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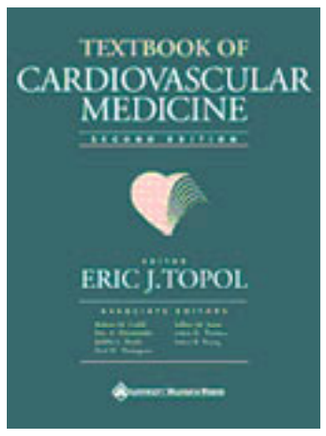

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Dedicated to the memory of
Jeffrey M. Isner, M.D., associate editor for the first and second editions, and one
of the most extraordinary researchers and individuals in the history of cardiovascular medicine

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PREFACE

Textbook of Cardiovascular Medicine, *2nd Edition*
A Pioneering Concept in the Era of Electronic Textbook Publishing

The success of the first edition of the *Textbook* was largely predicated on fulfilling its mission: “building a new, authoritative reference textbook in the field of cardiovascular medicine . . . based on the radical changes that have taken place in the past decade.” These changes not only include coverage of the largest specialty within medicine, but also the fully transformed electronic capabilities that have become both pervasive and prosaic. The CD-ROM version of the first edition of the *Textbook* received significant recognition and acclaim as a single disc that contained the entire expanded, two-volume *Comprehensive Cardiovascular Medicine* and hundreds of digital images and multimedia video clips to bring the text alive. Subsequent to the launch of this project, we were the first to make its entire contents fully available on the Internet at http://www.theheart.org/.

In this edition of the *Textbook* , we have developed an entirely new concept of electronic textbook publishing. This takes into account a broad embracing of digital technology, with a CD-ROM fully integrated with the textbook. The book and CD-ROM are a unit, with each component providing invaluable support for the other. The hard copy of the book is intended to capture the core material in our specialty; those sections of each chapter and whole chapters that are critical to providing a comprehensive reference source of the field are incorporated in the CD-ROM. This model of full integration of hard copy and an electronic medium has not been done before in medical textbook publishing. It is intended to cater to the realities of and need for rapidly looking up something in a book, which is simplified and limited in bulk, while at the same time providing in-depth probing of virtually all aspects of cardiovascular medicine, from its molecular areas to health care policy. Only via the electronic medium using the CD-ROM can all the detail be provided along with the extensive graphic support without being too voluminous.

The graphics are extensively hyperlinked to the text in an effort to broaden the presentation to not only words, but also multimedia imagery. The extent of this graphic support in magnitude has not been approached to date by any medical textbook, let alone the full integration concept. Clearly, this has been an ambitious and futuristic project for medical textbooks.

Beyond the book and electronic hybridization, there have been radical updates of nearly every chapter from the first edition (with the exception of such topics as history and physical examination!). New chapters include End-of-Life Care, Athlete’s Heart, Clinical Assessment of the Autonomic Nervous System, Percutaneous Coronary Intervention, Surgical Considerations in the Treatment of Heart Failure, Gene Therapy, and Molecular Basis of Heart Development. The updates and new chapters were built on the original framework of the eight sections of the book, which we believe continue to represent the optimal partitioning of the field’s major components. The digital anchoring of this project fully supports updates in the field, such as the significant advance in a clinical trial of rapamycin-coated stents that proved highly effective in reducing the incidence of restenosis after percutaneous coronary revascularization.

To execute this prodigious effort, we relied on nearly 200 expert contributing authors from all over the world. One of the most significant contributors to and editors of this project from its inception was Dr. Jeffrey M. Isner, who was a veritable pioneer in this field. His untimely death in late 2001 has sent shock waves throughout the biomedical community. Besides all the leadership he provided in gene therapy, angiogenesis, and translational research, he was deeply committed to this book and the value it would have for our field. Although it is only one dimension of Dr. Isner’s rich legacy, the editors and authors hope that this initiative will prove helpful in day-to-day care of patients with cardiovascular disease, serve as a stimulus for future research in basic and clinical science, and provide a utilitarian reference for all health care professionals, trainees, and biomedical researchers active in the field of cardiovascular medicine in the twenty-first century.

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As in the first edition, this project has been utterly consumptive and, without question, the most challenging and enormous undertaking that I have ever encountered. For it to be accomplished, a huge number of dedicated individuals came together in a highly synergistic fashion. The people behind the project include the superb section editors, nearly 200 contributing authors from all over the world, and two project teams. One, based at The Cleveland Clinic Foundation, included Donna Wasiewicz-Bressan, Managing Editor; Steve Nissen, CD-ROM Producer and Director; Suzanne Turner, Charlene Surace, Mary Ann Citraro, and Marion Tomasko, graphic artists; with extensive CD-ROM contributions from Timothy Crowe, Paula Shalling, Arman Askari, Ron Aviles, Keith Ellis, Murray Estess, Hitinder Gurm, Barbara Hesse, Matt Hook, Chris Jones, David Lee, Tom McRae, Chris Merritt, Adrian Messerli, David Rodriguez, Ravish Sachar, Niranjan Seshadri, Barb Srichai, Mike Yen, and Frank Zidar. Heart sounds were collected by Deb Mukherjee, Steve Lin, Khaldoun Tarakji, and Raymond Migrino. The other group, based at Lippincott Williams & Wilkins and Silverchair Science + Communications, included Ruth Weinberg, Executive Editor, and the editorial and production teams of Sonya Seigafuse, Brian Brown, Mary Ann McLaughlin, Alyson Langlois, Holly Hoe, and Lisa Cunningham. Only with the tight collaboration and dedication of all the editors, authors, and the project teams could such a vast endeavor come together so successfully. My personal appreciation to all of these people runs very deep and cannot be adequately expressed in words.

INTRODUCTION

CARDIOVASCULAR MEDICINE: A HISTORICAL PERSPECTIVE

W. BRUCE FYE

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Electrocardiograph
Challenge of Treating Heart Disease
United States Declares War on Heart Disease
Cardiac Catheterization
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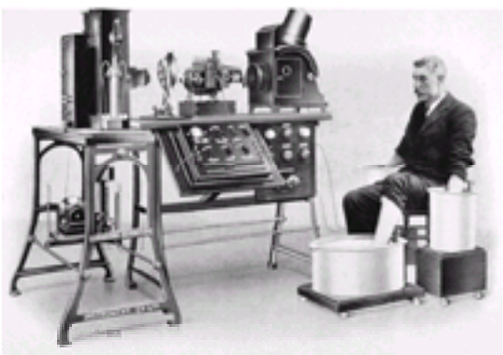
"Indicates text or graphics that appear only in the electronic versions of this text."

INTRODUCTION

This chapter provides a brief overview of some of the milestones in the history of cardiovascular disease. In it I describe several factors that stimulated cardiology's growth, especially in the United States, and set the stage for the discoveries and inventions that gave heart specialists so many powerful tools to help them diagnose and treat various cardiovascular diseases (1,2). Cardiology's remarkable growth in recent decades was fueled by new knowledge gained from research and controlled observation, the high prevalence of cardiovascular disease, and an impressive series of procedural and technological innovations. Social and economic factors (operative at local, regional, national, and international levels) also modulated the specialty's development. In the United States, a few doctors began to invent the specialty of cardiology in New York, Boston, and other large cities just before World War I. The process was dynamic and to some extent drew on European models of research and practice. The first physicians who identified heart disease as their main professional interest were a diverse group. Some focused on science, some on practice, and others on the socioeconomic consequences of cardiac disease. Their combined vision and contributions resulted in the differentiation of cardiology as a special field of endeavor.

ELECTROCARDIOGRAPH

Beginning with the electrocardiograph (ECG), invented in 1902 by Dutch physiologist Willem Einthoven, technology has played a major role in defining cardiology as a specialty (3,4 and 5). It became apparent within a few years that the ECG was a powerful research and clinical tool for studying cardiac arrhythmias (6). Within a decade, Einthoven's large and complicated instrument had migrated from the physiologist's laboratory to the hospital, where electrical cables connected it to patients. British physician and researcher Thomas Lewis was the first person in the English-speaking world to acquire an ECG machine for clinical investigation (in 1909). During the second decade of the twentieth century, his laboratory at University College Hospital, London, became a factory of new knowledge as a result of his passion for research and his possession of an ECG machine (eFig. 1). Lewis, a role model for aspiring cardiologists, did much to popularize the new diagnostic technique (7,8 and 9).



***e*FIGURE 1** A table-model Einthoven electrocardiograph made by the Cambridge Scientific Instrument Company (London) in 1911. [From an advertising leaflet in *Heart* 1912;4(2). Author's collection.]

World War I stimulated some Americans to become heart specialists. In 1917, several American internists with an interest in heart disease were assigned to the 700-bed Military Heart Hospital in Colchester, England. This huge facility offered unprecedented opportunities for the care and study of heart patients (10). It also meant that several dozen American physicians were exposed to Thomas Lewis and to James Mackenzie, who supervised two of the hospital's four services. Mackenzie, a Scottish general practitioner whose research focused on cardiac arrhythmias, was a role model for several of America's first-generation cardiologists (11).

During the 1920s, heart specialists began to appear in several of America's largest cities. Most were general practitioners or internists who focused their practice on cardiac disease; they were "partial" specialists. Very few physicians limited their practice to cardiology at this time; there simply was not enough specialty work. The career path to cardiology was informal. These first-generation heart doctors had little, if any, formal cardiology training. Most had completed an internship and a year of medical residency, and some had taken brief postgraduate courses on heart disease or ECG interpretation (12).

By the mid-1920s, a few teaching hospitals had appointed heart specialists to their staffs. These were part-time appointments; there were virtually no full-time academic posts for cardiologists until after World War II (13). Until then, academic cardiologists earned most or all of their income by seeing private patients and interpreting ECGs. The academic cardiologists' influence on the development of cardiology was substantial. They helped shape the specialty as lecturers and authors, as organizers of cardiac clinics and local heart associations, as consultants, and as role models. Through informal networks and through the American Heart Association (AHA), created in 1924, academic cardiologists had greater influence on the character of the emerging specialty than the much larger group of practitioner cardiologists.

The 1920s also resulted in additional opportunities for cardiologists in the United States, as more than 200 cardiac clinics opened in larger cities, and many hospitals sought electrocardiographers. Meanwhile, as public awareness of the frequency and implications of cardiac disease increased, more patients wanted to see a heart specialist (14). The AHA and other organizations encouraged apparently healthy persons to get periodic health examinations to identify unrecognized heart disease. Warning readers about the risk of heart attack and sudden death, a writer in the popular magazine *Hygeia* declared: "No business man who expects to succeed would think of neglecting to take inventory of his stock once a year." He urged them to get an annual examination supplemented by "instruments of precision" because "you can't get another heart" (15).

While heart specialists used the stethoscope, chest x-ray, and fluoroscope to help detect and classify heart disease, the ECG was the tool that set them apart from other practitioners. Because of its high cost, the ECG would not become the twentieth-century equivalent of the stethoscope—a diagnostic tool carried by all physicians (16). For many patients during the middle decades of the century, a doctor who possessed an ECG machine was, *de facto*, a heart specialist.

CHALLENGE OF TREATING HEART DISEASE

Between the world wars, the number of practitioner cardiologists in the United States increased significantly as a result of the public demand for cardiac evaluations, which usually included an ECG. Although doctors found the ECG helpful in detecting and characterizing heart disease, they still had few effective treatments to offer cardiac patients. James Herrick, a Chicago internist best known for his classic description of the clinical syndrome of acute myocardial infarction (AMI), told a group of doctors in 1928: “The cynic said to me, when he heard that I was to discuss the treatment of heart disease: ‘Why not condense and say there is no treatment for heart disease save rest and digitalis?’” Herrick admitted, “Really, the cynic is not far wrong” (17).

Three years later, Paul White (eFig. 2), America’s prototypical academic cardiologist, published a 931-page book on heart disease that revealed much about contemporary cardiology theory and practice. He divided cardiac disease into three main groups in order of frequency: coronary, hypertensive, and rheumatic heart disease were common; syphilitic and thyroid heart disease were fairly common; and bacterial endocarditis and congenital heart disease were uncommon. White’s sections on treatment show that practitioners used a wide variety of medicines and nonpharmacologic approaches to treat cardiac patients. But a close reading of the text reveals the serious limitations of contemporary therapeutics—something that White, like Herrick, acknowledged (18,19).

***e*FIGURE 2** Paul Dudley White. (From the Rare Books and Manuscript Division, Francis A. Countway Library of Medicine, Boston, Massachusetts, with permission.)

Although the sphygmomanometer (invented in the late nineteenth century) made it possible to detect hypertension, White conceded that treating hypertension was a “difficult and almost hopeless task.” Advances in electrocardiography, such as the introduction of precordial leads in the 1930s, helped doctors diagnose AMI and heightened their awareness of the spectrum of symptoms caused by coronary artery disease. But despite these new insights, White conceded that there was “no specific treatment for coronary disease” (18). In this preantibiotic era, infective endocarditis was invariably fatal, and there were no specific cures for syphilis or streptococcal infections. Valvular heart disease defied treatment, despite a few heroic attempts to operate for mitral stenosis.

Digitalis, quinidine, morphine, and nitroglycerin were the main cardiac drugs available to practitioners in the 1930s, and they are still used today. There were no antibiotics, potent diuretics, or antihypertensive agents. Congestive heart failure was treated with digitalis and diuretics (mercury compounds or purine derivatives like theophylline), but these drugs had significant side effects or had to be administered by injection. Rest was a mainstay of therapy for heart failure and angina.

UNITED STATES DECLARES WAR ON HEART DISEASE

The 1940s was a decade of transition in medical and surgical treatment of heart disease. It was also a time of great ferment in America’s small but expanding research community. There was a growing conviction that medical scientists could discover ways to cure or prevent many diseases, if only they had enough money and time for their research (20). Ambitious but largely unfunded, the medical scientists and clinical investigators who belonged to the AHA were becoming impatient.

During World War II, the leaders of the AHA decided that their association should follow the example of other disease-specific organizations, such as the National Foundation for Infantile Paralysis, which were raising huge sums of money from the public for research. During 1946 to 1948 they transformed the AHA from a professional society into a voluntary health organization whose public fund-raising drive would focus on research (21). The AHA leaders also joined forces with a group of legislators, government officials, and concerned citizens to form the “heart lobby.” Using a military metaphor to describe their goal, they told the American people and their political leaders that heart disease could be conquered if only enough money were given to support cardiovascular research (22).

The federal government’s role in financing cardiovascular research (and medical research in general) expanded dramatically after World War II. In 1948, Wisconsin Republican Frank Keefe claimed that “every member of Congress is thoroughly aware of the tremendous inroads that diseases of the heart are making upon the American people.” He urged the creation of a “heart control program” patterned after the government-sponsored cancer program (23). Later that year, Congress passed and Harry Truman signed the National Heart Act, designed “to support research and training in diseases of the heart and circulation.” The act established the National Heart Institute (NHI) as a division of the National Institutes of Health (NIH) and created the National Advisory Heart Council to review grant requests for research projects and training programs.

Paul White, Executive Director of the National Advisory Heart Council and Chief Medical Advisor to the NHI, first appeared before Congress in 1949. White, business woman and philanthropist Mary Lasker, and other members of the heart lobby stated and restated their simple message: If the nation invested in academic medical centers—facilities, researchers, and equipment were needed—practical discoveries were inevitable. Wartime programs had proved that systematic support of categorical research produced results. In the case of heart disease, the goals were prevention, earlier diagnosis, better treatments, and cures. Individuals would be helped, but the nation would be the real beneficiary. Lower mortality and morbidity from heart disease would result in a healthier and more productive work force.

The heart lobby worked tirelessly to ensure generous and consistent government support of the nation’s few organized cardiovascular research and training programs. Several medical advances helped White, Lasker, and their allies make their case to America’s citizens and their political leaders (24). In the decade after World War II, new drugs dramatically changed the way doctors cared for patients with cardiovascular disease. Antibiotics, oral diuretics, and effective antihypertensive medications were all introduced at this time (25). The significance of these and other advances is underscored by the case of Franklin Roosevelt. Crippled by polio, the president died from complications of malignant hypertension just before effective antihypertensive drugs and the Salk polio vaccine were developed (26).

At midcentury, heart specialists and their patients sensed they were entering a new era in the diagnosis and treatment of cardiovascular disease (27,28). The first truly dramatic therapeutic advances—ones that offered cardiac patients the possibility of cure—were in the emerging field of cardiovascular surgery (29,30). Although a few surgeons had tried to repair diseased heart valves in the 1920s, they abandoned the approach, because nearly all of the patients died. There was renewed interest in cardiovascular surgery after Boston surgeon Robert Gross successfully ligated a patent ductus arteriosus in 1938, and Swedish surgeon Clarence Crafoord successfully repaired a coarctation of the aorta 6 years later.

CARDIAC CATHETERIZATION

Meanwhile, a powerful new diagnostic technique—cardiac catheterization—was being developed (31). Just as the ECG made it possible to study cardiac electrophysiology in humans, the cardiac catheter allowed doctors to evaluate the heart’s structure and function. German surgeon Werner Forssmann had performed the first human cardiac catheterization in 1929—on himself. But his goal was not to advance cardiac diagnosis, it was to improve on a risky therapeutic procedure used in some cases of cardiac arrest. Forssmann had hoped to find a safer way than direct cardiac puncture to deliver medicines like adrenalin into the central circulation after cardiac arrest (32).

Twelve years later, André Cournand, Dickinson Richards, and their colleagues at Bellevue Hospital in New York City reported the results of the first series of heart catheterizations in humans. Although they were interested in cardiopulmonary physiology rather than cardiac diagnosis, these researchers showed that cardiac output and intracardiac pressures could be measured safely in patients (33). By 1945, the cardiac catheter was being used to study cardiopulmonary physiology in humans in Boston (Lewis Dexter), Atlanta (James Warren and Eugene Stead), London (John McMichael and Edward Sharpey-Schaefer), and Paris (Pierre Maurice and Jean Lenègre).

One surgeon’s desire for more accurate preoperative diagnosis helped to transform cardiac catheterization from an esoteric research tool into a standard clinical diagnostic technique. Johns Hopkins surgeon Alfred Blalock performed an operation in 1944 that inaugurated a new era in the treatment of cardiac disease. With

pediatric heart specialist Helen Taussig, he developed the “blue baby operation” for tetralogy of Fallot, the most common form of cyanotic congenital heart disease (eFig. 3) (34). News of the operation electrified the medical community and the public.

***e*FIGURE 3** An early Blalock-Taussig heart operation performed at the Johns Hopkins Hospital, 1945. (From the Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions, Baltimore, Maryland, with permission.)

Once surgeons began performing heart operations that were both life-saving and life-threatening, the limitations of standard diagnostic techniques (history, physical examination, auscultation, electrocardiography, x-ray, and fluoroscopy) became more apparent. Blalock knew that accurate preoperative diagnosis was crucial, and he thought the new technique of cardiac catheterization could provide useful physiologic information as part of the routine evaluation of his heart patients. He hired Richard Bing (eFig. 4) in 1945 to organize the world’s first *diagnostic* cardiac catheterization laboratory at Johns Hopkins (35).

***e*FIGURE 4** Richard J. Bing. (From the author’s collection.)

Later that year, Lewis Dexter developed a diagnostic cardiac catheterization program in Boston at the Peter Bent Brigham Hospital. He published a paper in 1946 that demonstrated the value of catheterization in the evaluation of children with congenital heart disease. Once catheterization was shown to be useful clinically, several innovations were introduced that enhanced the value of the cardiac catheter as a diagnostic tool. These included technical advances, such as improved pressure gauges and instruments to measure oxygen saturation, and new procedures, such as injecting dyes into the circulation to document intracardiac shunts (36).

ADVANCES IN THE TREATMENT OF CARDIOVASCULAR DISEASE

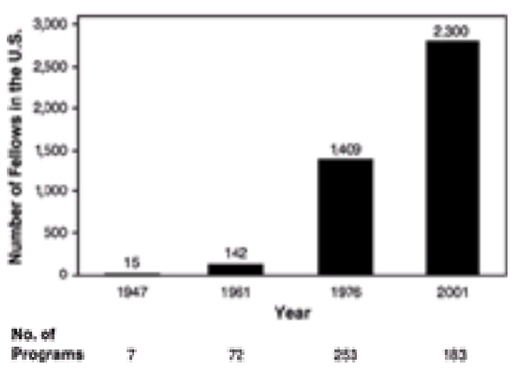
World War II contributed directly to the development of cardiovascular surgery, which in turn created demand for cardiologists trained to perform catheterization. Working in the European theater, Boston surgeon Dwight Harken adopted an aggressive approach for removing shell fragments from in and around the heart and great vessels. His experience proved that the heart was not the fragile organ that generations of doctors had assumed it to be. After the war, Harken resumed studies on the surgical treatment of mitral stenosis that Eliot Cutler had abandoned two decades earlier when almost every operated patient died (37). In 1948, Charles Bailey of Philadelphia and Harken independently performed successful operations on patients with mitral stenosis. Bailey used a special scalpel blade attached to his finger, whereas Harken relieved the obstruction by splitting the fused valve leaflets with his finger. Although several of their first patients died, they persisted and proved that such an operation could help some patients with mitral stenosis (38).

Meanwhile, the introduction of penicillin promised to change cardiology practice, because it was effective in treating (and preventing recurrent) streptococcal infections, by now recognized as the underlying cause of acute rheumatic fever. As the incidence of rheumatic fever declined, so did its cardiac complications (39). Penicillin also transformed bacterial endocarditis from a disease with a “hopeless prognosis” (Paul White, 1931) into “the most frequent curable cardiac disease” (Charles Friedberg, 1949) (18,40). Other medical advances also had important implications for patients with heart disease. For example, it was clear by 1950 that anticoagulants—intravenous heparin and oral dicumarol—were useful in the prevention and treatment of some forms of cardiovascular disease (41).

CONGRESS CATALYZES CARDIOLOGY

The federal government’s ambitious program of research funding after World War II energized academic medicine in the United States (42). Between 1945 and 1949, the NIH budget for extramural research increased 100-fold to $10 million. This resulted in discoveries and inventions that transformed medicine in general and cardiology in particular. The nation’s small but growing community of academic cardiologists and their institutions benefited from the creation of the NHI in 1948 and its program of extramural grants for researchers, facilities, equipment, and staff (43).

Specialty training also changed dramatically when the government began to subsidize research programs in university medical centers. The politicians who passed the National Heart Act wanted to be sure that their constituents benefited from the discoveries that academicians promised would result from the endowment of research. They thought this goal could best be achieved by producing more and better-trained heart specialists. Today, when 2,300 doctors are enrolled in the nation’s 183 cardiology fellowship programs, it is hard to comprehend that in 1947 there were just seven cardiology training programs that offered just 15 positions (eFig. 5) (44). The creation of the NHI (and the government funds it disbursed) had an immediate impact. In just 5 years, the number of cardiology training programs and fellowship positions quadrupled; by 1952, there were 27 training programs that offered 61 positions (45).



***e*FIGURE 5** Cardiology trainees and training programs.

Liberal government funding of academic medical centers led to an extraordinary expansion of the nation's capacity for biomedical research (eFig. 6). And the funds kept coming. In 1957, less than a decade after the creation of the NHI, the institute's budget exceeded $33 million (46). That year, the AHA budget was $20 million—half of it targeted to support research (21). The money was having the desired effect: more investigators, more research, and more well-trained heart specialists.

***e*FIGURE 6** United States Capitol. (From the author's collection.)

Basic and clinical research was paying off, and some of the most dramatic advances during the 1950s were in cardiovascular surgery. There were many challenges, however. Surgeons who hoped to develop operations for a variety of congenital and acquired cardiac defects knew they needed to *see* what they were doing inside the heart and *have time* to do it—no small feat in a beating, blood-filled organ. Open-heart surgery was possible once a heart-lung machine, which allowed surgeons to operate in a bloodless intracardiac field, was invented (47).

The earliest cardiac operations were performed on children with relatively simple congenital heart defects and middle-aged adults with rheumatic mitral stenosis. Before long, however, surgeons were developing procedures and inventing devices to treat other heart problems. The heart lobby could point with pride to these achievements, many of which represented the application of knowledge gained through basic research that was sponsored, at least in part, by the NHI (48).

Innovations in cardiac surgery catalyzed the further development and diffusion of cardiac catheterization and angiocardiography. These tests helped cardiologists and surgeons classify heart defects, quantitate their severity, and plan treatment. Referrals to heart specialists increased as cardiac patients and their family doctors learned about catheterization and heart surgery, as cardiologists and surgeons introduced these procedures into more hospitals, and as more Americans were covered by hospital insurance.

A 1964 survey of America's hospitals documented the rapid diffusion of cardiac catheterization and heart surgery from academic medical centers to community hospitals. There were 513 cardiac catheterization laboratories, 649 angiocardiography suites, 327 open-heart surgery programs, 777 closed-heart surgery programs, and 303 "fully equipped centers" offering all four procedures. That year, 30,654 catheterizations, 18,095 angiocardiograms, 8,792 open-heart operations, and 8,448 closed-heart operations were performed. More than half of these procedures were for congenital heart disease (49). This fact underscores how much cardiology and cardiac surgery would change when two new techniques—selective coronary angiography and saphenous vein coronary artery bypass graft (CABG) surgery—were introduced shortly after the survey was completed.

ASCENT OF CORONARY HEART DISEASE

During the 1960s, the focus of cardiology research and practice shifted from congenital and rheumatic heart disease to coronary artery disease. This trend was accelerated greatly by three innovations: selective coronary angiography, the coronary care unit (CCU), and CABG. Coronary angiography had the greatest impact on cardiology practice. Beginning in 1945, a few radiologists and cardiologists had developed techniques to visualize the coronary circulation by injecting contrast material in the proximal aorta. But these nonselective methods did not provide adequate images of the coronary arteries consistently, because most of the contrast material flowed down the aorta rather than into the coronary vessels (50).

Mason Sones, Jr. (eFig. 7), a cardiologist at The Cleveland Clinic, inadvertently performed a selective coronary angiogram in 1958, while doing an aortogram in a 26-year-old man with rheumatic heart disease. The catheter tip had migrated and contrast was injected directly into the right coronary artery. Sones was relieved when the patient experienced no ill effects—he expected his heart to arrest as a result of so much contrast entering the artery (51). Realizing he had discovered a technique for acquiring clear and detailed pictures of the entire coronary circulation, Sones published a description of his invention in 1962 (52). This procedure changed the practice—and the profession—of cardiology, just as the ECG had half a century earlier. Coronary angiography and other innovations in patient care placed coronary artery disease at the center of cardiology research and practice. The trend accelerated when the CCU concept was introduced almost simultaneously.

***e*FIGURE 7** Mason Sones, Jr. (*left*). (From the archives of The Cleveland Clinic Foundation, Cleveland, Ohio, with permission.)

AMI, with its risk of sudden death, is the most serious complication of coronary artery disease. Two innovations developed during the 1950s, the pacemaker and the external defibrillator, gave doctors the power to control some life-threatening arrhythmias that could complicate AMI and set the stage for the invention of the CCU (53,54). Boston cardiologist Paul Zoll published his method of using an external pacemaker to stimulate the heart of a patient who had developed asystole in 1952 (55). Two years later, he reported that ventricular fibrillation could be terminated by a shock delivered through the chest wall (56). The modern era of cardiopulmonary resuscitation began in 1960 when electrical engineer William Kouwenhoven and his colleagues at Johns Hopkins combined Zoll's defibrillation technique with closed-chest cardiac massage and mouth-to-mouth respiration (57,58).

These advances led to new strategies for delivering care to patients with AMI. In 1961, Desmond Julian of Edinburgh and Hughes Day of Kansas City, Kansas, independently developed a team approach for resuscitating hospitalized patients who had a cardiac arrest after an infarction (59,60). Their other innovation was to group vulnerable patients in a specific hospital setting—a CCU—equipped with cardiology's new electronic tools and staffed with nurses trained to use them and perform cardiopulmonary resuscitation. Continuous ECG monitoring of AMI patients in CCUs alerted nurses to sudden rhythm changes, and it also helped to clarify how they died. Whereas cardiac arrhythmias were shown to cause almost one-half of in-hospital AMI deaths, an equal number of patients died from shock and congestive heart failure. This finding led to new treatment strategies and stimulated research into ways to limit infarct size (61).

Although the advent of the CCU transformed the care of AMI patients and stimulated the job market for cardiologists, the nearly simultaneous expansion of indications for cardiac catheterization and coronary angiography had an even greater impact on the specialty. The major stimulus for the diffusion of coronary angiography in the late 1960s and early 1970s was the widespread adoption of a new surgical technique to treat angina.

Cleveland Clinic surgeon René Favaloro first described CABG as a treatment for angina in 1968, 6 years after his colleague Mason Sones, Jr., reported his technique of coronary angiography (62). As it became apparent that bypass surgery often improved anginal symptoms, the operation spread rapidly. Coronary angiography was a mandatory step if CABG was being considered, because it provided crucial information for deciding whether angina patients should be treated with medicines or surgery. If an operation was feasible, coronary angiography gave the surgeon a road map for the procedure. This stimulated the demand for cardiologists.

Meanwhile, echocardiography, another powerful diagnostic imaging technique, gave heart specialists a way to evaluate the heart's structure and function noninvasively. Diagnostic ultrasound evolved from military research that led to the invention of sonar and radar. The technique was first used to image the heart in 1954 by physicist Helmuth Hertz and cardiologist Inge Edler of the University of Lund, Sweden (63). Echocardiography migrated to the United States through the University of Pennsylvania, where biomedical engineers John Reid and Herman Schwann collaborated with cardiologist Claude Joyner to repeat and extend Hertz and Edler's work (64).

Harvey Feigenbaum, a cardiologist at Indiana University who became America's most vocal champion of echocardiography during the late 1960s and 1970s, was impressed with ultrasound's ability to detect pericardial effusion (65). The portable echocardiograph machine made it possible to detect a pericardial effusion promptly, noninvasively, and without risk. It also became apparent that the technique was useful in the evaluation of patients with congestive heart failure and heart murmurs. Meanwhile, other medical scientists and clinical investigators were inventing the important field of nuclear cardiology (66).

Technological innovations were not limited to diagnosis. Permanent, implantable electronic cardiac pacemakers were invented in Sweden and the United States in the late 1950s. Later in the decade, other researchers—most notably groups headed by Walton Lillehei in Minneapolis, Seymour Furman in New York City, and Ake Senning in Sweden—developed transvenous cardiac pacemakers for clinical use (67,68). University of Buffalo surgeon William Chardack reported the successful "implantation" of a battery-powered pacemaker built by engineer Wilson Greatbatch in 1960 (69). This report of a "permanent" pacemaker heralded a new era in the treatment of patients with symptomatic heart block and bradycardia.

During the second half of the twentieth century, market forces encouraged the rapid migration of these new cardiac diagnostic technologies and therapeutic procedures from academic medical centers to community hospitals across the country (70). Cardiovascular disease was common in middle-aged and older people—more than one million Americans had heart attacks each year. Citizens were becoming better informed about health care as the news media continued to emphasize medical "breakthroughs." The accelerating suburbanization of America also encouraged the spread of sophisticated heart care.

MEDICARE REVOLUTIONIZES AMERICAN MEDICINE

The increasing availability of health insurance as a benefit of employment also stimulated demand for specialized heart care. Between 1948 and 1965, the NHI had spent more than three-fourths of a billion dollars supporting its mission, and it could point with pride to many practical discoveries made by researchers it had funded. But as government-sponsored research led directly and indirectly to discoveries and innovations, concern grew that medical advances were diffusing too slowly into patient care (71). Congress passed laws in the mid-1960s designed to accelerate the practical application of new knowledge and to make health care more available to older and indigent Americans.

The Social Security Amendments of 1965 Act established Medicare, a program that entitled all U.S. citizens 65 years of age and older to government-funded hospital insurance benefits, and Medicaid, a program that paid for care delivered to the indigent. Medicare Part A paid for hospital-based diagnostic and treatment services provided to older Americans who were guaranteed "free choice" to "obtain health services from any institution, agency, or person qualified to participate." Medicare Part B covered many physicians' services through a voluntary "supplementary medical insurance" program eventually administered by nongovernment third-party payers (72).

Just as NIH research grants had helped many academic medical centers build and equip catheterization laboratories during the 1950s, Medicare made it possible for many larger nonteaching hospitals to install them after 1965. This fueled the demand for invasive cardiologists across the country. Cardiology technology and trainees went hand-in-hand. Liberal government funding had created an academic infrastructure capable of rapid expansion, and cardiology training programs were poised to meet the growing demand for practitioner cardiologists to diffuse new diagnostic tools like coronary angiography and echocardiography. Between 1961 and 1976, the number of cardiology training programs grew from 72 to 253, and the number of fellows increased *tenfold* from 142 to 1,409 (2).

Medicare had important implications for heart specialists, because it provided payment for office-based services and outpatient diagnostic tests, an area of cardiology that would expand rapidly during the 1970s. Medicare and private health insurance reimbursement policies helped transform cardiology from a technology-*oriented* into a technology-*dominated* specialty. The field was poised for growth as new equipment and techniques were invented, indications for their use were liberalized, and access to them was enhanced by expanding health insurance coverage. Cost was no longer a barrier to specialty care for many patients with an acute illness who required hospitalization. If they had (or got) heart disease, insured patients wanted access to "modern" cardiac care close to home, and this meant technology and heart specialists. By the mid-1970s, the nation's cardiology and cardiothoracic surgery training programs were producing a record number of practitioners to meet the demand. These doctors transferred innovations like coronary angiography, echocardiography, and open-heart surgery from academic centers to community hospitals across town and around the country.

Along with this explosion of technology and hospital-based care, the number of physicians increased dramatically in the United States, beginning in the late 1960s as a result of new government policies (73). The federal government first committed significant resources to augment the physician work force in 1963 with enactment of the Health Professions Educational Assistance Act. Congress gave medical schools more than $5 billion in direct funding between 1965 and 1971. This led to a dramatic increase in the number of medical schools and students (74). It also helped to swell the ranks of cardiologists and other specialists. By this time, the academics who taught America's medical students and residents were not part-time practitioners or primary care physicians—they were full-time clinical scientists and specialists.

CARDIAC CATHETER BECOMES A THERAPEUTIC TOOL

Cardiology entered a new era in the late 1970s when medical heart specialists began to perform *therapeutic* catheterization procedures. German cardiologist Andreas Grüntzig (*e*Fig. 8) performed the first percutaneous transluminal coronary angioplasty (PTCA) for the treatment of angina in September 1977 in Zurich, Switzerland (75). PTCA migrated to the United States within a few months of Grüntzig's first procedure. Powerful social and economic forces encouraged the spread of angioplasty before the procedure's efficacy had been proved scientifically. Understandably, many angina patients chose PTCA over CABG, because it seemed to work and meant they could avoid the discomfort, risks, and recovery time of open-heart surgery.

***e*FIGURE 8** Andreas Grüntzig. (From Willis Hurst, Emory University School of Medicine, with permission.)

Angioplasty revolutionized cardiology, much like open-heart surgery and the ECG had one and two generations earlier. But there were important differences. Before PTCA, cardiologists had used the catheter as a *diagnostic* tool to help channel patients to surgeons. Now, a new type of medical heart specialist, the interventional cardiologist, used a special catheter to perform *therapeutic* procedures on patients with angina. This changed the traditional relationship between medical and surgical heart specialists—collaborators suddenly became competitors who offered angina patients radically different treatment approaches (76).

During the 1980s, PTCA spread rapidly as many cardiologists learned the technique by attending "demonstration" courses or from their colleagues, and hundreds of fellows trained to perform the procedure entered practice. Meanwhile, clinical investigators and equipment manufacturers collaborated to develop new balloon

catheters to simplify the procedure, and innovators showed that multiple coronary lesions and multiple vessels could be safely dilated in a sequential fashion. Other important innovations in interventional cardiology, such as stents, are beyond the scope of this historical review. By the 1990s, the number of angioplasties equaled the number of bypass operations performed in the United States.

Concurrent with the development of PTCA, other medical scientists and heart specialists were inventing new techniques and refining old ones to study and treat arrhythmias (77). Beginning with the efforts of Benjamin Scherlag and his colleagues at the Staten Island Public Health Service Hospital, the field of invasive clinical electrophysiology had evolved into a formal subspecialty of cardiology by the mid-1970s. This field grew dramatically during the 1980s and 1990s with the invention of the automatic implantable defibrillator and the development of radiofrequency ablation (78).

Meanwhile, the treatment of AMI was being revolutionized by the introduction of thrombolytic therapy (79). This advance resulted from the efforts of many scientists and clinical investigators, beginning with bacteriologist William Tillett who discovered in 1933 that beta-hemolytic streptococci produced a fibrinolytic substance that he named *fibrinolysin*, later called *streptokinase* (80). Anthony Fletcher, Sol Sherry (who had worked with Tillett), and their associates first reported giving streptokinase to patients with AMI in 1958 (81). However, the clinical use of streptokinase was delayed because of concerns regarding the pyrogenicity and antigenicity of the substance.

Although E. I. Chazov and colleagues from Russia reported successful reperfusion of the infarct-related artery after intracoronary administration of streptokinase and heparin in 1976, their report was published in Russian with a brief English summary and went largely unnoticed. The modern era of thrombolytic therapy for acute myocardial infarction began 3 years later when Peter Rentrop and his associates from Göttingen, Germany, published a report on the intracoronary administration of streptokinase in five patients (82). The following year, Spokane cardiologist Marcus DeWood and his colleagues reported the high prevalence of total coronary occlusion during the early hours of AMI, documented by coronary angiography (83). The papers by Rentrop and DeWood led to widespread introduction of intracoronary streptokinase therapy.

Several European and American groups soon published studies that demonstrated the efficacy of intravenous streptokinase, an important observation for those AMI patients hospitalized in institutions without a cardiac catheterization laboratory (84,85). Meanwhile, other European groups were studying another thrombolytic agent, tissue plasminogen activator (t-PA), discovered in 1947 by Danish biologists Tage Astrup and Per Permin (86). A quarter of a century later, W. Weimar, Desire Collen, and their associates in Belgium and the Netherlands reported the successful intravenous administration of t-PA in an attempt to lyse a renal and iliofemoral thrombus in a renal transplant recipient (87).

Collen and his collaborators in the United States reported in 1983 that t-PA could lyse intracoronary thrombus that had been induced experimentally in dogs (88). The successful cloning and expression of the human t-PA gene that year meant that sufficient quantities of the substance could be produced for commercial marketing (89). The many clinical trials of thrombolytic therapy during the past two decades are beyond the scope of this review, but they proved that this approach saved lives (90).

EPILOGUE

Cardiology is one of modern medicine's greatest triumphs. During the second half of the twentieth century, cardiovascular mortality declined dramatically. Today, millions of heart patients are living longer and living better as a result of decades of research and specialty care. But medicine has entered a new era in the United States. The managed-care paradigm frames specialists and their tools and techniques as expensive resources. The issue is no longer what has been accomplished and what is still possible, but rather what is affordable. Practitioners and academicians share many concerns about how new health care delivery models, reimbursement strategies, and societal attitudes will affect cardiovascular research, education, and practice (91,92).

Resources are limited, and medical research and health care delivery must become more efficient. Now, more than ever, doctors must learn how to use technology wisely and prescribe cost-effective treatments. Outcomes research and practice guidelines, still in their infancy, will help them achieve this goal. But in this era of cost-containment, we must not lose sight of how the gains made against heart disease since World War II were achieved. By understanding the past, we will be better able to shape the future of health care and ensure that patients have access to the breakthroughs still to come.

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1

ATHEROSCLEROTIC BIOLOGY AND EPIDEMIOLOGY OF DISEASE

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JAMES H. F. RUDD

"Indicates text or graphics that appear only in the electronic versions of this text."

Epidemiology of Cardiovascular Disease
Biology of Atherosclerosis
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Atherosclerotic Vessel
Theories of Atherogenesis
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EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE

Atherosclerosis, with its complications, is the leading cause of mortality and morbidity in the developed world. In the United States, a snapshot of the population would reveal that 60 million adults currently suffer from atherosclerotic cardiovascular disease, which accounts for 42% of all deaths annually, at a cost to the nation of $128 billion. Fortunately, despite this catastrophic burden of disease, much evidence has emerged over the last decade suggesting that the progression of atherosclerosis can be slowed or even reversed in many people with appropriate lifestyle and drug interventions.

The origin of the current epidemic of cardiovascular disease can be traced back to the time of industrialization in the 1700s. The three factors largely responsible for this were an increase in the use of tobacco products; reduced physical activity; and the adoption of a diet high in fat, calories, and cholesterol. This rising tide of cardiovascular disease continued into the twentieth century but began to recede when data from the Framingham study identified a number of modifiable risk factors for cardiovascular disease, including cigarette smoking, hypertension, and hypercholesterolemia (1).

The number of deaths per 100,000 attributable to cardiovascular disease peaked in the Western world in 1964 to 1965, since which time there has been a gradual decline in death rates (Fig. 1.1) (2). The age-adjusted coronary heart disease mortality in the United States dropped by more than 40% and cerebrovascular disease mortality by more than 50%, with the greatest reductions being seen among whites and males. This reduction has occurred despite a quadrupling of the proportion of the population older than 65 years of age and has been due to a number of factors, particularly major health promotion campaigns aimed at reducing the prevalence of Framingham risk factors. Indeed, there has been a substantial change in the prevalence of population cardiovascular risk factors over the last 30 years (Table 1.1). The war is not won, however, and the decline in the death rate from cardiovascular disease slowed in the 1990s (Fig. 1.2). This is likely due to a large increase in the prevalence of both obesity and type 2 diabetes mellitus, as well as a resurgence of cigarette smoking in some sectors of society (3). Female death rates from cardiovascular disease overtook male death rates in 1984 and have shown a smaller decline over the last 30 years (4). The consequences of atherosclerosis are also beginning to be felt in less well-developed regions of the globe (5), with death from atherosclerotic cardiovascular disease set to replace infection as the leading cause of death in the Third World in the near future.

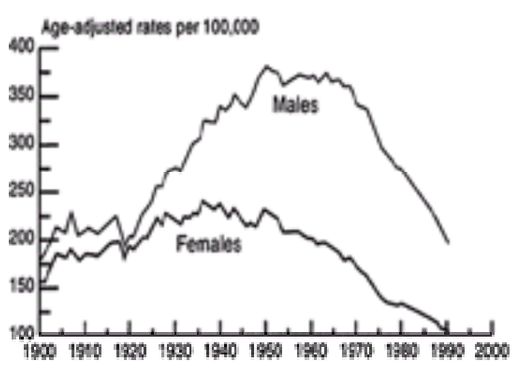


FIGURE 1.1 Trends in death rates for heart diseases: United States, 1900 to 1991. [From Feinleib M. Trends in heart disease in the United States (review). *Am J Med Sci* 1995;310(Suppl 1):S8–S14, with permission.]

Cigarette smoking	1960	Men: 55%; Women: 33%
	1990	Men: 30%; Women: 27%
Undiagnosed hypertension	1960	52%
	1980	29%
Mean serum cholesterol	1960	225 mg/dL
	1990	208 mg/dL
Diabetes mellitus	1970	2.6%
	1990	9.1%
Sedentary lifestyle	1970	41%
	1985	27%
Obesity	1960	25%
	1990	38%

From Miller M, Vogel RA. *The practice of coronary disease prevention*. Baltimore: Williams & Wilkins, 1996.

TABLE 1.1 TEMPORAL CHANGES IN CORONARY RISK FACTORS

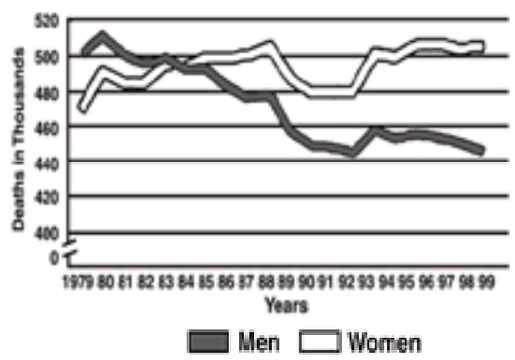


FIGURE 1.2 Cardiovascular disease mortality trends for men and women: United States, 1979 to 1998. (Source: CDC/NCHS and the American Heart Association, with permission.)

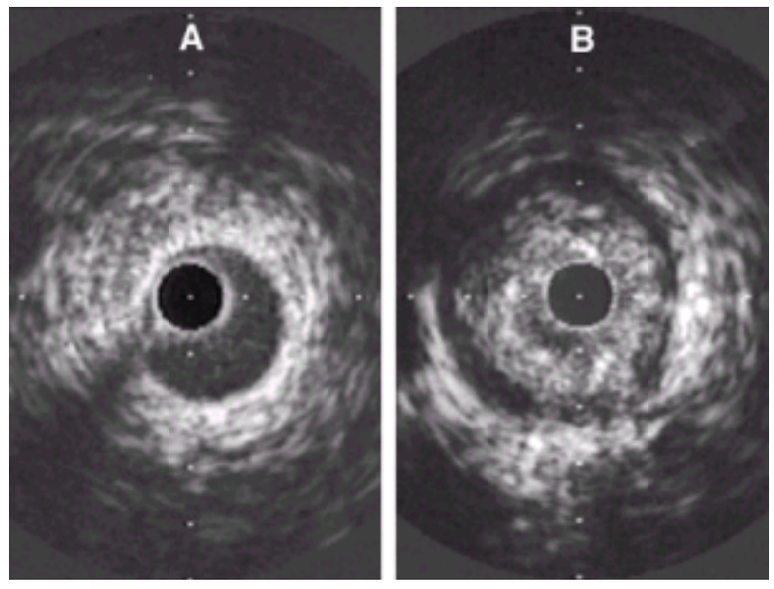
BIOLOGY OF ATHEROSCLEROSIS

Traditionally, atherosclerosis has been viewed as a degenerative disease, affecting predominantly older people, slowly progressing over many years, and eventually leading to symptoms through mechanical effects on blood flow. The perceived insidious and relentless nature of its development has meant that a somewhat pessimistic view of the potential to modify its progression by medical therapy has held sway. There has been little emphasis on the diagnosis and treatment of high-risk asymptomatic patients. Disease management has instead been dominated by interventional revascularization approaches, targeting the largest and most visible or symptomatic lesions with coronary angioplasty or bypass surgery.

Recently, for three reasons, this defeatist view of the pathogenesis and progression of atherosclerosis has begun to change. First, careful descriptive studies of the underlying pathology of atherosclerosis have revealed that atherosclerotic plaques differ in their cellular composition and that the cell types predominating in the plaque can determine the risk of fatal clinical events. Second, recent cellular and molecular biologic work has emphasized the importance of inflammatory cells and inflammatory mediators in the pathogenesis of atherosclerosis. The third and most important reason is because several large-scale clinical trials have reported that drugs—in particular, the HMG-CoA reductase inhibitors—are able to reduce the number of clinical events in patients with established atherosclerosis and do so without necessarily affecting the size of atherosclerotic plaques. These three strands of evidence have shown that, rather than being an irreversibly progressive disease, atherosclerosis is a dynamic, inflammatory process that may be amenable to medical therapy. Understanding the cellular and molecular interactions that determine the development and progression of atherosclerosis brings with it opportunities to develop novel therapeutic agents targeting key molecular and cellular interactions in its etiology. In addition, the recognition that the clinical consequences of atherosclerosis depend almost entirely on plaque composition argues for a new approach to diagnosis, with less emphasis placed on the degree of lumen narrowing and more interest in the cellular composition of the plaque.

NORMAL ARTERY

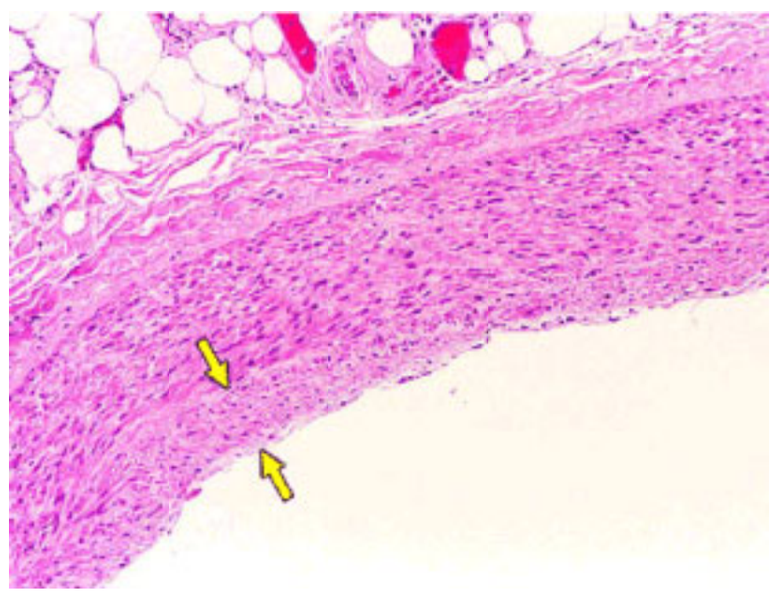
The healthy artery consists of three histologically distinct layers. Innermost and surrounding the lumen is the tunica intima, which comprises a single layer of endothelial cells in close proximity to the internal elastic lamina. The tunica media surrounds the internal elastic lamina, and its composition varies depending on the type of artery. The tunica media of the smallest arterial vessels, arterioles, comprises a single layer of vascular smooth muscle cells (VSMCs). Small arteries have a similar structure but with a thicker layer of medial VSMCs. Arterioles and small arteries are termed *resistance vessels* because they contribute vascular resistance and, hence, directly affect blood pressure. At the opposite end of the spectrum are large elastic or conduit arteries, named for the high proportion of elastin in the tunica media. The tunica media of all arteries is contained within a connective tissue layer that contains blood vessels and nerves and that is known as the *tunica adventitia*. In normal arteries, the vessel lumen diameter can be altered by contraction and relaxation of the medial VSMCs in response to a variety systemic and locally released signals.



Comparison of normal (A) vs. atherosclerotic coronary morphology (B).

ATHEROSCLEROTIC VESSEL

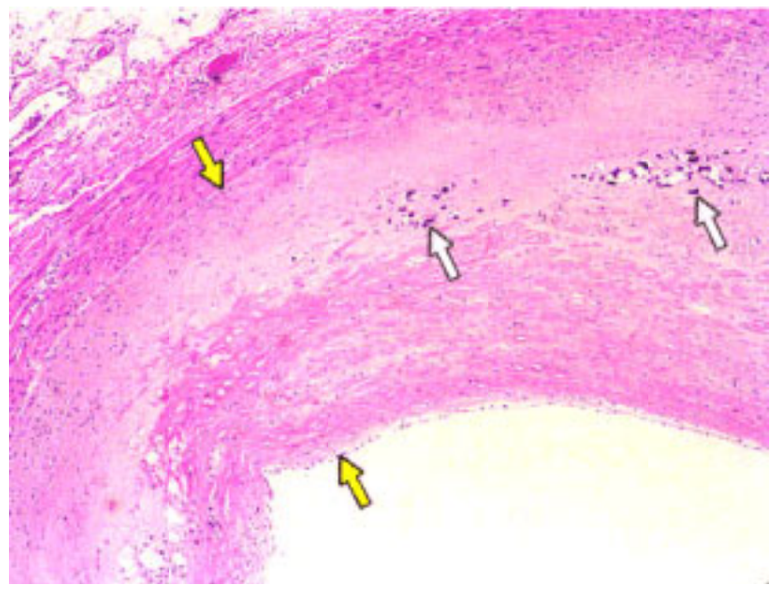
Atherosclerosis is primarily a disease affecting the intimal layer of elastic arteries. For reasons that remain largely unknown, some arterial beds appear more prone than others. Coronary, carotid, cerebral, and renal arteries and the aorta are most often involved. The arteries supplying the lower limb are also vulnerable to disease. Interestingly, the internal mammary artery is almost always spared, making it an invaluable vessel for coronary bypass surgery.



Early changes of coronary atherosclerosis. There is intimal proliferation (between the yellow arrows). The media and adventitia remain normal.

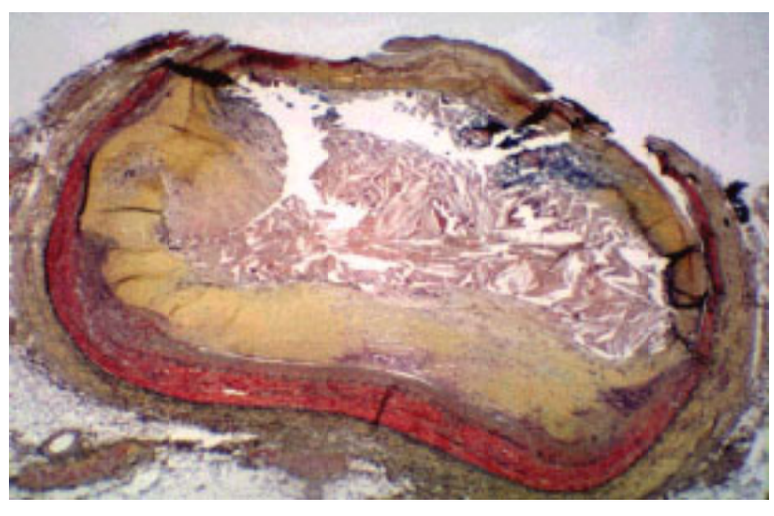
Atherosclerotic lesions develop over many years and pass through several stages. Histologically, the earliest lesion is a subendothelial accumulation of lipid-laden macrophage foam cells and associated T lymphocytes known as a *fatty streak*. Fatty streaks are asymptomatic and nonstenotic. Postmortem examinations have

shown that they are present in the aorta at the end of the first decade of life, are present in the coronary arteries by the second, and begin to appear in the cerebral circulation by the third decade. With time, the lesion progresses and the core of the early plaque becomes necrotic, containing cellular debris, crystalline cholesterol, and inflammatory cells, particularly macrophage foam cells. This necrotic core becomes bounded on its luminal aspect by an endothelialized fibrous cap, consisting of VSMCs embedded in an extensive collagenous extracellular matrix. Inflammatory cells are also present in the fibrous cap, concentrated particularly in the “shoulder” regions, where T cells, mast cells, and especially macrophages have a tendency to accumulate. Advanced lesions may become increasingly complex, showing evidence of calcification, ulceration, new vessel formation, and rupture or erosion. Thus, the composition of atherosclerotic plaques is variable and complex, and it is the interaction between the various cell types within a plaque that determines the progression, complications, and outcome of the disease.



Advanced coronary atherosclerosis. There is fibrotic intimal thickening marked by the yellow arrows with small areas of intimal calcification (*white arrows*).

Severe calcific atherosclerosis of aorta. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Severe atherosclerosis of saphenous vein graft. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

THEORIES OF ATHEROGENESIS

Over the years, several theories have been advanced to explain the process of atherosclerosis. None of these is able to account for all aspects of the disease. The most recent, which views atherosclerosis as a consequence of inflammation in the vessel wall, is supported by the results of large-scale clinical trials, as discussed below. Several of these hypotheses are discussed briefly below.

Lipid Hypothesis

The lipid hypothesis, proposed initially in 1913 by Anitschkow, holds that the development of atherosclerosis is the result of the gradual accumulation of lipid in the arterial wall, with its presence at that site being responsible for the generation of the characteristic tissue changes of atheroma. In animal models, hyperlipidemia, as a result of either a high-fat diet or genetic modification, reliably leads to the development of atherosclerotic lesions in many species. This idea is supported by the wealth of evidence that links elevated serum lipid levels with the risk of development of atherosclerotic lesions in humans (6).

Thrombogenic Hypothesis

The thrombogenic hypothesis holds that atherosclerotic lesions grow by the gradual incorporation of luminal thrombus into the arterial wall. It is supported by the finding of fibrin (7) and platelet-derived proteins in both developing and mature atherosclerotic plaques (8). In addition, thrombus contains large amounts of platelet-derived growth factor, a potent VSMC mitogen. However, this theory is difficult to prove because plaque infiltration by immature blood vessels is common in advanced lesions, and consequent hemorrhage and thrombosis also occur frequently. Therefore, thrombus may appear directly as a result of atherosclerosis rather than as a causative factor.

The initiating factor for atherosclerosis formation in both of the above theories can be considered to be endothelial dysfunction. In the lipidic theory, a defective endothelial cell barrier may permit the gradual seepage of lipid into the arterial intima layer, allowing the plaque formation process to begin. In the thrombogenic theory, a dysfunctional endothelium may allow local platelet aggregation and clot formation that might subsequently become incorporated into the arterial wall. The idea that endothelial dysfunction is central to atherosclerosis has dominated recent theories about the origin of atherosclerosis.

Response to Injury Hypothesis

The response to injury hypothesis was initially proposed by Virchow in 1856, who believed that the degenerative changes associated with atherosclerosis were due to a healing response of the arterial intima to a prior mechanical injury.

Modified Response to Injury Hypothesis

In 1973, Russell Ross and John Glomset published a modified version of the response to injury hypothesis (9). They noted histologic similarities between advanced native atherosclerotic plaques and those created in monkeys' aortas by balloon injury of the endothelium. They suggested that atheroma was the result of excessive VSMC proliferation in response to an endothelial injury. This idea was later revised, and subsequent versions of the theory have claimed that endothelial dysfunction from any cause—not necessarily a mechanical injury—is crucial for the development of atherosclerosis (10,11). These injurious agents are what we today regard as risk factors for atherosclerosis and include hypertension, hyperlipidemia, and cigarette smoking.

Inflammation Theory

In his most recent review of the pathogenesis of atherosclerosis (12), Ross continues to state the importance of endothelial dysfunction in the origin of atherosclerosis but also highlights the role played by inflammation at every step of the pathogenesis of atherosclerosis. The key roles played in this process by endothelial, inflammatory, and smooth muscle cells are reviewed in the next section.

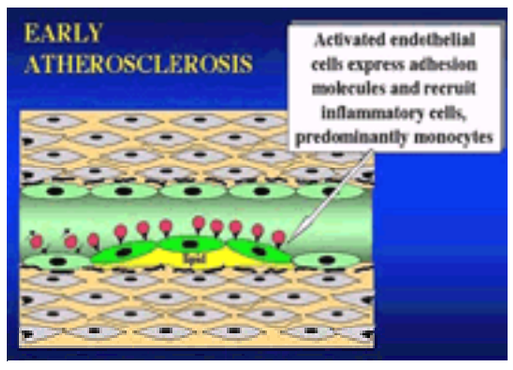
CELLULAR ROLES IN ATHEROGENESIS

Endothelial Cells

The endothelium plays a central role in maintaining vascular health by virtue of its vital antiinflammatory and anticoagulant properties. Many of these characteristics are mediated by the nitric oxide molecule (NO). This molecule was discovered in the 1980s, having been isolated from lipopolysaccharide-primed macrophages (13). NO is synthesized by endothelial cells under the control of the enzyme endothelial nitric oxide synthase and has a number of antiatherogenic properties. First, it acts as a powerful inhibitor of platelet aggregation on endothelial cells. Second, it can reduce inflammatory cell recruitment into the intima by abrogating the expression of genes involved in this process, such as those encoding intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin, and monocyte chemoattractant protein-1 MCP-1) (14,15 and 16). There is some evidence that NO may also reduce lipid entry into the arterial intima (17). NO is also a potent antiinflammatory molecule and, depending on concentration, may be a scavenger or a producer of potentially destructive oxygen free radicals, such as peroxynitrite (18,19 and 20).

The earliest detectable manifestation of atherosclerosis is a decrease in the bioavailability of NO in response to pharmacologic or hemodynamic stimuli (12). This may occur for two reasons. Either there may be decreased manufacture of NO because of endothelial cell dysfunction, or increased NO breakdown may take place. There is evidence that both mechanisms may be important in different situations (21). Many atherosclerosis risk factors can lead to impaired endothelial function and reduced NO bioavailability. For example, hyperlipidemic patients have reduced NO-dependent vasodilatation. This reduction is reversed when patients are treated with lipid-lowering medication (22). Patients with diabetes mellitus also have impaired endothelial function, occurring primarily as a result of impaired NO production. There is, however, some evidence to suggest that increased oxidative stress leading to enhanced NO breakdown may also be a factor (23). Similarly, other risk factors for atherosclerosis, such as hypertension and cigarette smoking, are associated with reduced NO bioavailability (24,25). In cigarette smokers, endothelial impairment is thought to be due to enhanced NO degradation by oxygen-derived free radical agents such as the superoxide ion. There are also other consequences of an increased reactivity between NO and superoxide species. The product of their interaction, ONOO– (peroxynitrite), is a powerful oxidizing agent and can reach high concentrations in atherosclerotic lesions. This may result in cellular oxidative injury.

Another consequence of endothelial cell dysfunction that occurs in early atherosclerosis is the expression of surface-bound selectins and adhesion molecules, including P-selectin, ICAM-1, and VCAM-1. These molecules attract and capture circulating inflammatory cells and facilitate their migration into the subendothelial space (eFig. 1.2.1) (12). Normal endothelial cells do not express these molecules, but their appearance may be induced by abnormal arterial shear stress, subendothelial oxidized lipid, and, in diabetic patients, advanced glycosylation products in the arterial wall. The importance of selectins and adhesion molecules in the development of atherosclerosis is demonstrated by experiments using mice, which lack their expression. These animals develop smaller lesions with a lower lipid content and fewer inflammatory cells than control mice when fed a lipid-rich diet (26). Animal models have reinforced the importance of inflammatory cell recruitment to the pathogenesis of atherosclerosis, but because inflammatory cells are never seen in the intima in the absence of lipid, the results suggest that subendothelial lipid accumulation is also necessary for the development of atherosclerosis.



***e*FIGURE 1.2.1** Early atherosclerosis. (From Weissberg PL. Atherogenesis: current understanding of the causes of atheroma. *Heart* 2000;83:247–252, with permission.)

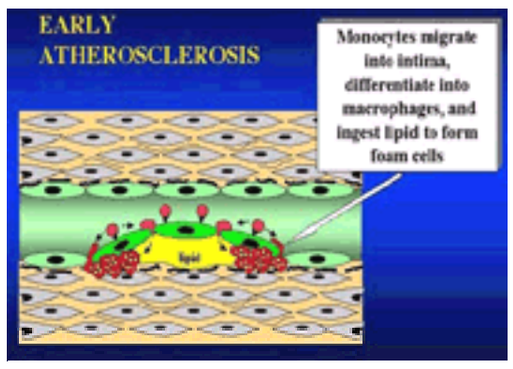
The tendency for atherosclerosis to occur preferentially in particular sites may be explained by subtle variations in endothelial function. This is probably caused by variations in local blood flow patterns, especially conditions of low flow, which can influence expression of a number of endothelial cell genes, including those encoding ICAM-1 and endothelial nitric oxide synthase (27,28). In addition to flow speed, flow type can have a direct effect on cell morphology. In areas of laminar flow, endothelial cells tend to have an ellipsoid shape, contrasting with the situation found at vessel branch points and curves, where turbulent flow induces a conformational change toward polygonal-shaped cells. Such cells have an increased permeability to low-density lipoprotein (LDL) cholesterol and may promote lesion formation (29).

These data are consistent with the idea that the primary event in atherogenesis is endothelial dysfunction. The endothelium can be damaged by a variety of means, leading to dysfunction and, by unknown mechanisms, subsequent subendothelial lipid accumulation. In this situation, the normal homeostatic features of the endothelium break down; it becomes more adhesive to inflammatory cells and platelets, it loses its anticoagulant properties, and there is reduced bioavailability of NO. Importantly, endothelial function is improved by drugs that have been shown to substantially reduce death from vascular disease, including statins and angiotensin-converting enzyme inhibitors (30,31).

Inflammatory Cells

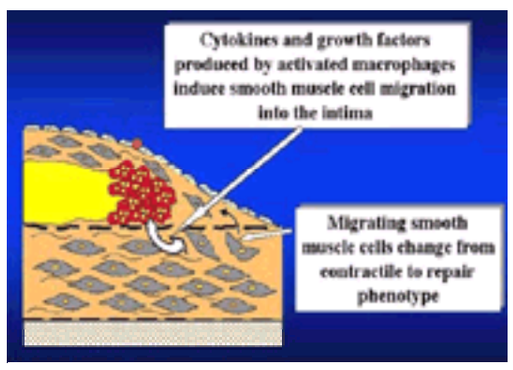
LDL from the circulation is able to diffuse passively through the tight junctions that bind neighboring endothelial cells. The rate of passive diffusion is increased when the circulating levels of LDL are elevated. In addition, other lipid fractions may be important in atherosclerosis. Lipoprotein(a) has the same basic molecular structure as LDL, with an additional apolipoprotein(a) element attached by a disulfide bridge. It has been shown to be highly atherogenic (32), to accumulate in the arterial wall in a manner similar to LDL (33), to impair vessel fibrinolysis (34), and to stimulate smooth muscle cell proliferation (35). The accumulation of subendothelial lipids, particularly when at least partly oxidized, is thought to stimulate the local inflammatory reaction that initiates and maintains activation of overlying endothelial cells. The activated cells express a variety of selectins and adhesion molecules and also produce a number of chemokines—in particular, MCP-1, whose expression is upregulated by the presence of oxidized LDL in the subendothelial space (36). Interestingly, the protective effect of HDL against atherosclerotic vascular disease may be partly explained by its ability to block endothelial cell expression of adhesion molecules (37,38). Chemokines are proinflammatory cytokines that are responsible for chemoattraction, migration, and subsequent activation of leukocytes. Mice lacking the MCP-1 gene develop smaller atherosclerotic lesions than normal animals (39). The first stage of inflammatory cell recruitment to the intima is the initiation of "rolling" of monocytes and T cells along the endothelial cell layer. This phenomenon is mediated by the selectin molecules, which selectively bind ligands found on these inflammatory cells. The subsequent firm adhesion to and migration of leukocytes through the endothelial cell layer is dependent on the endothelial expression of adhesion molecules such as ICAM-1 and VCAM-1 and their binding to appropriate receptors on inflammatory cells. Once present in the intima, monocytes differentiate into macrophages under the influence of chemokines such as macrophage colony-stimulating factor. Such molecules also stimulate the expression of the scavenger receptors that allow macrophages to ingest oxidized lipids and to develop into macrophage foam cells, the predominant cell in an early atherosclerotic lesion (eFig. 1.2.2). The formation of scavenger receptors is also regulated by peroxisome

proliferator-activated receptor-g, a nuclear transcription factor expressed at high levels in foam cells (40).



***e*FIGURE 1.2.2** Early atherosclerosis. (From Weissberg PL. Atherogenesis: current understanding of the causes of atheroma. *Heart* 2000;83:247–252, with permission.)

In early atherosclerosis at least, the macrophage can be thought of as performing a predominantly beneficial role as a “neutralizer” of potentially harmful oxidized lipid components in the vessel wall. However, macrophage foam cells also synthesize a variety of proinflammatory cytokines and growth factors that contribute both beneficially and detrimentally to the evolution of the plaque. Some of these factors are chemoattractant (osteopontin) (41,42) and growth-enhancing (platelet-derived growth factor) for VSMCs. Under the influence of these cytokines, VSMC migrate from the media to the intima, where they adopt a synthetic phenotype, well-suited to matrix production and protective fibrous cap formation (*e*Fig. 1.2.3).



***e*FIGURE 1.2.3** Smooth muscle cell migration and phenotype change.

However, activated macrophages have a high rate of apoptosis. Once dead, they release their lipid content, which becomes part of the core of the plaque, thereby contributing to its enlargement. The apoptotic cells also contain high concentrations of tissue factor, which may invoke thrombosis if exposed to circulating platelets (43).

Immunohistochemical studies have demonstrated that T lymphocytes are present in atheromatous plaques, located predominantly in the subendothelial space. The cells are in an activated state, as evidenced by expression of human leukocyte antigen-DR, CD-25 (interleukin-2 receptor), and CD-30 (44). The cells are mainly of the T-helper type 1 class, characterized by the production of interleukin-2 and interferon-g (IFN-g). These factors can alter plaque morphology and can also upregulate adhesion molecule expression by endothelial cells, thereby recruiting more cells to join the inflammatory process.

It is now generally recognized that the pathologic progression and consequences of atherosclerotic lesions are determined by dynamic interactions between inflammatory cells recruited in response to subendothelial lipid accumulation, and the local reparative “wound healing” response of surrounding VSMCs (Fig. 1.3).

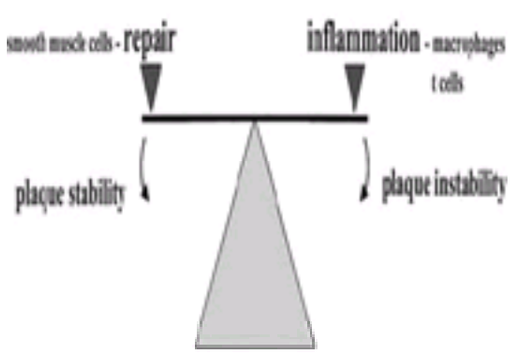
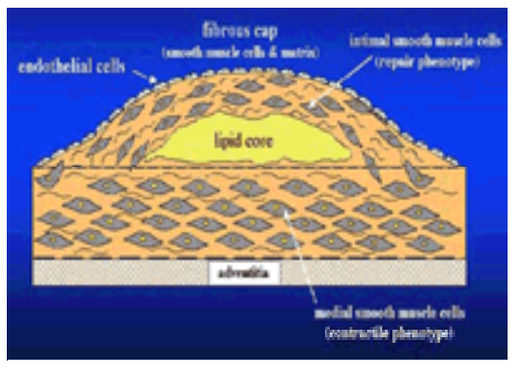


FIGURE 1.3 Factors influencing plaque stability.

Vascular Smooth Muscle Cells

VSMCs reside mostly in the media of healthy adult arteries, where their role is to regulate vascular tone. Thus, medial VSMCs contain large amounts of contractile proteins, including myosin, alpha-actin, and tropomyosin. Continued expression of this “contractile” phenotype is maintained by the influence of extracellular proteins in the media, which act via integrins in the VSMC membrane. In atherosclerosis, however, the cells become influenced by cytokines produced by activated macrophages and endothelial cells. Under these influences, VSMCs migrate to the intima and undergo a phenotypic change characterized by a reduction in content of contractile proteins and a large increase in the number of synthetic organelles (*e*Fig. 1.2.3). This migration of VSMCs from the media to the intima, and the consequent change from a contractile to a “synthetic” phenotype, was previously thought be a crucial step in the development of atherosclerosis in the modified response to injury hypothesis discussed previously. More recently, it has been recognized that intimal VSMCs in atherosclerotic plaques bear a remarkable similarity to VSMCs found in the early developing blood vessels (45), suggesting that intimal VSMCs may be performing a beneficial, reparative role rather than a destructive one in atherosclerosis. VSMCs are well-equipped for this action. First, they can express the proteinases that they require to break free from the medial basement membrane and allow them to migrate to the site of inflammation or injury in response to chemokines. Second, they can produce various growth factors, including vascular endothelial growth factor and platelet-derived growth factor, that act in an autocrine loop to facilitate their proliferation at the site of injury. Finally, and most important, they produce large quantities of matrix proteins, in particular glycosaminoglycans, elastin, and collagen isoforms 1 and 3, necessary to repair the vessel and form a fibrous cap over the lipid-rich core of the lesion. This fibrous cap separates the highly thrombogenic lipid-rich plaque core from circulating platelets and the proteins of the coagulation cascade and also confers structural stability to the atherosclerotic lesion. And because the VSMC is the only cell capable of synthesizing this cap, it follows that VSMCs play a pivotal role in maintaining plaque stability and protecting against the potentially fatal thrombotic consequences of atherosclerosis (*e*Fig. 1.3.1 and *e*Fig. 1.3.2) (46).



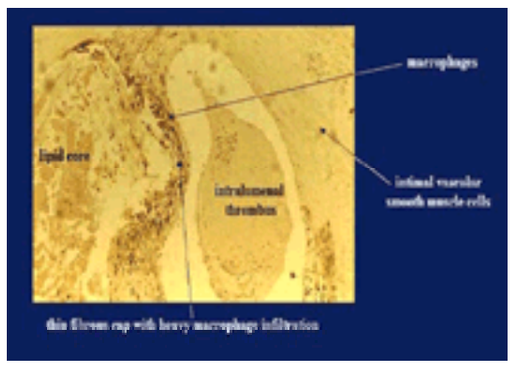
***e*FIGURE 1.3.1** Stable atherosclerotic plaque. (From Weissberg PL. Atherogenesis: current understanding of the causes of atheroma. *Heart* 2000;83:247–252, with permission.)

***e*FIGURE 1.3.2** Pathogenesis of atherosclerosis. VSMC, vascular smooth muscle cell.

CELLULAR INTERACTIONS AND LESION STABILITY

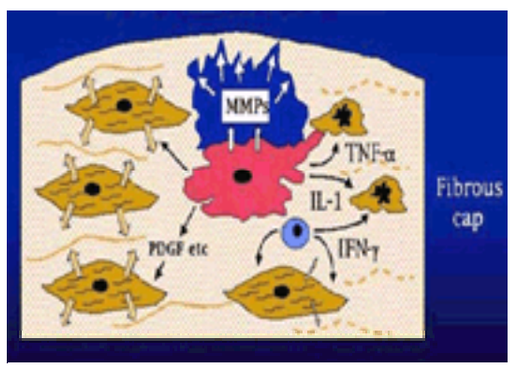
Generally, early atherosclerosis progresses without symptoms until a lesion declares itself in one of two ways. As discussed previously, macrophage foam cells may undergo apoptosis, especially in the presence of high concentrations of oxidized LDL. Their cellular remnants then become part of an enlarging lipid-rich core. Plaque size thus increases, and there may be a consequent reduction in vessel lumen area. At times of increased demand, such as exercise, this may be sufficient to cause ischemic symptoms such as angina. More hazardous is if the plaque presents with disruption of the fibrous cap, leading to exposure of the thrombogenic lipid core. This is likely to result in subsequent platelet accumulation and activation, fibrin deposition, and intravascular thrombosis. Depending on factors such as collateral blood supply, extent of arterial thrombus and local fibrinolytic activity, the end result may be arterial occlusion and downstream necrosis.

By studying the pathology of ruptured plaques, several characteristics have been identified that seem to be predictive of the risk of rupture in individual lesions (47). Plaques that are vulnerable to rupture tend to have thin fibrous caps with a high ratio of inflammatory cells to VSMCs and contain a lipid core that occupies more than 50% of the volume of the plaque. Of these, the most important is the cellular composition of the fibrous cap. Plaques containing a heavy inflammatory cell infiltrate and relatively few VSMCs have the highest risk of rupture (*e*Fig. 1.3.3) (48).

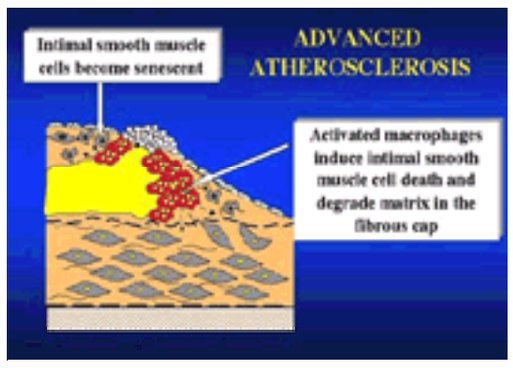


***e*FIGURE 1.3.3** Macrophages accumulate in the thin fibrous cap of unstable plaques.

Inflammatory cells in plaques act to promote plaque rupture by a number of synergistic mechanisms. First, activated T cells produce proinflammatory cytokines, typified by IFN-g, that directly inhibit VSMC proliferation (49) and almost completely shut down collagen synthesis (50,51). Thus, VSMCs in the vicinity of activated T cells in plaques are poorly able to lay down or repair extracellular matrix. Second, macrophage-derived inflammatory cytokines, in particular interleukin-1b and tumor necrosis factor-a, along with IFN-g from T cells, are synergistically cytotoxic for VSMCs, causing depletion in cell number by apoptosis (52). These cytokines are found at high levels in vulnerable plaques (53). Third, activated macrophages can induce VSMC apoptosis by direct cell-cell contact (54). Finally, and probably most important, macrophages secrete a variety of matrix metalloproteinases that degrade the matrix components of the fibrous cap by proteolytic cleavage of its protein components (46). The production of matrix metalloproteinases is upregulated by inflammatory mediators such as tumor necrosis factor-a. As well as being under threat from such an array of insults, VSMCs themselves within the fibrous cap of a mature plaque have a reduced ability to proliferate (55,56) and an enhanced susceptibility to apoptosis (57). Thus, inflammatory cells can destroy the fabric of the fibrous cap, and resident VSMCs are poorly equipped to compensate, particularly in the presence of inhibitory inflammatory cytokines (*e*Fig. 1.3.4 and *e*Fig. 1.3.5). It is important to note that all of these features can be present in small, hemodynamically insignificant plaques that are clinically silent and angiographically invisible. Thus, plaque composition is far more important than plaque size in determining outcome.



***e*FIGURE 1.3.4** Smooth muscle–inflammatory cell interactions in atherosclerosis. IFN-g, interferon-g; IL-1, interleukin-1; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; TNF-a, tumor necrosis factor-a.



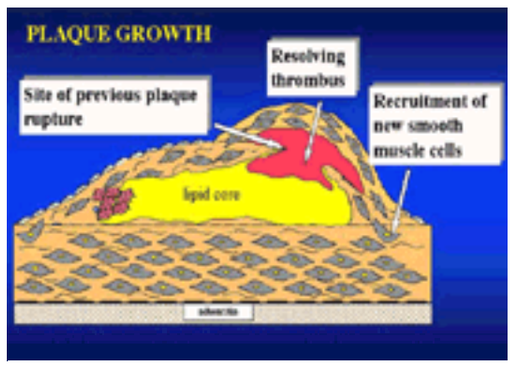
***e*FIGURE 1.3.5** Advanced atherosclerosis.

INFLAMMATORY MARKERS IN ATHEROSCLEROSIS

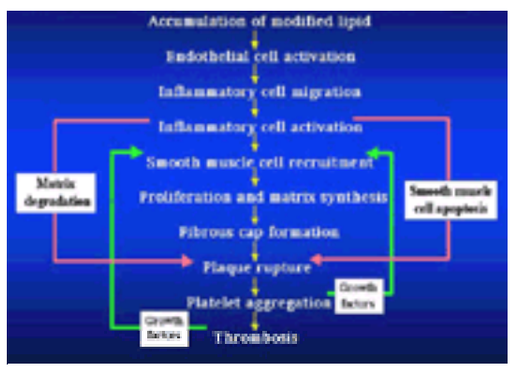
The cell biology of plaque development and subsequent rupture illustrates that atherosclerosis is fundamentally an inflammatory condition. Confirmation of the inflammatory basis of atherosclerosis has come from several studies that have all demonstrated a correlation between levels of markers of systemic inflammation, principally C-reactive protein (CRP), and risk of a clinical event due to plaque rupture (58,59,60 and 61). However, unlike in other systemic inflammatory conditions, such as rheumatoid arthritis, levels of CRP in atherosclerosis are characteristically not elevated above the conventional normal range, and a correlation between CRP level and coronary events was demonstrated only after development of a highly sensitive assay for CRP that was capable of measuring levels below the lower limit of detection of conventional assays. Similar, although less compelling, correlations with clinical events have also been published for other markers of inflammation, including soluble ICAM-1 (62), VCAM-1 (63,64), P-selectin (65), and interleukin-6 (the primary driver of CRP production) (66). Results of these studies have been interpreted by some as indicating that atherosclerosis arises as a consequence of a systemic inflammatory process, for example chronic infection, and by others that it reflects the inflammatory processes of atherosclerosis itself. However, there is accumulating evidence in favor of the latter interpretation.

TWO FORMS OF PLAQUE DISRUPTION: FIBROUS CAP RUPTURE AND ENDOTHELIAL EROSION

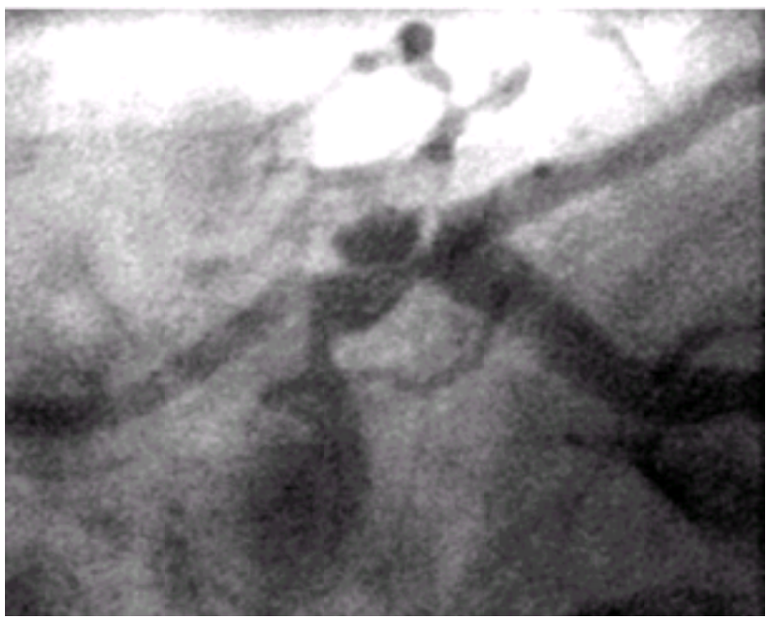
Atherosclerotic plaques become life-threatening when they initiate clot formation in the vessel lumen and disturb blood flow. This can occur in two different ways. Either there can be fibrous cap rupture, with consequent exposure of the thrombogenic extracellular matrix of the cap and the tissue factor–rich lipid core to circulating blood, or less commonly, there is erosion of the endothelial cells covering the fibrous cap, also potentially leading to the buildup of platelet-rich thrombus. Endothelial erosion probably accounts for approximately 30% of acute coronary syndromes overall and seems particularly common in females (67). Both forms of plaque disruption invariably lead to local platelet accumulation and activation. This may result in triggering of the clotting cascade, thrombus formation and, if extensive, complete vessel occlusion. Platelet-rich thrombus contains chemokines and mitogens, in particular platelet-derived growth factor and thrombin that induce migration and proliferation of VSMCs from the arterial media to the plaque and transforming growth factor-b that contributes to healing of the disrupted lesion (68). Platelets also express CD40 on their cell membranes, which causes local endothelial cell activation, resulting in the recruitment of more inflammatory cells to the lesion and perpetuating the cycle of inflammation, rupture, and thrombosis. However, fibrous cap rupture or erosion does not invariably lead to vessel occlusion. Up to 70% of plaques causing high-grade stenosis contain histologic evidence of previous subclinical plaque rupture with subsequent repair (69). This is particularly likely to occur if high blood flow through the vessel prevents the accumulation of a large occlusive thrombus. Thus, nonocclusive plaque rupture induces formation of a new fibrous cap over the organizing thrombus, which restabilizes the lesion but at the expense of increasing its size (*e*Fig. 1.3.6 and *e*Fig. 1.3.7). Because this occurs suddenly, there is little opportunity for adaptive remodeling of the artery, and the healed lesion may now impede flow sufficiently to produce ischemic symptoms. This explains why patients who have previously had normal exercise tolerance may suddenly develop symptoms of stable angina pectoris. It also follows that if lesions can grow as a consequence of repeated episodes of silent rupture and repair, a reduction of plaque rupture rate will reduce progression of atherosclerosis. Therefore, atheromatous plaques may become larger by two methods. The first is a gradual increase in size as a consequence of macrophage foam cell apoptosis and the plaques' incorporation into an enlarging necrotic lipid-laden plaque core. The second is a stepwise increase in size because of repeated, often silent episodes of plaque rupture or erosion with subsequent VSMC-driven repair.



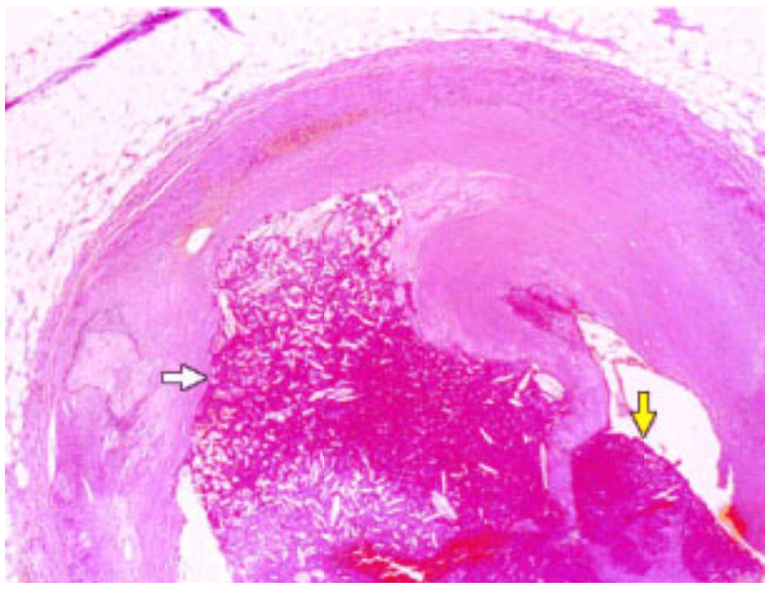
***e*FIGURE 1.3.6** Plaques may enlarge by repeated episodes of rupture and repair. (From Weissberg PL. Atherosclerosis involves more than just lipids: plaque dynamics. *Eur Heart J* 1991;1:T13–T18, with permission.)



***e*FIGURE 1.3.7** Pathogenesis of atherosclerosis. (From Weissberg P. Mechanisms modifying atherosclerotic disease—from lipids to vascular biology. *Atherosclerosis* 1999;147:S3–S10, with permission.)



Severe ulcerated plaque of the left main trunk discovered on diagnostic angiography.



Organized intraplaque thrombus (*white arrow*) with overlying, near-occlusive fresh thrombus (*yellow arrow*). Ruptured atherosclerotic lesion of the right coronary artery 5 days after a balloon angioplasty procedure.

BALANCE OF ATHEROSCLEROSIS: THERAPEUTIC IMPLICATIONS

Atherosclerosis is a dynamic process in which the balance between the destructive influence of inflammatory cells and the reactive, stabilizing effects of VSMCs determines outcome (Fig. 1.4 and (*e*Fig. 1.4.1). This balance can be tipped toward plaque rupture by factors such as an atherogenic lipoprotein profile, high levels of lipid oxidation, local free radical generation, and genetic variability in expression and activity of certain central inflammatory molecules. For example, an association between plaque progression and a polymorphism in the stromelysin-1 gene promoter has been described (70). It is also possible that infectious organisms might be involved in atherosclerosis, either as plaque initiators or as having some role in initiating plaque rupture. This fiercely debated question has still to be resolved. *Chlamydia pneumoniae* remains the most plausible candidate pathogen. It is found in plaques, localizing at high concentrations within macrophages, but is rarely found in normal arteries (71). Although these data imply a pathologic association between the presence of chlamydia infection and atherosclerosis, neither a causative role nor an association between serum markers of infection and ischemic heart disease has been established. Animal work has shown that healthy rabbits that are nasally inoculated with chlamydia develop extensive atherosclerosis (72). The situation appears to be somewhat different in humans. Two large prospective studies and an extensive metaanalysis of previous data failed to show any association between serum markers of infection with chlamydia and incidence of or mortality from ischemic heart disease (73,74). The results of these two studies effectively exclude a strong association but allow the possibility of a weaker link, and several trials of antichlamydial antibiotics for the prevention of ischemic heart disease are in progress (ACES, WIZARD, PROVEIT, MARBLE, STAMINA).

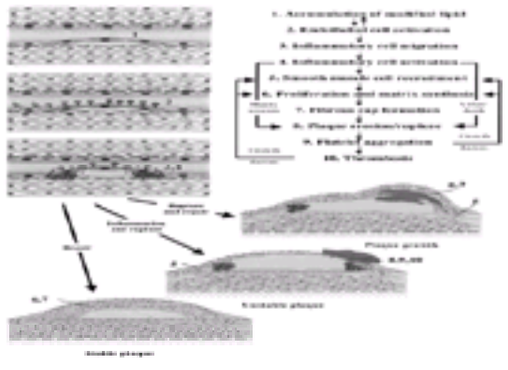
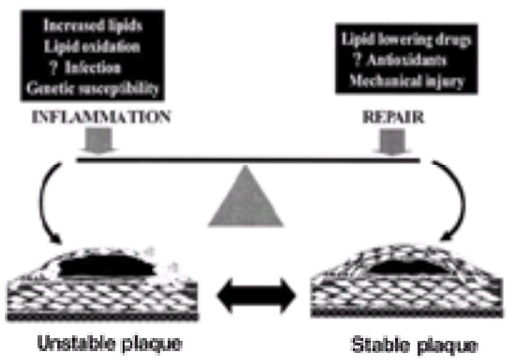


FIGURE 1.4 Cellular interactions in the development and progression of atherosclerosis. (From Weissberg PL. Atherogenesis: current understanding of the causes of atheroma. *Heart* 2000;83:247–252, with permission.)



***e*FIGURE 1.4.1** The balance of atherosclerosis.

The balance can be tipped toward plaque stability by a reduction in plaque inflammation or an increase in VSMC-driven repair. Lipid reduction, by whatever means, reduces clinical events. Evidence that this may be due to a plaque-stabilizing effect comes from animal studies that showed that statins reduced inflammatory cell and increased VSMC content of plaques (75,76), changes that would be expected to enhance stability. More important, however, evidence from human clinical studies also

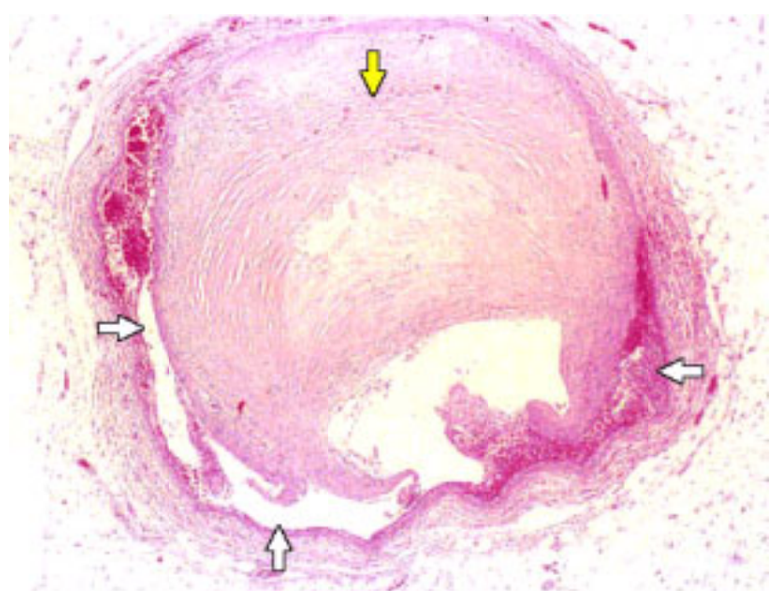
points to a plaque-stabilizing effect of statins. Angiographic studies have shown that statins produce only a small, hemodynamically insignificant reduction in progression of established stenoses (77,78 and 79). They also reduce new lesion formation, and, importantly, the number of new vessel occlusions. These arise after a plaque ruptures, leading to an occlusive thrombus in the context of a well-collateralized myocardial circulation. This seems to imply that statins are stabilizing plaques by reducing rupture rate. This conclusion is supported by the results of all the large primary and secondary prevention studies, which have demonstrated that statins (pravastatin, simvastatin and lovastatin) produce major reductions in events due to plaque rupture, such as myocardial infarction and stroke (30,80,81,82 and 83). Because statins have only a modest effect on plaque size but cause profound reductions in the number of clinical events, these studies highlight the inadequacy of angiography for the prediction of clinical events and suggest that statins have beneficial effects on plaque inflammation in addition to, or as a result of, their lipid-lowering effects. Importantly, this notion is supported by the observation that the reduction in clinical events due to statin therapy is accompanied by a parallel reduction in highly sensitive assay for CRP levels that is unlikely to be due to effects of statins on nonatherosclerotic inflammation (84,85). Also, in the first study of its kind, it has been shown that statins reduce inflammation and increase plaque collagen content in human carotid artery atherosclerosis (86).

Statin drugs may help stabilize plaques in a number of different ways (*e*Fig. 1.4.2). It is known that they can exert direct effects on endothelial cell function, inflammatory cell number and activity, VSMC proliferation, platelet aggregation, and thrombus formation (87,88,89,90 and 91). Evidence that non–lipid-lowering effects may be important *in vivo* comes from animal studies in which pravastatin caused beneficial changes in plaque composition (but not size), even when lipid levels were maintained at pretreatment levels (76). Additionally, in mice, simvastatin has direct antiinflammatory effects comparable to those of indomethacin (92). Recently, a newly recognized effect of statins as immune modulators has been described, whereby major histocompatibility complex class II mediated T-cell activation is reduced by a variety of statins (93). These observations point to potentially important effects of statins that are poorly understood and have yet to be fully defined.

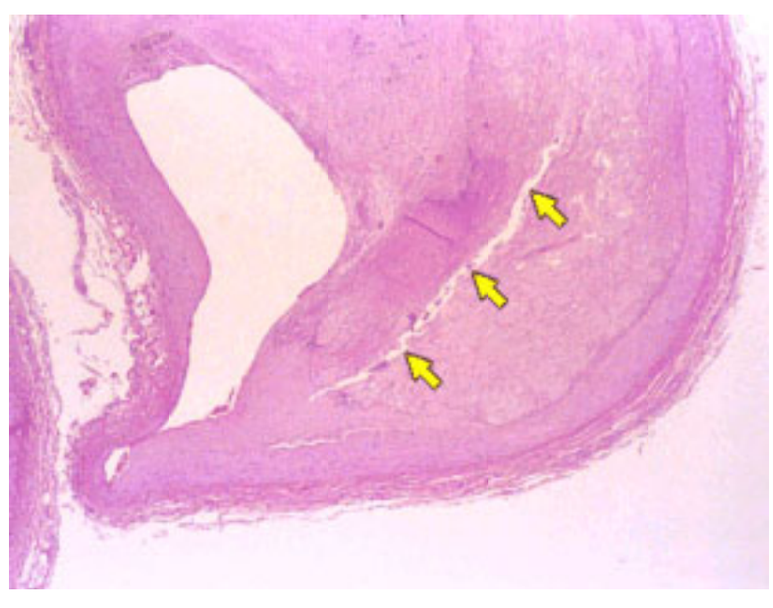
***e*FIGURE 1.4.2** The pleiotropic effects of statins on plaque biology. VSMC, vascular smooth muscle cell.

RESTENOSIS

Restenosis is the term used for the late loss of gain in lumen diameter achieved immediately after balloon dilatation of an atherosclerotic plaque. For many years, it has been thought of as an undesirable response to vascular injury. However, in effect, it represents an extreme form of plaque stabilization. Whether performed on a stable or unstable plaque, angioplasty causes endothelial disruption and often substantial damage to the full thickness of the vessel wall. The initial thrombotic response that would otherwise lead to early vessel occlusion is prevented by antiplatelet and antithrombotic therapy. There then follows a reparative response driven by medial VSMCs and adventitial myofibroblasts. The former form a matrix-rich neointima over the exposed plaque, whereas the latter produce a collagenous matrix in the adventitia. The net result is that the adventitial reaction “splints” the vessel and prevents the remodeling that would normally allow expansion of the vessel to accommodate the neointima. However, although this phenomenon may lead to angiographic or clinical restenosis, much more important, it renders the lesion stable, making the likelihood of a further plaque rupture at that site extremely remote. In effect, by stimulating a vigorous VSMC repair response, balloon angioplasty tips “the balance of atherosclerosis” in favor of plaque stability (Fig. 1.4 and (*e*Fig. 1.4.1). This phenomenon undoubtedly underlies the success of angioplasty in the treatment of acute myocardial infarction. Most of the adverse effects of the response to balloon angioplasty on remodeling can be countered by deployment of a stent. Nevertheless, the neointimal response remains problematic but is probably a worthwhile price for the stability achieved because restenosis is rarely life-threatening.



Linear, circumferential dissection 2 days after balloon angioplasty of a restenotic lesion. Note the extensive neointimal proliferation (*yellow arrow*) and dissection (*white arrows*).



Restenotic lesion. Residual tear in atherosclerotic plaque (*yellow arrows*) and large amount of neointimal proliferation 76 days after balloon angioplasty.

Video 1.1 Severe in-stent restenosis involving the distal right coronary artery **(A)** and successful angioplasty **(B)**. *This video must be viewed with QuickTime. If you do*

not have QuickTime you may download it here.

Video 1.2 Severe in-stent restenosis involving the distal right coronary artery **(A)** and successful angioplasty **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

CONTROVERSIES AND PERSONAL PERSPECTIVES

Many issues concerning the initiation and progression of atherosclerosis remain to be resolved. In particular, controversy persists over the extent to which endothelial dysfunction precedes or is the consequence of intimal lipid accumulation; the relative contributions of endothelial erosion and plaque rupture to clinical events; the specific role, if any, of infective agents such as *C. pneumoniae* in the pathogenesis and progression of atherosclerosis; and the extent to which statins achieve their plaque stabilizing effects directly via lipid lowering or by their so-called pleiotropic effects on the intercellular interactions that lead to plaque rupture. Integral to this latter issue is the outstanding question of what is the optimal level of lipid reduction. In other words, is greater always better?

Despite these controversies, it is certain that drug treatment will become increasingly prominent in the management of patients with, and at high risk of developing, atherosclerosis. Improvements in drug design will come from a number of complementary approaches. First, improvement will come by modifications of existing molecules, based on understanding how currently available drugs such as statins and angiotensin-converting enzyme inhibitors influence plaque progression. This will include evaluation of how other lipid-modifying strategies, such as inhibiting cholesterol absorption in the gut and modifying the balance between pro- and antiatherogenic lipoproteins and triglycerides, might influence the atherosclerotic process. Second, improvements will come by targeting molecular interactions known to be involved in atherogenesis. Likely candidates include endothelial adhesion molecules, matrix metalloproteinases, inflammatory cytokines and their signaling molecules, in particular, nuclear factor-kB and its downstream transcriptional activators. Here the challenge lies in identifying pathways or molecular species that are specific for atherosclerosis whose modification will not compromise the normal inflammatory response to pathogens. This approach will include developing regulators of VSMC behavior, such as modulators of transforming growth factor-b–driven matrix production, that may lead to enhanced maintenance of the fibrous cap. Another important example includes establishing the role of drugs targeting peroxisome proliferator–activated receptors in modifying inflammation and the vascular consequences of the metabolic syndrome that links insulin resistance, diabetes, hypertension, and dyslipidemia with premature atherosclerosis. The potentially beneficial effects of thiazolidinediones (the glitazones) on atherosclerotic events have yet to be determined. The third approach is to use new technologies such as proteomics to design new therapeutic molecules and gene array technologies to identify new molecular targets in vascular disease. In addition, as a consequence of sequencing the human genome, a number of “orphan” receptors have already been identified that might provide vascular specific targets for novel therapies.

THE FUTURE

It is almost inconceivable that the combination of these approaches will not lead to the development of new drugs that will act synergistically with statins and angiotensin-converting enzyme inhibitors. Furthermore, we predict that advances in genetics and diagnostics will combine with therapeutic advances to produce substantial reductions in premature cardiovascular deaths. Thus, new gene polymorphisms and mutations will be identified that confer increased likelihood either of developing atheroma or of experiencing its consequences. This will lead, in turn, to better prescription of lifestyle modifications and better targeting of current and new therapies for primary prevention of cardiovascular events. This approach will be aided by new diagnostic tests—based on specific circulating markers of vascular inflammation or imaging of the inflammatory process underlying plaque rupture—that will lead to better preclinical diagnosis of patients at greatest risk of cardiovascular events and better monitoring of plaque-modifying therapies.

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2

DIET, NUTRITIONAL ISSUES, AND OBESITY

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Diet plays an important role in the primary and secondary prevention of coronary artery disease (CAD). It has beneficial effects on the lipid profile and is a crucial part of the treatment of individuals who have multiple metabolic risk factors ("the metabolic syndrome"). Moreover, data on the value of diet in reducing oxidant stress, thrombotic tendencies, ischemic ventricular arrhythmia, and sudden death are encouraging.

The American Heart Association's (AHA) recommended population or "healthy" diet focuses on healthy eating patterns and foods. It replaces the older AHA Step I diet. It recommends an overall healthy eating pattern with general advice that should help prevent obesity, hypertension, and hypercholesterolemia (Table 2.1). For individuals who have medical problems that necessitate consumption of a therapeutic cardiovascular diet, consultation with a dietitian for medical nutrition therapy is recommended for guidance in making the necessary lifestyle changes. To reduce levels of low-density lipoprotein cholesterol (LDL-C), the earlier AHA Step II diet restricted saturated fatty acids to less than 7% of energy and dietary cholesterol to less than 200 mg per day. The current AHA dietary module to reduce LDL-C preserves this recommendation and also suggests a reduction in *trans* fatty acids (TFAs). For individuals with multiple metabolic risk factors and obesity, treatment begins with caloric restriction and increased energy expenditure. For those with elevated blood pressure, a low-salt regimen with increased emphasis on fruits and vegetables, nonfat dairy products, and weight reduction, if needed, is suggested.

Have a healthy eating pattern	Achieve and maintain a healthy body weight	Achieve a desirable blood cholesterol profile	Achieve and maintain a desirable blood pressure
Variety of fruits, vegetables, grains, low-fat or nonfat dairy products, fish, legumes, poultry, lean meats	Match energy intake to energy expenditures with appropriate changes to achieve weight loss when indicated	Limit foods high in saturated fat and cholesterol; substitute unsaturated fat from vegetables, fish, legumes, and nuts	Limit salt and alcohol; maintain a healthy body weight and a diet with emphasis on vegetables, fruits, and low-fat or nonfat dairy products

Adapted from Krauss RM, Eckel RH, Howard B, et al. Revision 2000: AHA dietary guidelines: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 2000; 102:2296–2311, with permission.

TABLE 2.1 REVISION 2000: AMERICAN HEART ASSOCIATION DIETARY GUIDELINES SUMMARIZED

The response to diet is variable and probably is genetically based. Therapeutic diets that reduce risk factors must be targeted to the specific characteristics of the individual [high LDL-C level, combined elevation of cholesterol and triglyceride (TG) levels, obesity, hypertension]. These individual characteristics may also underlie individual responsiveness to diet.

Understanding the response of the individual to various dietary components is useful, because some people may use the therapeutic diet to reach their LDL-C goal or reduce their need for medication to reach LDL-C goals. The response of LDL-C to dietary cholesterol is highly variable. People with combined forms of hyperlipidemia may be the most sensitive to diet. Dietary options such as plant sterol and stanol esters taken as margarines reduce cholesterol absorption significantly and can reduce LDL-C by 10% or more. Some saturated fats raise blood cholesterol more than others. Stearic acid is converted to oleic acid and may even lower blood cholesterol. Nonetheless, restriction of saturated fats is the hallmark of the cholesterol-lowering diet. TFAs, when consumed in high amounts, can raise LDL-C and lower high-density lipoprotein cholesterol (HDL-C). Sources high in TFAs, such as stick margarine, cookies, biscuits, and cakes, should be avoided. Butter contains cholesterol and saturated fat and is cholesterol-raising compared with soft margarine. Therapeutic diets should be low in both saturated fatty acids and TFAs.

Diets high in sources of monounsaturated fats such as canola and olive oil do not lower HDL-C as much as do high-carbohydrate diets. Such diets may be preferred for individuals with the metabolic syndrome or for diabetic patients, when weight control is not an issue. Patients need to be reminded, however, that an excess intake of fats—monounsaturated or not—can lead to weight gain. Reducing excess body weight can be a crucial factor in improving the lipid profile. The addition of regular exercise to changes in diet can be particularly beneficial in helping a patient maintain weight loss. Recent data suggest that omega-3 fatty acids, particularly docosahexaenoic acid (DHA) may reduce cardiovascular events by a mechanism other than improvement of lipid profiles. Several trials have shown a reduction in cardiac death among patients consuming DHA-supplemented diets, and animal models of coronary heart disease (CHD) suggest that an increase in the ventricular fibrillation threshold accompanies consumption of DHA.

Mild alcohol consumption, especially among middle-aged and older adults, is associated with decreased rates of CAD compared with rates among teetotalers. Approximately one-half of the benefit of alcohol can be attributed to increased levels of HDL-C. Benefit is not dependent on the kind of beverage consumed. Excess amounts of alcohol can lead to significant cardiovascular problems, including arrhythmias, cardiomyopathy, and left ventricular hypertrophy (LVH). Women are more

sensitive to alcohol than men and develop cardiomyopathy and a decrease in left ventricular function at a lower dose.

Large clinical trials have not shown beneficial effects of vitamin E or beta-carotene supplementation either on total mortality or on cardiovascular end points in both primary and secondary prevention trials. These supplements cannot be recommended for reduction of cardiovascular risk. Diets that emphasize sources of antioxidants in fruits, vegetables, nuts, and whole-grain products are recommended.

The prevalence of overweight and obesity is increasing. This is a serious concern; obesity is now considered to be the second leading cause of preventable death in the United States (after cigarette smoking). The use of the body mass index (BMI) to define overweight as a BMI of 25.0 to 29.9 and obesity as a BMI of 30 or higher is useful in clinical practice. Weight gain into the overweight range increases insulin resistance. The clinical presentation of insulin resistance includes multiple metabolic abnormalities such as high TG levels, low HDL-C levels, glucose intolerance, hypertension, and hypercoagulability. Treatment begins with regular physical activity and reduction of excess weight. The importance of prompt recognition and treatment of individuals with the metabolic syndrome is underscored by data showing that weight gain after the age of 18 years is an important precursor of diabetes and CAD. Most therapies for obesity result in benefits in the short term, with disappointingly low rates of success at 5 years. Popular diets can achieve short-term weight loss, but there is no convincing evidence of long-term efficacy. Medications such as fenfluramine and phentermine or dexfenfluramine are no longer used to treat obesity because of the associated occurrence of valvular lesions that resemble those seen with serotonin excess. Newer medical approaches to weight loss include use of sibutramine and orlistat, which may help the obese patient achieve a 5% to 10% weight loss in 1 year. Gastric bypass surgery is particularly useful for those with marked obesity. Lifestyle change is important even for individuals who are being treated with medication and/or surgery. Thus, a comprehensive approach to weight loss is recommended. Prevention of obesity should be a high priority for public policy, and physicians should consider intervention when patients initiate measures strongly associated with weight gain. Examples include smoking cessation, use of steroids, and initiation of certain antidiabetic or antidepressant medications known to promote weight gain.

GLOSSARY

Alpha-linolenic acid: Plant-based omega-3 polyunsaturated fatty acid.

Android or male pattern obesity: Increased waist-to-hip ratio associated with increased CAD risk and with hypertension, visceral obesity, glucose intolerance, and insulin resistance.

BMI: Body mass index. Calculated as weight/height^2. This index minimizes the effect of height on body weight and has become the preferred index for categorizing levels of obesity. It does not provide information, however, on the pattern of obesity.

Cis: Naturally occurring double bonds that produce a bend in the molecule that impairs crystallization.

DART Trial: Diet and Reinfarction Trial.

DASH Trial: Dietary Approaches to Stop Hypertension Trial.

Dietary cholesterol: A crucial waxy substance that is found in animal cells. Response of blood cholesterol to its consumption is highly variable.

Familial dyslipidemic hypertension: Hypertension and dyslipidemia aggregating in family members.

Gynoid or female pattern obesity: Waist to hip ratio is not increased as fat increases in femoral-gluteal regions. Not associated with increased heart risk.

Insulin-resistance syndrome: Increased insulin levels relative to glucose levels. In some studies, this is an independent predictor of CAD risk. Associated with atherogenic dyslipidemia, hypertension, and visceral obesity.

Linoleic acid: Major human polyunsaturated fatty acid; an essential fatty acid.

Mediterranean diet pyramid: Graphic summary of eating style that excludes all fats but olive oil; recommends fish, poultry, and red meat less frequently, and includes physical activity and consumption of wine in moderation.

Metabolic syndrome: Describes constellation of multiple metabolic risk factors likely due to insulin resistance. These include high TG levels, low HDL-C level, hypertension, glucose intolerance or diabetes, hypercoagulability, and increased inflammatory markers.

Monounsaturated fatty acids: Fatty acids, such as oleic acid, whose carbon chains have one double bond. Foods high in monounsaturated fats include canola and olive oil.

NHANES II, III: National Health and Nutrition Exam Surveys II (1976–1980) and III (1988–1994).

Oleic acid: A monounsaturated fatty acid.

Omega-3 or *n*-3 polyunsaturated fatty acid: Fatty acids whose first double bond is 3 carbon atoms from the methyl end of the fatty-acid chain. Fish oils and alpha-linolenic acid are *n*-3 fatty acids.

Omega-6 or *n*-6 polyunsaturated fatty acid: Polyunsaturated fatty acids whose first double bond is six carbon atoms from the methyl end of the fatty-acid chain. Linoleic acid is an example.

Partial hydrogenation: A process whereby hydrogen atoms are added to fatty acids. Produces TFAs.

Phytoestrogens: Plant compounds that have estrogen-like activity.

Polyunsaturated fatty acids: Fatty acids whose carbon chains have one or more double bonds.

Saturated fatty acids: Fatty acids whose carbon chains have no double bonds.

SCRIP: Stanford Coronary Risk Intervention Project.

STARS: St. Thomas Atherosclerosis Regression Study.

Syndrome X: Also known as the *metabolic syndrome*, with insulin resistance, glucose intolerance, dyslipidemia, and hypertension as its hallmarks. Patients have visceral obesity. The cardiologic syndrome X is microvascular angina. The link between the two syndromes may be insulin resistance.

***Trans* fatty acids:** Fatty-acid configuration in which the molecule is straightened out, leading to a more densely packed form. Solid at room temperatures.

USDA: United States Department of Agriculture.

USDA Diet Pyramid: Graphic summary of eating style based on the dietary guidelines of the USDA.

Waist to hip ratio: Measurement of waist or waist to hip ratio used to determine the pattern of obesity. Men with waist greater than 100 cm (approximately 40 in.) or waist to hip ratio greater than 0.9 and women with waist greater than 90 cm (35 in.) or waist to hip ratio greater than 0.8 are believed to have increased adiposity.

DIETARY PRESCRIPTION AND LIFESTYLE CHANGES TO REDUCE CORONARY ARTERY DISEASE

The contemporary practice of preventive cardiology requires an understanding of the use of dietary prescriptions to reduce the risk of CAD. Diets designed to lower cholesterol and improve multiple metabolic risk factors can lower the risk of CAD. A conference on dietary fatty acids and cardiovascular health reviewed in detail the epidemiologic, clinical trial, and nonhuman primate evidence supporting an important relationship between dietary fat and CAD (1). There are real benefits to an emphasis on solid nutritional principles. Cholesterol-lowering diets may allow therapeutic goals for LDL-C to be reached without additional medication (2). For example, a multicenter trial noted that the effects of intensive dietary therapy added to treatment with lovastatin resulted in a very modest gain of approximately 5% additional lowering of LDL-C levels (3). This trial had several design features that may have caused the value of diet to be underestimated. Nonetheless, even this modest lowering may allow LDL-C targets to be attained without the need to resort to an increased statin dose. For many patients, diet can reduce the expense of medication. In addition, for those with high TG, LDL-C, or HDL-C levels and associated features of the metabolic syndrome, diet, exercise, and weight loss may be particularly effective in normalizing lipid profiles or reducing the need for complex medication regimens (3). Finally, the use of dietary therapy alone, often in conjunction with either reduced tobacco intake or regular exercise, has been associated with significant cardiovascular benefit, including reductions in total mortality (4), angiographic progression (5,6), CHD end points [particularly CHD death (7,8 and 9)], and symptoms in patients with CAD (10). [See Table 2.2 and Table 2.3 for a comprehensive look at clinical and angiographic trials (11).]

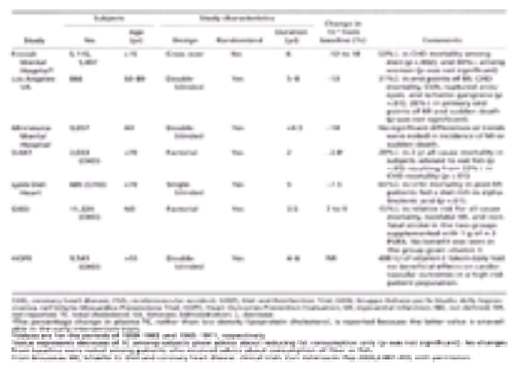


TABLE 2.2 SELECTED BLINDED, CONTROLLED DIETARY INTERVENTION TRIALS USING CHD MORBIDITY OR MORTALITY AS END POINTS

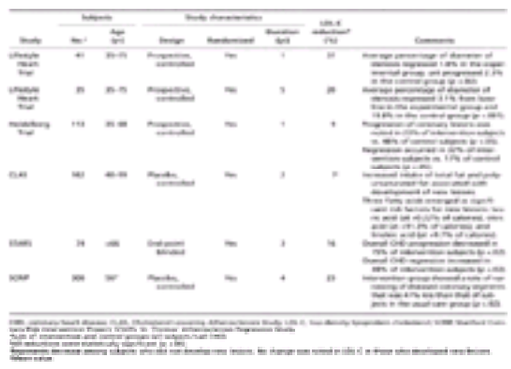


TABLE 2.3 SELECTED CONTROLLED DIETARY INTERVENTION TRIALS USING RESULTS OF ANGIOGRAPHY AS AN END POINT

For the population as a whole, the implications of a “healthy” diet that shifts the population mean for serum cholesterol are exciting to contemplate. It has been speculated that a shift in the population mean cholesterol level by 10% would prevent 30% of all CAD events, whereas lifelong treatment with cholesterol-lowering drugs of individuals with cholesterol values in the highest 10% would achieve only a 15% to 20% reduction in CAD events (12).

NATIONAL CHOLESTEROL EDUCATION PROGRAM GUIDELINES FOR DIET

Overall Goals

One major goal of the National Cholesterol Education Program (NCEP) guidelines for diet is to use diet and lifestyle to reduce both risk factors and morbidity and mortality from CHD. The NCEP, through its population and adult treatment panels (13,14), believes that adherence to its dietary recommendations could result in a 10% decrease in blood cholesterol levels (Fig. 2.1). Since those reports were published, emerging information on fiber, plant sterol/stanol esters, alcohol, fish oil, and antioxidants indicate continued relevance of dietary considerations in a total program to reduce CHD risk. Moreover, reducing or preventing obesity is a major goal because it not only indirectly affects CHD risk, through its link with risk factors, but also independently predicts CAD (15).

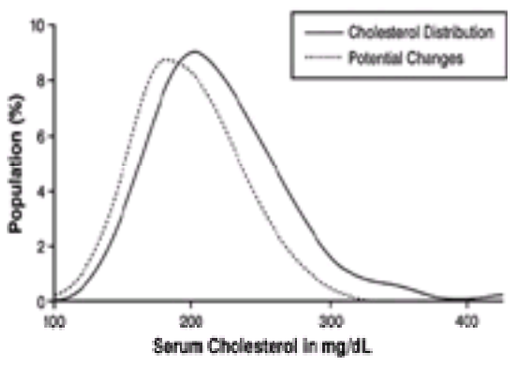


FIGURE 2.1 Cholesterol distribution in the U.S. population from the National Health and Nutrition Exam Survey, showing data from 1976 to 1980 and changes possible (*dotted lines*) if population goals for diet are attained. (Adapted from National Cholesterol Education Program. Report of the expert panel on population strategies for blood cholesterol reduction. Publication NIH 90–3046. Bethesda, MD: National Institutes of Health, US Department of Health and Human Services, 1990, with permission.)

Therapeutic Diets: Step I and II Diets Give Way to Revised Diets for Year 2000

The NCEP Adult Treatment Panel and the AHA previously recommended the Step I and Step II diets to lower cholesterol and to achieve LDL-C goals (13). The Step I diet restricted total fat to less than 30% of energy, saturated fat to less than 10% of energy, and dietary cholesterol to less than 300 mg per day. The Step II diet also restricted total fat to less than 30% of energy but limited saturated fat to less than 7% of energy, and dietary cholesterol to less than 200 mg per day. To put these diets in proper perspective, the Step I diet was really the “population diet,” designed to shift the mean cholesterol level of the population to a lower value, and the Step II diet was the therapeutic or “clinical” diet, designed to provide more optimal lowering of total cholesterol and LDL-C levels. For patients with TG levels that exceed 1,000 mg per dL, the Step II diet’s focus on LDL-C lowering was inadequate. Dietary control of severe hypertriglyceridemia requires weight loss, marked fat restriction, and possibly omega-3 fatty acids.

In the new AHA Dietary Guidelines known as “Revision 2000,” the Step I diet is supplanted by major guidelines for the general population (16) (Table 2.1). These

include the following population goals:

1. Achieve an overall healthy eating pattern
2. Achieve and maintain appropriate body weight
3. Achieve a desirable cholesterol profile
4. Achieve a desirable blood pressure

The revised guidelines stress three underlying principles. First, there are dietary patterns that all individuals can follow throughout their life span that promote and encourage cardiovascular health. This includes particular emphasis on patterns that help individuals avoid obesity. Second, the focus should shift to healthy dietary practices over an extended period of time, rather than insisting on "perfection" with each meal. This allows for the inclusion of a wide variety of healthy foods and avoids restricting the diet to repetitious and unsatisfying dietary experiences. Finally, the new guidelines form a framework on which specific recommendations can be made to individuals, based on their health and risk-factor status, and appropriately modified by their dietary preferences and cultural background.

The new NCEP Adult Treatment Panel III guidelines (17) essentially advocate the Step II diet for individuals with raised LDL-C but provide specific nutritional and lifestyle options for those who need more intensive nutritional efforts to lower LDL-C or who require an approach that more specifically targets the metabolic syndrome. Along with the DASH (Dietary Approaches to Stop Hypertension) diet (18) for individuals with high blood pressure and guidelines for obesity to guide those with weight excess, clinicians can individualize the dietary prescription to address not only an abnormal lipid profile, but also associated hypertension, obesity, and risk of sudden death.

Efficacy of Diets in Affecting Lipid Levels

Denke divided the efficacy studies of diet into those addressing healthy populations, those addressing high-risk populations, and finally, those addressing populations with known coronary disease (19). In all three categories, diet was effective if dietary counseling continued during the trial. Again, the crucial importance of weight loss in achieving the results with diet was emphasized.

Clinical and Biologic Factors Affecting Dietary Responsiveness

Any critical analysis of diet must include a consideration of the various factors that influence the results. Although a small study of men with elevated LDL-C and normal TG levels showed that restriction of saturated fat and dietary cholesterol in outpatients could achieve the results predicted by inpatient metabolic diet studies, the responsiveness for individuals was highly variable (20). Denke and Grundy suggested that this variability was influenced by both clinical and biologic factors (eTable 2.3.1). Clinical factors include compliance to diet and changes in body weight (20). Studies of compliance have documented the difficulty of maintaining adherence to a diet low in saturated fats (21,22).

***e*TABLE 2.3.1** GENETIC FACTORS DETERMINING RESPONSIVENESS TO DIET

Genetic mechanisms	Effect on cardiac health
Familial hypercholesterolemia[22]	Usually can't normalize LDL-C by diet.
Specific isoforms of apoprotein E[23]	Those with apolipoprotein E4 may absorb more dietary cholesterol than those with apolipoprotein E2.
Inherited changes in apoprotein A-IV[20]	Decreased cholesterol response to diet in patients heterozygous for this allele.
Changes in the gene encoding apoprotein B[20]	Reductions in TC and LDL-C; apolipoprotein B and HDL-C were greater in subjects homo- or heterozygous for the presence of the Xbal cutting site (X1X2 or X2X2 genotype, designated X2+) compared with those lacking the cutting site (X1X1 genotype, designated X2–).
Changes in gene encoding the apoprotein A-I promoter region[28]	Differences seen in LDL-C with diet in those with anadenine to guanine (A¬G) mutation in the promoter region of the apolipoprotein A-I gene.
LDL subclasses[39]	With low-fat diets, some men change from pattern A (large, buoyant LDL) to pattern B (small, dense LDL). Men with pattern B may respond unfavorably to a low-fat diet.

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Biologic factors include specific changes in dietary composition, the initial serum cholesterol concentration, metabolic responsiveness, and genetic factors. When Denke and Frantz (23) reexamined the Minnesota Coronary Survey Dietary Trial, taking into account the regression toward the mean phenomenon, they found that patients with high initial serum cholesterol levels had an 18% reduction in serum cholesterol levels, whereas those with lower levels had an 11% reduction. They found that subjects with high serum cholesterol levels were significantly more diet-responsive than those with normal values. Other studies have shown the importance of the presence of excess body weight (24,25) and the fractional catabolic rate of LDL with a diet high in saturated fatty acid in causing variability in diet-responsiveness (20).

A common cause of dietary resistance is familial hypercholesterolemia, in which affected children are unlikely to normalize their cholesterol values by diet alone (26). This highlights the importance of genetic factors in determining genetic response. Better knowledge of genetic determinants of dietary response may also permit targeting of specific dietary interventions toward different genotypes. An important genetic contribution appears to be associated with the presence of specific apoprotein E isoforms. Subjects with apoprotein E4 absorb more dietary cholesterol than do those with apoprotein E2 (27). Lopez-Miranda and coworkers (28) compared the responsiveness of men and women to a Step I diet and found that the apparent differences in mean LDL-C level reduction of 15% in men and 8% in postmenopausal women were related to the presence of the apoprotein E phenotype. Men with the apoprotein E3/4 genotype had a significantly greater reduction in LDL-C levels and the ratio of LDL to HDL than did men with the apoprotein E3/3 genotype or similarly affected women. A retrospective analysis reviewing diet and apoprotein E phenotype suggested that women with the apoprotein E3/2 phenotype derived little benefit from a diet with a high ratio of polyunsaturated fat to saturated fat because of reduction in the more protective HDL-C, whereas men with the apoprotein E4/3 phenotype showed the greatest improvement in the ratio of LDL to HDL. (29). Other factors shown to play a role in dietary responsiveness are apoprotein A-IV (30,31), changes in the gene-encoding apoprotein B (32) or the apoprotein A-I promoter region (33), and the LDL subclasses (34).

Using Diet to Alter Risk for Coronary Artery Disease

There are several principles that must be remembered in treating patients. First, the response of patients to diets is variable, as discussed earlier. Currently, we cannot predict how a given patient will respond to a particular therapeutic diet. Second, adherence to diets that produce an excellent reduction in serum lipids often also results in clinically important weight loss. Third, dietary factors that lower LDL-C levels include restriction of cholesterol-raising fatty acids and dietary cholesterol and inclusion of plant sterol/stanol esters to reduce cholesterol absorption. Other important factors include substituting mono- or polyunsaturated fats or complex carbohydrates for saturated fats, reducing intake of animal protein, and increasing intake of viscous fiber or cereal. Fourth, factors that affect HDL-C or TG levels include changes in body weight and consumption of sugars, alcohol, and omega-3 fatty acids or fish oils. Supplementation of the diet with fish may reduce cardiovascular end points independent of its effects on the lipid profile. Weight loss or restriction of simple sugars, for example, raises HDL-C levels and lowers TG levels. On the other hand, alcohol intake raises both HDL-C and TG levels. Fifth, changes seen in the first few months of a diet often are not sustained over time. This is particularly true for weight loss. The real hurdle for those with excess weight is not beginning a therapeutic program, it's maintaining the dietary habits and resulting weight loss. For weight maintenance, regular physical activity can be invaluable. The goal, of course, is sustained, not temporary, benefit.

EFFECT OF DIETARY FACTORS ON LIPIDS AND CORONARY ARTERY DISEASE

In published landmark studies, Keys (35) and Hegsted (36) quantified the response of serum cholesterol levels in humans to consumption of varying proportions of dietary fat and cholesterol. They demonstrated that saturated fatty acids (C12:0 to C16:0) are approximately twice as potent in raising cholesterol as polyunsaturated fats are in lowering them. Both investigators showed an independent effect of dietary cholesterol on serum cholesterol, although monounsaturated fats (*cis* C18:1) were believed to have no specific independent effect. These equations do not take into account the effects of behenic acid (22:0), caprylic acid (8:0), and capric acid (10:0) that are cholesterol raising as well (37). Moreover, as will be shown later, these equations do not account for the increase in LDL-C levels seen with intake of TFAs and *n*-3 fatty acids that should be considered in any contemporary review of current dietary habits.

Cholesterol-Raising Factors: Dietary Cholesterol

Mechanism

The most significant quantitative response to increased dietary cholesterol is the suppression of hepatic cholesterol synthesis (38). In addition, the effect of dietary cholesterol on receptor-mediated LDL clearance is strikingly affected by the proportion of saturated fat consumed. Studies of cholesterol feeding in humans, however,

are characterized by the great variability of their results (39). Hyper- and hyporesponders to dietary cholesterol are seen. Incredibly, significant within-person fluctuations may be found, even at the same level of serum cholesterol (40). Despite several attractive genetic mechanisms that might explain this variability, no simple test is available to discriminate responders in a quantitative fashion.

Feeding Studies

Age and gender may be important variables in determining the response to dietary cholesterol. Dietary studies involving healthy young men and women showed that consumption of one or two eggs daily, when added to a Step I AHA diet, may have only a small effect on blood cholesterol values (41,42). Unlike their male counterparts, in whom the rise in total cholesterol levels with consumption of eggs was almost completely accounted for by a rise in LDL-C, in young women, approximately 75% of the rise in total cholesterol levels was due to an increase in LDL-C, with a significant increase in HDL-C as well. On the other hand, when Lichtenstein and associates (43) added moderate amounts of dietary cholesterol to reduced-fat diets followed by hyperlipidemic middle-aged and elderly men and women, significant increases in LDL-C were seen, despite different dietary fat composition.

Other variables that help explain dietary responses to cholesterol include race and lipid profile. White individuals respond with higher cholesterol responses than individuals from other racial backgrounds (44). Careful egg-consumption studies suggest that people with combined hyperlipidemia are more sensitive to dietary cholesterol than those with elevations of cholesterol levels only (45).

Dietary Cholesterol and Coronary Artery Disease

Currently, the average daily consumption of cholesterol is 331 mg for men and 213 mg for women (46). Studies performed when average dietary cholesterol intakes were higher than they are now have shown that dietary cholesterol intake is clearly related to atherosclerosis. The Western Electric Study showed that dietary cholesterol was significantly associated with risk for CAD, independent of the serum cholesterol level (47). In three additional prospective studies, a 200 mg higher intake of cholesterol per 1,000 kcal at baseline was associated with a 30% higher rate of CAD (48). On the other hand, food frequency data gleaned from prospective cohort studies involving men and women suggested that one egg per day did not increase CHD risk (49), although subgroup analysis from this large cohort suggested that egg consumption was associated with increased CHD risk in diabetic men and women.

Plant Stanol/Sterol Esters

Cholesterol is the sterol component of mammalian cell membranes. Plant sterols are structurally similar to cholesterol and, when ingested by humans, inhibit cholesterol absorption. Of the many plant sterols found in nature, beta-sitosterol is particularly abundant and has been used since the 1950s to lower serum cholesterol (50). Stanols are saturated sterols without double bonds in the sterol ring structure. Recently, soybean and tall oils have been esterified to create fat-soluble plant sterols and stanols that facilitate cholesterol lowering in normo- and hypercholesterolemic men and women, individuals with diabetes, people with CHD, and children (51,52).

Mechanism

Plant sterol/stanol esters compete with dietary cholesterol for absorption via mixed micelles. They can reduce cholesterol absorption efficiency by as much as 65%. Only a small amount of plant sterols and an even smaller amount of plant stanols are absorbed. Ingestion of products enriched with plant sterol/stanol esters does not cause fat malabsorption.

Feeding Studies

The efficacy of the plant sterol/stanol esters appears to be similar. Using doses of 2 to 3 g per day, feeding studies show that reductions in LDL-C levels range from 6% to 20% in most studies.

Metaanalysis shows that the dose-response relation is continuous up to a dose of approximately 2 g of plant sterol or stanol per day, although there is considerable variability in response (50). The reduction in the concentration of LDL-C at each dose is significantly greater in older people than in younger people. Levels of TGs and HDL-C are not affected. A randomized clinical trial in the United States suggested a dose-dependent response after ingestion of 3 g per day lowered LDL-C by 10.1%, with no significant reduction in serum vitamin A or 25-hydroxyvitamin D levels (53). Consumption of plant sterol/stanol ester–enriched products appears to be generally safe, but a reduction in beta-carotene absorption occurs. This has prompted concern from the AHA about the use of these products by children and pregnant women. The AHA nutritional advisory committee has recommended that further studies and long-term monitoring be undertaken to determine the long-term safety of consumption of foods enriched with plant sterol/stanol esters (54,55).

Relationship to Coronary Heart Disease

Based on their proven ability to lower LDL-C, Law (50) suggested that a reduction of CHD of approximately 25% could be expected to accompany regular dietary supplementation with plant stanol esters. A subgroup analysis of the Scandinavian Simvastatin Survival Study indicated that patients with CHD who had evidence of low cholesterol absorption and high synthesis experienced reduced CHD events during simvastatin treatment. This suggested a combined role for plant sterols and statins in individuals with high cholesterol absorption and low synthesis (56).

Cholesterol-Raising Fatty Acids

Saturated Fats

The major saturated fats in the diet are lauric (C12:0), myristic (C14:0), palmitic (C16:0), and stearic fatty acids (C18:0) (eTable 2.3.2). They have no double bonds and are solid at room temperature. Foods that are rich in saturated fats primarily include those of animal origin, such as meat and dairy products, and selected vegetable fats, such as coconut oil, palm kernel oil, palm oil, and vegetable shortening. Palmitic acid is the predominant saturated fat in animal and dairy fats, whereas lauric acid is the predominant fat in coconut oil and palm kernel oil.

***e*TABLE 2.3.2** CHOLESTEROL-RAISING FATTY ACIDS

Fatty acid	Chain length	Examples
Lauric	12	Coconut oil, palm kernel oil
Myristic	14	Coconut oil, palm kernel oil
Palmitic	16	Palm oil, beef tallow, butter, chicken fat
Elaidic[a]	18:1	Shortening, partially hydrogenated oils and margarines
Behenic	22:0	
Caprylic	8:0	
Capric	10:0	

[a] This is a *trans* fatty acid that, like the other saturated fats, raises serum and low-density lipoprotein cholesterol levels.

Mechanism

Detailed studies have determined that saturated fats raise LDL-C by suppressing LDL-receptor activity (38).

Feeding Studies

When the lipid profiles of adult lactovegetarians, whose major sources of dietary saturated fat and cholesterol are dairy products, were compared with those of strict vegetarians, the lactovegetarians have 24% higher LDL-C levels and 7% higher HDL-C levels (57). The author of that study concluded that in vegetarian populations, the ingestion of dairy products rich in saturated butterfat raises the LDL-C level on a percentage basis approximately three times higher than it raises the HDL-C level. Indeed, changes in the dietary intake of saturated fat appear to have been instrumental in lowering CAD in eastern Finland, an area that historically had the world's highest rates of mortality associated with CHD (58). Recently, a multicenter, randomized, crossover trial of the effects of reducing dietary saturated fatty acids on

plasma lipid and lipoprotein levels in 103 healthy adults aged 22 to 67 years was carried out in older men and postmenopausal women, with both white and black subjects. Compared to an average American diet in which 15% of energy comes from saturated fatty acids, lowering saturated fatty acids to 6.1% reduced LDL-C levels by 11% (59). Interestingly, lipoprotein(a) [Lp(a)] increased in a stepwise fashion as LDL-C decreased.

Although most studies have examined saturated fat as a single entity, there are important differences among saturated fatty acids. Lauric acid (12:0) raises LDL-C levels more than oleic acid does, although it is not as potent in this regard as palmitic acid (16:0) (60). Lauric acid also raises HDL-C levels more than palmitic acid does (61). Stearic acid (18:0), the second most abundant saturated fatty acid in animal fats, is not a cholesterol-raising fatty acid and does not raise LDL-C levels relative to the effect of oleic acid (62). Myristic acid (14:0) is more potent in raising cholesterol than is palmitic acid (63). In middle-aged and elderly hyperlipidemic individuals, consumption of beef tallow–enriched diets produces higher concentrations of total cholesterol and LDL-C and a higher ratio of total cholesterol to HDL-C than consumption of corn oil–enriched diets does (64). Thus, curtailment of beef tallow consumption as part of a cholesterol-lowering diet seems appropriate. On the other hand, the amount of saturated fat and dietary cholesterol in lean beef is such that it need not be totally eliminated from cholesterol-lowering diets.

Saturated Fats and Coronary Artery Disease

Epidemiologic Data The Seven Countries Study showed a direct relationship between saturated fat intake and rates of CAD (65). In that trial, Finland had the highest rate of CAD mortality, Mediterranean groups were far lower, and the Japanese, who had low intakes of saturated fat, had the lowest rates of CAD. The Ni-Hon-San Trial compared the diets and clinical status of native Japanese men with Japanese men who had migrated to Hawaii or to California. After migration toward the mainland of the United States, the diet increased in calories and saturated fat and the resulting increases in weight and serum cholesterol levels paralleled increases in rates of CAD (66,67). A notable exception to the observation that national diet often predicts risk of CAD is France. Despite similar intakes of saturated fat and dietary cholesterol to those in other Western countries, the rate of CHD in France is lower. The inverse association between wine ethanol and CHD has been one possible explanation for what has become known as the “French paradox” (68). Artaud-Wild and colleagues (69) reviewed the cholesterol–saturated fat index scores for foods eaten in these countries. They speculated that consumption of milk and butterfat was markedly higher in Finland than in France. They suggested that the lower rates of fatal CAD in France were related to a less thrombogenic diet containing more plant foods and vegetables and small amounts of liquid vegetable oils. Law (70) noted that serum HDL-C levels explained little of the difference and offered a time-lag observation, suggesting that consumption of animal fat increased more recently in France than in Britain and that this accounted for the difference.

Clinical Trial Data As noted earlier, clinical trials using lipid-lowering drugs with the ability to markedly reduce LDL-C levels have shown more convincing results than have trials involving dietary adjustments alone (71). Nonetheless, the insights gained from the entire range of dietary trials are worth reviewing, even if any single trial is, by itself, not conclusive in proving that dietary reduction of saturated fats prevents CAD.

Interpretation of many of the dietary trials that used clinical end points is hindered by faulty design (Table 2.2 and Table 2.3). This is particularly true of early trials that were underpowered, so that achieving a positive result was more difficult. The Minnesota Coronary Survey, for example, did not have sufficient patients on the therapeutic diet for a sufficient length of time to achieve a significant effect—if, in fact, one was possible (72). Other examples of flawed study design that have made interpretation difficult include the Oslo Dietary and Smoking Intervention Trial, which changed smoking habits as well as diet (73), the Los Angeles Veterans Administration Trial, which combined both primary and secondary prevention (74), and the Finnish trial, which suffered from flawed randomization (75). Despite the fact that it was not a “pure” dietary trial, the results of the Oslo trial suggested that dietary reductions in cholesterol may be important in reducing rates of CAD. In this study, participants were randomly assigned to consume a diet low in saturated fat and counseled to reduce smoking. A 47% reduction in the incidence of sudden death and myocardial infarction (MI) was achieved in the intervention group, compared with the control group. The dietary change resulted in a net difference of 10% in serum cholesterol levels between intervention and control groups. The authors used statistical analysis to show that dietary change influenced the reduction in CAD events more than smoking did. At 5 years, the difference between both groups in total mortality became marginally significant, with a 33% lower mortality rate in the intervention group than in the control group.

Three large, multiple–risk factor intervention trials in which dietary change was a component also resulted in a smaller decrease of serum cholesterol values than was anticipated (76,77 and 78). When intervention trials (multifactorial or not) that use dietary changes are viewed as a whole, it appears that modest lowering of serum cholesterol by approximately 10% by dietary intervention over a short trial period is unlikely to show significant differences in CHD risk as compared to that seen in a control group.

Clinical trials with angiographic end points have the advantage of providing additional information about the potential beneficial effects of a diet low in total and saturated fat but involve sample sizes that are easier to recruit (Table 2.3). An individual’s initial response to a diet can decrease with time, as seen in the Heidelberg trial, in which total fat restriction to less than 20% of calories resulted in initial LDL-C level decrease of 25% in subjects after 3 weeks on a metabolic ward (7). At the end of 1 year, the decrease in LDL-C levels had fallen to 4% as adherence to diet fell sharply. This produced an average lowering of LDL-C levels of 8% over the course of the year. The intervention group also participated in intensive physical exercise. When follow-up angiograms were reviewed, a significant decrease in progression and an increase in regression were seen in the intervention group. In this study, apolipoproteins, lipids, and lipoproteins were measured. Although the exercise component was an important part of this study, the best metabolic predictors of angiographic disease progression were the ratio of total cholesterol to HDL-C and the level of LDL-C (79).

In the St. Thomas Atherosclerosis Trial (STARS), CAD patients were randomly assigned to received treatment with usual care, diet, or diet and cholestyramine resin (6). The diet restricted total fat intake to 27% of total energy and saturated fat intake to 8% to 10% of energy and was high in fiber, chiefly pectin. The primary end point of this angiographic trial was the per-patient change in the mean absolute width of coronary segments. Progression of angiographic CAD correlated significantly with in-trial plasma total cholesterol, LDL-C, apolipoprotein B, and Lp(a) levels. By multiple regression analysis, LDL-C level was the best predictor of change in the diameter of the coronary vessel, appearing to account for 24% of the variance.

Further detailed dietary analysis showed that total fat intake was higher in the usual-care group than in the diet group (97 g vs. 61 g) (80). Patients in whom disease progression occurred consumed 42 g per day of saturated fat, whereas patients who experienced regression consumed only 21 g per day. These distinctions were important, because there were linear correlations between decreased intake of saturated or total fat and increased size of the artery lumen. When multiple regression analysis was used, the associations between change in coronary vessel diameter and total or saturated fat intake persisted, despite adjustment for LDL-C and other clinical descriptors. Thus, in this study of middle-aged British men, progression of CAD was strongly influenced by the intake of saturated fatty acids, possibly mediated in part by mechanisms other than the effect of saturated fat on LDL-C levels.

These studies suggest a role for reducing saturated fatty acids and cholesterol in the diet. The effects seen with these dietary changes are not as great as those seen with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Moreover, they do not produce results as dramatic as those seen in individuals who consume diets supplemented with *n*-3 fatty acids, in which benefit appears to be mediated through a nonlipid effect (see Fish Oils).

Trans Fatty Acids

Saturated fatty acids are not the only cholesterol-raising fatty acids. TFAs are found in meat and dairy products (they are a byproduct of fermentation in ruminant animals) and in products containing partially hydrogenated oils. The most common TFA in the American diet is elaidic acid, the *trans* isomer of oleic acid, which is found in stick margarines, shortenings, milk, butter, cheese, commercially processed baked goods, and vegetable oils used for frying.

Feeding Studies

When TFAs are ingested as 7.7% or more of energy, they raise total cholesterol and LDL-C levels and lower HDL-C levels (81,82). At 3.8% of energy, TFAs raise LDL-C levels significantly less than do saturated fat and oleic acid and do not lower HDL-C levels (83). To put these findings into perspective, the average intake of TFAs in the United States is approximately 2% to 4% of energy. TFA may increase Lp(a) (84), although this has not been a consistent finding (85).

Mechanism

Partial hydrogenation has been used by the food industry to improve the texture acceptability and increase the oxidative and thermal stability of vegetable oils (86). Hydrogenation is accomplished by converting the naturally occurring *cis* double bonds, which produce a bend in the molecule, impair crystallization and keep the oil liquid, to their straighter *trans* isomers, which can be more tightly packed and hence are solid at room temperature. The change in HDL-C levels seen with TFA consumption appears to be mediated through an increase in cholesterol ester transfer protein (87).

Trans Fatty Acids and Coronary Artery Disease

Willet and colleagues (88) used dietary questionnaires in the Nurses Health Study to demonstrate that intake of *trans* isomers, after adjustment for age and total energy

intake, was directly related to risk of CAD. They noted that consumption of foods that are major sources of TFA [e.g., margarine, cookies (biscuits), cake, and white bread] were each significantly associated with higher risks of CAD.

How can this information on TFA be used to reduce CHD risk? Butter is clearly an undesirable choice in a cholesterol-lowering diet, because it contains both cholesterol and saturated fats. Stick forms of margarine, with their higher content of saturated fatty acids and TFA, also should be avoided. The preferred choices for spreads are either soft or tub forms of reduced-fat or *trans*-free margarines (89). The major focus of the public health message remains on restriction of sources of saturated fatty acids, but consumers should also be encouraged to keep calories from TFA low.

Cholesterol-Lowering Interventions

Unsaturated Fatty Acids

Unsaturated fatty acids lower LDL-C levels when they are exchanged for saturated fatty acids in the diet. The more unsaturated a fatty acid, the more liquid it tends to be at room temperature. There are important differences, however, in various groups of unsaturated fatty acids that should be considered in the design of therapeutic diets. The two major groups are the polyunsaturated fatty acids (PUFAs) and the monounsaturated fatty acids (MUFAs). A recent metaanalysis found no significant differences in total cholesterol, LDL-C, and HDL-C levels when MUFAs and PUFAs are directly compared (90). Real differences may relate to effects on oxidation and coagulation parameters.

Polyunsaturated Fatty Acids

PUFAs, however, are not a homogenous class but are divided into two groups by the position of the first double bond from the terminal end of the carbon chain. Examples of *n*-6 fatty PUFAs include corn, sunflower, safflower, sesame, and cottonseed oils. The major *n*-6 PUFA, linoleic acid (18:2) is an 18-carbon “essential” fatty acid that cannot be synthesized by the body. Linoleic acid is needed for normal immune response, and essential fatty acid deficiency impairs B and T cell–mediated responses (91). The *n*-3 PUFAs are often referred to as “marine lipids” or “fish oils.” Marine *n*-3 PUFAs have a major effect on TG levels, as is discussed later. Alpha-linolenic acid is a plant-based *n*-3 PUFA. Common sources of alpha-linolenic acid are tofu, soybean and canola oil, nuts, and flax seed. These are healthy additions to the diets of vegetarians and those who do not eat seafood; however, alpha-linolenic acid does not appear to lower TG levels as strikingly as do fish oils (92).

Feeding Studies

In the past, diets high in *n*-6 PUFAs were recommended to counterbalance the effect on serum cholesterol of a high intake of saturated fat. Today, diets high in *n*-6 PUFA are no longer recommended, for several reasons. First, there are no large populations that habitually ingest significantly more than 10% of energy as PUFAs. Second, excess PUFA intake can have unwelcome side effects, such as weight gain and cholelithiasis (93). Third, excess consumption of linoleic acid has been associated with tumor growth in animals, although this effect has not been verified in human trials (91). There was no association between PUFA intake and the mortality rate at 10.5 years in the large Multiple Risk Factor Intervention Trial (MRFIT) (94), but the AHA guidelines recommend restriction of total PUFA intake to <10% of calories, because there is also no conclusive evidence that high PUFA intake is safe.

Polyunsaturated Fatty Acids and Coronary Artery Disease

The *n*-6 PUFAs appear to reduce risk of CAD more than MUFAs in older epidemiologic trials (1). This was also seen in human primate studies. The benefits of consumption of *n*-3 PUFAs on CHD, particularly fatal CHD, are noteworthy. The dietary effects appear to be independent of improved lipid profiles. This is discussed in the section Fish Oils.

Monounsaturated Fatty Acids

The role of MUFAs in reducing risk of CHD has prompted an AHA Science Advisory (95). This class of fatty acids has only one double bond. Oleic acid is representative of the *cis* (hydrogen atoms are on the same side) forms of MUFAs. Common sources include canola (rapeseed) oil, olive oil, peanut oil, almonds, and avocados.

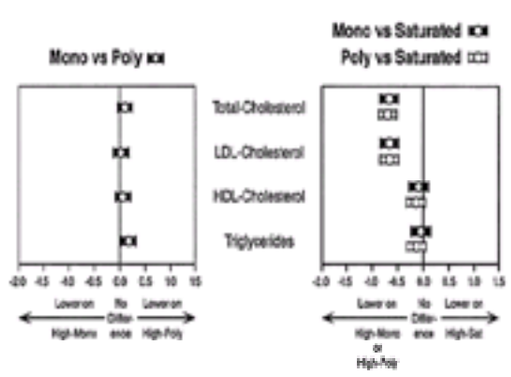
Mechanism

In contrast to PUFAs, MUFAs do not appear to lower HDL-C when they are added to the diet (96). Most important, LDL isolated from subjects on diets rich in MUFA is less susceptible to oxidation than LDL isolated from subjects on diets rich in polyunsaturated fats (97,98). This suggests that there are theoretical, but unsubstantiated, advantages to a diet high in MUFAs for individuals with small, dense LDL-C particles (99).

Feeding Studies

Grundy (100) noted that a high-carbohydrate diet raises TG levels and lowers HDL-C levels, whereas a diet high in monounsaturated fat does not. Mensink and Katan (101), in studying 57 outpatient volunteers, used foods enriched with olive oil. The olive oil–rich diet caused a specific decrease in non-HDL cholesterol and did not significantly change TG levels. Moreover, when a Step I diet in which total fat accounted for 30% of calories was compared with a Step I diet in which fat accounted for 38% of calories but that was enriched with monounsaturated fat, no significant difference was seen in the extent to which LDL-C was reduced, suggesting that monounsaturated fats have a neutral effect on LDL-C (102).

Gardner and Kraemer (90) performed a metaanalysis of 14 studies to demonstrate that there were no significant differences in lipid levels when a diet high in monounsaturated fats was compared with a diet high in polyunsaturated fats (*e*Fig. 2.1.1). A recent randomized, double-blind, five-period crossover design study in normocholesterolemic subjects with normal HDL-C levels compared the effects of three diets high in monounsaturated fat with an average American diet and the Step II diet (103). The high-MUFA diets lowered LDL-C by 14%, similar to the reduction seen with the Step II diet. TG concentrations, however, were higher with the Step II diet than with the high-MUFA diets. HDL-C levels were maintained by the high-MUFA diets, whereas they were lowered by 4% by the average American diet. Thus, with respect to HDL-C and TG levels, the high-MUFA diets had a more favorable response on these important cardiac risk factors.

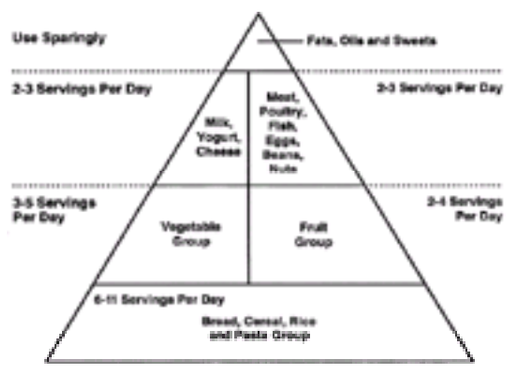


***e*FIGURE 2.1.1** Metaanalysis of the effects of high-monounsaturated (mono) versus high-polyfat (poly) diets on lipid levels. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Some investigators have suggested following a Mediterranean diet pyramid that differs from the one endorsed by the U.S. Department of Agriculture (104) (*e*Fig. 2.1.2 and *e*Fig. 2.1.3). A wholesale shift to the Mediterranean diet pyramid that excludes all fats but olive oil; recommends less frequent consumption of fish, poultry, and red meat; and includes physical activity and wine in moderation would require major changes in agricultural policy for the United States (105). Diabetic patients may benefit from an emphasis on more monounsaturated fats, such as canola or olive oil, in the diet (106). A high-carbohydrate, low-fat diet can worsen blood sugar control and increase levels of TG levels compared with a diet enriched with monounsaturated fat. With a high–monounsaturated fat diet, levels of HDL-C are likely to be maintained

better as well.

***e*FIGURE 2.1.2** The Mediterranean diet pyramid. This pyramid is based on the dietary traditions of Crete, circa 1960, structured in light of current nutrition research. *Olive oil is the region's principal fat. In the optimal Mediterranean diet, total fat can be as high as 35% to 40% of calories.



***e*FIGURE 2.1.3** The U.S. Department of Agriculture (USDA) diet pyramid. This pyramid is based on the dietary guidelines established in 1992 by the USDA.

Monounsaturated Fatty Acids and Coronary Artery Disease

Epidemiologists have long pointed to the favorable experiences among Mediterranean populations that subside on an olive oil–based, so-called Mediterranean-type diet, in which the incidence of CAD is lower than would be expected based on the cholesterol levels of the population (10). The AHA Scientific Advisory contrasted the favorable effects of MUFAs on lipid levels, factors related to thrombogenesis, *in vitro* LDL oxidative susceptibility (compared with high-PUFA diets), and insulin sensitivity, reporting that MUFAs have accelerated atherosclerosis in monkeys and have increased the presence of chylomicron remnants. They called for additional data to resolve this issue.

The Lyon Trial compared a Mediterranean-type diet rich in alpha-linolenic acid with the AHA Step I diet in 605 subjects with a history of MI (107). It supplied a canola oil–based margarine to the intervention group that was high in oleic acid and even higher in alpha-linolenic acid. The intervention group diet was also lower in saturated fat and cholesterol and higher in fiber than the diet of the control group. There was no significant difference in alcohol ingestion between the groups. The control group had a total and saturated fat intake higher than that recommended by a Step I AHA diet. A Step II diet would have been a more appropriate control diet for this CHD population; nonetheless, despite a lack of improvement in BMI and lipid profiles, there was a striking difference in mortality, with eight sudden deaths occurring in the control group and none occurring in the treatment group. A follow-up of the original results showed that the significant difference in CHD end points was maintained at 47 months (108). Although these results are impressive, it is hard to know what individual factor in intervention mediated the reduction in CHD. There were several interventions used, including more *n*-3 fatty acids, such as alpha-linolenic acid; more fiber; more MUFAs; and less saturated fatty acids and dietary cholesterol in the diet.

Low-Fat, High-Carbohydrate Diets

A diet low in fat and high in complex carbohydrates is typical of an "Asian-style" diet. Often the percentage of energy that comes from carbohydrates is 60% to 65%, allowing total fat calories to be as low as 15% to 20% of total energy. Thus, intakes of saturated fat and dietary cholesterol are very low.

Mechanism

The usual response of a subject to a high carbohydrate diet is an increase in TG levels, which lowers HDL-C levels. Yet when patients are *gradually* introduced to a high-carbohydrate, low-fat diet, significant reductions of plasma total cholesterol and LDL-C levels are seen without the invariable carbohydrate-induced hypertriglyceridemia that is characteristic of an abrupt transition to such a diet (109).

Feeding Studies

Pritikin espoused diets that were severely limited in fat to prevent CHD (110). With this regimen, initial improvements in total cholesterol and LDL-C can be dramatic. On the other hand, the strictness of the regimen makes it difficult to obtain high rates of adherence. Possible explanations for the short-term gains seen when patients embark on such diets include regression to the mean, the effect of institutionalization (if the diet was introduced in such a facility), reduction in saturated fatty acids and dietary cholesterol, regular exercise, acute caloric restriction, and weight loss (111). Weight loss may be crucial in obtaining desired lipoprotein profiles. When Lichtenstein and colleagues (112) compared a reduced-fat diet, a low-fat diet without change in energy, and a low-fat diet in which decreased caloric intake was allowed to occur, only in the third diet was the overall change in the ratio of LDL-C to HDL-C favorable. A metaanalysis of 37 dietary intervention studies in free-living subjects published from 1981 to 1997 showed that exercise resulted in greater decreases in LDL-C and TG levels and prevented the decrease seen in HDL-C levels that is associated with low-fat diets (113).

Low-Fat Diets and Coronary Artery Disease

Some studies have emphasized a total fat content less than 30% of calories and a lowered intake of saturated fat in the diet. The Leiden study was an uncontrolled study of the effects of a vegetarian diet in 39 men who had angina pectoris. The study demonstrated that subjects who improved the ratio of total cholesterol to HDL-C had the least progression of CAD on follow-up angiography (114). Blackenhorn and colleagues (115) noted a striking difference between the 18 men in the placebo group of the Cholesterol Lowering Atherosclerosis Study (CLAS), who developed new atherosclerotic coronary lesions, and the 64 men in the diet group, who did not. Their analysis of the nutritional data suggested that this was related to dietary choices. Subjects who did not show progression had substituted low-fat meats and dairy products for high-fat products. The effect of an increased intake of total, saturated, and polyunsaturated fat was to foster a greater likelihood of new lesion development. These observational results are consistent with, but did not prove, the premise that for individuals at risk, the diet should be low in both total fat and saturated fat to reduce the likelihood of coronary progression.

The value of a low-fat vegetarian-style diet as part of a comprehensive lifestyle intervention that includes exercise was examined in the Lifestyle Heart Trial (10). In this provocative study, a highly motivated group of patients with symptomatic coronary disease consumed a diet in which fewer than 10% of calories came from fat and no cholesterol was allowed. The treatment group lost 22 lb, whereas the control group, who were on what was essentially a Step II diet, did not lose any weight. The intervention subjects showed a decline in LDL-C levels of 37.8%, to 100 mg per dL.

At the end of 1 year, the intensively treated group had decreased progression and/or regression of angiographic CAD compared with the control group. The

improvement in angiographic appearance went beyond simple improvements in percentage of stenosis; the treatment group had complex shape-change and stenosis-molding characteristics suggestive of augmented flow reserve (116). At the end of 5 years, improvement was documented by both angiography and decreased size and severity of perfusion abnormalities as seen while the patient was at rest, using dipyridamole positron emission tomography (PET) (117). The small sample size, the difficulties caused when 49% of the subjects refused to participate after randomization, and the fact that multiple interventions were in place, including exercise, stress reduction, and the significant weight reduction seen in the treatment group, preclude any generalizations about the value of the very-low-fat diet to the coronary patient that might be based on the results of this study.

Singh and coworkers (118) performed a randomized, single-blind, controlled clinical trial in patients with acute MI to determine the effect of adding more fruits, vegetables, nuts, and grains to the usual post-MI fat-reduced diet. Both groups consumed a principally vegetarian diet, eating eggs four to five times per week and meat one to two times per week. The treatment group's goal was to eat at least 400 g per day of fruits and vegetables. The results were striking: blood cholesterol and the incidence of cardiac events were significantly lower in the treatment group. Even total mortality was significantly improved. It is important to note that weight fell by 6.3 kg in the treatment group versus 2.4 kg in the usual-care group. As seen in other trials, reduction in LDL-C, particularly when it is accompanied by loss of excess weight, appears to be associated with improvement in rates of CAD events.

The Stanford Coronary Risk Intervention Project was a 4-year multifactor intervention trial. The study used serial, quantitative coronary angiography in 300 men and women to show a significant reduction in new lesion formation in the coronary arteries of those randomly assigned to the risk-reduction group, compared with that in the usual-care group (119). All risk-reduction group subjects were instructed to consume a low-fat, low-cholesterol, and high-carbohydrate diet, with a goal of intake of less than 20% of energy from fat, less than 6% of energy from saturated fat, and less than 75 mg of cholesterol per day. Increased physical activity and a specific endurance exercise-training program were recommended. A staff psychologist supervised a stop-smoking program for smokers. Major goals were to decrease LDL-C levels to fewer than 110 mg per dL and TG levels to fewer than 100 mg per dL, and to increase HDL-C levels to greater than 55 mg per dL, using dietary and pharmacologic interventions. Multiple regression analysis identified in-study dietary fat intake as the best correlate with new lesion formation. Participants randomly assigned to the risk-reduction group preferentially increased complex carbohydrate intake to offset reduction in dietary fat restriction. The authors suggested that the reduction in dietary fat accomplished by subjects in their study, as in the CLAS placebo group, decreased the rate of new lesion formation by mechanisms not limited to LDL reduction.

In addition, a low-fat diet may help relieve symptoms through mechanisms apart from the lipid-lowering effects on atherosclerosis. Several studies that used low-fat diets as part of a multiple intervention approach showed early symptomatic improvements in cardiac status. Ornish (10) reported that patients in the experimental group of his Lifestyle Trial experienced a 91% reduction in frequency of angina, a 42% reduction in duration of angina, and a 28% reduction in severity of angina, whereas angina worsened in the control group. A decrease in angina was also seen in the Heidelberg Trial (7). Both of these studies used intensive exercise regimens. Interestingly, a beneficial effect on angina was seen in the intervention groups in STARS, but not in the control group, even though there was no difference in the exercise advice given to control and to intervention subjects. Gould and colleagues (120) showed that relatively short-term, intensive cholesterol lowering over the course of 90 days resulted in improved myocardial perfusion capacity, as measured noninvasively by dipyridamole PET.

A likely explanation for short-term improvement that occurs with changes in diet is improved endothelial regulation of vasomotion. In both animal and human studies of hypercholesterolemia, abnormal blood-vessel reactivity occurs early and involves both large vessels with overt atherosclerotic change and the microcirculation, where atherosclerosis does not develop (121). Harrison and coworkers demonstrated that dietary treatment of atherosclerosis in monkeys not only produced morphologic improvement of the atherosclerotic lesion, but also restored endothelium-dependent vascular relaxation to normal (122). Later work in rabbits also showed that cholesterol-lowering diets improved endothelium-dependent vascular relaxation (123).

The mechanism by which diet restores endothelium-dependent vascular relaxation to normal most likely involves diet-related reduction of LDL-C levels. Further studies have demonstrated the more potent effects of adding LDL-lowering therapy to diet. Leung and coauthors (124) demonstrated that impairment of endothelium-dependent relaxation in hypercholesterolemic patients with healthy coronary arteries can be reversed by cholesterol-lowering therapy with diet and a lipid-lowering resin that lowered LDL-C levels by 35.7%. In patients with CAD, adherence to a cholesterol-lowering diet and HMG-CoA-reductase therapy for 5.5 months significantly improved endothelium-dependent coronary reactivity in hypercholesterolemic patients, compared with patients whose condition was managed solely by adherence to a Step I diet (125). Anderson and colleagues (126) documented even greater improvement when probucol (which is no longer clinically available, but was used as an antioxidant in this study) was added to treatment with lovastatin. Because the effects of diet may be additive to the effects of drug therapy, these data support the notion that drug therapy should be added to dietary therapy and not given alone.

Dietary Fiber

Fiber, or nondigestible plant-based carbohydrate, is an important part of a balanced diet. Some believe that the ideal diet for both cancer and heart disease prevention is the 25/25 diet (i.e., intake of 25% of calories from fat and 25 g of total fiber per day) (127). However, for the optimal cholesterol-lowering diet, it is useful to think of fiber in terms of its viscous (formerly called "soluble") and nonviscous ("insoluble") forms. Nonviscous fiber aids in the treatment of constipation but is not lipid-lowering.

Mechanism

Viscous fiber in oat bran appears to act in the gastrointestinal tract by altering bile-acid metabolism and decreasing cholesterol synthesis (128). Fiber-rich foods have an increased ratio of protein to carbohydrate, and this has been suggested to have beneficial effects on insulin sensitivity (129). Good sources of viscous fiber include dried beans, oat products (they have more viscous fiber than any other grain), and certain fruits, vegetables, and grains. The latter items contain pectin, guar gums, and mucilages. Psyllium is a common source of viscous fiber used in dry cereals or obtainable as a dietary supplement.

Feeding Studies

Fiber lowers serum cholesterol levels modestly beyond the reduction expected from a cholesterol-lowering diet among patients who have elevated cholesterol levels. A metaanalysis that identified ten randomized, controlled trials in which oat products were included in the diet showed that the greatest lipid-lowering effects were seen when trials enrolled patients who had higher total cholesterol values (greater than 229 mg per dL) and when a dose of 3 g or more of viscous fiber was used (130). On average, an increase of viscous fiber of 5 to 10 g per day should lead to an approximately 5% reduction in LDL-C levels (131). Three grams of viscous fiber is equivalent to one large bowl of ready-to-eat oat bran or three packets of instant oatmeal. Psyllium is particularly useful in lowering LDL-C levels in both adults and children (132). When 5.1 g twice daily is added to a low-fat diet, it can lower LDL-C levels by 6.4%, a degree of LDL-C lowering equivalent to that achieved by doubling a statin dosage (133).

In addition, even when saturated fat and dietary cholesterol are greatly reduced, very high intakes of foods rich in viscous fiber lower LDL-C levels and also HDL-C levels, although to a lesser degree (134). Improvements that occur with increased consumption of fiber are not temporary. Hunninghake and associates (135) used 20 g of fiber daily, predominantly viscous guar gum and pectin, to treat 59 subjects who had mild to moderate increases in LDL-C levels (131 to 191 mg per dL) and were already on a Step I diet. After approximately 1 year, the mean percentage reductions from baseline were approximately 9% for LDL-C and 11% for the ratio of LDL to HDL.

Fiber and Coronary Artery Disease

The benefits of increased intake of dietary fiber for cardiovascular disease may extend beyond lowering of LDL-C levels. Khaw and Barrett-Connor (136) used 24-h dietary fiber intake by recall in a cohort of men and women in southern California aged 50 to 79 to show a significant inverse relationship between fiber intake and CAD. A 6-g increment in daily fiber intake was associated with a significant 25% reduction in mortality from CAD. A recent report of 43,757 U.S. male health professionals 40 to 75 years of age showed that there was a reduced risk of MI in men in the highest quintile for total dietary fiber intake (137). A 10-g increase in dietary fiber corresponded to a significant 19% reduction in risk. Within the three main dietary contributors to total fiber intake (vegetables, fruits, and cereals), *cereal fiber* was most strongly associated with reduced risk for MI. Finally, fruit and vegetable intake was found to reduce the all-stroke risk, including risk of transient ischemic attack, in men followed in the Framingham Trial, even after adjustment for multiple risk factors, including total fat, ethanol, and total energy intake (138).

Vegetable Protein

Soy protein has been consumed worldwide for centuries, and some Asian populations are known to consume 20 g of soy protein daily in products such as soy milk, tempeh, and tofu (139). This would seem to attest to the long-term safety of a diet enriched with soy protein. The mechanism by which soy lowers cholesterol levels is still unclear (140). The presence of the soybean isoflavone fraction appears to be important to cholesterol-lowering effects (141,142). In addition, high isoflavone intakes in soy breakfast cereals may reduce oxidized LDL levels, even though LDL-C is not significantly lowered (143). The benefit of this on atherosclerosis is not established.

Feeding Studies

A metaanalysis of clinical studies that examined the effects of consumption of a diet high in soy protein showed that cholesterol lowering may be one result in individuals who are hypercholesterolemic (144). In individuals who have cholesterol levels lower than 255 mg per dL, the changes were not striking. HDL-C levels remained unchanged. It is, of course, quite reasonable to choose soy-based food products within an overall balanced diet. In fact, textured vegetable-protein may have high acceptability.

Soy Protein and Coronary Artery Disease

There are no good data from clinical trials that examined the effects of soy protein on CAD end points. Although there are practical concerns regarding intake of sufficient soy protein to improve LDL-C values, products made with soy may prove useful as substitutes for products high in animal fat.

Additional Dietary Factors

Coffee

There has been considerable interest in whether coffee has deleterious effects on the coronary risk profile. A critical analysis must distinguish between filtered coffee and boiled coffee, such as is consumed in Scandinavia, France, or Turkey, which is associated with elevated cholesterol values.

Mechanism

Cafestol is a lipid-soluble diterpene present in coffee beans that is responsible for the cholesterol-raising effects associated with coffee consumption (145). In a special mouse model (apoE*3 Leiden), cafestol increases serum cholesterol levels by suppressing bile acid synthesis and decreases the LDL receptor by means of elevated secretion of cholesteryl esters in very-low-density lipoproteins (VLDLs) (146). Human studies using kinetic analysis of VLDL levels documented that cafestol increased plasma TG levels by increasing the mean rate of VLDL apolipoprotein B production (145).

Feeding Studies

Studies of filtered coffee have yielded conflicting results. Superko and coworkers (147) studied 186 coffee drinkers and found that a change from filtered, caffeinated coffee to decaffeinated coffee increased LDL-C and apoprotein B levels, whereas cessation of consumption of caffeinated coffee had no effect on these lipid parameters. A randomized, controlled study involving 119 students that examined intake of two types of filtered, decaffeinated coffee found no significant change when subjects were switched from filtered, caffeinated coffee (148). However, large amounts of filtered, caffeinated coffee may be associated with lipid changes. A randomized clinical trial involving 100 healthy male volunteers demonstrated that daily consumption of 720 mL of caffeinated coffee led to a small increase in plasma and total cholesterol levels, which was due to an increase in both LDL-C and HDL-C levels, even though this increase was not seen with an intake of 360 mL (149).

Coffee and Coronary Artery Disease

A prospective cohort analysis from the Health Professionals Study has provided the largest sample to date used to collect data about coffee's effects on cardiovascular disease (150). Although follow-up was only 2 years, they found that increased consumption of caffeinated coffee did not lead to higher risks for cardiovascular disease. They did note that greater consumption of decaffeinated coffee was associated with a marginally significant increase in the risk for CAD. A longer follow-up was used in the Nurses' Health Study, which documented 712 cases of CAD after 10 years of follow-up (151). There was no increase in CAD among women who drank six or more cups of caffeinated coffee, compared with that among women who drank none. The results of a study by La Croix and colleagues (152) that followed 1,130 male medical students for 19 to 35 years supported an independent, dose-responsive association between coffee and overt CAD among coffee drinkers who had more than 5 cups per day. In the absence of a placebo-controlled, clinical trial that would eliminate unknown confounding variables, it would appear that individuals who drink, on average, one to two cups of filtered coffee per day probably incur little change in lipid levels or CAD rates, as long as the coffee consumption is neither associated with the use of dairy creamers nor accompanied by cigarette smoking.

Garlic

The effects of garlic on cholesterol levels are inconsistent. One metaanalysis suggested that among individuals who have cholesterol levels greater than 200 mg per dL, one-half to one clove of garlic per day decreases total cholesterol levels by approximately 9% (153). Yet among 50 moderately hypercholesterolemic subjects, a double-blind, randomized, placebo-controlled trial of consumption of 300 mg of a standardized garlic tablet three times daily for three months showed that garlic therapy had no effect on major plasma lipoprotein levels (154). Moreover, clinical studies show that garlic has no impact on HDL subclasses, Lp(a), apolipoprotein B, postprandial TG, or LDL subclass distribution (155).

Dietary Factors That Affect High-Density Lipoprotein Cholesterol and Triglyceride Levels

The dietary factors that alter HDL-C and TG levels are not the same as those that alter LDL-C levels. The emphasis shifts to excess dietary energy, high carbohydrate intake, alcohol, and fish oil.

Excess Dietary Energy

Knuiman and colleagues (156) reviewed epidemiologic data on the relationship between diet and HDL-C levels and concluded that three partly opposing dietary factors determine the ratio of total cholesterol to HDL-C in an adult population. They convincingly argued that the proportion of energy from saturated fat raised total cholesterol and LDL-C levels, the proportion of energy from total fat raised HDL-C levels, and an excess in dietary energy, which produces obesity, lowered HDL-C levels. In addition, weight loss markedly affects TG levels and can improve HDL-C levels. A clinical study involving obese men and women quantified the effects of weight loss on the lipid profile as additive to those reducing fat and saturated fat (157). In this 13-week trial, weight loss in and of itself appeared to explain approximately 50% of the decrease in total cholesterol, 60% of the decrease in LDL-C, and 70% of the decrease in TGs. Moreover, although a low-fat, low–saturated fat diet alone reduced HDL-C by 11.1% and the ratio of HDL-C to LDL-C by 7.7%, weight loss reversed this trend, resulting in an increase in HDL-C of 12.5% and in the ratio of HDL-C to LDL-C of 24%. A metaanalysis of studies on the effects of weight loss on lipid and lipoprotein levels showed a significant negative correlation between weight loss and total cholesterol, LDL-C, and TG levels (158). HDL-C levels decreased during the active weight loss phase but increased by 0.009 mmol per L with every kilogram of weight loss when weight was maintained.

Mechanism

The means by which a low-fat diet reduces HDL-C is not clear. Brinton and colleagues (159) demonstrated that the mechanism by which diet lowers HDL-C differs substantially from the mechanisms that create differences in HDL-C among individuals who are on a fixed diet. Thus, the reduction in HDL-C that occurs quite commonly when a low-fat diet is begun may not be equivalent to the significance of an initial low HDL-C level on a usual diet when risk for CAD is being assessed.

High-Carbohydrate Diets

TG levels have a marked influence on HDL-C levels and are very sensitive to dietary change. Dietary influences on TG levels include high carbohydrate consumption, which, as noted earlier, can both elevate TG levels and lower HDL-C levels. Avoidance of simple sugars is particularly important, because they not only promote dental caries, but also can lead to caloric excess and obesity. The current trend toward fat-free foods has produced many food choices that are high in calories as a result of the addition of corn syrup solids or sucrose. Patients should be cautioned that such fat-free foods cannot be eaten in unlimited quantities. Although limited amounts of these foods can be part of a healthy dietary regimen, a diet that is fat-free is not necessarily nutritious.

Alcohol Intake

Alcohol consumption raises TG levels but, unlike a high-carbohydrate diet, also raises HDL-C levels. The Framingham Offspring Study's analysis of 1,584 middle-aged

men and 1,639 middle-aged women showed that TG levels, BMI, and alcohol intake all contributed significantly to fasting HDL-C and apoprotein A-I variability (160).

Mechanism

Alcohol consumption increases VLDL and TG levels by increasing VLDL synthesis (161). A metaanalysis of studies that assessed biomarkers consistently modified by alcohol showed that an experimental daily dose of 30 g of ethanol increased HDL-C by almost 4 mg per dL, apolipoprotein A-I by 8.8 mg per dL, and TGs by 5.7 mg per dL (162). Several hemostatic factors were modestly affected by alcohol intake.

Feeding Studies

Excess alcohol consumption is a common cause of secondary hyperlipidemia (163). Alcohol not only exacerbates fasting hypertriglyceridemia, but also augments postprandial lipemia. Delayed TG clearance, however, appears to occur in inactive, but not in exercise-trained, subjects, and the effect of alcohol on plasma HDL subfractions may differ between these groups (164). For individuals prone to severe hypertriglyceridemia, alcohol use must be prohibited to prevent the occurrence of the chylomicronemia syndrome, which can lead to acute pancreatitis.

Alcohol and Coronary Artery Disease

Dietary and alcohol consumption data from 21 countries indicate that alcohol consumption has a strong negative correlation with CAD mortality (68) (Fig. 2.2). Among middle-aged or older British men whose average intake of alcoholic beverages was 1 to 2 U per day, consumption of alcohol was associated with significantly lower all-cause mortality than was consumption of no alcohol or of greater amounts of alcohol (165). A genetic “proof of principle” was seen in a study of individuals with a polymorphism for the gene for alcohol dehydrogenase-3 that alters the rate of alcohol metabolism. Men homozygous for the allele, which is associated with a slow rate of oxidation, who consumed at least one drink per day had the greatest reduction in risk and the highest plasma HDL-C levels (166). This interaction was confirmed in an independent study of postmenopausal women.

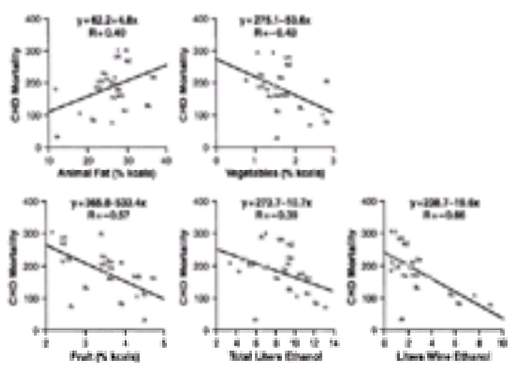


FIGURE 2.2 Graphs showing epidemiologic correlations between intake of fat, vegetables, fruit, alcohol, and wine ethanol. Au, Australia; Ca, Canada; CHD, coronary heart disease; De, Denmark; Fi, Finland; Fr, France; Ic, Iceland; Ir, Ireland; Is, Israel; It, Italy; Ja, Japan; Ne, The Netherlands; No, Norway; NZ, New Zealand; Sp, Spain; Sw, Sweden; Sz, Switzerland; UK, United Kingdom; US, United States; WG, West Germany. (From Criqui MH, Ringel BL. Does diet or alcohol explain the French paradox? *Lancet* 1994;344:1719–1723, with permission.)

In the MRFIT prospective experience among middle-aged men who were light-to-moderate drinkers, HDL-C levels largely demonstrated the inverse association between alcohol consumption and death from CAD (167). Metaanalysis of 42 experimental studies suggested that 30 g of alcohol per day would cause an estimated reduction of 24.7% in risk of CHD (162). There has been speculation that an effect of alcohol on platelet function could explain the low mortality from CAD that is seen among the population in France despite consumption of a diet that is comparable in intake of saturated fat to those of other nations in which CAD rates are higher (168). Other effects of alcohol on coagulation include a positive association between moderate alcohol intake and plasma levels of endogenous tissue-type plasminogen activator (169).

Various reports indicate that one kind of alcoholic beverage is not preferred over others. A systematic review of 12 ecologic, 3 case-control, and 10 separate prospective cohort studies indicates that *all* alcoholic drinks are linked with lower risk (170). Indeed, a study comparing red and white wine did not show that red wine selectively decreased the susceptibility of LDL to oxidation (171).

Although older men and women may benefit from the effects of mild-to-moderate alcohol intake in reducing rates of CAD, public health considerations argue against an uncritical encouragement of alcohol consumption (172). In men and women younger than 40 years, alcohol consumption has a particularly negative benefit/risk profile; the cardiovascular risk is already low, and the increase in all-cause mortality that accompanies drinking more than offsets any possible health advantage (173). Moreover, individuals who consume five or more drinks per occasion are nearly twice as likely to die from injuries than persons who drink less (174). Cardiac patients, in particular, may suffer from aggravation of hypertension, as well as increased arrhythmia, stroke risk, cardiomyopathy, and LVH, with excess drinking (175).

An important caveat pertains to alcohol intake among women. Women reporting any amount of alcohol consumption in the First National Health and Nutrition Exam Survey had an approximately 20% decrease in risk for CAD compared with women who abstain (176). A recent study that examined asymptomatic alcoholic women and men noted a similar prevalence of cardiomyopathy and myopathy in both groups (177). The threshold dose for the development of cardiomyopathy was significantly lower among women, and the decline in ejection fraction with increasing amounts of alcohol was significantly steeper than among men. These data suggest an increased sensitivity in women to the toxic effects of alcohol on cardiac muscle (Fig. 2.3).

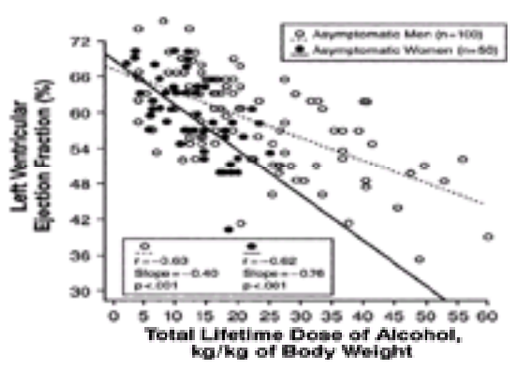


FIGURE 2.3 Lifetime dose of alcohol and left ventricular ejection fraction in men and women.

Fish Oils

The omega-3 PUFAs known as *n*-3 fatty acids can be obtained from either plant or marine sources. Alpha-linolenic acid is a plant-based omega-3 PUFA found in tofu, soybean, canola oil, and nuts. Plant-based omega-3 PUFAs do not lower TG levels in a striking fashion in contrast to the marine-based omega-3 fatty acids known as “eicosapentenoic acid” and DHA (92). The sum of these long-chain *n*-3 PUFAs in a capsule or fish product determines the amount of omega-3 PUFAs present. Fatty fish such as salmon and mackerel are good sources of *n*-3 fatty acids.

Feeding Studies

Marine lipids lower elevated TG values. This can be of particular clinical importance for individuals with TG values greater than 1,000 mg per dL for whom secondary-cause correction, diet, exercise, and gemfibrozil have proven inadequate (178). Marine lipids also have important effects on coagulation parameters. Populations who consume a diet rich in marine lipids show reduced platelet aggregation and prolonged bleeding times (179).

There are detrimental aspects to the wider use of fish oils for milder forms of hypertriglyceridemia. In one study, the beneficial decrease in TG levels was accompanied by a rise in LDL-C levels (180). In other studies, increased blood sugars were seen in diabetic patients, although this was not invariably the case (181,182). Nevertheless, in these studies, a rise in LDL-C levels that was associated with fish oil ingestion was seen. Finally, a careful analysis of the immunologic effects of fish supplementation of a Step II AHA diet demonstrated changes in delayed hypersensitivity (183). Additional studies are needed to understand the long-term consequences of these effects. Finally, there is concern about mercury contamination.

Fish Oil and Coronary Artery Disease

Studies using fish or fish oil capsules challenge the traditional diet-lipid-heart paradigm, although fish oil capsules are useful in the control of moderate to severe hypertriglyceridemia. The relationship between fish intake and lowered rates of CHD stemmed from early observational studies comparing Greenland Inuit with their Danish counterparts. The Inuit diet included a strikingly higher intake of *n*-3 PUFAs, in which marine sources, such as seal and whale, are rich. The biochemical and hematologic profiles of the Inuit showed lower values for total cholesterol, TG, LDL-C, and VLDL-C, increased values for HDL-C, increased bleeding times, and lower rates of CAD (184). In addition, prospective epidemiologic studies confirmed that men who ate at least some fish every week had a lower mortality from CAD than did men who ate none (185,186,187 and 188). In two studies, however, in which fish intake was high, a beneficial effect was not documented (189,190).

Despite these intriguing results, the results of most primary prevention studies of fish, fish oil, and CAD have been negative. The Health Professionals Follow-up Study, a large-scale prospective cohort study, reported no association between increases in consumption of fish and CAD (191). The authors concluded that increasing fish intake beyond one or two servings per week is not beneficial in the primary prevention of CAD. A nested case-control study among the 14,916 participants of the Physician's Health Study also showed no beneficial effect from consumption of fish oil on CAD (192). No association was found between fish oil levels and the incidence of MI, even when results were adjusted for major cardiovascular risk factors. Fish oil has not always produced beneficial results in trials of secondary CAD prevention. A clinical trial large enough to find a significant effect if one existed showed that 8 g per day of *n*-3 PUFA was well-tolerated, but not helpful in preventing clinical restenosis after angioplasty (193). Among normocholesterolemic men with angiographically documented CAD, fish oil treatment (6 g of *n*-3 PUFAs for 2 years) did not produce significant changes in the diameter of the coronary arteries (194).

Yet the ability of fish and fish oil capsules to reduce all-cause mortality in two intervention trials and a putative relationship between increased omega-3 fatty acid ingestion and CHD mortality in a third trial are compelling data that must be examined carefully (8,9,195). The Diet and Reinfarction Trial (DART) noted that those men who were instructed to eat fish after they had experienced MI showed a 29% decline in all-cause mortality compared with those in the placebo group (8). The mechanism for this beneficial effect was independent of lipid levels. In this trial, a group of the men (25%) who could not tolerate fish were given 875 mg of fish oil in capsule form. This study raised speculation that the beneficial effect of fish oil in survivors of MI may relate to its effects on thrombosis and/or risk for arrhythmia. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI)–Prevenzione Trial, a large-scale open-label, randomized, controlled trial involving 11,324 MI survivors, demonstrated that 875-mg fish oil capsules, but not vitamin E, reduced the primary cumulative end point of all-cause mortality, nonfatal MI, and nonfatal stroke (9). Neither intervention significantly reduced the other primary end point, the cumulative rate of cardiovascular death, nonfatal MI, and nonfatal stroke. Analysis of secondary end points suggested that the benefit lay in reduction of mortality and not in reduction of nonfatal MI. It was a safe intervention, although LDL-C levels were slightly increased as TG levels were decreased.

The Lyon Trial, which was mentioned previously in the section on Mediterranean diet, used a diet rich in a vegetable-based omega-3 fatty acid known as *alpha-linolenic acid* (107). The striking reduction in sudden death, similar to that seen in DART, suggested a beneficial effect on cardiac health from intake of omega-3 fatty acids, independent of any lipid-lowering effect. Viewed critically, the Lyon results seem almost too good to be true: When the major primary and secondary end points are combined, 59 events occurred in control subjects and 14 events occurred in study patients—a risk reduction of 76% (195). Although these data seem to overestimate the true effect of such dietary change, they do suggest that certain components of the Mediterranean-type diet, such as omega-3 fatty acids, oleic acid, and dietary antioxidants, may play important roles in reducing the risk for CAD. Moreover, a cohort questionnaire study involving 43,757 male health professionals aged 40 to 75 years and free of cardiovascular disease or diabetes reported that subjects who consumed diets high in alpha-linolenic acid had a reduced risk of CAD (196).

These provocative findings were followed by a carefully done population-based case-control study from Seattle and King County, Washington (197). Among 334 patients who had experienced primary cardiac arrest, the monthly intake of *n*-3 PUFAs was significantly less than that seen in age- and sex-matched community controls. The equivalent of one fatty-fish meal per week was associated with a 50% reduction in the risk for primary cardiac arrest after adjustment for potential confounding factors. These findings were consistent with experimental evidence suggesting that the *n*-3 PUFAs have an important effect on the vulnerability to ventricular fibrillation in the setting of myocardial ischemia (198).

Recommending consumption of one or two fish-based meals weekly is reasonable, particularly if it substitutes for sources of protein in the diet such as fatty meats, which increase total saturated fat intake. Patients should be cautioned to avoid fish contaminated with mercury and other toxins. Mercury contamination not only could prove an important hazard to susceptible persons (children, pregnant women), but has been shown to attenuate the cardiac benefits of fish (199). The use of fish oil capsules can be considered for MI survivors, based on the GISSI trial, but additional studies and standardized, widely available preparations are needed before this is a routine recommendation (200). The potential benefit of decreasing sudden cardiac death using fish oil therapy is exciting to contemplate. Additional research studies are awaited.

Antioxidants, Vitamins, and Coronary Artery Disease

The available data support the hypothesis that oxidation of LDL by cells in the arterial wall is a pivotal step in the initiation of the early lesions seen in coronary atherosclerosis (201). Thus, there has been a heightened interest in antioxidants, which may work to prevent or retard this process. Several lines of evidence support an important role for vitamin E (or alpha-tocopherol), which is carried on LDL and is a potent lipid-soluble antioxidant. There is also considerable interest in beta-carotene, which is lipid soluble, and in vitamin C, which is a water-soluble vitamin. Food sources of vitamin E include seed oils, nuts, avocados, whole-grain and fortified cereals, eggs, and green vegetables. Food sources of beta-carotene include carrots and boiled broccoli. Vitamin C is widely available in fruits and vegetables, but losses of vitamin C can occur with cooking.

Mechanism

Two putative mechanisms are involved in the effect of antioxidants on reduction of oxidative stress and improvement of endothelial dysfunction. When added to plasma, vitamin E, but not vitamin C or beta-carotene, seems to make LDL more resistant to oxidation (202). Moreover, in one study, 2.0 g of ascorbic acid improved brachial artery endothelial-dependent response to ischemia in 46 patients 2 h after ingestion (203).

Vitamin E and Coronary Artery Disease

The effects of vitamin E on atherosclerosis and clinical CAD are controversial and do not support enthusiastic recommendation of the vitamin. To be sure, early observational studies suggested a beneficial effect of vitamin E (204,205 and 206). Furthermore, a prospective study of postmenopausal women from Iowa showed that the intake of vitamin E from foods is inversely associated with the risk by death from CAD. Importantly, the data suggested that such women might lower their risk without using vitamin supplements (207). These were not randomized clinical trials, and unforeseen bias may have influenced the results.

The Cambridge Heart Antioxidant Study used a randomized, double-blind design in 2,002 patients with angiographic CAD who were assigned to receive 400 IU of alpha-tocopherol daily or placebo. Nonfatal MI decreased significantly at 1 year among subjects who took vitamin E (208). One feature of the study that is worthy of concern was the lack of a significant reduction in either total mortality or cardiovascular deaths in the alpha-tocopherol group. In fact, a slight, nonsignificant increase was seen in these categories in the treatment group. Since publication of the results of this trial, two large randomized trials have shown no benefit from vitamin E on primary end points. In the previously mentioned GISSI trial, vitamin E did not affect either of the two primary combined end points. Although benefit was suggested in a secondary analysis that examined cardiovascular death, the authors speculated that a longer trial would be required to show beneficial effects from vitamin E on cardiovascular end points. The Heart Outcomes Prevention Evaluation Study found no significant effect associated with daily ingestion of 400 U of vitamin E on cardiovascular end points in 9,541 high-risk subjects older than 55 years who were randomly assigned to receive vitamin E or placebo and followed for 4.5 years (209). Moreover, a substudy of this trial showed no differences in atherosclerosis progression rates, as determined by carotid ultrasound, associated with ingestion of vitamin E, whereas a beneficial effect was seen with the angiotensin-converting enzyme inhibitor ramipril (210). Because strong evidence for effects associated with vitamin E on subclinical atherosclerosis as well as clinical rates of CHD is lacking, a routine recommendation for its use is not reasonable at this time.

Vitamin C and Coronary Artery Disease

A large prospective observation of 19,496 men and women in a nine-country study showed that plasma ascorbic acid levels were inversely related to mortality from all causes, from cardiovascular disease, and from ischemic heart disease (211). The authors speculated on the potential benefits of a small increase in intake of fruits and vegetables. The Atherosclerosis Risk in Communities Study examined the relationship between the intake of dietary and supplemental vitamin C, alpha-tocopherol, and provitamin A carotenoids and average carotid artery–wall thickness among 6,318 women and 4,989 men aged 45 to 64 years (212). Among men and women older than 55 years, but not among individuals younger than 55 years, who had not recently begun a special diet, there was a significant inverse relationship between vitamin C intake and average carotid artery wall thickness, adjusted for pertinent variables. In Kuopio, in Eastern Finland, men and postmenopausal women in a double-masked, two-by-two factorial trial were randomly assigned to four strata and received either 136 IU daily of D-alpha-tocopherol, 250 mg of slow-release vitamin C, a combination of these, or placebo for 3 years. Progression of common carotid atherosclerosis was decreased significantly among men who received a combination of D-alpha-tocopherol and slow-release vitamin C (213).

Beta-Carotene and Coronary Artery Disease

The European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer was a controlled study that looked at adipose tissue levels of beta-carotene and alpha-tocopherol in individuals with a history of MI (214). The data suggested that consumption of foods rich in beta-carotene, such as carrots and green leafy vegetables, might reduce the risk for MI.

In contrast, three carefully done trials using beta-carotene supplementation did not show beneficial effects on cancer or cardiovascular disease (215,216 and 217). Moreover, the Beta Carotene and Retinol Efficacy Trial showed that the combination of beta-carotene and vitamin A may have led to an adverse effect on lung cancer and the risk of death from lung cancer, from cardiovascular disease, and from all causes in both cigarette smokers and workers exposed to asbestos. Thus, the time and expense necessary to obtain clinical trial data to document or refute contentions derived from observational data was clearly worth it. There is no good evidence to support the endorsement of beta-carotene supplementation to reduce cardiovascular disease end points.

Flavonoids

Flavonoids are strong antioxidants that occur naturally in foods such as vegetables (onions) and fruits (apples) and in beverages such as tea and wine. On a milligram per day basis, the intake of antioxidant flavonoids still exceeds that of the antioxidants beta-carotene and vitamin E (218). Thus, flavonoids represent a potentially important source of dietary antioxidants.

Flavonoids and Coronary Artery Disease

In the Zutphen Elderly Study, flavonoid intake was measured in 805 men aged 65 to 84 years who were then followed for 5 years (219). Flavonoid intake was significantly inversely associated with mortality from CAD, and an inverse association was seen with MI that was of borderline significance (219). In a larger sample from the Seven Countries Study, flavonoid intake contributed only slightly to reduction in CAD risk (approximately 8%), whereas saturated fat contributed the major dietary risk (approximately 73%) (220).

Minerals and Coronary Artery Disease

Minerals such as iron and selenium have been implicated in heart disease.

Iron

Menstrual loss of iron has been proposed as an explanation for the reduced risk for CAD among women (221). Menstrual loss of iron may reduce oxidative stress on LDL and hence lower rates of atherosclerosis. A review of the literature noted that 18 of 25 epidemiologic studies showed either a negative association or no association between CAD and indicators of body iron (222). In a 4-year prospective study that collected data from diet questionnaires completed by 44,933 men aged 40 to 75 years who had no history of cardiovascular disease, iron intake in the form of non-*heme* iron was not related to the incidence of CAD (223). However, incidence of fatal CAD or nonfatal MI was higher among men in the top quintile of *heme* iron intake compared with men in the lowest quintile, despite adjustment for dietary cholesterol and fats. That iron intake is associated with CAD appears to be a testable hypothesis, but more data from various population groups will be required before firm conclusions can be reached (224).

Selenium

Selenium is an essential trace element. It is a cofactor of the enzyme glutathione peroxidase. Deficiency of selenium has been associated with a cardiomyopathy described in China called “Keshan disease” (225). Data relating it to risk for CAD are scanty, and more detailed studies are required before recommendations can be made.

OBESITY, LIPIDS, CORONARY ARTERY DISEASE, AND CARDIOVASCULAR DISEASE

The terminology of the obesity literature can be confusing. Terms useful to the following discussion are summarized in *e*Table 2.3.3. Bray has proposed a classification of obesity that avoids misleading descriptors such as “progressive” or “morbid” (226). Using the BMI, obesity can be classified from Class 1 to Class 4, at the extreme. This system is summarized in *e*Table 2.3.4.

***e*TABLE 2.3.3** TERMS ASSOCIATED WITH OBESITY AND EXAMPLES

Term	Definition
Obesity	BMI ³30
Overweight	BMI 25–30
BMI	Weight (kg) divided by height^2 (m)
Increased waist circumference	>102 cm (>40 in.) for men; >88 cm (>35 in. for women)
Abdominal obesity	Male pattern or android obesity; metabolically active abdominal fat; increases risk of coronary artery disease
Gluteal-femoral obesity	Female pattern or gynecoid obesity; fat concentrated in hips and thighs; cosmetic problem
Morbid obesity or class IV obesity	BMI ³40

Body mass index (BMI) is calculated in kg/m^2 or 703 ¥ lb/in.^{2}

***e*TABLE 2.3.4** CLINICAL CLASSIFICATION OF OBESITY

Class of obesity	Body mass index (kg/m^2)	Mortality and coronary heart disease risk class
0	20–25	Not obese
1	25–30	Mild risk
2	30–35	Moderate risk
3	35–40	High risk
4	³40	Very high risk

From Bray G. Pathophysiology of obesity. *Am J Clin Nutr* 1992;55[Suppl]:488S–494S, with permission.

According to recent data, 50% of all adult Americans are overweight or obese (227). This reflects an increasing prevalence over the course of the past decade. This finding is worrisome, because obesity, over the long term, increases the risk for death (228,229,230 and 231). In addition, obesity contributes to at least one-half of the diseases that are chronic in Western societies (232). Although abdominal obesity is cause for particular concern, noncentral obesity is not metabolically benign. A cross-sectional study in Manitoba showed that, in its survey of adults aged 18 to 74 years, the BMI as an overall measure of obesity compared favorably with waist-to-hip ratio in predicting effects of obesity on blood pressure, glucose, and plasma lipids (233).

A review published in 1993 of 13 reports from 11 diverse populations looked at weight changes in subjects aged 17 years or older (234). It concluded that the highest mortality rates occur in adults who either have lost weight or have gained excessive weight. Andres (235) believed that data suggesting that the lowest mortality rates in these studies accompanied modest weight gains in adulthood supported his previously held views. This was disputed by a detailed analysis of U.S. women enrolled in the Nurses' Health Study (236) (eTable 2.3.5). The data showed that body weight and all-cause mortality were directly related. Lean women did not show excess mortality, and a weight increase ³10 kg after the age of 18 was associated with increased mortality in middle adulthood. When the BMI exceeded 27, mortality was substantially elevated. In terms of attributable risk, 53% of deaths among women with a BMI greater than 29 could be attributed to their obesity. Mortality from CAD in this study was more strongly related to waist-hip ratio, which is a measure of abdominal obesity.

***e*TABLE 2.3.5** EFFECT OF WEIGHT CHANGE ON RISK OF DEATH AND CORONARY HEART DISEASE (CHD): NURSES' HEALTH STUDY DATA

Weight change	No. of deaths	Relative risk for all causes	Relative risk for CHD
Lost >10 kg	16	0.7	0.3
Lost 4–9 kg	54	1.2	0.6
Stable	224	1.0	1.0
Gained 4–9 kg	269	1.0	0.7
Gained 10–19 kg	292	1.2 (1.0–1.4)	2.6 (0.7–12.8)
Gained >20 kg	204	1.6 (1.3–1.9)	7.4 (2.4–21.7)

From Pouliot MC, Despres J-P, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;73:460–468, with permission.

The Nurses' Health Study data should be compared with observations from the Honolulu Heart Program, in which men who had a weight loss of 4.5 kg or more, large fluctuations in weight, or both over the course of a 6-year period were in poorer health than those whose weight was more stable (237). Like the Nurses' Health Study, an increase in mortality occurred primarily among subjects with a BMI greater than 27. Subjects whose weight fluctuated the most had a significantly higher risk for death from cardiovascular causes. This relationship was not seen in healthy men who had not smoked. In fact, one of the problems with analyzing "weight cycling" is the inability to distinguish between intentional and unintentional weight loss. Stunkard (238) noted that evidence that weight cycling is a cause of either upper-body obesity with metabolic changes or increased mortality is lacking.

In a prospective cohort study of Dutch men and women aged 30 to 54 years, with an average follow-up of 12 years, all-cause mortality was increased among obese men (BMI greater than 30) and among underweight men, but not among women (239). The Framingham Heart Study looked at the relationship of weight at age 65 among 1,723 nonsmokers who were followed for a mean of 9.5 years (240). The study found that the risk of death was increased twofold over the course of the entire follow-up period for persons with a BMI higher than the 70th percentile at both 55 and 65 years of age. This works out to a BMI greater than or equal to 28.5 that is attained by a 5-ft 9-in. man who weighs at least 193 lb.

Mechanism

To be sure, obesity and the response to overfeeding have a definite genetic component (241). A detailed discussion of the genetic component is beyond the scope of this section. Instead, we focus on environmental influences in susceptible subjects. The impact of the environment on the prevalences of obesity and non–insulin-dependent diabetes (NIDDM) was dramatically illustrated by a comparative study of Pimas in Arizona with their distant relatives living in a remote mountainous location in northwestern Mexico (242,243). Arizona Pimas eat a higher-fat diet and have a higher prevalence of diabetes than do their Mexican relatives, who are lighter, shorter, more active, and expend more energy. The increases in obesity, cholesterol, and glucose intolerance seem directly related to environmental factors. This suggests that the high rate of obesity among Arizona Pimas may be due to genetic susceptibility promoted by an unhealthy lifestyle.

Physiologic changes related to gender and aging must be considered as well. A study of 427 healthy men aged 17 to 90 years and women aged 18 to 88 years showed that fat mass increased with age, and that the rate of increase was higher among women (244). The increase in waist circumference with age was also greater among women. Increasing waist circumference with age among men and women was most strongly associated with declines in leisure-time physical activity and in peak volume of oxygen utilization.

Obesity is also associated with a multiplicity of risk factors for CAD. Although it is often incorrectly assumed that obese patients uniformly have hypercholesterolemia, Grundy and Barnett (245) observed that significant hyperlipidemia in obesity was usually associated with an underlying defect in lipid metabolism. Because obesity and excess calories lead to an overproduction of VLDL, dyslipidemia is seen among individuals who have defects in the clearance of TG (impaired lipolysis) or cholesterol (deficient LDL receptors). Thus, it is possible for a Class 4 obese patient who is 40% overweight to have a normal LDL-C level (246).

Nonetheless, a major health hazard of obesity is a result of the metabolic changes that accompany the deposition of abdominal or visceral fat. Despres and coworkers have stressed the need to focus on high-risk abdominally obese patients (247). Their group has proposed that the waist circumference or the abdominal sagittal diameter, rather than the waist-to-hip ratio, be used as an index of abdominal visceral adipose-tissue deposition in the assessment of risk for CAD (248). Bouchard and colleagues (249) noted that waist circumference values greater than approximately 100 cm, or abdominal sagittal diameters greater than 25 cm, are most likely to be associated with potentially atherogenic metabolic disturbances. The crucial distinction, however, is that for a given level of body mass, subjects with anthropomorphic measures of visceral obesity such as waist-to-hip ratio or the more precise waist circumference represent the subgroup of individuals at highest risk for CAD (250). This is likely conferred through multiple risk factors, including dyslipidemia, hypertension, and glucose intolerance. Walton and associates (251) measured lipid and lipoprotein levels in 103 healthy men aged 21 to 77 years who underwent dual energy x-ray absorptiometry to determine the ratio between total body fat tissue and total body lean tissue. Both adiposity and fat distribution correlated with total serum cholesterol and TG concentrations. Fat distribution negatively correlated with HDL2 cholesterol. On multivariate analysis, waist-to-hip ratio was independently associated with elevated total TG and decreased HDL2 levels.

The association of dyslipidemia, hypertension, and glucose intolerance with visceral adiposity and insulin resistance is a recognizable multiple metabolic risk factor syndrome, or simply, "the metabolic syndrome" (4). This was initially designated "syndrome X" by Reaven (252). Data from the Bogalusa Heart Study show that clustering of risk factors for CAD begins in children and young adults and persists throughout life (253). The lipid abnormalities seem to fit best with a constellation of findings called "atherogenic dyslipidemia." Grundy (254) has characterized the typical picture as borderline total cholesterol, high TG, low HDL-C, and increased small, dense LDL-C particles. The second component is insulin resistance, both with and without impaired glucose tolerance (255). The insulin-resistance syndromes were recently reviewed, and several points are worth emphasizing (256). Genetic predisposition, sedentary lifestyle, and central obesity are viewed as determinants, with insulin resistance being the measurable abnormality that leads to metabolic dysregulation with a compensatory hyperinsulinemia, dyslipidemia, hypertension, glucose intolerance, and hyperuricemia. Also seen are abnormalities of coagulation with increased plasminogen activator inhibitor type 1 and decreased tissue plasminogen activator accompanying hypertriglyceridemia.

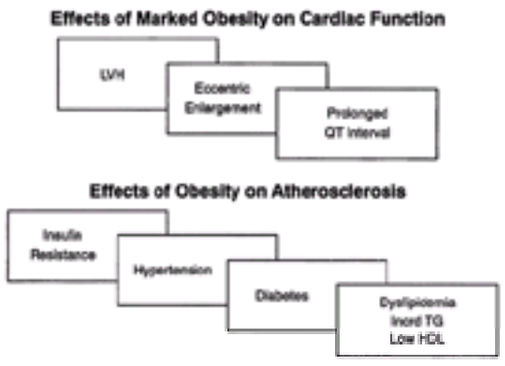
Williams and colleagues (257) have described a subset of hypertension associated with metabolic abnormalities involving lipids, insulin, and often obesity, all of which aggregate strongly in families. They called this "familial dyslipidemic hypertension" and noted an association with a particularly high risk for early coronary disease. They observed that the clinical and biochemical features of familial dyslipidemic hypertension shared similarities with Reaven's Syndrome X: (a) familial combined hyperlipidemia, (b) dense LDL subfractions, (c) diabetes, (d) impaired glucose tolerance, (e) central and general obesity, (f) prediabetes, (g) prehypertension, and (h) genetic deficiency of lipoprotein lipase (heterozygous). Interestingly, women who had microvascular angina (the cardiology syndrome X, with chest pain and an abnormal exercise electrocardiogram despite normal appearance of vessels on coronary angiography) tend to be insulin resistant and have lower HDL-C levels, although not all of the other features of the metabolic syndrome X previously described are seen (258).

The presence of multiple metabolic risk factors, such as raised fasting insulin levels, apolipoprotein B concentration, and an increased proportion of small, dense LDL particles are associated with a 20-fold increase in the risk of developing CHD in initially asymptomatic middle-aged men who were followed for 5 years (259). This underscores the need for more-effective prevention of adult-onset weight gain. Although drug therapy for these risk factors is usually required, the additive beneficial effects of weight loss, regular exercise, and diet should be recognized.

Obesity and the Heart

Cardiac output and blood volume increase in obesity to supply the increased adipose stores (eFig. 2.3.1). Systolic function is generally preserved, even in patients with marked obesity. Nonetheless, in a small subgroup who had low left ventricular fractional shortening before surgical therapy for morbid obesity, the mean fractional shortening increased significantly when body weight decreased from 13 to 79 kg of the amount over ideal body weight. Blood pressure and left ventricular internal dimension in diastole also decreased (260). Obesity affects diastolic function and is a strong stimulus for LVH. Messerli (261) noted, among subjects matched for blood pressure values, that LVH was found in more than 50% of all obese subjects and only in less than 20% of nonobese subjects. When heart size is examined, eccentric enlargement is seen in obese patients with hypertension, compared with symmetric LVH in hypertensive patients who were not obese. In addition to magnitude of obesity, the duration of obesity must also be taken into account (262). In the Framingham Heart Study, BMI was strongly associated with echocardiographic LVH,

particularly when the BMI was greater than 30 kg per m^2 (263). Finally, obesity leads to a prolonged QT interval, which may increase the potential for arrhythmias (264).



***e*FIGURE 2.3.1** Obesity and the heart. HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; TG, triglycerides.

For the Class 4 obese patient, the situation is especially grim. Cardiovascular disease is the most frequent cause of death (265). Life-table techniques that compare the mortality among Class 4 obese individuals with that among men in the general population demonstrated a 12-fold excess mortality among obese patients aged 25 to 34 years, and a sixfold excess among those aged 35 to 44 years. This ratio diminished with advancing age. Postmortem examination of 12 Class 4 obese patients aged 12 to 59 years disclosed dilated left ventricular and right ventricular cavities, but only two patients had one or more epicardial coronary arteries that had narrowed at least 75% in cross-sectional diameter (266). Kasper and colleagues (267) looked at patients greater than 35% overweight who presented with congestive heart failure and compared them with patients whose weight was normal. A significantly higher percentage of the obese patients had a dilated cardiomyopathy. Among patients with similar degrees of cardiomyopathy, obese patients had elevated right-heart pressures, cardiac outputs, and pulmonary vascular resistance index. On biopsy, the most common finding in the obese group was mild myocyte hypertrophy.

Importantly, the cardiac dysfunction associated with obesity may occur with weight loss (268). Cardiac studies were repeated in 12 Class 4 obese patients after a 54.8 ± 1.9-kg weight loss. Echocardiography documented a decrease in dilatation (27.3% to 9.1%) and a significant decrease in hypertrophy. After the weight loss, radionuclide and right-heart catheterization studies demonstrated improved cardiac function with reduced filling pressures and increased left ventricular work during fluid and exercise challenges. In addition, the prolonged QT interval seen in obese patients may shorten after weight reduction (269).

The Class 4 obese patient may present with significant noncardiovascular problems as well. The Pickwickian syndrome, involving sleep apnea, pituitary/gonadal dysfunction, acanthosis nigricans, and pronounced osteoarthritis, is well described (226). Weight loss achieved by consumption of a very-low-calorie diet improves lung volumes in morbidly obese patients but may not be enough to improve arterial oxygenation (270). In one study, hypoxemia was not relieved in patients who assumed a supine position but was significantly relieved when patients stood up, both before and after weight loss. Comorbidity seen with significant obesity includes respiratory disease, gout, osteoarthritis, and gallbladder disease (271). The presence of obesity more than doubles the risk for gallstones, because it increases the flux of cholesterol through the biliary tree. In fact, after 8 weeks of dieting, sludge was detected in three subjects and gallstones in 25.5% of subjects, compared with nonfasting control subjects (272). Depression commonly accompanies significant obesity. Individuals more likely to show symptoms of emotional illness include patients with a history of obesity from childhood, those undergoing severe caloric restriction, and those undergoing outpatient treatment (273).

Treatment of Obesity

The Obesity Education Initiative from the National Heart, Lung, and Blood Institute noted that obesity-related conditions are significantly improved with a weight loss of only 5% to 10% (274). Yet successful weight loss is not easy to achieve. A survey of 192 participants in the Sandoz Nutrition Diet Program showed that, on average, the group lost 22 kg during the diet program (275). After 3 years of follow-up, the mean weight was within 3.3 kg of initial weight at the start of the diet. Only 12% of the subjects maintained 75% of the weight loss after leaving the diet program; 57% maintained at least 5% of the loss; and 40% gained back more weight than they lost while on the diet. The best predictor of recidivism was television viewing, whereas frequency of exercise was the strongest predictor of weight loss maintenance. The long-term results of behavioral treatment are also discouraging. Resumption of the obese state occurs, and only less than 5% of subjects remain lean for more than 4 years (276).

What about popular diets? A scientific review prepared for the U.S. Department of Agriculture divided these diets into three categories:

1. High-fat (55% to 65%), low-carbohydrate, high-protein diets
2. Moderate-fat (20% to 30%) diets, high in carbohydrates and moderate in protein
3. Low-fat (11% to 19%) and very-low-fat (<10%) diets; very-high-carbohydrate, moderate-protein diets

This report concluded that caloric balance is the major determinant of weight loss, and that any of the diets that result in reduced caloric intake will result in weight loss. In the absence of physical activity, it was estimated that an optimal diet would contain approximately 1,400 to 1,500 kcal per day. It was further noted that all low-calorie diets result in loss of body weight and body fat. Macronutrient composition did not appear to play a major role. On the other hand, low-carbohydrate, ketogenic diets cause a greater loss of body water than body fat. Moreover, although the moderate-fat diet is nutritionally adequate, high-fat, low-carbohydrate diets are nutritionally inadequate and require supplementation, and very-low-fat diets are deficient in vitamins E and B_{12}, and zinc. Despite various claims, there does not appear to be an optimal diet for reducing hunger. Long-term compliance is likely a function of psychological issues rather than macronutrient composition.

Emphasizing the basic strategies mentioned in this chapter was shown to be particularly effective in a study of 522 overweight subjects with impaired glucose tolerance who were randomly assigned to receive either frequent individualized dietary and exercise counseling or occasional general recommendations over the course of an approximately 3-year period (277). Individualized counseling was aimed at reducing weight by 5% or more, reducing total fat intake to less than 30% of energy intake, reducing saturated fat intake to less than 10% of energy intake, increasing fiber intake to greater than 15 g per 1,000 kcal, and increasing regular exercise to more than 4 h per week. This resulted in a reduction in new diabetic cases of 58% in comparison with the rate among control subjects.

The very-low-calorie diet promised a more intensive approach to weight loss, but the early experience with very-low-calorie diets was problematic; at least 58 deaths were reported among very obese patients who underwent rapid weight loss by consuming diets low in protein of good biologic value (278). Current very-low-calorie diets provide 400 to 800 kcal per day of energy and 45 to 100 g per day of high-quality protein and are associated with only minor complications when administered in selective fashion by physicians trained in their use (279). These diets should be limited to use in patients who are at least 30% overweight. The appropriate duration for most patients is approximately 12 to 16 weeks. Careful monitoring with attention to electrolytes during the treatment, refeeding, and weight maintenance periods is important. These diets may prove to be valuable for patients who have serious respiratory abnormalities or NIDDM. Nonetheless, the recidivism rate is still high, as it is for all dietary strategies that are used in obese patients, prompting concern that the long-term benefits may not outweigh the risks.

Why does diet therapy for obesity fail over the long term? Hirsch and colleagues (280), in elegant experiments, showed that maintenance of either a reduced or increased body weight is associated with compensatory changes in energy expenditure that oppose the maintenance of a body weight that is different from the usual weight. This seems to explain the results of a study in which obese and nonobese subjects were followed for 5 years; in 19% of the subjects, weight varied no more than 5 lb higher or lower during that 5-year period (281). This group included three times as many normal-weight subjects as obese subjects. Eckel (282) suggested that metabolic reasons for patients' return to original weight include maintenance of raised concentrations of fasting adipose tissue lipoprotein lipase, the enhanced responsiveness of adipose tissue lipase to insulin, and failure of corn-oil ingestion to inhibit the insulin-stimulated adipose tissue lipoprotein lipase–response, all of which support accelerated uptake and storage of lipid fuels.

Interventions that focus on health behaviors have the advantage of emphasizing the positive aspect of voluntary actions. Wing (283) noted that behavioral approaches to obesity are usually used in the context of short-term (10 to 20 week) treatment interventions. These programs produce weight losses averaging 10 kg at the end of the program and 6.6 kg at 1-year follow-up. These have proven useful in NIDDM; at 1 year, patients who lost more than 6.9 kg or had a greater than 5% reduction in body weight had significant improvements in glycosylated hemoglobin values (284). Kayman and colleagues (285) studied obese women who regained weight after successful weight reduction. Most subjects who maintained the weight loss exercised regularly, used available social support, and confronted problems directly, whereas most subjects who relapsed did not. The authors noted that subjects who maintained weight loss were more likely to use personally developed strategies to help themselves. When obese children aged 8 to 12 years were randomly assigned to treatment groups that targeted increased exercise, decreased sedentary behavior, or both, the greater decrease in percentage of overweight was seen in the group that targeted sedentary behavior (286). However, reported estimates of diet

and activity may overestimate exercise and underestimate caloric intake (287), which is a real problem in interpretation.

There are many benefits to regular exercise for the obese patient. Lifestyle changes that increase the level of physical activity may be advantageous in blunting age-related increases in total-and central-body fatness. Bouchard and associates (288) carefully studied young men who developed negative energy balance through exercise and a maintained energy intake. They showed clearly that it is quite possible to lose fat while preserving fat-free mass through regular, prolonged exercise of moderate intensity, when energy intake is kept constant at a baseline level. They underscored the importance of individual differences in response to negative energy balance. Foreyt and colleagues (289) undertook a prospective 4-year natural history study that examined psychological correlates of physical activity. They noted that individuals who reported participating in physical activity had a better psychological profile at 1 and 5 years, with improvements in eating self-efficacy and well-being. When diet and exercise are combined, the results are encouraging. Tremblay and colleagues (290) noted in four obese women who had been previously trained in exercise that addition of a low-fat diet could normalize the glucose/insulin profile of obese women, even if their adiposity remains higher than that of lean women. It seems prudent that every physician should encourage patients to engage in 30 minutes or more of moderate-intensity physical activity on most, and preferably all, days of the week (291).

For much of the 1990s, appetite suppressant drugs that acted via a serotonergic mechanism were prescribed for weight control (292). The association by Mayo investigators of unusual valvular morphology and regurgitation after approximately 12 months of fenfluramine and phentermine therapy led physicians to reconsider the pharmacologic approach to obesity (293). In that investigation, five patients who went to surgery had valvular abnormalities reminiscent of those associated with the carcinoid syndrome. Devereaux (294) summarized well the lessons learned from the careful studies that were done to determine the severity and extent of the problem. First, he noted that the investigations validated the decision of the U.S. Food and Drug Administration to pull these appetite suppressants from the market. Second, he noted that clinically overt valvular disease after the use of appetite suppressants for 3 or fewer months was low after 4 years of follow-up. He concluded that clinically important valvular disease would probably not develop after short-term exposure to these drugs. Third, the converse appears to be true. Exposure to a high dose or a long duration of use makes valvular abnormalities more likely. He suggested that patients who have taken these drugs be followed carefully, that those with clinical or echocardiographic evidence for valvular heart disease be given endocarditis prophylaxis instructions, and that caution should be urged before other appetite suppressant drugs that act via serotonergic mechanisms are used. Further investigation has established that activation of 5-HT_{2B} receptors is necessary to produce these valvular lesions, and that serotonergic medications that do not activate 5-HT_{2B} receptors are unlikely to create the difficulties seen with the offending drugs. It has been suggested that all clinically available medications with serotonergic activity and their active metabolites be screened for agonist activity at 5-HT_{2B} receptors, so that clinicians can consider suspending their usage if necessary (295). Of historical note, before the discovery of valvular abnormalities associated with use of these drugs, there was a historical concern relating to primary pulmonary hypertension and certain appetite-suppressant drugs (296).

Currently, the two major drugs available to clinicians for patients who require assistance with weight loss are sibutramine and orlistat. It is instructive to compare the results of 1-year clinical trials with each drug. Sibutramine is a norepinephrine-serotonin reuptake inhibitor and is approved for long-term use. To determine efficacy and safety in obese patients with drug-controlled hypertension, both white and black subjects between 27 and 40 years old were randomly assigned to receive sibutramine (n = 150) or placebo (n = 74) with minimal behavioral intervention for 52 weeks (297). Among subjects receiving sibutramine, 13.4% lost 10% or more of their body weight, compared with 4.3% of subjects in the placebo group (p <.05). The benefits of sibutramine-induced weight loss included reduced waist circumference and improvement in quality-of-life measures, as well as significant improvements in TG, HDL-C, glucose, and uric acid levels. Subjects treated with sibutramine had small but statistically significant mean increases (similar among blacks and whites) in diastolic blood pressure (2.0 mm Hg) and pulse rate (4.9 beats/min) compared with placebo-treated patients (–1.3 mm Hg and 0.0 beats/min). The most common adverse event resulting in discontinuation among subjects receiving sibutramine was hypertension (which occurred in 5.3% of patients receiving sibutramine, vs. 1.4% of patients receiving placebo).

Orlistat inhibits pancreatic lipase and can block 30% of the triacylglycerol hydrolysis in subjects consuming a 30% fat diet. This unique mechanism of action appears to teach patients how to reduce their intake of fat due to fecal leakage of unabsorbed fat if they exceed the 30% limitation on fat calories. In a five-center study in the United Kingdom, 228 obese adult subjects were randomly assigned to receive orlistat, 120 mg three times daily, versus placebo after run-in diet of 30% fat designed to produce an energy deficit of 600 kcal per day (298). After 1 year of treatment, 28% of the orlistat group lost at least 10% of body weight, compared with 17% of the placebo group (p = .04). Orlistat-treated subjects had significant decreases in LDL-C levels and in the ratio of LDL-C to HDL-C. More gastrointestinal events occurred in the orlistat group, but these were mild and transient. After 1 year, the decrease in vitamin E and beta-carotene levels was significantly greater in orlistat-treated patients than in the placebo group, and fat-soluble vitamins were given to supplement the diet of subjects in the orlistat group. In summary, both sibutramine and orlistat can produce and maintain weight loss over the course of a 12-month period that is greater than that obtained with placebo.

Surgery for obesity is becoming increasingly common in the United States, with the number of operations growing to approximately 40,000 in the year 2000 (299). This is results of the recognition that, if left untreated, patients who are the most obese (BMI greater than 40) have only a 1 in 7 chance of reaching their normal life expectancy and of increased acceptability of current surgical techniques (300). One current surgery involves the gastric bypass, in which a partition is created across the upper stomach by using surgical staples. Another way to limit food intake is to place a constricting ring around the fundus of the stomach, a procedure known as “gastric banding.” Approximately 80% of the patients who undergo these surgeries are women. The complications of gastric bypass are much less severe than those of the older jejunoileal intestinal bypass procedure, which is no longer performed due to the high morbidity and mortality associated with it. Laparoscopic techniques hold the promise of reducing the morbidity seen with these procedures but require special training and should be performed by practitioners who are experienced in this technique.

The selection criteria for obesity surgery include a BMI greater than 40 or of 35 to 40 in a patient with serious comorbidity that is treatable by weight loss (301). Other criteria are a minimum of 5 years’ duration of obesity, a history of conservative treatment that failed, no history of alcohol misuse or major psychiatric illness, and age between 18 and 55, with an acceptable operative risk. Women are asked to avoid becoming pregnant within 2 years of the operation. The surgery must be performed in a multidisciplinary environment with a team that includes dietitians or specialist nurses, physicians, anesthesiologists, radiologists, and psychologists experienced with the special problems that are seen in these patients.

CONCLUSIONS

What diet can cardiologists recommend at present? For those with coronary disease or who are greatly at risk for coronary disease, a healthy AHA diet is inadequate. A therapeutic diet that is nutritionally adequate and contains from 25% to 35% of calories as fat is recommended, but less than 7% of calories should come from saturated fat and intake of dietary cholesterol should be less than 200 mg per day. There should be at least five servings of fruits and vegetables daily, along with nonfat dairy products and salt restriction, if the patient is hypertensive. Whether the patient prefers an Asian regimen with more-complex carbohydrates or a Mediterranean-type regimen with more olive or canola oil is best decided on a case-by-case basis. Two servings of fatty fish per week should be recommended. For individuals who have experienced MI and cannot eat fish, consideration should be given to use of approximately 875 mg of omega-3 fatty acids as a fish oil capsule. Sugar calories are “empty” calories and should be eliminated from the diet. Because weight reduction is given high priority in the overweight heart patient, calories in excess of energy expenditure must be discouraged. An alcoholic drink with dinner is not prohibited, and moderate alcohol consumption may prove to be salutary. Nonetheless, as noted earlier, the negative effects seen in individuals who cannot limit alcohol consumption and in special circumstances (e.g., pregnancy) should make physicians wary about casual, global endorsement of alcoholic drinking to improve risk for CAD.

Although some patients may do well with highly restricted low-fat diets (as recommended by Ornish and Pritikin), there are no available data to show that this is the preferred nutritional choice for the patient with CAD. Nonetheless, these programs have taught us the value of a real commitment to a low-fat diet. As is seen even with drug therapy, individuals who adhere most consistently to a therapeutic regimen often get the best results (10). A possible danger of advising a very-low-fat regimen to patients who do not receive adequate instruction is the adoption of a dietary regimen that is too low in protein and too high in carbohydrates. If detailed individualized instruction is provided and there is a comprehensive approach to lifestyle changes, the dietary and lifestyle changes achieved can be impressive in the short term (302). Certainly, when noninvasive testing such as PET can monitor the efficacy of these regimens, the potential for improvement in coronary status can motivate patients considerably (301,303). Most often, surrogates such as improved risk factors (and possibly markers of subclinical disease) should provide the reassurance that patients often require to continue with these regimens. In addition, we need further studies of the Mediterranean-type diet used in the Lyon Trial (107). We need to understand whether the crucial intervention was the increase in omega-3 fatty acids, MUFAs, or both together with the low–saturated fat, low-cholesterol, low-fiber regimen that produced the striking results.

The growing weight of evidence suggests that lifestyle changes should be recommended to the coronary patient that encourage the avoidance of excess calories and promote regular exercise to reduce the likelihood of excessive weight gain. These are crucial supplements to dietary advice. Also helpful would be the presence of a registered dietitian to help the patient learn how to deal with external cues from the environment and to develop important skills such as label reading, wise restaurant menu selections, and recipe modification. This cannot be emphasized enough; individualized recommendations for lifestyle change and feedback are crucial to obtaining good results. Many excellent books on eating a healthier diet are available. Sources such as the AHA; the National Heart, Lung, and Blood Institute; and the American Dietetic Association should be consulted (by phone or through the Internet) to obtain help.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Several major controversies need to be resolved. The first is whether we should adopt the Mediterranean diet pyramid (*e*Fig. 2.1.2) instead of our current pyramid for primary prevention of CAD. As noted in this chapter, there are aspects of the Mediterranean-type diet that are particularly helpful for certain patients. However,

although the potential cardioprotective effects associated with a diet supplemented with omega-3 fatty acids and oleic acid are exciting to contemplate, their efficacy needs to be explored with more data from clinical trials.

Many physicians are under the false impression that basic nutrition principles do not work in clinical practice. Well-meaning but poorly reinforced suggestions about diet are certainly likely to fail. As noted in earlier sections of this chapter, failure is much less likely when individualized counseling and follow-up are provided. Results can occasionally be dramatic. In a recent small study involving healthy, motivated individuals that was designed to determine whether use of the Dietary Guidelines for Americans and the Food Guide Pyramid, combined with exercise training, could result in significant reductions in cardiovascular risk compared with a regimen of exercise therapy alone, subjects randomly assigned to the diet and exercise group fared better than those assigned to exercise alone (302). In the half of the group that received individualized dietary counseling using the Food Guide Pyramid as a primary educational tool, the percentage of energy intake from fat decreased from 39% to 23% (*e*Fig. 2.1.3). This was associated with significant reductions in BMI, total cholesterol levels, and LDL-C levels, whereas no change was observed in the group who used exercise alone.

Another controversial aspect of medical nutritional therapy is whether patients with CAD require a very-low-fat diet. Again, the data supporting this approach are inadequate at present because of the highly selected nature of the patients who have been involved in studies of the effect of such diets. Although these patients have been able to make the major lifestyle changes required for these regimens, it is not clear that this is feasible for the population at large. In fact, diets with less than 15% fat are not likely to have wide appeal. For those with CAD, a diet markedly restricted in saturated fats is still the primary approach and retains the appropriate focus. Well-motivated patients should be encouraged to learn the basics of a vegetarian lifestyle and supplement their diets with small amounts of lean meat, fish, and skinless fowl. The use of exercise as an adjunct to diet cannot be stressed enough. The best diets will invariably be the ones that promote loss of excessive weight while augmenting the use of drugs to lower LDL-C and TG levels and to raise subnormal levels of HDL-C.

An important controversy that appears to be resolving is whether it is better to have a diet supplemented with fish, vegetables, and fruits as a supply of antioxidants, or to load up on a handful of pills each morning that contain megadoses of minerals and vitamins. The adverse experience with beta-carotene and the lack of data confirming cardiovascular benefit from vitamin E supplementation in large-scale clinical trials should make all cardiologists more cautious about the supplements they recommend for their patients. Physicians should remember that, although tempting, recommendation of interesting but unproved nutritional supplements may not work to a patient's advantage.

A word of caution should be given about "fad diets" that are presented to cardiologists by their patients. Many diets have had glowing testimonials in the short term only to fall short of the mark in the long term. In addition, at the extremes of the life cycle, children and the elderly are likely to do poorly with dietary plans that may not have the proper nutritional balance for their age group. This can lead to unwanted nutritional deficiencies. Many patients look for endorsement because they feel the most important hurdle is getting started on weight loss. Actually, the most formidable hurdle is *maintaining* weight loss. As a general rule, diets that promise dramatic short-term weight loss fail to teach our patients the proper behaviors that are needed for long-term weight maintenance. Should it be surprising that so many regain lost weight and become even heavier?

A final controversy relates to the treatment of obesity. As the prevalence of obesity increases, its impact will be seen in cardiology practices. As noted earlier, the increase in insulin resistance with accompanying dyslipidemia, hypertension, and glucose intolerance (i.e., the metabolic syndrome) greatly increases coronary risk. The risk factors in turn magnify the negative effects of obesity on cardiac status. Moreover, for individuals with CAD, obesity limits or adversely affects the accuracy of diagnostic procedures. Although more vigorous attempts at adhering to dietary recommendations under the watchful eye of a registered dietitian are very useful, they have not proven as productive as might be wished. The current antiobesity drugs may be useful if 5% to 10% weight loss is required to improve risk-factor status. I do not recommend sibutramine in patients with CHD, because of its small but definite effects on blood pressure and heart rate. Further clinical trials of the newer generations of obesity drugs are needed to determine their proper place in both primary and secondary prevention of CAD. More widespread use of surgical techniques by qualified surgeons with appropriate multidisciplinary support may prove most helpful to severely obese patients. Given the high recidivism rate in weight-loss programs, the focus for the obese patient should be on learning new behaviors, such as dietary changes, exercise, and stress management. Increasing social support may be extremely helpful in this regard. Most important, the cardiologist should use every opportunity to endorse prevention of obesity through regular exercise and diet among individuals who are just beginning to increase their weight status as they age. Given the difficulty of successfully treating obesity, prevention of obesity should remain a high priority for public policy. Physicians should play a role as well and try to anticipate the expected weight gain from patients who stop smoking or start medications such as steroids, antidepressants, and antidiabetic drugs. These patients constitute a high-risk group to which heightened attention should be given.

THE FUTURE

As we approach the year 2010, the United States is well on its way to attaining an even lower overall serum cholesterol level through improved diet. The ongoing change in health care delivery toward a system of managed care has the potential to improve the nutritional health of the population through innovative, low-cost nutritional programs. The ability to document improved outcomes associated with such endeavors is an important task that lies ahead. Finally, exciting advances in medical genetics hold the promise of more-targeted nutritional advice, not only for the general population, but particularly for those at high risk for heart disease.

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3

LIPID DISORDERS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Lipid disorders are common and are an important risk factor for coronary heart disease (CHD) and all types of atherosclerotic cardiovascular disease (ASCVD). Intervention with diet and drugs to reduce low-density lipoprotein (LDL) cholesterol has been proven to decrease the risk of subsequent cardiovascular events, including the total mortality. In patients who have established ASCVD or are at a high risk for developing it, treatment to reduce LDL cholesterol is effective not only when the LDL cholesterol level is elevated, but also when the cholesterol level is average. On the basis of a wealth of clinical trial data, it is widely agreed that virtually all patients with ASCVD should be treated with lipid-lowering drug therapy to reduce the risk of subsequent cardiovascular events. However, sudden cardiac death at the time of the first myocardial infarction (MI) is common, and, therefore, waiting to reduce cholesterol until symptoms of CHD have developed is not an acceptable strategy. Drug therapy to reduce cholesterol in primary prevention has also been shown to reduce cardiovascular events, even when LDL cholesterol levels are only moderately elevated. Thus, the major challenge in primary prevention is to perform an accurate risk assessment so that high-risk patients can be treated with an appropriate level of aggressive drug therapy, and low-risk patients can avoid drug therapy. Traditional risk factors are useful but do not always permit accurate risk assessment; additional tests to assess cardiovascular risk, such as laboratory tests and noninvasive imaging tests of subclinical atherosclerosis, have a role to play. It is likely that those individuals at highest risk for developing premature CHD will be able to be prospectively identified. Cholesterol reduction is a cornerstone of cardiovascular risk reduction. Strategies to achieve cholesterol reduction must include both broad-based public health measures oriented around diet and lifestyle and highly focused, aggressive intervention targeted toward those at highest risk for developing premature CHD.

GLOSSARY

Apolipoprotein: Major protein component of lipoproteins; apolipoproteins have a variety of functions.

Cholesteryl ester transfer protein (CETP): Protein that transfers lipids among lipoproteins, especially cholesteryl ester from high-density lipoprotein to very low-density lipoprotein, in exchange for triglycerides.

Chylomicron: Intestinal triglyceride-rich lipoprotein; elevated when triglycerides are >1,000 mg per dL.

Hepatic lipase (HL): Endothelial-anchored enzyme in liver that is primarily responsible for hydrolysis of triglycerides and phospholipids in intermediate-density lipoprotein and high-density lipoprotein.

High-density lipoprotein (HDL): Small lipoprotein thought to participate in "reverse cholesterol transport"; levels are inversely associated with risk of coronary artery disease.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase: Rate-limiting enzyme in cholesterol biosynthesis; inhibition by statins results in reduction of plasma LDL-cholesterol levels.

Intermediate-density lipoprotein (IDL): Lipoprotein formed by hydrolysis of triglycerides in very low-density lipoprotein; elevated in type III hyperlipoproteinemia.

Lecithin-cholesterol acyltransferase (LCAT): Enzyme that converts free cholesterol to cholesteryl ester on high-density lipoprotein.

Lipoproteins: Complexes responsible for transporting lipids (cholesterol, triglyceride, phospholipids) within the blood.

Lipoprotein lipase (LPL): Endothelial-anchored enzyme primarily responsible for hydrolysis of chylomicron and very-low-density lipoprotein triglycerides, especially in muscle and adipose tissue.

Low-density lipoprotein (LDL): Major cholesterol-containing lipoprotein and major atherogenic lipoprotein.

Primary prevention: Treatment to prevent atherosclerosis and coronary artery disease events in persons who do not have evidence of coronary artery disease.

Secondary prevention: Treatment to prevent recurrent coronary artery disease events in persons who have documented coronary artery disease.

Very-low-density lipoprotein (VLDL): Major triglyceride-containing lipoprotein when fasting triglycerides are <1,000 mg per dL; made by the liver.

HISTORICAL PERSPECTIVE

Cholesterol was first postulated to be related to atherosclerosis when it was found to be a major component of advanced atherosclerotic plaques. The association between elevated serum cholesterol and atherosclerotic disease was first reported in the 1930s. Subsequent large epidemiologic studies such as the Seven Countries Study (1) and the Framingham Heart Study (2) confirmed the strong relationship between serum cholesterol and CHD. In the Multiple Risk Factor Intervention Trial, 356,222 men with no history of MI were screened and followed for the development of CHD over the course of 6 years. The relationship between serum cholesterol level and subsequent CHD was found to be continuous, graded, and strong (3). The Lipid Research Clinics Prevalence Study demonstrated in a 10-year follow-up that cholesterol level at baseline was strongly associated with CHD death in men who did and men who did not have CHD when they entered the study (4). In the Johns Hopkins Precursors Study, cholesterol levels determined in young men in their early twenties were predictive of the risk of developing CHD three to four decades later (5). In the Bogalusa Heart Study, aortic fatty streaks in young individuals (mean age, 18 years) were found to be strongly correlated with serum cholesterol level (6). These and many other epidemiologic and observational studies formed the basis of the “cholesterol hypothesis,” which states that the relationship between serum cholesterol and atherosclerosis is causal and that reduction of serum cholesterol reduces atherosclerotic disease.

The subfractionation of serum cholesterol into cholesterol contained within specific lipoproteins, such as LDLs and high-density lipoproteins (HDLs), was a major clinical advance. Risk for CHD was found to be strongly associated with LDL cholesterol levels. The seminal observation that HDL cholesterol levels were inversely associated with cardiovascular risk was made in the 1950s and rediscovered in the 1970s (7). Subsequent studies from many parts of the world have confirmed this observation (8) and have ultimately resulted in the use of HDL cholesterol levels as a key laboratory marker for the screening of cardiovascular risk in all adults (9).

The relationship between fasting serum triglycerides and cardiovascular risk has been confounded by the inverse association between triglycerides and HDL cholesterol, as well as by the association of triglycerides with other risk factors, such as diabetes mellitus and body mass. Earlier epidemiologic studies demonstrated that fasting triglycerides were not independently associated with cardiovascular risk. However, in the last several years, several prospective studies have indicated that triglyceride levels are an important independent predictor of risk (10). Although formal guidelines have not yet established the use of triglycerides as an independent risk factor, many clinicians now incorporate the fasting triglyceride level into a comprehensive cardiovascular risk assessment (see below).

LIPID-MODIFYING THERAPY AND EFFECTS ON ATHEROSCLEROSIS AND CARDIOVASCULAR EVENTS

Despite the wealth of epidemiologic and pathologic data linking serum cholesterol to atherosclerotic disease, proof of the “cholesterol hypothesis” required demonstration that reduction of cholesterol decreased atherosclerosis and clinical cardiovascular events. Over the past two decades, multiple trials have been reported that were designed to test this hypothesis, and more recent studies have been designed to test whether modification of HDL cholesterol and triglyceride levels would reduce atherosclerosis or cardiovascular risk. Many studies have assessed the impact of lipid-modifying therapy on a quantitative measure of atherosclerotic disease (as assessed by coronary angiography or carotid ultrasound) (*e*Table 3.0.1). Other, larger trials have been focused on the effect of lipid-modifying therapy on clinical cardiovascular events (nonfatal MI, CHD death, and total mortality rate) (Table 3.1). These studies encompass both secondary prevention trials (in patients with clinically established CHD) and primary prevention trials (in patients without established CHD).

***e*TABLE 3.0.1** CLINICAL TRIALS OF CHOLESTEROL REDUCTION IN WHICH QUANTITATION OF ATHEROSCLEROTIC DISEASE WAS THE PRIMARY END POINT

Coronary angiography

Study	No. of subjects	Intervention	Control	Change in the percentage of patients treated for stenosis	Reduction in events (%)
NHLBI Type II (159)	143	R	NA	NA	33
CLAS I (160)	188	R + N	NA	NA	25
FATS (161)	146	R + N	+2.1	–0.9	80
		R + L	+2.1	–0.770	70
Lifestyle Heart Trial (162)	48	Mult	+3.4	–2.2	NA
UCSF-FH (163)	97	R + N ± L	+0.8	–1.5	NA
STARS (164)	90	D	+5.8	–1.1	69
		D + R	+5.8	–1.9	89
SCRIP (165)	300	Mult	+4.8	+3.0	43
MARS (166)	270	L	+2.2	+1.6	24
CCAIT (167)	331	L	+2.9	+1.7	25
MAAS (168)	381	S	+3.6	–2.6	24
PLAC I (169)	408	P	+3.3	+2.1	60
REGRESS (170)	885	P	+3.5	+2.1	42

Carotid ultrasonography

Study	Intervention	IMT (mm/yr) treated	control	Reduction in events (%)
ACAPS (143)	L	+0.006	–0.009	64
PLAC II (144)	P	+0.067	+0.059	60
KAPS (145)	P	+0.031	+0.017	38

ACAPS, Asymptomatic Carotid Artery Progression Study; CCAIT, Canadian Coronary Atherosclerosis Intervention Trial; CLAS, Cholesterol Lowering Atherosclerosis Study; D, diet; FATS, Familial Atherosclerosis Treatment Study; IMT, intimal-medial thickness; KAPS, Kuoppio Atherosclerosis Prevention Study; L, lovastatin; MAAS, Multicentre Anti-Atheroma Study; mult, multiple therapies; N, niacin; NA, not applicable; NHLBI, National Heart, Lung, and Blood Institute; P, provastatin; PLAC, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; R, resins; REGRESS, Regression Growth Evaluation Statin Study; UCSF-FH, University of California San Francisco Familial Hypercholesterolemia; S, simvastatin; SCRIP, Stanford Coronary Risk Intervention Project; STARS, St. Thomas’ Atherosclerosis Regression Study.

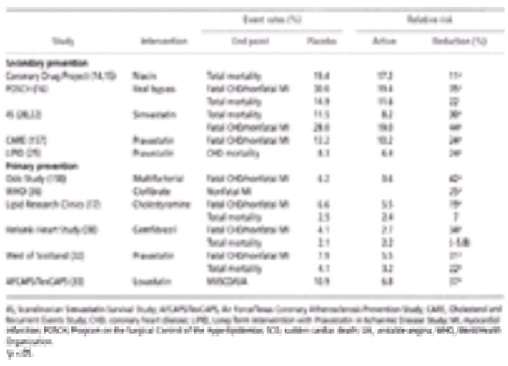


TABLE 3.1 CLINICAL TRIALS OF CHOLESTEROL REDUCTION WITH CLINICAL EVENTS AS THE PRIMARY END POINT

Trials Using Quantitation of Atherosclerotic Disease as the Primary End Point

Quantitative Coronary Angiography

A large number of angiographic trials have been performed that address whether treatment to lower cholesterol or modify serum lipids influences the course of angiographic coronary disease (*e*Table 3.0.1). These trials have consistently demonstrated that cholesterol reduction resulted in slowing of the progression of coronary disease compared with the rate of progression in a control group. Some trials have even demonstrated modest regression of coronary atherosclerotic disease in a subset of the treated subjects. Although the results were statistically significant, the magnitude of the differences between treated and control groups in these studies has generally been rather small and of uncertain clinical significance. However, many of these studies have subsequently reported their secondary endpoint clinical cardiovascular event rates. In most trials, a substantial reduction in clinical events was seen in the treated group that was out of proportion to the small quantitative

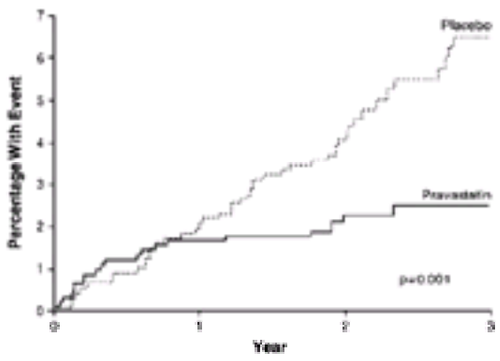
changes in luminal diameter of lesions. This consistent angiographic-clinical dissociation has led to the concept of “plaque stabilization,” in which cholesterol reduction alters the vulnerable plaque in a way that may not substantially change its angiographic stenosis but nevertheless makes it substantially less likely to rupture and cause an acute coronary event (11). The mechanisms by which cholesterol reduction reduces the likelihood of acute coronary events are not well understood but may include lipid depletion of the core of the lesion, stabilization of the endothelium, inhibition of platelets, and effects on vascular smooth muscle cell behavior (11,12).

Carotid Ultrasonography

Several trials have been performed that address the question of whether cholesterol reduction influences the progression of carotid atherosclerosis as assessed by B-mode ultrasonography for quantitation of the intimal-medial thickness (IMT) (eTable 3.0.1). All studies demonstrated a statistically significant effect of treatment on the primary end point of quantitative carotid intimal thickening. Interestingly, as noted in the coronary angiographic studies, secondary endpoint cardiovascular events were also substantially reduced in these trials (although the total number of events was relatively small).

Pooled Analysis

A pooled analysis of four atherosclerosis trials using pravastatin was prospectively planned and subsequently performed (13). These four trials (two involving coronary angiography and two involving carotid ultrasound) included a total of 1,891 subjects, all of whom had some evidence of atherosclerosis and elevated cholesterol levels, who were followed for 2 to 3 years. In this pooled analysis, the major end point was the combined end point of nonfatal or fatal MI. A total of 46 events in the placebo group and 21 events in the pravastatin group were reported, resulting in a 62% reduction in relative risk of nonfatal or fatal MI after 2 to 3 years of treatment (p = .001) (eFig. 3.0.1).



***e*FIGURE 3.0.1** Rate of nonfatal or fatal myocardial infarction in the pooled analysis of four pravastatin atherosclerosis trials. (From Byington RP, Jukema W, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy: pooled analysis of clinical events of the pravastatin atherosclerosis intervention program. *Circulation* 1995;92:2419–2425.)

Taken together, these trials indicate that cholesterol reduction has a quantitative effect on the progression and even regression of atherosclerosis, and that the reduction in clinical cardiovascular events is disproportionately greater than the modest changes in measurable atherosclerosis.

Trials Using Clinical Events as the Primary End Point

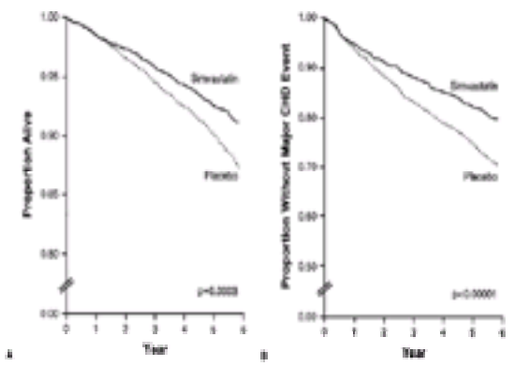
Early Clinical Trials: Niacin, Bile Acid Sequestrants, and Partial Ileal Bypass

The early clinical trials used niacin, bile acid sequestrants, and even the surgical approach of partial ileal bypass to reduce serum cholesterol levels (Table 3.1). The Coronary Drug Project demonstrated a modest benefit of niacin in reducing nonfatal MI after 6 years of treatment (14) and in reducing the total mortality rate after 15 years of follow-up (15). The Program on the Surgical Control of the Hyperlipidemias trial used partial ileal bypass surgery to reduce LDL cholesterol levels and demonstrated a significant 35% relative reduction in fatal CHD and nonfatal MI, although no significant reduction was seen in the total mortality rate (the primary end point of the trial) (16). In the Lipid Research Clinics Coronary Primary Prevention Trial, which studied the effect of cholestyramine administration in hypercholesterolemic men (17,18), combined fatal CHD and nonfatal MI (the primary end point) was reduced by 19%, but the total mortality rate was not reduced (68 deaths among patients receiving cholestyramine vs. 71 deaths among patients receiving placebo). A higher noncardiovascular mortality rate was seen in patients who were treated with cholestyramine (36 deaths) than in patients who received placebo (27 deaths), mostly because of a higher number of suicides and violent deaths among patients treated with cholestyramine (11 vs. 4 deaths). Extension of the follow-up period to a total of 13.4 years (19) demonstrated that the total number of deaths in the group of patients receiving cholestyramine (143 deaths) was not significantly different from that in the control group (156 deaths).

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitor (Statin) Trials

Secondary Prevention

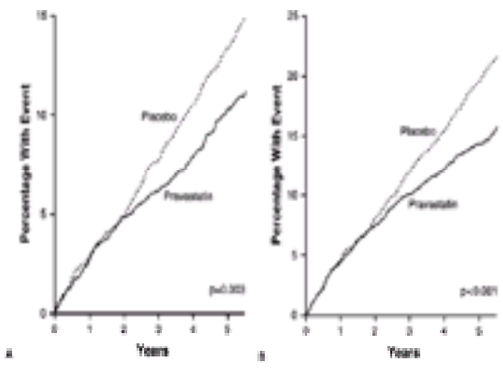
Five major clinical outcome trials with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) performed during the 1990s definitively established that reduction of LDL cholesterol reduced cardiovascular risk in both secondary and primary prevention (Table 3.1). Three of these trials were secondary prevention trials, and two were primary prevention trials. The Scandinavian Simvastatin Survival Study (4S) (20) was designed to address the question of whether cholesterol reduction with simvastatin in persons with CHD and elevated cholesterol would reduce the total mortality rate (the primary end point). A total of 4,444 patients with angina or previous MI whose total cholesterol levels were between 212 and 310 mg per dL were randomized to placebo or simvastatin. The simvastatin dose was titrated to reduce the total cholesterol level to <200 mg per dL. Subjects were followed for a mean of 5.4 years. One hundred and eighty-nine deaths occurred in the group receiving placebo, and 111 deaths occurred in the group receiving simvastatin, resulting in a highly significant 30% relative reduction in the total mortality rate (p <.00001) (eFig 3.0.2A). The relative risk of a major coronary event (the secondary end point) such as CHD death or MI was reduced by 44% (p <.00001) (eFig 3.0.2B). The number of revascularization procedures such as coronary bypass surgery and angioplasty also dropped significantly, by 34%. An economic analysis based on the 4S study concluded that in the United States, the reduction in hospital costs alone as a result of the treatment would virtually offset the cost of the medication (21). Importantly, the reduction in risk was not only seen among subjects who had the highest cholesterol levels; the quartile with the lowest LDL cholesterol levels at baseline had proportionately as much benefit from treatment as the highest quartile (22).



***e*FIGURE 3.0.2** Proportion of subjects with all-cause mortality **(A)** and major coronary heart disease events **(B)** in the Scandinavian Simvastatin Survival Study involving patients with coronary heart disease (CHD) and elevated cholesterol levels. [From the Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.]

This issue is important, because the majority of patients with CHD do not have particularly elevated cholesterol levels; in fact, approximately 35% of all persons with

CHD have total cholesterol levels <200 mg per dL (23). Therefore, another major trial, the Cholesterol and Recurrent Events study (24), addressed the previously unanswered question of whether patients who had experienced MI and who had average cholesterol levels would benefit from further cholesterol reduction with pravastatin. In this study, 4,159 patients who had experienced MI 3 to 20 months before the trial and had total cholesterol levels <240 mg per dL were randomly assigned to receive placebo or pravastatin, 40 mg daily, and followed for an average of 5 years. The mean total cholesterol level was 209 mg per dL in each group, and the mean LDL cholesterol level was only 139 mg per dL (range, 115 to 174 mg per dL). After 5 years, 274 subjects in the placebo group had nonfatal MI or CHD death (the primary end point), compared with 212 subjects in the group of patients treated with pravastatin, resulting in a significant 24% reduction in relative risk (p = .003) (eFig 3.0.3A). Revascularization procedures were reduced by 27% (p <.001) (eFig. 3.0.3B). These results demonstrated that the benefit of cholesterol-lowering therapy extends even to CHD patients who have average cholesterol levels.



***e*FIGURE 3.0.3** Rate of fatal coronary artery disease or nonfatal myocardial infarction **(A)** and revascularization procedures **(B)** in the Cholesterol and Recurrent Events Study in patients with myocardial infarction and average cholesterol levels. (From Sacks FM, Pfeffer MA, Moye L, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009.)

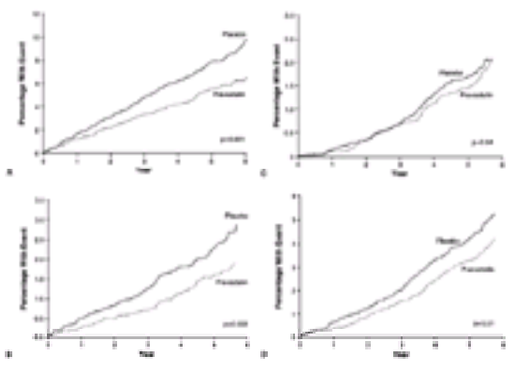
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study (LIPID) (25) was the largest secondary prevention study performed to date. It included 9,014 patients aged 31 to 75 years who presented with either acute MI or unstable angina and who had baseline cholesterol levels spanning the wide range of 155 to 271 mg per dL. Subjects were randomly assigned to receive placebo or pravastatin, 40 mg daily, and followed for 6 years. Treatment with pravastatin significantly reduced the CHD mortality rate (the primary end point) by 24% (p <.001) and the total mortality rate by 22% (p <0.001). The study was terminated early by the data and safety monitoring committee because of the highly significant difference in total mortality between the two groups. The occurrence of revascularization was reduced by 20%, and the occurrence of stroke of any type was reduced by 19%.

These three studies definitively established the efficacy of statin therapy in reducing cardiovascular events and the total mortality rate in patients who had established CHD over a very wide range of baseline LDL cholesterol levels. Not only is cholesterol-lowering drug therapy clinically effective in secondary prevention, it is cost-effective as well. Aggressive cholesterol reduction in patients with patients with CHD or other ASCVD is now the standard of care, as agreed on in a joint statement issued by the American Heart Association and the American College of Cardiology (26). The majority of patients with ASCVD should be considered candidates for lipid-lowering drug therapy. Current debate in secondary prevention centers around not whether to treat, but how far to reduce the LDL cholesterol level (27). Studies designed to address this issue are currently under way.

All of the statin trials reviewed earlier excluded patients who were within 3 to 6 months of an acute coronary event. The LIPID trial was, in fact, the only secondary-prevention trial to include patients who had presented with unstable angina. In LIPID, the relative risk reduction for total mortality with pravastatin therapy was 20.6% among patients who had experienced MI and 26.3% among patients who had experienced unstable angina, suggesting a trend for even greater benefit in those patients who presented with unstable angina (28). In patients in LIPID who had previous unstable angina, the CHD mortality rate, the total mortality rate, the incidence of MI, the need for coronary revascularization, the number of admissions to the hospital, and the number of days spent in the hospital were all significantly lower in the group of patients receiving pravastatin. One question of substantial clinical interest is whether patients presenting with acute coronary syndromes would benefit from immediate initiation of statin therapy. In a small study called the Randomized Lipid-Coronary Artery Disease Study, patients were randomly assigned, an average of 6 days after presenting with an acute coronary syndrome, to receive pravastatin, 40 mg daily (combined, when necessary, with cholestyramine and/or nicotinic acid to achieve LDL cholesterol levels <130 mg per dL), or usual care (29). After 2 years, 52% of patients in the group receiving usual care but only 23% of patients in the group being aggressively treated experienced a recurrent cardiovascular event (p = .005). In a larger study called the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study, patients who presented with acute coronary syndromes and did not undergo revascularization were randomly assigned to receive immediate therapy with atorvastatin, 80 mg, or placebo and followed for 4 months (30). A 16% reduction in recurrent coronary events was associated with immediate statin therapy, a difference that barely achieved statistical significance (p = .048). Additional studies that include patients undergoing revascularization are under way that also address the important question of the benefit of immediate initiation of statin therapy.

Primary Prevention

Primary prevention of CHD is also important, because approximately one-fourth to one-third of first MIs result in death (31), precluding the opportunity for secondary prevention. Nevertheless, the use of drug therapy in primary prevention has been controversial; before the mid-1990s, relatively few data were available that demonstrated clinical benefit. The West of Scotland Coronary Prevention Study (32) was a landmark trial in primary prevention of CHD. This study involved 6,595 healthy Scottish men aged 45 to 64 years, with total cholesterol levels >252 mg per dL and LDL cholesterol levels of 174 to 232 mg per dL. Although none of the study subjects had documented CHD, 5% had positive results of a Rose questionnaire indicating probable angina. Subjects were randomly assigned to receive pravastatin, 40 mg per day, or placebo and were followed for an average of 5 years. The primary end point of the study was nonfatal MI or CHD death. Two hundred and forty-eight definite events were reported in the group of patients receiving placebo (7.9% of the subjects) and 174 events in the group receiving pravastatin (5.5% of the subjects), resulting in a 31% reduction in relative risk of nonfatal MI or CHD death (p <.001) (eFig. 3.0.4A). In addition, a significant 32% reduction in CHD death (p <.033) (eFig. 3.0.4B) and a 37% reduction in revascularization procedures (p <.009) were seen. Importantly, no significant difference was found in the noncardiovascular mortality rate (eFig. 3.0.4C), indicating that cholesterol reduction with pravastatin did not increase the risk of death from other causes. In fact, the relative risk of death from any cause (total mortality rate) was reduced by 22% among patients treated with pravastatin (p = .051) during the 5-year period of the trial (eFig. 3.0.4D). This trial clearly established that drug therapy for hypercholesterolemia is an effective method of decreasing risk of cardiovascular events in persons who do not have prior evidence of CHD.



***e*FIGURE 3.0.4** Rates of nonfatal myocardial infarction or coronary artery disease death **(A)**, cardiovascular mortality **(B)**, noncardiovascular mortality **(C)**, and all-cause mortality **(D)** in the West of Scotland Coronary Prevention Study in men without myocardial infarction and with elevated cholesterol levels. (From Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301–1307.)

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) extended these findings to a population with modestly elevated to average cholesterol levels (33). A total of 6,608 men and women with LDL cholesterol levels of 130 to 190 mg per dL and HDL cholesterol levels <45 mg per dL in men and <47 mg per dL in women were randomly assigned to receive lovastatin, 20 mg, or placebo and were followed for an average of 5.2 years. The dose of lovastatin was

titrated to 40 mg in an attempt to reduce LDL cholesterol levels to <100 mg per dL. A 37% relative risk reduction was seen in the primary end point of combined cardiovascular events in the group of patients who were treated with lovastatin. Interestingly, only 17% of the subjects in this trial would have met National Cholesterol Education Program Adult Treatment Panel II (NCEP-ATPII) 1993 guidelines for drug therapy. Therefore, the major clinical challenge in the use of drug therapy to reduce cholesterol levels in primary prevention of CHD is the accurate identification of individuals who are likely to develop clinical CHD and who are therefore most likely to benefit from drug therapy.

Pooled Analyses

Previous trials have included insufficient numbers of coronary events to address definitively the effect of lipid-modifying therapy on CHD in subgroups of patients with varying baseline characteristics. The data from three large randomized trials of pravastatin that involved 19,768 patients and 2,194 primary end points (coronary death or nonfatal MI) were pooled and analyzed with the use of a prospectively defined protocol (34). Pravastatin significantly reduced relative risk in patients regardless of age, sex, smoking habits, and presence of diabetes mellitus or hypertension. Relative risk reduction was significant in predefined categories of baseline lipid concentrations and was similar throughout most of the baseline LDL cholesterol range (125 to 212 mg per dL). Therefore, treatment is effective in reducing CHD events in patients with high- or low-risk factor status across a wide range of pretreatment lipid concentrations.

Fibrate Trials

Fibrates have been used as lipid-lowering drugs for several decades. They are particularly effective in reducing triglyceride levels and have modest effectiveness in reducing cholesterol levels and raising HDL cholesterol levels (35). Relatively few clinical endpoint trials examining the use of fibrates have been published. In the World Health Organization cooperative trial using clofibrate to treat hypercholesterolemic men (36), a 25% reduction was seen in relative risk of nonfatal MI (the primary end point) after 5 years, but a substantial 47% increase in noncardiovascular deaths was also found. Extension of the follow-up period to 13 years did not reveal a persistent effect of the drug on the excess mortality rate (37). The Helsinki Heart Study (38) treated men who had elevated non-HDL cholesterol levels, >200 mg per dL, with gemfibrozil and demonstrated a significant 34% reduction in combined fatal and nonfatal MI (the primary end point) but no difference in the total mortality rate (45 deaths among patients receiving gemfibrozil and 42 deaths in the control group). A small trend toward an increase in the noncardiovascular mortality rate was seen (31 vs. 23 deaths, respectively), which was largely due to a difference in accidental and violent death (10 vs. 4 deaths, respectively). Extension of the follow-up period to 8.5 years (39) demonstrated an increased mortality rate in the group treated with gemfibrozil (101 deaths) compared to the group receiving placebo (83 deaths) that was not statistically significant (p = .19) and was due to a small increase in cancer deaths among patients receiving gemfibrozil. Neither of these trials were designed with adequate power to assess the impact of fibrates on the total mortality rate. Nevertheless, the lack of effect on the total mortality rate and the small trends toward an increased noncardiovascular mortality rate resulted in uncertainty about the broad use of fibrates for cardiovascular risk reduction in hypercholesterolemic patients.

Two trials of fibrates in the late 1990s provided more data but also generated more questions. The Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) tested the benefit of gemfibrozil therapy in patients who had CHD and reasonably well-controlled LDL cholesterol levels but low HDL cholesterol levels (40). Two thousand five hundred and thirty-one patients with CHD, low levels of HDL (mean, 32 mg per dL), low LDL cholesterol levels (mean, 112 mg per dL), and triglyceride levels <300 mg per dL were randomly assigned to receive treatment with a sustained-release gemfibrozil formulation (1,200 mg daily) or placebo and followed for an average of 5.1 years. Gemfibrozil therapy was associated with a significant 22% reduction in the primary end point (nonfatal MI and coronary death) compared with placebo. Gemfibrozil resulted in a 6% increase in HDL cholesterol levels, a 31% decrease in triglyceride levels, and no change in LDL cholesterol levels. This important study suggests that lipid-modifying drug therapy using fibrates in patients with CHD and low LDL and HDL cholesterol levels reduces cardiovascular events.

In contrast, the Bezafibrate Infarction Prevention (BIP) trial involved 3,090 patients with established CHD, total cholesterol levels of 180 to 250 mg per dL, HDL cholesterol levels <45 mg per dL, triglyceride levels <300 mg per dL, and LDL cholesterol levels <180 mg per dL who were randomly assigned to receive either bezafibrate, 400 mg daily, or placebo and followed for a mean of 6.2 years (41). The primary end point was fatal or nonfatal MI or sudden death. Bezafibrate therapy was associated with a reduction in the primary end point of only 7.3%, which was not statistically significant (p = .24). A post hoc analysis in the subgroup with high baseline triglyceride levels (>200 mg per dL) suggested a reduction in events of 39% (p = .02).

These trials differed in a number of important ways, including the agent used and the mean baseline LDL cholesterol levels, which in BIP were 150 mg per dL and in VA-HIT were only 111 mg per dL. A reasonable conclusion is that fibrates are effective as monotherapy in reducing events in secondary prevention if the LDL cholesterol is low, but not if it is elevated. A number of additional studies are under way that address the role of fibrates in reducing cardiovascular events, both as monotherapy and in combination with statins.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF LIPOPROTEIN METABOLISM AND RELATIONSHIP TO ATHEROSCLEROSIS

Clinical management of patients with lipid disorders requires a general working knowledge of normal lipoprotein metabolism (42). Lipoproteins are large macromolecular complexes that transport cholesterol and triglycerides within the blood. They contain a neutral lipid core consisting of triglycerides and cholesteryl esters that is surrounded by phospholipids and specialized proteins known as *apolipoproteins*. The five major families of lipoproteins are chylomicrons, VLDLs, intermediate-density lipoproteins (IDLs), LDLs, and HDLs. Chylomicrons are the largest and most lipid-rich lipoproteins, whereas HDLs are the smallest lipoproteins and contain the least amount of lipid. The major metabolic pathways of lipoproteins are shown in Figure 3.1,Figure 3.2, and Figure 3.3 and described in detail in the accompanying legends.

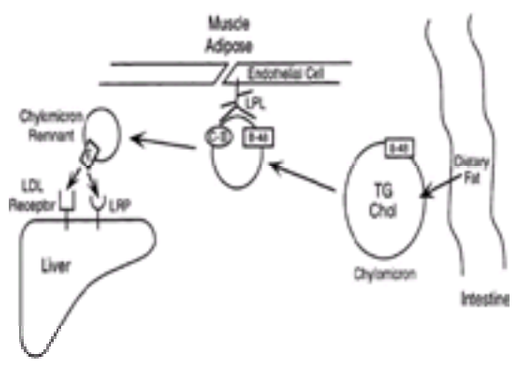


FIGURE 3.1 Exogenous pathway of lipid transport. Dietary fat is absorbed into chylomicrons, which contain the major structural apolipoprotein B-48. Chylomicrons bind to lipoprotein lipase (LPL) on the luminal surface of the capillary endothelium of tissues, especially muscle and adipose tissue. The LPL hydrolyzes the triglycerides [apolipoprotein C-II (C-II) on the chylomicron surface is a required cofactor for LPL]. The free fatty acids enter the tissue to be used for energy (muscle) or storage (adipose), and the triglyceride-depleted chylomicron remnant is released. Chylomicron remnants are taken up by the liver by binding of apolipoprotein E (E) to the low-density lipoprotein (LDL) receptor and the LDL receptor–related protein (LRP). TG Chol, triglyceride cholesterol.

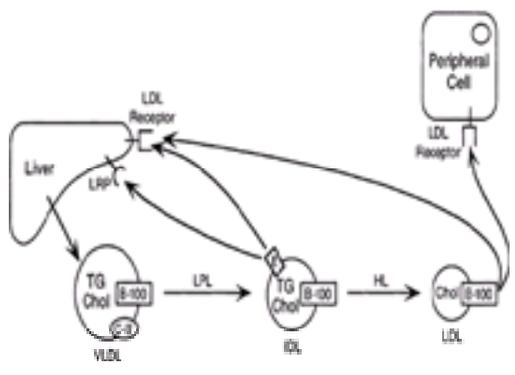


FIGURE 3.2 Endogenous pathway of lipid transport. The liver synthesizes triglycerides and cholesteryl esters and packages them into very-low-density lipoproteins (VLDLs), which contain the major structural apolipoprotein B-100. VLDLs are hydrolyzed by lipoprotein lipase (LPL) to form intermediate-density lipoproteins (IDL). IDLs can be taken up by the liver via binding of apolipoprotein E (E) to the LDL receptor or LDL receptor–related protein (LRP). Alternatively, the triglyceride and

phospholipid in IDL can be hydrolyzed by hepatic lipase (HL) within the hepatic sinusoids to form LDL. LDL can be taken up by peripheral cells or by the liver through the binding of apolipoprotein B-100 to the LDL receptor. C-II, apolipoprotein C-II; TG Chol, triglyceride cholesterol.

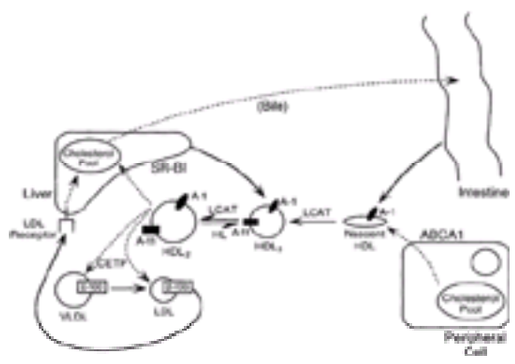


FIGURE 3.3 High-density lipoprotein (HDL) metabolism and reverse cholesterol transport. HDL and its major apolipoprotein, apolipoprotein A-I, are synthesized by both the intestine and the liver. A second major HDL protein, apolipoprotein A-II, is made only by the liver. Nascent HDL interacts with peripheral cells to facilitate the removal of excess free cholesterol through a process that is facilitated by the cellular protein ABCA1. Some of the acquired free cholesterol is esterified to cholesteryl ester on the HDL particle by the action of the enzyme lecithin-cholesterol acyltransferase (LCAT), and the nascent HDL particle becomes the larger HDL3. HDL acquires further cholesteryl ester by continued LCAT action and eventually becomes the even larger HDL2. HDL2 can selectively transfer both cholesteryl ester and free cholesterol to the liver via an HDL receptor in the liver called *scavenger receptor BI*. Cholesteryl esters can also be transferred from HDL2 to apolipoprotein B–containing lipoproteins such as very-low-density lipoproteins (VLDLs) and LDLs via the action of the cholesteryl ester transfer protein (CETP) and then returned to the liver by hepatic uptake of LDL. HDL2 triglycerides and phospholipids can be hydrolyzed by hepatic lipase (HL) to remodel HDL2 to HDL3. Cholesterol derived from HDL contributes to the hepatic cholesterol pool used for bile acid synthesis, and the cholesterol is eventually excreted into the bile and feces as bile acid or free cholesterol. Solid lines indicate the metabolism of the lipoprotein particles, and broken lines indicate the flux of cholesterol independent of lipoprotein particle metabolism.

Apolipoproteins are required for the structural integrity of lipoproteins and direct their metabolic interactions with enzymes, lipid transport proteins, and cell surface receptors (*e*Table 3.1.1). Apolipoprotein A-I (apoA-I) is a major component of all HDL particles and serves as a marker for this lipoprotein family. In contrast, apolipoprotein B (apoB) is the major apolipoprotein for all the remaining non-HDL lipoproteins. There are two forms of apoB, apoB-48 and apoB-100, both of which are derived from the same gene. In the liver, the apoB messenger RNA is translated to produce the larger apoB-100, which is found in lipoproteins derived from the liver (VLDL, IDL, LDL). However, in the intestine, the apoB messenger RNA is “edited” by a complex that introduces a stop codon sequence slightly before the midpoint of the coding sequence, resulting in the synthesis of a smaller protein (apoB-48), which is then found in lipoproteins derived from the intestine (chylomicrons).

***e*TABLE 3.1.1** CHARACTERISTICS OF MAJOR APOLIPOPROTEINS

Apolipoprotein	Lipoprotein association	Primary source	Functions
ApoA-I	HDL	Intestine, liver	Structural protein for HDL, activator of LCAT
ApoA-II	HDL	Liver	Unknown
ApoA-IV	HDL, CM, VLDL	Intestine	Unknown
ApoB-48	CM	Intestine	CM synthesis and secretion
ApoB-100	VLDL, IDL, LDL, Lp(a)	Liver	VLDL synthesis and secretion, ligand for binding to LDL receptor
ApoC-I	CM, VLDL, HDL	Liver	Unknown
ApoC-II	CM, VLDL, HDL	Liver	Cofactor for LPL
ApoC-III	CM, VLDL, HDL	Liver	Inhibitor of lipoprotein binding to receptors
ApoE	CM, IDL, HDL	Liver	Ligand for binding to LDL receptor and LRP
Apo(a)	Lp(a)	Liver	Unknown

CM, chylomicron; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; LRP, low-density lipoprotein receptor–related protein; VLDL, very-low-density lipoprotein.

Lipoprotein receptors are a class of cell surface proteins that bind lipoproteins. The known lipoprotein receptors bind regions of apolipoproteins on the lipoprotein particles. The best-understood lipoprotein receptor is the LDL receptor, which is responsible for catabolizing both chylomicron and VLDL remnants as well as LDL (43). The LDL receptor binds apolipoprotein E and apoB and has sometimes been called the “apoB/E receptor.” The level of LDL receptor expression in the liver plays a major role in regulating the plasma level of cholesterol (43). The LDL receptor–related protein (LRP) has a variety of ligands, including apoE (44). It serves as a second pathway for clearance of apoE-containing chylomicron and VLDL remnants, especially in the deficiency of LDL receptors (45). The VLDL receptor is expressed in several extrahepatic tissues and may play a role in the delivery of fat to peripheral cells (44). The scavenger receptor binds modified or oxidized LDL (in addition to other ligands) and is thought to play a role in the development of the macrophage into the foam cell (46). Several other types of lipoprotein receptors have been postulated, but none has been convincingly demonstrated to play a role in lipoprotein metabolism or atherosclerosis.

Lipid-modifying enzymes and lipid transport proteins play a major role in lipoprotein metabolism and potentially in atherosclerosis. Lipoprotein lipase (LPL) is an enzyme that hydrolyzes triglycerides in chylomicrons and VLDL. It is bound to the surface of the capillary endothelium, especially in muscle and adipose tissue, and binds to the chylomicrons as they traverse the capillary bed. Apolipoprotein C-II (apoC-II), found on the chylomicrons, serves as a required cofactor for LPL. The free fatty acids generated by triglyceride hydrolysis enter the tissue to serve as a source of energy or fat storage, and the resulting chylomicron remnant is released and is eventually taken up by the liver. Hepatic lipase (HL) is found primarily on the endothelium of the hepatic sinusoids. HL has both triglyceride and phospholipid hydrolytic activity. One major substrate for HL is IDL, possibly resulting in conversion to LDL or in some cases promoting the catabolism of IDL. The other major substrate for HL is HDL, in which the phospholipid hydrolysis results in conversion to smaller HDL particles that may be more rapidly catabolized. Lecithin-cholesterol acyltransferase (LCAT) converts free cholesterol to cholesteryl ester on lipoproteins (especially HDL) by transferring fatty acids from phospholipids to cholesterol (47). One major role of LCAT is thought to be the esterification of free cholesterol that is acquired by HDL from cells, thus creating a gradient for free cholesterol and enhancing further cholesterol efflux from cells. The cholesteryl ester transfer protein (CETP) transfers cholesteryl esters and other lipids among lipoproteins (48). One major role of CETP is thought to be the transfer of cholesteryl esters from HDL (formed as a result of LCAT activity) to VLDL and IDL in exchange for triglycerides. This may be a major pathway by which cholesterol obtained from cells by HDL is eventually returned to the liver in a process that has been termed “reverse cholesterol transport.” However, some cholesteryl esters are transferred by CETP to VLDL and LDL, and therefore CETP could promote atherogenesis; the relationship of CETP to atherosclerosis remains uncertain. The phospholipid transfer protein transfers phospholipids among lipoproteins (48), although its role in lipoprotein metabolism and atherosclerosis has not yet been fully elucidated. These lipoprotein-modifying enzymes and lipid transport enzymes act in concert to modulate lipoprotein metabolism and probably have important effects on atherosclerosis.

Disorders of lipoprotein metabolism involve perturbations that cause elevation of triglyceride and/or cholesterol levels, reduction of HDL cholesterol levels, or alteration of properties of lipoproteins, such as their size or composition. These perturbations can be genetic (primary) or may occur as a result of other diseases, conditions, or drugs (secondary). Many (but not all) lipoprotein disorders have as their most important clinical consequence the increased risk of premature ASCVD. The next section of this chapter focuses specifically on the identification and diagnosis of specific lipid disorders, and the subsequent section focuses on the management of lipid disorders, especially with regard to the prevention of atherosclerosis and its associated clinical events.

The mechanisms by which elevated serum cholesterol promotes atherosclerosis has been a subject of intensive research for decades. Much of this work has traditionally focused on the mechanisms by which lipoproteins promote foam-cell formation. *In vitro* studies by several investigators demonstrated that native LDL is not taken up by macrophages in culture and does not promote their conversion to foam cells. However, modification or oxidation of the LDL was demonstrated to result in cholesterol loading and foam-cell formation. This led to the “oxidized LDL hypothesis,” which states that LDL must be oxidized before it becomes atherogenic, and a large body of research has supported this general concept (49). Observational data suggest that intake of antioxidant vitamins is associated with decreased incidence of ASCVD. However, controlled clinical trials have not yet conclusively proven the hypothesis that inhibition of LDL oxidation reduces progression of atherosclerosis or risk of clinical cardiovascular events (see below). It is not certain that oxidation is required for all of the atherogenic effects of lipoproteins to take place. For example, some evidence suggests that certain lipoproteins, such as remnant lipoproteins, may promote foam-cell formation without prior modification or oxidation (50). In addition, LDL and other lipoproteins are likely to have other atherosclerosis-promoting effects that are distinct from foam-cell formation and may not require oxidation, such as effects on endothelial function, platelets, and smooth muscle cells (51). For example, cholesterol reduction has beneficial effects on coronary endothelial function (52,53) that may be at least partially independent of LDL oxidation. However, dissection of these mechanisms remains an active area of basic and clinical

research.

Although the epidemiologic inverse association of HDL cholesterol with CHD is well established, the mechanistic relationship of HDL metabolism to atherogenesis is not well understood (48). The leading hypothesis for decades has been the “reverse cholesterol transport hypothesis,” in which HDL removes excess cholesterol from cells within the arterial wall and returns it to the liver for excretion in the bile. Although this process occurs in tissues throughout the body, its direct relationship to HDL metabolism and atherogenesis remains uncertain. Even if reverse cholesterol transport is one mechanism by which HDL retards atherosclerosis, HDL may work by other mechanisms as well. For example, HDL has been demonstrated *in vitro* to inhibit LDL oxidation, stabilize prostacyclin, and inhibit endothelial adhesion molecule expression (48). Finally, it has been proposed that the HDL cholesterol level may simply be a good marker for other disorders associated with increased cardiovascular risk, such as the metabolic syndrome and abnormal postprandial lipemia, and may not be directly associated with inhibiting atherogenesis (48). Active research is ongoing in these important areas.

SECONDARY DISORDERS OF LIPOPROTEIN METABOLISM

Lipid disorders can be grouped into primary disorders (genetic or inherited) and secondary disorders (caused by disease or environmental factors). Clinically, it is useful to consider and exclude secondary causes. Some of the most important secondary causes of hyperlipidemia are reviewed here and listed in Table 3.2.

Disorder	Cholesterol	Triglycerides	HDL
Metabolic/endocrine			
Hypothyroidism	++	N	N
Diabetes mellitus, type II	+	++	−
Cushing's syndrome	+	++	−
Renal			
End-stage renal disease	+	+	−
Nephrotic syndrome	++	++	−
Hepatic			
Obstructive liver disease	++	N	−
Primary biliary cirrhosis	++	N	+
Drugs			
Alcohol	N	++	+
Thiazide diuretics	N	+	−
Beta-blockers	N	+	−
Cyclosporin	++	N	N
Isotretinoin and etretinate	N	++	−
HIV protease inhibitors	+	++	−

−, decreased; +, increased; ++, substantially increased; HDL, high density lipoprotein; HIV, human immunodeficiency virus; N, not affected.

TABLE 3.2 SELECTED DISORDERS ASSOCIATED WITH SECONDARY HYPERLIPIDEMIA

Hypothyroidism

Hypothyroidism causes elevated LDL cholesterol levels primarily because of down-regulation of the LDL receptor (54). Because hypothyroidism can be subtle in its clinical presentation, patients presenting with hypercholesterolemia should be screened with a thyroid-stimulating hormone to rule out hypothyroidism. Thyroid replacement therapy usually results in resolution of the hypercholesterolemia. Hypothyroid patients who remain hypercholesterolemic after adequate replacement probably have an underlying lipoprotein disorder and may require lipid-lowering drug therapy.

Diabetes Mellitus

Several forms of hyperlipidemia are recognized clinically in patients with diabetes mellitus (55,56). Patients with type I diabetes mellitus who are under adequate glycemic control do not usually have hyperlipidemia, and the presence of hyperlipidemia in such patients suggests the presence of an underlying genetic lipoprotein abnormality. In contrast, patients with type II diabetes mellitus frequently have associated hyperlipidemia. Insulin resistance results in impaired capacity to catabolize chylomicrons and VLDL, as well as excess hepatic triglyceride and VLDL production (57). Type II diabetes mellitus and even glucose intolerance are often associated with a constellation of lipid abnormalities, including elevated triglyceride and VLDL cholesterol levels, increased small, dense LDL levels, and decreased HDL cholesterol levels. These lipid abnormalities are also common in persons with impaired glucose tolerance and insulin resistance in whom frank diabetes is not present. Occasionally, the triglyceride levels may be extremely elevated (>1,000 mg per dL) and predispose the patient to acute pancreatitis. Significant elevation of LDL cholesterol levels in the diabetic patient often suggests the presence of an additional lipoprotein abnormality. All patients who present with hyperlipidemia should be screened for diabetes using a fasting glucose test. Aggressive control of diabetes often results in improved control of hyperlipidemia. Furthermore, hyperlipidemia is a major risk factor for diabetic patients, and lipid disorders in patients with diabetes should be aggressively treated to decrease the risk of ASCVD (55).

Renal Diseases

Chronic renal insufficiency and especially end-stage renal disease are often associated with moderate hypertriglyceridemia caused by a defect in triglyceride lipolysis and remnant clearance (54). Nephrotic syndrome is associated with a more pronounced hyperlipidemia involving both elevated triglyceride and cholesterol levels caused by hepatic overproduction of VLDL (58). Both types of renal disease should be considered and excluded when they are suspected in patients who present with hyperlipidemia. Resolution of the nephrotic syndrome improves the lipid profile, but patients with chronic nephrotic syndrome often require lipid-lowering drug therapy. Although the lipid abnormalities in end-stage renal disease are more modest, cardiovascular risk is high, and lipid-modifying drug therapy should be seriously considered. It has been suggested that lipid-lowering therapy could slow the progression of chronic renal insufficiency (59), but clinical trials have not yet been performed to test this hypothesis.

Alcohol Consumption

Alcohol intake often exacerbates hyperlipidemia, but its effects are highly variable (60). The greatest effects of alcohol are on triglyceride levels. Alcohol consumption inhibits oxidation of free fatty acids by the liver, which stimulates hepatic triglyceride synthesis and secretion of VLDL. The usual lipoprotein pattern associated with alcohol consumption is moderate hypertriglyceridemia, although it can raise total and LDL cholesterol levels as well. Regular alcohol use also raises the HDL cholesterol level by a mechanism that is not completely understood. Patients with hyperlipidemia who drink alcohol regularly should be advised to reduce their alcohol intake.

Drug Use

Several drugs are known to influence plasma lipid levels; these are listed in Table 3.2. Retinoids such as isotretinoin and etretinate, used for acne, are known to induce substantial hypertriglyceridemia in susceptible persons. Immunosuppressive therapy used in the posttransplantation setting is well known to cause hypercholesterolemia and hypertriglyceridemia. Finally, since the introduction of the protease inhibitors for therapy for human immunodeficiency virus, it has been recognized that many of these patients develop hyperlipidemia, which appears to result from a complex and poorly understood interaction between the disease and the effect of the drugs.

PRIMARY (INHERITED) DISORDERS OF LIPOPROTEIN METABOLISM

The classification of lipoprotein disorders is useful as a guide to accurate diagnosis and effective treatment. The Frederickson and Levy classification (Table 3.3) is based on the type of lipoprotein that is elevated. This classification system has been used for several decades. It is now gradually being replaced by a classification based on the understanding of the molecular etiology and pathophysiology of the lipoprotein disorders (Table 3.4). In this section, lipoprotein disorders are presented in a way intended to facilitate a practical clinical approach. This approach is based on classifying patients first according to triglyceride levels and can lead to a more rational approach to differential diagnosis and choice of appropriate therapy.

Phenotype	Lipoprotein	Triglyceride	Cholesterol	Xanthomas	Pancreatitis	Atherosclerosis	Molecular defects
I	CM	+++	+++	Eruptive	+++	0	LPL, apolipoprotein C-II
IIa	LDL	N	++	Tendon	0	+++	LDL receptor, apolipoprotein B-100
IIb	LDL and VLDL	+	+	None	0	+++	Unknown
III	Remnants	+	++	Palmar and tuberoeruptive	0	++	Apolipoprotein E
IV	VLDL	++	+	None	0	±	Unknown
V	CM and VLDL	+++	+++	Eruptive	+++	±	Unknown

+, mildly elevated; ++, moderately elevated; +++, severely elevated; CM, chylomicron; LDL, low-density lipoprotein; LPL, lipoprotein lipase; N, not affected; VLDL, very-low-density lipoprotein; 0, minimal to no risk.

TABLE 3.3 FREDERICKSON AND LEVY CLASSIFICATION OF LIPOPROTEIN PHENOTYPES

Genetic disorder	Molecular defect	Lipoproteins elevated	Lipoprotein phenotype	Clinical findings	Genetic transmission	Estimated incidence
Familial chylomicronemia syndrome	LPL deficiency, apolipoprotein C-II deficiency	Chylomicrons	Type I	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	Autosomal recessive	Rare
Familial dysbetalipoproteinemia	Abnormal apolipoprotein E (i.e., E2/2)	Chylomicron and VLDL remnants	Type III	Palmar and tuberoeruptive xanthomas, premature atherosclerosis	Autosomal recessive or autosomal codominant	1/5,000
Familial combined hyperlipidemia	Unknown	VLDL and LDL	Type IIb, sometimes IIa or IV, rarely V	Premature atherosclerosis	Autosomal dominant	1/200
Familial hypertriglyceridemia	Unknown	VLDL, occasionally chylomicrons	Type IV, occasionally V	Usually none	Autosomal dominant	1/500
Familial hepatic lipase deficiency	Hepatic lipase	VLDL remnants	Type III deficiency	Premature atherosclerosis	Autosomal recessive	Rare
Familial hypercholesterolemia	LDL receptor	LDL	Type IIa	Tendon xanthomas, premature atherosclerosis	Autosomal codominant	1/500
Familial defective apolipoprotein B-100	Abnormal apolipoprotein B-100 (i.e., $Arg_{3500} \rightarrow Gln$)	LDL	Type IIa	Tendon xanthomas, premature atherosclerosis	Autosomal codominant	1/700

Arg, arginine; Gln, glutamine; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.

TABLE 3.4 PRIMARY LIPID DISORDERS

Disorders Associated with Triglyceride Levels >1,000 mg per dL

Severe hypertriglyceridemia (fasting triglyceride levels >1,000 mg per dL) is virtually always an indication of hyperchylomicronemia in the fasting state and points to an underlying genetic predisposition, often exacerbated by another medical condition or a hormonal or environmental factor. The major clinical complication of severe hypertriglyceridemia is acute pancreatitis, and initial treatment is focused on decreasing the triglycerides below 1,000 mg per dL to prevent this serious complication. In addition, some but not all patients with severe hypertriglyceridemia are at risk for premature ASCVD and require more aggressive therapy, even after triglyceride levels have been decreased below the 1,000 mg per dL threshold.

Familial Chylomicronemia Syndrome: Lipoprotein Lipase Deficiency and Apolipoprotein C-II Deficiency

The familial chylomicronemia syndrome (61) is characterized by presentation in childhood with acute pancreatitis and triglyceride levels >1,000 mg per dL. Recurrent abdominal pain is a common feature in children with this disorder. On physical examination, eruptive xanthomas (small papular lesions that occur in showers on the buttocks and back) are often seen. Lipemia retinalis (a pale appearance to the retinal veins) is a clue to the existence of severe hypertriglyceridemia, and hepatosplenomegaly caused by ingestion of chylomicrons by the reticuloendothelial system is often found. Premature ASCVD is not a feature of this disease.

Eruptive xanthoma. Bulbous cutaneous eruptions associated with hyperlipidemia.

Two different genetic defects can cause the familial chylomicronemia syndrome: LPL deficiency and apoC-II deficiency (Table 3.4). The hydrolysis of triglycerides in chylomicrons requires the action of LPL in tissue capillary beds, and apoC-II is a required cofactor for the activation of LPL (Fig. 3.1). Mutations in either the LPL gene or the apoC-II gene result in functional deficiency of LPL, inability to hydrolyze triglycerides in chylomicrons, and consequent massive hyperchylomicronemia. The disorder is autosomal recessive, meaning that both alleles of the LPL or apoC-II gene must be affected for the disorder to be present. Therefore, the parents of children with this disorder generally have normal or near normal triglyceride levels. Both are rare disorders, but of the two, LPL deficiency is much more common (approximately 1 case in 1 million persons) than apoC-II deficiency.

The diagnosis of the familial hyperchylomicronemia syndrome is usually made based on clinical presentation and some key laboratory features. The plasma is often lactescent, and after overnight refrigeration, a cake of chylomicrons forms on the surface. Triglyceride levels are >1,000 mg per dL and may be 10,000 mg per dL. Total cholesterol levels are also elevated, due to the presence of cholesterol in chylomicrons. Lipoprotein electrophoresis demonstrates markedly elevated chylomicrons at the origin but is not essential for making the diagnosis. The diagnosis of LPL and apoC-II deficiency can be confirmed at specialized centers by the quantitation of LPL activity in the plasma after intravenous heparin injection (postheparin lipolytic activity). Patients with suspected familial chylomicronemia syndrome should be referred to a specialized lipid center for diagnosis and management of the disorder.

The mainstay of therapy for familial chylomicronemia syndrome is restriction of total dietary fat. Consultation with a registered dietitian familiar with this disorder is essential. Caloric supplementation with medium-chain triglycerides, which are absorbed directly into the portal vein and therefore do not promote chylomicron formation, can be useful. If dietary fat restriction alone is not successful, some patients may respond to a cautious trial of fish oils (62). For patients with apoC-II deficiency, an attack of acute pancreatitis can be treated with infusion of fresh-frozen plasma to provide apoC-II in an attempt to clear severe hypertriglyceridemia and promote resolution of the pancreatitis.

Type V Hyperlipoproteinemia

Type V hyperlipoproteinemia (HLP) is a common diagnosis which continues to use the nomenclature of the Frederickson classification system. The label “type V hyperlipoproteinemia” is generally used to describe the disorder of an adult in whom triglyceride levels are >1,000 mg per dL and who does not have known familial chylomicronemia syndrome caused by LPL or apoC-II deficiency (see above). Type V HLP is also associated with risk of acute pancreatitis, which can be the initial presentation of this syndrome and is the major criterion for aggressive treatment of this condition. Type V HLP can also be associated with increased risk of

cardiovascular disease, although some patients with type V HLP do not appear to be at significantly increased risk.

Most but not all patients with type V HLP have a family history of hypertriglyceridemia, although specific genetic mutations causing type V HLP have not yet been identified. Type II diabetes mellitus or glucose intolerance frequently accompanies type V HLP, but type V HLP also occurs in people who have normal glucose tolerance. Some patients with nephrotic syndrome can develop severe hypertriglyceridemia. Estrogen replacement therapy can exacerbate moderate hypertriglyceridemia and lead to a more severe type V HLP, as can heavy alcohol consumption. Finally, treatment with isotretinoin or etretinate sometimes causes severe hypertriglyceridemia. Rarely, patients with familial dysbetalipoproteinemia (type III hyperlipidemia; see below) due to a mutation in apoE can have triglyceride levels >1,000 mg per dL, particularly if another factor is superimposed on the apoE mutation. The diagnostic evaluation of an adult patient presenting with triglyceride levels >1,000 mg per dL should be focused on a search for underlying predisposing factors and an attempt to establish a history of complications (pancreatitis and cardiovascular disease). A comprehensive personal and family history should be obtained, and all medications should be reviewed. On physical examination, lipemia retinalis and tiny eruptive xanthomas on the back or buttocks are the most specific findings for type V HLP. In contrast, larger tuberoeruptive xanthomas on the elbows or knees or palmar xanthomas (orange coloration to the creases of the palms) are more suggestive of familial dysbetalipoproteinemia (see Familial Dysbetalipoproteinemia, later). Diabetes and renal disease should always be excluded as potential contributing factors. No specific laboratory tests are required for the diagnosis of type V HLP except possibly lipoprotein centrifugation to exclude familial dysbetalipoproteinemia.

The management of type V HLP is first targeted at decreasing triglycerides to reduce the risk of pancreatitis, followed by further lipid lowering depending on the presence of CHD or other risk factors for cardiovascular disease. Women who are taking estrogens and patients taking isotretinoin or etretinate should be encouraged to discontinue these medications if triglyceride levels are >1,000 mg per dL. Diabetes mellitus should be controlled as optimally as possible. Metformin is a useful agent in the treatment of type II diabetes mellitus associated with severe hypertriglyceridemia, because it improves control of diabetes and also has a direct effect in lowering triglyceride levels. Patients should be referred to a registered dietitian for dietary counseling. In general, dietary management includes restriction of total fat as well as simple sugars in the diet. Alcohol should be avoided. Regular aerobic exercise can have a significant impact on triglyceride levels and should be actively encouraged. If the patient is overweight, weight loss can help to decrease triglyceride levels as well.

When fasting triglyceride levels remain >1,000 mg per dL despite institution of appropriate dietary and lifestyle measures and control of secondary causes, drug therapy must be considered to decrease the risk of acute pancreatitis. Drug therapy is usually straightforward, although a subset of patients is remarkably resistant to treatment. Three major drug classes should be considered for treatment of very high triglyceride levels: fibrates, nicotinic acid, and fish oils (see below). In practice, fibrates are generally recommended as the first-line agent. Nicotinic acid or fish oils should be considered for patients who fail to respond adequately to fibrates.

Frequently, patients remain significantly hypercholesterolemic after triglyceride levels are adequately controlled. This raises the difficult question of whether a second medication is needed to better control the LDL cholesterol levels. The NCEP guidelines are useful in making decisions about whether to institute further drug therapy in this setting (9). In patients who have CHD or diabetes mellitus or are at high risk for the development of CHD, who continue to have an LDL cholesterol level >130 mg per dL, most specialists recommend consideration of a second drug (usually a statin). Although it is important to recognize that an increased risk of myopathy is associated with this combination, it can be minimized by careful patient selection and by advising the patient to call the physician immediately in the event of generalized muscle pain.

Disorders Associated with Triglyceride Levels of 200 to 1,000 mg per dL

Fasting triglyceride levels <1,000 mg per dL are not generally associated with risk of acute pancreatitis. Therefore, the significance of elevated triglyceride levels of 200 to 1,000 mg per dL is their potential association with risk of ASCVD. There has been increasing recognition of the importance of elevated fasting triglycerides in this range as an independent cardiovascular risk factor (10). The major primary causes of elevated triglycerides of 200 to 1,000 mg per dL are familial hypertriglyceridemia (FHGT), familial dysbetalipoproteinemia (type III hyperlipidemia), and familial combined hyperlipidemia (FCHL). It is important to differentiate among them, because familial dysbetalipoproteinemia and FCHL are both definitely associated with increased risk of premature atherosclerosis, whereas the risk associated with FHGT is variable. The clinical approach to a patient with triglyceride levels of 200 to 1,000 mg per dL generally involves ruling out secondary causes (and, when they are found, treating them), differentiating among major primary causes, assessing the patient for the presence of ASCVD and other cardiovascular risk factors, and managing the lipid disorder based on the clinical assessment of cardiovascular risk. Because no clinical endpoint trials based on treatment of hypertriglyceridemia have been carried out and no formal guidelines for the clinical management of patients with hypertriglyceridemia are available, the clinical approach to reducing cardiovascular risk is focused on decreasing LDL cholesterol levels. However, elevated triglyceride levels can make the determination of the LDL cholesterol level difficult; can be associated with increased risk, even in the presence of a normal LDL cholesterol level; and can complicate the therapeutic approach.

Familial Hypertriglyceridemia

FHTG is a relatively common disorder characterized by moderately elevated triglyceride levels, usually with an average or only moderately elevated total cholesterol level. FHTG occurs in approximately 1 in 500 persons. It is inherited as an autosomal dominant trait but is not usually expressed until adulthood. The molecular etiology is unknown. In patients with FHTG, the VLDL level is elevated because of increased production, impaired catabolism, or a combination of the two. The LDL cholesterol level is generally not increased in patients with this disorder. Increased intake of simple carbohydrates, a sedentary lifestyle, obesity, insulin resistance, alcohol use, and estrogens can all exacerbate hypertriglyceridemia.

The diagnosis is suggested by elevated triglyceride levels (200 to 1,000 mg per dL) with normal or only mildly increased cholesterol levels (<240 mg per dL) and almost always a low HDL cholesterol level. A history of hypertriglyceridemia in at least one first-degree relative of the patient is useful in making the diagnosis. It is important to consider and rule out secondary causes of hypertriglyceridemia. In the differential diagnosis, both familial dysbetalipoproteinemia (type III HLP) and FCHL should be considered. This is not simply an academic exercise; these two conditions are associated with a significantly increased risk of ASCVD, whereas FHTG often is not. The total cholesterol level relative to the triglyceride level is usually lower in FHTG, compared with that in familial dysbetalipoproteinemia and FCHL, and the plasma apoB level is usually lower in FHTG than in the other two conditions. Determination of lipoprotein particle size using NMR reveals an increase in VLDL as the major lipoprotein abnormality.

Therapy for FHTG should begin with diet and lifestyle changes. Intake of simple carbohydrates should be reduced. Regular aerobic exercise can be very effective in decreasing triglyceride levels, as can weight loss. Alcohol use should be discouraged. Diabetes mellitus should be aggressively controlled. Lipid-lowering drug therapy can often be avoided if appropriate diet and lifestyle changes are made. However, drug therapy should be considered for patients who have triglyceride levels higher than 400 to 600 mg per dL after an adequate trial of diet and exercise changes. A fibrate is a reasonable choice as a first-line drug for FHTG, and niacin can also be considered in this condition.

Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

Familial dysbetalipoproteinemia is also commonly called *type III hyperlipidemia* (63). It is the best understood of the genetic lipid disorders that cause moderate elevation of triglyceride levels and can usually be definitively diagnosed based on a combination of clinical and laboratory parameters. Patients with familial dysbetalipoproteinemia usually present in adulthood with distinctive xanthomas or premature atherosclerosis, or asymptomatic hyperlipidemia is discovered on routine screening. Two types of xanthomas are seen in patients with familial dysbetalipoproteinemia. Tuberoeruptive xanthomas begin as clusters of small papules on the elbows, knees, or buttocks and can grow to the size of small grapes. Palmar xanthoma, orange-yellow discoloration of the creases of the palms and wrists, may also be present. Either of these xanthomas is highly suggestive of familial dysbetalipoproteinemia. Premature ASCVD is often seen in this disorder. Compared with other lipid disorders, peripheral vascular disease is particularly common in patients with familial dysbetalipoproteinemia.

The pattern of hyperlipidemia can be another clue to the diagnosis of familial dysbetalipoproteinemia. Patients generally have both hypertriglyceridemia and hypercholesterolemia, and in contrast to most other lipid disorders, the cholesterol and triglyceride levels are often elevated to a relatively similar degree. In addition, the HDL cholesterol level is often relatively normal, in contrast to most hypertriglyceridemic conditions, in which the HDL cholesterol level is usually reduced. Hyperlipidemia can be relatively mild or very severe, depending on the presence of other metabolic conditions and unknown factors.

Familial dysbetalipoproteinemia is caused by mutations in the gene for apoE (63,64). ApoE is present on chylomicron and VLDL remnants and mediates their removal from the plasma by binding to receptors in the liver (Fig. 3.1 and Fig. 3.2). Defective apoE is impaired in its ability to bind to these receptors, resulting in accumulation of chylomicron and VLDL remnants in the plasma. The most common form of familial dysbetalipoproteinemia is related to a common polymorphism of apoE. The “normal” form of apoE is known as *apoE3*, but another form, called *apoE2*, has an allele frequency of approximately 7%. The apoE2 protein, which differs from apoE3 by a single amino acid, does not bind adequately to lipoprotein receptors, resulting in defective removal of chylomicron and VLDL remnants. Homozygosity for the E2 allele (the E2/E2 genotype) is the most common cause of familial dysbetalipoproteinemia. However, most persons with the apoE2/E2 genotype do not have familial dysbetalipoproteinemia; development of this disorder appears to require an additional factor. Some of these factors include obesity, diabetes mellitus, hypothyroidism, renal disease, and alcohol use, but many patients with familial dysbetalipoproteinemia do not have an obvious predisposing factor other than the E2/E2 genotype. Another common variant of apoE, known as *apoE4*, has an allele frequency of approximately 14%. Although it is associated with elevated LDL cholesterol levels and increased risk of both CHD and Alzheimer’s disease (65), the common apoE4 allele is not associated with familial dysbetalipoproteinemia.

Because familial dysbetalipoproteinemia is treated somewhat differently from other lipid disorders, it is important to consider this diagnosis and confirm it when it is suspected. The diagnosis can be made with reasonable confidence by one of three methods. The traditional approach is to use lipoprotein electrophoresis, which demonstrates a broad beta band due to the presence of remnant lipoproteins but is expensive and not always definitive. In a second, and preferred, method, often referred to as a "beta quantification," plasma is subjected to ultracentrifugation and the cholesterol level is measured in the VLDL fraction. Because this disorder is associated with increased numbers of VLDL remnants that are rich in cholesterol relative to triglycerides, an elevated ratio of VLDL cholesterol:triglycerides of >0.3 confirms the diagnosis. A third approach is to perform lipoprotein analysis using NMR, which reveals a substantial increase in IDL sized particles. Finally, the apoE2/E2 pattern can be determined by using protein methods (apoE phenotype) or DNA-based methods (apoE genotype). The finding of an apoE2/E2 pattern by phenotyping or genotyping in a patient in whom familial dysbetalipoproteinemia is suspected confirms the diagnosis.

The absence of the apoE2/2 genotype decreases the likelihood but does not absolutely rule out the diagnosis of familial dysbetalipoproteinemia, because mutations in apoE other than E2 can also cause this condition (66). These mutations, which are much less common than apoE2, generally result in the synthesis of an apoE protein that is severely defective in its ability to bind to lipoprotein receptors. Often the inheritance of only one mutant allele is adequate to cause familial dysbetalipoproteinemia; hence the term "dominant type III hyperlipoproteinemia." Several different mutations in the apoE gene, all in the region of the protein that binds to the receptors, have been described in kindreds with this dominant form of the disease (66). Finally, several families have complete deficiency of apoE, which causes a severe form of familial dysbetalipoproteinemia (63).

Because familial dysbetalipoproteinemia is associated with increased risk of premature ASCVD, it should be actively treated. General therapeutic measures include decreased intake of dietary fat, regular aerobic exercise, weight loss (if required), and discontinuance of alcohol use. Postmenopausal women who have familial dysbetalipoproteinemia respond very favorably to estrogen replacement therapy. Although estrogens generally elevate triglyceride levels, familial dysbetalipoproteinemia is unusual in that estrogen replacement often decreases the triglyceride levels. Fibrates and niacin are each very effective in the treatment of familial dysbetalipoproteinemia. HMG-CoA reductase inhibitors have also been used with success, but they may be somewhat less effective than in other forms of hyperlipidemia.

Familial Combined Hyperlipidemia

FCHL is the most common primary lipid disorder, occurring in approximately 1 in 200 persons. Approximately 20% of patients with CHD who are younger than 60 years have FCHL (67). FCHL is characterized by a mixed dyslipidemia, usually associated with moderately elevated fasting triglycerides, moderately elevated cholesterol, and reduced HDL cholesterol. In most cases, at least one first-degree relative also has hyperlipidemia, and there is often a family history of premature CHD as well. Xanthomas are not generally seen in patients with this disorder. Visceral obesity, glucose intolerance, insulin resistance, hypertension, and hyperuricemia are sometimes associated with FCHL. Patients with FCHL almost always have a significantly elevated plasma level of apoB that is disproportionate to the LDL cholesterol level (68). This indicates the presence of small, dense LDL particles, which are characteristic of this syndrome and are considered to be highly atherogenic. The term "hyperapobetalipoproteinemia" has been used to describe the syndrome of elevated apoB with normal lipid levels, and that disorder is probably a subset of FCHL. FCHL is inherited as an autosomal dominant trait and can be expressed in childhood, but it sometimes is not fully expressed until adulthood.

The genetic basis of FCHL is not known. Studies of lipoprotein metabolism in carefully selected individuals have indicated that hepatic overproduction of VLDL is a common metabolic basis of this condition (68). It has been suggested that a subset of patients with the FCHL phenotype may be heterozygous for LPL deficiency, but LPL mutations are probably not a common cause of FCHL (69). It is likely that more than one genetic etiology of the FCHL phenotype exists (70).

The diagnosis of FCHL is suggested by the presence of a mixed hyperlipidemia with fasting triglyceride levels of 200 to 800 mg per dL, cholesterol levels of 200 to 400 mg per dL, and decreased HDL cholesterol levels in the absence of secondary causes of hyperlipidemia. A family history of hyperlipidemia and premature coronary disease is often present and supports the diagnosis. The finding of an apoB level that is elevated relative to the LDL cholesterol level suggests increased levels of small, dense LDL. The size and concentration of LDL can be determined using an NMR technique, which helps confirm the diagnosis and assists in decisions regarding therapy.

Because individuals with FCHL are at significantly increased risk of premature CHD, they should be treated aggressively. Decreased dietary intake of saturated fat and simple carbohydrates, regular aerobic exercise, and weight loss can all have beneficial effects on the lipid profile. However, many patients with FCHL require lipid-lowering drug therapy for adequate control. HMG-CoA reductase inhibitors (statins) are effective in lowering LDL cholesterol and apoB levels. Nicotinic acid decreases both LDL cholesterol and triglyceride levels and raises the HDL cholesterol level, and it is often used in combination with statins for this condition (71).

Hepatic Lipase Deficiency

HL deficiency is a very rare autosomal recessive disorder characterized by a mixed hyperlipidemia and the accumulation of lipoprotein remnants in plasma (72). HL hydrolyzes triglycerides and phospholipids in VLDL remnants and IDL and promotes their conversion to LDL (Fig. 3.2). Genetic deficiency of HL impairs the metabolism of VLDL remnants and IDL and results in their accumulation in the plasma. HL also metabolizes HDL lipids, so levels of HDL cholesterol are often slightly elevated in HL deficiency. The diagnosis of HL deficiency is suggested by a mixed hyperlipidemia with elevation in both triglyceride and cholesterol levels but an HDL cholesterol level that is normal or elevated rather than low. Familial dysbetalipoproteinemia should be excluded by apoE genotyping. Measurements of HL can be made in postheparin plasma by specialized laboratories. The association of HL deficiency with atherosclerosis is uncertain, but patients should be treated for hyperlipidemia with an approach similar to that used for familial dysbetalipoproteinemia. Acquired (usually partial) defects in HL can be seen in hypothyroidism, chronic renal insufficiency, and chronic liver disease.

Disorders Associated with Triglyceride Levels <200 mg per dL

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is caused by mutations in the gene for the LDL receptor that prevent its appearance on the cell surface or impair its ability to bind and internalize LDL (73). More than 200 different mutations in the LDL receptor have been described in patients with FH (74). FH is an autosomal codominant disorder, meaning that heterozygotes have hypercholesterolemia but homozygotes have even more severe hypercholesterolemia. The presence of one mutant LDL receptor allele results in the production of only approximately one-half the normal number of LDL receptors, whereas the presence of two mutant alleles severely reduces or eliminates functional LDL receptors. The reduction in functional hepatic LDL receptors leads to reduced clearance of plasma LDL by the liver and substantial elevations in LDL cholesterol. Elevated LDL cholesterol levels lead directly to the major complication of this condition, premature ASCVD.

Heterozygous FH occurs in approximately 1 in 500 persons in North America and worldwide, making it one of the most common single gene disorders. It is characterized by elevated LDL cholesterol levels (usually 200 to 400 mg per dL) with normal triglyceride levels and a family history of hypercholesterolemia or premature cardiovascular disease. The finding of tendon xanthomas is virtually diagnostic of FH (although these can also been seen in another disorder, as discussed later). Tendon xanthomas are most easily recognized within the Achilles tendons, where they cause thickening and irregularity. Another common location for tendon xanthomas is the digit extensor tendons of the metacarpophalangeal joints on the dorsa of the hands. Premature arcus corneae is frequently seen in patients with heterozygous FH. There is no definitive diagnostic test for heterozygous FH; the disorder is diagnosed on clinical grounds.

Heterozygous FH is strongly associated with premature ASCVD, especially CHD. Therefore, patients should be aggressively treated to lower the LDL cholesterol level. Most heterozygous FH patients require lipid-lowering drug therapy. Statins are especially effective in treatment of heterozygous FH, inducing up-regulation of the normal LDL receptor allele in the liver. If further lowering of the LDL level is required, the addition of a bile acid sequestrant to the statin is often beneficial. Niacin is also effective in FH and is often used in combination with statins and resins. The combination of all three drug classes (statin, resin, and niacin) is sometimes required to achieve LDL cholesterol level goals. If combination drug therapy is not tolerated or fails to adequately control the cholesterol levels, LDL apheresis should be considered (75) (see below).

Homozygous FH is caused by the inheritance of two mutant LDL receptor alleles, which results in the production of few or no LDL receptors and a severe defect in the catabolism of LDL. Homozygous FH occurs in approximately 1 in 1 million persons worldwide and is a much more severe clinical disorder than heterozygous FH. Patients with homozygous FH are often classified into one of two groups, based on the amount of LDL receptor activity measured in their skin fibroblasts: "Receptor negative" patients have <2% of normal LDL receptor activity, whereas "receptor defective" patients have 2% to 25% of normal LDL receptor activity (73). This classification is important, because LDL receptor–defective patients have a much better prognosis than LDL receptor–negative patients. LDL receptor–defective patients sometimes have small responses to drug therapy and can survive into the third decade of life and even beyond. In contrast, survival of the untreated LDL receptor–negative patient with homozygous FH into the third decade of life is very unusual. Clinical heterogeneity among homozygous FH patients is due to the significant genetic heterogeneity of the LDL receptor gene mutations (74).

Patients with homozygous FH usually present in childhood with cutaneous xanthomas on the hands, wrists, elbows, knees, heels, or buttocks. Some patients with

homozygous FH do not have cutaneous xanthomas but develop tuberous or tendon xanthomas on the elbows, knees, or Achilles tendons as older children or adolescents. Some degree of arcus corneae is usually present. Total cholesterol levels are usually >500 mg per dL and can be as high as 1,200 mg per dL. The devastating complication of homozygous FH is accelerated atherosclerosis, which can result in clinical sequelae even in childhood. Atherosclerosis often develops first in the aortic root and can cause aortic valvular or supravalvular stenosis. It frequently extends into the coronary ostia, which can develop significant stenoses. Carotid and femoral disease usually occurs somewhat later; the presence of femoral bruits has been reported to be a poor prognostic sign. Children with homozygous FH often develop symptoms of vascular disease before puberty, but symptoms can be atypical or go unreported, and sudden death is common. Untreated LDL receptor–negative patients with homozygous FH rarely survive beyond the second decade. LDL receptor–defective patients have a better prognosis but invariably develop clinical ASCVD by the age of 30 years and often much sooner.

A child who has severe hypercholesterolemia, relatively normal triglyceride levels, and cutaneous or tendon xanthomas should be suspected of having homozygous FH. The biologic parents and other relatives should be tested for hypercholesterolemia. A diagnosis of homozygous FH can be confirmed at specialized centers through assay of the LDL receptor activity on the skin fibroblasts after a skin biopsy is performed. Obstructive liver disease should be excluded by appropriate tests if its presence is suspected. Patients in whom homozygous FH is suspected should be referred to a specialized center. Drug therapy including a statin and a bile acid sequestrant should be tried. Atorvastatin, a new long-acting, potent statin, has been reported to have greater efficacy in homozygous FH than other statins and should be considered. Liver transplantation is effective in decreasing LDL cholesterol levels but is associated with the substantial risks of surgery and long-term immunosuppression. The treatment of choice for homozygous FH is LDL apheresis, which can promote regression of xanthomas and retard progression of atherosclerosis (76,77). The age at which LDL apheresis should be initiated is uncertain. Venous access is often problematic in young children, and central venous catheters can promote infections, which are especially risky, given the frequent aortic valvular and supravalvular flow disturbances. It is generally recommended that initiation of LDL apheresis be delayed until the patient is approximately 5 years old, except when evidence of ASCVD is present.

Because of its well-understood pathophysiology, serious consequences, and poor options for treatment, homozygous FH is a model for the development of somatic liver-directed gene therapy. Five patients with homozygous FH were treated in a gene therapy protocol involving *ex vivo* reconstitution of the LDL receptor gene into autologous hepatocytes with subsequent reimplantation (78). At 4 months, all patients had evidence of LDL receptor transgene expression by liver biopsy. LDL cholesterol levels were decreased in two patients by 17% and 22%, but in the other three patients, LDL cholesterol levels were essentially unchanged. Metabolic turnover studies in three patients documented an increased rate of LDL catabolism in the patient whose LDL cholesterol level decreased by 22% but no substantial difference in LDL kinetics in two of the patients whose LDL cholesterol levels showed little change (78). Although this pilot protocol demonstrated the feasibility of somatic gene transfer and expression of the LDL receptor in humans and some impact on LDL cholesterol levels and metabolism, future gene therapy trials await further improvements in technology. In the future, even low-level expression of the LDL receptor in an LDL receptor–negative FH patient could have the potential for substantial clinical benefit to the patient once it is combined with potent cholesterol-lowering drugs.

Familial Defective Apolipoprotein B-100

Familial defective apoB-100 (FDB) resembles heterozygous FH clinically. It is characterized by elevated LDL cholesterol levels with normal triglyceride levels, possible tendon xanthomas, and increased risk of premature ASCVD (79). In contrast to FH, FDB is caused by mutations in the receptor-binding region of apoB-100, the ligand for the LDL receptor, which impairs its binding and delays the clearance of LDL from the blood. The most common mutation that causes FDB is a substitution of glutamine for arginine at position 3500 in apoB-100 (79). However, other mutations have been reported that have a similar effect on binding of apoB to the LDL receptor. FDB is a dominantly inherited disorder and occurs in approximately 1 in 700 persons in Europe and North America.

Patients who have FDB clinically resemble those with heterozygous FH, and these disorders cannot be differentiated on purely clinical grounds. The apoB mutation can be detected in specialized laboratories so that a specific diagnosis of FDB can be made. However, there is no compelling reason to make a specific molecular diagnosis, because the clinical management of patients with FDB is similar to that of patients with heterozygous FH. If future therapies are found that are more effective in one condition than in the other, molecular diagnosis could be indicated to guide specific therapy.

Polygenic Hypercholesterolemia

Most forms of hypercholesterolemia are not single-gene disorders, but rather are caused by a complex interaction of several genetic and environmental factors. For example, genetic differences in cholesterol absorption, cholesterol synthesis, or rates of bile acid synthesis may result in very different cholesterol levels in people challenged with a diet rich in fat. Polygenic hypercholesterolemia is characterized by a cholesterol level exceeding the 95th percentile for age and gender, with triglyceride levels that are usually relatively normal. In polygenic hypercholesterolemia, LDL cholesterol levels are usually not as elevated as they are in heterozygous FH and FDB, and tendon xanthomas are not observed. In the differentiation of polygenic hypercholesterolemia from the these single-gene disorders, family studies are useful. Only approximately 7% of first-degree relatives of patients with polygenic hypercholesterolemia are hypercholesterolemic, whereas approximately one-half of the relatives of patients with FCHL, heterozygous FH, and FDB have dyslipidemia. Treatment of polygenic hypercholesterolemia follows the same guidelines as the approach to any patient with hypercholesterolemia.

DISORDERS OF HIGH-DENSITY LIPOPROTEIN METABOLISM

HDL cholesterol levels are inversely associated with CHD, independent of LDL cholesterol levels. The National Cholesterol Education Program recommends that all adults older than 20 years should be screened not only for total cholesterol levels, but also for HDL cholesterol levels. As a result of screening, patients with low HDL cholesterol levels are frequently identified. However, formal guidelines for the approach to the patient with a low HDL cholesterol level have not yet been developed. Many causes of low HDL cholesterol are secondary to other factors. Cigarette smoking, obesity, and physical inactivity contribute to a low HDL cholesterol. Type II diabetes mellitus, end-stage renal disease, and hypertriglyceridemia from any cause are all associated with low HDL. Beta-blockers, thiazide diuretics, androgens, and progestins can all reduce HDL cholesterol levels. Importantly, a low-fat diet often results in a low level of HDL cholesterol; for example, most vegetarians have low levels of HDL cholesterol. In this case, the low HDL is not considered to be associated with an increased risk of CHD, because persons who eat low-fat diets are at substantially reduced risk of premature CHD. However, many persons with low HDL cholesterol levels have a genetic cause for the low HDL cholesterol. Only a few of the genes responsible for inherited syndromes associated with low HDL levels have been identified (*e*Table 3.4.1).

***e*TABLE 3.4.1** GENETIC DISORDERS ASSOCIATED WITH LOW HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL LEVELS

Genetic disorder	Molecular defect	Metabolic abnormalities	Lipoprotein findings	Clinical findings	Premature atherosclerosis	Genetic transmission
Familial apoA-I deficiency	ApoA-I absence	Absent apoA-I biosynthesis	HDL <5 mg/dL, TG normal	Planar xanthomas, corneal opacities	++	Autosomal codominant
Familial apoA-I structural mutants	Abnormal apoA-I	Rapid apoA-I catabolism	HDL 15–30 mg/dL, TG normal or increased	Often none; sometimes corneal opacities	No	Autosomal dominant
Familial LCAT deficiency	LCAT deficiency (complete)	Rapid HDL catabolism	HDL <10 mg/dL, TG increased	Corneal opacities, anemia, proteinuria, renal insufficiency	No	Autosomal recessive
Fish-eye disease	LCAT deficiency (partial)	Rapid HDL catabolism	HDL <10 mg/dL, TG normal or increased	Corneal opacities	No	Autosomal recessive
Tangier disease	ABCA1 mutants	Very rapid HDL catabolism	HDL <5 mg/dL, TG usually increased	Corneal opacities; enlarged, orange tonsils; hepatosplenomegaly; peripheral neuropathy	+	Autosomal codominant
Familial hypoalphalipoproteinemia	Unknown	Usually rapid HDL catabolism	HDL 15–35 mg/dL, TG normal	Often none; sometimes corneal opacities	No to ++	Autosomal dominant

+, moderately increased risk of premature atherosclerosis; ++, markedly increased risk of premature atherosclerosis; ApoA-I, apolipoprotein A-I; LCAT, lecithin-cholesterol acyltransferase; TG, triglycerides.

Primary Disorders That Cause Low High-Density Lipoprotein Cholesterol Levels

Familial Apolipoprotein A-I Deficiency and Structural Apolipoprotein A-I Mutations

Complete genetic deficiency of apoA-I due to deletions of the apoA-I gene or nonsense mutations that prevent the biosynthesis of apoA-I protein result in a virtually absence of plasma HDL (80,81 and 82). The rare patients with this syndrome have corneal opacities and sometimes cutaneous or planar xanthomas. The risk of premature cardiovascular disease in patients with apoA-I deficiency is increased, but onset of CHD symptoms in these kindreds has varied from the third to the seventh decade of life. Mutations in the apoA-I coding sequence have been described in association with low levels of HDL cholesterol (usually 15 to 30 mg per dL) but are a very rare cause of low HDL cholesterol levels in the general population (83). The first of these mutants to be described was apoA-I_{Milano}, which was not found to be associated with increased risk of premature CHD, despite the low levels of HDL cholesterol seen in persons who bear this mutation. Increased premature

cardiovascular disease has not been reported in any kindred with an apoA-I mutation causing low HDL levels, suggesting that the mechanism that causes the low HDL levels may be an important determinant of the associated CHD risk. Most of these individuals do not appear to have clinical sequelae, other than corneal opacities, that are related to the apoA-I mutations. Interestingly, a few apoA-I mutations have been described in association with systemic amyloidosis, and the mutant apoA-I has been found as a component of the amyloid plaque.

Familial Lecithin-Cholesterol Acyltransferase Deficiency and Fish-Eye Disease

HDL facilitates the removal of unesterified cholesterol from cells, after which the cholesterol is esterified by the lipoprotein-associated enzyme LCAT (Fig. 3.3). Two general types of genetic LCAT deficiency have been described in humans: complete deficiency (also called *classic LCAT deficiency*) and partial deficiency (also called *fish-eye disease*) (84). Progressive corneal opacification, very low plasma levels of HDL cholesterol (usually <10 mg per dL), and variable hypertriglyceridemia are characteristic of both types. In partial LCAT deficiency, there are no other known clinical sequelae. In contrast, complete (classic) LCAT deficiency is characterized by anemia and progressive proteinuria and renal insufficiency. The diagnosis of LCAT deficiency can be made in specialized laboratories by quantitation of LCAT and cholesterol esterification activity in the plasma. Several different mutations in the LCAT gene have been described in patients with fish-eye disease and classic LCAT deficiency. Remarkably, despite the extremely low levels of HDL cholesterol and apoA-I that are seen in these patients, there is no apparent increased risk of premature ASCVD in either complete or partial LCAT deficiency. This demonstrates once again that the relationship between low HDL cholesterol levels and increased risk of CHD is complex and depends in part on the specific cause of the low HDL levels.

Tangier Disease

Tangier disease is a very rare disorder associated with accumulation of cholesterol in the reticuloendothelial system, resulting in hepatosplenomegaly, intestinal mucosal abnormalities, and pathognomonic enlarged orange tonsils (85). Intermittent peripheral neuropathy can also be seen that is caused by cholesterol accumulation in Schwann cells. Patients with Tangier disease have HDL cholesterol levels <5 mg per dL and extremely low levels of apoA-I because of their markedly accelerated HDL catabolism. Tangier disease is caused by mutations in the gene encoding ABCA1, a cellular transporter that facilitates the efflux of unesterified cholesterol and phospholipids from cells to apoA-I as an acceptor (86). Tangier disease is associated with increased risk of premature ASCVD, but this risk does not seem to be proportional to the markedly decreased HDL cholesterol and apoA-I levels. Tangier disease is an autosomal codominant disease; obligate heterozygotes have moderately reduced HDL cholesterol levels but no evidence of reticuloendothelial cholesterol accumulation. The risk of premature atherosclerosis in obligate heterozygotes is also be increased. Importantly, a substantial number of persons with low HDL cholesterol levels may have mutations in ABCA1 (87).

Primary Hypoalphalipoproteinemia

The most common inherited syndrome associated with low HDL levels is termed *primary hypoalphalipoproteinemia* or *familial hypoalphalipoproteinemia* (88,89). It is defined as an HDL cholesterol level below the 10th percentile in the setting of relatively normal cholesterol and triglyceride levels, no apparent secondary causes of the low HDL level, and no clinical signs of LCAT deficiency or Tangier disease. This syndrome is often referred to as *isolated low HDL*. A family history of low HDL cholesterol levels facilitates the diagnosis of an inherited condition, which usually follows an autosomal dominant pattern. The genetic etiology of this syndrome is unknown, although the metabolic etiology appears to be primarily accelerated catabolism of HDL and its apolipoproteins (47,90). Several kindreds with this syndrome have been described in association with an increased incidence of premature ASCVD (89), but other families have been described in which there was no evidence of increased ASCVD (91). Therefore, the direct relationship of primary hypoalphalipoproteinemia to premature CHD is uncertain and may depend on the specific nature of the gene defect or the metabolic cause of the low HDL cholesterol level.

SCREENING AND MANAGEMENT OF PATIENTS WITH LIPID DISORDERS

Screening

A general approach to the screening and management of hyperlipidemia has been developed by an expert panel convened by the NCEP of the National Institutes of Health, and the original recommendations (92) underwent one revision in 1993 and another revision in 2001 (9). These guidelines have been widely endorsed by other professional organizations, including the American Heart Association and the American College of Cardiology (26). Alternative screening guidelines issued by the American College of Physicians (93,94) were based on a number of tenuous assumptions and have not been widely accepted.

All adults older than 20 years should be screened through measurement of fasting total, LDL cholesterol, HDL cholesterol, and triglyceride levels. The initial classification according to the NCEP-ATPIII guidelines is described in Table 3.5.

Cholesterol (mg/dL)	Classification
Total	
<200	Desirable
200–239	Borderline high
≥240	High
LDL	
<100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
≥190	Very high
HDL	
<40	Low
≥60	High

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TABLE 3.5 CLASSIFICATION BASED ON TOTAL, LDL, AND HDL CHOLESTEROL LEVELS

The LDL cholesterol is usually estimated from the other lipid values using the following equation: LDL cholesterol = total cholesterol – (triglycerides/5) – HDL cholesterol. (Because VLDL usually contains triglyceride and cholesterol in a ratio of approximately 5:1, “triglycerides/5” is an estimate of the VLDL cholesterol). This formula is reasonably accurate if test results are obtained from fasting plasma and if the triglyceride level is less than 400 mg per dL. The determination of LDL cholesterol levels in patients who have triglyceride levels >400 mg per dL usually requires application of ultracentrifugal techniques in specialized laboratories, although direct assays for LDL measurement have recently become available. All further evaluation and treatment is based on other cardiovascular risk factors (Table 3.6) and the LDL cholesterol level (Table 3.7).

Age
Men ≥45 yr
Women ≥55 yr
Family history of premature CHD (CHD in male first-degree relative ≤55 yr or female first-degree relative ≤65 yr)
Cigarette smoking
Hypertension
Low high-density lipoprotein cholesterol[a]

CHD, coronary heart disease.
[a]If the high-density lipoprotein cholesterol is ≥60 mg/dL, subtract one risk factor.
Note: Diabetes mellitus is considered a CHD risk equivalent; see Table 3.7.

TABLE 3.6 MAJOR CARDIOVASCULAR RISK FACTORS TO CONSIDER IN THE TREATMENT OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Risk category	LDL-C Goal (mg/dL)	Lifestyle therapy (mg/dL)	Drug therapy (mg/dL)
CHD or CHD risk equivalent (10-yr risk >20%)	<100	≥100	≥130 (100–129 optional)
2+ risk factors (10-yr risk 10–20%)	<130	≥130	≥130
2+ risk factors (10-yr risk <10%)	<130	≥130	≥160
0–1 risk factors	<160	≥160	≥190 (160–189 optional)

CHD, coronary heart disease.

TABLE 3.7 LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C) GOALS AND CUTPOINTS FOR THERAPY

Diagnosis and Classification of Lipid Disorders

Most patients with hyperlipidemia have a primary or genetic cause for the lipid disorder. However, the clinician should always first consider whether a secondary medical disorder could be causing or contributing to the hyperlipidemia. Treatment of the underlying medical condition can often result in substantial improvement in the lipid profile and obviate the need for therapy directed at the lipids themselves. Once secondary causes have been considered, the fasting triglyceride level can be used as an initial method of stratifying patients. This approach guides both the initial diagnostic evaluation and the selection of the most effective therapy. It is important to consider the differential diagnosis of hyperlipidemia before treatment is started, because the inherited disorders discussed earlier are associated with different risks of developing CHD, different responses to drug therapy, and differences in family and genetic history.

Although extremely elevated triglyceride levels (>1,000 mg per dL) are associated with a risk of acute pancreatitis, the most important clinical consequence of lipid disorders is ASCVD, including coronary, cerebrovascular, and peripheral vascular disease. The clinical approach to a patient with a lipid disorder is significantly influenced by the presence of established ASCVD and other risk factors. Treatment of hyperlipidemia in patients with ASCVD is called *secondary prevention*, whereas treatment in patients without established ASCVD is known as *primary prevention*.

Management of lipid disorders should be based, whenever possible, on clinical trials that indicate the benefit of treatment in decreasing the risk of cardiovascular morbidity and death, although reasonable extrapolation of these data to specific subgroups is sometimes required (95). LDL cholesterol levels are strongly associated with increased risk of cardiovascular disease, and abundant data exist to show that treatment aimed at lowering LDL levels decreases the risk of clinical cardiovascular events in both secondary and primary prevention (51). Elevated triglyceride levels are also associated with increased risk of cardiovascular disease, but this relationship weakens considerably when statistical corrections are made for LDL and HDL cholesterol levels (96). Furthermore, no trials have been performed specifically to determine whether treatment to decrease triglyceride levels decreases the risk of cardiovascular disease. HDL cholesterol levels are inversely associated with cardiovascular disease, but no clinical trial data exist to date indicating that treatment aimed at elevating HDL levels leads to decreased risk of cardiovascular disease events. However, elevated triglyceride levels, decreased HDL cholesterol levels, or both are important clues to the existence of a lipid disorder and can help to identify individuals who may be at higher risk of cardiovascular disease and therefore are candidates for more aggressive therapy aimed at lowering the LDL cholesterol level. The clinical management of lipid disorders is a major component of an overall strategy directed toward the treatment or prevention of complications related to ASCVD. Some general guidelines for the nonpharmacologic management of patients with lipid disorders are given in the next section.

General Issues in the Nonpharmacologic Management of Lipid Disorders

Identify and Treat Secondary Causes of Hyperlipidemia

Secondary causes of hypercholesterolemia should be considered and excluded with appropriate laboratory testing. Many lipid experts recommend routine screening of all hyperlipidemic patients with a thyroid stimulating hormone to exclude hypothyroidism. Treatment of hypothyroidism usually results in substantial improvement in hypercholesterolemia. A fasting glucose level should always be obtained in the initial workup of a patient with hyperlipidemia. Diabetes mellitus should be controlled as effectively as possible, which often results in substantial improvement in hyperlipidemia. Nephrotic syndrome and chronic renal insufficiency should be excluded if they are clinically suspected. Patients with hyperlipidemia, especially hypertriglyceridemia, who drink alcohol should be encouraged to decrease their intake. Sedentary lifestyle, obesity, and smoking are all associated with low HDL cholesterol levels.

Counsel Patients on an Appropriate Diet

Dietary modification is an important component of the effective management of patients with lipid disorders. It is important for the physician to make a general assessment of the patient's diet, to provide suggestions for improvement, and to recognize whether a patient may benefit from referral to a dietitian for more intensive counseling. The dietary approach depends on the type of hyperlipidemia. For predominant hypercholesterolemia, the major approach is restriction of saturated fat intake. For moderate hypertriglyceridemia, it is also important to restrict intake of simple sugars. For severe hypertriglyceridemia reflecting hyperchylomicronemia, restriction of total fat intake is critical.

To lower the LDL cholesterol level by diet modification, restricting the intake of saturated fats and cholesterol is necessary. The most widely used diet is the "step I diet" developed by the American Heart Association (Table 3.8). If possible, the patient should receive specific instruction in the diet from a dietitian or qualified professional. Periodic review of the diet may be needed to reinforce the need for its continued use. Responses to a step I diet vary widely among individuals, and it can be difficult to predict which persons are most likely to benefit from dietary intervention. However, the majority of patients has relatively modest (<10%) decreases in LDL cholesterol levels on a step I diet. If therapeutic goals for LDL cholesterol are not reached after 3 to 6 months on a step I diet, the patient may be referred to a registered dietitian for more detailed dietary instruction, including the introduction of a step II diet, which is further restricted in total and saturated fat (Table 3.7). Patients with established ASCVD should be instructed on how to maintain a step II diet from the first. Almost all persons experience a decrease in HDL cholesterol levels when they decrease the amount of total and saturated fat in their diets. Patients should be reassured that a low-fat diet is beneficial in terms of reducing overall cardiovascular risk. For patients with hypertriglyceridemia, dietary counseling should also include restriction of simple sugar intake. Treatment of severe hypertriglyceridemia (triglyceride levels >1,000 mg per dL) includes restriction of all fat intake, both saturated and unsaturated.

Dietary constituent	Step I diet	Step II diet
Total fat	<30% of total calories	<30% of total calories
Saturated fatty acids	<10% of total calories	<7% of total calories
Polyunsaturated fatty acids	<10% of total calories	<10% of total calories
Monounsaturated fatty acids	10–15% of total calories	10–15% of total calories
Carbohydrates	50–60% of total calories	50–60% of total calories
Protein	15–20% of total calories	15–20% of total calories
Cholesterol	<300 mg/day	<200 mg/day
Total calories	As required to achieve and maintain desired body weight	As required to achieve and maintain desired body weight

TABLE 3.8 DIETARY GUIDELINES FOR MANAGING HYPERCHOLESTEROLEMIA

Certain types of foods and dietary additives can be used to modestly reduce cholesterol levels and in some cases obviate the need for drug therapy. Plant stanol esters were shown to reduce LDL cholesterol levels in randomized controlled trials when the esters are taken three times per day (97); are not absorbed; and are available in a variety of foods, such as spreads, salad dressings, and snack bars under the trade label Benecol. Plant sterol esters also can reduce LDL cholesterol but have not been as extensively studied, and they can be absorbed, so they are not as desirable an option. Chinese red yeast rice has been shown to reduce LDL cholesterol levels and is known to contain small amounts of lovastatin, which probably accounts for its modest cholesterol-lowering properties. Addition of psyllium to the diet can reduce cholesterol levels. Soy protein has been shown to reduce cholesterol levels. Certain types of nuts, such as walnuts, have been shown to reduce cholesterol

levels, but this approach requires the daily consumption of a very large amount of nuts and is not practical. Despite some enthusiasm, controlled trials of garlic have not demonstrated a significant cholesterol-lowering effect. Other herbal approaches, such as gugulipid, are interesting but require further study. No controlled studies have been carried out that combined several of these nonpharmacologic options to address their additive or synergistic effects.

Encourage Regular Aerobic Exercise

Regular aerobic exercise can have a positive effect on lipids. Elevated triglyceride levels are especially sensitive to aerobic exercise, and persons with hypertriglyceridemia can substantially lower their triglyceride levels by initiating an exercise program. The effect of exercise on LDL cholesterol levels is more modest. Although aerobic exercise is widely believed to raise HDL cholesterol levels, the effects on HDL are relatively modest in most individuals. Patients should also be reminded that aerobic exercise has cardiovascular benefits that extend well beyond its effect on lipid levels (98).

Encourage the Patient to Achieve and Maintain an Appropriate Weight

Obesity is often associated with dyslipidemia, especially with elevated triglyceride levels, low HDL cholesterol levels, and small, dense LDL levels. In individuals who are overweight, weight loss can have a significant favorable impact on the lipid profile and should be actively encouraged. In addition to providing counseling on other dietary issues, a dietitian should advise patients about the caloric restriction necessary for effective weight loss.

Consider Hormone Replacement Therapy in Postmenopausal Women

The effects of hormone replacement therapy (HRT) on lipid metabolism are complex (99). HRT generally decreases LDL cholesterol levels and modestly increases HDL cholesterol levels. However, HRT raises triglyceride levels, and, in women with underlying triglyceride disorders, can precipitate severe hyperchylomicronemia and acute pancreatitis. Therefore, HRT is relatively contraindicated in women with triglyceride levels >500 mg per dL, until the triglyceride levels are better controlled. When triglyceride levels are between 250 and 500 mg per dL, estrogens can be administered cautiously, but triglyceride levels should be monitored carefully. One exception to this rule is in women with type III HLP, in whom estrogen replacement can substantially improve the lipid profile, including the triglyceride levels. HRT also decreases levels of lipoprotein (a) [Lp(a)] in women (100).

The relationship of HRT to cardiovascular risk has been the topic of substantial debate. On the basis of observational data, HRT was believed to confer substantial cardiovascular benefit associated with an approximately 50% reduction in clinical cardiovascular disease events (101). However, randomized controlled trials with estrogen replacement have not duplicated the positive results seen in observational studies. Both the Heart and Estrogen/Progestin Study clinical outcome trial (102) and an angiographic study (103) have failed to show a benefit of combination estrogen/progestin HRT in secondary prevention. Therefore, prospective studies do not support a role for HRT in the secondary prevention of cardiovascular disease, at least over the short to medium term. However, many experts feel that estrogen replacement may still have a clinical role, especially in primary prevention. Understanding of the long-term role of HRT and the effect of HRT in primary prevention of cardiovascular disease awaits the results of ongoing studies, including the Women's Health Initiative Study of >50,000 asymptomatic postmenopausal women (104).

Drug Therapy for Lipid Disorders

Deciding to Initiate Drug Therapy for Dyslipidemia

The decision to use drug therapy is highly dependent on whether established CHD is present and, if it is not, on the global cardiovascular risk of the patient. Drug therapy for hypercholesterolemia in patients with established CHD is well supported by clinical trial data. Randomized controlled clinical trials have demonstrated conclusively that lowering LDL cholesterol levels in patients with established CHD reduces not only cardiovascular events and CHD mortality rates but also the total mortality rate after only 5 years. Even patients with CHD who have average LDL cholesterol levels benefit from treatment. Drug treatment to lower LDL cholesterol levels in patients with CHD is also highly cost-effective (21,105). Current guidelines (9) call for drug therapy in all patients who have established CHD and LDL cholesterol levels >130 mg per dL (9,26), with consideration given to treating patients with LDL cholesterol levels 100 to 130 mg per dL (Table 3.7). Based on these guidelines, the majority of patients with established CHD should be treated with cholesterol-lowering drug therapy. Nevertheless, it has been estimated that at least 50% of patients who have CHD are not receiving cholesterol-lowering drug therapy (106).

The decision to initiate lipid-lowering drug therapy in primary prevention is more difficult. However, data now exist that demonstrate a substantial benefit with drug therapy, even in individuals without preexisting CHD. Therefore, persons at high risk for the development of cardiovascular disease are excellent candidates for lipid-modifying drug therapy. For example, patients with diabetes mellitus have a level of absolute cardiovascular risk that is similar to that of patients with established CHD (107). Therefore, lipid disorders in diabetic patients should be treated as aggressively as in patients with established CHD; the NCEP, the American Heart Association, the American College of Cardiology, and the American Diabetes Association all have endorsed this view. Absolute global cardiovascular risk can be quantitated using a simple approach based on the Framingham Heart Study database (108) and used as a guide in the decision about whether to initiate cholesterol-lowering drug therapy. A 10-year risk of less than 20% should be considered a "CHD risk equivalent," and such patients should be treated like those with CHD or diabetes targeting the LDL to <100 mg per dL (Table 3.7). Drug therapy should be used for most individuals who have markedly elevated LDL cholesterol levels (>190 mg per dL), even if the short-term absolute risk is not particularly elevated. However, it is often difficult to decide whether to initiate drug therapy in patients who have LDL cholesterol levels that are in the gray zone between 130 and 190 mg per dL. Although it is desirable to avoid drug treatment in patients who are unlikely to develop CHD, a very high proportion of patients who eventually develop CHD have LDL cholesterol levels in this range (23). Therefore, the use of certain blood and vascular imaging tests may be useful in helping to refine the risk assessment, and therefore the decision about drug therapy (see below). In persons considered to be at low risk, the emphasis should remain primarily on dietary and lifestyle modification.

In certain patients, drug therapy should be targeted initially toward reduction of triglyceride levels rather than the LDL cholesterol level. For example, when triglyceride levels are >1,000 mg per dL, the patient has a primary triglyceride disorder and should be treated with drug therapy to prevent acute pancreatitis. When triglyceride levels are 400 to 1,000 mg per dL, the decision to use drug therapy depends on the assessment of cardiovascular risk; however, if drug therapy is used, it should usually be targeted first at reducing the triglyceride levels, because cholesterol reduction is difficult in the setting of substantially elevated triglycerides. Importantly, all of the five major clinical endpoint trials with statins have excluded persons with triglyceride levels >350 to 450 mg per dL. Therefore, no data are available regarding the effectiveness of statins in reducing cardiovascular risk in persons with triglyceride levels greater than approximately 400 mg per dL. If the triglyceride levels are <400 mg per dL, the initial emphasis in treatment should be on reduction of the LDL cholesterol level, not the triglyceride levels.

In general, a low level of HDL cholesterol justifies the use of more aggressive therapy to decrease an elevated LDL cholesterol level. In AFCAPS/TexCAPS, subjects were recruited in part on the basis of relatively low HDL cholesterol levels, and individuals with the lowest HDL cholesterol levels at baseline had the highest relative risk reduction with lovastatin therapy (109). Drug therapy targeted primarily toward raising HDL cholesterol is a potentially important strategy for reducing cardiovascular events. The VA-HIT study has provided data to support the initiation of pharmacologic therapy in patients in whom LDL cholesterol levels are controlled but HDL cholesterol levels are low. More data are required before broad recommendations are made about the use of drug therapy targeted specifically toward raising HDL cholesterol levels to prevent cardiovascular events.

Choosing a Lipid-Lowering Drug

Once the decision to initiate drug therapy has been made, the drug must be chosen. A summary of the major drugs for treating dyslipidemia is provided in Table 3.9, and the major classes of drugs are discussed here.

Drug	Major indications	Starting dose	Maximal dose	Mechanism	Common side effects
HMG-CoA reductase inhibitors	Elevated LDL			Inhibit cholesterol synthesis and up-regulate LDL receptors in liver	Myositis, arthralgias, GI upset, elevated liver function tests
Lovastatin		20 mg daily	80 mg daily		
Pravastatin		10 mg qhs	40 mg qhs		
Simvastatin		10 mg qhs	40 mg qhs		
Fluvastatin		20 mg qhs	40 mg qhs		
Atorvastatin		20 mg qhs	80 mg qhs		
Cerivastatin		0.2 mg qhs	0.8 mg qhs		
Bile acid sequestrants	Elevated LDL			Promote bile acid excretion and increase LDL receptors in liver	Bloating, constipation, flatus, elevated triglycerides
Cholestyramine		4 g daily	As tolerated		
Colestipol		5 g daily	As tolerated		
Colesevelam		3.75 g daily	As tolerated		
Nicotinic acid	Elevated LDL and triglycerides, low HDL			Decrease VLDL synthesis	Cutaneous flushing, GI upset, elevated glucose, uric acid, transaminases
Immediate-release		100 mg t.i.d.	1,000 mg t.i.d.		
Sustained-release (Niaspan)		500 mg qhs	2,000 mg qhs		
Fibric acid derivatives	Elevated triglycerides			Stimulate lipoprotein lipase; may decrease VLDL synthesis	Myositis, GI upset, gallstones
Gemfibrozil		600 mg b.i.d.	600 mg b.i.d.		
Fenofibrate		200 mg qd	200 mg qd		
Fish oils	Elevated triglycerides	1 g daily	12 g daily	Decrease triglyceride synthesis	Diarrhea, GI upset, fishy odor to breath

GI, gastrointestinal; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

TABLE 3.9 MAJOR DRUGS USED FOR THE TREATMENT OF HYPERLIPIDEMIA

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors (Statins)

HMG-CoA reductase is the rate-limiting step in cholesterol biosynthesis, and inhibition of this enzyme decreases cholesterol synthesis. There are six HMG-CoA reductase inhibitors currently available: lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), fluvastatin (Lescol), atorvastatin (Lipitor), and cerivastatin (Baycol). By inhibiting cholesterol biosynthesis, these drugs lead to increased hepatic LDL receptor expression and in some situations to decreased hepatic production of VLDL as well. Their major effect is reduction of LDL cholesterol, which they do in a dose-dependent fashion. There is wide interindividual variation in the initial response to statins, but once a patient is on a statin, the doubling of the statin dose produces a very predictable 6% further reduction in LDL cholesterol (110). Statins also reduce triglyceride levels in a dose-dependent fashion that is proportional to their effect in decreasing LDL cholesterol levels. Statins have a modest effect in increasing HDL cholesterol levels by 5% to 10% that is not dose dependent. As was reviewed earlier, considerable evidence of efficacy of statins in reducing the risk of clinical cardiovascular events is now available.

Patient acceptance of these drugs is high, because they can be taken in tablet form once a day and are generally well tolerated. Potential side effects include gastrointestinal upset, headaches, sleep disturbance, fatigue, and muscle or joint pains. Severe myopathy and even rhabdomyolysis have been reported with HMG-CoA reductase inhibitors, but these side effects are very rare. The risk of statin-associated myopathy is increased by the administration of drugs that interfere with the cytochrome P450 metabolism of statins, such as erythromycin, and related antibiotics, antifungal agents, immunosuppressive drugs, and fibrates. Severe myopathy can usually be avoided by carefully selecting the patients who will receive treatment with statins, by avoiding interacting drugs, and by informing patients of the potential of severe myopathy and advising immediate discontinuance of the drug in the event of new generalized muscle pain. Serum creatine kinase (CK) levels need not be monitored on a routine basis, because an elevated serum CK level in the absence of symptoms does not predict the development of myopathy and does not suggest the need for discontinuing the drug. The serum CK level can be measured in a patient who is taking a statin and complains of muscle pain, but a normal level does not exclude the possibility that the symptoms are caused by the drug. By convention, liver transaminases (alanine aminotransferase and aspartate aminotransferase) are monitored in patients taking statins (for example, 8 weeks after initiation of the drug and every 6 months thereafter). Other liver function tests, such as those for alkaline phosphatase and gamma glutamyl transpeptidase, are not useful and need not be used to monitor the patient. Substantial elevation (more than three times normal levels) in transaminases is relatively rare, and mild to moderate elevation (one to three times normal levels) in transaminases in the absence of symptoms need not mandate discontinuation of the medication. Severe clinical hepatitis associated with statins is exceedingly rare, if it occurs at all, and the trend is toward less-frequent monitoring of transaminases in patients taking statins.

A careful review of the five major trials with statins indicates a high level of safety (111). These five trials included a total of more than 30,000 subjects, one-half of whom were treated with active statin therapy for an average of 5 to 6 years. A review of this experience demonstrates that the incidence of suicide and fatal trauma did not differ between the patients being treated with statin and those receiving placebo. Likewise, the incidence of cancer did not differ between the two groups.

Bile Acid Sequestrants (Resins)

Bile acid sequestrants include cholestyramine (Questran), colestipol (Colestid), and colesevelam (WelChol). They bind bile acids in the intestine, interrupt their enterohepatic circulation, and accelerate the loss of bile acids in the stool. To maintain an adequate bile acid pool, the liver diverts cholesterol to bile acid synthesis. The decreased intracellular cholesterol content results in up-regulation of the hepatic LDL receptor and enhanced LDL clearance from the plasma. Bile acid sequestrants primarily reduce LDL cholesterol levels and should not be prescribed for patients with triglyceride levels higher than approximately 300 mg per dL, because this exacerbates hypertriglyceridemia. The bile acid sequestrants are very safe drugs that are not systemically absorbed. However, cholestyramine and colestipol are insoluble resins that must be suspended in liquid and are therefore often inconvenient and unpleasant to take. Colestipol is also available in large tablets, but multiple tablets must be taken each day to achieve a substantial effect. The newest bile acid sequestrant, colesevelam, was designed to combat the limitations of the traditional resins by providing a molecule able to bind a larger number of bile acids. Colesevelam is available in smaller tablets than colestipol, and because it binds more bile acids per molecule, fewer tablets are required each day to achieve the desired effect. Most side effects of resins are limited to the gastrointestinal tract; bloating and constipation can occur and are ultimately dose limiting. In addition, bile acid sequestrants may bind some other drugs (e.g., digoxin and warfarin) and interfere with their absorption, so that other medications must be taken 1 hour before or 4 hours after the bile acid sequestrants are taken.

Bile acid sequestrants can be useful in young, highly motivated patients with moderate hypercholesterolemia who wish to avoid systemic drug therapy. These are also the cholesterol-lowering drug of choice in children and in women who are pregnant, could become pregnant, or are lactating. Bile acid sequestrants are especially effective in combination therapy, and their major clinical role has evolved to use in combination with HMG-CoA reductase inhibitors, with which they are synergistic in the reduction of LDL cholesterol.

Nicotinic Acid (Niacin)

Nicotinic acid, or niacin, is a B-complex vitamin that in high doses is a lipid-lowering drug. Niacin reduces triglyceride and LDL cholesterol levels and is the most effective of the available lipid-modifying drugs in raising HDL cholesterol. Niacin is also the only lipid-lowering drug currently available that decreases Lp(a) levels (34,35,36 and 37). Its safety and efficacy were documented in the Coronary Drug Project, which demonstrated a modest benefit to the use of niacin to reduce nonfatal MI after 6 years of treatment (14) and a decrease in the total mortality rate after 15 years of follow-up (15).

The use of immediate-release crystalline niacin has been limited by the occurrence of cutaneous flushing. However, with proper administration and patient education, flushing can be minimized. The starting dose of immediate-release niacin should usually be 100 mg three times per day and always at the end of meals. Food delays the absorption and makes it much easier to tolerate with less flushing. Patients should be told to expect some flushing initially but that it will improve quickly with continued administration. Every 4 to 7 days, the dosage should be increased by 100 mg per dose, eventually reaching 500 mg three times per day. After 1 month of treatment with this dose, lipid and other pertinent levels (e.g., glucose, uric acid, and liver transaminases) should be measured. It is frequently necessary to increase the dose to 3 g per day to achieve a substantial beneficial effect on lipid levels. Rarely, immediate-release niacin is used in doses of up to 4.5 g per day. Despite adherence to the dosing protocol, some patients may continue to have flushing with certain doses (often the morning dose) and may benefit from taking aspirin 30 minutes before the niacin.

Sustained-release forms of niacin are associated with less flushing and therefore are better tolerated. However, the use of over-the-counter sustained-release niacin preparations, which are usually administered twice a day, has been limited because of several cases of severe hepatotoxicity. Niaspan is a prescription sustained-release niacin that is administered once daily at bedtime. Niaspan is better tolerated than immediate-release crystalline niacin and is probably safer than over-the-counter sustained-release niacin because of its pharmacokinetics, the once-a-day dosing, and superior quality control. In one study, Niaspan decreased triglyceride levels by 29% and increased HDL cholesterol levels by 26% at a dose of 2 g (112). Niaspan has also been directly compared to gemfibrozil and had a significantly greater effect on HDL cholesterol levels (increase of 26%), compared with 1,200 mg of gemfibrozil (increase of 13%), although gemfibrozil had a more pronounced effect on triglyceride levels (decrease of 40%) than Niaspan (decrease of 29%) (113).

Use of niacin can be limited by side effects other than flushing. It has been associated with elevation in uric acid and precipitation of gouty attacks and can also exacerbate peptic ulcer disease and symptoms of gastroesophageal reflux. Mild elevations in transaminases occur in as many as 15% of treated patients, but these elevations rarely require cessation of treatment with the medication. Niacin potentiates the effect of warfarin and should be used cautiously for patients taking warfarin. Acanthosis nigricans, a dark-colored, coarse skin lesion, is a rare side effect of niacin that is not dangerous but can be bothersome.

Niacin can elevate fasting glucose in patients with diabetes and therefore has traditionally been avoided in the treatment regimens of these patients. However, the Arterial Disease Multiple Intervention Trial confirmed the benefits of short-acting niacin and extended the safety and efficacy of this therapy to patients with diabetes (114). In this study, niacin given at an average dose of 2,500 mg per day resulted an increase in HDL cholesterol of 29% and a decrease in triglycerides of 25% in patients with and without diabetes. Interestingly, although patients with diabetes who were treated with niacin had a small increase in fasting glucose, their glycosylated hemoglobin levels did not change from baseline but were 0.3% higher than those in patients with diabetes who received placebo. No changes in hypoglycemic agents were required during the 48-week follow-up period.

Successful therapy with niacin requires careful education and motivation on the part of the patient. Its advantages are its low cost, long-term safety, and efficacy in treatment of combined hyperlipidemia and in raising HDL cholesterol levels. It is particularly useful in the secondary prevention of CHD in motivated patients who have combined hyperlipidemia and low HDL levels. Niacin can also be used successfully in combination with bile acid sequestrants and statins. In particular, patients already receiving a statin who require further LDL cholesterol reduction, in whom triglyceride levels remain elevated, or who have low HDL cholesterol levels can benefit substantially from the addition of niacin to treatment regimen (71).

Fibric Acid Derivatives (Fibrates)

Fibric acid derivatives, or fibrates, are agonists of peroxisome proliferator–activated receptor-a, a nuclear hormone receptor involved in metabolic regulation (35). This

class includes clofibrate (Atromid-S), gemfibrozil (Lopid), fenofibrate (TriCor), and bezafibrate (not available in the United States). Fibrates work by activating peroxisome proliferator–activated receptor-a to stimulate LPL activity (enhancing triglyceride hydrolysis), reduce apoC-III synthesis (enhancing lipoprotein remnant clearance), and possibly reduce VLDL production. Fibrates decrease triglyceride levels effectively (up to 40%) and generally increase HDL cholesterol levels modestly (up to 15%), but they have less ability to decrease LDL cholesterol levels.

The most straightforward clinical role of fibrates is in the treatment of severe hypertriglyceridemia to prevent acute pancreatitis. They are also highly effective in patients who have type III HLP. Fibrates are first-line agents for individuals with triglyceride levels >400 to 600 mg per dL who need drug therapy. The role of fibrates in the treatment of dyslipidemia for prevention of cardiovascular disease is supported by the Helsinki Heart Study and the more recent VA-HIT trial. Additional clinical endpoint trials with fibrates are under way.

Fibrates are generally well tolerated; the most common side effect is dyspepsia, which occurred in 6% more patients receiving treatment with fibrates than patients receiving placebo in the VA-HIT study. Myopathy has occurred, but in the absence of treatment with other drugs, it is very rare. In both the VA-HIT and BIP studies no statistically different occurrence of muscle complaints was seen between the group of patients receiving fibrates and those receiving placebo. Elevated results of liver function tests can also occur, but the frequency of elevations in transaminases more than three times the upper limit of normal was no different among patients receiving fibrates than those receiving placebo in both the VA-HIT and the BIP trials. Fibrates have also been associated with an increased risk of gallstones, but this was not seen in VA-HIT over the course of 5 years. Fibrates can potentiate the effect of warfarin and interact with certain oral hypoglycemic agents. In the World Health Organization study (37), clofibrate was associated with an increase in gastrointestinal tumors and in the total mortality rate, and therefore clofibrate is rarely used.

Omega-3 Fatty Acids (Fish Oils)

W-3 Polyunsaturated fatty acids (**W**-3 PUFAs) are useful tools in the management of severe hypertriglyceridemia. **W**-3 PUFAs are found naturally in high concentrations in fish and in flax seeds, and their use in the form of concentrated fish-oil capsules has been at the center of active investigation. Both epidemiologic and experimental studies have demonstrated the benefit of dietary fish intake and concentrated fish oils in the management of CHD (115). Most of the attention has been focused on the two active molecules in fish oil, eicosapentanoic acid (EPA) and decohexanoic acid (DHA).

W-3 PUFAs in doses of 3 to 6 g per day consistently decrease fasting and postprandial triglyceride levels (116). Fish oils are useful as a third-line therapy for patients who have severe hypertriglyceridemia that is resistant to fibrates and niacin or who are intolerant of these drugs. At least 6 g per day is usually required for a substantial effect, and many patients require 9 to 12 g per day. Fish oils should not be used to treat hypercholesterolemia and have been reported to raise LDL cholesterol levels. Interestingly, a large randomized controlled trial demonstrated that one fish-oil capsule daily was associated with a significant reduction in cardiovascular events (117).

In general, supplemental **W**-3 PUFAs are well tolerated, with patients reporting dyspepsia and a fishy aftertaste at doses of more than 3 g per day. Despite concerns, large trials have not reported increased bleeding. Supplemental **W**-3 PUFAs have been studied in a wide range of populations, including postmenopausal women who are receiving HRT, patients with diabetes, and patients who are already receiving statins and antiplatelet agents. The U.S. Food and Drug Administration (FDA) has decided that up to 3 g daily of EPA and DHA is “generally regarded as safe.” What limits the generalized use of **W**-3 PUFAs is the large number of capsules that must be ingested. Because most commercially available fish-oil preparations in the United States contain 30% to 50% EPA and DHA, patients have to take at least two to three tablets (1 g) three times daily to get the desired decrease in triglyceride levels. Fish-oil supplements are best used in patients with primary triglyceride abnormalities who cannot tolerate or chose not to take fibrates or niacin. Fish-oil supplements can also be used in combination with fibrates, niacin, or statins in patients who do not reach target triglyceride levels during treatment with those drugs.

Combination Drug Therapy

Some patients with dyslipidemia may require therapy with more than one drug. Patients with FH often have difficulty achieving LDL cholesterol goals with a statin alone but respond very well to the addition of a bile acid sequestrant. In some cases, the addition of niacin to this regimen is required for further decreases in LDL levels (71). Patients with FCHL can often reach their LDL cholesterol goal with a statin alone but frequently have persistent moderate hypertriglyceridemia, low HDL cholesterol levels, or both. In this situation, the addition of niacin to the statin can be highly effective in reducing the triglycerides and increasing the level of HDL cholesterol (71,118). Many patients with triglyceride levels higher than 400 to 600 mg per dL require initial therapy with a fibrate to decrease the triglyceride levels, but once the triglycerides are reduced, the LDL cholesterol often remains elevated. In this situation, the addition of a statin to the fibrate is effective in decreasing the level of LDL cholesterol. Although the risk of myopathy with this combination is a concern, it can be minimized with appropriate patient selection and education (118). Patients should be told of the potential for myopathy and advised to stop the medication and call their physician in the event of unexplained or generalized muscle pain. Practicing physicians are encouraged to consider combination therapy in appropriate high-risk patients or consider referring patients who may benefit from such therapy to a specialized lipid center.

Approaches to Reducing Cholesterol When Drugs Are Not Tolerated or Are Ineffective

Some patients cannot tolerate any of the existing lipid-lowering drugs at the doses required for adequate control of their lipid levels. A larger group of patients, most of whom have genetic lipid disorders, remain significantly hypercholesterolemic despite combination drug therapy. These patients, many of whom already have established CHD, are at high risk for disease progression and clinical events and should be referred to a specialized lipid center. The approaches discussed in the next sections have been used or are being developed for use in such patients.

Partial Ileal Bypass

Partial ileal bypass was developed as a surgical procedure to decrease LDL cholesterol levels in the 1960s (119). Like the mechanism of the bile acid sequestrants, partial ileal bypass interrupts the enterohepatic circulation of bile acids, resulting in up-regulation of the hepatic LDL receptor. One controlled trial of partial ileal bypass in moderately hypercholesterolemic patients who had established CHD demonstrated a 38% decrease in LDL cholesterol and a 35% decrease in the combined end point of nonfatal MI and CHD death (16). The procedure is ineffective in patients with homozygous FH (73), probably because partial ileal bypass works by up-regulating the LDL receptor (which is absent in homozygous FH). Partial ileal bypass has not been proven to be effective in patients with severe hypercholesterolemia who did not respond adequately to HMG-CoA reductase inhibitors. Diarrhea is a common side effect of this procedure, and the incidence of kidney stones, gallstones, and intestinal obstruction increases in patients who have undergone the surgery. The clinical usefulness of partial ileal bypass is limited to treatment of hypercholesterolemic patients who have established CHD, are unable to tolerate standard lipid-lowering medications, and do not wish to undergo LDL apheresis.

Low-Density Lipoprotein Apheresis or Plasma Exchange

The preferred option for management of patients who have refractory or drug-resistant hypercholesterolemia is LDL apheresis (or, if LDL apheresis is not available, plasma exchange). Plasma exchange involves removing a large volume of plasma and replacing it with an albumin/saline solution. It results in acute reduction in plasma cholesterol levels and has been used for decades on a repetitive basis for the management of severe hypercholesterolemia (120). However, plasma exchange also removes all other plasma constituents, such as HDL cholesterol and other plasma proteins, and is often associated with fatigue and other systemic symptoms. In 1996, the FDA approved a device for selective LDL apheresis (Kaneka) as an alternative to plasma exchange. In this approach, the patient’s plasma is passed over dextran sulfate columns that selectively remove LDL, and then the LDL-depleted plasma is returned to the patient (121). More recently, another device (Braun) that uses heparin columns was also approved by the FDA. Both methods are in use in many countries around the world. In contrast to plasma exchange, LDL apheresis does not decrease the levels of HDL cholesterol or other plasma constituents and is often better tolerated by patients. Clinical trials have indicated that LDL apheresis can retard progression or cause regression of CHD in patients who have severe drug-resistant hypercholesterolemia (76,77) and have even suggested a decrease in clinical cardiovascular events (77). Patients on maximally tolerated combination drug therapy who have CHD and an LDL cholesterol level >200 mg per dL or no CHD and an LDL cholesterol level >300 mg per dL are considered candidates for LDL apheresis (75). The procedure is usually performed every 2 weeks, although some patients with very severe hypercholesterolemia may benefit from undergoing the procedure every week. LDL apheresis is safe, but it requires a major time commitment on the part of the patient and a substantial expense on the part of the insurer. Nevertheless, it is considered the therapy of choice for patients with severe refractory hypercholesterolemia, and these patients should be referred to a specialized lipid center for management of their condition, including consideration of LDL apheresis.

Future Developments in the Treatment of Dyslipidemia

Small molecules that target new molecular pathways are under development for use in therapy for dyslipidemia. One example is a molecule that inhibits the intestinal bile acid transporter. These molecules inhibit the reuptake of bile acids by the intestine and therefore result in LDL receptor up-regulation and reduction of LDL cholesterol. They are expected to be particularly effective in combination with statins. Somatic gene therapy is a logical treatment of the future for patients with major genetic lipid disorders who cannot be treated adequately with available drugs (122). Homozygous FH due to deficiency of LDL receptors has been a disease model for the development of liver-directed somatic gene therapy, and a pilot clinical trial involving five patients has been completed (123). However, the development of effective

gene therapy for severe genetic dyslipidemias requires advances in the technology of gene delivery and expression.

Approach to the Patient with Low High-Density Lipoprotein Cholesterol

Many individuals are found to have a low HDL cholesterol level during routine lipid screening. The finding of a low HDL cholesterol level can be useful when it is recognized as an independent risk factor in the assessment of CHD risk and in the clinical management of LDL cholesterol levels that are in the gray zone. However, no formal guidelines have been developed specifically for the classification and management of patients with isolated findings of low levels of HDL cholesterol.

Secondary causes of low HDL levels should always be considered. Specifically, the patient should be asked about medications, smoking habits, dietary patterns, and physical activity. Decreased HDL cholesterol levels in patients with substantially elevated triglyceride levels (>500 mg per dL) are common and should not be directly addressed until the triglyceride levels have been reduced. Once secondary causes and hypertriglyceridemia are excluded, the differential diagnosis and management of low HDL cholesterol can be divided into moderately decreased HDL cholesterol levels (20 to 35 mg per dL) and severely decreased HDL levels (<20 mg per dL). Severely decreased HDL cholesterol levels <20 mg per dL accompanied by triglyceride levels <400 mg per dL usually indicate the presence of a specific genetic etiology for the condition, such as mutations in apoA-I, LCAT deficiency, or Tangier disease. A patient in whom one of these diagnoses is suspected should be referred to a specialized lipid center for further evaluation.

No formal clinical practice guidelines are available for the management of the condition of patients with isolated low HDL cholesterol. However, some general guidelines can be proposed. Secondary factors should be sought and corrected when possible. Smoking should be discontinued, obese persons should be encouraged to lose weight, and sedentary persons should be encouraged to exercise. HRT can substantially raise HDL cholesterol and should be considered in postmenopausal women. When possible, medications associated with reduced HDL cholesterol should be discontinued. Diabetes mellitus should be optimally controlled. Isolated low HDL cholesterol levels that are not a result of a secondary factor or a very low-fat diet are often associated with modestly elevated LDL cholesterol levels. In this situation, a finding of decreased HDL cholesterol levels is useful clinically as an additional independent cardiovascular risk factor supporting the use of drug therapy to reduce a slightly increased or even average LDL cholesterol level. If the LDL cholesterol level is well controlled, it can be difficult to decide whether pharmacologic intervention should be used to raise an isolated finding of a low HDL cholesterol level. In individuals with established ASCVD, drug therapy may be a reasonable approach, especially in light of the results of the VA-HIT study. In healthy individuals, no published clinical trials have demonstrated any benefit from treatment targeted specifically at increasing the level of HDL cholesterol. Every effort should be made to assess the risk of future CHD in patients with isolated findings of low HDL cholesterol levels so that appropriate clinical decisions about medical management can be made. In high-risk individuals, drug therapy targeted toward HDL cholesterol could be reasonably considered.

Statins increase HDL cholesterol levels modestly, by approximately 5% to 10%, and are not generally regarded as HDL cholesterol–raising drugs. Fibrates also increase HDL cholesterol modestly, by approximately 5% to 15%, but are most effective when triglyceride levels are elevated. Change in HDL in response to fibrate therapy is relatively slight in many patients who have low HDL cholesterol and normal triglyceride levels. Niacin is the most effective therapy targeted at increasing HDL cholesterol levels that is currently available; increases in HDL cholesterol levels up to approximately 30% have been seen. But some patients who have isolated findings of low HDL cholesterol levels do not even respond significantly to niacin therapy. New molecules designed to raise HDL cholesterol levels or promote reverse cholesterol transport are under active development.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The case for aggressive cholesterol reduction has become much stronger over the past few years as a number of new clinical studies have been published. These studies have contributed to the paradigm shift away from a focus on angiographic disease and degree of luminal stenosis and toward the concept of plaque stabilization in the prevention of acute coronary events. The enthusiasm for using aggressive lipid lowering to markedly reduce the burden of coronary morbidity and death has been apparent in a variety of editorials written by prominent scientists. Nobel laureates Drs. Michael Brown and Joseph Goldstein stated in an editorial in *Science* that “Exploitation of recent breakthroughs—proof of the cholesterol hypothesis, discovery of effective drugs, and better definition of genetic susceptibility factors—may well end coronary disease as a major public health threat early in the next century” (124). Dr. William Roberts, editor of the *American Journal of Cardiology*, has called the statin drugs “miracle drugs” that are to atherosclerosis “what penicillin was to infectious disease” (125). The purpose of this section will be to outline the issues, make practical suggestions based on current knowledge, and point out needs for future basic and clinical research.

Assessment of Cardiovascular Risk

It is widely agreed that drug therapy to reduce cholesterol is indicated in secondary prevention of clinical events and death in individuals with established CHD (26). Most experts also agree that drug therapy is indicated for primary prevention in certain high-risk individuals (such as diabetics and those with multiple risk factors) who have hypercholesterolemia that cannot be controlled adequately with diet and exercise. Therefore, in primary prevention, the major emphasis has turned to the more precise identification of high-risk individuals who are most likely to benefit from more aggressive therapy. It is now generally recognized that although traditional risk factors are reasonably good at predicting excess risk above the baseline for particular populations, they allow clinicians to predict only approximately 50% to 60% of the variation in absolute risk in individual patients (126). Therefore, factors that enhance predictive ability in an additive fashion over traditional risk factors would have considerable clinical usefulness, allowing better decisions to be made regarding the use of proven preventive therapies. Although traditional risk factors are useful in identifying some high-risk individuals, they identify only approximately one-half of the individuals who are destined to develop premature CHD. Therefore, there is great interest in the use of additional tests to identify high-risk individuals. Such information has immediate implications with regard to decisions about the use and intensity of lipid-lowering drug therapy. Those individuals at the highest risk for future CHD will benefit the most from aggressive lipid-lowering drug therapy (127). This section will briefly review some of the tests that have been proposed and are being used for the purpose of cardiovascular risk assessment.

Low-Density Lipoprotein Particle Concentration and Size

A given level of LDL cholesterol could be caused by a small number of large LDL particles or a large number of small LDL particles. A large body of epidemiologic data indicates that the latter is associated with substantially greater cardiovascular risk than the former. Therefore, determination of LDL particle concentration and size could potentially be used to aid the diagnosis of lipid disorders and to refine the identification of individuals at risk for premature CHD, who therefore deserve more aggressive therapy (128). ApoB is the major protein component of LDL, and each LDL particle has one molecule of apoB per particle. Thus, the apoB concentration is an indirect measure of the number of LDL particles. Although epidemiologic studies have been conflicting, apoB levels are probably predictive of CHD risk independent of LDL cholesterol levels (128,129). Assays to measure apoB have not yet been fully standardized. An NMR imaging–based method has become the gold standard for the quantitation of LDL particle size and LDL particle number (130). Some clinicians choose to use this test, which is FDA-approved and commercially available, to assist them in the treatment of patients with LDL cholesterol levels that are in a borderline range. The finding of an increased concentration of small, dense LDL particles could reasonably lead to the initiation of drug therapy, even if the LDL cholesterol level itself were not significantly elevated.

Lipoprotein(a)

Lp(a) is similar to LDL, but it is characterized by the presence of an additional protein called “apolipoprotein(a)” (131). Lp(a) levels are highly genetically determined, and the gene for apolipoprotein(a) is the major genetic factor controlling the plasma levels of Lp(a). A large number of epidemiologic and observational studies have indicated that Lp(a) levels are associated with premature ASCVD, independent of LDL cholesterol levels (131). A recent prospective study of the Framingham offspring cohort confirmed that the relative risk for premature CHD was increased in the presence of an elevated Lp(a) level (132). The mechanism by which Lp(a) promotes cardiovascular disease is not well understood, although it may inhibit activation of plasminogen to plasmin. Elevated Lp(a) levels may not have the same significance in all ethic groups; in studies of African-Americans, Lp(a) levels have not been associated with CHD. In contrast, elevated levels of Lp(a) are common in Asian Indians who have premature CHD and may play an important role in the early CHD often seen in this population. End-stage renal disease is strongly associated with elevated levels of Lp(a), which may play a role in the cardiovascular disease common in patients with such disease. Lp(a) levels increase in women after menopause and can be reduced with HRT. Some data suggest that an elevated Lp(a) level invites less risk after decrease of an elevated LDL cholesterol level (133). Therefore, an elevated Lp(a) level should be considered in decisions about whether to initiate drug therapy aimed at lowering the LDL cholesterol level. Although there is no proof that reducing levels of Lp(a) reduces the risk of cardiovascular disease, niacin is the only lipid-lowering drug that consistently lowers the Lp(a) level, and it should probably receive extra consideration as a treatment in the hypercholesterolemic patient who has an elevated Lp(a) level. Finally, postmenopausal women with elevated Lp(a) levels should receive special consideration for estrogen replacement therapy. However, the major emphasis in the setting of an elevated Lp(a) should remain on reduction of the LDL cholesterol level.

Homocysteine

Homocysteine levels have a continuous graded relationship with all types of ASCVD (134). This association is independent of known risk factors, and the mechanism has not yet been established. Homocysteine levels are inversely associated with folic acid intake and serum folate levels (135). Therefore, in addition to providing evidence of higher CHD risk, an elevated serum homocysteine level may have therapeutic implications with regard to folic acid supplementation. Randomized controlled clinical trials of the use of folic acid supplementation to lower homocysteine levels in the prevention of CHD are under way, but results have not yet been

reported.

Inflammatory Markers

There has been increasing interest in the concept of atherosclerosis as an inflammatory disease (136). This concept has been fueled by the finding that serum markers of inflammation predict future cardiovascular events (137,138). The most-studied marker has been the high-sensitivity C-reactive protein, which has been found to be associated with increased cardiovascular risk in multiple prospective studies. Other inflammatory markers that have also been found to be predictive of risk include interleukin-6, serum amyloid A, and soluble intercellular adhesion molecule 1 (139). In a head-to-head comparison of different serum-based markers, inflammatory markers were clearly additive to lipid markers in predicting future cardiovascular risk (140). The clinical use of certain markers, such as high-sensitivity C-reactive protein, in selected patients for improvement of cardiovascular risk assessment may be reasonable.

Fibrinogen

Fibrinogen levels have been found to have a significant association with premature CHD in several studies (141). The mechanism by which fibrinogen promotes CHD is not well understood but may involve at least in part its effects on plasma viscosity.

Genetic Polymorphisms

Genetic variation plays a role in determining cardiovascular risk. A variety of single-nucleotide polymorphisms in different candidate genes have been reported to be associated with CHD in univariate analyses. In theory, a panel of a large number of single-nucleotide polymorphisms could be used to predict future cardiovascular risk. This type of panel is not yet ready for use in clinical decision-making but is under active study.

Noninvasive Vascular Imaging

In theory, the use of noninvasive tests to examine vascular beds for presence of atherosclerotic plaque before the development of symptoms is an attractive way of identifying high-risk individuals who may be candidates for more aggressive therapy to reduce LDL cholesterol levels (142). Several different modalities are under development and clinical investigation with regard to this concept. Because acute coronary events are frequently caused by lesions that represent <50% stenosis of the vessel, the goal in identifying individuals at high risk for coronary events is not to identify those with significant coronary stenoses (as for exercise testing), but rather to identify individuals who are at higher statistical risk of developing vulnerable coronary lesions and having acute coronary events. Therefore, the most promising methods are likely to be those that sensitively and specifically detect and quantitate atherosclerosis. B-mode carotid ultrasound can be used to quantitate carotid IMT in asymptomatic individuals, and this technique has been used to demonstrate that lowering lipid levels can retard the progression of intimal thickening in comparison with that in control patients (143,144 and 145). Prospective studies based on large populations, such as the Atherosclerosis Risk in Communities (ARIC) study and Cardiovascular Health Study (CHS), have shown that carotid IMT is predictive of future coronary events, independent of known cardiovascular risk factors. Another marker for coronary atherosclerotic plaque is coronary calcification (146). Electron-beam tomography can detect and quantitate coronary calcification as a specific marker for atherosclerotic plaque (147). Coronary calcification is highly correlated with the extent of atherosclerotic disease on autopsy (148,149) and with the extent of angiographic coronary disease (147). Several prospective studies have indicated that the extent of coronary calcification is associated with the probability of a future coronary event (150). Therefore, both carotid IMT and coronary calcification could potentially be used as noninvasive methods for stratifying selected asymptomatic persons according to cardiovascular risk, to aid physicians in making more informed decisions regarding drug therapy for cholesterol reduction.

Use of Lipid-Lowering Drug Therapy in Underrepresented Subgroups

Women

Women have been traditionally underrepresented in lipid-lowering trials, although trials such as 4S, Cholesterol and Recurrent Events, LIPID, and AFCAPS/TexCAPS included women. Subgroup analyses have indicated that women are as likely as men to benefit from cholesterol reduction. On the basis of available data, women with CHD or diabetes or who have high cardiovascular risk should receive treatment as aggressive as that in men. Premenopausal women are, on average, at substantially lower risk of developing premature CHD than men of the same age, and therefore the threshold of LDL cholesterol levels for institution of drug therapy should probably be higher for women than for men. Nevertheless, in women at high risk, such as those with diabetes mellitus or strong family histories of premature CHD, it is appropriate to consider more aggressive therapy. HRT may be considered for postmenopausal women before initiation of lipid-lowering drug therapy, because estrogens can lower LDL cholesterol levels (as well as raise HDL cholesterol). Postmenopausal women who are not receiving estrogen replacement are at similar risk to that in men for developing CHD and therefore should be treated for hypercholesterolemia with a similar degree of intensity.

Elderly Individuals

Some secondary prevention trials have included patients as old as 75 years. Subgroup analyses have indicated that age is not a determinant of benefit from therapy and that patients in older age groups derive benefit similar to that in younger patients. Given the wealth of data demonstrating the benefit of cholesterol reduction in secondary prevention, it is rational to treat elderly persons with CHD as aggressively as younger persons with CHD. However, the decision to use cholesterol-lowering drug therapy should be influenced by the general health of the patient, the need for other medications, and the patient's ability to tolerate the lipid-lowering medication. Primary prevention of CHD using cholesterol-lowering drugs is a more difficult issue in elderly patients. The West of Scotland study included patients as old as 64 years; a subgroup analysis of patients older than 55 years indicated a significant reduction in MI and CHD death, similar to that seen in the group of patients younger than 55 years (32). The approach to hypercholesterolemia in elderly persons without CHD should probably be influenced primarily by the general health and vigor of the patients as well as by their degree of interest in being treated aggressively. For example, a healthy, active 80-year-old with an elevated LDL cholesterol level who wants to do everything possible to prevent his or her first MI should not be denied drug therapy simply on the basis of age.

Role of Antioxidants in Reduction of Risk of Coronary Heart Disease

The Probucol Quantitative Regression Swedish Trial used probucol as an antioxidant to treat patients who had femoral atherosclerosis. No difference was seen between the group of patients who were treated with probucol and the control group with regard to the extent of femoral atherosclerosis (151). Two large trials failed to demonstrate any effect on cardiovascular disease from beta carotene supplementation with relatively low doses of either 50 mg every other day (152) or 30 mg daily (153). The Cambridge Heart Antioxidant Study compared the use of two different doses of vitamin E supplementation (400 and 800 IU per day) to placebo in 2,002 patients with established CHD (154). The analysis was performed by pooling the two different treatment groups and comparing them to the placebo group. Combined CHD death and nonfatal MI (the primary end point) was significantly reduced (by 47%; $p < .005$) in the groups treated with vitamin E. This difference was entirely due to a reduction in nonfatal MI (14 events in the group of patients receiving treatment vs. 41 events in the control group). Although the trial was not powered to address the total mortality rate, the rate was actually increased in the group of patients receiving vitamin E (36 deaths) compared with that in the control group (27 deaths). In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Prevenzione Trial (117), 11,324 Italian subjects with recent MI (<3 months before enrollment) were randomly assigned to receive 300 mg per day of synthetic vitamin E, 1 g per day of **W**-3 PUFA, or both, or placebo in a 2-by-2 factorial design and followed for 3.5 years. The primary combined efficacy end points were death, nonfatal MI, and stroke. Treatment with **W**-3 PUFAs without vitamin E significantly lowered the risk of the primary end point. The Heart Outcomes Prevention Evaluation study (155) involved 9,541 subjects aged 55 years or older with both symptomatic and asymptomatic cardiovascular disease. Subjects were randomly assigned to receive naturally occurring vitamin E (400 IU) or placebo and followed for 4.5 years. This trial used a two-by-two factorial design that also involved the angiotensin-converting enzyme inhibitor ramipril. No clinical benefit or adverse events were noted in the group of patients treated with vitamin E. The Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) trial (156) investigated the effect of high-dose vitamin E supplementation on cardiovascular disease outcomes in hemodialysis patients with preexisting heart disease. One hundred and ninety-six hemodialysis patients aged 40 to 75 years were randomly assigned to receive 800 IU per day of vitamin E or placebo in a double-blind design. Patients were followed for approximately 17 months. The primary end points included fatal and nonfatal MI, ischemic stroke, peripheral vascular disease, and unstable angina. Secondary outcomes included cardiovascular mortality and total mortality rates. Results of this study demonstrated a highly significant reduction in the composite primary outcome measure that was chiefly attributable to a 70% reduction in acute MI. No effect on the total mortality rate or the cardiovascular mortality rate was seen. Therefore, although most of the results of vitamin E supplementation trials have been negative to date, the results of the SPACE trial suggest that patients who have elevated levels of oxidant stress may benefit from therapy with vitamin E. Additional clinical trials are under way that are examining the important question of whether antioxidant therapy will reduce cardiovascular events in both secondary and primary prevention.

THE FUTURE

Virtually all experts agree that cholesterol-lowering drugs are underused and that more frequent use will lead to even more impressive reductions in coronary events in the future. Nevertheless, many clinical issues remain unresolved in the treatment of lipid disorders. Although a thorough discussion of all of these issues is beyond the scope of this chapter, several are discussed here: (1) the use of additional diagnostic tests for determining CHD risk as a guide to intensity of lipid-lowering drug therapy in primary prevention, (2) the use of lipid-lowering drug therapy in particular subgroups underrepresented in clinical trials, and (3) the use of antioxidant therapies.

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4

EXERCISE AND PHYSICAL ACTIVITY

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Physical activity results in increased exercise capacity and physical fitness, which may lead to many health benefits. Individuals who are more physically active appear to have lower rates of all-cause mortality, probably due to a decrease in chronic diseases, including coronary artery disease (CAD). This low rate may result from an improvement in cardiovascular risk factors, enhanced fibrinolysis, improved endothelial function, decreased sympathetic tone, and other as-yet-undetermined factors.

Regular endurance and resistance exercise leads to favorable alterations in the cardiovascular, musculoskeletal, and neurohumoral systems. These alterations result in a training effect that allows an individual to do increasing amounts of work at a lower heart rate and blood pressure. Such an effect is particularly desirable in patients with CAD, because it allows increased activity with less ischemia.

Current recommendations from the Centers for Disease Control and Prevention (CDC) (8) state that every American should participate in at least moderately intense physical activity for at least 30 minutes on most, if not all, days of the week. Unfortunately, too many Americans are sedentary and perform too little physical activity. This is especially true among racial minorities, low-income groups, the elderly, and women. It is important to educate the public regarding the benefits of physical activity and to help encourage more leisure-time exercise in underactive individuals.

GLOSSARY

Calorie: a unit of energy equal to the amount of heat required to raise the temperature of 1 kg of water 1°C.

- 1,000 cal = 1 kcal
- 5 kcal = 1 L oxygen consumed
- 7,000 kcal = 1 kg fat (2.2 lb)

Endurance exercise: Dynamic exercise involving high-repetition movements against low resistance. Endurance exercise also is called *isotonic exercise* because muscle shortening develops predominantly without much muscle tension. Examples include walking, jogging, swimming, and cycling. The term also is referred to as *aerobic exercise*.

Exercise: A form of physical activity; planned physical activity with the goal of achieving or preserving physical fitness.

Maximal oxygen uptake ($\dot{V}O_2$max): Maximal rate of oxygen consumption per minute. $\dot{V}O_2$max is a reliable, reproducible, and objective measure of physical fitness.

Metabolic equivalent (MET): One MET is equal to the amount of oxygen per minute required by the body during resting conditions.

1 MET = 3.5 mL oxygen/kg body weight/minute

Physical activity: Skeletal muscle contraction resulting in bodily movement that requires energy utilization.

Physical fitness: A set of attributes that enables an individual to perform physical activity.

Resistance exercise: Exercise involving low-repetition movements against a high resistance. An example is weightlifting.

Training effect: The ability to achieve a higher peak workrate and $\dot{V}O_2$max with lower heart-rate responses to submaximal levels of exercise compared with pretraining conditions.

Volume of oxygen ($\dot{V}O_2$): Amount of oxygen consumed per minute and expressed as the absolute value or as liters per kilogram of body weight per minute.

$\dot{V}O_2$ = stroke volume × heart rate × arteriovenous oxygen difference

Work: Force × distance.

Workrate: Work per unit of time.

INTRODUCTION

Physical Activity and Public Health

Nearly 60 million (approximately one of every four) persons in the United States have cardiovascular disease (CVD). Of these, 50 million suffer from hypertension, 12 million have CAD, and more than 4 million have suffered a stroke (1). Despite the declining mortality rate observed since 1950 and due to cardiovascular illness, 43% of all deaths are currently attributed to CVD. The morbidity and subsequent disability incurred from cardiovascular illness have far-reaching medical and socioeconomic implications and an estimated total cost of $327 billion in 2000. Thus, continued major efforts in preventing CVD are needed to reduce the overall incidence of atherosclerotic disease and stroke (1).

Physical inactivity is a risk factor for CVD. Regular exercise results in an increase in exercise capacity and lower myocardial oxygen demand, leading to cardiovascular benefits such as lower mortality rates and fewer symptoms of CAD (2,3 and 4). Moreover, the long-term cost-effectiveness of an unsupervised exercise training program has been estimated to be less than $12,000 per year of life saved for all individuals (5). The Surgeon General's report on physical activity and health (6) has summarized the findings of five national surveys by the CDC. The results indicate that too many American adults lead sedentary lifestyles, with only 14% of respondents reporting regular vigorous physical activity (i.e., activity performed at 50% of maximum cardiorespiratory capacity for 20 minutes at least three times per week). Approximately 25% of adults report regular moderate physical activity (i.e., activity performed at 3 to 6 METs for 30 minutes on most days of the week), and 25% participate in no leisure-time physical activity (6). More recent data from the National Health Interview Survey (7) estimate that 40% of American adults are sedentary.

Many factors contribute to physical inactivity in adults, but the most-cited reasons are lack of time and risk of injury. Although most Americans are aware that exercise is beneficial for good health, this knowledge does not strongly correlate with physical activity. Other important barriers are lack of companionship or encouragement and the absence of an appropriate environment for exercise (e.g., no available paths for walking or biking, poor weather, or dangerous neighborhood). Regular physical activity is more strongly associated with enjoyment of exercise, confidence in athletic ability, and participation in low to moderate levels of activity (8).

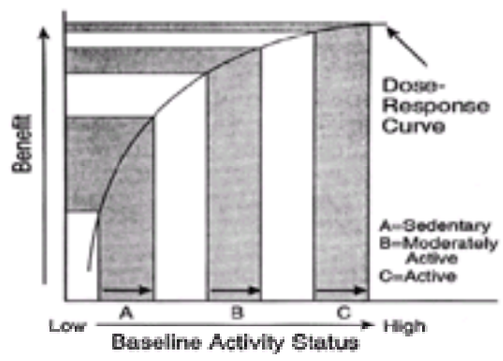
Organizations, including the CDC, the American College of Sports Medicine (ACSM) (8), and the American Heart Association (AHA) (9), have published consensus reports and recommendations for the promotion of physical activity in an attempt to increase the leisure-time activity of all Americans. In a joint statement (8), the CDC and ACSM recommend that all adults participate in at least 30 minutes of moderate-intensity exercise on most, if not all, days of the week. Moderate-intensity physical activity is achievable for most adults and can be accomplished with many routine activities such as walking briskly (i.e., 3 to 4 miles per hour) for 2 miles, biking at 10 miles per hour, swimming, house cleaning, lawn mowing, and gardening. These recommendations emphasize that the 30 minutes of activity can be obtained intermittently throughout the day in 10-minute increments or in one continuous session. Thus, physical activity can become part of the daily routine and may involve using stairs instead of an elevator, walking or biking instead of driving, calisthenics, or use of exercise equipment while watching television (8) (*e*Table 4.0.1). An increase in lifestyle physical activity can be as effective as participation in traditional, structured exercise in improving caloric expenditure, blood pressure, and cardiorespiratory fitness (10).

***e*TABLE 4.0.1** EFFORT INTENSITY FOR VARIOUS COMMONLY PERFORMED PHYSICAL ACTIVITIES

Light (<3.0 METs[a] or <4 kcal/min)	**Moderate (3.0–6.0 METs or 4–7 kcal/min)**	**Hard/vigorous (>6.0 METs or >7 kcal/min^{-1})**
Walking, slowly (strolling)(1–2 miles/h)	Walking, briskly (3–4 miles/h)	Walking, briskly uphill or with a load
Cycling, stationary (<50 W)	Cycling for pleasure or transportation (£10 miles/h)	Cycling, fast or racing (>10 miles/h)
Swimming, slow treading	Swimming, moderate effort	Swimming, fast treading or crawl
Conditioning exercise, light stretching	Conditioning exercise, general calisthenics, racket sports, table tennis	Conditioning exercise, stair ergometer, ski machine, racket sports, singles tennis, racquetball
Golf, power cart	Golf, pulling cart or carrying clubs	
Bowling		
Fishing, sitting	Fishing, standing/casting	Fishing in stream
Boating, power	Canoeing, leisurely (2.0–3.9 miles/h)	Canoeing, rapidly (³4 miles/h)
Home care, carpet sweeping	Home care, general cleaning	Moving furniture
Mowing lawn, riding mower	Mowing lawn, power mower	Mowing lawn, hand mower
Home repair, carpentry	Home repairs, painting	

MET, metabolic equivalent.
[a] 1 MET = 3.5 kcal/kg/min.
From Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;273:402–407, with permission.

It is advised that individuals who are inactive should increase their physical activity gradually until they are moderately active for 30 minutes per day. Those who participate in light levels of exercise or who are irregularly active should attempt to exercise more regularly, at least at moderate levels. The beneficial effects depend on how active the individual is at baseline. For example, sedentary people will gain the most, followed by moderately active individuals, and then active individuals (8) (*e*Fig. 4.0.1).



***e*FIGURE 4.0.1** The relationship between baseline physical activity and health benefits is depicted. The greatest benefits are observed in patients who are least active and increase their physical activity. (From Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;273:402–407, with permission.)

Physical Activity, Exercise, and Fitness

Physical activity, fitness, and exercise are related entities but have different definitions. The definitions described below are as defined in the Surgeon General's report on physical activity and health (6).

Physical Activity

Physical activity is skeletal muscle contraction resulting in bodily movement that requires energy use. Further classification can be based on mechanical and metabolic aspects of contraction. Mechanical properties relate to whether limb movement occurs and includes isometric contraction (i.e., muscle tension without limb movement) and isotonic contraction (i.e., limb movement without change in muscle tension). Metabolic properties of physical activity are divided into categories of aerobic contraction (i.e., energy derived in the presence of oxygen) and anaerobic contraction (i.e., energy derived in the absence of oxygen). Most activity involves a

combination of the above parameters (6).

The intensity of physical activity can be described as the energy required per unit of time for the performance of an activity and can be obtained by measuring the oxygen uptake required for the activity. This intensity can be expressed in units of oxygen, kilocalories (measure of heat), or kilojoules (measure of energy). In addition, intensity of activity can be expressed by measuring the force of muscle contraction and is expressed in pounds or kilograms. Alternatively, physical activity can be measured in relative terms by relating the amount of activity in relation to the individual's capacity and is usually expressed as a percentage, such as the percentage of $\dot{V}O_2$max or the percentage of maximum heart rate (6) (Table 4.1).

	Endurance-type activity					
	Relative intensity		Absolute intensity (METs) in healthy adults (age in yr)			
				Middle-aged		
Intensity	$\dot{V}O_2$max/heart rate reserve (%)	Maximum heart rate (%)	Young (20–39)	(40–64)	Old (65–74)	Very old (80+)
Very light	<25	<50	<3.0	<2.5	<2.0	≤1.25
Light	25–39	50–63	3.0–4.7	2.5–4.4	2.0–3.5	1.26–2.20
Moderate	40–59	64–76	4.8–7.1	4.5–5.9	3.6–4.7	2.30–2.95
Hard	60–84	77–93	7.2–10.1	6.0–8.4	4.8–6.7	3.00–4.25
Very hard	≥85	≥94	≥10.2	≥8.5	≥6.8	≥4.25
Maximal[a]	100	100	12.0	10.0	8.0	5.0

MET, metabolic equivalent; $\dot{V}O_2$max, maximal oxygen uptake.
[a]Based on 8 to 12 repetitions for persons <60 years old and 10 to 15 repetitions for persons >60 years old.
[b]Maximum values are mean values achieved during maximum exercise by healthy adults. Absolute intensity (METs) values are approximate mean values for men. Mean values for women are approximately 1 to 2 METs lower than those for men.
Adapted from U.S. Department of Health and Human Services. Physical activity and health: a report of the surgeon general. Atlanta: Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Promotion, 1996.

TABLE 4.1 CLASSIFICATION OF PHYSICAL ACTIVITY INTENSITY[a]

Physical Exercise

Physical exercise is a form of physical activity and is defined as planned physical activity with the goal of achieving or preserving physical fitness. *Exercise training* may be a more accurate term, because similar activity may be viewed as exercise by one person and not by others (6).

Physical Fitness

Physical fitness is a set of attributes that enables an individual to perform physical activity (8). Physical fitness is best assessed by measures of $\dot{V}O_2$max. Many studies estimate fitness levels by measurement of the peak workrate or MET level achieved during graded exercise tests. Numerous exercise training studies have evaluated the frequency, intensity, and duration of the training sessions. Based on these data, it appears that the most consistent benefit on $\dot{V}O_2$max is observed when exercise training is performed at least three to five times per week for 12 or more weeks at an intensity of approximately 60% of the maximum heart rate, or 50% of $\dot{V}O_2$max, for 20 to 60 minutes (11). Improvements in $\dot{V}O_2$max of 15% to 30% are usually achieved using the above guidelines (11). It also appears that intermittent activity can confer fitness benefits similar to those of continuous activity at similar exercise intensities and total duration (12).

Physical Activity Patterns in the United States

In the past, most physical activity was occupationally related. However, technological advances of the twentieth century have rendered many jobs less physically demanding; thus, exercise must now be obtained during leisure time. General awareness of the benefits of physical activity has increased over the past 30 years; however, data regarding trends before 1980 are limited. Several studies between 1988 and 1992 have addressed the patterns in adult Americans and are summarized in the 1996 Surgeon General's report on physical activity and health. The patterns of physical activity in American adults vary with regard to sex, age, ethnicity, socioeconomic status, education, and a variety of other social factors (6) (eTable 4.1.1). These data concur with those from the more recent National Health Interview Survey (7).

***e*TABLE 4.1.1** ACTIVITY PATTERNS AMONG VARIOUS DEMOGRAPHIC GROUPS IN THE UNITED STATES[a]

	No leisure-time physical activity	Regular, moderate physical activity	Regular, vigorous physical activity
Total	28.7	23.5	14.2
Males	26.5	24.9	12.6
Females	30.7	22.3	15.6
White	27.4	24.3	14.8
Black	38.4	17.6	9.4
Hispanic	34.8	23.4	11.9
<12 years education	28.7	17.0	8.0
College education	22.6	28.3	21.6
Income <$10,000	41.5	20.3	8.8
Income >$50,000	17.8	27.7	20.3
Employed	25.8	22.5	13.8
Unemployed	36.0	21.6	10.1
Married	28.5	22.5	15.3
Never married	22.4	28.1	11.0

[a]Values represent % of Americans over the age of 18 who participate in no physical activity, moderate physical activity, or vigorous physical activity.

When the surveys were analyzed according to gender, it appeared that more women than men were inactive, more men than women engaged in regular, moderate physical activity, and approximately an equal number of men and women exercised vigorously (6). According to age, adolescents are less active than children—an observation that is more pronounced in girls than boys. The percentage of physically inactive adults increases with age, with no leisure-time physical activity reported among 38% to 50% of people older than 75 years. Interestingly, vigorous activity increases with age in both men and women up to 74 years of age and then decreases after age 75 (6). This may be because the elderly have more leisure time or because activity that is considered moderate in middle age, such as walking, is considered vigorous in the elderly due to the diminished cardiorespiratory capacity that occurs with aging.

Approximately 16% of the United States population consists of racial minorities, and the impact of CVD among these individuals is now being realized (13). Levels of physical activity are lower in blacks and Hispanics compared with whites and lower in minority women compared with men of these groups. Whereas approximately 25% of whites are inactive, approximately 40% of minority women and 30% of minority men participate in no leisure-time physical activity (6). In addition, 25% of whites participate in moderate leisure-time physical activity, but only 21% of black men and 15% of black women are moderately active. The trend for Hispanics is similar to that for whites (6).

Groups reporting the lowest amounts of exercise are at highest risk for CVD. The estimated age-adjusted prevalence of CVD in adults for non-Hispanic whites is 30% for men and 24% for women; for non-Hispanic blacks, 41% for men and 40% for women; and for Mexican Americans, 29% for men and 27% for women (1).

Physical inactivity also appears to correlate with various socioeconomic factors. Participation in leisure-time physical activity is positively associated with higher education, higher income, employment status, and marriage (6). Evidence to date suggests that socioeconomic status is an important and independent factor in the etiology and progression of CVD. When socioeconomic status is characterized by the principal measures of education, occupation, and income, there appears to be a consistent, inverse relation between these indicators and CVD risk factors—primarily hypertension, obesity, cholesterol levels, and cigarette smoking (14). Keil et al. (15) have demonstrated that among men in the Charleston Heart Study, there were no differences in all-cause or cardiovascular mortality between black and white men when socioeconomic status was controlled. The pathophysiologic mechanisms linking socioeconomic status to CVD are unclear. In addition to the greater prevalence of risk factors in persons of lower socioeconomic status, issues of behavior, coping, and access to health care should also be considered.

Finally, physical activity varies with the geographic location and season of the year. Highest levels of inactivity are reported in the South and the lowest levels are

reported in the West. Americans are more physically active during the spring and summer months than during the winter (6).

PHYSICAL ACTIVITY AND HEALTH: EPIDEMIOLOGIC OBSERVATIONS AND BIOLOGIC MECHANISMS

All-Cause Mortality

Data accumulated over the past 50 years have confirmed the health benefits of exercise. Epidemiologic studies have shown that active individuals are at lower risk for developing many chronic diseases (8). In addition, all-cause mortality rates are higher in less active people than in those who are more active (16,17). A large-scale epidemiologic study involving 13,375 women and 17,265 men between the ages of 20 and 93 years reported a significant inverse association between leisure-time physical activity and all-cause mortality (18). Approximately 12% of deaths per year in the United States are associated with inactivity (19). The risk for all-cause mortality decreases among inactive individuals who become more physically active (20). Importantly, recent data from an evaluation of 5,209 men and women demonstrate that the performance of recent activity confers a reduction in all-cause mortality, whereas activity performed decades earlier without subsequent maintenance appears to have no long-term benefit (21).

Cardiovascular Disease

Many studies have demonstrated that regular exercise and physical activity prevent primary and secondary cardiac events. In one of the most well-known studies, male Harvard University alumni without a history of CVD were followed for 16 years (16). There was a 39% reduction in cardiovascular morbidity and a 24% reduction in cardiovascular mortality in subjects with exercise energy expenditures of more than 2,000 kcal per week. Oldridge et al. (4) performed a metaanalysis of ten randomized clinical trials that examined the effects of cardiac rehabilitation after myocardial infarction (MI). No differences in nonfatal MI were apparent; however, there was a 24% reduction in all-cause mortality and a 25% reduction in cardiovascular mortality among exercise rehabilitation patients compared with controls. Wannamethee et al. (22) have also demonstrated that in men with established CAD, an increase in leisure-time physical activity was associated with a significant reduction in all-cause mortality.

Several population-based studies show that incremental levels of regular physical activity are inversely proportional to long-term cardiovascular mortality when controlled for the presence of other risk factors in both men and women (2,8,16,20,23) (Fig. 4.1). Among male alumni, the risk of death became progressively lower as physical activity levels increased from 500 to 3,500 kcal per week of energy expended (16). Alumni who were initially inactive and later increased their activity levels demonstrated significantly reduced cardiovascular risk compared with those who remained inactive (20). Moreover, when measured by an exercise tolerance test, higher levels of physical fitness are associated with significantly reduced subsequent cardiovascular mortality among men and women (17,25). In the Nurses' Health Study (24,26), 73,029 women (aged 40 to 65 years) were followed for 4 years. Physical activity in women was inversely related to the risk for stroke and CAD. The largest benefit was seen between the lowest and second-lowest quintile groups, suggesting that the incremental value of exercise is greatest in the least-active subjects compared with the most-active subjects. In a general population of elderly men, the 10-year CVD and all-cause mortality rate was inversely related to increasing levels of physical activity (27).

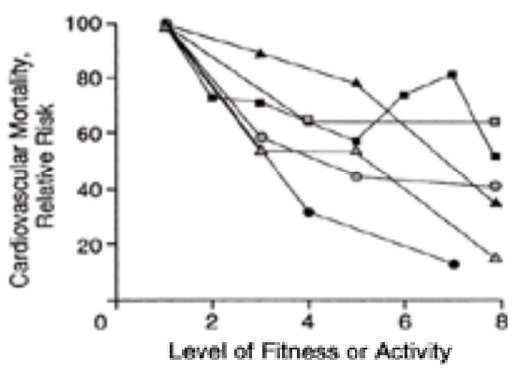


FIGURE 4.1 The relationship between physical activity or fitness and the relative risk for cardiovascular mortality. As fitness improves, the risk for cardiovascular death diminishes. ■, Paffenbarger et al. (1993); ▲, Morris et al. (1990); ●, Blair et al. (1989); □, Leon et al. (1987); △, Ekelund et al. (1988); ○, Sandvik et al. (1993). (From Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;273:402–407, with permission.)

The relative risk of CAD in physically inactive subjects compared with active individuals is approximately 2.0 (2,8,9). Importantly, the relative risk for cardiovascular mortality in the least-fit or least-active individuals compared with the most-fit or most-active subjects approaches 6.0 (8,9,17). Paffenbarger et al. (20) have reported encouraging data that demonstrate that, when habitual physical activity levels are increased, subsequent mortality is decreased relative to those who remained physically inactive. These data strongly support the need to increase physical activity and fitness levels among both women and men, with the most mortality benefit to be derived by those who are the least fit.

The specific mechanisms by which physical activity reduces CAD mortality are not known. Exercise improves lipid profile, glucose tolerance, obesity, and elevated blood pressure. In a cross-sectional analysis of a large cohort of men and women, increasing levels of physical fitness assessed by maximal exercise treadmill testing were found to protect against elevations in most coronary heart disease (CHD) risk factors in persons with and without CAD (28). However, modification of atherosclerotic risk factors does not fully explain the benefits that have been observed. Other possible mechanisms—including effects on thrombosis, endothelial function, and autonomic tone—may play an important role (*e*Table 4.1.2).

***e*TABLE 4.1.2** PHYSICAL ACTIVITY AND REDUCED CARDIOVASCULAR RISK: BIOLOGIC MECHANISM
Lower blood pressure
Improved glucose tolerance
Reduced obesity
Improvement of lipid profile
Enhanced fibrinolysis
Improved endothelial function
Enhanced parasympathetic autonomic tone

Cardiovascular Risk Factors

Hypertension

Three cohort studies have demonstrated that regular physical activity prevents the development of hypertension. In the Harvard University alumni study (21), there was a 35% increased risk for the development of hypertension in sedentary versus active individuals. This risk was more pronounced in obese subjects. Blair and colleagues (30) found that, compared with physically-fit patients, subjects who were less fit had a relative risk of 1.5 for the development of hypertension. In a prospective study of Japanese men aged 35 to 60 years, Hayashi et al. (31) showed that milder forms of physical activity such as walking are associated with a reduction in the risk of developing hypertension. As a result of these and other studies, the National Institutes of Health now recommends regular physical activity for the prevention of hypertension (32).

In addition to preventing hypertension, regular exercise has also been found to lower blood pressure. In mildly hypertensive men, short-term physical activity decreases blood pressure for 8 to 12 hours after exercise, and average blood pressure is lower on exercise days than on nonexercise days (33). In severely hypertensive black men, moderate physical activity performed for 16 to 32 weeks results in a decrease in diastolic blood pressure that is sustained even after reduction in antihypertensive medications. In addition, a significant decrease in left ventricular (LV) hypertrophy has been reported as early as 16 weeks after the initiation of exercise (34).

Diabetes Mellitus

Physical activity has beneficial effects on glucose metabolism and insulin sensitivity, including increased sensitivity to insulin, decreased production of glucose by the liver, larger numbers of muscle cells that use more glucose than adipose tissue, and reduced obesity (35). In addition, there is evidence that regular exercise may

prevent the onset of diabetes mellitus. A study of male alumni from the University of Pennsylvania (36) found that for every 500 calories of energy expended per week participating in leisure-time physical activity, the age-adjusted risk for the development of type 2 diabetes mellitus decreased by 6%. Lynch et al. (37) found that men who participated in moderate physical activity for at least 40 minutes a week were at lower risk for developing type 2 diabetes. This risk reduction was even more pronounced in men at high risk for developing diabetes. In a population-based prospective study, men in the lowest level of cardiorespiratory fitness, as measured by maximal exercise treadmill time, had a 3.7-fold higher risk of developing diabetes compared with men in the highest fitness level (38). In a large prospective cohort study of women, the risk of developing type 2 diabetes was substantially decreased in women who either walked or exercised vigorously, as long as the total energy expenditure was the same (40). Among physically inactive men who already have type 2 diabetes, those with a low fitness level have higher all-cause mortality than those who exercise and are physically fit (39). However, the role of exercise in the prevention and treatment of type 1 diabetes mellitus is unclear.

Overweight and Obesity

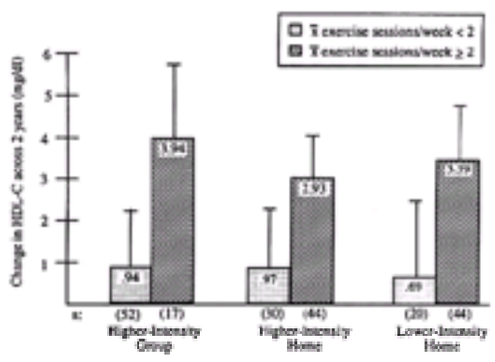
The prevalence of obesity has increased over the past 25 years, despite a reduction in fat intake. The most likely explanation for this national trend is an increase in total caloric intake, along with a reduction in physical activity (41). Using a body mass index of 25 or higher as “overweight” and a body mass index of 30 or higher as “obese,” nearly 106 million American adults age 20 and older are considered overweight (55 million men and 51 million women), and more than 43 million are considered obese (18 million men and 25 million women). In addition, an estimated 4.9 million children ages 6 to 17 are considered overweight (1).

Exercise training appears to be an important component for weight loss, although the effect of exercise is quite variable. Most controlled exercise training studies show only modest weight loss (approximately 2 to 3 kg) in the treated group versus the control group. When diet is added to exercise programs, the average weight loss is 8.5 kg (42,43). A well-controlled, 1-year randomized trial (44) that included 231 subjects demonstrated a significant 8.7-kg weight loss, most of which was body fat, in the exercise and diet intervention group and a significant 5.1-kg weight loss in the diet-only group. Those in the control group increased their weight by an average of 1.7 kg. Another randomized controlled trial involving 40 obese women demonstrated that moderate-intensity lifestyle activity combined with a low-fat diet resulted in favorable effects on weight loss, systolic blood pressure, and serum lipoprotein concentrations at 16 weeks and 1 year. Remarkably, the magnitude of benefit was similar to that observed in patients randomized to diet plus a structured program of aerobic exercise (45). These data strongly support the role of both exercise and diet in weight-loss programs.

Body composition and fat distribution are also linked to cardiovascular mortality (43) and are favorably affected by exercise. On average, exercise training programs reduce body fat by approximately 1.6% (42). Physically active men and women have a more favorable waist-hip ratio (p <0.9) than do sedentary individuals (46,47,48 and 49). Although significant, these changes are rather small, even after 1 year of diet and exercise (47). Importantly, physical activity appears to have favorable effects on lipoproteins, glucose metabolism, and blood pressure, even when weight loss is only modest (50).

Lipids

The effect of exercise on lipid levels has been an area of continued research. There is much variability in the results of exercise–lipid-lowering studies, at least in part due to the heterogeneity of the study methods, populations, exercise interventions, and the use of adjunctive interventions such as diet or pharmacologic lipid-lowering agents. A metaanalysis of 95 studies (51), most of which were not randomized controlled trials, concluded that exercise leads to a 6% reduction in total cholesterol, 10% in low-density lipoprotein cholesterol, and 13% in cholesterol/high-density lipoprotein cholesterol (HDL-C), and a 5% increase in HDL-C. The greatest changes in lipids were noted in patients who also lost weight during their exercise program. When body weight increased, lipid levels worsened. Intermediate changes were noted when body weight remained constant. It appears that the training intensities required to yield modest improvements in lipids are not as high as those that lead to improvements in fitness levels, as HDL appears to increase across a broad spectrum of exercise intensities (52,53) (eFig. 4.1.1). Moderate-intensity exercise (i.e., equivalent to briskly walking 10 miles per week), Step 2 AHA diet, and the combination of exercise plus diet were studied in a randomized controlled trial of postmenopausal women and middle-aged men. The most favorable changes in low-density lipoprotein (8% to 12% reduction) occurred among subjects in the diet and exercise group after 1 year. HDL levels decreased by 2% among women in the diet plus exercise groups, but among men there was a favorable increase of 2% (54).



***e*FIGURE 4.1.1** Graph depicts the relationship between the mean change in high-density lipoprotein cholesterol and frequency of exercise over a 2-year period of exercise training. Although the absolute change is small, the change was greater for subjects who exercised ³2 times per week compared with those who exercised <2 times per week, despite the intensity or location of exercise. HDL-C, high-density lipoprotein cholesterol. (From King AC, Haskell WL, Young DR, et al. Long-term effects of varying intensities and formats of physical activity on participation rates, fitness, and lipoproteins in men and women aged 50 to 65 years. *Circulation* 1995;91:2596–2604, with permission.)

In a study of 82 male and female patients with coronary disease, a 3-month exercise training program in conjunction with diet resulted in an 8% increase in HDL and a 22% decrease in triglycerides in subjects who had baseline triglyceride elevations. However, there was no significant improvement in body weight, low-density lipoprotein cholesterol, glucose level, or insulin level (55).

Few investigations of the effect of exercise on lipids and lipoproteins have been performed in women. Available prospective studies are contradictory (56,57 and 58). Because estrogen causes an increase in HDL-C (58), studies regarding women are also confounded by menopausal status and estrogen use, which are frequently not reported. A cross-sectional study examined the effects of vigorous exercise on HDL-C in female runners (59). HDL-C levels increased with increasing amounts of exercise and continued to rise, even in women who ran more than 64 km per week. For every additional kilometer run, the HDL-C increased by 0.133 to 0.200 mg/dL. This dose-response relation persisted in premenopausal and postmenopausal women, as well as in subjects on oral contraceptives and estrogen replacement therapy. Although these studies suggest an improvement in lipid profile with exercise training, the effects are quite modest. These improvements may have a favorable effect on cardiovascular risk; however, exercise is unlikely to normalize cholesterol levels in patients with true lipid disorders.

Thrombosis

Mounting evidence suggests that hemostatic parameters are important cardiovascular risk factors. Hemostasis is a balance between clot formation (thrombosis) and clot dissolution (fibrinolysis). This balance is especially important in CAD, in which the fibrinolytic system plays a protective role. The Framingham Study (60) has shown that elevated fibrinogen levels increase the risk for CAD in men and women between the ages of 47 and 59 years. In fact, patients in the upper tercile of fibrinogen levels had a two- to threefold higher incidence of CVD. Emerging evidence suggests that exercise training favorably affects the fibrinolytic system, which may help to explain the reduction in cardiac events observed in subjects who are more physically active. Strenuous endurance exercise for 6 months in healthy older patients (i.e., aged 60 to 82 years) resulted in a significant improvement in hemostatic parameters, a reduction in plasma fibrinogen levels of 13%, an increase in mean tissue-plasminogen activator (t-PA) of 39%, an increase in active t-PA of 141%, and a reduction of plasminogen activator inhibitor-1 of 58% (61). In contrast, younger patients (i.e., aged 24 to 30 years), whose baseline fibrinolytic variables were lower than the older group, had no significant change in fibrinogen, t-PA, or plasminogen activator inhibitor-1 activity. However, other studies have shown favorable effects of fibrinolytic enzymes after exercise training in younger subjects (62) and in patients after MI (63).

There is also evidence that acute and chronic exercise affect platelet activation. Platelet activation is important in the pathophysiologic mechanisms of unstable coronary syndromes and acute MI. Kestin et al. (64) studied the effects of treadmill exercise on platelet activation in sedentary and physically fit individuals. After acute strenuous exercise of similar duration and intensity, platelet activation and hyperreactivity were increased in sedentary subjects but remained unchanged in physically fit subjects. Rauramaa et al. (65) demonstrated that regular, moderate-intensity physical activity in middle-aged, overweight, mildly hypertensive men results in decreased platelet aggregation. After the 12-week exercise program, the study subjects demonstrated a 52% reduction in secondary platelet aggregation compared with a 17% decrease for the control group. Thus, it appears that, although acute exercise can lead to increased platelet activity, especially in sedentary individuals,

regular exercise may abolish or improve this response.

Inflammation

Growing evidence suggests that inflammation plays a role in atherosclerosis. In a recent study, serum levels of cytokines and C-reactive protein levels were measured in 52 volunteers in a 6-month, moderate-intensity exercise program who were at risk for ischemic heart disease. Atherogenic cytokine production fell significantly after the training period, as did levels of C-reactive protein (66).

Endothelial Function

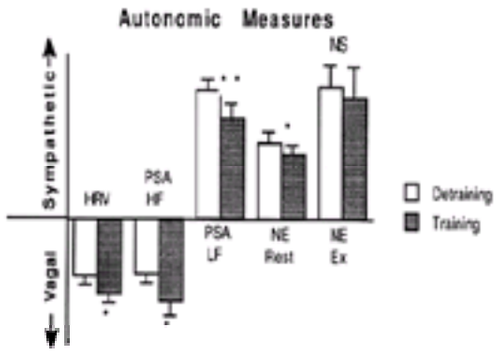
The vascular endothelium plays an important role in the regulation of arterial tone and local platelet aggregation, in part through the release of nitric oxide (NO) (67). NO produces vasodilation and inhibits platelet adhesion and aggregation by a guanylyl cyclase–dependent mechanism in vascular smooth-muscle cells and platelets. These effects are associated with an increase in platelet cyclic–guanosine monophosphate. Release of NO is stimulated by serotonin, thrombin, acetylcholine, and other receptor-dependent agonists (67). NO release is also stimulated by increased shear stress associated with acute and chronic increases in blood flow (68,69). Endothelium-dependent dilation is impaired in patients with coronary atherosclerosis or coronary risk factors, including hypercholesterolemia, diabetes mellitus, cigarette smoking, and hypertension (70,71 and 72). Patients with peripheral arterial disease have also been shown to have impaired endothelium-dependent vasodilation in the presence of cardiac risk factors (73). Convincing evidence exists that impaired NO action in atherosclerosis contributes to the pathophysiology of myocardial ischemia in patients with stable and unstable coronary syndromes (71,72,74).

An improvement in endothelial function in such patients has the potential to improve outcome. Growing evidence suggests that exercise improves endothelial function (75). Recent animal studies suggest that an important consequence of chronic exercise is an improvement in vasomotor function. This manifests by increased endothelium-dependent vasodilation in response to increased blood flow and clinically relevant NO agonists (76,77). High-resolution brachial artery ultrasound assessment of flow-mediated dilation has been used and validated as a model to evaluate endothelial function (78,79). Brachial artery diameter is measured at baseline and after reactive hyperemia produced by 5 minutes of cuff occlusion of the upper arm. Relative increases in diameter from baseline are used as measures of endothelium-dependent, flow-mediated dilation. Using this method, Clarkson et al. (80) showed that exercise training improved endothelium-dependent, flow-mediated dilation in young, healthy men. This effect was present in patients with and without CAD risk factors and was not related to lipid levels. Similar effects were demonstrated in patients with heart failure (HF) (81). Aging has been associated with a progressive decline in endothelium-dependent vasodilation, which may partially explain the increased risk of atherosclerosis in the elderly. A cross-sectional study of 68 healthy men demonstrated that regular aerobic exercise prevented this age-associated decline in endothelial function (82). A separate study suggests that the mechanism of the improvement in endothelial function in trained elderly athletes may be an increase in the availability of NO (83).

A seminal study by Hambrecht et al. (84) assessed whether exercise training affects endothelial function in the coronary circulation. In a randomized controlled trial, improvement in coronary endothelial function and coronary flow reserve in men with CAD was demonstrated. After 4 weeks of exercise training, significantly less coronary vasoconstriction in response to acetylcholine was observed.

Autonomic Function

The balance between sympathetic and parasympathetic activity modulates cardiovascular activity. Enhanced sympathetic nervous system activity, which may occur with aging, may be a risk factor for cardiac events. Heart-rate variability (HRV) is a well-accepted noninvasive technique for assessing autonomic tone. HRV increases with higher parasympathetic tone and decreases with sympathetic stimulation. Thus, higher HRV implies augmentation of parasympathetic tone, which may protect against cardiovascular morbidity and mortality. In healthy subjects, HRV appears to be related to exercise training. In a cross-sectional study, Goldsmith et al. (85) evaluated HRV in eight endurance-trained men and eight age-matched controls. Using 24-hour Holter monitors, they found that the standard deviation of the RR intervals, the average RR interval, and the high-frequency power were greater in the trained group, suggesting that exercise training increases parasympathetic tone. In another cross-sectional study, DeMeersman et al. (86) compared HRV in 72 male runners with sedentary age-matched controls. HRV was significantly higher in the physically fit patients, implying higher parasympathetic tone. Whether exercise affects autonomic tone in patients with CVD is unclear. Coats et al. (87,88) found that exercise training increased HRV in 17 patients with chronic HF (eFig. 4.1.2). However, in a recent randomized controlled trial of 25 men with new-onset LV dysfunction after MI, 2 months of high-intensity exercise training did not alter HRV at 1, 2, and 12 months compared with controls (89).



***e*FIGURE 4.1.2** Bar graph demonstrates the effect of exercise training and detraining on parameters of autonomic function. Training results in higher heart-rate variability (HRV) but lower spectral power of the low-frequency component of HRV (PSA LF) and norepinephrine (NE) spillover. This indicates higher vagal and lower sympathetic tone in exercise-trained subjects compared with detrained subjects. Ex, exercise; NS, not significant; PSA HF, spectral power of the high-frequency component of HRV. [From Coats AJS. Exercise rehabilitation in chronic heart failure. *J Am Coll Cardiol* 1993;22(Suppl A):172A–177A, with permission.]

Other markers of sympathetic tone, such as responses to various stressors, are influenced by physical training. In one study, 37 men with type A personalities were randomized to aerobic or weight-training programs for 12 weeks (90). The aerobic group showed improvement in functional capacity and lower sympathetic responses to a variety of mental stressors compared with the weightlifters. This response manifested as lower heart rate, rate-pressure product, diastolic blood pressure, and epinephrine levels in the aerobically trained individuals during the performance of mental arithmetic. Compared with sedentary individuals, subjects who exercise daily have been found to have lower norepinephrine spillover rates—a measure of sympathetic activity (91). These data suggest that regular aerobic exercise reduces sympathetic responses, which may be an important factor in reducing the risk for CAD. Whether these benefits extend to patients with CVD is unclear.

Mental Health and Quality of Life

There is evidence that physical activity improves psychological well-being; however, these data are less convincing than those regarding physical benefits. In general, exercise is associated with decreased anxiety and depression and an increased sense of well-being (92). Psychological benefits have also been found in cardiac patients who are more physically active (93). Several studies also have evaluated the effect of exercise on quality of life among patients with CVD. In a recent randomized controlled trial of moderate exercise training in patients with HF, measures of quality of life were significantly improved in patients who exercised (94).

PHYSIOLOGY OF EXERCISE

Types of Exercise

Most types of exercise involve endurance and resistance training. However, usually one type of training predominates. The physiologic responses to exercise lead to specific muscular, neurohumoral, and cardiovascular adaptations that depend, in part, on the type of exercise performed.

Endurance

Endurance (aerobic, dynamic) training consists of dynamic or isotonic exercise, which involves high-repetition movements against low resistance. Examples include walking, jogging, swimming, or cycling. Isotonic exercise implies that muscles shorten but maintain a constant tension, although tension does change to some degree during exercise (11). Endurance exercise involves rhythmic contraction and relaxation of working muscles. This results in increased blood flow to active muscles during

relaxation and increased venous return to the heart from the working muscles during contraction. Regular dynamic exercise is referred to as *endurance training*, because it results in improved functional capacity, enabling the individual to exercise for a longer duration or at a higher workrate.

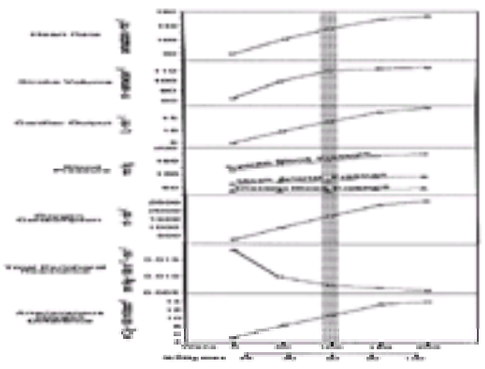
Resistance

Resistance training, also called *static exercise*, involves low-repetition movements against high resistance. This training may also be referred to as *isometric exercise*, because muscle tension develops predominantly without muscle shortening. An example of resistance training is weightlifting. The development of muscle tension during resistance training restricts blood flow during contraction. Regular resistance training leads to increased strength and is commonly referred to as *power* or *strength training*.

Cardiovascular Responses to Acute Exercise

Hemodynamic Changes

The cardiovascular system must respond in several ways to meet the demands of exercising muscles (95) (eFig. 4.1.3). The heart and peripheral blood vessels work together with neurohumoral stimuli and the muscle beds to increase oxygen supply to exercising muscles, clear byproducts of metabolism and heat produced by working muscles, and deliver neurohumoral substances to target tissues. The acute hemodynamic changes with exercise include increased $\dot{V}O_2$, heart rate, stroke volume, and systolic blood pressure. The amount that each of these parameters changes depends on which limbs are exercising (upper vs. lower), body position, and type of muscle contraction (isotonic vs. isometric).



***e*FIGURE 4.1.3** Cardiovascular and hemodynamic responses to acute exercise in the untrained subject. The shaded area represents the lactate threshold. Workrate is plotted along the x-axis. $\dot{V}O_2$max, maximal oxygen uptake. (From Durstine LJ, Pate RR, Branch JD. Cardiorespiratory responses to acute exercise. In: Durstine JL, King AC, Painter PL, et al., eds. *ACSM resource manual for guidelines for exercise testing and prescription*, 2nd ed. Philadelphia: Lea & Febiger, 1993:66–74, with permission.)

Contraction and relaxation of skeletal muscle are energy-dependent processes requiring the use of oxygen in the generation of adenosine 6-triphosphate. As a result, $\dot{V}O_2$—a measure of energy expenditure and oxygen use by exercising muscles—must increase from resting values. $\dot{V}O_2$ is linearly related to cardiac output (stroke volume × heart rate) and arteriovenous oxygen (AVO_2) difference (i.e., the amount of oxygen extracted from blood by peripheral tissues). Levels of $\dot{V}O_2$ 15 to 20 times higher than baseline can be attained during exercise due to augmented cardiac output or enhanced extraction of oxygen from the blood (96). The average resting AVO_2 difference is 5 mL/100 mL. During maximal exercise, enhanced oxygen extraction by exercising muscles can result in an increased AVO_2 difference up to 16 mL/100 mL (97). The $\dot{V}O_2$max of an individual is the best measurement of fitness and aerobic work capacity.

Cardiac output can augment four to five times from its baseline during endurance exercise and is influenced by body position, age, gender, fitness, and presence of cardiac disease. Higher cardiac output is the result of increased heart rate and stroke volume (97). As exercise increases, stroke volume increases until approximately 50% of maximum exercise capacity is reached, after which higher cardiac output is due to faster heart rate. The increase in stroke volume results from multiple neurohumoral stimuli, including sympathetic tone, epinephrine, and norepinephrine. In addition, endurance training results in augmented venous return from contracting muscles, leading to increased LV end diastolic volume. The greater stretching of the left ventricle results in increased stroke volume by 1.3 to 1.5 times baseline due to the Frank-Starling mechanism (97,98). Heart rate can increase 2.0 to 2.5 times baseline due to augmented sympathetic tone and diminished parasympathetic tone, in addition to increased epinephrine and norepinephrine (99).

Total peripheral resistance decreases during endurance exercise due to arteriolar vasodilation in exercising muscles. Vasodilation, which probably results from a decrease in local pH due to metabolic byproducts such as carbon dioxide and lactate, predominates over the vasoconstrictor effects of increased sympathetic tone. The net effect is a decrease in diastolic blood pressure—an indicator of peripheral resistance—and an increase in systolic blood pressure due to increased cardiac output (97). With resistance training, isometric contraction of skeletal muscle causes an increase in systolic and diastolic blood pressure, both of which fall abruptly during relaxation (100). This event results in increases in heart rate and blood pressure that are proportional to the intensity of contraction, size of the muscles involved, and duration of contraction (101).

The extent to which each of these hemodynamic parameters changes depends on body position and the specific muscle group that is being exercised. A comparison of dynamic arm and leg exercise can help to elucidate these differences. With submaximal dynamic arm exercise, there is less arteriolar dilation than with leg exercise because the muscle group is smaller. This characteristic results in higher total peripheral resistance due to vasodilation in the smaller vascular bed of the arm and vasoconstriction in the larger, nonexercising vascular bed. The increased total peripheral resistance, in turn, leads to a higher diastolic blood pressure than that seen with leg exercise. In addition, heart rate is faster during arm exercise due, in part, to differences in sympathetic tone. Arm exercise also leads to smaller increases in cardiac output because of lower volumes of blood returning to the heart from the smaller muscle mass of the arm (102). $\dot{V}O_2$max during arm exercise is approximately 70% of that during leg exercise (98), whereas, at a similar submaximal $\dot{V}O_2$, arm exercise requires lower workrates than does leg exercise.

Both age and gender have an effect on physiologic responses to exercise. Men can exercise to higher peak workrates and $\dot{V}O_2$ than can women. Peak workrates in older individuals are lower than in younger subjects. In addition, at matched workrates, $\dot{V}O_2$ is higher in older subjects (103,104).

Changes in Myocardial Oxygen Demand

As a result of increased oxygen demand by exercising muscles, the heart must augment stroke volume and heart rate, leading to an increase in blood pressure, LV contractility, and wall stress (98). These alterations, which increase with exercise, result in greater myocardial oxygen demand. A reliable estimate of myocardial oxygen demand is the rate-pressure product (i.e., the product of the heart rate and systolic blood pressure) (105). Coronary arteries respond to increased demand for oxygen by augmenting coronary blood flow, which is dependent on coronary perfusion pressure, the diameter of the coronary artery lumen, and distal coronary resistance. Coronary blood flow is controlled by neurohumoral stimuli and local endothelial factors—all of which regulate vasomotor tone. Neuromodulation of the coronary vasculature is regulated, in part, by the increase in sympathetic tone that occurs with exercise. The net effect of alpha- and beta-adrenergic stimulation in normal arteries is vasodilation. The endothelium produces various vasoactive substances that regulate vasomotor tone. Vasodilation in normal coronary arteries results from the release of NO and prostaglandins, which are produced in response to various stimuli such as increased flow and shear stress (68).

Myocardial responses to acute exercise in patients with CAD or reduced LV systolic function differ from responses of normal subjects. Luminal narrowing of the coronary artery results in a supply-demand mismatch for oxygenated blood during physical activity. This mismatch manifests as myocardial ischemia and myocardial dysfunction due to an inability of the coronary artery to deliver sufficient amounts of oxygenated blood to meet the increased oxygen demands of the heart. In patients with normal LV function, functional capacity may be limited by symptoms of angina. Myocardial dysfunction may lead to increased LV end diastolic pressure, resulting in dyspnea. Alternatively, diminished myocardial contractility may lead to a reduced cardiac output, thereby limiting the supply of oxygenated blood to exercising muscles and producing fatigue (99). Patients with reduced systolic function and HF have altered hemodynamic responses to exercise that may impair exercise tolerance. These individuals have reduced cardiac outputs with exercise due to a blunted heart-rate response and failure to increase stroke volume. As a result, systolic blood pressure is reduced; however, the total peripheral resistance is elevated. Thus, a smaller portion of the cardiac output reaches the exercising muscles, leading to

increased anaerobic metabolism and lactate production. The resulting acidosis causes muscle fatigue and discontinuation of exercise (99,106).

Responses to Exercise Training

Regular endurance or resistance training results in specific changes in the muscular, cardiovascular, and neurohumoral systems that lead to improvement in functional capacity and strength. These changes are referred to as the *training effect* and allow an individual to exercise to higher peak workrates with lower heart rates at each submaximal level of exercise.

Muscular Adaptations

Regular endurance training results in changes in skeletal muscle, including increases in mitochondria, myoglobin, capillary density, and metabolic enzymes (107). The increased mitochondrial number is specific to the muscle group exercised. For example, runners have more mitochondria in their lower-extremity muscles than in their arm muscles. Additional capillaries in skeletal muscle serve to aid in the exchange of nutrients and metabolic byproducts during exercise (108). Increased metabolic enzymes enhance a muscle's capacity for converting glycogen and fatty acids to adenosine 6-triphosphate. With endurance training, more energy is derived from fatty-acid metabolism, and glycogen stores are spared (107). As a result, less lactate is produced, and endurance is enhanced. The net effect of the changes in skeletal muscle is to promote aerobic metabolism, which, in turn, improves exercise capacity.

In contrast to endurance training, regular resistance training leads to muscle-cell hypertrophy due to increased synthesis of contractile proteins and connective tissue (109).

Cardiovascular Adaptations

Endurance training results in increased venous return to the heart, which leads to higher LV volumes. Resistance training exposes the patient to chronic increases in afterload due to increased total peripheral resistance and elevated blood pressure, yielding a greater LV wall thickness. These effects result in increased LV mass in both training groups. However, the LV mass–lean body mass ratio is elevated in the endurance trainer, whereas it is normal in the resistance trainer (110). The increase in LV mass in the resistance trainer is proportional to the increase in skeletal muscle mass.

Along with changes in myocardial mass, certain hemodynamic effects are observed from endurance and resistance training. Wall stress at rest in endurance trainers is normal; however, it is lower in resistance trainers due to increased wall thickness without ventricular dilation (111). Systolic function and fractional shortening at rest are normal in both groups. However, compared with nonathletes, stroke volume is increased due to greater end diastolic volumes (111,112). Despite increased LV wall thickening, diastolic function appears to be normal in both groups (113). A cross-sectional study comparing the effects of long-term training among distance runners and wheelchair athletes demonstrated that long-term arm exercise and leg exercise yield increases in LV volume and mass—although to a lesser degree in arm-trained athletes—compared with untrained control subjects (114).

The decline in $\dot{V}O_2$max (exercise capacity) seen with aging has also been shown to be attenuated by habitual exercise. A recent study (115) aimed to explain this observation and noted that, after exercise training, peak leg blood flow increased by 50%, although there was no change in peak cardiac output. This occurrence suggests that exercise yields a reversible deconditioning effect on the distribution of cardiac output to exercising muscle. In patients with CAD, there appears to be less ischemia for a given rate-pressure product after exercise training compared with that before training. Improvements in ischemic threshold manifest as less angina (116), ST-segment depression (117), and thallium defects (118) at the same levels of exercise. These findings suggest that exercise training improves myocardial oxygen supply in patients with CAD. The specific mechanisms responsible are unclear; however, possible explanations include improvement in endothelial function and vasomotor tone, decreased sympathetic tone, and alterations in blood rheology.

Neurohumoral Adaptations

Neurohumoral responses to exercise manifest as lower resting heart rate and reduced heart rate at any level of submaximal exercise. The diminished heart rate at rest and with exercise is due to increased resting parasympathetic tone and decreased sympathetic tone. Lower levels of circulating catecholamines are observed in trained versus untrained individuals (90,91), whereas the number and sensitivity of beta-adrenergic receptors appear unchanged with exercise training (119).

Detraining

Cessation of exercise training for as little as 3 weeks can lead to some loss of the training effect. This may be partially due to the reduction in LV size and stroke volume as a consequence of the absence of increased cardiac filling, which occurs with exercise (120). The lower preload results in less stretching of the myocardium and a lower stroke volume, according to the Frank-Starling mechanism.

PHYSICAL ACTIVITY AND EXERCISE: PRESCRIPTION FOR HEALTH AND FITNESS

Energy Expenditure

Major public health statements have generated recommendations regarding the amount of exercise and physical activity that should be performed each week to generate health benefits. It is important to note that these recommendations are based on studies performed almost exclusively on men, although recent years have witnessed an increasing number of studies performed on women.

Intensity, Frequency, and Duration of Physical Activity

The CDC, ACSM (8), and Surgeon General (6) recommend that adults exercise for 30 minutes at moderate-intensity levels on most, if not all, days of the week to achieve a weekly energy expenditure of at least 1,000 kcal. These statements stem from evidence stating that regular moderate physical activity provides many health benefits. In addition, these recommendations stress that physical activity can be accomplished in multiple short intervals—which may be more feasible for many individuals—rather than continuous 30-minute exercise sessions. Low-intensity exercise should be performed more frequently and for longer duration.

The CDC recommendations are based on data that suggest that the benefits of exercise are related to the total energy expenditure or dose measured in calories or duration of physical activity. Observational studies have shown that cardiovascular mortality decreases when duration of exercise increases from 15 to 47 minutes per day and when caloric expenditure increases from 500 to 2,000 calories per week (16). A recent study of 7,307 Harvard University alumni demonstrated that brief durations of physical activity—as short as 15 minutes—conferred as much of a reduction in CHD risk as longer sessions, as long as the total energy expenditure was equivalent (121). However, an important question remains regarding the intensity of physical activity required to incur a mortality benefit. Intensity can be defined in terms of reflecting the rate of energy expenditure during exercise (expressed in METs or kcal per minute) or the relative percentage of maximum aerobic capacity that is maintained during the exercise or activity (expressed in terms of percentage of maximum heart rate or percentage of $\dot{V}O_2$max achieved on exercise tests) (8). The data regarding exercise intensity are much less clear than those addressing dose. Lee et al. (122) have reported that only energy expended during vigorous activity (>6 METs) yielded a mortality benefit among Harvard University alumni. More recent data from this cohort similarly demonstrate that moderate activities (<6 METs) have no clear association with risk of CHD and that men older than 60 years with coronary risk factors who expended more than 1,000 kcal per week had less CHD risk, as did men without risk factors. The intensity of physical activity was associated with a 20% reduction in CHD risk (29). Conversely, walking also has been shown to reduce the incidence of coronary disease in a large sample of elderly subjects, with a proportionately lower incidence of CVD in men who walked more than 1.5 miles per day (29). One must consider however, that brisk walking in elderly persons may be at moderate-intensity relative to their peak exercise capacity but, in absolute terms, is <6 METs. Similarly, prospective data from the Nurses Health Study suggest that brisk walking (3 to 4 miles per hour; 2.5 to 4.5 METs), as well as vigorous exercise (>6 METs), is associated with a substantial reduction in the risk for CVD (124).

Training Modalities

Modalities for training can be categorized by the specific muscle groups that are exercised, such as arms, legs, or both. In addition, different modalities emphasize predominantly endurance or resistance exercises (*e*Table 4.1.3).

***e*TABLE 4.1.3** TYPES OF EXERCISE
Lower extremity
Endurance Walking
Jogging/running

	Climbing stairs
Resistance	Leg extension, curls, press
	Adductor/abductor
Upper extremity	
Endurance	Arm ergometry
Resistance	Biceps curls
	Triceps extension
	Bench/overhead press
	Lateral pull down/raises
	Bench-over/seated row
Combined upper and lower extremity	
Endurance	Rowing
	Cross-country ski machines
	Combined arm/leg cycle
	Swimming
	Aerobics

Endurance Lower-Extremity Exercise

Endurance leg exercise is the most common form of physical activity performed. Examples include walking, running, cycling, and climbing stairs. When calculating workrate (force × distance/time), it is important to take into consideration whether the activity is a weight-bearing exercise (walking or running) or a non–weight-bearing exercise (cycling). This consideration is due to the fact that during weight-bearing exercise, body weight is a major component of force; during non–weight-bearing exercise, body weight is supported and, consequently, is a much smaller component of force (125).

Walking

Walking is a common form of exercise that is highly feasible for the general population, because it does not require special equipment or the mastery of a new technique. Brisk walking (3 to 4 miles per hour) is considered moderate exercise for most individuals. A slower pace is frequently an adequate intensity for the elderly, because they have a lower maximum peak heart rate and $\dot{V}O_2$; thus, less exercise is needed to achieve a training effect. Walking is commonly prescribed in cardiac rehabilitation programs.

Individuals can walk indoors or outdoors. Exercise intensity can be regulated using a treadmill, because the speed and grade can be altered. It should be kept in mind that holding onto the handrail of a treadmill reduces the amount of work performed. Ideally, one should walk without holding the handrail or use it for balance only. Hand-held weights and elevations in grade can increase training intensity. A recent study in healthy volunteers compared energy expenditure at various perceived exertion levels for various indoor exercise machines (126). Although the results suggest that energy expenditure was highest with treadmill exercise compared with cross-country ski machines, rowing, stair-climbing machines, and stationary bicycles, additional studies are needed to confirm these results.

Jogging and Running

Jogging and running are higher-intensity forms of exercise than walking. As with walking, no special equipment or instruction is needed to begin. However, due to the higher impact, injuries are more common than with walking. Jogging on shock-absorbing surfaces can help to decrease the impact.

Stair-Climbing

Stair-climbing has become popular due to the advent of stair-climbing machines. Different intensities and exercise programs can be performed. In this type of exercise, holding onto the handrails decreases exercise intensity. Stair-climbing is used in many fitness programs and provides exercise diversity to prevent boredom.

Cycling

Cycling is another popular dynamic lower-extremity exercise. Stationary bicycles take up little space and are relatively inexpensive compared with other types of training equipment. These bicycles are ideal for individuals who are insecure on a treadmill or who have orthopedic or neurologic impairments that cause unsteady gait. The workrate is dependent on the force exerted on the flywheel, the resistance of which can be altered. Off-road cycling has become extremely popular. Unlike walking or jogging, cycling must be learned and involves muscle groups that are not usually required for everyday activity. As a result, the initial exercise capacity during cycling may be low, especially in the elderly.

Endurance Upper-Extremity Exercise

As previously discussed, the physiologic responses of endurance upper-extremity exercise are different from those of lower-extremity exercise in that the arms have a smaller muscle mass. Given the location of the arms, arm exercise often requires the use of other muscle groups (e.g., chest, back, legs, and buttocks) for stabilization. This requirement results in a curvilinear response of the $\dot{V}O_2$ with increasing workrates, leading to less predictable changes in heart rate and blood pressure (103). Consequently, the $\dot{V}O_2$ for any submaximal arm work exceeds that for leg work, resulting in expenditure of more calories for the amount of external work performed during arm exercise. Compared with leg exercise, arm exercise at matched submaximal workrates also leads to higher ventilation, blood pressure, heart rate, total peripheral vascular resistance, and cardiac output. The total peripheral resistance is higher with arm exercise than with lower-extremity exercise, because there is less vasodilation in the smaller vascular bed of the arm. The smaller muscle bed also results in less blood returning to the heart and, thus, smaller increases in cardiac output (102).

Arm Ergometer

An arm ergometer is a commonly used device for upper-arm exercise. The workrate can be adjusted by altering the resistance against the flywheel. Revolution rates of 60 to 80 per minute for 5- to 10-minute intervals are recommended for upper-extremity endurance training. This exercise is performed with the individual seated and the fulcrum of the handles set at shoulder height.

Many training modalities combine endurance exercise of the upper and lower extremities. Examples include cross-country ski machines, rowing machines, combined arm-leg ergometers, swimming, and aerobic dance. Given the strenuous nature of many of these exercises, they are not recommended for individuals with low functional capacity who are beginning an exercise program or with serious disabilities.

Resistance Exercise

By improving strength and muscle endurance, resistance training can be beneficial to all individuals because routine, daily activities frequently involve a combination of isotonic and isometric effort. Although weight training was believed to be unsafe for cardiac patients, recent data have documented its safety and efficacy in cardiac rehabilitation programs. Resistance exercise performed 2 to 3 days per week is now advised to complement aerobic training in individuals with and without CVD (127).

Equipment for resistance training may include free weights, wall-mounted pulleys, or exercise machines with stackable weights. Exercise should be performed in a manner that isolates specific muscle groups, using movements of slow to moderate speed and encompassing full ranges of motion. Special instruction is recommended to avoid musculoskeletal injury. The exercises should involve the anterior and posterior of each large muscle group, such as the biceps and triceps of the arm, the chest and back of the torso, and the hamstrings and quadriceps of the legs. Resistance intensity can be varied by changing the amount of weight, the number of repetitions, and the number of sets.

Risks of Exercise

The inherent risks of physical activity must be considered to promote the health benefits of exercise while minimizing injury. Because nearly every activity carries some risk, the risk-benefit ratio must be examined for each individual. Major hazards involve the cardiovascular and musculoskeletal systems.

Cardiovascular Risks

The risks of cardiovascular morbidity and mortality depend on whether one studies the general population or individuals with CAD. Although the risk of death during exercise is low, death in individuals over 35 years of age is usually the result of atherosclerotic CAD, whereas younger individuals are more likely to suffer from congenital cardiac malformations (128). The incidence of sudden cardiac death during exercise for the population at large is 1 in 565,000 events per hour (129). The risk of sudden death during exercise is much lower for young individuals than for middle-aged and older adults. Among high school and college athletes, the sudden death rate is estimated to be 1 in 133,333 male athletes and 1 in 769,230 female athletes (130). The exertionally related sudden death rate in previously healthy middle-aged men is approximately 6 to 7 in 100,000 events per year (131,132).

For healthy sedentary men, the risk of cardiac arrest is 56 times higher during exercise compared with times of inactivity. In contrast, the risk for active men during exercise is five times the risk during times of inactivity. Despite this transient increased risk during strenuous exercise, regularly active men have a cumulative cardiac arrest risk that is 40% lower than the risk in inactive men (132). In a prospective study of 21,481 male physicians who were reportedly free of CAD, the relative risk of sudden death after an episode of heavy exertion was 1.9. However, the absolute risk of dying was extremely low (1 in 1.5 million episodes of exertion). Furthermore, habitual vigorous exercise was associated with a significant reduction in the incidence of sudden death (133). This and other studies (132,134) demonstrate that the risk of primary cardiac arrest during exertion is reduced among those who are physically active.

There is also evidence that heavy exertion may trigger acute MI. Two studies have found that the relative risk for MI within 1 hour after strenuous physical exertion was increased by two to six times that of patients who were sedentary or less active during that hour (135,136). However, the risk was inversely related to the amount of leisure-time physical activity performed by the subjects. Thus, the more active the individual, the lower the risk for developing acute MI during strenuous exertion. There is also evidence that sexual activity can trigger acute MI; however, the risk is low (137). The relative risk for MI within 2 hours of sexual activity was 2.5 in healthy subjects, 2.1 in those with a history of angina, and 2.9 in those with a history of MI. The absolute risk for MI in all groups was low and was not increased in individuals with CAD. In addition, the risk was reduced in individuals who exercised regularly.

In individuals with known CAD, exercise training is relatively safe. In a study of 167 cardiac rehabilitation programs involving 51,000 patients, the incidence of cardiac arrest was 1 in 112,000 person-hours, with a successful resuscitation rate of 86% (138). The incidence of MI was 1 in 294,000 person-hours, and the incidence of death was 1 in 784,000 person-hours. More recent data from a single cardiac rehabilitation center report the incidence of major cardiovascular complications to be 1 in 60,000 participant-hours, with no deaths occurring (139). Limited data are available regarding home exercise in patients with cardiac disease. Using heart-rate monitors and transtelephonic electrocardiographic transmission, DeBusk and colleagues (140) found a similar rate of reinfarction and death after 26 weeks in patients randomized to home training versus subjects randomized to group training. Similarly, Ades et al. reported no major cardiac arrest or death during 3,100 hours of home exercise (141).

Musculoskeletal Risks

The risk of musculoskeletal injury depends on the type of exercise performed, as well as the intensity. The incidence of injury to runners is high, with approximately 35% to 65% of individuals sustaining injuries per year (142). Injuries tend to increase as running distance increases; injuries also increase in sedentary individuals who begin a vigorous exercise program (143). In runners, the most common site of injury is the knee (143); however, the foot, ankle, and lower leg are also at risk (144). Upper-extremity exercise (e.g., racquet sports, baseball, and swimming) may lead to difficulties with the hand, wrist, elbow, and shoulder.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Promotion of Physical Activity

The message from America's leading scientists is clear, unequivocal, and unified: physical inactivity is a risk factor for CVD. It is highly prevalent and is a matter of public health. This unprecedented focus on physical activity and exercise is the product of copious research, including epidemiologic observational studies, cohort studies, randomized controlled trials, and basic research. It is clear that the promotion of physical activity has reached the forefront of our national public health agenda, as manifested by the publication of the 1996 Surgeon General's report on physical activity and health (6). Much work remains to promulgate this message and implement strategies to achieve the ambitious goals of the Healthy People 2010 objectives (145). Broad-based efforts that affect every level of our social infrastructure are needed ultimately to impact the health status of the United States. Although educational and media campaigns that directly target youth and adults are essential, these efforts must be supported by policy makers, legislators, educators, health care providers and insurers, employers, community leaders, and researchers.

Federal, state, and local governments must adopt policies that foster the promotion of physical activity. Physical education programs in schools throughout our nation are vital for the development of positive attitudes and the acquisition of appropriate knowledge and skills that foster active and healthy lifestyles throughout adult years. All individuals should develop an understanding and appreciation of the benefits that can be derived from the wide range of physical activity options. The nature of these activities range from everyday house chores to organized sports, from walking the dog to running on a treadmill. Physicians, nurses, and allied health care providers play a pivotal role in counseling their patients on physical activity and influencing subsequent behavior. These initiatives by the health care team must, in turn, be supported by government and private health insurance providers, who must realize that appropriate lifestyle interventions can reduce or eliminate a large number of health risks and, ultimately, reduce health care costs. Communities and employers have remarkable opportunities to provide environments and incentives to promote physical activity. Finally, scientists and researchers should be stimulated to answer the many remaining questions regarding physical activity, exercise, and health. Of course, such work cannot be done without the much-needed support of federal and private funding agencies. Funding opportunities and initiatives for clinical, behavioral, and basic research in this area are essential to transform present-day goals into future reality.

Dose and Intensity of Physical Activity

Despite the large body of literature from more than half a century of research in the area of physical activity, large gaps in the knowledge base remain. A prudent conclusion has been drawn from the studies to date: moderate-intensity activity for 30 minutes a day leads to health and, presumably, mortality benefits. Inherent properties in this recommendation are dose (i.e., total energy expanded per week) and intensity (i.e., the energy requirements per unit of time for a given activity). Prospective, randomized controlled trials are needed to evaluate variations of dose versus intensity of activities on specific health outcomes—including definite cardiac events—in any large representative cohort of the population or among any specific subgroup (e.g., youth, elderly, patients with known CVD). Recent studies indicate that exercise training of low to moderate intensity can increase physical fitness and result in improvements in several health variables (e.g., insulin sensitivity, HDL levels, blood pressure). Epidemiologic data support the relation of moderate-intensity activity to lower mortality; however, intensity of activity in these studies is not directly measured, but it is categorized based on estimated energy requirements per unit of time or subjective perception of activity intensity. Indeed, the lowest threshold for dose or intensity to achieve specific cardiovascular benefit is not known, nor is the ideal dose-intensity prescription for specific biologic outcomes or total cardiovascular health.

Considering the high prevalence of physical inactivity among American youth and adults, the existing broad-based public health recommendations are reasonable and scientifically sound. However, it is hoped that customized activity prescriptions tailored to individual needs, risks, and benefits will someday replace the current generic recommendations.

Medical Screening before Exercise

It is anticipated that the public health efforts to promote physical activity will impact all Americans, including the one in four who have some form of CVD. Although regular exercise leads to health benefits, the incidence of cardiovascular events during exercise is estimated to be 10 times greater than that at rest among otherwise healthy persons (129). The CDC (6) and AHA (129) conclude that most persons do not need to see their physician before starting a moderate-intensity physical activity program. However, it is advised that men older than 45 years and women older than 55 years who plan to start a program of vigorous intensity (>60% $\dot{V}O_2$max) or individuals with risk factors, signs, or symptoms of cardiovascular or chronic disease consult their physician to design an exercise program. These recommendations seem reasonable, yet are they practical? Should asymptomatic men and women, based on their age, undergo a screening exercise test before participation in exercise training programs designed to improve fitness, strength, or both? Indeed, the utility of the exercise test in screening asymptomatic individuals may often result in false-positive tests, which may cause undue concern and lead to further, more expensive and invasive tests. Conversely, are the many individuals with CVD who do not seek regular evaluation by a health care professional placing themselves at significantly increased risk by beginning an unsupervised exercise program at home or at a fitness club? The specific answers to these questions remain unknown, as there are no scientific data that evaluate the benefits, costs, and potential risks of specific medical screening practices—or the lack thereof—for individuals who are about to begin or who are actively participating in moderate- to vigorous-intensity exercise programs. As such, current recommendations must be left to expert consensus opinion until more data are available. General medical screening guidelines (6,127,129) and those directed at cardiovascular screening at fitness facilities (146) must be promulgated to the public and the health care professional in concert with efforts promoting physical activity.

THE FUTURE

Evidence regarding the health benefits of physical activity is overwhelming; however, there are many unanswered questions, and future research is needed. For example, further study of the specific mechanisms responsible for the decrease in cardiovascular events, as well as total mortality, is needed. In addition, whether specific physiologic and biochemical changes differ among the various types of exercise is undetermined. For instance, what are the effects of chronicity, intensity, and duration of activity on these parameters? The effects of physical activity in persons of different age, gender, race, and ethnicity are unknown (9). Moreover, no prospective, randomized controlled trial has compared the effects that the high-dose versus low-dose range of these exercise recommendations has on fitness levels or modifiable cardiovascular risk factors (including weight, body composition, and lipid profile). Importantly, no study has evaluated the cardiovascular benefits of these recommendations on racial minorities.

The economic effects of physical activity on various diseases need additional investigation. Knowledge of the cost-effectiveness of exercise for the treatment or prevention of atherosclerotic diseases is important (9).

The U.S. Department of Health and Human Services has published recommendations for the promotion of health and prevention of disease in Americans (145). A major objective is to enhance the physical activity of inactive individuals in an attempt to reduce chronic diseases and improve quality of life. Certain special populations have been targeted due to their lack of participation in leisure-time physical activity, including ethnic minorities such as blacks, Hispanics, Native Americans, low-income groups, the elderly, the disabled, and obese individuals. Methods that aid in promoting, implementing, and maintaining physical activity are needed.

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5

HYPERTENSION: CONTEXT, PATHOPHYSIOLOGY, AND MANAGEMENT

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LARS G. OSTERBERG

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Hypertension is a major cardiovascular risk factor that directly contributes to myocardial infarction (MI), cerebrovascular accidents, congestive heart failure (CHF), peripheral arterial insufficiency, and premature mortality. Optimal and cost-effective management of the condition depends on careful diagnosis, treatment minimization, optimized adherence, parsimonious selection of tests and treatments, and practice efficiency.

Over the natural history of hypertension, early endothelial dysfunction and elevations of cardiac output (CO) usually give way to increased peripheral vascular resistance, reflecting an array of genetic, environmental, and homeostatic factors. Early perturbations may be slight and reversible; subsequent chronic changes tend to be larger, slower, and irreversible.

Successful reduction in blood pressure (BP) and other cardiovascular risk factors can dramatically reduce the incidence of cerebrovascular and coronary morbidity and mortality, especially for individuals with the highest elevations of BP, individuals with multiple risk factors, and the elderly. Nondrug therapy is often sufficient for mild or labile elevations of BP. The large number of antihypertensive drug options necessitates individualization for particular patients and a thoughtful balancing of hypotensive efficacy, impact on key vascular beds, patient cost and convenience, and long-term consequences on metabolic and other baseline functions.

Secondary hypertension with curable potential makes up <2% of unselected hypertensive populations and usually produces characteristic clues or refractoriness to therapy. Suboptimal compliance with prescribed medications and suboptimal drug combinations are more common causes of apparent resistance to standard treatment than is secondary hypertension.

Continued controversy surrounds the optimal threshold of treatment and the optimal choice of antihypertensive medications.

INTRODUCTION

Hypertension is a major cardiovascular risk factor that contributes to MI, cerebrovascular accidents, CHF, peripheral arterial insufficiency, and premature mortality (1). Of all the known cardiovascular risk factors, hypertension is the most prevalent: it occurs in up to 30% of the United States population (approximately 80 million Americans), when using a threshold of 140/90 mm Hg (2). Hypertension is the most common reason cited for office visits to American internists (3) and the most common indication for the use of prescription medication in the United States (4). In 1995, direct costs of American antihypertensive management and treatment of its complications totaled $24 billion (2).

Definitions of hypertension continue to evolve as more epidemiologic data and randomized controlled trials clarify the distributions of BPs and the thresholds for net benefit from treatment. Traditional definitions have used systolic BP (SBP) ³140 mm Hg and/or diastolic BP (DBP) ³90 mm Hg to delimit the upper bounds of normal. More recently, the recommendation has shifted to defining normal BP as mean daytime SBP <135 mm Hg and DBP as <85 mm Hg (5).

Recent reanalysis suggests that hypertensive patients fall in two groups. Approximately one-fourth consists of individuals under the age of 50 who are predominantly male and have diastolic hypertension. The remaining three-fourths are older than the age of 50, are slightly more than half (58%) women, and often display isolated systolic hypertension. From Framingham data, the best predictors of coronary heart disease differ in the three age clusters: <50 years old, 50 to 59 years old, and ³60 years old. Among patients <50 years old, DBP predicted subsequent coronary heart disease better than SBP. Among patients 50 to 59, SBP, DBP, and pulse pressure served equally well as predictors. At age 60 years and older, pulse pressure was the best predictor followed by SBP (6,7).

On the basis of its high prevalence, responsiveness to treatment, and financial impact, hypertension deserves our attention (8). Perhaps most importantly, hypertension represents a success story in which evolving therapies and concerted public and professional educational efforts have combined to reduce its disease burden of morbidity and mortality (9). The overall cost-effectiveness of antihypertensive management depends on five factors: correct diagnosis, treatment minimization, optimized adherence to therapy, parsimonious selection of tests and treatments, and practice efficiency (10).

HISTORICAL PERSPECTIVE

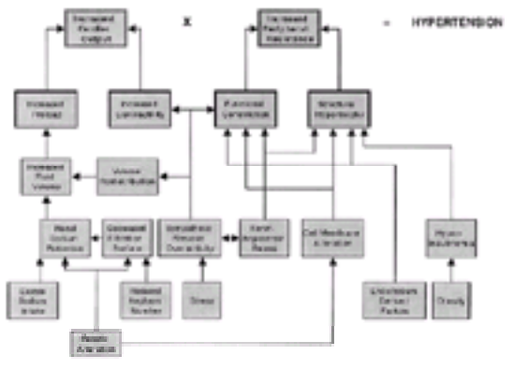
The first report of direct BP measurement dates back to 1726, when Stephen Hales cannulated a horse's crural artery and assessed the height of the blood column before and after hemorrhage. The monaural stethoscope appeared in the early nineteenth century; the binaural stethoscope came to America in 1852, well before Riva-Rocci's introduction of the sphygmomanometer cuff in 1896. Firmly shifting attention away from assessing the pulse wave (11), Korotkoff reported the auscultatory method of measuring arterial pressure in 1905, permitting measurement of diastolic pressure and systolic levels for the first time (12).

As early as 1827, Bright recognized that patients who had high BP also had contracted kidneys and hypertrophied left ventricles. By 1852, Johnson had described medial hypertrophy of the renal afferent arterioles from high BP, and Traube associated left ventricular hypertrophy (LVH) with increased arterial tension in 1856. In 1913, Janeway described 500 of his private practice patients followed for 9 years, concluding, "It does not seem to me that any very definite prognostic conclusions can be drawn from the height of the blood pressure" (13). Fully 26 years later, Keith, Wagener, and Barker published their landmark study of survival curves for four groups of hypertensive patients classified by eyeground patterns (14). With these and many subsequent advances, the medical focus shifted from simple measurement of BP to its clinical consequences.

Early efforts to reduce extreme hypertension by adrenalectomy or sympathectomy frequently led to disastrous results. Some early authorities concluded that such hypertension was not merely primary but "essential," because brusque pressure reductions were deleterious. Serious work on experimental hypertension started with Goldblatt's description of the renal artery clip model in 1934 (15). Thus began a series of discoveries of one intriguing complexity after another: renin, angiotensin, atrial natriuretic factor, cation fluxes, endothelial factors, vascular remodeling, central monoaminergic, and hypothalamic factors, among others.

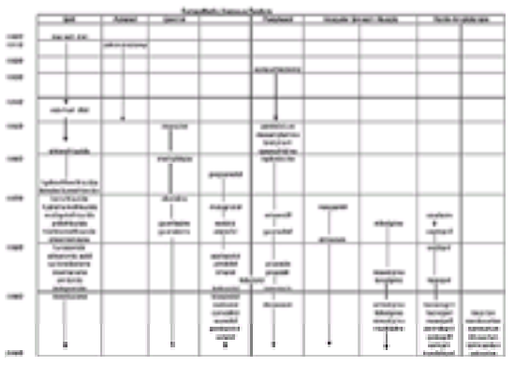
With each decade, new potential culprits were identified, each carrying some plausible basis for a role in causing or maintaining BP elevations. For most hypotheses, the perspective remained the same as that proposed in 1960 by Page in his "mosaic theory" of hypertension: a disease of regulation in which abnormal regulatory systems fail to reduce BP once it is elevated (16). More precisely, the control of arterial pressure was likened to a kaleidoscope of interlocking, dynamic equilibria that determined the net effect while continually shifting from one set of relations to another. Although the regulatory factors were limited, their changing interplay was not (17).

The strength of the model lies in its adaptability to new data. Because there is likely to be no unique cause for most cases of hypertension but many potentially contributing factors, one struggles to integrate all the possible components. The mosaic concept offers a way to combine diverse factors—from genetic and physiologic to emotional and environmental. eFigure 5.0.1 lays out some of the major factors affecting BP.



***e*FIGURE 5.0.1** Interactions among the genetic, environmental, and physiologic factors that affect blood pressure in health and in disease. (Adapted from Kaplan NM. Primary hypertension: pathogenesis. In: Kaplan NM, ed. *Clinical hypertension*. Baltimore: Williams & Wilkins, 1994:47–108.)

Despite no unanimity on the causation of hypertension, the field of antihypertensive therapeutics evolved exponentially from humble beginnings. eFigure 5.0.2 summarizes these developments. Many of the medications were originally developed for other purposes and later applied to hypertension as an afterthought or via serendipity. Most of the reported drug toxicity has been dose related and, therefore, potentially avoidable; perhaps this reflects an early, excessive enthusiasm for high doses not always coupled by close follow-up (18).



***e*FIGURE 5.0.2** Time frame of major developments in antihypertensive therapy by sites or mechanisms of pharmacologic action.

The early array of therapeutic options was severely limited, often poorly tolerated, and inconsistently effective. Progress really began with the arrival of thiazide diuretics, leading to the first therapeutic trials for key clinical outcomes by the late 1960s. Most early trials used diastolic BP criteria (19,20). The decision reflected controversy about how best to approach isolated systolic hypertension that was common among the elderly, who least tolerated the available antihypertensive agents. The results of pioneering clinical trials were wildly encouraging. By starting with patients with greatest diastolic elevations and highest cardiovascular risk, the studies successively demonstrated large benefits for severe elevations (DBP >114 mm Hg) in 6 months (19), moderate elevations (DBP 105 to 114 mm Hg) in 3 years (20), and mild elevations (DBP 95 to 104 mm Hg) in 5 years (21,22).

Each successful trial offered further expectation that extending treatment to other, untested patient groups would yield attractive benefits at acceptable societal and personal cost. In recent years, investigators returned to the elderly—especially those with isolated systolic hypertension—and confirmed net benefit from treatment (23,24,25 and 26). Despite previous worries, the benefits from treating isolated systolic hypertension occurred without demonstrable impact on mood, cognitive function, basic self-care, or leisure activity (27).

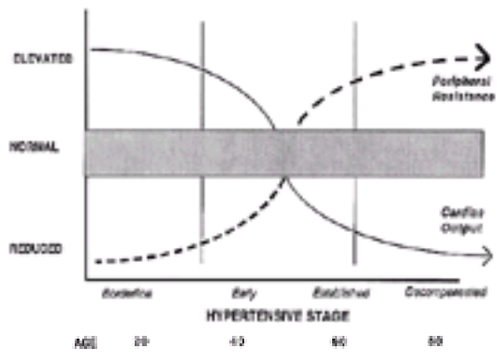
Despite the many advances, hypertension still largely epitomizes the "triple paradox" by which a condition (a) easy to diagnose often remains undetected, (b) simple to treat often remains untreated, and (c) for which, despite available and potent drugs, treatment all too often is ineffective (28).

ANATOMIC CONSIDERATIONS

At its simplest level, the circulatory system consists of a pump, an array of outgoing and returning vessels, and regulatory mechanisms to modify flow and pressure. These components constitute the hemodynamic core: BP as the product of CO (itself made up of stroke volume and heart rate) and peripheral vascular resistance. The vascular smooth muscle of smaller arterioles serves as the principal determinant of peripheral resistance. In large arteries, the structure of the arterial wall determines the pulsatile hemodynamics of pressure and flow. Mechanical wall stiffness, wall thickness, and elastin and collagen content vary along the arterial tree, further contributing to regional differences in pressure and blood flow.

Over the natural lifetime of many hypertensive subjects, the relative proportion of these components undergoes a predictable evolution. The early predominance of

elevated CO gives way to normal or even reduced levels, whereas peripheral resistance rises. This sequence is summarized in *e*Figure 5.0.3 (29).



***e*FIGURE 5.0.3** Evolution of hemodynamic patterns from borderline or early hypertension through its advanced or decompensated states. (Adapted from Messerli FH, Garavaglia GE, Schmieder RE, et al. Disparate cardiovascular findings in men and women with essential hypertension. *Ann Intern Med* 1987;107:158–161.)

This model provides insight into the hypertension of early pregnancy and hyperthyroidism. Both conditions reflect high CO with relatively normal or even reduced peripheral resistance. In contrast, most patients with chronic primary hypertension exhibit reduced CO and elevated peripheral resistance.

The hypertensive patient responds to interventions for lowering BP in predictable ways, often as if to restore BP to its elevated, preintervention level. Most commonly, the body compensates with fluid retention, increased heart rate, or both.

PATHOPHYSIOLOGY

As summarized in *e*Figure 5.0.1, the numerous factors affecting BP control are complex in themselves and their interrelationships. Striking examples of the interdependencies include observations that insulin resistance precedes hypertension in individuals genetically predisposed to it (30) and that hyperinsulinemia, salt sensitivity, obesity, and increased sympathetic drive are covariants (31).

Genetic Factors

BP has been called “a quantitative multifactorial trait” with environmental and genetic determinants (32). Essential hypertension occupies simply one extreme of the BP distribution (33). Variation in BP represents the combined effects of multiple genes rather than single gene disorders with discrete separation (34). A strong family history (³2 first-degree relatives with hypertension before age 55 years) predicts a future occurrence of hypertension with a relative risk (RR) of 3.8 (35). Obesity, hypertension, and the associated metabolic syndrome occur from childhood through to adult life, underscoring the importance of early prevention (36). In the majority of hypertensive patients, the hereditary determinants of BP elevations remain unknown. The search for genetic determinants is handicapped by the absence of a marker to identify prehypertensive individuals before the pressure rises because, thereafter, the initiating factor may be rendered unrecognizable.

To date, four gene mutations have been implicated in human hypertension: (a) syndrome of apparent mineralocorticoid excess, (b) glucocorticoid-remediable aldosteronism (from ectopic expression of aldosterone synthetase enzymatic activity), (c) Liddle’s syndrome (b-subunit mutations of the amiloride-sensitive epithelial sodium channel), and (d) primary hypertension in some whites (variants at the angiotensinogen locus) (37,38). Family pedigrees indicate that greater left ventricular (LV) wall thickness and mass, altered vascular capacity, and pressor responsivity all occur more commonly among normotensive individuals with a positive family history than among normotensive controls (39).

Sodium Intake

Primitive societies have had diets characterized by low salt (10 to 30 mmol per day) and high potassium intakes. In such settings, hypertension is rare. Only a subset of people (20% to 50%) appears to be salt sensitive by showing a pressor response when fed diets of more than 50 mEq sodium per day (~1/2 tsp of salt per day, because 1 tsp of salt = 6 g salt = 2.4 g sodium = 104 mEq sodium = 104 mmol sodium). Most Americans consume substantially more than this level. Proving the unique contribution of excessive salt intake, however, is difficult. Some have argued that the sodium-potassium ratio or the chloride intake may be crucial. Still, most data support a role for dietary sodium excess in producing hypertension in some individuals (40,41).

Despite attractive theories to the contrary, Intersalt—the superbly executed, worldwide study of salt intake and BP (10,079 subjects from 32 countries)—was unable to confirm a consistent relationship between dietary salt intake and BP in diverse settings (42). In other studies, no single marker has predicted salt sensitivity with accuracy. Even the reproducibility of salt loading in such individuals leading to pressor responses has been questioned (40). A recent metaanalysis of 56 published trials could confirm only 3.7/0.9 mm Hg reductions in systolic and diastolic pressures among 1,131 hypertensive subjects who reduced dietary salt intake by 100 mmol per day (41).

Given these small differences, testing for salt sensitivity cannot be justified in routine clinical practice, especially because the standard protocol is difficult to administer: determination of baseline BP after a 4-hour infusion of 2 L of normal saline, and then comparison with BP after 1 day of a 10-mmol sodium diet coupled with three oral doses of furosemide at 10 a.m., 2 p.m., and 6 p.m. in search of ³10 mm Hg decline in mean BP.

Natriuresis and Renal Function

In healthy individuals, homeostasis prevails. When BP rises, sodium and water excretion via the kidneys increases to return BP to baseline. This process is termed *pressure natriuresis*. Among hypertensives and prehypertensives, renal blood flow appears reduced compared to normotensives. The causative sequence may include preferential constriction of efferent arterioles (perhaps via the renin-angiotensin system), reduction in renal blood flow, and increased filtration fraction. The peritubular capillary blood with less sodium and water develops higher oncotic pressure and facilitates sodium reabsorption, leading to higher blood volume and higher BP. Pressure natriuresis occurs but only to sustain BP at a higher level.

In some individuals, renal function may contribute to elevated BP after reductions in filtration surface area from lower numbers of functioning nephrons. Controversy surrounds whether both the number and the function of nephrons are reduced, either globally or in a patchy distribution (43). Intrarenally, prostaglandin function—especially prostaglandin E_2 influencing natriuresis and prostaglandin I_2 modulating renin release—may serve as intermediary derangements (44). Regardless of the precise mechanism, the kidney acts to return the pressure all the way back to a balance of input and output—the “set point” of the system—even if disease has deranged the set point to pathologic levels (45).

Renin-Angiotensin System

Since its discovery in 1898, renin has assumed growing importance as a pressor hormone and a growth factor. A single-chain polypeptide, renin is secreted from the renal juxtaglomerular apparatus in response to macula densa signals of lowered cytosolic calcium, decreased renal arteriolar pressure, or increased renal alpha- or beta-adrenergic nerve activity. Renin likely has no physiologic effect except for stimulating the activation of angiotensin I from angiotensinogen. Angiotensin I, in turn, undergoes conversion to the four–amino acid angiotensin II (AII, sometimes called *angiotensin 1-8*) in multiple tissues, especially the lung. AII becomes inactivated by angiotensinases that are present in many tissues, especially red blood cells. Complete renin-angiotensin systems operate in the brain, reproductive tract, and heart and play physiologic roles in epithelial, fibroblast, and macrophage cell function (46).

The principal effects of AII consist of the following: (a) vasoconstriction that leads to elevated BP by inhibiting adenylate cyclase mediated through G proteins, particularly for the kidney’s efferent arterioles; (b) volume retention via promoting aldosterone secretion by the adrenal and stimulating antidiuretic hormone and thirst; and (c) vascular hypertrophy, especially in the heart, peripheral vessels, and renal vasculature (47,48). Of the two AII receptors, the AT_1 subtype mediates all the known actions of AII on BP control and is widely distributed in the body (49).

From first principles, one would predict that renin levels would be low among most hypertensive patients because the kidney “sees” higher than normal pressures. This is not the case. Renin levels may remain normal despite hypertension from abnormal modulation in response to AII by renal and adrenal tissues, both of which blunt aldosterone secretion in response to sodium restriction and do not increase renal blood flow after sodium loading (50). Compared to normotensive controls, hypertensive patients and offspring of hypertensive parents exhibit lower levels of renin and renal blood flow and a greater responsiveness to subpressor doses of AII (51). Thus, available data support a view of distorted homeostatic mechanisms within the renin-angiotensin system that contribute to establishing and maintaining hypertension.

Over more than two decades, controversy has raged about the utility of renin profiling in predicting cardiovascular prognosis and optimal therapy for hypertensive patients. One study reported differential rates of MI among 1,717 mild to moderate hypertensives followed for more than 8 years; these rates were based on high, normal, or low renin-sodium profiles (52). Pending confirmatory reports from other studies, renin profiling is still not standard practice, although it is useful in some cases of refractory disease (53).

Sympathetic Nervous System

In parallel with the renin-angiotensin systems, the sympathetic nervous system (SNS) may couple with high sodium intake to raise BP. Often, stress activates the SNS, especially in patients genetically or environmentally predisposed to respond with increased levels of epinephrine, norepinephrine, and neuropeptide Y (54). Baroreceptor sensitivity—both sinoaortic and cardiopulmonary—rapidly undergoes resetting and decreased sensitivity among hypertensives, predisposing to heightened BP variability (55). Catecholamine-mediated vasoconstriction may contribute to changes in efferent arterioles. In parallel with diurnal cortisol variation, increases in a-sympathetic activity likely play a role in early morning pressor responses. Higher BP, higher pulse rates, and increased risk for cardiovascular events all ensue (56,57).

Increased sympathetic activity serves as initiator and sustainer of hypertension, promotes the development of LVH, and predisposes to dysrhythmias and sudden death. The link between obesity and hypertension may reflect increased renal sympathetic tone without suppression of cardiac norepinephrine spillover (58).

The precise role of psychological stress remains largely undefined. Most likely, its effects depend on complex interactions among the nature of the stressor, the individual’s perception of the stress, and the individual’s physiologic susceptibility (59). In this way, people may become hypertensive because they respond differently to stress, not merely because of the stress itself. Such hyperreactivity is demonstrable among hypertensives and their normotensive offspring when compared to normal controls (60). The most common pattern is one of greater anger and hostility, along with greater suppression of these emotions. These patterns are more sustained among hypertensives and their offspring than among controls.

As hypertensive patients age, their sympathetic system tone—as measured by neurotransmitter levels—tends to fall, as if less sympathetic drive is needed to maintain neurogenic hypertension once it is established (61).

Vascular Constriction and Vascular Remodeling and Hypertrophy

The simple notion of the circulatory system as a collection of passive pipes attached to a pump is incorrect. *In vivo*, systemic resistance vessels depend on complex interactions among smooth muscle contractility, the vessels’ geometric design, vessel wall distensibility, and distending pressure (62). Structural changes increase the ratio between wall thickness and lumen diameter, in turn producing higher wall stress and intraluminal pressure when resistance vessels are sympathetically stimulated.

The vascular tree acts like a Windkessel system, in which there is a distensible component that absorbs energy during systole and releases it during diastole. The net effect is to sustain perfusion to peripheral vascular beds, despite the rhythmic cardiac contractions. In hypertension, vessel wall compliance (i.e., the change in vessel diameter for a given change in pressure) falls. This reduction occurs throughout the arterial side but predominantly among smaller, distal, resistance vessels, rather than large or medium-sized vessels, and increases dramatically with age (63). These changes result from a multitude of vasoactive trophic factors originating within the vessel wall itself (64).

Regardless of the specific initiating events, hypertension is maintained by vascular hypertrophy, which sustains elevated peripheral resistance. In such a pathophysiologic formulation, hypertension proceeds in two steps: (a) an initiating step by which any one of an array of possible small, largely undetectable perturbations occurs, especially in the context of those genetically or environmentally predisposed to derangement; and (b) an amplification step, which is slow, progressive, ultimately large, and likely nonspecific (65).

Cell Membrane Alteration

Abnormal ionic fluxes across cell membranes potentially affect both vessel tone and hypertrophy. The contractile machine of vascular smooth muscle consists of thick and thin filaments, similar to the model of skeletal muscle. The force of contraction reflects cycling activity of myosin bridges, which is initiated by an increase in intracellular calcium concentration and determined by the degree of phosphorylation of the myosin light chain (66). Most attention, therefore, has focused on fluxes of sodium and calcium ions.

Despite more than a decade of *in vitro* studies, there remains considerable skepticism about the relevance of the findings to human hypertension (67). Five sodium transport systems have potential involvement: (a) Na^+ channel, (b) Na^+-H^+ antiport/Na^+-Li^+ countertransport exchange, (c) Na^+-K^+-Cl^- cotransport, (d) Na^+-Ca^{2+} exchange, and (e) Na^+-K^+ ATPase pump. If dysfunctional Na^{2+}-H^+ transport occurs, increased intracellular Na^+ accompanies intracellular alkalinization (a recognized stimulus for cell growth) and increased intracellular Ca^{2+} (a stimulus for vascular reactivity). In this way, defects in sodium elimination might be unmasked only when sodium intake rises substantially, perhaps above a threshold level.

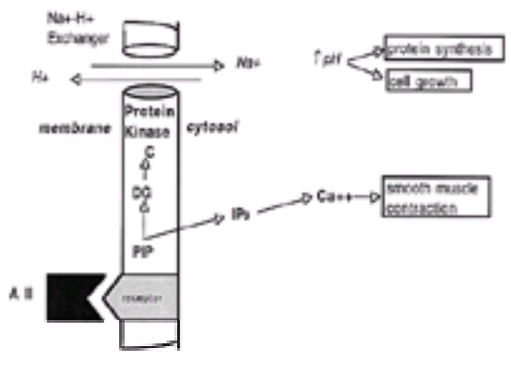
Some authors challenge that intracellular sodium is increased in hypertension. The multitude of other reported abnormalities may be nothing more than markers for the disturbed physicochemical properties of the cell membrane (68). More intriguing are the correlations between ion transport defects and plasma lipid levels that further link dyslipidemia and hypertension (69). Na^+-Li^+ countertransport appears to be increased in subsets of patients with hypertension, dyslipidemia, pregnancy, and diabetes mellitus (70).

Similarly, three reported defects in calcium transport have emerged that involve (a) the Ca^{2+} pump, (b) the Na^+-Ca^{2+} exchange, and (c) the dynamic release and sequestration of free Ca^{2+} between cytosol and mitochondria (71). As little as a 5% increase in intracellular Na^+ by inhibiting the sodium pump could inhibit Na^+-Ca^{2+} exchange enough to increase the resting tone of vascular smooth muscle by 50% (72). The two cation regulatory clusters may be linked through at least two interrelated cellular pathways: the kinase/phosphatase cascade and the Ca^{2+}/calmodulin system (73). While the specifics remain debatable, strong and plausible links among cell membrane alterations, vascular reactivity, and cell growth continue to appear.

Vascular Hypertrophy

Many of the same factors that produce immediate pressor responses also yield trophic influences for protein synthesis and cell growth. *In vitro* studies confirm that AII can increase protein synthesis within aortic cells by 80% within 24 hours of application (74) and induce protooncogene and growth factor genes within 30 minutes (75). At least seven distinct growth factors for vascular smooth muscle have been described, including platelet-derived growth factor, insulin-like growth factor, and transforming growth factor-b (47).

At a cellular level, the sequence generally follows this order: (a) once stimulated, the growth factor (e.g., AII) occupies its membrane receptor; (b) receptor occupancy activates membrane phosphodiesterase, which hydrolyzes phosphatidylinositol biphosphate; (c) the hydrolysis introduces inositol triphosphate into the cytosol and retains 1-2-diacylglycerol in the membrane; (d) inositol triphosphate releases calcium from nonmitochondrial organelles, producing smooth muscle contraction; (e) as a second messenger, diacylglycerol activates protein kinase C, which controls the Na^+-H^+ exchanger; (f) Na^+ enters the cell and H^+ leaves it; and (g) the cell becomes more alkaline, stimulating the nucleus to initiate protein synthesis and division. eFigure 5.0.4 schematically summarizes the process, although the process and components likely are more complex (76).



***e*FIGURE 5.0.4** Schematic of intracellular mechanism by which angiotensin II (AII) produces enhanced Na^+-H^+ exchange, smooth muscle contraction, protein synthesis, and cell growth. See text for details. DG, 1-2-diacylglycerol; IP_3, inositol triphosphate; PIP, phosphatidylinositol biphosphate. (Adapted from Kaplan NM. Primary hypertension: pathogenesis. In: Kaplan NM, ed. *Clinical hypertension*. Baltimore: Williams & Wilkins, 1994:47–108.)

Two components are distinguishable. The contraction stimulus and response are finite and short-term, whereas cellular growth occurs once tissue stimulation is prolonged. Antihypertensive treatment may partially reverse structural changes (77).

Much of the smooth muscle cell growth and remodeling occurs as a consequence of endothelium-derived growth factors in response to shear forces, intravascular pressure, circulating hormones, and platelet factors (78). One of the most critical is endothelium-derived relaxing factor—later determined to be nitric oxide (NO)—released into the lumen to inactivate platelets and into the vessel wall to relax vascular smooth muscle. Hypertensive subjects often display blunted vasodilatory response to various stimulations of endothelially dependent factors (79)—a defect not corrected by antihypertensive therapy (80). As another link to cardiovascular risk, hypercholesterolemia produces NO inactivation by the lysolecithin component of oxidized lipoprotein that is, in turn, reversed by L-arginine stimulating NO production (81).

A growing litany of endothelial mediators has emerged with many postulated interactions and interdependencies. The major factors include prostacyclin, NO, superoxide anion, endothelin, endothelium-derived hyperpolarizing factor, prostaglandin H_2, thromboxane A_2, serotonin, and platelet-derived factors.

Hyperinsulinemia and Insulin Resistance

Hyperinsulinemia and insulin resistance commonly coexist with essential hypertension, augmenting the overall cardiovascular risk profile. In contrast, secondary hypertension does not lead to insulin resistance. Prospective follow-up of individuals with elevated fasting insulin demonstrated a high correlation with subsequent development of hypertension at two- to threefold higher rates than controls (82). The association is not perfect; individuals from ethnic groups with high prevalence of diabetes mellitus (e.g., Mexican Americans and Pima Indians) do not display higher incidences of hypertension. Undoubtedly, complex interactions among genetic, environmental, and other factors determine the clinical outcomes (83), because insulin's ability to mediate glucose disposal can differ by as much as tenfold among subjects with normal glucose tolerance (84).

Obese individuals' degree of insulin resistance does not increase if hypertension is present. This lack of additive effect suggests that hypertension, exogenous obesity, and diabetes mellitus may act independently but along a final, common pathway (85). A review of 25 prospective studies correlating plasma insulin levels with heart disease did not support hyperinsulinemia by itself as a major cardiovascular risk factor (86). In contrast, insulin resistance correlates closely with atherosclerosis, thrombogenesis, hypertension, obesity, and diabetes mellitus (87,88).

The vasodilatory effects of insulin appear blunted among hypertensives, compounded by the increased SNS tone of obesity and the insulin resistance all three conditions share (89). Other proposed mechanisms by which insulin resistance and hyperinsulinemia may lead to hypertension include (a) increased sensitivity to dietary salt intake, (b) heightened renal sodium and water reabsorption, (c) augmented pressor and aldosterone responses to AII, (d) increased Na^+-H^+ pump activity and decreased Na^+-K^+ ATPase activity leading to augmented intracellular Na^+, (e) increased intracellular Ca^{2+}, (f) stimulation of vascular smooth muscle growth factors, (g) stimulation of SNS activity, (h) reduced vasodilatory prostaglandins, (i) increased endothelin secretion, and (j) impaired vasodilation (90). Not surprisingly, given the several overlapping effects, hypertension may be clustered with obesity, dyslipidemia, glucose intolerance, and type II diabetes mellitus; sometimes, these conditions are lumped together as "metabolic syndrome X" or "insulin resistance syndrome." Individually and collectively, these conditions lead to accelerated atherosclerosis and cardiovascular disease (91).

Other Potential Contributors

The list of other potential causes of primary hypertension is long and diverse, although the evidence in support of their role is less convincing.

Atrial natriuretic factor is one of several natriuretic peptides that can increase glomerular filtrate without increasing renal blood flow, relax preconstricted vasculature (especially in the renal bed), reduce systemic BP, and suppress renin levels and its secretion (92). Despite a number of attractive hypotheses linking decreased levels or altered responsiveness of atrial natriuretic factor to the pathogenesis of hypertension (93), strong evidence remains elusive (94).

Prostaglandins undoubtedly play important roles in circulatory control and thrombosis. Their role in primary hypertension is less clear, although it likely contributes to preeclampsia (95). Prostacyclin inhibits platelet aggregation, relaxes vascular smooth muscle, and promotes natriuresis. Prostaglandin E_2 causes vasodilation, whereas prostaglandin F_2a causes vasoconstriction.

Interleukins, such as interleukin-1, may inhibit angiotensinogen synthesis, whereas interleukin-6 may enhance the protein-producing messenger RNA transcription rate (96).

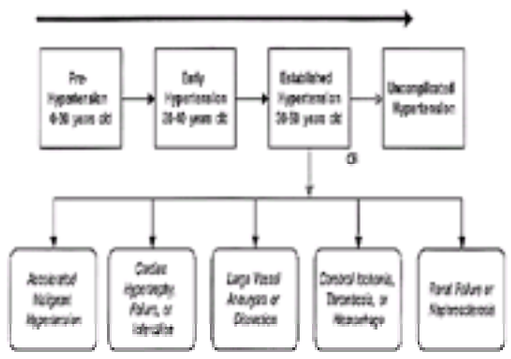
Medullipin serves as a counterbalance to AII. It is secreted from renal medullary cells but requires activation by the hepatic cytochrome P-450 system for its effect, independent of renin-angiotensin or autonomic nervous function (97).

To date, there have been no convincing data on the role of dietary calcium, potassium, magnesium, lead, zinc, or cadmium in causing primary hypertension. Caffeine may cause pressor effects in the uninitiated but rapidly accommodates (90). In contrast, chronic alcohol use, especially in excess of two drinks per day, may elevate BP and increase mortality (98).

CLINICAL PROFILE

Natural History of Hypertension

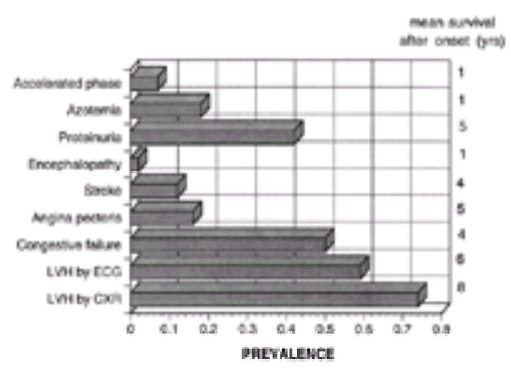
Whether viewed as a distinct disease or as a cardiovascular risk factor, hypertension commonly produces structural changes in arteries and target organs in a variety of patterns. This sequence appears in *e*Figure 5.0.5.



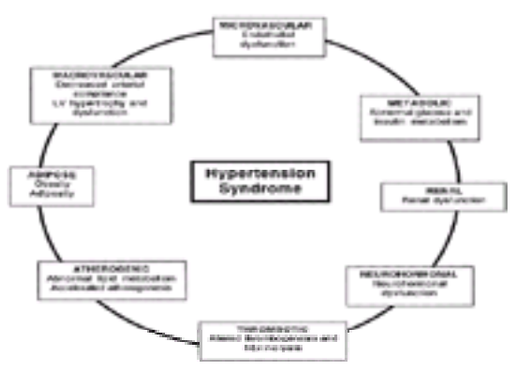
***e*FIGURE 5.0.5** Sequence of stages by which hypertension may evolve and affect one, some, or all key target organs. (Adapted from Kaplan NM. Natural history, special populations, and evaluation. In: Kaplan NM, ed. *Clinical hypertension*. Baltimore: Williams & Wilkins, 1994:109–143.)

During the prehypertension phase, repetitive perturbations of cardiovascular homeostasis occur, reflecting an array of hereditary and environmental factors. In time, these small changes accumulate and yield larger changes that are recognizable as early hypertension. If the BP elevations are caught in time and reversed by lifestyle changes, normalization may occur. In the Australian Therapeutic Trial, 13% of screenees with entry DBP >95 mm Hg had spontaneous BP reduction that continued for at least 1 year. An additional 48% of subjects' BPs remained <95 mm Hg while on placebo treatment for 3 years (21).

Patients with sustained elevations may progress to established hypertension. Subsequent events are somewhat difficult to predict in individual patients, because BP on its own provides only the most crude index of prognosis. Observed log-linear associations between BP and risk of coronary heart disease death display approximately constant risk regardless of the specified definition of hypertension (99). A few individuals (<5%) enter a fulminant course with rapid deterioration in cardiac, renal, and neurologic function. Another distinct subset (»20%) undergoes a more subdued course, commonly producing moderate to severe target organ changes with progression over years, rather than over weeks to months. The most common organ systems involved with these destructive processes include (a) the heart itself (diastolic dysfunction, LVH, endocardial scarring, CHF, and coronary insufficiency), (b) the large and medium-sized arteries (accelerated atherosclerosis, aneurysm formation with or without dissection), (c) the brain and intracranial circulation (ischemia, infarction, whether hemorrhagic or thrombotic), and (d) renal circulation (nephrosclerosis, with or without renal failure). These target organ complications reflect a wide array of contributing factors, often inherited, that extend well beyond elevated BP alone. This cluster has been termed *hypertension syndrome* (100). One patient series antedating effective antihypertensive therapy gives a glimpse of the array and progression of events, as summarized in eFigure 5.0.6. eFigure 5.0.7 displays the cluster of pathophysiologic derangements of the hypertension syndrome.

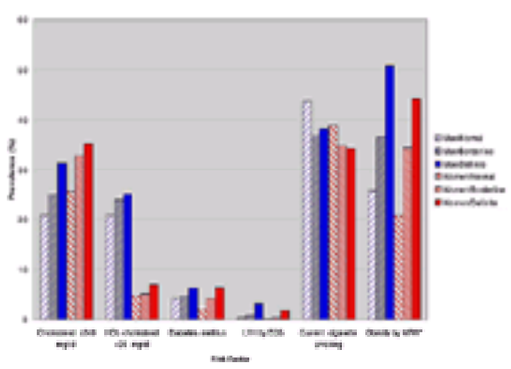


***e*FIGURE 5.0.6** Data from era before effective antihypertensive therapy, highlighting the array of major hypertension-related complications and the mean survival after onset. CXR, chest x-ray; ECG, electrocardiogram; LVH, left ventricular hypertrophy. (Adapted from Perera GA. Hypertensive vascular disease: description and natural history. *J Chron Dis* 1955;1:33–42.)



***e*FIGURE 5.0.7** *Hypertension syndrome* refers to a complex of inherited alterations of physiology that affects multiple tissues and target organs. The alterations emerge, persist, and sometimes even progress, even if the elevated blood pressure is reduced to normal levels. Consequently, such individuals remain at increased risk for cardiovascular morbidity and mortality; their conditions may partially explain the limited success in reducing coronary heart disease despite antihypertensive therapy. LV, left ventricular. (Adapted from Neutel JM, Smith DH. Hypertension control: multifactorial contributions. *Am J Hypertens* 1999;12:164S–169S.)

The majority of individuals displays an indolent course in which changes occur over decades; these changes usually are mediated by diffuse atherosclerosis and predispose to stroke, heart attack, congestive failure, renal dysfunction, and peripheral arterial insufficiency. The specific events and time course for an individual are greatly affected by comorbidities, especially dyslipidemia, cigarette smoking, diabetes mellitus, and exogenous obesity, as well as other factors such as sedentary lifestyle, salt intake, and situational stress. In addition, the occurrence of target organ damage such as LVH or peripheral arterial insufficiency makes subsequent target organ damage more likely (101). eFigure 5.0.8 illustrates the prevalence of many of these factors in the Framingham cohort.



***e*FIGURE 5.0.8** Data from the Framingham Heart Study (1970–1982) summarizing the prevalence of key cardiovascular risk factors by hypertensive status among adults aged 35 to 64 years. ECG, electrocardiogram; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; MRW, Metropolitan relative weight. (Adapted from Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996;275:1571–1576.)

Most hypertension first appears before age 50 years. Early stages are commonly labile or borderline in the degree of elevation. Only 20% of new cases present over age 60 years in the context of regular BP checks (102). As the population ages, individuals—hypertensive or not—are more likely to sustain a cardiovascular event. At all ages, women display a better prognosis for hypertension-related complications, providing the basis for higher treatment thresholds (eFig. 5.0.8). Adult blacks in the United States display higher levels of BP and a higher prevalence of hypertension, as well as higher rates of hypertension-related complications (103). A number of hypotheses to explain the higher rates include (a) unique genotypes, (b) differences in sodium sensitivity and sodium transport, (c) stress, (d) increased vascular responsiveness, (e) growth factor responsiveness, (f) diet, and (g) insulin resistance (104). The American Southeast has long displayed especially high prevalence of hypertension and its complications, perhaps in part because of suboptimal access to medical care and close follow-up (103).

Among hypertensives, as with most other Americans, death usually results from ischemic heart disease. Individuals with severe, resistant disease often die of strokes, whereas those with severe retinopathy or renal dysfunction at first presentation tend to die of renal failure. The presence of demonstrable atherosclerosis (e.g., carotid stenosis, lower extremity arterial insufficiency) substantially increases mortality among patients with hypertension. Over a 4-year follow-up, mortality among patients with atherosclerosis was fivefold higher (23% vs. 5%) than those without atherosclerosis (105).

The pathologic changes include (a) hyperplastic or proliferative arteriosclerosis; (b) hyaline arteriosclerosis affecting intima and media and narrowing the lumen; (c) miliary aneurysms especially in small, penetrating, cerebral arterioles; (d) atherosclerotic or nodular arteriosclerosis producing plaques that narrow the lumen and trap thrombi; and (e) other media changes such as cystic medial necrosis predisposing to dissections.

Effective treatment that reduces BP dramatically changes the natural history of hypertension-related end points, especially for cerebrovascular events and, somewhat less so, for coronary events. Hypertension carries a high population-attributable risk for subsequent CHF, accounting for 39% of cases in men and 59% in women. The overall RR of CHF in 12 randomized controlled trials between 1967 and 1991 was reduced to 0.48 [95% confidence interval (CI), 0.38–0.59] among treated versus control subjects (106). As in most situations, preventing the end organ damage is more effective than trying to reverse the changes once they are established. There continues to be controversy about the optimal drug therapy for hypertension, especially to prevent major target organ damage, as occurs in stroke, MI, and renal dysfunction (107). The proportions of American hypertensives who are aware of their condition (50% to 82%) and who are treated for it (37% to 72%) have increased dramatically in the last two decades, but the percentage of patients consistently controlled with their medications remains at <30% (108), illustrated by Figure 5.1. The benefits of treatment accrue to both genders (109).

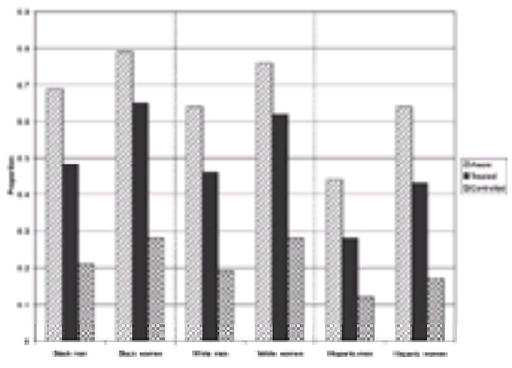
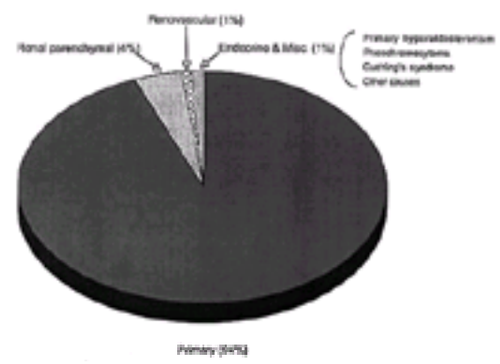


FIGURE 5.1 Data from National Health and Nutrition Examination Survey III (NHANES III) Study classifying American hypertensives by gender, ethnic group, and hypertensive status: Aware of hypertension, under treatment for hypertension, and controlled by treatment. (Adapted from Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995;25:305–313.)

Common Presentations

The vast majority of hypertensive patients (93% to 95%) displays no demonstrable, curable abnormality of anatomy or physiology (110). Termed *primary hypertension*, the condition carries no consistent hallmark symptoms or signs, except for the elevated BP itself. Most cases are detected incidentally as part of routine examinations and generally in the absence of target organ damage at initial presentation. Reports of headache, dizziness, fatigue, palpitations, and chest discomfort occur commonly among hypertensive and nonhypertensive patients. Because the symptoms prompt clinician attention, hypertension is more likely to be detected among patients with symptoms. For the majority of hypertensives, symptoms and symptom levels do not correlate well with BP level (111).

Even among individuals with proven secondary hypertension, clinical presentations are often nonspecific. Together accounting for 5% to 7% of all hypertensives, secondary causes represent a diverse collection of conditions. Renal parenchymal disease is the most common condition and occurs often in the context of known predisposing illnesses such as diabetes mellitus, connective tissue disease, or drug toxicities. The early (<age 30 years) or late (>age 65 years) onset of hypertension moderately raises the likelihood of secondary causes. The section Evaluation for Secondary Forms of Hypertension explores specific constellations of symptoms and signs by secondary cause (eFig. 5.1.1).



***e*FIGURE 5.1.1** Prevalence of primary versus secondary hypertension among unselected adult patients, based on composite data from several studies in diverse international sites. See text for references.

Establishing the Diagnosis and Risk Profile

The Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure has defined hypertension as indirect, sphygmomanometric levels of ³140 mm Hg systolic, ³90 mm Hg diastolic, or both (5). Other groups have urged more stringent thresholds for high-risk populations such as diabetics in special danger of target organ damage, infants, children, and pregnant women. The standard criteria, cardiovascular risk factors, and consequent treatment and risk categories are summarized in Table 5.1, *e*Table 5.1.1, and Table 5.2.

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Optimal	<120	<80
Normal	<130	<85
High normal	130–139	85–89
Hypertension		
Stage 1	140–159	90–99
Stage 2	160–179	100–109
Stage 3	≥180	≥110

[a]When systolic and diastolic pressures fall into different categories, the higher category should guide the classification.
Adapted from Joint National Committee. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413–2446.

TABLE 5.1 BLOOD PRESSURE CLASSIFICATION—ADULTS ³18 YEARS OLD[a]

***e*TABLE 5.1.1** CARDIOVASCULAR RISK STRATIFICATION IN PATIENTS WITH HYPERTENSION

Major risk factors	Target organ damage or clinical cardiovascular disease
Smoking	Heart diseases
Dyslipidemia	Left ventricular hypertrophy
Diabetes mellitus	Angina or prior myocardial infarction
Age >60 yr	Prior coronary revascularization
Gender (men and postmenopausal women)	Heart failure
Family history of cardiovascular disease: women <65 yr old or men <55 yr old	Stroke or transient ischemic attack
	Nephropathy
	Peripheral arterial disease
	Retinopathy

Adapted from Joint National Committee. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413–2446.

Blood pressure stage	Risk group A[a]	Risk group B[b]	Risk group C[c]
High normal (130–139/85–89 mm Hg)	Lifestyle modification	Lifestyle modification	Drug therapy
Stage 1 (140–159/90–99 mm Hg) (72% of all hypertensives)	Lifestyle modification (12 mo	Lifestyle modification (6 mo	Drug therapy
Stage 2 (160–179/100–109 mm Hg) (22% of all hypertensives)	Drug therapy	Drug therapy	Drug therapy
Stage 3 (≥180/110 mm Hg) (6% of all hypertensives)	Drug therapy	Drug therapy	Drug therapy

[a]Risk group A: No cardiovascular (CV) risk factors; no clinical CV disease; no target organ damage.
[b]Risk group B: One CV risk factor; no clinical CV disease; no target organ damage; no diabetes mellitus.
[c]Risk group C: Clinical CV disease or target organ damage or diabetes mellitus (± CV risk factors).
Adapted from Ovrga SG, Black HR, Cohen JD, et al. The sixth report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. Am J Hypertens Suppl 1998;6:348–375S.

TABLE 5.2 DEFINITIONS AND RISK STRATIFICATION FOR HYPERTENSION

By single BP determinations, nearly one in every four adult Americans have hypertension. Using the somewhat more stringent criteria of intercurrent antihypertensive drug therapy or ³2 occasions with sustained BP elevations, the prevalence falls to 35 to 45 million Americans. Its prevalence rises with advancing age, from <5% among individuals under age 29 to >50% among those over age 60 (113). On average, black women develop hypertension 10 years before white women do. As the population ages and women tend to outlive men, the number of hypertensive women continues to predominate with higher attributable risk than that of men, even though men and women develop hypertension at comparable rates (3). Each year, approximately 2 million new hypertensive patients are added to the pool of Americans who may benefit from antihypertensive intervention (114).

When assessing a hypertensive patient, the clinician seeks to (a) confirm the existence and magnitude of hypertension, (b) assess the extent of end organ damage, (c) evaluate for contributing comorbidities and risk factors, (d) screen for secondary causes of hypertension, (e) understand any special circumstances that may impact treatment over time, and (f) help create professional trust and the patient's commitment for reducing cardiovascular risk over time. The most important components of initial and follow-up visits in the ambulatory setting are enumerated in Table 5.3.

Initial visit
Evidence for secondary hypertension?
Evidence for target organ damage at presentation?
Clues for optimal future management?
Follow-up visits
Interim symptoms/signs from hypertension-related pathology?
Interim symptoms/signs attributable to antihypertensive treatment?
Obstacles to optimal medication/diet/exercise/other compliance?

TABLE 5.3 COMPONENTS OF AMBULATORY ANTIHYPERTENSIVE MANAGEMENT

Not all patients require drug therapy. For individuals with sustained elevations not responding to nondrug treatments over 3 to 6 months, consistent support has emerged for antihypertensive drug therapy as producing net benefit—even among the elderly with isolated systolic hypertension (23,24,25 and 26)—without compromising quality of life (115). The benefit is especially marked in patients with higher pretreatment BPs (116) or multiple risk factors, rather than in patients with hypertension alone (117).

The critical components of history and physical examination are summarized in *e*Table 5.3.1 and *e*Table 5.3.2; recommended baseline tests are summarized in *e*Table 5.3.3. The highest priorities in gathering history surround the presence or absence of major cardiovascular risk factors, duration and extent of past BP determinations, age of onset, and clinical context, including major comorbidities such as pregnancy, renal insufficiency, or need for chronic medications with pressor effects. Other important components include prior antihypertensive treatments and their effectiveness and tolerability, and patients' perceptions, hopes, and fears about hypertension, its prognosis, and its treatment.

***e*TABLE 5.3.1** INITIAL HISTORY FOR HYPERTENSIVE PATIENTS

Sociodemographics	Age, gender, race, occupation, education, psychosocial constraints
Hypertension history	Duration, monitoring intervals, past evaluations, response to past therapy, recent weight changes
Symptoms of hypertensive complications	TIA, CVA, angina, CHF, arterial PVD, claudication

Symptoms of secondary hypertension	Episodic headaches, palpitations, sweating, weight loss (pheochromocytoma); muscular weakness, cramps, paresthesia, and polyuria (first-degree hyperaldosteronism); weight gain, acne, bruising, hirsutism (Cushing's syndrome); and lower-extremity claudication (coarctation of aorta)
CV risk factors	Dyslipidemia, diabetes mellitus, smoking, high salt intake, saturated fat intake, stress, low activity level, alcohol use, gout; family history of hypertension, CAD (especially if <60 yr old), CVA, diabetes mellitus, dyslipidemia
Complicating comorbidity	Renal or hepatic dysfunction, COPD or asthma, obesity, gout
Medications	All, including pressors (e.g., amphetamines, cocaine, appetite suppressants, diet and cold capsules, nasal sprays), fluid retainers (e.g., oral contraceptives, corticosteroids, NSAIDs), and other (e.g., cyclosporine tacrolimus, MAO inhibitors, erythropoietin, licorice, thyroid hormones)

CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVA, cerebrovascular accident; MAO, monoamine oxidase; NSAIDs, nonsteroidal antiinflammatory drugs; PVD, peripheral vascular disease; TIA, transient ischemic attack.

***e*TABLE 5.3.2** INITIAL PHYSICAL EXAMINATION FOR HYPERTENSIVE PATIENTS

Vital signs, including ³2 BP determinations (averaged) both supine or sitting and standing, separated by ³2 min; notation and selection of "higher" arm if asymmetric BPs; ankle-brachial index or arm and leg BP
Weight and height, calculation of BMI (weight in kg/height in m^2)
Funduscopic examination for retinopathy
Neck examination for carotid artery, jugular venous distention, thyromegaly
Cardiac and chest examination for heart size, murmurs, gallops, arrhythmias, and rales
Abdominal examination for masses, bruits, abnormal aortic pulsations
Extremity examination for peripheral vascular pulses, bruits, edema, and radial-femoral pulse delay
Neurologic examination for baseline assessment and focal findings
Check for stigmata of gout, dyslipidemia, thyroid dysfunction, Cushing's syndrome, neurofibromatosis

BMI, body mass index; BP, blood pressure.

***e*TABLE 5.3.3** INITIAL TESTS FOR HYPERTENSIVE PATIENTS TO ESTABLISH BASELINE LEVELS AND SEARCH FOR CARDIOVASCULAR RISK FACTORS

	Specific tests
Initial	Serum potassium, creatinine
	Blood glucose (preferably fasting) or hemoglobin A1c
	Total, LDL-C, and HDL-C, urinalysis
Desirable but not essential	Complete blood cell count, uric acid, triglycerides, electrocardiogram
Sometimes useful	Plasma renin/urinary sodium ratio, echocardiogram, home or ambulatory blood pressure monitoring

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

The principal components of the focused physical examination are summarized in *e*Table 5.3.2. The most critical component is attention to optimal techniques of BP determination, including properly sized cuff, preparation of the patient, and multiple determinations (118). During the initial visit, the examiner should obtain BP in the supine and upright positions and compare BPs in the arms, noting discrepancies of ³10 mm Hg and taking future BP determinations in the arm with the higher BP. Although it is a time-consuming extra step, the measurement of BP in supine and standing positions offers two insights: (a) the amount, if any, of orthostatic drop and, therefore, the safety margin to start or increase the antihypertensive dose, especially in the frail or elderly; and (b) the less common compensatory responses of tachycardia or even BP elevation when standing. If the heart rate increases but the BP remains unchanged, or if the BP rises rather than falls when the patient stands, one may consider starting or increasing an antiadrenergic agent to slow the compensatory tachycardia or blunt the exaggerated baroreceptor response. The cuff bladder should encircle at least 80% of the arm circumference, and its width should be ³15 cm in the average adult. Rolled sleeves constricting the arm may distort BP values, but thinly sleeved arms display no significant effect (119).

All manometers, especially aneroid units, may lose accuracy over time. Periodic recalibration offers reassurance against some diagnostic errors. In one study of physicians' office practices, 8% of mercury sphygmomanometers were out of calibration by ³4 mm Hg, and 30% of aneroid sphygmomanometers deviated by ³10 mm Hg. In the same study, only 3% of the physicians used the appropriate cuff size on all patients (120). The examiner's characteristics may play an additional role. Higher BP readings may result when the examiner is male rather than female and wearing a white coat rather than dressed in casual clothing (121). The prevalence of "white-coat hypertension" and the degree of transient BP elevations appears consistently higher among women than men (122).

Many problems arise as artifacts of measurement techniques themselves. Perhaps the most critical factors are selection of optimal cuff size for the patient's arm (123), sufficient initial elevation of cuff pressure with confirmation by palpation to avoid auscultatory gaps (124), and proper preparation of the patient (i.e., avoiding full bladder or bowel conditions; cold or uncomfortable ambient temperature; and caffeine compounds, smoking, or physical exertion within 30 minutes of measurement) (125). Arriving late for an appointment, fighting traffic, or having parking difficulty may also cause transiently higher pressures.

To avoid underestimating SBP within an auscultatory gap, the examiner should palpate the radial or brachial pulse during inflation and begin auscultation only after noting the pressure at which the pulse first appears. The systolic pressure is the point at which the Korotkoff sounds first become audible with each heart beat; diastolic pressure is recorded when heart sounds disappear, except in unusual circumstances in which disappearance (phase V) extends close to zero. In such circumstances, using phase IV (muffling) reasonably approximates DBP. When obtaining ³2 BP determinations, the second reading is almost always lower than the first, sometimes by 5 to 10 mm Hg with little subsequent change (126). *e*Table 5.3.4 lists potential errors in BP measurement.

***e*TABLE 5.3.4** POTENTIAL ERRORS IN BLOOD PRESSURE (BP) MEASUREMENT

Equipment
- Inaccurate or uncalibrated manometer
- Improper sphygmomanometer bladder size

Patient preparation
- Not resting for ³5 min in quiet, comfortable environment

Drinking caffeine-containing beverage or smoking within 30 min
Observer technique
- Not supporting arm or torso to decrease muscle artifact
- Not keeping arm position at heart level
- Not centering cuff bladder on brachial artery
- Not estimating systolic BP by palpating radial pulse before auscultation to detect ausculatory gap
- Not keeping eyes at level of mercury manometer
- Not consistently using phase V sounds for diastolic BP (use Korotkoff phase IV if sounds continue until close to 0 mm Hg)
- Inflating bladder too slowly or deflating it too fast
- Not measuring in both arms at first to establish symmetry of BP is present
- Not completely deflating cuff and waiting 1–2 min before remeasurement

General caveats
- Ignoring distortion from any cardiac dysrhythmias
- Ignoring observer bias and digit preference

Clinicians' office settings, even when protected from distractions, interruptions, and irritations, often yield higher BP levels than when determinations occur in less stressed environments such as home. On one hand, office recordings remain the basis for most epidemiologic correlations with subsequent cardiovascular morbidity and mortality. On the other hand, office BP values correlate less well with target organ damage [e.g., eye (127), heart (128), arteries (129), and kidney (130)] than do BPs obtained from home determinations or ambulatory monitoring.

Home or ambulatory monitoring provide the benefit of additional data, especially over a variety of physiologic conditions, compared to the relatively brief times spent in clinicians' offices (131). Home determinations may reduce the need or frequency of physician visits with improved BP control and reduced costs (132). Important cautions about using home BP determinations include the need for thorough instruction in proper BP-taking technique and validation that the specific BP measuring device is accurate (133,134). Most indirect methods using arms cuffs tend to underestimate SBP and overestimate DBP when compared to direct assessment of BP by intraarterial measurement, which is usually reserved for research settings or rare situations in which validation of BP is essential (135).

Ambulatory BP monitoring by electronic technology is rarely necessary for the diagnosis of hypertension (136), but it may prove valuable in isolated cases for whom

white-coat hypertension (137) needs to be excluded (5). No consensus currently exists about the optimal analysis for ABPM data, although the concept of BP load has gained special prominence. The *load* refers to the percentage of readings during which the SBP or DBP exceeds predefined limits (e.g., 140/90 mm Hg while awake and 120/80 mm Hg during sleep). In one study, when the BP load exceeded 40%, the probability of increased LV mass index or decreased LV filling rate was 61%, compared to only 17% when the load was <40% (138). BPs tend to be highest at work, lower at home, and lowest during sleep in most individuals (139).

The remainder of the physical examination should search for target organ damage and evidence of atherosclerotic disease, concentrating on evidence for cardiomegaly, vascular insufficiency, bruits, and possible stigmata of secondary hypertension or comorbidities such as hepatic or renal dysfunction that can complicate therapy. Recent reports indicating increased risk of dementia among the hypertensive elderly (140) and risk of lacunar infarction underscore the importance of a careful baseline neurologic examination.

Hypertension often keeps close company with other cardiovascular risk factors, including diabetes mellitus, dyslipidemia, hyperinsulinemia, and exogenous obesity (82). In the National Health and Nutrition Examination Survey II, the prevalence of hypertension (BP ³160/95) was 2.9 times higher among patients who were overweight compared to those who were not. Obesity brings a two- to sixfold increase in the probability of developing hypertension (141) and may account for 65% to 78% of its attributable risk (142). Upper-body or android fat patterns (apple-like) are more dangerous cardiovascularly than lower-body or gynoid patterns (pear-like) (143), perhaps more in women than in men (144).

The obese patients were also 2.9 times more likely to have diabetes mellitus and 1.5 times more likely to have hypercholesterolemia, whether mediated through relative insulin resistance (145) or changes in cytosolic calcium (146). Most of the individual factors (e.g., hypercholesterolemia, obesity) exhibit an exponential relation to subsequent rates of adverse outcomes, rising disproportionately as the number of risk factors increases. In combination, these risk factors are multiplicative rather than simply additive (147).

Smoking and alcohol use also contribute to hypertension. Cigarette smoking directly and indirectly leads to endothelial damage and accelerated atherosclerosis. Epidemiologically, smoking is negatively associated with BP, relative body weight, and physical activity during leisure; smoking is positively associated with total cholesterol, psychological stress, and alcohol abuse (148). The use of alcohol itself is associated with higher BP (149). Consuming three or more alcoholic drinks a day (»40 g ethanol per day) increases BP, even when controlling for body mass index, cigarette smoking, and age (150).

PRINCIPLES OF MANAGEMENT

Goal of Antihypertensive Therapy

The overall goal of antihypertensive therapy is to prevent cardiovascular morbidity and mortality. Management generally combines nonpharmacologic and drug therapy to optimize BP control. Table 5.4 summarizes recommendations for nondrug therapy.

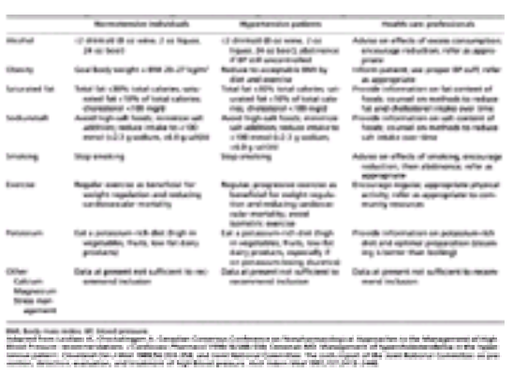


TABLE 5.4 RECOMMENDATIONS FOR NONDRUG THERAPY

Nonpharmacologic Treatment

Most studies confirm that nondrug therapy may be effective for mild or labile hypertension but that combined nondrug and drug therapy is generally more powerful in controlling BP than nondrug treatment alone (151) and more cost-effective for more severe disease (152).

Weight Reduction

Loss of excess weight reduces SBP and DBP. The Trials of Hypertension Prevention (153) produced an average weight loss of 3.8 kg at 18 months, reduction of SBP and DBP by 2.9 mm Hg and 2.3 mm Hg respectively, and a 51% reduction in hypertension incidence among individuals with high normal BP by using caloric restriction and modest physical activity. Similar results have been reported by two other randomized controlled trials of nondrug therapy (154,155) and among patients with morbid obesity (156). None of these trials reported adverse effects from weight loss. Other benefits of weight loss generally include improvement in lipid profile (157) and reduced rates of developing diabetes mellitus, breast cancer, and gout (113).

Most trials confirm that BP reduction is directly related to the weight loss achieved, although less-than-optimal weight loss may still reduce BP to levels below the need for supplemental treatment. If weight gain recurs, hypertension may return, but most trials suggest that the regain is only partial and that long-term benefits of BP reduction persist (153,154 and 155,158).

Exercise

Adding physical activity to a weight-loss program accelerates the weight loss and augments BP reduction (159). An addition of even a 20-minute daily walk can reduce the risk of incident hypertension by 29% (160). The precise mechanism likely involves decreases in CO and peripheral resistance, as well as modifications in serum norepinephrine levels, insulin sensitivity, electrolyte balance, neural and baroreflex mechanisms, and vascular structure (161).

After increased physical activity, BP falls as much as 6 to 7 mm Hg for SBP and DBP, independent of any weight changes (113). Escalating daily activity level may be superior to concentrated workouts three times per week (162), and moderate-intensity endurance exercise proves as effective as higher-intensity exercise for reducing BP (163). To plan exercise programs, summaries of energy expenditures for representative activities and lists of contraindications may be helpful (164).

Dietary Adjustment

Some of the most dramatic evidence supporting nondrug therapy has emerged from the Dietary Approaches to Stop Hypertension trial (165). The study evaluated 459 subjects with mild hypertension (<160/80–95) randomized to usual diet or to a diet with increased fruits and vegetables with or without reduced total and saturated fat intake. Despite lasting only 8 weeks, the combined dietary intervention reduced BP by 11.4/5.5 mm versus 7.2/2.8 mm achieved by increasing fruits and vegetables alone (p <.01). Fully 70% of subjects on combination diet—versus only 45% on increased fruits and vegetables alone and 23% on usual diet—were normotensive at the end of 8 weeks (166). The Dietary Approaches to Stop Hypertension combination diet emphasizes fruits, vegetables, and low-fat dairy products; it includes whole grains, poultry, fish, and nuts and decreases fat, red meat, sweets, and sugar-containing beverages. The precise mechanisms by which such dietary changes can rapidly lower BP remain uncertain.

Sodium Restriction

More than 70 published studies have addressed the impact of reducing sodium intake on BP (40,167). Despite crossover and parallel group comparisons in normotensive and hypertensive trial populations, most trials have been too small to assess definitively the sodium hypothesis of hypertension causation. A metaanalysis of 32 randomized controlled trials of reducing salt intake estimated the net effect of decreasing intake by 100 mmol per day as –6 mm Hg systolic (168). Another review of 56 trials found the BP reduction at –3.7 mm Hg for a mean 95 mmol salt intake reduction (41). A metaanalysis of nine trials of 24-hour urinary sodium

excretion suggested that salt intake was an independent determination of LV mass (169).

Pooled estimates suggest that BP reductions are most impressive among older individuals, those with higher baseline levels of BP, and particularly those who are salt-sensitive (167). Most important, sodium restriction often allows reduction in the need for antihypertensive medications, regardless of combination with weight loss (170). In one trial of sodium reduction with or without weight reduction among elderly hypertensives, 34% to 44% of patients were able to remain off their antihypertensives, compared to only 16% who continued on their usual diet (171). The principal hurdles include maintaining such reductions over the long haul and dealing with the high sodium content of most processed foods (36). Despite these data, the optimal guideline for salt use remains controversial (172).

Alcohol Restriction and Smoking Cessation

Restricting habitual consumption to two or fewer alcohol drinks per day can reduce BP in normotensive and hypertensive individuals and may help prevent hypertension (113). Whereas stopping smoking generally does not reduce BP, its cessation dramatically reduces overall cardiovascular risk. An important caution surrounds the weight gain that commonly accompanies the cessation of smoking and creates a major hurdle to individuals otherwise willing to stop.

The impact of alcohol use occurs in both genders, increases with age, combines with obesity, and may be aggravated by cigarette smoking (36). Among individuals consuming four to six standard drinks a day, the pressor effect lasts throughout the 24-hour period (173). There may also be a withdrawal component to patients exhibiting higher pressures after binge intake (36).

Stress Reduction/Relaxation Training

Some benefit of relaxation, meditation, or biofeedback has been reported from workplace and clinical settings (174,175). One review of 25 published randomized controlled trials enumerated 823 subjects on active treatment, but the studies had many methodologic limitations: small sample sizes (17 of 25 studies had <40 subjects), short duration (average = 3 months), and small effects (176). Only two of five studies with >15 subjects per treatment arm and ³12 months of treatment duration exhibited significant BP reductions. The one randomized controlled trial testing the value of stress management in preventing the development of hypertension could not demonstrate a clear benefit (153). There is insufficient current evidence to support stress reduction as a principal treatment modality for hypertension. Conflicting data exist as to whether high job stress alone is a powerful predictor of subsequent hypertension or whether the methods for coping with stress are more determinant (36).

Other Dietary Changes

Most of the published trials of potassium supplementation have been small, short, and limited to normotensives or subjects with mild BP elevations. Even when the trials were larger, longer, or pooled for data analysis, the net effect of potassium supplementation was modest: 3 to 5 mm Hg net reduction in BP (113,177).

The data in support of calcium's beneficial effect for hypertension are scant. Although 25 randomized controlled trials of calcium supplementation have been reported, most show small or inconsistent results. Even when pooling results from 23 of the trials, the average net reduction in BP was 0.5 to 1.0 mm Hg (113).

Similarly disappointing results have emerged about magnesium supplementation. Of the nine published clinical trials, many are confounded by intercurrent use of antihypertensive medications (113,153). Magnesium supplementation, moreover, frequently caused indigestion, diarrhea, or other gastrointestinal complaints.

No association for BP was demonstrable for total dietary fat (178). Replacing saturated fats with mono- or polyunsaturated fats has produced no significant change in BP, although replacing these fats still is beneficial for reducing overall cardiovascular risk. Similarly, reductions in dietary protein or increases in dietary fiber show no net effect on BP. Fish oil supplements of ³3 g per day (at least two 100-g servings of fish or 6 to 10 fish oil capsules) produced net reductions of 3 to 5 mm Hg among hypertensives that were accompanied by flatulence and a taste and smell found disagreeable to many patients and their families (179).

Selecting Drug Therapy

If 3 to 6 months of nondrug therapy fail to reduce BP to acceptable levels, the clinician should consider antihypertensive medications. *e*Table 5.4.1 summarizes the objectives for antihypertensive drugs (180).

***e*TABLE 5.4.1** OBJECTIVES FOR ANTIHYPERTENSIVE DRUGS

Display efficacy as monotherapy in more than 50% of all patients
Provide 24-h blood pressure control during all activities
Reduce vascular resistance and improve arterial compliance
Preserve cardiac output and maintain perfusion to critical organs
Reverse the pathologic structural changes (e.g., cardiac hypertrophy)
Minimize target organ damage
Avoid tolerance or pseudotolerance
Avoid reflex volume retention or stimulating neurohumoral mechanisms
Reduce ventricular ectopy if present and maintain normal hemodynamic response to exercise
Display favorable biochemical and metabolic effects and favorable profiles in comorbidities
Offer few side effects and good quality of life
Facilitate optimal compliance with drug regimen and offer once-per-day dosing

Adapted from Houston MC. Hypertension strategies for therapeutic intervention and prevention of end-organ damage. *Prim Care* 1991;18:713–753.

No single strategy for selecting antihypertensive drug therapy is relevant and helpful for all patients. Four principal approaches have emerged as useful: stepped care, demographic analysis, renin profiling, and individualization.

Stepped Care

Over the past two decades, the concept of progressive, stepped care has evolved from a narrow set of incremental options to a broader set of guidelines by the Joint National Committee VI (JNC VI) (5):

Step 1—Prescribe lifestyle modifications, including weight reduction, moderated alcohol intake, regular physical exercise, reduced sodium intake, and smoking cessation.

Step 2—If response is inadequate, continue the lifestyle modification and add monotherapy for mild to moderate (stage 1–2) hypertension with thiazide diuretics or beta-blockers, unless there is a contraindication. Other agents [e.g., angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, $alpha_1$-blockers, and alpha-beta-blockers] are satisfactory substitutes for patients with contraindications, although the long-term net benefit of these drugs is not established.

Step 3—If response to initial treatment is inadequate, increase drug dose, substitute another antihypertensive drug, or add a second agent from a different drug class.

Step 4—If response is still inadequate, add a second or third agent from a different drug class, including an appropriate diuretic (if not already administered).

This approach carries several major advantages: simplicity of understanding and implementation, emphasis on administration of complementary drug classes for synergism, and titration to minimize toxicities. The JNC VI offers limited sensitivity to three issues: hemodynamic diversity among hypertensives, negative metabolic effects of thiazides and beta-blockers, and the need for direct testing of stepped care versus alternative approaches.

Demographic Analysis

Several investigators have propounded useful, if simplistic, heuristics that summarize relative responsiveness of demographic subgroups to different antihypertensive drug classes. Although helpful as generalizations, these guidelines reflect relative, not absolute, effectiveness.

Younger patients may exhibit high or normal CO, which is often associated with a sympathetically activated, hyperkinetic circulation. Such individuals may be responsive to ACE inhibitors or antiadrenergic agents such as beta-blockers. Older patients more commonly display low or normal plasma renin activity (PRA), volume expansion, and increased peripheral resistance. Such patterns often respond to diuretic or calcium antagonist therapy. A majority of black hypertensive patients shows volume-dependent, low-renin patterns, compared to about 10% of white hypertensives. Whereas diuretic therapy may be especially effective, other drug classes (e.g., beta-blockers, calcium antagonists, and ACE inhibitors) may also control BP among black hypertensives (181). Such differences in demographic responsiveness to medications decrease when more than one class of antihypertensive agents are used. The demographic and hemodynamic differences offer modest support for the principles summarized in eTable 5.4.2.

***e*TABLE 5.4.2** DEMOGRAPHIC/HEMODYNAMIC CLUSTERING OF RELATIVE RESPONSIVENESS TO MONOTHERAPY BY ANTIHYPERTENSIVE DRUG CLASS

Factor	Diuretics	Beta-blockers	Alpha$_1$-blockers	ACE inhibitors or AII receptor antagonists	Calcium antagonists
Older age (vs. younger)	+++	+	++	++	+++
Black race (vs. white)	+++	+	++	++	+++
Volume dependency (vs. not)	+++	+	++	+	++
High renin (vs. low)	+	+++	+	+++	+
- Sympathetic activity (vs. -)	+	+++	+++	++	++

AII, angiotensin II; ACE, angiotensin-converting enzyme; +, less effective; ++, effective; +++, more effective than comparison group.
Modified from Dzau VJ. Evolution of the clinical management of hypertension. Emerging role of “specific” vasodilators as initial therapy. *Am J Med* 1987;82:36–43.

Renin Profile Analysis

Classification of hypertensive patients into renin-sodium strata may carry prognostic and therapeutic implications (52,183). The process requires assessment of PRA and 24-hour urinary sodium excretion on a stable diet. By such evaluation, hypertensive populations have been categorized as low-renin (20% to 30% of group), normal-renin (50% to 60%), or high-renin (10% to 15%) subtypes. Pretreatment renin-sodium profiles predict differential rates of subsequent MI among high (14.7/1,000 person-years), normal (5.6), and low (2.8) renin-sodium profile subjects (52). These differences occur despite comparable success in BP control among all three groups. No significant differences were observed over more than 8 years of follow-up for stroke or noncardiovascular events.

Therapeutically, high-renin hypertensives reportedly respond better to ACE inhibitors, central alpha$_2$-agonists, peripheral alpha$_1$-blockers, beta-blockers, and nondihydropyridine calcium antagonists. In contrast, hypertensives with low-renin profiles display higher responsiveness to dihydropyridine calcium antagonists and diuretics. Despite the conceptual attractiveness and prognostic implications, renin profiling has not achieved wide acceptance as a method for selecting drug therapy (184). Practical obstacles to the use of renin profiling include cost, inaccuracies and logistics of 24-hour urinary collections, and suboptimal predictive characteristics. Most clinicians find therapeutic trials of particular medications more feasible and less expensive.

Individualized Approach

Perhaps the most comprehensive strategy for selecting antihypertensive therapy is the individualized approach. It factors in patients’ profiles of hemodynamics and pathophysiology, cardiovascular risk analysis, concurrent medical conditions and therapies, demographics, quality-of-life analysis, and cost. In essence, the customized approach corresponds to a type of “mosaic” model of treatment, incorporating a large number of variables that differ for each individual.

The strategy consists of six components. Responding to the projected *pathophysiology and hemodynamics*, the clinician chooses medications to reverse the underlying circulatory dysregulation, lowering the vascular resistance, if elevated, while preserving CO and maintaining perfusion to critical target organs, both at rest and with exercise and over the entire 24 hours.

Reflecting *cardiovascular risk profile analysis*, the clinician should avoid medications that worsen the known risk profile, such as using high-dose thiazides in a patient with elevated low-density lipoprotein cholesterol. In addition, the clinician should prospectively monitor those regimen- affected factors that impact risk and continuously adjust the regimen to minimize overall risk, whether related to atherosclerosis, major arrhythmias, congestive failure, or sudden death (184).

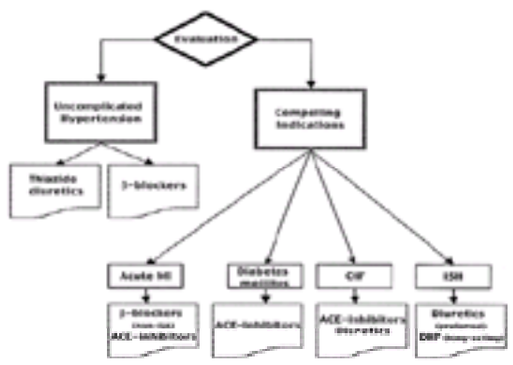
Aware of *concurrent medical conditions and therapies*, the clinician prescribes the fewest antihypertensive drugs to treat the greatest number of concomitant conditions, such as using beta-blockers when angina and hypertension are present in the absence of heart failure, peripheral vascular insufficiency, or bronchospasm. Such therapeutic parsimony facilitates medication adherence by simplifying the overall regimen and minimizes adverse drug reactions and drug-drug interactions. This approach uses the *demographic* patterns previously described but integrates the options related to age and race with the other factors as well (185).

To optimize adherence to the regimen, the clinician seeks to optimize the patient’s *quality of life* by considering physical, mental, social, emotional, and sexual functions (186,187 and 188).

Finally, the strategy considers cost: the sum of drug acquisition cost, required concomitant treatment (e.g., potassium supplementation for thiazide diuretics) and tests (e.g., monitoring serum potassium and renal function), clinician visits, hospitalizations and emergency evaluations, missed work from disease or side effects, and direct and indirect costs of long-term morbidity and mortality, as well as lost wages and productivity (10,189).

The guidelines for initial drug therapy promulgated by the JNC VI reflect these considerations. They incorporate consideration of patient comorbidities and the use of agents proven to reduce mortality in randomized controlled trials.

The JNC VI suggests three pathways for initiating medical treatment in patients requiring drug therapy for hypertension. First, patients with uncomplicated hypertension should be initiated with a beta-blocker or a diuretic. Second, patients with coexisting conditions and “compelling indications” should be started on medications that have been shown to reduce mortality. The choice of these drugs are “compelling” in that they have been shown by randomized controlled trials to reduce mortality in the specific condition (e.g., use of ACE inhibitors in patients with heart failure) and should be used unless strong contraindications to their use exist. Third, patients with comorbidities should be started on medications that are favorable to other medical conditions present (e.g., use of alpha$_1$-blockers in patients with coexisting prostatism) (eFig. 5.1.2).



***e*FIGURE 5.1.2** Flow diagram distinguishing selected “compelling indications” that steer selection of initial antihypertensive monotherapy away from the default choices of thiazide diuretics or beta-blocker treatment. ACE, angiotensin-converting enzyme; CHF, congestive heart failure; DHP, dihydropyridine; ISA, intrinsic sympathomimetic activity; ISH, isolated systolic hypertension. (Adapted from Joint National Committee. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413–2446.)

One controversial strategy to minimize medication-related cost and toxicity is to attempt cautious “step-down” therapy with progressive reduction and, sometimes, discontinuation of therapy—especially for patients with mild elevations (190) or good control, despite imperfect medication compliance (191,192).

Hemodynamics of Essential Hypertension/Drug Effects

Table 5.5 summarizes the effects of antihypertensive drug therapy on concomitant medical conditions and metabolic disorders, and Table 5.6 lists common drug interactions for antihypertensive therapy. Table 5.7 indicates the dosing guidelines and relative advantages and disadvantages by drug.

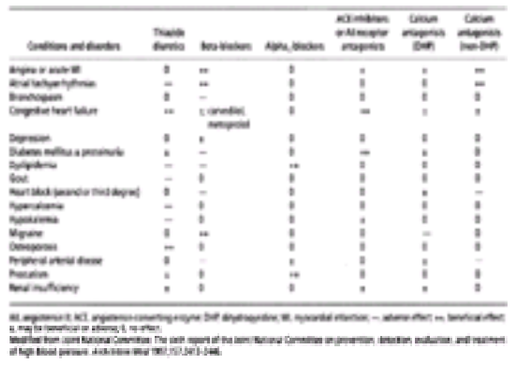


TABLE 5.5 EFFECTS OF ANTIHYPERTENSIVE DRUG THERAPY ON CONCOMITANT MEDICAL CONDITIONS AND METABOLIC DISORDERS

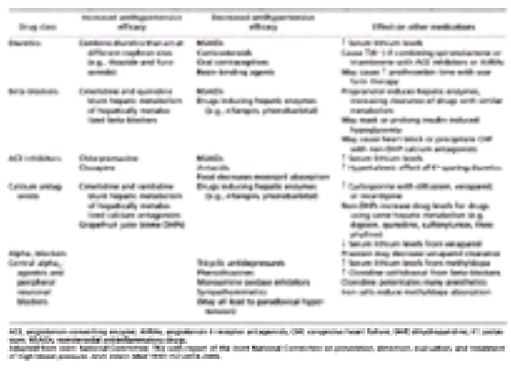


TABLE 5.6 IMPORTANT DRUG INTERACTIONS IN ANTIHYPERTENSIVE THERAPY

TABLE 5.7 ANTIHYPERTENSIVE DRUG THERAPY: A PHARMACOLOGIC SUMMARY

The optimal hemodynamic approach to antihypertensive drug treatment is to reduce systemic vascular resistance (SVR) while preserving CO and perfusion of critical target organs such as brain, heart, and kidney. Available medications for lowering BP conveniently fall into three subgroups by hemodynamic alterations, as summarized in *e*Table 5.7.1.

***e*TABLE 5.7.1** ANTIHYPERTENSIVE DRUGS BY HEMODYNAMIC CLUSTER

Drugs reducing SVR, preserving CO and organ perfusion
- Alpha$_1$-blockers
  - Prazosin, terazosin, doxazosin rimazosin
- Alpha$_2$-central agonists
  - Clonidine, guanabenz, guanfacine, methyldopa
- Diuretics
  - Thiazides, spironolactone
- ACE inhibitors
  - Captopril, enalapril, lisinopril, ramipril, benazepril, quinapril, etc.
- Angiotensin II receptor antagonists
  - Candesartan, eprosartan, irbesartan, losartan, valsartan, etc.
- Dihydropyridines
  - Nifedipine, nicardipine, amlodipine, nitrendipine, nimodipine, isradipine, etc.
- Direct vasodilators
  - Hydralazine, minoxidil, pinacidil

Drugs elevating SVR and reducing CO
- Beta-blockers
  - Without ISA
    - Propranolol, metoprolol, timolol, atenolol, nadolol, betaxolol, penbutolol, etc.
  - With ISA

Pindolol, acebutolol, carteolol, etc.

Drugs reducing SVR and reducing CO
- Combined alpha/beta agents
  - Labetalol, carvedilol, etc.
- Other sympatholytic agents
  - Reserpine, guanethidine, guanadrel
- Nondihydropyridine calcium antagonists
  - Diltiazem, verapamil

ACE, angiotensin-converting enzyme; CO, cardiac output; ISA, intrinsic sympathomimetic activity; SVR, systemic vascular resistance.

The first group of medications *reduces SVR while preserving CO and organ perfusion*. Most of these agents may be administered as initial monotherapy with little compensatory neurohumoral response—except for the direct vasodilators, which induce reflex tachycardia, fluid retention, and increased myocardial work. Diuretics initially produce modest contraction of intravascular volume, but antihypertensive effect may be delayed for weeks or even months as SVR falls and CO returns to near

normal levels. Although calcium antagonists share a common name, the subgroup of dihydropyridines distinctively produces vasodilatation, decreased SVR, and reflex sympathetic stimulation with possible tachycardia, fluid retention, and vasodilatory headache.

The second group of medications *elevates SVR and reduces CO*. Recent studies indicate that all beta-blockers share an unfavorable hemodynamic response to exercise and may compromise perfusion to skeletal muscle, liver, and kidneys. Distinctions between selective and nonselective beta-blockers are dose-dependent and tend to converge on nonselective features as administered dose increases (180).

The third group of medications *reduces SVR and reduces CO*. Whereas unpleasant side effects generally limit the utility of guanethidine and guanadrel, reserpine has received some renewed attention because of low cost, long duration of action to compensate for partial compliance, and demonstrable long-term efficacy, especially in combination with diuretic therapy (193). Combined alpha/beta agents, such as labetalol, offer the convenience of reduced SVR from $alpha_1$-blockade and controlled heart rate from beta-blockade (194), as well as recent reports of better survival in heart failure (195). Finally, the nondihydropyridine calcium antagonists promote vasodilatation and negative inotropic and chronotropic cardiac effects.

There is a growing body of data exploring the duration of drug effect and seeking insights into the optimal dosing pattern. Not all drugs lead to consistent and satisfactory BP control for 24 hours, despite pharmacokinetic patterns justifying once-daily administration (196).

EVALUATION FOR SECONDARY FORMS OF HYPERTENSION

Prevalence

Curable secondary hypertension is relatively rare (197). Among unselected patient series, primary hypertension is the ultimate cause in 93% to 94% of cases, renal parenchymal disease in an additional 5% to 6%, and all other causes of presumably reversible secondary hypertension accounting for only 1% to 2% of the total, as summarized in eFigure 5.1.1 (197,198,199,200 and 201). There is little justification for aggressive evaluation of every hypertensive patient for secondary hypertension in the absence of important clues. The diagnostic process may resume if patients later exhibit new clues or refractoriness to treatment. Several important clues from history, physical examination, or baseline testing may indicate a higher-than-usual likelihood of secondary hypertension. The differential for secondary hypertension appears in eTable 5.7.2, and the clues are summarized in Table 5.8.

***e*TABLE 5.7.2** DIFFERENTIAL DIAGNOSIS OF SECONDARY HYPERTENSION

Renal parenchymal disease
- Anephric
  - Volume dependency
- Chronic dialysis
  - Volume dependency
  - Autonomic dysfunction
- Posttransplantation
- Chronic renal failure
- Acute renal failure
- Other

Vascular
- Renovascular
- Coarctation of the aorta

Endocrinologic
- Glucocorticoid excess
- Mineralocorticoid excess
- Catecholamine secreting tumors
- Hyperthyroidism
- Hyperparathyroidism

Pharmacologic
- Vasoconstrictors
- Volume expanders
- Other

TABLE 5.8 SECONDARY HYPERTENSION: AN OVERVIEW

Renal Parenchymal Disease

Renal parenchymal disease constitutes a collection of diverse conditions, and it is the single largest cause of secondary hypertension (202). Most of these conditions may not be reversible.

A large array of clinical situations affect renal parenchyma and produce hypertension. Acute renal failure may result from acute glomerulonephritis (especially postinfectious, crescentic, or focal segmental changes), vasculitis (especially systemic lupus erythematosus, scleroderma, or polyarteritis), or acute obstruction. When the renal dysfunction is more insidious, ultimately destroying ³80% of the nephrons, chronic renal failure occurs. The most common causes are vasculitis, glomerular disease (especially diabetic nephropathy and crescentic or focal segmental glomerulitis), and polycystic renal disease (203). Two patient clusters predominate. Most patients have a volume-dependent form of hypertension that is indicative of chronic glomerulonephritis and is usually relatively easy to control. A less common subset of patients has nephrosclerosis that is dependent on renin rather than volume and is often more difficult to control. Most patients requiring chronic dialysis display a volume dependency and variable degrees of autonomic dysfunction, whereas those with no functional kidneys or post bilateral nephrectomy usually are volume-dependent.

Other, less common causes of hypertension associated with chronic renal disease include pyelonephritis, membranous and membranoproliferative glomerulonephritis, immunoglobulin A nephropathy, renin-secreting tumors, or drug-induced renal dysfunction (e.g., phenacetin-associated analgesic nephropathy) (204). Even after renal transplantation, hypertension may result from continuation of prior hypertension, excess renin from the native kidney if not removed, posttransplant renal artery stenosis, immunosuppressive therapy [e.g., corticosteroids, cyclosporine, and tacrolimus (205)], chronic rejection, recurrent intrinsic renal disease, or volume overload.

Screening tests usually reveal azotemia, microalbuminuria, proteinuria, or abnormal urinary sediment. The most important management decisions usually revolve around the desirability and timing of dialysis or transplantation, as well as the optimal management of the volume component of the hypertension. The volume component usually responds to diuretics or to dialysis, whereas the renin component may require beta-blockers, ACE inhibitors, AII receptor antagonists, or minoxidil. Several of the standard antihypertensive agents may need dose adjustments in chronic renal failure (204). Optimizing BP control—usually to a lower target pressure (120–130/70–80 mm Hg) than for other hypertensive patients—may slow progression of the renal disease. Proteinuria itself serves as an independent risk factor for renal dysfunction (206), as well as for overall risk of cardiovascular disease (207). Direct comparison of the calcium antagonist nisoldipine versus the ACE inhibitor enalapril revealed that BP control was more important than the specific agent used for preserving creatinine clearance (208). More importantly, the trial demonstrated

that renal function can be stabilized in type II diabetes over 5 years before frank albuminuria by achieving BPs no higher than 138/86 mm Hg.

Vascular Causes of Hypertension

Hypertension may result from physiologically significant stenosis of the renal arteries, the aorta, and a variety of other vascular structures.

Renovascular Causes of Hypertension

Activation of the renin-angiotensin-aldosterone system can result from compromise of arterial flow to either or both kidneys. Depending on the status and participation of the contralateral kidney, the ischemic stimulus may elevate renin, promote fluid retention, or both.

Two clinical subgroups comprise the majority of patients with renovascular hypertension: fibromuscular dysplasia and atherosclerotic disease. Fibromuscular dysplasia of the renal arteries accounts for less than 10% of all renovascular hypertension and occurs almost exclusively in younger patients, especially females. Although five pathologic subtypes are described, 70% of affected individuals display medial fibroplasia, and an additional 20% show perimedial fibroplasia. Both of these subtypes exhibit classical beaded appearance on angiography (209). Although the precise pathogenesis is uncertain, the natural history usually consists of slow progression of stenosis without frank occlusion (210).

Atherosclerotic disease, making up about 90% of the total causes, usually involves the proximal third of the renal artery with or without encroachment of the ostium itself. Lesions generally arise bilaterally, although one side may predominate. Atherosclerosis disease may extend for years without signaling its presence with hypertension or even elevated serum creatinine. Left untreated, most lesions progress, including complete occlusion and renal failure (210). If stenosis exceeds 75%, the probability of progression to full occlusion approaches 40% over 1 year (211). As many as 5% to 15% of individuals entering dialysis programs have previously undetected renovascular hypertension (210).

Less common causes of renovascular hypertension include Takayasu's arteritis, polyarteritis nodosa, aneurysms, radiation fibrosis, thromboemboli (including cholesterol emboli), and extrinsic compression of the renal arteries by tumor.

Two scenarios are most likely to herald renovascular hypertension: (a) recent onset of hypertension in a young white woman with no family history of hypertension; or (b) late onset or exacerbation of hypertension in an older man with strong evidence of coronary, cerebrovascular, or peripheral vascular insufficiency. Although abdominal bruits modestly increase the odds of significant stenosis, the presence or absence of bruits holds limited predictive value. Other potential clues include marked hypertensive retinopathy, marked or progressive worsening of renal function after ACE-inhibitor therapy, progressive worsening of azotemia despite adequate BP control, history of unilateral small kidney from incidental studies, history of smoking, and history of pulmonary edema in a difficult to control hypertensive (212).

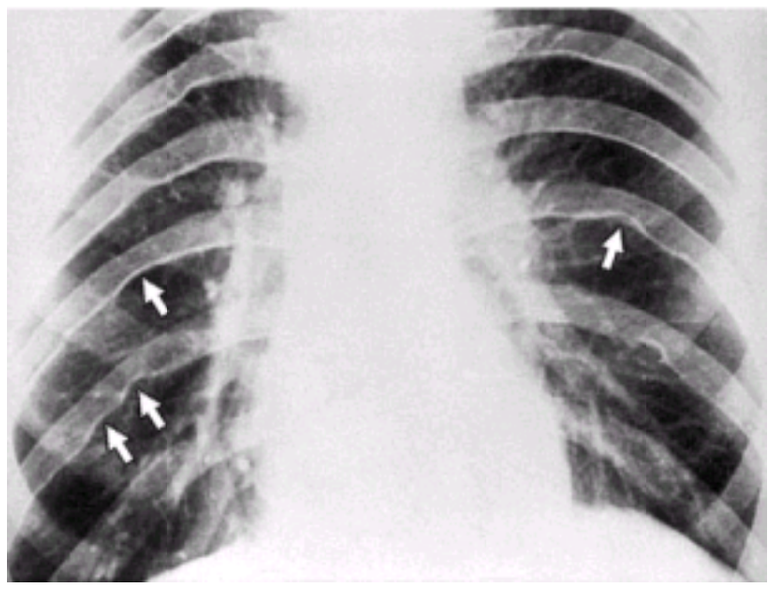
No perfect screening test exists. Baseline testing may demonstrate mild azotemia, proteinuria, or hypokalemia in <20% of individuals with the condition—modestly higher rates than among others with essential hypertension. Proponents exist for elevated peripheral PRA with or without captopril stimulation (213), renal scans, renal digital subtraction angiography (214), intravenous pyelography, and prompt progression to arteriography (215). Although it is an invasive test, arteriography remains the gold standard, searching for critical stenoses of ³80% (216). Given its poor positive and negative predictive value, the marginal utility of obtaining renal vein renins to confirm unilateral versus bilateral disease has been questioned (217). One alternative to direct angiography is the use of captopril scintigraphy, which combines radionuclide scanning of the kidney (especially with mercaptoacetyltriglycine) with captopril stimulation to enhance differences in renal blood flow (218). The ACE inhibitor produces a fall in glomerular filtration rate on the affected side more than a reduction in renal blood flow. A positive scan correlates with successful angioplasty or surgical intervention in ³90% of fibromuscular cases, but it may be less definitive in the elderly or in the presence of renal dysfunction (219). Its sensitivity can approach 100%, with specificity of 68% in selected series (220). Doppler ultrasound and magnetic resonance angiography offer promising results, but some consider them not yet cost-effective alternatives (221).

Preserving renal function preferentially involves endarterectomy, stenting, aortorenal bypass with saphenous vein or hypogastric artery, or partial nephrectomy when multiple distal stenoses occur. Rates of overall improvement and rapidity of improved glomerular filtration are superior among patients with fibromuscular dysplasia compared with those with atherosclerosis (222,223). The latter carry a worse prognosis because of progression of the arteriosclerotic process. Higher rates of successful repairs by angioplasty occur for fibromuscular dysplasia than for atherosclerotic disease. Another advantage of angioplasty is that it may take place at the same time as diagnostic angiography, with or without stenting (224).

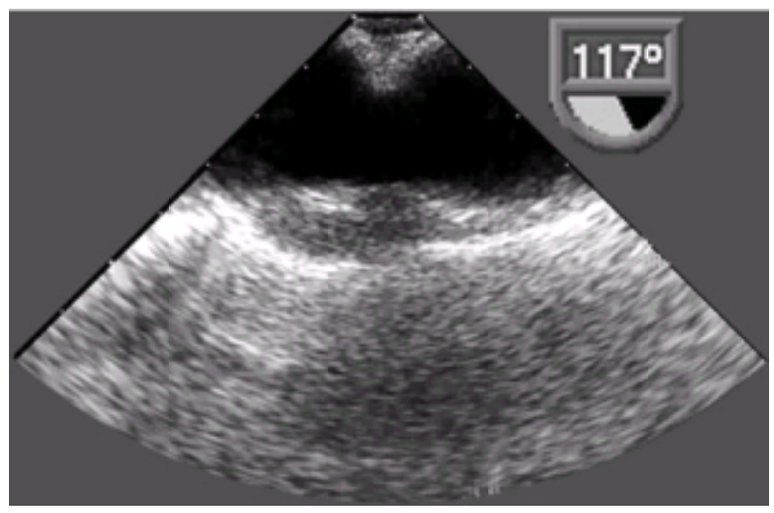
The trade-offs for medical management are especially acute for atherosclerotic disease. Progression of arteriosclerosis with occlusion and renal failure may occur even with adequate BP control. There have been no randomized controlled trials directly comparing the two treatment strategies (210). Useful drug classes have included ACE inhibitors or AII receptor antagonists (with cautions about hypotension, dose adjustment with renal dysfunction, and actual deterioration in renal function), beta-blockers, and dihydropyridine calcium channel blockers.

Aortic Coarctation

A variety of congenital and acquired malformations of the aorta may produce hypertension. Although the majority of patients presents during childhood, an important minority may pass into adulthood before definitive diagnosis (225). The variations include a left, right, or double aortic arch, which produces tracheal, bronchial, and esophageal compression. These conditions can be recognized on chest radiographs or esophagrams and confirmed by ultrasound, angiography, computed tomography (CT), or magnetic resonance imaging (MRI). Other congenital lesions of the aortic arch are characterized by aortic obstruction and include supravalvular aortic stenosis, aortic arch interruption or atresia, and coarctation (226).



Chest x-ray in coarctation of the aorta. There is prominent rib notching (*white arrows*).



A still frame of a transesophageal echo demonstrating a coarctation of the aorta. Note the local narrowing of the aorta located at the junction of the distal arch and descending aorta. There was a 100–mm Hg pressure gradient across the coarctation as determined by continuous wave Doppler.

Color Doppler interrogation of the coarctation demonstrating the high-velocity, turbulent flow across the focal narrowing in the aorta.

Angioplasty and surgery remain the treatments of choice, although complications of these procedures include functional impairment, aortic rupture, aneurysmal formation, and restenosis (227). Useful, noninvasive ways to confirm the diagnosis and monitor for complications include Doppler ultrasound with exercise for arm-leg differences (228), transesophageal echocardiography (229), and MRI (227).

Endocrinologic Causes of Hypertension

Cushing's Syndrome

Spontaneous Cushing's syndrome may be classified into (a) corticotropin-dependent forms (e.g., Cushing's disease, ectopic corticotropin syndrome, and the rare ectopic corticotropin-releasing hormone syndrome); and (b) corticotropin-independent forms (e.g., unilateral cortisol-producing adenomas and carcinomas). Rarely, bilateral adrenal hyperplasia—especially with functioning nodules—may yield the same clinical constellation of hypercortisolism, including hypertension. As the spectrum of conditions causing ectopic adrenocorticotropic hormone (ACTH) hypersecretion has filled in and expanded, even these distinctions have been become blurred (230). Fully 70% to 90% of patients with ACTH-dependent hypercortisolism have a pituitary tumor, but sophisticated special testing and endocrinologic consultation may still be necessary, once the syndrome is confirmed.

In most patients, the physical stigmata are striking: truncal obesity, moon facies, acne, buffalo hump, striae, and ecchymoses are coupled with osteoporosis, hyperglycemia, and hypertension (231). Up to 70% of individuals with the syndrome display hypertension, regardless of the subtype and independent of salt intake. Increased pressor responsiveness has been reported, probably due to local postsynaptic effector mechanisms in the resistance vessels; circadian BP variations have been decreased, absent, or even reversed (232). Initial screening for the diagnosis is best performed by a 1-mg, overnight dexamethasone suppression test or a 24-hour urinary-free cortisol after 2-mg dexamethasone suppression. Further distinctions require repeated plasma ACTH measurements by radioimmune assay, along with the 8-mg dexamethasone suppression test (233) or a corticotropin-releasing hormone stimulation test with inferior petrosal sinus sampling (234). Localization maneuvers include CT, MRI, or scanning using [^{131}I]6b-iodomethyl-19-norcholesterol—a marker of adrenocortical cholesterol uptake that accurately localizes adrenal cortex dysfunction (235).

Cholesterol emboli. Purpura secondary to cholesterol emboli are shown (*yellow arrows*).

The majority of individuals with Cushing's disease undergoes transsphenoidal exploration with remission rates of about 80%, especially for localized, relatively small tumors (236). Postoperative courses, particularly for patients undergoing adrenalectomy, may be stormy, in part because of cardiac complications associated with LVH (237). Recently described medical options include metyrapone, bromocriptine, and ketoconazole (238).

Primary Aldosteronism

Whereas Cushing's syndrome reflects glucocorticoid excess, a variety of other conditions exhibit mineralocorticoid excess. These conditions include primary hyperaldosteronism (adenoma, carcinoma, or bilateral hyperplasia), enzymatic deficiencies (11-OH-hydroxylase deficiency, 17-OH-hydroxylase deficiency, and 11-OH-dehydrogenase deficiency syndromes), or chronic licorice ingestion containing glycyrrhetinic acid (239). Although all of these conditions are relatively rare, the most common (60% to 90% of the total) is benign unilateral adenoma of the adrenal [aldosterone-producing adenoma (APA)], which yields inappropriately large and autonomous secretion of aldosterone with predictable metabolic and pathophysiologic consequences. Less common variants include idiopathic hyperaldosteronism (IHA or bilateral hyperplasia), nodular adrenocortical hyperplasia, aldosterone-producing renin-responsive adenoma, and glucocorticoid-suppressible hyperaldosteronism (240).

The autonomous secretion of plasma aldosterone (PA) occurs in distinction to its usual diurnal variation that is linked to plasma cortisol concentrations. Nonhormonal factors, such as increased serum potassium or decreased serum sodium, can stimulate aldosterone synthesis directly. Once secreted, aldosterone increases distal tubular sodium resorption and potassium secretion, increases intravascular volume, and suppresses renin secretion. When secreted in excess, aldosterone produces a volume-dependent hypertension, although there is physiologic escape from incessant sodium retention before frank edema develops.

Patients with primary hyperaldosteronism have no distinguishing symptoms from individuals with hypertension, although they may display nonspecific weakness, fatigue, polyuria, or cramps, presumably reflecting hypokalemia. APA is more common in women than in men, generally presenting in the third to sixth decade (241). An excessive loss of potassium or refractoriness to treatment may prompt further investigation. Hypokalemia may reach panic values (£2.8 mEq per L), especially after diuretic therapy, but may be in the low normal range (£4.0 mEq per L) without provocation or after salt restriction in up to 38% of patients (242).

The diagnostic process for primary hyperaldosteronism consists of three components: confirmation of inappropriately high aldosterone secretion, distinction between excisable tumor and nonsurgical glandular hyperplasia, and exclusion of rare variants suitable for medical therapy (other than aldosterone antagonists) (243). Because of many other causes of hypokalemia and low-renin hypertension, the single best screening test for the condition is a 24-hour urinary collection for aldosterone (244). The collection should occur after withdrawing all diuretics and ACE inhibitors for ³2 weeks and all aldosterone antagonists for ³6 weeks and repleting fluid status, sodium, and potassium to normal levels, if necessary, with 3 to 5 days of salt loading to ensure 24-hour urinary sodium of ³200 mEq/L (241). These steps are essential to avoid stimulation of aldosterone secretion by hyperkalemia or its inhibition by hypokalemia. Noninterfering antihypertensive drugs, including alpha$_1$-blockers and ganglionic antagonists such as guanadrel, may be used to control BP before the test. Alternatively, a logistically simpler screening test may be the PA to PRA ratio, if patients can be withdrawn safely from antihypertensive medications for ³2 weeks. A PA/PRA ratio >30 and a PA >20 ng/mL may yield a sensitivity of 90%, a specificity of 91%, a positive predictive value of 69%, and a negative predictive value of 98%. Some investigators have reported both consistent differentiation from essential hypertension and separation between APA and IHA—the two most common forms of primary hyperaldosteronism (245).

Once the triad of hypertension, high aldosterone, and low renin has been confirmed, the clinician can shift attention to detecting adenomata for which surgical excision is the treatment of choice and curative in 70% of cases (241). The hypertension, hypokalemia, and hyperaldosteronism are generally higher in APA than in IHA, but the distinctions are usually too small to be clinically useful. Imaging studies such as CT scans can detect adenomata of ³0.7 cm, but £8% of the normal population may have nonfunctioning, incidental adrenal adenomata. MRI scanning offers no clear advantage. Dexamethasone and Lugol's solution pretreatment and [^{131}I]6b-iodomethyl-19-norcholesterol scanning may highlight a functioning mass while suppressing surrounding adrenal tissue and protecting the thyroid. Unfortunately, scanning must proceed over 2 to 5 days and carries only a 72% accuracy that is highly dependent on the tumor's size (241).

Indirect confirmation of the pathophysiologic significance of such masses may come from orthostatic tests or selective venous sampling. Orthostatic tests for APA versus IHA are based on two complementary features: (a) APA usually displays autonomous aldosterone secretion unaffected by physiologic stimuli such as standing but is exquisitely sensitive to the diurnal variation in cortisol secretion; and (b) IHA exhibits no particular diurnal variation but marked responsiveness to renin-based stimuli such as standing. Most critically, the change in PA from 8 a.m. to noon after overnight recumbency must be interpreted in combination with the concomitant changes in PRA and plasma cortisol (239). An increase in plasma cortisol during the procedure invalidates the test because the procedure seeks to compare the relative strength of two stimuli: orthostatic stimulation from standing versus the physiologic fall in cortisol over the morning hours. Some investigators have reported sensitivities of 85% with the criterion of <30% orthostatic increase in PA (246).

Venous sampling of the adrenals may be justified despite the expense and risks if the CT scan is normal, despite unsuppressible PA. Worrisome complications of the procedure include adrenal infarction. Technically difficult, the catheterization may fail to cannulate the right adrenal vein in up to 25% of cases, but if it is successful, it permits direct measurement of aldosterone-cortisol ratios with ratios of >10:1 to lateralize the overproduction to one adrenal. Concomitant infusion of ACTH or cosyntropin minimizes stress-related changes in PA.

For the subset of patients with APA, unilateral total adrenalectomy is the treatment of choice in surgical candidates. High-dose spironolactone (200 to 600 mg per day in divided doses) for 2 to 6 weeks preoperatively corrects hypertension and hypokalemia, thereby predicting the surgical result (247). Despite careful workups and uncomplicated perioperative courses, long-term cure rates average <70%, even though most patients display improved BP control and simplified regimens. The BP may require 3 to 6 months postoperatively to fall to normal values (241).

For the remaining patients, no cure is available, although outcomes are often satisfactory (248). Treatment usually consists of a low-sodium diet (£80 mEq per day), maintenance of near-optimal body weight, and aldosterone antagonist therapy. Spironolactone is the drug of choice in the form of 200 to 600 mg per day in divided doses. Correction of hypokalemia occurs within days, whereas normalization of BP may require 1 to 2 months. Common side effects include painful gynecomastia, impotence, decreased libido, menstrual irregularities, and gastrointestinal discomfort. Alternative therapies include amiloride (10 to 40 mg per day), dihydropyridines (e.g., nifedipine 30 to 180 mg per day), or ACE inhibitors. In patients with the rare syndrome of glucocorticoid-suppressible aldosteronism, spironolactone therapy may be as effective and better tolerated than dexamethasone 2 mg daily (241).

Pheochromocytoma

Pheochromocytomas and other catecholamine-secreting tumors—termed *paragangliomas* when arising outside the adrenal—may prompt some of the most dramatic moments in hypertension. The clinical spectrum is wide, ranging from previously unsuspected tumors, which first gain recognition from hypertensive crisis after a procedure like anesthesia, to incidentally discovered, slow growing, sometimes large, almost metabolically inactive masses. Nearly 80% of the tumors are limited to the adrenal glands, usually unilaterally. The tumors are more likely to be bilateral or multiple in pediatric presentations or in familial forms such as neurofibromatosis, von Hippel-Lindau disease, or multiple endocrine neoplasia type 2a or 2b. An additional 10% to 20% arise in other intraabdominal sites, and <5% appear from intrathoracic sites along the neurosecretory crest or bladder. A small number come from intracranial sites. Up to 20% of tumors are multiple. Less than 10% of all catecholamine-secreting tumors are malignant, although their presentation may be difficult to distinguish from their more benign equivalents. Prompt diagnosis and definitive treatment is essential to avoid cardiomyopathy, CHF, and other potentially lethal outcomes (249).

Disease manifestations reflect the direct and indirect effects of catecholamines, either hypersecreted at random intervals for variable durations or tonically released. The classic triad of episodic headache, palpitations with or without tachycardia, and inappropriate perspiration accompanying the hypertension may suggest pheochromocytoma. The full textbook description, however, occurs less than half of the time. Other findings that may indicate pheochromocytoma include nervousness and anxiety, tremor, nausea, abdominal or chest pain, orthostatic drops in BP, glucose intolerance, weight loss, pallor, and fatigue (249). Usually the most spectacular symptoms accompany the most dramatic BP elevations. Although less likely without one or more of the classical symptoms, the diagnosis of pheochromocytoma should be considered in patients unresponsive to appropriate triple-drug therapy, patients with paroxysmal hypertension associated with clinical procedures, or patients with hypertension developing after phenothiazine, tyramine, or tricyclic medications. Pregnancy may unmask the disease, as the growing uterus applies pressure on the adrenal, or after micturition in the rare presence of bladder wall-based tumors. Tumors that are nearly silent metabolically may grow to large size before detection, whereas metabolically active lesions generate enough early symptoms to be small when first discovered.

Under most circumstances, the diagnosis of catecholamine-secreting tumor receives first confirmation by elevated urinary levels of one or more of the vasoactive hormones. Most tumors secrete norepinephrine and epinephrine, although the former usually predominates. Because any single hormone may or may not be elevated, most published guidelines call for collecting an array, usually consisting of metanephrine, normetanephrine, total catecholamines, vanillylmandelic acid, norepinephrine, and epinephrine. Some have argued that a negative assay for a single catecholamine has a 98% predictive value for ruling out the disease in a primary care population (250). Optimally, the diagnostic procedure consists of a 24-hour collection that includes a catecholamine and creatinine to monitor sufficiency of urine collection. Shorter timed intervals (e.g., 4 to 8 hours) may be useful when full-day collections are impractical or if episodic symptoms are short-lived and potentially diluted by longer collections. Using µg of catecholamine/mg creatinine, the clinician may extrapolate to a full day's collection. Urine collections should occur at times of sustained hypertension. Plasma catecholamines may be equally diagnostic, as long as collection procedures are assiduously followed to minimize false-positives and false-negatives (249). Recent reports suggest that plasma metanephrine is more sensitive (»100%) than serum catecholamines or urinary metanephrines for the diagnosis of pheochromocytoma and retains specificity (»85%) similar to that of serum catecholamine determinations (251). Newer biochemical techniques usually obviate the need for dietary or drug restrictions (252).

The majority of patients with pheochromocytoma has dramatic elevations of catecholamines that are at least twice normal. If the clinical suspicion is high but the urinary concentration is only equivocally elevated, use of an oral clonidine suppression test (plasma catecholamine levels before and after clonidine, 0.3 mg orally) (253) or overnight clonidine suppression test (clonidine, 0.3 mg orally, at 9 p.m. with overnight urine collections) (254) to minimize hypotensive reactions may distinguish clonidine-suppressible versus irrepressible secretion. Clonidine serves to reduce central sympathetic outflow among patients with essential hypertension, but it leaves autonomous secretion unaffected. The provocative tests commonly recommended in prior decades are now relegated only to the small number of individuals with ambiguously mild elevations but strong clinical suspicion.

Definitive diagnosis and full localization usually require biochemical tests for catecholamines and scanning of potential sites by CT or MRI. On occasion, these scans may fail to localize the tumor. Scanning by [^{131}I]-metaiodobenzylguanidine (MIBG) uses a guanethidine analog with affinity for chromaffin tissue to search the entire body, rather than a more focal anatomic study that generally requires a lesion ³1 cm in diameter for detection. A number of antihypertensive drugs—including labetalol, nifedipine, reserpine, diltiazem, verapamil, and tricyclic medications—may interfere with the test (255).

In most situations, patients with catecholamine-secreting tumors undergo curative resection as definitive therapy. Perioperative management usually includes several weeks of alpha$_1$-blocker therapy, especially phenoxybenzamine, and rehydration to avoid abrupt hypotension from withdrawal of the elevated catecholamines once the tumor pedicle is clamped. Often, the degree of alpha-blockade—using phentolamine or nitroprusside—is only partial to assist the surgeon in localizing the tumor by direct palpation during the exploration and to ensure that BP falls with complete excision. Persistent BP elevations may indicate additional catecholamine-secreting tumors. Beta-blockade can control arrhythmias during the perioperative period but should be administered only in conjunction with alpha-blockers to avoid unopposed alpha-agonist influence. Up to 25% of patients with benign, resected tumors remain hypertensive postoperatively; perhaps this percentage is related to primary hypertension or hypertensive nephropathy (252).

Other Endocrinologic Causes of Hypertension

A variety of other conditions may cause hypertension, including hyperthyroidism and hyperparathyroidism. Usually, hypertension is not the most prominent manifestation of the hormonal derangement but responds over 1 to 2 months after correction of the underlying disease. Screening tests for hyperthyroidism consist of a supersensitive thyroid stimulating hormone assay or, more traditionally, a free thyroxine concentration supplemented by a free triiodothyronine assay, only if the hormonal excess is suspected despite normal screening values. An ionized calcium and parathormone assay by immunoradiometric assay constitute the best screening tests for hyperparathyroidism.

Pharmacologic Causes of Hypertension

A wide variety of medications may produce drug-mediated hypertension, which is correctable once the condition is recognized and the offending agent withdrawn. The drugs logically cluster into several groupings.

1. Vasoconstrictors [e.g., phenylephrine, pseudoephedrine (at higher-than-usual doses), phenylpropanolamine, beta-agonist bronchodilators, ephedrine, and other sympathetic amines, as well as cocaine, stimulant abuse, antiadrenergic agent withdrawal, and monoamine oxidase inhibitor cotreatment with tyramine-containing foods or medications]
2. Volume expanders [e.g., glucocorticoids, estrogens (especially at high doses, as in oral contraceptives), nonsteroidal antiinflammatory agents that inhibit prostaglandins and thromboxane A_2 via cyclooxygenase, and, potentially, cyclooxygenase 2 and cyclooxygenase 1 agents] (256,257 and 258)
3. Miscellaneous other agents [e.g., estrogen-containing compounds, psychotropic drugs that interfere with sympatholytic antihypertensive agents, or drugs with poorly specified mechanisms (cyclosporine, tacrolimus, or erythropoietin)] (259)

Although the newer formulations of oral contraceptives generally have lower estrogen concentrations than their predecessors, the incidence of oral contraceptive–related hypertension is estimated at 5% of users, with rapid reduction of risk once they discontinue contraceptive use (260).

Hypertension related to the immunomodulating drugs cyclosporine and tacrolimus has assumed special importance, because of the critical utility of these agents in many posttransplantation settings and because the incidence of hypertension in such a context can exceed 50%. Possible mechanisms of producing elevated BP include (a) direct nephrotoxicity, (b) renal vasoconstriction by imbalanced production of renal vasoconstrictor eicosanoids or by failure of vasodilatory prostaglandin synthesis, (c) altered renin-angiotensin-aldosterone system status, (d) interference with physiologic mediators such as endothelial-derived relaxation factor, or (e) increased renal sympathetic nerve activity with resultant vasoconstriction (261). Perhaps as a consequence of the binding of cyclosporine to cyclophilin, an intracellular calcium binding protein, hypertensive patients treated with cyclosporine may be particularly sensitive to treatment by dihydropyridine therapy (262). In contrast, ACE-inhibitor therapy may worsen renal function, and diuretic therapy may exacerbate hypomagnesemia. In the presence of worsening renal function or hyperkalemia, the clinician should reduce cyclosporine doses (261).

SPECIAL SITUATIONS

Hypertensive Crises

True hypertensive emergencies are unusual. Many reflect mismanagement—sometimes from patient nonadherence, sometimes from medical system failures, sometimes from both factors (263). Rather than a search for secondary causes, the clinical priority should be the safe, prompt, and gradual lowering of BP without major side effects or complications.

Dangers exist from both undertreatment and overtreatment. Diuretic therapy usually is not needed, unless it is applied in the presence of frank fluid overload or with diazoxide or minoxidil therapy to combat fluid retention. Centrally acting antiadrenergic agents (e.g., clonidine) carry the possibility of sedation, confounding the interpretation of altered mental status in hypertensive crisis. Such drugs, therefore, should be avoided in favor of nonsedating alternatives. The principal drug classes useful in hypertensive crisis reduce peripheral resistance. The clinician selects among them by assessing the need for (a) *prompt* (e.g., diazoxide) versus *less prompt* (e.g., minoxidil) treatment, (b) *precisely* controlled (e.g., nitroprusside) versus *less controlled* (e.g., hydralazine) treatment, and (c) *equipment-intensive* (e.g., nitroprusside) versus *uncomplicated* (e.g., fenoldopam) procedures. Most drug-induced complications may be minimized by anticipating which organs will receive pharmacologic effects in the short erm and the long term.

Clinical decompensation rather than BP level alone should define the situation as urgent (i.e., no target organ damage) or emergent (i.e., target organ damage present). Others have emphasized the term *malignant hypertension* in reference to the association with encephalopathy or nephropathy (264). Although systolic pressures often exceed 180 to 200 mm Hg and diastolics are ³110 to 120 mm Hg, the absolute level is less important than the rate of rise and the absolute difference in BP between the patient's usual level and those observed during crisis. The typical patient in hypertensive crisis is a middle-aged male with inconsistent access to medical care. All sociodemographic groups, however, are at risk.

Early pathophysiologic changes reflect arteriolar spasm, whereas later decompensation results from fibrinoid necrosis, release of vasoactive substances, further vasoconstriction, and myointimal proliferation. Target organ damage may affect brain, eye, kidney, heart, and gut, among other tissues. Most patients offer few specific symptoms. Sometimes cardiovascular decompensation produces palpitations, angina, or congestive failure; neurologic manifestations may include headache, nausea, seizures, or obtundation. Clinical examination may demonstrate retinopathy, CHF, arrhythmias, or focal neurologic deficits. Most screening laboratory tests are normal or nonspecific, such as mild azotemia, proteinuria, and hypokalemia.

Several patterns of clinical presentations deserve emphasis. New onset of hypertension in the absence of prior BP elevations is most consistent with acute drug reactions (e.g., cocaine, amphetamines, phencyclidine, monoamine oxidase inhibitor–tyramine reactions) or acute glomerulonephritis. If BP worsening rather than improvement occurs after diuretic therapy, extra stimulation of the renin-angiotensin-aldosterone system from volume depletion may be the cause from prior vasoconstriction.

There is no single recipe for managing hypertensive crises. Each situation should be assessed individually for critical organ involvement, desired time frame for lowering BP (minutes, hours, or days), and available options, including personnel and equipment. A summary of preferred treatments for hypertensive emergencies appears in Table 5.9. Notably, the use of short-acting nifedipine may cause precipitous falls in BP and should be avoided (265).

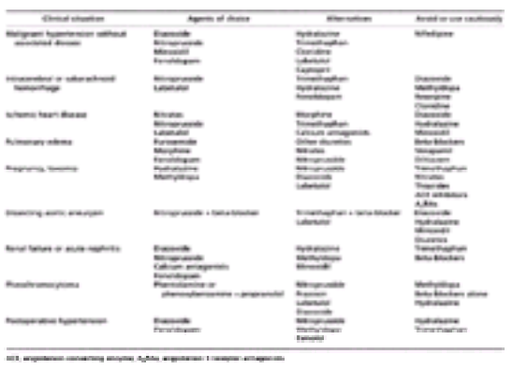


TABLE 5.9 ANTIHYPERTENSIVE THERAPY OF CHOICE FOR HYPERTENSIVE EMERGENCIES

Accelerated hypertension without major target organ damage is the most common situation. It usually occurs in the context of inadequately treated primary hypertension, but it may also reflect renal parenchymal disease, withdrawal from antiadrenergic agents, vasculitis or renovascular disease. In the absence of significant retinopathic, cardiovascular, or neurologic abnormality, the clinician may elect close follow-up rather than automatic hospitalization (266).

More ominous are central nervous system catastrophes. These may result from hypertensive encephalopathy with failure of autoregulation by cerebral blood flow (CBF). There may be focal neurologic findings. Less commonly, transient hypertension can follow any cerebral insult, such as cerebrovascular accident (thrombotic, embolic, or hemorrhagic), trauma, subdural hematoma, neoplasia, encephalitis, vasculitis, or drug withdrawal. Whereas autoregulation generally maintains CBF within narrow limits over a wide range of BPs, chronic BP elevations shift the curve to higher settings, and abrupt changes in BP carry risks of dangerous rises or falls in CBF (267). Therapeutically, the clinician seeks a 10% to 20% reduction in BP over the first hour, then further, stepped reductions over 12 to 24 hours; this therapy is preferred over prompt and full normalization because more aggressive treatment may impair CBF (268).

Hypertension carries extra hazards for *ischemic heart disease*. Angina, like other acute pain, may briefly elevate BP, but MI usually lowers CO and subsequently BP. If persistent, hypertension may increase periinfarction morbidity and mortality. In pulmonary edema or CHF, the priority should be to ameliorate the LV failure. BP

reduction usually follows. Diuretic therapy plays an important role in situations of fluid overload, even though most other hypertensive crises offer little place for diuresis.

Dissecting aortic aneurysms affecting the proximal ascending aorta comprise surgical emergencies and carry poor prognoses. Medical management in that context serves mainly to stabilize the patient as much as possible before transfer to the operating room when surgery is feasible. When localized distal to the left subclavian artery, such aneurysms may be triaged to surgery (good surgical risk) or medical (poor surgical risk) therapy (269). Drug therapy seeks to decrease the rate of pulse wave propagation to limit aneurysmal extension, as well as to lower BP overall.

Less than 5% of pregnant women present with preexisting chronic hypertension (270). During pregnancy, hypertension usually presents among primiparas after the twentieth week. Up to 40% of gestational hypertensives experience sustained hypertension within the subsequent two decades. Preeclampsia, especially when superimposed on chronic hypertension or renal disease, carries substantial risks to mother and fetus, whereas transient hypertension appearing near term is usually mild (271). Pregnancy may unmask previously unrecognized chronic renal disease, renovascular hypertension, and other secondary causes of hypertension. Whereas delivery is the ultimate treatment of choice, interim therapy may include bedrest, methyldopa, or hydralazine. In one study using atenolol, lower birth weights and smaller placentas were observed without demonstrated long-term differences in outcomes (272). ACE inhibitors are specifically contraindicated in pregnancy because of congenital malformations and fetal growth retardation (273).

In the *perioperative period*, hypertension constitutes a relative contraindication to elective surgery. The occurrence of abrupt hypertension during induction may suggest an occult pheochromocytoma. Sudden cessation of beta-blockers, methyldopa, or clonidine in the immediate preoperative period may precipitate hypertensive crises (274).

Refractory Hypertension

Resistant or *refractory hypertension*—defined as failure to lower BP to <140/90 mm Hg despite a regimen of ³3 antihypertensive agents—may occur from factors related to the prescribing clinician, the patient, the disease, or combinations of all three (275). Such a definition assumes that careful and appropriate measurement of BP has occurred on several occasions, including adequate patient preparation, elimination of interfering substances, and use of proper instruments and techniques.

The differential diagnosis of refractory hypertension heavily depends on selective factors of primary care versus referral practice. Whereas partial compliance with prescribed regimens may figure prominently in primary care, the most common cause of resistant hypertension is usually inappropriate or inadequate drug regimens in a referral practice (259). Other causes of refractory hypertension are summarized in *e*Table 5.9.1. Even in the context of refractory hypertension, specific, identifiable secondary causes of hypertension comprise only approximately 10% of the total. Although not common, correctable secondary forms of hypertension may first appear more likely after treatment has started. For example, increased BP after starting ACE-inhibitor therapy may suggest occult, bilateral renovascular hypertension, especially in association with drug-induced renal insufficiency.

***e*TABLE 5.9.1** DIFFERENTIAL DIAGNOSIS OF REFRACTORY HYPERTENSION

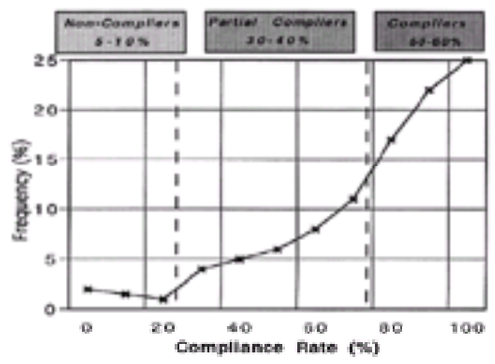
Specific identifiable disorder (second-degree hypertension)	10%
Exogenous substances	15%
Agents that raise blood pressure in susceptible persons	
Agents that interfere with antihypertensive drug action	
Complicating biologic factors	5%
Inappropriate or inadequate drug regimen	45%
Noncompliance or partial compliance with regimen	25%

Adapted from Setaro JF, Black HR. Refractory hypertension. *N Engl J Med* 1992;327:543–547.

Once the diagnosis of resistant disease is confirmed, the clinician should review the regimen to confirm its sufficiency. If the dose or dosing frequency of prescribed medications is submaximal, they may be reasonably increased, as long as adverse drug reactions have not occurred. When prescribed as monotherapy, most antihypertensive medications prompt physiologic compensation. These compensatory reactions usually involve reflex tachycardia, fluid retention, or other stimulation of the renin-angiotensin-aldosterone system. Perhaps the most common difficulty surrounds unrecognized “pseudoresistance” from subclinical fluid retention, especially after the use of vasodilators or antiadrenergic agents. BP control usually follows quickly the (re)institution of adequate diuretic therapy, commensurate with the level of renal function. Most thiazide diuretics lose antihypertensive potency as creatinine clearance falls below 40 mL per minute. Inappropriate antihypertensive combinations may also occur. Using more than one drug of the same drug class or creating adverse drug-drug interactions, as summarized in Table 5.6, may blunt BP control.

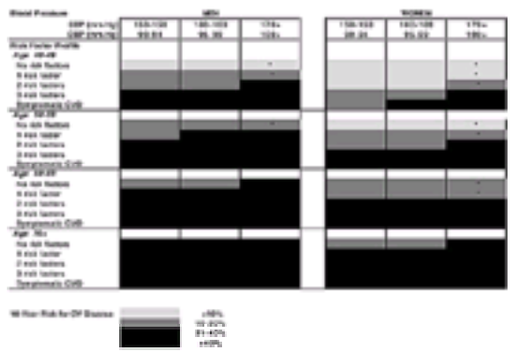
A patient’s failure to adhere to prescribed regimens—sometimes termed *partial compliance* or *adherence*—frequently reflects suboptimal knowledge of the regimen or of the importance of consistent medication taking. When queried nonconfrontationally, many patients acknowledge that a variety of “hassle” factors interfere, such as complex regimens, disruption of daily schedules, side effects, and cost (276). Other concerns for some patients may include health beliefs discordant from those of the treating clinician, especially about the significance of the “hypertension” diagnosis or the effectiveness of the prescribed treatment (277).

Electronic monitoring of medication-taking behavior has demonstrated several important epidemiologic patterns, as summarized in *e*Figure 5.1.3. Whereas 50% to 60% of individuals appear to take their regimens consistently and accurately, an additional 5% to 10% of the total demonstrate poor adherence with negligible compliance and early dropout from treatment. An intermediate group of partially compliant patients, comprising 30% to 40% of the total, exhibits highly variable medication-taking behavior—from perfect patterns to “drug holidays” (278). These patients appeared to accept the principle of antihypertensive therapy but had difficulty with consistent adherence. Their important gaps in medication taking—sometimes lasting for days—predispose to withdrawal, rebound, or other side effects, as well as to submaximal benefit (279). Recognition of the problem is often confounded by physicians’ disinterest in noncompliance, as well as by the insensitivity of patient self-report, clinician opinion, and prescription refill rates (280).



***e*FIGURE 5.1.3** Remarkably similar distributions of compliance rates have been reported with electronic monitoring of patients with hypertension, seizure disorders, glaucoma, and congestive failure. (Reviewed in Rudd P. Clinicians and patients with hypertension: unsettled issues about compliance. *Am Heart J* 1995;130:572–579.)

Compliance-enhancing strategies for the clinician include (a) watching for nonattenders and nonresponders, (b) inquiring nonconfrontationally about compliance barriers, (c) encouraging the development and use of the patient’s own medication-taking system, (d) providing simple and clear instructions, (e) simplifying the regimen as much as possible, (f) guiding behavioral changes in “small packets,” (g) monitoring progress to goal, both in BP and in compliance, (h) reinforcing desirable behaviors and outcomes whenever possible, (i) making explicit the value of the regimen and adherence to it, (j) applying help from all possible sources, (k) emphasizing the importance of dose-timing when appropriate, and (l) customizing the regimen to the patient’s needs and preferences (281) (*e*Fig. 5.1.4).



***e*FIGURE 5.1.4** Guidelines for selecting patients for antihypertensive therapy, based on cumulative risk of major cardiovascular morbidity and mortality. CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; *, treatment advised if blood pressure sustained above these levels despite low absolute risk. (Adapted from Alderman MH, Cushman WC, Hill MN, et al. International roundtable discussion of national guidelines for the detection, evaluation, and treatment of hypertension. *Am J Hypertens* 1993;6:974–981.)

Confronted with a patient demonstrating refractory hypertension, the clinician should review the regimen, goal BP, and past patterns of BP control. Subsequent steps include ruling out confounding conditions such as drug-related side effects, excess salt intake, drug-drug interactions, and secondary hypertension. Inquiring about toxicities should be nonconfrontational and assess potentially embarrassing symptoms such as altered libido, impotence, or incontinence (282). When relevant, the clinician should consider a change in regimen—especially the inclusion of an appropriate diuretic—commensurate with the level of renal function. Adjusting the regimen should permit simplification, tailoring the regimen details to the patient's daily lifestyle, and minimizing side effects. On occasion, powerful additional hypertension agents such as minoxidil may be necessary. Table 5.10 summarizes guidelines for management of refractory hypertension.

Principle 1	Increase the dose of drug A to the maximal tolerated dose before adding drug B (selected for complementary mechanism of drug action).
Principle 2	Review the fluid/volume/diuretic status for "pseudoresistance." Thiazide diuretics are superior antihypertensive agents than loop diuretics when glomerular filtration rate (GFR = C_{cr}) >50 mL/min. Longer-acting metolazone or indapamide may be useful when GFR <50.
Principle 3	Simplify the regimen (number of drugs, frequency of dosing).
Principle 4	Decrease out-of-pocket costs (consider using free medication samples as test).
Principle 5	Inquire about side effects (especially awkward symptoms, like decreased libido, impotence, or incontinence) and adjust regimen to reduce them.
Principle 6	Use nonconfrontational phrasing to help detect partial compliance and to explore useful options to reduce it.
Principle 7	Consider formal monitoring of compliance (diary vs. pill count vs. biologic assay vs. electronic dispenser).

C_{cr}, creatinine clearance; GFR, glomerular filtration rate.

TABLE 5.10 GUIDELINES FOR MANAGEMENT OF REFRACTORY HYPERTENSION

CONTROVERSIES AND PERSONAL PERSPECTIVES

In a field as vast and rapidly changing as hypertension, controversies thrive, and new ones emerge just as the old ones appear less compelling. Two of these controversies deserve special attention.

Significance of White-Coat Hypertension

The phenomenon of labile hypertension is familiar, as when patients exhibit a degree of hour-to-hour variability in excess of the usual 15% to 20% variation. Such variation includes physiologic dipping of the BP to lower levels during sleep. In 1983, Mancia et al. (283) proposed the term *white-coat syndrome* to reflect the systolic and diastolic BP increases of 27 mm Hg and 15 mm Hg, respectively, when a physician entered the patient's room during intraarterial BP monitoring. Over time, *white-coat hypertension* has come to mean elevated BP occurring in a medical setting despite normal ambulatory BP monitoring (284). The prevalence of such discrepant BP levels may affect up to 20% of men and 54% of women in reported series (122).

The difficult question then arises: what is the significance of such discrepancies? Unfortunately, the data are murky (284). The original prospective series of Verdecchia et al. (285,286) restricted white-coat hypertension to patients with elevated BP during clinic visits but normal ambulatory BPs (daytime pressures <130/80). Such patients had the same cardiovascular morbidity as patients with normal office BP (<140/90) on at least three visits on different days. Liberalizing the criteria even slightly (£136/87 for men or £131/86 for women) raised CV risks close to those of sustained hypertensive patients. Several additional investigators (287,288 and 289) have reported intermediate risk for patients with white-coat hypertension, as reflected in abnormal levels of carotid stiffness and LV relaxation.

Accordingly, some have challenged the assumption that office hypertension among patients with normal ambulatory BP need not be treated. This argument starts with the reminder that office BPs are the basis for most published clinical trials in which treating hypertension appears beneficial (284). Several additional studies suggest that home BPs of £ 135/85 (290) or 137/82 (291) represent the upper limit of normality. Finally, to confound the matter, other investigators report that "white-coat normotension" (i.e., elevated ambulatory pressures despite normal office BP) correlates with augmented LV mass index and relative wall thickness compared to patients with sustained normotension (292). For the moment, there is no simple resolution. Given a curvilinear relation between BP and cardiovascular risk, no simple or universal threshold is likely to emerge.

Best Options for Initial Monotherapy

The JNC VI unambiguously recommended diuretics and beta-blockers as drugs of choice for initial monotherapy in the absence of specific contraindications (5). With the exception of diabetics, for whom the use of ACE inhibitors or AII receptor antagonists are particularly advantageous (147,293), a large number of other primary prevention trials found strong and consistent support for endorsing diuretics and beta-blockers over the alternatives. Diuretics and beta-blockers have been evaluated in 18 long-term randomized trials (294). Compared with placebo, beta-blocker therapy was effective in preventing stroke (RR, 0.71; 95% CI, 0.59–0.86) and CHF (RR, 0.58; 95% CI, 0.40–0.84). The findings were similar for high-dose diuretic therapy (for stroke, RR, 0.49; 95% CI, 0.39–0.62; and for CHF, RR, 0.17; 95% CI, 0.07–0.41). Low-dose diuretic therapy prevented not only stroke (RR, 0.66; 95% CI, 0.55–0.78) and CHF (RR, 0.58; 95% CI, 0.44–0.76), but it also reduced coronary disease (RR, 0.72; 95% CI, 0.61–0.85) and total mortality (RR, 0.90; 95% CI, 0.81–0.99).

Several other randomized controlled trials highlight reduction in stroke risk with the use of the calcium antagonist nitrendipine (295) and reduced rates of stroke, coronary disease, and heart failure among patients receiving the ACE inhibitor ramipril (296), but not in those receiving captopril (297). Concomitantly, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) investigators reported the elimination of the $alpha_1$-blocker doxazosin treatment arm because of unexpectedly higher rates of congestive failure compared to the diuretic chlorthalidone (298). Together, these reports create ambiguities as to whether alternative drug classes offer net benefit versus risk as initial monotherapy for hypertension. At least 2 more years will pass before the final ALLHAT results are published, allowing head-to-head comparisons of the remaining treatment arms among more than 24,000 patients at 625 centers: the calcium antagonist amlodipine, the ACE inhibitor lisinopril, and chlorthalidone. The controversy continues.

Finally, the contention about calcium antagonists and their linkage to higher mortality has greatly softened in recent years. Early reports of higher rates of MI, gastrointestinal hemorrhage, and breast cancer (299) have not been confirmed in larger trials of nitrendipine (300), nifedipine gastrointestinal therapeutic system, amlodipine (301), or verapamil (302). The risks of shorter-acting dihydropyridines remain debated.

THE FUTURE

As one tries to predict the future of hypertension management, there will continue to be exciting developments in three major areas. First, basic scientific advances in molecular and genetic medicine will likely shed light on the initial and initiating events that cause the deranged physiology of hypertension. Second, evolving insights from epidemiology will refine definitions of high-risk groups and clusterings to focus efforts that produce the greatest positive yield for a population, despite resource constraints. Finally, the development of more effective and better tolerated antihypertensive medications will almost certainly combine with more sophisticated behavioral approaches to enhance adherence. In so doing, patients may enjoy the full benefits of risk reduction while maintaining an excellent quality of life.

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6

SMOKING

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OVERVIEW

Worldwide, there are approximately 1 billion individuals who smoke cigarettes. The overall prevalence of smoking in the United States in 1994 was 25.5%. Cigarette smoking remains the most important preventable contributor to premature death, disability, and unnecessary health expense in this country, and it is a major risk factor for all manifestations of coronary artery disease (CAD), stroke, and peripheral artery disease. Smoking also has been estimated to cause between 17% and 30% of all deaths due to cardiovascular disease. Although the risk of CAD after smoking cessation drops by approximately 50% 1 year after cessation, it approaches that of a person who has never smoked within 3 to 4 years. Smoking contributes to the pathogenesis of CAD and sudden death through a variety of mechanisms, including the promotion of atherosclerosis, the triggering of coronary thrombosis, coronary artery spasm, and cardiac arrhythmias, and through reduced capacity of the blood to deliver oxygen.

Nicotine is a powerful pharmacologic agent with a wide variety of stimulant and depressant effects involving the central and peripheral nervous, cardiovascular, endocrine, and other systems. These effects contribute to nicotine's addictive properties. The characteristics and patterns of chronic nicotine use have much in common with the use of other psychotropic drugs, and nicotine dependence is a recognized psychiatric disorder. Chronic nicotine use associated with smoking produces tolerance and a characteristic withdrawal syndrome that contributes to difficulty in achieving abstinence.

Cardiologists have an especially important role to play in smoking cessation. Because cardiologists frequently encounter patients in the setting of an acute cardiovascular event, they have the opportunity to take advantage of these "teachable moments" when patients may be most receptive to smoking cessation advice or intervention. In 1996, a *Clinical Practice Guideline on Smoking Cessation* was released by the Agency for Health Care Policy and Research based on an extensive review of the scientific literature. The guideline was recently updated and released by the U.S. Department of Health and Human Services, Public Health Service (*Treating Tobacco Use and Dependence: Clinical Practice Guideline*). The guideline recommends that clinicians determine and document the tobacco-use status of every patient treated in a health care setting; provide a minimal intervention to every patient who uses tobacco; offer several first-line pharmacotherapies—including bupropion and nicotine replacement therapy (NRT)—to all patients willing to make a quit attempt; provide a brief intervention designed to increase motivation to quit to all patients unwilling to commit to quitting; and use problem-solving and skills-training strategies, clinician-provided support, and help in securing social support outside of treatment to aid the smoker's quitting efforts. Because most patients seen for routine care are not motivated to make a quit attempt, clinicians should match their counseling interventions to patient's level of readiness for change. Motivational interventions that include personalized feedback and use an empathic style are most likely to be effective for patients not committed to quitting smoking.

NRT (e.g., gum, transdermal nicotine, inhaler, and nasal spray) and bupropion are efficacious smoking cessation treatments. Clonidine and the antidepressant nortriptyline are also efficacious but are considered second-line treatments. Other pharmacotherapies, such as buspirone and the combination of nicotine and mecamylamine, have shown some promise. Among behavioral or psychosocial treatments, problem solving and skills training, clinician-delivered social support, and aversive therapies have the most evidence of efficacy. Multicomponent groups are highly effective, especially when combined with nicotine replacement treatment. Intensive case management for myocardial infarction (MI) patients has produced excellent smoking cessation outcomes. Finally, organizational systems to support office-based smoking interventions are useful for insuring optimal delivery of these interventions in medical care settings.

GLOSSARY

Aversive therapy: A behavioral treatment for smoking cessation that uses aversive experiences to make smoking unpleasant and less reinforcing. Techniques used to produce the aversive experience include rapid smoking, smoke holding, and rapid puffing.

Fagerstrom Tolerance Questionnaire: A scale for measuring the level of nicotine dependence; helpful in determining risk of relapse after attempted cessation and likelihood of benefit from high-dose nicotine gum or nicotine nasal spray.

Nicotine dependence: A well-defined psychiatric disorder characterized by physical dependence on nicotine (i.e., tolerance and withdrawal), as well as a maladaptive pattern of nicotine use.

Nicotine replacement therapy (NRT): Pharmacotherapy that delivers doses of nicotine to help manage nicotine withdrawal and promotes smoking cessation in tobacco users who are attempting to quit. Currently approved forms of NRT are nicotine gum, transdermal nicotine, and nicotine nasal spray.

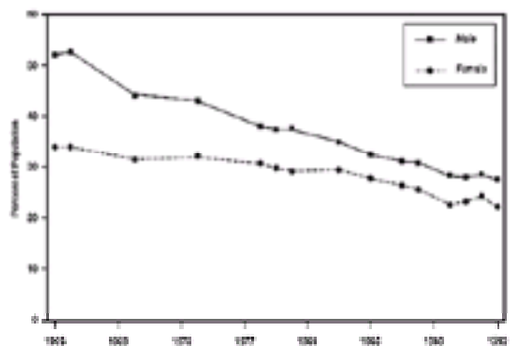
Nicotine withdrawal: A syndrome of disturbing symptoms that occur in the setting of abstinence from nicotine.

Stimulus control: A behavioral smoking cessation strategy that involves identification of cues associated with smoking and removal or avoidance of these cues during attempts at smoking cessation.

EPIDEMIOLOGY OF SMOKING

Smoking Prevalence and Incidence

There are approximately 1 billion individuals who smoke cigarettes worldwide, with approximately one-third living in China (1). An estimated 48 million adults (25 million men and 23 million women) were current smokers in the United States in 1994 (2); another 46 million adults were former smokers, indicating that almost one-half of all individuals who had ever regularly smoked cigarettes had successfully quit. After a steady decline in the prevalence of cigarette smoking from the late 1960s to the early 1990s, there has been little to no change in these rates from 1990 to 1997 (2) (*e*Fig. 6.0.1). The overall prevalence of current smoking among adults in 1994 was 25.5% (28% of men, 23% of women) (2). In 1997, the prevalence was 24.7% (27.6% for men, 22.1% for women) (3). Because the proportion of “ever-smokers” who are now former smokers is increasing at a yearly rate of less than 1%, smoking prevalence is likely to remain high well beyond the year 2000 (4). In developing countries, prevalence rates of cigarette smoking is actually increasing at an alarming rate; for example, in China, cigarette consumption increased from 700 cigarettes per adult in 1970 to approximately 2,000 per year in 1992 (1).



***e*FIGURE 6.0.1** Smoking prevalence among adults in the United States, 1965–1993.

Several factors contribute to the relatively slow decline in smoking prevalence in the United States. Although approximately 70% of current smokers say they want to quit smoking (2), only approximately 20% are actively attempting to do so (5). Relapse rates for those who do attempt to quit approach 80%, even when smokers use pharmacologic agents or seek assistance from formal treatment programs (6). Moreover, among the 90% of smokers who attempt to quit smoking on their own, only 3% to 5% achieve successful abstinence after 1 year (7). Other factors contributing to the slow decline in smoking prevalence in the United States include tobacco corporations’ aggressive marketing and high rates of smoking initiation among youth. In the 1980s, approximately 1 million young persons per year were recruited to regular smoking—the equivalent of about 3,000 new smokers each day (4). Also, as the prevalence of smoking has declined, a greater proportion of smokers are likely to have conditions that make quitting more difficult, such as high levels of physical dependence on nicotine, dependence on other psychoactive substances, depression, and other psychiatric comorbid conditions (8,9).

The decrease in smoking prevalence in the United States since the 1960s has not been equal among demographic groups. Smoking prevalence has declined more rapidly among men than women, and the decline has been highest among persons with 16 or more years of education. Currently, smoking prevalence is almost 40% among individuals with 9 to 11 years of education (2). Smoking prevalence is also much higher among those living below the poverty level (35%) than among those at or above the poverty level (24%) (2).

Several factors may explain the slower decline in smoking prevalence among women than men: Over the last decade, young girls initiated smoking at a greater rate than young boys (10,11); women quit smoking at the same rate as men but were less likely to maintain long-term abstinence (10,11); smoking prevention and cessation programs may not have adequately addressed weight concerns and tension reduction—the issues of greatest concern to women (10,11); and women were the targets in tobacco industry marketing campaigns (12). The increased rate of smoking among disadvantaged groups (e.g., low income, low education) may be related to decreased access to information about the negative health effects of smoking and decreased access to smoking cessation resources, increased use of smoking as a strategy to manage stressful life situations, and targeting of these groups by tobacco company marketing efforts (12).

Morbidity and Mortality Associated with Smoking

Cigarette smoking remains the most important preventable contributor to premature death, disability, and unnecessary medical expense in this country (13). In developed countries as a whole, tobacco was responsible for more than 1.8 million deaths in 1990, representing 24% of all male deaths and 7% of all female deaths (14). Although studies in the 1960s and 1970s reported that overall mortality rates in women were not as high as men at the same age and level of daily consumption, more recent epidemiologic studies show that overall mortality ratios in female smokers are similar to those seen in men (15). In the United States, cigarette smoking accounts for more than 400,000 deaths each year; in 1990, tobacco use accounted for 19% of all deaths (16). Smoking has also been estimated to cause between 17% and 30% of all deaths due to cardiovascular disease (16). The average loss of life for all cigarette smokers is approximately 8 years, whereas loss of life approaches 16 years for those whose deaths are attributed to tobacco (14). Approximately half of all smokers in developed countries die from a smoking-related illness (14). Based on current worldwide smoking patterns, epidemiologists have estimated that approximately half a billion of the world’s current population will eventually be killed by tobacco, and approximately half of them will be 35 to 69 years of age when they die (14).

Cigar smoking, which has become popular again in recent years, is also associated with increased mortality. Cigar smokers who smoke five to eight and nine or more cigars daily have mortality rates that are 22% and 40% greater, respectively, than nonsmokers (15). Former cigarette smokers who switch to cigars or pipes continue to have an increased risk for subsequent stroke (17), perhaps because they are more likely to inhale (18). A problem in estimating the risk of disease in individual cigar smokers is the wide variation in cigar size, nicotine content, nicotine concentration, and patterns of smoking (19). Because of variation in nicotine concentration, cigar size is not an accurate predictor of nicotine content (19). However, some fat cigars contain as much tobacco as a pack of cigarettes and may be smoked over the course of an hour, leading to significant exposure to toxic smoke (19,20).

Health Effects of Environmental Tobacco Smoke

Exposure to environmental tobacco smoke (ETS)—also known as *passive smoking*—is associated with an increased risk of death from heart disease, increased risk of lung cancer, and an increased frequency of respiratory infections in children (21).

In ten epidemiologic studies on the risk of death from CAD among nonsmokers living with smokers, the group exposed to tobacco smoke experienced a 20% to 30% increase in risk (21). Individuals with CAD who are exposed to ETS have increases in heart rate, blood pressure, and carboxyhemoglobin; angina patients exposed to ETS experience an approximately 20% to 40% reduction in exercise capacity (22). Moreover, physiologic and biochemical studies have documented deleterious effects of ETS on platelets, the endothelium, and cellular respiration (23).

The risk of lung cancer is increased approximately 30% for nonsmoking spouses of smokers relative to nonsmoking spouses of nonsmokers (21). In 1992, the Environmental Protection Agency reviewed 30 studies of passive smoking and lung cancer and concluded that ETS is a “known human carcinogen” that is responsible for 3,000 lung cancer deaths per year in never-smokers and ex-smokers (24). Among children of parents who smoke, ETS is estimated to produce approximately 300,000 additional cases of bronchitis and pneumonia, as well as up to 1 million exacerbated cases of asthma per year (21).

Smoking and Cardiovascular Disease

Cigarette smoking is a major risk factor for all manifestations of CAD, stroke, and peripheral artery disease (25,26). In ten major cohort studies in several countries, each found a higher incidence of MI and death from coronary heart disease among smokers, averaging 70% higher in cigarette smokers versus nonsmokers (27). The 1990 Surgeon General’s report on the health benefits of smoking cessation lists 25 prospective studies that documented the effects of smoking on CAD risk (eTable 6.0.1). Pooled data from five large studies demonstrated that middle-aged men (40 to 59 years of age) who smoked 20 or more cigarettes per day have two to three times the risk of experiencing a major coronary event, as compared with nonsmokers (28). An analysis of the 30-year Framingham data found that the relative risk for CAD was almost three times as great in male smokers aged 35 to 44 as nonsmokers, although the relative CAD risk for smokers declined for each succeeding age

group (29). The higher relative risk for CAD among younger smokers likely is due to the rather low risk for CAD among nonsmokers in this age group.

***e*TABLE 6.0.1** COHORT STUDIES OF CORONARY ARTERY DISEASE (CAD) RISK AMONG FORMER SMOKERS

Reference	Population	Follow-up	Number of cases among former smokers	Relative risks compared with never-smokers[a] Former smokers		Current smokers	Comments
Doll and Hill (1964)	British physicians: 34,445 men	10 yr for CAD deaths	28	Quit 1–4 yr	1.05	1.41	Smoking ascertained 1951, updated 1958
			61	5–9 yr	1.25		
			59	10–14 yr	1.16		
			40	³15 yr	1.12		
				Aged 30–54		3.5	Smoking data assessed at baseline and after 7 yr
Doll and Peto (1976)	British physicians: 34,440 men	20 yr for CAD deaths	7	Quit 1–4 yr	1.9		
			10	5–9 yr	1.3		
			10	10–14 yr	1.4		
			7	³15 yr	1.3		
				Aged 55–64		1.7	
			19	Quit 1–4 yr	1.9		
			34	5–9 yr	1.4		
			38	10–14 yr	1.7		
			45	³15 yr	1.3		
				Aged ³65		1.3	
			24	Quit 1–4 yr	1.0		
			76	5–9 yr	1.3		
			62	10–14 yr	1.2		
			148	³15 yr	1.1		
Doll et al. (1980)	British physicians: 6,194 women	22 yr for CAD deaths	26	0.91		1.0–2.2 depending on amount smoked	Smoking assessed at baseline and after 9 yr
				Previously <1 ppd		1.75 (143 cases)	
Hammond and Horn (1958a,b)	18,783 men aged 50–60	44 mo for CAD deaths	23	Quit <1 yr	2.09		
			80	1–10 yr	1.54		
			40	>10 yr	1.09		
				Previously ³1 ppd		2.20 (122 cases)	
			18	Quit <1 yr	3.00		
			64	1–10 yr	2.06		
			40	>10 yr	1.60		
				Previously 1–19 cigarette/d			
Hammond and Garfinkel (1969)	ACS CPS-I: 358,534 men free of diagnosed CAD	6 yr for CAD mortality	29	Quit <1 yr	1.62	1.90 (1,063 cases)	
			57	1–4 yr	1.22		
			55	5–9 yr	1.26		
			52	10–14 yr	0.96		
			70	³20 yr	1.08		
Dorn (1959); Kahn (1966); Rogot and Murray (1980)[b]		For CAD deaths		Stopped (overall)	1.16	1.58	No update of smoking information
				<5 yr	1.40		
				5–9 yr	1.40		
				10–14 yr	1.30		
				15–19 yr	1.20		
				³20 yr	1.10		
Doyle et al. (1962)	Framingham and Albany cohorts 4,120 healthy men aged 30–62	6–8 yr for fatal and nonfatal MI	10	0.9		2.3	Only baseline smoking data used
Doyle et al. (1964)	Framingham and Albany cohorts of 4,120 healthy men aged 30–62	10 yr (Framingham) 8 yr (Albany) MI and CAD deaths	13	1.1 (0.5–2.2)		2.0–3.0 depending on amount smoked	No data on duration
Gordon, Kannel, McGee (1974)	2,336 men in Framingham Heart Study, aged 29–62	18 yr for CAD excluding angina	24	0.7		1.3	Smoking information updated biennially
Rosenman et al. (1975)	3,154 healthy California men aged 39–59	8–9 yr for fatal and nonfatal CAD	16	Aged 39–40	1.9	2.5	Only baseline smoking data used
				Aged 50–59	1.1		
Cederlof et al. (1975)	Sample of 51,911 Swedish men aged 18–69	10 yr	97	Quit 1–9 yr	1.5 total	1.7	Only baseline smoking data used
				Smoked <20 cigarette/d	0.9		
				Smoked ³20 cigarette/d	1.6		
			86	Quit ³10 yr	1.0 total		
				Smoked <20 cigarette/d	0.9		
				Smoked ³20 cigarette/d	1.1		
Fuller et al. (1983)	Whitehall civil servants: 18,403 men aged 40–64	10 yr for CAD deaths	208	171 normoglycemic	1.3	2.5	Prevalent cases of CAD not excluded
				23 glucose intolerant	0.7	1.5	
				14 diabetics	3.8	2.9	
Friedman et al. (1981)	25,917 Kaiser-Permanente subscribers in the San Francisco area, aged 20–79	4 yr for CAD deaths	31		0.9	1.6	Prevalent cases of CAD not omitted; exclusion of those cases increased the apparent benefit of quitting
				Previously ³20 cigarette/d		2.55 (2822 cases)	
Hammond and Garfinkel (1969)			62	Quit <1 yr	1.61		
			154	1–4 yr	1.51		
			135	5–9 yr	1.16		
			133	10–14 yr	1.25		
			80	³15 yr	1.05		

				Men <21 cigarette/d		1.93	Persons with cancer, heart disease, and stroke excluded at baseline
ACS (unpublished tabulations)	ACS CPS-II: 1.2 million men and women	4 yr for CAD deaths	14	Quit <1 yr	1.43		
			48	1–2 yr	1.61		
			47	3–5 yr	1.49		
			88	6–10 yr	1.28		
			90	11–15 yr	0.99		
			359	³16 yr	0.88		
				Men ³21 cigarette/d		2.02	
			19	Quit <1 yr	2.56		
			33	1–2 yr	1.57		
			36	3–5 yr	1.41		
			67	6–10 yr	1.63		
			71	11–15 yr	1.16		
			182	³16 yr	1.09		
				Women <20 cigarette/d		1.76	
ACS (unpublished tabulations)			3	Quit <1 yr	2.13		
			7	1–2 yr	0.87		
			11	3–5 yr	1.31		
			12	6–10 yr	0.74		
			17	11–15 yr	1.20		
			82	³16 yr	1.17		
				Women ³20 cigarette/d		2.27	
			9	Quit <1 yr	1.41		
			10	1–2 yr	1.16		
			16	3–5 yr	0.96		
			24	6–10 yr	1.88		
			12	11–15 yr	1.37		
			32	³16 yr	1.12		
Dorn (1959); Kahn (1966); Rogot and Murray (1980)[b]	U.S. veterans: 248,046 men	16 yr for cardiovascular deaths	9,027	Stopped (overall)	1.15	1.58	Those who quit on doctor's orders were excluded
				<5 yr	1.40		
				5–9 yr	1.40		
				10–14 yr	1.30		
				15–19 yr	1.20		
				³20 yr	1.00		
Keys (1980)	7-Countries Study of 12,096 men free of CAD	10 yr for CAD deaths	About 13[c] (Northern Europe)		2.3	2.4–4.5 depending on amount	Relative risk based on only about 5 cases in never smokers, very small numbers
			Approximately 9 (Italy, Greece, Yugoslavia)		0.8	0.7–1.8 depending on amount	
			Approximately 7[c] (United States)		0.7	1.6–3.0 depending on amount	Numbers extrapolated from figures
Shapiro et al. (1969)	HIP cohort approximately 39,000 men aged 35–64	3 yr for MI	NR	1.0		1.8	
Jajich, Ostfeld, Freeman (1984)	2,674 poor persons in Cook County, IL, aged 64–75	4.5 yr for CAD deaths	20	1.11		1.94	Stroke excluded but prevalent CAD not excluded at baseline
Willett et al. (1987)	Nurses Health Study: 121,700 U.S. women aged 30–55	6 yr for nonfatal MI and CAD deaths	55	1.5 (1.0–2.1)		2.1–10.8 depending on amount smoked	
Floderus, Cederlof, Friberg (1988)	10,495 Swedish twins aged 36–75	21 yr for CAD deaths	188 men	1.0 (0.8–1.1)		1.4–1.8 depending on amount smoked	No reassessment of smoking during follow-up; no data on duration
			10 women	0.6 (0.4–1.0)			
Lannerstad, Isacsson, Lindell (1979)	703 Malmö men, aged 55	5 yr	0	CAD deaths		2.0	No cases among former smokers; only two in never-smokers
Holme et al. (1980)	14,816 healthy Oslo men, aged 40–49	4.7 yr	NR				Never- and ex-smokers had approximately 40% of the risk of cigarette smokers
Netterstrom and Juel (1988)	2,465 Danish bus drivers	7.75 yr for MI and CAD death	9	3.2 (0.4–25.6)		5.0 (0.7–36.0)	

ACS CPS-I and -II, American Cancer Society Cancer Prevention Studies I and II; HIP, health insurance plan; MI, myocardial infarction; NR, not reported; ppd, packs/day.

[a]95% confidence interval shown in parentheses when available.

[b]Breakdowns of relative risk derived from figure presented in paper cited.

[c]Extrapolated from figure presented in paper cited.

From U.S. Department of Health and Human Services. *The health benefits of smoking cessation: a report of the Surgeon General*, DHHS Publication no. (CDC) 90–8416. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1990, with permission.

The risk for CAD among smokers is dose-related (26) (Fig. 6.1), and smoking as little as one to four cigarettes per day significantly increases risk (30). Women whose smoking patterns are similar to patterns of men have a similar increased risk of CAD morbidity and mortality (15,26). Women in the Nurses' Health Study who smoked more than 25 cigarettes per day had 5.5 times the risk of fatal CAD and 5.8 times the risk of nonfatal CAD than nonsmoking women (30). Women who smoke and use an oral contraceptive have a 13-fold increase in risk of fatal CAD than oral contraceptive users who do not smoke (31). Smoking in the presence of other coronary risk factors (e.g., hypertension, hypercholesterolemia) appears to have a synergistic effect on cardiovascular disease (CVD) morbidity and mortality (15,26) (Fig. 6.2).

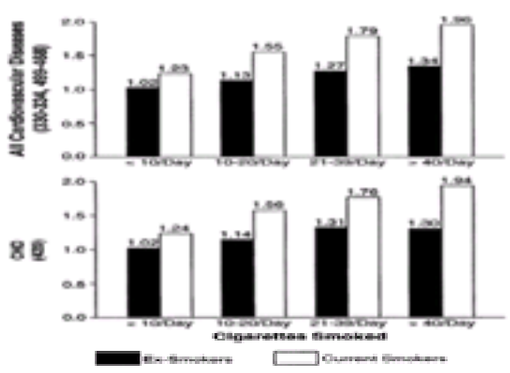


FIGURE 6.1 Mortality ratios for all cardiovascular diseases and congestive heart disease (CHD) by daily cigarette consumption, U.S. Veterans Study, 1954–1969. [From U.S. Department of Health and Human Services. *The health benefits of smoking cessation: a report of the Surgeon General*, DHHS Publication no. (CDC)

90–8416. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1990.]

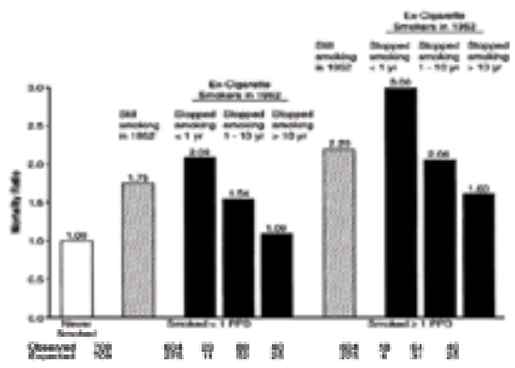


FIGURE 6.2 Mortality ratios due to coronary artery disease. Rates for men who have stopped smoking are compared with rates for men who have never smoked and rates for men still smoking in 1952. PPD, packs per day. [From U.S. Department of Health and Human Services. *The health benefits of smoking cessation: a report of the Surgeon General*, DHHS Publication no. (CDC) 90-8416. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1990.]

It has been estimated that 15% of the 150,000 stroke deaths that occur annually in the United States are directly related to smoking (15). Male and female cigarette smokers younger than 65 years experience stroke mortality rates that are 3.7 and 4.8 times greater, respectively, than those of nonsmokers (15). There is a clear dose-response relationship between smoking and mortality from stroke (26) (Fig. 6.3). Cigarette smoking is also associated with an increased risk of advanced atherosclerotic vascular disease in peripheral arteries (32). The likelihood of claudication, amputation, abdominal aortic aneurysm, and failure of vascular reconstruction is significantly higher in smokers than nonsmokers (32).

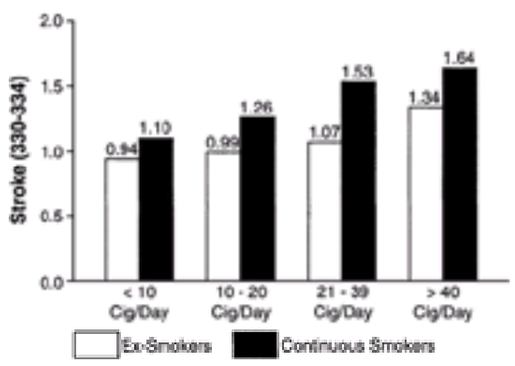
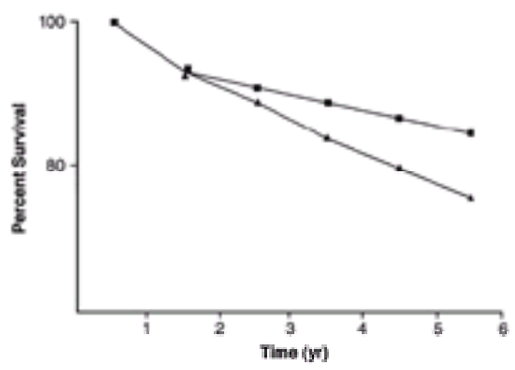


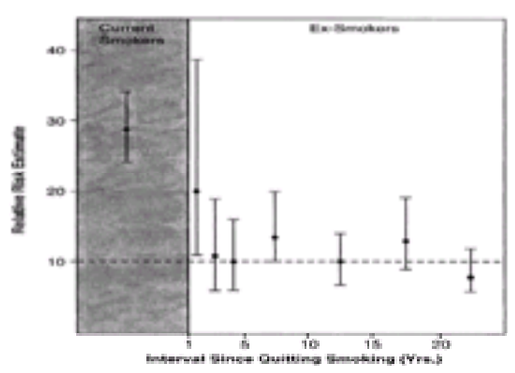
FIGURE 6.3 Mortality ratios for stroke for current smokers and ex-smokers compared with never-smokers by daily cigarette consumption, U.S. Veterans Study, 1954–1969. [From U.S. Department of Health and Human Services. *The health benefits of smoking cessation: a report of the Surgeon General*, DHHS Publication no. (CDC) 90-8416. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1990.]

Smoking Cessation and Reduction of Cardiovascular Disease Risk

Smoking cessation after the development of symptomatic CAD reduces the risk of mortality. Subjects in the Framingham Study who stopped smoking by the age of 65 years reduced their risk of initial or recurrent serious coronary events by 50%, compared to those who continued to smoke (29). Results from the Coronary Artery Surgery Study documented a 40% reduction in 5-year mortality in quitters compared to persistent smokers (33) (*e*Fig. 6.3.1). Although the risk of CAD after smoking cessation drops by approximately 50% 1 year after cessation, it approaches that of a person who has never smoked within 3 to 4 years (26) (Fig. 6.2 and *e*Fig. 6.3.2). The benefits of quitting on CAD risk are not limited to younger smokers. Even individuals older than 60 years experience significantly reduced CAD risks after smoking cessation (26). Smoking cessation also decreased the risk of recurrent cardiac arrest by approximately 30% in 310 survivors of out-of-hospital cardiac arrest who were followed for 3 years (34). Smoking cessation may also decrease the rate of restenosis after percutaneous transluminal coronary angioplasty (PTCA) (35) and recurrence of disease in saphenous vein bypass grafts after coronary artery bypass surgery (36). In the Nurses Health Study, more than one-third of the 31% decline in the incidence of coronary disease was explained by a reduction in smoking (37).



***e*FIGURE 6.3.1** Effect of smoking cessation on survival among men with documented coronary atherosclerosis; pooled survival among quitters (n) (n = 1,490) and continuers (D) (n = 2,675). [From U.S. Department of Health and Human Services. *The health benefits of smoking cessation: a report of the Surgeon General*, DHHS Publication no. (CDC) 90–8416. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1990.]



***e*FIGURE 6.3.2** Estimated relative risk of myocardial infarction after quitting smoking among men younger than 55 years, adjusted for age. Ninety-five percent confidence intervals are indicated by vertical lines; relative risk for men who never smoked is 1.0. [From U.S. Department of Health and Human Services. *The health*

benefits of smoking cessation: a report of the Surgeon General, DHHS Publication no. (CDC) 90–8416. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1990.]

Cessation rates after the diagnosis of clinical CAD range from 35% to 75% and appear to be related to the severity of disease at the time of hospitalization or coronary arteriography (38). Smoking cessation rates for patients with CAD are also related to the intensity of the smoking cessation interventions that are provided to patients. Ockene and colleagues (39) reported that an in-hospital smoking cessation intervention provided to patients who had just undergone coronary arteriography produced 12-month quit rates of 35%, compared with 28% for patients receiving usual care. In a study of patients hospitalized for an acute MI, DeBusk and colleagues (40) produced a 1-year smoking cessation rate of 70% using an intensive case-management system, compared to a rate of 53% for usual care. It must be noted, however, that both the usual care condition and the intensive case-management system in the DeBusk study included brief physician-smoking cessation counseling during hospitalization. In contrast to the high smoking cessation rates obtained post-MI or after angiography, 1-year smoking cessation rates produced by behavioral interventions delivered to ambulatory patients at risk for CAD range from 15% to 35% (41,42). Strategies for enhancing smoking cessation among cardiac patients is discussed in the section Intensive Case Management for Myocardial Infarction Patients.

HEALTH EFFECTS OF SMOKING

Cigarette Smoking and Nicotine: Effects on the Cardiovascular System

Smoking contributes to the pathogenesis of CAD and sudden death through a variety of mechanisms, including the promotion of atherosclerosis, the triggering of coronary thrombosis, coronary artery spasm, and cardiac arrhythmias, and reduced capacity of the blood to deliver oxygen (26). Smoking's effects on each of these mechanisms is described in the following sections.

Atherosclerosis

Acceleration or promotion of atherosclerosis due to smoking is attributed to a number of mechanisms: direct endothelial damage, increased proliferation of smooth muscle in atherosclerotic lesions, decreased endothelium-dependent coronary vasodilation, and reduced levels of high-density lipoprotein cholesterol (HDL-C) (26) (*e*Table 6.0.2). In animal models, endothelial damage was induced by blood nicotine levels, which are similar to those produced by human smokers (43,44), whereas studies in humans have demonstrated that smoking two cigarettes almost doubled the number of damaged endothelial cells found in circulating blood (45,46). A study that examined the effect of smoking on mothers' umbilical arteries and endothelium found pronounced degenerative changes among mothers who smoked that were not found in the arteries of nonsmoking mothers (47). Smoking-induced endothelial injury may result from oxidative damage caused by lipid peroxidation and the production of free radicals (48).

***e*TABLE 6.0.2** EFFECTS OF NICOTINE ON THE CARDIOVASCULAR SYSTEM
Atherosclerosis
Direct endothelial damage
Increased proliferation of smooth muscle in atherosclerotic lesions
Increased platelet adhesion to endothelium
Increased platelet aggregation
Decreased endothelium-dependent coronary vasodilation
Reduced levels of high-density lipoprotein cholesterol
Thrombosis
Increased platelet adherence to endothelium
Inhibits endothelial cell prostacyclin production
Increases thromboxane
Impairs platelet-derived nitric oxide release
Increased fibrinogen levels
Increased plasma viscosity
Decreased red cell deformity
Increased arterial wall stiffness, leading to increased risk for plaque rupture
Impairment of endothelium-dependent coronary vasodilation
Coronary artery spasm
Vasoconstrictor effect on coronary vasculature
Increased alpha-adrenergic tone
Increased platelet and plasma vasopressin, vasopressin carrier protein, and oxytocin
Arrhythmias
Release of catecholamines may decrease threshold for ventricular arrhythmias
Increased oxygen demand
Reduced oxygen carrying capacity

Smooth muscle proliferation—a primary feature of atherosclerotic lesions—appears to be stimulated by smoking-induced increases in the adherence of platelets to arterial endothelium (26). Blood drawn from persons after smoking two cigarettes results in a more than 100-fold increase in the adhesion of platelets to rabbit endothelium than does blood drawn from persons before smoking or from never-smokers (49). Platelets from smokers have a greater tendency to aggregate on an artificial surface than those from nonsmokers (50); in pigs, cigarette smoke increases the adhesion of platelets to arterial endothelium (51).

Smoking contributes to lipid infiltration of the arterial intima by reducing levels of HDL-C (26). An inverse relationship between smoking and HDL-C has been demonstrated in multiple cross-sectional and prospective studies (26). Prospective studies have also demonstrated an increase in HDL-C after smoking cessation in men and women (26). Although smoking and low-density lipoprotein cholesterol are not clearly related, smokers have twice the level of serum malondialdehyde as nonsmokers, which may promote the incorporation of low-density lipoprotein cholesterol into arterial wall macrophages (26,52,53). Smokers also have a decreased net transport of cholesterol from cell membranes into plasma, which could contribute to the accumulation of cholesterol in arterial walls (54).

Thrombosis

In addition to smoking's effects on atherosclerosis, smoking promotes coronary artery thrombosis by increasing platelet adherence to endothelium and platelet aggregation (26,46). Tobacco smoke appears to increase platelet aggregation by inhibiting endothelial cell prostacyclin production and increasing thromboxane (26). Recent research has demonstrated that platelet-derived nitric oxide release, which inhibits platelet aggregation, is significantly impaired in long-term smokers (55). Smoking also appears to decrease platelet monoamine oxidase, which may promote platelet aggregation by increasing catecholamine levels (55). Smoking also may promote thrombosis by increasing fibrinogen levels, increasing plasma viscosity, and decreasing red cell deformity (26). Short-term increases in arterial wall stiffness induced by cigarette smoking may increase the risk for plaque rupture, thereby triggering an acute ischemic event (56). Impairment of endothelium-dependent coronary vasodilation has also been shown in long-term smokers, which may also promote the development of atherosclerosis and thrombosis (57). This finding is likely due to reduced endothelial nitric oxide release (55). Although smoking promotes thrombosis, transdermal delivery of nicotine does not appear to do so (58).

The strong positive relationship between smoking and coronary artery thrombosis may paradoxically convey a "benefit" to smokers undergoing fibrinolytic therapy after acute MIs. Several studies have found that smokers who have an acute MI have a better prognosis than nonsmokers (59,60) and appear to be more responsive to fibrinolytic therapy than nonsmokers (61,62 and 63). Quantitative arteriographic analysis suggests that the mechanism of infarction in smokers is more often thrombosis of a less critical atherosclerotic lesion, as compared with nonsmokers (64). Smokers receiving thrombolysis for acute MI also appear to present significantly younger and have less comorbidity or severe CAD than nonsmokers (61). Two recent analyses of large thrombolytic trials found that smoking status was not associated with better outcome when results were adjusted for other baseline characteristics (61,64).

Coronary Artery Spasm

Both chronic and acute cigarette smoking have a vasoconstrictor effect on coronary vasculature (26). Current smokers have 20 times the risk of vasospastic angina compared to never-smokers (65). Smoking even a single cigarette has been demonstrated to produce coronary artery spasm during angiography (66). Smoking-associated vasoconstriction is mediated by an alpha-adrenergic increase in arterial tone and by smoking-associated increases in platelet and plasma vasopressin, vasopressin carrier protein, and oxytocin (26). In some cases of variant or Prinzmetal's angina, smoking induced a profound vasospastic effect; unless

cessation is assured, this may be refractory to medical management (67,68).

Arrhythmias and Reduced Oxygen-Carrying Capacity

Nicotine-induced release of catecholamines increases blood pressure and heart rate and may produce a lowered threshold for ventricular arrhythmias (26). In animal studies, cigarette smoke lowers the threshold for ventricular fibrillation (69). In a study of more than 10,000 men, smoking was associated with a 21% increase in ventricular premature beats on electrocardiographic rhythm strips (70). Moreover, nicotine's sympathetic effects increase myocardial oxygen demand, which is also accompanied by a reduction in oxygen carrying capacity due to the presence of 3% to 6% carbon monoxide in cigarette smoke (26). Carbon monoxide's high affinity for hemoglobin elevates levels of carboxyhemoglobin, interfering with oxygen exchange. The combination of increased myocardial oxygen demand and impaired oxygen exchange can produce or exacerbate myocardial ischemia. These effects on oxygen delivery may also lower the threshold for ventricular arrhythmias (26).

Smoking, Other Health Effects, and the Health Benefits of Smoking Cessation

In addition to cardiovascular diseases, smoking is also a direct cause of cancer of the lung, larynx, oral cavity, esophagus, and bladder; smoking also contributes to the development of cancers of the kidney, pancreas, stomach, and cervix (15,26). However, 10 years after smoking cessation, the risk of lung cancer is approximately 50% of the risk in continuing smokers; with further abstinence, the risk continues to drop (26). The risk of other cancers associated with smoking also declines substantially within several years after cessation (26).

Smoking is the major cause of chronic obstructive pulmonary disease and is responsible for approximately 90% of all deaths from these diseases (15,26). Smoking cessation reduces rates of respiratory symptoms and infections compared to continued smoking (26). With continued abstinence, the rate of decline in pulmonary function among ex-smokers returns to that of never-smokers (26).

Cigarette smoking during pregnancy increases the risks of low birth weight, spontaneous abortion, prematurity, and perinatal mortality, whereas cessation during pregnancy decreases the likelihood of these negative pregnancy outcomes (26,71). Smoking also causes women to have natural menopause 1 to 2 years earlier, which may be related to an antiestrogen effect (26,72). Smoking's antiestrogen effect, which appears to be due to an alteration in the metabolism of estradiol, leading to enhanced formation of the inactive catechol estrogens (72), may contribute to the increased cardiovascular disease risks associated with smoking in women.

Smoking also increases the risk of duodenal and gastric ulcers, osteoporotic fractures, infertility, cataracts, and macular degeneration (26,73). Among these conditions, improvement in clinical outcome after smoking cessation has been demonstrated for ulcer disease (26).

Nicotine as a Psychoactive Drug

Nicotine rapidly accumulates in the brain after cigarette smoking. Maximum brain concentrations are reached within 1 minute (13). This rapid accumulation of nicotine in combination with nicotine's effects on brain activity and function provide optimal conditions for the development of drug dependence (13). Acute and chronic tolerance to many effects of nicotine contribute to an increase in cigarette consumption, as individuals smoke more to obtain desired effects of nicotine (13,74).

Actions of Nicotine

Nicotine is a powerful pharmacologic agent with a wide variety of stimulant and depressant effects involving the central and peripheral nervous, cardiovascular, and endocrine systems, as well as other systems (13,74). These effects contribute to nicotine self-administration. Central effects include electrocortical activation (as noted on an electroencephalogram) and increases in brain serotonin, endogenous opioid peptides, pituitary hormones, catecholamines, and vasopressin (13,74). The rewarding properties of nicotine may be related to nicotine's stimulatory effects on dopaminergic pathways in the mesolimbic system (75). Nicotine has been shown to increase attention, memory, and learning in smokers—especially in the setting of low environmental demand, when stimulation is most desirable (26). Nicotine also has anxiolytic and antinociceptive effects, and there is evidence that smokers are more apt to use cigarettes during stressful situations or in situations involving negative mood (26). Recently, research has demonstrated an association between a history of clinical depression, depressive symptoms, and difficulty in quitting smoking (76,77 and 78). Nicotine's effects on negative mood states in some smokers may help to explain the relationship between smoking, depression, and other psychiatric disorders (77). There is considerable variability in nicotine's effects between and within individuals over time. This variability results from a number of factors including dose, biphasic pharmacologic effects of stimulation and blockade, the influence of setting, the current state of the individual, and individual differences in dependence, genetics, and learning history (79).

Nicotine as an Addicting Drug

The characteristics and patterns of chronic nicotine use have much in common with the use of other psychotropic drugs: Humans self-administer nicotine in the laboratory to reproduce desired effects, patterns of relapse to smoking after smoking cessation are quite similar to the patterns noted after treatment for other forms of drug abuse and dependence, chronic nicotine use produces tolerance, and a withdrawal state is noted with abstinence (13,74).

Nicotine recently has been included among the drugs that may produce psychoactive substance dependence in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (*DSM-IV*) (80). The diagnosis of nicotine dependence by these criteria require evidence for any three of nine criteria. The criteria are listed in *e*Table 6.0.3. Among older adult smokers, 87% are estimated to meet *DSM-IV* criteria for nicotine dependence (81).

***e*TABLE 6.0.3** DIAGNOSTIC CRITERIA FOR NICOTINE DEPENDENCE

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-mo period:

1. Tolerance, as defined by either
a. A need for markedly increased amounts of the substance to achieve desired effect.
b. Markedly diminished effect with continued use of the same amount of substance.
2. Withdrawal, as manifested by either
a. The characteristic withdrawal syndrome for the substance.
b. The substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is persistent desire or unsuccessful effort to cut down substance use.
5. A great deal of time is spent in activities necessary to obtain the substance or use the substance.
6. Important social, occupational, or recreational activities are given up or reduced because of substance abuse.

Adapted from American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 4th edition* (*DSM-IV*). Washington, DC: American Psychiatric Press, 1994:489.

The nicotine withdrawal syndrome is well characterized (Table 6.1 lists the *DSM-IV* criteria for nicotine withdrawal) and experienced by approximately 50% of the smokers who make a serious attempt to quit smoking (80,82). In addition, a craving for sweets and impaired performance on vigilance tasks can occur (82,83). The signs and symptoms of the nicotine withdrawal syndrome can appear within 2 hours after the last use of tobacco, usually peak between 24 and 48 hours after cessation, and usually last from a few days to 4 weeks, although craving and hunger can persist for months (82). The mean decrease in heart rate is eight beats per minute, and the mean weight gain is 2 to 3 kg (82).

1. Daily use of nicotine for at least several weeks
2. Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 h by four (or more) of the following signs:
   a. Dysphoric or depressed mood
   b. Insomnia
   c. Irritability, frustration, or anger
   d. Anxiety
   e. Difficulty concentrating
   f. Restlessness
   g. Decreased heart rate
   h. Increased appetite or weight gain
3. The symptoms in criterion 2 cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
4. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Reprinted from American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 4th edition* (*DSM-IV*). Washington, DC: American Psychiatric Press, 1994:489.

TABLE 6.1 DIAGNOSTIC CRITERIA FOR NICOTINE WITHDRAWAL

Women tend to gain more weight than men when they quit smoking (3.8 kg vs. 2.8 kg) (84). Subsets of both men and women (9.8% and 13.4%) are likely to gain a major amount of weight when they quit smoking (e.g., in excess of 13 kg). However, amount of weight gain is influenced by several factors, including race (blacks > whites), age (younger > older), and smoking rate (heavier > lighter) (84,85,86 and 88).

Fear of weight gain is an important deterrent to smoking cessation among women (88). Women report that they are less willing than men to tolerate weight gain if they quit smoking (89). Moreover, concerns about postcessation weight gain are particularly salient in younger and overweight women (90,91).

Some evidence suggests that weight gain during smoking cessation predicts an early relapse to smoking (92,93). Paradoxically, however, other studies suggest that longer-term abstinence is associated with greater weight gain (85). Behavioral weight-control interventions coupled with smoking cessation treatment appear to impede smoking cessation (94,95). However, vigorous exercise programs and pharmacologic adjunctive treatments (e.g., nicotine gum or serotonergic agents) may hold some promise in preventing postcessation weight gain (96,97 and 98).

There is a great deal of individual variation in the pattern and course of withdrawal symptoms. Moreover, future experiences with withdrawal cannot always be predicted from past quitting experiences (83). For many patients, the development of nicotine withdrawal is an important barrier to quitting smoking. Fortunately, the availability of effective pharmacotherapy for managing nicotine withdrawal has improved our capacity to assist patients in quitting smoking.

Nicotine dependence can be measured using the Fagerstrom Tolerance Questionnaire (99) (*e*Table 6.1.1). A high score on this scale predicts smoking cessation after attempted abstinence; it also predicts which smokers may benefit most from some forms of nicotine replacement (e.g., nicotine gum, 4-mg dose).

***e*TABLE 6.1.1** FAGERSTROM TOLERANCE QUESTIONNAIRE

Questions	Answers	Points
How soon after you wake up do you smoke your first cigarette?	Within 5 min	3
	6–30 min	2
	31–60 min	1
	After 60 min	0
Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	1
	No	0
Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
How many cigarettes per day do you smoke?	10 or fewer	0
	11–20	1
	21–30	2
	31 or more	3
Do you smoke more frequently during the first hours of waking than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

Adapted from Fagerstrom K, Schneider N. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. *J Behav Med* 1989;12:159–182.

Effects of Cigarette Smoking and Nicotine on Drug Metabolism

Smoking is known to accelerate the metabolism of many drugs (100,101), including several drugs used regularly in treating cardiovascular disease (e.g., propranolol, lidocaine, and theophylline). The blood levels of these medications may increase significantly when individuals stop smoking. Because hospitals are largely smoke-free, drug toxicity can develop if doses of these medications are not adjusted after hospitalization, whereas if an individual's dose of medication is stabilized in the hospital, drug levels may decrease after discharge if the patient resumes smoking. This effect was noted with propranolol in the Beta-Blocker Heart Attack Trial (102). The effects of smoking on metabolic pathways are likely due to nicotine and other constituents of cigarettes, including polyaromatic hydrocarbons (100). Because cigarette smoking's effects on metabolism are complex, it is difficult to generalize about the effects of cigarette smoking or nicotine use on entire classes of drugs. For example, although propranolol metabolism is affected by smoking, pindolol metabolism is not (100).

Smoking also appears to have an important independent effect on anticoagulation in response to intravenously administered heparin (103). Granger and colleagues (103) monitored the activated partial thromboplastin time in response to intravenous heparin in more than 29,000 patients participating in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial. Current smokers had significantly lower activated partial thromboplastin times than nonsmokers, even after adjustment for weight, age, and gender (103). This finding is consistent with previous studies of the pharmacokinetics of heparin, which have demonstrated that heparin is eliminated more rapidly among smokers (104). Therefore, when smokers are treated with heparin, anticoagulation parameters should be followed closely to ensure an adequate response.

SMOKING CESSATION

Role of the Cardiologist and Other Health Care Providers in Smoking Cessation

All physicians can play a central role in reducing the morbidity and mortality associated with cigarette smoking. Cardiologists have an especially important role in smoking cessation, for several reasons. Many cardiologists serve as primary care physicians for many of their patients. Because primary care providers have multiple opportunities over several years to intervene with their patients who smoke, they are in a unique position to provide smoking cessation advice and treatment. Moreover, because cardiologists frequently encounter patients in the setting of an acute cardiovascular event, they have the opportunity to take advantage of these "teachable moments," when patients may be most receptive to smoking cessation advice or intervention (39). *The Clinical Practice Guideline on Cardiac Rehabilitation*, published by the Agency for Health Care Policy and Research and the National Heart, Lung, and lood Institute, recommends the inclusion of smoking cessation interventions as an essential component of cardiac rehabilitation programs (105). Even if the patient is asymptomatic, health care providers can link the patient's smoking to increased risk for disease in the future (e.g., heart disease, if the patient has a family history of early CAD). Finally, the widespread adoption of smoke-free policies in hospitals and other health care institutions provides additional new opportunities for health care provider intervention.

Although physicians recognize the importance of smoking cessation as a disease-preventive measure, few physicians are confident in their ability to help patients stop smoking (106,107). Moreover, less than half of smokers report that they have ever been advised to quit smoking by their physician (108,109 and 110).

Smoking Cessation: Effectiveness of Brief Interventions

Perhaps the most compelling reason to focus on physician-delivered smoking cessation interventions is that they are effective (111,112 and 113). In April 1996, after a comprehensive and exhaustive review and analysis of the existing scientific literature, the Agency for Health Care Policy and Research Smoking Cessation Guideline Panel released the *Clinical Practice Guideline on Smoking Cessation* (113,114). The Panel was reconvened recently, and the Guideline was updated and reissued by the Department of Health and Human Services, Public Health Service (114). Table 6.2 outlines the principal recommendations of the Guideline.

Tobacco dependence is a chronic condition that often requires repeated intervention. However, effective treatments exist that can produce long-term or even permanent abstinence.

Because effective tobacco dependence treatments are available, every patient who uses tobacco should be offered at least one of these treatments. Patients willing to try to quit tobacco use should be provided with treatments identified as effective in the Guideline; patients unwilling to try to quit tobacco use should be provided with a brief intervention designed to increase their motivation to quit.

It is essential that clinicians and health care delivery systems institutionalize the consistent identification, documentation, and treatment of every tobacco user seen in a health care setting.

Brief tobacco dependence treatment is effective, and every patient who uses tobacco should be offered at least brief treatment.

There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness. Treatments involving person-to-person contact are consistently effective, and their effectiveness increases with treatment intensity.

Three types of counseling and behavioral therapies were found to be especially effective and should be used with all patients attempting tobacco cessation: provision of practical counseling (problem solving or skills training), provision of social support as part of treatment, and help in securing social support outside of treatment.

Numerous effective pharmacotherapies for smoking cessation now exist. Except in the presence of contraindications, these should be used with all patients attempting to quit smoking. Five first-line pharmacotherapies were identified that reliably increase long-term smoking abstinence rates: bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, nicotine patch. Two second-line pharmacotherapies were identified as efficacious and may be considered by clinicians if first-line pharmacotherapies are not effective: clonidine and nortriptyline.

Over-the-counter nicotine patches are effective relative to placebo, and their use should be encouraged. Tobacco dependence treatments are both clinically effective and cost-effective relative to other medical and disease prevention interventions.

Adapted from Fiore M, Bailey W, Cohen S, et al. *Treating tobacco use and dependence: clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Services, 2000.

TABLE 6.2 RECOMMENDATIONS OF THE AGENCY FOR HEALTHCARE AND RESEARCH QUALITY TREATING TOBACCO USE AND DEPENDENCE CLINICAL PRACTICE GUIDELINE

The Panel's recommendations were based on evidence that was derived primarily from metaanalyses of published randomized controlled trials (113,114). Highlights of the evidence is summarized in the following paragraphs. First, several studies have demonstrated that systems that identify and document smoking status result in significantly higher rates of smoking cessation interventions by clinicians (113,114). Further, the presence of these screening systems appears to result in higher quit rates among patients who smoke (113,114).

Second, even brief advice (e.g., less than 3 minutes) by a clinician significantly increases quit rates compared to the absence of such advice (113,114). The magnitude of the increase in quit rates with brief clinician advice is approximately 25% (113,114).

Third, smoking cessation interventions delivered by any type of health care provider increase cessation rates with no clear advantage to any single provider type (e.g., physician, nurse, psychologist, health counselor) (113,114). Moreover, interventions delivered by multiple types of providers more than double the likelihood of smoking cessation, suggesting that smoking cessation interventions should be delivered by as many clinicians and types of clinicians as feasible (113,114). This finding has implications for specialized inpatient cardiac units and cardiac rehabilitation programs, which provide unique opportunities to deliver interventions from multiple providers.

Fourth, there is a strong dose-response relationship between the intensity of person-to-person contact and a successful smoking cessation outcome (113,114). In Table 6.3, the results of a metaanalysis are presented that examine the relationship between smoking cessation outcome and level of intensity of contact across 43 randomized controlled trials. As noted above, even brief counseling significantly increases quit rates. However, more counseling is clearly even better, with rates exceeding 20.0% (compared with 10.9% for the no-contact reference group) for more than 10 minutes of counseling during a single clinical contact. Moreover, a separate metaanalysis that compared quit rates for varying amounts of the total time spent counseling across multiple visits found that 4 to 30 minutes of total contact time significantly increased quit rates over 1 to 3 minutes of total contact time (114). The estimated abstinence rates increased from 14.4% for 1 to 3 minutes to 18.8% for 4 to 30 minutes of total contact time (114). Although time, especially a physician's, is at a premium during office-based visits, the delivery of 10 or more minutes of counseling by other professional staff may be feasible, especially in cardiac rehabilitation or inpatient settings. Brief motivational messages from a physician followed by interventions delivered by an allied health professional can reduce physician burden, make counseling more likely, and produce significantly increased cessation rates compared with brief physician advice alone (115). Indeed, the addition of nurse-delivered interventions to brief physician advice in a primary care setting produced quit rates of 7.1% at 1 year compared to 3.9% for brief physician advice alone (115).

Level of contact	Estimated odds ratio (95% CI)	Estimated abstinence rate (95% CI)
No contact (reference group)	1.0	10.9
Minimal contact (<3 min)	1.3 (1.1–1.6)	13.4 (10.9–16.1)
Brief counseling (>3 min to <10 min)	1.6 (1.2–2.0)	16.0 (12.8–19.2)
Counseling (>10 min)	2.3 (2.0–2.7)	22.1 (19.4–24.7)

CI, confidence interval.

From Fiore M, Bailey W, Cohen S, et al. *Treating tobacco use and dependence: clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Services, 2000.

TABLE 6.3 SMOKING CESSATION RATES FOR VARIOUS INTENSITY LEVELS OF PERSON-TO-PERSON CONTACT

Based on their review and analysis of the scientific literature, the Guideline Panel also found evidence that four specific types of behavioral and psychosocial interventions were efficacious: problem solving or skills training, social support provided within the treatment setting, assisting the patient to access social support outside of treatment, and aversive smoking procedures (113,114). Components of the first three of these strategies can be delivered in medical care settings within the context of brief counseling. The Guideline has summarized the essential elements of these strategies, which are reproduced in *e*Table 6.3.1 and *e*Table 6.3.2. Behavioral and psychosocial strategies are discussed in more detail in the section Smoking Cessation: Behavioral and Psychosocial Treatments.

***e*TABLE 6.3.1** COMMON ELEMENTS OF PROBLEM-SOLVING AND SKILLS-TRAINING SMOKING CESSATION TREATMENTS

Problem-solving treatment component	Examples
Recognize danger situations—Identify events, internal states, or activities that are thought to increase the risk of smoking or relapse.	Being around other smokers Being under time pressure Negative affect Experiencing urges Drinking alcohol
Develop coping skills—Identify and practice coping or problem-solving skills. Typically, these skills are intended to cope with danger situations.	Learning to anticipate and avoid temptation Learning cognitive strategies that will reduce negative moods Accomplishing lifestyle changes that reduce stress, improve quality of life, or produce pleasure Learning cognitive and behavioral activities that distract attention from smoking urges
Provide basic information—Provide basic information about smoking and successful likelihood quitting.	The fact that any smoking (even a single puff) increases the likelihood of a full relapse The addictive nature of smoking Withdrawal typically peaks within 1–3 wk after quitting Withdrawal symptoms include negative mood, urges to smoke, and difficulty concentrating

From Fiore M, Bailey W, Cohen S, et al. *Treating tobacco use and dependence: clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Services, 2000.

***e*TABLE 6.3.2** COMMON ELEMENTS OF SUPPORTIVE COUNSELING FOR SMOKING CESSATION

Supportive treatment component	Examples
Encourage the patient in the quit attempt	Note that effective tobacco dependence treatments are now available Note that half of all people who have ever smoked have now quit

	Communicate belief in patient's ability to quit
Communicate caring and concern	Ask about how the patient feels about quitting
	Directly express concern and willingness to help
	Be open to the patient's expression of fears of quitting, difficulties experienced, and ambivalent feelings
Encourage the patient to talk about the quitting process	Ask about:
	Reasons the patient wants to quit
	Difficulties encountered while quitting
	Success the patient has achieved
	Concerns or worries about quitting

From Fiore M, Bailey W, Cohen S, et al. *Treating tobacco use and dependence: clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Services, 2000.

Finally, the Guideline Panel also found that bupropion hydrochloride and various forms of NRT (e.g., transdermal nicotine) were as efficacious as smoking cessation interventions, regardless of the intensity of adjuvant psychosocial interventions, and recommended their use with all smokers (113,114). Pharmacologic treatments for smoking cessation are discussed in more detail in the section Smoking Cessation: Pharmacotherapy.

Physician-delivered smoking interventions are not only effective, they are also highly cost-effective, especially when compared to such accepted medical practices as the treatment of mild to moderate hypertension or hypercholesterolemia (116,117). Using a very conservative estimate of the effectiveness of brief advice (2.7% increase in 1-year smoking abstinence rates), Cummings and colleagues estimated that the cost per year of life saved was $748 (116). This cost compares with costs of more than $11,000 per year of life saved for treating moderate hypertension and more than $65,000 per year of life saved for treating moderate hypercholesterolemia (116).

Smoking Cessation: Matching Interventions to the Patient's Readiness for Change

Although health care provider–mediated smoking cessation interventions are effective, only a small minority of patients who receive interventions from physicians are successful in achieving long-term abstinence. Frustration and feelings of ineffectiveness that result from these low rates of success are important barriers to provider intervention with smokers. The Transtheoretical Model of Change—developed by psychologists James Prochaska and Carlo DiClemente at the University of Rhode Island (118)—can help physicians and other health care providers to intervene more effectively with their smoking patients by offering strategies for the majority of smokers who are not ready to quit smoking when they visit a physician's office.

The Transtheoretical Model of Change identifies five discrete stages of smoking cessation: precontemplation, contemplation, preparation, action, and maintenance (118,119) (Fig. 6.4). Individuals at the precontemplation stage—representing as many as 40% of current smokers seen in a typical medical practice (5)—are not considering stopping smoking in the immediate future. These patients may be uninformed or underinformed, demoralized about their ability to change, or defensive and resistant to change (118). *Contemplation* is a stage of ambivalence that characterizes another 40% of smokers (5). Although individuals at this stage have given serious thought to giving up smoking, they are not yet ready to commit to quitting (118). Only approximately 20% of smokers who seek medical care are in the preparation stage and are intending to quit smoking in the next month. Many of these patients have attempted to quit in the past year or have taken small steps toward quitting, such as delaying their first cigarette in the morning or cutting down on the number of cigarettes that they smoke (118).

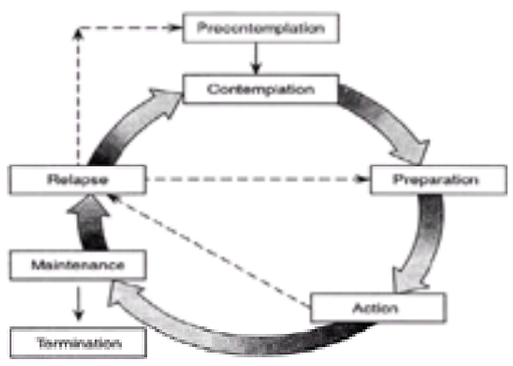


FIGURE 6.4 The Stages of Change (Prochaska and DiClemente). (From Prochaska JO, DiClemente CC. Towards a comprehensive model of change. In: Miller WR, Heather N, eds. *Treating addictive disorders: processes of change*. New York: Plenum Press, 1986.)

When individuals finally reach the action stage, they have overtly tried to quit smoking. Relapse is the rule during this stage, rather than the exception, especially during the first few days and weeks after quitting. *Maintenance*, defined as the stage reached 6 months after quitting, is characterized by continued use of processes to help individuals to change or modify their experience to prevent slips or relapse. The average smoker takes three or four cycles through the stages of change over several years before finally reaching a stable period of maintenance (119). By recognizing that the majority of smokers who visit a physician's office are not ready to take action, physicians can modify their expectations, back off on trying to get all of their patients to quit smoking, and develop strategies to attain intermediate outcomes, such as moving a precontemplator to the contemplation stage (118). Physicians using this approach are less likely to become frustrated and lose hope when the majority of their patients are unable to give up smoking in the short term. Additionally, matching intervention strategies to the stage of change may actually enhance movement through the stages that, in the long term, may shorten the time it takes to reach stable maintenance (118).

Patients in the precontemplation stage respond best to motivational interventions that help them to begin thinking about quitting smoking (120). Personalized information and feedback may help raise the smoker's awareness of the ways smoking affects his or her health and are more likely to be effective than minilectures about the health effects of smoking. Feedback can take several forms, including evidence of the effects of smoking on the patient's laboratory findings (e.g., carbon monoxide levels, pulmonary function tests, high-density lipoprotein), the impact of smoking on disease states (e.g., presence of angina, angiographic findings, transient ischemic attacks), and the relationship between smoking and risk (e.g., risk of sudden death, recurrent MI). Showing a smoker his or her coronary angiogram to demonstrate graphically the presence of diffuse atherosclerosis, as well as plaques in specific coronary arteries, may have a powerful motivating effect. Providing feedback about the deleterious effects of continued smoking should be paired with feedback about smoking cessation's beneficial effects on cardiovascular and other health outcomes. Asking the patient to reflect on his or her feelings about smoking and quitting is another useful intervention for the precontemplator (118). If feelings of demoralization are uncovered, they can be addressed by informing the patient that it may make several quit attempts before he or she is finally successful. It is also useful to offer empathic statements (e.g., "I recognize that it is difficult for many patients to quit") to provide praise for previous efforts to quit or cut down and statements of support (e.g., "When you are ready to quit, I'm willing to help"). An empathic style has been shown to be an important ingredient of effective motivational interventions (120).

Clarification and legitimization of feelings may also help patients in the contemplation stage to feel heard and understood (118). Statements such as "I'm glad that you're thinking about quitting" are especially useful because they reinforce the patient's interest in quitting. It is also useful to explore contemplators' reasons for smoking, as well as other barriers to quitting, so that potential solutions for overcoming barriers can be discussed (118). For example, if a patient reports that she depends on smoking to help manage her weight, the offer and provision of alternative weight-management strategies may precipitate a decision to quit smoking. Contemplators who become chronically stuck in this stage may benefit from encouragement to take small steps toward action, such as cutting down the number of cigarettes they smoke, delaying their first cigarette of the day, or trying to quit for just 24 hours (118).

When the patient is finally in the preparation stage or ready for action, appropriate action-oriented strategies can be advised or prescribed. Useful interventions for patients in the action stage include setting a specific quit date with the patient, writing a contract, providing self-help materials, prescribing or recommending nicotine replacement, teaching behavioral skills (*e*Table 6.3.1), referral to formal treatment programs, and enhancing social support. Individuals are most successful when multiple cognitive and behavioral strategies are used (8,121). As noted above, the *Treating Tobacco Use and Dependence Guideline* supports the use of problem solving, skills training, and supportive counseling (*e*Table 6.3.1 and *e*Table 6.3.2) as effective smoking cessation treatment components (113,114).

Five A's: A Strategy for Brief Provider Intervention

The Guideline (114) provides clinicians with a brief five-step strategy for smoking cessation intervention in medical care settings that includes the important step of assessing patients' readiness for making a quit attempt. This approach builds upon the "Four A's" of smoking cessation counseling that were developed for the National

Cancer Institute's Physician-Delivered Smoking Cessation Program (122). The five steps are as follows:

1. **Ask:** Systematically identify all tobacco users at every visit.
2. **Advise:** Strongly advise all smokers to quit and identify smokers willing to make a quit attempt (provide a motivational intervention if they are not willing to quit).
3. **Assess** willingness to make a quit attempt.
4. **Assist:** Aid the patient in quitting (set a quit date, encourage nicotine replacement, provide advice on successful quitting, refer to formal treatment if desired, and provide supplementary materials).
5. **Arrange:** Schedule follow-up contact.

The *Treating Tobacco Use and Dependence: Clinical Practice Guideline* is available in full text, along with references for the metaanalyses, on the Internet and can be found at http://www.surgeongeneral.gov/tobacco/default.htm. The *Clinical Practice Guideline*, the *Quick Reference Guide for Clinicians*, and the consumer version are also available from the Publications Clearinghouse, which can be reached at 1-800-358-9295 or P.O. Box 8547, Silver Springs, MD, 20907.

Smoking Cessation: Pharmacotherapy

Nicotine Replacement Therapy

NRT has been approved by the U.S. Food and Drug Administration (FDA) for use as an aid to smoking cessation. The four approved forms are nicotine gum, transdermal nicotine, nicotine inhaler, and nicotine nasal spray. As noted above, the Panel's review of the scientific literature found that nicotine gum and transdermal nicotine were efficacious as smoking cessation interventions across a variety of diverse settings and populations and regardless of the intensity of adjuvant behavioral and psychosocial interventions (113,114). This conclusion was based on the results of several published metaanalyses on the efficacy of transdermal nicotine (123,124,125,126 and 127) and nicotine gum (126,127,128 and 129). The American Psychiatric Association's *Practice Guideline for the Treatment of Patients with Nicotine Dependence* also endorsed the use of nicotine gum and patches as effective therapies (121). Moreover, the efficacy of the patch, gum, nasal spray, and inhaler were found to be statistically indistinguishable in the Guideline Panel metaanalyses and in a recent head-to-head clinical trial comparison (130).

Overall, compared with a placebo, transdermal nicotine doubles 6-month to 1-year quit rates, whereas nicotine gum increases long-term quit rates by approximately 50% (113,121). Although nicotine replacement with transdermal nicotine or nicotine gum is efficacious when provided with minimal adjuvant therapy, absolute smoking rates are enhanced when additional behavioral treatment is provided (113,121). A randomized placebo-controlled trial of transdermal patches and minimal supportive treatment (three 10-minute counseling sessions over 6 weeks) in 584 outpatients with cardiac disease found a significant treatment effect at 14 weeks (21% abstinence in the nicotine group vs. 9% in the placebo group), but abstinence rates were not significantly different at 24 weeks (14% vs. 11%) (131). Although they are disappointing, these results should not deter cardiologists from offering NRT to patients with cardiac disease due to the wealth of data regarding the efficacy of transdermal nicotine and nicotine gum. The increased relapse rate in the nicotine group between 14 and 24 weeks suggests that these patients, who were predominantly male veterans, may have required additional behavioral or other supportive treatment to maintain long-term abstinence. A more recent study (132) confirmed the safety and short-term efficacy of the nicotine patch among patients with CAD. One hundred and six patients with CAD were randomly assigned to received nicotine or placebo patches. The cardiovascular effects of nicotine patches were assessed by repeated ambulatory electrocardiographic monitoring and exercise testing. There were no changes in the resting heart rate and systolic or diastolic blood pressure between the active and placebo groups for the duration of the study. Repeated 48-hour ambulatory electrocardiographic monitoring revealed that there were no significant changes in the number and duration of ischemic episodes in both groups. There was no change in the frequency of atrial or ventricular arrhythmias in either group. More patients in the active patch group were abstinent at 2 weeks compared with the placebo group (27% vs. 13%).

Although patients with high levels of nicotine dependence (as measured by the Fagerstrom Tolerance Questionnaire) are less likely to be successful in quitting smoking, both high- and low-dependent smokers benefit from the use of transdermal nicotine (113,121). However, highly dependent smokers are more likely to benefit from the use of 4 mg of nicotine gum than a 2-mg dose (113,121). Most patients prefer the patch to the gum because of ease of use and decreased incidence of side effects (113,114). Side effects of nicotine gum include nausea, jaw soreness, mouth sores, gingivitis, and throat and gastrointestinal distress, whereas transdermal nicotine frequently produces skin reactions and vivid dreams (121). Because of anecdotal reports of MIs occurring in association with simultaneous smoking and nicotine patch use, the safety of NRT in patients with cardiovascular disease has been questioned. Nicotine has sympathomimetic effects that may lead to increases in heart rate and blood pressure and cause coronary vasoconstriction and arrhythmias (26,100,131). However, treatment with transdermal nicotine produces considerably lower peak plasma nicotine levels than cigarette smoking, even if the patient continues to smoke during treatment (131,133). Moreover, a careful study of transdermal nicotine in 156 patients with stable CAD found that transdermal nicotine did not affect angina frequency, overall cardiac symptom status, nocturnal events, arrhythmias, or episodes of ischemic ST-segment depression (134). Also, a recent randomized, double-blind, placebo-controlled trial of transdermal nicotine in 584 outpatients with at least one diagnosis of cardiovascular disease revealed that transdermal nicotine did *not* produce increased rates of death, MI, and cardiac arrest, increased admissions to the hospital due to increased severity of angina, arrhythmia, or congestive heart failure, increased admissions to the hospital for other reasons, or increased outpatient visits due to increased severity of cardiovascular disease (131). Moreover, nicotine gum use was not associated with any cardiovascular illness or events in more than 3,000 participants in the Lung Health Study (135).

Transdermal nicotine and nicotine gum are now available over the counter (OTC). Although pharmaceutical companies that produce nicotine gum and patches have provided the FDA with evidence of the effectiveness of OTC use of these products (121,136), health care provider monitoring and support is recommended and will likely lead to higher long-term quit rates (113,121). OTC preparations are virtually identical to the nicotine gum and transdermal products that were previously available only by prescription, although the Nicotrol 16-hour patch is only available OTC in the 15-mg (highest dose) preparation. Recommendations for use of transdermal nicotine are provided in *e*Table 6.3.3.

***e*TABLE 6.3.3** SUGGESTIONS FOR USE OF NICOTINE TRANSDERMAL PATCHES
Selection of patients: Avoid during pregnancy and breast feeding, in the presence of unstable angina or other unstable vascular disease. Patients with an allergy to adhesive or generalized skin diseases may be unable to use patches.
Dosage and duration: Initially, use highest dose patch *unless* smoking less than 10 cigarettes per day or if the patient weighs less than 100 lb. After 4 weeks at initial dose, taper to intermediate dose for 2 weeks and lowest dose for 2 weeks. Consider supplementing with nicotine gum if breakthrough craving or withdrawal occur. Use of more than one patch at a time can be considered for patients with significant withdrawal symptoms on single patch.
16- versus 24-hour patches: Base on patient preference. 24-hour patch is more likely to cause sleep disturbance or vivid dreams, whereas 16-hour patch may be associated with early morning withdrawal symptoms.
Instruct patient not to smoke while on patch and to discontinue patch if the patient smokes more than 5 cigarettes per day for several days.

Adapted from American Psychiatric Association. Practice guideline for the treatment of patients with nicotine dependence. *Am J Psychiatry* 1996;153[Suppl]:1–31.

Nicotine nasal spray was approved by the FDA in 1996 as a smoking cessation treatment. Nasal spray provides a more rapid rise in nicotine levels than transdermal or gum products, with peak levels of nicotine occurring within 10 minutes (121). Three published studies of nicotine nasal spray that meet the requirements for the Guideline metaanalyses have documented its efficacy when combined with adjunctive psychosocial treatment (121,114), and one study documented the efficacy of nicotine nasal spray in a minimal contact setting (137). Nicotine nasal spray has considerably more side effects than other forms of NRT and appears to have greater dependence liability (121). Side effects include nasal and throat irritation, rhinitis, sneezing, coughing, and watering eyes (121). However, tolerance to these side effects often develops within several days. At present, nicotine nasal spray seems best suited for individuals who have failed other forms of NRT. In a metaanalysis of four studies, nicotine inhalers—which produce a nicotine vapor when air is drawn through a tube into the mouth and throat—were found to be efficacious when combined with adjunctive behavioral therapy (114). In addition to its pharmacologic benefits in terms of nicotine replacement, the inhaler provides the user with an oral-handling substitute for cigarettes, which may confer additional therapeutic benefit. The inhaler is FDA-approved for use in the United States as a prescription product (121).

Bupropion and Other Pharmacotherapy

Bupropion recently received FDA approval for smoking cessation. Bupropion is a unique antidepressant with noradrenergic and dopaminergic activity. Clinical trials have demonstrated the efficacy of bupropion SR (a delayed release preparation) for smoking cessation with or without concomitant transdermal nicotine (121,138,139 and 140). The recommended dose of bupropion SR for smoking cessation is 150 mg twice daily. In clinical trials, medication was started 1 to 2 weeks before patients' quit days and was continued for 7 to 12 weeks. Because bupropion may lower the seizure threshold, it is contraindicated in patients with a seizure disorder and should be avoided when a patient has a condition predisposed to seizures (e.g., head injury, alcohol abuse or dependence) (Table 6.4). Common side effects include headache, insomnia, nausea, and restlessness. If sleep difficulty occurs, move the p.m. dose to the late afternoon or early evening. Bupropion has little or no adverse effects on the cardiovascular system (i.e., no significant alpha-adrenergic blockade, anticholinergic activity, or effects on cardiac conduction) (141,142 and 143), although elevations in blood pressure have been noted on occasion.

Selection of patients: Avoid during pregnancy and breast feeding unless increased likelihood of smoking abstinence, with its potential benefits, outweighs the risk of bupropion SR treatment and potential concomitant smoking. There is a small risk of hypertension. Contraindicated in patients with a history of seizure disorder, eating disorder, use of another form of bupropion (e.g., Wellbutrin), or use of a monoamine oxidase inhibitor in the past 14 days.

Dosage and duration: Begin with a dose of 150 mg q.a.m. for 3 days, increasing to 150 mg b.i.d. and continuing for 7–12 weeks after quit date. Patients should begin treatment 1–2 weeks before quitting. Use alcohol in moderation.

Adapted from Fiore M, Bailey W, Cohen S, et al. *Treating tobacco use and dependence: clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Services, 2000.

TABLE 6.4 SUGGESTIONS FOR USE OF BUPROPION SR

Clonidine is an alpha$_2$-agonist that dampens sympathetic activity and attenuates withdrawal symptoms associated with alcohol, opiate, and nicotine abstinence (121,144). Recent metaanalytic reviews (114,145) concluded that clonidine was more effective than placebo in promoting abstinence from smoking (144). Doses used for smoking cessation are 0.1 to 0.4 mg per day for 2 to 6 weeks in oral or transdermal formulations (121). The most common side effects are sedation, dry mouth, constipation, lightheadedness, and postural hypotension (144). Although it is uncommon, rebound hypertension after discontinuation is also a concern, especially in patients with cardiac disease. Clonidine is recommended as a second-line treatment for smokers who have failed NRT or bupropion (114,121) or as an alternative for smokers who prefer not to receive nicotine.

In addition to bupropion, other antidepressants have been evaluated as potential treatments for smoking cessation (121). Doxepin and fluoxetine have produced promising results in early clinical trials (121,138). However, further evidence of their efficacy is needed before they can be recommended as first-time treatments for smoking cessation. Two randomized double-blind clinical trials have demonstrated long-term (1-year) efficacy of nortriptyline versus placebo for smoking cessation (146,147). However, nortriptyline is recommended as a second-line treatment, largely because of its anticholinergic side effect profile. Nortriptyline's quinidine-like effects on cardiac conduction and its propensity to cause postural hypotension limit its safety and value as a smoking cessation treatment in patients with cardiac disease. Antidepressants may be useful for treating nicotine dependence for several reasons: a history of depression is associated with an increased difficulty with smoking cessation; depressive symptoms commonly occur during nicotine withdrawal, especially when there is a history of depression; nicotine appears to be a powerful regulator of negative effect; and antidepressants have been useful in ameliorating the withdrawal state associated with other drug withdrawal states (8,77,121).

Buspirone—a serotonergic agonist with anxiolytic properties—has also shown promise as a smoking cessation treatment, especially in high-anxiety smokers (121,138). Mecamylamine, a noncompetitive blocker of central and peripheral nicotine receptors, has produced promising results when combined with NRT (121,148,149).

Smoking Cessation: Behavioral and Psychosocial Treatments

As noted in the section Smoking Cessation: Effectiveness of Brief Interventions, the *Treating tobacco use and dependence guideline* panel found evidence that four specific types of behavioral and psychosocial interventions were efficacious: problem solving or skills training, social support provided within the treatment setting, assisting patients to access social support outside of treatment, and aversive smoking procedures (113,114). The essential elements of problem solving or skills training and supportive counseling are listed in *e*Table 6.3.1 and *e*Table 6.3.2. This section reviews the efficacy of aversive therapy and other behavioral and psychosocial treatments, including stimulus control, relaxation, hypnosis, acupuncture, and multicomponent groups.

Aversive Therapy

Aversive therapy is based on the premise that pairing smoking with aversive experiences makes smoking less reinforcing and unpleasant. Techniques used to produce the aversive experience include rapid smoking, smoke holding, and rapid puffing (150). Although these techniques have been shown to increase smoking cessation outcomes when compared to control conditions, compliance and safety issues have limited their acceptability and widespread use (113,121,150).

Stimulus Control

Stimulus control therapy includes identification of cues associated with smoking and removal or avoidance of these cues during attempts at smoking cessation to reduce urges to smoke (113,121,150). For example, patients who are preparing to quit are advised to discard all cigarettes, lighters, matches, and ashtrays and to avoid other smokers or settings where smoking is prevalent. Stimulus control strategies are often included in multicomponent behavioral treatment programs and can also be used as a component of brief problem-solving or skills-training treatments.

Relaxation

Strategies such as progressive relaxation and deep breathing often have been taught within the setting of multicomponent behavioral treatment programs. Although there is little evidence for their efficacy when used alone (113,121,150), some patients may find these strategies useful when dealing with trigger situations or craving.

Hypnosis

In isolation, hypnosis has not been demonstrated to be an efficacious smoking cessation treatment (113,121,150,151), although it may be of value when combined with behavioral skills training or in-treatment support. In a metaanalysis, acupuncture was also unproven as a smoking cessation treatment (114).

Multicomponent Treatments

Success rates are generally greater in multicomponent treatments than in programs using only one or two behavioral and psychosocial strategies (6,113,121,150). Six-month quit rates with multimodal group treatment are typically increased twofold over control groups, producing 6-month quit rates of approximately 20% to 25% (6,121). The combination of multimodal behavioral and pharmacologic interventions is likely more efficacious than either treatment strategy alone (114,121).

Group treatment settings have frequently been used to deliver multicomponent treatment. This approach takes advantage of the social support component of group treatment, is less costly than individual treatment, and facilitates the involvement of multiple therapists who may have overlapping, but distinct, therapeutic skills (e.g., a physician or nurse skilled in pharmacologic intervention and a psychologist skilled in behavioral interventions).

The *Treating Tobacco Use and Dependence Guideline* has developed recommendations for intensive multicomponent smoking cessation programs that include careful assessment of smokers' barriers to quitting, use of multiple types of clinicians, at least four sessions of at least 10 minutes each for a total contact time of at least 30 minutes, use of individual or group format or proactive telephone counseling (supplemented with self-help materials), use of multiple behavioral strategies (e.g., problem solving, skills training, and in-treatment and extratreatment social support), and use of pharmacotherapies endorsed in the guidelines (113,114) (*e*Table 6.4.1). These recommendations are especially relevant for the development of specialized intensive smoking cessation services for patients enrolled in cardiac rehabilitation programs.

***e*TABLE 6.4.1** RECOMMENDATIONS REGARDING INTENSIVE SMOKING CESSATION PROGRAMS

Assessment

Determine whether smokers are motivated to quit via an intensive smoking cessation program. Other assessments that may be used to guide treatment include level of nicotine dependence, presence of psychiatric comorbidity and emotional distress, presence of smoking-related medical conditions or risks, self-monitoring of smoking to identify important cues and triggers, reasons for smoking and quitting, level of social support for quitting, stressful life circumstances or events, and self-efficacy.

Program clinicians

Multiple types of clinicians are effective and should be used. One counseling strategy would be to have a medical or health care clinician deliver messages about health risks and benefits and deliver pharmacotherapy and to have nonmedical clinicians deliver additional psychosocial or behavioral treatments.

Program intensity
Because of evidence of a strong dose-response relation, the intensity of the program should be the following: session length longer than 10 minutes; 4 or more sessions; total contact time longer than 30 minutes.
Program format
Group or individual counseling may be used. Proactive telephone counseling is also effective. Use of adjuvant self-help material is optional.
Type of counseling and behavioral therapies
Counseling and behavioral therapies should involve practical counseling (problem solving or skills training) and social support.
Pharmacotherapy
Every smoker should be encouraged to use pharmacotherapies endorsed in the Guideline, except in the presence of special circumstances (e.g., pregnant adolescents). The clinician should explain how these medications increase smoking cessation success and reduce withdrawal symptoms. The first-line agents include bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch.

Adapted from Fiore M, Bailey W, Cohen S, et al. *Treating tobacco use and dependence: clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Services, 2000.

Intensive Case Management for Myocardial Infarction Patients

As noted in the section Smoking Cessation and Reduction of Cardiovascular Disease Risk, cessation rates after the diagnosis of clinical CAD range from 35% to 75%. Using an intensive case-management system, DeBusk and colleagues (40) produced a 1-year smoking cessation rate of 70% compared to a rate of 53% for usual care for patients hospitalized with acute MI (p = .03). The case-management system included the following components: in-hospital counseling (by a physician) lasting approximately 2 minutes, an in-hospital comprehensive assessment and counseling session conducted by a nurse trained in behavioral problem-solving skills, provision of a self-help manual focusing on relapse prevention and a relaxation audiotape, and telephone calls by the nurse 48 hours and 1 week after hospital discharge and monthly for 6 months. Patients who relapsed after discharge also were offered one additional visit with the nurse for further counseling, as well as nicotine gum or transdermal nicotine. The usual-care condition included physician counseling on smoking cessation, nutritionist counseling on dietary change during hospitalization, and physician-managed, lipid-lowering drug therapy after hospital discharge. Patients in the usual-care group also had access to a group smoking cessation program and group exercise rehabilitation at a number of community facilities.

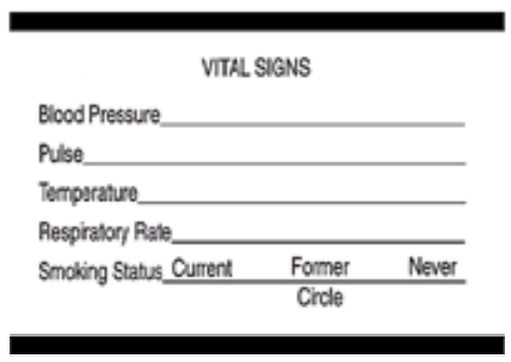
Organizational Systems to Support Office-Based Smoking Interventions

Barriers to the provision of smoking counseling in medical settings include lack of organizational support and limited availability of materials to aid physicians and patients in smoking cessation efforts. Kottke, Solberg, and Brekke have described the organizational components and systems that are essential to the delivery of effective and consistent counseling in primary care office settings (152,153). An amended list of these components is presented in *e*Table 6.4.2.

***e*TABLE 6.4.2** SOURCES OF SELF-HELP MATERIALS AND OTHER MATERIALS FOR PATIENTS AND STAFF

United States Department of Health and Human Services	Treating tobacco use and dependence clinical practice guideline
(800)358-9295	Quick reference guide for clinicians
http://www.surgeongeneral.gov/tobacco/default.htm	Consumer version (*English and Spanish*)
American Cancer Society	Smart move
(800)227-2345	The 50 most often asked questions about smoking and health and the answers
American Heart Association	Calling it quits
(214)822-9380	
American Lung Association (212)315-8700	Freedom from smoking for you and your family
	A healthy beginning: the smoke free guide for new parents
National Cancer Institute	Clearing the air
(800)4-CANCER	Why do you smoke?

As noted in the section Smoking Cessation: Effectiveness of Brief Interventions, research has demonstrated that the use of systems that identify and document smoking status result in significantly higher rates of smoking cessation interventions by clinicians and that the presence of these screening systems results in higher smoking cessation rates (113,114). The Guideline suggests the use of a vital-sign stamp that includes smoking status, along with blood pressure, pulse, and temperature, as a device to remind staff to assess and intervene with smokers (113,114) (*e*Fig. 6.4.1).



***e*FIGURE 6.4.1** Vital sign stamp. (From Fiore M, Bailey W, Cohen S, et al. *Smoking cessation: clinical practice guideline no. 18*. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, 1996.)

Resources for patients, physicians, and office staff are important tools that enhance the capacity of the health care provider to provide information and advice. Self-help manuals are available through voluntary agencies, the National Cancer Institute, and the Surgeon General (Table 6.5). Although most of these materials have been developed for smokers in preparation or action stages, materials such as the National Cancer Institute's *Why Do You Smoke?* pamphlet are geared toward precontemplators or contemplators. The pharmaceutical companies that produce nicotine transdermal patches and bupropion also have developed useful self-help materials that are available from their field representatives. As part of the purchase price, these products also support quitters' assessment and provide telephone counseling services tailored to the needs of the smoker.

TABLE 6.5 SOURCES OF INFORMATION ON TOBACCO CONTROL AND ADVOCACY

Action on Smoking and Health (ASH)
http://www.ash.org/
American Cancer Society
(800) 227-2345
American Heart Association
(214) 822-9380
American Lung Association
(212) 315-8700
Doctors Oughta Care (DOC)
(713) 528-1487
http://www.bcm.tmc.edu/doc/
National Clearinghouse on Tobacco and Health (Canada) (NCTH)
http://www.ncth.ca/NCTHweb.nsf
NicNet—Nicotine and Tobacco Network
http://www.nicnet.org/
Office on Smoking and Health (OSH), National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
http://www.cdc.gov/tobacco
Society For Research On Nicotine And Tobacco (SRNT)
http://www.srnt.org/

Once an office has decided to implement a system for supporting smoking cessation interventions, the establishment of a specific policy that is endorsed by all staff is a useful device for generating staff commitment and delineating specific roles among staff. For example, a policy might identify who is responsible for tasks such as ensuring that patients complete smoking questionnaires, ordering patient materials, or providing follow-up calls or letters. Identifying a single office staff person to be responsible for coordinating all smoking intervention activities is useful in larger offices or clinics. A policy to establish a smoke-free office is another useful step that clearly demonstrates a commitment to reducing the health risks for all patients, visitors, and staff. The presence of posters and prominent displays of patient-education materials also makes a "statement" that smoking cessation is a priority of the office's physicians and staff.

Finally, Kottke and colleagues have stressed the importance of developing a maintenance program once an office has implemented several systems for supporting smoking intervention efforts (152,153). A maintenance program may include regular audits of charts to provide feedback to staff, spirit-building activities (e.g., parties for achieving modest goals), and repeat training sessions to retain and enhance skills.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Harm Reduction

Proponents of a harm-reduction approach maintain that any decrease in smoking rate, even short of complete abstinence, is desirable. On the surface, this makes sense, given the clear dose-dependent relationship between the amount of tobacco smoked or consumed and the risk of cardiovascular diseases. However, this approach has several drawbacks. It is unlikely that most smokers can maintain a decrease in the amount that they smoke. Somewhere between 5% to 10% of all smokers smoke five or fewer cigarettes per day, but these "chippers" are more likely to have maintained this level of smoking for most of their smoking careers than to have decreased the amount that they smoked (154). Very few intervention studies have adopted decreases in smoking as a goal, largely because it is ineffective and because this strikes most smokers as unacceptable. Moreover, even though disease risk is reduced when smoking rate decreases, it is not eliminated. Smoking even one to four cigarettes a day increases risk of cardiovascular disease (30). Therefore, unlike with problem drinking—in which there is some evidence that a harm-reduction approach is feasible and that drinking moderate quantities of alcohol may be salubrious—complete abstinence from smoking should remain the desired outcome.

Another approach to harm reduction, ironically championed by the tobacco industry, is the low-tar and low-nicotine cigarette. However, considerable evidence now suggests that smokers compensate for decreased nicotine yield by smoking more effectively (e.g., more frequent and deeper puffing) and by blocking cigarette ventilation holes. Often, such compensation occurs outside of conscious awareness. In some cases, smokers even overcompensate by increasing their overall nicotine intake (i.e., smoking more cigarettes) after switching to a low-tar, low-nicotine brand. A study of women who smoked "low-yield" cigarettes produced a similar increase in the risk of having a first MI to those who smoked a higher-yield cigarette (155). Thus, there does not appear to be such a thing as a safe or even a safer cigarette, and this approach to harm reduction cannot be condoned because it is false.

Still another variation on harm reduction is the position that all nicotine replacement products should be sold as OTC medications. This includes not only slow-release formulations such as the nicotine patch and gum, but also the faster-release formulations such as nicotine nasal spray and inhaler, although abuse liability appears to be increased with the faster-release formulations. The argument in favor of this approach is simply that it is better to ingest pure nicotine rather than to be exposed simultaneously to carcinogens, carbon monoxide, and the other toxic components of tobacco during the combustion process, thereby increasing the risk of disease. However, because nicotine alone appears to increase the risk for cardiovascular disease by increasing adrenergic tone and by its effect on lipids, one has to question the wisdom of this suggestion. Moreover, an unknown number of non- and former smokers might use OTC nicotine delivery devices to boost memory and cognitive performance, to control weight, or for other "benefits," thereby risking addiction. Our perspective is that, although harm reduction appears laudable, it seems impossible to implement. Therefore, complete abstinence from smoking and nicotine should remain the treatment goal.

Policy, Regulation, and Advocacy

Should the sale of tobacco products be illegal? Can the sale of tobacco products be made illegal? The answer to the former question is a tentative yes; the answer to the latter is very probably no. A ban on tobacco products is extremely unlikely because (a) historically, they have been manufactured and sold legally, (b) a substantial number of Americans smoke, and (c) tobacco is very big business. Can tobacco products be regulated? Possibly. By calling nicotine an addictive drug, the FDA may be able to regulate aspects of tobacco manufacture and sales. However, governmental regulatory efforts face the challenge of the tobacco industry, its lobbyists, and politicians who are friendly toward the tobacco industry. The future of increased government regulation remains uncertain, given the vicissitudes of the political process. In our opinion, only "grass roots" reform will permit more effective regulation; unfortunately, there is as yet no evidence of an antitobacco groundswell.

Economic regulation (e.g., increasing taxes on tobacco products) is probably effective, to some degree, in motivating smokers to quit. However, this type of regulation has its limits. For example, recently the Canadian government substantially increased taxes on cigarettes, which increased the price of a pack of cigarettes two-to threefold. This resulted in a small decrease in smoking prevalence and a substantial increase in the cigarette black market, which is reminiscent of the effects of prohibition on alcohol use in the United States. The Canadian government repealed the high taxes on cigarettes when it was realized that tax revenues were decreasing. As a result, black market activity decreased. This scenario illustrates another reason why banning tobacco would be nearly impossible.

Another approach to regulation that has been debated is the application of a special tax on cigarette sales, which would then be used to offset the cost of smokers' disproportionately high use of health care resources as they become ill as a result of their smoking. In fact, variations on this theme are already in place (e.g., higher life insurance premiums for smokers). It is unclear to what degree such a tax would serve as a disincentive to smoke. There probably would be some effect, but we are not likely to see this form of regulation adopted anytime soon.

Should physicians advocate the control of tobacco? The answer is a resounding "yes!" Indeed, several physician organizations, including the American Medical Association (AMA) and the American Psychiatric Association, have drafted policy papers on this topic. Effective advocacy starts with education. Physicians are urged to learn about tobacco control by reading about the work of the AMA and established advocacy groups such as Doctors Oughta Care and the Action on Smoking and Health. The American Academy of Family Physicians has developed a model tobacco control program called Tar Wars. The principal goal of Tar Wars is to educate youth regarding tobacco-free lifestyles by developing partnerships between physicians, schools, and community agencies supporting tobacco control. The program supports physicians and other health care clinicians to deliver lessons to fifth- and sixth-graders on the effects of tobacco use on health and strategies for countering the advertising images that tobacco companies use to market their products. Physician-teachers also judge "counter-advertising" posters developed by the children as a follow-up activity. As enthusiastic participants in the Tar Wars program in our own communities, we strongly encourage cardiologists and other clinicians treating patients with cardiac disease to get involved in similar community-based tobacco control programs. It is a wonderful way to promote tobacco control, teach children about prevention, and have fun!

We also encourage physicians who are members of clinical and scientific societies to develop position papers similar to the AMA documents and to disseminate these papers to their membership. The AMA has also recommended divestiture of tobacco and tobacco-related stock. Does the American College of Cardiology or other similar societies own stock in tobacco and related industries? Do your employer-related retirement plans invest in tobacco-related stock? Recently, the Teacher's Insurance Annuity Association–College Retirement Equities Fund—the largest retirement fund for employees of educational institutions—was prompted by its membership to hold a vote on whether to divest all of its tobacco-related holdings. The motion was voted down.

An important but neglected topic is reimbursement for smoking cessation treatment provided by health care providers. The *Treating Tobacco Use and Dependence Guideline* recommends that those smoking cessation treatments found to be effective be included as paid services for all subscribers of health insurance programs (113,114). Lack of reimbursement is an important barrier, preventing the busy physician from spending more time motivating and assisting their patients to quit smoking. Physicians and other health care providers should push hard for third-party reimbursement. Voluntary agencies can provide more information on this issue (Table 6.5).

Finally, health care providers should not turn a blind eye to tobacco consumption on a worldwide scale. The United States enjoys one of the lowest smoking prevalence rates in the world, due in large part to increasing public awareness about the health risks of smoking and to considerable research on developing and disseminating effective smoking cessation treatments. Other countries, especially underdeveloped or newly developing ones, fare much worse in terms of smoking prevalence and efforts to educate and treat smokers. The American tobacco industry is one of the world's largest suppliers of tobacco. We should question American export practices, which actively promote the sale and distribution of tobacco products to developing countries, thereby directly contributing to a worldwide pandemic in tobacco-related diseases.

THE FUTURE

This is a time for considerable optimism. New behavioral and pharmacologic treatments for nicotine dependence are currently being developed to add to the many known effective treatments (58,156,157 and 158). Research is helping us to understand the biobehavioral mechanisms responsible for nicotine dependence and how to target these mechanisms for treatment. A few areas, however, stand out as especially important in terms of furthering our ability to help smokers to quit; one has to do with increased understanding of the biologic and psychological substrates of nicotine dependence. For example, symptoms of depression are associated with nicotine dependence and difficulty quitting, and promising new treatments for smoking cessation include antidepressant medications and psychosocial treatments that target depressive symptoms. Research on nicotine receptors in the mesolimbic areas associated with addiction suggest that more specific antagonists can be developed to block the reinforcing effects of nicotine, thereby helping smokers quit.

Another area of importance that dovetails with the study of biobehavioral mechanisms is patient–treatment matching. No single treatment proves effective for every smoker; there are many reasons why people smoke and become addicted. However, smokers with certain characteristics may respond more favorably to certain treatments. For example, smokers with symptoms of depression achieve better outcomes when treated with an antidepressant than smokers with no symptoms of depression. Better matching of treatment to patient will increase the chances of successful treatment.

Finally, if we are to truly have a significant impact on smoking, subpopulations in whom smoking prevalence has stabilized—or is even increasing—must be targeted for treatment (9). In particular, there is an epidemic of adolescent smoking in the United States. The adolescent smokers of today are the addicted smokers of tomorrow who will suffer from smoking-related cardiovascular and other diseases. Efforts to prevent the initiation of smoking are of paramount importance (the Tar Wars program described above is one such effort), but so is treatment of the adolescent smoker. Many of the same treatments that have proven effective among adult smokers, (e.g., nicotine replacement and bupropion) should be evaluated for efficacy among adolescent smokers. In addition, new innovative strategies for adolescent smokers need to be evaluated and tested.

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7

DIABETES

DORON ARONSON
ELLIOT J. RAYFIELD

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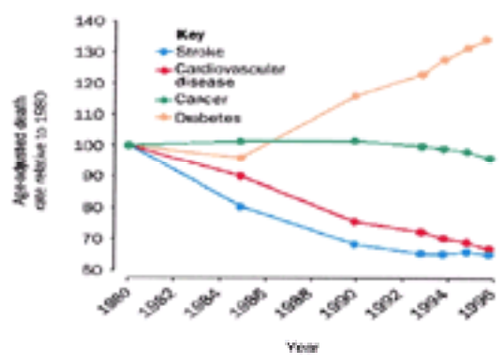
OVERVIEW

Both type 1 and type 2 diabetes are powerful and independent risk factors for coronary artery disease (CAD), stroke, and peripheral arterial disease (1,2). Atherosclerosis accounts for virtually 80% of all deaths among North American diabetic patients, compared with one-third of all deaths in the general North American population (3). More than 75% of all hospitalizations for diabetic complications are attributable to cardiovascular disease (3). Sixteen million people in the United States are estimated to have diabetes, and more than 90% of these patients have type 2 diabetes (4). In addition, it is estimated that up to one-half of type 2 diabetic patients have not been diagnosed. The World Health Organization estimates that the number of diabetic adults will more than double globally, from 143 million in 1997 to 300 million in 2025, largely because of dietary and other lifestyle factors.

Whereas other major multifactorial diseases (e.g., heart disease, stroke, and many cancers) have declined or remained stable, the age-adjusted death rate for diabetes in the United States has increased 30% since 1980 (5) (*e*Fig. 7.0.1). The decline in heart disease mortality in the general U.S. population has been attributed to the reduction in cardiovascular risk factors and improvement in treatment of heart disease. However, patients with diabetes have not experienced the reduction in age-adjusted heart disease mortality that has been observed in nondiabetic people, and an increase in age-adjusted heart disease mortality has been reported in diabetic women (6).



***e*FIGURE 7.0.1** Increasing number of deaths from diabetes, 1980 to 1996. (From National Center for Health Statistics, 1998. From McKinlay J, Marceau L. U.S. public health and the 21st century: diabetes mellitus. *Lancet* 2000;356:757–761, with permission.)

Several autopsy studies have shown that diabetic subjects have more extensive atherosclerosis of both coronary and cerebral vessels than age- and sex-matched nondiabetic controls. In the International Atherosclerosis Project, 23,000 subjects from 14 countries were examined. The severity of coronary atherosclerosis in diabetics varied in parallel with the severity of disease in subjects from the same country. However, the effect of diabetes was superimposed on any level of average severity of atherosclerosis (7).

Autopsy studies have shown that diabetics have a greater number of coronary vessels involved and more diffuse distribution of atherosclerotic lesions (8). Large angiographic studies comparing diabetics with matched controls have corroborated the autopsy studies. Thus, diabetic patients with established CAD undergoing cardiac catheterization for acute myocardial infarction (9), angioplasty (10), or coronary bypass (11) have significantly more severe proximal and distal CAD. Furthermore, postmortem (12) and angioscopic (13) evidence indicates a significant increase in plaque ulceration and thrombosis in diabetic patients.

CORONARY ARTERY DISEASE IN TYPE 1 DIABETES

In contrast to type 2 diabetes, cardiovascular risk in type 1 diabetes can be examined in relation to hyperglycemia *per se*. Long-term follow-up of patients with type 1 diabetes from the Joslin Diabetes Center has shown that an excess of cardiovascular mortality can only be observed after the age of 30 (14). The first cases of clinically manifest CAD occur late in the third decade or in the fourth decade of life, regardless of whether diabetes developed early in childhood or in late adolescence, suggesting that diabetes mainly accelerates the progression of early atherosclerotic lesions that occur at a young age in the general population (14). CAD risk increases rapidly after the age of 40; by the age of 55 years, 35% of men and women with type 1 diabetes die of CAD. This rate of CAD mortality far exceeded that observed in an age-matched nondiabetic cohort from the Framingham Heart Study (8% for nondiabetic men and 4% for nondiabetic women) (14). Similar to women with type 2 diabetes, the protection from CAD observed in nondiabetic women is lost in women with type 1 diabetes (14,15).

Diabetic nephropathy occurs only in a subset of 30% to 40% of type 1 diabetic patients and increases dramatically the prevalence of CAD. Data from the Steno Memorial Hospital showed that in patients with persistent proteinuria the relative mortality from cardiovascular disease was 37 times that in the general population, whereas in patients without proteinuria cardiovascular mortality was only 4.2 times higher (16). In a case-control study of type 1 diabetes patients who were followed from the onset of microalbuminuria (a urinary albumin excretion rate of greater than 20 µg per min but less than 200 µg per min or 30 to 300 mg per 24 hours), coronary heart disease (CHD) developed eight times more frequently than in a diabetic population of similar age, sex, and diabetes duration (17). In the Joslin clinic cohort, the risk of developing CAD in patients with persistent proteinuria was 15 times higher than in those without this renal complication (14). Microalbuminuria in type 1 diabetes is, therefore, not only a marker for renal disease, but it is also a potent risk marker of CAD.

Prospective studies demonstrated that in type 2 diabetes patients, microalbuminuria is also an independent predictor of increased cardiovascular mortality (18). Proteinuria in a patient with type 2 diabetes increases the risk of fatal CAD by a factor of only two to four.

When nephropathy is superimposed on diabetes, some of the atherogenic mechanisms present in diabetes are accentuated. An aggregation of cardiovascular risk factors for cardiovascular disease, including hypertension, lipid abnormalities, and a hypercoagulable state, are detectable in the early stages of diabetic nephropathy, when renal function is still normal (19). Hypertension is frequently present in diabetic nephropathy even when the creatinine concentrations remain normal and can intensify CAD in type 1 diabetes patients. In the World Health Organization Multinational Study on Vascular Disease in Diabetes, patients with both hypertension and proteinuria experienced 11-fold and 18-fold increased mortality for men and women, respectively (20). Microalbuminuria is associated with an atherogenic lipoprotein profile that includes elevated low-density lipoprotein (LDL) and chylomicron remnants levels, decreased high-density lipoprotein (HDL) levels, and elevated lipoprotein(a) levels (21,22). In addition, plasminogen activator inhibitor-1 (PAI-1) activity, factor VII, and plasma fibrinogen are significantly higher in microalbuminuric type 1 diabetes patients (23). Finally, nephropathy results in accelerated accumulation of advanced glycosylation end products (AGEs) in the circulation and tissue that parallels the severity of renal functional impairment (24). The accumulation of AGEs improves markedly with successful renal transplantation (25).

Contrary to other microvascular complications of diabetes (e.g., retinopathy), the risk for the development of diabetic nephropathy is only partially determined by glycemic control or disease duration and is highly influenced by genetic susceptibility (26,27). Familial clustering of cardiovascular disease occurs in diabetic patients with nephropathy. Parents of insulin-dependent diabetic patients with proteinuria have a significant excess of cardiovascular disease compared with parents of insulin-dependent diabetic patients who do not develop kidney disease. Among diabetics with nephropathy, those who had a cardiovascular event are six times more likely to have a familial history of cardiovascular disease than those who had no such event. A history of cardiovascular disease in both parents or in the father of type 1 diabetes patients increases the risk of nephropathy in the offspring ten- and threefold, respectively (28). Parents of diabetic offspring with nephropathy also have higher levels of arterial blood pressure than do parents whose diabetic offspring do not have diabetic nephropathy (29). Thus, a subgroup of type 1 diabetes subjects has a genetically determined predisposition to renal disease and hypertension, and this predisposition is linked to enhanced risk of CAD. The genetic link between diabetic nephropathy and CAD may be related, in part, to the ACE I/D polymorphism (see Genetic Factors). This inherited susceptibility to CAD might be more likely to be expressed in patients with poor glycemic control.

Patients with End-Stage Renal Disease and Postrenal Transplantation

In diabetic patients reaching end-stage renal disease, the overall mortality has been reported to be greater than in nondiabetic patients with end-stage renal disease. For example, in the age group of 35 to 44 years old, the 3-year survival rate of diabetic patients is 44% in men and 66% in women compared with 75% and 87% for nondiabetic patients with end-stage renal disease (30), and the majority of these deaths are secondary to CAD (31). The relative risk for age-specific death rate from myocardial infarction among all diabetic patients during the first year of dialysis is 89-fold higher than that of the general population (30).

The most common cause of death in diabetic patients who have undergone renal transplantation is also CAD, which accounts for 40% of deaths in these patients. In one study, a death rate of 30% was reported over a mean follow-up period of 4 years, and the majority of these deaths were from cardiovascular causes (32). Consequently, long-term survival of diabetic patients with renal allograft is substantially inferior to that of nondiabetic patients. In most centers, coronary angiography is performed in all diabetic transplant candidates (33), and coronary revascularization has been shown to be superior to medical therapy in this setting (34).

CORONARY ARTERY DISEASE IN TYPE 2 DIABETES

CHD is the leading cause of death among patients with type 2 diabetes, regardless of duration of diabetes. Several population-based studies have consistently shown that the relative risk ratio of cardiovascular disease in type 2 diabetes compared with the general population is increased twofold to fourfold (2,15,35). Patients with type 2 diabetes without previous myocardial infarction have CAD mortality as high as nondiabetic patients with a previous infarction (36).

The increased cardiovascular risk is particularly striking in women. A number of studies reported a disproportionate effect of CAD on diabetic women compared with diabetic men (37). Indeed, the usual protection that premenopausal women have against atherosclerosis is almost completely lost when diabetes is present (38).

Although the degree and duration of hyperglycemia are the principal risk factors for microvascular complications (39), in type 2 diabetes, there is no obvious association between the extent or severity of macrovascular complications and the duration or severity of the diabetes. An increased prevalence of CAD is apparent in newly diagnosed type 2 diabetes subjects (40). In fact, even impaired glucose tolerance carries an increased cardiovascular risk despite minimal hyperglycemia (41).

In individuals who are genetically prone to develop type 2 diabetes, insulin resistance is the earliest detectable metabolic defect and can occur 15 to 25 years or more before the clinical onset of overt diabetes (42). Although there is some uncertainty regarding the primary lesion and the relative importance of the different tissues, metabolic defects in the liver and peripheral tissues such as fat, muscle, and pancreatic beta cells all contribute to the syndrome.

The term *insulin resistance* usually connotes resistance to the effects of insulin on glucose uptake and metabolism in adipocytes and skeletal muscle and impaired suppression of hepatic glucose output (43). Insulin resistance is a common condition, associated with genetic predisposition, sedentary lifestyle, and aging. It is exacerbated and produced by obesity. Even in the absence of diabetes, insulin resistance is a major risk factor for CAD (44) because impaired insulin action coupled with compensatory hyperinsulinemia leads to a number of proatherogenic abnormalities referred to as the *insulin resistance syndrome* (Table 7.1). The association of insulin resistance with several established atherogenic risk factors (45,46 and 47) (Table 7.1) promotes atherosclerosis many years before overt hyperglycemia ensues (48) (Fig. 7.1).

Hypertension (45,46)
Abdominal obesity (47)
Dyslipidemia
Increased very-low-density lipoprotein triglyceride (52,71,72)
Decreased high-density lipoprotein (52,71,72)
Small dense atherogenic low-density lipoprotein particles (91,92)
Postprandial lipemia (82,87)
Prothrombotic state
Elevated plasminogen activator inhibitor-1 activity (158)
Fibrinogen (155)
von Willebrand factor (154)
Endothelial dysfunction (136)
Chronic subclinical inflammation (?) (51)

TABLE 7.1 CARDIOVASCULAR RISK FACTORS ASSOCIATED WITH INSULIN RESISTANCE

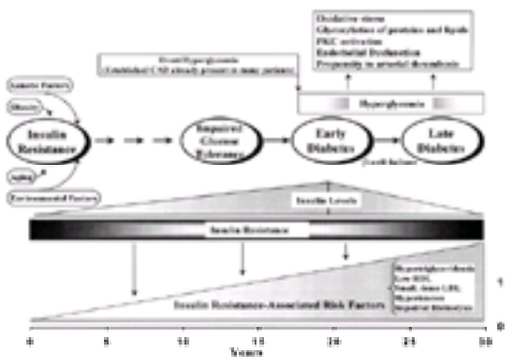


FIGURE 7.1 Schema of cardiovascular risk factors in patients with type 2 diabetes. Patients are exposed to the proatherogenic effects of the insulin resistance many years before the development of frank hyperglycemia. Therefore, macrovascular complications are commonly found when diabetes is diagnosed. When overt hyperglycemia ensues, it promotes atherosclerosis through several other mechanisms. CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PKC, protein kinase C.

The dyslipidemia associated with insulin resistance entails elevated very-low-density lipoprotein (VLDL)–triglyceride levels, low HDL levels, delayed postprandial clearance of triglyceride-rich lipoprotein remnants, and the presence of the very atherogenic, small, dense LDL particles (49) (Table 7.1). This atherogenic lipoprotein phenotype is the most common lipoprotein abnormality seen in patients with CAD and imparts a risk for CAD at least equal to that of isolated moderate to severe hypercholesterolemia (50) (see Lipoprotein Disorders in Diabetes).

Insulin-resistant subjects also exhibit endothelial dysfunction (see Vascular Endothelial Dysfunction in Diabetes) and a hypercoagulable state (see Diabetes as a Prothrombotic State). Chronic subclinical inflammation has emerged as part of the insulin-resistance syndrome. C-reactive protein, a sensitive marker of inflammation associated with cardiovascular events, is independently related to insulin sensitivity (51).

The proatherogenic metabolic risk factors in insulin-resistance subjects worsen continuously across the spectrum of glucose tolerance (52). In the Framingham Offspring Study, the deterioration of insulin resistance (and glucose tolerance) over time was associated with a continuous increasing gradient of metabolic atherogenic risk factors (Fig. 7.2).

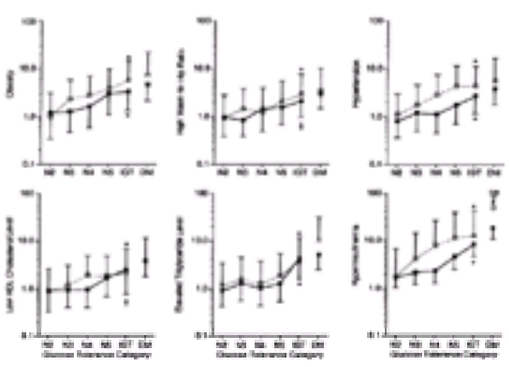


FIGURE 7.2 Multivariable odds ratios for metabolic risk factors by glucose tolerance category: odd ratios and 95% confidence intervals (*error bars*) of obesity (body mass index ³27.3 kg/m^2 in women or ³27.8 kg/m^2 in men, elevated waist-to-hip ratio (>0.9 for women and >1.0 for men), hypertension (two measurements of diastolic blood pressure >90 mm Hg, systolic blood pressure >140 mm Hg, or use of hypertensive medications), low high-density lipoprotein (HDL) cholesterol level (<45 mg per dL for women and <35 mg per dL for men), elevated triglyceride level (>200 mg per dL), and hyperinsulinemia (fasting insulin level greater than ninetieth percentile of its distribution among Framingham Offspring Study participants with normal glucose tolerance among women (*white squares* and *dotted lines*) and men (*black squares* and *solid lines*) are shown for each glucose tolerance category from lowest quintile (N1) to highest quintile (N5) of fasting plasma glucose level among participants with normal glucose tolerance, impaired glucose tolerance (IGT), and previously undiagnosed diabetes mellitus (DM). *p <.001; †p = .002; ‡p = .008 for trend from the lowest quintile of normal fasting glucose level to impaired glucose tolerance. (From Meigs JB, Nathan DM, Wilson PW, et al. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingham Offspring Study. *Ann Intern Med* 1998;128:524–533, with permission.)

Whether compensatory hyperinsulinemia promotes atherosclerosis in insulin-resistant subjects is still unclear. Several prospective studies reported the association between fasting or postprandial hyperinsulinemia and future CAD (53,54). Other studies reported inverse correlations between insulin sensitivity and atherosclerosis (55,56). In addition, it has been suggested that chronic hyperinsulinemia exerts a deleterious effect on the arterial wall (57) based on the ability of insulin at high concentrations to stimulate the insulin growth factor-1 receptor. However, the association between hyperinsulinemia and atherosclerosis has been demonstrated only in healthy male middle-aged white cohorts (53,54) but not in women (44,58), or in other ethnic groups such as Pima Indians (59) or Hispanic Americans (60).

The inconsistent association between plasma insulin levels and CAD may stem from the fact that hyperinsulinemia is only a compensatory response of pancreatic beta cells to the peripheral insulin resistance. Prospective studies have shown that type 2 diabetes progresses over a continuum of worsening insulin action, beginning with

peripheral insulin resistance and ending with a loss of insulin secretion. Thus, plasma insulin levels reflect not only the degree of insulin resistance but also the ability of beta cells to compensate. In fact, the natural course of type 2 diabetes is characterized by gradual loss of insulin secretion. Whereas hyperinsulinemia is characteristic in patients with impaired glucose tolerance and mild type 2 diabetes, increased glucose levels seen in patients with moderate-to-severe type 2 diabetes are associated with a progressive decline in both fasting and postprandial insulin concentrations as a result of pancreatic beta cell failure (43). Cross-sectional (52) and prospective (61) studies have shown that fasting and glucose-stimulated insulin concentrations have an inverted U-shaped curve when plotted against plasma glucose concentrations. This pattern has been termed the *Starling curve of the pancreas* (43). Thus, the insulin-resistance state itself—not the accompanying compensatory hyperinsulinemia—is more important than hyperinsulinemia as a risk factor for atherosclerosis (55).

Insulin-resistant individuals who go on to develop type 2 diabetes become exposed also to the atherogenic effects of hyperglycemia (Fig. 7.1). Indeed, the atherogenic risk factor profile observed in insulin-resistance patients accounts for only a portion of the excess risk for CAD in patients with type 2 diabetes (15,62), indicating that hyperglycemia itself plays a central role in accelerating atherosclerosis in these patients. Because many years of asymptomatic hyperglycemia may precede the clinical diagnosis of type 2 diabetes, the duration of diabetes is frequently underestimated. Furthermore, the threshold above which hyperglycemia becomes atherogenic is unknown but may be in the range defined as impaired glucose tolerance (63). Despite these confounding factors, many population-based studies in patients with type 2 diabetes have shown a positive association between the degree of glycemic control and CAD morbidity and mortality in middle-aged and elderly type 2 diabetic subjects (64,65 and 66).

LIPOPROTEIN DISORDERS IN DIABETES

The metabolic abnormalities associated with types 1 and 2 diabetes result in profound changes in the transport, composition, and metabolism of lipoproteins. Lipoprotein metabolism is influenced by several factors including type of diabetes, glycemic control, obesity, insulin resistance, the presence of diabetic nephropathy, and genetic background (67). Abnormalities in plasma lipoprotein concentrations are commonly observed in diabetic individuals and contribute to the atherosclerotic process.

Lipoprotein Profile in Type 1 Diabetes

The level of glycemic control is the major determinant of lipoprotein levels in type 1 diabetic patients (68). In well- to moderately controlled diabetes, lipoprotein levels are usually within the normal range (69). In poorly controlled type 1 diabetic patients, triglycerides are markedly elevated, LDL is modesty increased (usually when HbA_{1c} is greater than 11%), and HDL levels are decreased (69) (Table 7.2).

	Type 1 diabetes		Type 2 diabetes		
Lipoprotein	Conventional therapy	Intensive therapy	Poor control	Good control	Atherogenic modifications
VLDL	Normal or increased	Decreased	Increased	Normal or increased	Cholesteryl ester–rich VLDL
LDL	Normal or increased	Normal or decreased	Normal	Normal	Glycosylation of LDL, apolipoprotein B; LDL susceptible to oxidative modification; high proportion of small, dense LDL
HDL	Normal	Increased	Decreased	Normal or decreased	Decreased HDL, increased cholesteryl ester transfer protein activity; low paraoxonase activity (?)

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

TABLE 7.2 LIPOPROTEIN ABNORMALITIES IN DIABETES

Intensive insulin therapy normalizes all lipoprotein abnormalities. Hypertriglyceridemia and hypercholesterolemia are readily reversible with insulin therapy (69), and HDL levels may be higher than in normal controls (21). When high LDL levels exist in well-controlled type 1 diabetes, the existence of diabetic nephropathy or a separately inherited lipid disorder should be suspected (68).

Lipoprotein Profile in Type 2 Diabetes

In contrast to type 1 diabetes, the pathophysiology of dyslipidemia in type 2 diabetes results from a complex relationship between hyperglycemia and the insulin-resistance state (67). An atherogenic pattern of lipoprotein changes (Table 7.1) is often present for years before the development of fasting hyperglycemia and the diagnosis of type 2 diabetes (70).

The typical lipoprotein profile associated with type 2 diabetes includes high triglycerides, low HDL levels, and normal LDL levels (Table 7.2). The most consistent change is an increase in VLDL-triglyceride levels (71,72). Population studies, including studies of the Pima Indians who have virtually no forms of genetic hyperlipidemia, indicate that type 2 diabetes generally produces only a 50% to 100% elevation of VLDL or total triglycerides (73). Thus, type 2 diabetic subjects with total triglycerides greater than 350 to 400 mg per dL probably have other genetic disorders in lipoprotein metabolism that may be exacerbated by diabetes. HDL levels are typically approximately 25% to 30% lower than in nondiabetic subjects and are commonly associated with other lipid and lipoprotein abnormalities, particularly high triglyceride levels.

Very-Low-Density Lipoprotein Metabolism in Diabetes

Hypertriglyceridemia in type 2 diabetes results from high fasting and postprandial triglyceride-rich lipoproteins, especially VLDL (71). Type 2 diabetic subjects with hypertriglyceridemia have both overproduction and impaired catabolism of VLDL (67,72). Increased VLDL production is almost uniformly present in patients with type 2 diabetes and hypertriglyceridemia (72). Increased VLDL production in diabetes is a consequence of an increase in free fatty acid mobilization (because maintenance of stored fat in adipose tissue depends on the suppression of hormone-sensitive lipase by insulin) and high glucose levels (74) (Fig. 7.3). Because free fatty acid availability is a major determinant of VLDL production by the liver, VLDL overproduction and hypertriglyceridemia occur (72).

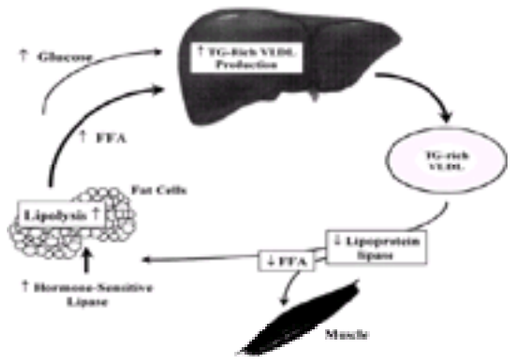


FIGURE 7.3 Mechanism of increased very-low-density lipoprotein (VLDL) triglyceride (TG) in diabetes. In the setting of insulin deficiency or insulin resistance, higher rates of glucose and free fatty acids (FFAs) flux to the liver lead to enhanced VLDL production and secretion. Decreased lipoprotein lipase activity contributes to the accumulation of these particles in the plasma.

The rest of the dyslipidemic phenotype that characterizes insulin resistance and type 2 diabetes (low HDL and small, dense LDL)—which has been termed *atherogenic lipoprotein phenotype* (50)—follows once VLDL secretion increases, mainly through the action of cholesteryl ester transfer protein and lipoprotein compositional

changes that occur in plasma (75).

Increased fatty acid flux to the liver also results in the production of large triglyceride-rich VLDL particles because the size of VLDL is also mainly determined by the amount of triglyceride available. VLDL size is an important determinant of its metabolic fate. Large triglyceride-rich VLDL particles may be less efficiently converted to LDL (76), thereby increasing direct removal from the circulation by non-LDL pathways. In addition, overproduction of large triglyceride-rich VLDL is associated with the atherogenic small, dense LDL subclass (50).

In type 2 diabetic subjects with more severe hypertriglyceridemia, VLDL clearance by lipoprotein lipase (LPL)—the rate-limiting enzyme responsible for the removal of plasma triglyceride-rich lipoproteins—is also impaired (71). LPL requires insulin for maintenance of normal tissue levels (77), and its activity is low in patients with poorly controlled type 2 diabetes (71). The result is enzymatic activity insufficient to match the overproduction rate, with further accumulation of VLDL triglyceride.

Although triglyceride concentrations are associated with premature CAD, the relation weakens when the strong inverse relation between HDL cholesterol and risk is taken into account (78). In addition, an important confounder of triglyceride and CAD risk is the heterogeneity of the triglyceride-rich lipoproteins. However, studies have shown that triglyceride-rich lipoproteins play an important role in the progression of atherosclerosis (79). Furthermore, in contrast to the controversy regarding hypertriglyceridemia as a risk factor for CHD in the nondiabetic population, several studies indicate that elevated triglyceride levels are independently associated with increased CHD risk in diabetic patients (71,80,81). Hypertriglyceridemia in diabetic patients often correlates with LDL density and subclass (i.e., small, dense LDL) and decreased levels of HDL_2 (50,78), which appear to increase overall risk synergistically (78).

Postprandial Lipemia

Exaggerated postprandial lipemia resulting from impaired remnant clearance is a factor in atherogenesis, involving endothelial dysfunction and enhanced oxidative stress (82,83,84 and 85). Several studies have shown that postprandial triglycerides may be a better predictor of CAD than fasting triglycerides (83,84). In support of this hypothesis is the observation that remnant lipoproteins are associated with impaired endothelial function (85).

Postprandial lipemia consists of a heterogeneous group of triglyceride-rich particles of different composition and origin. By definition, a remnant is an apolipoprotein B (apoB)–containing lipoprotein that has delivered some of its original triglyceride content to tissues by means of LPL-mediated lipolysis (82). After fat intake, the intestine secretes chylomicrons whose triglycerides are lipolyzed by LPL. The liver secretes triglyceride-rich VLDL particles that are also lipolyzed by LPL, forming VLDL remnant particles. This VLDL delipidation is reduced postprandially because of competition with chylomicrons for LPL-mediated lipolysis, and VLDL plasma residence is, therefore, prolonged. Consequently, although 80% of the increase in postprandial triglyceride levels is accounted for by chylomicrons (which carry a large number of triglyceride molecules), the number of endogenous (liver-derived) VLDL constitutes over 90% of the triglyceride-rich particles in the postprandial state (82). Delayed VLDL clearance results in the accumulation of partially catabolized VLDL remnants that are reduced in size and enriched in cholesteryl ester. A considerable body of evidence indicates that these small, cholesteryl ester–enriched VLDL particles are atherogenic.

Because type 2 diabetes is characterized by increased VLDL production and impaired removal, it is not surprising that patients with type 2 diabetes exhibit excessive postprandial lipemia and impaired remnant clearance (82,86). The increase in postprandial triglyceride concentrations strongly correlates with insulin resistance (87).

An inverse relation exists between lipoprotein particle size and their capacity of lipoproteins to enter the arterial wall. Accordingly, small VLDL (S_f 20–60) and intermediate-density lipoprotein (S_f 12–20) seem to share a similar mechanism and potential for penetrating the arterial intima. It is probable that the relative cholesteryl ester enrichment also contributes to their atherogenic potential. In the apoE knockout mouse the accumulation of triglyceride-rich lipoproteins that contain mainly cholesteryl ester and little triglyceride fatty streaks and complicated arterial lesions appear rapidly (88).

High-Density Lipoprotein Metabolism in Diabetes

As in nondiabetic subjects, low HDL levels are powerful indicators of CHD in diabetic patients (50,78). Decreased HDL levels in diabetes result from decreased production and increased catabolism of HDL and are closely related to the abnormal metabolism of triglyceride-rich lipoproteins (71,72) (Fig. 7.4).

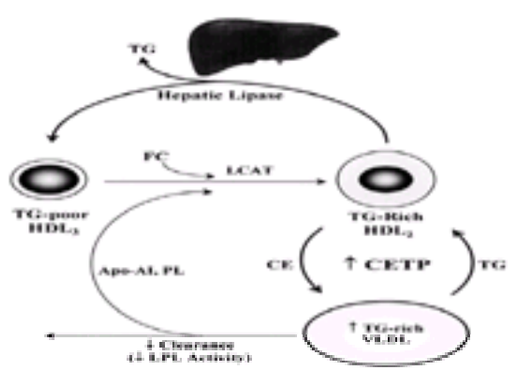


FIGURE 7.4 Mechanism of decreased high-density lipoprotein (HDL) in diabetes. The rate of HDL_2 formation is dependent on the rate of flux of surface components from lipolysis of triglyceride (TG)-rich lipoproteins. Inefficient low-density lipoprotein–mediated TG-rich lipoprotein catabolism reduces the rate of HDL_2 formation. Excess of TG-rich lipoproteins enhances cholesteryl ester transfer protein (CETP), resulting in the formation of HDL_2, which is a TG-rich particle that efficiently interacts with hepatic lipase. The result is the predominance of the small and dense HDL_3 in diabetic patients. A similar mechanism governs the predominance of small, dense species of low-density lipoprotein. Apo-AI, apolipoprotein AI; CE, cholesteryl ester; FC, free cholesterol; LCAT, lecithin-cholesterol acyltransferase; LPL, lipoprotein lipase.

During lipolysis of chylomicrons and VLDL, surface components (free cholesterol, redundant phospholipids, and apolipoproteins) are transferred into the HDL fraction. These components may enter nascent discoid HDL particles secreted by the liver. The free cholesterol is esterified by lecithin-cholesterol acyltransferase to generate mature spherical HDL. Alternatively, these surface components may be incorporated into preexisting HDL particles (see Chapter 3). The latter process results in an increase in size and decrease in density of HDL particles, leading to the conversion of preexisting HDL_3 (triglyceride depleted) to HDL_2.

Decreased HDL synthesis is related to the decreased LPL activity. Both genetic and acquired LPL (89) deficiencies are associated with low HDL because the rate of HDL_2 formation is dependent on the rate of flux of surface components from lipolysis of triglyceride-rich lipoprotein (Fig. 7.4). When LPL-mediated VLDL catabolism is inefficient, less surface material is transferred to HDL, impairing HDL formation.

Increased catabolism of HDL in diabetes can occur because increased secretion of VLDL into plasma promotes the transfer of triglycerides from these lipoproteins to HDL in exchange for cholesteryl ester. This exchange occurs in plasma and is facilitated by cholesteryl ester transfer protein, generating a triglyceride-enriched (and cholesteryl ester–depleted) HDL_2. This particle is highly susceptible to catabolism by hepatic triglyceride lipase (HTGL), an enzyme found primarily on endothelial cells of hepatic sinusoids (72,90). Hepatic triglyceride lipase has both triglyceride hydrolase and phospholipase activity and generates smaller HDL_3 particles that are depleted in triglycerides and phospholipids (Fig. 7.4).

Low-Density Lipoprotein Metabolism in Diabetes

As discussed, patients with types 1 and 2 diabetes in reasonable metabolic control have normal LDL cholesterol levels. However, although the absolute number of LDL particles is normal, alterations in LDL clearance and susceptibility to oxidative modification result in an increase in LDL atherogenic potential.

Low-Density Lipoprotein Composition and Insulin Resistance

In insulin-resistant patients with or without overt type 2 diabetes, the composition of LDL particles is altered, resulting in a preponderance of small, triglyceride-enriched and cholesterol-depleted particles (phenotype B). A preponderance of small, dense LDL particles is related to many characteristics of the insulin-resistance syndrome.

In nondiabetic subjects, LDL subclass phenotype B is associated with other components of the insulin-resistance syndrome, including central obesity, hypertension, glucose intolerance, and hyperinsulinemia (91,92 and 93).

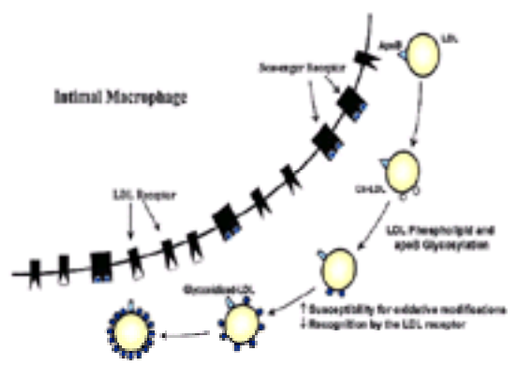
The formation of small, dense LDL in diabetes occurs in a similar fashion to the increased formation of small and dense HDL_3, as described previously. Cholesteryl ester transfer protein mediates the exchange of triglyceride from VLDL for cholesteryl ester in LDL. If sufficient LDL cholesteryl ester is replaced by triglyceride from VLDL, then when the particle comes into contact with hepatic lipase hydrolysis of newly acquired triglyceride in LDL and HDL by HTGL in turn decreases the size of LDL particles (94). The symmetry of the mechanisms for the formation of small, dense species of LDL and HDL (Fig. 7.4) helps to explain why low HDL levels and a preponderance of small dense LDL are both components of the insulin-resistance syndrome and why HDL cholesterol level is strongly correlated with LDL size (94).

Small, dense LDL has been associated with CAD risk independently of the absolute concentrations of LDL cholesterol or other CAD risk factors (50). Small, dense LDL particles are more susceptible to oxidative modification (95) and are particularly prone to induce endothelial dysfunction (96). In addition, there is enhanced arterial wall penetration by the small LDL particles (97).

Low-Density Lipoprotein Glycosylation

The glycosylation process (see Role of Advanced Glycosylation End Products in Diabetic Atherosclerosis) occurs both on the apoB (98) and phospholipid (99) components of LDL, resulting in profound functional alternations in LDL clearance and susceptibility to oxidative modification.

Clinical studies have shown an increased level of AGEs on LDL obtained from diabetics compared with healthy individuals (99,100). Glycosylation of LDL apoB occurs mainly on a positively charged lysine residue within the putative LDL receptor binding domain, which is essential for the recognition of LDL by the LDL receptor (100). LDL glycosylation increases with glucose levels and impairs LDL receptor–mediated LDL clearance (eFig. 7.4.1).



***e*FIGURE 7.4.1** Potential mechanisms by which low-density lipoprotein (LDL) glycosylation increases its atherogenicity. Advanced glycosylation of the phospholipid component of LDL is accompanied by the progressive oxidative modification of unsaturated fatty acid residues. Glycosylation of LDL apolipoprotein B (apoB) reduces its recognition by the LDL receptor.

Another atherogenic effect of glycation is to increase LDL susceptibility to oxidative modification. Advanced glycosylation of an amine-containing phospholipid component of LDL is accompanied by progressive oxidative modification of unsaturated fatty acid residues (99). Thus, glycation confers increased susceptibility of LDL to oxidative modification (101,102), which is considered a critical step in its atherogenicity.

Clinical Trials of Lipid Lowering in Diabetic Patients

In general, these trials suggest that aggressive lipid reduction has greater incremental benefit in diabetic than nondiabetic patients (eTable 7.2.1). However, with the exception of the Scandinavian Simvastatin Survival Study (4S), the number of diabetic subjects in these trials was too small to demonstrate statistical significance for this observation, and higher event rates were evident in diabetic patients even with lipid-lowering therapy.

***e*TABLE 7.2.1** SECONDARY PREVENTION TRIALS OF LIPID LOWERING IN DIABETIC PATIENTS

			Patients (n)		Risk reduction (%)	
Study	**End points**	**Follow-up (years)**	**No diabetes**	**Diabetes**	**No diabetes**	**Diabetes**
Scandinavian Simvastatin Survival Study (103,403)	Nonfatal MI/CAD death/total mortality/revascularization	5.4	4,242	202	29	43
Cholesterol and Recurrent Events trial (104)	Nonfatal MI/CAD death	5.0	3,573	586	23	25
Post–coronary artery bypass graft (353)	Composite cardiovascular events	4.3	1,235	116	13	43
Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group (404)	CAD death	6.1	4,116	386	19	25
AFCAPS/TexCAPS (410)	Nonfatal MI/unstable angina/CAD death	5.2	6,440	155	26	43
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group (112)	Nonfatal MI/CAD death, stroke	5.1	1,904	627	24	24
Helsinki Heart Study (111)	Nonfatal MI/CAD death	5.0	3,946	135	30	68

CAD, coronary artery disease; MI, myocardial infarction.

The 4S was the first to demonstrate the effectiveness of cholesterol-lowering therapy for secondary prevention of death and morbidity in diabetic patients. The risk reduction for CHD and overall mortality in diabetic subjects was 55% and 43%, respectively, compared with diabetic patients in the placebo group (103). Subjects in 4S had relatively high LDL cholesterol levels at baseline (approximately 185 mg per dL). However, the majority of patients with coronary disease (including diabetics) has lower LDL cholesterol levels. The Cholesterol and Current Events study examined the effect of cholesterol-lowering therapy in patients with coronary disease with average cholesterol levels (mean, 139 mg per dL). In 586 diabetic subjects with CAD, the mean baseline lipid concentrations (136 mg per dL LDL cholesterol, 38 mg per dL HDL cholesterol, and 164 mg per dL triglycerides) were similar to those in the nondiabetic group. The magnitude of LDL cholesterol reduction by pravastatin was also similar (27% and 28%) in the diabetic and nondiabetic groups. Pravastatin treatment reduced the absolute risk of coronary events for the diabetic and nondiabetic patients by 8.1% and 5.2% and the relative risk by 25% (p = .05) and 23% (p <.001), respectively (104).

These results demonstrate that cholesterol lowering improves the prognosis of diabetic patients with CAD. The absolute clinical benefit achieved by cholesterol lowering may be greater in diabetic than in nondiabetic patients with CAD, because diabetic patients have a higher absolute risk of recurrent CAD and higher case fatality rates (105) or because LDL cholesterol in diabetic patients is more atherogenic (91,92,99,101).

Management of Dyslipidemia in Diabetic Patients

The American Diabetes Association recommendations for the management of hyperlipidemia in patients with diabetes generally follow the guidelines of the National Cholesterol Education Program (see Chapter 3) with several differences (106).

Nonpharmacologic strategies to treat dyslipidemia in diabetics include dietary modification (similar to those recommended by the National Cholesterol Education Program), weight loss, physical exercise, and improved glycemic control (106). In patients with type 1 diabetes, optimal glycemic control should result in normal or below normal lipoprotein levels (68) and prevent the atherogenic state associated with lipoprotein glycosylation. Improved diabetic control in type 2 diabetes is beneficial but not always associated with reversal of lipoprotein abnormalities (Table 7.3). Improved glycemic control using sulfonylurea, insulin (21), metformin (107), or thiazolidinediones (e.g., pioglitazone, rosiglitazone) (108) therapy often causes a substantial reduction (20% to 50%) in VLDL triglyceride levels. The magnitude of improvement in triglycerides generally correlates with the change in glucose levels rather than the mode of therapy. However, agents that improve insulin sensitivity such as metformin (107) and thiazolidinediones (108) lead to greater lowering of triglyceride compared with sulfonylurea. The effect of improved glycemic control on HDL is more variable and often results in only a small increase (3 to 4 mg per dL) in HDL levels (21).

Drug	Therapeutic effect: Triglyceride level	Chl level	Chl size	HDL level	Main indication	Special considerations
Nicotinic acid	[illegible]	[illegible]	↑	[illegible]	Generally not indicated	Adverse effect on glycemic control May be used in refractory dyslipidemias No adverse effect on glucose metabolism Increased risk for cholesterol gallstones
Fibric acid derivatives*	[illegible]	↓ or ↑	↑	[illegible]	Probably the drugs of choice for the treatment of hypertriglyceridemia	
3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors	[illegible]	[illegible]	↑ or ↓	[illegible]	Drugs of choice for the treatment of hypercholesterolemia	
Bile acid resins	↑–↑↑	[illegible]	↓	↓	Mixed dyslipidemia, in combination with fibric acid derivatives	Extreme elevations in triglyceride level occur mainly in patients who already had marked hypertriglyceridemia The only drug therapy recommended for children and adolescents Impaired absorption of several drugs, including glycosides

↑, increased ↑↑, markedly increased ↓, decreased →, no change.
*Fibrates using 500 mg twice (see dosing regimen).
†Greatest reductions in patients with higher baseline levels.
‡Depending on initial triglyceride concentration (see text).
§Generally in relation to the magnitude of reduction in plasma triglyceride and very low-density lipoprotein levels.

TABLE 7.3 ANTIHYPERLIPIDEMIC DRUG THERAPY IN DIABETIC PATIENTS

Despite less than optimal response in lipids, optimal control of plasma glucose levels should be attempted before lipid-lowering agents are added to the therapeutic regimen. However, the physician should not wait too long to initiate concomitant drug therapy, because the significantly increased risk of macrovascular disease in type 2 diabetes has probably been present for many years before overt diabetes (70). In addition, “perfect” glycemic control is not attained in many type 2 diabetic patients. If 3 to 6 months of nonpharmacologic therapy fails to improve lipid level, drug therapy is warranted.

Relatively recent publications have argued against the relevance of the traditional classification to primary and secondary CHD prevention in the setting of diabetes (21,36). The rationale for this approach stems from both the high event rates in diabetic patients without clinical evidence of CAD (presumably because of the high rates of subclinical atherosclerosis) (21), as well as the worse prognosis in diabetic patients who have had a clinical event compared with nondiabetic subjects (105). These considerations led to the suggestion that LDL cholesterol should be lowered to less than 100 mg per dL in diabetic subjects without prior CAD (21,36).

Drug Therapy

Antihyperlipidemic drug therapy in diabetic patients is similar to that in nondiabetic subjects (see Chapter 3) with several specific considerations (Table 7.3). 3-Hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors are highly effective in lowering cholesterol levels in type 2 diabetic patients in whom the principal finding is elevated LDL cholesterol level. They do not adversely affect glycemic control (21,109).

The fibric acid derivatives are effective in the treatment of hypertriglyceridemia in diabetic patients (110) (Table 7.3). These agents decrease VLDL levels, increase HDL, and can increase LDL particle size in hypertriglyceridemic patients with small, dense LDL particles (110). In the Helsinki Heart Study, gemfibrozil reduced the incidence of cardiovascular events in patients with type 2 diabetes (111). The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial randomized 2,531 patients with CHD (25% of whom had diabetes) with low HDL cholesterol to gemfibrozil or placebo (112). Treatment with gemfibrozil over 5 years increased HDL 6% and reduced 22% of major coronary artery events, without lowering LDL cholesterol.

Fibric acid derivatives do not adversely affect glucose metabolism. In patients with normal triglyceride levels, these drugs lower LDL cholesterol by 5% to 15%. However, in hypertriglyceridemic patients, the decrease in triglyceride levels is frequently accompanied by an increase in LDL cholesterol levels (110). This increase probably reflects the elimination of small, dense LDL particles characteristic of the hypertriglyceridemic patients, resulting in less atherogenic LDL cholesterol (113).

Cholestyramine is efficacious in decreasing LDL cholesterol levels in diabetic patients (114). However, bile acid resins can increase VLDL triglycerides significantly, particularly if they are already elevated above 250 to 300 mg per dL or in patients with poorly controlled diabetes.

Nicotinic acid is the most effective drug in raising HDL levels in patients with hypertriglyceridemia and can increase particle size in patients with small, dense LDL particles (115). The use of nicotinic acid has been discouraged in patients with diabetes because of possible deterioration in glycemic control (21,116) secondary to the induction of insulin resistance. In one study of patients with type 2 diabetes, a niacin dose of 4.5 g per day reduced plasma cholesterol levels by 24% and triglyceride levels by 45% and raised HDL cholesterol by 34%. However, the glycosylated hemoglobin level increased by 21% (116). In another study, niacin at a lower dose (3 g per day) produced a 8% reduction in LDL, a 23% reduction in triglycerides, and a 29% increase in HDL level, whereas HbA_{1c} increased by only 0.3% (117).

Niacin therapy may be considered as an alternative to statin drugs or fibrates in patients with diabetes in whom these agents are not tolerated, or in whom they fail to sufficiently correct hypertriglyceridemia or low HDL (117). Glycemic status should be carefully monitored during niacin therapy and the dose modified or discontinued if glycemic control deteriorates.

VASCULAR ENDOTHELIAL DYSFUNCTION IN DIABETES

Endothelial cells situated at the vessel wall–blood interface participate in a number of important homeostatic and cellular functions that protect from atherosclerosis and intraluminal thrombosis (eTable 7.3.1). Endothelial dysfunction can promote both the formation of atherosclerotic plaques and the occurrence of acute events. Endothelial *injury*, which results in endothelial *dysfunction*, has a critical role in the pathogenesis of atherosclerosis.

***e*TABLE 7.3.1** DIABETES-INDUCED ALTERATIONS IN ENDOTHELIAL CELL FUNCTIONAL PROPERTIES

Endothelial function	Effectors	Diabetes-induced perturbations	Atherosclerosis/events promoting effects
Selective permeability barrier	Continuous endothelium with tight junctions in the lateral borders	Increased permeability; delayed regeneration (118,119,121,122)	Allow low-density lipoprotein or bloodborne mitogens to reach the subendothelial space
Provides a nonthrombogenic surface	EDRF, PGI_2 tissue-type plasminogen activator, heparan sulfate, thrombomodulin	Reduced antithrombotic and fibrinolytic phenotype (decreased EDRF, decreased PGI_2, increased plasminogen activator inhibitor-1, increased tissue factor) (409)	Promote thrombosis and inhibit fibrinolysis
Provides a nonadherent surface for circulating leukocytes	EDRF	Induction of adhesion molecules (e.g., vascular cell adhesion molecule-1, E-selectin) (122,123,124 and 125)	Recruit macrophages into the vascular wall
Regulation of vascular tone	EDRF, PGI_2, endothelin-1	Reduced vasodilator function (decreased EDRF, decreased PGI_2, increased endothelin-1) (128,131); increased advanced glycosylation end products quench nitric oxide (406)	Failure of vasodilation
Secrete growth inhibitors	EDRF, heparan sulfate	Inactivation of EDRF (406); reduced EDRF production (138)	Reduced antiproliferative activity of EDRF on vascular smooth muscle cells

EDRF, endothelium-derived relaxing factor; PGI_2, prostacyclin.

Endothelial dysfunction in diabetes entails profound perturbations in several critical functions of the endothelium (eTable 7.3.1, Fig. 7.5) that contribute to the initiation and progression of the atherosclerotic process, as well as to the occurrence of clinical events.

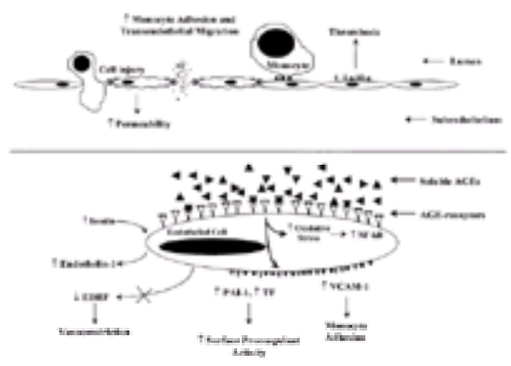


FIGURE 7.5 Generation of a dysfunctional endothelium in diabetes. See text for details. AGE, advanced glycosylation end product; EDRF, endothelium-derived relaxing factor; PAI-1, plasminogen activator inhibitor-1; TF, tissue factor; VCAM-1, vascular cell adhesion molecule-1.

Endothelial Permeability

The endothelial lining of the large arteries is of the continuous type characterized by tight junctions in the lateral borders, which restrict the movement of macromolecules from reaching the subendothelial space. Human vascular endothelial cells cultured in glucose concentrations comparable with those of uncontrolled diabetes exhibit delay in reaching confluence and in the rate of replication (118). Endothelial cell regeneration following deendothelialization (e.g., after balloon angioplasty) is slower (119). Endothelial cells in diabetic animals also exhibit morphologic abnormalities that include the presence of craters resulting from weakened intercellular junctions (120). Furthermore, AGEs, with their specific receptor, diminish endothelial barrier function (121,122). These abnormalities may explain the increased vascular permeability and transendothelial macromolecular transport (118).

Leukocyte Adhesion to the Vascular Endothelium

Among the earliest events in atherogenesis is the binding of mononuclear leukocytes to the endothelium with subsequent entry into the vessel wall. This is mediated through the expression of inducible adhesion molecules on the endothelial cell surface. Hyperglycemia stimulates the expression of vascular cell adhesion molecule-1 and E selectin (123). In addition, AGE interaction with the AGE receptor (see Advanced Glycosylation End Products) results in the induction of oxidative stress and, consequently, of the transcription factor NF-kB (124,125) and vascular cell adhesion molecule-1 (122). Thus, early events in the atherosclerosis process in diabetes may be mediated through enhanced adhesive interactions of monocytes with the endothelial surface. Indeed, monocyte binding to human aortic endothelial cells is increased by chronic incubation in high glucose (126). In addition, diabetic normolipidemic rabbits exhibit progressive adherence of mononuclear leukocytes to aortic endothelium and recruitment to the subendothelial space (127).

Impaired Endothelium-Dependent Vasodilation

Impairment of endothelium-dependent vasodilation in human coronary arteries has been demonstrated both in atherosclerotic segments of coronary arteries and in patients with risk factors for atherosclerosis and angiographically normal coronary arteries.

Impaired endothelium-dependent relaxation, which is mediated through the release of endothelium-derived relaxing factor (EDRF), is a consistent finding in animal models and in human diabetes (128,129) and occurs in a variety of vascular beds, including the coronary arteries (129). Impaired endothelium-dependent relaxation has been demonstrated in both type 1 and type 2 diabetes in the absence of clinical complications (129), while endothelium-independent vasodilation is preserved (128,129). Furthermore, impaired endothelium-dependent relaxation can be demonstrated in the insulin-resistant subject with normal glucose tolerance.

An attenuated effect of EDRF can render blood vessels vulnerable to spasm. However, the loss of EDRF has a much more profound effect on the arterial wall. EDRF is protective against the development of vascular disease because it inhibits platelet aggregation and adhesion, circulating monocyte adhesion to endothelial cells, and vascular smooth muscle proliferation (*e*Table 7.3.1).

Hyperglycemia Induces Endothelial Dysfunction

Hyperglycemia is recognized as the primary mediator of diabetic endothelial dysfunction. Impaired endothelium-dependent relaxation can be induced by short exposure (several hours) to high glucose concentrations, implying a hyperglycemia-dependent metabolic defect rather than irreversible damage to endothelial cells (130).

Similar to the mechanism of endothelial dysfunction observed in hypercholesterolemia, hyperglycemia-induced endothelial dysfunction is thought to result primarily from increased generation of oxygen free radicals that inactivate EDRF (131). Experimental and clinical data suggest that scavengers of oxygen radicals (132) and antioxidants such as vitamin E and vitamin C (131) improve endothelium-dependent relaxation in diabetic arteries. Angiotensin-converting enzyme (ACE) inhibition has also been reported to improve endothelium-dependent vasodilation in diabetic patients (133), probably through the reduction of oxidative stress.

Insulin-Resistant Subjects Exhibit Impaired Endothelium-Dependent Vasodilation

Insulin is a physiologic vasodilator of skeletal muscle vasculature in humans, and its vasodilatory effect is blunted in insulin-resistant subjects. The vasodilating effect of insulin is EDRF-mediated (134,135), and several studies have shown that in insulin-resistant *normoglycemic* subjects, vasodilatory responses to the endothelium-dependent vasodilator methacholine are also impaired (136,137) and the ability of insulin to enhance endothelium-dependent vasodilation is reduced (136). Thus, insulin resistance also contributes to endothelial dysfunction in diabetic patients.

The mechanism by which insulin resistance impairs endothelium-dependent vasodilation is not well understood. A positive correlation has been reported between endothelial nitric oxide production and insulin sensitivity in healthy subjects (138). Elevated circulating free fatty acids (139) and oxidized small, dense LDL (92) may mediate, in part, endothelial dysfunction in insulin-resistant subjects.

Endothelin

By maintaining a critical balance between relaxing and contracting factors, the endothelium regulates both vascular tone and growth. Endothelin-1, a potent cardiovascular peptide, mediates vasoconstriction, sodium retention, and mitogenesis. Key metabolic variables that are changed in diabetes, such as insulin and glucose, directly regulate the release of endothelin-1 from endothelial cells (140).

Insulin increases endothelin-1 gene expression in endothelial cells (141) and physiologic concentrations of insulin enhance the secretion of endothelin-1 from endothelial cells. Plasma endothelin concentrations are significantly increased in hyperinsulinemic patients with type 2 diabetes (142). Hyperglycemia has also been reported to enhance the production of endothelin-1 in endothelial cells (143) through a protein kinase C (PKC)–dependent mechanism.

DIABETES AS A PROTHROMBOTIC STATE

The coagulation and fibrinolytic systems are especially important in atherosclerosis because of the substantial contribution that mural thrombosis may make to the later stages of plaque progression, and because thrombotic occlusion plays a vital role in the development of clinical events. In the vast majority of cases, the fundamental mechanism in the development of potentially life-threatening events such as unstable angina or myocardial infarction is thrombosis arising at sites of plaque disruption. Not all disruptions of atherosclerotic plaques result in clinically apparent or symptomatic events. Thus, both local and systemic thrombogenic risk factors at the time of plaque disruption may determine the degree of thrombus formation; hence, the clinical outcome. Indeed, several hemostatic variables are powerful predictors of acute events in patients with established CAD (144,145 and 146).

Diabetes is characterized by a variety of individual alterations in the coagulation and fibrinolytic systems that combine to produce a prothrombotic state. These

alterations include increased platelet functional behavior, increased levels of several coagulation components, and impaired fibrinolysis (eTable 7.3.2).

***e*TABLE 7.3.2** COAGULATION AND FIBRINOLYTIC ABNORMALITIES OF PROGNOSTIC SIGNIFICANCE IN DIABETES

Factor	Prognostic significance	Diabetes effect
Platelet hyperactivity	Spontaneous platelet aggregation *in vitro* predicts coronary events and mortality in patients surviving myocardial infarction (146)	Platelet hyperaggregability in response to agonists (147) and increased fractions of circulating activated platelets (151)
von Willebrand factor	Increased concentrations of endothelium-derived von Willebrand factor reflect endothelial perturbation (23,144) and are associated with subsequent myocardial infarction (144)	Elevated von Willebrand factor levels, especially in the presence of vascular complications and endothelial dysfunction (23) or insulin resistance. Confers a high risk for cardiovascular events
Fibrinogen	High fibrinogen levels associated with increased risk for reinfarction and death (144,145)	Increased in diabetic patients (155)
Factor VII	High levels of factor VII coagulant activity are associated with increased risk for coronary events	Elevated and correlates with glycemic control and microalbuminuria
PAI-1	Reduced fibrinolytic capacity because of increased plasma PAI-1 levels predisposes to myocardial infarction in postinfarction patients or patients with angina (144,157)	Elevated PAI-1 levels occur mainly in the presence of insulin resistance (158,159,161)
Tissue factor	Expressed in coronary atherosclerotic plaques and may account for the magnitude of the thrombotic response to rupture of coronary atherosclerotic plaques	Advanced glycosylation end products and receptor for advanced glycosylation end products interaction induces cell surface expression of tissue factor (409)

PAI-1, plasminogen activator inhibitor-1.

Platelet Aggregation

Platelet hyperaggregability, including the presence of spontaneous platelet aggregation (144) and increased platelet aggregability induced by conventional stimuli (145), increases the risk for cardiovascular events.

Platelets from diabetic subjects exhibit enhanced adhesiveness and hyperaggregability in response to both strong [e.g., thrombin, thromboxane A_2 (TxA_2)] and weak (e.g., adenosine diphosphate, epinephrine, collagen) agonists (147,148). Shear-induced platelet adhesion and aggregation are increased in diabetic patients (149). Platelet hypersensitivity is more evident in diabetic patients with vascular complications. However, it is also observed in newly diagnosed diabetic patients, suggesting that altered platelet function may be a consequence of metabolic changes secondary to the diabetic state (147,150). Elevated fractions of $CD62^+/CD63^+$ (activated) platelets circulate in diabetic patients in the absence of clinically detectable vascular lesions (148,151). Enhanced activity of the arachidonic acid pathway with increased TxA_2 formation occurs in diabetic individuals (152). There is a significant correlation between TxA_2 production and fasting plasma glucose or HbA_{1c}, and TxA_2 production can be restored by strict glycemic control with continuous subcutaneous insulin infusion.

Alterations in Coagulation Factors

von Willebrand Factor

von Willebrand factor (vWF) is probably the most important among adhesive molecules mediating hemostatic interactions between platelets and vessel wall components. vWF is involved in the initial adhesion of platelets to the subendothelium of injured vessel wall and supports the progression of platelet-fibrin microthrombi to an occlusive thrombosis (153). High vWF levels are associated with subsequent myocardial infarction in patients with overt CAD (144,153).

vWF is synthesized and secreted by endothelial cells, and high circulating levels of vWF are considered markers of endothelial dysfunction. In diabetic patients plasma concentrations of vWF are elevated and are closely associated with the presence of vascular complications and endothelial dysfunction (23). Epidemiologic data have demonstrated a relation between plasma vWF and the insulin-resistance syndrome (154).

Fibrinogen

A large body of evidence indicates strong independent direct correlation between high fibrinogen plasma levels and an increased risk of CAD. Fibrinogen levels are often increased in diabetes, and this elevation is associated with poor glycemic control (155). Fibrinogen levels may decrease with intensive insulin therapy (156).

Altered Fibrinolysis in Diabetes

The intensity of endogenous fibrinolysis depends on a dynamic equilibrium involving plasminogen activators, primarily tissue-type plasminogen activator, and inhibitors. The principal physiologic inhibitor of tissue-type plasminogen activator is plasminogen activator inhibitor-1 (PAI-1). Attenuated fibrinolysis caused by an increase of PAI-1 activity has been associated with increased risk for myocardial infarction in patients with established CAD (144,157).

Reduced plasma fibrinolytic activity caused by increased PAI-1 levels is a characteristic feature of insulin resistance and hyperinsulinemia. Elevated concentrations of PAI-1 have been recognized consistently in the plasma of hyperinsulinemic type 2 diabetics (158) but occur also in normoglycemic insulin-resistant subjects (157,158). Increased plasma PAI-1 strongly correlates with parameters that define the insulin-resistance syndrome—in particular, body mass index and visceral accumulation of body fat, rather than with diabetes *per se* (158,159). Furthermore, interventions that lower insulin resistance, such as weight loss, are invariably accompanied by a reduction in plasma PAI-1 concentrations (160).

The mechanisms for the increased expression of PAI-1 in type 2 diabetes are complex. Insulin and especially proinsulin, a precursor of insulin, augment PAI-1 gene expression in hepatocytes resulting in an increased PAI-1 synthesis by the liver, which is the primary source of PAI-1 in plasma (161). Proinsulin levels are elevated in insulin-resistant subjects because of stimulation of pancreatic beta cells and in part because of the impaired processing of proinsulin to insulin that is typical of the condition. Exogenous insulin administration is accompanied by a decline in plasma PAI-1 levels, as stimulation of the pancreatic beta cells by hyperglycemia decreases. The production of PAI-1 by adipose tissue has been demonstrated and could be an important contributor to the elevated plasma PAI-1 levels observed in insulin-resistant patients (159). Hyperglycemia can also increase PAI-1 levels because it stimulates transcription of the PAI-1 gene through an effect on its promoter region (162).

Clinical Correlates of Hypercoagulability in Diabetic Patients

Although it remains possible that some of the hemostatic abnormalities in diabetes are partly markers of underlying vascular disease rather than the primary abnormalities, the clotting and fibrinolytic profile of diabetic patients bears a striking similarity to that of patients at high risk for future cardiovascular events (eTable 7.3.2).

The prothrombotic state in diabetes explains the observation that intracoronary thrombus formation is more frequently found by angioscopic examination in diabetic patients with unstable angina (13), and its clinical correlate, the higher risk of adverse outcome, namely death, nonfatal infarction (105), or recurrent unstable angina (163,164). In addition, high PAI-1 levels have been implicated in causing resistance to thrombolytic therapy (165).

HYPERGLYCEMIA AS AN ATHEROGENIC FACTOR

Hyperglycemia induces a large number of alterations in vascular tissue that potentially promote accelerated atherosclerosis. Currently, three major mechanisms have emerged that encompass most of the pathologic alterations observed in the vasculature of diabetic animals and humans: (a) nonenzymatic glycosylation of proteins and lipids; (b) oxidative stress; and (c) PKC activation. Importantly, these mechanisms are not independent. For example, hyperglycemia-induced oxidative stress promotes the formation of AGEs and PKC activation (166).

Role of Advanced Glycosylation End Products in Diabetic Atherosclerosis

One of the important mechanisms responsible for the accelerated atherosclerosis in diabetes is the nonenzymatic reaction between glucose and proteins or lipoproteins in arterial walls, collectively known as *Maillard's* or *browning reaction* (167). Glucose forms chemically reversible early glycosylation products with reactive amino groups of circulating or vessel wall proteins (Schiff's bases), which subsequently rearrange to form the more stable Amadori-type early glycosylation products.

Equilibrium levels of Schiff-base and Amadori products (the best known of which is hemoglobin A_{1c}) are reached in hours and weeks, respectively (168) (Fig. 7.6). Some of the early glycosylation products on long-lived proteins (e.g., vessel wall collagen) continue to undergo complex series of chemical rearrangements to form AGEs (168). Once formed, AGE-protein adducts are stable and virtually irreversible. Although AGEs comprise a large number of chemical structures, carboxymethyl-lysine-protein adducts are the predominant AGEs present *in vivo* (169).

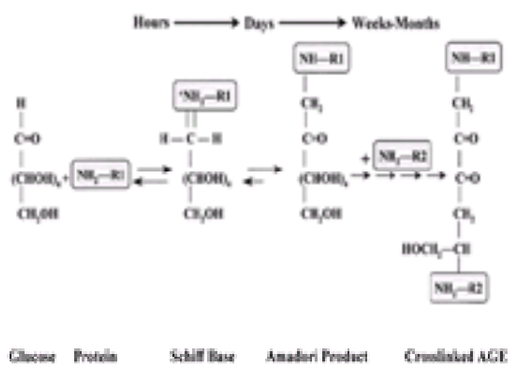


FIGURE 7.6 The formation of advanced glycosylation end product (AGE).

AGEs accumulate continuously on long-lived vessel wall proteins with aging and at an accelerated rate in diabetes (168). The degree of nonenzymatic glycation is determined mainly by the glucose concentration and time of exposure (168). However, another critical factor to the formation of AGEs is the tissue microenvironment redox potential. Thus, AGEs formation increases substantially in situations in which the local redox potential has been shifted to favor oxidant stress (166,170,171,172,173 and 174).

AGEs can accelerate the atherosclerotic process by diverse mechanisms that can be classified as non–receptor dependent (Table 7.4) and receptor mediated (Table 7.5).

Extracellular matrix
Collagen cross-linking (176)
Enhanced synthesis of extracellular matrix components (168)
Trapping of LDL in the subendothelium (405)
Glycosylated subendothelial matrix quenches nitric oxide (406)
Functional alterations of regulatory proteins
Basic fibroblast growth factor glycosylation reduces its heparin binding capacity and its mitogenic activity on endothelial cells (407)
Inactivation of the complement regulatory protein CD59 (175)
Lipoprotein modifications
Glycosylated LDL (99,100)
Reduced LDL recognition by cellular LDL receptors (98)
Increased susceptibility of LDL to oxidative modification (99)

LDL, low-density lipoprotein.

TABLE 7.4 ATHEROSCLEROSIS PROMOTING EFFECTS OF ADVANCED GLYCOSYLATION END PRODUCTS: NON–RECEPTOR-MEDIATED MECHANISMS

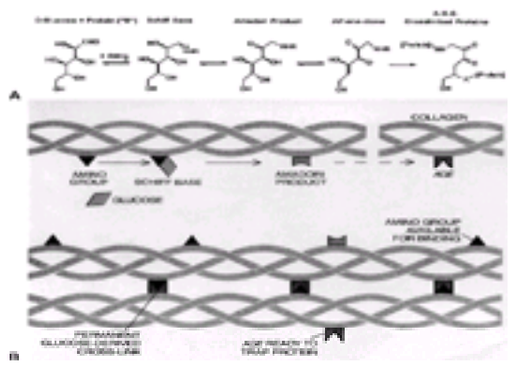
Promoting inflammation
Secretion of cytokines such as tumor necrosis factor-α, interleukin-1 (176)
Chemotactic stimulus for monocyte-macrophages (178,408)
Induction of cellular proliferation
Stimulation of platelet-derived growth factor (408) and insulin-like growth factor I secretion from monocytes and possibly smooth muscle cells
Endothelial dysfunction
Increased permeability of endothelial cell monolayers (121,409)
Increased procoagulant activity (409)
Increased expression of adhesion molecules (122)
Increased intracellular oxidative stress (121,124)

TABLE 7.5 ATHEROSCLEROSIS PROMOTING EFFECTS OF ADVANCED GLYCOSYLATION END PRODUCTS: RECEPTOR-MEDIATED MECHANISMS

Non–Receptor-Mediated Mechanisms

Glycosylation-modified proteins and lipoproteins can interfere with their normal function (Table 7.4). Examples are the proatherogenic effect LDL glycosylation described previously (see Low-Density Lipoprotein Metabolism in Diabetes) and glycation of the complement regulatory protein. Deposition of the membrane attack complex of complement (MAC) in blood vessels stimulates proliferation of fibroblasts and smooth muscle cells, in part by releasing growth factors such as fibroblast growth factor and platelet-derived growth factor from MAC-targeted endothelium. MAC deposition is normally restricted because cells express the regulatory membrane protein CD59, which limits complement activation and MAC formation. Glycation of the complement regulatory protein CD59 results in its inactivation (175) and may increase the sensitivity of the diabetic endothelium to MAC-induced release of growth factors and cytokines.

Another important consequence of AGEs formation is the ability to cross-link adjacent proteins. For example, collagen can become cross-linked because AGEs form covalent heat-stable intermolecular bonds (176) (*e*Fig. 7.6.1). The amount of cross-linked collagen peptides formed increases as a function of both time and glucose concentration (176). In contrast to normal cross-links within normal collagen, which occur only at two discrete sites at the N-terminal and C-terminal ends of the molecule, AGEs form cross-links throughout the collagen molecule (168). Collagen cross-linking plays an important role in changing the mechanical properties of tissues, leading to the increased vascular rigidity and the reduced left ventricular compliance in diabetic patients (see Diabetic Cardiomyopathy).



***e*FIGURE 7.6.1** Schematic description of the formation of collagen cross-links **(B)**. Glucose attaches to an amino group (NH_2) of a protein (*top*), such as collagen, to form Schiff's base, which subsequently transforms itself into an Amadori product [see **(A)** for chemical structure]. The latter can pass through several incompletely understood steps (*broken arrows*) to become an advanced glycosylation end product (AGE). AGEs can react with free amino groups on adjacent protein to form

cross-links (*bottom*). Cross-linking can lead to decreased compliance of large vessels and of the myocardium (see text). (From Cerami A, Vlassara H, Brownlee M. Glucose and aging. *Sci Am* 1987;256:90–96, with permission.)

Glycosylation of matrix components such as collagen VI, laminin, and vitronectin decreased binding of anionic heparan sulfate, leading to greater turnover of heparan sulfate (168). The absence of heparan sulfate is thought to stimulate a compensatory overproduction of other matrix components through altered partitioning of growth regulatory factors between matrix-bound proteoglycans and cells (168). AGEs on matrix also alter the normal interactions of transmembrane integrin receptors with three specific matrix ligands. For example, modification of the cell-binding domains of type IV collagen causes decreased endothelial cell adhesion (168).

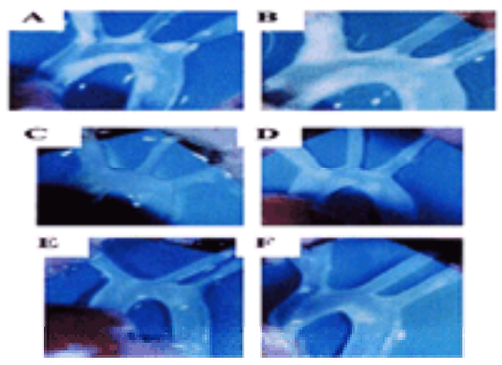
Receptor-Mediated Mechanisms

The cellular interactions of AGEs are mediated through a specific receptor for AGE determinants on cell surfaces (173). The presence of the AGE receptor (RAGE), a member of the immunoglobulin superfamily of receptors, has been demonstrated in all cells relevant to the atherosclerotic process including monocyte-derived macrophages, endothelial cells, and smooth muscle cells (173) (Table 7.5). In mature animals, RAGE expression on these cells is low (174). However, under certain pathologic circumstances, sustained upregulation of RAGE occurs. In pathologic lesions, abundance of RAGE-expressing cells is usually associated with sites of accumulated RAGE ligands. In diabetic vasculature, cells expressing high levels of RAGE are often proximal to areas in which AGEs are abundant (174).

The consequence of AGEs interaction with RAGE on endothelial cells has been previously discussed. Binding of soluble AGEs to RAGE induces monocyte chemotaxis (177), followed by mononuclear infiltration through an intact endothelial monolayer (178). Pathologic studies of human atherosclerotic plaques showed infiltration of RAGE-expressing cells in the expanded intima. Monocyte-macrophage interaction with AGEs results also in the production of mediators such as interleukin-1, tumor necrosis factor-a, platelet-derived growth factor, and insulin-like growth factor I (179,180).

In smooth muscle cells, binding of AGE-modified proteins to RAGE is associated with increased cellular proliferation. Although the precise mechanism of this response is unknown, the growth-promoting effects mediated by the RAGE are likely to be cytokine or growth-factor mediated. Thus, under conditions of enhanced tissue AGE deposition, receptor-mediated interaction of AGE proteins with vascular wall cells facilitates the migration of inflammatory cells into the lesion with the subsequent release of growth-promoting cytokines.

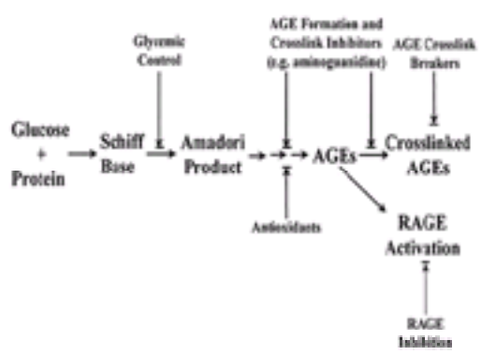
The potential role of RAGE in the atherogenic process in diabetes has been demonstrated by Park and associates (181). In the model of atherosclerosis-prone mice caused by homozygous deletion of apoE gene, the induction of diabetes using streptozotocin resulted in atherosclerosis of increased severity compared with euglycemic apoE controls. The development of vascular disease was more rapid with the formation of more complex lesions (fibrous caps, extensive monocyte infiltration, and so forth) and atherosclerosis extending distally in the aorta and major arteries (eFig. 7.6.2). Increased expression of RAGE and the presence of AGEs in the vessel wall, especially at sites of vascular lesions, were also evident. Blockade of AGE-RAGE interaction using a truncated soluble extracellular domain of RAGE resulted in a striking suppression of lesions in diabetic mice, with lesions largely arrested at the fatty streak stage and a large reduction in complex lesions (181).



***e*FIGURE 7.6.2** Effect of blockade of advanced glycosylation end product and advanced glycosylation end product receptor (RAGE) interaction using a truncated soluble extracellular domain of RAGE (sRAGE) on the development of atherosclerotic lesions in diabetic apolipoprotein E (apoE)-null mice. Diabetic mice without treatment **(A,B)**; diabetic mice treated with sRAGE at 20 µg per day **(C)** or 40 µg per day **(D)**; control euglycemic apoE-null mice without treatment **(E)** or sRAGE at 20 µg per day **(F)**. Also, note that diabetic apoE-null mice **(A,B)** develop atherosclerosis of increased severity compared with euglycemic controls **(E,F)**. (Modified from Park L, Raman KG, Lee KJ, et al. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. *Nat Med* 1998;4:1025–1031, with permission.)

Therapeutic Options

Normalization of blood glucose may decrease AGE formation and tissue accumulation. Aminoguanidine, an analog of the side chain of arginine and a small nucleophilic compound, is a potent inhibitor of AGEs formation and protein-to-protein and protein-to-lipid cross-linking (176,182). The terminal amino group of the compound reacts with glucose-derived reactive intermediates at the post-Amadori stage (Fig. 7.6 and eFig. 7.6.3). Aminoguanidine and other compounds such as pyridoxamine (183) have proved effective in animal models and clinical studies as inhibitors of AGE formation and the development of diabetic complications.



***e*FIGURE 7.6.3** Treatment strategies for blocking the formation of advanced glycosylation end products (AGEs), AGE cross-links, and the interaction of AGEs with AGE receptor (RAGE).

When tissue damage has already occurred, aminoguanidine-like compounds are not effective. In this setting, the development of cross-link “breakers” such as N-phenacylthiazolium bromide, which can cleave diketone bridges (184), may be a valuable therapeutic tool (eFig. 7.6.3). In diabetic animals, AGE breakers have been shown to reverse large artery stiffness (185) and increase left ventricular compliance (186). These results provide the conceptual basis for the design of drugs to reverse tissue damage that has already occurred (see Role of Advanced Glycosylation End Products in Pathogenesis of Diabetic Cardiomyopathy).

Antioxidant therapy may retard the formation of glycoxidation products formed by the combined processes of glycation and oxidation (187), and mitigate the oxidative stress generated by the interaction between AGEs and the cell surface AGE receptor.

The interaction between AGEs and RAGE may underlie chronic smoldering inflammatory responses that accelerate diabetic vascular disease (174). Blockade of AGE-RAGE interaction has been accomplished by administration of soluble, extracellular domain of RAGE and has been shown to block vascular permeability and

suppress the development of accelerated diabetic atherosclerosis in murine models (121,181).

PROTEIN KINASE C

The metabolic consequences of hyperglycemia can be expressed in cells in which glucose transport is largely independent of insulin. The resulting intracellular hyperglycemia has been implicated in the pathogenesis of diabetic complications through the activation of the PKC system (188,189).

High ambient glucose concentrations activate PKC by increasing the formation of diacylglycerol (DAG), the major endogenous cellular cofactor for PKC activation, from glycolytic intermediates such as dihydroxy-acetone phosphate and glyceraldehyde-3-phosphate. The elevation of DAG and subsequent activation of PKC in the vasculature can be maintained chronically (190).

PKC is a family of at least 12 isoforms of serine and threonine kinases. Although several PKC isoforms are expressed in vascular tissue, in the rat model of diabetes there is a preferential activation of PKC b2 in the aorta, heart, and retina, and PKC b1 in the glomeruli (191,192).

The PKC system is ubiquitously distributed in cells and is involved in the transcription of several growth factors and in signal transduction in response to growth factors (143,191,193). In vascular smooth muscle cells, PKC activation has been shown to modulate growth rate, DNA synthesis, and growth factor receptor turnover (189,191).

PKC activation increases the expression of transforming growth factor-b (TGF-b), which is one of the most important growth factors, regulating extracellular matrix production by activating gene expression of proteoglycans and collagen and decreasing the synthesis of proteolytic enzymes that degrade matrix proteins. Increased expression of TGF-b is thought to lead to thickening of capillary basement membrane, one of the early structural abnormalities observed in almost all tissues in diabetes. PKC b selective inhibitor (LY333531) attenuates glomerular expression of TGF-b and extracellular matrix proteins such as fibronectin and type IV collagen (192,193).

Hyperglycemia-induced PKC activation also results in increased platelet-derived growth factor-b receptor expression on smooth muscle cells and other vascular wall cells (e.g., endothelial cells, monocyte-macrophages) (194).

OXIDATIVE STRESS

Oxidative stress is widely invoked as a pathogenic mechanism for atherosclerosis. Among the sequelae of hyperglycemia, oxidative stress has been suggested as a potential mechanism for accelerated atherosclerosis (166,187,195). Importantly, there appears to be a strong pathogenic link between hyperglycemia-induced oxidant stress and other hyperglycemia-dependent mechanisms of vascular damage, namely AGEs formation and PKC activation (Fig. 7.7).

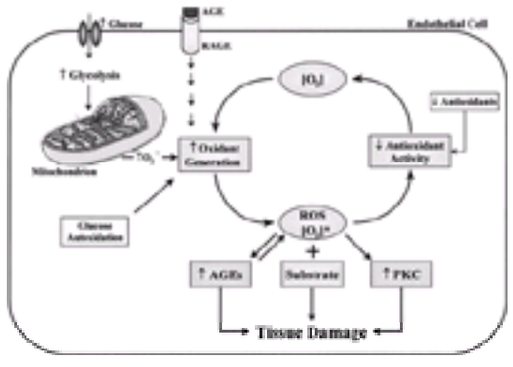


FIGURE 7.7 Relationship between rates of oxidant generation, antioxidant activity, oxidative stress, and oxidative damage in diabetes. *$[O_2]$** represents various forms of reactive oxygen species (ROS). The overall rate of formation of oxidative products leading to oxidative tissue damage is dependent on ambient levels of both $[O_2]$* and substrate. Increased generation of $[O_2]$* depends on several sources, including glucose autoxidation, increased mitochondrial superoxide production, and as a result of the receptor for advanced glycosylation end products activation. $[O_2]$* deactivation is reduced because antioxidant defenses are compromised in diabetes. Note that oxidative stress also promotes other hyperglycemia-induced mechanisms of tissue damage. Oxidative stress activates protein kinase C (PKC) and accelerates the formation of advanced glycosylation end products (AGEs).

Hyperglycemia can increase oxidative stress through several pathways. A major mechanism appears to be the hyperglycemia-induced intracellular reactive oxygen species, produced by the proton electromechanical gradient generated by the mitochondrial electron transport chain and resulting in increased production of superoxide (166).

Two other mechanisms have been proposed that may explain how hyperglycemia causes increased reactive oxygen species formation. One mechanism involves the transition metal-catalyzed autoxidation of free glucose, as described in cell-free systems. Through this mechanism, glucose itself initiates an autoxidative reaction and free radical production yielding superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) (196). The other mechanism involves the transition metal-catalyzed autoxidation of protein-bound Amadori products, which yields superoxide and hydroxyl radicals and highly reactive dicarbonyl compounds (195) (see Glycoxidation).

There is also evidence that hyperglycemia may compromise natural antioxidant defenses. Under normal circumstances, free radicals are rapidly eliminated by antioxidants such as reduced glutathione, vitamin C, and vitamin E. Reduced glutathione content (197), as well as reduced vitamin E (198), have been reported in diabetic patients. Plasma and tissue levels of vitamin C are 40% to 50% lower in diabetic patients compared with nondiabetic subjects (199).

Glycoxidation

Some of the individual advanced glycosylation products such as Ne-(carboxymethyl)lysine and pentosidine are formed in reactions of protein with glucose only under oxidative conditions (172,200,201). Thus, some AGEs are produced by combined processes of glycation and oxidation and have been termed *glycoxidation products* (187). Each AGE structure has its own formation mechanism and thus its own dependence on oxidative stress. However, because glycoxidation products on proteins are irreversible, it has been suggested that they may be an integrative biomarker for the accumulated oxidative stress to which the respective tissue has been exposed (171,195).

As previously discussed, the interaction between AGE epitopes and the cell surface AGE receptor upregulate oxidative stress response genes (124) and release oxygen radicals (202). Thus, hyperglycemia simultaneously enhances both AGEs formation and oxidative stress, and the mutual facilitatory interactions between glycation and oxidation chemistry can contribute synergistically to the formation of AGEs, oxidative stress, and diabetic complications (Fig. 7.7). Indeed, there are strong correlations between levels of glycoxidation products in skin collagen and the severity of diabetic retinal, renal, and vascular disease (203).

Oxidative Stress and Protein Kinase C Activation

Oxidative stress may also be involved in the activation of DAG-PKC in vascular tissue (166). Oxidants produced in the setting of hyperglycemia can activate PKC (204). Furthermore, several studies have shown that antioxidants such as vitamin E can inhibit PKC activation probably by decreasing DAG levels (166,205).

EFFECT OF OTHER CARDIOVASCULAR RISK FACTORS ON CORONARY ARTERY DISEASE RISK IN DIABETIC PATIENTS

Prospective studies indicate that all of the major cardiovascular risk factors continue to act as independent contributors to CAD in diabetic patients (2,206,207). Standard cardiovascular risk factors account for at least two-thirds of the excess risk from cardiovascular disease in diabetic subjects. In general, for any given degree of abnormality, individuals with diabetes have two to four times greater risk of developing CAD than individuals without diabetes (2).

Hypercholesterolemia

The U.K. Prospective Diabetes Study (UKPDS), including 2,693 patients with newly diagnosed type 2 diabetes, evaluated the significance of all major cardiovascular risk factors for CAD by stepwise multivariate Cox analysis (64). The most important risk factor for CAD—fatal and nonfatal myocardial infarction, angina pectoris—was high LDL cholesterol, followed by low HDL cholesterol, and HbA_{1c}. These results emphasize the contribution of concomitant classic risk factors for CAD in diabetic patients.

Hypertension

Hypertension occurs approximately twice as frequently in patients with diabetes as in the general population (208,209). Isolated systolic hypertension is considerably more common in diabetics. Type 1 diabetes mellitus is associated with hypertension only when albuminuria and early nephropathy develop, but type 2 diabetes mellitus may be associated with hypertension at or even preceding diagnosis (208,209).

The combined presence of hypertension and diabetes considerably accelerates the development of both macrovascular and microvascular diabetic complications. However, the most significant manifestation of this combination of diseases is that they confer a greater risk of ischemic heart disease, stroke, and peripheral vascular disease in affected individuals (208,209,210 and 211). The high cardiovascular risk associated with the coexistence of hypertension and diabetes led the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to include hypertensive patients with diabetes in the same risk group as hypertensive patients who have clinically manifest cardiovascular disease (212). These patients should be considered for prompt pharmacologic therapy, even if they have high-normal blood pressure (212).

Pharmacologic Therapy of Hypertension in Diabetic Patients

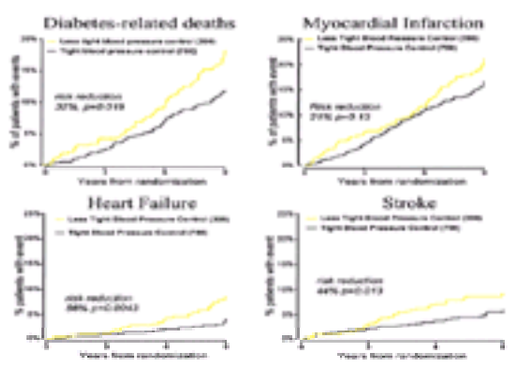
Current evidence suggests that for the prevention of cardiovascular events, ACE inhibitors (213,214), low-dose diuretics (215), or beta-adrenergic blockers (216) are the preferred first-line agents for hypertensive patients with diabetes, whereas a controversy exists with regard to the efficacy of calcium antagonists in preventing cardiovascular complications (217). In the Appropriate Blood Pressure Control in Diabetes trial, patients in the nisoldipine group had a fivefold higher risk of fatal and nonfatal acute myocardial infarction than did the enalapril group (213). The Swedish Trial in Old Patients with Hypertension 2 reported that ACE inhibitors were superior to calcium channel blockers in preventing myocardial infarction and congestive heart failure (CHF) in the subgroup of elderly patients with diabetes (218).

In the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial patients receiving fosinopril had half the risk of the combined outcome of acute myocardial infarction, stroke, or hospitalized angina than those receiving amlodipine (214). However, the combined therapy resulted in a lower incidence of cardiovascular events than either treatment alone and could be interpreted as evidence that combination therapy is a safe strategy (219). These results are important because hypertension control is not achieved by monotherapy in many diabetic patients, as demonstrated in Appropriate Blood Pressure Control in Diabetes trial (213) and UKPDS (216).

The Systolic Hypertension in Europe study compared outcomes of treatments with nitrendipine versus placebo in patients with isolated systolic hypertension. Endpoint reduction achieved by active treatment was significantly larger in the diabetic subgroup (–69% vs. –26% cardiovascular events), indicating a remarkable benefit from first-line treatment with a calcium antagonist (220). Similarly, the results of the Hypertension Optimal Treatment trial showed a reduction of myocardial infarction event rates in diabetic patients (n = 1,501, representing the largest calcium antagonist trial in diabetic patients) using the long-acting dihydropyridine calcium antagonist felodipine (221).

In the UKPDS, no difference was found between atenolol and captopril (216). In the Captopril Prevention Project study, no difference in outcomes was noted between subjects receiving a combination of diuretic and beta-blockers and those receiving captopril. By contrast, in the subgroup of patients with diabetes, captopril was associated with an approximately 40% decrease in the primary end point, fatal and nonfatal myocardial infarction, stroke, and cardiovascular deaths (222).

The evidence for aggressive antihypertensive treatment in patients with diabetes, hypertension, and nephropathy is now overwhelming (223,224). ACE inhibitors are particularly useful in this population, with clear evidence that these agents reduced the progression of kidney dysfunction and the number of patients who will develop end-stage renal failure (225,226 and 227). Furthermore, the UKPDS indicated that among patients with hypertension and type 2 diabetes, aggressive lowering of blood pressure (mean, 144/82 mm Hg vs. 154/87 mm Hg), either with ACE inhibitors or a beta-blocker, provides greater protection against death from cardiovascular causes and major nonfatal events than did less aggressive therapy (228) (*e*Fig. 7.7.1). A similar benefit was observed in the Hypertension Optimal Treatment study among hypertensive patients with diabetes, who were randomly assigned to intensive therapy with calcium channel blockers (221). In summary, ACE inhibitors appear to be the preferred antihypertensive therapy in diabetic patients, but other antihypertensive agents are also effective in reducing cardiovascular mortality and morbidity. In addition, aggressive blood pressure reduction may be more important than the specific agent being used.



***e*FIGURE 7.7.1** Effect of blood pressure control on morbidity and mortality of type 2 diabetic patients in the United Kingdom Prospective Diabetes Study. The mean blood pressure in the tight control group was 144/82 versus 154/87 in the less tight control group. (Modified from Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703–713, with permission.)

The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has incorporated these principles for the treatment of hypertension in the presence of diabetes and has included a more aggressive program of blood pressure reduction, aiming for a target of less than 130/85 mm Hg in both type 1 and type 2 diabetic patients (212,229). In addition, the guidelines included a target of 125/75 mm Hg in patients with greater than 1 g per day proteinuria (212,223,224).

Smoking

Cigarette smoking has a strong influence on the development of CAD in diabetic individuals (2,230,231 and 232). Furthermore, smoking increases the risk of microvascular complications (232). Several prospective cohort studies suggest that smoking is associated with the development of impaired glucose tolerance (233) and diabetes (232,234). This may be related to the ability of chronic cigarette use to induce insulin resistance (235), which also contributes to the excess CAD risk. In addition, smoking is known to stimulate release of counterregulatory hormones and consequently temporary elevation in plasma glucose levels (236).

Interestingly, both aqueous extracts of tobacco and cigarette smoke contain highly reactive glycation products (called *glycotoxins*) that can rapidly induce AGE formation on proteins *in vivo* and are readily absorbed through the lungs from cigarette smoke. In contrast to glucose, which induces AGE formation over a period of weeks, glycotoxins can induce AGE formation in hours (237). Thus, smoking can accelerate AGE-induced macrovascular and microvascular damage.

Hyperhomocysteinemia

Cross-sectional and prospective studies have shown that hyperhomocysteinemia appears to be a greater risk factor for CAD in diabetic patients compared with nondiabetic subjects (238,239). In a prospective population-based study with a 5-year follow-up, hyperhomocysteinemia was a stronger (approximately twofold) risk factor for death in diabetic than in nondiabetic subjects. For each 5 µmol per L (1 standard deviation) increment in serum homocysteine, the risk of 5-year mortality rose

by 17% in the nondiabetic and 60% in the diabetic subjects (238). High homocysteine concentrations may enhance prothrombotic state, oxidative stress, and endothelial dysfunction in diabetic subjects (240).

Genetic Factors

Complications of diabetes involve multiple organ systems, and their clinical presentation occurs after a period of time following onset (diagnosis) of diabetes. This delay may be short (a few years) or long (a few decades) in duration. Not all diabetic subjects develop a complication, although a portion have several complications. The distribution of complications in diabetic subjects—both in type of complications and in timing of their appearance—suggests that susceptibility to complications is partially controlled by complex unknown genetic factors.

For example, a subgroup of type 1 diabetes subjects have a genetically determined predisposition to renal disease and hypertension, and this predisposition is linked to a high risk of early CAD (see Coronary Artery Disease in Type 1 Diabetes). Studies have shown that an association between ACE I/D polymorphism, potentially affecting the level of angiotensins and kinins in the kidney, can affect the development of renal disease in type 1 diabetic patients (27). The same polymorphism has been linked to myocardial infarction in nondiabetic subjects, as well as in type 1 diabetic (241,242) and type 2 diabetic (243) patients.

Another example is the polymorphism in the paraoxonase gene. During a search for susceptibility genes for vascular disease in diabetes, a polymorphism in the paraoxonase gene was identified as a genetic risk factor for ischemic heart disease in type 2 diabetes (244). Paraoxonase, a serum enzyme entirely bound to HDL, retards the oxidation of LDL by preventing the generation of lipid peroxides (245). Decreased serum paraoxonase activity, caused by polymorphism in the promoter region of the paraoxonase gene, increases the risk of LDL oxidation, and consequently the risk of CAD. The reduced antioxidant capacity may be of particular relevance in diabetic patients because of the inherent propensity for increased oxidative stress (see Oxidative Stress).

DIABETIC CARDIOMYOPATHY

The risk for CHF and idiopathic cardiomyopathy is strongly increased in diabetes (246,247), particularly in women (246,248). In the Framingham Heart Study, although both young women and young men with diabetes had a greater incidence of heart failure than those without, the effect was greater in women (an eightfold versus a fourfold increase) (248).

Although data on the effect of diabetes on the prognosis of patients with CHF are limited, several studies suggest that diabetes is an independent predictor of poor prognosis in this setting. In the Studies of Left Ventricular Dysfunction study, diabetes was an independent predictor of morbidity and mortality in patients with symptomatic heart failure, asymptomatic patients with an ejection fraction less than or equal to 35%, and in the registry population (247). In the Framingham Heart Study, survival after the diagnosis of CHF was significantly worse only in diabetic women, with a 70% increase in mortality (249). Furthermore, one reason for the poor prognosis in patients with both diabetes and ischemic heart disease seems to be an enhanced myocardial dysfunction leading to accelerated heart failure (207).

The cardiomyopathic process associated with diabetes mellitus manifests initially as diminished left ventricular compliance in the presence of normal left ventricular systolic function (250,251 and 252). Diastolic abnormalities occur in 27% to 69% of asymptomatic diabetic patients (250,251). A lower ejection fraction in response to dynamic exercise in the presence of a normal resting ejection fraction has been demonstrated in several studies (252,253 and 254), suggesting that contractile reserve is decreased in many asymptomatic patients with diabetes. Systolic dysfunction may appear, usually in patients with long-standing disease who suffer from advanced microvascular complications (253,255). However, even subclinical cardiomyopathy with reduced myocardial reserve may become clinically important in the presence of myocardial ischemia (256) or with coexistent uncontrolled hypertension.

Pathogenesis of Diabetic Cardiomyopathy

Role of Hypertension and Insulin Resistance

The coexistence of hypertension and diabetes exerts a particularly deleterious effect on the heart. The coexistence of hypertension has been considered a major factor in the expression of diastolic dysfunction in diabetic patients (257). In hypertensive subjects, diabetes is an important precursor of CHF, with a greater relative risk in women than in men (258). The mechanisms responsible for the increased risk for the development of CHF are not fully understood, but may be related in part to an exaggerated increase in left ventricular mass (259).

Conventional clinical measurements of blood pressure have been only weakly related to echocardiographic left ventricular mass. Several observations suggest that insulin resistance and compensatory hyperinsulinemia may promote an increase in left ventricular mass. The association of increased left ventricular mass and hyperinsulinemia has been described in several rare genetic disorders such as leprechaunism (260) and total lipodystrophy (261). It also has been demonstrated in infants of diabetic mothers and in infants with nesidioblastosis and hyperinsulinemia (262). Obesity, which is characterized by insulin resistance and hyperinsulinemia (42,43), is strongly correlated with increased left ventricular mass independent of age and blood pressure (263). Furthermore, left ventricular mass in normotensive obese subjects is related more to the severity of insulin resistance than to the obesity itself as expressed by the body mass index (264). The reduction in left ventricular mass with weight loss (265,266) may be secondary to the improvement in insulin sensitivity.

In hypertensive patients with normal glucose tolerance, who commonly exhibit insulin resistance and hyperinsulinemia (45,48), left ventricular mass has been shown to correlate with the degree of insulin resistance (267,268). A similar association is also observed in nonhypertensive insulin-resistant subjects (267,269).

Hypertension, insulin resistance, hyperinsulinemia, and type 2 diabetes are commonly associated (45,48,270) and result in a high risk for cardiovascular complications (53,54,55 and 56,58,271). Left ventricular mass is a strong predictor of cardiac and cerebrovascular morbidity independent of blood pressure or other risk factors (272) and is a powerful risk factor for the development of symptomatic CHF (248). Thus, the association between insulin resistance and left ventricular hypertrophy may contribute to the increase risk of symptomatic CAD in insulin-resistant subjects.

Metabolic Abnormalities

Several investigators emphasize metabolic abnormalities including abnormal intracellular Ca^{2+} handling, defects in myocardial glucose use, and activation of PKC (273) as possible explanations for the pathogenesis of diabetic cardiomyopathy.

For example, hyperglycemia-induced activation of PKC-b isoforms (see) may contribute to the development of left ventricular dysfunction in diabetes. Transgenic mice overexpressing PKC-b isoform in the heart develop cardiac hypertrophy and accumulation of an excessive amount of extracellular matrix resulting in multifocal fibrosis (273) and decreased cardiomyocyte calcium responsiveness and contractility (274).

Role of Advanced Glycosylation End Products in Pathogenesis of Diabetic Cardiomyopathy

Part of the normal aging process of humans and other long-lived species is the gradual decrease in the elasticity of the cardiovascular system, which leads to increased arterial as well as to left ventricular stiffness and, consequently, diastolic dysfunction. Diabetic patients have increased arterial stiffness compared with nondiabetic individuals (275,276) and manifest diminished left ventricular compliance at a young age (250,251 and 252).

Several investigators have demonstrated that diabetes has several features of accelerated aging at the tissue level and at the level of collagen itself (277,278). Aging and diabetes mellitus are associated with cross-linking and nonenzymatic glycosylation of collagen. This led to the concept that glycosylation could explain the progressive cross-linking of collagen during normal aging and at an accelerated rate in diabetes, leading to changes in vascular tissue mechanical properties.

Thus, disturbances of vascular and cardiac mechanical properties in diabetes may be caused by a common mechanism. Among the structural alterations associated with AGEs formation is collagen-to-collagen cross-linking (168,176) (eFig. 7.6.1), which alters the structure and function of this protein, leading to tissue rigidity (176). Increased arterial stiffness in patients with diabetes strongly correlates with increased aorta and myocardial collagen advanced glycation (276).

Further evidence supporting the AGE hypothesis is the observation that agents that specifically inhibit AGE formation effectively prevent the pathologic stiffening process of diabetes and aging (279,280). For example, treatment of diabetic rats with aminoguanidine, an inhibitor of AGE formation, significantly increases carotid artery compliance, decreases aortic impedance (280), and prevents the decreased myocardial compliance (279).

To further substantiate this concept, studies have used the relatively newly developed AGE “breaker” compound (184). Treatment of rats with streptozotocin-induced

diabetes with the AGE breaker ALT-711 for 1 to 3 weeks reversed the diabetes-induced increase of large artery stiffness (185). Similarly, ALT-711 therapy resulted in a significant reduction in age-related left ventricular stiffness in dogs (186).

DIABETIC PATIENT WITH AN ACUTE ISCHEMIC EVENT

Acute ischemic events represent a major cause of death in the diabetic population (281). Diabetics who suffer myocardial infarction have a higher mortality than nondiabetic subjects both in the acute phase and on long-term follow-up (105).

Acute Myocardial Infarction

Numerous studies have shown that in-hospital mortality from myocardial infarction in diabetic patients is 1.5- to 2.0-fold higher than in nondiabetic patients (9,256,282,283). Diabetic women have a particularly poor prognosis, with an almost twofold increase in mortality compared with diabetic men (9,256,282,283).

Diabetes mellitus remains an independent predictor for a poor prognosis in the thrombolytic era. In the Thrombolysis and Angioplasty in Myocardial Infarction trials, the in-hospital mortality was nearly twice as high in patients with diabetes, with more CHF and twice the rate of clinically recognized reinfarction (9). In the GUSTO-I trial, mortality at 30 days was highest among diabetic patients treated with insulin (12.5%) compared with non–insulin-treated diabetic (9.7%) and nondiabetic (6.2%) patients (284). Similar results have been reported from the other large studies (285,286). Diabetes is also a risk factor for cardiogenic shock in the setting of acute ischemic syndromes (287). Despite the overall improvement in survival from an acute myocardial infarction with thrombolysis, the in-hospital mortality in diabetics remains 1.5 to 2.0 times higher than in nondiabetic subjects (9,284,286). Primary angioplasty appears to be an effective alternative to thrombolysis in diabetic patients (288,289).

The excess in-hospital mortality in diabetics correlates primarily with an increased incidence of CHF (105,256,282,283), although increased reinfarction, infarct extension, and recurrent ischemia also contribute (256,290,291).

CHF and cardiogenic shock are more common and more severe in diabetic subjects than would be predicted from the size of the index infarction (282,283,286). Indeed, studies using serial determinations of total creatine kinase activity, radionuclide ventriculography, or echocardiography have shown no evidence that diabetic patients sustain more extensive infarctions than their nondiabetic counterparts (105). However, a reduction in both left ventricular ejection fraction (256) and the regional ejection fraction of the noninfarcted myocardium occurs in diabetic patients following myocardial infarction compared with nondiabetic subjects. For example, early angiography in the Thrombolysis and Angioplasty in Myocardial Infarction trials has demonstrated worse noninfarct zone ventricular function in diabetics (9). These findings can be ascribed to several additional pathogenic processes that reduce the ability of the noninfarcted myocardium to compensate (Fig. 7.8). The observation that clinical manifestations of heart failure occur in diabetic patients despite a modest decrease in left ventricular ejection fraction led to the suggestion that preexisting diastolic dysfunction is a major culprit of the congestive symptoms (256). Subclinical diabetic cardiomyopathy, in which the salient finding is diastolic dysfunction (see Diabetic Cardiomyopathy) is likely to be an important factor in this setting.

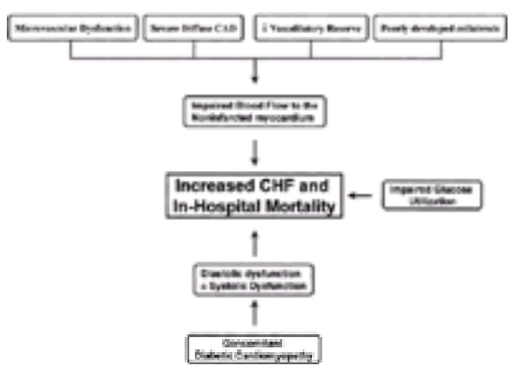


FIGURE 7.8 Factors promoting in-hospital and long-term mortality of diabetic patients following myocardial infarction. CAD, coronary artery disease; CHF, congestive heart failure.

The performance of the left ventricle following myocardial infarction is largely determined by the extent of coronary disease and the quality of collateral circulation. Thus, the diffuse nature of coronary atherosclerosis in diabetes may contribute to systolic dysfunction of the noninfarcted myocardium. Moreover, diabetic patients have a reduced ability to develop collateral blood vessels in the presence of CAD (292), a finding that may also explain the more frequent occurrence of postinfarction angina and infarct extension (105,256,291). Finally, an altered pattern of exogenous substrate use during ischemia and in the postreperfusion period may result in increased oxygen consumption by the myocardium and reduced contractility and may prevent myocardial preservation (see Abnormal Myocardial Substrate Metabolism).

Long-Term Outcome of Diabetic Patients after Myocardial Infarction

Diabetic patients surviving myocardial infarction suffer from higher late mortality than do their nondiabetic counterparts (256,291,293). Late mortality is mainly related to recurrent myocardial infarction and the development of new CHF (104,286).

Survival and recurrent cardiovascular events in diabetic patients after myocardial infarction are closely related to the following categories of risk: (a) extent of global pump dysfunction following the infarct; (b) multivessel CAD; (c) the diabetic hematologic milieu (see Diabetes as a Prothrombotic State); and (d) diabetic autonomic neuropathy, which may predispose to sudden death, especially in postinfarct patients (see Diabetic Autonomic Neuropathy and the Heart).

Medical Therapy in Diabetic Patients with Myocardial Infarction

Diabetic patients treated with fibrinolytic agents benefit by the same mortality reduction as nondiabetic patients (9,105,294). In an overview of fibrinolytic trials in patients with myocardial infarction, the proportion reduction in 35-day mortality was slightly, but not significantly, greater in diabetic patients than in nondiabetic patients (21.7% vs. 14.3%) (294). Importantly, no increase in serious bleeding complications or stroke has been observed in diabetics (9,285,294). Retinal bleeding is an extremely uncommon complication of thrombolytic therapy in diabetic patients. In the GUSTO-I study, 300 of 6,011 diabetic patients had proliferative retinopathy, but none developed intraocular hemorrhage (295). It is unlikely that thrombolytic therapy would increase vitreous hemorrhage, which is caused by vitreous detachment in patients with diabetic retinopathy. Thus, the concern that many clinicians have with regard to thrombolytic therapy in patients with diabetic retinopathy is not supported by the results of large clinical trials. It is probably unjustified to deny these patients the proven life-saving benefit of thrombolysis.

Beta-blockers are effective in reducing reinfarction and sudden death in diabetic patients, perhaps to a greater extent than in nondiabetic subjects (296,297 and 298). Early treatment of myocardial infarction with beta-blockers resulted in a 37% mortality reduction in diabetics compared with a 13% mortality reduction in all patients, whereas long-term mortality reduction was 48% and 33% in diabetics and all patients, respectively (296). Deterioration in glycemic control or blunted counterregulatory response to hypoglycemia are seldom a serious clinical problem, especially when cardioselective $beta_1$-blockers are used (296).

ACE inhibition is unequivocally associated with a substantial mortality reduction in patients surviving myocardial infarction with left ventricular dysfunction (ejection fraction less than 40%) (299). The GISSI-3 investigators compared the effect of early administration (within 24 hours of admission) of lisinopril in patients with and without diabetes presenting with myocardial infarction (300). Compared with placebo, lisinopril dramatically reduced both 6-week (30% vs. 5%) and 6-month (20% vs. 0%) mortality in diabetics versus nondiabetic subjects. These findings are corroborated by a retrospective analysis using data from the Trandolapril Cardiac Evaluation study, a randomized, double-blind, placebo-controlled trial evaluating trandolapril in patients after acute myocardial infarction with an ejection fraction less than or equal to 35%; it showed a 36% reduction of death from any cause and a 62% reduction in the risk of progression to severe heart failure (301). ACE inhibitors do not adversely affect glycemic control and lipid profile (3,208). In fact, ACE inhibitors may actually enhance insulin sensitivity in type 2 diabetic patients (302).

The Antiplatelet Trialists' Collaboration metaanalysis quantified the benefit of aspirin in diabetic patients who have had a previous cardiovascular event (303). The relative benefit on vascular events was 17% in the diabetic patients and 22% in those without diabetes. Although the number was lower for diabetic patients than for nondiabetic patients in terms of percentage benefit, the absolute number of events prevented was similar in the two groups (38 ± 12 per thousand compared with 36 ±

3 per thousand, respectively), probably because of the higher event rates in diabetic patients.

Unstable Angina in Diabetic Patients

Of all patients presenting with unstable angina, 20% to 25% have diabetes (163,304). Diabetes is an important risk factor for an adverse outcome (e.g., death, infarction, or readmission with unstable angina at 1 year; relative risk, 4.9) (164). Hospitalization for unstable angina or non–Q-wave myocardial infarction predicts a high 2-year morbidity and mortality in patients with diabetes. Diabetic patients with no previous cardiovascular disease have the same long-term morbidity and mortality as nondiabetic patients with established cardiovascular disease after hospitalization for unstable CAD (163).

These observations may be related to the higher proportion of ulcerated plaque (94% vs. 60%) and intracoronary thrombi (94% vs. 55%) observed by angioscopy in diabetic patients presenting with unstable angina (13). Coronary tissue obtained from culprit lesions of diabetic patients with unstable angina or myocardial infarction exhibit a larger content of lipid-rich atheroma, macrophage infiltration, and a higher incidence of coronary thrombus, which occupies a larger area (305).

ABNORMAL MYOCARDIAL SUBSTRATE METABOLISM

Tight coupling between cardiac work, coronary flow, and substrate oxidation is a central feature of cardiac physiology. Fatty acids are normally the predominant fuel for cardiac energy production, whereas glucose becomes the main substrate for oxidative metabolism of the heart when fatty acid levels are low and when the concentrations of glucose and insulin are high, as in the postprandial state, but also under ischemic conditions.

Transport of glucose across cell membranes is catalyzed by members of the facilitative glucose transporter family. The most important glucose transporters in cardiac myocytes are GLUT1 and GLUT4. GLUT1 is expressed ubiquitously and is mainly responsible for basal glucose transport. GLUT4, the insulin responsive glucose transporter, resides in intracellular membrane compartments, where it is prevented from contributing to cellular glucose transport. Insulin stimulates GLUT4 translocation from the intracellular pool to the plasma membrane, resulting in increased glucose uptake by myocardial cells. GLUT4 also translocates to the plasma membrane in response to increased metabolic demand such as increased workload, hypoxia, and myocardial ischemia (306,307 and 308). Mice with genetic ablation of the GLUT4 gene exhibit cardiac hypertrophy and heart failure, suggesting that GLUT4 is essential for normal cardiac function (309).

The ischemic myocardium relies largely on the anaerobic metabolism of glucose. The relative contribution of glucose to energy production in the ischemic heart is highly dependent on the severity of ischemia. In moderate ischemia glucose extraction increases and glucose metabolism is directed from oxidation to lactate production (306,307). Although ischemia results in a flow-dependent decrease in glucose delivery and a decrease in interstitial glucose levels, glucose uptake can still be accelerated, reflecting a greater capacity of glucose transport across the sarcolemmal membrane (306,307).

Under such ischemic conditions, myocardial glucose extraction is inversely related to coronary flow, until the degree of ischemia becomes so severe that glycolysis is inhibited by the accumulation of its products and glucose uptake progressively decreases. This “metabolic exhaustion” occurs before irreversible ischemic injury is observed and results from inhibition of glycolytic activity caused by accumulation of protons, Na^+, and Ca^{2+} and the inability to extrude the products of glycolysis (307). The decrease of glucose uptake during prolonged severe ischemia can be attenuated by an increase in extracellular glucose concentrations or the addition of insulin (310). Furthermore, the effect of physiologic hyperinsulinemia and ischemia on GLUT4 translocation and glucose uptake is additive (308).

Free fatty acids are commonly increased in most clinically relevant conditions of myocardial ischemia secondary to increased plasma catecholamine levels. Furthermore, heparin activates LPL and markedly increases circulating free fatty acid levels (311). The inhibition of glucose oxidation by fatty acids is a well-known phenomenon of mammalian metabolism (the glucose–fatty acid cycle). Indeed, increased free fatty acid levels have been shown to be toxic to ischemic myocardium and are associated with increased membrane damage, arrhythmias, and accelerated functional deterioration (312,313).

Increased glucose uptake and metabolism during acute myocardial ischemia are associated with preserved myocardial function (310,314). Hence, decreased GLUT4 translocation caused by insulin deficiency could limit glucose availability, thereby promoting myocardial damage, and possibly reducing the capacity of the noninfarcted myocardium to compensate. In addition, insulin deficiency reduces myocardial glucose use with a shift toward fatty acid metabolism. This altered pattern of exogenous substrate use may result in increased oxygen consumption by the myocardium, reduced contractility, and increased production of free radicals (313).

If specific metabolic abnormalities induced by diabetes can adversely affect mechanical performance or increase the myocardial vulnerability to ischemic insults, insulin administration and improved metabolic control may reduce myocardial damage, improve contractility, and decrease mortality. Noninvasive quantification of myocardial glucose uptake using positron emission tomography with the glucose analog ^{18}F-fluorodeoxyglucose has shown that myocardial glucose uptake can be significantly improved or normalized if adequate insulin substitution is provided (315).

These potential benefits—increased glucose uptake and decreased circulating fatty acid levels—have been exploited clinically with the use of glucose-insulin-potassium infusions in the setting of myocardial infarction.

In experimental studies, the protective effects of high glucose and insulin levels are much more apparent after reperfusion than during the preceding ischemic period (310). During reperfusion, fatty acid oxidation quickly recovers and again dominates as the source of energy. Therefore, glucose oxidation rates are markedly inhibited. The use of fatty acids instead of glucose strongly impairs the efficiency of the reperfused heart. Stimulation of glucose oxidation at the onset of reperfusion improves and accelerates functional recovery, whereas inhibition of glucose use induces a strong impairment of postischemic contractility (316). Thus, glucose-insulin-potassium may slow the rate of development of ischemic necrosis and prolong the time during which reperfusion therapy can salvage ischemic myocardium, as well as the amount of salvage that is achieved (312).

In the DIGAMI trial of diabetic patients with acute myocardial infarction (half receiving thrombolysis) in-hospital mortality was unchanged with insulin and glucose infusion. However, there was a trend to a decreased mortality at 3 months, which became significant at 1 year (29% relative mortality reduction, $p = .27$) (317). It is unclear, however, whether this mortality benefit is related to myocardial salvage or to other beneficial effects of improved glycemic control.

CORONARY REVASCULARIZATION IN DIABETIC PATIENTS

Because CAD is a major health problem in patients with diabetes, the need for revascularization procedures arises frequently. An increasing proportion of patients undergoing angioplasty are diabetics. In the 1977 to 1981 National Heart, Lung, and Blood Institute registry, 9% of patients undergoing angioplasty were diabetics (318). More recent large trials indicate that the prevalence of diabetes in patients undergoing angioplasty has increased to 17% to 26% (319).

Studies performed in the last decade have evaluated the relative efficacy of revascularization methods in diabetic patients. These studies reveal unique problems in diabetic patients, including higher periprocedural complication rates, a greater incidence of restenosis following successful angioplasty, and adverse long-term outcome after percutaneous and surgical revascularization, especially in the presence of multivessel disease, and suggest that the determination of optimal revascularization in these patients requires special attention.

Coronary Angioplasty

Procedural Outcomes and Complication Rates

In general, procedural success rates and completeness of revascularization do not significantly differ between diabetics and nondiabetic subjects (10,320,321,322 and 323). In-hospital complication (of death, infarction, and need for emergency surgery) rates have been reported to be higher in diabetic patients undergoing balloon angioplasty (10,320) and stenting (323). With stenting, a trend toward higher rates of subacute stent thrombosis was reported (323,324).

These differences are small and have not been confirmed in all studies. Based on data from the EPILOG study, Kleiman et al. concluded that with current angioplasty techniques, the in-hospital event rates for diabetic patients are comparable with those for nondiabetic patients (325). However, when acute ischemic complications occur during angioplasty, they may be poorly tolerated by diabetic patients, leading to a higher rate of periprocedural death (326).

Long-Term Results: Restenosis

Long-term outcomes have been disappointing because of the greater incidence of restenosis following successful angioplasty and adverse long-term outcome, especially in the presence of multivessel disease. The importance of diabetes as a consistent clinical predictor for restenosis after percutaneous transluminal coronary angioplasty (PTCA) has been demonstrated in multiple studies. The initial report from the National Heart, Lung, and Blood Institute Angioplasty Registry (327) that the

angiographic restenosis rate in diabetic patients was 47%, as compared with 32% in nondiabetic patients, was subsequently confirmed by many other studies that reported restenosis rates of 49% to 68% among diabetic patients undergoing balloon angioplasty (328,329 and 330). Diabetes is also a clinical predictor for restenosis with other percutaneous revascularization techniques, such as excimer laser angioplasty (331) and coronary atherectomy (321).

Intracoronary stents decrease restenosis compared with balloon angioplasty. However, even with stent use, the majority of studies has shown higher restenosis rates, compared with nondiabetic patients (324,332,333,334 and 335).

The full impact of the higher postangioplasty restenosis rates on the cardiovascular morbidity of diabetic patients is significant. Numerous studies have shown that diabetic patients experience a greater need than their nondiabetic counterparts for repeat revascularization [angioplasty or coronary artery bypass graft (CABG)], a high cardiac event rate, and lower overall survival rates after either balloon angioplasty (10,320,321,336) or stenting (333,334 and 335).

Whereas restenosis may explain the higher repeat angioplasty and CABG rates among diabetics, the exact relationship between restenosis and recurrent events or increased mortality is more complex. The majority of ischemic events outside the time frame of restenosis appears to be disease progression at other coronary sites rather than late restenosis at the original treatment site. Notwithstanding, percutaneous interventions may affect long-term prognosis through other mechanisms, including increased incidence of heart failure (330) and distal embolization (337). In a study of 485 consecutive patients with diabetes undergoing balloon angioplasty without stenting, at least one vessel with restenosis was found in 68% of patients (330). Many of these occlusions were clinically silent, with no angina in 36% and stable angina in 33% of patients. Occlusions were associated with a significant decrease in left ventricular function.

Because of the diffuse atherosclerotic process, poor collateralization, and preexisting microvascular dysfunction, diabetic patients may have reduced adaptive capacity for embolization during percutaneous interventions (337). Studies suggest that the combination of abciximab and stent placement reduces periprocedural myocardial infarction and short-term mortality (338,339). The beneficial effect of abciximab may be related to the reduction of distal embolization at the time of stenting (338,339). Target vessel revascularization rates were not different, suggesting that the risk for restenosis is not affected (338).

Mechanisms of Restenosis in Diabetes

Although vessel recoil may also contribute to loss of lumen, the markedly increased restenosis rate seen in diabetics following stent placement underscores the role of enhanced neointimal proliferation as the major mechanism for restenosis in these patients (334). In a study using intravascular ultrasound, exaggerated intimal proliferation was found in diabetic patients at the site of angioplasty-induced arterial injury, and this proliferative response was particularly striking in restenotic lesions (340).

Multiple potential mechanisms can contribute to intimal hyperplasia following arterial injury in hyperglycemic diabetic patients (reviewed in reference 341). The role of insulin resistance in the pathogenesis of restenosis is of major clinical importance not only for patients with type 2 diabetes or impaired glucose tolerance, but also for a large group of insulin-resistant subjects with normal glucose tolerance (48). Current data are limited and controversial, with studies both supporting (342) and refuting (119,331) the role of insulin resistance in the restenosis process.

When considering restenosis in diabetic patients, an important clinical issue is whether the effect of diabetes on accelerating the development of restenosis occurs in only a subset of patients. If this is the case, can this subgroup of diabetic patients who are at a particularly high risk for restenosis be identified? Restenosis may be predicted, at least to some extent, in diabetic patients based on clinical data, markers of metabolic control, and the presence of other diabetic complications (343) that may share similar pathophysiologic mechanisms (341).

Coronary Artery Bypass Graft

Perioperative Period

In an analysis performed on over 6,000 patients undergoing surgical revascularization, overall operative mortality was 2.3%, and diabetic status was not a predictive factor (344). Smaller studies reported higher operative mortality among diabetics, although only to a relatively small degree (345,346). In the largest series reported to date of 12,198 consecutive patients undergoing CABG at the Emory University Hospitals, the 2,278 diabetic patients had higher rates of postoperative death and stroke (347).

The most often cited complication associated with bypass surgery in diabetics is wound infection involving sternotomy (a complication associated with prolonged hospitalization, reoperation, and increased mortality) and graft harvest sites (348). The results of a large prospective study suggest that the incidence of deep wound infection in diabetic patients can be reduced with perioperative strict glycemic control (349). Renal failure, postoperative arrhythmia, respiratory failure, and intraaortic balloon pump use are mentioned only variably as complications seen more frequently in diabetics. The occurrence of both stroke and perioperative infarction is similar.

Vein Grafts

There are no prospective data on the influence of diabetes on disease progression in vein grafts. Animal studies suggest diabetes may be associated with accelerated intimal hyperplasia in vein grafts (350). Lytle et al. performed angiographic follow-up on 501 patients undergoing bypass surgery. Diabetes was found to be predictive of interval vein graft occlusion by multivariate analysis, although actual graft patency rates among diabetics were not specified (351). Other investigations have not found diabetes to be a significant predictor of progressive vein graft narrowing (352). These studies, however, are limited by total number of patients examined and even smaller numbers of diabetics. The post-CABG trial studied the effects of aggressive cholesterol lowering and low-dose anticoagulation on angiographic end points in patients 1 to 11 years after CABG. Angiographic changes in saphenous vein graft (SVG) conduits 4.3 years after entry were compared in 116 diabetic and 1,235 nondiabetic patients. There was no discernible difference between SVG disease in diabetic and nondiabetic patients for all three angiographic outcomes (substantial progression, occlusion, and change in minimum lumen diameter of SVGs) (353).

Internal Mammary Artery Grafts

Overall, long-term survival and freedom from subsequent cardiac events are better in patients receiving internal mammary artery (IMA) grafts compared with SVGs only. Even in patients with multivessel disease, the use of a single IMA graft conveys a significant survival benefit. Furthermore, the IMA appears to be virtually immune to the development of intimal hyperplasia, which almost universally occurs in aortocoronary vein grafts (354).

Although IMA graft patency rates have not been well documented in the diabetic population, the influence of IMA grafting on survival in diabetic patients was determined in a study of 5,654 consecutive patients of whom 1,132 (20%) were diabetic (355). Use of an IMA graft conveyed an independent long-term survival benefit to both nondiabetic and diabetic patients, and the magnitude of the survival benefit attributable to IMA grafting in the two groups did not differ (355). The importance of IMA grafting is also supported by the results from the Bypass Angioplasty Revascularization Investigation (BARI) trial, suggesting that a large mortality benefit is derived from IMA grafting in diabetic patients (see following discussion) (356).

Long-Term Outcome of Coronary Artery Bypass Graft in Diabetic Patients

The relative survival benefit of CABG surgery versus medical therapy is comparable in diabetic and nondiabetic patients (11,355). However, long-term survival rates after bypass surgery remain lower in diabetic than in nondiabetic patients (11,347,355,357). The BARI study demonstrated that surgically treated diabetic patients have a worse 5-year survival probability than nondiabetic patients (80.6% vs. 91.4%) (320).

Multivessel Angioplasty versus Coronary Artery Bypass Graft

In the last decade, angioplasty has been proposed and evaluated as an alternative to CABG in patients with multivessel disease. The influence of diabetes on outcome after PTCA for patients with multivessel disease received attention following the results of BARI study (358).

The BARI study enrolled 1,829 patients, including 353 diabetics with angiographically documented multivessel CAD and either clinically severe angina or objective evidence of marked myocardial ischemia requiring revascularization. A review of 5-year all-cause mortality showed a near doubling of mortality among diabetics on insulin or oral therapy assigned to multivessel angioplasty compared with those assigned to surgery (35% versus 19%, $p = .003$). In contrast, the 5-year mortality in nondiabetics and diabetics not on drug treatment was 9% with both revascularization strategies (358). Cause-specific 5.4-year cardiac mortality was 3.5 times higher in the PTCA group (20.6% vs. 5.8%) (322). These results raised concern about selection of angioplasty as a revascularization method in diabetic patients with multivessel

CAD.

Subsequent reports from the BARI investigators indicated that the survival benefit of CABG was limited to the 81% of diabetics receiving internal mammary grafts. Cardiac mortality after 5.4 years was 2.9% when internal mammary grafts were used and 18.2% when only SVG conduits were used. The latter rate was similar to patients receiving PTCA (20.6%) (322). The mortality benefit afforded by internal mammary grafting was most apparent in those experiencing myocardial infarction during follow-up, an effect seen also in nondiabetic patients.

The results of two other randomized trials comparing multivessel angioplasty to CABG are consistent with the BARI findings. Long-term follow-up of patients participating in the Emory Angioplasty versus Surgery Trial demonstrated an improved outcome in diabetic patients randomized to CABG (75.5% vs. 60.1% with PTCA at 8 years) (359). In the Coronary Angioplasty versus Bypass Revascularization Investigation, a trend toward a higher mortality was observed among diabetic patients randomized to PTCA (360).

In summary, an accumulating body of evidence points toward CABG as the preferred revascularization strategy in diabetic patients with multivessel disease. It should be emphasized, however, that it is still unknown whether the choice of the initial revascularization strategy in these patients should be based exclusively on a history of diabetes. Some of the questions regarding revascularization in diabetic patients with multivessel disease will be addressed in the BARI II study. This study is designed to examine the effects of revascularization plus aggressive medical therapy versus medical therapy alone, as well as the effect of insulin-providing (sulfonylurea and insulin) versus insulin-sensitizing (metformin and thiazolidinediones) strategies for tight glycemic control.

Mechanism of Coronary Artery Bypass Graft Protection

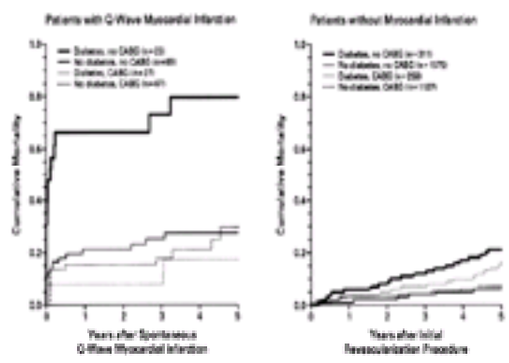
Two major mechanisms have been suggested to explain the apparent superiority of CABG over multivessel balloon angioplasty in diabetic patients: (a) high restenosis rates after angioplasty with incomplete revascularization of ischemic territories (336,361); and (b) accelerated progression of atherosclerosis of native arteries or SVGs (362).

Restenosis with Incomplete Revascularization

Previous CABG studies have shown that complete revascularization, which is accomplished almost exclusively through CABG surgery, is essential for obtaining survival benefit in patients with multivessel disease (363). The superiority of CABG over angioplasty in providing complete revascularization is exemplified in the BARI study itself. In the BARI population, 3.1 grafts were placed per patient undergoing CABG (364), whereas the mean number of successfully treated lesions in the PTCA group was 2.0 (322). Similar numbers are reported by other studies comparing multivessel angioplasty and CABG (336,357,365). In the Emory cohort, revascularization was achieved in 16% of patients undergoing PTCA, and 80% in the CABG group (365). In the study by Gum et al., complete revascularization was accomplished in 79% of patients undergoing CABG and in 42% of the angioplasty group (p <.001) (336).

Given the suboptimal revascularization with multivessel angioplasty compared with CABG, successful application of multivessel angioplasty—which entails a selective high-priority lesion-targeting strategy—requires that a comparable proportion of myocardium supplied through high-priority lesions be revascularized by each of the two strategies. Given the high restenosis rates in diabetic patients, and because when multivessel angiography is preformed, multiple treatment sites can become restenosed independently, it is likely that this goal is frequently not achieved in diabetic patients. Thus, the worse outcome of diabetic patients undergoing PTCA may be mediated in part by the frequent occurrence of incomplete revascularization (336,361). The effect of incomplete revascularization may be even more severe in view of the more diffuse and distal CAD (9,10 and 11,320,322), poor collateral development (292), and microcirculatory dysfunction in diabetic patients (see Vascular Endothelial Dysfunction in Diabetes).

The BARI investigators have analyzed the outcome of BARI-eligible patients, a larger group that included randomized patients and 2,010 additional eligible patients who declined randomization (361). This report identified two mechanisms for the protective effect of CABG in diabetes: (a) a strong protective effect with respect to survival in a small group of patients who sustained a Q-wave myocardial infarction, accounting for approximately 50% of the overall reduction in mortality attributable to the procedure; and (b) a moderate constant reduction in mortality throughout follow-up that occurred in the majority of diabetic patients who remained free of myocardial infarction during follow-up (eFig. 7.8.1). A steadily increasing advantage of CABG compared with PTCA was also apparent at 7-year follow-up (366). These protective effects were not present in nondiabetic patients (361).



***e*FIGURE 7.8.1** Mortality after the initial revascularization procedure in Bypass Angioplasty Revascularization Investigation (BARI) trial. The left panel shows Kaplan-Meier estimates of the cumulative mortality in patients with spontaneous Q-wave myocardial infarction according to diabetes status and coronary artery bypass grafting (CABG) status (the numbers in parentheses refer to the 186 spontaneous Q-wave myocardial infarctions that occurred in 176 patients). Patients who did not undergo CABG were treated only with percutaneous transluminal coronary angioplasty. The right panel shows the cumulative mortality in patients without Q-wave myocardial infarction, both according to diabetes status and with respect to CABG at the time of death. (From Detre KM, Lombardero MS, Brooks MM, et al. The effect of previous coronary-artery bypass surgery on the prognosis of patients with diabetes who have acute myocardial infarction. Bypass Angioplasty Revascularization Investigation Investigators. *N Engl J Med* 2000;342:989–997, with permission.)

Accelerated Atherosclerosis Progression

It has been suggested that accelerated progression of atherosclerosis leading to new plaque ruptures located within the native coronary arteries or vein grafts of diabetic patients accounts for the poor long-term prognosis after multivessel angioplasty (362). Bypass surgery offers some protection from atherosclerosis progression in native arteries by providing a bypass conduit beyond the epicardial coronary segment most vulnerable to future plaque development (usually within the proximal 6 cm of epicardial coronary arteries) (362). However, progression of native CAD in postbypass patients is mainly related to dyslipidemia (352). Currently, there is no evidence that in the group of patients who already have an advanced atherosclerotic process (multivessel disease) continued progression is more rapid in the presence of diabetes. Likewise, progression of vein graft atherosclerosis is mainly related to hypercholesterolemia, and aggressive lipid-lowering therapy reduces the progression of atherosclerosis in vein grafts (367), whereas the effect of diabetes on the accelerated atherosclerotic process that characterizes vein grafts is still unclear (see Vein Grafts). Indeed, in the BARI trial, the type of revascularization had no influence on the incidence of Q-wave myocardial infarction during follow-up (361). In a large study comparing the outcomes of 9,920 patients without diabetes and 2,278 diabetic patients after CABG surgery, there was no difference in myocardial infarction rates at 5 and 10 years (347). Of note is the fact that in post-CABG patients with evolving infarction, approximately two-thirds of culprit lesions are located within vein grafts (368).

Although the incidence of plaque disruption leading to a clinical acute coronary event is probably not affected, a greater proportion of the myocardium may become ischemic because of incomplete revascularization with PTCA. This is particularly important given the high long-term incidence of both fatal and nonfatal events among diabetic patients (10,320,322,361,365). For example, in the BARI study, although CABG offered no protection from myocardial infarction, patients with diabetes were 1.9 times as likely as those without diabetes to have a spontaneous (non–procedure-related) Q-wave myocardial infarction at 5 years (361).

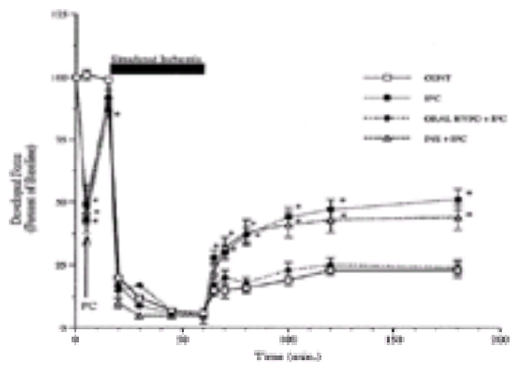
ISCHEMIC PRECONDITIONING

An essential mechanism for ischemic preconditioning is thought to involve the release of adenosine formed from net adenosine triphosphate (ATP) use during the preconditioning period of ischemia. Adenosine A_1 receptors are coupled through G proteins to K_{ATP} channels present on ventricular myocytes and smooth muscle cells (369). These channels are activated during ischemia by decreasing ATP levels in ventricular myocytes and adenosine receptor stimulation. Opening cardiac K_{ATP} channel ventricular myocytes initiates ischemic preconditioning of the myocardium for a subsequent ischemic event and in vascular smooth muscle contributes to

vasodilation (369,370).

In the pancreas, a surge in blood glucose leads to increased production of high-energy phosphate ATP and inhibits K_{ATP} channel opening. With channel closure, an excess of K^+ remains on the inner side of the plasma membrane, leading to depolarization of the beta cell plasma membrane. In turn, membrane depolarization results in opening of voltage-dependent Ca^{2+} channels followed by Ca^{2+}-dependent release of insulin through exocytosis. Sulfonylurea drugs as a class bind with high affinity to a subunit of the K_{ATP} channel known as the *sulfonylurea receptor* (371) and inhibit K^+ flux through the channel pore, leading to membrane depolarization and insulin release. In a similar fashion, sulfonylurea-induced inhibition of potassium efflux through K_{ATP} membrane channel may inhibit preconditioning of myocytes and vasodilation in response to hypoxia or ischemia (369).

Experimentally, sulfonylureas have been shown to increase infarct size and accelerate death of hypoxic cardiomyocytes (370). In humans, ischemic preconditioning during coronary angioplasty (decreased severity of ST-segment depression during second balloon inflation relative to the first) can be prevented by sulfonylureas. Long-term oral hypoglycemic agents abrogate preconditioning in isolated human myocardium (372) (eFig. 7.8.2).



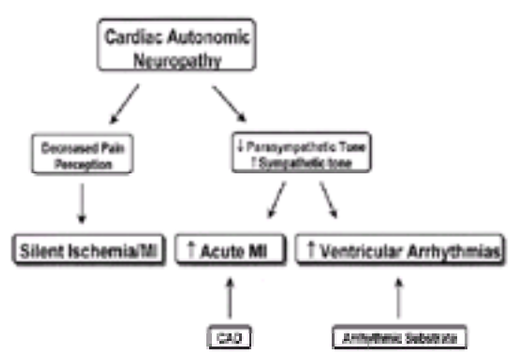
***e*FIGURE 7.8.2** Effects of ischemic preconditioning in trabeculae with and without long-term exposure to oral hypoglycemic agent (ORAL HYPO). Preconditioned trabeculae from patients without oral hypoglycemic exposure (IPC) show increased recovery of developed force relative to trabeculae not given preconditioning stimulus (CONT) after simulated ischemic injury. Conversely, trabeculae from patients with long-term ORAL HYPO + IPC are not functionally protected by ischemic preconditioning stimulus. Insulin (INS) + IPC does not inhibit protection by preconditioning. *p <.05 versus control. (Adapted from Cleveland JC Jr, Meldrum DR, Cain BS, et al. Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium. Two paradoxes revisited. *Circulation* 1997;96:29–32, with permission.)

In the early 1970s, the results of the University Group Diabetes Program study suggested that patients on sulfonylureas sustain an unexplained increase in cardiovascular mortality compared with diet treatment alone (373). No evidence of deleterious effect of sulfonylurea therapy on myocardial infarction, sudden death, or diabetes-related deaths has been found in the UKPDS (206). Notwithstanding, in the post–myocardial infarction setting, a paradoxical increase in mortality among diabetic patients on sulfonylureas has been observed in some (374), but not all, studies (375). At present, there are insufficient data regarding the effect of sulfonylureas on clinical outcome.

DIABETIC AUTONOMIC NEUROPATHY AND THE HEART

Although clinically apparent autonomic neuropathy (e.g., orthostatic hypotension and gastroparesis) generally occurs only in patients with diabetes of long duration, it has become evident that subclinical diabetic autonomic neuropathy, mainly in the form of cardiac autonomic neuropathy (CAN), evolves early in the course of diabetes (376) and in the absence of other microvascular complications (377). CAN is extremely common in both type 1 and type 2 diabetes, affecting up to 60% of unselected populations (376,378).

CAN involves parasympathetic dysfunction (379) as well as derangements of adrenergic cardiac innervation as assessed by myocardial meta-[^{123}I]iodobenzylguanidine scintigraphy (380). The presence of CAN in diabetic patients has been linked to increased risk of arrhythmias, cardiovascular events, and a high prevalence of silent ischemia and infarction (eFig. 7.8.3).



***e*FIGURE 7.8.3** Cardiac consequences of autonomic neuropathy. CAD, coronary artery disease; MI, myocardial infarction.

Propensity to Arrhythmias

Extensive experimental and clinical evidence suggests that changes in autonomic neural activity are important in the genesis of cardiac arrhythmias (381). In nondiabetic patients, clinical investigations have consistently shown that reduced heart rate variability is a marker of autonomic imbalance that favors the development of cardiac arrhythmias and sudden death, mainly in conjunction with left ventricular dysfunction and in patients surviving myocardial infarction (381,382). Reduced heart rate variability is a hallmark and the earliest indicator of CAN in diabetic patients (376,378,379) and may confer a higher risk for arrhythmic events. QT prolongation (383) and increased QT dispersion (384) have also been described in diabetic patients with autonomic dysfunction and may contribute to increased risk of arrhythmias.

Relation of Autonomic Neuropathy to Abnormal Circadian Rhythms in Diabetic Patients

Abnormalities in the circadian pattern of autonomic nervous system caused by the presence of CAN are associated with alterations in the temporal pattern of thrombotic events and in blood pressure regulation.

In the general population, the circadian pattern of acute myocardial infarction and other thrombotic events parallels the temporal pattern of the autonomic nervous system (385). Sympathetic tone predominates during the daytime, when the onset of cardiac events is maximal (385).

The circadian distribution of onset of symptoms of acute myocardial infarction is altered in the diabetic population with a shift from morning hours to the evening and night hours (386,387). Bernardi and colleagues (388) demonstrated that diabetic autonomic neuropathy is associated with a marked diminution of parasympathetic activation during sleep, which may result in a relative nocturnal sympathetic dominance. This finding led to the hypothesis that the relative nocturnal predominance of sympathetic activity might predispose diabetic patients to cardiovascular events at that time (388).

A nocturnal decline in blood pressure during sleep is characteristic of the 24-hour pattern of blood pressure. In hypertensive patients, this pattern is generally preserved, with an upward shift of the 24-hour mean around which the temporal changes are manifested. In a small proportion of patients with essential hypertension

the pattern of blood pressure is altered because of a blunted decline in nocturnal blood pressure (389). In these so-called nondipper patients, lack of nocturnal decline in arterial blood pressure is associated with left ventricular hypertrophy and increased cardiovascular complications (390). The decrease in plasma catecholamine levels and sympathetic nervous activity during sleep are thought to play a pivotal role in 24-hour changes of blood pressure. Indeed, subjects with autonomic failure lack the nocturnal blood pressure decline (391).

The physiologic nocturnal decrease in blood pressure is blunted or absent in many normotensive and hypertensive diabetic patients and has been linked to the presence of concomitant autonomic neuropathy (392). A high prevalence of nondippers has been documented in both type 1 (392) and type 2 (393) diabetic patients and has been associated with increased risk for the occurrence of various vascular events (393).

Silent Ischemia

The propensity of diabetic patients to present with silent or unrecognized myocardial infarction is well established (394). In the Framingham Study, a higher proportion of myocardial infarctions in diabetic patients was silent and unrecognized (395). Atypical symptoms such as confusion, dyspnea, fatigue, or nausea and vomiting were the presenting complaint in 32% to 42% of diabetic patients with myocardial infarction compared with 6% to 15% of nondiabetic patients. More recently, failure to use reperfusion therapy was observed in diabetic patients (396), which may be attributable, in part, to an atypical presentation.

Although silent ischemia frequently can be demonstrated in nondiabetic patients, several studies have shown that, whether assessed by treadmill exercise testing (377), ambulatory Holter monitoring, or exercise thallium scintigraphy (397,398), silent ischemia is more common in diabetic than in nondiabetic subjects. This finding, however, is not supported by all studies (399). For example, in the Asymptomatic Cardiac Ischemia Pilot study, there was a similar prevalence of asymptomatic ischemia during exercise treadmill testing and 48-hour ambulatory electrocardiographic monitoring (399).

Autonomic neuropathy with involvement of the sensory supply to the heart is a plausible explanation for painless infarction and ischemia episodes in diabetic subjects. In autopsies of diabetic patients who died of silent myocardial infarction, typical diabetic neuropathic changes were found in the intracardiac sympathetic and parasympathetic fibers (400), and several studies correlated abnormalities in autonomic function in patients with silent ischemia (377,401). The anginal perceptual threshold—the time from the onset of myocardial ischemia (assessed by ST-segment depression) to the onset of chest pain during exercise testing—is prolonged in diabetic patients compared with nondiabetic subjects. This delay in the perception of pain is related to the impairment of autonomic nervous function (401).

CONTROVERSIES AND PERSONAL PERSPECTIVES

In the last two decades, the advent of effective therapies of hypertension and hypercholesterolemia resulted in a substantial reduction in mortality and morbidity associated with these risk factors for CAD. Diabetes remains a major risk factor for which the optimal therapy has not been established and is increasingly becoming a research focus in the field of preventive and clinical cardiology.

A central issue in the treatment of diabetic patients is whether tight glycemic control will reduce CAD morbidity and mortality. Whereas randomized primary prevention trials have clearly shown that glycemic control reduces the incidence of microvascular complications in both type 1 and type 2 diabetes, the effect on macrovascular complications was small. Indeed, lipid lowering and aggressive blood pressure reduction appear to be more efficacious as primary prevention in diabetic patients.

There are two key questions with regard to the expected benefit of intensive glycemic control as part of the primary prevention of macrovascular disease. First, the threshold above which hyperglycemia becomes atherogenic is unknown and may be below the range defined as diabetes. It is also unknown whether a continuous relative risk reduction relationship over the range of hemoglobin A_{1c} exists for diabetic macrovascular complications. Second, the time necessary for the reversal of established hyperglycemia-induced vascular damage is not known. For example, in diabetic patients with functioning pancreatic transplants, renal pathology continues to progress for at least 5 years after diabetes has been cured (402). The mechanism for these observations is unclear but may be related to a slow replacement of glycosylated molecules or because phenotypic alterations in vascular cells may persist despite the return of normoglycemia (the so-called memory effect). Notwithstanding, intensive glycemic control as secondary prevention seems to be effective in reducing short-term mortality (317), suggesting that glycemic control may be valuable even in diabetics with established CAD.

The diffuse nature of the atherosclerotic process in diabetic patients is often emphasized. It is commonly accepted that angiographically severe CAD increases the propensity to develop acute coronary syndromes because the presence of the severe stenoses serves as a marker for the presence of angiographically modest or even inapparent noncritically stenotic plaques that are more prone to disruption. However, the striking excess of coronary events in diabetic patients with or without established CAD appears to be out of proportion to the severity of atherosclerosis. These observations raise the possibility that unique pathogenic mechanisms in diabetes operate to weaken plaque stability.

THE FUTURE

Basic and clinical research should be directed to elucidate the unique mechanisms causing accelerated atherosclerosis in insulin-resistant and diabetic individuals. Diabetes promotes initiation of atherosclerosis, progression of lesions, and thrombotic complications by multiple mechanisms. Current lines of investigation focus on the following interactions of diabetes and mechanisms of atherosclerosis: (a) the role of endothelial dysfunction in the pathogenesis of atherosclerosis and propensity to thrombosis; (b) the mechanisms involved in the abnormal hemostatic and fibrinolytic function observed in the diabetic setting; and (c) the role of AGEs and the receptor for AGEs in the pathogenesis of vascular disease in diabetes and the use of specific inhibitors of various steps in the glycosylation process (e.g., aminoguanidine or “AGE breakers”) as a potential therapy; (d) diabetes-induced augmentation of oxidative stress; (e) understanding the relationship between the components of the insulin-resistance syndrome and its importance as a cardiovascular risk factor for both diabetic and nondiabetic subjects; and (f) understanding the relation between inflammation and diabetes. Defining the molecular mechanisms responsible for insulin resistance may lead to the development of new “insulin-sensitizing” agents that can improve insulin action, resulting in a wide spectrum of beneficial metabolic effects and a reduced cardiovascular risk.

The pathogenesis, natural history, and clinical significance of diabetic cardiomyopathy remain to be determined. Likewise, the role of autonomic neuropathy in the cardiovascular complications of diabetes should be explored. More research is also needed with regard to the specific mechanisms involved in the pathogenesis of restenosis in diabetic patients and potential therapeutic approaches that will improve the results of angioplasty in diabetic patients.

Finally, the prevention of type 1 and type 2 diabetes is a major focus of basic and clinical investigations. Screening of the human genome can identify regions of genetic susceptibility, after which the final localization of disease genes can be carried out, followed by sequencing of candidate genes to identify the specific mutations. Multiple molecular defects can lead to type 2 diabetes, and the molecular details of several rare forms of type 1 diabetes have already been identified (e.g., pancreatic glucose “sensor” mechanism).

Diabetes prevention trials based on immunologic toleration to prevent type 1 diabetes, lifestyle changes, and pharmacologic interventions to prevent or delay type 2 diabetes are now being carried out.

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8

ESTROGEN, FEMALE GENDER, AND HEART DISEASE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Cardiovascular disease (CVD) across the entire lifetime is slightly more common as a cause of mortality in women than in men. In addition, CVD in women is a formidable problem because of difficulties in diagnosis and increased morbidity and mortality associated with CVD events at all ages. In the middle years, CVD is associated with multiple risk factors, generally more in women than in men of the same age. Diabetes appears to be a particularly more severe risk factor in women than in men, but smoking is still probably the worst CVD risk factor in any gender. Specific lipid management guidelines are available for the treatment of elevated low-density lipoprotein cholesterol (LDL-C) in women, but the management of combined hyperlipidemia is a more common condition and more important. Postmenopausal hormone replacement therapy, unfortunately, has not been beneficial in preventing progression of established coronary disease in prospective double-blind randomized studies. The evidence of benefit from experimental models may relate to the early rather than the late use of estrogen in the atherogenic process; this is analogous to the lower rates of heart disease in premenopausal women. There are many examples of interaction of sex steroids with lipid disorders that require care and thought and have long-term implications for the cardiovascular health of both men and women.

GLOSSARY

Combined hyperlipidemia: The concomitant elevation of total triglyceride level above 200 mg per dL and LDL-C level above 100, 130, or 160 mg per dL, depending on National Cholesterol Education Program risk factors.

Lipid transfer protein: Also known as *cholesterol ester transport protein*, lipid transfer protein facilitates the transfer of triglyceride from very-low-density lipoprotein (VLDL) to high-density lipoprotein (HDL) and cholesterol from HDL to VLDL and LDL, thereby maintaining a cycle of transport of cholesterol in the body.

Lipoprotein(a) [Lp(a)]: A nonfibrinolytic plasminogen analog that is attached to low-density lipoprotein (LDL) apoprotein B and plasminogen binding sites, inhibiting fibrinolysis and enhancing LDL trapping in the arterial wall.

Polycystic ovary syndrome (PCOS): Syndrome associated with the metabolic syndrome, obesity, and hyperandrogenemia in young women.

Remnant lipoprotein: A lipoprotein particle that is intermediate between VLDL and LDL (also known as *intermediate-density lipoprotein*) and has powerful atherogenic potential.

Syndrome X: The metabolic syndrome that is caused by insulin resistance. Syndrome X is associated with combined hyperlipidemia, obesity, hypertension, diabetes, and PCOS.

INTRODUCTION

The main points of this chapter are raised in the following true case. A 25-year-old woman who used oral contraceptives (OCs) and smoked one pack of cigarettes per day was having vague chest pains for a year, which were variously diagnosed as anxiety and acid reflux. On July 4, 2000, she was seen at an emergency room and sent away. Twelve hours later at the same emergency room, the possibility of a myocardial infarction (MI) was entertained as she went into shock. An emergency two-vessel angioplasty procedure was performed, saving the patient's life. Several other angioplasties and three-vessel bypass surgery have been done since, complicated by bilateral iliac vessel stenosis. She is now somewhat intellectually impaired. On presentation to clinic, the cholesterol was 182 mg per dL, triglyceride was 175 mg per dL, and high-density lipoprotein cholesterol (HDL-C) was 24 mg per dL on 40 mg atorvastatin. The Lp(a) was 19.2 (seventy-fifth percentile). Why did this patient have an MI? Why was it so severe? Why was the MI not recognized during the first emergency room visit? Is this case as rare as it might seem? Is the constellation of symptoms unique to this case or to women in general? What is the approach to managing this patient's lipid disorder? This chapter addresses these and other questions.

INCIDENCE OF CAD: WOMEN VS MEN

The perception persists that coronary artery disease is a rare occurrence in women, especially in young women, leading to the view that arteriosclerotic disease of the vascular tree is less important in women overall. Both perceptions are incorrect. CVD is an equal-opportunity killer in men and women over their lifetimes. In

Washington State in 1991, the incidence of CVD death was 42% in women and 39% in men (1). Nationwide, these numbers approach 50%. The slightly higher percentage of female cardiovascular deaths can be attributed to the greater longevity of women, which is an extremely powerful risk factor in its own right and allows female CVD mortality rates to “catch up” in old age.

A lower rate of CVD mortality in women is certainly observed in young women, especially premenopausally; still, the rates of CVD in women are not negligible and have defined relationships to cardiovascular risk factors. In fact, as shown in Figure 8.1, the increase in CVD with age in the Framingham study (2) lags behind the male age-associated increase by only 10 to 15 years. A similar pattern is seen even in high-risk conditions such as heterozygous familial hypercholesterolemia, again with a delay of 10 years in women compared to men. The delay in onset in women versus men is attributed to the premenopausal exposure to endogenous ovarian estrogen, but, even premenopausally, this effect diminishes with advancing age (Fig. 8.1). The most important point is that the rise in female CVD is highly parallel to the rise of CVD in men. A major inflection in the female risk curve around the time of menopause is not seen (Fig. 8.1). Possibly, some women develop menopause earlier (especially smokers), plasma estrogen levels decline in the 40s (a number of years before menopause), and any restraint of atherogenesis may take a few years to dissipate.

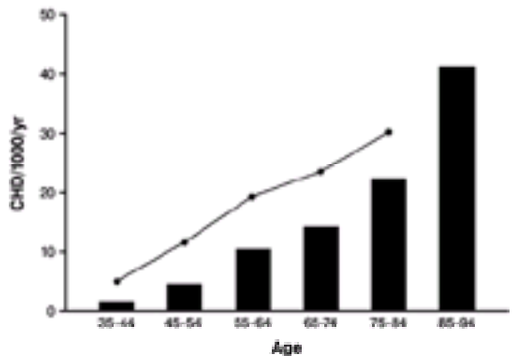
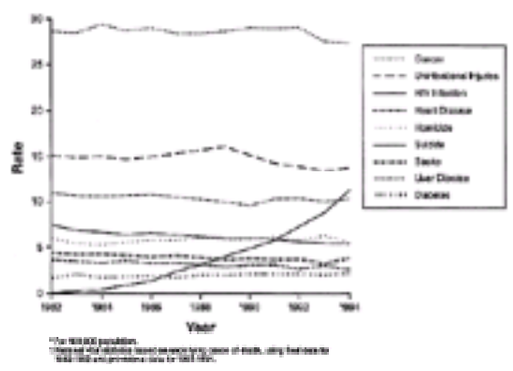


FIGURE 8.1 Annual rate of coronary heart disease (CHD) in men (*line*) and women (*bars*), from the Framingham Heart Study. (From Castelli WP. Cardiovascular disease in women. *Am J Obstet Gynecol* 1988;158:1553–1560, with permission.)

The importance of CVD in young women can be appreciated by comparing CVD death rates in women to other causes of mortality. These rates are shown in *e*Figure 8.1.1. Since 1982, heart disease mortality has occurred at a rate of approximately 11 per 100,000 in women ages 25 to 45 years with little decline, reflecting the level rates for CVD in women overall in the last decade (3). Among young women, approximately one-third of heart disease deaths are coronary in etiology. In men ages 25 to 44 years, the CVD rate is approximately 30 per 100,000—almost ten times more common than in women. As for other causes of mortality in women, cancer accounts for 29 per 100,000 and injuries for 14 per 100,000 (4). In a study of emergency room admissions among young persons (ages 18 to 45 years) for sudden death, 1 of 20 cases of coronary disease was in a young woman (5). In another study, one-fourth of all MI survivors younger than 40 years at a major hospital were women (6). The main point is that CVD incidence in younger women is not negligible, ranging from one-fourth to one-twentieth the rate in men.



***e*FIGURE 8.1.1** Death rates* from leading causes of death among women aged 25 to 44 by year—United States, 1982 to 1994. HIV, human immunodeficiency virus. [From Centers for Disease Control and Prevention. Update: mortality attributable to HIV infection among persons aged 25–44 years: United States, 1994. *MMWR Morb Mortal Wkly Rep* 1996;45(6):121–125, with permission.]

The early lesions of arteriosclerosis—the fatty streak and the fibrous arteriosclerotic plaque—are seen in young women and men. In teenagers and young adults who died traumatic deaths in Bogalusa (7), half of the men and one-fourth of the women were so affected. In blacks, half of men and women were affected and were equal in extent. In both genders, the fatty streak lesions were proportional in extent to the plasma LDL-C. However, the plasma level of VLDL-C (7), which is closely related to the plasma triglyceride level, was associated with lesions only in women (see the discussion of triglyceride as a CVD risk factor in women in the section Plasma Triglyceride Elevations). When coronary lesions are examined, female lesions are more lipid filled, rich in macrophages, and less densely fibrous (8). Thus, lesions in women could be more unstable under certain circumstances, as well as more readily reversed (9). Likewise, coronary calcification is half that of men on ultrafast computed tomography until age 60 years, when the difference between the genders narrows (10).

An excess in female acute MI susceptibility among young blacks is seen in the Bogalusa data (7). This trend is borne out by national mortality data, in which black women have consistently had a 50% to 75% greater risk of death from diseases of the heart since 1950 (11) and into the 1990s (3). The approximate rates (adjusted for age) for white and black women were 110 per 100,000 and 190 per 100,000, respectively, in 1988 (11). The reasons for this greater risk are unclear but could relate to higher blood pressure and Lp(a) levels in blacks.

DIFFERENCES IN DISEASE PRESENTATION

The tendency to overlook CVD in women because of its lesser frequency in youth and middle age is compounded by less classical presentation, which is more frequently angina in women and MI in men (*e*Table 8.0.1). In the Framingham study, the annual incidence of angina pectoris in women exceeded that of MI by a ratio of more than 2:1 in the age ranges of 45 to 54 years and 55 to 64 years. In men, frank MI exceeded angina for all four age groups examined, ranging from 1.5:1.0 between ages 45 and 64 years, 2.4:1.0 between ages 65 and 74 years, and 6.5:1.0 between ages 75 and 84 years (12,13). In a recent study, women presenting for stenting had fewer MIs than men (14). These data are consistent with the clinical impression that angina pectoris is an earlier and more common presentation of the arteriosclerotic process in women.

***e*TABLE 8.0.1** ANNUAL INCIDENCE OF ANGINA, MYOCARDIAL INFARCTION, AND SUDDEN DEATH IN MEN AND WOMEN PER 10,000 POPULATION

	Angina		**Myocardial infarction**		**Sudden death**	
Age (yr)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
45–54	30	21	54	9	11	3
55–64	74	54	91	25	21	6
65–74	52	51	119	51	31	13
75–84	25	94	168	90	43	32

Adapted from Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J* 1996;111:383–390.

Recognition of cardiovascular chest pain is difficult in women because (a) it is not expected, (b) it is often atypical, and (c) noncardiac chest pain seems to be more common in women than in men. As a result of atypical symptoms, misdiagnosis as chronic fatigue or a psychiatric disorder is not uncommon. The reason for the lack of classical anginal symptoms in many women—despite having validated myocardial ischemia—is unknown. The greater incidence of silent MI in women (13) may also be related to the atypicality of chest pain presentation. One of our patients had fatigue with exercise without ischemic electrocardiogram changes on treadmill testing that

did not resolve until she developed overt angina and had bypass surgery. A tip-off to performing anatomic studies earlier might have been recognition of her severe combined hyperlipidemia (see the section Lipid Screening Guidelines for Hyperlipidemic Women).

As this case suggests, the exercise tolerance test is not as useful in clarifying atypical chest pain in women as in men because it is too susceptible to false-positive and false-negative results. In general, radionuclide or echocardiographic imaging are recommended if an exercise test is to be done (15,16). On the other hand, a female patient with chest pain with a positive exercise test and a negative angiogram might have arteriosclerotic vasospasm with a normal lumen. In this instance, estrogen may be beneficial and even diagnostic if it eliminates the vasospasticity and the chest pain syndrome. In such cases, the long-term prognosis is favorable, and angina in women is collectively associated with approximately one-half the rate of subsequent MI as that in men (16).

Frank MI in women has more unfavorable consequences than in men. Sudden death is more frequent, and early post-MI mortality is greater in women than in men. In the Thrombolysis in Myocardial Infarction (TIMI)-II trial, the 6-week mortality rate was 9% in women versus 4% in men, and post-MI mortality was 1.54 times more likely in women compared to men when adjusting for age and other baseline inequalities (17). The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-I trial demonstrated a similar twofold excess that decreased to a relative risk of 1.4 when adjusted for age and 1.06 when adjusting predictors of 30-day mortality (18). In keeping with this observation, recent Scandinavian data (19) and experience from a Cleveland clinic (18) indicate that nearly all of the excess mortality in women is concentrated within the first 4 weeks post-MI (Fig. 8.2); these data influence all subsequent statistics. After 1 year, a mortality rate of 32% in women versus 16% in men has been observed in the Framingham study (20,21). Thus, postevent nonadjusted mortality is approximately 50% greater in women than in men for various intervals. These trends have been confirmed recently and extended (22) with a higher risk for death relative to younger men (23).

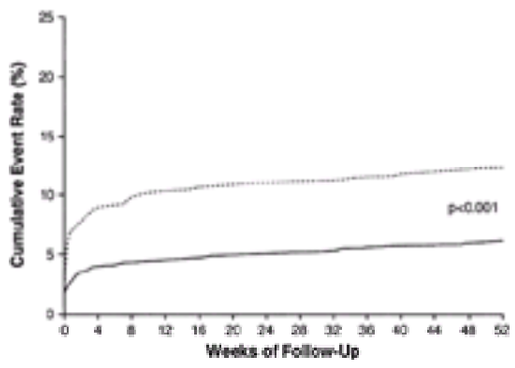
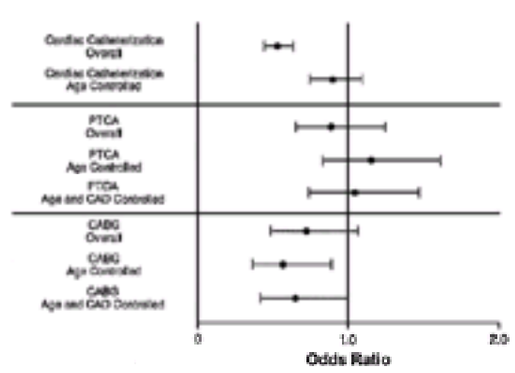


FIGURE 8.2 One-year Kaplan-Meier mortality curves for women and men. The solid line represents men; the dashed line represents women. (From Becker RC, Terrin M, Ross R, et al. Comparison of clinical outcomes for women and men after acute myocardial infarction. *Ann Intern Med* 1994;120:635–645, with permission.)

Regarding the cause for the greater female mortality, age and various risk factors interact, but the studies are not entirely consistent, as suggested above (17,18). In elderly Scandinavians with acute MI, a 28% versus 20% excess mortality in women and men, respectively, was eliminated by age adjustment alone (19). In a Spanish study of elderly post-MI outcome, a higher rate of congestive heart failure (CHF) in women explained the greater mortality (40% versus 23% in women and men, respectively), not gender itself (24). A metaanalysis of 27 reports between 1966 and 1994 seemed to rule out the effect of gender when age and other risk factors were taken into consideration (24). In summary, crude mortality post-MI is increased consistently in women versus men. The excess mortality is largely explained by age and other risk predictors, whether metabolic or relating to the severity of the incident MI, including CHF (24,25).

A variable literature has developed regarding the use of diagnostic testing and operative procedures in women versus men. Earlier studies from the 1970s and 1980s indicated that women were less likely to have Holter monitoring, exercise treadmill testing, cardiac catheterization, and angioplasty (26,27). In one study, the frequency of angioplasty in women was not reduced after age adjustment (26). In the Worcester, Massachusetts, area, angioplasty was less frequently performed in women, whereas coronary artery bypass grafting was performed as frequently in men as in women (27). On the other hand, in one Boston hospital, angiography was not performed less frequently in women than in men after age adjustment, angioplasty was performed as frequently in both genders, and bypass surgery was performed less frequently in women (*e*Fig. 8.2.1) (26). In a Seattle study, angiography and angioplasty were performed less frequently in women than in men, but among patients who had angiograms, equal proportions of men and women received bypass surgery (28). Thus, local conditions seem to influence some of the differences in treatment between the genders.



***e*FIGURE 8.2.1** Female-male odds ratios for cardiac procedures. Overall and age-controlled odds ratios are shown for cardiac catheterization. For percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG), overall odds ratios are shown, along with odds ratios adjusted for age and severity of coronary artery disease (CAD). Bars represent 95% confidence intervals. (From Krumholz HM, Douglas PS, Lauer MS, et al. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? *Ann Intern Med* 1992;116:785–790, with permission.)

As to whether a frank bias exists in physician management of coronary disease and cardiac catheterization of the genders, two investigators indicate that less-aggressive decision making is appropriate in women at low risk for cardiac death, with little probability of benefit (29,30), or with angina pectoris (31). A recent study found more do not attempt resuscitation orders, less aspirin prescription, and less thrombolytic therapy in women compared to men with acute MI (32). However, the issue is still little studied, and what happens in a woman's care depends greatly on the interaction between patient and physician (33).

Several recent studies have examined events surrounding MI treatment with thrombolysis in women and in men. In Kansas City, allocation of men and women to thrombolysis and angioplasty was equivalent (34). In the MITI study in Seattle, intravenous thrombolysis was performed within 6 hours of hospitalization in 57% of men and 54% of women (nonsignificant difference), whereas a total of all acute interventions was somewhat more common in men (72%) versus women (62%) (35).

Regarding outcome after thrombolysis, the recent GUSTO-I and Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI) studies revealed a number of features detrimental to women when unadjusted for age and risk factors, as shown in *e*Table 8.0.2. The two studies do not agree in all respects, but both indicate excess stroke, reinfarction, and unadjusted mortality in women (36,37). In addition, CHF, serious bleeding, and shock were more common in women than in men in the GUSTO-I trial. After adjustment for various factors in the TAMI trial, death was insignificantly more common (relative risk = 1.30), reinfarction significantly more common, and stroke approximately twofold more common. Thus, even after age and risk factor adjustment, there appears to be greater residual morbidity and marginally more mortality among acute-MI women treated with thrombolysis compared to men similarly treated (*e*Fig. 8.2.2) (37).

***e*TABLE 8.0.2** DIFFERENCES IN MYOCARDIAL INFARCTION IN MEN AND WOMEN AFTER THROMBOLYSIS IN TWO TRIALS

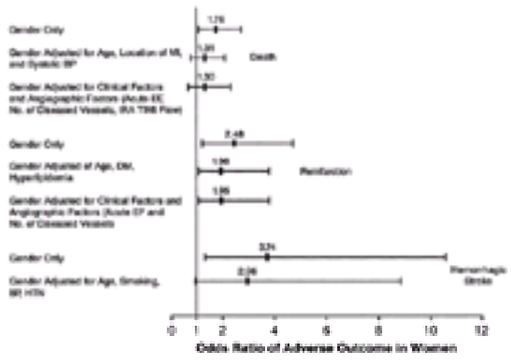
	GUSTO-I[a]			**TAMI**[b]		
	Men	**Women**	***p***	**Men**	**Women**	***p***
Age (yr)	59.00	66.00	<.001	55.80	61.00	<.001
Time to hospital (h)	1.80	2.00	<.001	3.02	3.13	NS
Shock (%)	5.00	9.00	<.001	—	—	—

Congestive heart failure (%)	14.00	22.00	<.001	32.70	33.90	NS
Bleeding (serious) (%)	7.00	15.00	<.001	12.10	12.10	NS
Reinfarction (%)	3.50	5.10	<.001	2.60	6.40	<.005
Stroke (%)	1.20	2.10	<.001	5.40	9.20	.014
Mortality (crude) (%)	5.50	11.30	<.001	1.00	1.30	NS
Mortality risk (adjusted) (%)	1.00	1.15	(CI, 1.0–1.31)	18.70	25.10	<.1

CI, confidence interval; GUSTO-I, Global Utilization of Streptokinase and Tissue Plasminogen Activator trial; NS, not significant; TAMI, Thrombolysis and Angioplasty in Acute Myocardial Infarction study.

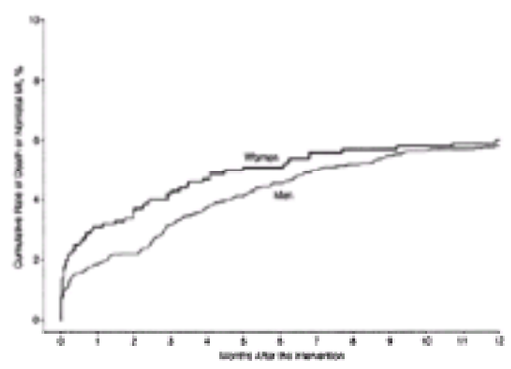
[a]From Weaver WD, White HD, Wilcox RG, et al. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. *JAMA* 1996;275:777–782.

[b]From Lincoff AM, Califf RM, Ellis SG, et al. Thrombolytic therapy for women with myocardial infarction: Is there a gender gap? *J Am Coll Cardiol* 1993;22:1780–1787.



***e*FIGURE 8.2.2** Multivariable model of the influence of female gender on mortality, reinfarction, and hemorrhagic stroke after acute myocardial infarction (MI), with adjustment for noninvasive clinical factors and angiographic variables. The relative odds ratio of death or reinfarction in women compared to men is plotted, along with 95% confidence intervals. A relative odds ratio of 1 denotes equal risk in men and women, an odds ratio >1 denotes higher risk in women, and an odds ratio <1 denotes higher risk in men. The 95% confidence intervals intersecting a relative odds ratio of 1 represent a nonsignificant influence of gender on mortality or reinfarction. BP, blood pressure; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; IRA, infarct-related artery; TIMI, Thrombolysis In Myocardial Infarction trial. (From Lincoff AM, Califf RM, Ellis SG, et al. Thrombolytic therapy for women with myocardial infarction: is there a gender gap? *J Am Coll Cardiol* 1993;22:1780–1787, with permission.)

Operative procedures also show greater short- and long-term morbidity and mortality in women than in men, though the probability of benefit remains high in both genders. At the Mayo Clinic, percutaneous transluminal coronary angioplasty was successful in 85% of women and 86% of men, but age-adjusted in-hospital mortality was 4.2% in women and 2.7% in men—a significant difference that persisted with multivariate analysis (38). In the case of bypass surgery, in-hospital mortality at Cedars-Sinai Medical Center was 4.6% and 2.6% in women and men, respectively, despite a difference in age of only 4 years (68.2 vs. 64.0) (39). However, more of the women had unstable angina and CHF, whereas more men were referred for abnormal exercise-test results. In this instance, the later stage of disease at the time of operation or the greater inherent severity accounted for the greater mortality in women (39). A recent analysis of stent experience from Germany found rates of death and MI greater in women at 30 days, (3.1% vs. 1.8% in men) but equal after 1 year (6.0 vs. 5.8%) (14) (*e*Fig. 8.2.3). Male-female differences in clinical presentation and prognosis are summarized in Table 8.1.



***e*FIGURE 8.2.3** Survival after coronary stenting, with 30-day and 1-year mortality statistics poststenting. *p* = .02 for comparison of men and women at 1 month; *p* = .77 for comparison at 12 months. MI, myocardial infarction. (From Mehilli J, Kastrati A, Dirschinger J, et al. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. *JAMA* 2000;284:1799–1805, with permission.)

	Comparison of W and M
Presentation	
Angina	W > M
Atypical chest pain	W > M
Death from MI	W > M
Sudden death	W > M
Exercise test false-positive	W > M
Angina prognosis for MI	W < M
Consequences	
MI morbidity	W > M
MI morbidity (unadjusted)	W > M
MI mortality (adjusted)	W = to slightly > M
Coronary artery bypass graft mortality	W = to > M
Angioplasty mortality (adjusted and unadjusted)	W > M
Stenting	W ≥ M[a]

MI, myocardial infarction.
[a]W > M at 30 days, W = M at 1 year.

TABLE 8.1 DIFFERENCES IN CARDIOVASCULAR DISEASE PRESENTATION AND OUTCOME IN WOMEN (W) VERSUS MEN (M)

The most important message from the greater morbidity and mortality associated with coronary disease in women is that high priority should be given to early recognition and treatment of risk factors and early ischemic symptoms in women, as well as in men. The other point is that obscure symptoms of fatigue or atypical chest pain should be worked up aggressively for potential coronary ischemia with exercise and performance imaging, particularly when risk factors for coronary artery disease are present and especially when present in combination.

CARDIOVASCULAR DISEASE RISK FACTORS IN WOMEN COMPARED TO MEN

Similarities in risk factor relationships to arteriosclerotic vascular disease in women and men include hypertension and smoking (12). In the Framingham study, smoking was the worst of any single risk factor among male subjects (40) but had less impact among females. However, in a study of 119,404 female nurses, the cardiovascular risk of smoking is clear (41) and may be increasing in severity in recent birth cohorts (42). The interaction of smoking with OC use is also strong (see the section Oral Contraceptive Use and Cardiovascular Disease Risk). Lp(a), fibrinogen, and homocystine all function as risk factors in women, as well as in men (43,44 and 45). Abdominal obesity, weight gain since age 18, and increments in body weight—even at body mass indexes less than 27—are all associated with increased CVD incidence in women (46). Recently, highly sensitive C-reactive protein (CRP) was found to be a stronger single risk factor than any other, including lipids and apoproteins (47). Marital stress (48) and being early in the menstrual cycle (49) are two other risk factors.

Differences between men and women have been identified for the impact of diabetes, plasma triglyceride, and HDL-C on female vascular health. Diabetes confers a greater increment of susceptibility to atherosclerosis in women than men, resulting in diabetic women having an absolute coronary disease rate equalling or

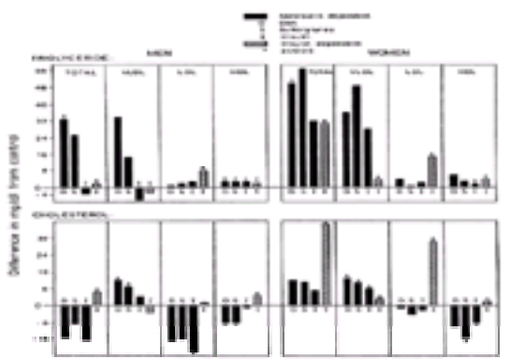
approaching that of men (50,51). The exaggerated diabetic effect on CVD in women is most marked in middle-aged women and attenuates with age (*e*Table 8.1.1), as does the cholesterol effect due to the increased incidence of coronary disease from other causes, especially age (25).

***e*TABLE 8.1.1** CARDIOVASCULAR DISEASE RISK RATIOS FOR DIABETES ACCORDING TO AGE IN A 20-YEAR FOLLOW-UP: FRAMINGHAM STUDY

	Average annual incidence of cardiovascular disease per 1,000			
	Men		**Women**	
Age (yr)	**Diabetic/nondiabetic**	**Risk ratio**	**Diabetic/nondiabetic**	**Risk ratio**
45–54	32/12	2.7	25/4	6.3
55–64	48/25	1.9	38/13	2.9
65–74	58/28	2.1	40/22	1.8
All ages (adjusted)	39/19	2.1	27/10	2.7

From Kannel WB. Cardiovascular sequelae in diabetes. In: Moskowitz J, ed. *Diabetes and atherosclerosis connection*. Rockville, MD: National Heart, Lung, and Blood Institute, 1981:5–15, with permission.

The greater impact of diabetes on CVD in women compared to men is not well understood but may be due to more greatly disturbed lipoprotein levels in the female diabetic than in the male diabetic (50). Specifically, the change experienced by diabetic versus nondiabetic women exceeds that for diabetic versus nondiabetic men for increases in total plasma triglyceride, cholesterol, and LDL-C and reductions in HDL-C (50,52), although insulin deficiency may affect lipoprotein metabolism equally in men and women (*e*Fig. 8.2.4). Whether other effects of gender bear on the atherogenic effects of lipoprotein oxidation and glycoxidation in diabetes requires further study



***e*FIGURE 8.2.4** Lipoprotein lipid changes in diabetic women and men. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein. (From Walden CE, Knopp RH, Wahl PW, et al. Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations. *N Engl J Med* 1984;311:953–959, with permission.)

Total plasma cholesterol relates to heart disease risk differently in women than in men. As shown in *e*Table 8.1.2, the increment in CVD in men from a low- to a high-cholesterol level is nearly tenfold in men aged 35 years but attenuates with increasing age to only 1.2-fold by age 65 years. In women aged 65 years, the increase in CVD risk associated with high cholesterol is twofold, but at an absolute increment similar to men: 2.4% versus 1.9%. This trend persists to old age, where LDL has stronger relative risk in women than men (53). Again, the decline in relative risk of cholesterol is due to the dilution of this effect by the increased rate of CVD with age, more so in men than in women.

***e*TABLE 8.1.2** CORONARY ARTERY DISEASE RISK IN MEN AND WOMEN WITH INCREASING AGE AT LOW VERSUS HIGH CHOLESTEROL LEVELS[a]

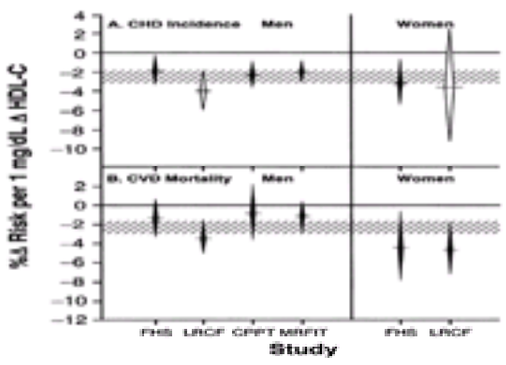
	Men		**Women**	
Age	**185**	**335**	**185**	**335**
35	0.5	4.0	—	—
40	1.2	6.5	—	—
45	2.3	9.3	—	—
50	3.9	11.5	0.8	2.4
55	5.7	12.5	1.3	3.3
60	7.3	11.9	1.9	4.2
65	8.1	10.0	2.6	5.0

Note: Values represent % probability of developing coronary disease in 6 years.
[a]No other risk factors. Based on Framingham—16-year follow-up.
From American Heart Association. *Coronary risk handbook: estimating risk of coronary heart disease in daily practice*. Dallas: American Heart Association, 1973, with permission.

The cluster of risk factors associated with CVD in middle age also differs between men and women. Because women tend to be protected compared to men and have a 10- to 15-year delay in the curve describing the rise in CVD (Fig. 8.1), it follows that for a woman to have coronary disease in middle age, she must have more risk factors or a greater risk burden than a man to experience coronary artery disease, as seen in many studies (14,54). The leading condition embodying multiple risk factors is the metabolic syndrome, also known as the *insulin resistance syndrome* or *syndrome X* (55,56,57 and 58). Along with insulin resistance, abdominal obesity, a propensity to hypertension, overt diabetes, and combined hyperlipidemia characterize this syndrome. Combined hyperlipidemia consists of elevated plasma triglyceride, VLDL-C, intermediate-density lipoprotein cholesterol, LDL-C, small dense LDL, and low HDL-C (56,57). Clotting factor abnormalities are also associated, including elevated factor VII and plasminogen activator inhibitor-1 levels. Thus, in a single entity, four to eight risk factors can be present, affecting approximately 25% of the population.

It is not known if the metabolic syndrome has a greater association with women versus men, but the presence of coronary disease in middle-aged women is highly associated with the metabolic syndrome. For instance, diabetes and hypertension are overrepresented three- and fivefold, respectively, in women with coronary disease compared to women without. In addition, diabetes, hypertension, and hyperlipidemia are present in more women than men with acute MI in virtually every study (14,17,18 and 19,28,29,33,36,37,59,60). In other words, for women to have “premature” coronary disease, they must have a greater number of risk factors; therefore, it is not surprising that the metabolic syndrome is so overrepresented.

The predilection of the metabolic syndrome for coronary disease in women contributes to plasma triglyceride being a stronger risk factor in women than in men—1.8-fold versus 1.2-fold, or even higher (61). Conversely, a reduction in HDL-C is more strongly associated with CVD risk in women than in men, such that a 1-mg-per-dL drop in HDL-C in women is associated with a 3% to 4% increase in coronary artery disease, whereas a 1-mg-per-dL decrease in HDL-C in men is associated with a 2% increment in coronary disease (62) (*e*Fig. 8.2.5). When coronary arteriosclerosis in men and women is graded according to angiographic severity, lipoprotein abnormalities correlating with disease severity in men are total cholesterol, LDL-C, and apoprotein B; in women, the abnormalities are VLDL-C, intermediate-density lipoprotein cholesterol, LDL triglyceride, and low HDL apoprotein (also termed *apoprotein A-I*) (63). Again, it is the combined hyperlipidemia phenotype that seems to predominate as the lipoprotein risk factor in women. The case presented in the introduction to this chapter is a striking and unfortunate example of this association.



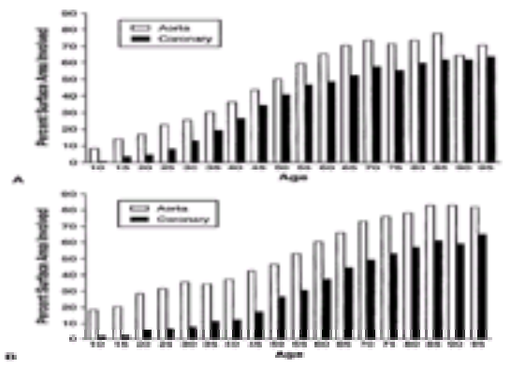
***e*FIGURE 8.2.5** Plots of 95% confidence intervals for the adjusted proportional hazards regression coefficients relating high-density lipoprotein cholesterol (HDL-C) levels to coronary heart disease (CHD) incidence rates **(A)** and cardiovascular disease (CVD) mortality rates **(B)** in Framingham Heart Study (FHS), Lipid Research Clinics Prevalence Mortality Follow-Up Study (LRCF), Lipid Research Clinics Coronary Primary Prevention Trial (CPPT), and Multiple Risk Factor Intervention Trial (MRFIT) participants. The shaded region (~1.9% to ~2.9%) is contained in all 12 confidence intervals. Note that the regression coefficients for LRCF in **(A)** are based on CHD mortality only because nonfatal events were not identified. (From Gordon DJ, Probstfeld JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;79:8–15, with permission.)

Triglyceride should not be rejected as a CVD risk factor because it is overtaken by HDL-C in some multivariate analyses (61). At the very least, triglyceride is a major and easily measured marker for CVD risk in the metabolic syndrome. Second, triglyceride-rich lipoproteins can be found as intact particles in the arterial wall (64). A third point is that regardless of which lipoprotein abnormality one may believe to be important, triglyceride and HDL are highly inversely associated, and treatment of one with lipid-lowering agents helps correct both abnormalities.

PCOS is the earliest manifestation of the metabolic syndrome in the young woman. Such individuals have the plasma lipid profile of combined hyperlipidemia, as described above. Conversely, women with coronary artery disease more frequently have PCOS (65). CVD risk is further aggravated by the excessive secretion of androgen, which attenuates the effect of endogenous estrogen, as discussed in the section Postmenopausal Sex Steroid Hormone Effects on Lipoproteins, Carbohydrate Metabolism, and Clotting.

Two treatments of the insulin resistance syndrome are at hand. Metformin (500 mg b.i.d. for the first week and 1 g b.i.d. thereafter) and the thiazolidinediones rosiglitazone (2 to 8 mg q.d.) and pioglitazone (15 to 45 mg q.d.) are associated with improved insulin sensitivity (even in normoglycemic individuals), a fall in plasma insulin, and a reduction in plasma free testosterone levels in PCOS (66,67). Weight loss is also important in obese individuals with serious CVD risk. The diet and lipid-lowering approach to the management of combined hyperlipidemia in women is discussed in the section Cholesterol-Lowering Interventions and Reductions in Coronary Artery Disease in Women.

A final argument that combined hyperlipidemia in association with insulin resistance syndrome is a major cause of premature coronary disease in middle-aged women is made from the distribution of arteriosclerosis in the vascular tree in women versus men (1,68). As shown in *e*Figure 8.2.6, the increase in arterial surface area affected by arteriosclerosis occurs later in women than in men by approximately 10 years, as does the clinical onset of coronary disease (2), but the distribution of arteriosclerosis in women is greater in the aorta and less in the coronary circulation than in men. The more peripheral distribution of arteriosclerotic vascular disease is typical of patients with diabetes and hypertriglyceridemia—both features of the insulin resistance syndrome.



***e*FIGURE 8.2.6** World Health Organization autopsy data comparing mean percent surface area involved with total atherosclerosis in the abdominal aorta and coronary disease in men **(A)** and women **(B)**. The surface area involved with atherosclerosis in the three coronary arteries has been averaged for comparison with the abdominal aorta. Ages represent a range of 5 years. For example, age 10 represents the age range 10 to 14 years, age 15 represents the age range 15 to 19 years, and so forth. (From Blankenhorn DH, Hodis HN. George Lyman Duff Memorial Lecture. Arterial imaging and atherosclerosis reversal. *Arterioscler Thromb* 1994;14:177–192, with permission.)

In summary, the metabolic syndrome and combined hyperlipidemia are more prevalent in women than in men with arteriosclerosis in middle age. The clinical management point is that treatment should be directed holistically toward the entire metabolic disorder (e.g., insulin resistance, obesity, hypertension, hyperglycemia, dyslipidemia) and not toward a single factor such as elevated LDL, as important as it is (69). Important risk factors in women are listed in Table 8.2.

The metabolic syndrome (syndrome X)
Insulin resistance
Obesity
Hypertension*
Diabetes*
Combined hyperlipidemias
Low high-density lipoprotein cholesterol (<40 mg/dL)*
Polycystic ovary syndrome (amenorrhea, hirsutism, infertility)
Smoking*
Inactivity
Age ≥55 yr*
Familial or polygenic hypercholesterolemia
Homocystine elevations
Family history of premature coronary disease: younger than 55 yr in men and 65 yr in women (first-degree relatives)*
Oral contraceptive use in the presence of other risk factors
Lipoprotein(a)

*Denotes official National Cholesterol Education Program risk factors. See Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497.

TABLE 8.2 RISK FACTORS FOR CARDIOVASCULAR DISEASE IN WOMEN

DIETARY RESPONSE AND CARDIOVASCULAR DISEASE

Some small-scale diet studies suggest that women are less responsive to diet than men. However, a large study from our own clinic indicates that the National Cholesterol Education Program (NCEP) Step II Diet lowers LDL-C equally in men and women, with LDL-C levels above approximately 160 mg per dL (70). On the other hand, HDL-C declined with Step II Diet to a greater extent in women—5% to 6% as compared to 1% to 3% in men after 6 and 12 months of diet—with the greatest reduction in HDL (2), the estrogen-exercise–sensitive portion of HDL (71).

This study indicates that chronic differences exist in the HDL-C response to diet between men and women. The mechanism and significance of the greater HDL-C decrease in women for CVD risk are not known. At this point, the recommendation for dietary intervention in men and women is not different. Nonetheless, in a woman with coronary disease needing dietary and drug management of hyperlipidemia, the greater propensity to HDL-C lowering with diet further reinforces the point that triglyceride and HDL—as well as LDL—be aggressively managed in the at-risk woman. The NCEP Adult Treatment Panel III (ATP-III) guidelines advocate a diet containing 35% of fat as calories rather than <30%, which is less likely to decrease HDL-C (71a).

EFFECTS OF GONADAL STEROIDS ON LIPOPROTEIN METABOLISM AND THEIR CLINICAL SIGNIFICANCE

The effects of estrogens and progestins on lipoprotein metabolism are shown in Figure 8.3. The main point from the illustration is that estrogen enhances the metabolic traffic of cholesterol transport in virtually every pathway except one, raising triglyceride, lowering LDL, and raising HDL, whereas progestins and androgens have the opposite effect (1,72,73). Details of the pathway effects are presented in the online version of this textbook and in the accompanying CD-ROM.

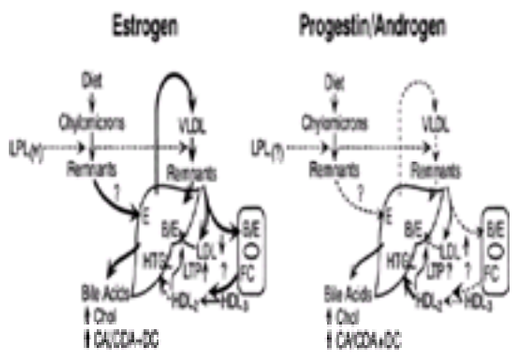


FIGURE 8.3 Effects of sex steroids on lipoprotein metabolism. Width of the lines indicates the rate of cholesterol traffic under the influence of estrogen or progestin/androgen. Question marks indicate effects for which documentation is uncertain or unclear. B/E, low-density lipoprotein receptor; CA, cholic acid; CDA, chenodeoxycholic acid; Chol, cholesterol; DC, deoxycholate; FC, free cholesterol; HDL, high-density lipoprotein; HTGL, hepatic triglyceride lipase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; LTP, leukocyte thromboplastin; VLDL, very-low-density lipoprotein.

Plasma Triglyceride Elevations

Probably the best-recognized effect of estrogen treatment is an increase in plasma triglycerides, one example of which is shown in *e*Table 8.2.1 (74). This effect is great when estrogen is given orally and less when given systemically by injection, patch, or natural ovarian secretion (1,72,73). The increase in plasma triglyceride concentrations is due to an increased hepatic triglyceride secretion in the form of increased entry of VLDL into the circulation. The most extreme, natural, estrogen-dominant condition is pregnancy (75,76).

***e*TABLE 8.2.1** EFFECTS OF 1 µG/KG ETHINYL ESTRADIOL GIVEN DAILY FOR 1 MONTH IN SIX WOMEN FED A HIGH-CHOLESTEROL DIET

	Diet (mg/dL)	**Diet + ethinyl estradiol (mg/dL)**
Triglyceride	98.00	154.0[a]
Cholesterol	255.00	225.0[a]
VLDL cholesterol	14.00	13.0
LDL cholesterol	173.00	130.0[a]
HDL cholesterol	68.00	82.0[a]
HDL(2)	33.00	46.0[a]
HDL(3)	35.00	36.0
Apo E	6.84	4.6[a]
Apo B	125.00	111.0[a]
Apo A-I	155.00	212.0[a]
Apo A-II	34.50	37.5[a]
LPL	125.00[b]	94.0[b]
HTGL	162.00[b]	51.0[a,b]
LCAT	5.40[c]	5.1[c]

Apo, apoprotein; HDL, high-density lipoprotein; HTGL, hepatic triglyceride lipase; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.
[a]$p < .05$.
[b]mmol/min/mL.
[c]ng/mL.
From Applebaum-Bowden D, McLean P, Steinmetz A, et al. Lipoprotein, apolipoprotein and lipolytic enzyme changes following estrogen administration in postmenopausal women. *J Lipid Res* 1989;30:1895–1906, with permission.

Estrogen treatment can interact with diabetes or genetic lipoprotein lipase deficiency to cause a marked exaggeration of hypertriglyceridemia that can result in pancreatitis if levels exceed 2,000 mg per dL. The clinical significance is that women given estrogen, especially postmenopausal estrogen, should be checked first for triglyceride elevations. If plasma triglyceride levels are >300 mg per dL, oral estrogen should be withheld. Patch estrogen can be given postmenopausally in this situation because it has little triglyceride-raising effect in the absence of the hepatic first-pass effect (77). The selective estrogen receptor modulator raloxifene can raise triglyceride in such patients, although not in most postmenopausal women (77).

In contrast to estrogen, androgens and androgenic progestins antagonize the effect of estrogen and tend to lower plasma triglyceride levels. For example, an anabolic steroid such as stanozolol or oxandrolone can be used as a last resort in the management of severe hypertriglyceridemia (>2,000 mg per dL) and recurrent pancreatitis, although undesirable effects on LDL and HDL may result. An example of an anabolic steroid effect is shown in *e*Table 8.2.2 (78).

***e*TABLE 8.2.2** EFFECT OF OXANDROLONE 7.5 MG DAILY IN PLASMA LIPOPROTEINS IN MEN

	Cholesterol (mg/dL)	
	Before	**During**
Very-low-density lipoprotein	65 ± 14[a]	37 ± 9
Low-density lipoprotein	179 ± 15	211 ± 17
High-density lipoprotein	43 ± 3	28 ± 2

[a]Mean ± standard error.
From Olsson AG, Oro L, Rossner S. Effects of oxandrolone on plasma lipoproteins and the intravenous fat tolerance test in man. *Atherosclerosis* 1974;19:337–346, with permission.

Remnant Lipoprotein Metabolism

Remnant lipoproteins are the product of the removal of triglyceride from chylomicrons and VLDL, as pictured in Figure 8.3. Hepatic LDL receptors recognize remnants by the presence of apoprotein E3 or E4 on the surface of the particle. Without this recognition, remnant removal disease, or type III hyperlipidemia, ensues. Because estrogen upregulates the LDL receptor, estrogen may correct remnant removal disease (1,74). Unfortunately, clinical experience indicates that estrogen-using hypertriglyceridemic women may present with remnant removal disease. This apparent discrepancy reflects the dual etiology of type III hyperlipidemia, which involves excessive entry of VLDL into the circulation and impaired remnant removal. Clinicians need to be alert to the possibility that estrogens may improve or aggravate type III hyperlipidemia.

A second step in the remnant removal process is the removal of triglyceride from the remnant by hepatic lipase (1). Hepatic lipase activity is reduced by estrogen (*e*Table 8.2.1 and *e*Table 8.2.3), causing lipoproteins in pregnancy, oral contraception, and postmenopausal hormone replacement to increase in triglyceride content. Clinically, hepatic lipase deficiency looks like remnant removal disease, but estrogen makes it worse, not better. Progestins have the opposite effect to increase hepatic lipase activity—an effect that is associated with increased cardiovascular risk in non–hormone-exposed persons with coronary disease (79).

***e*TABLE 8.2.3** EFFECTS OF FEMALE SEX STEROIDS AND ANDROGENS ON LIPOPROTEIN LEVELS AND METABOLISM

	Estrogen	**Estrogen + progestin**	**Androgen**
Levels			
Triglyceride	↑	=	↓
VLDL-C	↑	=	↓
LDL-C	↓	↑↓	↑
HDL-C	↑	=	↓
Apo A-I	↑	=	↓
Metabolism			
Cholesterol absorption	=	?	?

LPL activity	=↓	?	=↑
Chylomicron remnant clearance	↑?	↑	?↓
VLDL secretion	↑	↓	↓
VLDL remnant clearance			
Hepatic lipase mediated	↓	↑	↑
B/E receptor mediated	↑	↓	↓
LDL formation	↑	?↑	?
LDL removal	↑	↓	↓
HDL transport	↑	↓	↓
LCAT activity	↓	?	?
Hepatic lipase activity	↓	↑	↑
Lipid transfer protein activity	↑	?	?
Lp(a) concentration	↓	=	↓
Nitric acid synthase activity	↑	?	?

Apo A-I, apoprotein A-I; B/E, low-density lipoprotein receptor; HDL-C, high-density lipoprotein cholesterol; LCAT, lecithin-cholesterol acyltransferase; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; VLDL-C, very-low-density lipoprotein cholesterol; =, no change.

Adapted from Knopp RH, Zhu X, Bonet B. Effects of estrogens on lipoprotein metabolism and cardiovascular disease in women. *Atherosclerosis* 1994;110:S83–S91.

Low-Density Lipoprotein Metabolism

Decreased LDL-C concentrations with estrogen treatment are greatest with orally administered estrogen formulations due to increased LDL receptor activity. LDL reduction with patch formulations is due less to the lack of the first pass of estrogen through the liver that is associated with oral hormone administration.

Typical estrogen replacement doses are 0.625 mg of equine estrogen (Premarin) or 17b-estradiol (Estrace) 1 or 2 mg daily, both orally. Typical patch doses are Estraderm or Vivelle, 50 or 100 µg changed every third day; Climara, 50 or 100 µg changed every seventh day; or sublingual Estrace for women with patch sensitivity (see the section Clinical Advice). Costs range from $15 to $25 per month or more. Oral administration of estrogen replacement therapy appears to be preferable to patch or systemic administration for effects on LDL and HDL (see the section Postmenopausal Sex Steroid Hormone Effects on Lipoproteins, Carbohydrate Metabolism, and Clotting). However, oral estrogen can exaggerate hepatic synthesis of many other proteins, including VLDL and clotting factors. Thus, patch estrogen, which mimics the systemic entry of ovarian estrogen, may be preferable.

In contrast to estrogens, high-dose androgens increase LDL-C by diminishing the LDL receptor activity (*e*Table 8.2.2 and *e*Table 8.2.3). If the androgen is testosterone, which is partly converted to estradiol by tissue aromatases, no effect is seen on LDL levels (73).

Lipoprotein(a) Metabolism

Lp(a) is associated with LDL and exaggerates its inherent atherogenicity. Lp(a) is a nonfibrinolytic plasminogen homologue that is carried on LDL apoprotein B, thereby forming Lp(a) (40,43). Estrogen reduces Lp(a) levels in moderate to high doses (72,73). The selective estrogen receptor modulators raloxifene and tamoxifen also lower Lp(a) (72,73,77). Even more paradoxically, Lp(a) also is lowered by androgens (73).

High-Density Lipoprotein Metabolism

A well-known effect of estrogen is to increase plasma HDL cholesterol (HDL-C) concentrations—an example of which is shown in *e*Table 8.2.1. The HDL-C increase is confined to the more buoyant, lipid-rich HDL(2)-C. HDL(3)-C concentrations are unchanged. Because HDL(2)-C is also selectively increased with hygienic measures such as exercise, it was originally thought that HDL(2)-C was the only beneficial fraction of HDL-C. This conclusion no longer appears to be valid, but an increase in HDL(2)-C is associated, nonetheless, with a reduction in CVD risk. The increase in HDL(2)-C concentration is due to an increase in apoprotein A-I secretion from the liver and a reduction in hepatic lipase-mediated uptake of HDL(2)-C and phospholipid—quantitatively the two most important HDL lipids.

Cholesterol from HDL can also be recycled back to LDL and VLDL, where it is made available again to cells by the plasma enzyme that accomplishes this process: lipid transfer protein, which is estrogen dependent. With estrogen also reducing hepatic cholesterol uptake by a decrease in hepatic lipase activity, the overall effect is to enhance cholesterol transport and recycling in the bloodstream (see references 1, 72, and 73 for reviews). The effects of sex hormones on lipoprotein metabolism are summarized in *e*Table 8.2.3.

VASCULAR EFFECTS OF GONADAL STEROIDS

Some animal studies of estrogen effects on lipoprotein levels in plasma show little impact on the extent of atherogenesis and suggest that direct arterial wall effects of estrogen are more important (80). Whether this observation applies to humans is doubtful, but it is clear that estrogen has direct arterial wall effects. These effects include diminished penetration of arterial wall by LDL (80), diminished arterial wall LDL retention (81), and diminished inflammatory response (82) involving a diminished cytokine release and generation of inflammatory response molecules in arterial endothelium and intima-media (see reference 83 for review and Figure 8.4).

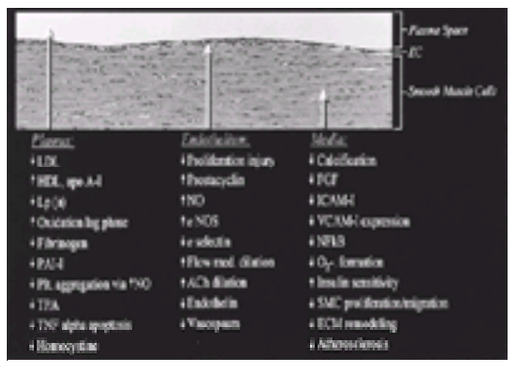


FIGURE 8.4 Beneficial effects of estrogen on arterial wall biology. In this scenario, estrogen-mediated events in plasma, endothelium, and intima-media are beneficial to the arterial wall. ACh, acetylcholine; apo, apoprotein; EC, epidermal cell; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; FGF, fibroblast growth factor; HDL, high-density lipoprotein; ICAM-1, intercellular adhesion molecule-1; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); NFkB, nuclear factor kappa B; NO, nitrous oxide; PAI-1, plasminogen activator inhibitor-1; Plt, platelet; SMC, smooth muscle cell; TNF, tumor necrosis factor; TPA, tissue plasminogen activator; VCAM-1, vascular cell adhesion molecule-1.

Some of these effects may be related to the antioxidant effect of estrogen, a non–receptor-mediated effect of estrogen believed to inhibit atherogenesis (83). Alternatively, estrogen effects may be mediated via genomic or nongenomic effects on estrogen receptors or macrophages and arterial walls (84,85). Importantly, estrogen receptors are found in diminished amounts or are absent in areas of atherosclerosis, which may explain the lack of vascular benefit from estrogen in recent clinical trials (86) (see the section Effects of Postmenopausal Hormone Use on Coronary Disease).

A moment-to-moment effect of estrogen increases endothelial nitric oxide synthase activity, nitric oxide generation, and vasodilation. This effect can reverse the paradoxical vasoconstrictor response to acetylcholine in arteriosclerotic arteries (87) (*e*Table 8.2.3 and Fig. 8.5). In fact, estrogen administration can reverse clinical vasospasm within minutes and may be a useful treatment in cardiologic syndrome X (88,89). Some of this benefit may also be due to the antioxidant effect of estrogen, which may slow the rate of oxidative destruction of endothelial nitric oxide (1,72,88,89 and 90). In addition, estrogen is associated with lower plasma levels of the vasoconstrictor endothelin (91). Surprisingly, testosterone and other androgens also have a vasodilatory effect in healthy arteries that is mediated directly and by an acetylcholine mechanism (92,93).

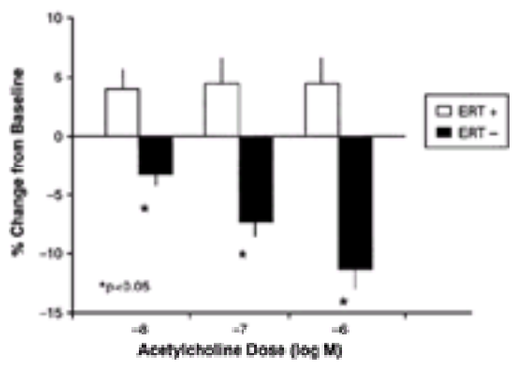


FIGURE 8.5 Mean percent change in coronary diameter after graded doses of acetylcholine. Vertical lines indicate standard error of the mean. Actual *p* values for comparison of estrogen replacement therapy (ERT)+ versus ERT– for each dose of acetylcholine are .03, .001, and .0004, respectively. (From Herrington DM, Braden GA, Williams JK, et al. Endothelial-dependent coronary vasomotor responsiveness in postmenopausal women with and without estrogen replacement therapy. *Am J Cardiol* 1994;73:951–952, with permission.)

Most recently, vasoconstrictive effects of progestins on arterial vasomotion have been reported (94), and medroxyprogesterone acetate (MPA) has been reported to abolish the antiatherosclerotic effect of estrogen in cholesterol-fed monkeys and rats (95,96). Testosterone and one androgenic progestin also promote atherogenesis in cholesterol-fed monkeys (97). We have found that progestins and androgens also have a weak prooxidant effect and oppose the antioxidant effect of estrogen (98).

Another way in which sex hormones affect arterial wall physiology is through the arterial wall–prostaglandin system, which can favor vasoconstriction and platelet aggregation if thromboxane formation is dominant and vasodilation and diminished platelet aggregation if prostacyclin is dominant. Consistent with its effects on nitric oxide metabolism and probably arterial wall redox state, estrogen favors prostacyclin dominance, whereas testosterone favors thromboxane formation, diminishes prostacyclin formation, and enhances platelet thromboxane receptor binding on platelets (see reference 93 for review). Again, the estrogen-androgen antagonism is borne out in another physiologic system.

In summary, ample evidence exists for the presence of estrogen receptors in healthy arterial walls and direct, almost moment-to-moment regulation of endothelial nitric oxide generation, vasomotion, arterial wall LDL penetration and metabolism, and underlying inflammatory response. Whether these effects are all estrogen receptor–mediated is unknown, but the fact that progestin and androgen can oppose some of the effects suggests receptor-mediated mechanisms.

ORAL CONTRACEPTIVE STEROID EFFECTS ON LIPOPROTEIN METABOLISM AND ATHEROGENESIS

The antagonism between estrogenic and progestogenic-androgenic effects on lipoproteins is played out in the three generations of OCs. The first generation contained high doses of estrogens and progestins, of which some were androgenic and some were not. Thus, some OCs were estrogen predominant with high triglyceride, high HDL-C levels, and normal LDL-C levels, whereas the progestin-androgen–dominant form had lower triglyceride, higher LDL-C levels, and lower HDL-C levels, consistent with antagonism of the two hormone classes described above.

The second-generation formulations showed less marked effects on triglyceride, LDL-C levels, and HDL-C levels, although the estrogen-versus progestin-androgen–mediated differences could still be seen. The third-generation pills now in use are associated with normal LDL-C levels and increased HDL-C levels and are believed to be estrogen dominant. As a result, triglyceride elevations of 30% to 40% are still seen. As mentioned above, a tendency to venous thrombosis (99) persists, but diminished risk from arteriosclerosis may be attained (100). In addition, estrogen-progestin balance affects insulin sensitivity and clotting factor levels (101), with estrogen dominance favoring insulin sensitivity and a reduction in plasma fibrinogen levels (101).

The main point is that OC steroids, depending on their composition, can affect several arteriosclerotic risk factor axes. It makes good sense for women taking OCs to have their lipoprotein and glucose levels checked at least once after starting because not all women respond the same, and sometimes the hormone-induced changes in lipoproteins can be marked. It also makes sense for women using OC steroids to manage aggressively concomitant heart disease risk factors.

ORAL CONTRACEPTIVE USE AND CARDIOVASCULAR DISEASE RISK

Shortly after the introduction of oral contraception in the early 1960s, a flurry of reports appeared of venous thrombosis and stroke among OC users. In light of today's experience, the occurrence of venous thrombosis is not surprising because the earliest OCs contained between 100 and 150 µg of ethinyl estradiol, which is approximately 20 to 30 times the postmenopausal replacement amount! Reports of an excess of coronary artery disease among OC users appeared in 1975, in which British epidemiologists found an approximately threefold excess of coronary disease among OC users (102,103). Most importantly, these researchers found that a basic tenet of the risk factor theory of arteriosclerosis applied to women and OC users, with single risk factors increasing coronary disease risk approximately threefold and combinations of risk factors increasing risk geometrically (102,103).

The doses of OC estrogen have declined over the ensuing decades to 20 to 35 µg daily of ethinyl estradiol, which is approximately 1.3 to 2.0 times postmenopausal replacement levels. Even at these doses, venous thrombosis still occurs (100) and may actually be somewhat promoted by the reduced androgenicity of certain third-generation OCs; this androgenicity allows the formulation to be more estrogenic, even though the estrogen dose is unchanged (101). The preferred initial formulations contain 35 µg of ethinyl estradiol and 0.250 mg of norgestimate (Ortho-Cyclen) or 0.250 mg of desogestrel and 30 µg of ethinyl estradiol (Ortho-Cept). The triphasic form of Ortho-Cyclen contains less progestin (0.180, 0.215, and 0.250 mg weekly). Other formulations containing less ethinyl estradiol or stronger progestin can be used—depending on gynecologic symptoms or requirements—such as Alesse 21 or 28 (20 µg ethinyl estradiol and 100 µg levonorgestrel).

Several studies in the mid- and late 1980s have verified the earlier epidemiologic surveys that show that, even with lower estrogen–dose OCs, the risk of coronary disease in a cigarette-smoking OC user is increased approximately 20- to 30-fold from baseline and approximately six- to eightfold above the risk of cigarette smoking alone for coronary disease (104,105). The data of Croft and Hannaford in *e*Table 8.2.4 (105) and Rosenberg et al. in Figure 8.6 are representative of the danger of combinations of risk factors for MI, even in young women (104).

***e*TABLE 8.2.4** RELATIONSHIP OF SMOKING TO MYOCARDIAL INFARCTION (RELATIVE RISK)

	Oral contraceptive use		
	Never	Former	Current
Nonsmokers	1.0	1.1	0.9
<15 cigarettes/d	2.0	1.3	3.5[a]
³15 cigarettes/d	3.3[a]	4.3[a]	20.8[a]

[a] Adapted from Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. *BMJ* 1989;298:165–168.

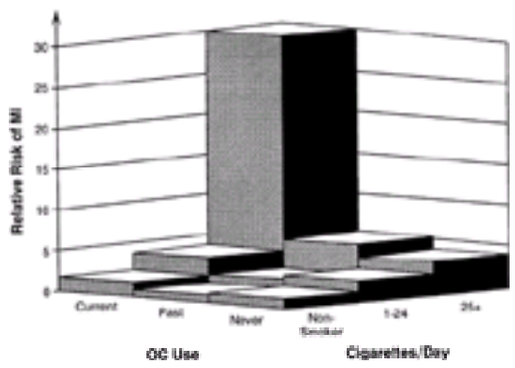
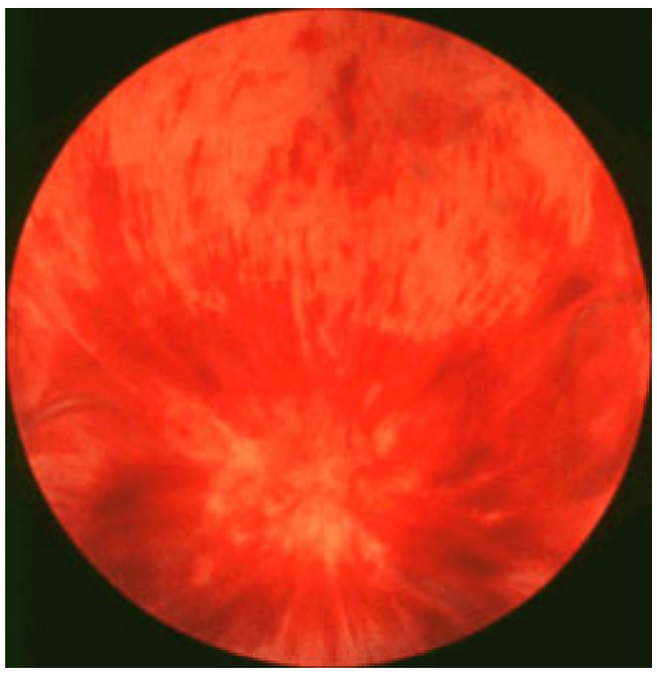


FIGURE 8.6 The effect of smoking and oral contraceptives (OCs) on the risk of myocardial infarction (MI) in women younger than 50 years. (Adapted from Rosenberg L, Kaufman DW, Helmrich S, et al. Myocardial infarction and cigarette smoking in women younger than 50 years of age. *JAMA* 1985;253:2965.)

The pathophysiologic mechanism for the increased risk for CVD with high- and mid-dose estrogen pills, especially with smoking, probably reflects the propensity for thrombosis at a site of arterial wall injury such as an endothelial erosion. Such erosion might arise from a toxic effect of cigarette smoke, smoke-induced depletion of antioxidant defenses, or enhanced LDL oxidation in the absence of major atherosclerosis. On the other hand, arteriosclerotic plaque rupture and thrombosis (106) and advanced arteriosclerotic disease (107) have been reported among OC users; this seems to be the situation in the case presented in the introduction to this chapter.



Retinal vein occlusion. There is severe venous congestion with an extensive exudate. The optic disc is nearly completely obscured.

Young women with high degrees of CVD risk should avoid the use of OCs, especially after the age of 35 years, unless the risk factors can be modified. It is the standard of clinical practice that OCs not be prescribed to cigarette-smoking women who are older than 35 years. A schema that takes this and other risk factors into account as a function of initial LDL-C is presented in *e*Table 8.2.5, which is modeled on the NCEP guidelines (108). The important message is that CVD risk factors must be considered seriously when prescribing OCs and that every woman should have her lipid profile checked when OC use is contemplated and then instituted. CVD risk factors in women are summarized in Table 8.2. Obviously, venous thrombosis due to an estrogen-containing OC is a separate contraindication to continued use of the drug. In the case mentioned in the introduction, the combination of cigarette smoking, OC use, and severe combined hyperlipidemia was nearly lethal, even at age 25 years. Had the patient's lipids been checked before OC use, her high-risk status might have been appreciated.

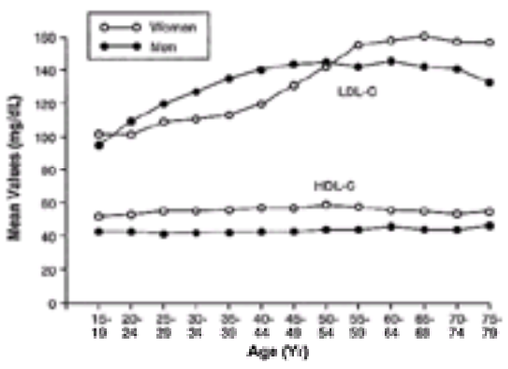
***e*TABLE 8.2.5** SUGGESTED GUIDELINES FOR ORAL CONTRACEPTIVE USE ON THE BASIS OF LDL-C LEVEL, NUMBER OF HEART DISEASE RISK FACTORS, AND AGE[a]

	Risk factors			
	<35 yr		**³35 yr**	
LDL-C (mg/dL)	**0–1**	**³2**	**0–1**	**³2**
<130	Yes	Yes	Yes[a]	Yes[a]
130–159	Yes	Yes with diet	Yes with diet[a]	No
160–190	Yes with diet	No	No	No
>190	No	No	No	No

LDL-C, low-density lipoprotein cholesterol.
[a]By established practice, smoking precludes oral contraceptive use in women older than 35 years.
From Knopp RH, LaRosa J. Burkman R. Contraception and dyslipidemia. *Am J Obstet Gynecol* 1993;168:1994–2004, with permission.

EFFECTS OF HRT ON LIPOPROTEINS

LDL-C levels are higher in postmenopausal women than in younger women—a condition likely due in part to the absence of endogenous estrogen (1,72,73) (*e*Fig. 8.6.1). When women have been studied through menopause and estrogen deficiency develops, the LDL-C level increases by 12.0 mg per dL (0.31 mmol), and HDL-C decreases by 3.5 mg per dL (0.09 mmol) (109). These differences reflect the absence of endogenous ovarian estrogen secretion into the systemic circulation. It is also noteworthy that plasma insulin, glucose, and body weight all increase more in women becoming menopausal than in those not becoming menopausal; this is consistent with a loss of insulin efficacy (discussed earlier).



***e*FIGURE 8.6.1** Lipoprotein cholesterol fractions and age trends in women and men. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. (Adapted from Kannel WB. Nutrition and the occurrence and prevention of cardiovascular disease in the elderly. *Nutr Rev* 1988;46:68–78.)

When hormone users are compared to nonhormone users, estrogen treatment raises the HDL-C level as much as 8 mg per dL (0.2 mmol). Compared to the smaller difference associated with menopause, the greater difference with hormone replacement may be due to higher doses of estrogen or to the oral route of administration. The Postmenopausal Estrogen-Progestin Intervention trial showed a 6-mg-per-dL (0.16-mmol) HDL-C increase above control in women given 0.625 mg of Premarin daily, as shown in *e*Table 8.2.6 (110). Premarin given with MPA (10.0 mg given cyclically or 2.5 mg given continuously) resulted in HDL-C increases to 1.6 and 1.2 mg (0.04 and 0.03 mmol) above baseline, respectively. Most interestingly, when micronized natural progesterone was given cyclically with Premarin, the Premarin effect on HDL-C was almost entirely preserved (5 mg per dL or 0.13 mmol increase above baseline). On the other hand, all of the postmenopausal hormonal formulations examined were associated with reductions in LDL-C concentrations of approximately 14.5 to 17.5 mg per dL (0.37 to 0.45 mmol) without any distinctions among the groups. Finally, the triglyceride elevations were minor, ranging from 11.4 to 13.7 mg per dL (0.13 to 0.15 mmol), and less than the triglyceride elevations associated with oral contraception.

***e*TABLE 8.2.6** RESULTS OF THE POSTMENOPAUSAL ESTROGEN-PROGESTIN INTERVENTION TRIAL[a]

	Change from baseline									
				Glucose (mg/dL)		**IRI (pmol/L)**				
	TG (mg/dL)	**LDL-C (mg/dL)**	**HDL-C (mg/dL)**	**0 h**	**2 h**	**0 h**	**2 h**	**Fibrinogen (mg/dL)**	**Weight (kg)**	**Waist-hip ratio**
Premarin 0.625 mg	13.7	–14.5	5.6	–2.8	2.0	–1.7	–8.0	–20	0.4	0.003
Premarin, micronized Pg (cyclic)	13.4	–14.8	4.3	–2.5	3.0	–3.5	–25.1	1	0.6	0.007
Premarin, Provera 10 (cyclic)	12.7	–17.7	1.6	–2.7	7.5	1.3	13.4	6	0.8	0.010

Premarin, Provera 2.5 (continuous)	11.4	–16.5	1.2	–2.1	6.9	–3.8	1.2	1	0.6	0.007
Placebo	–3.2	–4.1	–1.2	–0.5	–0.1	3.8	–13.7	10	1.3	0.010

HDL-C, high-density lipoprotein cholesterol; IRI, immunoreactive insulin; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
[a]Breast cancer incidence equal among groups (eight total cases) (total, n = 875, ~175/group).
Adapted from The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Intervention Trial. *JAMA* 1995;273:199–208.

In the Postmenopausal Estrogen-Progestin Intervention study (*e*Table 8.2.6), plasma glucose and insulin levels were lowest with estrogen alone and highest with high-dose progestin plus estrogen (110). Thus, the antagonism of estrogen and progestin on carbohydrate metabolism is seen with postmenopausal hormone replacement, as with OC steroids of varied composition.

The estrogen-progestin antagonism is also seen in the levels of clotting factors. Fibrinogen concentration is diminished among postmenopausal estrogen users, as with OC users (101), despite lower doses. Addition of natural progesterone or increasing doses of Provera (MPA) oppose these effects. Although the range of these effects is small, the data indicate that progestins can oppose the effect of estrogen on the clotting system. Recent work from our own laboratory indicates that progestins are prooxidants, opposing the antioxidant and anticytotoxic effects of estrogen (83,98).

An unexpected effect of estrogen—increased CRP levels—has been seen in several studies (111). This increase is said to drive an increase in activity in the complement pathway and favor inflammatory processes (112), and it may explain the strong predictive effect of CRP on atherosclerosis in women (47).

EFFECTS OF POSTMENOPAUSAL HORMONE USE ON CORONARY DISEASE

More than 30 case-controlled and prospective cohort studies have been performed over the last 20 years comparing arteriosclerotic vascular disease in estrogen users versus nonusers (1,72,73,113,114 and 115). These studies indicate that the incidence of coronary artery disease among estrogen users is approximately one-half of that among nonusers. Even before the recent negative clinical trials of estrogen efficacy on heart disease, it was postulated that the putative estrogen benefit was due in part to a “healthy user effect” (i.e., healthier women use estrogen). Barrett-Connor and associates (113) estimated that 50% of the lower rate of coronary artery disease among estrogen users might be ascribed to this selection bias.

Nonetheless, it was a great surprise that the Heart and Estrogen/Progestin Replacement Study (HERS) showed no benefit of equine estrogen (Premarin) 0.625 mg plus MPA (Provera, Cycrin) 2.50 mg continuously versus placebo (116). The results showed a hazard ratio of 0.99 with 95% confidence interval (CI) of 0.80–1.22, p = .91. Various CVD subgroups showed no significant differences with hormone replacement, but the number of subjects with unstable angina tended to be fewer with estrogen, whereas the number of individuals with CHF or cardiac death tended to be greater with estrogen (*e*Table 8.2.7). Because unstable angina involves plaque rupture and nonocclusive thrombus formation, it is hard to argue that the lack of overall benefit from estrogen was due to an enhanced susceptibility to thrombosis. It seems that the sicker or more vulnerable persons were at slightly greater risk from estrogen plus progestin therapy.

***e*TABLE 8.2.7** OUTCOMES BY TREATMENT GROUP AND YEAR SINCE RANDOMIZATION

	Estrogen-progestin		**Placebo**			
Outcome and period	**No.**	**Rates[a]**	**No.**	**Rates[a]**	**RH (95% CI)**	***p* value[b]**
Primary CHD event[c]						
Yr 1	57	42.5	38	28.0	1.52 (1.01–2.29)	.009
Yr 2	47	37.0	48	37.1	1.00 (0.67–1.49)	.009
Yr 3	35	28.8	41	33.1	0.87 (0.55–1.37)	.009
Yr 4 and 5	33	23.0	49	34.4	0.67 (0.43–1.04)	.009
Nonfatal myocardial infarction						
Yr 1	42	31.3	29	21.4	1.47 (0.91–2.36)	.01
Yr 2	34	26.8	37	28.6	0.94 (0.59–1.49)	.01
Yr 3	20	16.5	29	23.4	0.70 (0.40–1.24)	.01
Yr 4 and 5	20	13.9	34	23.9	0.58 (0.34–1.02)	.01
CHD death						
Yr 1	17	12.5	11	8.0	1.56 (0.73–3.32)	.34
Yr 2	19	14.4	13	9.7	1.48 (0.73–2.99)	.34
Yr 3	18	14.0	16	12.3	1.14 (0.58–2.24)	.34
Yr 4 and 5	17	11.0	18	11.6	0.95 (0.49–1.84)	.34

CHD, coronary heart disease; CI, confidence interval; RH, relative hazard.
[a]Event rates per 1,000 women-years in the estrogen plus progestin or placebo group.
[b]p values for tests of continuous trend in log-relative hazard.
[c]Primary CHD events include nonfatal myocardial infarction and CHD death.
From Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progesterone for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605–613, with permission.

Contrary to popularly held view, equine estrogen plus MPA was without benefit over the entire course of the study, particularly concerning CHD death (Fig. 8.7). Only in a secondary hypothesis-generating analysis was a downward trend detected in nonfatal coronary events, but this analysis included an adverse trend of excess nonfatal CHD events in the first year (116). The results of a HERS follow-up study will be reported in late 2001 and will address the questions of whether the downward trend in CHD events among hormone users continued after the conclusion of the main trial. At present, the conclusion is that coronary disease is not prevented by estrogen among older women (average age, 67 years) with established heart disease (116).

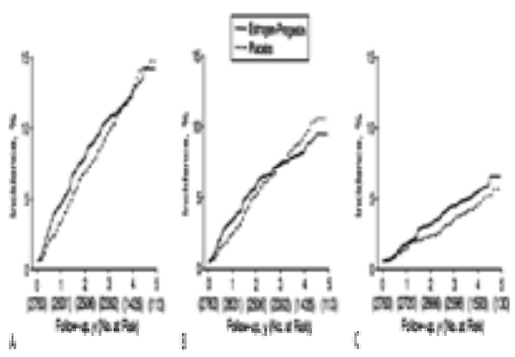


FIGURE 8.7 Heart and Estrogen/Progestin Replacement Study Kaplan-Meier curve estimates of the cumulative incidence of primary coronary heart disease and its constituents. **A:** All events. **B:** Nonfatal events. **C:** Fatal events. Numbers in parentheses are subjects followed to each time-point. Curves are fainter where the sample size falls to less than one-half of the original cohort. (From Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progesterone for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605–613, with permission.)

A similar negative result was observed on angiographically quantified coronary atherosclerosis after 3.2 years in 309 women randomized to placebo, 0.625 mg equine estrogen alone, or with 2.5 mg medroxyprogesterone acetate daily in the Estrogen Replacement Atherosclerosis trial (117). Again, these were women with established coronary disease, with mean ages ranging from 65.6, 66.3, and 65.5 years, respectively, in the three groups. Minimum coronary diameter change and change in percent stenosis were indistinguishable in the equine estrogen and placebo groups and slightly worse with the equine estrogen plus MPA group (Table 8.3).

				p values	
	Placebo	Equine estrogen (E)	E + MPA	E vs. placebo	E + MPA vs. placebo
Minimal coronary diameter adjusted change (mm)	-0.09 ± 0.02	-0.12 ± 0.02	-0.08 ± 0.02	.57	.38
% stenosis adjusted change	4.01 ± 0.52	4.75 ± 0.52	4.11 ± 0.53	.33	.56

MPA, medroxyprogesterone acetate.
[a]Data include all subjects with adjustments for baseline inequalities.
From Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med. 2000;343:522-529, with permission.

TABLE 8.3 EFFECTS OF POSTMENOPAUSAL HORMONE REPLACEMENT ON CORONARY LUMEN DIAMETER[a]

Possible reasons why neither the HERS nor the Estrogen Replacement Atherosclerosis studies were successful are listed in Table 8.4. These reasons range from too high an estrogen dose in older, estrogen-naïve women to an inflammatory effect of CRP. Not listed among these possibilities is an enhanced sensitivity to arterial thrombosis, because unstable coronary syndromes that are thrombotic in nature tended to be *less* frequent in the HERS hormone-treated group. Other possibilities include an adverse effect of progestin. In animal models, MPA completely blocks the cardioprotective effect of estrogen (95,96), and estrogen seems to be without benefit in animals who have been fed cholesterol and have established atherosclerosis (118,119).

The observational case-control and cohort studies are wrong and do not control for the "healthy user" effect (i.e., there may be no real benefit).
C-reactive protein is increased with estrogen and *may activate* complement and inflammatory response.
Estrogen receptors are reduced or absent in arteriosclerotic tissue.
Estrogen prevents atherosclerosis only in early animal models of atherosclerosis and not established disease.
The progestin opposes diverse effects of estrogen, possibly those that may benefit the arterial wall.
Too high an equine estrogen dose was given too late in secondary prevention studies in menopausal women (late 60s).
Estrogen appears to aggravate cardiovascular risk factor effects, whereas "statins" as an example yield extra benefit in women with high risk.
The oral estrogen route induces first pass effects on hepatic protein synthesis, including lipid and clotting effects; this route is not the systemic ovarian route and may actually diminish effective systemic estrogen delivery.

TABLE 8.4 REASONS WHY ESTROGEN MAY NOT PREVENT CORONARY DISEASE IN RANDOMIZED CLINICAL TRIALS

Another argument against arterial thrombosis being a factor in the negative HERS trial results is the rather low occurrence of venous thrombosis in the hormone-treated groups: 25 versus 8 cases in the placebo group and pulmonary embolism in 11 cases in the hormone-treated group versus 4 in the placebo group for totals of 34 and 12, respectively. These totals are well below the 172 and 176 primary CHD events in the two groups, respectively. Whereas these totals are low relative to coronary disease events, the approximately threefold increased rate of venous thrombosis is similar to that reported recently in a number of observational studies of postmenopausal estrogen use (120,121,122 and 123).

Notwithstanding the above data, Psaty et al. have reported association between a prothrombin polymorphism (20210 G→A) and first MI in hormone-treated postmenopausal women who are hypertensive (124). However, the patients are relatively few. Factor V Leiden was not a predictive factor.

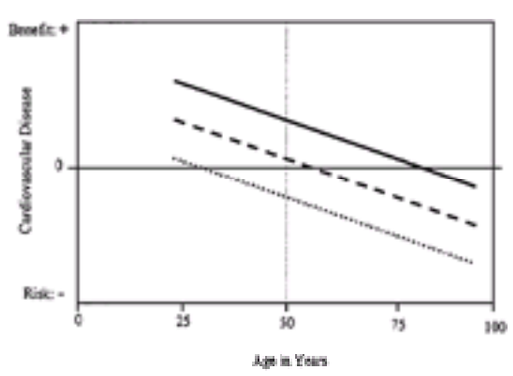
A much longer-term prospective randomized trial of estrogen and estrogen plus progestin replacement therapy is being conducted by the Women's Health Initiative in at least 40 centers nationwide. The larger number of 40,000 to 50,000 subjects is required because of the lower incidence of coronary disease in a primary prevention setting. This study will be reported in approximately 2004.

Clinical Advice

In the meantime, what do we tell patients? It does not seem possible dogmatically to recommend estrogen replacement therapy to prevent existing coronary disease, given the negative results of two prospective randomized trials. On the other hand, many reasons can be given for offering or suggesting estrogen replacement therapy, including sense of well-being, prevention of osteoporosis, preservation of skin turgor, prevention of senility and even Alzheimer's disease (1,72,73), preservation of vaginal mucosa, metabolic benefits (see below), and higher intellectual function (1,72,73). Most women come to this decision aware of at least some of these benefits and some of the side effects and often have their own well-established viewpoint about whether to take estrogen.

As to androgen effects on human atherosclerosis, more than 20 case reports of coronary artery disease have been documented among athletes taking androgen (125). This clinical experience and the atherogenic effects of androgens in animal models provide evidence against the use of excessive or pharmacologic amounts of androgen in young athletes and provides evidence for minimizing the exposure to androgenic progestins in hormone replacement and OC therapy.

The most frequently prescribed dose of postmenopausal estrogen replacement therapy is equine estrogen (Premarin) 0.625 mg daily. Whether generic equine estrogen is equivalent in the 8 to 10 estrogenic steroids of pregnant mares' urine is hotly debated. Occasionally, 0.9 or 1.2 mg daily of equine estrogens is necessary to control hot flashes in women entering menopause. Doses of 2.5 mg daily of equine estrogens have little or no use and may be associated with MI excess, especially in association with cigarette smoking, as found in the Framingham study—one of the few observational studies in which postmenopausal estrogen replacement was associated with an increased rate of coronary artery disease (126). This effect resembles the increase in coronary disease among men given 2.5 or 5.0 mg of equine estrogen in the Coronary Drug Project (127). These data are compatible with the idea that coronary disease is *worse* with high-dose estrogen and major CVD risk factors, as in the OC experience. Thus, one might predict diminished estrogen benefit or even harm with increasing estrogen dose, older age, and multiple CVD risk factors (eFig. 8.7.1).



***e*FIGURE 8.7.1** Postulated benefit or harm of estrogen on cardiovascular disease (CVD) as a function of age and inherent CVD risk. This hypothetical scenario takes into account the possibility that estrogen benefit diminishes with age (142), increased CVD risk (102,103), and high dose of estrogen with risk factors (102,103,126). Solid line, healthy women; dashed line, women with CVD, multiple risk factors, or possibly adverse progestins; dotted line, women with high-dose estrogen and risk factors for CVD.

Alternatives to equine estrogens are pure 17b-estradiol (Estrace), which is given in 1- to 2-mg-per-day doses, or estropipate (Ogen), which is estrone sulfate given in

doses ranging from 0.75, 1.50, or 3.00 mg daily (Ogen: 0.625, 1.250, or 2.50 mg). Ogen does not appear to be quite equivalent to equine estrogen, and doses higher than 0.75 mg daily may be needed to relieve flushing symptoms.

When women have oral intolerance to estrogens or have a metabolic contraindication (chiefly hypertriglyceridemia), then systemically administered estrogen is indicated by one of three routes: patch, injection, or sublingual. There are 3-day patches in the form of 50- or 100-µg doses of Estraderm or Vivelle or 7-day patches of Climara in 50 or 100 µg delivered daily. Most women prefer the longer duration patch, but, often, use is dictated by sensitivity to the patch adhesive. In this respect, Vivelle may be better tolerated. When no patch can be tolerated, sublingual estrogen in the form of Estrace (1 mg) is a viable alternative or 17b-estradiol valerate in oil (10 to 20 mg intramuscularly), although injectable preparations do not yield an even blood level over a month's time. Side effects of estrogen are most typically breast tenderness and, possibly, pelvic fullness. In postmenopausal women, and especially in elderly women, lower doses of estrogen are advisable to start (e.g., 0.3 mg of equine estrogen daily or every other day) to avoid these symptoms. Another advantage of patch estrogen is that a higher systemic dose can be obtained with better control of symptoms than the oral route, in which hepatic inactivation can limit symptom control.

Estrogen can be used without a progestin only in women without uteri. All other women require progestin in some form. The most popular form is 2.5 mg of MPA (Provera, Cycrin, or the combination formulation Prempro) given continually. This regimen is associated with vaginal spotting and bleeding in more than 50% of users during the first months of treatment and does not decline to a few percent until after 24 to 36 months of use. The unpredictability of this bleeding is the most troublesome aspect for older women. Cyclic progestin given 12 days out of each month can produce vaginal bleeding on a predictable basis in approximately 50% of the women who resume bleeding, but most women do not want this regimen, and the higher MPA doses of 5 and 10 mg daily have deleterious metabolic effects, as described above. Micronized natural progesterone taken cyclically in doses of 100 to 200 mg daily is an alternative form, as are 1 mg micronized 17b-estradiol with norgestimate (Ortho-Prefest) and 5 mg ethinyl estradiol with 1 mg norethindrone acetate (Femhrt)—a more androgenic progestin.

Side effects of progestins are not negligible and include weight gain, fluid retention, headache, and symptoms resembling premenstrual tension. Fortunately, most women are not bothered by these symptoms, but they can be virtually incapacitating when these symptoms are present. Oral progestin can be given with estrogen by any route. An alternative to oral progestin is Depo-Provera administered intramuscularly.

DEHYDROEPIANDROSTERONE

The adrenal and ovarian androgen precursor dehydroepiandrosterone (DHEA) has a divergent association with arteriosclerotic disease, depending on gender. In men, it has been shown that DHEA levels decline with age and are lower in subjects prone to coronary artery disease (128). On the other hand, female subjects with higher DHEA levels are obese and have overproduction of testosterone by the ovary, insulin resistance, and PCOS (65,66,129)—all markers of increased CVD risk in women. At the very least, in female subjects, DHEA seems to be a marker of the insulin resistance syndrome, which is associated with ovarian dysfunction, or it could be a risk factor in its own right as an androgen precursor. In contrast, DHEA may actually be beneficial to male subjects. When DHEA is given to animal models fed cholesterol, it prevents arteriosclerotic progression (73).

The clinical implication of these observations is that DHEA may protect against arteriosclerosis, at least in men. However, this hypothesis requires much more research and does not justify the almost black-market commerce in DHEA use.

CHOLESTEROL-LOWERING INTERVENTIONS AND REDUCTIONS IN CORONARY ARTERY DISEASE IN WOMEN

Diet

As mentioned earlier, some studies have found a diminished effect of diet on LDL-C and HDL-C levels in women compared to men. However, in a recent study of the largest group of free-living men and women studied to date, LDL-C lowering was equivalent in men and women, but the HDL-C lowering was greater in women (6% to 7%) than in men (1% to 3%)—even after 6 to 12 months, when the acute HDL-lowering effects of diet had worn off (70,71). These percentage differences are small in the aggregate but could be meaningful for atherosclerotic risk among individuals with marked HDL-C reductions. Monounsaturated fat supplementation is under investigation as a means to minimize this HDL-C decrease. The new NCEP guidelines favor a 35% fat diet, with only saturated fat restriction (71a).

Drug Therapy Efficacy

LDL-C reductions are at least as good in women as in men with heterozygous familial hypercholesterolemia treated with reductase inhibitor, niacin, and bile acid–binding resin. In the author's clinical experience, familial hypercholesterolemic women are more often successfully managed with single lipid-lowering agents (almost always reductase inhibitors) than are men, who often require combination therapy. The better response in women is not understood but could relate to lesser body mass.

Arteriosclerosis Prevention and Regression

In keeping with the usually good response of women to lipid-lowering drugs and equivalent LDL-C response to diet, studies of angiographic regression and heart disease prevention also show better responses in women than in men. In the SCOR study, the angiographic response of coronary arteries to lipid lowering in familial hypercholesterolemic women and men was analyzed in response to combination therapy (9). At baseline, the mean percent coronary artery stenosis was approximately 48% in women and 55% in men at equivalent ages (40 to 43 years), reflecting the later onset of disease in women. The angiographic improvement after several years of triple-drug therapy (reductase, resin, and niacin) was also greater in women (–2.1%) compared to men (–0.9%) (negative signs connote vessel enlargement). These were the first data to show that lipid-lowering treatments were as good as or better in women compared to men in attaining angiographic arteriosclerosis regression.

The prevention of clinical manifestations of coronary disease in men and women in the recent CARE study confirm and extend the angiographic study (130). In this investigation, a greater percentage of reduction in coronary artery disease was observed in women (46%) compared to men (20%) at equivalent doses (40 mg daily) of the reductase inhibitor pravastatin. The better preventive effect in women may be related to a less advanced stage of disease, to a greater LDL-C reduction, to a fixed reductase inhibitor dose, or to other inherent biologic differences. It is known that arteriosclerotic plaques in women are less fibrotic and contain more lipid-filled foam cells (131), implying greater potential for reversibility but also potentially greater vulnerability for plaque rupture and thrombosis. The main point is that impaired responsiveness to therapy cannot be used as a reason not to treat women at high risk for arteriosclerotic vascular disease.

Lipid Screening Guidelines for Hyperlipidemic Women

Based on the lack of association between coronary artery disease mortality and total plasma cholesterol levels in pooled epidemiologic surveys and the low CVD mortality rates of women before the menopause (132), it has been recommended by some that cholesterol screening not be done in premenopausal women unless a family history of coronary artery disease is present (133). In keeping with the lower expectation of coronary disease events and mortality, the previous NCEP recommendation was that premenopausal women be treated with lipid-lowering agents only if the LDL-C is >220 mg per dL, which means usually that only women with heterozygous familial hypercholesterolemia are candidates for treatment before menopause. Fortunately, the ATP-III guidelines remove this language (71a).

Additional factors must be kept in mind regarding the above guidelines. With respect to screening, other issues are in play besides CVD risk in women. One needs to know whether plasma triglyceride levels are elevated in the context of using sex hormones—either for oral contraception in the reproductive years or for therapy as ovarian function wanes, even before the menopause. In addition, combined hyperlipidemia is a real threat for coronary disease in middle-aged women (see the section Cardiovascular Disease Risk Factors in Women Compared to Men). This condition is now prominently addressed in the NCEP ATP-III guidelines (71a). Finally, it seems that knowing one's lipid profile is an important piece of basic health information that can influence one's health practices such as diet and exercise. Given these arguments, a triglyceride cholesterol, HDL-C, and calculated LDL-C measurement seems as reasonable to obtain as a hematocrit, urinalysis, blood pressure, or physical examination and is appropriate for all general health evaluations. Fortunately, the ATP-III guidelines recommend a full lipid panel in all initial screenings (71a).

Lipid-Lowering Treatment Guidelines

The NCEP guidelines for lipid lowering specify that risk factors apply equally for men and women—except for family history, in which, in contrast to men younger than 55 years, CVD under age 65 in a female relative is considered to be premature and a risk factor (71a). Likewise, age as a risk factor is later in women (age 55 years) than in men (age 45 years). Formerly, male gender was a risk factor at any age, but this guideline no longer applies. Finally, an unwritten difference exists in the application of the HDL-C <40 mg per dL rule as a risk factor. Because women have a mean HDL-C of approximately 55 mg per dL and men have a mean HDL-C of 45 mg per dL, fewer women qualify for low HDL-C as a risk factor than men. Similarly, more women qualify for subtracting one risk factor on the basis of HDL-C >60 mg per dL, yielding a significant number of women in population surveys (especially premenopausally) having a risk factor total of –1. Otherwise, the less than 160-, 130-,

and 100-mg-per-dL LDL-C target values apply equally to men and women, with the gender differences in risk being embodied in the risk factor assessments.

Gender Differences in Drug Treatment

Bile Acid–Binding Resin

Most patients object to the gustatory, upper gastrointestinal, and constipating side effects of bile acid–binding resin. Based on common sense, perhaps the most important point to keep in mind is that when resin is necessary, lower doses might be tried in women compared to men because of a woman's smaller size. Bile acid–binding resin tablets in the form of colestipol, although large, offer a somewhat more palatable alternative (1 capsule = 1 gm, 4 capsules = one scoop or packet). Recently, colesevelam (WelChol) has become available, which is the first well-tolerated, high-affinity bile acid–binding resin.

Niacin

In addition to the usual flushing, side effects of niacin include acanthosis nigricans, ichthyosis, thickening of the skin, and, more subtly, winter dryness. Most of these skin symptoms are more poorly tolerated in women than in men. Apart from scrubbing with pumice, there is no good solution except to tailor the dose to the level of tolerable side effects. Clinical experience indicates that lower doses of 1 to 2 gm daily are worthwhile because a beneficial effect on HDL and triglyceride levels can still be obtained at these doses, whereas the need for LDL-C lowering can be met by adding reductase inhibitor agents in combination. The tendency for plasma glucose levels to rise with niacin therapy does not have a known gender specificity, nor does it have a direct deleterious effect unless it provokes frank diabetes (134).

Fibric Acid Derivatives

Fibric acid derivatives are almost essential in the management of hypertriglyceridemia associated pancreatitis (>1,000 to 2,000 mg per dL). Whether these agents cause cancer in humans is moot in male subjects, and studies in women are lacking. More clear is the tendency of all fibrates to increase gallbladder bile saturation with cholesterol and cause gallstones (134). Because overweight, middle-aged women are more prone to this condition, gallstone disease from fibrate use adds to the reasons to try to find other approaches to high-triglyceride management, which includes weight-loss agents, insulin-sensitivity improvers such as metformin, and weak triglyceride lowerers such as fish oil and a low-fat diet.

Reductase Inhibitors

The largest available study of a reductase inhibitor is the Excel study of lovastatin. Results show a greater degree of lipid lowering in older women (135). As higher doses of reductases are being recommended (134), it may be anticipated that more hepatotoxicity and myotoxicity may occur in women because of their smaller body mass relative to dose than that of men. However, high-dose therapy may not be as necessary in women compared with men.

Reductase and Fibrate Combination Therapy

Myotoxicity is more common among women with impaired renal function who take the combination of gemfibrozil and lovastatin than among men (136). Clofibrate alone is highly myotoxic in renal failure because of its renal elimination. It is no longer manufactured. Gemfibrozil seems less so, but it can also produce myotoxicity under the conditions described above and with the additional potential for rhabdomyolysis and acute renal failure (136).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Postmenopausal Hormone Replacement Therapy

The view is still held by some that all women should be placed on sex hormone replacement therapy postmenopausally and, conceivably, supplemental estrogen premenopausally. Those who hold this view argue that the lipoprotein effects, the direct arterial wall effects, the antioxidant effects, the benefit on vasomotion, and the epidemiologic surveys are sufficient information and that the proposed cardiologic benefit is so great that side effects, some of which could be fatal, such as pulmonary embolism, can be ignored. This line of reasoning is flawed because, according to epidemiologic surveys, the benefit of estrogen may be overestimated by 50% due to the healthy user effect (113), side effects may possibly be underestimated, and clinical trials in women with advanced coronary disease do not show benefit. Younger women may benefit. The take-home message is that estrogen currently cannot be prescribed for CVD prevention with any assurance, especially in women with coronary disease. Nonetheless, I certainly prescribe hormone replacement to women for specific noncardiovascular indications, which are many.

When counseling patients, I tell them what I know, but I also listen to their concerns, fears, and family history, especially when it involves ovarian and breast cancer, venous thrombosis, and heart disease. If a patient declines to use postmenopausal hormone replacement therapy, she may be making the right decision for her! If hormone replacement therapy is initiated, it must be in conjunction with annual gynecologic evaluation, breast examination, and mammography.

Oral Contraceptives and Vascular Health

Over the years, the argument has raged over whether "undesirable" lipoprotein effects of androgenic progestin-dominant OCs have any material effect on the arterial wall. Given the absence of any arteriosclerotic carryover effect of prior OC use on subsequent risk for arteriosclerotic vascular disease, the possible deleterious effects of the progestin have been dismissed, especially in light of animal studies that show no arteriosclerotic effect in conjunction with estrogen administration (72). The reservations about this point of view are as follows: the monkey studies may not apply to humans, and the older, high-estrogen–dose OCs may have been sufficiently estrogen dominant to overcome any arterial wall progestogenic effect. We must recognize that our understanding of the interaction between estrogen and progestin in OCs and metabolic and vascular physiology is developing, as is our understanding of postmenopausal hormone replacement effects. For now, the clinical message is to minimize the estrogen exposure, the androgenicity of the progestin, and the presence of concomitant risk factors. In this context, not measuring a young woman's cholesterol because CVD mortality is not high enough to justify the expense (132,133) overlooks a vast area of biology and pharmacology that is pertinent to women's health. Greater refinement of our knowledge of new third-generation OC effects on vascular health is needed to secure the possibility that these OCs may be noninjurious and even beneficial to the arterial wall.

Future Directions

Clinical trials currently under way will better define the effects of postmenopausal hormone replacement therapy on cardiovascular health in healthy postmenopausal women without heart disease. We can also expect future development of estrogenic compounds that have hybrid or chimeric effects of estrogen and progestin or that only act on certain, but not all, estrogen-sensitive systems (e.g., the selective estrogen receptor modulators). A heart disease prevention study of one of these agents, raloxifene (Evista; 60 mg q.d.), is under way in high-risk women. These specific therapies may eventually be directed to the arterial wall or bone, for instance, without effects on clotting, hepatic lipoprotein production, or breast metaplasia. Knowledge is also developing rapidly in understanding the postreceptor signaling system of the estrogen receptor (137) and the specificities it entails that may eventually be used for pharmacologic benefit.

Female-Male Cardiovascular Disease Issues

As is apparent from the foregoing text, the epidemiology, management, risk predictors, and subsequent morbidities of CVD are incompletely distinguished in women compared to men. Although better descriptions are constantly appearing (17,36,37 and 38), we will never discover a better way to treat CVD in females without listening to and looking for the ways that early CVD presents differently in women than in men. In this regard, the basic skills of the practitioner must be joined with those of the epidemiologist, the clinical trialist, and the clinical and basic researchers to carry this field forward.

CONCLUSIONS

CVD can occur in women of all ages, depending on risk factor burden. The insulin resistance syndrome (syndrome X) appears to be more important as a risk factor in women than in men. Triglyceride and HDL levels are more important in women than in men until late in life, when the relationships are reversed. Because almost every category of CVD carries worse morbidity and mortality in women compared to men, it seems very important to use every means at hand to prevent its occurrence. The interplay of estrogen and progestin bears on this issue in all stages of life and has to be considered, along with all other cardiovascular therapies.

In general, estrogen at replacement hormone–dose levels is associated with a favorable effect on lipoprotein metabolism, arterial wall penetration of LDL, insulin

sensitivity, and plasma glucose concentrations; some clotting factors and progestins oppose these effects (138,139,140 and 141). The best available information from clinical trials is that estrogen is without cardiovascular benefit in women with established heart disease. It remains to be seen if estrogen or its selective estrogen receptor modulator relatives will have benefit in a primary prevention setting in younger women or those without heart disease.

Caution is also advised for clinicians giving estrogen in any case in which the patient has underlying hypertriglyceridemia or a history of thrombosis. Should hypertriglyceridemia result from estrogen administration or if the patient has a baseline plasma triglyceride level >300 mg per dL (3.38 mmol), an estrogen-patch regimen should be used as an alternative.

With the recent growth in understanding of the effects of sex steroid hormones on many body functions and of the many differences between the genders in arterial physiology and pathophysiology, there is an excellent prospect that this knowledge can be used to minimize coronary disease in both men and women if the undesirable side effects can be avoided.

THE FUTURE

The following statements are as much hopes as predictions. First, physicians and caregivers will remember that coronary disease and arteriosclerotic vascular disease are the most prevalent causes of death in women as well as in men but that the symptomatologies and presentations are likely to differ. Second, physicians and caregivers will have the patience to let patients tell us the story as they see it, so that we can better appreciate and describe the male-female difference and treat appropriately. The third expectation is that ongoing clinical trials will further refine the nature and extent of the heightened vulnerability of women for certain morbidities associated with coronary disease. The fourth expectation is that we will learn the reasons for these excessive morbidities and find better ways to prevent and treat them. The fifth hope is that caregivers will recognize that treatable CVD risk factors—especially hypertension, diabetes, and, in all probability, syndrome X with its associated dyslipidemia—are consistently more common among women with CVD than among men. The sixth expectation is that we will learn to use metabolic treatments more effectively and in combination to treat these risk factors. These treatments will include use of antihypertensives without adverse metabolic effect, agents to minimize insulin resistance, cautious use of existing and forthcoming appetite suppressants, and more informed, target-oriented treatment of diabetes and dyslipidemia. Treatments will also include management of female hyperandrogenic states premenopausally and hormone replacement postmenopausally, avoiding or minimizing the androgenic side effects of certain progestational agents. The future of hormone therapy of arteriosclerotic vascular disease may include the use of chimeric agents combining estrogenic and progestogenic effects and estrogens that are selective for specific tissues and organs. Seventh, women and men should be treated aggressively with lipid-lowering agents to target (while awaiting resolution of) the estrogen–heart disease enigma.

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9

ETHANOL AND THE HEART

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The influence of ethanol on the cardiovascular system generally has been attributed to its toxic action rather than to malnutrition. Whereas many individuals addicted to ethanol have subclinical diastolic dysfunction presumably related to interstitial fibrosis of the myocardium, a minority goes on to develop symptomatic cardiac problems such as heart failure and arrhythmias. In addition to supraventricular arrhythmias that often normalize spontaneously, there is an increased incidence of sudden death that apparently peaks at approximately 50 years of age in the alcoholic population. The combined use of tobacco and alcohol increases the risk of many of these clinical abnormalities. A significant degree of blood pressure elevation occurs in individuals who abuse alcohol. This tends to be transient and is normalized in most individuals during abstinence from alcohol. In addition to these risks, there is also a preventive effect of mild to moderate drinking on coronary heart disease.

GLOSSARY

Alcoholism: a disorder characterized by a pathologic pattern of alcohol use and resulting in serious impairment of social and occupational functioning.

Holiday heart: an acute arrhythmic process that appears after an episode of heavy drinking.

Light alcohol consumption: one to two drinks per day in women, two to three drinks per day in men.

PERSONAL PERSPECTIVES

Recent decades have seen a growing public awareness of the multiple negative consequences associated with excess intake of ethyl alcohol. Moreover, there has been some progress in the long-term management of this addiction. At the other end of the spectrum is the realization from multiple studies that low-dose alcohol intake can have positive effects in terms of prevention of cardiovascular disease in middle age and beyond.

HISTORICAL PERSPECTIVE

During the 1860s, controversy existed among members of the British medical profession on the therapeutic effects of alcohol, which had a prominent place in medical practice at the time. The debate focused mainly on the scientific basis that would support this practice (1). During the same period, new investigations called attention to the potential toxic effect of alcohol on the heart. Early studies in the nineteenth century demonstrated a relationship between excessive consumption of beer and the presence of cardiomegaly at autopsy (2). Clinical heart disease related to ethanol abuse was later described in the British medical literature (3). Since then, ethanol has been recognized as a toxic agent affecting different organ functions, both acutely and chronically.

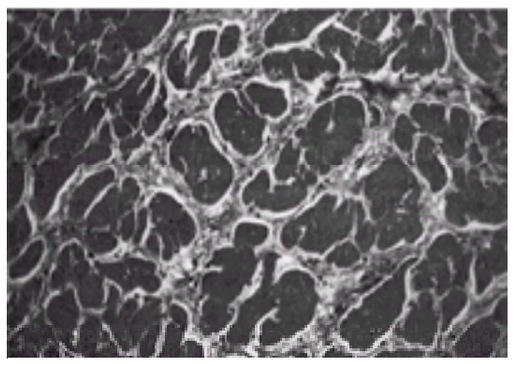
The discovery of the beriberi heart syndrome drew attention to the role of thiamine deficiency as an underlying factor in alcoholic heart disease. Diminished thiamine intake was common among alcoholics in a period when vitamin supplementation was uncommon. Since the middle part of the twentieth century, this confusion between the direct effects of alcohol and the effects of nutritional deficiency has been reduced by evidence of the direct deleterious effects of alcohol on the heart. Numerous studies performed during the late 1960s and early 1970s have confirmed the role of ethanol in the genesis of low-output heart failure, as opposed to the high cardiac output of wet beriberi (4,5). There is persistent controversy, however, about the roles that concomitant risk factors (e.g., tobacco) and lack of trace elements have in the development of cardiac abnormalities.

Recently, epidemiologic studies have reported beneficial effects of light to moderate alcohol consumption on cardiovascular risk. However, further evidence is required to recommend the use of alcohol as a general health policy.

ANATOMY

Specimens from autopsies and biopsies of alcoholic hearts have shown varying degrees of morphologic abnormalities, depending on the stage and progression of the disease. During the preclinical phase, left ventricular mass may be normal or moderately enhanced due to increased wall thickness. With progression of the disease, varying degrees of cardiomegaly reflecting chamber dilatation are seen, particularly when there is concomitant mitral insufficiency as part of the cardiomyopathic picture. On gross observation, the heart appears flabby, large, and pale.

Microscopic characteristics found in alcoholic hearts include focal and diffuse interstitial fibrosis, myocytolysis, and cardiac myocyte hypertrophy (6) (*e*Fig. 9.0.1). On electron microscopy, the sarcoplasmic reticula are dilated, and the mitochondria are swollen with fragmentation of the cristae and deposition of glycogen-filled vacuoles (*e*Fig. 9.0.2). Replacement fibrosis and loss of myofibrils appear with disease progression.



***e*FIGURE 9.0.1** Trichrome stain of left ventricular myocardium in a chronic alcoholic with heart disease (× 100).

***e*FIGURE 9.0.2** Electronic microscopy from the left ventricular myocardium of a long-term alcoholic animal highlights the dilatation of the sarcoplasmic reticulum. The mitochondria appear to be within normal limits. There is a diffuse distribution of glycogen particles. (From Regan TJ, Thomas G, Haider B, et al. Progression of myocardial abnormalities in experimental alcoholism. *Am J Cardiol* 1980;46:233, with permission.)

The degree of coronary atherosclerosis among these patients tends to be minimal. However, microscopic studies may show significant changes at the level of the microvasculature. The alterations noted in the microvascular compartment are, in order of frequency, vascular edema, perivascular fibrosis, vascular sclerosis, and subendothelial humps (7). These changes have prompted some investigators to consider chronic ischemia as a triggering factor in the development of this process, although histologic evidence of ischemia in tissue perfused by the abnormal vasculature has not been described.

PATHOPHYSIOLOGY

Acute ingestion of ethanol is responsible for a direct negative inotropic effect due to diminished ventricular contractile force. A modest increase in heart rate is commonly observed secondary to increased autonomic activity (8). Because these actions of ethanol tend to have opposing effects, evidence of direct acute damage from alcohol can be minimal in healthy individuals or asymptomatic alcoholics. However, clear demonstration of diminished contractility secondary to acute ingestion of alcohol has been shown in human and animal models under conditions of autonomic blockade (8,9 and 10).

The hemodynamic changes that alcohol produces are of greater clinical significance in the chronic user, especially in those with underlying cardiac disease. A potential morphologic basis for the increased diastolic stiffness observed early in the alcoholic heart is related to the accumulation of myocardial collagen in the extracellular matrix. Collagen accumulation has been associated with greater intermolecular cross-links, translating into an increased diastolic stiffness of the ventricle. Staining with Alcian blue shows the deposition of glycoprotein-like material in the interstitium of the ventricular wall (Fig. 9.1). The role of ethanol in the accumulation of collagen can be enhanced by the use of tobacco (11), which is commonly a coaddiction.

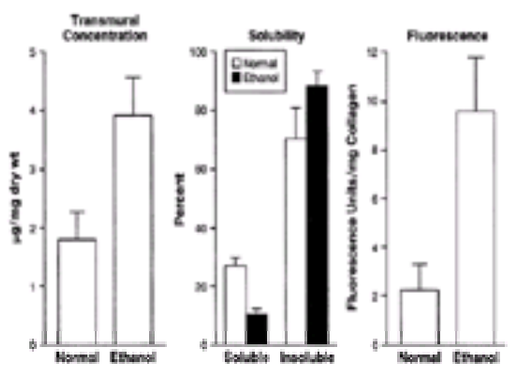
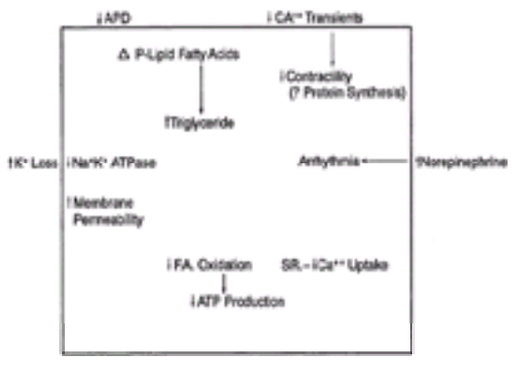


FIGURE 9.1 Differences in the concentration and solubility of collagen found in left ventricular muscle in comparison of healthy and ethanol-fed animals.

Whereas multiple biochemical mechanisms are altered, the specific pathways involved in clinical events are a matter of debate. Several steps in the excitation-contraction coupling system have been found to be acutely affected by ethanol: reduced capacity of the sarcoplasmic reticulum to accumulate calcium, direct inhibition of the interaction of actin and myosin, and an inhibition of the adenosine triphosphate–dependent Na^+/K^+ pump in the sarcolemma. A reduction of the respiratory ratio in mitochondria has also been described (12). Moreover, the synthesis of cell protein can be significantly reduced, thus suggesting that the appearance of hypertrophy must involve reduced protein degradation.

Ethanol is metabolized to other compounds with concomitant adverse effects on cardiac contractility. Acetaldehyde in high concentrations decreases the action potential of muscle fibers and inhibits the Na^+/K^+ adenosine triphosphatase activity. Abnormal fatty acids derived from ethanol, such as ethyl esters, can decrease mitochondrial activity in the affected cells (*e*Fig. 9.1.1). Phospholipase D catalyzes a transphosphatidylation between ethanol and natural phospholipids present in the myocardium, resulting in the formation of phosphatidyl ethanol, a compound that disrupts the properties of biologic membranes.



***e*FIGURE 9.1.1** Mechanism of action of ethanol and its metabolites on the cardiac cells. APD, action potential duration; ATP, adenosine triphosphate; ATPase,

adenosine triphosphatase; FA, fatty acids; SR, sarcoplasmic reticulum.

Electrolyte abnormalities are a common feature in the alcoholic patient, particularly hypomagnesemia, hypokalemia, and abnormal levels of selenium and cobalt. Changes in magnesium level are due to decreased intestinal absorption and increased renal excretion by a direct effect of ethanol on tubular reabsorption (13). Experimentally, the cardiac abnormalities seen in rats fed a low-magnesium diet are similar to those observed in alcoholic animals. Microscopic changes found in these specimens are mainly mitochondrial damage and myofiber degradation (13,14). Deficiency of the trace metal selenium can be observed in alcoholics. Selenium is known to be an essential component of glutathione peroxidase (15)—an enzyme considered to prevent oxidative cellular damage. A deficit of selenium may play a role in the enhancement of myocardial damage caused by ethanol toxicity.

Some beverage additives have been considered to play a role in the development of alcoholic cardiac disease. In the mid-1960s, outbreaks of an acute and fulminant form of cardiomyopathy were described among heavy beer drinkers (16,17). Cobalt chloride had been added to the beer as a foam stabilizer and was suspected to be the agent responsible for this presentation. Studies of the addition of cobalt salts failed to reproduce these manifestations (18), so it was hypothesized that concomitant nutritional deficiencies were required for the appearance of cardiac abnormalities secondary to cobalt. Alterations in the quality of protein intake may play a role, because amino acids such as cysteine decrease the uptake of cobalt ions by the myocardium. Lead has also been implicated in the pathogenesis of cardiac disease observed in “moonshine drinkers” (19). This effect has been shown in animals fed a combination of alcohol and lead: significant mitochondrial changes were seen in rats receiving this diet (20).

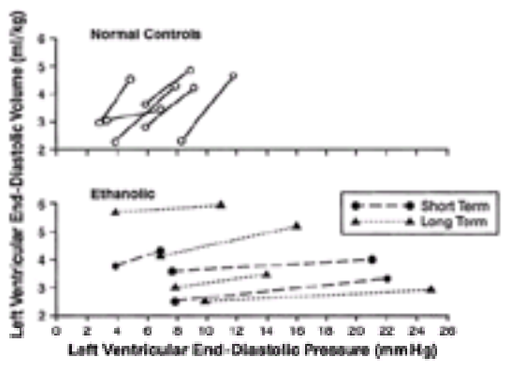
EPIDEMIOLOGY

Two-thirds of the population of the United States consume alcohol, and approximately 10% of these are considered heavy users. Among the identifiable etiologies of nonischemic dilated cardiomyopathy, alcohol is the most common in industrialized countries, accounting for almost half of those diagnosed at autopsy. Prevalence of alcohol consumption differs between genders; however, the risk of alcoholic cardiomyopathy is greater in women than in men.

CLINICAL PRESENTATION

Subclinical Cardiomyopathy

The development of cardiomyopathy is time dependent, with an early period characterized by a lack of symptoms or signs of disease. Evidence of early diastolic dysfunction has been demonstrated as an abnormal increase in left ventricular filling pressure during afterload increments (eFig. 9.1.2).



***e*FIGURE 9.1.2** Left ventricular response to saline in alcoholic and healthy individuals with no evidence of cardiac disease. Alcoholics exhibit a threefold increase in left ventricular end diastolic pressure with minimal stroke output increase. (From Regan TJ, Khan MI, Ettiger PO, et al. *J Clin Invest* 1974;54:740, with permission.)

Noninvasive methods have also demonstrated the existence of ventricular dysfunction during this early period of disease. Findings using these techniques require a stable state for valid assessment. Artifactual results, which can be obtained as a result of neurohormonal changes common after acute ethanol use, may obscure the underlying myocardial dysfunction.

Common echocardiographic findings in the asymptomatic individual include an increase in mean left ventricular and left atrial dimensions, as well as an increase in estimated ventricular mass (21). Characteristic of this stage is an increased mean septal and posterior wall thickness, while a normal percent fractional shortening of the left ventricle is maintained (22,23). Thus, studies of the subclinical state can indicate impaired diastolic function, impaired contractility index, and evidence of ventricular hypertrophy or dilatation, either singly or combined.

The importance of identifying this stage lies in the potential beneficial effect of abstinence. This has been partially demonstrated during serial studies of ejection fraction measured by radionuclide-gated heart scans and echocardiography (24,25). Patients at a rehabilitation center were assessed on the first days of admission, once a basal state was reached and after a 4- to 9-month period of abstinence. Follow-up radionuclide ventriculography after several months of abstinence revealed improved ventricular systolic function.

Congestive Heart Failure

With continuing ethanol abuse, the initial subclinical process eventually deteriorates in many patients with the development of heart failure (Fig. 9.2). Continuation of alcohol consumption at this stage produces a marked decrease of left ventricular function compared to normals (eFig. 9.2.1). Abstinence still plays a role during this period, resulting in evidence of partial improvement in ventricular function and reduced mortality. Cardiac decompensation commonly affects patients in the age range from 30 years to the mid-50s. Intake history averages 80 g of alcohol per day (approximately 8 oz of 86-proof whiskey or 1 L of wine) for a minimum of 10 years. Occasionally, an episode of intense drinking is reported before the development of symptoms, but a particular pattern of drinking has not been found to be associated with the onset of heart failure.

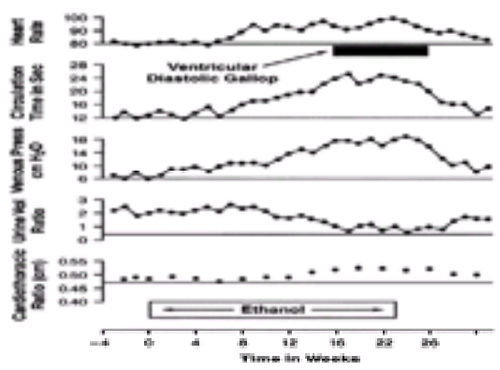
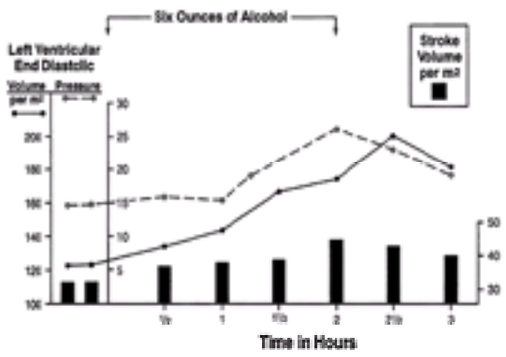
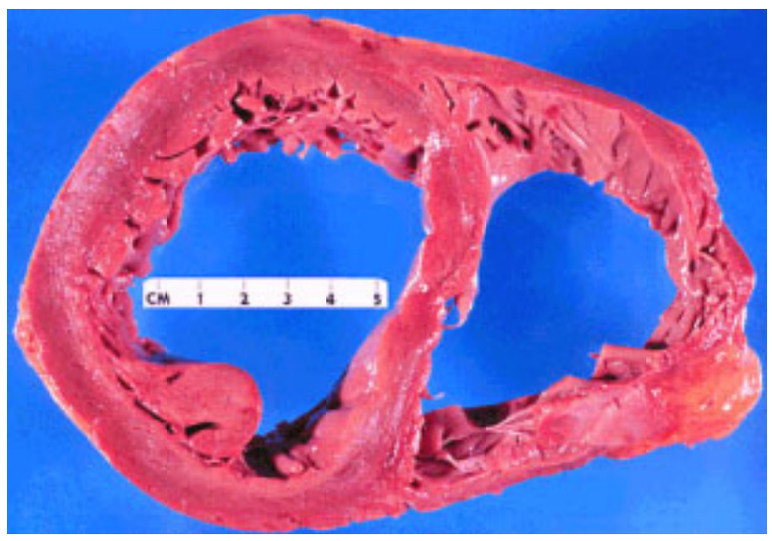


FIGURE 9.2 Evidence of cardiac depression developing as a result of chronic ethanol abuse. The various parameters became progressively abnormal after 8 weeks of alcohol ingestion. The abnormalities disappeared with abstinence.



***e*FIGURE 9.2.1** Observations made during the ingestion of 6 oz of scotch by an alcoholic patient with left ventricular failure, demonstrating a depressant effect on cardiac function at a dose that does not affect function in the addicted individual without heart failure. (From Regan TJ, Haider B. Ethanol abuse and heart disease. *Circulation* 1971;44:957, with permission.)

Physical findings and symptoms of left ventricular dysfunction are similar to those produced by other cardiac diseases. Fatigue and weakness secondary to reduced output may be part of the initial complaints, although these symptoms can be attributed to concomitant myopathy common in alcoholics (26). As the process progresses, dyspnea on exertion and orthopnea appear. Due to the fact that many alcoholics fail to seek medical attention early in the course of the disease, it is not uncommon to find evidence of right-side failure at the time of presentation, with jugular venous distention, leg edema, hepatomegaly, and ascites.



Dilated congestive cardiomyopathy. Both the left and right ventricles are significantly enlarged. In this example, the left ventricular wall thickness falls within normal limits.

VIDEO

Video 9.1 Apical long-axis view of a patient with severe left ventricular dysfunction and annular dilatation causing 4+, centrally directed mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Cardiomegaly may be moderate during the early stages. A greater degree of cardiac enlargement is found when there is concomitant mitral regurgitation secondary to papillary muscle dysfunction. Partial regression of ventricular dilatation can be achieved with therapy. An early diastolic gallop is frequently heard during this period. An atrial gallop can be auscultated if the patient is in sinus rhythm; on occasion, an atrial gallop is present in the absence of failure, indicating the existence of myocardial disease. The murmur of mitral insufficiency is rarely pansystolic, usually confined to one portion of systole, and tends to disappear as cardiac compensation is restored. A pansystolic murmur of tricuspid regurgitation, best heard in the third and fourth intercostal spaces, is found during signs of right-side failure and diminishes with effective therapy.

Electrocardiographic findings are, for the most part, nonspecific. Loss of septal Q waves and poor R-wave progression in the absence of coronary disease are common findings. Also noted are signs of left atrial and left ventricular enlargement, as well as varying degrees of intraventricular conduction defects. Low magnesium levels found frequently in the alcoholic produce characteristic electrocardiographic changes: tall, peaked T waves (not as narrow as the wave seen in hyperkalemia) and a normal QT interval. Prolonged hypomagnesemia produces an increased PR interval, wide QRS complexes, ST depression, and low-amplitude T waves.

A 41-year-old patient with hyperkalemia.

Hemodynamically, symptomatic subjects present with higher end diastolic pressures and volumes as compared to the subclinical stage. As might be expected, the ejection fraction and contractile indices are also more depressed. Another clinical manifestation described during this stage is the development of peripheral arterial or pulmonary embolism related to the formation of thrombi in the atrial or ventricular wall.

Thiamine Deficiency (Wet Beriberi)

Thiamine deficiency should be considered as a factor contributing to alcoholic cardiomyopathy. Approximately 15% of asymptomatic alcoholics are moderately deficient in thiamine, as determined by dietary history and excretion of vitamin metabolites (27). There has been no survey of patients with clinical heart disease. The physiologic derangements observed in beriberi heart disease are different from those seen in alcoholic cardiomyopathy; the hallmark is the existence of a hyperkinetic state affecting the cardiovascular system, characterized by decreased peripheral resistance, increased cardiac output, tachycardia, and biventricular failure. In addition to the findings of congestion, on physical examination, there is a wide pulse pressure with a bounding arterial pulse. Frequently, an early diastolic gallop and a systolic murmur can be heard in the apical area. A machinery-type murmur is heard in the peripheral arteries as a manifestation of the arteriovenous shunts that are common in this disorder. The electrocardiogram may show low voltage with an increased QT interval and nonspecific T-wave abnormalities. Cardiomegaly is the common finding in chest radiography.

For the diagnosis of beriberi heart disease, several criteria are required, including a history of thiamine deficiency for more than 3 months, absence of another etiology

of heart failure, evidence of peripheral neuropathy, and a therapeutic response to thiamine (28).

Arrhythmias

Dysrhythmias in the heart are associated with underlying changes in myocardial composition and electrophysiology as a consequence of chronic alcohol ingestion. Healthy subjects do not appear to be affected after mild to moderate intake. Arrhythmias tend to appear in the late stages of an episode of excessive drinking or in the subsequent hours. These episodes of intense drinking are particularly more prevalent among the middle-aged population, as compared to older individuals. A seasonal variability has been described, but similar episodes may not appear in the same individual, despite a similar drinking pattern. Frequent clinical presentations of alcoholics are dizziness and syncope, which are usually attributed to the individual's inebriated state. However, the arrhythmia is detected by electrocardiography.

The most common arrhythmia is atrial fibrillation. This condition can revert spontaneously to normal sinus rhythm, but, on occasion, electrical or pharmacologic cardioversion is required. With sustained abuse of alcohol, chronic atrial fibrillation can develop. *Holiday heart* describes the development of an acute arrhythmic process, generally atrial fibrillation, after an episode of heavy alcohol consumption (Fig. 9.3). These episodes frequently occur during long weekends or annual holidays, during which there is a rise in the consumption of spirits—thus the name *holiday heart* (29).

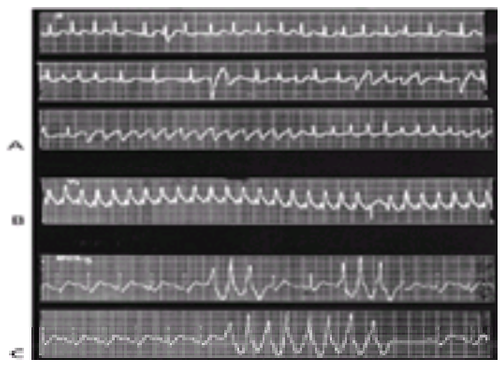


FIGURE 9.3 Electrocardiographic manifestations in alcoholic patients. **A:** The first strip demonstrates rapid atrial fibrillation with one aberrant beat (Ashman phenomenon); the following two strips show increased rate in the same patient with wide complex tachycardia (rate of 240 beats/min). **B:** Atrial flutter with 1:1 conduction (verified after carotid massage) at a rate of 250 beats/min with right bundle branch block aberration. **C:** Nonsustained ventricular tachycardia.

An increased incidence of sudden death has been found among the alcoholic population. It has been postulated that this increased incidence might be due to rapid degeneration of ventricular tachycardias anto ventricular fibrillation, because the former are rarely described in clinical practice. Two European studies have confirmed these observations. Cases of witnessed cardiac arrest were evaluated at the Pathology Institute of Moscow, showing that 17% of the deaths were related to alcohol abuse (30). The majority of the cases were in men younger than the age of 50 years and with alcoholemia. Autopsy revealed no significant coronary artery disease (CAD), but there was evidence of subclinical cardiomyopathy on light and electron microscopy. A large prospective study using a registration system established by the Swedish social authorities for alcoholism examined the role of alcohol as a general and specific cause of mortality (31). In a period of 11 years, the incidence of sudden death between the group registered for alcoholism was double that of the nonregistered group. This association was observed in men with and without coronary disease.

Dose is an important factor in determining the relationship of alcohol to the development of sudden death (Table 9.1). No effect on mortality was found with doses of <80 g of ethanol per day in an epidemiologic study (32). The mortality rate rose threefold with increased intake compared to that of those taking less alcohol. This finding was confirmed in an analysis of the Framingham population. Individuals consuming more than 2,500 g of alcohol per month had an increased risk of sudden death without evidence of CAD (33).

Beer (360 mL)	18 g
Wine (1 L)	100 g
Whiskey (90 mL)	36 g

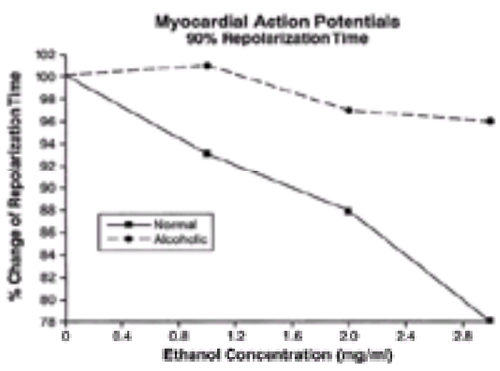
[a]1 oz = 30 mL.

TABLE 9.1 AMOUNT OF ALCOHOL IN DIFFERENT BEVERAGES[a]

High-fidelity electrocardiography has been performed in patients to determine the existence of occult disease. Varied conduction abnormalities have been found during sinus rhythm—mainly prolongation of the corrected PR, QRS, and corrected QT intervals. Also noted was notching and slurring of the QRS complex, indicating the existence of low-grade myocardial disease. In the absence of a dilated heart, these conduction disturbances appeared to be independent of ventricular mass (29).

Acute and chronic alcohol ingestion may trigger cardiac arrhythmias by several mechanisms. Smoking, electrolyte abnormalities, or sleep apnea may also contribute. Acute alcohol ingestion inhibits antidiuretic hormone–producing water diuresis with concomitant loss of sodium, potassium, and magnesium, which have a putative relationship with the development of a variety of arrhythmias. As described above, the existence of scarring, interstitial fibrosis, and cardiac autonomic dysfunction can act as a substrate for the genesis of dysrhythmias (7).

Effects on myocardial action potential are determined by the degree of ethanol intoxication and by the action of major metabolites of alcohol, such as acetaldehyde (34,35) (eFig. 9.3.1). Acute intoxication in alcohol-naïve animals affects the action potential differently within the cardiac tissue, with increases of the action potential at the level of the Purkinje system and decreases at the ventricular muscle (34). In chronic ethanol-exposed animals, acute ethanol administration does not alter the action potential, possibly because of an absence of acetaldehyde, which can produce adrenergic stimulation, or because of the unavailability of sarcolemmal receptors. The latter is thought to be secondary to downregulation because the receptors are occupied by high levels of circulating norepinephrine, thus reducing receptor uptake of exogenous catecholamines. Paradoxically, a decreased sensitivity to administered catecholamines is observed in terms of ventricular vulnerability (36).

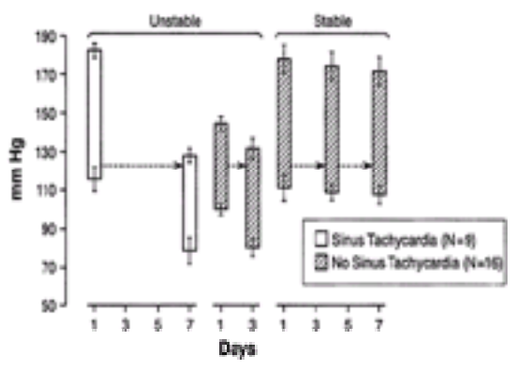


***e*FIGURE 9.3.1** Response of repolarization time in isolated superfused tissue to different doses of ethanol in alcoholic and healthy animals.

Reduction of basal repolarization time secondary to alcohol may be due to opening of voltage-sensitive calcium channels. This hypothesis has been confirmed by normalization of repolarization during calcium-channel blockade. A decrease in repolarization is also related to activation of adenosine triphosphate–sensitive potassium current by a potassium-channel opener.

Hypertension

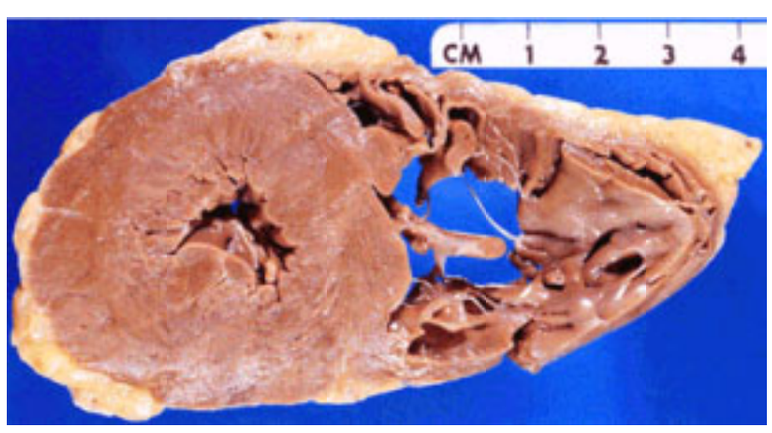
Elevated blood pressure is found in the majority of chronic alcoholics during late intoxication and during early withdrawal periods after acute ingestion. It is unclear whether bursts of elevated blood pressure during withdrawal eventually cause chronic hypertension. However, after a period of abstinence, no increase in blood pressure or end-organ damage was found in patients, irrespective of their underlying cardiac status (*e*Fig. 9.3.2).



***e*FIGURE 9.3.2** Arterial pressure in post–ethanol consumption state. The panel on the left indicates substantial elevation of arterial pressure, which declined without antihypertensive medication in 7 days. The middle panel shows that the moderate pressure elevation normalized in 3 days. The panel on the right indicates that in the essential hypertensive who is alcoholic, the blood pressure may remain stable.

A series of concomitant factors may play a role in the development of alcoholic hypertension, although the definite mechanism through which alcohol causes hypertension remains unclear. Hypertension may be due to a central nervous system (CNS) imbalance related to baroreceptors and CNS control of cardiac output and peripheral effects (37). Some researchers have found that alcohol induces increased postganglionic efferent sympathetic nerve activity accompanied by increased systolic and diastolic blood pressure (38). Stimulation of the renin-angiotensin-aldosterone system is controversial, but stimulation leads to increased extracellular fluid and hypertension. Elevated cortisol levels may occur with ethanol consumption and may be correlated to hypertension. Alcohol may cause increased intracellular calcium with increased vascular reactivity (39). There may be stimulation of endothelium to release endothelin or inhibit nitric oxide (NO) production. Reduced levels of circulating magnesium or changes at the level of the smooth muscle can affect intracellular calcium activity and promote vasoconstriction. Chronic subclinical withdrawal has been postulated as related to sympathetic overactivity.

Acute hypertensive episodes do not result in the development of ventricular hypertrophy, and it is unknown if there is a cumulative effect. Once a cardiomyopathic picture is established, hypertrophy eventually ensues; at that point, a similar pattern exists as in chronic hypertension. Echocardiography has shown that in the nonalcoholic hypertensive, left ventricular mass increments occur in 20% to 45% of patients. Consequently, the hypertrophy seen in some alcoholics may be at least partially related to coexistent hypertension.



Left ventricular hypertrophy secondary to chronic hypertension with secondary ectasia of the right ventricle.

Chest Pain

Underlying cardiac or gastrointestinal processes are often the cause of chest pain in alcoholics. Minimal CAD typically is found among these patients. However, transmural myocardial infarction associated with perivascular fibrosis of subepicardial vessels has been described (40). This fibrosis may limit the coronary blood flow during a period of high myocardial diastolic and systolic tension (Fig. 9.4). No evidence of spasm or embolization has been found.

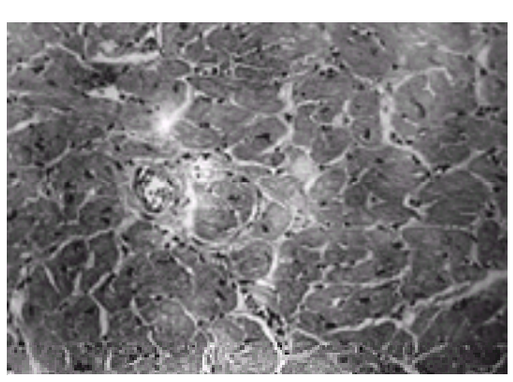


FIGURE 9.4 Periarterial interstitial collagen accumulation with distribution between myofibers (Alcian blue staining), graded as 2 to 3+, indicating increased deposition of glycoprotein material in the extracellular matrix. (From Regan TJ, Wu CF, Weisse AB, et al. Acute myocardial infarction in toxic cardiomyopathy without coronary obstruction. *Circulation* 1975;51:453, with permission.)

Elevations of creatine kinase (CK), CK-MB isoenzyme, troponin I, and lactate dehydrogenase have been described in individuals with alcoholic heart disease, both in clinical and in subclinical stages. Whereas its significance is debatable, the elevation of creatine kinase and CK-MB has been attributed to the existence of skeletal muscle myopathy that is common in alcoholics. Despite the absence of electrocardiographic changes, a cardiac origin is still possible because myocardial enzyme release is induced by acute alcohol administration (41,42 and 43). To make the diagnosis of coronary ischemia related to alcohol, physicians cannot rely entirely on

enzyme levels but must consider the entire clinical picture.

DIAGNOSIS AND MANAGEMENT

Identification of the alcoholic patient can often represent a challenge, because denial of the underlying problem is a common characteristic. It is estimated that approximately 60% to 80% of cases of alcoholism are undiagnosed. Physicians rarely use any screening method to identify the addiction. Screening tests have a sensitivity and specificity of 70% to 90%. Clinician specialists use the criteria established by the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* (44). These criteria require a maladaptive pattern of alcohol use associated with other typical characteristics (eTable 9.1.1).

***e*TABLE 9.1.1** *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS* DIAGNOSTIC CRITERIA FOR ALCOHOL ABUSE
Characteristics required to be present in a 12-mo period of a maladaptive pattern of alcohol abuse:
Recurrent drinking resulting in failure to fulfill major duties at work, school, or home
Recurrent drinking in hazardous situations
Recurrent alcohol-related legal problems
Continuation of alcohol use despite persistent social or interpersonal problems caused or exacerbated by alcohol

In clinical practice, there are clues that aid in the diagnosis: unexplained hepatic dysfunction, parotid enlargement, hypertension, seizures, anxiety, depression, tremors, and alcohol on the breath. Laboratory data have a low sensitivity and specificity, but they provide a hint of the existence of an alcoholic disorder when used in combination with the history and physical findings. Abnormal laboratory values include a high or slightly elevated mean corpuscular volume, aspartate aminotransferase, g-glutamyl transferase, serum uric acid, triglycerides, and high-density lipoprotein (HDL).

Development of withdrawal and delirium tremens are serious but relatively infrequent in alcoholic patients with heart failure (eTable 9.1.2). These complications are best managed in a hospital environment—especially if tremor, anxiety, tachyarrhythmias, fever, clouded sensorium, or concomitant medical problems (e.g., hepatic failure, pancreatitis) are present. In addition, patients who lack an adequate social support system or those who need psychiatric care benefit in an inpatient setting.

***e*TABLE 9.1.2** EFFECTS OF ABSTINENCE VERSUS CONTINUATION OF ALCOHOL USE ON MORTALITY OVER A 4-YEAR PERIOD

	Abstinent (22 patients; %)	**Active alcoholism (42 patients; %)**
Improved	44	5
Unchanged	36	28
Worse	9	10
Mortality	9	57

Acute withdrawal usually begins 6 to 8 hours after the reduction of ethanol consumption. Delirium tremens occurs in only 5% of these patients; a hallmark is the significant alteration of the patient's sensorium associated with dramatic CNS and autonomic hyperactivity. Seizure activity is of the tonic-clonic type and appears 7 to 48 hours after cessation or relative abstinence. In approximately 40% of these cases, the seizure is limited to a single episode. However, bursts of two to six events with normal sensorium between seizures are not an uncommon finding. Recurrent seizures lasting more than 6 hours are very rare and should raise the suspicion of other diagnoses (e.g., infection, trauma, subclinical hematoma). The seizures are treated with phenytoin or phenobarbital intravenously. Patients developing seizures as their initial manifestations may not have demonstrated earlier signs of withdrawal.

A basic strategy of the management of patients in withdrawal includes alleviating symptoms and prevention of the progression of the process and complications. To maintain a patent airway, care must be taken in patients with decreased mental status. Wernicke's encephalopathy and hypoglycemia have to be recognized, because they may appear concomitantly in alcoholics. The early administration of 100 mg of thiamine intravenously followed by 50 g of glucose (after quick evaluation of blood glucose level by fingerstick) is necessary. Aggressive hydration and correction of electrolyte abnormalities (e.g., of magnesium, potassium, and phosphate) is an important part of this therapy. A cornerstone in this process is the achievement of adequate sedation to prevent the development of complications secondary to agitation, such as trauma, rhabdomyolysis, and hyperthermia. Benzodiazepines are the drugs of choice to achieve this goal; chlordiazepoxide (Librium) at a dose of 25 to 100 mg orally or intravenously every 6 hours is recommended. Because lorazepam (Ativan) is the only benzodiazepine that can be given intramuscularly, it should be used in cases of liver disease or advanced age (>65 years old) or if the patient cannot tolerate oral medications. The use of beta-blockers or alpha$_2$-blockers has been proposed for control of the increased sympathetic tone present during the withdrawal period. However, these agents do not control hallucinations, seizures, or agitation. Experimental studies suggest that NO mediates part of the alcohol withdrawal syndrome and that inhibition of NO synthase during this period can diminish some of the signs and symptoms associated with withdrawal (45), although such therapy is not currently available.

The therapy of heart failure in alcoholic patients is guided by the same principles as other forms of cardiomyopathy. Initial management with diuretics and bed rest may be the only treatment required in patients with minimal clinical symptomatology. Although no clinical investigation has evaluated the efficacy of angiotensin-converting enzyme inhibitors or beta-blockade in the alcoholic heart, these medications' beneficial effect on heart failure patients in general should encourage their use.

Abstinence can result in reversibility of the underlying cardiomyopathic process, provided that the disease is not advanced. Once overt alcoholic heart disease develops, there is more than a 50% 4-year mortality with continuous use of ethanol (eTable 9.1.3). Recognition of the etiologic role in the development of heart disease and other organ failure may encourage abstinence from alcohol. Emphasis on the potential reversibility of the pathologic process may motivate the patient. Referral to addiction control groups such as Alcoholics Anonymous or Alanon (Alcoholics Anonymous groups for family members) can provide important support in the short- and long-term management. Pharmacologic agents such as disulfiram can be used in special situations.

***e*TABLE 9.1.3** RISK FACTORS FOR DEVELOPMENT OF SEVERE ALCOHOL WITHDRAWAL
Daily consumption of a fifth of liquor, a case of beer, or more than 3 L of wine
Heavy drinking for more than 5 mo
Poor nutrition
History of severe withdrawal
Use of other drugs

Reduction in the amount of alcohol consumed lowers blood pressure in the hypertensive alcoholic. A period of 2 to 4 weeks of abstinence should be allowed before considering antihypertensive medications in this population. In the absence of any specific data demonstrating the efficacy of any particular drug in the treatment of alcohol-induced hypertension, angiotensin-converting enzyme inhibitors could be considered the drugs of first choice due to the possibility of concomitant cardiomyopathy. It is important to note that a substantial portion of these patients may experience some degree of autonomic dysfunction secondary to alcohol, resulting in the development of orthostatic hypotension and making alpha-adrenergic blockers the least desirable drug in this population.

There are two objectives in managing patients who present with arrhythmias secondary to ethanol: control of the ventricular response and alcohol cessation. Control of the ventricular response in rapid atrial fibrillation or flutter is best achieved with medications that block atrioventricular nodal conduction, such as beta-blockers and calcium-channel antagonists. Atrial fibrillation in holiday heart tends to revert to sinus rhythm spontaneously, but chemical or electrical cardioversion should be considered if the arrhythmia persists. Ventricular tachycardia or fibrillation require aggressive management with electrical cardioversion or defibrillation. Individuals who are unresponsive to drug therapy or have experienced an episode of sudden cardiac death need to be considered for an implantable defibrillator. Correction of electrolyte abnormalities—especially potassium and magnesium—should ideally be done via intravenous infusion, because many patients present with clouded sensorium or gastrointestinal symptoms that limit oral therapy.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Light to Moderate Alcohol Consumption and the Prevention of Cardiovascular Diseases

A series of epidemiologic studies have suggested that one to two drinks a day of any alcoholic beverage helps protect against CAD (46,47,48 and 49,54). The low incidence of CAD seen in France (French paradox) (50,51) compared to other countries with similar dietary habits has been well publicized. This difference was initially attributed to red wine and its antioxidant components (e.g., tannins, anthocyanins, and flavonoids) (51). However, similar findings have been reported with the use of other alcoholic beverages (52,53).

This beneficial effect of moderate drinking also appears to have a secondary prevention effect by reducing total and cardiovascular mortality in individuals with a history of previous myocardial infarction (55). In this regard, a study of the myocardial response to ischemia in guinea pigs is of interest (56). Low-dose ethanol feeding for several weeks was followed by 45 minutes of no-flow ischemia in the isolated heart with a similar period of reflow. Compared to controls, the ethanol-fed group had

lower ventricular diastolic pressure and decreased myocardial damage measured as the level of creatinine-kinase. Adenosine A_1 receptors were required for this effect.

A biologically plausible basis for the effect of ethanol in reducing CAD is the rise of circulating HDL2 and HDL3 with moderate use. Both subfractions have been associated with a decreased incidence of CAD (57). Complementing this effect may be the increased incidence in thrombolytic activity secondary to enhanced endogenous tissue plasminogen activator (58,62), downregulation of plasminogen activator inhibitor-1 (59), prevention of mononuclear-macrophage activation (60), decreased platelet activity (61), and reduced fibrinogen levels after ethanol ingestion (62). A study by McConnell et al. demonstrated only increasing levels of HDL and its subfractions but no effect on hemostatic parameters in individuals exposed to light drinking over a period of 6 weeks (63).

Prospective studies on the relationship of ethanol consumption and incidence of CAD have demonstrated, in general, a U-shaped or J-shaped pattern with a lower risk among light to moderate drinkers. The increased incidence of cardiac mortality observed in heavy drinkers may be secondary to alcohol-related arrhythmias, hypertension, or cardiomyopathy. The benefit of moderate drinking compared to abstaining has been challenged on the basis that these studies did not separate true abstainers from ex-drinkers.

Major contributions to this field have been made by the Physicians' Health Study, which showed cardiovascular benefits of light ethanol consumption in men. These researchers have recently indicated that no further benefit was achieved above two drinks per day in men. Of greater interest is recent evidence showing no difference in benefit between the consumption of one drink per week and intake of one to two drinks per day. This evidence applies to cardiac events (64), stroke (65), and total mortality.

These findings have prompted others to evaluate the relationship of ethanol use and other cardiovascular diseases. A recent examination of carotid atherosclerosis by ultrasound did not find a significant difference in the wall thickness between patients with moderate drinking habits and the control group (66). In contrast, a recent prospective study on the relationship between alcohol use and peripheral artery disease among American physicians demonstrated that moderate ethanol intake appears to decrease the risk of peripheral artery disease in men (67). This inverse relationship is not affected by other known cardiovascular risk factors, except for smoking. Similarly, in a retrospective analysis of patients with mainly ischemic cardiomyopathy, light to moderate alcohol consumption was not associated with an adverse prognosis and decreased the risk of fatal myocardial infarction. However, a trend towards increasing hospitalization was seen with light to moderate alcohol intake among patients with nonischemic heart failure (68). In a large prospective study of apparently healthy males, a decrease in the incidence of sudden cardiac death was observed in those who reported a light consumption of ethanol. The nadir in risk occurred in those individuals who consumed two to six drinks per week (69).

An association between stroke and alcohol consumption has also been analyzed. In a study by Berger et al., approximately half of those individuals consuming alcohol were also using aspirin, making the absolute effect of ethanol *per se* unclear (65). The association with total stroke incidence showed a risk reduction of 20% after adjusting for important confounders. Benefit was observed among those consuming only one drink per week, and the degree of protection did not increase with higher doses.

The question of who may benefit from moderate alcohol consumption revolves around determinants such as age, gender, the influence of risk factors for disease, and the concomitant use of other drugs (70) (Table 9.2). Young adults have minimal risk for CAD but are at risk for vehicular accidents, which are commonly related to ethanol use. Individuals older than 50 years with coexisting cardiovascular risk factors may benefit from moderate ethanol intake (49). In fact, a major study in the United States indicated that a significant preventive effect was present only in subjects older than 60 years (48). Analysis of population subsets among women has revealed that only those with coronary risk factors experience a significant benefit from low-dose ethanol consumption (71,72) (*e*Table 9.2.1). Recent data also have shown a significant decrease in the risk of coronary disease among diabetics consuming one drink per week. The apparent lack of influence of light to moderate drinking on the regulation of blood glucose is especially important. In contrast to results of the Physicians' Health Study, these diabetics obtained apparent benefit with only one drink per day.

Quantity
Frequency
Duration
Ill-defined variables: nutrition, gender, cigarette use, age of onset

TABLE 9.2 FACTORS THAT CONTRIBUTE TO THE DEVELOPMENT OF ALCOHOLIC CARDIOMYOPATHY

***e*TABLE 9.2.1** NUMBER OF DEATHS FROM ALL CAUSES AND RELATIVE RISK (RR) OF DEATH ACCORDING TO CARDIAC RISK STATUS AND ALCOHOL INTAKE

Average alcohol intake (g/d)	**0**	**0.1–1.4**	**1.5–29.9**	**³30.0**
No risk factors				
No. of deaths	144	38	153	17
Multivariate RR (95% CI)	1.0	0.75 (0.52–1.00)	0.95 (0.75–1.10)	2.2 (1.3–3.7)
>1 Cardiac risk factor				
No. of deaths	693	283	1,088	242
Multivariate RR (95% CI)	1.0	0.93 (0.8–1.0)	0.84 (0.7–0.9)	1.1 (0.9–1.2)

CI, confidence interval.
Adapted from Fuchs CS, Stampfer MJ, Colditz GA, et al. Alcohol consumption and mortality among women. *N Engl J Med* 1995;332:1249.

At issue in the prevention of CAD by alcohol is the question of increased premature mortality rates from other alcohol-related causes, even at moderate doses. The risk-benefit ratio concept has been used to indicate the public health utility of a recommendation for light ethanol use. In a prospective study of 276,000 men aged 40 to 59 years, there was a benefit for reduction of coronary heart disease, but this was only at low dose (i.e., two to three drinks per day) (73). No additional benefit was achieved at higher levels of alcohol intake. Over the 12 years of follow-up, beginning at two drinks per day, there was a progressive increase in the risk of cancer (colon and breast), stroke, accidents, violence, and overall mortality with increasing use of alcohol (Fig. 9.5). Thus, the benefit was limited to low-dose consumption of alcohol. Particularly relevant is a French report that included a prospective cohort study of middle-aged men for nearly a decade and national mortality data from a single year. Whereas consumption of >60 g per day of ethanol correlated with an increase in mortality, lower levels of 26 to 60 mL per day (i.e., two to five drinks) were not associated with reduced total mortality (74).

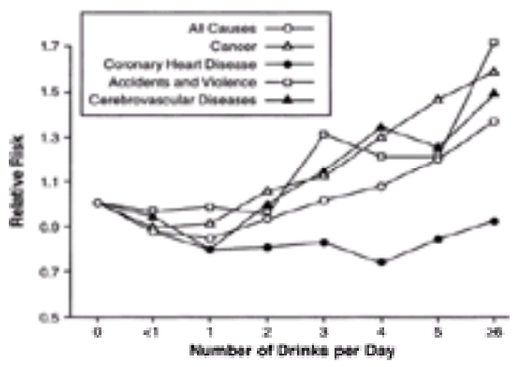


FIGURE 9.5 Alcohol consumption and relative risk of death over 12 years in an American Cancer Society prospective study of 276,802 men, ages 40 to 59 years. Mortality ratios are adjusted for age, smoking habits, the four most common causes of death, and death from all causes. (From Boffetta P, Garfinkel L. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. *Epidemiology* 1990;1:342–348, with permission.)

In the context of the positive epidemiologic message for moderate ethanol use, the statement of Castelli (75) provides a sobering perspective: “With 17 million alcoholics in this country, we perhaps have a message for which this country is not yet ready.” Moreover, the use of alcohol for cardioprotective purposes has been discouraged by some as a general public health measure, because alcohol abuse appears to correlate with overall ethanol consumption in the general population (76). Although the body of evidence supporting the cardiovascular benefits of light to moderate alcohol drinking appears to be reassuring, hazards of moderate intake must be weighed on an individual basis; even modest doses of two drinks per day are associated with an increase in blood pressure. Because of age-related body changes, the National Institute on Alcohol Abuse and Alcoholism recommends that individuals older than 65 years consume no more than one drink per day (77). Extrapolation of these epidemiologic findings to the general population has to take into account several issues: the potential beneficial effect of ethanol is likely to occur over several years; these reports are based on self-reporting habits, which tend to be inaccurate; consumption of ethanol varies among different cultures and societies, which, in turn, reflect different types of diet and lifestyles. Until the precise mechanisms by which ethanol affects cardiovascular diseases are determined, no public health recommendations should be established.

Cardiotoxicity of Alcohol in Women

A gender difference in the left ventricular function has been found among alcoholics (78), suggesting that there may be a varied prevalence of alcoholic cardiomyopathy between men and women, especially during the subclinical period. A lower prevalence of alcoholism among women may be responsible for the lower incidence of cardiac involvement. It is estimated that, currently, one-third of the alcoholics in the United States are women. Alcoholic heart failure is observed in postmenopausal women, but statistical data are lacking in terms of younger women.

However, a similar or slightly greater propensity for developing cardiomyopathy was seen in women, despite their consumption of lesser amounts of alcohol (79,80). In the study conducted by Urbano-Marquez et al. (80) in ethnically homogeneous and adequately nourished women, a decrease in the mean left ventricular ejection fraction was present, compared to that in a control group (men). However, the group was small (n = 4), and the women were at an age approximating menopausal years. Kupari et al. (79) found that the development of subclinical cardiomyopathy, as established by echocardiographic findings, was similar in alcoholics of both genders. The caveat to this study is the lack of data indicating whether the younger women ever developed clinical heart failure.

THE FUTURE

In the next decade, further diagnostic refinement should be developed for identification of cardiac patients who abuse alcohol. These developments include biochemical alterations in blood and specific histochemical changes identified on cardiac biopsy. Progress is needed in promoting abstinence in such patients. Pharmacologic interventions to reverse or impede progression of the pathophysiology in myocytes and extracellular matrix are likely to be forthcoming.

Although the research to demonstrate ethanol’s beneficial effect at low to moderate doses has been provocative (81), further extensive study is required to define the mechanisms involved and the precise subgroups of patients who may benefit.

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10

OTHER RISK FACTORS FOR CORONARY ARTERY DISEASE: HOMOCYSTEINE, LIPOPROTEIN(a), FIBRINOGEN, AND PLASMINOGEN ACTIVATOR INHIBITOR

KILLIAN ROBINSON
JOSEPH LOSCALZO

"Indicates text or graphics that appear only in the electronic versions of this text."

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KEY CONCEPTS

1. Nontraditional risk factors are now recognized as important determinants of coronary heart disease.
2. Hyperhomocysteinemia confers an independent risk for coronary heart disease, probably by imparting oxidative stress-induced endothelial dysfunction and inducing atherothrombosis.
3. Many patients with elevated homocysteine concentrations in plasma are relatively deficient in folate or pyridoxine; the possible benefits of treating patients with vascular diseases using vitamins is now being evaluated in clinical trials.
4. Lipoprotein(a) [Lp(a)] confers an independent risk for coronary heart disease in selected populations and may do so by impairing fibrinolysis, promoting thrombosis, or stimulating vascular smooth muscle cell proliferation.
5. Fibrinogen and other prothrombotic risk factors, including plasminogen activator inhibitor-1 (PAI-1) excess and factor VII, confer independent risk for coronary heart disease.
6. Thrombosis is a major determinant of atherogenesis; thrombin stimulates smooth muscle cell proliferation, activates platelets, and promotes plaque growth. In addition, a prothrombotic state in the vasculature supports thrombus propagation at sites of vascular injury.

OVERVIEW

Traditional risk factors are commonplace in patients with coronary artery disease. Their absence in many patients with vascular disorders provides a stimulus to search for other abnormalities that may also confer an increased risk of atherosclerosis. Several such abnormalities have received more widespread attention recently as their possible roles in the genesis of atherosclerosis and thrombosis become more evident. A high plasma homocysteine concentration has been proposed as a risk factor in most case-control studies and some prospective studies. Elevated levels of this sulfur-containing amino acid may cause vascular damage, perhaps by increasing intracellular oxidative stress in endothelial cells. High concentrations may be readily reduced by folic acid, either alone or combined with vitamin B_6 or vitamin B_{12}. The effects of such treatment on prognosis are being evaluated by a number of secondary prevention studies in patients with vascular diseases. An elevated Lp(a) level is also a recognized risk factor for atherosclerosis. The mechanism of vascular damage is unclear but may be related to enhancement of the toxicity of low-density lipoprotein (LDL) cholesterol or, because of structural homology to plasminogen, interference with normal thrombolysis. Although high Lp(a) levels may be reduced by certain drugs and LDL apheresis, such measures are not always successful, and no prognostic benefit has been demonstrated. High fibrinogen and factor VII concentrations are also independently linked with coronary artery disease by mechanisms that remain obscure. Prospective studies are needed to clarify the precise role of the elevated concentrations of PAI in patients with atherosclerosis and thrombosis. Levels of fibrinogen may be lowered by exercise and modest alcohol intake, but a specific fibrinogen-lowering agent is not yet available. The effect of reducing the levels of these prothrombotic clotting factors on prognosis is unknown. This chapter outlines the relationship between these risk factors and coronary artery disease.

HISTORICAL PERSPECTIVE

Associations between vascular disorders and traditional risk factors (e.g., diabetes, cholesterol, blood pressure, and smoking) are well known. Several plasma constituents discovered many years ago have undergone more extensive evaluation recently as their possible role in the development of atherosclerosis and thrombosis receives greater recognition. Although it was discovered in 1959, homocysteine began to receive greater attention only when patients with homocystinuria developed vascular abnormalities. Approximately 15 years later, these observations were broadened when higher homocysteine levels were detected in patients with coronary artery disease and other vascular diseases. Lp(a) was discovered in 1963 and has since been extensively investigated as a risk factor for atherosclerosis. Abnormalities of the clotting cascade are also associated with arterial occlusion. Indeed, more than 40 years ago, high fibrinogen concentrations were noted in patients with acute myocardial infarction (MI). It is now known that other clotting disorders—including excesses of prothrombin, factor VII, and inhibitors of plasminogen activation—may also contribute to thrombosis. These links with atherosclerosis and thrombosis are analogous to the early observations of elevated risk associated with hypercholesterolemia and hypertension. Concepts of risk associated with the latter have undergone considerable refinement and redefinition with time and may provide useful direction for the future evaluation of the risk factors discussed here.

HOMOCYSTEINE

Homocysteine, a sulfhydryl-containing amino acid, was first discovered as a product of demethylation of methionine (1), which is essential as a methyl donor (2).

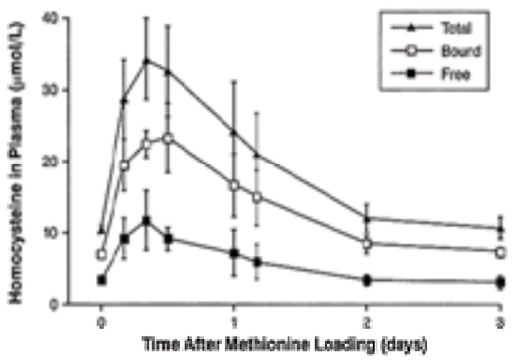
Excessive quantities of homocysteine were noted to accumulate in the blood of patients with homocystinuria—a rare disease characterized by skeletal, neurologic, and vascular abnormalities (3). From this initial observation, a link has been established between more moderate elevations of plasma homocysteine concentrations and atherosclerosis (4,5,6,7,8,9,10,11,12,13,14,15,16,17,18 and 19), even in patients without any apparent defined genetic trait for homocystinuria.

Nomenclature

P> The term *total homocysteine* refers to all species of this amino acid circulating in the blood (4,5,20) and may be abbreviated to *tHcy*. Approximately 80% of homocysteine is protein bound, principally to albumin. The sulfhydryl group of free, unbound homocysteine reacts readily with other sulfhydryl groups to form disulfides. Thus, homocysteine may combine with itself (forming homocystine) or with cysteine to form the mixed disulfide homocysteine-cysteine. Approximately 1% of all circulating homocysteine exists in the free, reduced state. The range of fasting homocysteine currently reported as normal is 5 to 15 µmol per L and includes all free, disulfide-linked and protein-bound species (4,5). Some evidence exists that this range may be too high, because concentrations as low as 12 µmol per L have been associated with atherosclerosis (4,5) and thrombosis in many of the studies of patients with vascular disease (4,5,11,12,13,14,15 and 16). A concentration above this range defines hyperhomocysteinemia; this is sometimes written as *hyperhomocyst(e)inemia* to emphasize the inclusion of all disulfide-linked bound and free species of the amino acid. Standard measurement is usually performed on blood drawn in the fasting state. Concentrations may increase if whole blood is stored at room temperature, as homocysteine may be exported from red blood cells (21). Therefore, blood should be placed on ice and centrifuged as soon as possible after collection for proper determination of fasting concentrations.

Methionine Loading Test

Homocysteine concentrations may also be measured after the administration of methionine (4,5). Methionine administration may be useful in identifying patients with normal fasting levels (*e*Fig. 10.0.1) but with latent abnormalities of homocysteine metabolism and a propensity for the achievement of higher concentrations under certain circumstances. The methionine loading test may also identify additional patients at risk for vascular disease (4,5,14) when combined with a fasting level alone, although the test is time consuming and expensive, which somewhat offsets its broad clinical applicability.



***e*FIGURE 10.0.1** The methionine loading test. After administration of a standard dose of methionine in the fasting state, homocysteine concentrations rise for several hours to a peak. Basal or fasting levels are usually restored after 24 hours. (From Ueland PM, et al. Plasma homocysteine and cardiovascular disease. In: Francis RB Jr., ed. *Atherosclerotic cardiovascular disease, hemostasis and endothelial function*. New York: Marcel Dekker, 1992:183–236, with permission.)

Homocysteine Metabolism

Following ingestion, methionine is converted to *S*-adenosylmethionine and then to *S*-adenosylhomocysteine, from which homocysteine is formed (Fig. 10.1). Methionine may be regenerated by the recycling of homocysteine via two remethylation pathways (2). One pathway uses vitamin B_{12}–dependent methionine synthase, using 5-methyltetrahydrofolate as a methyl donor; the presence of 5,10-methylenetetrahydrofolate reductase is also required. An additional pathway exists for methionine remethylation involving the enzyme betaine-methionine methyltransferase (2). This route is independent of folate and vitamin B_{12}, but it requires trimethylglycine (betaine) as a methyl donor. When methionine stores are adequate, homocysteine enters the transsulfuration pathway, where it is converted to cystathionine by vitamin B_6–dependent cystathionine b-synthase. Cystathionine, in turn, serves as a source for the generation of cysteine, which is required for the synthesis of many major biologic compounds, including glutathione—the most important and abundant intracellular thiol (Fig. 10.2). Ultimately, sulfur-containing amino acids are metabolized to water and sulphate and are excreted in the urine. Activity of cystathionine b-synthase is low or absent in classical homocystinuria. From a review of this metabolic pathway, it can be seen that plasma homocysteine concentrations may increase, owing to decreased activity of certain enzymes, reduced vitamin cofactor availability, or both.

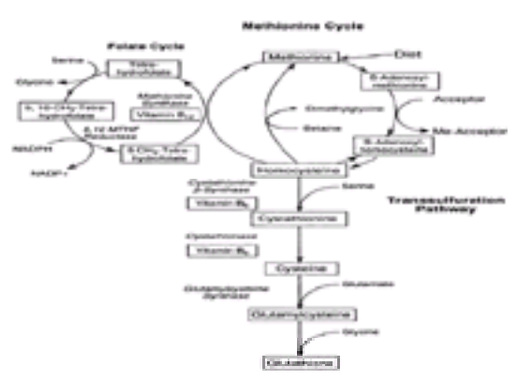


FIGURE 10.1 The metabolic pathway for the metabolism of methionine and homocysteine (see text for discussion). Me, methyl; MTHF, methylenetetrahydrofolate; NADP+, oxidized form of nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate.

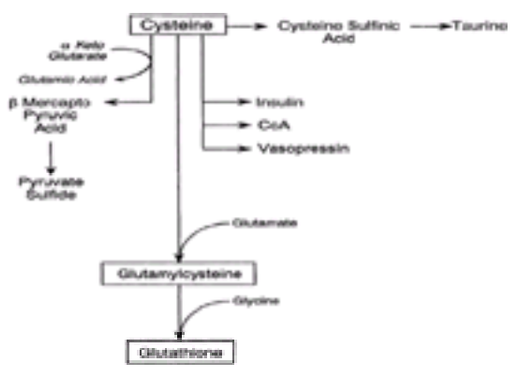


FIGURE 10.2 Pathways showing the fate of cysteine and its central role in the synthesis of essential metabolic compounds, including insulin, coenzyme A (CoA), and glutathione.

Causes of Altered Homocysteine Concentrations

See Table 10.1 for the causes of hyperhomocysteinemia.

Inherited causes
Disorders of transsulfuration
Cystathionine β-synthase deficiency
Disorders of remethylation
Defective vitamin B_{12} transport
Defective vitamin B_{12} coenzyme synthesis
Defective methionine synthase
5,10-methylenetetrahydrofolate reductase deficiency or defects
Acquired causes
Diseases
Chronic renal failure
Hypothyroidism
Chronic inflammatory bowel disease
Some malignant disorders
Systemic lupus erythematosus
Psoriasis
Vitamin deficiencies
Vitamin B_{12}
Folate
Vitamin B_6
Drugs
Cholestyramine, colestipol, and metformin (affect folate and cobalamin absorption)
Methotrexate (inhibits dihydrofolate reductase)
L-Dopa (increases transmethylation)
Niacin and theophylline (induce vitamin B_6 deficiency)
Androgens
Cyclosporine (reduces renal function)
Fibric acid derivatives (possibly after renal function)
Phenytoin and carbamazepine (antagonize folate)
Nitrous oxide (inactivates of methionine synthase)

TABLE 10.1 CAUSES OF HYPERHOMOCYSTEINEMIA

Genetic Factors

Classical homozygous homocystinuria is associated with low or absent activity of cystathionine b-synthase and leads to extremely high (>250 µmol per L) plasma concentrations of homocysteine (3). The heterozygous state is also associated with higher levels of the amino acid. Rare mutations in the remethylation enzyme methylenetetrahydrofolate reductase—which may be associated with excessively high homocysteine concentrations and early death—have also been reported (22). A more common abnormality yielding a temperature-sensitive enzyme (C677T mutation) is also associated with high homocysteine levels (23,24 and 25). Importantly, this abnormality leads to a requirement for high concentration of folate for optimal enzyme activity, and folate supplementation can correct the hyperhomocysteinemia observed in these individuals (26). Uncommon inherited abnormalities of cobalamin metabolism may produce similar clinical disorders (4,5). A genetic influence on plasma concentration has been observed in healthy subjects (27) and in patients with vascular disease (28).

Age

Plasma homocysteine levels rise with age in both men and women (4,5). This age-dependent increase may be secondary to decreases in vitamin cofactor levels or coexisting renal impairment; both are common in this age group. An age-related reduction in the activity of cystathionine b-synthase has also been reported (29).

Gender

Homocysteine concentrations are higher in men than women (4,5), which may be due to differences in muscle mass, renal function, essential vitamin cofactors, or even protein intake. Homocysteine levels are also higher in postmenopausal women than premenopausal women. Sex steroids play an important role in modulating homocysteine concentrations, as illustrated by one study of transsexual males and females in which homocysteine concentrations rose in the subjects treated with androgens but fell in the subjects treated with estrogens (30).

Lifestyle

Lifestyle is also an important determinant of plasma total homocysteine concentrations. In the Hordaland Homocysteine Study, gender, age, folate intake, smoking status, and coffee consumption were the strongest determinants of homocysteine concentration in apparently healthy subjects. A lifestyle of low folate intake, smoking, and higher coffee consumption was associated with a higher homocysteine concentration. Conversely, a high folate intake, nonsmoking status, and low coffee consumption were associated with a median homocysteine concentration that was 3.0 to 4.8 µmol per L lower (31).

Vitamin Deficiencies

Folate and vitamin B_{12} are required for remethylation of homocysteine to methionine. Concentrations of homocysteine rise with decreasing levels of these vitamins (4,5). Frank deficiency can give rise to a markedly increased homocysteine concentration (32). Levels also rise with a decreasing concentration of vitamin B_6 (4,5).

Drugs

Total plasma homocysteine concentrations may also be increased by drugs that affect the metabolism of folate or vitamin B_{12}, including methotrexate, phenytoin, carbamazepine, and nitrous oxide (4,5). Several preparations commonly used in patients with vascular disease—including the cholesterol-lowering agents cholestyramine and colestipol, niacin, and fibric acid derivatives—have also been shown to be associated with an increased homocysteine concentration (4,5). Metformin, theophylline, and L-dopa may have similar effects. A lower homocysteine concentration may be seen in patients taking hormone replacement therapy or penicillamine (4,5).

Renal Dysfunction and Other Disease States

Total plasma homocysteine concentration rises with declining renal function (4,5,33,34 and 35). The reasons for the increase remain unclear, as filtration and metabolism of homocysteine by the kidney are slight in humans (36,37). Some evidence exists that extrarenal metabolism of homocysteine may be impaired in uremia (38). Levels also rise in renal transplant patients (39). A high plasma homocysteine concentration has also been observed in patients with psoriasis, leukemia, systemic lupus erythematosus, hypothyroidism, and inflammatory bowel disease (4,5).

Homocysteine and Vascular Disease

Homocystinuria

Homocystinuria has been the paradigm of homocysteine-related atherosclerosis since the early work of Mudd and coworkers (20). The classical disorder—characterized by complete, or almost complete, absence of cystathionine b-synthase—is rare and occurs in the United States once in every 400,000 births (20). The condition is transmitted in autosomal recessive fashion. Reduced enzyme activity is observed in heterozygotes for the disorder and may be demonstrated by administering a methionine challenge. A markedly elevated plasma homocysteine concentration is typical and is accompanied by an increase in urinary homocystine. The clinical manifestations include skeletal abnormalities, ocular lens dislocation, and mental retardation. The other major complications of early atherosclerosis and a tendency to thromboembolic events soon became evident after the disorder was first described in a survey of mentally retarded children from Ireland (40). The plasma homocysteine concentration can be reduced by dietary methionine restriction or by the administration of vitamin B_6, which may protect against vascular complications (20).

Vascular Pathology

The premature atherosclerosis occurring in homocystinuria involves large, medium, and small arteries in any vascular territory. Pathologic features include marked intimal thickening, medial muscular fiber splitting and fraying, an increase in interstitial collagen, and changes in the internal elastic lamina (41). These lesions are associated with an increase in perivascular connective tissue and increased numbers of fibroblasts, collagen bundles, and small elastic fibers. Intimal and medial thickening may result in severe luminal narrowing. Similar findings have been reported in patients with homocystinuria secondary to the rarer remethylation defects (42). In these individuals, high homocysteine concentrations are also noted. In patients with a deficiency of cystathionine b-synthase, methionine levels are low, suggesting that homocysteine—not methionine—is responsible for the vascular damage.

Pathophysiology of Vascular Disease Due to Hyperhomocysteinemia

Although a high circulating level of homocysteine is associated with atherosclerosis and thromboembolic disorders, the underlying mechanism of vascular damage, if any, remains obscure (*e*Table 10.1.1). Most attention now focuses on possible endothelial dysfunction or damage related to hyperhomocysteinemia. Cystathionine b-synthase activity is absent from cultured endothelial cells and may predispose to intracellular homocysteine accumulation (43,44), especially with a lack of essential nutrients impairing remethylation.

***e*TABLE 10.1.1** HOMOCYSTEINE AND ATHEROTHROMBOSIS: POSSIBLE MECHANISMS

Vascular endothelium
Cytotoxic damage at high doses
Increased macrophage adhesion
Abnormal prostacyclin synthesis
Altered cytokine production
Changes mediated through adhesion molecules
Platelets
Increased synthesis of thromboxane B_2 and other eicosanoids
Increased levels of platelet-derived thromboxane A_2
Increased platelet adhesion and aggregation
Decreased platelet survival
Clotting factors
Activation of factor XII
Decreased antithrombin III levels
Factor V activation by a homocysteine-induced endothelial cell factor
Decreased activation of protein C
Inactivation of thrombomodulin production or activity
Increased affinity of lipoprotein(a) for plasmin-modified fibrin
Inhibition of vWF processing and secretion
Blocking of tissue-type plasminogen activator binding to endothelial cells
Reduction in plasma homocysteine is associated with a decrease in vWF, thrombomodulin, and endothelin

vWF, von Willebrand factor.

In vitro studies have shown the toxic effect of homocysteine on cells in culture; in animal models, homocysteine has been shown to cause vascular endothelial damage, resulting in desquamation and early atherosclerosis (45,46 and 47). Homocysteine is readily oxidized, leading to the formation of superoxide and hydrogen peroxide, which may cause endothelial damage. This oxidant stress may play an important role in endothelial cell damage (48) before the development of overt structural heart disease (49).

Welch and colleagues (50) have shown that homocysteine exposure produces a dose-dependent increase in intracellular reduced glutathione concentrations. An increase in the concentration of oxidized glutathione, however, was also observed. Overall, there was a decrease in the ratio between the two, consistent with an increase in oxidant stress. A number of mechanisms may protect against this oxidant stress, including release of nitric oxide, which may detoxify homocysteine by formation of *S*-nitrosohomocysteine, thereby inhibiting further generation of hydrogen peroxide. Endothelium-derived relaxing factor may be protective against the effects of homocysteine, but the protection may be lost with progressive endothelial damage (51). Catalase may also protect against the adverse effects of hydrogen peroxide, as may glutathione peroxidase. However, the expression of the latter enzyme may be inhibited by homocysteine (52).

In animals, reduced bioavailability of endothelial nitric oxide has been observed with a methionine-rich, folic acid–poor diet, which resulted in hyperhomocysteinemia (53). Human studies have also shown that high levels of homocysteine are associated with impaired endothelium-dependent vasodilation in healthy subjects (54). Endothelial damage may subsequently be expressed in various ways. Inhibited synthesis of prostacyclin by arterial tissues has been noted, which, in addition to a loss of bioactive nitric oxide itself, can predispose to thrombosis (55,56). Endothelial desquamation after homocysteine infusion in animals is associated with decreased platelet survival, suggesting that homocysteine-induced endothelial injury may cause a secondary increase in platelet consumption (46). In addition, homocysteine may promote procoagulant activity by inactivation of the endothelial cell anticoagulant protein C (57) or by disruption of the processing and secretion of von Willebrand factor (53). Increased factor V expression has also been observed (58), and tissue factor expression may be increased as well (59). Recent data also show that homocysteinylation of factor V impairs its inactivation by activated protein C (60). Other mechanisms by which homocysteine may promote thrombosis include inhibition of the cofactor activity of thrombomodulin and enhanced thrombomodulin expression in human umbilical vein endothelial cells (61), suppression of the expression of the anticoagulant heparan sulfate (62), modulation of tissue-type plasminogen activator (t-PA) binding to its endothelial cell membrane receptor (63), alteration of fibrinogen structure (64), and promotion of vascular smooth muscle cell growth (65). Homocysteine also enhances neutrophil adhesion and migration across the endothelium (66). These pathophysiologic mechanisms have been reviewed by Welch and colleagues in detail (67).

Major Clinical Studies of Homocysteine and Vascular Disease

In 1976, Wilcken and colleagues undertook the first studies of patients younger than 50 years with angiographically proven coronary disease (6) and found higher homocysteine concentrations in patients than in controls. In a later study, the same investigators were unable to confirm these results (68). However, many other studies have since been performed (7,8,9,10,11,12,13,14,15,16,17,18 and 19) that have reached conclusions similar to the initial investigation. In the study by Malinow and coworkers (8), after controlling for conventional risk factors, the odds ratio for vascular disease in patients with hyperhomocysteinemia was 3.3, which was higher than the ratio associated with smoking or hypercholesterolemia. In addition, the increased risk does not have a threshold and is present over much of the range of plasma homocysteine concentrations (Fig. 10.3). A European multicenter case-control study using an internationally accepted methodology and definitions of vascular disease has confirmed other case-control studies (14). Although some prospective studies have confirmed these findings (18,19), a number of major investigations have not (69,70), raising the question of whether an elevated homocysteine level may be causally related to the development of vascular disease or may simply be an epiphenomenon. There are a number of useful recent reviews of studies in this area to which we refer the interested reader (4,5).

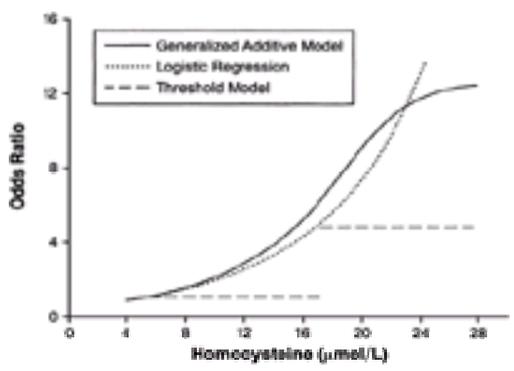


FIGURE 10.3 The relationship of rising plasma homocysteine concentrations to the risk of coronary heart disease. A higher risk is noted with higher concentrations. When homocysteine values are analyzed across the range of plasma concentrations, no threshold effect is evident. (From Robinson K, Mayer EL, Miller D, et al. Hyperhomocysteinemia and low pyridoxal phosphate: common and independent reversible risk factors for coronary artery disease. *Circulation* 1995;92:2825–2830, with permission.)

Interactions with Other Risk Factors

Large epidemiologic studies have also shown a correlation, albeit weak, between homocysteine and other risk factors (14,71) and significant interactions between high homocysteine concentrations and traditional risk factors. These findings are consistent with the enhanced oxidation of LDL in the presence of thiols, including homocysteine (72). Glueck and colleagues (73) have reported interactions of homocysteine with triglycerides. Harpel and colleagues have reported increased binding

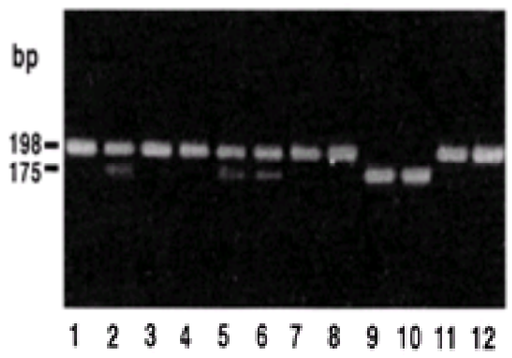
of Lp(a) to fibrin after homocysteine exposure (74).

Effect of Homocysteine on Prognosis in Patients with Atherosclerosis

An elevated homocysteine concentration is associated with an adverse prognosis in patients with established coronary artery disease. In patients with angiographically confirmed coronary artery disease, Nygard and colleagues found a graded relation between plasma homocysteine levels and overall mortality. After 4 years, 3.8% of patients with homocysteine levels below 9 µmol per L had died, as compared with 24.7% of patients with homocysteine levels of 15 µmol per L or higher (75). Stubbs and coworkers evaluated the relationship between plasma homocysteine and short-term (28 days) and long-term (median 2.5 years) prognosis in patients with acute coronary syndromes. Although the event rate within the first 28 days was unrelated to the homocysteine concentration, an apparent threshold effect was noted on long-term follow-up, with a 2.6-fold increase in the risk of cardiac events for patients in the upper two quintiles compared with the lowest three quintiles (76).

Mechanisms of Elevated Homocysteine Concentrations in Atherosclerosis

Wilcken and colleagues and other investigators (7,8) hypothesized a possible carrier state for cystathionine b-synthase deficiency to explain the high homocysteine concentrations in patients with atherosclerosis. The rarity of the genetic frequency for this condition and data from other recent studies, however, make this conclusion unlikely. In 1991, Kang and coworkers reported a thermolabile variant of the remethylation enzyme, methylenetetrahydrofolate reductase, in patients with coronary artery disease (*e*Fig. 10.3.1), which was associated with elevated homocysteine concentrations (23); other investigators have made similar observations (24,25,26 and 27), although a metaanalysis has shown no apparent increase in risk of vascular disease associated with this polymorphism (77). Nutritional abnormalities have also received attention. Because folic acid, vitamin B_{12}, and vitamin B_6 are important for the metabolism of homocysteine, concentrations of these substances have been measured in patients with vascular disease. Negative correlations with homocysteine have been found in many studies (4,5), demonstrating important links between plasma homocysteine, low B-vitamin concentrations, and vascular disease risk. In one study (78), higher homocysteine levels were noted in patients with vascular disease and correlated negatively with all three B vitamins. Low folate status was found in approximately 10% of patients and was associated with an increased risk of vascular disease explicable on the basis of higher homocysteine concentrations.



***e*FIGURE 10.3.1** Determination of 5,10-methylenetetrahydrofolate reductase genotypes. Results from 12 subjects are shown. The normal allele gives a fragment of 198 base pairs (bp), whereas the thermolabile allele gives a fragment of 175 bp. Subjects 1, 3, 4, 7, 8, 11, and 12 are homozygous for the normal allele (–/–); subjects 2, 5, and 6 are heterozygous (+/–); and subjects 9 and 10 are homozygous for the thermolabile allele (+/+). (From Adams M, Smith PD, Martin D, et al. Genetic analysis of thermolabile methylenetetrahydrofolate reductase as a risk factor for myocardial infarction. *QJM* 1996;89:437–444, with permission.)

Vitamin B_6 plays an important role in the metabolism of homocysteine. Early *in vivo* work showed that animals chronically deprived of vitamin B_6 also developed arteriosclerotic lesions (79). Epidemiologic studies have demonstrated a relation between vitamin B_6 deficiency and atherosclerosis in humans (10,15,78,80,81), and this association has been confirmed by prospective observation (70). The apparently common deficiency of vitamin B_6 in patients with vascular disorders may explain the high homocysteine concentrations observed after a methionine challenge in patients with vascular diseases previously ascribed to cystathionine b-synthase deficiency (7,9). This focus on the role of lower B-vitamin levels in hyperhomocysteinemia highlights the importance of functional vitamin deficiencies in the development of vascular disease.

Venous Thromboembolism

In homocystinuria, venous thromboembolic episodes are common; therefore, several studies have addressed homocysteine as a risk factor for venous thrombosis (82,83,84,85 and 86). Although not all of these case-control studies have reached similar conclusions, two metaanalyses have suggested that hyperhomocysteinemia may indeed be a risk factor for venous thrombosis (87,88). The mechanisms underlying this, however, require further study.

Renal Failure

High homocysteine concentrations occur frequently in patients with renal failure (89). Case-control studies have shown that higher levels of homocysteine are associated with an increased risk of atherosclerosis independent of traditional risk factors in dialyzed patients with end-stage renal disease (35). In addition, high homocysteine levels are closely related to B-vitamin metabolism in these patients. Prospective studies have also demonstrated a relationship between vascular complications of end-stage renal disease and elevated homocysteine concentrations (89,90). Recently, Suliman and colleagues (91) have shown that elevated homocysteine concentrations are a predictor of adverse outcomes in patients with end-stage renal disease and that nutritional status may also be an important determining factor of homocysteine concentrations.

Cardiac Transplantation

After cardiac transplantation, homocysteine concentrations rise (92,93 and 94) and are associated with abnormalities of B vitamins and renal function, suggesting a multifactorial etiology. Follow-up of these patients, however, has shown that low vitamin B_6—but not high homocysteine concentrations—predicted cardiovascular morbidity and mortality in this patient group (95).

Therapeutic Implications

Metabolism of homocysteine requires vitamin B_6, vitamin B_{12}, folate, and betaine. Vitamin B_6 and folate reduce homocysteine concentrations in homocystinuria, and vitamin B_6 may reduce the incidence of vascular complications in patients with atherosclerosis (20). The treatment of homocystinuria is reviewed extensively elsewhere (96).

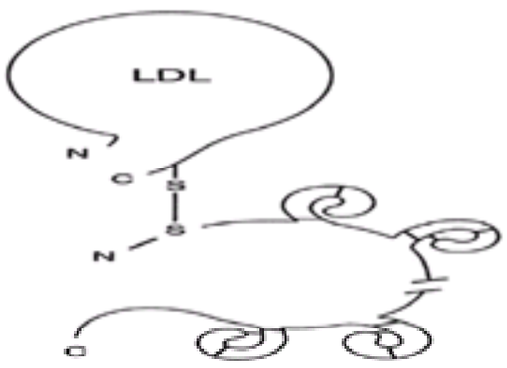
In healthy subjects and in patients with atherosclerotic vascular disease, homocysteine concentrations may be reduced by folic acid alone or in combination with vitamins B_6 or B_{12} (4,5,97,98). The effect is greatest with folic acid, which, in doses of only 0.5 mg per day, may reduce homocysteine concentrations by approximately 30% (98). Vitamin B_{12} may produce a more modest 10% reduction. Vitamin B_6 is most effective in reducing homocysteine concentrations after a methionine challenge. Other agents that may reduce homocysteine include betaine, choline (13), estrogen (99), and *N*-acetylcysteine (100). The use of penicillamine has also been associated with a reduction in homocysteine concentrations. A number of clinical trials are ongoing in patients with coronary artery disease and stroke using folic acid, vitamin B_6, and vitamin B_{12}. In addition, other studies are in progress using high-dose folic acid in patients with end-stage renal disease. These studies may help provide more definitive answers concerning the contribution of homocysteine to the development of atherosclerosis and whether the routine use of B-vitamin supplements is justified in these patients.

At the current time, measurement of homocysteine concentrations and use of these vitamins in patients with vascular disease remains speculative, although the American Heart Association has suggested that the measurement of homocysteine concentrations in high-risk individuals—such as those with a positive family history or the development of early atherosclerosis—may be reasonable. Until the ongoing treatment trials have been concluded, the benefit of routine use of vitamin supplements in these patients remains unproven (101).

LIPOPROTEIN(A)

Structure

Lp(a) was discovered in 1963 by Berg (102) and consists of two major components: an LDL particle containing the apoprotein B-100 molecule and an apoprotein(a) molecule (*e*Fig. 10.3.2) linked by a single disulfide bond to apoprotein B (103). Apoprotein(a) is a large protein with an amino-acid sequence similar to that of plasminogen. It contains several cysteine-rich domains of 80 to 114 amino acids in length that are referred to as *kringles*. Five kringles occur in plasminogen, and most of those in apoprotein(a) are largely similar to the fourth kringle of the plasminogen molecule. Lp(a) is synthesized in the liver, and its molecular weight varies from 400 to 700 kd. This range is due to variation in the number of copies of kringle 4 in apoprotein(a) and is inversely associated with Lp(a) levels in plasma. Plasma levels are determined by the balance between production (104) and removal (105). Variation in concentrations has also been noted in patients with the same apoprotein(a) isoform, which may be due to differences in the rates of production (105). It is unclear if this variation is caused by differences in gene transcription, protein translation, or assembly (106). The concentrations in plasma range from 1 mg per dL to 100 mg per dL. Most values lie below 20 mg per dL, and the concentration distribution is, therefore, markedly skewed in most populations [see the section Effects of Age, Gender, and Race on Lipoprotein(a) Levels]. The normal function of Lp(a) remains unclear.



***e*FIGURE 10.3.2** The structure of lipoprotein(a). The apolipoprotein(a) moiety is located in the lower portion of the diagram, together with four of its representative kringle (triple-loop) domains. Apolipoprotein(a) is linked to low-density lipoprotein (LDL) by a single disulfide bridge. [From Loscalzo J, Weinfeld M, Fless GM, et al. Lipoprotein(a), fibrin binding, and plasminogen activation. *Arteriosclerosis* 1990;10:240–245, with permission.]

Genetics

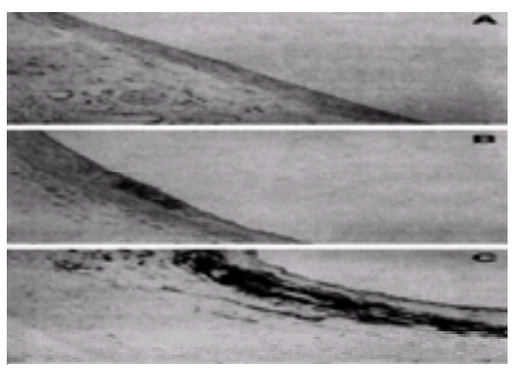
The gene for the apoprotein(a) is located on the long arm of chromosome 6 and is closely linked to the gene for plasminogen (106,107). There is a high degree of homology between these two genes. Utermann and colleagues (103) reported six size isoforms of Lp(a) that were inherited, but more than 30 isoforms have now been reported (106,108).

Effects of Age, Gender, and Race on Lipoprotein(a) Levels

Plasma levels of Lp(a) do not bear any clear relationship to age or gender, although levels are higher after menopause (109). Concentrations also increase with the levels of LDL cholesterol (109). A weak correlation with age in men and women was reported by the Northern Sweden World Health Organization (WHO) MONICA project investigators (110). Lp(a) levels vary substantially among ethnic groups and are higher in American and African blacks than in whites; levels are normally distributed rather than skewed in blacks. Despite the higher levels, the risk of coronary artery disease may not be increased in blacks compared with whites (110). In Asian populations, Lp(a) has also been associated with an increased incidence of coronary artery disease (111). Recent studies have shown that dietary fat content may increase Lp(a) concentrations, perhaps by modulating apoprotein(a) mRNA levels (106). Levels are higher in patients with nephrotic syndrome and chronic renal failure and may be three times higher than normal controls in patients undergoing dialysis (112). Higher levels have also been noted in patients with diabetes mellitus and immediately after MI (113,114). Lp(a) concentrations are higher in patients who have undergone renal transplantation treated with cyclosporin than in patients taking azathioprine or prednisone (115).

Epidemiologic Links with Coronary Artery Disease

Numerous case-control studies have shown a relationship between Lp(a) and coronary artery disease. Seed and colleagues (116) demonstrated that an elevated level is a strong risk factor for CHD in patients with familial hypercholesterolemia. There have been similar findings in a number of prospective and nested case-control studies. In one such study, serum Lp(a) was an independent risk factor for MI and CHD death (117). In another, the subsequent development of “severe” cardiovascular events was fourfold greater after 11 years of follow-up in randomly selected Swedish men with the highest levels (118). In an Icelandic study (119), 1,332 men were followed for 8.6 years, during which 104 patients experienced MI. Higher concentrations of apoprotein(a)—representing greater Lp(a) concentrations—were independent risk factors for developing MI (119). These findings were not reproduced in the Helsinki Heart Study, in which no relationship was noted between baseline levels of Lp(a) and subsequent development of fatal and nonfatal MI (120). An elevated risk of CHD associated with Lp(a) was not seen in the U.S. Physicians Health Study, although it should be emphasized that this was an unusual and narrowly defined population in which not even cholesterol conferred an increased risk of MI (121). This outcome could reflect biases related to the population studied, storage conditions for plasma, or even the use of aspirin. High levels of Lp(a) combined with high LDL cholesterol appear to confer a particularly high risk of coronary artery disease. There are conflicting reports concerning the relationship of Lp(a) and graft occlusion rates in patients who have undergone coronary artery bypass surgery (122,123). Lp(a) is found in atherosclerotic plaque (125,126; *e*Fig. 10.3.3), where it localizes with fibrinogen (127). Because of the heritability of Lp(a), Berg and colleagues (128) explored the frequency of this trait in siblings or offspring of patients with early coronary artery disease. Higher levels of Lp(a) combined with high LDL cholesterol appear to be associated with a particularly high risk of coronary disease and were found in patients with siblings or parents with CHD. Other studies have also shown higher levels of apoprotein(a) or Lp(a) in individuals with a positive family history of coronary artery disease.



***e*FIGURE 10.3.3** Photomicrographs showing immunohistochemical identification of lipoprotein(a) in early and advanced coronary atherosclerosis. Immunoperoxidase staining of coronary arteries with antilipoprotein(a) adsorbed with plasminogen from **(A)** normal monkey, **(B)** monkey fed an atherogenic diet (at necropsy, total plasma cholesterol = 200 mg/dL and high-density lipoprotein cholesterol = 45 mg/dL), and **(C)** monkey fed an atherogenic diet (at necropsy, total plasma cholesterol = 400 mg/dL and HDL cholesterol = 65 mg/dL). (× 150.) [From Nachman RL, Gavish D, Azrolan N, et al. Lipoprotein(a) in diet-induced atherosclerosis in nonhuman primates. *Arterioscler Thromb* 1991;11:32–38, with permission.]

Mechanism of Thrombosis and Atherosclerosis

The mechanism of thrombosis and atherosclerosis is unknown (*e*Table 10.1.2), but the structural similarity of apoprotein(a) to plasminogen suggests that high levels of Lp(a) may inhibit endogenous fibrinolytic activity (129). Unlike plasminogen, apoprotein(a) cannot be converted to a plasmin-like molecule. Indeed, it inhibits plasminogen activation by streptokinase and competitively inhibits plasminogen activation by t-PA. In addition, owing to its kringle-like domains, apoprotein(a) binds and displaces plasminogen from sites on fibrin and fibrinogen (130). Lp(a) may increase the endothelial release of PAI and downregulate plasmin generation (131). In one study, the rate of plasmin generation was most effectively inhibited by low-molecular-weight isoforms of Lp(a). However, it is important to point out that there is extraordinary polymorphism in apoprotein(a) with respect to kringle number and sequence heterogeneity within kringles—both of which can affect fibrin(ogen) binding properties (132). Alternatively, Lp(a) may affect the delivery of LDL cholesterol to the vessel wall, favoring atherogenesis by binding to plaque elements and enhancing cholesterol deposition (133). Recently, additional potential proatherothrombotic actions have been identified, including induction of monocyte chemotaxis by endothelial cells (134) and, possibly, control of angiogenesis (135).

***e*TABLE 10.1.2** LIPOPROTEIN(A) AND ATHEROTHROMBOSIS: POSSIBLE MECHANISMS
Binding to fibrin and cell surfaces where it competes with plasminogen for binding and reduces plasminogen activation
Inhibits transforming growth factor-b and promotes smooth muscle cell growth
Uptake by evolving foam cells
Stimulation of plasminogen activator inhibitor-1 release from endothelial cells
Induction of monocyte chemotactic activity in endothelial cells
Participation in control of angiogenesis

Treatment

Niacin and neomycin (136) may lower Lp(a) levels, as may stanozolol (137) and *N*-acetylcysteine (138). In one study, the angiotensin-converting enzyme inhibitor fosinopril lowered Lp(a) levels in patients with mild to moderate renal impairment, including blacks and diabetics (139). In a study of 31 postmenopausal women given conjugated equine estrogen for 3 months, Lp(a) concentrations fell by approximately 15% (140). In men with prostatic cancer, large doses of estrogen reduced Lp(a) concentrations by approximately 50% (141); androgens and androgenic progestins have similar effects (141,142). The effects of estrogen may be mediated by accelerated LDL-receptor–mediated clearance (140), as may the effects of the fibric acid derivative bezafibrate (143). Despite the potential for lowering Lp(a) levels, there are no data showing the clinical benefit of this treatment approach (144). In patients with a borderline LDL cholesterol level, an elevated Lp(a) level may provide a rationale for more aggressive LDL-lowering therapy (144). In one study (145), higher levels of Lp(a) did not confer greater cardiovascular risk if LDL had been lowered (Fig. 10.4).

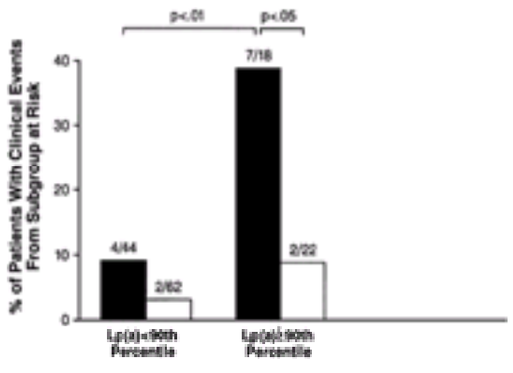


FIGURE 10.4 Relationship of in-treatment lipoprotein(a) [Lp(a)] level and low-density lipoprotein cholesterol (LDL-C) response to occurrence of clinical events. Dark bars indicate LDL-C reductions of £10% (i.e., minimal); light bars indicate LDL-C reductions of >10% (i.e., substantial). The number of clinical events divided by the number of patients at risk in subgroup is listed above each bar. It is assumed that patients dropping out of the study (n = 26) had LDL-C reductions £10%. [From Maher V, Brown BG, Marcovina SM, et al. Effects of lowering LDL cholesterol on the cardiovascular risk of lipoprotein(a). *JAMA* 1995;274;1771–1774, with permission.]

COAGULATION AND FIBRINOLYTIC ABNORMALITIES

Fibrinogen

As long ago as 1954, levels of fibrinogen were noted to be high in patients with acute MI (146). A large body of evidence has now accumulated that links fibrinogen independently to cardiovascular disease.

Structure

Fibrinogen is a glycoprotein synthesized in the liver and has a molecular mass of 340,000 d. The circulating concentration ranges from 200 to 400 mg per dL. Levels are higher in women than in men and increase with age, after menopause, and with increasing body fat. Elevated fibrinogen concentrations occur as a consequence of increased hepatic production or reduced clearance from the circulation. The fibrinogen molecule consists of three pairs of polypeptide chains (a, b, and g) linked by disulfide bonds (147).

Genetics

The three polypeptide chains are encoded by three separate genes on chromosome 4 band 4q32 (148). Genotype may be associated with significant differences in fibrinogen levels (149).

Function

Formation of a fibrin clot and support of platelet-platelet associations are the principal functions of fibrinogen. The proteolytic fragments of fibrinogen have several other functions, including stimulating hematopoiesis, promoting smooth muscle proliferation, and having a possible role in containing bacterial infection.

Effects of Race, Age, and Gender on Fibrinogen Levels

Fibrinogen levels are higher in blacks than in whites by approximately 0.2 g per L (150), and levels increase with age. Concentrations are also higher in women than in men and increase after menopause (151). Fibrinogen concentrations increase with body weight and are lower with exercise and in individuals who consume alcohol (151). Levels also correlate positively with other risk factors for vascular disease, increasing with concentrations of LDL cholesterol and Lp(a) and decreasing with increasing HDL cholesterol (151). Higher levels are found in the setting of stress, overweight status, and physical inactivity (152). Smoking also increases fibrinogen concentration (153), which may be reversible with smoking cessation (151,154).

A specific interaction of smoking and fibrinogen genotype has been observed (155). Higher concentrations of plasma fibrinogen have been observed in smokers with the T148-A455 allele compared with homozygotes for the common C148-G455 allele. The increased risk of vascular disease and smoking may be at least partially explicable by the higher fibrinogen concentrations in smokers (156). Fibrinogen levels are also higher in patients with hypertension (157) and diabetes mellitus (158). In addition to these diseases, fibrinogen is an acute phase reactant (151) that increases in a variety of acute disorders, including stroke (159), MI (160), acute infection, neoplasms, and hepatitis. Levels are higher in patients with end-stage renal disease on hemodialysis and peritoneal dialysis (161); these levels decrease after dialysis (162). A polymorphism in the beta-fibrinogen gene recently has been found to be associated with a progression of asymptomatic coronary atherosclerosis (163).

Epidemiologic Links with Coronary Artery Disease

Many studies have shown a link between fibrinogen and cardiovascular disease. In the Northwick Park Heart Study (*e*Table 10.1.3), an association was noted between fibrinogen and fatal or nonfatal MI, independent of other risk factors (164). Higher levels of factor VII coagulant activity also conferred an increased risk of ischemic heart disease in this study population. In this prospective study of 1,511 white men aged 40 to 64 years, the association between elevated levels of these clotting

factors and subsequent ischemic episodes was stronger than for cholesterol. Similar findings (eFig. 10.4.1) in relation to fibrinogen have been reported in other studies (165), including the Framingham study (156) and, more recently, the Bezafibrate Infarction Prevention Study (166). In a metaanalysis of six prospective population studies (167), odds ratios for cardiovascular events for the upper versus the lowest tertile were between 1.8 and 4.1 for the different studies. Despite the differences in design, sample sizes, and periods of follow-up, the summary odds ratio for all of these studies was 2.3. Only one of these studies involved women. Further work is needed in this area to determine the risk of vascular disease conferred by high fibrinogen and factor VII concentrations in black, Asian, and other populations.

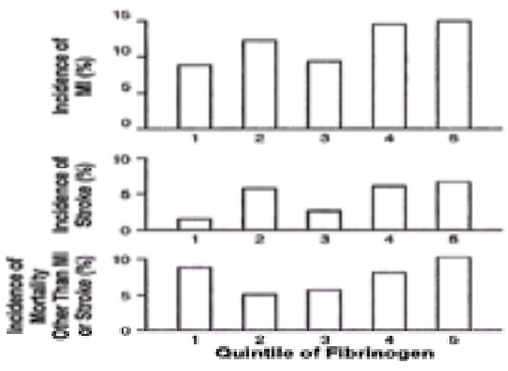
***e*TABLE 10.1.3** FACTORS ASSOCIATED WITH ISCHEMIC HEART DISEASE (IHD) FOR EVENTS OCCURRING WITHIN 5 YEARS AND IN A 13-YEAR TOTAL FOLLOW-UP PERIOD OF THE NORTHWICK PARK HEART STUDY[a]

Event	Age	Cholesterol	Systolic blood pressure	Fibrinogen	Factor VII
IHD death £5 yr					
SRE	1.92	1.36	1.21	1.67	1.55
p	.006	NS	NS	.02	.04
Total					
SRE	2.00	1.27	1.17	1.39	1.32
p	<.0001	.07	NS	.02	.03
Nonfatal IHD £5 yr					
SRE	1.48	1.16	1.14	1.68	1.28
p	.04	NS	NS	.004	NS
Total					
SRE	1.43	1.12	1.35	1.60	1.00
p	.02	NS	.04	.002	NS
All IHD £5 yr					
SRE	1.54	1.17	1.27	1.57	1.37
p	<.006	NS	.09	.003	.03
Total					
SRE	1.65	1.18	1.32	1.41	1.14
p	<.0001	NS	.008	.0002	NS

NS, not significant; SRE, standard regression effect.

[a]All five variables were included in the regression analysis, regardless of whether they were significantly associated with IHD in stepwise analyses. The SREs for different variables are comparable with each other and indicate the increased risk of an event for a 1 standard deviation rise in the variable in question. Thus, an SRE of 1.50 means that for a standard deviation rise in the variable concerned, the risk of an IHD event increases by 50%.

From Meade TW, Mellows S, Brozovic M, et al. Haemostatic function and ischemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* 1986;2:533–537, with permission.



***e*FIGURE 10.4.1** Myocardial infarction (MI), stroke, and death from cause other than MI or stroke among 792 men grouped according to quintile of fibrinogen levels. There was no clear trend for deaths other than those from MI or stroke. (From Wilhelmsen L, Svardsudd K, Korsan-Bengtsen K, et al. Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med* 1984;311:501–505, with permission).

Mechanism of Thrombosis and Atherosclerosis

The mechanism of thrombosis and atherosclerosis is unknown and reflects the complex interactions among plaque development, lipid abnormalities, and derangements of endothelium and the coagulation system (167) (*e*Table 10.1.4). Fibrinogen is the major determinant of plasma viscosity and binds to platelet glycoprotein IIb/IIIa receptors, which is a necessary prerequisite for platelet aggregation (168). In patients with type II hyperlipoproteinemia and familial hypercholesterolemia, fibrinogen binding to platelets is increased (169). In addition, fibrinogen is incorporated into arteriosclerotic plaques and stimulates smooth muscle cell proliferation and growth (151,170,171).

***e*TABLE 10.1.4** FIBRINOGEN AND ATHEROTHROMBOSIS: POSSIBLE MECHANISMS
Activation of factor XII
Promotion of platelet aggregation
Increased plasma viscosity and erythrocyte aggregation
Liberation of serotonin and platelet factors
Stimulation of smooth muscle proliferation and migration

Treatment

Several drugs lower plasma fibrinogen concentrations, including some beta-adrenergic blocking agents, platelet inhibitors (172), and fibric acid derivatives (especially bezafibrate) (167), but lifestyle interventions such as increased exercise and modest alcohol intake may be the most satisfactory initial treatment choice (172). A specific fibrinogen-lowering agent is not yet available.

Plasminogen Activator Inhibitor-1

Plasminogen activator inhibitors (PAIs) are specific inhibitors of t-PA and urokinase-type plasminogen activator. There are several PAIs: PAI-1, PAI-2, and PAI-3; the most extensively investigated in relation to atherosclerosis is PAI-1.

Structure

PAI-1 is a glycoprotein that belongs to the a_1-protease inhibitor class of serine protease inhibitors (i.e., serpins) (173). The gene for PAI-1 is located on chromosome 7 (174). PAI-1 has a molecular mass of 52 kd and consists of 379 amino acids. It is found in plasma, platelets, and extracellular fluid. The relatively high circulating levels of PAI-1 activity in pregnancy may be explained by the high concentrations in the placenta (173).

Synthesis

Synthesis and secretion of PAI-1 can be modulated by various substances that may exert their effects at the level of gene transcription (173,175). Some substances, such as insulin, may have a posttranscriptional effect by modification of mRNA stability (176). When synthesized in endothelium, PAI-1 is rapidly secreted, although it may also be stored in the alpha-granules of platelets and is released on activation (173).

Function

Under normal circumstances, fibrinolysis is tightly regulated by the balance between activation of plasminogen and inhibition of plasmin—the active serine protease derived from plasminogen. Inhibition of fibrinolysis may occur through inhibition of plasminogen activation. Plasma PAI-1 circulates bound to vitronectin (176); its

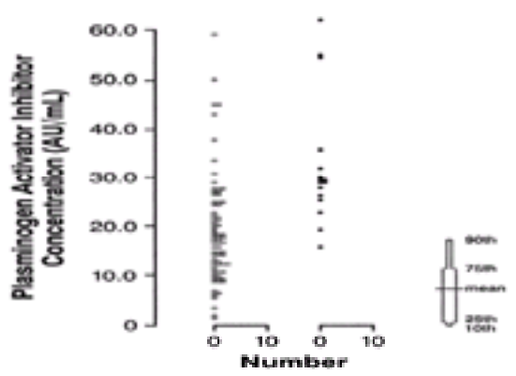
plasma levels exhibit a circadian variation reaching a peak in the morning and a trough in the evening. Importantly, this variation is opposite that for t-PA (173).

Age and Gender

Levels of PAI-1 increase with age (177,178) but are not related to smoking or cholesterol levels (179). Levels rise with increasing systolic blood pressure and are higher in patients with higher triglyceride and insulin concentrations and with higher body-mass indices (180). There is a correlation of PAI-1 with insulin resistance and with the components of this syndrome (181). Endothelial synthesis of PAI-1 may also be enhanced by Lp(a) (131), although plasma levels of these substances do not correlate with one another (182). The clinical value of measurement of PAI concentrations may be enhanced by drawing blood samples before and after venous occlusion for 10 minutes, using a blood pressure cuff inflated to 100 mm Hg (137). This maneuver should produce an increase in fibrinolysis expressed as increased plasminogen activator level and a fall in the concentrations of PAI-1. The test requires further evaluation, as it conceivably could be a better marker for vascular disease than the fasting value alone; the test has already been applied in therapeutic studies in which the fibrinolytic properties of drugs are being evaluated (137).

Epidemiologic Links with Coronary Artery Disease

Increased levels of PAI-1 have been reported in several thrombotic disorders, including venous thrombosis, coronary artery disease, and especially MI (*e*Fig. 10.4.2), although the mechanism remains unclear (*e*Table 10.1.5). Korninger and colleagues (183) described 121 patients with venous thrombosis or pulmonary emboli in whom impaired fibrinolysis was evident, although it was unclear if the findings were due to reduced release of t-PA or increased PAI-1. In addition, although other studies have shown higher levels of PAI-1 (184) in patients with venous thrombosis than in matched controls, confounding variables (e.g., obesity) may explain the findings. These studies of venous thrombosis recently have been reviewed, and the design of many may be flawed by the selection of inappropriate controls or the measurement of fibrinolytic activity after the thromboembolic event (185). Decreased fibrinolysis from increased PAI-1 is associated with an increased risk of postoperative thrombosis (185). Because PAI-1 is also an acute phase reactant, it remains unclear whether this increase is an effect of the surgery. Higher PAI-1 concentrations also have been noted in patients with coronary artery disease than in matched controls (186,187,188,189,190,191,192,193,194,195 and 196). An insertion/deletion polymorphism in the PAI-1 gene locus (5G/5G) has been associated with a family history of coronary artery disease (197), but this association has not been observed consistently (198). There are conflicting findings in relation to recurrent MI (196,199); in patients with angina, PAI activity was not predictive of increased risk of MI (199). Decreased levels of PAI-1 are actually associated with decreased rates of restenosis after coronary angioplasty (200). In addition, higher PAI-1 concentrations also have been noted within the vessel wall, although plasma levels do not correlate with the extent of atherosclerosis (201). Ridker and coworkers (202) have observed elevated plasma concentrations of t-PA in a prospective study of white men with stroke in the United States; these concentrations may simply be a marker of endothelial cell activation or dysfunction. Further prospective studies are required to explore the relationship between activators and inhibitors of plasminogen and the subsequent development of atherothrombotic disorders.



***e*FIGURE 10.4.2** Distribution of values for plasminogen activator inhibitor concentrations in plasma from patients with an uneventful course (*open dots*) and with recurrence of myocardial infarction (*solid dots*). (From Hamsten A, Walldius G, Szamosi A, et al. Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. *Lancet* 1987;2:3–9, with permission).

***e*TABLE 10.1.5** PLASMINOGEN ACTIVATOR INHIBITOR AND ATHEROTHROMBOSIS: POSSIBLE MECHANISMS
Interaction with lipoprotein(a)
Coincident expression of plasminogen activator inhibitor-1 and tissue factor may initiate and prolong thrombotic events in the vessel wall
May regulate extracellular proteolysis during growth or migration
Increased expression in atherogenic lesions may increase vessel wall damage

INFLAMMATORY MARKERS

Inflammatory responses within coronary atheromata are important determinants of plaque activation and subsequent acute atherothrombotic events (203). Systemic inflammation is also associated with atherogenesis and its acute thrombotic complications. Recent data suggest that circulating systemic markers of inflammation can identify subjects at high risk for clinical atherothrombotic events (204,205). In this regard, the acute phase reactants serum amyloid A protein and, more important, C-reactive protein (CRP) have been identified as independent risk factors for cardiovascular events among both apparently healthy individuals and patients with unstable angina pectoris (206,207). In addition, the increase in CRP after acute MI (208,209 and 210) or in the setting of unstable angina pectoris (211,212) correlates with adverse outcome. The association between CRP and cardiovascular disease is believed to be indirect, because circulating CRP reflects the extent of acute phase response to nonspecific stimuli that induce acute inflammation, including ischemia, plaque rupture, vascular injury, and necrosis. Nevertheless, CRP has been demonstrated to be an independent risk factor for atherothrombotic events (207) and may, therefore, be a direct mechanistic determinant of outcome by as yet poorly defined molecular processes. Importantly, aspirin suppresses CRP levels, and this effect may account, in part, for the benefits of aspirin in prevention (207).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Research into the relationship between homocysteine and vascular disorders has uncovered important links between folic acid and atherosclerosis. Although folate is important, it is not the sole determinant of plasma homocysteine levels. It is essential to realize that high homocysteine concentrations may reflect reduced activities of a number of enzyme systems and several B vitamins. By extension, the relationship between vitamin B_6 and atherosclerosis—although proposed almost 50 years ago by Rinehart and Greenberg (78) and since developed by others (79,80,216)—is largely unknown by clinicians and requires greater recognition. Controversy also surrounds the relationship of mutations in methylenetetrahydrofolate reductase and cystathionine b-synthase to hyperhomocysteinemia and vascular disease. Treatment of high homocysteine levels by the routine use of multivitamins in patients with atherosclerosis remains entirely speculative, although trials are now ongoing. Indeed, even the routine measurement of homocysteine, Lp(a), or the concentrations of fibrinogen, factor VII, or PAI-1 in patients with atherosclerosis cannot be recommended until controlled intervention studies have demonstrated a clinical benefit of therapy.

THE FUTURE

Whereas the elevated concentrations of homocysteine, Lp(a), and prothrombotic clotting factors may confer increased risk of atherosclerosis and thrombosis, much additional investigation is required before their role in these disorders can be fully understood. For example, the underlying abnormalities that lead to high homocysteine levels in patients with vascular disease are complex and involve nutritional and genetic factors (25,26,203,204,205,206,207,208,209,210 and 211). The cellular mechanism, if any, leading to vascular damage in patients with high homocysteine levels is also unclear. Interactions with traditional risk factors (e.g., smoking, hypercholesterolemia, and hypertension) may predispose to a greater likelihood of vascular disease (14,72), but attention should also focus on interactions with nontraditional risk factors. The increased risk of thrombosis in patients with homocystinuria possessing the R506Q (Leiden) mutation of factor V (212) highlights the possibility of multiple coexisting genetic abnormalities predisposing to atherosclerosis and emphasizes the evolving concept of disease-modifying genes as an explanation for the diverse manifestation of complex phenotypes. Perhaps the most important issue is whether reduction is associated with an improved prognosis in primary or secondary prevention studies, and these issues should now be tested by clinically appropriate trials.

The role of Lp(a) in atherosclerosis and thrombosis remains unclear, but complex interactions with nontraditional risk factors are evident. There is increased binding of Lp(a) to fibrin by homocysteine (73). In addition,Lp(a) regulates PAI-1 expression in endothelial cells (131) and accumulates with fibrinogen in atherosclerotic plaque (127). It is also possible that Lp(a) may be more atherogenic in the presence of specific cholesterol subfractions and that certain Lp(a) phenotypes may be more atherogenic than others. Different populations may be at varying risk; this also requires further study. Reduction of high Lp(a) levels is possible, but, at present, this may not confer any benefit if LDL is maximally reduced. Future development of more specific and effective treatment may alter this perspective.

High circulating levels of fibrinogen and PAI are frequently seen in patients with atherothrombotic disorders, but their origin is obscure. Genetic determinants and their relationship to environmental factors require further study. Newer genetic polymorphisms in platelet glycoproteins (213,214) and procoagulants (215) and other prothrombotic determinants are likely to gain importance as we unravel the complexities of gene-gene interactions in atherothrombotic risk. Therapeutic studies are also needed but are made more complex, as in the case of fibrinogen, by the lack of a specific agent that selectively reduces levels of this clotting factor. As with other heritable abnormalities, the atherosclerotic and thrombotic tendency associated with specific phenotypic abnormalities—alone or combined with other risk factors—requires further evaluation. Additional prospective study is required to define the specific role of high levels PAI in atherosclerosis and thrombosis.

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11

BEHAVIORAL MEDICINE AND HEART DISEASE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Behavioral medicine integrates behavioral sciences with the science of medicine. Thus, the behavioral medicine approach to cardiac disease includes evaluation of behavioral, psychological, and social functioning in relation to the etiology and treatment of disease. Behavioral and psychological factors associated with coronary artery disease (CAD) include personality [e.g., Type A behavior pattern (TABP)], affective state (e.g., depression, anxiety), and social or work environment.

Although global Type A (TA) behavior previously was found to be strongly associated with the development of CAD, refinements of the TA construct have indicated that hostility and cynicism may be the most toxic components of the TABP. In addition, negative emotions other than hostility, especially depression, and environmental factors such as work strain (high demand, low control) have been associated with the development of CAD. Social support, on the other hand, appears to mitigate the negative effects of stress and environment on CAD.

Comprehensive evaluation of stress usually includes a subjective appraisal of stress, as well as physiologic indicators of stress as measured in laboratory studies of cardiovascular (CV) function. Stress-related hemodynamic alterations are important to evaluate because CV reactivity of the sympathoadrenal and pituitary adrenal-cortical systems is thought to be a pathophysiologic mechanism linking stress with development of CAD. Recent data also reveal stress-related changes in neuroendocrine function and blood lipids, which may contribute to CAD.

Intervention studies suggest that relaxation training may have beneficial effects on CV reactivity to laboratory stressors and that stress-management training may be beneficial for reducing components of the TABP. Stress-management interventions can minimize the impact of depression on future cardiac events among post–myocardial infarction (MI) patients, and stress management is a central component of multimodal treatments for patients with CAD. Studies have not yet demonstrated the optimal components or dosage of stress-management interventions among patients with CAD, but ongoing research is documenting various aspects of stress-management interventions that may be important in the treatment of cardiac patients.

GLOSSARY

Appraisal: The mechanism by which social support is thought to mitigate the effects of stress on health. *Primary appraisal* refers to support that helps to prevent the individual from viewing an event as stressful. *Secondary appraisal* refers to social support facilitating reappraisal (in a less stressful way) after an event that was viewed as stressful.

Biofeedback-assisted relaxation training: The use of auditory and visual feedback from electromyographic sensors to enhance individual awareness and control of muscle tension.

Cognitive-behavioral counseling: An approach to stress management that includes increasing the patient's awareness of negative and stressful ways of thinking that are likely to result in unhealthy behavior and negative social interactions. Cognitive counseling is directed toward increasing the frequency of positive, rational thinking.

Health behavior model: A theoretical model linking hostility with CAD and suggesting that hostile individuals are less likely to engage in good health habits.

Progressive muscle relaxation (PMR): A technique for reducing muscle tension and subjective stress by means of focused, systematic relaxation of muscle groups throughout the body.

Psychophysiologic (CV) reactivity model: A theoretical model linking hostility with CAD and suggesting that individuals high in hostility manifest larger increases in heart rate, blood pressure, and stress hormones than individuals with low hostility.

Psychosocial vulnerability model: A theoretical model linking hostility with CAD and suggesting that hostile individuals experience a more conflict-laden environment with less available social support.

Self-efficacy: The individual judgment of one's ability to achieve a goal. This is a widely studied concept in health psychology literature that has been proved to be an important psychological factor in behavioral change (e.g., exercise, smoking cessation, diet).

Structured Interview: An interview assessment of TABP and related characteristics (e.g., potential for hostility) that is widely regarded as the best assessment tool for evaluating TA characteristics.

Thought stopping: A stress-management technique in which patients are trained to stop the rapid succession of negative thoughts and feelings associated with stressful circumstances and to substitute alternative behaviors (e.g., relaxation) or thoughts.

Type A behavior pattern (TABP): Also described as *coronary-prone behavior*, TABP includes a constellation of behaviors and personality traits (e.g., excessive

competitiveness, chronic feelings of time pressure and urgency, chronic feelings of anger and hostility) associated with increased rates of CAD.

HISTORICAL PERSPECTIVE

For more than 50 years, clinical researchers have acknowledged the importance of behavioral, psychological, and social factors in the pathogenesis, assessment, and treatment of physical illness. The past several decades have witnessed a proliferation of research evaluating behavioral aspects of medical conditions and describing the direct and indirect effects of behavior and psychological functioning on incidence and progression of disease. Due to the widespread prevalence and profound impact of cardiovascular disease (CVD) in our society, research into the behavioral and psychological aspects of CAD has received an exceptional amount of attention and has flourished. In an effort to explore the multidetermined nature of behavioral and psychological factors in CAD, research in this area has addressed a broad spectrum of topics, including stress effects, personality (e.g., TABP, hostility, neuroticism), affective function, social support, health behavior, cognitive function, and CV reactivity.

In the 1950s, cardiologists Friedman and Rosenman first suggested the probability of a coronary-prone personality (1). More recent work has identified specific affective states (e.g., depression, anxiety, chronic anger) that are predictive of CAD (2,3), as well as relevant social and environmental factors associated with CAD (4,5). In addition, psychophysiologic researchers during the past two decades have successfully documented important individual differences in physiologic and behavioral responses to stress and the relevance of CV reactivity for the etiology of CAD (6,7). This multidisciplinary approach to the study of CAD typifies the field of behavioral medicine. Behavioral medicine involves the integration of behavioral sciences with the practice and science of medicine to promote and maintain health, prevent and treat illness, and identify etiologic and diagnostic factors in illness and health (8).

This chapter elaborates on the historical perspective by delineating the contribution of each area of research toward understanding behavioral and psychological factors in CAD. Subsequent sections of the chapter address biobehavioral factors in the etiology of CAD, behavioral and psychological interventions, and select issues and controversies relevant to future behavioral medicine research.

Stress

Stress has been broadly defined as an experience in which the demands of a situation exceed the perceived ability to cope with the situation (9), most often resulting from a person-environment transaction and leading to overarousal or underarousal of the organism (10). Much research has been directed toward elucidating the nature of the *stress response*, first described by Cannon (11) and characterized as an innate “fight-or-flight” response in animals when confronted by a threatening situation of a physical or social nature. Although this fight-or-flight response is an adaptive response to physical threats, it is not adaptive in most modern social circumstances and often is suppressed. In human beings, the stress response is marked by a cognitive appraisal of a situation as threatening, followed by physiologic changes such as increases in blood pressure, heart rate, respiratory rate, output of stress hormones, blood homocysteine levels (12), and blood platelet activity. It has been hypothesized that stress-associated physiologic arousal may contribute to chronic elevations in blood pressure and increased risk of cardiac disease (6). Thus, the stress response is a function of personality and individual differences that may affect the appraisal of the situation, as well as influence person-environment interactions.

An expanded view of the stress response was proposed in a recent review (13), in which it was observed that the majority of studies describing the fight-or-flight phenomenon has included only men. After extensive review of animal and human research, Taylor and colleagues (13) have postulated that women respond to stress with a “tend-and-befriend” pattern of behavior. *Tending* is described as nurturing activities that enhance safety and alleviate distress to protect the self and offspring; *befriending* involves the development and maintenance of social relationships that facilitate tending.

The tend-and-befriend pattern is thought to be a product of the biobehavioral attachment-caregiving system involving oxytocin, estrogen, and endogenous opioid mechanisms, which, in turn, down-regulate sympathetic nervous system responses. Taylor and colleagues suggest an evolutionary basis for this behavioral pattern, speculating that the tend-and-befriend stress response may help to explain gender differences in CV reactivity and life span. At a minimum, this view of the stress response indicates the importance of evaluating responses to stressful circumstances in the context of gender.

Several studies provide data suggestive of the importance of stress—physical or mental—in the onset of cardiac symptoms. Stressful, frustrating interpersonal relations may elicit anger and general excitement among CAD-prone individuals (14). In addition, epidemiologic research suggests that the onset of symptoms of acute MI are triggered by external factors (e.g., heavy physical work, violent quarrel, unusual mental stress) in a substantial minority of cases (10%) (15).

Work environment has become one of the most commonly studied environmental precipitants of stress-related cardiac disease, and it has been argued that work environment is more important to evaluate than individual factors (16). Johnson and Hall (17) found that job strain (high demand and low control) was associated with increased rates of CVD prevalence and that workers with the lowest level of social support had higher prevalence rates, regardless of level of job strain. Figure 11.1 provides a schematic of relative job strain associated with various common professions.

FIGURE 11.1 Illustration of the Karasek job strain model. Based on a job characteristics scoring system, occupations are characterized according to level of job demand and control. Workers with high demand and low control are at greater risk for cardiovascular disease. (Adapted from *The New York Times*, 3 April 1983.)

This research shows promise in providing evidence of the complex interaction of factors (e.g., work stress and social support) associated with CAD. Longitudinal data from a 14-year follow-up study revealed that working Swedish men with low control in their jobs had a significantly elevated risk for CVD mortality compared to men with high-control jobs (5). CV risk factors may also be affected by work stress. A study of 715 male shipyard workers found that the threat of job loss was associated with increased serum cholesterol, especially among those men reporting sleep disturbance (18). Thus, data suggest that work and related environmental stressors may have a significant influence on the development of CAD. However, individual differences in the frequency and magnitude of the stress response also suggest the importance of personality variables such as the TABP.

Type A Behavior Pattern

The TABP was first described in the late 1950s by cardiologists Meyer Friedman and Ray Rosenman, who observed in their patients a number of common behavioral characteristics and personality traits, including excessive competitiveness, extreme desire for recognition and achievement, chronic feelings of time pressure and urgency, as well as chronic feelings of anger and hostility (1). Although early research suggested a strong association of TABP with development of CAD (19), more recent data suggest that global TABP may not be associated with CAD (20,21). Thus, there remains controversy regarding the prognostic importance of TABP in primary and secondary prevention settings. Data from a recent metaanalysis indicate that global TABP may not be as relevant as more specific aspects of TABP, especially hostility (2).

Hostility and Heart Disease

Epidemiologic data evaluating personality traits associated with CAD suggest that chronic hostility and cynicism are the most pathogenic components of the coronary-prone personality (22). Smith has reviewed evidence for several models to explain the association (23). The psychophysiologic reactivity model is founded on the notion that individuals high in hostility are more likely to manifest larger increases in heart rate, blood pressure, and stress hormones in response to stressors than individuals with low hostility (22). However, the nature of the stressor may be important, as demonstrated by studies finding no association of hostility with reactivity in the context of nonsocial stressors (24) but significant associations in the context of interpersonal stressors (25). Other theoretical models linking hostility with disease

include the psychosocial vulnerability model (i.e., hostile individuals experience a more conflict-laden environment with less social support) and a health behavior model (e.g., hostile individuals may engage in poor health habits). The transactional model—representing a synthesis of the psychophysiologic and psychosocial models—posits that hostile individuals tend to respond to daily stressors with heightened CV and neuroendocrine reactivity and that these individuals experience more frequent, extreme, and enduring episodes of stress due to their hostile cognitions and overt behavior (23). Thus, all of the models linking hostility with CAD emphasize the interaction of the hostile individual with environmental stressors; this interaction supports the importance of individual constitutional variation and environmental factors.

Gender

Several studies suggest that gender differences may mediate the relationship between hostility and psychophysiologic reactivity. Davidson et al. (26) examined correlations between hostility scores from a Structured Interview assessment (27), scores on antagonism and neuroticism scales, and resting blood pressure among 193 undergraduate women and men. Whereas hostility was related to antagonism and higher resting blood pressure in men, hostility was related to neuroticism and lower resting blood pressure in women. Siegman et al. (28) explored the relationships between Structured Interview component scores and CAD status among 196 men and women undergoing thallium stress testing. Results of separate logistic regressions suggested that men with overt anger expression were at greater risk for CAD, but women with indirect expression of antagonism were at greater CAD risk. Similar results were observed by Lahad et al. (29) in a study comparing 277 women with a history of nonfatal MI with 988 case-control women without CAD. Lahad and colleagues found that hostile affect (i.e., the experience of negative affect in relationships) was associated with increased risk for MI, but aggressive responding (i.e., the tendency toward anger and aggression in response to problems) was associated with reduced MI risk.

Blood Serum

Recent studies have explored the relationship between hostility and lipid reactivity. In a study of 77 healthy women, Suarez et al. (30) observed significant elevations in total serum cholesterol and low-density lipoprotein cholesterol among women assessed as high in cynical and antagonistic hostility. Among healthy men (n = 98), Richards et al. (31) found significant associations between angry reactions (i.e., the tendency to experience and express anger in response to criticism or unfair treatment) and elevated total serum cholesterol and low-density lipoprotein cholesterol levels. Data also indicate that healthy women and men with high levels of hostility and men with inhibited anger expression may have higher levels of blood homocysteine (32). One hypothesized mechanism for this effect may be increased hemoconcentration associated with stress (33).

Depression and Anxiety

Although much early research was devoted to the relationship of CAD to TABP and its components, more recent data have suggested additional important psychological factors associated with CAD, especially anxiety and depression. In a metaanalysis of studies evaluating psychological functioning and CAD, it was found that the effect size for depression was as great as that of TABP or other known risk factors for CAD (2). Although anxiety was related to CAD, it was not as strongly related as depression. Thus, the traditional image of the coronary-prone individual as time pressured, impatient, and work oriented is not consistent with the data. Instead, a more appropriate image is that of someone harboring negative emotions, such as depression, anxiety, hostility, or aggression. Thus, hostility or anger would be supported as the most important component of TABP, but depression and anxiety also may be important predictors of CAD (2).

Depression has been implicated as an important factor in the initial onset of CAD (34), as well as among patients with previously diagnosed CAD. Frasure-Smith and colleagues (35) confirmed the importance of negative emotions, including depression, anxiety, and history of depression, for prognosis of post-MI patients. Results from their longitudinal study, included in Figure 11.2, suggested that post-MI depression was more strongly associated with arrhythmic deaths (3), whereas anxiety was more strongly associated with acute coronary syndromes (30). Carney et al. (36) found that major depressive disorder was the best predictor of cardiac events during the 12 months following catheterization among patients with CAD. It has been suggested that dysregulation of the autonomic nervous system—particularly, elevated resting heart rate and decreased heart-rate variability associated with reduced parasympathetic nervous system activity—may be one mechanism explaining the association of major depression with CAD (37). In a study of medically stable patients with CAD, heart-rate variability was significantly lower among subjects with moderate to severe depression than among mildly depressed and nondepressed patients (38). Also, depressed patients have been found to manifest elevations in heart rate at rest and under orthostatic challenge (39).

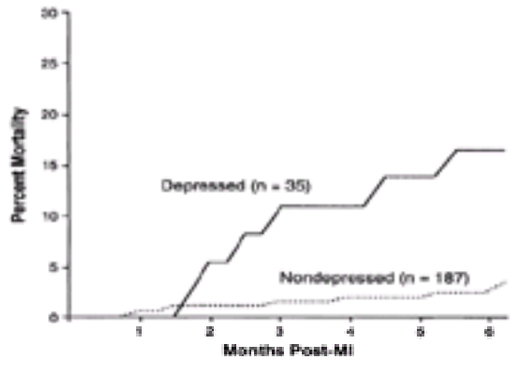

FIGURE 11.2 Cumulative 6-month mortality for depressed and nondepressed post–myocardial infarction (MI) patients. Depression was assessed with structured interviews during inpatient hospitalization (approximately 7 days post-MI). (Adapted from Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA* 1993;270:1821.)

The association of depression and CAD has continued to receive considerable attention and has led to current investigations of pharmacologic and behavioral interventions to treat depression among post-MI patients. Given the recent data indicating that exercise may be as efficacious as pharmacotherapy in the treatment of depression among healthy, older adults (40,41), exercise may be especially useful among cardiac patients in alleviating the physical and psychological symptoms associated with CAD. In addition, data from the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial should soon be available to evaluate the efficacy of cognitive-behavioral interventions among depressed patients with CAD. The ENRICHD trial is a multisite, randomized controlled clinical trial sponsored by the National Heart, Lung, and Blood Institute to examine the effect of cognitive-behavioral treatment for depression and poor social support on morbidity and mortality among post-MI patients. Participants were recruited for the study on the basis of having experienced acute MI and having clinical depression or being deficient in social support. Although results of ENRICHD and other clinical trials are not yet available, recent data underscore the importance of distinguishing long-standing depression and personality traits from acute, reactive depression after a cardiac event (34,42) and the relevance of examining interactions of depression with other psychosocial factors (e.g., social support). Acute depression in reaction to a cardiac event may be more amenable to relatively brief psychological intervention, whereas chronic depression is likely to involve a broader range of precipitating factors (e.g., other major life stressors in addition to health problems) and may require more intensive, long-term treatment.

Additional Psychological Factors

Numerous other studies have documented psychological and personality dimensions related to CAD. Among post-MI patients, data indicate that patients who experience distress and inhibited expression of emotion may have a higher rate of death than other personality types (43). Powell and Thoresen (44) found that the intensity of experiencing emotion was associated with reinfarction among coronary patients in the Recurrent Coronary Prevention Program, and Shekelle et al. (45) suggest the possibility of greater emotional susceptibility among post-MI patients based on data from a 10-year follow-up. Thus, the prospective data suggest that negative emotions, including hostility, depression, and anxiety, are predictive of coronary events. Among post-MI patients, inhibition of emotion and negative emotions, including cynicism, have been predictive of mortality. In addition, post-MI patients may be more emotionally vulnerable, potentially leading to greater intensity of emotional experience, which, in turn, is associated with cardiac events. The degree to which heightened emotional vulnerability is a cause or an outcome of MI remains unclear, based on the literature to date.

Social Support

During the past two decades, increased attention has been devoted to understanding the effects of social support on health, health behavior, and adherence to behavioral change programs. Cohen and Wills (46) have suggested that social support may have a beneficial effect on physical health by buffering the individual from the potentially pathogenic effects of stress. These researchers posit that the buffering effects of social support may act in two ways: (a) by preventing the appraisal of

stress immediately after an event (primary appraisal) or (b) by facilitating reappraisal (secondary appraisal) or inhibiting an emotionally linked physiologic response after an event is perceived as stressful. Cohen and Wills (46) note that social support may buffer stress by providing enhanced self-esteem, companionship, assistance in problem solving, and material aid. Several epidemiologic studies provide evidence to suggest that social support may act to mitigate the effects of chronic stress on the development of CAD. Population-based studies in Sweden have provided evidence that (a) low social support is associated with total and CV mortality in adults over the age of 35 (4); (b) men who reported feelings of loneliness had higher CV mortality rates than men not reporting loneliness (47); (c) low social activity, along with traditional risk factors, was associated with CV mortality (48); and (d) in a 3-year follow-up study of a CV risk reduction intervention, subjects who maintained health behavior changes had a larger support network and tended to be more family centered (49). A recent review of the literature suggested that social network is an important, independent risk factor for CVD in white middle-aged men and that the impact of social support is comparable to that of traditional risk factors for CVD (50). The effects of social support also have been found to interact with other risk factors for CAD among patients with symptoms of cardiac disease. In a sample of patients undergoing diagnostic coronary angiography, Blumenthal and colleagues (51) found that severity of CAD was negatively associated with perceived social support for TABP individuals, but no association of CAD and social support was found for type B participants.

In addition to its influence on appraisal of potentially stressful situations, social support may also affect CAD via the influence of caregivers and friends (a) encouraging appropriate health behavior change and use of medical care and (b) providing direct comfort and aid in tasks of daily living, thereby minimizing potential physical stresses (46,52). Relatedly, marriage may be an important source of social support associated with decreased risk of CAD. In a recent population-based study of risk factors for stroke among older adults in Australia, it was found that unmarried men had relatively low high-density lipoprotein cholesterol and relatively high systolic blood pressure, but widowed women did not have similar risk factors (53). In a population-based study pooling data from the Minnesota Heart Survey and the Minnesota Heart Health Program, separated or divorced persons had higher rates of hospitalization for heart attack or stroke than did married or widowed persons. However, separated or divorced persons also reported higher levels of smoking, drinking alcohol, and physical inactivity than did married persons (54). Thus, although spousal support may be important for facilitating health behavior changes in patients who are at risk of CAD and for supporting early identification of cardiac symptoms, data also indicate that hostile and antagonistic marital interactions may contribute to greater risk for CAD (55).

Psychophysiologic influences of social support on CV functioning via neuroendocrine or hemodynamic function also have been demonstrated. For example, among college-aged women, Kamarck et al. (24) found that CV reactivity (blood pressure and heart rate) to a mental stressor was attenuated by the presence of a friend. However, the study did not evaluate the extent to which this effect was cognitively mediated (i.e., the friend's presence minimized the cognitive stress of the task). A subsequent study (56) found that social support (e.g., the presence of a friend) influenced CV reactivity only in the presence of social threat and that the effect was most prominent among socially avoidant individuals. Thus, social support may interact with environmental or situational variables and individual personality dimensions to influence CV function.

Adherence and Risk-Factor Reduction

As awareness of risk factors for CAD has become more widespread through community education efforts, the need has grown for programs to support health behavior change. Most of the risk factors for CAD are behaviorally mediated and, thus, may be readily influenced and modified. For example, smoking, diet, and exercise activity all involve modifiable behaviors. However, it may be difficult to reach high-risk individuals in primary prevention, because it has been found that high-risk CAD groups (e.g., men, older adults, and individuals with less education) are less likely to make use of educational materials regarding CVD risk (57).

As shown in Figure 11.3, adherence to a behavioral program may be influenced by a number of factors, both individual and environmental. Among the most clearly identified individual factors affecting adherence are self-efficacy (i.e., the patient's belief that he or she will be able to achieve the behavioral goal) and self-motivation (58). Hellman (59) used a Stages of Change in Exercise Adherence (60) model to examine predictors of exercise adherence among cardiac patients who completed an inpatient rehabilitation program. This model consists of five stages of change in exercise adherence: (a) *precontemplation*—not exercising at present with no intent to begin exercising; (b) *contemplation*—not exercising at present but considering exercising in the future; (c) *preparation*—starting to exercise on a limited basis; (d) *action*—less than 6 months of regular exercise; and (e) *maintenance*—more than 6 months of regular exercise. Several predictor variables were shown to differentiate the stages of change in exercise adherence: perceived self-efficacy, perceived benefits of exercise, interpersonal support for exercise, and perceived barriers to exercise, with group means for exercise predictor variables increasing in a stepwise fashion from precontemplation to maintenance stages. Bock et al. (61) also used a stages of change model (60) to assess predictors of exercise adherence among 62 men and women who completed a 12-week cardiac rehabilitation program. At posttreatment assessment, 68% of patients had progressed at least one stage, with significant increases in self-efficacy and use of behavioral processes of change (e.g., reinforcement management, stimulus control) and significant reduction in ratings of the cons of exercise occurring from pre- to posttreatment. At a 3-month follow-up assessment, results indicated that patients who regressed toward earlier stages (42%) rated the cons of exercise higher than the pros, had decreased self-efficacy, and were less likely to use behavioral processes of change compared to patients who did not regress. Hershberger et al. (62) found significant associations between scores on a personality measure [e.g., Well-Being, Socialization, and Communality (i.e., similar views of self and others)] and percentage of exercise appointments kept among patients in cardiac rehabilitation.

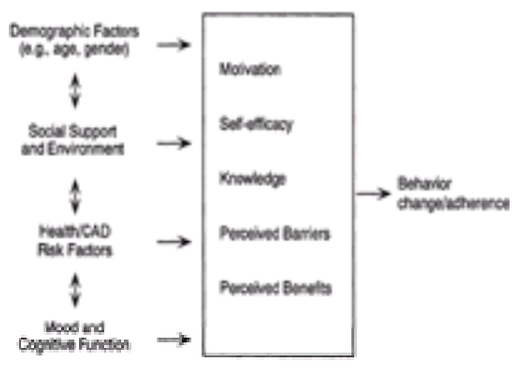

FIGURE 11.3 Hypothesized model of factors associated with adherence and behavior change. CAD, coronary artery disease.

Although studies of exercise adherence have been conducted among patients in cardiac rehabilitation programs, few studies have evaluated predictors of adherence outside of cardiac rehabilitation programs or adherence to health behaviors other than exercise. For example, environmental factors such as stress in the home or workplace may be associated with negative health behaviors (e.g., patient may resume smoking, overeating, or drinking to cope with stress at work) through the patient's reliance on previous maladaptive coping strategies. In a study of 118 healthy men enrolled in a CAD prevention program, Naslund et al. (63) noted that poor compliance with increased consumption of dietary fiber was associated with hostility, perceived barriers to diet modification, and little knowledge of CAD risk factors. Poor compliance with a low-fat diet was related to younger age, smoking, and negative family history of CAD. Poor compliance with exercise was associated with younger age and having children living at home. Further study is required to evaluate the complex interaction of psychological and social variables affecting adherence.

BIOBEHAVIORAL FACTORS IN THE PATHOPHYSIOLOGY OF HEART DISEASE

As theoretical advances have been made in evaluating physiologic mechanisms of behavioral and psychological effects in CAD, the major thrust of research has been directed toward studies of CV reactivity.

Cardiovascular Reactivity

Studies suggest that stress may contribute to the development of CAD via stress-associated, chronic, exaggerated reactivity of the sympathoadrenal-medullary and pituitary adrenal-cortical systems, triggering hemodynamic changes or biochemical alterations that lead to damage of artery walls (6). The impact of CV reactivity is thought to be cumulative, contributing to injury of the endothelium and to deposition of cholesterol on the artery wall. Among patients with CAD, CV reactivity may also contribute to myocardial ischemia and arrhythmias (23). Studies generally confirm an association of elevated CV reactivity in individuals with symptoms of CAD or hypertension (6). Indeed, among post-MI patients, CV reactivity to a cognitive task (the Stroop test) predicted subsequent clinical events (i.e., MI and stroke) (7). Furthermore, among mildly hypertensive subjects, CV reactivity was associated with elevated total cholesterol levels, as well as elevated low-density lipoprotein cholesterol and lower levels of high-density lipoprotein cholesterol (64). In research with cynomolgus monkeys fed an atherogenic diet, it has been demonstrated that monkeys responding to stress with high heart-rate reactivity had significantly greater coronary atherosclerosis than did low heart-rate reactors (65). In humans, laboratory studies have confirmed stress-associated CV and neuroendocrine changes (6), and it has been theorized that stressful interpersonal interactions and work environment may be potent precipitants of increased nervous system reactivity, leading to acute changes in CV or endocrine functioning. Thus, CV reactivity is viewed as a marker of the stress response and as a mechanism in the pathophysiology of heart disease.

In psychophysiologic studies of CAD, CV reactivity is a critical outcome measure that can be evaluated reliably in a laboratory setting. The methodology for measurement of CV reactivity may be specific to the clinical and research questions being addressed, and several methodologies have been summarized elsewhere (66). Because of the limited generalizability of laboratory measurement of CV reactivity, measurement of CV and neuroendocrine functioning in naturalistic settings is increasingly emphasized in clinical research studies.

Health-Damaging Behavior

The health behavior model described by Smith (23) suggests that the association between hostility and CAD is the result of poor health behavior among hostile individuals. In support of this model, Smith summarizes studies that have demonstrated associations between hostility and low physical exercise, low self-care, higher alcohol consumption, higher body mass index, and more cigarette smoking. However, the interrelationship of hostility, health behavior, and CAD has not been evaluated. Frasure-Smith et al. (3) suggest that health behavior change among cardiac patients also may be impaired by affective distress (e.g., depression and anxiety). Although social support may serve to moderate somewhat the negative effects of emotional state and personality on health behavior change, the effect of personality and emotions on adherence to preventive and rehabilitative health behaviors has not been investigated.

Cognitive functioning also may affect an individual's ability to conduct adequate self-care and follow prescribed health care regimens. Although several studies have documented cognitive deficits among cardiac patients (67,68), only one study has evaluated the association of cognitive functioning with health behavior in cardiac patients. In a sample of clinically stable cardiac rehabilitation patients, Barclay and colleagues (69) found that 35% were so cognitively impaired that they were unable to self-administer medications appropriately. The evaluation of interactions of cognitive performance with health and health behavior is especially important among older adults with or at risk for CAD.

Relationship among Areas of Behavioral Medicine

As the research data indicate, it is difficult to define psychosocial functioning by addressing only one of the many psychosocial factors in CAD because these factors are likely to be interrelated. For example, social support may mitigate the association of TABP with CAD, as well as minimize CV reactivity to laboratory stress. Figure 11.4 provides an illustration of the relationships among various behavioral factors suggested by the research data thus far.

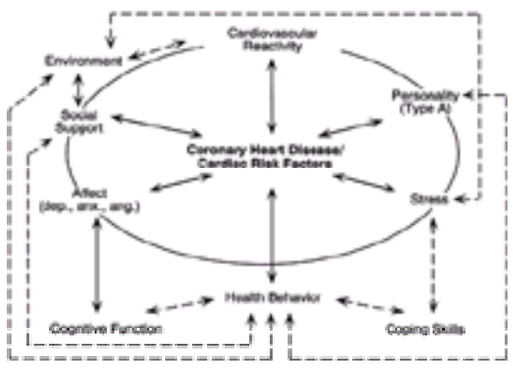

FIGURE 11.4 Psychosocial factors associated with coronary heart disease and cardiac risk factors. Stronger associations are depicted with solid arrows; less strong associations are depicted with hatched arrows. ang., anger; anx., anxiety; dep., depression.

CLINICAL PROFILE AND ASSESSMENT

The historical research data suggest that the typical CAD patient is likely to manifest one or more components of TABP—most likely hostility or cynicism, as well as other negative emotions such as depression or anxiety. In addition, the patient's work and home environments may present obvious or subtle stressors of a chronic nature, and social support may be limited. Although not all CAD patients present with psychosocial problems, the clinician addressing behavioral issues among CAD patients must use adequate assessment techniques to facilitate appropriate treatment strategies.

Several assessment instruments have been used by researchers to measure psychiatric symptoms, physical symptoms, psychological functioning, social support, and stress. A listing of common assessment instruments is included in Table 11.1. The Structured Interview assessment was the first instrument designed to measure TABP and remains the benchmark of global TABP assessment tools (70). In addition, the Structured Interview can be used to evaluate potential for hostility (i.e., tendency to experience anger and resentment, tendency to react to aggravating events with antagonism and rudeness) (71), which has been associated with CV outcomes (23). Use of more specific assessment tools has helped isolate anger and hostility as the potentially toxic components of TABP. The Cook-Medley Hostility Scale (72), derived from the Minnesota Multiphasic Personality Inventory (73), is one of the most widely used self-report instruments to assess hostility. The Beck Depression Inventory (74) is a 21-item, self-report questionnaire that measures severity of depressive symptomatology, although it is not designed to diagnose clinical depression. In a study by Frasure-Smith et al. (3), the Beck Depression Inventory predicted later post-MI mortality in patients who did not meet criteria for major depression. The Social Support Questionnaire (75) consists of a series of items that yield scores for a perceived number of social supports and satisfaction with social supports. Measures of work stress also have been included in assessments of psychosocial risk in CVD. The Job Content Questionnaire, developed by Karasek (76), includes two scales that define job strain: decision latitude and psychological job demands. Job strain as measured by the Job Content Questionnaire was shown to be a risk factor for hypertension and increased left ventricular mass in a sample of 215 working men employed in a variety of jobs at seven urban work sites (76).

Stress and coping
Hopkins Symptom Checklist-90-R (SCL-90-R)
Millon Behavioral Health Inventory (MBHI)
General Health Questionnaire (GHQ)
Sickness Impact Profile (SIP)
Schedule of Recent Life Events (SRLE)
Life Experiences Survey (LES)
Perceived Stress Scale (PSS)
Personality/type A
Structured Interview (SI)
Jenkins Activity Survey (JAS)
Cook-Medley Hostility Scale (Ho)
Buss-Durkee Hostility Inventory (BDHI)
Minnesota Multiphasic Personality Inventory (MMPI)
Eysenck Personality Questionnaire (EPQ)
Social support
Social Support Questionnaire (SSQ)
Perceived Social Support Scale (PSSS)
Dyadic Adjustment Scale (DAS)
Work
Job Content Questionnaire (JCQ)
Psychiatric comorbidity
NIMH Interview Schedule (DIS)
Beck Depression Inventory (BDI)
Center for Epidemiological Studies Depression Inventory (CES-D)
Profile of Mood States (POMS)
State-Trait Anxiety Inventory (STAI)

NIMH, National Institute of Mental Health

TABLE 11.1 PSYCHOSOCIAL ASSESSMENT INSTRUMENTS COMMONLY USED IN CARDIOVASCULAR MEDICINE

These measures represent a sampling of instruments available for assessment of behavioral and psychological factors among patients with CAD. Although there are no firm guidelines for selecting appropriate assessment instruments, it is important that behavioral and psychological evaluation be conducted. Assessment of hostility, depression, social support, and work strain is especially important, given these factors' relevance for patients with CAD.

BEHAVIORAL AND PSYCHOLOGICAL INTERVENTIONS

Most cardiac risk factors are modifiable, with the exceptions of age, gender, and family history. Primary prevention strategies tend to target at-risk behaviors, such as cigarette smoking, poor dietary habits, and sedentary lifestyle. Secondary prevention efforts also aim to reduce health-damaging behaviors and improve compliance with physicians' recommendations; these efforts often include additional therapeutic techniques to reduce the impact of psychological distress and other psychosocial risks that can interfere with a positive prognosis. Among the intervention strategies commonly used are stress reduction techniques, relaxation training, biofeedback, and other psychotherapeutic interventions. However, none of these techniques is mutually exclusive. Most studies of psychosocial interventions among cardiac patients have evaluated the effects of stress-management interventions encompassing relaxation training and selected other techniques, such as cognitive counseling (e.g.,

identifying and challenging irrational, stress-producing thought patterns) or behavioral counseling (e.g., modifying contingencies for desired behavior). Relaxation techniques typically include breathing exercises and PMR—a process of systematic tensing and relaxing of major muscle groups throughout the body. Cognitive and behavioral components of stress management have included specific skills training, such as public speaking training, stress-inoculation training emphasizing positive self-statements, biofeedback-assisted relaxation training with electromyography and heart-rate feedback, and affect regulation, including appropriate expression of anger and hostility. Few studies have been conducted to compare the relative efficacy of the stress-management components. The only study contrasting components of stress management among cardiac patients found no significant differences between a relaxation condition and a no-relaxation stress-management condition (i.e., monitoring negative self-statements) with regard to psychological functioning (i.e., decreases in social anxiety) (77).

Stress Management

The effects of stress management on cardiac outcomes have been studied mainly in secondary prevention. The Ischemic Heart Disease Life Stress Monitoring Program (35) examined the impact of stress monitoring and intervention in 543 male post-MI patients randomly assigned to a treatment condition or no-treatment control. Subjects in the treatment condition received monthly telephone calls from nurses who assessed stress levels. If the subject's monthly stress level was above the standard criterion (i.e., above 4 on the General Health Questionnaire; 78), he would receive individual counseling and advice designed to alleviate stress. Results indicated that the monitored group showed a greater decline in stress levels compared to no-treatment controls. Although the monitored group did not differ from the controls in the incidence and length of hospital readmissions, the rate of mortality for that group was significantly lower. Data from this study are depicted in Figure 11.5. The authors suggest that stress reduction interventions may play a greater role in lowering cardiac mortality than in preventing future nonlethal cardiac episodes. Unfortunately, the investigators did not control for the type of counseling offered to each subject; indeed, they suggested that the phone call itself might have been responsible for lowering stress levels.

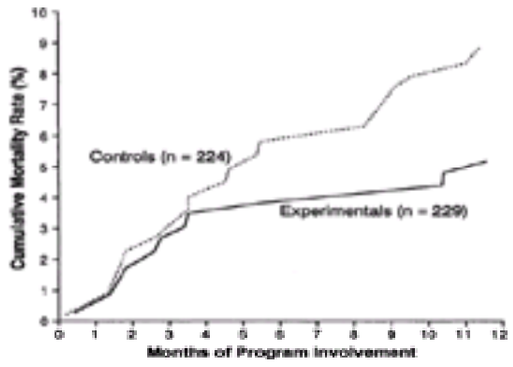

FIGURE 11.5 Life-table cumulative mortality rates for post–myocardial infarction patients randomly assigned to experimental group (stress monitoring) or no-treatment control group. (From Frasure-Smith N, Prince R. The ischemic heart disease life stress monitoring program: impact on mortality. *Psychosom Med* 1985;47:438, with permission.)

Among post-MI subjects, stress-management interventions (e.g., coping skills training, PMR, deep breathing exercises, biofeedback) have been found to provide greater cardiac benefit (i.e., significantly fewer arrhythmias, less chest pain, and better overall cardiac status) than cardiac education alone (79), and the effect of stress management on psychophysiologic reactivity has been found to be comparable to that of drug treatment (e.g., propranolol) (80). Stress management also has been evaluated as an adjunct to exercise rehabilitation in a study of 45 post–coronary artery bypass graft patients randomly assigned to (a) conventional medical therapy and exercise rehabilitation or (b) conventional therapy, exercise rehabilitation, and stress-management intervention (81). Exercise rehabilitation included three 1-hour workouts per week for 18 weeks. Stress-management intervention included eight 90-minute sessions that provided education about TABP, expression of anger and hostility, use of humor, and autogenic training—a form of relaxation training. Subjects received a booster session 1 month after the end of the program. Results indicated that subjects in the stress-management intervention experienced reduced blood pressure reactivity, as well as improved perceived health status and decreased triglyceride levels. The conventional treatment showed a decrease in high-density lipoprotein. Blumenthal et al. (82) compared the effects of stress management or exercise on myocardial ischemia and risk for cardiac events among 107 CAD patients exhibiting ischemia during mental stress tasks or ambulatory monitoring. Patients were randomized to stress management (i.e., psychoeducational group sessions, monitoring and modifying irrational thoughts, PMR, and biofeedback) or an exercise intervention (i.e., riding on a stationary bicycle, walking, and jogging three times per week) for 4 months. Patients residing at a distance from the study site comprised a nonrandom, usual-care control group. Patients were contacted at 4 months, 10 months, and at yearly intervals up to 5 years to assess cardiac morbidity and mortality. Compared to patients in the usual-care control group, patients in the stress-management group had significantly lower relative risk for cardiac events throughout the 5-year follow-up period. In addition, subjects in the stress-management condition experienced reductions in ischemia during mental stress and ambulatory monitoring.

Dusseldorp et al. (83) conducted a metaanalysis of 37 studies to evaluate the effects of stress-management and health-education programs on cardiac morbidity and mortality and risk-factor reduction. Stress-management programs were defined as psychotherapeutic or supportive interventions or as relaxation training. Health-education programs involved contact between professionals and patients for organized instruction on CAD risk-factor reduction and behavioral change. Results of this quantitative review found that stress-management and health-education programs provided an average of 34% reduction in cardiac mortality, a 29% reduction in recurrent MI, and significant improvements in blood pressure, cholesterol, weight, smoking cessation, exercise, and diet. Programs that had greater success in risk-factor reduction showed, in turn, the strongest effects on disease outcome variables.

In a primary prevention study, Patel and colleagues (84) examined the effects of relaxation training—including breathing exercises and meditation techniques—among 192 men and women with two or more coronary risk factors (e.g., high blood pressure, high cholesterol, or cigarette smoking). Subjects were randomly assigned to a treatment group that received health-education leaflets and 8 weeks of relaxation training or to a control group that received only the educational leaflets. In the relaxation group, systolic and diastolic blood pressure were significantly reduced after 8 weeks, as well as at 4-year follow-up. No significant blood pressure changes were observed in the control group; at 4-year follow-up, the control group had a significantly higher incidence of ischemic heart disease, fatal MI, or electrocardiographic evidence of ischemia.

Beneficial effects of relaxation-based stress management also have been observed among patients with diagnosed CAD. Trzcieniecka-Green and Steptoe (85) examined the effects of a 12-week stress-management program on various aspects of psychosocial functioning in 78 patients who had recently experienced MI, coronary artery bypass graft surgery, or coronary angioplasty. Results indicated that subjects experienced a reduction in anxiety, an improvement in activities of daily living and social activities, and greater satisfaction with sexual relationships; these effects were largely maintained at 6-month follow-up.

Relaxation training also has been evaluated as an adjunct to standard exercise-based cardiac rehabilitation programs. Progressive relaxation training among 18 post-MI patients in a cardiac rehabilitation exercise program was associated with lower State Anxiety scores and reduced somatization, anxiety, and depression scores compared with scores of 19 nonrandomized control subjects who were not provided relaxation training (86). Munro et al. (87) examined the effect of relaxation training among 27 subjects in cardiac rehabilitation compared to 30 nonrandomized controls who received standard treatment. At 3-month follow-up, the relaxation group sustained a significant reduction in diastolic blood pressure, but the control group did not. However, relaxation had no effect on psychosocial functioning.

Van Dixhoorn and colleagues examined the impact of relaxation training as an adjunct to exercise-based cardiac rehabilitation programs in a series of randomized trials. Post-MI patients who received exercise training plus relaxation and breathing therapy had less cardiac dysfunction (88) and a significantly lower rate of reinfarction (17%) than patients receiving exercise training alone (37%) (89). Exercise alone did not affect psychosocial variables, but exercise combined with relaxation training resulted in reductions in anxiety and improvements in well-being (90).

Behavioral Counseling and Therapy

The impact of behavioral and psychological factors on CVD outcomes suggests that mental health and behavioral interventions should be part of multidisciplinary treatment programs and secondary prevention strategies (91). Although data indicate that psychological counseling may be associated with improved prognosis, few published studies have examined the effects of psychotherapy in cardiac care. In one early study, a group of six post-MI patients showed improvements in psychosocial functioning after nondirective group therapy (92).

In a randomized block-design study, 46 post-MI patients were assigned to one of three groups: an educational intervention that included cardiac information and relaxation training, an education plus counseling intervention involving six to ten sessions of individual psychological counseling in addition to the educational

intervention, or a control condition of routine medical care (93). After 3-, 6-, and 12-month follow-ups, both intervention groups demonstrated significant improvements in psychological and lifestyle functioning and reported fewer cardiac symptoms compared to the control group.

Cognitive and behavioral counseling appears to have been effective in modifying TA behavior in the Recurrent Coronary Prevention Program (94). Post-MI patients (n = 862) were randomly assigned to group cardiac counseling, group cardiac counseling plus TA behavior modification counseling, or a waiting-list control condition. Cardiac counseling focused on strategies improving behavioral compliance with medical recommendations. TA counseling included relaxation, cognitive therapy, and graded behavioral assignments. The cardiac counseling group met biweekly for 3 months, monthly for 3 months, and bimonthly until the conclusion of the study; the TA behavior modification group met weekly for 2 months, biweekly for 2 months, and monthly through the conclusion of the study. After 1 year, results indicated significantly greater changes in global TA ratings, hostility, and anger in the TA modification intervention than in the cardiac counseling group. At the 41/2-year follow-up evaluation, the TA modification group had a significantly lower reinfarction rate than the cardiac counseling group (13% vs. 21%). The TA modification group also reported greater improvements in self-efficacy and social support and lower levels of depression than the cardiac counseling group. Although the results suggest that TA counseling was associated with a decreased reinfarction risk, the intervention may have affected other psychosocial indicators associated with CAD (95), such as depression and anxiety.

In a recent study, 22 highly hostile CAD patients were randomly assigned to a hostility intervention consisting of eight 90-minute, weekly group meetings or a one-session information control group (96). The intervention addressed behavioral, cognitive, and affective hostility factors, as well as relapse prevention. Immediately after treatment and at 2-month follow-up assessment, intervention patients had lower hostility on self-report and interview ratings and lower resting diastolic blood pressure compared to control patients. Moreover, significant positive correlations were found between reductions in hostility and diastolic blood pressure. Davidson et al. (97) subsequently examined patient interviews from this sample and found that the relationship between reductions in hostility and diastolic blood pressure was mediated by increased ability to express anger verbally in a constructive fashion.

Investigators have developed theories to explain the relationship between hostility, interpersonal interactions, and CV reactivity. Davidson et al. (97) theorize that when hostility and cynicism are minimized, previously hostile individuals' enhanced willingness to participate in problem solving reduces their exposure to interpersonal provocation, which, in turn, reduces blood pressure reactivity. Stoney and Engebretson (98) suggest that expressions of anger be considered in terms of two modes of expression: (a) "communicative" expressions that are nonthreatening or (b) "aggressive" expressions that involve the intent to inflict verbal or physical harm. The notion that verbal expressions of anger can be constructive is supported by the results of a recent study that found a positive relationship between anger expression and quality of social support among 246 undergraduate men and women (99).

Multidisciplinary Interventions

Recent cardiac intervention studies have incorporated several behavioral strategies into multidisciplinary efforts. Ornish and colleagues (100) conducted a randomized controlled clinical study of an intensive multidisciplinary intervention on patients with CAD. Twenty-eight subjects participated in the treatment group, and 20 subjects participated in the usual-care control group. Treatment subjects were provided an intensive 1-week retreat at which they were instructed in numerous areas of lifestyle change, including initiating a low-fat vegetarian diet (i.e., <10% calories from fat), practicing stress management for at least 1 hour per day (e.g., stretching and breathing exercises, meditation, progressive relaxation, and imagery), and exercising regularly (i.e., minimum of 3 hours per week with 30 minutes at target heart rate). After the retreat, intervention subjects participated in group support meetings for 4 hours twice a week. At 12-month follow-up, experimental subjects had reduced cholesterol, fewer angina episodes, and significant regression of coronary atherosclerosis, but control subjects were unchanged. Better adherence to the experimental regime was associated with greater decreases in stenosis of the arteries, as shown in Figure 11.6. Experimental subjects continued to exhibit regression of coronary atherosclerosis at 5-year follow-up; control subjects showed progressive coronary atherosclerosis and had twice as many cardiac events (101). Although the results are impressive, the study has been criticized for several reasons. The intensive nature of the treatment raises questions as to its viability, cost-effectiveness, and generalizability to larger samples. Only half of the 94 original subjects randomized to treatment and control conditions agreed to participate in the study, raising the possibility of selection bias. In addition, the study did not discriminate between the effects of individual components of the multidisciplinary treatment program.

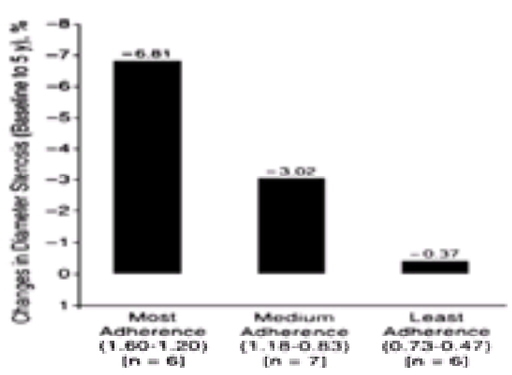

FIGURE 11.6 Percentage change in coronary arterial diameter stenosis over 5 years by adherence tertiles for coronary heart disease patients assigned to intensive lifestyle (exercise, diet, stress management) intervention. (Adapted from Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* 1998;280:2005.)

The Women's Lifestyle Heart Trial (102) used the methodology developed by Ornish et al. (100) in a study of 25 postmenopausal women with CAD. Fourteen women were randomized to the treatment group, and 11 were randomized to the usual-care control group. Results at 4-, 12-, and 24-month follow-up showed significantly greater improvement for the treatment group, as reflected by decreases in body mass, angina symptoms, and hypertension medications, as well as increases in self-reported quality of life. There were also trends toward lower lipids and blood pressure in the treatment group, as well as reductions in lipid-lowering medications.

Spoth et al. (103) assessed a minimal multidisciplinary intervention in 47 patients undergoing coronary angioplasty. Patients were randomized to one of three treatment conditions: minimal intervention (1-day risk-reduction educational workshop plus individual consultation on behavior change), minimal intervention plus biofeedback training (six 1-hour sessions), or waiting-list control. Both intervention groups showed greater increases in knowledge about CVD risk reduction strategies, but the group in the combined program had a greater benefit in self-reported lifestyle behavior change.

Several community-wide primary intervention trials aimed at reducing behavioral and psychosocial risk factors have been studied [e.g., Purdue Stepped Approach Model (104); Stanford Five-Cities Project (105)]. Although clinical interventions are more intensive and responsive to individual cognitive, behavioral, and psychological needs, community interventions have the advantage of reaching a much larger audience (104). The majority of these interventions is based on health-education and health-promotion strategies; the results are generally encouraging, revealing improved use of educational resources and compliance with health-promotion programs.

The intervention strategies reviewed show promising results, but they suffer from methodologic shortcomings. Most strategies are lacking randomized control groups; many have high dropout rates, small samples, and unbalanced sample sizes in treatment conditions and lack assessment of long-term cardiac outcomes. Ethical concerns may contribute to the methodologic problems, such as reluctance to include a no-treatment control group in clinical settings. There may also be a bias toward publishing only positive results. Despite these shortcomings, the findings are encouraging and suggest that stress-management approaches can be an effective component of primary and secondary efforts to minimize the impact of CAD. Specifically, the data suggest that clinical behavioral and psychological management of cardiac patients should include (a) relaxation training, (b) education regarding cardiac risk factors, (c) identification of social and environmental stressors, (d) facilitation of social support mechanisms, and (e) focused cognitive approaches to stressful interactions (e.g., positive self-talk, thought stopping, distraction). The data suggest that such interventions provide additional benefit to cardiac patients beyond the benefits of exercise per se. Although the efficacy of stress management and relaxation has been demonstrated, no studies have evaluated the appropriate "dose" required.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Psychological Influences in Heart Disease

Decades of research have helped to refine the TABP construct and delimit its components (e.g., hostility and cynicism), which appear to be associated with the etiology of CAD. Recent data suggest that depression also may be an extremely important psychological factor in the etiology of CAD, as well as in mortality post-MI. There is acknowledgment of the importance of environmental or interpersonal factors in the manifestation of coronary-prone behavior, as well as the importance of situational appraisal as a hypothesized modifiable link between stimulus and physiologic response. The transactional model described by Smith (23) posits that the hostile individual creates situations that are challenging and stressful. Although no studies have directly tested this model, it deserves further scrutiny to evaluate the full extent

to which the hostile or coronary-prone individual exerts control over physiologic responses and cognitive or emotional responses. In the treatment literature, it is assumed that individuals exert a considerable amount of influence over select aspects of physiology and cognition. However, the parameters of control must be explicated further to help direct future psychosocial interventions among patients at risk for cardiac disease.

Environmental influences also may affect the individual's health-promoting behavior, thereby having an indirect influence on the development or progression of CAD. Although the research literature has addressed various psychosocial components related to CAD, studies have not addressed more complex models integrating psychophysiologic, social, environmental, and personality variables. Thus, despite data suggesting the relevance of several psychosocial variables, there is minimal documentation of the way in which the variables interact or the relative importance of psychosocial variables. For example, O'Neil and Emery (99) found a positive relationship between anger expression and quality of social support among college undergraduates with a family history of CAD. This counterintuitive result of a higher quality of social support for people who express anger may reflect the positive aspects of a greater willingness to discuss problems and emotions with close friends. In addition, the presence of a curvilinear relationship between hostility and quantity of social support in this study suggested the possibility that social relationships may increase with a moderate degree of cynicism but not with a high degree of cynicism (99). Thus, it is important to recognize that factors associated with CAD may interact in unexpected ways.

Brummett et al. (106) found a directly inverse relationship between CAD patients' perceived social support during hospitalization and depressive symptoms 1 month after discharge; hostility was indirectly predictive of postdischarge depressive symptomatology due to its negative association with social support. In a comparative population study of Lithuanian and Swedish men (107), a four-fold higher CAD mortality rate for Lithuanian men was associated with poor social support, low self-esteem and quality of life, depression, vital exhaustion, and poor expectations for health and well-being. Data suggest that social support may have less impact than negative emotions on cardiac events among post-MI patients (3), but further research will help to clarify models describing the relative impact of psychological and social factors in CAD.

In clinical practice, data suggest the importance of teaching relaxation skills, addressing psychological distress, especially depression and anger, and working with patients in identifying social and environmental sources of stress and support. Although none of these areas is easily addressed by the practicing cardiologist, recent data suggest that cardiac patients' satisfaction with health care providers' support is associated with enhanced recovery times (108). Thus, it is important for the cardiologist to attend to the patient's concerns and provide support directed at those concerns while encouraging the patient to make positive steps forward in recovery and health-behavior change. The cardiologist may help the patient view the illness as an opportunity to reevaluate priorities and set new goals, thereby encouraging the patient to remain oriented toward the future instead of dwelling on perceived past mistakes. Perhaps the most important role for the cardiologist is to help the patient identify specific individuals (e.g., spouse, child, friend) who will be supportive of the patient and future behavioral changes. Toward that end, cardiac rehabilitation programs provide an excellent environment for the patient to receive emotional and physical support from staff members and fellow patients, in addition to learning further strategies for exercise, nutrition, and stress management.

Measurement and Data Analysis

Despite the availability of a wide range of psychosocial assessment procedures, implementation of the assessments may be restricted. For example, metaanalysis has indicated that self-report measures of TABP are not adequate and that the Structured Interview is a preferable assessment technique for TABP (2). However, the Structured Interview is a more cumbersome and expensive assessment because it requires a face-to-face interview conducted by trained interviewers and scoring of videotaped interviews. Thus, the Structured Interview may be impractical in many settings, and clinical investigations of TABP and related factors (e.g., potential for hostility) may be constrained by inadequate measurement. Studies of more specific psychological and personality factors (e.g., depression or neuroticism) are likely to be easier because of the availability of valid and reliable self-report measures.

Technological advances have enhanced the reliability of CV reactivity measurement, and CV reactivity may have utility as an outcome for the clinician to document changes over time in physiologic response to laboratory or environmental stress. However, analysis of reactivity data remains controversial due to conflicting methodologies for analysis of the complex data resulting from reactivity studies. In addition, measurement of CV parameters, especially determination of baseline values, may be subject to experimental bias or neglect (66). Although data indicate the importance of the cardiac patient's home and work environment as potential sources of interpersonal conflict and work stress, there is a lack of reliable measurement of environmental factors and a lack of agreement regarding choice of environmental factors to measure. Because the analysis of psychological-environmental interactions in the pathogenesis of CAD remains a critical area for further study, it is important for clinicians working with cardiac patients to help elucidate relevant environmental factors to consider for evaluation.

Implementation of Behavioral and Psychological Interventions

Evidence exists for the importance of psychological factors (e.g., depression, hostility) in the pathogenesis of CAD, as well as for the effectiveness of behavioral and psychological interventions in modifying psychosocial risk factors (109). Although behavioral and psychological approaches are increasingly embraced in the practice of CV medicine, there remains a bias against directly addressing psychological issues. This bias may stem from several sources, including (a) patients and family members who are reluctant to acknowledge that psychological or social factors may play a role in the patient's health and heart condition and (b) inadequate resources available for behavioral assessment and treatment. The result of this bias is that, often, only patients who are most distressed, most difficult to manage, or unresponsive to traditional medical care are referred for behavioral and psychological evaluation. Such patients may be angry at the health care system and less willing to address psychological issues, thereby undermining the efficacy of the intervention. However, data from randomized clinical studies support the utility of behavioral and psychological interventions for the average patient. Thus, the most efficacious approach for addressing behavioral and psychological issues among cardiac patients is to provide all patients with psychological evaluation, group support, and individual follow-up intervention as needed. The accumulated evidence supporting the relevance of behavioral and psychological factors in CAD indicates that a behavioral and psychological assessment and treatment model would be appropriate in primary care settings, as well as in rehabilitation settings. By making behavioral evaluation a routine part of practice, all patients would benefit without fear of being stigmatized.

Factors limiting the ability to implement a behavioral and psychological evaluation and treatment program among cardiac patients are the reluctance of third-party payers to reimburse for behavioral services and the difficulty that most patients have paying for medical costs out-of-pocket. This problem can be addressed, in part, by health care providers who are sensitive and responsive to behavioral issues. More important, systematic collection of behavioral and psychological outcome data can help to clarify the utility of behavioral and psychological assessment and treatment among cardiac patients and patients at risk for CAD. In addition, further clinical studies are needed that compare the effects of established behavioral interventions (e.g. relaxation training, cognitive therapy) and lifestyle interventions on the incidence and progression of CAD and that evaluate psychological factors associated with long-term adherence and behavior change among patients with CV risk factors and CAD. The accumulated evidence to date suggests that behavioral and psychological factors are of critical importance in the etiology and treatment of CAD and cardiac risk factors. By implementing and evaluating behavioral interventions, it is possible to refine intervention techniques and develop symptom- and illness-specific behavioral and psychological assessment and treatment protocols.

THE FUTURE

Empirical studies have documented the potent effects of negative emotions on the development and course of CAD, and studies support the importance of CV reactivity and related neuroendocrine changes as pathophysiologic mechanisms by which stressful events may contribute to the development of CAD. Future clinical research will be dedicated to the task of evaluating the complicated interactions of social, psychophysiologic, and health behavior factors in the development of CAD and the mechanisms explaining interactions of these factors with emotions and coping skills. In addition, future research will further explore the mechanisms by which gender may interact with behavioral, psychological, and physiologic factors in the etiology of CAD. Studies will also address treatment outcomes among cardiac patients to determine the most effective strategies for minimizing the influence of negative psychosocial factors in the epidemiology of CAD.

ACKNOWLEDGMENT

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12

CARDIAC REHABILITATION AND SECONDARY PREVENTION

PHILIP A. ADES

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Cardiac rehabilitation is a well-defined process that has changed over the years from a narrowly focused, closely monitored exercise program for coronary patients to a widely applied secondary prevention process, available to a broad range of patients with cardiovascular disease. Risk reduction outcomes are closely tied to specific individualized patient goals, often delivered in a case-management format. The greatest benefits are often manifest in the highest-risk patients and extend to women, elderly patients, and patients with chronic heart failure (CHF). The best determinant of patient participation in cardiac rehabilitation is the strength of the primary physician's recommendations, and these physicians should be actively recruited into the rehabilitation process from acute coronary event to participation in long-term preventive care.

Cardiac rehabilitation is highly cost-effective and is associated with a decrease in cardiac hospitalizations. The cardiac rehabilitation facility should be viewed as the clinical site at which systematic secondary prevention services are delivered in an outpatient setting in collaboration with the primary physician. The maintenance of physical functioning, the prevention of coronary disability, and the prevention of recurrent coronary events are the primary outcome goals.

BACKGROUND

Cardiovascular disease is the leading cause of death and premature disability in the United States for both men and women (1). It is also a major cause of disability in the rapidly growing elderly population (2,3). Coronary artery disease (CAD) usually presents clinically as angina pectoris or acute myocardial infarction and affects more than 13 million Americans, with many more cases remaining undiagnosed. More than 1 million individuals survive a myocardial infarction yearly in the United States, and another 750,000 undergo coronary revascularization procedures (4,5). The maintenance of physical functioning and the prevention of second coronary events and rehospitalizations in these populations are major preventive health challenges and require a systematic approach.

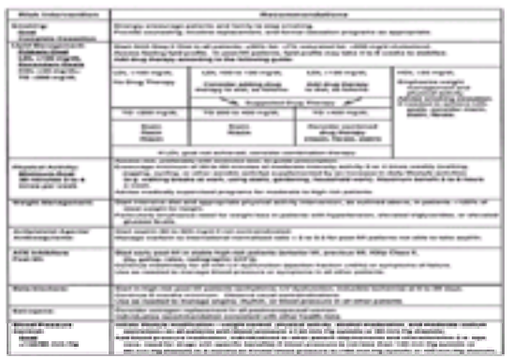
The current perspective of cardiac rehabilitation is that of a structured "secondary prevention" center, with on-site and home-based exercise programs, lipid clinics, weight loss programs, and other risk-factor modification components aimed at preventing second coronary events, cardiac rehospitalizations, and cardiac disability in patients with established CAD (6,7). Cardiac rehabilitation services include medical evaluation; prescribed exercise; and cardiac risk-factor modification, education, and counseling. Services are tied to a series of short-term and longer-term outcomes, which include return to work and measures of physical functioning, cardiac symptoms, psychological well-being, risk factors, progression of coronary atherosclerosis, recurrence of cardiac events, and number of rehospitalizations. Cardiac rehabilitation is prescribed for patients with myocardial infarction, coronary bypass surgery or percutaneous angioplasty, chronic angina pectoris, CHF, or heart transplantation and for selected patients who have had valvular heart surgery or exertional arrhythmias (8,9). Debate is ongoing as to whether early outpatient exercise training requires direct supervision or whether it could effectively be more widely applied, for low- and moderate-risk patients, in the home setting (10,11,12 and 13).

HISTORICAL PERSPECTIVE

Cardiac rehabilitation was conceived in an era when postmyocardial infarction activity prescriptions were evolving from 6 weeks of bed rest in the 1930s, to "chair" therapy in the 1940s, to 3 to 5 minutes of walking per day at 4 weeks in the 1950s (14,15 and 16). By the early 1960s, clinicians recognized that early ambulation helped patients avoid many of the complications of bed rest, such as pulmonary embolism and deconditioning, and in-hospital ambulation gradually displaced long-term bed rest as the standard of care (17,18 and 19). As the ambulation process extended beyond hospital discharge, concerns about the safety of unsupervised exercise resulted in the development of highly structured, physician-supervised, electrocardiographically monitored exercise programs in the 1970s. The focus was almost exclusively on exercise. By the 1990s, hospitalizations for acute myocardial infarction had shortened and are now as brief as 3 to 4 days (20), so that deconditioning is minimal. However, so is the opportunity to counsel patients about risk-factor modification. Smoking-relapse prevention programs, initiated in-hospital, have proven effective (21), but therapy and education for other modifiable risk factors are largely left for the postdischarge period.

With the development of a body of literature supporting the benefits of risk-factor modification in coronary patients (called *secondary prevention*), the cardiac rehabilitation center has evolved to become a clinical site for the systematic delivery of secondary prevention services. Recently demonstrated benefits of cardiac rehabilitation and secondary prevention in coronary patients are broad and compelling. Metaanalyses of exercise rehabilitation after acute myocardial infarction have demonstrated a 20% to 25% decrease in the overall mortality rate and in sudden cardiac death in the 3 years after infarction (22,23). Complementary trials of exercise and low-fat diets have demonstrated a slowing of the atherosclerotic process (24,25), and studies that incorporated multiple risk-factor interventions (10), pharmacologic lipid-lowering, or both, demonstrated a decrease in coronary events and a retardation of atherosclerosis (26). Despite these well-described advantages, fewer than 15% of patients who might benefit currently participate in formal cardiac rehabilitation (27).

In view of this, efforts have been made to develop physician-directed, nurse-coordinated home-based rehabilitation programs, with the goal of expanding the delivery of preventive cardiology services (10,11,12 and 13,28). In many cases, these services can be appropriately delivered through a physician's office, with a systematic approach to the detection and modification of coronary risk factors (29) (eFig. 12.0.1).



***e*FIGURE 12.0.1** Guide to comprehensive risk reduction for patients with coronary and other vascular disease. ACE, angiotensin-converting enzyme; AHA, American

Heart Association; CHF, congestive heart failure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; MI, myocardial infarction; TG, triglycerides. (From Smith SC, Blair SN, Criqui MH, et al. Preventing heart attack and death in patients with coronary disease. *Circulation* 1995;92:2–4, with permission.)

SCIENTIFIC FOUNDATION OF CARDIAC REHABILITATION AND SECONDARY PREVENTION

In the 1970s and 1980s, the scientific study of cardiac rehabilitation focused primarily on exercise, which was generally delivered in a 12-week program of three hourly sessions of aerobic exercise per week. Studies focused on physiologic mechanisms of conditioning in cardiac patients after 3 months of exercise and on the magnitude of the exercise training response, measured as exercise tolerance, or peak aerobic capacity on the treadmill. Outcomes of interest have gradually broadened to include longer-term effects on clinical parameters such as cardiac symptoms, clinical events, rehospitalization rates, quality of life, and measurement of coronary risk factors, such as blood lipids, that mediate progression of the atherosclerotic process (30).

Determinants of Exercise Capacity and Physical Functioning in Coronary Patients

In the period after a coronary event, when patients are most commonly identified for participation in cardiac rehabilitation programs, the incidence of exertional angina or ischemia is surprisingly low, owing to modern approaches including post-event risk-stratification, angiography, and interventional revascularization techniques aimed at improving coronary blood flow.

The cardinal symptoms of coronary heart disease (CHD), angina, and exertional dyspnea depend on a complex interplay of vascular biologic abnormalities and cardiac hemodynamics, compounded by deconditioning and psychological factors. Angina pectoris and ischemic left ventricular (LV) dysfunction result from an imbalance of myocardial oxygen supply and demand. In the presence of coronary atherosclerosis, exercise-induced increases in blood flow are limited both by the presence of atheroma and by an abnormal vascular endothelial response that paradoxically results in exertional vasoconstriction (31,32).

In the presence of chronic exertional angina, supervised aerobic exercise training programs have clearly been shown to increase the anginal threshold, and at a given workload, myocardial oxygen demand is lower (33) (Fig. 12.1). In one study, after 3 months of aerobic training, 7 of 18 patients who had exertional angina before conditioning could no longer reach their angina threshold after conditioning (34). In the 1-year study by Ornish and associates, a combination of aerobic exercise, a very low-fat diet, and meditation led to a 91% decrease in angina frequency and a 28% decrease in angina severity (25).

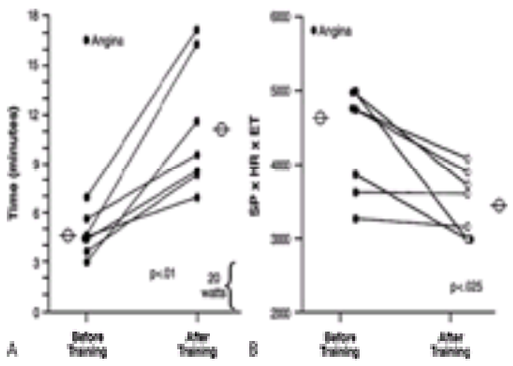


FIGURE 12.1 Effect of 6 weeks of training on exercise capacity **(A)** and triple product **(B)** in patients who have exertional angina. ET, ejection time; HR, heart rate; SP, systolic pressure. (From Redwood DR, Rosing DR, Epstein SE. Circulatory and symptomatic effects of physical training in patients with coronary-artery disease and angina pectoris. *N Engl J Med* 1972;286:959–965, with permission.)

Many patients with CAD are limited by coronary ischemia in the absence of angina, often manifested as dyspnea or fatigue. Furthermore, LV diastolic abnormalities, which are particularly common in older coronary patients, lead to exertional dyspnea, which may be exercise limiting (35,36). A smaller number of patients are limited by exertional arrhythmias, peripheral vascular disease, and comorbidities independent of their CAD.

More than 25% of patients with CAD appear to terminate exercise at treadmill testing before the attainment of a true physiologic maximal effort in the absence of coronary ischemia, heart failure, and arrhythmias (37,38). This effect is particularly notable in the older coronary population, in which as many as one-third of patients terminate exercise prematurely, before significant anaerobic metabolism has been measured, in the absence of angina or ischemia (37). These findings are supported by a study on cardiac disability in which many patients describe limiting their daily activities because of a fear of adverse cardiac consequences, based on advice or misinformation, rather than on account of specific symptoms, such as angina or dyspnea (38) (Fig. 12.2). Rehabilitation programs that counsel patients about the safety of specific employment-related and daily living activities and that reproduce these activities in a monitored setting are designed to facilitate return to premorbid activities (39,40). This is supported by improvements in patient-reported physical function scores after cardiac rehabilitation (11,13,41).

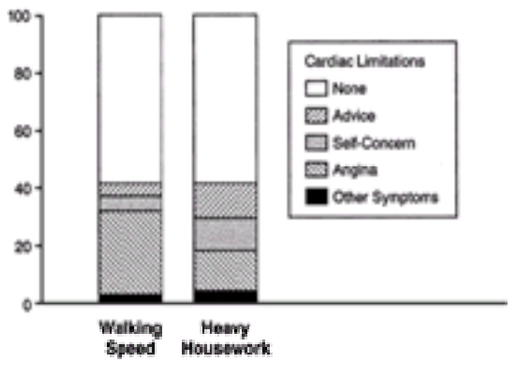


FIGURE 12.2 Patients' perception of reasons why heart disease limited them in walking speed and in heavy housework. (From Neill WA, Branch LG, De Jong GD, et al. Cardiac disability. The impact of coronary heart disease on patient's daily activities. *Arch Intern Med* 1985;145:1642–1647, with permission.)

The reasons for limitation of exercise performance in patients with significant LV dysfunction are complex. Although the initial insult results in a reduction in LV function, with a resultant decrease in rest and exercise cardiac output, secondary neurohormonal, peripheral muscular, and vascular abnormalities often predominate as the cause of exercise intolerance. Neurohormonal abnormalities include elevated circulating catecholamine levels that result in downregulation of cardiac b-adrenoreceptors and a decreased cardiac reserve. A diminished peripheral arterial vasodilatory capacity results in a decreased blood flow to skeletal muscle during exercise (42,43). Several observations suggest that peripheral abnormalities are primary determinants of exercise tolerance in CHF. First, exercise capacity correlates poorly with hemodynamic variables such as LV ejection fraction, cardiac output, and left-atrial filling pressures (44,45). Second, despite rapid improvements in central hemodynamics with medications, rapid parallel improvements in exercise capacity do not occur (46). Third, abnormalities in skeletal muscle histology and biochemistry are similar to those seen with deconditioning and improve with reconditioning (47,48).

In summary, exercise capacity and physical functioning in coronary patients are limited by the direct effects of coronary disease, such as angina and LV dysfunction, the indirect effects of CAD on skeletal muscle structure and function, and patient-centered psychological factors.

Adaptations to Exercise Conditioning in Patients with Coronary Heart Disease

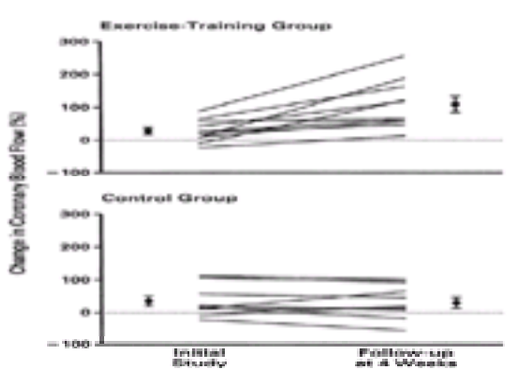
Physiologic adaptations to aerobic exercise training in middle-aged coronary populations include skeletal muscle and vascular adaptations, which result in a widened arteriovenous oxygen difference at maximal exercise (49,50 and 51), and cardiac adaptations, which result in an increased capacity to deliver bloodborne substrate to skeletal muscle (52,53,54 and 55). Peripheral adaptations include an increase in skeletal muscle fiber area, capillary density, and oxidative enzyme capacity (49,50 and 51), in addition to a probable increase in exercise-induced skeletal muscle vasodilatory capacity (56). Cardiac adaptations include increases in cardiac dimensions, stroke work, cardiac output, and afterload-corrected indexes of LV function (52,53,54 and 55). These are similar to training adaptations seen in healthy younger subjects (50). In coronary patients, these adaptations result in a lower heart rate and heart-rate systolic blood pressure product at a given submaximal exercise workload, the primary mechanism by which exercise conditioning decreases symptoms of angina and ischemia during physical exercise (*e*Table 12.0.1) (33,34,57).

***e*TABLE 12.0.1** MECHANISMS OF CLINICAL BENEFITS OF EXERCISE IN CORONARY ARTERY DISEASE

Direct
Decreased myocardial work and oxygen demand
Increased myocardial oxygen supply
Improved myocardial function
Enhanced endothelial vasodilatory capacity
Indirect
Delayed progression of coronary atherosclerosis
Improved lipid profiles
Improved carbohydrate metabolism
Increased fibrinolysis/decreased platelet adhesiveness
Decreased body adiposity
Increased skeletal muscle mass

In older coronary patients, CAD and peripheral vascular disease are superimposed on “normal” aging-related increases in LV and arterial wall thickness and stiffness (35,36). This has been shown to limit cardiovascular adaptations to aerobic conditioning in older coronary patients (58). Accordingly, in these patients, training mechanisms are primarily limited to the periphery and include an increase in arteriovenous oxygen extraction, capillary density, oxidative enzyme capacity, and individual fiber area, without an increase in maximal cardiac output or calf blood flow (58).

Much attention has been focused on whether exercise conditioning increases coronary flow during exercise in patients with CAD. Although several studies have documented improved thallium perfusion after conditioning (59,60), it is not clear whether this reflects an absolute increase in coronary flow in zones of prior ischemia or an improvement in myocardial metabolism during exercise. It has been demonstrated that healthy runners who exercise intensively on a regular basis possess a greater capacity to vasodilate coronary arteries in response to direct-acting vasodilators, such as nitroglycerin (61). A recent study in patients with CHD described improvements in endothelium-dependent coronary vasodilation after 4 weeks of exercise training, which may be a mechanism of the generalized protective effects of exercise in CHD patients (31,62) (*e*Fig. 12.2.1). Experimental studies in dogs similarly document enhanced coronary vasodilation after exercise training in association with an increased transcription of nitric oxide synthase in the vascular wall (63,64 and 65).

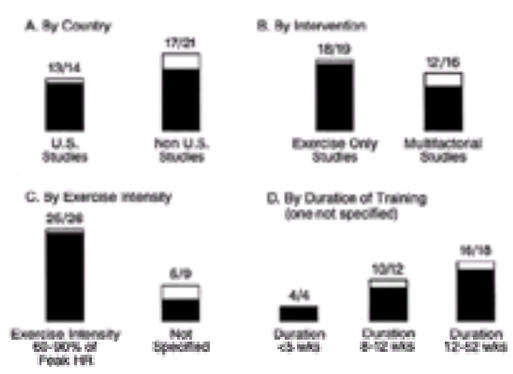


***e*FIGURE 12.2.1** Coronary blood flow in response to acetylcholine at initial study and after 4 weeks; exercise-training group vs. control group. The mean percentage change differed significantly between groups at 4 weeks (*p* <.01). (From Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med* 2000;342:454–460, with permission.)

Clinical Effects of Exercise Conditioning in Coronary Patients

Exercise Tolerance

The effect of supervised exercise conditioning programs on exercise tolerance in populations of patients with CAD has been extensively studied. The Federal Clinical Practice Guideline on cardiac rehabilitation describes a total of 35 randomized, controlled trials of cardiac rehabilitation exercise training on measures of exercise tolerance, and the vast majority documents a clear benefit of exercise training on the outcome measure of exercise tolerance (8) (*e*Fig. 12.2.2). These exercise conditioning studies consisted of uncomplicated patients after myocardial infarction who began their exercise program 4 to 52 weeks after the coronary event (22,23 and 24,66,67). After 3 months of aerobic conditioning three times weekly, at an intensity of 70% to 85% of maximal heart rate, exercise tolerance on the treadmill increased by 30% to 50%, and peak oxygen consumption increased by 15% to 20%. It should be noted, however, that in individual coronary patients the relationship between exercise tolerance and home-based physical activity profile is quite complex, with many patients limiting household activities for reasons other than angina, dyspnea, or fatigue (38). For example, many patients limit activities on the advice of family or physicians, not on the basis of objective evidence (38). Other patients develop elaborate support systems that minimize the need for physical activity, contributing to the vicious cycle of inactivity and deconditioning.



***e*FIGURE 12.2.2** Proportion of randomized controlled trials of cardiac rehabilitation reporting improvement of exercise tolerance in intervention groups. HR, heart rate. (From Wenger NK, Froehlicher ES, Smith LK, et al. *Cardiac rehabilitation: clinical practice guidelines*. AHCPR publication no. 96-0672. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, and the National Heart, Lung, and Blood Institute, 1995, with permission.)

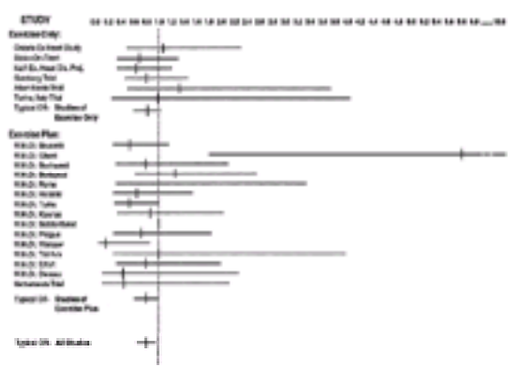
Studies in coronary patients older than 65 years have documented relative improvements in exercise tolerance similar to those seen in younger patients (37,68,69 and 70). Some authors suggest that older patients require longer training programs to attain training effects than younger patients (71), although this is not a universal

finding (72).

Efforts to predict which patients will make the greatest gains in exercise tolerance with cardiac rehabilitation have been somewhat disappointing. Patients with exertional ischemia at baseline appear to benefit somewhat less from a standard 3-month training protocol than do patients without exertional ischemia, although fitness levels and angina threshold nonetheless increase (34,73). The presence of LV dysfunction without exertional ischemia does not predict a lower relative response to conditioning (73). Whereas some studies suggest that patients with the poorest state of fitness show the most improvement with training (74), other studies, particularly in elderly patients, do not show a diminished relative training response in the least-fit patients (37,75). From the point of view of preventing or treating cardiac disability, patients at the lowest levels of physical functioning stand to gain the most if they can exercise at intensities adequate to stimulate a training response (41,76). The use of beta-adrenergic blockers or other pharmaceutical agents does not appear to alter conditioning response in coronary patients (77), despite the attenuation of conditioning in healthy subjects (78,79).

Morbidity and Mortality Rate

The effect of cardiac rehabilitation programs on long-term morbidity and mortality rates, particularly in patients who have experienced myocardial infarction, has been extensively studied. These studies, however, took place in the 1970s and 1980s, before the widespread use of thrombolytic therapy, coronary angioplasty, stents, and angiotensin-converting enzyme inhibitors. Although several individual randomized, controlled trials documented significant decreases in the long-term mortality rate (66,80,81 and 82), metaanalyses have provided the best data on the effect of cardiac rehabilitation on the mortality rate in patients who have experienced myocardial infarction. In the metaanalyses of Oldridge, O'Connor, and their coworkers, which included more than 4,000 patients in 21 randomized, controlled trials, cardiac rehabilitation was associated with a 25% reduction in the mortality rate compared with the rate among control subjects at an average follow-up of 3 years (22,23) (*e*Fig. 12.2.3). More than 80% of the patients in these studies were male, and they were primarily younger than 65 years. Studies in which the intervention involved exercise and risk-factor modification showed a greater benefit than studies in which the intervention was exercise only (23). It should be noted that all of the studies reported in these metaanalyses antedated current aggressive approaches to risk-factor modification, often centered at the cardiac rehabilitation facility. Exercise training per se is nonetheless a contributor to the improvement in mortality rate, because training-induced changes in peak exercise capacity that occur with cardiac rehabilitation are associated with lower mortality rates for patients who have the greatest training effect (83).



***e*FIGURE 12.2.3** Metaanalysis from randomized trials of the effect of cardiac rehabilitation on the mortality rate 3 years after randomization. OR, odds ratio; W.H.O., World Health Organization. (From O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989;80:234–244, with permission.)

Studies of the long-term effects of cardiac rehabilitation on morbidity rates, most commonly reinfarction rates, are less clear. Metaanalysis of 15 randomized, controlled trials of primarily exercise-only interventions from the 1970s and 1980s document no significant effects on reinfarction rates (23). These results are perhaps no longer relevant in the 1990s, when multiple studies of secondary prevention, consisting primarily of lowering of lipid levels, often in association with exercise, have documented a clear decrease in coronary events and cardiac rehospitalizations (10,26,84) (see below). A more recent large controlled trial of multifactorial rehabilitation, which included both aerobic exercise and risk-factor counseling, documented reductions in reinfarction rates (18% vs. 33%) and fewer hospitalization days for cardiac problems (11 vs. 16 days) over a 5-year follow-up period (85,86). At 5 years, there was also less smoking, less hypertension, and less use of antianginal medication.

The risks associated with the actual delivery of supervised exercise rehabilitation were well studied in coronary populations of the1980s and 1990s (87,88). A study of 142 U.S. rehabilitation programs reported a nonfatal myocardial infarction rate of 1 per 294,000 patient-hours and a mortality rate of 1 per 784,000 patient-hours (87). A similar study reported in 1998, after the widespread implementation of thrombolysis, beta-adrenergic blockers, and angiotensin-converting enzyme inhibitors, documents similar event rates (88). It should be noted that rehabilitation programs are now actively encouraging participation of higher-risk patients, including patients who have CHF or arrhythmias, elderly patients, and patients who have undergone transplantation, who were often excluded from rehabilitation in past years. Nonetheless, rates of exercise-induced coronary catastrophes in the rehabilitation setting remain exceedingly low.

Effects on Lipid Levels and Obesity

Studies of cardiac rehabilitation exercise programs on serum lipid levels in the absence of focused nutritional counseling document modest, though favorable, effects. Although exercise has no consistent effect on low-density lipoprotein (LDL) cholesterol levels, a consistent favorable increase of high-density lipoprotein (HDL) cholesterol of 8% to 23% has been demonstrated (89,90 and 91). Decreases of 3% to 21% in serum triglyceride levels after 1 to 2 years of exercise have also been demonstrated (92,93 and 94). Numerous studies that combined exercise with behavioral counseling and dietary instruction have documented consistent beneficial effects on serum lipid levels that include decreases in LDL cholesterol and serum triglyceride levels and maintenance or slight increase in HDL cholesterol (10,11,24,25,95). For example, in the diet-exercise studies of Schuler and Ornish, reductions in LDL cholesterol of 11% and 37%, respectively, were attained (24,25). In some patients, lipid-lowering medications are required to meet treatment goals (29), and the benefits of aggressive therapy include a retardation of the atherosclerotic process and a decrease in long-term coronary events (10,26).

Studies on the effect of cardiac rehabilitation exercise without intensive nutritional counseling on measures of obesity have documented only modest benefits (82,90,96,97). This may be because of the surprisingly low exercise-related caloric expenditure noted with cardiac rehabilitation exercise programs, particularly in female and older participants (98,99). A promising intervention that merits further study is the modification of cardiac rehabilitation exercise protocols to maximize caloric expenditure. This involves increasing the frequency and duration of exercise, at slightly lower intensities, and using non–weight-supported exercise such as walking (100). In studies that incorporated a very low-fat dietary intervention in addition to the exercise intervention, consistent improvements in body mass index [(weight in kg)/(height in m)^2] have been demonstrated (10,24,25). Although obesity is an independent risk factor for the development of CAD (101,102), in the setting of established CAD, reduction of obesity, particularly abdominal obesity, acts as a multifactorial intervention with associated improvements in lipid profiles and measures of insulin resistance and a lowering of blood pressure (96,103,104 and 105). Aerobic exercise training alone is associated with a reduction in abdominal obesity, even in the absence of major changes of weight in healthy elderly individuals and in CHD patients (90,106).

Psychological Effects

Many patients state that psychological effects of cardiac rehabilitation programs play a major role in their successful recovery from a cardiac event. In practice, the objective demonstration of measurable improvements in markers of psychological function has been difficult. Studies of exercise rehabilitation without psychological counseling have shown improvements in selected markers of psychological functioning, such as measures of depression and tension (107,108), although these findings have not been universal (109). Group psychological counseling in the rehabilitation setting has demonstrated objective improvements in selected psychological measures, such as depression and social adjustment (110,111 and 112). In addition, a metaanalytic study has noted that the addition of psychosocial treatments to standard cardiac rehabilitation regimens results in a reduction in mortality rates and morbidity over a 2-year period, along with a reduction in psychological distress (113). A randomized, controlled trial of relaxation training in cardiac rehabilitation resulted in a significant decrease in total cardiac events (114).

The magnitude of improvement in dysfunctional behavior in CHD patients is a function of the intensity of the counseling component of a multifactorial rehabilitation intervention. This generally includes group counseling on stress management, relaxation training, and guidance on social adjustment and recovery. Another important role of the group sessions is to identify patients who require more intensive counseling or pharmacologic therapy to avoid psychological symptoms and psychological disability. Depression, in particular, has been demonstrated not only to be a quality-of-life issue, but to predict 6-month mortality rates after myocardial infarction and rate of cardiac rehospitalizations, independent of the severity of cardiac disease (115,116).

Employment

A return to prior employment status is an important integrated measure of successful recovery from a coronary event. Numerous factors independent of the rehabilitation process are important predictors of failure to return to work after a coronary event. These include older age at the time of the coronary event, extended sick leave or unemployment at the time of the coronary event, lower educational level, employment in an unskilled position, or a prior myocardial infarction (86,117,118 and 119). On the other hand, several predictors of return to work may be favorably modified by the exercise rehabilitation process, particularly if work requirements are defined early in the rehabilitation process. These include a low physical function capacity, a lack of confidence in performing physical work, and high levels of depression or anxiety (86,117,118 and 119). A cardiac rehabilitation program that simulates elements of work during the training process has proven to be more effective at returning cardiac patients to work than standard cardiac rehabilitation without job simulation (39,40,117). Studies that have applied a generic exercise training routine to all participants have had little success in enhancing return-to-work rates (67,81,82,85,109,119).

An additional intervention that has been determined to be effective in accelerating return to work in patients with uncomplicated postmyocardial infarction is the performance of a symptom-limited electrocardiographic stress test 3 weeks after the coronary event, with explicit instructions regarding the timing of return to work (120). Patients who are defined as low risk, as determined by an absence of severe exertional ischemia (³2 mm of ST depression), are given explicit instructions to return to work within 2 weeks of the stress test. In a carefully controlled clinical trial, this lowered the time to return to work from 75 to 51 days (120). If the patient then proceeds into a rehabilitation program, a careful determination of work requirements and a training program designed to simulate work-related tasks with monitoring as needed can increase return-to-work rates (39,40). When anxiety or depression is deemed to be preventing a patient's return to work, psychological and vocational counseling may be helpful. Because CAD remains the major cause for premature disability in the United States, continued efforts at refining interventions aimed at returning patients to employment is a major health care issue.

Older Patients

More than one-half of the patients who are eligible for cardiac rehabilitation services are older than 65 years. According to the Framingham Disability Study, which defined disability by work and mobility limitations, disability rates in older coronary patients are extremely high (2). In patients older than 70 years, 79% of women and 49% of men with CAD were found to be disabled (Table 12.1). The direct causes of disability in older coronary patients have received little study, although preliminary work suggests that the best predictors of poor physical function in older coronary patients are a low aerobic fitness capacity and the presence of mental depression, both of which are treatable (121). Despite this, older coronary patients are far less likely to participate in cardiac rehabilitation than younger patients (122,123). The rate of participation for patients older than 62 years is less than one-half that seen in younger patients (122). The primary reason for nonparticipation is a low rate of physician referral (122).

	Men (%)	Women (%)
No CAD or CHF	27	49
CAD	39	61
Angina	56	84
CHF	57	88

CAD, coronary artery disease; CHF, congestive heart failure.
Adapted from Pinsky JL, Jette AM, Branch LG, et al. The Framingham Disability Study: relationship of various coronary heart disease manifestations to disability in older persons living in the community. *Am J Public Health* 1990;80:1363–1368.

TABLE 12.1 FRAMINGHAM DISABILITY STUDY DISABILITY RATES: AGES 70–88 YEARS

The cardiac rehabilitation literature clearly supports the safety and efficacy of exercise-training regimens in older coronary patients, with relative training benefits similar to those in younger coronary patients (37,68,69 and 70,72,75). Special considerations in the older population include frequent need to adjust training regimens to accommodate the presence of comorbidities such as arthritis, diabetes, and peripheral vascular disease. In addition, the least-fit elderly patients are often unable to sustain exercise for extended periods; these patients do well with intermittent brief bouts of exercise and a longer-term training program. Even patients who use canes and walkers can be exercise tested and trained on a treadmill that has surround bars. Resistance training is a promising intervention for older patients, owing to the frequent presence of sarcopenia and physical disability (see Resistance Training) (124,125). A combination of aerobic and resistive exercise training has been shown to improve physical function scores in both older and younger CHD patients (41).

Women

After menopause, the incidence of CAD rises steadily; by age 65 years, the prevalence of CAD in women approaches that in men (126,127). Despite this, women are a definite minority among cardiac rehabilitation participants (122). The primary reason for this appears to be lower referral rates by primary physicians rather than clinical differences between male and female patients (122). Relatively little study has been made of the relative benefits and special needs of women in cardiac rehabilitation, although women and men improve exercise capacity with training to a similar degree (122,128). Women, however, appear to experience less weight loss, and risk factors improve to a lesser degree, probably owing to a significantly lower exercise-related energy expenditure during cardiac rehabilitation sessions (90,99).

The current model of cardiac rehabilitation was developed primarily for middle-aged male coronary patients in the 1960s and 1970s. Early after myocardial infarction, women have a lower functional capacity than men, they are generally older, they are more likely to have residual angina, and they have more prominent risk-factor profiles; therefore, rehabilitation needs may differ from those of male participants (122,126,129,130). In addition, women are more likely to have a recurrent coronary event during the year after an initial myocardial infarction than are men (122,126,129,130).

Women's preferences in cardiac rehabilitation programming differ from those of men and need to be incorporated into programs designed to maximize adherence and attainment of clinical goals. Although both women and men describe that "frequent progress updates," "encouragement from professionals," and "flexibility in choosing exercise modality" are their most important cardiac rehabilitation features, women preferentially describe that their desires to "not have pain" and "not tire" are less well met than in men (131). As the population ages, the special needs of rehabilitating older female CAD patients will play an increasing role. Because of their high disability rates and diminished muscle mass and strength, older women may benefit from resistance training to a greater degree than other segments of the cardiac rehabilitation population (2,125,132).

Chronic Heart Failure

Patients with CHF are the most highly symptomatic group of patients with cardiovascular disease, and their activities are often limited by low-threshold exertional dyspnea and fatigue. Because of the progressive aging of the population and the improved prognosis of patients with CHF who receive pharmacologic therapy with angiotensin-converting enzyme inhibitors (133,134), the absolute size of the American population with CHF is gradually increasing. At present, more than 2 million Americans experience CHF, with 400,000 new cases diagnosed yearly (135). The mortality rate is high, at a 5-year mortality rate of roughly 50% (135).

Recent studies show that patients with CHF can safely undergo exercise conditioning and that regular exercise improves functional status and decreases symptoms (47,136,137 and 138) (Fig. 12.3). Furthermore, in a randomized, controlled trial, 1 year of moderately intense aerobic exercise improved patient-reported measures of quality of life and decreased overall mortality and hospital readmission rates (139) (Fig. 12.4). Neurohormonal activation and lactate production during submaximal exercise is also diminished by a regular, supervised, home-based exercise program (136), and exercise training augments the symptomatic and functional benefits of angiotensin-converting enzyme inhibitors (137). Peripheral (skeletal muscle) adaptations appear to mediate the improvement in exercise tolerance (47). In addition to improving the peripheral extraction of oxygen, aerobic conditioning in CHF is associated with an increase in cardiac output both during submaximal and maximal exercise (136).

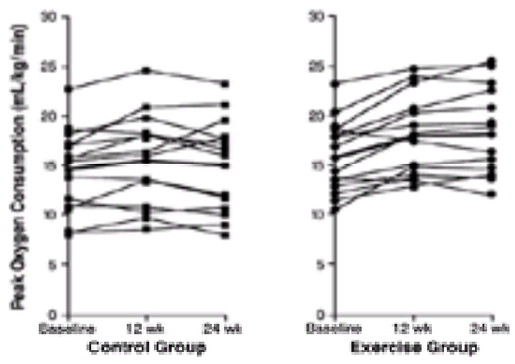


FIGURE 12.3 Peak oxygen consumption in patients with compensated heart failure who do not have exercise training (control group, n = 14) and who did have exercise training (exercise group, n = 15). The heavy line represents the mean value across time, with a significant difference between groups (*p* <.05). (From Keteyian SJ, Levine AD, Brawner CA, et al. Exercise training in patients with heart failure: a randomized, controlled trial. *Ann Intern Med* 1996;124:1051–1057, with permission.)

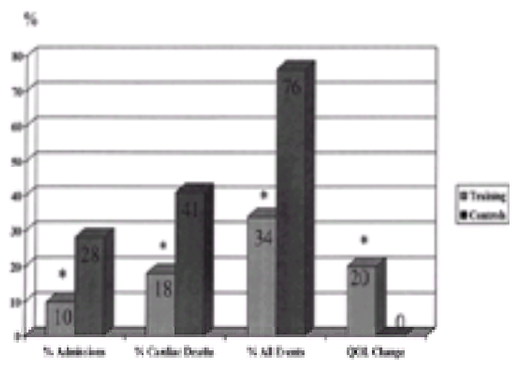


FIGURE 12.4 Randomized, controlled trial of exercise training in patients with chronic heart failure (n = 99; mean follow-up, 3.3 ± 0.15 years). **p* <.05 compared with control group. QOL, quality of life. (Adapted from Belardinelli R, Georgiou D, Cianci G, et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999;99:1173–1182.)

There is insufficient evidence to recommend a specific type of training program for patients with CHF, although existing studies have focused primarily on aerobic exercises such as cycling or treadmill walking rather than resistance training (47,136,137 and 138). Effects of combined strength and aerobic training in patients with CHF is a promising intervention that improves muscular strength, aerobic capacity, and endothelial-dependent and -independent vasodilator capacity (140,141). In addition to the benefits of supervised exercise training, rehabilitation programs can provide patient and family counseling and facilitate patient compliance with treatment recommendations (135).

An exercise conditioning trial involving CHF patients awaiting cardiac transplantation involved maximal medical therapy and a prescribed walking program. Patients gradually worked up to walking 20 to 30 minutes or 2 miles four times per week at a moderate exercise intensity for 6 months. Peak exercise tolerance improved in 38 of 68 clinically stable patients, and after an average of 6 months of follow-up, 31 of those 38 patients had improved sufficiently to be removed from the transplant list (142). After transplantation, exercise tolerance improves with aerobic exercise training, using perceived exertion as a guide to exercise intensity (143,144 and 145).

Resistance Training

Resistance- or weight-training protocols have long been discouraged in coronary patients because of fears of cardiac complications that can be caused by blood pressure elevations during the lifting phase of such exercise (146). However, carefully screened subsets of CAD patients younger than 65 years have safely participated in resistance-training programs, with impressive increases in strength and no adverse cardiac effects (146,147,148 and 149). Recent data also confirm increases in strength measures after 3 months of resistance training in older coronary patients of approximately 19% to 24% (124). It is important to note that when strength is low, it is a limiting factor in endurance activities, such as walking (150). Thus, in elderly patients, walking endurance improves with resistance training in the absence of aerobic training (151).

Resistance training is of particular importance in women, elderly patients, and coronary patients who plan to return to physically demanding employment (132,148). In healthy individuals, the conditioning response to resistance training includes fiber hypertrophy and an increase in oxidative enzyme activity without an increase in peak aerobic capacity (152). An important functional result is a decreased heart-rate response to a given resistive workload (147,151,152).

Cardiac responses to resistance training have been variable. Although cross-sectional studies of recreational weightlifters have generally shown measurable increases in LV mass, this has not been associated with alterations in LV diastolic filling patterns or in LV systolic function (153,154,155 and 156). Systolic blood pressure and heart-rate measures during exercise up to a training intensity of 80% of a single maximal lift have been found not to be excessive and, in fact, are lower than values measured during symptom-limited treadmill testing of the same individuals (157). A number of studies have assessed the safety and feasibility of weight training in middle-aged coronary patients, although no long-term studies of weight training on cardiac morphology or function have been reported (147,148,157). Because measurable increases in diastolic blood pressure during the lifting phase to levels beyond those seen with aerobic exercise have been demonstrated, the primary relative contraindication to weight training in coronary patients is uncontrolled hypertension (146). Although there is a theoretical concern of adverse LV remodeling caused by blood pressure rises during weight training in coronary patients, beneficial effects on skeletal muscle mass and function may override that danger, and LV dysfunction need not be considered a contraindication. The elevated diastolic blood pressure during the lift may, in fact, increase subendocardial perfusion and thereby contribute to the lower incidence of ischemic responses seen with isometric or isodynamic effort (158,159 and 160).

From a practical point of view, the onset of upper body resistance training should be delayed until 3 months after coronary bypass grafting surgery to allow full sternal healing to occur, whereas it can commence as early as 1 month after myocardial infarction or 1 to 2 weeks after a successful percutaneous coronary intervention, after performance of a satisfactory baseline exercise tolerance test. The resistance-training program should include training of the leg extensor muscles to assist with walking and stair climbing and upper body training to aid in the lifting and pushing required for the performance of daily household activities. A report on the results of resistance training in disabled older women with CHD documented increased strength, endurance, balance, coordination, and measures of physical performance during practical activities such as stair climbing and grocery carrying (125).

Secondary Prevention

The relative risk of developing myocardial infarction for patients with clinically manifest CAD is five to seven times higher than in matched individuals without established coronary disease (161). Thus, secondary prevention focuses preventive efforts in patients at the highest risk of recurrent cardiac events and cardiac death. The cardiac rehabilitation center needs to be structured in such a manner that program personnel systematically define and treat modifiable risk factors in participants, in coordination with primary physicians. The American Heart Association has defined “core components of cardiac rehabilitation,” which expand the mandate of cardiac rehabilitation programs to act as “secondary prevention centers” (6) (*e*Table 12.1.1). Individual programs need to develop treatment modules that screen for the presence of risk factors and define counseling, behavioral, and pharmacologic interventions related to the presence of hyperlipidemia, obesity, hypertension, smoking, diabetes, and psychological dysfunction.

***e*TABLE 12.1.1** CORE COMPONENTS OF CARDIAC REHABILITATION/SECONDARY PREVENTION PROGRAMS
Patient assessment
Evaluation
Medical history
Include cardiovascular (including peripheral vascular and cerebrovascular) diagnoses and prior cardiovascular procedures (including assessment of left ventricular function), comorbidities, symptoms of cardiovascular disease, risk factors for atherosclerotic disease progression, medications, and medication compliance (see below for physical activity and psychosocial assessment).

Physical examination
Include vital signs, cardiovascular and pulmonary examination, postprocedure wound sites, joint and neuromuscular examination (see below for specific examinations for hypertension, weight, and diabetes).
Testing
Obtain resting electrocardiogram, assess quality of life using standard questionnaires (e.g., Medical Outcomes Study Short Form 36; see below for specific tests for exercise, lipid levels, and diabetes).
Intervention(s)
Compose written records that reflect the patient evaluation and contain a patient-care plan with detailed priorities for risk reduction and rehabilitation.
Actively communicate this plan to the patient and the primary health care provider.
Expected outcome(s)
Development and implementation of short-term (i.e., weeks to months) and long-term (i.e., years) goals and strategies to reduce disability and subsequent cardiovascular disease risk.
Improvement in quality of life as identified by positive changes on follow-up questionnaire.
Generation of a written summary of patient outcomes on completion of the program that is provided to the patient and to the primary and referring health care providers. Written summaries should identify specific areas that require further intervention and monitoring.

Nutritional counseling

Evaluation
Obtain estimates of total daily caloric intake and dietary content of fat, cholesterol, sodium, and nutrients.
Assess eating habits, including number of meals, snacks, frequency of dining out, and alcohol consumption.
Assess target areas for nutrition intervention as outlined in the core components of weight, hypertension, and diabetes, as well as heart failure, kidney disease and other comorbidities.
Intervention(s)
Prescribe specific dietary modifications that aim to attain at least the fat and cholesterol content limits of the American Heart Association step II diet (9).
Individualize diet plan according to specific target areas as outlined in the core components of weight, hypertension, and diabetes (as outlined in this table), as well as heart failure and other comorbidities.
Educate and counsel patient (and family members) regarding dietary goals and how to attain them.
Incorporate behavior change models and compliance strategies in counseling sessions.
Expected outcome(s)
Patient adherence to prescribed diet.
Patient understanding of basic principles regarding dietary content of calories, fat, cholesterol, and nutrients.
Construct a plan to address eating behavior problems.

Lipid management

Evaluation
Obtain fasting measures of total cholesterol, HDL, LDL, and triglyceride levels. In patients with abnormal levels, as judged by the National Cholesterol Education Program (9), obtain a detailed history to determine whether diet, drug use, and/or other conditions that may affect lipid levels can be altered.
Assess current treatment and compliance.
Repeat lipid profiles at 4–6 wk after hospitalization, and at 2 mo after initiation or change in lipid-lowering medications.
Intervention(s)
Provide nutritional counseling and weight management, aiming for at least an American Heart Association step II diet in those patients with LDL levels ³ 100 mg/dL; consider adding drug treatment in patients with LDL levels 100–130 mg/dL; add or intensify drug treatment in patients with LDL levels >130 mg/dL.
Provide interventions to increase HDL >35 mg/dL. These include exercise, smoking cessation, and consideration of targeted drug therapy.
Provide interventions to reduce triglyceride levels <200 mg/dL. These include nutritional counseling and weight management, exercise, alcohol moderation, and drug therapy according to the National Cholesterol Education Program recommendations (9).
Provide and/or monitor drug treatment in coordination with primary health care provider.
Expected outcome(s)
Short term
Continued assessment and modification of intervention until LDL levels are <100 mg/dL.
Long term
LDL levels <100 mg/dL.
Secondary goals include HDL levels >35 mg/dL and triglyceride levels <200 mg/dL.

Hypertension management

Evaluation
Measurement of resting blood pressure on two or more visits.
Assessment of current treatment and compliance.
Intervention(s)
If blood pressure is 130–139 mm Hg systolic or 85–90 mm Hg diastolic:
Provide lifestyle modifications, including exercise, weight management, moderate sodium restriction, alcohol moderation, and smoking cessation.
Administer drug therapy in patients who have heart failure, diabetes, or renal failure.
If blood pressure is ³ 140 mm Hg systolic or ³ 90 mm Hg diastolic:
Assist in lifestyle modification and administer drug therapy.
Provide and/or monitor drug therapy in coordination with primary health care provider.
Expected outcome(s)
Short term
Continued assessment and modification of intervention until blood pressure is <130 mm Hg systolic and <85 mm Hg diastolic.
Long term
Blood pressure <130 mm Hg systolic and <85 mm Hg diastolic.

Smoking cessation

Evaluation
Document smoking status: never smoked, former smoker, or current smoker (which, because of the high rate of relapse, includes those who have quit smoking in the last 6 mo); specify both the amount of smoking (packs/d) and duration of smoking (number of years).
Assess frequency of cigar smoking, pipe smoking, and chewing tobacco use and exposure to secondhand smoke.
Assess for confounding psychosocial issues.
Determine readiness to change by asking every smoker whether he/she has considered quitting in the last 6 mo.
If the answer is no (precontemplation stage), firmly advise the patient that he/she give it some thought; plan to ask again after several visits.
If the answer is yes (contemplation stage), proceed with interventions below.
Ongoing contact
Update status at each visit during first 2 wk of cessation and periodically thereafter for at least 6 mo.
Intervention(s)
When readiness to change is confirmed, assist the smoker in setting a quit date and select appropriate treatment strategies (preparation):
Minimal
Provide individual education and counseling by program staff, supplemented by self-learning materials.
Encourage physician, staff, and family support.
Provide relapse prevention.
Optimal
Provide formal smoking cessation program using group and/or individual counseling.
Provide and/or monitor pharmacologic support as needed, in coordination with primary health care physician.
Offer supplemental strategies if desired (e.g., acupuncture or hypnosis).
Arrange follow-up by return visits or telephone contact for at least 6 to 12 mo.
Expected outcome(s)
Short term
Patient demonstrates readiness to change by initially expressing decision to quit (contemplation) and selecting a quit date (preparation). Subsequently, the patient quits smoking and use of all tobacco products (action); adheres to pharmacotherapy, if prescribed; practices strategies as recommended; and resumes cessation plan as quickly as possible when relapse occurs.
Long term
Complete abstinence from smoking and use of all tobacco products at 12 mo from quit date.

Weight management

Evaluation
Measure weight, height, and waist circumference.
Calculate body mass index.
Intervention(s)

In patients with body mass index >25 kg/m^2 and/or waistline >40 in. (102 cm) in men and >35 in. (88 cm) in women:
Establish reasonable short-term and long-term weight goals individualized to patient and associated risk factors (e.g., reduce body weight by at least 10% at a rate of 1–2 lb/wk over a period of time as long as 6 mo).
Develop a combined diet, exercise, and behavioral program designed to reduce total caloric intake, maintain appropriate intake of nutrients and fiber, and increase energy expenditure.
Aim for an energy deficit of 500–1,000 kcal/d.
Expected outcome(s)
Short term
Continued assessment and modification of interventions until progressive weight loss is achieved.
Provide referral to specialized, validated nutrition weight loss programs if weight goals are not achieved.
Long term
Adherence to a diet and exercise program aimed at attainment of established weight goal.
Diabetes management
Evaluation
Identify patients with diabetes using initial history, and note medication type, dose, and regimen; type and frequency of glucose monitoring; and history of hypoglycemic reactions.
Obtain fasting plasma glucose in all patients and hemoglobin A_1C in diabetic patients to monitor therapy.
Intervention(s)
Develop a regimen of dietary adherence and weight control that includes exercise, oral hypoglycemic agents, insulin therapy, and optimal control of other risk factors.
Drug therapy should be provided and/or monitored in coordination with the primary health care provider.
Monitor glucose levels before and/or after exercise sessions. Instruct patient regarding identification and treatment of postexercise hypoglycemia. Limit or prohibit exercise if blood glucose ³300 mg/dL.
Refer patients without known diabetes whose fasting glucose is >110 mg/dL to their primary health care provider for further evaluation and treatment.
Expected outcome(s)
Normalization of fasting plasma glucose (80 to 110 mg/dL or hemoglobin A_1C <7.0), minimization of complications of diabetes, control of associated obesity, hypertension (<130/85 mm Hg), and hyperlipidemia.
Psychosocial management
Evaluation
Identify psychological distress as indicated by clinically significant levels of depression, anxiety, anger, or hostility; social isolation; sexual dysfunction/adjustment; and substance abuse (alcohol or other psychotropic drugs) using interview and/or standardized measurement tools.
Intervention(s)
Offer individual and/or small-group education and counseling regarding adjustment to coronary heart disease, stress management, and health-related lifestyle change. When possible, include family members and significant others in such sessions.
Develop supportive rehabilitation environment and community resources to enhance patient's and family's level of social support.
Teach and support self-help strategies.
In coordination with the primary health care provider, refer patients who are experiencing clinically significant psychosocial distress to appropriate mental health specialists for further evaluation and treatment.
Expected outcome(s)
Evidence of emotional well-being indicated by the absence of clinically significant psychological distress, social isolation, or drug dependency.
Demonstration of self-responsibility for health-related behavior changes; relaxation and other stress-management skills; ability to obtain effective social support; compliance with psychotropic medication regimens, if such medications are prescribed; and reduction or elimination of alcohol, tobacco, caffeine, or other nonprescription psychoactive drugs.
Construction of a plan for ongoing management if important psychosocial issues are present.
Physical activity counseling
Evaluation
Assess current physical activity level and determine domestic, occupational, and recreational needs.
Question activities relevant to age, gender, and daily life, including: driving, sexual activity, sports, gardening, and household tasks.
Assess readiness to change behavior, self-confidence, barriers to increasing physical activity, and social support in making positive changes.
Intervention(s)
Provide advice, support, and counseling about physical activity needs on initial evaluation and in follow-up. Target exercise program to meet individual needs (see "Exercise training" in this table). Provide educational materials as part of counseling efforts. Consider simulated work testing for patients with labor-intensive jobs.
Set goals to increase physical activity that include 20–30 min/d of moderate physical activity on 5 or more days each week. Explore daily schedules to suggest how to incorporate increased activity into the patient's usual routine (e.g., parking farther away from entrances, walking up two or more flights of stairs, walking 15 min during lunch break).
Advise low-impact aerobic activity to minimize risk of injury. Recommend gradual increases in intensity over weeks.
Expected outcome(s)
Increased participation in domestic, occupational, and recreational activities.
Improved psychosocial well-being, reduction in stress, facilitation of functional independence, prevention of disability, and enhancement of opportunities for independent self-care to achieve recommended goals.
Exercise training
Evaluation
Obtain an exercise test (or another standard measure of exercise capacity) before participation and repeat as changes in clinical condition warrant. Test should include assessment of heart rate and rhythm, signs, symptoms, ST segment changes, and exercise capacity.
Intervention(s)
Develop a documented individualized exercise prescription for aerobic and resistance training that is based on evaluation findings, risk stratification, patient and program goals, and resources. Exercise prescription should specify frequency (F), intensity (I), duration (D), and modalities (M).
For aerobic exercise: F = 3–5 d/wk; I = 50% to 80% of exercise capacity; D = 20–60 min; and M = walking, treadmill, cycling, rowing, stair climbing, arm ergometry, and others.
For resistance exercise: F = 2–3 d/wk; I = 8–15 repetitions, maximum, for each muscle group (where repetition maximum is the maximum number of times a load can be lifted before fatigue occurs); D = one to three sets of six to ten different upper and lower body exercises (20–30 min); and M = elastic bands, cuff/hand weights, dumbbells, free weights, wall pulleys, weight machines.
Include warm-up, cool-down, and flexibility exercises in each exercise session. Provide updates to the exercise prescription routinely and when patient condition warrants. Structured outpatient or home-based programs are appropriate and may include electrocardiographic monitoring as deemed necessary. Regardless of program site, supplement the formal exercise regimen with at-home activity guidelines as outlined in the "Physical activity counseling" section of this table. Caloric expenditure of at least 1,000 kcal/wk should be a specific exercise program objective.
Expected outcome(s)
As a component of an overall program of cardiac rehabilitation/secondary prevention, exercise assists in lowering cardiovascular risk and improves overall outcomes.
Improved functional capacity through enhanced muscular endurance and strength, flexibility, and weight management improves symptoms and physiologic responses to physical challenges and should assist in the modification of various unhealthy behavior and psychosocial characteristics.
Patient understanding of safety issues during exercise.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
From Balady GJ, Ades PA, Comoss P, et al. Core components of cardiac rehabilitation/secondary prevention programs: a statement for healthcare professionals from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation Writing Group. *Circulation* 2000;102:1069–1073, with permission.

Lipids

It is now well established that lowering blood lipid levels reduces clinical events and mortality rates in patients known to have CHD. Numerous controlled clinical trials, most with quantitative coronary angiography, have demonstrated the efficacy of pharmacologic and diet-induced lipid lowering on slowing the progression of angiographic measures of atherosclerosis and on reducing clinical coronary events (10,24,25,84,162,163 and 164). Low-fat diets, without accompanying drug treatment, have been effective in reducing the prevalence of angiographic progression of CAD when combined with exercise (24,25) and stress management (25), which strengthens the case for widespread institution of lipid-lowering dietary therapy. The reduction in clinical coronary events was most conclusively demonstrated in the Scandinavian Simvastatin Survival Study, which reported a 30% to 35% reduction in deaths and major coronary events (84). Data from these studies suggest that even patients who have mild to moderate lipid abnormalities benefit from therapy in a manner similar to that in patients who have more severe abnormalities. The National Cholesterol Education Program recommends setting an LDL cholesterol level of <100 mg per dL as a goal of therapy for all coronary patients (165).

The cardiac rehabilitation program is an optimal site for systematic screening and treatment of hyperlipidemia. This includes dietary counseling and active participation by the patient in pharmacologic therapy. A rehabilitation-based screening and treatment program has been documented to triple the likelihood that, with the collaboration of the referring physician, patients for whom such treatment is appropriate receive lipid-lowering therapy (166). Affiliation with a clinician who is expert in

lipid management is necessary, and in many cases a lipid clinic can be organized at the rehabilitation facility itself.

Smoking Cessation

Cigarette smoking cessation is associated with a marked decrease in coronary event rates in coronary patients (167,168). In the study of Wilhelmsson and associates, patients who quit smoking after experiencing myocardial infarction reduced their 1-year mortality rate from 10% to 5% and their 1-year reinfarction rate from 18% to 9% (168). Exercise training in and of itself has minimal, if any, effect on smoking cessation rates in coronary patients (82). The best results with smoking cessation after a coronary event have been obtained using a physician-recommended, nurse-managed intervention that takes place during hospitalization for an acute coronary event (while patients are unable to smoke) and is aimed at relapse prevention (11,21). These interventions include teaching skills to deal with high-risk situations, relaxation training, provision of nicotine or bupropion when necessary, and long-term telephone contact. At the end of 6 months (21), and 1 year (11), cessation rates were significantly increased, from 32% to 61%.

Weight Reduction

Although no study has addressed the effect of weight reduction on second coronary events, its well-defined role in the treatment of hyperlipidemia, hypertension, and insulin resistance makes it an important multifactorial risk-factor intervention (97). In the studies of Haskell, Schuler, and Ornish that incorporated a low-fat dietary intervention and exercise, reductions in body mass index were demonstrated in coronary populations (10,24,25). For example, in the Stanford Coronary Risk Intervention Project, a sustained 4% decrease in body mass index was attained with a combination of nutritional counseling and home-based exercise (10). On the other hand, studies of exercise rehabilitation alone have generally not been associated with substantial weight change (82,90). When weight loss is accomplished in the rehabilitation setting, it is generally associated with improvements in lipid profiles, insulin resistance, and blood pressure (96). Nutrition education combined with behavioral interventions and prescribed exercise can achieve modest and sustained weight loss in the rehabilitation setting (169). However, the accomplishment of weight loss in cardiac rehabilitation is not a passive process, and it requires the development of a weight loss module for selected patients, staffed by appropriately trained professionals, with clear definitions of goals and desired outcomes and long-term follow-up. A well-established and effective behavior-based weight reduction program has been adapted to the cardiac rehabilitation setting (170,171). The intervention includes behavioral concepts of stimulus control, self-monitoring, problem-solving, and social support; a daily caloric goal; and a daily calorie count. The weight loss goal is not to reach ideal body weight, but rather to achieve improvements in obesity-related risk factors. In many cases, a relatively modest but sustained weight loss of 5% to 10% of body weight significantly improves risk factors such as lipid measures and insulin resistance. An advantage of cardiac rehabilitation–based weight reduction programs is that patients are already performing the exercise component needed to prevent them from regaining lost weight (172).

Diabetes

No clinical trials involving patients with established CAD have been carried out to determine whether tight control of diabetes, in patients with either type I or type II diabetes, prevents cardiac complications or slows the course of macrovascular disease. Results of a recent multicenter clinical trial of tight glucose control in patients with type I (insulin-dependent) diabetes who did not have CAD demonstrated improved lipid profiles, an increase in body weight, a decrease in microvascular complications (retinal and renal), and a trend toward decreased macrovascular events, with such events (cardiac and cerebrovascular) reduced by almost 50% (173). In patients with type II diabetes, exercise and weight reduction resulted in improved measures of insulin resistance and associated coronary risk factors, such as lipid abnormalities and hypertension (174,175). Poor glycemic control predicts an increased likelihood of cardiac events in type II diabetes (176,177). An important role of the cardiac rehabilitation program, beyond encouraging exercise and proper nutrition, is to assist primary physicians with monitoring and treatment of diabetes. Patients are taught self-monitoring techniques, and medications are adjusted as needed (6,178).

Hypertension

Rehabilitation programs assist primary physicians with the treatment and follow-up of coronary patients with hypertension. Although weight reduction, exercise, and salt restriction have all been associated with modest reductions in systemic blood pressure, definite benefits in the cardiac rehabilitation setting have not been demonstrated. Frequent surveillance of blood pressure, teaching of self-monitoring techniques, nutritional instruction, and adjustment of medications are all useful (6,179).

Psychological Factors

The effect of cardiac rehabilitation counseling and behavioral interventions on measures of psychological stress and psychological well-being has received much study. In particular, the type A behavior pattern, hostility, depression, social isolation, and lack of social resources have been identified as important targets of therapy. Psychosocial interventions in the cardiac rehabilitation setting are associated with lower mortality rates and a lower likelihood of recurrent cardiac events (113). The type A behavior pattern, which includes a heightened sense of time urgency and hard-driving competitiveness, has been the most studied psychological variable. In the Western Collaborative Group Study, men with type A behavioral patterns were five times more likely to have a recurrent myocardial infarction than men with type B behavioral patterns (180). Although other studies did not confirm this finding (181), an intervention trial aimed at altering type A behavior patterns was associated with a decreased rate of recurrence of cardiac events (182). The intervention included stress-management counseling in a group setting and avoidance of stressful situations in the home setting.

Depression is reported to precede myocardial infarction in 33% to 50% of cases. One study of patients hospitalized after myocardial infarction found that 18% had major depression and an additional 27% had symptoms of depression (183). In another study, postinfarction patients who met criteria for a major depressive disorder (16% of 272 patients) were five times more likely to die during the first 6 months after infarction than patients who were not experiencing depression (115). Depressive affect in the absence of a major depressive disorder also conferred a higher risk (115). Whether the treatment of depression is associated with a better long-term outcome is not yet known, but decreased depression would probably lead to better functional outcomes and an improved quality of life, independent of effects on orbidity and mortality rates.

Social isolation is also associated with a poor prognosis after a coronary event. In a follow-up study of patients with angiographically documented coronary disease, a 5-year mortality rate of 50% was noted among the patients who were most socially isolated, versus 17% in nonisolated patients (184). No association was seen in this study between social isolation and the severity of cardiac dysfunction.

Cardiac rehabilitation stress-management programs and psychological counseling are performed both in a group setting and in individualized sessions. Counseling sessions generally focus on stress management and relaxation skills, in addition to reintegration and socialization after a coronary event, both at home and at work. Individuals who are at high risk for prolonged depression or maladaptive recovery patterns are identified and referred for more specific therapy, such as pharmacologic antidepressant therapy or longer-term counseling. Studies in the rehabilitation setting have documented lower levels of self-reported emotional stress, lower levels of type A behavior, and improvements in measures of quality of life and anxiety (181,182).

PRINCIPLES OF MANAGEMENT, PROGRAM STRUCTURE, AND ORGANIZATIONAL ISSUES

Inpatient Rehabilitation

In-hospital rehabilitation, or phase I rehabilitation, has necessarily evolved in recent years in response to ever-shortening hospitalizations for acute myocardial infarction and coronary revascularizations. With many infarction patients hospitalized for only 4 to 6 days (20), and much of this period occupied by acute care and recovery from interventional techniques, it is no longer realistic to expect patients to participate in a comprehensive course providing information about coronary risk factors and cardiac diets, and a graded in-hospital exercise program. However, in addition to the economic benefits of a shorter hospitalization, less deconditioning occurs, and patients are more capable of resuming premorbid physical activities. Many patients report that in the current environment, the most important aspect of phase I rehabilitation is to be directed to the phase II outpatient program (185).

Nonetheless, several important interventions take place during this brief hospitalization. Most important is smoking-relapse prevention. Because essentially all American hospitals now prohibit smoking, the issue is no longer smoking cessation, but planning for continued cessation on hospital discharge. Well-designed studies demonstrate that in the setting of acute myocardial infarction, 32% of patients stop smoking without a program, which can be increased to 61% with a nurse-managed smoking-relapse prevention program, as demonstrated by Taylor and colleagues (21).

It is also important during this brief index admission to define coronary risk factors and to set up an outpatient plan for long-term therapy. Defining lipid profiles early on is of particular importance; studies of aggressive lipid lowering in coronary patients document decreasing secondary event rates beginning 6 months to 1 year after therapy is begun (84,164). Serum lipid values are accurate when measured within 24 hours of myocardial infarction. When they are measured later in a hospitalization for myocardial infarction, they are inaccurate, with total, LDL, and HDL cholesterol levels lower and triglyceride levels higher (186,187,188 and 189). For 1 month after coronary bypass surgery, serum cholesterol levels measure falsely low, and therefore baseline measures should be determined preoperatively, with follow-up

measures performed after 1 month (190).

Before the patient is discharged, a nurse clinician or physician should review a set of “survival skills” to outline proper use of medications, to define a plan for early physical activity profiles, and to review how to deal with symptoms, should they occur. If an exercise tolerance test was performed before discharge, it will be helpful in defining the early activity profile, although the exercise prescription needs to be updated during the physician’s visit or on the patient’s entry into outpatient/phase II rehabilitation. If phase II rehabilitation is not planned, a symptom-limited exercise tolerance test performed 3 to 6 weeks after the coronary event, while the patient is receiving his or her usual medications, is useful in constructing a long-term activity program. It is recommended that patients exercise regularly at approximately 60% to 85% of the intensity attained at the exercise test. Additionally, this stress test assists in making return-to-work recommendations and achieving a more rapid return to work for low-risk patients (104).

Outpatient Rehabilitation

Intake Evaluation

The cardiac rehabilitation intake evaluation is the optimal opportunity to stratify patients into risk categories and to systematically define secondary risk factors for the progression of CAD (Fig. 12.5). Therefore, as part of this evaluation, a fasting lipid profile and a glucose measure should be obtained for all patients. Other risk factors, such as smoking status, blood pressure, obesity, and diabetes-related measures, should also be assessed.

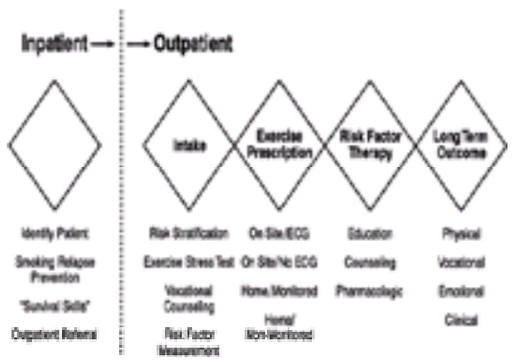


FIGURE 12.5 Elements of cardiac rehabilitation. ECG, electrocardiogram.

An exercise tolerance test needs to be performed so that an exercise prescription can be developed and the risk associated with exercise can be assessed. Patients in whom high-risk characteristics are identified at risk-stratification (Table 12.2) should participate in a supervised program in which electrocardiographic monitoring is available. Patients who are stratified to low- or intermediate-risk groups can be considered for a home-based exercise program. Although the requirements for electrocardiographic monitoring remain poorly defined, the American College of Cardiology, in its “Report on Cardiac Rehabilitation,” recommends electrocardiographic monitoring for high-risk patients (*e*Table 12.2.1) (191).

Risk level	Characteristics
Low	No significant left ventricular dysfunction (i.e., ejection fraction, >50%) No resting or exercise-induced myocardial ischemia manifested as angina and/or ST segment displacement No resting or exercise-induced complex arrhythmias Uncomplicated myocardial infarction, coronary artery bypass surgery, angioplasty, or atherectomy Functional capacity of 8 METs or greater exercise test 3 weeks after clinical event
Intermediate	Ability to moderately depressed left ventricular function (ejection fraction, 31–49%) Functional capacity 5–6 METs on graded exercise test 3 weeks after clinical event Failure to comply with exercise intensity prescription
High	Exercise-induced myocardial ischemia (≥2 mm ST segment depression or reversible ischemic defects seen on echocardiography or nuclear radiography) Severely depressed left ventricular function (ejection fraction, <30%) Complex ventricular arrhythmias while patient is at rest or appearing or increasing with exercise Decrease in systolic blood pressure of >15 mm Hg during exercise or failure to rise with increasing exercise workloads Patient is survivor of sudden cardiac death Myocardial infarction complicated by congestive heart failure, cardiogenic shock, and/or complex ventricular arrhythmias Severe coronary artery disease and marked exercise-induced myocardial ischemia (≥2 mm ST segment depression)

Adapted, modified and reprinted with permission. Position paper on cardiac rehabilitation. Committee on Rehabilitation of Cardiovascular Patients. Guidelines for cardiac rehabilitation programs. Chicago: American Heart Association, 1995, with permission.

TABLE 12.2 GUIDELINES FOR RISK-STRATIFICATION

***e*TABLE 12.2.1** CRITERIA FOR ELECTROCARDIOGRAPHIC MONITORING

1. Severely depressed left ventricular function (ejection fraction, <30%)
2. Complex ventricular arrhythmia while patient is at rest
3. Ventricular arrhythmias appearing or increasing with exercise
4. Decrease in systolic blood pressure with exercise
5. Patient is a survivor of sudden cardiac death
6. Patient is a survivor of myocardial infarction complicated by congestive heart failure, cardiogenic shock, serious ventricular arrhythmias, or some combination of the three
7. Severe coronary artery disease and marked exercise-induced ischemia (³2 mm ST segment depression)
8. Inability to self-monitor heart rate because of physical or intellectual impairment

From Parmley WW. Position report on cardiac rehabilitation: recommendations of the American College of Cardiology on cardiovascular rehabilitation. *J Am Coll Cardiol* 1986;7:451–453, with permission.

Only 15% of eligible patients in the United States receive cardiac rehabilitation services. In many cases, cardiac rehabilitation programs are not geographically available, whereas in other cases, formal rehabilitation is not recommended by the primary physician. For some patients, insurance coverage is incomplete or unavailable. Whereas cardiac rehabilitation services have classically been delivered on-site at a well-defined exercise training facility, the need to expand preventive cardiology services to include the majority of eligible patients necessitates a redefinition of this model.

The development of alternate approaches to delivery of cardiac rehabilitation services is an ongoing process, aimed at a goal of expanding the base of patients who receive services, at the lowest possible health care cost. Numerous investigators have documented the safety of home-based exercise programs for individuals who are at low to medium risk by use of varying degrees of transtelephonic monitoring (12,13,28,192). Case management (i.e., evaluation and management of risk factors for the individual patient) complements exercise conditioning and allows the individualization of preventive care in health care delivery systems that focus on efficiency and outcomes. Case management, whether delivered in an office practice or in a structured rehabilitation program, should focus on attainment of risk-factor goals (Table 12.3) and identification of highest risk patients (Table 12.2) (10,11). Exercise programs can be individualized for moderate- and higher-risk patients, and patients at highest risk of disability should be referred to a rehabilitation program for closer supervision and monitoring.

Variable	Minimum	Intermediate	Maximum
Body weight, % ideal	[illegible]	[illegible]	[illegible]
Systolic BP, mm Hg	[illegible]	[illegible]	[illegible]
Diastolic BP, mm Hg	[illegible]	[illegible]	[illegible]
Plasma cholesterol, mmol/L (mg/dL)	[illegible]	[illegible]	[illegible]
LDL cholesterol, mmol/L (mg/dL)	[illegible]	[illegible]	[illegible]
HDL cholesterol, mmol/L (mg/dL)	[illegible]	[illegible]	[illegible]
Plasma triglycerides, mmol/L (mg/dL)	[illegible]	[illegible]	[illegible]
Dietary fat, % calories	[illegible]	[illegible]	[illegible]
Saturated fat, % calories	[illegible]	[illegible]	[illegible]
Dietary cholesterol, mg/d	[illegible]	[illegible]	[illegible]
P:S ratio[a]	[illegible]	[illegible]	[illegible]
Sodium, mg/d[b]	[illegible]	[illegible]	[illegible]
Cigarette smoking, no./d	[illegible]	[illegible]	[illegible]
Exercise capacity (METs)			
Men	[illegible]	[illegible]	[illegible]
Women	[illegible]	[illegible]	[illegible]
Fasting glucose, mg/dL	[illegible]	[illegible]	[illegible]
1-h glucose, mg/dL	[illegible]	[illegible]	[illegible]
Physical activity			
Routine aerobic calories/wk	[illegible]	[illegible]	[illegible]
Training session, % MHR	[illegible]	[illegible]	[illegible]
	15–30-min sessions every other day	20–30-min sessions every other day	30–45-min sessions every other day

BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; METs, multiple of resting energy expenditure; MHR, maximal heart rate; P:S, polyunsaturated:saturated fat.
[a]Emphasis was placed on achieving the desired percentage of calories from unsaturated fat, with P:S ratio approximately 1:1.
[b]Hypertensive participants were encouraged to reduce sodium further, with attention also given to other aspects of their diet.
From Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease (the Stanford Coronary Risk Intervention Project [SCRIP]). *Circulation* 1994;89:975–990, with permission.

TABLE 12.3 RISK-FACTOR GOALS FOR PATIENTS IN RISK REDUCTION GROUP: STANFORD CORONARY RISK INTERVENTION PROJECT MODEL

Exercise Prescription

Classically, exercise programs for coronary patients have involved primarily aerobic exercise, with patients exercising at an intensity approximated by exercise heart rates measured at 70% to 85% of peak exercise heart rate while the patient is receiving his or her usual medications (8). It should be noted that in many cases, the early post–coronary event symptom-limited stress test is a submaximal stress test, and patients are often reluctant at this stage to exercise to a true physiologic maximum (37). Thus, it is useful to supplement heart-rate guided training with estimates of perceived exertion, as described by Borg (193). Lower-intensity training regimens, at 50% to 70% of maximal heart rate, have been shown to result in improvements in functional capacity similar to those produced by more intensive regimens and may be more acceptable for particularly unfit, obese, or older patients (194,195). Clinicians have a tendency to recommend lower-intensity exercise regimens to patients who are exercising in unsupervised settings, and although this appears reasonable, it has not been subjected to study. Probably more important than the absolute training intensity in the early recovery period is the issue of whether patients continue exercise over the long term, and whether they experience long-term improvements in outcomes such as measures of home-based physical functioning, improvement in symptoms, psychological benefits, and physiologic benefits, such as improved lipid profiles and body composition measures.

A baseline evaluation of physical functioning and health-related quality of life, usually using a standardized questionnaire (e.g., the Medical Outcomes Study questionnaire), is extremely helpful in defining a baseline for physical functioning (30,196). Measures of physical functioning improve in all age groups and in both genders after cardiac rehabilitation (41). An evaluation of physical functioning is quite distinct from an exercise tolerance test, and such an evaluation determines the actual activities that a patient can and cannot perform in the home environment. Thus, in the clinical setting, the need for aerobic exercise or resistance training can be determined for the individual patient, based on their at-home work requirements. For example, an older women with CHD is most likely to be limited in the performance of daily activities by decreased muscle mass and strength, and therefore a resistance training program would appropriately supplement an aerobic walking program. Although the exact exercise prescription for resistance training in coronary patients has not been fine-tuned, a common approach is to measure the single-repetition maximum lift for specific exercises after 1 to 2 weeks of acclimatization at low workloads, and then to begin resistance training at roughly one set of eight to ten repetitions at 40% to 50% of the single-repetition maximum. With training, the workload is gradually increased by increasing the number of repetitions and by increasing the resistance so that a steady level of perceived exertion during exercise is maintained. An area of future research is to define the effects of resistance training on physical functioning in specific subsets of patients, in addition to developing low-cost equipment for long-term home use.

Compliance with Exercise and Long-Term Follow-Up

Long-term adherence to cardiac rehabilitation exercise is approximately 50% at 1 year (197,198). This compares to 1-year adherence rates of 64% for antihypertensive medication regimens (199) and 82% for treatment with lipid-lowering agents (200). Several interventions have been shown to optimize compliance with cardiac rehabilitation exercises. A gradual transition to home-based exercise sessions with self-monitoring while the patient was still in the rehabilitation program increased 6-month compliance rates from 76% to 92% (201). The use of lower-intensity exercise (202), participation of nurse case-managers (10,11), and the signing of a written agreement (203) have all been associated with increased long-term compliance with the exercise component of cardiac rehabilitation.

Provisions for the long-term continuation of risk-factor modification also need to be specified. The long-term surveillance and treatment of coronary risk factors is generally transferred to the primary physician, in a case-management format, whereas the long-term surveillance and maintenance of the exercise component is often delegated to the rehabilitation program. Although long-term, institutional phase III programs successfully maintain patients in a supervised exercise program and are particularly useful for older patients because they provide supervision and social interactions, a fully “rehabilitated” patient exercises independently at home.

Strategies to improve participation in cardiac rehabilitation programs are of major importance in view of the relationship between adherence with preventive cardiology recommendations and better clinical outcomes (204,205 and 206). The most important determinant of early post–coronary event cardiac rehabilitation participation, studied in a population of patients ³62 years old, is the strength of the primary physician’s recommendation for participation (207). When the recommendation was graded as moderate to strong (4 to 5, on a scale of 1 to 5), participation was 70%; when the recommendation was weak (1 to 3), participation rate was 2% (Fig. 12.6). Other predictors of poor participation rates included older age; presence of comorbidities, especially arthritis; and the presence of mental depression (207). It should be noted, however, that nonadherence with formal cardiac rehabilitation does not necessarily mean that self-care preventive practices are not in place. It is suggested that successful strategies for enhancing long-term adherence with cardiac rehabilitation and long-term risk reduction include involving the patient and family in clinical decision-making, providing individualized and understandable explanations about regimens that are compatible with the patient’s values, acknowledging the patients’ social and cultural background, and integrating and coordinating patient care with primary providers, particularly during periods of transition (8).

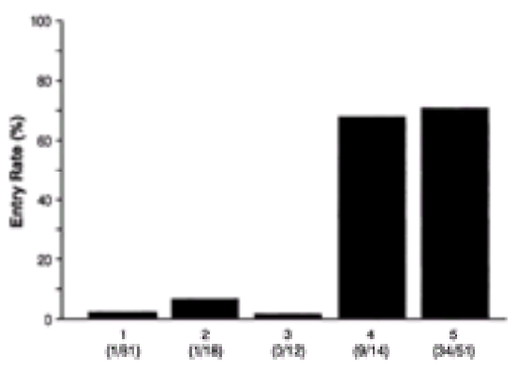
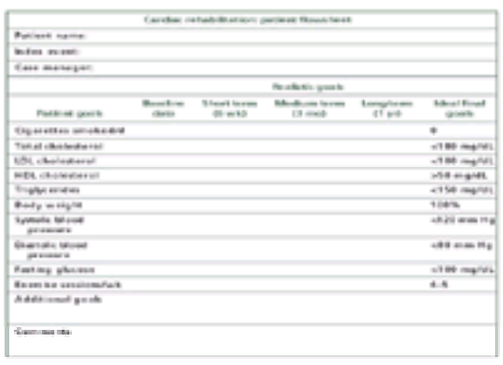


FIGURE 12.6 Cardiac rehabilitation participation by physician’s recommendation. The physician’s recommendation score was graded from 1 (not recommended, or recommended against) to 5 (strongly recommended). (From Ades PA, Waldmann ML, McCann W, et al. Predictors of cardiac rehabilitation participation in older coronary patients. *Arch Intern Med* 1992;152:1033–1035, with permission.)

Organizational Issues

Candidates for cardiac rehabilitation are identified in-hospital or referred directly to the outpatient rehabilitation facility. The cardiac rehabilitation program is usually physician directed but managed by a nurse, nurse-practitioner, or exercise physiologist. Patient care is individualized by a case manager who coordinates the implementation of the exercise prescription and the risk-factor treatment plan. Long-term risk-factor goals are set with regard to lipid measures, body weight, diet, and exercise (eFig. 12.2.2), but individualized short-term goals are realistic, with periodic adjustment (eFig 12.6.1). Consultants who have expertise in lipid management, nutrition, psychology, physical therapy, and exercise physiology supplement the expertise of the medical director and clinical coordinator. Outcome measures, such as exercise tolerance, employment status, recurrence of cardiac events, quality of life, and risk factors are updated periodically in coordination with the primary physician.



***e*FIGURE 12.6.1** Patient flowsheet: risk-factor goals.

Home-Based Cardiac Rehabilitation

So that cardiac rehabilitation services can be extended to increasing numbers of patients, the development of home-based programs is essential. The same principles of management described for facility-based rehabilitation apply. Specifically, an on-site intake evaluation is required, with risk-stratification, development of an exercise prescription, and delineation of long-term preventive cardiology goals (*e*Table 12.3.1). The Stanford Coronary Risk Intervention Project describes a model of health care delivery that has been successfully incorporated into a community setting (10). It is a physician-directed, nurse case-managed, multiple risk-factor modification program with well-defined short-term and longer-term individualized goals for specific risk factors (Fig. 12.3). It incorporates personal instruction, home-based programs, and periodic phone and office follow-up and requires no specialized exercise facilities. It has been successfully adapted for use in community programs (208).

***e*TABLE 12.3.1** HOME-BASED CARDIAC REHABILITATION (CASE-MANAGEMENT MODEL)

Intake	Intervention	Follow-up
Risk-factor assessment	Risk-factor therapy	Risk-factor outcomes
Exercise tolerance test	Education, counseling, medical therapy	Physical activity counseling
Risk-stratification	Exercise prescription	Vocational counseling
Vocational assessment		

Home-based rehabilitation can be coordinated either through a physician's office practice or an established rehabilitation program for patients who are unable to attend a facility-based program. In both cases, a case manager (usually a registered nurse), a physician, or both, coordinate the intake evaluation, which incorporates the same basic criteria as were described for facility-based patients. A baseline stress test is particularly useful for risk-stratification to rule out adverse effects of exercise, such as arrhythmias or ischemia, that may require treatment and to help design an appropriate exercise program. The exercise program should be tailored to the patient's needs, but in most cases exercise includes primarily a walking program. Intensity may be guided by exercise heart rate, with patients learning to take their pulse or using a heart-rate monitor to keep their exercise heart rate in the range of 65% to 80% of their maximal heart rate on the treadmill. Alternatively, exercise intensity can be monitored using the perceived exertion scale developed by Borg (193,209); patients should exercise at a perceived exertion of 12 to 14 Borg units (*e*Table 12.3.2). The importance of long-term exercise should be emphasized more than speed or the intensity of individual sessions.

***e*TABLE 12.3.2** BORG SCALE OF PERCEIVED EXERTION

Category scale	
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	Exhaustion

All but the highest-risk cardiac patients, such as those with exertional arrhythmias or low-threshold angina, may participate in home-based rehabilitation, although patients in the moderate-risk category, such as older individuals, those with exertional angina, or those with stable CHF, require more frequent periodic checks and a slower progression of exercise. New technologies include commercially available heart-rate monitors and transtelephonic monitoring and online nurse supervision for selected patients (13). Patients should be encouraged to keep records of their exercise sessions and to perform home monitoring of other individualized risk factors, such as body weight, dietary intake, and blood pressure measures. Short- and longer-term risk-factor goals should be realistic and individualized based on the current status of the patient, the patient's readiness for change, and the available resources. The use of community resources should be maximized to provide climate-controlled exercise spaces, assistance in measurements such as weight or blood pressure, and support groups. Appropriate consultations in the medical environment, such as nutritional instruction or physical therapy, should be available for selected patients to aid them in meeting risk-factor goals. The nurse case-manager should be capable of providing the majority of the necessary education about risk factors related to diet, exercise, and smoking cessation. Patients should be referred as needed to the physician director or the primary health care physician for medical therapy for lipid abnormalities, diabetes, and other risk factors.

COST-EFFECTIVENESS ANALYSIS

Expenditures for the treatment of patients with CAD accounts for approximately 7% of total U.S. health care costs in 1995 ($60 billion of $900 billion) (5). In an era in which containment of health care costs is a major goal, documentation of the cost-effectiveness of specific medical care strategies is a high priority. Cardiac rehabilitation is a clinically effective intervention for CAD that has been subjected to several cost analyses (8,210,211,212 and 213).

Economic evaluations of cardiac rehabilitation were performed both in the United States and in Sweden (210,211 and 212). In a randomized U.S. trial of 8 weeks of rehabilitation begun within 6 weeks of myocardial infarction, a mean per-patient increase of 0.052 quality-adjusted life-years was calculated (210). The cost-effectiveness of this intervention was measured at $9,200 per quality-adjusted life-year. A similar analysis performed in 1996 calculated cost-effectiveness for cardiac rehabilitation of $4,950 per life-year saved (213). These compare favorably with cost-effectiveness analyses calculated for other clinical interventions for CAD (*e*Table 12.3.3).

***e*TABLE 12.3.3** COST-EFFECTIVENESS OF SELECTED INTERVENTIONS FOR CORONARY ARTERY DISEASE

Intervention	Patient group	Cost-effectiveness[a]	Time period
Cardiac rehabilitation	Post-MI	$9,200	1980s–1992
Cardiac rehabilitation	Post-MI	$4,950	1980s–1995
Cholesterol-lowering simvastatin (217)	Angina, post-MI	$9,630	1985–1993
Thrombolytic therapy (t-PA) (218)	Acute MI	$32,700	1990–1994
Coronary bypass surgery (219)	Man, age 55 yr, three vessels	$18,700	1970s–1990s

MI, myocardial infarction; t-PA, tissue type-plasminogen activator.
[a]In dollars per quality-adjusted life-year saved.

A controlled trial of multifactorial cardiac rehabilitation performed in 580 U.S. patients documented a lower cardiac rehospitalization rate and a lower cost per hospitalization, over a mean follow-up of 21 months, for patients who participated in such rehabilitation, resulting in lower hospitalization charges averaging $740 per patient (211). These results are supported by a Swedish study that assessed the value of a 4-month nurse-managed intervention of education and exercise, performed after myocardial infarction in patients older than 65 years (214). At 1 year, rehospitalization rates were significantly lower in the group of patients who participated in intervention programs (13%) than in the control group (29%).

Finally, a comprehensive cost analysis of cardiac rehabilitation was performed in Sweden in patients who had experienced myocardial infarction or had undergone coronary bypass surgery (212). The intervention included twice-weekly group exercise and risk-factor counseling. After 5 years of follow-up, cardiac rehospitalizations were decreased in the group of patients who participated in intervention compared with the control group (11 vs.16 days), and patients participating in rehabilitation returned to work more frequently (53% vs. 38% at 5 years) and had lower sick-leave costs. In the overall cost analysis, rehabilitation costs were offset by the lower hospital admission rates and increased work productivity, which resulted in a 5-year cost savings to the Swedish system of $12,000 per patient.

Thus, cost analyses of the value of cardiac rehabilitation are highly favorable. The well-described clinical benefits of cardiac rehabilitation are attained at an economic cost that compares favorably with other medical interventions that are commonly used for patients with CAD.

CONTROVERSIES AND PERSONAL PERSPECTIVES

In a health care environment that is rapidly incorporating the precepts of managed care and other delivery models, cardiovascular services are undergoing a consolidation designed to maximize efficiency and minimize the use of expensive technologies. Advances in knowledge about the development of coronary atherosclerosis and the prevention of acute coronary events will drive continued interest in the delivery of efficient preventive cardiology services well into the new century. Furthermore, the patient population is aging, and the prevention of coronary disability and second coronary events in elderly patients is a major priority. In patients of all ages, costly cardiac rehospitalizations can be prevented, clinical event rates can be reduced, and coronary disability can be treated and prevented by the systematic application of secondary prevention services.

Many physicians question the need for distinct cardiac rehabilitation facilities, arguing that they can effectively measure and treat cardiac risk factors and recommend home-based exercise in the office setting. In reality, it is the rare physician whose practice is sufficiently regimented, who possesses sufficient expertise in preventive cardiology, and who has sufficient time available to meet the multidisciplinary medical, psychosocial, and vocational needs of the complex cardiac patient. Cardiac rehabilitation is a comprehensive process, and the complex patient benefits greatly from the expertise that is concentrated in the rehabilitation program, including specialists in preventive cardiology, exercise physiology, physical therapy, psychology, nutrition, and vocational counseling. The rehabilitation program has methods in place to maximize the likelihood of attaining outcome goals, and patients describe receiving great psychological support from the peer-group exercise and counseling sessions. Well-defined rehabilitation algorithms have been demonstrated to attain risk-factor goals more successfully than “usual care” in several clinical trials (10,11,24).

Successful modification of coronary risk is not a passive process. Care-management systems need to be established so that patients who would benefit from treatment are referred for care. Risk factors need not only to be identified and measured, but also to be actively treated according to systematic algorithms, with transition to primary health care providers for long-term care and follow-up.

Overall, only 15% of eligible patients participate in cardiac rehabilitation programs, whereas more than 30% of patients at academic medical centers participate (8). Alternative modes of delivery of cardiac rehabilitation services need to be developed to increase the availability of programs. These include home-based programs, with and without transtelephonic monitoring, and case-management systems coordinated through rehabilitation programs or physicians’ offices (208). Exercise programs and risk modification need to be individualized, with an emphasis on clinical outcomes.

In summary, the scientific foundations of cardiac rehabilitation and secondary prevention are on firm ground, supported by recent authoritative clinical practice guidelines and clinical trials (8,6,215,216). As is true of many other preventive interventions, we need not await a “magic bullet.” If currently available therapies can be systematically applied to targeted populations, recurrent coronary event rates will plummet, and coronary disability will be minimized.

THE FUTURE

An established body of scientific knowledge exists that supports the foundations of cardiac rehabilitation and secondary prevention for coronary patients. Systems of delivery need to be established so that patients are systematically involved in the prevention process. The future of cardiac rehabilitation will be defined by the medical care delivery system within which it operates and by the aging of the cardiac population. Prevention of costly rehospitalizations will be a high priority, as will preventing coronary disability in elderly patients. Ever-shortening lengths of stay for acute coronary events and interventional procedures will increase the need for prevention in the outpatient setting.

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13

AN INTEGRATED APPROACH TO RISK-FACTOR MODIFICATION

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The World Health Organization recognizes the two parameters needed to control a disease such as cardiovascular disease (1). First, a 100% efficacious intervention must be developed. Basic science studies and epidemiologic investigations have identified so-called risk factors, which can explain 60% to 80% of coronary heart disease (2,3). Randomized trials have tested and proven that interventions to modify these risk factors can prevent disease. Yet these increasingly efficacious interventions have fallen short of controlling this disease because of less success in the second parameter, namely, the requirement that 100% of the population be covered by the interventions. Our health systems are inefficient, and a portion of the population is not afforded risk-factor reduction because it is considered not cost effective. Risk factors are not assessed, treated, and controlled on current practice, even in high-risk patients. There are many opportunities for risk-factor management, however. These include the inpatient unit, in which risk factors should be assessed and interventions initiated, even at the time of the acute presentation of coronary disease. Risk-factor assessments and goals, as well as plans for their control, should be clearly communicated by the cardiovascular specialist to the primary care provider. Specialized units, including preventive cardiology clinics, cardiac rehabilitation units, and nurse case manager programs, can support the primary care provider's efforts in outpatient risk-factor management. Developments in electronic media open new avenues for patient education. Finally, health care organizations, professional societies, and third-party payers can favorably affect levels of risk-factor control through professional education programs, clinical guidelines, quality assurance standards, and reimbursement policies. The management of risk factors should be viewed as the management of the atherosclerotic disease process itself, emphasizing the role of risk-factor modification as the cornerstone of coronary care.

NEED FOR A SYSTEMATIC APPROACH TO PREVENTIVE CARDIOLOGY

The evidence base supportive of preventive cardiology has steadily become more comprehensive. Studies of vascular biology, natural history studies, and multicenter clinical trials have clearly delineated the role of factors in the atherosclerotic process and the effectiveness of practices to reduce the morbidity and mortality resulting from coronary artery disease. This evidence base has been used by the scientific community and the medical profession to develop a number of comprehensive clinical guidelines and scientific statements, which have been endorsed by the major cardiovascular associations (4,5,6,7,8,9,10,11,12 and 13) (*e*Fig. 13.0.1). But guidelines are not enough. The next step to realize these potential benefits are critical. Evaluations of the performance of health care providers and health care systems to implement prevention and rehabilitation from coronary artery disease have shown continuing deficiencies. This chapter focuses on these gaps, as well as the barriers causing them and the strategies to successfully implement effective preventive care. Although revascularization and thrombolytic interventions continue to revolutionize care of the acute coronary syndromes, preventive cardiology forms the backbone for lifelong management of this systemic disease process.

***e*FIGURE 13.0.1** Quality assurance in preventive cardiology.

Risk-Factor Modification as an Integral Part of Optimal Care of the High-Risk Patient

Cardiovascular disease, including stroke and peripheral arterial disease, has a multifactorial etiology. Most coronary disease patients have two or more risk factors. Yet any single coronary risk factor can contribute to coronary heart disease if left untreated. *e*Table 13.0.1 provides an updated overview of cardiovascular risk factors and the relative strength of evidence that supports their inclusion (14). The important points of note are, first, the sizable list of potentially modifiable risk factors that are strongly tied to the atherosclerotic process on the basis of sound evidence. Several of these risk-factor modifications require the knowledge and skills of a variety of health professionals, including physicians, nurses, behavioral scientists, exercise physiologists, and nutritionists. Thus, effective risk reduction usually requires a team approach. Second, new data suggest interventions such as hormone replacement therapy have shifted in prominence and practice. New factors, such as inflammatory markers, have been linked to clinical disease.

***e*TABLE 13.0.1** CARDIOVASCULAR RISK FACTORS: THE EVIDENCE SUPPORTING THEIR ASSOCIATION WITH DISEASE, THE USEFULNESS OF MEASURING THEM, AND THEIR RESPONSIVENESS TO INTERVENTION

	Evidence for association with CVD			Response to	
Risk factor	**Epidemiologic**	**Clinical trials**	**Clinical assessment useful?**	**Nonpharmacotherapy**	**Pharmacotherapy**

Category I (risk factors for which interventions have proven to lower CVD risk)					
Cigarette smoking	+++	++	+++	+++	++
LDL cholesterol	+++	+++	+++	++	+++
High-fat/cholesterol diet	+++	++	++	++	–
Hypertension	+++	+++ (stroke)	+++	++	+++
Left ventricular hypertrophy	+++	+	++	–	++
Thrombogenic factors	+++ (fibrinogen)	+++ (aspirin, warfarin)	+	+	+++ (aspirin, warfarin)
Category II (risk factors for which interventions are likely to lower CVD risk)					
Diabetes mellitus	+++	+	+++	++	+++
Physical inactivity	+++	++	++	++	–
Low HDL cholesterol	+++	++	+++	++	+
Triglycerides, small, dense LDL	++	++	+++	++	+++
Obesity	+++	–	+++	++	+
Category III (risk factors associated with increased CVD risk, which, if modified, might lower risk)					
Psychosocial factors	++	+	+++	+	–
Lipoprotein(a)	+	–	+	–	+
Homocysteine	++	–	+	++	++
Oxidative stress	++	–	–	+	+
No alcohol consumption	+++	–	++	++	–
Inflammatory markers	+ + +	+	+	–	+
Postmenopausal status (women)	+++	–	+++	–	+
Category IV (risk factors associated with increased CVD risk, but that cannot be modified)					
Age	+++	–	+++	–	–
Male sex	+++	–	+++	–	–
Low socioeconomic status	+++	–	+++	–	–
Family history of early-onset CVD	+++	–	+++	–	–

CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; +, weak, somewhat consistent evidence; ++, moderately strong, rather consistent evidence; +++, very strong, consistent evidence; –, evidence poor or nonexistent.
Modified from Pearson TA, Fuster V. Executive summary of the 27th Bethesda Conference: matching the intensity of risk-factor management with the hazard for coronary disease events. *J Am Coll Cardiol* 1996;27:961–963.

The evidence to support risk factors for which interventions have been proven to lower cardiovascular disease continues to grow and change. For example, a Mediterranean-type diet appears to be able to reduce recurrent myocardial infarction (MI) and death in coronary patients by over 60%, compared with the usual French diet (15). This is of similar or greater magnitude of reduction with pharmacologic agents such as lipid-lowering drugs and beta-blockers. Other recent additions to this table include further data emphasizing the importance of high-density lipoprotein (HDL) cholesterol in coronary disease (16). The Veteran Affairs High Density Lipoprotein Cholesterol Intervention trial showed an impressive 22% relative risk reduction in nonfatal MI and cardiac death with the use of gemfibrozil to raise HDL cholesterol (17). This has important ramifications for many patients with features of the metabolic syndrome (diabetes, glucose intolerance, hypertension obesity, high triglycerides or low HDL) who may have *normal* low-density lipoprotein (LDL) cholesterol but remain at high risk for future coronary events because of low HDL. Vitamin E was not found to alter coronary heart disease risk (18), although there is growing data supporting the importance of inflammatory markers such as high sensitivity C-reactive protein (19,20) providing further options for risk-stratification and management of coronary artery disease risk.

A major change in cardiovascular risk management for postmenopausal women occurred after the results of two randomized trials of estrogen and progestin for secondary prevention of coronary heart disease showed no benefit (21,22). This result came in the face of a wealth of observational studies that have found lower rates of coronary heart disease in women taking postmenopausal estrogen therapy. The known thrombogenic effects of estrogen and progestin were postulated as a potential cause, highlighting the complexities of risk-factor modulation of disease. Although estrogen replacement therapy is no longer recommended for women with established cardiovascular disease (7), their use in symptomatic women remains controversial. Results from The Women's Health Initiative and WELL-HART trials should provide better delineation of this problem (23).

Another development in preventive cardiology has been an emphasis on the modification of risk rather than just risk factors. The concept of primary and secondary prevention has become less applicable. High-risk groups have been identified by global risk assessment to identify individuals whose risk of coronary heart disease is so high that they should be treated as having presumptive coronary atherosclerosis. More specific and sensitive cardiac imaging methods are now widely used to identify people with atherosclerosis in a preclinical phase. The goal for the health professional is therefore to accurately place individual patients into categories of risk. The aggressiveness of risk-factor modification is matched to these categories, providing a cost-effective, evidence-based approach to prevention (14). The patient with symptomatic coronary artery disease is easily placed in the category of highest risk. The risk of future events after an ischemic episode is extremely high. Secondary end points of reduced myocardial ischemia and correction of arrhythmias, prompting fewer hospital admissions, leads to the primary objective of reduction of cardiac morbidity and mortality in these symptomatic patients.

The asymptomatic patient without evidence of vascular disease provides the cardiovascular specialist with additional challenges, because many of these patients have a coronary heart disease risk equivalent. Contribution and interaction of multiple risk factors has provided the impetus to globally assess the cardiovascular risk of a patient with multiple risk-factor scoring systems. These have provided better predictive ability for MI and death. An example of this is the Framingham risk scoring system for persons older than 30 years without prior cardiovascular disease (24,25). Points assigned to risk-factor levels are summed to produce a 10-year absolute risk for coronary heart disease end points for an individual patient. The Joint European Societies have established a 20% risk of coronary heart disease over 10 years as warranting aggressive risk-factor modification therapy (26). This is a risk similar to many persons with previous MI or stable angina and is therefore referred to as a *coronary heart disease risk equivalent*. These patients may be increasingly identified and referred to cardiovascular specialists for risk reduction. Risk-factor management will continue to be the primary means to reduce their high absolute risk of MI and death.

Rationale for a Comprehensive Risk Reduction Approach

What form should risk-factor modification take in the management of the high-risk patient? Several scenarios might be entertained, including intervention by a specialty clinic, for example, lipid management or preventive cardiology clinics, referral of this responsibility back to the primary care provider, or integration of modification efforts as part of the overall care of the high-risk patient. Table 13.1 identifies several of the many reasons to support the latter approach for all patients with symptomatic or high risk for atherosclerotic disease.

Treatment of the primary disease process (atherosclerosis) rather than the symptomatic complications of the disease
Long-term efficacy in reducing risk of events
Reduced risk of symptoms from disease in other vascular beds (e.g., cerebral, peripheral)
Improved effectiveness of acute coronary care
Risk-factor interventions efficacious over very short intervals
Risk-factor modifications may be more successful in the acute phases of coronary disease
Benefits additive to those of other cardiologic procedures
Improved safety of interventions
Reduce potentially deleterious interactions between risk-factor modifications
Reduce deleterious interactions between risk-factor modifications and other cardiologic therapies
Improve follow-up care and compliance by considering risk-factor modification as a cornerstone of cardiologic care worthy of initiation early in clinical course

TABLE 13.1 RATIONALE FOR COMPREHENSIVE RISK-FACTOR MODIFICATION INTEGRATED INTO THE OVERALL MANAGEMENT OF THE PATIENT WITH CORONARY ARTERY DISEASE

One important consideration deals with which disease is actually being targeted for intervention. Although acute syndromes of myocardial ischemia and their sequelae demand acute intervention to reduce the risk of death and disability over the short-term, long-term prognosis is dictated by the extent of the atherosclerotic disease in the coronary vasculature and the factors related to it. Perhaps a better concept is that risk-factor modification constitutes the *medical management of atherosclerosis* (14). After alleviation of the acute manifestations of ischemia, the focus of the physician should then turn to those pathophysiologic processes within the arterial wall that allowed the ischemic event to develop. Although invasive or surgical approaches to atherosclerosis have their place in cardiac care, a considerable array of interventions, both behavioral and pharmacologic, are now available. These focus on reestablishing normal endothelial function, inhibiting the initiation and growth of

atherosclerotic plaques, stabilizing these plaques to prevent ulceration and rupture, and reducing thrombogenicity of the blood. This represents the management of the atherosclerotic arterial system, in conjunction with the correction of myocardial ischemia, left ventricular dysfunction, ventricular arrhythmias, and other pathophysiologic processes. Clinical trials have proven the long-term benefits of this approach (eTable 13.0.1).

Second, limiting intervention to atherosclerotic disease that is symptomatic in one vascular bed ignores the fact that atherosclerosis is a systemic disease. Although the relief of symptoms through revascularization is important to the patient, without intervention on recurrence of the systemic atherosclerotic process itself, symptomatic disease in the coronary arteries or in other vascular beds is highly likely. It is well known that the leading cause of death in patients with atherosclerotic abdominal aneurysm or peripheral arterial disease is MI and sudden cardiac death (24). Moreover, reductions in risk factors in patients with symptomatic coronary disease have been shown to reduce events elsewhere in the vasculature. A metaanalysis of clinical trials observed that LDL cholesterol reduction with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in patients with coronary disease not only reduced MI and cardiac death but also reduced the occurrence of fatal and nonfatal stroke by approximately 30% (27). Clearly, the management of the atherosclerotic disease process must occur concomitantly with the management of its symptoms.

Third, the traditional approach has been to consider risk-factor modification as adjunctive therapy, to be provided only after the completion of diagnostic and therapeutic steps in the acutely ill patient. This is based on the old notion that risk-factor management acts on the slowly progressive atherosclerotic process, thereby taking months or years to benefit the patient. More recent evidence, suggesting that a number of modifiable risk factors affects endothelial function, plaque stability, and hemostasis, establishes the biologic plausibility for rapid benefits of risk-factor modification in the acute care of a coronary patient (28). Clinical studies corroborate the acute benefits of risk-factor modification. It has long been recognized that smoking cessation reduces the risk of reinfarction and death after MI in a matter of weeks or months (29,30). More recent randomized trials of lipid-lowering agents have demonstrated substantial reduction of myocardial ischemia on ambulatory electrocardiograms within months of MI (31). There is now agreement that these effective behavioral and pharmacologic measures should be instituted before hospital discharge for maximal benefit (32). Studies using HMG-CoA reductase inhibitors suggest that sizable reductions in clinical coronary events can be realized in a matter of weeks or months. The Pravastatin Multinational study showed a 95% reduction in coronary events with pravastatin after only 6 months, with sizable differences discernible at 8 weeks (33). In a prospective cohort study evaluating early statin use post-MI, a relative risk reduction of 25% in 1-year mortality was noted (Fig. 13.1) (34). Likewise, the preliminary results of a randomized trial of a high-dose statin within the first 48 hours after symptom onset showed a significant 16% reduction in events over the next 6 months (35). Several randomized double-blind placebo trials of early initiation of statins are currently being completed to further delineate the best time to introduce statin use. The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction trial showed a mortality reduction in those patients who had more aggressive management of their blood sugars post-MI, again highlighting short-term benefits of effective risk-factor management (36). The magnitude of these benefits is similar to that expected with angiotensin-converting enzyme (ACE) inhibitors or beta-blocker therapies. This shift in preference toward early risk-factor modification again highlights the need for an effective, structured risk reduction strategy to be in place.

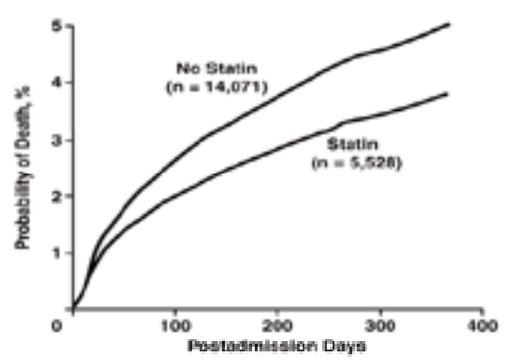


FIGURE 13.1 Statin treatment initiated early in the postinfarction period for patients with acute myocardial infarction. Data were calculated using multiple Cox regression analysis (relative risk, 0.75; 95% confidence interval, 0.63–0.89; *p* = .001). (From Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 2001;285:430–436, with permission.)

Next, there are a number of psychosocial benefits of integrating risk-factor modification into the overall management of acute and chronic ischemic heart disease. During acute phases of illness, the patient and his or her family members may be especially receptive to behavioral interventions. This is the concept of the *teachable moment*. For example, during hospitalization for acute ischemia, the coronary disease patient is prohibited from smoking. This may be a propitious time to initiate a program of behavior modification that can extend to the outpatient phases of the patient's treatment.

Another erroneous notion is that traditional cardiac interventions such as revascularization or beta-blocker therapies may somehow negate the need for risk-factor management. Risk factors and clinical factors both strongly influence the natural history of coronary disease (37,38). Although prevention of ischemia, congestive heart failure, and arrhythmia is an important goal in caring for the atherosclerotic patient, stabilization of the atherosclerotic process, slowing its progression, and prevention of thrombosis are discrete benefits of risk-factor management. Subanalyses in large clinical trials such as the Scandinavian Simvastatin Survival Study, for example, were able to examine the benefits of LDL cholesterol lowering in patients who were undergoing a variety of secondary preventive interventions such as treatment with aspirin, beta-blockers, ACE inhibitors, as well as those who were not (39). Consistently, cholesterol lowering was found to have benefits additive to other interventions. Another example is the prevention of saphenous vein bypass graft atherosclerosis. Both the Cholesterol Lowering Atherosclerosis Study (40) and the Post Coronary Artery Bypass Graft Study (41) have shown that the lowering of LDL cholesterol can prevent the initiation and progression of lesions in bypass grafts, preventing the need for repeated surgical revascularization. These observations point to the need to integrate risk-factor modification into the initial stages of therapy, with the expectation of short- and long-term benefits additive to those of traditional cardiac interventions.

On the other hand, another reason for coordination of efforts in comprehensive risk reduction is the potential deleterious interactions between risk-factor modifications and other therapies. Bile acid–binding resins, useful agents for reducing LDL cholesterol, can bind up coumadin, beta-blockers, and digoxin. Similarly, smoking cessation, a major means of reducing risk, can nonetheless lead to postcessation weight gain and deleterious effects on lipids and glucose. A diet that reduces saturated fat and cholesterol may also reduce HDL cholesterol. Proven antihypertensive therapies, namely, thiazide diuretics and beta-blockers, can also reduce HDL cholesterol and raise serum triglycerides in some patients. Clearly, when considering overall risk, a patient's entire risk-factor profile must be considered, especially because most patients with coronary disease have two or more risk factors (39). Intervention on one risk factor should take others into consideration, with the goal being maximal reduction of overall risk.

Finally, the cardiovascular specialist is looked to for leadership and advice in constructing the optimal treatment program for the high-risk patient. Because their care often deals with the acute or emergent management of ischemia, much of the communication to the primary care provider may deal with these interventions only. If a description of a risk-factor reduction program is not included in the overall care program, the impression is given that it is not important. The incorporation of risk-factor modification and other preventive interventions into a well-integrated, comprehensive program that seeks maximal risk reduction should be the mutual goal of both specialist and generalist. Risk reduction is the responsibility of everyone on the health care team.

Evidence for the Underutilization of Interventions to Reduce Risk

The American Heart Association (AHA), American College of Cardiology (ACC), and other organizations have released a number of consensus statements addressing prevention of coronary artery disease (4,5,6,7,8,9,10,11,12 and 13), based on basic epidemiologic and clinical trial evidence (14) (eFig. 13.0.1). Despite the increasing evidence supporting effective preventive therapies, their application has been disappointing. An example is the National Cholesterol Education Program (NCEP) Adult Treatment panel II guidelines for LDL cholesterol management (10). As an evidence-based document, these guidelines established LDL cholesterol thresholds for treatment and LDL cholesterol goals that should be attained for low-risk, high-risk, and coronary heart disease patients. A review of office visits from the National Ambulatory Medical Care Surveys showed that cholesterol screening, both for primary and secondary prevention, was much lower than predicted by NCEP guidelines (42). Cholesterol testing occurred in only 22.9% of office visits and counseling was infrequent (34%) in known hyperlipidemic patients. The Heart and Estrogen/Progestin Study trial enrolled women with coronary artery disease, identifying 91% of participants who had not achieved the NCEP LDL cholesterol goal of less than 100 mg per dL. (43). The Lipid Treatment Assessment Project, a survey to evaluate the proportion of 4,888 dyslipidemic patients receiving lipid-lowering therapy, also provided evidence of a low success rate, especially in high-risk, noncoronary, and coronary heart disease groups (44). Only 18% of patients with established coronary heart disease met the NCEP goal for LDL cholesterol. This was despite surveying 618 physicians who were among the most frequent prescribers of lipid-lowering drugs. The lack of use of medications, an inappropriate choice or dose of medication, or the infrequent use of combination therapy appeared to be the cause of the low success rates. The majority (80%) of participants did not receive dietary counseling.

This treatment gap does not appear to be limited to lipid management. Further review analyzed medication use and showed disappointing rates of use of well-established medications such as beta-blockers (45), ACE inhibitors (46), and aspirin (47), even when clearly indicated. Smoking cessation counseling is addressed

in less than one-half of smokers with coronary disease (48,49). A multicenter study conducted in Europe looked retrospectively at hospital records and conducted prospective interviews of patients to determine whether major coronary risk factors had been addressed (50). There was a striking twofold difference between countries' use of proven beneficial therapies such as beta-blockers post-MI. There was also a threefold variation in ACE inhibitor use in those patients with symptoms of heart failure that could not be explained. Reduced assessment and inappropriate modification of risk factors have also been documented in the elderly (aged 65 years and older) despite their high burden of disease and proven significant risk reduction with these therapies (51,52). An outpatient survey of predominately cardiology practices documented a reluctance to titrate the dose of ACE inhibitors for patients with congestive heart failure and of HMG-CoA reductase inhibitors in patients with lipid disorders (53). Only 26% of patients achieved the recommended target dose as described by a number of studies clearly showing mortality benefit (54). Finally, the majority of patients with premature coronary heart disease were not encouraged to have first-degree relatives screened for cardiac risk. This was further emphasized in a study using the ACC Evaluation of Preventative Therapeutics data, in which less than 1% of inpatient medical records contained a discharge plan detailing recommended screening of family members of patients younger than 55 years (55). Only 17.8% of these patients had their families screened within 6 months of their cardiovascular event, despite NCEP guideline recommendations to screen all patients with a recognized history of premature coronary artery disease (10).

Thus, the gap between the goals of treatment and the actual levels of risk-factor control appears large, and it must translate into considerable numbers of preventable cases of recurrence and death caused by atherosclerotic disease. Table 13.2 illustrates this gap by showing the numbers of lives potentially saved each year if proven preventions were optimally implemented, suggesting that tens of thousands of deaths might be averted merely by following guidelines (56).

Therapy	Ideal–actual use (%)	Relative risk reduction (%)	No. of additional lives saved/yr
Antiplatelet	15	15	13,500
Beta-blockers	10	21	12,600
Angiotensin-converting enzyme 1	30	17	30,600
Statins	20	23	27,600
Total			**84,300**

From Bahit MC, Granger CB, Alexander KP, et al. Applying the evidence: opportunity in US for 80,000 additional lives saved per year. Circulation 2000;102:11–874, with permission.

TABLE 13.2 ESTIMATION OF ADDITIONAL LIVES SAVED EACH YEAR BY IMPLEMENTATION OF PREVENTIVE CARDIOLOGY INTERVENTIONS

BARRIERS TO IMPLEMENTATION OF PREVENTIVE CARDIOLOGY SERVICES

Introduction

Unfortunately, the provision of appropriate and effective preventive cardiology care is affected by a large number of people and institutions, including the patient, physicians (both specialists and generalists), health care facilities (both inpatient and outpatient), and societal and community factors. For example, the motivated patient may not be supported by his or her physician, or the physician and patient may find the hospital environment hostile to preventive care (e.g., high-fat, high-cholesterol meals in the coronary care unit). Finally, all may be frustrated by the lack of reimbursement or standards set by third-party payers. Therefore, it is useful to identify the barriers to implementation of preventive services with proven efficacy and cost effectiveness (*e*Table 13.2.1) (57).

***e*TABLE 13.2.1** BARRIERS TO IMPLEMENTATION OF PREVENTIVE SERVICES
Patient
Lack of knowledge and motivation
Lack of access to care
Cultural factors
Social factors
Physician
Problem-based focus
Feedback on prevention is negative or neutral
Time constraints
Lack of incentives, including reimbursement
Lack of training
Poor knowledge of benefits
Perceived ineffectiveness
Lack of skills
Lack of specialist–generalist communication
Lack of perceived legitimacy
Health care setting (hospitals, practices, and so forth)
Acute care priority
Lack of resources and facilities
Lack of systems for preventive services
Time and economic constraints
Poor communications between specialty and primary care providers
Lack of policies and standards
Community/society
Lack of policies and standards
Lack of reimbursement

From Pearson TA, McBride PE, Houston-Miller N, et al. Organization of preventive cardiology service. *J Am Coll Cardiol* 1996;27:1039–1047, with permission.

Patient Factors as Barriers to Risk-Factor Modification

Often, the tendency is to blame the patient for lack of success with behavioral modifications and noncompliance with pharmacologic interventions. Surprisingly, in surveys of patients ascertaining satisfaction with treatment, preventive services, including counseling, were provided less often than recommended or by patient preference (58,59). For example, studies looking at smoking cessation in the primary care setting have shown that the majority of patients who smoke would attempt to stop if their physicians advised them how to do so (48). Only 40% to 55% reported that this advice was given, despite a number of studies illustrating that timely physician counseling on smoking cessation is an effective preventive intervention (49,60,61). In spite of this knowledge, a review of physician encounters showed that in only 67% of the cases was smoking status documented, and for those who did smoke, discussion in regard to stopping occurred in less than 25% of consultations (48). A number of reasons for these results have been cited by physicians, including a fear of antagonizing patients. However, one recent study has shown that smoking interventions during physician visits were associated with increased patient satisfaction with their care (58).

Coronary heart disease is the leading cause of death in American women (7). Despite this, several studies have documented that women with coronary artery disease were less likely to have invasive management of coronary atherosclerosis (62,63 and 64). Sueta et al. showed women to be less likely to be treated with lipid-lowering drugs (53). Strong associations between a low socioeconomic status and a poor prognosis after the onset of coronary heart disease have been consistently documented (65,66). For example, survival after admission for diagnostic coronary arteriography is strongly related to income, with 24% of patients with an income of $10,000 or less not alive after 5 years, in contrast with 9% mortality in those patients with an income of $40,000 or more (65). A variety of studies have documented a poorer prognosis after the onset of coronary disease in blacks as compared with whites (67,68). Also a major difference in use of medication was noted in the Heart and Estrogen/Progestin Study data, in which nearly one-half of the black women did not use lipid-lowering medication (43). It was postulated that this may have been secondary to cost or reduced access to care. In a review of physician encounters it was also noted that nonwhite populations were less likely to be referred for cardiac stress testing and had lower rates of treatment with medications such as beta-blockers when indicated (45,62). Private insurance was also seen to be an independent nonclinical variable that determined access to treatment for cardiac patients (45,62).

Surprisingly, less is understood about the pathways through which these social and cultural factors act (68). A lack of knowledge or motivation on the part of the patient

is frequently cited. High levels of noncompliance are common in a variety of settings (69,70). For example, a study from Australia noted that 58% of patients prescribed HMG-CoA reductase inhibitors were no longer taking them at the end of 12 months (71). The most frequent reason for this noncompliance was patient related; the patient simply did not understand why he or she was given the medication. Indeed, many patients are less likely to continue cardiac rehabilitation after MI and consequently are less likely to benefit from aggressive risk-factor modification. This has been seen in women (7) and also patients with lower incomes and education who are also less likely to pursue an exercise program on their own, when not enrolled in a cardiac rehabilitation program (72). Similarly, people with lower incomes perceive cost to be a barrier to access cardiac care and emergency care in the United States (73).

Patient confusion over conflicting information is also a significant cause for noncompliance. Unfortunately, the media provides a powerful source of provocative, memorable information that may not entirely provide a balanced picture. Although debate over such issues takes place within the confines of the medical profession, it is important to display a consistent, considered interpretation of the available data. Consensus statements have attempted to address this issue (4,5).

Clearly, a patient well educated and proactive in his or her health influences whether a physician addresses a problem (57). Therefore, efforts to empower patients to seek preventive health services remain a viable strategy. Addressing this imbalance is a key component to optimal preventive care. Laying blame at the feet of the patient is unlikely to remedy this. Targeting high-risk groups with special interventions tailored to their educational level or cultural group will provide better results.

Physician Factors as Barriers to Risk-Factor Modification

Preventive cardiology has indeed become more complex, with increased numbers of issues that should be considered in each patient. First, adequate assessment of patient risk factors and determining the degree of overall coronary heart disease risk is vital. Second, a clear understanding of the clinical guidelines for treatment that are constantly updated provides guidance to effectively manage patients. Frequently a lack of appreciation exists in regard to the benefits and magnitude of cardiac event reduction by risk-factor management (74). Risk-factor intervention rivals or exceeds that of more standard cardiologic intervention, in terms of magnitude of benefit. For example, the lowering of LDL cholesterol has shown reductions in recurrent MI, sudden death, and total mortality in the range of 25% to 40% in a wide variety of clinical subgroups of patients with coronary disease in contrast to a few subgroups of patients undergoing revascularization. Indeed, the Atorvastatin Versus Revascularisation and Treatment trial showed that aggressive lipid management was at least as effective (if not more) as angioplasty in reducing ischemic events in symptomatic coronary patients (75). Angioplasty and bypass surgery generally do not prevent infarction, and bypass surgery improves survival only in certain subgroups of patients.

Both the cardiovascular specialist and the generalist face considerable constraints on their abilities to implement risk-factor modification strategies. Time-consuming interventions, especially those involving behavior modification, place enormous burdens on the ever-shrinking time allotted for interactions with patients. The average length of stay in the hospital has dramatically decreased and in the ambulatory care setting, patient appointments are also brief. These interactions, both in inpatient and in ambulatory care settings, are increasingly focused on the acute problem, with the physician being pressured to treat that problem solely. A preventive therapy is therefore often forgotten and, if remembered at all, there is little continued assessment or progression of treatment (44,76).

High proportions (more than 90%) of physicians have expressed adequate knowledge about various guidelines, such as those related to the detection and management of hypercholesterolemia (77). Nevertheless, there remains a lack of self-confidence in their abilities to effectively implement a cholesterol-lowering diet or to use cholesterol-lowering drugs (78,79). Effective titration of dosages of medications or using combination therapy when goal cholesterol levels have not been achieved have been frequently cited causes of therapeutic failure (44,52). Risk-factor management strategies clearly have not been integrated into many cardiology training programs, and many cardiology trainees lack hands-on experience at risk-factor management in a cardiac rehabilitation or preventive cardiology clinic setting. Without this knowledge, the ability to effectively communicate a preventative strategy to the patient is limited. Furthermore, goals of the treating physician and patient may differ. Patients may be more inclined to seek and use medications that relieve discomfort rather than continue with a medication that lowers cholesterol but provides no detectable symptomatic relief. For both doctor and patient, monitoring of lipid levels as objective evidence of medication success is important to encourage compliance.

There also exist a number of disincentives for the physician to provide preventive interventions. Frequently, risk-factor management services are not recognized as part of the treatment of cardiac problems and are not reimbursed. This is especially true for services by nutritionists and nurses. Furthermore, the feedback to the physician is frequently neutral; the goal of prevention is the absence of further events. This delayed gratification is in stark contrast to the relief of angina or dyspnea brought about by acute interventions.

Finally, the notion persists that risk-factor management is the only legitimate bailiwick of the generalist, and that the specialist's activity in this arena may encroach on the generalist's area of responsibility, resulting in loss of patient referrals. This notion emphasizes the lack of specialist–generalist communication in this area and also the lack of clarity over whose role it is to provide and monitor preventative cardiac care. The real issue is whether risk-factor management is an integral part of the optimal care of the cardiac patient; cardiology societies appear unanimous in their opinion that this is true (14,76). Therefore, risk-factor management should be initiated as part of the management of acute coronary disease and included in the care plan communicated from the specialist to the generalist. Lack of this communication continues to adversely affect patient care (57).

FACTORS IN HEALTH CARE SETTINGS AS BARRIERS TO RISK-FACTOR MODIFICATION

Motivated patients and well-informed, skilled physicians may still fail to implement risk reduction strategies when faced with barriers inherent in acute care hospitals and ambulatory care offices. Today's emphasis on early discharge after treatment of the acute condition places tremendous pressures on the duration and content of inpatient interventions. That time available is frequently taken up by procedures or by periods of convalescence in which the patient is not receptive to health education because of pain or treatment with sedatives. These are clearly not high-quality opportunities for intervention, which formerly may have occurred in the additional day or two available before discharge. Increasingly, discharge occurs before risk reduction strategies can be implemented.

Other barriers in the health care setting may be more amenable to correction. These include a lack of organization and resources dedicated to achieving risk-factor management. The responsibility for risk-factor management is often not assigned to a specific person or unit within the hospital or clinic, leaving the physician to fend for him- or herself. This haphazard duty assignment, when actually undertaken, is often performed inadequately because of lack of training r experience. Nurses, nutritionists, physical therapists, and other professionals frequently have not received formal training materials or patient education manuals to ensure the quality of their service. Again, laboring under the false assumption that risk-factor management is adjunctive care, these professionals are often reassigned to other duties during times of staff reductions. The infrastructure for an effective preventive program is often not in place, and therefore interventions are sporadic and inconsistent. Finally, there is often little opportunity to monitor the outcomes of inpatient programs, because patients are rapidly discharged to ambulatory care settings without proper follow-up of their risk reduction care plan. Communication of interventions already performed or strongly recommended for outpatient initiation and instructions regarding later titration are often not included in the limited space on discharge summary forms. A lack of opportunity to address preventive interventions in hospital is thus propagated into the ambulatory setting.

SOCIETAL AND HEALTH SYSTEM FACTORS AS BARRIERS TO RISK-FACTOR MODIFICATION

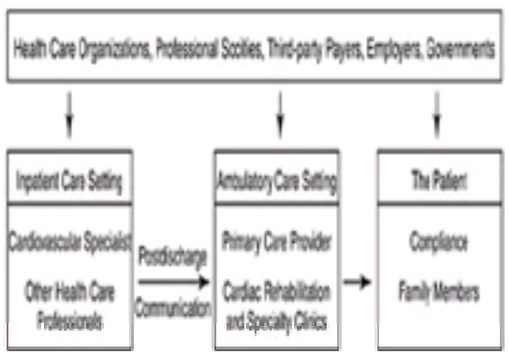
Until relatively recently there has been little impetus from health maintenance organizations to assess the adequacy of risk-factor modification in their patient population. Such an evaluation would be both costly and time consuming. This is especially unattractive without definitive cost-effectiveness data regarding secondary preventive measures. More recent analyses and studies of models for delivering preventive strategies have shown reduced hospitalizations, cardiology clinic visits, and other direct costs as well as improvement in symptoms (80). Frequently, for-profit (and some not-for-profit) health care systems have required a positive return from a preventive intervention within 18 to 24 months, assuming that a substantial portion of patients would be transferring to another health care payer by the end of that time. This in turn has led to lack of reimbursement for preventive services or the lack of designation of positions and resources to provide the risk reduction services. However, more recent studies have focused on initiating preventive interventions in the acute care setting because of early benefits seen (28,29,30,31,32,33 and 34). This has served to increase the importance of guidelines and recommendations that recognize risk-factor management as an integral part of optimal care over both the short- and long-term phases of the disease.

STRATEGIES FOR INTEGRATION OF COMPREHENSIVE RISK REDUCTION INTO CARDIOLOGIC PRACTICE

Introduction

After consideration of the barriers to implementation of risk-factor modification, a chain of opportunities for comprehensive risk reduction might be constructed (*e*Fig. 13.1.1). This would include assessment of the patient's risk factors at the time of admission for an acute coronary disease syndrome, when the cardiovascular specialist or a team of other health professionals might recommend and initiate a risk reduction program. Of special importance would be the communication to the primary care provider about the interventions required and the eventual goals of these interventions, e.g., frequency and duration of exercise, target LDL cholesterol level, and so forth. On an ambulatory care basis, the primary care provider then could initiate or continue the recommended interventions, with or without the help of

specialized entities such as cardiac rehabilitation units, preventive cardiology clinics, and nurse case manager programs. The patient then would be provided with tools to improve compliance with recommended interventions. Finally, health care organizations (e.g., health maintenance organizations and managed care organizations), health insurers and other third-party payers, professional societies, employers, and governments (including the legal system) likely could affect all links in the chain through reimbursement policies, guidelines, and quality assurance programs.



***e*FIGURE 13.1.1** The chain of opportunities for integration of comprehensive risk reduction strategies into the overall care of the patient with vascular disease.

Unfortunately, we have limited direct information on the performance of any of the specific components of this chain of opportunities. What we can infer from large clinical studies is that underuse of preventive interventions and unmet goals of risk-factor reductions currently result in preventable morbidity and mortality. This section discusses the opportunities for intervention at each step of the chain and provides evidence for effectiveness of these interventions to improve levels of risk-factor detection and management.

Opportunities in the Inpatient Care Setting

Role of the Hospital

An inpatient cardiology service can be organized to efficiently and reliably assess the levels of risk factors prevalent in patients admitted with acute coronary syndromes or for revascularization procedures. A convenient tool is the joint AHA–American Association of Cardiovascular Preventive Health statement regarding core components for secondary prevention (26), which includes strategies for optimal risk-factor management. These guidelines include the goals for each risk-factor intervention and have been modified to provide a form to comprehensively document the initial status of the risk factor as well as plans for intervention and follow-up (Fig. 13.2). The checklist format has been used successfully to improve levels of preventive care (81,82). In one study, computer-generated preventive-care reminders, individualized to the patient, increased preventive services provided by 126 physicians by 20% (83). Such a form could be filled out by physicians, nurses, or other health professionals. The AHA has provided a number of Web-based tools to quickly and efficiently document risk-factor assessments and interventions for individual patients (http://www.americanheart.org/CAP, “Get with the Guidelines Program”). These tools track compliance of risk-factor modifications and can even generate letters clearly outlining proposed programs. This provides a time-efficient, vital communication between physicians participating in care. Nurse-generated checklists also have been successful in increasing preventive services (84,85). Similar reminder messages and forms have also been used to implement a variety of acute care guidelines, suggesting their feasibility and desirability even in acute care settings (86). The Cardiac Hospitalization Atherosclerosis Management Program at the University of California Los Angeles has implemented such a system of early risk-factor intervention and has shown increasing rates of use of known effective interventions during long-term follow-up (Table 13.3) (87). Another approach is the development of more elaborate care protocols, or *critical pathways*, that comprehensively define care of a specific problem. The joint AHA-ACC guidelines for management of patients with acute myocardial infarction is an example of this, defining multiple dimensions of acute myocardial infarction management but including risk-factor assessment and management as part of the initial intervention (13).

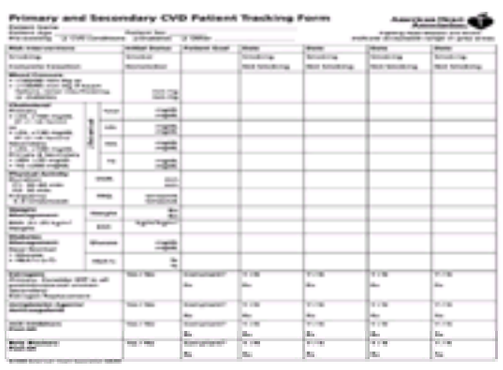


FIGURE 13.2 American Heart Association form to track risk-factor modification and secondary preventive intervention. ACE, angiotensin-converting enzyme; BMI, body mass index; CVD, cardiovascular disease; DUR, duration; ERT, estrogen replacement therapy; FRQ, frequency; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; Rx, prescription; TG, triglyceride.

Discharge therapy	Pre-CHAMP (1992–1993) (n = 256; %)	Post-CHAMP (1994–1995) (n = 302; %)
Aspirin	78	92
Beta-blocker	12	61
Nitrate	62	34
Calcium antagonists	68	12
Angiotensin-converting enzyme inhibitors	4	56
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor	6	86

From Fonarow GC, Gawlinski A. Rationale and design of the cardiac hospitalization atherosclerosis management program at the University of California Los Angeles. *Am J Cardiol* 2000;85:10A–17A, with permission.

TABLE 13.3 RATES OF APPROPRIATE AND INAPPROPRIATE CARDIOLOGIC MEDICATION USE BEFORE AND AFTER AN INPATIENT PROGRAM TO IMPROVE ATHEROSCLEROSIS: THE CARDIAC HOSPITALIZATION ATHEROSCLEROSIS MANAGEMENT PROGRAM (CHAMP) STUDY

Hospitals can also provide a variety of other opportunities to identify risk factors. One example is the chemistry laboratory. The AHA-ACC guidelines for management of acute myocardial infarction suggest a lipid profile at the time of admission to the hospital (13). This can be made automatic, so that serum collected for cardiac enzymes such as troponin and creatinine phosphokinase might also be analyzed for serum lipids. The importance of this lies in the observation that serum cholesterol levels (and most lipoprotein cholesterol levels) decrease 24 hours after an MI (88). The routine measurement of a lipid profile in the patient with the presumptive diagnosis of MI would ensure a baseline assessment of lipids and lipoproteins. Furthermore, laboratory reports can include various messages identifying abnormal levels and the steps needed to correct those levels. Cholesterol levels identified as abnormal serve as cues to change physician behavior and are more likely to lead to further diagnosis and treatment of a lipid abnormality than those values not identified as normal (89). This has taken on even more importance with increasing evidence of the benefits of in-hospital preventive interventions.

Another important reason for encouraging early assessment and treatment of risk factors is that hospitalization for an acute ischemic episode often represents an opportunity to change patient attitude and behavior. Patients are unable to smoke in the hospital and are subject to dietary restrictions. This provides as ideal

opportunity to begin the discussion of what permanent changes need to be made in their lifestyles (49,60,61).

Role of the Cardiovascular Specialist

The usual role of the physician admitting the patients acutely ill with vascular disease, or the cardiovascular consultant asked for advice, is to make and confirm the diagnosis, to set goals for treatment, and to formulate the optimal plan to achieve these goals. The same should be true for the modification of risk factors. In this way, the cardiovascular specialist plays a leadership role in the integration of risk reduction strategies into the overall plan. Those patients admitted with symptomatic coronary artery disease already fall into the high-risk group of patients likely to experience further cardiac events. Therefore, risk-factor modulation should aim to meet recommended goals over the next few months after the onset of symptoms and the diagnosis of a risk factor.

After the plan is constructed, the physician may or may not be the person implementing it. However, the physician does need to communicate the overall treatment plan to the patient, including the importance of risk-factor control in the prognosis of disease. Other supporting team members charged with counseling or other behavior-modifying activities need to emphasize the importance of nonpharmacologic life-style changes as well as pharmacologic interventions and revascularization procedures.

The duration of hospital stays is continuing to decrease, with many diagnostic and nonsurgical revascularization procedures being performed on a same-day basis. Much of the care plan, especially that dealing with long-term issues, is carried out by the specialist or by the primary care provider on an outpatient basis. This does not alter the need to integrate risk-factor management into the overall treatment plan of the patient. Rather, it emphasizes the importance of communicating to the ambulatory care provider the need for risk-factor management and the appropriate strategies to achieve specified goals. Frequently, discharge summaries describe findings of diagnostic or therapeutic procedures in great detail, only to ignore altogether the presence of risk factors and any plan to control them. The ambulatory care provider is then led to believe that risk-factor management is not an essential part of the patient's care. Discharge plans and letters to the referring physician should identify risk factors on the patient's problem list, including diagnostic tests performed (e.g., fasting lipid profiles at the time of admission for MI). Furthermore, steps taken, including counseling by members of the multidisciplinary team, should be recorded. Finally, additional interventions and the goals of these interventions, which still need to be completed, should be provided. Again, the emphasis is on communicating the optimal care plan for the patient with vascular disease and this includes risk-factor management.

Role of Other Health Professionals

Interventions on behavioral and physiologic risk factors require a broad range of expertise in such diverse areas as behavioral counseling, nutrition, exercise physiology, pharmacology, and genetics. As noted previously, physicians may not possess specific skills in all of these areas, as compared with the focused expertise of patient education nurses, nutritionists, and exercise physiologists. Therefore, there is much to recommend a multidisciplinary team to implement the care plans for many patients. The team should be well coordinated to ensure communication and avoid confusion between the physician, team members, and patient. This is where the concept of a nurse manager–based cardiac rehabilitation service has become more desirable. In major hospitals this is currently in effect, with the prevention team forming a link between inpatient and outpatient care.

Opportunities in the Ambulatory Care Setting

Role of the Primary Care Provider

The primary care provider plays a variety of important roles in risk-factor management. It is hoped that detailed notes on the recommendations and progress to date will be available from the specialist after discharge from an inpatient unit. Construction of this plan requires the ability to accurately assess an individual patient's risk factors and place them in a category of appropriate risk-factor intervention. Currently, many discharge forms are poorly organized. There are a number of easily accessible forms that provide more comprehensive communication and prompt the physician to consider a number of key issues (Fig. 13.2, http://www.americanheart.org/CAP). The primary care provider needs to integrate these new plans with the overall care plan. Monitoring and feedback of patients' progress are often best carried out by the primary care provider, who has more frequent and regular access to the patient. The primary care provider may also wish to organize his or her practice to provide preventive care more efficiently. The office nurse frequently serves as a counselor on smoking cessation, diet, exercise, medication compliance, and other risk factors. Additional training of nonphysician professionals can expand considerably the services provided by an ambulatory care practice.

In terms of preventive strategies in the patient without symptomatic coronary artery disease, the physician must be able to assess multiple risk factors and estimate an overall risk of future coronary artery disease events. In this instance, the calculation of a global risk-scoring equation using multiple risk-factor variables gives an overall estimate of absolute risk of developing coronary artery disease over a 10-year period (24,25). A variety of risk assessment instruments are available, including wall charts, slide rules, hand-held risk calculators, and software programs. With use of this risk-stratification, the physician is able to provide the appropriate level of risk-factor modification based on accepted guidelines, including the identification of the *coronary heart disease risk equivalent* patient who deserves aggressive risk-factor management.

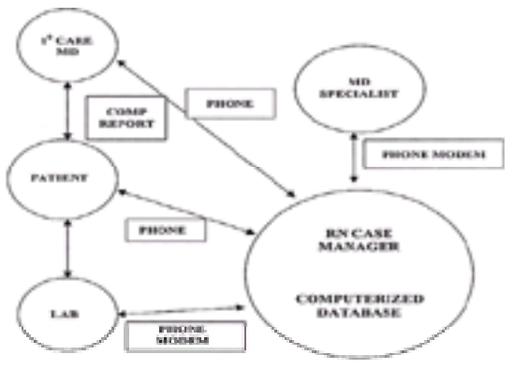
Role of Specialty Clinics and Cardiac Rehabilitation Units

Larger ambulatory practices, especially those tied to inpatient units, may have the opportunity to develop specialized programs for risk-factor management. The key element is the focus of risk-factor management expertise and resources in a person or team of people to whom problems can be referred. Clearly, most patients with vascular disease should be provided with risk-factor counseling and appropriate pharmacologic therapy as part of optimal cardiology care. However, there will continue to be a subgroup of patients in whom specialized expertise will likely be needed. These include patients who are resistant, recalcitrant, rare, or risky (the four Rs). Patients not responding to usual interventions for dyslipidemia or hypertension may benefit from an additional opinion. Patients who are recalcitrant may benefit from physicians, nurses, nutritionists, and exercise specialists skilled in behavior modification and counseling. Patients with rare risk-factor abnormalities, such as genetic hyperlipidemias, coronary disease without obvious risk factors, or coexisting medical diagnoses, may also require specialist expertise. Finally, patients at extreme risk of bad outcomes may have aggressive risk-factor management programs more successfully implemented by a multidisciplinary team (e.g., the patient with symptomatic vascular disease in the fourth or fifth decade of life and those patients with coronary heart disease and type 2 diabetes mellitus).

These specialized programs may take several forms. A preventive cardiology clinic is likely preferable over a clinic emphasizing a single risk factor, as most patients have several risk factors (90). In general, the staff includes one or more physicians with specialized training and expertise in risk-factor management, a coordinator, a nurse skilled in risk-factor counseling, a nutritionist knowledgeable about lipid-lowering diets, and an exercise physiologist who can develop an exercise prescription. The team may be supported by a variety of data collection tools, including computerized databases, patient education materials, and follow-up protocols.

Cardiac rehabilitation programs are often underused as sites for risk-factor management (see Chapter 12). Their efficacy in reducing total and cardiovascular mortality has been well documented in metaanalyses (91), especially when they include comprehensive risk-factor management services (92,93). Again, a team approach is optimal. Cardiac rehabilitation programs have the added advantage of providing considerable psychosocial support from other patients and their family members.

Nurse case managers are being used widely as a cost-effective means to provide comprehensive risk reduction with excellent continuity between inpatient and ambulatory care settings. Nurse-managed programs have been shown to be effective in the management of single risk factors, including smoking cessation (94), diabetes (95), hypertension (96), and lipid lowering (97). Specially trained nurses have implemented comprehensive risk-factor reduction programs targeting multiple risk factors. An example of such a program, the Stanford Cardiac Risk Intervention Program, is illustrated in *e*Figure 13.2.1 (98,99). During a 1-year period, patients received a combination of visits, telephone calls, and mailing reminders. Nurses formed the central point of contact, interacting with patients and other health professionals and laboratories. There was a clear delineation of professionals' responsibilities. The system successfully enhanced pharmacologic and dietary therapy and improved patient symptomatology and use of health services. DeBusk et al. (98) demonstrated a significantly higher rate of smoking cessation, a tripling of the proportion of patients reaching the LDL cholesterol goal of less than 100 mg per dL, and an improved exercise capacity among those patients managed by nurses trained in multiple risk-factor management (Table 13.4). Nurse case managers appear to be particularly effective in increasing patients' adherence to diet and drugs; in implementing a program of self-monitoring of weight, blood pressure, symptoms, and smoking cessation; and in teaching patients to recognize and respond to changes in their symptoms (100,101). Among the numerous advantages of such nurse case manager programs is the opportunity to initiate contact with the patient while he or she is still in the hospital (98,99), thereby integrating the inpatient and outpatient risk-factor management into a single, continuous program. Furthermore, patient satisfaction has been high, and significant cost savings, even over the short-term, can be realized (101).



***e*FIGURE 13.2.1** Organization of a nurse case-managed program for multiple risk-factor reduction. (From Miller NH, Warren D, Myers D. Home-based cardiac rehabilitation and lifestyle modification: the MULTIFIT model. *J Cardiovasc Nurs* 1996;11:76–87, with permission.)

	Intervention	
Risk-factor modification	Nurse case manager (n = 293)	Usual care (n = 292)
Smoking cessation at 12 mo (%)	70.0	53.0
Low-density lipoprotein cholesterol <100 mg/dL at 12 mo (%)	42.0	15.0
Functional capacity	9.3	8.4

From DeBusk RF, Houston-Miller N, Superko HR, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. *Ann Intern Med* 1994;120:721–729, with permission.

TABLE 13.4 LEVELS OF RISK-FACTOR MODIFICATION IN PATIENTS AFTER MYOCARDIAL INFARCTION: A TRIAL OF NURSE CASE MANAGER–BASED PROGRAMS VERSUS USUAL CARE

Opportunities for the Patient

Patient Compliance and Adherence to Interventions

A detailed discussion of patient compliance and adherence with behavioral and therapeutic regimens is beyond the scope of this review. It is an issue of enormous importance (69). First, the prevalence of noncompliance is exceptionally high, with estimates suggesting that only one-third of patients are fully compliant, another one-third are somewhat compliant, and one-third are fully noncompliant (102). This results in approximately 50% of the 2 billion prescriptions written in the United States annually being taken incorrectly (69). Compliance with behavioral interventions is even lower, with the maintenance of smoking cessation, weight-control diets, and low–saturated fat diets estimated at 10% to 20% over a 1-year period (103). The costs resulting from this noncompliance are staggering, with approximately 10% of hospitalization caused by patients' inability to follow therapeutic regimens (69). In the Beta Blocker Heart Attack Trial, both men and women taking fewer than 75% of their prescribed beta-blocker medication had 2.5- to 3.0-fold higher mortality than those who took their medications more than 75% of the time (104,105). The problem of noncompliance encompasses all diseases, risk factors, and therapies (70). Improving patient compliance and adherence is clearly a major challenge and opportunity for improving the outcome of any intervention program.

The determinants of noncompliance and nonadherence are multiple and complex (106). For example, patient factors (knowledge, beliefs, attitudes, and values), their families, the health care setting, the provider–patient relationship, characteristics of the disease, and nature of the treatment all play important roles (69,107). A 2-year study of patients with hypertension, diabetes, or cardiac disease showed that characteristics of health care providers (physician specialty, number of patients seen per week, willingness to answer patients' questions), the health care facility itself (scheduling a follow-up appointment, number of tests ordered), the seriousness of the illness, and the level of patient distress all have an effect on compliance (70).

Because of the complexity of this issue, no single intervention has been shown to be effective in solving the problem. Although a variety of strategies of varying sophistication have been proposed (102), some rather simple steps can be emphasized (Table 13.5) (107). These include clear communication of goals, simplification of the intervention, and monitoring with feedback to the patient. Special programs, such as those with nurse case managers, may succeed because of their abilities to carry out these compliance-enhancing steps. Increasingly, programs in the electronic media have been developed to ensure compliance. The AHA has also provided several Web-based tools that have a wide variety of applications for physicians, patients, and hospital staff. The *one-of-a-kind* program allows patients to enter data regarding their cardiac risk factors and track their progress as well as compare their values with a composite mean of the database (http://www.onelife.americanheart.org/). This compliance-enhancing, Web-based tool is versatile. Physicians and staff in busy practices can provide their patients with access to cardiovascular services by a brief but strong recommendation to enroll in this program, which prompts a wide range of risk-factor management issues based on current guidelines.

Initiation of treatment
Convey the importance of the recommendations
Emphasize required behaviors to provide the rationale for them
Simplify the regimen
Discuss costs
Record keeping
Use a systematic and consistent tracking form
Send reminders of follow-up appointments
Monitor effects
Follow-up
Reinforce treatment message
Probe about side effects, problems, and adherence

From Luepker RV. Patient adherence: a "risk factor" for cardiovascular disease. *Heart Dis Stroke* 1993;2:418–421, with permission.

TABLE 13.5 RECOMMENDATIONS TO IMPROVE PATIENT ADHERENCE TO TREATMENT

Family Members

Two objectives are served by involving the family unit in a risk reduction program. First, the patient's risk behaviors are subject to a number of influences. The patient's diet, exercise, and smoking habits are usually part of a family's behavior. A lasting behavioral change therefore usually requires family participation. Social support is an important part of any program to improve compliance with behavioral or pharmacologic interventions. Other family aggregating factors, such as diet and environmental tobacco smoke, affect the patient's health directly. Second, the familial aggregation of risk factors is well recognized. The screening of first-degree relatives clearly yields a high prevalence of undetected risk factors (108). A strong recommendation that siblings and children be screened for risk factors should be included in any patient presenting with premature coronary heart disease. Screening in this population has been disappointing (55) and perhaps should form part of the algorithm when documenting family history and risk-factor assessment.

Opportunities by Health Care Organizations, Professional Societies, and Third-Party Payers

Professional Education Programs

The training of physicians, nurses, and other health professionals responsible for the care of patients with vascular disease should include a working knowledge of risk-factor modification, including vascular biology and clinical evidence supporting such interventions. Guidelines for the education of cardiovascular specialists include this training for minimal competence in preventive cardiology (74). Frequently lacking from such programs are didactic and shell-building experiences to organize hospital services or interpret priorities or to improve physician performances in ensuring compliance with both behavioral and pharmacologic interventions.

The continuing education of professionals already in practice presents another set of challenges. In general, successful continuing education programs must identify a specific audience and learning need, express clear learning objectives, target physician performance rather than knowledge, be carried out in clinical settings, and measure changes in physician practices (108). Traditional lectures and mailed materials appear to be less successful unless tied to results of clinically relevant, randomized trials (109,110).

Many studies of continuing education suggest that the effectiveness of these educational programs can be boosted considerably if combined with some form of performance feedback. Forms of feedback include medical records audits (111) or physician knowledge assessment (112). Feedback should be as personalized as possible. In one study, performance feedback boosted the cholesterol management practice in house officers caring for patients with coronary disease, far exceeding the benefits of a reminder system (113).

The AHA and ACC have released a number of clinical guidelines and statements to aid and update physicians on current evidence-based preventive practice (4,5,6,7,8,9,10,11,12 and 13). These should provide ample targets for physician education. Programs to explore professional compliance with guidelines are increasingly available, such as the AHA's "Get with the Guidelines" program (http://www.americanheart.org/CAP).

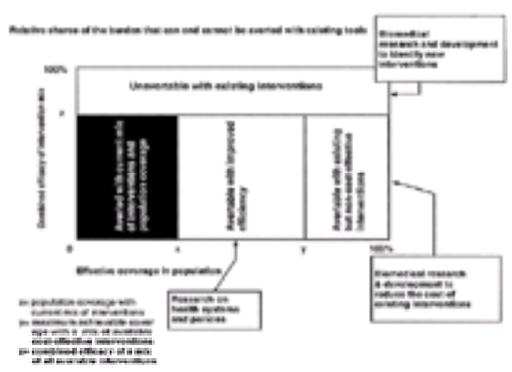
Clinical Guidelines

Fortunately, the AHA, ACC, and other bodies have issued joint guidelines on risk-factor management in patients with vascular disease (4) and without vascular disease (8), as well as for women (7) and diabetic patients (6). These guidelines are consistent with statements addressing individual risk-factor modification such as hypertension (9), hypercholesterolemia (10), sedentary lifestyle, smoking (11), and obesity (12). The essence of these guidelines has also been incorporated into recommendations for acute cardiac care (13).

Despite good consensus on risk-factor management, the efficacy of guidelines is mixed. It appears that they are least likely to succeed if no incentives (or removal of disincentives) are provided for the practicing physician (114). Guidelines need to be actively disseminated and implemented. They are most effective when coupled with evaluation of physician performance (115). As databases evaluating patient risk-factor modification become increasingly available, this may provide such an opportunity in the future.

Quality Assurance Standards

Some of the components of a quality assurance program are already in place, including substantial evidence from basic science, epidemiology clinical trials, cost-effectiveness analyses (14), and guidelines reflecting broad consensus on criteria for optimal risk-factor management (4). The next component in a quality assurance program is the feedback loop, in which levels of performance toward accepted criteria are linked to incentives, including credentialing, remuneration, or competitiveness (eFig. 13.2.2) (116,117). One performance report has been the Health Plan Employer Data and Information Set (HEDIS), which employers use in contracting for care with managed care organizations (118). Risk-factor management indices have become especially well represented, probably because of the presence of consensus statements and the evidence of nearly universal benefits of many of the interventions. HEDIS 3.0, for example, used a number of risk-factor levels and management practices as end points for the next *report card* (Table 13.6) (119). The National Committee for Quality Assurance is routinely developing new performance guidelines as part of the HEDIS process (118). This now requires a mandatory report from health maintenance organizations, quantifying the percentage of cardiac patients who have met HEDIS criteria. The National Committee for Quality Assurance have defined a difference between clinical and performance goals. Although they endorse the NCEP guidelines, they have stipulated a goal LDL of less than 130 mg per dL, rather than less than 100 mg per dL, in patients with coronary heart disease. The reason for this difference is to provide a realistic, attainable goal that allows physicians room for clinical judgment in individual cases. The important point to note, however, is the change in focus for health maintenance organizations and consequently physician practice in terms of evaluation of efficacy of risk-factor modification (120).



***e*FIGURE 13.2.2** World Health Organization view of disease control: roles of intervention efficacy and population coverage. (From Ad Hoc Committee on Health Research to Future Intervention Options: investing in health research development. Geneva: World Health Organization, 1996:1–18, with permission.)

Beta-blocker treatment after myocardial infarction
Advising smokers to quit
Controlling high blood pressure[a]
Aspirin treatment after myocardial infarction[a]
Prevention of stroke in patients with atrial fibrillation[a]
Angiotensin-converting enzyme inhibitors in patients hospitalized with congestive heart failure[a]
Cholesterol management in patients hospitalized with coronary disease[a]

[a]Being evaluated for inclusion in future Health Plan Employer Data and Information Set.
From Committee on Performance Measurement of the National Center for Quality Assurance. Health plan employer data and information set. HEDIS 3.0 Draft, 1996, with permission.

TABLE 13.6 MEASURES RELEVANT TO THE COMPREHENSIVE RISK REDUCTION OF PATIENTS WITH VASCULAR DISEASE PROPOSED FOR REPORTING IN HEALTH PLAN EMPLOYER DATA AND INFORMATION SET

Relatively recent medical-legal actions may be another example of use of quality assurance standards. One settled suit, successfully charging a wrongful death caused in part by the lack of treatment of hyperlipidemia, illustrates the use of guidelines in medical malpractice claims (121).

Reimbursement Policies

The lack of reimbursement can serve as a powerful disincentive to risk-factor management for practicing physicians (122). Statements, guidelines, and accreditation by professional societies and the acceptance of risk-factor management as quality indicators are powerful motivators for third-party payers to reimburse for preventive services. Such motivation will be needed for physicians, clinics, and hospitals to allocate personnel, space, and funds for risk-factor management programs.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The demand for risk modification is likely to continue to expand because of several irreversible trends. First, the prevalence of coronary heart disease and other vascular diseases will continue to expand for at least the next 30 years (123). Currently, among U.S. adults aged 45 years and older, 12% of men and 8% of women carry the diagnosis of coronary disease. Second, cardiovascular specialists are likely to be consulted in the management of a new cohort of patients in whom asymptomatic atherosclerotic disease has been identified by noninvasive means. Third, current guidelines are now identifying, on the basis of a global risk score, a potentially large group of patients who have a coronary heart disease risk equivalent. Thus, the demand for preventive services will only expand, necessitating efficacious, effective, and efficient methods to reduce risk. This chapter has identified gaps in the successful implementation of risk-factor modification. How might we do better? The controversy is not why, whether, or how to do it, but who should do it.

This author's personal impression is that this responsibility is a shared one. Although additional research is needed to identify specific barriers to preventive care and to test strategies to remove them, it is clear that we can organize ourselves to be more effective. For every coronary disease patient admitted to an inpatient service, we recommend an organized, comprehensive assessment of risk factors, which then triggers the development of a plan to manage the patient. Next, a nurse case manager either follows up on the patient from the inpatient to the outpatient setting or clearly communicates the plan to the referring generalist. The plan is then carried out by a coordinated, multidisciplinary team of physicians, nurses, nutritionists, and exercise physiologists either in the inpatient service or in the outpatient clinic. In general, the patient is cared for until risk-factor goals have been met.

Cardiovascular specialists often cite their lack of responsibility in this area. This position is increasingly untenable, because most or all of the goals of revascularization or cardiac pharmacotherapy are the same as those for risk-factor management. Risk-factor management alleviates chest pain, reduces the risk of MI, prevents disability caused by stroke and heart disease, prolongs survival, and, in many instances, reduces health care costs. Few invasive procedure and high-technology interventions can boast of such an effect. The cardiovascular specialist who does not integrate risk-factor management into his or her patient care then has the simple goal of performing procedures, rather than optimizing clinical outcomes.

The bedrock, which is unmoved by contemporary deficiencies in medical education, health care economics, and practice disorganization, will remain the scientific evidence defining the role of risk-factor management in beneficially altering the natural history of atherosclerotic disease. This is likely only to strengthen. In addition to studies of basic mechanisms and randomized clinical trials of new interventions, research on the implementation and maintenance of optimal care practices is needed to ensure the appropriate application of all that we have learned.

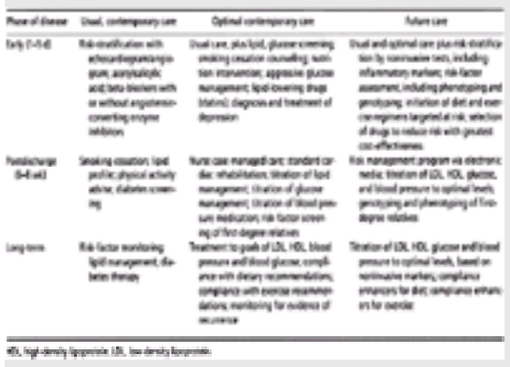
This would then require us to reform our research agenda. The World Health Organization perspective on disease control is illustrated in eFigure 13.2.2 (1). The WHO identified three areas for improvement. The first is to reduce disease currently unavoidable with existing interventions through biomedical research and the development of new interventions. Clearly, there are many opportunities to elucidate new disease mechanisms amenable to intervention, to identify new risk factors, and to test new drugs and technologies with randomized trials. Indeed, the vast majority of our research and development resources go into this activity. A controversial position may be that, as biomedical science advances, further development of interventions will result in only a modicum of disease reduction unless there is attention to two other causes of the disease burden, namely, disease that would be averted with improved efficiency and disease that would be averted if existing interventions were more cost effective. These two areas currently receive a small fraction of research and development funds. To really affect this disease, these sources of avoidable coronary heart disease must likewise be reduced.

THE FUTURE

Applications of the principles of vascular biology to the practice of cardiology will likely be of such priority that the two fields will become one. The concepts of *metabolic revascularization* and *risk-based intervention* will be cornerstones for care.

eTable 13.0.1 provides a view of contemporary interventions as well as those likely to evolve in the near future to become established modes of care. improved intervention and studies to establish their efficiency will be forthcoming in the next decade for diabetes, low hdl and high triglycerides, and obesity. improvements in compliance with physical activity and diet will also take place, it is hoped.

Table 13.7 furthers this vision, starting with current care using known strategies, expanded to optimal evidence-based care projected into the future. several trends clearly stand out. first, risk-stratification will improve through the use of noninvasive imaging and biochemical or genetic markers, such as inflammatory markers. likewise, risk-factor assessment in early and postdischarge periods will be sharpened by use of genetic markers and improved phenotypic indicators, for both probands and their relatives. selection of nonpharmacologic and pharmacologic interventions will be more precise, with clusters of interventions chosen to optimize prognosis and cost effectiveness. these interventions will be guided by knowledge of disease processes and by empirical data from clinical trials. compliance will be strongly emphasized, with the use of multidisciplinary teams led by risk-factor managers supported by a variety of electronic media. titration of drugs and lifestyle interventions may rely less on metabolic or behavioral end points and more on noninvasive measures of altered pathophysiology, such as endothelial dysfunction or disease progression.



Phase of disease	Usual, contemporary care	Optimal contemporary care	Future care
Early (1–5 d)	Risk-stratification with echocardiogram/angiogram; aspirin/clopidogrel; beta-blockers with or without angiotensin-converting enzyme inhibitors	Usual care, plus lipid, glucose screening; smoking cessation counselling; nutrition intervention; aggressive glucose management; lipid-lowering drugs (statins); diagnosis and treatment of depression	Usual and optimal care plus risk-stratification by noninvasive tests, including inflammatory markers; risk factor assessment, including phenotyping and genotyping; initiation of diet and exercise regimens targeted at risk; selection of drugs to reduce risk with greatest cost-effectiveness
Postdischarge (6–8 wk)	Smoking cessation; lipid profile; physical activity advice; diabetes screening	Nurse case-managed care; standard cardiac rehabilitation; titration of lipid management; titration of glucose management; titration of blood pressure medication; risk factor screening of first-degree relatives	Risk management program via electronic media; titration of LDL, HDL, glucose, and blood pressure to optimal levels; genotyping and phenotyping of first-degree relatives
Long-term	Risk-factor monitoring; lipid management; diabetes therapy	Treatment to goals of LDL, HDL, blood pressure and blood glucose; compliance with dietary recommendations; compliance with exercise recommendations; monitoring for evidence of recurrence	Titration of LDL, HDL, glucose and blood pressure to optimal levels, based on noninvasive markers; compliance enhancers for diet; compliance enhancers for exercise

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TABLE 13.7 PREVENTIVE CARE OF THE CORONARY DISEASE PATIENT: USUAL, OPTIMAL, AND FUTURE

this explosion of knowledge and technology should not lull us into a false sense that cardiovascular disease will be conquered without the continued reliance on interpersonal skills. preventive cardiology will still need to rely on the ability of the preventive cardiology team to modify the patient's behaviors that led to the disease in the first place. it is difficult to conceive of pharmacologic or surgical interventions that will even partially displace the need for effective smoking cessation counseling, the alteration of ingestion of dietary fats and cholesterol, and the increase in physical activity. although patients will benefit from the skills of a variety of health professionals, the cardiovascular specialist will still need to ensure optimal care through his or her implementation. thus, the integration of risk-factor modification will undoubtedly cease to be adjunctive therapy and take its rightful place as the cornerstone of cardiac care.

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14

THE HISTORY

ERIC J. TOPOL

Overview
General Perspective
Evaluation of Cardiovascular Symptoms
Chest Discomfort, Pain, and Related Symptoms
Dyspnea and Cough
Syncope and Palpitations
Edema, Fatigue, and Other Symptoms
Controversies and Personal Perspectives
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OVERVIEW

The history is the most essential part of the diagnostic evaluation. A careful interview with the patient not only lays the foundation for an appropriate further workup, but it also serves as the framework for a bond between patient and physician, thereby promoting mutual respect, trust, and understanding. Listening to the patient cannot be adequately emphasized, and this goes beyond what is verbally communicated through gestures and nonverbal language. The major symptoms to review with each patient include chest discomfort or pain, dyspnea or cough, and syncope or palpitations—each of which are discussed in more depth. It is hoped that directly obtaining a meticulous history will become more routine and prioritized in the years ahead.

GENERAL PERSPECTIVE

Obtaining a careful, detailed history is fundamental to the proper evaluation of the patient. This takes time, as it requires listening to the patient and, ideally, his or her family members without interruption. Beyond listening, it is vital to cue in to the patient's nonverbal communication, such as affect and gestures. The time spent with the patient and the attitude displayed set the tone for the whole relationship and, therefore, represent a critical investment for the long-term bond and mutual trust that need to be nurtured. It is important for the patient to understand that the physician is a compassionate person who frankly cares about his or her condition and who genuinely wants to help. The relationship that is built on strong communication with attention to details during the interview leads to a "full disclosure" history that often preempts the need for expensive, potentially hazardous, and certainly inconvenient diagnostic testing (1,2). History taking is a true art that yields unique and valuable information.

Before zooming in on the chief complaint, it is helpful to establish the patient's noncardiovascular history and medications and to query the risk factors for atherosclerosis. Pertinent conditions such as thyroid disease, anemia or gastrointestinal bleeding, asthma or chronic bronchitis, recent upper respiratory or viral illness, prostatitis, or arthritis frequently interrelate to the chief complaint and need to be fully characterized. Similarly, trauma or recent procedures such as oral surgery need to be surveyed. The entire list of medications with corresponding dosages must be known, given the preponderance of symptoms that can arise from side effects of drug therapy. Furthermore, the list of medications often serves as a checkpoint that all relevant medical conditions have been reviewed. Known allergies should be ascertained, and if coronary angiography is even a remote possibility, direct questioning about exposure to contrast dye or shellfish is imperative.

The risk factors for atherosclerosis must be carefully examined. As reviewed in detail in the first section of this textbook, each of the "big five"—hypertension, smoking, diabetes, hypercholesterolemia, and family history—is discussed. In this era of recognition of the primacy of genetics for influencing diseases, it is especially essential to obtain a detailed family history to consider for precocious atherosclerotic coronary disease (presenting at younger than 40 years for men or 45 years for women), any history of coronary artery disease, and other heart disease such as hypertrophic cardiomyopathy, arrhythmias, or other conditions (see Chapter 97 and Chapter 100). As recently noted, a family history of myocardial infarction may not be accurate (3,4).

The patient's weight at the time of graduation from high school and over the next few years (with any significant fluctuations) is helpful information. For women, determination of menstrual status and, if postmenopausal, of whether hormone replacement therapy has been recommended are important to resolve but are too frequently overlooked. The patient's diet and nutritional status are worthy of full review, providing some insight into a patient's level of commitment to a healthy lifestyle. Similarly, the level of physical activity and whether regular exercise is part of the patient's weekly routine frame the symptomatic assessment and corroborate the previous commitment to cardiovascular health. The pattern of alcohol use is a particularly worthwhile item about which to question the patient. Similarly, the potential for drug abuse should be explored in particular circumstances. Considerable revelation about the psychosocial makeup of the patient becomes evident, provided the physician is cueing in to the intensity level and manner in which the words and responses are being conveyed.

EVALUATION OF CARDIOVASCULAR SYMPTOMS

For each patient, a review of cardiovascular symptoms beyond the primary symptom is useful. The major symptoms are chest discomfort, dyspnea, syncope, edema, and fatigue. Other symptoms such as cough, palpitations, orthopnea, and dizziness or light-headedness are supportive and need to be ascertained in relation to the primary complaint. Often, a patient is not in touch with the symptoms or is in such fear or denial that he or she is unlikely to volunteer the information. For this reason, it is imperative to perform detailed questioning about chest discomfort or dyspnea in patients with a clustering of risk factors for atherosclerosis irrespective of the lack of a complaint. Symptoms of atherosclerosis of other arterial beds are systematically surveyed. For the cerebrovasculature, a check on symptoms such as transient loss of speech or motor function (suggesting a transient ischemic attack) or, for the peripheral blood vessels, calf discomfort on exertion that is promptly relieved by rest (suggesting intermittent claudication) help resolve the diffuseness of the atherosclerotic process, if present.

A functional classification of the patient's symptoms should be obtained (5,6). For angina, the Canadian Cardiovascular Society Functional Classification System is usually used (Table 14.1), whereas for dyspnea and other symptoms of heart failure, the New York Heart Association Functional Classification is relied on (Table 14.2).

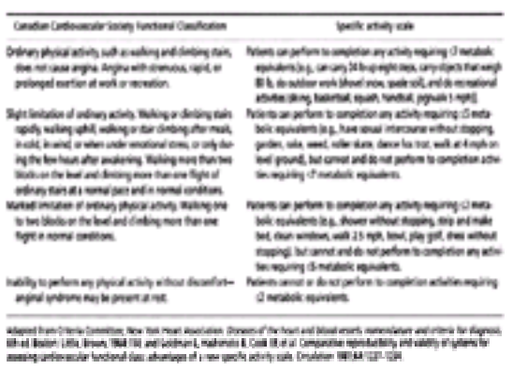

TABLE 14.1 ASSESSING CARDIOVASCULAR DISABILITY

Class	New York Heart Association functional classification
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activities. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to perform any physical activity without discomfort.

Goldman L, Hashimoto B, Cook EF, et al. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 1981;64:1227–1234.

TABLE 14.2 FUNCTIONAL CLASSIFICATION

Chest Discomfort, Pain, and Related Symptoms

One of the most frequent, yet difficult, symptoms to assess is chest discomfort or pain (7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22 and 23). Because this can be so frightening to patients, these symptoms may precipitate emergency evaluation. A variety of cardiac and noncardiac conditions can produce chest discomfort or pain, as summarized in Table 14.3. The key to determining whether the discomfort is cardiac is to review its character, location, and precipitating factors. Because conditions such as esophageal reflux and musculoskeletal abnormalities are quite common, it is not unusual for a given patient to have two or more different types of chest discomfort (22,23). In such instances, a careful assessment of each of the symptom complexes is necessary to determine the underlying condition(s).

Cardiac	Noncardiac
Angina	Esophagitis, esophageal spasm, or reflex
Acute myocardial infarction	Peptic ulcer
Aortic dissection	Gallbladder disease
Pericarditis	Musculoskeletal causes, including osteochondritis or cervical disk, thoracic outlet syndrome
Myocarditis	Hyperventilation
	Anxiety
	Psychogenic causes
Mitral valve prolapse	Pneumonia
	Pulmonary embolus
	Pneumothorax
	Pulmonary hypertension

TABLE 14.3 CAUSES OF CHEST DISCOMFORT AND PAIN

Character and Location

Although *angina* literally means “choking,” most patients with true angina do not use this term to describe their sensation. Despite Herberden’s early description in 1768 of a “painful and most disagreeable sensation in the breast” (24), the unpleasant sensation is more typically characterized as a pressure, tightness, heaviness, or burning. The pressure is not perceived by the patient as “pain,” such that the interviewer who specifically asks about pain may be misled. On the other hand, “pain” is much more apt to be used by the patient to describe a heart attack; on occasion, the patient may clench the fist while describing the discomfort—the so-called Levine sign. The discomfort of angina is usually easy to differentiate from the pain of acute myocardial infarction by the duration, radiation, and lack of precipitating or alleviating factors. As opposed to angina, which usually lasts for 1 to 3 minutes, heart attack pain lasts for longer than 10 minutes; rather than having one focus (usually the retrosternal region), there is commonly radiation of the pain, such as down the arm. Heart attack pain is described in more depth in Chapter 18. Angina most commonly is felt in the midline of the chest, but it can manifest exclusively in the jaw or neck, the left shoulder or arm, and, when present in the arm, particularly on the ulnar aspect of the forearm and hand (Table 14.4). Rather than in the chest, the principal pressure or burning can be perceived in the epigastrium, causing the patient to believe the problem is simple indigestion. More rarely, the back interscapular region or the right side of the chest, shoulder, arm, or forearm is involved. Unlike the chest discomfort of angina, severe pain that radiates to the back is a classic indication of aortic dissection. However, patients with aortic dissection or expanding aortic aneurysm can have predominant anterior chest pain that may be mistaken for acute myocardial infarction. In the course of evaluating patients with chest pain, it is helpful to adopt the philosophy of “aortic dissection until proven otherwise” so that this diagnosis is never missed, even though it is a relatively uncommon entity in the current era of improved control of hypertension.

Dyspnea
Jaw or neck discomfort
Shoulder, elbow, or arm discomfort, particularly along the side of the left forearm and hand
Epigastric discomfort
Back (interscapular) discomfort

TABLE 14.4 ANGINAL “EQUIVALENTS”

Chest pain or discomfort in women is more difficult to assess, and there have been studies to address the issue of whether there is gender bias resulting in inappropriate underinvestigation or undertreatment in women (25,26). A careful history and assessment of risk is especially critical among women, as the correct diagnosis is more elusive—even with noninvasive testing—and pivotal.

Acute pericarditis is a precordial pain that is typically left sided; it is usually worse with inspiration and described as sharp, often referred to the neck. Unlike angina or myocardial infarction pain, this pain is often positional in character such that if the patient sits up and leans forward, the pain may be relieved. Congenital absence of the pericardium is exceedingly rare, but the telltale symptom is chest pain produced by lying on the left side lasting only a few seconds or minutes (27). On occasion, patients with acute myocarditis may present with chest pain, which may be attributed to pericardial involvement or the actual inflammation of cardiac muscle. Mitral valve prolapse often is accompanied by atypical chest discomfort because it is sharp, stabbing, protracted in duration, and associated with a constellation of symptoms (see Chapter 21).

A long list of noncardiac causes of chest pain or discomfort (Table 14.3) is capped by the esophageal disorders of reflux, esophagitis, or spasm—all of which may coexist in certain patients with myocardial ischemia. Esophageal discomfort can fully mimic the character and location of myocardial ischemic symptoms, but, more commonly, the retrosternal burning or epigastric heaviness is brought on by food ingestion and recumbency, with relief by antacids and H_2-blockers. When there is a sour taste in the mouth (so-called water brash) as a result of the acid reflux, this is helpful in differentiating esophageal-induced symptoms from other etiologies. Other gastrointestinal disorders such as peptic ulcer disease, gall bladder disease, and pancreatitis can produce epigastric discomfort and need to be considered in the differential diagnosis.

The symptoms of chest discomfort may be the presenting feature for a host of musculoskeletal conditions. Costal chondritis, or Tietze’s syndrome (11), is characterized

by a chest-wall pain that includes point tenderness and, frequently, is exacerbated by movement or coughing. Chest wall syndromes are particularly common among cigarette smokers and seem to be responsive to cessation of smoking; the etiology remains unclear. A thoracic outlet syndrome is associated with ulnar distribution paresthesias in the arm and forearm that are worsened by arm abduction or lifting. Herpes zoster of the chest wall displays a specific dermatome pattern of the pain with exquisite sensitivity of the skin to touch and, ultimately, the development of characteristic skin vesicles.

In the continuum of musculoskeletal chest discomfort, terms frequently used for discharge diagnosis in emergency departments when the cause is uncertain are *hyperventilation*, *anxiety*, and the *Da Costa's syndromes* (also known as *neurocirculatory asthenia*) (10). Emotional stress precipitates pain characterized by a dull, persistent ache and may be accompanied by point or even diffuse chest-wall tenderness (28,29,30,31 and 32). This pain may last for hours or even days and may be quite localized (e.g., below the left nipple) with a "stabbing" quality. A component of hyperventilation may be diagnosed by eliciting the symptoms of circumoral or fingertip paresthesias with occasional carpal-pedal spasm and the response of the symptoms to breathing into a paper bag. Pulmonary causes of chest discomfort include pneumonia, pneumothorax, pulmonary hypertension, and pulmonary embolus. On occasion, pneumonia can present simultaneously with acute myocardial infarction such that the "either/or" process of ruling out one diagnosis should be considered carefully. Pulmonary hypertension may simulate angina, likely due to right ventricular ischemia. A pneumothorax presents with sudden onset of chest pain in the lateral chest with acute shortness of breath. Pulmonary embolism is also sudden, occurring at rest, and is usually associated with pleuritic chest pain exacerbated by coughing.

Exacerbating and Alleviating Factors

The most helpful aspect of angina is the classic precipitation by exercise or emotional stress. Interestingly, some patients never have angina with peak levels of robust exercise but, rather, experience the tightness or burning during a high-pressure business meeting or a stressful emotional incident. Cold weather, rushing to do an activity, and heavy meals are all common precipitants of angina. When angina occurs nocturnally or in the early morning hours on a cyclic basis, or when it occurs at rest, the possibility of coronary artery spasm or Prinzmetal's angina should be considered. This "variant" angina may be associated with a history of migraine headaches, Raynaud's phenomenon, or both, signifying a vasospastic tendency of multiple arterial beds. Coronary artery spasm, expressed as rest pain or discomfort, can occur concomitantly with classic exertional angina.

Alleviating factors that help in the diagnosis are relief by cessation of the activity or by sublingual nitroglycerin. Getting out of the cold or completing the uphill walk are excellent examples of ways that angina is usually relieved. Interestingly, lying down may not relieve angina and, at times, may precipitate it by the increase in venous return. The response to nitroglycerin is not specific, because esophageal spasm also is alleviated by nitroglycerin. However, the rapidity of relief for angina is quite impressive. The freshness of the nitroglycerin tablets needs to be ascertained in the context of whether the discomfort was responsive; if the tablets are old and did not induce mucosal tingling or a headache, it remains unclear whether a true effect was tested.

Precipitating Factors

There are several key subgroups of patients that deserve particular emphasis. Diabetes mellitus frequently leads to significant atherosclerotic coronary disease, but the symptoms are much less apt to be present and probably are related to a sensory neuropathy (13). Silent ischemia must, therefore, be considered in these patients, but careful interrogation for anginal equivalent symptoms (Table 14.4) is especially worthwhile. Of course, many diabetics have classic angina, but missing the underlying coronary disease in patients who are not fortunate enough to have an intact "alarm system" can have serious or even fatal consequences. Compared with men, women with documented coronary artery disease more often do not have the characteristic symptoms of angina, for unclear reasons. Whereas an exertional or emotional stress component is frequently elicited, the quality of the discomfort can be misleading and seem atypical. A full diagnostic evaluation and extra time to delineate fully the symptoms, precipitants, and risk factors are imperative.

After cardiac transplantation, patients cannot expect to experience chest pain or discomfort due to denervation, except in rare situations in which apparent reinnervation occurs (33,34). Systematic screening for coronary atherosclerosis has to be set up (see Chapter 94). For patients presenting with the chest pain of acute myocardial infarction, women, the elderly, and minority patients (particularly African-American and Hispanic) tend to present later in the course of the event and are more apt to have atypical or nonclassic features (15,16 and 17).

Dyspnea and Cough

Difficulty breathing is one of the cardinal symptoms of cardiac and pulmonary disease. Strictly, *dyspnea* denotes an abnormally uncomfortable awareness of breathing that is easily differentiated from normal, quiet, unnoticed breathing. The history can be particularly important in pinpointing the cause of dyspnea because there are a number of potential etiologies (35,36), including heart failure, pulmonary edema, obstructive airway disease, and pulmonary embolism.

Sudden dyspnea occurs not only with acute pulmonary edema but also with a pneumothorax, pulmonary embolism, or airway obstruction. In congestive heart failure, the onset of dyspnea is insidious and frequently precipitated by exertion. Conditions that simulate the chronic development of dyspnea are chronic obstructive pulmonary disease, pleural effusions, pregnancy, and obesity. Asthma or obstructive airway disease is suggested by inspiratory dyspnea, wheezing, and prior episodes responsive to bronchodilators. Although it is a rare symptom, sudden dyspnea while sitting rather than recumbent suggests the possibility of atrial myxoma, whereas dyspnea relieved by squatting is a classic indication for the congenital lesion of tetralogy of Fallot.

Paroxysmal nocturnal dyspnea is a classic sign of interstitial pulmonary edema and is most commonly due to heart failure. It usually begins 2 to 4 hours after going to sleep; is associated with sweating, cough, and, at times, wheezing; and can gradually improve (over 10 to 20 minutes) by getting out of bed or sitting on the side of the bed. The cough follows the dyspnea in heart failure but occurs in the opposite order in patients with chronic obstructive pulmonary disease. Of lesser severity is orthopnea due to pulmonary venous hypertension, and it occurs in the recumbent position with relief by sitting upright or standing. The number of pillows used by the patient is a good way to semiquantify orthopnea, because patients learn to use one or more extra pillows to combat their sense of breathlessness. Symptoms of heart failure that also cluster with dyspnea and orthopnea are nocturia, edema, and, more rarely, upper abdominal discomfort due to hepatosplenomegaly.

Dyspnea on exertion as a sole symptom may signify an anginal equivalent (Table 14.4); if it occurs with angina, there is an increased likelihood of a large myocardium in jeopardy, compared with angina and no symptoms of breathlessness.

Two alterations of breathing, both with a component of apnea, deserve mention. *Cheyne-Stokes respiration* refers to periods of hyperpnea followed by apnea. The pattern is a feature of the elderly who have heart failure, often with concomitant cerebrovascular disease. Sleep apnea has emerged as an important trigger of pulmonary hypertension and is characterized by episodes of snoring with prolonged periods of apnea due to upper airway obstruction. It typically occurs in patients who are overweight or mildly obese and can be responsive to measures that counter the upper airway obstruction. The diagnosis, however, can only be supported by obtaining a history from the patient's spouse or significant other.

Cough as a symptom is considerably more frequent but equally less specific (37). Perhaps the most common cause of cough today results from the side effect of angiotensin-converting enzyme inhibitors—popularly used for the treatment of hypertension and heart failure—that occurs as a result of activating bradykinin. The dry cough from this class of medications can be difficult to differentiate from that of pulmonary hypertension or mitral stenosis. Both types of cough are irritating and spasmodic, although the heart failure or mitral stenosis cough is more likely to be nocturnal, despite considerable overlap. Cough associated with hoarseness in the absence of upper respiratory disease may suggest a very enlarged left atrium with compression of the recurrent laryngeal nerve. Hoarseness without obvious upper respiratory infection in such patients is known as *Ortner's syndrome*, in which the large left atrium exerts pressure on an enlarged pulmonary artery and peribronchial lymph nodes to compress the recurrent laryngeal nerve. Dysphagia and right posterior chest pain occur only if left atrial enlargement is extreme due to severe chronic mitral regurgitation.

Sputum production and, particularly, hemoptysis are symptoms that tend to localize the disorder in the lungs, except for hemoptysis that is associated with severe mitral stenosis and is characterized by sudden increases in left atrial pressure and rupture of small bronchopulmonary veins. Frank hemoptysis that occurs with pulmonary arterial hypertension due to congenital left-to-right shunts may not share this pathophysiology, as bronchial arterioles rupture, in this case, to cause massive hemorrhage.

In patients with dyspnea and suspect valvular disease, determining whether there is a history of rheumatic fever is customary but can be misleading. Determination of whether there was scarlet fever with a rash, joint pains, chorea (St. Vitus' dance) with twitches or clumsiness, frequent sore throats, prolonged bed rest, or a family history of rheumatic fever are all in this line of questioning. However, frequently, the absence of these symptoms does not rule out rheumatic fever; a positive history can also be inaccurate (38).

Syncope and Palpitations

Syncope is a loss of consciousness due to inadequate perfusion of the brain. The history is fundamental for narrowing down a wide differential diagnosis (see Chapter 71). Sudden loss of consciousness without an aura or warning characterizes cardiac syncope. This condition can result from an arrhythmia such as ventricular

fibrillation, ventricular tachycardia, advanced atrioventricular block, or asystole (38,39). A family history of syncope raises the possibility of a long QT syndrome (see Chapter 97). Beyond arrhythmic causes of syncope, the hemodynamically significant lesions of aortic stenosis, hypertrophic cardiomyopathy, or primary pulmonary hypertension are important causes of cardiac syncope. With these disorders, syncope classically occurs just after exertion, and although hemodynamic lesions are present that can account for the loss of consciousness, serious arrhythmias should not be discounted as the primary trigger. Hypertrophic cardiomyopathy is usually familial such that the family history is important to raise or support this possibility. Besides the postexertional syncope, fainting during prolonged standing, posttussive, or even during exertion can occur with this condition.

The most common cause of cardiac syncope is known as *vasodepressor* and is mediated through the autonomic nervous system, with unconsciousness developing a bit more gradually and lasting for a few seconds; this condition can be induced by emotional stress or pain. It can be preceded by dim vision, sweating, nausea, light-headedness, giddiness, or yawning, reflecting autonomic nervous system hyperactivity, and can be fully alleviated by lying down. After the spell, it is common for the patient to be quite pale and to have a slow heart rate. Closely related in underlying pathophysiology is the syncope due to direct stimulation of the carotid sinus in patients who are “hypersensitive”; this syncope is manifested by fainting spells after sudden head motion or wearing of a tight collar. Hypovolemia in patients experiencing fainting while standing and orthostatic hypotension-related syncope are other possible and related etiologies of cardiac syncope.

Compared with cardiac syncope, neurologic causes often have an aura, as in the case of epilepsy (which, in some cases, is familial and in others posttraumatic) or associated neurologic deficits of transient cerebrovascular ischemia (e.g., vision loss, speech impairment, or motor weakness). Furthermore, after some neurologic causes of syncope such as a grand mal seizure, there is postictal confusion. Importantly, vasodepressor syncope is not typically linked with trauma, but patients with seizures or other forms of sudden cardiac syncope can sustain physical injury with a fainting spell. Near syncope, which is described by the patients as “nearly” losing consciousness or “graying” out, is similar in its differential to actual syncope but, overall, is less likely to be associated with serious pathologic conditions compared with true loss of consciousness.

Calkins and colleagues (39) studied the differentiating symptoms of the history to resolve the etiology of syncope. Features of the history predictive of syncope not due to ventricular tachycardia or atrioventricular block were palpitation, blurred vision, nausea, warmth, diaphoresis, and lightheadedness before syncope and nausea, warmth, diaphoresis, and fatigue after the syncopal event (40).

Palpitations represent an unpleasant awareness of the heartbeat and frequently are described as “skipping,” “jumping,” “pounding,” or “racing.” The skipping is often attributed to the postextrasystolic pause, whereas the pounding or forceful beat is accounted for by the postextrasystolic potentiation of contractility. A variety of rhythm disturbances may be considered, with the full spectrum from bradyarrhythmias to supraventricular or ventricular tachycardias being potential triggers. Palpitations are remarkably common and can simply occur with anxiety (e.g., palpitations occurring with the syndrome of hyperventilation previously described), with tingling around the mouth and in the hands, although the underlying rhythm is sinus tachycardia. Similarly, other benign forms occur with postural hypotension due to the reflex heart acceleration or in response to medications (e.g., amphetamines), cocaine, alcohol, tobacco, and caffeine. With physical exertion, a sense of the heart “pounding” may certainly be anticipated.

However, when the complaint occurs despite lack of exertion or with only minimal effort, other causes need to be surveyed, such as heart failure, anemia, thyrotoxicosis, and atrial fibrillation. A pulse rate of approximately 150 beats per minute suggests atrial flutter, whereas faster rates suggest paroxysmal supraventricular tachycardia. Rates slower than 140 beats per minute (as low as 100 beats per minute) are more suggestive of sinus tachycardia and, therefore, are more likely to be benign.

Edema, Fatigue, and Other Symptoms

Swollen legs manifesting at the end of the day are characteristic of heart failure or chronic venous insufficiency. Early on, this can sometimes be associated only with difficulty in getting one’s shoes on but can also be linked to appreciable weight gain due to fluid retention. Usually, the edema is symmetric and progresses “from the ground up.” In patients with prior bypass surgery who have had saphenous vein grafts harvested, the edema may begin unilaterally on the side of decreased venous competence. In patients confined to bed with heart failure, presacral edema is common. In the presence of hyperpigmentation of the legs, ulcers, and other changes suggesting venous stasis, chronic venous insufficiency may be the likely explanation, but, frequently, the coincident finding of heart failure and chronic venous insufficiency is present. This is especially true in patients who have had long-standing heart failure and other reasons for venous insufficiency (e.g., marked obesity). Generalized edema, known as *anasarca*, can occur with severe heart failure but also with cirrhosis and the nephrotic syndrome. Periorbital edema occurs with hypoproteinemia, myxedema, hereditary angioneurotic edema, and acute glomerulonephritis. Edema localized to the upper body, involving the face, arms, and neck, raises the possibility of a superior vena cava syndrome, which may herald carcinoma of the lung. Edema of cardiac origin that is not associated with dyspnea or orthopnea suggests a right-sided heart lesion such as constrictive pericarditis, tricuspid stenosis, or, for example, a tumor that has invaded the inferior vena cava or right atrium.

Fatigue is a nonspecific and common symptom that may not have cardiovascular basis. However, it may signal poor cardiac output or result from overdiuresis or from the use of beta-blocker drugs. In some cases, episodic fatigue from physical exertion or emotional stress disproportionate to the amount of effort expended may represent an anginal equivalent.

Nausea and vomiting can occur with acute myocardial infarction (see Chapter 18). Fever and chills, along with other constitutional signs, may be associated with infectious endocarditis (see Chapter 25).

CONTROVERSIES AND PERSONAL PERSPECTIVES

It is clear that taking a thorough history has become less of a priority for a few pivotal reasons. First, there is less time available for physician-patient direct contact as a result of the demands placed on a physician’s time. Frequently, a physician extender or nurse obtains part or all of the history to reduce the time burden on the doctor. Under the putative heading of “efficiency,” the priority of the detailed, thorough interview has been markedly reduced. Second, with advances in technology, the history and physical examination have been partially supplanted by rapid use of bedside tools such as the two-dimensional echocardiogram, a treadmill or dobutamine thallium test, a Holter recording, or even diagnostic angiography or electrophysiologic study—all instead of the meticulous history.

These two forces are unfortunate. The history is the most important way to create a physician-patient bond and is precious and irreplaceable. Ideally, the task should not be delegated to a physician extender, except for such perfunctory aspects as the medications and doses, risk factors, and minor details. It is absolutely essential to query the patient directly and in depth for the principal symptoms (e.g., chest discomfort, loss of consciousness, or dyspnea). Only in this way can there be the optimal accuracy and relationship building that are critical. Also, the use of advanced diagnostic technology easily can be imprudent with respect to cost and can uncover findings that, although accurate, have no bearing on the patient’s symptoms. The detailed history preempts or properly guides the use of more refined diagnostic tests. Intuitively, the history is the most cost-effective tool that one can use to lay soundly the foundation of the patient’s evaluation.

THE FUTURE

Although the history has been deemphasized in the past decade, it will become increasingly relied on in the future because of its relatively low cost and pivotal importance in guiding more diagnostic and therapeutic decision making. With the reduced sense of patient satisfaction and bonding with the physician, spending more time with the patient to relay information and develop mutual understanding and trust hopefully will override the forces that have deprioritized such a core component of high-quality cardiovascular medicine.

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15

PHYSICAL EXAMINATION

KANU CHATTERJEE

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OVERVIEW

A systematic approach to the bedside examination of a patient is essential in determining the significance of an abnormal physical finding, such as decreased or increased intensity of the first heart sound (S_1), a pathologic third heart sound (S_3), or a systolic or diastolic murmur. Assessment of the abnormalities of the systemic venous pressure and pulse, arterial pulse, precordial impulse, heart sound, and murmurs provides clues not only for the diagnosis of the anatomic abnormalities, but also for the determination of the severity of the hemodynamic abnormalities. It should be emphasized that appropriate investigations (e.g., echocardiography, radionuclide ventriculography and scintigraphy, and cardiac catheterization) should be considered to establish the diagnosis.

In the present era of technological advances, particularly in the various imaging modalities, there is a growing conception among practicing physicians in cardiovascular medicine that bedside physical examination is unnecessary. It should be emphasized, however, that for proper application and interpretation of various new and old tests that are available for cardiovascular evaluation in a given patient, a careful physical examination is essential. Furthermore, a careful, systematic, and methodical bedside clinical evaluation—including analysis of clinical history—can provide enough information to decide whether further investigations are necessary and, if necessary, which investigations are appropriate. Bedside clinical examination should be performed and practiced in the same way after similar sequences and usually begins with *general inspection* of the patient.

INSPECTION

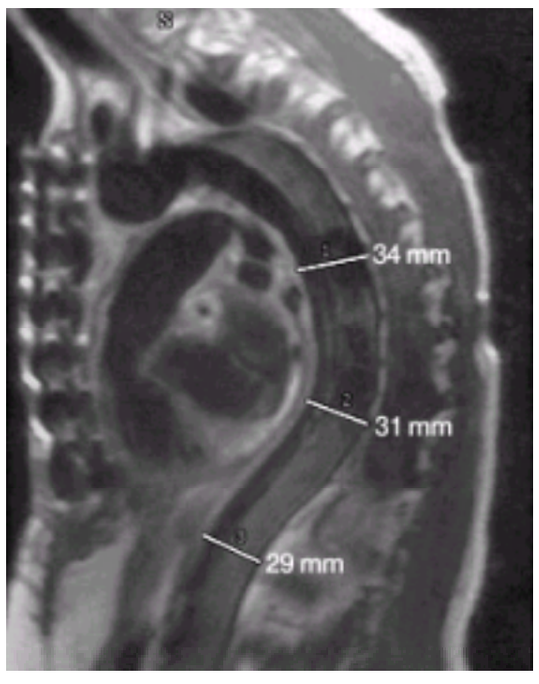
During general inspection (1,2), the stature, body habitus, approximate weight, and presence or absence of obesity are noted. An unusually short stature is seen in patients with osteogenesis imperfecta, which is associated with aortic and mitral regurgitation and calcification of the arterial system. Congenital heart disease, such as Noonan's syndrome, also occurs in association with short stature due to dwarfism. In Noonan's syndrome, short stature is associated with web-neck, dental malocclusion, antimongoloid slanting of the eyes, mental retardation, and hypogonadism. Pulmonary valve stenosis and obstructive and nonobstructive cardiomyopathy are also observed. Dwarfism is an essential phenotypic feature of the various types of mucopolysaccharidosis, which can be associated with various valvular and myocardial dysfunctions due to mucopolysaccharide deposition. An unusually tall stature, however, is seen in patients with Marfan's syndrome, which is frequently associated with aortic aneurysm, aortic regurgitation, and mitral regurgitation. When severe chest pain or back pain is the presenting symptom in a patient with Marfan's syndrome, acute aortic dissection should always be suspected. A tall stature, long extremities, and eunuchoid appearance is observed in patients with Klinefelter's syndrome, which can be associated with congenital heart diseases such as ventricular septal defects, patent ductus arteriosus, and tetralogy of Fallot. During initial cardiac evaluation, it is customary to notice any obvious musculoskeletal deformity, such as kyphoscoliosis, straight back, and pectus deformity of the chest. A higher incidence of mitral valve prolapse is observed in the presence of such musculoskeletal deformities. An increased incidence of mitral valve prolapse is also observed in females with smaller breasts. Muscular dystrophies such as pseudohypertrophic, fascioscapular humoral, or limb-girdles varieties can be suspected during general inspection. These muscular dystrophies may be associated with various cardiovascular abnormalities, including myocardial disease, mitral valve prolapse, ventricular septal defect, and dysrhythmias.

VIDEO

Video 15.1 Coronary ectasia. These angiograms were obtained in a 40-year-old patient with Noonan's syndrome and no coronary risk factors. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Ectopia lentis. This lens dislocation is associated with Marfan syndrome.

Arachnodactylia in Marfan syndrome. The ratio of finger length to hand size is markedly increased.



Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

Gait

Abnormalities of gait are also noted during inspection. Neurologic deficits resulting from cardioembolic strokes or hypertensive cerebrovascular disease may be associated with abnormalities of gait. A parkinsonian gait may indicate Shy-Drager syndrome, which may be associated with orthostatic hypotension (3). Certain metabolic disorders (e.g., hyperthyroidism, hypothyroidism, Cushing's syndrome, and acromegaly) can be suspected during inspection, and these metabolic diseases may be associated with various cardiovascular abnormalities, including systemic and pulmonary hypertension and myocardial and pericardial diseases.

Body Habitus

During inspection, the general nutritional status of the patient is also noted. Although marked weight loss, wasting, and cachexia occur more frequently from metabolic and neoplastic diseases, they can be manifestations of severe congestive heart failure. Cardiac cachexia (4) does not correlate to cardiac output as usually perceived, but to a marked neuroendocrine abnormality characterized by an activated renin angiotensin system as well as increased levels of cytokines, including tumor necrosis factor and interleukins. The presence and severity of obesity should be noted, as various cardiovascular abnormalities can be associated with obesity. Obesity, particularly abdominal and truncal types, is one of the components of the metabolic syndrome X, which comprises hypertension, hyperlipidemia, and insulin resistance (5,6). In patients with metabolic syndrome, there is increased risk of developing atherosclerotic macrovascular disease, including coronary artery disease. Furthermore, in markedly obese patients, there is increased incidence of sleep apnea, hypertension, and dilated cardiomyopathy. Truncal obesity, if associated with buffalo hump or moon facies, should raise the suspicion of Cushing's syndrome, which may be complicated by hypertension and hypertensive heart disease. In African-Americans, severe obesity and marked increase in body mass index and diabetes are more important predictors of primary diastolic heart failure than hypertension or coronary artery disease.

Respiration

During inspection, presence of respiratory distress and types of altered respiration should be observed. Labored and uncomfortable breathing, however, may be of

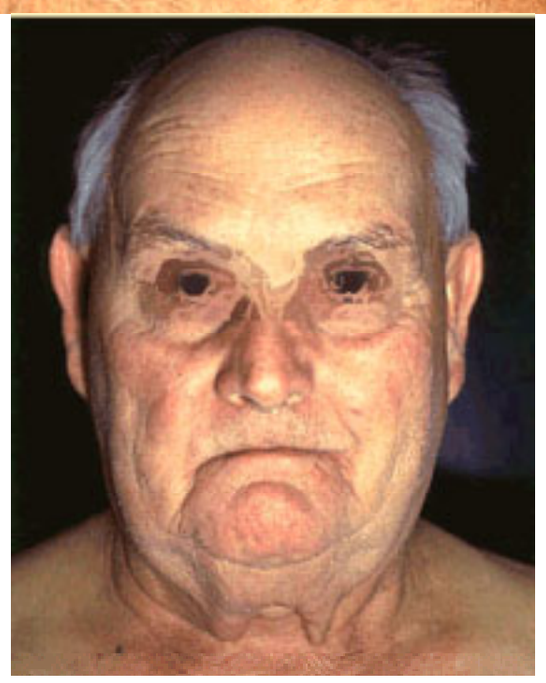
cardiac or noncardiac origin. Inability to lie down or a dry, irritating cough with dyspnea when in the supine position usually indicates pulmonary venous congestion. Sleep-disordered breathing is common in chronic congestive heart failure (7). Typical Cheyne-Stokes respiration with central sleep apnea is observed in 20% to 30% of patients with moderate or severe congestive heart failure with reduced left ventricular ejection fraction and, usually, elevated pulmonary capillary wedge pressure and lower cardiac output. Cheyne-Stokes respiration with central sleep apnea should be distinguished from obstructive sleep apnea, which is associated with inspiratory efforts during apneic phase, because central sleep apnea is a risk factor for increased mortality (7a). Also, patients with only central sleep apnea are likely to benefit from continuous positive airway pressure therapy (7b). Frequent sighing respirations and a restless, anxious look are more frequently encountered in patients with anxiety and neurocirculatory asthenia. The “blue bloater” and “pink puffer” appearances, which can be detected during inspection, usually indicate chronic obstructive pulmonary disease. During inspection, it is desirable to note any obvious changes in the color of the skin. A bluish discoloration of the skin usually indicates cyanosis, which can be either peripheral or central. Peripheral cyanosis is detected in exposed skin (e.g., lips, nose, and earlobes, and in extremities) and indicates impaired peripheral perfusion. A bluish discoloration of the tongue, uvula, and buccal mucus membrane suggests central cyanosis, which results from intrapulmonary or intracardiac right-to-left shunt. When differential cyanosis (i.e., cyanosis in the inferior extremities without cyanosis in the superior extremity) is observed along with differential clubbing, Eisenmenger’s syndrome associated with patent ductus arteriosus should be suspected.

Edema

Generalized edema is easily detected during inspection, usually results from nephrotic syndrome and sepsis, and rarely results from severe heart failure. Dependent edema, on the other hand, is associated with right heart failure. When dependent edema is discovered, careful evaluation of systemic venous pressure and pulse is essential for the diagnosis of right heart failure. The presence of ascites, which also may be a manifestation of right heart failure, can be suspected from the protuberant abdomen. Ascites in the absence of edema of the lower extremities is more frequently a manifestation of liver disease, such as cirrhosis, rather than of heart failure. However, in patients with constrictive pericarditis and restrictive cardiomyopathy, disproportionately large ascites with little or no edema of the lower extremities can be observed (8). Again, careful examination for the presence of systemic venous hypertension, pulmonary arterial hypertension, and physical findings suggestive of restrictive physiology is essential for the differential diagnosis between liver disease and cardiac failure.

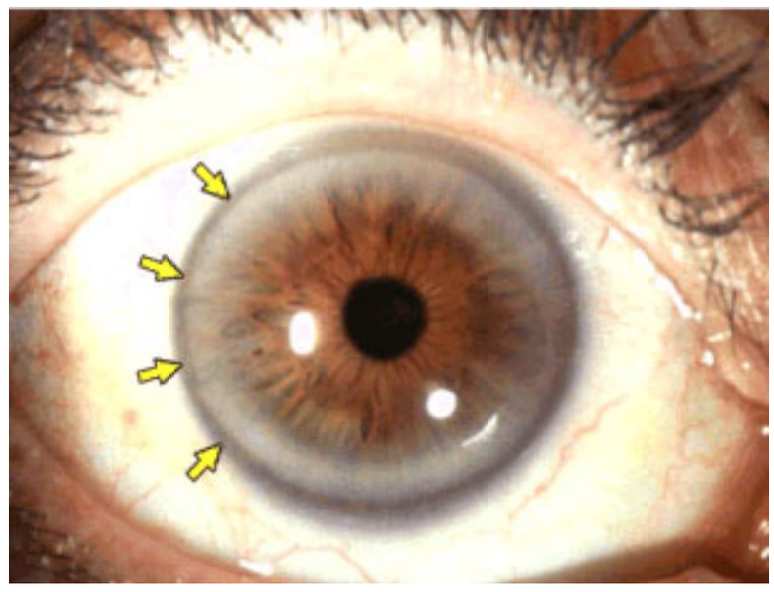
Skin

Slate or bronze pigmentation of the skin may suggest hemochromatosis, which may be associated with various cardiac complications (e.g., restrictive or dilated cardiomyopathy, arrhythmias, and conduction disturbances). It also should be appreciated that patients on chronic amiodarone therapy also develop similar discoloration of the skin with exposure to sunlight (9). Discoloration of the skin similar to marked suntan is also seen in patients with carcinoid syndrome. Mild jaundice may be observed in patients with heart failure with congestive hepatopathy and with pulmonary embolism. Prosthetic valve malfunction should be suspected if jaundice is detected in a patient with artificial heart valves. The livido reticulares with cyanosis of the toes and preserved peripheral pulses (blue toes syndrome) suggest cholesterol emboli (10). Acrosclerosis with taut, thickened, or edematous skin bound tightly to subcutaneous tissue in the hands and fingers suggests systemic sclerosis, which may be associated with pulmonary hypertension, pericarditis, right heart failure, systemic hypertension, restrictive cardiomyopathy, and dilated cardiomyopathy. If malar flush is detected, mitral stenosis with pulmonary hypertension should be suspected. Malar flush, however, can also occur in patients with severe precapillary pulmonary hypertension and may be confused with butterfly rash of lupus erythematosus. The presence of transverse or diagonal earlobe creases in a relatively young person (i.e., under 45 years of age), may suggest the presence of premature atherosclerotic coronary artery disease. The presence of arcus—a circumferential light ream around the iris that begins inferiorly—further increases the risk of premature atherosclerotic coronary artery disease. Arcus is also frequently associated with hypercholesterolemia and xanthelasma (i.e., deposits of cholesterol on the eyelids). When telangiectasia of the lips, tongue, and buccal mucosa are detected, Osler-Weber-Rendu disease, which is associated with pulmonary arteriovenous fistulae, should be suspected. Exfoliative dermatitis, purpura, and petechial rashes usually indicate drug reactions. Although an erythema marginatum is characteristic of acute rheumatic fever, erythema nodosum is a nonspecific finding and occurs in many systemic diseases. In patients with suspected bacterial endocarditis, searches should be made for conjunctival hemorrhages, skin purpuric, and petechial lesions, as well as for splinter hemorrhages. It should be realized that splinter hemorrhages in the nail beds may occur in normal patients after mild trauma and in patients with trichinosis or hemorrhagic disorders.



Jaundice. There is diffuse yellowing of the skin (A,B).

Livedo reticularis. Mottled reddish discoloration of the lower extremities with accompanying multiple ulcerations associated with atheroemboli.



Arcus juvenilis. This ring is associated with premature atherosclerosis.

Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia). Multiple dark red and slightly elevated telangiectasia in the back (*left panel*) and hands (*right panel*) are shown. These represent arteriovenous malformations of dermal microvasculature.

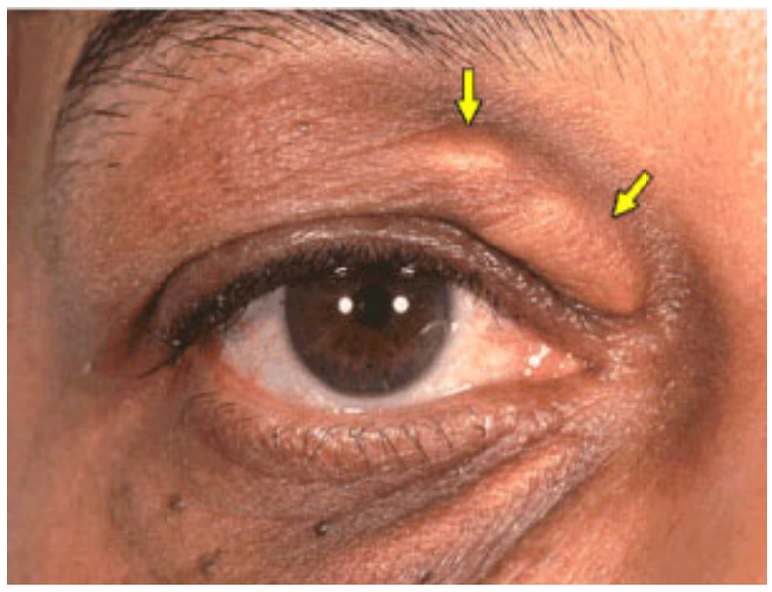
Splinter hemorrhages. Linear hemorrhages on the fingertips (*yellow arrows*) of a patient with infective endocarditis.

During examination of the skin, it is customary to check for the presence of cutaneous and subcutaneous nodular lesions, which may suggest some systemic and metabolic diseases that may also involve the cardiovascular system. The rheumatic nodules associated with acute rheumatic fever are small, nontender, and most frequently seen on the knuckles, extensor surface of the elbows, and suboccipital regions. Rheumatoid nodules, on the other hand, are large, nontender, and characteristically localized over points of pressure or friction—most commonly the extensor surfaces of the proximal forearms. If rheumatoid nodules are detected, attention should be directed to detect the cardiovascular complications of rheumatoid arthritis (e.g., pericarditis, aortic and mitral valvular disease, conduction disturbances, and, rarely, cardiomyopathy). Xanthomas, the cholesterol-filled nodules, occur in different types of abnormalities of lipoprotein metabolism, and recognition of the distribution of xanthomas aids in the diagnosis of these disorders. Tendon xanthomas, xanthomas occurring on digital extensors, and tuberous xanthomas occur in familial hypercholesterolemia (11). Eruptive xanthomas are small yellow papules in the skin that are surrounded by an erythematous halo. They occur in patients with primary familial hypertriglyceridemia that results from lipoprotein lipase deficiency and is associated with recurrent episodes of pancreatitis, but not with premature coronary artery disease. Eruptive xanthomas also occur in patients with endogenous and mixed hypertriglyceridemia, which can be associated with ischemic vascular disease. In patients with suspected bacterial endocarditis, it is desirable to search for Osler's nodes and Janeway's lesions. Osler's nodes are most frequently observed on the palms, soles of the feet, and pads of the fingers or toes. These nodes are tender, nodular, erythematous skin lesions and result from emboli. Janeway's lesions are nontender, raised, hemorrhagic nodules that usually occur on the palms of the hands and soles of the feet. These lesions were initially thought to be due to vasculitis, but they also appear to be of embolic origin. Café au lait spots—sometimes detected only in the axilla—occur in neurofibromatosis, which occasionally is associated with hypertrophic cardiomyopathy.

Xanthelasma. Yellow papules are seen below the eyelid (*arrows*) associated with elevated B lipoproteins.

Xanthoma disseminata. Crops of yellow papules associated with hypertriglyceridemia.

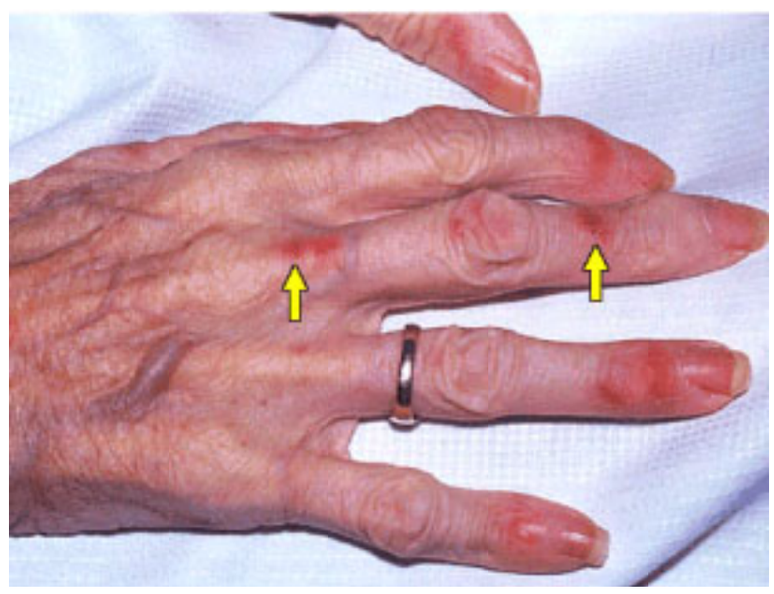
Xanthelasma. Yellowish discreet plaques in the orbital area resulting from hyperlipidemia.



Xanthelasma in association with hypercholesterolemia. The yellow arrows indicates yellowish deposits in this patient with hyperlipidemia.

Xanthoma. Nodular protuberance of the extensor surface of the leg (*left panel*) as well as multiple nodules of the arm (*right panel*).

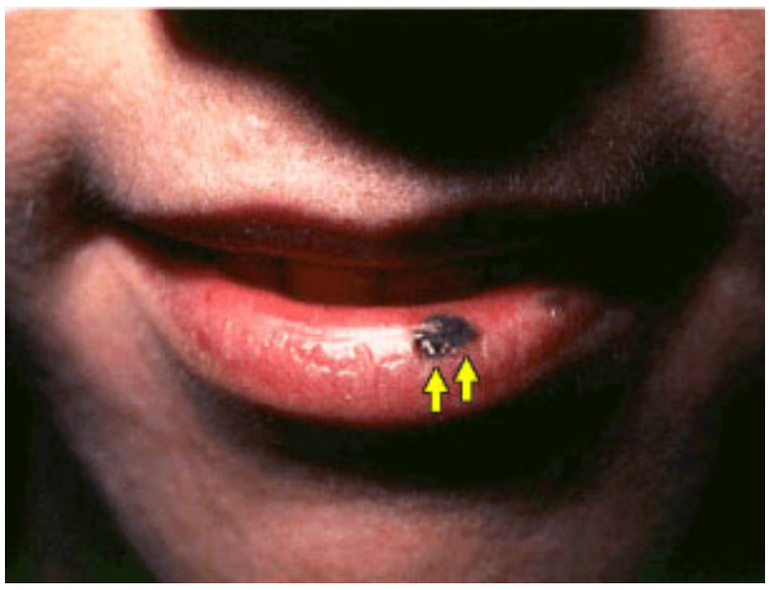
Eruptive xanthoma. Bulbous cutaneous eruptions associated with hyperlipidemia.



Septic emboli from infective endocarditis (*yellow arrows*).

Osler nodes. There are tender nodules on the toe pads (*yellow arrows*) secondary to infective endocarditis.

Janeway lesions of endocarditis. There are hemorrhages with nodular character at the fingertips (*arrows*).



Café au lait spot. There is a flat localized hyperpigmentation that is uniformly light brown in the lower lip (*yellow arrows*) that may be associated with neurofibromatosis, Albright syndrome, or pulmonary stenosis.

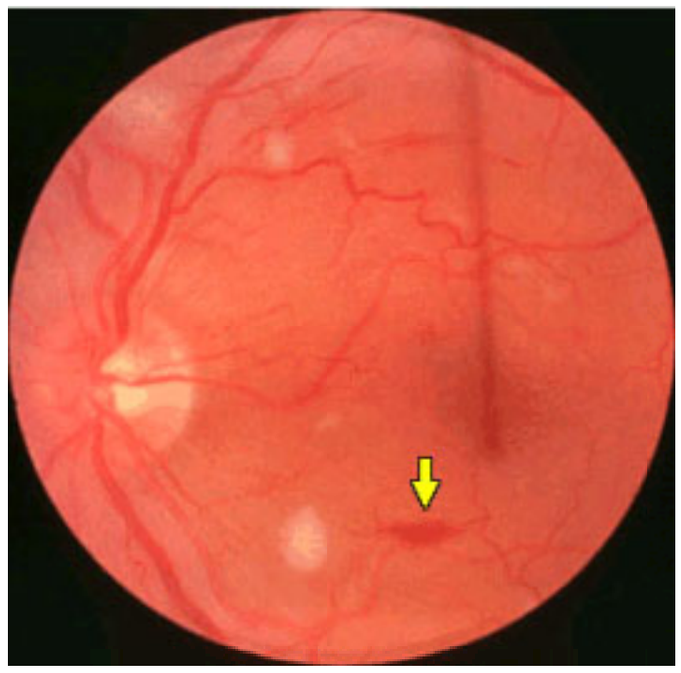
Funduscopy

In patients with established or suspected systemic hypertension, funduscopic examination should be performed. Based on the degree of narrowing or irregularities of retinal artery, the presence or absence of arteriovenous nicking or nipping, hemorrhages, exudates, and papilledema, four grades are recognized (12). Grade 1 consists of minimal irregularity of the arterial lumen and narrowing with increased light reflex. Grade 2 changes consist of arteriovenous nicking, more marked narrowing and irregularity of the arterioles, and distention of the veins. Grade 3 changes are characterized by the presence of flame-shaped hemorrhages and fluffy “cotton wool” exudates in addition to arterial changes. Hard exudates may also be present. Grade 4 funduscopic changes are characterized by the presence of papilledema and any other changes in grades 1 through 3. Generally, grade 1 and 2 changes are present in benign hypertension, whereas grade 3 or 4 changes are seen in accelerated or malignant hypertension. Funduscopic examination should also be performed in patients with suspected bacterial endocarditis and may reveal vascular occlusions and hemorrhagic areas with white centers (Roth’s spots), which result from emboli in the nerve fiber retinal layer. Roth’s spots, however, are not diagnostic of bacterial endocarditis and can be seen in hemorrhagic disorders, including leukemia. Mycotic aneurysms resulting from large emboli occasionally may be discovered in retinal vessels during funduscopic examination. Identification of such lesions should lead to further evaluation for the source of emboli, and appropriate investigations—including transthoracic and, occasionally, transesophageal echocardiography—must be undertaken. Occasionally, funduscopic examination may reveal unusual findings that may provide clues for the diagnosis of the underlying pathophysiology. Beading of the retinal artery may suggest hypercholesterolemia. Microinfarction in the peripheral retina is seen in sickle cell disease, which may also involve the cardiovascular system. Angioid streaks may suggest pseudoxanthoma elasticum, which may be associated with coronary artery calcification, systemic hypertension, intermittent claudication, and arrhythmias. A wreath-like arteriovenous anastomosis around the optic disk is a characteristic of Takayasu’s syndrome. In adult cardiology practice, the abnormal findings that are often detected during inspection, along with their significance, are summarized in Table 15.1.

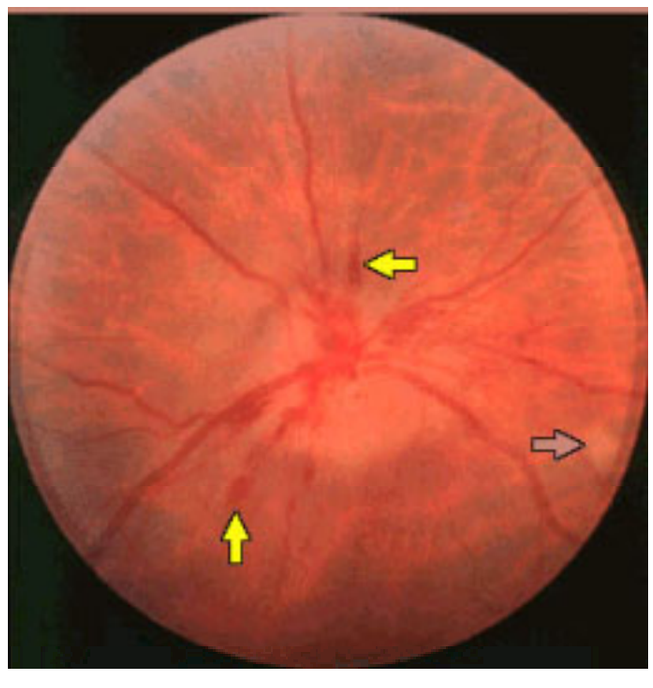
Cyanosis
Peripheral cyanosis only—suspect low cardiac output and impaired peripheral perfusion
Central cyanosis—suspect intrapulmonary or intracardiac right-to-left shunt
Differential cyanosis—suspect Eisenmenger’s syndrome with patent ductus arteriosus
Respiratory distress
Cheyne-Stokes respiration with central sleep apnea—suspect heart failure
Blue bloater and pink puffer—suspect pulmonary disease
Frequent sighing respiration—suspect anxiety syndromes
Nutritional status
Cachexia—suspect severe heart failure with abnormal neuroendocrine profile
Obesity—suspect metabolic syndrome X, sleep apnea, cardiomyopathy
Ascites and peripheral edema—suspect severe heart failure, constrictive pericarditis
Musculoskeletal deformity, kyphoscoliosis, straight back, pectus excavatum
Suspect mitral valve prolapse, aortic and mitral valve regurgitation, congenital heart disease such as atrial septal defect
Abnormal movement of the head and neck
Bobbing of the head coincident with each heart beat—suspect severe aortic regurgitation
Lateral movements of the earlobes with each cardiac cycle—suspect severe tricuspid regurgitation
Slate or bronze discoloration of the skin
Suspect chronic amiodarone therapy, hemochromatosis, carcinoid syndrome

TABLE 15.1 INSPECTION

Arteriovenous nicking in association with hypertension (*yellow arrow*).



Flame-shaped hemorrhage in association with severe hypertension (*yellow arrow*).



Papilledema from malignant hypertension. There is blurring of the borders of the optic disc with hemorrhages (*yellow arrows*) and exudates (*white arrow*).

EXAMINATION OF THE ARTERIAL PULSE

During initial evaluation, all accessible arterial pulses should be examined; in the inferior extremities, dorsales pedes, posterior tibials, and femoral pulses should be examined bilaterally. In the upper extremities, both brachial and radial pulses should be examined, and, in special circumstances, the ulnar pulses and axillary arterial pulses should also be examined. Temporal arteries are examined when temporal arteritis is suspected in patients with headache and jaw claudication. Carotid arteries should be examined sequentially in all patients. Diminished or absent pulses may result from atherosclerotic peripheral vascular disease, which is associated with increased incidence of atherosclerotic coronary artery disease. Loss of or decreased femoral pulse unilaterally or bilaterally most frequently suggests local obstructive lesions due to atherosclerotic disease. However, diminished amplitudes of the lower extremity pulses, including femoral, popliteals, posterior tibials, and dorsales pedes arterial pulsations, also occur from isolated aortoiliac diseases, such as Leriche's syndrome (13), postsubclavian coarctation of the aorta, aortic dissection, descending thoracic and abdominal aortic aneurysms, and abdominal aortic disease such as giant cell arteritis. When coarctation of the aorta is suspected, it is desirable to examine the radial and femoral pulses simultaneously to assess radial/femoral delay. In a normal adult, the pulse transmission time from aorta to the radial artery is approximately 75 ms and to the femoral artery is approximately 70 ms. Thus, in the presence of coarctation, delay in the onset of femoral pulse compared to that of radial pulse can be detected. The radial/femoral delay is rarely observed in patients with Leriche's syndrome and abdominal coarctation. Also in pseudocoarctation, the degree of obstruction is not severe enough to decrease the amplitude of the femoral pulse or to cause delay in the onset of femoral pulse compared with that of radial pulse (14). In patients with radial/femoral delay and suspected coarctation, blood pressure should be recorded in the upper and lower extremities. In the supine position, the inferior extremity pressure is normally slightly higher than that of the upper extremity arterial pressure. In coarctation, inferior extremity pressure is lower than upper extremity pressure. While examining the peripheral arterial pulses, it is desirable to assess the rigidity and elasticity of the arteries. The rigidity of the arterial pulses are best appreciated by examining the femoral, radial, brachial, and carotid pulses. In clinical practice, the thickness and firmness of the arterial walls are examined by rolling the vessel, usually the radial artery, against underlying tissue. The more rigid the artery, the less it is compressible. The appreciation of nonelastic, rigid peripheral arteries may indicate the presence of systolic hypertension. If the significant rigidity of the peripheral arteries is observed, it is desirable to perform Osler's maneuver. Osler's maneuver is performed by elevating the cuff pressure to obliterate the radial pulse; if, after obliteration of the pulse, the radial artery is easily palpable and appears rigid (i.e., a positive Osler's sign), then there might be a significant difference between indirect measurement of arterial pressure by cuff method and directly determined intraarterial pressure.

The peripheral arterial pulses are also examined at the bedside for detection of arrhythmias. If the pulse rate is regular but slow, sinus bradycardia, junctional rhythm, or complete atrioventricular block is suspected. Occasionally, bigeminy may produce an irregular slow pulse because of the nonconducted pulse associated with the ectopic beat. Careful examination of the venous pulse and simultaneous auscultation may be helpful for the differential diagnosis of slow regular pulse. If regular cannon waves with each cardiac cycle are recognized, junctional rhythm is suspected. In the presence of a slow regular pulse, if irregular cannon waves and changing intensity of the S_1 are observed, atrioventricular dissociation due to complete atrioventricular block is the most likely diagnosis. Bigeminy can be diagnosed easily by auscultation, which demonstrates the postectopic compensatory pause. Atrial fibrillation can be suspected if irregularly irregular pulses are appreciated. However, frequent premature beats or multifocal atrial tachycardia can also produce an irregularly irregular pulse similar to that of atrial fibrillation. If atrial fibrillation is suspected, it is desirable to determine the ventricular rate by simultaneous auscultation to assess the degree of pulse deficit. The difference between the heart rate by auscultation and the pulse rate is the pulse deficit. The rapid ventricular responses are the cause of the hemodynamic abnormalities of atrial fibrillation. A fast and regular pulse rate (150 beats or more) should raise the possibility of supraventricular or ventricular tachycardia. It is mandatory to do electrocardiographic evaluation of every patient with suspected arrhythmia.

Peripheral arterial pulses are also examined to detect any alteration of the character of the pulse, which can provide important diagnostic clues. Pulsus alternans is suspected when strong and weak amplitude pulses are appreciated with alternate beats in the presence of a regular pulse. Pulsus alternans can be confirmed by measuring blood pressure by sphygmomanometer. When the cuff pressure is slowly released, phase I Korotkoff's sound is heard initially only during the alternate strong beats; with further release of cuff pressure, the softer sounds of the weak beat also appear. The most important cause of pulsus alternans is left ventricular systolic failure. Pulsus alternans is rarely encountered in patients with cardiac tamponade. In patients with tamponade with pulsus paradoxus, if the respiratory rate is half of the heart rate, pulsus alternans may occur. However, in these patients, when respiration is held transiently, the pulsus alternans is resolved. Pulsus alternans (mechanical alternans) can also occur occasionally in aortic stenosis, in hypertrophic obstructive cardiomyopathy, with sudden increase of afterload, with ischemia, with abrupt fall of preload, and with the onset of a tachyarrhythmia. Rapid atrial pacing may induce pulsus alternans in the presence of normal left ventricular systolic function. However, clinically detectable sustained pulsus alternans almost always indicates left ventricular systolic dysfunction.

In experimental and clinical studies, alternating changes in preload, afterload, and contractility have been suggested as potential mechanisms for mechanical alternans (15); ventricular dyssynchrony with alternating contraction of the interventricular septum, incomplete relaxation in the alternate beats, partial asystole of the left

ventricle, alternating changes in action potential duration, and alternating amounts of Ca^{2+} sparks from the sarcoplasmic reticulum are the other proposed mechanisms (15a). The failing heart is sensitive to altered afterload and resistance to left ventricular ejection. The increased arterial pressure associated with a strong beat increases the resistance to left ventricular ejection for the following beat, which is thus associated with decreased forward stroke volume and decreased arterial pressure. This reduction in arterial pressure lowers the resistance to left ventricular ejection, which allows increase in forward stroke volume and, therefore, increase in arterial pressure. These changes in arterial pressure, reflecting changes in the ejection impedance with alternate beats, can perpetuate pulsus alternans (Fig. 15.1). It should be emphasized, however, that the absence of pulsus alternans does not exclude left ventricular systolic dysfunction. Nevertheless, the pulsus alternans is a reliable and helpful physical finding for the diagnosis of left ventricular systolic dysfunction.

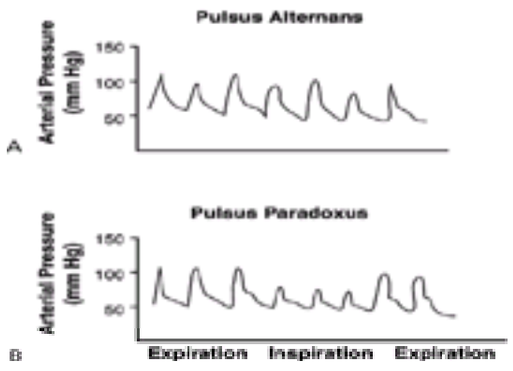


FIGURE 15.1 Schematic illustrations of pulsus alternans **(A)** and pulsus paradoxus **(B)**. In clinical practice, pulsus alternans usually indicates systolic ventricular failure and occurs in patients with chronic ischemic or nonischemic dilated cardiomyopathy, aortic stenosis, and acute myocardial infarction. Pulsus paradoxus, however, is observed in pericardial tamponade, constrictive pericarditis (rare), emphysema, asthma, marked obesity, and severe congestive heart failure (rare).

During examination of the peripheral arterial pulses, if there is a substantial reduction in the amplitude of the arterial pulse during inspiration, pulsus paradoxus should be suspected, and determination of arterial pressure by sphygmomanometry during inspiration and expiration should be performed. Systolic arterial pressure normally falls during inspiration; however, the magnitude of fall in arterial pressure during inspiration usually does not exceed 8 to 12 mm Hg. A more marked inspiratory decrease in arterial pressure exceeding 12 to 15 mm Hg is regarded as pulsus paradoxus and usually is detectable by palpation of the peripheral pulses. However, the magnitude of pulsus paradoxus should be measured by sphygmomanometry. When the cuff pressure is slowly released, the systolic pressure at expiration is noted. With further slow deflation of the cuff, the systolic pressure during inspiration can also be detected. The difference between the pressure during expiration and inspiration is the magnitude of the pulsus paradoxus. The abnormal pulsus paradoxus is an important physical finding of cardiac tamponade (16). The marked inspiratory decrease in arterial pressure in tamponade results from the marked inspiratory decline of left ventricular stroke volume due to a decreased end diastolic volume. In cardiac tamponade during inspiration, there is an increase in venous return to the right atrium and the right ventricle. Due to increased intrapericardial pressure, the intraventricular septum shifts toward the left ventricle during inspiration, which decreases left ventricular preload. There is also an expected decrease in venous return to the left ventricle during inspiration because of increased pulmonary venous reservoir capacity during inspiration. In clinical practice, besides cardiac tamponade, pulsus paradoxus is observed in patients with chronic obstructive pulmonary disease. It should be emphasized that pulsus paradoxus is a rare finding in patients with constrictive pericarditis. Pulsus paradoxus is rarely observed in pulmonary embolism, pregnancy, marked obesity, and partial obstruction of the superior vena cava. In hypertrophic obstructive cardiomyopathy, arterial pressure occasionally increases during inspiration (i.e., reversed pulsus paradoxus) (17). The precise mechanism for this phenomenon is not clear.

The amplitude of the peripheral arterial pulse may provide some information about stroke volume, systemic vascular resistance, and compliance of the arteries. A small-amplitude, rapid pulse usually indicates hypotension, reduced stroke volume, and increased systemic vascular resistance. A large-amplitude, arterial pulse suggests large stroke volume or decreased compliance. A large-volume, bounding pulse is noted after exercise; in high-output states such as chronic anemia, hyperthyroidism, and aortic regurgitation; and in patients with bradycardia (e.g., complete heart block). Decreased compliance and increased rigidity of the peripheral arteries may also increase the amplitude of the arterial pulse, as seen in elderly patients with systolic hypertension. In elderly patients, when the carotid pulse amplitude is decreased, local carotid disease or aortic stenosis should be suspected. Decreased amplitudes of the carotid pulse in elderly subjects should prompt further evaluation, such as echocardiography, to exclude aortic stenosis.

Changes in the contour of the arterial pulses (Fig. 15.2) should also be noted. In patients with significant aortic valve stenosis, a delayed upstroke of the ascending limb of the carotid pulse (so-called pulsus tardus), an anacrotic character of the carotid pulse, delayed peak, and small amplitude (pulsus parvus) of the carotid pulse are frequently appreciated. In patients with aortic stenosis, a thrill over the carotid pulse, which usually is termed a shudder, may also be detected. These abnormalities are best appreciated in the central pulse. In the central aortic ascending pressure pulse, normally there is a notch on the ascending limb: the anacrotic notch. On the upstroke of the carotid pulse, however, the anacrotic notch is not normally appreciated. An anacrotic carotid pulse gives the impression of interruption of the ascending limb or the upstroke of the carotid pulse. When the anacrotic notch is felt immediately after the onset of the upstroke, aortic stenosis is likely to be hemodynamically significant. An anacrotic radial pulse also suggests moderate to severe aortic stenosis. At the bedside, the delayed peak of the carotid pulse is appreciated by simultaneous auscultation of the duration of the systole. Normally, the peak of the carotid pulse is closer to the S_1. In the presence of significant aortic stenosis, the peak of the carotic pulse is delayed and is closer to the second heart sound (S_2). With increasing severity of aortic stenosis, the peak of the carotid pulse is not only further delayed and closer to the S_2, but the amplitude of the carotid pulse is also substantially reduced. It needs to be emphasized, however, that these changes in the contour of the carotid pulse may not be present in elderly patients with aortic stenosis with decreased and noncompliant carotid arteries. When aortic stenosis is suspected, whether in young or older patients, an echocardiographic evaluation is highly desirable.

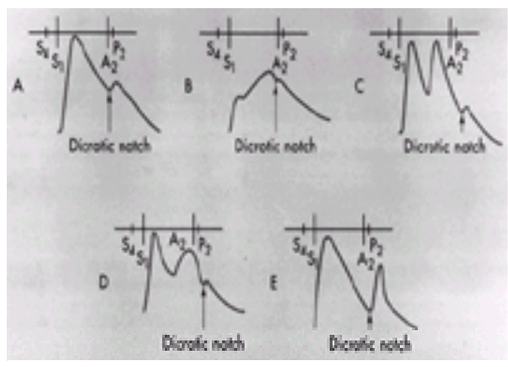


FIGURE 15.2 Schematic illustration of the configurational changes in the carotid pulse and their differential diagnoses. Heart sounds are also illustrated. **A:** Normal. **B:** Anacrotic pulse with slow initial upstroke and delayed peak, which is close to the aortic component of the second heart sound (A_2), indicate fixed aortic stenosis. **C:** Pulsus bisferiens with increased amplitude of percussion and tidal waves occurs during systole. This type of pulsus bisferiens carotid pulse is most frequently observed in patients with significant aortic regurgitation. **D:** Pulsus bisferiens in hypertrophic obstructive cardiomyopathy is rarely appreciated at the bedside. **E:** Dicrotic pulse results from an accentuated dicrotic wave and tends to occur in severe heart failure, hypovolemic shock, cardiac tamponade, sepsis, and after aortic valve replacement. P_2, pulmonary component of the second heart sound; S_1, first heart sound; S_4, atrial sound. (From Chatterjee K. Bedside evaluation of the heart: the physical examination. In: Parmley W, Chatterjee K, eds. *Cardiology*. Philadelphia: JB Lippincott Co, 1997;1:13, with permission.)

Pulsus bisferiens is appreciated by the presence of two positive impulses near the peak of the arterial pulse. These two positive impulses represent accentuated percussion and tidal waves, which can be recorded in the carotid arterial pulse tracing and the central aortic pulse waveform, even in normal subjects. The percussion wave results from the rapid left ventricular ejection, and a second, usually smaller peak represents the tidal wave that results from a reflected wave from the periphery. Normally, radial and femoral pulse tracings demonstrate a single sharp peak. In pulsus bisferiens, percussion and tidal waves are accentuated. At the bedside, it is often difficult to distinguish between anacrotic, pulsus bisferiens and dicrotic pulse. The anacrotic pulse, however, is characterized by a positive palpable wave during the ascending limb of the arterial pulse. Thus, it should be easily distinguished from pulsus bisferiens or the dicrotic pulse. However, if the two positive waves are felt near where the maximum amplitude of the pulse wave occurs, it is difficult to distinguish between pulsus bisferiens and dicrotic pulse. In these circumstances, one has to rely on detection of the etiologic conditions that can be associated with pulsus bisferiens or dicrotic pulse (18). The most frequent conditions associated with pulsus

bisferiens are isolated hemodynamically significant aortic regurgitation, mixed aortic stenosis and regurgitation with predominant aortic regurgitation, and obstructive hypertrophic cardiomyopathy. Pulsus bisferiens is rarely appreciated in patients with large patent ductus arteriosus with large left-to-right shunt, multiple arteriovenous fistulas, and, rarely, complete heart block. If these etiologies are excluded at the bedside, then one should consider dicrotic pulse if double-picked arterial pulse is appreciated. The arterial pressure waveform, when recorded, reveals a single percussion wave and a prominent, accentuated dicrotic wave. At the bedside, however, it is difficult to differentiate between dicrotic pulse and pulsus bisferiens. The dicrotic pulse is appreciated in some patients with severe heart failure, for example, due to dilated cardiomyopathy, low cardiac output, and increased systemic vascular resistance. On the other hand, dicrotic pulse is also appreciated in patients with septic shock with high cardiac output and low systemic vascular resistance. However, in clinical practice, a dicrotic pulse is appreciated frequently in patients after aortic valve replacement and usually indicates impaired left ventricular systolic function. In patients with aortic valve replacement, if a double-picked carotid pulse with sharp initial upstroke is appreciated, it is desirable to evaluate prosthetic valve and left ventricular function by echocardiography to exclude paraprosthetic leak, which usually is associated with pulsus bisferiens, or depressed left ventricular ejection fraction, which is associated with dicrotic pulse. The significance of altered character of the arterial pulse that is sometimes encountered at the bedside in adult patients is summarized in Table 15.2.

Pulsus alternans—suspect acute or chronic reduction in left ventricular ejection fraction
Anacrotic pulse, delayed upstroke, palpable thrill, delayed peak—suspect fixed left ventricular outflow tract obstruction such as aortic valve stenosis
Pulsus biferiens—suspect aortic regurgitation, aortic stenosis with dominant aortic regurgitation, dynamic left ventricular outflow tract obstruction (obstructive hypertrophic cardiomyopathy), large patent ductus arteriosus with left-to-right shunt, complete heart block, hyperkinetic heart syndrome (e.g., in hyperthyroidism)
Dicrotic pulse—suspect "low output syndrome" with increased systemic vascular resistance, "high output" with low systemic resistance (e.g., in septic shock), postaortic valve replacement with depressed left ventricular ejection fraction
Pulsus paradoxus—suspect tamponade, emphysema

TABLE 15.2 ALTERED CHARACTERS OF THE ARTERIAL PULSE AND THEIR CLINICAL SIGNIFICANCE

EXAMINATION OF JUGULAR VENOUS PULSE AND PRESSURE

Examination of jugular venous pulse and pressure (1,2) is essential to assess hemodynamic changes in the right side of the heart. Jugular venous pressure and pulses usually are examined with the patient in a 45-degree, semirecumbent position. However, if, in this position, the venous pulsations are not recognized, the examination of venous pressure and pulse should be done with the patient in a supine position or even with the head and neck tilted below the level of the chest. Occasionally, if the venous pressure is normal or low, the legs need to be raised to increase the venous return and increase right-sided venous pressure. When the venous pressure is extremely elevated and the veins appear to be distended, it is preferable to examine the jugular venous pulses with the patient in an upright position or even in a standing position. It is preferable to examine the internal jugular venous pressure and pulse. In adults, particularly in elderly patients, the external jugular venous pressure may be elevated due to partial obstruction at the level of the external jugular venous bulb due to partial thrombosis or even obstruction by the platysma muscle. The internal jugular venous pulse usually is located medial to the mandibular portion of the sternomastoid muscle. The proximal internal jugular venous pulse is located in the supraclavicular area between the two proximal heads of the sternomastoid muscle. Both right and left jugular venous pulsations need to be examined, because sometimes, disparity between left and right internal jugular venous pressures can be recognized. Occasionally in elderly patients, the left internal jugular venous pressure is higher than the right internal jugular venous pressure because of the partial obstruction of the left innominate vein by unfolded aorta. In these circumstances, with inspiration and descent of the diaphragm, partial obstruction of the left innominate vein is relieved, and the pressures in the right and left internal jugular veins become equal.

At the bedside, venous pulsation needs to be differentiated from carotid artery pulsation. By inspection, the venous pulse is characterized by a sharp inward movement, whereas the arterial pulse is characterized by a sharp outward movement. During inspection, the venous pulse is also recognized by its double undulation character in sinus rhythm. In the presence of atrial fibrillation, the double undulation character of the venous pulse is lost due to the absence of an 'a' wave associated with atrial systole. The venous pressure and the amplitude of the venous pulse can be decreased or increased by appropriate maneuvers. The pressure and amplitude can be decreased by raising the level of the head and trunk above the level of the right atrium (in a sitting or standing position), or they can be increased by enhancing the venous return to the right side of the heart by raising the legs or by abdominal compression. In the presence of low systemic venous pressure, when a patient is examined in a head-down position, it is possible to recognize the venous pulsation in the neck. When a pulsation in the neck is recognized, a gentle to moderate compression—by the fingers or stethoscope tubes—at the root of the neck obliterates the venous pulse, but the arterial pulse remains visible. This maneuver is extremely useful for differentiating between arterial and venous pulsations. Normally during inspection, the jugular venous pulse amplitude decreases during inspiration, whereas the arterial pulse amplitude does not change during respiration.

After recognizing the venous pulse, the venous pressure is estimated by noting the height of the oscillating top of the venous pulse above the sternal angle. Right atrial pressure is approximated by adding 5 cm to the height of the venous column, as it is assumed that the right atrium is located about 5 cm below the sternal angle. The normal right atrial pressure is <9 cm of water. If the jugular venous pressure is increased in the absence of obvious pulsation, it is desirable to exclude superior vena cava obstruction, which does not permit transmission of right atrial pulsation to the internal jugular veins. If pulsation of the neck veins can be recognized, the estimated venous pressure can be used to estimate right atrial pressure. It should be recognized that although jugular venous pressure reflects right atrial pressure, the cause of elevated right atrial pressure cannot be determined by simply noting the height of the jugular venous pulse. The character of the venous pulse and other physical findings need to be incorporated to assess the cause of elevation of systemic venous and right atrial pressures. The normal jugular venous pulse wave or right atrial pressure wave recordings usually consist of three positive waves ('a,' 'c,' and 'v') and two negative waves ('x' and 'y' descents)(Fig. 15.3). The 'a' wave is caused by transmitted right atrial pressure to the jugular veins during right atrial systole. The 'a' wave in the jugular venous pulse is appreciated by its occurrence just prior to the left ventricular ejection, which is recognized by simultaneous palpation of the carotid pulse upstroke. At the bedside, simultaneous palpation of the carotid pulse upstroke and inspection of the venous pulse give the impression that the 'a' wave of the venous pulse and the carotid pulse upstroke occur out of phase. On the other hand, the prominent 'v' wave in the venous pulse occurs more or less simultaneously with the carotid pulse upstroke. Atrial relaxation initiates the descent of the 'a' wave. Rarely, when the PR interval is markedly prolonged, the descent may continue until a plateau is reached: the 'z' point, which occurs just prior to the ventricular systole. The descent after atrial systole usually is interrupted by the 'c' wave. In the right atrial pressure pulse, the 'c' wave is recognized with the onset of right ventricular systole and occurs from bulging of the tricuspid valve into the right atrium. It should be emphasized, however, that the 'c' wave in the jugular venous pulse probably results from transmission of the carotid artery pulsation and not from the transmission of the right atrial 'c' wave. The 'v' wave is caused by the rise in right atrial and jugular venous pressure due to continued inflow of blood to the venous system during right ventricular systole when the tricuspid valve is still closed. Although in right atrial and jugular venous pressure tracings, the peak of the normal 'v' wave occurs immediately after ventricular systole; at the bedside, the normal or abnormal 'v' wave coincides with the carotid pulse upstroke and downstroke. Although the regurgitant wave of tricuspid regurgitation (a prominent 'v' wave) occurs earlier and coincides with the beginning of left ventricular ejection, at the bedside the tricuspid regurgitant wave is appreciated simultaneously with the carotid pulse upstroke (Fig. 15.3).

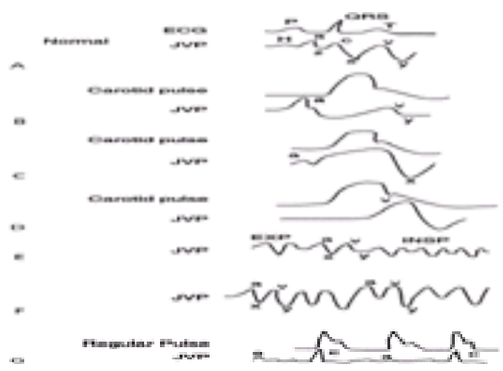


FIGURE 15.3 Schematic illustrations of a normal jugular venous pulse (JVP) and a few commonly encountered abnormalities of the JVP. **A:** Normal venous pulse along with electrocardiogram (ECG). The 'a' wave associated with right atrial systole occurs after the P wave and just before the upstroke of the carotid pulse. Normally, 'a' wave is dominant and appears more obvious during inspiration. During simultaneous palpitation of the carotid pulse at the bedside, an impression of "out of phase" between the 'a' wave and the carotid pulse upstroke is appreciated. During right atrial relaxation, the venous pulse descends and may continue up to a plateau interval (z) or can be interrupted by the 'c' wave, which is produced by the bulging of the tricuspid valve into the right atrium at the onset of the isovolumic systole and also transmitted from the carotid pulse when observed in the neck. After the 'c' wave, the venous pulse descends (x), which results from atrial relaxation. The 'v' wave occurs during right atrial filling with closed tricuspid valve and during right ventricular ejection. After the peak of the 'v' wave, which corresponds to the T

wave of the ECG, right atrial pressure exceeds right ventricular diastolic pressure, which causes opening of the tricuspid valve, rapid filling of the right ventricle, and subsequent ‘y’ descent. When diastole is long (e.g., with a slow heart rate), the ‘y’ descent may be followed by a brief positive wave (H) or a plateau. It should be recognized that, at the bedside, it is difficult to appreciate the ‘x’ descent, H wave, and ‘z’ wave; usually only ‘a’ and ‘v’ waves and ‘y’ descents are appreciated. **B:** A prominent ‘a’ wave precedes the carotid pulse upstroke; when jugular venous pulse is inspected during simultaneous palpitation of the carotid pulse upstroke, an impression of “out of phase” between pulses is appreciated at the bedside. Once a prominent ‘a’ wave is recognized, an increased resistance to right ventricular filling during atrial systole (e.g., tricuspid stenosis) and right ventricular hypertrophy from right ventricular outflow obstruction should be suspected. In adults, however, pulmonary hypertension is the most frequent cause. **C:** Prominent ‘v’ wave (regurgitant wave) followed by a sharp ‘y’ descent and coincident with the carotid pulse. At the bedside, venous pulse appears in phase with carotid pulse, and tricuspid regurgitation is the most common cause. **D:** In atrial fibrillation, a prominent ‘v’ in the JVP and even pulsatile liver in the absence of tricuspid regurgitation can be recognized in the absence of tricuspid regurgitation. **E:** In cardiac tamponade, mean jugular venous pressure (JVP) is elevated, and a lack of a sharp ‘x’ or ‘y’ descent is appreciated at the bedside. A quiet precordium and significant pulsus paradoxus are also usually appreciated. EXP, expiration; INSP, inspiration. **F:** Jugular venous pulsation in constrictive pericarditis usually reveals a marked elevation of the mean venous pressure and sharp ‘y’ descent. During inspiration, the venous pressure may not decrease and may even increase (Kussmaul’s sign). These altered characteristics of the JVP, however, are nondiagnostic of constrictive pericarditis and can be present in patients with right ventricular infarction, pulmonary embolism, restrictive cardiomyopathy, and severe tricuspid regurgitation. **G:** In a patient with a slow regular pulse, appreciation of irregular cannon waves (‘c’) in the jugular venous pulse suggests complete atrioventricular block.

The descending limb of the ‘v’ wave—the ‘y’ descent—is caused by the opening of the tricuspid valve and the rapid inflow of blood to the right ventricle from the right atrium. The ‘y’ descent is almost always recognized in the jugular venous pulse, and it follows the ‘v’ wave.

During examination of the jugular venous pulse at the bedside, if a prominent ‘a’ wave is appreciated, the conditions that are associated with increased resistance to right atrial emptying during atrial systole should be considered. The ‘a’ waves need to be distinguished from regular cannon waves, which occur in junctional rhythm or ventricular tachycardia with retrograde ventriculoatrial conduction. Cannon waves occur during atrial systole with closed tricuspid valve. Cannon waves, therefore, occur concurrently with the onset of ventricular systole (i.e., concurrently with carotid pulse upstroke). Cannon waves are distinguished from ‘v’ waves by lack of obvious ‘y’ descents that follow ‘v’ waves or regurgitant waves. In the presence of a regular pulse, if irregular cannon waves are recognized by a sudden appearance of a large positive wave coincident with ventricular systole (with carotid upstroke), atrioventricular dissociation should be suspected. Regular cannon waves also occur in patients with a prolonged PR interval when atrial systole occurs during the preceding ventricular systole. However, more frequent causes of regular cannon waves are junctional rhythm and ventricular tachycardia with retrograde conduction.

In an adult cardiac patient, when a prominent ‘a’ wave with large amplitude is appreciated, it is desirable to exclude tricuspid valve obstruction; this can be done by noting absence of a mid-diastolic rumble along the lower left sternal border, which increases in intensity during inspiration. Although in severe tricuspid stenosis the ‘y’ descent is abbreviated and presystolic hepatic pulsations can be observed, such degree of tricuspid stenosis is rarely encountered in adult patients. It should also be emphasized that isolated tricuspid stenosis is almost never encountered in rheumatic heart disease, and rheumatic tricuspid stenosis occurs almost always in the presence of mitral or aortic valve disease and in patients who are usually in atrial fibrillation. Thus, in rheumatic tricuspid stenosis, it is uncommon to appreciate a prominent ‘a’ wave. In adult cardiac patients, if isolated tricuspid stenosis is recognized with a prominent ‘a’ wave (in sinus rhythm) with a mid-diastolic rumble along the lower left sternal border that increases in intensity during inspiration (Carvello’s sign), right atrial myxoma or carcinoid heart disease should be considered in the differential diagnosis. However, the most common cause of a prominent ‘a’ wave in adults is right ventricular hypertrophy, which offers increased resistance to right atrial emptying during right atrial systole. Right ventricular hypertrophy may result from a right ventricular outflow tract obstruction, such as pulmonary valve stenosis or precapillary or postcapillary pulmonary hypertension. Significant pulmonary valve stenosis can be easily diagnosed by noting a long ejection systolic murmur, which is heard best over the left second intercostal space, a pulmonary ejection sound, and a widely split S_2 with reduced intensity of the pulmonary component of the S_2. Pulmonary stenosis is an infrequent cause of right ventricular hypertrophy in adult patients, and the most common cause of right ventricular hypertrophy is chronic pulmonary arterial hypertension. Pulmonary hypertension is also easily recognized at the bedside by noting the increased intensity of the pulmonic component of the S_2 and its transmission to the cardiac apex (mitral area).

If a prominent ‘v’ wave in the jugular venous pulse is recognized at the bedside, tricuspid regurgitation should be suspected, and physical findings that will confirm the diagnosis should be sought. In tricuspid regurgitation, jugular venous pulse always reveals a sharp ‘y’ descent after a prominent ‘v’ wave. In severe tricuspid regurgitation, lateral pulsatile motions of the earlobes coincident with each cardiac cycle are observed in many patients. There usually is a systolic murmur either early or pansystolic in duration, which is heard best over the left third and fourth intercostal space, along the left sternal border. Tricuspid regurgitation murmur frequently radiates to the epigastrium and the right side of the sternum. The tricuspid regurgitation murmur also increases in intensity after inspiration. When the diagnosis of tricuspid regurgitation is confirmed, it is desirable to assess carefully the intensity of the pulmonic component of the S_2 to distinguish between primary and secondary tricuspid regurgitation. Secondary tricuspid regurgitation is defined when tricuspid regurgitation occurs due to right ventricular dilatation and failure secondary to pulmonary hypertension.

Occasionally, a prominent ‘v’ wave is detected in patients with atrial septal defect in the absence of pulmonary arterial hypertension and tricuspid regurgitation (19). The mechanism of the prominent ‘v’ wave in atrial septal defect is not clear; however, a concomitant increase in systemic venous return and left-to-right shunt during ventricular systole may cause a rapid increase in right atrial pressure—hence, a prominent ‘v’ wave. It should be emphasized that a prominent ‘v’ wave in patients with atrial septal defect is not followed by a sharp ‘y’ descent.

Although a sharp ‘y’ descent most frequently occurs in tricuspid regurgitation, it can be observed in constrictive pericarditis and restrictive cardiomyopathy. In constrictive pericarditis and restrictive cardiomyopathy, systemic venous pressure is elevated, and inspection of the jugular venous pulse may reveal a sharp ‘y’ descent of brief duration. In the presence of sinus rhythm, the amplitudes of the ‘a’ and ‘v’ waves are similar. In patients with atrial fibrillation, because there is no ‘a’ wave present in the venous pulse, changes in the venous pulse character may seem similar to those in tricuspid regurgitation (i.e., a ‘v’ wave followed by a ‘y’ descent). In such circumstances, it is difficult to distinguish between constrictive pericarditis, restrictive cardiomyopathy, or primary or secondary tricuspid regurgitation. However, it is easy to recognize tricuspid regurgitation by other physical findings. In constrictive pericarditis or restrictive cardiomyopathy, the jugular venous pressure does not fall appropriately or even increase during inspiration (Kussmaul’s sign) (20) (Fig. 15.3). It should be recognized that Kussmaul’s sign is not diagnostic of constrictive pericarditis or restrictive cardiomyopathy. Kussmaul’s sign can be observed in patients with right ventricular infarction (21), primary severe right ventricular failure resulting from any cause, primary or secondary severe tricuspid regurgitation, partial obstruction of the vena cava, or right atrial and right ventricular tumors; in some patients with severe congestive heart failure without tricuspid regurgitation; and, occasionally, in patients with tricuspid stenosis. It should also be emphasized that Kussmaul’s sign is uncommon and seldom noted in cardiac tamponade. The mechanism of Kussmaul’s sign has not been adequately studied; however, increased resistance to right atrial filling during inspiration seems to be a common contributory factor. For practical purposes, in patients with chronic congestive heart failure, a presence of Kussmaul’s sign should raise the possibility of constrictive pericarditis or restrictive cardiomyopathy, and appropriate evaluations should be considered. The presence of physical findings of pulmonary hypertension (e.g., a sustained systolic left parasternal lift, a loud pulmonic component of the S_2, and severe tricuspid regurgitation with pulsatile hepatic impulse) favor the diagnosis of restrictive cardiomyopathy. In contrast, lack of findings suggestive of pulmonary hypertension, a quiet precordium or presence of a prominent diastolic left parasternal impulse, and absence of hepatic pulsation favor the diagnosis of constrictive pericarditis. In constrictive pericarditis, a pericardial “knock” (similar to right-sided S_3 gallop) and, rarely, a mid-diastolic murmur are heard. It should be emphasized that when constrictive pericarditis or restrictive cardiomyopathy are suspected, appropriate investigations—particularly cardiac catheterization—should be undertaken. After confirming the presence of constrictive or restrictive hemodynamics by cardiac catheterization, magnetic resonance imaging or computed tomography are appropriate noninvasive investigations to distinguish between constrictive pericarditis and restrictive cardiomyopathy (see Chapter 54).

In patients with suspected congestive heart failure but with normal resting venous pressure, it is desirable to perform the hepatojugular reflux test (22,23). With the patient breathing normally and in the semirecumbent position, a firm pressure is applied with the palm of the hand to the upper right quadrant of the abdomen for at least 10 seconds. In normal patients, there may be a transient increase in jugular venous pressure with rapid return to or near baseline in <10 seconds. The abnormal hepatojugular reflux is defined when there is a rapid increase in jugular venous pressure that remains elevated by 4 cm or more until abdominal compression is released. During abdominal compression with increased intraabdominal pressure, there is an increase in venous return to the right atrium and right ventricle. Concurrently, there is an increase in right ventricular afterload due to upward movement of the diaphragm, which reduces the intrathoracic volume capacity. The normally functioning right ventricle handles this increase in preload and afterload, and systemic venous pressure remains normal. The dysfunctioning right ventricle, however, fails to accept this increase in preload and afterload; therefore, there is a persistent elevation of systemic venous pressure. A positive hepatojugular reflux is most frequently associated with congestive heart failure resulting from left heart failure (24). In these circumstances, an abnormal sustained elevation of right atrial pressure during hepatojugular reflux indicates incipient right heart failure or abnormal compliance of the right ventricle in the presence of intact pericardium (Fig. 15.4). It should be emphasized that a positive hepatojugular reflux is noted in patients with isolated right heart failure due to precapillary pulmonary hypertension or right ventricular infarction. The abnormalities of the venous pressure and pulse and associated suspected cardiovascular disorders are summarized in Table 15.3.

Positive hepatojugular reflux—suspect congestive heart failure, particularly left ventricular systolic dysfunction (echocardiography recommended)
Elevated systemic venous pressure without obvious 'x' or 'y' descent and quiet precordium and pulsus paradoxus—suspect cardiac tamponade (echocardiography recommended)
Elevated systemic venous pressure with sharp 'y' descent, Kussmaul's sign, and quiet precordium—suspect constrictive pericarditis (cardiac catheterization and MRI or CT recommended)
Elevated systemic venous pressure with a sharp, brief 'y' descent, Kussmaul's sign, and evidence of pulmonary hypertension and tricuspid regurgitation—suspect restrictive cardiomyopathy (cardiac catheterization and MRI or CT recommended)
A prominent 'a' wave with or without elevation of mean systemic venous pressure—exclude tricuspid stenosis, right ventricular hypertrophy due to pulmonary stenosis, and pulmonary hypertension (echo-Doppler study recommended)
A prominent 'v' wave with a sharp 'y' descent—suspect tricuspid regurgitation (echo-Doppler study or cardiac catheterization recommended to determine the etiology)

CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 15.3 ABNORMALITIES OF THE VENOUS PRESSURE AND PULSE AND THEIR CLINICAL SIGNIFICANCE

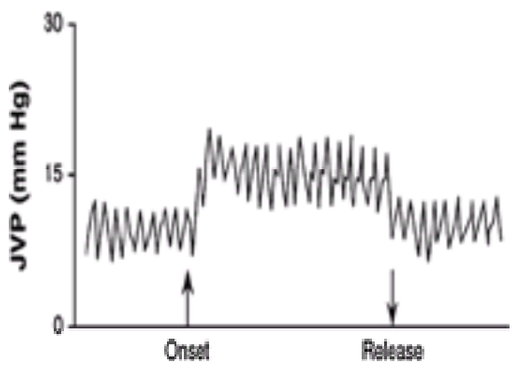


FIGURE 15.4 An example of a positive hepatojugular reflux (abdominojugular maneuver). Jugular venous pressure (JVP) increases with the onset of abdominal compression (↑) and remains elevated until it is released (⌒). In adults, the most common cause of positive hepatojugular reflux is left heart failure due to dilated cardiomyopathy. However, positive hepatojugular reflux also is observed in tricuspid stenosis and isolated right ventricular failure due to pulmonary hypertension and right ventricular infarction.

EXAMINATION OF THE PRECORDIAL PULSATIONS

Inspection and palpation of precordial pulsation during bedside cardiac evaluation may provide important diagnostic clues (1,2). Normally, a slight, abrupt, inward pulsation can be seen occasionally over the lower left parasternal area, particularly in children and thin-chested patients. Epigastric and subxyphoid pulsations are usually abnormal, although they can be seen in the absence of right heart failure in patients with chronic obstructive pulmonary disease. A pronounced epigastric or subxyphoid pulsation should raise the possibility of right ventricular failure or abdominal aortic aneurysm, and appropriate evaluations should be undertaken. A visible pulsation over the right second intercostal space or right sternoclavicular joint may indicate aneurysm of the ascending aorta. Aneurysm of the arch of the aorta may also cause suprasternal pulsation. The most common cause of right supraclavicular pulsation is a kinked, tortuous right carotid artery. A visible pulsation over the left second or third interspace may be due to dilated pulmonary artery, which may result from increased flow, such as with atrial septal defect or increased pressure, as in patients with precapillary or postcapillary pulmonary hypertension. Systolic outward parasternal and left ventricular outward movements are better appreciated by palpation. However, in many patients, an abnormal left ventricular apical impulse is visible and may result from a pronounced, sustained, outward movement or hyperdynamic left ventricular apical impulse. When cardiac pulsations are visible lateral to the left mid-clavicular line, cardiac enlargement should be suspected. Leftward displacement of the cardiac apex may occur due to fibrosis of the left lung, right-sided tension pneumothorax, or massive left pleural effusion. Absent left pericardium (a congenital anomaly) and thoracic deformity may also cause visible pulsations beyond the mid-clavicular line. Occasionally in patients with adhesive pericarditis, retraction of the ribs in the left axilla (Broadbent's sign) are recognized. In patients with severe dilated congestive cardiomyopathy, a double or triple impulse over the left ventricular apex can be recognized and represents a sustained left ventricular outward movement, a prominent atrial filling wave, and early diastolic filling impulse.

Although conventional teaching recommends palpation of the precordium to detect any abnormal impulse in the apical, mid-precordial, lower left and right parasternal, pulmonary, aortic, suprasternal, and epigastric areas, palpation of left ventricular impulse and left parasternal impulse provide the most useful information to assess changes in cardiac dynamics and function. The left ventricular apical impulse is best palpated when the patient lies in a partial left lateral decubitus position. The outward movement of the left ventricular apical impulse is normally brief and localized and does not extend significantly into the left ventricular ejection phase (Fig. 15.5). The beginning of left ventricular ejection at the bedside is appreciated by the onset of the carotid pulse upstroke. The normal outward movement of the left ventricular apical impulse recedes from the chest wall and becomes impalpable with the onset of ejection after the upstroke of the carotid pulse and during the downstroke of the carotid pulse (25). Thus, at the bedside, when carotid pulse and left ventricular apical impulse are examined concurrently, these two impulses appear out of phase or asynchronous. The sustained apical impulse is characterized by a prolonged duration of the outward movement extending into the ejection phase of the left ventricle. Usually, this outward movement is diffuse and occupies more than one intercostal space. When the carotid pulse upstroke and duration are evaluated simultaneously with the left ventricular outward movement, the sustained apical impulse appears in phase with the carotid pulse upstroke and remains palpable during the downstroke of the carotid pulse.

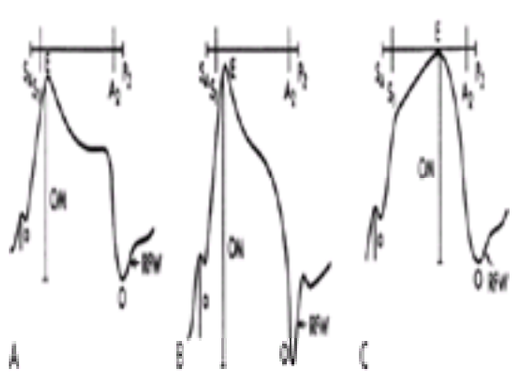


FIGURE 15.5 Schematic diagrams of normal, hyperdynamic, and sustained left ventricular impulse. Heart sounds are also illustrated. **A:** Normal apical impulse. The 'a' wave related to ventricular filling during atrial systole usually is not palpable. Similarly, the rapid filling wave (RFW) in early diastole is also not palpable. The E point, which coincides with the beginning of the left ventricular ejection, is brief in normal individuals. Normal apical impulse usually is associated with normal left ventricular ejection fraction. **B:** Hyperdynamic left ventricular impulse usually is seen in left ventricular volume overloaded conditions such as primary mitral regurgitation and aortic regurgitation. Left ventricular ejection fraction usually is normal. A palpable 'a' wave or presystolic wave indicates increased left ventricular end diastolic pressure. **C:** Sustained left ventricular impulse, which extends into the ejection phase, usually is seen in the presence of decreased left ventricular ejection fraction or when there is marked left ventricular hypertrophy. A palpable 'a' wave or early rapid filling spike is associated with increased diastolic pressure. A_2, aortic component of the second heart sound; P_2, pulmonary component of the second heart sound; S_1, first heart sound; S_4, fourth heart sound.

With a hyperdynamic apical impulse, the amplitude of the outward movement is increased, but the sequence between the onset of the carotid pulse and the outward movement remains normal. The hyperdynamic apical impulse is appreciated as a thrust of large amplitude that immediately disappears from the palpating fingers. When the duration of the ejection phase is estimated from the carotid pulse upstroke and downstroke or from the interval between the S_1 and S_2, the hyperdynamic apical impulse does not extend throughout systole. The sustained outward movement usually is felt as a heave. The duration of the outward movement of the apical impulse when it is sustained extends throughout the ejection phase. A sustained apical impulse usually is found when there is significant impairment of left ventricular

systolic function (i.e., reduced ejection fraction) (26,27). Another cause of sustained apical impulse is marked left ventricular hypertrophy resulting from systemic hypertension or left ventricular outflow tract obstruction. If, at the bedside, these conditions are excluded, a sustained apical impulse should be regarded as an indication of depressed left ventricular ejection fraction. In patients with known coronary artery disease or previous myocardial infarction, a sustained apical impulse almost invariably indicates reduced left ventricular ejection fraction. Similar hemodynamic correlates should be suspected in patients with known nonischemic dilated cardiomyopathy. In patients with angina pectoris, early systolic, late systolic, or combined early and late systolic bulges occasionally can be appreciated at the bedside when left ventricular apical impulse is analyzed carefully. These abnormal systolic motions are more frequently appreciated in patients with previous myocardial infarction. Systolic bulges occasionally may be appreciated in the absence of previous myocardial infarction and probably result from myocardial ischemia. If these abnormal apical impulses are transient and appreciated during anginal pain, reversible myocardial ischemia should be considered. At the bedside, however, these transient abnormal systolic motions are difficult to appreciate. Occasionally in patients with mitral valve prolapse, a deep notch in the systolic portion of the left ventricular apical impulse, which coincides with the mid-systolic click, is recorded in the apex cardiogram, but it is difficult to recognize at the bedside. The hyperdynamic apical impulse occurs in conditions associated with an increased stroke volume or volume overload. Hyperdynamic impulse is found in patients with hypermetabolic state, such as hyperthyroidism, anemia, primary mitral regurgitation, and aortic regurgitation, and in some patients with a patent ductus arteriosus and ventricular septal defect with a large left-to-right shunt. A hyperdynamic impulse, in general, suggests preserved left ventricular ejection fraction.

While examining the left ventricular apical impulse, particularly in the left lateral decubitus, a double impulse is felt and almost always represents a palpable ‘a’ wave (presystolic wave) and a prominent outward movement. The palpable ‘a’ wave is related to an accentuated atrial filling wave and is most frequently observed in patients with noncompliant left ventricle, such as in patients with aortic stenosis, hypertensive heart disease, or ischemic heart disease. The hemodynamic correlate of palpable ‘a’ wave is increased left ventricular end diastolic pressure. Occasionally, a palpable, rapid filling spike, which coincides with a prominent S_3 gallop, is appreciated during palpation of left ventricular apical impulse. At the bedside, this palpable early diastolic rapid filling spike is appreciated after the outward movement. The hemodynamic correlate of palpable S_3 gallop is also increased left ventricular diastolic pressure. The characteristics of the left ventricular outward movement, along with changes in the filling waves, are illustrated in Fig. 15.5.

Right ventricular impulse is appreciated by palpation of the lower left parasternal area. In children and in some adults with thin chest walls, a brief, gentle impulse may be palpable over the left third and fourth interspaces. This impulse usually is in diastole. A prolonged left parasternal impulse extending during the ejection phase (i.e., throughout the carotid pulse upstroke and downstroke or between S_1 and S_2) is distinctly abnormal and reflects right ventricular failure or right ventricular hypertrophy. It should be realized, however, that in the presence of significant mitral regurgitation, left atrial expansion during left ventricular systole may also produce a sustained systolic left parasternal impulse. Thus, at the bedside, before the diagnosis of right ventricular failure or right ventricular hypertrophy is suspected, it is necessary to exclude significant mitral regurgitation. In patients with right ventricular hypertrophy and failure, a sustained epigastric impulse is also appreciated. An inward systolic movement and an outward diastolic movement are sometimes appreciated in some patients with constrictive pericarditis. (28) The diastolic movement usually coincides in timing with the pericardial knock. The precise explanation for these unusual precordial impulses in constrictive pericarditis has not been clarified. It has been suggested that this unusual outward movement during isovolumic systole is inhibited by the constriction, and the outward movement during early diastole becomes accentuated. In patients with severe chronic constrictive pericarditis, however, the precordium usually is quiet, and no obvious precordial impulses are appreciated at the bedside. In patients with Ebstein’s anomaly, the precordium may also be quiet. In some patients with Ebstein’s anomaly, a right parasternal systolic outward movement resulting from a large, ventricularized right atrium is appreciated.

A left ventricular aneurysm can be associated with a systolic impulse in unusual locations, such as over the mid-precordium. Pulsation in the left second interspace usually reflects an enlarged pulmonary artery resulting from chronic severe pulmonary arterial hypertension or from increased pulmonary flow, as in atrial septal defect. Occasionally, a higher-frequency impulse is appreciated coincident with the downstroke of the carotid pulse in the left second interspace and usually reflects an accentuated pulmonary component of the S_2, as in patients with severe chronic pulmonary hypertension. A pulsatile mass in the suprasternal notch may indicate aneurysm of the ascending aorta. Aneurysm of the ascending aorta is sometimes associated with the tracheal tug, which is appreciated when the trachea is slightly pulled upward and the pulsation in the trachea is recognized with each cardiac cycle. A pulsatile mass in the right supraclavicular area is most frequently caused by a kinked right carotid artery. Such an abnormal impulse may indicate the presence of atherosclerotic peripheral vascular disease.

AUSCULTATION

A systematic and careful cardiac auscultation (1,29) is essential for the diagnosis of a cardiovascular abnormality. Auscultation should be performed whenever possible with the patient in the left lateral decubitus, supine, and sitting positions. However, in many clinical circumstances, particularly with patients with critical illness in intensive-care units, such approaches are not practical. Auscultation can begin over the cardiac apex—the so-called mitral area—and one can proceed counterclockwise to the left fourth interspace (tricuspid area), left third interspace, left second interspace, pulmonic area and right second interspace (aortic area), sometimes, over the right fourth interspace adjacent to the sternal borders, and, finally, over the epigastrium. It is customary to assess the intensity and splitting of the S_1 and S_2 and the presence of S_3 and the fourth heart sound (S_4). It is also desirable to listen for the presence of abnormal early systolic, mid-systolic, early diastolic, and late diastolic heart sounds. After the analysis of the normal and abnormal heart sounds, heart murmurs, if present, are analyzed. When certain diagnoses are suspected, areas of auscultation should include the left axilla, thoracic and lumber spine, vortex (mitral regurgitation), axilla and back (pulmonary artery branch stenosis), posterior chest (coarctation of aorta), left infraclavicular area (patent ductus arteriosus), and sternoclavicular joints (venous hum).

First Heart Sound

For the analysis of the S_1, the diaphragm is used, and auscultation is performed over the mitral and tricuspid areas. The intensity of the S_1 is determined primarily by the intensity of mitral component (M_1) of the S_1. Several factors contribute to the intensity of M_1 (30,31). The position of the mitral valve at the onset of systole, the rate of mitral valve closure, the mobility of the mitral valve, the PR interval, and the dP/dT of the left ventricle—all are important factors that influence the intensity of M_1. Of all these contributing factors, the position of the atrioventricular valves at the beginning of the ventricular systole, and the velocity of closure seem to be the major determinants of the intensity of the S_1. When the mitral valve remains fully open until the very end of diastole and then closes rapidly, the intensity of M_1 is increased. The greater the distance that the mitral valve leaflets have to travel from the open to closed positions and the greater the velocity of closure of the mitral valve, the louder the S_1. In clinical practice, if a substantial increase in the intensity of the S_1 is recognized at the bedside, an increase in transmitral valvular pressure gradient (e.g., in mitral stenosis), increased transvalvular flow (e.g., in the presence of large left-to-right shunt due to ventricular septal defect or a patent ductus arteriosus), a very short PR interval (e.g., in preexcitation syndrome), or markedly shortened left ventricular diastole (e.g., in tachycardia) should be suspected. When mitral valve obstruction and short PR interval are excluded, increased intensity of the S_1 may reflect an increased left ventricular dP/dT, as during adrenergic stimulation. The increased intensity of the tricuspid valve closure sound (T_1), which is appreciated over the left third and fourth interspaces along the lower sternal border, usually occurs when the transtricuspid valve pressure gradient is increased, as in patients with tricuspid stenosis or right atrial myxoma. A substantial increase in diastolic flow across the tricuspid valve, as in large atrial septal defect, may also increase the intensity of the T_1. Intermittent increased intensity of the S_1 in the presence of regular pulse and heart rhythms indicates atrioventricular dissociation, results from varying PR intervals, and is associated with variable rates of closure of atrioventricular valves. An increase in intensity of the S_1 has been observed in some patients with mitral valve prolapse, despite mitral regurgitation, and probably reflects increased adrenergic activity (32).

HEART SOUNDS

Audio 15.2 Auscultation performed at the apex in a 34-year-old man. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.3 Auscultation performed at the apex in a 34-year-old man. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.4 Auscultation performed at the apex in a 34-year-old man. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.5 Auscultation performed at the apex in a 34-year-old man. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Intensity of the First Heart Sound

A decrease in intensity of the S_1 can result from a substantial loss of the tissue mass of the atrioventricular valves, as occurs in severe rheumatic tricuspid and mitral valve diseases and bacterial endocarditis. This decrease can also result from the marked restriction of the movement of the atrioventricular valves due to calcification or sclerosis of the valve leaflets, which occasionally occurs in patients with rheumatic mitral valve stenosis and may be associated with decreased—rather than increased—intensity of the S_1. When the PR interval is prolonged (i.e., exceeding 200 ms), the intensity of the S_1 decreases because semiclosure of the mitral valve occurs after atrial systole and before ventricular systole begins. In severe aortic regurgitation, premature closure of the mitral valve may occur due to a rapid rise in left ventricular diastolic pressure, and the mitral valve may be virtually closed at the onset of ventricular systole, resulting in a markedly decreased intensity of the S_1. In patients with acute severe aortic regurgitation associated with marked increase in left ventricular diastolic pressure, the S_1 may be inaudible and should be regarded as an indication for surgical intervention (33). A substantial increase in left ventricular diastolic pressure and a reduction in transmitral valve pressure gradient are important mechanisms for decreased intensity of the S_1 in the absence of prolonged PR interval and restricted mitral valve mobility. Impaired pump and contractile function, as in dilated cardiomyopathy, is an important cause of reduced intensity of the S_1. In these patients, left ventricular diastolic pressure is also frequently elevated. In clinical practice, decreased intensity of the S_1 in the absence of prolonged PR interval should be regarded as indicative of increased left ventricular diastolic pressure with or without impairment of contractile function. Occasionally, decreased intensity of S_1 is observed in isolated left bundle branch block, probably reflecting impaired left ventricular function (34).

A variable intensity of the S_1 is common in atrial fibrillation. However, atrial fibrillation can be suspected at the bedside from analysis of the arterial pulse, which is irregularly irregular. Auscultatory alternans—in which the S_1 is soft and loud in intensity with alternate beats—is a rare finding of severe cardiac tamponade and is almost always associated with electrical alternans and pulsus paradoxus. Auscultatory alternans also has been observed in patients with pulsus alternans, in whom beat-to-beat alteration in the left ventricular dP/dT occurs (35).

Decreased conduction of sounds through the chest wall reduces the intensity of the S_1 in patients with chronic obstructive pulmonary disease, obesity, and pericardial effusion. In these circumstances, all heart sounds appear soft and distant. One of the practical difficulties in assessing the intensity of the S_1 at the bedside is the lack of any objective method to standardize its intensity. The S_1 normally is loudest at the apex and along the lower left sternal border. In the tricuspid and mitral areas, the intensity of the S_1 is louder than the intensity of the S_2. If the S_1 is softer than the S_2 over the mitral or tricuspid area, it can be assumed that the intensity of the S_1 is reduced. On the other hand, if the S_1 is much louder than the S_2 over the left or right second interspace, the intensity of the S_1 is likely to be increased.

Splitting of the First Heart Sound

The splitting of the S_1 (36) is best appreciated along the left parasternal areas and is most frequently observed in the presence of complete or incomplete right bundle branch block. In right bundle branch block, the S_2 is also widely split, and the A_2-P_2 interval widens during inspiration. Delayed closure of T_1 due to increased flow across the tricuspid valve (atrial septal defect) or increased transtricuspid valve pressure gradient (tricuspid stenosis) causes wide splitting of S_1 without splitting of the S_2. The widely split S_1 is recognized in patients with Ebstein's anomaly, not only because of right ventricular conduction disturbances but also from the delayed closure of the tricuspid valve due to atrialization of the right ventricle. In Ebstein's anomaly, the S_2 is also widely split, and, frequently, systolic and diastolic, scratchy, superficial sounds—so-called "sail sounds"—are present (37). In adult cardiac patients, however, Ebstein's anomalies are encountered infrequently. The diagnosis of Ebstein's anomaly can only be suspected at the bedside and needs to be confirmed by other investigations, including echocardiography. The reversed splitting of the S_1 is extremely rare and difficult to recognize at the bedside. Reversed splitting of the S_1 can result from severe mitral stenosis and is rarely due to left bundle branch block. However, in left bundle branch block, it is easier to appreciate the reversed splitting of the S_2 than that of the S_1. In patients with severe mitral stenosis, delayed closure of the mitral valve contributes to the reversed splitting of the S_1. However, earlier closure of the tricuspid valve resulting from secondary tricuspid regurgitation is also necessary for the reversed splitting of the S_1 in mitral stenosis. The severity of mitral stenosis at the bedside also is not diagnosed based on the presence or absence of reversed splitting of the S_2. The duration of the diastolic murmur, associated pulmonary hypertension, and the A_2–opening snap interval are assessed to determine the severity of mitral stenosis at the bedside. Furthermore, in all patients with suspected mitral valve obstruction, echocardiographic evaluation is mandatory.

Sounds Mimicking the First Heart Sound

At the bedside, it is necessary to distinguish between splitting of the S_1 and the presence of a loud atrial sound preceding the S_1 (Fig. 15.6). The left ventricular atrial sound (S_4) usually is localized over the cardiac apex and is heard best with the bell of the stethoscope. When auscultation is started with the use of the bell over the cardiac apex, S_1 and S_4 are heard easily. When the bell is converted to the diaphragm by applying firm pressure over the underlying skin, the S_4 decreases in intensity or disappears, whereas the splitting of the S_1 becomes more obvious.

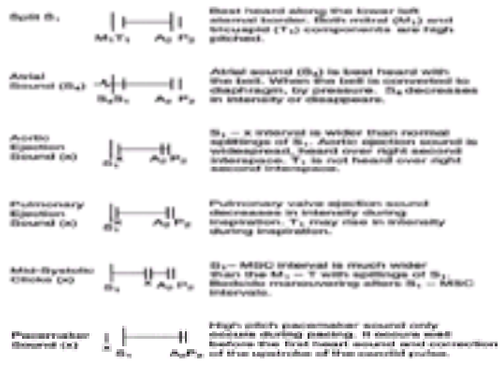


FIGURE 15.6 The causes and differential diagnosis of the first heart sound (S_1). A_2, aortic component of the second heart sound; P_2, pulmonary component of the second heart sound.

The combination of a systolic ejection sound and S_1 may also appear as split S_1. The S_1 and the ejection sound interval usually is greater than the normal M_1-T_1 interval. The aortic ejection sound is widely transmitted and, therefore, can be heard easily over the aortic area, along the left sternal border, and over the cardiac apex. On the other hand, the split S_1 is best appreciated along the lower left sternal border, over the left third and fourth interspaces. Pulmonary valvular ejection sounds can

be easily distinguished from T_1. Pulmonary ejection sounds are usually localized and heard best over the left second interspace. Pulmonary valvular ejection sounds decrease in intensity during inspiration, whereas the intensity of T_1 remains unchanged or increases after inspiration.

A combination of S_1 and a mid-systolic click due to mitral valve prolapse is rarely confused with a split S_1. The interval between S_1 and a mid-systolic click is much greater than the interval between M_1 and T_1. Furthermore, the S_1 to mid-systolic click interval can be changed by maneuvers such as standing and squatting. These maneuvers, however, usually do not alter the interval between M_1 and T_1 significantly enough to be appreciated at the bedside. The presence of a pacemaker sound preceding S_1 may seem like a widely split S_1. The pacemaker sound results from the stimulation of the intercostal muscles during pacing, precedes S_1, and occurs well before the upstroke of the carotid pulse (38). Furthermore, the pacemaker sound disappears with discontinuation of pacing. The causes and the differential diagnosis of the abnormalities of the S_1 are summarized in Table 15.4.

TABLE 15.4 USUAL CAUSES OF THE ABNORMALITIES OF THE FIRST HEART SOUND

SECOND HEART SOUND

The genesis of the S_2 appears to be related to closure of the aortic and pulmonary valves; thus, the S_2 traditionally is regarded to consist of two components designated as A_2 (associated with aortic valve closure) and P_2 (associated with pulmonary valve closure). The first high-frequency component of A_2 and P_2 is coincident with completion of closure of these semilunar valves (39). It should be appreciated that A_2 and P_2 are not produced by the clapping together of the valve leaflets but by the sudden deceleration of retrograde flow of the blood column in the aorta and pulmonary artery when the maximum tensing of these valve leaflets occurs. The abrupt deceleration of flow produces the vibration of the cardiohemic system, and the lower frequency vibrations are coincident with the incisura of the great vessels, whereas the higher frequency components cause A_2 and P_2. It should be recognized that left and right ventricular ejection ceases before the closure of the aortic and pulmonary valves.

Aortic Component

The amplitude and intensity of A_2 and P_2 are directly proportional to the rate of change of the diastolic pressure gradient that develops across the semilunar valves—that is, the driving force that accelerates the blood mass retrograde into the base of the great vessels (40). The rate of pressure decline in the ventricle and the level of the diastolic pressure in the great vessels determine the pressure gradient in the root of the great vessels. Normally, the diastolic pressure gradient in the aorta is significantly greater than that in the pulmonary artery, which explains the normal increased intensity of A_2 compared with that of P_2. The most common cause of the increased intensity of A_2 is systemic hypertension. Occasionally, in addition to the increased intensity, a tambour quality of A_2 is recognized in systemic hypertension. Such altered quality of A_2 also is appreciated in some patients with aneurysm of the ascending aorta without aortic insufficiency. The decreased intensity of A_2 most frequently occurs from immobility of calcified, sclerosed aortic valves in calcific aortic stenosis. It should be appreciated, however, that the degree of intensity of A_2 does not correlate well with the severity of aortic stenosis. In aortic regurgitation resulting from fibrosed and retracted aortic valve leaflets, as in syphilitic aortic regurgitation, the aortic component of the S_2 also is decreased in intensity. Normally, A_2 is widely transmitted and well heard at the cardiac apex. However, in patients with significant mitral regurgitation, A_2 may be drowned at the cardiac apex by the regurgitant murmur that frequently extends beyond the aortic valve closure. However, in these circumstances, the intensity of A_2 can be appreciated by listening over other areas of the precordium.

Pulmonic Component

The pulmonic component of the S_2—that is, P_2—is softer than A_2 and is rarely audible at the apex. Increase in the intensity of P_2 indicates pulmonary hypertension, irrespective of its etiology. When there is a substantial increase in its intensity, P_2 is also heard at the cardiac apex. Without pulmonary hypertension, it is uncommon for the P_2 to be transmitted to the cardiac apex. In only approximately 5% of healthy subjects, and only when they are young (i.e., under 20 years old), can P_2 be recorded by phonocardiography over the cardiac apex (41). Although an increased intensity of P_2 is the most important physical finding for the diagnosis of pulmonary arterial hypertension, other physical findings that support the diagnosis should be searched for at the bedside. A prominent ‘a’ wave in the jugular venous pulse, a sustained left parasternal outward impulse, epigastric pulsation, a palpable P_2 over the left second interspace, and auscultatory features of tricuspid regurgitation and secondary pulmonary insufficiency all support the diagnosis of significant pulmonary arterial hypertension. These secondary findings, however, result from severe pulmonary hypertension and are not present in all patients.

When the cardiac apex is occupied by the right ventricle—as in patients with large atrial septal defects—P_2 can be heard at the apex, even when the pulmonary artery pressure is not increased. Similarly, in patients with primary tricuspid regurgitation without pulmonary hypertension, P_2 occasionally is heard at the apex. In patients with a widely split S_2 due to right bundle branch block, P_2 rarely can be heard at the apex in the absence of pulmonary hypertension.

Decreased intensity of P_2 results from a reduction in the pulmonary artery diastolic pressure, as in patients with pulmonary valve stenosis. Decreased intensity of P_2 or absence of P_2 may also occur from the loss of the pulmonary valve leaflets or from the congenital absence of the pulmonary valves. In these clinical conditions, however, a loud pulmonary insufficiency murmur is appreciated over the precordium.

Splitting of the Second Heart Sound

The sequence of closure of the aortic and pulmonary valves (i.e., the splitting of A_2 and P_2 during respiratory phases) should be analyzed whenever feasible. Normally, A_2 precedes P_2 during expiration and inspiration. The A_2-P_2 interval also increases considerably during normal inspiration.

In adults, the splitting of the S_2 during the expiratory phase of respiration usually is not appreciated at the bedside, because the degree of splitting usually does not exceed 30 ms. However, during inspiration, the splitting is easily appreciated, particularly in the semirecumbent position and even in elderly patients. The splitting of the S_2 should be assessed during normal respiration with the diaphragm of the stethoscope over the left second and third interspaces close to the sternal border. Normally, the aortic component of the S_2 (A_2) precedes the pulmonic component (P_2). The normal splitting of the S_2 primarily results from the differences between pulmonary artery and aortic “hangout” times (42). The left ventricular ejection starts a few milliseconds before the onset of right ventricular ejection because of the earlier onset of left ventricular depolarization. The earlier onset of left ventricular ejection certainly contributes to the earlier completion of left ventricular ejection. However, this earlier completion of left ventricular ejection only accounts for 10 to 15 ms of the degree of splitting of the S_2. The hangout time is the interval between the end of ventricular ejection and the closure of the semilunar valves. The hangout time in the aorta is considerably shorter than that of the pulmonary artery. The hangout time in the pulmonary artery may be as long as 60 to 70 ms; the hangout time in the aorta may be as short as 15 to 30 ms. The difference between the pulmonary artery and aortic hangout times primarily determines the degree of splitting of the S_2, both in physiologic situations and in many pathologic conditions (Fig. 15.7). The hangout time also is determined by the compliance of the aorta and the pulmonary artery. Normally, the aorta is much stiffer than the pulmonary artery—a characteristic that accounts for the shorter hangout time in the aorta than in the pulmonary artery. When the pulmonary artery compliance decreases, as in chronic pulmonary

hypertension, the hangout time also decreases; thus, the degree of splitting of the S_2 may actually be shorter in the presence of significant chronic pulmonary arterial hypertension. The normal inspiratory splitting of the S_2 is explained by an increase in the pulmonary hangout time during inspiration that results from an increase in right ventricular stroke volume. An increase in the right ventricular ejection time after inspiration also contributes, to some extent, to the inspiratory splitting of the S_2. More negative intrathoracic pressure during inspiration is associated with an increased venous return to the right ventricle and an increased right ventricular stroke volume, which increases the ejection time and delays the P_2. During inspiration, A_2 occurs slightly earlier due to slight reduction of left ventricular ejection time associated with a transient, slight reduction of left ventricular stroke volume. After one to three cardiac cycles, the increase in right ventricular stroke volume with inspiration is followed by a similar increase in stroke volume of the left ventricle associated with a slight increase in left ventricular ejection time. During normal respiration, prolongation of left ventricular ejection time and a delayed A_2 usually occur during the expiratory phase, whereas lengthening of the right ventricular ejection time and delay in P_2 coincide with the inspiratory phase.

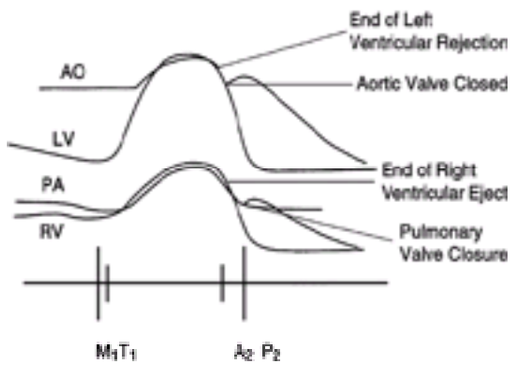


FIGURE 15.7 Schematic illustrations of “hangout” times, which are the time intervals between the end of ventricular ejection and closure of the aortic valve (A_2) and closure of the pulmonary valve (P_2). The hangout time is primarily determined by the compliance of the great vessels and the stroke volume ejected into the great vessels. The aortic hangout time is much shorter (aorta is less compliant than the pulmonary artery) than that of the pulmonary artery. The differences between the pulmonary and aortic hangout time may explain physiologic or pathologic splitting of the second heart sound. The mitral component (M_1) and the tricuspid component (T_1) of the first heart sound and left ventricular (LV), right ventricular (RV), aortic (AO), and pulmonary artery (PA) pressure waveforms are also illustrated.

Wide Splitting of the Second Heart Sound

When splitting of the S_2 is appreciated during expiration, abnormal wide splitting of the S_2 should be suspected. The longer the A_2-P_2 interval during expiration, the more abnormal is the splitting of the S_2. The inspiratory increase in the degree of splitting of the S_2 indicates the presence of physiologic delay in the pulmonary valve closure sound. The widely split S_2 during expiration (with further increase in splitting during inspiration) most frequently occurs in right bundle branch block. In right bundle branch block, the S_1 also is frequently split. A widely split S_2 may be present in Wolff-Parkinson-White syndrome with left ventricular preexcitation. Left ventricular pacing also produces right bundle branch block–types of conduction disturbances and is associated with widely split S_2. Premature beats and an idioventricular rhythm of left ventricular origin with QRS complex of right bundle branch block morphology are also associated with wide splitting of the S_2. The wide splitting of the S_2 in conduction disturbances occurs from delayed activation of the right ventricle and consequently delayed completion of right ventricular ejection.

The wide splitting of the S_2 may also result from increased resistance of right ventricular ejection, as in patients with pulmonary valve stenosis, infundibular stenosis, supravalvular stenosis, and pulmonary branch stenosis. In pulmonary valve stenosis, the intensity of the P_2 is substantially decreased, and pulmonary valve stenosis can be easily recognized from the presence of a long ejection systolic murmur. In pulmonary valve stenosis, the degree of expiratory splitting of the S_2 is directly related to the severity of stenosis and right ventricular systolic hypertension (43). If the expiratory splitting of the S_2 is approximately 40 to 50 ms, right ventricular systolic pressure is also 40 to 50 mm Hg. When the degree of splitting of the S_2 exceeds 70 to 80 ms, the right ventricular systolic pressure is extremely high and may exceed 80 mm Hg. In patients with pulmonary branch stenosis, the intensity of P_2 is increased, and, frequently, unilateral or bilateral continuous murmurs are appreciated. In adults, the most common cause of obvious expiratory splitting of the S_2 with increased intensity of P_2 is precapillary or postcapillary pulmonary arterial hypertension. In pulmonary hypertension, although the expiratory splitting is obvious, the degree of splitting is less than that expected from the degree of pulmonary hypertension. The relatively shorter splitting of the S_2—even in patients with severe pulmonary hypertension—is related to the substantial reduction in pulmonary hangout time due to decreased pulmonary arterial compliance. For the same reason, in patients with severe pulmonary hypertension, the magnitude of inspiratory widening of the interval between A_2 and P_2 is smaller. Wide expiratory splitting of the S_2 may also result from isolated reduction of the left ventricular ejection time, as in patients with hemodynamically significant mitral regurgitation (44). In patients with severe mitral regurgitation with relatively preserved left ventricular ejection fraction, as in patients with primary mitral regurgitation, left ventricular forward stroke volume may decrease with a substantial shortening of left ventricular ejection time and an earlier occurrence of A_2 (45). In patients with unrestricted ventricular septal defect with increased pulmonary flow and decreased pulmonary vascular resistance, a widely split S_2 is appreciated due to a decrease in left ventricular ejection time and an increase in pulmonary artery hangout time (46). In constrictive pericarditis, a wide inspiratory splitting of the S_2 occasionally is observed, and it results from marked reduction in left ventricular ejection time during inspiration (47). Decreased impedence of the pulmonary vascular bed resulting in an increase in pulmonary hangout time may also cause a wide splitting of the S_2 (29). In patients with idiopathic dilatation of the pulmonary artery, mild pulmonary valve stenosis, atrial septal defect with normal pulmonary artery pressure, and postoperative atrial septal defect, the increase in pulmonary hangout time is the principal mechanism for the wide splitting of the S_2. In patients with a primum or secondary type of atrial septal defect and also with common atrium, the interval between A_2 and P_2 during expiration and inspiration may not change significantly (widely split fixed S_2). The mechanism of wide expiratory splitting of the S_2 appears to be due to isolated shortening of the ejection time of the left ventricle, whereas the right ventricular ejection time remains normal. There is also an increase in the pulmonary hangout time, which results from the decreased pulmonary vascular impedence. During inspiration, P_2 is delayed, as in healthy patients, due to prolongation of the right ventricular ejection time. However, in atrial septal defect, A_2 does not occur earlier, suggesting the absence of inspiratory shortening of left ventricular ejection time (48). This lack of shortening of left ventricular ejection time may result from the transient increase in the venous return to the left ventricle due to a reduction in the magnitude in the left-to-right shunt. Thus, the A_2-P_2 interval may remain relatively constant during normal expiration and inspiration.

In adults, the most frequent cause of fixed splitting of the S_2 is the occurrence of severe right ventricular failure when there is little or no increase in right ventricular stroke volume after inspiration. The degree of splitting of the S_2 during expiration, however, usually is normal in the absence of right bundle branch block. In patients with severe right ventricular failure and right bundle branch block, a wide fixed splitting of the S_2 frequently is appreciated at the bedside.

Paradoxical Split of the Second Heart Sound

Reversed or paradoxical splitting of the S_2 is recognized when splitting of the S_2 during expiration is appreciated. However, during inspiration, the A_2-P_2 interval shortens, and the S_2 may appear single (48). The reversed splitting of the S_2 almost always occurs due to a delay in A_2. The sequence of these closure sounds is reversed, with P_2 preceding A_2 during expiration. During inspiration, P_2 moves toward A_2, and the splitting of the interval narrows. The reversed splitting of the S_2 may occur due to a delay in the electrical activation of the left ventricle, which results in a delay in the onset and completion of left ventricular ejection. The most common cause of reversed splitting of the S_2 in adults is left bundle branch block, which is associated with a prolonged electromechanical interval. Right ventricular ectopic beats and right ventricular pacing produce a delay in the onset of left ventricular contraction and result in reversed splitting of the S_2. The Wolff-Parkinson-White syndrome with right ventricular preexcitation is associated with reversed splitting of the S_2. In all of these conditions, conduction disturbance resulting in delayed activation of the left ventricle causes a delay in the onset and completion of left ventricular ejection and, thus, results in reversed splitting of the S_2. It should be appreciated that left ventricular systolic function may also be impaired and can accompany conduction disturbances (49). In these circumstances, the degree of expiratory reversed splitting may be significantly greater than when the conduction disturbances are present without myocardial dysfunction.

Reversed splitting of the S_2 may occur due to prolongation of the left ventricular ejection time, which is due to a selective increase in the left ventricular forward stroke volume or a marked increase in resistance to left ventricular ejection. A selective increase in left ventricular forward stroke volume can occur in patients with significant

aortic regurgitation or with patent ductus arteriosus with a large left-to-right shunt. Increased resistance to left ventricular ejection producing a reversed splitting of the S_2 occurs in patients with significant aortic stenosis and obstructive hypertrophic cardiomyopathy. In patients with aortic stenosis, reversed splitting in the absence of left bundle branch block indicates hemodynamically significant aortic stenosis. In patients with hypertrophic cardiomyopathy with left ventricular outflow tract obstruction, reversed splitting occurs despite significant mitral regurgitation (50). The systolic murmur associated with primary mitral regurgitation, ventricular septal defect, and hypertrophic obstructive cardiomyopathy may appear similar in character and duration at the bedside. The behavior of the S_2 may be useful in the differential diagnosis of these conditions. If the S_2 is paradoxically split in the absence of left bundle branch block, the diagnosis of hypertrophic cardiomyopathy is most likely. The presence of widely split S_2 favors the diagnosis of primary mitral regurgitation or ventricular septal defect. The reversed splitting also occurs in patients with severe chronic systemic hypertension with a marked increase in systemic vascular resistance, which increases resistance to left ventricular ejection. However, a compensatory increase in adrenergic activity and left ventricular wall thickness, which reduces left ventricular wall stress, may normalize left ventricular ejection time; therefore, S_2 may be normal. In systemic hypertension, the intensity of A_2 is always increased. If there is dilatation of the aortic root, a tambour quality of the A_2 frequently can be recognized. Acute elevation of systemic arterial pressure (e.g., during administration of methoxamine) has been shown to produce reversed splitting of the S_2, even in normal subjects, suggesting that acute increase in left ventricular afterload may cause a substantial prolongation of the left ventricular ejection time (51). Reversed splitting of the S_2 also has been recognized in patients with ischemic heart disease and during episodes of angina. These findings, however, are rarely encountered in clinical practice in patients with ischemic heart disease. Furthermore, the mechanism of reversed splitting in these patients remains unclear, but it may be related to a prolonged isovolumic systole of the ischemic left ventricle and an increase in left ventricular afterload. This mechanism may also be related to transient left bundle branch block. Poststenotic aortic root dilatation is associated with a decrease in the impedence in the systemic vascular bed; delayed A_2 can occur, which may contribute to the reversed splitting of the S_2 (52). Such mechanisms have also been entertained in explaining the reversed splitting of the S_2 in patients with chronic aortic regurgitation and patent ductus arteriosus. In clinical practice, however, when reversed splitting of the S_2 is clearly recognized at the bedside, it is desirable first to exclude left bundle branch block or any other conduction anomaly that can be associated with paradoxical splitting of the S_2. After exclusion of these conduction abnormalities, covert left ventricular systolic dysfunction should be suspected in the absence of left ventricular outflow tract obstruction or aortic regurgitation, which can be diagnosed easily at the bedside.

WIDELY SPLIT SECOND HEART SOUND

A marked increase in the intensity of the pulmonic component of the S_2 (P_2) with narrow expiratory splitting of the S_2 is a common and almost universally present physical finding in severe pulmonary hypertension. The degree of expiratory splitting (i.e., the A_2-P_2 interval) may even be <30 ms in patients with pulmonary hypertension, but the splitting is still clearly appreciated because of the marked increase in the intensity of P_2 (53). In some patients with pulmonary hypertension, a wide splitting with an increased amplitude of P_2 is present in the absence of right bundle branch block (54). It has been suggested that, in these circumstances, wide splitting may represent impairment of right ventricular systolic function. In some patients with severe pulmonary hypertension, fixed splitting of the S_2 has been observed, and it has been suggested that this fixed splitting occurs due to concomitant right ventricular failure secondary to pulmonary hypertension. In these patients, the altered pulmonary vascular impedence associated with severe pulmonary hypertension may also be contributory in the diminished inspiratory splitting of the S_2.

At the bedside, when pulmonary hypertension is suspected from the presence of the increased intensity of the P_2, it is desirable to search for other findings that may be associated with or result from chronic severe pulmonary hypertension. These findings include the pulmonary ejection sound, left parasternal systolic lift associated with right ventricular failure, pulmonary insufficiency murmur, right ventricular S_4, S_3 gallops, and tricuspid regurgitation. It is also desirable to investigate at the bedside the potential etiology of pulmonary hypertension. In adult patients, Eisenmenger's syndrome is suspected from the presence of cyanosis and clubbing and the characteristic changes in the S_2. In Eisenmenger's syndrome, central cyanosis occurs due to intracardiac right-to-left shunt. In Eisenmenger's syndrome associated with atrial and ventricular septal defects, peripheral cyanosis and clubbing involve fingers and toes bilaterally. In Eisenmenger's syndrome associated with patent ductus arteriosus, however, the cyanosis and clubbing are usually recognized in the toes, and the fingers are spared. Differential cyanosis and clubbing in adult patients almost always indicate patent ductus arteriosus and reversal of shunt due to marked increase in pulmonary artery pressure and pulmonary vascular resistance, which allows shunting of the desaturated blood from the pulmonary artery to the descending thoracic aorta. The S_2 in Eisenmenger's syndrome associated with atrial septal defect remains widely split, and the degree of splitting during expiration and inspiration usually does not change significantly (wide fixed splitting of S_2). In Eisenmenger's syndrome associated with a ventricular septal defect, the duration of right and left ventricular systole is essentially equal; therefore, a loud, single S_2 is appreciated because of simultaneous closure of the aortic and pulmonary valves (41). In Eisenmenger's syndrome associated with patent ductus arteriosus, the S_2 behaves like that in precapillary primary pulmonary hypertension.

It should be appreciated that pulmonary hypertension and central and peripheral cyanosis and clubbing can also occur from primary pulmonary disease, such as severe pulmonary fibrosis.

In adults, postcapillary pulmonary hypertension is much more frequent than precapillary pulmonary hypertension, including Eisenmenger's syndrome. Postcapillary pulmonary hypertension can be caused by mitral valve obstruction, such as rheumatic mitral stenosis, mitral regurgitation, aortic stenosis, and aortic regurgitation. These valvular abnormalities can be suspected at the bedside and subsequently confirmed by further investigations, such as echocardiography. If valvular heart disease is excluded, an increase in left ventricular diastolic pressure resulting from left ventricular myocardial dysfunction should be suspected. Systolic ventricular failure due to ischemic and nonischemic dilated cardiomyopathy, diastolic ventricular failure resulting from hypertrophic cardiomyopathy, hypertensive heart disease, and restrictive cardiomyopathy all can be associated with a substantial increase in left ventricular diastolic pressure, a passive increase in left atrial and pulmonary venous pressure, and an obligatory rise in pulmonary artery pressure. If a left ventricular S_3 gallop is appreciated in patients with suspected dilated cardiomyopathy or aortic valve disease, an abnormally elevated left ventricular diastolic pressure and, thus, postcapillary pulmonary hypertension, should be suspected. Careful analysis of the characters of the cardiac apex, diastolic and systolic murmurs, and gallop sounds is essential for exclusion of postcapillary pulmonary hypertension. The causes of precapillary pulmonary hypertension in adults include primary pulmonary diseases, such as chronic obstructive pulmonary disease, chronic thromboembolic pulmonary hypertension, and unexplained or primary pulmonary hypertension. When precapillary pulmonary hypertension is suspected at the bedside, it is desirable to look for conditions such as systemic lupus erythematosus, scleroderma, or CREST syndrome, which can also be associated with precapillary pulmonary hypertension.

Single S_2 may result from the absence of either of the two components of the S_2 or from the fusion of A_2 and P_2 without the inspiratory splitting. The most common cause of an apparently single S_2 is the inability to hear the faint pulmonic component because of chronic obstructive lung disease, obesity, or even normal but accentuated respiratory noise. Another common cause of single S_2 is advanced age and most likely occurs due to a decreased inspiratory delay in P_2, rather than a delayed A_2. Decreased inspiratory delay of P_2 probably results from a decreased right-sided hangout interval related to aging changes in the pulmonary artery compliance. However, all conditions that can delay A_2 may produce a single S_2 when the splitting interval becomes <30 ms. In conditions in which one component of the S_2 is absent or inaudible (e.g., in patients with severe tetralogy of Fallot, severe pulmonary valve stenosis, severe aortic stenosis, pulmonary atresia, and most cases of tricuspid atresia), S_2 is single. The abnormalities of the S_2 and their potential mechanisms and associated causes are summarized in Table 15.5.

TABLE 15.5 ABNORMALITIES OF THE SECOND HEART SOUND

EJECTION SOUNDS

The ejection sounds are relatively high-pitched sounds occurring with the onset of ejection or soon after ventricular ejection starts. The ejection sounds are classified as valvular (i.e., arising from deformed aortic or pulmonic valves) or vascular (i.e., caused by a forceful ejection of blood into the great vessels).

Aortic Sounds

Aortic valvular ejection sounds are recognized in bicuspid aortic valve and valvular aortic stenosis. The aortic valvular ejection sounds occur 20 to 40 ms after the onset of pressure rises in the central aorta, and they coincide with the sharp anacrotic notch on the upstroke of the aortic pressure curve. The aortic valvular ejection sounds also are coincident with the maximal excursion of the domed valve. When the aortic valve is immobile due to severe calcification, no excursion or pistol-like ascent of the deformed valve is present; therefore, in severe calcific aortic stenosis, ejection sound is frequently absent. The intensity of the aortic valvular ejection sound also correlates directly with the mobility of the valve. Thus, if the ejection sound is present in patients with aortic valvular stenosis, it indicates the presence of a mobile stenotic valve. In bicuspid aortic valve, the ejection sound usually is loud and is followed by a short ejection systolic murmur, normal S_2, and trivial aortic regurgitation. The aortic valvular ejection sound is widely transmitted and often heard best at the apex. Aortic vascular ejection sounds originate from the aortic root and are common in systemic hypertension, aortic aneurysm, and, sometimes, with aortic root dilatation resulting from hemodynamically significant aortic regurgitation. Aortic vascular ejection sounds occur later than aortic valvular ejection sounds and frequently are localized and poorly transmitted. Aortic vascular ejection sounds are sometimes confused with the tricuspid valve closure sounds. The differential diagnosis between tricuspid valve closure sounds and aortic vascular ejection sounds depends on the clinical circumstances when these sounds are expected to be present.

HEART SOUNDS

Audio 15.6 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.7 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.8 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.9 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.10 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.11 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.12 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first

heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*).(The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.13 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*).(The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.14 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*).(The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.15 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*).(The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.16 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth lip*).(The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pulmonic Sounds

Pulmonary valvular ejection sounds are observed in mild to moderate pulmonary valve stenosis and idiopathic dilatation of the pulmonary artery. Pulmonary valvular ejection sounds occur at the maximal excursion of the stenotic pulmonary valve. In contrast to the aortic valvular ejection sounds and to most right-sided sounds and murmurs, a pulmonary ejection sound or click decreases in intensity—or even disappears—with inspiration (55). The pulmonary valvular ejection sounds coincide with the movement of the domed pulmonary valve. During expiration, a pressure gradient between the pulmonary artery end diastolic pressure and right ventricular end diastolic pressure exists, allowing the deformed domed pulmonary valve excursion and, therefore, the presence of the ejection sounds. During inspiration, the pressure gradient between the pulmonary artery and the right ventricle in end diastole substantially decreases, and there is preopening of the pulmonary valve; there is no further excursion of the domed pulmonary valve, which explains the absence of pulmonary ejection sounds during inspiration. In severe pulmonary stenosis, the pulmonary valvular ejection sounds appear fused with the S_1, which may explain the lack of pulmonary valvular ejection sounds in these patients. Pulmonary vascular ejection sounds arise from the pulmonary artery and are associated with dilatation of the pulmonary artery. The dilated pulmonary artery can be seen in patients with idiopathic dilatation of the pulmonary artery or secondary to severe pulmonary hypertension. Vascular pulmonary ejection sounds are louder in the second and third left intercostal spaces. Echocardiographic studies have suggested that pulmonary vascular ejection sounds coincide with the complete opening of the pulmonary valve and occur during the upstroke of the pulmonary artery pressure recordings (56). It should be recognized that the intensity of pulmonary vascular ejection sounds may not vary substantially during the phases of respiration. In patients with pulmonary hypertension with vascular pulmonary ejection sounds, the intensity of P_2 is markedly accentuated. In idiopathic dilatation of the pulmonary artery, the S_2 intensity is normal and may or may not be associated with a short ejection systolic murmur and a short early diastolic murmur. In pulmonary valve stenosis with pulmonary valvular ejection sounds, there is a long ejection systolic murmur. The S_2 is widely split, and the intensity of P_2 is decreased.

NONEJECTION SOUNDS

Clicks

Systolic nonejection sounds (mid-systolic clicks) occur most frequently in mitral valve prolapse syndrome. Mid-systolic clicks also occur in prolapse of the tricuspid valve. The mechanism of the mid-systolic click is the tensing of the atrioventricular valves during systole.

At the bedside, when a nonejection or a mid-systolic click is recognized, the initial diagnosis, until proved otherwise, should be mitral valve prolapse. The sound has a sharp, high-frequency, clicking quality, and, although it is heard best over the cardiac apex, it can be transmitted widely. It may be an isolated finding occurring in mid- to late systole, or there may be multiple clicks resulting from prolapsing of the different areas of the large, redundant, scalloped mitral leaflets at different times. Echocardiographic studies have shown the presence of the mid- to late systolic prolapse, as well as pansystolic prolapse, in patients with mid-systolic clicks. All of these different types of prolapse of the mitral valve can occur in patients with only systolic clicks, with clicks and late systolic murmur, or with late systolic murmur alone (57,58 and 59). Mid-systolic clicks usually occur at the time of maximum prolapse. Valvuloventricular disproportion (i.e., a valve too big for the ventricle) has been thought to be the principal cause of mitral valve prolapse. It has been suggested that the ventricular volume or dimension associated with prolapse of the mitral valve (click dimension) is relatively fixed in a given patient. After the onset of ejection, the mitral valve prolapse occurs whenever this click dimension is reached (60). Thus, the S_1-click interval and the relative proportion of systole occupied by the regurgitant murmur vary with maneuvers (Fig. 15.8). When the patient maintains an upright posture and the ventricular volume is reduced, the S_1-click interval is shorter, and the duration of the murmur is longer. When the patient is supine and the ventricular volume is increased, the S_1-click interval is longer, and the duration of the murmur is shorter. With the postectopic beat—even though the ventricular volume is increased—the postectopic potentiation causes a rapid ejection; therefore, the S_1-click interval gets shorter, and the duration of the murmur gets longer (60). These bedside maneuvers are helpful for the differential diagnosis between nonejection click and early ejection sound, a split S_2, and an S_3.

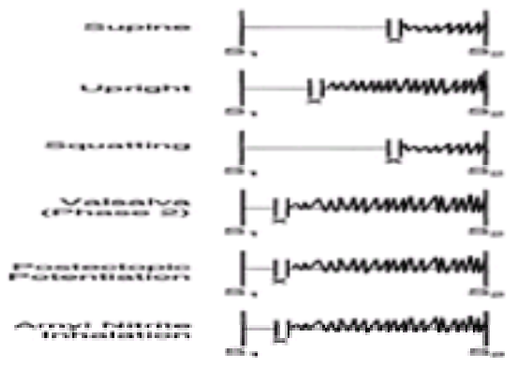


FIGURE 15.8 The influences of various bedside maneuvers on the first heart sound (S_1) and mid-systolic click (x) intervals and the duration of the late systolic murmur, which usually extends to the second heart sound (S_2). With an increase in left ventricular volumes (supine and squatting), S_1-x intervals are longer and the duration of the late systolic murmur is shorter. With a smaller left ventricular diastolic volume (upright, Valsalva phase 2, amyl nitrite inhalation), S_1-x intervals are shorter and the duration of the late systolic murmur is relatively longer.

Although mitral valve prolapse and tricuspid valve prolapse are the most frequent causes of mid-systolic clicks, nonejection sounds also have been observed in patients with left-sided pneumothorax, adhesive pericarditis, atrial myxomas, left ventricular aneurysm, and aneurysm associated with ventricular septal defects (61,62,63 and 64). These nonejection clicks vary in their timing, and the maneuvers that influence the mid-systolic click associated with mitral valve prolapse and the S_1 interval are not recognized in these patients. In some patients with hypertrophic cardiomyopathy, a nonejection sound has been observed to occur with systolic anterior motion of the anterior mitral leaflet. This sound, termed *pseudoejection sound*, begins considerably after the upstroke of the carotid pulse (65). The precise mechanism of this pseudoejection sound in hypertrophic cardiomyopathy remains unclear. It may result from the contact of the anterior leaflet with the septum or from the deceleration of blood flow in the left ventricular outflow tract. The S_1–pseudoejection sound interval also does not change with maneuvers. The effects of different maneuvers on the S_1–mid-systolic click interval and mitral regurgitation murmur associated with mitral valve prolapse are summarized in Figure 15.8.

Opening Snap

The opening snap is a high-pitched (high-frequency), early diastolic sound associated with mitral or tricuspid valve opening. These opening sounds of the atrioventricular valves are normally silent, but they become audible in the presence of mitral or tricuspid stenosis. The most common cause of opening snap is mitral stenosis, and the snap is heard best with the diaphragm of the stethoscope just medial to the cardiac apex. The opening snap associated with mitral stenosis usually is widely transmitted and frequently heard along the left sternal border and even over the left second interspace. Thus, the transmitted opening snap can be confused with the pulmonic component of the S_2. However, during the inspiratory phase of respiration, three high-frequency sounds can be recognized: The initial two sounds are the two components of the S_2, and the third is the opening snap. The opening snap coincides with the full opening of the mitral valve and usually occurs 40 to 100 ms after the S_2. The opening snap results from rapid opening of the mitral valve to its maximal open position; thus, the mobility of the valve contributes to its genesis. When the mitral valve is heavily calcified and immobile, the opening snap may be absent. A careful analysis of the interval between A_2 and the opening snap can provide information regarding the severity of mitral stenosis. The shorter the A_2–opening snap interval is, the more severe is the mitral stenosis. The A_2–opening snap interval is related to the difference in pressures at the time of the aortic valve closure and the opening of the mitral valve. When mitral stenosis is severe, left atrial pressure is higher, and the pressure crossover point between the left ventricle and the left atrium is closer to A_2, which reduces the A_2–opening snap interval. At the bedside, if the A_2–opening snap interval appears like widely split S_2, the A_2–opening snap interval is short and suggests severe mitral stenosis. On the other hand, if the opening snap seems to occur at the time when the S_3 gallop is expected, the A_2–opening snap interval is wide and indicates mild mitral stenosis. It needs to be emphasized that the A_2–opening snap interval should be assessed when the heart rate is relatively normal. When the heart rate is fast, the A_2–opening snap interval is shorter, even when the mitral stenosis is not severe. Similarly, in the presence of aortic stenosis, mitral regurgitation, or aortic regurgitation, it is difficult to assess the severity of mitral stenosis based on the A_2–opening snap interval (66) (Fig. 15.9). However, in the presence of significant mitral regurgitation or aortic stenosis, if the A_2–opening snap interval is wide, it is unlikely that significant mitral stenosis is present.

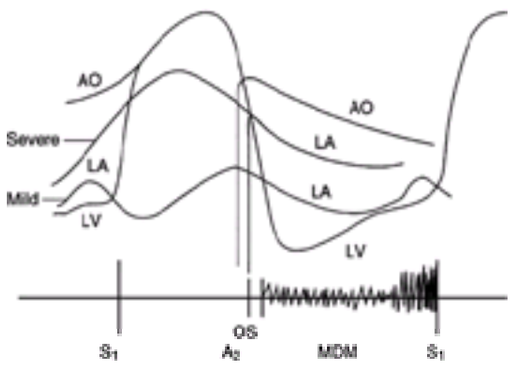


FIGURE 15.9 Schematic illustrations of left ventricular (LV), aortic (AO), and left atrial (LA) pressures to explain the relationship between the severity of mitral stenosis and the interval between the closure of the aortic valve sound (A_2) and the opening snap (OS). Compared to mild mitral stenosis, left atrial pressure is higher in severe mitral stenosis; thus, LA-LV pressures cross over at the end of isovolumic relaxation phase occur closer to A_2; thus, the A_2-OS interval is shorter with more severe mitral stenosis. The mid-diastolic murmur (MDM) is longer in more severe mitral stenosis and may extend to a loud first heart sound (S_1). The A_2-OS interval, however, is related to aortic pressure at the time of aortic valve closure; the interval is related to left ventricular pressure at the time of the opening of the mitral valve, which is also related to arterial pressure, ventricular relaxation, associated mitral regurgitation, aortic stenosis, and aortic regurgitation, as well as heart rate, which influences the duration of diastole. Thus, a relatively poor correlation exists between A_2-OS intervals and the mitral valve areas.

Although an opening snap is most frequently encountered in mitral stenosis, it also can occur in patients with tricuspid stenosis. Left atrial and right atrial myxomas may cause an early diastolic sound (tumor plop) and seem to occur when tumors move into the ventricle and come to a sudden halt. In patients with hypertrophic cardiomyopathy with a decreased left ventricular cavity, high-frequency, early diastolic sounds are heard in some patients; these sounds coincide with the time of contact of the anterior leaflet of the mitral valve to the interventricular septum (67). The tricuspid opening snap also can be heard in patients with atrial septal defect with a large left-to-right shunt. Rarely, a high-pitched diastolic sound can be heard in patients with mitral valve prolapse. This high-frequency sound seems to be related to the rapid, inward movement of the prolapsed mitral valve toward the left ventricular cavity before the opening of the mitral valve. Also, rarely in patients with severe mitral regurgitation due to ruptured chordae, a high-pitched, early diastolic sound similar to the opening snap can be heard (44). If a high-frequency, early diastolic sound is heard in clinical practice, one should exclude mitral valve stenosis by echocardiography.

Bioprosthesis and mechanical prosthesis also produce systolic and diastolic high-pitched sounds. The relative intensity of the opening and closing sounds vary according to the type and design of the prosthetic valve. With the ball-and-cage type of valve, the opening and closing sounds are loud and clicking in character. With the disc valve, however, the closing sound is louder and clickier than the opening sound. The artificial valve sounds are of high frequency and are much louder than normal valve sounds. The opening or closing sounds may consist of multiple clicks, which do not necessarily indicate valve malfunction. The absence of an opening click has been observed with normally functioning mitral valve prosthesis. Obstruction of a prosthetic valve in the mitral position may be associated with a markedly decreased A_2–opening click interval. For the diagnosis of the malfunction of prosthetic valve, however, one should not rely on the physical findings.

THIRD AND FOURTH HEART SOUNDS

S_3 and S_4 are of relatively low frequency, are lower-pitched sounds, and are related to early and late diastole filling of the ventricles (68). When these sounds are recognized in the pathologic states, they are termed *gallop sounds*. In certain pathologic conditions, the presence of gallop sounds provides useful information about

the hemodynamic and functional abnormalities. The S_3 is commonly heard in children, adolescents, and young adults in the absence of any pathologic condition or hemodynamic abnormality and is termed *physiologic* S_3. The physiologic or pathologic S_3 is a low-frequency sound that follows A_2 by 120 to 200 ms and occurs during the ventricular early rapid filling phase.

HEART SOUNDS

Audio 15.17 Third heart sound. Auscultation in a 39-year-old female patient with mild left ventricular hypertrophy. The third heart sound comes immediately after the second heart sound. It is heard best in this case at the apex and the left lower sternal border. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.18 Third heart sound. Auscultation in a 39-year-old female patient with mild left ventricular hypertrophy. The third heart sound comes immediately after the second heart sound. It is heard best in this case at the apex and the left lower sternal border. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.19 Third heart sound. Auscultation in a 39-year-old female patient with mild left ventricular hypertrophy. The third heart sound comes immediately after the second heart sound. It is heard best in this case at the apex and the left lower sternal border. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.20 Third heart sound. Auscultation in a 39-year-old female patient with mild left ventricular hypertrophy. The third heart sound comes immediately after the second heart sound. It is heard best in this case at the apex and the left lower sternal border. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The mechanisms for the production of physiologic and pathologic S_3 have not been precisely determined. The opening and tensing of the atrioventricular valves in early diastole, the tensing of the ventricular wall, and the impact of the ventricular wall with the chest wall at the end of the rapid filling phase had been proposed to explain physiologic and pathologic S_3. The fast cineangiographic, echocardiographic, and Doppler studies have indicated that the S_3 is most likely related to the rapid deceleration of flow in early diastole. During the early filling phase—when there is an abrupt deceleration of the column of blood entering the ventricle after the opening of the atrioventricular valves—the cardiohemic system is set into vibration, which contributes to the genesis of the S_3 (69). It also has been suggested that the dynamic impact of the heart with the chest wall at the end of the rapid filling phase may contribute to the genesis of the S_3 that is recognized at the bedside (70).

At the bedside, S_3 is best recognized when the bell of the stethoscope is pressed very lightly over the skin in the left lateral decubitus position. When the bell of the stethoscope is pressed harder and converted to a diaphragm, the intensity of the S_3 decreases and may even disappear. In a number of pathologic conditions, an S_3 gallop indicates an increase in left ventricular diastolic pressure (71). In patients with dilated cardiomyopathy, coronary artery disease, and aortic valve disease, a relatively crisper and sharper S_3 gallop indicates abnormally elevated left ventricular diastolic pressure. In patients with chronic aortic regurgitation, the presence of an S_3 gallop has been reported to reflect reduced left ventricular ejection fraction (72). An S_3 gallop is very common in aortic regurgitation and usually is followed by a mid-diastolic rumble of the Austin Flint murmur.

HEART SOUNDS

Audio 15.21 Fourth heart sound. Auscultation in a 43-year-old male patient with no structural heart disease. The fourth heart sound immediately precedes the first heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

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HEART SOUNDS

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An S_3 is frequently appreciated in patients with hemodynamically significant atrioventricular valvular regurgitation (mitral and tricuspid regurgitation) and in hyperkinetic states. In these conditions, there is an excessive early diastolic filling of the left ventricle that may not be associated with any impairment of ventricular systolic function or elevation of left ventricular diastolic pressure. An S_3 gallop also is heard in patients with a large left-to-right shunt due to high flow across the mitral valve with ventricular septal defect or patent ductus arteriosus and to high flow across the tricuspid valve with atrial septal defects. The presence of S_3 in these conditions does not imply abnormal ventricular function or congestive heart failure.

A pathologic S_3 is almost invariably recognized in patients with restrictive cardiomyopathy. The pathologic S_3 in constrictive pericarditis is termed the *pericardial knock*. However, the frequency of the pericardial knock is somewhat higher than the physiologic or other pathologic S_3. The pericardial knock or S_3 associated with restrictive cardiomyopathy may occur earlier and soon after A_2 and may be confused with opening snap; it usually increases in intensity with inspiration and occurs coincident with the 'y' descent of the jugular venous pulse.

The S_4 is related to ventricular filling during atrial systole and, therefore, is absent in patients with atrial fibrillation. The S_4 follows the onset of the P wave of the electrocardiogram and precedes the S_1; thus, it is frequently termed the *atrial diastolic gallop* or the *presystolic gallop*. The S_4 is heard best at the cardiac apex with the patient in the left lateral decubitus position. The right ventricular S_4 gallop, however, is heard best along the lower left sternal border over the third or fourth intercostal space. The intensity of the right-sided S_4 increases after inspiration. In contrast, the left-sided S_4 is heard best during expiration. Occasionally, a loud, audible S_4 is accompanied by a palpable presystolic apical impulse—the so-called palpable S_4. The precise mechanism for the genesis of the S_4 has not been identified; however, both the ventricular origin due to the abrupt deceleration of the incoming blood column during atrial contraction and the impact theory have been proposed (70,73). Regardless of the mechanism of genesis of S_4, its presence—particularly when associated with a palpable, presystolic, apical impulse—indicates abnormal hemodynamics and ventricular diastolic dysfunction. The common pathologic conditions in which a prominent left-sided S_4 is recognized are systemic hypertension, aortic valvular stenosis, and hypertrophic cardiomyopathy—the conditions that produce significant left ventricular hypertrophy. Similarly, pulmonary hypertension and pulmonary valvular stenosis, which produce right ventricular hypertrophy, are associated with right-sided S_4. Although it initially was thought that the presence of S_4 in a patient with aortic stenosis indicated hemodynamically significant aortic valvular stenosis with a gradient of 70 mm Hg or greater and a left ventricular end diastolic pressure of 13 mm Hg or greater, recent studies have suggested that S_4 is good evidence of significant aortic stenosis only in patients younger than age 40 (74).

An audible S_4 with or without a palpable presystolic impulse is common in patients during angina associated with ischemic heart disease. In the absence of acute ischemia, S_4 is uncommon, except in patients with ischemic dilated cardiomyopathy with elevated left ventricular diastolic pressure. In patients with left ventricular aneurysm or idiopathic or ischemic cardiomyopathy, the S_4 is often associated with a pathologic S_3, producing a quadruple rhythm. If there is also tachycardia or a markedly prolonged PR interval, S_3 and S_4 can be fused and give rise to a loud summation gallop. A gallop rhythm, which usually is associated with tachycardia and results from the fusion of S_3 and S_4 gallops, is most frequently observed in patients with dilated cardiomyopathy with clinical overt heart failure. With improvement in ventricular function and reduction in heart rate, as well as improved hemodynamics, gallop rhythm is no longer observed in these patients. Thus, clinical evaluation to assess the presence or absence of an S_3 gallop or gallop rhythm can provide information regarding response to therapy. In acute atrioventricular valve regurgitation, as in patients with mitral regurgitation due to ruptured chordae, an S_4 associated with a presystolic apical impulse is frequently present and results from vigorous atrial contraction into an acutely volume-loaded ventricle. In chronic mitral regurgitation, it should be appreciated that an S_4 is uncommon, whereas an S_3 is frequently present. In patients with first degree atrioventricular block, S_4 is more easily heard because of its separation of the S_1. In complete atrioventricular block, intermittent S_4 is recognized frequently. It is of interest that S_4 occasionally is recognized in patients with complete atrioventricular block with atrial contraction during ventricular systole with closed atrioventricular valves. These sounds associated with atrial contraction, therefore, cannot be due to ventricular filling, and different mechanisms need to be postulated for the genesis of these sounds (70). The pathophysiologic mechanisms and clinical significance of the gallop sounds are summarized in Table 15.6.

S_3 is common in children and young adults (physiologic), but it is uncommon in normal subjects older than 40 years.
S_3 usually indicates an increase in left or right ventricular diastolic pressure in the presence of impaired ejection fraction.
Chronic aortic regurgitation—the presence of S_3 indicates impaired left ventricular ejection fraction.
Right ventricular failure resulting from congenital heart disease and pulmonary hypertension or primary right ventricular failure—S_3 gallop indicates an increase in right ventricular diastolic pressure and reduced right ventricular ejection fraction.
In hyperkinetic states, hyperthyroidism, anemia, arteriovenous fistulae, left to right shunts, and chronic tricuspid or mitral regurgitation, S_3 does not indicate hemodynamic abnormalities.
Primary myocardial or pericardial disease (constrictive pericarditis)—S_3 and S_4 gallops indicate increased ventricular diastolic pressures.
In the presence of first-degree atrioventricular block, S_4 can be audible without any associated hemodynamic abnormality.

S_3, third heart sound; S_4, fourth heart sound.

TABLE 15.6 PATHOPHYSIOLOGIC MECHANISMS AND CLINICAL SIGNIFICANCE AFTER GALLOP SOUND

PERICARDIAL FRICTION RUB

Pericardial friction sounds are high pitched, leathery, and scratchy in quality and heard best with the patient leaning forward or in the knee/chest position during held, forced expiration. The pericardial rub may have three components: (a) during atrial systole, (b) during ventricular systole, and (c) during rapid ventricular filling. Frequently, the pericardial rub consists of two components; occasionally, it consists of only one component. Three-component pericardial rubs are more frequently observed in patients with acute primary pericarditis, uremic pericarditis, postoperative pericarditis, and traumatic pericarditis. In episternal pericarditis after acute myocardial infarction, it is more common to recognize one or two components of the pericardial rub. Episternal pericarditis, however, is transient, and persistent pericardial rub in acute myocardial infarction may indicate Dressler's syndrome or subacute rupture of the ventricular free wall.

A one-component pericardial rub occurring during ventricular systole can be confused with certain mid-systolic ejection murmurs with a scratchy quality, as recognized in some patients with hyperthyroidism (Means-Lerman sign) (75). Superficial, scratchy ejection systolic murmurs also are recognized in patients with Ebstein's anomaly.

Mediastinal crunch (Hamman's sign) is a series of scratchy sounds that occur with cardiac cycles and result from the presence of air in the pericardium and mediastinum (76). These sounds occur most frequently during ventricular systole. The mediastinal crunch sounds also are influenced by respiratory excursion. The pleuropericardial rubs are accentuated during inspiration. However, the character of the pleuropericardial rub is different from that of the mediastinal crunch. Mediastinal crunch is observed in patients with mediastinal emphysema, which may also be associated with chest pain syndrome similar to angina. Mediastinal emphysema is associated with crepitations in the neck, secondary to subcutaneous air. The most common cause of mediastinal crunch is the presence of air and blood in the open pericardial sac after cardiac surgery. In the postoperative patient, mediastinal crunch does not indicate any significant hemodynamic abnormality.

Pacemaker sounds are also high-frequency sounds of brief duration and are produced by the contraction of the intercostal muscles resulting from stimulation of the intercostal nerves by the transvenous pacemakers located in the right ventricular apex (38). The pacemaker sounds coincide with the pacemaker stimuli and are abolished when the pacing is discontinued. The stimulation of pectoral muscles and the diaphragm during epicardial or endocardial pacing may also produce extracardiac sounds.

EVALUATION OF HEART MURMURS

During bedside evaluation of a cardiovascular murmur, it is customary to assess the location of the maximum intensity, radiation, timing (systolic, diastolic, or continuous), intensity (loudness), and frequency (pitch) of the murmur, as well as its configuration (shape, quality, and duration). Although the exact mechanisms for the production of murmurs are not clear, it is generally agreed that turbulence is the principle determinant for the genesis of most murmurs. In clinical practice, six grades are used to assess the intensity of a murmur at the bedside. Grade 1 is the faintest murmur and can be heard only with special effort or maneuvers. A grade 2 murmur is faint but can be heard easily. A grade 3 murmur is moderately loud. A grade 4 murmur is very loud, and a grade 5 murmur is extremely loud and can be heard with a light touch of the stethoscope. A grade 6 murmur is exceptionally loud and can be heard with the stethoscope just removed from contact with the chest. Systolic murmurs of grade 4 or more usually are associated with a palpable thrill. The intensity or loudness of the murmur can vary depending on the hemodynamic determinants that govern the production of a given murmur. The frequency of the murmur determines its pitch, which may be high or low. During auscultation, a mental image is formed to recognize the shape of a murmur and its configuration. A crescendo murmur is recognized when there is increasing intensity; a decrescendo murmur is defined when the intensity of the murmur is diminishing. A crescendo/decrescendo murmur is defined when there is initial increasing intensity followed by decreasing intensity, and a plateau murmur is recognized when there is no change in intensity of the murmur. The quality of a murmur that is recognized during auscultation can be harsh, rumbling, scratchy, grunting, blowing, squeaky, and musical. The duration of a murmur is assessed by determining the length of systole or diastole that the murmur occupies. The murmur can be long or brief. The direction of radiation of a murmur follows the direction of blood flow and can provide information regarding the origin of the murmur. At the bedside, initially, it is essential to determine the timing of the murmur in relation to the cardiac cycle. A murmur can be systolic, diastolic, or continuous. Systolic and diastolic murmurs can be left-sided or right-sided. At the bedside, there usually is little difficulty in distinguishing between systolic and diastolic murmurs, because at normal heart rate, systole is much shorter in duration than diastole. However, when the heart rate is fast, the duration of systole and diastole may become equal; in these circumstances, the timing of the murmur can be determined by simultaneous palpation of the carotid pulse. In rare circumstances, a high-pitched, pandiastolic murmur can be confused with a pansystolic murmur. Whenever there is any doubt about the timing of a given murmur, it is desirable to auscultate with simultaneous palpation of the carotid pulse. After recognizing a systolic murmur at the bedside, it is desirable to determine whether the systolic murmur is of ejection type (mid-systolic) or regurgitant type (Fig. 15.10). The ejection systolic murmur starts after the S_1 and does not extend to the S_2. A left-sided ejection systolic murmur ends before A_2, and a right-sided ejection systolic murmur ends before P_2. The ejection, or mid-systolic, murmur is related to flow across the semilunar valves. Onset of the murmur coincides with the beginning of the ejection, and termination of the murmur coincides with the cessation of forward flow. The S_1 occurs at the onset of isovolumic systole, and the beginning of ejection occurs at the end of the isovolumic systole, explaining why ejection systolic murmur starts after the S_1. The ventricular ejection ends before closure of the semilunar valves; thus, an ejection systolic murmur cannot extend to the semilunar valve closure sounds. The configuration or shape of most ejection systolic murmurs is crescendo/decrescendo. The crescendo part of the ejection systolic murmur is related to the initial rapid ejection phase, and the decrescendo part of the ejection systolic murmur is related to the slower ejection phase.

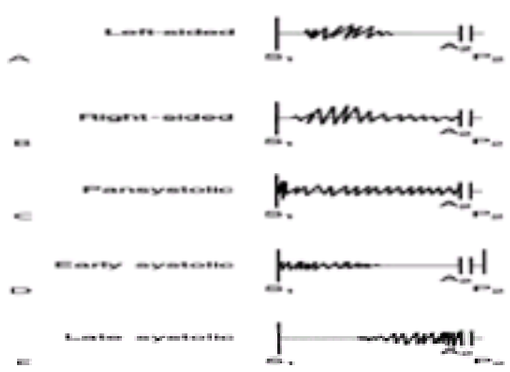

FIGURE 15.10 A left-sided ejection systolic murmur starts after the first heart sound (S_1) and terminates before the aortic component of the second heart sound (A_2). A right-sided ejection systolic murmur starts after S_1 and terminates before the pulmonary component of the second heart sound (P_2). A pansystolic murmur starts with S_1 and extends to the second heart sound. An early systolic murmur starts with the S_1 and terminates before the second heart sound. A late systolic murmur starts after the S_1 and extends up to second heart sound. **A:** Aortic stenosis, aortic sclerosis, flow murmur, innocent murmur, hypertrophic cardiomyopathy, and bicuspid aortic valve. **B:** Pulmonary stenosis, infundibular stenosis, flow murmur (ASD), idiopathic dilatation of the pulmonary artery, and innocent murmurs. **C:** Mitral regurgitation, tricuspid regurgitation, and ventricular septal defect. **D:** Mitral regurgitation, tricuspid regurgitation, and ventricular septal defect. **E:** Mitral regurgitation and tricuspid regurgitation.

Ejection Systolic versus Regurgitant Murmur

When the S_1 and S_2 are decreased in intensity, it is often difficult to distinguish between an ejection systolic murmur and a regurgitant murmur. There are a number of distinguishing features, however, that can be appreciated at the bedside (76). If A_2 is clearly audible over the cardiac apex, the murmur is likely to be ejection or mid-systolic (77). If A_2 is heard over the right and left second interspaces but not over the apex, it is likely that A_2 is drowned out by the holosystolic murmur of mitral regurgitation. If the patient is in atrial fibrillation, and if the intensity of the murmur substantially increases with longer RR cycle length, the murmur is likely to be an ejection murmur. Similarly, if the intensity of the murmur increases during the postectopic beat after a postectopic pause, the murmur is likely to be of ejection variety. At the bedside, a response to hand grip can be used to distinguish between left-sided ejection and regurgitant murmurs. In response to sustained hand grip, the intensity of a mitral regurgitation murmur increases, whereas the intensity of murmur associated with aortic stenosis usually decreases. The physiologic responses to hand grip are complex. In addition to an increase in systemic vascular resistance and arterial pressure, a reflex increase in contractility may also occur, which can increase the intensity of the stenotic murmur. Amyl nitrite inhalation is also a helpful bedside pharmacologic maneuver to distinguish between an ejection systolic murmur and a holosystolic regurgitant murmur of left ventricular origin. The intensity of the ejection systolic murmur increases, whereas the intensity of the regurgitant holosystolic murmur decreases. Amyl nitrite inhalation is associated with decreased systemic vascular resistance and arterial pressure, which decreases the severity of the regurgitation—hence, the intensity of the regurgitation murmur. In aortic stenosis, the intensity of the systolic murmur increases because of the increased flow across the stenotic aortic valve. In obstructive hypertrophic cardiomyopathy, the intensity of the murmur in response to amyl nitrite inhalation increases due to an accentuated left ventricular outflow obstruction. The intensity of an ejection systolic murmur is markedly influenced by the changes in stroke volume. With increased stroke volume—such as during exercise, anxiety, or fever; after volume loading or passive leg elevation; or with a long diastolic filling period—the intensity of the ejection systolic murmur increases. Likewise, conditions that decrease cardiac output and stroke volume (e.g., congestive heart failure, beta blockade, or other negative inotropic agents) decrease the intensity of the ejection murmur. The effects of different pharmacologic and nonpharmacologic interventions on systolic murmurs of fixed and dynamic left ventricular outflow obstruction and of mitral regurgitation are summarized in Table 15.7.

	Aortic stenosis		Hypertrophic obstructive cardiomyopathy		Mitral regurgitation	
Maneuver	ESM	CAR AMP	ESM	CAR AMP	PSM	CAR AMP
Leg raising	Increased	Increased	Decreased	Increased No change	Increased	Decreased No change
Standing	Decreased	Decreased No change	Increased	Decreased No change	Decreased	Increased No change
Squatting	Decreased No change	No change	Decreased	Increased No change	Increased	Decreased No change
Hand grip	Decreased Increased	Increased No change	Decreased	No change	Increased	No change
Supine position	No change	No change	Decreased	No change	No change	No change
Postectopic beat	Increased	Increased	Increased	Decreased No change	No change	No change
Valsalva (phase 2)	Decreased	Decreased	Increased	Decreased	Decreased	Decreased
Amyl nitrite	Increased	Increased	Increased	Decreased No change	Decreased	Increased No change

CAR AMP, carotid pulse amplitude; ESM, ejection systolic murmur; PSM, pansystolic murmur.

TABLE 15.7 EFFECTS OF MANEUVERS ON THE INTENSITY OF THE SYSTOLIC MURMURS AND CAROTID PULSE IN AORTIC STENOSIS, HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY, AND MITRAL REGURGITATION

Once the presence of an ejection systolic murmur is established, a systematic evaluation to establish its etiology should be undertaken (Table 15.8). In adults, it is desirable to search for the findings that might indicate fixed or dynamic left ventricular outflow obstruction. The conditions of congenital aortic, valvular, subvalvular, or

supravalvular stenosis, acquired aortic stenosis, and hypertrophic obstructive cardiomyopathy are all associated with an ejection systolic murmur. The murmur of fixed stenosis of the left ventricular outflow tract is crescendo/decrescendo in configuration and usually is heard best at the right second and left second and third interspaces near the sternal border. This murmur usually radiates widely into the neck and along the great vessels. The murmur of aortic stenosis is of lower pitch and has a harsh quality. With calcific aortic stenosis, particularly in the elderly, the murmur may radiate to the apex. Also in calcific aortic stenosis in the elderly, the high-frequency components of the murmur may predominate, and the apical murmur may have a high pitch and, often, a musical quality (78). This murmur has been frequently confused with the mitral regurgitation murmur. However, it should be emphasized that the murmur associated with aortic stenosis is an ejection murmur and not a regurgitant murmur. An aortic ejection sound is frequently appreciated in congenital and acquired valvular aortic stenosis. With increasing severity of aortic stenosis and with calcification of the aortic valves, however, the aortic ejection sound may not occur. In congenital aortic stenosis—whether valvular, subvalvular, or supravalvular—the S_2 splitting usually is normal or single. In acquired aortic stenosis, the S_2 usually is single, or it may be reversed with severe outflow obstruction. The intensity of A_2 in congenital valvular aortic stenosis usually is normal but may decrease with calcification. The intensity of A_2 in subvalvular and supravalvular aortic stenosis is normal or decreased. In acquired aortic stenosis, the intensity of A_2 is decreased, or it may be absent with calcification of the aortic valve. The murmur of aortic regurgitation frequently is present in congenital valvular and subvalvular aortic stenosis, as well as in acquired aortic valvular stenosis. A murmur of aortic regurgitation is uncommon in supravalvular congenital aortic stenosis. In supravalvular congenital aortic stenosis (William's syndrome), elf-like facial appearance, mental retardation, and hypercalcemia are common (79). The carotid artery upstroke is slow rising, the peak is delayed, and the amplitude is decreased in congenital valvular and subvalvular aortic stenosis, as well as in acquired aortic stenosis. In congenital supravalvular aortic stenosis, the right brachial and carotid pulsations have greater amplitudes than those of left brachial and left carotid pulsations. Left ventricular hypertrophy can occur in response to valvular, subvalvular, supravalvular, and acquired aortic stenosis; thus, it can be associated with a sustained left ventricular apical impulse. A significant hypertrophy and noncompliant ventricle may also be associated with a palpable presystolic impulse (S_4).

TABLE 15.8 DIFFERENTIAL DIAGNOSIS OF SYSTOLIC MURMURS—BEDSIDE EVALUATION

Severity of Aortic Stenosis

After establishing the diagnosis of aortic stenosis, attempts should be made to assess its severity (Fig. 15.11). The physical finding that indicates that hemodynamically significant aortic stenosis is a substantial increase in left ventricular ejection time. A palpable anacrotic character of radial pulse, slow-rising carotid pulse, and reduced amplitude and delayed peak of the carotid pulse indicate significant aortic stenosis. The decrease in intensity of the S_1 in the absence of prolonged PR interval (first degree atrioventricular block) indicates an increase in left ventricular end diastolic pressure, which indirectly suggests hemodynamically significant aortic stenosis. The intensity of the aortic valve closure sound (A_2) does not correlate with the severity of aortic stenosis. A longer and delayed peaking ejection systolic murmur suggests significant aortic stenosis. However, in the presence of heart failure and reduced stroke volume, the duration and intensity of the ejection murmur is decreased, and it may even be absent (silent aortic stenosis). Hemodynamically significant aortic stenosis usually is associated with left ventricular hypertrophy, which can be appreciated at the bedside by the presence of a sustained left ventricular apical impulse. The presence of an ejection systolic murmur with a musical quality along the left sternal border or over the cardiac apex strongly suggests calcification of the aortic valves. In elderly patients, diagnosis of hemodynamically significant aortic valve stenosis may be difficult (80). The ejection murmur is often of low intensity due to decreased stroke volume associated with impaired left ventricular ejection fraction. The murmur is often loudest at the apex, may have a high-frequency component, and may be difficult to define as ejection in nature because of decreased S_1 and S_2. In the elderly, the rate of rise of the carotid pulse may be normal or near normal because of the sclerotic changes in the carotid arteries. The carotid pulse amplitude may also be normal—even in the presence of significant aortic stenosis—because of the rigid, noncompliant carotid vessels. In elderly patients with aortic stenosis, hypertension may coexist and cause further difficulties in the diagnosis.

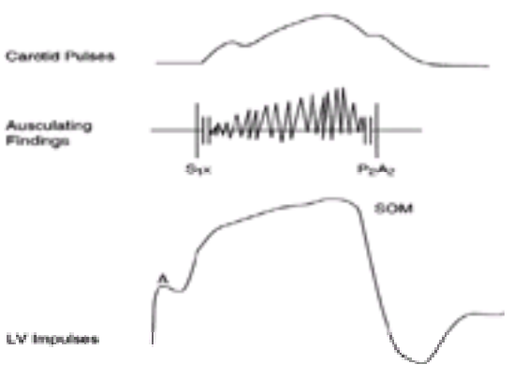

FIGURE 15.11 Schematic illustration of the physical findings of aortic stenosis at the bedside, which suggest hemodynamically significant aortic stenosis, are slow-rising, delayed-peaking anacrotic pulse (carotid pulse), palpable presystolic (A) and sustained outward movement (SOM) in left ventricular (LV) impulse and delayed-peaking ejection systolic murmur, reversed splitting of the second heart sound in the absence of left bundle branch block, and reduced intensity of the first heart sound (S_1)(see text). A_2, aortic component of the second heart sound; P_2, pulmonary component of the second heart sound; x, aortic ejection sound.

HEART SOUNDS

Audio 15.25 Severe valvular aortic stenosis. Auscultation at the right upper sternal border performed in a 70-year-old male patient with a calcified and degenerated aortic valve. The peak and mean systolic gradients across the aortic valve were 100 and 55 mm Hg, respectively. The valve area calculated by the continuity equation was 0.5 cm^2. Note the soft A_2 and the high-pitched mid-systolic crescendo-decrescendo murmur. Right upper sternal border (*first clip*) and left upper sternal border (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

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Audio 15.26 Severe valvular aortic stenosis. Auscultation at the right upper sternal border performed in a 70-year-old male patient with a calcified and degenerated aortic valve. The peak and mean systolic gradients across the aortic valve were 100 and 55 mm Hg, respectively. The valve area calculated by the continuity equation was 0.5 cm^2. Note the soft A_2 and the high-pitched mid-systolic crescendo-decrescendo murmur. Right upper sternal border (*first clip*) and left upper sternal border (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.27 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.28 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.29 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.30 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.31 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.32 Moderate valvular aortic stenosis. Auscultation in a 79-year-old female patient with moderate aortic valve stenosis (peak gradient of 41 mm Hg, mean gradient of 23 mm Hg, and aortic valve area of 0.9 cm^2. Note the systolic ejection murmur with crescendo-decrescendo pattern and distinct second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

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Audio 15.33 Moderate valvular aortic stenosis. Auscultation in a 79-year-old female patient with moderate aortic valve stenosis (peak gradient of 41 mm Hg, mean gradient of 23 mm Hg, and aortic valve area of 0.9 cm^2. Note the systolic ejection murmur with crescendo-decrescendo pattern and distinct second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

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HEART SOUNDS

Audio 15.35 Moderate valvular aortic stenosis. Auscultation in a 79-year-old female patient with moderate aortic valve stenosis (peak gradient of 41 mm Hg, mean

gradient of 23 mm Hg, and aortic valve area of 0.9 cm^2. Note the systolic ejection murmur with crescendo-decrescendo pattern and distinct second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 15.36 Parasternal short-axis view of a patient with senile calcific aortic stenosis. Note the heavily calcified, distorted leaflets with restricted motion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 15.37 Parasternal long-axis view of a stenotic aortic valve. Note the thickened, calcific aortic leaflets with markedly reduced excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Hypertrophic Cardiomyopathy

In adult patients, when aortic stenosis for the cause of the ejection systolic murmur is excluded, dynamic left ventricular outflow tract obstruction (obstructive hypertrophic cardiomyopathy) should be considered. It is generally believed that the systolic anterior motion of the mitral valve apparatus, impinging on the thickened interventricular septum and producing high-velocity flow and obstruction during mid-systole, causes the mid-systolic ejection murmur in hypertrophic cardiomyopathy. The maximum intensity of this ejection murmur is appreciated over the left second or third interspace along the sternal edge. In many patients with obstructive hypertrophic cardiomyopathy, the systolic murmur along the left sternal edge is longer in duration and may appear regurgitant in nature. In fact, in many patients with obstructive hypertrophic cardiomyopathy, mitral regurgitation occurs after the onset of left ventricular outflow tract obstruction. The sequence of dynamic events in these patients is rapid, high-velocity ejection in mid-systole followed by obstruction in the left ventricular outflow tract due to systolic anterior motion, which also produces incompetence of the mitral valve associated with mitral regurgitation (ejection, obstruction, regurgitation). The initial part of the systolic murmur seems to be related to left ventricular outflow tract obstruction, and the latter part is related to mitral regurgitation (81). The ejection murmur that is appreciated at the bedside is the summation of both murmurs as transmitted to the chest wall. In patients with obstructive hypertrophic cardiomyopathy, the intensity of the ejection systolic murmur resulting from outflow tract obstruction and the intensity of the systolic murmur resulting from mitral regurgitation vary directly with the degree of left ventricular outflow tract obstruction and pressure gradient and, therefore, the orifice size of the left ventricular outflow tract (82). The larger the size of the left ventricular outflow tract, the lower the pressure gradient and the lesser the intensity of the murmur. The narrower the left ventricular outflow tract, the higher the pressure gradient and the louder the murmur. The size of the left ventricular outflow tract is directly related to left ventricular volume and intraventricular pressure during systole, and it is inversely related to muscle tension and contractile state. The higher the distending pressure (i.e., the arterial pressure), the larger the left ventricular outflow tract and, therefore, the softer the murmur. Similarly, the larger the left ventricular volume, the larger the size of the left ventricular outflow tract and the softer the murmur. With increased inotropic state, such as during postectopic potentiation or during the challenge with positive inotropic drugs, the size of the left ventricular outflow tract decreases with an increase in the pressure gradient and intensity of the ejection systolic murmur. At the bedside, when obstructive hypertrophic cardiomyopathy is suspected from the presence of a loud ejection systolic murmur along the left sternal border, it is desirable to perform certain maneuvers that may confirm the diagnosis (Table 15.9). Auscultation for the changes in the intensity of the murmur during supine, sitting, standing, and squatting positions can demonstrate characteristic changes. The ejection systolic murmur in obstructive hypertrophic cardiomyopathy increases in intensity while standing and decreases in intensity in the supine and squatting positions. When the patient is standing, there is a reduction of intracardiac volume due to decreased systemic venous return associated with transient fall in blood pressure and an increase in heart rate. These hemodynamic changes decrease the size of the left ventricular outflow tract and increase the pressure gradient and intensity of the murmur. The supine and squatting positions, on the other hand, increase intracardiac volume by increasing venous return and left ventricular outflow resistance. The size of the left ventricular outflow tract, therefore, increases with a decrease in pressure gradient and intensity of the murmur. Valsalva's maneuver is another intervention that can be applied at the bedside to establish the diagnosis of obstructive hypertrophic cardiomyopathy. During phase 2 of Valsalva's maneuver, there is a decrease in venous return, which reduces left ventricular volume; a decrease in arterial pressure, which results from decreased stroke volume; and a reflex increase in heart rate. All of these hemodynamic changes enhance left ventricular outflow obstruction and increase the intensity of the murmur. Furthermore, there is a simultaneous reduction in the carotid pulse volume. In patients with aortic stenosis during phase 2 of Valsalva's maneuver, the carotid pulse volume decreases, but there is also a reduction in the intensity of the ejection systolic murmur. Similarly, during phase 2 of Valsalva's maneuver in patients with chronic primary mitral regurgitation, there is a reduction in the carotid pulse volume and the intensity of the regurgitant murmur (Table 15.7). If premature beats occur during clinical evaluation, it is desirable to assess the intensity of the ejection systolic murmur and the amplitude of the carotid pulse simultaneously during the postectopic beat. In obstructive hypertrophic cardiomyopathy, postectopic potentiation increases the left ventricular outflow pressure gradient; therefore, the intensity of the murmur is increased. However, the carotid pulse volume is either decreased or remains unchanged. In patients with aortic stenosis, the intensity of the murmur increases during the postectopic beat, but there is also a substantial increase in the carotid pulse volume. The most useful pharmacologic intervention that can be applied easily at the bedside is the use of amyl nitrite inhalation. After inhalation of amyl nitrite, the intensity of the ejection systolic murmur in obstructive hypertrophic cardiomyopathy increases along with decreased or unchanged carotid pulse volume. The murmur of mitral regurgitation, however, decreases with amyl nitrite inhalation as a decreased systemic vascular resistance, and arterial pressure decreases the severity of mitral regurgitation. In aortic stenosis, the intensity of the murmur tends to increase after amyl nitrite inhalation. The pharmacologic agents that increase the contractile state (e.g., isoprenaline, dobutamine, or dopamine) increase the intensity of the murmur; agents that decrease the inotropic state (e.g., intravenous beta blocker, or disopyramide) decrease the intensity of the murmur. Similarly, pharmacologic agents that increase left ventricular outflow resistance (e.g., methoxamine or phenylephrine) decrease the intensity of the murmur as the left ventricular outflow tract obstruction decreases (83). In clinical practice, however, these pharmacologic agents are rarely used or necessary for the differential diagnosis of obstructive hypertrophic cardiomyopathy, aortic stenosis, or mitral regurgitation. In patients with suspected or confirmed obstructive hypertrophic cardiomyopathy, careful analysis of the carotid pulse and left ventricular apical impulse may provide additional information about the severity of hypertrophic cardiomyopathy. In patients with significant left ventricular outflow tract obstruction, the carotid pulse usually has a sharp initial upstroke, a large volume, and, occasionally, a bisferiens quality. The left ventricular apical impulse frequently is sustained due to significant increase in left ventricular mass. A presystolic wave (a palpable S_4) also is frequently appreciated. The outward movement of the left ventricular apical impulse may occasionally have bifid character. If the left ventricular outward movement is associated with a presystolic wave, three distinct impulses can be appreciated in rare patients (triple ripple). It should also be realized that in patients with known obstructive hypertrophic cardiomyopathy, the carotid pulse character may be normal, and ejection systolic murmur may be absent. The only indication of hypertrophic cardiomyopathy may be a palpable S_4 or a sustained left ventricular apical impulse. In apical hypertrophic cardiomyopathy, the electrocardiogram may provide some clues for the diagnosis. The electrocardiogram in apical hypertrophic cardiomyopathy frequently reveals a giant T-wave inversion in the lateral precordial leads, along with large QRS voltages due to left ventricular hypertrophy (84). The absence of electrocardiographic changes, however, does not exclude nonobstructive hypertrophic cardiomyopathy. In all patients with suspected hypertrophic cardiomyopathy, echocardiographic evaluation is essential.

Maneuvers	Hemodynamic changes	LV outflow tract size	LV outflow pressure gradient	Intensity of the murmur
Standing	↓ LV volume ↑ Heart rate	↓	↑	↑
Squatting	↑ LV volume ↑ SVR, ART pressure	↑	↓	↓
Valsalva phase 2	↑ Heart rate ↓↓ LV volume	↓↓	↑↑	↑↑
Hand grip	↓ Heart rate ↑ ART pressure	↑	↓	↓
Post-PVC	↑↑ Contractility ↑ LV volume	↓↓	↑↑	↑↑
Amyl nitrite inhalation	↑ Heart rate ↓ LV volume ↓ ART pressure	↓↓	↑↑	↑↑

ART, arterial; LV, left ventricular; PVC, premature ventricular contraction; SVR, systemic vascular resistance; ↑, mild increase; ↓, mild decrease; ↑↑, marked increase; ↓↓, marked decrease.

TABLE 15.9 DIAGNOSIS OF OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

HEART SOUNDS

Audio 15.38 Left ventricular outflow tract obstruction in severe hypertensive heart disease. Auscultation in a 47-year-old female patient with severe concentric left ventricular hypertrophy with intracavitary velocity of 3.7 m/sec and pressure gradient across the left ventricular outflow tract of 50 mm Hg by catheterization. Note the systolic ejection murmur and normal second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.39 Left ventricular outflow tract obstruction in severe hypertensive heart disease. Auscultation in a 47-year-old female patient with severe concentric left ventricular hypertrophy with intracavitary velocity of 3.7 m/sec and pressure gradient across the left ventricular outflow tract of 50 mm Hg by catheterization. Note the systolic ejection murmur and normal second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.40 Left ventricular outflow tract obstruction in severe hypertensive heart disease. Auscultation in a 47-year-old female patient with severe concentric left ventricular hypertrophy with intracavitary velocity of 3.7 m/sec and pressure gradient across the left ventricular outflow tract of 50 mm Hg by catheterization. Note the systolic ejection murmur and normal second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.41 Left ventricular outflow tract obstruction in severe hypertensive heart disease. Auscultation in a 47-year-old female patient with severe concentric left ventricular hypertrophy with intracavitary velocity of 3.7 m/sec and pressure gradient across the left ventricular outflow tract of 50 mm Hg by catheterization. Note the systolic ejection murmur and normal second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.42 Hypertrophic cardiomyopathy. Auscultation performed in a 60-year-old male patient. The systolic gradient across the left ventricular outflow tract was 55 mm Hg at rest and increased to 121 mm Hg after amyl nitrate inhalation. The mid-systolic, crescendo-decrescendo ejection murmur is observed. Valsalva maneuver and sudden squatting are helpful in distinguishing this from fixed aortic valvular stenosis. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 15.43 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy (*first video*). Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy (*second video*) for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 15.44 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy (*first video*). Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy (*second video*) for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Other Left-Sided Ejection Systolic Murmurs

When aortic stenosis or obstructive hypertrophic cardiomyopathy is excluded as the cause of an ejection systolic murmur, other potential causes of left-sided ejection systolic murmur should be considered. Hemodynamically significant isolated aortic regurgitation can also be associated with an ejection systolic murmur, which usually reflects increased flow during systole. Predominant aortic regurgitation can be diagnosed at the bedside from the presence of characteristic physical findings of significant chronic aortic regurgitation, such as pulsus bisferiens, hyperdynamic left ventricular apical impulse, and a high-pitched, early diastolic murmur along the left sternal border. A bicuspid aortic valve may be associated with an ejection systolic murmur. The bicuspid aortic valve at the bedside is suspected from the presence of an aortic ejection sound, normal carotid pulse upstroke, a short early diastolic murmur, and no evidence of hemodynamically significant aortic stenosis. Once suspected, the bicuspid aortic valve should be confirmed by two-dimensional transthoracic echocardiography. A left-sided ejection systolic murmur is also recognized in the presence of normal valves when the flow across the aortic valve is significantly increased, as in anemia in pregnancy or thyrotoxicosis. In these clinical conditions, however, the findings suggestive of fixed or dynamic left ventricular outflow tract obstruction are absent. The murmur of so-called aortic sclerosis is also a mid-systolic ejection murmur. It is benign because it is not associated with hemodynamic abnormalities. In aortic sclerosis, the physical findings of left ventricular outflow tract obstruction are absent. The benign aortic systolic murmur results from the stiffening and degenerative fibrous thickening of the roots of the aortic cusps at the site of their insertions. These morphologic changes do not cause any impairment of mobility of the valve and, thus, no obstruction. The murmur of aortic sclerosis usually is heard best over the right second interspace, and the murmur usually does not radiate to the carotid arteries. In some patients, a musical, high-frequency murmur of brief duration can be heard along the lower left sternal border and cardiac apex. The S_1 and S_2 are normal, and there is no evidence of aortic regurgitation. Clinical recognition of aortic sclerosis is relevant, as it is an adverse risk factor for long-term prognosis probably due to increased atherothrombotic complications. When

diagnosis of aortic sclerosis is suspected, echocardiography for confirmation should be considered.

Right-Sided Ejection Systolic Murmurs

In the adult cardiac patient, it is infrequent to encounter pathophysiologic conditions that produce right-sided ejection systolic murmurs. Right-sided systolic murmurs can result from obstructions to right ventricular outflow, such as pulmonary valvular stenosis, subvalvular right ventricular outflow obstruction, or supravalvular pulmonary stenosis. Isolated infundibular pulmonary stenosis without ventricular septal defect is rare. Infundibular pulmonary stenosis usually is associated with ventricular septal defect, as in patients with tetralogy of Fallot. Pulmonary valvular stenosis, however, may be present in the absence of ventricular septal defect. One finding at the bedside that suggests the presence of pulmonary valvular stenosis is a long ejection systolic murmur that starts after the S_1 and terminates before the P_2 and which can be markedly decreased in intensity. Frequently, a pulmonic valvular ejection sound is also present, and, characteristically, the pulmonary valvular ejection sound decreases in intensity during inspiration. There may or may not be an associated early diastolic murmur due to pulmonary insufficiency. Depending on the severity of pulmonary valvular stenosis, evidence of right ventricular hypertrophy may be recognized at the bedside. Significant pulmonary valvular stenosis causing right ventricular hypertrophy frequently is associated with a prominent 'a' wave in the jugular venous pulse, which reflects increased resistance to right ventricular filling during right atrial systole. In severe pulmonary valvular stenosis, the pulmonary ejection sound may fuse with the S_1 and cannot be recognized at the bedside. Typically, in pulmonary valvular stenosis and isolated subvalvular right ventricular outflow obstruction, the S_2 is widely split. The degree of splitting of the S_2 roughly correlates to the severity of the pressure gradient across the pulmonary valve or the right ventricular outflow tract. In patients with valvular pulmonary stenosis or subvalvular infundibular fixed stenosis, the intensity of the P_2 is decreased substantially, as the pulmonary artery diastolic pressure in these circumstances is low. In patients with supravalvular pulmonary stenosis, however, the intensity of P_2 is not decreased. Supravalvular pulmonary stenosis, or pulmonary artery branch stenosis, is frequently associated with a continuous murmur. Pulmonary valve stenosis, or obstruction in the right ventricular outflow tract, and supravalvular pulmonary stenosis can be associated with significant right ventricular hypertrophy. Occasionally, the long, harsh ejection systolic murmur of pulmonary stenosis is confused with the holosystolic murmur of a ventricular septal defect. This confusion is more likely to occur with infundibular stenosis because of the lower location of the murmur. In ventricular septal defect the splitting of the S_2 and the intensity of the P_2 are normal. In infundibular pulmonary stenosis, the S_2 is widely split, and the intensity of P_2 is significantly reduced. Amyl nitrite inhalation—which usually decreases the intensity of the murmur associated with ventricular septal defect, whereas the intensity of the murmur due to right ventricular outflow obstruction remains unchanged—is sometimes helpful.

HEART SOUNDS

Audio 15.45 Subpulmonic stenosis. Auscultation performed in a 60-year-old female patient with infundibular pulmonic stenosis (double chamber right ventricle). Note the audible P2 and high-pitched mid-systolic ejection murmur. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.46 Supravalvular pulmonic stenosis. Auscultation performed in a 47-year-old male patient with supravalvular stenosis of the main pulmonary artery. The peak systolic gradient across the stenosis was 38 mm Hg. Note the loud P2 and the high-pitched mid-systolic ejection murmur. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 15.47 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.48 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.49 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.50 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The idiopathic dilatation of the pulmonary artery may be associated with a right-sided ejection systolic murmur. The usual findings of idiopathic dilatation of the pulmonary artery are a pulmonary ejection sound, a short ejection systolic murmur, a relatively widely split S_2 with normal intensity of P_2, and, occasionally, a short pulmonary insufficiency murmur. There is no hemodynamic abnormality. It should be noted that the auscultatory findings associated with idiopathic dilatation of the pulmonary artery are similar to those observed in patients with precapillary or postcapillary pulmonary hypertension—except that the S_2 is narrowly split, with P_2 markedly accentuated in intensity, and the pulmonary ejection sound is late due to vascular origin. Evidence of pulmonary insufficiency, right ventricular hypertrophy, and tricuspid regurgitation also is present in patients with significant pulmonary hypertension, but is absent in patients with idiopathic dilatation of the pulmonary artery. A right-sided ejection systolic murmur also is heard in atrial septal defect with relatively large left-to-right shunt. This ejection murmur occurs because of increased flow across the pulmonary valve, and it is not related to any pulmonary valve stenosis. Atrial septal defect can be suspected from the presence of wide fixed splitting of the S_2 and the evidence for right ventricular volume overload. Increased flow across the pulmonary valve associated with increased flow due to hyperthyroidism may also

be associated with an ejection systolic murmur. The ejection systolic murmur due to hyperthyroidism may have a scratchy quality (Means-Lerman scratch), and, frequently, the intensity of P_2 is increased due to mild to moderate pulmonary hypertension (75). The right-sided flow murmurs, however, usually are not associated with evidence of any hemodynamic compromise, such as right ventricular hypertrophy or right heart failure.

Innocent Murmurs

Innocent murmurs are, by and large, ejection in type and mid-systolic in timing. In adults, innocent ejection systolic murmurs are diagnosed when there is no evidence for right or left ventricular outflow tract obstruction. The short ejection systolic murmur associated with aortic sclerosis is often regarded as an innocent murmur. In children, a short, vibrating murmur can be heard over the mid-precordium, and it is not accompanied by any other abnormality. The precise mechanism of this murmur, termed *Still's murmur*, is not known (85,86). Another type of innocent systolic ejection murmur most frequently heard in children has a blowing quality and is heard best over the left second interspace. This murmur is thought to originate from the flow across the pulmonary artery. With increasing age, these innocent murmurs tend to decrease in intensity and, ultimately, disappear. In patients with straight back syndrome with a decreased anteroposterior diameter of the chest, a superficial ejection systolic murmur is heard over the left second interspace. The mechanism of this murmur remains unclear. It should be emphasized that whether an ejection systolic murmur is innocent should not depend on the duration or intensity of the murmur but on whether any other abnormal finding is present. If any abnormal finding coexists, such as an abnormality of S_2, even a short and sharp ejection systolic murmur should not be considered benign or innocent.

Regurgitant Systolic Murmurs

Regurgitant systolic murmurs can be pansystolic (holosystolic), early systolic, or late systolic in nature. A pansystolic murmur starts with the S_1 and lasts throughout the systole; the murmur extends to A_2 when it is left sided or to P_2 when it is right sided. In clinical practice, when a pansystolic or holosystolic murmur is recognized at the bedside, mitral regurgitation, tricuspid regurgitation, or ventricular septal defect should be considered in the differential diagnosis. The pansystolic mitral regurgitation murmur usually is of higher pitch and has a blowing character. The murmur frequently extends beyond the left ventricular systole, and A_2 is frequently drowned by the murmur. In patients with hemodynamically significant primary mitral regurgitation, the left ventricular pressure remains higher than the left atrial pressure throughout the systole and during the isovolumic relaxation phase. This hemodynamic abnormality explains the onset of pansystolic murmur with S_1 and extension of the murmur beyond A_2. Primary mitral regurgitation is defined when mitral regurgitation occurs due to the abnormalities of the components of the mitral valve apparatus, particularly of the mitral valve leaflets. Rheumatic mitral valve disease, bacterial endocarditis, and ruptured chordae due to idiopathic degenerations that produce pansystolic mitral valve prolapse are examples of primary mitral regurgitation. Hemodynamically significant chronic mitral regurgitation usually is associated with an S_3 gallop and left ventricular dilatation with preserved left ventricular ejection fraction. When mitral regurgitation results from mitral valve prolapse, particularly of the posterior leaflet, the radiation of the murmur occurs toward the base and occasionally radiates to the neck. Thus, this murmur can be confused with an ejection systolic murmur due to aortic stenosis. The murmur resulting from aortic stenosis is ejection in nature, and other findings for left ventricular outflow tract obstruction, such as delayed upstroke of the carotid pulse, are evident. The pansystolic murmur due to mitral valve prolapse occasionally can be confused with the ejection systolic murmur resulting from left ventricular outflow obstruction in hypertrophic cardiomyopathy. Bedside maneuvers (e.g., Valsalva's, hand grip, squatting, and standing) usually can differentiate between obstructive hypertrophic cardiomyopathy and primary mitral regurgitation. Posterior radiation of the mitral regurgitation murmur can be detected when auscultation is done over the thoracic spine or on the vortex. When the regurgitant murmur is heard over the lower back (i.e., on the lumbar spine), a substantial increase in left atrial size should be suspected. The S_2 in hemodynamically significant primary mitral regurgitation usually is widely split—a condition that results from decreased left ventricular ejection time. The intensity of P_2 remains normal until pulmonary hypertension develops, when its intensity is increased. Chronic primary hemodynamically significant mitral regurgitation is associated not only with an increase in left ventricular diastolic volume but also with normal ejection fraction. A displaced and hyperdynamic left ventricular apical impulse indicates normal ejection fraction and, therefore, primary mitral regurgitation. A displaced and sustained left ventricular apical impulse usually is associated with a decreased left ventricular ejection fraction, which, of course, can result from long-standing, severe mitral regurgitation, or it may indicate secondary mitral regurgitation due to dilated cardiomyopathy. Thus, normal left ventricular ejection fraction is helpful in establishing the diagnosis of primary mitral regurgitation. When the left ventricular ejection fraction seems to be decreased, further evaluation by echocardiography or cardiac catheterization is required to establish the mechanism of mitral regurgitation.

VIDEO

Video 15.51 Intraoperative transesophageal echo with color Doppler of a mitral valve with severe prolapse of the posterior mitral leaflet with 4+, anteriorly directed mitral regurgitation. A very prominent proximal convergence zone is seen in the left ventricle. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.52 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S_1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

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HEART SOUNDS

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HEART SOUNDS

Audio 15.55 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.56 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.57 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.58 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.59 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.60 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.61 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.62 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Tricuspid Regurgitation

The pansystolic murmur of tricuspid regurgitation usually is heard best at the lower left sternal border. Occasionally, the murmur is heard best near the cardiac apex because of significant right ventricular dilatation. The tricuspid regurgitation murmur, however, does not radiate to the left axilla. Frequently, the murmur of tricuspid regurgitation is heard along the right sternal border, over the epigastrium, and over the right subcostal region. The intensity of the murmur, as expected, increases during inspiration due to the increased venous return and right ventricular filling. Occasionally, a severe tricuspid regurgitation is associated with a diastolic flow murmur that is characterized as a short diastolic rumble along the lower left sternal border. When present, this murmur also increases in intensity during inspiration. Hemodynamically significant tricuspid regurgitation frequently is associated with right ventricular S_3 gallop, which also increases in intensity during inspiration. Tricuspid regurgitation is diagnosed at the bedside from the presence of a prominent ‘v’ wave followed by a sharp ‘y’ descent in the jugular venous pulse and systolic hepatic pulsation. Tricuspid regurgitation is most often secondary to pulmonary arterial hypertension; thus, a prominent left parasternal impulse and narrow splitting of S_2 with an accentuated P_2 suggest secondary tricuspid regurgitation. Although severe tricuspid regurgitation can be associated with reversed splitting of the S_2 due to a marked reduction in right ventricular ejection time, this finding is rarely observed at the bedside. Tricuspid regurgitation not accompanied by pulmonary hypertension (primary tricuspid regurgitation) can occur after right-sided bacterial endocarditis, right ventricular infarction, Ebstein’s anomaly, carcinoid heart disease, right ventricular papillary muscle dysfunction or infarction, and traumatic rupture of the chordae of the tricuspid valve. Predominant tricuspid regurgitation also can occur in rheumatic heart disease; however, rheumatic tricuspid regurgitation is almost always accompanied by aortic or mitral valvular disease. The diagnosis of primary tricuspid regurgitation depends on the demonstration of normal pulmonary artery pressure; thus, echo-Doppler evaluation is recommended.

HEART SOUNDS

Audio 15.63 Tricuspid stenosis and regurgitation. Note the holosystolic murmur of tricuspid regurgitation and soft diastolic blowing murmur of tricuspid stenosis. The loud second pulmonic sound connotes pulmonary hypertension. Apex. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and

Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Ventricular Septal Defect

Ventricular septal defect is associated with a pansystolic murmur, because the pressure in the right ventricle is lower than the pressure in the left ventricle throughout systole (87). This hemodynamic profile usually is observed in unrestricted ventricular septal defect with normal pulmonary vascular resistance. Thus, the S_2 in these patients usually is normal. The murmur is loud and may be accompanied by a thrill (46). The murmur is heard best over the left third or fourth interspace along the left sternal border. In supracristal ventricular septal defect, the maximum intensity of the murmur may be located over the left second interspace, and it can be confused with the murmur of pulmonary valve stenosis. The changes in the splitting of the S_2 may help in the differential diagnosis. A wide splitting of the S_2 with reduced intensity of P_2 is present in pulmonary stenosis, and a normal S_2 favors ventricular septal defect. The murmur of ventricular septal defect does not radiate to the axilla, as with mitral regurgitation, and does not increase in intensity with inspiration, as with tricuspid regurgitation. When the magnitude of the left-to-right shunt is large, wide physiologic splitting of the S_2 with normal intensity of P_2 is recognized. Furthermore, left ventricular S_3 gallop with or without a mid-diastolic rumble suggesting increased flow across the mitral valve can be heard at the cardiac apex. It should be appreciated that the intensity of the murmur correlates poorly with the degree of left-to-right shunt. A grade 5 murmur usually is associated with a high-velocity flow through a small hemodynamically insignificant ventricular septal defect (88). When the septal defect is large and the right and left ventricular pressures are equal, no murmur may be produced across the defect (89). Pansystolic murmur of mitral regurgitation and the murmur of ventricular septal defect decrease in intensity in response to amyl nitrite. Amyl nitrite inhalation reduces systemic vascular resistance and left ventricular/right ventricular pressure gradient associated with decreased left-to-right shunt. However, with certain vasodilators, which have the potential to decrease pulmonary vascular resistance by greater magnitude than systemic vascular resistance, the intensity of the murmur may increase. Nitroglycerin and sodium nitroprusside can cause a greater reduction of pulmonary vascular resistance than of systemic resistance and, therefore, may cause an increase in the magnitude of left-to-right shunt and the intensity of the murmur.

Early systolic regurgitant murmurs can occur in mitral and tricuspid valvular regurgitation and in certain types of ventricular septal defects. Early systolic regurgitant murmurs begin with the S_1 but do not extend to S_2 and generally have a decrescendo configuration. The early systolic murmur associated with mitral regurgitation is heard best at the cardiac apex, but it may have limited radiation. The early systolic murmur usually suggests relatively mild mitral regurgitation and results most frequently from left ventricular dilatation with or without annular dilatation. In some patients with mitral stenosis, an early systolic murmur is heard and probably represents mild mitral regurgitation. Mitral annular calcification may also be associated with an early systolic murmur, indicating mild mitral regurgitation. Mitral annular calcification is associated with lack of a reduction of the circumference of the annulus at the beginning of the systole, thus inducing mild mitral regurgitation.

Acute Severe Mitral Regurgitation

Early systolic murmur may also be associated with acute severe mitral regurgitation (90). The conditions producing acute severe mitral regurgitation include spontaneous rupture of the chordae, acute or subacute bacterial endocarditis of the mitral valve, papillary muscle rupture or infarction secondary to acute myocardial infarction, and disruption of the mitral valve apparatus due to chest trauma. In acute severe mitral regurgitation, there is regurgitation of a relatively large volume of blood into a normal-sized left atrium. As a result, there is a rapid increase in the magnitude of ‘v’ wave, and, during mid- or late systole, ‘v’ wave pressure may be similar to that of left ventricular systolic pressure; this loss of the pressure gradient between the left ventricle and left atrium during mid-systole stops the regurgitation, and, therefore, the murmur terminates before the A_2 (Fig. 15.12). In patients with ruptured chordae, left ventricular apical impulse usually is normal in character, indicating normal ejection fraction. In contrast, when mitral regurgitation occurs after acute myocardial infarction, left ventricular ejection fraction usually is depressed. In acute mitral regurgitation, a palpable S_4 and audible S_4 are commonly recognized. In contrast to chronic mitral regurgitation, an S_3 gallop may be absent. Acute severe mitral regurgitation almost always is associated with a substantial increase in the left atrial and pulmonary capillary wedge pressure and with postcapillary pulmonary hypertension. The S_2 is widely split, and the intensity of P_2 is increased (Fig. 15.12). The systolic murmur of acute mitral regurgitation may radiate to the axilla and back, especially if it is due to prolapse of the anterior leaflet of the mitral valve. When the murmur is loud, it may be conducted to the top of the head and to the lower back along the spinal column. Occasionally, the murmur is conducted to the base of the heart and over the neck vessels and can be confused with the murmur of aortic stenosis. However, the sharp initial upstroke of the carotid pulse and the wide physiologic splitting of the S_2 allow differentiation from aortic stenosis. The systolic murmur associated with primary tricuspid regurgitation is often early systolic and ends well before the S_2 (91). Early systolic murmur may also represent severe tricuspid regurgitation. When the right ventricular pressure is near normal and there is minimal gradient between right ventricular systolic pressure and right atrial pressure, the flow velocity is low and there is minimal turbulence, producing an abbreviated systolic murmur. In these patients, a large ‘v’ wave with a sharp ‘y’ descent frequently is encountered, indicating severe tricuspid regurgitation. There may also be a short mid-diastolic rumble (flow murmur) along the left sternal border, which increases in intensity during inspiration. Frequently, a right-sided S_3 gallop is appreciated. The early systolic murmur associated with severe tricuspid regurgitation also increases in intensity during inspiration. A right-sided S_4 with a prominent diastolic tricuspid flow rumble is appreciated when the tricuspid regurgitation is acute and severe, as occurs in endocarditis of the tricuspid valve. After total excision of the tricuspid valve, severe tricuspid regurgitation may not be associated with any systolic murmur, although there is a prominent ‘v’ wave in the jugular venous pulse, and systolic hepatic pulsations are easily appreciated. Palpable venous thrills and a murmur at the base of the neck are due to rapid retrograde flow to the jugular venous system (92).

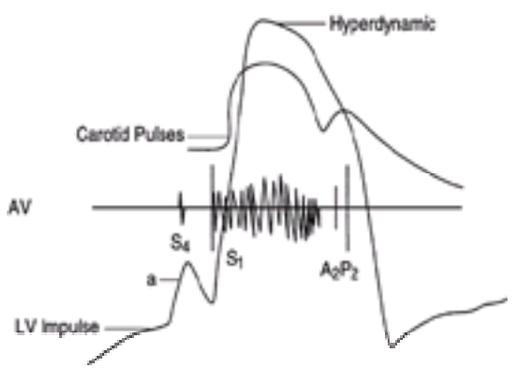

FIGURE 15.12 Schematic illustrations of the physical findings suggestive of acute or subacute severe primary mitral regurgitation (e.g., due to ruptured chordae). Examination of the carotid pulse reveals a sharp upstroke, but the amplitude is small. Palpation of the left ventricular (LV) impulse usually reveals a palpable ‘a’ wave and a hyperdynamic outward movement, indicating increased LV diastolic pressure and normal LV ejection fraction, respectively. Auscultation usually reveals a fourth heart sound (S_4), an early systolic murmur, and a relatively widely split second heart sound. The pulmonary component of the second heart sound (P_2) usually is accentuated, indicating pulmonary hypertension. A_2, aortic component of the second heart sound; AV, atrioventricular; S_1, first heart sound.

Other Systolic Murmurs

An early systolic murmur may occur in certain types of ventricular septal defects. The ventricular septal defects causing early systolic murmur usually are small and located in the muscular septa, which are sealed because of systolic thickening of the ventricular septa (93). This early systolic murmur associated with ventricular septal defect may indicate that the defect may eventually close spontaneously. The small ventricular septal defect causing early systolic murmur is not associated with any other hemodynamic compromise, such as right ventricular failure or pulmonary hypertension.

Late systolic murmurs are most frequently recognized in mitral regurgitation due to papillary muscle dysfunction or mitral valve prolapse. The late systolic murmur resulting from papillary muscle dysfunction in patients with ischemic heart disease may or may not be associated with mid-systolic clicks. The late systolic murmur due to papillary muscle dysfunction can be intermittent or constant and may occur only during myocardial ischemia. Late systolic murmur with or without mid-systolic clicks may occur due to fibrosis of the posterior left ventricular wall, as seen in patients with pseudohypertrophic muscular dystrophy. In these patients, the electrocardiogram always reveals evidence of posterior wall infarction (i.e., a tall R wave in the leads V_1 and V_2). Mitral valve prolapse associated with myxomatous disease of the mitral valve is the most common cause of late systolic murmur. The murmur is heard best at the apex and often has a late systolic crescendo character. Single or multiple mid-systolic clicks frequently accompany late systolic murmur associated with mitral valve prolapse.

Precordial whoop or honk also is associated with mitral valve prolapse. These murmurs are loud, high pitched, musical, sonorous, and vibratory. These murmurs are

heard best at the apex in late systole and can be intermittent. The unusual quality of this precordial whoop or honk is secondary to the high-frequency vibrations of the mitral apparatus.

Late systolic murmur with or without mid-systolic clicks can be observed in tricuspid regurgitation due to prolapse of the tricuspid valve. Isolated prolapse of the tricuspid valve is extremely unusual and almost always accompanies mitral valve prolapse. However, isolated tricuspid valve prolapse can be observed in patients with Ebstein's anomaly. Tricuspid valve prolapse may also produce precordial whoop or honk, as with mitral valve prolapse.

DIASTOLIC MURMURS

Early Diastolic Murmurs (Aortic Regurgitation)

Early diastolic murmurs typically start at the time of closure of the semilunar valves, and their onset coincides with S_2 (Table 15.10; Fig. 15.13). The aortic regurgitation murmur begins with the A_2, whereas the pulmonary regurgitation murmur begins with the P_2. The configuration of the aortic regurgitation murmur usually is decrescendo. The aortic regurgitation diastolic murmurs are high pitched and have a blowing character. Occasionally, these murmurs have a musical quality (diastolic whoop) and can be heard best with the diaphragm of the stethoscope. The musical quality of the aortic regurgitation murmur has been attributed to everted aortic cusps or perforated aortic cusps (94). The duration of the murmur is variable but usually terminates before the S_1. The low-intensity, high-pitched murmur of aortic regurgitation may not be heard easily until the patient sits and leans forward with the breath held during expiration and firm pressure with the diaphragm of the stethoscope is applied along the left sternal border or over the right second interspace. The radiation of an aortic regurgitation murmur is toward the cardiac apex. In some patients, the murmur can be heard best over the mid-precordium, along the lower left sternal border, or even over the cardiac apex. Radiation of the murmur along the right sternal border is more frequent in aortic regurgitation caused by aortic root abnormalities (95). After the diagnosis of aortic regurgitation is suspected at the bedside, it is desirable to assess the severity of aortic regurgitation (Fig. 15.14). In hemodynamically significant chronic aortic regurgitation, the carotid pulse upstroke is sharp, and the volume is increased. Frequently, a pulsus bisferiens quality of the carotid arterial pulse is appreciated. In patients with hemodynamically significant chronic aortic regurgitation, arterial diastolic pressure usually is <60 mm Hg. The pulse pressure is increased substantially in severe aortic regurgitation. The presence of water-hammer pulse or Corrigan's pulse is also suggestive of hemodynamically significant chronic aortic regurgitation. The various peripheral signs of chronic aortic regurgitation should also be determined at the bedside. Hemodynamically significant chronic aortic regurgitation is almost always associated with a considerable increase in left ventricular size, which should be determined at the bedside and by chest x-ray. The lack of cardiac enlargement usually suggests hemodynamically insignificant chronic aortic regurgitation. In severe aortic regurgitation, ejection systolic murmur along the left sternal border and over the aortic area indicates increased stroke volume rather than aortic stenosis. S_2 can be paradoxically split due to selective increase in the left ventricular stroke volume, which increases its ejection time. Frequently, it is difficult to appreciate A_2, which may be decreased in intensity or absent because of the lack of coaptation of the valve cusp (96). Left ventricular apical impulse usually is displaced downward and laterally and maintains the normal asynchronous sequence with the carotid pulse upstroke, indicating normal left ventricular ejection fraction. In severe chronic aortic regurgitation, there may be a substantial increase in left ventricular mass due to eccentric hypertrophy that may be associated with a sustained left ventricular apical impulse. In these circumstances, it is desirable to assess ventricular function by echocardiography or radionuclide ventriculography. The presence of S_3 gallop in patients with hemodynamically significant chronic aortic regurgitation usually indicates reduced left ventricular ejection fraction. The presence of S_3 may also indicate increased left ventricular diastolic pressure. A soft S_1 in the absence of a prolonged PR interval in chronic aortic regurgitation indicates elevated left ventricular diastolic pressure. The duration of the aortic regurgitant murmur does not correlate well with the severity of aortic regurgitation. The presence of a pandiastolic murmur is more likely to be associated with significant aortic regurgitation. The Austin Flint murmur is a mid-diastolic rumble with late systolic accentuation; it is heard best at the cardiac apex and results from relative functional mitral stenosis. Evidence of pulmonary venous congestion and pulmonary hypertension should also be considered indicative of hemodynamically significant aortic regurgitation if these hemodynamic abnormalities are related to aortic regurgitation.

TABLE 15.10 DIFFERENTIAL DIAGNOSIS OF THE DIASTOLIC MURMUR

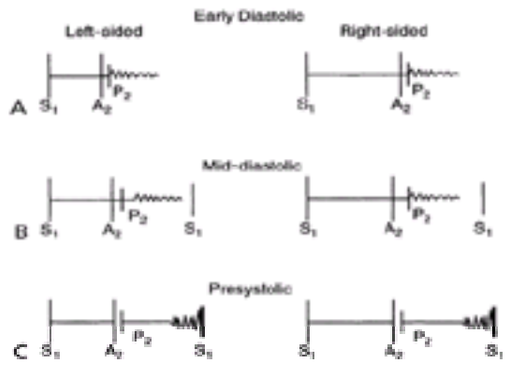

FIGURE 15.13 A: An early diastolic murmur, when the left-sided murmur starts with the aortic component of the second heart sound (A_2) and when the right-sided murmur starts with the pulmonary component of the second heart sound (P_2) or soon after P_2. **B:** A mid-diastolic murmur starts after A_2 when left sided and after P_2 when right sided and does not extend up to the first heart sound (S_1). **C:** A presystolic murmur starts before S_1 and terminates at S_1.

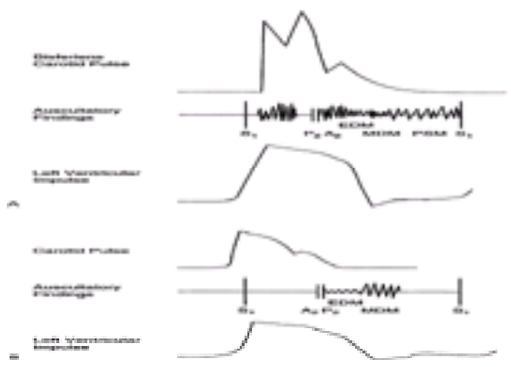

FIGURE 15.14 A: Schematic illustrations of the physical findings that can indicate hemodynamically significant chronic aortic regurgitation and can be appreciated at the bedside. The carotid pulse upstroke is sharp or may have bisferiens quality. The amplitude is increased. Left ventricular apical impulse reveals a hyperdynamic quality that suggests increased left ventricular volume with normal ejection fraction. Auscultation usually reveals an early diastolic murmur (EDM), and an Austin Flint murmur with both mid-diastolic (MDM) and presystolic (PSM) components are usually appreciated. The second heart sound can be paradoxically split (P_2-A_2), and the first heart sound (S_1) may be soft if left ventricular diastolic pressure is elevated. **B:** Schematic illustrations of the physical findings that may indicate hemodynamically significant acute aortic regurgitation. The carotid pulse usually is normal. Left ventricular apical impulse is also normal. The EDM of aortic regurgitation usually is brief.

Austin Flint murmur only consists of an MDM component. The S_1 is soft or absent as the second heart sound is physiologically split (A_2-P_2), but the pulmonary component of the second heart sound (P_2) may be increased in intensity, indicating pulmonary hypertension. A_2, aortic component of the second heart sound.

HEART SOUNDS

Audio 15.64 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

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VIDEO

Video 15.68 Transgastric view (transesophageal echo) of the mitral valve in a patient with severe aortic insufficiency. Note the fluttering of the anterior mitral leaflet (*left*) due to the jet of aortic insufficiency hitting it (color flow seen on the left). (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The hemodynamic consequences of acute severe aortic regurgitation are characterized by a sudden, severe volume overload to a nondilated left ventricle, which is associated with a rapid increase in left ventricular diastolic pressure and, often, equalization of left ventricular and aortic pressures in mid-diastole. The regurgitant murmur, therefore, can be brief (97). Because of a noncompliant ventricle and a substantial increase in left ventricular diastolic pressure, pulmonary venous pressure and pulmonary artery pressure may increase considerably—a condition that can be suspected from the increased intensity of P_2 as left ventricular wall stress increases due to the lack of compensatory eccentric hypertrophy—and forward stroke volume may decrease, which may cause a decrease in carotid pulse amplitude and arterial pulse pressures. Displacement of the left ventricular apical impulse is not appreciated. The apical impulse maintains the normal character, indicating normal ejection fraction. Decreased intensity of the S_1 or absent S_1 indicates acute severe aortic regurgitation and results from premature closure of the mitral valve due to a marked and rapid increase in left ventricular diastolic pressure (Fig. 15.14). A marked increase in left ventricular end diastolic pressure may also prevent effective left ventricular filling during left atrial systole; thus, an S_4 gallop may be absent in acute aortic regurgitation.

Mild aortic regurgitation without any hemodynamic compromise can occur in association with bicuspid aortic valve or systemic hypertension. The bicuspid aortic valve can be suspected at the bedside from the presence of an aortic ejection sound, a short ejection systolic murmur, and a normal S_2. Aortic regurgitation resulting from systemic hypertension usually is associated with an accentuated A_2, and the duration of the regurgitation is brief. However, the duration of the murmur varies with the degree of systemic hypertension. The higher the diastolic blood pressure, the longer the duration of the murmur.

Dock's Murmur

Diastolic murmur similar to murmurs of aortic regurgitation can be heard in some patients with stenosis of the left anterior descending coronary artery (Dock's murmur) (98). The murmur of left anterior descending coronary artery stenosis, however, is not transmitted widely and usually is heard best over the left second or third interspace, a little lateral to the left sternal border. This murmur is caused by turbulent flow across the coronary artery stenosis, and its duration may be short or long. After successful angioplasty or coronary artery bypass surgery, this murmur is abolished.

Pulmonary Regurgitation (Graham Steell's Murmur)

An early diastolic murmur also results from pulmonary regurgitation. In adult patients, pulmonary regurgitation occurs most frequently due to pulmonary artery hypertension (Graham Steell's murmur) (99,100). The early diastolic murmur associated with pulmonary hypertension is a high-pitched, blowing murmur that starts with an accentuated P_2 and can be of variable duration. In Eisenmenger's syndromes associated with atrial septal defect or patent ductus arteriosus, when right ventricular diastolic pressure may remain normal, the pulmonary regurgitant murmur may be pandiastolic. On the other hand, in the presence of modest precapillary or postcapillary pulmonary hypertension, the duration of the murmur may be brief. The pulmonary regurgitant murmur has a decrescendo configuration like that of aortic regurgitation. The murmur may increase in intensity during inspiration and may be very localized. It is heard best over the left second and third interspaces. Pulmonary regurgitation is suspected when other findings of pulmonary hypertension are present and peripheral signs of aortic regurgitation are absent.

Pulmonary regurgitation can occur in the absence of pulmonary hypertension, as in patients with idiopathic dilatation of the pulmonary artery. Pulmonary regurgitation is also frequently observed after pulmonary valvulotomy. It may occur as a complication of right-sided endocarditis and with the congenital absence of the pulmonary valve. In these conditions, the pulmonary artery diastolic pressure is normal or low, and the pulmonary regurgitant murmur is of lower pitch. The murmur usually begins after the onset of P_2 (101). The degree of pulmonary regurgitation associated with idiopathic dilatation of the pulmonary artery or after pulmonary valvulotomy usually does not produce any hemodynamic compromise. Congenital absence of the pulmonary valve may be associated with severe pulmonary regurgitation, and a loud "to

and fro" murmur and absent pulmonary component of the S_2 should raise the suspicion of absent pulmonary valve.

Mid-Diastolic Murmurs

The mid-diastolic murmurs result from turbulent flow across the atrioventricular valves during ventricular diastole. These murmurs result from either functional or organic mitral or tricuspid valve stenosis.

Mitral Stenosis

The mid-diastolic murmur of mitral stenosis has a rumbling character and is heard best with the bell of the stethoscope and over the left ventricular impulse and with the patient in the left lateral decubitus position. If the stenotic mitral valve is mobile, an opening snap and a loud S_1 are present. The mid-diastolic rumble starts with the opening snap and may extend to the S_1 with presystolic accentuation (Fig. 15.9). The presystolic component of the mid-diastolic murmur of mitral stenosis may be present in sinus rhythm and atrial fibrillation (102). The mechanism of the presystolic accentuation of the mid-diastolic murmur is not entirely clear. It was initially thought to be related to atrial systole. However, it may occur in the presence of atrial fibrillation. Doppler-echocardiographic studies have suggested that the presystolic murmur is related to antegrade flow through a progressively narrowing mitral orifice during the end of the ventricular diastole. It should be recognized that the onset of mitral valve closure starts approximately 60 ms before the valves close and produce S_1. With an obstructed mitral valve, the presence of a pressure gradient at end diastole allows antegrade flow across the closing mitral valve before the mitral valves close completely, explaining the presystolic murmur—even in patients with atrial fibrillation. The duration of the murmur correlates well with the severity of mitral stenosis. The longer the mid-diastolic murmur, the more severe the mitral stenosis. However, the duration of the murmur should be assessed during normal or slower heart rate. In the presence of sinus tachycardia or rapid ventricular response with atrial fibrillation, a pandiastolic rumble may not necessarily indicate severe mitral stenosis. Although duration of the mid-diastolic murmur correlates reasonably well with the severity of mitral stenosis, there is a poor correlation between the intensity of the murmur and the severity of mitral stenosis. The intensity of the murmur is related not only to the severity of the mitral valve obstruction but also to the flow across the valve. When there is a marked reduction in cardiac output resulting from severe mitral valve obstruction, the flow across the valve also is markedly reduced and may be associated with a soft murmur or absent murmur (silent mitral stenosis). At the bedside, the severity of mitral stenosis also can be assessed by noting the A_2–opening snap interval. The shorter the A_2–opening snap interval, the higher the left atrial pressure and the higher the pressure gradient across the mitral valve. In patients with severe postcapillary pulmonary hypertension associated with low cardiac output and calcified immobile mitral valve, the auscultatory findings of mitral stenosis may not be recognized at the bedside. The severity of mitral stenosis also should be suspected from the associated findings, such as evidence of pulmonary hypertension.

HEART SOUNDS

Audio 15.69 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm^2. Note the loud S_1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border (*first clip*) and apex (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.70 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm^2. Note the loud S_1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border (*first clip*) and apex (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.71 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.72 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.73 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.74 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Left Atrial Myxoma and Tumor Plop

Although rheumatic mitral stenosis is the most common cause of mitral valve obstruction, left atrial myxoma, left atrial ball valve thrombus, cor triatriatum, and congenital mitral stenosis all can be associated with findings of mitral valve obstruction. Left atrial myxoma may cause intermittent obstruction of the mitral valve and, therefore, may be associated with a mid-diastolic murmur. Indeed, the auscultatory findings may be identical to those of rheumatic mitral stenosis (103). A loud tumor plop sound at the beginning of the mid-diastolic rumble may be similar to opening snap. The presystolic component of the mid-diastolic murmur may occur when the tumor is ejected into the left atrium at the beginning of the systole. A systolic murmur of mitral regurgitation may also be present. The auscultatory findings of left atrial myxoma may vary from examination to examination and even with changes in the body position. Patients with left atrial myxoma may also present with positional syncope and intermittent pulmonary edema.

Video 15.75 Myxoma tumor blush from left circumflex artery. Contrast injection of left coronary showing perfusion of the tumor. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

OTHER DIASTOLIC MURMURS

Tricuspid valve stenosis is associated with a mid-diastolic rumbling murmur, which usually is heard best in the xyphoid area or over the lower left third and fourth interspaces along the sternal border. The diastolic murmur resulting from tricuspid valve obstruction increases in intensity during inspiration (Carvello's sign). The mid-diastolic murmur of tricuspid valve stenosis may be preceded by tricuspid opening snap. As right atrial systole occurs before the left atrial systole, the diastolic murmur of tricuspid stenosis may have a crescendo/decrescendo configuration without presystolic accentuation (104). Isolated tricuspid stenosis is infrequently encountered in clinical practice. Systemic lupus erythematosus and carcinoid heart disease may produce tricuspid stenosis. Rarely, constrictive pericarditis may cause functional tricuspid stenosis and may be associated with a mid-diastolic murmur. Tricuspid stenosis most frequently occurs in association with rheumatic mitral valve disease. Right atrial myxoma is an infrequent cause of tricuspid valve obstruction and may be associated with mid-diastolic murmur with presystolic accentuation preceded by a tumor plop sound. Both tumor plop sound and mid-diastolic murmur resulting from tricuspid valve obstruction due to right atrial myxoma increase in intensity during inspiration.

Diastolic rumbles may occur due to high flow across the atrioventricular valves. Diastolic murmurs at the cardiac apex are appreciated in patients with severe isolated mitral regurgitation or ventricular septal defect and patent ductus arteriosus with a large left-to-right shunt. Similarly, a large left-to-right shunt associated with atrial septal defect may cause a mid-diastolic murmur along the left sternal border due to increased flow across the tricuspid valve. Similar low-pitched, rumbling murmurs may be present in hyperkinetic states such as hyperthyroidism, chronic severe anemia, and arteriovenous fistulae. These flow murmurs occur not due to anatomic obstruction of the atrioventricular valves but due to functional stenosis.

Carey-Coombs Murmur

Mitral valvulitis associated with acute rheumatic fever may cause a short diastolic rumble (Carey-Coombs murmur) (105). This rumble usually is preceded by an S_3 gallop and most often is recognized in children in the presence of fever and anemia. These physical findings do not indicate mitral valve obstruction, but they do indicate rheumatic carditis.

Austin Flint Murmur

The mid-diastolic murmur associated with aortic regurgitation in the absence of organic mitral stenosis is called the *Austin Flint murmur*, after the man who first described this murmur in 1862 (106). It is heard best at the apex and can be mid-diastolic or presystolic in timing. In some patients, however, a long mid-diastolic rumble with presystolic accentuation is appreciated. Unlike organic mitral stenosis, the Austin Flint murmur is preceded by an S_3 gallop rather than opening snap. The S_1 in patients with aortic regurgitation and the Austin Flint murmur is normal or decreased in amplitude, but in mitral stenosis, S_1 usually is increased in amplitude. The duration and intensity of the Austin Flint murmur is directly related to the severity of aortic regurgitation. With amyl nitrite inhalation and when aortic regurgitation is decreased, the Austin Flint murmur is decreased in duration and intensity. The mid-diastolic murmur of organic mitral stenosis, however, increases in intensity and duration after amyl nitrite inhalation. In most cases of severe aortic regurgitation—particularly when there is a marked increase in left ventricular end diastolic pressure, as in acute severe aortic regurgitation—the presystolic component of the Austin Flint murmur is not appreciated. In this situation, there is reversal of the pressure gradient between the left ventricle and the left atrium in mid-diastole, which causes premature closure of the mitral valve and loss of the presystolic component of the Austin Flint murmur.

Video 15.76 Parasternal long-axis view (transthoracic echo) of a bicuspid aortic valve with prolapse of the anterior leaflet causing posteriorly directed aortic insufficiency. The aortic insufficiency hits the anterior mitral leaflet, causing deformation of this leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The mechanisms of the genesis of the Austin Flint murmur are incompletely understood and likely to be multifactorial (107). Although late diastolic mitral regurgitation has been excluded as one of the mechanisms, antegrade flow across the mitral valve with closing mitral orifice and incomplete mitral valve opening because of the regurgitant jet impinging on the anterior leaflet of the mitral valve may be contributory to the genesis of the Austin Flint murmur. In clinical practice, an easily appreciated Austin Flint murmur usually indicates hemodynamically significant aortic regurgitation.

Rytand's Murmur

Occasionally in patients with complete atrioventricular heart block, a mid-diastolic murmur is heard at the apex (Rytand's murmur) and may be confused with mitral stenosis. The slow heart rate, variable duration of the murmur, changing intensity of the S_1, and lack of opening snap are helpful findings for the differential diagnosis. The mechanism of Rytand's murmur is not clear, but increased flow due to slow heart rate and increased antegrade flow with atrial contraction, which occurs randomly, may be contributory (108).

CONTINUOUS MURMURS

Continuous murmurs (109) begin in systole and extend up to diastole without interruption. Continuous murmurs do not necessarily occupy the total duration of systole and diastole. These murmurs may result from blood flow from a higher-pressure chamber or vessel to a lower-pressure system associated with the persistent pressure gradient between the structures during systole and diastole. Patent ductus arteriosus is one relatively common cause of a continuous murmur that is occasionally encountered in adult patients. Descending thoracic, aortic pressure is higher than pulmonary artery pressure during both systole and diastole, and the blood flow from the high-pressure descending thoracic aorta to the low-pressure pulmonary artery causes the continuous machinery murmur (Gibson murmur) (110). The maximum intensity of the murmur usually occurs at the S_2, and the duration of the murmur is variable and depends on the pressure difference between aorta and the pulmonary artery. When pulmonary hypertension develops, pulmonary diastolic pressure increases, and the diastolic portion of the continuous murmur becomes shorter. When the diastolic pressure in the pulmonary artery is equal to the aortic pressure, the diastolic component of the continuous murmur is absent. With more severe pulmonary hypertension, the pulmonary artery systolic pressure may be similar to the aortic systolic pressure, and the systolic component of the murmur may be absent (silent patent ductus arteriosus). In patients with severe pulmonary hypertension with reversal of shunt across the patent ductus arteriosus (Eisenmenger's syndrome),

differential cyanosis and clubbing may provide clues for diagnosis.

Continuous murmurs may be present in patients with aorticopulmonary window or Lutembacher's syndrome, which consists of a small atrial septal defect and mitral valve obstruction (111), total anomalous pulmonary venous drainage, and mitral stenosis with a persistent left superior vena cava. These conditions, however, are rarely encountered in clinical practice. A communication between the sinus of Valsalva and the right atrium or right ventricle is associated with a continuous murmur. Systemic and pulmonary arteriovenous fistulae also produce continuous murmurs. Systemic arteriovenous communications usually produce loud continuous murmurs. The murmurs of pulmonary arteriovenous fistulae are softer and may be primarily systolic. Coronary arteriovenous fistulae are occasionally encountered in adult cardiac patients. The location, duration, and character of the continuous murmur due to a coronary atriovenous communication depend on the anatomic type of coronary arteriovenous fistulae. The right coronary and right atrial or coronary sinus communication produce continuous murmurs that usually are located along the parasternal areas. The circumflex coronary artery–coronary sinus communication, however, produces continuous murmurs in the left axilla (112).

VIDEO

Video 15.77 Calcified sinus of Valsalva aneurysm ruptured into the right atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.78 Ruptured sinus of Valsalva aneurysm. Auscultation performed in a 23-year-old male who presented with sudden onset of shortness of breath. Echocardiography reveals rupture of an aneurysm of the right coronary cusp into the right ventricle. The loud systolic murmur continues well into diastole. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.79 Ruptured sinus of Valsalva aneurysm. Auscultation performed in a 23-year-old male who presented with sudden onset of shortness of breath. Echocardiography reveals rupture of an aneurysm of the right coronary cusp into the right ventricle. The loud systolic murmur continues well into diastole. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.80 Ruptured sinus of Valsalva aneurysm. Auscultation performed in a 23-year-old male who presented with sudden onset of shortness of breath. Echocardiography reveals rupture of an aneurysm of the right coronary cusp into the right ventricle. The loud systolic murmur continues well into diastole. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 15.81 Ruptured sinus of Valsalva aneurysm. Auscultation performed in a 23-year-old male who presented with sudden onset of shortness of breath. Echocardiography reveals rupture of an aneurysm of the right coronary cusp into the right ventricle. The loud systolic murmur continues well into diastole. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Constriction in the systemic or pulmonary arteries can be associated with a continuous murmur due to a pressure gradient across the narrow segment during both systole and diastole. In coarctation of the aorta, a continuous murmur can be heard in the back overlying the areas of constriction. Continuous murmurs in coarctation of the aorta may also originate from the tortuous collateral arteries, which are heard in the back over the interscapular regions. Sometimes, large, tortuous intercostal vessels are visible when the shoulders are rotated and separated (Suzman's sign) (113). Pulmonary artery branch stenosis may also be associated with continuous murmur. Chronic obstruction of the pulmonary artery from pulmonary embolism has been shown to produce continuous murmur on rare occasions. Bronchial arterial collateral vessels develop in certain types of cyanotic congenital heart disease, as in tricuspid atresia and pulmonary atresia with ventricular septal defect; these collateral vessels can produce continuous murmur. An example of innocent continuous murmur is venous hum (114). The venous hum is heard with the patient in the sitting position and usually in the supraclavicular areas; it disappears when the patient is in the supine position. A loud, left-sided venous hum transmitted below the clavicle should not be mistaken for the patent ductus arteriosus. A venous hum is not heard in the supine position, and pressure on the internal jugular vein abolishes the venous hum. The mammary shuffle associated with pregnancy is another example of an innocent continuous murmur. These innocent murmurs are usually of higher frequency (i.e., high-pitched) and louder in systole. The causes of continuous murmurs and the mechanisms of their geneses are summarized in Table 15.11.

Continuous murmur due to flow from high- to low-pressure systems
Systemic artery to pulmonary artery connection—patent ductus arteriosus, aortopulmonary window, truncus arteriosus, pulmonary atresia, and coronary arteriovenous fistulae
Systemic artery to right heart connection—rupture of sinus of Valsalva coronary artery fistulae
Left-to-right atrial shunting—Lutembacher's syndrome
Venovenous shunts—anomalous pulmonary veins, portosystemic shunts
Arteriovenous fistulae—systemic or pulmonic
Continuous murmur secondary to localized arterial obstruction
Coarctation of the aorta, pulmonary artery branch stenosis, carotid stenosis
Continuous murmur due to rapid blood flow
Venous hum, mammary shuffle

TABLE 15.11 CAUSES OF CONTINUOUS MURMUR

HEART SOUNDS

Audio 15.82 Coarctation of the aorta. Auscultation performed in a 54-year-old female patient with coarctation of the aorta, status post Dacron graft replacement of the proximal descending aorta and persistent severe graft stenosis. The mid-systolic ejection murmur is a result of residual high-grade coarctation. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

CONTROVERSIES AND PERSONAL PERSPECTIVES

Often in today's clinical practice, bedside examination is considered unnecessary and a waste of time. Indeed, the investigative tools available today are far superior to the bedside examination in establishing the diagnosis of the anatomic abnormality and severity of the pathophysiologic consequences. However, only bedside examination allows you to know the patient, understand the patient's sufferings and expectations, and establish rapport with the patient. Thus, I believe that we should practice more—not less—bedside physical examination.

CONCLUSION

Bedside clinical examination of the cardiovascular system provides useful information about the potential etiology of valvular, myocardial, and pericardial diseases, which can be confirmed by further noninvasive and invasive investigations. Physical examination also is helpful in deciding the appropriate investigations to establish the diagnosis. Furthermore, appropriate clinical evaluations are helpful to assess the therapeutic response and prognosis of patients with cardiovascular disorders. There is no cost-effective substitute for the information and insight derived from a careful bedside examination.

THE FUTURE

The future of the physical examination as an investigation tool is likely to be compromised with the increasing availability of sonocardiographic and other allied imaging techniques. It should be remembered, however, that the bedside physical examination is still the cheapest and, in certain circumstances, most informative investigation.

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16

STABLE ISCHEMIC SYNDROMES

PAUL W. ARMSTRONG

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The phenomenon of coronary atherosclerosis mediates the development of myocardial ischemia through a complex interaction of fixed atherosclerotic plaque, impaired coronary vasomotion, and diffuse disease underestimated by conventional coronary angiography.

The frequency of angina grossly underestimates the frequency of ischemia; it is the composite impact of the latter that has an important impact on prognosis. Attention to the particular diagnostic and therapeutic strategies most appropriate to individual patient needs is warranted. Exercise testing remains the pivotal diagnostic test for assessment of patients with stable angina pectoris. Perfusion imaging and dobutamine echocardiography (ECHO) can complement exercise testing, especially in patients with inconclusive results or of intermediate risk. Although not routinely indicated, ambulatory ST-segment monitoring may be helpful in establishing the relationship between symptoms and objective manifestations of ischemia, quantifying the total ischemic burden and confirming the presence of Prinzmetal's variant angina.

Matching the intensity of risk-reduction strategies to an accurate assessment of individual patient risk is a fundamental responsibility of the practitioner. Intelligent medical (both pharmacologic and nonpharmacologic) management offers genuine benefits in controlling symptoms and ischemia. Revascularization is a valuable alternative in high-risk subsets and in those in whom symptoms and/or ischemia persist on effective medical management. Future opportunities of exciting potential that harness the results of ongoing research into the pathogenesis, diagnosis, and treatment of coronary disease offer exciting prospects for patients and physicians alike.

HISTORY AND BACKGROUND

But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and the sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris.

Those who are afflicted with it are seized while they are walking (more especially if it be uphill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes.

This elegant description by William Heberden first published 225 years ago eloquently captures the symptomatic characteristics of angina pectoris (1). It is a common and important symptom affecting many patients with coronary artery disease. Recent estimates indicate that there are 6.75 million Americans with angina pectoris, and an additional 350,000 new cases occur each year (2). These figures, however, are likely very conservative: Current estimates reveal that between 3.0% and 3.5% of patients with angina experience an acute myocardial infarction each year (3,4). Back-calculating from the observed rates of patients with acute myocardial infarction who survive to hospital admission suggests a more realistic prevalence for stable angina of at least 16.5 million individuals (5). The prevalence of angina pectoris in elderly men varies from 21.1% (aged 65 to 69 years) to 27.3% (aged 80 to 84 years), whereas in women the comparable figures are 13.7% (aged 65 to 69 years) and 24.7% (aged 85 years and older) (6). The socioeconomic implications of angina pectoris are staggering and in the United States alone likely extend to tens of billions of dollars. A comprehensive approach to diagnostic assessment, risk stratification, medical treatment, revascularization, and prevention of other cardiac complications through secondary prevention is a key priority and responsibility of the physician.

PATHOPHYSIOLOGY

Stable Angina

Cardiac ischemic pain is thought to arise from sensory afferents located in the coronary vessels and myocardium (7). These afferents were reasoned to be sensitive to both stretch and irritation promoted by local expression of noxious chemical stimuli. The latter theory has gained credence through the work of Crea and colleagues (8), who demonstrated that intracoronary adenosine reproduced typical cardiac ischemic pain in patients with stable angina pectoris yet did not promote electrocardiographic (ECG) signs of ischemia. Furthermore, in some of these same patients, prior treatment with aminophylline, an antagonist of adenosine P_1 receptors, attenuated exercise-induced angina without nullifying the ST-segment depression associated with the symptoms. Maseri and colleagues (7) have categorized cardiac ischemic pain into three components: (a) a diffuse visceral component, (b) a better-defined somatic component conforming to a distribution by dermatomes, and (c) an interpretive component modulated by psychological factors. Pain-producing stimuli traveling through afferent nerve endings converge with others from the same dermatome on the same dorsal horn spinal neurons. Cardiac afferents distributed from the first to the fourth thoracic spinal neurons interact with other afferents and descending signals from supraspinal sources, then ascend to the thalamus and from thence to the cortex, where the decoding is processed by a complex collage of physical, emotional, and other factors.

The symptomatic discomfort that represents angina pectoris is usually associated with inadequate oxygenation of the myocardium. Most often this reflects underlying coronary atherosclerosis that involves at least a 50% diameter stenosis sufficient to reduce maximal blood flow during exercise (9). Whereas fixed segmental coronary stenosis may preclude adequate myocardial blood flow to meet the increased oxygen requirements imposed by physical exercise, it is important to realize that coronary atherosclerosis is a diffuse vascular disease associated with deficient endothelial-dependent relaxation (10). It is this deficiency that may mediate exercise-induced coronary vasoconstriction of a narrowed coronary artery, with resultant imbalance between oxygen supply and demand culminating in angina. Moreover, it is clear that the reduction in coronary vascular reserve is not limited to angiographically abnormal vascular beds and may extend to apparently normal distant nonischemic coronary vascular regions in patients with single-vessel coronary disease with and without prior myocardial infarction, as well as in patients with mild coronary artery abnormalities (11,12).

In 1962, Smith and Papp (13) urged that clinicians develop a broader perspective of angina than one that focused solely on effort-induced symptoms. They emphasized the occurrence of sporadic attacks at night and with mental stress or emotion, highlighted the role of postural change in inducing angina, and examined in detail the

impact of angina linked to cervical spondylitis and a variety of gastrointestinal disorders. Experimental evidence was cited to implicate the role of distention of both the gut and biliary tree in reducing coronary flow and the potential for ameliorating this by section of the vagi nerve. Maseri and colleagues further elaborated on this issue by suggesting that angina could be classified into primary, secondary, and mixed forms. The term *primary* was used to implicate transient impairments of coronary flow, many of which were spontaneous, unpredictable, and unrelated to levels of physical activity, in contrast to *secondary angina*, which was deemed prototypically related to an increase in oxygen consumption with effort in the face of fixed coronary stenosis. Recognizing that the same patient might experience both forms of symptoms, a third category of mixed angina was also suggested.

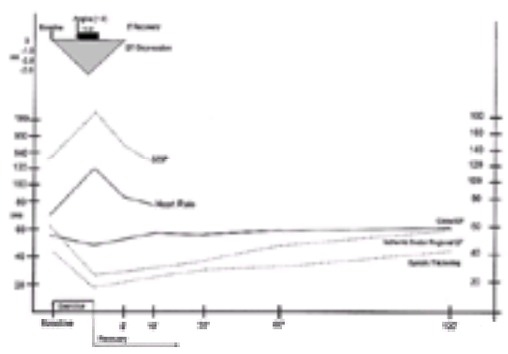
Exposure to cold results in the earlier development of exercise-induced angina at a similar rate pressure product in stable coronary disease patients, implying a failure to provide a commensurate increase in coronary blood flow due to an increase in coronary vascular resistance. In a study of 24 patients before formal testing, one-third was classified as sensitive based on an angina questionnaire (14). At approximately 8°C versus 20°C, these individuals demonstrated lessened time (by approximately 30%) to 1-mm ST depression yet had a similar exercise duration and rate pressure product, thereby implying a reduction in coronary flow (14). Similar findings are evident with cigarette smoking—that is, it produces an increase in myocardial oxygen consumption but restricts the commensurate increase in coronary flow. Importantly, in those individuals who were identified as cold sensitive, the phenomenon was prevented with phentolamine and aggravated by beta-blockers, clearly incriminating alpha-adrenergic stimulation of the coronary circulation as the operative mechanism (14).

Finally, exposure to carbon monoxide has been shown to have a deleterious effect on patients with angina pectoris (15). A blood carboxyhemoglobin of 6% seems to be approximately the threshold for exacerbating left ventricular dysfunction, exercise performance, and time to angina. This degree of exposure would be expected to be achieved in a variety of environmental situations such as closed automobiles amidst heavy freeway traffic, as well as during chronic smoking. Indeed, smoking has a direct and adverse effect on the frequency of angina and exercise performance (16). It interferes with the antianginal efficacy of beta-blockers as well as nifedipine, where the heart-rate increments associated with smoking seem especially marked (17).

Mental as well as physical stress is known to precipitate angina pectoris and ischemia; mental stress is mediated by sympathetic activation, with a commensurate increase in myocardial oxygen requirements resulting from tachycardia, hypertension, and increased contractility (18). This exerts a double jeopardy on the ischemic myocardium by also reducing regional coronary flow (19). Although failure of endothelial-dependent epicardial coronary vasodilatation is evident during mental stress in patients with stable angina, it seems likely that this is, by itself, inadequate to explain the genesis of ischemia (19). Hence, vasoconstriction of coronary resistance vessels is likely operational. Several neurohumoral factors may be at work to produce this, including serotonin, neuropeptide Y, norepinephrine, angiotensin II, thromboxane A_2, endothelin, and arginine vasopressin (20). Moreover, as many as one of five stable angina patients has been shown to have features of recent injury and/or repair in their culprit coronary lesions; hence, the stage is obviously set in such patients for both aggregation and activation of platelets (21). The demonstration of increased levels of both serotonin and thromboxane A_2 in the coronary sinus of patients with angina pectoris, coupled with the capacity of ketanserin, a selective serotonin II receptor antagonist, to blunt coronary vasoconstriction is further support for this reasoning (22).

Silent Ischemia

Ambulatory ECG monitoring of patients with established coronary disease and stable angina has revolutionized our understanding of myocardial ischemia in these individuals. In patients with established or a high likelihood of coronary disease, transient ST-segment depression of at least 1 mm persisting for at least 1 minute has been well validated as a marker of myocardial ischemia through concomitant studies involving positron emission tomography, radionuclide and echocardiographic assessment of ventricular function, and myocardial perfusion imaging (18,23,24 and 25). At least 75% of the ischemia occurring in patients with stable angina is clinically silent, and effective symptomatic control of angina notwithstanding, a substantial proportion (i.e., 40% of patients with stable angina) continue to demonstrate ischemia on ambulatory monitoring (26). On reflection, it is perhaps not surprising that evidence of ischemia occurs so frequently in the absence of symptomatic complaints, given prior pathophysiologic studies of myocardial ischemia in patients with stable coronary disease. Ample evidence in the literature predating the concept of silent ischemia clearly documents a chronologic sequence of events during ischemia that begins with diminished myocardial perfusion and is followed by diminished diastolic and systolic left ventricular function, abnormal myocardial lactate metabolism, ECG changes, and then finally symptoms of angina pectoris (26,27). Moreover, impairment of contractile function may persist for a surprisingly extended period of time—that is, 60 to 120 minutes after exercise-induced angina despite abrupt normalization of hemodynamic and ECG parameters. This temporal dissociation has been elegantly delineated by Ambrosio and colleagues (eFig. 16.0.1) (28), who have demonstrated delay in return of contractile performance despite normal perfusion after the development and relief of exertional angina—that is, myocardial stunning—which is thought to represent severe coronary artery disease.

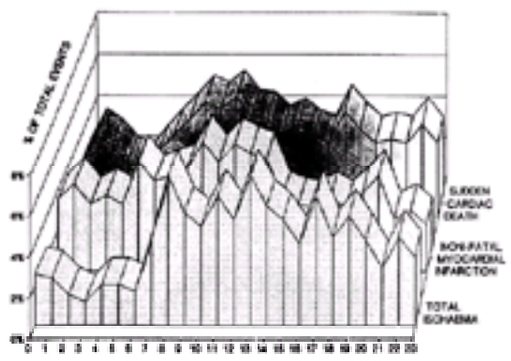


***e*FIGURE 16.0.1** Myocardial stunning in angina. Agenda chronology of physiologic response to the development of ischemia provoked by exercise. Note the extended delay in recovery of contractile function—that is, myocardial stunning after recovery from angina and disappearance of ST depression. EF, ejection fraction; SBP, systolic blood pressure.(From Ambrosio G, Betocchi S, Pace L, et al. Prolonged impairment of regional contractile function after resolution of exercise-induced angina. *Circulation* 1996;94:2455–2464, with permission.)

According to the classification of Cohn (29), ischemia detected on ambulatory monitoring in the absence of symptoms (i.e., silent ischemia) may be categorized into three types: Type 1 patients are totally asymptomatic, type 2 are those who are symptomatic after a prior documented myocardial infarction, and type 3 patients manifest silent ischemia but also have symptomatic ischemia (29). It is patients in the type 3 category who are further discussed here. In a series of insightful studies, Krantz et al. and Gabbay et al. (30,31) examined the relationship between symptomatic and silent ischemia during daily life activities, the role of triggers of myocardial ischemia, and the response and significance of mental stress testing. In a study of 63 patients, they found that 85% of episodes of ST depression were asymptomatic. Importantly, however, only one-third of 90 symptomatic reports of anginal symptoms was associated with ST-segment depression, yet the majority of these was associated with significant heart-rate increments (30). This bidirectional uncoupling of symptoms and ECG evidence of ischemia highlights the difficulties in developing a treatment program aimed solely at the modification of symptoms in patients with stable angina. Whereas some of these symptoms may have reasonably been attributable to noncardiac causes, ischemia can clearly occur, as documented by evidence of left ventricular functional abnormalities without ST-segment shift (i.e., so-called super-silent ischemia) (24). After adjusting for duration of time spent, intense physical activity was found far more likely to be associated with ambulatory symptomatic ischemia, most particularly walking, stair climbing, and related activities (31). Similar temporal adjustments associated with the evaluation of mental activity revealed that ischemia was evident approximately 5% of the time during intense mental activity such asanger or anxiety and only 0.2% of the time when low-intensity mental activities were occurring. A significant relationship existed between elevated heart rate at the onset of ischemic activities associated with physically and mentally intense activities. Finally, ischemia was fivefold more prominent when cigarette consumers smoked than when they did not. Mental stress induced in a laboratory setting, especially when it involves personally relevant speech, may induce abnormalities in regional and global left ventricular function at lower heart rates but comparable elevations in blood pressure to exercise (32). This has led to the suggestion that a decrease in myocardial oxygen supply may be as important or more important than an increase in myocardial oxygen demand and lends credence to the notion that a dynamic decrease in coronary flow mediates this phenomenon. Interestingly, the ability to demonstrate mental stress–induced ischemia has been found to be associated with a significantly higher prevalence, longer duration, and greater frequency of ambulatory ischemia during everyday activity (33). Gabbay and colleagues (31) have also demonstrated a relationship between ambulatory ischemia and intense mental activity unaccompanied by physical activity, as well as a similar proportion of ischemia during marked physical activity (accounting for roughly one-half of all ischemia).

It is now evident that the distribution of ambulatory ischemia among patients with stable angina conforms to a clear circadian pattern previously described for the temporal presentation of acute myocardial infarction and sudden cardiac death (34,35,36 and 37). The similarity in these patterns is demonstrated in eFigure 16.0.2. A variety of pathophysiologic factors for ischemia also display a similar circadian distribution, with a higher frequency in the early morning hours; these include increased coronary vasomotor tone, elevated plasma catecholamines, increased platelet aggregation, and decreased endogenous fibrinolysis. Although the greatest peak frequency of ambulatory ischemia is in the early morning hours coincident with the commencement of physical activities, further insight into mechanisms has been provided by Andrews and coworkers (38), who studied 933 episodes of ambulatory ischemia in 50 patients and found that 81% were temporally associated with periods of increased heart rate. These episodes clearly demonstrated a typical circadian distribution, whereas the 19% of episodes not associated with increased heart rate were evenly distributed throughout the 24-hour period of monitoring. The response to beta-blocker therapy in this and other studies has been further used to develop

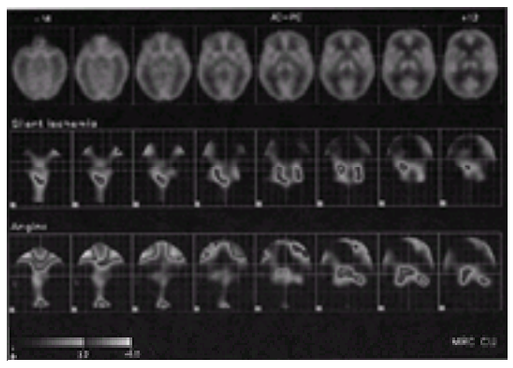
additional pathophysiologic insights; hence, beta-blockers seem to effectively reduce the frequency of ambulatory ischemia associated with increased heart rate by at least half and to remove the circadian distribution of this phenomenon (34,38). On the other hand, with ischemic episodes that are not associated with increased heart rate, they have either no effect or a potentially aggravating impact (39). This has led to the hypothesis that heart-rate–related ambulatory ischemia is primarily mediated by an increase in myocardial oxygen demand, whereas ischemia without circadian variation—that is, not associated with heart-rate increments—is largely attributable to a reduction in coronary flow (39,40). This interesting, albeit oversimplified, notion is deserving of further investigation.



***e*FIGURE 16.0.2** Circadian patterns of ischemic syndromes plotted as a percentage of total events during each hour of the 24-hour day. (From Mulcahy D, Keegan J, Cunningham D, et al. Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. *Lancet* 1988;2:755–758, with permission.)

The mechanism(s) of silent ischemia have been extensively studied and it seems unlikely that a single unifying hypothesis will emerge (41). A higher threshold for pain is explanatory in some: This in turn has been related to increased baseline beta-endorphin plasma levels and increased age (42,43 and 44). A linkage is known to exist between baroreceptor function and pain perception, potentially explaining the relationship that exists between increased systolic blood pressure, reduced sensitivity to ischemic pain, and the previous demonstration that carotid sinus stimulation relieves angina (45). Autonomic dysfunction and evidence of sympathetic cardiac denervation in patients with diabetes has been linked to the presence of silent ischemia in such patients and is another potential factor (25,46). Finally, the complexity associated with pain perception within the cerebral cortex and spinal tract and the role that dynamic gating plays in modulating the variability of perception of ischemic symptoms within different individuals in the face of similar objective manifestations of ischemia remain to be determined (41).

Rosen and colleagues conducted a landmark study (47) of patients with symptomatic and silent ischemia in which they evaluated regional cerebral blood flow via positron emission tomography [ironically the same imaging technique that Deanfield and coworkers (17) used in 1983 to validate ambulatory ST monitoring as the surrogate for myocardial ischemia] during dobutamine-induced myocardial ischemia. Ischemia was confirmed both electrocardiographically and echocardiographically in those without chest pain, whereas symptomatic patients experienced angina that in all cases was associated with ischemic ECG changes. The hemodynamic response to dobutamine was similar in both symptomatic and silent patients, but the cerebral blood flow findings were significantly different. Whereas in symptomatic patients both thalami were activated, in patients with silent ischemia, cortical activation was limited to the right frontal region. The absence of activation of basal frontal, anterior, and ventral cingulate cortices and the left temporal pole suggested that gating of the afferent signals at the thalamic level is a possible mechanism for silent ischemia (*e*Fig. 16.0.3). These findings open up new avenues of investigation aimed at evaluating, as suggested by Pepine (48), whether silent ischemia could be considered a conditioned autonomic response to environmental and psychosocial stressors (48). Hence, repeated ischemia could attenuate painful stimuli associated with ischemia, possibly through involvement of endogenous neurochemical analgesia.



***e*FIGURE 16.0.3** Cerebral areas activated during angina pectoris and silent ischemia. **Top:** Averaged blood flow maps from all patients and all conditions normalized into a standard stereotactic space. These pictures can be used for anatomical localization of the activation foci, which are shown as statistical parametric maps in the same stereotactic anatomical space shown in the averaged blood flow maps. **Middle:** Results for the patients with silent ischemia. **Bottom:** Results for the patients with angina pectoris. The magnitude of the Z scores is displayed for both patient groups according to the same linear color scale (threshold for significance, 3.7). Distances are expressed in millimeters from the intercommissural plane. AC-PC, intercommissural plane. (From Rosen SD, Paulesu E, Nihoyannopoulos P, et al. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. *Ann Intern Med* 1996;124:939–949, with permission.)

Other Causes of Ischemia

A variety of other causes of coronary artery narrowing that result in ischemia exist. Congenital abnormalities of the coronary artery take many forms and are prevalent in 1% to 2% of the general population. Anomalous origin of left or right coronary from the contralateral sinus of Valsalva with passage between the aorta and pulmonary trunk may produce ischemia and all its sequelae. Other aspects of congenital coronary abnormalities are extensively discussed in Chapter 31.

Bridging of a coronary artery within the myocardium occurs almost exclusively in the mid-portion of the left anterior descending vessel (49). Despite the fact that it is a relatively common finding at angiography (i.e., 0.5% to 5.5%), there is lack of unanimity on its physiologic significance (50). It is almost twice as common in patients with chest pain who have normal coronary arteries than in those with obstructive coronary disease. Investigation using intravascular ultrasound has revealed characteristic systolic compression of the bridged segment, especially in the second half of systole with delayed diastolic relaxation (51). Atherosclerotic plaques were evident (most of which were not seen on angiography) in the left anterior descending coronary artery segment proximal to the bridge but not involving the bridge or the distal segment. There is now clear evidence that systolic bridging can produce symptoms and other features of myocardial ischemia in some patients; interestingly, short-acting beta-blocker administration during atrial pacing–induced angina relieves both symptoms and ischemia, with a reduction in both systolic and diastolic compression (52).

VIDEO

Video 16.1 Severe myocardial bridging of the mid–left anterior oblique in a 30-year-old male patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Coronary arteritis associated with systemic collagen vascular diseases such as systemic lupus erythematosus, scleroderma, and polyarteritis nodosa may produce restriction in coronary flow, as may the coronary involvement associated with aortitis, Kawasaki disease, and Takayasu's arteritis. These are discussed elsewhere.

Coronary artery ectasia with or without concomitant obstruction may occasionally be found in association with angina pectoris. The frequency of this finding is estimated to be between 1.0% and 2.5% of consecutive coronary angiographic studies (53). Ectasia is characterized by irregular, diffuse, saccular, or fusiform dilatation

of the coronary arteries, which may coexist with obstructive disease (54). Pathologic studies reveal ectatic arterial enlargement, degeneration of the elastic lamina, medial atherosclerotic plaque formation or calcification, and thinning of the arterial wall (55). It has been hypothesized that this peculiar entity could be related to chronic elevation of acetylcholine concentrations in the coronary arterial interstitium. This interesting speculation arose from a cluster of ectasia cases in young Australian farmers and survivors of myocardial infarction who had been exposed to herbicide sprays containing an acetylcholinesterase inhibitor (56). Slow and delayed filling of the vessels is sometimes observed angiographically, as is thrombus formation and presumed distal embolization. Prior myocardial infarction and angina are common in patients with coronary ectasia, and the natural history is comparable with that of those with advanced coronary obstructive disease (55).

Thoracic radiotherapy with resultant cardiac injury can produce coronary arterial fibrosis with intimal proliferation that evolves over a variable time course and may result in important ischemia (57). A major emerging and recalcitrant problem in cardiac transplantation recipients is the development of a diffuse intimal fibrosis of the coronary arteries that becomes especially prevalent beyond 1 year after transplantation (58). The precise mechanism is unclear, but cyclosporin and steroid therapy along with infectious agents and elevated lipids have all been incriminated.

Syndrome X

Fully 25% of patients with stable angina have coronary lesions on angiography that are inadequate to alter exercise-induced coronary flow (59,60). It is appreciated that abnormalities of coronary vasomotor tone in arteries that are by angiography apparently normal may also mediate angina. Most commonly, angina, or angina-like chest pain in the presence of normal coronary arteries, has been related to so-called syndrome X, a term coined by Kemp in 1973 (61). Despite a host of investigative studies in these patients over the past quarter century, uncertainty remains regarding the exact etiology. Most likely, cardiac syndrome X represents a heterogeneous group of disorders best characterized by a reduced capacity of the coronary circulation to augment flow in the face of an increase in oxygen demand. Although some have argued that a positive exercise test should constitute part of the definition of syndrome X, it seems clear that this should not be a mandatory requirement given the demonstration of abnormal myocardial lactate production with isoproterenol stress in some symptomatic patients who do not have ischemic ECG changes during exercise (62). Evidence for myocardial ischemia in such patients has also been evident through the demonstration of reversible perfusion defects with thallium scintigraphy and transient impairment of global and regional left ventricular function by radionuclide ventriculography (63). Importantly, in a 4.5-year follow-up study, Cannon and coworkers (64) demonstrated a decline in left ventricular function in 15 of 61 patients with syndrome X accompanied by patchy myocardial fibrosis on left ventricular endocardial biopsy. Several lines of evidence support the notion of a pathophysiology for syndrome X distal to the level of the epicardial coronary conductance vessels. Cannon and coworkers (65) demonstrated no alteration in the dimensions of epicardial coronary vessels during ergonovine-induced anginal pain (with concurrent atrial pacing at 250 beats/min), thereby inferring support for their term “microvascular angina.” Egashira and colleagues (66), using a creative experimental protocol in patients with syndrome X, found a diminished coronary blood flow response to acetylcholine compared with controls, yet a similar degree of alteration in epicardial coronary vessels; comparable epicardial coronary dilatation with isosorbide dinitrate and papaverine in both patient groups, while at the same time showing evidence of myocardial lactate production after papaverine administration, led these workers to hypothesize that a defective endothelial-dependent dilatation of the coronary microcirculation existed. Further studies are ongoing to more definitively identify the microcirculatory functional abnormalities that modulate vascular smooth muscle. The absence of morphologic changes in the microvasculature and the coexistence of abnormal reactivity in other noncoronary vascular beds as well as in the bronchial tree and esophagus raise the specter of a more generalized smooth muscle disorder (65,67,68). A reduced pain threshold, heightened awareness of discomfort associated with cardiac catheterization, and a remarkable reproduction of typical pain produced by angiographic injection of the left coronary artery in more than half of patients studied further contributes to the multiplicity of causative factors associated with the genesis of symptoms in patients with syndrome X (63). It has been argued that such individuals constitute the other end of the nociceptive spectrum from those with silent ischemia. Recent evidence also supports previous speculations that endogenous adenosine may play a role because it seems to contribute to myocardial ischemia and perfusion abnormalities evident during exercise in a subset of patients with syndrome X (69). On balance, it is important to recognize that the demonstration of normal coronary arteries is associated with an excellent long-term prognosis (69a).

Although most studies of syndrome X have been careful to exclude patients with left ventricular hypertrophy, a history of hypertension is a common feature in one-fourth to one-third of individuals. Moreover, in patients with hypertension and left ventricular hypertrophy, stress-induced angina is common (30% of 60 patients), and so too is the demonstration of angiographically normal coronary arteries (63). Exercise thallium scintigraphy in such patients corresponds well geographically with reduced coronary flow reserve (70).

The relationship between cardiac syndrome X, endothelial dysfunction, and insulin resistance was first articulated by Reaven (71). In the 1988 Banting lecture he highlighted the role of insulin resistance in human disease and ironically used the term *syndrome X* to propose five consequences to insulin resistance that in turn had been previously documented to augment the risk of coronary artery disease—that is, (a) glucose intolerance,(b) hyperinsulinemia, (c) increased very-low-density lipoprotein (LDL) triglyceride, (d) decreased high-density lipoprotein (HDL) cholesterol, and (e) hypertension (71). It has since been clearly demonstrated by multiple groups that, compared with matched controls, patients with cardiac syndrome X show insulin resistance usually in the face of normal basal levels of glucose and insulin (72). The linkage between cardiac syndrome X and insulin resistance may be forged by reduced microvasculature endothelium-derived relaxing factor: Because blood flow modulates glucose uptake in skeletal muscle, it thereby serves as an important determinant of insulin sensitivity (73). Because it is estimated that approximately 25% of healthy individuals may be insulin-resistant and that physical fitness increases insulin’s sensitivity whereas obesity reduces it, we are likely to learn much more about the interaction of insulin resistance, vascular reactivity, and syndrome X in the future.

Prinzmetal’s Variant Angina

Originally described in 1959 by Prinzmetal and colleagues (74) in association with resting angina and ST-segment elevation, these workers noted organic obstruction of the proximal portion of the coronary artery supplying the territory of ST elevation. Subsequently, this uncommon but well-recognized syndrome, evident in approximately 2% to 3% of patients presenting with chest pain undergoing invasive study at large referral centers, is known to be usually associated with underlying fixed coronary obstruction, although a substantial cohort may have either normal coronary arteries or minimally evident disease angiographically (75). The evidence for focal coronary spasm as the mechanism for variant angina is clear, based on the association of transient ST elevation concurrent with symptoms and localized myocardial perfusion and function abnormalities (76). Although usually confined to a single epicardial vessel, multivessel spasm is well documented, as is the occurrence of spasm at different levels within the same vessel (77). Based on an exaggerated vasodilator response to nitroglycerin, it is evident that the resting tone of the coronary vessels is not only augmented in patients afflicted with variant angina, but also indeed is supersensitive to intracoronary acetylcholine, which reliably provokes spasm (78). Multiple etiologies have been proposed for variant angina, and the following have been established:

Video 16.2 Severe diffuse spasm of the right coronary artery after administration of ergonovine. In this example, the right coronary artery is significantly reduced in caliber with several areas of focal “stenosis.” *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

- The basal release of nitric oxide appears deficient in arteries where spasm occurs and is not corrected by provision of the substrate for nitric oxide, L-arginine, leading to the suggestion that basal nitric oxide synthetase may be a culprit (79).
- Low levels of intracellular magnesium and increased retained magnesium after an intravenous load as well as the therapeutic response to intravenous magnesium have led to the suggestion that it may also be involved (80).
- Low plasma levels of vitamin E in patients with active variant angina and improvement in symptoms when vitamin E is used supplementary to calcium channel blockers have been observed (81).
- Vagal withdrawal based on spectral analysis that reveals a reduction in the high-frequency component of heart-rate variability has been postulated as a trigger for spasm (82).
- Hyperinsulinemia and insulin resistance are thought to be risk factors (73).
- The circadian variation with an augmentation of symptoms during sleep and in the early morning hours correlates with elevated levels of plasma fibrinogen and plasminogen activator inhibitor activity (83).
- Hyperventilation, cigarette smoking, cocaine use and withdrawal, and alcohol withdrawal are also known to precipitate coronary spasm (84,85,86 and 87).

Whereas freedom from exercise-induced symptoms was initially thought to be prototypical of Prinzmetal’s angina, exercise-induced vasospasm with symptoms is well known to occur and also seems to follow a circadian variation (88). Yasue and coworkers (88) have demonstrated that propranolol aggravates attacks of exercise-induced coronary spasm, whereas alpha-blocking agents suppress such attacks, thereby highlighting the importance of alpha-adrenoceptors as key factors modulating disordered coronary arterial tone in such patients. Dopamine and ergonovine infusion are known to provoke coronary artery spasm angina (89,90).

CLINICAL PROFILE

Perhaps more than any other cardiac symptom, descriptions of angina are rich with history and a delicate mix of elegant clinical observation buttressed by an interesting and still-unfolding pathophysiologic foundation. A glossary of the terminology associated with the term *angina* is provided in *e*Table 16.0.1. Most patients with stable angina describe retrosternal chest discomfort or distress, not pain, that occupies a physical area of clenched-fist proportion or more. Anginal discomfort is sometimes characterized as a burning, tightness, choking, heaviness, and occasionally a hot or cold sensation. It may be exclusively located outside the chest, however, and reside in the epigastrium, neck, shoulders, back or arms, and, occasionally, the jaw or head. Patterns of anginal radiation from the chest typically spread to the neck, shoulders, arms (usually left), and jaw. Anginal equivalents characterized by dyspnea, profound fatigue, weakness, or syncope may occur in the absence of any discomfort whatsoever. Ischemic symptoms during stable angina are usually of brief duration, persisting for 3 to 5 minutes, and are typically relieved by rest, dissipation of emotional distress, or the administration of nitroglycerin. Typically the symptoms are produced by vigorous physical activity or emotional distress, and the threshold at which they occur may be lowered by exposure to cold weather, by smoking a cigarette, or after ingestion of a meal. Some patients experience walk-through angina such that they can characteristically maintain the same or a slightly lesser degree of physical activity while the symptoms disappear within a few minutes. Thereafter, they are able to continue for a sustained time at the same or even an accelerated pace. A variation on this theme is the warm-up, or so-called second-wind angina, which is evident in approximately 20% of patients; hence, the second exertional effort is predictably better than the first if there is separation of at least 2 to 5 minutes between them (91). However, if the second effort is initiated later than 30 to 60 minutes after the first, the improvement disappears. If the interval between symptom-limited exercise in chronic stable angina is separated by 30, 60, or 240 minutes, the impact on both exercise performance and left ventricular dysfunction presumed secondary to stunning diverges (92). Hence, after 30 minutes, exercise time is extended, and comparable depression in contractile and diastolic function recovers more quick Jaily. When the interval is separated by 60 minutes, total exercise time remains unchanged, but left ventricular performance is more severely depressed than initially and recovers more slowly, whereas if the interval is 240 minutes, both exercise time and cardiac performance behave in a fashion similar to controls. These data provide further physiologic underpinning for the warm-up phenomenon in patients with stable angina during exercise. Marber and colleagues (91), along with others (93,94), have suggested a pathophysiologic link triggered by favorable adaptive myocardial metabolic changes that result in less of a decline in high-energy phosphate and less lactate production despite recurrent ischemia. Experimental and clinical insights into the phenomenon of ischemic preconditioning suggest that enhanced ischemic adenosine production is a likely putative mechanism for warm-up angina, leading to reduced requirement for oxygenated substrate and attendant reduction in myocardial oxygen consumption and coronary flow (94,95).

***e*TABLE 16.0.1** ANGINA PECTORIS: A GLOSSARY

Stable angina	A predictable pattern regarding frequency and precipitating factors (sustained over 3 mo).
New-onset angina	Recently developed angina (within the previous 1 to 3 mo).
Primary angina	Angina at rest with obvious precipitating cause. If primary angina develops with exercise, the level at which it occurs is inconsistent. A synonym for this type of angina is “variable threshold” angina.
Secondary angina	Typical exertional angina associated with specific and usually predictable forms and levels of physical activity.
Mixed angina	Composite pattern of primary and secondary angina.
Emotional angina	Angina with specific psychological factors that precipitate symptoms.
Nocturnal angina	Angina that awakens and is sometimes associated with dreaming or sleep apnea.
Angina decubitus	Angina that occurs shortly after adopting the recumbent posture. May coexist with nocturnal angina.
Status anginosus	Frequent, recurrent, sustained angina refractory to usual treatment.
Walk-through angina	Angina with effort that disappears gradually during activity that is sustained (although usually at reduced intensity) and after which improved exercise tolerance results.
Second-wind angina	A brief rest after an initial attack results in a markedly improved threshold free from angina. A synonym is “warm-up” angina.
Caudal angina	Angina symptoms occurring in the scalp or head via referred pain.
Angina equivalents	Symptoms other than pain or discomfort that are ischemic-related and serve as angina surrogates (e.g., dyspnea, diaphoresis, fatigue, or lightheadedness).
Silent angina	Objective manifestations of ischemia without symptoms.
Crescendo angina	Synonym is “accelerated” angina. Change in the pattern of angina such that it comes on more easily, lasts longer, or is more frequent.
Acute coronary insufficiency	Sustained anginal pain (i.e., 20–30 min usually at rest), that may or may not be preceded by crescendo angina and obvious precipitating factors.
Unstable angina	A collection of symptoms of angina usually incorporating crescendo angina and/or acute coronary insufficiency. By definition, unstable angina includes rest pain.
Postinfarction angina	Symptoms that follow within 24 hr to 30 d of acute myocardial infarction.
Angina with normal coronary arteries	Syndrome X or microvascular angina.
Variant angina	Prinzmetal’s or vasospastic angina related to epicardial coronary spasm. Pain often at rest that is sustained and may have circadian variation. Exercise tolerance often is normal.
Right ventricular angina	Anginal symptoms developing in association with pulmonary hypertension thought to be secondary to right ventricular ischemia.

Another clinical feature is angina pectoris when first reclining in bed at night that is thought to be related to blood volume redistribution centrally and an increase in preload. Nocturnal angina may be provoked by an emotionally charged dream and is known to be exacerbated by sleep apnea in patients with severe disabling angina (96).

Angina is traditionally categorized into four grades based on the Canadian Cardiovascular Society grading scale (97). Hence, patients in class I experience angina only with strenuous or protracted physical activity; those in class II experience only slight limitation with vigorous physical activity such as walking up a hill briskly. Patients in class III have marked limitation, with symptoms during the activities of everyday living, and those in class IV have the inability to perform the activities of daily living because of symptoms as well as angina that may occur at rest. Although this classification has some virtue, it also has limitations; hence, it does not address changes in the pattern or frequency of angina or take into account the warm-up effect or the self-imposed alteration in activities of daily living that may subtly modify symptomatic status (98).

New-onset angina, defined as occurring within 2 to 3 months of presentation, has been found to be associated with at least a doubling of the risk of nonfatal myocardial infarction within the first year after onset (99). This accentuated risk over patients with chronic coronary disease appears in spite of a lesser extent of triple-vessel disease and a greater frequency of single-vessel disease than in patients with chronic stable angina (100). Within the broad rubric of patients with new-onset angina, a story of progressive symptoms with more frequent and more readily provoked pain, nocturnal pain, and sustained resting discomfort with an abnormal baseline electrocardiogram are indicators of increased risk and a need to investigate promptly. Noninvasive stratification (see the section Diagnostic Tests) is usually helpful and feasible, but direct interrogation of the coronary anatomy may also be desirable.

Evaluation of a general outpatient population of 5,125 patients with stable angina enrolled by 1,266 primary care physicians in the United States provides a basis for reevaluating the common notion that this is a disorder that largely occurs in middle-aged men (101). This population was nearly evenly split between men and women, with the mean age of women of 71 years and that of men of 67 years. Most patients had more than one cardiovascular-related illness, usually systemic hypertension, hypercholesterolemia, prior infarction, heart failure, or diabetes. The majority perceived their health to be either poor or fair and had experienced at least two episodes of angina per week, and although more than 90% had angina with activity, nearly half also experienced angina at rest, highlighting the commonality of mixed angina. One-third had mental stress–induced angina, and one-fourth reported sleep-related symptoms. Accordingly, the traditional requirement that stable angina conform to a pattern of exercise-induced symptoms is no longer tenable given the aforementioned new insights into its pathophysiology, as well as surveillance data from both ambulatory monitoring and symptomatic surveys.

The approach to women with angina has undergone careful scrutiny in recent years, especially as it relates to the vigor with which diagnostic studies and hospital admission are undertaken. Atypical pain is more common in women than in men and may be related to a higher prevalence of less common causes of ischemia such as vasospasm and microvascular and microcirculatory disturbances as well as causes of nonischemic chest pain such as mitral valve prolapse (102). In the Coronary Artery Surgery Study, 62% of women with definite angina had coronary disease compared with a much higher proportion (89%) in men (103). Women with chronic stable angina are more likely to have chest pain at rest, during sleep, or at times of emotional stress. Paradoxically, analysis of cardiovascular risk factors alone more correctly predicts the existence and extent of coronary disease in women than in men, especially in young women. Polycystic ovaries have been found to be more likely associated with advanced coronary disease; also linked to this observation was the finding of high testosterone and triglyceride levels, low HDL cholesterol levels, and a suggestion of insulin resistance (104). Diabetes mellitus is a more cogent predictor of the presence and prognosis of coronary disease in women than in men; hypertension also portends a worse prognosis from coronary disease in females. Importantly, women underestimate their own likelihood of coronary disease. This may explain both their reluctance to present early in the course of the disease as well as their lack of acceptance of invasive diagnostic procedures and preventive strategies (102).

Blacks, especially those born in the southern United States, have an excess of cardiovascular mortality compared with American whites (105). Less aggressive use of diagnostic procedures in blacks is known to occur. It has been suggested that, in addition to racial bias, blacks are less likely to request major procedures and have more of a tendency to decline them when offered (106,107). Asian Indians living outside of India have an excess risk of myocardial infarction (range of 2.5 to 5.0) and mortality for coronary artery disease (range of 1.5 to 3.0) compared with indigenous populations (108). Their disease is characterized by premature onset and a severe and diffuse nature such that it is less amenable to coronary artery bypass graft (CABG) and more likely to lead to permanent disability. Factors promoting this more

malignant course include increased triglycerides and lipoprotein(a) levels, low HDL cholesterol levels, insulin resistance, and more prevalent diabetes occurring earlier in life (108). A consistent inverse relationship exists between indicators of socioeconomic status and coronary artery disease (109). Although socioeconomic status is strongly linked to conventional risk factors such as cigarette smoking, hypertension, cholesterol, and obesity, it is likely to be an independent risk factor for cardiovascular disease.

PRINCIPLES OF MANAGEMENT

The clinical assessment of patients with angina pectoris should involve a systematic review of cardiac and extracardiac factors that might contribute to the genesis of symptoms. Hence, cardiovascular factors such as hypertension, left ventricular hypertrophy, aortic and other valvular disease, aortitis, and arteritis must be considered. Important associated confounding systemic illnesses such as anemia, thyrotoxicosis, renal disease, chronic volume overload, and high output states from other causes such as arteriovenous fistula need identification. Homocysteinuria (estimated prevalence of 1% to 2% of the population in a heterozygous state) has been found to be a relatively common and correctable factor associated with symptomatic coronary artery disease (110). In the U.S. Physician Health Study, the adjusted relative risk for disease in the highest 5% versus the lowest 90% of homocysteine levels was 3.4 (95% confidence interval, 1.3% to 8.8%, $p = .01$) compared with matched-paired controls (111). The impact of correcting this risk factor is under study and is as yet unknown.

In addition to identifying cardiac and systemic factors on clinical examination that might support the clinical suspicion of coronary disease, a survey for systemic hyperlipidemia; hypertension with associated signs of target organ damage; and concomitant vascular disease in the extracranial neck vessels, abdominal aorta, and peripheral vascular tree should be undertaken. Evidence of left ventricular dysfunction and elevated left ventricular filling pressure are commonly accompanied by a presystolic fourth heart sound gallop, cardiomegaly, mitral regurgitation, and paradoxical splitting of the second sound. If the clinician is presented with the opportunity to assess a patient during a typical attack of angina, physical examination may be rewarded by detection of transient signs of left ventricular dysfunction and pulmonary congestion.

Differential Diagnosis

The approach to the differential diagnosis of angina pectoris requires an alert and sensitive historian willing to take the time to establish the pattern and periodicity of the symptomatic complaint, the response to endogenous and exogenous provocative maneuvers, and the impact of therapy. The physical and psychological milieu of the individual patient can dramatically color the physician's diagnostic approach, and physicians should guard against diagnostic nonchalance, even though the patient's manner of presentation is atypical or histrionic (112). There are a number of major systems beyond the heart that warrant careful consideration in the ascertainment of the cause of symptoms potentially attributable to angina.

Common among these is musculoskeletal pain, which is thought to exist concurrent with angina in approximately half of individuals (113). Such pain is often sharp in character; fleeting in duration (although a background of chronic soreness or ache may exist); and often aggravated by respiration and movement of the torso, arms, or shoulders. Patients may be able to localize this pain to point tenderness on the chest (i.e., rib, costochondral junction, pectoral muscle, or xyphoid), and the pain may be reproducible by local pressure. Pain and tenderness associated with swelling of the costal cartilages (most often the second) as described by Tietze is rare (114). Musculoskeletal pain is a very common cause of chest and shoulder pain and may respond to simple reassurance, local applications or anesthesia infiltration, or a course of antiinflammatory therapy.

Cervical disc disease involving the seventh cervical nerve root can produce shoulder, anterior chest, and axillary pain with involvement of the arm and hand; this pain may be aggravated by coughing or sneezing. Neck movement is often compromised and may reproduce the discomfort. Clinical findings of local neck tenderness associated with paresthesia, muscle weakness, and objective neurologic findings are confirmatory.

Inflammatory processes involving the pericardium and pleura are generally associated with a sensation of sharp chest discomfort aggravated by inspiration, cough, and movement. Involvement of the phrenic nerve is associated with radiation of the pain to the shoulder. Pericardial pain is often relieved by sitting forward. Both pericardial and pleural pain are usually discernible from angina pectoris because of their persistence, character, and aggravating and relieving factors.

Emotional and psychological disturbances are a common milieu in which chest discomfort emerges. Persistent band-like chest tightness often with a sensation of air hunger or hyperventilation may be present in such individuals. The symptoms may emerge in response to tension-provoking circumstances or during anxiety attacks where sweating and a sense of impending doom may coexist (113).

The gastrointestinal sources of discomfort that may be confused with angina are many and include hepatic congestion secondary to heart failure; in this condition, the symptoms are typically aggravated by effort, right-sided abdominal in location, and associated with clinical findings of right-sided heart failure. The patterns of discomfort, relationship to meals, and associated symptoms are usually sufficient to provide diagnostic differentiation between peptic ulcer, chronic cholecystitis, and abdominal angina secondary to celiac and mesenteric vascular disease versus those of angina pectoris (115). Esophageal discomfort associated with reflux esophagitis and neuromuscular dysfunction of the esophagus are particularly challenging diagnostic problems given (a) their commonality, (b) the similarity with which sensory afferents travel (i.e., C8 to T10 for the esophagus vs. T1 to T4 for the heart), and (c) the linkage between the heart and the esophagus characterized by the cardioesophageal reflex(116). Recent studies by Chauhan et al. (117) in a small but carefully documented group of 14 patients with exercise-induced angina and angiographically established coronary disease revealed that esophageal acid perfusion evoked typical angina in nine of the 14 patients studied; each showed a substantial decline in coronary blood flow in the absence of any significant change in epicardial coronary diameter, leading to the conclusion that microvascular coronary constriction had occurred. This was presumed to be neurally mediated (117). When symptoms occur associated with meals and acid reflux, are aggravated by stooping or the recumbent posture, and are relieved by antacid therapy, the diagnostic distinction between esophageal and anginal pain is reasonably clear. Pain on swallowing or difficulty in swallowing liquids during an episode of pain are useful clues to pinpoint an esophageal source for the discomfort. Recent studies using sophisticatedesophageal impedance planimetry in patients with unexplained chest pain demonstrated that balloon distention was successful in reproducing typical chest pain in 20 of 24 patients studied (118). The fact that this discomfort occurred at significantly lower thresholds than in controls and in the absence of demonstrable esophageal pathology led the authors to hypothesize the presence of a hypersensitive esophagus. Once typical esophagitis and motility disorders have been eliminated, the balance of recent evidence suggests that specialized esophageal testing in patients with unexplained chest pain is not helpful because of the nonspecificity of the responses (119). Another approach to reflux esophagitis is to assess the response to a therapeutic trial of acid-suppressant therapy such as omeprazole [40 mg per day for 4 weeks (120)].

Diagnostic Tests

Whereas the ECG at rest may commonly be normal in patients with angina pectoris, it is useful to seek evidence of prior infarction and persisting ST-segment depression, which are both factors portending an unfavorable prognosis. T-wave change, intraventricular conduction defects, and atrial abnormalities may also be evident. ECG observations captured during an episode of angina permit evaluation of the location and extent of ECG changes. When the total amount of ST-segment change is extensive (i.e., more than 12 mm), there is a high positive predictive accuracy for the detection of three-vessel or left main coronary disease(121).

In the Rochester, Minnesota, area, 59% of 1,154 individuals presenting with chest pain were found to have normal resting electrocardiograms (122). In these individuals, assessment of clinical variables such as age, gender, and presence of diabetes, coupled with the results of an exercise electrocardiogram, can achieve a predictive value comparable with that of exercise thallium-201 scintigraphy in the estimation of three-vessel or left main coronary disease (123). It has been suggested that conventional exercise testing can readily triage patients into three major groups: (a) those who have normal or near-normal responses, comprising approximately 30% to 40% of patients with resultant mortality of less than 1% per year; (b) those with markedly abnormal tests, comprising 10% to 15% of the population who have a high risk of mortality (5% or more per year), and (c) the remaining population of approximately half the patients who are in an intermediate-risk area (124).

The graded exercise stress test forms the cornerstone of diagnostic testing in patients with known or suspected stable angina pectoris. It should be performed in all such patients before moving toward more detailed, costly, or invasive procedures. At least four important potential objectives may be achieved by conducting this test:

1. Correlation of patient symptoms with the presence of ischemia. When angina occurs with ischemic ECG changes, the prediction of coronary disease is more reliable (125).
2. Definition of risk of future events. Hence, those patients who are unable to exercise for more than 6 minutes on the Bruce protocol or demonstrate significant ischemia within this temporal window are at increased risk and deserving of further investigation (126). A summary of high-risk variables associated with unfavorable prognosis during exercise testing is shown in Table 16.1. A recent addition to this profile is the observation that a delay in the decrease in heart rate during the first minute after a graded exercise test was strongly predictive of mortality at 6 years (19% vs.5%; relative risk of –4.0). This finding occurred in 26% of 639 patients and was associated with 56% of the deaths(127).

Inability to complete 6 min (Bruce protocol)
Early positive test (i.e., 3 min)
Strongly positive test (i.e., 2-min ST depression)
Sustained ST depression 3 min after cessation of exercise
Delayed decrease in heart rate during first minute after cessation of exercise
Downsloping ST depression
Ischemia developed at a low heart rate (i.e., 120 beats/min)
Flat or lowered blood pressure response
Serious ventricular arrhythmia at a heart rate of 120 beats/min

TABLE 16.1 HIGH-RISK EXERCISE TEST

3. To provide the patient with an “exercise prescription” based on the level of activity and heart rate–blood pressure product at which ischemia develops.
4. To evaluate the efficacy of pharmacologic and revascularization therapy directed toward the subjective and objective manifestations of ischemia.

Deriving an index or score from information relating to the duration of exercise, the extent of ST-segment deviation, and the reproduction of limiting or nonlimiting angina has been shown to provide a more precise estimation of prognosis. Using such an approach (as depicted in Fig. 16.1), Mark and colleagues (128) in a series of 613 consecutively evaluated outpatients with suspected coronary disease found that two-thirds of patients had low risk, with a 4-year survival of 99%, whereas 4% had high risk, with a 4-year survival of 79%. In general, the location of ST depression during exercise testing is an unreliable guide to the location of coronary narrowing. By contrast, exercise-induced ST elevation (which is uncommon in the absence of prior Q-wave infarction, estimated variably between 1% and 19%) more reliably tracks underlying coronary anatomy (i.e., anterior ST elevation is predictive of left anterior descending, and inferior ST elevation is predictive of right coronary artery narrowing)(129). Although the incidence of false-positive examinations is higher in females with atypical chest pain, the finding of a negative test may be useful; the nonspecificity of the positive test in this situation commits the physician to consider pursuing radionuclide or other investigations with higher diagnostic specificity (102). The frequency of false-positive tests in women becomes similar to that in men when groups are matched for age and presence and extent of coronary disease (103). When considering which of the various supplementary diagnostic tests beyond exercise testing is desirable, it is useful to assess the characteristics of the patient; the specific question the test is to address; and finally the always-present factors of local experience, availability, and cost-efficacy. Patients with abnormalities in their resting electrocardiogram characterized by a prior Q-wave infarction; left ventricular hypertrophy; conduction abnormalities including left bundle branch block, baseline ST, and T-wave abnormalities associated with digitalis effect or other factors; female patients; and patients with renal insufficiency are likely to have specious results with conventional exercise ECG testing (126).

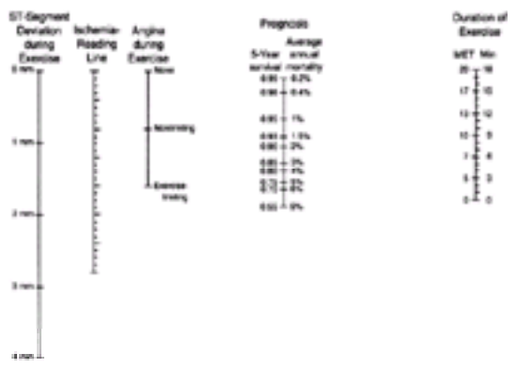
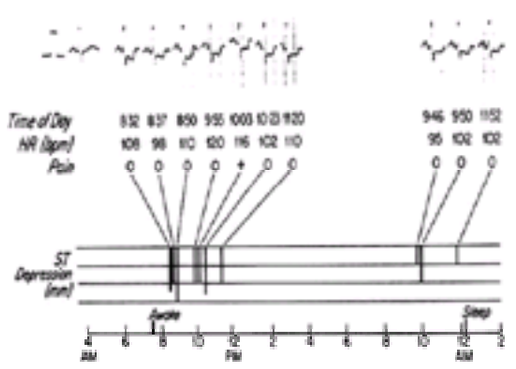
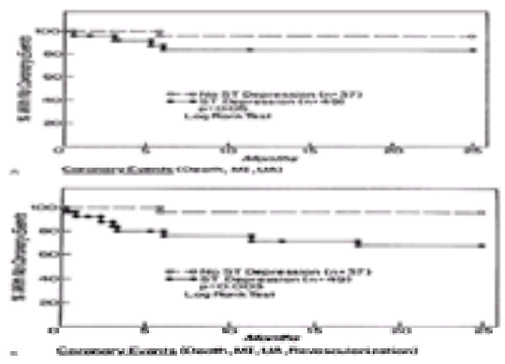


FIGURE 16.1 Nomogram of the prognosis relations embodied in the treadmill score. Determination of prognosis proceeds in five steps. First, the observed amount of exercise-induced ST-segment deviation (the largest elevation or depression after resting changes have been subtracted) is marked on the line for ST-segment deviation during exercise. Second, the observed degree of angina during exercise is marked on the line for angina. Third, the marks for ST-segment deviation and degree of angina are connected with a straight edge. The point where this line intersects the ischemia-reading line is noted. Fourth, the total number of minutes of exercise in treadmill testing according to the Bruce protocol [or the equivalent in multiples of resting oxygen consumption (METs) from an alternative protocol] is marked on the exercise duration line. Fifth, the mark for ischemia is connected with that for exercise duration. The point at which the line intersects the line for prognosis indicates the 5-year survival rate and average annual mortality for patients with these characteristics. (From Mark DB, Shaw L, Harrell FE, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991;325:850, with permission.)

Ambulatory Holter monitoring in patients with stable angina pectoris has received substantial attention as a result of its use in clinical investigation and trials. These studies have demonstrated a clear pattern of a circadian variation in ischemia, with increased frequency during the early morning hours (*e*Fig. 16.1.1) (34,36,37). Silent ischemia seems to be far more common than symptomatic ischemia, and the total amount of ischemia, or “ischemic burden,” bears a direct relationship to long-term prognosis in some studies (*e*Fig. 16.1.2) (130,131 and 132). The prognostic ability of silent ischemia in patients with low-risk stable angina, however, has been challenged, and it would not be expected to reflect the vulnerability of a nonobstructing plaque to rupture and cardiac event (133). Almost all episodes of silent ambulatory ischemia occur in patients with positive exercise tests, indicating this technique has little or no role as a screening test for coronary artery disease (134,135). Within the cohort of patients with positive exercise tests, the extent of ambulatory ischemia seems greatest among those who develop ischemia within 6 minutes of exercise at heart rates of less than 150 beats/min or in those with ischemic ECG changes persisting at least 5 minutes after cessation of exercise (136). In multivariant analysis of patients with stable angina who underwent ambulatory monitoring, exercise testing, and a myocardial perfusion scan, ambulatory ischemia was of additional predictive value in determining the extent of proximal coronary narrowing, suggesting that the unfavorable prognosis in these patients may be mediated by a greater amount of myocardium at risk (137). Suggestive evidence exists indicating an association between complex plaque formation in the coronary arteries of patients with ambulatory ischemia; the important pathophysiologic implications of these observations await confirmation but notably are in concert with what has previously been observed in patients with unstable angina pectoris (138,139). Silent ischemia is frequent among patients with stable angina pectoris whose symptoms are controlled with standard medical therapy, and this phenomenon has been associated with the identification of patients at high risk of subsequent cardiac death by some workers (131). Some evidence suggests that treatment that reduces the magnitude of ischemia as opposed to the relief of symptoms may afford improved prognosis; this seminal proposition is currently under further investigation and requires validation in large-scale clinical trials (136,140,141 and 142). Although ambulatory monitoring is not indicated as a routine test in patients with stable angina, its selective use in patients with non–high-risk exercise tests may define prognosis more precisely; it may also be helpful in uncoupling typical or atypical symptoms from objective manifestations of ischemia and in confirming the diagnosis of Prinzmetal’s variant angina.



***e*FIGURE 16.1.1** Results of a typical 24-hour recording session in a 65-year-old man. Ten ischemic episodes with ST-segment depression ranging from 1 to 4 mm occurred throughout the day, with the peak activity of ischemia during the first 4 to 5 hours after awakening. Only a single episode was accompanied by chest pain. HR, heart rate.



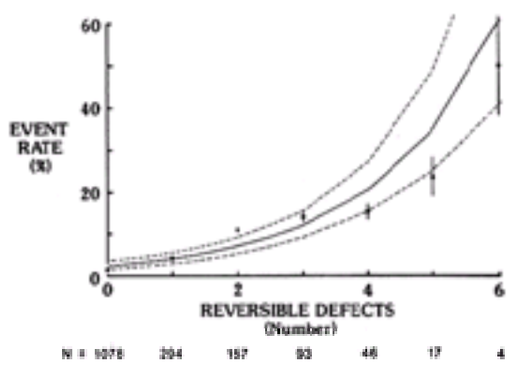
***e*FIGURE 16.1.2** Kaplan-Meier curves comparing the probability of not experiencing **(A)** an acute ischemic event [death, myocardial infarction (MI), unstable angina (UA)] and **(B)** progressive ischemic event (acute events or revascularization for worsening symptoms) during follow-up for the 37 patients without ST-segment depression (o—o) and the 49 patients with ST-segment depression (■—■) as detected by ambulatory monitoring. (From Rocco MB, Nabel EG, Campbell S, et al. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. *Circulation* 1988;78:882, with permission.)

There are a variety of circumstances where more specialized noninvasive assessment of the coronary circulation beyond that provided by conventional exercise testing may be warranted (*e*Table 16.1.1). If an adequate exercise test is feasible, it remains a highly effective, diagnostically accurate test when coupled with either myocardial nuclear imaging or two-dimensional echocardiography. Both exercise and the infusion of dobutamine induce ischemia through an increase in myocardial oxygen consumption mediated by augmented heart rate, systolic blood pressure, and contractility. However, exercise results in a 50% greater increment in heart-rate systolic blood pressure product versus dobutamine in direct comparisons, probably accounting for its greater sensitivity in detecting coronary artery disease in some series (143). The findings of lower end systolic volume and higher ratio of systolic blood pressure to end systolic volume index at the ischemic threshold during dobutamine echocardiography (compared with exercise) support the notion that there is greater augmentation of contractility as a contributor to the increase in myocardial oxygen consumption with dobutamine versus exercise (143).

***e*TABLE 16.1.1** INDICATIONS FOR SPECIALIZED NONINVASIVE ASSESSMENT OF THE CORONARY CIRCULATION
Abnormal resting electrocardiogram
Left ventricular hypertrophy
Inadequate response or inability to exercise
More precise prognostic assessment
Assessment of physiologic significance of stenosis
Assessment of viability in the presence of left ventricular dysfunction

Given that a high proportion of patients with stable angina have prior infarction and/or wall motion abnormalities at rest detected by two-dimensional echocardiography or resting perfusion defects, the question of whether such wall motion abnormalities possess residual myocardial perfusion and viability becomes highly relevant in therapeutic planning. Dobutamine enhancement of left ventricular dysfunction or inotropic stimulation evident after a ventricular premature beat is predictive of improvement in function with revascularization of the affected segment (144). Delayed imaging—that is, 18 to 24 hours after thallium exercise scintigraphy—reveals that 50% or more of segments (with apparently irreversible thallium defects on delayed imaging, i.e., at 3 to 4 hours) demonstrate isotope redistribution thought to be indicative of severe ischemia and predictive of favorable response to revascularization (145). Thallium reinjection at rest, 3 to 4 hours after stress imaging, has been demonstrated to provide similar information to delayed imaging in a more time-efficient and practical fashion (146). The use of thallium in this fashion to detect myocardial viability has been validated by concomitant metabolic imaging using positron emission tomography with oxygen-15–labeled water and exogenous glucose use with fluorine-18–labeled fluorodeoxyglucose (146).

By contrast, dipyridamole- and adenosine-induced hyperemia resulting in maldistribution of coronary flow occurs by maximally dilating normal vascular segments, whereas those with fixed coronary stenosis already have near-maximal dilatation, and hence, a resulting uneven flow pattern emerges. Adenosine's rapid onset of action and extremely short half-life, as opposed to that of dipyramidole, circumvents the need for theophylline reversal of troublesome side effects such as bronchial constriction (147). Two-dimensional echocardiography performed before and immediately after exercise testing and continuously before, during, and after dobutamine infusion is used to detect new or worsening preexisting wall motion abnormalities (24,148). These findings bear excellent concordance with the territory of the affected coronary vessel (143). Dobutamine stress echocardiography has been demonstrated to be of value in determining prognosis in patients with known or suspected coronary artery disease (149). In 108 medically treated patients with left ventricular dysfunction and known or suspected coronary disease observed for 16 months, Williams and coworkers (150) noted a significant relationship between cardiac events (death, myocardial infarction, and unstable angina requiring revascularization) and the development of ischemia or demonstration of viability—that is, enhanced myocardial thickening of a dysfunctional left ventricular segment. Marcovitz et al. (151) found an increased likelihood of death or myocardial infarction in 291 patients observed for a mean of 15 months who had a combination of fixed and inducible wall motion abnormalities with dobutamine stress echocardiography. Perfusion imaging with thallium-201– or technetium-99m–labeled radiopharmaceuticals [either sestamibi (MIBI) or tetrofosmin] provides visualization of myocardial blood flow. Injected immediatelybefore cessation of exercise or pharmacologic stress, these agents can delineate relative differences in myocardial blood flow conforming to areas of myocardial ischemia. With thallium-201, a late image associated with redistribution of blood flow 3 to 4 hours after exercise is commonly obtained to assess reversibility of defects observed during exercise (152). By contrast, with the technetium-99m–labeled MIBI, myocardial distribution is relatively fixed without significant redistribution; hence, imaging can be conducted for a few hours after the time of injection during pharmacologic or exercise stress (153) A second injection is necessary to characterize blood flow at rest. In addition to the value of perfusion scintigraphy in depicting coronary artery disease, it is useful in assessing ischemia in specific vascular segments when coronary disease has been established. In a study evaluating the prediction of cardiac events in patients without prior infarction presenting with suspicion of coronary artery disease, Ladenheim and coworkers (154) found that the frequency of cardiac events bore an exponential relationship to the number of reversible perfusion defects (*e*Fig. 16.1.3). Thus, substantial data are now available to support the role of myocardial perfusion imaging in more precisely defining prognosis; in this regard a high-risk scan may be especially useful, and the characteristics of this finding are depicted in Table 16.2 (155,156,157,158 and 159).



***e*FIGURE 16.1.3** Relationship between coronary event rate and extent of hypoperfusion as estimated by the number of hypoperfused regions that reverse by at least 1 on a 4-point ordinal scale. The extent of reversibility is exponentially related to event rate [cardiac death, nonfatal myocardial infarction, or referral for coronary bypass surgery more than 60 days after noninvasive testing (r = 0.97, *p* <.001)]. (From Ladenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1986;7:467, with permission.)

More than 15% of left ventricle involved
Multiple defects (two or more)
Both fixed and reversible defects
"Left main pattern" (i.e., mid/upper septum and upper postero-lateral wall involvement)
Left involvement dilatation after exercise
Lung uptake after exercise

TABLE 16.2 HIGH-RISK NUCLEAR SCAN

A well-conducted direct comparative evaluation of two-dimensional echocardiography and technetium-99m MIBI single-photon emission computed tomography, using the pharmacologic stressors dobutamine and adenosine in patients undergoing diagnostic catheterization without infarction, provided a comparison of the diagnostic accuracy of each technique and pharmacologic stress—that is, four separate approaches (147). Briefly, this study established similar accuracies for the detection of coronary artery disease (more than 50% narrowing of a major epicardial vessel) for adenosine MIBI (80%), dobutamine MIBI (77%), or dobutamine two-dimensional echocardiography (84%), all of which were superior to adenosine two-dimensional echocardiography (69%). The authors suggested the diagnostic approach of choice should depend on local experience but highlighted the superiority of dobutamine two-dimensional echocardiography when baseline left ventricular hypertrophy or left bundle branch block was present. Other patient characteristics favoring dobutamine stress are the presence of asthma and atrioventricular conduction defects, whereas those patients with systemic hypertension and arrhythmia are probably best stressed with adenosine. A scintigraphic approach is obviously preferred in nonechogenic subjects. In another direct comparison of exercise and pharmacologic stress echocardiography in detecting coronary artery disease, overall accuracy for exercise, dobutamine, and dipyramidole was 87%, 82%, and 77%, respectively (exercise vs. dipyramidole, p <.01) (143). When dobutamine infusion is unsuccessful in achieving 85% of the target heart rate, supplementary intravenous atropine is useful in enhancing the diagnostic information; it does so in approximately one-half of instances in which it is required (148). This tactic may be especially helpful in the face of concurrent treatment with beta-blockers.

Although coronary calcification has long been recognized as a marker of atherosclerosis, its clinical utility has been limited by the low sensitivity of cardiac fluoroscopy for detection. The availability of electron beam (ultrafast) tomography has dramatically increased the sensitivity of coronary calcium detection. Notwithstanding evidence supporting electron beam tomography's ability to predict both the presence and severity of coronary disease, other data indicate marked intrapatient variability on repeat testing. Its ultimate role remains both uncertain and controversial (5). Recently an American College of Cardiology/American Heart Association consensus document concluded that "the test has proven to have a predictive accuracy approximately equivalent to alternative methods for diagnosing coronary artery disease but has not been found to be superior to alternative non-invasive tests" (160).

Selective coronary angiography remains the most definitive diagnostic investigation to define the anatomic extent and severity of intrinsic coronary narrowing. In general, it should be performed in patients (a) when the diagnosis of coronary disease is important to establish yet remains in doubt after noninvasive assessment, (b) when high-risk coronary disease is suspected based on the results of clinical and noninvasive evaluation, and (c) when significant symptoms persist despite adequate medical therapy (or, alternatively, when compliance with medical therapy is problematic). Although angiography was originally considered to be an unequivocal gold standard, it is now evident (not surprisingly) that some tarnish has emerged on this valuable diagnostic tool. Hence, the physiologic importance of moderate apparently similar stenoses has been demonstrated to be markedly different (161). Advances in technology using miniaturized wires that permit measurement of coronary velocity and pressure change across a stenosis allow evaluation of coronary flow reserve in living humans (162). Coupling the physiologic importance of a lesion with its anatomic definition is a key step toward appropriate revascularization therapy (161). Provocative testing with ergonovine maleate in patients with known or suspected Prinzmetal's variant angina may be useful during coronary angiography to identify the location and extent of provokable coronary spasm (90). In patients without major anatomic narrowing and in the absence of Prinzmetal's variant angina, vasoreactivity of lesions may be provoked by intravenous ergonovine; in this regard, Harding and coworkers (90) identified a subset of patients with a 10% likelihood of provokable spasm; this occurred in 17% of their study group and was identified by a history of smoking and the presence of 50% or less coronary stenosis. Building on the insights provided by coronary angioscopy, intravascular ultrasound provides precise definition of not only the contents of the coronary lumen and the extent of its narrowing, but also the thickness and characteristics of the coronary arterial wall, thereby portraying coronary anatomy in an entirely new fashion (Fig. 16.2) (163,164).

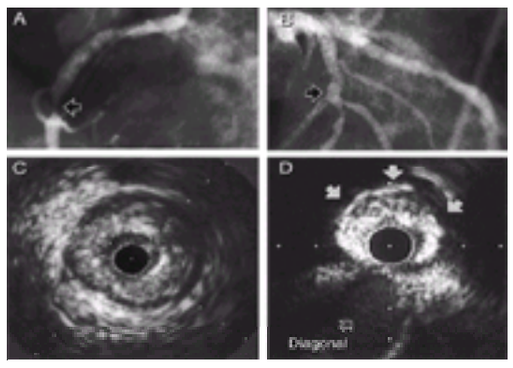


FIGURE 16.2 Angiographic and intravascular ultrasound patterns in stable angina. Stable lesions are often concentric **(A)** and have an echodense appearance and distinct fibrous cap **(C)**. In this example of a bifurcation lesion **(B)**, intravascular ultrasound examination reveals a significant and calcified plaque (*closed arrows*) at the mid left anterior descending artery opposite the origin of a large diagonal branch that was not angiographically apparent **(D)**.

Therapy

The traditional approach to therapy of angina is aimed at the relief of symptoms and the reduction of risk to future untoward events known to develop (i.e., unstable angina, myocardial infarction, and death). Early observations suggest that obliteration of silent as well as symptomatic ischemia may well be a desirable long-term objective. It is also now evident that merely retarding or halting the progression of underlying atherosclerosis is too modest a goal; hence, reversal of atherosclerosis is a feasible aim. Accordingly, this section deals first with medical therapy, then the approach to revascularization, and finally the natural history and potential for modifying it. Comprehensive recommendations for the management of stable angina have been developed both by task forces of the European Society of Cardiology (165) and the American College of Cardiology/American Heart Association (5). In approaching therapy of patients with stable angina, it is useful to develop an overall strategy that emerges from the individual patient profile (166). Developing this profile involves several issues:

1. A risk assessment (i.e., What is the natural history of this individual?).
2. What factors are modifiable that will favorably alter the likelihood of future adverse events?
3. A comprehensive review of the following:
   a. Systemic factors that may aggravate ischemia (i.e., intercurrent disease such as anemia, thyrotoxicosis, renal failure, and infection).
   b. Cardiac-specific issues (e.g., hypertension, heart failure, valvular disease, and arrhythmia).
4. What patient-specific characteristics need special consideration as one chooses a medical treatment program (i.e., the presence of peptic ulcer and gastrointestinal hemorrhage such that aspirin may be relatively contraindicated; advanced left ventricular failure, brittle insulin-dependent diabetes that would make the use of beta-blockers problematic; marked sinus bradycardia or atrioventricular conduction delay where beta-blockers and certain negative chronotropic calcium antagonists could be deleterious)?
5. What characteristics of the anginal pattern suggest typical exercise-induced angina in which attention to favorably modifying the determinants of oxygen consumption will result in treatment benefit versus mental stress–induced angina where coronary vasoconstriction may be operative? Is mixed angina present where both of the above may exist? Is nocturnal angina present?

All patients with stable angina should receive 80 to 325 mg per day of regular or enteric-coated aspirin unless contraindicated (167). Aspirin produces a sustained functional defect in the platelet associated with prolongation of the bleeding time (168). This is induced by cyclooxygenase inhibition and subsequent suppression of

thromboxane A_2, the key modulator of irreversible platelet aggregation. The Swedish Angina Pectoris Aspirin Trial, a prospective study of 2,035 patients with stable angina, revealed that 75 mg of aspirin added to sotalol produced a 34% decrease in primary outcome events of myocardial infarction and sudden death (95% confidence interval of 24% to 49%, $p = .003$) and a 32% reduction in secondary vascular events (169). Although 325 mg of coated aspirin is a common daily dose, this amount is in excess of what has been shown to be efficacious. Given the dose-related increase in gastrointestinal bleeding with aspirin, this dose could be administered on alternate days, or a daily dose of 75 to 100 mg would suffice. When aspirin cannot be used because of genuine allergy or gastrointestinal complications, ticlopidine or clopidogrel should be considered. These agents, which inhibit platelet aggregation induced by adenosine diphosphate collagen, arachidonic acid thrombin, and platelet aggregating factor, are known to reduce blood viscosity probably as a result of a reduction in plasma fibrinogen and an increase in red cell deformability. A number of trials have shown a consistent positive reduction with ticlopidine in a dose of 250 mg twice a day in nonfatal and fatal vascular events in peripheral, cerebral, and coronary vascular disease (170). Because hematologic changes including neutropenia, thrombocytopenia, and pancytopenia may occur (usually within 3 months of commencement of ticlopidine therapy), this therapy requires careful monitoring and is usually but not always reversible. Added to these concerns with ticlopidine have been a series of cases demonstrating a small but genuine increase in the risk of thrombotic thrombocytopenic purpura (171). Accordingly, an agent structurally similar to ticlopidine—that is, clopidogrel in a dose of 75 mg daily—is the preferred agent in this class because it does not have the hematologic problems associated with ticlopidine and has been demonstrated to have a favorable effect on vascular complications that is slightly superior to that of aspirin (relative risk reduction, 8.7%; $p = .043$) (172).

There are three main classes of drugs with demonstrated efficacy on the relief of the symptoms of stable angina. It is important to recognize the presence of a strong placebo effect associated with any new therapy: This was well typified by a 76% improvement in the placebo arm of an internal mammary ligation study conducted in 1958 (173,174).

Nitrates have a multitude of effects on the cardiovascular system that promote the relief of ischemia and angina (Fig. 16.3). They reduce left ventricular preload and afterload through effects on the venous and arterial circulation, thereby reducing the oxygen consumption of the heart; they also dilate epicardial coronary vessels through their smooth muscle relaxant effect and in selected circumstances may enhance intracoronary collateral flow, relieve epicardial vasoconstriction and spasm, and produce a favorable redistribution of transmural coronary flow from epicardial to endocardial layers. Finally, they have a direct effect on the compliance of the left ventricle, producing a downward shift in the pressure-volume relationship (175). This increase in compliance is thought secondary to a reduction in pericardial restraint. Nitrates are metabolized through a common intermediary and after reaction with a sulfhydryl moiety are converted to an S-nitrosothiol. This in turn stimulates guanylate cyclase, which catalyzes the conversion of guanosine triphosphate to guanosine monophosphate, resulting in a decrease in intracellular calcium (176). When this develops in smooth muscle, it results in relaxation; a similar biochemical reaction seems to mediate the antiaggregatory effects on platelets that nitrates have been demonstrated to possess (177). It is thought that the nitric oxide produced by nitrate metabolism is similar or identical to that endogenously produced by the vascular endothelium—that is, endothelium-derived relaxing factor. Initial enthusiasm for sustained nitrate therapy as effective prophylaxis against angina has abated in the face of evidence that this strategy produces tolerance to its hemodynamic and antianginal effects (178). Tolerance can appear rapidly within days of commencement of sustained nitrate therapy, and three major mechanisms have been implicated: (a) the depletion of sulfhydryl groups necessary to promote metabolism of nitrates to nitric oxide, (b) expansion of blood volume leading to attenuation of the hemodynamic effects of nitrates, and (c) activation of counterregulatory vasoconstrictor neurohumoral influences that would again attenuate the peripheral circulatory effects of nitrates (179,180). It is unlikely that a single unifying explanation can satisfactorily explain the phenomenon of tolerance, and controversy exists about the relative importance of the aforementioned hypotheses. Hence, the addition of a sulfhydryl donor, *N*-acetyl cysteine, to patients made tolerant to the antianginal effects of oral isosorbide was not successful in reversing the effect (181). Whereas chronic nitrate therapy is associated with an expanded intravascular volume and diuretic therapy was associated with improvement in exercise tolerance, it seems that this benefit is independent of any direct effect on nitrate tolerance (182). The addition of an angiotensin-converting enzyme inhibitor in patients with chronic stable angina receiving sustained nitrate therapy seems to restore short-term efficacy of nitrate effect (183,184). The long-term implications of this strategy are unclear.

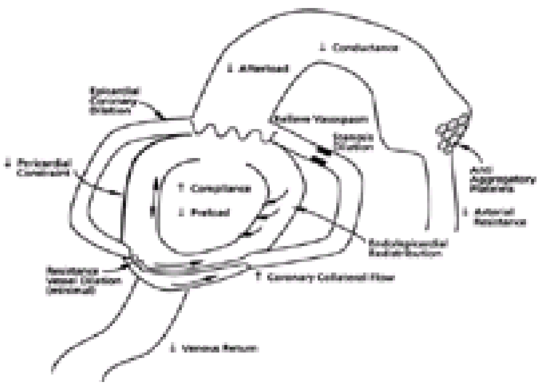


FIGURE 16.3 Mechanism of nitrates.

In Table 16.3, a summary of the variety of nitrate dosing preparations and strategies is demonstrated. Nitroglycerin, either sublingual or as an oral spray, remains the most effective remedy for relief of individual attacks. Nitroglycerin may also provide good short-term (i.e., 20-minute) prophylaxis when activities known to predictively produce symptoms are about to be commenced (e.g., physical exercise or sexual intercourse). Oral or buccal nitrates administered twice or three times a day can produce sustained and effective symptomatic relief, as can topical preparations (185,186). Care should be taken to avoid the tolerance associated with sustained use by ensuring a nitrate-free interval of at least 8 hours; this can be achieved by once-daily topical or asymmetric oral dosing in patients in whom nocturnal angina is especially problematic (187). Using a bedtime application of nitrate may be especially useful for patients with nocturnal angina. In addition, care should be taken to use the smallest effective dose of nitrate required to minimize tolerance development (187). The best approach to long-acting nitrate therapy is to begin with the minimally effective and tolerated dose and be prepared to individualize the timing of administration in accordance with the pattern of symptoms and/or ischemia one is aiming to relieve. Gradual upward adjustment to maximally tolerated doses should be undertaken within 6 to 12 weeks. Nitrates are the most venerable of the medical therapies for angina pectoris and, despite challenge, have stood the test of time very well.

Formulation	Dose	Frequency	Onset/action duration
Sublingual tablet GTN	0.3–0.6 mg	As required	2 min/20–30 min
Sublingual tablet ISDN	2.5–10 mg	As required	5–10 min/1–2 h
Oral spray GTN	0.4-mg metered dose	As required	2 min/20–30 min
Oral GTN SR	2.6 mg	Three times a day	2–5 min/3–5 h
Buccal tablet GTN	1, 2, 3, and 5 mg	Two or three times a day	2–5 h/3–5 h
Oral ISDN	10–30 mg	Two or three times a day	15 min/4–6 h
Oral ISDN SR	80–120 mg	Daily	Approximately 60 min/10–12 h
Oral IS-5-MN	20 mg	Twice a day	30 min/5–7 h
Oral IS-5-MN SR	60–240 mg	Daily	Approximately 60 min/10–14 h
GTN ointment 2%	0.5–2.0 in.	Twice a day	15 min/8 h
Transdermal GTN patch	0.2–0.8 mg/h[a]	Daily	30 min/12–24 h

GTN, nitroglycerin; ISDN, isosorbide mononitrate; IS-5-MN, isosorbide 5-mononitrate; SR, sustained release.
[a]A nitrate-free interval of at least 8 hours per 24-hour period should be provided to avoid tolerance.
Adapted from Abrams J. Therapy of angina pectoris with long-acting nitrates: which agent and when? Can J Cardiol 1996;12(Suppl C):9C–16C.

TABLE 16.3 NITRATE DOSING

The principal side effects associated with the use of nitrates are headache, flushing, and lightheadedness. Occasionally, nitrate syncope can occur with a rapid decline in systolic blood pressure in the upright position, associated with arterial dilatation and venous pooling. Patients who experience lightheadedness while taking sublingual or oral short-acting nitrates should be cautioned to sit or adopt a semirecumbent position when taking short-acting nitrates. Generally, concomitant analgesia for headache for the first several days or weeks is successful in circumventing this side effect, but approximately 30% of patients are unable to take sustained long-acting nitrate therapy because of troublesome side effects. Oral isosorbide should be taken with milk or meals to avoid the heartburn sometimes associated with its use.

The role of nitrate therapy in stable angina has recently undergone reexamination in conjunction with the availability of sildenafil (Viagra), a selective phosphodiesterase inhibitor indicated for the enhancement of sexual performance. The commonality of erectile dysfunction in males with stable angina presents a significant therapeutic challenge to the practitioner. Many men so afflicted have associated diabetes, have peripheral vascular disease, and/or are receiving beta-blockers, all or none of which may contribute to this symptomatic complaint. Because sildenafil releases endothelium-bound nitric oxide, concomitant use of nitrates (which also function as nitric oxide donors) may result in a synergistic decline in blood pressure (188). Accordingly, a recent American College of

Cardiology/American Heart Association consensus document (189) advises that sildenafil is contraindicated in patients receiving long-acting nitrates and should be used with substantial caution if patients require short-acting nitrates for symptoms that develop during mild or moderate exercise.

The introduction of beta-blockers more than 25 years ago has markedly improved the medical therapy of patients with stable angina. These agents have a variety of cardiovascular effects that ameliorate ischemia (Fig. 16.4) (190). Occasionally, unfavorable effects on the cardiovascular system occur—that is, (a) patients with impaired left ventricular function may develop cardiac dilatation with an increase in myocardial oxygen consumption and aggravation of angina and/or left ventricular failure and (b) the blockade of $beta_2$-adrenergic effects in the coronary circulation may lead to vasoconstriction in patients with coronary vasospasm (191). This tendency becomes unmasked by the unopposed impact of alpha-adrenergic–mediated vasoconstriction.

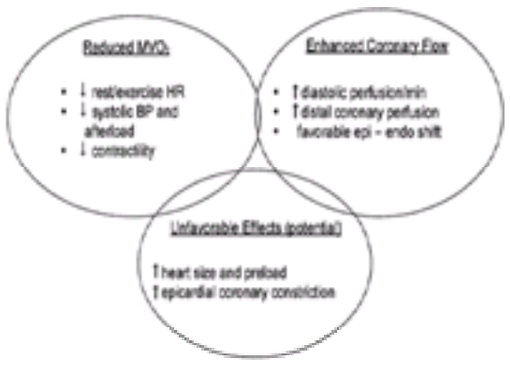


FIGURE 16.4 Mechanism of action—beta-blockers. BP, blood pressure; endo, endocardial; epi, epicardial; HR, heart rate; MVO_2, myocardial oxygen consumption. ↓, decreased; ↑, increased.

Because the catecholamines are so widely distributed in body organ systems, the use of beta-blockers is enhanced by an understanding of receptor pharmacology as it relates to how they exert their cardiovascular effects and what side effects, both cardiac and noncardiac, can be anticipated. Although there are a very large number of these agents now in use worldwide, this discussion focuses primarily on those used for angina pectoris and for secondary prophylaxis after myocardial infarction. As antagonists of beta receptors, beta-blockers attenuate the catecholamine-generated increase in intracellular cyclic adenosine monophosphate (190). It is important to identify the two classes of beta receptors—$beta_1$ and $beta_2$—to comprehend their effects. Beta receptor antagonists have been classified into those with nonselective properties, those with $beta_1$-selective effects, and agents with partial agonistic activity that produce an intrinsic sympathomimetic effect. Nonselective agents affect the heart, peripheral vasculature, bronchial tree, and modulation of hepatic and skeletal muscle glyconeogenesis. Use of a $beta_1$ antagonist tends to circumvent constriction of the bronchial tree and arterial smooth muscle. There are remarkable differences between different beta-blocker agents relating to their absorption from the gastrointestinal tract, first-pass hepatic biotransformation, renal clearance, water versus lipid solubility (the latter promotes central nervous system effects), protein binding, volume of distribution, and production of pharmacologically active metabolites (192). The physiologic effects of beta-blockers are maintained longer than their pharmacologic half-life would suggest, leading to a longer-than-anticipated time between dosing intervals.

Both propranolol and metoprolol, two first-generation beta-blockers, have relatively short pharmacologic half-lives, are metabolized by the liver, and are lipid soluble. Lipid solubility tends to be associated with enhanced central nervous system concentration of beta-blockers and has been linked to the side effects of lethargy, depression, sleep disruption with vivid dreaming, and hallucinations (190). By contrast, atenolol and nadolol are water-soluble agents that are excreted unchanged by the kidney, have relatively long half-lives, and can be administered once daily. It has been suggested that these agents may be associated with fewer central nervous system effects given their water solubility. This proposition has recently been buttressed by evidence from a randomized double-blind study of propranolol and nadolol in normal volunteers whose memory for emotional events was tested by observation of both a neutral and an arousal version of a slide show. The study confirmed that propranolol significantly impaired memory for an emotionally arousing but not a neutral story, whereas an equipotent beta-blocking dose of nadolol did not impair either type of memory and was comparable to placebo (193). Agents with $beta_1$-selective action, such as metoprolol and atenolol, may circumvent the undesirable consequences of nonselective beta-blockade (Table 16.4). Other side effects of beta-blockers include lightheadedness and postural hypotension, cold extremities and Raynaud's phenomenon, gastric upset with heartburn and diarrhea, decreased libido, impotence, and reversible alopecia. Selective $beta_1$-blocker effects, however, are only relatively selective, and at increased doses these agents produce $beta_2$-blockade. Beta-blocking agents with partial agonist activity such as pindolol and acebutolol do not lower resting heart rate or slow atrioventricular conduction and may obviate the untoward effects of beta-blockers on plasma lipids and the central nervous system (194).

Coronary vasoconstriction
Peripheral circulatory vasoconstriction
Bronchial constriction
Response to hypoglycemia
Impaired hepatic gluconeogenesis
Impaired general awareness
Triglycerides/high-density lipoprotein cholesterol

TABLE 16.4 UNTOWARD EFFECTS OF NONSELECTIVE BETA-BLOCKADE

Unless contraindicated or limited by unacceptable side effects, all patients should be considered as candidates for beta-blockers, given their demonstrated antianginal efficacy and favorable effect on long-term survival in patients after myocardial infarction (195,196). A variety of beta-blocker preparations are available for clinical use in angina, and an inventory of their characteristics, dosages, and frequency of administration is depicted in Table 16.5. Despite initial suggestions that four daily dosages were required, most beta-blockers can now be given either twice a day or once daily, both of which are well received by patients and therefore conducive to good compliance. Although those agents characterized as $beta_1$-selective lose their selectivity at the higher dose ranges, at more modest doses they may be advantageous in patients in whom nonselective beta-blockade is undesirable—those with chronic obstructive lung disease or brittle insulin-dependent diabetes. In general, beta-blockers with significant intrinsic sympathomimetic activity, such as pindolol, have fewer cardioprotective effects and seem to be less effective in control of symptoms and ischemia (194). Although sotalol may be useful in some patients because of its additional antiarrhythmic effects, its propensity to prolong the QT interval and be proarrhythmic limits its broad applicability (197). Whereas heart failure can occasionally be precipitated, there is now unequivocal evidence that the use of $beta_1$-selective beta-blockers—that is, metoprolol (sustained action) (198) and bisoprolol (199)—ameliorate the symptoms, morbidity, and mortality of heart failure. The introduction of carvedilol (200), a third-generation beta-blocker with $alpha_1$-adrenergic blocking activity (which produces vasodilatation), as well as antioxidant and antiproliferative properties, has shown an impressive reduction in cardiac mortality and morbid events in patients with chronic heart failure (201); this has recently been extended to include those with class IV symptoms (202). Recent data support the efficacy of carvedilol, as superior to placebo and comparable to metoprolol, as it relates to antianginal efficacy, exercise time, and time to 1-mm ST-segment depression (203,204).

Name (proprietary)	Property	Frequency	Daily dose (mg)
Propranolol (Inderal)	Nonselective	Twice a day	80–320
(Inderal LA)		Daily	60–320
Nadolol (Corgard)	Nonselective	Daily	80–240
Timolol (Blocadren)	Nonselective	Twice a day	15–45
Metoprolol (Lopressor)	Beta, selective	Twice a day	100–400
(Lopressor SR)		Daily	100–400
Atenolol (Tenormin)	Beta, selective	Daily	50–200
Bisoprolol (Zebeta)	Beta, selective	Daily	5–10
Acebutolol (Sectral)	Beta, selective partial ISA	Twice a day	200–400
Pindolol (Visken)	Nonselective ISA	Twice a day	15–45
		Three times a day (>30 mg total)	
Sotalol (Betapace)*	Nonselective with type II antiarrhythmic effect	Twice a day	160–480
Carvedilol (Coreg)	Nonselective with vasodilator effects	Twice a day	50–100

ISA, intrinsic sympathomimetic activity; LA, long acting; SR, sustained release
*Sotalol is not approved for angina pectoris use

TABLE 16.5 BETA RECEPTOR ANTAGONISTS FOR ANGINA PECTORIS

In a study of 306 patients with mildly symptomatic or asymptomatic ischemia and well-documented coronary disease, Pepine and coworkers (141) examined the effects of atenolol, 100 mg daily, versus placebo on event-free survival at 1 year. Because of a significant reduction in risk of adverse events with atenolol versus placebo [relative risk, 0.44; 95% confidence interval, 0.26 to 0.75 (p = .001)], this study was terminated earlier than planned. Importantly, these events were a composite of hard and soft outcomes—that is, death, resuscitation from ventricular arrhythmia, nonfatal myocardial infarction, hospitalization for unstable angina, aggravation of angina requiring known antianginal therapy, and the need for revascularization. Atenolol also significantly reduced heart rate, the number of ischemic episodes on ambulatory monitoring, and the average total duration of ischemia over 48 hours of monitoring. As in other studies, the frequency of ischemia on ambulatory monitoring was predictive of the long-term cardiac risk. Although this study was relatively small in size and underpowered to detect a significant change in death and myocardial infarction, the linkage in treatment response to silent ischemia and the clinical outcome was suggestive.

To ensure patient compliance and minimize adverse side effects, the use of once-daily atenolol or metoprolol twice a day (or a once-daily long-acting preparation) is usually an effective strategy. Titrating the dose to symptomatic relief and assessing the adequacy of beta-blockade based on the response of exercise (not resting) heart rate is a useful approach. Initial unfavorable adverse effects can sometimes be circumvented by dropping the dose to one-half the initial maintenance dose and building gradually over weeks such that full-dose therapy or maximally tolerated amounts can be reached within 6 to 12 weeks.

When symptoms persist or side effects limit treatment with beta-blockers and/or nitrates, the use of calcium antagonists may provide significant additional relief. It has been suggested that a special niche for calcium antagonists resides with Prinzmetal's variant angina patients and those in whom hyperventilation precipitates angina with ST depression during the recovery phase of this form of provocative stress (205). Although often considered as a single class of therapeutic agents for angina, calcium antagonists, like nitrates and beta-blockers, have substantial heterogeneity (206).

Calcium channel blockers inhibit intracellular entry of calcium ions primarily through the voltage-dependent L-type slow- or long-acting calcium channel. The subsequent reduction in intracellular calcium availability is critical to an activation process that binds actin to myosin, resulting in contraction of cardiac, skeletal, and smooth muscle. Each of these agents possesses significant smooth muscle relaxing effects, resulting in peripheral arterial vasodilatation and afterload reduction, as well as coronary vasodilatation with reduced potential for coronary vasospasm. In the intact circulation, each agent possesses negative inotropic effects; this is most marked with verapamil, least evident with nifedipine, and represents the composite impact of the latter agent's more prominent arterial unloading influence of the direct cardiodepressive effect.

In September 1995, a special announcement from the National Heart, Lung, and Blood Institute on the safety of calcium channel blockers proved a focus for major scientific debate on the safety of these agents. This announcement was fueled in part by a retrospective case control study of patients with hypertension, suggesting an increased risk of myocardial infarction for nifedipine, diltiazem, and verapamil (31%, 63%, and 61%, respectively) (207). Shortly thereafter, a metaanalysis by Furberg of 16 trials using short-acting nifedipine in patients with clinical coronary disease, primarily those with acute ischemic syndromes, revealed a dose-related influence on excess mortality (208). This analysis has been the subject of substantial scientific debate, and the weight of this and other evidence suggests that nifedipine's use as a short-acting preparation without concomitant beta-blocker therapy should be avoided (209). The resulting reflex tachycardia, increased cardiac output, and untoward precipitation of angina and ischemic events that are associated with its use all support this posture. Observational clinical evidence suggests increased ischemic activity during nifedipine therapy in patients who have well-developed coronary collaterals on angiography, implying a possible coronary steal phenomenon as an explanation for this observation (210).

Significant differences also exist between the electrophysiologic effects of dihydropyridines and the verapamil and diltiazem classes; these are absent with nifedipine, but both verapamil and diltiazem slow the resting and exercise heart rate and delay atrioventricular conduction (206). Verapamil and diltiazem also are effective in controlling the ventricular response to atrial fibrillation and in intravenous form are effective in converting reentry paroxysmal supraventricular tachycardia to sinus rhythm. Oral verapamil is effective as prophylaxis against paroxysmal supraventricular tachycardia as well. Sustained-release nifedipine preparations and newer longer-acting dihydropyridine agents such as felodipine and amlodipine have circumvented some of the untoward effects of dihydropyridines and, along with sustained-release formulations of verapamil and diltiazem, have facilitated patient use and compliance through once-daily dosing regimens (211,212). Although initial animal studies suggested calcium antagonists might have a role in retarding or reversing atherosclerosis, clinical studies of nifedipine and nicardipine have failed to show benefit on either lesion progression or regression (213,214). The dosing schedule and effects on heart, atrioventricular conduction, and blood pressure of the various calcium channel blockers available for angina are depicted in Table 16.6. Side effects of headache, dizziness, and flushing along with peripheral edema are most prominent with the dihydropyridines, whereas they are much less frequent with verapamil and diltiazem. Overall, diltiazem is the best tolerated of the first-generation calcium antagonists; constipation, which may be especially troubling in the elderly, is a significant side effect of verapamil. However, each of these first-generation calcium antagonists has negative inotropic effects. This is most pronounced with verapamil and least with nifedipine, and they are relatively contraindicated in patients with significant left ventricular dysfunction. Special note should be made of the propensity for bepridil to prolong the QT interval and promote proarrhythmic effects in a small proportion of patients; accordingly, the QT interval should be monitored during the initiation of therapy with this agent and the drug discontinued or dosage reduced if there is a more than 25% increment. Accordingly, bepridil should be reserved for patients with refractory angina. The newer-generation dihydropyridines exhibit less net negative inotropic effects, presumably attributable to their greater vascular selectivity. Opie has suggested that amlodipine has a more favorable side effect profile than beta-blocker therapy in angina based on overview of a number of small studies (215). Amlodipine has also been demonstrated to reduce the extent of postexercise ischemic-induced myocardial stunning as compared with isosorbide mononitrate: In 24 patients with chronic stable angina and normal resting left ventricular function, exercise was undertaken until limited by chest pain (216).

Blocker	Dose (mg/frequency)	Heart rate	Atrioventricular conduction	Blood pressure
Nifedipine	30–120 three times a day	↑	→	↓↓
Nifedipine GITS	30–180 daily	→	→	↓↓
Diltiazem	30–90 three or four times a day	↓↓	↓	↓
Diltiazem SR	60–120 twice a day	↓↓	↓	↓
Verapamil	80–120 three or four times a day	↓	↓↓	↓
Verapamil SR	120–240 daily or twice a day	↓	↓↓	↓
Amlodipine	2.5–10.0 daily	↑	→	↓↓
Felodipine	5–20 daily	↑	→	↓↓
Nicardipine	10–20 three times a day	↑	→	↓↓
Isradipine	2.5–10.0 twice daily	↑	→	↓↓
Bepridil	200–400 daily	↓	→↓	↓

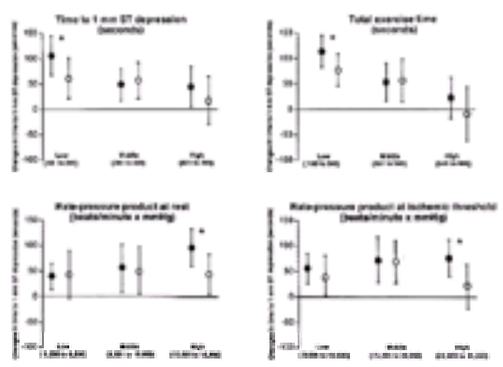
GITS, gastrointestinal system; SR, sustained release.

TABLE 16.6 CALCIUM CHANNEL BLOCKERS: DOSING AND PROPERTIES

Despite similar extent of radionuclide-confirmed perfusion abnormalities, comparable exercise duration, hemodynamic parameters, and ST-segment depression, postexercise stunning defined as a new wall motion abnormality in the area of a perfusion defect occurred less frequently and was less marked while receiving amlodipine than isosorbide mononitrate. These data support prior experimental work demonstrating a direct antistunning effect of calcium antagonists thought to be secondary to inhibition of calcium overload.

In summary, all three classes of antiischemic agents have been demonstrated to relieve symptoms, improve exercise tolerance, and reduce the frequency of silent ischemia. On balance, beta-blockers and, more specifically, the two $beta_1$-antagonists atenolol and metoprolol, seem to be most effective in the relief of ischemia.

Ardissino and colleagues (217) studied 280 patients with mild stable angina and compared long-acting metoprolol, 200 mg daily, versus nifedipine in a sustained formulation, 20 mg twice a day. Whereas both agents improved exercise tolerance, there was a greater effect for metoprolol, which seemed most prominent in patients with low exercise tolerance and high-rate pressure products either at rest or during exercise (eFig. 16.4.1). Interestingly, the same investigators (the International Multicentre Angina Exercise Study group) found that the benefit of combination metoprolol and nifedipine seemed to be mainly related to an enhanced response to one versus another agent in nonresponders and not a function of the additive effects of the two agents (218). (The total nifedipine dose in both these studies was somewhat modest, at 40 mg, compared with full 200-mg doses of metoprolol.) The Tibet study of patients with mild stable angina compared 100-mg atenolol to 40-mg nifedipine, and then the combination on exercise testing, ambulatory ECG monitoring, symptoms, and cardiac events (219). Both therapies were equally effective in reducing evidence of ischemia, and combination therapy did not further improve these measures. However, cardiac events at 2 years consisting of mortality, myocardial infarction, unstable angina, and the need for revascularization and further treatment showed a trend for benefit with combination therapy (8.5%) over that observed with atenolol and nifedipine alone (12.8% and 11.2%, respectively, $p = .14$). Hence, it would seem that once symptoms are adequately controlled, reassessment of the patient for continuing objective evidence of ischemia while on treatment may be warranted because such patients seem to be at high risk and potentially deserving of more aggressive intervention (220). This question is under active continuing clinical investigation.



***e*FIGURE 16.4.1** Changes in time to 1-mm ST-segment depression after 6 weeks of treatment with metoprolol (*closed circles*) or nifedipine (*open circles*). Bars indicate 95% confidence intervals. When a bar does not cross the 0 axis, the difference from baseline is statistically significant at a level of $p < .05$. Comparisons between drugs are made within each low, middle, and high tertile of the baseline exercise variables. Numbers in parentheses denote the range of each tertile. *$p < .05$ for comparisons between metoprolol and nifedipine within each tertile. [From Ardissino D, Savonitto S, Egstrup K, et al. Selection of medical treatment in stable angina pectoris: results of the International Multicenter Angina Exercise (IMAGE) Study. *J Am Coll Cardiol* 1995;25:1516–1521, with permission.]

Other Medical Therapy

Despite some initial enthusiasm, angiotensin-converting enzyme inhibitors have proved to be disappointing in ameliorating symptoms or evidence of myocardial ischemia in patients with chronic stable angina (221). However, their role in enhancing survival among patients with left ventricular dysfunction after myocardial infarction is well established. Importantly, angiotensin-converting enzyme inhibitors have been found in both the Survival and Ventricular Enlargement studies and Studies of Left Ventricular Dysfunction to reduce the long-term risk of developing unstable angina and myocardial infarction (222). These studies have now been confirmed and their implications broadened by the Heart Outcomes Prevention Evaluation study, which studied more than 9,000 patients with a history of coronary disease, stroke, peripheral vascular disease, or diabetes in conjunction with at least one additional cardiovascular risk factor and no evidence of heart failure or depressed ejection fraction. More than one-half of the patients had stable angina, and more than one-third had diabetes with coexisting hypertension and prior infarction also common. The treatment group received 10 mg of ramipril for a mean of 5 years, with a significant reduction in all-cause mortality, cardiovascular death, myocardial infarction, stroke, coronary revascularization, cardiac arrest, heart failure and, not only complications related to diabetes, but also the appearance of new-onset diabetes (223). Interestingly, the Heart Outcomes Prevention Evaluation study, which was a two-by-two design also studying vitamin E, found no difference for this therapy as compared with placebo on cardiovascular outcomes (224). It seems clear that angiotensin-converting enzyme inhibitors exert a multiplicity of effects on the vasculature at diverse sites that extend beyond any of their well-documented hemodynamic effects. These include a potential antiproliferative effect that may retard atherosclerotic plaque growth, an inhibitory effect on the endothelium that may attenuate both vasoconstriction and plaque rupture, and modulation of collagen deposition and left ventricular remodeling.

Amiodarone was initially introduced in 1967 as an antianginal agent, yet its clinical use has been primarily directed toward atrial and ventricular arrhythmias. Suggestive evidence from one trial of congestive heart failure indicated a favorable effect on survival (225). Amiodarone has multiple mechanisms of action as a class III antiarrhythmic that also decreases myocardial infarction oxygen consumption by reducing heart rate, contractility, and afterload. It also dilates the coronary vasculature through a direct relaxing effect. In a modest-sized placebo-controlled trial of patients with persisting angina despite double or triple medical therapy, amiodarone was administered for 2 months in a dose of 200 mg per day after initial loading (226). An increase in exercise tolerance in conjunction with a decrease in rate pressure product and ST-segment depression was accompanied by modest symptomatic improvement. Hence, in patients with refractory symptoms, this strategy may be a worthwhile alternative to explore, but careful monitoring for long-term side effects is required.

The role of postmenopausal hormone replacement therapy (HRT) is thought to have been important in secondary prevention among women with coronary disease based on impressive observational data. This thesis has finally been subjected to a randomized study in 2,763 women younger than 80 years of age with established coronary disease who were postmenopausal but possessed an intact uterus (227). HRT was provided by 0.625 mg of conjugated estrogen coupled with 2.500 mg of medroxyprogesterone acetate, and an evaluation of the primary outcome was evaluated over a mean of 4.1 years. Although no significant differences in the primary outcome were found, there was a statistically significant time trend for excess coronary events in the HRT group during the first year and less in years 4 and 5. This was largely modulated by an increase in nonfatal myocardial infarction and overall coronary deaths remained nonsignificantly higher for the HRT group compared with placebo throughout the study despite an 11% lower LDL cholesterol and 10% higher HDL cholesterol in the HRT group. Importantly, there was also an excess of venous thromboembolic events and gallbladder disease in the HRT group. As suggested in an accompanying editorial, “these findings are a sobering reminder of the limitations of observational research, the incompleteness of current understanding of the mechanisms of vascular disease, and the dangers of extrapolation” (228). Whereas there is now clearly no indication for commencing HRT for secondary prevention, sustaining such therapy in women who have received it for longer than a year may be reasonable. HRT in women with prior hysterectomy and as a strategy for primary prevention is the subject of ongoing study.

Hormone therapy in the form of supplemental testosterone in men has recently been demonstrated in a pilot study using low-dose supplemental testosterone (5 mg daily by transdermal patch) to improve exercise-induced ischemia in chronic stable angina (229). These findings were accompanied by a twofold increase in androgen levels, and the magnitude of the response was somewhat greater in those with lower baseline testosterone levels. As the coronary circulation appears more sensitive to the vasodilatory effects of testosterone in larger blood vessels and age-related decrements in androgens are common in elderly men, this interesting initial work deserves confirmation and wider study.

In patients with syndrome X and systemic hypertension, enalapril therapy has been shown to reduce left ventricular hypertrophy, normalize thallium perfusion defects, and increase exercise capacity (230). In a randomized double-blind study, Cannon and coworkers (231) demonstrated that imipramine, 50 mg every night, reduced chest pain frequency by half among patients with syndrome X; the mechanism is unknown but was speculated to relate to a visceral analgesic effect.

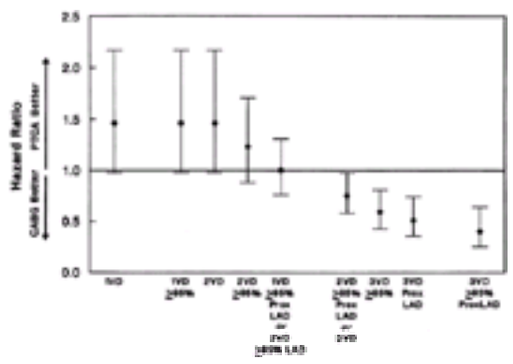
In Prinzmetal’s variant angina, when symptoms do not respond to nitrates and calcium antagonists, a variety of options have been suggested. Conflicting data exist regarding serotonin antagonism; hence, short-term intravenous ketanserin (232), a specific serotonin blocker, did not attenuate ischemic episodes, whereas chronic therapy with cyproheptadine, a nonselective serotonergic antagonist, has been reported to be of benefit in two case reports (233). Supplementary vitamin E therapy (vitamin acetate, 300 mg per day) added to calcium antagonist in patients with persisting attacks of variant angina significantly inhibited recurrent symptoms (81).

Nonpharmacologic Therapy

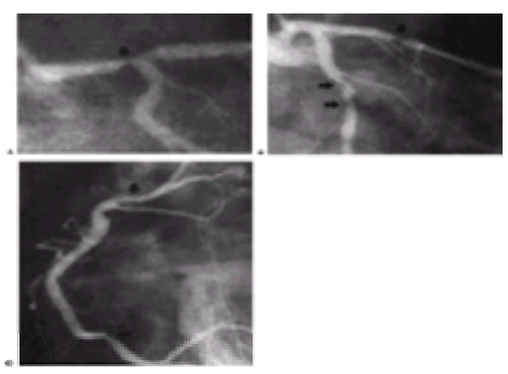
Factors associated with mental and physical stress are often underestimated in the therapeutic approach to stable angina. Similarly, the increased physical demands associated with obesity, an increasingly common and correctable risk factor, provide both patient and physician a significant opportunity for reducing cardiac work and enhancing a general sense of well-being. Diet, environmental manipulation, exercise conditioning, stress relaxation, and behavior modification applied appropriately and judiciously (in conjunction with patient and family counseling), may yield significant symptomatic benefit. A recent review of exercise as cardiovascular therapy outlines the physiologic effects of regular exercise and suggests an approach to a rationale for exercise prescription and how this may improve cardiac performance, quality of life, and secondary prevention (234). These considerations are too often neglected, yet they commonly comprise powerful opportunities for enhancing short- and long-term quality of life in stable angina (5).

Revascularization Therapy

Angiography plays a pivotal role in modulating the advisability and need for revascularization. Confirmation of significant epicardial coronary stenosis—that is, 50% or more diameter narrowing—helps to define patient risk and guide therapeutic decision making. If the patient falls into a high-risk anatomic subset where surgical revascularization is known to improve prognosis, the course of action is relatively clear. Hence, those patients with left main coronary stenosis or a triple-vessel coronary disease are best managed with coronary bypass surgery (234,235). This strategy may also be reasonably applied to patients with two-vessel disease involving the proximal left anterior descending coronary artery, given the recent report of the Coronary Artery Bypass Surgery Trialists Collaboration (236). In the first large-scale prospective observational assessment of angioplasty versus CABG for patients with coronary disease, Mark and colleagues (237) described the 5-year survival experience of patients in the Duke data bank evaluated between 1984 and 1990. As is evident from eFigure 16.4.2, a survival advantage was evident for coronary bypass grafting over angioplasty in patients with three-vessel disease and those with two-vessel disease that involved the proximal left anterior descending coronary artery. In 1995, Pocock and colleagues (238) conducted a metaanalysis of 3,371 patients from eight randomized trials comparing angioplasty with coronary bypass surgery for patients with angina observed for a mean of 2.7 years. Three of the trials and 22% of the patients had single-vessel disease and the remaining had multivessel disease. Those with high-risk proximal three-vessel disease and left main stenosis were excluded (eFig. 16.4.3). As is evident in Table 16.7, there was no difference in cardiac death and myocardial infarction at 1 year; however, patients receiving angioplasty had a substantially greater requirement for repeat revascularization and less complete relief of symptoms, which required more antianginal medical therapy. Examples of anatomic subsets well suited for surgical revascularization are depicted in eFigure 16.4.3.



***e*FIGURE 16.4.2** Hazard (mortality) ratios for coronary artery bypass graft surgery (CABG) versus medicine calculated from the Cox regression model to evaluate relative survival differences. Points indicate hazard ratios for each level of the coronary artery disease index; bars indicate 99% confidence intervals. Horizontal line at ratio of 1.0 indicates point of prognostic equivalence between treatments. Hazard ratios below the line favor CABG; those above the line favor medicine. Prox LAD, proximal left anterior descending coronary artery; PTCA, percutaneous transluminal coronary angioplasty; VD, vessel disease. (From Mark DB, Nelson CL, Califf RM, et al. Continuing evolution of therapy for coronary artery disease. *Circulation* 1994;89:2015–2125, with permission.)



***e*FIGURE 16.4.3** Anatomic subsets from angiography. Example of high-risk coronary anatomy leading to exclusion of patients from randomized trials comparing angioplasty with coronary artery bypass graft surgery. **A:** Distal left main trunk stenosis. **B:** Complex multivessel disease with main trunk equivalent, consisting of high-grade proximal left anterior descending and complex proximal left circumflex stenoses. **C:** High-risk complex stenoses in the right coronary artery, consisting of severe ostial stenosis followed by high-grade distal vessel lesion preceded by significant proximal tortuosity.

	Metanalysis (n = 3,371; mean follow-up duration 2.7 yr)		Bypass Angioplasty Revascularization Investigation (n = 1,829; mean follow-up duration 5 yr)	
	PTCA	CABG	PTCA	CABG
Mortality (%)	4.6	4.4	13.7	10.7
Myocardial infarction (%)	4.2	5.4	10.9	11.7
Need for PTCA/CABG (%)	33.7	3.3	54.0	8.0
Need for CABG (%)	21.2	1.5	31.0[b]	1.0

CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.
[a]Data are percentages and represent mean follow-up of 2.7 years for metanalysis (238) and 5 years for the Bypass Angioplasty Revascularization Investigation (239), except for Q-wave myocardial infarction (and need for PTCA/CABG, which is 1 year, in metanalysis.
[b]11.8% of the PTCA group underwent both PTCA and CABG.

TABLE 16.7 RANDOMIZED TRIALS COMPARING PTCA AND CABG[a]

The Bypass Angioplasty Revascularization Investigation trial compared the results of coronary bypass surgery with percutaneous transluminal coronary angioplasty (PTCA) in 1,829 patients with multivessel coronary disease and demonstrated superior survival with CABG in the 25% of the patients with diabetes mellitus (239). Hence, the 5-year survival with CABG versus PTCA (80.6% vs. 65.5%, respectively; $p = .003$) was substantially better. Summary results for the major 5-year outcomes of the Bypass Angioplasty Revascularization Investigation trial are depicted in Table 16.7. Subsequently, investigators in the Bypass Angioplasty Revascularization Investigation analyzed a subgroup of 353 patients (19% of the overall sample) who were diabetic with multivessel disease and found a substantial reduction in 5-year all-cause and cardiac mortality in those receiving CABG (especially with internal mammary artery grafts) as compared with PTCA; thus, for CABG, these mortalities were 19.1% and 5.8% and for PTCA 34.7% and 20.6%, respectively. Some, but not universal, support from post hoc analysis of this issue has merged from other trials; accordingly, caution should be exercised in applying PTCA to diabetic patients in the setting of multivessel or multilesion disease (240,241). A summary of the pros and cons of PTCA versus CABG for patients with multivessel disease who fit the criteria of the randomized trials to date is outlined in Figure 16.5 (242). Multivessel disease accounts for approximately 12% of all candidates for revascularization. It is conceptually useful to consider revascularization as a strategy rather than a choice of single procedure (243,244). Hence, in a young patient, angioplasty may be useful in avoiding early surgical procedure and the use of grafts that are of finite number, with the expectation that they will ultimately be required. Angioplasty may be extremely useful in dealing with the problem of graft stenosis that markedly accelerates in venous conduits after the first 6 years. Superior long-term patency with internal mammary as opposed to saphenous vein grafts unequivocally points to using this conduit wherever possible, especially when the left anterior descending coronary artery is being surgically revascularized (241). When revascularization is planned and the prognosis judged to be equal, irrespective of the procedure, the decision regarding the type of revascularization depends on a host of factors that are best left to an informed discussion between patient and physician, taking into account local expertise and experience. Such a discussion will involve the risk and morbidity of the initial procedure, the time for recovery, cost-benefit issues, acceptance of the need for follow-up, and the likelihood of need for ongoing medical therapy and repeat procedures as well as the completeness of revascularization.

PRO	CON
PTCA • Avoids or defers major surgery • Rapid recovery • Shorter initial hospitalization • Less early morbidity and MI • 80% less costly @ 2 yrs	PTCA • Incomplete revascularization • More angina • More medical therapy • More subsequent hospitalization • More subsequent revascularization • Possibly less long-term survival in MVD
CABG • More complete revascularization • Excellent symptom relief • Less anti-anginal meds • Less subsequent hospitalization • Less subsequent revascularization • Possibly better survival in multivessel CAD	CABG • More early morbidity/MI • Longer recovery • Longer initial hospital stay

FIGURE 16.5 Weighing the balance for revascularization. CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; MI, myocardial infarction; MVD, multivessel disease; PTCA, percutaneous transluminal coronary angioplasty. [Adapted from Simoons ML. Myocardial revascularization—bypass surgery or angioplasty? (editorial). *N Engl J Med* 1996;335:275–277, with permission.]

The evidence base for these revascularization decisions is now somewhat dated, and major changes in the content and application of medical therapy PTCA and CABG have occurred since its acquisition. These include the use of angiotensin-converting enzyme inhibitors and statins as part of a broad secondary prevention strategy. For percutaneous interventions they are composed of the use of intravenous glycoprotein IIb/IIIa inhibitors, which reduce acute complications, the use of coronary stenting to reduce the recurrence rate of restenosis, and the application of intracoronary radiation to reduce the risk of restenosis after coronary stenting (245,246 and 247). For CABG surgery, significant attempts have been made to diminish the morbidity of the operation by using smaller incisions and obviating the use of cardiopulmonary bypass. In particular, minimally invasive direct coronary artery bypass ("MID-CAB" operation) through a small left thoracotomy incision with a thoracoscope permits surgery on the left anterior descending coronary artery and its diagonal branches, whereas a right-sided incision allows access to the right coronary artery. Early results in appropriately selected patients are encouraging, with reduced morbidity and hospital stay and rapid return to normal activity (241).

In patients with single-vessel coronary disease, exclusive of the proximal left anterior descending and at low risk—that is, with normal left ventricular function, preserved exercise tolerance, and nondisabling angina—the evidence from two randomized trials supports contemporary medical therapy to be at least as effective as PTCA (248) with regard to the outcomes of death and myocardial infarction (249). In a third study, where the medical group received aggressive lipid-lowering therapy with 80 mg of atorvastatin (250), medically treated patients tended to have a lower frequency of ischemic events as well as a delay to their first occurrence. Relief of angina was superior with PTCA in all three trials, but the majority of this benefit attenuated over time. It should be emphasized that none of these trials used state-of-the-art interventional procedures with systematic concurrent intravenous glycoprotein IIb/IIIa platelet inhibition or intracoronary stenting (245,246). This composite approach has been shown to have a substantial effect on reducing the risk of 30-day myocardial infarction and death (246).

Three novel alternatives to conventional PTCA and CABG have recently been introduced: percutaneous transmyocardial laser revascularization (PTMR), enhanced external counterpulsation, and spinal cord stimulation (SCS).

Transmyocardial laser revascularization for patients with advanced and/or medically unresponsive angina has been suggested as a potentially promising new therapeutic modality (251). Reserved for patients who are not candidates for either percutaneous coronary or surgical revascularization, this approach creates small transmural channels in ischemic myocardium using carbon dioxide or holmium as the laser energy source during thoracotomy. Although modest improvements in functional classification of angina and symptomatic improvement have been observed in randomized studies, several caveats must be addressed before this therapy can be widely endorsed:

VIDEO

Video 16.3 Intraoperative transesophageal echo of a patient undergoing laser transmyocardial revascularization. Note the gas production as the laser beam penetrates the myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

- The incidence of perioperative death (2% to 20%) and myocardial infarction (5% to 15%) is substantial. In part this relates to patient clinical status and, not surprisingly, is increased with unstable coronary syndromes.
- Deterioration in left ventricular function and worsening heart failure have been observed in a number of reports.
- Objective demonstration of enhanced perfusion, although occasionally observed, has been an inconsistent finding.
- Because, by necessity, the active therapy is unblinded, the well-recognized placebo effect in angina pectoris is likely an important component of the symptomatic benefit observed (252,253,254,255,256 and 257).

Recently the transmyocardial laser revascularization procedure, which had been surgically based, was modified to use a PTMR approach. Using the holmium:YAG laser passed through a percutaneous flexible optical fiber system, 221 patients with reversible ischemia and class III or IV angina were randomized to PTMR versus medical therapy and followed for 12 months. Eleven deaths occurred (eight in the PTMR group), 11 patients versus seven had myocardial infarction, and 16 versus 11 had worsening heart failure in the PTMR versus medical group, respectively. There were three periprocedural myocardial perforations, one of which required pericardiocentesis. Patients in the PTMR group showed a 14.4% increase in exercise duration over their baseline of 379 seconds, compared with a 5.5% increase in the medically treated group. Twenty-eight PTMR patients versus 12 in the medical group had Canadian Cardiovascular Society angina class II or lower angina. These results were disappointing as compared with the surgical approach in that the magnitude of the symptomatic benefit was somewhat less and the mortality and morbidity unimproved (258).

Although enhanced external counterpulsation has also been suggested as a successful method to relieve angina, improve exercise tolerance, and reduce perfusion defects, a recent randomized control study of 139 carefully selected patients with mild to moderate angina was less encouraging (259). Exercise duration increased in both groups, but there was a slightly longer time to 1 mm of ST-segment depression during exercise and less frequent angina and use of nitroglycerin in the enhanced external counterpulsation arm. However, the relatively high frequency of device-related adverse events such as paresthesia, edema, skin abrasions, and leg and back pain make it unlikely that this therapy will be widely acceptable.

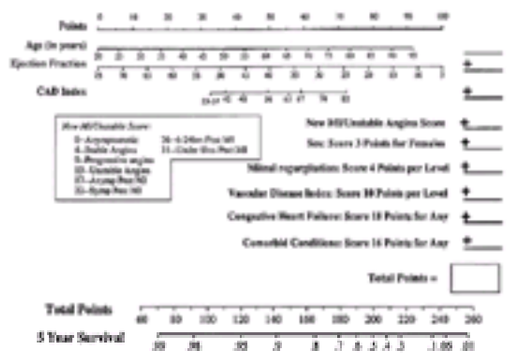
An additional surgical technique suggested for intractable angina, SCS, involves an electrical pulse generator inserted in a subcutaneous pouch below the left costal arch, attached to an electrode placed at the level of T1 to T2 in the epidural space. The pulse generator is activated for at least 2 hours, four times daily by an external magnet, which also allows switching between two preset stimulation strengths. A recent randomized study compared this therapy with coronary bypass surgery in 104 patients with symptomatic indication for CABG. These patients were believed to be unsuitable for PTCA, and their anatomy was configured in a way that increased surgical risk and was believed to preclude improved prognostics from CABG (260). Both groups had similar symptomatic relief, but the CABG group had increased exercise capacity with less ST-segment depression at comparable workloads and pressure product increments. Mortality rate and cerebral vascular morbidity were both lower in the SCS than in the CABG groups. Hence, SCS may play a role in these select circumstances.

NATURAL HISTORY, RISK ASSESSMENT, AND REDUCTION

Substantial progress has been made in the evaluation of the risk of fatal events in patients with coronary artery disease. A remarkable spectrum of risk exists within patients depending on the interaction of a variety of information that can be acquired from the history, clinical examination, electrocardiogram, and laboratory findings.

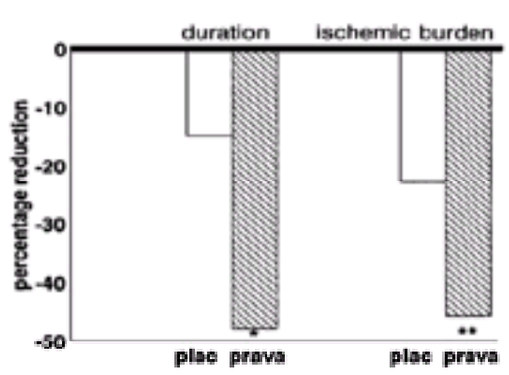
Whereas a 60-year-old patient with stable angina and no comorbid conditions may have a 98.7% 1-year survival, the presence of prior infarction, diabetes, heart failure, and a high-risk exercise treadmill can markedly reduce the 1-year survival (261). Nomograms developed during the twenty-seventh Bethesda, Maryland, conference, "Matching the Intensity of Risk Factor Management with the Hazard for Coronary Events," exist to assimilate the variety of factors known to predict outcome and permit the physician to practically apply such information for purposes of the assessment of an individual patient (*e*Fig. 16.5.1) (261). A defining principle of this strategy is the application of comprehensive risk management in direct proportion to the level of risk identified, giving both physician and patient the requisite knowledge and enthusiasm to initiate and sustain a risk-reduction program (262). This strategy is particularly important given the dramatic new developments in risk

reduction.



***e*FIGURE 16.5.1** Nomogram for prediction of 5-year survival from clinical, physical examination, and cardiac catheterization findings. CAD, coronary artery disease; MI, myocardial infarction. (From Califf RM, Armstrong PW, Carver JR, et al. Task Force 5: stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol* 1996;27:1007–1019.)

A rigorous effort to address correctable risk factors is a fundamental component of the overall management of the patient with stable angina. Smoking cessation is the single most powerful contribution patients can make to their own well-being and destiny. A variety of approaches including behavior modification and pharmacologic assistance have been used. Nicotine-replacement therapy using transdermal patches has had modest success without adversely affecting angina frequency (263). Achieving an ideal body weight through dietary modification, which also reduces cholesterol and saturated fat, controlling elevated blood pressure and blood sugar, along with incorporating regular physical activity into a patient's daily routine, can lead to enhanced quality of life with a higher threshold of physical activity before symptom development and improved prognosis (264). Improved cardiovascular conditioning such that the same degree of effort can be achieved at a lower rate pressure product may account in part for this phenomenon (265). The most important development in risk modification is the introduction of inhibitors of hydroxymethylglutaryl coenzyme A reductase, which have been substantially more successful in reducing LDL cholesterol than diet or prior drug interventions. Appreciation that reduction in total and LDL cholesterol of the order of 25% and 35%, respectively, can achieve a similar dramatic reduction in total and coronary mortality, myocardial infarction, and the need for coronary revascularization has provided the physician with important new opportunities and responsibilities (266). Sequential angiographic studies have demonstrated both a reduction in the frequency of progression and an increase in the frequency of regression of coronary atherosclerotic lesions in conjunction with clinical improvement (267). Because the extent of coronary arterial regression by sequential angiography seems too modest to explain the dramatic clinical benefit, it is presumed that this benefit relates to stabilization of coronary plaque and extraluminal remodeling with a commensurate reduction in the frequency of plaque fissuring and the coronary vascular accidents that ensue. It has been speculated that the interaction between hypercholesterolemia, lipid peroxidation, and platelet activation provides the statin drugs with an opportunity to favorably modulate the attendant prothrombotic state (268). The documentation of an antiaggregatory effect on platelets in patients with coronary artery disease after only 2 to 3 months of pravastatin therapy, coupled with evidence that statins can reduce fibrinogen levels, demonstrates their potential to behave as antithrombotic agents (269,270). This effect could be expressed temporally in advance of their effect on plaque stabilization and regression. Emerging data from two clinical studies have confirmed the ability of the statins to reduce ischemia detected by ambulatory monitoring. Andrews and coworkers (271) have shown in 96 patients with known stable coronary disease that lovastatin reduced the number of ischemic episodes by 65% in the control group versus 10% in placebo patients (p <.001) within only 4 to 6 months of commencing therapy. Van Boven and colleagues (272) assessed the efficacy of 40 mg of pravastatin in 768 male patients with stable angina and found a reduction in the duration and number of ischemic episodes coupled with a decline inischemic-related clinical events. They observed changes from baseline in the duration of ischemia (60 ± 13 mm per minute and 80 ± 12 mm per minute) and ischemic burden (34 ± 6 and 41 ± 5 mm per minute) for placebo and pravastatin, respectively (eFig. 16.5.2). Restoration toward normal coronary vasomotion as a result of lipid-lowering strategies with lovastatin has been unequivocally demonstrated after 6 months of therapy, and this improvement in endothelium-dependent vasomotion seems to be accentuated by combining cholesterol-lowering therapy produced by lovastatin with antioxidant therapy achieved with the use of probucol (273). Given that the majority of lesions responsible for acute myocardial infarction develops from noncritically stenosed coronary lesions, these observations from lipid-lowering trials acquire additional credibility and coherence (274). Targeting a reduction of total cholesterol to the range of 3.0 to 5.2 mmol per L as identified in the Scandinavian Simvastatin Survival Study of secondary prevention seems a legitimate goal (266). It is likely, however, that the risk associated with elevated total and LDL cholesterol is continuous. Hence, when other risk factors for coronary disease are present, more aggressive lipid lowering may be sensible. Pharmacologic management of serum cholesterol in patients older than 75 years remains of uncertain value and requires individualization of therapy. However, the benefit seen in the Scandinavian Simvastatin Survival Study was evident among all age groups up to the exclusion cutpoint of 70 years of age and, importantly, was also seen in both genders. A variety of endogenous factors known to play either a thrombogenic or coagulation inhibitory role have been identified as markers of increased risk (275). Serum fibrinogen is the most powerful and independent of these and has a particularly potent impact when present in association with increased cholesterol (276). Increased platelet aggregability, thrombin activity and generation, factor VII, and tissue-type plasminogen activator antigen have all been associated with increased risk of coronary events. The benefit of aspirin and warfarin and the interest in the development of oral antithrombin compounds relate to these risks. Continuing epidemiologic evidence provides considerable but not uniform weight to the role of homocysteine as a risk factor for cardiovascular disease. A recent American Heart Association Science Advisory cautions that there is as yet still no indication for population-wide screening or therapy (277). However, in high-risk patients, a strategy associated with dietary incorporation of a diet fortified with the recommendations of the Food and Nutrition Board of the Academy of Sciences Institute of Medicine that includes folic acid, vitamin B_6, and vitamin B_{12} of 400 µg, 1.7 mg, and 2.4 µg, respectively, is appropriate. In the event that this is unsuccessful in reducing basal homocysteine less than 10 µmol per L, supplementation with a multivitamin of 400 µg of folic acid, 2 mg of vitamin B_6, and 6 µg of vitamin B_{12} is suggested (277). The potential benefit of vitamin supplementation to reduce oxidation of LDL cholesterol is currently under investigation (262).



***e*FIGURE 16.5.2** Diagram of percent reduction in components of transient myocardial ischemia during the study in placebo patients [placebo (plac), *open bars*] and in pravastatin patients [pravastatin (prava), *hatched bars*]. The benefit of pravastatin persisted after adjustment for independent risk factors and cardiac interventions during the trial. (From Van Boven AJ, Jukema W, Zwinderman AH. Reduction of transient myocardial ischemia with pravastatin in addition to the conventional treatment in patients with angina pectoris. *Circulation* 1996;94:1503–1505, with permission.)

CONTROVERSIES AND PERSONAL PERSPECTIVES

Using symptoms as the solitary guide for appropriate therapy of stable angina is no longer an acceptable treatment strategy. Most ischemia is clinically silent, and its total extent bears a prognostic relationship to outcome. Hence, consideration should be given to assessing provocable or ambulatory ischemia as part of overall management. Validation that effective medical treatment of silent ischemia improves long-term outcome remains a promising and plausible hypothesis that is currently under study and requires confirmation.

Pharmacologic interventions such as the use of angiotensin-converting enzyme inhibitors and hydroxymethylglutaryl coenzyme A reductase inhibitors that reduce morbid events and the progression of coronary vascular disease have broad implications for huge populations. Movement of the gains achieved through secondary prevention toward primary prevention among patients at risk is one of the most fundamental and major future challenges. Realization of this goal requires incorporation of a collaborative approach with a variety of nonphysician health care providers, who are often better equipped to provide the necessary advice and follow-up (278).

Now that regression of disease and enhanced prognosis as a result of angiotensin-converting enzyme inhibitors and lipid-lowering strategies is a clinical reality, the

time is ripe for new prospective studies comparing this strategy with revascularization in selected anatomic subsets.

The growing epidemic of obesity and diabetes will place new emphasis not only on understanding the multiplicity of the effects of insulin resistance but also on how to modify this especially unhappy synergism between environmental factors and genetics. Further insights into the triggers of myocardial ischemia and their relationship to behavior and mental stress will lead to nonpharmacologic strategies aimed at stress relaxation and behavior modification with avoidance of ischemia (279).

Angiography with a view to revascularization of all lesions more than 50% diameter narrowing in patients with stable coronary disease irrespective of prognostic stratification is unwarranted. An appropriate profile of risk, including noninvasive documentation of left ventricular function, reversible ischemia, exercise tolerance, and the response to pharmacologic therapy, is sensible, cost-effective, and responsible stewardship of resources.

The promise of transmyocardial and percutaneous laser revascularization appears more elusive than 5 years ago given the attendant morbidity and mortality of the procedure(s) and uncertainty about long-term efficacy. Rigorous phase IV surveillance of this technique, now that it has been U.S. Food and Drug Administration–approved, will be necessary to establish its ultimate role.

Finally, care of the patient with chronic stable angina is a lifelong proposition. It takes time and patience to provide a comprehensive treatment plan, especially in non–high-risk patients. Issues associated with lifestyle, occupation, age, quality of life, the ability and motivation to comply with a complex medical program, and lifestyle preferences all require consideration. Active participation of the patient as a full partner in this collaborative venture is most likely to lead to a successful long-term strategy that couples symptom control, prevention of morbid events, improved survival, and retardation or reversal of the underlying disease based on targeting correctable risk factors.

FUTURE DIRECTIONS

The frequency of thrombus and complex plaque formation including inflammation within culprit lesions in patients with stable angina suggests a continuum between stable and unstable syndromes mediated by platelet activation, oxidative stress, dysfunctional endothelium, vasoconstriction, thrombus formation, and the potential for rapid acceleration in growth of atherosclerotic plaque (275). Endothelial injury and its interaction with inflammation, monocytes and mediators extruded from inflammatory cells, platelets, and other sources are an intense focus of investigation. It now appears that the proinflammatory milieu associated with unstable angina can also be demonstrated in some patients with stable angina as demonstrated by elevations in C-reactive protein, macrophage colony-stimulating factor, interleukin-6, and leukocyte elastase (280,281 and 283). There appears to be at least a modest relationship between serologic evidence of inflammation, the extent of coronary disease and ischemia, and the likelihood of future unfavorable cardiovascular events. Explosive developments in cell biology associated with better understanding of adhesion molecules and their role of the growth of the atherosclerotic plaque are likely to lead to entirely new classes of efficacious drugs (275). Despite its limitations, aspirin's venerability is likely to survive, possibly related, in part, to its antiinflammatory as well as its relatively weak antiplatelet effect (284). Notwithstanding the clinical disappointment associated with the introduction of oral glycoprotein IIb/IIIa antagonists during the convalescence of acute coronary syndromes (285), the identification and cloning of the P2Y subset 1,2 receptor and its demonstration of abundant expression on the surface of human platelets provides new opportunities for more rational drug design (286). So too is the future development of specific oral antithrombin agents likely to add usefully to our therapeutic armamentarium.

Further advances in the assessment of the coronary arterial tree will enhance our on-line assessment of coronary arterial plaque burden as well as its composition and stability (164,287). These will use novel ultrasonic measures, thermal detection interrogating temperature heterogeneity, and magnetic resonance imaging (288,289). These techniques will underscore the diffuse nature of coronary atherosclerosis and highlight the need for an appropriately broad strategy directed toward the total endothelial lining and what modulates its health and disease.

Major advances within the next 5 years are likely to be seen in association with the conduct of percutaneous coronary intervention (290). Further refinement in the development of intravascular stents that are biologically degradable and pharmacologically active may well additionally reduce the frequency of restenosis. The long-term effects of intracoronary radiation will establish whether enthusiasm concerning its short-term impact on restenosis after stent implantation is warranted. Advances in molecular biology coupled with the introduction of vascular endothelial growth factor provide creative new opportunities for revascularization in the face of inoperable diffuse disease and obstructed vessels (291). This will be especially applicable to the increasing cohort of patients who present with recurrent symptoms after prior revascularization. Less traumatic, minimally invasive coronary bypass surgery will become one component of an overall revascularization strategy: This will include percutaneous delivery of a melange of options such as mechanical dilation, stenting, radiation, and molecular modulation of both vascular and tissue growth. A central challenge for the practicing clinician and the majority of patients with stable angina will be how to apply and integrate a sensible, cost-effective solution from such a dazzling array of medical advances.

THE FUTURE

One of the most extraordinary features of stable ischemic syndromes is that our knowledge and approach are anything but stable!Since the publication of the first edition of this text, major new clinical trials and evidence have emerged to influence our thinking about pharmacologic therapy and approaches to revascularization. The sequencing of the human genome and the exploitation of the potential of molecular biology have begun to dramatically alter our thinking and, in some instances, management. This will accelerate progress toward closing the gap on the 50% of coronary atherosclerotic cases where known risk factors fail to account for its development. Polymorphisms of a variety of genes regulating the immune system, vascular tone, coagulation, and lipid metabolism are or will be uncovered (292). These discoveries will in turn spawn pharmacogenetic developments that provide "boutique" solutions for specific defects.

The future seems both challenging and filled with opportunity given the tremendous advances in cell biology that are enhancing our ability to comprehend the pathophysiology of coronary disease, better assess its long-term risk, and construct novel therapies (293). The therapeutic success of the past decade with its attendant prolongation of life will further accelerate the number of elderly patients seeking relief from symptomatic coronary disease. Further diagnostic advances will help discern the risk of future events and thereby guide the application of multiple therapeutic choices. Better strategies will be required to ensure practitioners apply evidence-based medicine to the broad population at risk; the emergence of two major guidelines concerning chronic stable angina management and the application of coronary artery bypass surgery are required reading for the clinical practitioner.

Engagement of the broad public in a response to the evidence supporting the promotion of healthy lifestyles and the adoption of behavior that reduces morbidity and mortality from atherosclerosis must surely constitute the centerpiece of our ongoing efforts.

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17

NON–ST-ELEVATION ACUTE CORONARY SYNDROMES: UNSTABLE ANGINA AND NON–ST-ELEVATION MYOCARDIAL INFARCTION

HARVEY D. WHITE

“ Indicates text or graphics that appear only in the electronic versions of this text.”

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OVERVIEW

The major pathophysiologic mechanism of acute ischemic syndromes is plaque rupture or fissuring with superimposed thrombus. Patients with non–ST-elevation acute coronary syndromes should be risk profiled at admission, and therapy should be tailored to individual patient characteristics and risk. Many low- and intermediate-risk patients can be managed without the need for interventions.

The goals of a conservative treatment strategy should be to risk-stratify all patients at admission, revascularize those at high risk, and “passivate” (i.e., inactivate) the platelet-active surface of the ruptured or fissured plaque in patients at intermediate risk. Patients at low risk should be discharged early.

Combination therapy with aspirin, a platelet glycoprotein IIb/IIIa receptor antagonist, and unfractionated heparin is effective for preventing myocardial infarction (MI) and death. The combination of aspirin and clopidogrel also reduces the risk of death/MI. Low-molecular-weight heparins are more convenient to use than unfractionated heparin, and the combined results of two trials showed that one low-molecular-weight heparin reduced the risk of death/MI compared with unfractionated heparin. Beta-blockers, nitrates, and calcium channel antagonists relieve angina but have no significant effect on intracoronary thrombus and do not necessarily reduce the risks of MI and death.

In high-risk patients, a revascularization strategy combined with a IIb/IIIa antagonist or an antithrombotic agent such as low-molecular-weight heparin prevents death/MI more effectively than a conservative medical strategy. The patient has less need for antianginal medications, a shorter hospital stay, and less need for readmission. This approach is cost effective in many health-care settings.

Better treatments and new therapeutic strategies are needed to improve the outcomes of patients with non–ST-elevation acute coronary syndromes. It is important that primary and secondary preventative measures are instituted to reduce the community burden of acute coronary syndromes.

GLOSSARY

Conservative management: Risk-stratification and medical therapy with selective use of angiography and revascularization procedures according to the patient's risk status.

Invasive management: Medical therapy plus early coronary arteriography and revascularization, irrespective of the patient's risk status.

Plaque instability: Propensity for atheromatous plaque to rupture or fissure.

Plaque passivation: Inactivation of the platelet-active surface of a ruptured or fissured plaque.

Rebound ischemia: Increase in ischemic events when heparin therapy is stopped.

Risk profiling: Estimation of the risk of coronary events—usually death or MI—by studying patient characteristics and the results of investigations.

INTRODUCTION

The first documented description of a patient with an acute ischemic syndrome is in the Ebers papyrus from 2600 BCE, which states, "If you find a man with heart discomfort, with pain in his arms, at the side of his heart, death is near." The description is still apt, but the prognosis has changed over the centuries. Today unstable angina is one of the most frequent causes of hospitalization (1), and the number of patients admitted with this condition is on the increase.

The syndromes of unstable angina, non–ST-elevation MI and ST-elevation MI are a continuum, and the pathophysiology is heterogeneous and dynamic. The clinical presentation depends on the severity of the arterial injury, the size and type of thrombus formed, the extent and duration of ischemia, and the amount of previous myocardial necrosis. The extent of ischemia depends on the myocardial distribution of the ischemia-producing artery, the severity of the ischemia-producing stenosis, the absence or presence of collateral circulation, factors that affect the supply of oxygenated blood, and increased myocardial demands, including the heart rate, blood pressure, and contractility. Patients may die, have an MI, require revascularization for refractory angina, or be readmitted with recurrent symptoms, and management continues to pose a major clinical challenge (1).

DEFINITIONS

The term *acute coronary syndromes* describes a spectrum of clinical syndromes that ranges from unstable angina to non–ST-elevation MI and ST-elevation MI. Patients who present with acute coronary syndromes are divided into those with ST elevation or new left bundle branch block and those with non–ST-elevation acute coronary syndromes including unstable angina and non–ST-elevation MI (2) (Fig. 17.1).

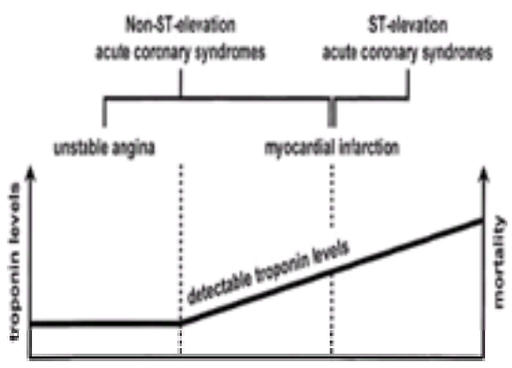


FIGURE 17.1 New terminology for coronary syndromes. [Adapted from Aroney C, Boyden AN, Jelinek MV, et al. Management of unstable angina: guidelines 2000. *Med J Aust* 2000;173(Suppl):S65–S88, with permission.]

The term *unstable angina* describes a syndrome that is intermediate between chronic stable angina and MI. It is a clinical diagnosis based on a history of chest pain and exclusion of the diagnosis of MI by electrocardiography (ECG) or cardiac enzyme testing. The chest pain may be prolonged at rest or of new onset, or it may represent accelerating symptoms of previously stable angina. It can also occur after MI. Patients who present without ST elevation are diagnosed as having either unstable angina or non–ST-elevation MI based on whether or not an elevation in myocardial protein levels, such as the troponins (3) or creatine kinase (CK)–MB, is detected. In 2% to 15% of patients, Q-wave MI subsequently develops. Braunwald (4) developed an unstable angina classification in 1989, which has proved to be clinically useful (5) and has been found to correlate with the underlying coronary angiographic findings in patients with unstable angina (6) (Table 17.1). This classification is based on the severity of symptoms, the clinical circumstances in which the unstable angina occurs, and the intensity of medical treatment. It has been updated to include troponin levels (7). Prinzmetal's angina (8) (i.e., recurrent rest angina accompanied by ST elevation on the ECG) is considered as a separate entity.

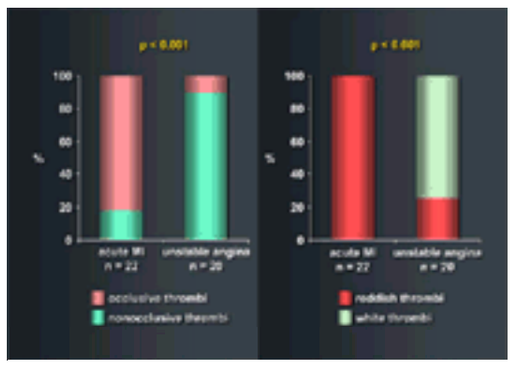
	Clinical circumstances		
Severity	A: Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary unstable angina)	B: Develops in absence of extracardiac condition (primary unstable angina)	C: Develops within 2 wk after acute myocardial infarction (postinfarction unstable angina)
I: New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II: Rest angina within past month but not within preceding 48 h (rest angina, subacute)	IIA	IIB	IIC
III: Rest angina within 48 h (rest angina, acute)	IIIA	IIIB (troponin negative) IIIB (troponin positive)	IIIC

Patients with unstable angina can also be divided into three groups, depending on whether unstable angina occurs (a) in the absence of treatment for chronic stable angina, (b) during treatment for chronic stable angina, or (c) despite maximal antischemic drug therapy. These three groups can be designated by subscripts 1, 2, or 3, respectively. Patients with unstable angina can be further divided into those with and those without transient ST-wave changes during pain.
Modified from Hamm CW, Braunwald E. A classification of unstable angina revisited. Circulation 2000;102:118–122, with permission.

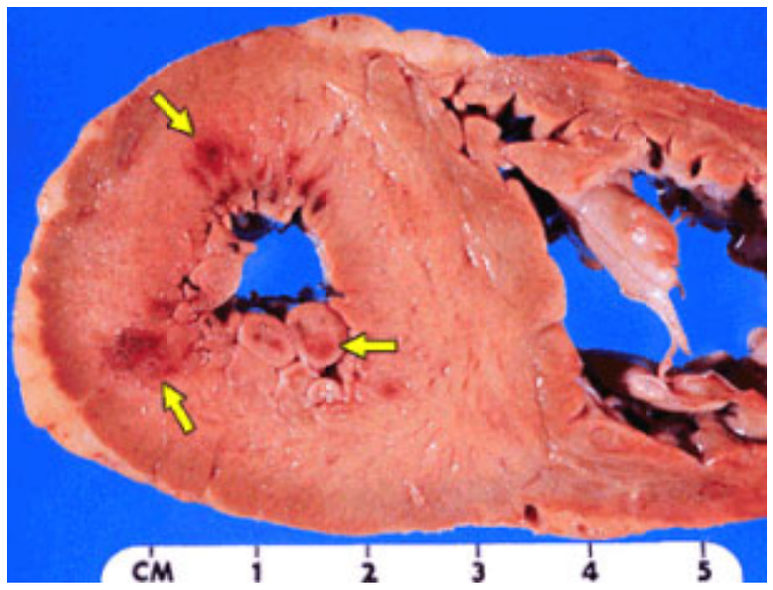
TABLE 17.1 CLASSIFICATION OF UNSTABLE ANGINA[a]

PATHOPHYSIOLOGY

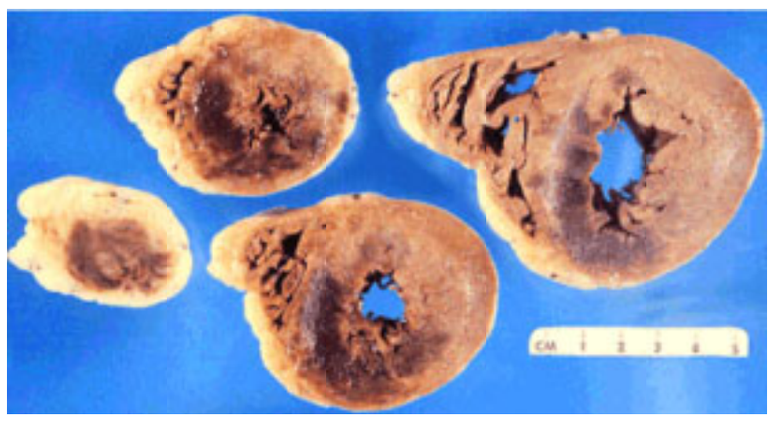
The five major causes of acute coronary syndromes are thrombus, mechanical obstruction, dynamic obstruction, inflammation, and increased organ demand (9). The major pathophysiologic mechanism is rupture or fissuring of an atheromatous plaque with superimposed thrombus (10,11,12 and 13). Superficial fissuring of a plaque usually results in platelet deposition, but there is less superimposed thrombus formation in patients with unstable angina than in those with Q-wave MI, which is usually associated with deep arterial injury and occlusive thrombus (12,13) (eFig. 17.1.1). Angioscopic findings show that the thrombus associated with unstable angina is white or gray and consists mostly of platelets, whereas the thrombus in patients with acute MI consists mostly of red blood cells (14) (eFig. 17.1.1).



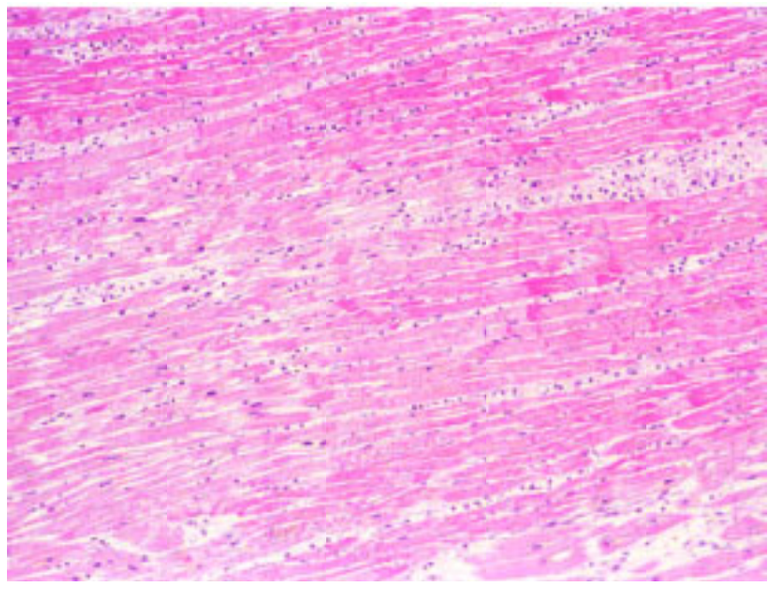
***e*FIGURE 17.1.1** Angioscopic findings in acute ischemic syndromes showing (*left*) the proportions of occlusive and nonocclusive thrombi and (*right*) the differing character of thrombi in acute myocardial infarction (MI) and unstable angina. (Redrawn from Mizuno K. Angioscopy in acute coronary syndromes. *Cardiology Today* 1992;20:1, with permission.)



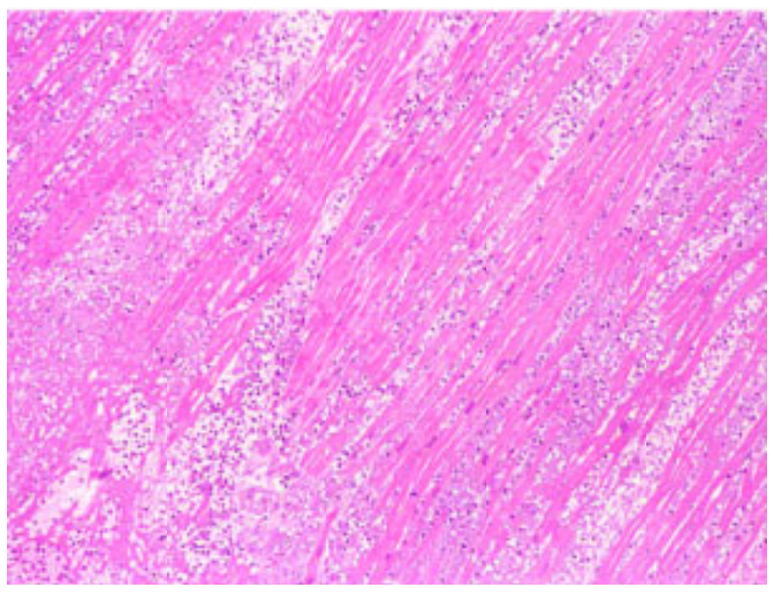
Extensive subendocardial myocardial infarction (*yellow arrows*).



Massive acute transmural anteroseptal myocardial infarction. Cross sections from multiple levels are shown in this chemical fixed preparation. The dark brown area represents the zone of infarction. In this example, approximately 50% of the myocardium is involved.

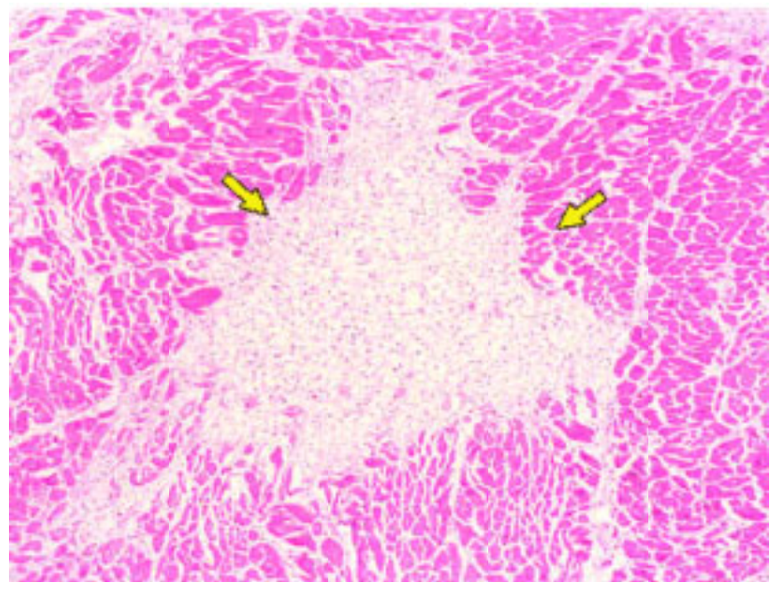


Early histologic changes after acute myocardial infarction. These changes are typically seen within a day of the acute event and show contraction band necrosis at the margins of the infarct.

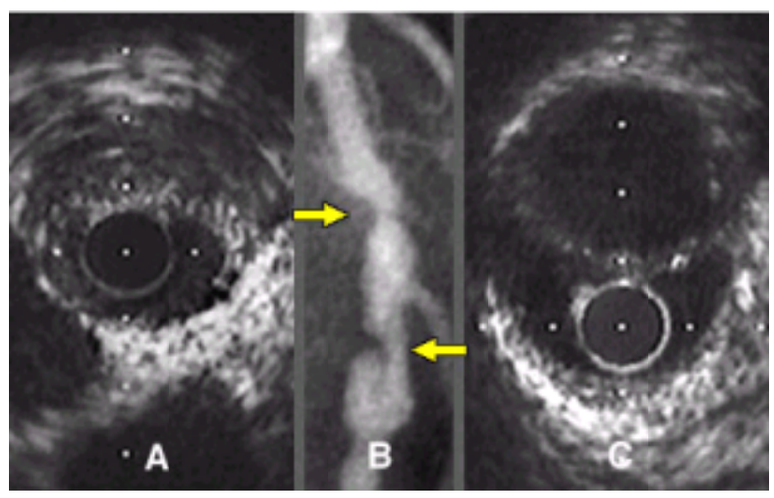


Histologic changes typically seen 2 to 3 days after acute myocardial infarction. There is a prominent acute inflammatory infiltrate and coagulation necrosis

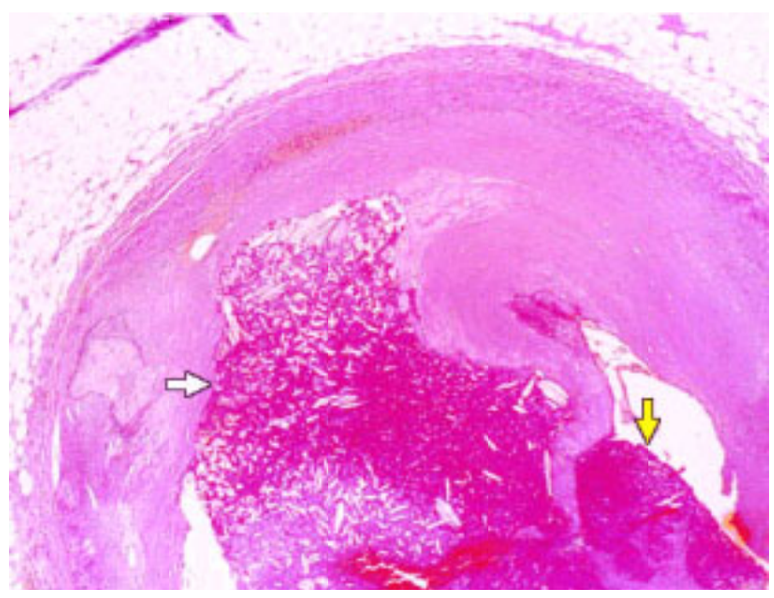
of myocytes.



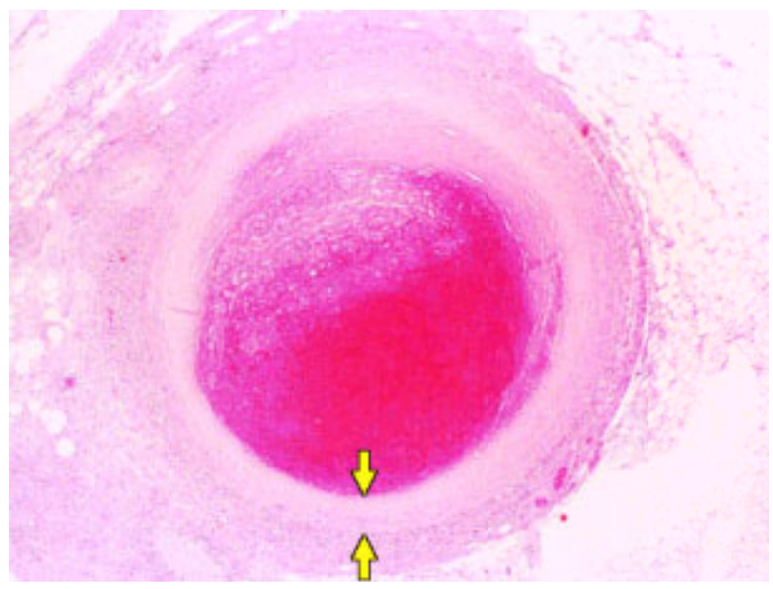
Histology showing the early stages of healing following myocardial infarction. These changes are typical in the second week after the acute event. This is a hematoxylin-eosin stain showing removal of the necrotic myocytes and early ingrowth of vascular tissue and fibroblasts, particularly evident at the edges of the lesion (*yellow arrows*).



Intravascular ultrasound interrogation of a complex coronary lesion. The proximal part of the lesion shows an eccentric soft plaque (A), whereas the distal end of the lesion (B) demonstrates rupture of the plaque with a double lumen.

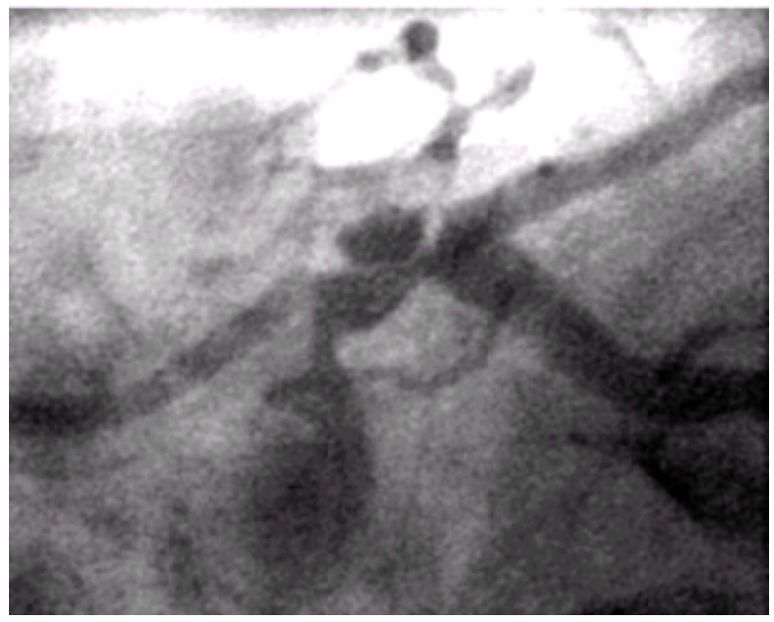


Organized intraplaque thrombus (*white arrow*) with overlying, near-occlusive fresh thrombus (*yellow arrow*). Ruptured atherosclerotic lesion of the right coronary artery 5 days after a balloon angioplasty procedure.

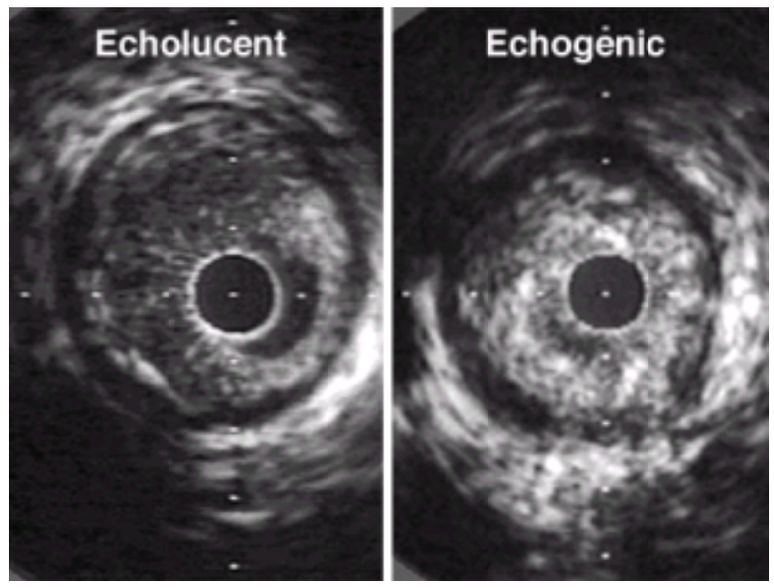


Acute thrombosis of the coronary artery in a transplant heart. The concentric thickening of the vessel wall is consistent with transplant associated vascular disease (*yellow arrows*).

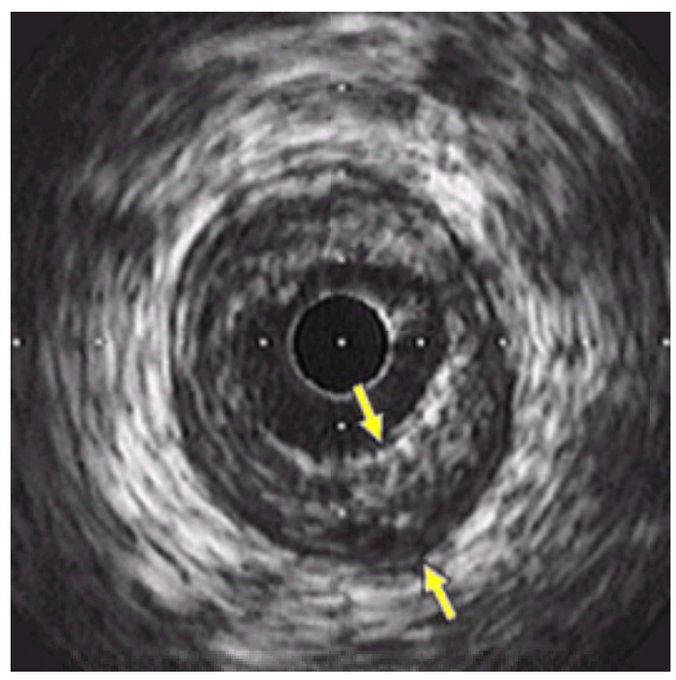
Inflammation plays a major role in atherosclerosis (15,16), and it is the activation of macrophages that triggers inflammatory processes that lead to plaque instability, procoagulation, and clinical events. Plaque rupture or fissuring can be triggered by increased shear forces with sudden changes in pressure or tone. The bending and twisting of coronary arteries in systole is likely to be a predisposing factor. Rupture most often occurs on minor plaques (17,18,19,20,21 and 22) that are eccentric (23) and have a large lipid core with a thin fibrous cap (24), increased concentrations of macrophages (25), and local expression of tissue factor. Macrophages produce metalloproteases such as collagenase, elastases, and stromelysins, which digest extracellular matrix (16). Macrophage-rich areas are more frequently found in atherectomy specimens from patients with unstable angina than from those with stable angina (26). Activated T-lymphocytes are also present at sites of plaque rupture (27) and release various cytokines, which activate macrophages and promote smooth muscle cell proliferation (16). Mast cells are also found at plaque edges at sites that are likely to rupture (28).



Severe ulcerated plaque of the left main trunk discovered on diagnostic angiography.



Differences in lesion composition. Intravascular ultrasonography can characterize lesions into soft (echolucent) and fibrous (echogenic). Available evidence demonstrates that sonolucent lesions exhibit a high lipid content, whereas more echogenic lesions have greater fibrous tissue content.

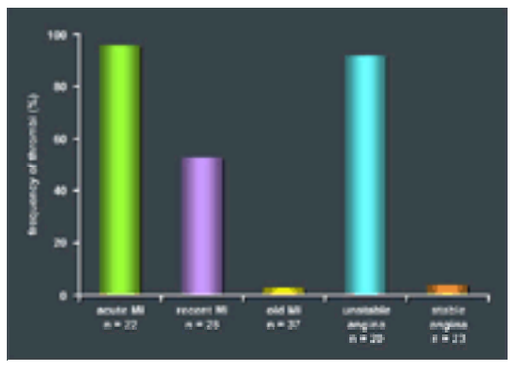


Plaque morphology. This image demonstrates a soft echolucent plaque.

Increased levels of C-reactive protein (29) and the major inducer, interleukin-6 (30), have been found in patients with unstable angina and are associated with higher rates of death and MI at hospital discharge and at 1 year (31,32 and 33). The inflammatory stimulus for triggering expression of soluble cell adhesion molecules has been shown to persist for 6 months after presentation with a non–ST-elevation acute coronary syndrome (34). The inflammatory nature of the cells at the site of plaque rupture and shared T-cell receptor sequences in clonotypes from different patients (35) have led to speculation that chronic stimulation by a common antigen or certain bacterial infections, such as *Chlamydia pneumoniae* or *Helicobacter pylori*, might be associated with an increased risk of plaque rupture (36,37 and 38). The T-cell response in patients with unstable angina is antigen driven and directed to antigens carried in culprit coronary atherosclerotic plaques (39). Cytomegalovirus has also been found in atheromatous plaque specimens, but active replication of the virus is not thought to be a major cause of plaque instability (40).

After plaque rupture or fissuring, subendothelial adhesive proteins, collagen tissue factor, and von Willebrand's factor are exposed, and tissue factor is released. Platelets adhere to glycoproteins Ia and Ib, change their shape, and release serotonin, thromboxane A_2, and adenosine diphosphate (ADP). Episodic platelet aggregation at sites of coronary artery stenosis has been shown to cause cyclic coronary blood flow in animal models (41). Platelet emboli have been found downstream from atheromatous plaques in small intramyocardial vessels from patients who have died suddenly (42). Platelet activation is also suggested by anginal episodes associated with increased urinary levels of thromboxane B_2 (43).

Released tissue factor combines with factor VII, stimulating the extrinsic coagulation cascade to form thrombin, a very potent stimulus of platelet aggregation. At the platelet surface, factors V and X are activated to form the prothrombinase complex, which generates more thrombin. Damage to endothelium without plaque rupture may also lead to thrombus formation (44). Evidence of a hypercoagulable state has been found in patients with unstable angina (45). During anginal episodes, there are increased levels of prothrombin fragments 1 and 2, signifying increased activity of factor X_a and thrombin formation, and fibrinopeptide A, a sign of increased thrombin activity and fibrin formation (46). Six months after an acute ischemic event, the levels of prothrombin fragments are still increased (46). Platelets remain activated after an acute coronary syndrome. In the Thrombolysis in Myocardial Infarction (TIMI) 12 trial, P-selectin assays showed that there was still evidence of platelet activation at 28 days (47). Intracoronary thrombus is visualized in 35% to 52% of patients who are undergoing coronary angiography for unstable angina (6,48,49 and 50), but the rate rises to 70% to 93% when angioscopy is performed (14,49,51,52 and 53) (eFig. 17.1.2). The presence of thrombus at angiography signifies that recurrent ischemia and MI are more likely to occur (48).



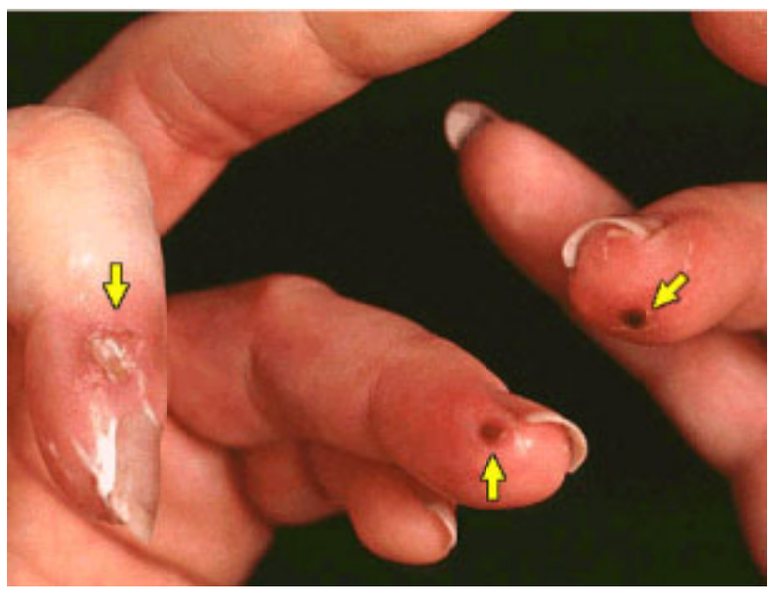
***e*FIGURE 17.1.2** Angioscopic findings in ischemic syndromes showing the frequency of thrombi. MI, myocardial infarction. (Redrawn from Mizuno K. Angioscopy in acute coronary syndromes. *Cardiology Today* 1992;20:1, with permission.)

Another potential mechanism is increased narrowing of a coronary artery from progression of atherosclerosis or plaque rupture (54). Patients whose chronic stable angina becomes unstable angina are likely to have severe multivessel disease, whereas those with new-onset angina may have single-vessel disease (55). Patients with unstable angina are often found to have complex lesions at coronary arteriography (6). Cocaine is toxic to the heart, and its use may be associated with acute ischemic syndromes, even in patients with angiographically normal coronary arteries (56).

A circadian variation is seen in the onset of acute ischemic syndromes (57). Platelet aggregation increases in the morning, heightening the risk of MI or sudden death (58). Activities such as heavy exertion, which produces acute physiologic effects, may also trigger ischemic events (59).

CORONARY ARTERY SPASM

In 1959, Prinzmetal et al. (8) described a variant form of angina characterized by chest pain predominantly at rest and usually associated with ST elevation on the ECG. Rarely, variant angina is associated with other vasospastic disorders, such as migraine or Raynaud's syndrome, in patients with angiographically normal coronary arteries.



Raynaud's disease. Ulcers and gangrene on the fingertips are shown (*arrows*) caused by vasospasm and abnormalities of digital vessels. Associated cardiac findings are coronary vasospasm and primary pulmonary hypertension.

Physiologic contraction of an epicardial coronary artery may occur in response to a number of stimuli, such as increased adrenergic activity (60), increased vagal activity (61), secretion of vasoconstrictor substances such as thromboxane A_2 (62), and increased production of endothelin-1 by endothelial cells (63). Increased vasomotor hyperreactivity may be localized to regions of coronary atheroma or may occur in angiographically normal segments (64). In the presence of endothelial dysfunction, stimuli such as acetylcholine that normally cause vasodilation may instead cause vasoconstriction (65). In the presence of a severe atherosclerotic stenosis (particularly one that is eccentric with an arc of normal coronary artery able to contract), increased coronary tone can result in a critical reduction of coronary blood flow. Cold-pressor testing has shown that patients with unstable angina have excessive vasoreactivity in comparison with patients who have stable angina (66).

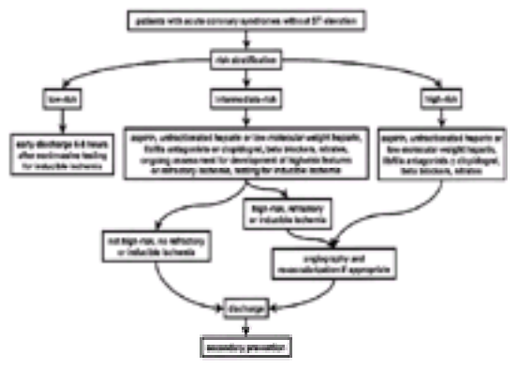
PATHOPHYSIOLOGIC IMPLICATIONS FOR CLINICAL MANAGEMENT

The management of patients with non–ST-elevation acute coronary syndromes should focus on etiology (9). The primary aims of treatment are to reduce initial symptoms and to prevent death or MI.

In individual patients, the mechanisms of plaque fissuring, platelet aggregation, thrombus formation, and increased vasomotor tone may play different roles at different times. A variety of therapeutic approaches are needed to modify these processes.

Platelet activation and aggregation and thrombus formation are central to the pathophysiology of unstable angina, and greater understanding of these mechanisms has led to improvements in treatment. The main emphases of medical management are antithrombotic therapy with aspirin and heparin (67) and antiplatelet therapy with IIb/IIIa antagonists or clopidogrel to reduce the risks of MI and death. Beta-blockers, nitrates, and calcium channel antagonists should be used for relief of symptoms.

Patients with an increased oxygen demand or a decreased oxygen supply (e.g., those with anemia or thyrotoxicosis) need to be managed differently from those with a severe coronary artery stenosis that is causing mechanical obstruction. Patients with vasospasm require therapies such as nitrates and calcium channel antagonists, whereas those with evidence of inflammation may be best treated with aspirin and statins (68). The choice of medical therapies also depends on whether an invasive or a conservative treatment strategy is planned. Risk-stratification is pivotal to triage, and the results determine whether patients should be discharged early, admitted and monitored closely, or undergo early angiography and revascularization (*e*Fig. 17.1.3). Revascularization reduces the likelihood of death, MI, and readmission (69,70).



***e*FIGURE 17.1.3** Risk-stratification in patients presenting with non–ST-elevation acute coronary syndromes.

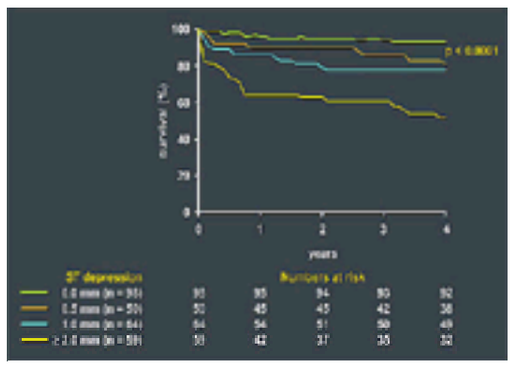
CLINICAL PROFILE

History and Physical Examination

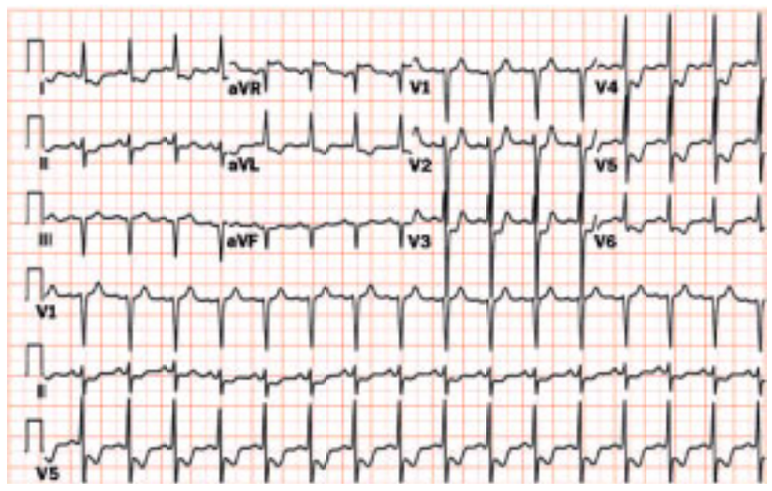
The site, character and radiation of the discomfort, and physical findings are similar to those in patients with MI, except that unstable angina may occur at rest with an unclear relationship to exercise or stress, and there may be little or no response to nitroglycerin therapy.

Electrocardiography

The ECG is a very important investigation and should be performed at admission and during episodes of ischemia. Patients with recurrent episodes of pain should have ECGs recorded while the pain is present. If there is sustained ST elevation or left bundle branch block (either new or old with evidence of troponin or myoglobin elevation), administration of thrombolytic therapy or transfer to a catheterization laboratory for primary percutaneous coronary intervention (PCI) should be considered. A normal ECG does not exclude the possibility of unstable angina. Transient ST depression (or, less frequently, elevation) and T-wave inversion occur commonly only during ischemia, and the prognosis and management are critically dependent on the ECG (71,72,73 and 74). ST depression of 0.5 mm or greater has been shown to be a significant risk factor for the composite end point of death/MI at 1 year (73), and 4-year follow-up has shown that patients with 0.5 mm or greater ST depression have a significantly higher mortality than those with normal ECGs or T-wave inversion (19% vs. 4% at 1 year and 18% vs.6% at 4 years) (74) (eFig. 17.1.4). Patients with isolated T-wave inversion usually have a benign course (72). The presence of inverted T waves in five or more leads has been shown to be associated with higher risk (75). Little information is available regarding the outcome of patients with deep T-wave inversion (0.2 mV), who are usually classified as being at intermediate risk.



***e*FIGURE 17.1.4** Survival over 4 years of follow-up in patients presenting with non–ST-elevation acute coronary syndromes with either a normal electrocardiogram or T-wave inversion and various degrees of ST depression. The *p* value is a log rank comparison over the follow-up period. (Redrawn from Hyde TA, French JK, Wong C-K, et al. Four-year survival of patients with acute coronary syndromes without ST-segment elevation and prognostic significance of 0.5-mm ST-segment depression. *Am J Cardiol* 1999;84:379–385, with permission.)



Subendocardial ischemia. Anterolateral ST-segment depression is consistent with diffuse subendocardial ischemia versus non–Q-wave myocardial infarction.

Unstable angina vs. non–Q-wave myocardial infarction. ST-segment depression in leads V_2 through V_5 supports acute ischemic syndrome.

Continuous Electrocardiographic Monitoring

Ischemic ST-segment changes are detected in 85% to 90% of patients with unstable angina who are undergoing continuous ECG monitoring, but these changes are often silent (76,77). Silent ischemia on Holter monitoring has been shown to correlate with reduced myocardial perfusion and ventricular function (77), and patients with this feature are more likely to die, develop MI, or require revascularization (77,78 and 79). The European guidelines for the management of acute coronary syndromes without persistent ST elevation (80) recommend that patients with suspected acute ischemic heart disease should have multilead continuous ST-segment monitoring if it is available or, failing that, frequent ECGs.

Troponins

The cardiac troponins are sensitive and specific markers of myocyte necrosis (81). Troponin levels are useful prognosticators, with a clear gradient of risk as levels increase (82,83), but because of their release pattern, patients who present within 6 hours of symptom onset may have a normal troponin test result despite being at high risk. For this reason, it is important that troponin tests be done at admission and repeated 6 to 8 hours later.

Only one troponin T assay is available. A number of different troponin I assays are available with a wide variety of cutoff values, and discrepancies have been found between the results obtained using different assays (84). The prognostic value of third-generation assays for troponin T (cutoff point, 0.03 mg per L) and troponin I (cutoff point, 1.0 mg per L) was confirmed in the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC II) study (85).

It is important to measure troponin levels because they correlate with the pathophysiology of acute coronary syndromes (i.e., the presence of thrombus in the coronary artery) (86) and may reflect the thrombogenic activity of ruptured or fissured plaques (86,87). The prognostic value of the troponins is greater than would be expected

from the extent of myocyte necrosis and impairment of left ventricular function, perhaps reflecting preceding episodes of micromyocyte necrosis following embolization of platelets from ruptured or fissured plaques (Fig. 17.2). Several angiographic studies have reported that evidence of thrombus, complex lesions, and impairment of TIMI flow were more common in patients with elevated troponin levels than in those with normal levels (86,87).

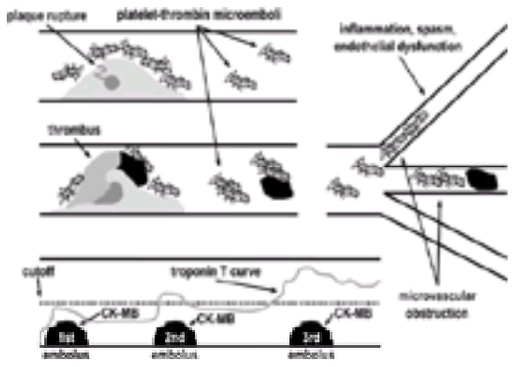
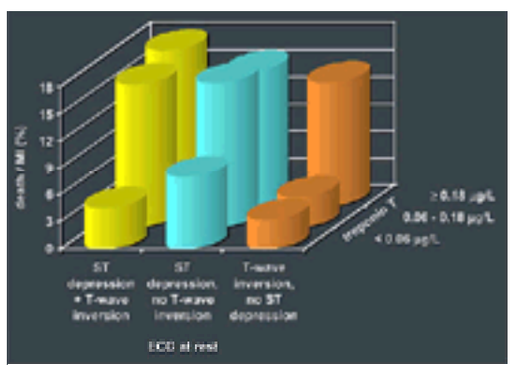


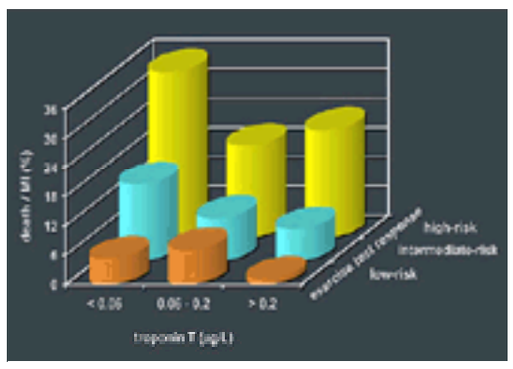
FIGURE 17.2 Microvascular obstruction after plaque rupture. CK-MB, creatine kinase-MB. (Adapted from Goldmann BU, Christenson RH, Hamm CW, et al. Implications of troponin testing in clinical medicine. *Curr Control Trials Cardiovasc Med* 2001;2:75–84, with permission.)

Troponin levels identify patients at short- and long-term risk (83,88,89,90,91,92,93 and 94), enabling therapies such as low-molecular-weight heparins (95), IIb/IIIa antagonists (83,91,96), and interventions (69,70) to be targeted toward those who are most likely to benefit. Troponin testing is thus a valuable addition to the history, examination, and ECG, and troponin levels have been added as a subclassification to the Braunwald definition of unstable angina (7) (Table 17.1). Thirty percent of patients who present with non–ST-elevation acute coronary syndromes and normal CK-MB levels have elevated troponin levels (82,95,97), and these patients have poor outcomes (95,98).

In the FRISC I study, the risk of cardiac death/MI within 5 months rose with increasing troponin T levels obtained in the first 24 hours (95). Troponin T, age, hypertension, the number of antianginal drugs, and ECG changes at rest were all independent predictors of death/MI. Patients with low troponin T levels (<0.06 mg per mL) had a 4.4% incidence of death/MI within 6 months. eFigure 17.2.1 shows the increase in risk according to troponin T levels and ECG findings at admission. The combination of troponin T testing and exercise testing further defines patients at low, intermediate, and high risk (99) (eFig. 17.2.2). In the FRISC I study, there was a 1.2% incidence of cardiac death/MI within 5 months in patients with troponin T levels of greater than 0.06 mg per L and a low-risk exercise test response (i.e., a maximal workload of 90 W or greater in men and 70 W or greater in women without ST depression of 0.1 mm or greater in three or more leads).



***e*FIGURE 17.2.1** Five-month risk of cardiac death/myocardial infarction (MI) in relation to resting electrocardiographic findings and maximal troponin T levels during the first 24 hours in the Fragmin during Instability in Coronary Artery Disease I study. (Redrawn from Lindahl B, Venge P, Wallentin L, et al. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. *Circulation* 1996;93:1651–1657, with permission.)



***e*FIGURE 17.2.2** Five-month risk of cardiac death/myocardial infarction (MI) in relation to exercise test response and maximal troponin T levels during the first 24 hours in the Fragmin during Instability in Coronary Artery Disease I study. (Redrawn from Lindahl B, Andrén B, Ohlsson J, et al. Risk-stratification in unstable coronary artery disease: additive value of troponin T determinations and pre-discharge exercise tests. *Eur Heart J* 1997;18:762–770, with permission.)

Figure 17.3 shows the risk of death/MI at various time points in trials of the IIb/IIIa antagonists, abciximab (88,93), tirofiban (89,90), and lamifiban (91), and the low-molecular-weight heparins, dalteparin (92) and enoxaparin (94). In all seven trials there was a clear association between elevated troponin levels and risk. However, a normal troponin test does not ensure a good clinical outcome, as shown by the event rates in these trials.

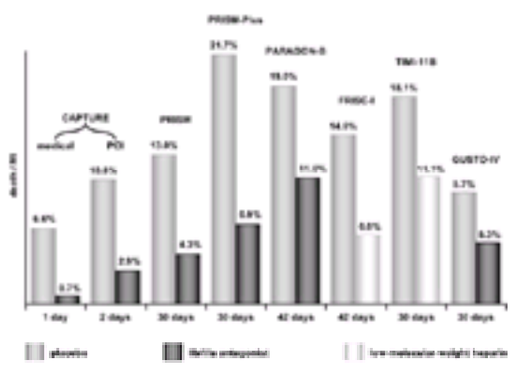


FIGURE 17.3 Rates of death/myocardial infarction (MI) at various time points in patients with elevated troponin levels in the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) study of abciximab (88), the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) (89) and PRISM-PLUS (90) studies of tirofiban, the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON-B) trial of lamifiban (88), the FRISC I study of dalteparin (92), the TIMI 11B trial of enoxaparin (94), and the Global Utilization of Streptokinase and t-PA for Occluded Coronary

Arteries (GUSTO) IV trial (93) of abciximab. PCI, percutaneous coronary intervention.

A metaanalysis of trials, totaling more than 5,000 patients, reported odds ratios of 4.19 [95% confidence interval (CI), 2.01 to 4.20] for the short-term risk of an event (i.e., inhospital or within 30 days) and 2.05 (95% CI, 1.98 to 4.11) for longer-term risk (up to 150 days). Troponins T and I were found to have equivalent prognostic values (100). An urgent troponin test should therefore be incorporated into the initial risk assessment, along with the clinical features, ECG changes, measures of left ventricular function, and extent of coronary disease. If the initial troponin test is negative, it should be repeated at 6 to 8 hours (3).

Cardiac Enzymes

Because troponin levels may remain elevated for 2 weeks, other measures of myocyte necrosis are required to diagnose reinfarction, such as CK levels (or preferably CK-MB, which is more cardiac specific). A myoglobin test may be helpful if troponin levels are not elevated, as this enzyme is the first to become elevated following ischemia. Baseline point-of-care testing with a multimarker strategy including myoglobin has been shown to be a more effective means of risk-stratification than a single-marker laboratory-based strategy (101). Other tests such as myosin light-chain assays (102) are not currently recommended as standard practice.

Chest X-Ray

Unless MI has occurred previously, the heart size is normal. Transient pulmonary edema may occur with global ischemia and should raise suspicions of left main coronary artery stenosis or mitral papillary muscle dysfunction.

C-Reactive Protein

C-reactive protein is an acute-phase protein produced by the liver when there is tissue injury, infection, or inflammation. High-sensitivity C-reactive protein levels have been shown to correlate with future risks of MI, stroke, and peripheral vascular occlusion in apparently healthy people (103), and elevated levels have been noted in studies of patients with unstable angina (31). C-reactive protein levels are elevated in 50% to 70% of patients with Braunwald class IIIB angina (31).

Patients with elevated C-reactive protein levels at admission have been shown to have worse inhospital and 1-year outcomes, and elevated levels at discharge have been linked to recurrent instability long term (32). The major application of C-reactive protein testing appears to be in determining the long-term strategy after hospital discharge. Reduced C-reactive protein levels have been observed with aspirin (104) and statin therapy (105).

Amyloid A

Amyloid A is an acute-phase protein that is produced by the liver. Its predictive value appears to be similar to that of C-reactive protein (31).

Fibrinopeptide A

Fibrinopeptide A is a polypeptide cleaved from fibrinogen by thrombin. It is a sensitive marker of thrombin activity and fibrin generation. Elevated urinary fibrinopeptide A levels have been shown to correlate with the presence of intracoronary thrombus (106) and are an individual predictor of death/MI/revascularization within 1 week (odds ratio, 4.8) and within 6 months (odds ratio, 9.6). Persistently elevated levels signify an increased risk of coronary events (46). A number of other markers that are currently under investigation include interleukin-6, intercellular adhesion molecule-1, lipoprotein-associated phospholipase A_2, and infectious seropositivity for *Chlamydia* (eTable 17.1.1).

***e*TABLE 17.1.1** FUTURE CANDIDATE MARKERS OF CORONARY RISK

Markers of endothelial injury	Markers of inflammation
Human neutrophil elastase	Antibodies to heat shock protein
Inducible nitric oxide synthase	C-reactive protein
Matrix metalloproteinases	Endothelial selectin
Thrombomodulin	Infectious agents
Markers of hemostasis	Intracellular adhesion molecule-1
Anti-IIa	Interleukin-6
Anti-Xa	Neopterin
D-dimer	Oxidized low-density lipoprotein
Fibrinogen	Platelet selectin
Fibrinopeptide A	Serum amyloid A
Platelet-derived growth factor	Tumor necrosis factor-a
Thromboglobulin	Vascular cell adhesion molecule-1
Tissue factor	Markers of necrosis
von Willebrand's factor	Fatty acid–binding proteins
Markers of platelet activation	Markers of hemodynamic stress
Glycoprotein IIb/IIIb receptor occupancy	Brain natriuretic peptide
Monocyte-platelet conjugates	
PAC-1	
P-selectin	
Soluble fibrinogen binding	

Other Laboratory Tests

The white cell count is normal unless myocardial necrosis has occurred or there is underlying infection. Primary risk factors should be assessed at admission, including cholesterol and glucose intolerance, and possible secondary causes of unstable angina should be investigated if appropriate to the clinical circumstances, for example, hemoglobin, thyroid function, oxygen saturation, and so forth.

Risk-Stratification

Risk-stratification is critically important because it determines the choice of treatment strategy and provides prognostic information for the patient and relatives. Risk-stratification should take into account clinical factors, ECG and serum markers, evidence of spontaneous or inducible ischemia, measures of left ventricular function, and coronary anatomy. Patients at low risk can be discharged early. They should be asked to report any changes in their symptoms (e.g., recurring discomfort at rest or at night) and be reviewed subsequently at n outpatient clinic. Patients at intermediate risk may either receive initial medical therapy and be closely monitored for high-risk features or undergo early angiography with a view to revascularization. Patients at high risk should undergo early angiography and revascularization if their anatomy is suitable.

A variety of risk factors have been identified, and various models for risk-stratification have been developed. Table 17.2 summarizes the guidelines for risk-stratification that were published by the American College of Cardiology (ACC) and American Heart Association (AHA) (1). Special emphasis is given to the tempo and momentum of ischemia, the patient's age (the most powerful determinant of risk), troponin levels, and ECG features, based on the TIMI IIIB study (73), which showed that ST depression of 0.5 mm or greater was a significant risk factor for the composite end point of death/MI at 1 year, and a study from Auckland (74), which showed that patients who presented with 0.5 mm or greater ST depression had a significantly higher mortality than those with normal ECGs or T-wave inversion (10% vs. 4% at 1 year and 18% vs. 6% at 4 years) (eFig. 17.1.4). Certain clinical features are not included in risk-stratification models, and the clinical assessment should always be regarded as paramount; for example, a patient who is gray, sweating, and anxious is at higher risk than one who is relaxed and appears well.

	High risk: At least one of the following features must be present	Intermediate risk: No high-risk features but must have one of the following features	Low risk: No high- or intermediate-risk features but may have any of the following features
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Previous MI, peripheral vascular disease or cerebrovascular disease, CABG, or prior aspirin use	
Character of pain	Prolonged (>20 min) rest angina	Prolonged (>20 min) rest angina now resolved, rest angina (>20 min) or angina relieved by rest or sublingual nitroglycerin	New-onset Canadian Cardiovascular Society class III or IV angina in the previous 2 wk without prolonged (>20 min) rest pain
Clinical features	Pulmonary edema (most likely due to ischemia), new/worse murmur of mitral regurgitation, third heart sound or new worsening rales, hypotension, bradycardia, tachycardia, age >75 yr	Age >70 yr	
ECG features	Rest angina with transient ST segment changes (>0.05 mV), new bundle branch block, sustained ventricular tachycardia	T-wave inversion (>0.2 mV), pathologic Q waves	Normal or unchanged ECG during an episode of angina
Cardiac markers	Markedly elevated troponin T or I (>0.1 ng/L)	Slightly elevated troponin T (>0.01 ng/L but <0.1 ng/L)	Normal

CABG, coronary artery bypass grafting; ECG, electrocardiography; MI, myocardial infarction.
Adapted from Braunwald E, Jones RH, Mark DB, et al. Diagnosis and management of unstable angina. AHCPR Publication No. 94-0602 (1994). Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute. US Public Health Service, US Department of Health and Human Services, 1994, with permission.

TABLE 17.2 AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION GUIDELINES FOR RISK-STRATIFICATION IN PATIENTS PRESENTING WITH NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

Different markers have been shown to have different prognostic values for acute risk and long-term risk, and the European Society of Cardiology guidelines (80) divide patients into these two categories (*e*Table 17.2.1). Patients should be assessed fully when first seen and then reviewed at 6 to 8 hours for recurrence of ischemia, response to treatment, and results of cardiac marker investigations, particularly the troponins. Further assessments should be done at 24 hours and again before discharge (*e*Table 17.2.2). Patients who have new-onset or accelerated angina without severe pain or pain at rest within 2 weeks and who have normal troponin levels and a normal ECG or an ECG that shows new T-wave changes are considered to be low risk and can be treated as outpatients (1,2) or in chest pain units (107).

***e*TABLE 17.2.1** EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES FOR RISK-STRATIFICATION IN PATIENTS PRESENTING WITH NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

Markers of thrombotic risk (i.e., acute risk)
Recurrent chest pain
ST depression
Dynamic ST-segment changes
Elevated troponin levels
Thrombus at angiography
Markers of underlying disease (i.e., long-term risk)
Clinical markers
Age
History of previous myocardial infarction
History of severe angina
Diabetes
Biologic markers
Level of C-reactive protein
Angiographic markers
Left ventricular dysfunction
Extent of coronary artery disease

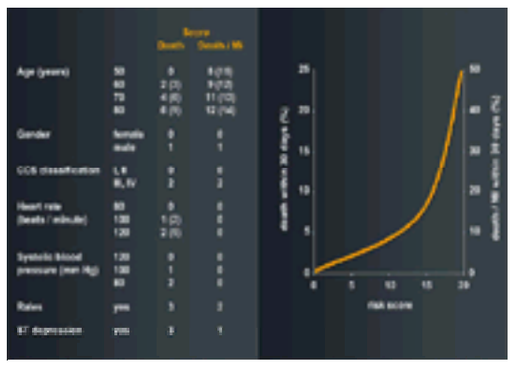
From Bertrand ME, Simoons ML, Fox KAA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation: recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000;21:1406–1432, with permission.

***e*TABLE 17.2.2** TIMING OF RISK-STRATIFICATION IN NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

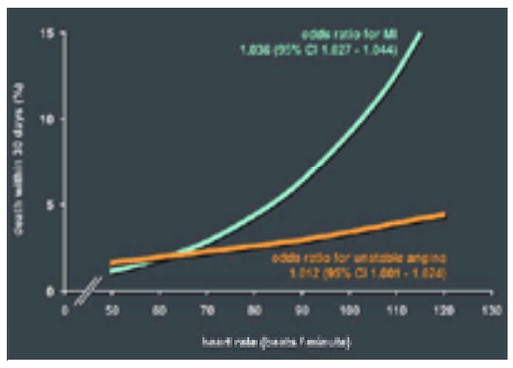
At presentation
Clinical examination
Electrocardiography
Cardiac markers
At 6–8 h
Recurrence of ischemia
Cardiac markers
At 24 h
Recurrence of ischemia
Cardiac markers
Response to therapy
Predischarge
Left ventricular function
Catheterization
Inducible ischemia

Clinical trials have provided further information to aid risk-stratification. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB trial, the ECG category and CK level at admission were found to be predictors of death/reinfarction within 30 days, which occurred in 5.5% of patients with isolated T-wave inversion, 9.4% of those with ST elevation, 10.55% of those with ST depression, and 12.4% of those with ST elevation as well as depression (p <.01) (108). Among patients with initially elevated CK levels, those without ST elevation had significantly higher rates of reinfarction within 6 months (9.8% vs.7.4%) and mortality within 1 year (11.1% vs. 9.6%) than those with ST elevation (109).

The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) investigators developed a multivariate model from 33 candidate variables (110). Most of the prognostic information was contained in seven variables: age, gender, Canadian Cardiovascular Society angina classification, heart rate, blood pressure, the presence of rales, and the presence of ST-segment depression. Different models were developed for the end points of death and death/MI (*e*Fig. 17.3.1), and for the admission diagnoses of MI and non–ST-elevation acute coronary syndrome without MI (*e*Fig. 17.3.2).



***e*FIGURE 17.3.1** Risk-stratification model for the end points of death and death/myocardial infarction (MI) within 30 days in the PURSUIT trial. Points were given for each predictive factor. With respect to age and heart rate, separate points were given for the enrollment diagnoses of unstable angina and MI (indicated in parentheses). CCS, Canadian Cardiovascular Society. (Redrawn from Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation: results from an international trial of 9461 patients. *Circulation* 2000;101:2557–2567, with permission.)



***e*FIGURE 17.3.2** Univariate relation between heart rates and 30-day mortality in patients with myocardial infarction (MI) or unstable angina in the PURSUIT trial. CI, confidence interval. (Redrawn from Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation: results from an international trial of 9461 patients. *Circulation* 2000;101:2557–2567, with permission.)

Using a different approach from those used by the PURSUIT (110) and GUSTO IIB investigators (109) (eTable 17.2.3), the TIMI 11B investigators evaluated 12 baseline characteristics (eTable 17.2.4) and devised a risk model based on the number of risk factors (111) (eFig. 17.3.3). The advantage of this model is its simplicity. It should be noted that these studies did not measure troponin levels in large proportions of their patients.

***e*TABLE 17.2.3** FACTORS INCLUDED IN RISK-STRATIFICATION MODELS FOR PATIENTS WITH NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

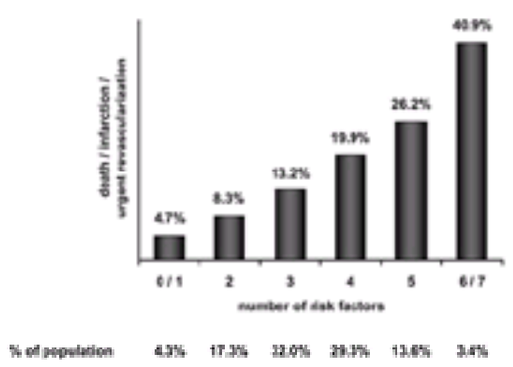
	GUSTO IIB (109)	**PURSUIT**(110)	**TIMI 11B** (111)
Age	✔	✔	✔
Cardiac markers	✔	✔	✔
ST-segment deviation	✔	✔	✔
Congestive heart failure	✔	✔	
Previous coronary artery disease or MI	✔	✔	✔
Risk factors	✔	✔	✔
Prior beta-blocker therapy		✔	
Prior aspirin therapy		✔	✔
Previous CABG	✔	✔	✔
Renal insufficiency	✔		
Severe chronic obstructive respiratory disease	✔		

CABG, coronary artery bypass graft; MI, myocardial infarction.

***e*TABLE 17.2.4** BASELINE CHARACTERISTICS INCLUDED IN THE TIMI RISK SCORE FOR UNSTABLE ANGINA/NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

Age ³65 yr
³3 risk factors for coronary artery disease
Known coronary stenosis of ³50%
ST-segment deviation
³2 anginal events within the previous 24 h
Aspirin therapy within the previous 7 d
Elevated cardiac markers

From Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–842, with permission.



***e*FIGURE 17.3.3** TIMI risk-stratification model for the composite end point of death/myocardial infarction/urgent revascularization in patients with non–ST-elevation acute coronary syndromes. (Redrawn from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–842, with permission.)

NONINVASIVE TESTING

Stress Testing

Exercise or pharmacologic testing with or without imaging can be performed when patients have been asymptomatic for 24 to 48 hours. Exercise stress testing on a treadmill or bicycle, with ECG monitoring for ischemia and arrhythmias, is adequate in most patients. Ischemia occurring at a low workload (<6 metabolic equivalents) is associated with a poor prognosis (112), and coronary angiography is recommended. When exercise testing for ischemia is negative in patients with a normal baseline ECG, the 5-year survival rate is 95% (112).

Exercise thallium imaging can predict the severity of coronary artery disease and the risk of subsequent cardiac events in patients with unstable angina (113). In a study of 126 men undergoing exercise technetium-99m sestamibi tomography, the 12-month rate of cardiac death/MI was 25% in those with a reversible defect and 2% in those with a negative scan (*p* <.001) (113). In another study of 102 patients who presented to the emergency room with chest pain and a normal or nondiagnostic ECG, the recurrent event rates [cardiac death/MI/thrombolysis/PCI/coronary artery bypass grafting (CABG)] were 71% in those with a positive scan and 1.4% in those with a negative scan (*p* <.001) (114).

A number of patients are unable to undergo exercise testing because of physical limitations, and others have ECG changes that are difficult to interpret because of baseline abnormalities such as left ventricular hypertrophy, left bundle branch block, preexcitation, or the effects of digoxin. Pharmacologic stress testing is of particular value in these patients (115). Dipyridamole can be administered intravenously to cause coronary artery vasodilatation and flow discrepancies on perfusion scintigraphy (116), or echocardiography may reveal wall motion abnormalities in myocardial segments that are supplied by stenosed coronary arteries. By increasing myocardial contractility and, to a lesser extent, the heart rate, dobutamine stress testing can also detect areas of ischemia (113,117,118).

Early noninvasive testing is an important part of risk-stratification and should be performed soon after stabilization. If it is performed 1 month later, events that occur during this time—which may amount to 50% of all events in the first year—cannot be predicted. Sensitivity is not lost if exercise tests are performed before discharge. Stress testing can determine whether severe coronary artery stenoses are present (119) and indicate the likelihood of multivessel disease but does not show whether

there is instability of coronary artery plaque with ongoing thrombosis.

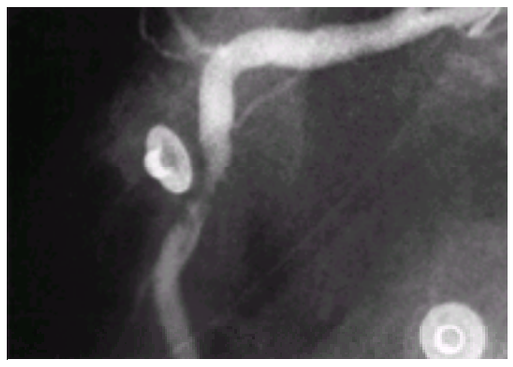
Echocardiography

Two-dimensional echocardiography can provide anatomic and functional information, which is helpful in determining the diagnosis and prognosis. Transient abnormalities of wall motion and changes in ventricular volumes can be detected during ischemia (120). These findings may be helpful if the symptoms are atypical or if the ECG findings are nondiagnostic. Echocardiographic changes may precede pain or ischemic ST-segment changes. Transesophageal echocardiography is particularly useful for evaluating the possibility of aortic dissection.

Coronary Arteriography

The findings at coronary arteriography depend on the population studied. Single-vessel disease has been demonstrated in 43% of those with new-onset angina (55), and angiographically normal coronary arteries are found in 10% of patients (121). However, angiography outlines only the arterial lumen, and there may be large plaques within the arterial wall. Intravascular ultrasound may show that some of these patients have ruptured plaques with probable thrombus. In others, even intravascular ultrasound and angiography are normal, and the likely pathophysiology is coronary spasm. Alternatively, there may have been a misleading history of false-positive ECG features.

In a selected group of patients from the Coronary Artery Surgery Study Registry who had CABG for unstable angina, 14% had left main coronary artery stenoses and 50% had triple-vessel coronary artery disease. In the TIMI IIIB trial, 19% of patients had no coronary artery stenoses of greater than 60% narrowing. Single-vessel disease was found in 38%, double-vessel disease in 29%, and triple-vessel disease in 15%. A left main coronary artery stenosis of greater than 50% narrowing was found in 4% (122). Eccentric plaques and complex plaques (*e*Fig. 17.3.4) are more commonly found in patients with unstable angina than in those with chronic stable angina (6). Coronary artery thrombi may be seen in 40% of patients if arteriography is performed soon after an episode of rest pain (48).



***e*FIGURE 17.3.4** Right coronary angiogram showing a complex midcoronary stenosis and protruding thrombus downstream.

Video 17.1 A 59-year-old male patient with acute inferior myocardial infarction. Large angiographically visible thrombus in the mid-portion of the right coronary artery distal to a severe stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Left Ventriculography

Abnormalities of regional wall motion may be detected, caused by previous MI or “hibernation” due to prolonged or recurrent ischemia. Wall motion abnormalities and changes in ventricular volumes may also occur during episodes of acute ischemia (123).

PROGNOSIS

The prognosis of patients who present with unstable angina depends on their risk factors. Within 1 month, 2% to 5% die and 5% to 16% experience an MI (70,90,124). Within 1 year, 26% to 35% require readmission to the hospital for recurrent symptoms (125) and 4% to 15% die (122,125,126,127,128 and 129). Patients with unstable angina and a normal coronary arteriogram have good short-term (130) and long-term prognoses (131).

CLINICAL VARIABLES

The most important variables are age (110), left ventricular function (110), coronary anatomy (132), diabetes, and comorbid conditions such as chronic obstructive pulmonary disease, renal failure, cerebrovascular disease, and malignancy. Diabetics with non–ST-elevation acute coronary syndromes are at higher risk of death/MI than are nondiabetics (70,90,124).

The GUSTO IIB trial (133) compared two antithrombotic regimens in 12,144 patients who presented with acute ischemic syndromes. For the first time in a concurrent trial, patients with or without classic ST elevation were included, providing a unique opportunity to compare the baseline demographics of these two groups of patients (*e*Table 17.2.5). Those without ST elevation were older and more likely to be female, with a much greater preponderance of risk factors (e.g., a prior history of MI, heart failure, cerebrovascular disease, PCI, or CABG), reflecting the fact that patients who present with unstable angina generally have more advanced multivessel coronary artery disease than do those with ST elevation. *e*Table 17.2.6 shows the rates of death/MI for the three Braunwald classes that were prospectively validated in the TIMI III registry (5). Patients with postinfarction angina are at the highest risk (5,134), and secondary angina is higher risk than primary angina.

***e*TABLE 17.2.5** DEMOGRAPHIC FEATURES OF PATIENTS WITH OR WITHOUT ST ELEVATION IN THE GUSTO IIB TRIAL

	ST elevation (n = 4,131)	**No ST elevation (n = 8,011)**
Age (yr)[a]	63 (53, 71)	65 (57, 73)
% Female	24%	33%
Hypertension	40%	48%
Diabetes	16%	19%
Current smoker	41%	27%
Hypercholesterolemia	36%	41%
Previous MI	17%	32%
Previous CABG	5%	12%
Previous PTCA	6%	11%

CABG, coronary artery bypass graft; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

[a]Median (25th, 75th percentiles).From The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;335;775–782. Copyright © 1996, Massachusetts Medical Society. All rights reserved, with permission.

***e*TABLE 17.2.6** BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA AND OUTCOME

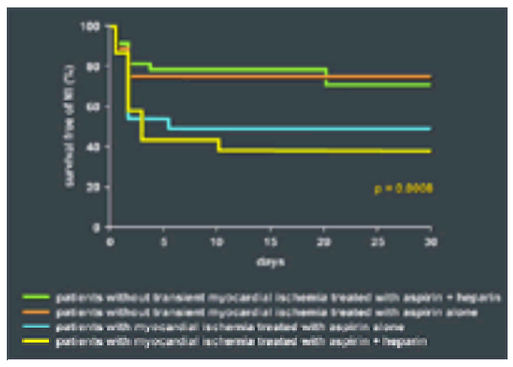
		Death or MI within 42 d			**Death or MI within 1 yr**		
	n	**Primary (n = 1,038)**	**Secondary (n = 317)**	**Postinfarction (n = 44)**	**Primary (n = 1,038)**	**Secondary (n = 17)**	**Postinfarction (n = 44)**
I: No rest pain	261	1.4%	7.7%	0%	7.3%	10.3%	0%
II: Subacute rest pain	47	8.1%	0%	0%	10.8%	0%	0%

III: Rest pain within 48 h	1,091	4.2%	7.0%	18.4%	10.9%	20.3%	26.3%

MI, myocardial infarction.Reprinted from Cannon CP, McCabe CH, Stone PH, et al. Prospective validation of the Braunwald classification of unstable angina: results from the Thrombolysis in Myocardial Ischemia (TIMI) III registry. *Circulation* 1995;92[Suppl I]:I-19(abst), with permission.

Rest pain at admission and recurrent episodes of ischemia are high-risk features (71,122,135,136 and 137). Patients with recurrent rest pain within 48 hours after admission have a 20% lower survival rate (135).

The incidence of MI is approximately 3% in patients with accelerating angina without ECG changes and about 18% in those with rest pain and ECG changes (136). Ischemic ST changes on the admission ECG are high-risk features (71,109,135). The presence of myocardial ischemia on continuous ST-segment monitoring increases the risk of death/MI significantly (79) (eFig. 17.3.5). Mortality at 1 year can be predicted by the extent of ST depression on the admission ECG (eTable 17.2.7). ECG changes of greater than 1 mm of ST depression after admission have an 89% sensitivity for predicting MI, further angina, or the need for revascularization (71). The number of ischemic episodes is related to outcomes (109).



***e*FIGURE 17.3.5** Rates of survival free of myocardial infarction (MI) in patients with unstable angina treated with aspirin or aspirin plus heparin. (Redrawn from Holdright D, Patel D, Cunningham D, et al. Comparison of the effect of heparin and aspirin versus aspirin alone on transient myocardial ischemia and in-hospital prognosis in patients with unstable angina. *J Am Coll Cardiol* 1994;24:39–45, with permission.)

***e*TABLE 17.2.7** OUTCOMES OF PATIENTS WITH ST DEPRESSION AT ADMISSION

Diagnosis of myocardial infarction	
³4-mm ST depression	97% specific, 20% sensitive
ST depression in ³7 ECG leads	95% specific, 21% sensitive
Mortality at 1 yr	
1-mm ST depression	14%
³2-mm ST depression	39%
ST depression in £2 ECG leads	11%
ST depression in ³3 ECG leads	30%

ECG, electrocardiographic.

In a pooled analysis of the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), PURSUIT, and Fibrinogen Receptor Occupancy (FROST) trials, death/MI occurred within 30 days in 5.7% of patients with no ischemic events, 9.5% of those with one to two events, 12.7% of those with three to five events, and 19.7% of those with more than five events (138).

ST-segment shifts increase the risk of death/MI (71). Patients with rebound ischemia during continuous ST-segment monitoring have an increased risk of death/MI at 1 year (18.4% vs. 8.3%, $p = .02$) (139).

The medicines that patients are taking when angina develops can be an important indicator of risk. In the TIMI IIIB trial, patients in whom unstable angina developed while they were receiving beta-blockers did worse, whereas those on angiotensin-converting enzyme (ACE) inhibitors at the time did better (122).

PRINCIPLES OF MANAGEMENT

Aims of Treatment

The immediate aims of treatment are to relieve pain with morphine and antianginal therapy and to prevent MI and death by stabilizing the thrombotic process with antithrombotic therapy (eTable 17.2.8). If MI develops, treatments to preserve the myocardium should be used, such as thrombolytic therapy or primary PCI in the event of ST elevation or left bundle branch block that is not preexisting. Revascularization is recommended for high-risk patients and can also be performed as primary treatment in intermediate-risk patients or reserved for use in those who are refractory to medical therapy.

***e*TABLE 17.2.8** GOALS OF TREATMENT IN UNSTABLE ANGINA

Acute treatment
To relieve angina
To prevent MI
To preserve viable myocardium in the event of MI
To prevent death
Nonacute treatment
To identify and treat precipitating factors
To determine the prognosis
To identify and treat coronary risk factors
To prevent recurrent admissions
To use the most cost-effective treatment strategy
Cardiac rehabilitation

MI, myocardial infarction.

Longer-term goals involve identification and treatment of cardiac risk factors such as hypertension, dyslipidemia, and smoking. Patients should also be enrolled in a cardiac rehabilitation program (eTable 17.2.8). It is incumbent on physicians to use the most cost-effective strategy that is available to them.

General Measures

Patients with rest pain or ECG changes, or both, within the previous 48 hours should be admitted to the hospital. Antithrombotic and antiischemic therapy should be commenced without delay when the patient is first seen in the emergency department, chest pain unit (107), or coronary care unit. Patients should be placed on bed rest, ideally with continuous ECG monitoring for arrhythmias and ischemia, or, failing that, 12-lead ECGs should be performed at baseline, 30 minutes, and 1 hour and repeated if further pain occurs.

Oxygen

Oxygen is commonly administered to all patients with acute chest pain. The Agency for Health Care Policy and Research guidelines recommend more selective use of oxygen in patients with obvious cyanosis, respiratory distress, or high-risk features (1) (Table 17.2).

Morphine

Morphine is very effective for relieving pain and anxiety. It may also reduce the cardiac workload and oxygen consumption by causing venodilation and slightly decreasing the heart rate and blood pressure. Morphine should be administered in intravenous (i.v.) doses of 2 to 5 mg if angina has not been relieved by nitroglycerin tablets or spray (see Nitrates), provided that there are no contraindications. The dose can be repeated every 5 to 30 minutes.

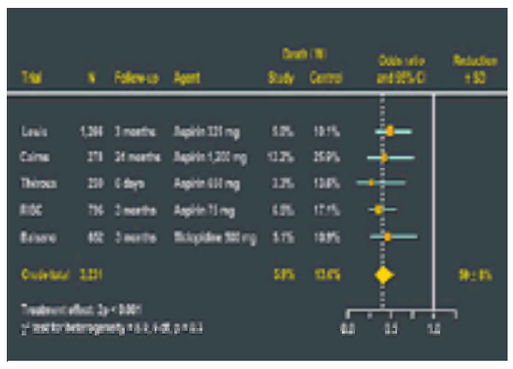
Antiplatelet Agents

Aspirin

Aspirin potently inhibits thromboxane A_2-dependent platelet aggregation by irreversibly inhibiting the platelet enzyme, cyclooxygenase, which reduces platelet synthesis of thromboxane A_2. Platelet adhesion to damaged endothelium is not affected (140). Aspirin does not prevent platelet degranulation (140) and does not inhibit platelet aggregation in response to stimuli such as thrombin, ADP, collagen, catecholamines, and shear-induced platelet aggregation (141). Aspirin resistance occurs in up to 40% of patients and is more common in women and the elderly, whereas patients with PIA_2 polymorphism of the IIb/IIIa receptor have been shown to be more responsive to aspirin (142). A significant proportion of patients (30% to 40% in some studies) do not respond to moderate doses (80 to 325 mg) of aspirin (143,144), and some patients cannot tolerate it because of gastrointestinal side effects, bleeding, or allergy (145,146 and 147). Despite these limitations, aspirin has been shown to reduce the risk of death/MI by approximately 50% in patients with non–ST-elevation acute coronary syndromes (69,126,127,148,154). It also reduces the risk of vascular events for at least 2 years in patients with previous MI, unstable angina, or stable angina (149).

Aspirin has a number of nonplatelet effects; for example, it inhibits prostaglandin, interleukin-6 synthesis in leukocytes (150), and the activity of endothelial nitric oxide inhibitors (151). These features could explain why its effects appear to be greater than might be expected from inhibition of thromboxane A_2-dependent platelet aggregation alone (152). However, aspirin can also have detrimental effects; for example, it reduces endothelial production of the vasodilating prostaglandin, prostacyclin, especially at high doses (153).

In a metaanalysis of five studies, aspirin or ticlopidine reduced mortality by 59 ± 8% (67,126,127,154,155) (eFig. 17.3.6). The dosages used varied from 75 mg per day (154) to 325 mg four times a day (127). The effect of aspirin is rapid. In normal volunteers, 162.5 mg aspirin inhibited 91% of arachidonic acid–induced platelet aggregation *ex vivo* within 15 minutes (156).



***e*FIGURE 17.3.6** Metaanalysis of the relative risk of death/myocardial infarction (MI) in placebo-controlled trials of aspirin or ticlopidine in patients with unstable angina (67,126,127,154,155). CI, confidence interval; RISC, Research Group on Instability in Coronary Artery Disease in Southeast Sweden; SD, standard deviation.

All patients with a diagnosis of unstable angina should receive aspirin as soon as possible unless there is active bleeding or documented hypersensitivity. The initial dose should be 150 to 325 mg because of the possibility of reduced intestinal blood flow during ischemia and to ensure complete inhibition of thromboxane A_2 production.

The Antiplatelet Trialists' Collaborative Overview reported that an aspirin dose of 75 to 150 mg per day reduced the rates of nonfatal stroke and MI by one-third and vascular death by one-sixth (149). However, the Coumadin Aspirin Reinfarction study (157), which randomized 8,803 patients 3 to 21 days after MI to receive either 160 mg per day of aspirin, 80 mg per day of aspirin plus 1 mg per day of warfarin (Coumadin), or 80 mg per day of aspirin plus 3 mg per day of warfarin, found no difference in mortality between the three treatment groups, with rates of 2.7%, 3.0%, and 3.1%, respectively. Ischemic stroke was more common in the two warfarin groups (1.5% with aspirin plus 1 mg warfarin and 1.1% with aspirin plus 3 mg warfarin vs. 0.5% with aspirin alone). It is possible that the 1-mg warfarin dose was thrombogenic, or these results could have occurred by chance. Another possibility is that the 80-mg aspirin dose that was used in combination with warfarin was too low. It is therefore recommended that the long-term maintenance dose of aspirin should be approximately 160 mg per day.

Ticlopidine and Clopidogrel

Ticlopidine and clopidogrel are thienopyridine derivatives, and both are prodrugs. They are selective antagonists of ADP-induced aggregation and also reduce responses to other agonists that require ADP.

In an open trial, 652 patients with unstable angina or non–Q-wave MI were randomized within 48 hours of hospital admission to receive either ticlopidine (250 mg twice a day) or standard therapy, which did not include aspirin or heparin (155). Ticlopidine had no effect during the first 15 days, but at 6 months the incidence of cardiovascular death/MI was reduced from 13.6% to 7.3% (p <.01).

Because of its side effects and delayed onset of action (2 to 3 days for maximal antiplatelet effect), ticlopidine is not recommended as initial therapy for patients with unstable angina.

Clopidogrel (75 mg per day) was compared with aspirin (325 mg per day) in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial of 19,000 patients with symptomatic peripheral vascular disease, recurrent MI, or a recent ischemic stroke. A modest reduction in vascular death/MI/ischemic stroke occurred with clopidogrel (5.32% vs. 5.83% with aspirin, p = .04; relative risk reduction, 8.7%; 95% CI, 0.3 to 16.5). The safety profile was similar to that of aspirin (158). Thrombotic thrombocytopenic purpura can occur when clopidogrel is commenced, but this is rare and tends to manifest within the first 2 weeks of therapy (159).

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial randomized 12,562 patients with acute coronary syndromes to receive either aspirin (75 to 325 mg per day) or aspirin plus clopidogrel, given as a 300-mg loading dose followed by 75 mg per day. At 9 months, the incidence of cardiovascular death/MI/stroke was reduced by 20% from 11.47% to 9.28% in the patients who had received aspirin plus clopidogrel (p <.01) (Fig. 17.4). The major component of this reduction was a 23% decrease in MI (Table 17.3). A 31% reduction in refractory ischemia (defined as ischemic ECG changes leading to intervention while receiving at least one antianginal and one antithrombotic agent) also occurred. The reduction in death/MI/stroke beyond 30 days was similar to that observed within 30 days, and the benefits of clopidogrel were seen across many subgroups. The effect was similar in patients with and patients without elevated markers. A 1% absolute increase in major bleeding occurred among patients who were given aspirin plus clopidogrel (3.6% vs.2.7% in patients given aspirin alone, p <.01) (160).

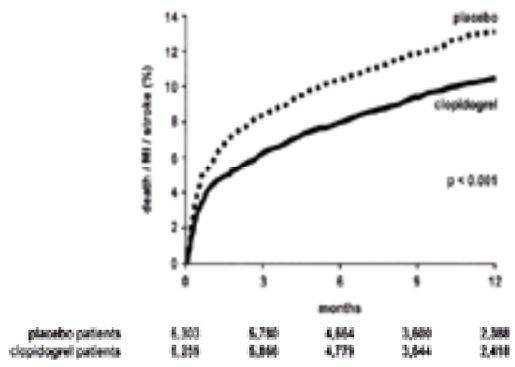


FIGURE 17.4 Rates of cardiovascular death/myocardial infarction (MI)/stroke within 9 months in patients given either aspirin alone or aspirin plus clopidogrel in the CURE trial. (Redrawn from The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502. Copyright © 2001, Massachusetts Medical Society. All rights reserved, with permission.)

End point	Aspirin (n = 6,303)	Aspirin + clopidogrel (n = 6,259)	Risk ratio
Cardiovascular death/MI/stroke*	11.40%	9.30%	0.80
Cardiovascular death	5.50%	5.10%	0.93
MI	6.70%	5.20%	0.77
Stroke	1.40%	1.20%	0.86
Noncardiovascular end point	0.70%	0.70%	0.91

CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; MI, myocardial infarction.
*Primary end point.
From The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502. Copyright © 2001, Massachusetts Medical Society. All rights reserved, with permission.

TABLE 17.3 RESULTS OF THE CURE TRIAL

Clopidogrel is thus indicated for acute and long-term use in addition to aspirin in intermediate-risk patients. It is not known whether it is superior to small-molecule IIb/IIIa antagonists in high-risk patients. In high-risk patients, its use should be considered in addition to IIb/IIIa antagonists. The use of clopidogrel should also be considered in patients in whom emergency surgery is likely, such as those with hemodynamic instability or widespread ST-segment changes. It is also recommended for adjunctive use with a IIb/IIIa antagonist in the setting of PCI (161,162). Approximately 1,500 patients undergoing CABG in the CURE trial received clopidogrel, with no increase in the relative bleeding excess (160). However, there is concern among surgeons about the possibility of increased bleeding in patients who have received clopidogrel, and there was a trend in the CURE trial toward increased bleeding in patients who received clopidogrel within 5 days of their surgery.

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

The final common pathway to platelet aggregation is the binding of fibrinogen to the IIb/IIIa receptors on the surface of platelets, with cross-linking and formation of a platelet thrombus. On the surface of each platelet are 50,000 to 80,000 of these receptors, but they are usually unreceptive unless activated by the conformational changes associated with disruption of endothelium. Inhibition of these receptors blocks the final common pathway to platelet aggregation (Fig. 17.5). The effects of thrombin, thromboxane A_2, collagen, ADP, catecholamine, and shear-induced platelet aggregation can be prevented by specific blockers of these receptors.

Dose-dependent inhibition of platelet aggregation can be achieved, and the effect of the nonantibody agents is reversible within a few hours of stopping the infusion. With the monoclonal antibody, abciximab, there is a gradual decline in the antithrombotic effect, with 50% recovery of ADP-induced aggregation at 24 to 48 hours.

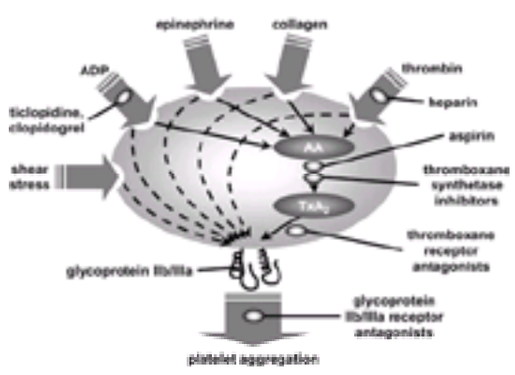


FIGURE 17.5 Stimuli that increase the affinity of the glycoprotein IIb/IIIa receptor for fibrinogen. AA, arachidonic acid; ADP, adenosine diphosphate; TxA_2, thromboxane A_2.

Glycoprotein IIb/IIIa antagonists can limit platelet aggregation at the site of plaque rupture, erosion, or fissuring and reduce the amount of platelet thrombus and embolization causing myocyte necrosis. Abciximab was shown in the CAPTURE study to reduce the amount of thrombus present at coronary arteriography (96), and the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study found that tirofiban reduced peak troponin levels (163). In 16 trials of IIb/IIIa antagonists in acute coronary syndromes, totaling more than 32,000 patients, mortality was reduced by 30% at 48 to 96 hours (p <.03), but the mortality reductions at 30 days and 6 months were not significant. The incidence of death/MI was significantly reduced by 24% at 30 days and at 6 months (164). Seven trials have shown that IIb/IIIa antagonists reduce the incidence of death/MI by approximately 35% at 30 days in patients who are undergoing PCI (162).

Abciximab

The efficacy of abciximab, a monoclonal antibody to the IIb/IIIa receptor, has been evaluated in several trials. Abciximab binds for the life of the platelet. The Evaluation of IIb/IIIa Platelet Receptor Antagonist (7E3) in Preventing Ischemic Complications (EPIC) trial (165) randomized 2,099 patients undergoing high-risk PCI (i.e., those with unstable angina, recent or evolving MI, or high-risk angiographic lesions of grade B2 or C) (166) to receive either a placebo, a bolus of abciximab, or a bolus and 12-hour infusion of abciximab. At 30 days, the patients who received the abciximab bolus and infusion had a 35% lower rate of death/MI/urgent revascularization than those who were given the placebo.

At 6 months, there was a 23% reduction in death/MI/urgent revascularization among the patients who received the abciximab bolus and infusion (27.0% vs. 35.1% in the placebo group, p = .001) (167). A reduction in the need for repeat PCI or CABG also occurred (16.5% vs. 22.3%, p = .007). An increase in major bleeding was, however, noted with the abciximab bolus and infusion (15.4% vs. 13.2% with bolus abciximab and 7.0% with the placebo).

The Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) trial, which compared abciximab with a low dose of weight-adjusted heparin (70 IU per kg bolus), was terminated prematurely after an interim analysis showed that abciximab reduced the incidence of death/MI from 8.1% to 2.6% (p <.001) (168). No increase in bleeding occurred with abciximab.

The CAPTURE study randomized 1,050 patients to receive either a placebo or abciximab before PCI. Thirty days after PCI the incidence of death/MI/need for intervention was reduced from 16.4% in the placebo group to 10.8% in the abciximab group (p <.05) (88).

In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial, 2,399 patients who were undergoing PCI were randomized to receive either a placebo plus stenting, abciximab plus balloon angioplasty, or abciximab plus stenting. At 30 days, death/MI/urgent revascularization had occurred in 10.8% of the placebo plus stenting group, 6.9% of the abciximab plus angioplasty group, and 5.3% of the abciximab plus stenting group. In the subgroup of patients who presented within 48 hours of symptom onset, the primary event rates were significantly reduced in those given abciximab plus stenting (4.5% vs. 7.3% in those given abciximab plus angioplasty and 14.8% in those given a placebo plus stenting) (169).

In the GUSTO IV trial (93), 7,800 patients who presented within 24 hours of the onset of chest pain that lasted at least 5 minutes and who had either 0.5 mm or greater ST depression or elevated troponin I or T levels were randomized to receive a placebo infusion, abciximab for 24 hours, or abciximab for 48 hours. The aim of the trial was to test an intensive medical regimen, and only 1.6% of patients underwent PCI in the first 48 hours. Abciximab was found to have no effect on the incidence of death/MI within 30 days (MI being defined as a CK-MB level of three times normal), with rates of 8.0% in the placebo group, 8.2% in the 24-hour abciximab group, and 9.1% in the 48-hour abciximab group. In patients with elevated troponin levels, the event rates were 10.0%, 10.0%, and 11.6%, respectively. Abciximab also had no effect in patients with ST depression, with event rates of 8.4%, 8.5%, and 9.9%, respectively, or in patients with both elevated troponins and ST depression.

These results are markedly inconsistent with previous trials, and at least three explanations have been proposed. Firstly, GUSTO IV had poor statistical power because of the low frequency of the primary composite end point. However, even when the results are analyzed using a more traditional definition of MI (namely, a CK-MB level of twice normal), raising the event rate in the placebo group to approximately 13%, there is still no evidence that abciximab was beneficial.

Secondly, the group of patients randomized was markedly different from those in previous trials in that a large proportion were women—37.6% overall and 49.1% of the patients randomized in Eastern Europe. In addition, this was the first trial to use troponin levels as an entry criterion. Previous trials have used evidence of ischemia (90) and evaluated outcomes in patients with elevated troponin levels (91,124,170). Although an elevated troponin level signifies that myocyte necrosis has occurred, it does not indicate the timing, which could have occurred up to 14 days previously (171), or the etiology of myocyte necrosis, which could be due to causes other than ischemia associated with thrombus, such as coronary spasm, pulmonary embolism with right ventricular MI, myocarditis, or heart failure. Furthermore, 20% of the patients in GUSTO IV did not have ST depression.

A third possible explanation for the lack of benefit seen with abciximab in GUSTO IV could be the effects of abciximab or the duration of treatment. Although the infusion was only given for 48 hours, abciximab can affect platelets for up to 2 weeks. Besides competitively blocking IIb/IIIa receptors, abciximab blocks vitronectin receptors and $a_M b_2$ integrin (Mac-1) receptors. However, abciximab may be procoagulant in low doses (172), and an *ex vivo* study has suggested that it may increase leukocyte rolling, which could outweigh the reduction in leukocyte aggregation caused by its anti–Mac-1 effect (173). Although no studies have precisely determined the optimal level of platelet inhibition, the effect of the abciximab bolus attenuates during the course of the infusion (174,175), and there is a possibility that a procoagulant state could ensue (176).

The CAPTURE study compared abciximab with a placebo in patients who were treated medically for 24 hours before PCI and showed that it reduced the frequency of MI (0.6% vs. 2.1%, p = .029). However, unlike the patients in GUSTO IV, all of the CAPTURE patients continued to have pain while receiving aspirin and heparin (88), and angiography showed that they also had anatomy suitable for PCI, and many had evidence of thrombus. Furthermore, any prothrombotic effects of abciximab may be unimportant after PCI when the coronary artery stenosis (and, thus, the shear-induced stimulation of platelet aggregation) has been reduced, and when clopidogrel is also given.

Tirofiban

Tirofiban is a small nonpeptide antagonist of the IIb/IIIa receptor that mimics the tripeptide arginine-glycine-aspartate sequence in fibrinogen. It is nonimmunogenic and has a high degree of selectivity for the platelet fibrinogen receptor, producing an acute effect within 5 minutes of administration. The effects are reversible in 4 to 6 hours.

The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) compared tirofiban with a placebo in 2,600 patients who were either postinfarction or had unstable angina and reported that tirofiban significantly reduced the incidence of death/MI/CABG/repeat PCI/bailout stenting at 48 hours (5.4% vs. 8.7%, p <.01) and at 7 days (7.4% vs. 10.1%, p <.05) but not at 30 days (10.3% vs. 12.2%, p = .15) (177). However, when the results were reanalyzed using a PCI end point similar to that used in the EPIC trial (165) (i.e., including only emergency revascularizations and not elective PCI), there was a significant 24% reduction in event rates at 30 days.

The PRISM study (89) compared tirofiban with heparin in 3,231 patients with unstable angina or non–Q-wave MI, using a placebo-controlled, double-dummy technique with adjustment of the activated partial thromboplastin time (APTT). All patients received aspirin, and 75% had ECG evidence of ischemia at randomization. The composite primary end point was death/new MI/refractory ischemia during the 48-hour infusion period, and tirofiban was found to reduce all components of this end point by approximately 33% (p = .007), with refractory ischemia being reduced from 5.3% to 3.6%, MI from 1.3% to 0.9%, and death from 0.6% to 0.4%. At 30 days, the incidence of death/MI was reduced by 21% from 7.0% to 5.7% (p = .1), and mortality was reduced by 40% from 3.6% to 2.3%. Revascularization procedures were performed in 39% of patients.

The PRISM-PLUS study was conducted in 1,560 high-risk patients with unstable angina (90). Three treatment arms compared tirofiban (0.6 µg per kg per minute for 30 minutes followed by 0.15 µg per kg per minute), heparin, and tirofiban plus heparin, all on a background of aspirin therapy. Angiography was encouraged with PCI if indicated, and tirofiban was to be continued until 12 to 24 hours after the revascularization procedure. Ninety percent of patients had angiography, and 54% underwent revascularization procedures within 7 days, at which time the incidence of death/MI/refractory ischemia was 44% lower in patients who were given tirofiban plus heparin than in those given heparin alone (12.9% vs. 17.9%, p = .004). At 30 days, the overall difference in event rates was 27%, and the incidence of death/MI was reduced by 30% from 11.9% to 8.7% (p = .03). The tirofiban arm had been terminated early because of a nonsignificantly higher mortality, but it should be noted that the PRISM study, which enrolled five times the number of patients, found that tirofiban significantly reduced mortality compared with heparin (89). Both studies reported that there was no increase in bleeding rates with tirofiban.

The PRISM and PRISM-PLUS studies showed that tirofiban is effective at reducing acute ischemic events during the infusion of the drug. Tirofiban was more effective than heparin in the PRISM study (89) and added to the effects of heparin in the PRISM-PLUS study (90). Because of the mortality increase observed with tirofiban in the dropped arm of PRISM-PLUS, which enrolled higher-risk patients than PRISM, it is recommended that adjunctive heparin be given with tirofiban.

In the Do Tirofiban and ReoPro Give Similar Efficacy (TARGET) trial (161), tirofiban was compared with abciximab in patients who were undergoing stenting. At 30 days, there was a 20% reduction in death/MI/rescue revascularization in the patients treated with abciximab (6.0% vs. 7.5% with tirofiban, p = .037). The difference was greater in the subgroup of patients with acute coronary syndromes (6.3% with abciximab vs. 9.3% with tirofiban). No difference was found in death/MI in patients undergoing elective PCI (5.6% with abciximab vs. 4.5% with tirofiban).

Eptifibatide

Eptifibatide is a cyclic peptide inhibitor of the IIb/IIIa receptor that exerts rapid platelet inhibition. It has a short half-life, with platelet aggregation returning to baseline within 2 to 4 hours.

The Integrilin (Eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT) II study compared eptifibatide with a placebo in 4,010 patients who were undergoing PCI for unstable angina. A high-dose eptifibatide regimen (135-µg-per-kg bolus followed by 0.75 µg per kg per hour) reduced the incidence of ischemic events/emergency revascularization within 24 hours from 6.8% to 5.% (p = .01), but there was no significant difference in the same end point at 30 days (9.9% with eptifibatide vs. 11.4% with the placebo, p = .18) (178).

The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial (162) was conducted in 2,064 patients who were undergoing stenting. All patients received aspirin, low-dose heparin, and loading doses of ticlopidine or clopidogrel and were randomized to receive either eptifibatide (2 boluses of 180 mg per kg followed by 2.0 mg per kg per hour) or a placebo for 18 to 24 hours. When an interim analysis showed that the 48-hour incidence of death/MI/urgent revascularization/thrombotic bailout IIb/IIIa inhibitor use was significantly lower in patients who were treated with eptifibatide (6.6% vs.10.5%, p = .0015), the trial was terminated early. Patients who presented within 2 days of an acute coronary syndrome made up 14% of the trial population, and eptifibatide nonsignificantly reduced their event rates from 20.4% to 11.4% (p = .24).

The PURSUIT trial compared eptifibatide with a placebo in 9,461 patients with ischemic chest pain and 1 mm or greater ST depression and reported that it reduced the incidence of death/MI from 15.7% to 14.2% at 30 days (*p* = .03).

Lamifiban

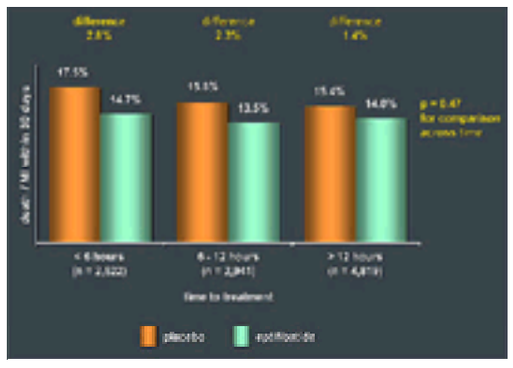
Lamifiban is a synthetic, nonpeptide, highly selective IIb/IIIa antagonist. It has been tested in several clinical trials (91,170) but is not yet available for clinical use. Its pharmacodynamic half-life is approximately 4 hours (179).

In the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)-A trial (170) of lamifiban in 2,282 patients who received background aspirin therapy, the rates of death/MI at 30 days were 10.3% in patients who were given low-dose lamifiban (300-µg bolus followed by 1-µg-per-minute infusion for 72 hours) with heparin, 10.8% in those given low-dose lamifiban without heparin, 12.3% in those given high-dose lamifiban (750-µg bolus followed by 5-µg-per-minute infusion for 72 hours) with heparin, and 11.6% in those given high-dose lamifiban without heparin [*p* = not significant (NS)].

In the PARAGON-B trial (91), 5,225 patients were randomized to receive either a bolus and 72-hour infusion of lamifiban or a placebo, adjusted for estimated creatinine clearance and body weight. Although there was no significant difference overall in the incidence of death/MI/severe recurrent ischemia within 30 days (12.6% with the placebo vs. 11.8% with lamifiban), lamifiban was beneficial in patients who were undergoing PCI and in those with elevated troponin T levels (³0.1 mg per mL), reducing their event rates from 18.5% to 11.6% and from 19.4% to 11.0%, respectively (both *p* = .01). No benefit was found in patients without elevated troponin levels.

Time to Treatment

The longer the delay before commencement of IIb/IIIa antagonist therapy, the longer patients are exposed to the risk of MI. In the PURSUIT trial, patients were randomized to receive eptifibatide either within 6 hours, between 6 and 12 hours, or more than 12 hours after symptom onset. A larger absolute reduction in death/MI occurred within 30 days in patients who received eptifibatide earlier (2.8%, 2.5%, and 1.4%, respectively) (124,180) (*e*Fig. 17.5.1).



***e*FIGURE 17.5.1** Rates of death/myocardial infarction (MI) at 30 days in patients given eptifibatide or a placebo within 6 hours of symptom onset, between 6 and 12 hours, and after 12 hours in the PURSUIT trial (180).

Upstream Treatment with IIb/IIIa Antagonists

IIb/IIIa antagonists may be beneficial in three situations: during PCI, before PCI ("upstream" treatment), and in patients who are treated with medical therapy alone. Upstream treatment was assessed in the CAPTURE (88), PRISM-PLUS (90), and PURSUIT (124) trials, totaling more than 12,000 patients, and the combined results demonstrated a substantial reduction in death/MI in the period before intervention (from 4.3% to 2.9%, equating to 14 fewer events per 1,000 patients treated) (181) (Fig. 17.6). Most of this reduction was in MI rather than death. From the time of the intervention up until 48 hours afterward, the effect was greater, but after that time there was no effect.

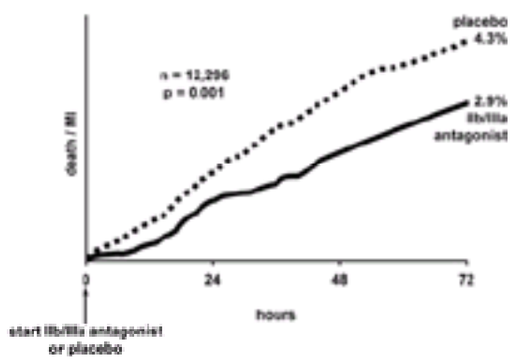


FIGURE 17.6 Event rates before intervention in the CAPTURE (88), PRISM-PLUS (90), and PURSUIT (124) trials of IIb/IIIa antagonists in patients with non–ST-elevation acute coronary syndromes. MI, myocardial infarction. (Redrawn from Boersma E, Akkerhuis M, Théroux P, et al. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999;100:2045–2048, with permission.)

Upstream treatment with a IIb/IIIa antagonist also reduces the incidence of MI before CABG (90) and may reduce the risk of perioperative events. Cardiopulmonary bypass activates platelets, leading to thromboembolism. Paradoxically, it may also lead to thrombocytopenia and increased bleeding via binding of platelets through the IIb/IIIa receptors. In the PURSUIT trial, 1,558 patients underwent CABG. Eptifibatide reduced the rate of death/MI within 30 days from 30.8% to 26.1%, and the effect was maintained at 6-month follow-up (*e*Fig. 17.6.1). The reduction in events was greatest among patients who received eptifibatide within 72 hours of CABG (23.8% vs.33.6%, *p* = .002). The incidence of major bleeding was not increased, occurring in 58.2% of the eptifibatide group and 56.6% of the placebo group (*p* = .7) (182). In the PRISM-PLUS study, tirofiban reduced the 30-day incidence of death/MI in patients who were undergoing CABG from 16.8% to 12.2% (90). Given the logistical difficulties in many hospitals of performing procedures at night and during the weekend, upstream use of a IIb/IIIa antagonist before procedures is very practical.

***e*FIGURE 17.6.1** Rates of death/MI at 30 days and at 6 months in patients given eptifibatide or a placebo in the PURSUIT trial (182). The reduction in events was

greatest among patients who received eptifibatide within 72 hours of coronary artery bypass grafting (CABG; 23.8% vs. 33.6%, *p* = .002). MI, myocardial infarction.

Use of IIb/IIIa Antagonists in Patients Treated without Interventions

In the PARAGON-A (170), PRISM (89), PRISM-PLUS (90), PURSUIT (124), PARAGON-B (91), and GUSTO IV trials (93), intervention was not recommended to be performed routinely, and only approximately 11% of patients underwent intervention while on randomized IIb/IIIa antagonist or placebo therapy. These trials were thus trials of medical therapy with intervention performed at the discretion of the treating physician, and so conclusions cannot be drawn from analysis of the medically managed patients alone. These trials showed that IIb/IIIa antagonists reduced the incidence of death/MI by 8% at 30 days (see Fig. 17.7). In the PURSUIT trial, in which PCI was performed at the discretion of the treating physician, an analysis with censoring for PCI across the 30-day follow-up period showed that eptifibatide accounted for a 31% reduction in the incidence of death/MI (from 16.8% to 15.1%, *p* = .035) (183). Correction of the event rates using a PCI propensity score produced no evidence that the eptifibatide treatment effect differed between the two groups.

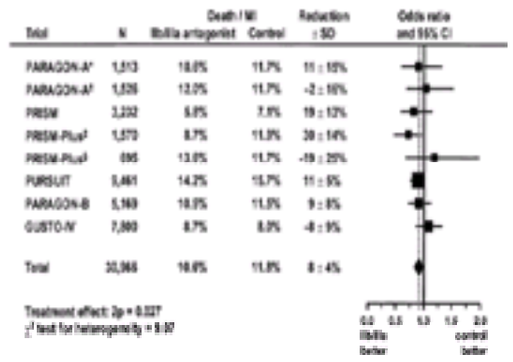


FIGURE 17.7 Metaanalysis of death/myocardial infarction (MI) at 30 days in trials (89,90 and 91,93,124,170) comparing IIb/IIIa antagonists with control treatment in patients with non–ST-elevation acute coronary syndromes who were also receiving aspirin therapy and in whom immediate percutaneous coronary intervention was not planned. *Low-dose lamifiban; †high-dose lamifiban; ‡tirofiban plus heparin versus heparin alone; §tirofiban alone versus heparin alone; CI, confidence interval; SD, standard deviation.

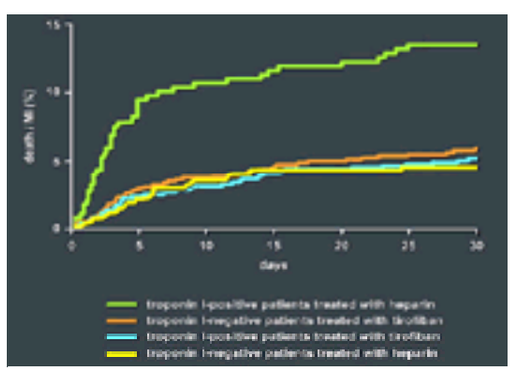
Which Patients Should Receive IIb/IIIa Antagonists?

IIb/IIIa antagonists should be targeted at patients who are undergoing PCI (184), patients at high risk, and, in particular, those with ST depression or elevated troponin levels (1,80,89,91,96) (Table 17.4). In the PRISM study (89), tirofiban reduced the risk of death/MI in patients with elevated troponins to a level similar to that of patients without elevated troponins (83) (eFig. 17.6.2). In the PARAGON-B trial, lamifiban had no beneficial effect overall, but in patients with troponin levels it reduced the incidence of death/MI/recurrent ischemia from 19.4% to 11.0% at 30 days (*p* = .01) (91). Diabetic patients are at high risk, and in PRISM-PLUS tirofiban reduced their incidence of death/MI from 19.2% to 11.2% at 30 days (90).

Elevated troponin levels
≥0.5-mm ST depression
Elevated cardiac enzyme levels
Patients undergoing PCI
Patients with high-risk features
Age >65 yr
Ejection fraction <50%
Hemodynamic instability
Angiographic evidence of thrombus
PCI within the previous 6 mo
Previous CABG
Previous myocardial infarction
Pulmonary edema
Diabetes
Patients already receiving aspirin at admission
Recurrent ischemia
Inpatients awaiting CABG

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

TABLE 17.4 HIGH-RISK EXERCISE TEST



***e*FIGURE 17.6.2** Event rate curves for death/myocardial infarction (MI) within 30 days in patients with troponin I levels above and below the diagnostic threshold of 1.0 mg per L treated with either heparin or tirofiban in the PRISM study. (Redrawn from Heeschen C, Hamm CW, Goldmann B, et al. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999;354:1757–1762, with permission.)

Patients who are already receiving aspirin therapy at admission are at particularly high risk (111,185) because the aspirin has usually been prescribed for secondary prevention due to a previous coronary event or known coronary artery disease or for primary prevention; for example, they are considered at high risk because of a strong family history of coronary disease (186). When such patients present with an acute coronary syndrome, it signifies that they have broken through the antiplatelet and antiinflammatory effects of the aspirin (103), and it could mean either that they are unresponsive to aspirin or that they have a large thrombus load associated with plaque rupture or fissuring. In patients who are already receiving aspirin, the rates of death/MI were reduced from 17.3% to 14.9% at 30 days with eptifibatide in PURSUIT (185) and from 21.8% to 14.8% at 7 days with tirofiban in PRISM-PLUS (90).

Patients with intracoronary thrombus detected at angiography are also at high risk. In PRISM-PLUS (187) the presence of thrombus was shown to increase the 30-day incidence of death from 2% to 5%, MI from 4% to 9%, and recurrent ischemia from 5% to 9%. IIb/IIIa antagonists have been shown to reduce the amount of thrombus detected at angiography (96), and their use may be indicated in patients with angiographic thrombus unsuitable for PCI who are awaiting CABG over the next few days.

More than 30,000 patients have been randomized into IIb/IIIa antagonist studies in which they received medical treatment primarily and underwent revascularization procedures only at the discretion of the treating physician. If all of the results are combined (including GUSTO IV), there was a significant 8% reduction in death/MI at 30 days in patients who were given IIb/IIIa antagonists, down from 11.8% to 10.6% (*p* <.02) (89,90 and 91,93,124,170) (Fig. 17.7). In the subgroup of patients with elevated troponin levels, analysis using a similar definition of MI in all of the trials (namely, a CK-MB level of twice normal) shows that the incidence of death/MI was reduced by 22% (83,90,91,93) (Fig. 17.8). A few studies have evaluated the cost effectiveness of IIb/IIIa antagonists and found it to be similar to that of other therapies

(188).

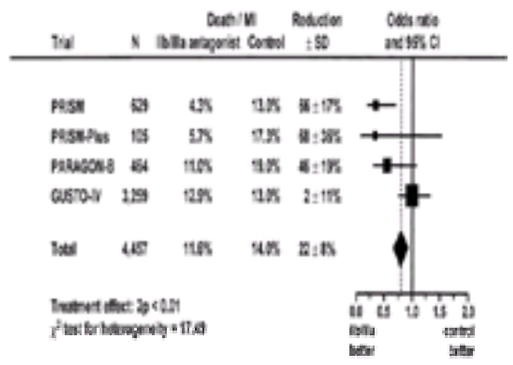


FIGURE 17.8 Metaanalysis of death/myocardial infarction (MI) at 30 days in patients with elevated troponin levels in the PRISM (83), PRISM-PLUS (90), PARAGON-B (91), and GUSTO IV (93) trials. In GUSTO IV, MI was defined as a creatine kinase (CK)–MB level of three times normal. Here, MI is defined as a CK-MB level of twice normal. CI, confidence interval; SD, standard deviation.

Guidelines

The guidelines issued by the European Society of Cardiology (80) and by the ACC and AHA (1) give a class A recommendation (i.e., based on at least one randomized controlled trial) for the use of IIb/IIIa antagonists and PCI in unstable angina or non–ST-elevation MI. Both guidelines also give a class A recommendation for the use of IIb/IIIa antagonists in patients with acute coronary syndromes who were managed without interventions, based on the data from PRISM (89), PRISM-PLUS (90), PURSUIT (124), and CAPTURE (88).

Combination Therapy with IIb/IIIa Antagonists and Clopidogrel

There have been no randomized trials of combination therapy with IIb/IIIa antagonists and clopidogrel, but retrospective analysis of several studies has suggested that this combination is both beneficial and safe. In the EPISTENT Trial, ticlopidine was found to be beneficial when given prior to stenting in patients who also received abciximab in the catheterization laboratory (188a). In the TARGET trial (161), patients who received clopidogrel prior to either abciximab or tirofiban had lower event rates. In the CURE trial (188b), there was less usage of IIb/IIIa antagonists in the clopidogrel treatment group, and no increase in major bleeding was observed in patients who did receive a IIb/IIIa antagonist. Upstream treatment with both clopidogrel and a IIb/IIIa antagonist prior to PCI should be considered in high-risk patients but avoided in those likely to require urgent CABG.

Heparin

A number of trials have compared unfractionated heparin with placebos or control aspirin therapy in patients with unstable angina (67,154,189,190,191,192 and 193). Heparin has been shown to be more effective than aspirin for relieving angina (67,194,195). The first study to demonstrate the efficacy of heparin was published in 1981 by Telford and Wilson (189). In a selected group of 214 patients who were not taking aspirin, 5,000 IU heparin every 6 hours reduced the incidence of death/MI from 17% to 3% (p <.05).

A placebo-controlled trial from the Montreal Heart Institute (67) randomized 479 patients to receive aspirin (650 mg followed by 324 mg twice a day) or heparin (5,000 IU i.v. bolus followed by 1,000 IU per hour), or both. Heparin was continued for 6 ± 3 days, reducing the risks of MI by 89% and refractory angina by 63%. No difference was found between aspirin and heparin, and the combination of the two was not superior to heparin alone.

A subsequent trial from Montreal (190) randomized two sequential cohorts of 484 patients with unstable angina to receive aspirin (325 mg twice a day) or heparin (5,000 IU i.v. bolus and infusion adjusted to an APTT of 1.5 to 2.5 times control). MI was less common in patients who received heparin than in those receiving aspirin (0.8% vs. 3.7%, p <.05), and the survival rate without MI during the treatment period was higher with heparin than with aspirin (p <.05).

The placebo-controlled Research Group on Instability in Coronary Artery Disease in Southeast Sweden (RISC) study (154) randomized 796 men with unstable angina or non–Q-wave MI to receive aspirin (75 mg per day) or heparin (5,000 IU i.v. bolus every 6 hours), or both. Aspirin reduced the risk of death/MI by 47% at 5 days. Heparin on its own had no apparent effect on event rates, but patients who were given both aspirin and heparin had the lowest event rates during the first 5 days.

The Antithrombin Therapy in Acute Coronary Syndromes (ATACS) trial (193) compared aspirin alone (n = 109) with aspirin plus heparin (n = 105) in patients with rest angina or non–Q-wave MI who were not already taking aspirin. At 5 days, death/MI had occurred in 8.3% of patients who were given aspirin alone and in 3.8% of those given aspirin plus heparin (p = NS).

In a small study of 219 patients with unstable angina, Gurfinkel et al. (192) compared aspirin alone (200 mg per day), aspirin plus i.v. unfractionated heparin (400 IU per kg per day), and aspirin plus subcutaneous low-molecular-weight heparin (nadroparin calcium, 214 IU per kg twice a day). MI occurred in 9.5% of patients who were given aspirin alone, 6.0% of those given aspirin plus unfractionated heparin (p = .5), and none of those given aspirin plus low-molecular-weight heparin (p = .01). Recurrent angina and silent ischemia were also less common with low-molecular-weight heparin than with aspirin alone or aspirin plus unfractionated heparin.

Neri Serneri et al. (195) found that heparin, administered either subcutaneously or intravenously, reduced the incidence of angina or silent ischemia in 108 patients with symptoms that were not controlled by 325 mg aspirin, 300 mg metoprolol, 40 mg isosorbide dinitrate, and 40 mg nifedipine daily. Aspirin did not reduce the incidence of angina or myocardial ischemia on ST-segment monitoring. Over the first 3 days, i.v. and subcutaneous heparin reduced the incidence of angina by 91% and 86%, respectively (*e*Table 17.4.1); episodes of silent ischemia by 56% and 46%, respectively; and the overall duration of ischemia by 66% and 61%, respectively. After 3 weeks of continued treatment, recurrent angina was less common among patients who received subcutaneous heparin than among those receiving aspirin (13% vs. 56%, p <.005).

***e*TABLE 17.4.1** EFFECTS OF HEPARIN VERSUS ASPIRIN ON THE FREQUENCY OF ANGINA

	Run-in day		Treatment days		Mean decrease	
No. of episodes of angina	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**% (SD)**	***p* Value**
Intravenous heparin (n = 37)	22	1[a]	3[a]	2[a]	91 (4)	<.001
Subcutaneous heparin (n = 35)	22	5[b]	2[a]	2[a]	86 (6)	<.001
Aspirin (n = 36)	24	19	18	15	28 (7)	NS

NS, not significant; SD, standard deviation.
[a]p <.005.
[b]p <.01.Reprinted from Neri Serneri GG, Modesti PA, Gensini GF, et al. Randomised comparison of subcutaneous heparin, intravenous heparin, and aspirin in unstable angina. *Lancet* 1995;345:1201–1204, with permission.

Dosing regimens have been tested in which the infusion rate of unfractionated heparin was reduced by 50% for 12 hours, or a subcutaneous dose of 12,500 IU was given within 4 hours of cessation and again 12 hours later, but these did not prevent thrombin generation (196). However, the response was modestly attenuated with the i.v. regimen.

A pooled analysis of heparin trials is shown in Figure 17.9. Overall, unfractionated heparin had no effect on the incidence of death/MI within 30 days (197).

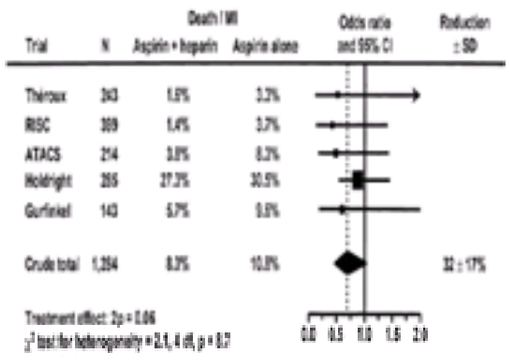


FIGURE 17.9 Metaanalysis of death/myocardial infarction (MI) in trials (79,154,190,192,193) comparing aspirin plus unfractionated heparin with aspirin alone in patients with unstable angina. Low-molecular-weight heparin was used in the trial by Gurfinkel et al. (192). CI, confidence interval; df, degrees of freedom; SD, standard deviation.

Duration and Monitoring of Heparin Therapy

Limited data are available regarding the optimal duration and intensity of heparin therapy. When administered for 6 to 7 days, heparin has been shown to reduce the incidence of death/MI (67,189,194). However, in two studies, 2 days of heparin therapy had no effect on myocardial ischemia or on the incidence of death/MI (79).

Low-Molecular-Weight Heparins

Although unfractionated heparin is standard therapy in acute coronary syndromes, the data for its use are not compelling (194). Its bioavailability varies because it binds to plasma proteins and to the endothelium, and this makes it difficult to use, necessitating precise dosage adjustment to maximize therapeutic efficacy while minimizing the risk of bleeding.

Low-molecular-weight heparins have a mean molecular mass of only 46 kd and lack the minimum 18 saccharides that are required for simultaneous binding of thrombin and antithrombin III, although they bind to and inhibit factor X_a more effectively than does unfractionated heparin. Because the different low-molecular-weight heparins have different chemical structures and different molecular weights, they have different biologic properties, antifactor X_a to antifactor II_a ratios, and effects on the release of tissue factor pathway inhibitor. The antifactor X_a effects of low-molecular-weight heparins can be partially reversed (by approximately 60%) by administration of protamine sulfate (198).

Low-molecular-weight heparins have a number of practical advantages over unfractionated heparin, including greater bioavailability and a more predictable dose response due to minimal protein binding, and higher antifactor X_a to antifactor II_a ratios with an enhanced ability to inhibit thrombin generation, inhibition of von Willebrand's factor release, resistance to inactivation by platelet factor 4, no heparin resistance, and no activation of platelets. They are more convenient to use because they require no monitoring of the APTT and no i.v. lines, and their use has been shown to save money in some health-care systems (199). The associated rates of thrombocytopenia and osteoporosis are lower (200), and rebound ischemia may be less common after cessation than it is with unfractionated heparin (139). The patients who benefit most are those older than 65 years (92,94,201); those who are currently receiving aspirin; those with elevated troponins, ST depression, or previous or current MI; and those waiting for interventions (69).

As of yet, there is no compelling evidence that the low-molecular-weight heparins as a group are superior to unfractionated heparin in the management of patients with acute coronary syndromes. The five trials that compared enoxaparin (94,201), dalteparin (202), and Fraxiparine (192,203) with unfractionated heparin yielded mixed results.

The TIMI 11B trial (94) compared enoxaparin (30-mg i.v. bolus followed by 1.0 mg per kg subcutaneously twice a day) with unfractionated heparin (70-IU-per-kg i.v. bolus followed by 15-IU-per-kg-per-hour i.v. infusion). The mean duration of treatment in the acute phase was 4.6 days in patients who were given enoxaparin and 3 days in those given unfractionated heparin. Subcutaneous enoxaparin was then continued for 6 weeks in a twice-daily weight-adjusted dose of 40 mg or 60 mg, and the unfractionated heparin group received matching placebo injections. At day 8, death/MI/urgent revascularization was less common in the enoxaparin group (12.4% vs.14.5%, p = .048). The incidence of major hemorrhage was similar in both groups (1.5% with enoxaparin vs. 1.0% with unfractionated heparin), but minor hemorrhage was more common with enoxaparin (9.1% vs. 2.5% with unfractionated heparin).

In the ESSENCE trial (201), 3,171 patients with unstable angina or non–Q-wave MI were randomized to receive either i.v. dose-adjusted unfractionated heparin or subcutaneous enoxaparin (1 mg per kg 12-hourly). All patients received aspirin. The treatment phase lasted a minimum of 48 hours and a maximum of 6 days (average, 2.6 days). At 14 days and 30 days, the rates of death/MI/recurrent angina were lower in the enoxaparin group [16.6% vs.19.8% at 14 days (p = .02) and 19.8% vs. 23.3% at 30 days (p = .02)], as were the rates of death/MI [4.9% vs.6.1% at 14 days (p = .131) and 6.2% vs. 7.7% at 30 days (p = .081)]. The incidence of major hemorrhage was similar in both groups (7.0% with heparin vs. 6.5% with enoxaparin), but the total hemorrhage rate was higher in the enoxaparin group (18.4% vs. 4.1% with heparin, p = .001). The benefit of enoxaparin was maintained at 1 year. A prospective metaanalysis of the TIMI 11B and ESSENCE trials (204) showed that enoxaparin reduced the incidence of death/MI by 18% at 43 days (p = .02)(Fig. 17.10).

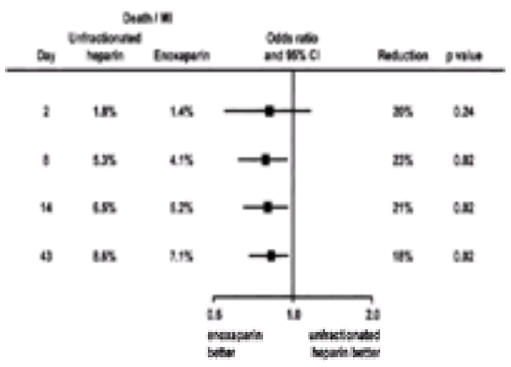


FIGURE 17.10 Metaanalysis of death/myocardial infarction (MI) at days 2, 8, 14, and 43 in the TIMI IIB (94) and ESSENCE (201) trials comparing enoxaparin with unfractionated heparin. CI, confidence interval. (Redrawn from Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999;100:1602–1608, with permission.)

In the Fragmin in Unstable Coronary Artery Disease (FRIC) study (202), subcutaneous dalteparin (120 IU per kg 12-hourly for at least 48 hours) was compared with unfractionated heparin in 1,482 patients who were also taking aspirin. At 6 days, death/MI had occurred in 3.9% of patients who were given dalteparin and in 3.6% of those given unfractionated heparin, and bleeding had occurred in 4.4% versus 4.3%, respectively (p = NS). Between days 6 and 45, there was no difference in the incidence of death/MI between the two groups.

As detailed previously (see Heparin), Gurfinkel et al. (192) compared nadroparin (Fraxiparine) with unfractionated heparin in a small study of 219 patients and reported that it reduced the rates of ischemic events and minor bleeding. However, the Fraxiparine in Ischaemic Syndrome (FRAXIS) study (203) found that nadroparin increased the rate of major bleeding (3.5% vs.1.6%) without reducing the incidence of death/MI/recurrent angina.

A metaanalysis of these five trials (94,192,201,202 and 203) concluded that there was no significant overall reduction in death/MI during short-term follow-up (odds ratio, 0.88; 95% CI, 0.69 to 1.12; p = NS) (197) (Fig. 17.11). The combined event rates in these trials—2.2% in patients given low-molecular-weight heparin and 2.3% in

those given unfractionated heparin—were much lower than the event rates in the IIb/IIIa antagonist trials.

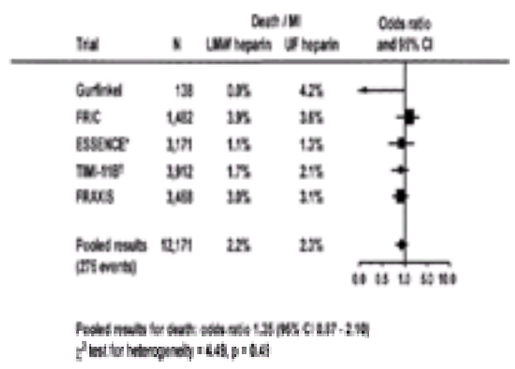


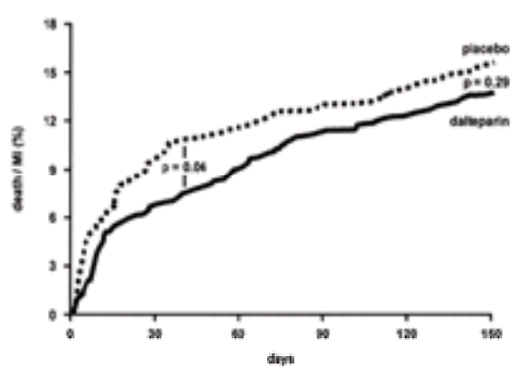
FIGURE 17.11 Metaanalysis of death/myocardial infarction (MI) at the completion of treatment in randomized trials (94,192,201,202 and 203) comparing short-term low-molecular-weight (LMW) heparin with unfractionated (UF) heparin in patients with non–ST-elevation acute coronary syndromes. *The median duration of therapy was 2.6 days in both groups. †Unequal duration of treatment. CI, confidence interval. (Redrawn from Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000;355:1936–1942, with permission.)

The disparate findings of these trials using various low-molecular-weight heparins may be partly due to differences in the trial methodologies and patient selection. Firm conclusions regarding the relative efficacy of the low-molecular-weight heparins will only be possible once directly comparative trials have been performed.

A number of differences between the agents, such as the doses of the drugs used, rates of clearance, amount of nonspecific binding, and effects on von Willebrand's factor (205) or tissue factor pathway inhibitor, could produce different clinical outcomes (206). A low-molecular-weight pentasaccharide with anticoagulant activity has been found to persist for several days after the administration of enoxaparin, but this has not been demonstrated with dalteparin or unfractionated heparin (207). More prolonged treatment with low-molecular-weight heparins has not been found to be beneficial (92,94,202,203).

A moderate increase in bleeding was found in TIMI 11B (94), FRAXIS (203), and FRISC II (208), and the only one of these trials to report any benefit was FRISC II, which compared a twice-daily dose of dalteparin with a placebo. The incidence of death/MI was significantly reduced from 5.9% to 3.1% at 30 days (p = .002) and nonsignificantly reduced from 8.0% to 6.7% at 3 months (p = .17). The incidence of death/MI/refractory angina was reduced from 33.4% to 29.1% at 3 months (p = .031), at the expense of a moderate increase in bleeding (3.3% vs. 1.5%, p = .01). The benefits of dalteparin were observed only in patients with elevated troponin T levels (208).

The FRISC I study (92) randomized 1,506 patients with unstable angina or non–Q-wave MI to receive either a placebo or 120 IU per kg dalteparin twice a day for 6 days followed by 7,500 IU per day for 35 to 45 days. All patients received aspirin. In the first 6 days of treatment, dalteparin was very beneficial, reducing the incidence of death/MI from 4.8% to 1.8% (relative risk, 0.37; 95% CI, 0.20 to 0.68). A survival analysis showed that the event rate increased when the dose of dalteparin was decreased. Although the reduction in death/MI persisted at 40 days, this benefit was confined to nonsmokers. At 150 days (4 to 5 months after the end of treatment), there was no difference in death/MI between the two groups (*e*Fig. 17.11.1). However, there was a significant reduction in death/MI/revascularization for angina in the patients who had received dalteparin (24.1% vs. 28.7%; risk ratio, 0.84; 95% CI, 0.70 to 0.98).



***e*FIGURE 17.11.1** Cumulative incidence of death/myocardial infarction (MI) within 150 days in patients treated with a placebo or dalteparin in the FRISC I study. [Redrawn from Fragmin during Instability in Coronary Artery Disease (FRISC) study group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996;347:561–568, with permission.]

Rebound Ischemia

Following the cessation of heparin therapy, there may be a rebound increase in ischemic events. In the first of the two Montreal Heart Institute trials that compared heparin with aspirin (209), there was a recurrence of angina at a median of 9.5 hours after stopping heparin in patients who were not taking aspirin. A number of hypotheses have been postulated to explain this phenomenon, including release of thrombin from the heparin-antithrombin-thrombin complex or from fibrin, reduction of antithrombin III, nitric oxide, or prostacyclin. Upregulation of platelet thrombin receptors and reduction of the thrombin-thrombomodulin complex, resulting in reduced protein C activation (thrombotic tendency), may also play a role.

Rebound ischemia was also noted with unfractionated heparin in the GUSTO IIB study despite concomitant aspirin therapy (133). In a group of patients who received 325 mg aspirin daily, the levels of fibrinopeptide A and prothrombin fragments 1 and 2 increased after cessation of heparin and then returned to baseline, indicating that rebound ischemia is not just a manifestation of ongoing prothrombotic activity that continues when heparin is stopped (210). This probably reflects failure to reduce thrombin generation via thrombin inhibitors, such that after cessation of the infusion, the accumulated thrombin serves to facilitate the extrinsic coagulation cascade and platelet accumulation.

Recommendations for Heparin Use

Patients with intermediate- or high-risk non–ST-elevation acute coronary syndromes (Table 17.2) should receive either low-molecular-weight heparin or weight-adjusted i.v. unfractionated heparin immediately, provided that they have no contraindications (1). The initial dose should be a 5,000-IU bolus followed by an infusion of 1,000 IU per hour in patients who weigh 80 kg or greater or 800 IU per hour in those weighing less than 80 kg to maintain the APTT between 50 and 70 seconds (210,211). The infusion should be continued for 2 to 5 days or until revascularization (1). The APTT should be measured 6 hours after any change in dosage, and the heparin dose should be readjusted if necessary.

If recurrent ischemia develops, the APTT should be measured immediately. A validated bedside APTT measurement can be used to expedite management. If the APTT is subtherapeutic, an appropriate weight-adjusted bolus of heparin should be administered. Urgent cardiac catheterization should be considered with a view to revascularization if the ischemic episode is prolonged or associated with ECG changes despite a therapeutic APTT. When i.v. heparin is stopped, patients should be monitored closely for ischemic events over the next 12 hours.

Low-molecular-weight heparin should be considered as an alternative to unfractionated heparin. The European Society of Cardiology and American College of Chest Physicians guidelines (212) recommend low-molecular-weight heparin as the antithrombotic agent of choice. However, patients with heparin-induced thrombocytopenia should not be given low-molecular-weight heparins, which have a high degree of *in vitro* cross-reactivity with the antibody that causes this disorder (213), and can cause heparin-induced thrombocytopenia in patients with a history of this condition (214,215 and 216).

Combination of IIb/IIIa Antagonists and Low-Molecular-Weight Heparins

No large clinical trials to date have compared aspirin plus low-molecular-weight heparin with aspirin plus unfractionated heparin plus a IIb/IIIa antagonist. However, several small trials have suggested that the combination of tirofiban and enoxaparin is safe.

In the Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE) I study (217), 55 patients were randomized to receive either tirofiban plus enoxaparin or tirofiban plus unfractionated heparin. At 48 hours, 84% of the patients who were given enoxaparin had *ex vivo* platelet inhibition of greater than 70%, compared with only 65% of those given unfractionated heparin, although this trend did not reach statistical significance ($p = .16$). Also, less variability was seen in the degree of platelet inhibition achieved with enoxaparin. In addition, although not closely related to clinical bleeding, bleeding times were less prolonged with enoxaparin (20.7 minutes vs. 30 minutes with unfractionated heparin, $p = .35$).

In the ACUTE II study (218), 525 patients were randomized to receive either tirofiban plus enoxaparin or tirofiban plus unfractionated heparin. No difference was seen in the incidence of death/MI/stroke, and the rates of thrombocytopenia and major and minor bleeding were similar in both groups.

In PARAGON-B (91), 410 patients received lamifiban and (nonrandomized) low-molecular-weight heparin. Patients who were given low-molecular-weight heparin had a lower revascularization rate than those given unfractionated heparin (33.7% vs. 44.3%, $p <.001$), and there was a trend toward a lower incidence of death/MI at 30 days (10.3% vs. 12.2%, $p = .13$) and at 6 months (12.8% vs. 15.5%, $p = .08$). The stroke and bleeding rates were similar.

In a GUSTO IV substudy of 974 patients, dalteparin was given for 5 to 7 days in conjunction with abciximab or a placebo. The combination of dalteparin and abciximab did not reduce the incidence of cardiac events but did increase the incidence of minor bleeding (4.0% vs. 1.3%, $p <.05$).

The A-Z trial is randomizing approximately 5,800 patients to receive either unfractionated heparin or enoxaparin on a background of tirofiban therapy. The primary end point will be a composite of death/MI/refractory ischemia requiring urgent revascularization.

Beta-Adrenoreceptor Blockers

Beta-blockers are effective when used singly in unstable angina (128,129,189,219) and in combination with nitrates (220) to reduce recurrent ischemia. They block beta-receptors on all cell membranes and reduce myocardial oxygen demands by slowing the heart rate, lowering the blood pressure, and reducing contractility.

Three double-blind trials have compared beta-blockers with placebos in patients with threatened MI (128,129,189). The Holland Interuniversity Nifedipine/Metoprolol (HINT) trial reported that metoprolol reduced the incidence of MI in patients who had not previously received beta-blocker therapy (128).

In a review of 4,700 randomized patients, beta-blockers reduced the percentage of those in whom MI developed by 13%, from 32% to 29% ($p <.05$) (219). It has not been clearly shown whether beta-blockers reduce mortality.

Patients should be started on a beta-blocker or have their existing dose adjusted to keep the resting heart rate at 50 to 60 beats/min. Intravenous beta-blockers should be considered in high-risk patients with rest pain and widespread ST-segment changes or tachycardia. The choice of beta-blocker should take into account the patient's characteristics and the pharmacologic profile and side effects of the particular agent. Esmolol (50 to 250 µg per kg per minute intravenously), which has an effect that lasts for only 20 to 30 minutes after discontinuation, can be considered for patients with relative contraindications. Standard contraindications include marked first- (>0.24 seconds), second-, or third-degree atrioventricular block, asthma, and severe left ventricular dysfunction. The degree of left ventricular dysfunction at which beta-blockers become contraindicated is not clearly defined, and they can and should be used in stable patients with heart failure provided that doses are carefully titrated. Therapy should be continued long term.

Nitrates

No large randomized trials of nitrates in unstable angina have been done, and there is no compelling evidence that these agents reduce the incidence of death/MI. They do, however, relieve angina.

Nitrates dilate normal and atherosclerotic epicardial coronary arteries and inhibit platelet-mediated thrombus formation. Their vasodilatory effect plays an important role in reducing the preload and afterload of the heart, and they are of particular value in patients with vasospasm or a physiologic increase in coronary artery tone. They reduce ischemia very effectively, but tolerance can develop within 24 hours.

Small doses or concomitant administration of the sulfhydryl donor, *N*-acetylcysteine, may augment the effect of nitroglycerin and decrease tolerance (221). Nitroglycerin should be given immediately, either as a sublingual tablet or spray, to relieve angina. If symptoms are not relieved, i.v. nitroglycerin can be infused to relieve pain and to optimize hemodynamics, commencing at an infusion rate of 5 to 10 µg per minute, with increases every 5 to 10 minutes depending on symptoms and side effects such as headache or hypotension. It is usually recommended that the infusion be decreased slowly, as abrupt cessation can precipitate ischemia. However, a study of 200 patients reported savings in nursing time and patient transfer time, with no compromise in safety, when i.v. nitroglycerin was discontinued abruptly as opposed to being tapered off with concurrent use of topical nitrates. To avoid tolerance, nitrate patches or oral therapy may be preferred, with nitrate-free periods of 6 to 10 hours.

Calcium Channel Antagonists

Calcium channel antagonists act as coronary artery dilators by reducing the cellular membrane influx of calcium. They have variable vasodilatory effects in peripheral arteries and negative inotropic, chronotropic, and atrioventricular conduction-slowing effects. They may also enhance diastolic relaxation and left ventricular compliance. Agents that increase the heart rate (e.g., short-acting nifedipine) may be associated with worse outcomes than those that reduce the heart rate (e.g., verapamil or diltiazem) (222,223).

Three trials have reported trends toward higher mortality when nifedipine was used alone (128,220,224). Short-acting nifedipine should therefore not be used as monotherapy except in patients who are suspected of having coronary artery spasm with ST-segment elevation during angina (225).

A study that compared diltiazem with propranolol found that both agents reduced the rates of death, MI, recurrent ischemia, and the need for CABG. In the HINT trial, the addition of nifedipine to standard therapy for unstable angina (including beta-blockers) was found to reduce symptoms of angina, the short-term risk of death/MI, and the need for CABG (225). Diltiazem has been shown to reduce the rates of reinfarction and refractory angina in patients with non–Q-wave MI (222,223).

Nicorandil, which has nitrate and potassium channel-opening effects, was compared with a placebo in 188 patients with unstable angina and found to reduce the incidence of recurrent ischemia but not death or MI (226).

Because there is a risk of excessive bradycardia or atrioventricular block when drugs such as verapamil or diltiazem are added to a beta-blocker, it may be appropriate to use dihydropyridines (e.g., nifedipine, amlodipine, or nicardipine) as combination therapy. If the patient cannot tolerate a beta-blocker, a non-dihydropyridine calcium channel antagonist with sinus node-slowing effects, such as diltiazem or verapamil, should be used.

Calcium channel antagonists should be used as needed in patients with ongoing ischemia despite beta-blocker and nitrate therapy or in combination with a beta-blocker if hypertension is present. Calcium channel antagonists should be avoided in patients with pulmonary edema or left ventricular dysfunction (222) but are the agents of choice in individuals with variant angina. The choice of agent should be based on the clinical profile of the patient and also depends on whether concomitant beta-blocker therapy is prescribed. Few published data are available evaluating the effects of newer agents on hard clinical end points.

Oral Anticoagulants

Because of their delayed onset of action, oral anticoagulants are not appropriate for acute treatment but can be considered for long-term use if aspirin is contraindicated. In an open, randomized controlled trial, warfarin [adjusted to an international normalized ratio (INR) of 2.0 to 3.0] reduced the incidence of cardiac events at 6 months from 34% to 12% ($p <.05$). Oral anticoagulants have also been shown to reduce the incidence of death/MI long term (227).

The use of low-dose oral anticoagulants together with aspirin has been disappointing. In the Coumadin Aspirin Reinfarction study of 8,803 patients (157), those who were given either 1 mg or 3 mg warfarin together with 80 mg aspirin 3 to 21 days after MI had similar outcomes to those given 160 mg aspirin alone. In the National Heart, Lung, and Blood Institute's Post Coronary Artery Bypass Graft trial (228), 1,351 patients who had undergone CABG between 1 and 11 years previously were randomized to receive either a placebo or low-dose warfarin with a target INR of 1.8 to 2.0. However, the anticoagulation target was frequently not achieved. Warfarin had no effect on the incidence of angiographic progression (defined as a decrease in minimal luminal diameter of 0.6 mm or more), which occurred in 32.5% of the placebo group and 34.2% of the warfarin group (p = NS).

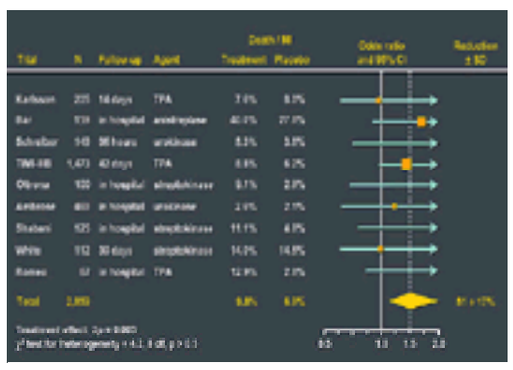
In the Stroke Prevention in Atrial Fibrillation (SPAF) III trial, 1,044 patients with atrial fibrillation and at least one thromboembolic risk factor (namely, a systolic blood pressure of greater than 160 mm Hg, prior thromboembolic events, poor left ventricular function, or being a women older than 75 years) were assigned to receive either 325 mg aspirin plus low-dose warfarin (with a target INR of 1.2 to 1.5, achieved in 55% of follow-up measurements) or adjusted-dose warfarin (target INR, 2.0 to 3.0, achieved in 60%). At 1.1 years, the incidence of ischemic stroke/systemic embolism was 7.9% per year in the patients who took aspirin plus low-dose warfarin versus 1.9% per year in those who took standard-dose warfarin alone (p <.0001) (229). Low-dose oral anticoagulants have therefore been tested with and without aspirin in three studies of different cardiac syndromes (157,228,229) but were found to be ineffective.

The ATACS trial randomized 214 patients with unstable angina or non–Q-wave MI to receive either aspirin (162.5 mg per day) or aspirin plus heparin (adjusted to an APTT of twice control) followed by warfarin (adjusted to an INR of 2.0 to 3.0) (193). At 12 weeks, the patients who were given combination therapy had a lower incidence of death/MI/recurrent angina with ECG changes (19% vs. 28%, p = .09) but a slightly higher incidence of bleeding complications.

In the Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot study (230), 309 patients who had received 3 days of unfractionated heparin or hirudin were randomized to receive aspirin with or without warfarin, with a target INR of 1.5. At 6 months, cardiovascular death/MI/refractory angina had occurred in 5% of patients who were given aspirin plus warfarin versus 3.9% of those given aspirin alone (p = .31). In phase II of this study, the target INR was 2.0 to 2.5, and the rates of the same composite end point were 5% in patients who were given aspirin plus warfarin versus 12.1% in those given aspirin alone (p = .08).

Thrombolytic Therapy

Thrombolytic therapy is not recommended for routine use in patients with unstable angina because it has been shown to increase the rate of MI (231). It is known to improve survival and left ventricular function in patients with ST elevation or bundle branch block pattern on their admission ECG (232), when occlusive coronary artery thrombus is usually present (233). Most patients with recent prolonged pain and ST depression on the ECG also have intracoronary thrombus, but it is usually nonocclusive (14,233,234). Thrombolytic therapy has been shown to decrease the amount of intracoronary thrombus (234), but in a heterogeneous group of patients with unstable angina it was found to increase the incidence of MI by 50% (122,235,236,237,238,239,240 and 241) (*e*Fig. 17.11.2).



***e*FIGURE 17.11.2** Metaanalysis of death/myocardial infarction (MI) in trials comparing thrombolytic therapy with a placebo in patients with unstable angina (122,235–241). CI, confidence interval; df, degrees of freedom; SD, standard deviation; TPA, tissue plasminogen activator.

The Fibrinolytic Therapy Trialists' overview (232) of the Second and Third International Studies of Infarct Survival (ISIS-2 and ISIS-3) (242,243), the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-1) study (244), and the Late Assessment of Thrombolytic Efficacy (LATE) study (245), which included 3,563 patients with ST depression, reported mortality rates of 15.2% in patients who received thrombolytic therapy and 13.8% in those receiving control therapy. (The 95% CI ranged from a 12% reduction to a 44% increase in mortality.) Within this heterogeneous group, there may be a subgroup of patients who would benefit from thrombolytic therapy. For example, approximately 30% of patients with thrombotic occlusion of a circumflex artery do not have ST elevation that fulfills the usual eligibility criteria for thrombolytic therapy (246,247,248 and 249), but they may well benefit from thrombolysis.

Why might thrombolytic therapy be harmful? First, in patients with ST depression and a patent ischemia-producing artery, it is unlikely that thrombolytic therapy would improve perfusion, and thus the concomitant risk of bleeding outweighs the possibility of benefit. Second, thrombolytic therapy is procoagulant in that platelets are activated by the generation of plasmin (250) and by exposure of clot-bound thrombin (251). These procoagulant effects could make a nonocclusive thrombus become occlusive, thereby increasing the risk of MI. Third, hemorrhage into a plaque could also theoretically elevate the plaque and exacerbate the coronary artery stenosis. Besides these adverse effects, thrombolytic therapy may be less effective in these patients because their thrombi are relatively platelet rich (14).

A post hoc analysis of the LATE study revealed an unexpected finding. Patients with confirmed MI who presented initially with ST depression of greater than 2 mm had a significant reduction in mortality at 1 year when tissue plasminogen activator was administered 6 to 24 hours after symptom onset (20.1% vs. 31.9%, p <.01) (252). This suggests that further trials should be conducted to examine the effect of thrombolytic therapy in specific subgroups. Meanwhile, thrombolytic therapy is not recommended for routine use in patients with unstable angina (231).

Intraaortic Balloon Counterpulsation

Intraaortic balloon pump counterpulsation (IABP) stabilizes patients and relieves symptoms very effectively (253). By increasing aortic diastolic pressure, coronary blood flow is improved distal to critical stenoses, and there is a decrease in myocardial oxygen demands due to reduction of afterload. No randomized trials of IABP have been done in patients with unstable angina.

A randomized trial of IABP for 48 hours in 182 patients who had infarct artery patency restored by thrombolytic therapy or by primary or rescue PCI found that there was less reocclusion at 5 days (8% vs. 21% in control patients, p <.03) (254). The Second Primary Angioplasty in Myocardial Infarction (PAMI-II) trial showed that IABP after primary PCI was safe and improved clinical outcomes in patients with multiple high-risk features such as an age of greater than 70 years and an ejection fraction of less than 45% (255). IABP should be considered in patients with refractory symptoms or hemodynamic instability to stabilize the patient on the way to the cardiac catheterization room or operating room (1).

Indications for Angiography

Coronary angiography determines the extent and severity of coronary artery disease and may detect thrombus. Assessment of valvular and left ventricular function can be performed at the same time. The information obtained is a useful indicator of prognosis and determines the choice of revascularization strategy. Patients who are more likely to have severe coronary artery stenoses, multivessel disease, or left main stenosis can be identified by ECG changes (71) or a recent history of rest angina (135,136). Angiography is not normally performed if revascularization is contraindicated due to comorbidity.

Possible indications for angiography (other than as part of an aggressive treatment strategy) are listed in *e*Table 17.4.2.

***e*TABLE 17.4.2** INDICATIONS FOR ANGIOGRAPHY
Suspicion of left main coronary artery disease
Two ischemic episodes of ³5 min
Pain lasting ³20 min
³1-mm ST-depression or T-wave inversion while on heparin with a therapeutic activated partial thromboplastin time

[3]2-mm ST-depression or T-wave inversion with or without pain
Pain with development of pulmonary edema, mitral regurgitation, or hypotension
Percutaneous coronary intervention within 6 mo
Previous coronary artery bypass graft
Significant ventricular arrhythmias
Impaired left ventricular function
Abnormal stress testing at the nonacute stage
Diagnosis of coronary artery disease in a patient with atypical symptoms

Revascularization

Despite the effectiveness of aspirin, heparin, and beta-blockers, refractory angina that requires an intervention commonly develops in patients with unstable angina (122,154,190,193). The FRISC II study (69) and the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) trial (70) have shown that patients at high risk should undergo interventions (1,80).

In the second Montreal study of aspirin and heparin (190), refractory angina occurred in 23% of patients who received nitrates, beta-blockers, or calcium channel blockers versus 9.6% of those receiving heparin. Such events commonly occur in the first 72 hours after admission (190). If refractory ischemia develops, the risk of MI rises ninefold and the risk of death eightfold (137).

The Duke Databank of outcomes in 6,200 patients with coronary artery disease who were treated with either PCI or CABG from 1984 through 1990 (256) showed that the interventions achieved similar 3-year survival rates in those with single- or double-vessel disease without a critical proximal left anterior descending artery stenosis. CABG achieved better survival rates in patients with triple-vessel disease or double-vessel disease with a critical proximal left anterior descending artery stenosis. PCI may be more appropriate for patients with single- or double-vessel disease because it is less invasive, less expensive, requires less time in the hospital and for rehabilitation, carries fewer risks of complications such as strokes, and preserves arterial and venous conduits for potential future use (257). In patients with triple-vessel disease, CABG achieves more complete revascularization and consequently better initial relief of symptoms (258,259).

Percutaneous Coronary Intervention

PCI techniques have evolved rapidly over the past several years, particularly with the advent of stenting and the use of adjunctive therapies such as IIb/IIIa antagonists and thienopyridines. A 1994 review of PCI procedures performed before the use of these therapies found a 90% success rate in patients with unstable angina, although their restenosis and complication rates were higher than in those with chronic stable angina (260). The rates of MI ranged from 5.1% in patients with unstable angina that had stabilized to 6.3% in those with early postinfarction angina. Emergency CABG was required in 5.8% of stabilized patients and 6.5% of those with postinfarction angina.

A subanalysis of 857 patients with unstable angina in the 1985–1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry showed that after adjustment for risk factors, the adverse event rates were similar in different subgroups such as patients with or without rest pain and those with new-onset angina, accelerating angina, or acute coronary insufficiency (261).

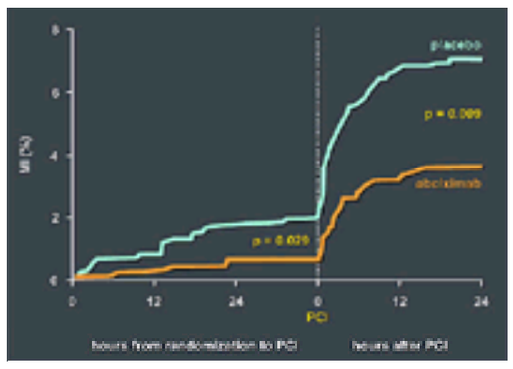
Higher complication rates have been observed when PCI is performed within 1 to 2 weeks after the onset of unstable angina (260,262,263,264 and 265). Abrupt closure was previously reported as being more common in patients with intracoronary thrombus (262). The presence of thrombus is no longer regarded as a contraindication against stenting (266). Complex coronary artery stenosis is a risk factor for abrupt closure (264,267,268,269,270 and 271).

Several studies have reported that abrupt closure was treated effectively with thrombolytic therapy and redilation (272,273,274 and 275). However, in the Thrombolysis and Angioplasty in Unstable Angina (TAUSA) trial, prophylactic administration of urokinase before PCI in patients with complex lesions actually caused higher rates of abrupt closure (15.0% vs. 5.9% with placebo, $p < .05$).

An infusion of i.v. heparin for 24 hours or longer before PCI may reduce the rates of abrupt closure and improve procedural success rates (276), particularly in patients with intracoronary thrombus (277). The TIMI IIIB trial reported similar complication rates in patients randomized to undergo an early revascularization procedure (18 to 48 hours after randomization) and in those who were treated conservatively and required revascularization after an initial stabilization period of aspirin and heparin. The procedural success rates were 96% in both groups. MI occurred in 2.9% and 3.6%, respectively, and emergency CABG was performed in 0.7% and 0.5%, respectively (122). A small study of high-risk patients with unstable angina found no advantage in delaying PCI for 3 to 7 days (278).

Stenting has improved patient outcomes (279,280,281 and 282), with low rates of abrupt closure when intravascular ultrasound guidance (283,284) or high deployment pressures are used (282). A small study of 105 patients with unstable angina or chronic stable angina found that the rates of acute complications or restenosis were similar in the two groups (285). It is therefore likely that the complication rates in patients with unstable angina in the current era are lower than in earlier reports. Culprit-lesion PCI on its own is appropriate in patients who are at risk of abrupt closure and in those who have an ischemia-producing artery that supplies a large territory. However, this may result in incomplete revascularization, meaning that another revascularization procedure may subsequently be required (286). If PCI is indicated on clinical grounds, the procedure should be performed expeditiously while the patient is receiving heparin, with adjunctive use of a thienopyridine and a IIb/IIIa antagonist (88,161,165,166,168,169,177,184).

Although PCI improves coronary flow by reducing the coronary artery stenosis, it is associated with periprocedural MI (eFig. 17.11.3) due to obstruction of branch vessels or distal embolization of plaque material and microvascular injury, or both. Acute thrombotic closure and MI associated with PCI are more common in patients with non–ST-elevation acute coronary syndromes than in those who are undergoing elective interventions (287,288). Furthermore, PCI may not treat the unstable plaques that cause the clinical syndrome, which may be non-flow limiting (289) and multiple (290). Revascularization is not recommended unless the benefits are likely to outweigh the risks.



***e*FIGURE 17.11.3** Incidence of myocardial infarction (MI) during treatment with abciximab or placebo before and in association with percutaneous coronary intervention (PCI). (Redrawn from The CAPTURE investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;349:1429–1435, with permission.)

In the OASIS registry, which compared revascularization rates in six countries, the countries with higher revascularization rates (Brazil and the United States) had higher bleeding and stroke rates (odds ratio, 3.0; $p = .012$)—but not lower rates of cardiovascular death or MI—than the countries with lower revascularization rates (Australia, Canada, Hungary, and Poland). A comparison of outcomes in Canadian and U.S. GUSTO IIB patients with non–ST-elevation acute coronary syndromes showed that angiography and revascularization were more common (49% vs.25%) and performed sooner in the United States than in Canada (291). The length of hospital stay was 1 day longer in Canada. At 6 months, the Canadian patients had higher rates of MI (8.8% vs. 5.8%, $p = .04$) and death/MI (13.1% vs. 9.1%, $p = .02$). The outcomes did not differ in patients with non–ST-elevation MI.

Six trials have compared an invasive treatment strategy with a conservative treatment strategy in which patients underwent revascularization procedures only if recurrent or inducible ischemia developed (Fig. 17.12). Four of these trials were conducted exclusively in patients with non–ST-elevation acute coronary syndromes (69,70,122,292), one was conducted in patients with postinfarction ischemia (293), and one was conducted in patients with ST elevation or depression (294). In one of

these trials, early PCI did not reduce the incidence of death/MI at 1 year (122). In two trials a conservative strategy was better (292,294), and three trials favored an invasive strategy (69,122). Both approaches are therefore supported by clinical trial evidence, but the weight of evidence, including recent trials that are relevant to contemporary practice, suggests that patients at higher risk do better with an invasive strategy.

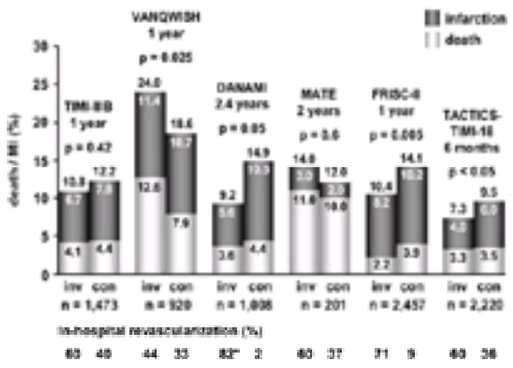


FIGURE 17.12 Rates of death/myocardial infarction (MI) at various time points in six trials comparing invasive (inv) with conservative (con) medical management in patients with acute coronary syndromes. Four of these trials were conducted in patients with non–ST-elevation acute coronary syndromes (69,70,122,292), one was conducted in patients with postinfarction angina (293), and one was conducted in patients with either ST elevation or ST depression who were ineligible for thrombolytic therapy (294). *At 2 months. DANAMI, Danish Trial in Acute Myocardial Infarction; MATE, Medicine versus Angiography in Thrombolytic Exclusion; VANQWISH, Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital.

The percentage of patients in these trials who were randomized to receive conservative treatment but then underwent revascularization procedures varied from 2% (293) to 40% (294) (Fig. 17.12). In some of the trials, there was little difference in revascularization rates between the invasive and conservative treatment groups; for example, in the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial, revascularization was performed in 33% of the conservative treatment group and 44% of the invasive treatment group. In the TIMI IIIB trial, the rates were 40% and 60%, respectively. In contrast, only 9% of the conservative treatment group in the FRISC II study underwent revascularization, as opposed to 71% of the invasive treatment group.

In the TIMI IIIB trial (122), 1,473 patients who presented within 24 hours of the onset of chest pain with ECG changes or previously documented coronary artery disease were randomized to undergo either conservative management or coronary angiography at 18 to 48 hours and PCI or CABG as appropriate. Patients in the conservative group underwent revascularization only for angina and 2 mm or greater of ST depression in two leads, pain lasting 20 minutes or more, or two anginal episodes that lasted 5 minutes or more with ECG changes of T-wave inversion or 1 mm or greater of ST depression in two leads, more than 20 minutes of ischemic (0.1 mm or more) ST deviation on a 24-hour Holter monitor recording, or an unsatisfactory predischarge stress thallium before completing stage II of a modified Bruce protocol. The rates of death and MI were similar in both groups, but the invasive strategy was found to reduce the rate of hospital readmissions from 14.1% to 7.8% (p <.001) and the incidence of death/MI from 14.8% to 7.9% (p = .05) in patients over the age of 65 years (122). Death, MI, or an unsatisfactory symptom-limited exercise stress test at 6 weeks occurred in 18.1% of the conservative treatment group and 16.2% of the invasive treatment group (p = NS). eTable 17.4.3 shows the components of this composite end point, with data on rehospitalization, antianginal therapy, and symptomatic class, all of which favored an early invasive strategy. At 42 days, 49% of patients in the conservative limb had undergone revascularization versus 61% in the early invasive limb.

***e*TABLE 17.4.3** OUTCOMES AT 6 WEEKS IN PATIENTS WITH NON–ST-ELEVATION ACUTE CORONARY SYNDROMES MANAGED EITHER INVASIVELY OR CONSERVATIVELY IN THE TIMI IIIB TRIAL

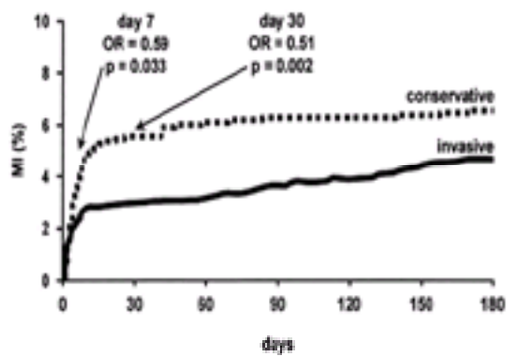
	Early invasive treatment (n = 740)	**Early conservative treatment (n = 733)**	***p***
Death	2.4%	2.5%	
Nonfatal MI	5.1%	5.7%	
Positive exercise test	8.6%	10%	
Initial hospitalization period	10.2 d	10.9 d	.01
Patients rehospitalized	7.8%	14.1%	<.001
Rehospitalization period	365 d	930 d	<.001
Antianginal medications			
0	19.3%	17.0%	.02
1	37.0%	31.0%	.02
2	25.5%	28.3%	.02
3	18.3%	23.7%	.02
Angina			
No angina	76.0%	71.4%	.02
CCS class I or II angina	16.4%	19.1%	.02
CCS class III or IV angina	7.6%	9.5%	.02

CCS, Canadian Cardiovascular Society classification (363); MI, myocardial infarction.
Adapted from the TIMI IIIB investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non–Q-wave myocardial infarction: results of the TIMI IIIB trial. *Circulation* 1994;89:1545–1556, with permission.

The Danish Trial in Acute Myocardial Infarction (DANAMI) (293) compared invasive treatment with conservative treatment in 1,008 patients under the age of 70 in whom postinfarction ischemia developed after they received thrombolytic therapy [namely, Braunwald class C angina (4)], including silent ischemia in 56.5% and exercise-induced ischemia in 28%. The incidence of MI was reduced by almost 40% (from 14.9% to 9.2%, p = .05) in the invasive treatment group.

In the VANQWISH trial, most of the mortality excess among patients who underwent early CABG was perioperative (11.6%). This may have been due to the urgency of the operation, as acuity is known to be one of the most powerful predictors of a poor outcome after CABG (295). The operative mortality among patients whose CABG was not performed acutely was 3.4%. At 23-month follow-up, there was no difference between the groups.

The FRISC II study (296) showed that intervention was beneficial after an initial period of dalteparin treatment (4 days in patients undergoing PCI and 7 days in those undergoing CABG). As noted above, the rate of inhospital revascularization in the conservative group (9%) was very low. The invasive group had a higher incidence of MI than the conservative group during the first month because of periprocedural events (eFig. 17.12.1) but a lower incidence from then on. At 6 months, the incidence of angina was reduced from 39% to 22% and hospital readmission rates from 49% to 31% (both p <.001). At 1 year, the mortality was reduced from 3.9% to 2.2% (p <.02), MI from 11.6% to 8.6% (p = .02), and readmissions from 57% to 37% (p <.001). The patients in FRISC II were at high risk, with 57.5% having elevated troponin T levels and 45.5% having ST depression. In addition, the angiograms of patients with ST depression showed that 13% of the invasive treatment group had left main coronary artery disease and 33% had triple-vessel disease—both of which are better treated with revascularization (297). The patients who benefited most from revascularization were those (n = 756) with ST depression and elevated troponin T levels (more than 0.03 mg per L) (87). No significant benefit was found in patients who had ST depression with normal troponin T levels (n = 301) or in patients who had elevated troponin T levels without ST depression (n = 800).



***e*FIGURE 17.12.1** Cumulative incidence of myocardial infarction (MI) within 6 months in patients treated conservatively or invasively in the TACTICS–TIMI 18 trial (70).

OR, odds ratio.

Based on these findings, the European Society of Cardiology Task Force (80) concluded that a modern invasive strategy preceded by modern antiischemic and antithrombotic medication in moderate- to high-risk patients with unstable coronary artery disease reduces death, MI, symptoms, and readmissions compared with a conservative strategy (evidence level B). The high-risk population was defined by the presence of arrhythmias, hemodynamic instability, recent MI, anginal instability, or prior CABG. The ACC/AHA guidelines (1) list a class I recommendation (indicating that intervention is useful and effective) for an invasive approach in patients with recurrent ischemia at rest despite intensive antiischemic therapy, recurrent ischemia with congestive heart failure or mitral regurgitation, high-risk findings on noninvasive testing, depressed left ventricular systolic function, hemodynamic instability, sustained ventricular tachycardia, PCI within 6 months, or prior CABG.

The TACTICS-TIMI 18 trial (70) enrolled 2,220 patients who presented with unstable or minimal-effort angina and ECG changes, elevated troponins, or a history of prior MI, PCI, or CABG, that is, largely intermediate/high-risk patients according to the ACC/AHA guidelines (1). The patients received heparin, aspirin, and tirofiban for 48 to 108 hours and were randomized to undergo either conservative or invasive treatment. Patients in the invasive treatment group underwent catheterization between 4 and 48 hours and were revascularized if their anatomy was suitable, whereas those in the conservative treatment group did not undergo revascularization procedures unless they had refractory angina (more than 10 minutes of rest pain with ECG changes), hemodynamic instability, a positive exercise test or stress echocardiogram, new MI, hospitalization with unstable angina, or class III or IV angina. The study prospectively evaluated the TIMI risk score (111) and the use of troponin levels in determining the optimal treatment strategy. The primary end point was a composite of death/MI/rehospitalization for an acute coronary syndrome during 6 months of follow-up.

During the initial hospital admission, 97% of the invasive group and 51% of the conservative group underwent cardiac catheterization. In the invasive group, the mean duration of the tirofiban infusion before catheterization was 24 hours, and 41% of patients underwent PCI, 19% had CABG, and 40% had no intervention. The 30-day mortality in patients who underwent CABG was 3.5%. In the conservative group, 36% of patients underwent revascularization procedures during the initial hospital admission. Although there was no difference in mortality at 6 months between the two groups, the incidence of death/MI/rehospitalization was reduced from 19.4% in the conservative group to 15.9% in the invasive group (odds ratio, 0.78; p = .025)(Fig. 17.13). Periprocedural MI was not increased among patients who were pretreated with tirofiban (*e*Fig. 17.12.1), unlike the FRISC II findings with dalteparin (69). The length of hospital stay was 1 day shorter in the invasive group (mean 7.4 days).

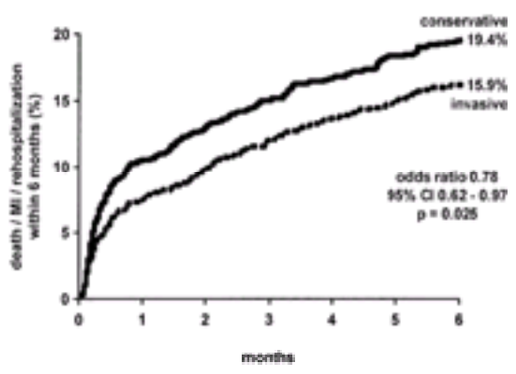
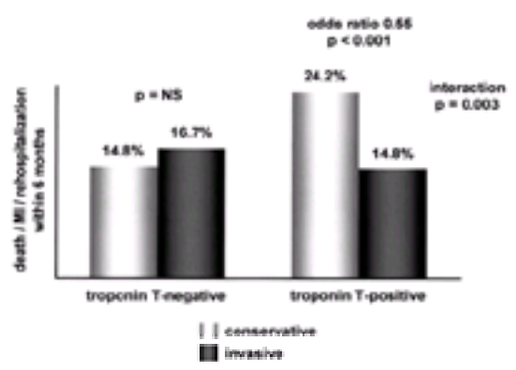


FIGURE 17.13 Cumulative incidence of death/myocardial infarction (MI)/rehospitalization for an acute coronary syndrome within 6 months in patients who were managed either conservatively or invasively in the TACTICS–TIMI 18 trial. CI, confidence interval. (Redrawn from Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879–1887. Copyright © 2001, Massachusetts Medical Society. All rights reserved, with permission.)

Invasive treatment was beneficial in patients with elevated troponin levels and in those with ST depression, reducing their rates of death/MI/rehospitalization from 24.2% to 14.3% (*e*Fig. 17.13.1) and from 26.3% to 16.4%, respectively—but not in patients with a low TIMI risk score of 0 to 2, who represented 25% of the study cohort. The odds ratios for death/MI/rehospitalization were 0.76 (95% CI, 0.57 to 1.00) in patients at intermediate risk and 0.56 (95% CI, 0.33 to 0.95) in those at high risk.



***e*FIGURE 17.13.1** Rates of death/myocardial infarction (MI)/rehospitalization for an acute coronary syndrome within 6 months in troponin–T-positive and -negative patients in the TACTICS–TIMI 18 trial (70).The troponin T cutoff point was 0.01 ng per mL, and 54% of patients tested positive for troponin T. NS, not significant.

In view of the TACTICS-TIMI 18 findings, early invasive treatment should be considered in high-risk patients after treatment with aspirin, unfractionated heparin, and a small-molecule IIb/IIIa antagonist for 4 to 48 hours. If catheterization facilities are not available, high-risk patients should be started on aspirin, unfractionated heparin, and a IIb/IIIa antagonist and then transferred to an appropriate center. An alternative approach for high-risk patients would be to transfer them promptly to a catheterization facility (preferably within 4 hours) (1) and to administer abciximab or eptifibatide if PCI is performed. The superiority of either approach is yet to be determined in clinical trials.

A powerful motivation for an early revascularization strategy is the evidence showing that patients can be discharged earlier and that readmissions are reduced (122,298). Hospital beds can thus be used more efficiently. In TACTICS-TIMI 18, inhospital costs were higher in patients who were treated invasively, but follow-up costs were higher in those treated conservatively; consequently, at 6 months there was no difference in cost between the invasive and conservative strategies (298). Intervention was most cost effective in patients with elevated troponin levels, ST depression, or diabetes. Angina scores, as measured by the Seattle Angina Questionnaire, improved in both treatment groups and were no different at 6 months.

Coronary Artery Bypass Grafting

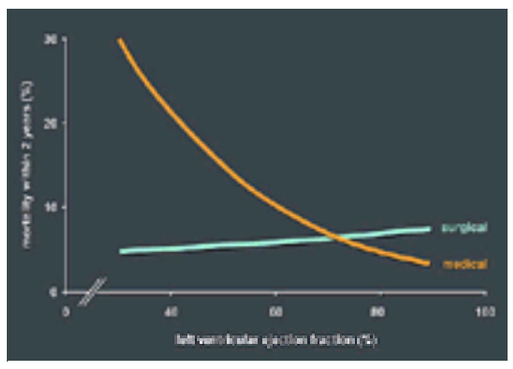
CABG is an excellent therapy for relieving angina and was an important component of the FRISC II and TACTICS-TIMI 18 trials, being performed in 35% of the invasive group in FRISC II (69) and in 20% of the invasive group in TACTICS-TIMI 18 (70). Both trials reported that revascularization was beneficial.

Early studies in unstable angina reported that the mortality at 1 year was 20% in patients who were managed without revascularization procedures (299). More recent studies have reported lower mortality rates but with considerable crossover of patients from medical therapy to revascularization procedures. Most randomized trials evaluating CABG have excluded patients with severe symptoms and have also involved substantial crossover of patients from medical treatment to CABG (300).

In the National Cooperative Study Group trial of 242 men and 46 women, 19% of patients who were randomized to the initial medical strategy had crossed over to

CABG by 1 year (301). The mortality was similar in both groups at 30 months.

The Veterans Administration Cooperative Study compared CABG with medical therapy in 468 men with ejection fractions of 30% or greater (302,303,304 and 305). By 2 years, 34% of those randomized to receive medical treatment had crossed over to CABG, and the mortality was similar in the two groups. At 5 years, the mortality among patients with triple-vessel disease was 11% in the CABG group and 25% in the medical therapy group ($p < .05$) (306). In the medical therapy group, patients with lower ejection fractions tended to have a higher mortality ($p < .01$), but there was no association between impairment of left ventricular function and mortality in the CABG group (eFig. 17.13.2).



***e*FIGURE 17.13.2** Mortality at 2 years according to the left ventricular ejection fractions of patients randomized to receive initial medical therapy or initial surgical therapy. (Redrawn from Luchi RJ, Scott SM, Deupree RH, et al. Comparison of medical and surgical treatment for unstable angina pectoris: results of a Veterans Administration cooperative study. *N Engl J Med* 1987;316:977–984. Copyright © 1987, Massachusetts Medical Society. All rights reserved, with permission.)

CABG was an important component of the FRISC-II and TACTICS-TIMI 18 trials, being performed in 35% of the invasive group in FRISC-II (69) and in 20% of the invasive group in TACTICS-TIMI 18 (307). Both trials reported that revascularization was beneficial.

Unstable Angina after Percutaneous Coronary Intervention

If angina develops in the first 6 months after PCI, it is likely that restenosis has occurred at the PCI site. Angiography should be performed expeditiously and repeat revascularization if indicated. Intravenous nitroglycerin has been shown to be superior to antithrombotic therapy in preventing recurrent or refractory angina in nonstented patients without restenosis (308).

Unstable Angina after Coronary Artery Bypass Grafting

In the first 12 months after CABG using venous conduits, 10% to 15% of grafts occlude due to technical reasons and fibroproliferation with or without superimposed thrombus formation (309). Internal mammary artery grafts have better long-term patency rates (approximately 92%) (310) but are also vulnerable to early stenosis. Long-term, late graft disease occurs as a result of atherosclerosis and superimposed thrombosis (311). Progression of atherosclerosis also occurs in the native coronary arteries.

Patients with unstable angina and subtotally occluded bypass grafts have a high risk of thrombotic occlusion, which is very difficult to treat. If important symptoms of angina develop, particularly with ischemic ST-segment changes in the distribution of a vein graft, the patient should undergo expeditious angiography to define the anatomy and to determine appropriate treatment. PCI with stenting may prevent occlusion of a vein graft with a severe stenosis, thereby avoiding reoperation and its associated risks. Unfortunately, progressive disease frequently occurs in nonstented segments of the vein graft within 2 years (312).

The Case for Conservative Management in Low- and Intermediate-Risk Patients

The good prognosis of many patients with unstable angina may justify a conservative treatment strategy provided that troponin levels are not elevated, symptoms settle, and left ventricular function is normal. Many patients can be managed with antithrombotic and antianginal therapy without the need for revascularization. For example, 40% of patients in TACTICS-TIMI 18 (70) and 46.5% of those in PRISM-PLUS (90), which encouraged angiography in everyone, were managed without the need for revascularization.

The aim of medical management is to passivate the plaque. Subsequent management can be based on the amount of inducible ischemia rather than the presenting clinical features and coronary arteriographic findings. If the symptoms settle, exercise testing, stress echocardiography, or dipyridamole sestamibi imaging can be performed to assess the hemodynamic significance of the residual coronary artery stenosis. Testing should be delayed until 24 to 48 hours after the last episode of angina. However, noninvasive stress testing does not predict plaque instability or the risk of future MI, and therefore it is important that patients are seen for review and instructed to report any continuing symptoms.

Early Lipid Lowering

The European (313), U.S. (314), and British guidelines (315) for the management of dyslipidemia in patients with ischemic heart disease recommend the use of lipid-lowering drugs only after diet and lifestyle modifications have been attempted. They do not recommend early drug treatment when patients are admitted with an acute coronary syndrome.

The concept that lipid lowering may stabilize plaques is supported by numerous statin trials showing that therapy reduces the risk of clinical events when used in secondary prevention, despite only modest angiographic reductions in the severity of coronary artery stenoses (316,317). The risk of death in patients with acute coronary syndromes is highest early after the onset of an acute coronary syndrome (1), but to date no randomized trials have shown whether survival is improved by early statin therapy. In the trials of longer-term statin therapy in patients with coronary artery disease, survival has been significantly improved, but in the Scandinavian Simvastatin Survival Study (4S) (318) and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study (319) it was 1 to 2 years before the event curves began to diverge. The times to enrollment were 6 months after MI in 4S and 3 months after MI or hospital admission with unstable angina in LIPID.

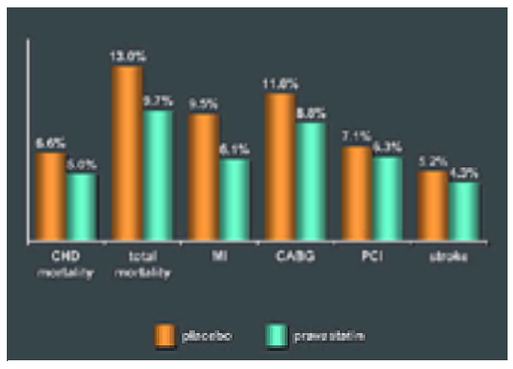
Statins have a number of pleotrophic effects that could result in better clinical outcomes independently of lipid changes in patients with acute coronary syndromes. A number of statin trials have reported rapid improvements in endothelial function (320,321,322 and 323), suggesting that statins may restore the vasodilatory properties of the endothelium in patients with coronary artery disease. In the Reduction of Cholesterol in Ischemia and Function of the Endothelium (RECIFE) study (320), pravastatin improved endothelial function within 6 weeks. Coronary flow reserve, as assessed by positron emission tomography, has been shown to be improved at 4 to 6 months in patients who are given statins (324,325 and 326), and a reduction in ischemia with statin therapy has been demonstrated on continuous ST-segment monitoring (323). However, some studies have found no reduction in ischemia with statin therapy (327). Statins have been shown to reduce the levels of inflammatory markers such as C-reactive protein (105) and may suppress inflammatory cell activity (328) and reduce thrombus formation (329).

A number of registries and retrospective studies have provided evidence that early lipid lowering may be beneficial. A Swedish registry of more than 12,000 patients reported a reduction in mortality in patients who received early lipid-lowering therapy, but despite adjustments for known baseline differences between the groups, a selection bias (e.g., the use of statins in lower-risk patients) cannot be excluded. A retrospective analysis from the PURSUIT trial also revealed a significant reduction in 6-month mortality in patients who were given lipid-lowering agents ($p < .001$) (330).

In a retrospective analysis of 12,630 GUSTO IIB patients with ST-elevation or non–ST-elevation acute coronary syndromes, the 6-month mortality (adjusted for other variables) was reduced by 52% in those who received lipid-lowering drugs (relative risk 0.48, 95% CI, 0.28 to 0.83) (330). In a retrospective analysis of 1,616 PRISM patients, the incidence of death/MI at 30 days was significantly lower in those who were continued on statin therapy ($p < .01$) (331).

In the LIPID study, 9,014 patients with an acute MI or a hospital discharge diagnosis of unstable angina 3 to 36 months previously and total cholesterol levels of 4.0 to 7.0 mmol per L were randomized to receive either pravastatin (40 mg per day) or a placebo for 6 years. Approximately one-third of the cohort (3,260 patients) were included in the unstable angina stratum, and pravastatin reduced their relative risk of mortality by 26.3% (332) (eFig. 17.13.3). Overall, the patients who received

pravastatin also had significantly lower rates of coronary heart disease mortality, MI, need for revascularization, admission to the hospital, and number of drugs received in hospital. In absolute terms, pravastatin prevented 33 deaths, 24 nonfatal MIs, and 26 revascularization procedures per 1,000 patients treated for 6 years.



***e*FIGURE 17.13.3** Cardiovascular outcomes in patients treated with pravastatin or placebo for 6 years in the LIPID study. CABG, coronary artery bypass grafting; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention. (Modified from Tonkin AM, Colquhoun D, Emberson J, et al. Effect of pravastatin in 3260 patients with unstable angina: results from the LIPID study. *Lancet* 2000;356:1871–1875, with permission.)

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (333), 3,086 patients were randomized to receive either 80 mg atorvastatin or a placebo 1 to 4 days after presenting with an acute coronary syndrome. On average, atorvastatin increased high-density lipoprotein cholesterol levels by 4% and reduced total cholesterol by 27%, low-density lipoprotein cholesterol by 40%, and triglycerides by 16%. At 16 weeks, the incidence of death/MI/resuscitated cardiac arrest/worsening angina/urgent rehospitalization was reduced from 17.4% to 14.8% (p = .048), but there was no reduction in the need for revascularization. Early atorvastatin therapy was confirmed as being safe, with no episodes of myositis, although 2.5% of patients who were given atorvastatin developed elevated liver transaminases (three times the upper limit of normal) as opposed to 0.6% of patients given the placebo.

The ongoing A–Z study will determine in the A phase whether enoxaparin is more effective and safer than unfractionated heparin when combined with tirofiban. In the Z phase, early institution of simvastatin (40 mg per day for 30 days followed by 80 mg per day) will be compared with a placebo for 4 months, with all patients being placed on a step I AHA diet. The primary end point is a composite of cardiovascular death/MI/readmission for acute coronary syndromes with ECG changes or positive cardiac markers.

A major rationale for beginning lipid lowering early is that it emphasizes to the patient that therapy is important and needs to be continued long term. A low-fat diet alone is usually inadequate to achieve the recommended cholesterol targets in patients with coronary artery disease (334). Compliance and achievement of target levels may be improved if therapy is begun in conjunction with dietary advice while the patient is still in hospital.

Antiinflammatory Agents

Some survivors of MI have been shown to have elevated levels of *Chlamydia pneumoniae* antibodies, and these patients have worse outcomes (335). A pilot trial of roxithromycin in patients with unstable angina reported reductions in ischemic events at 30 days and at 6 months (336).

A small randomized trial compared 48 hours of methylprednisolone therapy with a placebo in 166 patients with unstable angina and reported a reduction in C-reactive protein levels, but no effect on short-term outcomes (337). Large-scale trials are currently under way to establish whether antibiotics or antiinflammatory agents will improve outcomes.

Secondary Prevention

Smoking cessation and treatment of dyslipidemia and hypertension are important secondary preventative measures in all patients with coronary artery disease. The risk of dying is five times greater if patients with unstable angina continue to smoke than if they quit.

Other measures that should be instituted after presentation with a non–ST-elevation acute coronary syndrome include achievement of ideal weight, a regular exercise program, an appropriate low-cardiovascular-risk diet, and achievement of optimal diabetic control where necessary. If facilities are available, patients should be referred to a cardiac rehabilitation program (338). Appropriate education should also be undertaken.

Pharmacologic measures are also indicated, such as aspirin, beta-blockers, lipid-modifying agents (see above), and ACE inhibitors in patients with decreased ejection fractions or another risk factor. The Heart Outcome Prevention Evaluation (HOPE) study (339), which excluded patients who had experienced MI within the previous 30 days, showed that the ACE inhibitor, ramipril, reduced the rate of cardiovascular death/MI/stroke from 17.8% to 14.0% (p <.001) over 5 years in patients older than 55 years with a history of vascular disease or diabetes with one other risk factor.

Strong evidence has now been found that better outcomes are achieved with higher usage rates of proven therapies (340). Compliance with published guidelines has been shown to reduce mortality in patients with acute MI (341) and also offers the potential to improve outcomes in patients with non–ST-elevation acute coronary syndromes if physicians adhere to their recommendations (1,2,80).

AGENTS IN DEVELOPMENT

Despite the variety of therapeutic options that are currently available, many coronary events still occur, and there is an ongoing need for new and better therapies. A number of new agents are currently in development for the treatment of vascular disease.

Direct Antithrombins

Heparin has a number of limitations. It requires monitoring, has a poor effect on fibrin and platelet-bound thrombin (342), requires antithrombin III, is inactivated by platelet secretion products such as platelet factor 4 and thrombospondin, and carries a risk of thrombocytopenia.

Direct antithrombins do not require antithrombin III as a cofactor and are barely affected by plasma proteins or platelet factor 4 (343). These agents also have a more predictable and consistent effect on the APTT than heparin and are able to inactivate clot-bound thrombin.

Hirudin

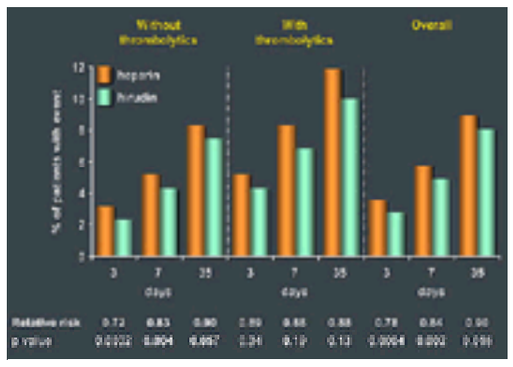
The prototypical agent is hirudin, a 65–amino acid peptide that is isolated from leech saliva. Topol et al. (344) randomized 166 patients with unstable angina to receive one of two different doses of heparin or one of four different doses of hirudin in a dose-escalating protocol. All patients had angiographic thrombus and stenoses of 60% or greater. A repeat angiogram at 72 to 120 hours showed a reduction in stenosis severity in the patients who were treated with hirudin, but there was no difference in the frequency of clinical end points.

In GUSTO IIB (133), 3,994 patients with acute ischemia without ST elevation were randomized to receive either heparin (5,000-IU bolus followed by 1,000 IU per hour) or hirudin (0.2-µg-per-kg bolus followed by 0.1 µg per kg per hour). Both infusions were adjusted to maintain an APTT of 50 to 75 seconds and continued for 75 hours. The patients who were treated with hirudin had a more consistent anticoagulant effect, and fewer required dosage adjustments. By 30 days, death had occurred in 3.4% of the heparin group and 3.7% of the hirudin group; MI in 6.4% and 5.6%, respectively; and intracranial hemorrhage in 0.02% and 0.2%, respectively (all p = NS). In the overall trial cohort of 12,142 randomized patients (including 4,131 with ST elevation), death/MI occurred within 30 days in 9.8% of the heparin group and 8.9% of the hirudin group (p = .006). The study was not sized to determine effects in the subgroup of patients without ST elevation.

In OASIS-2 (345), 10,141 patients who presented within 12 hours of the onset of suspected unstable angina or non–ST-elevation MI were randomized to receive either heparin (5,000-IU bolus and 15-IU/kg-per-hour infusion) or hirudin (0.4-mg-per-kg bolus and 0.15-mg-per-kg-per-hour infusion) for 72 hours. The doses were adjusted

to maintain an APTT of 60 to 100 seconds. The use of aspirin (80 to 325 mg per day) was recommended. By the end of the infusion at 72 hours, death/MI had occurred in 2.6% of patients who received heparin and 2.0% of those receiving hirudin (relative risk, 0.76; 95% CI, 0.59 to 0.99, $p = .039$). At 7 days, the rates were 4.2% and 3.6%, respectively (relative risk, 0.84; 95% CI, 0.69 to 1.02; $p = .077$), and at 35 days, 7.7% and 6.8%, respectively (relative risk, 0.87; 95% CI, 0.75 to 1.01; $p = .06$). Cardiovascular death/MI/refractory angina occurred within 72 hours in 4.0% of patients who were given heparin and 3.2% of those given hirudin (relative risk, 0.78; 95% CI, 0.63 to 0.96; $p = .019$) and at 7 days in 6.7% and 5.6%, respectively (relative risk, 0.82; 95% CI, 0.70 to 0.96; $p = .0125$). Minor and major bleeding were more common in patients given hirudin, but there was no difference in the incidence of life-threatening bleeding or bleeding that required surgical intervention, although the rates of intervention were low compared with those in the United States.

A metaanalysis of trials involving patients with non–ST-elevation acute coronary syndromes showed that hirudin reduced the incidence of death/MI by 20% during the treatment period (from 4.6% to 3.7%; odds ratio, 0.80; 95% CI, 0.70–0.92) (346) (eFig. 17.13.4).



***e*FIGURE 17.13.4** Pooled analysis of all large trials comparing hirudin with heparin in acute ischemic syndromes. The data for comparison in patients not receiving thrombolytics are based on the OASIS pilot (350), OASIS-2 (345), and GUSTO IIB (133) trials. The data for comparison in patients receiving thrombolytics came from TIMI 9B (364) and GUSTO IIB (365). The data are presented for the first 72 hours (the usual treatment period), 7 days, and 30 days (GUSTO IIB and TIMI 9B) or 35 days (OASIS). [Redrawn from Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularization procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999;353:429–438, with permission.]

Bivalirudin

Bivalirudin (formerly known as *Hirulog*) is a synthetic 20–amino acid peptide with a shorter half-life than hirudin (36 minutes as opposed to 2.3 hours) (347). The efficacy of escalating doses was evaluated in a study of 55 patients with unstable angina (348). Anginal symptoms were controlled in most patients, and there were no deaths, MIs, or bleeding complications.

The TIMI 7 trial randomized 410 patients with unstable angina to receive one of four different doses of bivalirudin infused for 72 hours (349). At hospital discharge, patients who were treated with the lowest dose had a 10.6% incidence of death/MI compared with 3.6% in those receiving the higher doses.

In the Hirulog Angioplasty study, 4,098 patients undergoing PCI for unstable or postinfarction angina were randomized to receive either heparin or bivalirudin (351). Bivalirudin reduced the incidence of primary end point events (death/MI/abrupt closure/CABG/IABP/repeat PCI) from 14.2% to 9.1% ($p <.05$) in patients with postinfarction angina. Overall, bivalirudin was associated with lower bleeding rates. Transfusions were required in 8.6% of patients who were given heparin and in 3.7% of those given bivalirudin ($p <.001$).

Argatroban, Inogatran, and Efegatran

Small trials of argatroban (352), inogatran (353), and efegatran (354) have reported no advantages over unfractionated heparin in terms of efficacy or safety.

Other Agents

Tissue factor is an integral protein of vascular endothelium. It is an essential cofactor for the proteolytic activity of factor VII toward its substrates, factors IX and X. Human plasma contains a tissue factor inhibitor, which inhibits coagulation. A recombinant tissue factor pathway inhibitor, targeted to exposed subendothelium, is currently in development (355).

An alternative strategy is to preserve ischemic myocytes. During ischemia, the myocyte switches to anaerobic metabolism, resulting in a lower intracellular pH level. This causes activation of the sodium-hydrogen exchange system (356,357 and 358), resulting in sodium accumulation within the cell, which, in turn, causes an increase in intracellular calcium via the sodium-calcium exchange system. The entry of calcium further impairs cellular function and, with prolonged ischemia, eventually leads to cellular necrosis. By inhibiting the sodium-hydrogen exchange system, cellular necrosis may be limited.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Upstream versus In-Laboratory Use of IIb/IIIa Antagonists

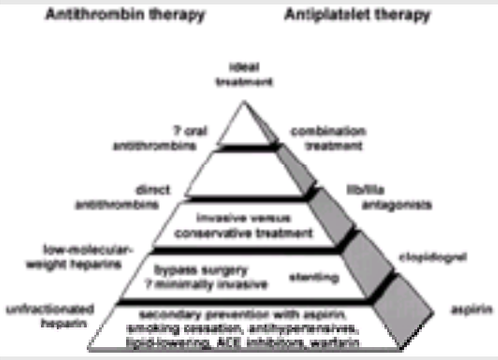
Revascularization by PCI or CABG is the preferred option in patients at high risk (219,292). Patients with non–ST-elevation MI are often treated by PCI, although in TACTICS-TIMI 18 only 41% of patients had PCI, 19% had CABG, and 40% had no intervention (70). When used appropriately, IIb/IIIa antagonists have been shown to improve outcomes in patients who are treated with revascularization procedures (70,162,165,168,177,182), but the optimal timing of therapy has not yet been established. A distinct advantage of starting IIb/IIIa antagonist therapy in advance of the procedure (upstream treatment) is that it allows even those patients who are not undergoing interventions to benefit from the drug. As seen in the TACTICS-TIMI 18 trial (70), upstream treatment with a small-molecule IIb/IIIa antagonist such as tirofiban reduces the risk of preprocedural MI and periprocedural events (69,88) in patients who are undergoing PCI, thereby allowing hospitals greater freedom in planning the timing of interventions in patients presenting at night or during the weekend.

In a metaanalysis of upstream IIb/IIIa antagonist therapy in more than 12,000 patients in the CAPTURE, PRISM-PLUS, and PURSUIT trials (181), the incidence of death/MI was reduced from 4.3% to 2.3% ($p = .001$). This equates to 14 fewer events (predominantly MIs) per 1,000 all-comers randomized in these trials. The risk reduction is far greater in patients at high risk (e.g., those with elevated troponins)—on the order of 100 fewer events per 1,000 patients, as seen in the PRISM study (83).

An alternative to upstream treatment with a small-molecule IIb/IIIa antagonist is to wait and give abciximab in the catheterization laboratory. This approach is based on the TARGET trial (161), which found that abciximab was superior to tirofiban for in-laboratory use, producing a greater reduction in the incidence of periprocedural MI. Dosing is critical when using small-molecule agents such as tirofiban, because there may be a dip in the level of platelet inhibition between the bolus dose and the infusion (359), unless a double bolus is administered or upstream treatment is continued for several hours before the procedure. No large randomized trials to date have addressed the issue of whether patients benefit more if catheterization is performed within 4 hours. In TACTICS-TIMI 18, patients underwent revascularization between 4 and 48 hours (70). It may well be appropriate to perform revascularization as expeditiously as possible and administer abciximab in the catheterization laboratory, but this approach has yet to be evaluated in comparison with upstream IIb/IIIa antagonist therapy before intervention.

THE FUTURE

Patient outcomes may well be improved by new combinations of current therapies such as clopidogrel with IIb/IIIa antagonists and low-molecular-weight heparin (eFig. 17.13.5). Predictors of plaque instability are needed so that patients at high risk can be targeted. The new biomarkers for risk assessment, ischemia, inflammation, thrombosis, necrosis, heart failure, and plaque instability will enable targeting of therapies for efficacy and safety, as will advances in pharmacogenomics.



***e*FIGURE 17.13.5** Evolution of treatment strategies for non–ST-elevation acute coronary syndromes, including new combinations of current therapies. ACE, angiotensin-converting enzyme. (Modified from White HD. Optimal treatment of patients with acute coronary syndromes and non–ST-elevation MI. *Am Heart J* 1999;138:S105–S114, with permission.)

High-resolution three-dimensional magnetic resonance imaging is able to distinguish intact thick fibrous plaque caps from intact thin and disrupted caps in human carotid arteries (360). This technology may allow the relationship between fibrous cap changes and clinical outcomes to be examined, enabling the development of therapies to stabilize plaques. Innovative work is also being done with noninvasive assessment of plaque temperature (361). Plaques with higher temperatures have increased numbers of macrophages and a greater propensity for rupture (362).

Further developments in noninvasive imaging may enable detection of coronary thrombi composed mostly of platelets, at which agents such as IIb/IIIa antagonists could be targeted. If imaging showed that a thrombus was composed mostly of red blood cells, a direct antithrombin might be more effective, whereas if the thrombus were a mixture of platelets and red blood cells, combination therapy might be more suitable. If imaging were able to show that there was an elevated plaque with little thrombus, PCI without adjunctive drug therapy might be the most appropriate first-line treatment.

Our knowledge of the mechanisms that lead to plaque instability will expand. Treatments that reduce the vulnerability of plaques to rupture include matrix metalloproteinase inhibitors and locally delivered growth factor inhibitors. Modulation of the ability of the myocardium to survive ischemia, including angiogenesis and metabolic manipulation, will be an area of active research. It may be possible to develop rapid bedside tests to obtain the genomic profile of patients so that therapies can be targeted to those who are most likely to benefit and least likely to experience side effects. Safer, more effective, cost-effective, and easily administered agents, including oral compounds, are needed. In the long term, however, greater emphasis must be placed on primary prevention.

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18

ACUTE MYOCARDIAL INFARCTION: EARLY DIAGNOSIS AND MANAGEMENT

ERIC J. TOPOL
FRANS J. VAN DE WERF

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Not only has our approach to the patient with acute myocardial infarction (MI) radically changed since the 1980s, but there continues to be steady refinement. The cardinal goal is to consider reperfusion therapy, either fibrinolytic or catheter-based, and to initiate such therapy as quickly as possible. Patients who present within the first 12 hours of symptom onset who have no contraindications for fibrinolytics are considered appropriate candidates, but the maximum benefit is achieved in patients treated within the first hour or two. The admission electrocardiogram (ECG), which provides the location and approximate size of the infarct, is remarkably important for prognosis, and combined with the main clinical parameters of age (the single most important parameter), heart rate, blood pressure, and Killip class, more than 90% of prognostic information is quickly assembled.

Patients without ST-segment elevation have non–Q-wave MI or unstable angina and are generally treated the same way, except without the use of fibrinolytic agents. Therapy with aspirin, anticoagulation, and beta-blockade is appropriate in most patients. Consideration for coronary angiography, either on an urgent or elective basis, and coronary revascularization, are key decisions that need to be made as a function of the patient's risk profile, the occurrence of recurrent ischemia, and resource availability.

Although there has been considerable progress in recent years, our current armamentarium leaves many patients with suboptimal reperfusion at the tissue level. This problem is currently being addressed with the assessment of platelet glycoprotein IIb/IIIa inhibitors and other antiplatelets, better anticoagulants, antiinflammatory agents, and emboli capture devices for catheter-based reperfusion. Undoubtedly, we will have more effective restoration of epicardial and tissue-level perfusion.

GLOSSARY

Myocardial reperfusion: Restoration of coronary blood flow through the infarct-related artery.

Primary angioplasty: Use of balloon angioplasty to achieve myocardial reperfusion.

Rescue angioplasty: For patients who fail thrombolytic therapy, the use of catheter-based reperfusion as a fallback approach in the early hours of the event.

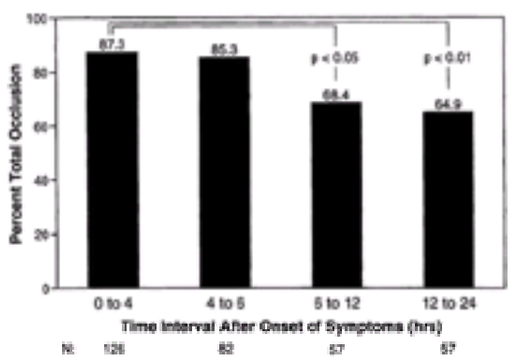
TIMI-3 flow: Brisk, complete flow as assessed by the Thrombolysis in Myocardial Infarction semiquantitative scoring system.

HISTORICAL PERSPECTIVE

Although the clinical syndrome of angina was described in the 1770s, it was not until 1912 that James B. Herrick described acute MI (1). This delay is largely attributed to the prevailing view that a sudden coronary occlusion would be uniformly fatal and to the lack of understanding of the pathophysiology. Just before Herrick reported the MI syndrome, two Russian physicians, Obrastzow and Straschesko, published cases of acute coronary thrombosis and the differential diagnosis of acute MI versus angina in the German literature (2). In the landmark paper by Herrick, he wrote, “The clinical manifestations of coronary obstruction will evidently vary greatly. . . depending on the size, location and number of vessels occluded. The symptoms and end-result must also be influenced by blood pressure, by the condition of the myocardium not immediately affected by the obstruction, and by the ability of the remaining vessels to properly carry on their work, as determined by their health or disease” (1).

For nearly 70 years, however, there was a failure to meaningfully build on Herrick’s visionary paper. There was considerable reluctance to accept the notion that coronary thrombosis was the proximate cause. There were a few isolated exceptions. Levine published a book on coronary thrombosis in 1929 (3); Fletcher and associates administered intravenous streptokinase (SK) in 24 patients with acute MI in 1958 (4), and Boucek, using an aortic root injection, nonselectively administered fibrinolysin (SK and human plasmin) to eight patients after acute MI in 1960 (5). Later, in 1976, Chazov and a Russian team administered direct, intracoronary fibrinolysin to two patients, and the paper was published in Russian (6). Rentrop, in 1979, reported the use of intracoronary SK in five patients with evolving MI (7), and this ushered in the reperfusion era that initially used intracoronary SK in selected centers in the early 1980s.

Nearly simultaneous to the development of a reperfusion therapy for MI was the other critical insight to its pathophysiologic underpinning. The classic angiographic study of DeWood and colleagues from Spokane (8), showing thrombotic occlusion in 87% of patients within 4 hours of symptom onset (*e*Fig. 18.0.1), provided the backbone for a revolutionary change to aggressive management of acute MI. This trial was powerful in convincing the medical community that coronary thrombus was indeed the proximate cause in nearly all acute MI patients.



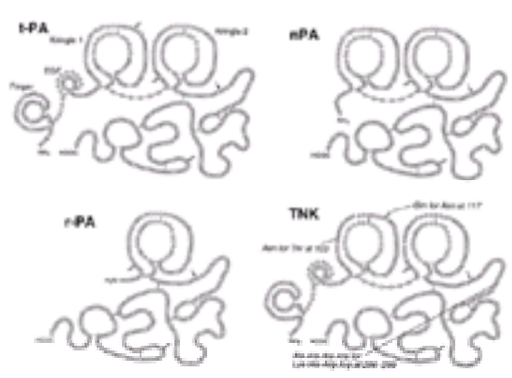
***e*FIGURE 18.0.1** Incidence of occlusion of the infarct vessel, as demonstrated by angiography, as a function of symptom onset. (From DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;303:897–902, with permission.)

But the initial therapy of intracoronary SK was highly impractical, requiring emergency coronary angiography with its intrinsic time delay, and restricted to a small number of hospitals with angiographic facilities and personnel equipped to rapidly intervene. Emergency coronary angiography laid the foundation in 1982 for primary angioplasty, pioneered by Hartzler et al. (9), as balloon angioplasty, only introduced in the United States in the late 1970s, was in the midst of a formative period. However, the need to identify a pharmacologic strategy that was immediately available and suitable for all hospitals led to the development of tissue plasminogen activator (t-PA) and brief high-dose intravenous SK. Both of these strategies were first used in the early 1980s (10,11 and 12); and subsequently, the landmark Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto (GISSI-1) (13) trial established the life-saving capacity of early intravenous thrombolytic therapy. Only in late 1987 did intravenous thrombolytic therapy receive U.S. Food and Drug Administration approval. The disparity in cost between t-PA and SK led to a decade-long debate over the superiority and the importance of early, complete infarct vessel patency (14). The primacy of achieving full, rapid, and sustained reperfusion has become evident from many trials conducted in the early 1990s.

From the last decade of large-scale, dedicated acute MI trials for which nearly 200,000 patients have been enrolled, we have learned considerably about reperfusion, adjunctive therapy, and the natural history of the disease, which have laid the groundwork for better treatments. Thus, our entire approach has radically changed from a supportive, passive one that was characteristic until the mid-1980s, in which the MI was simply accepted and the only measures taken were directed at preventing a second MI, to the modern era of acute intervention with thrombolytic therapy, or in suitable patients and facilities, emergency mechanical reperfusion. This aggressive therapy is designed to prevent the event or limit the extent of myocardial damage. Acute MI has become a veritable medical emergency with favorable clinical outcomes indexed to the efficiency of rapid restoration of myocardial blood flow. The patients with ST-segment elevation MI who are eligible for reperfusion therapy have been the primary target for intensive study, and only relatively recently has attention been directed toward the patients without ST-segment elevation, formerly known as having non–Q-wave MI. In this chapter, the spectrum of patients with MI is reviewed with specific attention to their diagnosis and early management.

PATHOPHYSIOLOGY

Coronary atherosclerotic disease is the underlying substrate in nearly all patients with acute MI. The initiating event is a crack or fissure in the diseased arterial wall, which occurs as a result of loss of integrity of the plaque cap, which is the fibrous tissue overlying the plaque and partitioning the atheroma from the arterial lumen (*e*Fig. 18.0.2) (15). The fissure or even frank plaque rupture leads to exposure of subendothelial matrix elements such as collagen, stimulating platelet activation, and thrombus formation. Furthermore, tissue factor is released with the arterial injury, which directly activates the extrinsic coagulation cascade and promotes the formation of fibrin (16). If an occlusive thrombus forms, patients may develop an acute ST-segment elevation MI unless the subtended myocardium is richly collateralized. On the other hand, the thrombus formed may not be occlusive, but rather mural, and the patient may develop unstable angina or non–ST-segment elevation changes on the ECG (ST-depression or T-wave changes), which denote the lack of a “current of injury” or full-thickness (subendocardial to epicardial) myocardial ischemia (Fig. 18.1).



***e*FIGURE 18.0.2** Coronary plaque rupture. **A:** Cross section showing the rupture site at 6 o’clock and thrombus in both the lumen and the lipid pool. **B:** Schematic demonstrates key cellular components. SMC, smooth muscle cell.

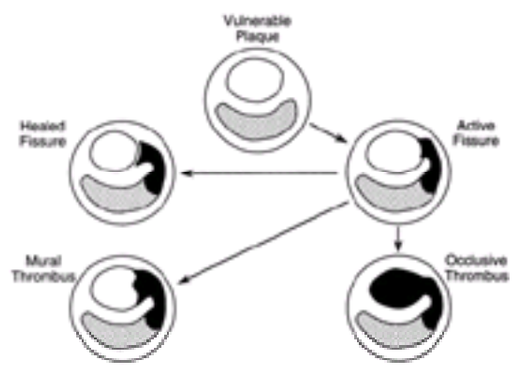
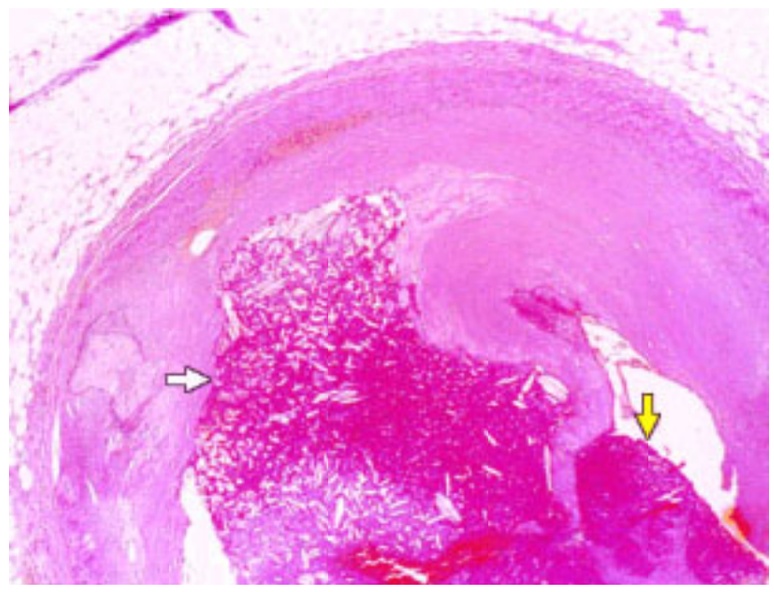
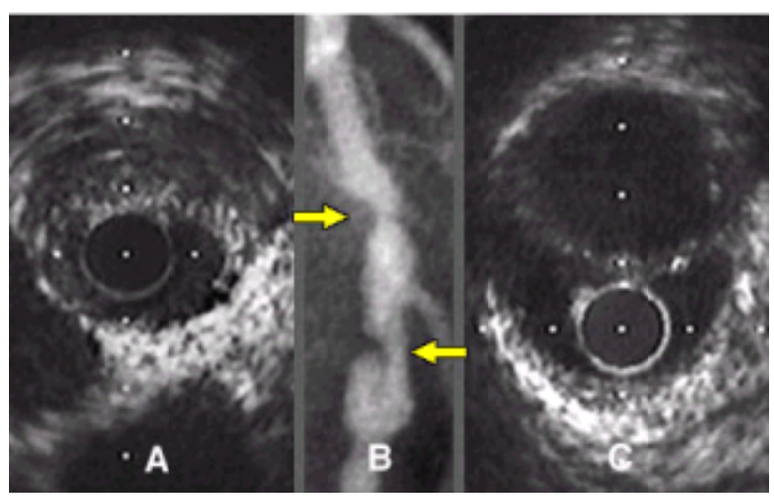


FIGURE 18.1 Different types of acute coronary syndromes as a function of mural versus occlusive thrombus. The vulnerable plaque develops a fissure, which can heal or result in a mural or occlusive thrombus. The fate of the plaque fissure depends, in part, on the extent of vessel wall disruption.



Organized intraplaque thrombus (*white arrow*) with overlying, near-occlusive fresh thrombus (*yellow arrow*). Ruptured atherosclerotic lesion of the right coronary artery 5 days after a balloon angioplasty procedure.



Intravascular ultrasound interrogation of a complex coronary lesion. The proximal part of the lesion shows an eccentric soft plaque (A), whereas the distal end of the lesion (B) demonstrates rupture of the plaque with a double lumen.

Understanding the reasons why plaques crack may provide a better means of preventing acute MI, rather than intervening at the late phase after the event has been initiated. Plaques that rupture or fissure tend to have a thin fibrous cap, a high lipid content, few smooth muscle cells, and a high proportion of macrophages and monocytes (17,18). These mononuclear cells are conceived as a major trigger in plaque rupture by their release of such proteases as monocyte chemotactic protein (MCP-1) and matrix metalloproteinases (examples are collagenases, stromelysin, elastases), which chemically digest the plaque cap. Of note, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to reduce the incidence of MI, and this is likely related to reduction in lipid content, as well as a favorable antiinflammatory effect on the cellular plaque constituents and chemokines (19,20,21 and 22). Loss of integrity of the arterial wall and platelet thrombus, with cessation of coronary blood flow through the infarct-related artery, thus drives myocardial ischemia and injury. As elegantly described by Reimer and Jennings, the *wavefront* of necrosis extends from the subendocardium to the subepicardium (23), and the extent of necrosis varies as a function of collateral flow, the length of time that coronary blood flow has halted, and the extent of diminution of coronary blood flow. In many patients, there is a stuttering quality of MI with severe pain often denoting the cutoff of blood supply, and less chest pain, with partial, albeit insufficient, reflow. This dynamic quality of the infarct vessel blood flow pattern in acute MI (altered vasomotor tone or spasm) is likely related to the release of vasoactive amines from the activated platelets and loss of endothelial function.

The thrombus that occludes the coronary artery is a mixture of white (platelet-rich) and red (fibrin- and erythrocyte-rich) clot. In some patients, there is a more dominant role of platelets, whereas in others predominantly fibrin-rich thrombus at the arterial injury site is found. Stagnation thrombosis results from the lack of blood flow through the infarct vessel, thus leading to calumniation of red thrombus proximal to the original occlusion site (24). There is rarely frank herniation of the plaque occluding the lumen, which is known as *plaque disaster* (24,25).

On the other hand, the mural thrombus in patients without ST-segment elevation MI is more apt to be platelet rich and not accompanied by stagnation as there is not sustained cutoff of coronary blood flow. Depending on the extent and duration of ischemia, the patient may not experience any myocardial necrosis (unstable angina) or develop myocardial damage (non–ST-elevation or non–Q-wave infarction). Beyond what is occurring at the arterial injury site and proximal to it, there is the potential for embolization of atheroma constituents or platelet thrombus distally. This is not typically found at postmortem but requires careful histologic inspection (26). When this occurs, a further explanation to cessation of myocardial blood flow is provided.

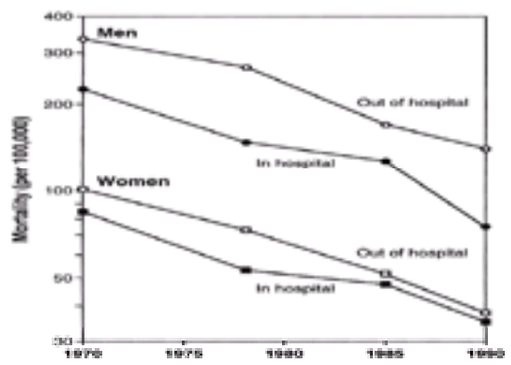
Although there is considerable variability in time of presentation, the plaque fissure events are more likely to happen in the early morning hours, especially on awakening, owing to the circadian rhythm, with its temporal cyclic-enhanced platelet aggregation, and reduced fibrinolytic potential related to higher plasminogen activator inhibitor levels (27). Surges of epinephrine may also have a role, as evidenced by a considerably higher rate of MIs during Scud missile attacks in the Gulf War and during the Los Angeles earthquake (28,29). Beyond catecholamine excess, there are several factors that ultimately may precipitate plaque fissure, including infection or inflammation of the diseased coronary artery segment.

INCIDENCE AND SIGNIFICANCE

The true incidence of acute MI is unknown. Beyond the significant proportion of patients who die before reaching the hospital, estimated at 200,000 to 300,000 patients in the United States per year (30), it is estimated that approximately 1 million patients present to a hospital each year with some type of MI as the principal diagnosis (31). Of these, we know that roughly 200,000 patients receive reperfusion therapy in the United States per year, and that this represents only 20% to 30% of the patients who are assessed for eligibility for aggressive management (32,33). The breakdown of infarctions is also unclear, with a split between the classic ST-segment elevation and the non–ST-segment elevation (also known as *non–Q wave*). The latter group is difficult to differentiate from unstable angina on presentation, but it is estimated that approximately one-half of patients present with either significant ST-segment elevation (greater than 1 mm) or fall into the latter category with abnormal ST-segment depression or T-wave inversion.

The incidence and mortality resulting from MI is on the decline. Not only has the fatality rate been reduced as better therapies have evolved (*e*Fig. 18.1.1), but the

absolute number of MI events has continued to decrease since the 1970s. This is likely attributable to the many advances in preventive cardiology, including treatment of hypertension, avoidance of smoking, management of hypercholesterolemia, improved diet and exercise, and the use of prophylactic aspirin. It may also be an outgrowth of the high rates of surgical and percutaneous coronary revascularization in the United States, where the treatment of angina is more apt to be bypass surgery or angioplasty, rather than medical management. Although prevention of MI is not a prominent effect of coronary revascularization, intervening early in the course of atherosclerotic coronary disease may change its natural history. The most pronounced effect on reducing the incidence of MI appears to have resulted from the use of HMG-CoA reductase inhibitors (19,20,21 and 22), which has led to the concept that acute MI may even be “extinct” someday (34). Clearly, the most important initiatives for the condition of MI are in its prevention, because once the process of plaque rupture is unleashed, it is much more difficult to interrupt.



***e*FIGURE 18.1.1** Trends in mortality due to coronary artery disease from 1970 to 1990, according to location of death, among residents of the Twin Cities area who were 30 to 74 years of age. Mortality (shown on a logarithmic scale) has been adjusted by the direct method to the age distribution of the total U.S. population in 1980. Deaths in the emergency room and on arrival at the hospital are included as out-of-hospital deaths. (From McGovern PG, Pankow JS, Shahar E, et al. Recent trends in acute coronary heart disease: mortality, morbidity, medical care, and risk factors. *N Engl J Med* 1996;334:884–890, with permission.)

Although the incidence is declining, acute MI remains the principal cause of death in Western society (35). With the many rapid advances that have occurred in this field, the serious and potentially catastrophic outcome of an MI event has been taken for granted in more recent years. Although reperfusion has made important progress in lowering mortality, most patients with acute MI are not eligible for this therapy and face in-hospital death rates of 10% to 20% (36,37 and 38). With the increasing proportion of our population being represented by the elderly, who have a high incidence of fatality even with reperfusion therapy, MI remains as the most critical single event in medicine. With the global burden of atherosclerotic disease, Beaglehole has predicted even greater prevalence and pervasiveness of MI by 2020 (38a).

DIAGNOSIS

Acute MI is a clinical syndrome for which a constellation of subjective and objective parameters need to be assessed. The diagnosis must be obtained rapidly and accurately, and misdiagnosis can have catastrophic sequelae. The individual components of making the diagnosis are discussed separately, but it is the integration of all of them that facilitates the accuracy and speed of the clinical syndrome recognition.

History

The classic symptoms of MI are intense, oppressive, excruciating chest pressure, with an impending sense of doom and radiation of the pain to the left arm. However, the other symptoms of chest heaviness or burning, radiation to the jaw, neck, shoulder, back, or both arms may be encountered. Indigestion is common, especially with inferior wall MI. Nausea and vomiting, particularly the former, are typical. Profuse diaphoresis is also a frequent characteristic. Taken together, the patient with a clear-cut presentation is experiencing a unique, discrete, painful event that has induced fear. However, the subtleties of the history are more common and challenging. It is important to ask whether there were premonitory signs of chest discomfort (not necessarily pain) in the preceding week or two. Pain or discomfort may be completely localized to the arm or shoulder. Quite commonly, only the symptoms of indigestion and nausea prevail, such that the patient attributes the episode to heartburn and resorts to taking antacids.

The identification of risk factors, such as smoking, known cholesterol elevation, diabetes, hypertension, and family history, is a supportive piece that helps to put the acute history into context. The chest discomfort that causes the patient to seek medical attention is usually sustained (greater than 20 minutes), but can be stuttering.

Other accompanying symptoms include dyspnea, which is of concern because it may denote incipient congestive heart failure or, alternatively, is an outgrowth of the patient’s anxiety. Palpitations or syncope are unusual, but a history of lightheadedness or dizziness and presyncope often reflects the underlying vagotonia or bradyarrhythmias. When syncope, or an out-of-hospital arrest has occurred, there is a high likelihood of ventricular tachycardia as an explanation.

The differential diagnosis is quite broad (because many conditions can masquerade as acute MI) including aortic dissection, pericarditis, esophagitis, myocarditis, pneumonia, cholecystitis, and pancreatitis. Of these conditions, it is always worth considering that the patient has aortic dissection until proven otherwise, so that this diagnosis is not missed. Although considerably less common than acute MI, the therapies for the two conditions are entirely different and, for example, the use of fibrinolytic therapy for aortic dissection could be disastrous.

Physical Examination

The patient appears to be in distress and may even be writhing in pain. Pallor is common. The pulse is usually regular, although ventricular extrasystoles may be present. Bradycardia or tachycardia is helpful in understanding the infarct location, the effect on the conduction system, the vagal tone, and the extent of myocardium at jeopardy. Significant tachycardia (pulse greater than 120) is worrisome and usually denotes an extensive MI, although a “hyperdynamic” subset of patients who have relatively small infarcts, but are hyperadrenergic, may be encountered. The blood pressure is typically elevated owing to the body’s response to pain. Hypotension is either due to vagotonia, dehydration, a right ventricular infarction, or impending power failure.

Major examination findings to be aware of include whether there is elevation of jugular venous pressure, the character and location of the apical impulse, the splitting of the second heart sound, the presence of a third or fourth heart sound, a mitral regurgitant murmur, and whether there are rales. Examination of the peripheral pulses and the extremities is important. Collectively, this information provides a sense of the size of the myocardial infarct. If a third heart sound is present, along with rales halfway up the posterior chest fields, a large anterior wall MI is likely present. On the other hand, a normal examination suggests either a small infarction or that more extensive myocardial damage has not yet occurred.

Electrocardiography

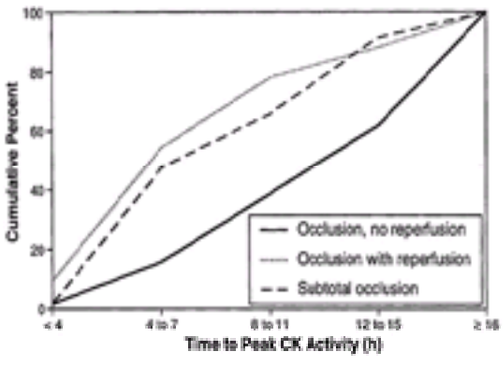
It is imperative to obtain the 12-lead ECG as quickly as possible to secure the diagnosis. The presence of a true normal ECG rules out the occlusion of a major epicardial vessel at the moment the tracing was obtained. Hyperacute, tall T-wave changes are the first manifestations of acute coronary occlusion, but are frequently not present when the patient reaches the hospital for medical attention. The presence of ST-segment elevation (*e*Fig. 18.1.2) is the principal feature that denotes “current of injury” and should be associated with reciprocal depression in contralateral leads. If only minimal (1 to 2 mm) ST elevation is present, then either the patient has collaterals to the infarct territory or the vessel is not fully occluded, or there has already been evolution of the ECG changes. If only ST-segment depression or T-wave inversion or both are manifest, this may denote either unstable angina or a non–ST-elevation (non–Q-wave) MI. This usually is not associated with an occluded infarct vessel, but rather one that is stenotic with myocardial ischemia. If a patient has a normal ECG, but the history is suggestive or even compelling, it is vital to observe the patient over an extended period (6 to 24 hours) to get additional ECG tracings and to determine if the chest discomfort or other symptoms recur. Certainly transient but marked ischemia can resolve before the patient has an ECG and a normal ECG can be recorded. It is worthwhile to give sublingual nitroglycerin (0.4 mg) to a patient with marked ST-segment elevation to see if this represents coronary artery spasm, while more definitive therapy (vide infra) is being initiated. If the patient’s chest pain and ECG quickly revert to normal after nitroglycerin, this strongly suggests vasospasm as the principal trigger.

***e*FIGURE 18.1.2** Serial electrocardiograms in the first patient to ever receive tissue plasminogen activator. **A:** Before tissue plasminogen activator, marked ST elevation V_1 to V_6, II, III, aVF suggested a large anterior myocardial infarction. **B:** Twenty minutes after tissue plasminogen activator, with sudden relief of chest pain, there was a run of accelerated idioventricular rhythm (not shown), the electrocardiographic results normalized, and the patient had angiographic evidence of brisk flow through the left anterior descending artery.

In patients with ST-segment elevation largely confined to the right precordial leads (V_1 to V_2), it is important to differentiate ST-segment elevation due to current of injury and fast (early) repolarization, which is a normal variant, especially common in young African-American men. Early repolarization is diminished or undetectable when the heart rate is increased, so that if the ECG remains equivocal it may be helpful to have the patient do some sit-ups to increase the heart rate, and then repeat the ECG.

Creatine Phosphokinase

The creatine phosphokinase (CPK) is unhelpful to make the initial diagnosis. It takes at least 6 hours for there to be an enzyme “leak,” which denotes myocardial cell necrosis. Enzymes should be assessed every 8 hours for the first 24 hours, and longer if the peak is not firmly established. The peak CPK occurs earlier when there has been successful reperfusion (*e*Fig. 18.1.3) (39). This enzyme is much more helpful in gauging the size of the MI than in making the diagnosis.



***e*FIGURE 18.1.3** Distribution of time to peak plasma creatine kinase (CK) activity from onset of symptoms according to angiographic perfusion status for each of the three groups. (From Gore JM, Roberts R, Ball SP, et al. Peak creatine kinase as a measure of effectiveness of thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1987;59:1234–1238, with permission.)

Troponin T and I

More sensitive measures of myocardial necrosis have become available, which have a similar obligatory lag in appearing in the blood (as CPK) but appear to detect cell damage more readily (40,41,42,43 and 44). The troponins are part of the tropomyosin-binding protein of the contractile apparatus of cardiac myocytes and therefore are highly specific for cardiac origin. A rapid, bedside assay for troponin is available and is a practical, rapid way to assess patients with ischemic symptoms and non–ST-segment elevation. The off-line quantitative assays of both troponin T and I have been particularly helpful in differentiating risk, better than CPK, in patients with unstable angina and non–ST-elevation MI (Fig. 18.2). Both are extremely promising for offering a more sensitive means of not only diagnosing whether infarction has occurred, but also discriminating the risk. However, the real utility of tests such as troponin goes beyond the determination of risk level to favorably alter the prognosis of the patient by knowledge of whether the test result is abnormal or not. Indeed, responses of patients to either IIb/IIIa inhibitors or low-molecular-weight heparins are predicted by abnormal troponin. These sensitive markers should be applied routinely for patients without ST-segment elevation. Troponins offer little incremental value in classic ST-elevation MI.

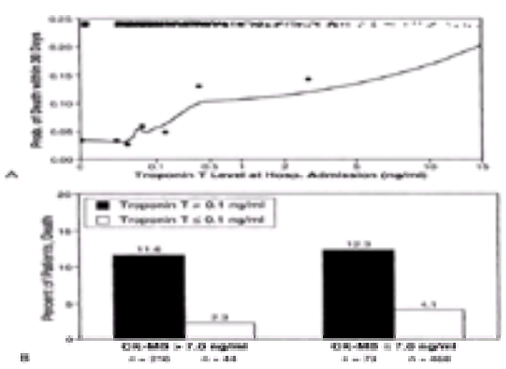


FIGURE 18.2 A: Probability of death within 30 days according to the troponin T level at hospital admission. Smoothed nonparametric estimates are shown. The troponin T levels are plotted on a cube-root scale. The density of the data is indicated at the top, with each mark representing one patient. The dots represent simple estimates of mortality derived from ranges of the troponin T level that contained at least 70 patients. (From Ohman EM, Armstrong PW, Christenson RH, et al. for the GUSTO-IIa Investigators. Risk stratification with admission cardiac troponin T levels in acute myocardial ischemia. *N Engl J Med* 1996;335:1333–1341, with permission.) **B:** Sensitivity of troponin compared with creatine kinase-myocardial band (CK-MB). Even in patients with a low CK-MB (less than 7.0 ng per mL), the troponin T–positive patients (greater than 0.1 ng per mL) had a worse outcome with respect to mortality. (Data from Ohman EM, Armstrong PW, Christenson RH, et al. for the GUSTO-IIa Investigators. Risk stratification with admission cardiac troponin T levels in acute myocardial ischemia. *N Engl J Med* 1996;335:1333–1341.)

Echocardiography

The diagnosis of acute MI cannot be made by echocardiography, as it is based on the combination of symptoms, the ECG findings, and the enzyme abnormalities. However, there are several findings that may be considered ancillary from a two-dimensional echo, including a segmental wall abnormality and hyperkinesis of the contralateral wall. If a segment is akinetic, dyskinetic, or severely hypokinetic, it is not possible to know whether there was ischemia, with attendant dysfunction or stunning, or irrevocable damage due to necrosis. This can only be differentiated by serial echocardiographic examination. However, the finding of lack of hyperkinesis of the contralateral territory (e.g., the anterolateral wall in an inferior MI) in the acute setting suggests that the infarct vessel has recanalized or that there is multivessel coronary disease. This finding may be especially valuable in assessing a patient with congestive heart failure or cardiogenic shock, as the main compensation of the ventricle to preserve its global ejection fraction is preempted if there is a significant stenosis of a major epicardial vessel supplying the noninfarct territory. In patients with inferior MI, the echocardiogram of the right ventricle is helpful in demonstrating dilation or hypocontractility and is more sensitive than the ECG (45). A significant

prior MI is also diagnosed by scarring and thinning of a specific territory and can easily be differentiated from an acute MI by its echocardiographic appearance.

Video 18.1 Apical long-axis view demonstrating an anteroseptal myocardial infarction. Note the akinetic anteroseptum to the right of the picture. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 18.2 Parasternal short-axis view of an anteroseptal myocardial infarction. Note the area of myocardial akinesis from 11 to 2 o'clock corresponding to the anteroseptum and anterior walls. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Angiography

On occasion, even with all of the tools outlined, the diagnosis is uncertain. This may be the result of atypical symptoms and an ECG that is difficult to interpret. In a patient in whom reperfusion therapy is contemplated, an approach that can rapidly establish the diagnosis is emergency coronary angiography. By demonstrating an acutely occluded infarct vessel, with the characteristic appearance of thrombus or a cutoff sign at the point of occlusion, coupled with left ventriculography to ascertain the segmental wall motion profile, angiography can at times be helpful for a difficult diagnosis. Examples of patients who may present with ambiguity are those with an acute myocarditis with diffuse ECG changes, or patients with prior bypass surgery and previous MI, or those without a characteristic pattern on ECG. Furthermore, angiography can serve as the foundation for primary balloon angioplasty to achieve reperfusion.

MAJOR SUBGROUPS AT PRESENTATION

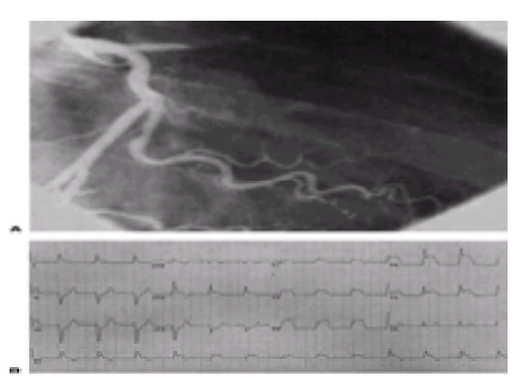
By Electrocardiography

In Table 18.1, the five types of ST-segment elevation MI are presented. These represent specific patterns of ECG abnormalities that correlate with a clinical presentation, the underlying coronary anatomy, and prognosis. The most worrisome type is the proximal left anterior descending (LAD) MI, often referred to as the *widow-maker* infarction, which carries a high mortality and is attributed to an occlusion of the LAD before or at the first septal perforator. All of the precordial leads and I and aVL show ST-segment elevation (eFig. 18.2.1). The proximal location of occlusion is associated with compromised perfusion to the His-Purkinje conduction tissue owing to loss of septal supply and often accompanied by a new bundle branch block. Usually, left anterior hemiblock or right bundle branch block is present, but bifascicular blocks, left bundle branch block, or Mobitz II atrioventricular block are all possible. Cardiogenic shock or power failure is not unexpected in this subgroup, unless there has been effective reperfusion established.

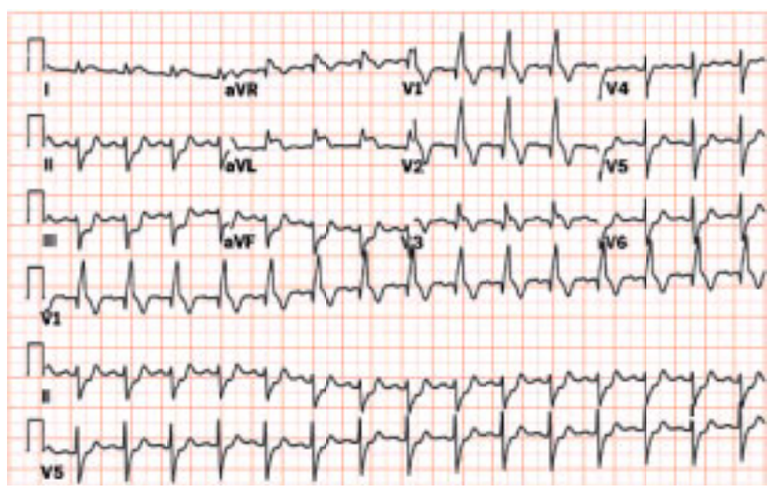
Categories	Anatomy of occlusion	Electrocardiographic entry	30-day mortality (%)[a]	1-year mortality (%)[a]
1. Proximal left anterior descending	Proximal to first septal perforator	ST↑ V_{1-4}, I, aVL and fascicular or bundle branch block	19.6	25.6
2. Mid-left anterior descending	Proximal to large diagonal, but distal to first septal perforator	ST↑ V_{1-4}, I, aVL	9.2	12.4
3. Distal left anterior descending or diagonal	Distal to large diagonal or of diagonal itself	ST↑ V_{1-4} or ST↑ I, aVL, II_{1-4}	6.8	10.2
4. Moderate to large inferior (posterior, lateral, right ventricular)	Proximal RCA or left circumflex	ST↑ I, II, aVF and any or all of the following: a. V_1, V_2, V_3 or b. V_3, V_4 or c. V_5 ≥ in V_1, V_2	5.4	8.4
5. Small inferior	Distal RCA or left circumflex, branch occlusion	ST↑ I, II, aVF only	4.5	6.7

RCA, right coronary artery.
[a]Based on Global Use of Strategies and t-PA for Occluded Coronary Arteries (GUSTO-I) cohort population in each of the 5-year categories, all receiving reperfusion therapy.

TABLE 18.1 A NEW CLASSIFICATION OF ACUTE MYOCARDIAL INFARCTION BASED ON ELECTROCARDIOGRAPHIC ENTRY CRITERIA WITH ANGIOGRAPHIC CORRELATION



***e*FIGURE 18.2.1** Category I myocardial infarction. **A:** Proximal left anterior descending occlusion before the first septal perforator. **B:** Electrocardiogram demonstrates large anterior infarction with conduction disturbance.

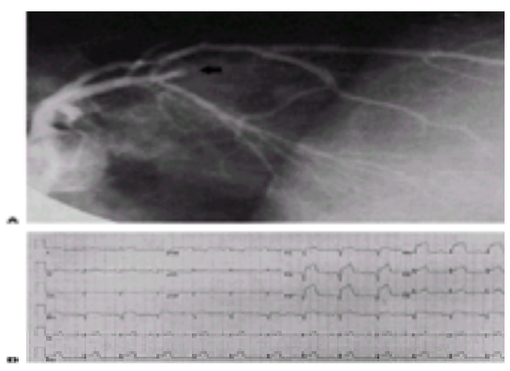


Acute anterolateral myocardial infarction complicated by conduction disturbance. ST-segment elevation in the anterior precordial leads as well as leads I

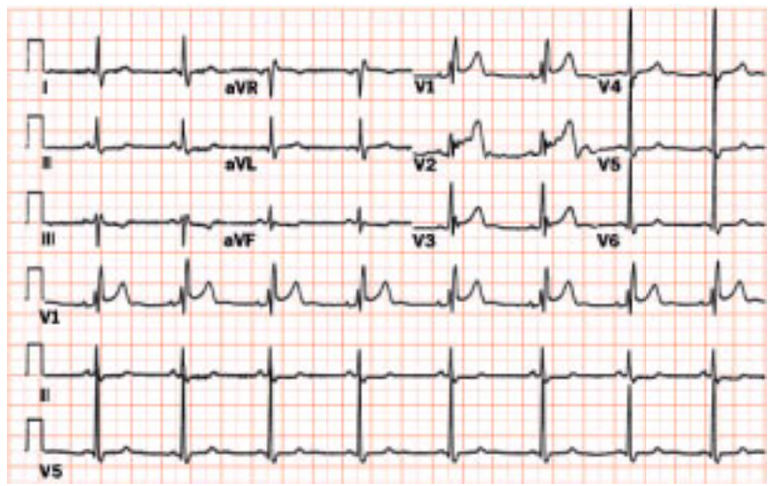
and aVL is associated with right bundle branch block and left anterior hemiblock.

Acute anterolateral myocardial infarction. Note ST segment elevation in the anterior precordial leads as well as leads I and aVL. New left anterior fascicular block suggests proximal left anterior descending infarct location.

In contrast, occlusion of the LAD just distal to the first septal perforator is an anterior MI, which is less serious and called the *mid-LAD infarction* (eFig. 18.2.2). Although the ECG may be indistinguishable from that of the proximal anterior MI patient with respect to the leads with ST elevation, there is no conduction disturbance. Cardiogenic shock in these patients is considerably less frequent, as restriction of the damage to the anterolateral and anteroapical segments spares the proximal interventricular septum. If shock is present, one should be concerned about prior myocardial damage or other noncardiac causes such as massive hemorrhage. Heart failure can occur, and the complications of ventricular aneurysm with potential of apical thrombus are common, especially if reperfusion has been delayed or is unsuccessful.



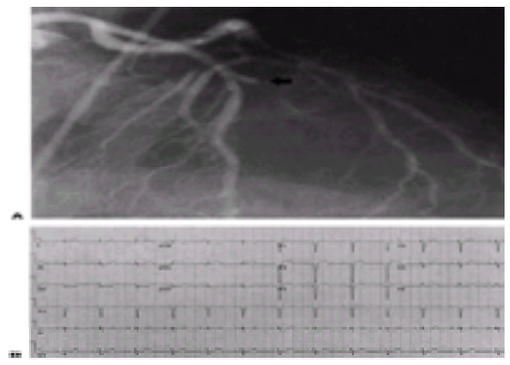
***e*FIGURE 18.2.2** Category II myocardial infarction. **A:** Mid-left anterior descending occlusion after the first septal perforator (*arrow*). **B:** Electrocardiogram demonstrates large anterior myocardial infarction without conduction disturbance.



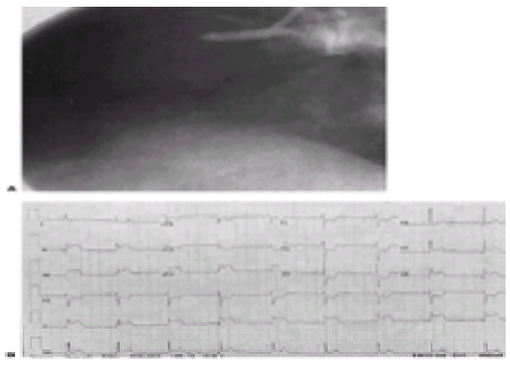
Anterior myocardial infarction in setting of right bundle branch block. ST-segment elevation in the anterior precordial leads as well as primary T-wave changes support acute anteroseptal myocardial infarction.

One segment distal in the LAD, sparing a large diagonal, represents the distal LAD infarction, which is less common. Only leads V_1 to V_4 are affected, but still there is the potential for apical hypokinesis, thrombus formation, and a milder form of the mid-LAD infarct clinical syndrome. Importantly, cardiogenic shock cannot result from this type of infarction per se.

Two types of infarcts that are relatively small are due to less significant territory affected. These are the LAD diagonal branch “lateral” MI, involving only leads I, aVL, V_5, and V_6 (eFig. 18.2.3), also classified in the distal LAD tensitory MI, and the small inferior MI, with ECG ST elevation confined to leads II, III, and aVF (eFig. 18.2.4). The latter is usually attributed to a distal right coronary artery lesion or branch (posterolateral or posterior descending), but in patients with a dominant left circumflex, it may be a branch from this vessel. Both of these types of MIs are usually uncomplicated and rarely associated with serious outcomes such as congestive heart failure or significant arrhythmias.



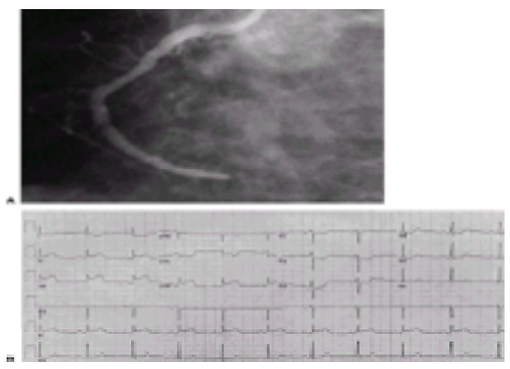
***e*FIGURE 18.2.3** Category III myocardial infarction. **A:** Occlusion of diagonal branch (*arrow*) and accompanying **(B)** electrocardiographic changes of ST elevation in I and aVL.



***e*FIGURE 18.2.4** Category V myocardial infarction. **A:** Proximal large right coronary occlusion. **B:** Significant ST elevation in leads II, III, aVF, V_5, and V_6 and prominent R wave in V_2 with precordial ST depression.

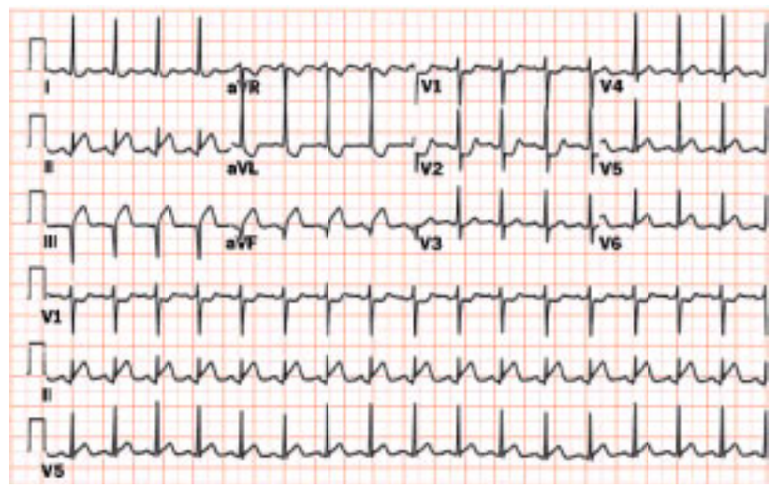
Lateral myocardial infarction. ST segment elevation in leads I and aVL associated with inferior reciprocal changes. Note preexisting anteroseptal myocardial infarction.

Patients with moderate or large inferior MIs are a key subgroup, which is heterogeneous, representing a spectrum of involvement of the inferior, posterior, lateral, and right ventricular myocardial involvement. The proximal, dominant right coronary artery is responsible for supplying all of these territories and can result in a large and potentially catastrophic event. The ECG leads involved include II, III, aVF, and additional changes in the V_5, V_6 lateral leads, right ventricular leads (V_1 or V_{3R}, V_{4R}), or posterior leads (R/S ratio greater than 1 in V_1, V_2, with or without ST depression, ST elevation in aVR). The largest inferior MI involves the composite of all of these territories (*e*Fig. 18.2.5). Dreaded complications, such as power failure or cardiogenic shock due to a large right ventricular infarct, or the development of a ventricular septal defect due to extensive distal septal necrosis, are possible. In all patients with inferior MI, a systematic approach to obtaining the right precordial ECG must be incorporated. Although right ventricular lead ST elevation of 1 to 2 mm in V_{3R} or V_{4R} is highly specific for right ventricular infarct, the sensitivity is still suboptimal, and one should carefully examine the patient for elevated jugular venous pressure, a right-sided S_3 gallop, and, in cases in which there is uncertainty, perform either or both echocardiography or right-sided heart catheterization. Inferior MI is characterized by hypervagotonia, with bradycardia and hypotension that is responsive to atropine (0.6 to 1.0 mg intravenously). Type I atrioventricular block (Wenckebach) is exceedingly common with inferior MI, particularly if continuous ECG monitoring is reviewed. The conduction disturbances and bradyarrhythmias of inferior MI are usually benign, most often not requiring specific therapy except occasional atropine.

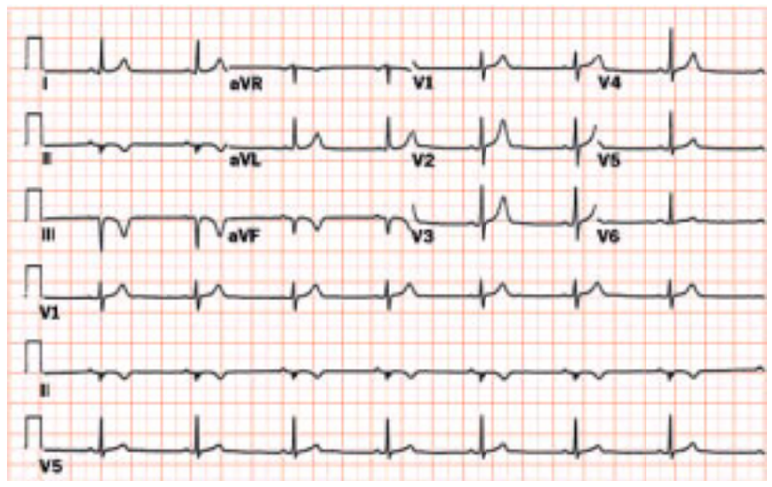


***e*FIGURE 18.2.5** Category IV myocardial infarction. **A:** Small inferior distal right coronary artery occlusion and **(B)** electrocardiographic changes in leads II, III, and VF.

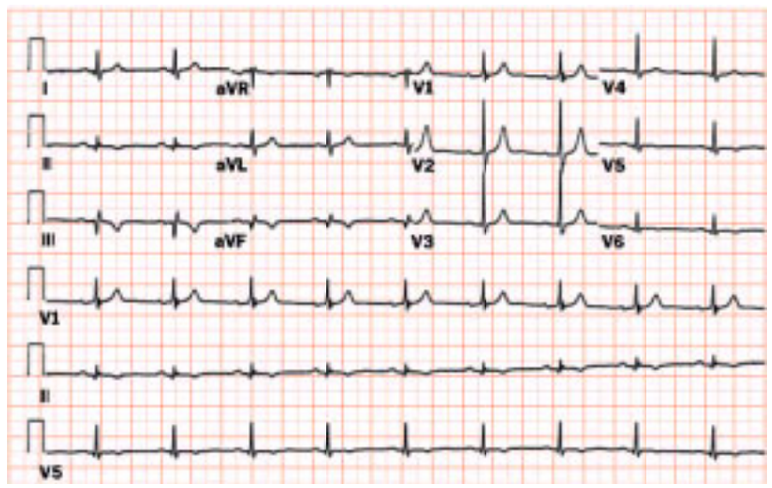
Right ventricular infarction. ST-segment elevation in leads V_{4R} and V_{5R} reveals right ventricular involvement complicating the inferior infarct.



Acute inferoposterior myocardial infarction. Note ST segment elevation in leads II, III and aVF with ST depression in leads V_1 and V_2.



Inferoposterior myocardial infarction, age undetermined. Inferior Q waves with T-wave inversions and R > S pattern in V_1 suggest this diagnosis.



Inferoposterior myocardial infarction. Note inferior Q waves and T wave inversions. R > S pattern in lead V_1 associated with upright T wave suggests posterior infarct.

Acute inferior myocardial infarction complicated by Wenckebach block. Note inferior ST-segment elevation and Q waves as well as progressive prolongation of the PR interval with grouped beating.

Diagnosis of a true posterior infarction is rare, but the posterior wall is the least well expressed on the 12-lead ECG, such that occlusion of the left circumflex branches, which are usually responsible for the true posterior myocardial territory, can be missed. When the findings of ST depression in V_1 to V_4 are present, especially when accompanied by an R greater than S wave in V_1 or V_2 (or both), the ECG is highly supportive of a posterior MI. The ST depression follows the “mirror rule” as the reflection of the tracing would fit the conventional ST-elevation pattern that one would expect in other MI locations. Posterior wall MIs are usually well tolerated, but it is imperative to interrogate the possibility of concomitant involvement of the right ventricle and free wall of the left ventricle.

All of the patterns described have associated reciprocal ECG changes, which are important to confirm the diagnosis. For example, most patients with inferior MI have ST depression in either leads I, aVL, or precordial leads V_1 to V_4, and the prognostic significance of this latter finding has been debated for many years (46). The extent of reciprocal changes is usually similar to the primary current of injury, such that if there is 5 mm of ST elevation, there is more pronounced evidence of contralateral, reciprocal ECG changes. For the most part, this finding is useful for confirming the diagnosis and represents an ECG contrecoup expression, which does not carry vital clinical prognostic information. In most series, however, there is some incremental risk of adverse outcomes as a function of the extent and severity of reciprocal ST-segment depression (46).

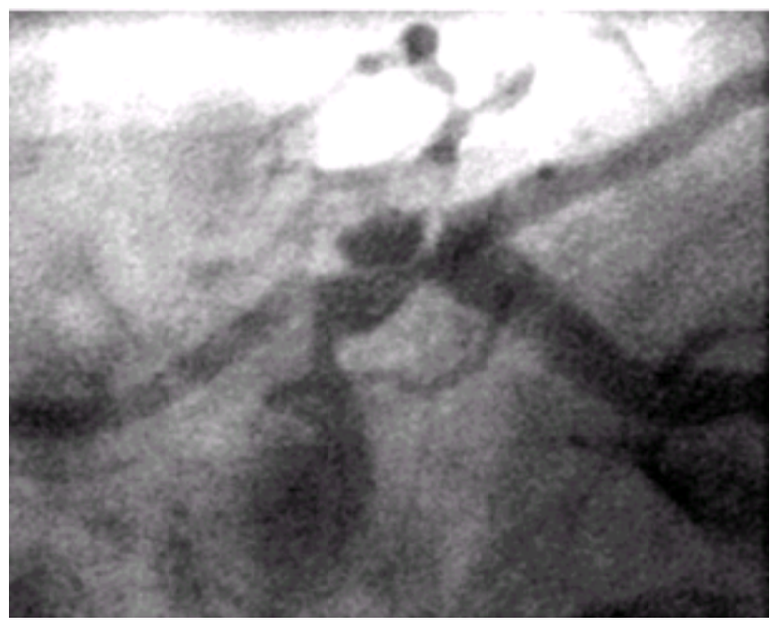
Repeat 12-lead ECGs are vital 60 to 90 minutes after administration of fibrinolytic therapy to detect whether tissue-level reperfusion has occurred. As shown in Table 18.2 with the early repeat ECG in many large-scale trials (47,48,49,50,51 and 52), the prognosis of patients is greatly differentiated by whether there has been greater than or equal to 70% resolution of ST-segment elevation. This has come to serve as the “lie detector” or “truth serum” as an inexpensive, readily available means of assessing tissue-level reperfusion. It is also worthwhile to recheck the ECG after catheter-based reperfusion because approximately 20% to 30% of patients do not achieve ST-segment resolution and carry an unfavorable prognosis (53).

Study (reference)	Time (min)	Complete	Partial	No.
ISAM (47)	180	2.8	4.3	9.2
INJECT (48)	180	2.5	4.3	17.5
HIT 4 (49)	180	2.8	6.0	14.3
GUSTO-III (50)	90	4.0	5.4	10.7
TIMI 14 (51)	90	1.0	4.2	5.9
InTIME (52)	60	1.7	4.5	7.7

TABLE 18.2 MYOCARDIAL REPERFUSION: ST RESOLUTION VERSUS MORTALITY (30 DAY)

Non–ST-Segment Elevation

Patients with acute ECG changes but without ST-segment elevation fit into the non–ST-elevation category. This was formerly known as *subendocardial, non–Q-wave MI*, but the reperfusion era has provided ample evidence that many patients with initial ST elevation do not go on to evolve a Q-wave MI (54). Giant T-wave inversion, characteristic of a proximal LAD lesion if occurring throughout the precordial leads, is an example of a non–ST-elevation MI with a discrete ECG pattern. However, many of the ECGs in this patient group do not fit a particular pattern of myocardial necrosis or ischemia, and at the time of evaluation, one is uncertain whether the changes are fixed or transient. Clearly, ST-segment depression is more ominous than T-wave inversion for 30-day mortality or nonfatal reinfarction (55). In a large-scale trial, the death rates were 6.8% versus 1.4%, and the composite event rates were 12.4% and 6.8%, respectively (55). Especially worrisome is the finding of global ischemia, when there is an ST depression in virtually every lead except aVR (where there is elevation); this frequently denotes a left main or equivalent non–ST-elevation MI.



Severe ulcerated plaque of the left main trunk discovered on diagnostic angiography.

By Hemodynamic (Killip) Class

Besides the ECG, which establishes the location of the infarct and often the precise location of the affected coronary artery, it is important to establish the patient's hemodynamic class. The Killip categories are most useful and validated for this purpose (56). Killip class I is the most common presenting class, occurring in 85% of patients with MI, and, by definition, with no evidence of heart failure. Early heart failure, as manifested by bibasilar rales and at times an S_3 gallop, is present in Killip II, the category that approximately 10% of patients present with. Pulmonary edema, as denoted by Killip III, and cardiogenic shock, classified as Killip IV, are uncommon, collectively accounting for 5% of patients in large-scale trials. In evaluating the patient's risk, five simple baseline parameters have been demonstrated, explaining more than 90% of the prognostic information for 30-day mortality. As shown in the pyramid (Fig. 18.3), the key five characteristics are age, systolic blood pressure, Killip class, heart rate, and location of the MI (57). Thus, evaluation of the patient's age, ECG, and hemodynamics provides crucial information that stratifies risk and may be helpful in guiding therapy.

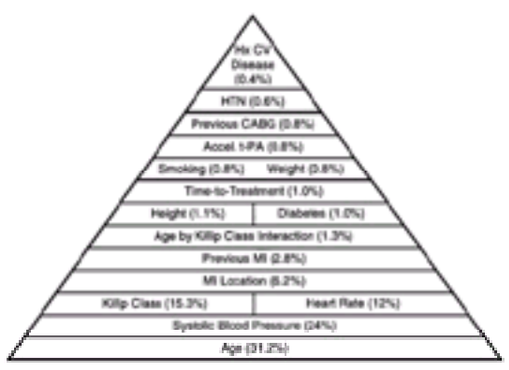


FIGURE 18.3 A multivariate model of mortality at 30 days in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial. The factors in the pyramid provide the relative importance in affecting mortality among the 41,021 patients studied. CABG, coronary artery bypass grafting; HTN, hypertension; Hx CV, history of cardiovascular disease; MI, myocardial infarction; t-PA, tissue plasminogen activator. (Data adapted from Lee KL, Woodlief L, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. *Circulation* 1995;91:1659–1668.)

TREATMENT

Analgesia and Supportive Measures

The first step in treating the patient, while more definitive therapy is being prepared (such as fibrinolytics or transfer to a cardiac catheterization laboratory), is to make the patient comfortable via supplemental oxygen (usually nasal cannula at 2 L per minute) and morphine (2 to 4 mg intravenously and repeat as necessary). Before using morphine, it is helpful to have quickly tried sublingual nitroglycerin to determine whether there is a reversible component of the ischemia, pain, and ECG changes. Furthermore, if the patient is Killip class I or II and has no bradycardia or hypotension (systolic pressure less than 110 mm Hg), then use of intravenous beta-blockade can be considered as a means of reducing the extent of ischemia and lessening the need for narcotic analgesia (58).

Aspirin

The use of aspirin is a cornerstone of therapy for patients with acute coronary syndromes. It should be initiated as quickly as possible when the diagnosis is made, at a dose of 160 mg by chewable administration (2 × 80 mg "baby" aspirin) or a 325-mg orally administered tablet. No enteric coated formulation of aspirin should be used. The validation for the importance of aspirin in this setting is derived from the landmark International Studies of Infarct Survival (ISIS-2) trial (Fig. 18.4), which showed it is lifesaving (59). Since this trial, aspirin has been used in all patients with acute MI, and other trials have provided strong evidence for its use in unstable angina and non–ST-elevation MI (60,61 and 62). The dose that has been routinely recommended is 325 mg per day, and it is continued indefinitely.

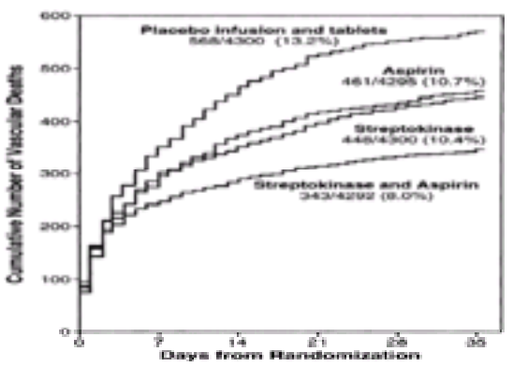


FIGURE 18.4 Second International Study of Infarct Survival (ISIS-2) showing significant reduction of mortality at 35 days for aspirin or streptokinase, and an additive effect for the two combined. [From ISIS-2 (Second international study of infarct survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet* 1988;11:349–360, with permission.]

Clopidogrel

The Clopidogrel in Unstable Angina to Prevent Recurrent Events trial (63) assessed the combination of aspirin plus clopidogrel compared with aspirin in patients without ST-segment elevation MI. With a 20% reduction of ischemic events, particularly MI (or reinfarction), there are supportive data to use this second antiplatelet (see Chapter 17). However, this has not been assessed in patients with ST-elevation MI.

Thrombolytics or Primary Mechanical Reperfusion

Patient Selection

All patients with ST-segment elevation MI who present within 12 hours from the onset of symptoms should be considered for myocardial reperfusion therapy (64,65). The list of absolute and relative contraindications is provided in *e*Table 18.2.1 and is quite straightforward in most respects. The only definite contraindications for thrombolytic therapy are active bleeding and recent stroke, trauma, or major surgery. Relative contraindications include severe or uncontrolled hypertension (systolic blood pressure greater than 180/110 mm Hg), any previous cerebrovascular history, prior gastrointestinal hemorrhage, active menstruation, pregnancy, prolonged cardiopulmonary resuscitation (CPR) (greater than 10 minutes), noncompressible vascular punctures, and coumadin therapy with an international normalized ratio of greater than 2 to 3. For patients with relative contraindications to thrombolytic therapy, consideration for primary angioplasty can be made.

***e*TABLE 18.2.1** CONTRAINDICATIONS AND CAUTIONS FOR FIBRINOLYTIC USE IN MYOCARDIAL INFARCTION

Contraindications
Previous hemorrhagic stroke at any time; other strokes or cerebrovascular events within 1 yr
Known intracranial neoplasm
Active internal bleeding (does not include menses)
Suspected aortic dissection
Relative contraindications
Severe uncontrolled hypertension on presentation (blood pressure >180/110 mm Hg) or chronic history of severe hypertension
History of prior cerebrovascular accident or known intracerebral pathology not covered in contraindications
Current use of anticoagulants in therapeutic doses (international normalized ratio 2–3); known bleeding diathesis
Recent trauma (within 2–4 wk), including head trauma or traumatic or prolonged (>10 min) cardiopulmonary resuscitation or major surgery (<3 wk)
Noncompressible vascular punctures
Recent (within 2–4 wk) internal bleeding
For streptokinase/anistreplase: prior exposure (especially within 5 d–2 yr) or prior allergic reaction
Pregnancy
Active peptic ulcer

Adapted from Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction. *J Am Coll Cardiol* 1996;28:1328–1428.

Patients with new bundle branch block are also considered suitable candidates for reperfusion on the basis of the collaborative overview of the large-scale controlled trials of thrombolytic therapy (65). However, right bundle branch block does not obscure ST elevation, and as pointed out by Sgarbossa et al., ST-segment elevation MI can frequently be diagnosed in the presence of left bundle branch block (see Chapter 59) (66). Thus, for the most part, ST-segment elevation is the hallmark ECG feature guiding the use of thrombolytic therapy along with symptoms, appropriate timing, and consideration of the clinical profile. Occasionally, left bundle branch block is present and the ST-segment elevation or ECG signs of acute MI are lacking. In these cases, a search for the old ECG is warranted; alternatively, or concomitantly, echocardiography may be considered.

The benefit of thrombolytic therapy or primary angioplasty is independent of age, gender, and most of the baseline characteristics. However, the patients who derive the most benefit are patients treated earliest, the elderly, those with anterior MI, and, in general, those with the highest risk. The critical dogma is to restore myocardial perfusion as quickly as possible. Accordingly, in a hospital with an experienced team for acute MI catheter-based intervention with an open laboratory, it may be the most rapid strategy to perform primary percutaneous transluminal coronary angioplasty (PTCA). Patient selection criteria will also be extended by the availability of primary PTCA owing to some relative exclusions of systemic fibrinolytic administration, which do not pose an incremental risk to mechanical reperfusion. Owing to the relative lack of efficacy of fibrinolytic intervention in specific settings, patients with cardiogenic shock and those with prior bypass surgery may be especially well suited for mechanical reperfusion, instead of fibrinolytic therapy.

Review of Clinical Trials

After the GISSI-1 (13) and ISIS-2 (59) trials, other placebo-controlled trials of 1,000 or more patients were pooled in the Fibrinolytic Therapy Trialists collaborative project (65,67,68,69 and 70). Collectively, the pooled data of more than 60,000 patients treated with different fibrinolytics (SK, t-PA, urokinase, or anistreplase) demonstrated an 18% reduction of mortality from 11.5% to 9.6% (13,59,65,67,68,69,70,71 and 72). Survival benefit was confirmed across a variety of subgroups, including the patients with ST elevation or bundle branch block, patients receiving therapy within 12 hours from symptom onset, diabetics, and patients with prior MI. Although patients with a systolic blood pressure less than 100 mg Hg had particular benefit, the GISSI-1 trial showed poor efficacy of thrombolytic therapy in patients with cardiogenic shock (13,65). Subsequent trials have confirmed minimal evidence for benefit of fibrinolytic therapy alone for cardiogenic shock (73,74). As discussed in the chapter by Hochman and Gersh (see Chapter 19), catheter-based reperfusion is preferred if it is available.

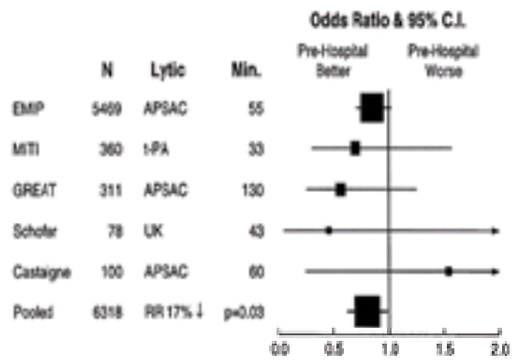
Time to Treatment

The time to treatment is a pivotal parameter in reperfusion. Patients treated in the first hour have the highest absolute and relative mortality benefit (75,76). This observation has led to the first 60 minutes to be referred to as the *golden hour* of reperfusion. The dominant explanation for the exaggerated benefit appears to be related to prevention of myocardial damage, as thallium studies have indicated the ability to prevent an MI in up to 40% of such patients (77). However, as judged from the high placebo group mortality of patients treated in the first hour, it may be that patients who present early (e.g., in less than 30 minutes from their onset of symptoms) have a larger MI and are therefore preselected to derive pronounced benefit. Certainly all of the trials convey an inverse relationship between treatment onset and survival benefit with little to no beneficial effect for patients treated at 12 hours or beyond. Two large-scale trials have been dedicated to the issue of late therapy (78,79), and both suggested that treatment benefit is restricted to the first 12 hours.

Prehospital Therapy

Taking a step backward in the chronology of presentation and management, it is noteworthy that the potential for improving outcomes is indexed to the rapidity of initiation of therapy, even with consideration for starting fibrinolytic therapy in the patient's home. A number of trials have prospectively addressed the out-of-hospital setting of reperfusion (77,80,81,82,83,84 and 85) and are summarized in *e*Figure 18.4.1. The pooled analysis demonstrates a 15% reduction of mortality in association with approximately 1-hour earlier initiation of therapy. This is a major, highly desirable effect that is difficult to attain using a system of paramedics and telemetry of the 12-lead ECG to a base station with 24-hour physician coverage to prescribe thrombolytic therapy. The problem with such a system is the marked consumption of resources and cost relative the number of patients who would qualify for out-of-hospital therapy (77,86). There is a ratio of at least 50 to 1 of patients with chest discomfort who call for ambulance transport compared with a patient who is a legitimate candidate for initiating fibrinolytics at his or her home. The time necessary to acquire the 12-lead ECG in the home is not substantial, or for transmitting the tracing to a medical center, but the commitment for training paramedics, using the cellular transmission of the ECG data, and physician staffing to interpret the tracings and the patient profile to make a decision are all cumbersome and represent a formidable expense. Few communities in the United States actually are capable of administering thrombolytic therapy in the patient's home (77,86). In some locations in Europe, where physicians staff the ambulances, this practice is more feasible; other models do not require a 12-lead ECG, but this is fraught with considerable potential for misdiagnosis and unnecessary exposure to thrombolytic therapy. As technology improves and the ECG is more readily interpreted (e.g., computer assessment combined with trained paramedic interpretation) and bolus thrombolytic therapy is commonplace, the practice of out-of-hospital thrombolytic therapy may

become more logistically attractive. Another factor that would promote its use would be a pharmacologic intervention that was more risk averse.



***e*FIGURE 18.4.1** Results of clinical trials comparing prehospital and in-hospital thrombolytic therapy. APSAC, anistreplase; C.I., confidence interval; EMIP, European Myocardial Infarction Project; MITI, Myocardial Infarction Triage and Intervention; GREAT, Grampian Region Early Anistreplase Trial; RR, relative risk; t-PA, tissue plasminogen activator; UK, urokinase. (Data adapted from The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med* 1993;329:383–389.)

In the meantime, there is an opportunity to apply the key data generated from these prehospital trials by facilitating the time to treatment. By having the ECG done in the field and transmitting this to the hospital receiving the patient, the decision for therapy can be implemented such that a thrombolytic is reconstituted and ready at the moment the patient arrives. This decision can significantly reduce the time to treatment, but again relies on the emergency medical service's capability and willingness to obtain the 12-lead ECG and transmit the recording.

Everything that can be done to shorten the time to treatment, once the patient has arrived at the hospital, has to be enacted. This includes a rapid assessment of the history and a physical examination, immediate ECG and interpretation, a quick decision of whether the patient qualifies for reperfusion and which type (pharmacologic or mechanical), and definitive therapy to achieve recanalization of the infarct vessel. Many hospitals have demonstrated a "door to needle" time of less than 20 to 30 minutes, which is the goal for all centers. However, the national average still exceeds 60 minutes, although this represents progress as in the past few years the time to thrombolytic treatment was well over 100 minutes (87).

Selection of Fibrinolytic Agents

There have been three large trials that studied the differences in effects on mortality for t-PA and SK (73,74,88,89). In the GISSI-2/International trial (73,74) 20,749 patients were randomly assigned to t-PA or SK, with a factorial design also randomized to subcutaneous heparin started after 12 hours or no heparin. The t-PA was alteplase given over 3 hours. Mortality at 30 days was 8.9% and 8.5%, respectively (74). The ISIS-3 trial evaluated 41,299 patients with three different thrombolytic agents: the duteplase form of t-PA, which has not been commercially developed; SK; and anistreplase. A factorial design for evaluating subcutaneous heparin started after 4 hours versus placebo was also used. There were no differences in mortality (10.3%, 10.5%, and 10.6%, respectively) (88). Subsequently, the Global Use of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial evaluated 41,021 patients randomly assigned to one of four thrombolytic strategies (89). Accelerated alteplase t-PA over 90 minutes, administered with intravenous heparin, was shown to significantly reduce 30-day mortality by 15% as compared with SK with intravenous or with subcutaneous heparin, or the combination of t-PA and SK with intravenous heparin (Fig. 18.5). The benefit was highly consistent across virtually all subcategories, including age, location of MI, and the time from symptom onset (*e*Fig. 18.5.1). Although the superiority of t-PA was contested because of the eight- to tenfold increase in its cost compared with SK ($2,200 vs. $300), the differences were highly significant, consistent, and durable at 1 year of follow-up (89,90,91 and 92). The mechanism for the benefit, with earlier complete infarct vessel patency, as discussed later in this chapter (see Importance of Early and Complete Reperfusion), was also fully characterized (83) (*e*Fig. 18.5.2 and Fig. 18.6). As would be expected, the patients with the higher risk derived the most substantial benefit of t-PA compared with SK (91). Formal cost-effectiveness analysis has shown that accelerated t-PA saved 14 additional years of life per 1,000 patients treated, which translates to a cost of $32,678 per year of life saved (90). This compares favorably with such benchmarks as the cost of hypertension treatment ($20,000 per year of life saved) or the cost-effectiveness ratio of hemodialysis for chronic renal failure ($35,000 per year of life saved), but still represents a significant toll on an individual patient basis and on a societal level.

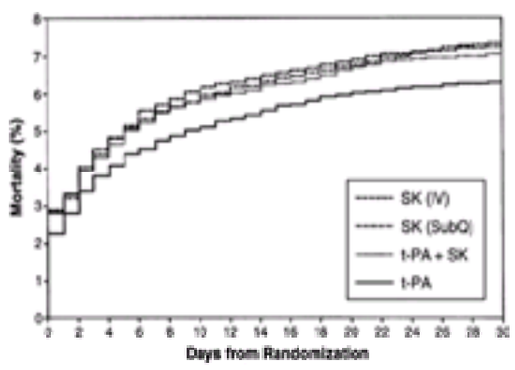
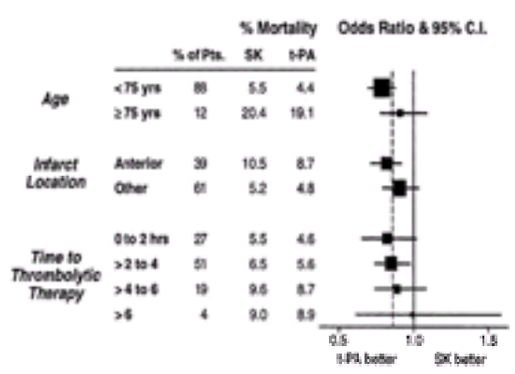
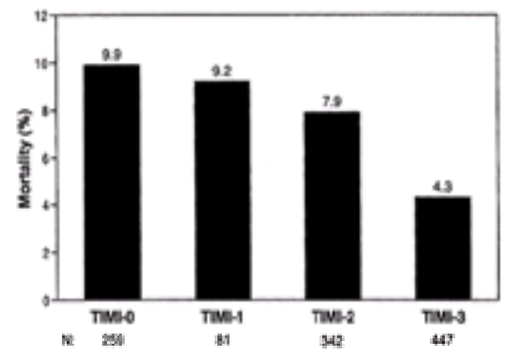


FIGURE 18.5 Thirty-day mortality in four treatment groups. The group receiving accelerated treatment with tissue plasminogen activator (t-PA) had lower mortality than both the two streptokinase (SK) groups (p = .001) and each individual treatment group: streptokinase and subcutaneous (SubQ) heparin (p = .009), streptokinase and intravenous (IV) heparin (p = .003), and tissue plasminogen activator and streptokinase combined with IV heparin (p = .04). (From The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:1615–1622, with permission.)



***e*FIGURE 18.5.1** Odds ratio and 95% confidence intervals (C.I.) for 30-day mortality in the prespecified subgroups defined by age, infarct location, and time to thrombolytic therapy. SK, streptokinase; t-PA, tissue plasminogen activator. (From The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:1615–1622, with permission.)



***e*FIGURE 18.5.2** Infarct vessel patency status at 90 minutes compared with mortality at 30 days in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) angiographic trial. TIMI, Thrombolysis in Myocardial Infarction semiquantitative scoring system. (Data from the GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:1615–1622.)

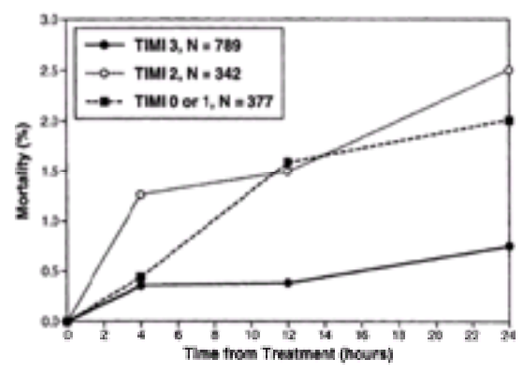


FIGURE 18.6 Plot of mortality according to Thrombolysis in Myocardial Infarction (TIMI) flow grade on the angiogram performed at 90 minutes in the angiographic study. Data are taken according to flow grade regardless of treatment arm. (Adapted from Kleiman NS, White, Ohman EM, et al. Mortality within 24 hours of thrombolysis for myocardial infarction: the importance of early reperfusion. *Circulation* 1994;90:2658–2665.)

New Plasminogen Activators

As shown in Figure 18.7, many new thrombolytic agents are being developed and these have been termed *third-generation* plasminogen activators (91,92,93,94,95,96,97,98,99,100,101 and 102). The mutants of native t-PA include reteplase (r-PA, Retevase, Roche/Centocor), lanoteplase (n-PA, Bristol-Myers Squibb), and TNK (a triple mutant Genentech; see Fig. 18.7). Other agents that are being developed include recombinant staphylokinase and vampire bat plasminogen activator.

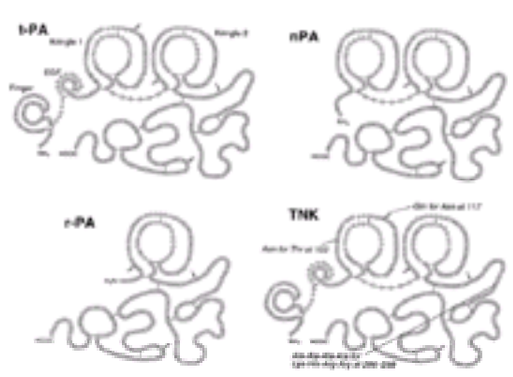


FIGURE 18.7 Structure of wild-type tissue plasminogen activator (t-PA) and three mutants. Reteplase (r-PA) is missing the finger, epidermal growth factor (EGF), and Kringle-1 domain. Lanoteplase (nPA) is similar to r-PA but maintains the Kringle-1. TNK is a triple site-directed mutagenic plasminogen activator with changes at three sites, as shown.

The common theme for many of these agents is their prolonged half-life and the ability to use a bolus-type administration. Three of the agents have remarkable fibrin specificity: TNK, staphylokinase, and bat PA, which affords almost no fibrinogenolysis. All have the theoretical potential to be more potent in lysing coronary thrombi and therefore are being pursued for acute MI as a chief indication. Each of the agents is briefly addressed.

Reteplase

r-PA was approved for use in the United States in 1996 and represents the first of the third-generation thrombolytics to become commercially available. As shown in Figure 18.7, it is a deletion mutant of t-PA and is given as two 10-MU boluses, 30 minutes apart. Like t-PA, intravenous heparin is used in conjunction with r-PA, and the results of two angiographic trials (103,104) indicate the potential of superiority for speed and extent of coronary thrombolysis for r-PA compared with conventional or accelerated t-PA. The International Joint Evaluation of Coronary Thrombolysis trial compared r-PA with SK in over 6,000 patients and demonstrated a small, but not statistically meaningful benefit for r-PA (105). The GUSTO-III trial compared r-PA and accelerated t-PA in 15,072 patients. No benefit for r-PA over t-PA was demonstrated (50) (Fig. 18.8). There was a higher mortality and hemorrhagic stroke rate in GUSTO-III compared with previous trials, probably owing to a more aged population enrolled. Both t-PA and r-PA cost approximately $2,200 per dose. The major benefit of r-PA over t-PA is the ease of use. Equivalence has not been established at 30 days or 1 year with respect to mortality point estimates, although the findings in GUSTO-III were supportive of a minimal gap.

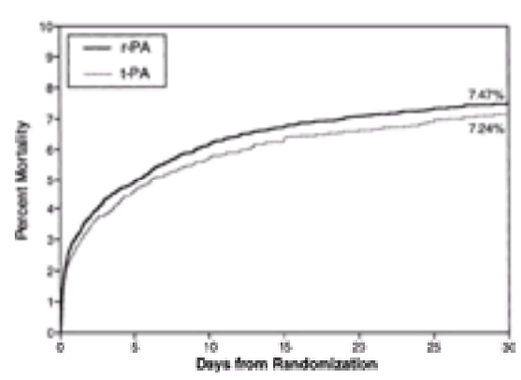


FIGURE 18.8 Primary results of Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-III) trial for 30-day mortality. r-PA, reteplase; t-PA, tissue plasminogen activator.

Tenecteplase

An outgrowth of the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) trial (106) was the validation of TNK as equivalent (or not inferior) to accelerated t-PA. As shown in Figure 18.9, the mortality at 30 days was remarkably similar with this single-bolus agent compared with the more complicated accelerated t-PA regimen. Furthermore, there was superiority established for patients presenting late (receiving therapy after 4 hours) and a significant reduction in noncerebral bleeding complications. Taken together, the profile of TNK is particularly favorable, and this is the most fibrin-specific agent currently available. Its cost, however, is similar to alteplase and r-PA.

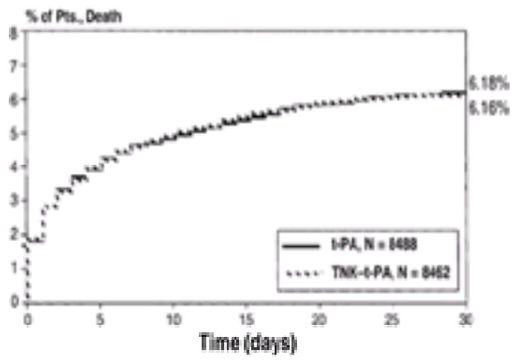


FIGURE 18.9 Mortality at 30 days for TNK as compared with accelerated tissue plasminogen activator (t-PA) in the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) trial.

Other Agents

n-PA was studied in the *I*ntravenous *n*PA for *T*reatment of *I*nfartcting *M*yocardium *E*arly (InTIME)-2 trial and did not fare particularly well against accelerated t-PA (52). Although the mortality at 30 days was within 0.3% absolute, possibly fulfilling noninferiority criteria, there was a significant excess in intracerebral hemorrhage with this single-bolus mutant t-PA. Thus far, n-PA has not become commercially available.

Staphylokinase has had promising phase II angiographic trial data and is a fibrin-specific agent such as TNK (107,108 and 109). However, it has yet to go forward with a mortality reduction trial and, despite efforts to reduce immunogenicity, has some intrinsic homology to SK. Saruplase, recombinant single-chain urokinase-type plasminogen activator, has been shown to provide better angiographic results than SK (110), but is not available on a commercial basis.

Importance of Early and Complete Reperfusion

The mechanism of benefit of accelerated t-PA in the GUSTO-I trial was clearly demonstrated to be the improvement in timely and complete restoration of coronary blood flow (111). As shown in eFigure 18.5.2, the proportion of patients in the angiographic trial who had TIMI-3 flow at 90 minutes after therapy was initiated, reflecting brisk infarct vessel blood flow, was considerably higher for the patients receiving t-PA compared with the other three strategies assessed. Nonetheless, even for accelerated t-PA, the rate of TIMI-3 flow was only 54%, leaving room for improvement in future pharmacologic reperfusion strategies (111). The patency status at 90 minutes was a critical index of outcomes, including survival at 24 hours, 30 days, and 1 and 2 years (Fig. 18.5, Fig. 18.6, and Fig. 18.10; eFig. 18.10.1) (89,111,112,113 and 114). Beside the salutary effects on improving survival, the TIMI-3 flow status was closely associated with global left ventricular function, cavity dilatation, and regional wall motion of the infarct zone (111,115) (eFig. 18.10.2). In eFigure 18.10.3, the linkage of early (90- to 180-minute) end systolic volume and 1-year mortality is shown (114).

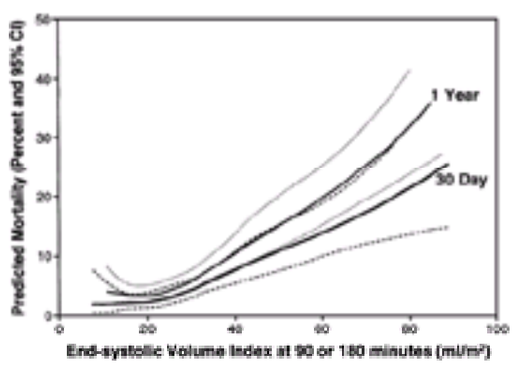
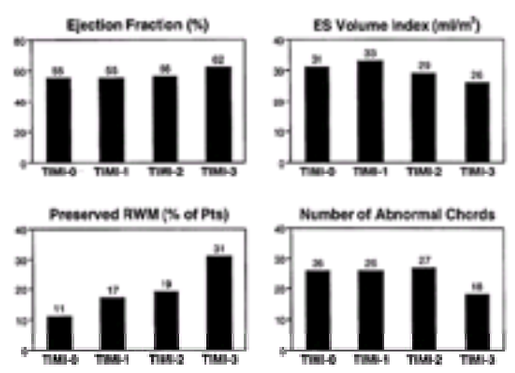
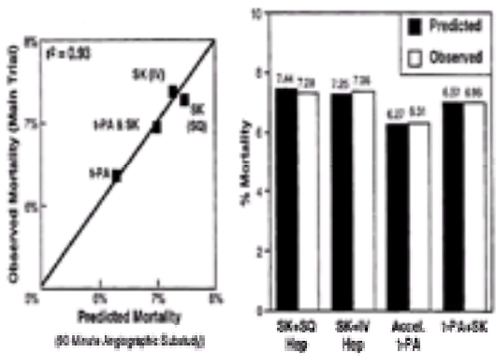


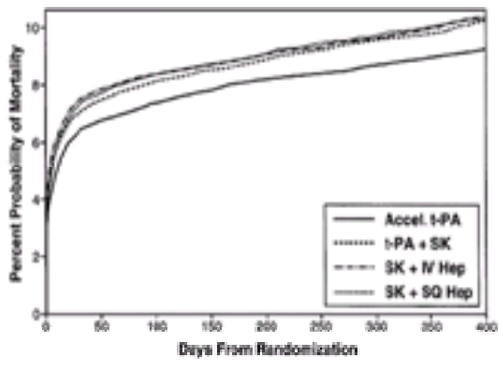
FIGURE 18.10 Model of the relationship between end systolic volume index and 30-day and 1-year mortality. Dashed lines represent 95% confidence interval (CI) for 1-year mortality, and dotted lines represent 95% CI for 30-day mortality. (From Migrino RQ, Young JB, Ellis SG, et al. End-systolic volume index at 90–180 minutes into reperfusion therapy for acute myocardial infarction is a strong predictor of early and late mortality. *Circulation* 1997;96:116–121, with permission.)



***e*FIGURE 18.10.1** Effect of 90-minute patency on ventricular function parameters at 90 minutes according to Thrombolysis in Myocardial Infarction (TIMI) grade. ES, end systolic; RWM, regional wall motion. (Adapted from The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:1615–1622.)



***e*FIGURE 18.10.2** Graphs showing predicted versus observed 30-day mortality results by treatment assignment. Predicted results are based on the 1,210 patients randomized to angiography at 90 minutes. Observed results refer to the remaining 39,811 patients in the main trial. Proportion of squared error explained (r^2) is 0.93. Accel. t-PA, accelerated tissue-type plasminogen activator with intravenous heparin; SK (IV), streptokinase with intravenous heparin; SK (SQ), streptokinase with subcutaneous heparin; t-PA & SK, t-PA plus streptokinase with intravenous heparin. (From Simes RJ, Topol EJ, Holmes DR, et al. The link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: the importance of early and complete infarct artery reperfusion. *Circulation* 1995;91:1923–1928, with permission.)



***e*FIGURE 18.10.3** Overall 1-year mortality in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial by treatment assignment. Accel. t-PA, accelerated tissue-type plasminogen activator with intravenous heparin; IV Hep, intravenous heparin; SK, streptokinase; SQ Hep, subcutaneous heparin; t-PA, tissue plasminogen activator. [From Califf RM, White HD, Van de Werf F, et al. One-year results from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) Trial. *Circulation* 1996;94:1233–1238, with permission.]

Approximately one-half of the patients who have fatal events with acute MI treated with thrombolytic therapy die within the first 24 hours (115). Many of these deaths are related to failure of reperfusion therapy or extensive myocardial damage in spite of reperfusion. In placebo-controlled trials of thrombolytic therapy, there has been an excess of deaths in the treated group during the first 24 hours. Although this phenomenon has been referred to as *early hazard* (65,115) and is not fully explained, the mechanism of death is usually related to power failure and to a lesser extent to myocardial rupture, arrhythmia, or intracerebral hemorrhage (115). Clearly, the early establishment of complete infarct vessel patency protects against death in the first 24 hours, just as it does during extended follow-up. The benefit of accelerated t-PA in the GUSTO-I trial was significant even at the 24-hour end point (Fig. 18.6), which accounted for nearly one-half of the survival benefit achieved by 30 days (89,115). There is no question that the first 24 hours is a critical time window in which much of the fate of a patient with acute MI is declared. Even in a patient with a large MI, assurance of brisk infarct vessel blood flow markedly reduces the chance of early fatality.

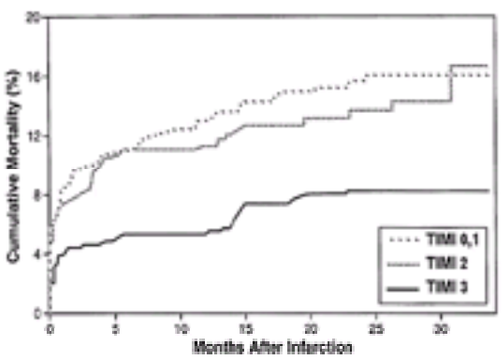
The left ventricular performance parameters at 90 minutes of therapy are insightful, as the TIMI flow pattern is closely linked with each index. In particular, TIMI-3 flow is predictive of significantly better ejection fraction, a smaller end diastolic and end systolic left ventricular cavity, and more intact regional motion of the infarct zone. Previous longitudinal studies have demonstrated the vital prognostic importance of ejection fraction and end systolic volume (116,117) for long-term survival, and this was confirmed in GUSTO-I (Fig. 18.10). Thus, these cardiac performance parameters provide a meaningful surrogate and mechanistic data for the subsequent reduction in mortality.

The link between early infarct vessel patency and 30-day mortality was studied by Simes et al. in the GUSTO-I trial (118) (*e*Fig. 18.10.2). In this analysis, the relationship between the relatively small cohort of patients with 90-minute patency evaluated in the angiographic trial was used to predict the mortality outcome for each thrombolytic strategy in the much larger mortality trial. The correlation coefficient of 0.93 indicates the tightness of this relationship, such that TIMI flow, irrespective of the pharmacologic strategy used, represents the main treatment determinant of clinical outcome.

VIDEO

Video 18.3 Angiogram demonstrating TIMI 1 flow. (Courtesy of Dr. Debabrata Mukherjee.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

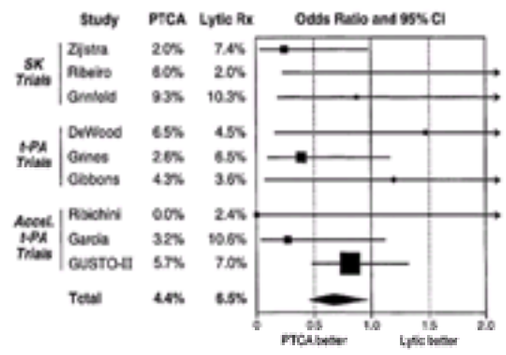
Following the patients beyond 30 days, the 1-year outcome according to thrombolytic strategy in the overall trial (*e*Fig. 18.10.3), along with the extended follow-up in the angiographic trial (*e*Fig. 18.10.4), provides further cogent evidence of the closeness and importance of the relationship between early TIMI flow and the outcome.



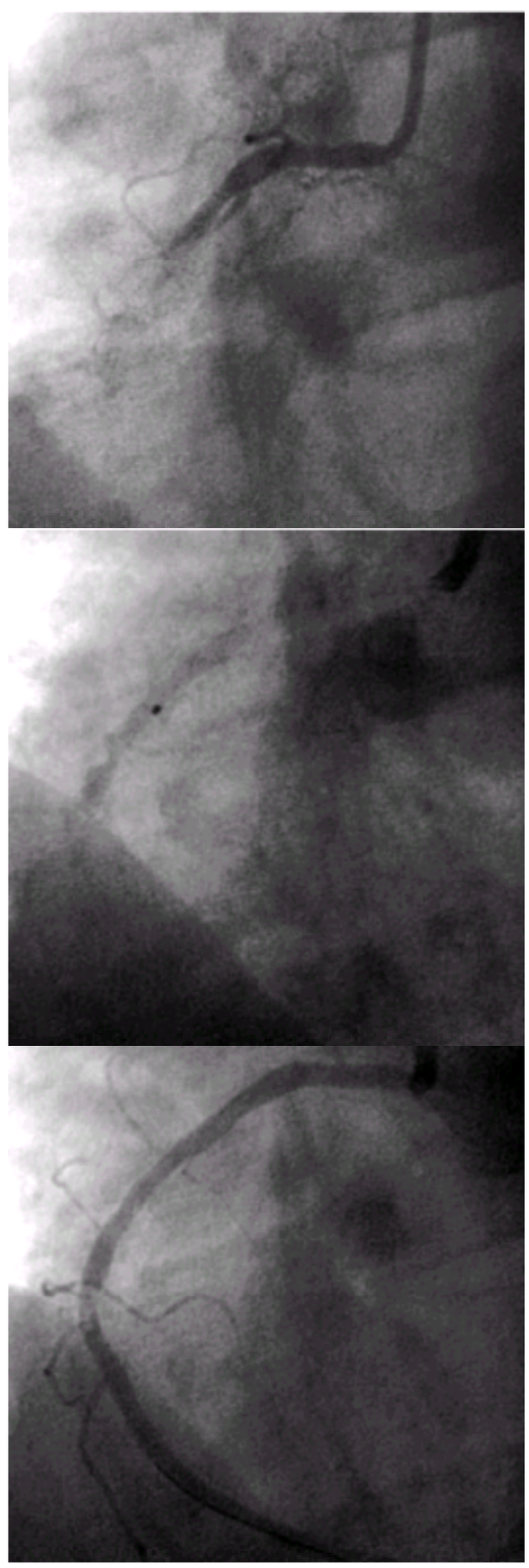
***e*FIGURE 18.10.4** Relationship of long-term infarct vessel patency and mortality at 3 years. Patients in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) angiographic trial with Thrombolysis in Myocardial Infarction (TIMI-3) flow had approximately one-half of the long-term mortality during extended follow-up. Furthermore, there was divergence of the event curves over time such that 4 lives per 100 patients were saved by achieving TIMI-3 flow at 30 days as compared with 8 lives per 100 patients at 3 years.

Primary Mechanical Reperfusion

Although thrombolytic therapy is a strategy that can be applied in virtually all hospitals, the 54% plateau of TIMI-3 flow (at 90 minutes) for even the most effective plasminogen activator available is a major shortcoming. The technique of mechanical reperfusion using balloon angioplasty that was introduced by Hartzler et al. in the mid-1980s (9) has been convincingly superior to thrombolytic therapy for establishing TIMI-3 flow in a greater proportion of patients. As assessed in the GUSTO-IIb substudy that directly compared accelerated t-PA and primary angioplasty, the rate of infarct vessel TIMI-3 flow was 80% (119), representing a near 50% proportionate improvement over accelerated t-PA. In *e*Table 18.2.1, the major features of the nine randomized trials of thrombolytics and primary angioplasty are summarized (119,120,121,122,123,124,125,126 and 127). In aggregate, approximately 2,500 patients have been incorporated in these trials, with two different thrombolytic agents, and, in the case of t-PA, both the 3-hour and accelerated dosing strategies. The number of patients assessed is thus two orders of magnitude less than the thrombolytic trial experience, and the scientific rigor of the trials, most of which had no central adjudication of clinical events or core angiographic laboratories, is suboptimal. The primary end point in these trials could not be mortality, owing to the small sample size, but pooling the studies affords a look into whether mortality is significantly affected. The pooled results of the trials are presented in *e*Figure 18.10.5, which shows a strong trend toward mortality reduction, and a significant reduction of the composite of death and reinfarction. Another benefit of major outcomes that has been unraveled in these trials has been the reduced incidence of intracerebral hemorrhage with balloon angioplasty as compared with thrombolytic therapy.



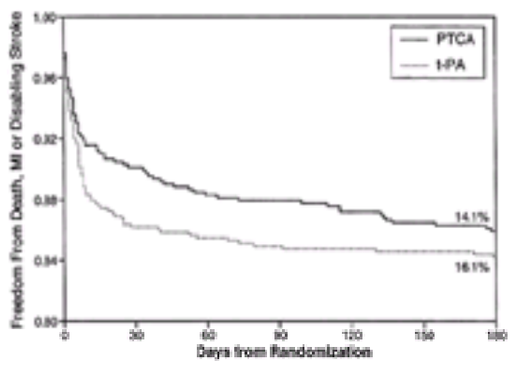
***e*FIGURE 18.10.5** Odds ratio for mortality with 95% confidence intervals (CI) for the nine randomized trials comparing percutaneous transluminal coronary angioplasty (PTCA) versus thrombolytic therapy. The size of the point estimate correlates with the sample size in the trial. Overall, there is a significant 32% reduction in mortality. Accel. t-PA, accelerated tissue-type plasminogen activator with intravenous heparin; GUSTO-II, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; Rx, treatment; SK, streptokinase; t-PA, tissue plasminogen activator.



The use of perfusion balloon angioplasty to treat an acute inferior myocardial infarction. Normal antegrade flow is restored (C) beyond the area of total

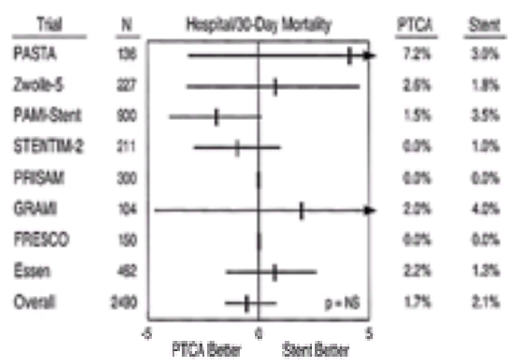
occlusion in the mid right coronary artery (A) after a prolonged inflation with a perfusion balloon catheter (B).

The early benefit of angioplasty over thrombolytic therapy is attenuated during more extended follow-up. As shown in eFigure 18.10.6, at 6 months' follow-up in the largest trial, GUSTO-IIb, there was near equivalence of the death and nonfatal reinfarction end point (119). In parallel, there was little difference in the actual cumulative costs associated with the two strategies ($18,643 vs. $19,395 for PTCA and t-PA, respectively, p = .19) (128).

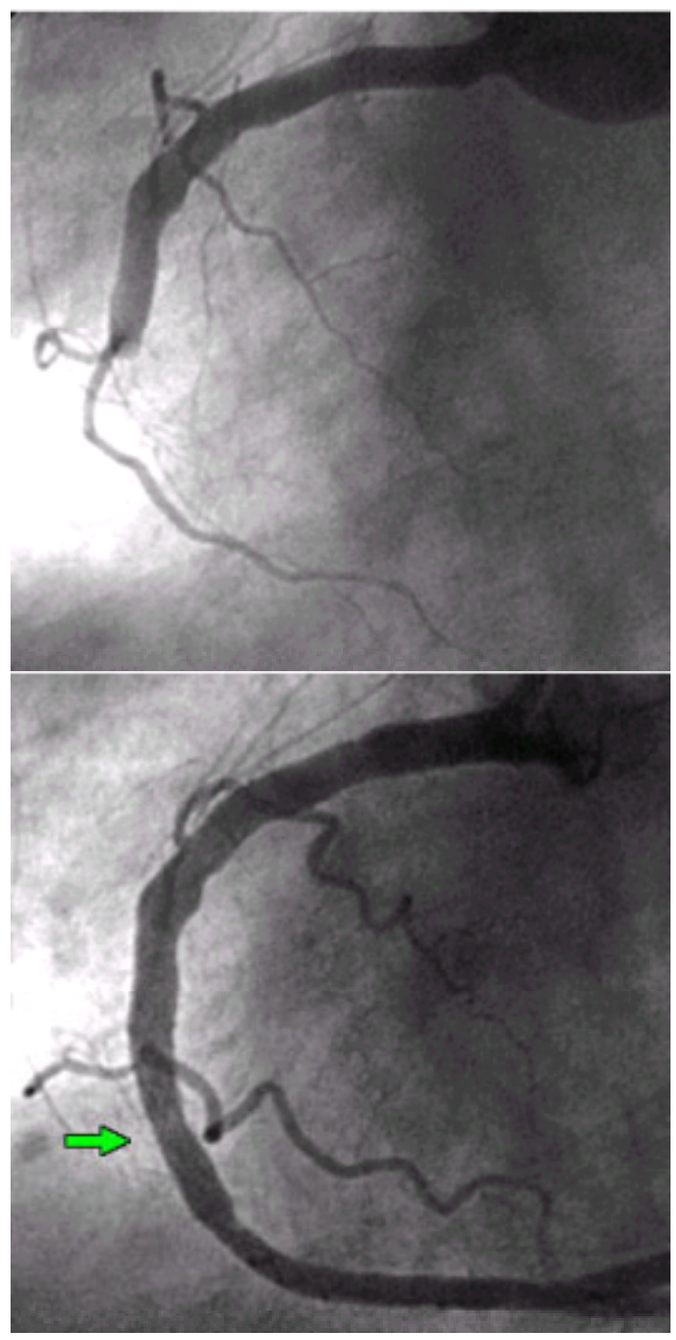


***e*FIGURE 18.10.6** Incidence of death or nonfatal myocardial infarction in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-IIb) substudy comparing percutaneous transluminal coronary angioplasty (PTCA) versus accelerated tissue plasminogen activator (t-PA). MI, myocardial infarction. (Data adapted from GUSTO II Angioplasty Substudy Investigators. An international randomized trial of 1138 patients comparing primary coronary angioplasty versus tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;336:1621–1628.)

A number of trials have compared balloon angioplasty with stenting for acute MI reperfusion (129,130,131,132,133,134,135 and 136), and the mortality data for eight of these trials are summarized in eFigure 18.10.7. Overall, the in-hospital or 30-day mortality did not favor stenting. On the other hand, all of these trials showed less need for repeat target vessel revascularization, and overall the rate of reinfarction was reduced from 2.5% to 0.9% (137). The *S*tent versus *T*hrombolysis for *O*ccluded Coronary Arteries in *P*atients with *A*cute *M*yocardial *I*nfarction (STOP AMI) trial trial compared alteplase with stenting and abciximab and demonstrated a substantial reduction of infarct size along with a trend of improved survival (138). The Controlled Abciximab and Device4 Investigation to Lower Late Angioplasty Complications (CADILLAC) trial compared balloon and stenting in a two-by-two factorial design with abciximab or control (not blinded) and showed an advantage for stenting for the primary end point (139). Overall, the mortality of stenting compared with balloon angioplasty has not been shown to be significantly reduced in the aggregate of all of the trials. Nevertheless, the overriding benefits of lessened reinfarction and the need for repeat revascularization have made stenting the standard for catheter-based reperfusion. As discussed subsequently (see Rescue Percutaneous Transluminal Coronary Angioplasty), more recent trials have incorporated IIb/IIIa inhibition, which may further ameliorate the results of stenting in acute MI.



***e*FIGURE 18.10.7** In-hospital or 30-day recurrent myocardial infarction in randomized trials of stenting in acute myocardial infarction. PTCA, percutaneous transluminal coronary angioplasty. (From Steinhubl S, Topol EJ. Primary angioplasty and stenting in acute MI. In: Topol EJ, ed. *Acute coronary syndromes*, 2nd ed. New York: Marcel Dekker, 2001:373–390, with permission.)



Primary stent placement for an acute inferior myocardial infarction. After the administration of abciximab, a Palmaz-Schatz biliary stent (B) is deployed across the area of acute occlusion in the mid right coronary artery (A), resulting in normal antegrade flow and no residual stenosis (C).

One major criticism that has been raised regarding primary PTCA is that the clinical trial experience may not be mirrored or replicated in community hospitals (140,141,142 and 143). It is clear that critical factors, such as the time from patient arrival ("door") to successful angioplasty-mediated reperfusion ("balloon") must be minimized and has been less than 60 minutes in the trials in which the most extensive advantage over thrombolysis was demonstrated. Many studies have shown that the average door-to-balloon time is approximately 2 hours for many hospitals, which may serve as the principal explanation for the failure to achieve excellent results (140,141,142 and 143). Furthermore, operator experience probably plays a meaningful role as the technical aspects of the procedure are important (140). Infarct vessels, as compared with diseased arteries in patients without acute coronary syndromes, are particularly prone to intimal dissection, vasospasm, and thrombosis. Furthermore, the complexity of the patient, with respect to hemodynamic management and arrhythmias, is heightened. Specific expertise in performing rapid, high-volume, high-quality (superior risk-adjusted outcomes) mechanical reperfusion probably accounts for some of the discrepancies between clinical trials and the community at large.

As far as recommendations for the use of mechanical reperfusion, it is clear that if a patient is in the right time and the right place with an evolving acute MI, then primary PTCA would be preferred. This is an infrequent phenomenon, however, as only a limited number of hospitals have the facilities, operators and teams, their timely availability, and the expertise. Nevertheless, if a patient presents to an appropriate center with these features, primary PTCA should be considered the superior strategy. In most cases, even in centers in which primary PTCA is used but the catheterization laboratory or personnel are not quickly available, thrombolytic fibrinolytic therapy is more easily implemented. It is worth bearing in mind, however, that for thrombolytic fibrinolytic therapy to actually dissolve the coronary thrombus and reestablish coronary blood flow it takes approximately 45 to 60 minutes. Therefore, in a situation in which the door-to-balloon time is anticipated to be 60 minutes, there is still legitimacy in using primary PTCA for more rapid and reliable reperfusion. This important triage decision must be made on an individual patient basis, but should not be accompanied by any delay.

Other patients who specifically benefit from primary PTCA are those with an absolute or relative contraindication to thrombolytic therapy (*e*Table 18.2.2), owing to safety concerns, and in patients with prior bypass surgery or cardiogenic shock, attributed to the markedly reduced efficacy of thrombolytic therapy in both of these settings (13,73,74,144,145,146 and 147). The reasons for poor efficacy are different. In cardiogenic shock, t-PA fibrinolytics have a high failure rate because their effect relies on adequate perfusion (148), whereas the failure rate of thrombolytics in saphenous vein grafts is attributed to the extensive clot burden and slow runoff (145). Furthermore, patients with a large MI (especially the proximal LAD; Table 18.1) should be considered for primary mechanical reperfusion because the risk profile is so high if successful reperfusion is not achieved.

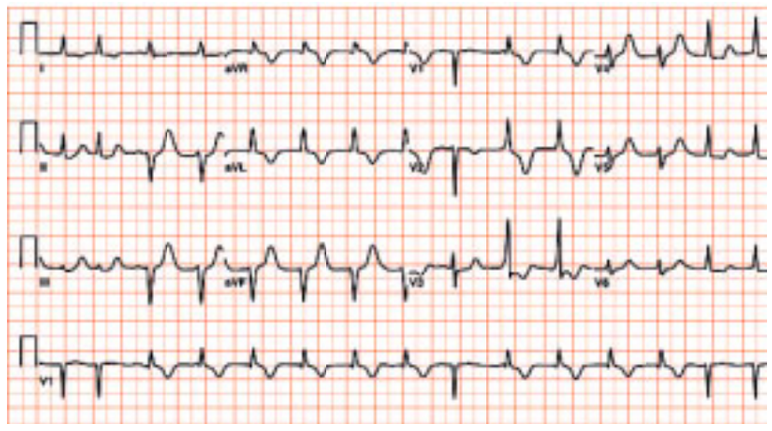
***e*TABLE 18.2.2** FEATURES OF THE RANDOMIZED TRIALS COMPARING PRIMARY PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) VERSUS INTRAVENOUS THROMBOLYSIS

Reference	Lytic agent and regimen	No. patients PTCA	No. patients thrombolysis	Time to PTCA (min)	Time to thrombolysis (min)
De Wood (125)	Duteplase over 4 h	46	44	126	84
Grines (120)	Alteplase over 3 h	195	200	60	32
Zijlstra (121)	1.5 M u SK over 1 h	197	192	62	30
Gibbons (122)	Duteplase over 4 h	47	56	45	20
Ribeiro (123)	1.2 M u SK over 1 h	50	50	238	179
Ribichini (127)	Alteplase over 90 min	41	42	40	33
Grinfeld (126)	1.5 M u SK over 1 h	54	58	63	18
GUSTO-II (119)	Alteplase over 90 min	565	573	114	72
Elizaga (124)	Alteplase over 90 min	95	94	84	69

GUSTO-II, Global Use of Streptokinase and t-PA for Occluded Coronary Arteries; M u SK, mega units SK; SK, streptokinase.

Clinical Detection of Reperfusion

Apart from administering thrombolytic therapy or performing PTCA as rapidly as possible after the diagnosis is established, it is important to emphasize that in most patients one cannot rely on bedside signs to reliably detect whether pharmacologic reperfusion has been successful (114,115,116 and 117). First, it is not possible to use the patient's chest pain as a guide to whether the therapy is effective. The reasons for this are multiple, including the confounding effects of narcotic analgesics, the partial denervation that occurs at some point after coronary thrombosis in some patients with MI (118), the stuttering pattern of infarct vessel blood flow in the early hours of infarction, and the natural evolution of the necrosis with eventual attenuation or relief from chest pain. Second, so-called reperfusion arrhythmias are a misnomer, such as ventricular tachycardia, as they more commonly occur in patients who either do not receive reperfusion therapy or fail to achieve successful reperfusion (119,120 and 121). One arrhythmia that has been correlated with restoration of infarct vessel patency is accelerated idioventricular rhythm (114,115). Third, resolution of the ST-segment elevation is an unreliable means of establishing reperfusion success. There may be partial resolution from natural, evolutionary features of the event or the dynamic blood flow pattern so characteristic of the first 12 hours of acute MI. If a patient develops sudden and near complete relief of chest pain, full resolution of the ECG abnormalities, and has a run of accelerated idioventricular rhythm, this is highly specific for successful reperfusion, but this only occurs in less than 10% of patients receiving thrombolytic therapy (example in Fig. 18.5) (114,115).



A 51-year-old patient with reperfusion accelerated idioventricular rhythm after thrombolytic therapy. Prior electrocardiogram documented ST elevation in leads II, III, and AVF, which resolved with thrombolytic therapy.

Accordingly, we do not have a sensitive bedside, clinical means of detecting reperfusion. A variety of enzymatic tests have been advocated, including myoglobin, creatine kinase isoforms, and troponin, but these have not yet been proven to be clinically useful (122,123,124,125,126,127,128,129,130 and 131). Continuous recording of the 12-lead ECG or serial assessment of the 12-lead ECG at baseline and 60 minutes into therapy may be more useful methods for the diagnosis of successful or unsuccessful reperfusion (132,133 and 134), but there is a suboptimal relationship between the extent of ST-segment resolution and the completeness of coronary blood flow. This may be related to the temporal instability of coronary blood flow in the early hours of acute MI, and that many of the studies that evaluated the correlation did not have simultaneous assessment of the ECG and angiographic indices. Alternatively, because up to one-third of patients with TIMI-3 flow on the angiogram do not have flow at the tissue level as evaluated with contrast echo perfusion imaging or positron emission tomography (135), it is possible that the ECG parameters are more indicative or authentically reflect the true myocardial perfusion status. Noninvasive markers continue to be intensely investigated, with more recent studies of cine magnetic resonance angiography (136,137), echocardiography (138), high-frequency QRS monitoring (139), and continuous vector ECG (140). Although in clinical practice there is frequent use of the term *clinical reperfusion*, it is essential to point out that this is usually based on quite soft criteria that may be misleading.

Heparin

Even though heparin was administered as early as 1916, it has only been in relatively recent years that we have generated data to study the appropriate ways of its use. A critical advance came with the analysis of the GUSTO-I trial in which more than 30,000 patients had intravenous heparin, serial measurements of the activated partial thromboplastin time (aPTT), and assessment of clinical outcomes (149). As shown in Figure 18.11, there is a relationship between aPTT and 30-day mortality, with the optimal range between 50 and 70 seconds. The same preferred range of 50 to 70 seconds proved to be associated with lower bleeding complications, and particularly intracerebral hemorrhage, than more aggressive heparin effects. These data, importantly, are not from a randomized trial of conservative or aggressive

heparin dosing strategies, but represent the largest data set that compares heparin effects and clinical outcomes.

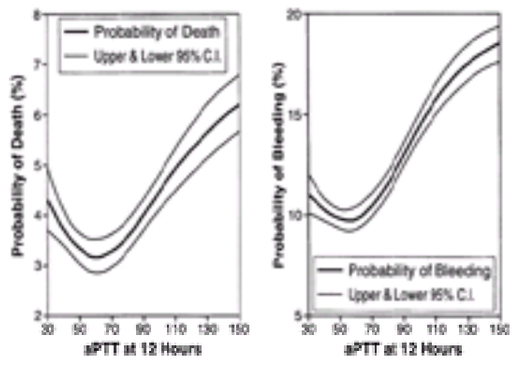


FIGURE 18.11 Activated partial thromboplastin time (aPTT) versus probability of death (30 days) or of severe or moderate bleeding. C.I., confidence interval. (Adapted from Granger CB, Hirsh J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction. *Circulation* 1996;93:870–878.)

When used in conjunction with thrombolytic therapy, heparin should be administered on a weight-adjusted basis at 60 U per kg bolus (maximum, 4,000 U) and followed by 12 U per kg per hour (maximum, 1,000 U per hour initially) (149a). Consideration for a lower bolus should be given in patients who are aged, lightweight (less than 50 kg), and female, as these are the major determinants of the aPTT after heparin administration (149). The use of intravenous heparin is essential with t-PA, as verified in a number of controlled angiographic trials (150,151,152 and 153), but less documented with SK (73,88,89,154,155 and 156). SK has considerably more fibrinogenolytic action, such that it will intrinsically elevate the aPTT to a higher extent than t-PA. In the GISSI-2 International and ISIS-3 controlled trials of high-dose subcutaneous heparin after SK, there was little evidence of mortality reduction and more bleeding complications (73,74,88). In GUSTO-I comparing SK with intravenous versus subcutaneous heparin, there were no significant differences for mortality even though predischarge infarct vessel patency favored intravenous heparin in the angiographic trial (88). There is considerable debate as to whether any heparin should be routinely conjunctively administered with SK (155,156 and 157), but more recent trials of direct thrombin inhibitors strongly suggest the potential for better adjunctive therapy with this plasminogen activator (158,159). Heparin is used for the first 48 hours, with serial assessment of the aPTT at 6,12, and 24 hours and active titration of the aPTT to the 50- to 70-second value. After 24 hours, in the uncomplicated patients, heparin can be discontinued. In patients with recurrent ischemia, however, atrial fibrillation, or those with an antero-apical MI who may require oral anticoagulation to prevent stroke (see Chapter 19 and Chapter 20), heparin should be continued until hospital discharge or the oral anticoagulation effect is fully established.

Bleeding Complications of Thrombolytics and Anticoagulation

With the judicious use of heparin, the potential for bleeding complications of thrombolytics is reduced. Nevertheless, the most feared complication of intracerebral hemorrhage occurs in approximately 1 of 200 patients (0.5%) treated with thrombolytic therapy. The incidence is definitely higher with t-PA (0.7%) than SK (0.4%) (73,74,88,89,160,161). Prompt recognition of this catastrophe can be helpful because there are case reports of successful neurosurgical evacuation of the hemorrhage or hematoma, and in many patients, the location of the event is one that will not incur long-term disability (162,163). Presentation can be heralded by the complaint of a headache, an acute confusional state, a seizure, visual disturbance, or any new, focal neurologic sign. Still, even with rapid recognition and immediate computed tomography or magnetic resonance brain imaging, approximately two-thirds of patients with an intracerebral hemorrhage will die or sustain fixed neurologic disability (89,161). In patients older than 75 years of age, the rate of fatality exceeds 90% (160,164). In the clinical trials that have evaluated thrombolytics, the mortality incorporates all causes, and the end point of death plus nonfatal, disabling stroke is important to consider (89,165) to understand the net clinical benefit of a particular reperfusion strategy. Other sites of serious bleeding, such as gastrointestinal or retroperitoneal, are unusual (less than 5%), but can be life threatening if not quickly diagnosed and treated. The most common cause of bleeding, periaccess site, is usually self-limiting (89,166).

Brachial artery hematoma. Hematoma complication after brachial artery catheterization and urokinase administration.

Beta-Blockade

Nearly all of the data available for the use of beta-blockers in acute MI are derived from the prereperfusion era. There is extensive support for the usefulness of beta-blockade to reduce recurrent ischemia and arrhythmias and improve survival (167,168,169,170,171,172 and 173). The largest trial of intravenous beta-blockade, ISIS-1, suggested that the predominant benefit was mediated via the reduction of cardiac rupture events (167). Only two placebo-controlled trials in the contemporary era of reperfusion therapy have been conducted, and one of these showed reduction in recurrent ischemia with the use of early intravenous followed by oral metoprolol (174). The trial was relatively small, however, and the primary end point of preserving cardiac function was not significantly affected. Likewise, a trial of intravenous metoprolol conducted by Van de Werf et al. was negative (175). In the GUSTO-I trial, the use of intravenous beta-blockade was associated with an adverse profile of clinical outcomes including worse mortality and congestive heart failure (175a). In this trial, the use of intravenous beta-blockade in 44% of patients was higher than many other large-scale thrombolytic studies, and it remains possible that the ill effects were related to administering therapy to patients with a large infarction or with marginal left ventricular function (73,88,89,175a). Current recommendations are to use beta-blockers orally in patients with a preserved left ventricular ejection fraction (estimated at >40%), and to initiate this on the first or second day after presentation. Intravenous beta-blockade is particularly useful in patients who are hyperdynamic and hyperadrenergic, representing the unusual subset of relatively young patients who have tachycardia and hypertension disproportionate to the smallness of their MI territory. But the potential for reducing intracerebral hemorrhage, as demonstrated in the TIMI-2 trial, has not been confirmed in subsequent large-scale efforts (174,175a).

Nitrates

Intravenous nitroglycerin is frequently used (89), but the data to support its use do not originate from trials conducted in the era of myocardial reperfusion. A review of trials that were conducted with nitrates in the period that antedated thrombolytic therapy suggested a significant 35% mortality benefit (176,177). The benefit is believed to be related to reduction of infarct size, improvement of regional myocardial function, along with reduction in right and left ventricular preload. More recent large-scale trials that have assessed either intravenous nitrates or long-acting oral nitrate preparations have failed to demonstrate benefit (178,179). However, in these trials there was extensive use of nitrates in the first few hospital days in the control group patients, confounding the assessment of the effect.

Often, intravenous nitroglycerin is inadequately administered, as the correct dose to achieve the desired hemodynamic benefit is to titrate the infusion to achieve at

least a 10% to 15% reduction in the systolic blood pressure for normotensive patients and a 30% reduction in hypertensive patients, not to exceed a systolic blood pressure less than 90 mm Hg. Appropriate administration is to use a bolus dose of 12.5 to 20.0 µg, followed by an infusion of 10 to 20 µg per minute with an increase in this infusion level by 5 to 10 µg every 5 to 10 minutes, along with careful surveillance of blood pressure, heart rate, and hemodynamic and clinical signs. In appropriate patients who do not have a large MI and are not at risk for congestive heart failure, it is especially helpful to combine beta-blocker therapy with the intravenous nitroglycerin to avoid the undesired tachycardia. Intravenous nitroglycerin is continued for the first 24 to 48 hours and replaced by oral or topical nitroglycerin preparations in patients with heart failure and recurrent ischemia.

Angiotensin-Converting Enzyme Inhibitors

One of the most important advances in cardiovascular medicine in the last decade has been the demonstration of survival benefit for angiotensin-converting enzyme (ACE) inhibitors in patients with left ventricular dysfunction. In several trials of acute MI (178,179,180,181 and 182) various ACE inhibitors have been tested and shown, in aggregate, to promote survival, reduce the incidence of heart failure, and, in selected trials, reduce the incidence of reinfarction and the need for revascularization. The details of these trials and the rationale are reviewed in Chapter 19 and Chapter 20. ACE inhibitors can be recommended in the first 24 hours of an anterior MI (proximal or mid-LAD, Table 18.1) or an MI complicated by either heart failure or ejection fraction less than 40%, or both. A graded dose schedule is used to avoid hypotension, especially with the first dose, with initiation of therapy on the first hospital day once the blood pressure is stabilized. The Heart Outcomes Preventions Evaluation (HOPE) trial findings of ramipril compared with placebo in a broad population of patients with coronary disease supports a greater than or equal to 20% reduction of death, recurrent MI, stroke, or need for revascularization (183). The combination of ACE inhibitors and beta-blockers with asymptomatic left ventricular dysfunction was studied in post-MI patients and appears to provide additive benefit (184).

Calcium Channel Blockade

Unlike ACE inhibitors, which have almost uniformly been shown to have salutary effects, the calcium channel blockers have limited data to support their use in this setting and, more recently, there has been heightened awareness of their potential for toxicity and risk of mortality (171,185,186,187,188,189 and 190). Nifedipine is contraindicated because of its intrinsic negative inotropic effects, reflex sympathetic activation, tachycardia, and hypotension. The excess of adverse outcomes in four placebo-controlled post-MI trials of nifedipine (none with reperfusion) (185,186,187,188,189 and 190) raised the possibility that coronary steal was occurring, referring to an imbalance in vasodilatation and reduction in coronary perfusion pressure. Other calcium channel beta-blockers, such as verapamil or diltiazem, may be used for specific indications, such as treatment of supraventricular tachyarrhythmia or relief of postinfarction angina, if nitrates and beta-blockers are ineffective or not adequately tolerated. All calcium channel blockers should otherwise be avoided, especially in patients who develop heart failure.

Management of Lipids

With the marked salutary effects on long-term survival, prevention of reinfarction, and subsequent coronary revascularization of HMG-CoA reductase drugs (19,20,21 and 22,191,192,193 and 194), it is important that a cholesterol panel (total, low-density lipoprotein, high-density lipoprotein) be obtained on admission and no later than the first 24 hours. This will be useful for predischarge planning, and the use of lipid-lowering drugs is discussed fully in Chapter 20.

Antiarrhythmics, Cardioversion, and Pacemaker Use

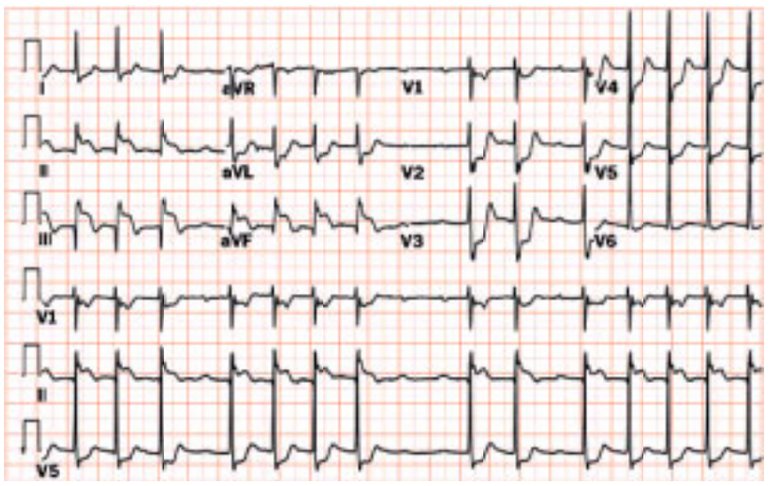
Most antiarrhythmic therapy is used to treat specific arrhythmias, which are fully discussed in Chapter 69, Chapter 70, Chapter 71, Chapter 72, Chapter 73, and Chapter 74, with the pharmacology of antiarrhythmic drugs in Chapter 72. For many years there has been debate over the use of prophylactic lidocaine for suppression of ventricular tachycardia and fibrillation. An overview of the randomized controlled prophylactic lidocaine trials showed a 33% reduction in the incidence of primary ventricular fibrillation, but the trend of increased mortality was also noted, suggestive of the potentiation of asystole (195). More recent data from the GUSTO trials, in the era of reperfusion, has suggested potential benefit of prophylactic lidocaine, but this was not a randomized, direct assessment (196). Still, in patients with acute MI who receive reperfusion therapy and manifest frequent extrasystoles or nonsustained ventricular tachycardia, lidocaine is frequently administered (89,196). But there is no adequate evidence base to support the prophylactic use of lidocaine. Importantly, accelerated idioventricular rhythm is a self-limiting arrhythmia that does not require therapy.

Atrial fibrillation is uncommon in the reperfusion era, with new onset in the first 24 to 48 hours occurring in less than 5% of patients in the GUSTO-I trial (197,198). This arrhythmia is markedly decreased in patients with successful early and complete reperfusion and carries an independent negative prognostic effect on adverse events in the first 30 days and 1 year after the index event (199,200). Many patients who develop this, especially when it is sustained, have a large MI and may not be considered good candidates for intravenous beta-blockade to achieve rate control. Digoxin is slower in achieving rate control, but certainly effective, and intravenous verapamil can be considered as a third alternative. In Europe, intravenous amiodarone is the preferred treatment for atrial fibrillation and a large acute MI.

One of the most frequent errors in management of arrhythmias in the first 24 hours of acute MI is the lack of prompt use of electrical cardioversion or defibrillation for specific arrhythmias. Ventricular fibrillation is immediately treated with 200 J of synchronized electric shock with increasing energies to 360 J if necessary. Patients who develop monomorphic ventricular tachycardia should undergo immediate synchronized electric shock of 100 J with increasing energies if this is not successful; polymorphic ventricular tachycardia is treated with unsynchronized initial energy of 200 J. Patients who develop atrial fibrillation or flutter should also be considered for immediate cardioversion if there is any sign of hypotension, chest discomfort or recurrent ischemia, or heart failure. Whenever possible, brief anesthesia is essential to ensure patient comfort and amnesia of the event.

Acute inferior myocardial infarction complicated by atrial fibrillation. Note ST-segment elevation in the inferior leads with reciprocal changes laterally. Atrial fibrillation has complicated this acute infarct.

A temporary pacemaker is infrequently needed in the contemporary management of MI that incorporates reperfusion. However, with occurrence of the following rhythm or conduction disturbances, temporary pacing is mandated because the risk of asystole is greater than 30%: symptomatic bradycardia, unresponsive to atropine, bilateral bundle branch block, new bifascicular block with first-degree atrioventricular block, or Mobitz II second-degree atrioventricular block (201). Less serious arrhythmias, such as right bundle branch block with first-degree block or new left bundle branch block, can be supported by transcutaneous standby pacing, as the chance for progression to asystole is much reduced. When transcutaneous standby pacing is used, it is important to check that it is operational (202).



Acute inferior myocardial infarction with Mobitz II atrioventricular block. Note ST-segment elevation in the inferior leads as well as intermittently dropped QRS complexes.

Magnesium

The use of intravenous magnesium has been controversial in more recent years, owing to conflicting results in large randomized trials (178,203,204,205 and 206). Several small trials, when considered in aggregate, suggested a more than 50% mortality reduction (207) and subsequently the Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) showed a 24% reduction in mortality (203). But in the ISIS-4 trial, which assessed magnesium, captopril, and nitrates, there were 58,050 patients enrolled and no beneficial effect in the patients receiving magnesium (179). In ISIS-4, magnesium was administered late, and there was a low control group mortality of only 7.2% (179,206). The principal effect of magnesium is to produce systemic and peripheral vasodilatation, but it also suppresses ventricular arrhythmias, especially polymorphic ventricular tachycardia (207), and by inhibiting myocyte calcium influx potentially reduces reperfusion injury. Further trials will evaluate the empiric use of magnesium, but until they are complete the recommendation is to check a serum magnesium level, especially important in patients who were taking diuretics before admission, and correct this with supplemental intravenous magnesium. If a torsades de pointes polymorphic ventricular tachycardia occurs, 1 to 2 g of magnesium as a bolus over 5 minutes can be administered and may be a definitive therapy, precluding the need for antiarrhythmic agents with more potential for side effects.

Inotropic Support, Vasodilators, Intraaortic Balloon Counterpulsation, and Hemodynamic Monitoring

Patients with Killip class III or IV require right-sided heart catheterization, as do patients with sustained hypotension without congestive heart failure. Patients in the latter group may well have a right ventricular infarction, but other causes of sustained hypotension, including tamponade, hemorrhage, or mechanical complications, should be considered.

In general, any patient who requires inotropic support or needs intraaortic balloon counterpulsation will also require right-sided heart catheterization. The choices for inotropic support are limited. Dopamine, which directly stimulates alpha- and beta-adrenergic receptors as well as dopaminergic receptors at doses higher than 5 to 10 µg per kg per minute, is associated with vasoconstriction, and dobutamine, like dopamine, induces tachycardia and is arrhythmogenic. Both of these agents produce modest improvement in contractility. Norepinephrine is rarely used as an inotrope because its principal -receptor effect leads to intense vasoconstriction. Phosphodiesterase inhibitors, such as amrinone or milrinone, which have combined vasodilating and inotropic action, are problematic because of their renal excretion in patients with low output and only viable if the other agents have failed to maintain adequate systemic pressure and forward output.

In general, these agents should be avoided whenever possible because of their effects on increasing myocardial oxygen demand and promotion of arrhythmias. An intraaortic balloon pump is preferred to the use of any inotropic support. If the primary problem is reduced myocardial contractility without hypotension, dobutamine remains the agent of choice. For hypotension, dopamine at doses up to 20 µg per kg per minute, with norepinephrine as a backup, if necessary, can be used. The main goal, however, should be to avoid these agents or reduce their need in terms of absolute dose and duration (201).

Digoxin is a useful adjunct in less serious circumstances, such as the patient with heart failure not controlled by the use of ACE inhibitors and diuretics. Although there has long been concern about the potential of digitalis toxicity in the peri-MI period (208), and the large-scale Digitalis Investigator Group excluded post-MI patients (209), there is no question as to the positive inotropic effects of digoxin and, in select patients, it should be considered useful.

The use of vasodilators, and particularly nitroprusside, is reviewed in Chapter 19, in association with the management of cardiogenic shock and mechanical complications such as acute mitral regurgitation and ventricular septal defect. Beyond the application of intraaortic balloon counterpulsation for the management of low output, cardiogenic shock, and these mechanical complications, more recent trials have indicated its potential for reducing post-MI angina and prevention of reocclusion of the infarct vessel after percutaneous revascularization (210). In patients with anatomy deemed to require emergency bypass surgery at the time of early angiography, such as critical left main stem disease or the equivalent, the use of counterpulsation as a bridge to surgical revascularization is advocated.

Left Ventricular Assist Devices and Emergency Transplantation

In select young patients with massive MI, there is a growing experience with a strategy of emergency transplantation (211). Although this can only be considered in special situations, it is important to recognize the potential from the outset. For example, if a 40-year-old patient presents in cardiogenic shock and with a massive MI (usually due to a proximal LAD occlusion), thrombolytic therapy should be avoided, if possible, as it will preempt the use or complicate the strategy of transplantation. Ideally, emergency angiography should be performed, and primary angioplasty should be considered. If the coronary anatomy is unsuitable or the attempt unsuccessful, or the myocardial damage is too profound for the patient to be sustained, consideration for the use of extracorporeal membrane oxygen support, a left ventricular assist device (left ventricular or biventricular), or HeartMate can be made while attempting to secure a donor heart. Prompt triage is vital, before there has been multiorgan damage (212).

HEART SOUNDS

Audio 18.4 Left ventricular assist device. Auscultation performed in a 48-year-old male patient with end-stage cardiomyopathy after implantation of a Novacor pneumatic left ventricular assist device as a bridge to transplantation. Left lower sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

EMERGENCY ANGIOGRAPHY AND REVASCULARIZATION

Emergency Angiography

The role of emergency angiography remains controversial, apart from its obligatory role in primary mechanical reperfusion. If a patient has received thrombolytic therapy, emergency angiography should be considered if there is recurrent chest pain or ECG changes, if there is new-onset hypotension or heart failure, or in an uncomplicated, large MI for which the success of pharmacologic reperfusion is unknown, but critical to the patient's outcome. As reviewed in the clinical assessment of reperfusion, in the vast majority of patients it remains unclear whether thrombolytic therapy has been effective.

The advantages of emergency angiography are that the coronary anatomy is fully defined, and a more precise assessment of the patient's status is determined regarding the presence of multivessel disease, which carries key independent prognostic information (213), and the patency status of the infarct vessel, which as reviewed is the most important treatment determinant of clinical outcome. On the other hand, disadvantages are the need for an emergency on-call team, as for primary PTCA, the cost, and potential for bleeding complications, which are usually in a periaccess site. Just as is the case with primary mechanical reperfusion, most hospitals do not have the potential to perform this procedure. However, transfer to a referral center may be appropriate for the categories of patients for whom this

strategy has the most potential benefit.

Rescue Percutaneous Transluminal Coronary Angioplasty

Rescue PTCA refers to using a mechanical strategy of balloon angioplasty as a fallback if thrombolytic therapy is unsuccessful (214). The decision to perform emergency angiography should be made promptly, as it sets up the foundation to achieve reperfusion mechanically even if thrombolytic therapy has proven ineffective. Ideally, the decision is made before a waiting period in a patient with a large MI (e.g., proximal LAD infarct) who is at considerable risk for adverse sequelae. If a waiting period of 60 to 120 minutes is interposed before making a decision, then the patient's potential gain from the rescue PTCA is substantially reduced.

The primary data supportive of the use of rescue PTCA are derived from a randomized trial of 150 patients with LAD artery occlusion after thrombolytic therapy (215). In this trial, the incidence of death at 30 days was 5.2% with PTCA as compared with 9.9% without PTCA. The composite of death or heart failure occurred in 6.5% versus 16.4%, respectively (p = .05). Although this trial was small, it was extremely difficult to do because it meant leaving half the patients with a known occluded LAD without reperfusion. These data, combined with many observational studies that provide a favorable clinical and left ventricular function profile, including long-term follow-up, for patients with successful rescue PTCA (216,217,218,219,220,221,222,223 and 224), support the application of rescue PTCA in select patients. The overall reocclusion rate in the studies with more than 560 patients in aggregate was 18%, and it should be noted that the reasons for failure of thrombolytic therapy are frequently more extensive intimal disruption, a large thrombus burden unresponsive to the plasminogen activator, or platelet-rich clot that is intrinsically resistant to current therapies. In right coronary artery occlusion, a higher incidence of periprocedural complications has been reported, as compared with the left coronary (225). But these complications of bradyarrhythmias, sustained hypotension, ventricular tachycardia, and fibrillation were responsive to therapy and do not represent a contraindication to rescue PTCA for patients with an inferior MI. However, the rationale for rescue PTCA in a patient with an uncomplicated inferior wall MI remains unclear, because this carries a low risk of fatality. It should also be pointed out that virtually all of the studies and the trial of rescue PTCA were performed in an era of suboptimal anticoagulation, one in which stents for intimal dissection were not available, and there was lack of antiplatelet coverage (215,216,217,218,219,220,221,222,223,224 and 225). With contemporary pharmacologic therapy, including platelet glycoprotein IIb/IIIa inhibitors, along with stents and in-laboratory monitoring of the activated clotting time, it is likely that the results of rescue PTCA will be improved. The safety, however, of combining full doses of fibrinolytic agents with IIb/IIIa inhibitors is unknown and will require careful study. The use of reduced lytic doses, judicious heparin, and IIb/IIIa inhibitors may be especially useful in maximizing benefit-risk ratio in these patients.

Immediate Angioplasty

The strategy of performing PTCA immediately after successful thrombolysis was essentially abandoned as a result of three randomized trials (218,226,227 and 228) that demonstrated a higher incidence of adverse events, including mortality and the need for emergency bypass surgery, and no improvement in left ventricular function. These trials were performed in the mid-1980s, and again the improvement in pharmacologic and catheter-based alternatives may lead to different results. However, the predominant benefit to the patient is restoration of TIMI-3 flow, such that alleviation of the underlying infarct vessel stenosis on an immediate basis provides little added benefit but certainly poses a risk. For these reasons, the practice of angioplasty after successful thrombolytic therapy in an uncomplicated patient has largely become unnecessary and obsolete.

H4>Emergency Bypass Surgery

Still an essential part of reperfusion strategies today, although infrequently reported on, is the use of emergency bypass surgery for patients who undergo early coronary angiography, with or without thrombolytic therapy. In patients who are intended to undergo primary mechanical reperfusion, but an unsuspected critical left main stem lesion is detected, or there is the equivalent scenario with advanced, diffuse, three-vessel coronary artery disease that is not approachable by percutaneous revascularization, emergency bypass surgery should be contemplated. In 1% to 2% of primary PTCA cases, emergency surgery proves to be necessary (119,120,121,122,123,124,125 and 126) and for this reason having a facility with rapid, in-house surgical capabilities is quite important. The results for emergency bypass surgery as a reperfusion treatment for acute MI are particularly encouraging, despite the lack of a randomized controlled design and the fact that these studies were reported in the 1980s before pharmacologic and catheter-based reperfusion was popularized (229,230,231,232 and 233).

PREDISCHARGE ASSESSMENT AND ELECTIVE REVASCULARIZATION

Functional Testing

Performing a functional test in an uncomplicated post-MI patient is advocated to determine whether there is provokable ischemia (201). However, this is uncommonly done in the United States (234,235), and a report from one administrative database showed that only 9% of patients underwent a functional test before having PTCA of the infarct vessel. The reasons for this are multiple and include the reliance of the cardiology community on coronary anatomic findings (236), the inability of patients to perform adequate tests, and our limited capacity to interpret the results (213,235,237). Most patients have an abnormal ECG and are thus not good candidates for a simple exercise stress test before discharge. Using dobutamine echocardiography or dipyridamole thallium scintigraphy adds to the cost of the test, and if the results are equivocal for ischemia or do not conform with the physician's assessment about ischemic viable myocardium, additional tests may be performed. According to the American College of Cardiology/American Heart Association Practice Guidelines of November 1996, a stress ECG before discharge for prognostic assessment or functional capacity is recommended (201). Although this may provide psychological benefit to the patient and permit detection of profound ischemia or inducible arrhythmia, it remains unclear whether this strategy is adequately sensitive and correlated with favorable long-term outcomes. There is indeed a wealth of data for the prognostic assessment of post-MI patients via stress testing; however, most of the studies were conducted before reperfusion therapy (238). More recent studies have been confounded by the use of PTCA and bypass surgery before the assessment (239,240).

The Danish Multicenter Study of Acute MI (241) investigators reported their randomized trial of thrombolytic-treated patients with a positive bicycle exercise test (performed at 2 to 3 weeks post-MI) who were assigned angiography and revascularization or medical therapy. The 3-year follow-up strongly favored the use of angiography and coronary revascularization, and this was the first trial that validated the use of the strategy of angiography and PTCA or bypass surgery post-MI. Multiple previous trials, performed in the 1980s, had not demonstrated any incremental benefit of the empiric "package" of angiography and revascularization (242,243,244 and 245).

In summary, there remains a dissociation between practice guidelines and what is common clinical practice, chiefly owing to the uncertain application of functional testing in this setting. The various functional tests for post-MI patients are reviewed in Chapter 48, Chapter 50, Chapter 53, and Chapter 56.

Elective Coronary Angiography and Revascularization

In the GUSTO-I trial of 21,722 patients in the United States with acute MI, 71% underwent coronary angiography (246), and most of this was elective, predischarge. The major determinants of angiography were the patient's age, hospital availability, and recurrent ischemia. The age characteristic is particularly troubling, as there was a pronounced reduction for use of angiography patients older than 73 years, and it is precisely these patients who have the highest risk of major events (164). Other studies have confirmed that hospital availability of the procedure is a key predictive factor of its use (247,248), which is also a sobering realization. Of note, recurrent ischemia, which could have been conceived as the most salient driving feature for performing coronary angiography, was third in importance (246). There is marked variability in the use of coronary angiography in the eight different regions of the United States, ranging from 52% to 81%, and reflective of the uncertainty of how this procedure should be applied (248).

When angiography is performed, patients can be categorized into five groups. An interesting group is the 15% of patients who have "minimal lesion syndrome" (249). These patients are usually young, quite often smokers, and of the male sex, who at the time of predischarge angiography have less than 30% residual stenosis. The underlying pathophysiology is likely to involve coronary vasospasm, or fissure, with subsequent thrombus formation overlying a minimally encroaching atherosclerotic plaque. Of course, revascularization is not necessary, but it is vital for smoking cessation to be achieved. The prognosis for these patients is excellent, but in 2% despite the use of nitrates, calcium channel blockers, or both, there is recurrence. The other angiographic subsets include patients with occluded infarct vessels and single-vessel disease, patients with single-vessel disease of the infarct-related artery, those with two- or three-vessel disease, and the small subgroup of patients with left main stem lesions.

Coronary angiography is advocated for all patients who have recurrent ischemia. For the reasons discussed for using emergency angiography, as far as establishing infarct vessel patency, extent of multivessel disease, and suitability for revascularization, angiography can be considered an integral part of the early post-MI assessment. Of note, if a patient has provocable ischemia, angiography is fully justified with the results of the Danish Multicenter Study of Acute MI trial (241).

A major question remains as to patients who do not have provokable ischemia or do not undergo functional testing but, by clinical criteria, have evidence of viable myocardium of the infarct zone. These criteria may include a lower peak CPK than expected, hypokinesia but not akinesia of the infarct zone by echocardiography, early thrombolytic therapy in the first 2 hours of symptom onset with rapid relief of chest pain and ECG findings, or the lack of development of Q waves on the ECG. These patients, on an empiric basis, may be suitable for coronary angiography because of the clinical judgment that they have sustained an "incomplete" infarct and

will likely have a significant residual stenosis of the infarct vessel. On the other hand, patients with a complicated MI, with such features as congestive heart failure or ventricular tachycardia, are at high risk for subsequent events and deserve consideration for angiography. The groups of patients who do not need angiography are those in whom revascularization, be it percutaneous or surgical, could not be considered or those patients with a small inferior or lateral infarct who do not have provokable ischemia. This analysis suggests that a substantial portion of patients probably deserve consideration for predischarge angiography, but this must be considered an unsettled controversy as there has not been a clinical trial to address this issue per se.

Coronary Angioplasty or Bypass Surgery

Revascularization is used commonly in hospitals in the United States, as evidenced by the GUSTO-I data of 30% use of PTCA and 13% use of CABG. The coronary anatomy strongly predicts which procedure is performed, with single-vessel disease resulting in PTCA for 86% of patients undergoing any revascularization, whereas CABG was used in 79% of patients with three-vessel disease who had some form of revascularization (246). Even though the use of coronary angiography and revascularization was much lower outside the United States in this large trial, the proportionate use of angioplasty and bypass surgery among patients undergoing angioplasty was similar (250). Bypass surgery carries a risk of mortality that is independent of the acute MI event and, even risk adjusted, in the first year after surgery there is a small excess of deaths (not statistically meaningful) compared with patients not undergoing surgery (251). However, the benefit of complete revascularization in these patients with advanced, multivessel disease is much more likely to be manifest over a more prolonged follow-up (251). One of the controversies in surgical revascularization in this setting is whether bypass surgery to the infarct-related vessel, especially if it was not successfully rendered patent from reperfusion therapy, is worthwhile. This dilemma is usually resolved by grafting the infarct-related territory, but determination of viability (see Chapter 50 and Chapter 55) may be helpful. In patients with spontaneous or provokable ischemia who have extensive and diffuse atherosclerotic involvement, bypass surgery should be strongly considered as the revascularization procedure of choice, provided that the distal vessels are suitable for grafting. It would be anticipated that the patients with compromised left ventricular function would stand the most to benefit from the standpoint of survival (251).

SPECIAL SUBGROUPS

The Aged

The highest risk group of patients with acute MI are clearly the elderly, as they account for more than one-half of the deaths of patients hospitalized (252), and age represents the single most important risk factor (57). In GUSTO-I, the 30-day mortality for patients between 75 and 85 years of age was 19.1% and for those older than 85 it was 27.9% (164). The risk of death in the aged was coupled with a higher risk of hemorrhagic stroke and bleeding complications. Overall, intracranial hemorrhage occurred in 3.3% of patients older than the age of 75 years and moderate or severe bleeding, as reflected by need for transfusion or significant blood loss, affected more than 20% of these patients. Of note, the elderly have more comorbidities and many have relative contraindications to thrombolytic therapy; they present later to the hospital by approximately 30 minutes and paradoxically have smaller infarcts based on creatine kinase measurements. The discrepancy between lower creatine kinase and higher mortality was explained on the basis of less muscle mass in the elderly (164,253). Some evidence suggests that the myocardial band fraction release is higher among elderly patients (164). These patients are much more apt to have multivessel disease, prior MI, diminished ejection fraction, and an increased risk of cardiac rupture (254,255). It has also been pointed out that advanced age is a major factor associated with the “early hazard” of thrombolytic therapy, such that in the first 24 hours after treatment, compared with placebo, there are actually more deaths in the elderly (65,115,164). Age is the single factor that most predicts whether a patient will undergo coronary angiography after acute MI, and it is the elderly, who by and large have the most to gain, who are at highest risk of not undergoing the procedure (246,256).

The most important issue is that reperfusion therapy should be used more aggressively in the elderly. The net benefit of reduction of death and disabling stroke is pronounced in the aged. In the ISIS-2 trial, the number of lives saved for SK was 16 per 1,000 in patients less than 65 years, but 36 lives per 1,000 in the older patients (59). For accelerated t-PA as compared with SK, the net clinical benefit of reducing the number of deaths or disabling strokes was 5 per 1,000 patients for those aged younger than 65 years as compared with 17 events per 1,000 patients for patients aged 75 to 85 years (164). The main explanations for this large amplification of net benefit include the considerably higher risk of the aged, and the fact that when hemorrhagic stroke occurs, it is much more likely to be a fatal event. Despite these findings, in several registries (257,258 and 259) the proportion of patients aged older than 75 years who do not receive therapy is one-half or more. It appears that there is more use of thrombolytic therapy in the elderly as based on the proportion of patients older than age 75 enrolled from the GUSTO-I to the GUSTO-III trials (an increase from 12% to 16%). Even patients up to the age of 110 years have been successfully treated (260), according to one of the most instructive case reports that have been published. After deciding on reperfusion for an elderly patient, the next choice is whether to use thrombolytic therapy or primary angioplasty. In GUSTO-I, for patients younger than 85 years, there is benefit of accelerated t-PA over SK (253). For patients older than age 85, the experience is limited and there are no cogent, statistically robust data to draw on. But in the 412 patients in GUSTO-I, the best regimen appeared to be SK and subcutaneous heparin (164). When fibrinolytic therapy is used in this subgroup, it is essential to lower the dose of heparin as age is a critical determinant to aPTT elevation (149), and SK with intravenous heparin (associated with the highest aPTTs) had a hemorrhagic stroke rate of 3.0% compared with 0.9% for accelerated t-PA and intravenous heparin (164). Alternatively, primary angioplasty can be used and is associated with a lesser risk of hemorrhagic strokes. Although early studies suggested that the risk of primary PTCA in the elderly might be excessive, more recent trials have pointed out the potential for heightened benefit over fibrinolytic therapy (261,262 and 263). The use of primary angioplasty is preferred in the appropriate settings as previously discussed and should be strongly considered if there is marked concern about hemorrhagic stroke or major bleeding, particularly in patients with absolute or relative contraindications to thrombolytic therapy.

More recently, there has been considerable debate about the use of fibrinolytic therapy in the elderly (264,265,266,267,268 and 269). This resulted, in part, from a report by Thiemann and colleagues of a large registry, which called into question whether the elderly were being harmed by fibrinolytic therapy. It is difficult to make a judgment from data in registries, although certainly important to reconsider the value and risk of the therapy in a population with a known high risk of intracerebral hemorrhage. The classic Fibrinolytic Therapy Trialists’ analysis of the data was originally hampered by inclusion of patients without certain criteria for reperfusion therapy. An update of the data from all of the large-scale fibrinolytic trials is shown in Figure 18.12. Among patients 75 years or older, there was an important 15% reduction of mortality (from 29.4% to 26.0%), and this translated to 34 deaths avoided per 1,000 elderly patients treated. This is an absolute benefit that compares favorably with the other age groups (Fig. 18.12). Furthermore, Krumholz and colleagues have demonstrated that at 1-year follow-up there is clear-cut advantage of therapy in the elderly (267). The issue is not completely settled, however, because of relatively limited data from the randomized trials. Overall, if catheter-based reperfusion were immediately available it would be considered preferable with the relative avoidance of intracerebral hemorrhage. Nonetheless, this is frequently not available on a timely basis and fibrinolytic therapy should still be considered as an established and important treatment for the aged with acute MI.

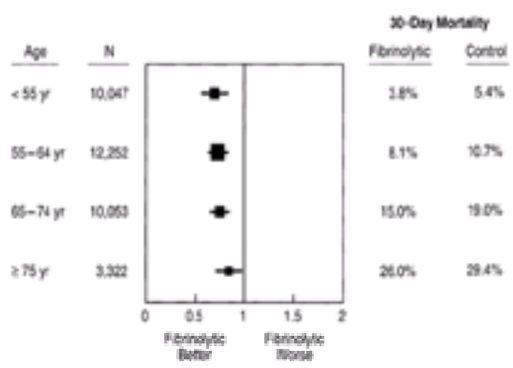


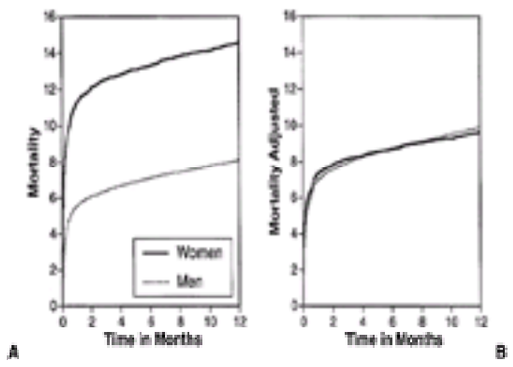
FIGURE 18.12 Revised Fibrinolytic Therapy Trialists’ data. [From Estess JM, Topol EJ. *Heart* 2001(*in press*).]

Women

The subgroup of women with acute MI has been a controversial one, and particularly the issue of whether gender differences were responsible for worse outcomes, including more than doubling of mortality (261,262 and 263). Beginning from presentation, it is clear that women are less apt to receive reperfusion therapy, even though their presenting symptoms and ECG manifestations are similar (261). The reasons for this appears to be that women are considerably older at presentation than men, on average 7 to 10 years, and as a result have more risk factors, including hypertension, smoking, and diabetes. They present later for medical attention, a median of 18 minutes, and have a longer time to treatment than men (263). Of note, by creatine kinase peak, women typically evolve a smaller MI (median, 1,223 U per L vs. 1,491 U per L for women vs. men, respectively, in GUSTO-I), even adjusted for weight, which is dissociated from their higher propensity for fatal and nonfatal complications, especially the more frequent but unexplained risk of heart failure (262).

The death rate for women in GUSTO-I, as shown in eFigure 18.12.1, at 30 days was 11.3% versus 5.5%, which seems like a major gender-specific adverse effect. However, by adjusting for the important differences in baseline characteristics (262), and especially age, these differences tended to disappear. After adjustment, the

mortality at 30 days was 15% higher in women, which was of marginal statistical significance. After 1-year follow-up, the differences were completely absent (eFig. 18.12.1) (263). Similarly, the excess in stroke of 2.1% versus 1.2% (p = .02) is canceled out by adjusting for the baseline feature differences, particularly age and weight.

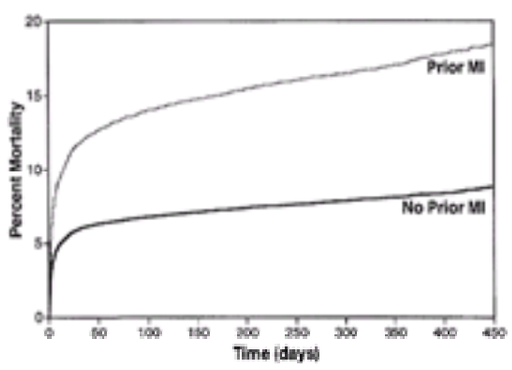


***e*FIGURE 18.12.1** Fate of women versus men in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial. **A:** Without adjustment, it appears that there is an approximate doubling of mortality for women. **B:** After adjusting for differences in age and other key covariates, such as hypertension and diabetes, there was no effect of gender. (From Moen EK, Miller DP, Asher CR, et al. Long-term follow-up of gender specific outcomes after thrombolytic therapy for acute myocardial infarction from the GUSTO-I trial. *J Womens Health* 1997;6:235–293, with permission.)

The use of the GUSTO-I trial to evaluate the gender differences is helpful because this trial enrolled almost fivefold the number of women as previous trials and registries (262). Importantly, there was no imbalance in the use of coronary angiography and only small differences in the use of revascularization (angioplasty in 35% vs. 32%, bypass surgery in 9% vs. 7%, for women compared with men, respectively). Accordingly, despite the marked controversy over the existence of a gender gap for acute MI patients in their diagnosis or treatment, more recent evidence suggests that this is not the case when adequate sized sample populations and differences in baseline features are appropriately analyzed.

Prior Myocardial Infarction

The patients with prior MIs denote a high-risk subgroup who have largely been understudied to date. The proportion of patients with prior MIs is at least 16% in thrombolytic trials (270), and the mortality for these patients is at least doubled (eFig. 18.12.2). Like the women subgroup, these patients are older (median increase of approximately 3 years) and have a greater preponderance of risk factors. In contrast to the elderly or women, they tend to present to the hospital earlier, probably owing to their familiarity with the symptoms. The chance for their presentation to be in Killip class III or IV is doubled (3.7% vs. 1.8%), as is the incidence of shock during the hospitalization (8.8% vs. 5.4%). Heart failure occurs much more commonly (22.6% vs. 14.9%), and ejection fraction is much lower (52% vs. 60%). As would be expected, the incidence of multivessel coronary disease is substantially increased (71.5% vs. 35.0%), but the response to coronary thrombolysis similar compared with the patients having de novo MI. As in the overall GUSTO-I and in this high-risk subgroup, the benefit of accelerated t-PA over SK for reducing mortality at 30 days and 1 year was significant (270). There is a gradient of prior MI with respect to risk, with the patients having an old inferior and new inferior MI having the lowest risk, and those with a prior inferior and new anterior MI demonstrating the highest risk of mortality (271).



***e*FIGURE 18.12.2** Incidence of death in Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) as a function of prior myocardial infarction (MI). Fatal events more than doubled in the prior MI subgroup (p <.001). (From Brieger DB, Mak K-H, White HD, et al. The benefit of early sustained reperfusion in patients with acute myocardial infarction superimposed on prior infarction. Insights from the GUSTO-I trial. *Am J Cardiol* 1998;81:282–287, with permission.)

This subgroup deserves emphasis because the risks are so exaggerated compared with the patients presenting with their first MI. Many of the patients have had prior CABG (17% of patients with prior MI) and already have the potential for a conduit that is resistant to thrombolytics owing to such an extensive clot burden (144,145). But even the patients with prior MI who have not had bypass surgery deserve special consideration for aggressive therapy. In the TIMI-2 trial comparing an invasive and conservative strategy of angiography and revascularization after thrombolysis, the subgroup of prior MI patients emerged as one with distinct benefit of the invasive approach (272). The group of patients with prior MI, like those who have Killip III or IV on presentation, or prior CABG, deserves careful consideration for emergency coronary angiography with an eye toward revascularization. If thrombolytic therapy is used, it should be thought of as only a temporizing measure because one cannot rely on either the success of the therapy (which leaves one-half of patients without early TIMI-3 flow) or our ability to clinically differentiate whether reperfusion has been achieved.

Cardiopulmonary Resuscitation

Administering fibrinolytics to patients with CPR (particularly when unsuccessful), has been quite controversial. A prospective study by Böttiger et al. (273) showed safety and supported efficacy in patients with initially unsuccessful out-of-hospital CPR. The odds ratio of return of spontaneous circulation was 2.7 for t-PA compared with controls. In patients with successful CPR, especially if brief (less than 5 minutes), fibrinolytics should not be considered contraindicated. This is an important area that has not been sufficiently studied (274).

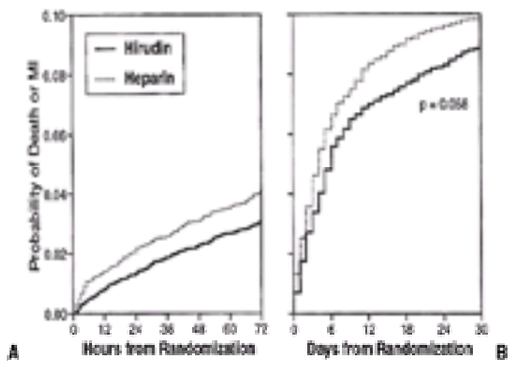
Non–ST-Elevation Myocardial Infarction

A considerable part of this chapter has been dedicated to ST elevation because of the pressing need to establish reperfusion therapy. Patients without ST elevation, unless they have true posterior MI (eTable 18.2.1), do not usually have an occluded infarct-related artery and have not been shown to benefit from thrombolytic therapy. In fact, the aggregate data suggest that these patients may be put at risk of reinfarction if thrombolytic therapy is used (275). The reasons for this include the presence of a mural thrombus, rather than an occlusive one, with the potential for a plasminogen activator to engender free thrombin and facilitate platelet aggregation and the autocatalytic formation of thrombin. Essentially, the prothrombotic effects of thrombolytic therapy pose a risk in this setting, and this class of agents should be avoided. One more recent study (276), which raised the potential salutary effects of t-PA in this setting, is difficult to interpret because it represents a post hoc analysis from a trial dedicated to testing reperfusion in patients presenting later after symptom onset (6 to 24 hours). More data would be necessary to condone the use of empiric thrombolytic therapy in this subgroup.

As we learned from the GUSTO-IIb trial (277), which enrolled more than 12,140 patients without ST elevation, they are clearly older and more frequently female, diabetic, and hypertensive than their ST-elevation counterparts. In many respects, their characteristics pull together the features of the three previous subgroups of the aged, women, and prior MI. They are twice as likely to have had a prior MI (32% vs. 17%) and have more than twice the frequency of prior CABG (12% vs. 5%). The outcomes for these patients are still indicative of the need for improved therapies, as the incidence of death and nonfatal MI in the first 30 days was 9.4% and quite similar to the patients with ST-segment elevation. Of this composite, the non–ST-elevation patients have more reinfarction than death as compared with the ST-elevation patients (277). The therapy for non–ST-elevation MI is the same as that delineated for the ST-elevation MI patients, with emphasis on the use of aspirin,

heparin, nitrates, and beta-blockade. The use of calcium channel blockers in this setting is supported by the results of one trial, albeit with marginal statistical significance (278).

With the pivotal importance of thrombin in these patients, it was thought that a direct inhibitor rather than heparin, which is effective on both circulating and clot-bound thrombin, would be associated with improved clinical outcomes. This was the focus of the GUSTO-IIb trial, which demonstrated a small but statistically insignificant benefit of hirudin over heparin (eFig. 18.12.3) (277). Although hirudin provided important benefits in the first few days of therapy while the infusion was being maintained, the lack of a robust effect at 30 days likely reflects the inability of hirudin or any direct thrombin inhibitor to block thrombin generation. Future trials directed at both antagonizing thrombin generation and activity might well build on the early phase, encouraging data on hirudin in the non–ST-elevation subgroup. Low-molecular-weight heparin (enoxaparin), given subcutaneously, has been shown to reduce death and nonfatal MI in patients with unstable angina or non–ST-elevation MI in the Efficacy Safety Subcutaneous Enoxaparin in Non-Q Wave Coronary Events study and TIMI-11 without an ill effect on major bleeding complications (279). Platelet glycoprotein IIb/IIIa inhibition is being actively studied in large-scale trials for reducing death and MI in this subgroup, and initial trials, as reviewed in Chapter 19, are encouraging. Patients without ST-segment elevation constitute a group with appreciable risk despite our current armamentarium. The use of troponin to differentiate risk among these patients may prove to be helpful for the purposes of triage to early coronary angiography, and when suitable, revascularization. While new therapies and diagnostics are being assessed, it is important to bear in mind that the absence of ST elevation does not, in any way, convey lower risk.



***e*FIGURE 18.12.3** Incidence of death or nonfatal myocardial infarction (MI) in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-IIb) trial. **A:** Significant (25%) reduction for hirudin in the first 72 hours while the thrombin inhibitors were administered. **B:** Borderline reduction of events for hirudin at 30 days. [From the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;335:775–782, with permission.]

Direct Thrombin Inhibitors and New Anticoagulants

The GUSTO-IIb trial was, in actuality, testing the thrombin activity hypothesis, rather than whether thrombin plays a pivotal role in acute coronary syndromes. Because it has been shown that hirudin does nothing to block thrombin generation, the beneficial effects that have been demonstrated in the trial, namely, an 11% reduction in death or reinfarction (eFig. 18.12.3), may be built on in the future.

The more substantial benefit realized in the first 24 hours and 3 days of therapy, while therapy was being administered, suggests that even directly blocking thrombin activity would be advantageous compared with our standard approach.

Several pilot studies have shown beneficial effects of low-molecular-weight heparins given in conjunction with fibrinolytics. In the ASSENT-3 trial, 2,040 patients were treated with full-dose TNK–t-PA and enoxaparin (30 mg intravenous bolus immediately followed by a subcutaneous dose of 1 mg per kg repeated every 12 hours until revascularization or discharge, with a maximum of 7 days). Enoxaparin cotherapy was associated with a significant 27% reduction in the composite of 30-day mortality, in-hospital reinfarction, or refractory ischemia when compared with unfractionated heparin. No excess of major bleeding complications or intracranial hemorrhage was observed, and a benefit was also present in patients above 75 years of age. These results suggest that prolonged administration of enoxaparin should be the anticoagulant treatment of choice in conjunction with TNK–t-PA. Whether it can replace unfractionated heparin with other less fibrin-specific agents needs to be determined (280).

Many agents work higher in the coagulation cascade and would be potentially more effective than hirudin. These include tissue factor pathway inhibitor, factor VII mimetics, factor X_a inhibitors, activated protein C, mutant thrombins that facilitate thrombomodulin or the protein C system, nematode anticoagulant protein (nAPc2), and factor IX inhibitors (281,282,283 and 284). Beyond the action of hirudin, these agents have the potential to be fully effective in blocking thrombin generation, and future clinical investigation will be devoted to extending the “thrombin hypothesis” and building on the encouraging GUSTO-IIb results. The better results obtained in the Efficacy Safety Subcutaneous Enoxaparin in Non-Q Wave Coronary Events study with the low-molecular-weight heparin (enoxaparin), which exerts a higher anti-X_a activity than standard heparin, seems to support the thrombin generation hypothesis.

Platelet Glycoprotein IIb/IIIa Inhibitors

There has been intensive clinical trial assessment of IIb/IIIa inhibitors in patients with acute MI. For the intravenous IIb/IIIa inhibitors, there are six trials of 29,855 patients (285,286,287,288,289 and 290) focusing on acute coronary syndromes: unstable angina and non–ST-segment elevation MI. The results of these six trials are summarized in Figure 18.13. Overall, there was only an 8% reduction of death or MI at 30 days. However, the benefit for patients with an abnormal troponin at entry (or the subsequent sample at 6 to 8 hours) and diabetics was striking, especially in the PRISM trials (troponin was not assessed in PURSUIT). Furthermore, the overall positive results for eptifibatide in *P*latelet IIb/IIIa in *U*nstable Angina: *R*eceptor *S*uppression *U*sing *I*ntegrilin *T*herapy (PURSUIT) and tirofiban in the *P*latelet *R*eceptor Inhibition for *I*schemic *S*yndrome *M*anagement (PRISM) trials were offset by the single trial with a trend of worsened outcome: In the GUSTO-IV study of abciximab an interesting paradox has arisen. Abciximab was associated with worse outcomes in the GUSTO-IV trial, while being regarded as the reference standard for superior outcomes in percutaneous coronary revascularization trials (291,292,293 and 294). This is likely due to the long (24- and 48-hour) infusions of abciximab in GUSTO-IV, given without percutaneous revascularization. The likely explanation involves subthreshold platelet inhibition (below 80% inhibition of platelet aggregation) and the link with proinflammatory expression of P-selectin and shedding of platelet CD40 ligand. This also probably explains the disappointing results of the oral IIb/IIIa inhibitors, which are subthreshold with respect to their IIb/IIIa receptor inhibition. Overall, these agents have induced a 35% excess of mortality for patients with acute coronary syndromes (295).

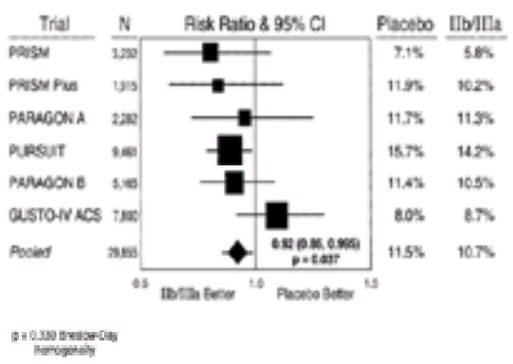


FIGURE 18.13 IIb/IIIa inhibition for acute coronary syndromes. Death or nonfatal myocardial infarction end point at 30 days. CI, confidence interval.

In acute MI, the GUSTO-V trial tested, for the first time in a large-scale definitive trial, low-dose fibrinolytic and IIb/IIIa inhibition. With enrollment of more than 16,000 patients comparing r-PA with r-PA at half-dose and abciximab, there was little difference in mortality (5.9% vs. 5.6%) (Fig. 18.14) (296). Noninferiority was established for the new strategy of combined therapy with respect to 30-day mortality, but superiority with respect to significantly less reinfarction and almost all MI complications

(Table 18.3) was demonstrated. On the other hand, there was an excess of bleeding complications (5.6% vs. 3.9%). Of note, no increase in intracerebral hemorrhage was encountered (0.6% in both groups). Overall, the GUSTO-V trial validated combined fibrinolytics (at reduced doses) with IIb/IIIa inhibition as an alternative therapy to traditional fibrinolytic monotherapy. This may be particularly well suited for younger patients, those with high-risk MIs such as anterior location, and patients who are being considered for acute transfer to a cardiac catheterization laboratory.

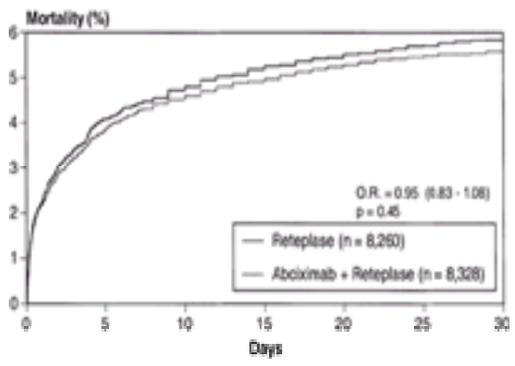


FIGURE 18.14 Kaplan-Meier mortality curves. O.R., odds ratio.

Complication	Reteplase (n = 8,260) (%)	Reteplase + abciximab (n = 8,328) (%)	Odds ratio	p Value
Reinfarction	3.5	2.3	0.67 (0.53, 0.80)	<.001
Recurrent ischemia	12.0	11.3	0.87 (0.79, 0.96)	.004
Sustained ventricular tachycardia	2.8	2.2	0.79 (0.63, 0.96)	<.02
Ventricular fibrillation	3.5	2.7	0.79 (0.64, 0.94)	<.008
Second- or third-degree atrioventricular block	3.3	2.7	0.80 (0.67, 0.96)	.018
Cardiogenic shock	0.2	0.2	0.76 (0.37, 1.56)	.45
Pulmonary embolism	0.04	0.06	1.43 (0.20, 6.92)	.49
Pericardial effusion	1.0	1.2	1.19 (0.89, 1.59)	.23
New, severe congestive heart failure	4.8	4.6	0.95 (0.82, 1.10)	.51
Tamponade	0.4	0.4	0.94 (0.59, 1.50)	.80
Angiotic	2.2	2.1	0.95 (0.77, 1.17)	.66
Ventricular septal defect	0.3	0.2	0.52 (0.26, 1.00)	.049
Papillary muscle rupture	0.07	0.029	0.44 (0.19, 2.34)	.32
Hypotension requiring therapy	9.4	9.1	0.96 (0.82, 1.07)	.49
Atrial fibrillation/flutter	4.4	4.2	0.95 (0.82, 1.11)	.52
Electromechanical dissociation	1.0	1.5	0.83 (0.63, 1.09)	.12
Myocardial rupture	0.6	0.4	0.67 (0.44, 1.03)	.065

TABLE 18.3 COMPLICATIONS OF MYOCARDIAL INFARCTION (THROUGH DAY 7)

The overall effect of abciximab given with half-dose TNK–t-PA in ASSENT-3 was similar to that in GUSTO-V. Significant reduction in in-hospital reinfarction and refractory ischemia rates as well as in the need for urgent intervention was observed, at the cost of a significant increase in major bleedings. Like GUSTO-V, there was no excess in intracranial hemorrhage with this combination. In the elderly no beneficial effects were seen. Major bleeding complications in this age category more than doubled as compared with full-dose TNK and unfractionated heparin (280).

This brings up the findings of IIb/IIIa used in conjunction with angioplasty or stenting in acute MI. Thus far, all of the five trials have tested abciximab, and the mortality results are summarized in Table 18.4. There is an overall reduction of mortality seen with all trials in aggregate, even though the open-labeled CADILLAC trial did not show an advantage of abciximab in the stent arm (297). Besides mortality as an end point, there was a significant reduction in reinfarction, recurrent ischemia, and stent thrombosis in these trials. The data from the various trials and the way in which clinical practice has evolved suggest that IIb/IIIa inhibition has evolved as an important adjunct for catheter-based reperfusion.

	Placebo		Abciximab				
	No.	Death (%)	No.	Death (%)	Hazard ratio	95% Confidence interval	p Value
RAPIDOC, 6 mo	242	4.6	241	4.2	0.91	(0.38, 2.13)	0.821
ISAR-2, 1 yr	200	8.5	201	6.0	0.69	(0.30, 1.45)	0.201
ADMIRAL, 6 mo	151	7.3	148	3.4	0.45	(0.16, 1.31)	0.144
CADILLAC, Balloon 6 mo	515	4.3	529	2.3	0.53	(0.26, 1.06)	0.073
CADILLAC, Stent 6 mo	513	2.8	525	3.8	1.38	(0.70, 2.74)	0.350
STOP-AMI, 6 mo	69	13	71	4.2	0.31	(0.08, 1.16)	–

TABLE 18.4 MORTALITY IN ALL ABCIXIMAB MYOCARDIAL INFARCTION TRIALS

The next phase of IIb/IIIa inhibition in clinical trials will take place with catheter-based reperfusion. A major issue is the time delay (from presentation to effective reperfusion) termed *door-to-balloon time*, which still averages almost 2 hours in most centers. Use of the combined strategy of half-dose fibrinolytic and full-dose IIb/IIIa inhibition may be a useful bridge to catheter-based reperfusion. Furthermore, the use of the IIb/IIIa inhibitor will likely be incorporated subsequently to deal with the microvascular embolization of platelet-thrombus and microscopic atheromatous debris.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The field of acute MI therapy has been characterized by a long-standing debate of pharmacologic versus catheter-based reperfusion. If a patient presents to a hospital with an experienced team and can be mobilized to the catheterization laboratory quickly, catheter-based reperfusion has emerged as a preferred strategy. It is hoped that there will be convergence established with the ability to have a strategy that facilitates mechanical coronary intervention and promotes early patency of the infarct vessel and the microvasculature. For this reason, the combination of IIb/IIIa inhibition and a low-dose fibrinolytic is an attractive foundation. This still remains to be demonstrated, but the hope is that one day there will be no “confusional” delays, deciding on whether to use drugs or the catheterization laboratory. The use of the 60-minute ECG after pharmacologic therapy is attractive in ferreting out the patients who do not yet have tissue-level reperfusion established, and who may indeed have considerable benefit from early catheterization laboratory transfer with consideration for rescue catheter reperfusion.

A considerable challenge exists in avoidance of microvascular obstruction with either pharmacologic or catheter-based reperfusion. To this end, emboli protection devices offer considerable promise to prevent the atheromatous and platelet-thrombus material from getting downstream at the time of the balloon or stenting procedure. Their use will probably become routine over the next few years as the devices go through iterative refinement and the results of the first vein-graft trial (298) become extrapolated to catheter-based reperfusion.

THE FUTURE

Patients with acute ST-segment elevation MI continue to have a compromised prognosis with a relatively constant rate of death or reinfarction by 30 days at 9% to 10%. Today MI remains as the number-one killer in Western society. The intrinsic delays of approximately 2.7 hours from onset of symptoms to initiation of therapy appear to have been immutable since the 1990s. Prehospital administration of pharmacologic reperfusion is frequently used in Europe, but has not been incorporated in practice at most centers in the United States. Once extensive damage has occurred, it is particularly hard to change the natural history. The *Sh*ould We Emergently Revascularize *O*ccluded Coronaries for *C*ardiogenic Shoc*k*? (SHOCK) trial shows benefit for aggressive therapy, but a persistent poor prognosis for those patients with extensive myocardial necrosis.

On the encouraging side, the incidence of classic MI appears to be decreasing, and this trend will likely continue with the use of statins, aspirin, clopidogrel, and ACE inhibitors. But even with improved preventive therapies, we will still need to improve the outcomes of patients with acute MI.

For therapeutic advances, the use of emboli protection devices is attractive and will likely become commonplace. Likewise, the early results of coated stents to control the local inflammatory response will likely become standard. Better antiinflammatory agents, such as selectin or complement inhibitors, may also afford improved outcomes of acute MI, and a focus on lessening heart failure and survival over a longer-term window (1 year rather than 30 days) is likely. For this reason, the early work with stem cells (CD34 positive) is very exciting (299,300,301,302 and 303) and may ultimately restore human heart tissue. It will be a challenge to perform autologous bone marrow transplantation in the early hours of acute MI, but it is nevertheless intriguing for patient with extensive necrosis.

A big change in the future is likely to be affected by the unraveling of the human genome. Although this is unlikely to affect the actual care provided on an emergency basis for acute MI, the ability to provide better primary and secondary prevention will be greatly enhanced. Tailored therapy according to the specific genotypic variant will likely markedly amplify the efficacy and safety of our preventive therapies.

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19

ACUTE MYOCARDIAL INFARCTION: COMPLICATIONS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Complications of myocardial infarction (MI) are related to myocardial factors including infarct size, transmural extent, and location and to coronary factors including extent and severity of coronary artery disease (CAD), as well as the status of the infarct-related artery (IRA) (i.e., patent or occluded). Arrhythmic complications, such as atrial tachyarrhythmias and ventricular tachycardia after the first day, are also largely related to infarct size and left ventricular (LV) function. Major complications include (a) pump failure [LV or right ventricular (RV)], which is the leading cause of death in hospitalized MI patients; (b) LV aneurysm; (c) systemic emboli; (d) reinfarction (infarct extension); (e) ischemia; (f) myocardial rupture (free wall, ventricular septal and papillary muscle); (g) pericardial effusion; and (h) pericarditis. Except for reinfarction and hemorrhagic complications, reperfusion therapy reduces the incidence of most complications.

Echocardiography with color flow Doppler is an excellent tool for rapidly assessing all complications and for evaluating hypotension, congestive heart failure (CHF), and cardiogenic shock. Mimics of shock complicating acute MI, such as aortic dissection, can be readily detected. Management of each complication must be related to its pathophysiology. Mechanical problems, such as ventricular septal rupture (VSR) and mitral regurgitation (MR), should be surgically corrected. A randomized trial of patients in cardiogenic shock demonstrated improved 6- and 12-month survival for those assigned to early angiography and revascularization compared with initial intensive medical therapy and delayed revascularization as indicated. After 20 years of unchanging high in-hospital mortality for shock, the Worcester community reported improved in-hospital survival in 1995 and 1997. Aspirin (ASA) therapy reduces the incidence of early reinfarction, which may be managed with percutaneous transluminal coronary angioplasty (PTCA) or thrombolysis when ST elevations occur. Future efforts must focus on preventing complications because mortalities are high once complications develop.

HISTORICAL PERSPECTIVE

The advent of cardiac care units in the 1960s with continuous electrocardiographic (ECG) monitoring and defibrillators has led to an overall improvement in the in-hospital mortality associated with acute MI. Cardiac care units were a direct result of new technologies available for detecting and treating cardiac arrest (1) including continuous ECG monitoring (2), transthoracic defibrillators (3), transthoracic and transvenous pace makers (4), and antiarrhythmic agents. Using these advanced technologies, patients with ventricular tachycardia and ventricular fibrillation, complete heart block, and asystole complicating acute MI have been successfully resuscitated.

Following the dramatic advances in the treatment of electrical instability in the 1960s, subsequent attention focused on infarct size and pump failure, because mortality among patients with these complications remained high (5). In the 1970s and 1980s, it was demonstrated that mortality and many other complications of MI were strongly associated with infarct size. The development of techniques to measure MI size—including ECG mapping, enzyme assays, and a wide variety of imaging techniques (e.g., radionuclide, ultrasound, and angiographic)—provided means for assessing prognosis and tools to evaluate new therapies to limit the size of the infarct.

The introduction of the intraaortic balloon pump (IABP) in the 1960s (6,7) was the first step in developing circulatory support for pump failure complicating acute MI. This was followed approximately 20 years later by use of many new circulatory assistance devices for cardiogenic shock. The era of hemodynamic monitoring for complicated acute MI began in 1970 with the introduction of the Swan-Ganz balloon-tipped pulmonary artery (PA) catheter (8). In time, complicated MIs (including cardiogenic shock) began to be treated with coronary artery bypass graft (CABG) surgery, with its first reported use in cardiogenic shock complicating acute MI in 1972 (9), and with PTCA, with its first reported use for treating cardiogenic shock in 1985 (10).

More recently, the widespread use of reperfusion therapy has led to a significant decrease in short- and long-term mortality. Overall, the incidence of MI complications, including pump failure, has decreased in the reperfusion era. Nevertheless, pump failure remains the leading cause of death in patients hospitalized for acute MI. This is especially true in patients who do not receive reperfusion therapy and for those in whom reperfusion therapy fails (i.e., those with a persistently occluded IRA). However, the primary cause of death in patients who undergo successful reperfusion is also pump failure, in most cases caused by extensive myocardial damage antedating restoration of myocardial blood flow. Despite the continued high mortality once cardiogenic shock develops, a randomized trial demonstrated that 1-year survival was markedly improved by early revascularization (11). Reperfusion therapy has changed the complexion of all acute MI complications, altering the pathophysiology and timing of cardiac rupture, reducing the risk for emboli, and increasing the incidence of hemorrhagic complications.

In this chapter, we review the pathophysiology and management of LV pump failure, RV infarction and failure, cardiac rupture (including rupture of the free wall, septum, and papillary muscle), pericarditis, and LV thrombus and embolization. We also examine how these complications have been lessened by reperfusion therapy. Arrhythmic complications associated with MI are discussed elsewhere in this textbook (see Chapter 67 and Chapter 74).

GENERAL PATHOPHYSIOLOGY

The spectrum of complications of myocardial necrosis from CHF to arrhythmias to post-MI angina is illustrated in Figure 19.1 (12). Complications of MI tend to occur when infarcts are large and extensively transmural (i.e., when they involve the full thickness of the myocardium). A large, transmural infarct is more prone to expansion (i.e., thinning and dilation) with its attendant increased risk for myocardial rupture, LV aneurysm, LV thrombus, pump failure, and pericarditis (Fig. 19.1) (12). Refractory, sustained ventricular tachycardia develops after MI most frequently in relation to large transmural infarcts that result in LV dilation. Although infarct size is a major determinant of complications, certain strategic locations of small, extensively transmural infarcts can result in devastating complications, such as LV free-wall rupture or rupture of the posteromedial papillary muscle, even when expansion does not occur (Fig. 19.1) (12). Indeed, in an autopsy study of patients dying of an acute MI, infarct size was substantially smaller in patients with cardiac rupture than in patients dying of primary pump function or arrhythmias (*e*Fig. 19.1.1). An anteroapical location of MI increases the likelihood of acute infarct expansion and mural thrombosis. Massive acute myocardial necrosis, multiple small infarcts (acute and prior), and recurrent ischemia or reinfarction may each lead to cardiogenic shock (Fig. 19.1) (12). New myocardial necrosis or infarct extension (i.e., reinfarction) may occur after the initial MI and result in a larger total area of infarction. In contrast, infarct expansion involves no additional myocardial necrosis but results in a larger functional infarct size with a greater percentage of the LV being composed of necrotic myocardium or scar (13). These two complications are compared in Figure 19.1 (12). Extent and severity of disease in noninfarct-related coronary arteries and important characteristics of the patient—including age, gender, and comorbidities (e.g., diabetes mellitus and prior hypertension)—also contribute significantly to the development of acute MI complications. These complications are not entirely independent, and each can lead to other complications (Fig. 19.2).

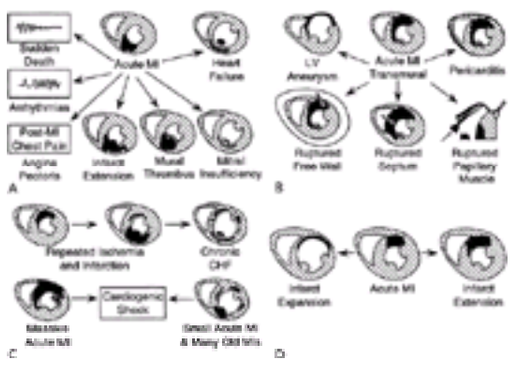
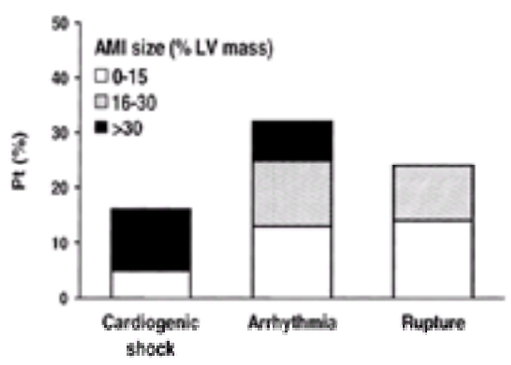


FIGURE 19.1 Complications of myocardial infarction (MI) (schematic). **A:** General complications. **B:** Complications of transmural infarctions. **C:** Cardiogenic shock as a result of either a massive acute infarction or a small acute process in a heart already involved by multiple old infarctions. **D:** Comparison of infarct expansion (aneurysm formation) and infarct extension (reinfarction). CHF, congestive heart failure; LV, left ventricle. (From Edwards WD. Pathology of myocardial infarction and reperfusion. In: Gersh BJ, Rahimtoola SH, eds. *Acute myocardial infarction*. Boston: Chapman & Hall, 1996:16–50, with permission.)



***e*FIGURE 19.1.1** Relationship of size of transmural acute myocardial infarction (AMI) to the mode of death in 78 necropsy patients dying of transmural myocardial infarction. Patients dying of cardiogenic shock had the greatest proportion of infarcts involving greater than 30% of the left ventricular (LV) mass, whereas among patients dying of rupture, the majority of infarcts were less than 15% of LV mass. Overall infarct size was 23% ± 14% of the LV mass; this was 37% ± 11% in patients dying of cardiogenic shock, and the smallest infarcts were in patients dying of cardiac rupture (15% ± 9%). (From Safitz JE, Fredrickson RC, Roberts WC. Relation of size of transmural acute myocardial infarction to mode of death, interval between infarction of death, and frequency of coronary arterial thrombus. *Am J Cardiol* 1981;57:1249–1254, with permission.)

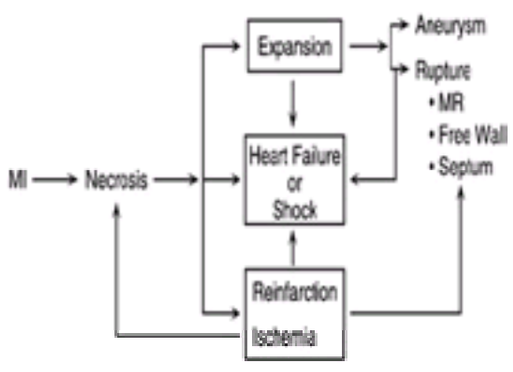
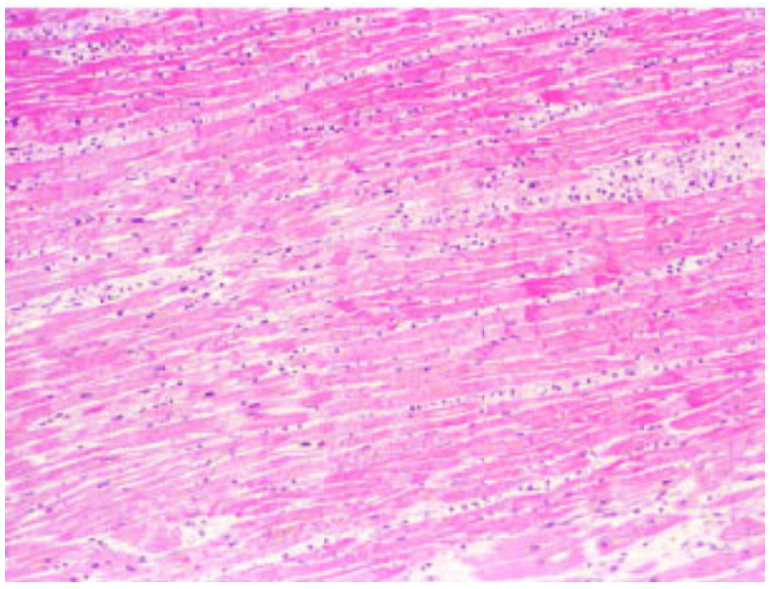


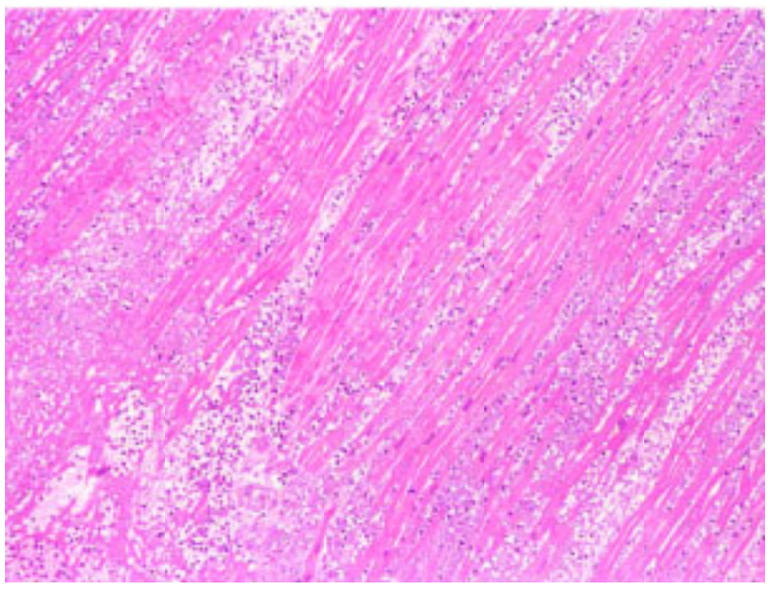
FIGURE 19.2 Overview of the interrelated nature of many complications of myocardial infarction (MI). One complication is often the substrate for another (e.g., expansion is the substrate for left ventricular aneurysms and myocardial rupture, or directly leads to another complication; reinfarction results in pump failure). MR, mitral regurgitation.

Myocardial Infarct Size and Characteristics

One major determinant of infarct size is the region at risk supplied by the acutely occluded coronary artery, which, in turn, is determined by vessel size and location of the occlusion within that vessel. For spontaneously, pharmacologically, or mechanically reperfused infarcts, the duration of total coronary occlusion is another major determinant of infarct size (14). Collateral blood flow from noninfarct-related coronary vessels ultimately affects infarct size. Absence of collateral blood flow in association with permanent total occlusion of the IRA results in infarcts that are extensively transmural. When the region at risk is large, a large, extensively transmural infarct results, with infarct segment dilation and an increased risk for pump failure. When there is no collateral blood flow and a permanent, total IRA occlusion, there is an increased risk for cardiac rupture even with a small vascular distribution. Rich, collateral blood flow with maintained myocardial perfusion may largely limit myocardial necrosis and result in a small subendocardial infarction, even in patients with a large region at risk (15,16). The rate of necrosis is also determined by metabolic demand, which is related to hemodynamic variables including heart rate (HR), LV size, filling pressure, and systemic arterial pressure. Ischemic preconditioning reduces infarct size (17).



Early histologic changes after acute myocardial infarction. These changes are typically seen within a day of the acute event and show contraction band necrosis at the margins of the infarct.



Histologic changes typically seen 2 to 3 days after acute myocardial infarction. There is a prominent acute inflammatory infiltrate and coagulation necrosis of myocytes.

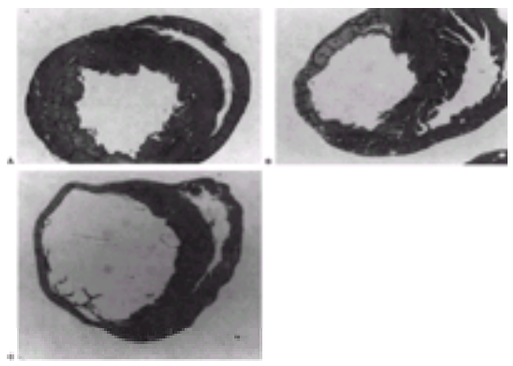
Survival of myocardial cells depends on coronary flow at the microvascular level. Patency of the IRA may be established, but the no-reflow phenomenon may occur (18,19) when relief of epicardial coronary artery occlusion does not result in restoration of myocardial blood flow. No reflow may result from (a) compression of the microvasculature by tissue swelling; (b) microvascular plugging by neutrophils or platelets and fibrin; or (c) microvascular spasm. Microvascular spasm may develop from platelet aggregates, thrombus, or ulcerated plaque fragments that may embolize, causing occlusion or spasm of small vessels. Capillary endothelial damage may occur before myocardial necrosis, and capillary cell swelling may obstruct flow. Tissue perfusion is ultimately determined by flow at the small vessel and interstitial myocardial level, which may result exclusively from collateral flow or may be absent, even in patients with a patent coronary artery and minimal stenosis. Studies have documented the independent prognostic effect of microvascular function and myocardial perfusion on prognosis (20,21 and 22).

Stunning, a temporary impairment of myocardial contraction that results from severe ischemia, may occur despite restoration of normal myocardial blood flow (23). Similarly, the more chronic process of impaired contraction, which manifests as chronic, low blood flow and hibernation, may result when a critical coronary stenosis remains after MI (24,25).

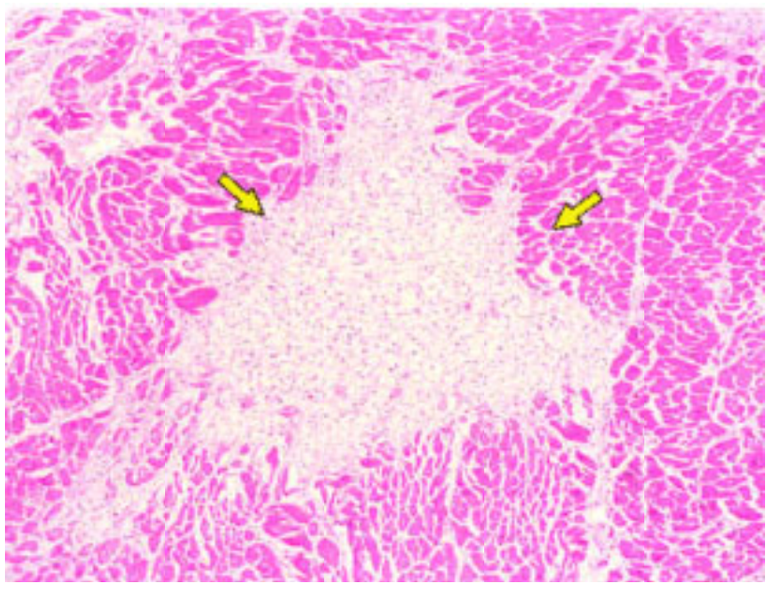
INFARCT EXPANSION, LEFT VENTRICULAR REMODELING, AND LEFT VENTRICULAR ANEURYSM

Pathophysiology

LV remodeling after MI refers to topographic and functional changes in the infarct zone and in remote, uninfarcted myocardium that begin minutes after MI and may continue for months or years later. These changes include (a) infarct expansion (i.e., thinning and dilation of the infarct zone) (eFig. 19.2.1); (b) subsequent dilation of the remote, uninfarcted myocardium with hypertrophy; (c) interstitial fibrosis and impairment of contraction; and (d) global change from a normal LV, elongated ellipse to a more spherical shape (26,27,28,29,30 and 31). LV aneurysm, a discrete bulge of the LV composed of fibrotic tissue, results when severe infarct expansion persists and scar is laid down on the topographic substrate.



***e*FIGURE 19.2.1** Infarct expansion and infarct extension. These photomicrographs of infarcts in rat hearts illustrate infarct expansion, infarct extension, and the effect of early and late reperfusion on infarct expansion. **A:** Subendocardial infarct, no expansion: cross-section through rat heart undergoing early reperfusion (30 minutes) after coronary ligation with resultant small subendocardial myocardial infarction, normal left ventricular free wall thickness, and normal cavity size (no infarct expansion). **B:** Late reperfusion, moderate infarct expansion: This left ventricular free wall myocardial infarction was reperfused late, without myocardial salvage. The infarct has thinned with left ventricular cavity dilation (compare with **A**); however, there is less infarct expansion than that seen in the same model with permanent left coronary ligation **(C)**. Infarct extension: This infarct has extended throughout the thickness of the left ventricular free wall (subepicardial extension) compared with the infarct in **A**, and at the superior aspect has extended laterally to reach the ventricular septum. **C:** Large infarct, severe expansion: This left ventricular free wall is severely thinned and the cavity severely dilatated in this rat with a permanent coronary occlusion.



Histology showing the early stages of healing after myocardial infarction. These changes are typical in the second week after the acute event. This is a hematoxylin-eosin stain showing removal of the necrotic myocytes and early ingrowth of vascular tissue and fibroblasts, particularly evident at the edges of the lesion (*yellow arrows*).

Infarct Expansion and Left Ventricular Remodeling

Infarct expansion occurs soon after onset of coronary occlusion (26,32). It is reversible if coronary flow is reestablished rapidly; however, it may progress in a time-dependent manner if flow is not reestablished or is reestablished late (33). Infarct size is a major determinant, with large infarcts expanding more frequently and more severely than small ones (27,30). Anterior infarcts and those involving the apex are at greatest risk for infarct expansion (13,26,34), probably as a result of a thinner LV wall and greater radius of curvature at the apex, which increase stress on the LV wall per Laplace's equation. Inferior, posterior, or lateral infarcts without apical necrosis less frequently expand. Transmural infarcts are more likely to expand; nontransmural infarcts are largely protected from expansion (27,33). The greater the extent of transmural infarct, the more likely it is to expand, even though a thin rim of noninfarcted subepicardial myofibrils helps to limit infarct expansion. Infarct expansion is the pathologic substrate for type III cardiac rupture. Disruption of the intercellular collagen matrix may lead to slippage of sheets of myofibrils and expansion of the affected area (31,35).

Infarct expansion results in early LV dilation (26,27 and 28). It is associated with CHF and LV intracavitary thrombosis (29,36,37). Long-term global remodeling with dilation and long-term impairment of uninfarcted, myocardial segment contraction begins soon after a large infarction and progresses for months to years (28,30,31,38). LV volume strongly correlates with long-term mortality (39,40).

Left Ventricular Aneurysm

Regional expansion of the infarct zone that results in a discrete diastolic and systolic bulge and that is not reversed by reperfusion or other measures produces chronic, true LV aneurysm. LV aneurysm pathologically is composed of scar that is laid down by fibroblasts on the topographic substrate formed early by infarct expansion (41). Scar laid down soon after infarction does not subsequently dilate to form aneurysms. Early LV aneurysms may be referred to as *functional aneurysms* (42) because they may be reversible. In fact, LV aneurysms resected years after MI sometimes contain viable and presumably hibernating myocardium (43). In contrast to true LV aneurysm, pseudoaneurysm or false LV aneurysm represents localized rupture of the myocardium and is discussed later in this chapter (Fig. 19.3) (44).

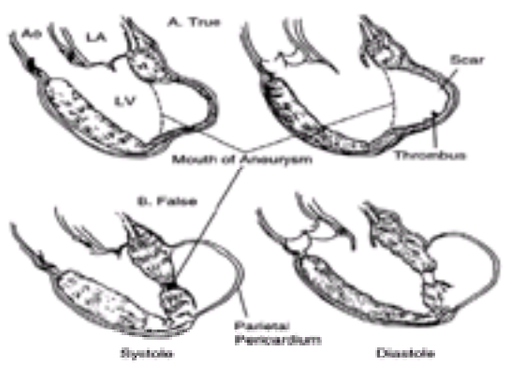
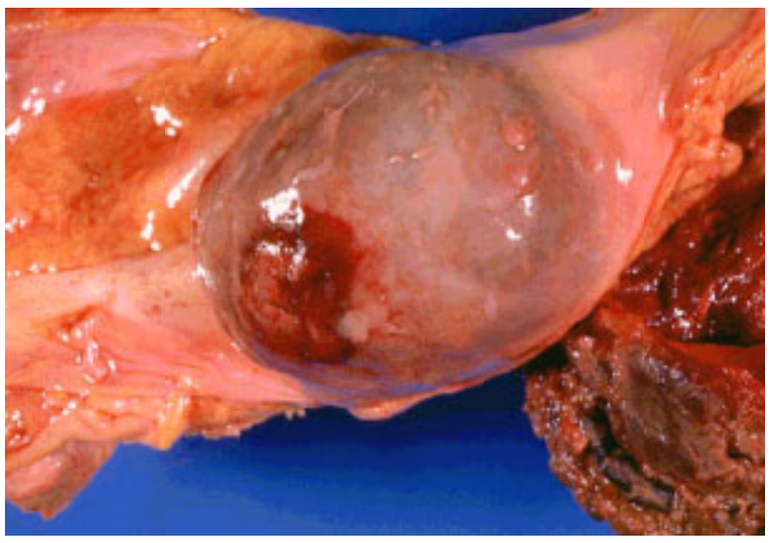


FIGURE 19.3 Hearts in systole and diastole with true and false anatomic left ventricular (LV) aneurysms and healed myocardial infarction. The true anatomic LV aneurysm protrudes during both systole and diastole, has a mouth that is as wide as or wider than the maximal diameter, has a wall that was formerly the wall of the left ventricle, and is composed of fibrous tissue with or without residual myocardial fibers. A true aneurysm may or may not contain thrombus and almost never ruptures once the wall is healed. The false anatomic LV aneurysm protrudes during both systole and diastole, has a mouth that is considerably smaller than the maximal diameter of the aneurysm and represents a myocardial rupture site, has a wall made up of parietal pericardium, virtually always contains thrombus, and often ruptures. Ao, aorta; LA, left atrium. (Adapted from Cabin HS, Roberts WC. Left ventricular aneurysm, intraaneurysmal thrombus, and systemic embolus in coronary heart disease. *Chest* 1980;77:586, with permission.)



False aneurysm of the aorta. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 19.1 A 61-year-old male patient with left ventricular pseudoaneurysm after acute anterolateral myocardial infarction. Patient underwent successful surgical repair. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Late and Early Open Artery Hypotheses

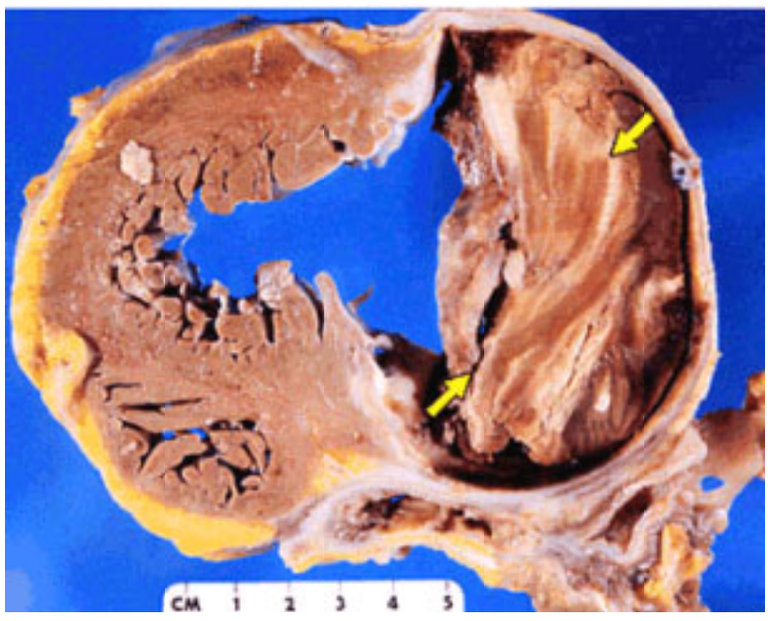
The *late open artery hypothesis* refers to the mechanisms whereby a patent IRA produces a beneficial effect on LV remodeling independent of myocardial salvage.

Infarct expansion and progressive LV dilation are associated with an occluded IRA, and inhibition of LV dilation has been associated with an open IRA (45,46 and 47). The *early open artery hypothesis* refers to the fact that *early* reperfusion results in myocardial salvage and inhibits infarct expansion (33) (eFig. 19.2.1), thus reducing mortality. *Late* reperfusion, beyond the time for myocardial salvage, may limit the degree of infarct expansion (33,48,49,50,51,52 and 53) (eFig. 19.2.1). There are multiple, potential causative mechanisms:

1. Immediate changes in the infarct characteristics with formation of contraction bands and possibly edema and hemorrhage, resulting in a shorter, thicker, and stiffer infarct segment
2. Preservation of small residual islands of myofibrils
3. Possible preservation of interstitial collagen
4. Accelerated healing
5. The scaffold effect of a blood-filled vasculature
6. Elimination of ischemia in viable dysfunctioning (hibernating) myocardium

Left Ventricular Thrombus

Inflammation of the endocardium resulting from myocardial necrosis in any location may produce layered, mural thrombus; however, thrombus most frequently develops in anterior infarcts (37,54) with expansion or aneurysmal dilation that involves the apex, caused by the combination of endocardial inflammation and stasis. More extensive thrombi with a protruding appearance are at increased risk for systemic embolization (37,55), and they typically occur in the apex. Mural thrombi are more frequently found in recently formed LV aneurysms than in older aneurysms (56).



Healed, atrophic posterolateral infarct and ventricular aneurysm containing a mural thrombosis (*yellow arrows*).

VIDEO

Video 19.2 A 54-year-old male patient with filling defect of the left ventricular apex consistent with left ventricular apical thrombus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 19.3 Post–myocardial infarction apical thrombus (long-axis). Akinesia of thin apical wall with adjacent thrombus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Clinical Profile

Risk Factors

Patients with myocardial infarcts that involve the apex of the left ventricle, particularly those with anteroapical, Q-wave (i.e., transmural) infarcts are at greatest risk for infarct expansion and aneurysm formation (34). A discrete, posterobasal aneurysm may less frequently develop following inferoposterior MI. Patients who do not receive reperfusion therapy or in whom reperfusion therapy fails are at greater risk for aneurysm formation.

High ventricular afterload states, such as hypertension during acute MI and elevated plasma angiotensin-converting enzyme (ACE) activity levels, are associated with infarct expansion (36,57,58). Administration of corticosteroids after acute MI is associated with delayed infarct healing and development of LV aneurysms (59). Both corticosteroids and nonsteroidal antiinflammatory drugs have been demonstrated experimentally to induce infarct expansion when administered acutely after coronary occlusion (60,61 and 62).

Diagnosis

Clinical Findings

The classic physical finding of LV aneurysm is a dyskinetic apical impulse on palpation. The ECG typically shows an extensive, anteroapical Q-wave MI with persistent ST-segment elevation. Persistent T-wave inversion is also a marker of progressive LV dilation (63). Chest roentgenography is insensitive but typically demonstrates a bulge in the LV silhouette.

A 78-year-old with left ventricular aneurysm status post anterolateral myocardial infarction.

Imaging

On imaging, LV aneurysm is defined as a discrete bulge in the LV contour during both diastole and systole, which typically exhibits dyskinetic (i.e., paradoxical) expansion during systole. Echocardiography with color flow Doppler is the imaging modality of choice and can be used to distinguish discrete, LV aneurysms from false aneurysms. Other techniques to assess an aneurysm include biplane left ventriculography, which is the traditional gold standard, radionuclide ventriculography, computed tomography (CT), and magnetic resonance imaging (MRI).

Video 19.4 Transesophageal echo view of a patient after a large left anterior descending coronary artery territory infarction with an apical aneurysm. Note the spontaneous echo contrast seen within the left ventricular cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 19.5 Apical left ventricular aneurysm in a 69-year-old female patient with history of anterior myocardial infarction. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

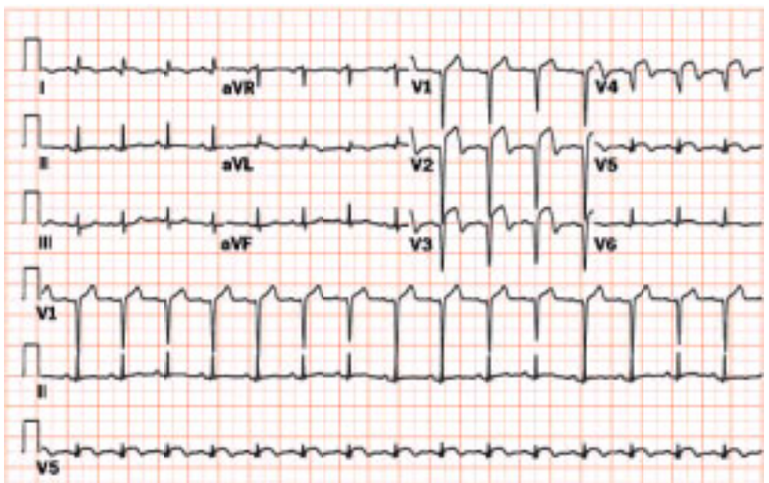
Video 19.6 Post–myocardial infarction true aneurysm (long-axis). Dyskinesia and thinning of the left ventricular apex due to an occlusion of left anterior descending artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 19.7 Post–myocardial infarction pseudoaneurysm (short-axis). Rupture of the inferolateral wall of the left ventricle due to circumflex artery occlusion. The pseudoaneurysm cavity is contained by pericardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

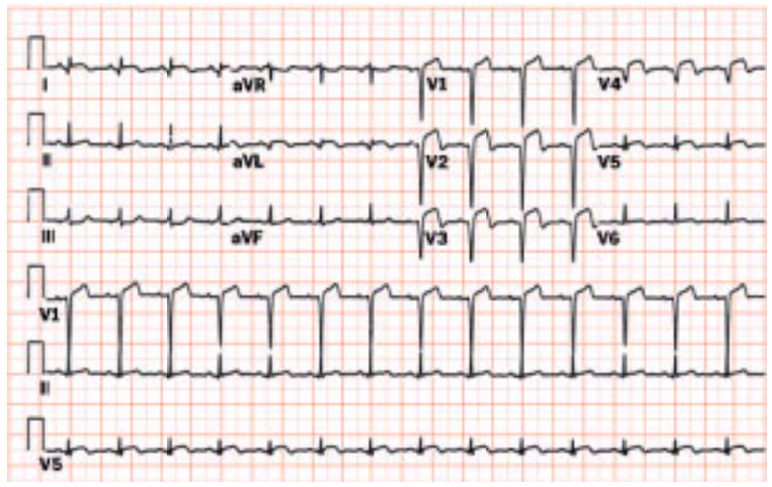
Clinical Consequences

Cardiac Rupture, Congestive Heart Failure, and Arrhythmias

Rupture of the myocardium may result from acute infarct expansion, but it does not occur in chronic LV aneurysms with scar. Acute CHF complicating MI more frequently occurs when infarct expansion is demonstrated (29,36). Infarct expansion and acute aneurysmal dilation may result in CHF caused by paradoxic systolic bulging with reduced mechanical efficiency of the left ventricle (i.e., wasted work) (43) and elevated wall stress in the remote, uninfarcted myocardium, causing global ischemia. Chronic LV aneurysms are associated with chronic CHF. In this context, the extent of systolic bulging with chronic scar is minimal and wasted work only plays a significant role when the aneurysm is composed of viable myocardium interspersed with scar tissue or of thin scar that expands with each systole (Fig. 19.3) (44).

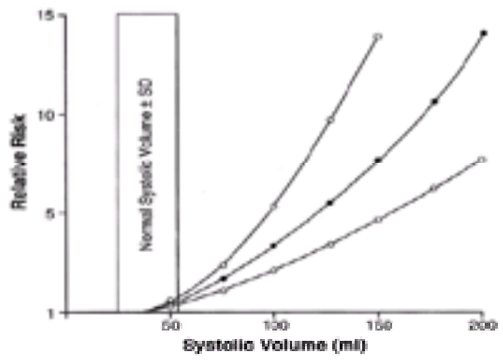


Evolution of acute anterolateral myocardial infarction at 24 hours. Prominent Q waves have developed across the anterior precordium and leads I and aVL. ST segment elevation persists, however.



Evolution of acute anterolateral myocardial infarction at 72 hours. Q-wave pattern in the anterolateral leads is well established. Persistent ST-segment elevation suggests complication by aneurysm or pericarditis.

Recurrent and sustained, monomorphic ventricular tachycardia may occur in acute infarct expansion or in chronic LV aneurysm and may be refractory to antiarrhythmic therapy (see Chapter 67). LV volume correlates strongly with short- and long-term mortality (eFig. 19.3.1) (39,40), with sudden cardiac death occurring at least as frequently as death from progressive pump failure. Early LV dilation results in late progressive LV enlargement with associated CHF and malignant ventricular arrhythmias late post-MI (64).



***e*FIGURE 19.3.1** Estimated relationships between end systolic volume 1 to 2 months after myocardial infarction and relative risk of cardiac death over the follow-up period (mean, 78 months). The risk is relative to that of an individual with an end systolic volume of 39 mL (normal for laboratory). SD, standard deviation. (From White HD, Norris RM, Brown MA, et al. Left ventricular end-systolic volume as the major determinant of survival after recover from myocardial infarction. *Circulation* 1987;76:44–51, with permission.)

Left Ventricular Thrombi and Systemic Emboli

Layered mural and protruding thrombi typically develop within the first week following acute anterior Q-wave MIs with expanded or aneurysmal akinetic or dyskinetic segments, especially those involving the LV apex. The estimated incidence in an echocardiographic study in 1986 was approximately 33% for anterior MI and less than 5% to 10% for other locations (65). Because LV thrombi more frequently occur with large infarctions, they have become less common in the reperfusion era. Of 8,326 patients in the Gruppo Italiano Per lo Studio Della Streptokinase nell'Infarto Miocardio (GISSI)-3 study who had a predischarge echocardiogram, the overall LV thrombus incidence was 5.1% of anterior MIs and 2.3% of nonanterior MIs. These rates were higher when the ejection fraction (EF) was less than 40%. Independent risk factors for LV thrombus are Killip class greater than I and early intravenous beta-blocker use (54). LV thrombi are associated with increased risk for systemic embolization (55), particularly when they have a protruding appearance (37). Stroke is the primary manifestation of cardiac emboli (occurring in 85% of cases); however, the overall incidence of arterial embolism is low (65,66,67,68 and 69), whether LV thrombus is visualized or not. The reported incidence (69) of systemic emboli associated with anterior MI in the prereperfusion era was 2% to 6%. Patients with atrial fibrillation (AF) after MI are at increased risk for systemic emboli from left atrial thrombi. Patients with chronic LV aneurysm are at low risk for systemic embolization (70), perhaps because the aneurysmal area containing thrombus is noncontractile and there is no longer endocardial inflammation. However, when global LVEF is reduced after MI (less than 40%), the rate of stroke is 1.5% per year even when CHF is not present. The risk increases with decreasing EF and older age (71). Patients with LVEF less than 28.0% have a 5-year stroke rate of 8.9%. These strokes, however, are undoubtedly caused by cerebrovascular disease, as well as cardiac emboli.

Video 19.8 Subcostal view of a patient with severe left ventricular dysfunction and multiple mobile thrombi within the left ventricular cavity. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Management

Medical Therapy

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors have been shown in experimental models and in clinical investigations (64,72,73) to reduce acute infarct expansion and progressive LV remodeling. When successful reperfusion has inhibited infarct expansion and aneurysm formation, ACE inhibitors have not been clearly shown to limit expansion further (74). A detailed discussion of the use of ACE inhibitors in MI can be found elsewhere in this textbook (see Chapter 20). Because infarct expansion begins early, therapy should be instituted within the first 24 hours of onset of MI in patients at risk for expansion and aneurysms (i.e., those with nonreperfused or large anteroapical Q-wave MIs, particularly with associated hypertension). A short-acting ACE inhibitor is recommended for initial therapy (e.g., captopril), so that it can be discontinued if hypotension develops, dissipating its effect more rapidly. The initial dose should be 6.25 mg followed by 12.5 mg, then 25 to 50 mg every 8 hours as tolerated. After several days, the patient may be switched to a long-acting ACE inhibitor. The use of ACE inhibitors in patients presenting with pulmonary congestion is discussed in Acute Left Ventricular Failure, later in this chapter.

Angiotensin Receptor Blockers

The effect of angiotensin receptor blocking agents on LV dilation following anterior MI has been investigated in two small trials. Losartan appeared efficacious when compared with captopril and results in greater reductions in end systolic volume when added to captopril after anterior MI (75,76). However, the combination results in a more marked decrease in blood pressure (BP). Larger trials are needed before they are routinely added to or replace ACE inhibitors. It is reasonable to use angiotensin-2 blockers instead of ACE inhibitors in patients who cannot tolerate ACE inhibitors.

Nitrates

Nitrates have also been demonstrated experimentally and in small clinical studies (77,78 and 79) to reduce infarct expansion, particularly in those with LV dysfunction. The data from both sources for the efficacy of nitrates in reducing infarct expansion and chronic LV remodeling are less compelling than are those for ACE inhibitors (80).

Anticoagulation: Prevention of Left Ventricular Thrombus

Full-dose heparin has been demonstrated on echocardiography to reduce the incidence of LV thrombus compared with low-dose subcutaneous (s.c.) heparin (11% versus 32%; $p = .0004$) (81). The full dosage can be administered s.c., as it was in this study, or by continuous intravenous (i.v.) infusion. Low-molecular-weight heparin may be used instead of full dose s.c. or i.v. unfractionated heparin.

Nonrandomized studies (66,67 and 68) of patients receiving thrombolytic therapy have reported variable results with respect to LV thrombus formation, with rates ranging from 8% to 28%. The development of LV thrombus in these patients despite thrombolytic therapy may be caused by large infarction and persistent, severe wall motion abnormality, particularly that involving the apex, resulting from failed or late reperfusion.

Anticoagulation: Therapy for Left Ventricular Thrombus

Full oral anticoagulation for 3 months significantly accelerated the resolution of LV thrombus in a small randomized trial (82) of acenocoumarol versus sulfinpyrazone versus placebo. Full-dose warfarin is recommended when LV thrombus is visualized, although there are no data from randomized trials of this subset demonstrating decreased events.

Anticoagulation: Prevention of Systemic Emboli

In the prethrombolytic era, the effect of anticoagulant therapy on systemic and pulmonary embolism (PE) was assessed in two major randomized trials. Patients assigned to heparin followed by high-dose phenindione had significantly lower rates of systemic and PE compared with those assigned to low-dose phenindione (4.8% vs. 11%; $p = .01$) (83). In the Veterans Administration Cooperative Trial (84), heparin followed by warfarin significantly reduced the rate of systemic embolism, including stroke (5.6% vs. 0.8%; $p = .001$). In the thrombolytic era, the GISSI (85) showed that the rate of pulmonary and systemic thromboembolism was significantly reduced by streptokinase (SK) alone compared with placebo (0.4% vs. 1.1%, respectively; $p = .05$).

The Survival and Ventricular Enlargement investigators (71) reported that long-term use of warfarin in patients with EF less than 40% after MI was strongly associated with a reduced 5-year stroke rate (relative risk, 0.19; range, 0.13 to 0.27; $p < .001$). Of note, ASA was also associated with a reduced risk (relative risk, 0.49; range, 0.29 to 0.65; $p < .001$) (71). In the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT 2) randomized trial, warfarin alone or in combination with ASA was superior to ASA alone post-MI in preventing stroke (0% versus 0.3% versus 1.5%) as well as MI and death (86). However, stroke, MI, and death were not reduced by warfarin (Coumadin) plus ASA compared with ASA alone in the Combined Hemotherapy and Mortality Prevention (CHAMP) trial (87). Larger trials comparing Coumadin with ASA and their combination are ongoing.

Anticoagulant Regimens

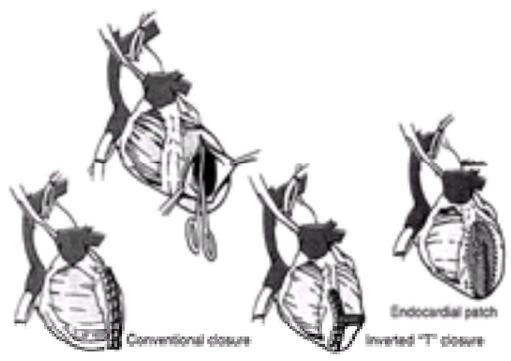
Heparin Dosing. We recommend a target activated partial thromboplastin time (aPTT) of 1.5 to 2.0 times control, typically 50 to 70 seconds, based on excessive hemorrhage and mortality for higher aPTTs after acute MI. However, there is variability in the aPTT based on the reagents used. Low body weight, older age, and female gender are independent risk factors for a high aPTT and hemorrhage (88). For patients who weigh less than 70 kg (e.g., women and the elderly), the dose should be reduced. The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (89,90) recommend a 60 U per kg bolus, maximum 4,000 U, followed by 12 U per kg per hour, maximum 1,000 U per hour, in conjunction with thrombolytic agents. When no thrombolytic agent is used, the recommended dose is 60 to 70 U per kg bolus, maximum 5,000 U, followed by 12 to 15 U per kg per hour, maximum 1,000 U per hour. Unlike its efficacy in non–ST-elevation syndromes (91), low-molecular-weight heparin has not been evaluated for preventing or treating LV thrombi or systemic emboli. Based on their ease of use, they are a practical alternative.

Warfarin Dosing. Warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0 is recommended following infarction in patients with anterior Q-wave MI (69) and, in particular, in those with akinetic or dyskinetic apical wall motion, or in the presence of ECG-documented LV thrombus. Warfarin is also recommended in patients with large, nonanterior infarcts complicated by depressed LVEF and CHF and in those with AF (65,69). Perhaps a higher target INR of 2.5 to 3.5 is appropriate for at least 6 months in patients with LV thrombi who have had systemic emboli. It is unclear whether patients with these high-risk characteristics should be treated with Coumadin indefinitely or 3 months of therapy followed by ASA. The former approach is supported by the ASPECT 2 study, which demonstrated reduction of vascular events, stroke, death, and MI with Coumadin plus ASA compared to ASA alone (86). However, the larger CHAMP study, which achieved lower INRs than ASPECT 2, showed similar event rates for Coumadin plus ASA compared with ASA alone (87). Long-term warfarin therapy should be strongly considered in asymptomatic patients with depressed EFs after MI, particularly EFs less than 30% (71). Until larger trials are completed, it is reasonable to continue warfarin indefinitely for the higher risk group patients who are suitable candidates.

Lower intensity warfarin (1 or 3 mg) combined with ASA (80 mg) in survivors of acute MI of any location (patients with LV thrombi are largely excluded) was associated with similar long-term outcomes when compared with ASA (160 mg) alone in the Coumadin Aspirin Reinfarction Study (92), except for a small excess of stroke in the two low-dose Coumadin with ASA (80 mg) arms.

Infarctectomy and Aneurysmectomy

It is our impression that the need for acute infarctectomy and aneurysmectomy has markedly decreased owing to successful reperfusion therapy as well as to other medical therapies. There is, however, renewed interest in ventricular reduction surgery to improve LV remodeling in chronic CHF patients. Indications for surgical resection include refractory CHF and refractory ventricular tachycardia (89). It may be considered in recurrent systemic thromboembolism. Improved techniques use the T closure and endocardial patch to close the LV and restore a more normal LV shape after aneurysm resection (*e*Fig. 19.3.2) (93).



***e*FIGURE 19.3.2** Operative techniques used in left ventricular aneurysm repair. The figure depicts resection of the ventricular aneurysm enclosure by one of three methods. The conventional closure is illustrated on the left. The T closure and the endocardial patch techniques were developed in an attempt to restore normal left ventricular geometry. (From Komeda M, David TE, Malik A, et al. Operative risks and long-term results of operation for left ventricular aneurysm. *Ann Thorac Surg* 1992;53:22, with permission.)

Aneurysm repair in a patient with a recent lateral wall myocardial infarction. "Packing material" is evident overlying the area of repair (*yellow arrow*).

Recognizing that stunned and hibernating myocardium may be present within the infarct zone, myocardial viability studies should be performed to determine whether revascularization of the infarct zone should be performed rather than infarctectomy in selected patients with apparent aneurysms and refractory CHF.

Revascularization

Late Open Artery Hypothesis

Observational data (94,95 and 96) demonstrate a strong association between outcome after MI and the status of the IRA. Patients with a patent IRA after MI have a markedly lower mortality at 1 year than those who have an occluded IRA. An open IRA correlates with improved electrical stability (96,97 and 98) and inhibition of infarct expansion and progressive LV dilation (45,46 and 47). *Late* spontaneous reperfusion is associated with recovery of function, and reocclusion is associated with progressive deterioration (51,52 and 53). However, there are conflicting observational data on whether the association of an open IRA late after MI and cardiac events is *independent* of other patient characteristics, including EF and coronary anatomy (94,96,99). The largest study, Global Use of Strategies to Open Occluded Coronary Arteries 1 (GUSTO 1), reported no independent association of an open IRA post-MI on 1-year survival (99). Studies of PTCA for totally occluded vessels days after onset of infarct have reported relatively high rates of unsuccessful PTCA and failure of sustained patency (i.e., in approximately 40% of patients) (47,100). Coronary stents have reduced these reocclusion rates (101). Failure of spontaneous reperfusion or sustained patency after *late* PTCA post-MI may be the result of more extensive myocardial damage with no reflow and autoregulatory decrease in coronary blood flow. Furthermore, failure of sustained patency has been associated with high lipoprotein(a) levels and the DD ACE gene allele and may simply be a marker of other prognostic variables (102,103). There are no data from large randomized trials demonstrating that late intervention (i.e., ³24 hours after MI) to reestablish flow in IRA with angioplasty or bypass surgery results in improved LV remodeling or outcome. Four small randomized trials assigned patients with total occlusions 2 to 45 days after MI to PTCA or medical therapy only (47,100,104,105,105a) (*e*Table 19.0.1). The most recent study used routine stenting following PTCA (104). Two trials were neutral for effects on ventricular size and function and clinical events (47,100). A single-center study of left anterior descending (LAD) infarcts in Japan reported improved LV volumes and clinical event rates with PTCA (105). A multicenter study in the United Kingdom reported adverse LV remodeling and clinical outcomes with PTCA and stents (104). In the latter study, 100% of patients were on ACE inhibitors, more than 80% on beta-blockers, and all had low-threshold ischemia excluded. If a benefit of late reperfusion was demonstrated, the clinical implication would be that asymptomatic patients with MI would need to undergo coronary angiography to establish the status of the IRA and, if it were occluded, to undergo revascularization (106). Large randomized clinical trials are ongoing.

***e*TABLE 19.0.1** RANDOMIZED CLINICAL TRIALS OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) FOR PERSISTENT TOTAL OCCLUSIONS OF THE INFARCT-RELATED ARTERY FOLLOWING MYOCARDIAL INFARCTION

Study	Reference number	Follow-up	Change in ejection fraction (%)	Change in end systolic volume (mL)	Change in end diastolic volume (mL)	Clinical events[a] (%)
TAMI-6	100	6 mo				
PTCA (n = 34)			+3.1	+7.0	+10.0	17.6
No PTCA (n = 37)			+3.8	–10.0	0.0	13.5
TOMIIS	47	4 mo				
PTCA (n = 25)			+5.3	NA	NA	4.0
No PTCA (n = 19)			+4.1			5.2
Horie et al.[b]	105					
PTCA (n = 44)		Ejection fraction and volumes, 6 mo	+5.4	–3.5[c]	–0.3[c]	9.1[c]
No PTCA (n = 39)		Clinical, 5 yr	+1.6	+3.8[c]	+9.0[c]	48.7[c]
TOAT	104	12 mo				
PTCA (n = 32)			+1.0	+12.0[c]	+17.0[c]	53.1[c]
No PTCA (n = 34)			+3.0	–5.0[c]	–3.0[c]	35.3[c]

NA, not available.
[a] The combined end point may include overlapping events in TAMI-6 and TOAT. Clinical events: TAMI-6 and TOMIIS, death and recurrent myocardial infarction; Horie et al., death, recurrent myocardial infarction, and congestive heart failure; TOAT, death, recurrent myocardial infarction, stroke, congestive heart failure, and revascularization.
[b] Volumes are indexed to body surface area; 50% of patients randomized to no PTCA had no baseline left ventricular ejection fraction and volumes reported.
[c] $p < .05$, comparison of the two groups.
Adapted from Sadanandan S, Buller C, Menon V, et al. The late open artery hypothesis—a decade later. *Am Heart J* 2001;142:411–421.

REINFARCTION AND ISCHEMIA

Pathophysiology

General

Reinfarction or recurrent ischemia may occur in the same region at risk as the index MI or less frequently in a remote vascular distribution (ischemia or infarction at a distance) (15,107,108). Reinfarction or infarct extension in the index region at risk may result from one of the following events:

1. Reperfusion of the IRA followed by reocclusion
2. Propagation of thrombus retrograde such that new branch vessel(s) are occluded
3. Distal embolization of thrombus or plaque contents to small vessels with occlusion of collateral blood inflow and microvascular dysfunction
4. Reduction in coronary perfusion pressure (e.g., hypotension) or in oxygen-carrying capacity (e.g., anemia from hemorrhage) in severe, residual IRA stenosis
5. Reduction in collateral flow from a stenosed coronary artery

The index infarct can extend laterally and subepicardially (*e*Fig. 19.2.1). Completion of the infarct to include the subepicardium results in an extensive transmural infarct that is at greater risk for infarct expansion, cardiac rupture, and pericarditis.

Although reinfarction occurs more frequently when the IRA reoccludes than when it remains patent, reocclusion of the IRA does not always result in reinfarction (109,110). This may be because of improved collateral flow after the index event, which protects the region at risk from further infarction, or it may be caused by the lack of any remaining viable myocardium in the region subtended by the reoccluded vessel. Following thrombolytic therapy for MI with ST elevation, reocclusion occurs in 5% to 30% of patients as demonstrated angiographically, and it is associated with a worse outcome compared with patients with sustained patency (110). Changes

in the supply and demand balance caused by an increase in HR and BP may cause recurrent ischemia.

Ischemia and Infarction at a Distance

Multivessel disease is present in most patients with MI as documented in both angiographic and autopsy studies (15,111,112). An angiographic study reported the presence of ulcerated or complex plaques in noninfarct-related arteries in 39.5% of patients with MI, suggesting that the potential for reinfarction is related in part to the presence of multiple potential culprit lesions in the presence of a prothrombic milieu (113). Infarction at a distance infrequently occurs and is more likely to develop at the time of the index infarction. Such infarction may be caused by

1. Interconnection of two vascular beds with a prior total or subtotal occlusion in the remote, recipient vessel and a fresh occlusion in the feeder IRA
2. Formation of a second coronary thrombosis resulting from the systemic hypercoagulable or inflammatory state of acute MI with multiple ulcerated plaques
3. Reduction in coronary perfusion pressure to vascular beds with preexisting coronary stenosis
4. Emboli from LV or left atrial thrombi (rare)

Post-MI recurrent ischemia that is remote from the index MI (i.e., in another vascular distribution) is associated with a worse outcome than recurrent ischemia in the periinfarct zone (107,108). It is associated with pump failure (114). This is consistent with the presence of multivessel (i.e., two-or three-vessel) CAD, which results in higher reinfarction and mortality. Ischemia at a distance may result from

1. Increased myocardial oxygen consumption ($\dot{V}O_2$) secondary to elevated wall stress resulting from LV dilation, increased LV end diastolic pressure (LVEDP), and HR from the index MI in patients with a fixed chronic stenosis
2. Diffuse, acute reduction in the vasodilator reserve response associated with recent MI (115,116)
3. Generalized platelet aggregability, inflammation, hypercoagulability, and increased viscosity
4. Reduction in collateral flow through occlusion of an interconnected vascular bed

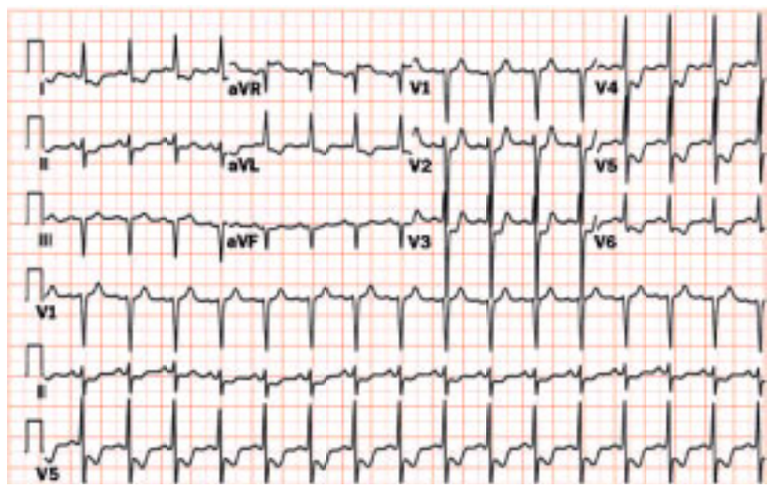
Importance of Coronary Perfusion Pressure

It is critical to maintain coronary perfusion pressure during acute MI to facilitate reperfusion and sustain patency of the IRA. Recurrent MI and ischemia may result from a decrease in coronary perfusion pressure in patients with a preexisting coronary stenosis. Reocclusion following reperfusion with PTCA may result from hypotension. Hypotension during thrombolytic therapy substantially reduces the rate of lysis of thrombi (117,118), as well as the overall reperfusion rate (119,120), and may predispose patients to reocclusion. There is also evidence of worse outcomes and larger MIs when hypotension occurs with use of nitrates and ACE inhibitors early in acute MI (74,121).

Clinical Profile

Diagnosis

The diagnosis and incidence of reinfarction or infarct extension vary widely depending on the clinical definition and the diligence with which it is sought. ECG changes alone are the least specific method of diagnosing infarct extension and they markedly overestimate its occurrence (13,122). ST-segment elevation that progresses days after MI may represent pericarditis or infarct expansion. Evolution of deepening T waves is typical after MI and does not usually represent ischemia or infarct extension. Recurrent chest pain is also nonspecific, with angina or pericarditis pain as other causes of post-MI chest pain. Recurrent elevations in creatine kinase with muscle and brain subunits (CK-MB) after its disappearance or to >50% of the prior value are regarded as the standard for reinfarction (89). Because troponin I and T may remain elevated for up to 2 weeks, they are not used to diagnose reinfarction (123). The full constellation of recurrent chest discomfort and recurrent elevation in ST segments followed by recurrent elevation in CK-MB infrequently occurs but constitutes the typical diagnosis, both in large clinical trials and in clinical practice. We recommend obtaining daily CK-MB measurements for 2 days after MI as well as 8-hour samplings for 24 hours if a recurrent event develops (e.g., chest pain, worsening ST elevations or depressions).



Subendocardial ischemia. Anterolateral ST-segment depression is consistent with diffuse subendocardial ischemia versus non–Q-wave myocardial infarction.

Incidence, Risk Factors, and Prognosis

The incidence of short-term reinfarction in the prereperfusion era in studies (124,125 and 126) in which it was carefully assessed by repeated CK-MB measurements is shown in Table 19.1 and is compared with rates reported in large clinical trials (84,85,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139 and 140). The rates reported in clinical trials are all relatively low probably because of (a) reporting of only those reinfarctions with the full clinical constellation of pain, ECG changes, and cardiac marker elevations in the same trials; (b) lack of adequate data collected; and (c) lower risk patients enrolled in clinical trials (141).

TABLE 19.1 REINFARCTION (INFARCT EXTENSION) RATES ≤6 MONTHS POST–MYOCARDIAL INFARCTION

Risk factors for recurrent MI in patients not receiving reperfusion therapy include diabetes, female gender, obesity, and non–Q-wave MI (125). In the thrombolytic era, recurrent ischemia after MI is associated with an increased risk for in-hospital reinfarction as demonstrated by a substudy of GISSI-2 (142) (28% vs. 2% reinfarction; p <.001). Among these 453 patients, aged 70 years or younger, there were no baseline or MI characteristics that predicted early recurrent ischemia. Recurrent ischemia and reinfarction increase the risk of death after MI (143,144).

Prevention

Recurrent MI is, in part, related to the early therapy used in treating the initial MI. Although there was originally some concern that thrombolytic therapy may increase the rate of reinfarction, with the residual active culprit lesion supplying an incomplete or aborted infarct zone, the large body of data does not support such concern (Table 19.1) (130,131,132,133 and 134) provided ASA is used adjunctively (130). Randomized trials (135,136,137 and 138) report slightly lower short-term reinfarction rates following tissue-type plasminogen activator (t-PA) compared with SK. After t-PA therapy, reocclusion is significantly reduced by full-dose i.v. heparin (145). However, there are no data demonstrating that heparin per se reduces the rate of reinfarction (146). Delayed, full-dose s.c. heparin after thrombolysis does not reduce reinfarction nor does i.v. heparin compared with full-dose s.c. heparin after administration of SK (135,136,137 and 138,146).

Hirudin, a direct thrombin inhibitor, has been found to significantly reduce the rate of very early reinfarction in patients with acute coronary syndromes whether or not they had received thrombolytics as well; however, the effect was attenuated at 30 days (147). Glycoprotein (GP) IIb/IIIa receptor antagonists have been shown to reduce the risk of reinfarction for patients with non–ST-elevation acute coronary syndromes and for patients who undergo percutaneous coronary intervention. Their efficacy in reducing reinfarction for ST elevation MI patients as an adjunct to thrombolysis was recently demonstrated in GUSTO V (147a). Glycoprotein IIb/IIIa receptor antagonists in combination with thrombolysis or percutaneous coronary intervention is discussed in Chapter 17 and Chapter 18 (148). Other antiplatelet agents, such as clopidogrel, have not been investigated for use in acute ST elevation MI to reduce short-term reinfarction; however, clopidogrel has been shown to be modestly superior to ASA for long-term reduction in vascular deaths (149).

For patients with ST-elevation MI who do not receive thrombolysis, full-dose heparin followed by warfarin has not been shown to reduce rates of reinfarction occurring over 6 weeks after the initial MI (84). ASA significantly reduced the rate of reinfarction in the International Study of Infarct Survival (ISIS) 2 (130). Beta-blockers in patients not receiving thrombolytic therapy did not reduce reinfarction in the large ISIS 1 or in the Metoprolol in Acute Myocardial Infarction trial (127,128). However, when patients in these trials were pooled with those in 26 small studies (127) of i.v. beta-blockade (greater than 27,000 patients), an 18% reduction in reinfarction was demonstrated (2.8% versus 3.4%; p <.02). In conjunction with thrombolysis, early i.v. beta-blockade followed by oral beta-blockade reduced reinfarction and recurrent ischemia compared with oral, deferred beta-blockade (129), particularly when administered less than or at 2 hours of symptom onset. In large-scale trials (139,140), neither nitrates nor ACE inhibitors reduced early reinfarction (Table 19.1). Long-term reinfarction is reduced with ACE inhibitors (150,151). Routine revascularization using PTCA or CABG following thrombolysis to prevent reinfarction at 6 weeks proved disappointing in several major randomized trials (129,152,153 and 154). Direct PTCA as an initial treatment for acute MI appears to result in lower early reinfarction rates compared with thrombolytic therapy (Table 19.1) (see Chapter 18).

Management

Reinfarction is managed using the same treatment modalities as those used for the initial MI, including ASA, heparin, and beta-blockers, but with the caveat that patients with recurrent ischemia are a high-risk group who merit early cardiac catheterization. Readministration of thrombolytics for recurrent MI with recurrent ST-segment elevations on ECG has been used (155,156), with high successful response rates. If SK is used previously, t-PA or recombinant plasminogen activator or tenecteplase should be administered because antibodies to SK may develop. Direct PTCA should be performed, if available for recurrent coronary artery occlusion.

GP IIb/IIIa antagonists and low-molecular-weight or unfractionated heparin are efficacious in reducing death and reinfarction when used in patients with non–ST-elevation acute coronary syndromes, which include patients with post-MI angina (see Chapter 17 and Chapter 18). Recurrent ischemia is initially managed with beta-blockers and nitrates. Calcium channel blockers may be added if recurrent angina occurs on maximal doses of beta-blockers and nitrates. IABP counterpulsation should be used for patients with ischemia and hemodynamic instability (i.e., hypotension, hypoperfusion, or low cardiac output) and for refractory ischemia if revascularization facilities are not immediately available. Recurrent ischemia postinfarction and reinfarction identifies a high-risk subgroup of patients in whom urgent cardiac catheterization is indicated to prompt revascularization with PTCA or CABG, depending on the coronary anatomy, LV function, and the extent of myocardial jeopardy. The Danish Trial in Acute Myocardial Infarction (DANAMI) trial demonstrated reduced long-term events for post-MI patients with spontaneous or stress-induced significant ischemia who underwent revascularization (157).

ACUTE LEFT VENTRICULAR FAILURE

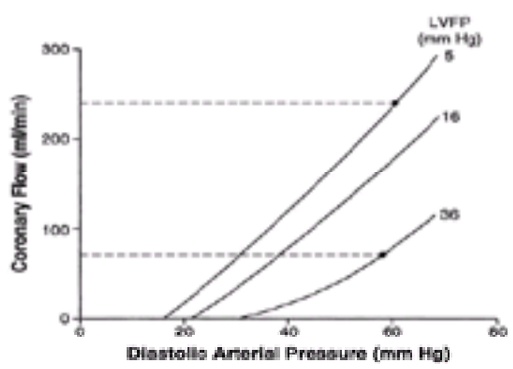
Pathophysiologic Principles

General

LV failure in acute MI varies widely in terms of pathophysiology and severity. Mild-to-severe pulmonary congestion may occur alone or in association with depressed stroke volume (SV) and cardiac output. Diastolic or systolic dysfunction may predominate. At the severe end of the spectrum of pump failure, cardiogenic shock is a state of severe tissue hypoperfusion caused by cardiac dysfunction.

Congestive Heart Failure

After acute coronary occlusion, LV systolic and diastolic functions change over minutes, hours, and weeks. Superimposed fixed or transient MR, recurrent ischemia, or reinfarction may have a major effect. Compliance of the infarct zone evolves over time (158,159 and 160), and stunned myocardium may recover function (161,162 and 163). Furthermore, elevations in LV filling pressures resulting from systolic or diastolic dysfunction may reduce the pressure gradient that maintains coronary blood flow (eFig. 19.3.3) (164) and thereby initiate a cycle of hypoperfusion and worsening LV dysfunction (Fig. 19.4) (165,166).



***e*FIGURE 19.3.3** Determinants of coronary artery blood flow. Coronary artery blood flow (*y*-axis) is proportional to aortic diastolic pressure (*x*-axis) and left ventricular filling pressure (LVFP; transmyocardial gradient). Reduced aortic diastolic pressure or increased left ventricular end diastolic pressure reduce coronary blood flow. Cardiogenic shock is characterized by hypotension and elevated left ventricular pressure with a markedly reduced gradient for coronary blood flow. (From McGhie AI, Goldstein RA. Pathogenesis and management of acute heart failure and cardiogenic shock: role of inotropic therapy. *Chest* 1992;102:626S–632S, with permission.)

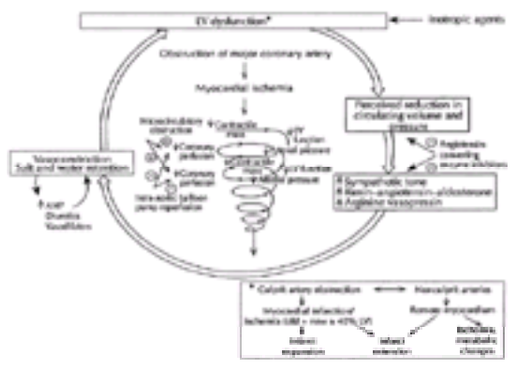


FIGURE 19.4 Pathophysiology of cardiogenic shock caused by primary left ventricular (LV) failure. The complex interplay of LV dysfunction, neurohormonal activation, and the vicious cycle of progressively worsening ventricular function that characterizes cardiogenic shock is illustrated. LV dysfunction results from dysfunction of the

infarct zone and remote myocardium, as illustrated in the inset in the lower, right-hand corner. For discussion, see text. ANP, atrial natriuretic peptide. (Adapted from Califf RM, Bengtson JR. Cardiogenic shock. *N Engl J Med* 1994;330:1724–1730; and Hochman JS, Palazzo A. Cardiogenic shock complicating acute myocardial infarction. In: Braunwald E, ed. *Atlas of heart diseases*. Boston: Current Medicine, 1996;8:12.1–12.23, with permission.)

Systolic Dysfunction

The composite number of dysfunctional myocardial segments—including hypokinetic, akinetic, and dyskinetic regions, as well as the hyperkinetic or normokinetic motion of the uninfarcted myocardium—determines global LV function. These abnormalities may be old (e.g., caused by prior infarctions) or new and may be reversible or irreversible. Global LV function is the strongest determinant of pump failure and death caused by MI (167,168,169 and 170). Lack of compensatory hyperkinesis of uninfarcted zones correlates with the development of pump failure (114). The LV typically dilates when significant systolic dysfunction is present, caused by early infarct expansion and the effect of the resultant increased wall stress on the remote myocardium. LV dilation plays an acute compensatory role by allowing the high end diastolic volume (EDV) to maintain SV when EF is significantly depressed.

$$EF = SV/EDV$$

The acute adaptive role of LV dilation is counterbalanced by deleterious long-term effects of LV dilation including increased wall stress, hypertrophy, and dilation, followed by failure of the remote myocardium.

The clinical manifestations of CHF when LV systolic function is depressed vary. Neurohormonal activation (171,172 and 173) (Fig. 19.4) and hydration status may explain why some patients with low EFs have pulmonary congestion and others do not (174). Varying degrees of diastolic dysfunction associated with infarction contribute substantially to alterations in LV compliance and filling pressure. Furthermore, alterations in peripheral circulation and in end organs, particularly those with prior LV damage, may influence the symptomatic response to the acute insult.

Recovery of contractile function in akinetic and even dyskinetic segments following acute MI is well documented and is caused by resolution of myocardial stunning and hibernation. Stunning may take weeks to months to resolve, and function of hibernating myocardium is only restored when coronary flow is normalized. Even late reperfusion may improve wall motion and global EF.

Diastolic Dysfunction

Diastolic dysfunction with reduced LV compliance is a relatively common cause of pulmonary congestion in acute MI. Ischemia causes impaired myocardial relaxation and diastolic dysfunction (175). Severe pulmonary edema may result from global subendocardial ischemia caused by three-vessel or left main CAD with a normal heart size. Additionally, the infarct zone undergoes alterations in compliance that result in varying LV distensibility over time following coronary occlusion (158,159 and 160). Reperfusion into areas of irreversible necrosis leads to contraction band necrosis, hemorrhage, and edema, resulting in acutely stiff infarcts (48,176) and, therefore, reduced LV compliance.

Diastolic abnormalities of the LV that impede LV filling may result in both an increase in LV filling pressures and a decrease in SV in the absence of global LV systolic dysfunction. Preexisting conditions that may cause reductions in ventricular compliance, such as hypertension and diabetes, result in an even greater shift of the pressure-volume curve when ischemia or infarction is superimposed.

Cardiogenic Shock Caused by Primary Left Ventricular Failure

LV failure is the most common cause of cardiogenic shock complicating acute MI. The prospective SHOCK Trial Registry identified LV failure as the etiology of shock in 78.5% of patients (Fig. 19.5) (177).

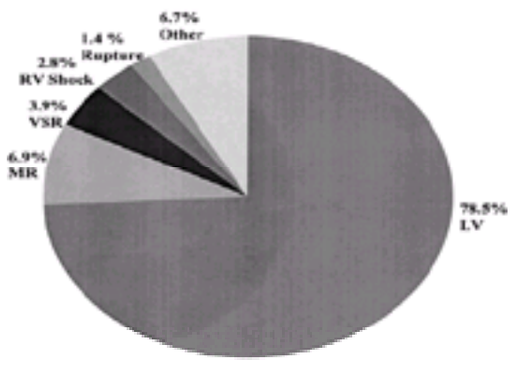
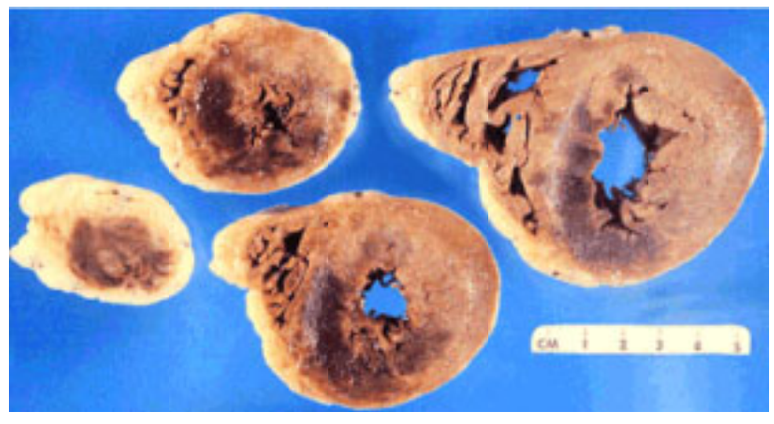


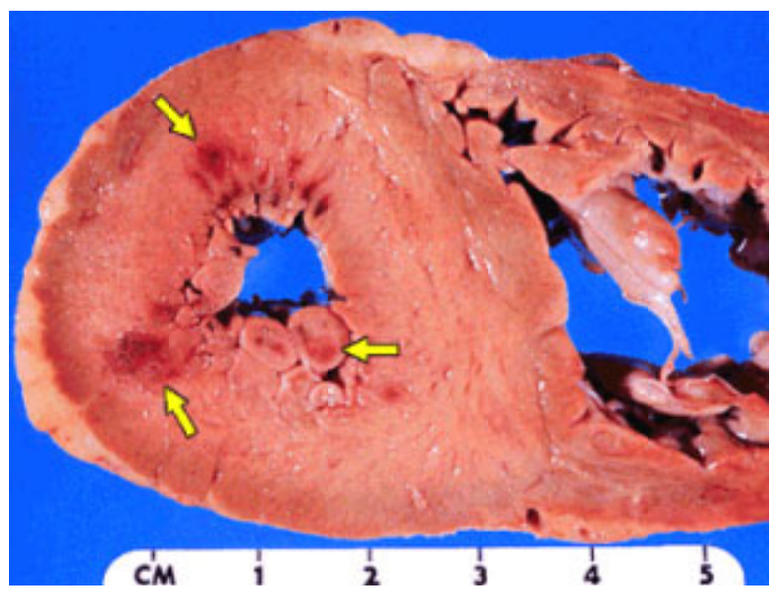
FIGURE 19.5 Etiologies of cardiogenic shock complicating acute myocardial infarction in the SHOCK Trial Registry (n = 1,190) and patients enrolled concurrently in the SHOCK Trial Registry (n = 232). The other category includes all other etiologies not noted (i.e., prior severe valvular heart disease, cardiomyopathy, or sustained arrhythmias). LV, left ventricular; MR, mitral regurgitation; RV, right ventricular; VSR, ventricular septal rupture. (Data from Hochman JS, Buller CE, Sleeper LA, et al. Cardiogenic shock complicating acute myocardial infarction— etiologies, management and outcome; overall findings of the SHOCK Trial Registry. *J Am Coll Cardiol* 2000;36:1063–1070.)

Patients with acute MI who develop cardiogenic shock typically have severe atherosclerotic disease involving all three major coronary arteries and often a severe stenosis in the LAD coronary artery. Significant stenosis in the left main coronary artery is seen in 16% to 21% of patients and single-vessel disease in approximately 13% to 22% of patients (178,179 and 180), with the LAD most often the IRA. Autopsy studies traditionally have demonstrated that at least 40% of the LV mass is affected in patients dying from cardiogenic shock complicating MI (179,181). Prior MI is present in approximately 40% of patients; when an old infarct is extensive, even a small, new infarction may lead to shock. Global ischemia, with or without minor infarction, may cause shock. In the GUSTO 2 trial one-third of patients with cardiogenic shock presented with a non–ST-segment elevation acute coronary syndrome (182).

Hemorrhage after left main infarct (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Massive acute transmural anteroseptal myocardial infarction. Cross sections from multiple levels are shown in this chemical fixed preparation. The dark brown area represents the zone of infarction. In this example, approximately 50% of the myocardium is involved.



Extensive subendocardial myocardial infarction (*yellow arrows*).

Pathologically, the infarct frequently is at varying stages of necrosis, often demonstrating a progressive, stuttering course of infarct extension (179,181,183). Infarct extension can be documented clinically as well, with continued myocardial necrosis reflected by persistently elevated cardiac isoenzyme levels (183). In the Multicenter Investigation of the Limitation of Infarct Size study (184), reinfarction occurred in 26% of 60 patients who developed cardiogenic shock more than 48 hours after onset of infarction in contrast to reinfarction in 7% of patients who did not develop cardiogenic shock (p <.0001). GUSTO 1 (185) also reported that recurrent myocardial ischemia or reinfarction occurred more frequently in patients who developed delayed cardiogenic shock compared with those who did not develop cardiogenic shock (29.3% vs. 6.1%, respectively; p <.05). Infarct extension and reinfarction are caused by mechanisms discussed previously (see Reinfarction and Ischemia). In addition, there are unique pathophysiologic considerations related to the interaction of abnormal hemodynamics of pump failure with infarct extension. Large infarctions result in a decrease in SV and an increase in LVEDP. When critical coronary stenoses are present, as they often are in patients with cardiogenic shock, and when the small resistance vessels are fully dilated, coronary blood flow is determined by the gradient between coronary perfusion pressure and LVEDP. With a decrease in cardiac output and arterial pressure and an increase in EDP, coronary perfusion significantly decreases (6). Hypoperfusion occurs within the vascular distribution of the infarct and in the vessels supplying the remote myocardium; global LV dysfunction results. The deterioration in LV function impairs coronary perfusion, precipitating the vicious downward spiral that is often the hallmark of the clinical course of cardiogenic shock (Fig. 19.4) (165,166).

A series of interrelated metabolic changes occur in the ischemic myocardium within the vascular distribution of the infarct as well as in remote myocardium (186,187). Under normal conditions, high rates of oxygen (approximately 65%) are extracted from coronary blood. Consequently, reduced coronary blood flow leads to anaerobic metabolism. Moreover, there is preferential use of glucose rather than fatty acids, and reduced coronary flow limits substrate delivery, potentially depleting Krebs cycle intermediates. Valuable insight into the role of metabolic abnormalities in cardiogenic shock is provided by experimental models evaluating the effects of different biochemical interventions on cardiac function. Progressive loss of contractile function has been demonstrated experimentally (188) in the uninfarcted circumflex distribution with a 50% stenosis in dogs with an occluded LAD. Infusion of Krebs cycle intermediate substrates including glutamate and aspartate with glucose, insulin, potassium, and coenzyme Q restores normal contractility (189). Similarly, in a rabbit model (190) of multiple coronary occlusions resulting in shock and a rapid progressive decrease in cardiac output, infusion of glucose, potassium, and insulin has been shown to maintain adequate cardiac output for a longer period of time.

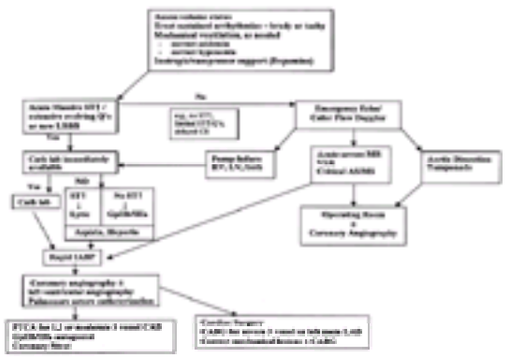
There are also major compensatory mechanisms involved in cardiogenic shock, with activation of the sympathetic nervous system and the renin-angiotensin system as well as release of antidiuretic hormone and atrial natriuretic peptide (Fig. 19.4) (165). Systemic vascular resistance is markedly increased and, as noted, SV is markedly depressed with a compensatory increase in HR. Over time, sodium and water retention results, with varying degrees of hyponatremia caused by increased water reabsorption from antidiuretic hormone.

Other Conditions

Conditions that result in high-output failure may occur in acute MI (Table 19.2). In particular, fever is common with large infarctions, and in the thrombolytic and aggressive anticoagulation era, acute anemia was sometimes seen. Excess use of negative inotropic agents, such as beta-blockers and calcium channel antagonists, particularly in combination, in patients with large infarctions may result in CHF and hypotension. When hypotension is present, noncardiogenic causes of shock must be excluded. These include volume depletion, particularly common in the elderly with or without hemorrhage, sepsis, and PE. Even when shock results from primary LV failure, MR caused by papillary muscle dysfunction (191,192) often contributes to shock. Each of the mechanical causes of cardiogenic shock discussed later in this chapter—including VSR, acute severe MR, pericardial tamponade, and PE—must be excluded. Aortic dissection with acute aortic regurgitation, tamponade, or both may mimic acute MI with cardiogenic shock (*e*Fig. 19.5.1, Table 19.2). An acute MI may occur in association with another catastrophic event (e.g., ruptured aortic aneurysm, ischemic bowel, and so forth), and the diagnosis may be difficult in an obtunded patient in shock.

Complications of acute myocardial infarction
Extensive left ventricular infarction and ischemia
Extensive right ventricular infarction and ischemia
Ventricular septal rupture
Acute, severe mitral regurgitation
Tamponade
With free wall rupture
Without free wall rupture
Other conditions
Aortic dissection
Myocarditis
Pulmonary embolism
Critical aortic or mitral stenosis
Acute aortic or mitral regurgitation
Pericarditis with tamponade
Metabolic/toxic
Calcium channel or beta-blocker overdose
Acidosis, hyperkalemia, hypoxemia
Thyroid storm, myxedema coma
Acute myocardial infarction with
Ischemic/infarcted bowel
Ruptured abdominal aortic aneurysm
Sepsis
Hemorrhage
Anaphylaxis
Excessive beta- or calcium channel blockade

TABLE 19.2 CARDIOGENIC SHOCK: DIFFERENTIAL DIAGNOSIS



***e*FIGURE 19.5.1** Overview of recommended diagnostic and treatment algorithm for patients with cardiogenic shock complicating acute myocardial infarction. AS, aortic stenosis; CABG, coronary artery bypass graft; CAD, coronary artery disease; CS, cardiogenic shock; Gp, glycoprotein; IABP, intraaortic balloon pump; LAD, left anterior descending; LBBB, left bundle branch block; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; PTCA, percutaneous transluminal coronary angioplasty; RV, right ventricular; VSR, ventricular septal rupture. (From Hochman JS, Califf R. Acute myocardial infarction. In: Antman EM, ed. *Cardiovascular therapeutics*. 2nd ed. Philadelphia: W. B. Saunders, 2001, with permission.)

Clinical Profile: Congestive Heart Failure and Cardiogenic Shock

The Killip clinical classification system (5) stratifies patients at risk based on severity of CHF and the presence of cardiogenic shock and provides a useful approach with continued applicability in the reperfusion era. In a classic study at a single center of 250 consecutive patients with acute MI, Killip et al. (5) defined criteria for risk-stratification based on clinical evidence of LV failure:

1. Killip class I is defined as no evidence of CHF.
2. Killip class II is defined as presence of a third heart sound gallop, basilar rales, or both.
3. Killip class III is defined as pulmonary edema.
4. Killip class IV is defined as cardiogenic shock (*e*Table 19.2.1 and *e*Table 19.2.2).

***e*TABLE 19.2.1** INCIDENCE OF PUMP FAILURE ON PRESENTATION BY KILLIP CLASS

Killip class (5)	Definition	GISSI-1 (1986) (85)	NMRI-2 (1998) (414)	GUSTO-III (1997) (407)	ASSENT-II (1997) (408)
I	No congestive heart failure	71.0	71	86.0	88.0
II	Third heart sound gallop or basilar rales	23.0	19	13.0	10.0
III	Pulmonary edema	3.7	7	1.0	1.0
IV	Cardiogenic shock	2.4	3	0.5	0.4

***e*TABLE 19.2.2** INCIDENCE OF PUMP FAILURE AT ANY TIME IN-HOSPITAL BY KILLIP CLASS

Killip class (5)	Definition	Killip and Kimball (1967) (5)	Killip class	GISSI-1 (1986) (85)	Israeli Cardiac Care Unit Registry (2000) (415)
I	No congestive heart failure	33	I	55	72
II	Third heart sound gallop or basilar rales	38	II–IV	45	28
III	Pulmonary edema	10	II–IV	45	28
IV	Cardiogenic shock	19	II–IV	45	28

The worst Killip class may be present on hospital admission or may develop at any point during hospitalization.

Incidence of Congestive Heart Failure and Cardiogenic Shock

The incidence of CHF by Killip class in the original description in 1967 is shown in *e*Table 19.2.2. The rates of CHF by Killip class reported 20 to 30 years later in large thrombolytic trials and two registries are shown in *e*Table 19.2.1. These data suggest that the incidence of CHF may be decreasing over time. However, this cannot be firmly established, as more complicated patients have been excluded from clinical trials (141), and the definition and diagnosis of CHF varies. Furthermore, the original description by Killip et al. (5) involved only 250 patients in a single, university hospital center. Data from placebo-controlled, randomized trials assessing the effect of thrombolysis on the occurrence of CHF after hospital admission demonstrate variable results (Table 19.3) (131,133,134,193,194,195,196,197 and 198). Overall, however, the short-term incidence of CHF is 20% for the placebo group and is slightly lower (17%) for the thrombolytic group. The 7-month to 1-year follow-up pooled data also appear to show a slight reduction in the incidence of CHF (Table 19.3).

Study	Reference	Thrombolysis		Placebo	
		Number	Percent	Number	Percent
In-hospital					
AIMS[T]	134	2,512	17.7	2,493	18.4
Guerci et al.	193	72	14.0	66	33.0
NHF	194	73	27.4	71	36.6
Simoons et al.	195	269	13.8	264	20.1
Meinertz et al.	196	162	20.0	151	29.0
Bassand et al.	197	112	6.7	119	13.4
Follow-up					
ISAM (7 mo)	133	859	6.6	882	9.1
AIMS (1 yr)	131	624	21.0	634	24.0
		Thrombolysis		Primary PTCA	
Study	Reference	Number	Percent	Number	Percent
GUSTO IIB PTCA substudy (30 days)	291	573	4.9	565	4.3

PTCA, percutaneous transluminal coronary angioplasty.
Modified from Bates ER, Topol EJ. Limitations of thrombolytic therapy for acute myocardial infarction complicated by congestive heart failure and cardiogenic shock. J Am Coll Cardiol 1991;18:1897–1904, with permission.

TABLE 19.3 INCIDENCE OF CONGESTIVE HEART FAILURE

From 1975 to 1988, which antedates the widespread use of reperfusion therapy, the incidence of cardiogenic shock in the Worcester community was relatively constant at 7.5%, with a consistently high mortality of 78% (199). This incidence is similar to that reported in more recent large thrombolytic trials (137). The Worcester

community studied 7 additional years (up to 1997) and reported no change in the incidence of cardiogenic shock (200). The U.S. National Registry of Myocardial Infarction (NRMI) data since 1989 demonstrate that 4.1% of patients not treated with thrombolysis (n = 228,512) died of cardiogenic shock, which represented 32.0% of deaths (201). Of those receiving thrombolysis (n = 91,218), 2.3% died of cardiogenic shock, which represented 39.0% of deaths. These data are consistent with a decrease in the incidence of cardiogenic shock in more recent years and a decrease in the incidence of shock associated with reperfusion therapy. Randomized trials (134,196) of thrombolysis versus heparin alone have demonstrated a significantly lower incidence of cardiogenic shock with thrombolysis, particularly of shock that develops 24 or more hours after MI.

Direct PTCA has not been compared with placebo in terms of its effect on pump failure or on the frequency of cardiogenic shock; however, by extrapolating from comparisons with thrombolysis, the incidence of shock is reduced compared with that following no reperfusion (202,203 and 204). Nevertheless, pump failure remains the leading cause of death in patients hospitalized with acute MI in the reperfusion era (201).

Congestive Heart Failure and Cardiogenic Shock: Risk Factors

Patient Profile

Risk factors for the development of shock have been studied extensively in the prereperfusion and postreperfusion eras and in ST-elevation and non–ST-elevation MI patients. Age, female sex, prior MI, and diabetes are consistently associated with risk of pump failure (184,185,199), as is anterior MI location (182,200,205). The characteristics of 1,190 patients with suspected cardiogenic shock in the prospective SHOCK Trial Registry, which includes all etiologies, infarct types, and therapies, were age 68.7, 40% women, history of MI in 37%, hypertension in 53%, and diabetes in 33% (177). Systolic BP, HR, and Killip class II or III on admission make up approximately 90% of the predictive information in thrombolytic-treated patients (205) (*e*Fig. 19.5.2). Other factors associated with the development of cardiogenic shock include EF less than or equal to 35%, persistent occlusion of the IRA, and the absence of hyperkinesis of the uninfarcted LV segments (114,168,184).

***e*FIGURE 19.5.2** Baseline predictors of cardiogenic shock. In panel 1, find the value most closely matching the patient's risk factors and circle the points. In panel 2, add the points for all predictive factors. In panel 3, determine the predicted occurrence of cardiogenic shock corresponding to the total number of points. For example, a 71-year-old 60-kg woman from the United States with a history of hypertension, who presents with a systolic blood pressure of 126 mm Hg, a diastolic blood pressure of 64 mm Hg, a heart rate of 123 beats/min, in Killip class III, and an anterior myocardial infarction who was then treated with intravenous streptokinase would have a total score of [37 + 17 + 39 + 5 + 10 + 5 + 8 + 17 + (3 + 2 + 5)] = 148. This score corresponds to predicted probability of 30% for cardiogenic shock occurring after thrombolytic therapy. SK, streptokinase; t-PA, tissue-type plasminogen activator; Tx, thrombolytic therapy. (From Hasdai D, Califf RM, Thompson TD, et al. Predictors of cardiogenic shock after thrombolytic therapy for acute myocardial infarction. *J Am Coll Cardiol* 2000;35:136–143, with permission.)

Non–ST-Elevation Myocardial Infarction. Cardiogenic shock complicates non–ST-elevation MI approximately half as often as it does ST-elevation MI (182). In the SHOCK Trial Registry, 17% of patients with predominant LV failure had non–ST-elevation MI (206). These patients are older and have more prior MI, CHF, CABG, and peripheral vascular disease than patients with ST-elevation MI. They more often have severe three-vessel and left main CAD. Importantly, in 35% the circumflex artery was the culprit vessel, reflecting the difficulty in diagnosing posterior ST-elevation infarction.

Prognosis. In patients with ventricular failure, age is strongly associated with death. A scoring system for predicting death when pump failure complicates the MI course of thrombolytic-treated patients in GUSTO 1 is shown in eTable 19.3.1 (207). The SHOCK Trial Registry of all consecutive patients with suspected cardiogenic shock complicating MI also demonstrated the prognostic importance of age, clinical signs of hypoperfusion as well as hemodynamic variables [BP, pulmonary capillary wedge pressure (PCWP), cardiac index (CI)] (208). Rupture of the ventricular septum was independently associated with death. Cardiopulmonary arrest is also associated with poor outcome (178). The prognosis is similar for non–ST-elevation and ST-elevation MI after adjusting for the marked patient differences (182,206).

***e*TABLE 19.3.1** PREDICTORS OF DEATH FOR THROMBOLYTIC-TREATED PATIENTS WITH CARDIOGENIC SHOCK COMPLICATING ACUTE MYOCARDIAL INFARCTION: POINTS FOR EACH PREDICTIVE FACTOR (WITH RIGHT-SIDED HEART CATHETERIZATION)

Predictive factors

Age (yr)	Points	Mean arterial pressure during shock (mm Hg)	Points	Heart rate during shock (beats/min)	Points	Lowest cardiac output (L/min)	Points	Highest pulmonary capillary wedge pressure (mm Hg)	Points	Factor	Points
20	0	20	20	20	5	2	42	10	31	Killip class	
30	11	40	38	40	11	4	13	20	0	I	7
40	22	60	25	60	16	6	0	30	24	II	26
50	33	80	17	80	22	8	7	40	26	II	25
60	44	100	19	100	27	10	13	50	25	IV	0
70	56	120	25	120	33	12	20	60	24	Prior infarction	15
80	67	140	32	140	38	14	27			Altered sensorium	15
90	78	160	38	160	43	16	33			Cold, clammy skin	15
100	89	180	44	180	49	18	40			Oliguria	23
										Ventricular septal defect	38

Risk corresponding to total points (with right-sided heart catheterization)

Points	30-Day mortality (%)
138	10
160	20
175	30
188	40
199	50
210	60
223	70
238	80
260	90

From Hasdai D, Holmes Jr D, Califf RM, et al., for the GUSTO-1 Investigators. Cardiogenic shock complicating acute myocardial infarction: predictors of death. *Am Heart J* 1999;138:21–31, with permission.

Congestive Heart Failure and Cardiogenic Shock: Timing

As noted, patients often develop CHF and cardiogenic shock after hospital admission. In the SHOCK Trial Registry, patients with cardiogenic shock caused by primary LV failure demonstrated a predominance of early shock: 47% within the first 6 hours and 72% within 24 hours of MI onset (209). Nevertheless, only 9% of those with cardiogenic shock presented to the hospital in shock. The large GUSTO 1 (185) thrombolytic trial reported that 0.8% of enrolled patients presented with cardiogenic

shock, and an additional 6.5% developed shock after hospital admission.

Clinical Assessment

Overview

Patients who develop pump failure must be assessed for other complicating conditions (Table 19.2; eFig. 19.5.1) (see Pathophysiologic Principles).

A history should be obtained and a physical examination should be performed rapidly as well as ECG, arterial blood gas analysis, and hematology and chemistry profiles. Chest roentgenography should be promptly performed.

Clinical Findings: Congestive Heart Failure

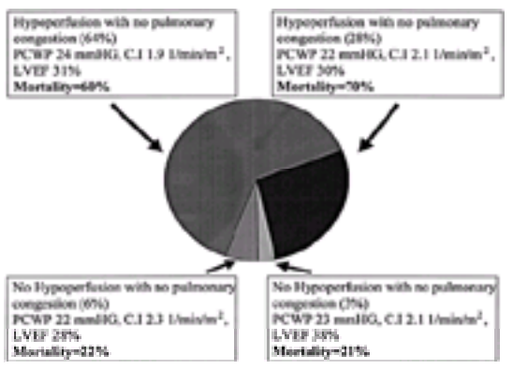
Pump failure most frequently manifests as pulmonary congestion with pulmonary rales on examination, and pulmonary vascular redistribution with interstitial edema on chest roentgenography, initially with a normal heart size. Patients with mild CHF (Killip class II) may or may not report dyspnea. Tachypnea is usually present, but the respiratory rate may be only mildly elevated. Tachycardia and hypertension may or may not be present. Pulmonary edema (Killip class III) with acute interstitial and alveolar edema is associated with tachypnea, tachycardia, and hypertension caused by sympathetic stimulation. Lack of hypertension suggests profound LV failure and impending cardiogenic shock.

Electrocardiographic Findings: Congestive Heart Failure

There are large variations in the ECG findings in patients with pulmonary congestion, although most patients have changes consistent with a large infarction. Extensive ST-segment depressions are not uncommon and may represent extensive subendocardial infarction or small infarcts with extensive ischemia.

Clinical Findings: Cardiogenic Shock

The patient with classic cardiogenic shock complicating acute MI has severe systemic hypotension, end-organ hypoperfusion with cool extremities and oliguria, and respiratory distress caused by pulmonary congestion. This syndrome may develop either as a sudden event or slowly *after* hospital admission. There is a wide range in the clinical manifestations and severity of cardiogenic shock, and all components for classic cardiogenic shock may not be present. Clinical pulmonary edema need not be present to diagnose or suspect cardiogenic shock. An adequate or elevated PCWP must be documented by right-sided heart catheterization in the setting of systemic hypotension to confirm the diagnosis when pulmonary edema is not present (unless RV cardiogenic shock is diagnosed) (see Right Ventricular Infarction). In the SHOCK Trial Registry, 29% of patients diagnosed with cardiogenic shock caused by predominant LV failure had no pulmonary congestion on physical or radiographic examination, despite having mean PCWP of 22 mm Hg and LVEF of 30% (210) (eFig. 19.5.3).



eFIGURE 19.5.3 Clinical findings in 537 patients in the SHOCK Trial Registry with a clinical diagnosis of cardiogenic shock caused by predominant left ventricular failure. Although most patients had the classic constellation of systemic hypoperfusion and pulmonary congestion, 28% had no pulmonary congestion despite an elevated pulmonary capillary wedge pressure (PCWP) and depressed left ventricular ejection fraction (LVEF) (30%); their mortality was similar to those with classic shock. Hypoperfusion denotes oliguria or cool extremities, and pulmonary congestion is noted on physical or radiographic examination. When shock is diagnosed based on hypotension, depressed cardiac index (CI), and elevated PCWP, but systemic hypoperfusion is not noted, the mortality is lower. (From Menon V, White H, LeJemtel T, et al. The clinical profile of patients with suspected cardiogenic shock due to predominant left ventricular failure. *J Am Coll Cardiol* 2000;36:1071–1076.)

Preshock. Categorization of patients is not absolute, and gray zones exist. Patients who develop delayed cardiogenic shock following MI often slowly slip into shock, with evidence of a low cardiac output clinically before the onset of hypotension. Sympathetic stimulation may result in maintenance of normal BP in patients with high systemic vascular resistance and low cardiac output. This preshock or nonhypotensive shock state is associated with predominately anterior MI and a 46% in-hospital mortality in the SHOCK Trial Registry (211). Sinus tachycardia and low urine output are clinical findings of reduced SV and cardiac output. It must be appreciated that these signs reflect severe depression of cardiac output and necessitate rapid evaluation of patients before the onset of frank hypotension.

Electrocardiographic Findings: Cardiogenic Shock

Most patients have ECG findings consistent with a transmural acute MI; however, 15% to 30% of patients who develop cardiogenic shock may have nonspecific ECG findings consistent with non–Q-wave MI (177,199,206) including widespread ST-segment depression. Anterior ST depression with upright T waves that improve across the precordium suggests acute posterior MI. More than one-half of all infarcts (55%) in the SHOCK Trial Registry (177) were anterior, 46% inferior, 19% posterior, and 32% lateral. Patients often have multiple infarct locations (50%) on ECG that are a composite of old and new MIs. Of note, ischemia in an old infarct zone may result in recurrent ST-segment elevations.

Patients with cardiogenic shock caused by *LV failure* should have extensive ECG abnormalities consistent with massive, acute infarct, severe and diffuse acute ischemia, or evidence of prior substantial damage (e.g., extensive pathologic Q waves or left bundle branch block). A relative lack of ECG abnormalities in contrast to the severity of the hemodynamic status should alert one to another cause of cardiogenic shock such as aortic dissection or rupture of the myocardium (i.e., free wall, ventricular septum, papillary muscle, or chordae) or hemorrhage (Table 19.2; eFig. 19.5.1).

Patients with first inferior or posterior or lateral MI do not develop cardiogenic shock caused by LV failure, and one should suspect acute severe MR. In patients with cardiogenic shock and mild ECG abnormalities, such as only limited ST-segment elevations, aortic dissection should be ruled out (Table 19.2).

Echocardiography with Color Flow Doppler

Echocardiography with color flow Doppler is an extremely valuable diagnostic tool and should be obtained as rapidly as possible once CHF or cardiogenic shock is suspected. LV and RV function can be visualized, and tamponade can be diagnosed (212,213 and 214). Color flow Doppler mapping can diagnose severe MR and VSR (214). Proximal aortic dissection with aortic insufficiency, pericardial tamponade, or both can also be visualized. In critically ill patients, who are often supported by mechanical ventilation, it may be difficult to obtain adequate images with transthoracic echocardiography, and transesophageal echocardiography may reveal a flail mitral leaflet with severe MR (215). Even adequate transthoracic echocardiography may miss localized MR caused by a flail mitral leaflet (212).

Congestive Heart Failure and Cardiogenic Shock: Hemodynamic Assessment and Monitoring

Hemodynamic subsets defined by Forrester et al. (216,217) in the prereperfusion era stratified patients based on a CI greater or less than 2.2 L per minute per m^2 and a PCWP greater or less than 18 mm Hg. Mortality was associated with severity of the hemodynamic abnormality. CI and PCWP were strongly associated with outcome in patients with shock in an adjusted mortality model in GUSTO 1 (205) and the SHOCK Trial Registry (208).

Patients in Forrester hemodynamic subset 1 with a PCWP <18 mm Hg and a CI >2.2 L per minute per m^2 are asymptomatic, and despite mild elevations in PCWP and

mild depression of CI compared with healthy patients, they have compensated pump dysfunction and a good prognosis, which corresponds to clinical Killip class I (5,216,217). Patients in hemodynamic subset 2 with an elevated PCWP and maintained CI have pulmonary congestion on examination (clinical Killip class II and III) and a significant component of diastolic dysfunction. Patients in hemodynamic subset 3 with a low CI and an inappropriately low PCWP have RV failure, hypovolemia, or profound venodilation. Patients in hemodynamic subset 4 with a low CI and high PCWP have severe LV dysfunction and may have cardiogenic shock.

Further subset classification of patients with LV pump failure is outlined in the ACC/AHA Task Force Guidelines for the Early Management of Patients with Acute MI (89). Patients are divided into those with an LV filling pressure (PCWP) >18 mm Hg, a systolic arterial BP >100 mm Hg, and a CI <2.5 L per minute per m^2, which represents LV failure without classic cardiogenic shock. Patients with PCWP >18 mm Hg, an arterial pressure <90 mm Hg, and a CI <2.5 L per minute per m^2 are in cardiogenic shock. This higher CI value compared with the Forrester classification is appropriate because most patients have already had inotropic support initiated before right-sided heart catheterization, and the measured CI reflects sympathomimetic stimulation. Those patients with an unsupported systolic arterial pressure of 90 to 100 mm Hg, an elevated PCWP, and a low CI have severe pump failure but not frank shock, by definition. When classic cardiogenic shock is present, the unsupported CI is typically lower (e.g., <2.0 L per minute per m^2) with a low SV index, and the PCWP is higher (e.g., >20 mm Hg). Mixed venous oxygen saturation is low in cardiogenic shock because of low cardiac output and increased oxygen extraction (218,219,220 and 221), and lactate levels are increased.

A PA (Swan-Ganz) catheter need not be placed in all patients with pump dysfunction during acute MI. Randomized clinical trial data assessing its efficacy in improving outcome are lacking, and nonrandomized data show an association between increased mortality and use of a Swan-Ganz catheter in a large series of critically ill patients with diverse etiologies. This excess risk is not demonstrated for cardiogenic shock and CHF (222) and may reflect a selection bias. However, complications during insertion, inaccurate interpretation of hemodynamic data, and inappropriate changes in therapy may contribute to the increased morbidity and mortality of PA catheterization in some studies. When cardiogenic shock is diagnosed, it has been routine practice to confirm the hemodynamic abnormality with a PA catheter and optimize medical management with inotropes, vasopressors, and subsequently vasodilators, using the hemodynamic values obtained (89,223). Other indications for PA catheterization include persistent hypotension despite fluid administration, refractory pulmonary congestion, and oliguria with tachycardia in large infarcts without obvious hypovolemia. Each patient's optimal PCWP is the lowest value that results in the highest cardiac output, provided the systemic arterial oxygen saturation is >90%. In acute MI with LV failure, the optimal PCWP most frequently is 15 to 20 mm Hg. Higher PCWPs are sometimes required to maintain optimal cardiac output and should be maintained provided pulmonary congestion with dyspnea and requirements for high F_{IO_2} do not result. Of note, the volume status is only one of multiple determinants of PCWP, and PCWP should *not* be equated with volume status alone. Ventricular compliance plays a large role and can be dynamic. Invasive monitoring of systemic arterial pressure is indicated in patients on vasopressors.

Coronary angiography is indicated when CHF or cardiogenic shock complicates acute MI based on the high incidence of severe CAD and depressed LV function in these patients. Emergency early coronary angiography should be performed on patients in cardiogenic shock in facilities that have experience performing PTCA and CABG on this high-risk group. This often involves rapid transfer of patients. The emergency transport of these unstable patients to tertiary care centers is a critical issue, with controversy focusing on whether to stabilize patients first with IABP or transfer those who may be rapidly deteriorating. We recommend *rapid* IABP placement before transfer when there are skilled staff and transport systems to accommodate this.

Placing patients in the supine position and injection of radiographic contrast dye put patients at risk for worsening pulmonary congestion. Contrast dye, particularly nonionic dye, may also be thrombogenic, negatively inotropic, and may induce nausea, vomiting, arrhythmias, heart block, and acute tubular necrosis. Therefore, low osmolality ionic contrast is recommended. Patients with respiratory distress should be intubated first. For patients in cardiogenic shock, intraaortic balloon counterpulsation and mechanical ventilatory support are advised before angiography. Continuous transcutaneous oximetric monitoring of systemic oxygen saturation is required. Subsequent angiography is recommended for those not undergoing emergency angiography and revascularization.

Management: Pharmacologic Therapy, Mechanical Support, and Revascularization

General Measures

Hypoxemia caused by pulmonary congestion must be corrected rapidly with mechanical ventilatory support to reduce the work of breathing and improve oxygenation, as necessary. In the presence of cardiogenic shock, lactic acidosis is common; this leads to further myocardial depression and renders patients resistant to the vasopressor effects of dopamine and norepinephrine. Rapid correction of acidosis is extremely important and empiric hyperventilation is appropriate until arterial blood gas results can be obtained. Ventilator settings can then be guided by arterial blood gas values. Hyperventilation is preferred to administration of sodium bicarbonate for correction of acidosis, because the buffering capacity of sodium bicarbonate is limited and short-lived, requiring a large sodium load.

Bradycardia and atrioventricular (AV) block must be corrected. If pacing is indicated, preservation of atrial contraction is an important goal; thus, AV pacing is preferred. New onset of AF should be rapidly cardioverted. An antiarrhythmic agent, such as amiodarone, may be required to maintain sinus rhythm. When severe LV dysfunction leads to reduction in SV, high HRs are necessary to maintain cardiac output. This needs to be taken into account when setting the HR for patients with hemodynamically significant bradycardia who require pacing. In general, HRs of approximately 90 to 100 beats/min are advisable.

Volume Status

Pulmonary Congestion. Pulmonary congestion with acute MI is caused by a transient or sustained increase in the PCWP. Patients who present with pulmonary edema who have no prior history of myocardial dysfunction and have not received fluid administration have a normal total body sodium and fluid status. There is acute redistribution of fluid into the lungs, and with diaphoresis and no oral intake, this results in *relative* intravascular depletion in the early phase. Diuretics can cause further intravascular depletion and hypotension and can precipitate cardiogenic shock. It must also be appreciated that there is a lag between normalization of the PCWP and resolution of interstitial and alveolar edema (224). Patients with findings on examination or on chest roentgenography suggesting congestion (e.g., basilar rales or interstitial fluid) for 24 hours do not necessarily require continued diuretic therapy provided dyspnea is resolving and respiratory status is improving. Excessive diuresis may result in severe intravascular depletion in patients who present with pulmonary edema, which initiates a vicious cycle of hypotension, hypoperfusion, infarct extension and ischemia, additional LV dysfunction, and so forth (Fig. 19.4). The best means of assessing volume status is careful measurement of the intake and output record including the prehospital and emergency department phases as well as the patient's weight. Measurement of PCWP is useful but reflects ventricular compliance as well as volume status. An elevated blood urea nitrogen to creatinine ratio may reflect intravascular depletion or poor renal perfusion caused by a low CI. However, a low blood urea nitrogen level in a patient with severely depressed LVEF and persistent pulmonary congestion reflects underdiuresis.

The volume status of patients with prior myocardial dysfunction and prior use of diuretics is more variable. These patients may be volume overloaded because of chronic CHF, or those on chronic diuretics may be intravascularly depleted at the time of onset of their acute MI, with a sudden increase in PCWP caused by acute infarction.

Hypotension. Hypotension complicating acute MI may be caused by hypovolemia as a result of vomiting, diaphoresis, use of diuretics, or associated hemorrhage. In addition, many of the medications (e.g., nitrates and morphine) administered during acute MI cause venodilation and preload reduction, which, in turn, causes hypotension. Placing the patient in Trendelenburg's position is appropriate for treatment of these causes of hypotension. For patients who do not have evidence on examination or on chest roentgenography of pulmonary congestion and who are not in respiratory distress, an empiric i.v. volume challenge of 250 mL of normal saline can be given. Repeated empiric fluid challenges may be used before PA catheterization, but caution must be exercised for those at increased risk for precipitation of CHF with volume infusion (e.g., older patients, patients with prior MI, prior CHF or impaired LV function, hypertensive heart disease, diabetes, and a small body size). Transcutaneous continuous oximetric monitoring of systemic oxygen saturation is advised. In some patients, hypotension and bradycardia are manifestations of Bezold-Jarisch reflex (225) or a vasovagal response to volume depletion. Although atropine may be helpful, the key to management is fluid administration. This is particularly true in patients with a first inferior MI and in association with the administration of nitrates, which accentuates preload reduction in an already volume-depleted patient. PA catheterization is needed only in refractory patients. Overly vigorous fluid challenges in patients with extensive LV infarction result in pulmonary edema and should be avoided. Elderly patients, in particular, are sensitive to excessive administration of fluids caused by reduced LV compliance.

Pulmonary Congestion and Hypotension—Cardiogenic Shock. When pulmonary congestion and hypotension are both present, cardiogenic shock is diagnosed; these patients should not have a fluid challenge. Diuretics have a limited role in the acute management of these patients because they can cause further hypotension and are ineffective when marked reduction in renal blood flow and glomerular filtration are present. The circulation must be first supported by pharmacologic and mechanical interventions discussed in the following sections, followed by i.v. diuretics.

Medications

General

Agents with negative inotropic properties should be avoided in patients with acute large infarctions and pump failure. These agents include both beta-blockers and calcium channel antagonists. This does *not* preclude the use of beta-blockers as secondary prevention at a later time in the clinical course once hemodynamics are stabilized. Beta-blockers, initiated in low doses, are indicated in these patients before hospital discharge (226). Amiodarone is the agent of choice for ventricular

tachycardia or fibrillation that occurs in patients with severe pump failure. Medications that are primarily cleared by the kidneys or liver must be used in reduced doses in patients with hepatic or renal dysfunction and end-organ hypoperfusion. In particular, lidocaine doses must be reduced when this agent is used to treat ventricular arrhythmias.

Morphine sulfate reduces preload and therefore improves pulmonary congestion. It also provides analgesia and lessens anxiety. To avoid hypotension, small incremental doses (2 to 4 mg) should be administered.

Medications that are used in acute MI patients with or without pump failure are discussed in Chapter 18.

Specific Medications

Diuretics. Furosemide, 20 mg i.v., should be the initial dose for patients who have not been given diuretics and who have normal creatinine levels; higher and repeated doses should be given as needed. Other loop diuretics, such as torsemide, bumetanide, or ethacrynic acid, are alternatives. After the early phase of acute MI with pulmonary congestion, continued doses of diuretics are necessary for patients with significantly impaired LV systolic function and persistent CHF. Potent loop diuretics also activate the renin-angiotensin-aldosterone system, thereby leading to an increase in cardiac afterload and promoting sodium retention once their short-term effects resolve. For refractory patients, a combination of a loop and a thiazide diuretic, such as hydrochlorothiazide or metolazone, produces additive effects. Diuretics should be withheld or the dosage reduced when ACE inhibitors are initiated to avoid hypotension and transient renal insufficiency.

Aspirin. ASA, 160 mg, given acutely, followed by 160 to 325 mg daily, has been shown to be effective in reducing mortality from acute MI (130) (see Chapter 18). Although ASA has not been specifically studied as a treatment for pump failure complicating acute MI, all patients should be given ASA. The optimal dose of ASA, however, has not been clearly defined. There is a theoretic concern regarding potential mitigation of the bradykinin-related beneficial effects of ACE inhibitors with concomitant use of ASA because ASA inhibits bradykinin formation. However, the Acute Infarction Ramipril Efficacy study (227) of acute MI complicated by CHF demonstrated that 1,543 of 2,006 patients who had received concomitant ASA had the same mortality benefit from ramipril as did those who did not receive ASA.

Glycoprotein IIb/IIIa Antagonists. The potent platelet inhibitors, GP IIb/IIIa antagonists, are indicated for selected patients with cardiogenic shock. Although not specifically tested in a shock population, a GP IIb/IIIa antagonist should be administered to patients undergoing percutaneous coronary intervention, based on the overall strong evidence of benefit when used in conjunction with percutaneous coronary intervention (228,229 and 230). These agents are also indicated for use in patients with non–ST-elevation MI. Analysis of the PURSUIT study suggests that patients with shock and non–ST-elevation acute coronary syndrome derive 30-day survival benefit from eptifibatide (231).

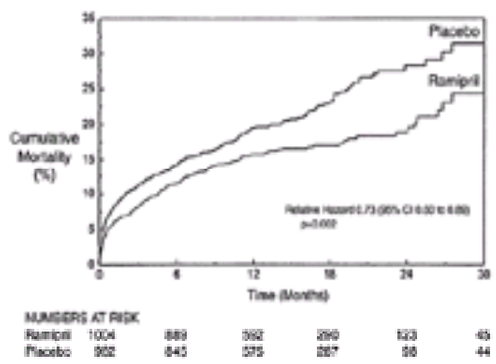
Anticoagulation. Heparin has not been specifically studied in patients with pump failure complicating MI. However, there are strong reasons why patients with pump failure, particularly those with cardiogenic shock or a severely low output, should be given full-dose i.v. unfractionated heparin. These patients have high circulating fibrinogen and catecholamine levels that render them hypercoagulable. Moreover, in patients with poor LV function and elevated PCWP and central venous pressure, the risk for deep venous thrombosis (DVT) and LV thrombosis is substantially increased. Additionally, heparin may be effective in maintaining coronary artery patency in patients with complex plaques with acute fissures. (For dosing, see Management in Infarct Expansion, Left Ventricular Remodeling, and Left Ventricular Aneurysm)

Intravenous Nitroglycerin. Sublingual followed by i.v. nitroglycerin is the ideal medication for patients with elevated LV pressures, moderate or no reduction in cardiac output, and normal or elevated systemic arterial pressure. Its acute use is preferred to i.v. loop diuretics for the treatment of pulmonary congestion for reasons discussed earlier (232). At low doses (<30 µg per kg), the dominant effect of nitroglycerin is on the venous circulation (233). At higher doses, i.v. nitroglycerin dilates the arteriolar circulation as well and therefore may significantly decrease systemic arterial pressure (77). PCWP and LVEDP decrease promptly, which rapidly improves symptoms of dyspnea. Myocardial ischemia is decreased by a reduction in myocardial wall diastolic tension, which decreases myocardial oxygen requirements. Nitroglycerin also may improve oxygen delivery by dilating coronary vessels and decreasing resistance in the coronary collateral circulation (234,235). Nitroglycerin reduces ischemic MR caused by LV dilation by reducing the LVEDV (236). Tolerance may develop after 24 hours of nitroglycerin administration, which may be overcome by increasing the dosage. Hypotension, which may result from sublingual or i.v. nitroglycerin, must be avoided, particularly during thrombolytic therapy or peri-PTCA. Patients with RV MI are sensitive to preload reduction (see Right Ventricular Infarction).

Sodium Nitroprusside. Cardiac afterload is reduced to a greater extent by administration of sodium nitroprusside than by nitroglycerin because of the former's balanced venous and arteriolar dilation properties (235,237,238). Unfortunately, sodium nitroprusside has been associated with coronary steal (i.e., redistribution of coronary blood flow away from ischemic areas) (234,237,239). Therefore, i.v. nitroglycerin is preferred for patients with pulmonary congestion complicating acute MI. However, in severely hypertensive patients, nitroprusside is highly effective in normalizing BP. Prolonged administration of nitroprusside, particularly when there is renal insufficiency, results in toxicity, with accumulation of thiocyanate and an attendant risk for neurotoxicity. In patients receiving nitroprusside who become confused, serum thiocyanate levels should be checked and infusion interrupted pending results.

Angiotensin-Converting Enzyme Inhibitors. ACE inhibitors, by reducing cardiac preload and afterload in patients with heart failure and acute MI, improve LV performance. The renin-angiotensin-aldosterone system is frequently activated in patients with acute MI (172) and further activated in patients with CHF. In addition to directly blocking the renin-angiotensin-aldosterone system, ACE inhibitors vasodilate by increasing circulating bradykinins (240,241 and 242). Other beneficial effects on atherogenesis and plaque rupture may occur at a cellular level and the long-term vascular event rate is reduced (151). ACE inhibitors produce a dilating effect on the cerebral, coronary, and renal circulation, decreasing blood flow in the hepatic and splanchnic circulations (243,244). ACE inhibitors should be instituted early in patients with pulmonary congestion and particularly in those with hypertension. They should be administered orally and initiated in low doses with rapid upward titration provided hypotension is not induced. ACE inhibitors should not be used acutely in patients who are hypotensive.

The only study that evaluated the effect of ACE inhibitors on morbidity and mortality in patients presenting with acute CHF complicating MI was the Acute Infarction Ramipril Efficacy study (227). Ramipril or placebo was instituted in 2,006 patients between days 3 and 10, and mortality was significantly reduced at 30 days (relative hazard, 0.73; 95% confidence interval: 0.602, 0.89; p <.002) (*e*Fig. 19.5.4) (227). This beneficial effect was seen in all subgroups analyzed, including those patients with or without thrombolytic and ASA therapy. Therefore, all patients with pump failure complicating acute MI, including those whose cardiogenic shock has resolved, should be treated with ACE inhibitors. The timing of initiation depends on the stability of the BP, with hypertensive or normotensive patients tolerating early initiation. Based on the excellent tolerance of early oral captopril and lisinopril in ISIS 4 and GISSI-3 and on the benefits on infarct expansion, we recommend early (£12 hours) oral initiation of captopril, 6.25 mg, for patients presenting with pulmonary congestion. The dosage may be doubled with each subsequent dosage, as tolerated up to 25 to 50 mg every 8 hours. Hypotension should be avoided, particularly during reperfusion, and we therefore recommend initiating oral ACE inhibitors after direct PTCA or thrombolysis has established reperfusion. If reperfusion fails or is not attempted, early administration of ACE inhibitors plays an important role. Long-acting ACE inhibitors (e.g., enalapril, lisinopril, ramipril, trandolapril) can be given after the acute phase.



***e*FIGURE 19.5.4** Angiotensin-converting enzyme inhibition for congestive heart failure complicating acute myocardial infarction. Patients with acute myocardial infarction complicated by congestive heart failure were randomly assigned to ramipril or placebo. The 30-day mortality curves demonstrate a significant reduction in mortality for those treated with ramipril. [From The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821–828, with permission.]

Cardiac Glycosides. Digoxin increases myocardial contractility to a lesser extent compared with dobutamine or phosphodiesterase inhibitors (245). Acute

administration is associated with alpha adrenergically mediated coronary and systemic vasoconstriction (246). However, in patients with CHF, the positive inotropic effects may result in reflex sympathetic withdrawal and vasodilation. Digoxin is associated with an increased risk for ventricular arrhythmias during the first 24 hours of acute MI. Therefore, digoxin has no clear role in acute pulmonary congestion or cardiogenic shock complicating MI. For patients with AF with a rapid ventricular response, digoxin has limited efficacy, but it is a good agent for rate control because it does not have the negative inotropic properties of beta-blockers or verapamil and diltiazem. The recommended dose for digoxin is 0.5 mg i.v., followed by 0.25 mg i.v. 4 to 6 hours later, until a 1-mg total loading dose has been administered or the target HR has been achieved (maximum dose, 1 mg). Of note, the target ventricular rate for a patient with pump failure is 90 to 110 beats/min to compensate for a depressed SV.

Pharmacologic Circulatory Support

General. The choice of a sympathomimetic agent for patients with pump failure depends on the patient's hemodynamics and, specifically, whether hypotension is present (*e*Table 19.3.2). Patients with pulmonary congestion without significantly depressed cardiac output should be treated with vasodilators alone. Patients in ACC/AHA hemodynamic subset 1 of pump failure (89) with an elevated PCWP and a CI £2.5 L per minute per m^2 and with systolic BP ³100 mm Hg can be treated with combined inotropic and vasodilating agents, such as dobutamine or milrinone if needed for hypoperfusion. Beta-adrenergic agents have been demonstrated to enhance contractility of stunned myocardium and therefore can provide temporary support for pump failure until stunned myocardium recovers (247). Patients with cardiogenic shock and profound hypoperfusion need initial vasopressor support with alpha-dose dopamine or norepinephrine.

***e*TABLE 19.3.2** SYMPATHOMIMETIC AMINES

Drug	Dose	Receptor stimulation	Hemodynamic effect	Adverse reaction
Dobutamine	2–20 µg/kg/min	Dominant: myocardial $beta_1$ other $beta_2$ alpha-adrenergics	↑ Contractility; ↑ CO; ↓ SVR; ↑, ↓, or → BP; ↓ PCWP	Tachycardia, ventricular arrhythmias, systolic hypertension, increased ventricular response in atrial fibrillation, nausea, headache
Dopamine	Low, <5 µg/kg/min	Dopaminergic	Renal and mesenteric vasodilation, ↑ diuresis	Occasional decreased BP
	Moderate, 5–10 mg/kg/min	Dominant: beta-adrenergic; other: norepinephrine release	↑ Contractility, ↑ HR, CO, and BP	Tachyarrhythmias, nausea, vomiting, headache, nervousness, myocardial and peripheral ischemia, oliguria; extravasation can cause tissue necrosis
		Dopaminergic	↑ Or → PCWP	
	High, >10 µg/kg/min	Dominant: alpha-adrenergic	↑ SVR, BP, contractility, HR, and PCWP	
Norepinephrine	0.03–0.15 mg/kg/min	Dominant: $alpha_1$- and $alpha_2$-adrenergic; other: $beta_1$-adrenergic, at lower doses	↑ SVR and BP; → or ↓ HR; ↑ or → CO	Tissue necrosis at injection site; tachyarrhythmias, bradycardia, headache, anxiety, tremor, myocardial and peripheral ischemia, oliguria, edema, hemorrhage, necrosis of intestine, liver, kidneys, plasma volume depletion
Drug	*Drug interactions*		*Treatment of tissue infiltration*[a]	
Dopamine and norepinephrine	Monamine oxidase inhibitors: reduce dopamine and norepinephrine dose to one-tenth; tolazoline: cardiac arrest report; potentiation of arrhythmias: anesthetics, tricyclics, digitalis		Antidote for peripheral ischemia caused by infiltration of dopamine or norepinephrine: 5–10 mg phentolamine infiltrated into affected area	

↑, increased; ¯, decreased; ®, unchanged; BP, blood pressure; CO, cardiac output; HR, heart rate; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

[a] Central vein administration is recommended to avoid this complication.

The lowest doses of sympathomimetic amines needed to maintain adequate cardiac output and adequate systemic perfusion should be used. For patients in cardiogenic shock, therapy should be guided with a PA catheter. Because each patient's response to different doses varies, systemic vascular resistance should be calculated, and the relationship between PCWP and CI should be defined repeatedly for patients as they remain on support. All sympathomimetic agents may cause atrial and ventricular tachyarrhythmias.

Dobutamine. This synthetic catecholamine increases myocardial contractility through preferential stimulation of myocardial $beta_1$-adrenergic receptors. $Beta_2$-peripheral vasodilator receptors and myocardial $alpha_1$-adrenergic receptors are also stimulated but to a lesser extent (248,249 and 250). Dobutamine has less chronotropic effect than does dopamine and typically does not cause significant changes in HR when the dose is less than 15 µg per kg per minute. The initial dosage of dobutamine is 2 µg per kg per minute followed by a gradual increase in dosage to 15 µg per kg per minute as needed. The lowest dosage required should be used for maintenance. Cardiac output should increase, and PCWP should decrease. Systemic vascular resistance decreases somewhat, and the balance of the increase in cardiac output and the decrease in systemic vascular resistance results in an unchanged BP. Dobutamine therefore is not the drug of choice for hypotension. Its short half-life, approximately 2 minutes, is highly desirable because it can be discontinued if ventricular tachycardia develops or it can be titrated down for excess increases in HR.

A concern with use of any inotropic agent is the risk for increase in myocardial oxygen requirements by increased myocardial contractility, tachycardia, and exacerbation of myocardial ischemia. However, when LV dilation and elevated diastolic filling pressures are present, wall tension decreases because EDV and pressure are reduced by dobutamine (251,252). Dobutamine can be combined with i.v. nitroglycerin when significant elevation in PCWP persists. Although dobutamine improves the patient's immediate hemodynamic status, there are no randomized trials assessing its effect on outcome.

Phosphodiesterase Inhibitors. Phosphodiesterase inhibitors, such as milrinone and amrinone, result in increased intracellular cyclic adenosine monophosphate caused by inhibited degradation and are therefore positive inotropes. They increase SV and cardiac output. They also result in venous and arteriolar vasodilation with a decrease in PCWP, systemic vascular resistance, and arterial pressure. Milrinone lowers the PCWP more than dobutamine (253). When cardiac output is severely reduced, the combination of lower doses of phosphodiesterase inhibitors and dobutamine may produce additive effects (254,255). Phosphodiesterase inhibitors have been studied in a limited number of patients with acute MI (253,256,257). Caution must be exercised when using these agents because they are potent vasodilators and may cause hypotension in patients with marginal BP. If milrinone, when administered concomitantly with dobutamine, increases CI further but results in untolerated vasodilation in refractory patients with low output, low-dose dopamine, norepinephrine, or vasopressin (258) can be added to normalize systemic vascular resistance. Milrinone and amrinone have longer half-lives than does dobutamine and have an even longer duration of action when renal insufficiency is present, as they are excreted by the kidneys. Other side effects include tachyarrhythmias and thrombocytopenia, with the latter seen less often with milrinone than with amrinone. Milrinone is preferred and is given as a 50 µg per kg slow bolus over 10 minutes followed by 0.375 to 0.75 µg per kg per minute. If BP is marginal, the bolus may be omitted.

Dopamine. The hemodynamic effects of dopamine are dose-dependent and vary from patient to patient. Low doses (i.e., 1 to 3 µg per kg per minute) result in renal vasodilation caused by dopamine receptor stimulation. Intermediate doses of 5 to 10 µg per kg per minute result in $beta_1$-adrenergic stimulation and increased myocardial contractility. High doses (i.e., ³15 µg per kg per minute) result in $alpha_1$-receptor stimulation and arterial vasoconstriction. High-dose dopamine increases pulmonary vascular pressures, including PCWP, as well as systemic arterial pressure. High-dose dopamine is required for cardiogenic shock with profound hypotension to support perfusion of the vital organs. Hypotension must be aggressively corrected during attempted reperfusion with thrombolytic therapy. As other support measures are instituted (e.g., IABP), dopamine should be titrated down to the minimum dosage required.

Norepinephrine and Epinephrine. Norepinephrine is a powerful $alpha_1$ stimulant that results in arterial vasoconstriction and is a $beta_1$-stimulant that increases inotropy (259). It is used primarily as a last resort if dopamine proves inadequate to maintain systemic and coronary perfusion pressures. Epinephrine also acts on the $beta_1$ myocardial receptors and on both $alpha_2$- and $beta_2$-receptors in peripheral blood vessels. Small amounts may constrict renal as well as cutaneous vessels while dilating skeletal and mesenteric vessels, which may result in a decrease in BP. At larger doses, epinephrine primarily acts as a vasoconstrictor. It causes tachycardia and arrhythmias, which limits its use in acute MI with cardiogenic shock, except in resuscitating patients in cardiac arrest.

Other Vasopressors. Vasopressin, an antidiuretic hormone, is a potent vasoconstrictor when used in high doses. It is indicated for one time use (40 U i.v.) for persistent ventricular fibrillation as an alternative to epinephrine (260). There is limited experience with its use in vasodilatory shock and milrinone-induced hypotension (258,261).

L-NMMA [*N*(*G*)-monomethyl-L-arginine], the nitric oxide synthase inhibitor, is being investigated for refractory hypotension in revascularized, IABP-supported patients

(262).

Although critical for initial stabilization, pharmacologic support has never been demonstrated to change outcome when pump failure complicates acute MI. In contrast, ACE inhibitors have been demonstrated to reduce mortality when CHF without cardiogenic shock complicates MI (227).

Mechanical Circulatory Support

Mechanical circulatory support plays an extremely important role in providing temporary support for patients in cardiogenic shock. Support devices are superior to pharmacologic support for cardiogenic shock in that perfusion is supported without increasing myocardial work and $\dot{V}O_2$. It must be noted, however, that mechanical circulatory support alone has never been demonstrated in randomized trials to improve outcome in patients with cardiogenic shock.

Intraaortic Balloon Counterpulsation

The IABP is placed in the descending thoracic aorta distal to the left subclavian artery and above the renal arteries through the femoral artery, with balloon inflations and deflations synchronized with the cardiac cycle. This augments diastolic blood flow in the coronary and systemic circulation, and reduces afterload and aortic impedance. Both mechanisms increase CI and systemic and coronary diastolic pressures and improve myocardial metabolism (9,263,264,265 and 266). It is not clear, however, whether coronary flow distal to a critical stenosis increases with IABP. There are conflicting results with Doppler flow wire measurements of coronary blood flow versus great cardiac vein thermodilution flow measurements (267,268 and 269). However, in hypotensive states an increase in aortic pressure by IABP should improve coronary blood flow (270), particularly when combined with PTCA.

A large, nonrandomized cooperative study (271) in the prethrombolytic and pre-PTCA era demonstrated that IABP therapy was extremely effective in reversing end-organ hypoperfusion in patients with acute MI and cardiogenic shock whose disease proved refractory to vasopressor therapy. However, when IABP was not combined with any coronary reperfusion and revascularization strategy, the mortality remained high at 83%. One small randomized trial (272), also in the prethrombolytic and pre-PTCA era, found that mortality was not reduced by IABP in patients who had CHF or cardiogenic shock complicating acute MI. A report (273) of nonrandomized patients suggested an improved survival rate in patients with cardiogenic shock complicating acute MI admitted to a unit in which IABP was used frequently compared with that in a similar unit in the same hospital in which IABP was not available (46% vs. 38% survival, respectively; *p* £.001). More than 40% of these patients received thrombolytic therapy, and counterpulsation was continued for longer periods than in previous studies to allow recovery of stunned myocardium.

IABP remains extremely effective in supporting patients undergoing coronary angiography, PTCA, and CABG in cardiogenic shock. It also provides bridging support until an LV assistance device can be implanted or cardiac transplantation can be performed.

A randomized trial (274) has demonstrated that IABP improves angiographic patency following PTCA of the IRA in patients not in cardiogenic shock. Reports have suggested that IABP may be combined with thrombolytic therapy to improve reperfusion rates when cardiogenic shock is present (see Thrombolysis). The GUSTO 1 thrombolytic trial investigators (275) reported that patients in the United States were more frequently treated with invasive therapy including IABP than patients not in the United States, and that use of IABP correlated with lower mortality in an adjusted model. The SHOCK Trial Registry also reported improved survival associated with IABP use (276). However, most of these patients were revascularized, which was the strongest determinant of survival. Use of IABP allows for rapid stabilization of cardiogenic shock patients so that they can survive long enough to undergo urgent revascularization. Rapid IABP insertion and transfer of patients from primary to tertiary care hospitals is associated with improved survival (277). ACC/AHA guideline indications for use of IABP include preparation for angiography and revascularization in cardiogenic shock that has not quickly reversed, acute MR or VSR, refractory post-MI angina (89), and refractory ventricular arrhythmias with hemodynamic instability. Less firm indications include hemodynamic instability without shock, poor LV function, or persistent ischemia with large regions at risk (89). Risks associated with IABP include (a) leg ischemia possibly necessitating thrombectomy, vascular surgery, or amputation; (b) dissection, perforation, or damage to the aorta with insertion; (c) hemorrhage; and (d) infection and thrombocytopenia. Full-dose i.v. heparin is required. IABP is contraindicated when significant aortic insufficiency is present or when peripheral vascular disease is severe or aortic pathology (e.g., aortic aneurysm) precludes it. IABP is not effective when there is no spontaneous circulation, and the timing of IABP inflation is difficult when there are uncontrolled tachyarrhythmias.

Other Circulatory Support Devices

Several types of devices are currently being used to provide improved circulatory support. They include (a) LV and biventricular assistance devices (278,279 and 280); (b) percutaneous cardiopulmonary bypass support with use of an extracorporeal membrane oxygenator (281,282,283,284 and 285); and (c) investigational devices such as the percutaneous transseptal ventricular assist system (286). The latter circulates oxygenated blood from the left atrium via a transseptal approach to the femoral artery, obviating the need for a membrane oxygenator. PCWP decreases and CI and mean arterial pressure increase (286). Cardiopulmonary bypass support is typically limited to several hours, and the left ventricle is not decompressed (i.e., unloaded) by this procedure. For patients with refractory shock or no spontaneous circulation, improved circulatory support with LV assistance devices or percutaneous cardiopulmonary bypass support with extracorporeal membrane oxygenator may be used as a bridge to cardiac transplantation.

Coronary Artery Reperfusion and Revascularization

Therapy that rapidly reestablishes blood flow in a totally occluded IRA is the single most important treatment of acute MI. This is true for patients with pump failure, in whom the absolute gain is large based on the high event rates (11,177,287,288 and 289). Observational data (287) demonstrate that an open IRA in patients with cardiogenic shock complicating MI correlates strongly with survival. Randomized trial results confirm that early revascularization, with either PTCA or CABG, improves 1-year survival compared with initial aggressive medical stabilization, including thrombolysis and IABP (11).

Congestive Heart Failure

The mortality among patients with CHF complicating acute MI (Killip classes II and III) has been only modestly reduced by thrombolytic therapy (Table 19.4) (5,85,135,156). However, GISSI-1 (85) provides the only randomized data available from patients with CHF on presentation that tested SK without ASA and included MIs with non–ST-segment elevations. Few patients with CHF have been enrolled in PTCA versus thrombolytic trials (202,203 and 204,290). One small trial (290) suggested benefit of PTCA over SK. In the GUSTO 2b PTCA substudy (291), patients who presented in Killip class II to III had similar relative reductions in mortality at 30 days from PTCA compared with front-loaded t-PA as was demonstrated in the overall study (292). Based on the higher event rates, the absolute reduction in events with direct PTCA was larger than for Killip class I patients. Unfortunately, the mortality remained high even with direct PTCA. It is likely that prior and acute *irreversible* myocardial damage in many of these patients will continue to result in mortality that is significantly higher than those among patients who present without CHF. Nevertheless, *early* successful reperfusion is the goal. We recommend direct PTCA when available; if direct PTCA is not available, thrombolytic therapy should be administered with rescue PTCA for failure of reperfusion. Based on the high event rate among patients with CHF complicating MI if early PTCA was not performed (Table 19.4), subsequent revascularization is indicated based on the anatomy. If CABG is indicated for multivessel disease, its timing must be individualized based on whether the IRA is patent and on the patient's degree of pulmonary congestion and clinical stability.

		Thrombolytic trials (30 days)			
		GISSI-1			
Killip class	Killip and Kimball (in-hospital)	Placebo	Thrombolytic	International thrombolytic	ASSENT-2 thrombolytic
I	6	7	6	5	5
II	17	20	16	18	13
III	38	39	33	32	26
IV	81	70	70	72	56

Data from references 5, 85, 135, and 488.

TABLE 19.4 MORTALITY BY KILLIP CLASS

Cardiogenic Shock

Thrombolysis

Early Shock. There is limited efficacy of thrombolysis in patients who present in shock. This appears to be the result of failure to reperfuse thrombosed arteries in the setting of low coronary perfusion pressure. Experimentally, the rate of dissolution of coronary artery thrombus is markedly depressed when hypotension is present (117,118). If BP is augmented (to a systolic pressure of 130 mm Hg as demonstrated in the canine model) by aggressive use of vasopressors (118) or by IABP (117) during reperfusion, the rate of thrombus dissolution can be restored to more normal values. In a nonrandomized study (119), the rate of reperfusion after intracoronary SK for 45 patients in shock was significantly lower than that among those not in shock (43% vs. 71%, respectively; *p* £.001). Patients in whom intracoronary SK proved successful in establishing reperfusion had a lower mortality than did those who had persistent occlusion (42% vs. 84%, respectively; *p* £.001) (119).

The GISSI-1 (85) study reported no mortality difference for those who presented in Killip class IV assigned to SK or placebo (70%). The Fibrinolytic Therapy Trialists' Collaborative Group (293) pooled nearly 60,000 patients from all large, placebo-controlled, randomized thrombolytic trials (including GISSI-1). They identified 276 patients with MI and ST-segment elevations and presenting with BP of less than or equal to 100 mm Hg and an HR greater than or equal to 100 beats/min. The mortality with thrombolytic therapy was 54% compared with 61% for placebo. This sample was relatively small and the difference did not reach statistical significance; however, the Fibrinolytic Therapy Trialists noted that the possibility of saving 7 lives in every 100 patients treated represents a large absolute benefit. Data from the large NRMI nonrandomized study of patients with shock complicating acute MI support an approach that combines early IABP and thrombolysis, as do data from small studies (273,277,294). The Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival (TACTICS) trial randomly assigned 57 patients with preshock or shock to thrombolysis alone or with IABP less than or equal to 3 hours. The trial was not completed (target n = 538), but there was a trend toward lower 6-month mortality for those randomized to thrombolysis with IABP (34% vs. 43%; *p* = .23) with a suggestion of a larger difference for the small subset enrolled in classic shock (39% vs. 80%; *p* = .05, n = 31) (295). When an IABP is inserted in a patient receiving a thrombolytic agent, care must be taken to reduce the risk for bleeding (e.g., puncture of anterior arterial wall only). The major bleeding rate in the IABP and thrombolysis arm of TACTICS was low (3%).

Choice of Thrombolytic Agent. In GUSTO 1 (185), although t-PA resulted in a lower mortality than did SK in patients who did not present with cardiogenic shock and also resulted in a lower rate of cardiogenic shock, this superiority was not seen among patients diagnosed with shock. Patients who were in shock on presentation or who developed shock had a tendency (*p* = NS) toward a lower mortality when treated with SK than did those treated with t-PA. This is likely caused by depression of t-PA clot lysis rates by hypotension (117,118) or to the problem of post hoc subset analyses. Nevertheless, the latter is less likely given similar findings from the International trial (296).

Mechanical Revascularization

Percutaneous Transluminal Coronary Angioplasty. The in-hospital mortality in mostly retrospective studies of patients undergoing PTCA for cardiogenic shock is 45% (10,177,178,287,288,297,298), which is lower than the historic mortality of 80% in controls (5,199). When PTCA is successful, mortality is significantly lower than when it is not (36% vs. 83%, respectively). The overall success rate for PTCA in shock is lower (75%), than for primary PTCA for acute myocardial infarction. GUSTO 1 investigators (185,275) also reported the association of revascularization (using PTCA or CABG) with lower mortality. Nonetheless, as shown in the SHOCK Trial Registry, selection bias plays a major role in improved outcomes following PTCA and CABG (177,299).

The randomized SHOCK Trial Registry compared a direct invasive strategy of emergency early revascularization to initial medical stabilization including thrombolysis and IABP, followed by delayed revascularization as clinically determined. Patients with shock (n = 302) caused by predominant LV failure that developed less than or equal to 36 hours after an ST elevation or Q wave or new left bundle branch block MI were enrolled (289). Angiography and early revascularization were performed in 97% and 87% of the invasive strategy group, respectively, and delayed revascularization was performed in 25% of the medical stabilization group. Both groups were supported with IABP (86%) and thrombolytic agents were used in 63% of the medical stabilization group and 49% of the invasive group. Although the difference in 30-day mortality of 9.3 percentage points between the groups (17% relative risk reduction, 46.7% vs. 56.0%) in favor of early revascularization did not reach statistical significance (*p* = .109), the difference increased over time. At 6 and 12 months, 13 lives were saved for every 100 patients treated with early revascularization compared with intensive medical therapy, including IABP, thrombolysis, and delayed revascularization (53% vs. 66%; *p* = .025 at 12 months) (11) (Fig. 19.6). This benefit is comparable with that seen at 1 year with CABG surgery for left main disease (300,301). The improved survival was seen for patients with early and late shock and regardless of infarct location or the presence of comorbidities (e.g., diabetes, prior hypertension, or MI) (Fig. 19.7). The small subgroup of those older than 75 years (n = 56) did not appear to benefit. However, the small sample size precludes firm conclusions. The larger nonrandomized Registry suggested a markedly lower in-hospital mortality for elderly patients who were carefully clinically selected for early revascularization, even after adjustment for their lower risk profile (302). In the SHOCK Trial Registry, more than 80% of 1-year survivors were in New York Heart Association CHF class I to II.

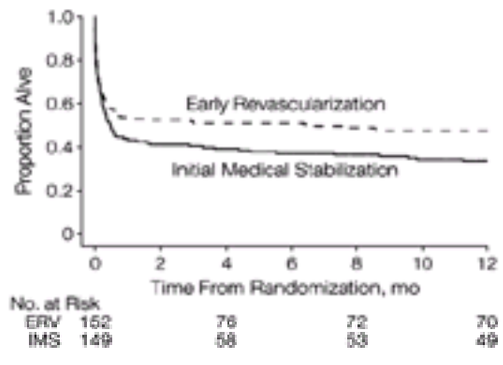


FIGURE 19.6 Kaplan-Meier survival curve 1-year postrandomization: 1-year survival of patients with acute myocardial infarction complicated by cardiogenic shock caused by predominant left ventricular failure. Patients were randomized to early revascularization (ERV) or initial medical stabilization (IMS) in the SHOCK Trial Registry (log rank, *p* = .043). (From Hochman JS, Sleeper LA, White HD, et al. One year survival following early revascularization for acute myocardial infarction complicated by cardiogenic shock. *JAMA* 2001;285:190–192, with permission.)

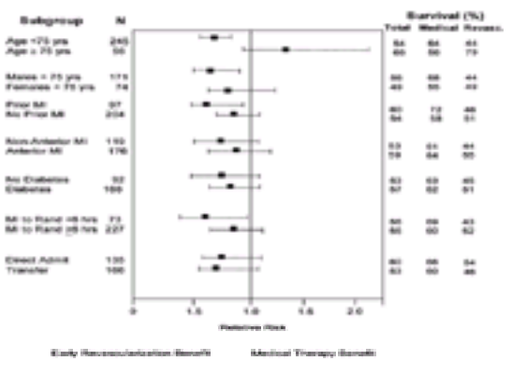


FIGURE 19.7 Relative risk of 6-month death with early revascularization compared with initial medical stabilization (medical therapy) for selected subgroups of patients with cardiogenic shock in the SHOCK Trial Registry. MI, myocardial infarction.

PTCA should be performed with IABP support. Although there are insufficient data in shock, we recommend use of stents and GP IIb/IIIa antagonists. The outcome of patients who underwent PTCA after thrombolysis was similar to those who underwent direct PTCA in the SHOCK Trial Registry (297). Most patients have triple-vessel disease (65%) and the options for revascularization include (a) PTCA of the IRA followed by complete revascularization by multivessel PTCA; (b) initial multivessel PTCA; (c) initial CABG; and (d) PTCA of the IRA followed by CABG. These strategies have not been directly compared. We recommend PTCA for patients with one-, two-, or moderate three-vessel disease and CABG for those with severe three-vessel or left main disease. Continuous, noninvasive monitoring of the systemic oxygen

saturation is required. Most patients with cardiogenic shock have required prior intubation; for others, intubation is recommended before injecting angiographic dye. Low osmolality, ionic contrast dye is recommended. Despite these measures, relatively low PTCA success rates and no reflow remain challenges. Some patients improve rapidly and dramatically after PTCA, whereas others show no immediate hemodynamic improvement. Patients may deteriorate hemodynamically after reperfusion is established, particularly if they are reperfused late. It is not uncommon for significant arrhythmias, including profound bradycardia and ventricular fibrillation, to develop during reperfusion in these patients. Immediate therapy must be available.

Coronary Artery Bypass Graft. In patients with shock, severe triple-vessel disease is present in most (65%), and left main disease is present in 20% (180,289). Such patients are often unsuitable for PTCA; hence, CABG is the preferred alternative. The in-hospital mortality among patients who underwent CABG at some time during their hospitalization for cardiogenic shock complicating acute MI was 35%. This constitutes the lowest mortality reported for cardiogenic shock in acute MI (9,177,287,298,299,303). In the SHOCK Trial Registry, early CABG surgery was performed in 40% of those who underwent emergency revascularization at a median of 2.7 hours after randomization. Despite significantly higher rates of left main (40% vs. 14%; $p = .001$) and triple-vessel CAD (79% vs. 59%; $p = .007$), the 30-day and 1-year mortality for those who underwent emergency CABG was the same as for those who underwent emergency PTCA (42% vs. 46% at 30 days; 52% vs. 55% at 1 year) (289,304).

We recommend emergency early CABG with IABP support for patients with cardiogenic shock and severe triple-vessel or left main disease. Although some surgeons prefer a period of medical stabilization, there is a high risk of death on the first day (almost 50% of all deaths). The SHOCK Trial Registry demonstrated that an initial intensive medical stabilization approach was associated with poorer 1-year survival than early revascularization (11).

Optimization of cardioprotection is most critical in patients with severe LV dysfunction and shock, and newer cardioprotective techniques including antegrade and retrograde cardioplegia, warm induction, prolonged vented bypass, and use of substrate-enriched blood have been advocated (303).

Metabolic Support

Severe metabolic abnormalities occur within the region at risk in the myocardium and in the remote uninfarcted myocardium as discussed previously (see Cardiogenic Shock Caused by Primary Left Ventricular Failure). Glucose, insulin, and potassium have been demonstrated in a rabbit model of cardiogenic shock to sustain cardiac output and survival significantly longer than dobutamine (190) and to improve postoperative hemodynamics when shock occurs after CABG (186,305,306). These two strategies correct depletion of Krebs cycle intermediates and the potentially deleterious role of free fatty acids, which are liberated during high catecholamine states (186,187). A nonrandomized study (303) using metabolic support solutions with glutamate and aspartate for controlled reperfusion during CABG has reported a remarkably low mortality of 9%. A randomized trial (307) of continuous insulin infusion and tight glucose control for patients with hyperglycemia and acute MI without shock also reported a significantly lower mortality than that among controls.

L-Carnitine restores adenine nucleotide translocase activity, which increases high-energy phosphate levels. One small, uncontrolled study (308) infused L-carnitine in 27 patients with cardiogenic shock and reported a 78% survival rate at 10 days. Administration of magnesium has not been evaluated for pump failure, but one trial (309) reported lower rates of failure in patients who received it. The large Magnesium in Coronaries trial includes patients with pump failure.

Agents that inhibit reperfusion injury (i.e., free radical scavengers and leukocyte inhibitors) have not been demonstrated to be efficacious for patients with routine, acute MI undergoing reperfusion therapy (310). However, these agents have never been investigated in patients with cardiogenic shock in whom reperfusion injury may play a greater role than in patients with uncomplicated MI.

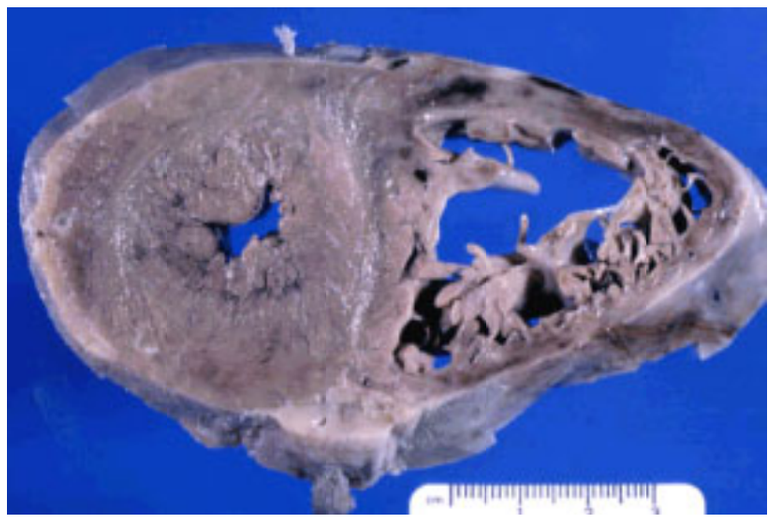
Summary

Rapid support of the circulation and restoration of IRA blood flow is the goal for managing patients with acute LV failure complicating acute MI. We strongly recommend rapid IABP support, coronary angiography, and revascularization, particularly for those aged less than 75 years. The choice of PTCA or CABG is based on the coronary anatomy and the experience of the personnel. For hospitals without the facilities for PTCA or CABG, thrombolytic agents should be administered with aggressive measures to augment BP, including IABP, followed rapidly by transfer to tertiary care facilities. For young patients who do not respond to available measures, LV assistance devices should be considered as a bridge to urgent cardiac transplantation. Despite the marked reduction in mortality and the good functional class of survivors, overall 30-day survival is only 45% with aggressive care. Patients, especially the elderly, and their families must be involved in the decisions regarding their care, which should be individualized.

RIGHT VENTRICULAR INFARCTION

Pathology

RV infarction is typically associated with an inferior MI involving the interventricular septum and with occlusion of the proximal, right coronary artery. The extent of infarction varies greatly depending on whether occlusion occurs before the RV free wall and RV marginal branches, whether collateral flow from the LAD is present, and on the extent of blood flow through the thebesian veins (311). Because the right ventricle is a thin-walled chamber that functions at low-oxygen demands and low pressure with coronary perfusion throughout systole and diastole, extensive irreversible infarction is unusual. Transient, ischemic dysfunction and stunning are more typical, with long-term recovery of function being the rule (312,313). RV infarction is typically seen in association with LV infarction, with isolated RV infarction reported in less than 5% of autopsies (314).



Right ventricular infarct. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Clinical Profile

Incidence

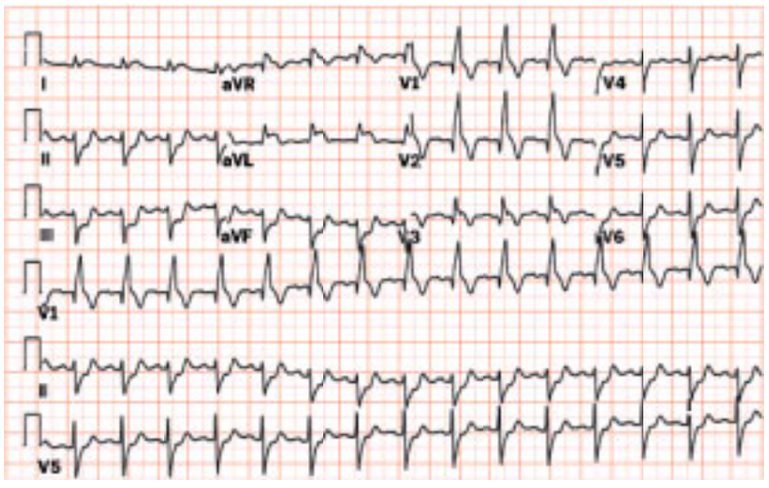
Depending on the diagnostic criteria used, the incidence of RV infarction in patients with inferior MI ranges from 10% to 50%. Most of these patients do not develop hypotension or cardiogenic shock. What is important is not the frequency of RV involvement but the identification of patients with dominant RV infarction in which dysfunction of the right ventricle is primarily responsible for hypotension and shock. The absence of preinfarction angina within 1 week in patients with inferior MI is independently associated with the development of RV infarction, hypotension, and shock (315).

In the SHOCK Trial Registry, 2.8% of 1,190 consecutive patients with suspected cardiogenic shock had shock caused by isolated RV failure (316).

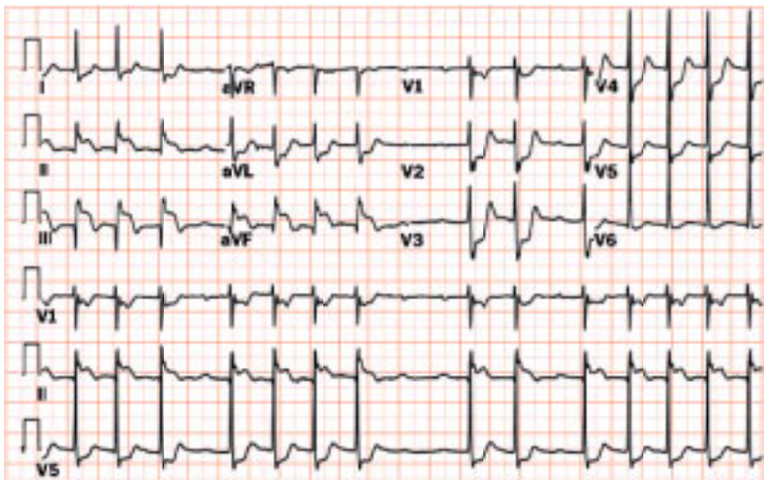
Clinical Findings

The clinical manifestations of RV infarction include marked sensitivity to preload reduction (nitrates, morphine sulphate, diuretics), hypotension, and, infrequently, cardiogenic shock (317,318 and 319). High-grade AV block and bradyarrhythmias are common (320,321 and 322) because they are both consequences of proximal, right coronary artery occlusion. Right atrial to left atrial shunting occurs infrequently in the presence of RV failure and a patent foramen ovale or atrial septal defect,

resulting in hypoxemia (323,324). RV free wall rupture and tamponade are rare, but patients with extensive RV necrosis are at risk for RV catheter- (i.e., pacemaker lead or PA catheter) related perforation.

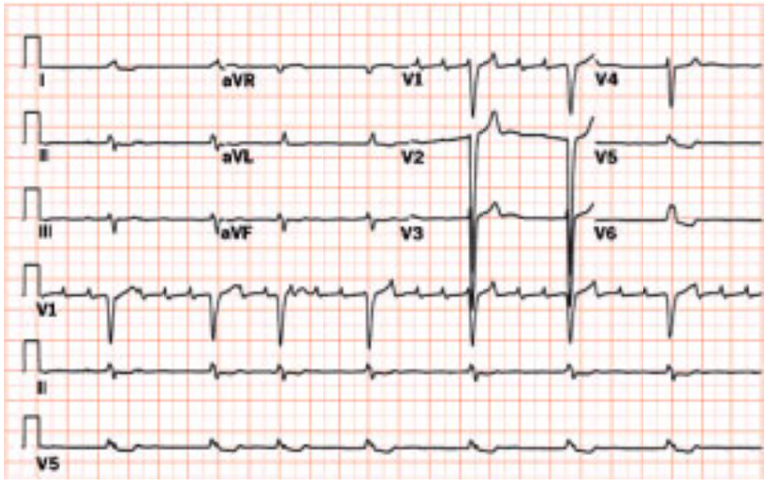


Acute anterolateral myocardial infarction complicated by conduction disturbance. ST-segment elevation in the anterior precordial leads as well as leads I and aVL is associated with right bundle branch block and left anterior hemiblock.



Acute inferior myocardial infarction with Mobitz II atrioventricular block. Note ST-segment elevation in the inferior leads as well as intermittently dropped QRS complexes.

Acute inferior myocardial infarction complicated by Wenckebach block. Note inferior ST-segment elevation and Q waves as well as progressive prolongation of the PR interval with grouped beating.

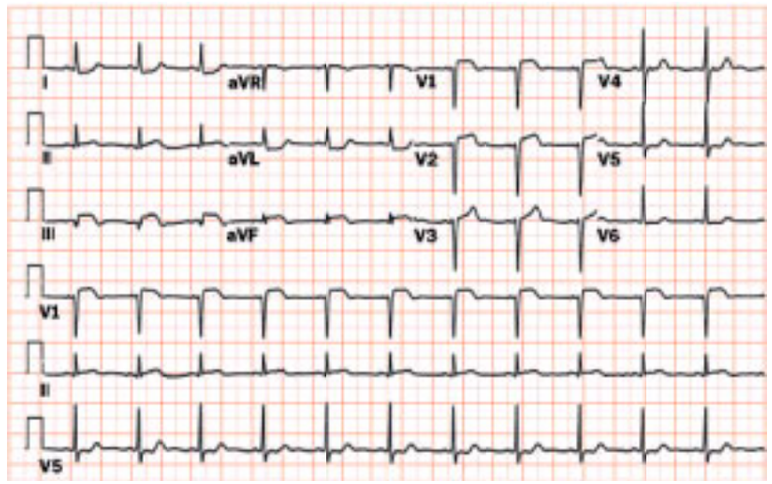


High-grade atrioventricular block. Note marked discrepancy between atrial and ventricular heart rates.

Diagnosis

The classic, clinical constellation of hypotension, elevated jugular venous pressure with clear lung fields, and no dyspnea (316) is highly specific but insensitive for RV infarction (325).

When performed early after onset of symptoms, ECG can be highly sensitive and specific. Right precordial (RV) leads should be obtained in patients with inferior MI. An ST elevation of greater than or equal to 0.5 mm in lead V_{4R} is highly sensitive (326,327) and correlates with major clinical complications (328). The added criteria of ST elevations greater than 0.5 mm in lead V_{4R} compared with leads V_1 to V_3 has higher specificity but lower sensitivity than does ST-segment elevation in lead V_{4R} alone (327). Technetium 99m pyrophosphate myocardial scintigraphy can diagnose RV infarction; however, at present, it is infrequently performed. Echocardiography and gated blood pool scintigraphy have proven to be efficacious (329) in diagnosing clinically significant RV infarction by assessing RV size and wall motion. Echocardiography is typically preferred because it can be performed at the bedside and simultaneously offers assessment of pericardial effusion and tamponade, which is the chief differential diagnosis when predominant RV infarction and hypotension are present. When this syndrome is found on acute presentation before cardiac marker confirmation, acute PE is part of the differential diagnosis as well. Echocardiography may also be useful because Doppler estimation of PA pressures may be obtained.



Acute inferior myocardial infarction with right ventricular involvement. Inferior ST-segment elevation associated with elevation in lead V_1. See right precordial leads.

Right ventricular infarction. ST-segment elevation in leads V_{4R} and V_{5R} reveals right ventricular involvement complicating the inferior infarct.

Accepted hemodynamic criteria for dominant RV infarction include a right atrial (RA) pressure >10 mm Hg, an RA/PCWP ratio ≥0.8, or an RA pressure that is no less than 5 mm Hg below the PCWP. These values may only be demonstrated after volume infusion (330). Equalization of RA pressure and PCWP is often seen, necessitating exclusion of cardiac tamponade. The CI will be ≤2.2 L per minute per m^2 in patients with severe RV dysfunction.

Prognosis

The prognosis for RV infarction is largely determined by the degree of associated LV infarction (321,331). Overall, RV infarction is an independent risk factor for death in patients with inferior MI, and this risk increases substantially with increasing age (328,332,333). Patients with isolated RV infarction and normal or near normal LV function infrequently have severe hemodynamic compromise leading to death. For the small subset with shock, the in-hospital mortality is 53% (316). This poor prognosis is despite the predominance of single-vessel disease (65%). For survivors of acute RV infarction, the long-term prognosis is excellent, with improved RVEF seen over time (312,334).

Hemodynamics and Management

Although RV cauterization in animal models with normal pulmonary vascular resistance and an open pericardium has not resulted in significant hemodynamic abnormalities, the clinical syndrome of hemodynamic compromise with RV infarction has been well described (335,336). A subsequent dog model (337) confirmed this hemodynamic profile and a favorable response of the systemic arterial pressure and cardiac output to volume administration. The difference between the animal model of isolated RV infarction and clinical isolated RV infarction is that in the latter, the inferior wall of the LV and the interventricular septum are almost invariably involved. This, in turn, may result in relatively elevated LV filling pressures and RV afterload, which further compromise RV SV. Contraction of the interventricular septum also contributes to normal RV function (338). The role of the pericardium and ventricular interdependence is important to the understanding of the pathophysiology of RV failure. As the size of the RV cavity increases because of extensive infarction and volume administration, flattening of the interventricular septum or bowing of the septum into the left ventricle develops, resulting in restriction of LV filling (339,340) (Fig. 19.8). This resolves when the pericardium is removed (339).

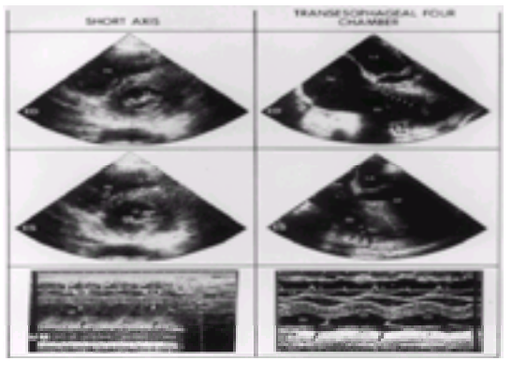


FIGURE 19.8 Transthoracic, transesophageal, and M-mode echocardiograms from a patient with right ventricular infarction, refractory shock, and right atrial infarction. In short axis at end diastole (ED), the right ventricle (RV) is markedly dilatated, and the interventricular septal curvature is reversed (*open arrow*) with a shift into the left ventricle (LV). The four-chamber view demonstrates marked right atrial (RA) enlargement as well as severe RV dilation and bowing of the septum into the LV (*white arrows*). At end systole (ES), the septum bulges paradoxically into the RV in both short-axis (*open arrow*) and four-chamber views (*white arrows*). RV free wall (FW, *dark arrows*) was dyskinetic in four-chamber view. These findings are confirmed in the M-mode views from the transthoracic and transesophageal images. Excess volume administration can cause RV dilatation, septal shift into the LV with impairment of LV filling, and paradoxic decrease in cardiac output despite an increase of pulmonary capillary wedge pressure. (From Goldstein JA, Barzilai B, Rosamound TL, et al. Determinants of hemodynamic compromise with severe right ventricular infarction. *Circulation* 1990;82:359–368, with permission. Original figure courtesy of Dr. J. Goldstein.)

Volume infusion became standard treatment for hypotension and low cardiac output in RV infarction based on the experimental data and early clinical series (317,337). In those patients who demonstrated the typical hemodynamic finding of an RA/PCWP ratio ≥0.8, the goal was to increase RV output and LV filling pressure. However, patients in these studies may have been receiving inappropriate preload-reducing therapy because RV infarction perhaps was not recognized initially. Dell'Italia et al. (341) demonstrated that despite progressive volume infusion with RA pressure rising from 11 to 15 mm Hg ($p \leq .001$) and PCWP increasing from 10 to 15 mm Hg ($p \leq .001$), the CI did not significantly increase (1.9 ± 0.5 L per minute per m^2 to 2.1 ± 0.4 L per minute per m^2). This was confirmed in patients. PCWP increased with i.v. volume infusion, but CI was unchanged (342) and RVEF decreased (343). This more contemporary experience probably reflects a patient population with more severely compromised RV function in contrast to earlier series of patients with milder RV infarction complicated by inappropriate diuresis in whom one would expect fluid administration to be beneficial. Radionuclide angiography demonstrated an increase in RVEDV, whereas LVEDV remained unchanged. The thin wall infarcted RV markedly dilates and, because of pericardial restraint, the interventricular septum shifts into the LV. This important finding demonstrates that PCWP may not accurately reflect LVEDV but, rather, impaired LV filling caused by the interventricular septal shift (Fig. 19.8). Therefore, echocardiographic imaging is critical for the diagnosis and management of patients with hemodynamic compromise caused by RV infarction, because the PCWP may be misleading. Nonetheless, an elevated PCWP is detrimental as a component of RV afterload. Hemodynamic monitoring is advisable. In patients with low output caused by dominant RV infarction, the RA should be maintained at 10 to 15 mm Hg and the PCWP should be maintained at less than or equal to 15 mm Hg. The finding of ventricular interaction and limitation of LV filling

by RV dilation has important therapeutic implications for the efficacy of volume infusion. Patients may deteriorate with excess volume administration. In addition, excess volume administration precipitates pulmonary edema when LV infarction is present in association with RV infarction.

The crucial management issue is not whether there is anatomic involvement of the right ventricle, but rather the pathophysiologic consequences of dominant RV infarction. If the jugular venous pressure is elevated in a patient with an inferior MI and hypotension, all that is necessary is to avoid preload reduction. For patients with hypotension and RV and first inferior MI, emergency empiric volume administration is indicated. These patients require variable amounts of fluid (200 mL to 1 L of fluid over the first several hours) depending on the estimated or measured RA pressure. If hypotension or evidence of low cardiac output persists, an emergency echocardiogram should be obtained, and subsequent management should be guided by PA catheter monitoring of cardiac output. As noted, additional fluid administration may be detrimental. Patients who are at risk for pulmonary edema should not receive this degree of rapid volume administration. These patients include those with (a) prior MIs; (b) acute, extensive LV infarction; (c) associated MR or other valvular lesions; (d) acute anterior MI; and (e) advanced age. If pulmonary congestion is not present, these patients may receive 200 to 250 mL of fluid, and an emergency echocardiogram should be obtained. If hypotension, evidence of a low cardiac output, or both persist, PA monitoring is required with further volume infusion.

The positive inotropic effects of dobutamine play an important role in managing patients with RV infarction and low cardiac output. Dobutamine significantly increases the CI and RVEF and is superior to afterload reduction therapy with nitroprusside (341). Patients in whom the initial central venous pressure or RA pressure are greater than 10 mm Hg or in whom an initial volume infusion fails and leads to an increase in RA and PCWP but a persistently low CI should be treated with dobutamine. When pacing is indicated for sinus bradycardia or complete heart block, it should be dual-chamber, AV sequential. Of note, there is an increased incidence of ventricular fibrillation with RV pacing caused by RV ischemia (344). IABP and PA counterpulsation have been used for RV shock (345,346 and 347). In rare cases of refractory shock caused by RV infarction, pericardiectomy should be considered (339).

Reperfusion Therapy

Rapid reperfusion with either thrombolytics or direct PTCA should be the initial treatment for RV infarction. RVEF improved in patients with successful intracoronary thrombolysis compared with no improvement in those in whom thrombolysis failed (348). Similarly, patients who received intracoronary SK had higher RVEFs than did those who did not receive intracoronary SK. Occluded IRAs at angiography correlated with evidence of RV infarction in contrast to a lower incidence of RV infarction in those with a patent IRA in Thrombolysis in Myocardial Infarction (TIMI) II (349). RV infarction is associated with low rates of reperfusion by thrombolysis, possibly caused by prolonged hypotension (120). Systemic arterial pressure should be augmented during thrombolytic administration for RV infarction with hypotension (117,118). Observational studies (350,351) of PTCA report marked improvement in hemodynamics and RV function after successful PTCA. In the SHOCK Trial Registry, 65% of those with RV shock had single-vessel disease with proximal right coronary artery occlusion (316). Based on extrapolation of the SHOCK Trial Registry results and the poor outcome if shock complicates RV infarction, we recommend direct (or rescue) PTCA for these patients.

MECHANICAL COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

Cardiac Rupture: Overview

Rupture may occur through a zone of necrosis in the LV free wall, interventricular septum, papillary muscle, or the contiguous chordae tendineae. Spontaneous RV free wall rupture rarely occurs. When one of these types of rupture occurs, it is typically referred to as a *mechanical complication* of acute MI; when shock results, this is termed a *mechanical cause* of shock. The relative infrequency of the often lethal mechanical complications of acute MI such as acute MR caused by papillary muscle rupture, VSR, or rupture of the free wall should not detract from their importance, because they are amenable to surgical repair. Moreover, these potentially catastrophic complications are, in turn, compatible with an excellent long-term prognosis among perioperative survivors. In a series (177) of 1,493 patients in 36 centers, acute septal rupture or MR accounted for only 11% of patients with cardiogenic shock. Acute MR without papillary muscle rupture can cause severe hemodynamic compromise and is discussed in this section as a mechanical complication. It is the etiology of MR in a substantial number of patients, although its exact frequency remains undetermined. Reperfusion therapy has reduced the overall incidence of cardiac rupture and shifted its occurrence to earlier after MI onset. Distinct clinical syndromes result, depending on the location and extent (i.e., partial or complete) of the rupture.

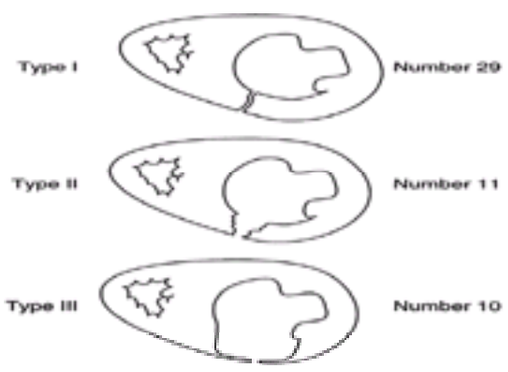
Left Ventricular Free Wall Rupture

Rupture of the LV free wall is not a uniformly fatal event, and early recognition of rupture with subacute tamponade may result in successful intervention.

Pathology

General

An autopsy study demonstrated that infarct size in patients dying of cardiac rupture is significantly less than in patients dying of arrhythmias or primary pump failure (352). Data such as these point to a potentially favorable long-term prognosis of rupture if it can be successfully treated initially with cardiac surgery. Three distinct types of cardiac rupture have been described (eFig. 19.8.1) in a classic study by Becker and van Mantgem (353). All types of cardiac rupture occurred in fully transmural infarcts. Type I is a slit through a full-thickness infarct, most frequently in anterior infarcts. These patients (17 of 29) most often had single-vessel disease. Type I rupture typically occurs during the first day and is likely responsible for the increased frequency of early rupture seen with thrombolysis (130,354). There is evidence to support the hypothesis that extensive disruption of interstitial matrix collagen may cause rupture as a result of both coronary occlusion and reperfusion. Early activation of proteolytic enzymes after coronary ligation has been demonstrated in an experimental study (35). Plasminogen activators activate metalloproteinases that degrade the interstitial myocardial matrix (355).



***e*FIGURE 19.8.1** Cardiac rupture. Three types of cardiac rupture have been characterized pathologically by Becker and van Mantgem (353). Type 1 rupture occurs early, within the first 24 hours of infarction, and is characterized by a slit through a normal thickness infarct. This may be the type of early rupture that occurs slightly more often with thrombolytic therapy. Type 2 rupture occurs more often in posterior infarcts and is less common than type 1. Type 2 is characterized by a localized erosion of infarcted myocardium. Type 3 rupture is most commonly seen in anterior infarcts and occurs in severely expanded (thinned and dilatated) infarcts. This type of rupture occurs later than type 1 rupture. Infarct expansion is inhibited by reperfusion, and it is likely that this is the type of rupture that is associated with the overall decrease in cardiac rupture after thrombolytic therapy. The number of each type of rupture cases observed is noted. (From Becker AE, van Mantgem JP. Cardiac tamponade: a study of 50 hearts. *Eur J Cardiol* 1975;15:349–358, with permission.)

Recent myocardial infarction with free wall rupture of the anterior wall of the left ventricle. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

An erosion of the myocardium at the borders of the rupture characterizes a type II rupture; the dominant location is posterior with multivessel CAD. Type I and II ruptures often occur in small-to-moderate sized infarcts. In contrast, type III rupture occurs in a severely expanded (i.e., very thin) infarct zone (356) and is usually associated with a large infarction. Anterior infarcts predominate, and single-vessel disease is present in more than one-half of cases. Type III rupture typically occurs later than do types I and II ruptures. Because reperfusion inhibits expansion (33) and thrombolytic therapy reduces the incidence of late rupture (130,354), it is likely that type III rupture is reduced with reperfusion therapy.

Cardiac rupture after acute transmural anteroseptal myocardial infarction. The yellow arrow indicates the site of rupture.

Pseudoaneurysm

Rupture that is sealed by the pericardium and then develops into a discrete aneurysmal outpouching with a narrow neck is referred to as a *pseudoaneurysm* or *false aneurysm* (Fig. 19.3) (44). The wall of a pseudoaneurysm is composed of pericardium and not infarcted myocardium or scar tissue, in contrast to a true LV aneurysm. The neck of a pseudoaneurysm is narrower than that of a true aneurysm.

Clinical Profile

Acute Ventricular Wall Rupture and Tamponade

Free wall rupture is a devastating complication that occurs in small-to-moderate sized MIs. Age is a strong risk factor for rupture, and free wall rupture is more common in women with MI than in men (357,358 and 359). Rupture can occur soon after coronary artery occlusion or days after onset of infarct. In a prospective study (360), the incidence of rupture was 6.2% in 1,457 patients, with 2% manifesting a subacute course. In the SHOCK Trial Registry, 1.4% of 1,422 patients had shock caused by cardiac rupture or tamponade. In a thrombolytic trial, patients with free wall rupture were much less likely to have been treated with beta-blockers before admission than those without rupture (359).

The incidence of cardiac rupture with death in patients not receiving thrombolytic therapy in the U.S. NRMI (357) (n = 350,755) was 0.8% compared with 0.7% in those treated with thrombolytics (p <.001). However, the timing of rupture changes with thrombolytic therapy; early rupture may be increased and late rupture may be decreased (130,354). The incidence of rupture in thrombolytic trials (130,354), including late administration, is 1.3% to 3.4%. This higher incidence than the NRMI may be related to time to treatment. The incidence of rupture in the Late Assessment of Thrombolytic Efficacy thrombolysis trial (354) in the first 24 hours was 1.5% with t-PA versus 1.0% in controls; after 24 hours it was 1.3% with t-PA versus 2.4% in controls (p <.04, interaction for treatment and time to death). ISIS 2 (130) reported a 0.5% incidence of rupture in the SK group and a 0.3% incidence of rupture in controls in the first 24 hours. When cardiac tamponade results from acute LV free wall rupture, the clinical presentation is sudden, electromechanical dissociation (EMD) or asystole, at times briefly preceded by severe chest pain.

Subacute Ventricular Wall Rupture and Subacute Tamponade

Rupture with a period of temporary pericardial sealing (less stable than pseudoaneurysm) and subacute tamponade has been characterized in the prospective, large series by Lopez-Sendon et al. (360). Of 1,457 consecutive patients with acute MI, 6.2% were diagnosed with free wall rupture; approximately one-third of these patients had a subacute presentation. Thirty-nine patients went to surgery and a myocardial rupture site was confirmed in 33. The clinical constellation in these patients may include transient hypotension, syncope, transient EMD, chest pain (360), and transient bradycardia, repetitive emesis, and restlessness (358). These clinical findings are sensitive but nonspecific. The ECG findings of pericarditis may be seen and include persistent or new ST-segment elevations, persistently positive T waves, or inverted T waves becoming positive. However, these findings are insensitive and nonspecific (360). Subacute rupture can often be identified on echocardiography and successfully repaired (eTable 19.4.1) (360,361). This is in contrast to the classic constellation of sudden chest pain and cardiovascular collapse with EMD seen in uncontained free wall rupture with tamponade. A right-sided heart catheterization can be performed to confirm tamponade hemodynamics with equalization of diastolic pressures, if the echocardiogram is not diagnostic.

Pericardial tamponade. Low QRS voltage and electrical alternans are characteristic findings of tamponade.

***e*TABLE 19.4.1** SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUE OF DIFFERENT VARIABLES FOR THE DIAGNOSIS OF SUBACUTE VENTRICULAR WALL RUPTURE

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Hypotension	93.9	81.5	12.2	99.8
Cardiac tamponade	69.7	99.5	79.3	99.2
PE by echocardiography				
5 mm	100	92.8	27.5	100
10 mm	78.8	98.2	54.2	99.4
15 mm	54.5	99.5	75	98.8
IP echocardiography	97	92.8	36	99.9
Wall compression				
RAWC	97	98.3	60.4	99.9
RVWC	87.9	99.1	72.5	99.7
Electromechanical dissociation	21.2	99.7	70	97.7
Hemopericardium (pericardiocentesis)	100	76.9	81.2	100
PE 5 mm + IP echoes	97	98.4	61.5	99.9
PE 5 mm + IP echoes + RAWC + RVWC	84.8	99.6	84.8	99.6
Tamponade + PE >5 mm	69.7	99.8	88.5	99.2
Tamponade + PE + IP echoes + RA or RVWC	66.7	99.8	91.7	99.1

IP, intrapericardial; PE, pericardial effusion; RA, right atrium; RAWC, right atrial wall compression; RVWC, right ventricular wall compression; Tamponade, hemodynamic criteria for cardiac tamponade. From Lopez-Sendon J, Gonzales A, Lopez DeSa E, et al. Diagnosis of subacute ventricular wall rupture after acute myocardial infarction: sensitivity and specificity of clinical, hemodynamic, and echocardiographic criteria. *J Am Coll Cardiol* 1992;19:1145–1153, with permission.

Management

Early recognition of subacute rupture with echocardiography is critical for early intervention before uncontained intrapericardial hemorrhage and acute tamponade. Pericardiocentesis has been used to confirm that effusion is hemorrhagic and to relieve tamponade. However, we recommend emergency open drainage and repair, when possible, for subacute rupture with subacute tamponade. A stabilized patient with temporary sealing of the rupture site by thrombus on the epicardial surface is at risk for dislocation of the thrombus and precipitation of acute tamponade. Surgical repair is often successful and is accepted therapy (360,361). That subacute rupture is accessible to surgical repair is not in dispute. Unfortunately, the diagnostic criteria are not specific, and the decision to undergo surgical exploration frequently has to be made on the basis of a high index of clinical suspicion without definitive documentation of a site of rupture. Echocardiography may be helpful with the demonstration of an effusion, RV and RA compression, and shaggy, intrapericardial echo densities consistent with thrombus, at times visualized as a thrombus on the epicardial surface of the heart. Whether coronary angiography should be performed first, enabling revascularization and rupture repair to be performed together, is determined by the stability of the patient. Unstable, hypotensive patients should have emergency repair. Patients with pseudoaneurysms are typically stable enough to have coronary angiography performed first. Pseudoaneurysms also require surgical repair, as they are at risk for rupture. Whether surgical intervention should be undertaken for acute free wall rupture with acute tamponade and EMD remains controversial because of the dismal survival rates and extensive consumption of resources.

Video 19.9 Ventriculography of a contained rupture of the left ventricle (false aneurysm). Contrast injection reveals a noncontractile portion of the left ventricular silhouette that fills with contrast but does not clear. This is consistent with a contained rupture of the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Acute Mitral Regurgitation

Pathophysiology

An autopsy study (362) in the precardiac surgical era established that among patients dying of papillary muscle rupture, the extent of LV infarction was relatively small; approximately one-half of patients had single-vessel disease, the annulus was usually not involved, and there was a marked predominance of inferior infarcts.

The conclusions that were drawn had major potential implications for surgical repair; patients dying of papillary muscle rupture died from MR and not from primary pump failure. The striking predominance of inferior infarcts in this autopsy study and in other studies (363) underscores the consequence of the vulnerability of the posteromedial papillary muscle because of its single blood supply from the posterior descending coronary artery, which is in contrast to the dual blood supply from both the LAD and left circumflex arteries to the anterolateral papillary muscle. Rupture of the papillary muscle may be partial or complete, but either condition results in severe MR (Fig. 19.9). These pathophysiologic features and, in particular, the limited extent of LV necrosis, highlight the potential for excellent long-term results from surgical correction and for the inefficacy of medical therapy (362,364).

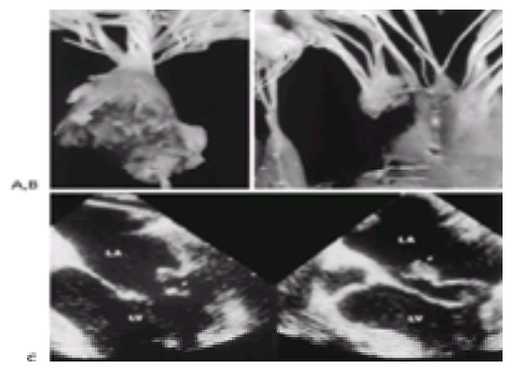


FIGURE 19.9 A, **B:** Examples of a ruptured belly of a papillary muscle **(A)** and a partial rupture **(B)** following acute myocardial infarction. **C:** The utility of transesophageal echocardiography. The ruptured belly of the papillary muscle can be seen prolapsing into the left atrium (LA) during systole and in the left ventricle

(LV) during diastole. (Pathology specimens courtesy of Dr. W. D. Edwards.)

There are multiple mechanisms by which MR can occur without papillary muscle or chordal rupture. One mechanism is ischemia causing transient papillary muscle dysfunction and an adjacent regional wall-motion abnormality, which alters the alignment of the mitral valve apparatus. An alternative explanation implicates infarct expansion and LV dilation (365,366). MR of sufficient severity to cause hemodynamic decompensation may be caused by (a) dilation of the mitral valve annulus secondary to LV enlargement; (b) papillary muscle dysfunction with an associated severe, ischemia-induced regional wall motion abnormality adjacent to the insertion of the papillary muscle; (c) partial or complete rupture of the head or belly of a papillary muscle; or (d) rupture of the head of a chordae tendineae (362) (Fig. 19.9).

Clinical Profile

Incidence, Patient Characteristics, and Prognosis

Acute MR often develops during the course of MI, and the frequency of a murmur during hospitalization has been reported to be 20% to 55% (367). Transient MR is common during the early phase of acute MI and is not usually the cause of hemodynamic compromise. Angiographic studies (368,369) reported incidences of MR of 13% and 18% within hours of MI, respectively; 13% of patients entering phase I of the TIMI trial (368) had MR documented on left ventriculography, and it was clinically silent in nearly all patients. When sought by Doppler echocardiography, a frequency of 39% has been reported (367).

MR is associated with a higher incidence of prior MI, infarct extension, recurrent chest pain, CHF, old age, and female gender. Nonetheless, in many series, irrespective of the methods of diagnosis, the presence of MR in a postinfarct patient has been associated with a highly significantly poorer prognosis. Although it would be intuitive to assume that the adverse effect of MR is mediated by the additional hemodynamic load it imposes on the left ventricle, even mild MR is associated with an increase in mortality (368,369). In one study (368), this was a powerful independent predictor of mortality. Possible mechanisms include an association between abnormal LV geometry, manifesting as an increase in sphericity leading to malalignment of the structures making up the mitral valve apparatus, and MR (366,370). This, in turn, may increase the hemodynamic load on the residual noninfarcted myocardium with a detrimental effect on long-term outcome and the development of CHF and ischemia, particularly in patients with multivessel disease.

Acute severe MR was the cause of shock in 7% of patients with cardiogenic shock complicating MI in the SHOCK Trial Registry (177,371) (Fig. 19.5). Compared with those with LV failure, MR patients were more often female and had inferior and posterior infarcts. Although the EF was higher in patients with MR, the mean EF for those in shock was only 37%. The in-hospital mortality (55%) was similar to those with shock caused by LV failure (59%) (177).

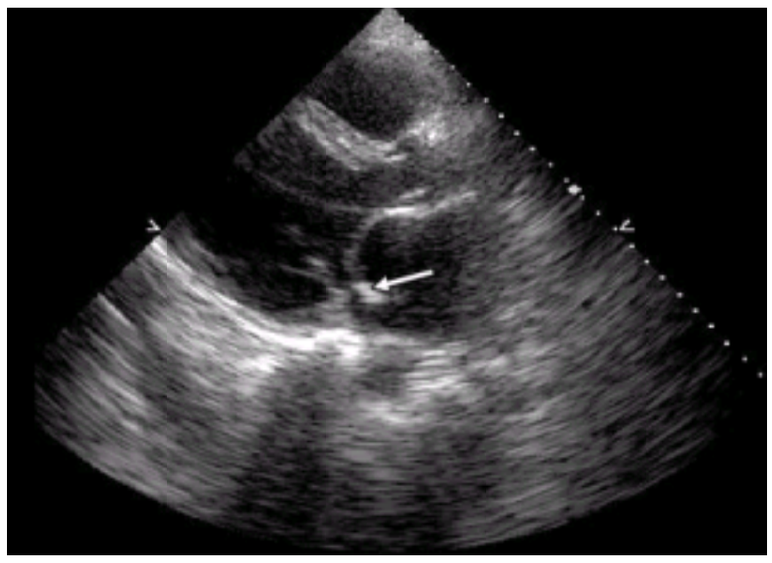
Clinical Presentation and Diagnosis

The clinical picture of acute papillary muscle rupture is characterized by the sudden onset of LV failure, hypotension, or both. Although older studies reported the onset approximately 2 to 7 days post-MI (362), the median time in the SHOCK Trial Registry is 22 hours (25%, 75%: 2, 36 hours) (371). As with other locations of myocardial rupture, thrombolytic therapy is associated with a shift in the time course to earlier occurrence, with an overall reduced incidence. Other clinical findings and physical examination are nonspecific. The apex beat may be dyskinetic, and heart sounds are usually soft, muffled, or masked by the auscultatory features of severe pulmonary edema. Accentuated pulmonary component of the second heart sound caused by pulmonary hypertension is often not appreciable. A harsh, but relatively short, systolic murmur typically is heard at the apex and left sternal edge; a thrill is uncommon. It should be strongly emphasized that the murmur may be soft or even absent as a result of the early pressure equalization between the left ventricle and left atrium caused by severe regurgitation into a nondilated atrial chamber and low-flow state. The key to the diagnosis is a heightened index of clinical suspicion, which should always be entertained in any patient with an inferior MI, particularly a first MI, who is hemodynamically compromised, particularly in the absence of any identifiable cause (e.g., an arrhythmia, PE, or tamponade) (Table 19.5).

Prior myocardial infarction
High-grade atrioventricular block/bradyarrhythmias
Acute severe mitral regurgitation
Right ventricular infarction (characterized by an absence of pulmonary edema)
Left ventricular pseudorupture/subacute rupture
Pulmonary embolism
Acute interventricular septal rupture

TABLE 19.5 DIAGNOSTIC CONSIDERATIONS IN PATIENTS WITH INFERIOR MYOCARDIAL INFARCTION AND CONGESTIVE HEART FAILURE OR CARDIOGENIC SHOCK

Two-dimensional, and often transesophageal, echocardiography is a pivotal noninvasive diagnostic tool (372,373) (Fig. 19.9). Identification of the freely mobile head of the papillary muscle either in the left atrium or the left ventricle or of a flail mitral leaflet is diagnostic (373). The addition of color flow imaging, with the aim of semiquantitation of the severity of MR is frequently helpful, and, in one series, it correctly identified MR in all patients. Transesophageal echocardiography may be particularly advantageous in patients on mechanical ventilation because transthoracic echocardiography may not provide adequate images. An extremely helpful clinical feature, particularly when the mitral valve apparatus is not well visualized, is the demonstration of reasonably well-preserved or even hyperdynamic LV function in the face of pulmonary edema, cardiogenic shock, or both. This constellation of clinical and echocardiographic features should point toward a mechanical complication as the putative cause of pulmonary edema or shock and is an indication for further diagnostic or confirmatory tests (e.g., left ventriculography). Those in shock often have depressed LV function (371). Documentation of tall V waves on PCWP tracing catheterization is a helpful finding but has limitations (374), and the role of PA catheterization as a diagnostic modality has been superseded by advances in echocardiography. Nonetheless, the former may be useful in monitoring the effects of pharmacologic therapy. Ventriculography may be required to confirm the severity of the MR in patients for whom surgery is being considered.



Parasternal long-axis view of a papillary muscle rupture after myocardial infarction. Note the piece of papillary muscle attached to the tip of the anterior mitral leaflet as it flails into the left atrium (demonstrated by the arrow).

Video 19.10 Parasternal long-axis view of a ruptured papillary muscle after myocardial infarction. Note the bright mass (papillary muscle) attached to the tip of the anterior mitral leaflet as it flails into the left atrium. This resulted in severe mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Management

The cornerstone of management is prompt diagnosis and aggressive medical therapy with a view to emergency cardiac surgery. The natural history of medically treated chordal or papillary muscle rupture, whether partial or complete, is poor and characterized by a volatile, unpredictable clinical course even when medical therapy results in initial stabilization (362). Sudden hemodynamic deterioration is frequent, and the consequences are usually catastrophic. There are several potential explanations, including (a) the progression from partial to complete rupture; (b) ischemia in the noninfarcted region of the heart; (c) development of adult respiratory distress syndrome caused by the markedly elevated left atrial pressures; (d) infarct extension as a result of tachycardia, hypotension, and hypoxia, which increase myocardial oxygen requirements and reduce myocardial oxygen supply; and (e) acute RV failure. Irrespective of the specific mechanisms underlying subsequent deterioration, the frequency of its occurrence should serve as a reminder that a period of apparent stabilization should not lull one into a sense of false security; rather, it should be seen as a window of opportunity before initiating prompt emergency cardiac surgery.

Video 19.11 This is an intraoperative transgastric transesophageal view of an ischemic ventricular septal defect after an acute inferior myocardial infarction. Note the location of the large defect in the inferior septum. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

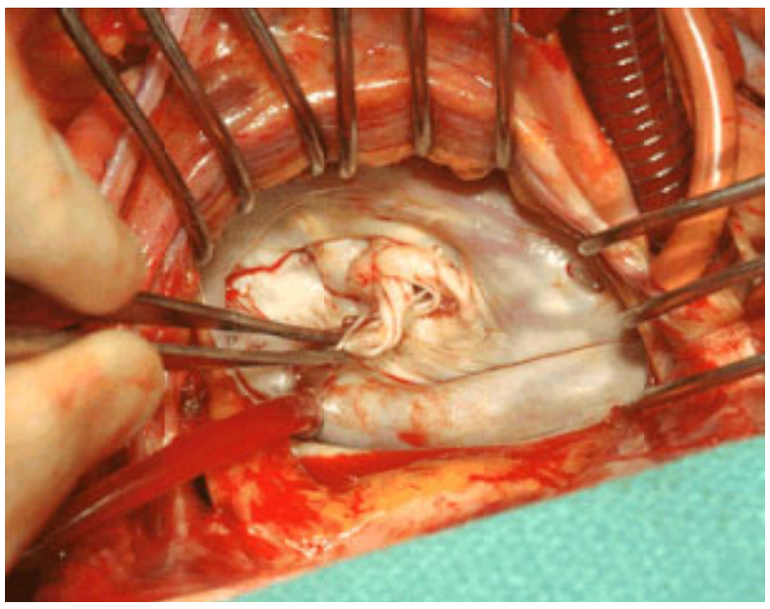
Video 19.12 Color Doppler view of a post infarct ventricular septal defect in the inferior septum. Note the color flow thru the large defect. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Earlier surgical studies (375) reported that results of delayed surgical intervention were superior to those obtained with emergency surgery; however, they did not take into account the attrition rate of more severely ill patients who died awaiting surgical intervention. The most logical approach—which may be associated with an increased surgical mortality but which has the potential to improve *overall* salvage—is to proceed with immediate cardiac surgery after confirming the diagnosis (364). Stabilization should be attempted before induction of anesthesia, using vasodilators, diuretics, intermittent positive pressure ventilation, with frequent use of positive end-expiratory pressures and IABP. Use of coronary angiography remains an issue of debate but is advisable providing hemodynamics are suitable, because the information obtained may be helpful in assessing whether coronary bypass surgery in conjunction with mitral valve replacement is necessary. Nevertheless, decisions must be individualized according to the patient's condition and the imperatives of the surgeon. Of those in shock, approximately 40% have three-vessel and 10% have left main disease (180).

Studies (364,376) have demonstrated a perioperative mortality of less than 10% and a 1-year survival of approximately 90%; one study reported a 64% 7-year survival rate among perioperative survivors. The underlying, relatively small size of the infarcted area and the fact that surgery does not involve the area of necrosis contribute to the relatively low perioperative mortality. However, the presence of cardiogenic shock is often associated with depressed LV and RV function, and mortality is higher (39%) (371). However, those treated medically had a much higher mortality (71%) (adjusted odds ratio for death with surgery 0.30, CI 0.13 to 0.73; $p = .008$). The duration of shock before surgery likely affects outcome by virtue of multisystem compromise. Surgery before the onset of shock is therefore advised.

One would intuitively expect that successful surgical correction of a mechanical defect in patients with reasonably well-preserved LV function would be in most cases followed by a smooth perioperative course. However, the contrary holds true. In a small Mayo Clinic series (364) of nine patients, seven of whom had papillary muscle rupture and two who had interventricular septal rupture, despite a 0% perioperative mortality, the average duration of IABP support in eight patients was 3.1 days (range, 1 to 5 days). The average duration of inotropic support was 5 to 7 days (range, 1 to 9 days), and three patients required prolonged respiratory support, ranging from 17 to 30 days. The explanations for such complex postoperative courses remain unclear, but they may relate to myocardial stunning and the consequences of markedly elevated, preoperative filling pressures resulting in massive transudation of fluid into the pulmonary interstitium followed by a lag phase before lung compliance and oxygenation normalize (i.e., a form of adult respiratory distress syndrome).

Papillary muscle rupture remains a potentially catastrophic and fatal complication of acute MI; however, there is a window of opportunity for emergency surgical correction with the encouraging prospect of excellent long-term survival and a return to an active life.



Intraoperative field demonstrating a mitral valve with a torn papillary muscle prolapsing across the mitral valve into the left atrium. The surgeon has the papillary muscle in forceps demonstrating the chordae attached to the posteromedial commissure, predominantly attached to the anterior mitral leaflet. (The patient's head is to the left of the screen and feet to the right.)

Surgical pathology specimen demonstrating a torn papillary muscle seen to the lower right of the screen, attached via chordae to a portion of the anterior mitral leaflet. Note the torn "ragged edges" at the bottom of the papillary muscle head.

In contrast, patients with moderate or severe MR in the face of severely compromised LV function (i.e., EF <30% to 35%), in whom clear evidence of papillary muscle or chordal rupture is not documented by echocardiography, pose a particularly difficult problem in diagnosis and management. The mechanism of MR in these patients may be underlying LV failure with dilation of the annulus or malalignment of the mitral valve apparatus caused by a severe regional wall motion abnormality adjacent to a papillary muscle or multiple areas by dyssynergy (366). A more prudent approach in these patients is aggressive medical therapy, including high-dose vasodilators and perhaps IABP. This may give time for LV function to improve and for additional diagnostic testing to help avoid the dilemma of a surgical procedure in the absence of a clearly delineated correctable cause of CHF. Factors to be addressed before performing surgery are the extent and reversibility of LV dysfunction, the potential for revascularization to improve LV size and function, the degree of MR, and the extent of structural abnormalities of the mitral valve apparatus.

Acute Interventricular Septal Rupture

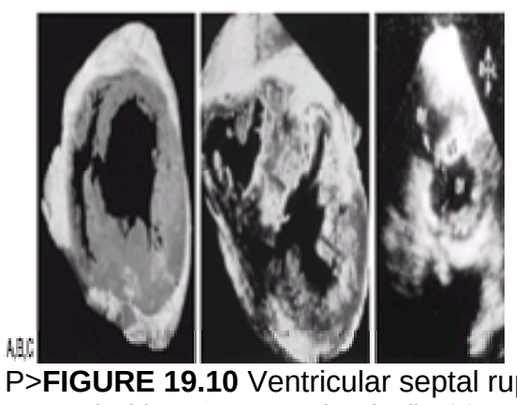
Incidence, Timing, Clinical Profile, and Prognosis

Acute rupture of the interventricular septum occurs in approximately 1% to 3% of all infarcts (377). In the GUSTO 1 trial in which all patients received thrombolytic therapy, the incidence was 0.2% (378). In the SHOCK Trial Registry, VSR was the etiology of shock in 3.9% of those with shock complicating MI (Fig. 19.5). Patients with VSR are more often older, female, with less prior MI and comorbidity compared with those without mechanical complications of MI (379) and with those with shock caused by LV failure. Older reports suggested that rupture occurred several days post-MI. However, in GUSTO 1 the median time was 1 day (378). When VSR causes shock, it occurs early after MI onset. The median time was 16 hours (25%, 75%: 2, 45 hours) for patients in the SHOCK Trial Registry. Once shock has developed, the prognosis is grim (87% mortality) (379).

Pathophysiology

Interventricular septal rupture is nearly always a complication of a transmural MI, particularly a first MI; however, in contrast to papillary muscle rupture, anterior or anterolateral infarcts are slightly more frequent than are inferior infarcts (378,379,380,381 and 382). A history of prior angina is uncommon, and hypertension may be a predisposing factor (378,382). Concomitant involvement of other structures including the papillary muscles and free wall of the left and right ventricles has been well described (381). Septal rupture may occur in patients with single-vessel disease, but multivessel disease is common. Two- or three-vessel CAD was present in 43% and 31%, respectively, in the SHOCK Trial Registry (379) and in 51% in GUSTO (378).

Interventricular septal rupture has been categorized morphologically into simple and complex forms (Fig. 19.10). The former is a discrete defect with a direct through-and-through communication across the septum, usually the apical septum. The ventricular openings are therefore at the same level on both sides of the septum. Complex ruptures are characterized by extensive hemorrhage around irregular, serpiginous tracts that extend in different directions within extensive necrotic tissue; they more frequently involve the inferobasal septum as a complication of inferior MIs. Complex ruptures are more likely to involve associated structures including extensive areas of the right ventricle (381).

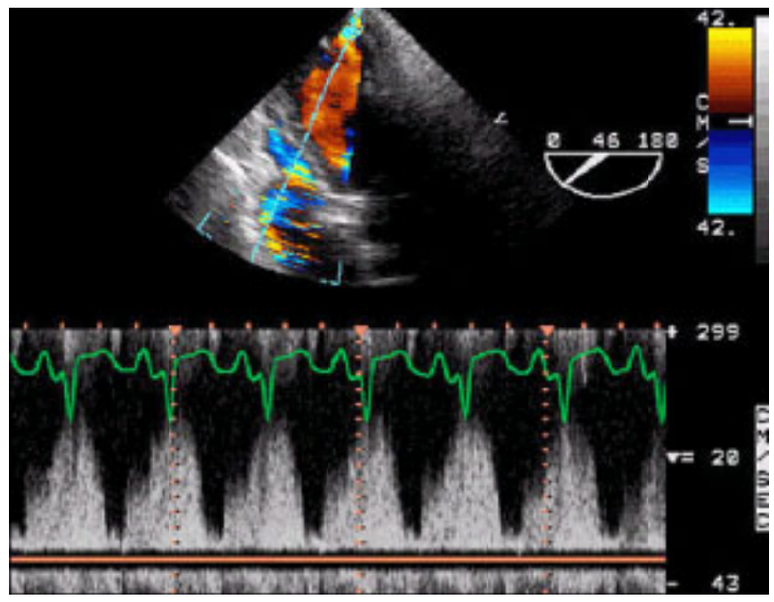


P>**FIGURE 19.10** Ventricular septal rupture complicating acute myocardial infarction. This illustrates two types of rupture of the ventricular septum, which in 53 autopsied hearts were simple (in 28 patients) or complex (in 25 patients). **A:** Simple rupture is a direct through-and-through defect. **B:** Complex ruptures are associated with serpiginous dissection tracts, which are remote from the primary site of tear of the ventricular septum. Complex ruptures are more frequent with inferior infarcts involving the inferobasal portion of the septum and may be associated with rupture of a second structure, such as the free wall of the right ventricle (RV) in this patient. **C:** The marked utility of two-dimensional echocardiography in the diagnosis, illustrating a parasternal short-access view using transthoracic echocardiography. The echocardiogram illustrates a complex ventricular septal rupture. LV, left ventricle; PW, posterior wall; VS, ventricular septum. (From Edwards BS, Edwards WD, Edwards JE. Ventricular septal rupture complicating acute myocardial infarction: identification of simple and complex types in 53 autopsied hearts. *Am J Cardiol* 1984;54:1201–1205, with permission.)

Clinical Presentation and Diagnosis

The typical presentation is the acute development of shock and pulmonary edema in the face of severe right-sided heart failure and a new systolic murmur. The murmur is usually loud and pansystolic and is accompanied by a thrill in 50% of patients. The distinction between papillary muscle rupture and acute interventricular septal rupture can be made clinically on the basis of the intensity and characteristics of the murmur and the presence of a thrill and right-sided heart failure in most patients with septal rupture. Nonetheless, physical findings may be unreliable, particularly in a low-output state. PA catheterization is helpful in diagnosing acute VSR with demonstration of a step-up in oxygen saturation in the right ventricle and in the PA in patients with acute VSR. The location of the step-up is important, whether it is in the right ventricle or in the proximal artery, because there is a report of a step-up in oxygen saturation in the peripheral PAs in a patient with severe, acute MR. PA catheterization is less helpful in diagnosing acute MR by documenting large V waves, which are nonspecific (374).

Two-dimensional and Doppler echocardiography have become the mainstays of diagnosis, and PA catheterization has been relegated to monitoring the results of therapy, as opposed to its previous role as a diagnostic modality (214). The use of transesophageal echocardiography, particularly in severely ill patients on ventilators, is well documented. In one series, two-dimensional echocardiography visualized the defect in 40% of patients, and the addition of Doppler color flow mapping correctly detected 100% of VSD with accurate localization in 98% of patients (214).



Doppler recording of flow through an ischemic ventricular septal defect before surgical repair.

In summary, echocardiography is highly sensitive and specific in assessing acute interventricular septal rupture. The defect is almost invariably localized. In papillary muscle rupture, however, echocardiography documents MR with a high degree of accuracy, but the specific anatomic abnormality causing the MR (i.e., partial or complete papillary muscle rupture, rupture of the head of the chordae tendinea, or dilation of the mitral annulus, or a malalignment of the papillary muscle caused by localized dyssynergy) may not always be evident. Nonetheless, severe MR, cardiogenic shock, or severe CHF, particularly in patients with first inferior MIs, and reasonably well-preserved LV function (i.e., EF ≥35% to 40%) should alert the clinician to the probability of a mechanical cause and, by implication, rupture involving the mitral valve apparatus.

Among patients with acute septal rupture, left-sided heart catheterization and left ventriculography confirm the diagnosis, but the decision to employ these diagnostic modalities depends on the patient's hemodynamic stability and the need to identify the coronary anatomy in the event that concomitant coronary artery bypass surgery is being considered.

Management

The key to management is prompt diagnosis, an aggressive approach to stabilization, rapid angiography, and surgery. Medical therapy consists of diuretics, vasodilators, and frequently inotropes in addition to intermittent positive-pressure ventilation and IABP in patients with severe CHF or cardiogenic shock. As is the case with papillary muscle rupture, initial stabilization on medical therapy may provide only a temporary respite.

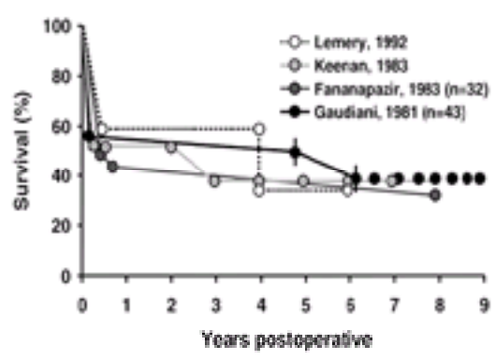
A small, asymptomatic VSR may be managed without surgery. For most patients with VSR who are severely symptomatic, the need for surgical repair has never been questioned, but its timing has been an issue of debate (383). Patients with interventricular septal rupture frequently have more extensive infarcts than do patients with papillary muscle rupture, and involvement of the RV and LV free walls with extensive necrosis in the inferobasal septum, particularly in patients with inferior infarcts, contributes to a high surgical mortality (384) (Fig. 19.10). Approximately 30 years ago, initial reports (385) demonstrated that delaying surgery for several weeks to allow time for healing of friable tissue in the infarcted area reduces surgical mortality. Nonetheless, it is likely that the lower surgical mortality was the result of a selection bias toward patients who were less ill and able to survive for several weeks. However, the onset of shock is unpredictable, and once shock develops, mortality is high (210).

The current approach, therefore, is to advocate early or emergency surgery in all patients, preferably before decompensation (90). It must be accepted that an aggressive approach may be associated with a high perioperative mortality but may have the potential for an overall reduction in mortality (379,382). This is particularly relevant in patients with cardiogenic shock as opposed to pulmonary edema alone in whom short-term survival with medical therapy is extremely poor and among whom apparent stabilization is usually transient (380,386,387,388,389 and 390).

There is little consensus in the literature (391) regarding the need for concomitant coronary revascularization during surgical repair of postinfarction VSR. Theoretically, revascularization of residual and viable but ischemic myocardium should facilitate weaning the patient off cardiopulmonary bypass and should accelerate recovery during the perioperative period as well as provide a beneficial effect on long-term outcome. There are, however, no prospective studies documenting the merits of such an approach. On balance, preoperative coronary angiography with a view to concomitant CABG appears reasonable and may be indicated, provided the patient is sufficiently stable as to tolerate the procedure.

David et al. (392) described the use of large pericardial patches without infarctectomy to simplify surgical management of VSR. Endocardial patch with infarct exclusion leaves the RV geometry unchanged and reshapes the LV wall and interventricular septum. The excellent clinical outcome in this series was attributed, therefore, to LV remodeling and decreased RV damage. Moreover, the rate of recurrent septal defects with this technique has been low. However, there are no randomized trials comparing this technique with other approaches.

Overall, perioperative mortality among patients with interventricular septal rupture is much higher than among those with papillary muscle rupture or shock caused by LV failure (177,379). This is particularly the case in patients with complex septal ruptures and inferior MI in whom extensive necrosis of the right ventricle contributes to a mortality of approximately 70% in contrast to approximately 30% in patients with anterior infarcts and simple apical ruptures (380,382,383,384,385,386,387,388,389,390,391,392 and 393). For patients in shock, the operative mortality in the SHOCK Trial Registry was 81% versus 95% for those without surgery. Five of six surgical survivors had anterior MI. Nonetheless, excellent long-term results have been obtained in perioperative survivors including a low late mortality and well-preserved functional capacity (380,386,388,393,394 and 395) (eFig. 19.10.1).



***e*FIGURE 19.10.1** Cumulative survival after surgery for septal rupture in acute myocardial infarction. This figure demonstrates the high perioperative mortality of 40% to 60%, but an encouragingly low late mortality thereafter. (Data from references 386 and 393–395.)

In summary, the approach to patients with acute septal rupture and hemodynamic decompensation is rapid stabilization and prompt surgery. Rarely, patients with small shunts and without CHF who remain hemodynamically stable may be managed medically over the long term.

MISCELLANEOUS COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

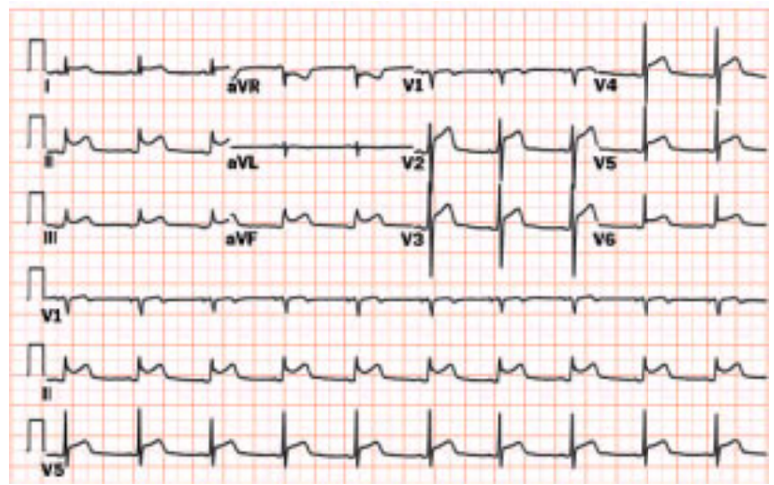
Pericarditis

Inflammation of the pericardium may occur acutely during acute MI and may be largely localized to the pericardium adjacent to the infarction, or it may occur as a

delayed, more generalized inflammatory syndrome (i.e., Dressler's syndrome). Pericarditis associated with acute infarction results from the infarction extending to the epicardial surface of the heart, with an associated inflammatory response.

Diagnosis

The diagnosis is made clinically by history, physical examination, and ECG. Pericarditic chest pain is typically sharp, severe, substernal pain that may radiate to the neck, shoulders, and back, increasing with inspiration and on reclining. Patients with pericarditis are often severely distressed and uncomfortable. A typical three-component pericardial friction rub may be heard but may be absent when effusion develops. The typical ECG changes of pericarditis are uncommon when the pericarditis is localized to the infarct zone (396). Nonetheless, persistent or new ST-segment elevations in multiple leads may be seen when pericarditis is more generalized. Pericarditis should heighten the index of suspicion for subacute rupture and warrants echocardiography. Atypical T-wave evolution, either with T waves remaining consistently positive for 48 hours or longer after onset of acute MI or with initially inverted T waves gradually becoming positive deflections, has been described in postinfarction pericarditis (358,397). An effusion may or may not be present on echocardiography; presence of effusion is more common than is clinical pericarditis (398). Most cases of acute pericarditis are diagnosed within 3 days of acute MI (399) but may occur as early as day 1.



Acute pericarditis. Note diffuse, marked ST-segment elevation with PR-segment elevation in lead aVR.

Incidence

Clinical studies (399) report a higher incidence of pericarditis in patients with Q-wave MI than in patients with non–Q-wave MI; it is more common with large infarcts. Its clinical incidence varies depending on the diagnostic criteria. Most studies require a pericardial friction rub to be present. Large clinical trials such as GISSI-1 (85) define pericarditis as either a friction rub or as typical pericarditis chest pain. The incidence of postinfarction pericarditis has decreased by approximately 50% in patients treated with thrombolytic therapy (85,131,195,396,399,400) (Table 19.6). Reperfusion therapy results in smaller infarcts that less often extend to the epicardial surface, resulting in less localized pericarditis.

Prethrombolytic era	Reference	Number	Incidence (%)		
Krainin	396	423	7.3		
MILIS	399	760	20.0		
			Q-wave MI	Non–Q-wave MI	*p* value
			25.0%	5.0%	<.001
			Incidence (%)		
Thrombolytic era	Reference	Number	Control	Thrombolysis	*p* value
Streptokinase	152	503	17.4	7.0	0.0004
GISSI-1	85	11,483	12.0	6.7	<.001
ECSG	400	721	11.0	6.3	<.005
AIMS	131	1,258	15.3	6.9	<.001
ASSENT-4	408	16,949	—	2.0	
			Incidence (%)		
Primary PTCA			PTCA	Thrombolysis	*p* value
PAMI	203	396	1.5	1.5	0.31

PTCA, percutaneous transluminal coronary angioplasty

TABLE 19.6 PERICARDITIS IN ACUTE MYOCARDIAL INFARCTION (MI): INCIDENCE

Pericardial Effusion

Pericardial effusions occur relatively frequently after acute MI (incidence, up to 45%) (398). They are more common with large, anterior, or both large and anterior infarcts and when CHF is present. They are typically asymptomatic. If tamponade develops, it is usually caused by free wall rupture or hemorrhage into the pericardium. Effusions most frequently occur without clinical pericarditis. Conversely, patients with clinical pericarditis frequently do not have associated effusion.

Risk for Hemorrhagic Effusion and Cardiac Tamponade

Widespread use of thrombolysis, anticoagulation, and ASA has raised concerns regarding the potential for hemorrhagic effusions and cardiac tamponade. A series (398) of 192 patients with first Q-wave MIs included 152 patients treated with thrombolytic therapy; serial echocardiography taken over 3 years revealed a 43% incidence of pericardial effusion and an 8% incidence of a pericardial friction rub or typical pericarditic chest pain. Patients treated with thrombolytic therapy less frequently had effusion and clinical pericarditis, and when effusion occurred, it was of similar size compared with that in patients who were not treated with thrombolytic therapy. There were no cases of tamponade in this series. Similarly, there were no cases of tamponade reported by the Thrombolysis and Angioplasty in Myocardial Infarction investigators (401) in 810 patients examined, including 5% of patients who developed pericardial rubs despite anticoagulation following thrombolysis. The large, placebo-controlled, randomized trials (293) do not demonstrate increased events consistent with tamponade including shock and EMD in those patients treated with thrombolytic therapy. Nevertheless, in the literature (402,403) there are several cases of hemorrhagic effusion with localized or generalized cardiac tamponade after thrombolytic administration. Therefore, when anticoagulation is continued in patients who have postinfarction pericarditis or pericardial effusions, careful monitoring for worsening pericardial effusions and tamponade is required.

Dressler's Syndrome

Dressler's syndrome is clinically indistinguishable from postcardiotomy syndrome, and both have been termed *postcardiac injury syndrome* (404). Some have argued that all forms of postinfarction pericarditis are related (404). Dressler's syndrome consists of clinical pericarditis with fever, leukocytosis, and a high erythrocyte-sedimentation rate and may be associated with pulmonary infiltrates, effusion, or both. It develops days to months after MI. The natural history is generally benign, but occasionally it can lead to tamponade or constrictive pericarditis. The postcardiac injury syndromes have been associated with antiheart antibodies. Viral infection has been proposed as a predisposing factor. Cardiac tamponade is uncommon and may occur with or without anticoagulant therapy (404). A prospective study (405) of 201 patients—all of whom were treated with thrombolytic therapy and who were followed for a minimum of 3 months for signs of Dressler's syndrome—reported this syndrome in only one patient, who had no evidence of reperfusion. It appears that the incidence of Dressler's syndrome has been dramatically reduced in the reperfusion era for reasons that remain unclear. A less striking reduction in early postinfarction pericarditis has been noted in patients undergoing reperfusion therapy (Table 19.6). Pericarditis remains associated with large infarctions.

Treatment

Treatment is only needed for postinfarction pericarditis to relieve symptoms. In a prospective study (406), ASA was equally as effective as indomethacin in relieving symptoms. ASA is strongly preferred over nonsteroidal antiinflammatory drugs or prednisone because of the potential of the latter for exacerbating infarct expansion (406). If nonsteroidal antiinflammatory drugs are used when ASA fails, they should be administered for as short a time as possible, with reassessment after each dose.

Analgesics may be used concomitantly as needed. Corticosteroids should be reserved for refractory cases.

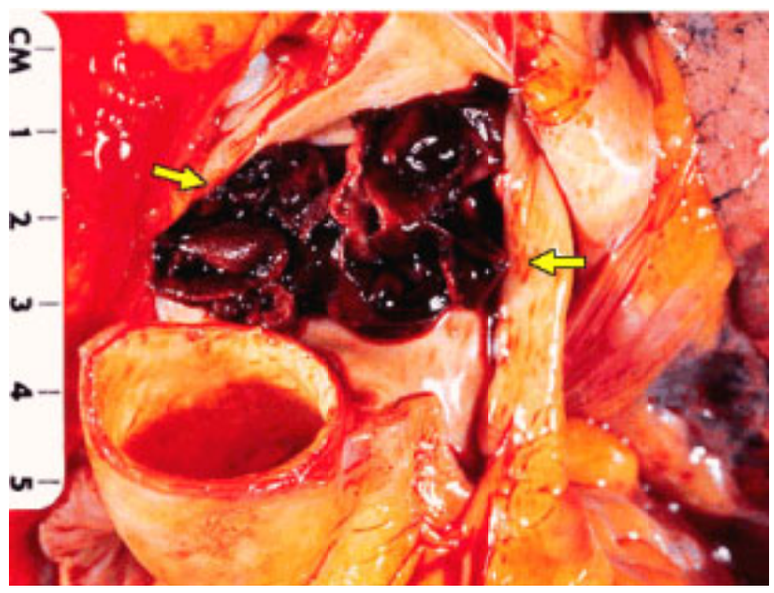
PULMONARY EMBOLISM

Prevention

At present, with early ambulation following MI, frequent use of full-dose i.v. heparin or low-molecular-weight s.c. heparin, thrombolytic therapy, and early hospital discharge, PE is an uncommon complication. However, patients with acute right- or left-sided CHF, elevated central venous pressure, or a low-output state remain at risk for DVT and PE. Furthermore, these patients may remain at bed rest in the cardiac care units for days. Therefore, full-dose heparin is recommended when pump failure complicates acute MI, because there is evidence that it decreases DVT and PE. Low-molecular-weight heparin is efficacious in preventing DVT and PE in other clinical settings and is likely to be efficacious in this setting. Heparin followed by high-dose phenindione resulted in significantly lower rates of PE after MI compared with low-dose phenindione (83). In the Veterans Administration Cooperative Trial (84), heparin followed by warfarin significantly reduced the rate of certain or suspected PE or infarction (7.0% versus 2.8%; $p = .005$). As evidenced by the data from GISSI (85), thrombolytic therapy also reduced the risk for PE, in which the rate of pulmonary thromboembolism was significantly reduced by SK.

Clinical Findings, Diagnosis, and Management

PE after MI can mimic reinfarction, or less frequently pericarditis, pneumonia, or pulmonary hemorrhage, with the constellation of chest pain, ECG abnormalities, and shortness of breath. The chest pain is typically pleuritic, but may be ischemic in nature. ECG abnormalities may include ST elevation or depression, T-wave inversion in the RV leads, V_1, V_2, or II, III, aVF, or all. Massive PE may be confused with acute RV infarction, with hypotension, elevated jugular venous pressure, and clear lung fields. Dyspnea and tachypnea should be present with PE but not with RV infarction unless LV failure is also present. An emergency echocardiogram with Doppler estimation of PA pressures may prove helpful to the diagnosis, followed by a lung scan or pulmonary angiography as needed. A spiral or cine CT scan is highly sensitive and specific for the diagnosis of proximal thrombi, but logistic constraints limit its use. The management of postinfarction PE involves the standard care for PE, with anticoagulation and thrombolysis for massive PE. If PE occurs with anticoagulation, inferior vena cava interruption should be accomplished.



Saddle embolism of the pulmonary artery. The pulmonary artery has been opened via an anterior incision. Multiple fragments of thrombi protrude from the open pulmonary artery and are wedged into both the left and right pulmonary artery branches (*yellow arrows*).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Pump Failure

We now have randomized trial evidence that a direct invasive strategy, with IABP-supported rapid angiography, PTCA, or CABG markedly improves 1-year survival when post-MI shock develops caused by predominant LV failure. The treatment benefit is derived despite comorbidities such as diabetes and despite profound hemodynamic abnormalities. Although the long-term survival is improved by intervention, even successful procedures are associated with high in-hospital mortality, and operators may be reluctant to intervene. Quality improvement measures must track not only procedural death rates but the rate of refusals for interventions based on the high-risk profile. However, when the outcome is grim even with intervention, such as surgery for VSR with inferior MI once shock is present, treatment may be deemed futile.

Reperfusing Occluded Infarct-Related Arteries in Asymptomatic Patients: Any Benefits?

Despite the wealth of data implicating a beneficial effect of an open artery independent of myocardial salvage, the late open artery concept remains a tantalizing but unproven hypothesis. The implications for clinical practice, however, are far reaching. If it could be demonstrated that reperfusion of a closed IRA in asymptomatic patients without stress-induced ischemia reduces mortality or improves LV function, routine angiography in all MI survivors might then be recommended to identify those with an occluded IRA. To accomplish this, a randomized trial is ongoing.

Reinfarction

In contrast to the efficacy of heparin (low-molecular-weight heparin or unfractionated) and GP IIb/IIIa antagonists demonstrated in non–ST-elevation acute coronary syndrome, their role after ST-elevation MI is less clear. Full anticoagulation is recommended for patients treated with t-PA and for those with large anterior MIs and other MI locations complicated by pump failure. Based on beneficial trends and the knowledge that the ulcerated plaque is thrombogenic, for other patients we recommend full-dose i.v. unfractionated or s.c. low-molecular-weight heparin for 48 hours in addition to ASA, 160 mg every day. However, patients at risk for intracranial or other hemorrhagic events should not be fully anticoagulated in an attempt to prevent reinfarction.

GP IIb/IIIa receptor antagonists and low-molecular-weight heparin are superior to i.v. unfractionated heparin in preventing reinfarction in the non–ST-elevation acute coronary syndromes. Their role in ST elevation MI is still being defined. Other antiplatelet agents, such as clopidogrel, have been reported to reduce long-term death rates compared with ASA in patients with vascular disease (149). The efficacy of clopidogrel in reducing short-term reinfarction rates after unstable angina and non–ST elevation has recently been demonstrated (416). The role of these antiplatelet agents in acute ST elevation MI is being evaluated.

When recurrent chest pain with ST reelevation develops after MI, the efficacy of readministering thrombolytic agents versus performing emergency PTCA remains an issue of debate. We recommend emergency PTCA when immediately available. When there is inherent delay, however (e.g., at hospitals that do not perform PTCA), we recommend thrombolytic administration (t-PA, tenecteplase, or recombinant plasminogen activator if SK has been used previously) followed by transfer for coronary angiography and PTCA or CABG.

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THE FUTURE

Pump Failure

Prevention of Pump Failure

Strategies to prevent pump failure in patients at high risk need to be further investigated. Such strategies should include (a) agents that inhibit reperfusion injury (e.g., leukocyte inhibitors, free radical scavengers, and magnesium); (b) metabolic support solutions (e.g., glucose, insulin, and potassium; carnitine; dichloroacetate; sodium-proton pump exchange inhibitors); (c) early coronary angiography and revascularization with and without circulatory support (e.g., IABP); and (d) other strategies to reduce reinfarction, such as newer antiplatelet and antithrombotic agents.

Treatment of Pump Failure

Use of magnesium, metabolic support for the remote, ischemic, and reperfused myocardium, and agents that inhibit reperfusion injury need further evaluation. The role of alternative vasopressors such as the nitric oxide synthase inhibitor L-NMMA and vasopressin should be investigated.

The role of newer LV support devices compared with IABP and criteria for selecting appropriate patients for newer LV support devices need to be defined.

Cardiac Rupture and Left Ventricular Remodeling: Basic Mechanisms

Measures to prevent cardiac rupture in patients at increased risk need to be evaluated. The role of interstitial matrix degradation by metalloproteinases in myocardial rupture should be explored further and metalloproteinase inhibitor evaluated in high-risk patients. Similarly, the effects of disruption of the intercellular collagen struts that link myofibrils with potential slippage of myocytes, infarct expansion, and LV remodeling and the role metalloproteinase inhibitors for patients at risk need to be investigated. Aging and female gender are associated with an increased incidence of rupture and pump failure. The basic myocyte and interstitial myocardial changes that may be associated with such increased incidence need to be elucidated. The development of improved techniques for the noninvasive diagnosis of subacute cardiac rupture is a priority.

In summary, despite the dramatic advances in the treatment of acute MI, reinfarction, pump failure, and myocardial rupture remain major challenges for the future and their basic mechanisms, prevention, and management must be explored and elucidated.

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20

POST–MYOCARDIAL INFARCTION MANAGEMENT

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ERIC J. TOPOL

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The management of acute ST-segment elevation myocardial infarction (MI) has been revolutionized in the past decade. Advances in pharmacologic and mechanical reperfusion therapy have improved the survival of patients who experience MI. As more patients survive the initial myocardial insult, subsequent medical care has increased in importance. An appreciation of pathologic left ventricular remodeling after MI has permitted the study of medications that preserve left ventricular function. The role of plaque stabilization with lipid-lowering therapy has been established. The use of antiplatelet therapy to prevent recurrent atherothrombotic events continues to grow. Appropriate control of risk factors such as diabetes and hypertension remains prominent. Additionally, inflammation has been identified as having a significant role in the pathogenesis of ischemic events. Controversy over noninvasive risk-stratification versus the need for invasive assessment continues, although the pendulum seems to be swinging toward aggressive management. Despite impressive technological advances, lifestyle modification remains a key component of secondary prevention after MI.

GLOSSARY

Acute coronary syndrome: Plaque rupture leading to various degrees of coronary artery thrombosis. Most often refers to unstable angina and non–Q-wave myocardial infarction, although sometimes meant also to include ST-segment elevation myocardial infarction.

Non–Q-wave myocardial infarction: Older nomenclature for myocardial infarction believed to be caused by nonocclusive coronary arterial thrombus. Now often referred to as *non–ST-segment elevation myocardial infarction*.

Q-wave myocardial infarction: Older term for myocardial infarction meant to imply transmural myocardial necrosis.

Remodeling: The process of left ventricular cellular and geometric adaptation to compensate for damage sustained during myocardial infarction.

ST-segment elevation myocardial infarction: Myocardial infarction resulting from coronary arterial occlusion by thrombus, manifested on the surface electrocardiogram as ST-segment elevation.

GENERAL PRINCIPLES

Historical Perspective

Because of the use of fibrinolytic therapy and, in communities where it is available, primary percutaneous intervention, the past decade has seen dramatic decreases in deaths resulting from MI. However, in the recent Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries III (GUSTO III) trial of acute MI, in which two different fibrinolytic regimens were tested, the 1-year mortality rate was still 11% (1). In fact, the additional 4% mortality rate observed in GUSTO III between 30 days and 1 year was quite high, illustrating the importance of initiating secondary preventive efforts during a patient's hospitalization for acute MI. Outside the context of clinical trials, mortality rates are even higher, with a 9.4% in-hospital mortality rate seen in the National Registry of Myocardial Infarction (NRMI) in 1999 (2). Therefore, despite improved therapies for acute MI, risk-stratification and secondary prevention are still critically important in improving the outcomes of patients with acute MI by decreasing the likelihood of recurrent ischemic events, in both the short term and the long term.

Pathophysiology

An appreciation of the pathophysiology of acute MI is necessary to understand how specific therapies may be used to target different components of the cascade of events that lead to acute MI. Plaque rupture, arterial thrombosis, myocardial necrosis, and adverse left ventricular remodeling are part of the continuum that leads to

symptomatic manifestations and long-term sequelae of acute MI.

Plaque Rupture and Thrombosis

The inciting event of acute MI is plaque rupture. Numerous factors, which are only partially understood, determine the occurrence of plaque rupture in a susceptible individual. Production of matrix metalloproteinases leads to degradation of the shoulder of a coronary plaque, leading to exposure of its lipid-rich core to flowing blood (3,4 and 5). This triggers formation of platelet-rich thrombus. When the degree of thrombus is flow-occlusive, ischemia occurs, and myocardial stunning and necrosis follow.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) may exert part of their benefit by decreasing the lipid content of plaques, making them less prone to rupture (6,7). Antithrombotic therapy decreases the tendency for occlusive thrombus formation. Antiplatelet therapy, in particular, decreases platelet aggregation at the site of ruptured plaque. Thus, in concert, statin therapy and antiplatelet therapy decrease the chance of MI occurring.

Left Ventricular Remodeling

When occlusive thrombus has developed and caused ischemia for several hours, myocardium is damaged. When this necrosis is transmural, the left ventricle may undergo a process of remodeling. This adaptation occurs at both the cellular level and the whole-organ level (8). Angiotensin-converting enzyme (ACE) inhibitors greatly decrease this process of adverse remodeling. This explains, at least in part, the marked benefits ACE inhibition has on patients who have ventricular dysfunction after MI.

Arrhythmogenic Substrate

The zone of myocardium surrounding the infarcted area is particularly prone to electrical instability. This often manifests as premature ventricular contractions (PVCs) and predisposes the patient to ventricular arrhythmia. Beta-blockers are useful in reducing the electrical irritability of the damaged myocardium, as is amiodarone. Implantable cardioverter-defibrillators (ICDs) are the last line of defense in treating electrical excitability that causes potentially lethal arrhythmia.

Open-Artery Hypothesis

Even if the left ventricular muscle supplied by an occluded artery is dead, revascularization may still favorably effect ventricular remodeling and promote electrical stability. Depending on the duration of ischemia, among other factors, the myocardial cells either die or go into a state of hibernation. In this latter stage, revascularization can restore contractile functionality to what otherwise appears to be dead myocardium. Thus, there are a number of reasons, both established and theoretical, why vessel patency can improve prognosis (Fig. 20.1) (9).

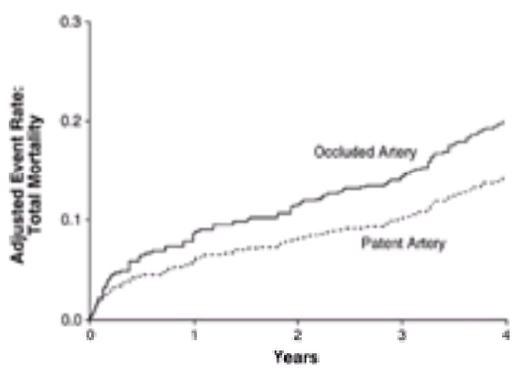


FIGURE 20.1 An occluded coronary artery is associated with a much lower survival rate, as illustrated by these data from the Survival and Ventricular Enlargement (SAVE) Trial, which provides indirect evidence supporting the “open-artery hypothesis.” (From Lamas GA, Flaker GC, Mitchell G, et al. Effect of infarct artery patency on prognosis after acute myocardial infarction. The Survival and Ventricular Enlargement Investigators. *Circulation* 1995;92:1101–1109, with permission.)

CLINICAL MANAGEMENT

Exercise stress testing, noninvasive imaging, and coronary angiography are all used to risk-stratify patients and determine their subsequent management. Risk-stratification models may help determine the most appropriate in-hospital and long-term management of patients with acute MI (10).

Assessment of Left Ventricular Function and Reperfusion

Echocardiography has assumed a large role in the management of the condition of patients who have experienced an acute MI. In addition to its role in determining the presence of mechanical complications of MI, echocardiography is able to provide an estimate of left ventricular systolic and diastolic function. Indeed, at least on a population level, the left ventricular ejection fraction has been shown to be a powerful predictor of outcome (Fig. 20.2) (11).

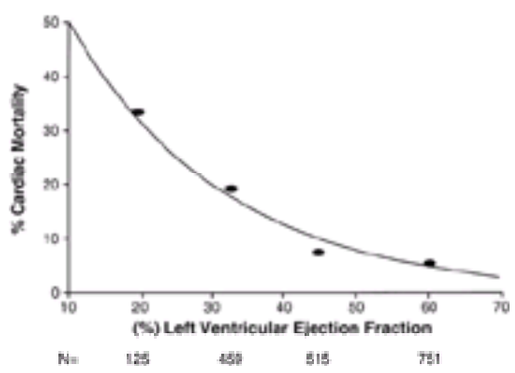


FIGURE 20.2 Diminished left ventricular ejection fraction after myocardial infarction is a powerful predictor of death after myocardial infarction. (From Gottlieb S, Moss AJ, McDermott M, et al. Interrelation of left ventricular ejection fraction, pulmonary congestion and outcome in acute myocardial infarction. *Am J Cardiol* 1992;69:977–984, with permission.)

Contrast echocardiography may, additionally, allow an assessment of whether successful tissue-level reperfusion has occurred (12,13). In conjunction with ST-segment resolution, important insights may be gained by gauging reperfusion with contrast echocardiography (14). Magnetic resonance imaging appears to be even more sensitive than contrast echocardiography in detection of microvascular obstruction (15). The *in vivo* study of microvascular function is not an arcane exercise in physiology, but rather adds important prognostic ability to more conventional determinants of infarct size (16). These newer modalities will refine assessment of left ventricular function so that an evaluation of microvascular integrity will become part of analyzing the state of the infarcted myocardium, at both a whole-organ and a cellular level.

Stress Testing

The role of stress testing in the management of patients after MI has been extensively studied. The value of exercise stress testing depends greatly on whether the patient has undergone revascularization (17). Guidelines have been developed to aid in the appropriate use of stress testing (18). As a practical point, based on data

from the NRMI, predischarge stress testing currently is performed in fewer than 10% of American patients, with the majority undergoing in-hospital revascularization or outpatient stress testing (2).

Certain features on a stress test identify patients at high risk of recurrent ischemic events. Left ventricular dilatation, pulmonary uptake of thallium-201, ejection fraction less than 40%, and reversible defects in the territory of the infarction are all markers of high risk on postexercise nuclear imaging scans. Additionally, large fixed defects and multivessel disease considerably raise the risk profile of the patient. Normal or low-risk results of a dipyridamole stress test predict an annual rate of death, MI, or urgent revascularization of less than 2%.

Video 20.1 Parasternal short-axis view of a dobutamine stress echo showing three-vessel coronary artery disease. Note the chamber enlargement and the deterioration of all walls. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 20.2 Apical two-chamber view of a dobutamine stress echo of a patient with peri-infarct ischemia in the distal anterior and distal inferior walls. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 20.3 Stress echo of a patient with left anterior descending coronary artery ischemia, parasternal long-axis and short-axis views. Note the deterioration of the anteroseptal wall (*upper right panel*) and the anteroseptum and anterior walls (*lower right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 20.4 Parasternal long-axis view of a dobutamine stress echo demonstrating viability and ischemia in the left anterior descending coronary artery territory. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 20.5 Parasternal short-axis view of a dobutamine stress echo demonstrating a biphasic response (viability and ischemia) in the left anterior descending coronary artery territory. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 20.6 Stress echo of a patient with right coronary artery ischemia. *Upper panels*: Apical four-chamber view showing worsening of basal septum (rest images to left, stress images to right). *Lower panels*: Apical two-chamber view demonstrating deterioration of the basal and mid inferior wall. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 20.7 Stress echo (parasternal long- and short-axis views) of a patient with right coronary artery ischemia. Note the normal response to stress in the anteroseptal and posterior walls. The inferior ischemia is difficult to see in this short axis because of the papillary muscle. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 20.8 Parasternal long-axis view of a dobutamine stress echo of a patient with three-vessel coronary artery disease. Note the deterioration of the anteroseptal and posterior walls in this view and the chamber dilatation. The images are arranged from upper left image = rest, to upper right and lower left = low-dose infusion, to lower right = peak infusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The Danish Trial in Acute Myocardial Infarction (DANAMI) randomly assigned 1,008 patients who had received fibrinolysis for MI and had inducible ischemia on stress testing to receive either invasive or conservative treatment (19). Those patients assigned to the invasive arm had a statistically significant reduction in the primary end points of death, MI, or readmission for unstable angina. The authors appropriately concluded that patients who have inducible ischemia detected before discharge should undergo coronary angiography.

Exercise stress testing can provide valuable information, primarily because the inability to exercise confers a poor prognosis (20,21). Although rare, myocardial rupture is possible during exercise stress testing or dobutamine stress testing in the post-MI period (22). As an alternative to submaximal exercise stress testing before hospital discharge, pharmacologic stress testing with dipyridamole 2 to 4 days after MI may be performed safely (23). In fact, dipyridamole stress testing outperformed submaximal exercise testing with nuclear imaging in its ability to predict postdischarge cardiac events (23). Therefore, if predischarge stress testing instead of invasive evaluation is the approach, dipyridamole stress testing may be the noninvasive test of choice.

Coronary Angiography

As noted, the DANAMI study showed that patients with inducible ischemia after acute MI had better outcomes if they were treated with an invasive strategy as opposed to a conservative one (19). Revascularization, either percutaneously or surgically, was found to be beneficial. An analysis of the patients from the DANAMI study who underwent coronary artery bypass grafting (CABG) was performed (24). The median time to CABG after acute MI was approximately 6 weeks. Patients who had

inducible ischemia, including silent ischemia, after acute MI benefited from CABG.

Similarly, spontaneous ischemia in the form of postinfarction angina is a serious development that warrants invasive investigation. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 3 (GISSI-3) trial prospectively analyzed patients with early angina after MI who were managed conservatively (25). Patients with post-MI angina suffered a higher rate of in-hospital reinfarction. Although the condition of many patients who developed post-MI angina was successfully controlled medically while the patient was in the hospital, these patients nevertheless had a higher rate of death or reinfarction at 6 months. In fact, the presence of early post-MI angina was an independent predictor of the 6-month rate of reinfarction or death. In patients with early angina, the rate of reinfarction was 12%, versus 5% in patients without early angina (p <.0001). The rate of death was also higher in patients with early angina than in those without early angina (13% vs. 7%, respectively; p <.0001). The presence of post-MI angina is a strong indication for coronary arteriography. Angiography for ischemic symptoms after MI is appropriately given a class I indication in the American College of Cardiology/American Heart Association guidelines for coronary arteriography (26).

Indirect evidence from comparative studies favors an invasive approach to treatment of MI. Compared with Canadian patients, American patients are more likely to undergo catheterization and angioplasty. This difference in approach appears to lead to better outcomes in American patients (27). A study comparing outcomes after MI in areas in France and Spain with different rates of angiography reached a similar conclusion regarding the superiority of an invasive approach (28).

However, older, randomized studies such as the Treatment of Post-Thrombolytic Stenoses (TOPS) trial do not favor routine angiography after successful fibrinolysis, even when angiography demonstrates a "significant" stenosis (29). The Should We Intervene following Thrombolysis (SWIFT) trial did not find a benefit for routine angiography after fibrinolysis either (30). Likewise, the Thrombolysis in Myocardial Infarction (TIMI) II-B and European Cooperative Study Group (ECSG) trials were unable to demonstrate an advantage to a routine invasive approach (31,32). The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study found no advantage to immediate angioplasty after fibrinolysis in comparison with delayed angioplasty 5 to 10 days later (33). Perhaps the prothrombotic effects at the site of ruptured plaque that systemic fibrinolysis can create, coupled with further arterial trauma from balloon angioplasty, led to lack of favorable outcomes with invasive therapy (34). Therefore, the results of these trials may no longer apply in an era marked by greater use of stents and intravenous glycoprotein IIb/IIIa inhibition, but this issue needs to be examined prospectively (35). Nevertheless, in patients who appear to have successfully reperfused after fibrinolysis, or those who have received no reperfusion therapy acutely, it is still reasonable to use noninvasive risk-stratification before invasive therapy, with its attendant risk. An algorithm for risk-stratification is shown in Figure 20.3.

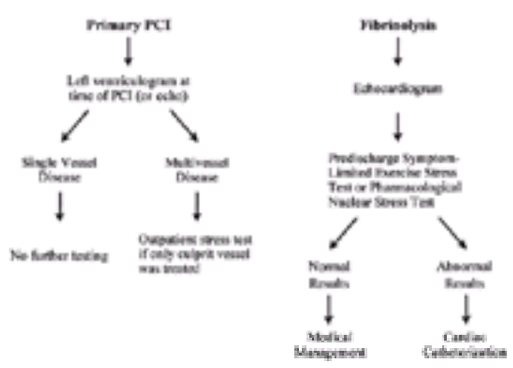


FIGURE 20.3 Risk assessment algorithm for the post–myocardial infarction patient, depending on the primary mode of reperfusion. echo, echocardiogram; PCI, percutaneous coronary intervention.

One of the benefits of an invasive strategy is that it can provide diagnostic information and definitive therapy in the form of percutaneous intervention. While Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease II (FRISC-II) and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) were studies demonstrating the superiority of an invasive approach over a conservative strategy in non–ST-segment elevation acute coronary syndromes, it may prove to be legitimate to extrapolate these results to the management of patients after acute ST-segment elevation MI (36,37 and 38). In the future, ST-segment resolution may be used to guide the need for invasive therapy. Contrast echocardiography or perfusion magnetic resonance imaging may also prove to have clinical usefulness in assessing lack of tissue-level perfusion and the need for invasive therapy. Biochemical markers of myocardial necrosis, such as troponin elevation on admission, may help determine the need for invasive therapy.

Assessment of Inflammatory Activity

Although an assessment of myocardial necrosis and microvascular obstruction is useful, measures of heightened inflammation, such as an elevated C-reactive protein (CRP) level, may provide additional ability to risk-stratify patients. The value of CRP levels was examined in a study of 64 patients with an uncomplicated MI (39). All patients had normal left ventricular function with no evidence of ischemia on a predischarge ergometer test. Interestingly, with each successive increase in quartile of CRP, the risk of cardiac death, recurrent MI, or new-onset angina in the ensuing year increased (Fig. 20.4). Even cruder indices of inflammation, such as the white blood cell (WBC) count, appear to help risk-stratify patients (40). A study of 975 patients with acute MI found that those who had angiographic thrombus were more likely to have an elevated WBC count, perhaps illustrating the interplay between inflammation and thrombosis (40). Furthermore, increasing elevation in levels of WBCs were associated with higher rates of death.

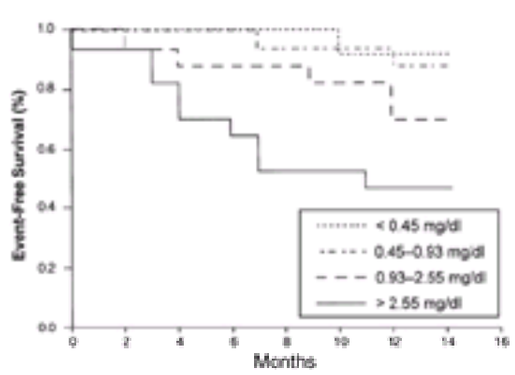


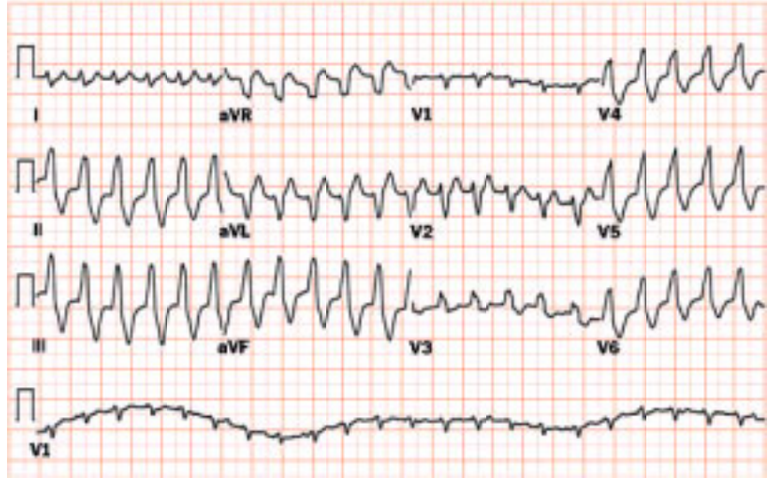
FIGURE 20.4 Even in patients who have an uncomplicated myocardial infarction, the risk of subsequent cardiac events increases with each successive quartile elevation of the C-reactive protein level. (From Tommasi S, Carluccio E, Bentivoglio M, et al. C-reactive protein as a marker for cardiac ischemic events in the year after a first, uncomplicated myocardial infarction. *Am J Cardiol* 1999;83:1595–1599, with permission.)

Beyond their role in risk-stratification, markers of inflammation may help gauge the incremental benefit of invasive therapy, in a manner complementary to troponin elevation. This paradigm has been shown to be true for non–ST-segment elevation acute coronary syndromes in two separate analyses, the results of which may apply to the acute MI setting also. In an analysis of almost 12,000 patients with acute coronary syndromes, an elevated WBC count correlated with 6-month mortality (177). However, in those patients undergoing in-hospital revascularization, the deleterious effect of an elevated WBC count were substantially lessened (177). Similarly, in FRISC-II, an invasive strategy (compared with a conservative approach) was seen to be of particular benefit in patients with elevated CRP, troponin T, or interleukin-6 levels (41).

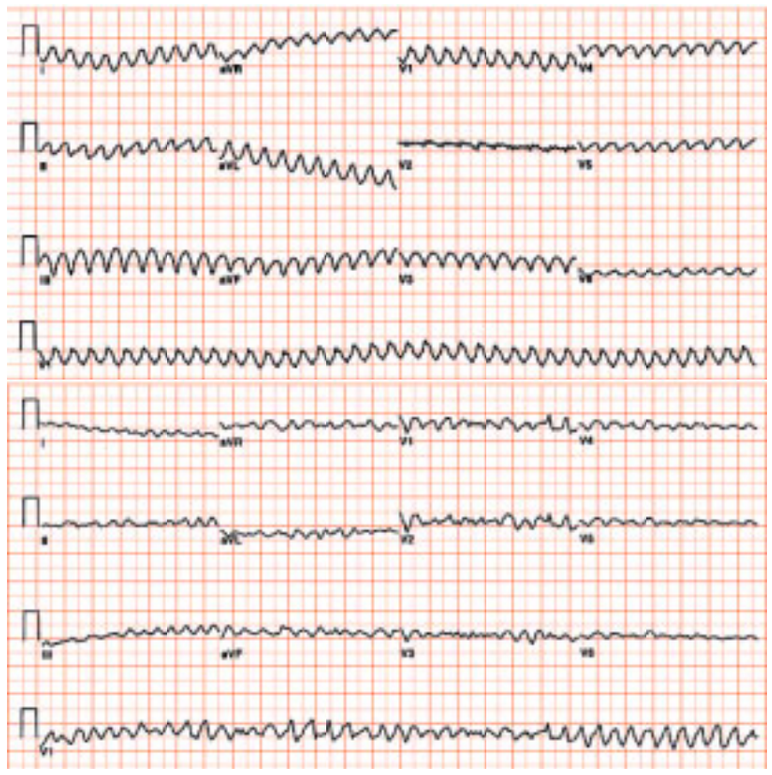
Risk of Arrhythmia

The role of routine telemetry in patients after MI is well established. In fact, perhaps the major advance of the cardiac intensive care unit was the development of continuous monitoring for ventricular arrhythmia, allowing prompt defibrillation. High-grade heart block may develop after anterior wall MI, and permanent pacemaker implantation may be necessary. Atrial fibrillation may complicate MI, often as a result of concomitant ventricular dysfunction from a large infarction. The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) Study Group found that dofetilide, a class III antiarrhythmic drug, did not affect the mortality rate

among MI patients who had ventricular dysfunction, although it did aid in restoring normal sinus rhythm (42).

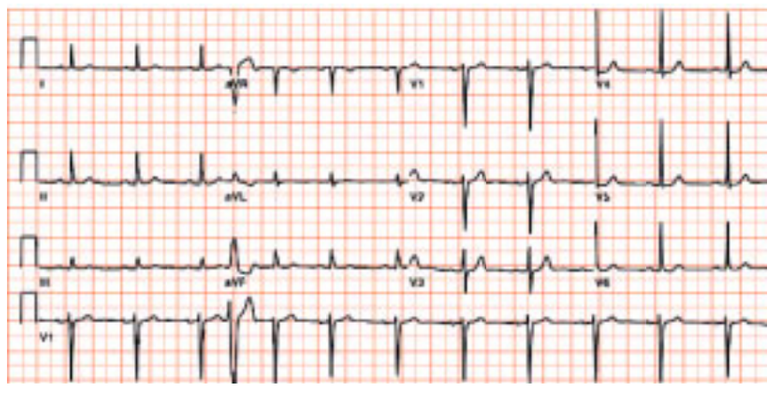


Wide complex tachycardia. Atrioventricular dissociation confirms ventricular origin.



Ventricular flutter (A). Same patient with degeneration into ventricular fibrillation (B).

PVCs after an MI are commonly observed on telemetry, and an increased frequency definitely increases the risk of subsequent arrhythmic death (43). It was logical to think, therefore, that decreasing or eliminating PVCs would be desirable. However, the Cardiac Arrhythmia Suppression Trial (CAST) I and CAST II showed that routine suppression of PVCs was not beneficial and that when the agents studied were used, suppression was in fact associated with an increased mortality rate (44,45 and 46). Therefore, routine suppression of asymptomatic ventricular arrhythmias was abandoned.



A 79-year-old patient with an interpolated premature ventricular contraction.

Methods to gauge proarrhythmic potential have been developed. The signal-averaged electrocardiogram (SAECG) is an older method used to help determine risk of subsequent arrhythmia. Normal results of an SAECG portend a very low risk of arrhythmia; however, although abnormal results of an SAECG do place a patient at increased risk of arrhythmia, the test is not very specific (47). Heart-rate variability, T-wave alternans, and QT dispersion are newer modalities to help assess arrhythmic risk. For example, depressed heart-rate variability may help allocate patients to amiodarone after infarction in a cost-effective manner (48).

Electrophysiologic studies have also been used to determine arrhythmic risk and to allocate patients to ICD therapy. An ICD may be indicated to prevent life-threatening arrhythmia in certain high-risk patients after acute MI. In patients with ventricular fibrillation or symptomatic sustained ventricular tachycardia, the Antiarrhythmics versus Implantable Defibrillators (AVID) Trial demonstrated the superiority of ICD over antiarrhythmic therapy, with a 3-year mortality rate of 24.6% versus 35.9%, respectively (49). The Multicenter Automatic Defibrillator Implantation Trial (MADIT) randomly assigned 196 patients with prior MI; an ejection fraction £35%; documented nonsustained ventricular tachycardia; and results of an electrophysiologic study that demonstrated inducible, nonsuppressible ventricular arrhythmia to receive either an ICD or standard therapy (50). MADIT found a significant 54% reduction in the mortality rate among highly selected patients receiving an ICD. The Multicenter Unsustained Tachycardia Trial (MUSTT) found that electrophysiologically guided therapy, namely ICD implantation, decreased sudden arrhythmic death and cardiac arrest in patients who had coronary artery disease, an ejection fraction £40%, and nonsustained ventricular tachycardia (51,52). Patients with runs of asymptomatic, nonsustained ventricular tachycardia noted on telemetry who have an ejection fraction <40% should be considered for electrophysiologic testing, and, if ventricular tachycardia is induced, an ICD should be implanted (53). Although this strategy definitely has a favorable impact on mortality rates, the cost-effectiveness of such an approach, especially if it were applied broadly to all MI patients, remains to be determined.

An 81-year-old male patient with ventricular tachycardia.

MEDICAL THERAPY

Several classes of medications designed to improve outcomes after acute MI have undergone rigorous evaluation in large, randomized, controlled trials. It is imperative that physicians screen post-MI patients for criteria that indicate that specific medications should be prescribed (Fig. 20.5).

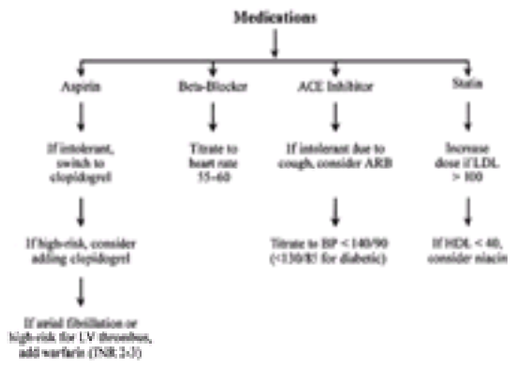


FIGURE 20.5 Flow chart for appropriate medications in patients after myocardial infarction. If left ventricular (LV) dysfunction is not present, it is not clear whether both beta-blockers and angiotensin-converting enzyme (ACE) inhibitors are necessary. ARB, angiotensin-receptor blocker; BP, blood pressure; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein.

Afterload Reduction

Angiotensin-Converting Enzyme Inhibitors

Use of ACE inhibitors after acute MI is supported by a vast amount of evidence (Table 20.1) (54,55 and 56). The Acute Infarction Ramipril Efficacy study found that ramipril decreased mortality rates after MI among patients with heart failure (57). The Survival and Ventricular Enlargement trial demonstrated the significant benefit, with regard to mortality rates, of administration of captopril after MI among patients with asymptomatic left ventricular dysfunction as well (58). The Trandolapril Cardiac Evaluation study showed that the benefit of ACE inhibition persisted through 2 years of therapy, suggesting that ACE inhibition should be continued indefinitely (59). In fact, the results of the Heart Outcomes Prevention Evaluation (HOPE) study suggest that ACE inhibitors may be indicated in all patients who have had an MI (60).

Study	ACE inhibitor	No. of patients	Length of follow-up	Mortality rates (%)	
				Placebo	ACE inhibitor
AIRE (57)	Ramipril	2,006	15 mo	22.4	16.8
CCS-1 (61)	Captopril	13,634	4 wk	9.6	9.1
CONSENSUS II (64)	Enalapril	6,090	6 mo	10.2	11.0
GISSI-3 (54)	Lisinopril	18,895	6 wk	7.1	6.3
ISIS-4 (55)	Captopril	58,050	5 wk	7.7	7.2
SAVE (58)	Captopril	2,231	42 mo	24.6	20.4
SMILE (293)	Zofenopril	1,556	1 yr	14.1	10.0
TRACE (294)	Trandolapril	1,749	24–58 mo	42.3	34.7

AIRE, Acute Infarction Ramipril Efficacy Study; CCS-1, Chinese Cardiac Study; CONSENSUS II, Cooperative New Scandinavian Enalapril Survival Study II; GISSI-3, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 3; ISIS-4, Fourth International Study of Infarct Survival; SAVE, Survival and Ventricular Enlargement Trial; SMILE, Survival of Myocardial Infarction Long-Term Evaluation Study; TRACE, Trandolapril Cardiac Evaluation Study.

TABLE 20.1 LARGE TRIALS OF THE USE OF ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS AFTER ACUTE MYOCARDIAL INFARCTION, DEMONSTRATING MORTALITY RATES FOR PLACEBO AND ACE INHIBITOR ARMS

Early initiation of oral ACE inhibitors is recommended for these patients, unless hypotension is present (61,62 and 63). However, the data do not support the early administration of intravenous ACE inhibitors (64). The early benefit of ACE inhibition on minimizing left ventricular dilatation is most marked when reperfusion has not occurred, but other beneficial effects of ACE inhibitors likely apply to all patients (65). Despite all these favorable data, ACE inhibitors are underprescribed after acute MI (66). Unless systolic blood pressure is <100 mm Hg, ACE inhibition should generally be initiated within 24 hours of acute MI (63).

Angiotensin-Receptor Blockers

At the present time, the role of angiotensin-receptor blockers (ARBs) appears limited to use in those patients who are unable to tolerate ACE inhibitors because of the side effect of cough. Whether any incremental benefit occurs with the addition of an ARB to the treatment regimen for patients who are on an ACE inhibitor is being evaluated in clinical trials. The Valsartan in Acute Myocardial Infarction Trial (VALIANT) will compare the ARB valsartan, captopril, or the combination in MI patients with heart failure (67).

Beta-Blockers

The role of beta-blockers in patients who have experienced MI is well established (Table 20.2) (68). Beneficial effects result from decreases in heart rate, blood pressure, myocardial oxygen demand, and arrhythmogenesis (69). Newer evidence suggests a favorable influence on left ventricular remodeling as well (70). The Beta-Blocker Heart Attack Trial (BHAT) demonstrated that propranolol safely decreased cardiac mortality, sudden death, and all-cause mortality rates (71). Furthermore, side effects caused by propranolol that prompted drug discontinuation were relatively infrequent. The BHAT investigators recommended continuation of therapy for at least 3 years. In aggregate, the data suggest that beta-blockade reduces nonfatal MI by approximately 25%, which is paralleled by a 25% reduction in the mortality rate (72). Although these data were gathered largely before the fibrinolytic era, TIMI II-B found that even in patients who have received fibrinolysis, compared with later administration of beta-blockers, early beta-blockade reduced recurrent chest pain and reinfarction (73). Furthermore, early beta-blockade appears to reduce the incidence of intracranial hemorrhage after fibrinolysis, as well as the incidence of reinfarction (74).

Study	Beta-blocker	No. of patients	Length of follow-up	End point	Event rate (%)	
					Placebo	Beta-blocker
BHAT (295)	Propranolol	3,837	24 mo	Death	9.8	7.2
Göteborg Trial (296)	Metoprolol	1,395	3 mo	Death	8.9	5.7
ISIS-1 (297)	Atenolol	16,027	7 d	Vascular death	4.6	3.9
MIAMI (298)	Metoprolol	5,778	15 d	Death	4.9	4.3
Norwegian Multicenter Study (65,299)	Timolol	1,884	3 yr	Death	32.3	26.4
TIMI II-B (73)	Metoprolol	1,434	6 d	Reinfarction	5.1*	2.7

BHAT, Beta-Blocker Heart Attack Trial; ISIS-1, First International Study of Infarct Survival; MIAMI, Metoprolol in Acute Myocardial Infarction Trial; TIMI II-B, Thrombolysis in Myocardial Infarction II-B Study.
*The placebo was delayed administration of metoprolol on day 6 after myocardial infarction versus immediate intravenous administration followed by oral dosing on day 1.

TABLE 20.2 EVENT RATES FOR SELECTED LARGE TRIALS OF THE USE OF BETA-BLOCKERS VERSUS PLACEBO AFTER ACUTE MYOCARDIAL INFARCTION

Beta-blockers remain underused after MI, sometimes because of unfounded concerns regarding relative contraindications such as diabetes or chronic obstructive pulmonary disease (75,76 and 77). Beta-blockers have a similar relative benefit in the presence and in the absence of heart failure, although the absolute benefit is magnified in those with heart failure (78). Underuse is a problem particularly among elderly patients (79,80). Numerous studies have confirmed that use of beta-blockade is safe in elderly patients and in diabetic patients (81). The optimal dose of beta-blockade, particularly in elderly patients, is not known, but doses lower than those that were used in several of the early randomized trials may be just as effective (82,83). If all eligible patients received beta-blockers after MI, thousands of recurrent MIs and deaths could be averted.

The limited available evidence suggests that beta-blockade and ACE inhibition are complementary (84,85,86,87,88 and 89). In patients who experience congestive heart failure after MI, both classes of medication seem to be indicated. At the other end of the spectrum, in patients with normal left ventricular function, perhaps only one of these classes of medication is needed. Without prospective data examining the incremental value of combination therapy, other patient factors, such as history of arrhythmia or diabetes, should also be considered in deciding which of these agents to use.

Calcium Channel Blockers

Given the large amount of data supporting the use of ACE inhibitors and beta-blockers, calcium channel blockers should not be considered first-line therapy in post-MI patients (90). Particularly unfortunate is the use of calcium channel blockers instead of beta-blockers, which has resulted largely from excellent marketing efforts by the makers of calcium channel blockers and from the lack of advertising on behalf of off-patent beta-blockers (91,92). In particular, the use of calcium channel blockers should be avoided in patients who experience heart failure after acute MI, because they do not confer a protective effect and may be deleterious (90,93,94). The Danish Verapamil Infarction Trial II (DAVIT-II) found that verapamil may have a benefit in those post-MI patients who do not have heart failure (95,96). The short-acting calcium channel blockers, especially nifedipine, should not be used for acute or chronic therapy, because these agents do not decrease mortality rates and appear to raise the risk of cardiac events, as seen, for example, in the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) (97,98,99,100 and 101). Long-acting calcium channel blockers do not appear to reduce mortality rates convincingly (102). Nevertheless, use of the calcium channel blocker verapamil is once again being studied for acute MI, now in conjunction with fibrinolysis (103). Potentially, when used in conjunction with fibrinolysis or ACE inhibition, long-acting calcium channel blockers may yield some clinical benefit (104). The Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis (INTERCEPT) examined the role of diltiazem in acute MI patients who had not experienced heart failure (105). A trend toward a reduction in ischemic events was seen in those patients randomly assigned to receive diltiazem in INTERCEPT. Nevertheless, without further supportive evidence, the only role of calcium channel blockers is as a second-line agent for control of hypertension in post-MI patients, or as primary therapy in the very rare patient with coronary artery spasm (106).

Nitrates

No study has provided compelling evidence that nitroglycerin reduces mortality rates after acute MI. GISSI-3 did not find any benefit from the use of transdermal nitroglycerin on the mortality rate or the incidence of left ventricular dysfunction (54). The Fourth International Study of Infarct Survival (ISIS-4) found no benefit from use of an oral mononitrate preparation on mortality rates in any subgroup examined (55). Nevertheless, because of the acute antiischemic effect of these agents, every patient who has experienced an MI should be instructed to carry a bottle of sublingual nitroglycerin at all times and should be instructed in its safe use.

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors

Statins are strongly indicated for use as secondary prevention after acute MI. The Cholesterol and Recurrent Events (CARE) trial demonstrated that pravastatin, compared with placebo, reduced the rate of death or MI in patients with previous MI (107). In addition to beneficial effects on reinfarction, the CARE study showed that statin use decreases the risk of stroke in survivors of acute MI (108,109). Several other trials have validated the role of statins in secondary, and even primary, prevention (110). Whether there are benefits specific to one statin or whether the protective attributes result from a class effect remains to be elucidated.

Timing of Initiation of Therapy

Until recently, the appropriate time in which to measure lipid parameters had been controversial (111). MI, as is true of most acute illnesses, can lower total cholesterol and low-density lipoprotein (LDL) cholesterol levels temporarily. This fact had led many doctors to avoid measurement of lipids during the hospitalization phase and defer decisions regarding lipid-lowering therapy to a subsequent outpatient evaluation. However, lipid-lowering therapy may not be started by the outpatient physician, who may assume that if it were necessary, it would have been started by the hospital specialist (112). The difference in lipid values is minimized if blood tests are drawn within 48 hours of hospital admission for acute MI (111). Furthermore, in a study of 294 MI patients, the in-hospital cholesterol levels were higher than the National Cholesterol Education Program target LDL for secondary prevention in 83.7% of patients anyway. Thus, there is no good reason to defer cholesterol measurements, although repeating them in the outpatient setting is not unreasonable. The argument could even be made that all patients should be treated with a statin, regardless of the initial in-hospital cholesterol measurement.

It appears logical to start therapy immediately, during the initial hospitalization, rather than wait to obtain a lipid measurement once the patient has left the hospital. Data from a Swedish registry of post-MI patients indicates that the combination of statin therapy for hyperlipidemia initiated during the hospitalization and revascularization within 14 days dramatically reduced the 1-year mortality rate after MI by two-thirds (113). After adjustment for baseline differences, the investigators found a 25% reduction in the mortality rate with early statin use and also reported a 36% reduction with early revascularization, both of which were highly statistically significant.

Additionally, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial suggests that an early benefit accrues to initiation of statin therapy in the acute setting (114,115). MIRACL randomly assigned more than 3,000 patients who had acute coronary syndromes to receive 80 mg of atorvastatin within 4 days. Patients who had recent or planned revascularization were excluded from the trial. A reduction in the composite end point of nonfatal MI, cardiac arrest with resuscitation, or angina requiring hospitalization was seen (p = .048), driven almost entirely by a reduction in rehospitalization for angina. Although these results were not overwhelming, the trial adds to the evidence suggesting a benefit from early initiation of statin therapy, with no downside other than cost.

The Effects of Fluvastatin Administered Immediately after an Acute MI on Myocardial Ischemia (FLORIDA) trial of treatment with fluvastatin within 24 hours of MI did not show a significant reduction in clinical events (116). With only 540 patients, this trial likely was underpowered to detect a difference between early fluvastatin administration and placebo. Additionally, patients undergoing revascularization were not enrolled in this trial, and it appears that both statin use and revascularization are necessary to optimize outcomes. The *P*revention of *Re*i*n*farction by Early Treatment of *Ce*rivastatin *S*tudy (PRINCESS) trial with cerivastatin will enroll 4,000 patients within 48 hours of MI and test the strategy of early statin use. The A to Z trial of simvastatin and the Pravastatin Acute Coronary Treatment (PACT) trial of pravastatin will be large, placebo-controlled trials that evaluate early initiation of statins in patients with acute coronary syndromes, including ST-elevation MI. These and other trials will determine the merit of initiating statin therapy immediately, across a broad range of baseline cholesterol values.

Although the rate of statin use has been increasing, many patients still do not receive them. The National Registry of Myocardial Infarction 3 found that in 1999, only 36.2% of patients with acute MI were discharged while a statin was being administered (2). Statins are cost-effective even in elderly patients who have had an MI, although they are particularly underused in this population (117). The Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) project in Germany has demonstrated that statin use after an acute MI can be increased by dissemination of practice guidelines. Early statin use after acute MI has increased in the MITRA registry from 15% to 76% between 1994 and 2000 (118). This resulted from study meetings that were used to discuss current treatment recommendations and compare practices in different centers. Interestingly, the physician involved had to document on a case report form whether statin therapy was used, and if not, to provide a brief explanation. This mental exercise likely forced physicians to realize that there are usually no contraindications to statin therapy, but rather clear indications for use in most post-MI patients. Such measures may be useful to increase prescription of statins, as well as other indicated therapies.

Other Lipid-Directed Therapy

Sitostanol ester margarine is able to reduce cholesterol effectively and was found in one study to normalize LDL cholesterol levels in one-third of women with previous MI (119). Potentially, other therapies that decrease LDL levels might be used to supplement or replace statins. Decreased LDL levels may not be the only important result of lipid-directed therapy. The Bezafibrate Coronary Atherosclerosis Intervention Trial randomly assigned male patients younger than 45 years who had previously experienced an MI to receive bezafibrate or placebo and found a significant reduction in the number of coronary events (120). This beneficial effect was not accompanied by a reduction in LDL levels, but rather by reductions in triglyceride and fibrinogen levels and increases in high-density lipoprotein (HDL) cholesterol levels. Whether patients with elevated triglyceride levels derive particular benefit from fibrates still needs to be confirmed (121). The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) randomly assigned men who had coronary artery disease and a low HDL level to receive gemfibrozil or placebo and found that gemfibrozil reduced the rate of cardiac death or MI (122,123). This study validated the importance of treating low HDL levels, although it is still not clear whether this relationship holds true if a patient is also receiving a statin to decrease LDL levels. Extended-release niacin may be even more effective at increasing HDL

levels than gemfibrozil (124). Statins may also have a modest effect on increasing the HDL level (125).

Therefore, if a post-MI patient has an LDL level higher than 100 mg per dL, a statin should be prescribed, and its use should be initiated in the acute phase. If the HDL level is lower than 40 mg per dL despite statin therapy, use of niacin or gemfibrozil should be considered. If triglyceride levels are elevated, gemfibrozil, rather than niacin, is preferred; otherwise niacin, because of its effects on decreasing fibrinogen and lipoprotein(a) levels, may be preferable (124).

Antithrombotic Therapy

Because of the important role that thrombosis plays in acute MI, much research has been done on the use of antithrombotic therapy for the secondary prevention of MI (126).

Antiplatelet Therapy

Aspirin

With its metaanalysis of 174 randomized trials of antiplatelet therapy for cardiovascular disease, the Antiplatelet Trialists' Collaboration conclusively demonstrated the value of aspirin use after MI (127). Approximately 20,000 patients with acute MI were included in this metaanalysis; aspirin reduced the rate of recurrent ischemic events from 14% to 10%. Because the majority of trials included in this metaanalysis lasted an average of 2 years and a significant benefit of aspirin therapy was found between years 1 and 3, aspirin should be continued for at least several years after MI, and, in the absence of bleeding complications, should be continued indefinitely. The Second International Study of Infarct Survival found that aspirin therapy given for 1 month after acute MI was beneficial (128). The benefit was on the same order of magnitude as the benefit of administration of fibrinolysis with streptokinase. The dose of aspirin should be no greater than 325 mg per day, although it is unclear whether more than 81 mg per day is actually necessary for chronic therapy. Thus, aspirin is a simple, highly cost-effective intervention in MI patients. Nevertheless, aspirin remains underused after MI (129).

Clopidogrel

Clopidogrel is an antiplatelet agent that works by blocking the adenosine diphosphate receptor. In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study, 19,185 patients with established atherosclerosis of the coronary, cerebral, or peripheral circulation were randomly assigned to undergo secondary prevention with either aspirin or clopidogrel (130). After a mean follow-up period of 1.9 years, this trial found an overall 8.7% relative risk reduction in the primary end point of vascular death, MI, or ischemic stroke (p = .043). Interestingly, the CAPRIE study found a 19.2% relative risk reduction in fatal or nonfatal MI (p = .008) (131). Thus, compared with aspirin, clopidogrel's ability to reduce the incidence of MI in patients with previous ischemic events is particularly notable. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) is currently enrolling approximately 30,000 patients within 6 hours of acute ST-elevation MI in China and randomly assigning them to therapy with either clopidogrel or placebo, in addition to aspirin, for 4 weeks. Whereas CAPRIE showed that clopidogrel was more effective than aspirin in secondary prevention of MI, COMMIT will help determine whether clopidogrel should be used in the acute setting in combination with aspirin.

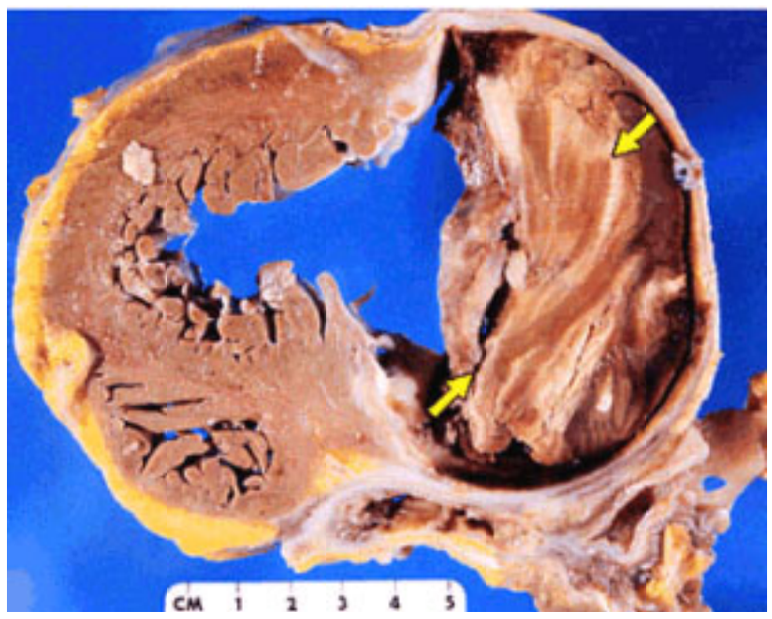
In a subgroup analysis from CAPRIE, patients who were on statin therapy and were randomly assigned to clopidogrel had a lower rate of recurrent ischemic events than patients who were randomly assigned to aspirin (132). Furthermore, the relative risk reduction for MI was slightly greater than 50% with this combination. Thus, the benefits of statin therapy and clopidogrel appear to be complementary. In patients who have had an MI while taking aspirin or who are intolerant to aspirin, it is therefore reasonable to consider long-term therapy with clopidogrel, in addition to statin therapy (133). Whether aspirin plus clopidogrel plus a statin should be standard care after an acute MI will be determined in part by the results of the COMMIT trial. The results from the recently presented Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial demonstrate that clopidogrel plus aspirin was superior to aspirin alone in patients presenting with non–ST-elevation acute coronary syndromes (134). After an average of 9 months, the rate of cardiovascular death, MI, or stroke was reduced from 11.5% in the aspirin-only group to 9.3% in the group assigned to receive both aspirin and clopidogrel (p = .00005). Furthermore, the rate of life-threatening bleeding was low: 2.1% in the dual antiplatelet therapy group versus 1.8% in the aspirin group. These findings from CURE are likely applicable to the ST-segment elevation MI population as well.

Warfarin

When atrial fibrillation is present, the role of warfarin is established (135). In the case of a large anterior wall MI with anterior akinesis or dyskinesis, warfarin is typically used, although this scenario is less common in the reperfusion era. Whether warfarin should have a larger role in the routine secondary prevention of post-MI patients has been extensively studied, although with no clear conclusion.

VIDEO

Video 20.9 Post–myocardial infarction apical thrombus (long-axis). Akinesia of thin apical wall with adjacent thrombus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Healed, atrophic posterolateral infarct and ventricular aneurysm containing a mural thrombosis (*yellow arrows*).

VIDEO

Video 20.10 A 54-year-old male patient with filling defect of the left ventricular apex consistent with left ventricular apical thrombus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The Sixty Plus Reinfarction Study Research Group found that anticoagulation was more effective after MI than placebo in reducing rates of recurrent MI and death (136). The Warfarin Re-Infarction Study (WARIS) also found that, compared with placebo, anticoagulation reduced mortality rates after MI, as well as rates of reinfarction (137). Additionally, the occurrence of stroke was reduced with warfarin therapy, perhaps because of the decreased occurrence of embolization of left ventricular thrombus. The Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial also found warfarin to be better than placebo in reducing recurrent MI and stroke, but again, an increase in bleeding complications was seen (138). The optimal international normalized ratio (INR) to minimize both

thromboembolic and bleeding events in ASPECT was between 3 and 4 (139). However, in the postfibrinolytic patient with an initially patent artery, the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT) study demonstrated the superiority of aspirin over warfarin (140). The Coumadin Aspirin Reinfarction Study (CARS) found that aspirin plus a fixed dose of either 1 or 3 mg of warfarin was no better than aspirin alone (141). Similarly, the Combination Hemotherapy and Mortality Prevention (CHAMP) study found no benefit with the use of warfarin adjusted to an INR of 1.5 to 2.0 in addition to aspirin after MI, although the addition of warfarin did cause more gastrointestinal bleeding (142). Recent studies have revisited the role of warfarin in MI patients. The 308-patient APRICOT-2 study found that the combination of warfarin, with a dose calculated to achieve an INR of 2 to 3, and aspirin was superior to the use of aspirin alone in maintaining the angiographic patency of culprit infarct arteries (143). WARIS-II will examine various intensities of warfarin anticoagulation with or without aspirin versus aspirin alone after MI (144).

Compared with placebo, adjusted-dose warfarin does appear to be beneficial in patients after MI if the patients are compliant and the dose of warfarin is carefully regulated, although bleeding remains a concern. Aspirin appears to be superior to warfarin as an antithrombotic strategy after MI, particularly if patients have undergone reperfusion therapy and are at lower risk for thrombus formation in a dyskinetic left ventricle. Potentially, a strategy of dual antiplatelet therapy with aspirin and clopidogrel would enhance the benefits seen with aspirin alone, without the large bleeding penalty incurred by warfarin. The value of a strategy including clopidogrel and aspirin over a strategy including warfarin and aspirin would be further enhanced in the setting of aggressive percutaneous revascularization with stent use, where dual antiplatelet therapy has been proven superior to warfarin plus aspirin (145,146).

Hormone Replacement Therapy

Although estrogen replacement may have a role in health maintenance in postmenopausal women, it can no longer be recommended for the secondary prevention of ischemic heart disease. Estrogen replacement affects the lipid profile favorably and lowers fibrinogen levels (147). But despite favorable effects on LDL and HDL cholesterol levels, estrogen replacement does not decrease progression of angiographic coronary artery disease, nor does it reduce clinical cardiovascular events (148). It appears that the use of conjugated equine estrogens actually increases the risk of thrombotic events and thus is particularly inappropriate for a woman with a recent MI (149).

Estrogens also have an effect on raising certain serum markers of inflammation, such as the CRP (150). The Heart and Estrogen/Progestin Replacement Study (HERS) found no cardiovascular benefit to estrogen replacement versus placebo after 4.1 years of therapy. An increase in risk of cardiovascular events was seen in the first year of estrogen therapy in the HERS trial, possibly as a result of a prothrombotic effect or a proinflammatory effect, followed by fewer events after 2 years of estrogen replacement therapy in the treated group, possibly as a result of beneficial effects on lipid levels and endothelial function (151). Other doses and formulations of estrogen, phytoestrogens, or selective estrogen-receptor modulators may therefore have a role in secondary prevention, but no randomized clinical data are currently available to evaluate them in this regard (152).

Antioxidants

The HOPE study did not find any benefit from use of vitamin E among patients with vascular disease (60). Although vitamins are relatively inexpensive and reasonably safe at normal doses, they do require patients to take even more pills, potentially instead of prescribed medication that has proven benefit. Therefore, at this time, routine vitamin supplementation in the healthy patient with an adequate diet cannot be recommended.

Amiodarone

Amiodarone is effective at reducing PVCs after MI (153). A number of trials have examined the effect of amiodarone on arrhythmia and survival after MI, with conflicting results. This is partly because of the fact that some studies have compared amiodarone to other antiarrhythmic agents that may themselves have toxic instead of beneficial effects which would have been apparent had there been a placebo arm.

The Basel Antiarrhythmic Study of Infarct Survival (BASIS) found that low-dose amiodarone decreased mortality rates among patients with complex ventricular ectopic activity seen on 24-hour telemetry after MI (154,155). The Polish amiodarone study of post-MI patients with contraindications to beta-blockers found that amiodarone reduced the occurrence of cardiac death (156). The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial showed that amiodarone decreased resuscitated ventricular fibrillation or arrhythmic death in patients with MI who had at least ten PVCs per hour or a run of ventricular tachycardia (157). The European Myocardial Infarct Amiodarone Trial found a reduction in arrhythmic death but not in cardiac death or overall mortality rates with amiodarone use in patients who had left ventricular dysfunction after MI (158).

A metaanalysis of the amiodarone trials demonstrated that amiodarone is in fact associated with a decrease in mortality rates, although much more so in patients who have ventricular ectopy (159). There is certainly no role for routine use of amiodarone in acute MI that is not complicated by arrhythmia (160,161). The clinical benefit of the use of amiodarone after MI is seen primarily in patients who have depressed left ventricular function (162). Amiodarone reduces rates of sudden death and arrhythmic death, which may translate into an overall decrease in mortality rates among patients at high risk for arrhythmia, although ICD therapy may be better in such patients (163). Beta-blockers and amiodarone can be used safely together. In fact, if amiodarone is necessary, beta-blockers should be used, unless they cannot be tolerated, because these two types of medication appear to interact in a positive manner (164).

RISK FACTORS

Hypertension

Hypertension is a risk factor for death after MI (165,166 and 167). Additionally, hypertension places patients at greater risk for development of heart failure after MI (168). Treatment with ACE inhibitors seems particularly important in this subgroup of patients (169). In addition to benefits from long-term secondary prevention, immediate treatment of hypertension may decrease the risk of hemorrhagic stroke after fibrinolysis (170).

Diabetes

The use of effective medical therapies to treat hyperglycemia and concomitant risk factors is suboptimal in the post-MI diabetic patient (171). Other risk factors that may be present in diabetic patients should be identified and aggressively treated (172). Subgroup analyses of major trials have confirmed that diabetic patients may benefit from the use of beta-blockers, ACE inhibitors, statins, and aspirin (173,174 and 175). For example, a retrospective analysis of 2,790 diabetic patients from GISSI-3 demonstrated a reduction in mortality rates with ACE inhibition that was significantly larger than for patients without diabetes (173). Similarly, clopidogrel was shown to be superior to aspirin in a subgroup analysis of diabetic patients from CAPRIE, further illustrating that high-risk patients derive amplified benefit from aggressive pharmacotherapy (176).

Inflammation

The role of inflammation in MI is being investigated, with identification of several markers that appear to correlate with adverse outcome after episodes of coronary instability (40,41,177,178). The possibility of using agents to treat inflammation to decrease the risk of recurrent ischemic events is appealing. Potential targets include tumor necrosis factor-a, CD 40, and peroxisome proliferator–activated receptor alpha and gamma (178,179 and 180). Additionally, agents already in use may have beneficial effects on inflammatory pathways. Statins may possess clinically relevant antiinflammatory properties (181). Antiplatelet agents such as clopidogrel and low-dose aspirin may have secondary antiinflammatory actions mediated through their ability to interfere with platelet activation and subsequent triggering of inflammatory processes. Ultimately, revascularization may prove to be the best “antiinflammatory” therapy (41,177).

Infection

Administration of influenza vaccine during the influenza season was shown in a case-controlled study of 218 patients to decrease independently the risk of recurrent MI (182). Therefore, vaccinating all eligible patients before hospital discharge seems prudent. Whether infection per se is a cause of MI is unclear. Perhaps more likely, infection is one pathway that leads to inflammation, which may trigger MI.

LIFESTYLE MODIFICATION

The post-MI patient must incorporate several elements of lifestyle modification into daily practice (Fig. 20.6). Physician involvement in this process is crucial. Although counseling a patient and family can be time-consuming for the busy clinician, the likelihood of effecting change is highest during the first few days after MI, and this

opportunity must not be lost.

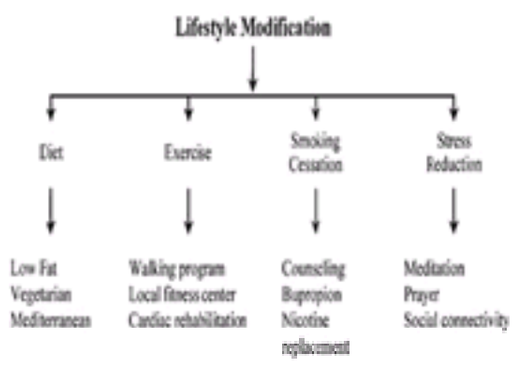


FIGURE 20.6 Lifestyle modification should consist of a multipronged effort to eliminate behaviors that are likely to contribute to adverse cardiac events. Although a comprehensive approach is mandatory, substantial latitude exists in specific recommendations, which allows therapy to be tailored to individual patients.

Smoking Cessation

It is critical for patients who smoke to stop. The physician must always counsel the patient about the importance of this step, the message should be repeated often during the hospitalization and subsequent outpatient visits, and smoking status should be documented on follow-up (183). The patient is particularly receptive to such messages while in the cardiac care unit (184). The risk of recurrent MI is greatly increased if smoking is continued. However, if the post-MI patient ceases smoking, the risk of death is decreased by almost one-half (185,186). The deleterious effects of smoking include elevation of fibrinogen, which is particularly undesirable in someone who is recovering from an MI (187).

The physician should emphasize the immediate cardiovascular and other health benefits associated with smoking cessation. In fact, the increased cardiovascular risk attributable to smoking decreases immediately after cessation, approaching the same level of risk as that of a nonsmoker by 4 years (188,189,190,191 and 192). Immediate economic benefits are also seen in terms of health care use (193). Living in a household in which other members smoke decreases the chances of successful smoking cessation. The physician should counsel family members who smoke to stop as well. Patient concerns regarding possible weight gain after smoking cessation should also be addressed. Cigar smoking and the chewing of tobacco are also to be avoided. Additionally, illicit drug use, such as cocaine, should also be considered in the etiology of MI and, if present, should be discontinued. Passive smoking should also be avoided (194).

Despite the importance of counseling about smoking cessation, rates of relapse are high. Formal smoking-cessation programs are useful in increasing long-term abstinence. A study of 100 post-MI patients with a history of smoking randomly assigned participants to receive either conventional care or inpatient counseling with telephone follow-up (195). At 1 year, 34% of the patients receiving conventional care were abstinent, versus 55% of those who were enrolled in the hospital-based counseling program ($p < .05$). Thus, smoking cessation programs do improve cessation rates, and methods to promote and fund such programs are needed. Furthermore, smoking cessation programs are highly cost-effective (196).

The use of pharmacologic adjuncts such as nicotine replacement and bupropion can help increase the rates of smoking cessation, especially when it is combined with behavioral counseling (197). Transdermal nicotine appears to be safe in patients who have cardiac disease and decreases the rates of smoking cessation in the short term, although this benefit diminishes with time (198). Nicotine gum, nicotine nasal spray, and nicotine inhalers are other nicotine-replacement options. The patient should be reminded not to smoke while receiving nicotine replacement, because this can trigger MI (199). Bupropion is an antidepressant that has been shown to be more effective than placebo at maintaining abstinence at 1 year (200). It may even be more effective than transdermal nicotine (201). It has no significant cardiac effects and can be used safely in patients who have recently had an MI (200). Persistent smoking after MI has been linked with depression and anxiety, and this may be one reason that bupropion is effective (202).

Exercise

Ambulation in the hallways should begin as soon as the patient is hemodynamically stable and shows no evidence of ischemia. Prolonged bed rest is undesirable and leads to deconditioning and an increase in the risk of deep vein thrombosis. Simple measures, such as a daily walking program, may lead to weight loss (203). Exercise can trigger acute MI, which is something patients fear, but this occurs most often from sudden bursts of exercise, rather than from a gradual increase in the intensity of an exercise program. If a patient has been revascularized, the decision to proceed with an exercise program is simplified. Some have asserted that a preentrance exercise test may not be absolutely necessary in an appropriately monitored cardiac rehabilitation program (204). However, if no invasive investigation has occurred, standard practice consists of use of an exercise stress test to guide the decision about beginning an exercise program. Even a structured weight-training program appears safe when it is started 6 or more weeks after acute MI in low-risk patients, with a rate of complications lower than that for aerobic exercise (205). The importance of exercise training is most pronounced in post-MI patients who have left ventricular dysfunction. Exercise training improves exercise capacity without causing left ventricular dilatation or increasing left ventricular wall thickness, which were concerns raised by older studies (206). Beta-blockade does not attenuate the benefits of exercise training (207).

Exercise rehabilitation has been studied extensively, although the overall quality of the studies has been less than rigorous (208). Furthermore, many studies of cardiac rehabilitation consisted of exercise as well as other behavioral and risk factor modifications, thus making it impossible to determine the individual contribution of a specific intervention (209,210 and 211). Some analyses have suggested that cardiac rehabilitation can decrease the risk of death in post-MI patients by up to 25% (212,213 and 214). Long-term follow-up showed a reduction in sudden death and cardiac mortality rates in another study (215). The benefits of exercise training extend to elderly patients, although high-risk patients appear to be referred to cardiac rehabilitation infrequently (216,217). A cost-effectiveness analysis found that cardiac rehabilitation costs as little as $4,950 per life-year saved, making it very economically attractive (218,219).

Resumption of Sexual Activity

An often unspoken fear of patients (and their spouses) is that sexual activity may trigger an acute MI (220,221). Both men and women describe decreased frequency of sexual activity and diminished satisfaction after MI (222). Sexual activity may usually be resumed 6 weeks after an infarction, or after 2 weeks if the risk of residual ischemia is low and no symptomatic heart failure or arrhythmia is present (223). If a patient has an exercise capacity of at least 6 metabolic equivalents, sexual activity should be well tolerated (224). The possibility of medication-induced sexual dysfunction, such as can be caused by beta-blockers, should be investigated during outpatient follow-up. For men (or women) taking sildenafil (Viagra), the patient should be educated about the possible interaction with nitrates (oral, topical, or sublingual) that can cause life-threatening hypotension and trigger MI. No convincing evidence exists that sildenafil itself causes MI, although the subsequent sexual activity may rarely trigger MI (225,226). In fact, the actual risk of MI as a result of sexual activity, even in patients who have prior MI, is small, and regular exercise appears to decrease this risk further (227,228). Thus, in most patients who have had an MI, sexual activity can be resumed safely. Furthermore, some evidence suggests that regular sexual activity can even reduce cardiovascular risk, although the data are not compelling (229).

Return to Work

How soon a patient is able to return to work depends on the patient and the exact degree of physical exertion required by the patient's job, although occupation per se does not appear to influence the risk of MI (230). A major determinant of returning to work is the perception by the patient of the severity of the MI (231). Importantly, cardiac rehabilitation increases the likelihood of returning to work (232).

Driving is permissible if no increased risk of arrhythmia is present. Air travel would not be recommended but is probably safe 2 to 3 weeks after an MI, if reversible ischemia has been excluded (233).

Alcohol and Coffee Consumption

Patients often ask whether resumption of alcohol consumption is permitted. Consumption of moderate quantities should not be problematic. Moderate consumption of any type of alcoholic beverage, not just red wine, appears to decrease the risk for cardiovascular death in patients with a history of MI, perhaps in part as a result of

beneficial effects on the HDL cholesterol level (234,235). However, one study found that consumption of more than two drinks per day was associated with a 50% increase in mortality rates in men with prior MI (236). Thus, it appears that two or fewer drinks per day is safe for patients who have experienced an MI and may even be protective against future MI. An alternative hypothesis is that concomitant psychosocial factors, such as lower degrees of stress, account for the observed benefits of moderate alcohol consumption, or that alcohol abstainers have other medical comorbidities (237,238 and 239). No compelling data suggest that patients who do not drink should start consuming alcohol.

Although moderate, regular consumption of alcohol may have antiplatelet effects and may enhance endogenous fibrinolytic activity, ingestion of a large amount of alcohol may increase platelet activation transiently (240,241 and 242). Therefore, binge drinking is to be avoided (243,244). Regular heavy drinking leads to elevations in blood pressure and is associated with increases in MI, stroke, and mortality rates and should be avoided as well (245,246 and 247). Alcohol may also have untoward effects on systolic performance of recently infarcted myocardium (248).

Coffee consumption has been linked to an excess risk of MI, although this association is in part confounded by concomitant cigarette smoking (249,250). Increased cholesterol levels in coffee drinkers may also account for some of the association (251). Heavy coffee consumption, four or more cups per day, is probably best avoided (252,253).

Diet

Diet is an important part of realigning the patient's lifestyle after MI. Ideally, nutritional change should be implemented in the cardiac unit setting to emphasize the importance of this component of the patient's care. Consultation with a nutritionist can help the patient make practical changes and can ensure that the person who is most involved with food preparation in the household also understands the changes that must take place.

The usual recommendation is for a low-fat diet. Dietary change after an MI was shown to decrease all-cause mortality rates in a small study (254). Compared with patients randomly assigned to a diet that was simply low in fat, patients assigned to a low-fat diet that was high in fruits, vegetables, nuts, and grains had a decrease in cholesterol levels and body weight, accompanied by decreased cardiac event and mortality rates (254). Thus, although a low-fat diet is important, other components appear to be necessary in a heart-healthy diet. A Mediterranean diet also seems to confer cardioprotection. Fish consumption does not convincingly decrease the risk of MI (255). Vegetarianism does appear to decrease the risk of an MI, in part by favorable effects on glucose intolerance and the waist-to-hip ratio (256).

Psychosocial Aspects

Patients who have completed high school education fare better after MI than those who have not graduated from high school (257). Higher rates of smoking only partially accounted for this difference in outcome between patients who graduated from high school and those who did not. Thus, a patient's socioeconomic background does influence the outcome after MI.

Whether mental stress has a role in MI has been debated, and data are available that support both sides of the argument. Psychological distress does appear to increase the risk of rehospitalization, MI, cardiac death, and sudden death in patients who have had acute coronary events (258,259). In fact, psychological distress may have more to do with the failure to return to previous levels of functioning than the extent of myocardial damage (260). Patients' self-perception of their level of functioning after MI contributes to actual levels of function (261).

Stress management decreases depression and anxiety and improves the quality of life after MI (262). Anger and hostility have been shown to increase the risk of MI and death (263,264). The aggressive type A personality also has been seen to increase the risk of MI in a few, but not most, studies, although this relationship may be confounded by HDL levels (265,266,267 and 268). Meditation techniques can help relieve stress, as can prayer. Some, but again not all, studies have linked an elevated risk of MI in patients with a type D personality, the tendency to suppress emotional distress (269).

Depression appears to increase the risk of MI. Similarly, MI can lead to depression. Therefore, the physician must be vigilant for signs of depression and not merely assume that it is "normal" for a patient to be depressed after a heart attack. The options for treating depression pharmacologically include the use of selective serotonin reuptake inhibitors (270). Although concerns exist over the cardiac side effects of tricyclic antidepressants, use of selective serotonin reuptake inhibitors after acute MI appears safe (271). Additionally, the social support provided by a spouse can have substantial effects on recovery after MI. Interestingly, the social support provided by a pet can have a tremendous positive influence on survival after MI as well (272).

Ideally, all the aforementioned aspects of lifestyle modification can be incorporated into a comprehensive cardiac rehabilitation program. Whether this will be a formal or informal program depends largely on patient preference and local availability of resources, but in either case, the commitment to change on the part of the patient and physician is most critical.

CONTROVERSIES AND PERSONAL PERSPECTIVES

In the patient who appears to have experienced clinical reperfusion after fibrinolysis, the value of routine angiography remains controversial. Newer methods to assess microvascular reperfusion, such as electrocardiographic ST-segment resolution, contrast echocardiography, and magnetic resonance imaging, may help further clarify which patients will benefit from early angiography. Patients with recurrent spontaneous ischemia or abnormal results of a stress test should definitely undergo cardiac catheterization, with the goal of performing revascularization. After initial treatment, much of the distinction between therapy for ST-segment elevation MI and non–ST-segment elevation acute coronary syndromes will continue to be blurred as an early invasive approach becomes the standard treatment for chest pain syndromes associated with electrocardiographic deviation or elevated markers of myocardial necrosis and inflammation.

Efforts to increase the use of beta-blockers and ACE inhibitors should continue, given the widespread availability of these proven medications, and, unless new data emerge, calcium channel blockers should not be used as first-line agents for secondary prevention in patients with MI. Whether both beta-blockers *and* ACE inhibitors are necessary in every patient requires clarification from clinical trials. Because beta-blockade has been shown to decrease adverse ventricular remodeling and ACE inhibition has been shown to decrease sudden death, the two classes of drugs may have overlapping protective effects, and both may not be necessary in the patient who has normal left ventricular function after MI. The role of warfarin in acute MI should be limited to specific indications, such as atrial fibrillation or left ventricular thrombus. Instead, oral antiplatelet therapy should be continued after acute MI. Aggressive identification and treatment of hypertension, hypercholesterolemia, and diabetes should occur, with medical therapy begun in the hospital phase.

Quality improvement initiatives directed at the physician and the patient can increase the use of appropriate medications and lifestyle measures (273). Measures to improve quality do appear to be able to affect "hard" end points such as mortality rates (274). Communication between the hospital-based specialist and the outpatient physician is necessary to ensure a smooth transition of care for the patient. Effective methods to enhance such communication need to be developed and integrated into health care delivery systems (275). The availability of guidelines to aid the practitioner in management of MI should be welcomed (276,277). In fact, one of the few measurable differences between treatment of patients with MI in "top" hospitals and mediocre hospitals appears to be a difference in the use of medications such as aspirin and beta-blockers, and this appears to translate into better outcomes, including reduced mortality rates (278). Although physician resistance to implementation of guidelines is often the result of a perceived intrusion into the "art" of medicine, in reality, much of the variation in physician practice stems from a failure to incorporate new data (279). For example, a large degree of geographic variation exists in the prescription of medications that have been proven to be effective in multiple, randomized clinical trials (280,281). Payer status also appears to influence management after acute MI (282). A comprehensive approach that integrates care at multiple levels in the health care system will help standardize and optimize the care of patients after MI.

THE FUTURE

Early revascularization will become the favored strategy throughout Western health care systems. Optimal medical management begun early in the hospital course after MI will include statin therapy, beta-blockade, ACE inhibition, and antiplatelet therapy. The coupling of early revascularization with aggressive medical therapy will lead to dramatically improved outcomes after MI. Efforts targeting thrombus formation will continue to be an important part of secondary prevention and will consist of antiplatelet therapy with aspirin, clopidogrel, or possibly a combination. Inflammatory markers will help stratify risk beyond current measures, and therapies directed specifically at inflammatory pathways will be developed. A more refined understanding of the role of inflammation will complement efforts directed at treating thrombosis. The relative effectiveness, cost-effectiveness, incremental benefit, and potential for interaction of all these different medications in combination remain to be determined, although industry is unlikely to fund this type of research (283,284). Potentially, pharmacogenomics will allow targeting of patients most likely to benefit from therapy. Initially, based on the knowledge of the human genome, efforts will be directed toward the development of pharmaceuticals tailored to specific genotypes. For example, factor VII, glycoprotein IIIa (PlA2 allele), and thrombospondin genes have all been demonstrated to have clinically relevant single-nucleotide polymorphisms that could guide the use of different antithrombotic cocktails (285,286,287,288,289,290 and 291). Eventually, therapies designed to modify or enhance an individual's genetic structure will be created. Lifestyle modification will remain an important part of secondary preventive efforts, although pharmaceutical adjuncts to aid in smoking cessation and weight loss will continue to be tested. The appreciation of psychosocial factors in the well-being of post-MI patients will grow. The aging of the population will continue to challenge the health care system. The mortality rate among aged patients with acute MI remains extremely high, and a shift toward more aggressive management in both the acute and chronic phases of therapy will be necessary (292). Use of practice guidelines and critical care pathways, aided by developments in medical informatics, will play an even larger role in reducing variability in physician management and improving the care of the post-MI patient.

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21

MITRAL VALVE DISEASE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Mitral stenosis is almost invariably the result of chronic rheumatic heart disease secondary to one or more prior episodes of acute rheumatic fever. The beginning of modern cardiology is defined by the earliest clinical studies of mitral stenosis (1,2). The disease can be recognized and its severity appreciated from a careful history and physical examination (3). In more recent years, it has become possible to obtain a highly accurate assessment of the pathologic status of the mitral valve by means of a Doppler-echocardiographic examination.

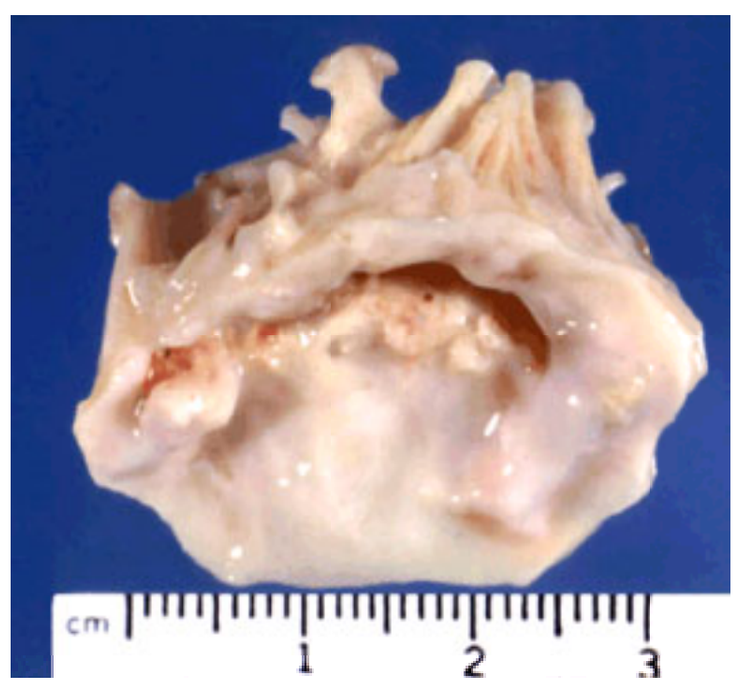
Rarely, mitral stenosis can be the result of entities other than rheumatic heart disease. For example, congenital mitral stenosis, infective endocarditis with large vegetations that obstruct the mitral orifice, massive mitral annular calcification, and a variety of rare inborn errors of metabolism (e.g., Fabry's disease, Hurler-Scheie syndrome) can all lead to clinically important mitral stenosis (4). Deposition of mucopolysaccharidoses within the valve structure itself leads to thickening and eventual fibrosis with consequent valve obstruction. Other rare causes of mitral stenosis include the malignant carcinoid syndrome, systemic lupus erythematosus, and rheumatoid arthritis, all of which can lead to mitral valvular fibrosis (5,6). Amyloid deposits may also thicken the mitral valve and lead to modest stenosis (7). Left atrial myxoma and ball-valve thrombus of the left atrium reproduce the pathophysiologic changes of mitral stenosis, although the valve itself is often normal (8).

VIDEO

Video 21.1 Atrial myxoma (long-axis). A myxoma attached to the interatrial septum is seen. During diastole, the myxoma moves through the mitral orifice into the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

NATURAL HISTORY OF MITRAL STENOSIS

The natural history of untreated mitral stenosis was carefully studied before the advent of cardiac surgical techniques for relieving mitral stenosis (1,9). Children who developed acute rheumatic fever had a 30% chance of dying over the subsequent 20 years, with more than 90% of these deaths attributed to heart disease (1). Forty-five percent of survivors had clinical evidence of rheumatic heart disease; almost invariably, mitral stenosis was present in these latter patients.



Rheumatic mitral valve. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 21.2 Parasternal long-axis view of a rheumatic mitral valve with thickened, restricted, doming leaflets. Severe mitral regurgitation is the primary functional problem with this valve with only mild mitral stenosis. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 21.3 Parasternal long-axis view of a rheumatic mitral valve with color Doppler. Mitral regurgitation is the primary problem seen by color Doppler, with only mild mitral stenosis due to the thickened and doming leaflets. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 21.4 Apical four-chamber view of a patient with severe rheumatic mitral stenosis with marked thickening and doming of the mitral leaflets, with severe ALE and spontaneous echo contrast within the left atrium. Note the left ventricle remains small. Because of long-standing severe mitral stenosis, the patient has severe pulmonary hypertension with right ventricular hypertrophy and right ventricular failure and severe right atrial enlargement. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Prospective clinical studies of patients with known mitral stenosis have shown that approximately one-half of these individuals are asymptomatic at the time of diagnosis if a young population (mean age, 28 years) is examined (9). An additional 47% of patients had mild or moderate symptoms. Mortality was 39% at 10 years and 78% at 20 years. Most of the deaths were the result of heart failure or arterial embolism. If an older population (mean age, 42 years) is followed, more of the patients are symptomatic at the time of diagnosis (86%), and the 10-year mortality is higher (70%) (10). The mortality at 20 years was only slightly higher (83%) than in the younger population, however. The 10-year mortality in a more recent observational study was 60% (11).

The average patient with mitral stenosis develops acute rheumatic fever for the first time at age 12. In general, the murmur of mitral stenosis is heard approximately 20 years later (2). Cardiac symptoms usually appear in the fourth or fifth decade in patients who live in industrialized nations. In developing countries, particularly tropical areas, the disease progresses more rapidly. This may be the result of prolonged or repetitive episodes of untreated acute rheumatic fever. In developing countries, one commonly observes teenagers or young adults with severe mitral stenosis. Symptoms develop gradually in approximately one-half of the patients; sudden development of symptoms is often the result of new onset atrial fibrillation.

The progression of mitral stenosis is generally slow, although wide variation in clinical progression exists among different patients. In Rowe's series, 40% of patients were clinically unaltered after 10 years (9). Grant followed 238 British servicemen with mitral stenosis for 10 years and noted that disease in one-third had progressed, one-third were unchanged, and one-third had died (12). More recent serial hemodynamic and Doppler-echocardiographic studies have demonstrated annual mitral valve area loss ranging from 0.09 to 0.32 cm^2 (13,14). The rate of progression of mitral valve narrowing was variable among individuals, however. Patients with the most stenotic valves and the largest mitral valve gradients tended to progress the most rapidly (14).

Anatomic Considerations

As already noted, stenotic mitral valves are the result of relatively few conditions, with rheumatic heart disease as the etiology in all but a rare patient. With respect to operatively excised rheumatic mitral valves, 83% were stenotic with or without accompanying mitral regurgitation; 17% were purely regurgitant (4,15). Because of a decreasing incidence of acute rheumatic fever in the United States, the percentage of operatively excised valves that are stenotic is declining in comparison with valves that are purely regurgitant.

The anatomic features of rheumatic mitral stenosis are listed in Table 21.1. The initial valvular pathologic lesion in acute rheumatic fever consists of valvulitis manifesting as a series of translucent nodules along the line of closure of the mitral valve. With chronic mitral stenosis, the mitral valve is thickened, fibrotic, and often calcified. Aschoff bodies in the myocardium demonstrate that an attack of rheumatic fever has occurred in the past. Aschoff bodies consist of zones of fibrinoid necrosis associated with histiocytes and giant cells; they are located within the myocardium, the endocardium, or both (4). Calcific valvular deposits are generally seen in both leaflets; the amount of leaflet calcium correlates directly with the severity of valvular obstruction and inversely with leaflet mobility. Valvular calcification is more common in men, in older patients, and in individuals with large mitral valve gradients (16).

Diffuse fibrous thickening of the margins of closure
Fibrous thickening involving the entire anterior and posterior leaflets, producing leaflet rigidity
One or both valve commissures fuse, reducing the size of the mitral orifice
Shortened, thickened, and fused chordae tendineae leading to subvalvular stenosis
Calcific deposits in one or both leaflets
Presence of Aschoff's nodules (bodies) in the myocardium

TABLE 21.1 ANATOMIC FEATURES OF RHEUMATIC MITRAL STENOSIS

The process of valvular fibrosis produces a funnel-shaped valve with the base at the left atrial–left ventricular boundary and the narrowed apex within the left ventricular cavity. The left atrium is almost always dilated, and thrombus in a variety of shapes may be present within this chamber. Initial formation of left atrial thrombus often occurs within the auricular appendage. Pulmonary hypertension, associated with severe mitral stenosis, leads to right ventricular hypertrophy and dilatation.

Pathophysiology

It has been suggested that the mitral valvulitis associated with an episode of acute rheumatic fever leads to abnormal flow patterns across the valve. These altered flow patterns place increased tension on an already damaged valve. Furthermore, valve inflammation can lead to fibrin deposition on the valve surface, thereby further increasing abnormality of flow patterns across the valve. The eventual outcome from years of abnormal tension and stress placed on the mitral valve is fibrosis and thickening. It is also possible that smoldering rheumatic immunologic activity continues to damage the valve, leading to progressive fibrosis (3).

In adults, the normal mitral valve area is approximately 4 to 6 cm^2. As mitral stenosis progressively narrows the valve orifice, a gradient develops between the left atrium and the left ventricle. This gradient is usually small and clinically unimportant until the mitral valve area is narrowed to less than 2.0 cm^2. Cardiac output and heart rate also affect the mitral valve gradient: The greater the cardiac output, the larger the gradient; faster heart rates are associated with shortened diastolic filling times and hence larger mitral valve gradients. Atrial fibrillation with fast ventricular response markedly shortens the diastolic filling time, thereby leading to a large increase in the mitral valve gradient. Of course, the larger the mitral valve gradient, the higher the left atrial, pulmonary venous, and pulmonary capillary pressures.

Exercise augments cardiac output and heart rate simultaneously. This can lead to marked increases in left atrial pressure with resulting pulmonary congestion and dyspnea on exertion. When the mitral orifice is reduced to 1.0 cm^2 or less, severe mitral stenosis is said to be present: Left atrial pressure is elevated at rest. At this point in the natural history of mitral stenosis, the gradient across the valve is approximately 20 mm Hg, depending, of course, on the magnitude of the cardiac output. Because normal left ventricular mean diastolic pressure is usually 5 mm Hg, left atrial and pulmonary capillary wedge pressure in these patients is approximately 25 mm Hg (3). Pulmonary capillary wedge pressure in this range leads to marked transudation of fluid into the pulmonary interstitium. The pulmonary lymphatic drainage increases in size and capacity in response to the increased volume of interstitial fluid. Despite this increase in lymphatic capacity, total lung water increases and pulmonary compliance declines (3). Dyspnea is present with minimal exertion. As noted in *e*Table 21.1.1, increasing mitral valve obstruction leads to

progressive elevation in pulmonary capillary pressure and augmented symptoms.

***e*TABLE 21.1.1** PATHOPHYSIOLOGIC CLASSIFICATION OF MITRAL STENOSIS

Class	Mitral valve area (cm^2)	Resting pulmonary capillary pressure (mm Hg)	Cardiac output at rest	Symptoms
Class I: mild	>2.0	<10–12	Normal	Asymptomatic or mild dyspnea on exertion
Class II: moderate	1.1–2.0	~10–17	Normal	Mild to moderate dyspnea on exertion; with smaller mitral valve area: orthopnea, paroxysmal nocturnal dyspnea, hemoptysis
Class III: severe	<1.0	>18	Decreased	Dyspnea at rest; possible pulmonary edema
Class IV: very severe	<0.8	>20–25	Markedly decreased	Severe pulmonary hypertension; right ventricular failure, marked dyspnea at rest; severe fatigue; cyanosis

Elevations in pulmonary venous and capillary pressures lead to increases in pulmonary arterial pressures because pulmonary arterial systolic and diastolic pressure must exceed pulmonary capillary pressure if forward flow is to continue across the pulmonary vascular bed. Initially, increases in pulmonary arterial pressures are commensurate with increases in pulmonary capillary pressure. This is termed *passive pulmonary hypertension*, because the observed increase in pulmonary arterial pressure is completely explained by the increase in left atrial pressure (3,17). After some time with passive pulmonary hypertension, pulmonary arteriolar vasoconstriction develops, adding a precapillary component to the preexisting venous pulmonary hypertension. This form of pulmonary hypertension is said to be reactive, with pulmonary arterial pressure increasing out of proportion to the increase in left atrial pressure. Reactive pulmonary hypertension only develops in patients with severe mitral stenosis who have pulmonary capillary pressures in excess of 18 to 25 mm Hg. However, not all patients with markedly elevated pulmonary capillary pressure develop reactive pulmonary arterial hypertension. It remains unclear why some patients with pulmonary venous hypertension develop pulmonary arteriolar vasoconstriction and others do not.

In some patients, left atrial compliance appears to play an important role in determining pulmonary arterial pressure. Thus, the less compliant the left atrium, the higher the pressure will be within this chamber for any given mitral valve area. In this manner, noncompliant left atria lead to earlier and more severe pulmonary arterial hypertension (17a).

Because the right ventricle does not tolerate increased afterload as well as the left ventricle, it is not surprising that pulmonary hypertension eventually leads to right ventricular dilatation and failure often associated with tricuspid regurgitation. Severe tricuspid regurgitation may develop as right ventricular enlargement produces dilatation of the tricuspid valve annulus.

Left ventricular volumes are normal or decreased in patients with mitral stenosis (18). Left ventricular ejection fraction and other contractile indices are modestly reduced in approximately one-fourth of patients with mitral stenosis (19). Posterobasal hypokinesis is common, perhaps secondary to tethering or extension of the fibrotic valvular process into the adjacent myocardium. All in all, however, left ventricular function remains normal or near normal in the overwhelming majority of patients (20). Concomitant ischemic heart disease, systemic arterial hypertension, or regurgitation of the aortic or mitral valve can also result in left ventricular dysfunction.

Patients with mitral stenosis and normal sinus rhythm have prominent ‘a’ (atrial) waves in the left atrial or pulmonary capillary wedge tracing. The ‘y’ descent following mitral valve opening is slow secondary to valvular obstruction leading to left ventricular filling that is more gradual than normal.

The etiology of a number of complications of mitral stenosis can be explained by examining the abnormal hemodynamic state produced by severe mitral stenosis (Table 21.2). Thus, pulmonary edema develops when the pulmonary capillary pressure exceeds 25 mm Hg, thereby favoring transudation of fluid from the capillary lumen into the pulmonary interstitium and alveoli. Atrial fibrillation is the result of left atrial dilatation and hypertrophy. Systemic embolism occurs as a result of left atrial thrombosis, which, in turn, is the result of sluggish flow in the dilated, fibrillating left atrium. Factors that increase the risk of systemic embolism for patients still in sinus rhythm include advanced age, the presence of left atrial thrombus, decreasing mitral valve area, and the presence of significant aortic regurgitation. For individuals in atrial fibrillation, the risk of arterial embolism increases if there is a history of a previous embolic episode. Mitral commissurotomy decreases the risk for arterial embolism (20a). Hemoptysis results from the rupture of small venules secondary to sudden increases in pulmonary venous pressure, such as might occur in a patient with moderate to severe mitral stenosis who performs strenuous exercise. In industrialized countries, progression of the mitral stenotic process is slow as is the development of pulmonary hypertension. Pulmonary venules gradually thicken in response to increased pulmonary venous pressure. Thus, rupture of venules secondary to sudden accentuation of pulmonary venous hypertension (e.g., in response to exercise) is uncommon, as is hemoptysis. As noted earlier, the pathophysiologic sequence of mitral stenosis occurs at an accelerated pace in patients living in developing nations where the symptom of hemoptysis is more common. An unusual complication of mitral stenosis is hoarseness that develops secondary to compression of the left recurrent laryngeal nerve by a dilated left pulmonary artery, thereby leading to vocal cord paralysis. Rarely, patients report dysphagia, which is the result of esophageal compression by a dilated left atrium.

Elevated left atrial, pulmonary venous, and pulmonary capillary pressure leads to dyspnea, pulmonary edema, hemoptysis
Dilated left atrium leads to atrial fibrillation, systemic embolism, dysphagia (rare)
Pulmonary hypertension leads to right ventricular failure (fatigue, peripheral edema, ascites, cyanosis, venous thromboembolism), vocal cord paralysis secondary to left recurrent laryngeal nerve compression
Abnormal valvular structure with roughened surface leads to infective endocarditis

TABLE 21.2 PATHOPHYSIOLOGY OF SYMPTOMS AND COMPLICATIONS OF MITRAL STENOSIS

As the severity of mitral stenosis increases and left atrial pressure increases, the left atrium gradually dilates. This dilatation, combined with fibrosis within the wall of the atrium, leads to electrical inhomogeneity within the atrial myocardium. Left and right atrial rheumatic inflammation (carditis) also fosters this intramural fibrosis. Atrial conduction velocities and refractory periods are disparate and abnormal in such patients, thereby favoring atrial arrhythmias such as premature atrial contractions, atrial flutter, and, most commonly, atrial fibrillation. Atrial fibrillation is initially paroxysmal in nature. As mitral stenosis progresses and left atrial dilatation increases, atrial fibrillation becomes sustained. Atrial fibrillation contributes to its own persistence because the arrhythmia itself leads to diffuse atrophy of atrial musculature, further atrial dilatation, and increasing inhomogeneity of atrial conduction and refractoriness (21).

Clinical Profile

History

Fifty percent or more of patients with mitral stenosis do not recall having had acute rheumatic fever. In midlife, these patients report dyspnea on exertion. Younger female patients may report an unusual degree of dyspnea during pregnancy. The onset of atrial fibrillation with a rapid ventricular response may also produce marked dyspnea and even pulmonary edema. This is the result of a marked decrease in diastolic filling period, resulting in a concomitant increase in left atrial pressure. Cardiac output may also decrease, producing the sensation of fatigue.

As already noted, frank hemoptysis is the result of ruptured pulmonary venules, whereas blood-tinged sputum is secondary to pulmonary capillary disruption. An occasional patient with severe pulmonary hypertension complains of angina-like chest pain, which is often the result of a marked increase in right ventricular oxygen demand in the absence of arteriosclerotic heart disease. Hoarseness or dysphagia are rarely reported. Arterial embolism usually results from thrombus formed in a dilated, fibrillating left atrium. Arterial embolism may be asymptomatic, or it may lead to symptoms associated with stroke, splenic or renal infarction, or peripheral arterial occlusion. The occurrence of arterial embolism does not correlate well with the severity of mitral valvular obstruction. Thus, even patients with moderate mitral stenosis may suffer an episode of arterial embolism. The risk of embolism increases with age, left atrial size, and the presence of atrial fibrillation (3,22).

Before anticoagulant and surgical therapy were available, approximately one-fourth of patients with mitral stenosis died of complications of arterial embolism. Fortunately, such deaths are unusual in the current era. Patients with moderate or more severe mitral stenosis, particularly those older than age 35 or with dilated left

atria, should be strongly considered for chronic warfarin therapy. Given their high risk for arterial embolism, such therapy is nearly always mandatory in individuals with mitral stenosis and atrial fibrillation (see Medical Therapy of Mitral Stenosis). A rare patient develops a persistent, free-floating, or pedunculated ball thrombus within the left atrium. Such ball thrombi may suddenly obstruct left atrial outflow, leading to marked exacerbation of symptoms, syncope, or even death (8,23).

Physical Examination

Patients with mitral stenosis have a number of characteristic physical findings (Table 21.3). The malar flush may be observed in patients with fair complexions. Jugular venous distension is the result of right ventricular failure. Prominent cardiovascular waves are noted in patients with concomitant tricuspid regurgitation. Peripheral cyanosis is a late finding resulting from low cardiac output. The dilated hypertrophied right ventricle may be palpated during systole along the left sternal border. A systolic impulse from the dilated pulmonary artery can occasionally be felt in the second or third left intercostal space.

Inspection
Malar flush
Peripheral cyanosis (severe mitral stenosis)
Jugular venous distension (right ventricular failure)
Palpation
Parasternal right ventricular impulse
Palpable pulmonary arterial impulse
Palpable first heart sound, pulmonary component of the second heart sound, and occasionally, the diastolic rumble
Auscultation
Increased intensity of the first heart sound
Opening snap
Low-pitched diastolic rumbling murmur

TABLE 21.3 FINDINGS ON PHYSICAL EXAMINATION IN PATIENTS WITH MITRAL STENOSIS

The low-pitched, diastolic rumble of mitral stenosis is best heard at the apex with the patient in the left lateral decubitus position. It is usually accompanied by an accentuated first heart sound (S_1), which is the result of rapid closure of a thickened but pliable valve. The more severe the mitral stenosis, the shorter the interval between the second heart sound (S_2) and the opening snap (OS). As the stenotic valve becomes progressively fibrotic, calcified, and “fixed” (i.e., minimal to no valve mobility), the intensity of the S_1 diminishes and the OS may become inaudible. This is the result of ever-decreasing cardiac output and excursion of the mitral valve leaflets at the time of valve closure. The rumbling diastolic murmur may also be extremely difficult to hear in patients with severe “end-stage” mitral stenosis accompanied by low cardiac output and right ventricular failure.

The OS is the most characteristic feature of mitral stenosis. It occurs when the mitral valve reaches its maximum opening excursion into the left ventricular cavity. The OS may occur between 0.03 and 0.13 seconds after the S_2. An S_2-OS interval (time from the S_2 to the OS) of less than 0.08 seconds implies a markedly elevated left atrial pressure and severe mitral stenosis (24,25). The OS is unfortunately not pathognomonic for mitral stenosis. It can also be heard in patients with mitral regurgitation, ventricular septal defect, second- and third-degree heart block, tricuspid atresia with a large atrial septal defect, and tetralogy of Fallot treated with a Blalock-Taussig shunt (26,27). The OS of mitral stenosis is best heard using the diaphragm of the stethoscope and searching between the left sternal border and the apex. The OS can be differentiated from the pulmonic component of the S_2 because the latter occurs earlier.

The mitral stenotic diastolic rumble may be difficult to hear, particularly in a thick-chested or obese individual. A brief period of exercise may accentuate the murmur. In the early stages of mitral stenosis, the murmur is confined to mid-diastole; as the stenotic valve worsens, the murmur becomes holodiastolic with presystolic accentuation (25). The intensity of the murmur does not correlate with the severity of mitral stenosis, but the duration of the murmur does; patients with severe mitral stenosis often display a holodiastolic murmur (25). The murmur of mitral stenosis is best heard with the bell of the stethoscope held lightly against the skin over the apex impulse with the patient in the left lateral decubitus position. The murmur can be accentuated by exercise, deeply held expiration, or inhalation of amyl nitrite. Presystolic accentuation of the murmur is normally heard when the patient is in sinus rhythm. However, presystolic accentuation is occasionally observed in patients with moderately regular atrial fibrillation (28,29).

Mitral stenosis may be accompanied by other valvular lesions (i.e., aortic regurgitation, aortic stenosis, mitral regurgitation, tricuspid regurgitation, and rarely, tricuspid stenosis). Hence, other murmurs, systolic and diastolic, may accompany the diastolic rumble of mitral stenosis. As right ventricular hypertrophy and dilatation develop, a right ventricular fourth heart sound and, eventually, an S_3 can be heard. When severe pulmonary hypertension is present, a short, early diastolic murmur of pulmonic regurgitation may be appreciated. This is called the *Graham Steell’s murmur*. Another sign of pulmonary hypertension is a pulmonic ejection click that decreases in intensity during inspiration secondary to dilatation of the pulmonary artery (30).

Diastolic rumbles can be the result of other conditions besides mitral stenosis, including left atrial myxoma, atrial or ventricular septal defect, patent ductus arteriosus, cor triatriatum, severe aortic regurgitation (the Austin Flint murmur), or tricuspid stenosis. Mitral stenosis may go unsuspected in patients who are elderly, obese, emphysematous, or have other complicating pulmonary, cardiovascular, or chest wall diseases (31).

VIDEO

Video 21.5 Parasternal long-axis view (transthoracic echo) of a bicuspid aortic valve with prolapse of the anterior leaflet causing posteriorly directed aortic insufficiency. The aortic insufficiency hits the anterior mitral leaflet, causing deformation of this leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 21.6 Transgastric view (transesophageal echo) of the mitral valve in a patient with severe aortic insufficiency. Note the fluttering of the anterior mitral leaflet (*left*) due to the jet of aortic insufficiency hitting it (color flow seen on the left). (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Electrocardiography

Many patients with mitral stenosis are in atrial fibrillation. Those in sinus rhythm usually demonstrate left atrial enlargement on electrocardiography (ECG) (Table 21.4). Left atrial enlargement by ECG correlates more closely with atrial volume than with atrial pressure (32). ECG signs of left atrial enlargement often regress following successful valvulotomy (2). Left ventricular hypertrophy is notably absent. When pulmonary hypertension leads to right ventricular hypertrophy and dilatation, the pattern of right ventricular hypertrophy may be seen in the ECG (Table 21.4). The sensitivity of the ECG diagnosis of right ventricular hypertrophy is not high. However, right ventricular hypertrophy by ECG is almost always present if right ventricular systolic pressure exceeds 100 mm Hg.

Atrial fibrillation is common
In sinus rhythm, P mitrale is present
Prolonged M-shaped P wave (duration >0.12 sec in lead II)
Marked terminal negative component to the P wave in lead V_1 (1.0 mm wide and 1.0 mm deep)
P wave axis between +45 and −30 degrees
Severe mitral stenosis is often accompanied by findings of right ventricular hypertrophy
Right axis deviation (QRS axis >80 degrees)
R wave >S wave in lead V_1

TABLE 21.4 ELECTROCARDIOGRAPHY IN MITRAL STENOSIS

Mitral stenosis. Left atrial enlargement and right ventricular hypertrophy have developed secondary to mitral stenosis, causing fixed pulmonary hypertension.

A 62-year-old female patient with mitral stenosis.

Chest Roentgenography

Chest roentgenographic findings in mitral stenosis include left atrial enlargement, redistribution of pulmonary vascular flow to the upper lung fields, calcification of the mitral valve, an enlarged pulmonary artery, and an enlarged right ventricle (3). Other signs of elevated pulmonary venous pressure may be present, such as Kerley A and B lines and interstitial pulmonary edema (Fig. 21.1).

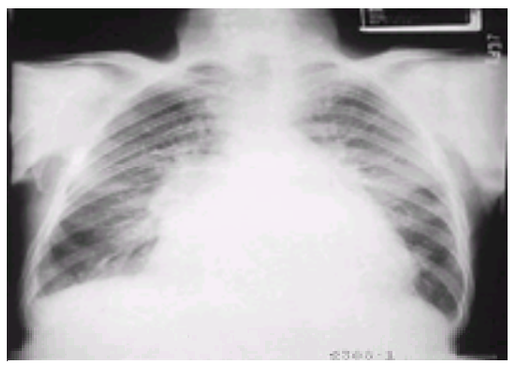


FIGURE 21.1 Chest roentgenogram from a 50-year-old woman with severe, long-standing mitral stenosis complicated by pulmonary hypertension. The overall cardiac silhouette is enlarged secondary to right atrial, right ventricular, left atrial, and pulmonary arterial dilatation. The left ventricle was found to be normal in size during an echocardiographic examination. Marked pulmonary congestion is present.

Although overall heart size is often normal, left atrial enlargement is usually evident. Left atrial enlargement in chest roentgenography is characterized by straightening of the left-sided heart border, a double density within the cardiac silhouette on a postero-anterior film, and elevation of the left main stem bronchus. Posterior displacement of the barium-filled esophagus is also indicative of left atrial enlargement. Massive left atrial enlargement is almost invariably the result of predominant mitral regurgitation and not mitral stenosis, in which atrial dilatation is more modest. Pulmonary arterial dilatation is best appreciated in the postero-anterior view, whereas right ventricular enlargement is best identified on the lateral view. Severe mitral valvular calcification can often be identified on the chest roentgenography; however, more modest calcium deposits require fluoroscopy for identification.

Echocardiography

A modern two-dimensional Doppler-echocardiographic examination of the heart can accurately characterize the severity and extent of the pathologic process in patients with mitral stenosis. A variety of M-mode and two-dimensional findings have been shown to correlate quite well with the hemodynamic determination of mitral valve area (33,34,35,36 and 37). Severe mitral valvular calcification, fibrosis, and limited leaflet excursion can also be identified. The anatomic abnormalities of the stenotic mitral valve (i.e., thickening, diastolic doming, and restriction of leaflet motion) are usually well defined by transthoracic echocardiography. The size of the stenotic mitral valvular orifice is often clearly visualized and quantitated. Doppler-echocardiographic analysis identifies the presence and severity of regurgitation of the aortic, mitral, and tricuspid valves. Two-dimensional echocardiography is more accurate than M-mode echocardiography in defining the severity of mitral stenosis (38). This is especially true when Doppler studies are added to the two-dimensional echocardiographic analysis. An occasional patient requires a transesophageal study to visualize the stenotic mitral valve. Transthoracic echocardiography is sufficient for diagnosis in the vast majority of patients with mitral stenosis. Valvular vegetations can almost invariably be seen with the aid of transthoracic or transesophageal echocardiography in mitral stenosis patients whose course has been complicated by infectious endocarditis.

Echocardiographic study also yields important information concerning left and right ventricular systolic and diastolic function and size, left atrial size, and the presence

of other valvular lesions. Transesophageal echocardiography is quite accurate in identifying thrombus in the left atrium and the left atrial appendage, as well as spontaneous echoes in the left atrial cavity that can predict thrombus formation in the future (39,40). Factors that correlate with spontaneous left atrial echoes and hence an increased risk for thrombus formation and eventual arterial embolism include decreasing degrees of mitral regurgitation, absence of left atrial appendage blood flow, and decreasing mitral valve area (40a). Finally, an accurate measure of mean pulmonary arterial pressure can be obtained from a Doppler examination of a tricuspid valve regurgitant jet. Only a small regurgitant jet is required for this analysis. Many patients do not require invasive study once a thorough Doppler-echocardiographic examination is completed. Coronary arteriography may be the only form of diagnostic catheterization performed in the patient with severe mitral stenosis.

Doppler-echocardiographic analysis is highly accurate in predicting mitral valve area. The value obtained, however, is not predictive of the rate of progression of the stenotic process (41), nor is it predictive of the onset or progression of right ventricular dysfunction. The mitral valvular gradient and the echocardiographic severity score for mitral stenosis are likewise *not* predictive of progression of mitral stenosis or right ventricular dysfunction (41). Transthoracic three-dimensional echocardiography can provide highly accurate and reproducible measurements of mitral valve area (41a).

Cardiac Catheterization

Cardiac catheterization was formerly the gold standard for determining the severity of mitral stenosis. The accuracy of Doppler-echocardiographic techniques has resulted in only selective use of cardiac catheterization in patients with mitral stenosis, however. As noted in Table 21.5, cardiac catheterization is most useful in identifying concomitant coronary artery disease and quantifying the degree of mitral regurgitation that is present. Assessing the level of pulmonary hypertension is also of considerable importance. Less important is the evaluation of left and right ventricular function, because this information is often obtained with considerable accuracy from the echocardiographic study. Quantifying the amount of aortic regurgitation that is present can also be of value, because the Doppler-echocardiographic study may underestimate the aortic regurgitant volume. Most centers accept the echocardiographic assessment of severity of aortic regurgitation, and only an occasional patient requires aortic root cineangiography.

Important
Assessment of coronary artery disease
Quantification of mitral regurgitation
Confirmation of presence or absence of pulmonary hypertension (pulmonary vascular disease)
Moderately important
Assessment of right ventricular and right atrial pressures: presence of right ventricular failure
Assessment of aortic valve function: presence and quantity of aortic regurgitation
Modestly important
Confirmation and quantification of the degree of mitral valve obstruction

TABLE 21.5 INFORMATION THAT MAY BE OBTAINED FROM CARDIAC CATHETERIZATION IN PATIENTS WITH MITRAL STENOSIS THAT MAY NOT BE ALREADY AVAILABLE FROM A DOPPLER-ECHOCARDIOGRAPHIC STUDY

A full hemodynamic and angiographic study for mitral stenosis consists of a left and right heart catheterization with determination of the pressures in all four cardiac chambers. Special attention is paid to the measurement of the diastolic gradient across the mitral valve. Heart rate and cardiac output are also determined, and the mitral valve area is calculated using the Gorlin's formula (42).

Cineangiographic studies are rarely performed if a technically adequate Doppler-echocardiographic study is available for assessment of left and right ventricular function and the severity of aortic, mitral, and tricuspid regurgitation. As already noted, mitral stenosis can be associated with modestly decreased left ventricular contractile function (18,19 and 20), perhaps as the result of tethering of the basal portion of the left ventricle by the fibrotic and calcified mitral valve. Reduced preload or other cardiac lesions are commonly cited reasons for impaired left ventricular systolic function. Coronary arteriography is performed to ascertain if any coronary arterial stenoses are present. Coronary arteriography is omitted if the patient's age (younger than 40 to 45 in men; 50 to 55 in women) or absence of risk factors for atherosclerosis makes it quite unlikely that arteriosclerotic coronary artery disease is present.

Differential Diagnosis

The symptoms and signs of mitral stenosis may be mimicked by several rare clinical entities: left atrial myxoma, cor triatriatum, and primary pulmonary hypertension. Left atrial myxoma is a rare condition in which the usually pedunculated myxoma obstructs the mitral valve orifice. A tumor "plop" in early diastole mimics the OS, and a diastolic rumble is often present. Patients complain of dyspnea and fatigue. Arterial embolism may occur. An echocardiographic examination leads to the correct diagnosis (43,44).

Cor triatriatum is a rare congenital disorder in which a membrane subdivides the left atrium and partially obstructs normal blood flow from the pulmonary veins to the mitral orifice. Thus, the pathophysiology closely resembles that of mitral stenosis. Patients with cor triatriatum are usually symptomatic during early childhood; hence, they are rarely misdiagnosed with mitral stenosis. An OS and a diastolic rumble are not present. The characteristic murmur is systolic as blood crosses the perforation(s) in the intraatrial membrane (45).

Patients with primary pulmonary hypertension occasionally present with right ventricular failure of recent onset. Severe, silent mitral stenosis is considered in the differential diagnosis but is invariably ruled out following an echocardiographic study.

Therapy

Medical Therapy of Mitral Stenosis

Medical therapy of mitral stenosis seeks to prevent and treat complications associated with the disease (Table 21.6). In general, symptomatic mitral stenosis is best treated by relieving the mitral valvular obstruction either by means of balloon valvuloplasty or surgical intervention (valvuloplasty, valve replacement). However, prevention or treatment of a variety of complications associated with mitral stenosis is often necessary (Table 21.6).

Reduce symptoms of pulmonary congestion (dyspnea on exertion, paroxysmal nocturnal dyspnea, pulmonary edema): diuretics, nitrates
Prevent arterial embolism (cerebral or peripheral arterial embolism): anticoagulation
Prevent infectious endocarditis: prophylactic antibiotics
Treat bacterial endocarditis: antibiotics
Prevent/treat atrial fibrillation: digoxin, beta-blockers, antiarrhythmic agents, anticoagulants

TABLE 21.6 THERAPEUTIC GOALS IN PATIENTS WITH MITRAL STENOSIS

Symptomatic dyspnea can be ameliorated with diuretics, as well as short- or long-acting nitrate preparations, but these agents are usually only of temporary benefit. Patients with dyspnea associated with bronchospasm may respond to inhaled corticosteroids (45a). Mitral valvuloplasty or replacement is indicated in symptomatic

patients with mitral stenosis. Cerebral embolism is often a devastating complication of mitral stenosis, accounting for 60% to 70% of episodes of systemic embolism (46). Episodes of systemic embolism can occur in patients with moderate, severe, and even mild mitral stenosis; the risk for this complication increases markedly when atrial fibrillation develops. Embolism can be fatal. In the series of patients with mitral stenosis followed by Rowe et al., 19% of the deaths were attributed to arterial embolism (9). Increasing age and left atrial size both augment the risk of systemic embolism (47,48).

Prophylactic antibiotics are administered to patients with mitral stenosis before dental work, as well as a variety of other interventions (see Chapter 25), to minimize the risk of developing infectious endocarditis. Prolonged courses of intravenous antibiotics are given to patients who develop infectious endocarditis, which is more likely to develop in patients with concomitant mitral or aortic regurgitation (46). Mitral regurgitation usually develops or worsens in patients with mitral stenosis who develop infectious endocarditis.

Atrial fibrillation is a commonly occurring complication in patients with mitral stenosis. Initially, it develops as transient paroxysms; later in the course of the illness, atrial fibrillation is sustained. Often the ventricular response is rapid (>140 beats/min), resulting in a shortened diastolic filling period with concomitant pulmonary venous hypertension. Many of these patients complain of dyspnea at rest, and pulmonary edema may develop.

The loss of atrial contraction has little effect on mitral valve flow in the patient with mitral stenosis in whom left atrial pressure is already quite elevated (49). The size of the fibrillatory waves in the ECG are unrelated to left atrial size (50). In most series of patients with mitral stenosis, approximately 40% of patients have sustained atrial fibrillation with the incidence of the arrhythmia increasing with age and left atrial size (51,52). Patients with mitral stenosis and atrial fibrillation, paroxysmal or sustained, should receive prophylactic anticoagulation with warfarin unless a strong contraindication exists. Some authorities favor prophylactic anticoagulation for all patients with mitral stenosis—even those in sinus rhythm—once they are older than 35 to 40 years, because cerebral or peripheral arterial embolism can occur at any time in the course of the illness (50). Patients who are candidates for warfarin anticoagulation should receive 5 mg per day for 3 days. Thereafter, the daily dose of warfarin is determined by the measured prothrombin time (52). An international normalized ratio between 2.0 and 3.0 should be maintained long-term (52).

Attempts to maintain sinus rhythm with antiarrhythmic medication are often unrewarding and carry the risk of proarrhythmia, syncope, and even sudden death. Many clinicians favor controlling the ventricular response with digoxin combined with beta-blockers or diltiazem. Verapamil may also be employed for this purpose. Chronic anticoagulation with warfarin is also employed. Patients who develop pulmonary edema secondary to a rapid ventricular response are candidates for urgent electrical cardioversion. In less urgent circumstances, reversion to sinus rhythm can often be achieved by administering 1,000 mg of intravenous procainamide over 30 to 60 minutes. Once sinus rhythm is reestablished, it can usually be maintained with intravenous procainamide, 2 mg per minute. Blood pressure and QRS duration should be followed closely during procainamide infusion. The dosage should be decreased if arterial blood pressure falls below 100 mm Hg systolic or if QRS duration exceeds 0.10 seconds. If the clinical decision is in favor of elective cardioversion, patients who have been in atrial fibrillation for 48 hours or more should be anticoagulated with warfarin for 3 to 4 weeks before and for 4 weeks after cardioversion.

Beta-blocker therapy has occasionally been used to slow the heart rate in patients still in sinus rhythm. Because the size of the mitral valvular gradient is directly proportional to heart rate, interventions that lower the heart rate, such as beta-blockade, lead to a reduction in the valvular gradient and hence to a lower pulmonary capillary wedge pressure.

Nonrheumatic Mitral Stenosis

As noted earlier, almost all cases of mitral stenosis are the result of rheumatic heart disease. Tumors, vegetations from infectious endocarditis, and ball-valve thrombi can obstruct the mitral orifice, thereby mimicking the pathophysiologic changes of mitral stenosis (4). Severe mitral annular calcification can occasionally obstruct the mitral orifice as well. Patients with Hurler's syndrome may develop mitral stenosis secondary to deposition of mucopolysaccharides within the valve itself (4). Similar alterations in valvular structure can develop in patients with systemic amyloidosis (7). Congenital mitral stenosis is usually one component of a complex set of malformations involving the left ventricle (4). Case reports have documented mitral stenosis in association with giant cell myocarditis (53). It is unclear whether the mitral stenosis in these individuals was the result of a viral endocarditis or myocarditis or whether the giant cell lesions developed in patients with preexisting rheumatic mitral stenosis. Mitral stenosis has been noted in a rare patient with pseudoxanthoma elasticum, carcinoid syndrome, systemic lupus erythematosus, and rheumatoid arthritis (4,5 and 6,54).

Interventional Therapy: Percutaneous Balloon Mitral Commissurotomy

Percutaneous transvenous valvotomy is usually performed with specially designed balloon catheters that are advanced across the stenotic mitral valve from the left atrial side. The catheter is placed in the left atrium using a venous transseptal technique. The balloon is inflated, thereby separating the stenotic leaflets (55,56 and 57). However, the procedure can also be performed by placing the balloon catheter across the mitral valve using a retrograde, transaortic, arterial route. Early results with this retrograde technique have been good, although local arterial complications were more common than with the transvenous technique (57a,57b). A new percutaneous technique, employing a metallic valvulotome attached to a catheter, has given excellent short-term results. Multiple uses are possible with this device, thereby reducing the cost for percutaneous mitral commissurotomy. Comparison with the traditional balloon technique and long-term results are not available as yet (58c). The procedure resembles surgical, closed mitral valvuloplasty. In some patients, leaflet calcification may also fracture.

Patients should be carefully selected for this procedure by means of two-dimensional echocardiography. Individuals with symptomatic mitral stenosis and pliable, mobile, relatively thin, and minimally calcified valves are the best candidates for balloon valvuloplasty. Some clinicians favor studying the patient with transesophageal echocardiography before balloon valvuloplasty to ensure that no thrombus is present in the left atrium. Short-term and intermediate-term results are quite good when compared with surgical valvuloplasty (55,56 and 57). Long-term results are excellent as well (58,59). In one study, two-thirds of patients treated with percutaneous balloon mitral commissurotomy were in good clinical condition and free of any major event 7 years after the procedure. However, the mitral valve area decreased progressively with time, although mitral regurgitation did not progress (58a). Similar good long-term results have also been observed by other investigators (58a,58b,58d). However, Hildick-Smith and coworkers reported more modest but still acceptable long-term results in a western European population with unfavorable characteristics (58e). In addition to the usual adult population of patients with mitral stenosis, balloon valvulotomy has been successfully employed in children and pregnant women (58e,58f and 58g).

Mitral valve area usually increases to 2.0 cm^2 or more following balloon valvuloplasty, whereas left atrial pressure declines and cardiac output increases (60,61). Symptoms of pulmonary congestion are relieved. A small residual atrial septal defect can be identified in a small number of patients. It is of considerable interest that relief of mitral stenosis is associated with improvement in both systolic and diastolic measures of left ventricular performance (62,63 and 64). Repeat balloon valvuloplasty can be performed successfully in patients who develop restenosis (64b).

Goto and coworkers observed increased left ventricular end diastolic volumes and improved left ventricular ejection performance following successful mitral balloon valvulotomy (62). arious measures of left atrial function also improve after successful balloon commissurotomy (62a). Tischler and associates noted increases in both left ventricular end diastolic volume and mass following balloon valvulotomy (63). Liu and coworkers attributed improved left ventricular compliance following valvotomy to a more mobile mitral valve apparatus (64). Moreover, increased sympathetic nerve activity normalizes following successful balloon valvuloplasty (64a).

Failure rates range from 1% to 17% and are usually the result of inexperience. Patients with symptomatic mitral stenosis are candidates for balloon valvuloplasty, even if they have undergone previous mitral valvuloplasty by surgical or catheter technique. Patients who have had an episode of arterial embolism should be avoided. Pulmonary hypertension is not a contraindication. Individuals with more than mild mitral regurgitation or clinically significant aortic stenosis should be referred for surgery (65,66 and 67). Predictors of long-term, event-free survival include mitral valve morphology as reflected in the echocardiographic score, baseline and postprocedural valve area, and the presence of chronic atrial fibrillation, preexisting mitral regurgitation, or both (67a,67b and 67c).

Surgery for Rheumatic Mitral Stenosis

The pioneering work of Souttar, Cutler, Harken, and Bailey (68,69,70 and 71) began the era of the surgical treatment of mitral valve disease. Their early operations were closed mitral commissurotomies for rheumatic mitral stenosis. Today, with the assistance of cardiopulmonary bypass and myocardial protection, surgeons are no longer blinded to the valve pathology but can directly inspect the mitral valve and repair or replace the valve. Techniques for mitral valve repair have evolved to such a degree that severely regurgitant or stenotic mitral valves may be repaired with excellent long-term results. For mitral valves unsuitable for repair, both bioprosthetic and prosthetic valves are available.

The standard approach to mitral valve surgery is through a median sternotomy. Cardiopulmonary bypass is performed with direct aortic cannulation for arterial return and bicaudal cannulation for venous drainage. During the cross-clamp period, the heart may be protected with either antegrade cardioplegia or a combination of both antegrade and retrograde cardioplegia. Exposure for the mitral valve may be through a standard left atriotomy or through a transseptal approach, as advocated by Guirdon.

Mitral Valve Replacement

Two types of valves may be used to replace the mitral valve: prosthetic or bioprosthetic valves. The prosthetic valves are the mechanical valves and come in three main types: tilting single disk valves, bileaflet valves, and ball valves (see Chapter 24). Although excellent durability has been reported with the mechanical valves, the major drawback of these valves is that patients with mechanical valves must be anticoagulated with coumadin for life to prevent thromboembolic events. The bioprosthetic valves are stented, glutalderhyde-treated porcine valves (see Chapter 24) or trileaflet, glutalderhyde-treated bovine pericardial valves. Although the bioprosthetic valves lack the durability of the mechanical valves, patients in sinus rhythm with bioprosthetic valves do not need to be systemically anticoagulated with coumadin to prevent thrombosis or embolism. The major drawback of bioprosthetic porcine valves is that 20% to 40% fail over 10 years secondary to structural deterioration and require reoperation (72). In patients over the age of 70, however, structural deterioration is rare (73,74). Results of bovine pericardial mitral valve use suggest better long-term durability compared with porcine valves. In one study, actuarial freedom from structural valve deterioration at 10 years in patients with bovine pericardial mitral valves was 95% in patients 61 to 70 years old and 100% in patients greater than 71 years old (74a).

Although attempts have been made at establishing guidelines to assist surgeons as to which type of valve is best for certain patients, valve selection must be individualized for each patient. The selection of which type of valve to insert in which patient is based on weighing the disadvantages of anticoagulation-related complications associated with mechanical valves against the disadvantages of decreased longevity of the bioprosthetic valves. Mechanical valves are usually inserted in younger patients (<70) who have no contraindications to anticoagulation or in any patient who is already systemically anticoagulated for another reason, such as atrial fibrillation. Bioprosthetic valves are usually placed in older patients (>70) or in any patient who has a contraindication to systemic anticoagulation, such as a history of gastrointestinal hemorrhage.

To preserve left ventricular function, when replacing a mitral valve, the mitral valve leaflets and chordae tendineae should be preserved. Although first suggested by Lillihei et al. in 1964 (75), chordal-sparing techniques to preserve left ventricular function after mitral valve replacement did not become widely accepted until the 1980s. The deterioration in left ventricular function seen after mitral valve replacement was originally felt secondary to the elimination of regurgitant flow into the left atrium (76). However, as mitral valve repair techniques became popular and no decrease in left ventricular function was observed after regurgitant mitral valves were repaired (77,78), the contribution of the chordae to left ventricular function was again appreciated. Many clinical studies have demonstrated that preserving mitral valve chordae during mitral valve replacement not only results in better left ventricular function postoperatively, but also results in decreased operative mortality and decreased incidence of left ventricle rupture following mitral valve replacement (79,80,81,82,83 and 84).

The native, diseased mitral valve should be débrided of calcium and any fibrous material that has formed on the valve. This restores leaflet flexibility and allows insertion of an artificial valve without having to excise the mitral valve leaflets and their subvalvular attachments. When inserting a mechanical valve, it is important to ensure that the remaining mitral valve leaflets or chordae do not interfere or become entrapped in the valve mechanism, thus preventing proper valve functioning.

The prosthetic or bioprosthetic mitral valve is sutured into place by placing the sutures first through the valve annulus and then through the sewing ring of the valve. The valve is then seated in the annulus and the sutures are tied. A variety of suture techniques may be used. Simple interrupted sutures or pledgeted mattress sutures with the pledgets placed on either the atrial or ventricular surface of the annulus may be used. To avoid interfering with valve function, when using pledgeted sutures with a mechanical valve, the pledgets are usually placed on the atrial surface of the annulus.

Results of Mitral Valve Replacement

Operative mortality correlates directly with the preoperative functional class of the patients undergoing mitral valve replacement. Patients in functional class three or less have a reported operative mortality of £2% (85,86 and 87). However, patients in functional class four have an operative mortality of 25% (85).

Five-year survival rates of 80% to 85% have been reported for patients undergoing mitral valve replacement (88,89,90 and 91). Surprisingly, long-term survival is independent of the type of valve inserted, but it is directly related to preoperative myocardial function (88,89,90 and 91). This emphasizes that patients with significant mitral valvular lesions should undergo mitral valve surgery before a significant decrease in their left ventricular function.

Thromboembolic complications occur in 2% to 4% of patients with mechanical valves per year who are adequately anticoagulated with coumadin (72). Of these thromboembolic events, however, 50% are minor, without any residual deficit or complication. Patients with porcine mitral valves who are not anticoagulated have a yearly thromboembolic rate of 1% to 3% (72,89,92). In patients in sinus rhythm with bioprosthetic valves and no anticoagulation, however, Cohn et al. observed no embolic events in patients followed for a mean of 3 years (89). For patients anticoagulated with warfarin, the risk of a major hemorrhage is 1.5% per year, and the risk of a fatal hemorrhage is 0.5% per year (93,94).

Structural valve deterioration is rare in mechanical valves, except for the 70-degree Björk-Shiley convexo-concave valve. This valve had structural failure of the welded outflow strut, and this mechanical valve has been removed from the market.

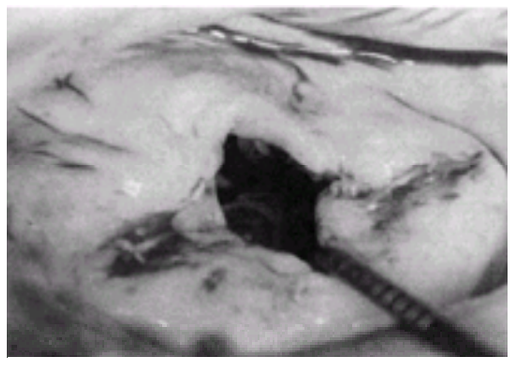
Mitral Valve Repair

Unlike mitral valve replacement, mitral valve repair surgical techniques are individualized to the specific mitral valve pathology. Both stenotic and regurgitant valves may be successfully repaired with excellent long-term results. The ability to successfully repair the valve depends not only on the severity of the valve pathology, but also on the experience and ability of the surgeon.

Mitral Repair for Rheumatic Mitral Stenosis

The first operations performed on the mitral valve were closed mitral valve commissurotomies to relieve mitral valve stenosis secondary to rheumatic mitral valve disease (68,69,70 and 71). Today, mitral valve repairs for rheumatic mitral stenosis not only correct commissural fusion, but also restore leaflet mobility and pliability and relieve subvalvular chordal and papillary muscle fusion.

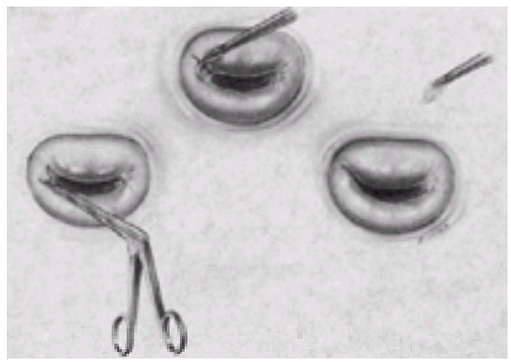
The dominant features of rheumatic mitral stenosis are commissural fusion and leaflet thickening (eFig. 21.1.1). Commissural fusion is the earliest phase of rheumatic mitral valve disease and is also the most amenable to surgical therapy. Commissurotomies of the involved commissures are performed by incising the area of fusion between the anterior and posterior leaflets. To avoid mitral insufficiency after commissurotomies, the commissurotomies should not be extended to the annulus. If areas of commissural regurgitation occur after commissurotomies, they may be corrected with annuloplasty sutures or an annuloplasty ring.



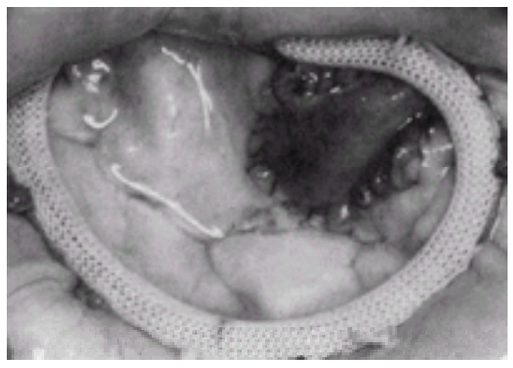
***e*FIGURE 21.1.1** Rheumatic mitral valve with leaflet thickening and commissural fusion.

When rheumatic disease involves the mitral valve leaflets, the leaflets become thickened, scarred, and often calcified. These pathologic changes lead to immobile, restricted leaflets, resulting in mitral stenosis, mitral insufficiency, or both. The goal of surgical repair is to restore the pliability of the mitral valve leaflets. This leaflet thickening and scarring results from a fibrous layer that forms on the leaflets. This fibrous layer can often be excised from the thickened and scarred leaflets, leaving the leaflets more translucent, thinner, and pliable (95) (eFig. 21.1.2). As the disease progresses, areas of calcification occur on the leaflets. These areas may be

excised and replaced with glutaraldehyde-treated autologous pericardium (eFig. 21.1.3).



***e*FIGURE 21.1.2** The fibrous layer that forms on the mitral valve leaflets may be excised.



***e*FIGURE 21.1.3** Areas of calcification on the leaflet are excised and replaced with a pericardial patch.

The greatest problem in the reconstruction of the rheumatic mitral valve is repair of chordal and papillary muscle fusion. The fibrous layer that is often present on the leaflets may extend down onto the chordae. This peel may be teased off the chordae, restoring the mobility of the chordae. To restore normal chordal and papillary muscle mobility, the chordae and papillary muscle may be split (96). used chordae may also be replaced by artifical Gore-Tex chordae or replaced by normal chordae from another area of the mitral valve (96).

Results of Valve Repair for Rheumatic Mitral Stenosis

Although the results of valve repair for rheumatic mitral valve disease have been less satisfying than for other etiologies of mitral valve disease, they are still favorable. Of all patients with rheumatic mitral stenosis presenting for surgery, 60% to 80% of the stenotic valves have been reported to be successfully repaired (97,98 and 99). Operative mortalities of under 1% (97,99,100,101 and 102) and 10-year survival rates of >95% (97,99,100,101 and 102) have been reported for patients undergoing mitral valve repair for rheumatic mitral stenosis. In addition, the durability of the repair has been encouraging. Freedom from reoperation at 10 years for mitral valve failure has ranged from 84% to 90% (97,99,102). Duran et al., however, noted an increased rate of repaired mitral valve failure in young patients (<20 years of age) who underwent mitral valve repair for rheumatic mitral stenosis (103).

The timing of surgical repair for rheumatic mitral stenosis may affect the long-term results, and some suggest that early surgery may not only improve long-term survival, but also increase the likelihood of successful valve repair, decrease the long-term complication rate, and decrease the rate of valve repair (97,99). Eguaras et al. (99), in a retrospective review, divided patients with severe mitral stenoses (valve area <1.3 cm^2) into two groups. The first group consisted of patients in sinus rhythm with few or no symptoms. All of these patients underwent successful valve repair. There were no operative deaths, and 100% were alive at 11 years. There were no recurrences of mitral stenosis at 10 years, and only 1 patient of 40 required reoperation for mitral regurgitation. Actuarial freedom from complications at 11 years was 97%. Similarly, group II consisted of patients with severe mitral stenosis who also had a history of clinical symptomatology (functional class III or IV) or a history of thromboembolism. In contrast, only 70% of these valves were successfully repaired. Operative mortality was 1.9%. Actuarial freedom from reoperation and complications at 11 years was 86.1% and 73.4%, respectively. When mortality, reoperation, embolism, or poor clinical condition were included as complications, group I did significantly better than group II. Although not a randomized comparison, these observations support the hypothesis that early rather than late surgical valve repair for rheumatic mitral stenosis improves not only the ability to successfully repair the valve but also the long-term outcome.

Comparison of Mitral Valve Repair and Percutaneous Balloon Mitral Commissurotomy

In recent years, percutaneous balloon commissurotomy has largely replaced surgical repair of the stenotic mitral valve. Farhat et al. performed a randomized controlled trial comparing percutaneous balloon mitral commissurotomy with surgical closed and open commissurotomy in 90 patients with mitral stenosis and pliable valves (103a). The best long-term results were obtained with balloon and open surgical commissurotomy, with only a 6.6% restenosis rate after 7 years as compared with a 37% restenosis rate for closed mitral commissurotomy. Moreover, larger initial mitral valve areas were obtained with the percutaneous and open surgical techniques as compared with the closed surgical procedure. The authors concluded that the procedure of first choice was the percutaneous balloon technique because of the lower costs and the elimination of the need for thoracotomy and cardiopulmonary bypass. Ommen et al. observed no difference in long-term, event-free survival between patients with mitral stenosis treated by percutaneous balloon versus closed surgical mitral commissurotomy (103b).

MITRAL REGURGITATION

During the first half of the twentieth century, textbooks of cardiovascular disease emphasized mitral stenosis over mitral regurgitation. Moreover, during the 1950s and 1960s, some clinicians stated that mitral regurgitation was a relatively unimportant valvular lesion rarely requiring therapy. As rheumatic fever has waned in the United States and the understanding of the multiple etiologies of mitral regurgitation has increased, the latter lesion has assumed greater importance than the former. Current thinking distinguishes the various causes of mitral regurgitation and the difference between acute and chronic forms of this pathophysiologic entity (Table 21.7).

Chronic
Inflammatory
Rheumatic heart disease
Systemic lupus erythematosus
Progressive systemic sclerosis
Methysergide therapy
Degenerative
Myxomatous degeneration of the valve
Calcification of the mitral valve annulus
Marfan's syndrome
Ehlers-Danlos syndrome
Pseudoxanthoma elasticum
Ankylosing spondylitis
Infiltrative amyloidosis
Infectious
Infectious endocarditis
Structural
Ruptured chordae tendineae (acute mitral regurgitation that can become chronic)
Dysfunction of a papillary muscle (ischemic (acute mitral regurgitation that can become chronic)
Dilatation of mitral valve annulus secondary to left ventricular dilatation (cardiomyopathy)
Hypertrophic cardiomyopathy
Paravalvular prosthetic valve leak
Congenital
Cleft mitral valve (associated with other congenital heart disease (e.g., ostium atrial septal defect))
Parachute mitral valve (associated with other congenital heart disease (e.g., endocardial cushion defect, endocardial fibroelastosis, transposition of the great arteries))
Acute
Structural
Trauma
Dysfunction or rupture of a papillary muscle (ischemic heart disease)
Prosthetic valve malfunction with paravalvular leak or leaflet malfunction or disruption
Infectious
Infectious endocarditis
Acute rheumatic fever
Degenerative
Myxomatous degeneration with chordal rupture

TABLE 21.7 CAUSES OF MITRAL REGURGITATION

During the last 25 years, the incidence of rheumatic mitral regurgitation has declined steadily. Conversely, degenerative and structural etiologies (Table 21.7) have increased in number. Mitral valve prolapse is the most common form of valvular heart disease in the United States. Consequently, in addition to material cited throughout the section on mitral regurgitation, a separate section is dedicated to mitral valve prolapse.

Anatomic Considerations

Anatomic changes in patients with mitral regurgitation vary according to the underlying etiology. Thus, patients with rheumatic mitral regurgitation develop progressive fibrosis, contracture, and calcification of the mitral valve and the chordae tendineae, which can lead to predominant mitral stenosis, predominant mitral regurgitation, or mixed stenosis and regurgitation.

Patients with floppy or prolapsing mitral valves demonstrate redundant myxomatous tissue with excess deposits of proteoglycans within the spongiosa layer of the valve (104,105). This excess tissue impinges on the supporting fibrosa layer of the valve, resulting in the laxity and redundancy of the leaflets. There is associated mitral annular dilation. Moreover, all major components of mitral valvular connective tissue are abnormal in patients with floppy mitral valves.

The presence of excessive amounts of proteoglycans may interfere with the normal synthesis of collagen and elastic fibers. These valves are characterized by disorganization of bundles of collagen fibers and alterations in the aggregation and organization of elastic fibers (105). The posterior leaflet is affected more often and more severely than the anterior leaflet (106). Myxomatous change can affect the chordae tendineae as well as the tricuspid and aortic valves. Myxomatous chordae are prone to spontaneous rupture, thereby producing an acute and marked increase in the amount of mitral regurgitant blood flow.

Floppy valves occur in association with Marfan's syndrome, Ehlers-Danlos syndrome, thoracic skeletal abnormalities, acute rheumatic carditis, and a variety of congenital cardiac conditions (107,108,109 and 110). Marfan's syndrome is associated with a dilated mitral valve annulus and severe myxomatous changes in the valve leaflets. Similar myxomatous alterations are found in patients with other connective tissue disorders such as Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. Other conditions that have been reported in association with mitral valve prolapse include periarteritis nodosa, myotonic dystrophy, von Willebrand's disease, hyperthyroidism, and various intracardiac congenital malformations such as atrial septal defect and Ebstein's anomaly of the tricuspid valve. Patients with primary mitral valve prolapse have an increased incidence of asthenic habitus, straight back, and pectus excavatum (107,108,109,110,111,112,113,114,115 and 115a). One group of investigators has even suggested that mitral valve prolapse is an acquired condition, the result of a growth disproportion between the heart and the chest cavity (115b). However, another group of investigators (115c) has reported an inherited form of myxomatous degeneration of the mitral valve located on the X chromosome (locus Xq28).

Some patients develop end systolic mitral valve prolapse secondary to elongated chordae tendineae or papillary muscles, or both, whereas others have small left ventricular cavities with normal sized mitral valve apparatus. Young, asthenic women and older men have a tendency to develop this latter form of mitral valve prolapse. Thus, one can characterize this latter type of mitral valve prolapse as resulting from mitral valve–left ventricular cavity size mismatch.

Calcification of the mitral annulus interferes with the normal closure of the valve leaflets. Moreover, the sphincter-like action of the annulus, which occurs during ventricular systole, is lost. Mitral annular calcification is commonly seen in patients with Marfan's syndrome and in elderly women. In the latter group, mitral annular calcification often parallels the presence of coronary arterial and aortic atherosclerosis. On occasion, mitral annular calcification spreads into the conduction system, leading to varying degrees of heart block (116,117). Mitral annular calcification is accelerated in patients with diabetes, arterial hypertension, calcific aortic stenosis, and Marfan's and Hurler's syndromes. Mitral annular calcification is also common in patients with chronic renal failure and secondary hyperparathyroidism. Calcified protrusions may extend from the heavily calcified annulus into the adjacent myocardium, with resulting conduction system abnormalities (118). In most patients, calcification is modest as is the degree of mitral regurgitation.

Infectious endocarditis involving the mitral valve can cause mitral regurgitation secondary to leaflet destruction, perforation, or chordal rupture (119). Acute mitral regurgitation may gradually give way to subacute and chronic valvular insufficiency. Large vegetations can prevent appropriate leaflet coaptation, whereas healed vegetations may lead to valvular fibrosis and deformity (119a).

A variety of uncommon congenital abnormalities can lead to chronic mitral incompetence. For example, clefts of the anterior leaflet are often associated with partial or total AV canal or anomalous mitral arcade (120). Other congenital malformations associated with mitral regurgitation include endocardial fibroelastosis, transposition of the great arteries, and anomalous origin of the left coronary artery from the pulmonary artery.

Trauma may lead to acute, severe mitral regurgitation as a result of disruption of a chordae tendineae or a mitral valve leaflet. Ischemia or infarction is commonly associated with acute as well as chronic mitral regurgitation. Abnormal papillary muscle contractile function is often accompanied by hypokinesis or akinesis of the adjacent left ventricular wall. If papillary muscle ischemic necrosis is present, partial or total papillary muscle rupture may occur (119). The latter almost invariably leads to cardiogenic shock secondary to severe, acute mitral regurgitation with the subsequent demise of the patient. The former may be associated with mild, moderate, or severe mitral regurgitation (119). Papillary muscle rupture usually occurs during the first week after infarction (see Chapter 19). Healing and fibrosis of an infarcted papillary muscle can lead to chronic mitral insufficiency.

The posterior papillary muscle has a single blood supply (i.e., the posterior descending coronary artery), whereas the anterior papillary muscle has a dual blood supply: diagonal branches of the left anterior descending and marginal branches of the left circumflex coronary arteries. Hence, the posterior papillary muscle is more susceptible to ischemia and rupture. Dyskinesis of left ventricular myocardium adjacent to the papillary muscle contributes to the development of mitral regurgitation (121).

In experimental papillary muscle ischemia in dogs, mitral regurgitation is the result of complex geometric alterations in the three-dimensional relations of the papillary muscles to each other and to the various axes of the left ventricle (121a). Discoordination of papillary muscle function also contributes to the development of mitral regurgitation by distorting leaflet coaptation sufficiently to produce severe mitral regurgitation (121b).

Mitral regurgitation can be expected in approximately 30% of patients who are undergoing evaluation for coronary bypass surgery (121). In most of these individuals, mitral regurgitation is mild. The presence of severe mitral regurgitation is associated with reduced left ventricular function and a worsened prognosis (122). However, even milder degrees of mitral regurgitation that develop following acute myocardial infarction are associated with a worsened 1- and 4-year prognosis (122a,122b).

Left ventricular dilatation, such as that which occurs in patients with dilated cardiomyopathy, can cause mitral regurgitation by altering the position and axis of the papillary muscles. Moreover, ventricular dilatation causes dilation of the mitral annulus with resulting incomplete coaptation of the mitral leaflets. Mitral regurgitation leads to left atrial dilatation and thereby results in retraction of the posterior mitral leaflet by the dilated left atrium. In this manner, mitral regurgitation amplifies itself (i.e., "mitral regurgitation begets more mitral regurgitation") (119). Abnormal position of the papillary muscle, combined with altered hydraulic forces in the left ventricular outflow tract, results in mitral regurgitation in patients with hypertrophic cardiomyopathy. The presence and degree of this type of mitral regurgitation (often termed *functional*) is unrelated to the severity of left ventricular dysfunction. Rather, local left ventricular remodeling with apical and posterior displacement of the papillary muscles leads to valvular tenting. This, combined with decreased or absent mitral annular contraction, results in mitral insufficiency that may be mild, moderate, or severe (119a).

Pathophysiology

Chronic mitral regurgitation is a form of volume overload that affects the left ventricle and the left atrium. The lesion is well tolerated for years but eventually leads to failure of the left ventricle. In patients with mitral incompetence, a portion of each systolic stroke volume is ejected retrograde into the left atrium. This results in abnormal left atrial expansion with resulting left atrial dilation (123). Left ventricular eccentric (dilated as opposed to concentric) hypertrophy develops as new myocardial sarcomeres are added end to end (i.e., in series). Total left ventricular volume increases progressively (124). Increased left ventricular dilatation changes the spatial relationship between the papillary muscles and the mitral valve annulus (124a). These spatial changes lead to increases in the volume of mitral regurgitant flow. Thus, mitral regurgitation worsens over time as a result of left ventricular remodeling.

Enlargement of the left ventricle increases that chamber's diastolic compliance, allowing it to fill to a greater volume at a lower filling pressure than would otherwise be allowed. Mitral regurgitant volume is delivered into the low-pressure left atrium during the earliest phase of systole, before aortic ejection commences. As much as 50% of the regurgitant volume can be ejected into the left atrium *before* aortic valve opening. This may represent as much as 20% of the total left ventricular stroke volume in patients with severe mitral incompetence (125). Preload is increased in patients with severe mitral regurgitation as a result of left ventricular dilatation and the addition of new sarcomeres in series. Afterload is maintained in the normal range by the addition of these new left ventricular sarcomeres. Left ventricular contractile function remains within the normal range for many years despite the presence of severe mitral insufficiency (124). Late in the course of the disease, interstitial fibrosis of the left ventricle, which accompanies long-standing pathologic hypertrophy, results in a decline in left ventricular contractile function. At this point in the natural

history of mitral regurgitation, left ventricular ejection fraction declines (124).

Left atrial size and compliance increase in response to large volumes of regurgitant mitral blood flow. Left atrial pressure remains within the normal range as a result of the increases in left atrial size and compliance. In patients with long-standing mitral incompetence, left ventricular systolic function deteriorates slowly. However, because of the low-pressure outlet from the left ventricle into the left atrium, left ventricular afterload is maintained at a lower level than would be observed for a ventricle of similar size that lacked the left atrial “escape valve” (126). Consequently, left ventricular ejection fraction may be normal or near normal despite a significant reduction in ventricular contractile function. Mildly reduced left ventricular function is a serious finding in patients with chronic mitral regurgitation. It implies a greater loss of myocardial integrity than would be the case with a similar decrease in ejection fraction in a patient with coronary artery disease or aortic stenosis. Therefore, the prognosis is poorer for the patient with chronic mitral regurgitation and reduced left ventricular function.

Ejection phase indices such as ejection fraction are afterload dependent. Patients with chronic mitral regurgitation have reduced afterload secondary to the left atrial escape valve, which can lead to falsely reassuring normal values for left ventricular ejection fraction. Because preoperative left ventricular function is an important determinant of survival, a number of investigators have sought a more accurate index of left ventricular contractile function in patients with chronic mitral regurgitation. The end systolic volume relation is useful in this setting (127,128,129 and 130). Indeed, this relation is quite insensitive to afterload and, hence, ideal for following patients with chronic mitral regurgitation. The simple measurement of end systolic volume is also of considerable use in this regard. Patients with severe, chronic, compensated mitral regurgitation and an end systolic volume of 40 mL per m^2 or less have a considerably better prognosis than individuals whose end systolic volume exceeds 80 mL per m^2 (129). An end systolic volume of 55 mL per m^2 or less serves to separate patients who do well after mitral valve surgery from those with a higher rate of postoperative complications such as heart failure.

The presence of left ventricular dilatation per se does not identify a patient with reduced left ventricular function unless the left ventricular end diastolic echocardiographic dimension exceeds 70 mm or the angiographic end diastolic volume approaches 200 mL per m^2. Left ventricular afterload is reduced as a result of partial ejection of the ventricular stroke volume into the low-pressure left atrium. Ejection fraction is consequently increased early in the course of chronic mitral regurgitation. Late in the course, afterload increases secondary to ventricular dilatation, and ejection fraction declines. Therefore, a left ventricular ejection fraction of approximately 50% denotes mild left ventricular dysfunction; ejection fractions of 40% to 50% reflect moderate ventricular dysfunction; an ejection fraction less than 40% indicates marked ventricular dysfunction.

Once left ventricular contractile performance begins to deteriorate, diastolic filling pressure increases as do left atrial and pulmonary capillary wedge pressures. Cardiac output declines, and patients report symptoms of left ventricular failure (e.g., dyspnea on exertion and fatigue). Reduced left ventricular contractile function leads to further ventricular dilatation. Afterload increases, thereby leading to worsening contractile performance and higher filling pressures. Symptoms are accentuated.

The amount of left ventricular dilatation and eccentric hypertrophy are less in patients with severe mitral regurgitation than in individuals with severe aortic regurgitation (126). Nevertheless, chronic aortic regurgitation is better tolerated and has a better long-term prognosis. Myocardial failure is apparently more easily reversible following successful valve replacement in patients with aortic regurgitation than in individuals with mitral regurgitation (130,131).

Increases in pulmonary capillary wedge pressure lead to pulmonary arterial hypertension, and eventually to right ventricular dilatation and failure. The development of pulmonary vascular disease and right ventricular failure is less common than in patients with mitral stenosis, presumably because the compliant, dilated left atrium maintains a lower left atrial pressure than is observed in individuals with mitral stenosis.

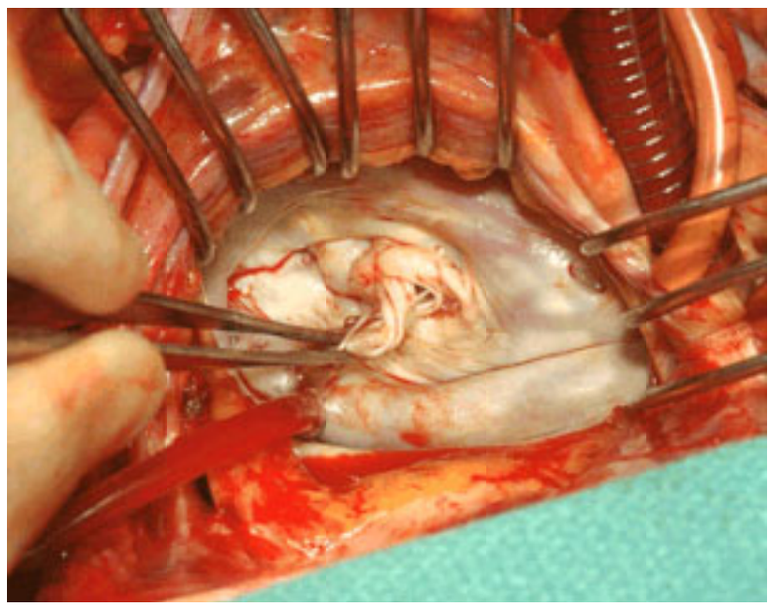
Mitral regurgitation, but not mitral valve prolapse, is associated with systemic platelet activation. The degree of platelet activation correlates positively with the severity of the regurgitant lesion, but is independent of the underlying etiology of the valvular abnormality (131a).

Acute Mitral Regurgitation

The pathophysiologic consequences of acute, severe mitral incompetence—such as that observed in patients following rupture of a chorda tendineae—differ from those of chronic mitral insufficiency. With acute mitral regurgitation, a sudden volume overload is imposed on an unprepared, nondilated, nonhypertrophied left ventricle and left atrium. Preload is increased, whereas afterload decreases as a result of the newly developed low-pressure runoff to the left atrium during systole (132). In the absence of coronary artery disease or myocardial infarction, left ventricular contractile function can be normal or even supranormal secondary to augmented sympathetic nervous stimulation of the myocardium (132,133).

Despite increased left ventricular preload and contractility and decreased afterload, overall left ventricular pump function declines in acute mitral regurgitation. This decline is considerably greater if recent or previous myocardial infarction is present. Total left ventricular stroke volume increases, but a large amount of this flow is directed into the left atrium rather than the aorta. Forward cardiac output declines. Pressures in the noncompliant, nondilated left atrium and left ventricle increase, often dramatically. Pulmonary congestion results with the development of dyspnea at rest or with minimal exertion. At times, acute pulmonary edema may be observed. Large, regurgitant CV waves are observed in the pulmonary capillary wedge pressure tracing secondary to the arrival of a large bolus of regurgitant blood flow in the small noncompliant left atrium. In most patients with chronic mitral regurgitation, the left atrium dilates progressively so that left atrial and pulmonary capillary wedge pressures remain normal or only modestly elevated.

Major complications in patients with long-standing mitral regurgitation include left ventricular failure, atrial fibrillation, arterial embolism, and infectious endocarditis. Left ventricular failure usually develops when mitral regurgitation has been present for decades and marked left ventricular and left atrial dilatation are present. At that time, left ventricular systolic and diastolic function are almost always abnormal (137).



Intraoperative field demonstrating a mitral valve with a torn papillary muscle prolapsing across the mitral valve into the left atrium. The surgeon has the papillary muscle in forceps demonstrating the chordae attached to the posteromedial commissure, predominantly attached to the anterior mitral leaflet. (The patient’s head is to the left of the screen and feet to the right.)

Clinical Profile

Natural History

Chronic Mitral Regurgitation

The clinical course of patients with chronic mitral regurgitation is determined by the severity of the regurgitant lesion and its etiology. Many patients with mild to moderate amounts of mitral regurgitation remain asymptomatic for their entire lives. Patients with moderate to severe mitral regurgitation are usually without symptoms for decades. During this time period, the left ventricle and left atrium slowly dilate and hypertrophy, thereby maintaining left ventricular filling pressures at or near the normal range. Mitral regurgitation tends to increase with time, although considerable individual variation occurs from patient to patient. Independent predictors of progression include flail leaflet, progression of the underlying cardiac disease (e.g., arteriosclerotic coronary artery disease), and increase in mitral valve annulus

diameter (137a). Depending on the severity of the regurgitant lesion, the state of left ventricular and left atrial function, and the disease entity producing mitral regurgitation, symptoms of left ventricular failure begin to develop usually during the fourth through the sixth decade of life. This course is quite different from that observed in patients with mitral stenosis, who often become symptomatic in their 30s.

The prognosis is often worse for patients whose mitral regurgitation is the result of ischemic heart disease. In patients with connective tissue disease, the severity of mitral regurgitation tends to increase with time. Patients with coronary artery disease may suffer complications related to the latter entity (e.g., myocardial infarction), thereby worsening mitral regurgitation or left ventricular function; hence the prognosis. In Rapaport's unselected series of patients with aortic and mitral valve disease, patients with chronic mitral regurgitation had approximately an 80% 5-year survival (11). Survival for patients with mixed mitral stenosis and regurgitation was worse than for individuals with predominant mitral regurgitation, approximately 70% at 5 years. Patients with myxomatous degeneration and mitral regurgitation usually have a more benign prognosis than individuals in whom mitral regurgitation results from other entities. Zuppiroli and coworkers followed more than 300 patients with mitral valve prolapse for more than 8 years (138). The risk of morbid or mortal events, including death, mitral valve replacement, infectious endocarditis, or cerebral ischemia, was low in this series of patients, approximately 1% per year. The risk for morbid or mortal events is higher in men, older patients, and individuals with greater degrees of mitral regurgitation. In patients with mitral valve prolapse, even mild degrees of mitral regurgitation may be associated with increased risk of complications. Thus, patients with mitral valve prolapse with exercise-induced mitral regurgitation, but none at rest, have more clinical events during a 3-year follow-up compared with patients who fail to develop regurgitation during exercise (139).

Acute Mitral Regurgitation

As noted earlier, the clinical course of patients with acute forms of mitral regurgitation differs greatly from that of individuals with chronic mitral regurgitation. The acute form of the illness is usually associated with the sudden development of severe left ventricular failure. Patients are often in pulmonary edema when initially seen, and cardiogenic shock may ensue. The "unprepared" left ventricle and atrium cannot accept the large quantity of mitral regurgitant blood flow and maintain low or modestly elevated filling pressures as in patients with chronic mitral incompetence. Patients with acute mitral regurgitation have marked elevations in left ventricular filling pressures and decreased cardiac output (Table 21.8). Their clinical course is marked by the development of sudden disability; they are almost invariably hospitalized and undergo urgent mitral valve repair or replacement.

	Chronic	Acute
Time to symptoms	Decades	Immediate
Symptoms	Often asymptomatic	Highly symptomatic
Left ventricular size	Enlarged	Normal
Left atrial size	Enlarged	Normal
Left ventricular filling pressure	Normal to increased	Invariably increased
Left atrial pressure	Normal to increased	Invariably increased
Cardiac output	Normal to decreased	Invariably decreased
Ability of the cardiovascular system to compensate	Usually compensated	Usually not compensated
Echocardiography	Left ventricular hypertrophy	No left ventricular hypertrophy
Chest roentgenography	Left ventricular, left atrial enlargement	No cardiac enlargement, pulmonary edema
Therapy	Medical-surgical	Usually urgent surgical

TABLE 21.8 COMPARISON OF ACUTE AND CHRONIC MITRAL REGURGITATION

History

Chronic Mitral Regurgitation

Patients with symptomatic chronic mitral regurgitation develop dyspnea on exertion as their initial complaint. Later, these individuals report orthopnea and paroxysmal nocturnal dyspnea. Dyspnea at rest and even pulmonary edema may develop if medical therapy is not instituted or if atrial fibrillation with a rapid ventricular response occurs. These symptoms are the result of increased left ventricular diastolic and left atrial pressures. Decreased cardiac output produces fatigue and generalized weakness. Pulmonary hypertension develops late in the course of the illness and can lead to right ventricular failure with associated peripheral edema and even ascites.

Acute Mitral Regurgitation

Acute mitral regurgitation is associated with the rapid development of symptoms resulting from markedly increased left ventricular filling pressures: severe dyspnea at rest and anxiety.

Physical Examination

Chronic Mitral Regurgitation

Patients with chronic mild mitral regurgitation may have a normal physical examination except for the characteristic murmur. At the other end of the spectrum are patients with chronic, severe, or acute mitral regurgitation who often manifest signs of left ventricular failure (i.e., pulmonary rales and pleural effusion). Patients with long-standing left ventricular failure and associated pulmonary hypertension may have signs of right ventricular failure: distended neck veins, hepatomegaly, ascites, and peripheral edema.

The typical patient with chronic, severe, compensated mitral regurgitation often displays many of the physical findings listed in Table 21.9. The characteristic murmur of chronic mitral regurgitation begins with the S_1 and ceases at or slightly after the aortic component of the S_2 (140). The intensity of the murmur of mitral regurgitation is usually constant throughout systole. Patients with mitral valve prolapse are an exception to this rule: The murmur commences in mid- to late systole and has a brief ejection quality. It is often associated with one or more early systolic clicks.

Head, eyes, ears, nose, throat	Anxious facies; diaphoresis secondary to left ventricular failure
Jugular venous pulse	Distended in patients with right ventricular failure
Carotids	Small or normal volume; brisk upstroke with more rapid than normal falloff
Chest	Rales; dullness and decreased breath sounds at lung bases and e to a change resulting from pleural effusions
Cardiac	Apex impulse laterally displaced, enlarged apical impulse; ↓ intensity of first heart sound; holosystolic murmur loudest at apex with radiation to the axilla, a third/fourth heart sound; T_P, if pulmonary hypertension is present
Abdomen	Hepatomegaly, ascites if right ventricular failure is present
Extremities	Peripheral edema if right ventricular failure is present

↓, decreased; ↑, increased.

TABLE 21.9 FINDINGS ON PHYSICAL EXAMINATION IN PATIENTS WITH CHRONIC SEVERE MITRAL REGURGITATION

Patients with long-standing mitral regurgitation often have an easily palpable, enlarged, and laterally displaced apical impulse resulting from left ventricular dilatation. Right ventricular dilatation may be inferred if a left parasternal impulse is felt. An occasional patient demonstrates a modest systolic left parasternal lift secondary to anterior displacement of the heart by a markedly enlarged left atrium. It is often difficult to distinguish this left atrial impulse from a right ventricular lift (140).

he murmur of mitral incompetence is rarely affected by respiration or variations in the cardiac cycle unless hypertrophic cardiomyopathy or mitral valve prolapse

is present. The intensity of the murmur does not correlate well with the quantity of regurgitant blood flow. In contrast to the murmur of aortic stenosis, the mitral regurgitant murmur does not vary in intensity with different cycle lengths. Moreover, the murmur of mitral regurgitation usually increases in intensity when left ventricular afterload is increased (e.g., by squatting, leg elevation, isometric exercise, or phenylephrine administration). Conversely, the murmur is softer during standing or amyl nitrite inhalation. The timing and direction of the murmur of mitral valve prolapse vary with left ventricular cavity size. Maneuvers that decrease left ventricular cavity size (i.e., standing or amyl nitrite) cause the murmur to begin earlier in systole, whereas maneuvers that increase left ventricular cavity size (i.e., squatting or leg raising) delay the onset of the murmur. In chronic mitral regurgitation, the intensity of the S_1 is often reduced. A third heart sound (S_3) is also frequently appreciated. This latter finding is the result of an accentuated rapid filling wave entering the left ventricle from the dilated left atrium. In this setting, left ventricular function is preserved, and the murmur of mitral regurgitation is loud. When the S_3 is produced by a decompensated left ventricle, the murmur is often soft (141). The pulmonic component of the S_2 is accentuated in patients with pulmonary hypertension.

HEART SOUNDS

Audio 21.7 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S_1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.8 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S_1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left lower sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.9 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S_1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Apex. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.10 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.11 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Left lower sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.12 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Apex. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.13 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.14 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.15 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the

medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Left lower sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.16 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Apex, supine. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 21.17 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Apex, left lateral. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Acute Mitral Regurgitation

In individuals with acute mitral regurgitation, the physical examination is dominated by findings associated with left ventricular failure. The heart size is usually normal by palpation; tachycardia and tachypnea are common. The murmur is usually loud if normal left ventricular function is present. The murmur may be soft if left ventricular function is markedly reduced (e.g., with mitral regurgitation secondary to papillary muscle dysfunction following an extensive myocardial infarction). The murmur of acute mitral regurgitation may be harsh and even ejection in quality with wide radiation (142). The S_2 is often widely split secondary to early aortic valve closure. Both the S_3 and the fourth heart sound are also frequently present.

Electrocardiography

Long-standing mitral regurgitation with associated left atrial and left ventricular dilatation alters the morphology of the P waves and the QRS complex: The patterns of left atrial dilatation and left ventricular hypertrophy are usually observed. Atrial fibrillation is often present in patients with chronic mitral regurgitation. Other ECG findings may relate to the pathologic entity producing mitral regurgitation (e.g., myocardial infarction with associated papillary muscle dysfunction). Patients with mitral valve prolapse often manifest nonspecific ST-T changes on the ECG. Individuals with acute mitral regurgitation demonstrate neither left atrial enlargement nor left ventricular hypertrophy.

Chest Roentgenography

Chest roentgenography in patients with chronic mitral insufficiency is usually characterized by left ventricular and left atrial enlargement. Cardiac chamber enlargement is rarely noted in patients with acute mitral regurgitation. Left atrial size is a reasonable gauge to the duration and severity of mitral regurgitation. The larger the atrium, the more severe and chronic is the regurgitation. An occasional patient with very severe and long-standing mitral incompetence is noted to have a giant left atrium.

The pulmonary vasculature is usually normal in patients with chronic mitral regurgitation reflecting normal or only minimally elevated pulmonary venous pressure. Pulmonary vascular redistribution and interstitial pulmonary edema are observed late in the course of the illness or in patients with acute mitral regurgitation. Cardiac fluoroscopy may reveal mitral leaflet or annular calcification. These findings may often be inferred from the postero-anterior chest roentgenogram as well. Patients with mitral valve prolapse usually demonstrate a normal cardiac silhouette, clear lungs, and an abnormal chest configuration (i.e., narrow anteroposterior diameter or pectus excavatum). Patients with acute mitral regurgitation usually have a normal cardiac silhouette as well as signs of left ventricular failure (e.g., interstitial edema and Kerley A and B lines).

Echocardiography

Chronic Mitral Regurgitation

A Doppler-echocardiographic study is useful in patients with chronic mitral regurgitation (143,144,145,146 and 146b). Such examinations reveal (a) abnormalities of valvular architecture, (b) left atrial size, (c) left ventricular size and function, (d) a semiquantitative estimate of the severity of mitral regurgitation, (e) size and function of the right ventricle, (f) a rather accurate estimate of pulmonary arterial systolic pressure, and (g) associated valvular lesions (e.g., mitral stenosis, tricuspid regurgitation) (Table 21.10). This information can be obtained from a transthoracic Doppler-echocardiographic study in the overwhelming majority of patients. A number of individuals require a transesophageal echocardiographic examination (e.g., patients with prosthetic mitral valves and paravalvular leaks or individuals in whom mitral valve repair is being contemplated). Transesophageal Doppler-echocardiographic studies provide more accurate anatomic assessment of all types of mitral regurgitant lesions as well as prosthetic valves than can be obtained with transthoracic examinations (see Chapter 52) (146a). As noted earlier, end systolic volume is an excellent discriminator of prognosis in patients with chronic mitral regurgitation. Serial determination of this variable is of considerable value in determining the timing of mitral valve surgery (127,128,129 and 130).

Mitral valve	Prolapse; myxomatous thickened valve; fibrotic or calcified valve (rheumatic); valvar vegetations; ruptured chordae; mild, moderate or severe mitral regurgitation (Doppler)
Left atrium	Dilatation; thrombus
Left ventricle	Dilatation; hypertrophy; normal or reduced contractile function
Right ventricle	Dilatation; hypertrophy; normal or reduced contractile function
Pulmonary artery	Dilatation, estimated pulmonary arterial systolic pressure (Doppler analysis of tricuspid regurgitant jet)
Right atrium	Dilatation
Tricuspid valve	Mild, moderate, or severe tricuspid regurgitation (Doppler)
Pulmonary veins	Reduced systolic and diastolic flow ratios and reversed systolic flow (Doppler)

TABLE 21.10 SPECTRUM OF ECHOCARDIOGRAPHIC FINDINGS IN PATIENTS WITH MITRAL REGURGITATION

Echocardiographic examination is important in patients with suspected mitral valve prolapse. Two-dimensional echocardiographic study reveals systolic posterior displacement of one or both leaflets of the valve into the left atrium. The leaflets coapt on the atrial side of the mitral annular plane in the parasternal, long-axis view. The diagnosis of mitral valve prolapse is considerably less accurate in the apical four-chamber view (147). The diagnosis is reasonably certain when mitral valve leaflet thickness is 5 mm or more during ventricular diastole. Patients with 5-mm thick valves are at risk for complications associated with mitral valve prolapse such as infectious endocarditis (147). Other echocardiographic findings include leaflet redundancy, annular dilatation, and chordal elongation. For screening purposes, a single view, two-dimensional, transthoracic echocardiographic study has been shown to be both accurate and cost effective (147a).

Intraoperative transesophageal echo showing bileaflet prolapse of the mitral valve. The color Doppler showed centrally directed mitral regurgitation.

(Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)

Acute Mitral Regurgitation

In patients with acute mitral regurgitation, Doppler-echocardiographic studies frequently demonstrate the etiology of the acute regurgitant lesion (e.g., vegetations in patients with infectious endocarditis or ruptured chordae in individuals with mitral valve prolapse). Transesophageal echocardiographic examination is more sensitive than transthoracic study for revealing pathologic entities associated with acute mitral regurgitation. Other subtle findings may also be observed in patients with acute mitral incompetence: decreased pulmonary venous systolic and diastolic flow ratios and reversed pulmonary venous systolic flow (143).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) produces quantitative estimates of regurgitant valvular flow. Hundley et al. studied 23 subjects with varying degrees of mitral regurgitation and compared regurgitant volume indices obtained from cardiac catheterization and MRI (148). MRI estimates of mitral valvular regurgitant flow were highly accurate.

Cardiac Catheterization

Noninvasive techniques almost invariably confirm the diagnosis of mitral regurgitation and help to quantitate its severity. Cardiac catheterization is rarely employed as a diagnostic technique for mitral regurgitation. Rather, catheterization is employed to confirm the status of left ventricular function and the possible presence of associated coronary artery disease. In addition, pulmonary arterial and capillary wedge pressures and cardiac output can be determined. All of these variables have prognostic implications in the patient being considered for mitral valve surgery.

Patients with acute mitral regurgitation usually have a prominent CV wave in the pulmonary capillary wedge pressure tracing. This results from the decreased compliance of the relatively small left atrium. Patients with chronic mitral regurgitation usually have dilated, capacious left atria that accommodate the regurgitant bolus of blood without a marked increase in pressure (i.e., with small CV waves in the pulmonary capillary pressure tracing).

Quantitative angiographic techniques allow one to calculate the volume of regurgitant blood flow and the regurgitant fraction (i.e., regurgitant blood flow divided by total left ventricular stroke volume) (see Chapter 78 and Chapter 79). In this manner, the relative severity of mitral regurgitation can be quantitated. In general, a regurgitant fraction less than 20% denotes mild mitral regurgitation, 20% to 40% represents moderate regurgitation, 40% to 60% connotes moderately severe regurgitation, and greater than 60% defines severe regurgitation. Left ventricular cavity size and wall thickness can also be ascertained, although this information is often more easily obtained by echocardiography. Using Laplace's relationship, and determinations of left ventricular pressures, dimensions, and wall thickness, the physician can calculate systolic and diastolic wall stress, which can be related to left ventricular myocardial shortening. As already noted, such stress-shortening relationships reflect overall left ventricular function (133). Moreover, the ratio of end systolic stress to end systolic volume is an important measure of left ventricular systolic function that carries major prognostic implications (149,150). Indications for invasive study are listed in *e*Table 21.10.1.

***e*TABLE 21.10.1** SPECTRUM OF DIAGNOSTIC METHODS AT CARDIAC CATHETERIZATION IN PATIENTS WITH MITRAL REGURGITATION

Ascertain the presence of atherosclerotic coronary artery disease before mitral valve surgery
Establish the etiology of chronic mitral regurgitation[a]
Define the state of left ventricular function[a]
Define the severity of mitral regurgitation[a]
Help determine if mitral regurgitation is the primary problem in a patient with a dilated hypokinetic left ventricle and mitral regurgitation[a]
Help determine if mitral regurgitation is a major contributing factor to the pathophysiologic abnormality of a patient with hypertrophic cardiomyopathy[a]
Define the etiology and hemodynamic status of a patient with suspected acute mitral regurgitation

[a] This information may often be obtained more easily and safely with a Doppler-echocardiographic study.

Left atrial size can also be ascertained from cineangiographic study. Left atrial size predicts the severity of mitral regurgitation and cannot be predicted accurately from ECG, chest roentgenography, or pulmonary capillary wedge pressure measurements (151).

Invasive study is also of value in patients with acute mitral regurgitation. The etiology of mitral regurgitation is usually defined or confirmed, and the hemodynamic status of the patient is ascertained. This information is important in the preoperative evaluation of such patients. Patients with mitral valve prolapse rarely undergo cardiac catheterization except for coronary arteriography performed to ascertain if recurrent episodes of chest discomfort are caused by atherosclerotic coronary artery disease.

Differential Diagnosis

Patients with mitral regurgitation must be distinguished from individuals with other entities that produce systolic murmurs. The murmur of aortic stenosis is usually loudest at the base and radiates to the carotid arteries. It increases following longer cycle lengths (e.g., in patients with atrial fibrillation or extra systoles with compensatory pauses). Echocardiography usually defines the presence or absence of aortic stenosis. Hypertrophic cardiomyopathy can produce two systolic murmurs: a left ventricular outflow tract murmur and a mitral regurgitant murmur. It may be difficult to distinguish these two murmurs during an auscultatory examination. Echocardiography reveals the correct diagnosis and helps to define the severity of mitral regurgitation.

In patients with acute myocardial infarction, a loud systolic murmur of recent onset may be the result of acute mitral regurgitation, or it may result from an acute ventricular septal rupture. The murmur of an acute septal rupture is often more localized than that of mitral regurgitation; the former murmur has its greatest intensity along the lower left sternal border. A systolic thrill is often palpable in patients with septal rupture. Echocardiographic study or right-sided heart catheterization with blood-oxygen content determination in the right atrium, right ventricle, and pulmonary artery defines the cause of the systolic murmur in these patients.

Medical Therapy of Mitral Regurgitation

Chronic Mitral Regurgitation

Medical therapy for the patient with chronic mitral regurgitation involves a number of different strategies: antibiotic prophylaxis with various interventions in order to prevent infectious endocarditis; antiarrhythmic therapy to maintain sinus rhythm in the patient who develops atrial fibrillation (see Medical Therapy of Mitral Stenosis); anticoagulation for the patient with sustained atrial fibrillation; and vasodilators, digoxin, and diuretics for the patient with left ventricular failure.

From an understanding of the pathophysiology of mitral regurgitation, it seems reasonable that chronic therapy with a vasodilator, particularly an angiotensin-converting enzyme (ACE) inhibitor, or hydralazine, would reduce left ventricular wall stress and thereby delay or obviate entirely the need for mitral valve surgery (152,153). Studies in patients with chronic aortic regurgitation have demonstrated such an effect (see Chapter 22). Unfortunately, minimal long-term outcome data are currently available involving patients with chronic mitral incompetence. Tischler et al. observed significant reduction in left ventricular end diastolic and end systolic volumes and mass following 6 months of ACE inhibitor therapy (153a). Levine et al. noted improvement in severe functional mitral regurgitation following 1 year of ACE inhibitor and nitrate therapy in 19 patients with chronic heart failure and severe mitral regurgitation (153b). Despite the modest volume of evidence, the rationale for such therapy seems compelling and can be recommended for patients with chronic, asymptomatic mitral regurgitation of moderate or greater severity. Such therapy is particularly rational if some degree of left ventricular dilatation is present (152,153,154,155,156,157,158,159 and 160). We favor ACE inhibition for this indication.

Management of mitral valve prolapse is often straightforward because the degree of valvular incompetence present is usually mild in most of these individuals. Antibiotic prophylaxis for dental and other interventions and reassurance are usually all that is required. Antibiotic prophylaxis is probably required only in patients with mitral valves 5 mm or more in thickness. Some patients describe orthostatic symptoms or fatigue with only modest exertion. Once normal left ventricular function and minimal mitral regurgitation have been documented by echocardiography, such individuals should be reassured. Liberal salt and water intake (i.e., a normal U.S. diet) and regular exercise should be prescribed. The rare prolapse patient who suffers a neurologic event should receive life-long aspirin or warfarin anticoagulation.

Acute Mitral Regurgitation

In patients with acute mitral regurgitation, left ventricular failure is almost invariably present. Intravenous vasodilator therapy with nitroprusside can produce dramatic benefit with subsequent reduction in ventricular cavity dilatation, diastolic filling pressures, and mitral regurgitant orifice (154,155). The nitroprusside infusion is

continued until the patient is stabilized by either surgical intervention (e.g., mitral valvuloplasty or replacement) or long-term oral medical therapy (e.g., ACE inhibitors, digoxin, and diuretics). Intravenous nitroglycerin is often effective in reducing pulmonary vascular congestion in these patients, particularly if the underlying etiology for mitral regurgitation is ischemic heart disease. Surgical therapy is almost always required.

It is essential that the clinician serially monitor left ventricular function and cavity size by echocardiography when following patients with chronic mitral regurgitation of moderate severity or greater. Declining left ventricular function or progressive left ventricular dilatation should prompt the clinician to consider mitral valve surgery seriously.

MITRAL VALVE PROLAPSE

The syndrome known as *mitral valve prolapse* has been characterized and studied for more than 30 years. It has been given a variety of names including the floppy valve syndrome, Barlow's syndrome, the click-murmur syndrome, and myxomatous mitral valve, among others (106,161,162,163,164,165 and 166). There is great variability in the expression of this syndrome, with some patients demonstrating severely involved valves that often require surgical intervention. The overwhelming majority of individuals with this entity, however, has only a minor derangement of mitral valvular structure, which is usually clinically insignificant. The syndrome in any of its manifestations is quite common, with 3% to 5% of the adult U.S. population affected (164,167). Female subjects are affected twice as commonly as male subjects. The Framingham Heart Study employed strict echocardiographic criteria to determine the prevalence of mitral valve prolapse. They noted a prevalence of 2.4% in their population; 60% of the patients with mitral valve prolapse were women (167a).

The clinical finding of a mid-systolic click and a late systolic murmur is associated with mid- to late systolic prolapse of one or both of the mitral leaflets posteriorly into the left atrium. Prolapse is often associated with mitral regurgitant blood flow, but this is not required for the syndrome to be present. Under normal circumstances, there is slight bowing of the mitral valve posteriorly into the left atrium during systole. Exaggeration of this bowing results in systolic prolapse of one or both leaflets into the left atrium. Perloff and coworkers have refined the clinical criteria for the diagnosis of this syndrome (162) (*e*Table 21.10.2). As noted in *e*Table 21.10.2, three classes of clinical finding should be sought in these patients: major, minor, and nonspecific criteria. The presence of one or more major criteria establishes the presence of the mitral valve prolapse syndrome. Minor criteria raise the clinician's suspicion that the syndrome may be present but do not establish its presence. The nonspecific findings are often associated with the syndrome but also fail to establish the diagnosis. As noted in *e*Table 21.10.2, the diagnosis can be made on clinical grounds alone (i.e., the presence of mid- to late systolic clicks and a late systolic murmur or "whoop"). However, mitral valve prolapse is usually diagnosed by means of a two-dimensional echocardiographic study demonstrating clear posterior displacement of one or both leaflets in the parasternal view. Apparent but false posterior displacement may be seen on the four-chamber view (168,169).

***e*TABLE 21.10.2** DIAGNOSTIC METHODS USED IN ESTABLISHING THE DIAGNOSIS OF MITRAL VALVE PROLAPSE

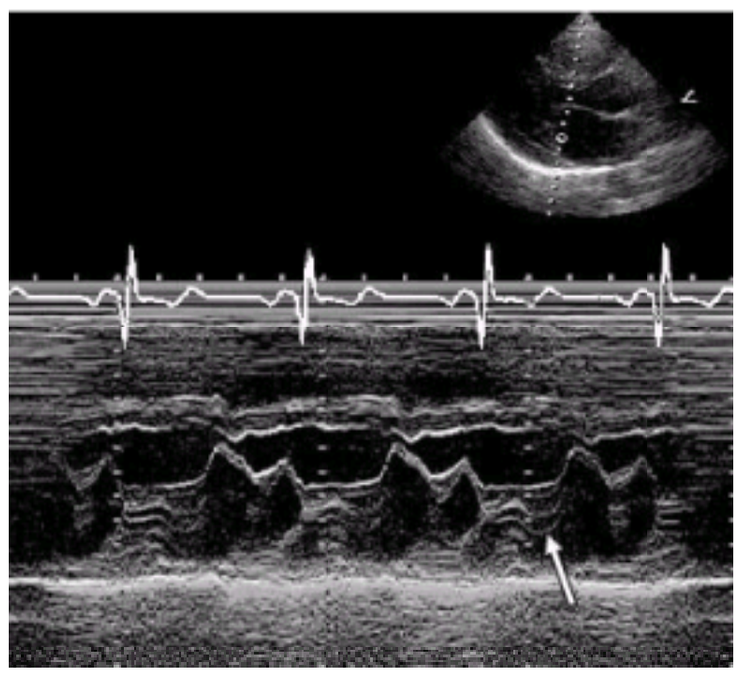
Major criteria
Auscultation
Mid- to late systolic clicks and late systolic murmur or "whoop" alone or in combination at the cardiac apex
Two-dimensional echocardiography
Marked superior systolic displacement of mitral leaflets with coaptation point at or superior to annular plane
Mild to moderate superior systolic displacement of mitral leaflets with
Chordal rupture
Doppler mitral regurgitation
Annular dilatation
Echocardiography plus auscultation
Mild-to-moderate superior systolic displacement of mitral leaflets with
Prominent mid- to late systolic clicks at the cardiac apex
Apical late systolic or holosystolic murmur in the young
Late systolic whoop
Minor criteria
Auscultation
Loud first heart sound with an apical holosystolic murmur
Two-dimensional echocardiography
Isolated mild-to-moderate superior systolic displacement of the posterior mitral leaflet
Moderate superior systolic displacement of both mitral leaflets
Echocardiography plus history of mild-to-moderate superior systolic displacement of mitral leaflets with focal neurologic attacks or amaurosis fugax in the young
First-degree relatives with major criteria
Nonspecific findings
Symptoms
"Atypical" chest pain, dyspnea, fatigue, lassitude, giddiness, dizziness, syncope
Psychological disturbances
Physical appearance
Thoracic bony abnormalities
Hypomastia
Electrocardiography
T-wave inversions in inferior limb leads or lateral precordial leads
Premature ventricular beats at rest, during exercise, or on ambulatory electrocardiography
Supraventricular tachycardia
Roentgenography
Scoliosis, pectus excavatum or carinatum, or loss of thoracic kyphosis
Two-dimensional echocardiography
Mild superior systolic displacement of anterior or anterior and posterior mitral leaflets

From Perloff JK, Child JS, Edwards JE. New guidelines for the clinical diagnosis of mitral valve prolapse. *Am J Cardiol* 1986;57:1124, with permission.

Mitral valve prolapse has been associated with a number of different conditions, including Marfan's syndrome, Ehlers-Danlos syndrome, acute rheumatic carditis, and a variety of congenital, intracardiac anomalies. A number of these entities are the result of genetic defects in connective tissue structure that produce, among other anatomic abnormalities, mitral valve prolapse. Other entities associated with mitral valve prolapse (e.g., straight-back syndrome or atrial septal defect) may cause mitral valve prolapse by virtue of a small left ventricle with a normal sized mitral valve (107,108,109,110,111,112,113,114,115 and 115b). The syndrome may be hereditary: One family had the gene for myxomatous valve dystrophy mapped to chromosome Xq28 (169a).

Dysfunction of the autonomic nervous system has been reported in patients with mitral valve prolapse. It is said that some of the symptoms reported by these individuals (i.e., anxiety, atypical chest pain, and palpitations) are the result of these abnormalities in autonomic nervous function (134,135 and 136).

As noted earlier, patients with mitral valve prolapse have redundant myxomatous tissue with excess deposits of proteoglycans within the spongiosa or middle layer of the mitral valve (105). This layer, therefore, increases in size, enlarging the valve and leading to systolic prolapse. The mitral annulus is also enlarged. Electron microscopic examination of these valves demonstrates widespread disruption and haphazard organization of the collagen fibrils within the valve itself. Moreover, the endothelial layer overlying the valve is often disrupted, thereby predisposing the valve to local thrombus formation and bacterial invasion that may lead to endocarditis (170). The valve leaflets, the chordae tendineae, and the annulus may also demonstrate extensive myxomatous change and disruption of normal collagen structure. Such changes in the chordae tendineae can lead to chordal rupture with the development of severe, acute mitral regurgitation. Degenerative changes in the mitral valve annulus can lead to premature annular calcification, which may exacerbate preexisting mitral regurgitation.



M-mode tracing of posterior leaflet mitral valve prolapse. Note the posterior displacement of the posterior mitral leaflet after the leaflets close in systole.

Video 21.18 Severe angiographic mitral valve prolapse with mitral regurgitation. In the angiogram there is a prolapse of the posterior leaflet accompanied by severe mitral regurgitation (4+). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 21.19 Mitral valve prolapse with severe mitral regurgitation (right anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Myxomatous changes may not be restricted to the mitral valve. Indeed, the tricuspid, aortic, and pulmonic valves can also be affected. The myxomatous valve syndrome has a strong genetic transmission; in some cases, familial inheritance is by an autosomal dominant mechanism (161,171). An occasional patient demonstrates mitral valve prolapse as well as rheumatic mitral valve disease or ischemic heart disease. It is still unclear whether prolapse in this setting is the result of rheumatic or ischemic heart disease or merely the simultaneous occurrence of two common entities (172,173 and 174).

Patients with mitral valve prolapse may have absent, mild, moderate, or severe mitral regurgitation. The majority of patients have mild or no mitral regurgitant blood flow. These individuals are at risk for bacterial endocarditis but will almost certainly not require mitral valve surgery unless chordal rupture develops with attendant acute mitral regurgitation. In patients with minimal or absent mitral regurgitation, left ventricular size and function should remain normal because there is no, or only the most minimal, increase in left ventricular volume work and wall stress. In patients with moderate or severe mitral regurgitation, left ventricular dilatation and dysfunction may develop as described for other individuals with chronic mitral regurgitation.

Clinical Profile

Natural History

Mitral valve prolapse can be recognized in children, adolescents, and adults. The outlook in children is excellent, with the overwhelming majority remaining asymptomatic and without complications for many years (138,161,175). Increasingly severe mitral regurgitation is the result of progressive mitral valvular degeneration. This complication occurs in 10% to 15% of patients and can require mitral valvular surgery if symptoms of left ventricular dysfunction develop (138,176,177). Correlates with severe mitral regurgitation and the need for mitral valve surgery include male gender, older age, and the presence of obesity and hypertension (177a). Patients with posterior mitral valve leaflet prolapse have a worse prognosis than patients with anterior leaflet prolapse (177b). As already noted, chordal rupture with the development of acute, severe, mitral regurgitation is also a feared complication. Severe regurgitation requiring consideration of mitral valve repair or replacement is more common in men over age 50 than in any other group (177). Mitral valve prolapse is the most common underlying etiology in patients who undergo mitral valve surgery for mitral regurgitation. When chordal rupture occurs, the affected leaflet begins to flail with marked systolic prolapse into the left atrium, leading to severe mitral regurgitation. This complication is associated with a poor prognosis if medical therapy alone is employed. Indeed, sudden death is relatively common in these patients. Surgical intervention with valve repair or replacement should be strongly considered for these patients early in the course of their illness (178,178a and 178b). All patients with mitral valve prolapse are at risk for developing infectious endocarditis; however, patients with isolated systolic clicks appear to have a low risk for this complication. Endocarditis is more common in men and in patients older than age 50 (179,180). As might be expected, endocarditis exacerbates the degree of mitral regurgitation present and can lead to chordal rupture.

Cerebral embolism occasionally occurs in patients with mitral valve prolapse. It is manifested as either a transient ischemic attack or a permanent neurologic deficit (181,182). Amaurosis fugax may also occur. Platelet or fibrin thrombi probably form on the surface of the myxomatous valve in regions of endothelial disruption. Cerebral embolism can be a devastating complication in patients with mitral valve prolapse, most of whom will not have other cardiovascular symptoms at the time the cerebrovascular accident develops. Acute myocardial infarction can be another manifestation of arterial embolism in these patients (183). As noted earlier, Zuppiroli et al. followed 300 patients with mitral valve prolapse for more than 8 years and found a serious complication rate of only 1% per year in this population (138). Similar low rates of this and other possible complications of mitral valve prolapse have been noted in the Framingham Heart Study population (167a). In fact, Gilon et al. were unable to demonstrate any association between the presence of mitral valve prolapse and acute ischemic neurologic events in a young population of patients (183a).

Arrhythmias are also quite common in patients with mitral valve prolapse. Both supraventricular and ventricular arrhythmias have been reported. Because arrhythmias occur quite commonly in the general population, it remains unclear to what degree mitral valve prolapse is the actual cause of these rhythm disturbances. It is quite possible that arrhythmias in patients with mitral valve prolapse are merely the result of two common events occurring simultaneously (184,185). An occasional patient with mitral valve prolapse suffers sudden death. Because this event can occur in the absence of obvious structural heart disease, it is unclear what role mitral valve prolapse plays in the etiology of such sudden deaths. Evaluating the relationship between mitral valve prolapse and sudden death, Kligfield et al. have concluded that patients with mitral valve prolapse and significant mitral regurgitation, complex ventricular arrhythmias, prolongation of the QT interval, and a history of syncope were at increased risk for sudden death (184,185). In this regard, it is of interest that abnormal late potentials have been recorded by means of signal-averaged ECG in patients with mitral valve prolapse (184). Supraventricular arrhythmias are quite common in patients with mitral valve prolapse and nonspecific ST-T wave changes on the ECG (184). Atrial premature beats and paroxysmal supraventricular tachycardia are the most common supraventricular arrhythmias observed in these patients. There is an increased incidence of left-sided atrioventricular bypass tracts in patients with mitral valve prolapse (184). There is also an increased incidence of mitral valve prolapse in patients with the Wolff-Parkinson-White syndrome (186). This may be, in part, responsible for the paroxysms of atrial tachycardia that have been observed.

History

The overwhelming majority of patients with mitral valve prolapse are asymptomatic (138,164,177). Many patients have symptoms that seem unrelated to the cardiac manifestations of the syndrome. For example, anxiety, easy fatigue, palpitations, and orthostatic hypotension have all been ascribed to this syndrome. Some authorities ascribe these symptoms to dysfunction of the autonomic nervous system with inappropriately increased sympathetic nervous activity at rest and with mild exertion

(134,135 and 136,180,187).

A relationship to neurocirculatory asthenia, commonly diagnosed in an earlier era, has been postulated (163,166). The exact relationship of these autonomic abnormalities to mitral valve prolapse is unclear. It is possible that abnormally heightened sympathetic tone leads to a decrease in left ventricular volume with resulting mitral valve prolapse. In this scenario, mitral valve prolapse is merely an epiphenomenon related to the abnormality in sympathetic nervous function. It is also possible that some of the symptoms reported by patients with mitral valve prolapse are psychosomatic in origin, resulting from anxiety generated when the patient was informed that he or she had heart disease. Some patients report chest discomfort that, at times, is obviously musculoskeletal in origin and at other times seems anginal in nature. Some authorities have suggested that anginal chest discomfort is cardiac in origin, resulting from abnormal tension and traction on papillary muscles (174).

Physical Examination

Patients with mitral valve prolapse are often asthenic in habitus with low body weights. Arterial blood pressure is often low and orthostatic hypotension may be present. Straight-back syndrome, pectus excavatum, scoliosis, and a narrow thoracic anteroposterior diameter may be present. If severe mitral regurgitation is present, the carotid pulse may be brisk in upstroke with a hint of rapid falloff. Palpation of the precordium may reveal a brief inward movement of the apex impulse in mid-systole coinciding with the occurrence of the mid-systolic click.

Auscultation of these patients is best performed using the diaphragm of the stethoscope with the patient lying and standing. The left lateral decubitus position while lying and movement from standing to squatting may assist the examiner in clarifying the relationship between the ausculted clicks and murmurs. The usual finding is a sharp, systolic click heard 0.14 seconds or more after the S_1. This click differs from the ejection click of aortic valve disease because it occurs well after the onset of the carotid arterial upstroke. At times, more than one click is heard. The click(s) is best heard along the lower left sternal border. It is thought that they are generated by tensing of the chordae tendineae and billowing of the mitral valve leaflets. The click(s) is usually, but not always, followed by a mid- to late systolic crescendo murmur heard best at the apex. The duration of the murmur correlates directly with the severity of mitral regurgitation: The earlier and more prolonged the murmur, the more severe the regurgitation.

The physical manifestations of this syndrome vary considerably. Some patients demonstrate only a systolic click, whereas others have multiple clicks and a prominent, prolonged murmur. The findings can vary from examination to examination, depending on the volume of the left ventricle and the position of the patient. Thus, with dehydration or standing, the click occurs earlier in systole, as does the murmur, because the valvular prolapse is occurring earlier secondary to a smaller left ventricular cavity. Other maneuvers can move the click and murmur earlier or later into systole, depending on the influence of the maneuver on left ventricular cavity size. Decreases in systemic blood volume, increases in myocardial contractility, or decreases in venous return all decrease left ventricular cavity volume, thereby moving the click and murmur earlier in systole. Thus, inhaling amyl nitrite produces marked vasodilatation with a resulting decrease in left ventricular cavity size and movement of the click and murmur earlier in systole. Maneuvers that increase left ventricular cavity size (i.e., increases in systemic blood volume, decreases in myocardial contractility, and increases in venous return) move the click and murmur later in systole. Thus, an infusion of phenylephrine or squatting augments peripheral arterial resistance, resulting in an increase in left ventricular cavity size and the movement of the click and murmur later into systole.

In general, factors that move the click and murmur later into systole decrease the severity of mitral regurgitation; hence the intensity of the murmur. This is not always the case, however. For example, inhalation of amyl nitrite shrinks left ventricular cavity size and moves the murmur and click earlier into systole. Because left ventricular systolic pressure is reduced by this drug, the systolic gradient between the left ventricle and the left atrium is reduced, thereby lessening the quantity of mitral regurgitant flow and hence decreasing the intensity or loudness of the systolic murmur. Valsalva's maneuver decreases left ventricular cavity size and thus leads to an earlier click and a more prolonged murmur in patients with mitral valve prolapse. This response should not be confused with that observed in patients with hypertrophic cardiomyopathy whose murmur usually becomes louder but not longer during the strain phase of Valsalva's maneuver. Diastolic filling sounds, similar in timing to an S_3, may occasionally be heard in patients with mitral valve prolapse.

Electrocardiography

Most patients with mitral valve prolapse have normal ECG results. In a small number of patients, and particularly in those with symptoms, the ECG demonstrates nonspecific ST-T changes in the inferior leads (II, III, augmented voltage unipolar left foot lead) and rarely in the anterolateral leads (V_4–V_6) (163,166,174). It has been suggested that these findings are the result of increased papillary muscle tension with resulting ischemia (151). Few data support this supposition, however, and it is just as reasonable to believe that these ECG findings are the result of altered autonomic tone in some patients or ventricular dilatation in individuals with more marked degrees of mitral regurgitation. Some investigators report that arrhythmias and even sudden death are more common in patients with mitral valve prolapse.

Chest Roentgenography

Chest roentgenography is usually normal in patients with mitral valve prolapse unless severe, chronic, or acute mitral regurgitation is present. If chronic severe mitral regurgitation is present, cardiomegaly secondary to left ventricular enlargement, left atrial enlargement, and pulmonary congestion are often noted. If severe acute mitral regurgitation secondary to chordal rupture is present, heart size is usually normal, but severe pulmonary congestion with or without frank pulmonary edema is often observed.

Echocardiography

As already noted, echocardiography yields important diagnostic and prognostic information in patients with mitral valve prolapse. Echocardiography confirms the diagnosis of mitral valve prolapse by demonstrating systolic posterior displacement of one or both leaflets into the left atrium (168,169). The mitral leaflets are usually thickened. Indeed, risk for complications in this syndrome is correlated with thickened leaflets. Patients with mitral valve prolapse but without leaflet thickening have a benign prognosis (147,168,169). Patients with thickened leaflets and dilated mitral valve annuli are at highest risk for complications such as infectious endocarditis and progressive mitral regurgitation. The echocardiographic findings in patients with mitral valve prolapse are quite variable, with individuals at one end of the spectrum demonstrating only mild prolapse, whereas patients at the other end of spectrum manifest thickened valves, dilated mitral valve annuli, and left atrial and left ventricular dilatation.

Color flow Doppler examination is usually combined with two-dimensional echocardiographic study in patients suspected of having mitral valve prolapse. The color flow Doppler analysis identifies and quantitates the severity of mitral regurgitation that is present. It helps define the location of the regurgitant jet, a finding that may be useful if surgical repair is being considered. Mitral regurgitation is usually mild in degree in most patients with mitral valve prolapse. Approximately 10% of patients, however, have moderate to severe regurgitation; this occurs most commonly in men over age 50 (165,175,176). If one performs echocardiographic examinations on first-degree relatives of patients with mitral valve prolapse, a large number have echocardiographic findings consistent with previously unsuspected mitral valve prolapse. Prolapse of the tricuspid and aortic valves is occasionally demonstrated during echocardiographic study in patients with mitral valve prolapse. This is the case in approximately 20% of patients with mitral valve prolapse (161,163).

Most patients with this syndrome have mild mitral valve prolapse and, in the absence of any change in their physical examination results, only a single echocardiographic examination is necessary. For screening purposes, often an abbreviated, single-view echocardiographic study is all that is required (163a). Individuals with moderate to severe mitral regurgitation require more careful monitoring, and serial echocardiographic examinations should be undertaken. Asymptomatic patients with severe mitral regurgitation should have a yearly echocardiographic study. Individuals with more moderate degrees of mitral regurgitation can be studied less frequently.

Radionuclear Imaging

Patients with mitral valve prolapse and angina-like chest discomfort may benefit from a thallium or sestamibi exercise or pharmacologic stress test. The resulting normal study result reassures the clinician and the patient that the chest discomfort is the result of the mitral valve prolapse syndrome and not coronary artery disease.

Cardiac Catheterization

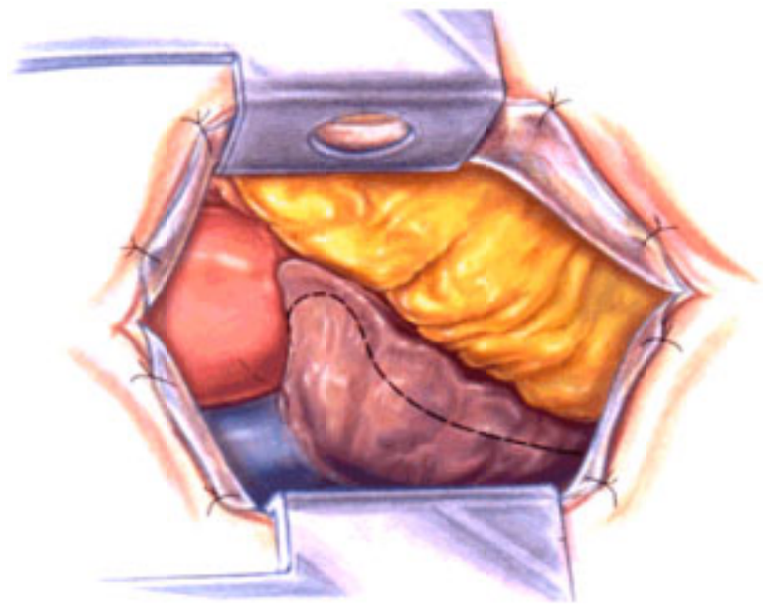
Invasive hemodynamic and angiography study is usually not necessary in patients with mitral valve prolapse because all manifestations of this syndrome can be exquisitely defined by echocardiography. When angiography is performed, mitral valve prolapse is clearly seen in the right anterior oblique left ventriculogram. Mitral valve redundancy is also often observed in this projection. If severe acute mitral regurgitation secondary to chordal rupture is present, the pulmonary capillary wedge and left ventricular diastolic pressures are markedly elevated. Pulmonary hypertension of moderate degree is also present. Large regurgitant CV waves are present in the pulmonary capillary wedge pressure tracing. If chronic severe mitral regurgitation is present, findings similar to that already discussed for other forms of chronic mitral regurgitation are observed: left atrial and left ventricular dilatation often with associated left ventricular dysfunction. Coronary angiography may be undertaken in

selected patients who are being considered for mitral valve surgery.

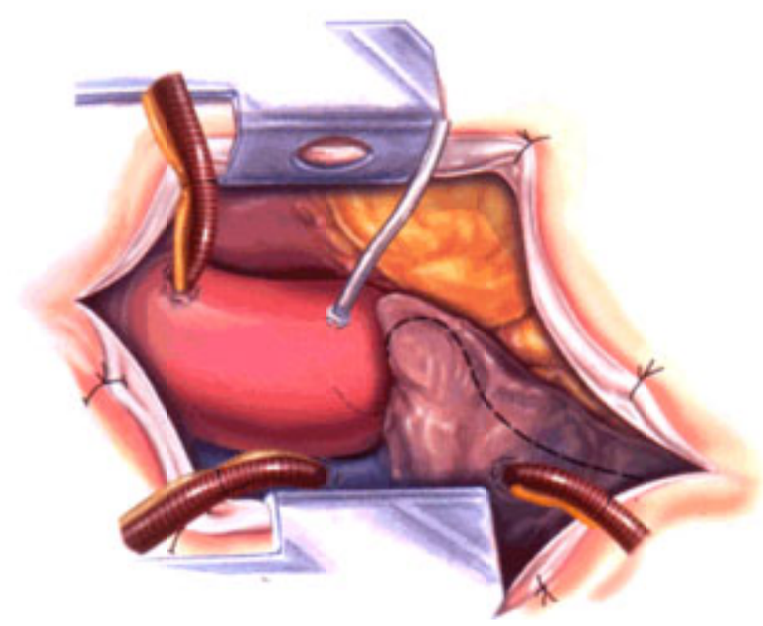
Therapy

Most patients with mitral valve prolapse have an excellent prognosis. Therefore, they should receive strong reassurance concerning the usually benign nature of their condition. The importance of such reassurance cannot be overemphasized because cardiac neurosis is common in these patients, often as a result of inadequate time spent by the physician when the diagnosis was initially explained to the patient. Individuals with mitral valve prolapse should be carefully instructed concerning antibiotic endocarditis prophylaxis for dental work or surgical procedures. Some physicians believe that patients with isolated clicks without a late systolic murmur or without a thickened valve by echocardiography do not need endocarditis prophylaxis (179,179a). Opinion is divided in this regard, however, and many physicians still provide prophylaxis to the latter group of patients.

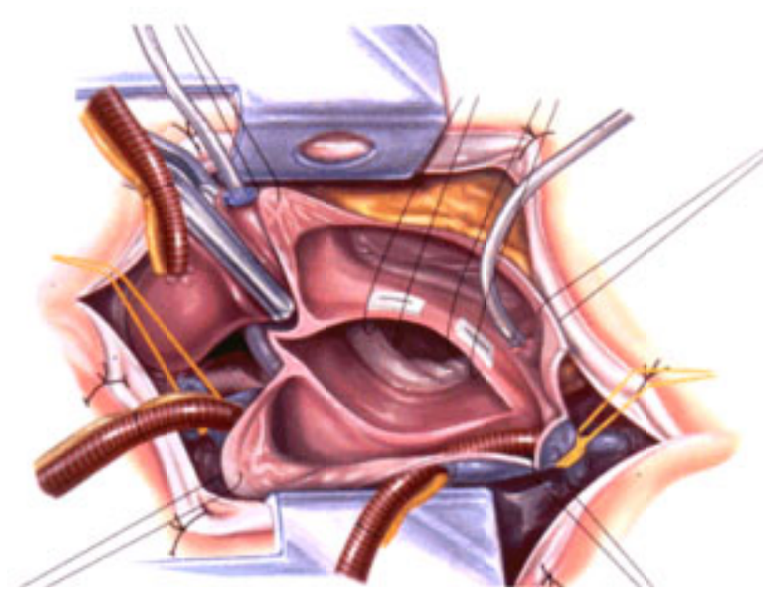
Patients with severe mitral regurgitation, particularly if a flail leaflet is present, should be considered for mitral valve surgery (see Results of Mitral Valve Repair for Mitral Insufficiency) (178,178a and 178b). If left ventricular size and function are normal or nearly so, the patient can be observed with careful and frequent follow-up, including at least yearly echocardiographic study. Mitral valve prolapse is now the most common underlying etiology observed in patients who undergo mitral valve surgery for mitral regurgitation. Most patients with mitral valve prolapse who require surgery can have their valves repaired rather than replaced with a prosthetic valve. Older individuals should have coronary arteriography before surgery so that clinically significant coronary arterial obstructions can be bypassed at the time of mitral valve surgery.



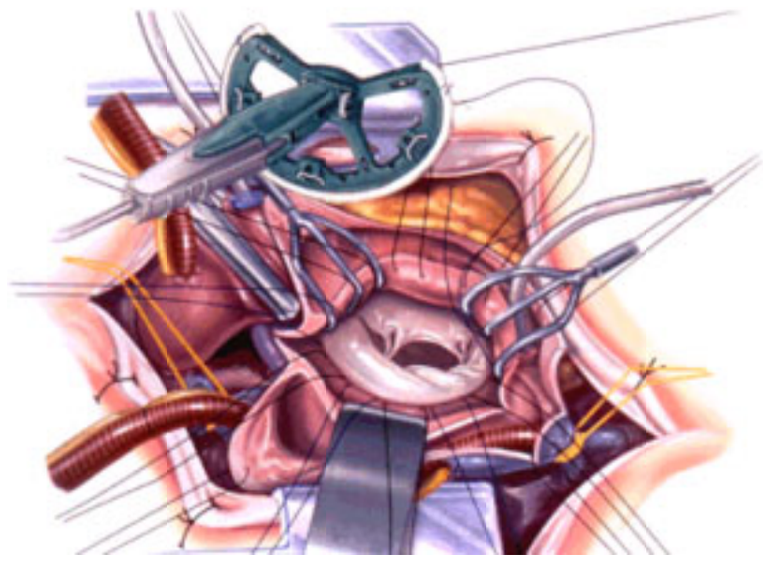
After the hemisternotomy is performed, the pericardium is incised and sutured to the skin edges. A retractor is placed, which brings the aorta, right atrium, superior vena cava, and right ventricle into view. The dashed line represents the site of the right atrial incision for the transseptal approach.



Cannulation is performed with direct aortic, superior vena cava, and inferior vena cava cannulation.



After the right atrium is incised, the septum is incised, exposing the left atrium and mitral valve.

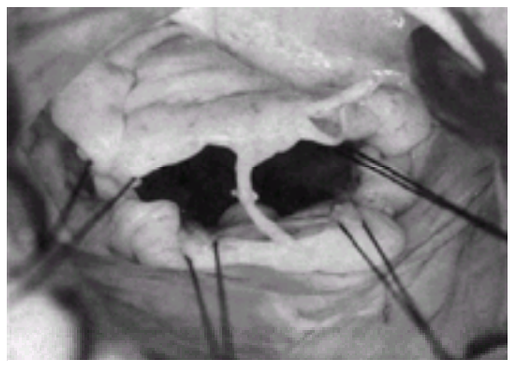


Mitral valve exposure.

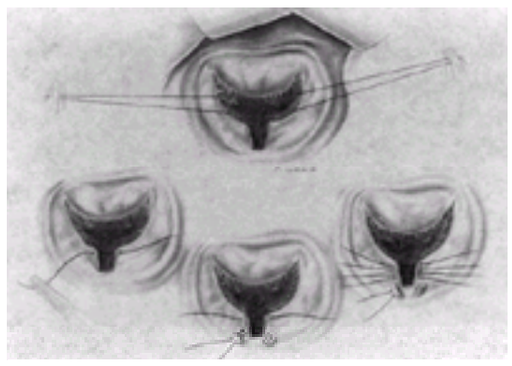
Individuals with a history of palpitations, particularly if syncope or presyncope has occurred, should undergo evaluation for arrhythmia, including ambulatory monitoring and routine ECG. If a prolonged QT interval, or repetitive ventricular ectopy such as ventricular tachycardia is detected, further evaluation is indicated, including signal-averaged ECG and possibly an invasive electrophysiologic arrhythmia evaluation to assess the risk for sudden death (184,185). Beta-adrenergic–blocking agents in modest dose are often effective in abolishing these arrhythmias as well as episodes of supraventricular tachycardia. Patients who are resuscitated from sudden death or whose electrophysiologic study demonstrates sustained ventricular tachycardia should be considered for aggressive antiarrhythmic therapy (i.e., amiodarone and an implantable defibrillator) (see Chapter 75). If paroxysms of atrial fibrillation or if an episode of arterial embolism have occurred (e.g., a transient or permanent neurologic deficit), life-long anticoagulation with warfarin should be strongly considered.

Mitral Valve Repair for Mitral Insufficiency

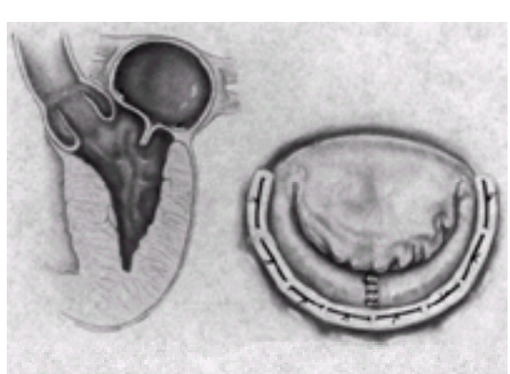
The most common etiology of mitral insufficiency that presents for mitral valve repair in the United States is degenerative or myxomatous mitral valve disease (186). In degenerative mitral insufficiency, the mitral valve regurgitation is caused by mitral valve leaflet prolapse. The etiology of the prolapsing leaflet is chordal rupture or elongation (eFig. 21.1.4). Although any segment of the mitral valve may prolapse, the middle scallop of the posterior mitral valve leaflet is the most commonly involved. Surgical repair involves resection of the prolapsing segment of the posterior mitral valve leaflet and reapproximation of the posterior leaflet and annulus (eFig. 21.1.5). An annuloplasty is performed to reinforce the repair, correct any posterior annular dilatation, and prevent any further annular dilatation (eFig. 21.1.6).



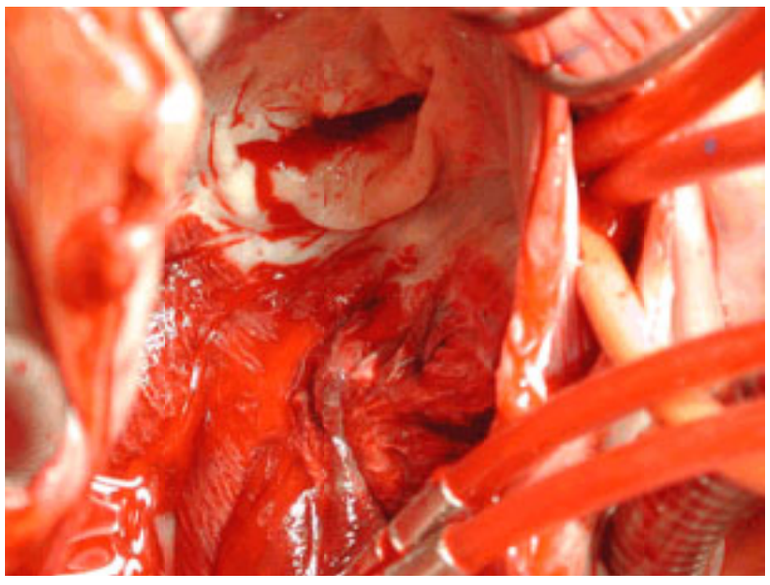
***e*FIGURE 21.1.4** Ruptured chordae to the anterior leaflet of mitral valve, resulting in anterior leaflet prolapse and mitral regurgitation.



***e*FIGURE 21.1.5** Quadrangular resection of prolapsing middle scallop of posterior mitral valve leaflet. The posterior annulus and leaflet are reapproximated.

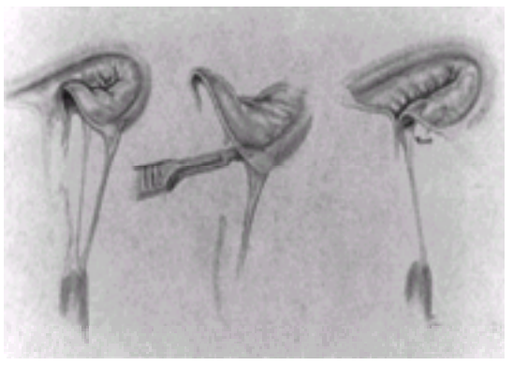


***e*FIGURE 21.1.6** After quadrangular resection and leaflet and annual reapproximation, a posterior annuloplasty is performed.

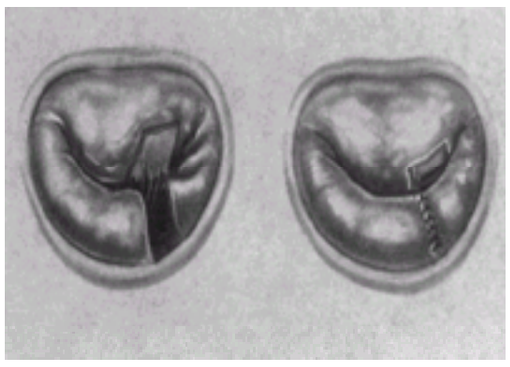


Intraoperative field looking into the left atrium after the large left atrial thrombus was resected demonstrating the rheumatic mitral valve at the top of the screen. Note the scarred, thickened, restricted mitral leaflets. This patient had severe mitral stenosis with a mean pressure gradient of 20 mm Hg across the valve and a mitral valve area of 0.7 cm^2.

In degenerative mitral valve insufficiency, anterior leaflet prolapse may also occur. Like posterior leaflet prolapse, the anterior leaflet prolapse is caused by chordal rupture or elongation. However, because the anterior leaflet is attached to the annulus of the aortic valve, it is not possible to repair anterior leaflet prolapse by segmental resection and annular plication. Instead, reconstruction is directed at restoring normal chordal length. Although some have advocated chordal shortening procedures, chordal transfer procedures have been demonstrated to result in superior long-term outcomes (187,188 and 189). Secondary chordae from the anterior leaflet can be advanced to the location of the elongated or ruptured primary chordae (*e*Fig. 21.1.7). Alternatively, normal chordae from the posterior leaflet may be transferred to the anterior leaflet to repair anterior leaflet prolapse (*e*Fig. 21.1.8). The defect created in the posterior leaflet is repaired by leaflet and annular approximation and a posterior annuloplasty.



***e*FIGURE 21.1.7** Secondary chordae from the anterior leaflet are used to repair ruptured primary chordae.

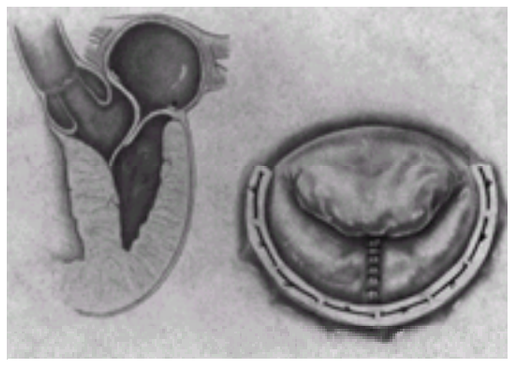


***e*FIGURE 21.1.8** Normal chordae from the posterior leaflet are transferred to the anterior leaflet to replace ruptured or elongated anterior leaflet chordae.

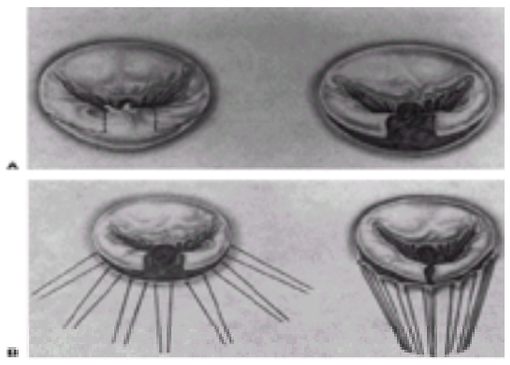
Video 21.20 Color Doppler of 0-degree intraoperative transesophageal echo with prolapse and flail of the posterior mitral leaflet causing very eccentric, anteriorly directed mitral regurgitation. This valve was successfully repaired. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 21.21 Postpump echo (with color Doppler) after repair of the flail posterior mitral leaflet. There is a Cosgrove-Edwards annuloplasty ring in place. There is no residual mitral regurgitation and there is no systolic anterior motion of the mitral leaflets, which can sometimes complicate mitral valve repair. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

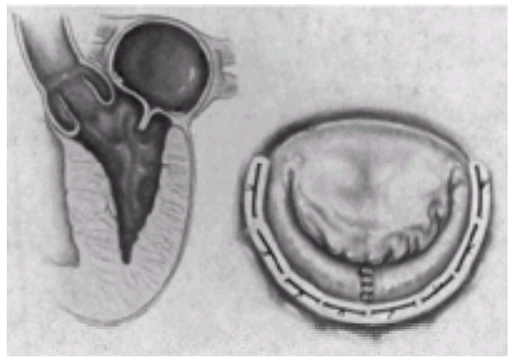
Systolic anterior motion of the anterior leaflet of the mitral valve occurs occasionally after mitral valve repair for degenerative mitral insufficiency, resulting in obstruction of the left ventricular outflow tract (190,191,192 and 193). This complication of degenerative mitral valve repair is secondary to the anterior displacement of the site coaptation of the anterior and posterior leaflets (*e*Fig. 21.1.9). In patients with excessive height of the posterior leaflet, there may be anterior displacement of the mitral valve leaflet coaptation. To prevent this complication in patients undergoing mitral valve repair, if the height of the posterior leaflet is greater than 1.5 cm, the height of the posterior leaflet is decreased by performing a sliding repair of the posterior leaflet. In this repair, the prolapsing segment of the posterior leaflet is excised. The height of the remaining posterior mitral valve is decreased by detaching the remaining posterior mitral valve leaflet from the annulus, advancing the detached segments toward each other, and then reattaching the remaining leaflet to the annulus (*e*Fig. 21.1.10). This effectively decreases the height of the posterior leaflet and decreases the amount of anterior displacement of the anterior leaflet. A flexible posterior annuloplasty is performed to correct similarly any posterior annular dilatation, support the repair, and prevent future annular dilatation (*e*Fig. 21.1.11).



***e*FIGURE 21.1.9** Systolic anterior motion of the anterior leaflet of the mitral valve after mitral valve repair, resulting in left ventricular outflow tract obstruction.

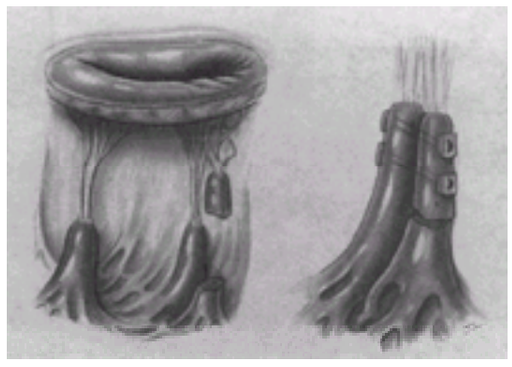


***e*FIGURE 21.1.10 A:** After quadrangular resection, the posterior leaflet is detached from the annulus. **B:** The annulus is plicated, and the leaflets are reattached to the annulus.



***e*FIGURE 21.1.11** Reducing the height of the posterior leaflet results in normal coaptation of the mitral valve leaflets and correction of left ventricular outflow tract obstruction.

Chronic or acute ventricular ischemia may result in mitral insufficiency. Papillary muscle infarction with papillary muscle rupture can lead to acute mitral valve leaflet prolapse and severe mitral regurgitation. When papillary muscle infarction occurs, it occurs four times more commonly to the posterior medial muscle than to the anterior lateral papillary muscle (194,195). Papillary muscle rupture occurs in less than 1% of patients with fatal acute myocardial infarctions (196). To repair this injury, the ruptured papillary muscle is sutured to the immediately adjacent papillary muscle or the left ventricular wall (eFig. 21.1.12).



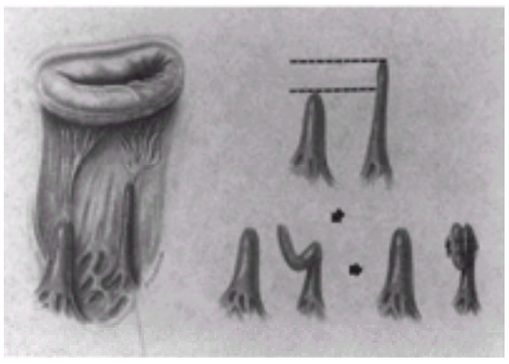
***e*FIGURE 21.1.12** The ruptured papillary muscle head is sutured to the remaining papillary muscle head.

Video 21.22 Mitral valve repair. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

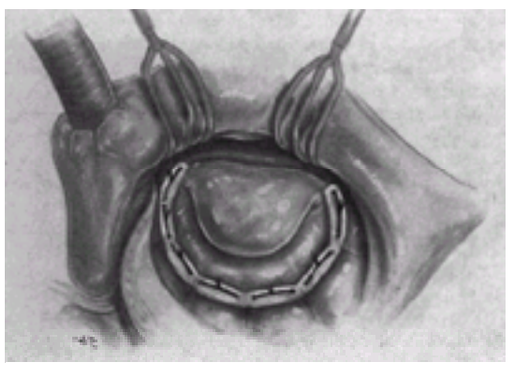
Surgical pathology specimen demonstrating a torn papillary muscle seen to the lower right of the screen, attached via chordae to a portion of the anterior mitral leaflet. Note the torn "ragged edges" at the bottom of the papillary muscle head.

Video 21.23 Parasternal long-axis view of a ruptured papillary muscle after myocardial infarction. Note the bright mass (papillary muscle) attached to the tip of the anterior mitral leaflet as it flails into the left atrium. This resulted in severe mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Chronic ischemia or healed papillary muscle infarction can result in papillary muscle fibrosis and elongation, and mitral valve prolapse with regurgitation. To correct this defect, the height of the papillary muscle is reduced by folding the papillary muscle to itself (eFig. 21.1.13). Central regurgitation with normal papillary muscle function may occur in patients with left ventricular dilatation secondary to ischemic heart disease. Left ventricular dilatation results in displacement of the papillary muscles laterally, causing restricted excursion of the leaflets. This prevents leaflet coaptation and results in central mitral regurgitation. A posterior annuloplasty is performed to increase leaflet coaptation and decrease the mitral insufficiency (eFig. 21.1.14).



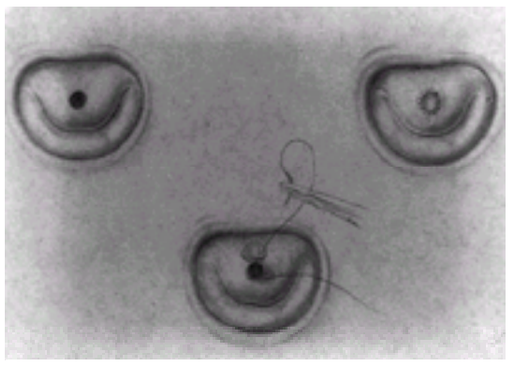
***e*FIGURE 21.1.13** The length of elongated papillary muscles may be reduced by folding the papillary muscle onto itself.



***e*FIGURE 21.1.14** To correct central mitral regurgitation from ventricular dilatation, a posterior annuloplasty is performed.

Rheumatic mitral valve disease may result in mitral insufficiency by annular dilatation or restricted motion of the mitral valve leaflets. Because of fibrosis and thickening of both the posterior leaflet and subvalvular apparatus, the posterior leaflet of the mitral valve is more commonly restricted in its mobility than is the anterior leaflet. If there is still restrictive motion of the posterior leaflet after leaflet debridement and chordal debridement, the posterior leaflet may be augmented with a glutaraldehyde-treated or autologous pericardial patch. Annular dilatation is treated with a flexible posterior annuloplasty.

Mitral insufficiency caused by acute or healed endocarditis may often be repaired. Leaflet perforations may be patched with pericardium after adequate debridement (eFig. 21.1.15). As experience with repair of infected valves has increased, large portions of the anterior leaflet have been replaced with pericardium. When chordae are destroyed, normal leaflet coaptation can be obtained by leaflet resection or chordal transposition. The use of autologous tissue for repair of mitral valve insufficiency secondary to endocarditis may lead to eradication of infection in a greater percentage of patients.



***e*FIGURE 21.1.15** A perforation in the anterior mitral valve leaflet is repaired with a pericardial patch.

Results of Mitral Valve Repair for Mitral Insufficiency

The ability to perform mitral valve repair for mitral insufficiency successfully depends on the valve pathology and the experience of the surgical team (197). Degenerative or myxomatous mitral valves are the most likely to be repaired, followed by mitral insufficiency secondary to ischemia (186). In 1995, at The Cleveland Clinic Foundation, 86% (247 of 286) of patients with mitral insufficiency secondary to degenerative mitral valve disease were successfully repaired, whereas 76% (29 of 38) of patients with ischemic mitral regurgitation underwent successful repair, 59% (10 of 17) of patients with mitral insufficiency secondary to endocarditis underwent successful mitral valve repair, and 42% (13 of 31) of patients with mitral insufficiency secondary to rheumatic disease underwent successful valve repair. In addition, the ability to perform mitral valve repair for mitral insufficiency successfully depends also on the experience of the surgical team. At The Cleveland Clinic Foundation, the percentage of patients with mitral valve disease undergoing mitral valve repair increased from 20% in 1980 to 71% in 1995 (186). Others have reported a similar trend (187).

The operative mortality of mitral valve repair has been documented to be low, with reported rates of 0% to 6.3% (80,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215 and 216). Although it had been speculated that the operative mortality for mitral valve repair would be greater than that for mitral valve replacement secondary to the increased operative time required for mitral valve repair and greater incidence of patients undergoing mitral valve repair with mitral insufficiency, this concern has not been substantiated. The literature demonstrates an overall decreased operative mortality in patients undergoing mitral valve repair versus mitral valve replacement (Table 21.1) (200,201,202 and 203,205,206,208,209 and 210). From 1985 to 1995 at The Cleveland Clinic Foundation, 2,131 patients underwent isolated mitral valve surgery. Operative mortality for patients undergoing mitral valve repair was 0.8% as compared with the operative mortality of 6.4% for patients undergoing mitral valve replacement. In addition, the mortality for degenerative disease, rheumatic disease, and ischemic disease was lower in patients who had mitral valve repair than in those who had mitral valve replacement for each pathology. Ischemic disease was found to be associated with the highest operative mortality. The lower operative risk for patients undergoing mitral valve repair versus mitral valve replacement may be attributable to maintaining the entire mitral valve mechanism and its beneficial influence on left ventricular function. Patients with organic mitral regurgitation and preoperative functional class III and IV symptoms have excess short- and long-term mortality following mitral valve surgery (210a). These observations argue for surgical intervention at an earlier stage in the clinical course of patients with mitral regurgitation. Decreased preoperative right ventricular function predicts increased postoperative mortality following mitral valve surgery (210b).

The long-term results for mitral valve repair for mitral insufficiency have been encouraging. Five-year survival rates of 86% to 91% have been reported, and rates of freedom from reoperation for structural valve failure at 5 years have been reported at 83% to 95% (186,213,214). Cohn et al. noted an increased rate of valve failure in patients undergoing mitral valve repair who did not undergo a ring annuloplasty at the time of surgery (54). This finding has been confirmed by Marwick et al. (217). Cohn reported a 5-year rate of freedom from reoperation of 88% in patients who underwent an annuloplasty as compared with 67% for patients who did not undergo an annuloplasty ring at the time of mitral valve repair (213). In a multivariate analysis, David et al. noted an increased risk of valve failure in patients with advanced myxomatous changes (214).

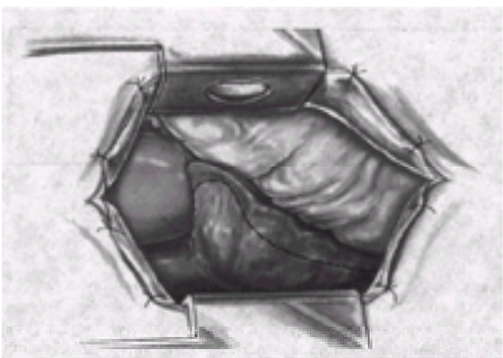
Complication rates after mitral valve repair have also been low, with a 93% to 94% rate of freedom from thromboembolic complications after 5 years (213,214). Freedom from endocarditis at 5 years has also been low with reported rates of 7% to 100%.

Minimally Invasive Mitral Valve Surgery

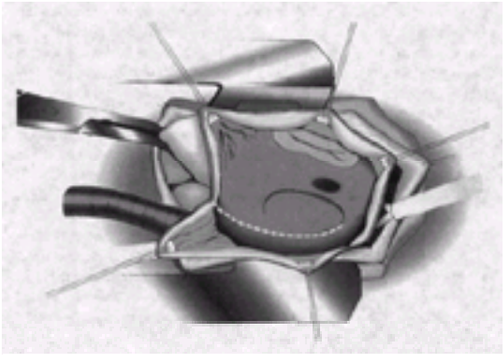
To decrease the morbidity associated with cardiac surgery, minimally invasive procedures for coronary artery bypass surgery, aortic valve surgery, and mitral valve replacement and repair are being developed. In minimally invasive mitral valve operations, the median sternotomy is avoided, and the operations are performed through an 8-cm hemisternotomy or right lateral thoracotomy. These incisions are associated with less morbidity than the median sternotomy, and the hope is that the decreased morbidity associated with the minimally invasive approaches will result in less postoperative pain, decreased need for postoperative ventilatory support, shorter intensive care unit stays, shorter hospitalizations, decreased hospital costs, and quicker functional patient recovery.

The minimally invasive approach for mitral valve surgery at The Cleveland Clinic Foundation evolved from a right parasternotomy to a hemisternotomy (218). The skin incision is 8 cm in length and extends from the junction of the manubrium and sternum to the level of the fourth intercostal space. The sternum is divided from the sternal notch down to the level of the fourth intercostal space, and then the left side of the sternum is divided in a horizontal direction into the fourth intercostal space. The pericardium is incised, and tension is placed on the pericardial edges with sutures, bringing the heart into view (*e*Fig. 21.1.16). Cannulation for cardiopulmonary bypass is performed with direct aortic and superior and inferior vena caval cannulation (*e*Fig. 21.1.17). Similar to mitral valve surgery performed through a median sternotomy, the aorta is cross-clamped, and myocardial protection is performed with antegrade cardioplegia, retrograde cardioplegia, or a combination of both. The approach to the mitral valve is a transseptal approach (*e*Fig. 21.1.18). After placement of retractors, the mitral valve is exposed, and mitral valve replacement or repair may be performed (*e*Fig. 21.1.19).

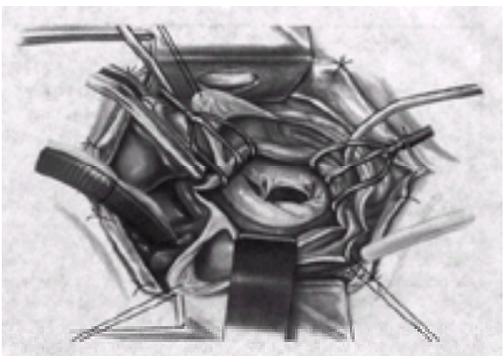
***e*FIGURE 21.1.16** The incision for minimally invasive mitral valve operations. An 8- to 10-cm incision is made, extending from the lower border of the second costal cartilage to the upper border of the fifth costal cartilage.



***e*FIGURE 21.1.17** The pericardium is sutured to the skin edges. This brings the right atrium, superior vena cava, and aorta into the operative field. The dashed line denotes the site of the incision in the right atrium for the transseptal approach to the mitral valve.



***e*FIGURE 21.1.18** After the right atrium has been incised, the septum is incised from the fossa ovalis to the roof of the left atrium. The dashed line denotes site of incision.

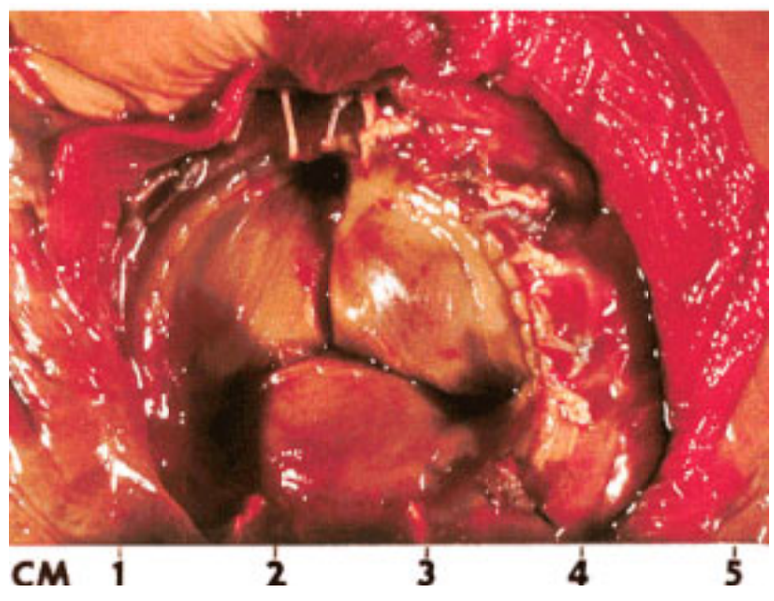


***e*FIGURE 21.1.19** After the septum has been incised, retractors are placed, and the mitral valve is exposed.

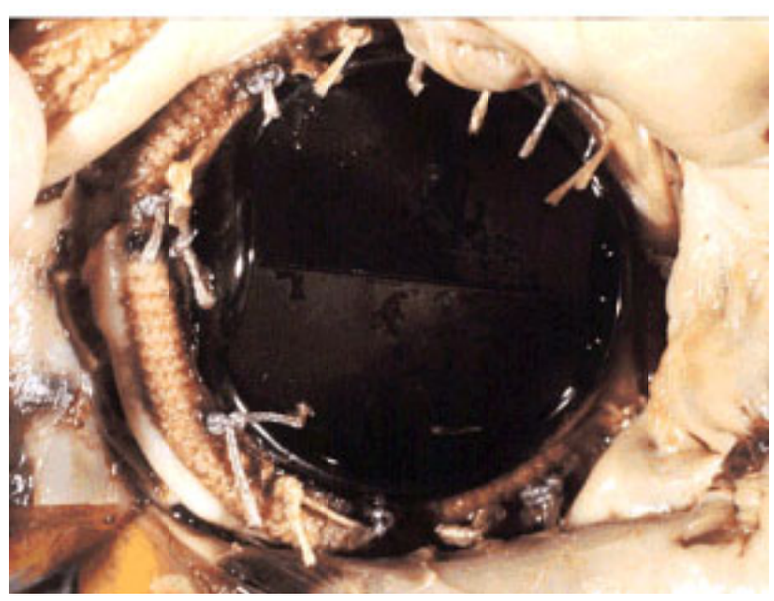
Another minimal access approach to mitral valve surgery is through an 8- to 10-cm right lateral thoracotomy (219,220). With this approach direct access to the aorta and right atrium is not obtained, and cannulation for cardiopulmonary bypass is via the common femoral artery and vein. The aorta cannot be directly accessed and, therefore, a standard aortic cross-clamp cannot be applied. The mitral valve surgery may be performed with hypothermic fibrillatory arrest or under ischemic arrest with myocardial protection with the aid of an endovascular aortic occluder catheter (219,220), or with a transthoracic aortic clamp that is placed through a small intercostal incision (220a). The endovascular aortic occluder is a catheter that is passed from the femoral artery into the ascending aorta with the assistance of fluoroscopy or transesophageal echocardiography. At the end of the catheter is an inflated balloon that effectively occludes or cross-clamps the aorta from inside the aorta. Cardioplegia is delivered directly into the aortic root through a central port in the endovascular clamp. Alternately, cardioplegia may be administered by a coronary sinus catheter that can be placed into the coronary sinus with the assistance of fluoroscopy from the internal jugular vein. The mitral valve is approached through a standard left atriotomy. Both mitral valve repairs and replacements have been successfully performed with this approach.

The early results with minimally invasive mitral valve surgery have been encouraging. Cosgrove et al. at The Cleveland Clinic Foundation have reported the results of their first 50 patients who underwent mitral valve surgery via a minimally invasive right parasternal incision (221). The majority of the patients were men and were in functional class II or III. Forty-nine patients underwent successful mitral valve repair, and one patient underwent a mitral valve replacement. The valve repair techniques performed through the minimally invasive incision included leaflet resection in 94% of patients, chordal transfer in 15%, and annuloplasty in 100%. There were no hospital deaths. Patients were extubated early after surgery, and intensive care unit stays were short. The median hospital stay was 5.7 days. Patient acceptance was high with the more cosmetically appealing incision.

From 1996 through 1999, a total of 898 patients have undergone minimally invasive mitral valve repair at The Cleveland Clinic Foundation. Similar to our early report, the majority were men (64%), and most patients underwent mitral valve repair (88%). All techniques of mitral valve repair were able to be performed through the minimally invasive incision. Leaflet resection was performed in 86%, chordal transfer in 10%, and annuloplasty in 100%. Operative mortality was only 0.1%, and morbidity was also low, with a 0.9% rate of perioperative myocardial infarction, a 1.2% rate of perioperative stroke, and a 0.7% rate of respiratory complications. Nineteen patients (2.1%) required conversion to a full median sternotomy to complete the operation.



Porcine prosthetic mitral valve. In this example, the valve is normal and the suture line is intact.



Normal St. Jude valve in the mitral position.

Explanted Carpentier-Edwards mitral valve regurgitation in a patient with severe infective prosthetic valve endocarditis. The patient had severe mitral stenosis due to the large vegetations on the prosthesis.

The results of minimally invasive mitral valve operations performed through a small right thoracotomy with the assistance of endovascular aortic occlusion have also been reported. Galloway et al. reported the results of a multicenter study in which 321 patients underwent mitral valve surgery through a right thoracotomy with femoral perfusion and endovascular aortic occlusion (221a). Operative mortality for the 137 patients undergoing mitral valve repair was 1.5% and 3.3% for the 184 patients undergoing mitral valve replacement. The overall risk of perioperative stroke was 2.2%, and the risk of postoperative atrial fibrillation was only 7.2%. Twenty-two patients (6.8%) required conversion to a median sternotomy to have their procedure completed.

Video 21.24 Transesophageal view of a Starr-Edwards prosthesis in the mitral position. (The left atrium is toward the upper right side of the screen and the left ventricle is toward the lower left.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 21.25 Normal-functioning Starr-Edwards prosthetic valve in the mitral position. Note the full motion of the valve pop-it within the cage. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Future Directions

As technology and instrumentation continue to develop, further refinements in minimally invasive mitral surgery will be made. New techniques involving robotic assisted mitral valve surgery are being developed. These robotic assisted mitral valve operations are performed through multiple ports, small 1- to 2-cm incisions in the chest. Without a large incision and the need for chest wall retraction, the hope is that these robotic assisted operations will result in less patient morbidity and quicker patient recovery.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Mitral Stenosis

Although clinicians have been quite successful in managing mitral stenosis for the last 50 years, a number of controversial aspects remain. As already noted, some clinicians favor prophylactic warfarin anticoagulation for all but the most mild forms of mitral stenosis. Others prefer to await the onset of atrial fibrillation, the development of marked left atrial dilatation, or age 35 to 40 before instituting anticoagulant therapy. The recommendations of the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy are reasonable and favor this course of action (52). Patients are anticoagulated when the following criteria are met: Individuals with rheumatic mitral valve disease with a history of either systemic embolism or paroxysmal or sustained atrial fibrillation should receive chronic warfarin anticoagulation with an international normalized ratio maintained between 2.0 and 3.0. Individuals with rheumatic mitral valve disease in normal sinus rhythm but with a left atrial size exceeding 5.5 cm in diameter should also receive chronic warfarin therapy as previously mentioned. Other patients with rheumatic mitral valve disease may be considered candidates for chronic warfarin anticoagulation if they are older than 65 to 70 years and have more modest but nonetheless definite left atrial dilatation. This is particularly the case if moderately severe or severe mitral stenosis is present. If recurrent systemic embolism occurs, the international normalized ratio range should be increased to 2.5 to 3.5, or 81 to 100 mg of aspirin daily should be added to long-term warfarin therapy. Patients with nonrheumatic mitral disease and paroxysmal or sustained atrial fibrillation should also be anticoagulated with warfarin (see Chapter 64).

A number of randomized trials are currently evaluating the role of transesophageal two-dimensional echocardiography in the management of patients with atrial fibrillation (see Chapter 52 and Chapter 64). One school of thought favors immediate cardioversion if left atrial thrombus is not identified during a transesophageal study. Other investigators point out that an occasional patient has an episode of arterial embolism following cardioversion despite a negative transesophageal study. The correct strategy will evolve from the results of ongoing trials. The traditional approach is 3 to 4 weeks of warfarin anticoagulation before and 4 weeks following elective cardioversion. Routine transesophageal echocardiographic studies are not obtained in these patients.

The long-term results of balloon valvuloplasty are still not available. Some patients are now 10 years from this procedure; but the numbers are small, and definitive long-term comparisons between balloon and surgical valvotomy await further follow-up results. Essop and coworkers anticipate that the long-term results of these two procedures will be similar, and it seems reasonable to concur with their arguments (222). Whether surgical repair of the mitral stenotic valve will largely displace prosthetic valve replacement also awaits the results of further clinical trials. Surgical advances, including minithoracotomies and endoscopic techniques are currently being developed and evaluated. What role, if any, these procedures will play in the future remains to be seen.

Mitral Regurgitation

The most controversial decision for patients with chronic mitral regurgitation involves the timing of surgical intervention. At one time, it was commonly taught that mitral regurgitation was a benign lesion rarely, if ever, requiring mitral valve replacement. Subsequently, a number of clinician investigators argued for relatively early mitral valve replacement before insidious, irreversible left ventricular dysfunction developed. At the present time, most authorities favor serial, noninvasive follow-up for patients with chronic mitral regurgitation. Mitral valve repair or replacement is advised when early left ventricular dysfunction (left ventricular ejection fraction £50%) or dilatation (left ventricular end systolic volume index ³55 mL per m^2; end diastolic dimension between 65 and 68 mm; end systolic dimension between 44 and 45 mm) develops (160). Patients may be symptomatic or asymptomatic when significant left ventricular dysfunction or dilatation is observed. Controversy remains, however, concerning the level of left ventricular dysfunction or dilatation that should trigger an evaluation leading to mitral valve surgery (223). Long-term data from the Mayo Clinic suggest that patients with a flail mitral leaflet should be considered for surgery early in the course (224). As data accumulate, it is possible that evaluation of left

ventricular function or size during and after a stress echocardiographic study will yield discriminating information, thereby making it easier to select patients for mitral valve repair.

Another controversy involves the decision for medical or surgical therapy in patients with mitral regurgitation and an already dilated hypokinetic left ventricle. Is this entity the result of a congestive cardiomyopathy with mitral regurgitation secondary to ventricular and mitral annular dilatation, or did this patient once have normal left ventricular function with severe, chronic mitral regurgitation leading to marked left ventricular dysfunction? Patients in the latter group may still be surgical candidates, whereas individuals in the former category are rarely offered surgical intervention. Moreover, to what degree, if any, is left ventricular dysfunction or dilatation reversible following surgery? Most of these patients are better served by aggressive vasodilator therapy with ACE inhibitors than with mitral valve surgery unless severe mitral regurgitation is present.

Yet another controversial topic is the role of vasodilator therapy (e.g., ACE inhibition) in delaying or entirely obviating the need for mitral valve surgery. Should prophylactic ACE inhibitor therapy be given to all patients with moderate to severe chronic mitral regurgitation? The answer to this question awaits an appropriately designed randomized clinical trial.

Finally, a number of arguments surround the entity of mitral valve prolapse: How many of the myriad individuals with echocardiographic prolapse actually have myxomatous degeneration of the valve? What intensity of follow-up is required for these individuals? How should they be counseled and what therapy should they receive? Is their exercise intolerance and orthostatic hypotension the result or the cause of their mitral valve prolapse? These and many other questions await the results of further clinical and pathologic studies (225).

THE FUTURE

Further research, in the form of clinical trials, is needed to determine the appropriate role of vasodilator therapy in delaying or completely removing the need for mitral valve surgery. Continuing clinical and pathologic studies will provide data for improving therapy in patients with mitral valve prolapse as well as mitral regurgitation.

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22

AORTIC VALVE DISEASE

WILLIAM J. STEWART
BLASE A. CARABELLO

"Indicates text or graphics that appear only in the electronic versions of this text."

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Prophylactic Valve Replacement in Patients with Coronary Disease
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AORTIC STENOSIS

Historical Perspective

Until the advent of aortic valve replacement (AVR) in 1960, patients with aortic stenosis (AS) who developed classic symptoms of angina, syncope, or congestive heart failure (CHF) had only a few years to live, and survival was unaffected by medical therapy. Outcome has evolved from this dismal prognosis to the present, with the age-corrected survival after successful AVR for patients with pure AS being the same as that for the normal population (1). Excellent outcome is predicated on proper timing of surgery, use of dependable "substitute" valves with excellent hemodynamic profiles, and the advent of effective cardioplegic protection of the hypertrophied heart during surgery. These developments are fortunate because AS is primarily a disease of aging, and its incidence is increasing in our population, which is also aging. It is estimated that some degree of AS exists in approximately 3,000,000 Americans.

Paralleling the development of successful therapies for AS, diagnosis of this disease has also undergone substantial refinement. Hemodynamic assessment of AS initially was limited because retrograde catheterization of the stenotic aortic valve was thought to be contraindicated. Therefore, a number of other approaches, including transbronchial atriotomy (2), transthoracic left ventricular (LV) puncture (3), and the transseptal approach through the atrial septum (4), were devised to obtain LV pressure. These methods had their own complications that limited the procurement of intraventricular hemodynamic data until retrograde LV catheterization was revisited with success. Routine use of the retrograde approach to catheterization enabled physicians to measure the pressure gradient directly and to approximate aortic valve area (AVA). In addition, the ability to obtain catheter-provided pressure data simultaneously with angiographic volumetric data (5) allowed sophisticated pressure-volume analysis of systolic and diastolic function in patients with AS. In concert with the development of invasive hemodynamic measurements, noninvasive approaches also improved. By 1981, Doppler techniques were developed to provide an accurate estimation of both the transvalvular gradient (6,7), based on valvular velocity and the modified Bernoulli equation, and the AVA (8), based on the continuity equation. Thus, the physician's bedside assessment of the severity of AS could be confirmed noninvasively.

VIDEO

Video 22.1 Congenital bicuspid aortic valve with mild aortic regurgitation (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 22.2 A 76-year-old female patient with bicuspid aortic valve, aortic stenosis, and coarctation of aorta. Left anterior oblique aortogram revealed coarctation of the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

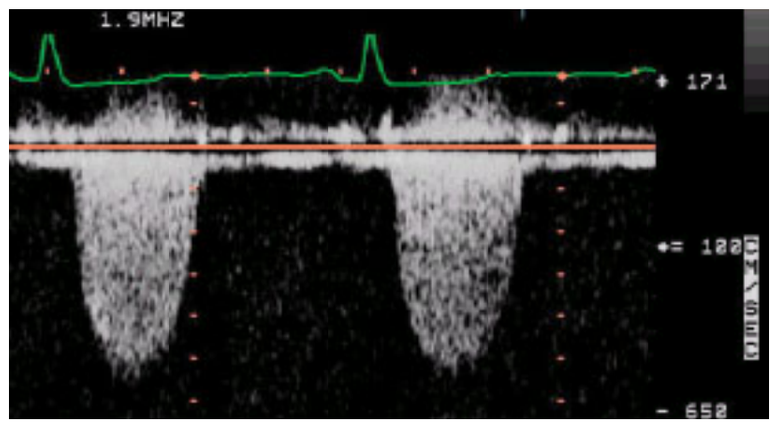
VIDEO

Video 22.3 A short-axis 60-degree transesophageal echo view of a normal, tri-leaflet aortic valve. The noncoronary cusp of the aortic valve is located toward the upper left of the screen, the left coronary cusp is towards the upper right, and the right coronary cusp is towards the bottom. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

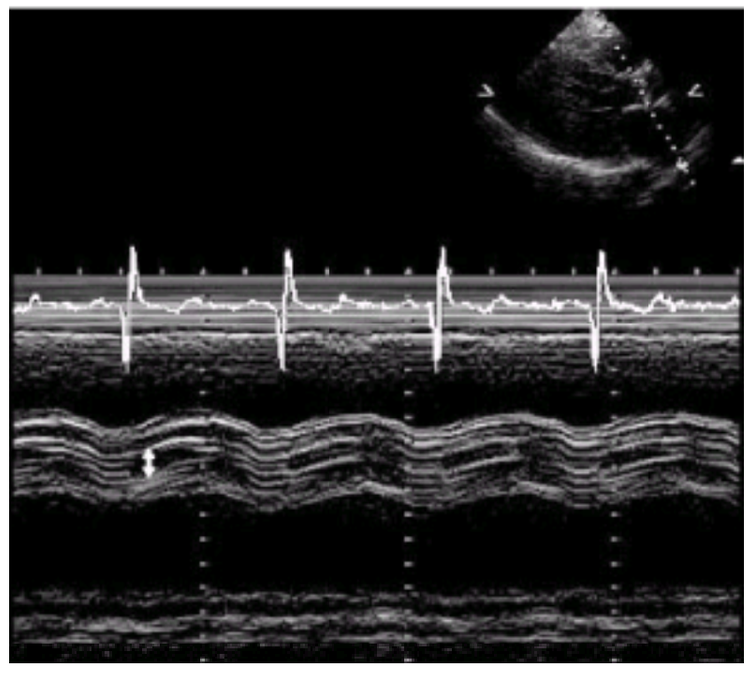
VIDEO

Video 22.4 A normal 120-degree transesophageal echo demonstrating a normal aortic valve in long-axis view and a normal mitral valve. The posterior mitral leaflet is

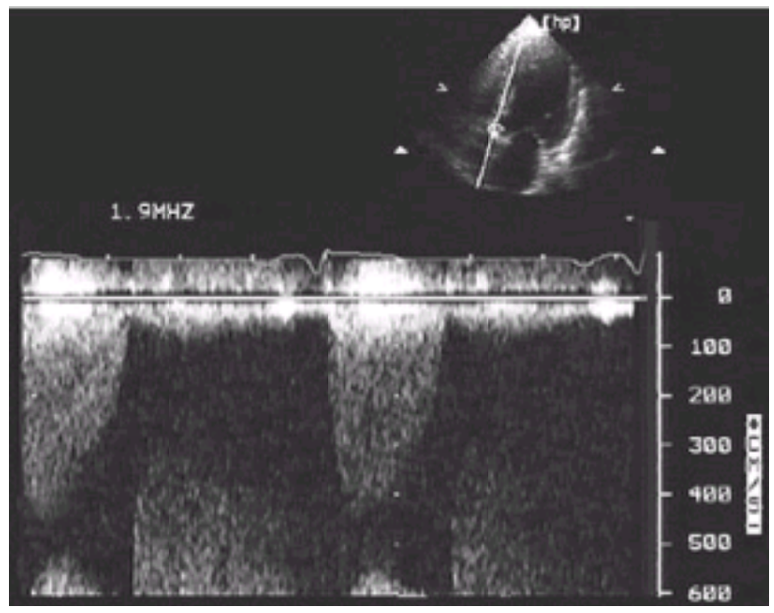
towards the left of the screen, and the anterior mitral leaflet is in the center of the screen. The anterior/anteroseptal wall of the left ventricle is in the center of the screen, and the posterior wall is to the left. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



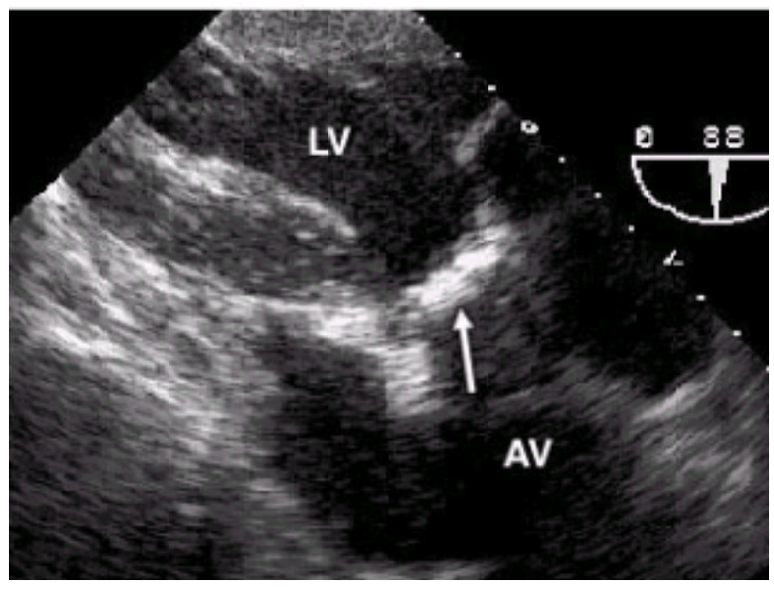
Continuous wave Doppler through a stenotic aortic valve. The maximal velocity is 5.5 m/sec, consistent with a peak pressure gradient of 121 mm Hg.



M-mode through a stenotic aortic valve. Note the thickened aortic leaflets with decreased excursion. (The small arrow designates the limited excursion of the aortic leaflets.)



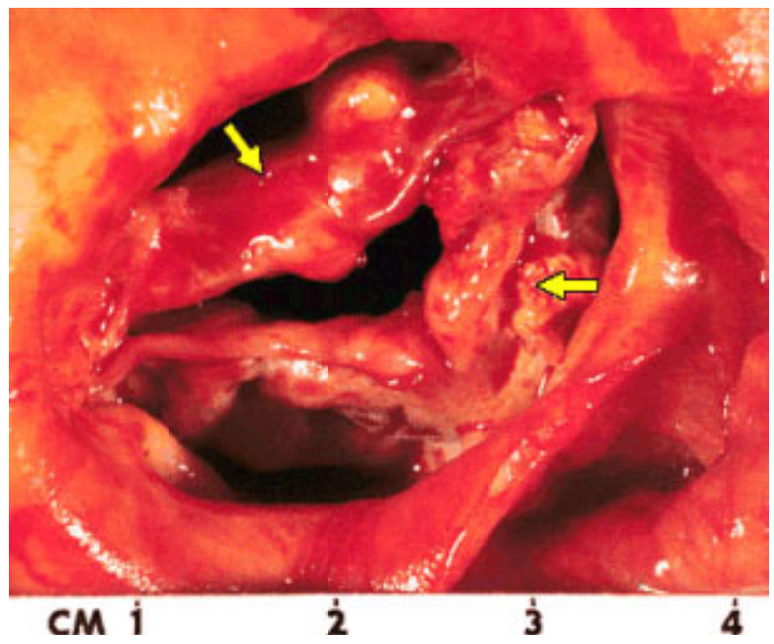
Apical continuous-wave Doppler spectrum of aortic valve disease. Note high forward velocities in systole (V_{max} 4.5 m/sec) and early peak of aortic stenosis. At the bottom, wrapped-around diastolic flow velocities from aortic regurgitation are seen.



Deep transgastric transesophageal echo view of the aortic valve in a patient with aortic stenosis. Note the heavily calcified aortic valve in the center of the screen (*arrow*); the posterior wall is at the top of the screen and the anterior/anteroseptal wall is towards the bottom. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)

Initial attempts to surgically treat aortic valve disease consisted of blind mechanical dilation of stenotic aortic valves. In 1952, Huffnagel and Harvey (9) inserted a ball valve prosthesis in the descending thoracic aorta in a patient with aortic regurgitation. After the development of cardiopulmonary bypass by Gibbon in 1953, dilation of the aortic valve under direct vision, debridement of calcific deposits, and replacement of individual valve leaflets were attempted, all without significant success. The modern era of aortic valve surgery began in 1960 when Harken and colleagues (10) reported successful AVR with a mechanical prosthesis implanted in the subcoronary position. Although in 1956 Murray (11) had reported the use of a homograft (allograft) valve in the descending thoracic aorta, Ross (12) in 1962 was the first to use the aortic valve homograft in the orthotopic position. Ross (13) also reported as early as 1967 transfer of the pulmonary valve to the aortic position

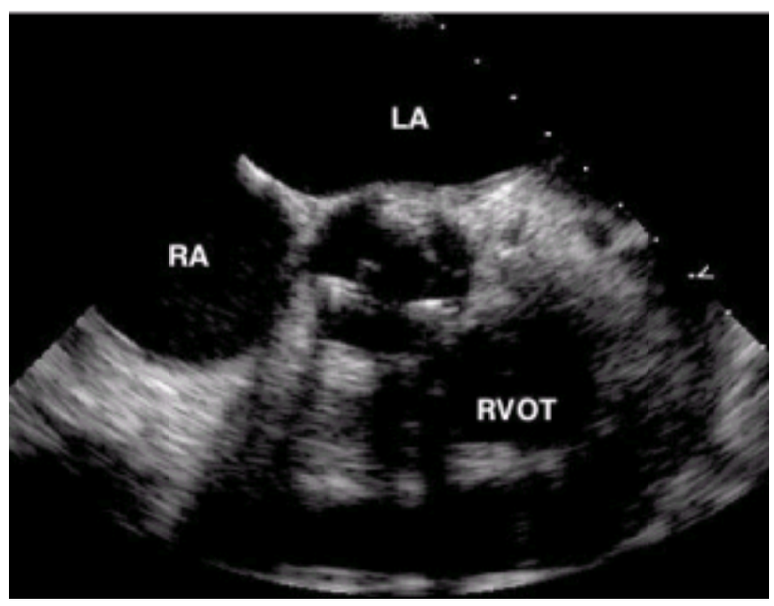
(pulmonary autograft), but this approach only recently gained appreciable, although qualified, acceptance.



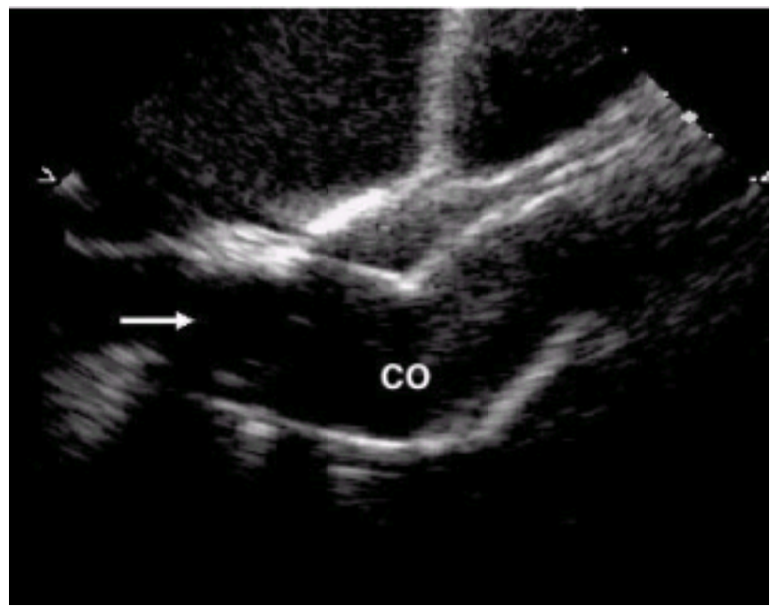
Bicuspid aortic valve with calcific stenosis. The yellow arrows identify each of the valve leaflets.

Aortic valve calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Many different types of aortic valve prostheses have been developed over the years; however, various drawbacks caused most of these prostheses to be discarded. Even still, the original Starr-Edwards ball-and-cage prosthesis has remained in use essentially unmodified for the last 30 years. In 1969 Carpentier and colleagues (14) described the use of glutaraldehyde-preserved porcine (heterograft) valves. Bovine pericardium was first used by Ionescu et al. (15) to construct a biologic valve, and although the original bovine pericardial valve has been discontinued, similar devices (Carpentier-Edwards pericardial prosthesis) are widely used today. Modern mechanical valves include, among others, the St. Jude, Medtronic Hall, and Carbomedics prostheses. Tissue valves available today include stent-mounted pericardial valves, stent-mounted porcine valves (e.g., Carpentier-Edwards valve), as well as stentless heterograft valves, cryopreserved homografts (allografts), and pulmonary autografts.



A short-axis –60 degree transesophageal echo of a Carpentier-Edwards (CE) aortic valve. One can see the three mobile leaflets suspended from the struts.



Postpump intraoperative transesophageal echo demonstrating an aortic valve replacement conduit. The arrow designates the aortic valve replacement,

and CO designates the conduit.

Video 22.5 A 120-degree postpump intraoperative transesophageal echo after placement of an aortic valve replacement conduit. The St. Jude aortic valve replacement is toward the left of the screen, and the aortic graft can be seen in the center of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Etiology

Valvular Degeneration and Calcification

Several etiologies of valvular AS have been described, including senile calcific, bicuspid, rheumatic, and congenital varieties. In developed countries, the most common cause of adult-acquired AS at present is idiopathic degeneration and calcification of the aortic valve (16), a process that can occur on a bileaflet or a trileaflet valve. Among the 1% of Americans born with a bicuspid aortic valve, the valve opens well at birth, but gradual and progressive degeneration leads to stenosis in approximately one-third (17,18). Because bicuspid aortic valves occur more frequently in men, AS also has a male predominance. When it occurs, clinically significant stenosis of a bicuspid valve usually develops in the fifth and sixth decades of life. Presumably, the flow characteristics of the valve increase the process of degenerative changes. In contrast, rheumatic AS, on average, becomes symptomatic in the fourth decade, and congenital AS becomes symptomatic in the first to third decades (Fig. 22.1) (19).

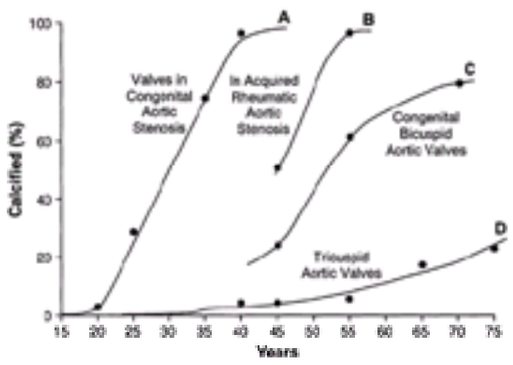
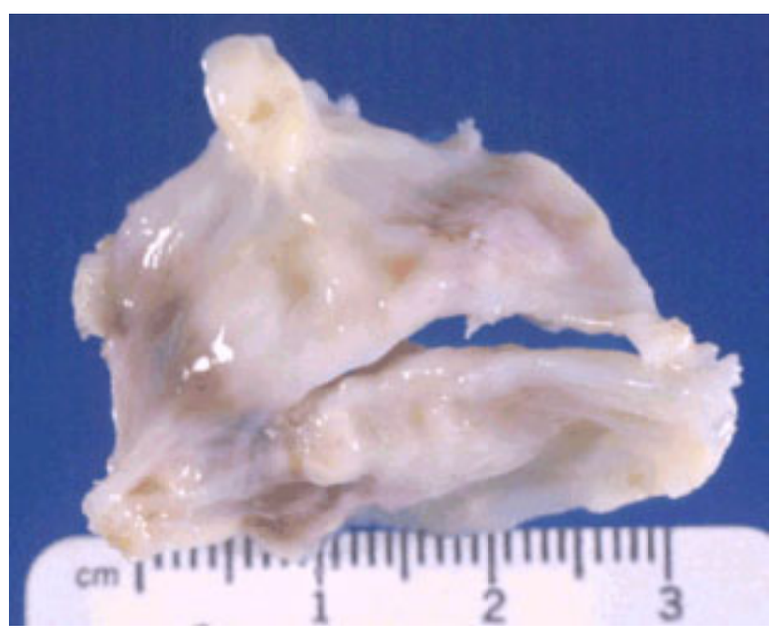


FIGURE 22.1 This figure shows the timing of onset of symptoms and significantly calcified and stenotic valves versus the major etiologies of aortic stenosis, including (A) congenital, (B) bicuspid, (C) rheumatic, and (D) senile. (From Campbell M. Calcific aortic stenosis and congenital bicuspid aortic valves. *Br Heart J* 1968;30:606–616, with permission.)



Bicuspid aortic valve with calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 22.6 Intraoperative transesophageal echo of a bicuspid aortic valve. There is fusion between the right coronary cusp (RCC) and left coronary cusp (LCC) with a raphe at 4 o'clock. This is the most common combination of leaflets to be fused. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Although the exact incidence of AS in patients born with tricuspid aortic valves is unknown, it is probably less than 1%. In patients with a previously normal tricuspid aortic valve who eventually develop AS, the same process of degeneration and calcification leads to symptoms of critical disease in the seventh and eighth decades (19). Why some patients with previously normal trileaflet valves develop AS whereas others do not remains a mystery. Otto and colleagues (20) have noted that the early lesion of AS is characterized by subendothelial thickening on the aortic side of the leaflet. Thickening occurs as the elastic lamina is displaced by the accumulation of cellular lipid infiltration and extracellular mineralization. There is proliferation of smooth muscle cells and lipid-laden foam cells resembling the plaque of coronary atherosclerosis (17).

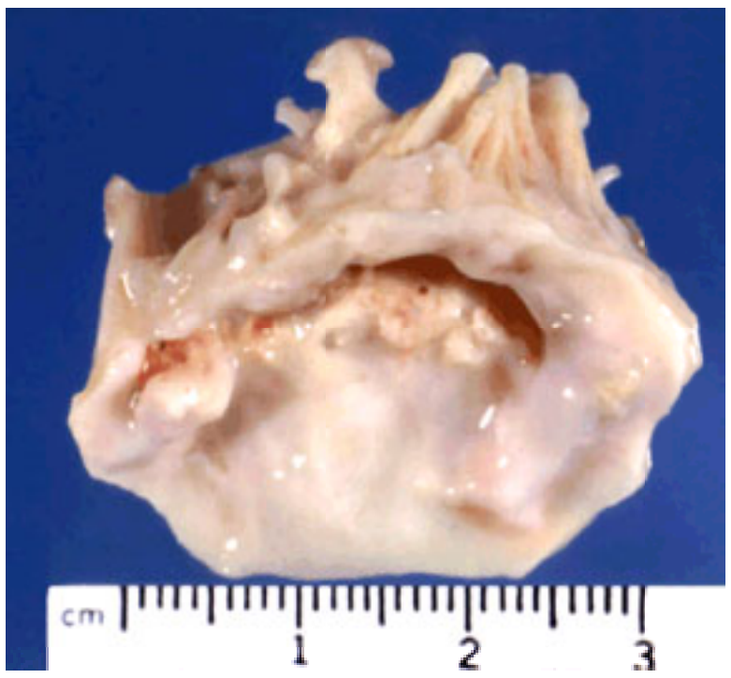
An association has been discovered between the standard risk factors for coronary disease and development of AS, suggesting that thickening of the aortic valve as aortic sclerosis, eventually leading to AS, is often a manifestation of an atherosclerotic process on the aortic valve (21,21a,21b and 21c). Cholesterol, lipoprotein disorders, smoking, male gender, and age may accelerate the age-related degenerative effects (21d). Duration of exposure to high cholesterol concentrations correlates with development of AS in patients with familial hypercholesterolemia (21e). In fact, even mild degrees of fibrosis, termed *aortic sclerosis*, have a major impact on prognosis, probably due to its link to atherosclerosis in all parts of the cardiovascular system (21c).

The same histologic changes occur in bicuspid valves at an earlier age, and there is no evidence to suggest that the valve pathology differs in bicuspid versus tricuspid disease or that the ultimate outcome of these two types of acquired AS differs.

Rheumatic Disease

In developed countries, rheumatic fever is the cause of AS in a minority of patients, accounting for less than 20% of the total (16). When rheumatic fever is the cause of AS, the mitral valve is almost always affected. Thus, the diagnosis of rheumatic AS should probably not be made in the presence of a completely normal-appearing

mitral valve by echocardiography unless a diagnosis of previous rheumatic fever is ironclad (18).



Rheumatic mitral valve. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

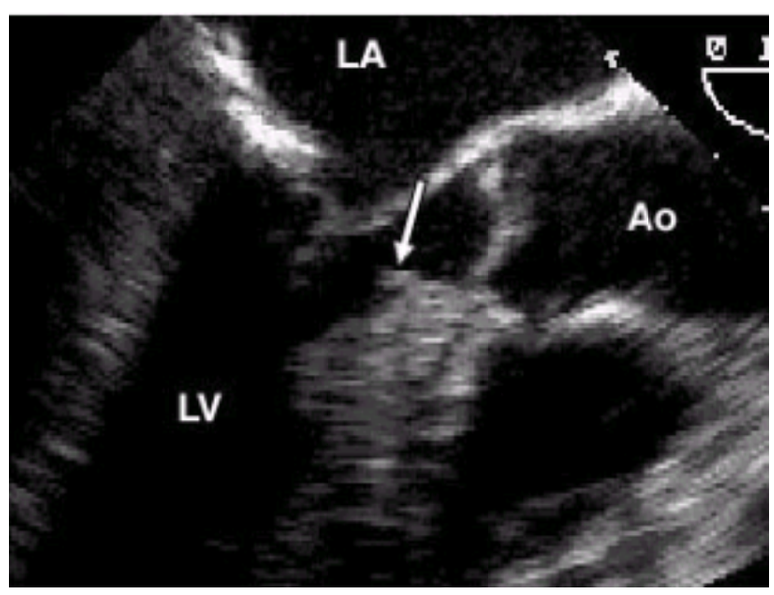
Congenital Aortic Stenosis

Congenital LV-outflow tract obstruction occurs at valvular, subvalvular, and supravalvular levels. Williams syndrome is the association of supravalvular AS with elfin facies and hypercalcemia. It is sometimes associated with peripheral pulmonary arterial stenosis, which tends to improve with time, whereas the supravalvular AS tends to progress with time, probably due to failure of growth of the sinotubular junction (18a).

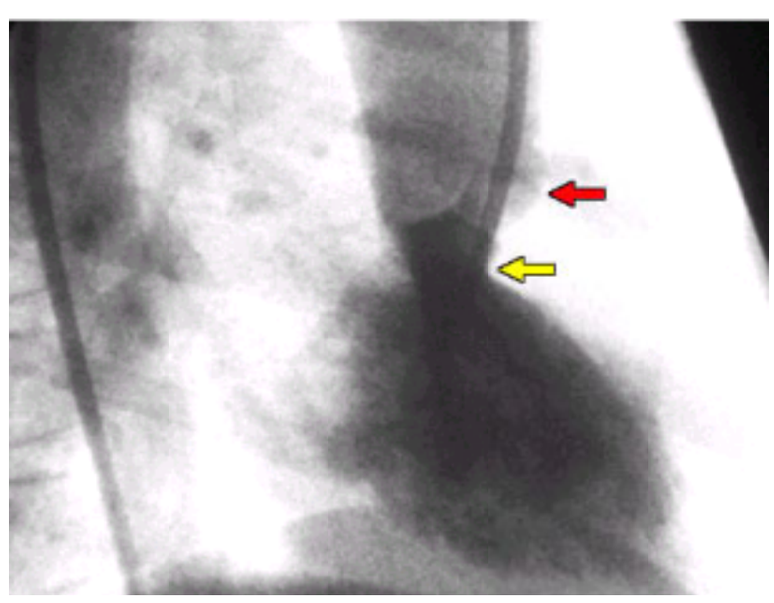
Subvalvular AS can be caused by a membranous ring or by a fibromuscular tunnel. In addition, some patients are born with small aortic roots, representing the spectrum of aortic atresia (see Chapter 32). Valvular congenital AS is usually caused by cusp fusion of tricuspid, bicuspid, or unicuspid valves. Each may present with severe obstruction and heart failure in infancy. Congenital valvular AS differs greatly from adult-acquired AS. The key differences are the following:

Video 22.7 Subaortic stenosis. A radiolucent membrane is visualized just below the aortic valve cusps (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

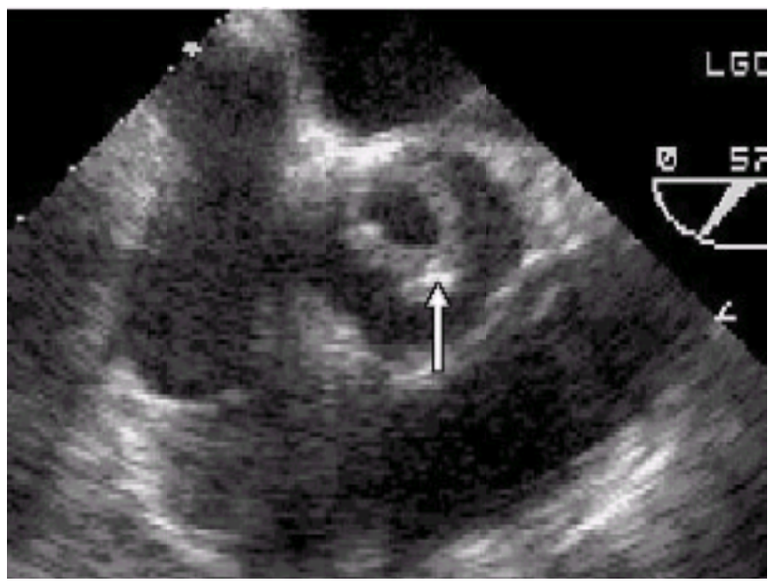
Video 22.8 Transesophageal echo in a patient with a subvalvular membrane in the left ventricular outflow tract. Note the normal mobility of the aortic valve. This patient had a significant pressure gradient across the left ventricular outflow tract/AV. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Transesophageal echo at 120 degrees of the aortic valve with a subaortic membrane in the left ventricular outflow tract (designated by the arrow).



Subaortic stenosis. This right anterior oblique left ventriculogram demonstrates the presence of a stenosis in the left ventricular outflow tract (*yellow arrow*) just below the level of the aortic valve (*red arrow*).



Short-axis transesophageal view of a unicuspid aortic valve with aortic stenosis. The arrow designates the single commissure present in this aortic valve. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)

Unicuspid aortic valve (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 22.9 A 60-degree intraoperative transesophageal echo of a patient with aortic stenosis due to a unicuspid valve (seen in short axis). Note the single commissure at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.10 Fixed left ventricular outflow tract obstruction. Auscultation performed in a 43-year-old female patient with subaortic membrane and bicuspid aortic valve. Left heart catheterization revealed a peak systolic gradient across the membrane of 60 mm Hg and a transvalvular gradient of 20 mm Hg. Note the distinct A_2 and the mid-systolic ejection murmur. Left upper sternal border (*first clip*), left lower sternal border (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.11 Fixed left ventricular outflow tract obstruction. Auscultation performed in a 43-year-old female patient with subaortic membrane and bicuspid aortic valve. Left heart catheterization revealed a peak systolic gradient across the membrane of 60 mm Hg and a transvalvular gradient of 20 mm Hg. Note the distinct A_2 and the mid-systolic ejection murmur. Left upper sternal border (*first clip*), left lower sternal border (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

- Extensive hypertrophy and supernormal ejection performance are the rule in congenital AS (22,23). Systolic dysfunction is unusual unless severe obstruction is present at birth.
- Sudden cardiac death in the absence of symptoms is more common in infants and children than in adults (24). Thus, in pediatric patients, valve replacement

should be recommended in the absence of symptoms if the mean transvalvular gradient exceeds 50 mm Hg.

Although most patients with congenital AS are diagnosed in childhood, occasionally these patients are seen for the first time as adults. It remains unknown whether patients with congenital AS who have reached adulthood are at lower risk, thus making timing of valve replacement difficult. This management problem is compounded by the fact that valve replacement in a 20-year-old patient may subject that patient to having a prosthetic valve for 50 to 60 years and may require multiple subsequent reoperations.

Fortunately for patients with valvular congenital AS, the commissural fusions are not densely calcified. Therefore, balloon aortic valvotomy is a reasonable option in asymptomatic patients with congenital AS whose mean transvalvular gradient exceeds 50 mm Hg, provided fluoroscopy or echocardiography does not show valvular calcification (25).

Clinical Presentation

Natural History

The natural history of acquired AS determines management of the disease. Depicted by Ross and Braunwald in Figure 22.2 and confirmed by recent studies (25a,26,27 and 28), the patient with asymptomatic AS has a nearly normal survival for a long latency period. During this time, the valve is slowly developing fibrosis and calcification, but the patient remains well. Once the symptoms of angina, syncope, or CHF develop, however, survival is dramatically shortened. Approximately 35% of patients who become symptomatic present with angina (29). In this group, 50% survive for only 5 years unless AVR is performed. In the 15% of patients who present with syncope, 50% survive for only 3 years; for the 50% with AS who present with symptoms of CHF, mean survival is less than 2 years unless the aortic valve is replaced. The risk of sudden cardiac death in asymptomatic or minimally symptomatic patients is rare, being less than 2% (28). Because this risk is less than that associated with AVR in many centers, there is usually no indication for surgery before the development of symptoms.

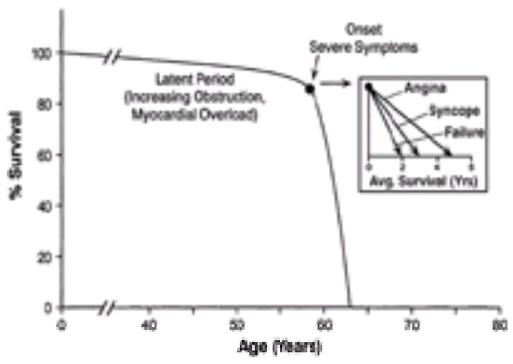
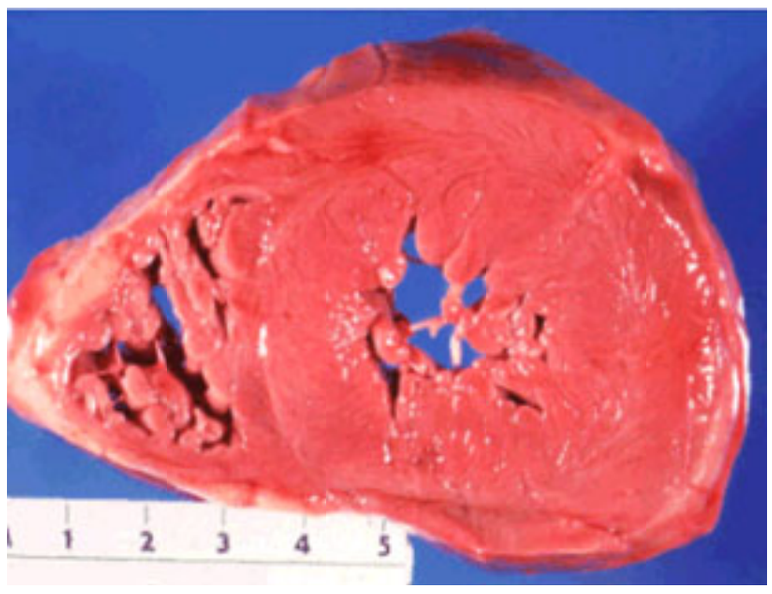


FIGURE 22.2 The natural history of aortic stenosis. A long latent period with a nearly normal survival rate is present until the symptoms of angina, syncope, or congestive heart failure develop. At that time, a precipitous decline in survival occurs unless the problem is surgically corrected. **Inset:** The prognosis is worst with presenting symptoms of congestive heart failure, second worst with syncope. [From Ross J Jr, Braunwald E. Aortic stenosis. *Circulation* 1968;38(Suppl 5):V-61, with permission.]

The progression of AS is more rapid, and prognosis with medical therapy is worse in patients who have moderate or severe valvular calcification and in those who have a rapid increase in their Doppler-derived gradient compared with previous studies (29a,29b and 29c). Similarly, smoking, hypercholesterolemia, and elevated serum creatinine and calcium levels have been associated with a more rapid rate of progression of AS (29d).

Pathophysiology of Aortic Stenosis and Its Relation to Symptoms

Understanding the pathophysiology of the symptoms of AS is key to understanding the disease. As stenosis worsens and the gradient increases, a progressive pressure overload is placed on the left ventricle. Pressure overload and increased systolic wall stress are thought to signal the development of concentric LV hypertrophy (LVH) (30). The mechanism is not apparently dependent solely on the renin-angiotensin system (30a,30b). Rather, the signaling cascade is complex, and hypertrophy can develop by activation of a variety of pathways. The pressure overload appears to selectively influence myocardial matrix metalloproteinase activity and expression and therefore the LV myocardial remodeling process (30c). The increased muscle mass that develops allows the ventricle to generate increased pressure while maintaining normal wall stress; thus, the hypertrophy compensates for the increased pressure load. The Laplace equation for wall stress is the following:



Massive left ventricular hypertrophy as well as concentric hypertrophic cardiomyopathy. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 22.12 Parasternal short-axis view of a patient with senile calcific aortic stenosis. Note the heavily calcified, distorted leaflets with restricted motion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

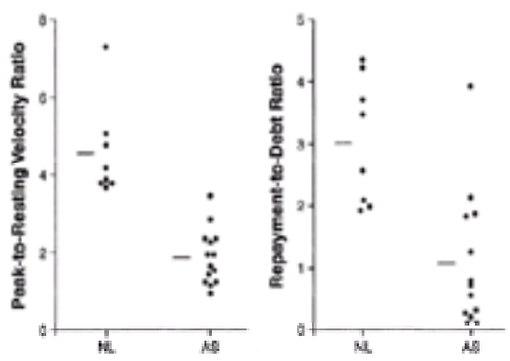
Video 22.13 Parasternal long-axis view of a stenotic aortic valve. Note the thickened, calcific aortic leaflets with markedly reduced excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

$$\text{stress} = \frac{\text{pressure} \times \text{radius}}{2 \times \text{thickness}}$$

This equation is used to approximate afterload on a given area of myocardium. As pressure in the numerator increases, increased thickness in the denominator offsets the pressure overload, and wall stress remains normal. However, as the pressure overload progresses, the hypertrophy that develops takes on pathologic characteristics, becomes involved in the pathogenesis of symptoms (e.g., subendocardial ischemia and arrhythmias), and thus is associated with a worsened outcome.

Angina

Angina, which stems from myocardial ischemia, occurs when myocardial oxygen supply is outstripped by demand either because demand increases or supply decreases. In AS, both factors probably play a role. With the development of concentric hypertrophy, coronary blood flow reserve becomes reduced from its normal five- to eightfold increase above baseline to just a two- to threefold increase (eFig. 22.2.1) (31). Reduced flow reserve may derive from the endocardial compression caused by increased diastolic filling pressure, or it may be due to a relative lack of capillary ingrowth to compensate for the increased muscle mass (32,33). In either case, limited flow reserve helps to precipitate ischemia during exertion. On the other side of the equation, myocardial oxygen demand is determined by heart rate (HR), contractile state, and wall stress. Patients with AS and angina have lower LV mass, increased peak systolic pressure, and increased wall stress than do patients without angina (34). Although hypertrophy initially helps to normalize wall stress in AS, in many patients the hypertrophy is inadequate to offset the increase in pressure, and stress and myocardial oxygen demand increase, precipitating ischemia and angina during exercise (35).



***e*FIGURE 22.2.1** Shown here are ratios of peak-to-resting velocity and of repayment-to-debt, demonstrating the coronary reactive hyperemia responses [after a 20-second occlusion of the left anterior descending coronary artery in control patients (NL) and in patients with aortic stenosis (AS)]. (From Marcus ML, Doty DB, Hiratzka LF, et al. Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. *N Engl J Med* 1982;307:1362–1367, with permission.)

Syncope

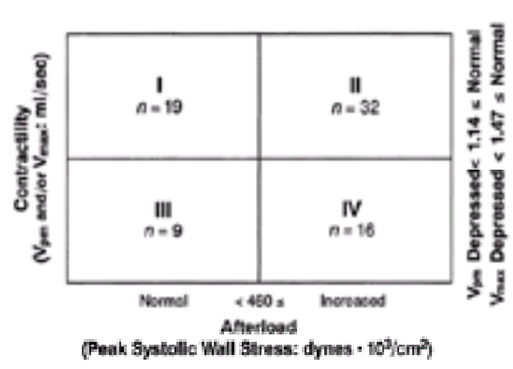
The cause of syncope in patients with AS remains controversial and is probably multifactorial. When syncope occurs in patients with AS, it is almost always precipitated by exertion. In the simplest sense, syncope occurs when blood pressure and cerebral perfusion fall. One presumed mechanism is that the reduced valve orifice area inhibits the normal increase in cardiac output that occurs during exercise. Because total peripheral resistance decreases during exercise, failure of cardiac output to increase leads to a drop in blood pressure and thus syncope. In elderly patients with systolic murmurs who present with syncope, AS should be ruled out. Although AS is a rare cause of syncope in the majority of patients who complain of this symptom, AS should always be considered in the differential diagnosis.

An alternative etiology of syncope in patients with AS could be that increased intraventricular pressure during exercise triggers a vasodepressor response, and syncope ensues (29,36,37). If excessive vasodilation of the venous capacitance bed occurs from any cause, cardiac output may drop because the hypertrophied LV in AS requires increased preload to maintain adequate forward flow because of the fixed obstruction. In some cases, the cause of this vasodilation is iatrogenic, from medications. Syncope may be caused in other cases by supraventricular or ventricular arrhythmias, which may precipitate hypotension.

Congestive Heart Failure

Both systolic and diastolic myocardial dysfunction may occur in AS. The concentric hypertrophy that develops invariably leads to diastolic dysfunction because the thicker ventricle requires a high diastolic pressure for filling. Initially, overall chamber stiffness is increased due to increased wall thickness, and myocardial stiffness remains normal (38) because the properties of the muscle itself have not changed. However, as the disease progresses, increased collagen deposition reduces muscle compliance, and thus filling of the left ventricle becomes impaired both because it is thicker than normal and also because the myocardium itself is stiffer (38,39).

The extent of ventricular shortening during systole depends on both afterload and contractility. In approximately 80% of patients with AS, there exists some degree of afterload excess defined as increased peak systolic stress (eFig. 22.2.2) (40). In these patients, increased pressure in the numerator of the Laplace equation has not been normalized because of an inadequate increase in wall thickness in the denominator, and afterload increases. Increased afterload in turn reduces ejection performance and cardiac output. Afterload excess may occur alone or together with decreased LV contractile function. Why the degree of hypertrophic compensation varies from patient to patient is only partially understood (40a). Perhaps there is an inherent variability in the set point for pressure regulation of cardiac growth (41).



***e*FIGURE 22.2.2** Here, contractility assessed as maximum dP/dT/P (V_{pm} and/or V_{max}) is plotted against afterload assessed as peak systolic wall stress in 76 patients with aortic stenosis. Of the 57 patients with some abnormality, 48 (85%) had increased afterload. (From Huber D, Grimm J, Koch R, Krayenbuehl HP. Determinants of ejection performance in aortic stenosis. *Circulation* 1981;64:126, with permission.)

The etiology of the decrease in contractility when it exists also remains controversial. Impaired calcium handling, subendocardial ischemia, and densification of microtubules comprising the cytoskeleton of the myocardium are some of the mechanisms that have been implicated (42,43 and 44). When microtubular densification occurs, it does so only in the context of inadequate hypertrophy and persistently increased systolic wall stress (44a,44b).

Hemodynamics

The best measurements for assessing the severity of AS are the mean systolic gradient and AVA, which are obtained accurately both by catheterization and Doppler methods. The invasive and noninvasive techniques for establishing the severity of stenosis are derived from similar principles. The Gorlin formula uses direct pressure measurements from a catheter and pressure manometer. The continuity equation uses direct velocity measurements from Doppler echocardiographic instruments (8).

Both methods derive AVA from Torricelli's equation:

$$F = A \times V, \text{ or } A = F/V$$

where *A* is orifice area, *F* is flow, and *V* is velocity.

Using Doppler methods, velocity is measured directly (by determining the amount of shift in the frequency of reflected ultrasound), both in the valve orifice (by continuous wave Doppler) and in the LV outflow tract (by pulsed Doppler). The area is calculated by measuring a diameter of the LV outflow tract directly from a two-dimensional echo image and assuming circular symmetry. Outflow tract area and velocity are multiplied and divided by valvular velocity to obtain the valve area using the continuity equation.

Using catheter methods, cardiac output is measured using the Fick or indicator dilution (thermodilution) technique. Pressure gradient is measured and converted to velocity:

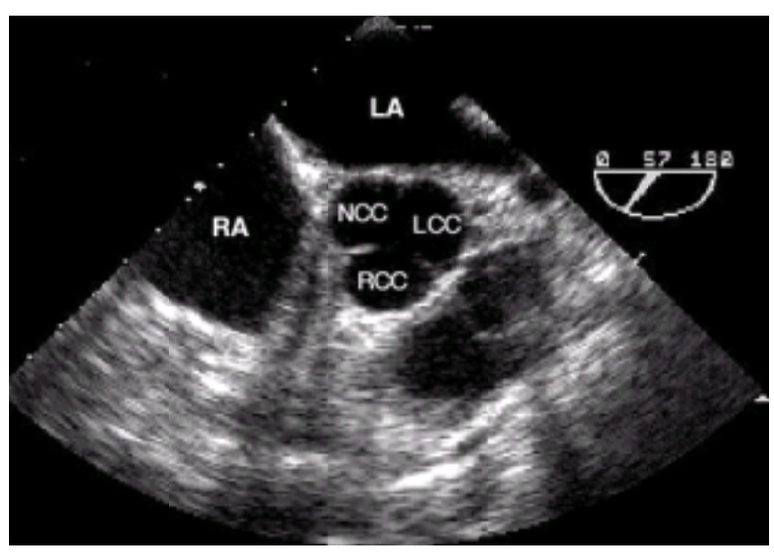
$$V = \sqrt{gh}$$

where *g* is acceleration due to gravity, and *h* is mean gradient. These are combined in the Gorlin formula for calculating AVA (45), which is the following:

$$AVA = \frac{Q}{K\sqrt{h}}$$

where *Q* is cardiac output, and *h* is the mean valve gradient.

An alternative, third method for determining AVA is transesophageal echocardiography (TEE). Using careful planimetry of the multiplane systolic TEE short-axis views of the aortic valve, the accuracy approaches that of the above-mentioned methods (46a). In addition, TEE from deep transgastric views can accurately determine transvalvular pressure gradients, a method that may be useful in patients with technically difficult transthoracic echo studies or when the data from transthoracic echo do not correlate with other information such as the physical examination.



Short-axis transesophageal echo view of the aortic valve seen in diastole. Note the closed leaflets of the aortic valve.

Video 22.14 Deep 90-degree transgastric view of the aortic valve obtained by starting with the transgastric long-axis view of the left ventricle and advancing the probe and retroflexing. This view is useful to measure aortic valve gradients. This patient has a heavily calcified aortic valve seen at the center of the screen. (Reproduced with permission from the Adult Clinical ardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

To obtain pressure gradient, the catheter-derived pressures on both sides of the valve are compared. For Doppler methods, velocity is converted to gradient using the simplified Bernoulli equation (Fig. 22.3) (6,7,46).

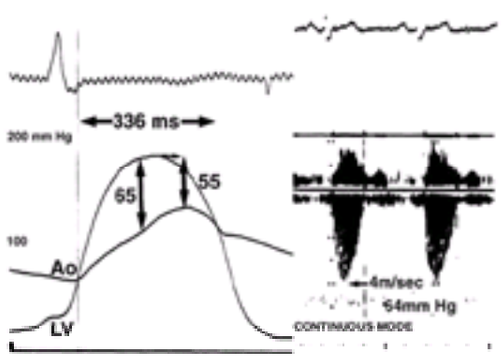


FIGURE 22.3 Micromanometer recordings of left ventricular and ascending aortic pressure tracing (*left*) and continuous-wave Doppler velocity envelope (*right*) demonstrate correspondence of Doppler-derived peak instantaneous gradient (64 mm Hg) with peak instantaneous gradient determined by catheter measurements (65 mm Hg), which differs from the peak-to-peak gradient (55 mm Hg). The catheter- and Doppler-derived mean gradients matched perfectly (42 mm Hg). (From Assey ME, Usher BW, Carabello BA, Spann JF Jr. The patient with valvular heart disease. In: Pepine CJ, Hill JA, Lambert CR, eds. *Diagnostic and therapeutic cardiac catheterization*, 2nd ed. Baltimore: Williams & Wilkins, 1994:692, with permission.)

$$\text{Gradient} = 4 \times V^2$$

Both methods can accurately derive the mean systolic gradient. Instantaneous gradient measured by Doppler has no convenient direct-pressure measurement counterpart and specifically is not the same as peak-to-peak gradient.

Progression of Aortic Stenosis

As shown in Table 22.1, reduction in aortic orifice area from its normal 3.0 cm^2 by 50% to approximately 1.5 cm^2 results in only a small gradient. However, from that degree of stenosis, small additional increments in the reduction of orifice area lead to progressively more dramatic increases in gradient. The average increase in

gradient is 7 to 10 mm Hg per year across a wide group of patients (47). However, there is a large and unpredictable individual variation.

Cardiac output (L/min)	Aortic valve area (cm^2)	Gradient[a] (mm Hg)
5.0	1.5	14.0
5.0	1.0	21.0
5.0	0.7	42.0
5.0	0.5	82.0

[a]Calculated at a heart rate of 76 beats/min and a systolic ejection period of 330 ms.

TABLE 22.1 MEAN SYSTOLIC PRESSURE GRADIENT AND ORIFICE AREA IN AORTIC STENOSIS

Although it is not uncommon for some patients to advance from mild AS with a small gradient of 10 mm Hg to severe AS with a gradient of 70 mm Hg in 3 or 4 years, in other patients the rate of progression is considerably less. Occasionally, the transvalvular gradient increases by as much as 25 mm Hg in 1 year, depending, in part, on the amount of stenosis already present (48). A rapid rate of progression of stenosis, as reflected by an increase in aortic-jet maximum velocity of more than 0.3 m per second in the course of a year, is significantly higher in patients who have clinical cardiac events (29a).

The unpredictable rate of progression of stenosis mandates careful follow-up by the physician and education of the patient who should be counseled to inform the physician of the onset of symptoms as soon as they occur. Although most patients with critical AS who require surgery have an AVA of less than 0.7 cm^2 and a mean systolic gradient of more than 50 mm Hg, patients may develop symptoms and therefore require surgery before or after reaching those thresholds.

Diagnosis

Physical Examination

The presence of AS is frequently first suspected when a systolic ejection murmur that radiates to the neck is heard during physical examination. Early in the disease when cardiac output is high, the murmur may be quite loud, typically peaking in early to mid-systole and is associated with a systolic thrill. The murmur often has a harsh quality and is lower in pitch than the higher-frequency blowing sound of mitral regurgitation. As the disease progresses, the murmur peaks progressively later until it becomes loudest during the later half of systole. The murmur may become softer as cardiac output through the stenotic valve decreases. The murmur is frequently well heard in the aortic area, disappears over the sternum, and becomes louder again over the apex, thus mimicking coexisting mitral regurgitation (Gallivardin's phenomenon). In some cases, the murmur is actually louder at the apex than it is in the aortic area. In congenital AS, the murmur is usually preceded by an early ejection sound.

HEART SOUNDS

Audio 22.15 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.16 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.17 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.18 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.19 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The

patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.20 Aortic ejection click and ejection murmur. Auscultation in a 30-year-old male patient with congenital bicuspid aortic valve. There is aortic stenosis with peak and mean gradients of 70 and 30 mm Hg, respectively. The aortic valve area is 1.5 cm^2. An ejection click followed by a systolic ejection murmur is heard. The patient also has 3–4+ aortic insufficiency and a soft diastolic high-pitched murmur is heard over the left upper sternal border. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border, sitting (*third clip*); left upper sternal border, supine (*fourth clip*); left lower sternal border (*fifth clip*); and apex (*sixth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

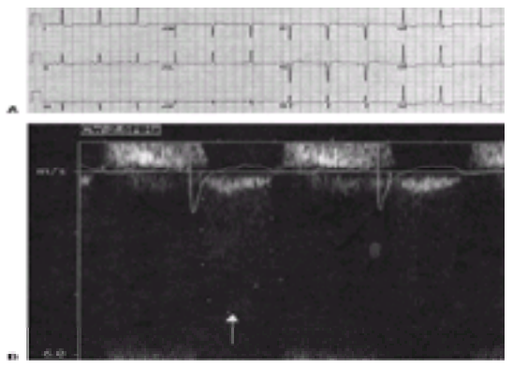
The severity of AS is best estimated at the bedside by palpation of the carotid arteries. As ejection begins, work is lost at the stenotic valve, and the carotid upstroke becomes reduced in amplitude and delayed in timing (*parvus et tardus*) (Fig. 22.3). In one controlled study, the only predictor of outcome based on physical examination was carotid upstroke amplitude (48a). Occasionally in elderly patients, inelasticity of the carotid arteries causes the carotid contour to maintain a more brisk upstroke, causing the examiner to underestimate the severity of the disease.

The intensity of the second heart sound may also be helpful in assessing the severity of AS. The aortic component typically becomes diminished in intensity (because leaflet mobility is reduced). The second heart sound may also be single, when the aortic component is absent, and only the soft pulmonic component of the second heart sound (S_2) is heard. In some cases, prolongation of LV ejection time, caused by severe outlet obstruction in conjunction with LV dysfunction, leads to a paradoxically split S_2. In severe congenital AS, the valve is still quite mobile, so both components of the S_2 are preserved.

Palpation of the cardiac apex reveals a powerful, enlarged, and sustained point of maximum impulse, which is usually not displaced in position. The simultaneous palpation of a strong apical impulse together with a weakened and delayed carotid pulse should alert the examiner to the fact that severe AS exists even if the murmur is atypically soft. A fourth heart sound is common and may be palpable as well as audible. Other findings on physical examination include pulsus alternans if LV dysfunction is present, as well as evidence of pulmonary artery (PA) hypertension and right ventricular (RV) failure in patients with far-advanced disease.

Electrocardiogram

The electrocardiogram (ECG) in AS usually demonstrates LVH and sometimes left atrial abnormality (eFig. 22.3.1). However, ECG signs of LVH may be absent in patients with AS even though severe LVH exists, presumably because the left ventricle usually is not dilated. The relatively normal ECG of a patient with severe symptomatic AS is shown in eFigure 22.3.2.



***e*FIGURE 22.3.1** Shown here is a typical electrocardiogram from a patient with severe symptomatic aortic stenosis showing left ventricular hypertrophy **(A)**, which was a continuous-wave Doppler spectrum from the same patient **(B)** showing a mean gradient of 47 mm Hg, derived from tracing the velocity envelope (*dots*), and a maximum instantaneous gradient of 70 mm Hg, calculated from the highest velocity (*arrow*) using the Bernoulli equation ($G = 4 \times V^2$).

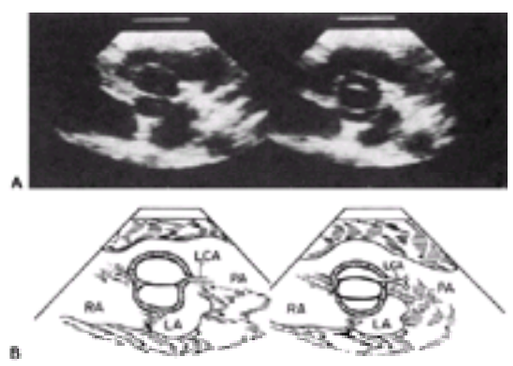
***e*FIGURE 22.3.2** Shown here is an atypical electrocardiogram from a patient with severe symptomatic aortic stenosis whose Doppler study showed a mean systolic aortic valve gradient of 90 mm Hg. Except for slightly increased QRS voltage, the electrocardiogram is remarkably normal.

Chest X-Ray

The cardiac silhouette is usually normal in size but may demonstrate a boot-shaped silhouette consistent with concentric LVH. Poststenotic dilation of the aorta is common. Calcification in the aortic valve occasionally may be visualized in the lateral view. Significant cardiomegaly and pulmonary venous congestion occur later in the course of the disease.

Echo-Doppler Studies

Ultrasonic examination of the heart in AS is the most important diagnostic modality in confirming the diagnosis and for quantifying disease severity. Two-dimensional echocardiography demonstrates thickened and calcified aortic valve leaflets with reduced leaflet motion. The aortic annulus and sometimes the surrounding aortic walls are echodense and often calcified. Distinction between bicuspid and tricuspid anatomy is often possible (eFig. 22.3.3) when the amount of calcification is small but is difficult in many patients with severe fibrosis and calcification. In addition, the extent of concentric LVH can be quantitated by calculating LV mass (48b). LV ejection performance can be evaluated and the ejection fraction (EF) measured. Doppler studies (6,7,32,46,49) can accurately quantify the transvalvular pressure gradient (Fig. 22.4) and the valve area, using the formulas listed above. Doppler assessment of diastolic dysfunction is also useful, often defining the presence of abnormal LV relaxation (49a).



***e*FIGURE 22.3.3** Shown here are echocardiographic images **(A)** and schematics **(B)** taken from the parasternal short-axis view from a patient with a bicuspid aortic valve in diastole (*left*) and in systole (*right*). (LA, left atrium; LCA, left coronary artery; PA, pulmonary artery; RA, right atrium.) (From Stewart WJ, King ME, Weyman AE. Prevalence of aortic valve prolapse with bicuspid aortic valve and its relation to aortic regurgitation: a cross-sectional echocardiographic study. *Am J Cardiol* 1984;54:1277–1282, with permission.)

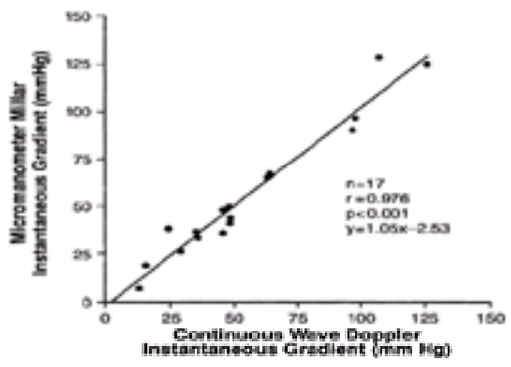


FIGURE 22.4 This figure shows correlation of peak instantaneous aortic valve gradient determined at cardiac catheterization using a micromanometer catheter technique with Doppler-derived estimated peak instantaneous gradient. (Data from the Medical University of South Carolina.) (From Assey ME, Usher BW, Carabello BA, Spann JF Jr. The patient with valvular heart disease. In: Pepine CJ, Hill JA, Lambert CR, eds. *Diagnostic and therapeutic cardiac catheterization*, 2nd ed. Baltimore: Williams & Wilkins, 1994:693, with permission.)

In practice, an initial Doppler echocardiographic study should be performed when AS is first suspected to confirm the diagnosis and assess the hemodynamics. Clinical follow-up should be frequent enough to ascertain development of symptoms. Echo follow-up should be frequent enough to detect the development or worsening of problems such as LV dysfunction, LVH, or mitral regurgitation (47). Repeat echo studies do not need to be performed every year because quantifying the progression of the disease in the absence of symptoms does not normally influence management. A case can be made for periodic echo examination of asymptomatic patients: yearly in patients with severe AS, every 2 years or so in patients with moderate AS, and every 5 years or so in patients with mild AS (49b). Once symptoms develop, a repeat echo-Doppler helps confirm worsening of disease severity.

Stress Testing

Stress testing has traditionally been avoided in AS for fear of complications (50). Indeed, stress testing *should be avoided* in obviously symptomatic patients. However, stress testing can be performed safely in patients with AS and equivocal symptoms to more clearly establish symptom status and to evaluate exercise tolerance (51,52). Nuclear imaging has also been used to evaluate the presence of coronary disease, which may coexist with AS; one study of perfusion imaging (53) suggests a sensitivity and specificity of approximately 80% for concomitant coronary disease. Stress echo can be done safely in stable patients with AS. Dobutamine echo is often a useful way to redefine valve area and gradient at a higher cardiac output, especially useful in patients with moderate to severe AS with a low gradient and depressed LV function (134).

Cardiac Catheterization

Because all of the information needed to quantify the extent and severity of AS can usually be obtained by physical examination combined with echo-Doppler studies, the need to perform invasive hemodynamics in this population has declined to a small number of patients for whom the data are conflictive (53a,53b). However, most patients with AS fall into the age range in which coronary disease is likely. Unfortunately, the presence or absence of angina pectoris is a poor indicator of the presence or absence of coronary disease. Coronary disease may be present in as many as 25% of AS patients who do not complain of angina, and it is present in 40% to 80% of AS patients who complain of angina (54,55 and 56). Although coronary revascularization at the time of AVR does not improve prognosis compared to that of patients who have isolated AS without coronary disease, coronary revascularization of severe coronary stenoses is conventionally performed at the time of AVR and is probably beneficial (57,58 and 59). Thus, coronary arteriography is performed in most adult patients with AS to assess coronary anatomy. If the severity of AS is in doubt, the transvalvular gradient should be measured at the time of cardiac catheterization and a right-heart catheterization should be performed to measure cardiac output for the AVA calculation.

Differential Diagnosis of Aortic Stenosis versus Hypertrophic Cardiomyopathy

The fixed obstruction caused by valvular AS may be confused clinically with the dynamic outflow obstruction of hypertrophic cardiomyopathy. Although the issue is almost always settled during cardiac echo-Doppler study, it is important to avoid misdiagnosing these very different diseases with very different outcomes. With respect to pathophysiology, AS is a valvular disease with fixed obstruction to aortic outflow. Hypertrophic cardiomyopathy (HCM) is a myocardial disease in which the obstruction varies indirectly with LV volume and directly with contractility. In HCM obstruction to outflow occurs as the anterior leaflet of the mitral valve contacts the hypertrophied intraventricular septum. Thus, conditions that reduce ventricular volume or increase contractility worsen the obstruction in HCM. Distinctions between valvular AS and HCM are outlined in *e*Table 22.1.1.

***e*TABLE 22.1.1** VALVULAR AORTIC STENOSIS VERSUS HYPERTROPHIC CARDIOMYOPATHY: A COMPARISON

Characteristic	Aortic stenosis	Hypertrophic cardiomyopathy
Orifice area	Relatively fixed	Varies with ventricular volume
Carotid upstroke	Upstroke delayed	Sharp upstroke with spike and dome quality
Valsalva maneuver	Murmur decreases in intensity	Murmur increases in intensity
Post–extrasystolic beat	Obstruction unchanged	Obstruction worsens
	Stroke volume increases	Stroke volume decreases (increased contractility)
	Pulse pressure increases	Pulse pressure decreases
	Murmur increases	Murmur increases
Electrocardiogram	Sometimes normal	Almost always shows LVH
Hypertrophy	Concentric	Asymmetric septal hypertrophy, or concentric LVH
Angina	Typical	Often atypical
Syncope	With exertion	Postexertion
Congestive heart failure and preload reduction	Diuretics helpful	May worsen obstruction

LVH, left ventricular hypertrophy.

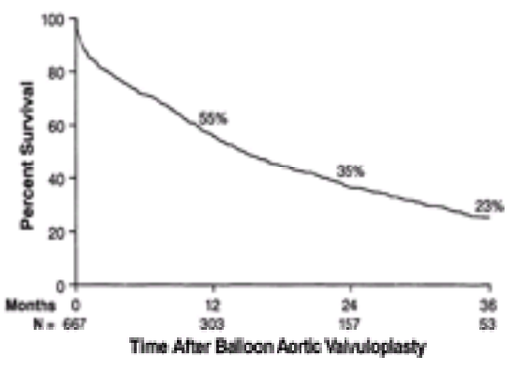
Management

Medical Therapy

There is no effective medical treatment for AS. Most patients who are asymptomatic do not require therapy. The onset of symptoms should prompt a recommendation for performing AVR (59a). In some patients who are deemed not to be surgical candidates, digitalis and diuretics may transiently improve CHF, and nitrates may be used cautiously to treat angina pectoris. However, these therapies provide no long-term benefit. Although vasodilators, especially angiotensin I–converting enzyme inhibitors, are widely used in treating most forms of CHF, they are relatively contraindicated in patients with AS. In patients with AS, vasodilators lower peripheral pressure without increasing cardiac output. In addition, adequate cardiac output may depend on a high LV filling pressure; thus, vasodilators that reduce preload may cause potentially dangerous hypotension. Like other types of valvular heart diseases, prophylactic antibiotics are indicated as pretreatment for dental or surgical procedures that have a moderate likelihood of causing bacteremia.

Balloon Valvotomy (Valvuloplasty)

After considerable initial interest, enthusiasm for aortic balloon valvotomy (valvuloplasty) in treating adult-acquired AS has waned. Although balloon valvotomy may be effective in relieving congenital AS, results have proved disappointing in adults, most of whom have valve calcification. In most patients, balloon valvotomy reduces severe AS to moderately severe AS (60), producing an AVA of 0.8 to 1.0 cm^2. The gradient typically is reduced by 50% and averages approximately 35 mm Hg after the procedure. Unfortunately, in 50% of patients, restenosis occurs within 6 months (61). Overall, balloon valvotomy has not reduced the high mortality seen in patients who do not undergo surgery for symptomatic AS, as shown in *e*Figure 22.4.1 (62). At present, balloon valvotomy should be reserved for patients with advanced CHF who are not candidates for surgery because of other comorbid conditions or because of unacceptably high perioperative risk. In these patients, balloon valvotomy may be performed, carrying a 2% to 5% risk of mortality; it may be effective in allowing bedridden patients to be discharged from the hospital. It may also be used in a palliative way in patients with treatable acute illnesses that are likely to resolve, thus eventually permitting elective aortic valve surgery.



***e*FIGURE 22.4.1** Plot of survival after balloon aortic valvuloplasty in 674 patients with aortic stenosis, censored at the time of aortic valve surgery. Numbers below the x-axis indicate the number of patients surviving at each time point. (From Otto CM, Mickel MC, Kennedy JW, et al. Three-year outcome after balloon aortic valvuloplasty: insights into prognosis of valvular aortic stenosis. *Circulation* 1994;89:642–650, with permission.)

Aortic Valve Replacement: Surgical Procedures

AVR is the definitive therapy for symptomatic AS. It is mandatory for all symptomatic patients. Very few patients with symptomatic severe AS should defer aortic valve surgery unless there are compelling contraindications for operation. Surgery for acquired aortic valvular disease usually requires AVR because the thickened aortic valve is difficult to repair (62a). Aortic valve débridement for calcific AS enjoyed a brief period of popularity in the mid-1980s but has since been abandoned because of early and progressive postoperative regurgitation from leaflet fibrosis and retraction (63). Aortic repair for true aortic regurgitation (64) is discussed later in this chapter (see Aortic Valve Replacement and Repair).

Aortic valve surgery is usually a mechanical or bioprosthetic valve, performed through a median sternotomy incision, although recently less invasive techniques have been carried out through smaller hemisternotomy incisions or anterior thoracotomies in the right second or third intercostal space (65) (see the section Aortic Valve Surgery: Minimally Invasive Procedures)

In the usual approach, the sternum is opened vertically in the midline, the pericardium is opened, and the anatomy is carefully inspected. The patient is anticoagulated with heparin, and the right atrium and inferior vena cava are cannulated with a single two-stage catheter inserted through the right atrial appendage. This catheter is used for venous return to the heart-lung machine; arterial return to the patient is provided through a cannula inserted into the ascending aorta. The patient is placed on a cardiopulmonary bypass and is usually cooled to 28°C to 32°C. The aorta is cross-clamped, and the myocardium is protected by antegrade or retrograde myocardial perfusion with hyperkalemic blood or crystalloid cardioplegia solution at 4°C. Cardioplegia infusion is generally repeated at approximately 20-minute intervals, or, alternatively, myocardial temperatures may be monitored directly to determine the frequency of reinfusion. Cardioplegia may also be administered directly into the coronary ostia; however, this technique may produce subsequent ostial stenosis and should be avoided when possible. After opening the aorta, the aortic valve is inspected, and when repair is not possible, the valve is excised. When the valve annulus is heavily calcified, it should be thoroughly débrided to obtain secure seating of the prosthetic valve as well as to maximize the size of the prosthesis that can be inserted. Meticulous care must be taken to avoid excessive fragmentation of the calcium, which can become dislodged into the left ventricle or into the coronary ostia. The aortic valve annulus is sized with a series of graduated obturators corresponding to the appropriate size of the prosthetic valve. For mechanical valves and stent-mounted tissue valves (porcine, pericardial), a row of interrupted sutures most commonly backed with small polytetrafluoroethylene (Teflon) felt pledgets is placed around the annulus of the aortic valve and then through the sewing ring of the selected prosthesis. The prosthesis is then slid down these sutures until it is firmly and securely seated at the annulus, and the sutures are tied. The valve leaflets are carefully inspected to ensure that they function appropriately and that there is no interference or obstruction of the coronary ostia. A running-suture technique is used by some surgeons to secure the prosthetic aortic valve; however, the interrupted technique is by far more frequently used. The aortotomy is closed with a running monofilament suture. The patient is rewarmed as the air is evacuated from the heart. Once this has occurred, the cross-clamp is removed, and cardiac action resumes, sometimes requiring electrical defibrillation; subsequently, the patient is weaned from cardiopulmonary bypass and decannulated, and the incision is closed.

Aortic Valve Replacement with Homograft (Allograft)

Valve replacement with homograft (allograft) valves is more complex because the tissue implanted is entirely biologic (*e*Fig. 22.4.2) without a stiff stent or sewing ring. Sizing is much more important and made more difficult by the frequent lack of availability of all sizes of homografts. Although early homograft AVRs were sutured in place using a free-hand technique, today nearly all are inserted as a mini-root replacement. In this technique, the homograft and proximal aortic root are implanted as a unit. This replaces the lowermost portion of the aortic root, or the patient's own root is closed around the implanted homograft root as an inclusion cylinder. The patient's coronary arteries are reimplanted into the sinuses of Valsalva of the homograft aortic root.

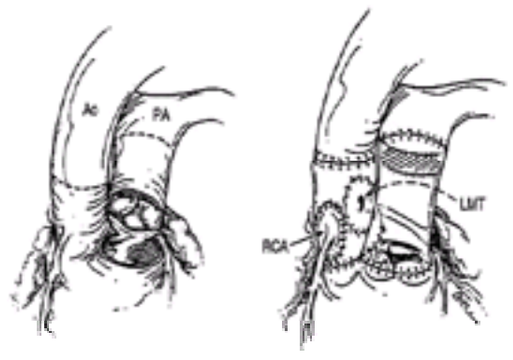
VIDEO

Video 22.21 Postpump intraoperative echo after placement of an aortic valve homograft. Notice that the leaflets look like a native valve. The only clue that it is a homograft is the thickening at the annulus and the proximal ascending aorta due to the double thickness of the graft cuff with the native aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

***e*FIGURE 22.4.2** A homograft conduit is shown before implantation. Most homografts are implanted as a mini-root that includes only a few centimeters of the tubular ascending aorta above the sinotubular junction excluding the great vessels. In this example, the great vessels are still attached.

Aortic Valve Replacement with Pulmonary Autograft (Ross Procedure)

Use of the pulmonary autograft (Ross procedure) is even more complex (*e*Fig. 22.4.3). First, the patient's PA must be divided at its bifurcation and the main PA and pulmonary valve removed as a unit from the RV outflow tract while scrupulously avoiding injury to septal perforators of the left anterior descending coronary artery. The pulmonary autograft is then inserted into the aortic root using a mini-root technique with reimplantation of the coronary arteries, similar to that used with homografts. Continuity of the RV outflow tract must then be restored by employing a pulmonary homograft, also implanted as a mini-root to replace the pulmonic valve and the main PA.



***e*FIGURE 22.4.3** Methods of performing the Ross procedure. Schematic at left shows resection of the pulmonic valve and main pulmonary artery (PA). At right, schematic shows implantation of the pulmonary autograft in the aortic position (with reimplantation of the coronary arteries) and a homograft implanted as another mini-root to replace the pulmonic valve. (Ao, ascending aorta; LMT, left main trunk; RCA, right coronary artery.) (From DeLeon SY. Adaptation of the Ross procedure. *Ann Thorac Surg* 1995;59:1007, with permission.)

Because significant coronary artery disease may be present in 25% to 30% of patients undergoing aortic valve surgery, especially in those with AS, it is frequently necessary to combine coronary artery bypass of the diseased vessels at the time of AVR.

Results of Surgery

Surgical Mortality

Operative mortality after aortic valve surgery should be less than 3% to 5%, depending on a variety of factors, including the individual surgeon's skill. The risk of operative mortality is higher in elderly or debilitated patients; in the presence of significantly impaired LV function; and in patients with extensive coronary artery disease or other valvular disease, infective endocarditis, or other associated diseases (e.g., renal failure). Operative mortality is slightly higher in patients with aortic regurgitation compared with that in patients with AS, but it is not influenced by the type of prosthesis used.

After surgery there is an improvement in symptoms, a drop in LV mass, and an increase in EF, although not necessarily an increase in exercise capacity (65a). Long-term survival is affected by many of the same variables that affect operative mortality. In general, actuarial survival is approximately 80% to 85% at 5 years and 70% at 10 years postoperatively. As noted, coronary artery disease that is not treated at the time of AVR adversely affects long-term survival.

Postoperative Valve-Related Complications

Postoperative valve-related complications include (a) structural deterioration of the valve; (b) hemodynamic valvular dysfunction; (c) valve thrombosis; (d) thromboembolism; (e) anticoagulant-related bleeding; (f) infection; (g) prosthetic valve endocarditis; (h) hemolysis; and (i) heart block.

VIDEO

Video 22.22 Björk-Shiley Convexo-Concave prosthetic valve in the aortic position in a left anterior oblique view. Abnormal function is demonstrated by less than a 60-degree opening excursion and incomplete closure. The differential diagnosis includes tissue in growth versus thrombosis of valve leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 22.23 This is a long-axis 134-degree transesophageal view of a patient with prosthetic valve endocarditis of the aortic valve. Note the very large mobile mass or vegetation on the prosthesis accompanied by prosthetic stenosis and moderate insufficiency. The peak and mean pressure gradients across this valve were 90/27 mm Hg, and there was also a paravalvular abscess. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 22.24 The short-axis 56-degree transesophageal view demonstrating the very large vegetation attached to the Carpentier-Edwards aortic valve replacement involving both aortic stenosis and aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

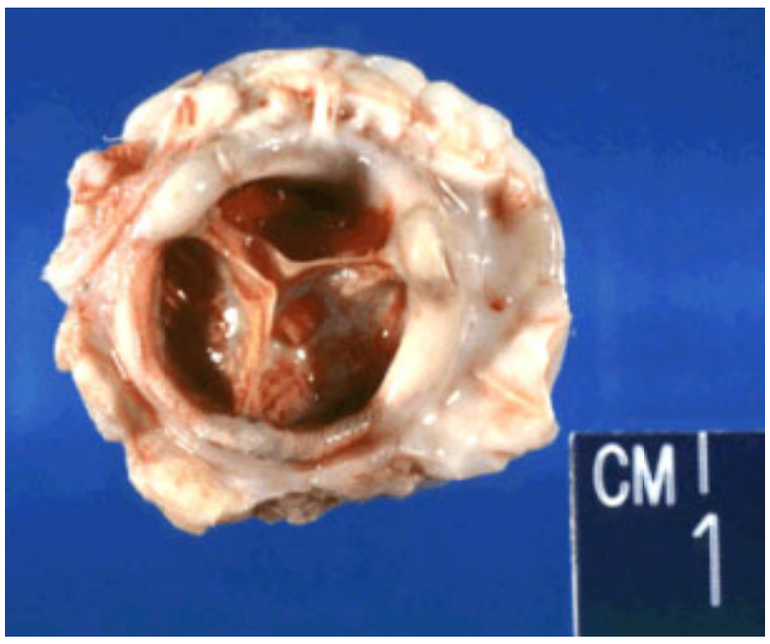
Unlike earlier valves, such as some models of the Björk-Shiley prosthesis, structural deterioration of currently available mechanical prostheses is extremely unusual (66,67,68 and 69). In contrast, virtually all tissue valves are prone to progressive, gradual deterioration, usually due to leaflet calcification. For the porcine bioprosthesis, the first primary valve failures usually occur at 7 to 8 years postoperatively and occur at a rate of approximately 2% per year thereafter (69a); freedom from hemodynamically significant structural tissue valve deterioration in the aortic position has been reported to be 80% to 85% at 10 years and 54% to 58% at 15 years (70,71 and 72). For currently available aortic pericardial valve bioprostheses, freedom from significant structural tissue valve deterioration has been reported to be 91% to 96% at 10 years (73,74 and 75). Structural deterioration of both porcine and pericardial valves in infants, children, and young adults occurs more rapidly than in older patients. Even in adults, the rate of deterioration varies indirectly with age so that a bioprosthesis placed in a 50-year-old might fail in 5 to 10 years, whereas the same valve implanted in a 70-year-old might last for 10 to 15 years. When structural deterioration results in significant and recurrent AS and/or regurgitation, reoperation for replacement of the deteriorated prosthesis may become necessary.

VIDEO

Video 22.25 Normal Björk-Shiley prosthetic valve in the aortic position. On fluoroscopy, the single valve disc moves normally with complete opening and closing. Björk-Shiley valves open 60 degrees or 70 degrees, depending on the model **(A,B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 22.26 Normal Björk-Shiley prosthetic valve in the aortic position. On fluoroscopy, the single valve disc moves normally with complete opening and closing. Björk-Shiley valves open 60 degrees or 70 degrees, depending on the model **(A,B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Porcine prosthetic valve with severe fibrosis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Structural deterioration with the development of aortic regurgitation also occurs after AVR with homograft valves. Its incidence varies widely in different reports depending on different techniques of homograft valve procurement, preservation, and implantation (76,77). The exact incidence of structural valve deterioration with homograft valves remains unknown because little long-term follow-up is available. In some reports (78) the rate of reoperation at 10 years is as low as 10%. Nevertheless, progressive degeneration of the homograft tissue does occur, and it may be more accentuated in younger patients (79) in whom homografts are otherwise an attractive alternative. Ross (80) has estimated that the useful life of a homograft valve is approximately 15 years.

Being native tissue, the pulmonary autograft has less calcific degeneration; however, it is not without some risk of functional deterioration, and the patient is susceptible to postoperative problems with valve replacements in both the pulmonic and the aortic position. Therefore, long-term follow-up of a large series of patients who have undergone the Ross procedure is necessary to determine how long these valves remain functional (81,82).

All standard prosthetic valves (mechanical valves as well as standard stented tissue valves) are stenotic compared with the native aortic valve because part of the potential orifice area of prosthetic valves is occupied by struts, stents, hinge mechanisms, sewing rings, and valve leaflets. Accordingly, all of these valves have a measurable gradient, which is inversely proportional to prosthesis size. Small-sized standard porcine bioprostheses (i.e., sizes 19 and 21) may be associated with gradients that are unacceptable in adult patients. Bioprosthetic valve gradients would be even higher, except for the substitution in manufactured processing of the right coronary valve leaflet (which contains a muscle bar in pigs) with the noncoronary leaflet from another pig. This so-called modified orifice porcine valve appears to have improved hemodynamic function and no increase in structural dysfunction compared with the standard porcine valve prosthesis (71,72). Tissue valves manufactured from glutaraldehyde-preserved bovine pericardium have improved hemodynamic function and may be adequate even in smaller sizes (73,74 and 75).

In general, modern bileaflet mechanical valves are also relatively stenotic but have better hemodynamic function than that of porcine bioprostheses and similar function compared with that of pericardial bioprostheses. Accordingly, smaller sizes of these valves are adequate in most adults, especially those who are elderly and those with smaller body surface area. Relatively little hemodynamic data are available from direct postoperative catheterization in patients with current mechanical prostheses because of the difficulties and dangers associated with crossing these delicate valves with stiff catheters. The echo-Doppler technique remains the best way to follow the function of an AVR noninvasively but provides a numerically higher gradient compared with a catheter-derived gradient due to pressure recovery, the “airplane wing” effect (83,83a). This discrepancy between catheter- and Doppler-derived gradients is most substantial in small aortic mechanical prosthetic valves such as bileaflet valves, where there is a localized area of low pressure at the mouth of the orifice between the two open prosthetic leaflets, creating higher velocity recordings.

VIDEO

Video 22.27 Normal St. Jude prosthetic valve in aortic position. Fluoroscopy shows a bileaflet valve that fully opens and closes with normal leaflet excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The aortic valve homograft and the pulmonary autograft are natural valves and their hemodynamic function is excellent. Excellent hemodynamic function may be obtained from the stentless porcine valve because of the absence of sewing ring and stent (84,85). However, there is less experience with its implantation.

Some evidence suggests that LVH regresses more rapidly and functional improvement is better postoperatively in a valve such as the stentless AVR or the aortic homograft, where the gradient across the prosthetic valve is minimized (85a,85b and 85c). Other data (86) suggest that operative and postoperative mortality may be increased in patients in whom smaller prostheses (with higher gradients) are inserted. These data imply that the prosthesis that is inserted should have the largest orifice area (lowest gradient) possible, which affects the choice of prosthesis in some patients. Some prostheses, such as the modified orifice porcine valve, have been modified to increase the effective orifice area. Another example is the St. Jude high-performance valve, which is implanted in a supraannular position in contrast to the intraannular position for the standard model. This effectively increases the orifice area by one size such that a size 19 St. Jude high-performance valve

hemodynamically functions similarly to the standard size 21 valve (87).

Alternatively, the annulus can be enlarged to allow insertion of a larger prosthesis. The simplest procedure (Nicks) is to extend the aortotomy across the aortic valve annulus for several millimeters and then use a patch [e.g., polyethylene terephthalate fiber (Dacron)] to close the aortotomy. This usually allows a prosthesis that is one size larger to be implanted (e.g., from size 21 to 23) (88). If the incision is extended further into the dome of the left atrium and the mitral valve, an even larger prosthesis can be inserted (89). In the Konno procedure (90), the aortotomy is altered so that it crosses the aortic valve annulus just to the left of the right coronary artery orifice and extends across the ventricular septum into the right ventricle. The resulting ventricular septal defect, right ventriculotomy, and aortotomy are closed by a double patch, which allows an increase of several sizes of the prosthetic valve to be inserted. Each of these annulus-enlarging procedures increases operative mortality, which must be weighed against the benefit of a larger valve size.

The aortic valve homograft and pulmonary autograft yield essentially normal hemodynamic function and therefore represent an alternative to the need for annulus enlargement procedures in patients with a small annulus.

At present, no blanket statement can be made regarding the relatively small aortic root/annulus. However, common sense dictates that the prosthesis be matched to the patient's needs. For example, it may be perfectly appropriate to insert a 19-mm pericardial prosthesis in an inactive elderly patient who has a small body surface area, especially because an annulus-enlarging procedure would increase operative risk. However, if the patient is younger, is active, and has a relatively large body surface area, a stentless valve such as a homograft might be chosen, or larger prosthesis with an annulus-enlarging procedure. The lower gradients are also a solid argument for the nonstented tissue valves, including the homograft, the pulmonary autograft, and the nonstented heterograft.

Thromboembolism

Thromboembolism remains a significant problem in patients undergoing AVR. Thromboembolism most frequently takes the form of a cerebrovascular accident but may also occur in other peripheral arteries. The resulting neurologic defects range from transient and mild to permanent and disabling, or even fatal. The incidence of systemic thromboembolism after AVR with a modern mechanical prosthesis ranges from 1% to 2% per patient-year even with adequate anticoagulation (66). The incidence is less in patients with pericardial and porcine bioprostheses even though these patients are not anticoagulated (70,71,73,74). Human homograft aortic valves and pulmonary autograft valves have a negligible incidence of thromboembolism and no valve thrombosis (76,79,81,82); hence, anticoagulation is not required.

Thrombosis of mechanical valves occurs at an incidence of less than 0.5% per patient-year. Although usually associated with inadequate anticoagulation, it may occur even when anticoagulation is considered optimal. Valve thrombosis may occur suddenly and be fatal, or it may occur gradually. The thrombus material may prevent normal movement of the valve leaflets, thus causing AS and/or aortic regurgitation and subsequently CHF (91). Valve thrombosis has been treated successfully by administering thrombolytic agents, although there is a significant incidence of thromboembolism, bleeding, and stroke associated with this form of treatment (92). The other alternative is reoperation with either débridement of the clot from the valve, leaving it in place, or removing the valve and replacing it with another prosthesis. Reoperation under these circumstances is associated with increased operative risk.

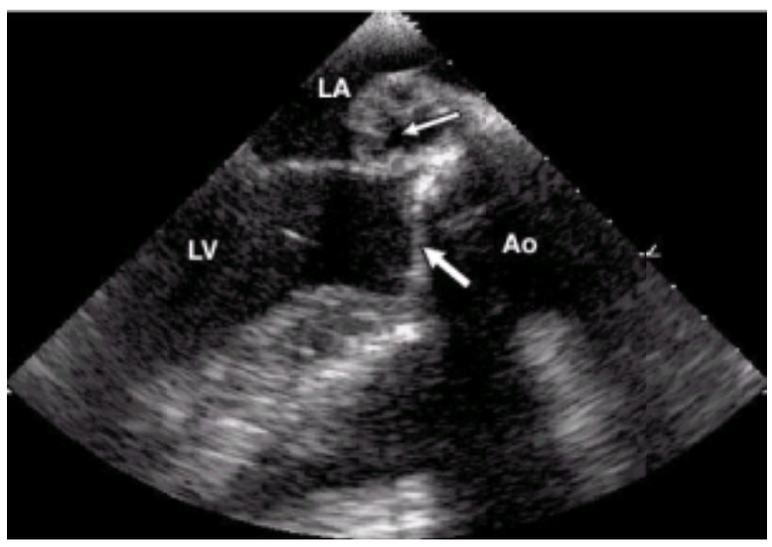
In an attempt to decrease the incidence of thromboembolism, all patients undergoing AVR with mechanical prostheses are anticoagulated with warfarin or one of its derivatives. Anticoagulation is usually not necessary with porcine and pericardial bioprostheses, homografts, and pulmonary autografts, unless it is indicated for other reasons such as atrial fibrillation.

In the past, anticoagulation was monitored by frequently assessing the prothrombin time, attempting to prolong the prothrombin time by approximately two (1.5 to 2.5) times the control value. However, the internationalized normalized ratio, a more accurate measurement that varies less between laboratories, is now used. In most patients with modern mechanical aortic valve prostheses, maintenance of the internationalized normalized ratio at 2.5 to 4.0 provides adequate protection from thromboembolism while minimizing the incidence of anticoagulant-related hemorrhage.

Anticoagulation is associated with an increased rate of bleeding, and the complications relating to anticoagulation occur at a linearized rate of 1% to 3% per patient-year. The incidence of anticoagulant-related complications increases with the degree of anticoagulation. Recent studies (67,69,93) have demonstrated that with modern mechanical valves, a decreased level of anticoagulation may provide a similar level of protection from thromboembolism, thus decreasing the incidence of anticoagulant-related bleeding.

Heart Block

The conduction system lies in close proximity to the junction of the non- and right coronary leaflets. The incidence of heart block after an uncomplicated AVR ordinarily is less than 1%. However, extensive débridement because of heavy calcification of the annulus increases the risk of heart block. Heart block after AVR also commonly occurs in patients with endocarditis, especially those who develop abscesses in the aortic root. Because all infected material must be thoroughly débrided, anatomic landmarks may be obliterated by the infectious process, and sutures have to be placed deeply to secure the prosthesis; understandably heart block develops more frequently in these patients.



A 120-degree transesophageal echo of an aortic valve abscess seen in the inner annular fibrosa. The thin arrow designates the abscess cavity, and the thicker arrow demonstrates the aortic valve.

Video 22.28 A 120-degree transesophageal echo demonstrating an abscess cavity in a patient with endocarditis of an aortic valve. Note the systolic expansion of the cavity located between the aortic and mitral valved in the inner annular fibrosa. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

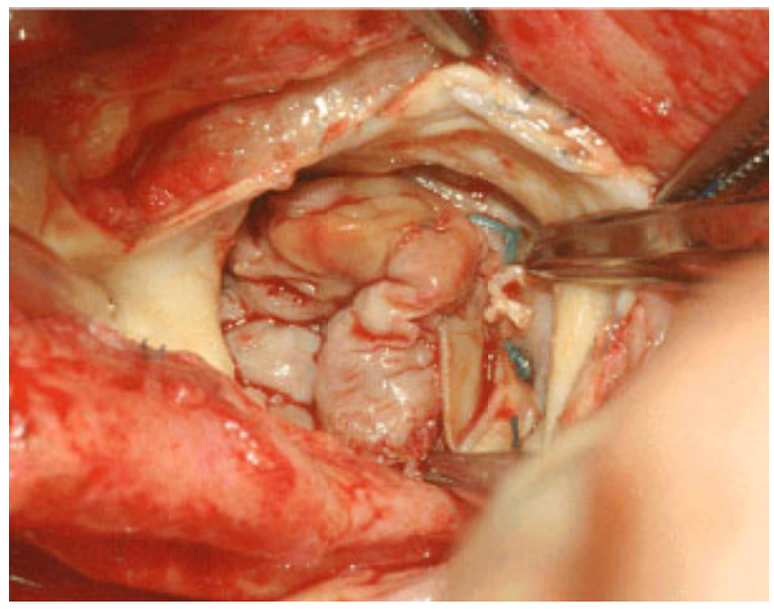
Hemolysis

Clinically important hemolysis after uncomplicated AVR is uncommon. A normally functioning mechanical prosthesis may produce a small amount of red blood cell destruction, usually not clinically apparent, which is enough to raise the LDH level to 1.5 or 2.0 times normal. Tissue prostheses are not generally associated with hemolysis. However, hemolysis may more frequently occur in patients with increased red blood cell fragility (i.e., sickle cell disease). Thus, mechanical prostheses should probably not be used in these patients. Clinical hemolysis after uncomplicated AVR is most frequently associated with a paravalvular leak and may be well tolerated. If such hemolysis occurs and severe clinical anemia or jaundice is present, reoperation may be necessary to correct the leak even though the hemodynamic effect of the leak may be insufficient to cause heart failure. However, the risk of surgery must be weighed against the risk of the transfusions and whatever treatment

program is required to maintain health.

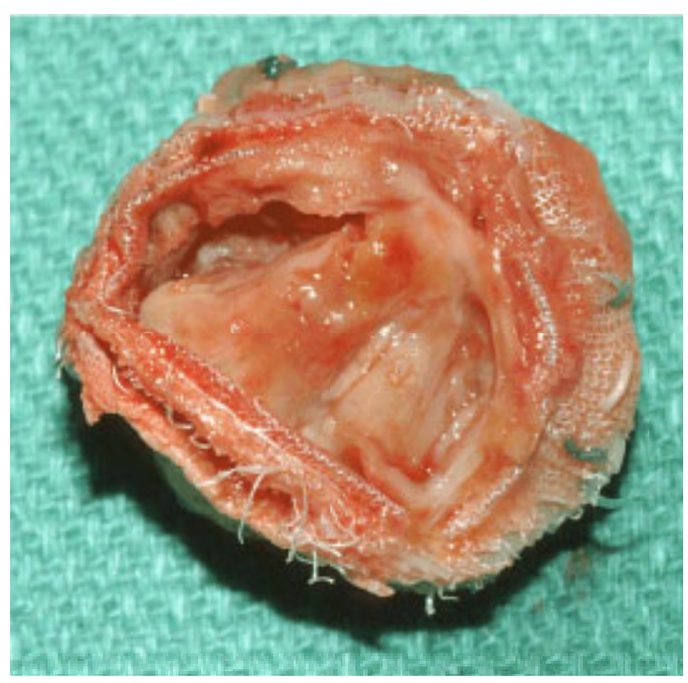
Infection

Postoperative infection of prosthetic valves (i.e., prosthetic valve endocarditis) occurs at a rate of 0.5% to 1.0% per patient-year in patients with mechanical and bioprosthetic valves (66,94). Infection is uncommon in homograft and autograft valves. Infection occurring within 6 months (early prosthetic valve endocarditis) frequently requires reoperation and results in decreased long-term survival. Infection occurring after 6 months (late prosthetic valve endocarditis) may sometimes be treated successfully with antibiotics and does not always require reoperation, thus yielding better long-term outcomes. To minimize the incidence of endocarditis associated with surgery, prophylactic antibiotics are administered for 24 hours before and after surgery.



Intraoperative view of a severely damaged aortic prosthesis in a patient with coagulase positive *Staphylococcus* endocarditis. This view is through the aortotomy looking down on the aortic side of the prosthesis.

Surgical specimen showing the aortic side of the tissue prosthesis destroyed by endocarditis. The marked scarring and distortion of the leaflets caused mixed aortic stenosis and aortic insufficiency.



Surgical specimen of a tissue prosthesis destroyed by Staphylococcus endocarditis. This is the ventricular side of the aortic prosthesis. Note the thickened, scarred prosthetic leaflets causing both aortic stenosis and regurgitation.

Choice of Valve

Multiple factors may be considered when choosing the most appropriate valve for a patient undergoing AVR. There is no perfect prosthesis, and each one has advantages and disadvantages. Valve repair is rarely applicable in patients with AS and degenerated valves and is reserved primarily for a highly selected subgroup of patients with noncalcified, purely insufficient valves (64,95).

Mechanical Valves

Aortic prostheses made by St. Jude (66,96,97), Medtronic-Hall (69,98,99), and Carbomedics (100) are readily available in all sizes, generally yield excellent hemodynamic function even in the smaller sizes, and are easily implanted in most situations. The Medtronic-Hall valve is a single-leaflet tilting-disc valve, whereas the other two are double-leaflet tilting discs. However, these prostheses have a significant incidence of valve thrombosis or thromboembolism that is not entirely prevented by anticoagulation and that, in turn, may cause postoperative anticoagulation-related bleeding. On the other hand, these valves are extremely durable and are rarely associated with structural dysfunction or hemolysis. The advantages of the different types of currently available mechanical valves have been reviewed by Akins (66). Although there are some differences among the currently available mechanical valves, the choice remains largely one of personal preference of the surgeon and of the individual characteristics of the patient.

Porcine Bioprostheses

Porcine bioprostheses do not require long-term anticoagulation and thus avoid anticoagulant-related bleeding problems. However, there is a small but definite

incidence of thromboembolism associated with tissue valves. These valves are available in all sizes and are relatively easily implanted. However, structural dysfunction, which increasingly appears after 8 to 10 years, limits the life span of tissue valves, especially in young patients and in those with renal dysfunction. Hemodynamic function in smaller porcine valve prostheses may be inadequate (66,67 and 68). Operation-free intervals are longer in older than in younger patients.

VIDEO

Video 22.29 Transesophageal short-axis view of a normal Carpentier-Edwards aortic valve replacement. Note the pliable three leaflets suspended on the struts. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Bovine Pericardial Bioprostheses

Pericardial bioprostheses are also available in all sizes, are easily implanted, and afford excellent hemodynamic function even in smaller sizes. They do not require anticoagulation, and they have a low incidence of thromboembolism. Although they appear to be more durable than porcine bioprostheses, particularly in older patients, these valves also eventually deteriorate (73,74 and 75).

Stentless Porcine Prostheses

Stentless porcine prostheses are relatively new, and follow-up is limited. They afford improved hemodynamic function because they are not mounted on a strut with a sewing ring. In addition, the incidence of thromboembolism may be decreased. However, long-term durability remains undetermined (85).

Cryopreserved Homograft Valves

Cryopreserved homograft valves duplicate the normal aortic valve. As they are human valves, harvested from cadavers, tested, and frozen, hemodynamic function is excellent, and the incidence of thromboembolism and endocarditis is extremely low. However, this valve is in short supply and is not usually available in all sizes. From a technical standpoint, these valves are considerably more difficult to implant. The degree to which homografts undergo structural deterioration remains unknown, but it is clear that their durability is limited, although significantly better than that of porcine and perhaps pericardial bioprostheses (76,77,80).

Pulmonary Autograft

Also called the *Ross procedure*, pulmonary autograft involves placing the patient's own pulmonic valve into the aortic position, then using a homograft in the pulmonic position. This option is nearly always available, and the autograft is nearly identical to the naturally occurring aortic valve. Accordingly, hemodynamic function of a normally functioning autograft is excellent, and there is a very low incidence of thromboembolism and postoperative endocarditis. Anticoagulation is not required. It has been demonstrated (81,82) that pulmonary autografts have the potential for growth, a significant advantage in the small child who requires an AVR. However, the surgical procedure is technically complicated and has the potential for significant injury to branches of the left anterior descending coronary artery, thus adversely affecting ventricular function. Although the pulmonary homografts used to replace the pulmonary valve are less frequently used and therefore much more readily available than are aortic homografts, they also have a finite durability; hence, reoperation may be necessary, particularly in younger patients. Furthermore, with this procedure, one trades one abnormal valve for two postoperative valves with an uncertain risk of valve dysfunction. Some aortic regurgitation and pulmonic stenosis have been observed after the Ross procedure; thus, long-term follow-up is needed to know its proper role relative to other options.

There is no perfect aortic valve substitute. Each alternative has significant advantages and disadvantages. Multiple factors, including (a) the patient's age, (b) anatomy, (c) ventricular function, (d) lifestyle, (e) fear of reoperation, and (f) possible contraindications to anticoagulation, must be considered when choosing the most appropriate option for each individual patient. This decision should be made jointly by the patient, the cardiologist, and the surgeon, and it should be very carefully discussed before surgery.

Management of Aortic Stenosis in Patients with a Small Hyperdynamic Ventricle

As noted above, the law of Laplace states that

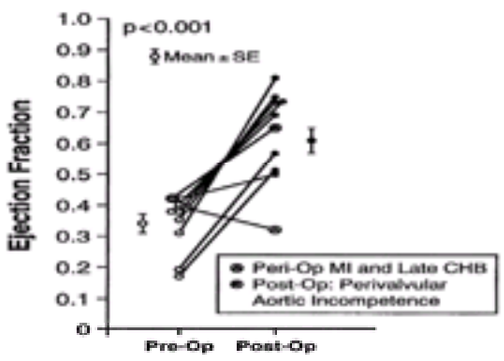
$$\text{stress} = \frac{\text{pressure} \times \text{radius}}{2 \times \text{thickness}}$$

If LVH were perfectly regulated, then just enough concentric LVH would develop to normalize wall stress. However, in some patients the LVH that develops is inadequate to maintain wall stress; thus, stress increases, and ejection performance decreases (125). In other patients, wall thickness increases markedly, and stress actually becomes subnormal despite the pressure overload from the lesion. Reduced systolic stress enhances LV performance, and EF may become supernormal. The small hyperdynamic ventricle with a decreased ratio of radius-to-thickness (decreasing wall stress) is found more frequently in women than in men (126).

At first glance, the patient with a small ventricle manifesting excellent ventricular performance would seem to have a clinical advantage, especially after AVR. Paradoxically, some studies (127) have suggested an increased mortality in such patients. Other investigations (128) suggest that the presence of a small hyperdynamic ventricle complicates the postoperative management of such patients but does not lead to excess mortality or morbidity. Postoperative management is difficult because the small hyperdynamic ventricle does not respond to usual postoperative strategies for treating depressed cardiac output. In the usual patient with low postoperative cardiac output secondary to systolic myocardial dysfunction, catecholamines are used to increase output because they enhance cardiac emptying. However, in the group of patients in whom preoperative hyperdynamic ejection performance has already been further augmented by relief of outflow obstruction, inotropic agents cannot increase cardiac output. Instead, such patients respond to aggressive volume replacement, which normalizes cardiac output without the need for pressor agents. Many such patients have diastolic dysfunction as a result of severe LVH and require high filling pressure to achieve adequate forward output. In many patients, volume replacement requires guidance by hemodynamic monitoring or by echocardiography.

Management of Aortic Stenosis Patients with Low Cardiac Output, Low Ejection Fraction, and Low Transvalvular Gradient

In most patients with even far-advanced AS that has resulted in reduced LV EF and severe CHF, outcome after surgery is remarkably good (129). Surgical intervention relieves the afterload excess on the left ventricle, allowing an increase in LV performance (*e*Fig. 22.4.4), which results in a stable postoperative course and rapid improvement in the symptoms of CHF. Unfortunately, this positive outlook frequently does not extend to patients with reduced EF who also have a small transvalvular gradient (125,130). Only about 50% of these patients improve after surgery; the other 50% suffer perioperative death or have persistent symptoms of CHF (131).



***e*FIGURE 22.4.4** In patients with aortic stenosis and poor left ventricular function, reduced ejection fraction (preoperative) increased dramatically after aortic valve replacement (postoperative), except for one patient (●) who had a perioperative myocardial infarction (MI). (CHB, complete heart block.) (From Smith N, McAnulty JH,

Rahimtoola SH. Severe aortic stenosis with impaired left ventricular function and clinical heart failure: results of valve replacement. *Circulation* 1978;58:255–264, with permission.)

Connolly et al. published a paper on 154 patients with severe AS and LV systolic dysfunction, finding a perioperative mortality of 9% and a high incidence of postoperative death, with 50 patients dying in follow-up. Coronary artery disease and a reduced preoperative cardiac output were primarily correlated with adverse outcome (131a). However, a subsequent study of valve replacement in 52 patients with a low gradient found a 21% operative and a 50% 4-year mortality (131b). Pereira et al. found a better prognosis in a series of somewhat different patients, including a perioperative mortality of 5.9%, compared with 4.0% in patients with similarly severe AS without bad LV function (131c). Serum creatinine level and RV systolic function may be more important predictors of outcome after AVR than LV systolic function and valve gradient.

The obvious challenge is to distinguish preoperatively between those patients who may benefit from AVR while avoiding surgery in patients for whom the outcome will be poor. Although at present there is no universally accepted means of distinguishing these patients, surgical candidates can be selected by making the distinction between AS and aortic "pseudostenosis" (132,132a). In true AS, severe valve disease has led to progressive LV dysfunction. Accordingly, correcting the valve lesion, the primary etiologic agent, may be expected to improve the patient's condition. Alternatively, an AVA may be calculated either during echocardiography or cardiac catheterization, which suggests that the valve is severely stenotic when, in fact, it is not (pseudostenosis). Underestimation of the AVA made by hemodynamic calculations occurs at low cardiac output because the Gorlin formula and continuity equation are flow-dependent and will therefore overestimate severity, obtaining an artificially low calculated AVA in low output states (133).

Flow dependence can reflect a true change in orifice area with differing flows. Lower flow can truly cause a smaller orifice area. At higher flows with increased force of contraction, the valve orifice may open to a wider area, and thus the formula may accurately reflect changing area with changing flow. Alternatively, flow dependence may be inherent in the Gorlin formula for which the discharge coefficients for the aortic valve were never experimentally determined (45). An example of aortic pseudostenosis is demonstrated in eTable 22.1.2 (132). In this case the patient's initial hemodynamic data at low cardiac output indicated severe AS with a calculated AVA of 0.6 cm^2. However, when cardiac output was increased with cautious infusion of nitroprusside, the gradient actually fell despite a large increase in cardiac output; thus, the new calculated AVA increased into the mild or moderate range of stenosis. Other investigators (134) have found similar results using an infusion of dobutamine.

***e*TABLE 22.1.2** HEMODYNAMIC DATA FROM A THEORETICAL PATIENT WITH AORTIC PSEUDOSTENOSIS

Hemodynamic data	**Baseline**[a]	**Nitroprusside**[b] **(0.5 mg/kg/min)**
Cardiac output (L/min)	3.0	4.5
Left ventricular pressure (mm Hg)	130/30	120/20
Aortic pressure (mm Hg)	90/60	90/50
Aortic valve area (cm^2)	0.6	1.0
Valve resistance (dynes/sec/cm^{-5})	200	160

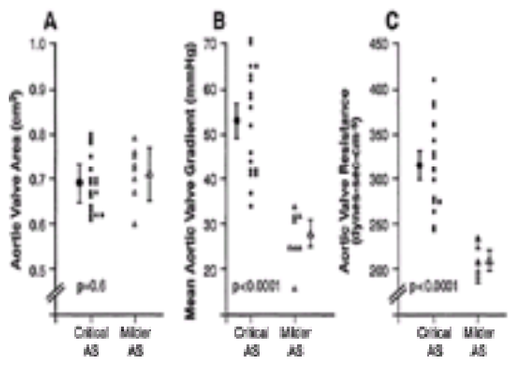
[a]Baseline values suggest severe stenosis.
[b]Values recorded during cautious afterload reduction suggest only moderate stenosis.
From Carabello BA, Ballard WL, Gazes PC. In: Shan SA, Heffner JE, eds. *Cardiology pearls*. Philadelphia: Hanley & Belfus, 1994:142, with permission.

At present, we use two methods to help discern AS from aortic pseudostenosis. First, as shown in eTable 22.1.2, we use pharmacologic manipulation of the patient in the cardiac catheterization laboratory or the echocardiography laboratory to derive a new calculated AVA at a higher cardiac output. Increased output can be accomplished either by infusion of a pressor agent, such as dobutamine, or by use of a vasodilator, such as nitroprusside. If nitroprusside is administered, it must be given with caution to avoid hypotension. Dobutamine has the advantage over nitroprusside of not producing hypotension; however, unfortunately, dobutamine may produce angina or arrhythmias in patients with or without coronary disease. In patients in whom nitroprusside or dobutamine substantially increases cardiac output with little increase in gradient, one can be relatively certain that the patient does not have as much AS as had originally been calculated. On the other hand, if output and gradient increase concomitantly, the calculated AVA remains small and severe AS probably exists (134). One group has suggested that the LV function that is demonstrated preoperatively during dobutamine infusion is predictive of postoperative LV function (134a).

As an adjunct to recalculation of valve areas and gradients under pharmacologic manipulation, aortic valve resistance may be used to help distinguish AS from aortic pseudostenosis (135,136,136a). Aortic valve resistance (*R*) is proportional to mean transvalvular gradient and inversely proportional to systolic flow:

$$R = \frac{\text{mean gradient} \times \text{heart rate} \times \text{systolic ejection period} \times 1.33}{\text{cardiac output (L per minute)}}$$

Valve resistance may be a helpful adjunct to the Gorlin formula because resistance does not assume any discharge coefficients. In several, but not all, studies, *R* has been shown to be less flow-dependent than AVA and may help distinguish severe AS from milder pseudostenosis in low-flow states (eFig. 22.4.5) (136). An *R* of less than 250 dynes per second per cm^{-5} usually indicates milder stenosis.



***e*FIGURE 22.4.5 A:** Aortic valve area for patients with severe aortic stenosis (AS) (*circles*) is compared with that of patients with milder AS (*triangles*) appearing to be aortic pseudostenosis. Aortic valve area calculated at catheterization was nearly identical in the two groups. **B:** Aortic valve gradient for the same patient groups. The gradient was substantially higher in the group with severe AS. **C:** Aortic valve resistance for the same two patient groups. Nearly complete separation is provided by this measure of severity of stenosis. (From Cannon JD Jr, Zile MR, Crawford FA Jr, Carabello BA. Aortic valve resistance as an adjunct to the Gorlin formula in assessing the severity of aortic stenosis in symptomatic patients. *J Am Coll Cardiol* 1992;20:1517–1523, with permission.)

Prophylactic Valve Replacement in Patients with Coronary Disease

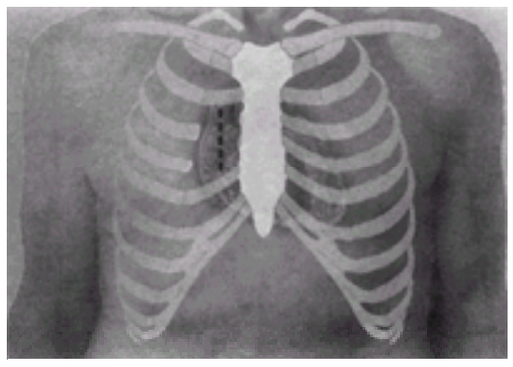
As noted in this chapter, AS frequently coexists with coronary disease. In many cases severe coronary disease requiring revascularization is present at a time when the patient has only mild or moderate AS or regurgitation. Although isolated AVR would not be considered in such a patient in the absence of coronary disease, the question arises as to the proper management of the aortic valve during bypass surgery. Prophylactic valve replacement has been considered because in some patients the severity of their AS may progress very rapidly and reoperation with a very high mortality rate [as high as 20% (137)] may be required just a few years after bypass surgery. These reoperations also have more chance of damage to bypass grafts implanted during the first surgery. On the other hand, in patients whose severity of AS does not progress rapidly, prophylactic surgery results in the presence of an unneeded valve prosthesis with all of its attendant risks and limited durability. Unfortunately, it is impossible to know preoperatively in which patients the severity of AS will progress rapidly and in which patients it will not. Although prophylactic valve replacement would probably be considered appropriate in most patients in whom the mean transvalvular gradient exceeds 40 mm and inappropriate if it were less than 10 mm, this leaves a broad middle range where clinical judgment must hold sway because there are few data for guidance. In general, aortic valve surgery should probably be done with the initial operation if the AS is at least moderate in severity. It also seems more reasonable in patients with higher transvalvular gradients and

calcified valves (137a).

A preliminary report suggested that patients with mild to moderate AS actually have a better outcome with prophylactic valve replacement (137b). However, we make this decision on a case-by-case basis, considering the age of the patient and the morphology of the valve. An older patient is less likely to undergo a prophylactic valve operation as is a patient with a more structurally normal valve as determined by echocardiography, surgical inspection, or both. Long-term studies are needed to resolve these issues.

Aortic Valve Surgery: Minimally Invasive Procedures

The minimally invasive procedure (MIP) is a new way of performing cardiac surgery through a smaller incision than the usual midsternal thoracotomy. Several varieties have been described. In the most popular, called the hemisternotomy method, an 8- to 10-cm vertical incision is made at the location of the lower sternum (eFig. 22.4.6) (65). Eligible patients are those undergoing first-time isolated aortic or mitral valve operations, and more than 1,700 patients have now been operated on in this way. Excluded are patients undergoing reoperation, which involves too much scarring, and those requiring additional procedures, such as coronary bypass or mitral surgery combined with aortic valve surgery, which usually requires the standard, larger incision. With the MIP, one can accomplish aortic valve repair or AVR with a bioprosthesis, a mechanical prosthesis, or a homograft. A Ross procedure requires more surgical exposure and cannot be performed through this small incision. The overall risks of MIP appear to be similar to those of the same surgery using the standard midsternal incision. It appears that this new approach has a number of short-term advantages. Because the MIP avoids splitting the sternum, the extent of perioperative pain and bleeding is less. In addition, the length of hospital stay, the duration of time before returning to work, and overall hospital costs are reduced. However, it is not clear what, if any, long-term advantages are reaped from the MIP. It may merely be a different approach to the same set of operations. At this point it also remains unclear whether the MIP will affect the timing of surgery for aortic valve disease. The threshold for performing aortic valve operations should probably not be changed because of the availability of the MIP for valve surgery until additional data on long-term outcomes are available.



***e*FIGURE 22.4.6** Location of incision for the minimally invasive procedure for aortic valve operations. A vertical incision approximately 3 to 4 in. long is made through the third and fourth ribs to the right of the sternum. (From Cosgrove DM, Sabik JF. Minimally invasive approach for aortic valve operations. *Ann Thorac Surg* 1996;62:596–597, with permission.)

CHRONIC AORTIC REGURGITATION

Etiology

Aortic regurgitation results from failure of leaflet coaptation either due to diseased valve cusps or a diseased aortic root, which distorts cusp suspension (Fig. 22.5) (101). Common causes of cusp disease include bicuspid aortic valve, rheumatic heart disease, infective endocarditis, or calcification of the leaflets, which often causes mixed AS and aortic regurgitation (AR). Although a congenitally bicuspid aortic valve frequently leads to AS in adulthood, approximately 10% of bicuspid valve patients who require surgery present with pure aortic regurgitation without stenosis; these patients are usually younger, averaging approximately 40 years of age. Aortic regurgitation from a bicuspid aortic valve often results from leaflet prolapse, especially when one cusp is larger than the other (102). Although rheumatic heart disease primarily attacks the mitral valve, leading to mitral stenosis, many patients with rheumatic involvement also have some degree of aortic regurgitation, and in some patients aortic regurgitation is the predominant lesion. As mentioned earlier, the presence of rheumatic mitral valve findings is the hallmark of diagnosing rheumatic aortic valve involvement. Infective endocarditis is the most common cause of acute aortic regurgitation. If infection is tolerated acutely without requiring surgery, it becomes a cause of chronic aortic regurgitation.

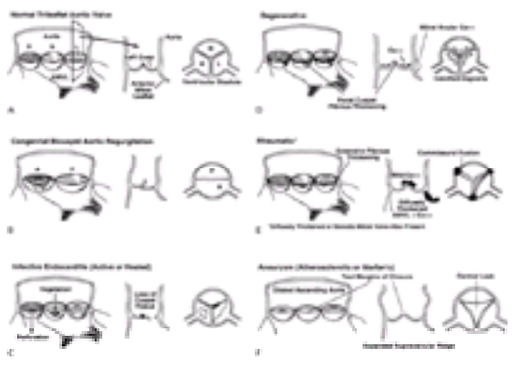
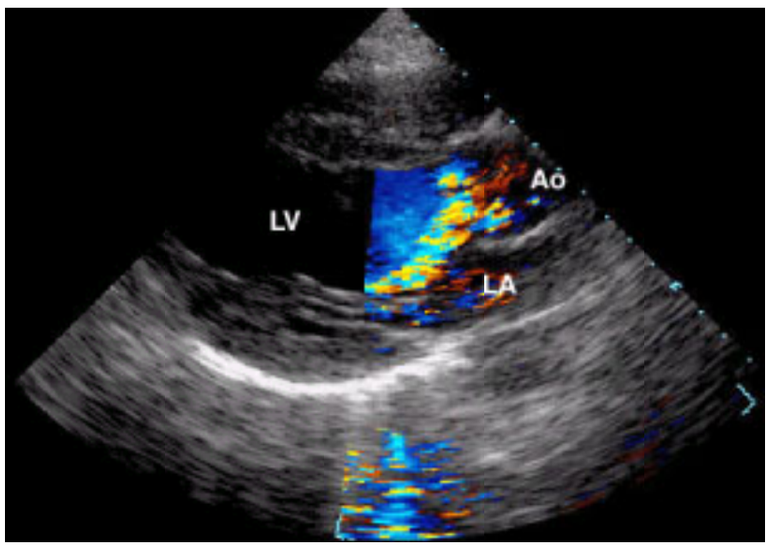


FIGURE 22.5 Diagrams showing various etiologies of aortic regurgitation (AR). Each of the six panels shows a long axis of the aortic root opened up to show all the leaflets (*left*), a schematic of the long axis of the sinus of Valsalva (*middle*), and a schematic of the short axis of the aortic valve (*right*). **A:** Normal trileaflet aortic valve. **B:** Congenital bicuspid valve with a raphe between what would be the right and left coronary cusps in an anterior cusp that is larger than the posterior cusp, causing prolapse and AR. **C:** Endocarditis causes AR through disruption of valve suspension or leaflet perforation. **D:** Degenerative changes cause AR by restricting leaflet motion and coaptation. **E:** Rheumatic valvulitis causes AR with postinflammatory leaflet fusion and fibrosis. **F:** Aneurysms from atherosclerosis or cystic medial necrosis (Marfan's type) cause AR by outward displacement of the leaflet suspension, with central noncoaptation, or by dissection causing failure of leaflet support. (A, anterior; AMVL, anterior mitral valve leaflet coronary cusp; Ca^{++}, calcification; L, left; N, noncoronary cusp; P, posterior; R, right coronary cusp.) (Modified from Frankl WS, Brest AN, eds. Valvular heart disease: comprehensive evaluation and management. *Cardiovasc Clin* 1986;30–31, with permission.)

VIDEO

Video 22.30 A 120-degree intraoperative transesophageal echo of a patient with aortic insufficiency due to blunt trauma causing a flail left coronary cusp. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Parasternal long-axis view (transthoracic echo) with color Doppler demonstrating the posteriorly directed aortic insufficiency caused by prolapse of the anterior leaflet of a bicuspid aortic valve. Note that the jet hits the anterior mitral leaflet.

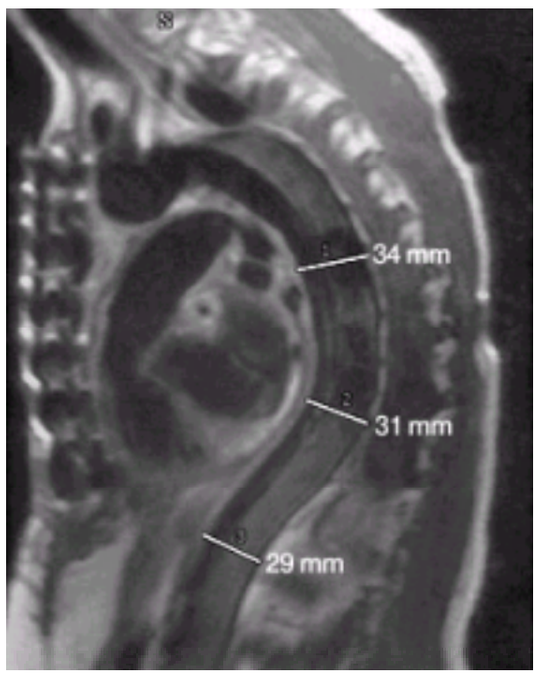
VIDEO

Video 22.31 Long-axis 120-degree transesophageal view of a rheumatic aortic valve with central aortic insufficiency due to furled, restricted leaflets. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

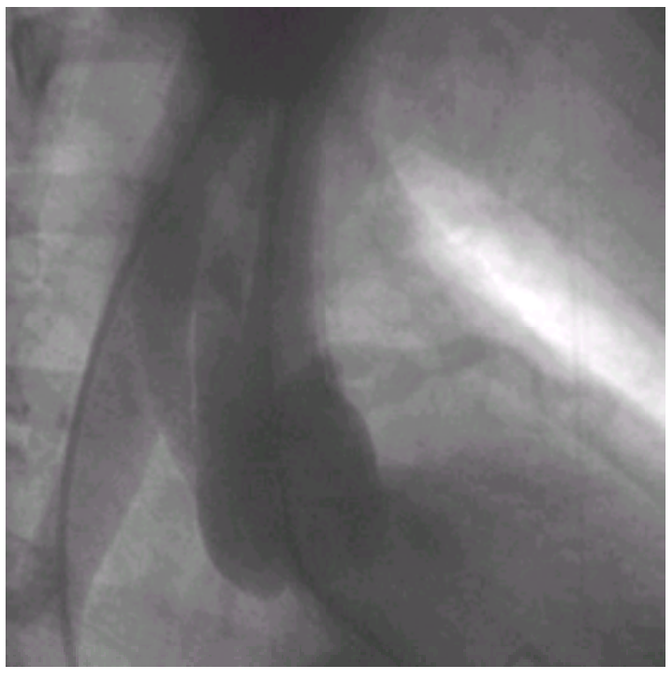
VIDEO

Video 22.32 Apical four-chamber view of a patient with severe rheumatic mitral stenosis with marked thickening and doming of the mitral leaflets, with severe ALE and spontaneous echo contrast within the left atrium. Note the left ventricle remains small. Because of long-standing severe mitral stenosis, the patient has severe pulmonary hypertension with right ventricular hypertrophy and right ventricular failure and severe right atrial enlargement. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Diseases of the aortic root leading to aortic regurgitation include atherosclerosis, Marfan's syndrome, aortic dissection, hypertension with associated annuloaortic ectasia, syphilitic aortitis, ankylosing spondylitis, osteogenesis imperfecta, and systemic lupus. In Marfan's syndrome and in annuloaortic ectasia, dilation of the proximal root increases the aortic diameter at the level of the sinotubular ridge, which lifts the cusp suspension superiorly, causing cusp separation and lack of central coaptation (103). Although annuloaortic ectasia is often associated with hypertension, its presence usually correlates better with age than with elevated blood pressure. In Marfan's syndrome, in hypertension, and in some patients with bicuspid aortic valves, cystic medial necrosis of the aorta occurs, and in some patients, it arises in isolation. Whether an aneurysm is caused by atherosclerosis or cystic medial necrosis, an intimal tear can occur, producing aortic dissection. Proximal dissection may undermine aortic valve cusp support if the aortic dissection affects the commissural ridge. Ankylosing spondylitis and syphilis also cause ascending aortic dilation, but they also produce aortic wall thickening, which, in turn, distorts the commissures and prevents leaflet coaptation.



Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

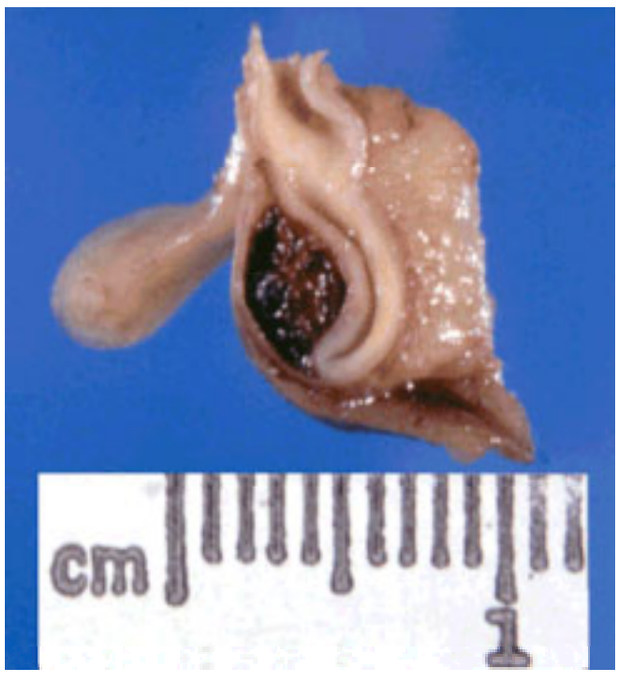


A 77-year-old male patient presented to the emergency department with severe chest pain and hypertension. Aortogram revealed type A aortic dissection.

Video 22.33 Aortic insufficiency associated with annuloaortic ectasia of aortic root (oblique-coronal). An “onion-bulb” dilatation of the proximal ascending aorta and the sinuses of Valsalva is observed. A signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricular cavity during diastole. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 22.34 Aortic dissection (left anterior oblique). Type A dissection of the aorta is manifested on the cine image loop by a mobile intimal flap extending from the mid-ascending aorta to the descending thoracic aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 22.35 Aortic dissection (left anterior oblique). Type B dissection of the aorta extending distally from the isthmus, just after the left subclavian artery, to the abdominal aorta. A communication between the true and false lumen is seen in the proximal portion of the descending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Ascending aortic dissection extending into the left main. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 22.36 Intraoperative transesophageal echo with color Doppler of an ascending aortic dissection. Note the mobile flap with the color flow separation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 22.37 Transesophageal echo in a patient with severe left ventricular dysfunction and a descending aortic aneurysm with severe spontaneous echo contrast within the aorta (seen in short axis). Note the significant layering of thrombus along the wall of the aneurysm (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 22.38 Short-axis transesophageal echo view of a type I aortic dissection. Note the flap originating within the noncoronary cusp (leaflet, upper left screen) and extending towards the ostium of the left main trunk. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 22.39 Intraoperative 120-degree transesophageal echo of an ascending aortic dissection. Note the large, complex flap in the ascending aorta seen originating near the origin of the right coronary artery. There is a small amount of aortic insufficiency. Flow is seen in the true lumen (*left*), whereas no flow is seen in the false lumen (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

TABLE cellSpacing=0 cellPadding=0 align=left border=0 hspace="10" vspace="5">

Video 22.40 Contained rupture of aorta (false aneurysm). The aorta ruptured into the pericardium, which was localized and contained by post–coronary artery bypass grafting adhesions. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pathophysiology

The pathophysiologic stages of acute and chronic aortic regurgitation are shown in Figure 22.6 (104). At the time of severe acute aortic regurgitation, there is a small increase in end-diastolic volume as the volume overload of aortic regurgitation increases LV preload. Increased filling volume allows only a modest increase in total stroke volume (SV), which is not enough to compensate for the volume that is regurgitated. Because pulse pressure is proportional to SV, which is only slightly increased, there is usually no perceptible increase in pulse pressure at this stage of the disease. The large regurgitant volume entering the relatively small LV chamber greatly increases LV and left atrial diastolic pressure, leading to pulmonary congestion.

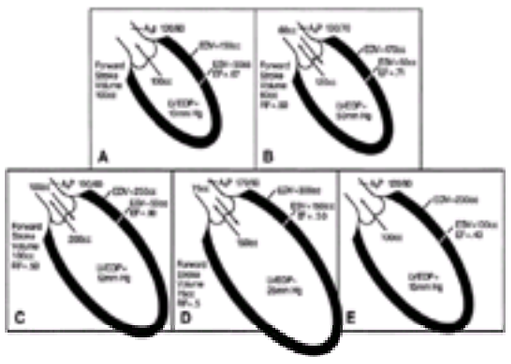


FIGURE 22.6 Hemodynamics of the clinical stages of aortic regurgitation (AR). **A:** Normal conditions. **B:** Severe acute AR, although total stroke volume (SV) is increased, forward SV is reduced. Left ventricular end-diastolic pressure (LVEDP) rises dramatically. **C:** Chronic, compensated AR. Eccentric hypertrophy produces increased end-diastolic volume (EDV), which permits an increase in total as well as forward SV. The volume overload is accommodated, and LVEDP is normalized. Ventricular emptying and end-systolic volume (ESV) remain normal. **D:** Chronic, decompensated AR. Impaired LV emptying produces an increase in ESV and a decrease in ejection fraction (EF), total SV, and forward SV. There is further cardiac dilation and recurrence of moderately elevated LVEDP. **E:** Immediately after aortic valve replacement, preload estimated by EDV decreases, as does LVEDP. ESV is also decreased but to a lesser extent, resulting in an initial decrease in EF. Despite these changes, elimination of AR leads to an increase in forward SV. (A_oP, aortic pressure; RF, regurgitant fraction.) (Modified from Carabello BA. Aortic regurgitation: hemodynamic determinants of prognosis. In: Cohn LH, DiSesa VJ, eds. *Aortic regurgitation: medical and surgical management*. New York: Marcel Dekker, 1986, with permission.)

If aortic regurgitation develops more slowly or if the patient can be managed successfully through the acute episode without surgery, the patient enters the chronic compensated phase. In this phase, eccentric cardiac hypertrophy in addition to increased preload allows a large increase in LV end-diastolic volume. Because muscle function remains normal in this phase, normal performance of an enlarged ventricle permits ejection of a very large total SV. The large total SV allows forward SV to be normal despite a large regurgitant volume. The enlarged left ventricle accommodates filling at a lower pressure, more normal than in acute AR. In this stage, the patient may be entirely asymptomatic even during fairly strenuous activity. The large total SV interacts with the aorta to produce a wide pulse pressure causing systolic hypertension. The wide pulse pressure produces most of the physical signs of aortic regurgitation.

The combined pressure and volume overload stimulates the development of both concentric and eccentric hypertrophy (*e*Table 22.1.3). In this regard, aortic regurgitation differs markedly from mitral regurgitation, which is a pure volume overload (105) without pressure overload and without an increase in LV wall thickness. AR also differs from AS, which is a pure pressure overload without volume overload. The hypertrophy that occurs in both appears to be related to changes in LV myocardial matrix metalloproteinase activity and inhibitory control, but with some differences—for example, in interstitial collagenase activity and stromelysin levels (30c).

VIDEO

Video 22.41 Parasternal long-axis view of a rheumatic mitral valve with color Doppler. Mitral regurgitation is the primary problem seen by color Doppler, with only mild mitral stenosis due to the thickened and doming leaflets. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 22.42 Left ventriculography with severe mitral regurgitation. After contrast injection in the left ventricle, the left atrium achieves the equal opacity to the left ventricular cavity indicative of severe (4+) mitral regurgitation. Before contrast injection, calcification in the mitral annulus and descending aorta is evident. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

***e*TABLE 22.1.3** HYPERTROPHY IN HUMAN LEFT-SIDED OVERLOAD VALVE LESIONS

Valve lesions	Mass index: g/m^2 (no. of patients analyzed)	Ratio of LV radius to thickness (no. of patients analyzed)	Ratio of LV mass to volume (no. of patients analyzed)
Normal subject	86 (259)	3.05 (88)	1.25 (225)
Mitral regurgitation	158 (146)	4.03 (64)	0.87 (117)
Aortic regurgitation	230 (148)	3.52 (31)	1.00 (141)
Aortic stenosis	178 (302)	2.35 (93)	1.55 (296)

LV, left ventricular.
From Carabello BA. The relationship of left ventricular geometry and hypertrophy to left ventricular function in valvular heart disease. *J Heart Valve Dis* 1995;4[Suppl II]:S132–S139, with permission.

Although the patient may remain in the compensated phase for many years, LV dysfunction eventually develops. In this stage, LV dilation increases further, LV filling pressure becomes elevated, and EF decreases, reducing both total and forward SV. Although most patients develop symptoms at this time, some still may enter this decompensated phase without complaints.

The final panel of Figure 22.6 depicts the patient after AVR has been performed. Shortly after AVR, there is a fall in both end-diastolic volume and end-systolic volume (ESV), with a greater decrease in the former. This results in a temporary reduction in ejection performance. However, if AVR has been performed before LV dysfunction has become permanent, additional remodeling occurs, resulting in an additional fall in ESV, with a return of ejection performance toward normal (106).

To summarize, in chronic aortic regurgitation, there is a large increase in total SV ejected into the aorta, which produces a widened pulse pressure and systolic hypertension accounting for the physical signs of the disorder; the widened pulse pressure and systolic hypertension are responsible for adding a pressure overload to this volume-overloaded state. Although initially compensated by cardiac dilation to increase total SV, eventually afterload mismatch and contractile dysfunction lead to reduced ejection performance and cardiac decompensation (107). If the aortic regurgitation is recognized and corrected surgically in a timely fashion, decompensation is reversed after AVR, afterload is reduced, and EF returns to normal (Fig. 22.7).

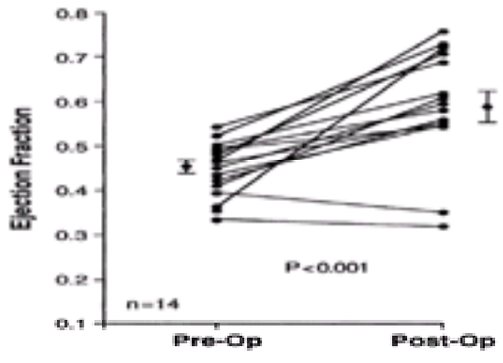


FIGURE 22.7 Shown here is preoperative and postoperative ejection fraction from 14 patients with aortic regurgitation. (From Carabello BA, Usher BW, Hendrix GH, et al. Predictors of outcome for aortic valve replacement in patients with aortic regurgitation and left ventricular dysfunction: a change in the measuring stick. *J Am Coll Cardiol* 1987;10:991–997, with permission.)

Clinical Profile: Symptoms

Congestive Heart Failure

Patients with aortic regurgitation in the chronic compensated phase are often entirely asymptomatic and can remain so for many years, even after myocardial dysfunction develops. As LV decompensation proceeds, in many patients symptoms occur, typically including dyspnea on exertion, orthopnea, and in advanced cases, paroxysmal nocturnal dyspnea and peripheral edema.

Angina and Aortic Regurgitation

Angina with normal epicardial coronary arteries is less frequent in aortic regurgitation than in AS (108). Aortic regurgitation results in rapid diastolic runoff with a rapid fall in aortic diastolic pressure. Because coronary blood flow occurs primarily in diastole, the aortic diastolic pressure serves as the pressure head for coronary flow. Thus, diastolic hypotension may be responsible for impaired coronary flow, leading to angina. In addition, the increased LV muscle mass may increase the resistance to coronary flow. When angina does occur with aortic regurgitation it is often associated with vasoactive phenomena such as flushing (a pseudo-Nothnagel attack). Other symptoms of aortic regurgitation include an unpleasant awareness by the patient of his or her heartbeat and occasionally of carotid artery pain.

Physical Examination

Chronic and severe aortic regurgitation results in a dramatic physical examination. Cardiac dilation and large total SV produce a hyperdynamic circulation. The point of maximum impulse is forceful, enlarged, sustained, and displaced downward and to the left. The typical murmur of aortic regurgitation is a diastolic, blowing, decrescendo murmur heard best at the left sternal border with the patient sitting upright. The length of the murmur is in part related to the severity of the aortic regurgitation. In mild disease a short, early diastolic murmur is the rule. As the degree of valvular regurgitation worsens, the murmur may become pandiastolic. With the late onset of LV dysfunction and in acute, severe aortic regurgitation, high LV diastolic pressure causes earlier equilibration of the aortic and LV diastolic pressures in mid-diastole, reshortening the length of the diastolic murmur. Many patients with aortic regurgitation also have a systolic murmur even if they do not have AS because of the increase in antegrade flow. A second diastolic murmur, an apical mitral rumble (Austin Flint murmur), usually indicates that the aortic regurgitation is severe. Although still debated, the Austin Flint murmur is probably the result of the aortic jet impinging on the mitral valve, causing it to vibrate or causing diastolic turbulence without true LV inflow obstruction.

HEART SOUNDS

Audio 22.43 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border-sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.44 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border-sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.45 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border-sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 22.46 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border-sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 22.47 Transgastric view (transesophageal echo) of the mitral valve in a patient with severe aortic insufficiency. Note the fluttering of the anterior mitral leaflet (*left*) due to the jet of aortic insufficiency hitting it (color flow seen on the left). (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 22.48 Parasternal long-axis view (transthoracic echo) of a bicuspid aortic valve with prolapse of the anterior leaflet causing posteriorly directed aortic insufficiency. The aortic insufficiency hits the anterior mitral leaflet, causing deformation of this leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 22.49 Parasternal long-axis view (transthoracic echo) of a bicuspid aortic valve with prolapse of the anterior cusp (right and left coronary cusps fused) causing posteriorly directed aortic insufficiency. Note the posterior displacement of the anterior mitral leaflet (AML) caused by the AI jet hitting this leaflet. The left ventricular cavity is dilated. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The large forward SV and wide aortic pulse pressure affect the process of taking the patient's blood pressure with a sphygmomanometer, during which Korotkoff's sounds are often heard almost down to a pressure of zero. The widened pulse pressure is also responsible for a myriad of signs, listed in Table 22.2, resulting from the hyperdynamic pulse contour. Among them, Hill's sign and Duroziez's sign seem to be the most useful as a bedside gauge of the presence of severe aortic regurgitation. However, when LV decompensation occurs, the pulse pressure may narrow and become pseudonormalized by a reduction in the systolic hypertension. This accrues from reduced total SV by the weakened left ventricle. Elevated LV diastolic pressures often cause an early diastolic apical filling sound [third heart sound (S_3) or gallop].

Sign	Finding
Corrigan's pulse	Rapid forceful carotid upstroke followed by rapid decline
Quincke's pulse	Systolic plethora and diastolic blanching in nail bed when nail is slightly compressed
de Musset's sign	Bobbing of head
Duroziez's sign	Systolic and diastolic bruit heard over femoral artery when compressed by bell of stethoscope
Hill's sign	Augmentation of systolic blood pressure in leg by ≥30 mm Hg compared with that in arm

TABLE 22.2 SIGNS OF AORTIC INSUFFICIENCY

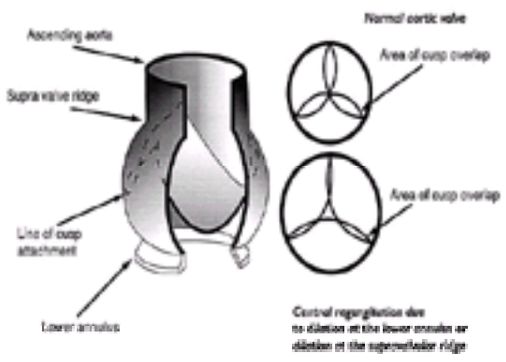
Electrocardiogram

The ECG in chronic aortic regurgitation is nonspecific, but it almost always demonstrates LVH.

Echocardiography and Doppler Examination

At present, echocardiography with Doppler interrogation of the aortic valve is the most important test to diagnose this disease. Two-dimensional echocardiography is able to visualize the structure, thickness, and mobility of the aortic valve leaflets and the size of the aortic annulus and ascending aorta.

Normal leaflets are thin and mobile, moving to an orientation parallel to flow during systole. During diastole, each cusp is suspended like a hammock from the valve commissures above, at the level of the sinotubular ridge. The belly of each cusp hangs down to the level of the annulus in diastole, with the centers of each cusp meeting in the middle and an oval-shaped segment of overlap between each adjacent leaflet (eFig. 22.7.1).



***e*FIGURE 22.7.1** Aortic regurgitation in normal and thoracic aortic aneurysms.

With each etiology of aortic regurgitation, there are typical structural changes that are definable by echo. In the patients with bicuspid aortic valve, rheumatic heart disease, infective endocarditis, or calcific degeneration of the leaflets, typical imaging features of the aortic cusps have become well recognized. Aortic dilation can also be easily detected when it is a cause of valvular regurgitation.

Video 22.50 Intraoperative transesophageal echo (120-degree view) with color Doppler demonstrating aortic insufficiency due to aortic dilatation (sinuses measure 5.0 cm) causing failure of leaflet coaptation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

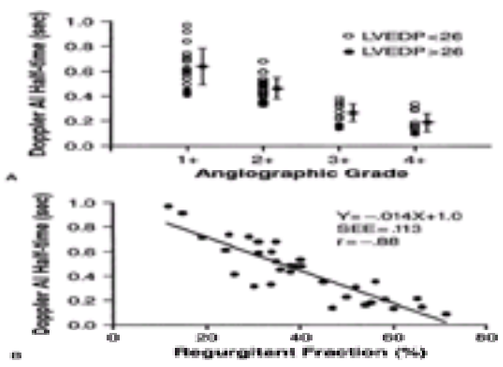
Video 22.51 Intraoperative short-axis 60-degree transesophageal echo of an aortic valve in a patient with a dilated ascending aorta (sinuses measure 5.0 cm) causing failure of the aortic leaflets to coapt centrally. This central gap caused severe aortic insufficiency. *This video must be viewed with QuickTime. If you do not have*

QuickTime you may download it here.

Video 22.52 Intraoperative 120-degree transesophageal echo showing a long-axis view of the aorta in a patient with a dilated aorta causing failure of aortic leaflet coaptation resulting in severe aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Echo also gauges LV performance, chamber dimensions, and the extent of LVH, which are used with clinical data to time aortic valve surgery (see Aortic Valve Replacement and Repair). Doppler interrogation is used to gauge the degree of aortic regurgitation in several ways. First, the spatial extent of the color Doppler aliasing in the outflow tract is used as a rough guide to the severity of aortic regurgitation (109). A semiquantitative scale of mild, moderate, moderately severe, and severe regurgitation is predicated primarily on the width (in long axis) and the area (in short axis) of the proximal portion of the jet of disturbed flow in the outflow tract. To a lesser extent, the depth to which the jet penetrates toward the apex of the left ventricle is also important.

Other echo methods for judging severity of AR include continuous-wave Doppler interrogation of the aortic jet, based on the decay of the diastolic velocity, and therefore gradient, across the aortic valve. In mild aortic regurgitation, the decay of the gradient is gradual and incomplete, whereas in severe aortic regurgitation the decay occurs rapidly, equilibrating relatively early in diastole (110). This qualitative difference can be quantified by measuring the time it takes for the regurgitant velocity to reach the pressure half-time, at which time the velocity is 71% (one divided by the square root of two) of its peak value. A pressure half-time of less than 400 ms usually indicates at least moderate aortic regurgitation (eFig. 22.7.2) and a pressure half-time of less than 300 ms indicates severe regurgitation. Unfortunately, pressure half-time is also shortened by LV diastolic dysfunction because of a faster rise in LV diastolic pressure. Descending aortic flow reversal in diastole, measured by pulsed Doppler from the suprasternal notch, is another useful gauge of severity of aortic regurgitation. When the reversal is pandiastolic, or the diastolic velocity integral equals the systolic integral, regurgitation is usually severe.



***e*FIGURE 22.7.2 A,B:** Correlation of aortic insufficiency (AI) pressure half-time by continuous wave Doppler, in seconds, with the degree of regurgitation on angiography. Note inverse correlations. Patients with left ventricular end-diastolic pressure (LVEDP) of more than 26 mm Hg are indicated by the filled circles in **(A)**. (From Teague SM, Marty W, Sandatmanesh V, et al. The effects of mean pressure gradient, chamber compliance, and orifice size upon the Doppler half-time method. *J Am Coll Cardiol* 1988;11:204A, with permission.)

Cardiac Catheterization

In patients with severe aortic regurgitation in whom the diagnosis is obvious from the physical examination and the noninvasive results, cardiac catheterization need not be performed before AVR. In general, valve surgery without catheterization is more reasonable in men younger than 40 years or in women younger than 50 years, but atherosclerotic risk factors and symptoms should also be considered in this decision. In patients in whom severity of aortic regurgitation is in question or for the purposes of defining concomitant coronary disease, catheterization should be performed. During cardiac catheterization, additional assessment of the severity of aortic regurgitation is made using aortography. Unlike echocardiography, which visualizes the velocity of flow, aortography visualizes regurgitant flow by opacifying the left ventricle with contrast injected into the aorta. The denser the opacification, the worse the aortic regurgitation (111). At least 60 mL of contrast should be injected to opacify both the enlarged left ventricle and aortic root.

Video 22.53 A 49-year-old male patient with bicuspid aortic valve and severe aortic regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Management

Timing of Surgery

Although severe chronic aortic regurgitation may be tolerated for years in many patients, the combined LV pressure and volume overload eventually leads to muscle damage and LV dysfunction. Aortic valve surgery should be performed when symptoms develop, but before muscle dysfunction becomes irreversible. If the patient with aortic regurgitation develops New York Heart Association class II symptoms of CHF, surgery should be performed to help improve the quality of the patient's life and functional status. However, surgery should be performed even in the asymptomatic patient if there is evidence that contractile dysfunction has begun to develop (112,113,114 and 114a). Contractility is the ability of the myocardium to develop force independent of preload. Unfortunately, there is no easily applied device or index to measure this property. Moreover, because of individual differences among patients with aortic regurgitation in the abnormalities of preload and afterload and the patient's hemodynamic response to the disease, the standard clinical indices of LV function, such as EF, may be confounded. Despite these problems, reliable guides to the timing of surgery have been developed.

Use of Echocardiography

During the past 15 years, echocardiography has become preeminent in predicting outcome and in timing surgery because it provides a safe, noninvasive method for frequent periodic interrogation of LV size and function. The two indices that have demonstrated efficacy in predicting outcome in patients with chronic asymptomatic or minimally symptomatic aortic regurgitation are echocardiographic shortening fraction or EF and end-systolic cavity size (either LV diameter or volume) (112,113 and 114a). Shortening fraction and systolic diameter are the minor axis one-dimensional equivalents of EF and ESV, respectively. A patient with a shortening fraction of less than 27% or a resting EF of less than 55% has presumed LV dysfunction. Aortic valve surgery should be considered even in the asymptomatic patient before systolic function declines further. End-systolic diameter, a more preload-independent index than EF, has also proved helpful in timing surgery (112,113 and 114). When the combination of eccentric hypertrophy and LV dysfunction has developed so that the left ventricle has an end-systolic diameter of 55 mm or larger, postoperative survival is significantly decreased. To avoid the prospects of a higher risk of perioperative mortality, surgery should be strongly considered when the end-systolic diameter reaches or exceeds 50 mm. It should be noted that there is a window of time of approximately 18 months after either of these thresholds is crossed during which surgery can be performed and systolic function will likely still return to normal (115). Although echocardiographic and clinical follow-up must be tailored to the needs of individual patients, Bonow et al. (113) have recommended that frequency of echo studies be gauged by the end-systolic diameter. When this dimension is less than 40 mm, it is very unlikely that dysfunction will develop within the next 2 years, and thus echocardiography should be performed biannually. When

echocardiographic end-systolic diameter ranges from 40 to 50 mm, yearly follow-up is recommended. If end-systolic diameter is more than 50 mm, the patient should also be given the option of surgery, but if delay is chosen, echocardiography should be performed every 6 months.

Use of Exercise Ejection Fraction

Some experts use exercise EF (116) for the timing of surgery in patients with asymptomatic or minimally symptomatic aortic regurgitation; however, use of this test remains controversial. In normal persons, EF usually increases and ESV decreases during exercise due to the catecholamine-mediated increase in contractility. In theory, a fall in exercise EF may indicate an exhaustion of myocardial reserve. However, a fall in EF may also result from changes in loading conditions that occur during exercise, especially when excessive afterload and hypertension develop during exercise due to failure to vasodilate and decrease peripheral resistance.

Recommendations for the timing of surgery in patients with relatively asymptomatic aortic regurgitation must be made individually for each patient based on the benefits and risks of the surgical and the medical approach. At present, we recommend AVR if the patient either becomes symptomatic or if echocardiographic examination demonstrates that LV dysfunction is developing, indicated by an end-systolic diameter approaching 50 to 55 mm or by an EF of less than 0.55.

Aortic Valve Replacement and Repair

Today, surgical treatment of most cases of aortic regurgitation entails valve replacement. Options for aortic valve surgery include (a) bioprosthetic valves of the standard stented variety; (b) mechanical prosthetic valves; (c) homograft valves; (d) pulmonary autografts; (e) stentless bioprosthetic valves; and (f) aortic valve repair. Transthoracic echocardiography may be used to determine anatomic information that may predict the likelihood of which surgical option can be used.

AVR is performed identically as discussed in this chapter in the section on AS. However, unlike the situation in AS, valve repair may be possible in some patients with aortic regurgitation. The best candidates for successful aortic valve repair are a highly selected group with one of three types of anatomy: a structurally normal valve with aortic dilation, a simple valve perforation, or a noncalcified valve with AR due to prolapse.

Cosgrove et al. and Fraser et al. (64,95) have reported success with aortic valve repair in a highly selected group of patients with either bileaflet or trileaflet valves that are not calcified where the aortic valve regurgitation is caused by aortic valve prolapse. In this group, the AR results from elongation of one of the aortic valve leaflets along its free edge, thus causing lower suspension of that leaflet during diastole.

Repair in these patients is performed by excising or excluding a V-shaped wedge of the prolapsing portion of the leaflet and then reestablishing leaflet continuity with a running suture to make the leaflet edge length match the opposing leaflets. The repair is supported by performing a commissural plication with pledgeted mattress sutures at the aortic valve commissures. These commissural sutures create an annuloplasty-like effect on the sinotubular ridge, thus lowering the level of suspension of diastolic leaflet position, which improves leaflet coaptation.

In patients with infectious endocarditis, aortic regurgitation may occasionally be caused by leaflet perforation. In these cases, the leaflet may be repaired with small patches of glutaraldehyde-treated autologous or bovine pericardium sutured over the perforation. In patients with aortic root dilation with normal aortic leaflets, the valve often can be resuspended at the time of aortic root replacement.

Because aortic regurgitation in patients with aortic dilation often results from increased diameter of the sinotubular ridge, causing superiorly directed tethering of normal cusps and central failure of coaptation (eFig. 22.7.1) (116a), repair can also be accomplished by commissural plication if the dilation is mild. When the dilation is moderate or more, root replacement is usually needed. Valve resuspension can be accomplished by implanting a supracoronary conduit, the lower edge of which is sewn to the patient's sinotubular ridge, fixing it to a smaller, more normal, diameter, which reestablishes leaflet coaptation. Other valve-sparing operations have been used in patients with aortic aneurysms that also reconstruct the sinuses of Valsalva (116b).

In any case of valve repair or in more technically difficult aortic valve surgery, such as the Ross procedure or aortic homograft implantation, there exists the potential for immediate failure of the attempted surgery, with persistent aortic regurgitation. Immediate assessment of the repair is obtained in the operating room with TEE. This provides a safety net to detect unsuccessful repair (see Chapter 57), allowing further surgery to be performed during the same thoracotomy to ensure a good clinical outcome.

Medical Therapy

Use of vasodilators in treating patients with asymptomatic aortic regurgitation has been found to forestall the development of LV dysfunction. The premise in their use is that arteriolar vasodilation reduces regurgitant flow and diminishes the severity of the lesion. Hydralazine, nifedipine, and angiotensin-converting enzyme inhibitors have been investigated for this purpose. The most compelling data point to nifedipine, although it is likely that angiotensin-converting enzyme inhibitors and other dihydropyridine calcium blockers would also be effective. In a randomized 2-year study of hydralazine (117), asymptomatic patients given hydralazine had less ventricular dilation and better ejection performance than did a placebo group. Similar results have been reported with angiotensin-converting enzyme inhibitors (118). A large controlled study of nifedipine versus digoxin (119) recently found that nifedipine substantially delayed the time when surgery was required and reduced the number of patients requiring surgery. Thus, there is evidence supporting long-term use of vasodilators in asymptomatic patients with severe, chronic aortic regurgitation who do not yet have LV dysfunction or other clear indications for surgery.

ACUTE AORTIC REGURGITATION

Background

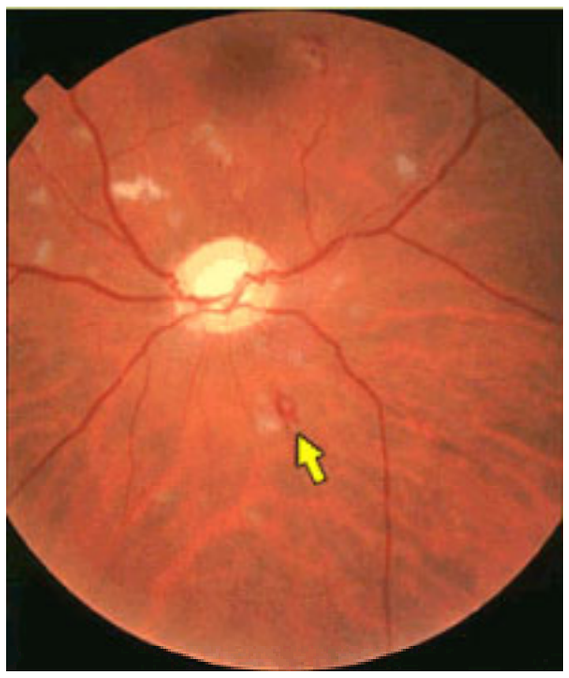
Severe, acute aortic regurgitation frequently constitutes a surgical emergency. Mortality may be as high as 75% in medically treated patients but only 25% after surgery. Thus, recognition of acute aortic regurgitation and its proper management are crucial in ensuring good patient outcome (120).

Etiology

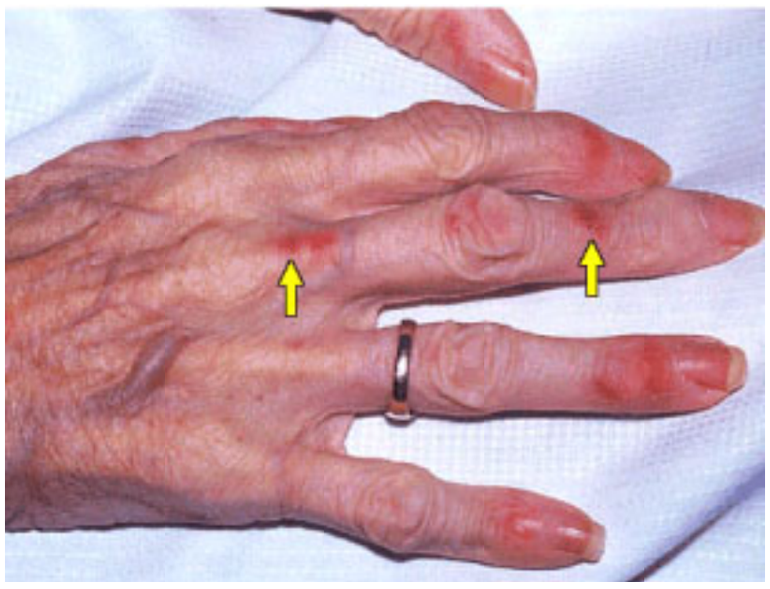
Infective Endocarditis

Infective endocarditis is the most common cause of acute aortic regurgitation. Frequently occurring in younger patients, especially those that practice illicit intravenous drug use, acute endocarditis may develop on a previously bicuspid valve or a normal valve, especially if aggressive organisms, such as *Staphylococcus aureus* or enterococcus, are the etiologic agents. Often mistaken for influenza, the sudden development of a high fever, malaise, and the early symptoms of CHF should be given immediate attention, especially in the patient with a previously known abnormal aortic valve or a valve prosthesis. Cutaneous manifestations of endocarditis, systemic emboli, a new or changing murmur of aortic regurgitation, positive blood cultures, and echocardiographic demonstration of aortic valve vegetations all help to make the diagnosis (see Chapter 25) (120a).

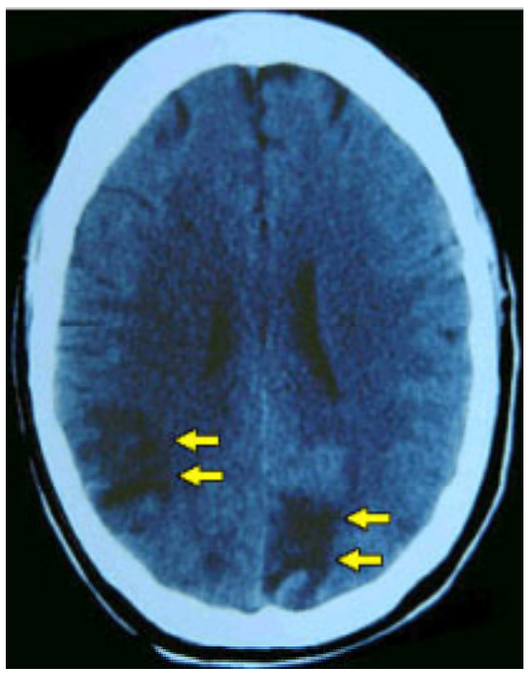
Janeway lesions of endocarditis. There are hemorrhages with nodular character at the fingertips (*arrows*).



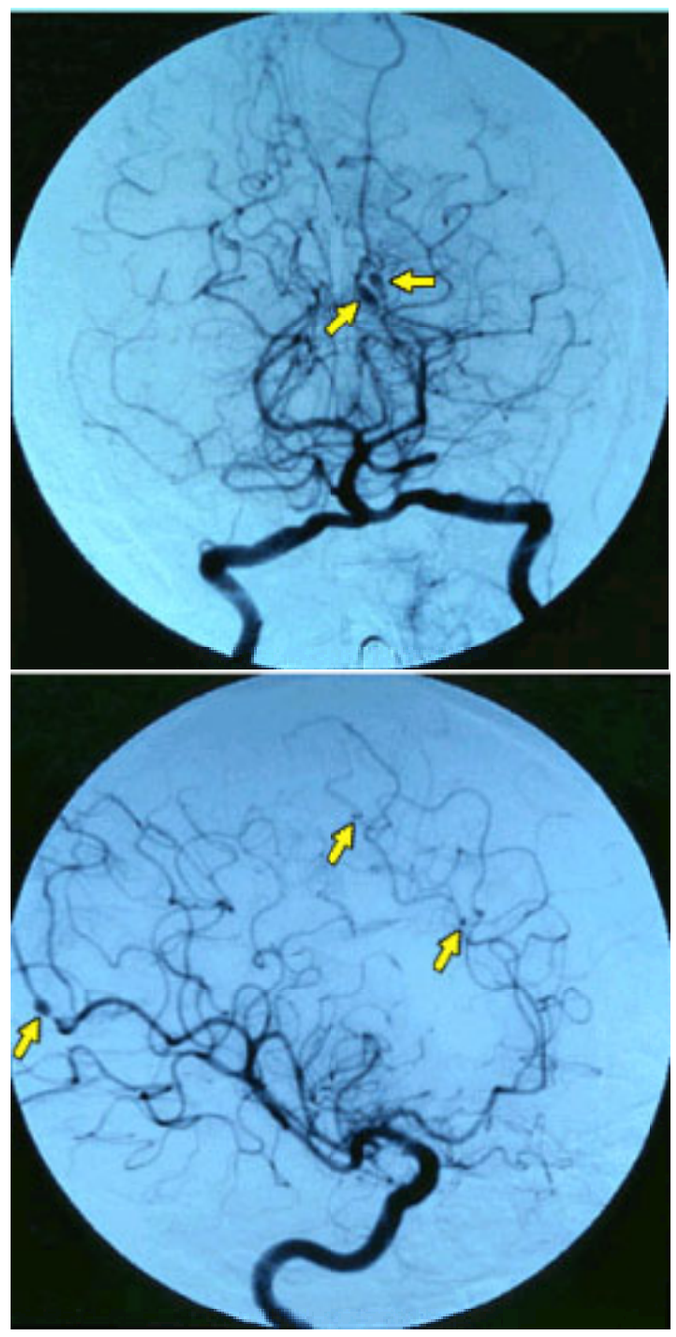
Roth spot. The yellow arrow indicates a hemorrhage with a white central spot typical of subacute bacterial endocarditis.



Septic emboli from infective endocarditis (*arrows*).



Ruptures mycotic aneurysms. Several areas of hypodensity representing ruptured mycotic aneurysms as a result of endocarditis (*arrows*).



Mycotic aneurysms from infective endocarditis. Localized aneurysmal dilatation of cerebral vessels as a result of endocarditis (*arrows*, A,B).

Osler nodes. There are tender nodules on the toe pads (*arrows*) secondary to infective endocarditis.

Splinter hemorrhages. Linear hemorrhages on the fingertips of a patient with infective endocarditis.

Aortic Dissection

Acute proximal aortic dissection is the other major cause of acute aortic regurgitation. However, unlike endocarditis, other hemodynamic manifestations of proximal dissection, such as hemopericardium with tamponade, myocardial infarction from coronary dissection, or progression to aortic rupture, are usually more problematic than aortic regurgitation.

Pathophysiology

In chronic aortic regurgitation, the development of eccentric LVH permits compensation of the left ventricle by allowing it to generate a large total SV. Apart from being compensatory, this large SV causes a wide pulse pressure, the source of most of the signs of chronic aortic regurgitation. However, in acute regurgitation, eccentric LVH and compensatory LV dilation have not yet developed. Thus, most of the signs of chronic aortic regurgitation, such as a widened pulse pressure, Quincke's pulse, and so forth, are absent. Indeed, the new murmur of aortic regurgitation may be the only clue that this deadly disease is present (121). However, the murmur may be

quite short or heard only in very early diastole because of the rapid equilibration of LV and aortic pressures.

At the bedside, considerable attention should be paid to the first heart sound (S_1). In severe, acute aortic regurgitation the high LV diastolic pressure closes the mitral valve before the onset of LV systole (preclosure). Preclosure of the mitral valve is an ominous sign, almost always indicating the need for urgent surgery.

Management

Echocardiography

Once the diagnosis of acute aortic regurgitation is suspected, echocardiography should be performed immediately. In either bacterial endocarditis or in aortic dissection, the echocardiogram is invaluable in helping to define the etiology and severity of the valve dysfunction. Aortic valve vegetations are key to the diagnosis in endocarditis. In aortic dissection, enlargement of the aorta, the intimal flap, and distinguishing true from false lumen velocities by color flow Doppler are keys to diagnosis, which may require TEE (see Chapter 52).

In either etiology, M-mode echo is useful in demonstrating premature mitral valve closure as a sign of high LV diastolic pressure (122). Occurring for the same reason, diastolic mitral regurgitation by Doppler and other signs of elevated LV pressure can be recorded in some cases. Endocarditis patients with severe AR may be followed medically if they have no heart block, mitral valve preclosure, or evidence of CHF on physical examination or chest x-ray. However, a repeat echocardiogram should be performed to look for an increase in vegetation size, especially if new evidence suggests that aortic regurgitation has worsened. Echocardiography, and particularly TEE, is helpful in diagnosing endocarditis, perivalvular abscesses, and aortic dissection (120a,120b).

Medical Therapy

In the case of endocarditis, multiple blood cultures should be drawn before antibiotics are started. Thereafter, broad-spectrum antibiotics are begun empirically and are adjusted later when blood cultures identify the least toxic antibiotic regimen to which the organism is sensitive. In the absence of CHF or mitral valve preclosure, careful daily assessment for progression of the disease is mandatory. This should include a careful history and physical examination, looking for symptoms and signs of even mild CHF, as well as an ECG rhythm strip looking for prolongation of the PR interval, which might indicate the development of an aortic ring abscess. In some patients, aggressive management with vasodilators may temporarily allow for improvement; however, this therapy should be used to better prepare the patient for surgery rather than as an attempt to delay surgery.

Surgical Therapy

If CHF or mitral preclosure develops, immediate AVR should be contemplated. Although there is always a concern that implantation of a prosthesis in an infected patient may lead to prosthetic endocarditis, reinfection of a prosthetic valve has an incidence of approximately 10%, even if surgery is performed within 48 hours of the last positive blood culture (123). In patients with aortic valve endocarditis, particularly those with extension of the infection into heart tissue (i.e., annular ring abscess), valve replacement with an aortic homograft may be advantageous because it entails implantation of less foreign body and reduced early postoperative valve infection (124).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Aortic Valve Replacement in Asymptomatic Aortic Stenosis Patients

Some change has occurred recently in our understanding of the optimum time for surgery in patients with AS (59a). With the mortality and morbidity risks of valve surgery declining due to improved technology and methods, the question has arisen whether patients with no symptoms should be considered candidates for surgery. In AS, there is a widely recognized risk of sudden death. Although most patients have antecedent symptoms before their event, in many patients the symptoms are not significant enough to bring them in for medical attention before their death and are therefore just as bad as the less common collapse and immediate death. As mentioned above, some factors have been associated with worse prognosis, including the presence of moderate or severe valvular calcification and a rapid increase in aortic jet velocity between two echocardiographic studies (29a). In addition, the flow-dependent rate of change in AVA measured during the ejection phase of a cardiac cycle predicts the rate of hemodynamic progression in patients with asymptomatic AS (25a). Exercise testing may also reveal latent symptoms or hemodynamic instability. If further studies confirm these findings, consideration for early valve replacement in some asymptomatic patients may be appropriate, rather than delaying surgery until symptoms develop.

THE FUTURE

In the future, improvements in our understanding of the contributing factors of the “atherosclerosis-like” process of AS will fuel prevention strategies. Innovations in cardiac surgery and perioperative medical management will promote the ongoing trend for surgical techniques for AS and AR to become safer, with less perioperative mortality and morbidity. No longer should surgery be put off until the patient’s symptoms cannot be managed medically, late in the course of the disease. New valvular replacement options will become more physiologic, with less prosthetic valve “penalty” in terms of persistent gradients, postoperative hypertrophy, and limited durability. Reoperations for a second, third, or even sixth time will continue to become more frequent and with acceptable operative risk. In addition, our abilities to monitor hemodynamics of surgery patients noninvasively and repeatedly and to study groups of patients to understand the disease processes will improve. These factors will further improve the prognosis for patients with aortic valve disease. The progress continues.

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23

ACQUIRED TRICUSPID AND PULMONARY VALVE DISEASE

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JOHN S. MACGREGOR

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Acquired disease of the tricuspid and pulmonary valves is uncommon. Tricuspid valve (TV) disease can be due to intrinsic disease of the valve or to functional tricuspid regurgitation (TR) secondary to right ventricular dysfunction. This condition, in turn, is due to intrinsic disease of the right ventricle (e.g., cardiomyopathy or coronary disease) or to pulmonary hypertension and right ventricular dilatation. Tricuspid stenosis is rare; when seen, it is often due to carcinoid heart disease rather than to rheumatic heart disease. Rarely, infective endocarditis—especially with fungal etiology—can result in tricuspid stenosis. Pulmonary stenosis is overwhelmingly congenital in etiology. Pulmonary regurgitation is rarely due to acquired organic disease of the valve, but when it occurs, it is most often iatrogenic due to surgery on a congenitally stenotic valve. Carcinoid can involve the pulmonary valve, causing pulmonary stenosis, regurgitation, or both. Most frequently, pulmonary regurgitation is secondary to pulmonary hypertension.

TR can result in right ventricular systolic and diastolic dysfunction and right heart failure. When cardiac output falls, with a rise in systemic venous pressure, hepatic congestion, ascites, and edema can result, requiring TV surgery, either annuloplasty or replacement. Long-term results of replacement of the TV are not as favorable as with left-sided valve replacement. With tricuspid stenosis, balloon valvotomy, surgical commissurotomy, or valve replacement can be beneficial. With pulmonary stenosis, almost always congenital in etiology, balloon valvotomy has replaced surgical commissurotomy and is probably as successful in the long term. With pulmonary regurgitation, usually due to pulmonary hypertension, it is rarely necessary to consider pulmonary valve surgery; treatment of the pulmonary hypertension is the most beneficial approach. With medically or surgically created pulmonary regurgitation with systolic dysfunction of the right ventricle, pulmonary valve replacement is indicated.

INTRODUCTION

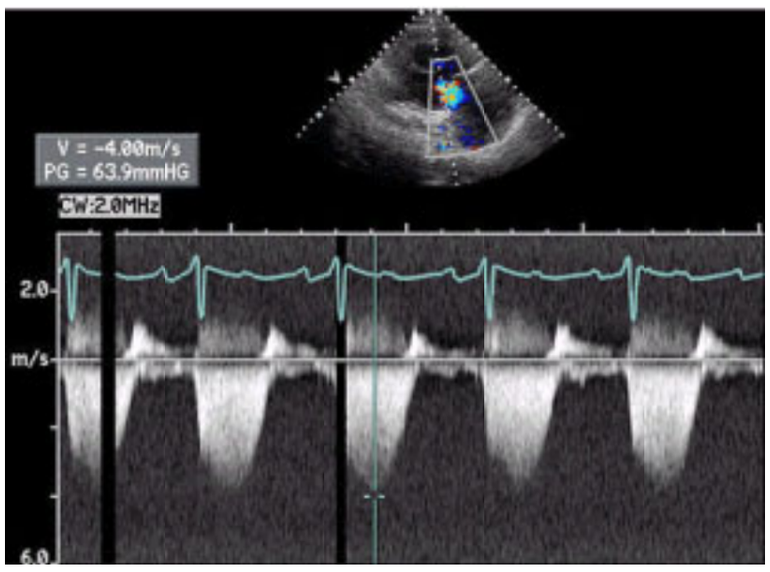
Acquired disease of the tricuspid and pulmonary valves is much less common than that of left-sided mitral and aortic valves. The exact reason for this is not totally understood, but it is true that the frequency of involvement of the cardiac valves with rheumatic heart disease and with infective endocarditis is related to the stress that these valves sustain in the course of normal function. Thus, the mitral valve (MV) is subject to the left ventricular systolic pressure, the aortic valve is subject to the aortic diastolic pressure, the TV is subject to the right ventricular systolic pressure, and the pulmonary valve is subject to the lowest pressure (the pulmonary arterial diastolic pressure). It is in this order that the frequency of valvular involvement occurs in rheumatic disease and infective endocarditis.

ANATOMY

The right ventricle lies anterior to the left ventricle and leftward of the right atrium. It consists of an inflow tract (including the annulus, TV, and chordal and papillary muscles) and an outflow tract (including the infundibulum of the right ventricle and the pulmonary valve). The outflow and the inflow tracts are separated by four muscle bands: the infundibular septum, the parietal and septal bands of the crista ventricularis, and the moderator band. The blood supply of the right ventricle is mainly from the acute marginal branch of the right coronary artery, with small bands of right ventricle adjacent to the septum receiving blood from the posterior descending and the left anterior descending coronary arteries. In approximately 10% of hearts, the posterolateral branches of the circumflex supply portions of the posterior right ventricle. The moderator band is supplied by a branch of the first septal perforator of the left anterior descending coronary, and the conus artery from the right coronary artery supplies the anterior wall of the right ventricle.

The TV arises from a fibrous annulus and has the largest circumference of all the valves: 10.0 to 12.5 cm, with an estimated valve area of approximately 7 cm^2. The TV has three leaflets separated by commissures: anterior, posterior, and septal leaflets. The chordae tendineae from the anterior and posterior leaflets arise from a large anterior papillary muscle, which itself arises from the anterior wall of the right ventricle. The posterior papillary muscles are variable in number, arising from the posterior wall of the right ventricle and contributing chordae that insert on the posterior and septal leaflets. There is a conal papillary muscle arising from the septum, its chordae inserted on the anterior and septal leaflets. Frequently, these chordae arise from the septum itself, without a defined papillary muscle. The valve cusps are thin and consist of a dense collagen layer facing the right ventricle (the fibrosa) and a loose matrix composed of mucopolysaccharides (the spongiosa). The TV on the atrial surface has a variable, sparse layer of fibroelastic fibers adjacent to the annulus (1).

By Doppler echocardiography, it is possible to see a jet of TR in approximately 75% of healthy people (2), because the valve ring is so large and the leaflets are relatively narrow. Because the volume of regurgitant blood is so small and the regurgitant pressure gradients are so low, there is normally no murmur of TR. Because the tricuspid annulus forms the orifice of the right ventricular inflow tract, dilatation of the right ventricle, for any reason, worsens the failure of coaptation of the tricuspid leaflets and increases the volume of TR. Any disease affecting connective tissue can be associated with TR, because the TV and chordae are composed of connective tissue.



Continuous wave Doppler trace through the tricuspid valve of a patient with pulmonary hypertension. The maximal jet velocity of 4 m/sec corresponds to a pressure gradient of 64 mm Hg or a PA pressure of approximately 80 mm Hg.

The pulmonary valve is a semilunar valve with three cusps of equal arc similar to the aortic valve; these cusps align approximately 1.5 cm superior, anterior, and leftward of the aortic valve. The cusps have similar histologic structure to the TV, with a dense fibrosa facing the pulmonary artery and the spongiosa facing the right ventricle. Because the stress sustained by the valve is far less than that of the aortic valve, the pulmonary leaflets are thinner and more delicate. Because the pulmonary annulus acts as the root of the pulmonary artery, anything enlarging the root or increasing the diastolic pulmonary arterial pressure causes commissural separation and pulmonary valve insufficiency. Obviously, any disease altering the structure of the pulmonary leaflets also results in pulmonary valve insufficiency.

ETIOLOGY OF ACQUIRED TRICUSPID STENOSIS

Because the tricuspid ring is so large, there are very few diseases that can cause enough obstruction to the opening of the leaflets—either by commissural fusion, fibrosis, and calcification or by vegetative mass—to result in tricuspid stenosis. Etiologies of tricuspid stenosis are presented in Table 23.1.

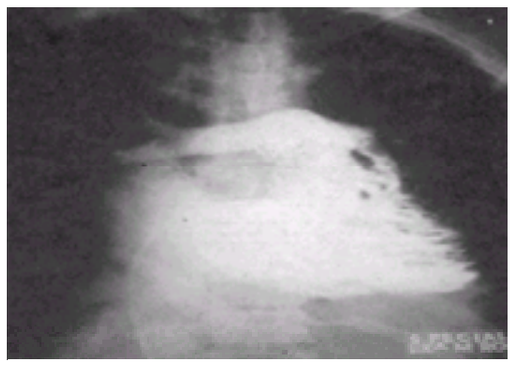
Rheumatic heart disease
Carcinoid heart disease
Metabolic abnormalities
Fabry's disease
Whipple's disease
Methysergide
Eosinophilic myocarditis (Loeffler's myocarditis)
Prosthetic valve thrombosis
Infective endocarditis
Prosthetic valve degeneration and/or calcification
Trauma produced by pacemaker leads or indwelling right-sided transvenous catheters
Tumors (differential diagnosis)
Right atrial tumors
Extracardiac tumors
Constrictive pericarditis

TABLE 23.1 DISEASES CAUSING ACQUIRED TRICUSPID STENOSIS

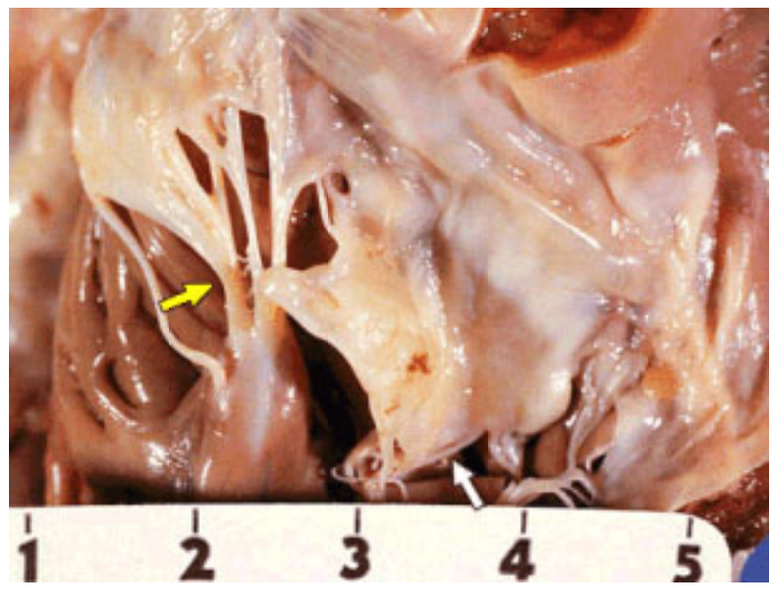
In more than 90% of cases, TV stenosis is caused by rheumatic heart disease. In 92 excisions of the TV for tricuspid stenosis reported by Hauck and colleagues (3), 85 (93%) were due to rheumatic heart disease.

Rheumatic tricuspid stenosis occurs almost always in association with mitral stenosis and is rare as an isolated finding (4). With rheumatic heart disease, the TV is involved pathologically in up to 67% of patients with MV disease (5). Functionally important TR occurs in 56%, combined TR/tricuspid stenosis occurs in 41%, and isolated tricuspid stenosis occurs in only 3% (3).

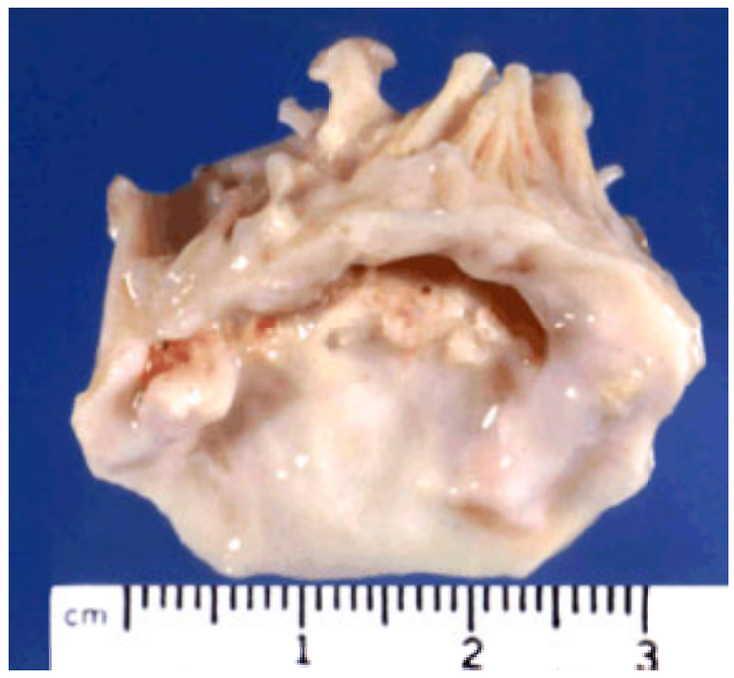
The pathology of tricuspid stenosis in rheumatic heart disease is similar to that of mitral stenosis (with diffuse leaflet thickening and fibrosis) and commissural fusion. Usually two or three of the commissures are fused (3,5,6). An autopsy specimen demonstrating rheumatic TV disease is shown in eFigure 23.0.1. Histologically, the leaflets are composed of fibrous collagen and elastic fibers. The chordae tendineae may be thickened and fused but less so than in mitral stenosis; although fibrosis and retraction of the valve is common, calcification is usually absent, unlike in mitral stenosis (6,7). The extent of the fibrosis and commissural fusion, together with the chordal fusion and leaflet retraction, determines whether the TV will be regurgitant, stenotic, or both.



***e*FIGURE 23.0.1** Rheumatic tricuspid valve disease. The chordae are fused and shortened. The leaflet edges are rolled, thickened, and fibrotic. [From Farb A, Burke AP, Virmani R. Anatomy and pathology of the right ventricle (including acquired tricuspid and pulmonic valve disease). *Cardiol Clin* 1992;10:1–21, with permission.]



Rheumatic disease of the tricuspid valve. Note the shortened cordae (*yellow arrow*) and thickened valve leaflet (*white arrow*).



Rheumatic mitral valve. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 23.1 Parasternal long-axis view of a rheumatic mitral valve with thickened, restricted, doming leaflets. Severe mitral regurgitation is the primary functional problem with this valve with only mild mitral stenosis. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 23.2 Parasternal long-axis view of a rheumatic mitral valve with color Doppler. Mitral regurgitation is the primary problem seen by color Doppler, with only mild mitral stenosis due to the thickened and doming leaflets. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 23.3 Apical four-chamber view of a patient with severe rheumatic mitral stenosis with marked thickening and doming of the mitral leaflets, with severe ALE and spontaneous echo contrast within the left atrium. Note the left ventricle remains small. Because of long-standing severe mitral stenosis, the patient has severe pulmonary hypertension with right ventricular hypertrophy and right ventricular failure and severe right atrial enlargement. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 23.4 Transthoracic right ventricular inflow view demonstrating rheumatic tricuspid valve disease. Note the doming of the tricuspid valve leaflets as well as their restricted closure causing both tricuspid stenosis and regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Carcinoid heart disease is the second most common etiology for tricuspid stenosis. It is almost always accompanied by TR. Carcinoid heart involvement occurs in 10% to 50% of patients with carcinoid syndrome (1,8,9 and 9a), depending on whether the patients with isolated carcinoid tumors are included or only those with a diagnosis of metastatic carcinoid tumors. Thus, the incidence of carcinoid heart disease depends on the method of diagnosis, either by physical examination or by Doppler echocardiography.

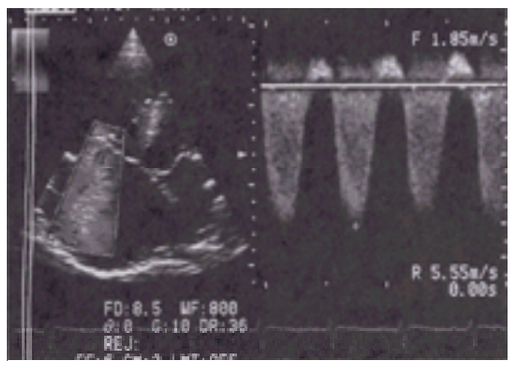
The primary site of origin for malignant carcinoid tumor is the gastrointestinal tract, including the appendix, ileum, small intestine, colon, and stomach. The tumor secretes vasoactive amines, including bradykinin, 5-hydroxytryptamine (serotonin), and histamine, which are responsible for the systemic manifestations of flushing, diarrhea, and bronchospasm. These substances are largely detoxified in the liver and, therefore, reach the right heart in low concentration. However, when the carcinoid tumor metastasizes to the liver, these substances are released directly into the hepatic venous system and reach the right heart in massive concentration; there, they cause endocardial injury, resulting in the development of fibrous plaques on the endocardium and on the surfaces of the TV and pulmonary valve. Plaques are mostly fibrous tissue, but they also contain smooth muscle cells, and there are no elastic fibers. They are present on the atrial and ventricular sides of the TV and on the arterial and ventricular sides of the pulmonary valve. The plaques are applied to, but do not destroy, the normal valve. However, the lesion can extend into the endocardium and myocardium (9b). The valves then become thickened and rigid, with a reduced valve area. An autopsy specimen demonstrating a TV in a patient with

carcinoid heart disease is shown in eFigure 23.0.2.

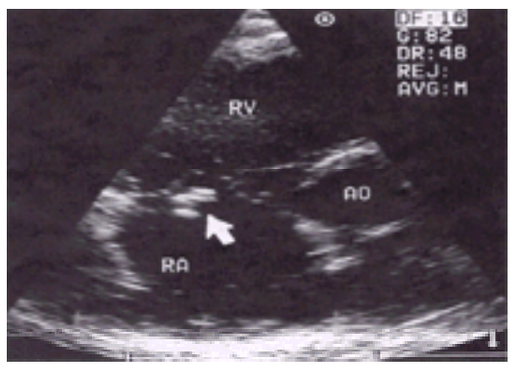
***e*FIGURE 23.0.2** Tricuspid valve from a patient with carcinoid heart disease who had severe tricuspid regurgitation. The valve leaflets are thickened, and the chordae are fused. Pathologically, the normal valve and endocardium are thickened by the deposition of plaques composed of a collagenous stroma rich in glycosaminoglycans but devoid of elastic fibers. [From Farb A, Burke AP, Virmani R. Anatomy and pathology of the right ventricle (including acquired tricuspid and pulmonic valve disease). *Cardiol Clin* 1992;10:1–21, with permission.]

Although it has been postulated that serotonin is the agent toxic to the endocardium, only recently has more direct evidence been found to support this assumption. Laudin and colleagues (9) reported the correlation of the functional severity of right-sided carcinoid heart disease to increased circulating levels of substance P and neural peptide and to an increased excretion of 5-hydroxyindoleacetic acid, a principal metabolite of serotonin. Robiolio and colleagues (10) reported strikingly higher serotonin levels in their patients with carcinoid heart disease compared with levels in their patients with carcinoid tumor and no cardiac involvement. Typical carcinoid syndrome symptoms were almost three times as common in the group with cardiac involvement as in the noncardiac group.

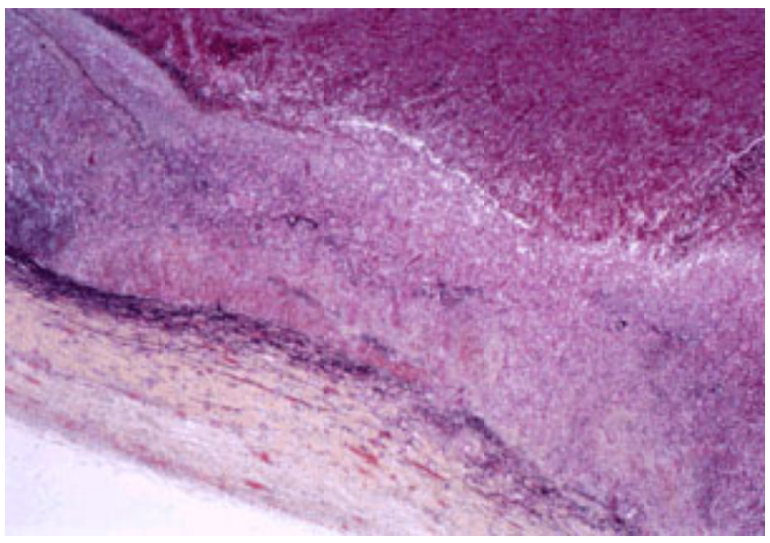
Other etiologies of TR/stenosis are much less common. Loeffler's eosinophilic myocarditis can affect both ventricles and frequently causes tricuspid and mitral valve insufficiency; however, it can so encase the TV that some degree of stenosis is also formed. There are two forms of eosinophilic syndrome: the tropical eosinophilic endomyocardial fibrosis and the nontropical eosinophilic endomyocardial disease (the type referred to in Loeffler's myocarditis). Both forms are characterized by peripheral blood eosinophilia and endocardial disease consisting of an eosinophilic infiltration, necrosis, and fibrosis causing thrombus formation and obliteration of the ventricular cavity by scar and thrombus (11–12a). The chordae tendineae and valves can be involved in this process. It is believed that the eosinophils produce cytotoxic substances that cause the myocardial necrosis (13). Marked eosinophilia from any cause—including parasites, leukemia, drug hypersensitivity, and allergic reactions—may be associated with endomyocardial disease. Eosinophilic myocarditis has also been seen associated with pregnancy (13a). It is believed that the disease seen in equatorial Africa and called *endomyocardial disease* is really an advanced form, or burnt-out stage, of Loeffler's myocarditis (14). Gross anatomic and microscopic specimens demonstrating Loeffler's myocarditis are shown in eFigure 23.0.3 and Figure 23.0.4, respectively.



***e*FIGURE 23.0.3** The right ventricle and tricuspid valve of a patient with Loeffler's myocarditis. A fibrous, opaque mass is visible at the apex of the right ventricle and involves the chordae tendineae and portions of the tricuspid valve. Tricuspid regurgitation occurs as a consequence of involvement of the valve leaflets, chordae, and papillary muscles with the myocarditis. (Courtesy of Renu Virmani, M.D.; from Cheitlin MD, MacGregor JS. Acquired tricuspid and pulmonic valve disease. In: Rahimtoola SH, Braunwald E, ds. *Atlas of heart diseases, vol. 11. Valvular heart disease*. St. Louis: Mosby, 1997, with permission.)



***e*FIGURE 23.0.4** Microscopic section of myocardium from a patient with Loeffler's myocarditis. A granuloma surrounded by eosinophils is present. (Courtesy of Renu Virmani, M.D.; from Cheitlin MD, MacGregor JS. Acquired tricuspid and pulmonic valve disease. In: Rahimtoola SH, Braunwald E, eds. *Atlas of heart diseases, vol. 11. Valvular heart disease*. St. Louis: Mosby, 1997, with permission.)



Loeffler's syndrome. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Finally, thrombosis or pannus formation on a prosthetic TV, calcification, and degeneration of a biologic TV can result in tricuspid stenosis (15,16 and 17). Occasionally,

large vegetations on an infected TV can cause obstruction (17a). Methysergide can cause endocardial fibrosis similar to that seen in carcinoid syndrome. Finally, severe tricuspid stenosis with calcification of the valve can be related to chronic trauma and has been reported in patients with permanently indwelling catheters across the TV for ventriculoatrial shunts (18), peritoneal venous shunts (19), and pacemaker leads (20).

VIDEO

Video 23.5 Four-chamber transesophageal view of a patient with a cystic-appearing mass on the tricuspid valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 23.6 Intraoperative transesophageal echo of a highly mobile echodensity seen on the tricuspid valve in a patient with lupus anticoagulant. On pathology, this turned out to be a calcified clot that had been present on the tricuspid valve for a long time, and the patient presented clinically with a pulmonary embolus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pathophysiology

When the TV becomes stenotic by fibrosis, disease, or commissural fusion, the blood flow from systemic veins and the right atrium into the right ventricle is obstructed; with atrial contraction against this stenotic valve, a large ‘a’ wave is seen. A pressure gradient develops between the right atrium and right ventricle in diastole. This results in a low-pitched diastolic rumbling murmur that is generated by the entire stroke volume crossing the obstructive valve under a low-pressure gradient. The gradient can be accentuated in inspiration, when there is an increase in systemic venous return to the right atrium and a drop in right ventricular filling pressure, and decreased in expiration; therefore, the murmur may become louder during inspiration and decrease in expiration. If the valve is flexible, a high-pitched tricuspid opening snap may be generated at the time of the opening of the TV (21). With severe tricuspid stenosis, there is a drop in cardiac output. With the elevation of pressure in the right atrium, right atrial dilatation occurs. With increasing right atrial pressure, systemic venous pressure, and systemic capillary pressure, edema develops, first in the dependent areas (e.g., the ankles) and then progressively advancing to the thighs, abdomen, and thorax. Finally, edema advances to the face, a condition known as *anasarca*. There is also the development of ascites and pericardial effusions (4,22).

HEART SOUNDS

Audio 23.7 Tricuspid stenosis and regurgitation. Note the holosystolic murmur of tricuspid regurgitation and soft diastolic blowing murmur of tricuspid stenosis. The loud second pulmonic sound connotes pulmonary hypertension. Apex. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

History and Physical Examination

In patients with tricuspid stenosis, the history depends on the severity of the tricuspid stenosis and the symptoms associated with the etiology and concomitant cardiac lesions. Therefore, patients with rheumatic heart disease almost always have concomitant MV disease, usually mitral stenosis. The symptoms of shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea due to the mitral stenosis may dominate the patient’s symptomatology (22). Decrease in cardiac output in the patient with severe mitral stenosis results in a lower-than-expected left atrial pressure and protects against pulmonary congestion (23).

In metastatic carcinoid tumors, the symptoms of flushing and diarrhea may be the most impressive symptoms. In the patient with mitral stenosis, atrial fibrillation and its concomitant palpitations may occur.

From the tricuspid stenosis alone, the symptoms alone are increased fatigability due to a decreased cardiac output and the effects of fluid retention and elevated systemic venous pressure. Edema—in the most severe cases, anasarca—may be the patient’s major complaint. Ascites and abdominal enlargement, hepatic distention, and right upper quadrant discomfort may dominate the history.

The physical findings due to tricuspid stenosis are an abnormally large ‘a’ wave in the jugular venous pulse. The ‘a’ wave occurs at the time of the first heart sound and is rapid-rising, resembling a carotid arterial pulse. The difference is that the ‘a’ wave can be eliminated by firm pressure on the jugular vein, whereas an arterial pulse cannot. The ‘v’ wave, without accompanying TR, is inconspicuous, and the ‘y’ descent is slow or absent (24).

The classic finding is that of a low-pitched diastolic murmur, usually along the left sternal border in the third and fourth intercostal spaces (25,25a). In sinus rhythm, it is most prominent at end diastole, whereas in atrial fibrillation, it is usually more prominent in early and mid-diastole. If the valve is flexible, an opening snap can be heard along the lower left sternal border, although this is more unusual than the opening snap heard with mitral stenosis. If the right atrium is very large, an impulse can be felt in diastole along the lower right sternal border. With pure tricuspid stenosis, there is no right ventricular lift.

Because mitral stenosis is almost always present when tricuspid stenosis is due to rheumatic heart disease, the physical findings of mitral stenosis (the diastolic murmur, the loud first heart sound, and opening snap at the apex) are more conspicuous than the findings of tricuspid stenosis. However, tricuspid stenosis should be suspected when mitral stenosis is present when the elevation in the jugular venous pressure is greater than the signs of pulmonary congestion and the patient complaints of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. The accentuation with inspiration of a diastolic murmur along the lower left sternal border is known as the *Rivero-Carvallo sign*; it is characteristic of tricuspid stenosis (26), even in the presence of mitral stenosis, in which inspiration does not affect the loudness of the murmur. Also, the presence of a large ‘a’ wave in the jugular venous pulse in the presence of mitral stenosis should raise suspicion of concomitant tricuspid stenosis. Because of the elevation in systemic venous pressure, there may be hepatomegaly, edema, or ascites. If the tricuspid stenosis is due to a metastatic carcinoid tumor, then a large nodular liver is frequently present, and a ruddy cyanotic flush of the face may be seen periodically.

HEART SOUNDS

Audio 23.8 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm2. Note the loud S1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border (*first clip*) and apex (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 23.9 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm2. Note the loud S1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border (*first clip*) and apex (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime*

you may download it here.

Laboratory Findings

Chest X-Ray

Cardiomegaly due to right atrial enlargement is frequent. The superior vena cava and azygous vein may be prominent. With pure tricuspid stenosis, the left atrium and right ventricle are not enlarged, and the pulmonary vascular markings are normal or decreased (23). With concomitant mitral stenosis, there is left atrial enlargement, although signs of pulmonary congestion are less prominent and without tricuspid stenosis.

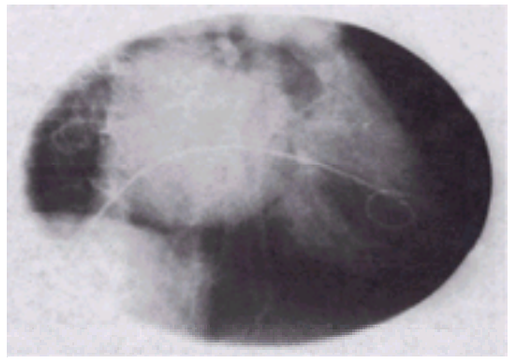
Electrocardiogram

A large, peaked P wave in lead II is consistent with right atrial abnormality. A peaked, broad, notched, or biphasic P wave with terminal negative potential in the V_1 lead is consistent with left atrial abnormality and may be present, especially if there is concomitant mitral stenosis. Atrial arrhythmias, especially atrial fibrillation, are often present with severe tricuspid or mitral stenosis.

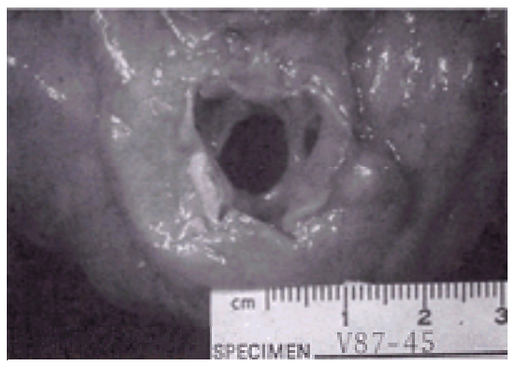
Doppler and Two-Dimensional Echocardiography

The findings on Doppler echocardiography depend on the etiology of the tricuspid stenosis. With rheumatic heart disease, the TV is domed in diastole. The leaflets are often thickened, with decreased mobility due to fusion along the commissures by the inflammatory process. The chordae tendineae may appear shortened and thickened. There is increased flow velocity across the TV in diastole; from this, by the modified Bernoulli equation, the diastolic gradient can usually be accurately estimated. With M-mode echocardiography, the E-F slope of the anterior leaflet is reduced, and there is increased reflectance from the valve. If rheumatic mitral stenosis or mitral regurgitation is present, the characteristic echocardiographic findings of these diseases can also be seen.

With carcinoid involvement, the valve is thickened and rigid, frequently fixed in the open position and acting like a washer, neither opening nor closing. Most often, TR is the predominant finding, along with an increase in diastolic velocity across the valve, with a reduced E-F slope that is consistent with tricuspid stenosis (8,27). A two-dimensional Doppler echocardiographic examination of a patient with carcinoid heart disease and tricuspid stenosis and regurgitation is shown in *e*Figure 23.0.5 and Figure 23.0.6.



***e*FIGURE 23.0.5** Two-dimensional echocardiogram of a patient with carcinoid heart disease and a thickened tricuspid valve (TV), which is both stenotic and regurgitant. The right atrium (RA) is markedly enlarged, and the atrial septum bulges to the left, indicating that the right atrial pressure exceeds the left atrial pressure—a finding consistent with tricuspid stenosis. RV, right ventricle; SL, septal leaflet.



***e*FIGURE 23.0.6** Doppler examination of the patient in *e*Figure 23.0.5 with carcinoid heart disease and tricuspid stenosis and regurgitation. The peak gradient is calculated to be 18 mm Hg, and the mean gradient is 10 mm Hg. RA, right atrium; RV, right ventricle; TV, tricuspid valve. (From Cheitlin MD, MacGregor JS. Acquired tricuspid and pulmonic valve disease. In: Rahimtoola SH, Braunwald E, eds. *Atlas of heart diseases, vol. 11. Valvular heart disease*. St. Louis: Mosby, 1997, with permission.)

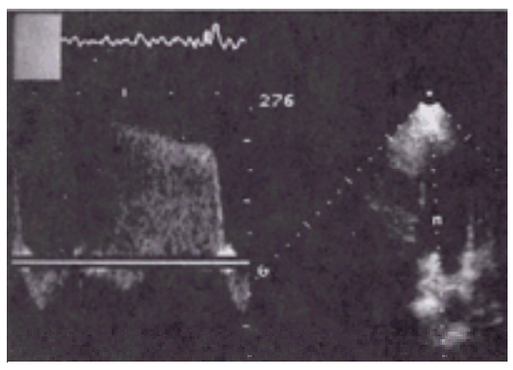
Echocardiography of stenotic bioprosthetic valves in the tricuspid position shows increased diastolic velocity, abnormal reflectance from the biologic leaflets, and, occasionally, calcification. Thrombus and vegetations from infective endocarditis can cause functional stenosis of a bioprosthetic valve. A large, obstructive vegetation on a bioprosthetic valve is shown in *e*Figure 23.0.7.

***e*FIGURE 23.0.7** A bioprosthetic valve in the tricuspid position is shown with a large, nearly obstructive vegetation. The Doppler examination is consistent with a gradient of approximately 20 mm Hg. The patient was an intravenous drug addict, and her blood cultures grew *Staphylococcus aureus*.

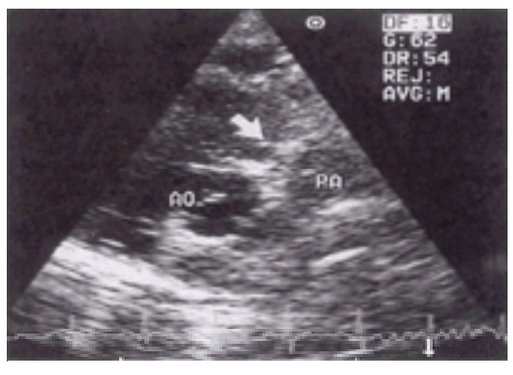
Echocardiography is particularly helpful in identifying those diseases that can simulate tricuspid stenosis, such as right atrial tumor, either growing up from the inferior

vena cava across the TV (e.g., renal carcinoma) or from a right atrial myxoma obstructing diastolic flow across the TV. A two-dimensional echocardiogram demonstrating a large tumor that almost totally obstructs the TV is shown in *e*Figure 23.0.8. *e*Figure 23.0.9 and *e*Figure 23.0.10 show the gross anatomic and microscopic features of this tumor, which was found to be a rhabdomyosarcoma.

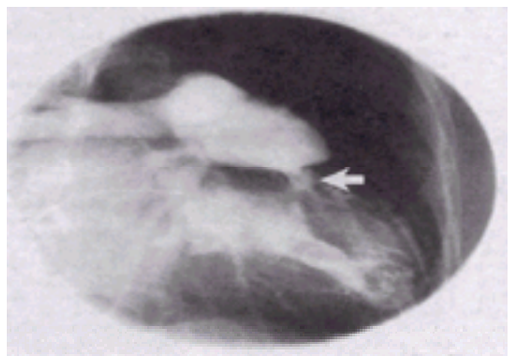
Video 23.10 Transesophageal echo of a large mobile mass seen in the right atrium, entering from the inferior vena cava. This patient had renal cell cancer that invaded the inferior vena cava. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 23.0.8** Two-dimensional echocardiogram of a large tumor that extends from the right atrium (RA) into the right ventricle and almost totally obstructs the tricuspid valve. This tumor produced a clinical syndrome of fatigue, malaise, abdominal distention, and edema that closely resembles the signs and symptoms found in patients with tricuspid stenosis. LA, left atrium; LV, left ventricle.



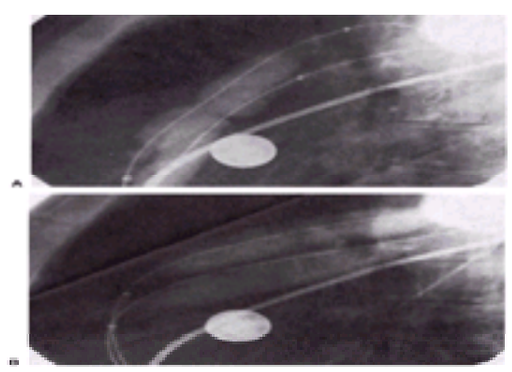
***e*FIGURE 23.0.9** Gross anatomic specimen removed at surgery from the patient described in *e*Figure 23.0.7. The tumor was adherent to the superior wall of the right atrium and measured approximately 8 cm in its longest dimension.



***e*FIGURE 23.0.10** Microscopic section of the tumor described in *e*Figure 23.0.8, stained with hematoxylin-eosin. The tumor was identified as a rhabdomyosarcoma.

Cardiac Catheterization

At the present time, the diagnosis and estimation of severity of tricuspid stenosis are made by physical examination and confirmed by Doppler echocardiography. Cardiac catheterization is usually not necessary. When catheterization is done, the right atrial pressure is characterized by a large ‘a’ wave with an inconspicuous ‘v’ wave and a slow ‘y’ descent. The cardiac output is low, and the right ventricular and pulmonary artery pressures are normal or low. The TV area is decreased, and clinical tricuspid stenosis does not occur until the valve area is reduced to approximately 1.5 cm^2. Depending on the cardiac output, the diastolic gradient can be quite low (3 to 5 mm Hg) and should be measured with simultaneous catheters in the right atrium and right ventricle (21). An example of right atrial and right ventricular pressure tracings in a patient with carcinoid heart disease and tricuspid stenosis is shown in *e*Figure 23.0.11. The gradient is accentuated by increasing the cardiac output and decreasing the diastolic filling period by exercising, lifting the legs, and increasing the heart rate with atropine. Because the gradient is so low, gradients estimated by pullback of the catheter across the TV from the right ventricle to the right atrium can miss significant tricuspid stenosis.



***e*FIGURE 23.0.11** Simultaneous right atrial (RA) and right ventricular (RV) pressure tracings in a patient with carcinoid heart disease and tricuspid stenosis and regurgitation. The diastolic pressure gradient is characteristic of tricuspid stenosis.

DIFFERENTIAL DIAGNOSIS OF TRICUSPID STENOSIS

Any disease that delays emptying of the right atrium in diastole can simulate tricuspid stenosis; this includes right atrial myxoma, which can prolapse into the tricuspid orifice in diastole and obstruct diastolic flow across the valve. In this situation, an early diastolic sound, or “tumor plop,” may simulate the opening snap of tricuspid stenosis. A tumor growing up from the inferior vena cava (e.g., renal cell carcinoma) can involve the TV and simulate tricuspid stenosis. Other intracardiac tumors, including lymphoma and sarcoma, can obstruct TV flow and mimic tricuspid stenosis. Constrictive pericarditis can involve primarily the right ventricle and stimulate tricuspid stenosis (27a).

Atrial myxoma. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Etiology of Tricuspid Regurgitation

In contrast to tricuspid stenosis, TR can be due to a number of different etiologies. Diseases affecting any part of the tricuspid apparatus can result in TR, including pathology of the annulus, leaflets, chordae, and papillary muscles of the right ventricular wall.

Video 23.11 Postoperative four-chamber transesophageal echo after tricuspid valve repair with placement of an annuloplasty ring. Note that although there is still prolapse of tricuspid valve tissue, there is only minimal residual tricuspid regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The etiologies of TR can be classified as (a) diseases causing pulmonary hypertension and right ventricular failure with tricuspid annular dilatation, or (b) primary diseases of the tricuspid apparatus (28). Table 23.2 lists diseases under each group. The most common etiology for TR is failure of the right ventricle due to pulmonary hypertension caused by left heart failure. Common causes of left heart failure are hypertension, coronary artery disease, mitral and aortic valve disease, and cardiomyopathy. Diseases causing an increase in pulmonary vascular resistance and pulmonary hypertension are listed in Table 23.2. The latest additions to this list have been acquired immunodeficiency syndrome (28a,28b) and anorexic drugs (e.g., fenfluramine or phentermine) (28c).

Diseases causing pulmonary hypertension
An left ventricular disease with left ventricular failure followed by right ventricular failure (coronary heart disease, cardiomyopathy, aortic stenosis and insufficiency, hypertension, mitral regurgitation)
Mitral stenosis
Pulmonary venous obstruction
Diseases causing an increase in pulmonary vascular resistance
Anorexic agents (e.g., fenfluramine or phentermine)
Acquired immunodeficiency syndrome
Primary pulmonary hypertension
Congenital heart disease with increased pulmonary vascular resistance (atrial septal defect, ventricular septal defect, patent ductus arteriosus)
Intrinsic pulmonary disease (chronic obstructive pulmonary disease, pulmonary fibrosis, pulmonary resections)
Collagen vascular disease (systemic sclerosis)
Sleep apnea and hypoventilation syndromes
Pulmonary emboli, acute and chronic
Diseases of the tricuspid apparatus
Rheumatic heart disease
Carcinoid heart disease
Trauma, penetrating and nonpenetrating
Infective endocarditis
Right atrial myxoma
Connective tissue disorders (Marfan and Ehlers Danlos syndromes)
Eosinophilic myocarditis
Right ventricular endomyocardial fibrosis
Prosthetic and bioprosthetic valve malfunction, both thrombotic and degenerative
Right ventricular myocardial infarction
Radiation therapy
Right ventricular cardiomyopathy (right ventricular dysplasia, Uhl’s disease)
Myxomatous tricuspid valve (tricuspid valve prolapse)
Congenital diseases (Ebstein’s anomaly, non-Ebstein’s tricuspid regurgitation, cleft tricuspid leaflet, atrioventricular canal defects)

TABLE 23.2 DISEASES CAUSING TRICUSPID REGURGITATION

The pathologic changes of the TV seen in rheumatic heart disease, carcinoid heart disease, and eosinophilic myocarditis have been described. Endomyocardial fibrosis is a rare disease that is found mainly in women. It is characterized by endocardial fibrosis that affects mainly the left ventricle (but also the right ventricle) and may involve the atrioventricular valves, causing mitral regurgitation or TR. It is also characterized by mural thrombus, which can obliterate the ventricular apices (28d). With TR, there is thickening, shortening, and increased stiffness of the valve without significant commissural fusion (29). With pulmonary hypertension, the tricuspid leaflets and chordae tendineae are normal. There is right ventricular hypertrophy, dilatation of the right ventricle and tricuspid annulus, and TR. Malalignment and decreased force of contraction of the papillary muscles are also factors (30). With right ventricular infarction—which is almost always associated with diaphragmatic wall infarction because the acute marginal artery from the right coronary artery is the major source of blood supply to the anterior wall of the right ventricle—there is infarction and, later, fibrosis of the right ventricular papillary muscles and dilatation of the right ventricle (31,32). With right ventricular cardiomyopathy or dysplasia and Uhl’s disease, which may be the most severe form of right ventricular dysplasia, the patient can present right ventricular failure and TR (33,34). Myxomatous changes in the TV are similar to changes seen in the MV, with thickening of the spongiosa and undermining support of the chordae tendineae insertions (3). The floppy TV is seen almost exclusively in the presence of a myxomatous prolapsing MV. The incidence of floppy TV in an autopsy population is as high as 3.2% of consecutive autopsies (35,36). An example of a myxomatous TV is shown in Figure 23.1. With connective tissue diseases like Marfan syndrome, there can be dilation of the tricuspid annulus, prolapsing valve leaflets, and elongated chordae (37).

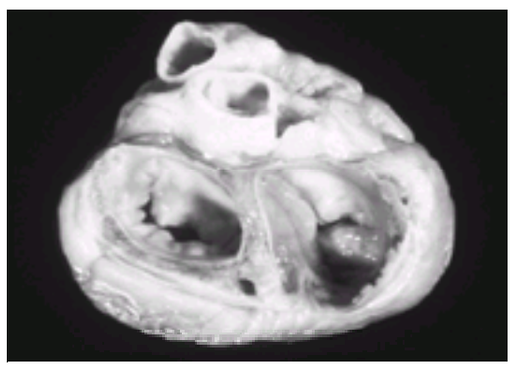
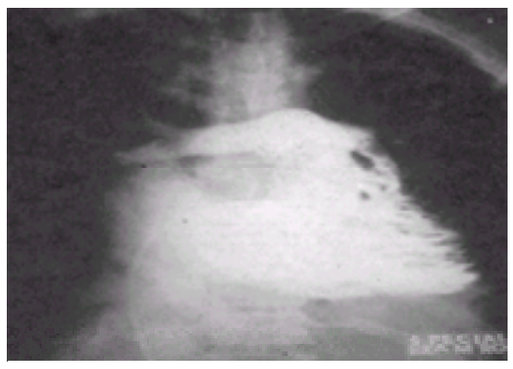


FIGURE 23.1 Autopsy specimen demonstrating the tricuspid valve (*right*) with three myxomatous prolapsed leaflets and the mitral valve (*left*) with both the anterior and the posterior leaflets myxomatous and prolapsed. (Courtesy of William Nelson, M.D.; from Cheitlin MD, MacGregor JS. Acquired tricuspid and pulmonic valve disease.

In: Rahimtoola SH, Braunwald E, eds. *Atlas of heart diseases, vol. 11. Valvular heart disease*. St. Louis: Mosby, 1997, with permission.)

Penetrating trauma can puncture the leaflets, rupture the chordae, or sever the papillary muscles (38). With blunt trauma (most frequently due to motor vehicle accidents), the right ventricle is the most common site of myocardial contusion. If right ventricular myocardial contusion is extensive, right ventricular failure and dilatation occur. With nonpenetrating injury (usually compressive injury or deceleration injury), complete fracture of the papillary muscles is not uncommon (39). A right ventriculogram from a patient with traumatic rupture of a tricuspid papillary muscle with resultant TR is shown in *e*Figure 23.1.1.



***e*FIGURE 23.1.1** Angiogram (posteroanterior projection) demonstrating severe tricuspid regurgitation in a patient with a ruptured tricuspid papillary muscle after an automobile accident. (From Cheitlin MD. The internist's role in the management of the patient with traumatic heart disease. *Cardiol Clin* 1991;9:675–688, with permission.)

Infective endocarditis is seen almost exclusively in intravenous drug users and, occasionally, in patients who have trauma to the TV from the jet of a ventricular septal defect or an indwelling catheter across the TV (Fig. 23.2). Chronic alcoholism and hereditary immunodeficiency disease are also associated with an increased incidence of tricuspid endocarditis (40,41). *Staphylococcus aureus* is the most common organism seen. Hecht and colleagues reported *S. aureus* to be responsible for tricuspid endocarditis in 82% of 132 cases seen in intravenous drug users (40). An autopsy specimen demonstrating a large vegetation on the TV is shown in *e*Figure 23.2.1.

VIDEO

Video 23.12 Transesophageal echo of a large tricuspid valve vegetation in a patient with infectious endocarditis. This patient was an intravenous drug user, which is common in patients with right-sided endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

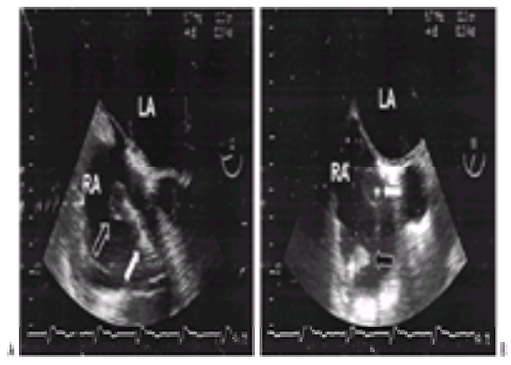
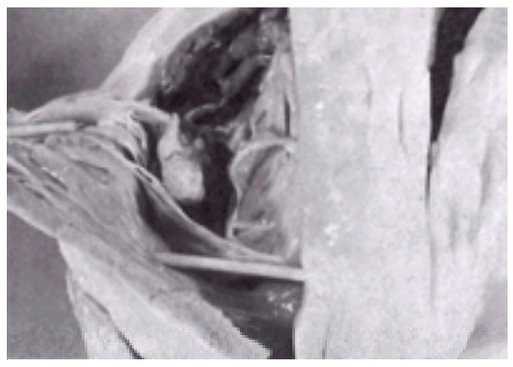
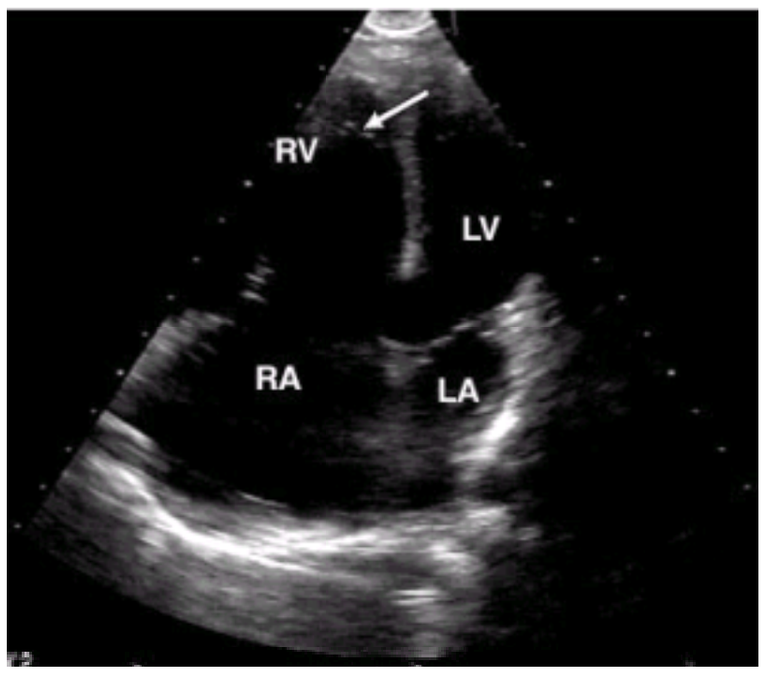


FIGURE 23.2 A: Transesophageal echocardiogram of a patient with right ventricular pacemaker wire and tricuspid valve endocarditis. The white arrow points to the pacemaker wire on tricuspid leaflet. The open arrow indicates vegetation/thickening on wire. **B:** Transesophageal echocardiogram of the same patient. The white arrow indicates the pacemaker on end with halo of thrombus, or vegetation, around it. The open arrow points to vegetation on tricuspid leaflet. LA, left atrium; RA, right atrium.



***e*FIGURE 23.2.1** Autopsy specimen with the right heart opened to demonstrate a large vegetation on the posterior leaflet of the tricuspid valve. Beta-hemolytic *Streptococcus* was isolated from blood cultures of the patient, who was an intravenous drug user. (From Cheitlin MD, MacGregor JS. Acquired tricuspid and pulmonic valve disease. In: Rahimtoola SH, Braunwald E, eds. *Atlas of heart diseases, vol. 11. Valvular heart disease*. St. Louis: Mosby, 1997, with permission.)

Congenital heart lesions (e.g., Ebstein's anomaly, primary TR, and cleft leaflets with endocardial cushion defects) are developmental defects due to malformation of the TV with displacement of the attachment of septal and posterior leaflets into the body of the right ventricle (e.g., Ebstein's anomaly) (28), tethering of the tricuspid leaflets (e.g., congenital non-Ebstein primary TR), or abnormal formation of the leaflets and clefting (e.g., endocardial cushion defects). Congenital lesions of the TV are not discussed further in this chapter.



Ebstein's anomaly of the tricuspid valve. Note marked apical displacement of the tricuspid leaflets, especially the septal leaflet. The arrow designates the septal leaflet of the tricuspid valve.

There are other etiologies of TR that are unusual, such as mediastinal radiation (42,43), systemic lupus erythematosus (44), and methysergide-induced valvular fibrosis (45).

Pathophysiology of Tricuspid Regurgitation

The primary problem in TR is the presence of a regurgitant orifice during systole, resulting in a jet of regurgitant blood from the right ventricle to the right atrium. This is the cause of the systolic murmur. When TR is secondary to pulmonary hypertension, the initial response to increased afterload on the right ventricle depends on the acuteness of the development of the pulmonary hypertension. If it is acute and sudden, as is the case with acute pulmonary embolism, the right ventricle suddenly dilates, and there is increased right ventricular wall stress and a marked increase in right ventricular filling pressure. The right ventricular annulus dilates, TR occurs, there is a marked drop in cardiac output, and there is no time for compensatory right ventricular hypertrophy to occur. In addition, with a sudden increase in right ventricular diastolic volume, there is a shift in diastole of the septum so that it bulges toward the center of the left ventricle. With an intact, stiff pericardium, the sudden increase in right ventricular volume occupies more space within the pericardial sac and, thus, interferes with the filling of the left ventricle. This leads to a decrease in stretch of the left ventricle and possibly a decrease in diastolic volume, thus decreasing left ventricular stroke volume (46,47,48 and 49).

When the pulmonary vascular resistance is gradually increased, and, therefore, pulmonary hypertension gradually develops, compensatory right ventricular hypertrophy occurs; without right ventricular dilatation, there may be little or no TR until right ventricular systolic dysfunction and right ventricular failure occur. With right ventricular dilatation, as the tricuspid annulus enlarges, there is reduction of the narrowing of the tricuspid os in systole and failure of coaptation of the TV leaflets (30,50). Displacement of the papillary muscles and alteration in direction of the chordal tension on the valve may also contribute to TR. With treatment and decrease in the volume of the right ventricle, the degree of TR can diminish or completely disappear.

With primary disease of the TV, chordae, or papillary muscles, the primary event is the development of a systolic tricuspid regurgitant jet into the right atrium, which causes a prominent 'v' wave, the height of which is related to the volume of the blood and compliance of the right atrial–systemic venous system. In diastole, the regurgitant volume is added to the systemic venous return, thereby increasing the diastolic right ventricular volume. The larger right ventricular volume causes the right ventricle to contract more forcefully, increasing the right ventricular stroke volume sufficiently to accommodate the regurgitant volume and maintain the effective stroke volume ejected into the pulmonary artery; therefore the cardiac output remains normal. With increased diastolic volume, there is increase in the diastolic wall stress, which is compensated for by eccentric right ventricular hypertrophy, finally resulting in a larger diastolic right ventricle with normal filling pressure. Eventually, right ventricular systolic dysfunction occurs, with failure of the right ventricle. With this, the diastolic filling pressure of the right ventricle increases, increasing the mean pressure in the right atrium and systemic veins and resulting in the clinical picture of right ventricular failure.

History and Physical Examination in Tricuspid Regurgitation

The patient with primary valve regurgitation can do very well for prolonged periods without significant symptomatology until right ventricular dysfunction occurs. Occasionally, the patient may notice active neck vein pulsations due to the marked 'v' wave in the jugular venous pulse (51). Even pulsating eyeballs have been reported by the patient (52). In the presence of pulmonary hypertension with right ventricular dilatation and TR, there is a marked decrease in the cardiac output and an increase in the mean right ventricular and right atrial filling pressures. This results in the signs of right ventricular failure: increased central venous pressure, hepatomegaly, edema, and ascites.

The clinical picture may be dominated by the symptoms related to the various etiologies of TR. If the patient has MV disease, the symptoms of pulmonary congestion may dominate the clinical picture. With severe TR and decreased cardiac output, there is reduction in left atrial pressure in a patient with mitral stenosis and, therefore, reduction in the symptoms of pulmonary congestion with a concomitant increase in easy fatigability and malaise. In patients with carcinoid syndrome, the systemic symptoms of facial flushing, diarrhea, and bronchospasm may predominate. In intravenous drug users with infective endocarditis, fever is the usual symptom that brings the patient to medical attention.

The physical examination is dominated by evidence of the regurgitant systolic jet and its effects. On palpation of the precordium, there is a precordial lift due to the increased diastolic right ventricular filling and increased right ventricular stroke volume. Depending on the severity of the TR and compliance of the right atrial–systemic venous system, there may be a large 'v' wave seen in the jugular venous pulse, with maximal height at the time of the second heart sound. It can be distinguished from a carotid pulse by pressure over the lower neck, which eliminates the 'v' wave but cannot change the carotid pulse. The descent of the 'v' wave, the 'y' descent, is rapid. With inspiration, the 'y' descent becomes more prominent due to a decrease in right ventricular pressure (53). With failure of the right ventricle, the mean central venous pressure is elevated, and the large 'v' wave occurs over and above the elevated mean venous pressure. Frequently, the external jugular vein is also distended when right ventricular failure occurs; this is not true when right ventricular function is normal, because the valves in the external jugular vein prevent the regurgitant blood from distending the vein. Because the systolic jet of regurgitant blood is directed mostly into the right innominate vein, there may be a peculiar right-to-left pulsation of the head that is different from the to-and-fro bobbing of the head seen in severe aortic regurgitation. Also, due to systolic distention of the cranial veins, pulsation of all veins—and even pulsation of the eyeballs—can be present (52). With auscultation over the jugular veins, a transmitted systolic murmur may be audible (54).

A pansystolic murmur is often present, usually in the third and fourth interspaces at the left sternal border and, occasionally, loudest to the right of the sternum or in the subxyphoid region. If the right ventricle is dilated, or if Ebstein's anomaly is present, the murmur may be heard best toward the apex and may be confused with the murmur of mitral regurgitation. The murmur may be increased with deep inspiration as a result of increased venous return and diastolic right ventricular filling with a more forceful contraction (the Rivero-Carvallo sign) (51). Other maneuvers, such as lifting of the legs or application of abdominal pressure (hepatojugular reflux), also increase venous return and increase the murmur (55). When the right ventricle can no longer respond with increased contraction to the increased venous return, the murmur does not augment. There may be a right-sided third and fourth heart sound gallop along the left sternal border, increasing in loudness with inspiration. Because of the increased diastolic flow across the TV, there may be a short, low-pitched, early diastolic rumble along the lower left sternal border. In patients with minimal TR, the systolic murmur may be short or inaudible. In patients with massive TR, because there is little pressure gradient between the right ventricle and right atrium in systole (the so-called ventricularization of the right atrium), the systolic murmur may be minimal or absent. Occasionally with TV prolapse, one or more nonejection clicks may be present at the beginning of the murmur; at times, the murmur may be vibratory, loud, and "honking" in quality.

If the TR is secondary to mitral or aortic valve disease, the auscultatory and other signs of mitral stenosis, mitral regurgitation, or aortic valve disease may be heard. With cardiomyopathy, there is frequently a left-sided third and fourth heart sound gallop, as well as mitral regurgitation. With pulmonary hypertension, a loud second heart sound, occasionally with a high-pitched diastolic murmur of pulmonary regurgitation, can be heard. With carcinoid heart disease, a large multinodular liver is commonly present. Atrial fibrillation is especially common with MV disease. Signs of right heart failure—with dependent edema, hepatomegaly, and, frequently, a pulsatile liver and ascites—may be present. With severe pulmonary hypertension and terminal right ventricular failure, cachexia and stasis cyanosis frequently are seen.

Laboratory Findings

Chest X-Ray

The effect on the cardiac silhouette depends on the severity of the TR. With severe pulmonary hypertension, there is frequently enlargement of the main pulmonary artery and primary branches. With further increases in pulmonary vascular resistance, the lung fields in the lateral third are diminished, and that part of the lung field is clear (pruning). The right ventricle is enlarged both anteriorly and to the left so that the retrosternal space is encroached upon. With dilatation of the right ventricle, the cardiothoracic ratio is increased, and the apex of the heart is formed by the dilated right ventricle. The right atrium may be enlarged to the right; with right ventricular failure, the azygos vein may be prominent as it enters the superior vena cava. A chest x-ray of a patient with severe TR and pulmonary hypertension is shown in Figure 23.3. With TR due to infective endocarditis, multiple infiltrations and densities in both lung fields due to septic embolic pulmonary infarction may be present. The appearance of the chest x-ray in patients with septic pulmonary emboli changes over time. Initially, multiple, peripherally based discrete nodules may be present. Depending on the identity of the infecting organism, these nodules may cavitate or become confluent diffuse infiltrates. An example of this process is shown in Figure 23.4. Hecht and Berger reported infiltrates compatible with septic pulmonary emboli in 72 (55%) of 132 patients with right-sided endocarditis (40).

FIGURE 23.3 Posteroanterior **(A)** and lateral **(B)** chest x-rays of a patient with pulmonary hypertension and severe tricuspid regurgitation. The pulmonary arteries and right heart are markedly enlarged.

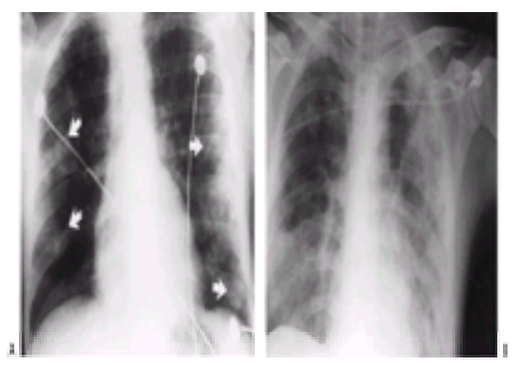


FIGURE 23.4 A: Chest x-ray (posteroanterior view) of a patient with infective endocarditis involving the tricuspid valve with septic emboli. Multiple, somewhat nodular, peripheral infiltrates are indicated by arrows. **B:** Chest x-ray of the same patient 2 days later (posteroanterior view). The relatively discrete nodules have now formed more confluent, diffuse infiltrates.

Electrocardiogram

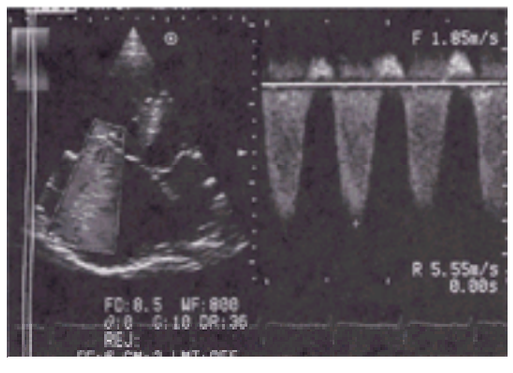
In isolated mild-to-moderate TR, the electrocardiogram may be normal. With moderate-to-severe TR and dilation of the right ventricle, an rSR' in the V_1 lead consistent with incomplete right bundle branch block and delayed activation of the right ventricle is seen. In normal sinus rhythm, a peaked P wave consistent with right atrial abnormality can be seen, but it is most common with TR due to pulmonary hypertension in which right ventricular hypertrophy is present. If mitral stenosis is the underlying etiology, biatrial abnormality or atrial fibrillation is present, as well as right ventricular hypertrophy.

Doppler Echocardiography

The findings on Doppler echocardiography depend on the severity of the TR, the presence of pulmonary hypertension, and the etiology of the disease producing the TR.

With minimal TR, the two-dimensional echocardiogram can be entirely normal. Pulsed-wave Doppler or color imaging shows the presence and direction of the regurgitant jet. An estimation of severity can be made by measuring the size of the regurgitant orifice, as outlined by the jet at the valve, and the area of the right atrium occupied by the turbulent and increased regurgitant jet velocities (56,57). Also, the detection of reverse blood-flow velocity in the inferior vena cava and hepatic veins is a measure of the severity of the TR (58). In severe TR, the shape of the velocity-time jet envelope is characteristically that of a dagger, with a high initial velocity and rapid dropoff due to rapid equalization of right atrial and right ventricular pressures in systole.

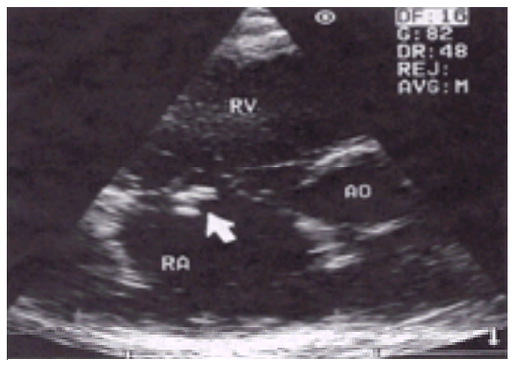
To quantify the regurgitant-jet velocities precisely, continuous-wave Doppler is needed. The peak pressure gradient from right ventricle to right atrium in systole can be estimated accurately by the modified Bernoulli equation (pressure gradient = 4 × velocity^2) (59,60). When added to the estimated jugular venous pressure (which equals the right atrial pressure), this formula gives an accurate estimate of right ventricular and pulmonary artery systolic pressure (PASP) in the absence of pulmonary stenosis. The literature suggests that PASP can be accurately measured in approximately 60% of patients. With attention to detail, a cardiologist, or even a well-trained echocardiographic technician, can obtain measurable TR signals—and, therefore, a measure of PASP—in more than 75% of patients (60a). A two-dimensional echocardiogram with Doppler and color-flow study for a patient with pulmonary hypertension is shown in *e*Figure 23.4.1. Injection of agitated saline or contrast intravenously causes microcavitations in the blood returning to the right heart, greatly enhancing the ability to visualize the regurgitant-jet velocities (2,61).



***e*FIGURE 23.4.1** Two-dimensional echocardiogram with Doppler and color-flow studies in a patient with pulmonary hypertension (same patient as in Fig. 23.3). The right atrium is enlarged, and the color flow reaches the most posterior portion of the right atrium. The Doppler shows a flow velocity of more than 4 m per second, corresponding to a systolic pulmonary artery pressure in excess of 64 mm Hg.

With moderate-to-severe TR, there is an increase in the size of the right atrium and right ventricle; with increased diastolic filling of the right ventricle, the interventricular septum is moved toward the center of the left ventricle in diastole. With rounding out of the left ventricle in systole, there is systolic “paradoxic motion” of the interventricular septum seen in right ventricular overload lesions (e.g., TR and atrial septal defect).

The echocardiogram can show dilatation of the TV annulus. In diseases affecting the TV itself, an echocardiogram can show thickening and increased reflectance caused by fibrosis, retraction and lack of coaptation of the leaflets, prolapse of the tricuspid leaflets and myxomatous changes (62), vegetations with infective endocarditis, and flail cusps due to ruptured chordae or papillary muscles. The thickened, immobile valve and fused chordae characteristic of carcinoid syndrome can also be detected (8,9a). With isolated right-sided infective endocarditis, the size of the vegetation is predictive of the development of a complication. In one study, vegetations >1.0 cm were present in 80% of tricuspid endocarditis in intravenous drug users. Vegetations >2.0 cm were associated with a significantly higher mortality than those £2.0 cm (33.3% vs. 1.3%; p <.001) (40). Furthermore, in right-sided infective endocarditis, the association of fever that persists for 3 weeks in the presence of a vegetation ³1.0 cm identifies those patients who require surgical intervention (62a). A two-dimensional echocardiogram demonstrating a large vegetation on the TV is shown in eFigure 23.4.2. Right atrial myxoma or thrombus can also be detected. With pulmonary hypertension, there is enlargement of the right ventricular outflow tract, right ventricular hypertrophy, and characteristic W-shaped motion of the pulmonary valve on M-mode echocardiography. There may also be pulmonary regurgitation.

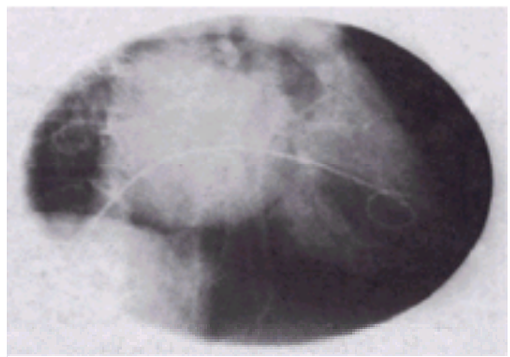


***e*FIGURE 23.4.2** Two-dimensional echocardiogram showing a large vegetation on the tricuspid valve (*large arrow*). The patient was an intravenous drug user with *Staphylococcus aureus* isolated from his blood. AO, aorta; RA, right atrium; RV, right ventricle.

Cardiac Catheterization

Invasive studies are not needed to make the diagnosis of TR or to estimate its severity. In the presence of a tricuspid regurgitant jet on echocardiography, the right ventricular and PASPs can be estimated accurately from the modified Bernoulli equation. With severe TR, there is a dominant ‘v’ wave in the right atrial pressure curve. With increasing severity of TR, the right atrial pressure becomes ventricularized and resembles the right ventricular pressure curve. An increase in right atrial pressure occurs on deep inspiration in patients with severe TR, especially with right ventricular systolic dysfunction (63). Right ventricular end diastolic pressure is elevated; with right ventricular failure, the mean filling pressures in the right ventricle and right atrium are elevated. Right ventricular and pulmonary artery pressures are normal or low in isolated TV regurgitation, but they may be elevated with septic emboli to the lungs. With diseases causing pulmonary hypertension, the pulmonary artery pressure and pulmonary vascular resistance can be accurately measured at catheterization. Usually the forward, or effective, cardiac output is normal or low, especially with severe TR.

With angiocardiography, injection of contrast is made in the right ventricle, films are taken in the right anterior oblique projection, and the tricuspid regurgitant jet can be seen and semiquantitatively estimated. However, because the catheter is across the TV and the injection produces premature ventricular complexes, there is the possibility of spurious TR (64). A right ventricular angiogram demonstrating severe TV regurgitation in a patient with carcinoid heart disease is shown in eFigure 23.4.3. Because calculation of right ventricular volume from angiography is unreliable (unlike left ventricular volume in mitral regurgitation), it is difficult to make an accurate estimate of regurgitant volume.



***e*FIGURE 23.4.3** Angiogram (right anterior oblique 30-degree projection) of the right ventricle in a patient with carcinoid heart disease and severe tricuspid valve regurgitation. The right atrium is densely opacified after contrast injection into the right ventricle. There is marked right atrial enlargement.

TREATMENT OF TRICUSPID VALVE DISEASE

Because most patients with tricuspid stenosis have rheumatic heart disease as the etiology, almost all have concomitant MV disease—mostly mitral stenosis. In these patients, indications for surgery or balloon valvotomy are mainly determined by the severity of the MV disease; however, tricuspid stenosis, when severe, can markedly reduce the cardiac output and cause severe limitation of physical activity, as well as eventually result in right-sided heart failure. Diuretics can be helpful, but, eventually, the valvular obstruction must be relieved. Until recently, with organic involvement of the TV, TV surgery, either commissurotomy or valve replacement, was necessary. Recently, there have been case reports (65) of balloon valvuloplasty in patients with tricuspid stenosis with encouraging results: The right atrial–right ventricular gradient has fallen, and the calculated TV area has increased. When mitral stenosis and tricuspid stenosis are both present, the valvotomy can be done with the same balloon (66,67). With the few cases and in the relatively short time the procedure has been available, it is not known whether balloon valvotomy will have long-term results equal to or better than those of open commissurotomy or TV replacement.

With tricuspid stenosis due to carcinoid syndrome, there have been reports of valve replacement (68,69); with tricuspid stenosis, there have even been attempts at balloon valvuloplasty (70). Connolly and colleagues (69) reported valve replacement in 26 patients with carcinoid TV disease. There were nine (35%) perioperative deaths, primarily from bleeding and right ventricular failure. Of the 17 survivors, eight were alive at a mean follow-up of 25 months, with substantial improvement in functional class. Late deaths were due to hepatic dysfunction due to metastatic disease. Compared to 40 patients with TV disease medically treated, the surgical group displayed a trend toward increased survival (69). In a review of the literature, Robiolio et al. described 47 carcinoid patients with valve replacement. The 30-day mortality was 56% in patients older than 60 years and 0% for those 60 years or younger (p <.001). Valve replacement in carcinoid syndrome has appreciable mortality but can afford prolonged palliation of symptoms (68).

With carcinoid heart disease, mechanical prosthetic valves were originally favored because of the fear that tissue valves would be damaged by the vasoactive carcinoid peptides (71). This has not proved to be the case (72). Bioprosthetic valves are now favored because of reduced incidence of valve thrombosis and, therefore, lack of need for systemic anticoagulation, because these patients are more prone to bleeding because of hepatic dysfunction (69). With the introduction of somatostatin and its derivatives—which inhibit the release of numerous peptides and improve symptoms and survival of patients with metastatic carcinoid tumors (73)—it is possible that the biologic tissue valves would be protected (69). Because of the small number of patients available, it is difficult to know what additional survival advantage there will

be with surgery, together with debulking of the tumor by hepatic artery embolization (74), in these patients with carcinoid heart disease.

Bioprosthetic valve degeneration with fibrosis and calcification, with or without thrombus, has been an indication for reoperation to replace the valve with a new prosthetic valve. However, there have been case reports of successful balloon valvuloplasty in patients with bioprosthetic TVs developing stenosis, with reduced right atrial pressure, increased cardiac output, and improved symptomatology (75,76 and 77).

Finally, in patients with thrombosed mechanical valves, there has been success in using fibrinolysis (78,79). The largest number of these studies has been of patients with mechanical left-sided valves, with a few patients with thrombosed mechanical TVs. Initial success rates of 75% have been reported, with a 15% to 20% incidence of rethrombosis (80). The danger with thrombolysis in left-sided valves is systemic embolization with serious consequences, such as stroke. The incidence quoted in the literature of systemic embolization occurring with thrombolysis in left-sided thrombosed valves is 15% (81,82). With the TV, there is probably also embolization to the lung, but so far, there have been no reports of clinically significant embolization, probably because the emboli have been small enough not to cause hemodynamic problems. At the present time, Silber and colleagues (81) suggest that thrombolysis is the treatment of choice for a thrombosed mechanical valve, even a thrombosed left-sided mechanical valve.

With TR due to organic involvement of the TV, it is generally agreed that surgical repair or replacement of the TV is necessary. Unfortunately, it is not always possible to tell preoperatively, even with two-dimensional Doppler echocardiography, that the TV regurgitation is due to organic TV disease. In a study of 306 patients requiring TV surgery, Duran (83) stated that only 42% were preoperatively diagnosed by Doppler echocardiography as having organic involvement of the valve, with the rest diagnosed only at the time of surgery. Similar findings were reported by Georgeson and colleagues (84).

In patients who have had surgery for MV stenosis, regression of pulmonary hypertension and a decrease in functional TR have been described (85). Patients with mild TR due to pulmonary hypertension usually do not need a surgical procedure (85,86). Eventually, numerous patients with mitral stenosis potentially have a reduction in pulmonary hypertension (87); however, whether moderate-to-severe TR in these patients will be reduced is not predictable (88). Porter et al. reported 65 patients with rheumatic heart disease who had undergone mitral valve replacement (MVR) between 1 and 30 years before. The predominant lesion was mitral stenosis in 44 patients and mitral regurgitation in 21 patients. Echocardiography showed significant late TR in 44 patients (67%), moderate TR in 16 patients (25%), and severe TR in 28 patients (43%). Age was the most significant predictor of TR likely to persist after MVR in patients with advanced right ventricular failure (88a). For these reasons, in patients with MV surgery with moderate-to-severe TR, an attempt at the time of surgery to reduce the TR with De Vega annuloplasty or TV replacement should be done (88). The same criticism has been raised after balloon valvuloplasty of mitral stenosis. Sagie and colleagues (89) studied 98 consecutive patients with balloon valvuloplasty for mitral stenosis who had Doppler echocardiography preoperatively. Thirty-two patients had moderate or severe TR before the valvuloplasty for mitral stenosis. There was a successful opening of the MV in 20 of the 32 patients. A follow-up study performed 18.4 ± 13.0 months after the procedure showed that TR did not improve in 88% of the patients, indicating that once significant TR has occurred, its persistence is less dependent on the pulmonary hypertension than on the pathologic change in the right ventricle.

With minimal distortion of the TV by organic disease or with moderate-to-severe TR in the patient with MV disease, MV surgery, together with repair of the TV with or without an annuloplasty ring, the De Vega annuloplasty procedure, is necessary. TV repair is successful in reducing perioperative and late mortality to approximately the same risk as the patient with MV surgery with minimal TR who did not have a TV procedure (90).

In Duran's study (83) of 306 patients requiring TV surgery, half of the subjects had organic TV disease. It was possible to repair the valve with annuloplasty in 291 patients (95%). Obviously, the success of annuloplasty depends on the expertise of the surgeon. Hospital mortality in this series was 7.5%, and actuarial survival was 77.7% at 48 months (83). Pellegrini and colleagues (90) studied 100 patients with MVR who required TV surgery. Late mortality was 15.4%, with actuarial survival of 85.6% at 5 years and 73.8% at 9 years; 8.6% required reoperation. In follow-up, whereas 97.0% were New York Heart Association (NYHA) class III or IV preoperatively, 90.4% were NYHA class I or II postoperatively. Bajzer et al. (90a) studied 401 patients who underwent TV surgery and other concomitant cardiac surgery, usually MV surgery. Ninety percent of the TV operations were annuloplasties. Overall 8-year survival was 50%. Decrease in survival was associated with higher preoperative NYHA class (relative risk, 2.02), increased left ventricular dysfunction by echocardiography (relative risk, 1.28), and use of TV replacement (relative risk, 2.92).

The long-term results of TV replacement reported in the past were not as good as with MVR. At least in part, this finding is related to the fact that patients with TV replacement are operated on at a later stage of their MV disease. Other reported reasons for poorer results are increased thrombosis seen in tricuspid mechanical valves and degenerative calcification seen in biologic valves (91). Van Nooten and colleagues (92) studied 146 consecutive patients undergoing TV replacement from 1969 to 1987, 69 of whom had bioprosthetic valves and 77 of whom had mechanical ball, disc, or bileaflet valves. Ninety-seven percent were NYHA functional class III or IV, and 40% had previous cardiac surgery. Hospital mortality was 16.1%. In a follow-up of 92 months, there were 70 late deaths, for an actuarial survival of 74% at 5 years and less than 25% at 14 years. Mortality was affected by the type of valve (mechanical worse than biologic), preoperative functional classification, and type of operative myocardial protection. The recommendation was that a large bioprosthetic valve was preferable to a mechanical valve (92).

A smaller study reported by Scully and colleagues (93) was of 60 patients, 47% of whom had bioprosthetic TV replacement and 53% of whom had mechanical valves. Eighty-two percent were NYHA functional class III or IV, and 25% had urgent operations. Hospital mortality was 27%. In a mean 75 ± 45 months' follow-up, there were 14 late deaths (32%)—nine with mechanical valve and five with bioprosthetic valve. Actuarial survival was 37% ± 9%; for hospital survivors, it was 50% ± 12% at 15 years. There were no significant differences in mortality or valve-related morbidity between the patients with mechanical valves and those with biologic valves (93). A retrospective study from the U.K. Heart Valve Registry identified 425 patients undergoing TV replacement, with 52.9% with biologic valves and 47.1% with mechanical valves. The 30-day mortality for TV replacement was 17.3%; 1-, 5- and 10-year survival rates were 72.2%, 59.9%, and 42.9%, respectively. Freedom from death or reoperation was 71.2% at 1 year and 41.9% at 10 years. There were no significant differences for survival or reoperation between biologic or mechanical prostheses (93a).

McGrath and colleagues (91) studied 154 patients with bioprosthetic valve replacement in the tricuspid position. Ninety percent had TR, and 10% had tricuspid stenosis or regurgitation; 54% had Carpentier-Edwards prostheses, and 35% had Ionescu-Shiley valves. Concomitant procedures were performed in 95% of cases. Preoperatively, 90% were NYHA class III or IV. There were 20 in-hospital deaths (13%). All survivors were followed for a mean of 66 months. There were 70 late deaths (52%), and the deaths were related to earlier date of surgery, more complex repairs requiring prolonged aortic occlusion, and signs of increased right heart failure. Valve-related events were thrombosis (1%) and endocarditis (2%). Seventeen patients (12.7%) had structural degeneration of the bioprosthetic valves, with 15 having a second operation at a mean of 74 months after the first operation. Actuarial freedom from TV replacement was 70% at 10 years. McGrath and colleagues concluded that patients with bioprostheses in the tricuspid position are at a relatively low risk for valve-related events but are at considerable risk for decreased overall survival from their underlying heart disease.

Jegaden and colleagues (94) studied 58 patients with TV bioprostheses (42 Hancock valves, 16 Carpentier-Edwards valves). Perioperative mortality was 12%, with an actuarial survival of 81% ± 11% at 5 years and 60% ± 17% at 10 years. In 21 patients after 88 ± 40 months of follow-up, the bioprosthesis was normal. In seven patients after follow-up of 129 ± 40 months, there was mechanical dysfunction of seven Hancock prostheses, with leaflet sclerosis and grade II TR. Only one patient had tricuspid stenosis. Jegaden and colleagues considered that the bioprosthesis in the tricuspid position had an acceptable long-term durability and that late valve dysfunction correlates with the length of follow-up of patients and the presence of fixed pulmonary artery hypertension (94). Others have similarly concluded that porcine bioprostheses have a remarkably low incidence of valve thrombosis, and valve durability is reasonable for up to 15 years in a population with limited life expectancy (94a).

Finally, although Duran (83) successfully repaired (rather than replaced) the TV in 291 (95%) of 306 patients with TV disease, there are significant problems. The annuloplasty ring is rigid, making systolic decrease in the tricuspid orifice impossible, and 30% to 70% of patients have some degree of tricuspid stenosis (95). This is obviously of greatest concern in children, in which fixation of the annulus does not allow for future growth. Because patients with TR secondary to MV disease and pulmonary hypertension unpredictably will have a decrease in TR with MV surgery, it is important to avoid an unnecessary permanent annuloplasty. To this end, Duran and colleagues are developing a time-limited annuloplasty made of biodegradable material. Recently, 2-0-polydioxanone was used as suture to perform a De Vega annuloplasty in sheep. In 5 months, the disruption of the sutures was advanced so that the tricuspid orifice dilated to its original size (95). Whether this will be useful in temporarily decreasing TR until annuloplasty is no longer needed is yet to be determined.

Tricuspid Regurgitation Due to Infective Endocarditis

TR caused by endocarditis is almost always seen in intravenous drug users; the etiologic organism most commonly is *S. aureus*, which readily responds to appropriate antibiotic therapy. TR can be severe, and if the pulmonary vascular resistance is normal, hemodynamically severe TR can be present with few or no symptoms. This condition is best seen in those patients who have resistant organisms such as *Serratia marcescens* or fungal endocarditis, in which removal of the infected valve without valve replacement allows for bacteriologic cure (96,97). Months or years later, a tricuspid prosthesis can be safely placed. As previously mentioned, in patients with TV endocarditis, persistent fever on antibiotics for more than 3 weeks and a vegetation ≥1.0 cm identifies those patients requiring surgical intervention (62a).

If pulmonary hypertension is present, as could be the situation with multiple septic emboli and hypoxia, then cardiac output decreases, exercise intolerance occurs, and right ventricular failure can occur rapidly. A less common problem is the development of a right-to-left shunt through a blown-open foramen ovale with arterial

desaturation and even cyanosis. There is also the possibility of systemic embolization.

Most patients with infective endocarditis of the TV are treatable with appropriate antibiotics and do not need TV replacement (40). Hecht and Berger (40), in their report of 132 episodes of right-sided endocarditis in intravenous drug users, had only one patient with an infected porcine TV who underwent surgery. There were ten deaths due to multiorgan failure, adult respiratory distress syndrome, pulmonary embolism, or persistent sepsis (40). If right ventricular failure occurs with severe TR, diuretics, preload reduction, digoxin, and afterload reduction can be initiated. In these patients, valvuloplasty or valve replacement is indicated (97a).

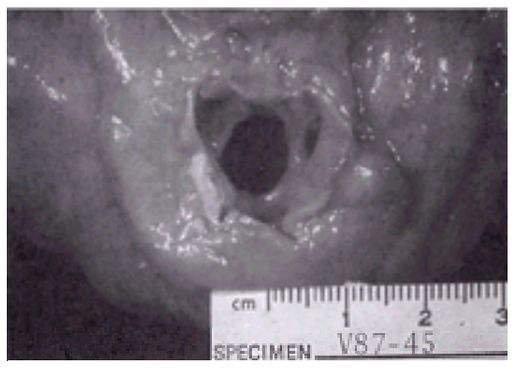
Treatment of Traumatic Tricuspid Regurgitation

TR can occur as a result of penetrating or nonpenetrating trauma to the valve, chordae, or papillary muscles. Right ventricular myocardial contusion can also occur, leading to right ventricular dilatation and TR. Because the pulmonary vascular resistance is usually normal, acute TR may be present without symptoms (98). Surgery to repair or replace the valve is indicated if progressive right ventricular dilatation and systolic dysfunction occur or if the patient develops right ventricular failure or exercise intolerance (39,98a).

Etiology of Acquired Pulmonary Valve Stenosis

With few exceptions, pulmonary valve stenosis is congenital in etiology (*e*Table 23.2.1). Of 116 excised pulmonary valves, 95% were congenital or associated with congenital heart disease, as reported by Altrichter (99). There are reported instances, however, of pulmonary valve stenosis due to rheumatic heart disease, but this is the rarest of all the rheumatic valve diseases. Carcinoid heart disease can cause pulmonary valve stenosis: of the 74 patients with carcinoid heart disease studied by Pellikka and colleagues (8), a murmur of pulmonary stenosis was noted in 24 patients (32%). Echocardiography showed valvular thickening and retraction or stenosis with narrowing of the pulmonary annulus in 36 patients (49%). The pulmonary valve was diminutive to where it could not be visualized in 29 of the patients (39%). In the 47 patients with carcinoid heart disease who underwent Doppler echocardiography of the pulmonary valve, regurgitation was seen in 81% and stenosis in 53% (8). The pathology is similar to that seen in carcinoid involvement of the TV, leaving the valve thickened, retracted, and immobile. A gross anatomic specimen from a patient with carcinoid heart disease and pulmonary stenosis and regurgitation is shown in *e*Figure 23.4.4.

***e*TABLE 23.2.1** DISEASES CAUSING ACQUIRED PULMONARY STENOSIS
Rheumatic heart disease (rare)
Carcinoid heart disease
Calcification of a congenitally abnormal pulmonary valve
Externally compromised pulmonary artery or right ventricular outflow tract by mediastinal mass



***e*FIGURE 23.4.4** Autopsy specimen showing the pulmonary valve from a patient with carcinoid heart disease and pulmonary stenosis and regurgitation. The cusps are thickened and deformed. (Courtesy of James B. Atkinson, M.D.; from Cheitlin MD, MacGregor JS. Acquired tricuspid and pulmonic valve disease. In: Rahimtoola SH, Braunwald E, eds. *Atlas of heart diseases, vol. 11. Valvular heart disease*. St. Louis: Mosby, 1997, with permission.)

Most acquired pulmonary stenosis is not valvular but the result of obstruction to the right ventricular outflow tract (100,101) or compression of the main pulmonary artery by mediastinal masses (100,102). Marshall and Trump (103) reviewed the literature reporting mediastinal masses causing acquired extrinsic pulmonary stenosis. Teratomas and Hodgkin's disease were responsible for more than 50% of the cases, although carcinoma of the lung, thymoma, pericardial sarcoma, and non-Hodgkin's lymphoma have all been reported.

Etiology of Acquired Pulmonary Regurgitation

All diseases of the left heart or lungs causing pulmonary hypertension can cause pulmonary valve regurgitation (*e*Table 23.2.2). In addition, rheumatic heart disease, carcinoid heart disease, trauma, infective endocarditis, and rheumatoid arthritis have all caused pulmonary valve regurgitation (104). Congenital dilatation of the main pulmonary artery can cause isolated pulmonary valve regurgitation (105,106). The most common etiology of acquired pulmonary valve regurgitation is the postoperative sequela of repair of pulmonary valve stenosis, tetralogy of Fallot, or pulmonary atresia (106a).

***e*TABLE 23.2.2** DISEASES CAUSING PULMONARY REGURGITATION
Diseases causing acquired pulmonary hypertension
Diseases of the pulmonary valve region or cusps
Rheumatic
Carcinoid
Trauma
Infective endocarditis
Rheumatoid arthritis
Idiopathic dilated pulmonary tract
Marfan syndrome
Postoperative pulmonary valve stenosis
Postoperative infundibulectomy/valvotomy for tetralogy of Fallot

Pathophysiology of Pulmonary Stenosis

With obstruction of the pulmonary outflow tract, there is increased afterload on the right ventricle, resulting in right ventricular hypertrophy. The degree of right ventricular hypertrophy depends on the severity and the duration of the pulmonary stenosis. In congenital pulmonary valve stenosis, infundibular stenosis, and even double right ventricle with anomalous pulmonary band obstructing the outflow tract, the obstruction is present from birth; therefore, with severe obstruction, right ventricular hypertrophy is almost always present.

With acquired pulmonary stenosis, the obstruction occurs gradually and is frequently not severe; thus, right ventricular hypertrophy is frequently not present. In carcinoid heart disease, for example, in 36 patients with pulmonary valve involvement (53% of whom had pulmonary stenosis), the gradients were 7 to 37 mm Hg (mean, 14 ± 9 mm Hg), and none of the patients had right ventricular hypertrophy (8). The same is true for external compression of the right ventricular outflow tract or pulmonary artery, causing pulmonary stenosis (100,101 and 102). Although large systolic pressure gradients across the right ventricular outflow tract can be generated (100), most of the patients had only a mildly dilated right ventricle on two-dimensional echocardiography.

Infants with severe pulmonary valve stenosis, especially those with right-to-left shunts through a blown-open patent foramen ovale, can have a high mortality. With congenital pulmonary valve stenosis, the patients have done well, with a low incidence of complications. In the Second Natural History Study of Congenital Heart Defects, 325 patients had a two-dimensional Doppler echocardiography examination. One hundred fifteen were followed medically, 209 had a valvotomy, and one had a pulmonary valve replacement. A visual estimate of right ventricular systolic function revealed 91% with normal right ventricular function, 8% with a modest decrease in right ventricular function, and 1% with severely depressed function. Eighty-eight percent of those with depressed right ventricular function were in the group who had a valvotomy (106b). With severe congenital pulmonary valve stenosis that remains surgically uncorrected, the most common cause of death is right heart failure as a result of systolic dysfunction, usually occurring after the fourth decade (107).

Pathophysiology of Pulmonary Valve Regurgitation

Isolated pulmonary valve regurgitation is rare; the most common form occurs after pulmonary valve surgery. In pulmonary valve regurgitation, there is a volume overload of the right ventricle, resulting in dilatation of the right ventricle and, eventually, eccentric right ventricular hypertrophy. With the increased right ventricular stroke volume, there is dilatation of the proximal pulmonary arteries. The regurgitant volume depends on the size of the regurgitant orifice, the diastolic filling period, and the pressure gradient driving the regurgitant volume from the pulmonary artery to the right ventricle. Other important factors are pulmonary artery distensibility and right ventricular compliance (105,106). With the large right ventricular stroke volume, a small systolic gradient can be generated, even without pulmonary stenosis (106). With severe pulmonary regurgitation, there is equalization of the pulmonary artery pressure and the right ventricular pressure in diastole. In the absence of pulmonary hypertension, even severe volume overload of the right ventricle is well tolerated for many years (108); however, the prognosis is not entirely benign, because right ventricular dysfunction and right heart failure can occur (109).

With pulmonary hypertension, the patient has right ventricular hypertrophy, and pulmonary regurgitation occurs with dilatation of the pulmonary valve annulus. The degree of the pulmonary regurgitation is usually not severe and is rarely hemodynamically significant. Right ventricular dilatation and dysfunction leading to right ventricular failure are more frequent in these patients as a result of the right ventricular systolic overload rather than as a result of the pulmonary regurgitation.

History and Physical Examination in Pulmonary Valve Stenosis

As stated before, the patient with pulmonary valve stenosis most often is asymptomatic. The patient may have symptoms such as palpitations and chest discomfort with acquired pulmonary stenosis, especially when the stenosis is caused by extrinsic or intrinsic compression due to mediastinal or cardiac masses.

The quintessential physical finding in the patient with pulmonary stenosis is a systolic ejection murmur that is usually loudest at the second and third interspaces at the left sternal border. The more severe the pulmonary stenosis, the louder the murmur and the later it peaks in intensity. With extremely tight pulmonary stenosis, especially with a decreased stroke volume, the murmur may become softer and higher pitched. Although the loud systolic murmur can be heard over the carotid arteries, it is weak compared to the similar loud murmur of aortic stenosis. As with most right-sided events, the loudness of the murmur of pulmonary stenosis may be increased by inspiration. If the valve cusps are flexible, as is usually the case in congenital pulmonary valve stenosis, there is frequently a systolic ejection sound that tends to increase in intensity with expiration and decrease with inspiration. This peculiar finding is explained by the fact that with inspiration, there is increased venous return to the hypertrophied right ventricle, with an increased end diastolic right ventricular pressure that decreases the gradient between the pulmonary artery and the right ventricular outflow tract in end diastole, placing the pulmonary valve in a semiopen position. With systole, the flexible cusps have less distance to go before they are checked by the fused commissures; the ejection click, therefore, is diminished in intensity. With expiration, the systemic venous return is decreased, the right ventricular end diastolic pressure falls, and the increased intrapleural pressure compresses the pulmonary arteries, increasing the pulmonary artery pressure. Thus, the gradient across the pulmonary valve just before systole is at maximum; with systole, the leaflet excursion is greatest, thus increasing the intensity of the ejection sound (109a).

HEART SOUNDS

Audio 23.13 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 23.14 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 23.15 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

With thickening of the pulmonary cusps, as is present with a dysplastic pulmonary valve or with carcinoid involvement of the pulmonary valve, there is no ejection click; the loud, harsh systolic ejection murmur is frequently followed by a short, harsh diastolic murmur.

With severe pulmonary stenosis, there is right ventricular hypertrophy, together with the precordial lift of right ventricular hypertrophy, and a right-sided fourth heart sound can be heard. Frequently, there is a prominent ‘a’ wave in the neck veins. With right ventricular dilatation and failure, the mean venous pressure rises, the jugular venous distention occurs, and the murmur of TR is heard with the signs of right ventricular failure.

History and Physical Examination of the Patient with Pulmonary Regurgitation

The symptomatology that the patient develops is dependent on the cause of the pulmonary regurgitation. Patients with pulmonary hypertension have symptoms related to the cause of the pulmonary hypertension; that is, with pulmonary disease or primary pulmonary hypertension, the patient with pulmonary hypertension can have syncope, dyspnea, hemoptysis, and right heart failure. The patient with mitral stenosis can have a history of orthopnea and paroxysmal nocturnal dyspnea. Patients with pulmonary regurgitation due to endocarditis have symptoms related to the infection such as fever, left heart failure if the mitral or aortic valve is infected, or septic pulmonary emboli with an infected TV. When the patient has pulmonary regurgitation due to carcinoid tumor, the symptoms are dominated by those seen with metastatic carcinoid tumor.

The patient with isolated pulmonary regurgitation has no symptoms if the regurgitant volume is small. With a large regurgitant volume, the majority of patients remains asymptomatic. Only 40% of patients with isolated pulmonary regurgitation present with exertional dyspnea, easy fatigability, and intermittent nonexertional left upper chest pain, possibly due to pounding of the enlarged main pulmonary artery and right ventricle against the chest wall (106).

The physical findings in isolated pulmonary regurgitation are those of a prominent right ventricular anterior precordial lift, frequently with a lift in the second left interspace that is caused by the dilated pulmonary artery and its exaggerated expansion due to the increased right ventricular stroke volume. There is also a diastolic murmur along the left sternal border in the second and third interspaces. With isolated pulmonary valve regurgitation, this murmur starts 0.04 to 0.06 seconds after the aortic second sound and is characteristically short and low-pitched (25a). The pulmonary second sound may be audible before the diastolic murmur. If the pulmonary valve cusp is fibrotic and retracted, the pulmonary second sound may be absent.

If pulmonary hypertension is present, the second heart sound is single and accentuated, and the diastolic murmur is high-pitched and decrescendo and cannot be distinguished from aortic regurgitation. This is called the *Graham-Steell murmur*.

If the pulmonary regurgitant volume is large, an early-peaking systolic ejection murmur ending before the second heart sound may be heard and can be grade III to

IV/VI in loudness. Such a systolic murmur was heard in 84% of isolated pulmonary valve regurgitation patients, accompanied by a systolic thrill in 10% (106). The murmur can be loud and late-peaking, sounding much like that in pulmonary stenosis. On rare occasions, a low-frequency late presystolic rumbling murmur (110) has been described, analogous to a right-sided Austin-Flint murmur. This murmur is said to increase with inspiration (110).

Laboratory Findings

Electrocardiogram

With pulmonary valve stenosis, the electrocardiogram reflects the hemodynamic severity of the lesion. With severe pulmonary stenosis, the electrocardiogram shows right axis deviation and right ventricular hypertrophy with a qR wave in the V_1 lead. With moderately severe pulmonary stenosis, there is an rSR' in the V_1 lead. With severe right ventricular hypertrophy, peaked P waves in the II, III, and augmented voltage unipolar left foot leads reflect right atrial abnormality (111). With acquired pulmonary stenosis, the obstruction is usually not severe, and the obstruction is present for a shorter period; therefore, severe right ventricular hypertrophy is less frequently present.

An 83-year-old female patient with hyperkalemia.

With TR with pulmonary hypertension, right ventricular hypertrophy is usually present. If the pulmonary regurgitation is an isolated lesion (which is very uncommon), and if the regurgitant volume is small, the electrocardiogram remains normal. With a large regurgitant volume, an rSR' may be seen in the V_1 lead.

Chest X-Ray

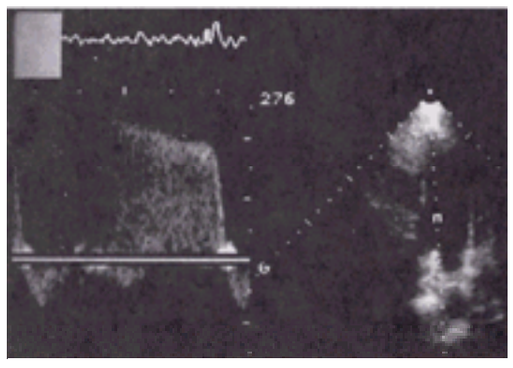
The chest x-ray with pulmonary valve stenosis shows poststenotic dilatation of the main pulmonary artery and, frequently, the proximal left pulmonary artery. With severe pulmonary stenosis, right ventricular hypertrophy manifested by lifting of the apex off the left hemidiaphragm and filling in of the retrosternal space in the lateral chest x-ray can be seen. With right ventricular failure, dilatation of the right ventricle results in an increased size of the cardiac silhouette in the posteroanterior film and encroachment of the retrosternal space. The chest x-ray of a patient with combined valvular and subpulmonary stenosis is shown in *e*Figure 23.4.5. With pulmonary regurgitation, dilatation of the main pulmonary artery with clear lung fields can be seen, together with right ventricular dilatation.

***e*FIGURE 23.4.5** Chest x-ray of a patient with combined valvular and infundibular pulmonary stenosis. The x-ray features are similar to those of pulmonary valve stenosis, including poststenotic dilatation of the pulmonary arteries and enlargement of the right heart.

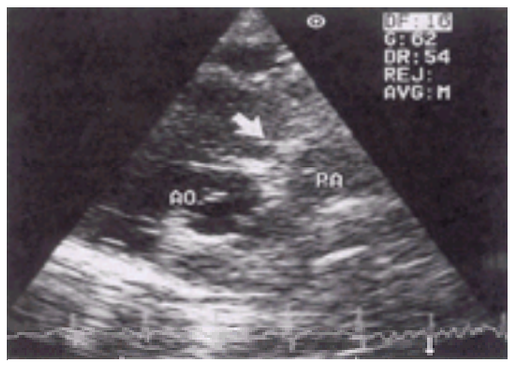
Doppler Echocardiography

With pulmonary stenosis, the two-dimensional echocardiogram, in the parasternal long-axis view and in the four-chamber view, can show right ventricular hypertrophy. Dilatation of the right atrium can be present, and the main pulmonary artery may be dilated in a short-axis view at the level of the aortic ring. At times, doming of the pulmonary valve can be seen. With carcinoid involvement of the pulmonary valve, thickening and lack of flexibility can be seen (8,10,27). With pulsed-wave and color Doppler echocardiography, the exact location of the obstruction to the right ventricular outflow tract can be seen, and obstruction can be seen locally at the valvular, subvalvular, or supravalvular level. Also, if there are masses, either intrinsic to the myocardium or extrinsic to the heart, these can be localized. With intrinsic masses causing obstruction to the right ventricular outflow tract, computed tomography and nuclear magnetic resonance imaging are extremely useful (112,113). With right ventricular failure, right ventricular dilatation and decreased contractility of the right ventricle can be seen. With continuous-wave Doppler echocardiography, the systolic gradient across the right ventricular outflow tract can be determined accurately by the modified Bernoulli equation (114).

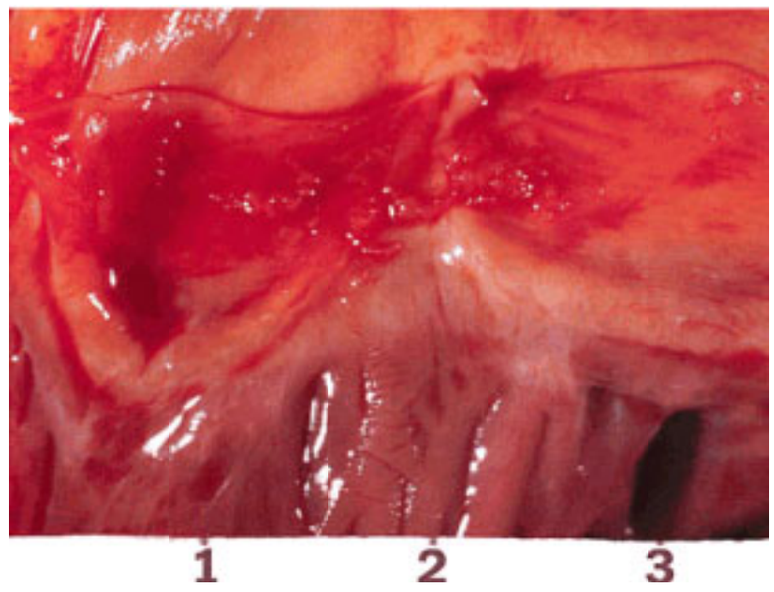
With pulmonary regurgitation due to pulmonary hypertension, right ventricular hypertrophy can be seen with dilatation of the main pulmonary artery. With pure pulmonary regurgitation, the right ventricle and the main pulmonary artery are dilated. With pulsed-wave and color Doppler echocardiography, the presence and magnitude of the pulmonary incompetence can be estimated both by the extent of the turbulence of the regurgitant jet in the right ventricle and by the width of the jet under the valve (115). Caution must be exercised because it is possible to detect minimal jets of pulmonary regurgitation in the majority of healthy people (116). With pathologic pulmonary regurgitation, the depth of the jet into the right ventricle is usually 1 to 2 cm below the pulmonary valve, and the duration of the jet usually occupies 75% or more of the entire duration of diastole (117). A Doppler echocardiographic examination demonstrating pulmonary regurgitation is shown in *e*Figure 23.4.6. Two-dimensional echocardiography is also useful in demonstrating vegetations on the pulmonary valve in patients with infective endocarditis (*e*Fig. 23.4.7).



***e*FIGURE 23.4.6** Doppler echocardiographic examination of the pulmonary valve demonstrating regurgitant flow in a patient with infective endocarditis. (From Cheitlin MD, MacGregor JS. Acquired tricuspid and pulmonic valve disease. In: Rahimtoola SH, Braunwald E, eds. *Atlas of heart diseases, vol. 11. Valvular heart disease*. St. Louis: Mosby, 1997, with permission.)



***e*FIGURE 23.4.7** Two-dimensional echocardiogram of an intravenous drug user with infective endocarditis involving the pulmonary valve. The large arrow points to the vegetation. *Staphylococcus aureus* was isolated from blood cultures. AO, aorta; PA, pulmonary artery.

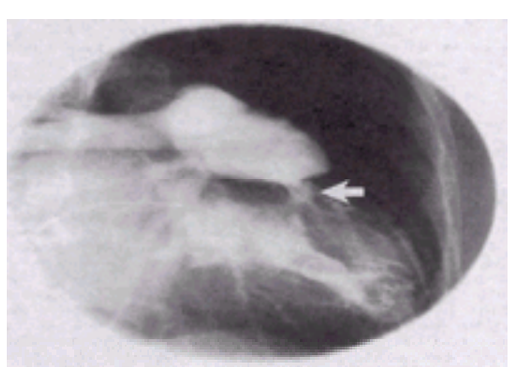


Marantic (nonbacterial) endocarditis of the pulmonic valve. Multiple vegetations are seen on the pulmonic valve in this patient with no bacterial growth from multiple blood cultures.

Catheterization and Angiocardiography

Catheterization and angiocardiography are usually not necessary in the diagnosis or estimation of severity of pulmonary stenosis or pulmonary regurgitation. However, in planning surgery (especially for an extrinsic mass), angiocardiography and coronary arteriography used to see the position of the coronary arteries in relationship to the extrinsic mass can be valuable. Cineangiography may be useful in localizing the level of pulmonary stenosis. A cineradiograph showing congenital pulmonary valve stenosis is shown in Figure 23.5. The domed appearance is characteristic of pulmonary valve stenosis, and the right ventricular outflow tract shows no infundibular stenosis. In eFigure 23.5.1, the pulmonary valves are normal, and the pressure gradient of 160 mm Hg between the right ventricle and pulmonary artery is due to infundibular stenosis. With pulmonary stenosis, the exact position of the obstruction can be seen; with pullback across the right ventricular outflow tract, the gradient can be accurately calculated. With pulmonary hypertension, pulmonary vascular resistance can be accurately measured. With angiocardiography and an injection into the right ventricle in the posteroanterior and left lateral views, the outflow tract, pulmonary valve, and main pulmonary artery can be seen, and the flexibility of the pulmonary valve can be judged.

FIGURE 23.5 Right ventricular angiogram (left lateral projection) of a patient with congenital pulmonary stenosis. The doming pulmonary valve (*top*) is characteristic of congenital pulmonary valve stenosis. The right ventricular outflow tract shows no infundibular stenosis. (From MacGregor JS, Ports TA. Catheter balloon valvuloplasty. In: Parmley WW, Chatterjee K, eds. *Cardiology: physiology, pharmacology, diagnosis*. Philadelphia: Lippincott, 1993:1–24, with permission.)



***e*FIGURE 23.5.1** Right ventricular angiogram (right anterior oblique projection) of a patient with infundibular subpulmonary stenosis. The pulmonary valve in this patient is normal, and the open leaflets are seen as thin, dark shadows above the infundibular stenosis (*arrow*) in this end systolic frame. The pressure gradient between the right ventricle and pulmonary artery was 160 mm Hg. The pulmonary artery is dilated and distal to the stenosis, and the right ventricle is enlarged and hypertrophied.

With pulmonary valve regurgitation, if the regurgitation is severe, the pulmonary artery pressure curve becomes ventricularized and takes on the configuration seen in the right ventricle, with end diastolic pulmonary artery pressure and right ventricular end diastolic pressure equilibrating. Evaluation of pulmonary regurgitation by angiocardiography is more difficult because the catheter is across the pulmonary valve; with injection into the pulmonary artery, any regurgitation into the right ventricle may be artifactual. Here, Doppler echocardiography is more reliable.

It is also possible to quantify the magnitude of pulmonary regurgitation by radionuclide angiography with the inversion of the left ventricular stroke volume–right

ventricular stroke volume ratio, called the *radionuclide regurgitation index*. In patients with pulmonary valve regurgitation, this index is usually 0.59 ± 0.23, which is significantly different from that seen in control subjects (1.49 ± 0.32) (118).

Treatment

With pulmonary stenosis, the prognosis depends on the etiology. With pulmonary valve stenosis that is mild or moderate, the patient does well without surgery. In the minority of cases, the degree of stenosis increases in severity with growth of the patient (119). With severe unrepaired pulmonary stenosis, right ventricular failure most commonly occurs after the fourth decade (107). With severe pulmonary valve stenosis, surgical repair in the past has given good long-term results, usually with residual moderate pulmonary regurgitation. If the operation occurs in childhood, the patient's long-term survival is similar to that of age-and sex-matched controls (120). In adults, long-term prognosis is not as good after surgery because right ventricular dysfunction can still lead to late-life right ventricular failure and death.

At present, balloon valvotomy is the treatment of choice, even in the adult with congenital pulmonary valve stenosis. Immediate and intermediate results are similar to those of surgery (121). Simultaneous right ventricular and pulmonary artery pressure tracings are shown in Figure 23.6 for a patient with congenital pulmonary stenosis. The pressure tracing on the left was obtained before pulmonary valvuloplasty, and the tracing on the right was obtained immediately after balloon valvuloplasty. The peak gradient after the procedure had decreased by 162 mm Hg. The sequence of balloon inflation is demonstrated in *e*Figure 23.6.1.

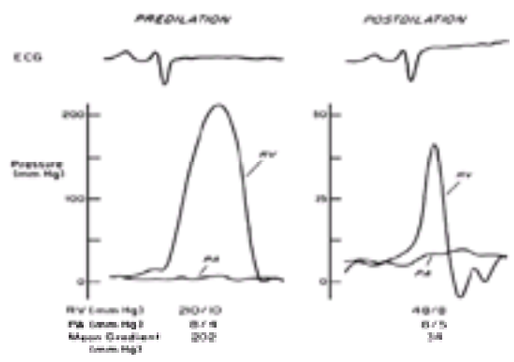
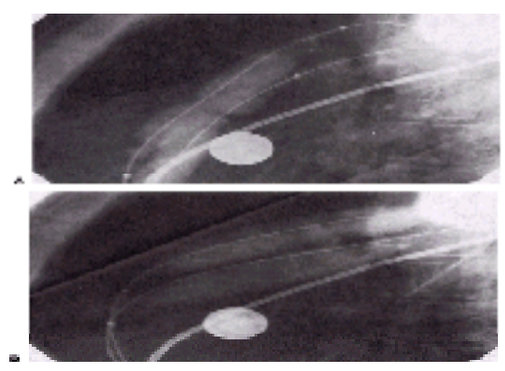


FIGURE 23.6 Simultaneous right ventricular (RV) and pulmonary artery (PA) pressure tracings in a patient with congenital pulmonary stenosis before (*left*) and immediately after (*right*) percutaneous balloon valvuloplasty. The mean pressure gradient across the pulmonary valve fell by 168 mm Hg after the procedure. ECG, electrocardiogram. (From MacGregor JS, Ports TA. Catheter balloon valvuloplasty. In: Parmley WW, Chatterjee K, eds. *Cardiology: physiology, pharmacology, diagnosis*. Philadelphia: Lippincott, 1993:1–24, with permission.)



***e*FIGURE 23.6.1** Cineradiographs showing the sequence of pulmonary balloon valvuloplasty in the left lateral projection. **A:** Two balloons are partially inflated across the stenotic pulmonary valve. A point of constriction is present in the middle of the balloons at the site of the stenosis. **B:** The balloons are fully inflated, and the constriction is no longer present. A penny (19 mm in diameter) is in the field to help estimate the diameter of the pulmonary annulus. The balloons in this case were 20 mm and 18 mm in diameter; both were 5 cm in length. (From MacGregor JS, Ports TA. Catheter balloon valvuloplasty. In: Parmley WW, Chatterjee K, eds. *Cardiology: physiology, pharmacology, diagnosis*. Philadelphia: Lippincott, 1993:1–24, with permission.)

With carcinoid heart disease, the prognosis is very poor (27). In the report by Pellikka and colleagues (8), in 74 patients with carcinoid heart disease, the median survival was 1.6 years. Balloon valvuloplasty has been reported in carcinoid pulmonary stenosis (68,70), but with the thickened, immobile valve, it is frequently unsuccessful, and valve replacement (rather than valvuloplasty) has been recommended (122). With extrinsic or intrinsic compression, surgical removal of the mass—or radiation therapy, if the neoplasm is sensitive—is indicated.

With pulmonary regurgitation, surgery is rarely necessary (106). Treatment of the primary condition is indicated; for instance, with pulmonary regurgitation due to pulmonary hypertension from mitral stenosis, valvuloplasty of the MV is needed. With endocarditis, treatment of the infection is necessary. If the pulmonary valve regurgitation is severe and right ventricular systolic dysfunction or failure is present, diuretics and digitalis are helpful, and pulmonary valve replacement is indicated (106a).

CONTROVERSIES AND PERSONAL PERSPECTIVES

As with left-sided valve replacement, a durable nonthrombotic prosthetic valve to be used in the pulmonary or tricuspid position would be a major advance in the treatment of severe TR or pulmonary regurgitation. TR secondary to pulmonary hypertension due to mitral stenosis or some other left-sided lesion may diminish or disappear after treatment of the left-sided lesion. An annuloplasty that would spontaneously reverse after a period of time, as suggested by Duran, could avoid the problems of a permanent annuloplasty ring, which can create relative tricuspid stenosis, especially if placed in children or adolescents. With the increased popularity of the Ross procedure (123), in which the patient's pulmonary valve is used to replace a diseased aortic valve and a bioprosthetic valve is placed in the pulmonary area, the question of how long the tissue valve will function in the pulmonary position will become increasingly important with continued investigation. Recent research of growing the patient's fibrocytes in cell culture on a biodegradable scaffold shaped in the form of a semilunar valve promises, one day, to lead to a bioprosthetic valve of the patient's own tissue, which could be as free of complications and as durable as the patient's original valve. Continued investigations of medications that reverse the vasoactive effects of amines produced in the patient with metastatic carcinoid tumor and of whether this approach will prevent tissue valves placed in the tricuspid or pulmonary regions from becoming diseased are important in the treatment of carcinoid heart disease. Continued investigation into possible vasoactive drugs that can reduce pulmonary resistance in patients who have severe pulmonary hypertension, as well as the development of successful lung transplantation, will be important in the control of severe functional TR. Finally, the most important advance to decrease the incidence of TR from infective endocarditis is in the control and eradication of intravenous drug use, which may be the most intractable problem of all.

THE FUTURE

The development of a durable nonthrombotic prosthetic valve would be a major advance in the treatment of severe tricuspid and pulmonary regurgitation. Research into developing a bioprosthetic valve of the patient's own tissues is promising a valve as durable and free of complications as the patient's own valve. Continued investigation into medical therapies for disease processes such as metastatic carcinoid tumor and pulmonary hypertension, as well as the successful development of lung transplantation, will be important in the treatment of tricuspid and pulmonary valve disease. The control and eradication of intravenous drug use would be the most important step toward decreasing the incidence of TR from infective endocarditis.

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24

PROSTHETIC VALVE DISEASE

MARIO J. GARCIA

"Indicates text or graphics that appear only in the electronic versions of this text."

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HISTORICAL PERSPECTIVE

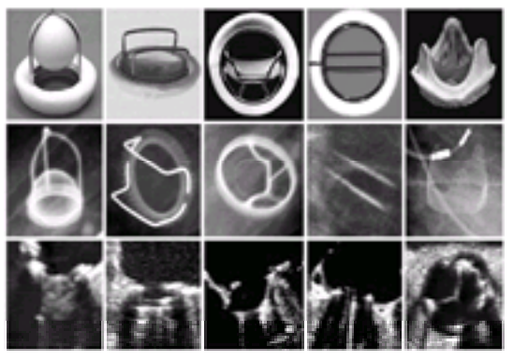
After a decade of research, in 1952 (1) Charles Hufnagel successfully inserted the first prosthetic valve in the descending aorta of a patient with aortic regurgitation. Since then, more than 80 different types of heart valve prostheses have been developed. Valve replacement surgery today represents the primary treatment modality for most types of valvular heart disease and is performed in 60,000 Americans each year.

Shortly after the introduction of the pump oxygenator in cardiac surgery, the first aortic valve replacement was performed by Harken (2) in 1953, and the first mitral valve replacement was performed by Starr (3) in 1960. The bare-strut ball valves that were initially used underwent further refinement for the next several years, leading to the development of the Starr-Edwards ball-and-cage valve. The first nontilting-disc valves were introduced shortly afterward, in an attempt to improve the profile of the ball-and-cage valve in the mitral and tricuspid positions. Although these are no longer implanted, nontilting-disc valves such as the Kay-Suzuki, Kay-Shiley, and Beall valves are occasionally found in a patient (4). The tilting-disc valves developed in the late 1960s represented a significant advance, demonstrating a hemodynamic performance far superior to that of the ball-and-cage and nontilting-disc valves. The Björk-Shiley (5) and Lillehei-Kaster (6) hingeless tilting-disc valves had a basic design similar to that of the Medtronic-Hall prosthesis that is commonly used today (7). Double-leaflet hingeless tilting-disc valves were developed in the early 1970s, and in 1977 the first St. Jude Medical bileaflet mechanical prosthesis (8) was made available for clinical use, becoming the most popular mechanical heart valve over the last two decades.

The undesirable thromboembolic complications of the mechanical valves raised interest in the development of tissue valves. The first tissue valve was an aortic homograft inserted by Ross in 1962 (9). The limited availability of fresh homografts made their use impractical until the development of cryopreservation in 1987. Advances in methods of preservation led to the development of the stented porcine valve xenografts, first implanted in 1965 by Carpentier (10) and later marketed as the Hancock and the Carpentier-Edwards valves. Although these valves eliminated the need for anticoagulation, they were limited to suboptimal hemodynamic performance at smaller sizes because of the bulk and position of their supporting stents. The Ionescu-Shiley (11) and the Carpentier-Edwards bovine valve, which were fashioned from bovine pericardium, were later developed to improve the hemodynamic profile of the tissue heterografts. Aortic homografts, aortic pulmonary autografts (12), and, more recently, stentless porcine valves are capable of providing hemodynamic performance comparable to that of native valves, although these are mostly available for use in the aortic position and have less durability than mechanical valves. A few institutions have limited experience with the use of a mitral valve homograft (13). The long-term results of this operation still need to be determined. Thus, efforts to improve the design and performance of prosthetic valves continue, because none of the options currently available can match the hemodynamic performance, durability, low risk of infection, and low thrombogenicity of native human valves.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

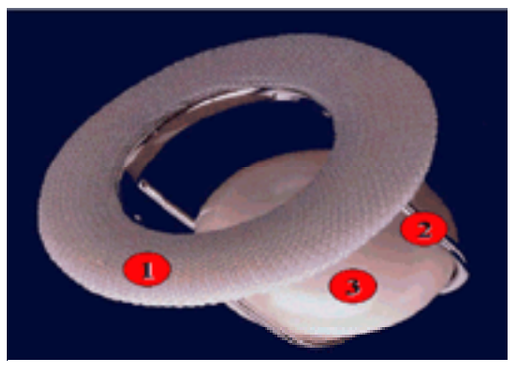
Prosthetic valves are classified into two major subgroups: mechanical prostheses and tissue prostheses. The predominant advantages of mechanical prostheses are higher durability and better hemodynamic performance. The main disadvantage is higher thrombogenicity, which necessitates the use of long-term anticoagulation. Each valve within these groups has unique design characteristics that convey specific differences in performance, durability, and thromboembolic risk. These variations in design translate into auscultatory, radiographic, and echocardiographic findings that make identification of these prostheses possible and, most important, permit recognition of changes that may represent prosthetic malfunction (eFig. 24.0.1).



***e*FIGURE 24.0.1** Photographic (*top row*), radiographic (*middle row*) and echocardiographic (*bottom row*) appearance of different mechanical and bioprosthetic valves. From left to right: Starr-Edwards ball and cage, Kay-Suzuki disc and cage, Björk-Shiley single-tilting disc, St. Jude's Medical bileaflet tilting-disc mechanical valves, and Carpentier-Edwards xenograft. (Radiographs are provided courtesy of Dr. Carolyn van Dyke.)

General Principles

Valve prostheses have three main components: a sewing ring, a supporting strut, and an occluder device (eFig. 24.0.2). Sewing rings are constructed from metallic alloys or plastics and covered with a cloth through which sutures are passed to implant the valve to the annulae fibrosa. These rings are common to all prosthetic devices, with slight variations in the frame and cloth materials. The size of the prosthesis is determined by the diameter of the suture ring. The type of occluder determines the anatomic and functional characteristics of each valve type. The occluders may be composed of plastic balls or discs in a metallic cage, single or dual tilting discs, or biologic tissue mounted in a frame. Each type of prosthesis has specific features that may permit its recognition by means of auscultation, two-dimensional and Doppler echocardiography, or cinefluoroscopy.



***e*FIGURE 24.0.2** Basic components of a prosthetic valve: (1) sewing ring, (2) supporting strut, and (3) occluder. Example of a Starr-Edwards valve.

Magnetic resonance imaging can be performed safely in most patients with prosthetic valves (14). This test may be of clinical advantage in patients in whom valvular regurgitation is suspected when the results of Doppler echocardiographic studies are inconclusive (15,16). Uncommonly, invasively obtained catheter gradients are needed to determine prosthetic valve dysfunction. Retrograde catheter crossing of tissue prostheses and ball-and-cage prostheses may be performed safely to determine transvalvular gradients. Tilting-disc prostheses should not be crossed with these catheters because of the risk of catheter entrapment (17). Direct left ventricular puncture using a percutaneous approach may be performed in some cases to measure pressure gradients. Fortunately, in most instances, transvalvular gradients can be determined by Doppler echocardiography, obviating the need for catheterization.

When evaluating the function of prosthetic valves, the following general principles should be taken into consideration:

1. With the exception of the aortic homograft and stentless porcine valves, all currently available tissue and mechanical prosthesis have a smaller effective orifice than a native valve in the same position. This reduction in effective orifice is caused by the profile of the suture ring and the supporting stents in tissue valves or the occluders in mechanical valves. Thus, most tissue and mechanical prostheses in a semilunar position generate a systolic flow murmur. Diastolic murmurs in atrioventricular prosthetic valves are uncommonly heard unless prosthetic stenosis, high forward flow caused by severe valvular regurgitation, or patient-prosthesis mismatch is present (18). The normal auscultatory findings of prosthetic valves may be altered by factors such as chest wall thickness, emphysema, stroke volume, heart rate and rhythm, and the presence of other prostheses.
2. Transvalvular gradients may be estimated from continuous-wave Doppler velocities by means of the modified Bernoulli equation ($DP = 4V^2$), where *P* represents pressure and *V* represents velocity. Transvalvular gradients are determined by several factors: the effective orifice of the prosthesis, the stroke volume, and the presence of intravalvular obstruction. Thus, the published normal ranges of transvalvular gradients are only general guidelines that are applicable to normally functioning prostheses at average resting cardiac outputs. Transvalvular gradients are often higher in patients in high output states, such as in patients with anemia, hyperthyroidism, or pregnancy. Forward transvalvular flow may be increased also in the presence of large paravalvular regurgitant leaks. Doppler-derived and catheter-derived peak and mean gradients are comparable, with perhaps the single exception of small ball-and-cage and bileaflet tilting-disc valves that are in the aortic position, in which Doppler gradients have been shown to exceed transcatheter gradients by as much as 44 mm Hg (19). This discrepancy between catheter-derived gradients and Doppler gradients is the result of pressure recovery upstream from the prosthesis.
3. The ratio of Doppler velocity across the valve and velocity proximal to the valve orifice, or “dimensionless index,” is independent of flow and should remain relatively constant over time; thus, it is useful in detecting changes in effective valvular orifice (20). The continuity equation of flow (21) provides accurate estimates of the effective valve orifice in single-leaflet tilting-disc mechanical valves and in bioprostheses but underestimates the orifice of the bileaflet tilting-disc valves by approximately 0.5 cm^2 (20). A decrease in effective valve orifice is often seen in bioprosthetic valves at low flow rates, suggesting that bioprosthetic leaflets do not open fully in these cases because of the increased resistance (22).
4. All normally functioning mechanical prosthetic valves have a certain amount of intravalvular regurgitation. This regurgitation is generated by the closure flow backwash and by built-in mechanisms that prevent the deposition of thrombogenic material. Small paravalvular leaks are commonly detected intraoperatively by transesophageal echocardiography immediately after surgical implantation, most of which improve after reversal of anticoagulation (23).
5. Prosthetic valve suture rings, cages, discs, and stents may produce echocardiographic shielding or make it impossible to visualize structures or flow beyond the location of the ultrasound reflecting surface. This limits the ability to detect transvalvular or paravalvular regurgitation, thrombi, or vegetations of infective endocarditis in some prostheses by transthoracic echocardiography, particularly in prostheses that are in the mitral position (24). In those cases, transesophageal echocardiography offers a superior visualization.
6. Certain types of prosthetic valves and their locations may be identified using plain chest radiography (Fig. 24.1, eFig. 24.1.1 and eFig. 24.1.2). Suture rings are always radiopaque, as are prosthetic cages and some tissue valve supporting stents. Tilting discs may or may not be seen in a plain film, depending on the angle of the prosthesis, the construction material, and the radiographic penetration. Cinefluoroscopy may be useful in evaluating the mobility of the occluder of mechanical valves in patients in whom obstruction is suspected. This technique, however, may not necessarily detect subvalvular obstruction by pannus and cannot be used to assess valvular regurgitation.

VIDEO

Video 24.1 Physiologic regurgitation of a St. Jude’s mechanical valve in the mitral position. Transesophageal echocardiography demonstrates two converging regurgitant jets in the left atrium (LA). AO, aorta; LV, left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.2 Normal leaflet motion of a St. Jude’s prosthesis in the mitral position demonstrated by cine-fluoroscopy. A St. Jude’s aortic prosthesis is also seen in the background. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

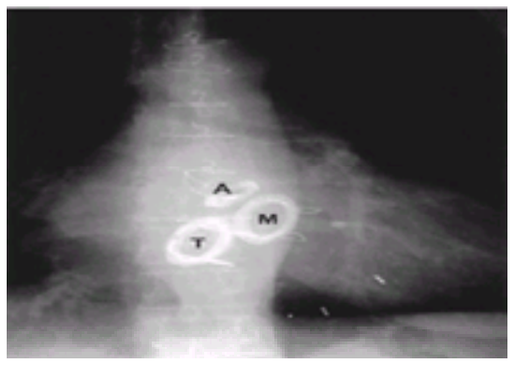
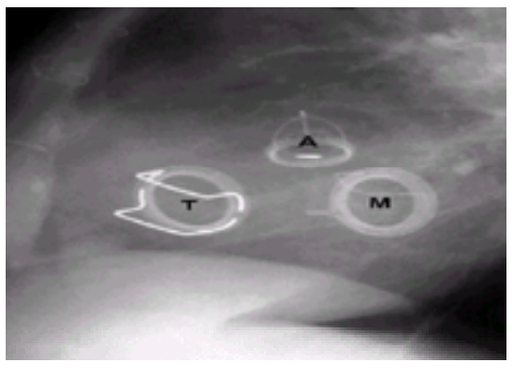


FIGURE 24.1 Radiographic appearance in the anteroposterior projection of mechanical valves in the aortic (A), mitral (M), and tricuspid (T) positions.



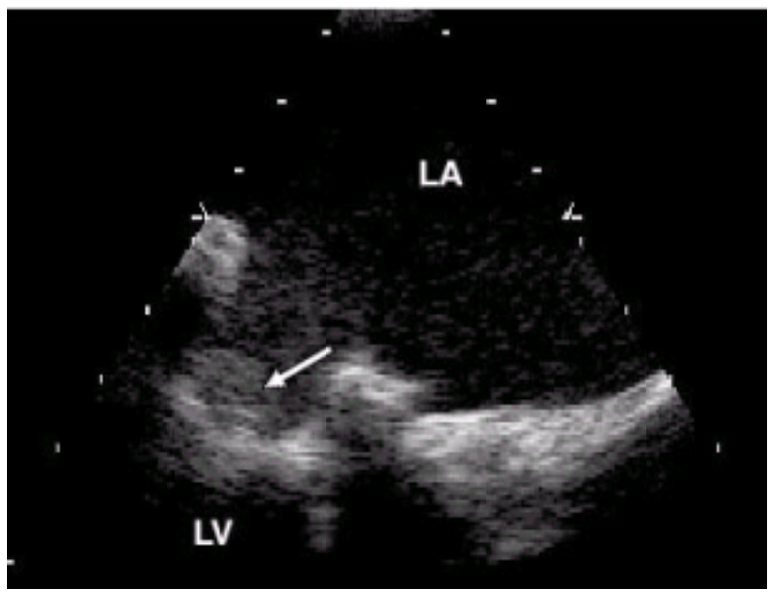
***e*FIGURE 24.1.1** Radiographic appearance in the lateral projection of mechanical valves in the aortic (A), mitral (M), and tricuspid (T) positions.

***e*FIGURE 24.1.2** Radiographic appearance in the lateral projection of Starr-Edwards prostheses closed in aortic (A) and opened in mitral (M) positions during diastole.

Mechanical Valves

Ball-and-Cage Valves

The Starr-Edwards valve prosthesis consists of a metallic alloy ring attached to a cage in which either a metallic or a silastic ball moves from a closed position occluding the ring to an open position in the outer end of the cage. A cloth that allows suturing of the prosthesis to the annulus covers the outside edge of the ring. Flow across the prosthesis is directed circumferentially around the ball, assuming a lateral angle. Model 6120 is manufactured in several different diameters, from 26 to 34 mm, for implantation in the mitral or tricuspid position. Four equidistant struts joined at the distal end make the cage in this model. Model 1260 has three struts in its cage and is available in different diameters, from 16 to 27 mm, for use in semilunar positions. Other models of these valves that contain metallic balls or cloth covered struts were discontinued because of the rapid degeneration or embolic complications associated with their use (25). The Starr-Edwards ball-and-cage prosthesis has the longest proven durability, in many instances exceeding 30 years, of all the prosthetic valves (26). Mechanical failure of this valve is rare and is caused by either degeneration of the ball due to abrasion and lipid infiltration, also known as “ball variance” (27), or by obstruction by thrombus or pannus formation that results in valve incompetence.



Magnified transesophageal view of a Starr-Edwards prosthesis (ball-and-cage valve) in the mitral position. This image was taken in systole with the ball (shown by the arrow) in the ventricular side of the cage.

VIDEO

Video 24.3 Transesophageal view of a Starr-Edwards prosthesis in the mitral position. (The left atrium is toward the upper right side of the screen and the left ventricle is toward the lower left.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.4 Normal-functioning Starr-Edwards prosthetic valve in the mitral position. Note the full motion of the valve pop-it within the cage. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

One of the major disadvantages of ball-and-cage valves is their suboptimal hemodynamic profile. Because of their configuration, flow is obstructed between the ring and the ball and again between the ball and the left ventricular cavity in the mitral position or the aorta in the aortic position. In patients with a small ventricular cavity,

the mitral prosthesis may also partially obstruct and create a pressure gradient across the left ventricular outflow tract (28). The mean transvalvular gradient for Starr-Edwards ball-and-cage prostheses in the mitral position is 4.6 + 2.4 mm Hg, and the estimated effective orifice is 1.4 to 2.9 cm^2 (29,30,31,32 and 33). In the aortic position, the mean gradient is 23 + 8 mm Hg, and the estimated effective orifice is 1.2 to 1.6 cm^2 (34,35). On auscultation, ball-and-cage valves produce a loud opening click, followed by multiple clicks of variable intensity, produced by the ball bouncing in the cage and a flow murmur in the aortic position. A less intense click occurs with the closing of the valve. Frequently, a systolic ejection murmur may be noted in patients with a mitral prosthesis. This murmur is produced by turbulence in the left ventricular outflow tract. Small prostheses or high cardiac output may produce soft diastolic flow murmurs in the mitral position.

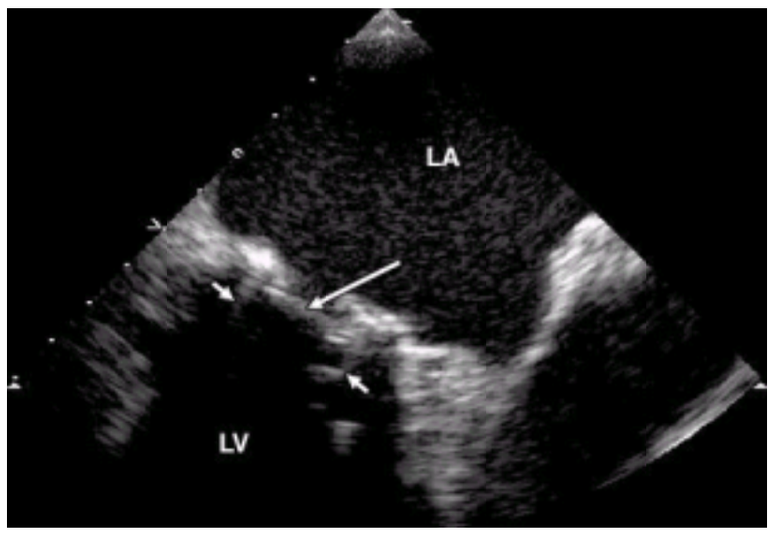
Radiographically, the support ring and cage can be detected in plain films (eFig. 24.1.2). In certain models of ball-and-cage prostheses, the ball is metallic or barium-impregnated, allowing visualization. Two-dimensional echocardiography can demonstrate the highly reflective echoes produced by the metallic struts and the less intense reflective echoes produced by the proximal surface of the ball. From the apical four- and five-chamber imaging views, M-mode echocardiography may detect the opening and closing displacement of the prosthetic ball. Doppler interrogation of forward flow velocities to estimate pressure gradients must be directed at a lateral angle between the prosthetic ring and the ball, where the highest velocities are expected (36). Color Doppler examination may be used to detect the direction of flow and to assess the presence of prosthetic regurgitation or flow turbulence in the left ventricular outflow tract with prostheses in the mitral position. In normal ball-and-cage prostheses, regurgitation is minimal and limited to the closure backflow (37). Other models of ball-and-cage prostheses, which were used in the 1960s and early 1970s, include the double-caged Cutter (38), Magovern-Cromie (39), and the cloth-covered Braunwald-Cutter (40) valves.

VIDEO

Video 24.5 Normal motion of the occluder of a Smeloff-Cutter valve in the mitral position. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Tilting-Disc Valves

These valves consist of a metallic ring attached to one or two flat or concave discs that pivot from the occluded position to an open position at an angle of 60 to 85 degrees. The Björk-Shiley valve (5) has been manufactured in six different models, four of them available in the United States. The original models had a flat disc made of Delrin or pyrolytic carbon, which was later replaced with a convexo-concave disc. The disc tilts through the retaining welded or unwelded struts to an angle of 60 to 70 degrees, depending on the model. The occurrence of fractures of the welded struts and embolization of the disc resulted in the withdrawal of these valves from the market. The Björk-Shiley Monostrut model (41) has excellent hemodynamics and a low risk of mechanical failure and thromboembolism. The Omniscience tilting-disc valve (42) has a free-floating concave-convex disc in titanium housing. The Omniscience valve has a 3% risk of thrombosis, which is considerably higher than the risk associated with other tilting-disc valves, probably because of the smaller built-in volume of regurgitation (43). The Medtronic-Hall (7) valve has a one-piece housing that is manufactured from titanium and a rotatable Teflon sewing ring. A small orifice in the center permits regurgitant flow to “wash” potentially thrombogenic material from the disc. Currently available single-tilting-disc valves have excellent hemodynamics and low risk of mechanical failure.



Beall mitral valve prosthesis showing the single disc within the cage in a 90-degree transesophageal view. The single arrow demonstrates the single disc of the prosthesis, and the two small arrows show the cage in which the disc is held.

VIDEO

Video 24.6 Normal Björk-Shiley prosthetic valve in aortic position and normal porcine valve in the mitral position. Depending on the vintage, the Björk-Shiley tilting-disc valve opens either 60 degrees or 70 degrees shown here. Prosthetic porcine valves are not radiopaque are therefore excursion cannot be ascertained fluoroscopically. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.7 Normal St. Jude prosthetic valve in aortic position. Fluoroscopy shows a bileaflet valve that fully opens and closes with normal leaflet excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

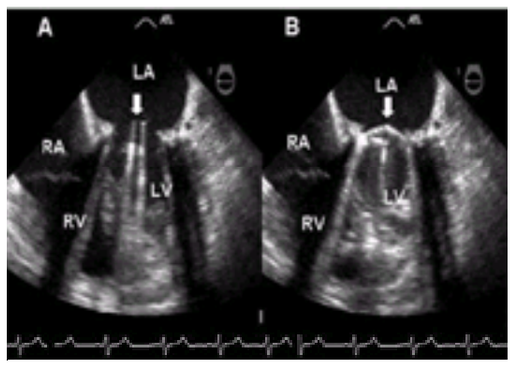
Video 24.8 Normal Björk-Shiley prosthetic valve in the aortic position. On fluoroscopy, the single valve disc moves normally with complete opening and closing. Björk-Shiley valves open 60 degrees or 70 degrees, depending on the model **(A,B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.9 Normal Björk-Shiley prosthetic valve in the aortic position. On fluoroscopy, the single valve disc moves normally with complete opening and closing. Björk-Shiley valves open 60 degrees or 70 degrees, depending on the model **(A,B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The St. Jude Medical (44) and the Carbomedics (45) valves are the only bileaflet tilting-disc valves. The leaflets of the St. Jude Medical prosthesis are manufactured

from pyrolytic carbon impregnated with tungsten for radiopacity. These semicircular leaflets open to an 85-degree angle, leaving two larger lateral orifices with a narrow rectangular slit between them (eFig. 24.1.3). The flow across bileaflet tilting-disc valves is symmetric, providing excellent hemodynamic performance (46). The rates of mechanical failure and thromboembolism associated with these valves are very low. Because of these favorable characteristics, this valve was the most commonly used mechanical prosthesis in the United States during the last decade. The Carbomedics bileaflet valve has characteristics and hemodynamic performance similar to those of the St. Jude's Medical valve, and it has also shown a low rate of mechanical failure and thromboembolism.



***e*FIGURE 24.1.3** St. Jude's valve in the mitral position shown by transesophageal echocardiography during opening **(A)** and closing **(B)**. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Tilting-disc prostheses are available in diameters from 19 to 33 mm for implantation in the mitral or aortic positions. Their mean transvalvular gradient is significantly lower than that of equally sized Starr-Edwards ball-and-cage valves, from 6 to 15 mm Hg in the aortic position and from 2 to 7 mm Hg in the mitral position. The estimated effective orifices range from 2.1 to 3.9 cm^2 for mitral prostheses and from 1.3 to 2.5 cm^2 for aortic prostheses. The Carbomedics "Top-Hat" valve is mechanically designed to increase the effective orifice in relation to the annular size, due to the supraannular location of the occluder (47). The auscultatory findings of tilting-disc prostheses include a loud single or double closing click and a soft mid-systolic ejection murmur in the aortic position or a low-frequency diastolic rumble in the mitral position. Tilting-disc prostheses also produce a softer opening click. The radiographic appearance of these valves differs according to the number and position of the struts and the tilting discs. In some valves, such as the Björk-Shiley valve and the Wada-Cutter valve, the discs may be radiolucent. The two half discs of bileaflet valves can be observed from a tangential plane. The motion of the valve ring and the opening angle of the discs can be evaluated under fluoroscopic guidance. The movement of the tilting discs also can be detected by two-dimensional echocardiography. Two-dimensional echocardiography frequently demonstrates microcavitations in the left ventricular cavity of patients with mechanical tilting valves in the mitral position (48). These microcavitations appear to be gaseous and do not cause any clinical symptoms. However, transcranial Doppler often detects these microembolic signals, and some cases have been reported in which this phenomenon appeared to be related to episodes of amaurosis fugax (49).

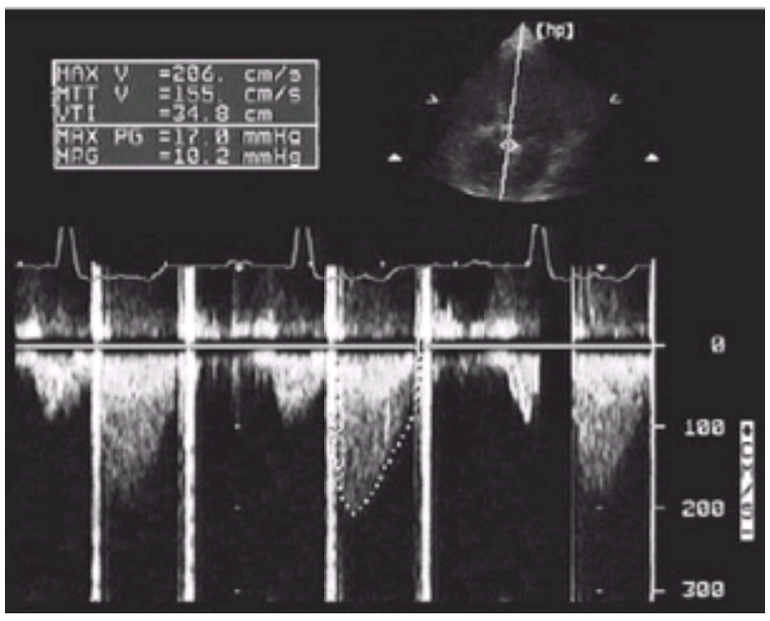
Video 24.10 Beall mitral valve prosthesis with normal antegrade flow seen with color Doppler by transesophageal echo. Note the typical antegrade flow around the disc with marked shadowing beyond the disc. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 24.11 Beall mitral valve regurgitation seen in the 90-degree transesophageal echo view. Note the disc within the prosthesis moving with each cardiac cycle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

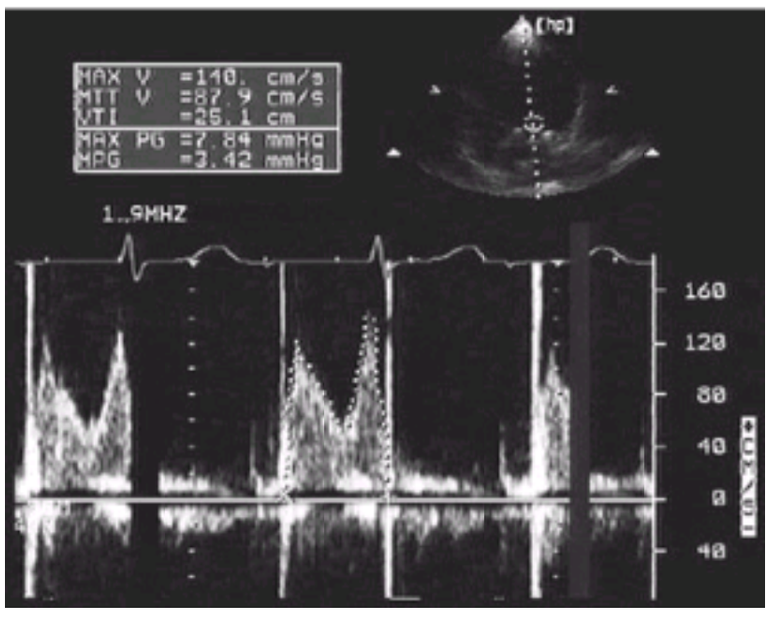
Video 24.12 Normal motion of the discs of a St. Jude's valve in the mitral position shown by transesophageal echocardiography. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 24.13 Microcavitations seen in the left ventricle (LV) of a patient with a St. Jude's mitral prosthesis in the mitral position. LA, left atrium; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Color Doppler imaging may help to identify the type of prosthesis. The Medtronic-Hall tilting-disc valve has a characteristic regurgitant flow jet through its central orifice. The St. Jude's Medical valve has two central divergent and multiple peripheral convergent regurgitant jets that may be visualized depending on the imaging angle. The amount of intravalvular regurgitation may vary according to heart rate and cardiac output. The regurgitant fraction of single tilting-disc valves averages approximately 12% under normal hemodynamic conditions, but it may be as high as 37% at high heart rates and low cardiac output (50). Continuous-wave Doppler imaging is useful for estimating transvalvular gradients using the modified Bernoulli equation. Mean pressure gradients obtained by Doppler imaging generally have a good correlation with catheter-derived gradients (51). Doppler imaging may overestimate the gradient, however, in small prostheses in the aortic position, particularly in those with bileaflet valves. The mean Doppler gradient may be 10 mm Hg higher than the catheter gradient in these circumstances (52). This apparent overestimation is caused by the effect of pressure recovery, which determines that part of the kinetic energy present at the valve level is converted back to pressure distal to the valve if the geometry of the valve prevents turbulence (53). Thus, discrepancy exists because the Doppler imaging method measures the highest gradient at the intravalvular level, whereas the catheter method measures the gradient distal to the valve. Extended M-mode and Doppler recordings are important in excluding intermittent entrapment of the discs.



Continuous wave Doppler spectrum of mechanical prosthesis in the aortic position. Note opening and closing clicks and calculation of mean and maximal pressure gradients.



Apical pulsed wave spectral Doppler recording of a St. Jude medical bileaflet prosthesis in the mitral position. Note opening and closing clicks and calculation of mean gradient.

Tissue Valves

Heterografts

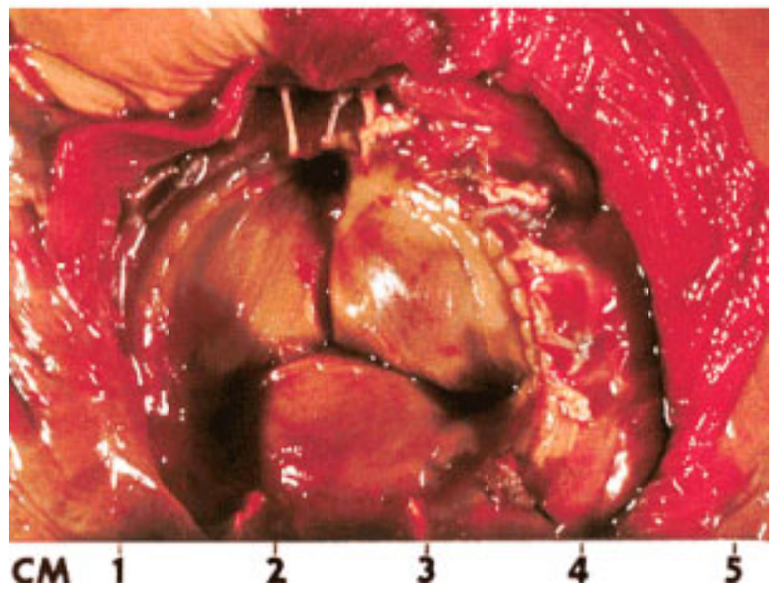
The biologic nonhuman tissue valves currently available are manufactured either from porcine valvular tissue or from bovine pericardium mounted in supporting stents or preserved *in situ* in a segment of the porcine ascending aorta. The Carpentier-Edwards porcine valve (54) consists of a cloth-covered silicone-rubber sewing ring attached to three cloth-covered steel alloy flexible stents and is available for both annular and supraannular implantation (55). The stents serve as a base for a porcine semilunar valve, which has been preserved in a glutaraldehyde solution to strengthen the tissue and to reduce its antigenicity. The Hancock valve has very similar characteristics, but the stents are manufactured of polypropylene. Early experience with other porcine valves more recently introduced to the U.S. market, such as the Medtronic Mosaic valve, has been favorable (56).

VIDEO

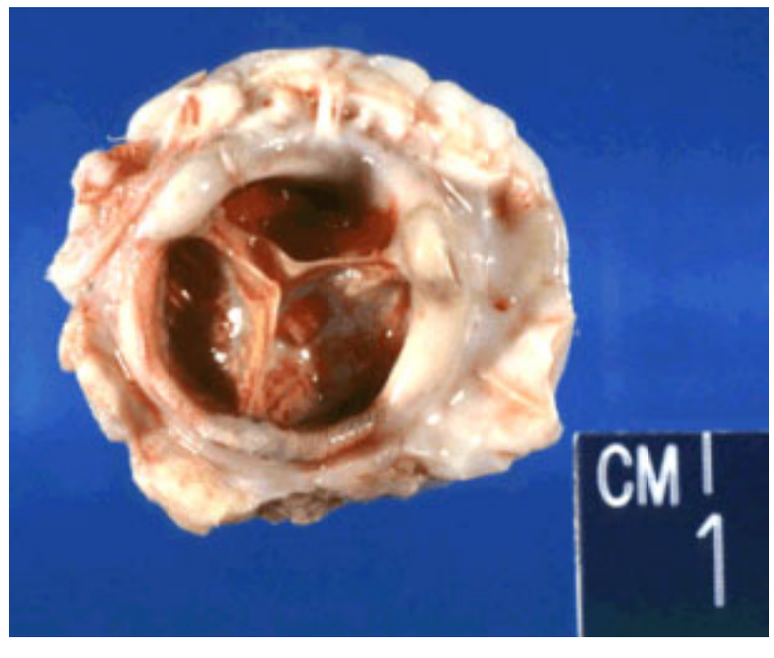
Video 24.14 Transesophageal echo of a patient with a Carpentier-Edwards mitral valve regurgitation. The pliable leaflets are suspended on the metallic struts. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

All bioprosthetic valves are structurally similar to human semilunar valves. A pressure gradient forces the movement of the three cusps to an open position, and flow occurs through the central orifice. A gradient reversal results in closure by backflow. Despite their resemblance to human anatomy, these valves have suboptimal hemodynamic performance in comparison to tilting-disc mechanical prostheses of the same diameter (57,58). This limitation results primarily from the reduction in their profile caused by the interposed stents and is more significant in valves smaller than 23 mm. The bioprosthetic leaflets are also stiffer than native human semilunar valves, exhibiting an incomplete opening at low flow rates. The durability of porcine bioprosthetic valves has improved significantly with newer changes in design and preservation techniques. Actuarial probability of freedom from structural valve degeneration at 5, 10, and 15 years has been reported at 99%, 79%, and 57%, respectively (59). According to this study, in patients younger than 50 years, freedom from structural valve dysfunction at 15 years was 16%, whereas in patients older than 70 years, the rate was 87%. The durability is reduced in mitral prostheses because of the greater closing pressure in this position, in younger patients, and patients with increased calcium metabolism (60,61).

Bovine pericardial bioprostheses were initially developed in an attempt to improve the hemodynamic profile of the porcine valves. The Ionescu-Shiley valve (62) was constructed from bovine pericardium preserved in glutaraldehyde mounted in a titanium frame with the cusps attached to the external surface of the stents to increase the internal diameter of the orifice. Although this design provided an improved hemodynamic performance (63), it also resulted in premature valve failure secondary to stress fracture of the cusps (64). The Carpentier-Edwards bovine pericardial valve (65) resembles structurally the porcine tissue valves and has comparable hemodynamics and durability.Advances in tissue valve preservation are expected to increase the longevity of these valves. Intermediate follow-up of the Hancock II porcine bioprostheses suggests that their durability will be superior to that of their predecessors. Freedom from reoperation has been reported to be 100%, 97%, and 89% after aortic, mitral, and combined valve replacement, respectively, after 7 years of follow-up (66).



Porcine prosthetic mitral valve. In this example, the valve is normal and the suture line is intact.

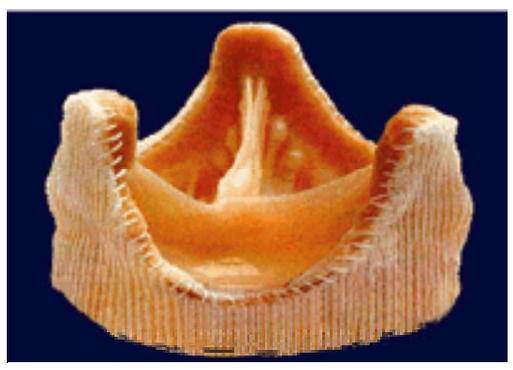


Porcine prosthetic valve with severe fibrosis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 24.15 An 85-year-old female patient status post aortic valve replacement with Ionescu-Shiley valve 13 years ago. Aortogram showing the Ionescu-Shiley valve in the aortic position with moderate aortic regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Bioprosthetic valves are available in diameters of 19 to 31 mm. The effective orifice area for bioprostheses ranges from 1.4 to 2.5 cm^2 in the mitral position and from 0.9 to 1.8 cm^2 in the aortic position. The auscultatory findings of bioprosthetic valves include a systolic ejection murmur in the aortic position and an opening sound in the mitral position. Frequently, a systolic murmur is heard in patients who have mitral bioprostheses, which is caused by turbulent flow in the left ventricular outflow track. The bioprosthetic valve sewing ring is radiopaque in radiographic films. In some models, wire-framed stents may also be seen. The three equidistant stents seen on two-dimensional echocardiography are the hallmark of bioprostheses. The three leaflets can also be imaged, although they are less echogenic than the native aortic valve. Normal bioprostheses showed no or minimal intravalvular regurgitation on color Doppler imaging.

Stentless heterograft prostheses consist of a tubular segment of a porcine proximal ascending aorta containing its *in situ* aortic valve, which is sutured proximally to the aortic annulus and distally to the mid-ascending aorta (eFig. 24.1.4). Although surgical implantation of these valves is technically more demanding, studies have failed to show higher in-hospital morbidity or mortality rates (67). Short and intermediate follow-up of stentless valves have, thus far, demonstrated better hemodynamics with smaller resting and exercise gradients and greater regression of left ventricular hypertrophy than stented tissue valves of similar size (68,69). One study suggested that patients with severe aortic stenosis and left ventricular dysfunction who receive a stentless valve demonstrate a greater early improvement in left ventricular systolic function than patients who receive a stented valve (70). Stentless aortic root bioprostheses can be used safely to replace the aortic root for aortic valve and aortic root pathology (71). Freedom from structural valve degeneration has been reported to be approximately 85% at 9 years (72).



***e*FIGURE 24.1.4** St. Jude Toronto stentless porcine valve.

Aortic Homografts

Human aortic valves are harvested from cadaveric hearts and cryopreserved (73). Like stentless heterografts, these valves are supported by a short segment of the donor's aortic root, in which the recipient's coronary arteries are reimplanted. The homograft endothelial cells and fibroblasts are antigenic (74) and are gradually destroyed by immunologic reactions. The antigenicity may be reduced by antibiotic sterilization and cryopreservation, resulting in a reduced rate of leaflet degeneration of approximately 2% to 10% by 10 years after implantation (75). Langley and associates recently reported freedom from structural valve degeneration at 10, 15, and 20 years of 81%, 62%, and 31%, respectively (76). The durability of the homograft is also influenced by the age of the donor. The incidence of valve degeneration at 10 years is 8% if the donor is younger than 20 years and 40% if the donor is older than 50 years (77). The flow characteristics, auscultatory findings, and radiographic appearance of aortic homografts are similar to those of native aortic valves. On echocardiography, the walls of a homograft may appear thicker at the level of the proximal anastomosis (78). Although the durability of homografts may be higher than that of heterografts in younger adults (79), the rate of degeneration has been shown to be similarly high in young children, particularly when grafts are used in the pulmonary position. Severe regurgitation may be detected in up to 50% of children

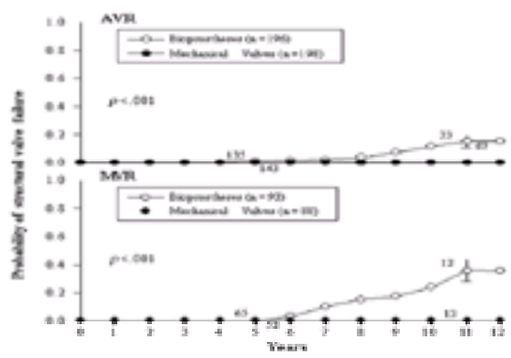
who are younger than 18 months at the time of implantation and in up to 15% of older children at 15 months' follow-up (80). Homografts have a reduced rate of reinfection when they are used to replace valves in patients with endocarditis (81). Langley and colleagues reported a freedom from endocarditis at 10, 15, and 20 years of 99%, 96%, and 95%, respectively (76).

Pulmonary Allografts

A healthy pulmonary valve may be transplanted to the aortic position to substitute for a diseased aortic valve, while a cadaveric homograft is placed in the pulmonary position. Late follow-up has shown no evidence of primary tissue degeneration and normal cusp cellularity. This evidence suggests that the cusps not only survive permanently but can grow with the patient, making the operation ideal for children. Among 339 operations performed from 1969 to 1991 in London, with a cumulative follow-up of 3,774 patient-years, freedom from reoperation was 85%, and the actuarial patient survival was 80% at 20 years after implantation (12). However, mild to moderate valvular regurgitation of the allograft is not uncommon and is usually associated with donor-recipient size mismatch. Degeneration of the implanted homograft in the pulmonary position and stenosis of the pulmonary trunk anastomotic site are also potential limitations and causes of reoperation in these patients. Most importantly, this operation is technically more demanding and thus requires longer circulatory arrest time, which could potentially lead to greater perioperative morbidity. In addition, longer follow-up is needed to determine whether reoperation after this surgery may be associated with greater morbidity.

Selection of Prosthetic Valve Type

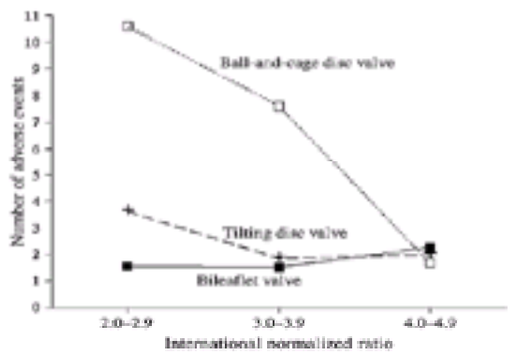
Because each prosthetic valve type has specific advantages and disadvantages, the selection of a prosthetic valve should always be individualized to each patient on the basis of age, anatomic considerations, lifestyle, expected longevity, and relative risks of anticoagulation. The in-hospital mortality and complication rates after valve replacement are similar to the rates seen among patients with mechanical and bioprostheses (26,82) and therefore should not be considered determining factors in the selection of a valve. Several retrospective and prospective studies have shown that the risk of death and major complications, including systemic embolization, endocarditis, and valve thrombosis, are also comparable in long-term follow-up (eFig. 24.1.5).



***e*FIGURE 24.1.5** Probability of structural valve degeneration of mechanical and bioprosthetic valves in aortic (*upper panel*) and mitral position (*lower panel*). AVR, aortic valve replacement; MVR, mitral valve replacement. (From Hammermeister KE, Sethi GK, Henderson WG, et al. A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. *N Engl J Med* 1993;328:1293, by permission of The Massachusetts Medical Society.)

In the Edinburg Heart Valve Trial (82), 541 consecutive patients undergoing valve replacement were randomly assigned to receive either a Björk-Shiley 60-degree spherical tilting-disc prosthesis or a Carpentier-Edwards porcine valve. A trend towards improved actuarial survival after 12 years was found in patients with Björk-Shiley valves, although this was not statistically significant. Reoperation was more frequent among patients with bioprosthetic valves (8.5% vs. 37.1%, p <.001), but bleeding complications occurred more frequently among patients with mechanical valves (18.6% vs. 7.1%, p <.01). No significant differences were seen in the rates of other complications, including embolism (mechanical vs. bioprosthetic valves, 21.1% vs. 26.4%) and endocarditis (3.7% vs. 4.6%).

In the Veterans Affairs Cooperative Study (26), in which 575 patients undergoing valve replacement were randomly assigned to receive mechanical valves (Björk-Shiley) or bioprostheses (Hancock), the risk of systemic embolism among patients with mechanical valves was 17% and the risk among patients with bioprostheses was 15% after a mean follow-up interval of 11 years. The risks of endocarditis were 8% versus 11%, respectively, and the risk of prosthetic valve thrombosis was 2% versus 1%. The most significant differences occurred in the incidence of structural failure, reoperation, and hemorrhagic complications related to the use of anticoagulant medication. Structural failure occurred in 21% of bioprostheses, and the rate was significantly higher among prostheses in the mitral position (36%) than among those in the aortic position (15%) (eFig. 24.1.6). Reoperation was required in 26% of the cases. In contrast, no cases of mechanical valve failure occurred, and only 11% of the patients in this group required reoperation, either because of periprosthetic regurgitation, valve thrombosis, or endocarditis (eTable 24.0.1). As anticipated, the risk of hemorrhagic complications was greater in patients with mechanical prostheses (42% vs. 25%).



***e*FIGURE 24.1.6** Incidence of adverse events (thromboembolism, major bleeding, and stroke) according to mechanical valve type. (From Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995;333:15, by permission of The Massachusetts Medical Society.)

***e*TABLE 24.0.1** CAUSES OF REOPERATION IN PATIENTS WITH MECHANICAL AND BIOPROSTHETIC VALVES

Cause	Mechanical prostheses	Bioprostheses
Operations	46	662
Prostheses	49	717
Structural valve degeneration	1 (2.0%)[a]	518 (72.2%)
Nonstructural dysfunction	32 (65.3%)	82 (11.4%)
Prosthetic valve endocarditis	9 (18.4%)	74 (10.3%)
Thromboembolism	5 (10.2%)	10 (1.4%)
Incidental removal	1 (2.0%)	31 (4.3%)
Miscellaneous	1 (2.0%)	2 (0.3%)

[a]Percentages relate to operations, not number of prostheses replaced.
Adapted from Tyers GF, Jamieson WR, Munro AI, et al. Reoperations in biological and mechanical valve populations: fate of the reoperative patient. *Ann Thorac Surg* 1995;60:S465.

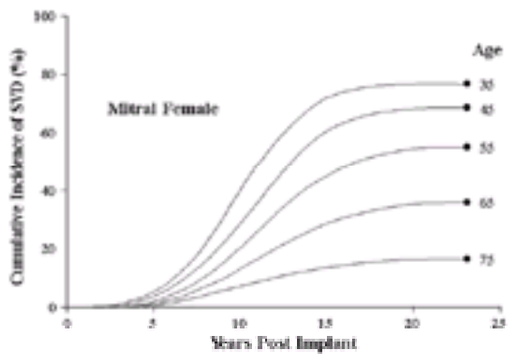
The slightly higher rates of death, endocarditis, and bleeding complications found in the Veterans Affairs Cooperative Study probably reflect an older population and a more intense anticoagulation regimen (prothrombin time, 2.0 to 2.5 times control, vs. 1.3 to 2.0 times control in the Edinburgh trial). The overall mortality rates for reoperation in the Edinburgh trial and the Veterans Affairs Cooperative Study were 30% and 25%, respectively. Other studies have reported valve reoperation mortality rates from 4.7% to 20.0% (83,84 and 85). The results of the Edinburgh Heart Valve Trial and the Veterans Affair Cooperative Study indicate that reoperation rates are higher among patients with bioprosthetic valves, and the risk of hemorrhagic complications is higher among patients with mechanical prostheses. The cumulative

mortality rate associated with reoperation in long-term survival is similar among patients with mechanical valves and patients with bioprostheses. Reoperation is performed less often in patients with mechanical prostheses, but it carries a higher individual mortality rate, because the cause of reoperation is more frequently endocarditis and abrupt mechanical failure.

It is important to consider, however, that significant advancement has occurred since these studies were conducted. The widespread use of anticoagulation clinics and, more recently, the introduction of home anticoagulation testing kits will likely result in a lower risk of embolic and hemorrhagic complications. At the same time, improved surgical expertise will likely reduce the relative risk of reoperation. Nevertheless, prosthetic valve durability and risks of hemorrhage remain the main determinants in the selection of heart valve prostheses.

Age

Children who require valve replacement benefit most from mechanical prostheses (86). Tilting-disc mechanical valves provide better hemodynamic performance than bioprostheses, particularly at smaller sizes, thus delaying the need for reoperation. Structural valve deterioration of bioprosthetic valves also occurs more rapidly in children and young adults (eFig. 24.1.7) (61,82,83,84,85,86 and 87). The main cause of dysfunction of porcine valves appears to be calcification of the leaflets. Premature calcification of porcine valves in children is thought to be caused by the patients' accelerated metabolism of calcium, reduced mobility of the leaflets due to lower cardiac output, and stronger immune reactivity to porcine valve tissue. The life expectancy of bioprostheses increases linearly with the patient's age at the time of implantation, from a mean of 6 years at age 20 years to 12 years at age 80 years. Approximately 60% to 80% of patients who are younger than 40 years at the time of bioprosthetic valve replacement will experience structural valve deterioration, versus 5% to 40% of patients older than 60 years (87,88). Therefore, as a general rule, mechanical valves are preferred in younger patients, and bioprosthetic valves are recommended in older patients, in whom the risk of anticoagulation therapy is higher. In young adults who may want to avoid the risks associated with long-term anticoagulation therapy, valve repair and homograft replacement may offer longer durability than replacement with heterograft prostheses.



***e*FIGURE 24.1.7** Cumulative incidence of structural degeneration of porcine bioprosthetic valves (SVD) in the mitral position by age group. Data is shown for female patients. (From Grunkemeier GL, Jamieson WR, Miller DC, et al. Actuarial versus actual risk of porcine structural valve deterioration. *J Thorac Cardiovasc Surg* 1994;108:714, by permission of Mosby-Year Book, Inc.)

Gender

The use of mechanical or bioprosthetic valves in women of childbearing age has disadvantages. Pregnant women with mechanical valves require rigorous control of their anticoagulation and are at higher risk for thromboembolism and for fetal hemorrhage and embryopathy (89,90). Bioprosthetic valves may obviate the need for anticoagulation therapy (89,90 and 91), but they have the disadvantage of limited durability. Hanania and coauthors (92) found an 18% rate of structural valve failure among 74 women who had bioprosthetic valves during pregnancy. In 7 of 13 patients (54%), structural valve failure occurred before the end of the expected life span of the prosthesis (2.5 to 8.0 years; all valves were in the mitral position). In this particular study, fetal loss also occurred in 16% of pregnant women who had bioprosthetic valves. More recent studies have failed to attribute a greater risk of prosthetic valve degeneration caused by pregnancy itself, demonstrating instead that the increased risk is solely dependent on the patient's age (93). Nevertheless, a significant increase in fetal and maternal morbidity is seen with the use of either mechanical or bioprosthetic valves during pregnancy. Therefore, ideally, valve replacement should be postponed until after delivery. Women with regurgitant valves can be managed medically during pregnancy; regurgitant lesions are well tolerated because of the decreased peripheral vascular resistance that occurs during pregnancy (94). Mitral valve repair should be the procedure of choice in patients with nonrheumatic mitral regurgitation (95). Stenotic mitral valves should be treated first by percutaneous balloon dilatation, when possible (96). For patients with aortic stenosis, homografts and pulmonary allografts (97) may be good alternative choices, although their durability may be less than that of mechanical valves.

Indications and Contraindications for Long-Term Anticoagulation Therapy

Bioprosthetic valves should be used in patients at higher risk for anticoagulation-related hemorrhage. These include patients with intestinal angiodysplasia, familial polyposis, inflammatory bowel disease, liver disease, and hereditary blood dyscrasias. Patients with a history of noncompliance or severe ethanol abuse and patients whose anticoagulation therapy cannot be adequately monitored should also receive bioprostheses. Mechanical valves are also relatively contraindicated in patients who are at high risk for trauma because of their particular occupation or lifestyle.

In most patients with chronic atrial fibrillation and other conditions that require long-term anticoagulation, there are no advantages to the use of bioprosthetic valves. Therefore, mechanical prostheses are usually the preferred option in this group.

Calcium Metabolism

Accelerated calcium turnover is associated with rapid degeneration of bioprosthetic valves. This is frequently seen in patients with chronic renal failure, Paget's disease, and other chronic illnesses associated with hypercalcemia. Mechanical valves offer an advantage to those patients who have no contraindications for anticoagulation and do not have a short life expectancy. Although mechanical valve replacement traditionally has been recommended for patients who require hemodialysis, most of these patients have a limited survival, and few live long enough to develop bioprosthetic valve degeneration (98). Thus, in this patient population, the choice of valve prosthesis should be individualized according to life expectancy and the relative risk of thrombotic and hemorrhagic complications.

Prosthetic Valve Position

Structural valve failure occurs earlier in bioprosthetic valves in the mitral position than in those in the aortic position (eFig. 24.1.6) (82,99,100), probably because of the higher stress forces to which they are subjected during closure at systolic pressure. In the Veterans Affairs Cooperative Study (82), mitral valve bioprostheses required replacement because of structural degeneration twice as often as aortic bioprostheses. Because most patients who require mitral valve replacement have atrial fibrillation, left atrial enlargement, or both, chronic anticoagulation therapy often cannot be avoided. Thus, mitral valve replacement with a bioprosthetic valve should be considered mainly for patients who have contraindications to anticoagulation therapy, particularly in older age groups and among patients with sinus rhythm.

Uncommonly, congenital or acquired tricuspid valve disease requires prosthetic replacement. The tricuspid annulus is larger than the mitral annulus, usually requiring prostheses of 33 or 35 mm in diameter. Flow across these large-orifice prostheses occurs at lower velocity, increasing the risk of prosthetic valve thrombosis. The geometry of the right ventricle and the presence of dense trabeculae may also impede the normal opening of mechanical prosthetic discs. Therefore, bioprosthetic valves are preferred by most for tricuspid valve replacements. Pulmonary valve replacement is rarely needed for the management of pulmonary valve stenosis or regurgitation; often these are done as part of surgical reconstructive procedures in patients who have congenital heart disease. Pulmonary valve insufficiency can be managed conservatively in most cases. On the other hand, pulmonary stenosis responds well to balloon valvuloplasty (101). Small surgical series, however, have reported improvement in right ventricular function after valve replacement in patients with pulmonary valve stenosis or regurgitation. In most cases, bioprosthetic valves have been used. Carcinoid syndrome is a unique indication for pulmonary valve replacement in many instances. Of note, carcinoid involvement of implanted homograft valves in the pulmonary position has been reported (102).

PATHOPHYSIOLOGY AND PRINCIPLES OF THERAPY

Complications related to prosthetic heart valves can occur as early as in the immediate postoperative period. Their relative frequency and timing vary with each type of prosthesis and determine the manner in which patients with prosthetic valves should be clinically followed.

Antithrombotic Therapy in Patients with Prosthetic Valves

Thromboembolism represents one of the most important causes of morbidity and death in patients with prosthetic valves. In one of the largest follow-up series of patients with Starr-Edwards ball-and-cage valves, 44% of patients had experienced a thromboembolic episode within 10 years after implantation (103). Of these episodes, 50% resulted in permanent neurologic sequelae and 10% resulted in death. The incidence of thromboembolic events is significantly higher in patients with mechanical prosthesis who are not receiving anticoagulation therapy, ranging from 7% to 34% per year (104,105 and 106). Several mechanisms are involved in the pathogenesis of prosthetic valve–mediated thromboembolism, including platelet activation by the synthetic surfaces of the sewing ring, sutures and mechanical occluders, flow stagnation, increased shear stress, and activation of intrinsic clotting factors by the prosthetic material or the damaged endothelium (107). Patient-related contributing risk factors include older age, atrial fibrillation, and left ventricular dysfunction (108). The risk of thromboembolism is higher with both mechanical valves and bioprostheses in the early postoperative period and declines after the first 3 months for bioprosthetic valves. The risk also varies with the type, size, position, and synthetic components of the valve.

Mechanical Valves

The first generation of Starr-Edwards ball-and-cage valves demonstrated a very high incidence of thromboembolic complications in the absence of anticoagulation therapy (104,105,109). In an attempt to reduce this risk by promoting endothelialization of the prosthetic surface, cloth-covered strut models (models 2300 and 6300) were introduced in the late 1960s. However, rapid destruction of cloth fragments resulted in a much higher embolization rate (110), requiring the discontinuation of these models. Oral anticoagulation therapy with warfarin significantly reduces the risk of thromboembolism in patients who have mechanical heart valves. Improved prosthetic design and anticoagulation therapy reduced the rate of embolism to 2.5% to 4.0% per patient-year in patients receiving anticoagulation therapy who had Starr-Edwards valves that were implanted after 1970 (111). The incidence of thromboembolic complications with Björk-Shiley tilting-disc valves is approximately 4% per year for valves in the mitral position and 2.5% per year for valves in the aortic position, and an average of 1% to 3% with Medtronic-Hall valves in patients receiving anticoagulation therapy (112). Bileaflet mechanical valves have a risk of approximately 2.5% per year in the mitral position and 1% per year in the aortic position (113,114 and 115).

Whether the small difference in these rates is associated with intrinsic properties of the prostheses or merely represents differences in patient characteristics, level of anticoagulation therapy, or study design is unclear. For example, Horstkotte and associates (116) reported a lower rate of embolism with the St. Jude's Medical valve, but their study did not include transient ischemic attacks as an outcome. On the other hand, another study, which involved a large group of patients in atrial fibrillation, showed a rate of 3.9 events per 100 patient-years with the same valve (117). Regardless of the type of mechanical prosthesis, the incidence of thromboembolism is lower than 1% in patients who maintain therapeutic anticoagulation (116,117 and 118). Studies have shown that the majority of patients with mechanical valves who experience thromboembolic complications has a subtherapeutic INR (international normalized ratio) at the time of the event (103). However, chronic anticoagulation therapy increases the long-term incidence of hemorrhagic complications. Pooled data from 46 studies that observed more than 13,000 patients with mechanical heart valves for more than 50,000 patient-years have shown an incidence of major bleeding complications of approximately 1.4 per 100 patient-years (119). Cannegieter and coworkers (120) reported a risk of intracranial and spinal hemorrhage of approximately 0.6% per 100 patient-years. In their study, 72% of hemorrhagic strokes resulted in permanent neurologic damage and 44% in death, compared to 21% and 5% of ischemic strokes, respectively (Table 24.1). Other common sites of bleeding are the gastrointestinal and genitourinary tracts and the retroperitoneal, intramuscular, subcutaneous, nasopharyngeal, and joint spaces.

Event	No.	Incidence (per 100 patient-yr)[a]
Thromboembolism		
Cerebral infarction	43	0.68
Peripheral embolism	2	0.03
Valve thrombosis	0	—
Any thromboembolism	45	0.71
Fatal thromboembolism	2	0.03
Bleeding episode		
Intracranial and spinal bleeding	36	0.57
Extracranial bleeding	128	2.11
Any bleeding	64	2.68
Fatal bleeding	20	0.30
Unclassified stroke	14	0.23
First events	210	3.50

[a]Because follow-up ended when the event of interest occurred, the denominators differ for the various endpoints.
Adapted from Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995;333:11.

TABLE 24.1 INCIDENCE OF ADVERSE EVENTS (THROMBOEMBOLISM, MAJOR BLEEDING, AND STROKE) IN PATIENTS WITH MECHANICAL VALVES RECEIVING CHRONIC ANTICOAGULATION

In the absence of a predisposing factor, hemorrhagic complications occur significantly more frequently in patients with an INR higher than the therapeutic range (121). In the study by Cannegieter and associates (120), in which 1,608 patients with mechanical valves were observed during 6,475 patient-years, the incidence of adverse events (hemorrhagic and thromboembolic) increased from 2 per 100 patient-years among patients with INRs of 2.5 to 4.9, to 7.5 per 100 patient-years among patients with INRs of 2.0 to 2.4, and to 27 per 100 patient-years among patients with INRs of 1.0 to 1.4 (Fig. 24.2). Similarly, adverse events increased to 4.8 per 100 patient-years among patients with INRs of 5.0 to 5.5 and to 75 per 100 patient-years among patients with INRs >6.5. Predisposing conditions such as trauma or underlying illness were identified in one-half of the patients who experienced hemorrhagic events, regardless of the INR level. Both hemorrhagic and thromboembolic complications are more frequent in older patients (120). Patients younger than 50 years had an incidence of thromboembolism of 0.1 per 100 patient-years and an incidence of hemorrhage of 2.5 per 100 patient-years, compared with incidences of 1.1 and 5.6, respectively, among patients older than 70 years.

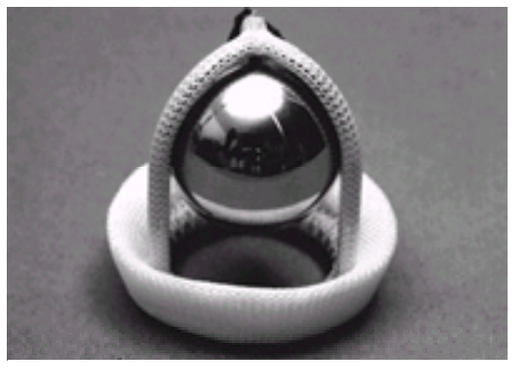
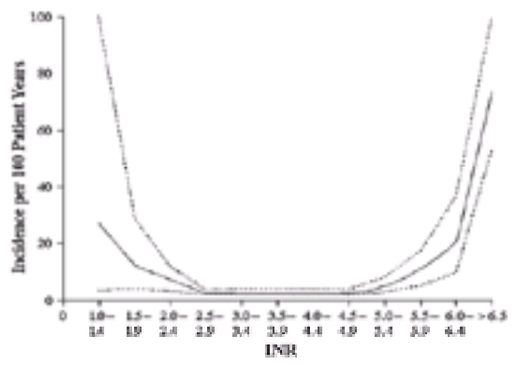


FIGURE 24.2 Cloth-covered Starr-Edwards ball-and-cage valve. This mechanical prosthesis was discontinued due to the high incidence of hemolysis and embolization of cloth fragments.

Accomplishing optimal anticoagulation requires not only achievement of a target INR but also maintenance of that level through careful patient education and rigorous monitoring. Monitoring anticoagulation by means of the INR eliminates uncertainty about the intensity of anticoagulation therapy that is caused by variability in the results of different commercial thromboplastins. The intensity of anticoagulation therapy should vary according to the type of mechanical device and to the presence of other predisposing factors (eFig. 24.1.6). In patients with ball-and-cage prostheses, the incidence of thromboembolic events is lowest when the INR is maintained between 4.0 and 4.9 (121). This higher INR also appears to reduce the rate of embolic events in patients who have multiple mechanical prostheses. An INR of 3.0 to 3.9 is associated with a very low incidence of thromboembolic events in patients with Medtronic-Hall or Björk-Shiley valves, whereas an INR of 2.0 to 2.9 appears to be sufficient in patients with St. Jude's Medical valves. Because the risk of thromboembolic events is higher for patients with any mechanical prostheses in the mitral position and for patients who have chronic atrial fibrillation, efforts should be made to maintain a higher anticoagulation level in these patients. Most hemorrhagic and thromboembolic complications can be avoided by maintaining a stable level of anticoagulation (eFig. 24.2.1).

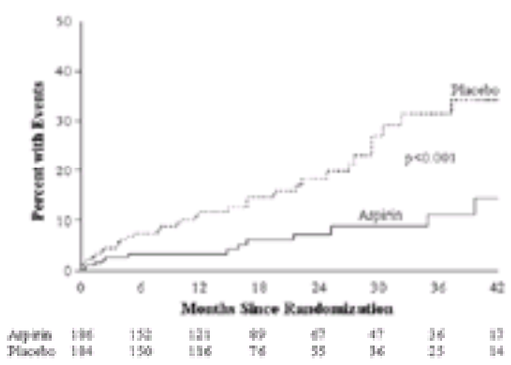


***e*FIGURE 24.2.1** Incidence of adverse events (thromboembolism, major bleeding, and stroke) in patients with mechanical heart valves according to the international normalized ratio (INR). Dotted lines represent 95% confidence limits. (From Cannegieter SC, Rosendaal FR, Wintzen AR, et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995;333:14, by permission of The Massachusetts Medical Society.)

Studies have shown that patients with prosthetic valves who receive chronic anticoagulation therapy that is monitored in a specialized clinic experienced a lower incidence of thromboembolic and hemorrhagic complications compared with patients who are followed sporadically by primary care physicians (122). Recently, studies have shown that weekly self-testing and self-dosing leads to a better control of anticoagulation therapy than standard treatment in an anticoagulation clinic (123). Whether the widespread use of home-monitoring anticoagulation kits will result in a reduction of thromboembolic complications, bleeding complications, or both remains to be determined.

Video 24.16 Thrombosis of bioprosthetic valves in the mitral and tricuspid position (arrows) in a patient with antiphospholipid syndrome in the early postoperative period demonstrated by transesophageal echocardiography. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Antiplatelet therapy may be used in combination with warfarin in patients who have mechanical heart valves. Aspirin may have a beneficial effect by reducing the platelet-mediated activation of the coagulation cascade. Turpie and colleagues (124) demonstrated that low-dose aspirin (100 mg per day) in patients with a target INR of 3.0 to 4.5 has been shown to reduce the annualized risk of death and major systemic thromboembolic events from 11.7% to 4.2% (*e*Fig. 24.2.2). Although the risk of all hemorrhage increased in the group of patients receiving aspirin in this study from 22% to 35%, the risk of major hemorrhagic events (cerebrovascular bleeding, gastrointestinal bleeding, and major bleeding requiring transfusion) appeared to be similar in both groups (13% vs. 10%; 95% confidence interval, –30% to 132%; p = .43). The additive benefit of aspirin appeared to be greater in patients who had experienced previous embolic events and were at higher risk for thromboembolism. The reduction in death rate in the group of patients receiving aspirin may also be associated with the prevention of myocardial infarction in patients with coronary artery disease, which present in at least 35% of the patients in this study. Another study has demonstrated that patients randomly assigned to receive oral anticoagulation therapy with a target INR of 2.5 to 3.5 and 200 mg per day of aspirin after mechanical mitral valve replacement had a lower risk of visualization of periprosthetic thrombi by transesophageal echocardiography 9 days after surgery (5% vs. 13%), compared with patients who received standard anticoagulation therapy without aspirin (125). The risk of thromboembolic events was also lower after 1 year of follow-up (9% vs. 25%). Nevertheless, these results have to be interpreted with caution; the incidence of thromboembolism with anticoagulation therapy alone in this study was considerably higher that previously reported. In addition, with the combination treatment, the rate of gastrointestinal hemorrhage was significantly increased (7% vs. 0%). High-dose aspirin (500 mg per day) may reduce the risk of thromboembolism in patients with a low INR (1.8 to 2.3), but it results in a higher incidence of gastrointestinal bleeding (126,127). There is no apparent benefit, but certainly a higher risk of hemorrhage, with the use of high-dose aspirin in patients who have high-intensity INR.



***e*FIGURE 24.2.2** Cumulative risk of major embolism or death in patients with mechanical valves or bioprosthetic valves with history of thromboembolism or atrial fibrillation randomized to warfarin versus warfarin plus low-dose aspirin. (From Turpie AG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med* 1993;329:528, by permission of The Massachusetts Medical Society.)

The use of other antiplatelet agents alone or in combination with warfarin in patients with prosthetic valves has been studied. The value of dipyridamole in preventing thromboembolism in patients with mechanical valves is controversial (128,129). A study by Hayashi and coauthors suggested that both dipyridamole and ticlopidine have beneficial effects similar to those of low-dose aspirin in combination with warfarin therapy (130). Because of the high cost and significant side effects of these drugs, their use should be reserved for high-risk patients who are intolerant to aspirin.

Bioprosthetic Valves

Patients with heterograft bioprostheses have an increased risk of thromboembolism during the first 3 months after implantation. This risk is attributed to the thrombogenic surface of the prosthetic sewing-ring cloth, transient hypercoagulable state after surgery, platelet activation during cardiopulmonary bypass, flow stagnation due to chamber enlargement, and postoperative atrial fibrillation (129). The risk of thromboembolism appears to be higher for mitral prostheses (7%) than for aortic prostheses (3%) during this period (131), decreasing to approximately 2% per year thereafter. Anticoagulation therapy with warfarin at a target INR of 2 to 3 has been shown to significantly reduce the thromboembolic risk (131,132). Because postoperative anticoagulation increases the risk of hemorrhagic pericardial effusion and cardiac tamponade, the decision as to whether a given patient should receive anticoagulation therapy should be individualized. After 3 months, intermediate-dose aspirin (325 mg per day) may be used to further reduce the risk (133). In patients who have experienced previous embolic events, atrial fibrillation, and severe left ventricular dysfunction, long-term oral anticoagulation should be maintained. Thromboembolism occurs rarely in patients with stentless valves.

Special Situations

Anticoagulation Therapy during Pregnancy

Because pregnancy causes relative hypercoagulability (134), rigorous anticoagulation therapy is required throughout gestation (89,92) in patients with mechanical valve prostheses. Anticoagulant therapy is associated, however, with higher fetal morbidity and mortality rates, especially if the drugs are administered during the first trimester (135). Warfarin has teratogenic effects in the embryo and may result in fetal death when the embryo is exposed between the sixth and ninth week of gestation (90). Pregnant women with mechanical valves who receive warfarin during this period carry a risk of embryopathy as high as 30% (136) and a risk of spontaneous

abortion of 25% to 30% (136). Therapeutic abortion should be considered if advanced gestation is discovered accidentally while the patient is receiving this drug. Anticoagulation should be maintained during pregnancy with either continuous intravenous or subcutaneous heparin, administered twice daily starting at 17,500 to 20,000 units and adjusted to a target activated partial thromboplastin time greater than two times control 6 hours after administration (137). Subtherapeutic doses of heparin are associated with a significant risk of thromboembolism. Large doses of heparin are commonly required because of the relatively hypercoagulable state during pregnancy (138). The risk of major hemorrhagic complications in pregnant patients treated with heparin is approximately 2% (139). Substituting heparin from the sixth week until the twelfth week of gestation eliminates the risk of embryopathy in pregnant women with mechanical valves (90). Larrea and coworkers (140) also found a reduction in the risk of spontaneous abortion from 34.6% in patients receiving warfarin to 9.5% in those receiving intravenous heparin. Warfarin appears to be safe during the second trimester and the first half of the third trimester, and it reduces the risk of thromboembolism that is associated with inadequate anticoagulation with heparin. Heparin should be substituted for warfarin again after the thirty-eighth week and until delivery, because warfarin crosses the placenta and may cause fetal intracranial hemorrhage in the peripartum period (92,141). Heparin should be discontinued 24 hours before elective induction of labor. Both heparin and warfarin can be used safely by nursing mothers, because they do not appear to be secreted into breast milk (139).

Low-molecular-weight heparins have been shown to be safe and effective for the prevention and treatment of deep venous thrombosis in pregnant women (142). Because they have a longer plasma half-life, they provide steady levels of anticoagulation and a more predictable dose response than unfractionated heparin. Low-molecular-weight heparins do not cross the placenta, and they carry lower risks of heparin-induced thrombocytopenia, but they are considerably more expensive. Studies are needed, however, to determine whether low-molecular-weight heparins are safe and effective during pregnancy in patients who have mechanical valves. Low-dose aspirin has been shown to be safe when used in combination with heparin or warfarin in pregnant patients who have a high risk of thromboembolism (143).

Perioperative Management of Anticoagulation

Patients who have mechanical valves and are undergoing minor surgical procedures in which blood loss is anticipated to be minimal and easily controlled do not require discontinuation of anticoagulation therapy. Otherwise, warfarin should be discontinued 3 days before major surgical procedures during which significant bleeding is expected. This is based on the half-life of warfarin, which varies from 18 to 36 hours (122). Although the overall risk of thromboembolism when anticoagulation therapy is discontinued for less than 10 days is reported to be low (144), the risk may be significantly higher in patients with mitral prostheses, ball-and-cage valves, and atrial fibrillation. Therefore, in these cases, and in patients who have left ventricular dysfunction, who have a history of embolic events, or who are otherwise considered to be at high risk, warfarin should be substituted with intravenous heparin until 3 hours before the procedure and resumed postoperatively until adequate oral anticoagulation is resumed. In emergency situations, small parenteral doses of vitamin K or fresh-frozen plasma may be used to quickly reverse anticoagulation.

Anticoagulation after Stroke

After a nonhemorrhagic stroke, the risk of recurrent stroke is approximately 1% per day if anticoagulant therapy is discontinued (145). Maintaining anticoagulation reduces this risk to one-third, but carries an increased risk of hemorrhagic transformation (8% to 24%), particularly during the first 48 hours, if the initial stroke is large in size and involves the basal ganglia (146,147). Although few objective data exist, it is thought that hemorrhagic transformation is usually a fatal or disabling complication. Because the risk of hemorrhagic transformation with continued anticoagulation appears to be higher than the risk of recurrent embolism in patients who are not receiving anticoagulation therapy, such therapy should be discontinued for 5 to 7 days in these patients. In patients who have smaller cerebral infarcts, controlled blood pressure, and absence of hemorrhage on a cranial computed tomographic (CT) scan, anticoagulation therapy should be continued. In patients with hemorrhagic strokes, most authorities recommend discontinuing anticoagulation therapy for 1 to 2 weeks and resuming when there is resolution of mass effect and no evidence of hemorrhage extension on a repeated cranial CT scan.

Anticoagulation in Patients with Prosthetic Endocarditis

The risk of thromboembolism in patients with mechanical valve endocarditis who are not receiving anticoagulation therapy has been reported to be as high as 50% in different studies (148,149). These studies suggest that anticoagulation may reduce this risk to less than 10%, although such therapy may be associated with a 14% risk of cerebral hemorrhage. The risk of hemorrhage is particularly high in patients who have clinical or radiographic evidence of cerebral embolization. In these patients, anticoagulation therapy should be discontinued for 48 to 72 hours, until resumption is considered safe. Because patients with prosthetic valve endocarditis are hospitalized, oral anticoagulation therapy should be replaced by intravenous heparin, which can be quickly discontinued if necessary. Low-molecular-weight heparins should be used in patients developing heparin-induced thrombocytopenia.

Prosthetic Valve Thrombosis

Prosthetic valve thrombosis is a serious complication associated with both mechanical and bioprosthetic valves (Fig. 24.3). The incidence is higher, approximately 6% per year, for patients with mechanical prostheses who are receiving suboptimal anticoagulation therapy (150,151). Thrombosis occurs more frequently in patients with older models of Björk-Shiley (150,151) and Omniscience (152) single-tilting-disc valves than with Starr-Edwards ball-and-cage, Medtronic Hall single-tilting-disc, and St. Jude's Medical bileaflet valves. Patients with mechanical prostheses who are receiving adequate anticoagulation therapy, regardless of the type of valve, have a lower risk, 0.1% to 2.0% per 100 patient-years, similar to the risk among patients with bioprosthetic valves who are not receiving anticoagulation therapy (25). Valve thrombosis occurs more commonly among patients with prostheses in the mitral position than among patients with prostheses in the aortic position. The incidence of thrombosis appears to be much higher (4% per year) among patients with prostheses in the tricuspid valve position (153).

Video 24.17 Frozen St. Jude prosthetic valve leaflet **(A)**. Image was obtained 5 days postoperative with suspected prosthetic valve dysfunction by echocardiography. Fluoroscopy reveals only one of the two leaflets moving normally (*arrow*). St. Jude prosthetic valve after reoperation **(B)**. Both leaflets now show normal excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 24.18 Frozen St. Jude prosthetic valve leaflet **(A)**. Image was obtained 5 days postoperative with suspected prosthetic valve dysfunction by echocardiography. Fluoroscopy reveals only one of the two leaflets moving normally (*arrow*). St. Jude prosthetic valve after reoperation **(B)**. Both leaflets now show normal excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

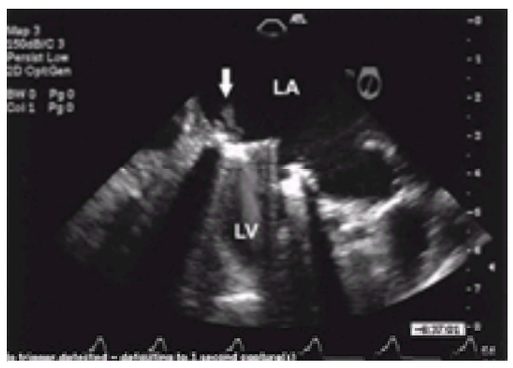


FIGURE 24.3 Thrombosis of a bileaflet mechanical valve in the mitral position. There is partial opening of one of the hemidiscs to a 45-degree angle while the other is stuck in the closed position. The arrow demonstrates the presence of a predunculated thrombus. LA, left atrium; LV, left ventricle.

The thrombus may directly obstruct the valve orifice, cause entrapment of the pivoting mechanism of tilting-disc prostheses, or interfere with the occluding mechanism, causing valvular stenosis, regurgitation, or both. Many patients who have prosthetic thrombosis also have redundant endocardial tissue growth (pannus) that partially obstructs the prosthesis. In the series by Deviri and coworkers (154), thrombus alone was seen in 54% of 106 patients undergoing reoperation for prosthetic valve obstruction. A combination of thrombus and pannus was present in 39%, and pannus alone was found in 6% of the patients. Pannus may be detected as early as 6 weeks and may cause prosthetic valve obstruction as early as 6 months after valve replacement (154). Patients with prosthetic valve thrombosis manifest systemic or pulmonary embolization and symptoms of congestive heart failure and cardiovascular collapse. The onset of symptoms may be insidious, occurring over a period of several weeks, or, more commonly, abrupt, presenting as cardiovascular collapse (155). Acute pulmonary edema appears to be more frequent with single-tilting-disc than with dual-tilting-disc thrombosed prostheses. A murmur of prosthetic stenosis, regurgitation, or both and decreased or absent opening and closing sounds are found on auscultation.

VIDEO

Video 24.19 Björk-Shiley Convexo-Concave prosthetic valve in the aortic position in a left anterior oblique view. Abnormal function is demonstrated by less than a 60-degree opening excursion and incomplete closure. The differential diagnosis includes tissue in growth versus thrombosis of valve leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.20 Intraoperative 90-degree transesophageal echo of a patient with a St. Jude mitral valve prosthesis with a stuck metallic leaflet due to a small clot. (The immobile leaflet is to the right of the screen; the left leaflet moves normally.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The diagnosis is easily established by two-dimensional and Doppler echocardiography; transesophageal imaging is frequently required. Single or multiple echo densities representing thrombus are often visualized within the valve. Incomplete or intermittent opening and closing of the occluder mechanism may be detected by two-dimensional or M-mode imaging (156). Thorough examination should be performed from different examining positions and angles. Thrombosis of a bileaflet mechanical valve may only affect the excursion of one of the discs. In these cases, careful identification and imaging of both discs should be performed to avoid false-negative results. M-mode images should be recorded for a reasonably long interval, because the valve mechanism may be impaired only intermittently. Continuous-wave Doppler examination is useful, demonstrating elevated transvalvular gradients, and color Doppler imaging may demonstrate abnormal regurgitant flow if there is incomplete closure of the prosthesis.

Prosthetic valve thrombosis carries a significant morbidity and mortality rate. Small thrombi of less than 5 mm in diameter often resolve with administration of intravenous heparin if they are not obstructing the occluding mechanism of the valve (157). Larger thrombi, particularly those that interfere with the mechanical function of the prostheses, are associated with a high incidence of embolization and death by cardiovascular collapse and rarely resolve with administration of intravenous heparin alone. Thrombolytic therapy or surgery is required in these patients. Successful thrombolysis has been reported with use of intravenous streptokinase, urokinase, and tissue plasminogen activator (158,159,160,161 and 162). Thrombolysis is effective and has a low complication rate in the treatment of right-heart prosthetic thrombosis. Thrombolytic therapy is effective in the treatment of aortic and mitral valve thrombosis, with an initial success rate of 70% to 80%. It appears to be more effective in patients who have thrombosed prostheses in the aortic position (160) and in patients who have had symptoms for less than 2 weeks (159). The efficacy of thrombolysis appears to be higher with the use of tissue plasminogen activator and streptokinase than with urokinase, although this difference may be caused by different patient characteristics, dosage, or both (163). Thrombolytic therapy for left-heart prosthetic valve thrombosis carries a significant morbidity and mortality rate. Pooled data from several retrospective studies (158,159,160,161,162,163,164 and 165) have shown an incidence of embolism of 5% to 22% and a 5% to 10% risk of disabling stroke or death (*e*Table 24.1.1). Incomplete resolution, recurrent thrombosis, or both occur in approximately 10% to 20% of patients. Many of these reported studies, however, are small series or a collection of reported cases (158), raising the question of whether the true incidence of complications is larger because complicated cases are most likely to be underreported. The combined risk of either death or stroke in these studies was 15%. Failure of thrombolysis occurred in an additional 11% of the cases. The highest failure and complication rates occurred in those patients presenting in New York Heart Association functional class IV. Death or stroke occurred in 7 (11%) of 65 patients presenting in New York Heart Association classes I to III versus 20 (26%) of 76 patients presenting in class IV. Transesophageal echocardiography is useful in monitoring the efficacy of thrombolysis in these patients (166). Recent studies have shown a higher success rate and a lower complication rate for thrombolytic therapy guided by transesophageal echocardiographic monitoring in treating patients with nonobstructive, small, and nonmobile thrombi (167,168). Pooled data from large surgical series (158,159,160,161,162,163,164 and 165) show a combined risk of death or stroke of 9%, although this risk also is higher in class IV patients [14 of 86 (16%) for class IV patients vs. 3 of 63 (5%) for patients in classes I to III]. On the basis of these data, surgical replacement appears to be very effective and carries a lower risk of recurrent thrombosis. However, the lower morbidity and mortality rate among surgically treated patients could be influenced by patient-selection bias. Surgery carries a low morbidity and mortality rate among patients who are hemodynamically stable and have no other significant comorbidities, and it should be the treatment of choice for patients who have large, mobile, and obstructive thrombi (158,159,160,161,162,163,164,165,166,167,168 and 169). The surgical mortality rate may be higher with emergency operations. The choice of treatment in these patients is controversial, because the morbidity and mortality associated with thrombolytic therapy in this group are also higher and the success rate is lower. The decision in this group should be based on the relative institutional availability and expertise of cardiac surgery and with respect to the age and other comorbidities of the patient.

***e*TABLE 24.1.1** INCIDENCE OF STROKE AND DEATH ASSOCIATED WITH THROMBOLYTIC THERAPY VERSUS SURGICAL REPLACEMENT OF THROMBOSED MECHANICAL VALVES

	New York Heart Association class at presentation	
Series	**I–III**	**IV**
Medical		
Reddy (160)	1/11	10/33
Vitale (165)	0/8	0/0
Roudaut (161)	4/36	7/27
Guerrero Lopez (164)	1/2	1/8
Vasan (158)	1/8	2/8
Ozkan (167)	1/31	1/5
Shapira (168)	0/6	1/6
Total	8/102 (8%)	20/87 (25%)
Surgical		
Vitale (165)	0/7	1/13
Deviri (154)	2/43	11/63
Kontos (155)	1/13	2/9
Total	**3/63 (5%)**	**14/85 (16%)**

Structural Degeneration

Mechanical Valves

Malfunction of a mechanical valve prosthesis is relatively uncommon during the first decade after implantation. Prosthetic failure of a mechanical valve resulting in stenosis, regurgitation, or both may occur as a result of ball degeneration, strut fracture, or impaired mechanical function due to thrombus, pannus formation, or infection. The Starr-Edwards ball-and-cage prosthesis has a very low incidence of mechanical failure (170). Degeneration of the silastic valve as a result of lipid infiltration or abrasion injury was common in models manufactured before 1965 (Fig. 24.4) (27). The incidence of ball degeneration, also called “ball variance,” is very low with the more recent models 1260 and 6120, but it may be a concern with valves that have been in use for 20 years or more. Auscultatory findings that suggest malfunction of a ball-and-cage valve include decreased intensity or absence of the opening or closing clicks; new diastolic murmurs, indicating incomplete closure and regurgitation with valves in the aortic position; or new diastolic rumbling murmurs or systolic regurgitant murmurs with valves in the mitral position. Two-dimensional and M-mode echocardiography may show diminished mobility of the ball. It is of paramount importance to register extended Doppler recordings, M-mode recordings, or

both of the prosthesis, because obstruction may occur intermittently. Color M-mode Doppler imaging may indicate abnormal intravalvular regurgitant jets.

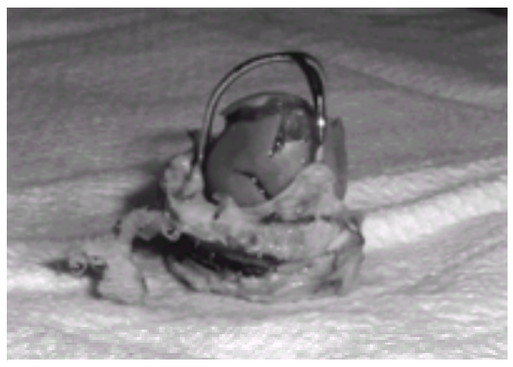


FIGURE 24.4 Structural degeneration of a Silastic ball in a Starr-Edwards valve.

Degeneration of the occluding disc of nontilting-disc valves is common. Abrasion of the edges of the disc results in incomplete occlusion and regurgitation. Entrapment of the disc by thrombus occurs also more commonly than in ball-and-cage prostheses. Tilting-disc valves may fail for a variety of reasons because of their complex structure. Immobilization of a disc can result from entrapment of the pivoting mechanism by free-floating sutures or chordae tendineae (171), resulting in valvular stenosis or regurgitation. Intermittent closure of the disc and a reduced opening angle are diagnostic features that may be found on echocardiographic and cinefluoroscopic examinations. Abnormal intravalvular regurgitation may be observed by color Doppler imaging. Although dislodgment and embolization of a disc has been reported with the Harken (172), the Duromedics (173), and the Omnicarbon (174) tilting-disc valves, most instances of disc escape due to strut fracture have been associated primarily with the Björk-Shiley convexo-concave tilting-disc valve.

Björk-Shiley Valve and Risk of Strut Fracture

In 1978, the disc used in Björk-Shiley valves underwent modifications in an attempt to reduce the risk of valve thrombosis with use of such valves and to improve their hemodynamic profile (175). These modifications included a change to a convexo-concave shape, relocation of the retaining struts 2.5 mm away from the orifice ring, and a disc opening angle of 60 degrees. Another model introduced in Europe in 1980 has an opening angle of 70 degrees. Although these modifications resulted in an improved effective orifice area, the increased stress forces led to frequent fracture of the supporting struts (176). By 1987,213 reports had been made of fracture of the valve ring strut, resulting in withdrawal of the Björk-Shiley tilting-disc valve from the market. By December 1994, 564 complete strut fractures were reported, two-thirds of which were fatal (177). Approximately 40,000 patients are carrying these valves worldwide. The risk of strut fracture appears to be greater in larger-diameter Björk-Shiley prostheses, particularly in those manufactured from 1981 through 1982 (176). Valves with a diameter between 21 and 27 mm and a 60-degree opening angle carry the lowest risk, approximately 0.02% per year (*e*Table 24.1.2). The risk is slightly higher (0.05% to 0.50%) for larger valves with a 60-degree opening angle manufactured before 1981 and after 1982. Larger valves (diameter, 29 to 33 mm) with a 60-degree opening angle manufactured between February 1, 1981, and June 30, 1982, have an intermediate risk of fracture (0.32% per year). Large valves (diameter, >29 mm) with a 70-degree opening angle carry the highest risk, approximately 2% per year. This risk is also higher in patients who are younger than 50 years at the time of implantation (177,178). Prophylactic valve replacement should be considered in patients in whom the risk of embolization exceeds the risk of reoperation.

***e*TABLE 24.1.2** OBSERVED AND EXPECTED 8-YEAR PROBABILITIES OF OUTLET STRUT FRACTURE FOR BJöRK-SHILEY CONVEXO-CONCAVE VALVES

Valve type	Observed 8-yr probability[a] (%)	Expected 8-yr probability (%)
Mitral valves		
Small 60 degree (n = 305)	0 (0.0–1.5)	0.9
Large 60 degree (n = 677)	4.2 (2.7–6.5)	3.3
Small 70 degree (n = 55)	7.2 (3.4–20.8)	5.8
Large 70 degree (n = 93)	17.3 (9.1–31.6)	19.8
Aortic valves		
Small 60 degree (n = 1,241)	0.2 (0.0–0.8)	0.3
Large 60 degree (n = 86)	0 (0.0–5.1)	1.5
Small 70 degree (n = 115)	3.7 (1.2–11.1)	1.7
Large 70 degree (n = 16)	8.3 (1.2–46.1)	8.1

[a]Values in parentheses are 95% confidence interval.
Adapted from van der Meulen JH, Steyerberg EW, van der Graaf Y, et al. Age thresholds for prophylactic replacement of Björk-Shiley convexo-concave heart valves. A clinical and economic evaluation. *Circulation* 1993;88:158.

In May 1994, the U.S. District Court in Cincinnati, Ohio, approved a settlement agreement between a worldwide class of Björk-Shiley heart valve patients and Shiley Inc. Under this agreement, a supervisory expert panel was appointed to establish guidelines for prophylactic valve replacement. Under these guidelines (last amended in June 2000), recipients of Björk-Shiley concave-convex valves qualify for monetary benefits to cover prophylactic valve replacement if their estimated risk of outlet strut fracture exceeds their life-expectancy adjusted risk of reoperation (*e*Table 24.1.3). The risk of fracture is estimated according to the size of the prosthesis, position, specific welder group and shop order fracture rates, and the patient's current age and gender. Risk factor multipliers for 60-degree models are listed in *e*Table 24.1.4. These guidelines must be applied, however, after the characteristics of the individual patient have been considered, which may determine different risk or normal life expectancy.

***e*TABLE 24.1.3** ESTIMATED OUTLET STRUT FRACTURE RATE (PERCENT PER YEAR) BY AGE, VALVE POSITION, AND GENDER, ABOVE WHICH A PATIENT WITH A SINGLE BJöRK-SHILEY VALVE QUALIFIES FOR VALVE REPLACEMENT SURGERY BENEFITS ACCORDING TO BOWLING-PFIZER SETTLEMENT[a]

Age (yr)	Aortic (male/female)	Mitral (male/female)
30	0.26/0.25	0.27/0.26
35	0.37/0.36	0.39/0.38
40	0.43/0.42	0.46/0.44
45	0.51/0.49	0.54/0.52
50	0.61/0.58	0.66/0.62
55	0.75/0.71	0.81/0.76
60	0.94/0.89	1.02/0.96
65	1.20/1.12	1.31/1.22
70	1.57/1.45	1.72/1.59
75	2.08/1.92	2.30/2.11
80	2.81/2.59	3.14/2.87

[a]Based on life expectancy and estimated risks of reoperation for an otherwise healthy patient. Reproduced by permission of the Bowling-Pfizer supervisory panel.

***e*TABLE 24.1.4** DETERMINATION OF OUTLET STRUT FRACTURE RATE FOR BJöRK-SHILEY CONVEXO-CONCAVE 60-DEGREE VALVES ACCORDING TO THE BOWLING-PFIZER SUPERVISORY PANEL RECOMMENDED METHOD[a]

Factor	Subgroup	Risk multiplier
Constant	All	0.097
Size (mm)	21 or 25	1.00
	23 or 27	3.03
	29	4.20
	31	6.01
	33	10.60
Position	Aortic	1.00
	Mitral	2.37
Weld date	<1980, 7/82 to 3/84	1.00

	1980	0.51
	1/81 to 6/82	1.67
	>4.84	0.00
Welder group	A, B	1.00
	C	1.54
Shop order rate[b]	<1.0%	1.00
	1.0–5.0%	1.76
	>5.0%	2.62
Current age	<35 yr	1.00
	>35 yr	$(0.943)^{(Age-35)}$
Gender	Male	1.00
	Female	0.47

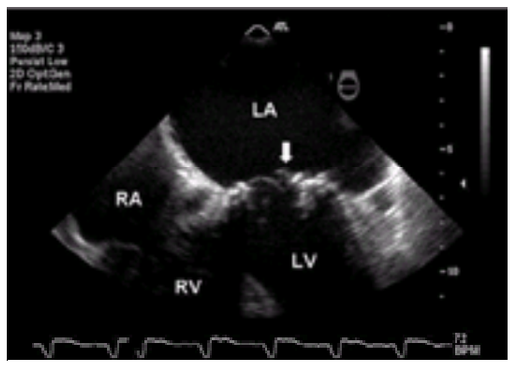
[a]The rate for an individual is estimated by multiplying the constant by each of the seven corresponding risk multipliers. (Reproduced by permission of the Bowling-Pfizer supervisory panel.)
[b]Percent of other valves in the same shop order that have fractured (data available from the manufacturer).

Strut fracture and disc embolization of an aortic prosthesis is usually fatal. Patients with strut fracture of a mitral prosthesis often survive (179). Acute pulmonary edema, syncope, shock, and acute neurological deficits are often the presenting signs and symptoms. Absence of the opening and closing clicks on auscultation, absence of the disc on radiographic or echocardiographic examination, and severe regurgitation found on color Doppler imaging help establish the diagnosis. Emergency valve replacement is required in these patients.

Incomplete fracture of the strut may be detected by high-resolution cineradiography (180) and also is an indication for valve replacement. This method appears to be very specific when specimens that have been explanted are analyzed. However, its sensitivity is unknown. Of 315 patients with mitral convexo-concave valves who were examined cineradiographically every 6 months after implantation, 11 who showed probable or definite single-leg separations underwent prophylactic explantation. In ten of these, the fracture was confirmed. The mortality rate was slightly lower than the expected mortality rate for this group, for which the fracture rate is estimated to be 0.46% per year or higher. However, two complete outlet-strut fractures occurred 3 and 7 months after radiographic examination yielded apparently normal results, which indicates that some cases were not detected or that complete outlet-strut fracture may not necessarily be preceded by incomplete fracture for a significant period of time. Thus, further studies are necessary to establish specific guidelines about the use of this method as an effective screening procedure. Acoustic analysis has been more recently proposed as a cost-effective method for detecting strut fracture (181).

Bioprosthetic Valves

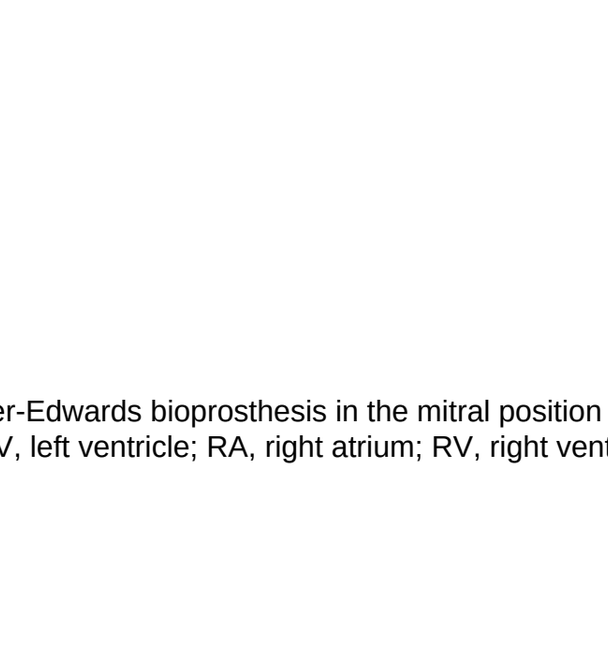
Structural failure of bioprosthetic valves is common and eventually necessitates prosthetic replacement (*e*Fig. 24.4.1). After implantation of these valves, the leaflets exhibit progressive fibrosis and calcification (182,183). The thickened leaflets become less compliant and either lose their mobility, resulting in prosthetic valve stenosis, or fracture, causing valve incompetence (184). Severe intravalvular prosthetic regurgitation tends to be clinically more significant than stenosis (85). Structural valve failure can occur as early as 4 years after implantation. The incidence of structural failure requiring valve replacement for heterograft bioprostheses increases linearly thereafter, approaching approximately 30% at 10 years and reaching as high as 60% at 15 years (87,185). Approximately 10% to 20% of stentless aortic homografts degenerate and require replacement at 10 years after implantation (185,186). The bioprosthetic valve failure rate is higher among prostheses in the mitral position (187,188) and among younger patients. Approximately 50% of patients who are in the second decade of life at the time of surgery experience structural valve deterioration requiring valve replacement before 6 years (87). Recent studies suggest that structural degeneration for bioprostheses implanted in the mitral valve position may be lower for porcine supraannular bioprostheses than pericardial bioprostheses (189). Thereafter, the incidence of structural failure of heterograft bioprostheses decreases linearly with increasing age of the patient. The incidence of structural failure for stentless porcine bioprosthesis appears to be reduced, according to a few nonrandomized studies (72). However, structural degeneration leading to prosthetic stenosis has also been described with these valves (190).



***e*FIGURE 24.4.1** Structural valve degeneration of a Carpentier-Edwards bioprosthesis in the mitral position demonstrated in a transesophageal echocardiogram. The arrow demonstrates a flail prosthetic leaflet. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

VIDEO

Video 24.21 Structural valve degeneration of a Carpentier-Edwards bioprosthesis in the mitral position demonstrated in a transesophageal echocardiogram (TEE). The arrow demonstrates a flail prosthetic leaflet. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Explanted Carpentier-Edwards mitral valve regurgitation demonstrating the left atrial side of the prosthesis. It is easy to see from this view that the markedly distorted valve leaflets would cause severe stenosis.

Bioprosthetic valve failure is usually insidious, presenting as progressive heart failure. Auscultation may reveal a stenotic or a regurgitant murmur and a soft or absent

closing sound. Leaflet thickening, calcification, and restricted motion is seen with stenotic valves by two-dimensional echocardiography. Leaflet fracture appears as excessive mobility and fluttering during opening and closing (191). Increased transvalvular gradients can be detected by continuous-wave Doppler imaging or by catheterization. Color Doppler imaging may demonstrate intravalvular regurgitation. Bending of the polypropylene stents may occur in certain models of the Hancock bioprosthesis and lead to functional stenosis (192). The incidence of this phenomenon, known as stent "creep," is unknown, but it should be suspected when transvalvular gradients are elevated in the presence of apparently normal prosthetic leaflets.

Video 24.22 Structural valve degeneration of a Carpentier-Edwards bioprosthesis in the mitral position demonstrated in a transesophageal echocardiogram (TEE). Color Doppler demonstrates intravalvular regurgitation. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Prosthetic Valve Endocarditis

Approximately 3% to 6% of patients with prosthetic heart valves will experience prosthetic valve endocarditis during their lifetimes (193,194). Prosthetic valve endocarditis represents approximately 15% of the cases of endocarditis in developed countries (195). The incidence of prosthetic valve endocarditis peaks at 5 weeks after surgery and levels off at 9 months after surgery. This probably occurs because of different factors related to the initial perioperative period, including contamination of the surgical wound, exposure to nosocomially acquired pathogens, and depressed immune system. The different frequencies and types of causative organisms support this concept and lead to the arbitrary classification of prosthetic valve endocarditis as "early" and "late" endocarditis. The overall risk of endocarditis is similar among patients with mechanical and patients with heterograft bioprostheses (194), although some studies suggest that the early endocarditis is more frequent among patients with mechanical valves, whereas late endocarditis is more common among patients with heterograft bioprostheses (195,196). The risk of endocarditis has been reported to be much lower among patients with stentless aortic homografts.

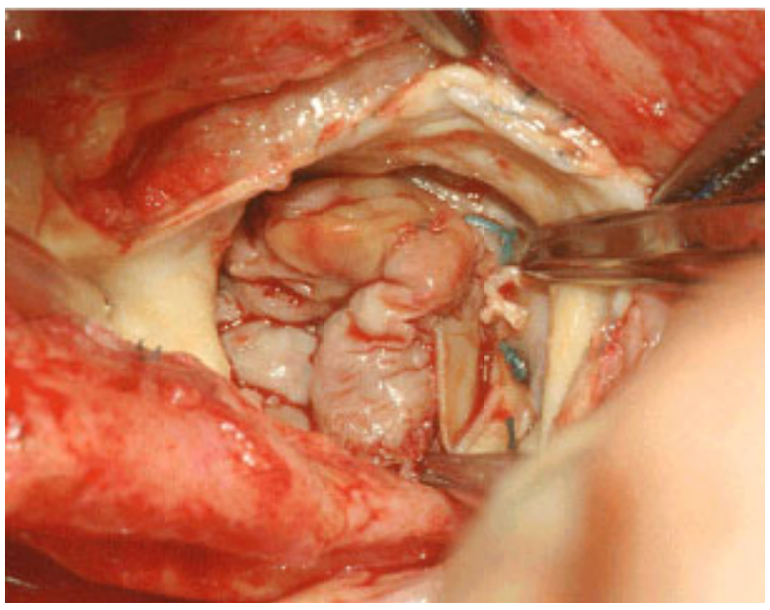
The diagnosis of prosthetic valve endocarditis is based on Duke's criteria, which require the combination of two major (evidence of endocarditis by echocardiography, positive blood cultures), one major and three minor (predisposition, fever, embolism, immunologic phenomena, suggestion of endocarditis by echocardiography, suggestive microbiology), or five minor criteria. Major echocardiographic criteria include the appearance of a new oscillating mass with independent motion attached to the prosthetic material, the detection of perivalvular tissue swelling indicative of an abscess, dehiscence of the prosthetic suture ring, or the appearance of new paravalvular or intravalvular regurgitation.

Early Prosthetic Valve Endocarditis

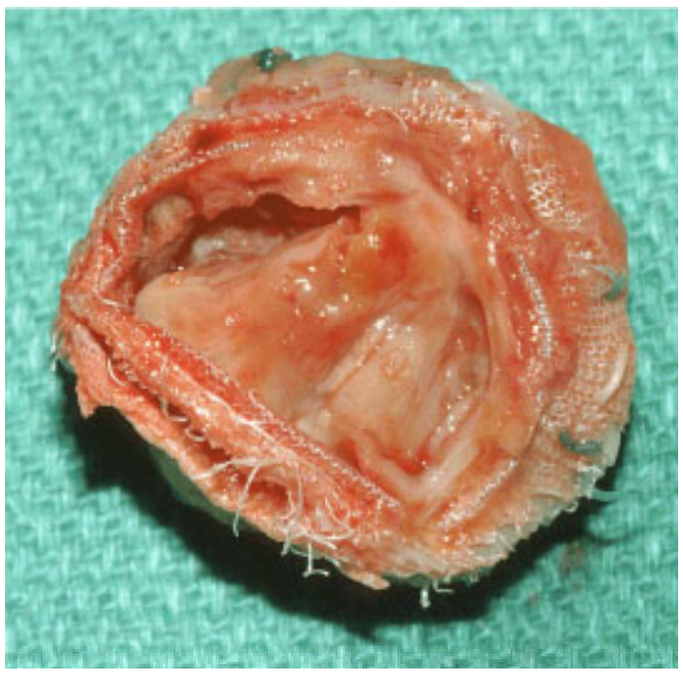
By definition, early endocarditis occurs during the first 60 days after valve implantation. It carries a higher mortality rate, ranging between 20% and 70% (195,196 and 197). The classic signs of endocarditis may be masked by the signs of extracardiac sites of infection, such as sternal osteomyelitis and indwelling catheter infections. Symptoms are usually less typical in early prosthetic valve endocarditis. Fever is the most common symptom, occurring in 97% of patients with this condition, followed by diaphoresis and back pain. Anemia is found in 74% of patients, although most of these patients are anemic because of recent blood loss during surgery. Elevated sedimentation rate is uncommonly found in early prosthetic valve endocarditis. Peripheral findings occur in approximately 10% of the cases. The clinical course tends to be more fulminant, with congestive heart failure observed in 60% and shock in 33% of patients (195). Cerebral thromboembolism is more frequent among patients with mechanical valves who are receiving inadequate anticoagulation (38% to 71%), compared to 10% among patients with therapeutic INR. The severity of neurologic deficits is higher, however, in patients receiving anticoagulant therapy, because of the increased risk of hemorrhagic complications. The differential diagnosis of early prosthetic valve endocarditis includes sternal wound, indwelling line infection, and pneumonia. Endocarditis is more frequently associated with sustained bacteremia, which is usually transient with extracardiac infections. Other features of endocarditis include (a) a longer interval between the time of surgery and the onset of symptoms (>25 days), (b) the presence of a new murmur, (c) identification of a microorganism known to be causative, and (d) the absence of an obvious extracardiac source of infection. Gram-negative organisms are not frequently associated with prosthetic valve endocarditis and most likely indicate an extracardiac source.

The incidence of early prosthetic valve endocarditis decreased steadily during the last two decades. This decrease has been attributed to the administration of prophylactic antibiotics in the perioperative period. However, no randomized study has been done to prove this belief. Studies have shown, however, that a shorter course of antibiotics (1 to 2 days) is not associated with a significant increase in risk compared to a longer course (5 to 6 days) (198). The risk of early prosthetic valve endocarditis in prostheses in the aortic position is similar to that of prostheses in the mitral position and is higher in multiple-valve recipients (193,194 and 195). Early prosthetic valve endocarditis is more common in men, perhaps as a result of skin infections related to shaving of chest hair during surgery.

Staphylococcus epidermidis is the most common causative organism of early prosthetic endocarditis, accounting for approximately 40% of the cases (199). These organisms have a particularly high affinity for implanted or indwelling synthetic surfaces. They are also the most common organisms causing infection throughout the first year after surgery. The majority of infections caused by *S. epidermidis* during the first year (80%) is resistant to methicillin. In contrast, methicillin resistance is low (20% to 30%) among these organisms after 1 year, suggesting that most infections occurring during the first year after surgery are nosocomial in origin. *Staphylococcus aureus* is the second most common causative organism of both early and late prosthetic valve endocarditis, accounting for 20% of the cases. Gram-negative organisms, diphtheroids, and fungi may also be causative organisms during the first 2 months after surgery. *Mycoplasma, Legionella* pneumonia, and atypical mycobacteria and enterococci are less frequent causative organisms during this period. Culture-negative endocarditis most commonly occurs as a result of antibiotic therapy. However, *Mycoplasma*, *Legionella*, fungi, *Coxiella burnetii*, and mycobacteria may cause prosthetic valve endocarditis with negative blood cultures.



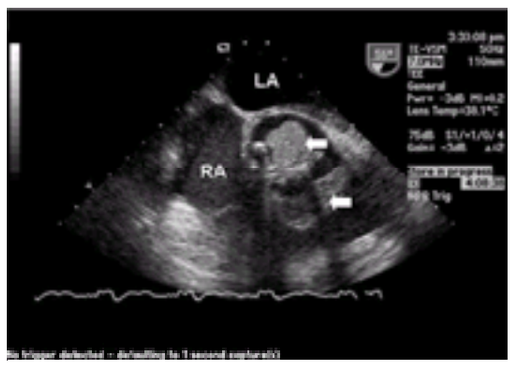
Intraoperative view of a severely damaged aortic prosthesis in a patient with coagulase positive *Staphylococcus* endocarditis. This view is through the aortotomy looking down on the aortic side of the prosthesis.



Surgical specimen of a tissue prosthesis destroyed by *Staphylococcus* endocarditis. This is the ventricular side of the aortic prosthesis. Note the thickened, scarred prosthetic leaflets causing both aortic stenosis and regurgitation.

Late Prosthetic Valve Endocarditis

Late prosthetic valve endocarditis occurs most commonly in patients who have bioprosthetic valves, valves in the aortic position, and multiple prostheses (eFig. 24.4.2). The clinical features of late prosthetic valve endocarditis resemble those of endocarditis of native valves. The incidence of late prosthetic valve endocarditis for mechanical valves is approximately 0.45% per patient-year for valves in the mitral position, 0.54% for valves in the aortic position, and 0.64% for double implants (196). The incidence for bioprosthetic valves is 0.49% for valves in the mitral position, 0.91% for valves in the aortic position, and 0.90% for double implants. The lower incidence of late endocarditis observed with mechanical valves may be explained by the resistance of the mechanical surface materials to adherence of microorganisms. Thus, infections of mechanical prostheses usually originate from the annular tissue around the sewing ring or as a complication of thrombi. A probable source of infection can be found in 25% to 80% of patients who have late prosthetic valve endocarditis (196). Dental procedures, urinary tract infections, and urologic procedures are the most common identifiable sources.



***e*FIGURE 24.4.2** Endocarditis involving a Carpentier-Edwards bioprosthesis in the aortic position demonstrated by transesophageal echocardiography. The arrows indicate a large vegetation and a paravalvular abscess, respectively. LA, left atrium; RA, right atrium.

Explanted Carpentier-Edwards mitral valve regurgitation in a patient with severe infective prosthetic valve endocarditis. The patient had severe mitral stenosis due to the large vegetations on the prosthesis.

VIDEO

Video 24.23 This is a long-axis 134-degree transesophageal view of a patient with prosthetic valve endocarditis of the aortic valve. Note the very large mobile mass or vegetation on the prosthesis accompanied by prosthetic stenosis and moderate insufficiency. The peak and mean pressure gradients across this valve were 90/27 mm Hg, and there was also a paravalvular abscess. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.24 The short-axis 56-degree transesophageal view demonstrating the very large vegetation attached to the Carpentier Edwards aortic valve replacement involving both aortic stenosis and aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.25 Transesophageal echo of a St. Jude mitral valve replacement in a patient with endocarditis. Note the large vegetation on the atrial side of the valve that prolapses across the prosthesis in systole causing prosthetic mitral stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.26 Transesophageal 138-degree view showing the Carpentier-Edwards mitral valve replacement with thickened leaflets with multiple mobile echo densities consistent with vegetations and a clot in a patient with prosthetic valve endocarditis. The mean transesophageal gradient was 20 mm Hg on surface echo. Note the large left atrial thrombus to the right of the screen with significant spontaneous echo contrast in the left atrial cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.27 Deep transgastric view showing the mitral valve replacement in short axis within the sewing ring. One can see the multiple mobile echo densities consistent with vegetation and/or thrombus causing the mitral stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Late prosthetic endocarditis is caused by organisms similar to those that cause endocarditis in native valves. Streptococci are the most common, followed by gram-negative bacteria, enterococci, and *S. epidermidis*, organisms usually found in the dental, gastrointestinal, and skin flora. Culture-negative endocarditis, caused by fastidious gram-negative organisms, is also more frequent during the late period. Symptoms in patients with prosthetic valve endocarditis are similar to those in patients with native valve endocarditis. In patients with mechanical valves, prosthetic valve endocarditis is associated with a high rate (50% to 60%) of annular tissue invasion (195). These rates are similar to those associated with prosthetic valve endocarditis of heterograft bioprostheses during the early period (194). Interestingly, the incidence of tissue invasion seems to be lower (27%) in late endocarditis in bioprosthetic valves. These findings suggest that late endocarditis in bioprosthetic valves may be more amenable to medical management. Congestive heart failure has been reported in approximately 30% to 70% of patients with prosthetic valve endocarditis (193). Cerebrovascular embolization is common in late prosthetic valve endocarditis, occurring in 28% of patients (195). Other common complications include hemolytic anemia (200), prosthetic dehiscence, and heart block (201).

Transthoracic and transesophageal echocardiography are very useful in (a) establishing a diagnosis in patients who have culture-negative endocarditis that is caused by fastidious organisms or the use of antibiotics, (b) detecting the presence of complications such as myocardial abscess, prosthetic dehiscence, fistulae, and large vegetations that are at risk for embolization, (c) monitoring the efficacy of medical therapy, and (d) helping in the planning of surgery. The sensitivity of transthoracic echocardiography for detecting vegetations is significantly lower than its sensitivity for detecting native valve endocarditis (202). This limitation stems from the acoustic shadowing caused by the prosthetic valve components and is more significant with mechanical prostheses. For imaging infective vegetations, the sensitivity and specificity of transesophageal echocardiography are approximately 95% and 90%, respectively. Transesophageal imaging is superior in detecting small vegetations, tissue invasion, and fistula formation (203,204 and 205). Prosthetic valve endocarditis is usually associated with large vegetations, because microorganisms are particularly protected from host defense mechanisms. In patients with both mitral and aortic prostheses, transthoracic imaging may provide a better visualization of the aortic prosthesis and assist in evaluating aortic regurgitation. Transesophageal echocardiography may fail to detect vegetations in patients who present early after the onset of symptoms (206). In these patients, performing a repeated study 48 to 72 hours after presentation should be considered. Prosthetic valve endocarditis carries a very high mortality rate, reported to be between 20% to 80% in different series (205,207,208). The risk of death is higher with early prosthetic valve endocarditis and decreases over time. Congestive heart failure, cerebral embolization, extensive tissue invasion, and infection with *S. aureus* also increase the mortality rate.

VIDEO

Video 24.28 Chest wall transesophageal echocardiogram of patient with endocarditis on a prosthetic mitral valve. A very large mobile mass is seen attached to the annulus on the left atrial side of the St. Jude mitral valve. This mass was not visible on the chest wall echocardiogram. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.29 Endocarditis involving a Carpentier-Edwards bioprosthesis in the aortic position demonstrated by transesophageal echocardiography. The arrows indicate a large vegetation and a paravalvular abscess, respectively. LA, left atrium; RA, right atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.30 Complicated prosthetic aortic valve endocarditis. Transesophageal echocardiography demonstrates fistulous tracts communicating the left ventricular outflow tract (LVOT) with left (LA) and right atria (RA). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Treatment of Prosthetic Valve Endocarditis

Medical treatment of prosthetic valve endocarditis requires longer courses of antibiotics than are used for treatment of native valve endocarditis. The presence of large vegetations usually requires a longer course of antibiotics to achieve sterilization. Regardless of the size of vegetation, however, medical cure is unlikely if there is extensive tissue invasion or if the organism is relatively insensitive to the antibiotic of choice (minimum bactericidal concentration, >4 µg per mL). Treatment of prosthetic valve endocarditis frequently requires surgical replacement of the prosthesis. Streptococcal prosthetic endocarditis is perhaps the only exception; this condition responds to medical treatment alone in 50% of the cases. Medical cure of prosthetic valve endocarditis caused by *Staphylococcus*, gram-negative organisms, or fungi is rare. In patients who are receiving antibiotics and are hemodynamically stable at the time of diagnosis, antibiotics should be withheld briefly to attempt the isolation of an organism from blood cultures. The duration, dosage, and choice of antibiotics is similar to those used in treatment of native valve endocarditis caused by the same organisms, with the following exceptions: (a) treatment of prosthetic valve endocarditis caused by *S. aureus* should include rifampin (300 mg three times per day) and either a semisynthetic penicillin or vancomycin and an aminoglycoside, and (b) in patients who have culture-negative endocarditis associated with a prosthetic valve, vancomycin should be added to ampicillin and gentamycin (209). In cases of penicillin allergy, vancomycin should be used as a second choice.

Surgical replacement should be promptly performed if (a) bacteremia persists after 5 days of intravenous antibiotic therapy; (b) infection recurs after discontinuation of antibiotic therapy; (c) there is evidence of tissue invasion or fistulous tracks; (d) recurrent embolization occurs on antibiotic therapy; (e) infection is caused by a fungal organism; or (f) prosthetic obstruction, dehiscence, heart block, or congestive heart failure develops (210,211). Patients with vegetations that are larger than 10 mm in diameter carry a high risk of embolization, and treatment is less likely to be successful. In these patients, early surgical replacement should be performed. Patients with prosthetic valve endocarditis who have experienced an embolic event while receiving antibiotics and who have residual vegetations carry a significant risk of recurrent

embolization and should be considered candidates for early surgical replacement. Patients in whom bacteremia persists for more than 2 days despite effective antibiotic therapy have a better prognosis with early surgical intervention (199). The overall mortality rate of patients treated with antibiotics alone is 61%, compared with 38% among patients who undergo valve replacement (212). In earlier surgical series, however, the mortality rate was high because of delayed operations in patients in whom medical therapy failed. Surgery should not be delayed in any of these circumstances, with perhaps one exception: Patients with cerebral embolization have a significant risk of intracranial hemorrhage during surgery, particularly if they have large neurologic deficits, large abnormalities on a cranial CT scan, or evidence of mycotic aneurysms on a cerebral angiogram. Aggressive removal of all infected tissue should be performed to avoid recurrence of the infection. Occasionally, the annular tissue needs to be reconstructed with autologous pericardium. The stentless aortic homograft is an excellent choice for replacement of infected aortic prostheses. The risk of recurrent endocarditis in aortic homografts is very low (213). Antibiotic treatment should be administered for 6 weeks after surgery. If the organism is methicillin-sensitive *Staphylococcus*, gentamycin should be also administered for 2 weeks. Vancomycin should be used to treat infections caused by methicillin-resistant strains.

Prosthetic valve endocarditis remains a serious complication of valve replacement, but the in-hospital mortality rate associated with reoperations for prosthetic valve endocarditis has declined. In experienced centers, most patients in whom prosthetic valve endocarditis is surgically treated have a favorable outcome. Of 146 patients reoperated for the treatment of prosthetic valve endocarditis by Lytle and colleagues (214) from 1975 through 1992, only 13% died in-hospital (eTable 24.1.5). In this study, the surgical mortality rate decreased from 20% between 1975 and 1984 to 10% between 1984 and 1992. The improvement in the prognosis of patients with prosthetic valve endocarditis during the last decade was probably caused by advancements in surgical techniques, including extensive débridement of infected tissue, use of homografts, and improved antibiotic therapy, as well as earlier surgical intervention and patient selection. Both homograft (215) and allograft (216) replacement are associated with a low risk of recurrence in aortic valve endocarditis. Recent efforts have aimed at reducing the incidence of early prosthetic valve endocarditis, such as coating the suture ring with silver (217). However, a higher than expected incidence of paravalvular regurgitation and dehiscence lead to the withdrawal of silver nitrate–impregnated mechanical valves from the market (218).

***e*TABLE 24.1.5** IN-HOSPITAL MORTALITY FOR SURGICALLY TREATED PROSTHETIC VALVE ENDOCARDITIS ACCORDING TO OPERATIVE YEARS

	1975–1984 (%)	**1984–1992 (%)**	***p* value[a]**	**Total (%)**	***p* value[b]**
Early	4/11 (36)	3/35 (9)	.046	7/46 (15)	
Late	5/33 (15)	7/67 (10)	.524	12/100 (12)	.591
Active	8/33 (24)	9/70 (13)	.146	17/103 (16)	
Healed	1/11 (9)	1/32 (3)	.451	2/43 (5)	.052
Extent of infection	2/19 (10)	2/47 (4)	.373	4/66 (6)	
Prosthesis alone					
Annulus	4/17 (24)	3/29 (10)	.397	7/46 (15)	
Invasive	3/8 (38)	5/26 (17)	.355	8/34 (24)	.04
Surgical specimen culture					
Negative	4/29 (14)	2/65 (3)	.071	6/94 (6)	
Positive	5/15 (33)	8/37 (22)	.483	13/52 (25)	.001
Total	9/44 (20)	10/102 (10)	.079	19/146 (13)	

[a]*p* value for comparison of mortality per variable for the two surgical periods.
[b]*p* value for comparison of mortality between variables for the entire patient group.
Adapted from Lytle BW, Priest BP, Taylor PC, et al. Surgical treatment of prosthetic valve endocarditis. *J Thorac Cardiovasc Surg* 1996;111:200.

Antibiotic Prophylaxis in Patients with Prosthetic Valves

To date, no adequate controlled studies testing the effectiveness of prophylactic antibiotics in patients with prosthetic valve endocarditis have been carried out. Antibiotic prophylaxis is recommended, however, based on observations determining that (a) transient bacteremia occurs after certain invasive procedures and (b) patients with prosthetic valves in whom bacteremia is documented have a 10% risk of developing late endocarditis (219). Antibiotic prophylaxis is recommended during invasive procedures that carry a high risk of bacteremia, including dental extractions and professional cleaning and gastrointestinal, genitourinary, and oral surgery. Prophylaxis is no longer recommended before flexible endoscopy or bronchoscopy or normal vaginal delivery. For dental, oral, and respiratory tract procedures, oral antibiotics are effective and are preferred in ambulatory patients. According to the new recommendations issued by the American Medical Association (220), amoxicillin (2 g) administered 1 hour before and after the procedure is the treatment of choice. Erythromycin or clindamycin is recommended for use in patients who are allergic to penicillin. For genitourinary and gastrointestinal procedures, ampicillin (1 g intravenously) and gentamycin (80 mg intravenously) should be given 1 hour before surgery and 8 hours after the initial dose. Vancomycin (1 g intravenously) should substitute for ampicillin in patients who are allergic to penicillin.

Hemolysis

Several mechanisms may contribute to the development of hemolysis in normal and malfunctioning prosthetic valves, including shear stress, turbulence, pressure fluctuations, interaction with foreign surfaces, and intrinsic abnormalities of the erythrocyte membrane (221). With the first class of ball-and-cage prosthesis that was implanted, the observed incidence of hemolysis was between 6% and 15% in different series (222,223 and 224). The improved hemodynamic performance and surface materials of the newer mechanical and bioprosthetic valves have resulted in a significant reduction of this risk (225,226). Subclinical hemolysis (increased reticulocyte count and lactate dehydrogenase, decreased haptoglobin) is found in most patients who have mechanical valves, but it rarely results in significant anemia. However, hemolytic anemia still represents a relatively common complication among patients with malfunctioning prostheses. Hemolysis is commonly found in association with paravalvular regurgitant leaks. In a series published by Kastor and coauthors (222), 40% of patients with prosthetic valves and paravalvular regurgitation had significant hemolysis that required surgical repair or resulted in death.

VIDEO

Video 24.31 Paravalvular regurgitation demonstrated by color Doppler in a patient with severe hemolysis. LA, left atrium; LV, left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 24.32 Intraoperative transesophageal echo (transgastric short-axis view) of a CarboMedics mitral valve replacement with both physiologic prosthetic mitral regurgitation (two jets from within the sewing ring) and an abnormal, lateral paravalvular jet (outside the sewing ring to the right of the screen). Note that the paravalvular jet is arising between the sewing ring and an area of mitral annular calcification, making it difficult for the prosthesis to be in close contact with the annulus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Shear stress that causes morphologic alterations in the erythrocyte membrane and results in hemolysis has been well documented. By means of transesophageal echocardiography and fluid dynamic simulation, it has been demonstrated that flow acceleration, deceleration, and fragmentation may be important causes of increased shear stress associated with periprosthetic leaks (227). Patients with clinical hemolysis demonstrate patterns of flow that are associated with peak shear stresses of 4,500 to 6,000 dynes per cm^2. Direct collision with cardiac structures, such as the limbus of the left atrial appendage, that caused rapid flow deceleration was the most common flow pattern associated with hemolysis in this study. Regurgitation through several small orifices or orifices of irregular shape is associated with greater hemolysis than regurgitation through large, round orifices, perhaps because of the higher acceleration required for passage through the small orifice.

Other factors are also important in the development of hemolytic anemia with prosthetic valves. The surface area and the type of prosthetic material are important factors in the genesis of hemolysis. This phenomenon was noted with the introduction of the completely cloth-covered ball-and-cage prosthesis (Starr-Edwards, series 2300, 2310; Fig. 24.2) (110). These valves, which were developed in an attempt to decrease the incidence of thromboembolism, were associated with a 15% incidence of severe hemolytic anemia. The foreign surface effect is of greater importance when considering the probability of a patient developing hemolysis with malfunctioning prostheses. Teflon and other prosthetic materials that are used to construct the sewing ring and to partially cover the struts in some contemporary valve models become rapidly endothelialized within several weeks after implantation. However, regurgitant jets from paravalvular leaks may denude this endothelium, revealing the

prosthetic surface and increasing the propensity to develop hemolysis.

Abnormal flow through a partially thrombosed prosthetic valve may cause hemolytic anemia. Hemolytic anemia is also a common finding in patients who have prosthetic valve endocarditis (228) and in patients who have bioprosthetic valves with structural failure (229). The presence of multiple prosthetic valves or unusually small mechanical prostheses is also associated with higher incidence and severity of hemolysis (230). Mild hemolytic anemia may be treated medically with erythropoietin, iron and folic acid supplementation, and blood transfusions. Control of hypertension with beta-blockers may reduce the severity of hemolysis, probably by reducing the velocity of regurgitant flows and thus the shear stress (231). Closure of paravalvular regurgitant leaks or valve replacement is indicated in patients with severe hemolysis that requires repeated blood transfusions or in patients with congestive heart failure.

Dehiscence and Periprosthetic Regurgitation

Separation of the sewing ring from the annular tissue may occur in the early postoperative period, due to poor surgical techniques, excessive calcification and fragility of the annular tissue, or infection. Inadequate nutritional status and use of steroids may impair surgical healing and promote early dehiscence. Late dehiscence occurs commonly as the result of infective endocarditis. Polypropylene sutures increase the risk of dehiscence to approximately 10% within 4 years of operation (232). On the other hand, fractures of Dacron polyester sutures are rare. A new regurgitant murmur may herald the presence of prosthetic valve dehiscence. Abnormal rocking of the sewing ring relative to the annular tissue is the characteristic finding observed by means of two-dimensional echocardiography or cinefluoroscopy (233,234). Color Doppler echocardiography demonstrates abnormal paravalvular flow seen as a regurgitant jet distal to the prosthesis or a region of proximal flow convergence (234). Prosthetic valve dehiscence requires prosthetic replacement, although resuturing of the free portion of the sewing ring with or without a pericardial patch may have satisfactory results. In patients at high risk for reoperation percutaneous catheter, closure of the paravalvular orifice with a double-umbrella device has been successfully performed (235).

VIDEO

Video 24.33 On this cine-fluoroscopy, note the extreme motion of the Lillehei-Kaster prosthetic valve apparatus. This is consistent with a partial dehiscence of the valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Conduction Abnormalities

Heart block may occur after replacement of aortic valves that have become severely calcified, as a result of trauma to the bundle of His that occurs during removal of calcium from the region of the right trigone, beneath the commissure between the noncoronary and the right coronary cusp. Fortunately, complete heart block is uncommon and is usually transient and caused by postoperative edema of the periannular tissue.

Myocardial Infarction

Embolization of air through the right coronary artery is a relatively common cause of perioperative infarction of the inferior wall myocardium, but it rarely results in permanent systolic dysfunction. Myocardial infarction due to obstruction or dissection of the coronary ostia after reimplantation of the coronary trunks in stentless aortic homografts or prosthetic valve conduits may rarely occur. Intraoperative echocardiography is useful demonstrating the presence of postoperative wall motion abnormalities and the patency of flow in the coronary arteries of such patients (236). Myocardial infarction may also be caused by coronary embolization of thrombotic material or infective and aseptic vegetations of endocarditis (237). Coexisting coronary artery disease represents, however, the most common cause of myocardial infarction in patients with prosthetic heart valves.

Ventricular Pseudoaneurysm

Perforation of the posterior mitral annular region may occur after mitral valve replacement, particularly when severe calcification of the mitral annulus is present (238). The posterior pericardium may initially contain the rupture, preventing cardiac tamponade and death. The diagnosis of this infrequent complication is often incidentally made on the basis of a routine echocardiogram. Pseudoaneurysms detected early after mitral valve prosthetic implantation require prompt surgical repair.

Patient-Prosthesis Mismatch

All prosthetic valves, with the exception of the stentless aortic homograft, have effective orifices that are smaller than those of native valves of the same annular dimensions. Thus, prosthetic valves are inherently stenotic and have a residual transvalvular pressure gradient. Occasionally this gradient is significant enough to cause symptoms, particularly when small prostheses are implanted in patients of large size. Pressure gradients that are of moderate magnitude at rest may increase significantly during exercise.

Patient-prosthetic valve mismatch occurs most frequently after valve replacement for aortic stenosis. The aortic annulus is often small in these patients, and, after replacement, the effective orifice may have an area between 1.0 and 1.5 cm^2. Dobutamine or exercise echocardiography may be useful in evaluating patients whose symptoms persist after valve replacement by obtaining an estimate of the transvalvular gradients at high cardiac outputs and by evaluating the impact of these gradients in left ventricular systolic function (239). In patients with small annular size, special consideration should be given to the hemodynamic profile when the replacement valve is selected. Stented bioprosthetic valves and ball-and-cage mechanical prostheses are intrinsically more stenotic. Patients with small tilting-disc mechanical aortic prostheses often have increased resting and exercise gradients. However, recent studies have failed to demonstrate aerobic exercise impairment in these patients in comparison with age-matched healthy cohorts (240).

Surgical techniques including supraannular implantation and supraannular and annular enlargement may be performed at several institutions to permit the implantation of larger prosthetic devices and avoid patient-prosthesis mismatch (241,242). Stentless valves are probably the best choice for active patients who want to avoid anticoagulation therapy. Studies have shown better exercise hemodynamics and greater regression of left ventricular hypertrophy in patients who receive stentless valves than in patients who receive stented valve prostheses (68,69). In general, stented aortic valve prostheses smaller than 21 mm in diameter are not recommended for patients of larger size who are physically active (243,244).

Left Ventricular Outflow Obstruction

Some patients with aortic valvular stenosis have significant hypertrophy of the basal muscular septum, either as a result of long-standing pressure overload or as a separate, coexisting condition. In these patients, left ventricular outflow tract obstruction may be subtle before valve replacement because of the high afterload imposed by the stenotic valve. After replacement, the decrease in afterload may result in significant obstruction of the left ventricular outflow tract caused by systolic anterior motion of the anterior mitral valve leaflet. Intraoperative transesophageal echocardiography is useful in diagnosing this complication and should be considered in patients undergoing aortic valve replacement who have severe septal hypertrophy and a small left ventricular outflow tract. Septal myectomy is usually successful correcting this problem when the obstruction is severe. Patients with mitral stenosis and small left ventricular cavities may also develop left ventricular outflow tract obstruction that is caused by one of the supporting struts of a bioprostheses. In these patients, replacement with a mechanical valve is preferred.

ROUTINE FOLLOW-UP OF PATIENTS WITH PROSTHETIC VALVES

After replacement, a transthoracic echocardiographic examination is recommended before the patient is discharged from the hospital to exclude potential postoperative complications such as cardiac tamponade, ventricular pseudoaneurysm, prosthetic paravalvular regurgitation, and perioperative myocardial infarction. A follow-up clinical and echocardiographic evaluation 6 to 8 weeks after discharge is also recommended. At this time, careful determination of the transvalvular gradient, effective valvular orifice, and dimensionless transvalvular velocity index should be made for future comparisons. Further echocardiographic studies should not be required for several years unless there is failure of functional recovery after surgery or development of new symptoms that may indicate myocardial or valvular dysfunction. Additional information obtained from the echocardiogram, such as the left and right ventricular systolic function, chamber sizes, and the estimation of the right ventricular systolic pressure, are helpful to determine the etiology of symptoms. Failure of mechanical valves is rare, and therefore the value of routine echocardiographic follow-up of asymptomatic patients is controversial. Routine echocardiographic evaluation is most useful for patients with bioprosthetic valves because of the earlier and more gradual structural degeneration of such prostheses.

Follow-up routine echocardiographic examinations performed as early as 5 years after surgery, particularly in younger patients and patients who have valves in the mitral position, is recommended. These studies should be repeated every 2 years if the leaflets appear to be morphologically normal and every 6 to 12 months if evidence of prosthetic degeneration (e.g., leaflet thickening and calcification), intravalvular regurgitation, or stenotic flow is seen. Transesophageal echocardiography provides a more accurate assessment when regurgitation is suspected in patients with mitral prostheses or when unexplained congestive heart failure or pulmonary hypertension occurs. Anticoagulation should be monitored rigorously by specialized clinics or physicians. Maintaining adequate anticoagulation requires not only periodic monitoring of the INR but continuous patient and physician education, including knowledge of drug interactions.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Selecting a Prosthetic Valve

The choice between mechanical and bioprosthetic valves should be an early point of discussion between the cardiologist, the cardiac surgeon, and the patient. Multiple factors need to be considered in the decision-making process, including the age of the patient; the probability of future pregnancy in young women; and the patient's occupation, lifestyle, and life expectancy. The risk of a future reoperation should also be considered and may be greater after more extensive surgery such as stentless valve or allograft replacements. When feasible, valve repair should be considered. Otherwise, with very few exceptions, such as a patient who is already receiving chronic anticoagulation therapy or whose anticipated life expectancy is short, no absolute advantages are associated with a specific valve type. Mechanical valve prostheses have a longer durability but require a lifelong commitment to chronic anticoagulation therapy. They should be chosen for younger patients who do not have contraindications and are expected to be medically compliant. The relative benefit-to-risk ratio shifts earlier toward bioprosthetic valves in the aortic position. We recommend bioprosthetic valves for aortic replacement in patients older than 65 years and for mitral valve replacement in patients who are 70 to 75 years old. Middle-aged or younger patients who wish to avoid long-term anticoagulation therapy and who require aortic valve replacement are good candidates for homograft or allograft replacement, because the durability of theses valves appears to be greater than that of bioprostheses. It remains to be determined whether the durability of stentless porcine valves is comparable.

Prosthetic Valves and Pregnancy

The risk of complications to the mother and to the fetus is significant with both mechanical and bioprosthetic valves. Anticoagulation therapy carries a risk to the fetus even when heparin is substituted for warfarin in the first and third trimesters. Bioprosthetic valves undergo rapid structural degenerative changes in young patients and still carry a higher than expected fetal mortality rate. Women of childbearing age who have mild or regurgitant valvular heart disease should carry their pregnancies earlier in their childbearing years and undergo tubal ligation before prosthetic valve replacement with a mechanical valve. Valve repair should be performed whenever feasible. If valve replacement cannot be avoided, bioprosthetic valves should be used, because they carry a smaller risk of fetal and maternal complications.

Medical versus Surgical Treatment of Prosthetic Valve Complications

Most hemorrhagic and embolic complications seen in patients who have mechanical valves are managed medically, although a few patients with mechanical valves who experience recurrent embolic or hemorrhagic events may benefit from replacement with a bioprosthetic valve. With rare exceptions, other prosthetic valve complications, such as prosthetic valve degeneration, dehiscence, severe hemolysis, and most cases of endocarditis are best treated surgically. No adequate treatment for prosthetic valve degeneration is available. Balloon valvuloplasty of bioprosthetic valve stenosis has been attempted but carries an unacceptably high risk of systemic embolization, acute severe regurgitation, and early restenosis. Thrombolytic therapy of left heart prosthetic valve thrombosis carries a significant risk of stroke. In our opinion, thrombolytic therapy should be reserved for patients who have right-heart prostheses, who are otherwise at high risk for surgery, or for whom skilled surgical treatment is not readily available. Medical cure of prosthetic valve endocarditis occasionally may be accomplished, depending on the valve type and the infecting organism. *Streptococcus viridans* endocarditis in patients with bioprosthetic valves usually responds well to antibiotic therapy. In our experience, these patients should be followed closely; they frequently require valve replacement because of recurrence of infection, incomplete cure, or premature structural degeneration. Valve-induced hemolysis is frequently insidious in onset and may be managed medically, often for several years. The rate of hemolysis and thus requirements for blood transfusion tend to increase steadily over time. Often, the diagnosis of hemolysis is missed in these patients; because of chronic iron losses in urine, they present with predominant signs of iron-deficiency anemia. Because of the risks associated with repeated blood transfusions, valve replacement should be considered early in these patients.

THE FUTURE

The development and refinement of prosthetic valves during the last three decades have resulted in a remarkable improvement in survival and quality of life for millions of patients who have valvular heart disease. Replacement of a malfunctioning native valve with a prosthesis, however, substitutes one disease for another. None of the available mechanical or biologic valves has the performance and durability of the native human semilunar and atrioventricular valves. Stentless valves appear to have better hemodynamic performance than mechanical valves and stented heterografts, but their long-term durability is still unknown. Refinement of the mitral valve homograft will likely occur in the near future. Mitral homografts may become the procedure of choice for young patients and women of childbearing age who have mitral stenosis that is not amenable to commissurotomy or mitral insufficiency that is not amenable to surgical repair. Future improvements in prosthetic valve design are likely to provide less thrombogenic mechanical materials and better hemodynamic profiles. Future generations of mechanical valves may not require chronic anticoagulation therapy with warfarin. At the same time, chemical and biologic preservation techniques will continue to improve the longevity of bioprostheses. Newer advances in surgical techniques may reduce the morbidity and mortality rates associated with valve surgery. Improved surgical instruments, limited incision surgical techniques, and robotic surgery are now available in many specialized centers and likely will reduce the morbidity associated with heart valve surgery.

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INFECTIVE ENDOCARDITIS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Despite many improvements in diagnostic and therapeutic advances, infective endocarditis (IE) remains a disease with high morbidity and mortality. Whereas formerly a younger population with rheumatic heart disease was the victim, an older population and a number of illicit drug users now present with the disease. Vegetations are usually located on the atrial surface of atrioventricular valves, the ventricular surface of semilunar valves, or in areas of the heart where jet lesions disrupt the endothelial surface. Occasionally, apparently normal valves are infected (especially in intravenous drug users). More recent diagnostic criteria have been developed that use clinical findings, pertinent laboratory data, and echocardiographic findings to diagnose endocarditis with a high degree of sensitivity and specificity. Transesophageal echocardiography (TEE) has been a major advance in diagnosing vegetations in prosthetic valve disease and in describing intracardiac complications, such as annular abscess, in all cases of IE.

Prevention of endocarditis using established criteria remains the standard of care despite lack of definitive studies. Antimicrobial therapy continues to evolve as efforts are being made to develop long-acting antibiotics that would be suitable for home therapy. Home intravenous therapy has been shown to be feasible and cost effective when the family situation allows such an approach. Advances in cardiothoracic surgery may result in earlier surgical intervention in many instances. Patients with IE often have many complicating features. The formidable challenge they often present is best met by using a team approach involving cooperation among cardiologists, cardiothoracic surgeons, and infectious disease specialists.

GLOSSARY

***Actinobacillus*:** A nonmotile, fastidious, gram-negative rod that can cause endocarditis in humans.

***Actinobacillus actinomycetemcomitans*:** A species of *Actinobacillus*.

Adenovirus: A family of double-stranded DNA viruses.

Aminoglycosides: A group of antibiotics made from species of *Streptomyces* or *Micromonosporum*. Effective against many gram-negative bacilli and *Mycobacterium tuberculosis*.

Amoxicillin: A semisynthetic penicillin with an antimicrobial spectrum similar to ampicillin.

Ampicillin: A semisynthetic penicillin that has a broader spectrum of antimicrobial activity than penicillin G.

***Bacillus*:** A genus of anaerobic, spore-forming gram positive rods found in the soil.

***Bartonella*:** A genus of bacteria that is difficult to grow in the laboratory. These bacteria cause infection in cats and can be transmitted to humans by scratches or louse bites.

Blalock-Taussig shunt: A shunt created by routing the left or right subclavian artery to the pulmonary artery.

***Brucella*:** A genus of encapsulated, gram-negative bacteria that are pathogens of humans and a variety of animals.

***Candida*:** A genus of fungi found on the skin and in feces, vaginal, pharyngeal, and gastrointestinal tracts.

Cefazolin: A broad-spectrum cephalosporin.

Ceftriaxone: A semisynthetic parenteral cephalosporin antibiotic.

Cephalosporin: One of several antibiotic substances obtained from *Cephalosporium* species of fungi. Effective against many gram-positive and gram-negative organisms.

***Chlamydia*:** A genus that includes all the agents of the psittacosis, lymphogranuloma, trachoma group.

Clindamycin: A class of antibiotics with broad activity against anaerobic bacteria and many gram-positive cocci.

***Corynebacterium*:** A genus of gram-positive rods found widely in nature; can be found in oropharynx.

***Coxiella burnetii*:** The bacteria that causes Q fever in humans.

Coxsackie B: A picornavirus responsible for a variety of diseases in humans.

***Eikenella*:** A nonmotile, gram-negative, anaerobic rod part of normal oral cavity.

Endarteritis: Inflammation of the intima of an artery.

***Enterococcus*:** A genus of gram-positive cocci that inhabits the intestinal tract of humans.

***Escherichia coli*:** A gram-negative rod widely found in nature; inhabits the intestines and causes infections of the urogenital and gastrointestinal tract.

Fibronectin: A fibrous-linking glycoprotein found in connective tissue, basement membranes, and cell surfaces; acts as an adhesive.

Gentamicin: An aminoglycoside antibiotic that inhibits growth of gram-negative and some gram-positive bacteria.

***Haemophilus*:** A gram-negative rod in the respiratory tract.

Histoplasma: A dimorphic fungus normally found in soil; it causes pulmonary infections.

Janeway lesion: Erythematous, nontender lesions on fingers, palm, or sole.

Keyhole surgery: Surgery performed through a small thoracotomy rather than large median sternotomy or large lateral thoracotomy.

Laminin: A large polypeptide glycoprotein component of basement membrane.

***Legionella*:** An aerobic gram-negative bacillus that is found in fresh water. It can cause pulmonary wound or renal infections.

***Listeria*:** A genus of motile bacteria containing small gram-positive rods; can cause meningitis, encephalitis, septicemia, endocarditis, abortion, and abscesses.

MacCallum's patch: Vegetations found along the mural surface of a cardiac chamber.

***Mycoplasma*:** A genus of gram-negative organism that lack a true cell wall; may cause pulmonary or genitourinary and postpartum infections.

Mycotic aneurysms: Aneurysmal dilatation of a vessel caused by invasion of the vascular wall from infective endocarditis.

Nafcillin: A semisynthetic penicillin resistant to penicillinase and effective against some strains of *Staphylococcus aureus*.

Osler's nodes: Small, tender, purple erythematous subcutaneous nodules visibly found on the pulp of digits.

Penicillin G: An antibiotic produced from cultures of the molds' *Penicillium* species.

***Propionibacterium*:** A genus of nonmotile, non–spore-forming gram-positive rods found on the skin and in the intestinal tract.

***Proteus*:** A genus of gram-negative bacteria that can cause genitourinary and nosocomial infections.

***Pseudomonas aeruginosa*:** A species of gram-negative, aerobic bacteria found in soil, water, and clinical specimens.

***Rickettsia*:** A genus of intracellular gram-negative bacteria that causes a variety of diseases such as spotted fever and typhus.

Roth's spots: Retinal hemorrhages with a clear center.

***Salmonella*:** A genus of gram-negative bacilli that can cause gastrointestinal and bacteremic illnesses.

***Serratia marcescens*:** Gram-negative rods that may produce infection in immunocompromised and hospitalized patients.

Splinter hemorrhage: An embolic subungual hemorrhage located proximally in the nailbed.

***Staphylococcus aureus*:** Gram-positive bacteria that may colonize the nasal mucous membranes and skin (hair follicles) and cause serious skin, soft tissue, blood, and endocardial infections.

***Streptococcus bovis*:** Gram-positive bacteria found in the gastrointestinal tract.

***Streptococcus milleri*:** A gram-positive coccus found in human throat, mouth, and nasopharynx.

***Streptococcus pneumoniae*:** A gram-positive, lancet-shaped diplococcus frequently occurring in chains; normal inhabitant of the respiratory tract.

***Streptococcus sanginosus*:** A gram-positive coccus found on oral and nasopharyngeal mucous membranes.

***Streptococcus sanguis*:** A gram-positive coccus found normally in oral and nasopharyngeal mucous membranes.

***Streptococcus viridans*:** Name applied to a group of alpha-hemolytic streptococci describing organisms isolated from the mouth and intestines.

Streptomycin: An antibiotic agent from *Streptomycesgriseus* active against *Mycobacterium tuberculosis* bacillus and a large number of gram-negative bacteria.

Type 4 collagen: A protein with a less distinct fibrillar form, characteristic of basement membranes.

Vancomycin: An antibiotic with activity against most gram-positive organisms.

Vegectomies: Surgical removal of endocarditis vegetations from a valvular surface.

Vegetations: Growth consisting of fused platelets, fibrin, and other bacteria adherent to a heart valve or other vascular structure.

HISTORICAL PERSPECTIVE

The first descriptions of infection of the heart valves in humans appeared over 300 years ago (1). Riveriere described autopsy findings associated with endocarditis in 1723, and Morgagni provided classical descriptions in 1761. In 1806, Jean Nicolause Corvisart first used the term *vegetations* to describe the characteristic macroscopic excrescences that are typically seen in patients with IE (2). During the next 75 years physicians such as Laennec, Bouillaud, Charcot, and Virchow described many of the clinical and pathologic features of IE, even though recognition of the relationship between microbes and this disease was delayed until the birth

of microbiology in the latter part of the nineteenth century. Rosenow (3) and Luschka (4), among others, thought microbes infected the valves by invading what was the network of capillaries that existed within the valves. It was not until 1937 that Gross (5) concluded that heart valves were avascular structures and the previously observed capillary network was merely a function of an inflammatory response. Subsequently, experiments by investigators such as Rosenbach, Wyssokowitsch, and Weichselbaum led to the realization that most patients with IE had preexisting damage to their heart valves and that the initiating event was the entry of microbes into the bloodstream from a site of local infection or a mucosal surface (2).

Through a series of three famous Goulstonian Lectures in 1885, William Osler was the first person to explain the clinical features of endocarditis in a clear and precise manner. He identified four cardinal manifestations of endocarditis: the presence of persistent bacteremia, the presence of active valvulitis, the occurrence of large vessel emboli, and immunologic vascular phenomena (6). These manifestations remain the cornerstones of clinical diagnosis to this day. Osler also coined the term *mycotic aneurysm* to describe the focal endarteritis that may complicate endocarditis (6). He not only noted emboli to multiple internal organs, such as the brain, spleen, kidneys, and retina, he also described “small swollen areas, some the size of a pea, others a centimeter and a half in diameter, raised, red, with a whitish spot in the center. . . . The commonest situation is near the tip of the finger.” These areas have been known as *Osler’s nodes* ever since (7).

The clinical features and morbid anatomy of endocarditis were extensively studied in the preantibiotic era of the twentieth century (6,8). Perhaps Soma Weiss reported the most famous early case. The patient was a medical student who had chronic rheumatic heart disease and then developed *Streptococcus viridans* endocarditis (9). In his diary, the budding physician noted clubbing of his fingernails followed by a host of peripheral embolic phenomenon. The diary describes his emotional reaction to the realization he has endocarditis. On discovering the cutaneous manifestations of the disease, he turned to his sister-in-law and proclaimed, “I shall be dead in 6 months.” His declaration was prophetic.

IE was invariably fatal until the discovery of penicillin and the subsequent development of other beta-lactams and antimicrobial agents. Thereafter, steady incremental advances in cardiac surgery and innumerable improvements in the technology of medical care collectively have had an enormous impact on the clinical management of this disease. During the past 15 years, new diagnostic methods such as transthoracic echocardiography and TEE have improved and simplified the diagnosis and management of endocarditis. Unfortunately, common causes of endocarditis such as enterococci and viridans streptococci have acquired resistance to standard antimicrobial agents. Clinicians who treat this potentially lethal, yet often curable, disease need to be aware of these developments and the fact that IE will remain a disease in evolution.

ANATOMIC CONSIDERATIONS

Vegetations in patients with preexisting valvular lesions are usually located on the atrial surface of incompetent atrioventricular valves or the ventricular surfaces of incompetent semilunar valves. This is likely because of the fact that these surfaces are subjected to injury from regurgitant jets. In patients with ventricular septal defects, vegetations tend to occur on the orifice of the defect, on the right ventricular side of the opening, and secondarily on the tricuspid and pulmonic valves (10). Vegetations may occasionally localize on the chordae tendineae of the anterior leaflet of the mitral valve in patients with aortic insufficiency. Patients with mitral regurgitation may also develop a vegetation (MacCallum’s patch) on the wall of the left atrium where the regurgitant jet strikes the atrial wall and results in endocardial thickening (Fig. 25.1).

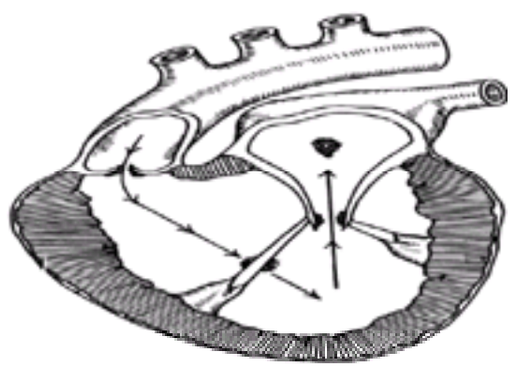


FIGURE 25.1 Sites of high-velocity streams where endocardial injury occurs in mitral and aortic insufficiency. (From Robard S. Blood velocity and endocarditis. *Circulation* 1963;27:24, with permission.)

The source of infection in some patients with endocarditis may be clinically evident (e.g., an infected vascular catheter, a dental abscess, or an infected skin lesion), but in many patients, there is no history of an antecedent localized infection. In most such instances, the source is presumed to be from minor trauma to the oropharyngeal, gastrointestinal, or genitourinary mucosa.

Endocarditis in injection drug users is dominated by one pathogen: *S. aureus*. *S. aureus* is known to have a predilection for normal as well as abnormal cardiac valves (11). This phenomenon may explain why the majority of injection drug–using patients with endocarditis has no known prior valvular disease (12). Endocarditis in injection drug users is presumed to result as a consequence of the trauma to heart valves from contaminating inorganic debris and bacteria injected along with the illicit drugs, from the paraphernalia used for drug injection, or via bacteria on the skin surface at the site of injection. Tricuspid valve involvement has been noted in 78%, mitral in 24%, and aortic in 8% of drug addicts with endocarditis (12). Simultaneous involvement of more than one valve may occur in approximately 20% of drug-abusing patients (13), and some of these infections are polymicrobial (14).

Approximately three-fourths of all patients with endocarditis have a preexisting structural cardiac abnormality at the time that endocarditis begins (15,16). During the period from 1938 to 1967, rheumatic heart disease was the underlying cardiac lesion in 39% of patients hospitalized with endocarditis at the Presbyterian Hospital in New York (17). In contrast, the authors of a large case series from Tennessee reported that only 6% of patients with endocarditis had underlying rheumatic cardiac lesions (16). Simultaneously, preexisting degenerative valvular lesions such as mitral valve prolapse (usually with coexistent mitral regurgitation) have become relatively more important as a predisposing cause for endocarditis. For example, preexisting mitral valve prolapse was the underlying cardiac lesion in 22% and 29% of cases of endocarditis in two case series (16,18). The estimated risk of endocarditis in patients with mitral valve prolapse and regurgitation has been estimated to be five to eight times higher than the normal population (19,20). However, mitral valve prolapse is a common abnormality and the overall risk of endocarditis in an individual with this lesion is quite small. Aortic valve disease (with stenosis, regurgitation, or both) is a predisposing cause for endocarditis in 12% to 30% of cases (21).

Congenital heart disease is now the underlying lesion in 10% to 20% of cases of endocarditis (10). The most common congenital heart lesions predisposing to endocarditis include bicuspid aortic valves, patent ductus arteriosus, ventricular septal defects, coarctation of the aorta, and tetralogy of Fallot. Unlike most other congenital defects, secundum atrial septal defects are not associated with an increased risk (21).

A succession of new surgical techniques for correction of congenital and acquired valvular lesions has affected the distribution of cardiac abnormalities now seen in patients with infective endocarditis (IE). The risk of endocarditis in patients with mechanical or bioprosthetic valves is similar. In a multicenter follow-up study of over 1,000 patients who were randomized to receive mechanical or bioprosthetic cardiac valves, the overall rate of prosthetic valve endocarditis was similar in both groups (0.8 cases per year of follow-up) (22). Duration of follow-up averaged 7.7 years; the cumulative percentage of patients who developed prosthetic valve endocarditis was 5.8% (22). However, other authors have suggested that mechanical prosthetic valves are more susceptible to endocarditis initially, whereas after 1 year, bioprosthetic valves are more likely to develop endocarditis (23,23a). In another study, endocarditis was more common after 11 years in patients with mechanical valves than in patients with bioprosthetic valves (23b).

A limited amount of data exists on the risk of endocarditis in patients with defined cardiac lesions. In a recent study in which 2,401 patients with congenital heart lesions were followed prospectively for a total of 40,855 days, the overall incidence of endocarditis was 135 cases per 100,000 person-years. The highest rates of endocarditis occurred in patients with aortic stenosis (4.8% of 462 cases, or 271 cases, per 100,000 person-years) and with ventricular septal defects (2.4% of 1,347 cases, or 145 cases, per 100,000 person-years). The lowest rate of endocarditis was observed in patients with pulmonic stenosis; only 1 of 592 patients developed endocarditis during the follow-up period (24). Horstkotte estimated that the risk of infective endocarditis in patients with aortic regurgitation was approximately twice as high (73 per 100,000 person-years) (25). The peak gradient across the aortic valve has been linked with the risk of infective endocarditis: The higher the gradient, the higher the risk of developing endocarditis (24).

A history of endocarditis is an additional important predisposing cause for endocarditis. Recurrent endocarditis occurred in 4.5% of patients in a follow-up study of a large cohort of patients who survived their initial episode of endocarditis (26). Other studies have reported rates of recurrence of endocarditis ranging from 2.5% to 9.0% (27). Also, not surprisingly, prosthetic valve endocarditis occurs more frequently when the original indication for the valve replacement was active endocarditis

(28).

Other uncommon but notable predisposing causes for endocarditis include pregnancy (10), arteriovenous fistulas used for hemodialysis (29), the use of central venous and pulmonary artery catheters (30), the presence of peritoneovenous (LeVeen) shunts for the control of intractable ascites (31), and the use of ventriculoatrial shunts for the management of hydrocephalus (32). In addition, patients with ulcerative lesions of the colon caused by carcinoma or inflammatory bowel disease have a poorly understood predilection to develop endocarditis caused by *S. bovis* (33,34). Infective endocarditis has also been reported in patients undergoing liver, heart, and heart–lung transplantation (35).

A number of cases of endocarditis in patients with human immunodeficiency virus (HIV) have also been reported (36). Some patients with HIV and endocarditis have had infection with unusual organisms such as *Salmonella* and *Listeria* (37,38). Although one study suggested that HIV infection was an independent risk factor for IE in injection drug abusers (39), the results of another study of a large cohort of injection drug users found no evidence that supported this concept (37). Cocaine use may be an additional risk factor for IE in injection drug users. In a study of a large number of injection drug users with fever, those who used cocaine were significantly more likely to have endocarditis (40).

PATHOPHYSIOLOGY

The endothelial lining of the heart and its valves is normally resistant to infection with bacteria and fungi. Experiments in animal models have demonstrated that a sequence of interrelated events must occur before microbes can establish an infective nidus or vegetation on the endocardium. Although a few highly virulent organisms such as *S. aureus* are capable of infecting normal human heart valves, the initial step in the establishment of a vegetation is injury to the endocardium followed by focal adherence of platelets and fibrin. This sterile platelet–fibrin nidus, in turn, becomes infected by microorganisms circulating in the bloodstream from a distant source of focal infection or as a result of a transient bacteremia from a mucosal or skin source (41,42).

Following colonization of the platelet–fibrin aggregate, microbial growth results in the secondary accumulation of more platelets and fibrin until a macroscopic excrescence or vegetation is present. The culmination of this process is mature vegetation consisting of an amorphous collection of fibrin, platelets, leukocytes, red blood cell debris, and dense clusters of bacteria. The surface of most vegetations consists of fibrin and scant numbers of leukocytes. Clumps of bacteria, histiocytes, and monocytes are usually found deep within the vegetation. Giant cells containing phagocytic bacteria may be found in some vegetations. Extremely high concentrations of bacteria (e.g., 10^9 to 10^{11} bacteria per g of tissue) may accumulate deep within vegetations. Some of these bacteria exist in a state of reduced metabolic activity. Following therapy and during the process of healing, capillaries and fibroblasts appear within vegetations, but without treatment, vegetations are avascular structures.

Infectious endocarditis of aortic valve. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Vegetations often prevent proper valvular leaflet or cusp coaptation, resulting in worsening valvular incompetence and congestive heart failure (43). Vegetation growth may result in leaflet perforation that can manifest as acute congestive heart failure (44). Patients with mitral or tricuspid valve vegetations may develop chordal rupture when infection progresses beyond the valve orifice. Extension of infection may also occur into surrounding structures such as the valve ring, the adjacent myocardium, the cardiac conduction system, or the mitral-aortic intravalvular fibrosa (45). Rarely, cavitation of periaortic abscesses may occur into the adjacent aortic wall, resulting in the formation of a diverticulum or aneurysm. Even more rarely such aneurysms may perforate into surrounding structures resulting in aortic-atrial or aortic-pericardial fistulae (44).

Endocarditis on prosthetic valve tissue differs from native valve endocarditis in that infection commonly extends outside the actual valvular apparatus, resulting in valvular dehiscence, abscess formation, and myocardial invasion (46) (Fig. 25.2). Endothelial cell proliferation overgrowing the valvular cuff of the bioprosthesis may provide a nidus that explains this propensity for valvular ring involvement (28). In addition, bioprosthetic valves are vulnerable to infection of the leaflets themselves (47).

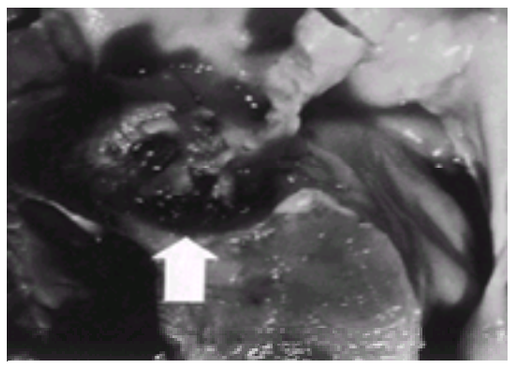


FIGURE 25.2 Pathology of a staphylococcal abscess (*arrow*) involving the annulus of the mitral valve. (From Kissane JM. Staphylococcal infections. In: Connor DH, et al., eds. *Pathology of infectious diseases.* Vol 1. Stamford, CT: Appleton & Lange, 1997:811, with permission.)

The stress placed on bioprosthetic valves is thought to be greater in the mitral position than aortic, possibly accounting for the observation that mitral bioprostheses are more prone to endocarditis than aortic bioprostheses (48). Prosthetic valvular infection may in turn result in secondary valvular thrombosis.

Microbial adherence is a crucial early event in the pathogenesis of endocarditis. The mechanism of this adherence is poorly understood and may vary among different organisms. Bacterial adherence to a platelet–fibrin nidus involves a complex interaction of components of the microbial cell wall. Bacteria such as *S. aureus*, viridans streptococci, enterococci, and *P. aeruginosa* adhere more avidly to excised canine heart valves *in vitro* than species such as *E. coli*, which rarely causes endocarditis (49).

The relative frequency with which different species of bacteria cause endocarditis in humans is directly correlated with the ability of these same organisms to cause endocarditis in an experimental rabbit model (50). One explanation for these phenomena may be related to the interaction between dextran in the cell wall of gram-positive organisms and the valvular endothelium. The amount of dextran production of streptococci grown in broth is proportional to the intrinsic ability of various species of streptococci to cause endocarditis in an experimental rabbit endocarditis model (51). A second explanation may be the intrinsic binding affinity of the organisms to fibronectin. Mutants of *S. aureus* with decreased ability to bind fibronectin have less ability to cause endocarditis in a rat endocarditis model than parent strains with higher binding affinity to fibronectin (52).

Components found in damaged endothelium, platelet–fibrin aggregates, or both that may mediate bacterial adherence include fibrinogen, laminin, and type 4 collagen. Bacterial platelet interactions also appear to be important in the pathogenesis of endocarditis, both in the induction of a vegetation and in its enlargement after colonization of a fibrin–platelet nidus has occurred.

Preexisting antibodies against certain bacteria may increase the predisposition to IE in some instances. For example, horses that are given repetitive injections of live pneumococci often spontaneously develop pneumococcal endocarditis (53). However, in some animal models of endocarditis, preexisting high antibody levels increase the median infective dose required to induce endocarditis (54).

It is virtually impossible to induce endocarditis in experimental animals unless the valvular endocardium is first traumatized with a polyethylene catheter inserted into the right or left side of the heart (41). If bacteria such as viridans streptococci, which have the inherent ability to adhere to fibrin–platelet matrices on damaged endocardium, are injected into animals with prior catheter-induced valvular lesions, vegetations predictably develop within a few days at the sites of valve injury. Similar lesions probably occur naturally in bacteremic humans with congenital or acquired cardiac lesions that induce constant endocardial trauma through regurgitant flow or high-pressure jets of blood through stenotic lesions.

Vegetations tend to occur when blood travels from an area of high pressure through a narrow orifice into an area of lower pressure. The explanation for this phenomenon can be deduced from *in vitro* experiments that demonstrate the physics of turbulent flow. If nebulized *Serratia marcescens* are injected into an air stream passing through an agar-coated Venturi tube, the highest concentration of bacteria is found in the low-pressure area immediately distal to the narrowing (55). A similar phenomenon is presumed to occur when bacteria circulate in the blood. The propensity for vegetations to form at specific sites may also relate to a decrease in lateral pressure downstream from the regurgitant flow, which causes a decrease in the perfusion of the intimal lining at these sites (49).

CLINICAL PROFILE

Classification of Infective Endocarditis

Various terms have been used to describe the many forms of endocarditis encountered by clinicians. The term *IE* should now replace the older terms *subacute* and *acute bacterial endocarditis* for several reasons. First, not all cases are caused by gram-positive and gram-negative bacteria; fungi, rickettsia, and *Chlamydia* may also cause endocarditis. Second, presentation and duration of endocarditis are not easily categorized. Although rapidly progressing (acute) endocarditis is usually due to *S. aureus*, the clinical utility of separating cases on the basis of the activity of the presentation is limited because pathogens such as *S. aureus* and streptococci can cause either fulminant or indolent disease in different patients. However, there is clinical utility in separating cases as to whether there is involvement of native or prosthetic valves; for in the latter group, the causative organisms vary if the infection occurs early (during the first 60 days after surgery) or late. In addition, right-sided endocarditis in intravenous drug users results in such a characteristic illness that it is useful to separate it from infection solely involving the left-sided structures of the heart. Although heart valves are the usual sites of infection, vegetations may also appear on pacemaker leads (56), in the mural endocardium (57), in arteriovenous shunts or fistulae (58), in vascular structures such as a patent ductus or a Blalock-Taussig shunt (59), or in coarctation of the aorta, or even in intracardiac masses such as myxomas (60).

Infective endocarditis is a highly variable disease. Its clinical course is dependent on numerous factors, including the causative pathogen, the age and underlying health of the patient, and the nature and extent of the underlying valvular disease. Decisions concerning clinical management are directly related to an accurate diagnosis. Underdiagnosis can lead to catastrophe. Overdiagnosis can lead to weeks of unnecessary therapy at great cost and risk of drug-related toxicity. Distinguishing between IE and an alternate focus of infection in a bacteremic patient with underlying heart disease can be extremely difficult. To help distinguish endocarditis from other bacteremic syndromes, consistent definitions are important. Clinical research concerning the natural history, complications, epidemiology, and treatment outcomes of endocarditis all depend on the accurate identification of patients with this disease. Definitions that are specific but not sensitive may lead to biased conclusions, as can definitions that are sensitive but not specific.

Petersdorf and Pelletier (61) developed the first diagnostic criteria for IE. Their schema classified cases as definite, possible, and probable. Surgical or autopsy confirmation was required to classify a case as definite. Designation of a case as probable or possible was based on the presence of one or more of the following criteria: predisposing valvular disease, bacteremia, the presence of emboli, and the presence of indirect evidence of an active endocardial disease process such as a new regurgitant murmur. In practice, many patients with presumed endocarditis did not meet these criteria. Thus, although this classification was reasonably specific, it lacked sensitivity.

In 1981, the Beth Israel criteria were proposed by von Reyn and colleagues (62). Four diagnostic categories were created: definite, probable, possible, and rejected. As in the Petersdorf and Pelletier schema, histologic or microbiologic confirmation either at autopsy or at surgery were required to categorize a case as definite. Other criteria included the presence of (a) persistent bacteremia, (b) predisposing valvular heart disease, (c) vascular phenomena such as emboli or splinter hemorrhages, and (d) evidence of active endocardial pathology such as a new regurgitant murmur. Echocardiography was not used as a diagnostic criterion nor was the use of illicit intravenous drugs considered to be a predisposing risk factor for endocarditis. The Beth Israel criteria were widely used during the following decade, but despite modifications by various investigators, this classification system still lacked sufficient sensitivity.

In 1994, investigators at Duke University developed a new diagnostic schema that addressed weaknesses in the Beth Israel classification: The Duke criteria used echocardiography as a major criteria for diagnosis, expanded the list of predisposing heart conditions to include intravenous drug use, and devised a system by which cases could be classified as definite using purely clinical criteria (63). The pathologic criteria used in the Duke classification were virtually identical to those proposed by Pelleteir, Petersdorf, and von Reyn. Cases were classified as definite in the Duke schema using major and minor criteria in a manner analogous to the Jones criteria for rheumatic fever (Table 25.1 and Table 25.2). In 2000, investigators from the Duke Endocarditis Service further modified the Duke criteria.

Definite
Pathologic criteria
Microorganism: demonstrated by culture, in a vegetation at surgery, from an embolized vegetation, or from an intracardiac abscess
Pathologic lesions: vegetations or intracardiac abscess present and confirmed by histology showing active endocarditis
Clinical criteria, using specific definitions listed in Table 25.2
Two major criteria, or
One major and three minor criteria, or
Five minor criteria
Possible
Findings consistent with infective endocarditis that fall short of *definite*, but not *rejected*
Rejected
Firm alternate diagnosis for manifestations of endocarditis, or
Resolution of manifestations of endocarditis, with antibiotic therapy for 4 d or less, or
No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 d or less

TABLE 25.1 DUKE CRITERIA FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS

TABLE 25.2 DEFINITIONS OF TERMINOLOGY USED IN THE DUKE CRITERIA FOR INFECTIVE ENDOCARDITIS

Several studies have compared the clinical utility and validity of the Duke criteria with those of von Reyn et al. (63,64,65,66 and 67). In each of these studies, a substantial number of cases that were considered as rejected when the Beth Israel criteria were applied prospectively were simultaneously classified as clinically definite by the Duke criteria (67). The negative predictive value of the Duke criteria was subsequently assessed in a follow-up study of patients considered to be rejected for a diagnosis of IE. None of 52 patients who had been considered as rejected by the Duke criteria had proven IE in follow-up (68). In another study of 100 cases of acute fever or fever of unknown origin, the specificity of the Duke criteria was found to be 99% (69).

The utility of the Duke criteria was subsequently assessed in patients with prosthetic valve endocarditis, pediatric patients, and hospitalized patients. Modifications (such as the use of serologic criteria for diagnosing endocarditis caused by *Coxiella burnetii*) have been adopted (70), and it is likely that further modifications will occur in the future (67). However, the Duke schema is currently the most sensitive and specific diagnostic criteria available and is particularly useful in diagnosing endocarditis in patients with *S. aureus* bacteremia, those with right-sided endocarditis, and those with negative blood culture results (67).

Epidemiology of Infective Endocarditis

An estimated 10,000 to 15,000 new cases of endocarditis are diagnosed in the United States each year (71). However, the precise incidence of IE is difficult to ascertain because case definitions have varied from decade to decade, among different authors, and among different medical centers. Also the incidence of predisposing conditions such as rheumatic heart disease and injection drug use has varied over time and between different areas. For example, a prospective study of the incidence of IE among patients admitted to 51 hospitals in Philadelphia and the surrounding area estimated that the incidence of endocarditis was 11.6 cases per 100,000 person-years (72). The incidence of endocarditis in Olmsted County, Minnesota, in a similar study during the period from 1950 to 1981, was 3.2 cases per 100,000 person-years (15). Other studies have reported incidence rates ranging from 0.6 to 6.0 cases per 100,000 person-years (73,74 and 75). Men predominate in most case series of endocarditis, with male to female ratios ranging from 2:1 to 9:1 (76,77). Although 50% to 70% of children less than 2 years old who develop endocarditis have no obvious underlying cardiac disease (78), most children over the age of 2 with endocarditis have coexistent congenital heart disease. Thus, the overall incidence of endocarditis in children and young adults is low (15).

Despite the discrepancies in incidence rates reported by the studies cited previously, there is general agreement that new trends in the epidemiology of endocarditis have occurred during the past 30 years. Most of these changes relate to the numbers and types of susceptible hosts rather than to shifts in the virulence of the infecting microorganisms. In addition, the age distribution of endocarditis has clearly changed. Endocarditis has increasingly become a disease of the elderly. More than one-half of all endocarditis cases in the United States now occur in persons over the age of 60, and the median age of patients has increased steadily during the past 40 years (79). The proportion of cases that present with an indolent course and the proportion caused by streptococci have declined, whereas simultaneous increases have occurred in the proportion of cases caused by *S. aureus*, fungi, and gram-negative bacilli.

The increase in the incidence of injection drug use has also had a major effect on the overall incidence of endocarditis. For example, the incidence of IE in injection drug users in Philadelphia and the surrounding areas has been estimated to be 5.3 cases per 100,000 person-years, accounting for nearly one-half of all recognized cases (72). Similar proportions of cases related to injection drug use were seen in a study from a hospital in Los Angeles (64). Other authors have estimated the incidence of IE in intravenous drug users may be 30 times higher than the general population and four times higher than the risk of endocarditis in young adults with rheumatic heart disease (80). In some areas of the United States, drug addiction is the most common predisposing cause for IE in patients less than 40 years old (81).

More than 100,000 heart valves are implanted annually in the United States (82). The presence of prosthetic valves as an important predisposing cause of endocarditis is substantial and is likely to increase in future years. Although still an uncommon disease, prosthetic valve endocarditis makes up a small but important segment of all cases of endocarditis in the United States. The overall incidence of prosthetic valve endocarditis in the Philadelphia area was estimated to be 0.9 cases per 100,000 person-years (72). Prosthetic valve endocarditis develops in 1% to 4% of prosthetic valve recipients in the first year following valve replacement and in approximately 1% of recipients annually thereafter (22,71).

Advances in medical technology have paradoxically resulted in the appearance of a new form of endocarditis (nosocomial endocarditis) that was extremely rare 25 years ago (68,83). Nosocomial endocarditis is usually a complication of bacteremia induced by an invasive procedure or a vascular device and now accounts for nearly 10% of cases of endocarditis in some areas (68,72). Nosocomial endocarditis is a particularly difficult problem to diagnose and manage in patients with prosthetic heart valves. In a multicenter study of patients with nosocomial bacteremia and underlying prosthetic heart valves, 18 of 171 (11%) developed prosthetic valve endocarditis after bacteremia occurred (84). In a review of nosocomial endocarditis in patients in intensive care units, 21 of 22 patients developed endocarditis as a consequence of bacteremia related to a medical or surgical procedure. The overall mortality was 68% (84a).

Laboratory Diagnosis

Infective endocarditis is usually a “syndrome diagnosis” based on the presence of multiple findings rather than on a single definitive test result. The diagnosis of IE is usually obvious when a patient has numerous positive blood culture results in the presence of a well-recognized predisposing cardiac lesion and the absence of infection elsewhere.

The bacteriologic diagnosis of IE is facilitated by the relative constancy of bacteremia originating from vegetations. Bacteria are discharged from vegetations at a relatively constant rate rather than haphazardly (85). A minimum of three blood cultures should be obtained. If the tempo of illness is subacute, and the patient is not critically ill, it is reasonable and often preferable to delay therapy for 1 to 3 days awaiting the results of blood cultures and other diagnostic tests. If the patient is acutely ill, three blood cultures should be obtained at least 1 hour apart before beginning empiric therapy. The constancy of bacteremia in patients with endocarditis makes it unnecessary to await the arrival of a fever spike or chills to obtain blood cultures; in addition, prior studies may have shown that venous blood culture results give approximately the same yield as arterial blood cultures.

Many patients with bacterial endocarditis have low-grade bacteremia (i.e., 1 to 10 colony-forming units per mL of blood) (86); thus, a minimum of 10 mL, and preferably 20 mL, should be obtained from adults and 0.5 to 5.0 mL from infants and children. Blood cultures inoculated with at least 5 mL of blood have a significantly higher detection rate for bacteremia than bottles inoculated with less than 5 mL of blood (92% vs. 69%; $p < .001$). The estimated yield of blood cultures in bacteremic adults increases approximately 3% per mL of blood cultured (87).

Not all microorganisms have the same propensity to cause endocarditis. For example, organisms such as viridans streptococci and *S. aureus* are more likely to cause endocarditis than are gram-negative rods such as *E. coli* and *Proteus*. This distinction has clinical importance. For instance, the Duke Criteria distinguishes among the type of organism isolated from blood cultures. The following organisms are considered to be *likely causes* of IE when isolated from two or more blood cultures: *S. aureus*, viridans streptococci, and enterococci (if the infection was acquired in the community and not nosocomially).

The setting in which bacteremia occurs also has an effect on the probability that an individual patient will have endocarditis. For example, patients who present with community-acquired enterococcal bacteremia are significantly more likely to have endocarditis than are patients who develop enterococcal bacteremia while hospitalized for another cause. The probability of endocarditis in a given patient with streptococcal infection also varies by the infecting species. For example, *S. sanguis* bacteremia is more often indicative of endocarditis than is bacteremia caused by *S. milleri* (also known as *S. anginosus*). Also, bacteremias to groups A, B, and C streptococci are seldom associated with IE, whereas bacteremia caused by group G streptococci is often indicative of the presence of endocarditis (88). The risk of endocarditis in patients with *S. aureus* bacteremia (regardless of source) is particularly high, and all such patients should be clinically evaluated for this possibility.

The interpretation of positive blood culture results in patients with suspected endocarditis is confounded by the fact that false-positive results occasionally occur despite the most exacting techniques for collection and processing. Each set of cultures should be obtained from separate venipuncture sites in order to minimize the risk of misinterpreting contaminating skin flora as pathogens.

False-positive results are likely to be present when organisms such as *Propionibacterium* species, *Corynebacterium* species, and *Bacillus* species and coagulase-negative staphylococci are recovered from a single blood culture or a minority of blood culture bottles. As all of these organisms are capable of causing endocarditis, it is important to determine if the bacteremia is persistent. Persistent bacteremia is present if (a) positive blood culture results for an organism likely to cause endocarditis are obtained from two samples collected more than 12 hours apart, or (b) if (for all other organisms) all of three or a majority of four or more separate blood culture results are positive, and if the first and last samples are collected at least 1 hour apart (63).

Culture results may remain negative in 2% to 5% of patients with IE even when the utmost care is taken in obtaining the proper number and volume of blood cultures (89). Certain organisms (e.g., *Coxiella burnetii* and *Tropheri whippelii*) with the occasional ability to cause endocarditis will not grow using cell-free media; other organisms (e.g., *Brucella*, *Mycoplasma*, *Chlamydia*, *Histoplasma*, *Legionella*, and *Bartonella*) will not grow unless special media or microbiologic methods are employed; and still other organisms (e.g., *Corynebacterium* species, *Haemophilus* species, *Actinobacillus, Cardiobacterium, Eikenella*) will not grow unless blood cultures are incubated for 7 to 21 days. The microbiology laboratory should be notified when such organisms are suspected, as most laboratories routinely discard

blood cultures when there has been no growth after 7 days of incubation.

Although unusual or fastidious organisms are an important consideration when patients with clinical findings of endocarditis are found to have negative routine blood culture results, the most common cause for negative blood culture results in patients with IE is prior antimicrobial therapy. Thus, it may be necessary to delay the institution of therapy for several days for such patients while additional blood cultures are obtained.

A total of three blood cultures is usually adequate to diagnose IE in most cases. In a study of 206 cases of endocarditis, all blood culture results were positive in 91% of the patients. In patients with streptococcal endocarditis, the first blood culture result was positive in 96% of cases and one of two culture results was positive in 98% of patients. In endocarditis, with organisms other than streptococci, the first blood culture obtained was positive in 82% of cases and one of two was positive in 100% of patients (86).

The white blood cell count is rarely helpful in making a diagnosis of endocarditis. Some patients with streptococcal endocarditis may have normal white blood cell counts when they seek medical attention. In contrast, most patients with staphylococcal endocarditis have leukocytosis (90).

The utility of other laboratory tests in the diagnosis of endocarditis is limited. An elevated erythrocyte sedimentation rate, an elevated level of C-reactive protein, or both are usually present, but these findings alone have little specific diagnostic or monitoring value. Most patients with endocarditis quickly develop a normochromic normocytic anemia, but this finding is equally nonspecific. Elevated levels of serum globulins, the presence of cryoglobulins and circulating immune complexes, hypocomplementemia, and false-positive serologic test results for syphilis may also occur in some patients with IE, but none of these findings is diagnostic or particularly helpful by itself. However, an elevated level of rheumatoid factor may occasionally be useful in diagnosis, particularly when the duration of illness is greater than 6 weeks (91). When present in individuals without a known prior rheumatologic disorder, this finding is considered to be one of the six minor criteria in the Duke Endocarditis Service diagnostic schema (63).

Most patients with endocarditis have an abnormal urinalysis result. Urinary sediment examination may disclose microscopic or gross hematuria, proteinuria, or pyuria. Microscopic hematuria and mild proteinuria occur in many cases and are often found in the absence of other renal complications (48). Like the erythrocyte sedimentation rate, all of these urinary findings lack specificity. However, the presence of red blood cell casts and a low serum complement level may be an indicator of immune-mediated glomerular disease. When present, this uncommon finding is an important minor diagnostic criterion (63).

Electrocardiography should be part of the initial evaluation of all patients with suspected endocarditis, even though this test rarely shows diagnostic findings. Besides the presence of changes suggestive of ischemia or infarction, the electrocardiogram may also reveal the presence or new appearance of heart block, an important clue to extension of infection to the valve annulus and adjacent conduction system. The presence of new prolongation of the PR interval in a patient with endocarditis, if unrelated to drug therapy or recent surgery, is virtually diagnostic of the presence of a ring abscess.

Chest radiography occasionally reveals important diagnostic clues. For example, patients with tricuspid valve endocarditis often present with radiographic evidence of septic pulmonary emboli. In such cases, there may be a few or multiple focal lung infiltrates. Some of these infiltrates may reveal central cavitation. Rarely, chest radiography discloses calcification in a *native* cardiac valve that may in turn raise the suspicion of endocarditis in a febrile patient.

Since its introduction in 1973, echocardiography has greatly simplified the process of diagnosing IE (44). Echocardiography is often of crucial importance in detecting a vegetation that is usually defined as a mass of echoes of distinct echogenicity from the adjacent valve >5 mm in its largest dimension with independent motion from the valve itself (92) (Fig. 25.3). Echocardiography should be obtained in all patients suspected of having endocarditis. Echocardiography not only may confirm the presence of vegetations in the setting of bacteremia, but it may also provide important physiologic information regarding right and left ventricular function and an estimate of valvular obstruction or regurgitation severity. Mitral valve preclosure in the setting of acute aortic insufficiency implies a marked increase in left ventricular diastolic pressure and the likely need for more urgent intervention (93) (*e*Fig. 25.3.1).

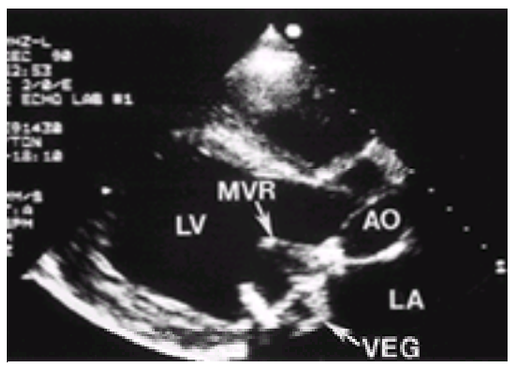
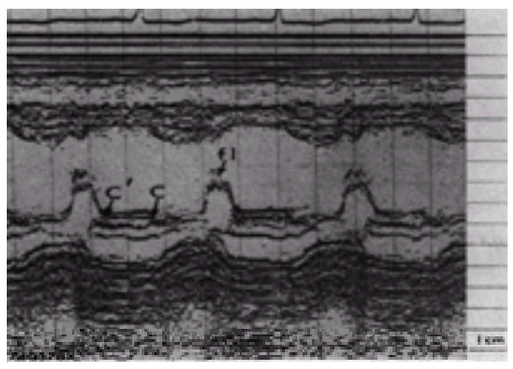
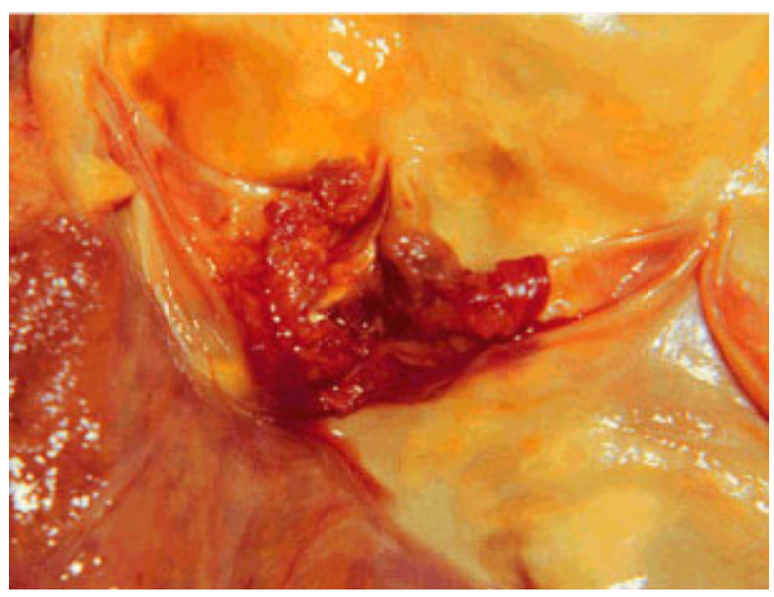


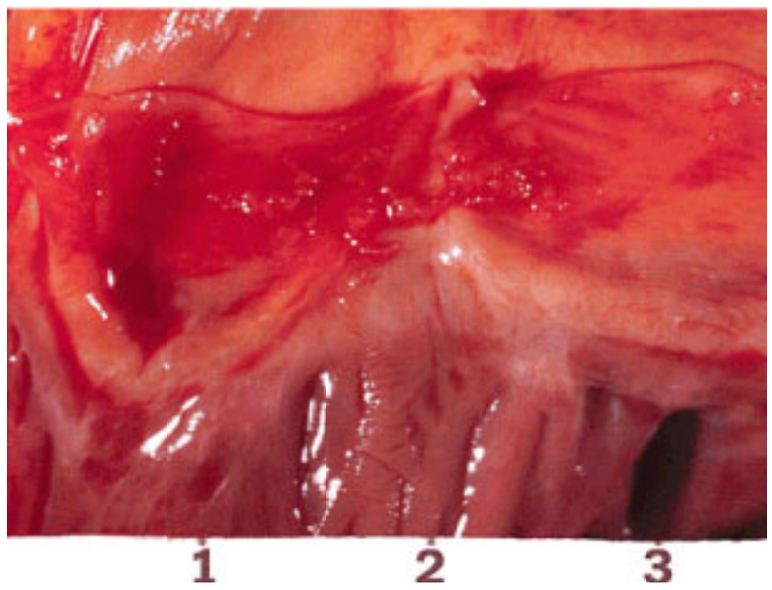
FIGURE 25.3 A vegetation (VEG) is shown on a prosthetic porcine mitral valve. The large mobile vegetation is noted to prolapse into the left atrium (LA). AO, aorta; LV, left ventricle; MVR, mitral valve replacement. (Courtesy of Dr. Thomas Ryan, Duke Medical Center.)



***e*FIGURE 25.3.1** Mitral valve preclosure in acute aortic insufficiency. The M-mode echocardiography allows timing of the mitral closure with the QRS. C, normal closure point; C”, early closure; fl, fluttering of the mitral valve from the aortic regurgitant jet. (From Feigenbaum H, ed. *Echocardiography*, 5th ed. Philadelphia: Lea & Febiger, 1994:289, with permission.)



Verrucal endocarditis of the aortic valve. Multiple vegetations are seen on the aortic valve cusps in this patient with subacute bacterial endocarditis.



Marantic (nonbacterial) endocarditis of the pulmonic valve. Multiple vegetations are seen on the pulmonic valve in this patient with no bacterial growth from multiple blood cultures.

Video 25.1 Intraoperative 90-degree transesophageal echo of a patient with a St. Jude mitral valve prosthesis with a stuck metallic leaflet due to a small clot. (The immobile leaflet is to the right of the screen; the left leaflet moves normally.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

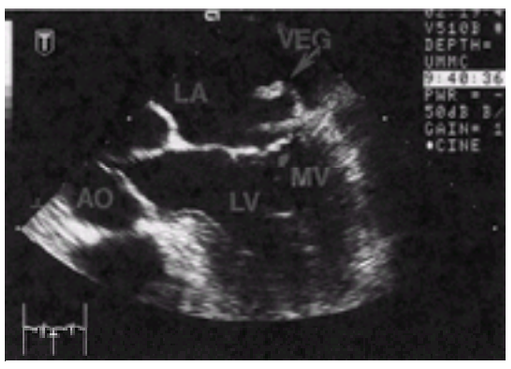
Three major incremental advances have occurred in echocardiographic technology in the past 25 years: (a) the advent of two-dimensional echocardiography, (b) the institution of color flow Doppler technology, and (c) the introduction of TEE. M-mode echocardiography has now largely been replaced by two-dimensional echocardiographic methods. M-mode methods detect vegetations in approximately one-half of patients with IE. Although transthoracic two-dimensional echocardiography provides a remarkable improvement in visualizing spatial anatomic relationships compared with M-mode methods, the sensitivity of transthoracic two-dimensional echocardiography is still only approximately 60% (94,95). Furthermore, two-dimensional echocardiography is often of limited utility in the detection of vegetation in patients with obesity, emphysema, and chest wall deformities.

TEE, especially when biplane probes are used, has improved the rate of detection of vegetations on native valves to 90% to 95% (95,96,97,98,99 and 100) (*e*Fig. 25.3.2). TEE is particularly useful in visualizing right-sided heart structures and masses on pacemaker leads or intravenous lines and in visualizing abnormalities on the pulmonic valve (101,102). The superiority of TEE over transthoracic imaging methods is particularly important in the detection of small vegetations. However, the sensitivity of both methods is approximately equal when vegetations are ³5 mm in size (35). In a study of 112 patients with 114 episodes of endocarditis, all of whom underwent transthoracic and TEE, Roe and colleagues reported that the findings on TEE resulted in reclassification of 22 patients from possible to definite endocarditis. Three patients were reclassified from rejected to possible (102a).

Video 25.2 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis (*first video*) showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. **Second video:** intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 25.3 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis (*first video*) showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. **Second video:** intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 25.4 Intraoperative transesophageal echo of a mitral valve with multiple, large, highly mobile vegetations from endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 25.3.2** Transesophageal echocardiography revealing large mobile vegetation (VEG, *long arrow*) on a native mitral valve (MV, *short arrow*). AO, aorta; LA, left atrium; LV, left ventricle. (Courtesy of Dr. Carolyn Donovan, Duke Medical Center.)

Transthoracic echocardiography in patients with prosthetic valve endocarditis often produces poor images, as shadowing of the echo beam may prevent adjacent structures from being adequately visualized and the mass effect from the prosthetic valve can obscure the identification of vegetations. As a result, transthoracic echocardiography has a sensitivity of only 35% for detecting vegetations in patients with prosthetic valve endocarditis.

TEE improves the sensitivity of detecting vegetations on prosthetic valves to up to 96% (103,104). TEE is especially useful in detecting ring abscesses or intracardiac fistulae (105,106,107,108 and 109). In one study of 44 patients with endocarditis complicated by perivalvular abscesses, transthoracic echocardiography identified only 28% of the abscesses, whereas TEE detected 87% (Fig. 25.4). Most such perivalvular abscesses communicate with the intravascular space (as evidenced by color flow turbulence observable within the lesion). These may be referred to as *pseudoaneurysms* by some. This phenomenon is not always evident, however. TEE is a particularly sensitive method for the detection of mitral regurgitation in the presence of mitral annular calcification or when a prosthetic mitral valve is present (110,111) (Fig. 25.5). The presence of spontaneous echo contrast in the atria of patients with endocarditis may imply a higher risk for systemic emboli in such patients (112).

VIDEO

Video 25.5 This is a long-axis 134-degree transesophageal view of a patient with prosthetic valve endocarditis of the aortic valve. Note the very large mobile mass or vegetation on the prosthesis accompanied by prosthetic stenosis and moderate insufficiency. The peak and mean pressure gradients across this valve were 90/27 mm Hg, and there was also a paravalvular abscess. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 25.6 The short-axis 56-degree transesophageal view demonstrating the very large vegetation attached to the Carpentier-Edwards aortic valve replacement involving both aortic stenosis and aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 25.7 Transesophageal 138-degree view showing the Carpentier-Edwards mitral valve replacement with thickened leaflets with multiple mobile echo densities consistent with vegetations and a clot in a patient with prosthetic valve endocarditis. The mean transesophageal gradient was 20 mm Hg on surface echo. Note the large left atrial thrombus to the right of the screen with significant spontaneous echo contrast in the left atrial cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 25.8 Transesophageal 98-degree view demonstrating the markedly thickened and distorted leaflets of a Carpentier-Edwards mitral valve replacement with multiple mobile echo densities attached in a patient with prosthetic endocarditis. Note the restricted leaflet motion with a diminished orifice causing the mitral stenosis. In addition, there is a left atrial thrombus to the right of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 25.9 Transesophageal echo of a large tricuspid valve vegetation in a patient with infectious endocarditis. This patient was an intravenous drug user, which is common in patients with right-sided endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 25.10 Intraoperative transesophageal echo of a rocking prosthetic mitral valve due to infectious endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 25.11 Intraoperative transesophageal echo showing a Carpentier-Edwards mitral prosthesis in a patient with infectious endocarditis. The mitral prosthesis is rocking, and there is a paravalvular jet of mitral regurgitation to the left of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 25.12 Transesophageal echo of a St. Jude mitral valve replacement in a patient with endocarditis. Note the large vegetation on the atrial side of the valve that prolapses across the prosthesis in systole causing prosthetic mitral stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 25.13 A 120-degree transesophageal echo demonstrating an abscess cavity in a patient with endocarditis of an aortic valve. Note the systolic expansion of the cavity located between the aortic and mitral valved in the inner annular fibrosa. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

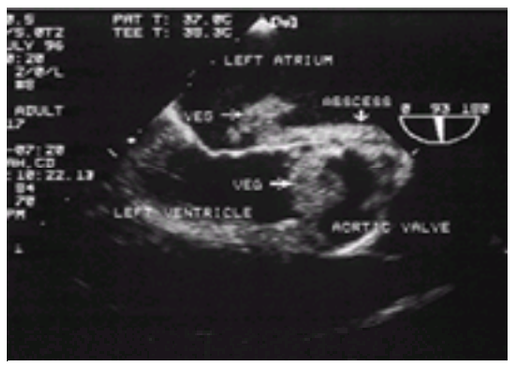


FIGURE 25.4 Transesophageal echocardiogram of a large aortic valve vegetation (VEG) with erosion through the aortic wall into the left atrium. Associated with this is an abscess. (Courtesy of Dr. Carolyn Donovan, Duke Medical Center.)

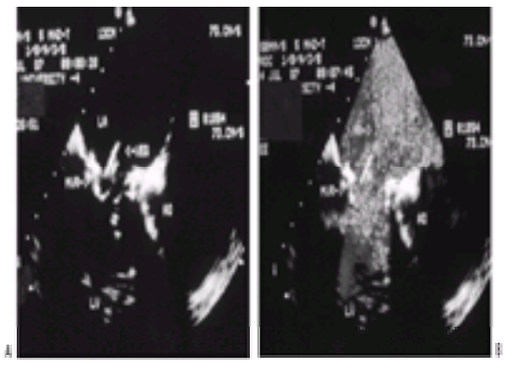


FIGURE 25.5 A: A linear vegetation (VEG) is shown on the St. Jude mitral valve. This was not visible by chest wall echocardiogram. **B:** Same view with color flow Doppler revealing marked mitral insufficiency. AO, aorta; LA, left atrium; LV, left ventricle; MVR, mitral valve replacement. (Courtesy of Dr. Joseph Kisslo, Duke Medical Center.)

Echocardiography cannot always differentiate between vegetations caused by active IE and abnormalities caused by other noninfectious valvular lesions such as those that occur in patients with malignancies or burns, or with valvular lesions associated with acute rheumatic fever, systemic lupus erythematosus, the antiphospholipid syndrome (113,114), or protein C deficiency (10,115). In addition, valvular thickening, valve aneurysms, ruptured chordae, benign leaflet nodules, suture material around a sewing ring (especially after mitral valve replacement), valvular thrombus, or pannus formation on valve structures may mimic vegetations. Although some experts believe that chronic (healed) vegetations cannot be differentiated from lesions caused by active valvular infection (92), other echocardiographers believe that active vegetations can be differentiated from chronic or healed vegetations using two-dimensional echocardiography (115a). The distinction may be subtle.

It is also important to emphasize that a negative transthoracic echocardiographic result does not eliminate the possibility that IE is present. In a study of 65 patients with clinical symptoms and signs of IE, in whom an initial TEE result was negative, an alternate diagnosis was made in 56 patients. However, 5 of the 65 patients were ultimately found to have IE by a repeat TEE in three of five, by pathologic findings, or a diagnostic clinical course (116).

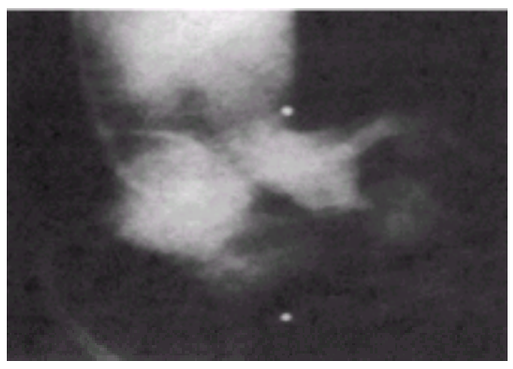
After endocardial lesions have been detected by echocardiography, their appearance during and after the completion of therapy is highly variable. The results of serial echocardiographic examinations done 3 to 16 months after the initial detection of the vegetations suggest that valvular lesions persist in approximately one-third of patients; in others, vegetations disappear during or after therapy; and rarely vegetations enlarge despite curative medical therapy (92). Thus, the presence of persistent vegetations should *not* be interpreted as indicative of persistent infection. Furthermore, neither the presence nor persistence of vegetations during or after therapy should, in itself, be a cause for clinical alarm (92,117).

It remains controversial as to whether the echocardiographic characteristics of vegetations are predictive of the risk of subsequent embolic phenomenon. A few studies have suggested that one or more of the following characteristics increase risk of emboli: size, appearance (e.g., pedunculated or sessile), and mobility (e.g., prolapsing or not) (118). Vegetations of large size (i.e., greater than 10 mm) have been associated with slower resolution during antimicrobial therapy and a greater incidence of embolism in some studies. The authors of other studies, however, have not been able to confirm the clinical value of assessing vegetation morphology in predicting such subsequent embolic events (119,120).

As a general rule, transthoracic echocardiography with Doppler flow studies should be the *initial study* performed in patients suspected of having endocarditis. However, if the clinical suspicion of endocarditis is high, a TEE may be obtained, as the initial study in selected patients. The TEE is often repeated during therapy if response to antimicrobials is inadequate, intracardiac complications are suspected, or both. Otherwise, it has been our practice to repeat the transthoracic echo Doppler (or TEE, if vegetations were not seen on the transthoracic) only at the completion of therapy.

Other imaging modalities such as gallium scanning (121,122), technetium-99m pyrophosphate scans (123), labeled antigranulocyte antibodies (124), technetium-99m labeled granulocytes (125,126), indium-111 labeled leukocytes (127), computed tomography (128), or magnetic resonance imaging (129,130) have been used to assess the presence of periaortic complications such as a ring abscess or emboli from a suspected cardiac source. Such tests are rarely clinically necessary, but they are occasionally of value in patients who cannot undergo TEE or in those whom echocardiography produces inconclusive results. Magnetic resonance imaging may be particularly useful in assessing embolic phenomenon to the central nervous system (CNS) (131).

The role of cardiac catheterization in the evaluation of patients with endocarditis remains controversial. Traditionalists have argued that intracardiac vegetations should not be crossed with intracardiac catheters; this view makes good sense, even though there are no data to confirm the danger of such maneuvers. Echocardiographic color flow Doppler methods that define the severity of regurgitation are helpful. However, it has been our experience that aortic regurgitation and mitral regurgitation often appear more severe using color flow Doppler methods than the estimates using contrast angiography. Thus, if the severity of aortic insufficiency or mitral regurgitation observed by Doppler methods is inconsistent with the clinical findings, then catheterization should be undertaken to clarify the degree of valvular competence. In addition, cardiac catheterization may occasionally be a useful tool to visual abnormal intracardiac anatomy or flow if these features are ambiguous or uncertain after use of routine clinical assessment and echocardiography (132). Aortography may reveal the presence and extent of a perivalvular abscess (eFig. 25.5.1) or fully outline fistulous channels in patients before surgical intervention.



***e*FIGURE 25.5.1** Aortography of large perivalvular ring abscess. The cavity is well seen from the contrast aortogram.

As endocarditis has progressively become a disease of the elderly, concomitant coronary artery disease is often present. It has become our practice to perform coronary angiography routinely in all patients over age 55 before surgery for endocarditis or in those at high risk for coronary artery disease based on their coronary risk factors. Coronary angiography may also be important to delineate coronary emboli from vegetations, if the clinical syndrome is suspected. In younger patients, the anatomic information provided by both transthoracic echocardiography and TEE usually provides adequate information to safely proceed to surgical repair or valve replacement without the need for invasive studies.

Explanted Carpentier-Edwards mitral valve regurgitation in a patient with severe infective prosthetic valve endocarditis. The patient had severe mitral stenosis due to the large vegetations on the prosthesis.

Clinical Manifestations

The clinical presentation of IE ranges from an illness characterized by subtle, chronic fatigue with low-grade fevers, weight loss, and malaise to one of abrupt fulminant acute pulmonary edema brought on by massive acute aortic regurgitation. The virulence of the infecting organism generally determines the acuteness of the presentation. However, the interval from onset of infection to onset of symptoms is usually short. Most patients with endocarditis develop symptoms within 2 weeks of the inciting bacteremia (133). Symptoms in staphylococcal endocarditis may even begin within a few days of the onset of infection.

A variety of nonspecific constitutional complaints may dominate the clinical presentation in individual cases (eTable 25.2.1) (133a,133b). Fever is the most common constitutional complaint. Fevers are usually low grade. Fever may be absent in the elderly and those with congestive heart failure, uremia, severe debility, and infection with coagulase-negative *Staphylococcus* (10,134). Chills, night sweats, and weight loss are also commonly present, as are a variety of neurologic and musculoskeletal complaints.

***e*TABLE 25.2.1** CLINICAL FEATURES AND COMPLICATIONS OF INFECTIVE ENDOCARDITIS

Signs and symptoms	**“Ballpark” estimates of incidence (%)**
Fever	85–97
Murmurs (acute, on presentation)	85–90
Murmurs (subacute)	90–95
Musculoskeletal symptoms	40–50
Neurologic symptoms	30–40
Weight loss	25–30
Peripheral stigmata	20–40
Splinter hemorrhages	15–20
Petechiae	10–15
Osler’s nodes	8–10
Janeway lesions	5
Clubbing	5
Roth’s spots	5
Splenomegaly	5
Complications	
Congestive heart failure; aortic insufficiency >mitral regurgitation >tricuspid regurgitation	50–60
Embolization	20–25
Glomerulonephritis	15–25
Annular abscess	10–15
Stroke	5–15
Mycotic aneurysm	15
Cerebral	5
Limbs	4–5
Mesenteric	2–3
Descending aorta	1–3
Splenic	1–2
Conduction system disturbances	5–10
Central nervous system abscess	3–4
Other rare complications	<1–2
Pericarditis	
Myocarditis	
Myocardial infarction	
Intracardiac fistula	
Metastatic abscess	

Heart murmurs are frequently noted but may be difficult to hear under certain conditions. As many as 15% or more of patients may not have a murmur at the time of initial evaluation (76,135). In acute staphylococcal endocarditis, it is even rarer to recognize a new or changing murmur in the first few days of illness (133c). Right-sided endocarditis, for instance, may be associated with inaudible tricuspid regurgitation. The diagnosis of tricuspid valve endocarditis should therefore be based on a careful clinical examination that includes analysis of the jugular venous pulse, precordium, and liver. When tricuspid regurgitation is present, the neck veins are usually distended and the venous waveforms reveal a C-V wave. The presence of a C-V wave is best detected by observing the jugular venous pulse and

simultaneously palpating the opposite carotid or auscultating the heart to define systole. The jugular venous pulse should fall during ventricular systole (the ‘x’ descent); if tricuspid regurgitation is present, right ventricular ejection into the right atrium results in systolic expansion of the jugular venous pulse (the C-V wave).

Similarly, the hemodynamics that result from acute aortic regurgitation may result in a soft or absent murmur because the rapid increase in left ventricular diastolic pressure results in minimal gradient between the aortic diastolic pressure and left ventricular end diastolic pressure. The rapid increase in left ventricular diastolic pressure in such patients also results in the softening of the first heart sound (as the mitral valve begins to close before ventricular systole begins). In patients with severe aortic insufficiency, the mitral valve may even close before the QRS of the electrocardiogram (preclosure). M-mode echocardiographic techniques may detect such preclosure. This finding may be an important indicator of the need for valve replacement in patients who are in heart failure (93).

Acute aortic insufficiency should be suspected in the presence of four clinical findings: (a) fulminant pulmonary edema, (b) a short or barely audible diastolic murmur, (c) soft or absent first heart sound, and (d) hypotension. A changing heart murmur in the setting of fever or sepsis may be an important clue to the presence of endocarditis. In such circumstances, it is important to distinguish between a new organic regurgitant murmur and an old murmur that is simply affected by a change in body temperature, hematocrit, or cardiac output.

A variety of other clinical features are seen in IE (*e*Table 25.2.1). Reports in the preantibiotic era noted that splenomegaly was almost invariably present in patients with IE (136); more recent case series report a much lower incidence, probably because the diagnosis of endocarditis is now usually made relatively soon after onset. Similarly, clubbing of the nailbeds appears to be related to chronic infection and is now also an uncommon finding in patients with endocarditis (137). Although in our experience splenomegaly and clubbing are rarely diagnostic findings in patients with IE, others have reported these findings along with a high C-reactive protein test result, and petechiae still have diagnostic utility in clinical practice (136a).

A variety of musculoskeletal complaints are common in patients with IE. In one case series, bone or joint complications occurred in 15 of 104 patients with IE; all 15 of the patients were injection drug users (138). Symptoms such as arthralgias, myalgias, and acute synovitis are common. When joint aspirates are done in patients with acute synovitis and endocarditis, the joint fluid is usually sterile, although rarely cultures reveal the same organism that is causing their endocarditis. Low back pain is common in patients with endocarditis. Such pain may be confused with the generalized arthralgias or may rarely be an indicator of concurrent vertebral osteomyelitis. Lumbar pain usually resolves without sequelae during treatment of endocarditis.

Neurologic symptoms occur in 30% to 40% of patients with endocarditis in most series. Headache is the most common of these neurologic complaints. Cerebral embolic events occur in one-fourth of patients and may be the cause of the presenting symptoms in an important number of patients (139). In a review of 218 episodes of IE from one center, 55 of 218 episodes (25%) had a neurologic complication. An embolic event was responsible for 25 of 55 (42%) of the events. In 45% of the 55 neurologic events, the neurologic manifestations were present before antimicrobial therapy had begun (139a).

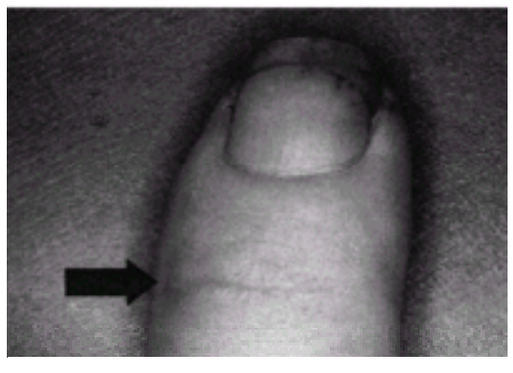
Peripheral stigmata are important in the recognition of endocarditis, but individual findings are neither diagnostic nor common. Petechiae are seen in approximately 10% to 15% of cases. Such lesions probably represent microemboli. Their presence should be sought for in the conjunctivae, on the palatal and buccal membranes, and on the extremities, especially the tops of the finger and toes in all patients. However, the presence of petechiae is not a highly specific finding. For example, petechiae may be present in many patients who undergo cardiopulmonary bypass, in some patients with staphylococcal bacteremia without coexistent endocarditis, and in patients with thrombocytopenia due to myriad causes (140).

Splinter hemorrhages—so called because they resemble a splinter being introduced into the nailbed—were first described in 1926 by Blumer (141). *e*Figure 25.5.2 depicts splinter hemorrhages caused by endocarditis. Splinter hemorrhages differ from traumatic subungual hemorrhages by being located more proximally in the nailbed. This finding is not specific, however, and splinter hemorrhages may be seen in patients with thrombocytopenia from any cause.

***e*FIGURE 25.5.2** Splinter hemorrhages. These are often seen in the middle third of nail beds and may migrate distally as the nail grows. (From Braverman IM, ed. *Skin signs of systemic disease*, 2nd ed. Philadelphia: WB Saunders, 1981:848, with permission.)

Splinter hemorrhages. Linear hemorrhages on the fingertips of a patient with infective endocarditis.

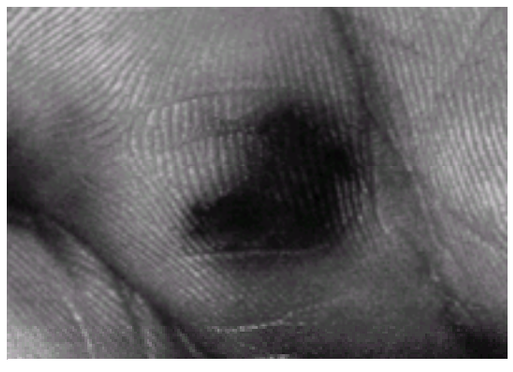
Osler’s nodes occur less commonly than petechiae and splinter hemorrhages in patients with endocarditis (*e*Fig. 25.5.3). The pathophysiology of Osler’s nodes remains controversial. Some authors believe that they result from immune complex deposition. However, other investigators have recovered bacteria from biopsies of these focal lesions (142,143). Osler’s nodes are small, tender, purple, erythematous subcutaneous nodules usually found on the pulp of the digits. Rarely, they may be seen in other areas such as the palms, soles, and ears. Even more rarely, they may become necrotic. Osler’s nodes are not pathognomonic of endocarditis; in fact, they can also be seen in other immunologic diseases (144). In some instances, their appearance is heralded by severe focal pain.



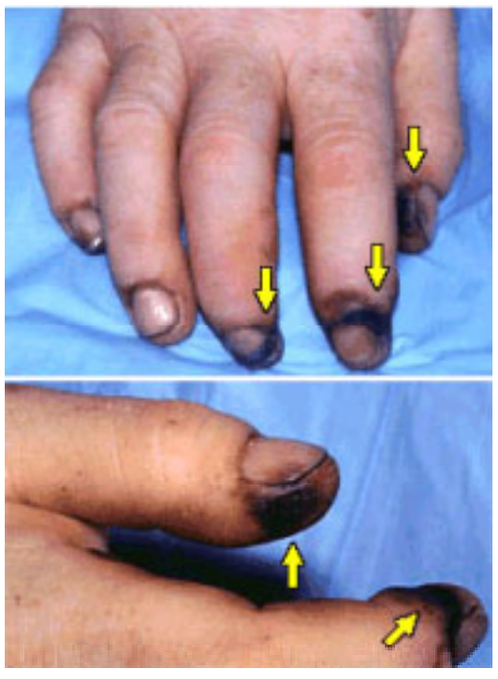
***e*FIGURE 25.5.3** Osler's node (*arrow*) and splinter hemorrhages. These are painful, wheel-like lesions in the pads of fingers and toes and may last from a few hours to days. The Osler's node is on the side of the finger with splinter hemorrhages noted in nail bed. (From Sanders CV, Nesbitt LT, eds. *The skin and infection*. Baltimore: Williams & Wilkins, 1995:45, with permission.)

Osler's nodes. There are tender nodules on the toe pads (*arrows*) secondary to infective endocarditis.

Janeway lesions were first described in 1899 (145). They are erythematous, macular, nontender lesions on the fingers, palm, or sole (eFig. 25.5.4). Similar to the controversy over the pathogenesis of Osler's nodes, some authorities believe they represent septic embolic and microabscesses (146), whereas others maintain they are caused by hypersensitivity angiitis (147,148). Regardless of their pathogenesis, both Osler's nodes and Janeway lesions are characterized histopathologically as localized vasculitis, often with central necrosis (147). The most important distinguishing difference between a Janeway lesion and Osler's node is lack of pain associated with the Janeway lesion (149).

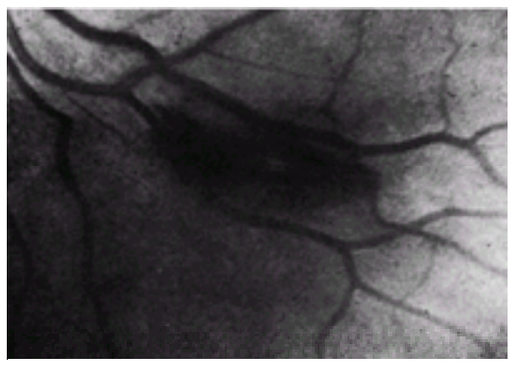


***e*FIGURE 25.5.4** Janeway lesion. These are nontender, nocular or nodular lesions on the palms or soles. (From Fitzpatrick TB, et al., eds. *Color atlas and synopsis of clinical dermatology*, 2nd ed. New York: McGraw-Hill, 1991:267, with permission.)

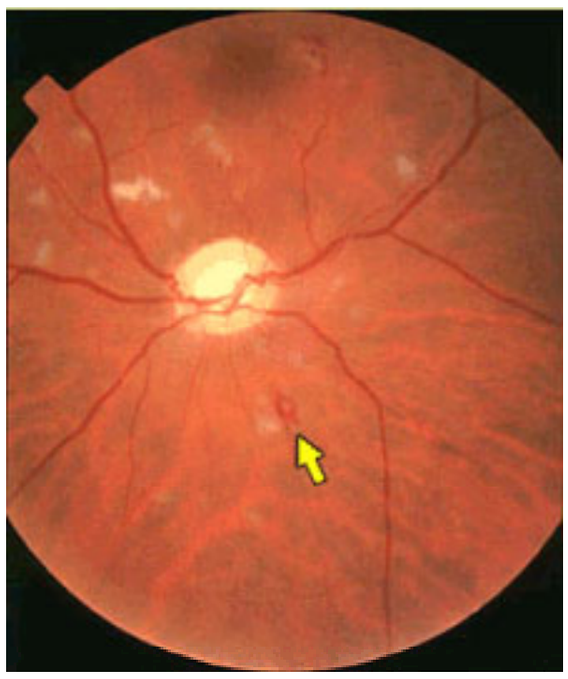


Janeway lesions of endocarditis. There are hemorrhages with nodular character at the fingertips (*arrows*).

Roth's spots, also known as *Litten's sign* (150), are retinal hemorrhages with a clear center. Roth's spots, originally described in 1872 (151), are classically associated with endocarditis (eFig. 25.5.5), but identical lesions may also occur in patients with severe anemia, a variety of other hematologic conditions, and collagen vascular disorders (147). The incidence of Roth's spots in endocarditis is low, appearing in 2% to 5% in various series. Roth's spots are presumed to occur as a result of capillary rupture, with secondary extravasation of blood and the formation of a central fibrin–platelet plug (150). Although a full ophthalmologic examination using direct ophthalmoscopy would likely improve the diagnostic yield for detecting Roth's spots, its infrequency in modern practice means the cost of ophthalmologic consultation is outweighed by the benefit.



***e*FIGURE 25.5.5** Roth's spot. Note hemorrhage with pale white center. (From Kritzinger EE, Wright BE, eds. *The eye and systemic disease*. Chicago: Yearbook Medical, 1984:27, with permission.)



Roth's spot. The yellow arrow indicates a hemorrhage with a white central spot typical of subacute bacterial endocarditis.

Clinical Complications

Surprisingly, the overall incidence of complications related to IE may not have changed significantly in the past three or four decades despite improvements in diagnostic techniques and in medical and surgical therapy (152). However, the types of complications seen in modern practice have changed substantially since the preantibiotic era. Patients now rarely die of sepsis. As a result of medical therapy, patients with IE often live longer and, thus, develop complications such as emboli, mycotic aneurysms, and heart failure more frequently. Estimates of the incidence of complications in the modern antibiotic era are presented in eTable 25.2.1.

Patients with endocarditis who undergo surgery are susceptible to a wide array of complications that were largely unknown 30 years ago (43). In a study of 287 patients treated for 300 episodes of IE in a tertiary cardiology referral center, a total of 386 complications occurred in 223 episodes. Most patients had either one (57%) or two (26%) complications, but 8% of patients had four or more complications (153). The most important and frequent cardiac complication of endocarditis is congestive heart failure. Heart failure in patients with endocarditis may be insidious or rapid in onset, but in both instances its primary cause usually is valvular insufficiency, rather than myocardial dysfunction. Patients with prosthetic valve endocarditis or endocarditis caused by fungal infection occasionally develop large bulky vegetations that may functionally occlude a valve orifice and secondarily cause heart failure. Regardless of the mechanism, the development of heart failure in patients with IE is an ominous sign. Unless valve replacement or valve repair is undertaken, most patients with this complication die, even if effective antimicrobial therapy is administered. Congestive heart failure may occur as a result of infection of any cardiac valve, but is most common in patients with aortic valve endocarditis and is least common in patients with tricuspid valve endocarditis (154).

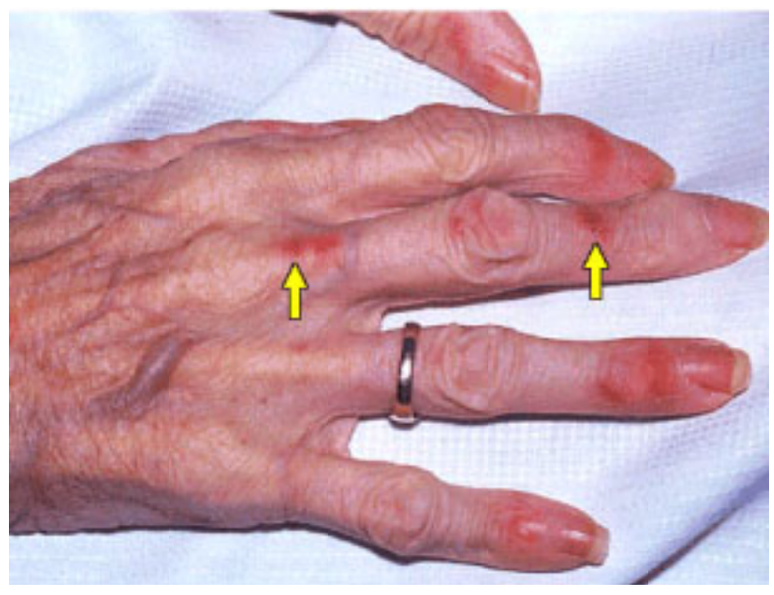
Most other cardiac complications in IE are related directly or indirectly to extension of infection from the valve leaflets or other areas of initial endocardial injury to surrounding cardiac structures such as the valve annulus, the adjacent cardiac conduction system, the sinus of Valsalva, or the mitral aortic intervalvular fibrosa. Rarely, vegetations on the aortic valve enlarge to the point that they occlude the left main coronary ostium (155).

Abscess in or adjacent to the valve annulus is often heralded by the appearance of first or second degree heart block, fever that persists despite appropriate therapy, or both. Rarely, patients with annular abscesses develop purulent pericarditis (89,156,157). Annular abscesses are more common in patients with aortic valvular infection than in those with mitral valve endocarditis (43). If infection extends beyond the valve ring, erosion may occur into the ventricular septum and secondarily into the cardiac conduction system. If the abscess extends into the lower portion of the septum, varying degrees of heart block may ensue. Extension of infection into the upper portion of the septum is less likely to produce electrocardiographic abnormalities (43). The new onset of atrioventricular or bundle branch block in a patient with endocarditis has a specificity of greater than 80% for the presence of an abscess (158). Furthermore, patients with perivalvular abscesses have higher rates of embolization and a higher risk of death than patients with endocarditis without abscess formation (116).

Uncommon cardiac complications of endocarditis include separation of the valve annulus from the surrounding myocardium with massive valvular insufficiency, myocardial infarction due to embolism to one or more coronary arteries, myocarditis, and pericarditis. Other uncommon intracardiac complications of endocarditis include fenestration of the valve leaflets, rupture of chordae tendineae, or aneurysm of the sinus of Valsalva. In the latter circumstance, aortocardiac fistulas may suddenly or gradually appear if the infective process ruptures into adjacent structures or chambers (43).

Myocarditis may occur as a result of coronary vasculitis, embolic coronary occlusion, or the effects of microbial toxins or immune complex deposition. Antisarcolemma antibodies have also been implicated in the pathogenesis of myocarditis in some cases of endocarditis (159). Pericarditis in patients with endocarditis may be either frankly purulent or follow a benign course with the formation of sterile pericardial effusions.

The most feared and most common extracardiac complication of endocarditis is embolism. Although valvular vegetations are the source of cerebral and systemic emboli in patients with endocarditis, rarely septic pulmonary arteriovenous fistulae may also provide a conduit for left-sided emboli (160). Cerebral infarction in patients with IE is usually caused by embolism that is later complicated by cerebral hemorrhage. Approximately three-fourths of all cerebral emboli involve the distribution of the middle cerebral artery. Cerebral infarction, caused by emboli or mycotic aneurysm, is the presenting sign of endocarditis in 4.5% to 14.0% of all cases of IE (161). Patients with endocarditis who develop cerebral emboli have clinically apparent evidence of systemic emboli in approximately one-half of cases; in contrast, only 2% of patients with other causes of stroke have associated systemic emboli (162).



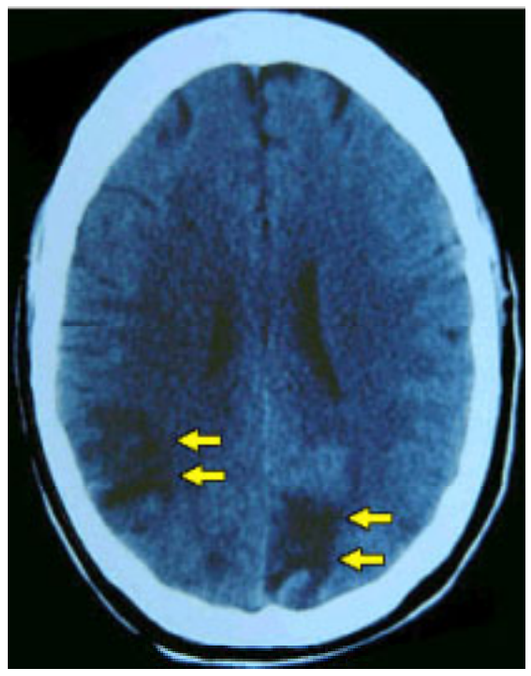
Septic emboli from infective endocarditis (*arrows*).

Septic emboli. Raised nodules from septic embolization from infective endocarditis.

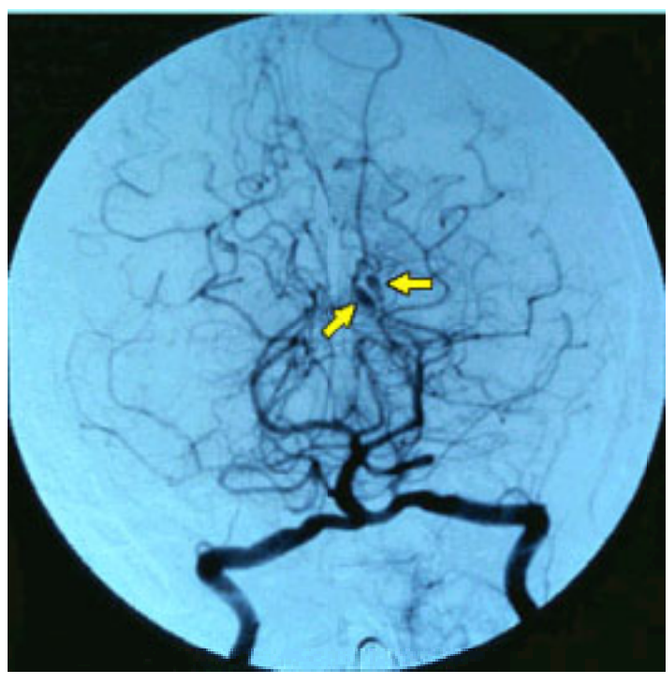
The risk of symptomatic embolism decreases rapidly after effective therapy for endocarditis is initiated. In a study that used transthoracic echocardiography to detect vegetations, the overall risk of embolism was 6.2 per 1,000 patient-days. The rate of embolism fell from 13 per 1,000 patient-days during the first week of therapy to less than 1.2 per 1,000 patient-days at the completion of therapy (163). Emboli to retina, coronary arteries, spinal cord, and the large arteries of the mesenteric circulation occasionally can produce sudden dramatic and catastrophic clinical findings such as blindness, paralysis, and signs and symptoms of an intraabdominal disaster. Peripheral large vessel embolism is uncommon in bacterial endocarditis but may be both the presenting symptom and the key to diagnosis in patients with fungal endocarditis. Microscopic examination or culture of material removed by thrombectomy may revel the fungal pathogen in some patients who simultaneously and paradoxically have negative blood cultures.

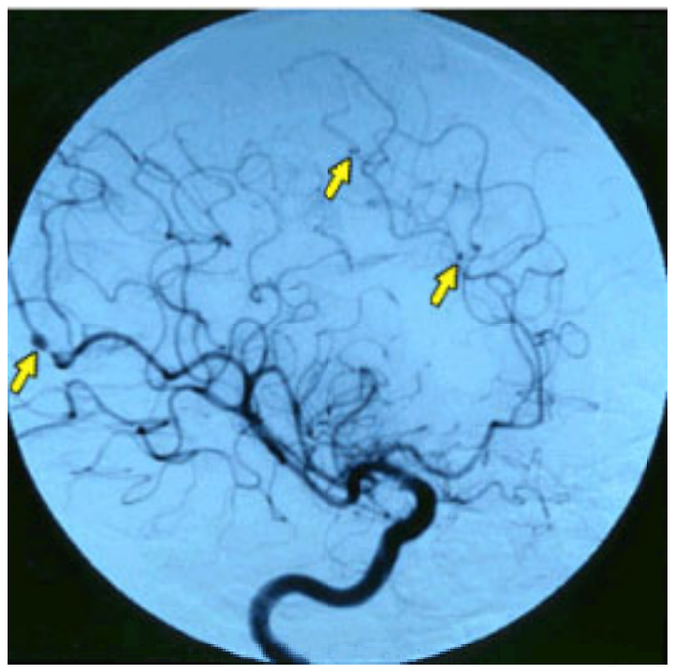
Patients with IE may also develop mycotic aneurysms in the cerebral, systemic, or both circulations, often at points of vessel branching. Mycotic aneurysms form when an arterial wall is damaged by septic emboli, which either occludes the vasa vasorum or the entire arterial lumen. Following the metastatic arrival of microbes, the vessel wall becomes secondarily infected and weakened. Thereafter, the lumen may dilate because of the combined effects of intraarterial pressure and destruction of the muscular layer. Estimates of the incidence of mycotic aneurysms vary between 1.2% and 5.4% in different studies, yet the true incidence of mycotic aneurysms is likely much higher, as many aneurysms remain asymptomatic (164). Mycotic aneurysms may decrease, increase, remain the same size, or even disappear during therapy for IE. The most significant complication of mycotic aneurysms is bleeding that may occur days, weeks, months, or rarely even years after successful therapy for the underlying endocarditis (165). When bleeding occurs, surgical intervention is often necessary, but surgery should be postponed whenever possible while antibiotic therapy is administered. Even a short period of medical therapy often makes surgical excision easier, possibly because the aneurysm wall becomes thicker from fibrosis during antibiotic treatment (164).

An array of other neurologic complications of endocarditis has been described. These include toxic metabolic encephalopathy due to sepsis, meningoencephalitis, purulent or aseptic meningitis, brain abscess, seizures, headache, and acute cranial or peripheral mononeuropathy (161). Such neurological abnormalities often are the presenting complaint. For example, a focal neurologic deficit, altered mental status, or a headache were the presenting complaint in 28% and 29%, respectively, in two large series of patients with endocarditis (166,167). Purulent meningitis is often a clue to the presence of staphylococcal endocarditis, but it may occur with any etiologic agent causing endocarditis; thus, the possibility of endocarditis should always enter the mind of clinicians when they treat patients with bacterial meningitis.



Ruptures mycotic aneurysms. Several areas of hypodensity representing ruptured mycotic aneurysms as a result of endocarditis (*arrows*).





Mycotic aneurysms from infective endocarditis. Localized aneurysmal dilatation of cerebral vessels as a result of endocarditis (*arrows*, A,B).

The renal complications of IE include focal areas of renal infarction (that often manifest as hematuria) and acute and chronic proliferative glomerulonephritis secondary to immune-mediated injury with deposition of IgG, IgM, and complement in the glomerular membrane. Chronic renal failure caused by immune complex glomerulonephritis was a common contributing cause to the death of patients with endocarditis who presented with classic subacute bacterial endocarditis in the preantibiotic era. This complication has become uncommon in modern practice. However, the presence of immune complex and secondary glomerulonephritis-mediated renal injury still occasionally occurs. Many patients with endocarditis have full or substantial return of renal function following temporary dialysis and treatment of their endocardial infection (168). As aminoglycosides are commonly used to treat staphylococcal and streptococcal endocarditis, it may be extremely difficult to separate drug-induced nephrotoxicity from renal impairment caused by the underlying disease. The development of renal insufficiency during IE is associated with a fivefold increase in the risk of a false outcome in one retrospective study of 204 consecutive episodes of IE from one medical center. Factors associated with increased risk of renal insufficiency include advanced age, the presence of *S. aureus*, severe thrombocytopenia, and prosthetic valve infection (168a).

Metastatic abscesses develop in the kidneys, spleen, or soft tissues (e.g., the psoas muscle) of some patients with IE. Surprisingly, patients with splenic abscesses often do not have marked abdominal pain or splenomegaly. Splenic abscesses usually require splenectomy for cure (43). In contrast, splenic infarcts, which are far more common than splenic abscesses in left-sided endocarditis, usually resolve spontaneously. Splenic infarct, on occasion, may be the presenting manifestation of endocarditis. Most metastatic abscesses in other locations require open or percutaneous drainage procedures.

Patients with tricuspid valve endocarditis may develop septic pulmonary emboli that later cavitate and produce hemoptysis. Such patients may also develop sterile or purulent, bloody or nonbloody pleural effusions (169). Septic pulmonary emboli may also result in the occurrence of a pneumothorax (170).

Clinical Course and Prognosis

Most patients with IE become afebrile within a few days after the institution of antimicrobial therapy. However, a small number of patients, particularly those with endocarditis caused by *S. aureus*, may remain febrile for 7 to 10 days and occasionally even longer. Drug fever, a secondary nosocomial infection, or intracardiac or extracardiac abscess formation should all be considered in such patients.

Congestive heart failure may first appear after an initial positive clinical response to medical therapy. Similarly, emboli to the CNS, coronary arterial, and systemic circulation may all occur after an initial response to antimicrobial therapy.

The prognosis in IE is related to the virulence of the infecting microorganism, the general health of the host, the valvular structures that are involved, the duration of the infection, and the presence or absence of congestive heart failure. *S. aureus* endocarditis is still fatal in 20% to 40% of cases, despite the best available medical and surgical therapies. In contrast, the prognosis of streptococcal endocarditis is substantially better. Between 90% and 95% of patients with endocarditis caused by viridans streptococci are now cured with medical or combined medical and surgical therapy. A similarly good prognosis exists for patients with endocarditis caused by other species of streptococci. Fungal endocarditis is virtually impossible to cure with medical therapy; only a small minority of such patients is currently cured with combined antifungal and surgical therapy (171). Some of these patients remain on antifungal treatment for extended periods of time on the assumption that sterilization of the infection is otherwise impossible.

The prognosis of patients with right-sided endocarditis, even those with infections caused by *S. aureus*, is remarkably good. In an analysis of 11 studies involving 362 cases of right-sided endocarditis, Chambers was able to document only two treatment failures (0.6%) and seven deaths (2.0%) in the same series (40).

Despite early surgical intervention, the prognosis of late-onset prosthetic valve endocarditis is better than for patients who acquire infection within 60 days of their replacement valve surgery. For example, in a review of 56 cases of prosthetic valve endocarditis that occurred among 3,200 recipients of bioprosthetic valves, the mortality for cases that occurred within 2 months of surgery was 75%, whereas only 25% of cases with late-onset prosthetic valve endocarditis were fatal (172).

Overall mortality for prosthetic valve endocarditis has ranged from 18% to 57% in different case series, but averages 30% to 45% in most reports (22,173,174). Although some authors have emphasized a more favorable outcome of prosthetic valve endocarditis with prompt surgical therapy (23,174,175), other authors have concluded that *long-term* outcomes of medical therapy are similar to outcomes in patients treated with combined medical and surgical therapy. It has been our experience that selected cases of prosthetic valve endocarditis can be cured medically. However, with prosthetic valve endocarditis caused by highly resistant organisms, cases complicated by congestive heart failure, or cases associated with perivalvular abscesses, surgery is usually necessary.

In a study of 49 episodes of definite prosthetic valve endocarditis (by the Duke criteria) treated at one institution, ten patients were treated with medical therapy alone and 39 patients received combined medical and surgical therapy. Long-term follow-up showed no significant differences between the two groups regarding late mortality risk of recurrent endocarditis at 5 years or the need for reoperation (175a).

PRINCIPLES OF MANAGEMENT

Prevention of Infective Endocarditis

Antimicrobial prophylaxis before selected dental and invasive surgical and diagnostic procedures has become standard and routine in most countries, despite the fact that no prospective study has been performed that proves that such therapy is clearly beneficial. Only one-half of all patients who develop endocarditis have a cardiac disorder that would have prompted endocarditis prophylaxis in the first place (176). Furthermore, follow-up incidence of endocarditis is low even if patients with predisposing valvular lesions do not receive prophylactic antibiotics: One in five untreated patients develops endocarditis after having had an invasive procedure. Thus, perhaps only one in ten endocarditis episodes can be prevented by the appropriate use of antibiotic prophylaxis before an invasive procedure.

It is our view that maintenance of meticulous dental hygiene is of equal importance to antibiotic prophylaxis in the prevention of IE. It has been our experience that some patients with valvular and congenital heart disease actually visit their dentist less often, rather than more often, when the infectious risks of dental procedures are explained to them. Vigorous brushing of teeth or even chewing gum may result in transient bacteremia in patients with periodontal disease; it is important to emphasize to the patient that maintenance of good dental hygiene is vital. In addition, it is advisable to instruct all patients to avoid gingival trauma with toothpicks and high-pressure water irrigation devices (177).

The guidelines for antimicrobial prophylaxis for endocarditis formulated by an expert committee of the American Heart Association (178) are the regimens most widely used by clinicians in the United States. Expert groups in Europe (45) have published similar guidelines. Both guidelines are based on results of *in vitro* studies, clinical experience, data from experimental animal models, and clinical assumptions concerning the bacteria most likely to produce bacteremia and cause endocarditis. These recommendations should not be assumed to be the standard of care in all clinical situations. Clinicians can reasonably deviate from these guidelines in

individual cases. For example, clinicians must often use judgment in selecting dose and duration of antimicrobial therapy in elderly or obese patients or in those with underlying renal disease. Furthermore, there are sometimes instances in which the risk of prophylactic therapy may actually outweigh the risk of postprocedure endocarditis. Patients in such circumstances often have cardiac lesions of questionable or little hemodynamic consequence, have a documented or possible drug allergy, or are undergoing procedures in which the risk of bacteremia is extremely low.

The primary justification for prophylactic therapy to prevent endocarditis is based on the results of animal experiments. If bacteria with a known ability to cause endocarditis are injected into animals after their heart valves have been abraded using vascular catheters, the animals predictably develop endocarditis (179). If antimicrobial therapy is given immediately before or for up to 30 minutes after this experimental bacteremia has been induced, endocarditis does not ensue (180). However, if therapy is delayed for several hours after a bacteremia has been produced in an animal rendered susceptible by cardiac valvular damage, endocarditis is likely to occur. These data suggest that antimicrobial therapy can prevent endocarditis by either killing bacteria before they establish a nidus of infection in a susceptible heart, or by killing organisms shortly after they adhere to a localized area of damaged endothelium (180).

No studies have conclusively demonstrated that prophylactic antibiotics are effective in preventing endocarditis in humans after dental procedures. Furthermore, currently recommended antibiotic regimens might fail to prevent endocarditis, even if such therapy is given immediately before an invasive procedure. For example, in a study of 52 cases of endocarditis that occurred despite prophylactic antimicrobial therapy, two-thirds of the cases had pathogens that were susceptible *in vitro* to the agents the patients had received prophylactically (23).

Three studies have been published in an attempt to measure the efficacy of prophylactic antibiotic therapy in the prevention of endocarditis. Two of these studies (8,181) produced results that suggested a benefit of prophylactic antibiotics; the third (182) found no benefit of such therapy. However, all three studies had serious limitations in their design or lacked appropriate numbers of patients to achieve necessary statistical power (180).

*e*Table 25.2.2 outlines the current clinical situations wherein antibiotic prophylaxis is recommended based on the risk involved. The precise risk of endocarditis following invasive dental or surgical procedures in patients with any of the listed conditions cannot be precisely measured; in fact, differences in opinions continue to exist as to whether even patients with each of the listed predisposing conditions should receive antibiotic therapy before an invasive procedure. There is general agreement, however, that those patients with a prior history of endocarditis and those with prosthetic heart valves are at higher risk than patients with acquired congenital and valvular lesions.

***e*TABLE 25.2.2** CARDIAC CONDITIONS AND THE NEED FOR ENDOCARDITIS PROPHYLAXIS[a]

Endocarditis prophylaxis recommended
Prosthetic cardiac valves, including bioprosthetic and homograft valves
Previous bacterial endocarditis, even in the absence of heart disease
Most congenital malformations
Rheumatic and other acquired valvular dysfunction, even after valvular surgery
Hypertrophic cardiomyopathy
Mitral valve prolapse with valvular regurgitation
Endocarditis prophylaxis not recommended
Isolated secundum atrial septal defect
Surgical repair without residua beyond 6 mo of secundum atrial septal defect, ventricular septal defect, and patent ductus arteriosus
Previous coronary artery bypass graft surgery
Mitral valve prolapse without valvular regurgitation[b]
Physiologic, functional, or innocent heart murmurs
Previous Kawasaki's disease without valvular dysfunction
Previous rheumatic fever without valvular dysfunction
Cardiac pacemakers and implanted defibrillators

[a]This table lists selected conditions but is not meant to be all inclusive.
[b]Individuals who have mitral valve prolapse associated with thickening, redundancy, or both of the valve leaflets may be at increased risk for bacterial endocarditis, particularly men who are 45 years of age or older.

In general, risk of IE is considered to be highest for oral or dental procedures in which the oral mucosa is penetrated and in which gingival or mucosal bleeding is likely to occur. Invasive dental procedures in which the risk of transient bacteremia is above 50% include tooth extractions, periodontal surgery, and cleaning of teeth with removal of tartar. The risk of bacteremia is substantially lower for invasive genitourinary procedures such as dilation of strictures, insertion of endoscopes and catheters, and prostatectomy. The risk of bacteremia following invasive gastrointestinal procedures such as colonoscopy with biopsy and endoscopic retrograde cholangiopancreatography is generally less than 5% to 10%. The American Heart Association has listed those invasive procedures in which endocarditis prophylaxis is and is not recommended (*e*Table 25.2.2). Clinicians may choose to use antimicrobial prophylaxis in some patients with a high risk for endocarditis who undergo a procedure with a low or intermediate risk of bacteremia, yet reasonably forego antimicrobial prophylaxis in patients with a very low risk of endocarditis (e.g., those with a history of drug allergy) who undergo a procedure with an intermediate or high risk of bacteremia (*e*Table 25.2.3).

***e*TABLE 25.2.3** DENTAL OR SURGICAL PROCEDURES AND ENDOCARDITIS PROPHYLAXIS

Endocarditis prophylaxis recommended
Dental procedures known to induce gingival or mucosal bleeding, including professional cleaning
Tonsillectomy, adenoidectomy, or both
Surgical operations that involve intestinal or respiratory mucosa
Bronchoscopy with a rigid bronchoscope
Sclerotherapy for esophageal varices
Esophageal dilatation
Gallbladder surgery
Cystoscopy
Urethral dilatation
Urethral catheterization if urinary tract infection is present
Prostatic surgery
Incision and drainage of infected tissue
Vaginal hysterectomy
Vaginal delivery in the presence of infection
Endocarditis prophylaxis not recommended
Dental procedures not likely to induce gingival bleeding, such as simple adjustment of orthodontic appliances or fillings above the gum line
Injection of local intraoral anesthetic (except intraligamentary injections)
Shedding of primary teeth
Tympanostomy tube insertion
Endotracheal intubation
Bronchoscopy with a flexible bronchoscope, with or without biopsy
Cardiac catheterization
Endoscopy with or without gastrointestinal biopsy
Cesarean section
In the absence of infection for urethral catheterization, dilatation and curettage, uncomplicated vaginal delivery, therapeutic abortion, sterilization procedures, or insertion or removal of intrauterine devices

The antimicrobial regimens suggested by the American Heart Association for endocarditis prophylaxis are listed in Table 25.3. Although the evidence supporting the routine use of antibiotic prophylaxis is spotty, failure to adhere to these guidelines in the current medicolegal climate may invite litigation. Other expert groups such as the British Society for Antimicrobial Chemotherapy proposed guidelines that differ only slightly. For example, the American Heart Association guidelines recommend that the primary antibiotic regimen for patients undergoing dental, oral, or upper respiratory procedures should be amoxicillin, 2 g orally, 1 hour before the procedure, whereas the British Society for Antimicrobial Chemotherapy recommends a single 3-g oral dose of amoxicillin (183). Some authors (184) have suggested that prophylaxis in patients with prosthetic heart valves should always be parenteral (184), but such recommendations are certainly not a consensus opinion, and we do not routinely use parenteral therapy in such patients.

- Standard regimen for dental/oral/upper respiratory tract procedures
  - Standard regimen in patients at risk (includes those with prosthetic heart valves and other high-risk patients): amoxicillin, 2.0 g, orally 1 h before procedure
  - For amoxicillin/penicillin-allergic patients: clindamycin (600 mg orally), cephalexin or cefadroxil (2 g orally), or azithromycin (500 mg orally) taken 1 h before procedure
- Alternate standard regimens for dental/oral/upper respiratory tract procedures
  - For patients unable to take oral medications: ampicillin, 2.0 g i.v. (or i.m.) 30 minutes before procedure; then ampicillin, 1.0 g i.v. (or i.m.) 6 h after initial dose
  - For ampicillin/amoxicillin/penicillin-allergic patients unable to take oral medications: clindamycin, 600 mg i.v., or cefazolin, 1 g i.v., 30 min before procedure
- Standard regimen for genitourinary/gastrointestinal procedures
  - Standard regimen in patients at high risk: ampicillin, 2.0 g i.v. (or i.m.), plus gentamicin, 1.5 mg/kg i.v. (or i.m.) (not to exceed 120 mg) 30 min before procedure; then amoxicillin, 1 g orally, i.m. or i.v. 6 h after initial dose
  - For amoxicillin/ampicillin/penicillin allergic patients: vancomycin, 1.0 g i.v. administered over 1 h, plus gentamicin, 1.5 mg/kg i.v. (or i.m.) (not to exceed 120 mg) 1 h before procedure
  - Alternate oral regimen for genitourinary/gastrointestinal patients at moderate risk: amoxicillin, 3.0 g orally; ampicillin, 2 g i.v.; or vancomycin, 1 g i.v. to be completed 30 min before the procedure

Adapted from Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997;277:1794–1801.

TABLE 25.3 RECOMMENDED BACTERIAL ENDOCARDITIS PROPHYLAXIS REGIMENS

Medical Therapy during the Course of Infective Endocarditis

General Principles

Individuals with IE often present with unique issues that must be addressed while treating the disease. For that reason, cases of endocarditis caused by the same organism may not be treated in precisely the same manner. On the other hand, common medical and social issues often arise while treating individuals with endocarditis caused by dissimilar pathogens. Table 25.4 outlines a typical approach that might be used for the patient without complications.

- Initial evaluation
  - Establish diagnosis (including history, physical, blood cultures, echocardiogram, supportive laboratory studies)
  - Initiate appropriate antibiotic therapy using minimum inhibitory concentration levels as guide
  - Obtain other baseline studies (electrocardiography, sedimentation rate, complete blood cell counts, electrolytes, chest roentgenography)
  - Continue chronic medications except warfarin
  - If on warfarin, discontinue and let international normalized ratio drift down to 2.0, then begin therapeutic heparin
  - Begin search for source of valvular infection
  - If significant valvular regurgitation present, begin angiotensin converting enzyme inhibitor
  - Cardiovascular surgical consult in most instances, particularly if resistant organism, prosthetic valve endocarditis, evidence of hemodynamic instability, or perivalvular abscess is present
  - Evaluate home situation and lifestyle regarding potential for home therapy
- Once therapy has begun
  - Daily vital signs, physical examination; telemetry at least the first week
  - Insert percutaneous indwelling central venous catheter line (or Hickman's) for intravenous antibiotic use
  - Continue search for source of valvular infection if appropriate
  - Repeat blood cultures after 72 h of therapy and repeat if fever persists
  - Obtain trough and peak antibiotic drug levels initially, and if dosage altered
  - Ongoing laboratory studies: Every 3 d, complete blood cell counts, electrolytes. Weekly, electrocardiography, chest roentgenography.
  - Continue i.v. antibiotic therapy 5 to 14 d in hospital, then arrange for completion of course (usually 4 wk) as outpatient
  - If patient on chronic warfarin, may resume after first week of therapy if surgery not apparently required
  - As outpatient on therapy, continue daily vital signs and weekly complete blood cell counts and electrolytes
  - Once therapy complete, follow-up echocardiography

TABLE 25.4 REPRESENTATIVE THERAPEUTIC APPROACH FOR UNCOMPLICATED NATIVE VALVE INFECTIVE ENDOCARDITIS

After establishing the initial diagnosis, as previously described, a search should be undertaken for the source of the valvular infection. This extent and nature of this search is dependent on the infecting organism. For instance, a dental abnormality is often associated with *S. viridans* endocarditis; a skin infection, deep abscess, or infected vascular catheter may be the origin if the organism is *Staphylococcus*, whereas a gastrointestinal source, such as colon cancer, may be the source of *S. bovis* endocarditis. If a source for the endocarditis can be found, then its treatment or eradication should be undertaken before cardiac valve repair or replacement is undertaken. For example, if an infected catheter or foreign body is the source of *S. aureus* endocarditis, this source should be removed before proceeding to valve replacement.

In the 1990s, it became acceptable and often necessary to reduce the length of hospitalization by use of a home health agency to administer home intravenous therapy. The patient's home situation should to be evaluated and the suitability for home intravenous therapy should be assessed soon after the diagnosis of IE is established. For most native valve endocarditis, at least 5 to 7 days of in-hospital intravenous therapy is given, followed typically by several more weeks of intravenous antibiotics that, in selected patients, may be completed at home. Criteria for outpatient treatment of endocarditis include the following: (a) unequivocal clinical response to initial therapy, (b) stable hemodynamic status, (c) absence of metastatic or intracardiac complications, and (d) ability to comply with the mechanics and scheduling of outpatient antibiotic therapy. For some patients home therapy is simply not an option because of their social situations. In patients with those home environments, completing the entire antibiotic course as an inpatient or in a convalescent care facility is preferred. Six weeks of therapy is used for most prosthetic valve endocarditis or when a relatively resistant organism causes native valve endocarditis. At times, more than 6 weeks of therapy may be needed, especially when a virulent or relatively resistant organism such as a gentamicin-resistant enterococcus is present.

Once the diagnosis of endocarditis is established, a baseline electrocardiogram, complete blood count with differential, sedimentation rate, electrolytes, and chest roentgenography should be obtained. A chest wall echocardiogram should be obtained in all patients. TEE should be employed in accordance with the guidelines noted previously. After the initial blood cultures, repeat blood cultures should be obtained in most patients after 3 days of treatment to ensure that bacteremia has resolved. Persistent bacteremia on surveillance cultures should raise concern that the antibiotic therapy is less than adequate. After that, blood cultures are usually only obtained again if fever resumes or if other signs of active infection, such as recurrent leukocytosis, occur.

Persistent fevers in the face of seemingly appropriate therapy are an occasional clinical dilemma. When fever is accompanied by mental confusion or congestive heart failure, therapy with antipyretics such as acetaminophen is warranted, but in general it is preferable to avoid antipyretics in order to monitor the clinical response to therapy. The blood counts and electrolytes are repeated every 3 days until the results are stable or normal. Patients are usually monitored with telemetry for the first week of therapy; electrocardiography and chest roentgenography are repeated weekly. Prolongation of the PR interval on electrocardiography (unrelated to drug usage) or radiographic or clinical signs of congestive heart failure may in turn lead to other studies and more careful clinical assessment. When aminoglycosides or vancomycin are used as therapy, antibiotic drug levels should be monitored at least once during therapy. Specialized microbiologic testing of the etiologic agent should be assessed with certain organisms such as viridans staphylococci and enterococci. Repeat echocardiography may be necessary if there is confusion regarding the clinical status of the patient, but, in most instances, serial echocardiograms are not necessary while therapy is ongoing.

Early surgical consultation should be obtained in most cases. Such consultation may be helpful regarding timing of future surgical intervention and the risks involved. Surgical consultation is mandatory when a virulent organism is the causative pathogen, in all cases of prosthetic valve endocarditis, or if there are extenuating circumstances, such as significant comorbid illnesses that could significantly increase surgical morbidity and mortality. Surgical consultants should also be involved in decisions concerning the need for cardiac catheterization. If a surgical indication arises early in the treatment of endocarditis, there is no advantage in waiting for "sterilization" of the valve before proceeding to surgery.

Few medications are contraindicated in the treatment of endocarditis; however, one frequent exception is warfarin (Coumadin). After the diagnosis of endocarditis is established, warfarin is usually discontinued and when the international normalized ratio drops to 2.0, heparin (either unfractionated or low-molecular-weight) is started in its place. Should cardiovascular or other surgery (e.g., placement of a Hickman's catheter) be needed, heparin anticoagulation can be quickly reversed by its discontinuation or the use of protamine. Warfarin is then restarted in patients with metallic prosthetic valves once the clinical course stabilizes, surgery appears unlikely

to be needed, or the patient is being readied for home antibiotic therapy.

An indwelling central line is usually placed soon after a diagnosis of endocarditis is established. In general, a peripheral indwelling central catheter is used for vascular access, although a Hickman's catheter or other devices [e.g., peripheral venous reservoirs such as the Passport (Wilson-Cook Medical, Inc., Winston-Salem, NC)] may be used in selected patients.

Most patients are monitored during home antimicrobial therapy with the assistance of personnel in home health organizations. However, it may also be appropriate to manage selected patients using a local infusion center or in a convalescent care facility. Patients receiving outpatient therapy typically should be seen weekly in the outpatient clinic during the course of their home therapy, and as necessary after the completion of treatment. A repeat chest wall echocardiogram following completion of the antimicrobial therapy should be obtained to assess the magnitude of residual valvular and ventricular dysfunction and to provide a baseline for subsequent follow-up evaluations.

The previously mentioned strategy is a broad overview of how uncomplicated patients with native valve IE caused by a susceptible organism should be managed. This approach is frequently modified as the clinical situation warrants. Other issues frequently arise during the course of treatment for IE and may require an alternative approach.

Antimicrobial Therapy

Before the availability of antimicrobial therapy, IE was invariably fatal. Even today a substantial percentage of patients with IE die because of highly virulent organisms such as *S. aureus*, despite having received appropriate antimicrobial therapy in a timely manner and despite the skillful use of modern diagnostic techniques, surgical methods, and supportive care. However, the majority of patients with endocarditis now survives infections.

Following the establishment of a diagnosis using clinical deduction and microbiologic and echocardiographic methods, antimicrobial therapy should be administered in a dose designed to give sustained bactericidal serum concentrations throughout much of or the entire dosing interval. The duration of this therapy has to be long enough to eradicate microorganisms growing in the valvular vegetations.

Soon after the discovery of sulfonamides and penicillins, it was apparent that bactericidal therapy was more effective than bacteriostatic therapy in treating endocarditis. Although early clinical trials showed that a few patients with streptococcal endocarditis could be cured with low doses of penicillin administered for as short a period as 6 days, longer therapy was necessary to ensure cure in all patients. For example, the results of two early landmark treatment trials performed in the 1940s and early 1950s revealed that approximately 20% of patients with viridans streptococcal endocarditis relapsed when penicillin was administered for only 14 days (185,186). In contrast, in a later study of patients with viridans streptococcal endocarditis, none of 66 consecutive patients who survived a 4-week course of penicillin G relapsed, and only 1 of 77 patients treated with this regimen died of active infection. Similarly, 4 to 6 weeks of bactericidal therapy with a single drug is highly effective as treatment for endocarditis caused by other streptococcal species and staphylococci. Such prolonged therapy is presumed to be necessary because bacterial concentrations within vegetations may be as high as 10^9 to 10^{10} colony-forming units per g of tissue, and because organisms deep within vegetations are not accessible to phagocytic cells and often are in a state of reduced metabolic activity (187).

The need for prolonged therapy in treating endocarditis and the problem of reduced *in vitro* sensitivity to commonly used antimicrobial agents has stimulated interest in using combination therapy to treat endocarditis. Combination therapy using a beta-lactam agent such as penicillin with an aminoglycoside has been shown to be highly effective in streptococcal endocarditis and somewhat effective in a small subset of patients with staphylococcal endocarditis. Combination therapy with penicillin or ceftriaxone and an aminoglycoside for 2 weeks is highly effective in viridans streptococcal endocarditis (188,189 and 190).

Combination therapy with nafcillin and an aminoglycoside for 2 weeks has been shown to be effective in patients with right-sided endocarditis caused by *S. aureus* (191). One study suggests that aminoglycoside therapy is not critical to the success of these short-course regimens. In a randomized trial, cloxacillin therapy alone for 2 weeks was as effective as the combination of cloxacillin and gentamicin (192). However, combined therapy with vancomycin and an aminoglycoside administered for 2 weeks does not appear to be effective. Also, combined therapy with nafcillin and an aminoglycoside is not effective in left-sided endocarditis if treatment is given for only 2 weeks.

Several reports have described the successful use of oral regimens for selected patients with IE (193). Despite reports of success with such regimens, oral regimens should not be used as initial therapy for endocarditis. Nonconventional regimens should only be used in highly selected cases in which the causative organism is known, in which the antimicrobial susceptibility has been carefully studied, and in which *in vitro* studies show high levels of susceptibility. Generally, there should be a compelling reason to use oral therapy over conventional intravenous therapy now that home health agencies allow for home antibiotic infusions. We do not believe there are adequate data to support a preference for oral antibiotic usage.

Until more recently, most patients with endocarditis received the entire duration of their antimicrobial therapy while in the hospital. However, the development of systems and equipment that allows for prolonged and safe administration of intravenous therapy to outpatients has made it acceptable and appropriate to treat selected patients with endocarditis as outpatients during much or even all of their therapy (190). Patients selected for outpatient therapy should have responded clinically to inpatient therapy and without evidence of metastatic or intracardiac complications. In addition, they should be hemodynamically stable, compliant, and capable of managing the technical aspects of intravenous therapy (188). Such patients still require careful and regular monitoring and must have ready access to full medical care should complications such as drug allergy, emboli, or cardiac failure occur.

Endocarditis Caused by Streptococcus Viridans and Streptococcus bovis

The various species of streptococci that make up the viridans group and *S. bovis* account for approximately 40% to 50% of all cases of native valve endocarditis in community practice. Endocarditis caused by these organisms can usually be microbiologically cured if one of four different regimens is used (eTable 25.4.1). Most of these organisms are highly penicillin-susceptible [i.e., have a minimum inhibitory concentration (MIC) £0.1 µg per mL].

***e*TABLE 25.4.1** SUGGESTED REGIMENS FOR THERAPY OF NATIVE VALVE ENDOCARDITIS CAUSED BY PENICILLIN-SUSCEPTIBLE VIRIDANS STREPTOCOCCI AND *STREPTOCOCCUS BOVIS* (MINIMUM INHIBITORY CONCENTRATION £0.1 µG PER ML)

Antibiotic	Dosage and route	Duration (wk)	Comments
Aqueous crystalline penicillin G sodium or	12–18 million U/24 h i.v. either continuously or in six equally divided doses	4	Preferred in most patients older than 65 yr and in those with impairment of the eighth nerve or renal function
Ceftriaxone sodium	2 g once daily or i.m.	4	
Aqueous crystalline sodium	12–18 million U/24 h i.v. either continuously or in six equally divided doses	2	When obtained 1 h after a 2- to 30-min i.v. infusion or i.m. injection, serum penicillin concentration of gentamicin of approximately 3 µg/mL is desirable; trough concentration should be <1 µg/mL
With gentamicin sulfate	1 mg/kg i.m. or i.v. every 8 h	2	
Vancomycin hydrochloride	30 mg/kg per 24 h i.v. in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4	Vancomycin therapy is recommended for patients allergic to beta-lactams (see text); peak serum concentrations of vancomycin should be obtained 1 h after completion of the infusion and should be in the range of 30–45 µg/mL for twice-daily dosing

Endocarditis caused by highly penicillin-susceptible streptococci can be reliably cured using aqueous crystalline penicillin G at a dose of 12 to 18 million units daily for 4 weeks. This regimen or an equally effective regimen consisting of ceftriaxone, given as a 2-g daily dose for 1 month, remains the preferred treatment for elderly patients or in other patients in whom aminoglycoside therapy is considered risky or contraindicated.

Selected patients with native valve endocarditis without evidence of intracardiac or extracardiac complications or preexisting renal or otic disease can be treated with shorter courses of combination therapy consisting of either aqueous crystalline penicillin G or ceftriaxone with gentamicin. The latter agent should be given at a dose (usually 1 mg per kg) designed to give a peak gentamicin serum level of 3 µg per mL. Although streptomycin can also be used with either of the previously mentioned beta-lactam antibiotics to achieve the same effect, gentamicin is currently more widely used in clinical practice. Furthermore, determinations of gentamicin serum levels are more widely available and dosing regimens are more familiar to clinicians than streptomycin.

Patients with histories of penicillin allergy can usually be treated with other beta-lactam antibiotics, such as cefazolin, if their prior history of penicillin allergy consists of skin rash without other signs of immediate-type hypersensitivity. Patients with histories of immediate-type hypersensitivity may be treated either with vancomycin for 4

weeks or desensitized to penicillin and treated with a standard regimen.

Patients with endocarditis caused by viridans streptococci and MICs >0.1 µg per mL and patients with endocarditis caused by streptococci with nutritional deficiencies that hinder their growth in routine laboratory culture media should receive aqueous penicillin G for a total of 4 weeks. Gentamicin should be added to this regimen for the first 2 weeks. As for other patients with streptococcal endocarditis with immediate-type hypersensitivity reactions to beta-lactams, vancomycin is an acceptable alternative (eTable 25.4.2).

***e*TABLE 25.4.2** THERAPY FOR NATIVE VALVE ENDOCARDITIS CAUSED BY STRAINS OF VIRIDANS STREPTOCOCCI AND *STREPTOCOCCUS BOVIS* RELATIVELY RESISTANT TO PENICILLIN G (MINIMUM INHIBITORY CONCENTRATION >0.1 µG PER ML AND <0.5 µG PER ML)

Antibiotic	Dosage and route	Duration (wk)	Comments
Aqueous crystalline penicillin G sodium	18 million U/24 h i.v. either continuously or in six equally divided doses	4	Cefazolin or other first-generation cephalosporins may be substituted for penicillin in patients whose penicillin hypersensitivity is not of the immediate type
With gentamicin sulfate	1 mg/kg i.m. or i.v. every 8 h	2	
Vancomycin hydrochloride	30 mg/kg per 24 h i.v. in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4	Vancomycin therapy is recommended for patients allergic to beta-lactams

Other streptococcal species (e.g., groups A, B, C, and G and *Streptococcus pneumoniae*) are occasional causes of endocarditis. Therapy should always be based on the results of susceptibility tests. As most such organisms are highly sensitive to penicillin, regimens used to treat endocarditis caused by viridans streptococci are usually effective. However, increasing numbers of isolates of *S. pneumoniae* have become relatively or highly penicillin resistant. Such organisms may be simultaneously resistant to other beta-lactams as well as to other antimicrobial agents. Therapy in such cases usually requires the input of an infectious disease specialist or a microbiologist. A few strains of *S. pneumoniae* only respond to vancomycin therapy.

Endocarditis Caused by Enterococci

Unlike streptococci, members of the genus *Enterococcus* are uniformly resistant to low concentrations of penicillin. Enterococci are also relatively resistant to expanded spectrum penicillins and vancomycin. Furthermore, they are uniformly highly resistant to all cephalosporins and typically resistant to aminoglycosides at concentrations achieved after standard dosing regimens. However, if penicillin, ampicillin, or vancomycin is given in synergistic combination with aminoglycosides such as gentamicin, most strains of enterococci are killed both *in vitro* and *in vivo* (eTable 25.4.3).

***e*TABLE 25.4.3** STANDARD THERAPY FOR ENDOCARDITIS CAUSED BY ENTEROCOCCI

Antibiotic	Dosage and route	Duration (wk)	Comments
Aqueous crystalline penicillin G sodium	18–30 million U/24 h i.v. either continuously or in six equally divided doses	4–6	
With gentamicin sulfate	1 mg/kg i.m. or i.v. every 8 h	4–6	4-wk therapy recommended for patients with symptoms <3 mo in duration; 6-wk therapy recommended for patients with symptoms >3 mo in duration
Ampicillin sodium	12 g/24 h i.v. either continuously or in six equally divided doses	4–6	
With gentamicin sulfate	1 mg/kg i.m. or i.v. every 8 h	4–6	
Vancomycin hydrochloride	30 mg/kg per 24 h i.v. in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4–6	Vancomycin therapy is recommended for patients allergic to beta-lactams; cephalosporins are not acceptable alternatives for patients allergic to penicillin
With gentamicin sulfate	1 mg/kg i.m. or i.v. every 8 h	4–6	

During the past 10 to 15 years, a number of new trends in the resistance pattern of enterococci have appeared. Some strains (particularly strains of *Enterococcus faecalis*) have acquired genetic material that allows them to produce beta-lactamase. Other strains, particularly strains of *E. faecium*, have acquired high-level resistance to streptomycin, gentamicin, or both. In addition, intrinsic high-level resistance to penicillin and ampicillin has appeared in some strains of enterococci. Finally, increasing numbers of enterococci have acquired high-level resistance to vancomycin. Some, but not all, of these highly resistant strains are also resistant to the investigational glycopeptide antibiotic, teicoplanin.

The previously mentioned microbiologic characteristics have a direct effect on the guidelines for treatment of enterococcal endocarditis. Standard therapy for enterococci with “typical” low-level penicillin resistance consists of a combination of intravenous aqueous penicillin G or ampicillin combined with gentamicin for 4 to 6 weeks. Patients with symptoms for less than 3 months can usually be treated successfully with 4 weeks of therapy. Patients with symptoms of more than 3 months’ duration before the initiation of treatment, those with a relapsed infections, and those patients with prosthetic valve infection should receive a 6-week course of therapy. Gentamicin therapy should be given at doses designed to achieve peak serum levels of approximately 3 µg per mL and trough serum concentrations <1 µg per mL. Patients with a history of penicillin allergy should be treated with a combination of vancomycin and gentamicin for 4 to 6 weeks.

Enterococcal endocarditis caused by strains with intrinsic high-level penicillin resistance (MIC >16 µg per mL) should be treated with a combination of vancomycin and gentamicin. Organisms that are resistant to penicillin via the production of beta-lactamase can be treated with either ampicillin-sulbactam, gentamicin, or vancomycin and gentamicin (188).

Endocarditis caused by enterococci with high-level aminoglycoside resistance, vancomycin resistance, or both may require special evaluation by microbiologists or infectious disease specialists. Some strains of enterococci that are streptomycin-resistant are gentamicin-susceptible and vice versa. When endocarditis is caused by enterococci that are highly resistant to both streptomycin and gentamicin, the addition of an aminoglycoside is not beneficial. Such patients may be treated with high doses of penicillin or ampicillin for 8 to 12 weeks and surgical resection of the involved valve may be necessary for cure. Other patients with vancomycin-resistant enterococcal endocarditis have been successfully treated with the oxazolidinone antibiotic linezolid (188a).

Staphylococcal Endocarditis

The success of therapy for staphylococcal endocarditis is dependent on numerous factors. These include whether the right-or left-sided valvular structures are involved, whether the staphylococcus is coagulase-negative or -positive, whether the infection occurs on a native or prosthetic valve, and whether there is favorable antimicrobial susceptibility to the staphylococcal isolate (eTable 25.4.4 and eTable 25.4.5).

***e*TABLE 25.4.4** THERAPY FOR ENDOCARDITIS CAUSED BY STAPHYLOCOCCUS IN THE ABSENCE OF PROSTHETIC MATERIAL

Antibiotic	Dosage and route	Duration	Comments
Methicillin-susceptible staphylococci			
Regimens for non–beta-lactam-allergic patients			
Nafcillin sodium or oxacillin sodium	2 g i.v. every 4 h, 4–6 wk		Benefit of additional aminoglycosides has not been established
With optional addition of gentamicin sulfate	1 mg/kg i.m. or i.v. every 8 h	3–5 d	
Regimens for beta-lactam–allergic patients			
Cefazolin (or other first-generation cephalosporins in equivalent dosages)	2 g i.v. every 8 h	4–6 wk	Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin
With optional addition of gentamicin	1 mg/kg i.m. or i.v. every 8 h	3–5 d	

Vancomycin hydrochloride	30 mg/kg per 24 h i.v. in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4–6 wk	Recommended for patients allergic to penicillin
Methicillin-resistant staphylococci			
Vancomycin hydrochloride	30 mg/kg per 24 h i.v. in two equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	4–6 wk	

***e*TABLE 25.4.5** TREATMENT OF STAPHYLOCOCCAL ENDOCARDITIS IN THE PRESENCE OF A PROSTHETIC VALVE OR OTHER PROSTHETIC MATERIAL

Antibiotic	Dosage and route	Duration (wk)	Comments
Regimen for methicillin-resistant staphylococci			
Vancomycin hydrochloride	30 mg/kg per 24 h i.v. in two or four equally divided doses, not to exceed 2 g/24 h unless serum levels are monitored	>6	
With rifampin	300 mg orally every 8 h	>6	Rifampin increases the amount of warfarin sodium required for antithrombotic therapy
And gentamicin sulfates	1.0 mg/kg i.m. or i.v.	2	
Regimen for methicillin-susceptible staphylococci			
Nafcillin sodium or oxacillin sodium	2 g i.v. every 4 h	>6	First-generation cephalosporins or vancomycin should be used in patients allergic to beta-lactam
With rifampin	300 mg orally every 8 h		Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin or with gentamicin methicillin-resistant staphylococci
And with gentamicin sulfate	1.0 mg/kg i.m. or i.v. every 9 h		

Native valve endocarditis caused by *S. aureus* is best treated with a semisynthetic penicillin such as nafcillin or oxacillin for 4 to 6 weeks. As methicillin-susceptible strains of *S. aureus* are more rapidly killed both *in vitro* and *in vivo* in a rabbit experimental model of endocarditis, many authorities recommend the addition of gentamicin for the first 3 to 5 days of therapy.

The combination of nafcillin and gentamicin given for the first 2 weeks of therapy in a multicenter collaborative study of native valve endocarditis caused by methicillin-susceptible strains of staphylococcal endocarditis was associated with more rapid clearing of the bacteremia than in patients randomized to receive monotherapy with nafcillin, but such combination therapy did not improve cure rates. Furthermore, combination nafcillin and gentamicin therapy was associated with a higher incidence of renal dysfunction.

Patients with native valve endocarditis caused by *S. aureus* who have histories of penicillin allergy can be treated with either first-generation cephalosporins such as cefazolin (if there is history of penicillin reaction that is not typical of an immediate-type allergy) or vancomycin. Vancomycin should not be used on the basis of convenience related to its pharmacokinetics in patients without a history of penicillin allergy, as clinical experience and *in vitro* studies have suggested that vancomycin is a less effective antistaphylococcal antibiotic than either nafcillin or oxacillin (188,194).

Selected patients with native valve endocarditis caused by *S. aureus* that involves the right-sided heart valves can be successfully treated with a 2-week treatment regimen using the combination therapy of nafcillin and gentamicin (191). Regimens that substitute vancomycin or cefazolin for nafcillin are not considered to be reliably effective in such patients if only 2 weeks of therapy are given (195). It is important to realize that short-course regimens using combination therapy are not suitable for patients with simultaneous infection of both left-sided heart valves, in patients with isolates that demonstrate high-level gentamicin resistance (MIC >500 µg per mL), or in patients with metastatic infection outside of the lungs.

Patients with prosthetic valve endocarditis caused by methicillin-susceptible *S. aureus* should be treated with nafcillin or an equivalent beta-lactamase–resistant beta-lactam antibiotic for at least 6 weeks. Because such infections are notoriously difficult to cure with medical therapy, most authorities recommend simultaneously treating with oral rifampin. In addition, many experts advise the addition of gentamicin for the first 2 weeks of therapy. A first-generation cephalosporin or vancomycin can be substituted for nafcillin in patients with a history of penicillin allergy.

The only effective therapy for patients with endocarditis caused by methicillin-resistant staphylococci is vancomycin. Monotherapy with vancomycin for 4 to 6 weeks is usually adequate for therapy with endocarditis caused by methicillin-resistant native valve endocarditis caused by either *S. aureus* or coagulase-negative staphylococci. However, when methicillin-resistant staphylococci cause infection in patients with prosthetic valves or other prosthetic material, combination therapy is generally used. Such patients can be treated with intravenous vancomycin and oral rifampin therapy for 6 to 8 weeks. The addition of gentamicin is recommended for the first 2 weeks of this therapeutic regimen. The appearance of strains of *S. aureus* that have intermediate- or high-level resistance to vancomycin has raised the possibility that such organisms could cause endocarditis for which all currently available therapy is ineffective. At present, there is little *in vivo* information available on the optimal treatment of human infection with such organisms.

Endocarditis Caused by HACEK Organisms

A number of fastidious gram-negative bacilli, collectively grouped by the acronym *HACEK*, accounts for 5% to 10% of all cases of native valve endocarditis in individuals who do not use illicit intravenous drugs. Organisms in this category include the following: *Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. All of these organisms grow slowly in blood culture media, and incubation for 7 to 14 days may be required to detect their growth. This delayed growth makes standard antibiotic susceptibility testing difficult. Although in the past most HACEK organisms were ampicillin-sensitive, this is no longer true, as many species in this group have acquired the ability to produce beta-lactamase. However, virtually all of these organisms are highly susceptible to third-generation cephalosporins such as ceftriaxone and cefotaxime (Table 25.5). Either agent is usually effective when given for 3 to 4 weeks to patients with native valve endocarditis; patients with prosthetic valve endocarditis should be treated for 6 weeks (188).

Antibiotic	Dosage and route	Duration (wk)	Comments
Ceftriaxone sodium	2 g once daily i.v. or i.m.	4	Cefotaxime sodium or other third-generation cephalosporins may be substituted
Ampicillin sodium	12 g/24 h i.v. either continuously or in six equally divided doses	4	
With gentamicin sulfate	1 mg/kg i.m. or i.v. every 8 h		

TABLE 25.5 THERAPY FOR ENDOCARDITIS CAUSED BY HACEK MICROORGANISMS (*HAEMOPHILUS PARAINFLUENZAE*, *HAEMOPHILUS APHROPHILUS*, *ACTINOBACILLUS ACTINOMYCETEMCOMITANS*, *CARDIOBACTERIUM HOMINIS*, *EIKENELLA CORRODENS*, AND *KINGELLA KINGAE*)

Serum Bactericidal Levels

A commonly asked question in clinical practice relates to serum bactericidal levels. In general, serum bactericidal levels are of little clinical benefit since there is a relatively poor correlation between bactericidal levels and outcome and because results obtained when performing serum bactericidal levels may vary depending on

laboratory technique.

Surgical Therapy

Surgery was not an option in the management of endocarditis until 1964 when Yeh and colleagues first reported their success in surgical correction of an aortic valve perforation caused by endocarditis (196). The following year, Wallace and colleagues reported their success with valve excision and replacement in a patient with active endocarditis (197). In the ensuing 30 years, valve replacement has become routine in the management for patients with endocarditis who develop congestive heart failure, perivalvular abscesses, or intracardiac fistulae. In addition, surgery is now often used to manage extracardiac complications such as mycotic aneurysms and metastatic abscess formation.

The classic indications for cardiac surgery in patients with IE have remained relatively constant for the past two decades. Surgery is recommended for patients who develop congestive heart failure, who exhibit recurrent emboli during the course of therapy, and who fail to achieve an adequate bactericidal response to therapy. Most clinicians, including the authors, believe that abscess formation or the presence of a fungal endocarditis is a relative indication for surgical intervention. There is now a general consensus that the indication for surgery in active endocarditis differs little between native valve (Table 25.6) and prosthetic valve infection (Table 25.7). Large bulky vegetations—especially if they represent infections with organisms with a propensity to embolize, such as HACEK—may be an indication for surgical intervention, although no adequately controlled prospective study has examined this question. Congestive heart failure is the most common indication for surgery in patients with left-sided endocarditis, whereas refractory infection is the most frequent indication for surgery in right-sided endocarditis. There is widespread consensus that surgical intervention has been shown to improve patient survival in virtually every instance in which congestive heart failure complicates endocarditis. Before the routine use of surgery in patients with complicated endocarditis, congestive heart failure caused over 90% of all deaths. At times, congestive heart failure may be subtle, clinically evident only by a persistent tachycardia for no other reason. Thus, careful daily assessment by experienced clinicians is necessary for patients with hemodynamic instability or unexplained tachycardia or dyspnea.

Major indications
Congestive heart failure (New York Heart Association Functional Classification III or IV) caused by valve dysfunction
Persistent sepsis while receiving antimicrobial therapy
Recurrent embolism
Minor indications
Intracardiac abscess or fistula formation
Rupture of sinus of Valsalva aneurysm
Pathogen not susceptible to antimicrobial therapy
Fungal endocarditis
Acute *Staphylococcus aureus* endocarditis on left-sided heart valves with congestive failure
Relapse after an adequate course of antimicrobial therapy
Culture-negative endocarditis with persistent (>10 d) fever

TABLE 25.6 INDICATIONS FOR CARDIAC SURGERY IN NATIVE VALVE ENDOCARDITIS

Major indications
Congestive heart failure caused by unstable prosthesis
Fungal endocarditis
Significant perivalvular dehiscence
Recurrent septic emboli
Evidence for intracardiac abscess or fistula formation
Persistent sepsis (>3 d on antimicrobial therapy)
Interference with valve function caused by vegetation
Pathogen not susceptible to antimicrobial therapy
Minor indications
Nonstreptococcal pathogen
Relapse after adequate course of antibiotic therapy
Culture-negative endocarditis with persistent (>10 d) fever

TABLE 25.7 INDICATIONS FOR CARDIAC SURGERY IN PROSTHETIC VALVE ENDOCARDITIS

It is important to realize that the severity of cardiac and extracardiac manifestations of heart failure and the degree of hemodynamic stability of the individual patient are the major determinants of the optimal timing for surgery (198). In most case series, congestive heart failure caused by endocarditis-induced aortic insufficiency has a worse prognosis than endocarditis-induced mitral insufficiency. However, regardless of the valve involved, valve replacement should be undertaken in most patients as soon as signs and symptoms of congestive heart failure appear. It has been our experience that clinical signs of heart failure are more important than the echocardiographic assessment of left ventricular function. However, when aortic insufficiency is severe enough to result in preclosure of the mitral valve as detected by echocardiography, then operative intervention is likely to be required (137).

Recurrent emboli are a difficult criterion on which to base the need for surgical intervention. Some patients who experience episodes of peripheral embolism after the institution of antimicrobial therapy can be successfully managed without surgery. Furthermore, there is no precise threshold for the number of embolic events that mandate surgery. However, the authors share the opinion of Weinstein that surgery is usually indicated when a second episode of embolization occurs, especially in patients with endocarditis caused by *S. aureus*, any fungal pathogen, or *Haemophilus* species (43). The optimal timing of surgery for recurrent cerebral embolism is often problematic, because full heparinization during bypass surgery may exacerbate the clinical course of a recent cerebral infarct regardless of whether it is hemorrhagic or ischemic. However, it is our experience, and that of others, that surgery can usually be safely undertaken in such patients (199).

Despite the availability of an array of antimicrobial agents, failure to control infection is still a problem in the treatment of endocarditis. Such failure remains an indication for surgical intervention as one is removing the source of the bacteremia. The definition of bacteriological failure though is not clear-cut. Some organisms, such as *S. aureus*, may persist in the bloodstream for up to 5 days after initiation of therapy that will ultimately be curative. However, in general, persistently positive blood culture results after 5 to 7 days of therapy are an indication of the need for surgical intervention. Fungal endocarditis is notoriously difficult to cure with medical therapy alone. A few cases of endocarditis caused by *Candida* species have been cured without surgery (200,201 and 202), but most patients with *Candida* endocarditis, and virtually all patients with endocarditis caused by *Aspergillus*, require surgery to control their infections. Even combined surgical and medical therapy often leads to a poor outcome in patients with fungal endocarditis. For example, in a review of the outcome of 108 cases of fungal endocarditis, 97 of 108 (90%) died (35).

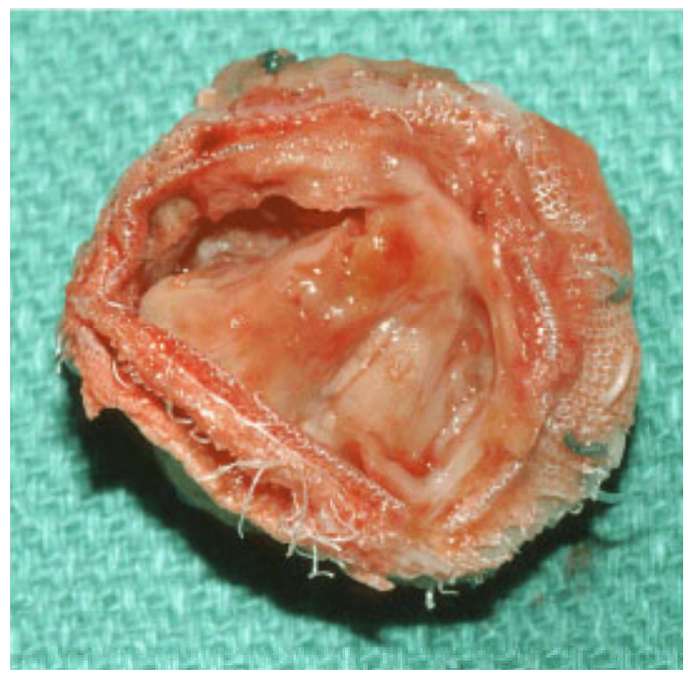
Bacteriological cure may be particularly difficult to achieve in patients with prosthetic valve endocarditis. The authors agree with others that prosthetic valve endocarditis caused by organisms other than viridans streptococci and that the HACEK group is difficult to cure with medical therapy. Most such patients eventually require surgery to achieve cure (203). In addition, when prosthetic valve endocarditis relapses after a course of medical therapy, a perivalvular infection is usually present. Such patients almost always require surgery. Certain organisms such as vancomycin-resistant enterococci cannot be effectively treated with any currently available agent. Patients with endocarditis caused by this organism should undergo early surgery whenever this is feasible.

The principal goals of surgery in patients with endocarditis are as follows: (a) valve repair or replacement, (b) drainage or repair of intracardiac abscesses, (c) excision of necrotic tissue, and (d) closure of intracardiac fistulae (204). The operative mortality for surgery in patients with endocarditis has varied widely from decade to decade and between different authors and medical centers. Some authors of more recent reports have reported operative mortality as low as 4.0% to 5.7% (198,205,206), whereas other authors have reported mortality of 20% to 30% (173,207,208). However, it is important to note that some case series included many patients who underwent emergency surgery, whereas other series included patients who underwent valvular replacement or repair for mild to moderate symptoms of congestive heart failure after lengthy periods of antimicrobial therapy (203). In general, surgery is of the highest risk and poorest outcome in patients with acute endocarditis caused by *S. aureus* complicated by the acute onset of congestive heart failure or perivalvular or aortic root abscess formation. In fact, abscess formation itself, regardless of causative organism, has been found to be an independent predictor of operative mortality by multivariate analysis in one study (204).

Most patients who undergo surgery for endocarditis require valve replacement. However, selected patients, particularly those with mitral valve endocarditis, can be effectively treated with mitral valve repair or vegectomy (209,210). Patients who have extensive damage to the aortic root and aortic valve may require placement of a homograft of the aortic root and ascending aorta (211). A variety of surgical procedures have been devised to deal with the problem of perivalvular abscess, aneurysm,

or fistula formation. These procedures include translocation of the aorta (212), valve conduit replacement of ascending aorta (213), and patch closure of annular mycotic aneurysms (214). Although some authors have found higher rates of recurrent endocarditis in patients receiving bioprostheses for infected heart valves than in those who receive mechanical valves (215), others have found the exact opposite (173). The authors agree with Mullany and colleagues who believe that the decision to place a bioprosthetic or a mechanical prosthesis should be dictated by the usual criteria (e.g., age, annular size, and ability to take anticoagulants) rather than by theoretical concerns about the risk of reinfection (204).

Patients with endocarditis who undergo valve replacement and survive through the early operative period have a reasonably good long-term prognosis. In a study of 151 patients who underwent valve replacement for endocarditis, the 5-year survival was 53% and the 10-year survival was 44%. Predictors of poor long-term survival in this group of patients using multivariate analysis included renal impairment, aortic valve involvement, and congestive heart failure at the time of surgery and surgery for an infected prosthetic valve (204). Others have also found that long-term outcome after valve replacement for endocarditis is heavily dependent on left ventricular function (203).



Surgical specimen of a tissue prosthesis destroyed by *Staphylococcus* endocarditis. This is the ventricular side of the aortic prosthesis. Note the thickened, scarred prosthetic leaflets causing both aortic stenosis and regurgitation.

FUTURE DIRECTIONS

Despite advances in echocardiography and surgery, IE remains a serious and often fatal disease. In one surgical study of 65 patients with aortic valve endocarditis complicated by periannular abscesses who underwent aortic valve replacement, the 30-day mortality was 24% in those who received aortic allografts and 8.5% in those patients who received prosthetic valves only. The 11-year survival rate was 82% in the allograft recipients and 65% in those receiving prosthetic valves (204a). Our basic understanding of the disease process thus remains incomplete, and our therapy is imperfect. Although there is a basic understanding of the nature of the vegetations, there is a great need to better understand exactly how vegetations propagate and result in valvular and perivalvular invasion. As noted in this chapter, it is generally accepted that vegetations begin on damaged heart valve tissue, often in an area where a jet effect from a high- to low-pressure system is present. A sterile platelet–fibrin thrombus forms and in the presence of bacteremia and circulating agglutinating antibodies specific for the invading organism, the thrombus then becomes infected as the organism adheres to the platelet aggregation (216). Studies suggest that *in vitro* resistance to thrombin-induced platelet microbicidal protein has an effect on the ability to cause endocarditis (216a). Moreover patients with endocarditis caused by infected intravascular devices are more likely to become infected with strains of *S. aureus* resistant to platelet microbicidal protein (216b). More research is needed in this area.

Nonbacterial thrombotic endocarditis lesions are seen in other conditions unrelated to IE, such as terminal cancers, congestive heart failure, pyelonephritis, or pneumonia (217). In addition, active collagen vascular diseases such as systemic lupus erythematous can result in vegetations (Libman-Sacks disease) that are similar to those seen in IE (113). Clearly, our understanding of the pathophysiology of vegetation remains incomplete.

More research is needed to learn whether agents such as anticoagulants that directly affect the vegetation might reduce their size or growth or prevent their occurrence all together. As vegetations also occur on apparently normal heart valves (218), our current understanding of the local hemodynamic and immunologic factors that lead to vegetations needs expanding. Similarly, it is not fully understood why some patients with endocarditis exhibit little or no immunologic response to their intravascular infection, whereas others demonstrate an array of immunologic complications that affect the kidney, skin, and joints. The precise mechanism and pathophysiology of this immunologic response in individual patients need further explanation.

More research is also needed to develop better therapies for the treatment of IE. Better drugs than are currently available are needed with less toxicity, especially renal, to treat enterococcal and staphylococcal endocarditis. There is a need for agents that can be given orally at infrequent intervals to facilitate use on an outpatient basis. As the age of the population with endocarditis grows older, the effects of antibiotics on this geriatric population also need to be clarified.

The value of prophylactic antimicrobial therapy in the prevention of endocarditis is still an unresolved issue. Successful medical malpractice claims continue to be litigated despite an absence of valid scientific data that prophylactic antimicrobial therapy is effective and of more benefit than risk. Indeed, every study on the value of prevention, even following dental work, has been underpowered. A true definitive study on the benefits of prophylaxis is needed.

Additional agents that are now responsible for culture-negative endocarditis will likely be recognized in the future. The role of viruses as causes for endocarditis has been debated for years (11). Viruses, such as HIV, can result in nonbacterial thrombotic endocarditis lesions (219), and endocarditis in mice has been produced by coxsackie B and adenoviruses (220). It is probable that new causes of endocarditis will be recognized as advances in diagnostic microbiology occur.

The surgical approach to IE will also likely evolve as advances in valvular and cardiovascular surgery occur. Given the high incidence of emboli from mitral valve endocarditis, surgery may become an early treatment option in more patients. Advances in less invasive cardiothoracic surgical techniques (221) and renewed interest in valvular preservation with improvements in valve repair and vegectomies (222) will likely continue, and these advances may alter the current surgical approach to endocarditis. Robotics may evolve to the point that the procedure of repair could be performed with less trauma to the patient. Prosthetic valve endocarditis often occurs in the prosthetic sewing ring, yet there are no studies to date examining whether improvements in prosthetic materials could reduce the risk of the endocarditis and the valve ring extension of infection.

Because endocarditis is an uncommon heterogenous disease there is a need for national and international registries or databases that prospectively collect data to answer important questions about management and outcome of frequent and uncommon pathogens that cause endocarditis, as well as frequent and uncommon complications such as cerebral embolism, mycotic aneurysms, and congestive heart failure.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Controversies revolving around the diagnosis and treatment of IE include the duration of therapy needed, the use of outpatient therapy, the use of expensive diagnostic tests such as TEE, the risks and benefits and indications for prophylactic antibiotic therapy (especially in the mitral valve prolapse syndrome), the timing of surgical intervention (including when surgical colleagues should be consulted), and the ethical issues that arise when ecurrent endocarditis results from destructive or erratic patient behavior such as often seen among illicit drug users.

All but the ethical issues have been addressed in detail in this chapter. It is our belief that endocarditis requires intravenous therapy. Until conclusive data showing efficacy of oral therapy are published or presented, we do not advocate therapy with any currently available oral antibiotic agent. We also advocate inpatient therapy for at least 5 to 7 days before considering outpatient intravenous therapy. The use of once-a-day administration of drugs with a long half-life, such as ceftriaxone, greatly assists in the administration of outpatient therapy. If there is any question regarding the suitability of the patient and family regarding home therapy though, we favor completing the entire antibiotic course as an inpatient or in a convalescent facility or infusion center.

We believe that TEE provides a substantial and clinically important identification of vegetations on leaflets and involvement of contiguous structures so that its routine

use makes some sense even though the chest wall echo may be adequate for diagnosis alone. This is particularly true for aortic valve endocarditis in which annular abscess may be discovered. The presence of abscess by TEE has prompted us to recommend surgery when other indications may not have been present.

Despite few data supporting prophylactic antibiotic usage to prevent endocarditis, our practice is to be quite liberal in its use. As prevention potentially protects from a serious disease that is seemingly much easier to potentially prevent than treat, the risk-benefit ratio of antibiotic usage, especially with dental procedures, seems in favor of antibiotic usage. Antimicrobial prophylaxis for mitral valve prolapse often presents a true therapeutic dilemma given the high prevalence in the population. Because the presence of mitral regurgitation in this disease is dependent on the relationship between the valve apparatus and left ventricular volume, mitral regurgitation may be audible at one time but not another. Given the reduction in emphasis on the physical examination in the majority of training programs in this country, the ability to properly auscultate also is troublesome if the criteria for use of antibiotic prophylaxis in patients with mitral valve prolapse require careful auscultation for murmur detection. For that reason, we are quite liberal in the use of antibiotic prophylaxis in patients with mitral valve prolapse.

We also believe that a close relationship with cardiovascular surgery is mandatory to ensure proper care of these often complex patients. We have formed an endocarditis team that includes cardiologists with an interest in valvular and congenital heart disease, specialists in infectious disease and bacteriology, and cardiovascular surgeons. We believe that consultation with cardiovascular surgeons should be done in almost all patients, regardless of their current clinical status. As mentioned in this chapter, this is particularly important in prosthetic valve endocarditis or when a potential complication, such as ring abscess, fungal valvular infection, or mycotic aneurysm, is present. Issues surrounding the surgical options can be complex, especially if there has been CNS bleeding or significant comorbid disease.

Finally, the debate on the treatment of recurrent endocarditis in patients who chronically use illicit intravenous drugs should be openly discussed and resolved. Ethical dilemmas and controversies often arise in patients with endocarditis who clearly indicate that their illicit drug use will continue. Our current policy is to replace or repair the infected heart valve in intravenous drug abusers only once; the ethical and financial issues that such an approach raise need to be resolved. We believe that every effort should be made to provide medical care for all intravenous drug abusers with special emphasis on efforts at rehabilitation. However, in an era of managed care and reduced resources, it is critical that personal responsibility for health become the accepted norm. Our policy at this time is to involve the ethics committee to provide a forum to understand the specifics for each individual who abused intravenous drugs and also has recurrent infective endocarditis.

THE FUTURE

Despite advances in echocardiography and surgery, IE remains a serious and fatal disease. Our basic understanding of the disease process remains incomplete. More research is needed to better understand vegetation propagation and the role of anticoagulant therapy. Refinements in antibiotic prophylaxis and treatment as well as surgical techniques are also important areas of research currently being pursued.

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26

PERICARDIAL AND RESTRICTIVE DISEASE

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CRAIG R. ASHER

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Diseases of the pericardium and restrictive cardiomyopathies cause impairment of diastolic function of the heart. Myriad underlying etiologies, via several mechanisms, result in final common clinical presentations, making specific diagnosis difficult. Historically, in the realm of invasive cardiac investigation (1,2), these disorders have become illuminated by several evolving noninvasive techniques including echocardiography (3,4) and magnetic resonance imaging (MRI) (5). This chapter discusses the general principles of diastolic heart failure including the biology and physiology, clinical presentation, epidemiology, investigation, and treatment. Specific diseases of the myocardium and pericardium that may cause diastolic dysfunction are reviewed.

GENERAL PRINCIPLES OF DIASTOLIC HEART DISEASE

Historical Perspective

Since the heart was determined to be a pump, physicians and biologists of the last century focused on systolic cardiac function. In an early reference to cardiac chamber filling by Wiggers in 1949, the term *inherent elasticity* was proposed to describe the passive elastic properties of the heart (6). In the 1970s, physiologists assessed the properties of active ventricular relaxation and passive filling using invasive quantification of intracavity pressure and volume (7). In the following decade, clinicians recognized that diastolic heart failure was an important cause of congestive heart failure (8,9 and 10), and Doppler echocardiography emerged as an important noninvasive method to assess diastolic function and the filling properties of the left and right ventricle (11,12,13 and 14). The term *diastology* was coined in the 1990s, and imaging modalities such as tissue Doppler echocardiography (TDE), color M-mode Doppler, and MRI were advancing our understanding of diastolic function (4,15,16) (*e*Table 26.0.1). Currently, new techniques and indices for assessing diastolic function continue to evolve (17,18,19,20 and 21), and there has been a shift toward evidence-based medicine with larger scale clinical trials to determine targeted treatment for diastolic heart failure.

***e*TABLE 26.0.1** HISTORICAL DEVELOPMENTS IN THE IDENTIFICATION, INVESTIGATION, AND TREATMENT OF DISORDERS OF DIASTOLIC FUNCTION

100 BCE	Galen suggested that the heart filled by active dilatation of the right ventricle.
1628	Harvey speculated that most ventricular filling occurred during atrial contraction.
1877	François-Franck concluded that most of left ventricular filling occurred in early diastole.
1906	Henderson described the three phases of diastole.
1921	Wiggers and Katz proposed that the atrial contribution to left ventricular filling varied.
1927	Meek proposed that the "contraction remainder" extended into diastole, thus suggesting active relaxation.
1949	Wiggers coined the term *inherent elasticity* to describe the passive diastolic properties of the myocardium.
1970s	*In vivo* and *in vitro* studies were performed on left ventricular relaxation and passive properties in health and disease.
1980s	Diastolic dysfunction was recognized as a common cause of heart failure in the presence of intact systolic function. Doppler echocardiography emerged as an important noninvasive method to assess diastolic function.
1990s	The *diastology* term was coined. Newer imaging modalities, including tissue Doppler echocardiography, color M-mode Doppler, and magnetic resonance imaging, emerged.

Modified from Shah PM, Pai RG. Diastolic heart failure. *Curr Prob Cardiol* 1992;17:783–868, with permission.

Definition of Diastolic Dysfunction

Clinical congestive heart failure is most often secondary to impairment of left ventricular (LV) systolic function (22). Diastolic impairment, although less common, is associated with significant morbidity and mortality (23). Clinically, it is important to distinguish isolated diastolic heart failure (normal ejection fraction) from systolic heart failure; although combined, systolic and diastolic heart failure will be more commonly observed (24,25). Several pathophysiologic definitions of diastolic heart failure have been proposed: (a) impaired capacity of the ventricles to fill without a compensatory increase in left atrial pressure (26); (b) abnormal ventricular filling that would produce inadequate cardiac output with a mean pulmonary venous pressure of less than 12 mm Hg (27); and (c) resistance to filling of one or both ventricles with an inappropriate upward shift of the pressure-volume loop, especially with exercise (28). These definitions have in common an abnormal resistance to filling causing elevated left-sided filling pressures and congestion. Diastolic dysfunction impairs filling of the ventricle by impairing relaxation (early diastole), reducing compliance (early to late diastole), or by external constraint from the pericardium (28,29). Numerous pathologic processes and disease states may produce the clinical constellation of diastolic dysfunction (Table 26.1).

Condition	Mechanism of diastolic dysfunction
Restrictive cardiomyopathy (idiopathic, restrictive cardiomyopathy, cardiac amyloidosis)	Increased resistance to ventricular inflow
Constrictive pericarditis	Increased resistance to ventricular inflow, with decreased ventricular diastolic capacity
Ischemic heart disease	
Flash pulmonary edema, dyspnea during angina	Impaired myocardial relaxation Diastolic calcium overload
Postinfarction scarring and hypertrophy (remodeling)	Increased resistance to ventricular inflow
Hypertrophic heart disease (hypertrophic cardiomyopathy, chronic hypertension, aortic stenosis)	Impaired myocardial relaxation Diastolic calcium overload Increased resistance to ventricular inflow due to thick chamber walls, altered collagen matrix Activation of renin-angiotensin system
Volume overload (aortic or mitral regurgitation, arteriovenous fistula)	Increased diastolic volume relative to ventricular capacity Myocardial hypertrophy, fibrosis
Dilated cardiomyopathy	Impaired myocardial relaxation Diastolic calcium overload Myocardial fibrosis or scar
Mitral or tricuspid stenosis	Increased resistance to atrial emptying

Adapted from Grossman W. Diastolic dysfunction in congestive heart failure. N Engl J Med 1980;303:1027–1030, with permission.

TABLE 26.1 CONDITIONS INVOLVING DIASTOLIC HEART FAILURE

As a framework to design and implement treatment trials, diagnostic criteria for patients with diastolic heart failure have been proposed. The 1998 European Study Group on Diastolic Heart Failure required (a) clinical evidence of congestive heart failure, (b) normal or mild LV dysfunction, and (c) the presence of impaired relaxation, filling, or compliance to diagnose diastolic heart failure (30) (*e*Table 26.1.1). All three components as assessed by noninvasive testing or cardiac catheterization were necessary for a diagnosis. Vasan and Levy subsequently proposed a less rigid criteria using similar inclusions but defining diastolic heart failure as definite, probable, or possible depending on the number of elements present (31). It has been suggested that the incorporation of exclusionary criteria will be required before using these standards for selection of patients for drug therapies to understand the specific effects on various pathologic conditions (32).

***e*TABLE 26.1.1** DIAGNOSTIC CRITERIA FOR DIASTOLIC HEART FAILURE

Signs or symptoms of congestive heart failure:

Exertional dyspnea [eventually objective evidence by reduced peak exercise oxygen consumption (<25 mL kg^{-1}•min^{-1})], orthopnea, gallop sounds, lung crepitations, pulmonary edema

and

Normal or mildly reduced left ventricular systolic function:

LVEF = 45% and LVEDIDI <3.2 cm•m^{-2} or LVEDVI <102 mL•m^{-2}

and

Evidence of abnormal left ventricular relaxation, filling, diastolic distensibility, and diastolic stiffness:

Slow isovolumic left ventricular relaxation:

LV dP/dt_{min} <1,100 mm Hg•s^{-1}

and/or $IVRT_{<30\ yr}$ >92 ms, $IVRT_{30–50\ yr}$ >100 ms, $IVRT_{>50\ yr}$ >105 ms

and/or t >48 ms

and/or slow early left ventricular filling:

PFR <160 ml•s^{-1}•m^{-2}

and/or $PFR_{<30\ yr}$ <2.0 EDV•s^{-1}, $PFR_{30–50\ yr}$ <1.8 EDV•s^{-1}, $PFR_{>50\ yr}$ <1.6 EDV•s^{-1}

and/or $E/A_{<50\ yr}$ <1.0 and $DT_{<50\ yr}$ >220 ms, $E/A_{>50\ yr}$ <0.5 and $DT_{>50\ yr}$ >280 ms

and/or $S/D_{<50\ yr}$ >1.5, $S/D_{>50\ yr}$ >2.5

and/or reduced left ventricular diastolic distensibility:

LVEDP >16 mm Hg or mean PCW >12 mm Hg

and/or PV A flow >35 cm•s^{-1}

and/or PV A t >MV A t + 30 ms

and/or A/H >0.20

and/or increased left ventricular chamber or muscle stiffness:

b >0.27

and/or b” >16

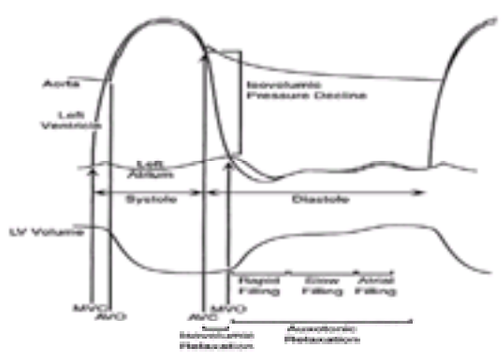
A/H, ratio of atrial wave to total signal excursion on the apexcardiogram; b, constant of left ventricular (LV) chamber stiffness; b”, constant of muscle stiffness; E/A, ratio of peak early to peak atrial Doppler flow velocity indexed for age groups; EDV, end diastolic volume; IVRT, isovolumic relaxation time indexed for age groups; LV dP/dt_{min}, peak negative left ventricular dP/dt; LVEDIDI, left ventricular end diastolic internal dimension index; LVEDP, left ventricular end diastolic pressure; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; MV A t, mitral atrial flow velocity duration; PCW, pulmonary capillary wedge pressure; PFR, peak LV filling rate indexed for age groups; PV A flow, pulmonary venous atrial flow velocity; PV A t, pulmonary venous atrial flow velocity duration; S/D, ratio of pulmonary vein systolic and diastolic flow velocities indexed for age groups; t, time constant of LV pressure decay.

From European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998;19:990–1003, with permission.

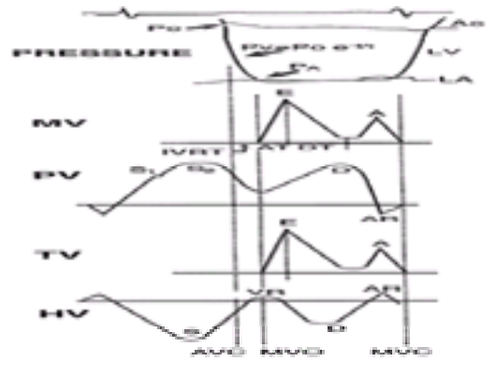
Pathophysiology of Diastolic Function

Phases of Diastole

The exact onset of diastole has been a matter of controversy over the years. Early definitions were provided by Wiggers (including isovolumic relaxation time in systole) (33) and Brutsaert et al. (including rapid filling phase in systole according to the triple control of relaxation) (34,35). A more contemporary clinical definition proposes that diastole is the period from the closure of the aortic valve to the end of mitral inflow and divided into two periods; an isovolumic relaxation period, and an auxotonic period that includes rapid filling, diastasis (slow filling), and atrial systole (36) (*e*Fig. 26.0.1). These phases are shown relating LV and left atrial pressure tracings and mitral, tricuspid, pulmonary, and hepatic venous Doppler echocardiography profiles (*e*Fig. 26.0.2). Each phase may be influenced by multiple factors including the effects of myocardial relaxation (37,38), the passive filling characteristics of the left ventricle (7,39), dynamics of the left atrium (40,41 and 42), pulmonary veins (43), mitral valve (44), and heart rate (45). The influence of the determinants of LV diastolic function on the phases of diastole are shown in *e*Figure 26.0.3.

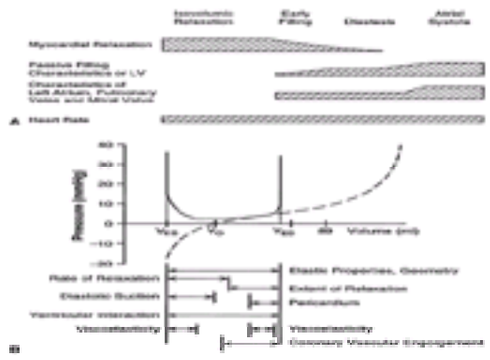


***e*FIGURE 26.0.1** Schematic drawing of the cardiac cycle in systole and diastole with left ventricular (LV) and left atrial pressures and LV volumes. Diastole is divided into two phases: an isovolumic relaxation period from aortic valve closure (AVC) to mitral valve opening (MVO) when the LV pressure falls with no change in volume; and an auxotonic period from MVO to mitral valve closure (MVC) when the LV volume increases with a variable increase in pressure and includes a rapid filling phase, slow filling, and atrial filling. AVO, aortic valve opening. (From Zile MR. Diastolic dysfunction: detection, consequences, and treatment. Part 1: definition and determinants of diastolic function. *Mod Con Cardiovasc Dis* 1989;58:68, with permission.)



***e*FIGURE 26.0.2** Diastole using Doppler echocardiography: combined schematic displaying left atrial (LA), left ventricular (LV), and aortic (Ao) pressure during diastole. Instantaneous LV pressure (Pv) falls exponentially through the isovolumic relaxation period (IVRT), from the Po [LV pressure at aortic valve closure (AVC)] to P_A [LV

pressure at mitral valve opening (MVO)] via the equation shown. Transmitral (MV) Doppler demonstrates an early rapid filling wave (E) broken into an acceleration time (AT) and a deceleration time (DT); a diastasis period with little inflow; and an atrial contraction wave (A) associated with an elevation of LA pressure above LV pressure until mitral valve closure (MVC) is induced by the onset of ventricular systole. Pulmonary vein (PV) demonstrates a systolic wave (S_1) related to atrial relaxation and a second systolic wave (S_2) related to mitral annular descent, a diastolic wave (D) associated with atrial emptying through an open mitral valve, and an atrial reversal wave (AR) associated with atrial systole causing regurgitation of flow back up the pulmonary veins. Transtricuspid (TV) inflow has a similar pattern velocity to transmitral. Hepatic vein (HV) flow is similar to pulmonary vein flow, with a more prominent reversal of flow between the S and D waves associated with ventricular systole (VR).



***e*FIGURE 26.0.3 A:** Influence of the determinants of diastolic function on the different phases of diastole (clinical definition). Note that the effect of myocardial relaxation extends into the early or rapid filling phase. LV, left ventricle. (From Little WC, Downes TR. Clinical evaluation of left ventricular diastolic performance. *Prog Cardiovasc Dis* 1990;32:276, with permission.) **B:** Effect of the different factors that influence LV diastolic pressure during diastole, using the pressure-volume loop format. The wavy lines refer to the time period when each factor is important (i.e., the elastic properties and geometry of the ventricle are important for all of diastole). Note: During early diastole, the combination of active relaxation and the elastic recoil from the elastic energy stored in the muscle from the previous systole (diastolic suction) determine the atrioventricular pressure gradient and ventricular filling. The dashed line refers to the purely elastic pressure-volume curve of the myocardium in the absence of relaxation. Note that there are negative pressures resulting from the stored elastic energy. V_{ED}, end diastolic volume; V_{ES}, end systolic volume; V_O, equilibrium volume. (From Gilbert JC, Glantz SA. Determinants of left ventricular filling and of the diastolic pressure-volume relation. *Circ Res* 1989;64:827, with permission.)

Isovolumic Relaxation

The isovolumic relaxation time period occurs from the time of aortic valve closure to mitral valve opening with no change in LV volume (46). During this period, active, energy-dependent myocyte relaxation occurs until mid-diastole. Ventricular pressure (P_v) decay during the isovolumic period follows an approximately exponential curve that can be characterized by its starting pressure (P_o) and its time constant (tau, t) (47). This curve may be fitted with the assumption of either a zero asymptote $P_v = (P_o\, e^{-t/t})$ (47), where P_o is the LV pressure at the time of aortic closure or peak negative dP/dT, *t* is the time after the onset of relaxation, and t is the time constant of relaxation. A more physiologic description with a nonzero value asymptote (to account for subatmospheric pressure and the effects of pericardial pressure) is shown in equation 1 (27,48).

$$P_v = (P_o\, e^{-t/\tau}) + P_b$$

A low value of tau is indicative of fast relaxation, whereas a high value represents slow relaxation. Isovolumic relaxation duration can be obtained invasively and by several noninvasive modalities including phonocardiography, M-mode, and Doppler echocardiography (49,50 and 51). Manipulation of the nonzero equation ($P_o\, e^{-t/t} + P_b$) has allowed the calculation of tau from the Doppler-derived isovolumic relaxation time (IVRT), systolic blood pressure, and left atrial pressure (P_{LA}) via tau = IVRT/[ln(systolic blood pressure) – ln(P_{LA})] (52). This estimate of relaxation may be useful in patients in the intensive care unit with hemodynamic monitoring. The time constant seems to be less preload dependent than the IVRT (46,47). Other noninvasive methods for determining LV relaxation have used the aortic and mitral regurgitant velocity profiles (53). Newer modalities including the color M-mode slope (Vp) (54) and TDE annular early velocity have been shown to relate closely to the time constant of relaxation (16). Isovolumic relaxation ends when the LV pressure falls below the left atrial pressure, resulting in mitral valve opening and the start of rapid filling phase (27).

Rapid Filling

The auxotonic period occurs from mitral valve opening until mitral valve closure (36). The rapid filling phase begins at mitral valve opening, when the LV pressure falls below left atrial pressure. LV pressure continues to fall because of ongoing relaxation and elastic recoil, with blood accelerating because of the development of a left atrial to LV pressure gradient (27). This gradient is influenced by the level of left atrial pressure at mitral valve opening and the rate of decline of LV pressure (55,56). Blood rapidly enters the left ventricle from the left atrium during the early filling period, with approximately 70% of the stroke volume received by the left ventricle during the first third of diastole (3). Active ventricular suction (pulling of blood) may play an important role in the rapid filling phase (57,58) (*e*Fig. 26.0.3B). It has been shown that if mitral flow is prevented, the LV pressure decreases to a subatmospheric asymptote (59). Ventricular suction may occur because of the recoil of the compressed elastic elements during contraction (39). Rapid filling ends as atrial and ventricular pressures equilibrate (27).

Diastasis (Slow Filling)

Diastasis, or the slow filling period, occurs between the rapid filling phase and atrial contraction and accounts for less than 5% of filling. After rapid filling, left atrial and ventricular pressure are almost equal, yielding no immediate forward driving gradient (27).

Atrial Filling (Contraction)

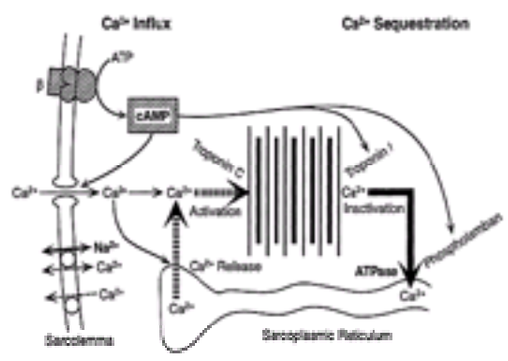
The atrial filling phase of diastole occurs when the left atrial pressure rises above ventricular pressure, forcing or pushing blood across the mitral valve and a small amount of regurgitation into the pulmonary veins. This late diastolic transmitral flow increases ventricular end diastolic volume by 25% in healthy subjects with only a small rise in mean pulmonary venous pressure. Diastole ends with onset of ventricular systole when the rapid increase in ventricular pressure closes the mitral valve (27).

Determinants of Diastolic Function

Diastolic function is dependent on four major factors: (a) active myocardial relaxation; (b) passive pressure-volume relationships (i.e., LV compliance); (c) left atrium (including atrial function), pulmonary vein, and mitral valve characteristics; and (d) heart rate (27) (*e*Fig. 26.0.3). Each variable can be in turn affected by different physiologic states and organic heart diseases. The physiology of ventricular diastolic function is exceedingly complex, involving interactions at the subcellular, myocyte, myocardial tissue, and whole chamber levels (29,60). Pericardial contributions to diastolic physiology are discussed in the section Pericardial Disease.

Myocardial relaxation is mediated by intracellular adenosine triphosphate (ATP) and calcium (61,62). Contraction is initiated by calcium release in large quantities from the sarcoplasmic reticulum (*e*Fig. 26.0.4). This free ionized calcium ion binds to the troponin-tropomyosin complex, removing the inhibitory effect of that complex on the actin-myosin myofilaments (37). Active cross-bridges form between actin and myosin with consequent contraction of the myofilaments. This rapid increase of intracellular calcium is countered by calcium sequestration into the sarcoplasmic reticulum by the calcium-ATPase pump (63), which is tonically inhibited by the phospholamban. Abnormal relaxation and diastolic tone may result from either elevated cytosolic levels of calcium in diastole or inadequate intracellular ATP levels to dissociate actin from myosin (62). Enhanced relaxation of the LV myocytes results in a reduction of an intracavitary pressure gradient within the left ventricle during

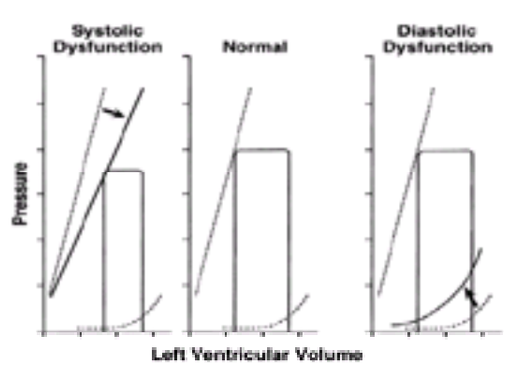
early diastole, and a pressure gradient is generated across the mitral valve pulling in blood from the left atrium (64). It has been demonstrated that relaxation is asynchronous, occurring earliest in apical segments and resulting in the intracavitary suction of blood from middle and basal regions toward the apex (64). Because relaxation is an energy-dependent process, it is influenced by many factors including ischemia and LV mass (65,66 and 67).



***e*FIGURE 26.0.4** Role of calcium ions in activation and inactivation of contractile proteins in myocytes. Calcium influx across the sarcolemma and release of calcium contained in the sarcoplasmic reticulum allow cross-linking of actin and myosin, causing active contraction. Calcium is then rapidly resequestered into the sarcoplasmic reticulum by calcium adenosine triphosphatase (ATPase), allowing active relaxation. Beta-adrenergic receptor stimulation increases intracellular cyclic adenosine monophosphate (cAMP) and further enhances the action of the calcium ATPase via the protein phospholamban. ATP, adenosine triphosphate. (From Bonow RO, Udelson JE, et al. Left ventricular diastolic dysfunction as a cause of congestive heart failure. *Ann Intern Med* 1992;117:505, with permission.)

The passive filling characteristics of the ventricle describe the late diastolic volume-pressure relationship of the chamber. This is determined by the viscoelastic nature of the myocardium; chamber size, shape, and wall thickness; right ventricular (RV) and LV pressure-volume interaction; intrathoracic pressure and pericardial constraint; and any active myocardial relaxation that remains incomplete (7). *Compliance*, the ratio of change in volume per change in pressure, quantifies the net result of all the previously mentioned factors. Intrinsic myocardial stiffness relates to the amount of collagen within the myocardium. Collagen plays an essential role in converting the contractile force of the myocytes into intraventricular pressure, as well as determining overall ventricular size and shape (68,69). Collagen fibrils coil around myofibrils. Little force is needed initially to stretch the coil, whereas large forces are required at full stretch, yielding an exponential stress-strain relationship (70). Pressure-induced hypertrophy is associated with increased collagen content and secondarily increased overall stiffness. Local collagen scarring following myocardial infarction is threefold stiffer than the surrounding myocardium (71).

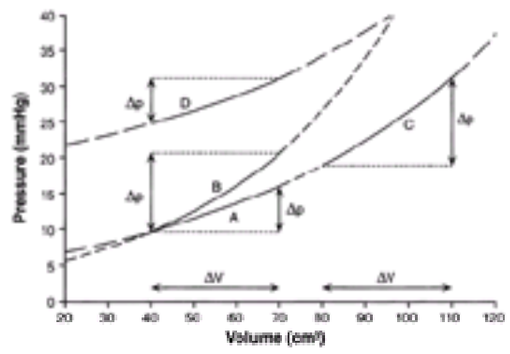
Diastolic properties of the ventricle have been studied and quantified extensively using pressure-volume loops (eFig. 26.0.5) (72,73 and 74). Simultaneous recording of ventricular pressures and volumes (contrast angiography, radionuclide imaging, or echocardiography) yield the loops that have traditionally been the benchmarks for quantifying systolic and diastolic function of the heart.



***e*FIGURE 26.0.5** Schematic representation of ventricular pressure-volume loops. The center panel demonstrates the normal situation. Note the exponential nature of the curve through late diastole. In systolic dysfunction (*left*), the end systolic pressure line is displayed downward and is manifest by a decreased ability of the left ventricle to generate high pressures for a given volume. Diastolic dysfunction involves an upward and leftward shift of the exponential curve—a result of elevated filling pressures for a given volume. (From Katz AM. Influence of altered inotropy and lusitropy on ventricular pressure volume loops. *J Am Coll Cardiol* 1988;11:438, with permission.)

There is a curvilinear relationship between the volume and pressure in the ventricle that is determined by the stress-strain relationship. As the volume increases in the left ventricle during diastole, there is an increase in LV pressure (70). The slope of the pressure-volume curve during diastole (dP/dV) is the chamber *stiffness*, and the inverse of this relation is the chamber *compliance* (14).

If we represent the ventricle as a thin-walled sphere with wall thickness *h* made up of tissue with a linear stress-strain relationship (constant stiffness, E), chamber stiffness (dP/dV) is approximately equal to the product of wall thickness multiplied by wall stiffness, *hE*, demonstrating that both myocardial stiffness and wall thickness influence chamber stiffness (29,75). The slope (dP/dV), or stiffness of the left ventricle, is not constant, but rather follows an exponential curve upward as volume increases (eFig. 26.0.6). Thus, when end diastolic volume increases without intrinsic change in the mural stress-strain relationship, stiffness increases along this exponential curve (eFig. 26.0.6). Conversely, an increased stiffness constant *E* moves the loop to a steeper curve with no change in volume (eFig. 26.0.6). Finally, it can be seen that increasing loading pressure without changing volume moves the loop directly upward, with no change in dP/dV or stiffness (eFig. 26.0.6).



***e*FIGURE 26.0.6** Relationship between chamber stiffness and the diastolic pressure-volume curve. Stiffness is the local slope of the curve, given by dP/dV (Dp, DV) (A). Stiffness increases (along the same exponential curve) with increased volume loading, without any innate change in the chamber properties (C). Intrinsic chamber changes may change the underlying exponential curve, increasing stiffness at normal loading volumes (B). Finally, increasing pressure, without changing volume or the intrinsic characteristics of the chamber, moves the entire curve upward, without any change in stiffness (D). (From Thomas JD. Assessment of diastolic heart failure by echocardiography. *Heart Failure* 1991;7:195, with permission.)

Pulmonary vein, left atrium, and mitral valve characteristics determine the volume of blood that enters the left ventricle (27). Early rapid filling is largely dependent on the pressure gradient between the pulmonary veins and left atrium and the left ventricle and the rate of myocardial relaxation and ventricular suction (55,57,58,76).

Diseases of the mitral valve such as mitral stenosis delay LV filling and prevent early rapid filling (27).

The left atrium acts as a reservoir of blood, as a passive conduit during early LV filling and as an active pump at end diastole (77). Atrial systolic function (active phase) may be essential to maintain cardiac output in disease states (78,79). Atrial function relates to its compliance (80), preload, afterload, and intrinsic contractility. Atrial preload, the volume and pressure at the time of atrial activation, has been shown in animals to influence the strength of atrial contraction in a manner analogous to Starling's law in the ventricle (81). Thus, a high left atrial pressure at the time of atrial contraction (e.g., due to delayed ventricular relaxation, elevated heart rate, or first-degree atrioventricular block) leads to a more forceful contraction and a larger mitral A wave. A strong relationship between left atrial (+) dP/dT, an invasive measure of left atrial contractility, and a combination of mitral inflow A wave and pulmonary venous atrial reversed flow has been demonstrated (82). The left atrial peak + dP/dT showed a linear relationship with left atrial pressure before atrial contraction, suggesting the presence of the Frank-Starling mechanism of the left atrium. Atrial afterload, in effect ventricular stiffness, impedes transmitral flow (83). Atrial contractile performance varies considerably in health and disease (78,79). In young and healthy normal individuals, the atrial contribution is less than 20% of the total volume, whereas in older healthy subjects, the atrial "kick" accounts for a greater proportion of the total LV filling (84). Atrial contractile function has delayed recovery following electrical cardioversion (42). Decreased atrial systolic function due to infiltration plays a role in the reduction in forward transmitral atrial contraction wave by Doppler echocardiography seen in advanced cardiac amyloidosis (85).

Heart rate bears directly on cardiac output in cases of diastolic dysfunction (45,86,87). As heart rate increases, the diastolic filling period preferentially decreases with respect to the systolic ejection period. As ventricular filling is functionally delayed, adequacy of inflow deteriorates and cardiac output paradoxically falls.

Neurohormonal activation, conduction abnormalities, and pericardial constraint may also influence diastolic function. Catecholamines may enhance relaxation and increase heart rate, thus decreasing the diastolic period (88). Conduction abnormalities may also influence diastole (89). LV relaxation may be impaired by conduction abnormalities by causing segmental asynchrony (90,91), which may contribute to decreased exercise tolerance in patients with left bundle branch block or RV paced rhythms. The pericardium (see below) considerably affects diastolic function, notably in constrictive pericarditis (13).

Diagnostic Approach to Diastolic Function

Clinical heart failure with normal systolic function (usually by echocardiography or nuclear techniques) would suggest diastolic dysfunction. The goals of investigation should include identification and quantification of diastolic dysfunction using the LV filling patterns (92,93 and 94) and newer Doppler techniques (16); semiquantitation of mean left atrial and end diastolic filling pressures (17,95,96,97 and 98); determination of underlying pathophysiologic mechanisms (constriction vs. restriction) (99,100,101 and 102); and stratification and prognostication and monitoring and guidance of therapy (103,104). Cardiac catheterization, echocardiography, radionuclide angiography techniques, and MRI are discussed in the following sections (24,105).

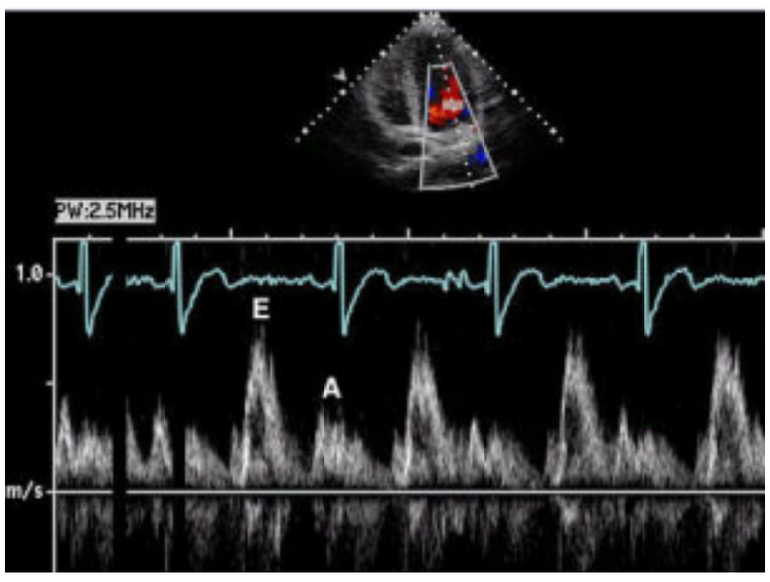
Echocardiography

Echocardiography has emerged as the main technique in the evaluation of patients with diastolic dysfunction and can be used as an alternative to cardiac catheterization (4,15). This modality encompasses M-mode, two-dimensional echocardiography, and Doppler echocardiography. This noninvasive modality quickly and safely assesses systolic ventricular function, atrial size, and function and valvular function; indirectly infers filling pressures and inflow patterns; and offers information to identify specific pathologies such as constrictive pericarditis, pericardial effusion, cardiac amyloidosis, and sarcoidosis (15,51).

With its enhanced spatial and temporal resolution, M-mode echocardiography has been used to time cardiac events such as the period of LV contraction and relaxation and the timing of valve opening and closing. Digitized M-mode echocardiography of the endocardium has been used to characterize diastolic filling in various diseases (106,107 and 108). M-mode echocardiography has been used to demonstrate abnormal RV diastolic collapse in cardiac tamponade (109), the abnormal septal bounce in constrictive pericarditis (110), and decreased annular motion in coronary artery disease (111). Ultrasound systems with high frame rate imaging now have the ability to generate anatomic M-mode tracings in any plane from digitally acquired two-dimensional images (112).

A complete two-dimensional echocardiogram is part of the diastolic function evaluation. It allows for assessment of global and regional systolic evaluation, LV mass and volumes, atrial dimensions, and pericardial thickness. Two-dimensional echocardiography helps exclude other causes of heart failure such as valvular heart disease (15,16). Diastolic dysfunction is unlikely with no organic heart disease, as documented by echocardiography. Similarly, there is a significant relationship with increasing left atrial size and stage of diastolic dysfunction (113). Inferior vena cava (IVC) plethora by echocardiography is closely associated with elevated right atrial (RA) pressure (114).

An integrated approach to the Doppler evaluation of diastolic function includes an evaluation of filling of both the left and right ventricles. The phase of respiration can be assessed simultaneously with Doppler flow velocities using a nasal thermistor to measure the change in temperature between inspiration, expiration, and apnea. Respiratory variations are crucial in differentiating constrictive pericarditis from restrictive cardiomyopathy (4). Transmitral flow is assessed in the apical four-chamber view with the pulsed Doppler sample volume (1 to 2 mm) at the leaflet tips along a laminar flow stream into the LV cavity. Optimal recordings depend on many technical features including sample volume placement, transducer alignment, and machine settings (115). Peak velocities of E and A, E/A ratio, and deceleration times are obtained and can be compared with age- and gender-matched subjects (84). Isovolumic relaxation time can be measured by placing a continuous wave Doppler beam between the LV outflow tract and the LV inflow to measure the time from the aortic valve closure to mitral valve opening. An alternative approach to measuring isovolumic relaxation time is to use pulsed wave Doppler (116).



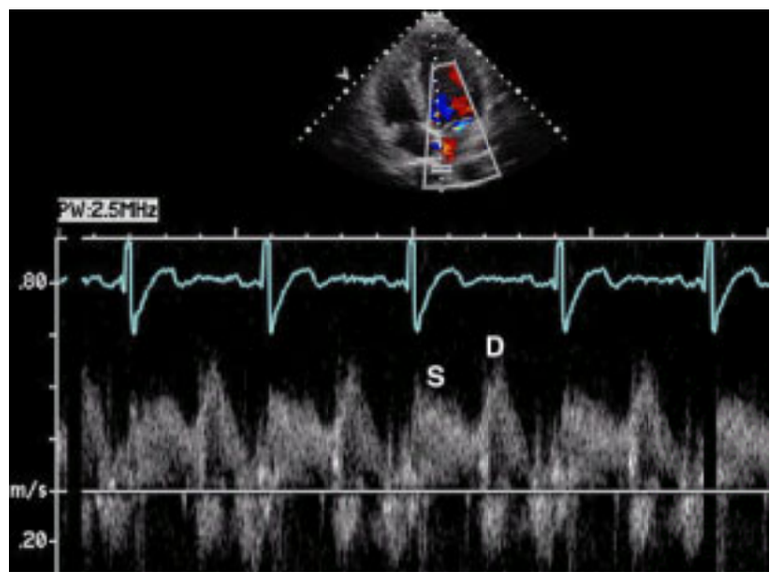
Pulsed wave Doppler signal from the mitral valve inflow. Note the E (early) and A (atria) waves.

Pulmonary venous flow can be assessed by transthoracic echocardiography by placing the sample volume (3 to 4 mm) into the right upper pulmonary vein from the apical four-chamber view. Adequate recordings can be achieved in up to 80% to 90% of patients, especially with the use of contrast echocardiography (15,117,118). Failure to obtain this information, critical to some cases, is an indication to proceed to transesophageal echocardiography (119).

RV inflow is assessed by placing the sample volume (1 to 2 mm) at the leaflet tips of the tricuspid inflow from the apical four-chamber view or the RV inflow view (120). The inferior vena cava diameter can be measured from the subcostal view and its respiratory variation calculated using M-mode echocardiography. Also from the subcostal position, hepatic venous flow sample volume (3 to 4 mm) can be recorded by placing the sample volume 1 to 2 cm into the right superior hepatic vein. The patient may have to control his or her depth of respiration to maintain the sample volume in a stable position. Finally, superior vena cava flow can be measured by placing the sample volume (3 to 4 mm) at a depth of 5 to 7 cm into the vein from the supraclavicular position (4). The diastolic filling variables that are typically measured are shown in Table 26.2.

Left ventricular filling	Right ventricular filling
Left ventricular inflow	Right ventricular inflow
E-wave velocity (cm/sec)	E-wave velocity (cm/sec)
A-wave velocity (cm/sec)	A-wave velocity (cm/sec)
E/A ratio	E/A ratio
Deceleration time (ms)	Deceleration time (ms)
Isovolumic relaxation time (ms)	Superior vena cava and hepatic vein
Pulmonary vein flow	Forward flow
Forward flow	S-wave velocity (cm/sec)
S-wave velocity (cm/sec)	D-wave velocity (cm/sec)
D-wave velocity (cm/sec)	Reverse flow
Reverse flow	V-wave reversal (cm/sec)
Atrial reversal wave velocity (cm/sec)	Atrial reversal wave velocity (cm/sec)
Atrial reversal wave duration (ms)	Tissue Doppler echocardiography (cm/sec)
Tissue Doppler echocardiography (cm/sec) of	of tricuspid annulus
mitral annulus	
Color M-mode flow propagation velocity (cm/sec)	

TABLE 26.2 DIASTOLIC FILLING VARIABLES



Pulmonary vein pulsed wave Doppler flow. Note the S (systolic) wave and the D (diastolic) wave.

Color M-mode Doppler is increasingly performed as a routine component of the diastolic function assessment. Pulsed wave Doppler records flow at a single spatial location in time. In contrast, color M-mode Doppler provides a map of LV filling velocities across a scan line with enhanced spatial and temporal resolution. In the apical four-chamber view with a standard depth, the M-mode cursor is aligned with the mitral inflow color Doppler flow, with the color Doppler sector size covering only the left ventricle and mitral valve. The positioning of the image should be adjusted to align the scan line parallel to the direction of flow. The color Doppler Nyquist limit is set below the mitral E wave peak velocity to allow for color Doppler aliasing of flow. The scan line from the mitral leaflet tips to the LV apex is obtained. LV filling is measured from the slope of the early propagation velocity (Vp) at the mitral valve plane to 4 cm into the LV cavity. Measurements are made at a sweep speed of 100 mm per second using the slope of the first aliasing velocity (17,121). Care must be taken to avoid measuring intracavitary flow starting before the onset of the mitral inflow. This may be prominent in some patients with hypertrophic cardiomyopathy or restrictive cardiomyopathy. It may be difficult to obtain accurate recordings in patients with sinus tachycardia as well as first-degree heart block because of fusion of the E and A waves (similar to mitral inflow).

TDE allows for evaluation of myocardial performance by evaluating myocardial rather than blood flow velocities. By means of a filter and amplification method, low-velocity and high-amplitude signals of tissue are preferentially displayed. A pulsed wave or color-encoded M-mode or two-dimensional map can be displayed and is superimposed over the two-dimensional image (122). TDE is able to provide myocardial velocities at different locations of the myocardium from different acoustic windows. Both systolic and diastolic patterns are displayed. For the assessment of diastolic function, Doppler velocities are obtained from the apical four-chamber view where the myocardium is near parallel with the transducer. The sample volume is approximately of 10-mm length, and the filter is set at 100 Hz or lower with a sweep speed of 100 mm per second. Sampling can be done at the lateral and septal annulus as well as the anterior and inferior annulus in the two-chamber view (16,123). TDE has the same limitations as the standard Doppler techniques. There are several limitations of TDE, including the effect of translation motion, Doppler angle of incidence, sample volume size, and inability to interrogate the apical segment (16,21).

Transesophageal echocardiography can complement transthoracic echocardiography in the comprehensive assessment of diastolic filling, providing both a physiologic assessment using Doppler echocardiography and excellent anatomic delineation. Optimal pulmonary venous flow recordings can be obtained by pulsed Doppler in virtually all patients from both the left and right upper veins from multiple planes. Isovolumic relaxation time, using continuous wave Doppler, is difficult to record using the transesophageal approach, but sometimes can be recorded from the apical five-chamber view from the deep transgastric approach. The pericardium can be visualized and measured when it is thickened by constrictive pericarditis (124). This is especially obvious over the RA and ventricular free walls, which are often seen to be “tethered” (101,119).

Acoustic Quantification and Color Kinesis

Acoustic quantification and color kinesis are automated boundary techniques that can provide complementary information about global and regional diastolic function (125). Acoustic quantification uses ultrasonic backscatter to allow instantaneous calculation of LV cavity areas during the cardiac cycle (126). Early studies showed good correlation between change of total area that occurred during rapid filling and atrial filling phases obtained by acoustic quantification and the mitral inflow patterns (127). Acoustic quantification evaluation of diastolic function has been also used in patients undergoing cardiac transplantation (126,128). Color kinesis is another echocardiographic technique (based on acoustic quantification) that encodes endocardial motion and is able to evaluate regional and global diastolic function (129,130).

TEI Index

The Doppler-derived index of combined systolic and diastolic myocardial performance is a relatively new index based on an old concept (ejection time intervals) (131). This index is the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time [(ICT + IRT)/ET]. It is easily measured from the LV outflow and mitral inflow using Doppler echocardiography. The TEI index has been shown to correlate with invasive measures of diastolic performance (18) and has been shown to be a useful predictor of survival in patients with cardiac amyloidosis (132) and dilated cardiomyopathy (133).

Exercise Capacity and Diastolic Function

Dyspnea on exertion is often the only symptom in patients with diastolic dysfunction and, accordingly, evidence of diastolic dysfunction may only be discernible by exercise. The normal hemodynamic response to exercise is an increase in ejection fraction and cardiac output with a decrease in the diastolic filling period. LV pressure in early diastole falls, allowing increased diastolic filling without increased left atrial pressure. However, in the presence of diastolic dysfunction, ventricular pressure fails to fall and an abnormal rise in left atrial pressure is required to maintain adequate inflow in the shortened filling period. Exercise testing with invasive hemodynamic monitoring (134) showed patients with diastolic dysfunction to have a significantly lower stroke volume index and end diastolic volume index than controls, whereas the end systolic volume index was not different. Patients, but not controls, had a markedly increased capillary wedge pressure with peak exercise. Exercise echocardiography may enable the examination of patterns of ventricular filling during or immediately after exercise and may prove to be a useful tool in detecting latent ventricular dysfunction, which may not be evident at rest.

Several studies have shown that baseline diastolic function is an important determinant of exercise capacity in various diseases (135,136,137,138 and 139). Other studies have focused on the role of medications, including angiotensin receptor blockers, on exercise tolerance and quality of life in patients with hypertensive response on a treadmill exercise test (140). Regional diastolic function has been evaluated with TDE in patients to detect LV ischemia during dobutamine stress testing (141). There has been recent interest in using TDE ratio E/Em during exercise to assess LV filling pressure (141a).

The difficulty with performing diastolic function measurements during exercise stress testing is the effect of tachycardia on the filling parameters (causing fusion of the

E and A waves), and the lusitropic effects of dobutamine as a stressor.

Cardiac Catheterization

The hemodynamic diagnosis of diastolic dysfunction requires measurement of LV volumes and pressures using high-fidelity micromanometer-tipped catheters (142). An elevated pulmonary capillary wedge pressure (PCWP) or mean left atrial pressure suggests diastolic dysfunction. Invasive measures can determine the passive elastic properties of the left ventricle from the pressure-volume relationship and the rate of myocardial relaxation from the time course of the fall of LV pressure during isovolumic relaxation (7).

The net passive diastolic properties of the left ventricle can be assessed by constructing pressure-volume loops and calculation of the LV chamber stiffness (dP/dV) and the modulus of chamber stiffness (K) (143). The passive diastolic properties of the myocardium can be assessed by calculation of the myocardial stiffness and the constant of myocardial stiffness (k) using the myocardial stress-strain relationship. Isovolumic relaxation can be assessed by the time course of isovolumic pressure decline by the negative dP/dT and the time constant of relaxation (14,144). Quantitative analysis of filling can be performed by using frame by frame analysis of the contrast angiogram or using volumes derived from conductance catheters (27,145). LV filling rates can be derived from the first derivative of LV volume with respect to time (dV/dT) (146). Several technical and theoretical problems have limited the usefulness of invasive measures in the clinical assessment of diastolic function.

Radionuclide Angiography

Radionuclide angiography can be used to document a normal ejection fraction and evaluate LV diastolic function using analysis of the LV time-activity curve (147). First-pass and gated equilibrium radionuclide imaging techniques have been used to noninvasively measure LV volume. The count activity over the left ventricle minus the background counts can be used to derive the relative LV volume and the time-activity curve. The parameters that can be generated from the time-activity curves include the peak rate of rapid diastolic filling and time to peak filling rate and an estimate of filling in early and late diastole to total stroke volume (147). Peak filling rates are usually normalized to end diastolic counts. Regions of interest in different sectors can be used to delineate regional time-activity curves and the spatial and temporal heterogeneity of diastolic function (147,148). Diastolic filling by radionuclide angiography relates generally to the diastolic filling parameters by Doppler echocardiography, especially the timing of events and the relative contributions of the early and late filling phases to total stroke volume (149). Extensive literature has been published showing the utility of clinical evaluation of LV diastolic filling by radionuclide angiography in coronary artery disease at rest and with exercise (150,151 and 152), in hypertrophic cardiomyopathy (153,154 and 155), hypertension (156,157), and dilated cardiomyopathy (158). Limitations include technical factors such as variations in the heart rate, smoothing, and effect of loading conditions. Also an increase in the peak filling rate may not necessarily suggest improvement of diastolic function (159), but rather an increase in left atrial pressure (160).

Magnetic Resonance Imaging

MRI has an increasingly valuable role in the assessment of diastolic function in restrictive cardiomyopathy and pericardial diseases. In particular, it can define the anatomic and functional abnormalities of diastolic function, especially in pericardial (pericardial effusions, constriction) and myocardial diseases (cardiac amyloidosis, hemochromatosis). It has been useful in differentiating constrictive pericarditis from restrictive cardiomyopathy (161,162).

In restrictive cardiomyopathy, the absence of increased pericardial thickening in the presence of abnormal filling is suggestive of restrictive cardiomyopathy (5,163,164). MRI provides excellent visualization of the pericardium and thus can define the presence and extent of pericardial effusions and increased pericardial thickness in constrictive pericarditis (161,165,166). Ancillary evidence includes conical or tubular narrowing of the ventricles from the constricting pericardium (5). Velocity-encoded cine MRI can be used to demonstrate diastolic flow patterns similar to Doppler echocardiography (167).

Diastolic Filling Patterns

Extensive literature exists regarding the empirically observed patterns of transmitral flow observed in normal individuals and patients with diastolic dysfunction. These patterns are the end result of the complex events only briefly described previously and are nonspecific for any particular physiologic perturbation. Diastolic filling patterns may be influenced by technical (sample volume placement) and hemodynamic factors (heart rate, volume status, conduction disorders) and not always be concordant with diastolic function (115).

Most simply, investigators have measured the peak velocity of the E wave and A wave by transmitral pulsed wave Doppler and their relationship, the *E/A ratio* (168). These basic parameters vary with age and within the spectrum of diastolic filling (Fig. 26.1) (84,92). Taken alone, the normal situation (E/A ratio greater than 1) passes through a delay relaxation phase (E/A ratio less than 1), then through a “pseudonormal” pattern (E/A ratio greater than 1) to the most abnormal “restrictive” pattern (E/A ratio greater than or equal to 1). Thus, the E/A ratio demonstrates a U-shaped curve, making it impossible to tell from this single parameter where in the spectrum a given patient lies (16). The pulmonary venous pattern is an important source of added information (43) that may overcome the limitations of the E/A ratio for determining diastolic function in many patients. An increased pulmonary atrial reversal (AR) flow, reversal velocity, or width, as well as Valsalva maneuver, may aid to differentiate “pseudonormal” from normal diastolic function, corresponding to elevation of mean left atrial or LV diastolic pressures, respectively (113,169,170).

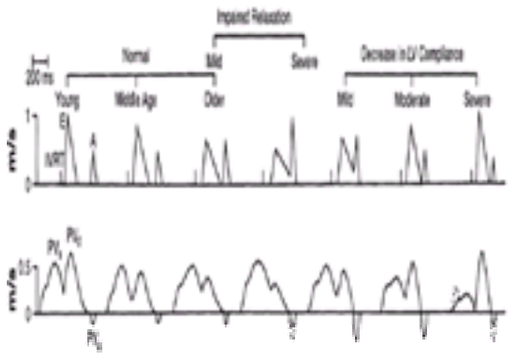


FIGURE 26.1 Natural history of left ventricular (LV) filling. Schematic representation of transmitral and pulmonary venous Doppler profiles, demonstrating the progression of the patterns with the normal aging process, and with diseases of diastolic function showing impaired relaxation and decrease in LV compliance. Isovolumic relaxation time (IVRT), E wave (E), A-wave (A) filling, pulmonary venous systolic (PV_s), diastolic (PV_d), and atrial reversal (PV_a) waves are shown. *Left*: In young healthy subjects, the E/A is greater than 1, the deceleration time and IVRT are short, and there is mild blunting of pulmonary venous systolic flow. With age, ventricular relaxation becomes impaired and the E/A ratio reverses, the A wave increases, the mitral deceleration time and IVRT lengthen, and the pulmonary venous systolic flow increases. *Middle*: With diseases showing impaired relaxation, there may be similar findings with a further decrease in E/A ratio. *Right*: With more severe derangements of diastolic function, as chamber compliance decreases, left-atrial pressure rises, the deceleration time decreases, the E/A ratio increases, and IVRT becomes shorter (restrictive physiology). PV_s flow becomes progressively blunted as mean left atrial pressure and the PV_a increases, helping to differentiate the “pseudonormal” pattern from normal. (From Appleton CP, Hatle LK. The natural history of left ventricular filling abnormalities: assessment by 2-D and Doppler echocardiography. *Echocardiography* 1992;9:453, with permission.)

Still, exceptions and limitations to the utility of pulmonary venous flow diminish the capability of distinguishing diastolic flow patterns in all individuals. Some patients may not have adequate pulmonary venous flow profiles, particularly the AR wave may not be well delineated. Blunting of pulmonary venous systolic waves may be present in young individuals due to rapid diastolic “suction,” and AR may be absent in advanced diastolic dysfunction due to the loss of atrial function with amyloid infiltration (169,171). Therefore, newer modalities for assessment of diastolic function including color M-mode Doppler and TDE have evolved that provide important adjunct information to determine diastolic function and LV filling pressures (16) (Fig. 26.2).

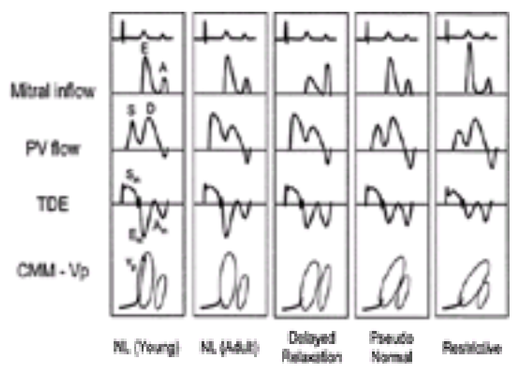


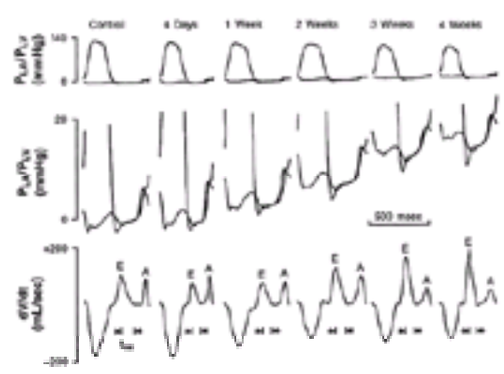
FIGURE 26.2 Stages of diastolic function. Schematic representation of the typical patterns seen with mitral inflow, pulmonary venous flow, tissue Doppler echocardiography (TDE), and color M-mode (CMM) – propagation velocity (Vp) for normal (NL, young and adult), impaired relaxation, pseudonormal, and restrictive diastolic function. Using an integrated approach with these four different modalities for assessment of diastolic flow pattern the stages of diastolic dysfunction can be determined. A, late mitral filling; A_m, diastolic filling during atrial contraction; D, diastolic filling; E, early mitral filling; E_m, early diastolic; S, systolic filling; S_m, systolic. (Adapted from Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998;32:865–875.)

Transmitral Flow Assessment in Health and Diastolic Dysfunction

Determination of pulsed Doppler mitral inflow pattern is a standard component of most echocardiographic studies. The components are an E wave, which represents the early diastolic filling velocity, and an A wave, which represents atrial contraction. As the ventricular myocardium relaxes during early diastole, the LV pressure (P_v) falls below left atrial pressure (P_a). The atrioventricular pressure gradient ($P_a – P_v$) is influenced by the degree of relaxation and left atrial pressure and ventricular suction (see the section Phases of Diastole). Slow relaxation (long tau) generates a high LV minimal pressure gradient, thus decreasing the pressure gradient. In contrast, an elevated left atrial pressure, which can be seen in patients with volume overload, shows an increased pressure gradient.

Thus, the E wave results from the acceleration of blood across the mitral valve due to the atrioventricular pressure gradient in early diastole and myocardial relaxation (55,75). As the volume of blood enters the left ventricle, the LV pressure increases and the left atrial pressure decreases until the pressure gradient equalizes and the blood column decelerates. The deceleration time (DT) of the E wave can be measured as the time from the peak velocity to return to the baseline and is related to the operating LV stiffness in clinical studies (169).

In vitro studies have demonstrated that the rate of early transmitral flow deceleration through a restrictive orifice is proportional to the net atrioventricular stiffness (S_{NET}) (40,172). More recent studies in a dog model of dilated cardiomyopathy have validated that LV stiffness is related to 1/DT in nonrestrictive orifices (146,173). eFigure 26.2.1 shows a shortening of the deceleration time in an animal model with progressive heart failure because of increasing LV stiffness.



***e*FIGURE 26.2.1** Recording over a 4-week period in a canine model of pacing-induced heart failure of the left atrial (P_{LA}) and left ventricular (P_{LV}) pressures and the time derivative of left ventricular volume (dV/dt). The dV/dt indicates the filling pattern (similar to Doppler), with peak filling rate in early diastole (E) and during atrial contraction (A) and the deceleration time (DT) of the E wave. Note that at 4 days, there is a slowing of relaxation, which results in a decreased left atrial–left ventricular (LA-LV) driving pressure and a decreased E wave. With progressive heart failure over the 4-week period, there is an increase in left atrial pressure, which increases the LA-LV driving pressure and the peak E wave, and a shortening of the deceleration time, which reflects increasing stiffness of the left ventricle. (From Ohno M, Cheng CP, Little WC. Mechanism of left ventricular filling during the development of congestive heart failure. *Circulation* 1994;89:2245, with permission.)

Following diastasis, the left atrium contracts, increasing left atrial pressure and the gradient ($P_a – P_v$) across the mitral valve (A wave). This atrial contraction is proportional to the atrial preload and atrial function and is inversely related to LV end diastolic stiffness (see the section Phases of Diastole) (75).

Physics of Mitral Inflow

Transmitral flow by pulsed Doppler relates to pressure gradients as determined by the Bernoulli flow equation:

$$P_A - P_V = [1/2\rho \times (v_V^2 - v_A^2)] + \left(\rho \int_A^V \frac{d\vec{v}}{dt \times d\vec{s}}\right) + [R \times \vec{(v)}]$$

This equation has three basic components: a convective, inertial, and resistive component. Of these, the convective component [$1/2p \times (V_V^2 – V_A^2)$] is important for spectral Doppler. When evaluating flow across stenotic valves, the convective component is much larger than the inertial component:

$$\left(\rho \int_A^V \frac{d\vec{v}}{dt \times d\vec{s}}\right)$$

thus allowing a quantitative assessment of pressure gradients (174). In contrast to nonstenotic valves, the inertial component has been shown to represent greater than 50% of the actual pressure gradient (175). Thus, spectral Doppler cannot be used to obtain a quantitative assessment of pressure gradients across a nonstenotic orifice; however, there still remains a qualititative relationship between the convective and the total pressure gradients across the mitral valve. This indirect qualitative relationship underlies the basis for using transmitral flow in the assessment of diastolic function (75).

Pulmonary Venous Velocity Patterns in Health and Diastolic Dysfunction

The pulmonary venous velocity pattern provides important adjunctive information to the transmitral pattern, particularly in distinguishing the normal transmitral pattern from the “pseudonormal” pattern (43) and evaluation of LV end diastolic pressures (96).

Pulmonary venous flow can be recorded by transthoracic echocardiography in 80% to 90% of cases (118,176) and by transesophageal echocardiography (119,177).

The pulmonary venous velocity profile typically has three distinct waves (Fig. 26.2).

The S wave has two components that are temporally separated: early systolic (S_1) and late systolic (S_2) waves. This wave occurs during ventricular systole and is an antegrade wave reflecting the fall in left atrial pressure due to atrial relaxation (S_1) and descent of the mitral annulus during ventricular contraction ('x' descent) and RV stroke volume (S_2) (178,178a). The D wave occurs during ventricular diastole shortly following the peak of the forward E wave through the mitral valve, reflecting the fall in atrial pressure with atrial emptying into the left ventricle ('y' descent). The height of pulmonary venous D wave is proportional to the height of the transmitral E wave (15). During this phase, the left atrium functions largely as a conduit between the pulmonary veins and the left ventricle (43,178) (*e*Table 26.2.1).

***e*TABLE 26.2.1** HEMODYNAMIC FACTORS INFLUENCING PULMONARY VENOUS FLOW

	Atrial factors	**Ventricular factors**
Systolic phase	LA contractility	LV contractility (mitral annular motion)
	LA relaxation	Right ventricular stroke volume
	LA pressure	
	LA compliance	
	Compliance of pulmonary veins	
	Rhythm	
Diastolic phase	LA pressure	LV compliance
	LA compliance	LV relaxation
Atrial reversal phase	LA pressure	LV compliance
	LA contractility	
	LA relaxation	
	LA compliance	
	PR interval, rhythm	

LA, left atrial; LV, left ventricular.
Modified from Klein AL, Tajik AJ. Doppler assessment of pulmonary venous flow in healthy subjects and in patients with heart disease. *J Am Soc Echocardiogr* 1991;4:381, with permission.

The AR wave represents retrograde flow into the pulmonary veins during atrial contraction. The degree of retrograde flow is proportional to the relative impedance to flow presented by the left ventricle versus the pulmonary veins. If pulmonary venous impedance is considered relatively constant, then the ratio of forward to reversed A wave should relate to the operating compliance of the ventricle at the time of atrial contraction. Furthermore, the sum of the forward and reversed blood velocity should relate to the total stroke volume of atrial contraction and thus reflect, to some degree, atrial systolic function.

Pulmonary venous flow is dictated physically by Newton's second law, force = mass × acceleration, where force is the pressure difference between the central pulmonary veins and the left atrium, and the mass relates to the inertance of blood within the distal pulmonary veins. Pulmonary venous inertance is approximately equal to the length of the distal pulmonary veins (179). Furthermore, pulmonary venous flow demonstrates a significant phase lag behind its driving pressure gradient.

Right-Sided Doppler Flows

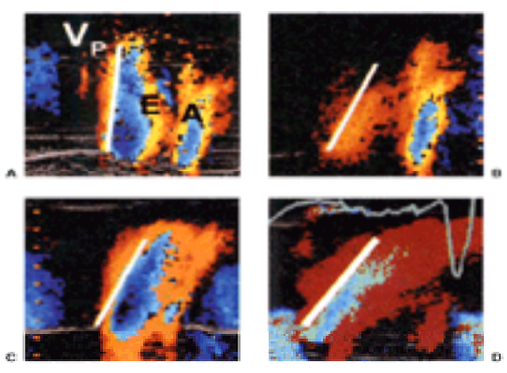
Diastolic function of the right-sided heart can be evaluated by the interrogation of the tricuspid inflow, hepatic vein flow, and superior vena cava (120,180). The Doppler flow patterns in the hepatic veins and superior vena cava are somewhat similar to the pulmonary venous flow patterns (4,15). In addition to the S, D, and AR waves, a second reversed flow is often seen between the S and the D wave at the end of ventricular contraction (VR) (120). Right-sided flow velocities normally increase during inspiration and decrease with Valsalva manuever (120,181).

As with the pulmonary venous flow, the S wave is related to RA relaxation and tricuspid annular descent, and the D is related to early RV filling velocity (E). The magnitude of AR and VR varies according to RV stiffness, RA contractility, and central venous pressure (182). The effect of respiration of the right-sided flows is useful in differentiating constriction from restriction and estimating right-sided filling pressures (4,15).

Color M-Mode Doppler

In more recent years, a number of investigators have studied the use of the color Doppler M-mode to characterize the spatiotemporal distribution of blood velocity throughout the ventricular inflow region in diastole (16,54,183,184,185 and 186).

A typical color Doppler M-mode echocardiogram has a temporal resolution of 5 ms, a spatial resolution of 300 µm, and a velocity resolution of approximately 4 cm per second. In normal sinus rhythm from the apical four-chamber view, the color Doppler M-mode demonstrates a characteristic pattern consisting of two filling waves, propagating from the left atrium to the left ventricle, corresponding to the E and A waves. The Vp changes with the different stages of diastolic dysfunction (*e*Fig. 26.2.2). The velocities are highest above the mitral valve and lowest as they approach the apex as shown by the change in color. The onset of flow occurs earlier at the mitral valve level than at the apex (16). The flow does not propagate instantaneously, but rather propagates with a velocity (Vp) given by the slope of the leading edge of the blood wave.



***e*FIGURE 26.2.2** Color Doppler M-mode transthoracic echocardiography in normals **(A)** and patients with delayed relaxation **(B)**, pseudonormalization **(C)**, and restrictive physiology **(D)**. Vp, propagation velocity (*white line*). Color M-mode display shows the column of blood flow over time and space from the mitral valve into the left ventricular cavity. There is a delay in time for blood to reach the apex and thus a slower propagation velocity with stages of decreasing relaxation and advanced diastolic impairment. (From Garcia MJ. Diastolic dysfunction and heart failure: causes and treatment options. *Cleve Clin J Med* 2000;67:727–738, with permission.)

Using digital processing of the color M-mode Doppler display, numerical values can be obtained to quantify pressure gradients using the Bernoulli's equation (187,188 and 189) or the simplified Euler equation:

$$-\frac{\partial p}{\partial s} = \rho\left[\frac{\partial v}{\partial t} + v\frac{\partial v}{\partial s}\right]$$

Previous clinical studies have shown that there is a poor relationship between the flow propagation velocity (Vp) and the peak E wave by pulsed Doppler (17,185). Vortex formation in the left ventricle may partly explain why the velocities of blood particles moving in a circular motion (E wave) may exceed the velocity of flow propagation (Vp) (16). Contrast echocardiographic studies in dilated left ventricles and apical dysfunction have also shown increased vortex formation (190).

Several qualitative and quantitative parameters have been proposed to characterize transmitral filling by color Doppler M-mode echocardiography. These studies have been used to characterize ventricular relaxation compared with cardiac catheterization (54,191). Brun et al. identified the leading edge of the E wave as representing the propagation velocity (54). This parameter is measured by identifying the boundary of the leading edge of color as it propagates into the ventricle, drawing a tangent to this line and measuring its slope on the M-mode. A negative correlation was demonstrated between this propagation velocity and the time constant of relaxation (tau)

in patients with coronary disease and cardiomyopathy. This propagation velocity parameter has been reported to be altered in conditions of delayed relaxation and ischemia, with a more rapid decrease in ventricular pressure allowing a greater propagation of flow into the left ventricle (54,191).

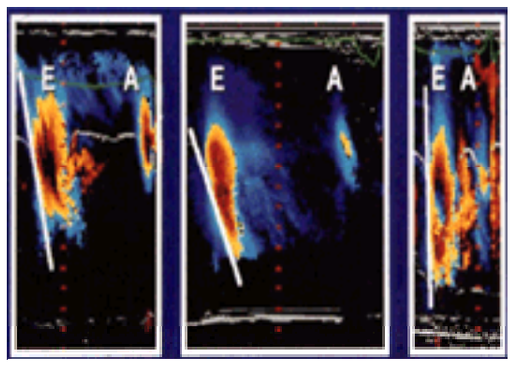
Another approach quantifying the propagation velocity (183) measured the delay required for the point of maximum velocity to traverse from the mitral valve to the apex. These investigators demonstrated that the time for flow to propagate from the mitral annulus to the ventricular apex was delayed significantly during ischemia associated with angioplasty, reverting to normal when the angioplasty balloon was deflated. They postulated that ischemia eliminated the physiologic early diastolic intraventricular pressure gradient pulling blood into the ventricle and thus there is a slower propagation of flow into the ventricle.

In contrast to the standard mitral inflow velocities, color M-mode propagation velocity has been determined to be relatively preload independent, validated by hemodynamic measurements in humans and animals (185,192).

In the study by Takatsuji et al., color M-mode flow propagation (Vp) was compared with the standard pulsed Doppler parameters for patients with abnormal relaxation and elevated filling pressures (diastolic dysfunction) and a control group with normal diastolic function. Color M-mode Doppler (Vp) was significantly lower in the patients with diastolic dysfunction than in the control group, whereas the mitral inflow velocities were similar (185).

When coupled with the ratio of the mitral inflow E wave over the color M-mode propagation velocity in patients in the intensive care unit, it provided a good estimate of PCWP (17). A more recent study showed that an E/Vp ³1.5 to be the single best predictor of in-hospital clinical heart failure in patients with their first myocardial infarction (186).

It appears that the propagation velocity may also be a discriminating feature between restrictive and constrictive diseases. Constrictive pericarditis is characterized by relatively normal early diastolic relaxation (and thus early diastolic filling) with an abrupt mid-diastolic cessation of inflow. Restrictive diseases have abnormal relaxation and impaired inflow from the opening of the mitral valve. These pathophysiologies seem to be reflected in the propagation velocity profile. Constrictive pericarditis is associated with extremely rapid flow propagation (a slope of greater than 100 cm per second), whereas restrictive cardiomyopathy shows markedly slowed propagation of the E wave (15,121) (eFig. 26.2.3).

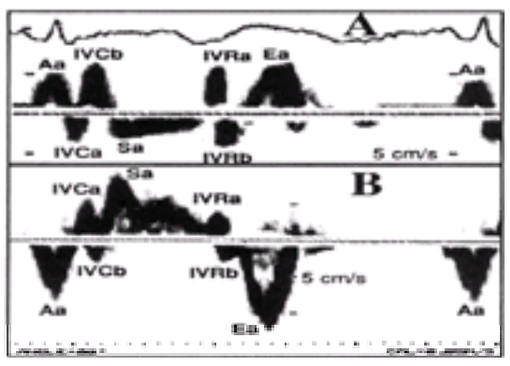


***e*FIGURE 26.2.3** Color Doppler M-mode transesophageal echocardiography of diastolic flow from the left atrium (*top*, left atrium) toward the ventricular apex (*bottom*, left ventricular apex) is imaged in a four-chamber view. Flow propagation is seen during early (E) and late (A) filling with normal filling (*left*), restriction (*center*), and constriction (*right*). Scale markers indicate 1 cm. (From Cohen GI, Pietrolungo JF, Thomas JD, et al. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. *J Am Coll Cardiol* 1996;27:1753–1760, with permission.)

Tissue Doppler Echocardiography

TDE quantifies the low velocity and high amplitude of tissue such as the ventricular myocardium or the motion of the mitral annulus (21,123,193). It provides a detailed spatial map of velocity in the myocardium, which can be further temporally enhanced with the color M-mode Doppler and pulsed wave Doppler.

The TDE myocardial velocities are composed of several waves (eFig. 26.2.4). Following the electrocardiographic QRS, a short-amplitude multiphasic signal coincides with the closure of the mitral and tricuspid valve (194) and is caused by translational motion and geometric LV changes assuming a more spherical shape during isovolumic contraction. Following this signal, a larger positive wave represents ventricular systole (S_M). A second multiphasic signal during isovolumic relaxation coincides with aortic valve closure and tricuspid valve opening. In sinus rhythm, two waves corresponding to early filling (E_M) and atrial contraction (A_M) appear as a mirror image of the mitral inflow early (E) and atrial (A) filling velocities. In healthy subjects, the peak of the E_m occurs earlier than the peak mitral inflow E wave (20 ms), suggesting that fast relaxation of the myocardium generates suction that pulls blood into the ventricle (E wave). However, in patients with diastolic dysfunction, the mitral inflow E wave coincides with or precedes the E_m, suggesting more passive filling (16).



***e*FIGURE 26.2.4** Doppler tissue imaging velocity spectrum recorded from parasternal short-axis view at mid-ventricular level from **(A)** anteroseptal and **(B)** posterior left ventricular wall. (From Garcia M, Rodriguez L, Ares M, et al. Myocardial wall velocity assessment by pulsed Doppler tissue imaging; characteristic findings in normal subjects. *Am Heart J* 1996;132:648–656, with permission.)

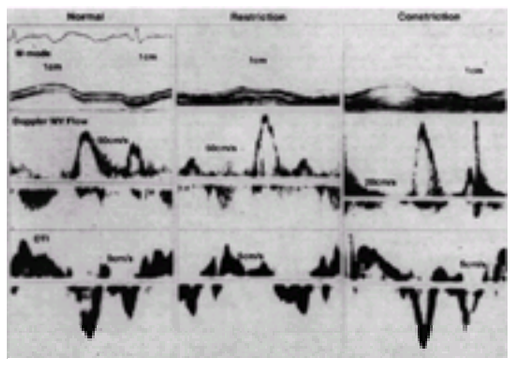
A major limitation of TDE is the effect of translation and rotation of the heart, in particular from the parasternal long-axis view. Thus, motion of the LV myocardium and annulus in the longitudinal plane can be measured from the apical four-chamber view. Because the apex is relatively fixed throughout the cardiac cycle and the axial plane of motion of the LV myocardium is parallel with the axis of the transducer, the velocities obtained from this acoustic window represent motion secondary to contraction and relaxation and do not require angle correction (16).

Color Doppler TDE provides a color map with high spatial resolution that is able to provide velocity data simultaneously from multiple segments of the myocardium. To decode the data, digital storage and off-line analysis are necessary. In contrast, pulsed wave TDE is much simpler, providing high temporal and velocity resolution with the data being stored using digital or video format. A limitation is that it measures only one point in time compared with the multiple information obtained from color TDE (195).

Our preference has been to use pulsed wave TDE from the mitral annulus medial and lateral walls for the assessment of diastolic function. In healthy subjects, the tissue Doppler echocardiographic velocities are a mirror image of the mitral inflow velocities. With the aging process, there is an inverse effect on the E_m/A_m ratio similar to that reported for the mitral inflow (194); however, there are significant differences in patients with organic disease, distinct from transmitral flow velocities (196). In patients with impaired relaxation, the E_m velocity decreases with E_m/A_m ratio less than 1. In patients with advanced diastolic dysfunction (see following discussion) the E_m remains low, even in the presence of elevated filling pressures (194).

Tissue Doppler E_m is less affected by preload than standard Doppler LV filling indices. Similar to color M-mode Doppler, tissue Doppler E_m has been shown to correlate with the time constant of relaxation in both patients with normal or increased preload (197,198 and 199). In hemodynamic studies performed by Oki et al., the time constant of relaxation correlated well with E_m in all patients independent of filling pressures (197). Sohn et al. demonstrated the relative preload insensitivity of E_m by infusing volume in patients with abnormal relaxation patterns and nitroglycerin in patients with normal or pseudonormal patterns. While mitral inflow E/A ratio and deceleration time were affected by volume changes, there was no significant change in E_m, demonstrating the utility of this parameter to differentiate normal from pseudonormal patterns. Patients with abnormal diastolic function (elevated preload and t greater than or equal to 50 ms) could be discriminated from those with normal filling (normal preload and t less than 50 ms) by a lower E_m (less than 8.5 cm per second) with a sensitivity of 88% and specificity of 67% despite having similar mitral inflow Doppler patterns (198). In an animal experiment, Garcia et al. showed that both peak mitral E-wave and E_m changes decreased with preload reduction (IVC occlusion); however, the effect of preload was less with more prolonged relaxation. When tau was less than 50 ms, the changes in E_m with preload reduction were significantly greater (DE_m = 2.83 ± 0.62 cm per second) than when tau ranged from 50 to 65 ms (DE_m = 1.21 ± 0.25 cm per second) or was greater than 65 ms (DE_m = 0.49 ± 0.09 cm per second, p <.05). Therefore, it appears that although E_m may be affected by alterations in preload, the effect is minimal in ventricles with impaired relaxation (192,200). In patients with various degrees of diastolic function, the tissue Doppler E_m was the best discriminator between healthy subjects (16 cm per second) and patients with abnormal diastolic function (7.5 cm per second) compared with the standard mitral inflow or pulmonary vein flow (201). Other groups have confirmed that a TDE E_m of 8 cm per second was a useful cutoff between normal and abnormal filling pressures (202).

We have used TDE myocardial velocities to differentiate constrictive pericarditis from restriction. In patients with restriction, both relaxation and compliance are abnormal, whereas relaxation is normal in constriction. We showed that patients with restriction had slow early diastolic motion of the annulus, whereas patients with constriction had normal or rapid early diastolic annular velocity (greater than 8 cm per second), suggesting preserved relaxation (121,123) (eFig. 26.2.5). Recently, another study showed that annular motion may not always distinguish constriction from restriction, especially if the annulus is involved with the pericardial process (202a).



***e*FIGURE 26.2.5** Samples of mitral annular M-mode tracings, Doppler tissue imaging (DTI) velocities in the longitudinal axis, and transmitral Doppler flow velocities in a normal volunteer, a patient with restrictive cardiomyopathy, and a patient with constrictive pericarditis. There is a marked difference in early diastolic longitudinal axis velocities, despite similar early transmitral flow velocities. MV, mitral valve. (From Garcia MJ, Rodriguez L, Ares M, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy: assessment of left ventricular diastolic velocities in longitudinal axis by Doppler tissue imaging. *J Am Coll Cardiol* 1996;27:108–114, with permission.)

Preliminary studies suggest that TDE of the myocardial velocities may be used in detecting rejection in cardiac transplantation (203). Because of the effects of translation and rotation on TDE, the myocardial velocity gradient has been developed as a measure of regional myocardial diastolic function, which is independent of translational motion. It is the velocity gradient between the endocardium and epicardium across the myocardial wall and is measured as the slope of the regression line for the transmural velocity profile across the myocardium (204,205 and 206). It is given by the follwoing equation: MVG = $(V_{end} - V_{epi})/L$.

The peak negative myocardial velocity gradient is a good noninvasive measure of diastolic function that is less preload dependent than mitral inflow (205). It has been used to differentiate myocardial hypertrophy in athletic hearts from patients with hypertrophic cardiomyopathy with an accuracy of greater than 0.9 (20), as well as patients with hypertension and dilated cardiomyopathy (205), and to differentiate patients with constriction from restriction (206). It has also been used to differentiate transmural from nontransmural acute myocardial infarction after reperfusion therapy (207).

Strain imaging is another newer modality that measures the deformation properties of a myocardial segment independent of translation or rotation. It is given by the equation $S = (L_0 - L_1)/L_0$, where L_0 is initial length and L_1 is compressed length (21,208). The strain rate measures the velocity in a certain direction dV/dX (sec^{-1}) of the longitudinal or circumferential fibers of the myocardium from parasternal or apical views. This technique has been used in patients with hypertrophic cardiomyopathy (209) and patients with coronary artery disease (21,210,211).

Interpretation of Diastolic Filling Patterns

Using information from mitral inflow, pulmonary vein flow, color M-mode, and tissue Doppler imaging, four patterns of diastolic function can be determined (Fig. 26.2). These patterns are dependent on age and hemodynamic conditions and represent stages of relaxation and compliance abnormalities and filling pressures. A classification was proposed that diastolic dysfunction be graded in four stages that correlate with diastolic impairment and symptom class (212) (Fig. 26.3).

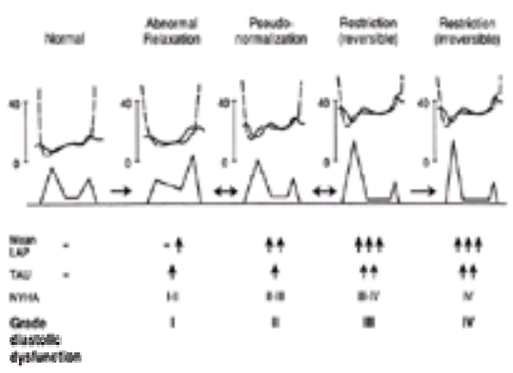


FIGURE 26.3 Proposed grading system for diastolic dysfunction based on progression of clinical disease patterns. Top row shows the high-fidelity left atrial and left ventricular pressure curves for the four grades of diastolic dysfunction, graded on a scale of I to IV, representing a progression from abnormal relaxation, pseudonormalization, restrictive (reversible), and restrictive (irreversible) disease. Below are the corresponding mitral flow velocity profiles; below these are the mean left atrial pressure (LAP), time constant of relaxation (TAU), and New York Heart Association (NYHA) class. Measurements are given in mm Hg. (From Nishimura RA, Tajik AJ. Evaluation of diastolic filling of the left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta stone. *J Am Coll Cardiol* 1997;30:8–18, with permission.)

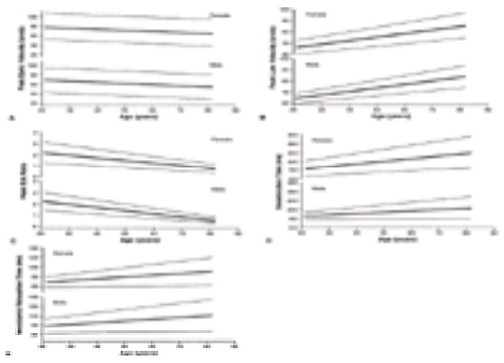
Normal Pattern

The normal filling pattern is seen in healthy subjects with normal relaxation, compliance, and filling pressures. Healthy individuals demonstrate a briskly accelerating E wave, relatively rapid deceleration, and an A wave significantly smaller in magnitude than the E wave. The E/A ratio is greater than 1, the mitral deceleration time is typically between 150 and 220 ms, and the IVRT less than 100 ms. The S/D ratio is generally greater than 1, and the AR wave should be less than 35 cm per second. The color M-mode propagation is relatively fast (greater than 45 cm per second), and the tissue Doppler E_m is greater than 8 cm per second consistent with normal

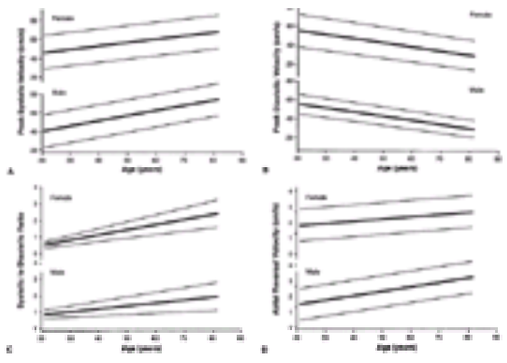
ventricular relaxation (16).

In young healthy subjects, there is a greater predominance of early diastolic filling due to the rapid “suction” effect of the ventricle (more enhanced relaxation with Vp greater than 55 cm per second and E_m greater than 10 cm per second) and little additional filling during atrial contraction. This results in an even greater E/A ratio with further shortening of the deceleration time. Because atrial contribution is minimal, the mitral inflow A wave and pulmonary vein AR are small. The S/D ratio may be less than 1, representing the large contribution of early filling.

Normal left-sided values with 95% confidence intervals with age are graphically shown in eFigure 26.3.1 and eFigure 26.3.2, and right- and left-sided normal values are listed in eTable 26.2.2 (4,84,92,120). eFigure 26.3.3 shows the left- and right-sided Doppler tracings in healthy subjects.



***e*FIGURE 26.3.1** Peak early velocity **(A)**, peak late velocity **(B)**, peak E/A ratio **(C)**, deceleration time **(D)**, and isovolumic relaxation time **(E)** (*boldface lines*, mean values; *lightface lines*, 95% confidence intervals) in female and male healthy subjects with increasing age. Note the peak early velocity and E/A ratio decrease with age, whereas the peak late velocity, deceleration time, and isovolumic relaxation time increase. (From Klein AL, Burstow DJ, Tajik AJ, et al. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc* 1994;69:219, with permission.)

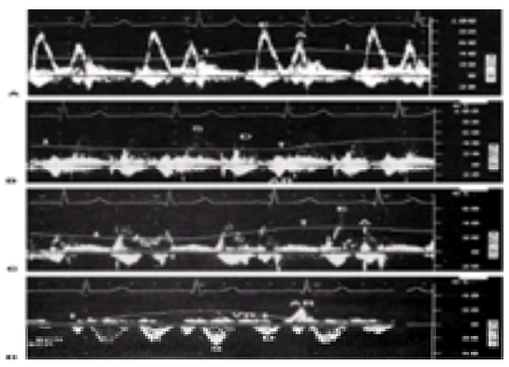


***e*FIGURE 26.3.2** Pulmonary venous peak systolic velocity **(A)**, diastolic velocity **(B)**, systolic to diastolic ratio **(C)**, and atrial reversal velocity **(D)** (*boldface lines*, mean values; *lightface lines*, 95% confidence intervals) in female and male healthy subjects with increasing age. Note that the peak systolic velocity, the systolic to diastolic ratio, and the atrial reversal velocity increase with age, whereas the peak diastolic velocity decreases with age. (From Klein AL, Burstow DJ, Tajik AJ, et al. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc* 1994;69:217, with permission.)

***e*TABLE 26.2.2** LEFT AND RIGHT VENTRICULAR FILLING DYNAMICS IN HEALTHY SUBJECTS[a]

	Age 21–49 yr	**Age greater than or equal to 50 yr**
Left ventricular inflow[b]	n = 61	n = 56
Peak E (cm/s)	72 (44–100)	62 (34–90)
Peak A (cm/s)	40 (20–60)	59 (31–87)
E/A ratio	1.9 (0.7–3.1)	1.1 (0.5–1.7)
DT (ms)	179 (139–219)	210 (138–282)
IVRT (ms)	76 (54–98)	90 (56–124)
Pulmonary vein	n = 44	n = 41
Peak S (cm/s)	48 (30–66)	71 (53–89)
Peak D (cm/s)	50 (30–70)	38 (20–56)
S/D ratio	1.0 (0.5–1.5)	1.7 (0.8–2.6)
Peak AR (cm/s)	19 (11–27)	23 (–5–51)
Right ventricular inflow[c]	n = 43	n = 45
Peak E (cm/s)	51 (37–65)	41 (25–57)
Peak A (cm/s)	27 (11–43)	33 (17–49)
E/A ratio	2.0 (1.0–3.0)	1.3 (0.5–2.1)
DT (cm/s)	188 (144–232)	198 (152–244)
Superior vena cava	n = 59	n = 53
Peak S (cm/s)	41 (23–59)	42 (18–66)
Peak D (cm/s)	22 (12–32)	22 (12–32)
Peak AR (cm/s)	13 (7–19)	16 (10–22)

A, atrial contraction; AR, atrial reversal flow velocity; D, diastolic flow velocity; DT, deceleration time; E, early transmitral flow velocity; IVRT, isovolumic relaxation time; S, systolic flow velocity.
[a]Values represent mean values (and confidence intervals).
[b]Data from Klein AL, Burstow DJ, Tajik AJ, et al. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc* 1994;69:212–224.
[c]Data from Klein AL, Leung DY, Murray RD, et al. Effects of age and physiologic variables on right ventricular filling dynamics in normal subjects. *Am J Cardiol* 1999;84:440–448.
From Cohen GI, Pietrolungo JF, Thomas JD, et al. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. *J Am Coll Cardiol* 1996;27:1753–1760, with permission.



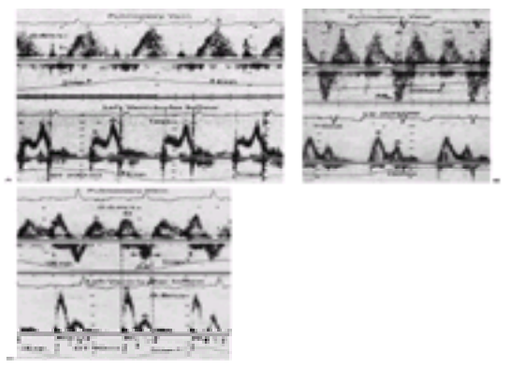
***e*FIGURE 26.3.3** Normal Doppler flow profiles of the transmitral **(A)**, pulmonary venous flow **(B)**, tricuspid inflow **(C)**, and hepatic venous flow **(D)** in healthy subjects. A, atrial flow velocity; AR, atrial reversal flow velocity; D, diastolic flow velocity; down arrow, expiration; E, early filling velocity; S, systolic flow velocity; up arrow, inspiration; VR, venous flow reversal during late ventricular systole.

Delayed Relaxation Pattern (Stage I)

The delayed relaxation pattern is seen in patients with delayed LV relaxation but with relatively normal compliance and filling pressures (213). With normal aging and various pathologic states, the time constant of relaxation is lengthened, the E wave shows a slower acceleration and a lower peak velocity, a prolonged deceleration time (greater than 220 ms), and isovolumic relaxation time (greater than 100 ms). To the extent that emptying may not be complete by the end of diastasis, an increased left atrial volume is present at the time of atrial contraction, leading to a larger A wave, compensating in large part for the smaller E wave. Thus, the E/A ratio is less than 1 and concomitantly the S/D ratio is greater than 1, because if E is small, the corresponding D is small. Because relaxation is impaired, the color M-mode Vp is prolonged (less than 45 cm per second) and E_m is decreased (less than 8 cm per second).

Impaired relaxation may occur with normal or elevated filling pressures. If LV end diastolic pressure is normal, pulmonary vein AR is less than 35 cm per second; although if it is elevated, the AR is greater than 35 cm per second or the duration of AR is greater than the duration of the mitral inflow A duration (96).

This pattern is seen in normal aging (4,84), ischemia (214), hypertrophic cardiomyopathy (215,216), and secondary hypertrophy (217) and is usually seen in patients who typically have only mild symptoms or are asymptomatic (113) (*e*Fig. 26.3.4). It can also be seen with hypovolemia because of a decreased left atrial to LV pressure gradient with greater filling during atrial systole (15,218).



***e*FIGURE 26.3.4** Transmitral filling and pulmonary venous flow patterns. **A:** Abnormal relaxation, with the transmitral flow showing an early (E) filling wave less than the late filling (A) wave with a prolonged deceleration time (DT, 300 ms); pulmonary venous flow shows greater systolic than diastolic flow. **B:** Pseudonormal pattern with E wave greater than A wave, resembling a normal pattern; pulmonary venous flow shows a normal systolic (S) flow with an increased and prolonged atrial reversal (AR). **C:** Restrictive pattern with E wave markedly increased with a small A wave with shortened DT (90 ms); pulmonary venous flow shows a blunted pulmonary venous flow with an increased and prolonged AR. Exp., expiration; Insp., inspiration; LV, left ventricular.

Pseudonormal Pattern (Stage II)

The pseudonormal pattern is difficult to recognize because it is similar to the normal pattern. As left atrial pressure increases further to compensate for deteriorating diastolic function, the peak E-wave velocity increases. Therefore, abnormalities of relaxation and compliance and elevated filling pressures are present. This is associated with a normal appearance of the transmitral inflow with an E/A ratio between 1 and 2, a deceleration time between 150 and 220 ms, and an isovolumic relaxation time between 60 and 100 ms (15,92,113) (*e*Fig. 26.3.4). One important feature to distinguish this pattern from normal is the pulmonary venous AR wave, which in pseudonormal filling displays a prolonged and increased AR greater than 35 cm per second (84), whereas the pulmonary vein S/D ratio could be normal or less than 1. The AR wave prominence may not be present if atrial systolic failure occurs, although the duration of AR greater than the mitral A wave may still occur. In addition, the Valsalva maneuver may be useful in differentiating normal from pseudonormal by reducing the preload, causing the normal-appearing E/A ratio to be greater than or equal to 0.5, and thus exposing a delayed relaxation pattern (4,92,170,219). Color M-mode propagation velocities and tissue Doppler imaging are particularly helpful to detect pseudonormal filling with a Vp less than 45 cm per second and E_m less than 8 cm per second (201).

Usually in patients with pseudonormal patterns, the left atrial size is increased, the LV function may be impaired or wall thickness increased, and the patient may have dyspnea (97,113). This pattern may represent an intermediate stage between impaired relaxation and restrictive filling as a result of disease progression, ischemia, or a change in loading conditions (15,100,113).

Restrictive Filling Pattern (Stage III)

The restrictive filling pattern is seen in the presence of severely reduced LV compliance and elevated filling pressures and ongoing delayed relaxation. It is characterized by a very elevated peak E-wave velocity with extremely rapid deceleration indicative of increased LV operating stiffness and diminutive (often absent) A wave (*e*Fig. 26.3.4). The E/A ratio is usually greater than 2, with a deceleration time less than 150 ms, and isovolumic relaxation time less than 60 ms (15). Pulmonary venous flow usually shows markedly blunted systolic flows with large and prolonged ARs (except in conditions of atrial systolic failure) (4). A pulmonary venous systolic fraction 0.40 to 0.55 of the of the sum of the systolic plus diastolic fraction is consistent with significant elevation of PCWP (96,220). Similar to pseudonormal patterns, the color M-mode propagation velocity and E_m are reduced.

Reduced filling due to increased ventricular stiffness may be counteracted by increases in heart rate, inotropic state, or most commonly left atrial pressure. This preload compensation dramatically changes the morphology of the E wave from a pattern consistent with delayed relaxation to one consistent with the restrictive pattern (221). Diastolic mitral and tricuspid regurgitation may occur as a result of ventricular pressure rising rapidly in a stiff ventricle and exceeding atrial pressure in mid- or late diastole (15).

The restrictive filling pattern is equivalent to the “square-root sign” or “dip and plateau” pattern seen in the ventricular pressure tracing at cardiac catheterization (92). The association between the restrictive filling pattern and the need for elevated filling pressures perhaps explains the poor prognosis connoted by the restrictive pattern (103). This pattern can be seen in patients with advanced stages of diastolic dysfunction due to restrictive, dilated, or ischemic cardiomyopathy, and usually the patients have dyspnea at rest and high New York Heart Association functional class (113). Severe enlargement and hypocontractility of the left atrium may be seen, and this pattern carries a poor prognosis in ischemic (222), dilated (223,224), and restrictive cardiomyopathies (103). In hypertrophic cardiomyopathy, there is a less clear prognostic potential of the filling patterns because of the complex interplay between systolic outflow tract obstruction, mitral regurgitation, and diastolic dysfunction (225).

Restrictive Filling Pattern (Stage IV)

As noted previously, restrictive filling patterns are associated with a poor prognosis for patients with various types of cardiac diseases. Additional prognostic information can be obtained in patients with restrictive filling patterns evaluated under different hemodynamic conditions. Failure to convert a restrictive mitral inflow filling pattern to a nonrestrictive pattern substantially increased the risk of death greater than twofold in a study of patients with chronic heart failure (226,227).

Estimating Left Atrial and Left Ventricular Filling Pressures

Transmitral inflow and pulmonary venous flow by Doppler echocardiography have been used to noninvasively estimate left heart filling pressures, including mean pulmonary capillary wedge and left atrial pressure and LV end diastolic pressure, primarily in patients with cardiac disease (96,97,220,228,229 and 230). A notable exception in the use of Doppler flow patterns to predict filling pressure is patients with hypertrophic cardiomyopathy in whom Doppler mitral flow patterns do not correlate well with LV filling pressures due mainly to the exaggerated relaxation abnormalities and other variables affecting diastolic function in this disease (225).

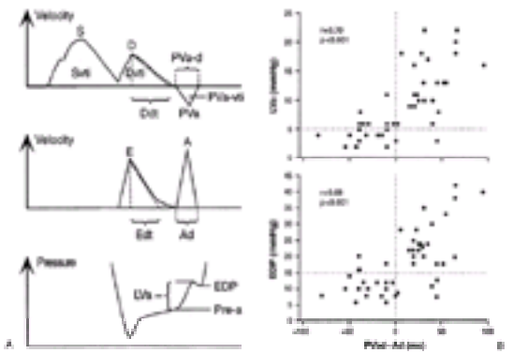
An increased E/A ratio, a shortened deceleration and isovolumic relaxation time, a decreased atrial filling fraction, a decreased pulmonary venous systolic fraction, an elevated and prolonged AR flow velocity, and increased left atrial volume may suggest an elevated mean left atrial pressure. Because these parameters are influenced by left atrial pressure and ventricular relaxation, these correlations work best for patients with abnormalities of LV relaxation in which left atrial pressure is the only variable. This includes mostly patients with structural heart disease. In the setting of isolated diastolic dysfunction with normal systolic function, mitral inflow and pulmonary venous inflow parameters are poorly related to LV filling pressures. By combining the mitral E wave, a variable that correlates modestly with left atrial

pressure and one that is associated with ventricular relaxation (color M-mode propagation velocity or TDE early filling velocity), closer approximations of left atrial pressure can be obtained.

Garcia and colleagues studied patients in intensive care units with a variety of medical or cardiac diseases and a mean LV ejection fraction of 40%. Using the regression equation, PCWP could be estimated by the equation, PCWP = 5.27 × (E/Vp) + 4.6, with an r = 0.80, *p* <.001 (17). Similar studies have confirmed these findings and included patients with atrial fibrillation (231,232). In a more recent study of 100 patients undergoing cardiac catheterization, Ommen et al. compared various mitral inflow and pulmonary venous flow measurements to the ratio of E/E_m to assess mean LV filling pressure (a surrogate for left atrial pressure). Ratios of E/E_m greater than 15 were associated with increased LV filling pressure, whereas E/E_m less than 8 correlated with normal pressures. These associations were best for patients with LV dysfunction (202).

LV filling pressures can be estimated even in patients with atrial fibrillation. One study showed a correlation between PCWP and mitral deceleration time for patients with LV dysfunction and atrial fibrillation (231). A subsequent study showed an even better correlation with the initial deceleration slope of the pulmonary venous diastolic wave (233).

End diastolic LV pressure has been estimated by echocardiography independent of left atrial pressure. Several studies have shown that the difference between the duration of the pulmonary venous AR and transmitral inflow A-wave duration can be used as an estimate of elevated LV end diastolic pressure (96,97 and 98) (*e*Fig. 26.3.5). When the duration of the pulmonary venous reversal wave is prolonged with respect to that of the forward mitral A-wave duration (greater than 20 to 30 ms), then the LV end diastolic pressure is usually elevated (greater than 15 mm Hg) (96). This variable has been shown to be relatively age independent (234) and not affected by mitral regurgitation (234a). Studies have demonstrated that the difference in duration between the pulmonary venous AR and mitral A wave of greater than or equal to 30 ms is a predictor of severity of disease in cardiac amyloidosis (235) and cardiac mortality in patients with coronary artery disease (236).



***e*FIGURE 26.3.5 A:** Measurements of pulmonary venous (*upper*) and mitral (*middle*) flow velocities and left ventricular pressure curve (*bottom*). A, peak velocity of late mitral flow; Ad, duration of late mitral flow; D, peak diastolic velocity of pulmonary venous flow; Ddt, deceleration time; Dvti, diastolic velocity time integral; E, peak velocity of early mitral flow; EDP, end diastolic pressure; Edt, deceleration time of early mitral flow; Pre-a, pressure before atrial contraction; PVa, peak velocity of reversed flow at atrial contraction; PVa-d, duration of reversed flow; PVa-vti, reversed flow time-velocity integral; S, peak systolic velocity; Svti, systolic time-velocity integral. **B:** Left ventricular pre 'a' wave (LVa, *top*) and EDP (*bottom*) versus the difference in duration between reverse pulmonary venous and mitral A waves (PVad – Ad). (From Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol* 1993;21:1687–1696, with permission.)

Clinical Presentation and Significance

Patients with impaired diastolic function present with the typical syndromes of congestive heart failure including dependent edema, limited exercise tolerance, ascites and effusions, orthopnea, and flash pulmonary edema. In general, the clinical examination is unreliable in differentiating systolic from diastolic dysfunction. The jugular veins are distended, and dependent pitting edema may be severe. Rales may be present on chest auscultation. Cardiac auscultation may demonstrate an S_3, S_4, or a pericardial knock (15,26). The typical clinical characteristic of patients with diastolic heart failure include the elderly, women, and those with hypertension, diabetes, and renal dysfunction (237). One study in Olmsted County, MN, of patients with diastolic heart failure found that nearly 50% of patients were 80 years of age or older (238). The presentation of heart failure may be with flash pulmonary edema and hypertensive heart disease (239,240), advanced ischemic heart disease, or hypertensive hypertrophic cardiomyopathy (241). Those patients who do not respond to treatment for heart failure include patients with diseases such as aortic stenosis or hypertrophic cardiomyopathy, infiltrative cardiomyopathy, and constrictive pericarditis (242) (Table 26.1). Patients with diastolic heart failure may present with new onset of atrial fibrillation or flutter, especially with more advanced diastolic dysfunction (238,242a).

More specific signs of individual disease states are discussed in the following sections.

Management of Diastolic Heart Failure

The general goal of treatment is twofold: to reduce the variables responsible for the underlying diastolic dysfunction and to reduce the clinical manifestations of the process. Treatment consists of reducing elevated filling pressures, maintaining atrial contraction, decreasing heart rate, preventing ischemia, improving relaxation, and causing the regression of ventricular hypertrophy (28,62,243,244). Therapy must be targeted to the specific pathologic process as some medications may be inappropriate for certain conditions. For instance, a beta-blocker or calcium channel blocker would be preferable to an angiotensin-receptor blocker in patients with hypertrophic cardiomyopathy since the latter medication may contribute to LV outflow obstruction.

Diuretics produce symptomatic relief but should be used judiciously, as noncompliant ventricles, by definition, require higher pressures to achieve adequate filling. Nitrates may be beneficial secondary to their effects on reducing preload and ischemia (22). Beta-blocking agents slow heart rate, decrease myocardial oxygen demand, control blood pressure, and produce regression of LV hypertrophy. Calcium channel blockers have multiple benefits as negative chronotropic agents, controlling blood pressure, decreasing myocardial oxygen demand, dilating the coronary arteries, and regressing hypertrophy (26). Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have direct and indirect effects. These include blood pressure control and substantial ventricular mass regression. The degree of myocardial mass regression of these agents appears more potent than any other antihypertensive agents for similar blood pressure reduction (245). Data have demonstrated improvement in diastolic function with lisinopril by reduction in myocardial fibrosis (including decreased collagen volume) independent of LV regression (246). Preliminary data support further investigation of nitric oxide donors, which produce improved myocardial relaxation (244,247).

Doppler flow patterns may be useful in guiding therapy (15) (*e*Table 26.2.3). Patients with abnormal relaxation with fusion of the E and A wave may need a calcium channel or beta-blocker to slow the heart rate, whereas patients with pseudonormal or restrictive filling may need diuretics or angiotensin-converting enzyme inhibitors to lower the elevated filling pressures. If there is a prolonged PR interval in the setting of dilated cardiomyopathy, dual-chamber pacing may be beneficial (248). There may be some additional benefit of the use in Doppler flow patterns in the evaluation of biventricular pacing (249).

***e*TABLE 26.2.3** POTENTIAL TREATMENT STRATEGIES OF DIASTOLIC FUNCTION ACCORDING TO DOPPLER FILLING PATTERN AND CLINICAL AND TWO-DIMENSIONAL ECHOCARDIOGRAPHIC CONTEXT

Doppler finding	Clinical/echocardiographic context	Treatment
Impaired relaxation	Hypovolemia	Fluids
	Excessive afterload	Antihypertensive drugs to regress hypertrophy; relieve outflow
	Coronary artery disease	Antianginal drugs; revascularization
	Infiltrative cardiomyopathy	Nitrates; diuresis; treat metabolic or immunologic derangement
(E-, A-wave fusion)	Inadequate filling time	Slow heart rate (beta-blockers, verapamil, diltiazem)
Pseudonormal filling or restriction	Volume overload	Nitrates; diuresis; dialysis; correct valvular regurgitation
	Coronary artery disease	Antianginal drugs; revascularization; transplantation
	Infiltrative cardiomyopathy	Nitrates; diuresis; treat metabolic or immunologic derangement; transplantation
	Dilated cardiomyopathy	Reduce afterload; angiotensin-converting enzyme inhibitors; correct outflow obstruction; optimize preload; treat coronary artery disease; inotropes for systolic dysfunction; transplantation

(End diastolic mitral regurgitation)	Prolonged PR interval	Dual-chamber pacing to reduce PR interval
Constriction	Thickened pericardium; chamber compression	Medical treatment of cause, especially if acute (antibiotics, antiinflammatory agents; hormonal therapy, chemotherapy, radiotherapy); pericardial stripping, if chronic
Tamponade	Pericardial effusion; chamber compression	Pericardiocentesis; pericardial window if recurrence likely; medical treatment of cause, evacuate hematoma after heart surgery or rupture; achieve hemostasis

From Cohen GI, Pietrolungo JF, Thomas JD, et al. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. *J Am Coll Cardiol* 1996;27:1753–1760, with permission.

Prognosis

Patients with congestive heart failure secondary to diastolic dysfunction generally have a better prognosis than patients with systolic dysfunction (250); however, they may have recurrent congestive heart failure and recurrent chest pain despite coronary revascularization (23,240). eTable 26.2.4 summarizes the mortality in a number of studies in patients with diastolic dysfunction. The prognosis of diastolic heart failure varies, depending on the population studied with an annual mortality varying from 1.3% to 17.5%, which is lower than patients with systolic dysfunction (19%) (22). The lower mortality with diastolic function has been shown in a large number of population-based studies including the Veterans Administration Cooperative Study and Coronary Artery Surgery Study (22,251). The addition of coronary artery disease in patients with congestive heart failure adds considerable risk to diastolic dysfunction; however, it does not approach the risk of patients with low ejection fractions (250). A study by Senni et al. showed similar mortality in older patients with diastolic and systolic dysfunction (238).

***e*TABLE 26.2.4** MORTALITY AND ITS DETERMINANTS IN PATIENTS WITH CONGESTIVE HEART FAILURE AND NORMAL LEFT VENTRICULAR SYSTOLIC FUNCTION

Study	No. of patients[a]	Follow-up duration (yr)	Mean age per patient (yr)	Coronary artery disease, % of patients	Cumulative mortality (%) 1 yr	Cumulative mortality (%) 4 yr	Average annual mortality (%)	Mechanism of death	Predictors of mortality
Warnowicz et al.	16	0.75	63	100	25	NR	NR	All cardiac (myocardial infarction 75%; sudden cardiac death 25%)	NR
Kinney et al.	44	4	64	NR	35	17	17.5	Majority cardiac	NR
Aronow et al.	68	4	84	100	22	56	14	95% cardiac	Age, HTN
Cohn et al.	83	5.7	59	26	8	27[b]	8	84% cardiac (sudden cardiac death 75%; pump failure 25%)	Ventricular tachycardia on Holter
Judge et al.	284	6	56	67	5[b]	12[b]	3	NR	Wall motion score, number of diseased vessels, age, HTN, lung disease, diabetes mellitus
Taffet et al.	40	3	82	65	25[b]	45[b]	15	45% cardiac (sudden cardiac death 20%; pump failure 73%)	Age, recurrent admissions
Brogan et al. (23)	53	5.6	55	0	3	5	1.3	44% cardiac	NR
Setaro et al.	52	7	71	52	20[b]	40[b]	6.5	90% cardiac (mostly pump failure)	Coronary artery disease not predictive
Ghali et al.	72	4	60	14	22	36	9	75% cardiac (pump failure 84%; sudden cardiac death 16%)	HTN
Vasan et al.[d]	37	6.2	72	57	—	32[c]	8.7	47% cardiovascular	NR

HTN, hypertension; NR, not reported.
[a]Patients, survival.
[b]Data obtained by interpolation of Kaplan-Meier survival curves.
[c]Five-year mortality.
[d]Vasan RS, Larson MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948–1955.
From Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565–1574, with permission.

Large prospective epidemiologic studies have provided significant insight into the clinical outcomes of patients with diastolic heart failure. One study group of 2,498 patients with functional class II to IV symptoms and LV ejection fractions greater than or equal to 40% were analyzed from the Duke University Cardiovascular database. A 5-year mortality of 28% was observed with predictors of mortality in a multivariable model including advanced age, minority status, coronary artery disease, severe heart failure or lower ejection fraction, diabetes, and peripheral vascular disease (252). An ongoing study (Candesartan in Heart Failure, Assessment of Reduction in Mortality and Morbidity) will address the effect of an angiotensin II type I receptor blocker in patients with systolic and diastolic dysfunction (253).

SPECIFIC DISEASE STATES

Restrictive Cardiomyopathy

Classification

The definition and classification of restrictive cardiomyopathy and other cardiomyopathies has evolved over time (254). Restrictive cardiomyopathy was originally classified as a group of primary muscle diseases of unknown etiology (255,256,257 and 258). According to the 1980 World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) task force on the definition and classification of cardiomyopathies (255), restrictive cardiomyopathy could exist either with or without obliteration and included endomyocardial fibrosis and Löffler's cardiomyopathy. This classification, which excluded "specific heart muscle diseases" of known cause or associated with other forms of myocardial disease, was becoming more blurred by more recent advances in imaging techniques such as Doppler echocardiography and radionuclide imaging (259). Indeed, the presence of restrictive physiology was by no means diagnostic of restrictive cardiomyopathy and restrictive cardiomyopathy may be diagnosed in the absence of demonstrable restrictive physiology. Thus, the WHO/ISFC classification of cardiomyopathy was not universally accepted and the number of cases with overlapping and unusual features was not insignificant (259,260).

Based on the problems outlined previously and increased knowledge, the 1995 WHO/ISFC Task Force found that the distinction between cardiomyopathy and specific heart muscle disease was not well delineated as previously thought; therefore, the current classification of cardiomyopathies now includes mention of the predominant pathophysiology, etiology, and provision for specific cardiomyopathies (254).

Restrictive cardiomyopathy is defined as a disease of the myocardium, which is characterized by "restrictive filling and reduced diastolic volume of either or both ventricles with normal or near-normal systolic function" (254). Systolic function may be normal in the early stage of disease, while wall thickness may be normal or increased depending on the etiology of the disease (254,261,262). The disease may be "idiopathic or associated with other disease" such as amyloidosis (254,261).

Despite this controversy of classification, in clinical practice, *cardiomyopathy* is a more loosely applied term. Dilated, hypertrophic, restrictive, and RV cardiomyopathies encompass the major categories of disease, although unclassified and specific cardiomyopathies (such as valvular, ischemic, hypertensive, and so forth) are also included (254). Restrictive cardiomyopathies are recognized as primary and secondary where the secondary forms include the specific heart muscle diseases in which the heart is affected as part of a multisystem disorder (e.g., infiltrative, storage, and noninfiltrative disease) (263).

A "working classification" of restrictive cardiomyopathy is shown in Figure 26.4 (261,263). Infiltrative cardiomyopathies can be further divided into interstitial and storage disorders. In interstitial diseases, the infiltrates localize to the interstitium (between myocardial cells), as with cardiac amyloidosis and sarcoidosis, whereas in storage disorders, the deposits are within cells, as with hemochromatosis and glycogen storage diseases (51). These secondary forms of restrictive cardiomyopathies are probably more common than the primary form (264) and display the classic restrictive hemodynamics only in their advanced form. The prototypical secondary

restrictive cardiomyopathy is cardiac amyloidosis (51).

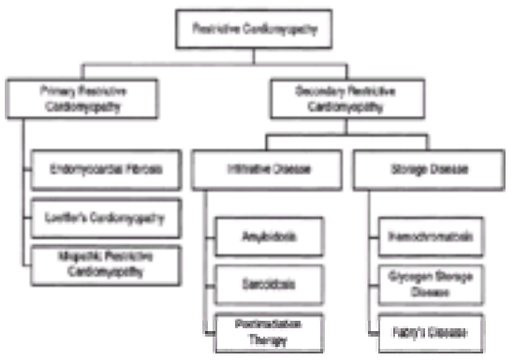


FIGURE 26.4 Working classification of restrictive cardiomyopathy. (From Leung DY, Klein AL. Restrictive cardiomyopathy; diagnosis and prognostic implications. In: Otto CM, ed. *Practice of clinical echocardiography*. Philadelphia: WB Saunders, 1997:474, with permission.)

Anatomic Considerations

In idiopathic restrictive cardiomyopathy, pathologic studies have shown mild to moderate degrees of hypertrophy and fibrosis (259) with the hemodynamic findings unrelated to the histopathologic abnormalities detected (259). In cardiac amyloidosis (see the section Cardiac Amyloidosis), there is interstitial infiltration of amyloid fibrils in the ventricles and atria causing a firm, rubbery consistency of the heart (265,266), whereas in the endomyocardial diseases there is an endocardial fibrotic shell with extension into the myocardium (267).

Pathophysiology

The characteristic feature of restrictive cardiomyopathy is a marked increased stiffness of the myocardium or endocardium that causes the ventricular pressure to rise dramatically with only small changes in volume causing an upward shift of the LV pressure-volume relationship and a dip and plateau or square-root hemodynamic pattern (268,269). As mentioned, there is a controversy about whether this restrictive hemodynamic pattern is necessary (270,271) to be included as a restrictive cardiomyopathy; however, the 1995 WHO/ISFC classification does include restrictive hemodynamics as an absolute criterion for the diagnosis. Both ventricles are affected with the restrictive process, but usually the pressures are higher on the left than the right (272), which may reflect the relatively decreased compliance of the left ventricle compared with the right ventricle. An exception may be tropical endomyocardial fibrosis in which the right ventricle may be predominantly involved (273).

Clinical Profile

The clinical signs and symptoms of restrictive cardiac diseases relate closely to the degree of left atrial hypertension required to compensate for poor ventricular filling (274). This gives rise to the typical clinical features of exercise intolerance in early cases and dyspnea at rest and symptoms of low cardiac output state such as fatigue in advanced cases (263). Left atrial dilatation, pulmonary congestion, distention of central veins, hepatic distention, ascites, peripheral edema, and anasarca are seen in advanced cases. Exertional chest pain is usually absent. Atrial fibrillation is common because of the atrial enlargement. Ventricular arrhythmias or heart block are not uncommonly present in advanced cases and are often the cause of death in these patients. Symptoms of the underlying multisystem disorder, if present, may also be evident (263). Examination may reveal jugular venous distention, S_4, or S_3 depending on the filling characteristics (275). Kussmaul's sign (272) can be detected, whereas apical retraction (as in constrictive pericarditis) is not seen (276).

In our experience, the main laboratory test to diagnose restrictive cardiomyopathy is echocardiography (4). Transthoracic or transesophageal echocardiography with respirometry has successfully been used to differentiate restriction from constriction (101,119). In patients with restriction, there is no significant respiratory variation as there is in constriction (13,101). Newer imaging modalities, including TDE and color M-mode Doppler (15,16,121,123), appear promising to further distinguish these disorders. MRI and computed tomography (CT) scanning may also be useful to exclude pericardial thickness (124,277,278). Cine MRI may show abnormal patterns of filling in early and advanced stages of restrictive cardiomyopathy similar to echocardiography (279). MRI may also be capable of distinguishing tissue characteristics of infiltrative processes, such as amyloid, differentiating it from other forms of cardiomyopathy (163).

Management

The prognosis of restrictive cardiomyopathy depends on whether there is early or advanced stage of the disease as shown with cardiac amyloidosis (103). The prognosis is variable, but usually progressive (280). Diuresis may help with symptomatic relief, while angiotensin-converting enzyme inhibitors may be of benefit with LV dysfunction. Vasodilators should be used cautiously because they may cause hypotension. Reversible underlying conditions such as hemochromatosis should be addressed. Transplantation can be considered; however, often the restrictive cardiomyopathy is part of a systemic illness (281). Signs or symptoms of ischemia in children with restrictive cardiomyopathy predict sudden death and should be managed aggressively with beta-blockers, an implantable defibrillator, or consideration for transplantation (282).

Primary Restrictive Cardiomyopathy

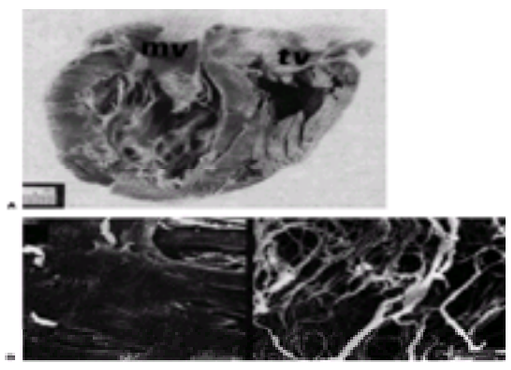
Idiopathic Restrictive Cardiomyopathy

Idiopathic restrictive cardiomyopathy is a disease in patients with diastolic heart failure that is often characterized by familial transmission and the association with skeletal myopathies (259,283,284). It was first described by Benotti et al. (285), who described nine patients with heart failure, with elevated RV and LV filling pressures with normal systolic function and dip and plateau hemodynamic tracing.

Other investigators have described similar findings using strict hemodynamic criteria (270,286,287,288 and 289). Some series have excluded patients with hypertrophy, and others have not shown the dip and plateau pattern in all patients (271,284). Thus, there is a lack of consensus on the type of diastolic filling pattern and the degree of LV hypertrophy in this disease (259).

Anatomic Considerations

The diagnosis of this disease is confirmed by the lack of any specific pathology on endomyocardial biopsies or autopsy specimens. The atria are disproportionately large with normal or near-normal ventricular cavity size (eFig. 26.4.1A). The left ventricle shows normal systolic function and there may be hypertrophy of the left or right ventricles (259). Thrombi may be present in the atrial appendages (261). Histologic examination is unremarkable or shows nonspecific degenerative changes seen in other cardiomyopathies, including myocyte hypertrophy, interstitial fibrosis, and nuclear changes (259) (eFig. 26.4.1B). Some series have reported myofibrillar disarray, increased fibrosis, and some hypertrophy of myocytes (270,286,287,288 and 289). Fibrosis may occur in the sinoatrial and atrioventricular nodes (283).



***e*FIGURE 26.4.1 A:** Gross pathology specimen removed at transplantation, fixed in physiologic shape, of nondilated, nonhypertrophic heart with hemodynamics typical of idiopathic restrictive cardiomyopathy. mv, mitral valve; tv, tricuspid valve. (From Keren A, Popp RL. Assignment of patients into classification of cardiomyopathies. *Circulation* 1992;86:1626, with permission.) **B:** Scanning electron micrographs of the myocytes (*left*) and the interstitial collagen fibrils (*right*) in a patient with idiopathic restrictive cardiomyopathy. Note that there is a thick collagen fiber network, which results in the hemodynamics of restriction. (From Hirota Y. Restrictive cardiomyopathy, cardiac amyloidosis and hypereosinophilic heart disease. In: Abelman WH, Braunwald E, eds. *Cardiomyopathies, myocarditis and pericardial disease. Atlas of heart diseases*. Vol 2. Philadelphia: Current Medicine, 1995, with permission.)

Pathophysiology

The classic hemodynamic filling pattern is the dip and plateau pattern (285). The pathogenesis of the stiff ventricle may be secondary to myocyte abnormalities including abnormal calcium handling, accumulation of desmin, which is a cytoskeletal component, and myofiber disarray, as well as abnormalities of the extracellular matrix including proliferation of collagen fibers and elastic elements (273). As mentioned, it is believed that a restrictive filling pattern should not be an absolute requirement for the diagnosis. However, there must be abnormalities of diastolic filling, whether restrictive or abnormal relaxation on Doppler echocardiography or abnormal filling pressures on cardiac catheterization (259,290).

Clinical Presentation

Idiopathic restrictive cardiomyopathy is usually a sporadic disease, but it can occur in families with autosomal dominant transmission. There may be a family history, the presence of a distal skeletal myopathy, and heart block in this condition, which has been reported in five generations of an Italian family (261,283,284). Another restrictive cardiomyopathy with autosomal dominance with variable penetrance is associated with Noonan's syndrome (291).

There may be differences in idiopathic restrictive cardiomyopathy in children compared with adults. In children, the disease may be more common in girls (292,293), and children may have a worse prognosis with the disease than adults (292,293).

Diagnosis

Cardiac catheterization, echocardiography, or both, and endomyocardial biopsy should be done to make the diagnosis. Atrial enlargement with nondilated ventricles with near-normal systolic function is uniformly present on echocardiography. In one series, the ejection fraction ranged from 40% to 55% in patients with advanced disease needing heart transplantation (294). Variable degrees of hypertrophy may be present (259,286,288,289). Cardiac catheterization and Doppler echocardiography may show restrictive hemodynamics; however, other patterns may be present as well (259). Biopsy is important to exclude other diseases and to assess myocyte hypertrophy and interstitial fibrosis (259).

Differentiation between Restrictive Cardiomyopathy and Constrictive Pericarditis

It is important to differentiate idiopathic restrictive cardiomyopathy from secondary forms such as cardiac amyloidosis, as well as constrictive pericarditis, because of different treatment regimens and prognosis (259). As a result of the rapid early ventricular filling, a prominent 'y' descent is often seen in the jugular venous pulse and the RA pressure tracing. Left atrial pressure is usually greater than 15 mm Hg, right atrial pressure is greater than 7 mm Hg, and the pulmonary wedge pressure is greater than 12 mm Hg (295,296 and 297). LV end diastolic pressure is usually 5 mm Hg higher than the right-sided pressures (259), although the absence of this difference does not suggest constriction (298). Moderate pulmonary hypertension is usually present in advanced restrictive disease (274,299). In restrictive cardiomyopathy, the RV end diastolic pressure is often less than one-third of the peak RV systolic pressure (274,299). In early stage restrictive disease or with marked diuresis, these characteristic changes may only be unmasked by intravenous fluid challenge, exercise, or pharmacologic interventions (297,300). A comparison of hemodynamic abnormalities in restrictive and constrictive disease is shown in Table 26.3. The hemodynamic findings show much overlap in distinguishing these two similar conditions (13,301).

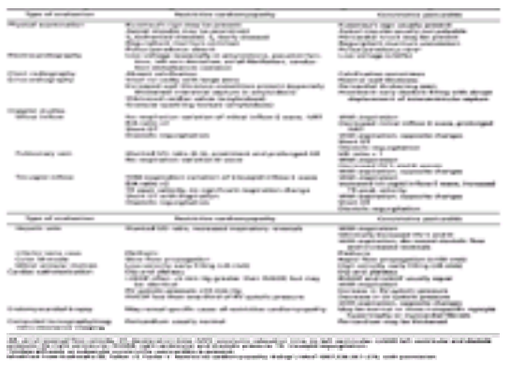


TABLE 26.3 DIFFERENTIAL DIAGNOSIS OF RESTRICTIVE CARDIOMYOPATHY AND CONSTRICTIVE PERICARDITIS

Management

Most small series show a protracted clinical course in adults, with a mean survival of 4 to 14 years (mean, 9 years) (285,288). Patients have symptoms of congestive heart failure, elevated jugular veins, and mitral and tricuspid regurgitation (288). Progressive heart failure that responds poorly to medical management and complete heart block requiring a pacemaker may occur (283,288). In one series, the mean follow-up time to transplantation or death was 117 months compared with 44 months for cardiac amyloidosis (284). In a large series of 94 patients with echocardiographically defined idiopathic restrictive cardiomyopathy, predictors of poor prognosis included advanced age, male gender, left atrial enlargement, and advanced functional class (302). The 5-year survival rate for this group was 64%. Heart transplantation can be considered in patients with idiopathic restrictive cardiomyopathy (284).

Endomyocardial Disease

There are two forms of the hypereosinophilic syndrome: endomyocardial fibrosis and Löffler's endocarditis (303). Endomyocardial fibrosis (Davies' disease) is a disease endemic to equatorial countries (Uganda, Nigeria, and Brazil) with rare appearance in nontropical countries (274,304). In contrast, Löffler's endocarditis is a disease of temperate countries, but occurs sporadically across the world (305). The common theme to this disease is an abnormal eosinophilia in the blood and the endocardium causing a restrictive (obliterative) cardiomyopathy, with endocardial fibrotic thickening at the apex and subvalvular regions causing impairment of ventricular inflow (303,306).

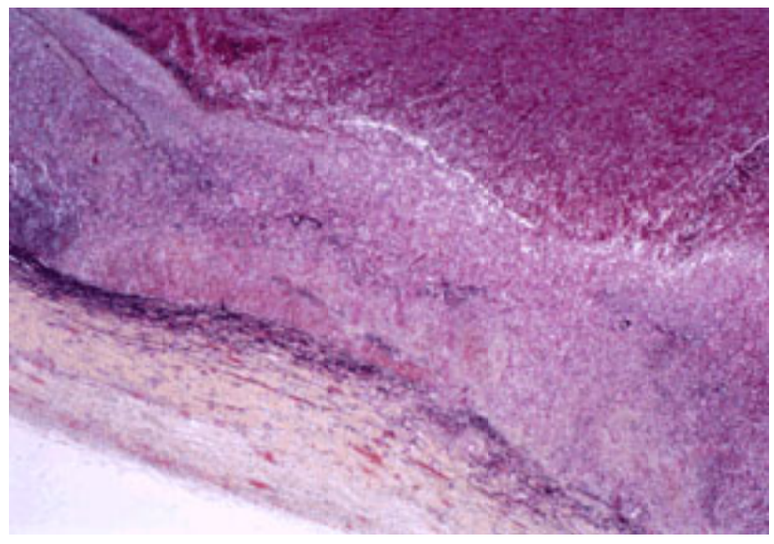
It has generally been thought that the two conditions are different forms of the same disease that result from tissue damage from the toxic effect of eosinophils and result in identical pathologic findings in advanced disease (303,307). However, despite the similarities of the two conditions, there are important differences. Eosinophilia is present in Löffler's endocarditis (308). In contrast, endomyocardial fibrosis affects younger patients without regard for gender and has no significant eosinophilia (303,308).

The eosinophil in these disorders is an abnormal cell, with fewer granules than normal (309). The abnormal eosinophil is thought to be cardiotoxic with the release of toxic substances from the granules (310) producing the necrotic reaction, followed by thrombosis and then fibrosis (303).

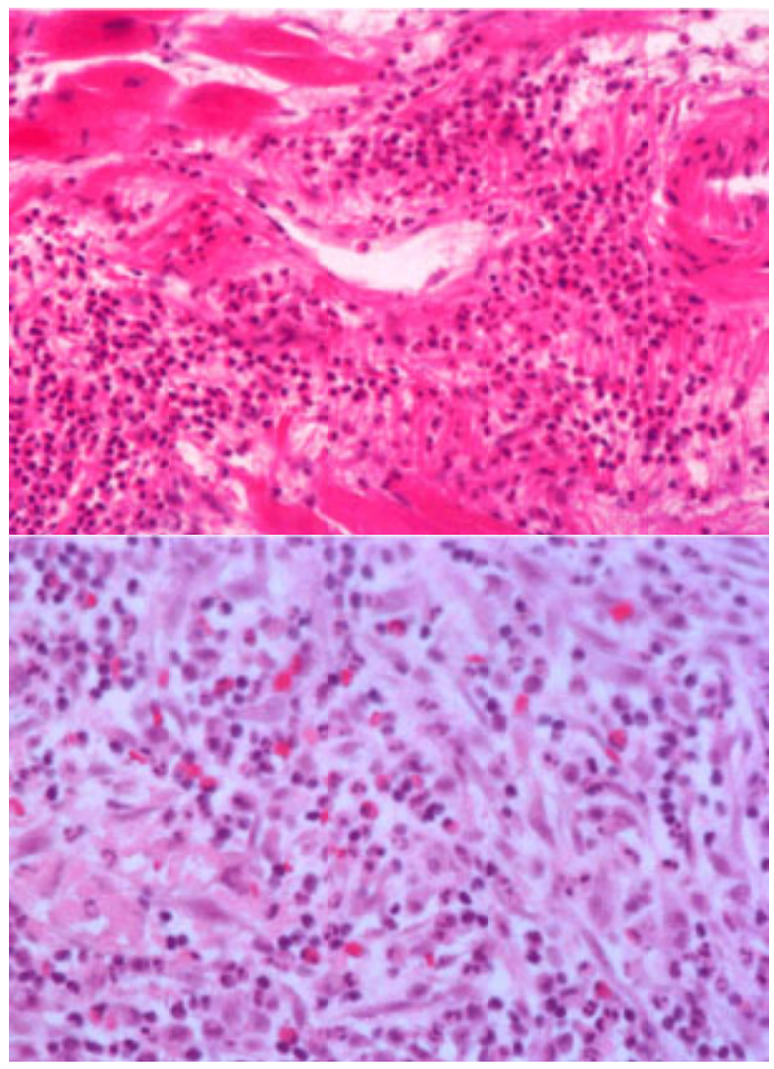
Löffler's Endocarditis

Löffler's endocarditis is considered to be part of the idiopathic hypereosinophilic syndrome that is characterized by a persistently elevated blood eosinophil count

without recognizable cause, despite a careful workup with signs and symptoms of organ involvement, especially in the heart, nervous system, and bone marrow (274,311,312). Cardiac involvement occurs in more than 75% of the cases of the syndrome (303).

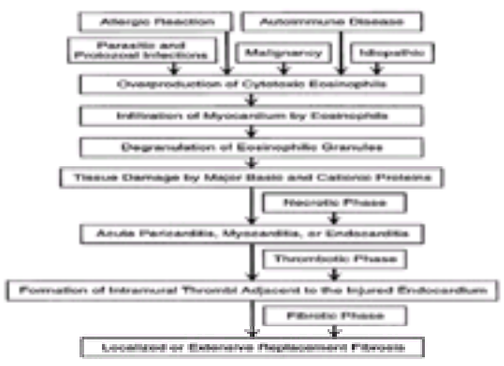


Löffler's syndrome. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



A case of Löffler's syndrome demonstrating extensive infiltration of the myocardium by eosinophils (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

The etiology of the eosinophilia is unknown, but may be related to parasitic and protozoal infections, malignancy (leukemia), or allergic or autoimmune reactions (313,314). For example, the eosinophilia-myalgia syndrome is associated with eosinophilia and restrictive cardiomyopathy, supporting the role of the eosinophil in the pathogenesis of this disorder (315). The pathogenesis resulting from the toxic eosinophil is shown in eFigure 26.4.2.



***e*FIGURE 26.4.2** Pathogenesis of Löffler's syndrome showing the effect of tissue damage from the cytotoxic eosinophil resulting in a necrotic, thrombotic, and fibrotic phase. (From Hirota Y. Restrictive cardiomyopathy, cardiac amyloidosis and hypereosinophilic heart disease. In: Abelman WH, Braunwald E, eds. *Cardiomyopathies, myocarditis and pericardial disease. Atlas of heart diseases.* Vol 2. Philadelphia: Current Medicine, 1995;5.3–5.15, with permission.)

Pathology

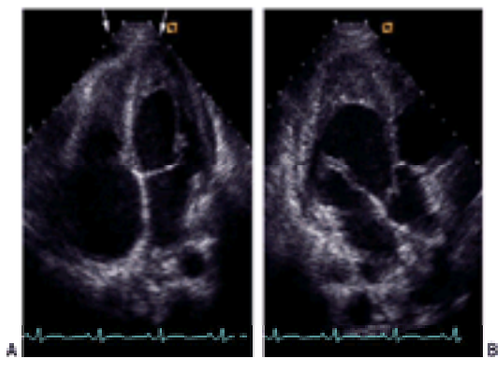
Cardiac involvement includes biventricular endocardial thickening of the inflow portion and the apex of both ventricles (316). The stages of the disease include necrotic, thrombotic, and fibrotic phases (273,316): (a) acute eosinophilic myocarditis involving the myocardium and endocardium with necrosis; (b) thrombosis overlying the endocardium, which is infiltrated with eosinophils; and (c) endocardial thickening with collagen fibrils and chronic inflammation and fibrosis of several millimeters (312) (eFig. 26.4.2).

Clinical Manifestations

The typical presentation is a man less than 50 years of age who lives in a temperate climate and has the hypereosinophilic syndrome (274,305). Right- and left-sided congestive heart failure, mitral regurgitation, systemic embolism, cardiac enlargement on the chest radiography, and T-wave inversions on the electrocardiogram are the main clinical manifestations of this disorder, which depends on the stage of disease (264,317).

Echocardiography commonly demonstrates mural thrombosis (eFig. 26.4.3). There may be obliteration of the apex and immobility of the posterior leaflet of the mitral

valve with entrapment against the thickened posterobasal endocardium, thus resulting in mitral regurgitation (264,318). These findings were described in a review of 29 patients with classic echocardiographic features of the hypereosinophilic syndrome (319). LV systolic function is often preserved, and restrictive physiology may be demonstrated by Doppler echocardiography, usually in the fibrotic phase (320).



***e*FIGURE 26.4.3** Transthoracic echocardiogram in a patient with endomyocardial fibrosis. **A:** Apical four-chamber view. **B:** Apical long-axis view. There is obliteration of the left and right ventricular apices with thrombosis and fibrosis (*arrows*), which is typical of endomyocardial fibrosis. Note also the marked right atrial enlargement. [From Thamilarasan M, Klein AL. Restrictive cardiomyopathy: diagnosis and prognostic implications. In: Otto CM, ed. *The practice of clinical echocardiography: transthoracic and transesophageal imaging*, 2nd ed. Philadelphia: WB Saunders (in press), with permission.]

Cardiac catheterization typically shows the dip and plateau physiology with reduced LV compliance because of the dense scarring of the ventricle, and mitral and tricuspid regurgitation may be present as well (303,312). Endomyocardial biopsy may be necessary to confirm the diagnosis; however, it may be difficult to obtain an adequate tissue sample (312).

Management

The treatment options depend on the stage of the disease; early Löffler's disease is treated medically with corticosteroids, whereas surgery is reserved for the fibrotic stages. Corticosteroids and hydroxyurea may be used to treat the myocarditis when associated with the hypereosinophilia (312,313,321). Also, interferon has been used in a limited number of patients with promising results (314,322). Standard supportive medical therapy should include digoxin, diuretics, afterload reducers, and anticoagulants (303,312). Surgical treatment involves debriding the fibrous plaque from the endocardial surface and replacement of the valves and pacemaker insertion (305,312,313).

Endomyocardial Fibrosis

Endomyocardial fibrosis is endemic to tropical and subtropical Africa and occurs less frequently in South America and Asia (300,323,324). It is a common cause of congestive heart failure and death in equatorial Africa, accounting for 15% to 25% of the deaths secondary to heart disease (274,305). Endomyocardial fibrosis involves both ventricles in 50% of the cases, followed by involvement of the left ventricle in 40% and right ventricle in 10% of the cases (274,307).

Endomyocardial fibrosis occurs in three distinct areas: the LV apex, subvalvular apparatus, and the RV apex (274,325). The fibrosis at the ventricular apex extends to the lower ventricular septum and to the posteromedial papillary muscle. The fibrosis also extends in the area behind the posterior mitral valve, causing tethering of the chordae tendineae and resulting in mitral regurgitation. The anterior leaflet of the mitral valve and the outflow tract is often spared. It also may involve the RV apex, causing impairment of filling of the tricuspid inflow and encasement of the papillary muscles of the tricuspid valve and resulting in tricuspid regurgitation (307,319).

A classification scheme according to the location of fibrosis was proposed by Shaper et al. (326). Usually, the right ventricle is obliterated more than the left ventricle (307). Microscopically, there is a thick layer of collagen tissue over a layer of connective tissue in the endocardium, with granulation tissue extending into the myocardium (327).

Clinical Profile

The clinical presentation in the endomyocardial fibrosis depends on whether the left, right, or both ventricles are involved. The disease affects both male and female subjects, usually children and young adults (308). Left-sided disease results in pulmonary congestion, whereas right-sided disease results in right-sided heart failure simulating constrictive pericarditis. Often, mitral and tricuspid regurgitation is present because of the involvement of the valves. Atrial fibrillation is not uncommon, occurring in one-fourth of patients with endomyocardial fibrosis, especially when there is RV involvement. Embolism is a frequent finding with endomyocardial fibrosis. A pericardial and pleural effusion may also be present (274,305,324).

Two-dimensional echocardiography shows the obliteration of the apices of the ventricles and dilated atria, whereas Doppler echocardiography shows evidence of mitral and tricuspid regurgitation. The posterior leaflet shows decreased mobility in left-sided disease (274,305). The basal ventricle may be hypercontractile due to the obliterated apex (328). Cardiac catheterization and Doppler echocardiography may show the restrictive hemodynamics of the disease.

Management

The prognosis is poor in endomyocardial fibrosis, with progressive disease and death caused by heart failure, or sudden death (274,305,326). The 2-year mortality is between 35% and 50% in patients with advanced disease (308,329). Surgery may improve symptoms in the fibrotic stage with excision of the fibrous endocardium and repair or replacement of the mitral and tricuspid valves (314,330,331); operative mortality has been reported in the range of 15% to 25% (332,333). However, one study of 11 patients undergoing surgery with endocardial resection and valve replacement reported a 10-year survival of near 70% (334).

Secondary Restrictive Myocardial Diseases

Infiltrative Conditions

Interstitial Diseases

Cardiac Amyloidosis. Cardiac amyloidosis is the prototype of restrictive myocardial diseases and the most frequently encountered in clinical practice (51).

Etiology and Classification of Amyloidosis. Amyloidosis is a multisystem disease in which linear, nonbranching, aggregated fibrils with a cross-beta pleated configuration are deposited in various organs of the body including the heart (335,336). The fibrils deposit between cells (interstitial) with a replacement of the normal tissue structures. Amyloidosis can be classified by the type of protein deposited. The primary type is the most common one, occurring in 85% of cases with amyloid, with fibrils composed of kappa or lambda immunoglobulin light chains (AL type), often associated with multiple myeloma. Recent work has suggested that circulating light chains from patients with amyloidosis (AL type) may directly cause diastolic dysfunction independent of extracellular fibril deposition (336a). There may be extracellular deposition of amyloid protein in the kidney, heart, liver, nerve, skin, and tongue resulting in tissue damage and organ malfunction (337). The most common manifestations include nephrotic syndrome or renal failure, congestive heart failure, sensorimotor peripheral neuropathy, and orthostatic hypotension. Most of the following discussion focuses on cardiac amyloidosis (AL type).

Secondary amyloidosis (AA type) is rare, with the fibrils consisting of protein A, a nonimmunoglobulin (336,338). Familial amyloidosis results from the production of a mutant prealbumin protein (transthyretin; TTR) (339), and there are six different types that present with a cardiomyopathy, neuropathy, or nephropathy. More than 50 mutations of this TTR protein have been described (340,341). This type of amyloid is important to recognize because liver transplantation may be life-saving. Senile systemic amyloidosis results in the elderly from the production of a normal TTR protein or atrial natriuretic-like protein and has become increasingly common as the population ages (335).

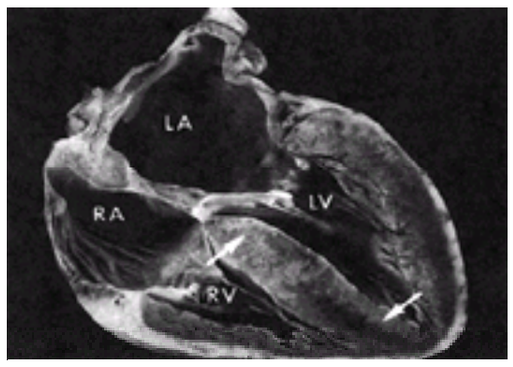
The heart is commonly involved in primary amyloidosis (AL type) (335). One-third of patients manifest cardiac involvement and one-fourth have congestive heart

failure; however, the heart is involved in most patients by pathologic examination (342). Death from cardiac involvement secondary to congestive heart failure or arrhythmia occurs in greater than 50% of patients with systemic amyloidosis (335). Cardiac involvement is unusual in secondary amyloidosis, with the renal manifestations being more predominant (338).

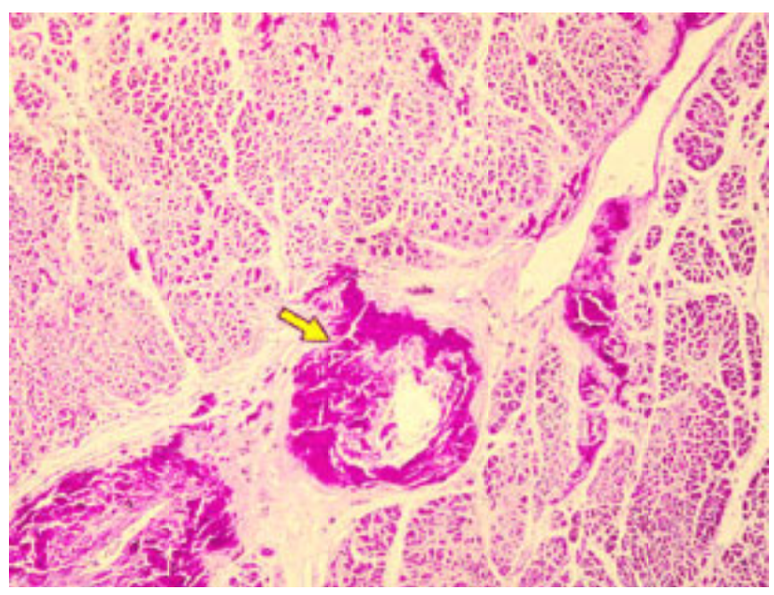
In familial amyloidosis, cardiac involvement occurs in 28% of patients at the time of diagnosis; however, it usually presents late in the course of the disease (339). Peripheral neuropathy and renal failure are the usual presenting features; however, cardiac features may predominate (343). It was reported over 30 years ago from a Danish family (344) but has been described in a family from Appalachia (345) and, more recently, in an Italian family (343). Cardiac failure or cardiac arrhythmia is responsible for the deaths in over 50% of patients (339). Familial amyloidosis has been reported in elderly blacks in the United States as a cause of heart failure secondary to a mutation in TTR isoleucine (122,346,347).

Senile cardiac amyloidosis may have extensive deposits in the heart producing congestive heart failure or may have minor deposits in the atria with no symptoms (335). It is important to differentiate senile cardiac amyloidosis from nonsecretory immunoglobulin-derived amyloidosis (AL type) and familial amyloidosis because of different treatment regimens (335,348).

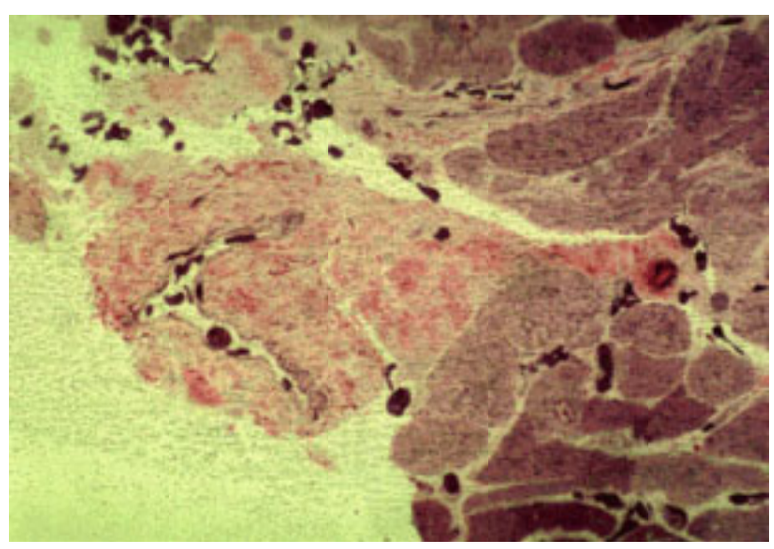
Pathology. Pathologic examination shows focal and diffuse deposits, microscopic and macroscopic interstitial deposits of amyloid in the myocardium, endocardium, and pericardium (51,265,266) (eFig. 26.4.4). The amyloid protein can be seen histologically between myocytes, particularly in the papillary muscles (349). Endocardial involvement occurs frequently in the ventricles and the atria (171), and the valves may also show focal thickening. The coronary arteries and veins may have interstitial deposits of amyloid protein in the media and adventitia, which may occlude the lumen of these vessels (343,350). Macroscopically, in advanced cases, the heart has a firm, rubbery consistency and is mildly to moderately enlarged with enlarged atria and thickened myocardium, interatrial septum, and valves (51).



***e*FIGURE 26.4.4** Gross necropsy specimen showing diffuse amyloid infiltration in a four-chamber view of 67-year-old woman's heart with diffuse amyloid infiltration. Note the pale transmural and subendocardial areas (*arrows*) indicating amyloid infiltration in the ventricular septum, left ventricular (LV) free wall, and apex. Note enlarged atria. LA, left atrium, RA, right atrium; RV, right ventricle. (From Click RL, Olson LJ, Edwards WD, et al. Echocardiography and systemic diseases. *J Am Soc Echocardiogr* 1994;7:201–216, with permission.)

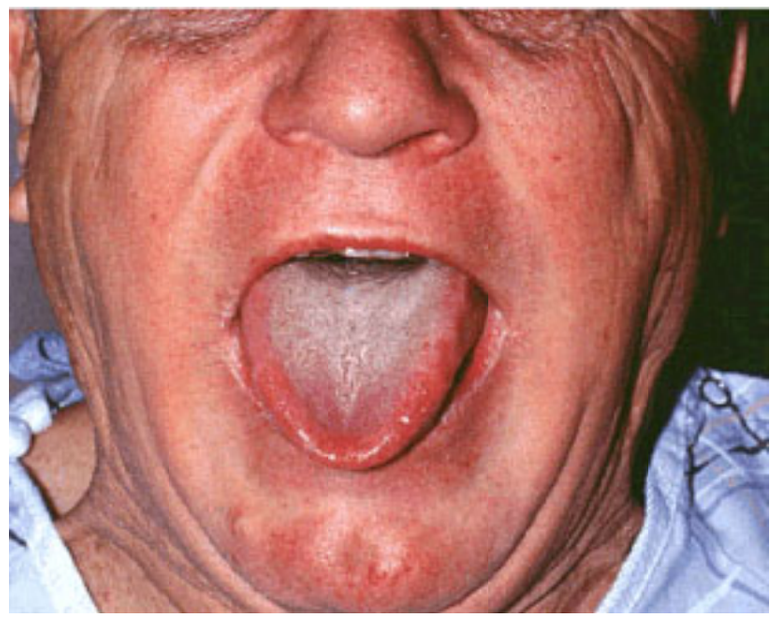


Amyloidosis of the heart. This is cresyl violet stain of the left ventricular myocardium. The yellow arrow indicates a metachromatic red-violet homogenous deposit around an intramyocardial arteriole with similar interstitial deposits.



Amyloid deposition. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

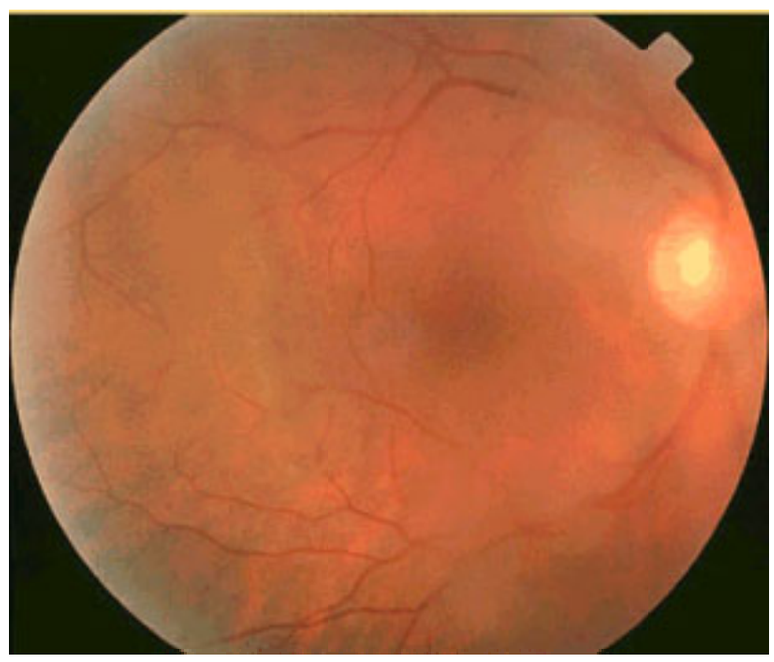
Clinical Presentation. Cardiac amyloidosis usually presents in men over 30 years of age (336,342) and occurs in older patients in the familial form (339). Patients with cardiac amyloidosis present with diastolic heart failure and the "stiff heart syndrome" resulting from amyloid infiltration. Patients may present with various degrees of progressive biventricular heart failure depending on the stage of disease as shown by two-dimensional and Doppler echocardiography (275). In early cardiac amyloidosis, patients may be asymptomatic, whereas patients with advanced disease have the typical evidence of restrictive cardiomyopathy with severe right-sided heart failure, ascites, and peripheral edema (305). During cardiac catheterization a square-root sign is present, and restrictive hemodynamics by Doppler echocardiography are detected only in the advanced stages of the disease (275). In addition, there may be an intermediate stage in which patients have more symptoms as left atrial pressure increases. Individual patients may actually evolve through the different stages of involvement (100). Often, it may be difficult to differentiate advanced cardiac amyloidosis from constrictive pericarditis (101,123). As the disease progresses, there are both systolic and diastolic heart failure (351). Chest pain resembling angina pectoris may also be present despite normal epicardial coronary arteries during cardiac catheterization (350), or there may be partial obliteration of the distal coronary arteries by amyloid infiltration (266,343,352). Involvement of the intramyocardial vessels may be an another explanation for this presentation (325,353). In 10% to 15% of cases, orthostatic hypotension is detected in patients with cardiac amyloidosis. This is secondary to amyloid infiltration of the autonomic nervous system with symptoms of syncope, diarrhea, lack of sweating, and impotence (337). Kidney, adrenal, and cardiac involvement with amyloid deposition may aggravate the postural hypotension. Refractory supraventricular and ventricular arrhythmias or conduction defects may also be another mode of presentation (354). Sudden death secondary to arrhythmias may also be the cause of death, especially in familial amyloidosis (339).



Amyloidosis. Infiltration of the tongue occasionally leads to macroglossia. Cardiac manifestations include cardiomegaly, congestive heart failure, and arrhythmias.

Amyloidosis. Infiltration of the skin results in raised waxy papules or plaques that are usually in clusters.

Physical examination may reveal an S_4 (early disease) or S_3 (advanced disease) on auscultation, depending on the stage of the illness (275). Mitral and tricuspid valvular regurgitation may also be present (51). There is evidence of biventricular heart failure with often predominant right-sided heart failure (305), an elevated jugular venous pulse with a prominent 'y' descent, hepatosplenomegaly, ascites, and peripheral edema, especially in advanced disease. The blood pressure may also be decreased.



Vitreous opacities in association with amyloidosis.

The cardiac silhouette on chest radiography is usually enlarged in patients with advanced disease with evidence of pulmonary congestion (297). Electrocardiography typically is of low voltage and shows a pseudoinfarction pattern with Q waves simulating a myocardial infarction in the precordial leads (325,355). Arrhythmias especially atrial fibrillation are common (30% of patients) and a sick sinus syndrome may be present (325).

Atrioventricular conduction defects may be present, especially in familial amyloidosis associated with polyneuropathy (339). Also, ventricular arrhythmias consisting of ventricular tachycardia may be present in advanced disease and may be a forewarning of death (343).

A 68-year-old male patient with amyloidosis.

Investigations: Echocardiography. Two-dimensional and Doppler echocardiography is the procedure of choice in the noninvasive diagnosis, serial follow-up, and prognosis of patients with cardiac amyloidosis (51,100,103,180,275,351,356). Cardiac amyloidosis gives a distinctive appearance on two-dimensional echocardiography and is associated with abnormal LV and RV diastolic function. The findings of a normal or small LV cavity size with markedly thickened myocardium

associated with a highly abnormal texture that is often described as “granular sparkling” in appearance is the classic presentation (51) (Fig. 26.5).

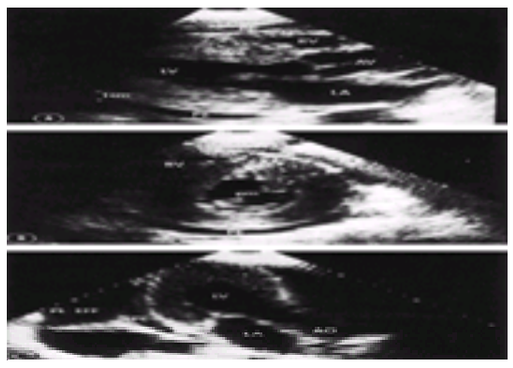


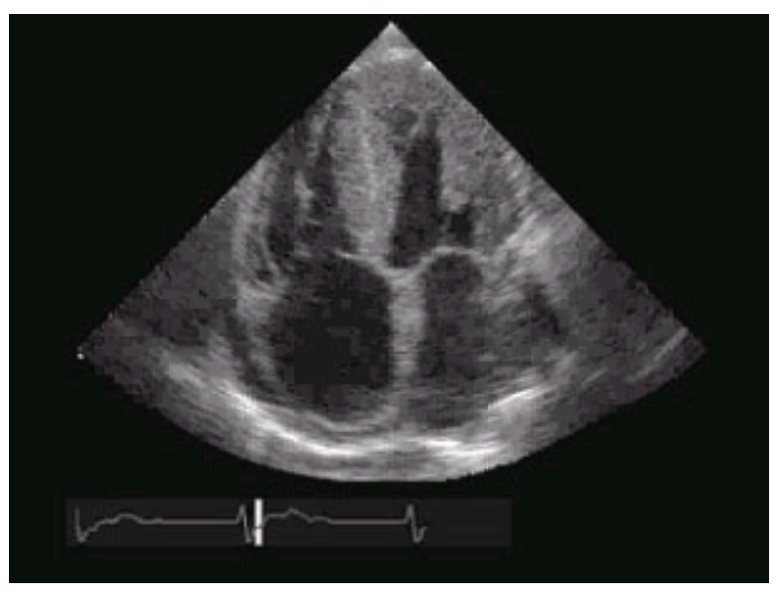
FIGURE 26.5 Parasternal long-axis **(A)**, short-axis **(B)**, and apical long-axis **(C)** views show typical echocardiographic features of advanced cardiac amyloidosis. Note left ventricle (LV) size is normal with markedly thickened ventricular walls [ventricular septum, 22 mm; posterior wall, 18 mm; and right ventricular (RV) free wall, 15 mm] and its characteristic granular sparkling appearance. Small pericardial effusion (PE) and left pleural effusion (PL EFF) are also present. AO, aorta; AV, aortic valve; LA, left atrium; pm, papillary muscle; VS, ventricular septum. (From Klein AL, Oh JK, Miller FA, et al. Two-dimensional and Doppler echocardiographic assessment of infiltrative cardiomyopathy. *J Am Soc Echocardiogr* 1988;1:48–59, with permission.)

VIDEO

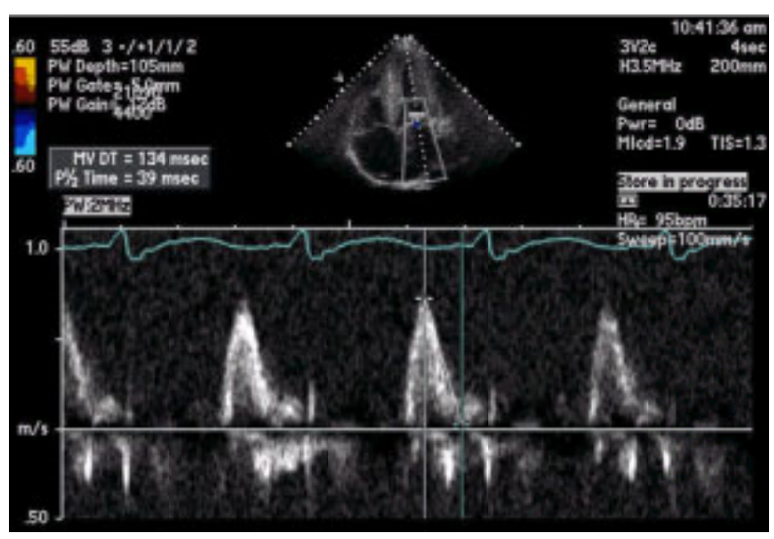
Video 26.1 Transthoracic apical four-chamber view of a patient with amyloidosis. Note the thickened “sparkling” walls of the right and left ventricles. Both the mitral and tricuspid valves are mildly thickened, and there is biatrial enlargement and a trivial pericardial effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 26.2 Transthoracic subcostal view of a patient with amyloidosis showing markedly thickened right and left ventricular walls, showing the characteristic “sparkle.” The right ventricle is towards the top of the screen, and the right ventricle free wall is 1.5 cm thick. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Apical four-chamber view of amyloid heart disease. Note the significant thickening of the left ventricle and right ventricle walls due to infiltration. There is also characteristic thickening of the valves and biatrial enlargement. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)



Pulsed wave Doppler of the mitral valve inflow in a patient with amyloidosis demonstrating a short deceleration time (134 ms) consistent with restrictive physiology.

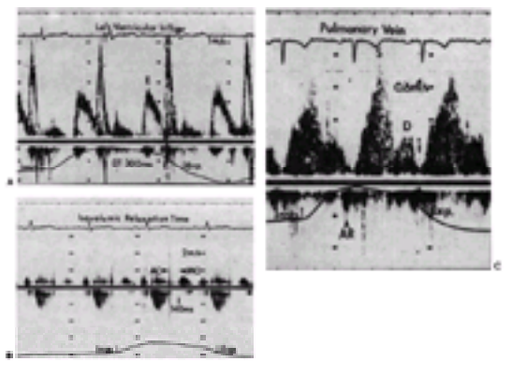
The sparkling granular appearance is thought to be caused by the acoustic mismatch between the highly reflective amyloid deposits in the endocardium, myocardium, and pericardium and the normal tissue (357). Moreover, autopsy and clinical biopsy series have demonstrated the presence of amyloid fibrils in the myocardium at the site of the granular sparkling echoes. Ultrasonic tissue characterization has been used to identify patients with cardiac amyloidosis (358).

Global LV systolic function is usually preserved in early disease, whereas systolic function is usually impaired in advanced disease. The interatrial septum and valve leaflets are also thickened. Both atria are enlarged, and small to moderate pericardial effusions are usually present (351,356).

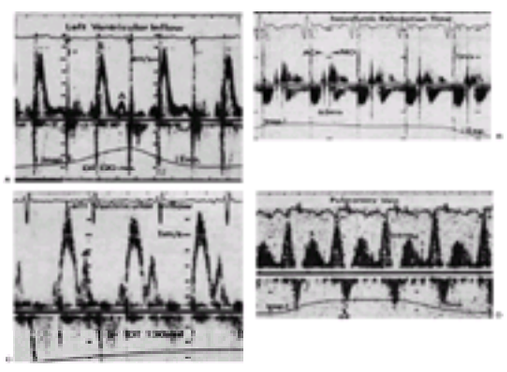
Patients with cardiac amyloidosis have a low ratio of electrocardiographic voltage to LV wall thickness ratio, which is thought to be specific to cardiac amyloidosis and suggested to be predictive of clinical symptoms and prognosis (359,360). However, the usefulness of this ratio is limited by the presence of coexisting diseases that may result in decreased electrocardiographic voltage.

Left Ventricular Diastolic Dysfunction. Cardiac amyloidosis has traditionally been considered to be associated with a restrictive pattern of ventricular filling (361); however, a spectrum of LV filling abnormalities using pulsed wave Doppler echocardiography is detected in patients with cardiac amyloidosis (51,275,361). In a study of

53 patients with the classic echocardiographic features of cardiac amyloidosis (275), patients with a mean LV wall thickness between 12 and 15 mm showed a transmitral flow pattern consistent with abnormal relaxation. The peak E-wave velocity was decreased while the A-wave velocity increased, giving rise to a lower E/A ratio. The isovolumic relaxation time (greater than 86 ms) and deceleration time (greater than 240 ms) were also prolonged. The pulmonary vein flow velocity profile also showed increased peak systolic and decreased diastolic forward filling (275) (eFig. 26.5.1). In contrast, in patients with advanced disease (i.e., a mean LV wall thickness of greater than 15 mm) a “restrictive” physiology pattern of LV filling was observed (275). The mitral E-wave velocity was increased while the A wave decreased with a shortened deceleration time (less than 150 ms) and isovolumic relaxation time (eFig. 26.5.2). The pulmonary vein systolic forward flow velocity was markedly decreased with an increase in the diastolic forward flow velocity. Furthermore, in serial studies of individual patients, patients with the “impaired relaxation” pattern gradually evolved into a restrictive pattern through a pseudonormal or intermediate phase with the progression of the disease (100). The mechanism for this serial change in LV filling pattern is thought to be due to a gradual decrease in the compliance of the left ventricle with progressive deposition of amyloid fibril in the myocardium leading to subsequent loss of myocardial cells from pressure necrosis (362). As compliance decreases, LV end diastolic and left atrial pressure increase. When the duration of the pulmonary venous AR wave is longer than the mitral A-wave duration, filling pressures are elevated and the disease is advanced with restrictive physiology (235).



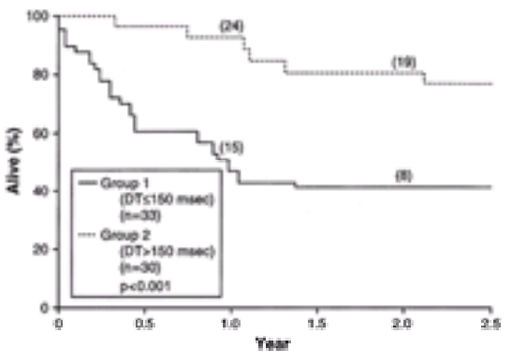
***e*FIGURE 26.5.1 A:** Early case of cardiac amyloidosis associated with impaired relaxation pattern of mitral inflow with a decreased E/A ratio and prolonged deceleration time (DT) of 300 ms. **B:** Continuous wave Doppler recording of the aortic valve and mitral valve flows. The isovolumic relaxation time is markedly prolonged (140 ms). **C:** A relatively normal pulmonary venous Doppler flow pattern with a small atrial reversal wave (AR). AC, aortic valve closure; Exp., expiration; Insp., inspiration; MO, mitral valve opening. (From Klein AL, Hatle LK, Burstow DJ, et al. Doppler characterization of left ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol* 1989;13:1017–1026, with permission.)



***e*FIGURE 26.5.2 A:** Advanced case of amyloidosis associated with a restrictive pattern of mitral inflow with an increased E/A ratio and a shortened deceleration time (DT) of 120 ms. **B:** Shortened isovolumic relaxation time. **C:** An example of an advanced case of amyloidosis with a normal E/A, but a shortened deceleration time. **D:** Note the blunted pulmonary venous systolic (S) flow and increased atrial reversal (AR). AC, aortic valve closure; Exp., expiration; Insp., inspiration; MO, mitral valve opening. (From Klein AL, Hatle LK, Burstow DJ, et al. Doppler characterization of left ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol* 1989;13:1017–1026, with permission.)

Right Ventricular Diastolic Function. Patients with cardiac amyloidosis also have been shown to have abnormalities of RV diastolic function (180). The RV filling pattern is often similar to that of the left ventricle or may be less advanced. In early cases (i.e., patients with RV free wall thickness of less than 7 mm), there is abnormal relaxation. In advanced cases, when the RV wall is greater than or equal to 7 mm in thickness, restrictive physiology is present. The systolic forward flows in the superior vena cava and hepatic vein were also decreased, and the diastolic flow increased compatible with restrictive physiology. Flow reversals were increased compared with normal values and showed further increase with inspiration (180).

Prognostic Stratification. The mean LV wall thickness has been suggested as a useful variable in assessing the degree of cardiac involvement and prognosis (363). In a study of 132 patients with biopsy-proven amyloidosis, patients with a mean wall thickness of 15 mm had a median survival of 0.4 years compared with a median survival of 2.4 years for those with a mean wall thickness of 12 mm. Doppler echocardiography has also been shown to be useful in prognostic stratification of patients with cardiac amyloidosis (103). Patients with a deceleration time of the mitral early filling wave at baseline study of less than or equal to 150 ms had a significantly reduced survival compared with those whose deceleration time was greater than 150 ms (1-year probability of survival 49% vs. 92%, p <.001) (eFig. 26.5.3).



***e*FIGURE 26.5.3** Survival in 63 patients with cardiac amyloidosis subdivided on the basis of the deceleration time (DT) of 150 ms. Patients with a shortened DT of less than or equal to 150 ms (*bold line*) had a significantly reduced survival compared with the patient subgroup having a DT greater than 150 ms. (From Klein AL, Hatle LK, Taliercio CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis. A Doppler echocardiographic study. *Circulation* 1991;83:808–816, with permission.)

Bivariate analysis showed that the combination of shortened deceleration time of less than or equal to 150 ms and an increased mitral E/A ratio were stronger predictors of cardiac death than two-dimensional variables of mean LV wall thickness and fractional shortening. The prognostic significance of a shortened deceleration time can most likely be explained by its association with elevated left atrial and LV diastolic pressures (296).

A new Doppler index (isovolumetric contraction time plus isovolumetric relaxation time/ejection time) combining systolic and diastolic performance for predicting outcome has been described in cardiac amyloidosis (364). RV enlargement has also been identified as an independent predictor of poor outcomes among patients with

primary amyloidosis (365).

Differentiation from Hypertrophic Cardiomyopathy. LV hypertrophy and hypertrophic cardiomyopathy are also associated with an increased myocardial all thickness, and differentiation from cardiac amyloidosis may be important as treatment and prognosis of these conditions are different (366). The presence of low voltage on the electrocardiogram favors a diagnosis of amyloidosis rather than hypertrophic cardiomyopathy; however, endomyocardial biopsy may be necessary in some cases to give a definitive diagnosis because of the grim prognostic implications of a diagnosis of cardiac amyloidosis (366). Consideration should be given to screen patients with serum and urine protein electrophoresis if they have increased wall thickness on echocardiography and unexplained congestive heart failure (336).

Nuclear medicine techniques may also be useful in the diagnosis of cardiac amyloidosis, and these include radionuclide angiography and technetium-99m pyrophosphate scintigraphy and indium-labeled antimyosin antibodies (163,367,368 and 369).

Cardiac amyloidosis can be diagnosed noninvasively antemortem in most cases from the classic appearance on two-dimensional echocardiography, electrocardiography, and an abdominal fat aspirate showing systemic amyloidosis (51,342). However, there has been a report of endomyocardial biopsy-proven AL type amyloid without echocardiographic features (370). Other sites of biopsy can include the rectum, gingiva, bone marrow, kidney, and liver (342). Fat aspirate and bone marrow biopsy may detect amyloidosis in most patients (371). If the echocardiogram is not diagnostic or the fat pad aspirate is negative and cardiac amyloidosis is still suspected, then an endomyocardial biopsy can be performed to make the diagnosis.

Serum and urine protein electrophoresis is recommended to assess for the secretion of a monoclonal protein (335). In 10% of cases, there is no monoclonal protein secreted (nonsecretory primary amyloidosis). For accurate classification of the different type of amyloid, antisera against TTR, the kappa and lambda light chains, and protein A in the biopsy should be performed (335,336).

Magnetic Resonance Imaging. MRI can be used to identify the increased myocardial thickness and small LV cavity in cardiac amyloidosis. It can be used to demonstrate the lack of increased pericardial thickening with the ancillary findings of biatrial enlargement and inferior cava dilatation, similar to echocardiography (372). Usually, the myocardial image has normal MRI properties (T2-weighted images) (373). Myocardial wall thickening due to hypertrophy or amyloid infiltration may be distinguishable (163).

Management. The prognosis of cardiac amyloidosis is uniformly poor but does depend on the type of disease, with AL amyloidosis having the worse prognosis (335,336,338,339,342). In a series of over 800 patents with primary amyloidosis over a 10-year period, the median survival was 2.1 years (374). The treatment for cardiac amyloidosis (AL type) includes alkylating agents, such as melphalan and prednisone (374).

There have been two randomized trials of chemotherapy showing benefit in AL amyloid (341,375,376). A trial of 100 patients with primary amyloidosis using melphalan, prednisone, and colchicine showed improvement of systemic disease when the major features were not cardiac or renal (377). Colchicine has also been used to prevent amyloidosis associated with familial Mediterranean fever (374); however, there is no evidence that it halts the progression of amyloid deposition in primary amyloidosis. Dose-intensive melphalan with blood stem cell support is currently being evaluated (378).

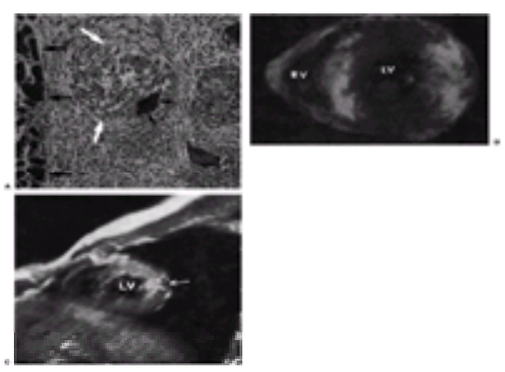
Cardiac transplantation is generally not performed for patients with AL type amyloidosis, because this is a systemic illness with progressive amyloidosis in other organs (281). However, it has been considered in select patients without extracardiac disease (379,380). Liver transplantation has been suggested for the familial type (TTR variant) since the circulating TTR is produced in the liver. Thus, the new liver replaces the variant TTR with a normal TTR. There is no specific treatment for the senile type (381,382).

Avoidance of digoxin is recommended since digoxin-induced arrhythmias may occur because the digoxin may bind to the amyloid fibrils (305,383). However, it has been used to control heart rate in patients with atrial fibrillation with careful monitoring (336). Also, patients with cardiac amyloidosis may be sensitive to the negative inotropic effects of calcium channel blockers either because of their abnormal binding to amyloid fibrils or the vasodilator effects (305,384). Vasodilator agents and diuretics should be used judiciously because of the risk of postural hypotension. Pacemakers may be useful to treat symptomatic high atrioventricular block (385), and anticoagulation should be considered because of the risk of thrombus formation with atrial amyloid involvement and atrial standstill (171,386).

Cardiac Sarcoidosis. Sarcoidosis is a noncaseating granulomatous disorder of unknown etiology that may involve the lung, lymph nodes, skin, liver, spleen, parotid glands, and heart (387,388). Pulmonary manifestations are the predominant finding, with pulmonary hypertension and pulmonary fibrosis resulting in right-sided heart failure (389). Sarcoid granulomata are found in the myocardium at autopsy in up to 25% of the patients with sarcoidosis and are often clinically silent (390,391,392 and 393).

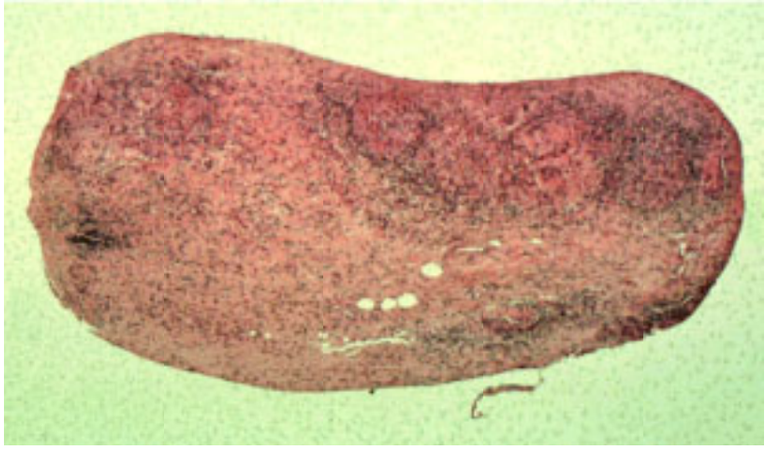
Sarcoidosis. Skin plaques with purple, raised lesions seen in sarcoidosis (*arrows*).

Pathology. Characteristically, the noncaseating granulomata infiltrate the ventricular walls and become fibrotic (393). They are typically found in the LV free wall and the superior interventricular septum, although other areas—including the papillary muscles, atria, conduction system, and pericardium—can also be affected (394,395 and 396). Clinical evidence of heart disease is only seen in approximately 5% of patients with sarcoidosis, whereas 25% have microscopic evidence (390). There may be transmural involvement with portions of the myocardium replaced by scar tissue and secondary aneurysm formation (396) (*e*Fig. 26.5.4A and *e*Fig. 26.5.4B). The interstitial inflammation of the granulomata in the heart may cause initially abnormal diastolic function with preserved systolic function (397). Systolic function becomes impaired with the injury and fibrosis of advanced disease.



***e*FIGURE 26.5.4 A:** Sarcoidosis: histologic section of cardiac biopsy showing noncaseating granuloma (*white arrows*), multinucleated giant cells (*small black arrows*), and normal myocardial border (*large black arrows*). **B:** Sarcoidosis: gross pathologic specimen. White indicates patchy areas of myocardium replaced by sarcoid. (**A**

and **B** from Click RL, Olson LJ, Edwards WD, et al. Echocardiography and systemic diseases. *J Am Soc Echocardiogr* 1994:7:201–216, with permission.) **C:** Cardiac sarcoidosis (spin-echo; short-axis). An area of increased signal intensity (*arrow*) of the free wall of the left ventricle (LV) represents acute inflammation from sarcoid involvement of the myocardium. RV, right ventricle. (Courtesy of R. D. White, MD, The Cleveland Clinic Foundation.)



Endomyocardial biopsy demonstrating multiple granulomas in a case of sarcoidosis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Clinical Manifestations. The clinical presentation of cardiac sarcoidosis is variable and may depend on the amount of myocardium replaced with granulomata and the amount and the location of scar tissue (264,394,396,398,399). Most patients are asymptomatic; however, rhythm abnormalities and conduction disorders may predominate (264,394). The most common arrhythmia is ventricular tachycardia (396,400,401), while complete heart block is the most common conduction disorder (393). Sudden death is the most feared complication (395,402) and occurs in 17% of patients when there is extensive myocardial involvement. Valvular dysfunction and pericardial effusions are less common manifestations in this disease (394,396,398,399).

Patients with congestive heart failure may show clinical features of restrictive cardiomyopathy, dilated cardiomyopathy, or both (393). Patients with marked disease may develop aneurysm formation and papillary dysfunction and mitral regurgitation (393,403). The electrocardiogram may show T-wave abnormalities, atrioventricular (AV) block, or Q waves mimicking myocardial infarction (393,404).

The echocardiographic findings consist of systolic and diastolic ventricular dysfunction, LV aneurysm formation, small to moderate pericardial effusions, and abnormal ventricular wall thickness (51,405,406,407 and 408). Regional wall motion abnormalities (suggestive of coronary artery disease) may be detected in the basal septum with sparing of the apex (409). There may be RV dilatation and increased wall thickness consistent with cor pulmonale (389). LV diastolic function abnormalities may be present in 14% of patients with pulmonary sarcoidosis without evidence of cardiac disease, suggesting subclinical sarcoid cardiomyopathy (410).

Thallium-201 or gallium-67 scanning may show segmental defects suggestive of sarcoid infiltration (411,412,413 and 414). The gallium-67 uptake in the myocardium may be able to predict the efficacy of corticosteroids. MRI may also be useful to identify areas of high intensity in the LV septum and the free wall of the ventricle in the inflammatory phase, while detecting thinning and aneurysm formation in the chronic phase (415). The findings on MRI may be useful in guiding endomyocardial biopsy (416). Endomyocardial biopsy may be useful although the sensitivity is reported to be in the range of 20% to 30% and thus does not exclude the diagnosis if negative (393,404).

Management. The finding of pulmonary involvement with bilateral hilar adenopathy and evidence of myocardial disease may suggest sarcoidosis involving the heart in a young person (393). Echocardiography shows LV dilatation, regional wall motion abnormalities, or aneurysm formation (264,408). Treatment of sarcoidosis may include the use of corticosteroids, especially with myocardial involvement; conduction abnormalities and ventricular arrhythmias are present, however, this remains controversial (404,417,418 and 419). Permanent pacemakers may be needed to treat the conduction abnormalities (392,393). Implantable defibrillators may be needed to prevent sudden death (420,421), whereas heart transplantation is reserved for intractable heart failure (392,420).

Gaucher's Disease Gaucher's disease is a rare disease of ceramide metabolism with a deficiency of the beta-glucosidase enzyme, which causes deposition of the cerebrosides in the myocardium, liver, spleen, bone marrow, lymph nodes, and brain (422). Deposition of the cerebrosides in the myocardium may cause diastolic impairment. The cardiac manifestations may include LV dysfunction, increased LV wall mass, restrictive cardiomyopathy, pericardial effusions, constrictive pericarditis, thickening or calcification of the left-sided valves, and pulmonary hypertension (which may also be due to treatment) (274,423,424 and 425) (*e*Fig. 26.5.5). There has been progress in treating this disorder with aglucerase or the recombinant form of glucocerebrosidase imiglucerase (426).

***e*FIGURE 26.5.5** Patient with Gaucher's disease. An 18-year-old man with a family history of Gaucher's disease who presented with congestive heart failure. Cardiac magnetic resonance imaging revealed severe mitral stenosis and insufficiency, severe aortic stenosis, and relative hypoplasia of the entire thoracic aorta with wall thickening and calcification. (From Cho L, Lytle BW, Moodie DS. Type IIIC Gaucher's Disease. *Circulation* online 2000;102:e69–e70, with permission.)

Hurler's Syndrome Hurler's syndrome is an autosomal recessive disorder of mucopolysaccharide metabolism caused by a deficiency of the enzyme alpha-iduronidase in the lysosomes of the cell. Thus, Hurler cells filled with mucopolysaccharides infiltrate interstitial tissues and cause a rubbery consistency, decreased compliance, and restrictive physiology (274). Clinical manifestations may include coarse facial features, short stature, clouding of the cornea, and cardiac involvement, and survival into adulthood is rare. Cardiac manifestations may include premature coronary disease, mitral and aortic regurgitation and stenosis (427,428), decreased systolic function, and low voltage on the electrocardiogram. Echocardiography reveals thickened right and LV walls, mitral valve leaflets, and decreased systolic function (274,429,430).

Metastatic Malignancies. Metastatic malignant involvement of the myocardium causing an impairment of diastolic filling and a restrictive cardiomyopathy with interstitial deposition is rare. The more common metastatic tumors are leukemia, malignant melanoma, lymphoma, and lung and breast carcinomas (274,431). More commonly, pericardial involvement is seen as a by-product of radiation. Metastatic involvement can be documented with echocardiography, CT scan, and MRI (432).

Storage Diseases

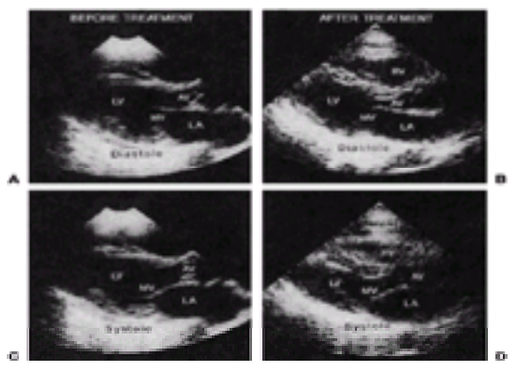
Hemochromatosis. Hemochromatosis is an iron storage disease that affects the heart, pancreas, liver, gonads, and skin (433). Primary idiopathic hemochromatosis is an autosomal recessive disorder related to the human leukocyte antigen on chromosome 6, whereas secondary hemochromatosis results from hemoglobin synthesis abnormalities leading to ineffective erythropoiesis, chronic liver disease, excessive intake of iron, or multiple blood transfusions (433,434).

Pathology. Iron is deposited within the sarcoplasmic reticulum in myocardial cells, especially in the subepicardium, subendocardium, papillary muscles, conduction system, and less commonly in the myocardium and the atria (435) (*e*Fig. 26.5.6). On gross examination, the "iron heart" is usually dilated, with normal or

increased wall thickness (435,436). The severity of myocardial involvement is related to the rate of iron deposition in the heart (436).

Clinical Presentation. Manifestations of cardiac involvement occur when there is a large amount of iron deposited over a long time period. One-third of patients manifest cardiac symptoms with evidence of congestive heart failure, supraventricular or ventricular arrhythmias, and conduction defects (433). One-third of patients die from cardiac involvement. A dilated or restrictive cardiomyopathy may be present with evidence of systolic and diastolic dysfunction. Cardiomegaly may be seen on chest radiography. Electrocardiographic findings have included arrhythmias, conduction disorders, and low voltages (51,433).

Echocardiography is a useful noninvasive technique in the assessment of cardiac involvement in primary hemochromatosis, detecting clinically occult heart involvement, following patients serially, and assessing LV function after phlebotomy (437,438 and 439) (eFig. 26.5.6).



***e*FIGURE 26.5.6** Hemochromatosis: Parasternal long-axis echocardiographic images of hemochromatosis before **(A,C)** and after **(B,D)** treatment (5-year period between studies). AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. (From Click RL, Olson LJ, Edwards WD, et al. Echocardiography and systemic diseases. *J Am Soc Echocardiogr* 1994;7:201–216, with permission.)

Olson et al. described 19 patients with primary hemochromatosis and demonstrated that 7 (37%) had chamber dilatation and systolic dysfunction secondary to the hemochromatosis, whereas 12 patients did not (440). Increased ventricular wall thickness and mass may also be observed, although Olson and coworkers suggested that increased ventricular wall thickness is not always present with cardiac hemochromatosis (440). Patterns consistent with dilated or restrictive cardiomyopathy have also been described in patients with primary hemochromatosis (441). Ventricular dysfunction and increased ventricular mass may normalize after successful venesection (441). The presence of systolic dysfunction usually signifies poor prognosis (439). Secondary hemochromatosis manifestations in the heart include increased LV wall thickness and mass, cavity dimension, and left atrial enlargement. Most patients have normal systolic function, and those with the depressed systolic function have the worst prognosis (442).

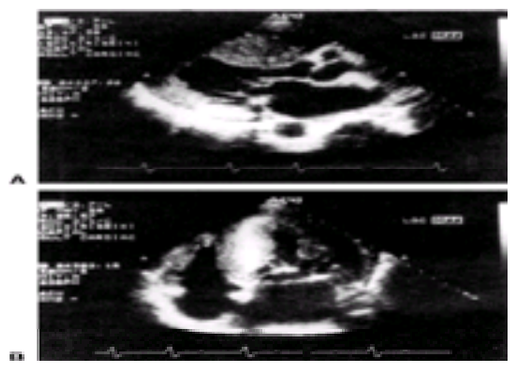
Other noninvasive tests, including CT scan or MRI, may be useful in demonstrating subclinical involvement of hemochromatosis (443). The MRI may show a low myocardial signal on the cine gradient-echo consistent with myocardial iron deposition. Endomyocardial biopsy may be useful to exclude the diagnosis, especially when the echocardiographic or clinical features are not evident (444,445). Laboratory tests show an elevated serum ferritin and increased ratio of plasma iron level to total iron-binding capacity, urinary iron, liver iron, and saturation of transferrin (445).

Management. Treatment by repeat phlebotomies in primary hemochromatosis or the use of chelating agents (desferrioxamine) in secondary hemochromatosis may result in improvement of the cardiac involvement, thus making early diagnosis important (433,446,447). Heart transplantation may be considered when the heart involvement is life-threatening (447) or combined heart and liver transplantation may be useful in patients with heart and liver failure (448).

Glycogen Storage Disease Glycogen storage diseases are autosomal recessive disorders of carbohydrate metabolism in which there is deposition of glycogen in the heart and the skeletal muscle (449). Cardiac involvement can occur in type II glycogenosis (Pompe's disease), but also can occur in type III glycogenosis (Cori's disease) with glycogen debranching enzyme deficiency (450). Detection of the debranching enzyme activity in muscle can be used to predict whether patients will develop cardiac involvement (451). The echocardiogram shows thickened walls and papillary muscles resembling hypertrophic cardiomyopathy, whereas the electrocardiogram demonstrates LV hypertrophy (425,450,452).

Fabry's Disease. Fabry's disease is a rare X-linked recessive disorder of glycolipid metabolism, secondary to a deficiency of the lysosomal enzyme alpha-galactosidase A. This disease severely affects homozygous male subjects with milder symptoms occurring in female subjects (453). Abnormal deposition of glycolipid occurs in the heart, skin, and kidney (454). Histologic examination shows diffuse involvement of the myocardium, conduction system, vascular endothelium, and the mitral valve secondary to deposition in the lysosomes of the affected tissue.

Patients may develop angina and myocardial infarction with normal epicardial coronary vessels, mitral regurgitation, and congestive heart failure and increased wall thickness on echocardiography, mimicking hypertrophic cardiomyopathy and cardiac amyloidosis (eFig. 26.5.7) (454,455 and 456). The electrocardiogram may show atrioventricular block and a short PR interval (457). Studies in adult patients have shown a correlation between age, the degree of alpha-galactosidase activity, and the degree of LV hypertrophy (458). Similarities in the structure of the glycolipid, ceramide trihexoside, and the amyloid fibril may account for their similar appearance (455). MRI may show mildly increased signal intensity in the myocardium (459). Endomyocardial biopsy may show low alpha-galactosidase A levels (274,460,461).



***e*FIGURE 26.5.7** Echocardiographic example of Fabry's disease. A 57-year-old man with exertional dyspnea and renal failure. Parasternal long-axis view **(A)** and apical four-chamber view **(B)** of patient with Fabry's disease. Both views show severe asymmetric increased wall thickness of the interventricular septum due to infiltration of glycosphingolipid. This feature may be indistinguishable from hypertrophic cardiomyopathy by echocardiography. (From Nakayama Y, Tsumura K, Yoshimaru K. Images in cardiology: echocardiographic features of cardiac involvement in Fabry's disease. *Heart* 2000;83:695, with permission.)

Noninfiltrative Diseases

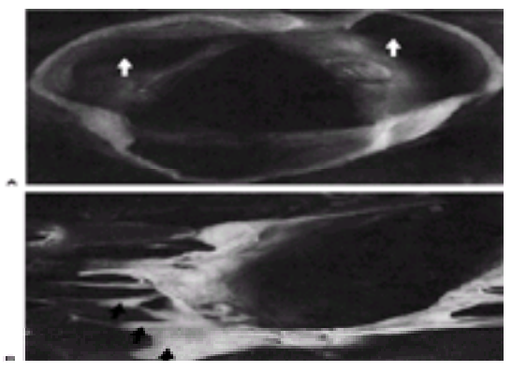
Carcinoid Heart Disease

Carcinoid heart disease is a rare cause of restrictive cardiomyopathy (462,463). Carcinoid syndrome results from metastatic carcinoid tumors that cause cutaneous flushing, diarrhea, bronchoconstriction, and fibrous endocardial plaques in the heart (464,465). Cardiac disease is detected by echocardiography in over 50% of patients with carcinoid syndrome, whereas clinically apparent heart disease with right-sided heart failure is detected in 25% of patients (464,466).

The carcinoid tumors most commonly originate in the small bowel and appendix in over 60% of cases, but they also may arise in the bronchus, biliary tract, pancreas, testis, and ovary (463,464). Carcinoid tumors from the ileum are the ones that metastasize to the liver and lymph nodes. These tumors contain cytoplasmic

granules that take up and reduce silver salts (463). Carcinoid heart disease results from hepatic metastases that produce large amounts of humoral substances that can reach the right side of the heart and are not inactivated by the liver but by the lungs (464). The humoral substances may include 5-hydroxytryptamine, serotonin, bradykinin, and other substances. Rarely, left-sided disease may occur when the humoral substances can cross right to left through a patent foramen ovale or when produced by carcinoid tumor of the bronchus or when there is extensive right-sided involvement (465,467,468,468a).

Pathology. Pathognomonic lesions in carcinoid heart disease are usually right-sided and are composed microscopically of fibrous plaques superimposed on mural and valvular endocardium (*e*Fig. 26.5.8). Histologically, the fibrous plaques are composed of smooth muscle cells that are mixed with mucopolysaccharide and collagen material (469). The fibrous plaques may be related to increased expression of transforming growth factor-b causing stimulation of fibroblasts and their matrix production (470). These white-yellow deposits affect the surface of the tricuspid and pulmonic valves, causing regurgitation and stenosis (471), with resultant RV overload and failure (464). Infiltration into the underlying mural endocardium and myocardium of the right atrium and right ventricle has also been demonstrated. Extensive involvement of the myocardium may result in restrictive physiology (462,463 and 464), whereas involvement of the mitral valve may also cause regurgitation and stenosis (463).



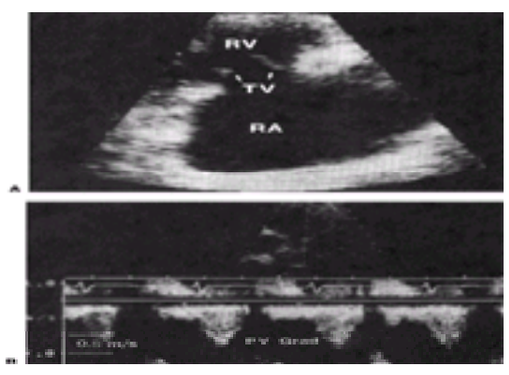
***e*FIGURE 26.5.8** Carcinoid. **A:** Gross pathologic specimen of carcinoid heart disease. Pulmonic valve leaflets are thickened, retracted, and shortened (*arrows*), with a fixed opening. **B:** Tricuspid valve leaflets and chordae are thickened and retracted. (From Click RL, Olson LJ, Edwards WD, et al. Echocardiography and systemic diseases. *J Am Soc Echocardiogr* 1994;7:201–216, with permission.)

Clinical Presentation. Carcinoid heart disease is difficult to diagnose until there is evidence of right-sided heart failure with an elevated jugular venous pulse with a prominent 'v' wave and tricuspid regurgitation (463). A systolic murmur along the left sternal border that shows inspiratory augmentation (tricuspid regurgitation) followed by an early diastolic sound and a diastolic rumble (tricuspid stenosis) may be detected. Also, there may be murmurs of pulmonic stenosis and regurgitation (464). Chest radiography may show cardiac enlargement, pleural effusions, and nodules. The pulmonary trunk is normal in size. The electrocardiogram is nonspecific with evidence of RA enlargement, nonspecific ST- and T-wave abnormalities, and sinus tachycardia (464). The hemodynamic findings are that of significant tricuspid regurgitation with a large RA 'v' wave and diastolic gradient (464).

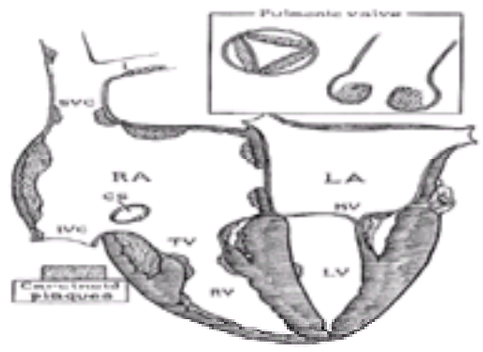
Echocardiography is a sensitive technique to document the combined tricuspid and pulmonic abnormalities and RV overload, as well as to follow the progression and detect subclinical involvement (464,472).

Using echocardiography in one series, right-sided disease was detected in 66% of patients with carcinoid syndrome, and the patients with more severe valvular disease were more associated with higher levels of bradykinins and serotonin (466,473). In another series of 132 patients with carcinoid syndrome, Pellikka et al. found that 56% of patients had cardiac involvement, which was associated with higher levels of 5-hydroxy-indoleacetic acid. The 3-year survival of patients with echocardiographic evidence of carcinoid heart disease was reduced compared with those without cardiac involvement (464). Other studies have shown a correlation between posttreatment 5-hydroxy-indoleacetic acid levels and progression of disease assessed by an echocardiographic score of valvular involvement (474).

The echocardiographic features of cardiac involvement are remarkable (475). The tricuspid valve leaflets are thickened, shortened, and retracted and show incomplete coaptation and decreased excursion, resulting in stenosis and regurgitation. The pulmonic valve also shows thickening, retraction, and commissural fusion and stays open in a partly fixed position, resulting in both stenosis and regurgitation. The predominant lesions seen are tricuspid regurgitation and pulmonary stenosis (476) (*e*Fig. 26.5.9). Carcinoid plaques causing these lesions are usually seen on the ventricular surface of the tricuspid valve and the pulmonary artery surface of the pulmonary valve (476) (*e*Fig. 26.5.10). The Doppler findings show severe tricuspid regurgitation with a distinctive dagger-shaped Doppler spectral profile with an early peak pressure and rapid decline. In addition, the pressure half-time is prolonged, which is consistent with associated tricuspid stenosis (464). Also, there is evidence of RV volume overload from the associated tricuspid regurgitation (264). Transesophageal echocardiography may be useful in assessing the thickness of the valvular leaflets and the superficial wall layers on the cavity side of both atria (472,477).



***e*FIGURE 26.5.9** Carcinoid. **A:** Two-dimensional echocardiogram of right ventricular (RV) inflow tract view. The tricuspid leaflets are thickened, retracted, and rigid (*arrows*). **B:** Mild pulmonic stenosis with a peak gradient (PV Grad) by continuous wave Doppler of 9 mm Hg and mean gradient of 5 mm Hg. RA, right atrium; TV, tricuspid valve. (From Gaos CM, Nasser MM, Wilansky S. Images in cardiovascular medicine. Carcinoid heart disease. *Circulation* 1997;95:1346, with permission.)



***e*FIGURE 26.5.10** Diagram showing the location of carcinoid fibrous plaques in carcinoid heart disease. CS, coronary sinus ostium; I, innominate vein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve. (From Ross EM, Robert WC. The carcinoid syndrome: comparison of 21 necropsy subjects with carcinoid heart disease to 15 necropsy subjects without carcinoid heart disease. *Am J Med* 1985;79:339–354, with permission.)

Management. Carcinoid heart disease can be diagnosed in the presence of the right-sided heart findings with the classic systemic features. There may be urinary excretion of 5-hydroxy-indoleacetic acid, the principal metabolite of serotonin (463,476).

The long-term prognosis is poor, regardless of treatment modality (478). Chemotherapy may be partially effective in treating the hepatic metastasis, while removal of the primary tumor is rarely indicated. Occasionally, the liver metastasis is removed; more commonly, hepatic arterial embolization is performed (463,479). Medical therapy often includes digitalis and diuretics for mild congestive heart failure. The effects of the carcinoid syndrome can be treated with the use of somatostatin analogs, serotonin antagonists, and alpha-adrenergic blockers (463,480,481 and 482).

Interventional and surgical therapy has also been performed for patients with carcinoid valvular heart disease. Balloon valvuloplasty of the tricuspid stenosis and pulmonic stenosis can also be performed (483,484,485 and 486). Tricuspid valve replacement and pulmonary valvotomy is recommended with advanced disease (487,488). Implantation of a biologic valve or allograft is not recommended because of carcinoid developing on the new valve (463,476,489). Surgical mortality for symptomatic patients with severe valve disease is high (490); however, there can be marked improvement in symptoms in survivors (478).

Radiation Heart Disease

Therapeutic radiation for malignancies such as Hodgkin's and non-Hodgkin's lymphoma can cause damage to the pericardium, myocardium, endocardium, and coronary arteries (491,492). Specific risk factors for cardiac involvement include prior chemotherapy, left-sided chest radiation field, and greater than 4,000 rad of exposition (492). Myocardial involvement with interstitial fibrosis, especially in the right ventricle (493), may cause a restrictive cardiomyopathy (494,495) or a mixed picture of pericardial and myocardial disease, which can be documented by echocardiography (119) and MRI (274).

Anthracycline Cardiomyopathy

Anthracyclines, which are used to treat acute leukemias and lymphomas, can cause myocardial toxicity, which is dose related and can be detected by endomyocardial biopsy. Myocardial toxicity usually results in a dilated cardiomyopathy, restrictive cardiomyopathy, or both. Restrictive physiology can be confirmed with echocardiography or cardiac catheterization (496). Fibrous thickening of the endocardium and interstitial fibrosis, loss of myofibrils, and vacuolation of the cytoplasm are the histologic basis for restrictive cardiomyopathy (274,497). Diastolic abnormalities often precede the abnormalities of systolic function in this disease and are unrelated to the dose (496,498). Dobutamine echocardiography, radionuclide angiography, and heart-rate variability analysis have been used to detect subclinical disease in children (499,500,501 and 502). Some data exist that show that antioxidants such as probucol may reduce the toxicity of anthracyclines on the myocardium (503,504).

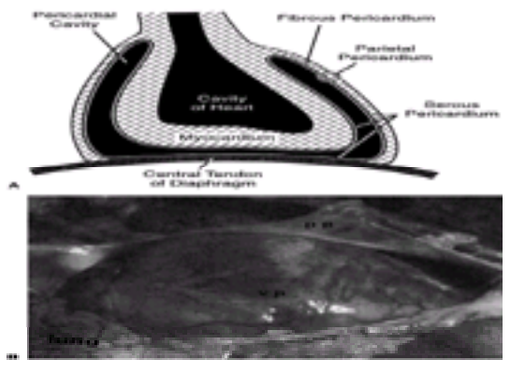
Scleroderma

Scleroderma is a rare cause of restrictive cardiomyopathy resulting from myocardial fibrosis (505). Pericardial involvement and atrioventricular conduction defects are more frequent (see the section Pericardial Disease) (274).

Pericardial Disease

Anatomic Considerations

The pericardium is a closed fibroserous membrane sac in the middle mediastinum, posterior to the sternum and the second to sixth costal cartilages and anterior to the fifth to eighth vertebrae (506). During embryologic development, the heart invaginates the sac, based on a pedicle of the great vessels, cavae, and pulmonary veins. A layer of the serous sac becomes densely adherent to the myocardium, forming the visceral pericardium or epicardium. This layer envelopes the entire heart apart from a bare area on the posterior aspect of the left atrium (eFig. 26.5.11), between the pulmonary veins, the oblique sinus. The visceral layer reflects back on itself and is continuous with the parietal pericardium. This reflection forms a second cleft between the great vessels and the left atrium, the transverse sinus (507).



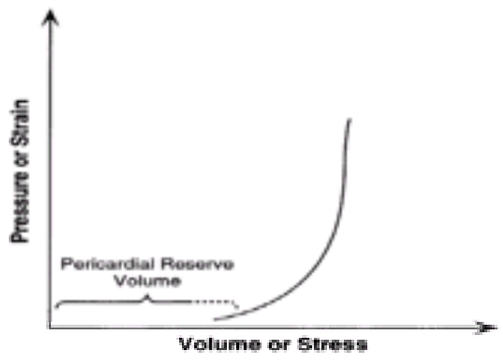
***e*FIGURE 26.5.11 A:** Anatomic structure of the pericardium, a double-walled fibroserous sac that encloses the heart and the great vessels (pulmonary artery and aorta). The pericardium is composed of two layers: an outer layer called *fibrous pericardium* and a double-layered sac called *serous pericardium*. (From Moore KL. *Clinically orientated anatomy*. Baltimore: Williams & Wilkins, 1980, with permission.) **B:** Anatomy of the normal pericardium *in situ* with the sternum and ribs removed. The parietal pericardium (pp) is made of fibrosa lined by mesothelial serosa, which is continuous with the serosa of the visceral pericardium (vp), which lines the pericardial sac. Note the transparent serosa of the visceral pericardium. (From Spodick DH. *The pericardium: a comprehensive textbook*. New York: Marcel Dekker, 1997:8, with permission.)

The parietal pericardium consists of an outer fibrous layer composed of multiple layers of collagen, aligned in different directions, and interspersed with elastin fibrils. This fibrous layer has ligamentous attachments with the central tendon of the diaphragm inferiorly, the sternum anteriorly by the superior and inferior sternopericardial ligaments, and the pleural membranes laterally. The inner layer of the parietal pericardium is a serous mesothelial membrane, with microvilli, to aid fluid secretion (508). The normal pericardium contains approximately 50 mL of pale serous fluid to minimize friction and restrict excessive cardiac motion. The fluid is low in protein, with a relatively high proportion of albumin, consistent with a ransudate.

The pericardium is innervated by branches of C4-5 via the phrenic nerve. This may explain the conscious perception of pericardial pain in the left shoulder tip. Arterial supply to the pericardium is via the internal (thoracic) mammary arteries and multiple branches of the bronchial, esophageal, and phrenic arteries. Venous drainage is via the azygous system.

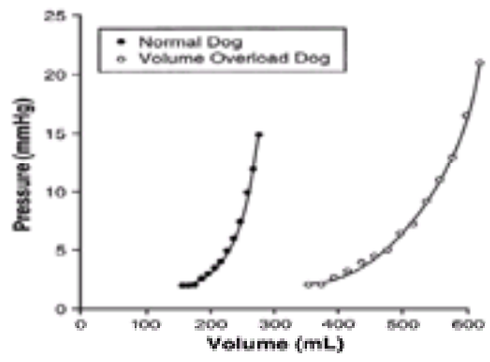
Normal Physiology of Pericardium

The normal pericardium consists of a mesothelial fluid-secreting layer, inside of several layers of collagen fibers, aligned in different directions (509). The mesothelium may secrete large amounts of prostacyclin and other substances that may have a regulatory role in sympathetic neural regulation, cardiac contractility, and coronary vasodilatation (510,511). This directionality of the collagen fibers imparts the interesting physical property called *anisotropia*: differential stress-strain relationships for different directions of applied load (512). For the pericardium as a whole, there is an exponential stress-strain relationship. At normal cardiac volumes, the pericardium is on the flat portion of the curve, and physiologic changes in volume are associated with minimal changes in intrapericardial pressure. However, with abrupt large increases in volume (such as in acute overhydration or valve rupture), the pericardium quickly reaches the exponential portion of the curve and significantly restricts further cardiac dilatation. In this way, it can be argued that the pericardium plays a small role in limiting cardiac filling at normal physiologic volumes and only exerts a constraining effect on filling when abrupt changes in volume occur (eFig. 26.5.12). The pericardial pressure usually approximates pleural pressure and varies with the respiratory cycle being approximately –6 mm Hg at end inspiration and –3 mm Hg at end expiration. The lowering of pericardial pressure more than atrial pressure and transmural pressures in inspiration allows increased filling of the right side of the heart while there is increased aortic transmural pressures and pooling of the RV output and consequently decreased left-sided heart filling (513,514).



***e*FIGURE 26.5.12** Schema of stress-strain and pressure-volume curves of the normal pericardium. After the relatively small pericardial reserve volume is exhausted by filling of the pericardial sinuses and recesses, the curve at first rises gently; with continued filling at some point more acutely, the time scale and exact proportions are variable depending on the rate of filling of the intact pericardial sac. (From Spodick DH. *The pericardium: a comprehensive textbook*. New York: Marcel Dekker 1997:19, with permission.)

As the heart slowly enlarges in the face of a chronic process such as cardiomyopathy or chronic valvular insufficiency, so too the pericardium increases in volume and mass (515). Thus, even in cardiomegalic states, the pericardial stress-strain curve shifts to the right, and during normal daily living, exerts very little constraining effect to filling. Similarly, abrupt changes in cardiac volume superimposed on a chronically dilated heart move the pericardium into the steep portion of the pressure-volume curve, and a constrictive effect on cardiac filling is observed (*e*Fig. 26.5.13).



***e*FIGURE 26.5.13** The pressure-volume relation of the pericardium in dogs under normal conditions (*left curve*) and after a period of cardiac dilatation resulting from a chronic abdominal aortic arteriovenous fistula (*right curve*). (From Freeman GL, LeWinter MM. Pericardial adaptations during chronic cardiac dilation in dogs. *Circ Res* 1984;54:294–300, with permission.)

When the cardiac volume causes the pericardium to reach the steep portion of its pressure-volume curve, a phenomenon of ventricular interdependence is observed (516). Put simply, the ventricles, with their common interventricular septum, are forced to exist in a finite volume cavity. Therefore, increased filling of one chamber (e.g., right ventricle during inspiration) shifts the septum into the left ventricle, impeding its filling and therefore output. A similar effect is seen in cardiac tamponade and constrictive pericarditis and is the pathophysiologic mechanism underlying pulsus paradoxus and “flow paradoxus” (13,517,518 and 519).

Clinical Presentations of Pericardial Disease

Acute Pericarditis

Inflammation of the layers of the pericardium, from any of myriad causes, yields a common clinical syndrome termed *acute pericarditis*. The causes of acute pericarditis are listed in Table 26.4. The classic symptom complex represents an important differential diagnosis in the assessment of chest pain presentations. However, the relatively common finding of pericardial inflammation at autopsy suggests that the majority of cases is subclinical.

Malignant tumor
Idiopathic pericarditis
Uremia
Bacteria infection
Anticoagulant therapy
Dissecting aortic aneurysm
Diagnostic procedures
Connective tissue disease
Postpericardiotomy syndrome
Trauma
Tuberculosis
Other
Radiation
Drugs inducing lupus-like syndrome
Chylopericardium
Postmyocardial infarction syndrome (Dressler's)
Fungal infections
Acquired immunodeficiency syndrome–related pericarditis

From Kowlgi NG. Pericardial disease. Heart Dis Stroke 1994;3:83–94, with permission.

TABLE 26.4 CAUSES OF ACUTE PERICARDITIS

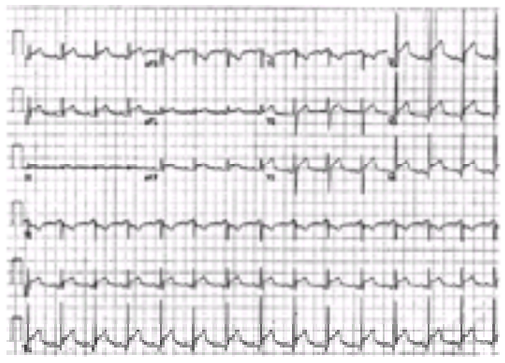
Pathology. The histopathology of pericarditis is dependent on the underlying etiology. The majority of cases is manifested by hyperemia and increased microvascularity, polymorpholeukocyte accumulation, and fibrin deposition. Adhesions can form between the layers of the pericardium and between pericardium and adjacent structures such as pleura and mediastinum.

Clinical Presentation. Acute pericarditis classically presents with progressive, often severe, chest pain over hours. This mechanical pain is typically postural, being worse on lying supine and relieved by sitting forward. It is often pleuritic and aggravated by coughing, motion, and swallowing. It is described as sharp, “stabbing,” or “knife-like” in character. The pain my radiate to the neck and less frequently to the arms and back and even left shoulder, making differentiation from coronary ischemic pain more difficult. There is often a low-grade fever associated with viral and idiopathic pericarditis, while purulent pericarditis is associated with high fevers and systemic sepsis.

The presence of a pericardial rub is pathognomonic for pericarditis, although its absence does not exclude the syndrome. This “to and fro” rasping sound has a timing consistent with the cardiac cycle. It is best appreciated with the diaphragm of the stethoscope applied to the lower left sternal edge and is creaking in nature, like leather on leather. It is heard best with the patient leaning forward in end expiration. The sound classically has a triple cadence (520) with components related to (a) atrial systole, (b) ventricular systole, and (c) ventricular diastole. In 33% of the cases, the rub is biphasic, whereas in 10% it is monophasic. The intensity of the sound can be attenuated by subcutaneous tissue thickness and hyperinflated lung volume. Furthermore, the development of a pericardial effusion as part of the inflammatory syndrome can lead to waxing and waning of the rub over days, although a loud pericardial rub can be still be heard occasionally in the presence of a significant effusion. The sound should be differentiated from a pleural rub, which, although similar in character, is timed with the respiratory cycle; subcutaneous emphysema, which may be an associate in postsurgical or traumatic cases; and loud intracardiac murmurs such as ventricular septal defect.

Investigations. Electrocardiography represents the most useful diagnostic test in acute pericarditis (*e*Fig. 26.5.14). Inflammation of the subepicardial myocardium is thought to be the mechanism producing ST- and T-wave changes, while inflammation of the atrium is thought to cause the PR-segment changes (521). The

PR-segment deviations may precede the ST changes (522). In contrast to the regional ST changes of myocardial ischemia, pericarditis produces widespread electrocardiographic changes in limb and precordial leads. Four phases of electrocardiographic abnormalities have been recognized (Table 26.5) (521,523): Stage I, with ST elevation and upright T waves, is present in 90% cases. Over days, the ST changes resolve and the electrocardiogram may look normal (stage II). There may be further evolution to T-wave inversion (stage III) and finally to normal (stage IV).



***e*FIGURE 26.5.14** Electrocardiographic recording of a 50-year-old man in sinus tachycardia with T-wave abnormality and findings of stage I pericarditis.

Sequence stage	Leads of "epicardial" derivation: at least I, II, aV_F, aV_L, V_3–V_6			Leads reflecting "endocardial" potential: aV_R often V_1, sometimes V_2		
	J-ST	T waves	PR segment	ST segment	T waves	PR segment
I	Elevated	Upright	Depressed or isoelectric	Depressed	Inverted	Elevated or isoelectric
II early	Isoelectric	Upright	Isoelectric or depressed	Isoelectric	Inverted	Isoelectric or elevated
II late	Isoelectric	Low to flat to inverted	Isoelectric or depressed	Isoelectric	Shallow to flat to upright	Isoelectric or elevated
III	Isoelectric	Inverted	Isoelectric	Isoelectric	Upright	Isoelectric
IV	Isoelectric	Upright	Isoelectric	Isoelectric	Inverted	Isoelectric

J-ST, junction of S/J or T wave with the end of the QRS complex.
Modified from Spodick DH. Electrocardiogram in acute pericarditis. Distributions of morphologic and axial changes by stages. Am J Cardiol 1974;33:776–781, with permission.

TABLE 26.5 FOUR-STAGE (“TYPICAL”) ELECTROCARDIOGRAPHIC EVOLUTION OF ACUTE PERICARDITIS

The electrocardiographic abnormalities should be differentiated most importantly from acute myocardial ischemia. The ST changes are more widespread in pericarditis and have a typical saddle-shaped or upward concave appearance. Unlike myocardial infarction, there are no Q waves or loss of R-wave progression. The other important differential diagnosis of these electrocardiographic changes is the early repolarization pattern. Although it is difficult without clinical correlation, differentiation can be made by the presence of PR-segment elevation (especially aV_R) and ST elevation in V_6, which is uncommon in the early repolarization syndrome (524). Most patients with acute pericarditis remain in sinus rhythm (525) (Fig. 26.6).

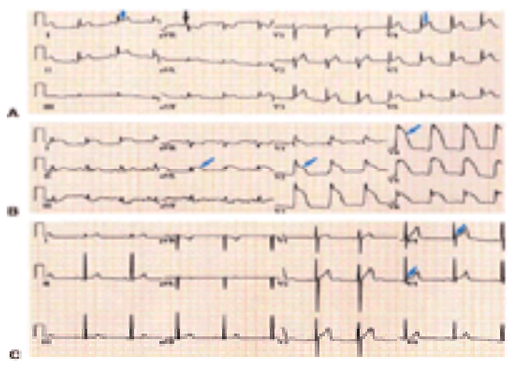


FIGURE 26.6 Differential diagnosis of acute pericarditis. **A:** Acute pericarditis. Note the upward concavity ST elevations in limb leads I, II, aVF, and aVL and in precordial leads V_3–V_6. (*blue left and right arrows*) and the PR segment elevation in aVR (*green middle arrow*). **B:** Acute myocardial infarction. Note the convex ST elevation in leads I, aVL, V_1–V_6 (*blue left, right, middle arrows*), indicating a large anterior myocardial infarction. **C:** Early repolarization. Note the elevation of the J point (*blue right arrows*) with pseudonormalization of the ST segment in V_4–V_6. (From Aikat S, Ghaffari S. A review of pericardial diseases: clinical, ECG and hemodynamic features and management. *Cleve Clin J Med* 2000;67:903–914, with permission.)

Chest radiography contributes relatively little to the diagnosis of acute pericarditis. The presence of cardiomegaly may be seen in the minority of cases in which a significant pericardial effusion has accumulated. Laboratory analysis of blood often shows a modest leukocytosis and raised C-reactive protein and sedimentation rate.

Radionuclide scanning with In-111 (526) and Ga-67 (527,528) has been reported to be useful in identifying the pericardium as the source of an inflammatory syndrome of unknown diagnosis in some patients. Serum troponin I has been reported to be elevated in patients with ST elevation and acute pericarditis, reflecting a degree of myocardial injury (529). MRI, with gadolinium-diethylenetriaminepentaacetic acid enhancement, has identified specific regions of the pericardium involved in the inflammatory process (530).

Diagnostic Algorithm. The following sequence has been proposed (531). All patients should have a complete history and physical examination, electrocardiography, and chest radiography. Diagnosis-specific testing may include tuberculin skin testing, rheumatoid factor and antinuclear antibody, and viral studies from pharyngeal and fecal swabs. In more complex cases (i.e., symptoms and signs lasting longer than 1 week, clinical evidence of tamponade, or purulent pericarditis), echocardiography, sputum and gastric aspirate for tubercle bacillus examination, and blood cultures *should be considered*. Pericardiocentesis (either percutaneous or surgical) is indicated for clinical tamponade, evidence for purulent pericarditis, high suspicion of tumor, or illness lasting longer than 1 week.

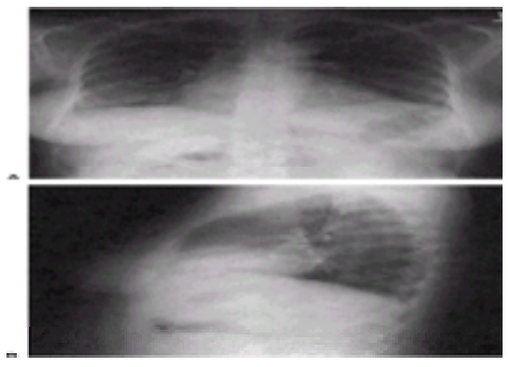
Pericardial Effusion

Pericardial effusion is diagnosed in routine echocardiographic practice in almost one in ten patients (532,533 and 534). Large pericardial effusions that develop slowly can be remarkably asymptomatic, while rapidly accumulating smaller effusions can present with tamponade.

Massive chronic pericardial effusion is a diagnosis ascribed to a syndrome consisting of a large pericardial effusion present for at least 3 months, not attributable to any systemic cause (535). This is an uncommon presentation of pericardial disease, accounting for 2.0% to 3.5% of all cases of large effusion (535). These effusions can be present for many years and were well tolerated in one series, with tamponade a rarity (536). However, in two series of patients, cardiac tamponade occurred in nearly 33% of the patients (535,537). In the larger study, 28 patients with large idiopathic chronic pericardial effusions were followed for a median of 7 years. Unexpected tamponade occurred in eight patients (29%) and pericardectomy was performed in 20 patients. Chronic nonspecific pericarditis was found in all patients evaluated by histology (537).

Clinical Presentation. Pericardial effusions that are not causing hemodynamic embarrassment to the heart are usually asymptomatic. Patients may describe dyspnea or dysphagia due to space-occupying effects in the chest. Physical compression may cause hoarseness (recurrent laryngeal nerve), hiccups (phrenic nerve), or nausea

(diaphragm). Physical examination of patients with large effusions demonstrates muffled heart sounds. Ewart's sign—dullness on auscultation under the left scapula—is a result of compression of the base of the left lung. This may be associated with coarse crepitations due to local atelectasis. Chest radiographic findings include cardiomegaly, which may be massive, often with a characteristic globular shape to the heart silhouette (eFig. 26.6.1). The cardiac margins are unusually sharp, as the pericardium is free of the cardiac motion that usually blurs the silhouette radiographically. Electrocardiography demonstrates diminished QRS and T-wave voltages. Electrical alternans is a marker of massive pericardial effusion.



***e*FIGURE 26.6.1** Pericardial effusion [posterior-anterior **(A)** and lateral **(B)** chest radiographs]. Globular enlargement of the cardiac silhouette without evidence of pulmonary venous hypertension suggests pericardial effusion. (Courtesy of R. D. White, MD, The Cleveland Clinic Foundation.)

Echocardiography is the diagnostic tool of choice for pericardial effusion. Initially, M-mode was the standard, with a high sensitivity for posterior pericardial fluid (533). The advent of two-dimensional echocardiography has shown the various presentations of effusion, including circumferential, posterior, and loculated (Fig. 26.7). Loculated effusions are more common when scarring has supervened (e.g., postsurgical, posttrauma, postpurulent pericarditis). The size of effusions can be graded as small (less than 10 mm of echo-free space in systole and diastole), moderate (greater than or equal to 10 mm at least posteriorly), large (greater than or equal to 20 mm), or very large (compression of the heart) (538). Furthermore, two-dimensional echocardiography can give information about the nature of the fluid, suggesting the presence of fibrin, clot, tumor, air, and calcium. Care must be taken to differentiate pericardial fluid from pleural fluid and ascites. Left pleural effusions can be difficult to differentiate from pericardial fluid. By transthoracic echocardiography in the parasternal long-axis view, pericardial fluid can be seen to reflect at the posterior atrioventricular groove, while pleural fluid continues under the left atrium, posterior to the descending aorta. Spin-echo and cine MRI can also be used to assess the size and extent of simple and complex pericardial effusions similar to echocardiography (161). The effusions by MRI may tend to be larger than by echocardiography (539).

VIDEO

Video 26.3 Apical four-chamber view (transthoracic) in a patient with metastatic lung cancer demonstrating a moderate to large pericardial effusion and a very large, highly organized pleural effusion encasing the heart. (Pleural effusion is towards the right of the screen.) Note the extensive fibrinous network in the pleural effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 26.4 Subcostal short-axis view demonstrating the left ventricle surrounded by an organized pericardial effusion, which is adjacent to highly organized pleural effusion in a patient with metastatic lung cancer. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

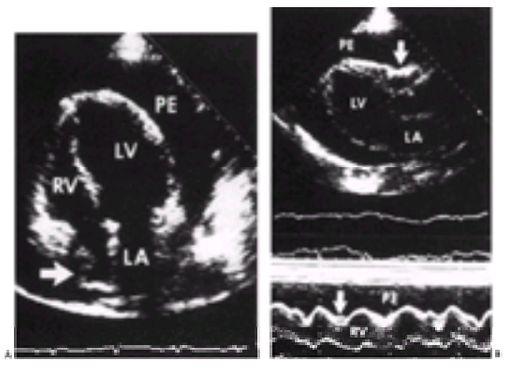


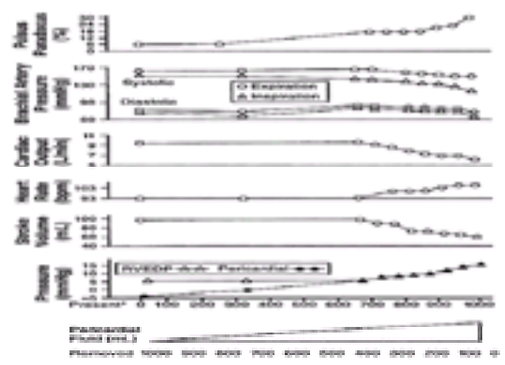
FIGURE 26.7 A: Apical four-chamber view of a large pericardial effusion (PE) with right atrial collapse (*arrow*). **B:** Parasternal long-axis view of a large PE with right ventricular (RV) collapse (*arrows*). LA, left atrium; LV, left ventricle. (From Schutzman JJ, Obarski TP, Pearce GL, et al. Comparison of Doppler and two-dimensional echocardiography for assessment of pericardial effusion. *Am J Cardiol* 1992;70:1353–1357, with permission.)

Management. The action taken after finding a significant pericardial fluid collection depends on the underlying etiology, the presence of hemodynamic compromise, and the volume of fluid. Pericardiocentesis may not be necessary in all cases, particularly when the diagnosis can be made based on other systemic features. Where doubt remains, particularly in cases in which malignancy or purulent pericarditis is suspected, pericardiocentesis is indicated. Hemodynamic compromise is an absolute indication for drainage (see following discussion).

Pericardial Tamponade

Fluid accumulation in the finite pericardial space causes an increase in pressure with subsequent cardiac compression. Tamponade is not a binary phenomenon, with a spectrum existing from mild cardiac compression and embarrassment to cardiovascular collapse.

Pathophysiology. Information regarding the cardiovascular response to pericardial tamponade is mostly derived from animal data (540). As fluid is infused into the pericardium, intrapericardial pressure rises and cardiac output falls (540). Systemic pressure is preserved by alpha-adrenergic–mediated peripheral vasoconstriction until eventually systolic pressure drops as a premortal event. As noted previously, the pericardial pressure-volume curve has a flat and a steep portion (515). Once intrapericardial volume passes this critical transition point, small increments in volume result in large increases in pressure. The actual volume at which this transition occurs depends on the current finite volume for the pericardium, itself a function of its degree or lack of chronic distention (*e*Fig. 26.7.1). The rise in extracardiac intrapericardial pressure results in decreased transmural distending pressures and thence poor diastolic ventricular filling (541). Because of the finite volume available in the pericardial space, there is an equalization of filling pressures of the four cardiac chambers and the pericardium.



***e*FIGURE 26.7.1** Hemodynamic changes during serial fluid withdrawals in a patient with cardiac tamponade. Pulsus paradoxus is expressed as a percentage decrease in the systolic arterial pressure with inspiration. Note that there is significant pulsus paradoxus and changes in the cardiac output, heart rate, and stroke volume when there is equalization of right ventricular diastolic pressures (RVEDP) and pericardial pressure. (From Fowler N. Pericardial disease. In: Abelman WH, ed. *Cardiomyopathies, myocarditis, and pericardial disease*. *Atlas of heart diseases*. Philadelphia: Current Medicine, 1995, with permission. Adapted from Reddy PS. Hemodynamics of cardiac tamponade in man. In: Reddy PS, Leon DF, Shaver JA, eds. *Pericardial disease*. New York: Raven Press, 1982:161;177.)

Systemic venous flow occurs in two phases: *systolic*, related to filling of the atrium with a closed tricuspid valve ('x' descent on central venous pressure trace, S wave on hepatic venous Doppler), and *diastolic*, related to filling of the right atrium as it empties through the open tricuspid valve ('y' descent on central venous pressure trace, D wave on hepatic venous Doppler). In tamponade, the heart is compressed and remains in a finite volume. Ventricular ejection decreases the relative proportion of the pericardial space occupied by the heart, allowing a fall in intrapericardial and atrial pressure and a rapid inflow of blood (large 'x' descent and S wave). During diastole, the pericardium contains filled ventricles that increase its pressure and thus forward flow from the systemic veins decreases (blunted 'y' descent and D waves) (519,542). The systemic venous flow in cardiac tamponade should be distinguished from constrictive pericarditis with prominent 'x' and 'y' descents (S and D on hepatic venous Doppler) (4,15).

Pulsus paradoxus, defined as an inspiratory drop of systolic blood pressure of greater than 10 mm Hg, is a hallmark of cardiac tamponade (*e*Fig. 26.7.1). With inspiration, intrathoracic pressure becomes subatmospheric. Intrapericardial pressure, pathologically high in this syndrome, is reduced during inspiration (as it is physiologically reduced in the normal state), allowing increased RV filling. Systemic venous diastolic flow ('y' descent, hepatic vein D wave) increases, and RV size and stroke volume increase. Again, because of the finite volume of the pericardium, the left ventricle is partially compressed by the enlarging right ventricle (due to leftward displacement of the intraventricular septum) causing an inspiratory decrease in systemic stroke volume (543). An alternative mechanism is that the pulmonary venous to left atrial pressure gradient is decreased because the changes in intrathoracic pressure are not transmitted to the left ventricle due to shielding by the pericardial fluid and because of the increased pulmonary vascular compliance. There is reciprocally increased flow on the right side of the heart because of interventricular interdependence (544,545). Pulsus paradoxus is also seen in severe lung disease, in which intrathoracic pressure swings are supraphysiologic, and in pulmonary embolus, in which RV filling pressures are disproportionately higher than left (543,546).

Clinical Presentation. The spectrum of presentation of patients with cardiac tamponade ranges from dyspnea and edema to frank circulatory collapse. The classic triad of cardiac tamponade was described by Beck including hypotension, elevated jugular venous pressure, and distant heart sounds (547). Early tamponade is manifest by tachycardia, tachypnea and dyspnea, edema and elevated venous pressure, and quiet cardiomegaly. Examination of the central venous waveform shows a prominent 'x' descent and absence of the 'y' descent.

Pulsus paradoxus is examined using the stethoscope over the brachial pulse and measuring the pressure gap between the appearance of the Korotkoff's sounds during expiration only and their continuous presence. It is defined by a fall in systolic blood pressure of 10 mm Hg with inspiration, an exaggeration of the normal situation. False-positive pulsus paradoxus without cardiac tamponade may occur with obstructive lung disease, RV infarction, and pulmonary embolism, and a false-negative finding may occur with high LV pressures as with LV dysfunction or hypertrophy, severe hypotension, severe aortic regurgitation, or in the case of an atrial septal defect (548).

Profound circulatory collapse or shock is more common in patients with acute tamponade related to cardiac or pericardial trauma. In the most extreme cases, such as acute aortic dissection into the pericardium, patients may present with electromechanical dissociation. Patients who develop the syndrome subacutely tend to present in a less dire status and manifest signs of right-sided heart failure with edema, hepatomegaly, ascites, and pleural effusion. Rarely, low-pressure cardiac tamponade, without the typical signs, can develop in the presence of dehydration and hypovolemia (549). Other variant forms of tamponade may include hypertensive cardiac tamponade (with high blood pressure), tamponade with ventricular dysfunction (RV or LV dysfunction), regional cardiac tamponade (localized effusions), or effusive constriction (538).

With an increase in invasive cardiac procedures in the electrophysiology and cardiac catheterization laboratories, the complication of cardiac tamponade is more frequent. A report of near 7,000 patients undergoing percutaneous coronary intervention found an incidence of 0.2% with cardiac tamponade developing 2 to 36 hours after the procedure (550).

Investigations. Electrocardiography and chest radiography do not differentiate tamponade from noncompressive pericardial effusion. Large pericardial effusions allow "swinging" of the heart on its vascular pedicle, causing in some cases electrical alternans.

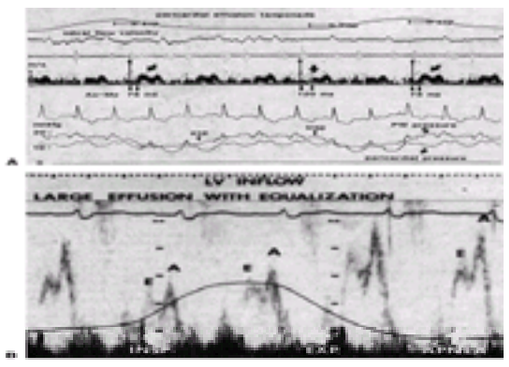
Echocardiography is a fast and noninvasive modality to accurately diagnose tamponade (519) (*e*Fig. 26.7.2, Table 26.6). The presence of pericardial fluid should be documented and its location defined. The classic signs of cardiac tamponade are RA and RV collapse (109,551,552). Postsurgical effusions may be loculated (e.g., behind the left atrium) and sometimes difficult to visualize from the transthoracic window. Indeed, if the diagnosis of tamponade is suspected in this scenario, transesophageal echocardiography is indicated (4). Two-dimensional echocardiography can also exclude pericardial masses and ventricular and valvular dysfunction as the cause of hemodynamic compromise. Doppler echocardiography allows direct quantitation of mitral and tricuspid inflows, pulmonary venous and systemic venous flows; and with the use of a nasal thermistor, variation with respiration can be assessed (553). Respiratory variation of transmitral E waves is minimal in healthy subjects, and greater than 25% variation (increasing on the first beat of expiration and conversely on inspiration) is highly suggestive of significant tamponade (*e*Fig. 26.7.2). Tricuspid E waves often exhibit some degree of respiratory variation in healthy subjects. Cardiac tamponade is present when there is greater than 40% variation (opposite pattern to the left side) and increased hepatic venous flow reversals in expiration (519) (Table 26.6).

VIDEO

Video 26.5 Apical four-chamber view demonstrating a large pericardial effusion causing tamponade. Note the inability of the right side to fill. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 26.6 Subcostal short-axis view of a large pericardial effusion causing tamponade. Note that the right side is small and under filled. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 26.7.2 A:** Patient with severe cardiac tamponade. *Upper panel*: Mitral inflow with respirometer, electrocardiogram, and phonocardiogram. Note the decrease in mitral early flow velocity (*middle large arrow*) on the first beat of inspiration (insp) compared with the first beat of expiration (exp) (*left and right large arrows*). Also note the marked difference in the isovolumic relaxation time (Ac-Mo interval) associated with these beats is shown by the smaller arrows. *Lower panel*: Phasic pulmonary wedge pressure (PW) and pericardial pressures with the electrocardiogram in the same patient, but they are not simultaneous with the mitral inflow recordings. Note the respiratory variation in pulmonary capillary wedge pressure is larger than that in pericardial pressure. This results in a decreased wedge to pericardial pressure gradient with inspiration and an increased gradient with expiration. (From Appleton CP, Hatle LK, Popp RL. Cardiac tamponade and pericardial effusion: respiratory variation in transvalvular flow velocities studied by Doppler echocardiography. *J Am Coll Cardiol* 1988;11:1020–1030, with permission.) **B:** Pulsed Doppler tracing of left ventricular (LV) inflow of a large pericardial effusion with right-sided equalization showing a marked decrease in LV inflow velocity from expiration (EXP.) to inspiration (INSP.). A, late diastolic flow; E, early diastolic flow. (From Schutzman JJ, Obarski TP, Pearce GL, et al. Comparison of Doppler and two-dimensional echocardiography for assessment of pericardial effusion. *Am J Cardiol* 1992;70:1353–1357, with permission.)

Abnormal inspiratory increase of right ventricular dimension with abnormal inspiratory decrease of left ventricular dimension
Inspiratory decrease of mitral valve DE excursion (M-mode) (anterior leaflet opening) and ejection fraction slope (initial anterior leaflet closing)
Right atrial collapse
Right ventricular early diastolic collapse
Left atrial collapse
"Flow paradoxus" with abnormal inspiratory increase of tricuspid valve flow and abnormal inspiratory decrease of mitral valve flow
Inferior vena cava plethora (failure to decrease proximal diameter by 50% or more on sniff or deep inspiration)

Modified from Fowler NO. Pericardial disease. *Heart Dis Stroke* 1992;1:85–94, with permission.

TABLE 26.6 ECHOCARDIOGRAPHIC FINDINGS IN PATIENTS WITH CARDIAC TAMPONADE

MRI may also be used to detect the signs of tamponade from hemopericardium and compression of the cardiac chambers by hematoma (165,554).

Cardiac catheterization has historically been the diagnostic standard for tamponade and remains useful, particularly in cases in which noninvasive modalities are not conclusive. Right-sided heart catheterization is often performed simultaneously with pericardiocentesis, allowing monitoring of improvement as the effusion is drained. Typically, patients demonstrate an elevated RA pressure, with a prominent 'x' descent and diminished or absent 'y' descent (542). The PCWP is also elevated and often equal to intrapericardial and RA pressure. As pericardial fluid is drained, intrapericardial pressure falls below biatrial pressure. If this does not occur, the diagnosis of effusive constrictive disease should be considered (see below).

Pericardiocentesis. While preparing the equipment for pericardiocentesis, the patient in tamponade may be supported with cautious fluid loading and inotropes (such as norepinephrine or isoproterenol). Percutaneous pericardiocentesis should be performed in an environment in which advanced cardiac life support equipment and personnel are immediately available. Historically, these procedures have been performed in the cardiac catheterization laboratory, with arterial and right-sided heart catheters in situ. More recently, the procedure has tended to be performed in the procedure room of the cardiac or intensive care unit, or even at the bedside, using echocardiographic guidance (555,556 and 557). Surgical drainage of the pericardium (either by a subxyphoid approach or using a complete pericardectomy) is indicated for loculated effusions, patients at risk of excessive bleeding, and in situations in which fluid has recurred after previous drainage procedures (558).

Echocardiography can demonstrate the most accessible window for passage of the needle (555,556,559). Historically, the subxyphoid approach has been used most commonly, with a long needle passed under the xiphoid and directed toward the left shoulder at a 30-degree angle to the skin. Echocardiography performed at the cardiac apex can often identify a window where the pericardium can be entered (usually in the sixth or seventh rib space in the anterior axillary line) without risk of cardiac puncture. A short needle is passed through the rib space under constant negative pressure until fluid is aspirated. It is important to confirm that the fluid aspirated is intrapericardial (i.e., the blood should not clot).

By either approach, once the pericardial space is reached a soft-tipped guidewire is passed and the needle removed. A multiholed catheter is then introduced and the pericardial fluid suctioned out. It is prudent to drain the fluid in steps of less than 1 L at a time to allow cardiovascular equilibrium to be restored at each stage and to avoid the rare complication of acute RV dilatation (560,561). Clinical improvement usually occurs after the aspiration of only 100 to 200 mL of fluid. The fluid should be drained completely, and specimens sent for chemistry, cytology, culture, and acid-fast bacilli staining. It is common practice to leave the catheter in for some hours, connected to a free drainage bag, to allow further drainage as the patient assumes different postures. It is important to avoid allowing air into the pericardium because this is most uncomfortable for the patient.

Percutaneous pericardiocentesis is a rapid and safe procedure when performed by trained personnel (559). In a study of patients undergoing urgent pericardiocentesis following cardiac perforation, tamponade was relieved in 99% of patients. A major complication rate of 3% occurred and included pneumothorax and RV laceration. No deaths resulted directly from pericardiocentesis (562). A similar review of 245 pericardiocenteses performed in patients with postoperative effusions showed that anticoagulant therapy was the most common contributing factor to early pericardial effusions (less than 7 days), and postpericardiotomy syndrome contributed most often to late effusions (563). The rate of major complications from pericardiocentesis was 2% in this study.

Surgical Procedures. A median sternotomy or anterolateral thoracotomy approach provides good visualization for pericardial surgery including pericardiectomy for constrictive and effusive disease (564). However, less invasive procedures are available for drainage of pericardial effusions when pericardiocentesis is not feasible or recurrent fluid accumulates.

Subxyphoid pericardiectomy is a safe and efficacious method of draining large pericardial effusions. A small vertical incision is made in the upper epigastrium and the pericardium approached by posterior retraction of the diaphragm from the sternum. A pleuropericardial window is often created to allow ongoing drainage (565).

Alternative nonthoracotomy techniques for formation of a pericardial window include percutaneous pericardiotomy using an inflatable balloon from a subxyphoid approach (566,567,568,569,570,571,572 and 573) and a video-assisted thoracic surgical pericardiectomy. These procedures are effective for the management of malignant and other large pericardial effusions.

Constrictive Pericarditis

Dense fibrosis and adhesion of the parietal and visceral layers of the pericardium create a rigid "case" around the heart, limiting its filling and causing profound disturbances of cardiac function (eFig. 26.7.3). This final common pathway may be the end result of one (or more) of many etiologic agents including infections, postcardiac surgery, or radiation. The constrictive process can follow the etiology acutely, subacutely (months), or chronically (years) (538). The clinical presentation is well recognizable, with debilitating right-sided heart failure and a poor prognosis. Voluminous literature exists about the many methods of differentiating this constellation from that of restrictive cardiomyopathy, which presents with similar clinical signs and symptoms (Table 26.3).

***e*FIGURE 26.7.3** Postmortem excised specimen of constrictive pericarditis demonstrating unusually thickened pericardium (Pm). (From Spodick DH. *The pericardium: a comprehensive textbook*. New York: Marcel Dekker, 1997, with permission.)

Pathophysiology. The fundamental abnormality in constrictive pericarditis is limited filling and enhanced interventricular dependence of the heart because of the rigid encasement of the heart by thickened pericardium, effectively isolating it from the normal respiratory swings in pressure and allowing a finite filling volume for the ventricles (13). Within the pericardium, the myocardium is intrinsically normal (unless there is a combined abnormality such as in radiation myocarditis), with no specific abnormality of systolic or diastolic function. In constriction, the ventricle fills abruptly on valve opening (often more abruptly than normal due to elevated atrial filling pressures). However, in mid-diastole, the chambers reach the maximum volume that the constraining pericardium will allow, and filling abruptly ceases. This can be appreciated visually on two-dimensional echocardiography as wall motion ceases with a shudder in mid-diastole. In contrast, restrictive myocardial diseases involve abnormal ventricular filling from the onset of diastole, as the chamber relaxes slowly and stiffness increases with a compensatory increase in left atrial pressure (272).

However, it is the effect of respiration on cardiac flows that is the major hallmark for differentiating constrictive from restrictive cardiac diseases. As the heart is effectively isolated from the thorax by its rigid encasement, it does not experience marked respiratory swings in pressure. Thus, on inspiration, intrathoracic (and therefore pulmonary vein) pressure decreases, but left atrial pressure does not. Thus, the pulmonary vein to left atrial pressure gradient that drives left atrial inflow diminishes, as does mitral inflow. The resultant decreased LV filling during diastole allows more room for RV filling because of a septal shift and enhanced ventricular interdependence and thus right-sided inflows increase. The exact opposite sequence occurs in expiration (4,13,101,102,166).

Filling pressures rise to compensate for the decrease in cardiac output via renal retention of salt and water. The finite space of the pericardium causes the filling pressure of the four chambers (and the pulmonary wedge pressure) to equalize. Intraventricular pressure recordings demonstrate the classical dip and plateau or square-root sign morphologies. The dip represents the abrupt early filling at atrioventricular valve opening related to high filling pressures and corresponds to a deep ‘y’ descent on the central venous tracing. The plateau phase represents a period of unchanging pressure and volume related to the finite volume of the pericardial encasement. The ‘x’ descent on the venous trace may also be prominent, as systolic emptying of the ventricles allows filling of the atria. The ‘x’ and ‘y’ descents are sometimes referred to as the *W pattern* (574) (Fig. 26.8).

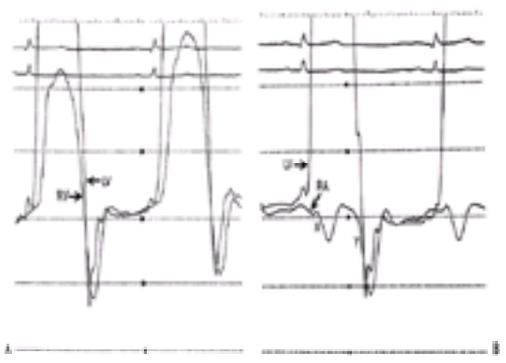


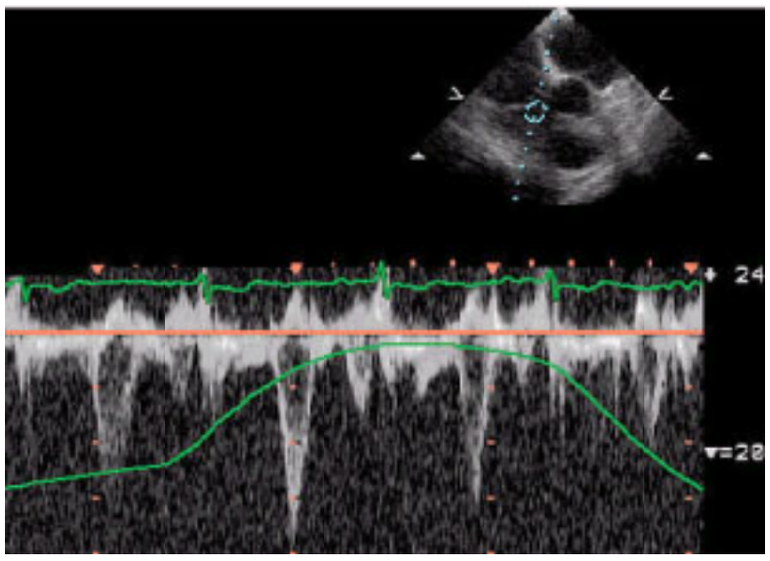
FIGURE 26.8 A,B: Simultaneous right ventricular (RV) and left ventricular (LV) pressure recordings demonstrating equalization of diastolic pressures and dip and plateau physiology. Simultaneous right atrial (RA) and LV pressure recordings demonstrating equalization during diastole and prominent ‘x’ and ‘y’ descents in the RA tracing. (From Vaitkus PT, Cooper KA, Shuman WP, et al. Images in cardiovascular medicine. Constrictive pericarditis. *Circulation* 1996;93:834–835, with permission.)

Differentiating Restriction from Constrictive Pericarditis.

Hemodynamics. Cardiac catheterization has been traditionally the gold standard in distinguishing between these two similar diseases; however, there can be overlap of the hemodynamics (13). These hemodynamic findings have been shown in Table 26.3. Simultaneous recordings of the right and left heart pressures have revealed elevation and equalization of pressures (within 5 mm Hg) of the RA, right ventricle diastolic, PCWP, and pre–‘a’ wave LV diastolic pressure. The RA pressure contour typically shows an M or W configuration with a preserved systolic ‘x’ descent and a prominent ‘y’ descent with small ‘a’ and ‘v’ waves. The RV and LV pressure tracings show a dip and plateau contour. The RV and pulmonary artery systolic pressures are mildly elevated, with a pressure of less than 50 mm Hg compared with a pressure greater than 50 mm Hg in restriction. Administration of saline over 6 to 8 minutes can enhance the classic findings of constriction in a patient with occult constriction (542). The respiratory changes in cardiac flows have been shown to be useful in the hemodynamic diagnosis of pericardial constriction. One study demonstrated that, although conventional hemodynamic variables failed to accurately diagnose constriction, differences between left and RV pressures on inspiration, a marker of ventricular interdependence, were highly specific and sensitive for the syndrome (301).

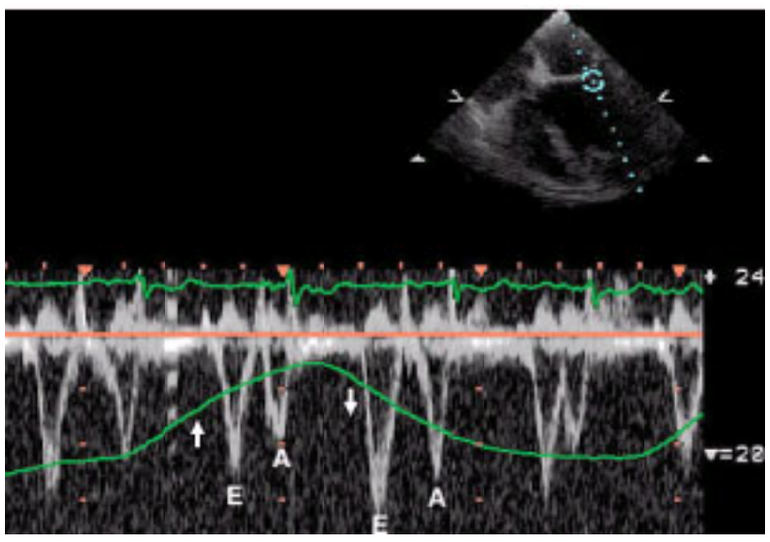
Echocardiography. There have been many M-mode and two-dimensional signs that have been used to differentiate these two conditions; however, these signs have proven to be nonspecific and insensitive (575,576,577 and 578). The important two-dimensional echocardiographic features of constriction that may provide clues to the diagnosis include pericardial thickening, myocardial tethering, a septal bounce with respiration, and inferior vena cava plethora (272,579).

Video 26.7 Transesophageal echo (four-chamber view) demonstrating constrictive pericarditis. Note the abnormal septal bounce and the tethering of the right atrium and right ventricle by the thickened pericardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Pulsed wave Doppler through the tricuspid valve of a patient with constrictive pericarditis. Note the decrease of the E wave with inspiration due to interventricular dependence.

Doppler Echocardiography. As described earlier, Doppler echocardiography with respirometry has emerged as a useful tool in these conditions (13,101,580). Limited ventricular filling and enhanced ventricular interaction account for the Doppler findings in constrictive pericarditis, whereas decreased distensibility of the ventricles accounts for the Doppler findings in restriction (13).



Pulsed wave Doppler of the mitral valve inflows of a patient with constrictive pericarditis. Note the decrease of the E wave during inspiration (*upward arrow*) due to interventricular dependence, and the increase in the E wave during expiration (*downward arrow*) for the same reason.

The classic Doppler echocardiographic findings are shown in Figure 26.9 and Figure 26.10. The similarities with restriction by Doppler echocardiography include a short deceleration time indicative of the dip and plateau hemodynamic pattern and limited filling. The main differences include enhanced respiratory variation in mitral inflow and pulmonary venous flow (greater than or equal to 25% at the onset of inspiration and expiration) in constriction, but not with restriction (unless a concomitant pericardial effusion accounting for respiratory variation is present). In restriction, there is a markedly blunted pulmonary venous systolic flow with greater diastolic forward flow indicative of a prominent ‘y’ descent and elevated left atrial pressures, whereas in constriction, there are usually both systolic and diastolic flows present (4) (Fig. 26.11). Because of enhanced ventricular interdependence, there is a decreased transtricuspid flow in expiration and enhanced expiratory flow reversals in the hepatic vein with constriction, while there are increased inspiratory flow reversals in restriction. Respiratory variation in the tricuspid regurgitation peak velocity and velocity duration has been noted in constriction but not in restriction (581). Superior vena cava Doppler can help distinguish respiratory variation of mitral inflow in patients with chronic obstructive lung disease and constrictive pericarditis (582). The systolic forward component of superior vena cava flow varies significantly with chronic obstructive lung disease, whereas there is little change with constrictive pericarditis. The newer modalities of color M-mode Doppler and TDE have provided complementary information in the evaluation of patients with constrictive pericarditis (see the section Phases of Diastole) (121,123,206,583,583a) (*e*Fig. 26.11.1). Recently, in patients with constrictive pericarditis, the mitral inflow E/Em was shown to be inversely correlated with PCWP (annulus paradoxus).

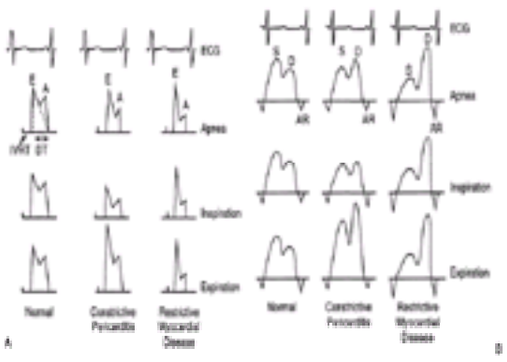


FIGURE 26.9 A,B: Left ventricular inflow velocities and pulmonary venous flow during different phases of respiration. (From Klein AL, Cohen GI. Doppler echocardiographic assessment of constrictive pericarditis, cardiac amyloidosis, and cardiac tamponade. *Cleve Clin J Med* 1992;59:278–290, with permission.)

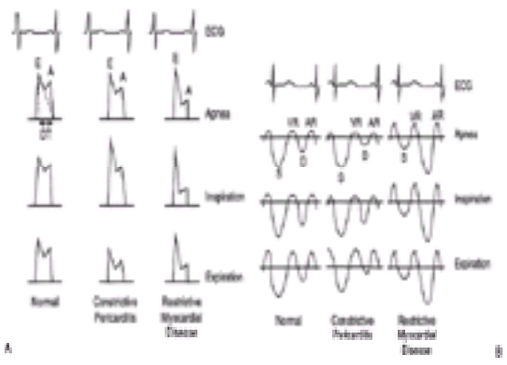


FIGURE 26.10 A,B: Right ventricular inflow velocities and hepatic venous flow during different phases of respiration. (From Klein AL, Cohen GI. Doppler echocardiographic assessment of constrictive pericarditis, cardiac amyloidosis, and cardiac tamponade. *Cleve Clin J Med* 1992;59:278–290, with permission.)

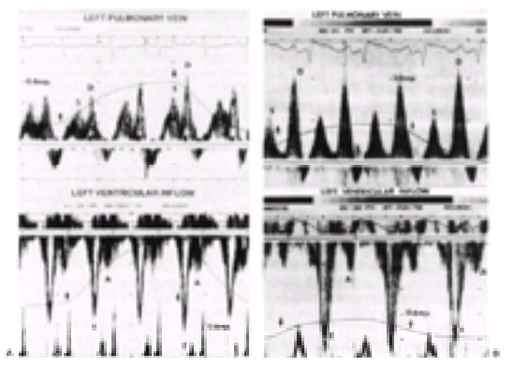
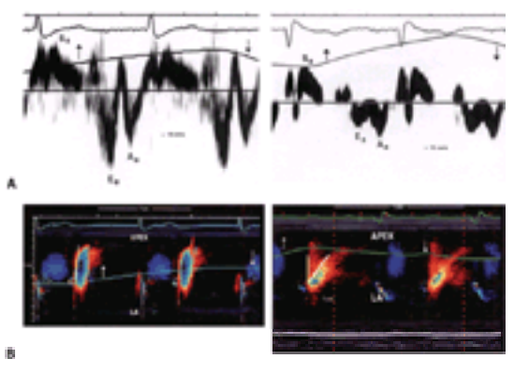
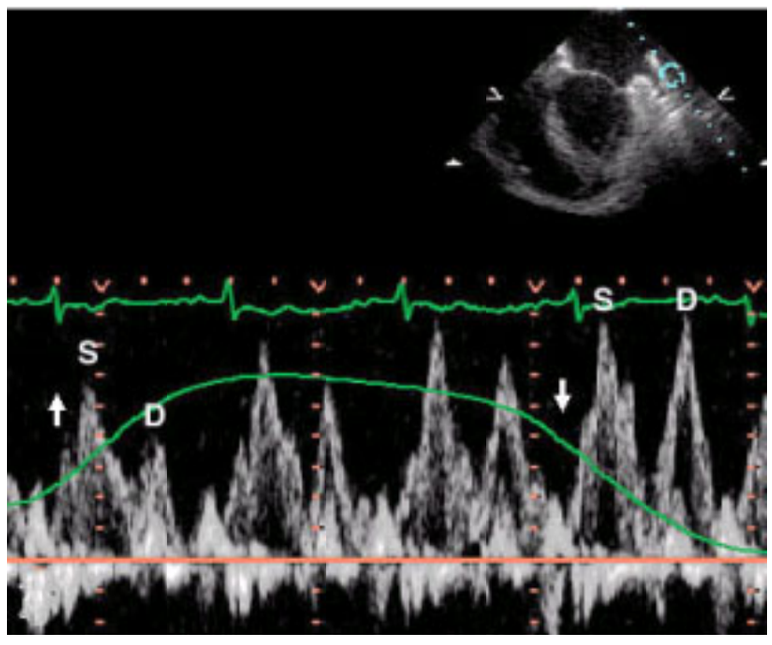


FIGURE 26.11 A: Constrictive pericarditis. Doppler transesophageal echocardiogram of the left upper pulmonary venous flow (*top*) and left ventricular inflow (*bottom*) in a 30-year-old man with constrictive pericarditis with respiratory monitoring with inspiration (*up arrow*) and expiration (*down arrow*). **B:** Restrictive cardiomyopathy. Doppler transesophageal echocardiogram of the left upper pulmonary venous flow (*top*) and left ventricular inflow (*bottom*) in a 64-year-old man with restrictive cardiomyopathy secondary to advanced cardiac amyloidosis during inspiration (*up arrow*) and expiration (*down arrow*). A, late filling velocity, D, peak diastolic; E, early filling; S, peak systolic. (From Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flow. *J Am Coll Cardiol* 1993;22:1935–1943, with permission.)

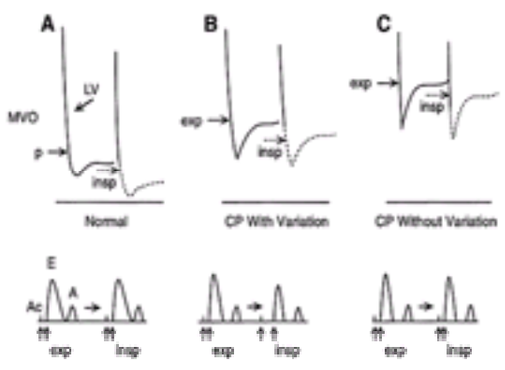


***e*FIGURE 26.11.1 A:** Representative tracings of the tissue Doppler echocardiographic velocities in the longitudinal axis in a patient with constrictive pericarditis (*left panel*) and a patient with restrictive cardiomyopathy (*right panel*) with respiratory monitoring with inspiration (*up arrow*) and expiration (*down arrow*). Note the peak systolic velocities are similar in both patients (10 cm/s), but a marked difference in early diastolic longitudinal axis velocities E_a was noted for the patient with constriction (15 cm/s) compared with the patient who had restrictive cardiomyopathy (5 cm/s). **B:** Color Doppler M-mode echocardiography of diastolic flow from the left atrium (LA) toward the ventricular apex as imaged from the four-chamber view with constriction (*left panel*) and restriction (*right panel*), with respiratory monitoring with inspiration (*up arrow*) and expiration (*down arrow*). The flow propagation slope of the first aliasing contour (*white line*) is steep (110 cm per second) for constrictive pericarditis (*left panel*) but the slope is significantly slower (35 cm per second) in restrictive cardiomyopathy (*right panel*). Note the color/no color transition (*yellow line*) is rapid for restrictive cardiomyopathy and represents isovolumic flow. A significant difference in the time delay of the maximal velocities is evident as well. (From Rajagopalan N, Garcia MJ, Rodriguez L, et al. Comparison of new Doppler echocardiographic methods to differentiate constrictive pericardial heart disease and restrictive cardiomyopathy. *Am J Cardiol* 2001;87:86–94, with permission.)



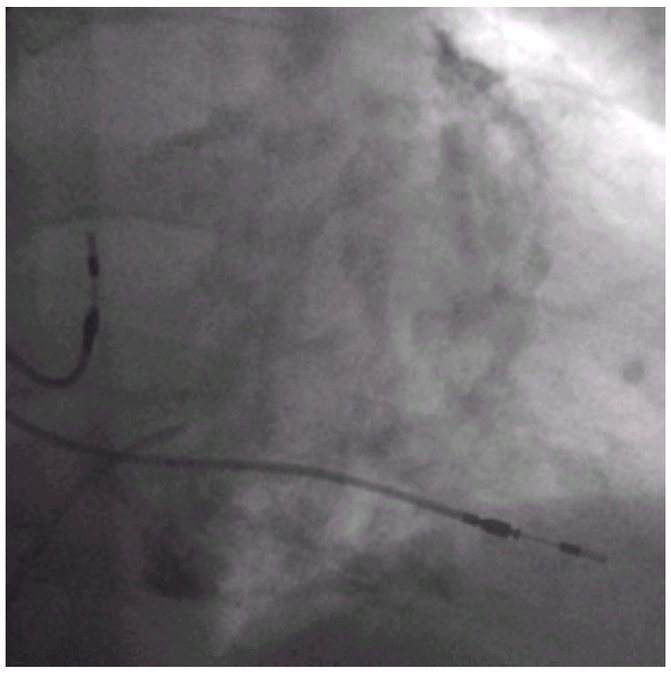
Pulsed wave Doppler of the pulmonary veins of a patient with constrictive pericarditis. Note the inspiratory decrease of the S and P waves and the expiratory increase due to interventricular dependence. (Inspiration is denoted by the upward arrow and expiration by the downward arrow).

There are several pitfalls in using Doppler echocardiography with respiratory monitoring in distinguishing constriction from restriction (eTable 26.6.1). Factors including depth of respiration, position of the sample volume, level of left atrial pressure, presence of concomitant myocardial disease, and atrial fibrillation may influence the accuracy of the diagnosis. Transesophageal echocardiography may be used to delineate the anatomy (pericardial thickening) as well as describe the physiology better than transthoracic echocardiography (101). In a large series of 192 patients undergoing transesophageal echocardiographic evaluation of complex diastolic function, 39% of patients had evidence of restrictive physiology, 30% had constriction, and 12% had mixed constriction and restriction, whereas the remainder had abnormal relaxation, pseudonormalization, or large pericardial effusion or tamponade (119). Preload reduction maneuvers may be useful in lowering the left atrial pressure to enhance the respiratory variation, whereas volume loading may be used if the filling pressures are decreased (584,585) (eFig. 26.11.2). Mixed restriction and constriction may occur postirradiation and may have features of localized pericardial thickening with restrictive physiology (119). Also, atrial fibrillation may make it difficult to perform a Doppler evaluation of constriction and restriction; however, a series of 31 patients with constrictive pericarditis showed a similar respiratory variation of pulmonary venous flow and mitral inflow in patients with atrial fibrillation compared with normal sinus rhythm (586). Occasionally, ventricular pacing can be used to regularize the RR intervals in patients with atrial fibrillation. Constrictive pericarditis can also be evaluated in the operating room during mechanical ventilation. In a series of 15 patients, it was noted that positive pressure ventilation reverses the pattern of respiratory variation of the mitral inflow and pulmonary venous flow velocities (587).



***e*FIGURE 26.11.2** Possible mechanism of decreased mitral flow velocity variation in some patients with constrictive pericarditis (CP). Left ventricular (LV) pressure

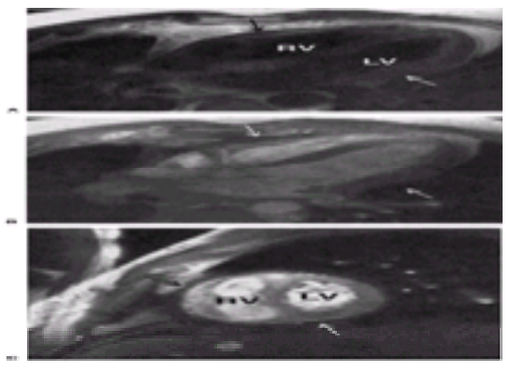
decrease and pressure at mitral valve opening (MVO; *horizontal arrows*) are shown during expiration (exp; *solid lines*) and inspiration (insp; *dashed lines*) together with mitral flow velocity and the time from aortic closure (Ac) to the start of mitral flow. Vertical arrows indicate LV isovolumic relaxation time. **A:** In healthy persons, the inspiratory decrease in LV minimal pressure and pressure at MVO is approximately equal, so that there is little change in early diastolic transmitral pressure gradient, mitral flow E velocity, or LV isovolumic relaxation time. **B:** In contrast, most patients with CP have less inspiratory change in LV minimal pressure than in pressure at MVO, resulting in increased variation in the early diastolic (transmitral) pressure gradient and early mitral flow velocity. **C:** However, if the constrictive process is severe and filling pressures are markedly increased, the flow velocity variation could be blunted because MVO occurs on a steeper portion of the exponential LV pressure gradient. In these cases, decreasing left atrial and MVO pressure by head-up tilt or diuresis may result in increased respiratory variation in mitral flow velocities and LV isovolumic relaxation time, as seen in **(B)**. (From Oh JK, Tajik AJ, Appleton CP, et al. Preload reduction to unmask the characteristic Doppler features of constrictive pericarditis; a new observation. *Circulation* 1997;95:796–799, with permission.)



Cine image showing severe calcification in the pericardium of a 71-year-old male patient with constrictive pericarditis.

***e*TABLE 26.6.1** PITFALLS OF DOPPLER ECHOCARDIOGRAPHY TO DIFFERENTIATE CONSTRICTION FROM RESTRICTION
Technical factors
Attention to detail
Sample volume movement
Depth of respiration
False-positive
Chronic obstructive pulmonary disease
Movement of sample volume
False-negative
High filling pressures
Localized constriction
Rhythm abnormalities
Atrial fibrillation

Magnetic Resonance Imaging for Pericardial Disease Direct visualization of the pericardium is possible with MRI in health (588,589) and disease states (590). This imaging modality is evolving as part of the routine workup of suspected pericardial disease (5,166,591). In constrictive pericarditis, the pericardium is seen as a thickened low-intensity signal band, related to its fibrocalcific nature (162) (eFig. 26.11.3).



***e*FIGURE 26.11.3** Constrictive pericarditis (spin-echo and cine; horizontal long-axis and short-axis). On the “dark blood” image **(A)**, thickened pericardium is represented by curvilinear signal void (*arrows*) separated by the bright signal of the epicardial and pericardial fat. There is associated conical/tubular compression deformity of the basal and middle portions of the right ventricle (RV) and left ventricle (LV). On the “bright blood” images **(B,C)**, the fibrous/calcified nature of the pericardium is confirmed by the dark appearance of the pericardium (*arrows*). The abnormal pericardium caused abrupt limitation of diastolic filling of the ventricles on the cine image loops. (Courtesy of R. D. White, MD, The Cleveland Clinic Foundation.)

The increased pericardial thickening can be measured easily by MRI, but does not necessarily indicate pericardial constriction (161). Ancillary findings by MRI include the conical or tubular narrowing of the ventricular cavities by the thickened pericardium, atrial dilatation, IVC enlargement, hepatomegaly, and ascites. The sensitivity, specificity, and accuracy of MRI in the diagnosis of constrictive pericarditis was 88%, 100%, and 93%, respectively, in one study (5). Cine MRI is useful in assessing the functional impairment of the abnormal filling in constriction compared with restriction (592), whereas phase flow mapping may show abnormal flow patterns in the superior vena cava that improve postpericardial stripping (593). However, MRI may have difficulty distinguishing between calcification and fibrous tissue and thus, CT scanning may be better to assess pericardial thickening, when calcification is present (102,554,594). Gadolinium-enhanced MRI has been used in the diagnosis of tuberculous constrictive pericarditis (595).

Clinical Presentation Patients with significant pericardial constriction present with congestive heart failure. Gross dependent edema, effusions and ascites (596), hepatic congestion with dysfunction, splenomegaly, poor exercise tolerance, and cachexia constitute anasarca, of which constriction is one of the few remaining causes in developed nations. Jugular venous distention is common with a prominent ‘y’ descent (Friedreich’s sign) (597), and the classical Kussmaul’s sign, a rise in central venous pressure with inspiration due to the inability of the right atrium to receive volume, is seen in some cases. The syndrome is relentless and progressive, responding poorly to conservative medical therapy.

Pulsus paradoxus is seen in one-third of cases. Auscultation of the chest reveals quiet heart sounds, often with a pericardial knock, which correlates with the abrupt cessation of early diastolic filling (E wave), when the ventricles reach their finite volume limit.

Electrocardiography demonstrates low voltages with nonspecific T-wave changes. Atrial fibrillation is seen in a minority of patients. Chest roentgenography may demonstrate “eggshell” calcification of the pericardium, particularly in tuberculous pericarditis, and pleural effusions (598).

There may be variation in the presentation of constriction. These variants include localized constriction (localized scarring) (599), effusive constriction (after the

pericardial fluid is drained), elastic constriction (thick pericardial fluid), latent or occult constriction (volume depleted), and transient constriction (600).

Treatment. Conservative medical management of constrictive pericarditis is at best palliative, with no substantial effect on the natural history of the disease. Diuretics decrease the intensity of fluid overload symptoms and atrioventricular blocking agents and antiarrhythmics are useful for the management of atrial fibrillation. Surgical pericardiectomy remains the only definitive management of this problem and should be performed before calcification and myocardial involvement progress (102,601,602 and 603).

In one series, a worse prognosis following pericardiectomy was associated with inadequate resection, higher New York Heart Association functional class, radiation, myocardial involvement, residual coronary artery disease, older age, chronic disease, and arrhythmias (600). A second contemporary series of 135 patients with constrictive pericarditis found a 6% 30-day perioperative mortality for pericardiectomy, and a 78% and 57% 5- and 10-year survival, respectively, with improvement in functional class in most patients. Predictors of poor prognosis, similar to prior studies, included advanced age, New York Heart Association class, and postradiation etiology. Symptomatic benefit postpericardiectomy has been correlated with improvement in diastolic filling pattern and shorter duration of symptoms (604).

Specific Causes of Pericardial Disease

Idiopathic and Viral Pericarditis

The majority of cases of acute pericarditis has no specific cause detected and is designated idiopathic. Many of these cases represent acute viral pericarditis. Attacks of this syndrome follow the seasonal epidemics of enterovirus infection (coxsackie B and echovirus) (605). Proven viral cases are more likely to occur in immunocompromised hosts. Cytomegalovirus pericarditis has increased in frequency in association with immunocompromised hosts and early human immunodeficiency virus infection (606,607 and 608). *e*Table 26.6.2 shows the most etiologies of infectious pericarditis.

***e*TABLE 26.6.2** ETIOLOGY OF INFECTIOUS PERICARDITIS
Viral diseases (coxsackie A and B viruses, echovirus, influenza, adenovirus, Epstein-Barr virus, chicken pox, psittacosis, acquired immunodeficiency syndrome, mumps, infectious mononucleosis)
Mycobacterial infections (*Mycobacterium tuberculosis*, *M. avium*, *M. intracellulare*)
Protozoa (toxoplasmosis, *Entamoeba histolytica, Trypanosoma cruzi*)
Fungal infections (histoplasma, *Coccidioides,* blastomycosis, *Candida*, *Aspergillus*)
Bacterial infections (*Staphylococcus*, *Streptococcus*, gram-negative bacilli, *Meningococcus*, *Pneumococcus*, *Salmonella* species, *Brucella*, *Legionella*, *Campylobacter*, *Haemophilus influenzae,* Lyme disease)
Rickettsial infections
Parasitic infections (trichinosis, microfilaria, echinococcus disease)
Anaerobic organisms (*Clostridium*, anaerobic *Streptococcus*)
Miscellaneous infections (*Nocardia*, *Actinomyces*, *Mycoplasma*, *Psittacosis-lymphopathia venereum* group)

From Fowler NO. Pericardial disease. *Heart Dis Stroke* 1992;1:85–94, with permission.

Pathology. Viral infection of the pericardial layers is associated with a polymorpholeukocyte accumulation followed by a mononuclear perivasculitis. Pericardial fluid is often observed, usually in small amounts. In a minority of cases, large effusions cause the clinical presentation of cardiac tamponade. The fluid is typically serosanguineous, often with a leukocytosis (with variable polymorpholeukocyte and monocyte composition). Biochemical analysis of the fluid typically shows elevated lactate dehydrogenase and protein levels. It is possible to culture cytomegalovirus from the pericardium or fluid in some cases. Serology in viral cases may demonstrate high titers of cytomegalovirus IgG by latex agglutination, cytomegalovirus IgM by enzyme-linked immunosorbent assay, influenza A or B antibodies by complement fixation, or coxsackie B antibodies by complement fixation (605,607).

Clinical Presentation. Idiopathic and viral pericarditis in the immunocompetent host is typically a self-limited illness, beginning with a nonspecific flu-like illness. There is often a history of a prodromal upper respiratory tract infection. There may be associated arthralgias and myalgias. Patients present with a syndrome of chest pain as described previously. The pain is often severe, distressing, and associated with sympathetic activation such as clamminess, pallor, and tremor. There is often an associated low-grade fever. Significant dyspnea is uncommon in simple cases, unless there is hemodynamic compromise by a large pericardial effusion or associated viral pneumonitis (609).

The specific diagnosis of viral pericarditis should be entertained in all cases, after other etiologic agents have been considered. However, the identification of the viral agent from serologic markers or from pericardial fluid occurs infrequently in clinical practice. A fourfold rise in serum antibody levels is highly suggestive of an underlying viral cause. Associated myocarditis is often associated with modest elevation of cardiac isoenzymes (529,605,610).

Pericardial collections in viral and idiopathic pericarditis are usually relatively small, being diagnosed and sized simply by transthoracic echocardiography. Having detected an effusion, it is important to exclude significant hemodynamic compromise or tamponade. Because of the relatively acute time frame of the fluid accumulation, tamponade may be present with only modest volumes of pericardial fluid. Pericardiocentesis is not usually indicated unless there is hemodynamic compromise, which occurs in up to 15% of cases of acute viral pericarditis (531). In a series of 57 patients, pericardial biopsy and fluid sampling identified cytomegalovirus in only four cases (607).

Uncomplicated acute pericarditis is a self-limited benign illness, with few sequelae and a course ranging from days to a few weeks. Complications are infrequent and include relapsing attacks of acute pericarditis (see following discussion), acute tamponade, acute myocarditis with ventricular dysfunction and late cardiomyopathy, and chronic constrictive pericarditis (609).

Management. Specific antiviral therapy is not indicated for viral idiopathic pericarditis in the immunocompetent host. Treatment is directed toward symptom relief. The mainstay of therapy has always centered on the oral antiinflammatory drugs, particularly aspirin (325 to 650 mg every 4 to 6 hours) or most often nonsteroidal antiinflammatory agents including ibuprofen (600 to 800 mg every 6 to 8 hours) (611). Indomethacin (25 to 50 mg four times per day) should be reserved in adults due to deleterious effects on coronary blood flow and myocardial infarcts. Thus, other nonsteroidal agents are commonly used. No specific studies have used the COX-2 inhibitor agents. Colchicine (0.6 mg every 12 hours), with or without a load of 2 to 3 mg, may be used when added to the antiinflammatory agent or by itself in treating the initial attack or preventing recurrences (612,613 and 614). There is no role for antibiotics, unless purulent pericarditis has been documented. Systemic corticosteroid therapy with prednisone has been used in severe and intractable cases (609,615). Some patients may have recurrent or incessant pericarditis that may be related to an immunopathic etiology (616). Frequently, these patients may be corticosteroid dependent. Colchicine may be an effective drug to attempt to wean patients off corticosteroids (617).

Purulent Pericarditis

Epidemiology and Etiology. The incidence and spectrum of purulent pericarditis have changed considerably with the advent of the antibiotic era and the increasing frequency of cardiac surgery and immunocompromised hosts (618,619). Previously, the most common presentation of purulent pericarditis was as an associate of pneumococcal pneumonia (619). A wide variety of organisms has been implicated as etiologic agents, depending on the clinical scenario. Following cardiac surgery, staphylococcal infection, including multiply-resistant strains, gram-negative rods including *Pseudomonas*, *Escherichia coli*, and *Klebsiella* (618), and streptococcal groups A and B (620) have been documented. Sporadic cases of other infectious agents have included *Legionella* (621,622), *Neisseria gonorrhoeae* (623), *Salmonella* sp (624), Lyme disease (625), anaerobes such as *Bacteroides fragilis* (626,627), and nonbacterial agents such as *Candida albicans* (628,629), *Nocardia*, *Asteroides* (630), *Mycoplasma pneumoniae* (631), and *Aspergillus* species (632). Meningococcal infection has been associated with purulent pericarditis (633,634), with or without clinical meningitis.

In a large hospital-based series of patients from 1972 to 1991 (619), purulent pericarditis was seen in only 33 of 600,000 patients reviewed and was detected premortem in only 19 of these. All but two patients had a remote source of infection such as pneumonia, skin infection, or oral sepsis as the probable primary source. In 8 of 33 cases, no bacteria could be isolated or grown from pericardial, pleural, cervical, or blood cultures. The outcome for the group was poor, with constriction requiring surgery developing in 6 patients, and only 16 surviving to be discharged from the hospital. Notably, only approximately one-third of the patients presented with the typical symptom complex of acute pericarditis.

Direct trauma to the chest may cause pericarditis directly, via penetration (635,636), or extensive soft tissue injury with secondary superinfection. An indirect, often late form of inflammatory sterile pericarditis is seen in blunt trauma cases (637,638). This is thought to be an autoimmune phenomenon, similar to Dressler's syndrome (see the section Dressler's Syndrome).

Management. A provisional diagnosis of purulent pericarditis is an indication for a drainage procedure, either percutaneous or preferably surgical. Complete clearance

and lavage of the pericardial space should be attempted (636,639). Urgent bacterial, acid-fast, and fungal staining of the fluid, followed by complete culture is mandatory. Broad-spectrum antibiotic therapy should be narrowed on identification of the specific etiologic agent. Pericardectomy may be indicated in cases with significant pericardial adhesions to avoid late constriction.

Fungal Pericarditis

Pericarditis due to fungal infection is a relatively uncommon condition, occurring in areas where certain strains are endemic. Histoplasmosis pericarditis—a usually benign self-limited clinical syndrome—is seen in young healthy adults who present with a typical acute pericarditis syndrome. Patients should be observed in-hospital, as large, hemodynamically significant effusions can accumulate rapidly, requiring drainage (640). This organism is endemic in the Ohio and Mississippi river valleys, Arkansas, and the western Appalachians (641). Other fungal agents such as coccidioidomycosis (642), *Candida* species, (628,629), and *Aspergillus* species (632) have been documented to cause pericarditis, particularly in immunocompromised hosts.

Tuberculous Pericarditis

Although tuberculosis is not endemic in many developed countries, it remains a major public health issue in nonindustrialized nations (643), and typical and atypical mycobacterium infection is an increasing problem in immunocompromised hosts (644,645 and 646). Pericardial involvement is responsible for up to 4% of acute pericarditis and 7% of tamponade presentations (647,648). The feared long-term sequelae of tuberculous pericarditis is calcific pericardial constriction, occurring in 30% to 50% of cases (647,649,650).

Pathology. Tuberculous pericarditis develops either from lymphangial spread from mediastinal or peribronchial nodes or direct or hematogenous spread from pulmonary lesions. The inflammatory process has four stages (651). Initially, the inflammation is dry or fibrinous, with little fluid accumulation and the presence of live acid-fast bacilli. The inflammatory response comprises a mononuclear infiltrate with typical giant cells and foci of caseating necrosis. Pericardial fluid accumulates in large volumes (600 to 1,500 mL), often causing significant hemodynamic compromise. With time, the effusion resolves, and fibrous adhesions develop between visceral and parietal layers and between pericardium and surrounding tissues. Late, the adhesions become dense, and calcification occurs with the appearance of clinical constriction and radiographic calcification (650).

The pericardial fluid has a high specific gravity with high protein levels and has a high white cell count comprising a majority of lymphocytes. The fluid appears serous in the majority of cases. The majority of cases has high levels of antimyolemmal and antimyosin antibodies (652). Polymerase chain reaction technology has successfully been employed to amplify and identify *Mycobacterium tuberculosis* DNA from pericardial fluid (653,654).

Clinical Presentation. Tuberculous pericarditis may present in several ways. Early involvement is often manifest by a nonspecific systemic syndrome of lethargy, fever, night sweats, weight loss, tachycardia, and dyspnea. Pericardial chest pain is seen in less than one-half of cases. Most cases present later, as pericardial fluid accumulates with the clinical manifestations of tamponade with elevated venous pressure, pulsus paradoxus, and anasarca. A pericardial rub is present in approximately one-half of all patients (655).

Approximately one-half of patients with treated tuberculous pericarditis proceed to constrictive pericarditis, even with treatment. This can occur over a prolonged period or may occur rapidly over weeks. The clinical manifestations of constrictive pericarditis have been discussed previously. The presence of pericardial tamponade at presentation and the degree of fibrosis at the start of treatment are predictors of late constriction (655).

Investigations. The diagnosis of tuberculous pericarditis can be made if one or more of the following criteria are met: (a) histologically proven tuberculous pericarditis at surgery or pericardial biopsy; (b) positive *M. tuberculosis* culture from pericardial fluid; (c) pericarditis with proven extracardiac tuberculosis (lymphadenopathy, pleural or peritoneal effusion, pulmonary infiltrate, positive tuberculin skin test result); (d) pericardial effusion without obvious cause, responding to antituberculous therapy (656,657). The presence of high levels of adenosine deaminase activity (greater than 50 U per L) in the pericardial fluid is supportive of the diagnosis (658). Tuberculin skin test results may be negative in one-third of patients with tuberculous pericarditis (659) and positive in one-third of patients with idiopathic or viral pericarditis (531), making it less than useful in this diagnostic algorithm.

Management. Before the availability of antituberculous agents, tuberculous pericarditis was almost universally fatal. Even with modern therapy, death occurs from tamponade and late constriction. The goals of management are to treat the active infection, monitor and treat developing effusions, and prevent and treat late constriction (650,660,661). A nonrandomized trial suggests a beneficial effect for supplementary corticosteroid therapy and complete open surgical pericardial drainage.

Human Immunodeficiency Virus–Associated Pericardial Effusion

Human immunodeficiency virus infection is a common cause of pericardial effusion. In one series of 122 patients with pericardial effusion, 33% had human immunodeficiency virus infection as the underlying condition. Cardiac tamponade is common in this disease population associated with various infectious agents including *Mycobacterium*, fungi, viruses, lymphoma, and Kaposi's sarcoma (662).

Uremic Pericarditis

Pericardial involvement in patients with end-stage renal disease has been recognized for 150 years to be a marker of preterminal disease (663,664). With the introduction of modern dialytic therapy, the incidence of pericarditis and effusion in these patients has decreased significantly, from almost one-half (663) to approximately 10% (665,666). Pericarditis is responsible for the death of a similar proportion of patients (666).

Pathophysiology. Uremic pericarditis and effusion occur in patients with severe renal failure and abate with dialysis or successful transplantation. However, among patients with severe uremia, those who suffer pericarditis are not biochemically discernible from those who do not (665). Established pericardial effusions in patients on dialysis often resolve with increased frequency of dialysis (665,666). Stressors such as surgery, trauma, or intercurrent illness are often seen to precipitate pericarditis (664,667).

Insults other than elevated serum urea levels have been postulated as causal in pericarditis in renal failure patients. Hypercalcemia, hyperuricemia (668), and heparin-associated hemorrhagic pericarditis have all been cited (664). The immunocompromised state has been suggested as a mechanism, allowing viral infection to become active (669). This latter mechanism does not fully explain the abatement of the syndrome with increased dialysis therapy. Finally, end-stage renal disease is an associate of many multisystem diseases, particularly immunologic syndromes such as lupus, which are well recognized to have an associated autoimmune serositis.

Gross inspection of the pericardium in cases of uremic pericarditis shows the classic "bread and butter" appearance. This is caused by the fibrin exuding into the pericardium forming fine adhesions between the visceral and parietal layers. The pericardium itself may have focal hemorrhagic areas or generalized erythema. The process may organize and calcify to a chronic constrictive state (670).

Clinical Presentation. Pericardial chest pain is the most common presenting feature of this syndrome, occurring in three-fourths of cases. This pain has the typical features of acute idiopathic pericarditis as discussed previously. The majority of cases has a pericardial rub heard at some point in the clinical course. Fewer than 30% have fever. Dyspnea is commonly experienced, particularly as pericardial tamponade develops. The presentation and diagnostic workup of cardiac tamponade is discussed earlier in this chapter (see the section Pericardial Tamponade). Tamponade poses a significant risk to the patient, especially at times of hemodynamic stress, such as during hemodialysis. Small asymptomatic pericardial effusions are seen in many dialysis patients (671,672) and of themselves are not diagnostic of uremic pericarditis.

Management. The approach to patients with uremic pericarditis is governed by the hemodynamic stability of the individual. In stable cases, intensive hemodialysis has been shown to reduce the size of effusions and severity of symptoms and is recommended (668,673,674), being successful in only 50% to 60% of cases (665,666). Such dialysis should use a minimal dose of heparin to avoid intrapericardial bleeding. Ongoing pericarditis and increasing pericardial fluid collection is predicted by high fever (greater than 39°C), significant leukocytosis (greater than 15,000 per mm^3), and the use of peritoneal dialysis alone (675). Large pericardial effusions are less likely to resolve with such medical therapy than small collections (666,676,677).

Pericarditis Associated with Myocardial Infarction

Differentiation of pericardial chest pain from that of acute myocardial ischemia is important for the clinician. Pericarditis as an associate of acute myocardial infarction occurs in up to 30% of cases at autopsy (678,679), significantly complicating the situation. In life, pericarditis is observed clinically in 7% to 10% of acute infarcts (680,681). An incorrect diagnosis of primary pericarditis has important implications in this setting as it will most likely preclude the patient from receiving timely revascularization therapy. Conversely, an incorrect diagnosis of myocardial ischemia in the setting of simple acute pericarditis may lead to the patient suffering the consequences of thrombolytic or anticoagulant therapy. In 16 such cases reported in the decade ending in 1995, there has been one death (in a young man), one hemorrhagic tamponade, and two nonhemorrhagic effusions managed conservatively (682,683,684,685,686 and 687). Two forms of pericardial involvement have been observed in association with myocardial infarction.

Early Acute Pericarditis

Pathophysiology. An early pericarditis syndrome is seen in the days following an acute infarction, resolving over approximately 1 week. Pathologically, a fibrinous exudate is seen, localized over the area of the infarct. Small pericardial effusions, without clinical pericarditis, are quite common after myocardial infarction, occurring in 25% to 40% of such patients (688,689). These effusions are usually of little clinical significance and are frequently detected incidentally on echocardiography assessing regional wall motion abnormalities. In such cases, it is important to consider and exclude contained rupture into the pericardium.

Clinical Presentation. The clinical presentation of pericardial-type pain often occurs after the abatement of ischemic pain. This syndrome should be considered during each physical examination of the postinfarct patient. The presence of a pericardial rub is diagnostic, occurring more commonly than the pericardial pain. It is important to differentiate this sound from intracardiac murmurs, which may represent mechanical complications of infarction such as acute mitral regurgitation and ventricular rupture. The typical electrocardiographic changes of pericarditis are seen in a small minority of cases of postinfarct pericarditis (680). In a large retrospective series of autopsy-proven postinfarct regional pericarditis, a pattern of atypical T-wave evolution was observed: specifically at 48 hours, persistent upright T waves *or* normalization of transiently inverted T waves (690).

The clinical course of early postinfarct pericarditis is usually benign. However, pericarditis seems to be associated with larger transmural infarcts and therefore more complications. Despite this, poorer prognosis is not predicted by the presence of periinfarct pericarditis or effusions (688,689,691,692 and 693). In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trials of thrombolytic therapy for myocardial infarction, pericardial involvement was associated with a higher long-term mortality, but was not an independent risk factor when infarct size was considered (694). Further evidence that pericarditis is a by-product of more severe myocardial damage and not an independent prognostic factor is provided by the data from analysis of incidence of pericardial involvement in patients treated with thrombolytic therapy compared with those who did not receive this treatment. In the GISSI trials, the incidence of periinfarct pericarditis was halved by the use of thrombolytic therapy, and this effect was more pronounced with earlier institution of treatment (694,695).

Management. Management is symptomatic, with aspirin or nonsteroidal antiinflammatory drugs. Caution is recommended with the latter as there have been anecdotal reports of pronounced thinning and even rupture of infarct sites when these drugs have been used (696). For similar reasons, corticosteroid therapy (697) is not recommended.

Dressler's Syndrome. The second pericardial associate of myocardial infarction is the late-appearing Dressler's syndrome (698). Dressler suggested an incidence of 4% of infarct patients, but more recent studies have shown rates of 1% or less (699,700). Indeed, in patients treated with thrombolytics, this syndrome has been observed at rates of less than 0.5% (701).

Clinical Presentation. Dressler's syndrome of chest pain, pleurisy, pericarditis with friction rub, severe malaise, moderate fever, and leukocytosis occurs at 3 weeks to several months postinfarct (681). Pericardial collections of fluid are not uncommon and can be hemodynamically compromising.

Management. Consideration should be given to hospital admission, as these patients are often severely debilitated. Furthermore, recurrent ischemia, significant pericardial effusion, bacterial superinfection, and hemorrhagic complications need to be examined for and excluded. Anticoagulant therapy should be temporarily discontinued. Symptoms are relieved usually with aspirin or nonsteroidal antiinflammatory drugs (see the section Acute Pericarditis for doses). Because of the recurrent nature of the syndrome and the possible immunologic nature of the insult, some authors recommend corticosteroid therapy (prednisone, 40 to 60 mg daily, tapering over a week) (702). Pericardiocentesis is indicated only for hemodynamic compromise or tamponade.

Trauma and the Postpericardiotomy Syndrome

After open or closed pericardial trauma or cardiac surgery requiring pericardotomy, a late inflammatory process may be observed, with fever and clinical pericarditis (703). his phenomenon is probably mediated by similar mechanisms to Dressler's syndrome following myocardial infarction (704). The syndrome usually presents with fever, malaise, and pericarditic chest pain 2 to 3 weeks after the inciting event. There is often a pericardial rub. The patient may exhibit leukocytosis, eosinophilia, and elevated sedimentation rate (705). Chest radiographic examination may show cardiomegaly related to pericardial effusion, associated pleural effusion, or both. Such fluid is usually serous and may be of sufficient volume to cause hemodynamic compromise in up to 1% of cardiac surgical patients (706). Patients should be treated with nonsteroidal antiinflammatory drugs, with corticosteroids being reserved for intractable cases and pericardiocentesis for cases with tamponade.

Radiation Pericarditis

Thoracic and mediastinal radiation for hematologic and breast malignancies has been routine practice for three decades. Accordingly, there is a growing population of patients suffering the late consequences of radiation to the heart and pericardium (707). Indeed, the heart and spinal cord appear to be the dose-limiting organs for thoracic radiation (708). The severity of these complications is variable from individual to individual and relates to the volume of heart exposed to the source, the total dose, duration and fractionation of the therapy, and nature of the source (^{60}Co being worse than linear accelerator). Early large studies of patients with Hodgkin's disease showed radiation-induced pericardial abnormalities in 6.6% (709), whereas more current series report an incidence of 2.2% (710). The modern use of anterior and posterior fields combined with subcarinal and apical shielding has contributed significantly to this improvement (711).

Pathology. The common pathogenetic feature of radiation-induced complications is microcirculation injury with endothelial cell damage, platelet adhesion, and capillary rupture. Radiation injury to the pericardium has an acute inflammatory phase with associated hyperemia and thickening of the serosal membranes, fibrin deposition, and pericardial fluid, which may be serous or bloody (712). This inflammatory response may resolve or may organize to form adhesions between the visceral and parietal pericardium, with late constriction. Pericardial effusions may resolve or become chronic. Myocardial fibrosis with diastolic dysfunction and scarring of the valves leading to poor coaptation are associated features of cardiac radiation injury.

Clinical Presentation. Acute pericarditis associated with radiation therapy is usually asymptomatic and self-limiting. When clinically evident, patients present with a typical acute pericarditis syndrome with pain, fever, lethargy, and electrocardiographic changes. Delayed pericardial involvement, usually occurring within 1 year of therapy (713), but with latent periods of up to 45 years reported (714), presents most commonly as a chronic pericardial effusion. This presentation is most commonly in the setting of an elevated sedimentation rate, elevated lymphocyte count, presence of bulky mediastinal disease, and concomitant chemotherapy (715). Such effusions most commonly present with hemodynamic compromise causing dyspnea, edema, and poor exercise tolerance. A smaller number of patients present with full-blown tamponade. Most cases of pericardial effusion secondary to radiation resolve spontaneously (715). Superinfection of the pericardial space with *Staphylococcus aureus* can lead to abscess formation. Thyroid dysfunction is common after mantle irradiation (15% to 25%) (710,716) and must be considered as a possible contributor to pericardial effusion.

Organization of the process may lead to the typical presentation of constrictive pericarditis, with congestive cardiac failure. An intermediate stage with pericardial fibrosis and effusion under pressure is manifest as the effusive-constrictive syndrome (717). Constrictive pericarditis evolves 5 to 10 years after therapy (718,719) and is not surprisingly predisposed to by the presence of pericardial fluid. Radiographic evidence of pericardial calcification is uncommon. A new condition of mixed constriction and restriction has been described that may occur from radiation injury to the myocardium and pericardium (119).

Diagnosis and Management. Pericardial effusion, with or without tamponade following radiotherapy, suggests either malignant or radiation pericarditis. Malignant pericarditis can be diagnosed by percutaneous pericardiocentesis with cytology in 85% of cases (720). Malignant effusions tend to be larger in volume and associated with other evidence of tumor recurrence. Percutaneous pericardiocentesis offers adequate relief of tamponade. Recurrent large pericardial collections should be treated with surgical pericardiectomy, as the pleuropericardial window procedure is associated with a high rate of progression to constriction (721). Pericardial stripping for constriction is associated with a higher mortality and poorer outcome than for constriction of other causes because of wound dehiscence and

infection and myocardial dysfunction related to associated radiation injuries.

Pericardial Involvement in Autoimmune Diseases

Pericardial involvement in the multisystem connective tissue diseases is not uncommon. Pericarditis, with or without effusion, is commonly a component of a multiserositis, together with pleuritis and ascites.

Rheumatoid Arthritis. Autopsy studies show evidence of some pericardial involvement in up to one-half of all patients with rheumatoid arthritis (722). This involvement consists of acute and chronic inflammatory changes, effusions, adhesions, and scar and, rarely, rheumatoid granulomata. In life, pericardial involvement is detected in 2.0% of adult cases and 7.6% of juvenile rheumatoid arthritis (Still's disease) (723).

Clinical Presentation. Classic pericarditis is not typically manifest in these patients. Chest pains are often atypical for pericarditis and may be confused with the myriad musculoskeletal pains suffered by these patients. Pericardial effusions are often small, with tamponade being uncommon. The fluid has high protein levels, low glucose, and high titers of rheumatoid factor. Rheumatoid arthritis may be associated with cholesterol ("yellow paint") pericarditis (724,725 and 726). Elevated levels of interleukin-6 in the pericardial fluid has been associated with tamponade (727).

Chronic pericardial involvement in rheumatoid arthritis may manifest as constrictive pericarditis. This has been associated with the presence of subcutaneous rheumatoid nodules (728). The diagnosis and management of constrictive pericarditis are discussed in detail earlier in this chapter. In addition, abnormal diastolic filling patterns have been noted in adults and children with rheumatoid arthritis compared with matched controls, suggesting undetected myocardial involvement (729,730).

Systemic Lupus Erythematosus. Pericardial involvement in lupus (both idiopathic and drug-induced) occurs in approximately one-third of all patients (731), being the most common cardiovascular complication of the disease. The process involves a serositis, with a fibrous exudate high in protein, low in glucose, and a polymorpholeukocyte count less than 10,000 per mm^3. This volume of fluid may be large and cause tamponade in a small minority of cases (less than 10%) (732). Pericardial fibrosis and thickening with constriction are rare late sequelae (733).

Clinical Presentation. In large series of patients with SLE, documented pericarditis is present in one-fourth to one-fifth and tamponade in 2.5% (734,735 and 736). The clinical presentation is often indistinguishable from simple idiopathic acute pericarditis, manifesting the characteristic symptom complex and electrocardiographic changes (737). Pericarditis can be the presenting feature of systemic lupus erythematosus and should be excluded in all cases of suspected idiopathic pericarditis, especially in women. The presence of antiphospholipid antibody in serum has been associated with cardiac complications of lupus (738) but not with a higher prevalence of pericardial effusion. Pericardiocentesis is not specifically indicated unless complications such as sepsis or tamponade are apparent (739).

Myocardial disease may also occur in patients with systemic lupus erythematosus or antiphospholipid antibodies without apparent systolic dysfunction or pericardial disease. Abnormal diastolic filling patterns have been demonstrated relative to controls in these patients, suggesting subclinical myocardial disease (740,741).

Management. Attacks of pericarditis parallel the systemic activity of the illness. Pericarditis usually abates with systemic immunosuppressive therapy. Pericardial drainage is reserved for cases with hemodynamic embarrassment. Close observation, often in the hospital, for the development of tamponade is warranted (733).

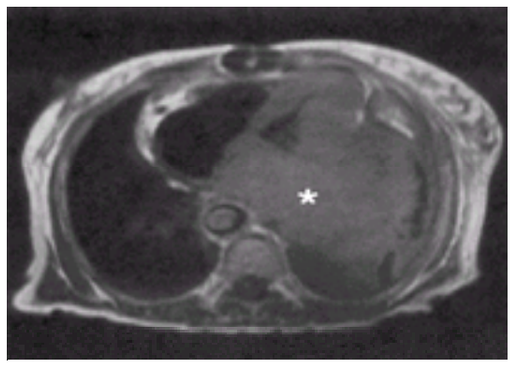
Scleroderma. Cardiac involvement in scleroderma (progressive systemic sclerosis) is seen in approximately 50% of cases, whereas clinical pericarditis occurs in 10% (742). Pericardial effusion detected by echocardiography, sometimes massive, has been reported in up to 40% of patients (743,744,745,746 and 747). Late pericardial constriction has an extremely poor prognosis. Associated cardiac abnormalities include myocardial fibrosis with diastolic dysfunction, conduction system abnormalities, valvular fibrosis, and arrhythmias (748,749 and 750). Acute scleroderma pericarditis is managed with antiinflammatory measures, in a manner similar to idiopathic pericarditis.

Myxedema

Untreated hypothyroidism is associated with peritoneal, pleural, and pericardial serous fluid collections related to sodium and water retention and increased capillary permeability (751,752). The fluid may be straw colored, with fibrin strands or have a gold paint appearance (753) related to a high cholesterol content (754). The pericardium may be coated with cholesterol deposits, related to the hypercholesterolemia of hypothyroidism. Associated cardiac abnormalities include accelerated coronary disease (755) and cardiomyopathy (756). Clinically, pericardial involvement is often silent, being detected as cardiomegaly on chest radiography. Fluid accumulation is gradual and may reach enormous volumes (greater than 4 L) (757). Pericardial effusion may be the presenting symptom of hypothyroidism and thus thyroid function testing should be routine in the workup of pericardial effusion of unknown origin. With institution of adequate thyroid hormone replacement therapy, the effusions usually resolve slowly (758). Pericardiocentesis should be reserved for cases with hemodynamic compromise.

Malignant Pericarditis

Malignant invasion of the heart and pericardium occurs in one-tenth of all cancer patients, and one-third of these die as a consequence of such involvement (759,760). Primary tumors of the pericardium are exceedingly rare. Angiosarcomas (including hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma), rhabdomyosarcomas, and fibrosarcomas are malignant primary cardiac tumors that involve the myocardium and may directly invade the pericardium. Medical and surgical management of these tumors is at best palliative, with a poor short-term prognosis. Primary malignant tumors of the pericardium (including fibrosarcoma and mesothelioma) have a similarly poor outcome (761) (*e*Fig. 26.11.4). Secondary or metastatic malignant pericardial disease arises from lung, breast, melanoma, or hematologic malignancies in the majority of cases (759,762). Malignancies from below the diaphragm (gastrointestinal tract and renal) rarely reach the pericardium. Autopsy studies show that less than one-third of cases are diagnosed antemortem (760).



***e*FIGURE 26.11.4** Primary pericardial malignancy (spin-echo; horizontal long-axis). A large heterogeneous mass (*asterisk*) represents a malignant fibrous histiocytoma originating in the pericardium and extending into the cardiac chambers at the level of the left atrium and outward into the left lung. (Courtesy of R. D. White, MD, The Cleveland Clinic Foundation.)

Clinical Presentation. The majority of patients with malignant involvement of the pericardium is asymptomatic (760,763,764 and 765). Malignant pericarditis may present as effusion, with or without tamponade, cardiac encasement with constrictive physiology, impaired coronary circulation, and cardiac denervation. Clinical manifestations include dyspnea, cough ascites, and edema (760). Indeed, malignancy is a leading cause of cardiac tamponade in developed nations. Electrocardiography demonstrates low voltages in the majority of patients, but classical electrical alternans in only 5% (766). Radiographic cardiomegaly is common. Echocardiography easily diagnoses pericardial effusion and can often identify a tumor mass in the pericardial space or encasing the heart. MRI has emerged as a useful diagnostic tool for assessing mass lesions in the pericardium (161).

Pericardiocentesis is useful as a diagnostic and therapeutic tool. Diagnostic information includes the nature of the fluid (exudate, transudate, serous, sanguineous, chylous), cellularity, infection, and presence of tumor cells by cytology. Pericardial tamponade is an indication for urgent pericardiocentesis from the apical or subxyphoid approach. Effusions may be large in volume and should be drained over hours. Loculated effusions may not drain completely. Fluid recurrence after

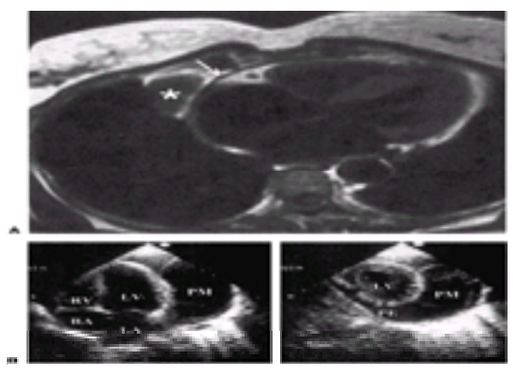
pericardiocentesis has been managed with pericardial sclerosis using several instillations of 500 to 1,000 mg of tetracycline over 8 days (767,768).

In situations in which no suitable percutaneous window exists for pericardiocentesis or fluid recurrence is significant, a surgical pleuropericardial or pleuroperitoneal window may be created. This procedure can be performed under local anesthetic in less than 1 hour with minimal risk. It is highly efficacious with a low recurrence rate. These advantages have led many clinicians to favor this as a first approach bypassing pericardiocentesis (766). Radiotherapy is a third treatment option for malignant pericardial effusions. External beam therapy of 25 Gy over 3 to 4 weeks gave short-term relief (mean, 4 months) in 60% of a series of 38 patients (765).

Prognosis. The diagnosis of malignant pericardial disease has ominous implications. Nonhematologic tumors involving the pericardium respond poorly to all therapeutic interventions, with life expectancies in the weeks to months range (720). Patients presenting with tamponade have an even worse outlook.

Congenital Abnormalities of the Pericardium

Cysts of the pericardium are rare, and clinically benign lesions usually present as asymptomatic masses along the cardiac margin on chest radiography (eFig 26.11.5). The most frequent sites of occurrence are the right followed by the left cardiophrenic angles (769,770). Nonspecific symptoms such as chest pain, dyspnea, and cough may occur (769). Serious complications such as airway obstruction, erosion into cardiovascular structures, and cardiac tamponade have been reported (770).



***e*FIGURE 26.11.5 A:** Pericardial cyst (spin-echo; transaxial). A well-circumscribed, oval-shaped mass lesion (*asterisk*) is seen along the right cardiac margin, separate from the pericardium (*arrow*); it represents a simple pericardial cyst. (Courtesy of R. D. White, MD, The Cleveland Clinic Foundation.) **B:** Two-dimensional echocardiography. *Left*: Apical four-chamber view. *Right*: Parasternal short-axis view. Echolucent structure seen adjacent to the left ventricle (LV) that was identified as a pericardial cyst. LA, left atrium; PE, pericardial effusion; PM, pericardial mass; RV, right ventricle; RA, right atrium. (From Bava GL, Magliani L, Bertoli D, et al. Complicated pericardial cyst: atypical anatomy and clinical course. *Clin Cardiol* 1998; 21:862–864, with permission.)

Complete or partial absence of the pericardium is rare, occurring in male more often than female subjects, and is associated with congenital cardiac abnormalities such as atrial septal defect and bicuspid aortic valve and lung malformations. Patients may develop chest pain while lying on the left side, and the character of the pain may be described as “stabbing” (771). Complete absence of the pericardium is associated with leftward displacement of the heart and RV dilatation. Partial absence usually occurs over the atria and may lead to herniation and pseudoaneurysm formation (772), which must be differentiated from true atrial aneurysms (773). Connolly et al. described the echocardiographic features most commonly seen in patients with congenital absence of the pericardium. They included unusual imaging windows, hypermobility or swinging of the heart, and abnormal septal motion (774).

Drugs

Pericardial reactions to drugs are rare and idiosyncratic. Pericarditis is seen in patients who develop lupus syndrome in response to procainamide, hydralazine, reserpine, and methyldopa (775). Other drugs such as penicillin, dantrolene, minoxidil, and practolol produce pericardial reactions by non-lupus mechanisms (776).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Definition, Prevalence, and Utility of Diastolic Function

In 2001, the exact definition and prevalence of diastolic heart failure are controversial, as well as the appreciation of its importance in clinical practice. A good working definition of diastolic dysfunction has been proposed by the European Working Group (30), but modification of this definition has been proposed by other investigators and will likely continue to evolve (31,32,250).

The exact prevalence of diastolic function is still debatable (31,250,777). The prevalence of diastolic function has varied widely from 13% to 74% (250). The reasons for this heterogeneity include variability in the criteria, duration and chronicity of congestive heart failure, the effect of age, the presence of coronary artery disease, selection bias in obtaining the patients, the type of imaging modality, the variables for assessing systolic performance, and the timing of the study (250). Despite this variability, it is the authors’ opinion that in a tertiary referral practice, elderly patients with hypertension and coronary disease commonly have diastolic heart failure, in keeping with the estimated 40% prevalence. A large population-based study (Cardiovascular Health Study) in older patients (66 to 103 years) found a prevalence of 55% of patients with heart failure and normal systolic function, and a total of 80% with normal or mildly reduced systolic function, especially in women (778).

Furthermore, the prognosis of patients with diastolic dysfunction is uncertain. The annual mortality was reported to vary from 1.3% to 17.5% (250). A worse prognosis is associated with older patients, men, coronary artery disease, and valvular heart disease (250). Relatively recent work in elderly patients (50% greater than 80 years age) with heart failure from Olmstead County showed similar poor prognosis in patients with normal (greater than or equal to 50%) or reduced systolic function. Despite the variability of these studies, the mortality of patients with diastolic dysfunction is generally lower than in patients with systolic dysfunction, with an annual mortality of 15% to 20% (24). It is the authors’ opinion that it is important to recognize an episode of diastolic heart failure so that early detection of underlying causes and treatments can be initiated.

The newer noninvasive tools to diagnose diastolic function including TDE and color M-mode Doppler are less load dependent than mitral inflow and pulmonary vein flow and have now been increasingly validated by hemodynamic standards. They may be useful especially in patients with isolated diastolic dysfunction, because they are more closely associated with myocardial relaxation. This will permit these techniques to be included into consensus and guideline papers in the measurement and reporting of diastolic dysfunction. The goal of determining diastolic function and estimating cardiac filling pressures in patients with depressed and normal systolic function by means of a comprehensive echocardiographic evaluation can be achieved for most patients (Fig. 26.12).

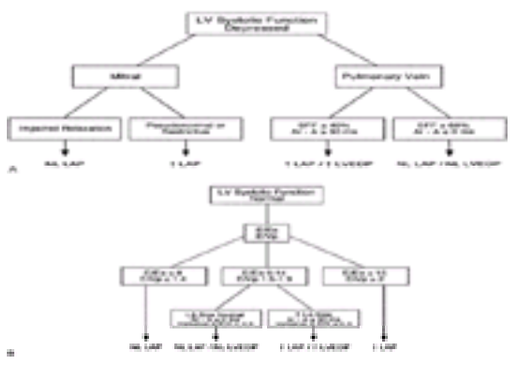


FIGURE 26.12 A: An algorithm for assessment of left atrial pressure and left ventricular end diastolic pressure (LVEDP) in patients with depressed LV systolic function. Ar-A, difference in duration of the atrial reversal wave (pulmonary vein) and of the atrial wave of mitral inflow; NL LAP, normal left atrial pressure; SFF, systolic filling fraction; ↑ LAP, increased left atrial pressure. **B:** Algorithm for estimation of LAP and LVEDP in individuals with normal LV systolic function using the new indices of diastolic function, mitral inflow E velocity (E), pulmonary vein velocity and left atrial size. Ea, early diastolic velocity at the mitral annulus; Vp, flow propagation velocity.

(Adapted from Nagueh SF, Zoghbi WA. Clinical assessment of LV diastolic filling by Doppler echocardiography. *ACC Curr J Rev* 2001;10:45–49.)

Treatment of Diastolic Function and the Need for Clinical Trials

The treatment of patients with diastolic heart failure is also controversial and limited to small studies (250). In fact, there have been no published clinical trials of patients with diastolic heart failure; thus the treatment is highly empiric. It is not generally appreciated that Doppler echocardiography may be useful in guiding medical therapy depending on the filling pattern, LV dimensions, and etiology of diastolic function (15).

There are ongoing studies to evaluate the role of new therapies including angiotensin receptor blockers, beta-blockers, including carvedilol and nitric oxide donors in patients with diastolic heart failure (104). These studies will evaluate not just the hemodynamic, biochemical, and histologic effects on the myocardium, but also exercise capacity and prognosis (246,779). Recent studies have targeted the direct cellular mechanisms leading to diastolic dysfunction. Animal experiments have shown that diastolic function can be improved in senescent rat hearts through adenoviral gene transfer of sarcoplasmic reticulum Ca^{2+} ATPase protein (SERCA 2a) (780) and through the use of the advanced glycation end-product cross-link breaker (ALT-711) in older dogs (781).

Controversies in Restrictive Cardiomyopathy and Constrictive Pericarditis

In 2001, the classification of restrictive cardiomyopathy still remains a controversial issue (see previous discussion) (269). The exact definition of restrictive cardiomyopathy has evolved over time and is not uniformly accepted by clinicians (255,256,257,258 and 259). Furthermore, there is still confusion about separating restrictive cardiomyopathy with diastolic heart failure from other cardiac diseases that manifest diastolic heart failure and restrictive hemodynamics (dip and plateau physiology) such as dilated cardiomyopathy with restrictive hemodynamics (263). The WHO/ISFC 1995 classification allays some of the confusion and preserves the old clinical entities of dilated, hypertrophic restrictive cardiomyopathies, and arrhythmogenic RV cardiomyopathy, but now considers the dominant pathophysiology or pathologic factors (254). Now, restrictive cardiomyopathy can be either idiopathic (which is rare) or more commonly be associated with an etiology (i.e., amyloidosis). Using this approach, restrictive cardiomyopathy is a disease within a large group of disorders which manifest diastolic heart failure.

There is also controversy about whether restrictive hemodynamics should be considered as a mandatory part of the disorder, as dictated by the 1995 WHO/ISFC classification (254). For example, as mentioned previously, cardiac amyloidosis may have an early (not restrictive) and advanced stage (restrictive) pattern (275). Similarly, hemochromatosis may present as a dilated cardiomyopathy in the majority of cases, and as a restrictive cardiomyopathy in others (439). It is the authors' opinion that a definite diagnosis of restrictive cardiomyopathy should show restrictive filling in a nondilated, nonhypertrophied ventricle with near-normal systolic function and dilated atria.

Differentiation of Restrictive Cardiomyopathy from Constrictive Pericarditis

Distinguishing restrictive cardiomyopathy from constriction is still an important clinical problem (119,166,269,272). The importance of this distinction is that in restrictive cardiomyopathy, the disease is often treated medically and has a poor prognosis, whereas in constriction, the disease is treated with surgery and usually has a good prognosis (269). Furthermore, to highlight the importance of this differentiation, making the wrong diagnosis in sending a patient with restrictive cardiomyopathy for pericardial stripping is totally unacceptable and dangerous. Since the 1970s, there have been countless diagnostic tests that have been used to differentiate these two similar conditions (166,261). It is the authors' opinion that no single test is perfectly reliable in making the distinction, and good clinical judgment and a stepwise approach should be used (119). The history and physical examination often provide clues to the diagnosis but by no means are definitive. The history of a systemic disorder such as amyloidosis may favor restriction, whereas a history of idiopathic pericarditis or previous cardiac surgery may favor constriction. On the other hand, a history of radiation may show evidence of both constriction and restriction (119,269). It is also the authors' opinion that the noninvasive workup is most important in distinguishing restriction from constriction (15). In most patients, diastolic functional abnormalities can be adequately characterized using noninvasive modalities such as transthoracic echo, transesophageal echo with respirometry, and MRI (119). Furthermore, they have added new information regarding the actual structure and physiologic function of the myocardium and pericardium. MRI may be better suited to demonstrate the abnormal pericardial thickness, whereas echocardiography may show the physiologic abnormalities including interventricular dependence, limited filling, and dissociation between intrathoracic and intracardiac pressures. As with most tests, there may be some overlap (584); other noninvasive tools have also emerged such as color M-mode and tissue Doppler imaging to help distinguish these disorders (121). Finally, endomyocardial biopsy may be necessary for cases in which other modalities are inconclusive or ambiguous (295).

THE FUTURE

There will be further recognition of the importance of diastolic function and the prevalence of diastolic heart failure, especially in the elderly. Future refinements in the noninvasive modalities will aid the consistent diagnosis of patients with diastolic dysfunction and elevated filling pressures, thus allowing for more uniform criteria for organization of large clinical trials. A diastolic stress test may be used as part of the assessment of patients with exertional dyspnea. There will be greater use of these newer modalities as part of the treatment algorithms for patients with diastolic dysfunction. There may be specific targeted therapies derived from the cellular, biochemical, neurohormonal, and physiologic mechanisms in these patients. There will be ongoing refinements in the differentiation of constrictive pericarditis and restriction. The genetic framework for all restrictive cardiomyopathies will aid in the assessment, prognosis, and treatment of these patients.

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27

PULMONARY HYPERTENSION AND COR PULMONALE

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VICTOR F. TAPSON

“ Indicates text or graphics that appear only in the electronic versions of this text.”

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OVERVIEW

Pulmonary arterial hypertension causes an increased pressure load on the right ventricle (RV) that subsequently results in the normal adaptive response of hypertrophy and dilation. Right ventricular failure occurs when the ventricle is unable to respond further to the hemodynamic burden (1). *Cor pulmonale* is defined as right ventricular hypertrophy, dilation, and dysfunction as a result of pulmonary hypertension secondary to a variety of chronic lung diseases (Table 27.1). Pulmonary hypertension may also develop in the absence of cardiac or pulmonary parenchymal disease.

TABLE 27.1 PULMONARY HYPERTENSION: NOMENCLATURE AND CLASSIFICATION

HISTORICAL PERSPECTIVE

In 1852, Beutner recorded the pulmonary artery pressure in dogs during open thoracotomy and demonstrated that the pulmonary artery pressure was considerably lower than that in the systemic circulation (2). Similar observations were made in the horse by Chauvau in 1856 (2). Measurement of the pulmonary artery pressure in humans was ultimately accomplished with the development of right atrial catheterization by Cournand and Ranges in 1941 (3), followed by pulmonary artery catheterization in 1946 by Bloomfield and colleagues (4). In 1953, Fowler and associates (5) found that the pulmonary artery systolic pressure in healthy individuals ranged from 11 to 29 mm Hg, the diastolic pressure from 4 to 13 mm Hg, and the mean pulmonary artery pressure from 8 to 19 mm Hg. These developments, followed by the widespread use of the pulmonary artery catheter (6), led to enhanced understanding of the pulmonary circulation in chronic lung disease and in primary pulmonary vascular disorders.

Because of the diverse causes of pulmonary hypertension and cor pulmonale, the historical perspective is complex. Fishman (1) outlined the state-of-the-art approach to cor pulmonale in 1976 after years of research dedicated to the understanding of the pulmonary circulation. Investigations into the pathophysiology of cor pulmonale have, to a significant extent, involved the influence of hypoxemia or pharmacologic agents on the pulmonary circulation in chronic lung disease (7,8,9,10,11 and 12). Fishman (13) also described in detail the history of research efforts in patients with pulmonary hypertension, particularly primary pulmonary hypertension (PPH) as it has evolved since the beginning of the twentieth century. Syphilitic arteritis had frequently been invoked as the cause of pulmonary hypertensive disorders. Interest in determining the cause of “Ayerza’s disease” ultimately led to the conclusion that most of these cases were secondary pulmonary hypertension caused by either congenital or acquired heart disease or by chronic obstructive pulmonary disease (COPD) (14). Significant contributions by Motley et al. (11), as well as by von Euler and Liljestrand (12), led to further studies that involved the hypoxic pressor response and pulmonary vasomotor reactivity. Experimental studies by Dresdale et al. (14) evaluating tolazoline, and by Harris (15) and Wood (16) with acetylcholine, led to the ultimate concept that vasodilator therapy was effective in some patients with PPH. In the late 1960s, a pulmonary hypertension epidemic occurred in Switzerland, Germany, and Austria and was attributed to aminorex, an over-the-counter diet pill (17).

In 1973, prompted in part by this epidemic, the World Health Organization (WHO) assembled a working group to assess the current understanding of PPH. The knowledge base for this disease was rather limited at that time, but this effort resulted in the initial pathologic classification of PPH (18). In 1998, on the 25-year anniversary of the original WHO meeting, the World Symposium on PPH, cosponsored by the WHO, was held in Evian, France (19). Substantial progress had been

made since the prior meeting. One of the significant outcomes of this most recent symposium was to propose a new, more clinically useful classification system for pulmonary hypertension. Over recent years, a number of therapeutic vasodilator agents have been investigated, with the hope that selective pulmonary arterial vasodilation could be achieved. The advent of prostacyclin therapy appears to have come the closest to accomplishing this goal. The importance of vascular remodeling in addition to vasoconstriction has been realized. Lung transplantation has become the final therapeutic step for PPH.

INCIDENCE AND RISK FACTORS

Right ventricular failure is an important predictor of increased mortality in patients with chronic lung disease. It commonly occurs in individuals with COPD, which causes an estimated 70,000 deaths each year in the United States (20). A study of patients with COPD found that 40% had evidence of cor pulmonale at autopsy (1). Furthermore, in the National Institutes of Health (NIH) Primary Pulmonary Hypertension National Registry, mortality was found to correlate best with indices of right ventricular hemodynamic function (21). Cor pulmonale is also associated with increased morbidity in patients with chronic lung disease leading to reduced exercise tolerance, increased sensation of dyspnea, and reduced functional status (22). Other causes of cor pulmonale are less common. The incidence of PPH is estimated to be one to two cases per million in the general population (21). Pulmonary vascular disease that is clinically and pathologically indistinguishable from PPH can occur in association with human immunodeficiency virus infection, portal hypertension, cocaine inhalation, monocrotaline (a compound from the plant *Crotalaria* that is found in bush tea), and drugs, including appetite suppressants and chemotherapeutic agents (23,24,25,26 and 27). In the 1960s, the anorexigenic agent aminorex was found to be associated with an increased risk of pulmonary hypertension (28). Use of the appetite suppressants fenfluramine and dexfenfluramine has been found to be associated with an increased risk of pulmonary hypertension (odds ratio 6.3) (27). This risk increased to an odds ratio of greater than 20 when the drugs were taken for more than 3 months, independent of body mass index. Other entities such as progressive systemic sclerosis and CREST (*c*alcification, *R*aynaud's, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasis) may present with progressive, severe pulmonary hypertension, often without associated parenchymal lung disease.

GENETICS OF PRIMARY PULMONARY HYPERTENSION

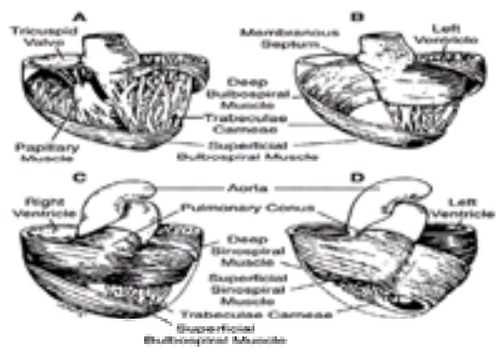
The genetics of PPH are becoming unraveled. Approximately 6% of patients with PPH have the familial variety. This disease is transmitted in the autosomal dominant manner with a risk of clinical expression of approximately 10% to 20% and demonstrates genetic anticipation. Studies of genetic linkage revealed that the locus for familial PPH is on chromosome 2q31–32. The known genes in this region have been surveyed for biologically plausible candidates. The results of a detailed genetic study of a large kindred of familial PPH patients has now provided additional information (28a). The gene that is associated with a unique member of the transforming growth factor-b (TGF-b) receptor family, known as *bone morphogenetic protein receptor II* (BMPR2), appears to be a likely candidate. Investigators have detected a missense mutation that involves a substitution of guanine for thymine at position 354 of *BMPR2*. This mutation was located in exon 3 of the gene and was present in all of the affected family members. More recently, it was discovered that the sporadic form of PPH is also associated with germline mutations of *BMPR2* (28b).

Bone morphogenetic proteins were previously identified as cellular products found in normal bone that promote ectopic bone formation and healing of fractures. Members of the TGF-b receptor superfamily of circulating proteins regulate growth and repair of tissue in all organs (28c,28d). Bone morphogenetic proteins exert their effects through the activation of receptors I and II, which are expressed adjacent to each other on cell surfaces and transduce intracellular signaling. The effect of activation of these receptors depends on the cell type and the circumstances and can result in either promotion or inhibition of growth. It appears that clinical PPH develops in only 10% to 20% of carriers of BMPR2 mutations; it has been speculated that gene modifiers, such as environmental factors, estrogens, or other mutations in unknown regulatory genes, may be required for clinical expression of the disease (28a). It may be that the normal function of bone morphogenetic receptor protein II in the pulmonary vasculature is antiproliferative. Based on these genetic discoveries, genetic testing and counseling will become increasingly important for PPH patients and their families.

PATHOPHYSIOLOGY

Normal Right Ventricular Anatomy and Function

The RV can be divided into an inflow tract, consisting of the tricuspid valve, papillary muscles, chordae tendineae, and trabeculated myocardium, and an outflow tract, consisting of the infundibulum (eFig. 27.0.1). It has a pyramidal geometric configuration, with the inflow region constituting the triangular base and the three sides composed by the interventricular septum and the anterior and the posterior aspects of the free wall. The thin free wall of the RV anchors anteriorly and posteriorly to the interventricular septum, which bulges into the RV cavity. Thus, on a cross-sectional view, the RV has a crescentic shape. It is this configuration and its thin wall that make the RV highly compliant and able to accommodate large volumes and filling pressures (20,29). Under normal circumstances, the pulmonary vasculature is a low-pressure system, thus providing low vascular resistance to right ventricular outflow (30). The pulmonary vascular bed is also able to accommodate large increases in blood flow without much change in pressure, preventing pressure overload of the RV. Cardiac output can increase substantially during exercise in normal individuals, with increases of up to fivefold in pulmonary blood flow (31,32). Recruitment of vessels in the poorly perfused upper lung and distention of the compliant vessels in the dependent areas appear to be the major mechanisms involved in accommodating increases in cardiac output and pulmonary blood flow (1,33). With the development of pulmonary disease, alterations in the pulmonary vasculature develop, often leading to pulmonary arterial hypertension and right ventricular pressure overload. The mechanisms that lead to the development of pulmonary arterial hypertension are complex and not completely understood.



***e*FIGURE 27.0.1** Spiraling muscle fibers are shown **(A–D)** that enclose both ventricles and help the two contract in synchrony. (From Rushmer RF. *Cardiovascular dynamics*. Philadelphia: WB Saunders, 1970, with permission.)

Mechanisms of Pulmonary Hypertension

Vascular Bed Destruction or Obliteration

Destruction or obliteration of the pulmonary vascular bed appears to account for some of the increase in pulmonary artery pressure as pulmonary disease develops. Nonetheless, the extent of pulmonary disease, as in COPD, does not correlate with the degree of pulmonary hypertension (34). In addition, in the absence of significant underlying lung disease, pulmonary artery pressure and pulmonary vascular resistance (PVR) remain normal after pneumonectomy (1), although right ventricular ejection fraction (RVEF) at rest can be significantly decreased up to 3 weeks postoperatively. Right ventricular dysfunction during exercise also occurs with increases in right ventricular end diastolic volume, pulmonary artery pressure, and PVR (35). Significant elevation in mean pulmonary arterial pressure develops only after one-half to two-thirds of the pulmonary vascular bed is occluded experimentally (36,37). Therefore, vascular bed obliteration does not appear to be a major mechanism in the development of pulmonary hypertension and cor pulmonale.

Hypoxic Pulmonary Vasoconstriction

Alveolar hypoxia is a major contributor to the development of pulmonary hypertension. In 1947, Motley and associates (11) found in five human subjects that breathing 10% oxygen for 10 minutes caused increases in pulmonary artery pressure with a concomitant decrease in cardiac output as determined by the Fick method. This was subsequently confirmed, in 1952, by Fishman and colleagues (7) in the steady state, despite the finding that the application of the Fick principle by Motley and associates was found to be erroneous. Hypoxic pulmonary vasoconstriction involving small arteries and arterioles is thought to be a defense mechanism that determines local ventilation-perfusion ($\dot{V}/\dot{Q}$) relationships, as first suggested by von Euler and Liljestrand (12) in 1946. It is unclear, however, if the vasoconstriction is due specifically to the hypoxia or whether it is caused by vasoactive mediators, including prostaglandins, endothelin, bradykinin, acetylcholine, angiotensin,

catecholamines, histamine, or serotonin, which lead to calcium influx (30).

In recent years, advances have been made in understanding the regulation of pulmonary vascular tone with the discovery of nitric oxide (NO). Endothelium-derived relaxation factor, discovered in 1980 (38), is produced by endothelial cells in a constitutive manner from arginine and is now identified as NO (39) or a nitroso compound that ultimately releases NO (40). NO synthase produces NO and citrulline from L-arginine, and the endothelial form of this enzyme depends on calcium and calmodulin to regulate NO production in a constitutive manner (41,42 and 43). Endothelium-dependent relaxation has been found in isolated pulmonary arteries from most mammalian species, including humans (44,45,46,47 and 48). Studies have demonstrated that inhibition of NO production by L-arginine analogs markedly enhances the pulmonary pressor response to acute hypoxic challenges, which demonstrates the role that NO has in regulating pulmonary vascular tone at rest and during acute hypoxia (49,50,51,52 and 53). In addition, impaired NO production or release by endothelial cells, or both, is seen in chronic hypoxic vasoconstriction (54,55 and 56). A number of mediators cause calcium influxes into vascular smooth muscle cells, activating the endothelial constitutive NO synthase (43). Impairment of NO production allows for excessive vasoconstriction and reduces the ability of the pulmonary vasculature to relax.

Chronic vasoconstriction eventually leads to structural changes in the walls of the pulmonary vasculature. Changes in the vasculature begin to appear even 1 hour after the onset of hypoxia in experimental models (57). Although the mechanisms that lead to these changes are not fully understood, lack of NO production may allow mitogenesis and proliferation of cells within the vessel walls (55). The changes in the pulmonary vasculature include increases in the percentage of vessels with a muscular layer due to proliferation of vascular smooth muscle cells, medial hypertrophy, and eccentric intimal fibrosis (58). These changes may also allow for increased platelet aggregation and development of thrombi, causing further increases in PVR (58,59). As a result, the cross-sectional area of the pulmonary vasculature decreases, and pulmonary arterial hypertension is irreversible (30).

Myocardial Blood Flow

Inadequate blood supply to the RV may also contribute to the development of right ventricular failure. The RV responds to chronic increases in PVR with dilation and hypertrophy. With increases in muscle mass, oxygen demands increase (60,61). Oxygen also demands an increase in the LV with the development of systolic hypertension. Nonetheless, left ventricular coronary perfusion pressures are maintained or even increased because of increased diastolic pressures (60,62). Unlike the case with the LV, the perfusion (diastolic) pressure of the right coronary artery is unchanged or reduced when oxygen demands increase because right ventricular cardiac output remains unchanged or is diminished (62). In addition, the systolic component of right ventricular coronary blood flow is reduced due to the increase in chamber pressure that occurs with dilation of the RV (63).

The relationship between right coronary blood flow and right ventricular performance was studied in experimental animal models by Brooks et al. (37,64). Pigs were subjected to increases in pulmonary artery pressure by pulmonary artery occlusion. Right ventricular failure and shock developed at or above a pulmonary artery pressure of approximately 70 mm Hg. Hemodynamic collapse occurred at a lower pulmonary artery pressure when the right coronary was occluded. With reinstitution of coronary blood flow by a coronary artery perfusion pump, the RV could be resuscitated despite maintenance of high pulmonary artery pressures (37) (Fig. 27.1). This would also explain the findings that right ventricular failure and hemodynamic compromise are more likely to develop in patients with coronary artery disease in the setting of pulmonary embolism.

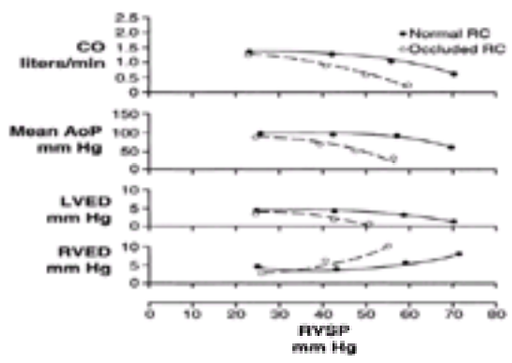


FIGURE 27.1 Effect of increasing right ventricular systolic pressure (RVSP) on cardiac output (CO), aortic pressure (AoP), left ventricular end diastolic pressure (LVED), and right ventricular end diastolic pressure (RVED). Solid lines join points with an intact right coronary artery (RC). Decompensation occurs at a much lower level of RVSP, with an occluded compared with intact RC. (From Brooks H, Kirk G, Vokonas P, et al. Performance of the right ventricle under stress: relation to right coronary flow. *J Clin Invest* 1971;50:2176–2182, with permission.)

Afterload and Preload

Increasing PVR increases afterload for the RV. By increasing preload and dilating, right ventricular function can improve via the Frank-Starling mechanism with increased cardiac output (29,65). Myocardial wall hypertrophy allows for reduction in wall stress and maintains adequate stroke volume. Spann and colleagues (66) showed that cardiac output and stroke volume were not different in cats who had pulmonary artery banding for 30 days compared with the normal control subjects. Nonetheless, right ventricular end diastolic volume and weight were significantly increased; in addition, contractile performance of the intact ventricles and isolated papillary muscles was reduced (66). Thus, normal hemodynamics were maintained by compensatory dilation and hypertrophy.

Severe right ventricular hypertrophy resulting from pulmonary hypertension. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Chronic Obstructive Lung Disease and Interstitial Lung Disease

COPD and interstitial lung disease (ILD) are common causes of pulmonary parenchymal disease. In the United States, COPD is the most common pulmonary disease that results in right ventricular dysfunction, and it is a factor that adversely affects survival (1,30). In 1966, a Veterans Administration cooperative trial found that patients with cor pulmonale had a 4-year mortality of 73% (67). These findings were reproduced by Lindsay and Read in 1972 (68), as well as by Traver and colleagues in 1979 (69).

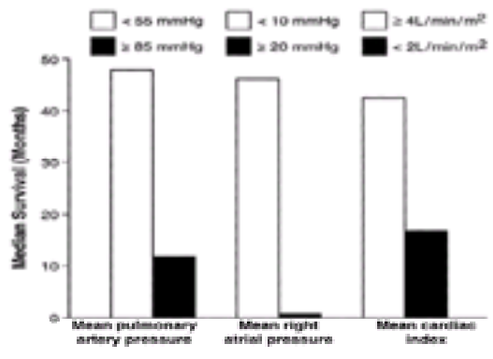
Assessment of right ventricular systolic function is commonly done in patients with pulmonary disease by measuring the RVEF. Despite the variability of RVEF in patients with COPD, it has been shown that those with clinically evident cor pulmonale consistently have a reduced RVEF (70). In addition, patients without clinical cor pulmonale, but with a depressed RVEF, have severe obstructive ventilatory defects. In COPD patients with a history of cor pulmonale and elevated pulmonary artery pressure, the latter measure is inversely related to arterial oxygen tension, and increased PVR has been found to correlate with mortality (71). Therefore, it appears that increased right ventricular afterload leads to a depressed RVEF. Nonetheless, when right ventricular contractility was measured with load-independent methods, it did *not* appear to correlate with RVEF (72). Thus, RVEF may be a poor indicator of intrinsic contractility, although it is usually depressed in the setting of pulmonary artery hypertension.

The ILDs are disorders that cause thickening and fibrosis of the alveolar walls, resulting in disruption of the alveolar-capillary unit. The majority of these is of unknown etiology. The fibrosis can entrap segments of the pulmonary vasculature, compressing the vessels and subsequently leading to thrombosis and fibrous organization of the vessels with complete obliteration of some areas of the vasculature (73). This leads to hypoxemia from diffusion impairment and $\dot{V}/\dot{Q}$ mismatching. Patients with ILD die from respiratory failure or right ventricular failure. Initially, hyperventilation at rest allows for normal oxygenation, and desaturation occurs during exercise. As the disease progresses, oxygen consumption increases as the work of breathing increases, leading to hypoxemia at rest (1,30). Eventually, pulmonary artery hypertension develops that correlates with the degree of hypoxemia. The pulmonary artery pressure is moderately elevated in such patients until late in the disease. Again, as in their counterparts with COPD, pulmonary artery pressures are important predictors of survival (74). Sarcoidosis may result in significant parenchymal disease with hypoxemia and pulmonary hypertension. Alternatively, the predominant abnormality may appear to be intrinsic to the vasculature or due to compression/tethering of the vessels. Pulmonary hypertension may also result from left ventricular dysfunction in sarcoidosis.

Pulmonary Arterial Hypertension

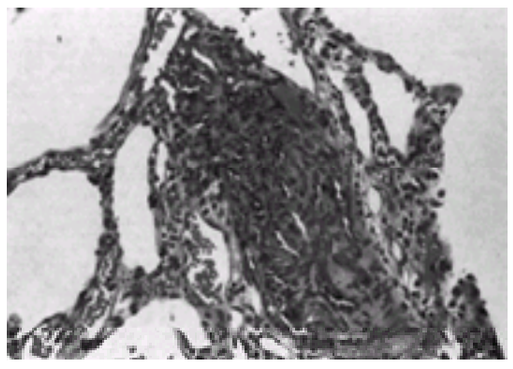
In 1998, on the 25-year anniversary of the original WHO meeting, the World Symposium on PPH, cosponsored by the WHO, was held in Evian, France (19). Substantial progress had been made since the prior meeting. One of the significant outcomes of this symposium was to propose a new, more clinically useful classification system for pulmonary hypertension. Traditionally, pulmonary hypertension has been classified as being either “primary” or “secondary.” Although PPH is relatively rare, secondary pulmonary hypertension is distinctly more common and includes a heterogeneous group of diseases. A consensus was reached at the 1998 symposium to develop a more inclusive and clinically useful classification system (Table 27.1). An important result was to emphasize the significance of the entity of pulmonary *arterial* hypertension. The latter indicates that the disease is a pulmonary *vascular* process caused by direct involvement of the pulmonary arteries.

PPH is a clinical condition characterized by an unexplained persistent elevation of pulmonary artery pressures. The criteria for the diagnosis established by the NIH PPH Registry include a mean pulmonary artery pressure of greater than 25 mm Hg at rest or 30 mm Hg or greater with exercise and the exclusion of any known cause of pulmonary hypertension, including left-sided cardiac valvular disease, myocardial disease, congenital heart disease, and clinically important pulmonary, connective tissue, or thromboembolic disease. According to this registry, the median survival of 187 patients was estimated at 2.8 years and was independent of age, sex, age at onset of symptoms, symptom duration, or family history of PPH (21). The hemodynamic profiles of these patients demonstrated an average mean pulmonary artery pressure of 60 mm Hg, and those with worse functional class had higher pulmonary artery pressures. The abnormalities in pulmonary hemodynamics persist over time, leading to decline in cardiac output and increase in PVR. Very high correlations with mortality were obtained for the independent variables of pulmonary artery pressure, right atrial pressure, and cardiac index as determined by catheterization (eFig. 27.1.1). Additional studies have shown a correlation between mixed venous oxygen saturation, functional class, exercise tolerance, and response to vasodilators (75,76,77,78 and 79). Patients with PPH die primarily of right ventricular failure or, less commonly, of sudden death. It is unusual for patients who are clinically stable, and who have early New York Heart Association class III or milder symptoms, to die unexpectedly.

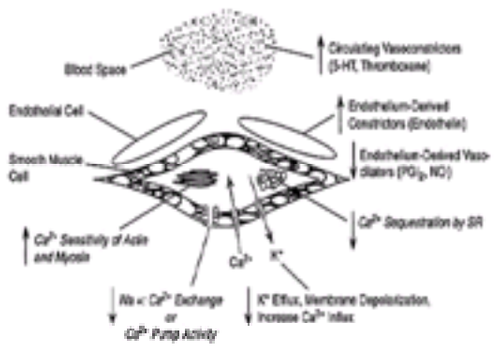


***e*FIGURE 27.1.1** Median survival in months for patients with primary pulmonary hypertension compared with three hemodynamic variables. It is likely that long-term mortality in patients fitting one or more of these categories is significantly improved on continuous intravenous prostacyclin. (From D’Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. *Ann Intern Med* 1991;115:343–349, with permission.)

The pathology of PPH is not unique to this disease entity. It includes medial hypertrophy of the pulmonary arteries, intimal hyperplasia, muscularized pulmonary arterioles, thrombotic microangiopathy, and plexiform lesions (eFig. 27.1.2). Increased PVR is thought to occur as a result of a combination of vasoconstriction, vascular wall remodeling, and *in situ* thrombosis (58). Sustained vasoconstriction may be due to several mechanisms that can lead to altered vasoreactivity (eFig. 27.1.3). The proposed mechanisms include an imbalance in the production of specific vasodilators, such as prostacyclin, endothelium-derived relaxation factor or NO, and vasoconstrictors, such as thromboxane, endothelin, or serotonin (55,58,80,81). Another mechanism that has been considered includes impaired smooth muscle relaxation as a primary event or secondary to endothelial cell injury (58). Nonetheless, the lack of supportive data makes this hypothesis less likely. Finally, alterations that are present in potassium ion channels may lead to calcium influx causing smooth muscle contraction (82).



***e*FIGURE 27.1.2** A plexiform lesion in primary pulmonary hypertension. Experimental evidence suggests that these abnormalities arise from repair, recanalization, and formation of small collateral channels that may originate or be predominantly from the bronchial circulation.



***e*FIGURE 27.1.3** Mechanisms that might increase pulmonary vascular tone. 5-HT, serotonin; NO, nitric oxide; PGI_2, prostacyclin. (Modified from Voelkel NF, Tuder RM, Weir EK. Pathophysiology of primary pulmonary hypertension: from physiology to molecular mechanisms. In: Rubin LJ, Rich S, eds. *Primary pulmonary hypertension.* New York: Marcel Dekker Inc, 1997:83–133, with permission.)

A thrombophilic state that contributes to the formation of microthrombi may contribute to the development of PPH. Abnormalities in the coagulation system, such as abnormal fibrinolysis or von Willebrand's factor production, have been found in some PPH patients (83,84,85 and 86). Microthrombi are frequently noted in advanced vascular lesions of patients with PPH, making this finding difficult to categorize as a cause or a secondary event in the disease process (87).

Smooth muscle migration and proliferation can be a consequence of the increased production, increased availability or upregulation of receptors, or increased production of growth factors (88). Growth factors, such as TGF-b, basic fibroblastic growth factor, platelet-derived growth factor, and insulin-like growth factor-1, have been implicated (89,90 and 91). These growth factors, in turn, can lead to increased levels of extracellular matrix proteins, such as thrombospondin, tropoelastin, and fibronectin, which have been found in patients with PPH (92). The increased levels of extracellular matrix proteins can also be due to increased proteolytic activity (93).

In a distinct minority of patients with pulmonary hypertension, the vascular lesions involve predominantly the pulmonary veins with occlusive intimal lesions. This disorder has been termed *pulmonary venoocclusive disease* and mimics classic PPH in many respects (94). The pathologic diagnosis is based on the presence of obstructive, eccentric, fibrous intimal lesions and sinusoidal channels that fill long segments of the pulmonary vein and venule lumina. Arterialization of pulmonary veins may occur, with the development of a distinct medial muscle coat bounded by internal and external laminae. Because of pulmonary venous flow obstruction, the alveolar capillaries are markedly congested, the interstitial space is edematous, and the lymphatics are dilated. This may lead to interstitial and alveolar hemorrhage.

Chronic Thromboembolic Pulmonary Hypertension

In normal patients without prior cardiopulmonary disease, acute pulmonary vascular obstruction results in an increase in PVR, pulmonary artery pressure, and right ventricular work (30). The degree of afterload increase is related to the degree of obstruction of the vascular bed, as well as the degree of vasoconstriction apparently due to vasoactive substances released from the thrombus. When previously healthy patients with pulmonary embolism were studied angiographically and hemodynamically, an increase in mean pulmonary artery pressure was found in 14 of 20 patients (95).

Patients with obstruction of greater than 25% of the vascular bed had increases in pulmonary artery pressures. Nonetheless, the mean pulmonary artery pressure did not exceed 40 mm Hg, even in patients with greater than 50% occlusion of the vascular bed. Therefore, a mean pulmonary artery pressure of greater than 40 mm Hg is rarely generated acutely by the previously normal, thin-walled RV. The RV dilates and increases its filling pressure, and there is a linear correlation between right atrial pressure (and pulmonary artery pressure) and the degree of obstruction by angiography (95). Patients with acute pulmonary embolism and mean pulmonary artery pressure greater than 40 mm Hg nearly always have prior cardiopulmonary disease (96). In such patients, less obstruction is required to increase the pulmonary artery pressure. In patients with right ventricular hypertrophy, however, no correlation is seen between the extent of obstruction and the elevation in pulmonary artery pressure (95). On the other hand, right atrial and pulmonary artery pressures correlate closely, indicating that the RV still makes use of its preload reserve in the setting of increased afterload (30).

Pulmonary Hypertension and Normal Lung Parenchyma

A number of entities can result in pulmonary hypertension in the absence of structural cardiac disease and with normal lung parenchyma. These include sleep apnea, chronic alveolar hypoventilation, high-altitude sickness, and neuromuscular disease. Chest wall and neuromuscular disease as well as sleep apnea are briefly discussed, offering some potential explanations for the resulting pulmonary hypertension.

Thoracic Cage Deformities and Neuromuscular Disease

Neuromuscular diseases, including muscular dystrophy, amyotrophic lateral sclerosis, postpolio syndrome, and numerous others, can result in respiratory failure, hypoxemia, and, occasionally, pulmonary hypertension (97), as may thoracic cage deformities including severe kyphoscoliosis. The management of hypoventilation in neuromuscular and chest wall disorders is based on the premise that preventing further reductions in alveolar ventilation during sleep will result in an improvement in nocturnal and subsequently daytime arterial blood gases, a reduction in pulmonary hypertension and cor pulmonale, and the prevention of premature death. Patients who have been previously disabled by profound dyspnea, sleep fragmentation, cor pulmonale, and unstable respiratory failure have in many instances returned to full-time activities.

Hypoventilation and Sleep Apnea

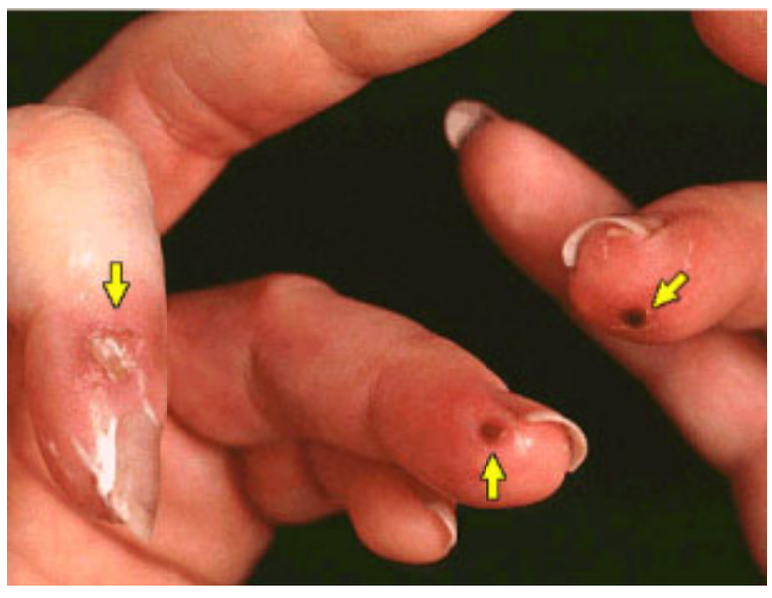
Sleep apnea may lead to the development of pulmonary hypertension and right ventricular failure (98). In obstructive sleep apnea, airflow ceases as a result of complete occlusion of the upper airway despite continued activity of the inspiratory muscles. In central sleep apnea, airflow ceases because there is transient loss of central drive to the respiratory muscles. Most individuals with sleep apnea have a mixed obstructive and central picture. Obstructive apneas are often accompanied by intermittent elevations in pulmonary artery pressure above the baseline level that occur during wakefulness. The maximum increase in pulmonary artery pressure occurs at, or shortly after, the onset of arousal and ventilation, which usually coincides with the maximum extent of arterial oxyhemoglobin desaturation. Supplemental oxygen markedly attenuates but does not abolish these increases in pulmonary artery pressure. Hypoxia-induced pulmonary vasoconstriction certainly plays a role in the pathogenesis of these elevations in pulmonary artery pressure, but it is probably not the only contributing factor. Hypercapnia and acidosis can also induce pulmonary vasoconstriction, leading to elevations in pulmonary artery pressure (1). Thus, it is not surprising that elevations in pulmonary artery pressure are not completely abolished by supplemental oxygen. Although a number of factors contribute to the development of chronic hypercapnia and cor pulmonale in patients with obstructive sleep apnea, reversal of the obstruction alone is sufficient in most cases to alleviate symptoms and reverse right ventricular failure.

CLINICAL PROFILE: EVALUATION OF THE PATIENT WITH PULMONARY HYPERTENSION

History and Physical Examination

Because the development of right ventricular failure and pulmonary hypertension in the patient with chronic pulmonary disease has important prognostic implications, it is important to assess for symptoms that can herald such development. One of the main difficulties is that, in general, symptoms tend to develop gradually. In the NIH PPH Registry, a period of 2 to 5 symptomatic years before diagnosis was documented (99). This is also true of other chronic lung diseases including COPD.

Dyspnea is commonly reported early in the pulmonary patient. With the development of hypoxemia and right ventricular failure, this symptom increases in severity and is uniformly present in nearly all patients. Chest pain is also common and can be difficult to distinguish from angina. Orthopnea is relatively common in patients with severe COPD, although it is not necessarily accompanied by worsening cardiac function. Orthopnea in these patients is believed to be related to hyperinflation of the lungs and the subsequent effects on ventricular function or reduction, or both, in venous return. Evidence of right ventricular dysfunction with increased venous and hepatic congestion can present with the development of early satiety, increasing lower extremity edema and fluid overload. Finally, in patients with PPH, Raynaud's phenomenon is common but also suggests the possibility of collagen-vascular disease. Presyncope and syncope are usually exertional in patients with severe pulmonary hypertension due to the inability to increase cardiac output in response to the increased demand.



Raynaud's disease. Ulcers and gangrene on the fingertips are shown (*arrows*) caused by vasospasm and abnormalities of digital vessels. Associated

cardiac findings are coronary vasospasm and primary pulmonary hypertension.

Certain physical findings may suggest pulmonary hypertension or cor pulmonale, independent of their cause. The presence of a loud and occasionally palpable pulmonic valve closure sound is a common finding in patients with pulmonary hypertension. A parasternal or epigastric lift may be present due to the hypertrophied RV. With progression to cor pulmonale, tricuspid valvular regurgitation develops as a result of dilation of the RV, which causes a prominent jugular V wave. Progressive signs of chronic right ventricular dilation and failure include pulmonic valve insufficiency, a right ventricular third heart sound, jugular venous distention, hepatojugular reflux, hepatomegaly, lower extremity edema, ascites, and eventually anasarca.

Patients with cor pulmonale and pulmonary hypertension due to COPD invariably have findings that are associated with their obstructive lung disease, including decreased breath sounds and hyperinflation. Individuals with cor pulmonale secondary to ILD often have dry crackles at the lung bases. Auscultation of the lungs in PPH and chronic thromboembolic pulmonary hypertension are generally unremarkable, although bruits may be evident over the peripheral lung in the latter group. Clubbing is a common finding in chronic pulmonary disorders, particularly pulmonary fibrosis, cystic fibrosis, and other bronchiectatic disorders. It is also very common in individuals with pulmonary hypertension due to congenital heart disease. Cyanosis, either peripheral or central, may be present in individuals with hypoxemia due to advanced cardiopulmonary disease. Other pertinent physical findings include those associated with collagen-vascular disease, such as telangiectasias, sclerodactyly, or calcinosis, and findings that might suggest alveolar hypoventilation, such as muscle weakness, kyphoscoliosis, and extreme obesity. Algorithms for determining the presence and the cause of pulmonary hypertension are presented (Fig. 27.2 and Fig. 27.3).

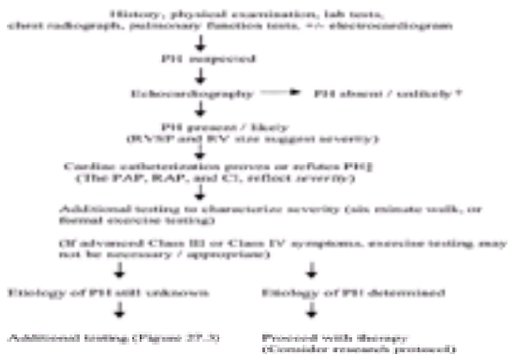


FIGURE 27.2 An approach to the diagnosis of primary pulmonary hypertension (PH). CI, cardiac index; PAP, pulmonary artery pressure; RAP, right atrial pressure; RV, right ventricle; RVSP, right ventricular systolic pressure. †The absence of perceived tricuspid insufficiency by echocardiography may not absolutely exclude PH. ‡Other tests may already have revealed potential etiology(ies) of PH. These tests may also strongly suggest the etiology. (From D'Alonzo GE, Dantzker DR. Diagnosing primary pulmonary hypertension. In: Rubin LJ, Rich S, eds. *Primary pulmonary hypertension.* New York: Marcel Dekker Inc, 1997:227–252, with permission.)

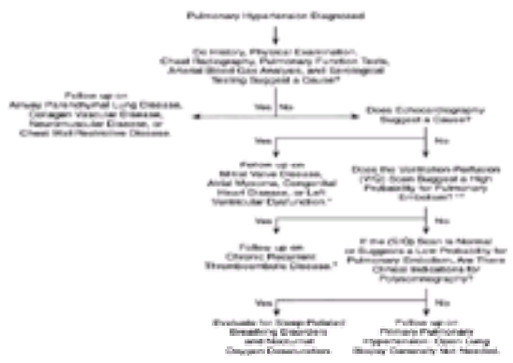
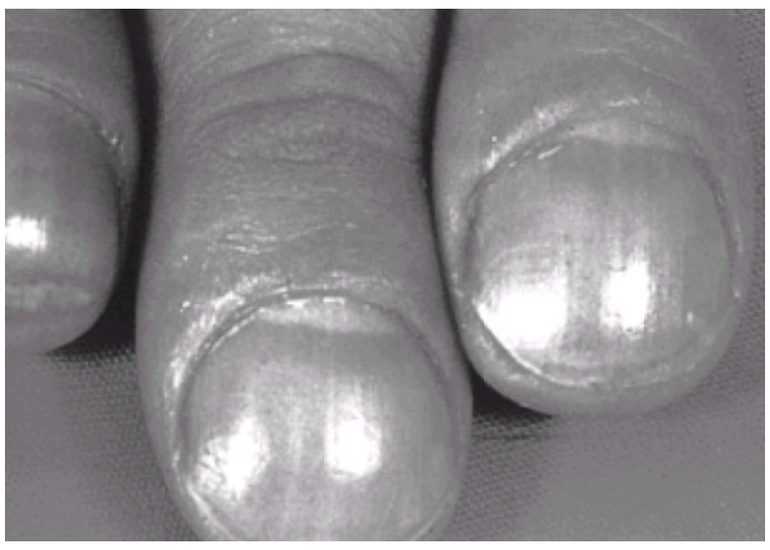


FIGURE 27.3 An approach to determining the cause of primary pulmonary hypertension. *Radionuclide ventriculography may be needed to confirm. **** Spiral computed tomography may also suggest pulmonary embolism. In addition to emboli, a mosaic perfusion pattern may indicate chronic thromboembolic pulmonary hypertension. † Pulmonary angiography may be needed to confirm. (From D'Alonzo GE, Dantzker DR. Diagnosing primary pulmonary hypertension. In: Rubin LJ, Rich S, eds. *Primary pulmonary hypertension.* New York: Marcel Dekker Inc, 1997:227–252, with permission.)



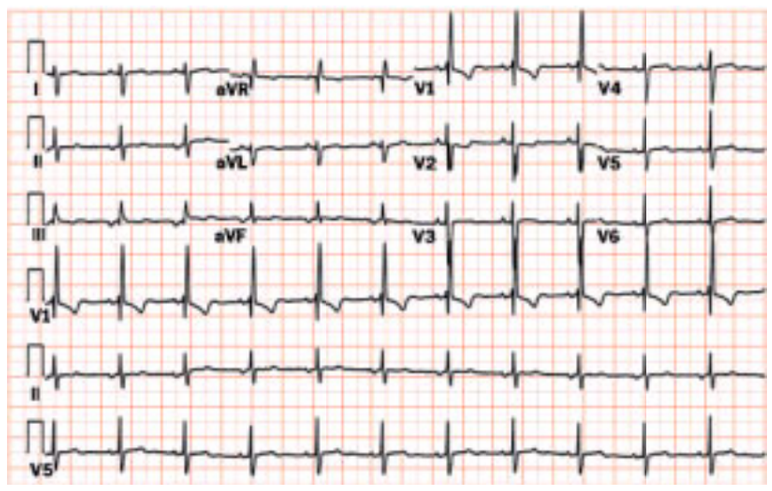
Clubbing. There is bullous enlargement of the distal portion of the digit as a result of increased soft tissue. This may be associated with cyanotic heart disease.

Clubbing. There is enlargement of the distal digits as a result of long-standing endocarditis.

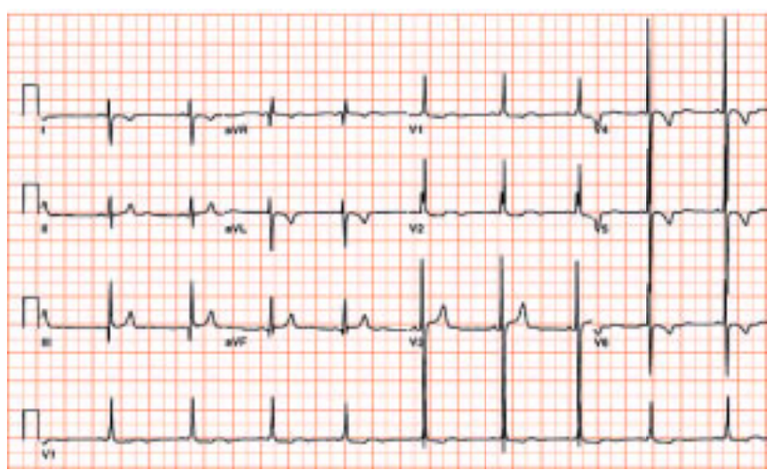
Electrocardiography

The electrocardiogram in the patient with pulmonary hypertension and cor pulmonale reveals evidence of right heart strain, including P-pulmonale, right-axis deviation, right ventricular hypertrophy, and a right ventricular strain pattern. In addition, atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia often occur in the setting of chronic pulmonary disorders. Although the electrocardiogram may not be sensitive in the presence of mild or early pulmonary hypertension, it is more often abnormal in those with advanced disease. In PPH patients, evidence of right heart strain appears to be present in approximately 80% of patients (99). However, particularly with the ready availability of echocardiography, electrocardiography does not offer much useful information regarding the cause or severity of pulmonary hypertension in the vast majority of settings.

A 22-year-old Caucasian female patient with primary pulmonary hypertension.



Right ventricular hypertrophy. Note incomplete right bundle branch block pattern, right axis deviation, and ST-T–wave changes secondary to right ventricular hypertrophy.



A 16-year-old male patient with biventricular hypertrophy secondary to ventricular septal defect and Eisenmenger's syndrome.

A 19-year-old Caucasian female patient with primary pulmonary hypertension.

Mitral stenosis. Left atrial enlargement and right ventricular hypertrophy have developed secondary to mitral stenosis, causing fixed pulmonary hypertension.

Chest Radiography

The chest radiograph is an important tool in the evaluation of patients with suspected pulmonary hypertension or cor pulmonale (Fig. 27.4). It may be helpful in identifying parenchymal lung abnormalities such as pulmonary fibrosis or hyperinflation associated with emphysema. Skeletal abnormalities that may lead to right ventricular failure, such as kyphoscoliosis, can also be identified. In addition, the chest radiogram allows for assessment of cardiac size, especially of the RV. Abnormalities in distribution of pulmonary blood flow may offer clues to the presence of vascular obstruction due to thromboembolic disease. Prominence of the proximal pulmonary arteries is usually present in patients with pulmonary hypertension and may be accompanied by pruning of the distal vessels (100). Unlike classic PPH, even rarer entities such as pulmonary venoocclusive disease may be associated with interstitial infiltrates and Kerley B lines due to alveolar septal lymphatic edema.

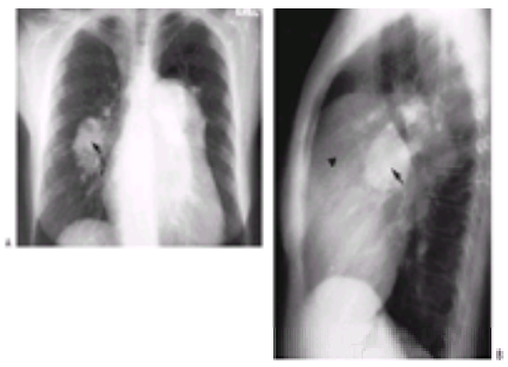


FIGURE 27.4 Chest radiograph in a patient with primary pulmonary hypertension. The proximal pulmonary arteries are dramatically enlarged. This is evident on the posteroanterior **(A)** and the lateral **(B)** views (*arrow*). The lateral film also reveals severe right ventricular enlargement (*arrowhead*).

Pulmonary Function Testing

Pulmonary function tests sometimes suggest the presence of pulmonary vascular disease and may aid in identifying the etiology of pulmonary hypertension and right ventricular failure. Spirometry may reveal evidence of, as well as determining the extent of, obstructive abnormalities. Measurement of lung volumes may identify restrictive lung disease as well as its severity. An isolated reduction in the carbon monoxide diffusing capacity is often noted in PPH, although mild reductions in lung volumes or spirometric values may be present also (101).

Pulmonary gas exchange abnormalities are commonly found in patients with pulmonary hypertension and cor pulmonale. Hypoxemia is frequently observed in patients with significant pulmonary hypertension and cor pulmonale, although the severity depends on the underlying disease. Nevertheless, arterial oxygen tensions are normal or mildly abnormal early in the disease process. Patients with PPH may have normal oxygen tension values until very late in the disease. In patients with sleep-related disorders, oxygen desaturation occurs during apneic or hypopneic episodes. Therefore, abnormalities may not be present during wakeful periods. In the majority of such patients, gas exchange abnormalities with hypercarbia are present early in the course of the disease. Mild sleep apnea in the setting of more severe pulmonary hypertension could represent either coincident disease or an unusually low threshold for the development of pulmonary hypertension. Clinically significant hypoxic vasoconstriction occurs at an arterial oxygen tension of less than 60 mm Hg, which may further exacerbate pulmonary hypertension, regardless of the cause.

Echocardiography: Anatomic Correlations and Clinical Use

Cor pulmonale is defined to some extent by structural changes of the RV including right ventricular hypertrophy and dilation. On gross inspection, right ventricular hypertrophy is usually defined as a posterior wall thickness of greater than or equal to 5 mm at the level of the inferior border of the posterior leaflet of the tricuspid valve, excluding the papillary muscles (102). However, the sensitivity of this measurement as an indicator of pulmonary hypertension has been shown on multiple occasions to be poor (103,104,105 and 106). The most accurate method to determine the presence of cor pulmonale pathologically includes measurement of the weight of the free wall of the RV and the ratio of the combined weight of the septum and the free left ventricular wall to the right ventricular weight (104). These measurements in normal adult hearts are right ventricular weight less than 65 g, combined ventricular weights less than 250 g, and the ratio (as defined above) of 2.3 to 3.3. Evidence of right ventricular failure, defined by the presence pathologically of chronic hepatic congestion, was seen in 27% of cases with a right ventricular weight of 75 to 99 g, in 64% of those with weights of 100 to 150 g, and in 93% of cases with weights greater than 150 g (107). Gross examination of the RV also reveals a change in its shape with the development of cor pulmonale. The volume of the RV appears to decrease relative to its mass; in addition, it becomes less C-shaped and more concentric, the so-called left ventricularization of the RV (107).

VIDEO

Video 27.1 Apical four-chamber transthoracic view demonstrating a patient with severe pulmonary hypertension with a markedly dilated right ventricle with right ventricular dysfunction and a dilated tricuspid annulus. This annular dilatation causes severe tricuspid regurgitation. Because of the severe tricuspid regurgitation, there is significant right atrial dilatation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 27.2 Apical four-chamber view with color Doppler demonstrating severe tricuspid regurgitation due to annular dilatation. There is right ventricular dilatation and significant right ventricular dysfunction. Note the large zone of proximal flow convergence on the right ventricular side of the tricuspid valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In the past, the echocardiographic evaluation of the RV was more difficult because of its crescentic shape and substernal location, which limited adequate visualization of its chambers and subjected it to near-field acoustic artifacts. With the advent of two-dimensional echocardiography—Doppler and color Doppler imaging—came a growing interest in right heart function and evaluation. The echocardiographic views that best depict right-sided anatomy include the apical four-chamber, the right ventricular inflow long-axis, the oblique short-axis, the subcostal, the long-axis pulmonary, the short-axis view of the great vessels, the angulated short-axis view of the pulmonary artery, and the short-axis ventricular view (108).

The ideal method to evaluate the RV in cor pulmonale adequately includes measurement of chamber sizes, volumes, flow, and pressures. The echocardiogram is helpful in establishing secondary causes for pulmonary hypertension, such as left ventricular dysfunction, mitral valve abnormalities, or congenital heart disease. Although echocardiography is not foolproof in detecting mild to moderate pulmonary hypertension, it is quite sensitive in detecting severe elevations in pulmonary artery pressure. Patients with pulmonary hypertension exhibit an early peak velocity on pulsed-wave Doppler patterns in the proximal pulmonary artery because of poor compliance of the pulmonary vascular bed (108). The majority of such patients has tricuspid regurgitation, thereby allowing a reasonably accurate estimate of pulmonary artery systolic pressure. In the absence of right ventricular outflow tract obstruction, the relationship of the squared peak velocity of the tricuspid jet multiplied by four (Bernoulli equation) equals the pressure gradient across the valve. In a study by Currie et al. (109), analyzable Doppler regurgitant velocities were accurate in 80% of patients with elevated right ventricular systolic pressures, compared with 57% of normal patients. Such predictions, however, are only accurate for outflow tract waveforms. Pulmonary artery flow patterns do not allow for accurate predictions of systolic pressures, but they do allow for accurate predictions of diastolic pressures (108). Pulmonary hypertension can also be estimated by studying the flow characteristics in the inferior vena cava, although this technique has not been studied prospectively. Other echocardiographic findings that are associated with pulmonary hypertension and cor pulmonale include the presence of a dilated pulmonary artery and dilation and hypertrophy of the RV, even though the posterior wall often is not adequately visualized. Diastolic flattening of the interventricular

septum also occurs with progressive pulmonary hypertension, eventually leading to a concave septal configuration.

Video 27.3 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Because echocardiography is noninvasive, it is generally used early to determine the presence and severity of pulmonary hypertension and cor pulmonale. It is also extremely useful for following patients with established pulmonary hypertension after therapeutic interventions. Patients with markedly depressed RVEF measurements (10% or less) who have undergone lung transplantation appear to have considerable improvement of right ventricular function by echocardiography (110). Another study in patients who underwent pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension compared catheterization data with echocardiography. Strong correlations were seen between the maximal velocity of the regurgitant tricuspid jet by Doppler and the measurements of pulmonary artery pressures by cardiac catheterization postoperatively (111). Although transesophageal echocardiography can be used to evaluate the RV, there do not appear to be any major advantages with the latter technique for this particular indication. Three-dimensional echocardiography is being increasingly investigated, and although the technique has not yet been systematically investigated in patients with right ventricular dysfunction, this approach appears promising (112).

Nuclear Imaging Modalities

Ventriculography

The gold standard for the measurement of cardiac volumes and ejection fractions is usually considered to be contrast ventriculography. These measurements are normally calculated from geometric models that closely resemble the shape of the structure being studied (113). Nonetheless, unlike the left ventricle, the complex shape of the normal RV renders the methods that make use of such mathematical models prone to error. Additionally, in cor pulmonale, the changes in the shape of the RV can further invalidate measurements derived from models of the normal ventricle. Nuclear imaging techniques may overcome some of these difficulties because they are count based and relatively independent of the geometric constraints of the RV. Images in the septal left anterior oblique view are used in determining RVEF (114). Because inclusion of right atrial counts can falsely lower RVEF, the gated first-pass technique minimizes activity in adjacent structures. This technique performed with a multicrystal scintillation camera with high count rate capacities is the best way to measure RVEF.

Ventilation-Perfusion Scanning

When evaluating a patient with pulmonary hypertension, $\dot{V}/\dot{Q}$ scanning is only useful in differentiating whether the cause of the pulmonary hypertension is secondary to chronic thromboembolic disease (115). The latter patients typically have significant $\dot{V}/\dot{Q}$ abnormalities. The high-probability scans of such patients have at least one major perfusion defect. In contrast, patients with PPH generally have either normal or low-probability lung scans. Patients with cor pulmonale due to significant obstructive or restrictive lung diseases may have large perfusion defects, but these correlate with ventilation abnormalities. It is difficult to exclude thromboembolism using the $\dot{V}/\dot{Q}$ scan in the setting of severe COPD.

Computed Tomography

The use of computed tomographic (CT) scanning is increasingly being used to characterize the lung vasculature and parenchyma in patients with pulmonary hypertension. The pulmonary vasculature can be examined for thromboembolism, and the nature and extent of parenchymal disease can be evaluated. For example, patients with scleroderma and pulmonary hypertension may have variable degrees of interstitial disease; CT scanning may help determine whether the process is related primarily to pulmonary vascular involvement or to underlying fibrosis. The CT scan may reveal a mosaic perfusion pattern that suggests the presence of chronic thromboembolic pulmonary hypertension. In spite of the ability to visualize the pulmonary arteries with contrast-enhanced CT scanning, pulmonary arteriography should be performed if there is any question about proceeding with a potentially curable pulmonary thromboendarterectomy.

Pulmonary Arteriography

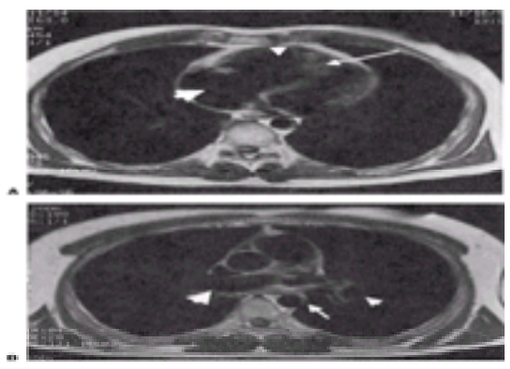
The role of the pulmonary arteriogram in the evaluation of the patient with pulmonary hypertension and cor pulmonale is to diagnose thromboembolic disease, and it is especially useful if the $\dot{V}/\dot{Q}$ scan is nondiagnostic. In chronic thromboembolic disease, the arteriogram can reveal convex-bordered occlusions, stenoses, intravascular webs, and large central thrombi with filling defects and vessel cutoffs (116). The arteriogram in the PPH patient reveals dilation of the proximal vessels with pruning of the distal vessels. Performing pulmonary arteriography in patients with severe pulmonary hypertension carries a small risk, although it is enerally safe in the absence of overt, severe right ventricular failure. In the NIH PPH Registry, 50 patients underwent the procedure without significant adverse events (99). One patient experienced transient hypotension. The risk is likely inversely proportional to the experience of the center performing the procedures (116). Pulmonary angioscopy may be necessary to determine the precise extent of thromboembolism (117).

Right Heart Catheterization

The gold standard for the diagnosis of pulmonary hypertension remains the right heart catheterization. This technique uses a thermodilution balloon catheter to measure right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures (6). Patients with pulmonary arterial hypertension should have normal wedge pressures. The presence of an abnormal capillary wedge pressure usually requires left heart catheterization for further evaluation. In addition, right heart catheterization allows for comparisons between the oxygen saturations in the central veins, right atrium, RV, and pulmonary artery. This helps determine if a left-to-right shunt is present. The right heart catheterization may supplement the echocardiographic data in the diagnosis and evaluation of congenital heart disease.

Magnetic Resonance Imaging

The use of magnetic resonance imaging (MRI) has been introduced to evaluate ventricular volume and ejection fraction (118) (eFig. 27.4.1). The potential use of MRI in the evaluation of right ventricular function is suggested by a study in 11 patients in which a correlation coefficient of 0.86 was found between measurements of RVEF by MRI compared with radionuclide ventriculography (119). The measurement of stroke volumes in healthy subjects, including children, by MRI has been validated in numerous studies (120). MRI has also been used for the determination of wall stress, by measuring end systolic and end diastolic wall size (121). A study in seven patients who underwent single-lung transplantation for pulmonary hypertension revealed significant reductions in right ventricular wall stress and remodeling of the RV within 3 to 6 months (121). However, unlike the case with the left ventricle, such data with regard to the RV have not been validated. MRI is also being used in the evaluation of patients with thromboembolic disease, especially those with emboli in the proximal pulmonary arteries (122).



***e*FIGURE 27.4.1** Cardiac magnetic resonance image (MRI). The image was acquired using a T1-weighted, gated spin-echo technique. The patient has moderately severe primary pulmonary hypertension with a pulmonary artery pressure of 65/35 (mean 43). Mild obstructive lung disease is present, but the pulmonary hypertension is disproportionately severe. All other causes of secondary pulmonary hypertension were ruled out. A high natural contrast exists between the blood pool and the

cardiovascular structures, making MRI a favorable technique for cardiac imaging. In **(A),** the right atrium (*large arrowhead*) and right ventricle (*small arrowhead*) are enlarged, resulting in septal flattening (*arrow*) with encroachment on the left ventricle. In **(B)**, the pulmonary arteries are enlarged (*large arrowhead*). The left descending pulmonary artery (*small arrowhead*) is as large as the descending aorta (*arrow*).

PRINCIPLES OF MANAGEMENT

Oxygen

As was previously stated, a low arterial oxygen tension value is a predictor of reduced survival in patients with cor pulmonale. Supplemental oxygen not only relieves tissue hypoxia but can also reduce hypoxic pulmonary vasoconstriction, thereby reducing PVR, pulmonary artery pressures, and afterload. The reduction in such hemodynamic parameters might then allow right ventricular dysfunction to reverse. Two large trials have demonstrated the benefit of supplemental oxygen therapy in patients with hypoxemia and cor pulmonale: the Nocturnal Oxygen Therapy Trial Group (NOTT) (123) and the Medical Research Council Working Party (MRC) (124). The NOTT study enrolled 203 patients with hypoxemia and COPD at six treatment centers in the United States. The patients were randomized to continuous versus nocturnal oxygen therapy. Mortality was significantly reduced in patients who received continuous oxygen when compared with the other treatment group (Fig. 27.5). Nonetheless, statistically significant differences in mortality between each group were not evident when considering the specific subset of patients with altered pulmonary hemodynamics, despite an improvement in PVR with continuous oxygen therapy.

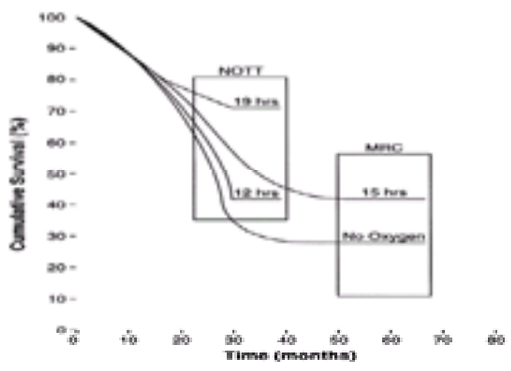


FIGURE 27.5 Composite graph of the British Medical Research Council Working Party (MRC) and the U.S. Nocturnal Oxygen Therapy Trial (NOTT) studies. Survival was poor with no oxygen, better with some oxygen, and best as they approached continuous oxygen (19 hours). (From Tiep BL. Long-term home oxygen therapy. *Clin Chest Med* 1990;11:505–521, with permission.)

The MRC trial performed in the United Kingdom enrolled 87 patients with COPD and severe arterial hypoxemia and hypercarbia (124). The patients were randomized to oxygen therapy for at least 15 hours per day versus no oxygen. Again, mortality was significantly reduced in the treatment group versus the control group (Fig. 27.5) after 500 days of therapy. When examining the hemodynamic data, mean pulmonary artery pressure in the treatment group remained stable, whereas it increased significantly in the control group. Therefore, in both trials the decrease in mortality did not appear to correlate with improvement in pulmonary hemodynamics. However, Weitzenblum and colleagues (125) subsequently evaluated a small group of patients with pulmonary hypertension and underlying COPD. Twelve of the 16 patients had improvement in their pulmonary hypertension after the institution of oxygen therapy of 15 to 18 hours per day. During long-term oxygen therapy, there was a yearly decrease in pulmonary artery pressures of 2.15 ± 4.4 mm Hg. Thus, long-term oxygen therapy is recommended when the arterial oxygen tension is 55 mm Hg or less or when the oxygen tension is 60 mm Hg or less in patients with cor pulmonale, polycythemia, or other evidence of cardiac disease.

Treatment of Airflow Obstruction and Parenchymal Lung Disease

The therapy of patients with cor pulmonale due to COPD involves maximizing lung function. Several classes of drugs are used in patients with obstructive lung diseases for their bronchodilatory properties. Theophylline has been shown in animal models to have a bronchodilator effect and inotropic effects and to improve diaphragmatic contractility (126,127 and 128). The effects on ventricular function are attenuated by beta-receptor or calcium channel blockade (126). However, the use of this agent to improve diaphragmatic as well as cardiac function appears to be controversial in humans. Beta-adrenergic receptor agonists are primarily used for their bronchodilator properties. These are also vasodilators of the systemic and pulmonary vascular beds, although the latter effect does not appear to be clinically significant when used at standard doses via the inhaled route. The development of tolerance with the use of these agents is common, and potential hemodynamic effects seem unlikely to be long term. These agents, including albuterol, salmeterol, terbutaline, and others, can be used for acute exacerbations of COPD or for chronic maintenance therapy. Ipratroprium bromide is also commonly used in the setting of acute and chronic airflow obstruction. A major advantage of this agent is the paucity of adverse effects, even at relatively high doses. Finally, steroid therapy plays a role in certain patients with obstructive as well as interstitial lung disease. Treatment of the underlying lung disease may improve airflow and potentially oxygenation, theoretically offering a chance for improvement in cor pulmonale.

Digoxin

The use of digoxin as an agent to improve cardiac contractility in patients with impaired right ventricular function is controversial. A randomized placebo-controlled trial studied the effect of digoxin on RVEF after 8 weeks of treatment in COPD patients (129). Improvement in RVEF was seen in those patients with concomitant left ventricular dysfunction, but not in individuals with isolated right ventricular dysfunction. In addition, digoxin does not improve cardiac function or oxygen consumption during exercise in patients with COPD (130). Finally, patients with chronic lung disease and gas exchange abnormalities tend to develop digoxin toxicity at lower serum levels than patients with right ventricular dysfunction without gas exchange abnormalities. Additional clinical trials would appear warranted.

Vasodilator Therapy

Because pulmonary arterial muscularization and vasoconstriction are believed to be major pathophysiologic mechanisms for the development of pulmonary hypertension and pressure overload of the RV, a number of vasodilator agents have been studied. Guidelines for their use are provided in *e*Table 27.1.1 and *e*Table 27.1.2 and in *e*Figure 27.5.1.

***e*TABLE 27.1.1** ASSESSMENT OF VASODILATOR RESPONSE IN PULMONARY HYPERTENSION

Parameter	Desired acute change	Comments
Mean pulmonary artery pressure (MPAP)	>25% decrease ↓	Avoid ↓ systemic BP
Pulmonary vascular resistance (PVR)	>33% decrease ↓	Should be associated with ↓ MPAP and ↑ CO
Right atrial pressure (RAP)	No change or ↓	↑ RAP suggests impending RV failure
Pulmonary capillary wedge pressure (PCWP)	No change	↑ PCWP may suggest PVOD or LV failure and may be dangerous
Systemic blood pressure (BP)	Minimal ↓ (keep systolic BP >90 mm Hg)	Significant ↓ BP precludes use of agent
Cardiac output (CO)	Increase	↑ CO should be related to ↑ stroke volume, not ↑ HR
Heart rate (HR)	No significant change	Chronic ↑ HR may precipitate RV failure
Systemic arterial O_2 saturation (Sa_{O_2})	If baseline is ↓, Sa_{O_2} may ↑	↓ Suggests right-to-left shunt or underlying lung disease
Pulmonary artery (mixed venous) O_2 saturation ($P\bar{v}_{O_2}$)	Increase	Reflects ↑ CO and ↑ tissue O_2 saturation

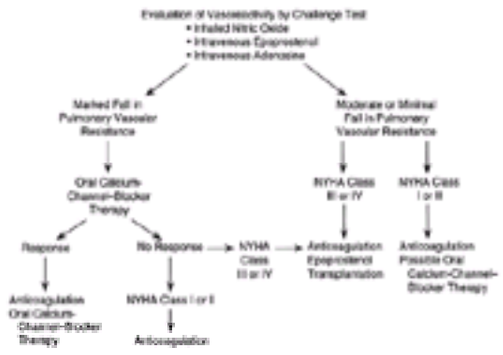
LV, left ventricle; PVOD, pulmonary venoocclusive disease; RV, right ventricle; ↑, increase; ↓, decrease.
Adapted from Rubin LJ, Rich S. Medical management. In: Rubin LJ, Rich S, eds. *Primary pulmonary hypertension.* New York: Marcel Dekker Inc, 1997, with permission.

***e*TABLE 27.1.2** ACUTE DOSING OF VASODILATORS IN PRIMARY PULMONARY HYPERTENSION

Agent	Route	Dose range	Half-life

Prostacyclin	Intravenous	2–10 ng/kg/min[a]	3–5 min
Adenosine	Intravenous	50–200 µg/kg/min	5–10 sec
Nitric oxide	Inhaled	5–80 ppm	15–30 sec
Nifedipine[b]	Oral	30–240 mg/kg	2–5 h
Diltiazem[b]	Oral	120–900 mg/d	2.0–4.5 h

[a]Many cardiac catheterization laboratories infuse prostacyclin only at 2 ng/kg per minute without dose titration to ascertain that the patient tolerates the drug. The lack of a vasodilator response to this drug does not preclude a long-term response. Dose increases at weekly intervals may lead ultimately to doses as high as 100 ng/kg per minute.
[b]The half-life values shown refer to preparations dosed every 6 to 8 hours. If the medication is tolerated, it can be changed to a sustained-release preparation administered once a day.
Adapted from Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997;336:111–117. Copyright © 1997 Massachusetts Medical Society. All rights reserved.



***e*FIGURE 27.5.1** Algorithm for the management of primary pulmonary hypertension. (Note: The use of endothelin antagonists, such as bosentan, will frequently be added to the long-term therapy of class III and IV patients. At present, there are no data to suggest that these medications should not be used in nonresponders whose condition is not severe enough for treatment with epoprostentol.) NYHA, New York Heart Association. (From Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997; 336:111–117. Copyright © 1997 Massachusetts Medical Society. All rights reserved.)

Calcium Channel Blockers

Calcium channel blockers have been the most widely tested and used group of drugs in patients with PPH. In such individuals, sustained improvement occurs in 25% to 30% (76,87). Nifedipine and diltiazem are the most commonly used, because verapamil has been shown to have negative inotropic effects. Typically, the patients who experience the most sustained improvement in hemodynamics during an acute vasodilator challenge are those who show improvement in symptoms and prolonged survival (76). However, these agents may also result in significant adverse effects such as hypotension, which can be life threatening in patients with severely compromised right ventricular function. Therefore, indiscriminate use of these agents should be avoided.

Data from the NIH PPH Registry suggested that patients with greatly depressed right ventricular function are at greatest risk of adverse outcomes with acute administration of vasodilators (131). If oral calcium channel blocker doses are changed in PPH patients who have already undergone right heart catheterization, the change should take place with careful monitoring of the blood pressure. In patients with other causes for pulmonary hypertension and cor pulmonale, the use of these agents is controversial. A study of 11 patients with COPD and cor pulmonale who were treated with nifedipine revealed no improvement in survival over age- and disease-matched control subjects despite improvements in PVR (132,133 and 134). Other studies have shown improvement in the hemodynamics of COPD patients, but these were accompanied by worsening of arterial oxygenation due to $\dot{V}/\dot{Q}$ mismatching. Therefore, treatment of COPD patients should be carefully considered on an individual basis. Other oral vasodilators have been evaluated. Despite a possible role of angiotensin-converting enzyme in the pathophysiology of pulmonary hypertension (135), the evaluation of inhibitors of this enzyme has not revealed significant benefit, and these drugs have not been studied in large prospective, randomized trials (136).

Prostacyclin

The use of prostacyclin (epoprostenol, PGI_2) as long-term therapy developed from observations of hemodynamic parameters during its acute administration (137). It has a very short half-life, and it is rapidly inactivated by the low gastric pH. Therefore, it must be given as a continuous intravenous infusion via a permanent indwelling catheter with a portable infusion pump. Substantial preliminary data (138,139) led to a large prospective, randomized multicenter trial that compared prostacyclin plus conventional therapy with conventional therapy alone in patients with class III and IV PPH (79). The patients who were treated with prostacyclin had significant improvements in exercise capacity, hemodynamics, and survival (Fig. 27.6). More recently, patients with severe pulmonary hypertension due to the scleroderma spectrum of diseases were randomized in a similar prospective trial (140). Improvement in exercise capacity and hemodynamics at 3 months was demonstrated in the prostacyclin cohort. Long-term benefits have also been reported, even in patients who have not demonstrated hemodynamic improvement during the acute infusion. The dose of the drug is increased, generally once or twice per week, and tolerance develops if it is not increased. The long-term effects have been suggested to be due not only to the vasodilator properties but also to antiplatelet or anti–smooth muscle proliferation properties. Adverse events are related to catheter-related infections and thrombosis and pump malfunction. Dose-related side effects include diarrhea, jaw pain, flushing, and arthralgias. This drug should be administered by a team of individuals who are experienced with its use and aware of the time commitment that is required for proper teaching and maintenance. Alternatives to this form of prostacyclin are under investigation and include inhaled prostacyclin (141,142), nebulized iloprost (a prostacyclin analog) (142), and oral prostacyclin in the pill form (143). Subcutaneous prostacyclin delivered by a small pump (UT-15/Remodulin) is pending approval by the U.S. Food and Drug Administration.

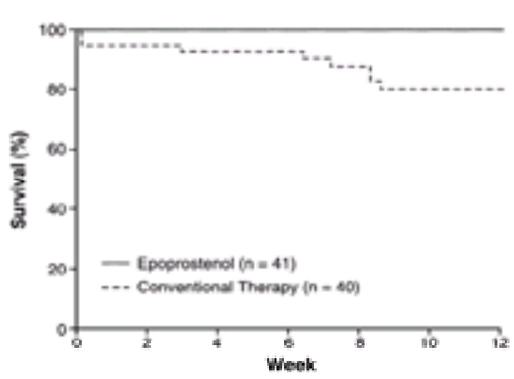


FIGURE 27.6 Survival among the 41 patients treated with epoprostenol and the 40 patients receiving conventional therapy. Data on patients who underwent transplantation during the 12-week study were censored at the time of transplantation. Estimates were made by the Kaplan-Meier product-limit method. The two-sided *p* value from the log-rank test was .003. Survival analysis with data on patients receiving transplants not censored at transplantation resulted in the same level of significance (two-sided *p* = .003 by the log-rank test). No deaths occurred in the epoprostenol group, and there were eight deaths in the conventional therapy group. [From Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;334:296–301, with permission.]

Endothelin Antagonists

Because endothelin levels have been shown to be elevated in patients with PPH, and because the production and activity of this substance may be two of several important mechanisms in the development of pulmonary hypertension, endothelin antagonism has been studied as potential therapy in pulmonary arterial hypertension. Results in animal models with pulmonary hypertension have appeared to be favorable (144). Channick and colleagues (145) conducted a large randomized, double-blind, placebo-controlled multicenter trial that compared bosentan, an orally active antagonist receptor of both endothelin receptor subtypes (A and B). The Borg dyspnea index, 6-minute walk distance, WHO functional class, and PVR all improved to a statistically significant degree in patients who received the drug compared with placebo. Ultimately, it may prove most effective to combine this form of treatment with therapies that use other mechanisms of action for optimal therapy. Bosentan

(Tracleer) was recently approved by the U.S. Food and Drug Administration for use in patients with New York Heart Association class III and IV PPH and those with pulmonary arterial hypertension due to the scleroderma spectrum of diseases.

Inhaled Nitric Oxide

Because abnormalities in NO production, regulation, and effect appear to be involved in the pathophysiology of pulmonary hypertension, its use as a therapeutic agent is being investigated. It is a selective pulmonary vasodilator (146,147), delivered via inhalation, with a short half-life. It appears to be useful as a “screening vasodilator” in the therapy of pulmonary hypertensive states (148). Two prospective randomized trials using inhaled NO in neonates with pulmonary hypertension revealed no reduction in mortality but a decrease in the need for more invasive therapy such as extracorporeal membrane oxygenation (149,150). The delivery of the inhaled gas has been a major obstacle in its use, because administration has been via ventilators or face masks. An ambulatory delivery system is being developed for the widespread use of inhaled NO, and it appears to be a promising alternative in the future (151,152). The effects of pulsed inhaled NO in eight patients with PPH revealed improvement in hemodynamic parameters over a short period of time (151). Long-term effects have not been studied, but a few patients have been maintained on this therapy.

Anticoagulation

Anticoagulation is recommended in the treatment of patients with pulmonary hypertension due to their increased risk of *in situ* thrombosis. In a subgroup of these patients, microscopic thrombi may play a role in the pathogenesis of the disease (152). In addition, these individuals appear to be at risk of thromboembolism due to right ventricular dilatation and dysfunction as well as relative immobility. A retrospective clinical trial and a nonrandomized prospective study have suggested improved survival with anticoagulation therapy (76,152). Despite the fact that heparin is beneficial in animal models of hypoxic pulmonary hypertension due to its inhibitory effects on smooth muscle proliferation (153), the drug of choice is warfarin; an international normalized ratio of 1.5 to 2.5 is considered therapeutic (76). The risk-benefit ratio has to be considered on an individual basis when using anticoagulant therapy.

Atrial Septostomy

Patients with PPH often begin to shunt blood from right to left as the pulmonary artery pressure rises. This is due to the opening of a patent foramen ovale. It is likely that, in some patients, this serves as a means by which to “unload” the RV to some degree. Creation of a shunt, atrial septostomy, has been performed as palliation in a few cases with severe PPH (154,155 and 156). In such patients, the RV is massively dilated, thereby encroaching on left ventricular filling. A right-to-left shunt is created in an attempt to improve forward output and allow for better filling of the left ventricle. The unfortunate tradeoff is the potential for causing profound systemic arterial hypoxemia or pulmonary edema by overloading the left ventricle. Therefore, this procedure is still considered investigational but may be used in extreme cases.

Surgical Treatment

Pulmonary Thromboendarterectomy

Thromboendarterectomy has been the treatment of choice for pulmonary hypertension that is associated with chronic thromboembolic disease. Anticoagulation should be instituted and inferior vena cava filters are recommended in patients with this entity, but the only means by which to alleviate symptoms and to have an impact on survival is surgery. Pulmonary thromboendarterectomy is performed via median sternotomy on cardiopulmonary bypass. The overall mortality continues to improve and is now less than 5%. The response to therapy is often impressive, with dramatic reversal of right ventricular dysfunction (157,158). Lung transplantation can be performed in patients in whom thrombi are too distal to extract.

Lung Transplantation

Lung transplantation and heart-lung transplantation are being used as surgical therapy for patients with a variety of pulmonary parenchymal and vascular disorders (159). Patients should be referred for evaluation for transplantation if class III or class IV symptoms are present. The length of the waiting list at a given center (generally 6 to 18 months) helps to determine the appropriate time for listing and transplantation. Patients with PPH or pulmonary arterial hypertension due to the scleroderma spectrum of diseases should undergo a trial of prostacyclin therapy by continuous infusion before proceeding to lung transplantation, because this drug has proved so efficacious in these settings. Single and bilateral lung transplantation, rather than heart-lung transplantation, are the procedures of choice due to the limited availability of organs. The RV has a tremendous capacity to recover in spite of severe dysfunction once the afterload posed by the abnormal pulmonary vasculature is removed. Single-lung transplants are done in all patients with pulmonary parenchymal disorders, except those with suppurative diseases such as cystic fibrosis, in which case bilateral lung transplantation is performed. Most centers prefer bilateral lung transplantation for PPH as well. One advantage of the bilateral approach may be that the new lung is less likely to suffer from reperfusion pulmonary edema immediately after operation. Chronic rejection may also be more easily tolerated with a bilateral transplant than when the extremely abnormal native PPH lung remains (160). However, the waiting time on the list is shorter for a single-lung transplant, and a set of donor lungs can be offered to two patients when single-lung transplantation is used for PPH. Many transplant teams prefer the single-lung procedure. Heart-lung transplantation is reserved for patients with associated left heart disease or congenital heart disease with pulmonary hypertension when the atrial or ventricular septal defect cannot be repaired. Markedly depressed right ventricular function is not a contraindication to single or bilateral lung transplantation because right ventricular function improves considerably after transplantation (159). Right ventricular shape also appears to normalize after single and bilateral lung transplantation. One-year survival rates for lung transplantation are approximately 80%. Obliterative bronchiolitis (chronic rejection) is the major long-term complication of transplantation. Patients with PPH appear to have higher mortality as well as a higher frequency of obliterative bronchiolitis. Recurrence of the primary pulmonary disorder in the transplanted lung can occur in certain conditions but has not been reported in PPH.

SUMMARY

Pulmonary hypertension and cor pulmonale result in substantial morbidity and mortality. The etiologies are numerous because nearly any chronic lung disease can result in cor pulmonale. Other entities such as neuromuscular disease and thoracic cage abnormalities can result in hypoxemia and ultimately in pulmonary hypertension with right ventricular failure. Basic scientific efforts indicate the importance of growth factors and of smooth muscle proliferation in the pathogenesis of PPH. The diagnosis and an assessment of severity begin with the history and physical examination. Chest radiography and echocardiography may be useful in elucidating the etiology and severity of pulmonary hypertension, and pulmonary function testing may clarify the physiology and severity of underlying lung disease. Certain diseases such as chronic thromboembolic pulmonary hypertension require specific diagnostic testing, including $\dot{V}/\dot{Q}$ scanning and pulmonary arteriography. Helical CT scanning and MRI may be useful in diagnosing and characterizing the extent of this disease. Right heart catheterization remains the gold standard for quantifying the severity of pulmonary hypertension. Appropriate therapy involves treatment of underlying lung disease as well as direct measures to reduce pulmonary artery pressures without causing systemic hypotension. The prognosis depends to some extent on the nature of the underlying disease. The underlying causes of pulmonary hypertension and cor pulmonale followed by the diagnostic and therapeutic approaches are described. Continuous intravenous prostacyclin has revolutionized the treatment of primary and some forms of secondary pulmonary hypertension. Finally, newer diagnostic and therapeutic modalities, some of which remain theoretical or unproven, are emphasized. The recently approved endothelin antagonist will likely be used in substantial numbers of patients with PPH and with pulmonary arterial hypertension due to scleroderma and related diseases.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Despite tremendous progress in basic scientific and clinical research, pulmonary hypertension and cor pulmonale remain among the more difficult cardiopulmonary disorders to treat. Because (except in the case of PPH) they are the result of *other* disease processes, they may go clinically undetected for months or years, with the assumption that the COPD or ILD itself, for example, is responsible for the dyspnea, fatigue, and other clinical symptoms. The implications of missing the diagnosis of pulmonary hypertension and right ventricular failure are substantial. For PPH, prostacyclin and anticoagulation appear to improve mortality, and listing for transplantation is important because waiting lists are increasing in length. Patients with PPH are often young, do not have hypoxemia or abnormal pulmonary function testing early in the course of the disease process, and may not have glaring chest radiograph abnormalities. Thus, in the past, these individuals were often labeled as having psychogenic dyspnea until symptoms were quite advanced. Over the past decade, the level of awareness for PPH among cardiology and pulmonary specialists has increased, particularly with the advent of newer therapies. However, the diagnosis is more difficult for general practitioners, who may see only one case in a lifetime. It is appropriate for patients with PPH to be evaluated and followed at centers with expertise in this area, particularly as the disease advances.

Organizations such as the Pulmonary Hypertension Association have made tremendous progress in the education and support of patients with PPH. Their biannual conference is a very unique one, at which physicians as well as patients and their family members mutually attend lectures and conferences about pulmonary hypertension, ranging from drug therapy and lung transplantation to coping with a potentially fatal disease. Among the important controversies that clinicians continue to struggle with at present are the timing of the initiation of intravenous prostacyclin and the timing of lung transplantation. A massive effort is currently under way to evaluate all patients who have received intravenous prostacyclin in the past and to evaluate future patients prospectively to better characterize appropriate dosing of the drug and to examine the mortality and outcome. Although lung transplantation is the final therapeutic step for many patients with PPH and other patients with cor pulmonale, conquering the ultimate cause of death in many of these patients (chronic rejection) will be crucial. The genetics of PPH are being unraveled; this may

contribute substantially to disease prevention and treatment in the future.

THE FUTURE

The diagnostic and therapeutic approach to pulmonary hypertension and right ventricular failure will change substantially over the next 10 years. Noninvasive technology, including multidimensional echocardiography, ultrafast CT, and MRI techniques, will facilitate accurate characterization of right ventricular size and function, eliminating the need for invasive testing with cardiac catheterization. With the advent of this technology, evaluation of the RV and pulmonary circulation will, when necessary, be performed more frequently, permitting more effective assessment of therapeutic benefit. At the present time, the need for right heart catheterization for evaluation of pulmonary hypertension and cor pulmonale prevents rigorous accurate follow-up in these patients.

Clinical trials will be conducted, enabling better understanding of the utility of older treatment modalities, such as digoxin and other inotropes, on right ventricular function, as well as enhancing our knowledge base with regard to newer therapies, such as oral, subcutaneous, and inhaled prostacyclin; endothelin antagonism; and inhaled NO; and related therapies. Treatment of underlying lung disease that leads to cor pulmonale may become more feasible. Enhanced understanding of the role of various inflammatory mediators in primary pulmonary vascular disease as well as chronic fibrotic lung disorders will also have an impact on therapy. Surgical therapy will continue to become more sophisticated. Advances in lung transplantation (including xenotransplantation), pulmonary thromboendarterectomy, and lung volume reduction surgery for emphysema may lead to increases in survival in patients with end-stage lung disease. Perhaps direct right ventricular surgery with removal of hypokinetic myocardial tissue will enhance the function of the ventricle.

Our understanding of the basic biology of the vascular endothelium and its role in the development of pulmonary hypertension as well as the importance of its interaction with red blood cells is essential. The respective roles of platelet-derived growth factor B, TGFs, insulin-like growth factor-1, and basic fibroblast growth factor will be clarified, as will the regulation of endothelin and NO. The key elements of tissue repair and vascular remodeling will be elucidated. The relative role of the coagulation pathway in PPH will be essential to determine. The genetics of PPH are already becoming clearer. The *BMPR2*, a component of the TGF-b family, plays a key role in cell growth. This gene has been shown to be associated with familial PPH (28a). MORE RECENTLY, IT HAS BEEN DISCOVERED THAT THE SPORADIC FORM OF PPH IS ALSO ASSOCIATED WITH GERMLINE MUTATIONS OF *BMPR2* in a significant minority of patients (28b). The importance of this gene and its relationship to pulmonary hypertension will be clarified. Regulation of gene expression may be a key method through which pulmonary hypertension can be controlled. The basic mechanisms that underlie hypoxic vasoconstriction are essential to understand; if this process can be unraveled, it may permit us to prevent right ventricular failure *completely*.

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28

VENOUS THROMBOEMBOLISM

VICTOR F. TAPSON

"Indicates text or graphics that appear only in the electronic versions of this text."

Historical Perspective
Incidence
Risk Factors and Pathophysiology
Risk Factors
Gas Exchange and Hemodynamic Alterations in Acute Pulmonary Embolism
Clinical Profile
History and Physical Examination
Laboratory Testing
Chest Radiography, Ventilation-Perfusion Scanning, and Pulmonary Arteriography
Echocardiography in Acute Pulmonary Embolism
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HISTORICAL PERSPECTIVE

In 1819, Laennec wrote about "pulmonary apoplexy," stating, "The disease I call by this name is very common, but nevertheless its features are almost unknown" (1). Ten years later, Cruveilhier began his work meticulously describing thrombi in central and peripheral veins as well as describing multiple pulmonary emboli pathologically (2). Despite their important discoveries, neither Laennec nor Cruveilhier made the association between the development of deep venous thrombosis (DVT) and pulmonary embolism (PE). The true discovery of this association is attributed to Virchow, who described it in 1858 (3). Virchow also determined that PE did not always result in infarction because of the dual circulation of the lung. Several years later, Trousseau reported the high incidence of DVT in patients with gastric carcinoma (4). In 1880, Beniamino Luzzatto described at least 160 cases of PE in a manuscript titled "Embolism of the Pulmonary Artery," in which he emphasized the predilection for the lower lobes and the predisposing role of stasis and preexisting cardiopulmonary disease (5). He also credited a number of other individuals for their observations. Shortly after the turn of the century, Trendelenburg attempted pulmonary embolectomy (6), and in 1924, Kirschner, a student of Trendelenburg, performed the first successful embolectomy for acute PE (7). Ljungdahl described the concept of chronic PE in 1928 (8). In 1931, Moniz et al. reported the first pulmonary angiogram, although this technique did not become widely used for PE until decades later (9). In 1940, Bauer, a Swedish surgeon, diagnosed DVT by venography and investigated the natural history of untreated venous thrombosis using serial venography (10). He was also among those who first reported the use of heparin therapy for this disease (11,12) despite the discovery of heparin in 1916 by McLean, then a medical student (13).

The ability to diagnose PE changed dramatically with the development and availability of new diagnostic techniques after 1960. The advantages of pulmonary angiography became more widely recognized in 1963, when Chrispin and colleagues (14) injected contrast material into the right atrium and pulmonary arteries, delineating emboli within the large pulmonary arteries. Williams, Sasahara, and their respective associates reported the utility of selective pulmonary angiography exclusively for the diagnosis of PE (15,16). Stein et al. (17) evaluated the angiographic signs of PE in 1967 and concluded that an intraluminal filling defect and vessel cutoff with a trailing edge were the only two primary angiographic criteria that could be relied on to diagnose PE. Radionuclide imaging was further explored in 1964 when Taplin developed a method of generating and radiolabeling macroaggregated albumin particles (18). Wagner et al. (19) reported the diagnosis of PE in humans by radioisotope scanning the same year. These diagnostic discoveries helped to usher in a new era in the approach to venous thromboembolism (VTE). Substantial research has been undertaken since. Although much more has been learned about this entity, it remains elusive and is all too frequently discovered at autopsy.

INCIDENCE

VTE constitutes a clinical spectrum encompassing DVT and PE. This disorder occurs extraordinarily commonly in hospitalized patients particularly after major surgery, and the care of these patients spans all specialties and subspecialties. PE most commonly results from DVT occurring in the veins of the proximal lower extremities—that is, including and proximal to the popliteal veins. Both DVT and PE are frequently clinically unsuspected, leading to significant diagnostic and therapeutic delays and accounting for substantial morbidity and mortality. Although there are as many as 260,000 patients in the United States in whom VTE is diagnosed and treated each year, more than half of the cases that actually occur are never diagnosed, and as many as 600,000 cases may therefore occur. Many patients dying from acute PE have coexisting terminal illnesses; however, it would appear that this disease entity is responsible for the deaths of 50,000 to 100,000 patients with an otherwise good prognosis, and many of these deaths would appear preventable (20,21). Autopsy studies have repeatedly documented the high frequency in which PE has gone unsuspected and undetected (22). Despite advances in diagnostic technology and therapeutic approaches, VTE remains underdiagnosed, and prophylaxis continues to be dramatically underused (23).

RISK FACTORS AND PATHOPHYSIOLOGY

Risk Factors

The pathogenesis of DVT as proposed by Virchow is based on several potential initiating events, including stasis, venous injury, and hypercoagulability. Risk factors for DVT are based on these processes (Table 28.1). Frequently more than one risk factor is present, and knowledge of these risk factors provides the rationale for both prophylaxis and clinical suspicion.

Clinical factors
Age >40 yr
History of venous thromboembolism
Prior major surgical procedure/trauma
Hip fracture
Immobilization/paralysis
Varicose veins
Congestive heart failure
Myocardial infarction
Obesity
Pregnancy/postpartum
Oral contraceptive therapy
Cerebrovascular accident
Cancer
Paroxysmal nocturnal hemoglobinemia
Antiphospholipid antibody syndrome (including lupus anticoagulant)
Genetic/molecular factors
Antithrombin III deficiency
Factor V Leiden (activated protein C resistance)
Protein C deficiency
Protein S deficiency
Prothrombin gene (G20210A) defect
Dysfibrinogenemia
Disorders of plasminogen
Elevated factor VIII levels
Elevated factor XI levels

TABLE 28.1 RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Clinical Factors

Most venous thrombi arise in valve pockets, where blood flow tends to stagnate. The increased frequency of thrombosis with advanced age and immobilization further suggests the causal relationship between stasis and thrombogenesis. Immobility of any cause results in decreased venous return and stasis. Patients with acute cerebrovascular accidents commonly develop venous thrombi in the paralyzed lower extremity but only rarely in the unaffected limb. Acute paraplegia may be associated with a significantly increased risk of developing DVT, and the period of highest risk appears to be the first two weeks after the onset of the illness (24). Prolonged bedrest or long automobile or airplane trips may lead to the development of thromboemboli. The risk presented by air travel has been somewhat controversial (25,26 and 27). Although one recent trial suggests that the risk is not significant (25), more than 5 hours was the longest travel time evaluated, and this group of patients was not further subdivided. Thus, longer travel times were not independently analyzed. A more recent clinical trial does demonstrate a relationship between distance traveled and incidence of PE (27a). Obesity also appears to increase the risk of VTE. Information extrapolated from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) suggests that the role of obesity as a risk factor requires further clarification; there were not enough patients with morbid obesity included to draw firm conclusions (28). Immobility and resultant stasis are likely contributing factors. Age appears to increase mortality due to PE (29). This risk is particularly high in those with cardiac disease or cancer. It appears that PE is suspected premortem less commonly in the elderly patient (30).

Previous thromboembolic disease predicts a substantial risk of recurrence in the hospitalized patient. Surgical patients with a history of VTE who do not receive prophylaxis develop postoperative DVT in more than 50% of cases (31). Surgery itself places a patient at significantly increased risk. General surgery patients not receiving pharmacologic or mechanical prophylaxis have been shown to develop venography-proven DVT in as many as 19% of cases (32). Traditionally, heparin prophylaxis has been initiated perioperatively to prevent the development of intraoperative and early postoperative thrombosis. Patients undergoing spinal or pelvic surgery appear to be at particularly high risk (31). Total hip and total knee replacement patients not receiving prophylaxis develop DVT in more than 50% of cases (33). These orthopedic settings have been extensively investigated, prompted by clear evidence in clinical trials that low-molecular-weight heparin (LMWH) preparations are more effective than standard heparin in the setting of total joint replacement (33).

Lower extremity and pelvic trauma enhance the risk of DVT. Emboli are discovered at autopsy in as many as 60% of patients with fractures of the lower extremities (34), and mortality has been attributed to PE in 38% to 50% of patients dying after hip fracture (35). The duration of immobility after trauma influences the development of DVT. The frequency of autopsy-confirmed PE in patients surviving for less than 24 hours after trauma has been shown to be 3.3%, increasing to 5.5% in those surviving up to 7 days. Pulmonary emboli occurred in 18.6% of those surviving for a longer period (36). Other causes of venous trauma include placement of central venous catheters in the jugular, subclavian, or femoral veins. Clinically significant PE arising from upper extremity thrombosis can occur but is significantly less likely than from a lower extremity source.

Other disease processes are associated with a high risk of VTE. Autopsy studies as well as recent epidemiologic analyses suggest that patients with cardiac and malignant disease are particularly susceptible to VTE (29,37). Although myocardial infarction without anticoagulation resulted in a significant incidence of DVT, more recent therapeutic strategies have had a favorable impact (38). A reduction in the incidence of VTE resulting from the use of thrombolytic therapy was demonstrated in a number of large placebo-controlled trials for acute myocardial infarction, including the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico and the second International Study of Infarct Survival (39,40). Patients with malignancies have an increased risk of developing VTE (41). Cancers of the pancreas, lung, stomach, genitourinary tract, and breast are associated with a particularly high risk of DVT and PE. In addition to thrombophilia, these disorders are frequently associated with significant weakness and decreased ambulation with venous stasis. Treatment with chemotherapy with resulting neutropenia and sepsis often necessitates hospitalization and bedrest, which contributes further to the high risk of VTE. A recent analysis based on data from the PIOPED trial revealed that of 399 patients with PE, 73 (18.3%) had cancer (29).

Pregnancy and the postpartum period are the most common settings in which women younger than age 40 develop DVT or PE. DVT develops in these settings five times more often than in women not on oral contraceptives (42). Thrombosis appears to be more common in the third trimester and postpartum than before delivery, but the risk is clearly significant throughout pregnancy (42). Delivery by cesarean section further increases the risk. Oral contraceptives are associated with the development of VTE (43). The risk increases with third-generation agents (agents containing desogestrel or gestodene as the progestin component) (44,45). In a clinical trial evaluating hormonal replacement therapy, it was determined that such therapy increased the incidence of VTE in women 45 to 64 years of age. It appears that an annual total of 16.5 cases of VTE out of 100,000 individuals may be attributed to hormonal replacement therapy (46). The risk of VTE also appears to be highest in the first year of exposure to hormonal replacement (47). Past use may not increase the risk (48). Although such therapy is associated with clear benefits, physicians should take risk factors for VTE into account before prescribing hormonal replacement therapy. A recent review of oral contraceptive use and VTE further emphasizes that, with the increased risk associated with third-generation progestins in combination preparations, these agents should not be the first choice for new users (49).

Disease states associated with the development of VTE include paroxysmal nocturnal hemoglobinuria, inflammatory bowel disease, homocystinuria, Behçet's syndrome, polycythemia, and thrombocythemia. Most intensive care unit patients can be considered at risk for VTE because of their multiple risk factors, including significant underlying disease, immobility, and the frequent presence of venous injury due to trauma. With few exceptions, these patients should receive some form of DVT prophylaxis, and a high index of suspicion for VTE should be maintained in appropriate clinical circumstances. Hospitalized general medical patients represent an increasingly ill population frequently requiring medical prophylaxis.

Molecular Defects

Inherited coagulopathies result in variable degrees of VTE risk (50). Patients with antithrombin III or protein C or S deficiency may remain free of thromboembolic disease until another risk factor such as immobilization is superimposed. Factor V Leiden is a common genetic polymorphism associated with activated protein C resistance and appears to be present in approximately 4% to 6% of the general population (51). The relative risk of a first idiopathic venous thrombosis among men heterozygous for the mutation has been shown to be three- to sevenfold higher than those not affected (51). The more recently identified prothrombin gene mutation (G20210A) and factor V Leiden are common among healthy whites but are rare among Asians and Africans. The presence of these genetic defects does not at present, in and of itself, mandate lifelong anticoagulation therapy, nor does it mandate increased intensity of prophylaxis, although more data are needed and patients should be scrutinized individually and carefully (50).

Gas Exchange and Hemodynamic Alterations in Acute Pulmonary Embolism

The hypoxemia occurring in the majority of patients with PE has been explained by various mechanisms. In patients without previous cardiopulmonary disease, regions with low ventilation-perfusion (V/Q) ratios and shunting secondary to perfusion of atelectatic areas are likely the dominant mechanisms of hypoxemia.

When emboli obstruct a significant portion of the pulmonary arterial bed, profound hemodynamic alterations occur. The impact of the embolic event depends on the extent of reduction of the cross-sectional area of the pulmonary vasculature as well as on the presence or absence of underlying cardiovascular disease. Submassive emboli in normal individuals may actually augment cardiac output (CO). Hypoxemia leads to an increase in sympathetic tone with systemic vasoconstriction and an increase in venous return with augmentation of stroke volume. With massive emboli, CO is diminished but may be sustained as the mean right atrial pressure increases. The ensuing increase in pulmonary vascular resistance impedes right ventricular outflow and reduces left ventricular preload. In a patient without previous cardiopulmonary disease, occlusion of 25% to 30% of the vascular bed by emboli is associated with a significant rise in pulmonary artery pressure (PAP). With increasing vascular obstruction, hypoxemia worsens, stimulating vasoconstriction and a further rise in PAP. More than 50% obstruction of the pulmonary arterial bed is usually present before substantial elevation of the mean PAP evolves. When the extent of obstruction of the pulmonary circulation approaches 75%, the right ventricle must generate a systolic pressure in excess of 50 mm Hg and a mean PAP of greater than 40 mm Hg to preserve pulmonary perfusion (52). The normal right ventricle

is unable to achieve this and ultimately fails (52). Patients with underlying cardiopulmonary disease are more inclined to experience more substantial deterioration in CO than normal individuals in the setting of massive PE. A depressed CO *without* elevation of the right atrial pressure suggests cardiac dysfunction superimposed on PE. Right ventricular failure is more common in the setting of PE in patients with coronary artery disease (53). It is important to realize that although supportive measures may sustain a patient with massive embolism, any additional increment in embolic burden may be fatal.

CLINICAL PROFILE

The diagnostic technology for acute DVT has developed considerably with the evolution of convenient and inexpensive techniques such as compression ultrasound as well as highly accurate yet more expensive diagnostic modalities such as magnetic resonance imaging (MRI). For PE, V/Q scanning followed by pulmonary arteriography remains the gold standard approach to the diagnosis, although newer techniques such as MRI and helical computed tomography (CT) scanning are being used increasingly. The presence of risk factors together with the history and physical examination generally leads to further diagnostic testing in the setting of suspected VTE.

History and Physical Examination

The clinical diagnosis of both DVT and PE based on the history and physical examination are notoriously insensitive and nonspecific. Patients with lower extremity DVT often do not exhibit erythema, warmth, pain, swelling, or tenderness. These findings, however, although not specific for DVT, merit further evaluation. PE should always be considered whenever unexplained dyspnea is present. Dyspnea as well as pleuritic chest pain and hemoptysis are common in PE but are nonspecific. Anxiety, lightheadedness, and syncope are all symptoms that may be caused by PE but may also result from a number of other entities that result in hypoxemia or hypotension. Tachypnea and tachycardia are the most common signs of PE but are also nonspecific. PE should always be considered in the setting of syncope or sudden hypotension. The cardiac and pulmonary physical examinations are both nonspecific. The index of clinical suspicion does, however, become a more useful parameter when considered in conjunction with V/Q scanning (54). Diagnostic efforts directed at possible VTE may be appropriate despite alternative explanations if risk factors and the clinical setting are suggestive. Dyspnea, tachypnea, clear lung fields, and hypoxemia may often be attributed to a flare of chronic obstructive disease or asthma when underlying PE is present.

Venous stasis eczema. Stasis dermatitis as a result of chronic edema and venous incompetence. There is erythema, scaling, pigmentation, crusting, and exudation.

Varicose veins. There are dilated, tortuous, superficial lower-extremity veins as a result of dysfunction of the valves of the saphenous veins.

Laboratory Testing

Electrocardiographic findings in acute PE are generally nonspecific and include T-wave changes, ST-segment abnormalities, and left or right axis deviation. In the Urokinase Pulmonary Embolism Trial, electrocardiographic abnormalities were documented in 87% of patients with proven PE who were without underlying cardiac or pulmonary disease (55). These findings were not specific for PE, however. In this clinical trial, 26% of patients with massive or submassive PE and 32% of those with massive PE had manifestations of acute cor pulmonale such as the S1 Q3 T3 pattern, right bundle branch block, P-wave pulmonale, or right axis deviation. Such changes are thus seen in a minority of patients. The low frequency of specific electrocardiographic changes associated with PE was confirmed in the PIOPED study (56).

Hypoxemia is common in acute PE. Some individuals, particularly young patients without underlying lung disease, may have a normal partial pressure of arterial oxygen (PaO_2). In a retrospective study of hospitalized patients with PE, the PaO_2 was greater than 80 mm Hg in 29% of patients younger than 40 years old, compared with 3% in the older group (57). The alveolar-arterial (A-a) difference was elevated in all patients, however. A subset of patients participating in the PIOPED study suspected of PE with no history or evidence of preexisting cardiac or pulmonary disease was evaluated and the PaO_2 and A-a difference values compared (54). Patients with and without PE could not be distinguished based on either of these values. The A-a difference was elevated by more than 20 mm Hg in 76 of 88 (86%) patients with PE, however. The diagnosis of acute PE cannot be excluded based on a normal PaO_2, and although the A-a difference is usually elevated, it may rarely be normal in patients without preexisting cardiopulmonary disease.

The usefulness of plasma measurements of circulating D-dimer, a specific derivative of cross-linked fibrin, as a diagnostic aid in PE has been extensively evaluated. A normal enzyme-linked immunosorbent assay appears sensitive in excluding PE. When the D-dimer level is 500 µg per liter or greater, the sensitivity and specificity for PE have been shown to be 98% and 39%, respectively (58). The sensitivity of the plasma D-dimer appears to remain high up to 1 week after presentation. In another prospective analysis, 96% of 79 patients with high-probability V/Q scans had an elevated D-dimer concentration (59). Thus, increased levels of cross-linked fibrin degradation products are an indirect but suggestive marker of intravascular thrombosis in addition to indicating fibrinolysis. A D-dimer assay together with a respiratory rate of less than 20 breaths per minute and a partial pressure of oxygen of more than 80 mm Hg was shown to be very sensitive in ruling out acute PE (60). Wells and

colleagues (60a) have refined simple but very useful pretest probability criteria with a scoring system and found that, in the setting of a low score and a negative simplified D-dimer, PE is exceedingly unlikely. Although the sensitivity of the D-dimer appears high, the specificity is not high enough to be diagnostic. Thus, symptoms, signs, radiographic findings, electrocardiographic measurement, and the plasma D-dimer measurement cannot be considered diagnostic of PE or DVT, and when these entities are suspected, further evaluation with noninvasive or invasive testing is necessary. A recent exhaustive review of the various D-dimer assays and clinical trial results reinforces the above findings (61).

Chest Radiography, Ventilation-Perfusion Scanning, and Pulmonary Arteriography

Most patients with PE have abnormal but nonspecific findings on chest radiograph. Common radiographic findings include atelectasis, pleural effusion, pulmonary infiltrates, and mild elevation of a hemidiaphragm (56). Classic findings of pulmonary infarction such as Hampton's hump or decreased vascularity (Westermark's sign) are suggestive but infrequent. Normal chest radiograph findings in the setting of severe dyspnea and hypoxemia without evidence of bronchospasm or anatomic cardiac shunt are strongly suggestive of PE. The presence of a pleural effusion increases the likelihood of PE in young patients who present with acute pleuritic chest pain (62). Under most circumstances, however, the chest radiograph cannot be used to conclusively diagnose or exclude PE. Although exclusion of other processes such as pneumonia, pneumothorax, or rib fracture, which may cause symptoms similar to acute PE, is possible, PE may frequently coexist with other underlying lung diseases.

V/Q scanning should be performed when PE is suspected. Normal and high-probability scans are considered diagnostic. A normal perfusion scan rules out the diagnosis of PE with a high enough degree of certainty that further diagnostic evaluation is unnecessary. Matching areas of decreased ventilation and perfusion in the presence of a normal chest radiograph generally represent a process other than PE. However, low- or intermediate-probability (nondiagnostic) scans are commonly found with PE, and in such situations further evaluation with pulmonary arteriography is often appropriate. Normal, high-, low-, and intermediate-probability lung scans are shown in Figure 28.1, Figure 28.2, Figure 28.3, and Figure 28.4. In the PIOPED study, the use of V/Q scanning combined with clinical assessment of patients with suspected PE was prospectively evaluated (54). Patients with PE had scans that were high, intermediate, or low probability, but so did most patients without PE. Although the specificity of high-probability scans was 97%, the sensitivity was only 41%. Of interest, 33% of patients with intermediate-probability scans and 12% of patients with low-probability scans were diagnosed definitively with PE by pulmonary arteriography. When the clinical suspicion of PE was considered very high, PE was found to be present in 96% of patients with high-probability scans, 66% of patients with intermediate scans, and 40% of patients with low-probability scans. The diagnosis of PE should be rigorously pursued, even when the lung scan is low or intermediate probability, if the clinical scenario suggests PE. Therefore, although the V/Q scan may sometimes be diagnostic of PE or exclude the possibility with sufficient certainty, it is often nondiagnostic. Even in such circumstances, however, it may serve as a useful guide for limited pulmonary arteriography.

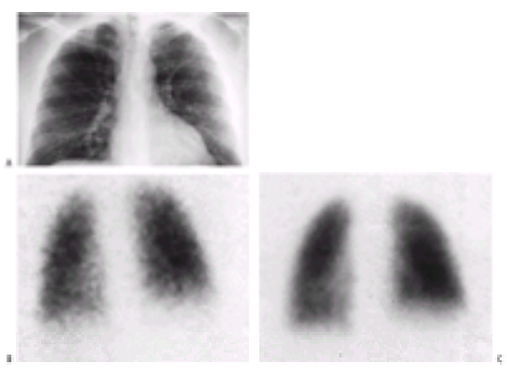


FIGURE 28.1 Normal ventilation-perfusion scan. Multiple views are always performed for the perfusion images; only the posterior view is shown in each of these cases. Ventilation scans are done as breath-hold, equilibrium, and washout phases; only one phase is shown in each of these cases. The chest radiograph **(A)**, ventilation scan **(B)**, and perfusion scan **(C)** are normal in this patient. Pulmonary embolism is excluded.

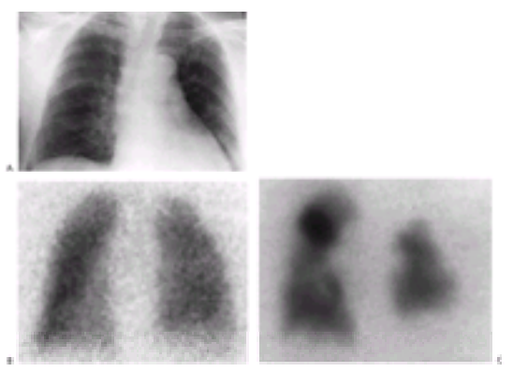


FIGURE 28.2 High-probability lung scan. This patient with metastatic cancer developed sudden dyspnea and unexplained hypoxemia after prolonged bedrest. The chest radiograph **(A)** reveals a right hilar mass. The ventilation scan **(B)** is normal, but the perfusion scan **(C)** demonstrates multiple bilateral perfusion defects, virtually diagnostic of pulmonary embolism.

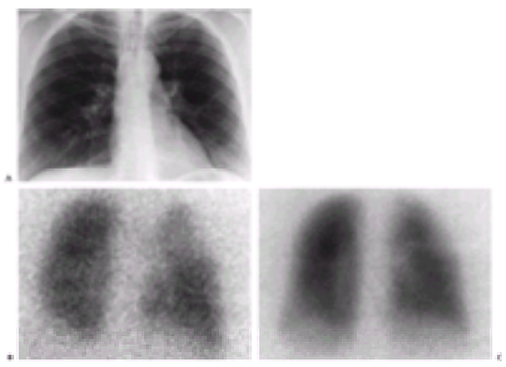


FIGURE 28.3 Low-probability lung scan. This patient had a significant smoking history and developed dyspnea with hemoptysis. The chest radiograph **(A)** reveals enlarged central pulmonary arteries consistent with pulmonary hypertension. The ventilation scan sequence revealed xenon retention consistent with chronic obstructive lung disease, and the image shown **(B)** demonstrates ventilation abnormalities, especially at the bases. Matched perfusion abnormalities were present on the perfusion scan **(C)**. Because of purulent sputum and a rapid response to bronchodilator therapy, pulmonary embolism was believed unlikely, and further evaluation was deemed unnecessary. Obstructive lung disease commonly results in nondiagnostic ventilation-perfusion scans. Further studies depend on level of clinical suspicion.

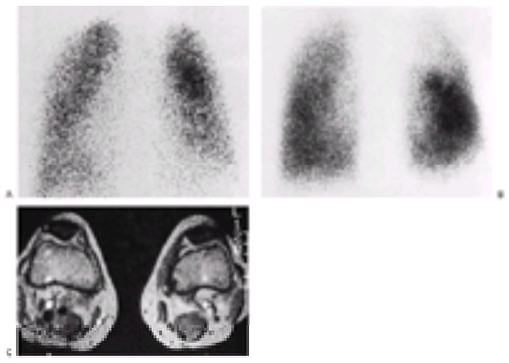


FIGURE 28.4 Intermediate probability. This patient developed sudden dyspnea and pleuritic chest pain after surgery. The chest radiograph (not shown) was clear. The ventilation scan **(A)** reveals a defect at the right base. The perfusion scan **(B)** reveals a solitary defect in the right upper lobe; this unmatched defect was not large enough to qualify as a high-probability reading. The clinical suspicion was high for pulmonary embolism, but pulmonary arteriography could not be performed because of significant renal insufficiency. Magnetic resonance imaging **(C)** was used to document proximal deep vein thrombosis of the right lower extremity. The completely occlusive thrombus (*arrow*) appears as a hypodense region adjacent to the high-intensity white signal representing normal arterial flow. The patient was heparinized for acute deep vein thrombosis (and presumed pulmonary embolism).

Pulmonary arteriography has remained the accepted gold standard technique for the diagnosis of PE. It is a very sensitive, specific, and safe test. Complications of pulmonary arteriography among 1,111 patients suspected of PE in the PIOPED study included death in 0.5% and major nonfatal complications in 1% (63). An alternative to pulmonary arteriography is to perform lower extremity studies when the lung scan is nondiagnostic, and if these are negative, the chances of significant PE or morbidity from a subsequent event appear unlikely (64). This practice is gaining acceptance and in patients with cardiopulmonary stability may be appropriate. Finally, pulmonary angiography has been performed at the bedside using a Swan-Ganz catheter (65). This may prevent the need to transport critically ill patients. A pulmonary arteriogram diagnostic of PE is shown in Figure 28.5.

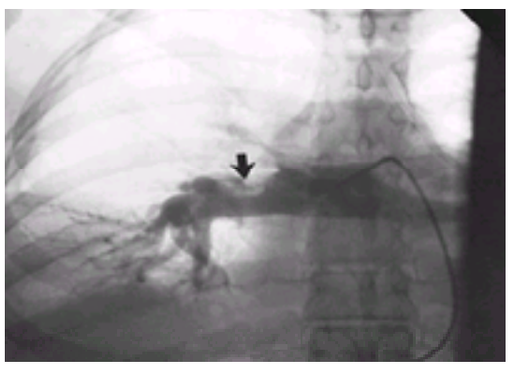


FIGURE 28.5 Pulmonary arteriography demonstrating acute pulmonary embolism. There is a large filling defect in the right pulmonary artery (*arrow*) and marked hypoperfusion to the right upper and middle lobes. A ventilation-perfusion scan had been performed and was nondiagnostic because of extensive air space disease in the right lung.

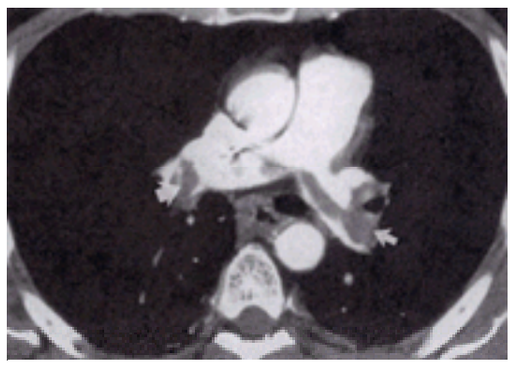
Echocardiography in Acute Pulmonary Embolism

Other diagnostic techniques sometimes prove useful particularly in the setting of massive PE. Echocardiography, which can often be obtained more rapidly than either lung scanning or pulmonary arteriography, may reveal findings that strongly support hemodynamically significant PE (66). Studies of patients with documented PE have revealed that more than 80% of patients have imaging or Doppler abnormalities of right ventricular size or function that may suggest acute PE (66,67). Unfortunately, because patients with PE often have underlying cardiopulmonary disease such as chronic obstructive lung disease, neither right ventricular dilation nor hypokinesis can be reliably used even as indirect evidence of PE in such settings. Goldhaber and colleagues (68) demonstrated that echocardiography could be used to document improvement in right ventricular wall motion in patients with PE treated with recombinant tissue-type plasminogen activator (t-PA). Intravascular ultrasound imaging has been shown in both the experimental and clinical setting to adequately image large emboli (69,70 and 71). This procedure may be performed at the bedside. Although the technique may be less sensitive and specific and more time-consuming in the setting of smaller emboli, further investigation may be warranted.

Computed Tomography and Magnetic Resonance Imaging

The usefulness of CT scanning and MRI for diagnosing PE has recently been explored. Preliminary data suggest comparable accuracy for these techniques (72). Helical (spiral) CT has been explored in patients with both acute and chronic PE. This technique involves continuous movement of the patient through the scanner with concurrent scanning by a constantly rotating gantry and detector system that takes 1 second for a 360-degree rotation (73). A helix of raw projecting data is obtained. Continuous volume acquisitions can be obtained during a single breath and rapid scans can be obtained, facilitating imaging in critically ill patients. Retrospective reconstructions can be performed. A contrast bolus is required for vascular imaging. Limitations of helical CT scanning include poor visualization of horizontally oriented vessels in the right middle lobe and lingula because of volume averaging. The peripheral areas of the upper and lower lobes may be inadequately scanned and intersegmental lymph nodes may result in false-positive studies. Multiplanar reconstructions in coronal or oblique planes may aid in differentiating lymph nodes from emboli.

Helical and electron beam CT may reveal emboli in the main, lobar, or segmental pulmonary arteries with more than 90% sensitivity and specificity (74,75,76 and 77). Others have reported very accurate results for large PE (78,79). Oser and colleagues (80) determined retrospectively that of 76 consecutive pulmonary angiograms, 23 (30%) revealed only subsegmental emboli. Nineteen studies (25%) revealed only a single PE. Thirteen of the 19 single emboli were subsegmental only. The PIOPED study, however, revealed that only 6% of patients had isolated subsegmental emboli (54). The latter prospective evaluation is likely more representative. Interestingly, however, two referee angiographers from the PIOPED agreed on the presence or absence of subsegmental emboli in only 66% of cases (54). Using selective pulmonary arteriography, Quinn and colleagues (81) emphasized excellent agreement on main, lobar, and segmental emboli but only 13% agreement on subsegmental emboli. Thus, this apparent limitation with helical CT scanning is also a concern with angiography. Goodman and others (82) have strongly endorsed the incorporation of CT scanning into diagnostic algorithms for PE. Examples of bilateral, central emboli imaged by helical CT are shown in *e*Figure 28.5.1. Sensitivity and specificity data from several large studies evaluating helical CT scanning for acute PE are shown in *e*Table 28.1.1. Contrast-enhanced electron beam CT also appears useful in diagnosing acute PE (77,83). The rapid (100 ms) scanning time makes breath holding unnecessary, and respiratory and cardiac motion artifact are minimized. In one comparison with pulmonary angiography, only 8 of 720 vascular zones (1.1%) were considered inadequately visualized with electron-beam CT. The entire chest examination took approximately 10 to 15 minutes in each case. As with helical CT, three-dimensional reconstruction techniques can be applied to the opacified pulmonary vasculature to better define vessels located within the plane that has been sectioned. Another important advantage of these CT techniques includes the concomitant ability to define nonvascular structures such as airway abnormalities, lymphadenopathy, lung tumors, and other parenchymal abnormalities, as well as pleural and pericardial disease. One recent helical CT study suggested a significantly lower sensitivity for acute PE than previous studies (84). Two sets of readers performed with 53% and 61% sensitivity, respectively. The specificities were 97% and 81%. It is feasible that reading cut films instead of evaluation of the images at the computer workstation accounted for the low sensitivity by these experienced readers. Prospective, randomized, clinical trials comparing these techniques with the standard diagnostic approach to PE are currently under way. PIOPED II is a prospective clinical trial sponsored by the National Institutes of Health in which approximately 1,000 patients with suspected PE will undergo V/Q scanning and helical CT to better assess the appropriate role of the latter modality. Data from a large European CT scan clinical trial is currently being analyzed also. These efforts will help to determine their precise role.



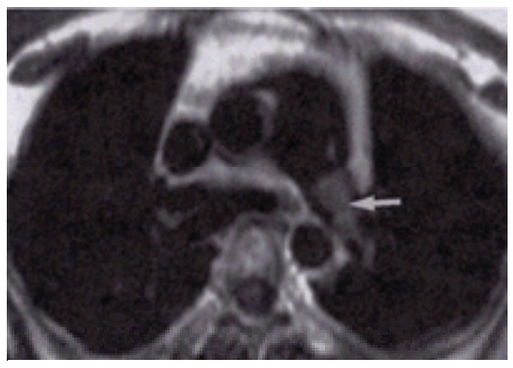
***e*FIGURE 28.5.1** Helical computed tomography scan demonstrating acute pulmonary emboli. The low-density emboli are easily visualized in both the left and right pulmonary arteries (*arrows*) surrounded by the dense white contrast.

***e*TABLE 28.1.1** SENSITIVITY AND SPECIFICITY FOR COMPUTED TOMOGRAPHY SCANNING FOR ACUTE PULMONARY EMBOLISM

References	Number of patients	Sensitivity (%)	Specificity (%)
Helical computed tomography			
Goodman (75)	20	86[a]	92[a]
	—	63[b]	89[b]
Remy-Jardin et al. (74)	72	90	86
van Rossum et al. (78)	124	97	98
Sostman et al. (72)	28	73	97
Remy-Jardin et al. (76)	42	100	96
van Rossum et al. (79)	45	95	97
Drucker et al. (84)[c]	—	60	81
	—	53	97
Electron-beam computed tomography			
Teigen et al. (77)	60	65	97
Teigen et al. (83)	25	95	80

[a]Main, lobar, and segmental emboli.
[b]All emboli, including peripheral.
[c]Two sets of readers from different institutions were used, resulting in two sensitivity/specificity values.

MRI is also being used to evaluate clinically suspected PE (72). In a comparison with helical CT, the average sensitivity of CT for five observers was 75% and of MRI 46%. The average specificity of CT was 89%, compared with 90% for MRI. Sensitivity and specificity values for expert readers were higher, however (72). Helical CT may be somewhat more useful than MRI for detecting PE at the present time, but MRI has several attractive advantages, including excellent sensitivity and specificity for the diagnosis of DVT (see Detection of Deep Venous Thrombosis). This technique may ultimately allow simultaneous accurate detection of both PE and DVT. PE proven by MRI is demonstrated in *e*Figure 28.5.2. Future investigation will determine the roles of these modalities in the evaluation of PE.



***e*FIGURE 28.5.2** A T2-weighted magnetic resonance image of a large pulmonary embolus (*arrow*) in the left pulmonary artery. No contrast is necessary for these images.

Detection of Deep Venous Thrombosis

The available technology used to pursue the diagnosis of DVT has expanded over the past several decades. Each technique has advantages and limitations. Impedance plethysmography has been shown to be reliable for detection of DVT occurring above the knee. Early studies suggested greater than 90% sensitivity and 97% specificity for DVT involving the proximal lower extremity, although less than 30% of isolated calf vein thromboses were detected (85,86). Other reports have emphasized the limitations of impedance plethysmography (41). In a more recent retrospective analysis at a university-based tertiary care center, impedance plethysmography was abnormal in only 37 of 56 patients, with proximal vein thrombosis confirmed by venography for a sensitivity of only 66% (87). The specificity was equally poor. Although this modality is sometimes portable, it does require access to the calf and thigh for electrode and cuff placement. The specificity is affected by disorders that obstruct venous outflow such as tumor or hematoma. External fixation or plaster immobilization of extremities reduces the usefulness of this technique. It is being used decreasingly.

Compression ultrasonography is a portable and accurate diagnostic technique for proximal lower extremity DVT. The sensitivity and specificity for symptomatic proximal DVT have been well above 90% in most recent clinical trials (88,89). Limitations include insensitivity for asymptomatic DVT, operator dependence, the inability to accurately distinguish acute from chronic DVT in symptomatic patients, and the insensitivity to calf vein thrombosis (90,91). A recent prospective evaluation of the utility of bilateral color Doppler ultrasound in asymptomatic high-risk (elective unilateral hip or knee replacement) patients revealed that ultrasound was only 38% sensitive for proximal DVT using contrast venography as the diagnostic standard (92). Compared with other technology, it is relatively inexpensive and is the preferred diagnostic modality for the straightforward case of symptomatic presumed proximal DVT.

Although contrast venography remains the gold standard technique for the diagnosis of DVT, it is less commonly performed since the advent of compression ultrasonography (93). Venography should be performed whenever noninvasive testing is nondiagnostic or impossible to perform. It is an invasive procedure that may result in superficial phlebitis or hypersensitivity reactions, but it is generally safe and accurate.

MRI is being increasingly used to diagnose DVT and appears to be an accurate noninvasive alternative to venography (94). A major advantage of this technique is excellent resolution of the inferior vena cava (IVC) and pelvic veins (95,96). Preliminary experience with this technique suggests that it is at least as accurate as contrast venography or ultrasound imaging and perhaps more sensitive than either for pelvic vein thrombosis. It offers the opportunity for simultaneous bilateral lower extremity imaging and appears to accurately distinguish acute from chronic DVT. It offers the additional advantage of lower extremity and lung imaging during the same session. DVT imaged by MRI is shown in Figure 28.4C.

At Duke University Medical Center, duplex ultrasound is commonly used as the first test to evaluate suspected acute DVT. MRI is frequently used subsequently when the ultrasound is nondiagnostic or to distinguish acute from chronic DVT. Another useful aspect of MRI lies in distinguishing other entities such as cellulitis or a Baker's cyst from acute DVT. The utility of this technique depends to a certain degree on the experience of the reader. Finally, helical CT scanning has been studied for suspected acute DVT. The contrast dye from the bolus injected for lung imaging is followed into the deep veins of the legs for viewing. Initial data are promising (97) and the utility of "CT venography" will be further studied in PIOPED II. These techniques may fit into diagnostic algorithms for DVT and PE, but these algorithms are

institution-specific at present, depending on resources and expertise with certain techniques.

PRINCIPLES OF MANAGEMENT

Prophylaxis of Deep Venous Thrombosis

A significant reduction in the incidence of DVT can be achieved when patients at risk receive appropriate prophylaxis. Such preventive measures appear to be grossly underused. A review of the use of prophylaxis for DVT in 16 Massachusetts hospitals indicated that such therapy was administered to only 44% of high-risk patients in teaching hospitals and only 19% in nonteaching hospitals (98). The frequency of prophylaxis ranged from 9% to 56% among hospitals. Patients can be stratified according to DVT risk, and certain prophylactic measures are more appropriate for some patients than for others. In general, for medical patients at risk for DVT, subcutaneous heparin at 5,000 U every 8 to 12 hours is generally adequate. Intermittent pneumatic compression devices should be used in the unusual situation when such prophylactic doses of heparin are contraindicated. Both methods combined would be reasonable in patients deemed to be at exceptionally high risk, but an additional reduction in risk in such patients has not been well substantiated.

In the general surgery population, a number of prophylactic methods have been used. In a large metaanalysis, Colditz et al. (99) not only confirmed the value of prophylaxis to reduce the incidence of DVT but also suggested that intermittent pneumatic compression plus gradient compression stockings may result in the lowest incidence of postoperative DVT. Other combined treatments were associated with lower rates than heparin alone. Another overview of the results of randomized trials in surgical patients demonstrated the benefit of DVT prophylaxis (100). In this review of more than 70 randomized trials involving 16,000 patients, it was demonstrated that perioperative use of subcutaneous heparin can prevent approximately half of all pulmonary emboli and approximately two-thirds of all DVT.

A number of investigators have evaluated the efficacy and safety of LMWH for DVT prophylaxis (101). LMWH may have an advantage in producing a more predictable dose response and is administered subcutaneously once or twice per day depending on the preparation (eTable 28.1.2 and eTable 28.1.3). Enoxaparin has been approved by the U.S. Food and Drug Administration (FDA) for three surgical prophylaxis indications, including elective total hip or knee replacement and general abdominal surgery (eTable 28.1.4). The approved dose is either 30 mg subcutaneously twice daily or 40 mg once daily for the orthopedic indications and 40 mg once daily for abdominal surgery. Prophylaxis is generally recommended for 7 to 10 days. Longer regimens may be appropriate depending on associated additional risk factors and on whether the patient is ambulatory. A large, randomized, placebo-controlled trial in patients undergoing total hip replacement compared enoxaparin prophylaxis during hospitalization (average, 10 to 11 days) with more prolonged outpatient prophylaxis (102). Blinded outpatient therapy (or placebo) was continued long enough that the total treatment period (inpatient plus outpatient) was 1 month for each patient. In the 233 patients with adequate venography, there were 43 episodes of DVT and two PE in the placebo group compared with only 21 episodes of DVT and no PE in the group receiving 1 month of prophylaxis. The incidence of thromboembolic events was 39% and 18%, respectively (p <.001). Another clinical trial recently confirmed the potential benefit in these patients (103). Thus, more prolonged outpatient prophylaxis may be appropriate in this patient population. Further investigation in such high-risk patients appears warranted. A second preparation, dalteparin, has been approved for once-daily use as prophylaxis for elective abdominal surgery. A number of other preparations are currently being investigated. Recent clinical trials emphasize the increased thromboembolic risk of general medical patients (104). Although this concept is not new, it is important to stress, as the population of hospitalized patients is becoming increasingly complex. The recent MEDENOX (Prophylaxis of Medical Patients with Enoxaparin) clinical trial compared two doses of enoxaparin (20 mg and 40 mg) with placebo in 1,102 hospitalized medical patients at moderate risk for VTE (104). Most of these patients had acute respiratory failure, congestive heart failure, or acute infectious diseases. The primary outcome was DVT detected by venography or ultrasonography between day 6 and 14 or PE. VTE developed in 14.9% of the patients receiving placebo, in 15% of patients receiving 20 mg of enoxaparin, and in only 5.5% of patients receiving the 40-mg enoxaparin dose (p <.001 for enoxaparin vs. placebo). There was no difference in major bleeding or death between the three groups. Enoxaparin is now FDA-approved for prophylaxis in this group of patients. Preliminary results from two European studies suggest that enoxaparin is at least as effective and as safe as standard heparin as VTE prophylaxis at a dose of 5,000 U every 8 hours in medically ill patients (105,106). Further prophylaxis studies in the medically ill evaluating LMWH preparations and standard heparin at 5,000 U every 12 hours would appear appropriate. It is important to realize that LMWH preparations are not identical and the results of clinical trials with one agent cannot be extrapolated to another agent. Evidence-based recommendations for DVT prophylaxis have recently been published (American College of Chest Physicians Consensus) and are updated every 2 years (33).

***e*TABLE 28.1.2** COMPARISON OF LOW-MOLECULAR-WEIGHT HEPARIN WITH UNFRACTIONATED HEPARIN

Characteristic	Unfractionated heparin	Low-molecular-weight heparin
Mean molecular weight	12,000–15,000 daltons	4,000–6,000 daltons
Protein binding	Substantial	Minimal
Anti-X_a activity	Substantial	Substantial
Anti-II_a activity	Substantial	Minimal
Platelet inhibition	Substantial	Minimal
Vascular permeability	Moderate	None
Microvascular permeability	Substantial	Minimal

***e*TABLE 28.1.3** POTENTIAL ADVANTAGES OF LOW-MOLECULAR-WEIGHT HEPARINS OVER UNFRACTIONATED HEPARIN

Comparable or superior efficacy
Comparable or superior safety
Superior bioavailability
Once- or twice-daily dosing
No laboratory monitoring[a]
Less phlebotomy
Subcutaneous administration
Earlier ambulation
Home therapy in certain patient subsets

[a]Measurement of anti–factor X_a levels is recommended in significantly obese patients, very small patients (e.g., <40 kg), and patients with renal insufficiency.

***e*TABLE 28.1.4** GUIDELINES FOR USE OF ENOXAPARIN PROPHYLAXIS AFTER KNEE OR HIP REPLACEMENT

Dose: 30 mg subcutaneously twice daily or 40 mg once daily
Duration: 7–10 d (or until discharge or risk of postoperative deep venous thrombosis has diminished[a])
Initial dose: Begin 12–24 h after surgery
Delivery method: Deep subcutaneous administration
Monitoring: None

[a]Several randomized, prospective, placebo-controlled trials strongly suggest that extending prophylaxis in total hip replacement patients to a total of 1 mo (inpatient plus outpatient) significantly reduces the incidence of venous thromboembolism (102,103).

Anticoagulation Therapy

Anticoagulation has been proven to reduce mortality in acute PE. When VTE is diagnosed or strongly suspected, heparin therapy should be promptly instituted unless contraindications exist. Confirmatory testing should always be planned if anticoagulation is to be continued. Heparin exerts a prompt antithrombotic effect, preventing thrombus growth. Although it does not directly prevent the development of acute PE or dissolve thrombus, it allows the fibrinolytic system to act unopposed and more readily reduces the size of the thromboembolic burden (107). Although thrombus growth can be prevented, early recurrence can develop even in the setting of therapeutic anticoagulation.

With the institution of continuous intravenous heparin, the activated partial thromboplastin time (aPTT) should be aggressively followed at 6-hour intervals until it is consistently in the therapeutic range of 1.5 to 2.0 times control values (107). This range corresponds to a heparin level of 0.2 to 0.4 U per mL as measured by protamine sulfate titration. In general, heparin should be administered as an intravenous bolus of 5,000 U followed by a maintenance dose of at least 30,000 to 40,000 U per 24 hours by continuous infusion (108). The lower dose is administered if the patient is considered at high risk for bleeding. This aggressive approach decreases the risk of subtherapeutic anticoagulation, and although supratherapeutic levels are sometimes achieved initially, bleeding complications do not appear to be increased (109). More recent data continue to support aggressive heparin dosing. An alternative regimen consisting of a bolus of 80 U per kg followed by 18 U per kg per hour has been recommended (110). Further adjusting of the heparin dose should also be weight-based (Table 28.2). This weight-adjusted approach is recommended in the recent American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (111). Warfarin therapy may be initiated as soon as the aPTT is

therapeutic, and heparin should be maintained until a therapeutic international normalized ratio of 2.0 to 3.0 has been overlapped with a therapeutic aPTT for 2 consecutive days. Although proximal lower extremity thrombus is more likely to result in PE, calf thrombi should either be followed for proximal extension over 10 to 14 days with noninvasive testing, or anticoagulation should be instituted (112,113). Documented proximal DVT or PE should be treated for at least 3 months. Longer treatment is appropriate when significant risk factors persist. Both short- and long-term anticoagulation guidelines are outlined in the American College of Chest Physicians Consensus Conference guidelines (111).

Initial heparin dose = 80 U/kg bolus, then 18 U/kg per h		
Subsequent modifications		
aPTT		
(sec)	(times control)	Heparin dose adjustment
<35	<1.2	80 U/kg bolus, then increase by 4 U/kg per h
35 to 45	1.2 to 1.5	40 U/kg bolus, then increase by 2 U/kg per h
46 to 70	1.5 to 2.3	No change
71 to 90	2.3 to 3	Decrease infusion rate by 2 U/kg per h
>90	>3	Hold infusion 1 h, then decrease rate by 3 U/kg per h

aPTT, activated partial thromboplastin time.
From Dalen JE, Hirsh J, Guyatt GH. Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy. Chest 2001;119:1S-376S; and Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. Ann Intern Med 1993;119:874, with permission.

TABLE 28.2 WEIGHT-BASED NOMOGRAM FOR HEPARIN THERAPY IN ACUTE VENOUS THROMBOEMBOLISM

A number of clinical trials have strongly suggested the efficacy and safety of LMWH for treatment of established acute proximal DVT using recurrent symptomatic VTE as the primary outcome measure (111,114,115 and 116). The incidence of DVT and recurrent bleeding in these trials indicates that LMWH preparations are at least as effective and as safe as unfractionated heparin. These agents can be administered once or twice per day subcutaneously even at therapeutic doses and do not require monitoring of the aPTT. Antifactor X levels appear reasonable to monitor in certain settings such as in obese patients, in very small patients (less than 40 kg), and in those with renal insufficiency. There is no proven benefit in monitoring other patients. In two large randomized (Canadian and European) trials, therapy with LMWH was safely initiated at home or continued at home after a brief hospitalization (114,115). A number of outpatient studies have followed these two pivotal trials. Four metaanalyses examined the use of LMWH compared with unfractionated heparin in the initial treatment of acute proximal DVT (117,118,119 and 120). Although there was overlap between the analyses, they have helped to confirm the efficacy and safety of LMWH for the treatment of established DVT. The most recent of these studies has suggested a reduced mortality in patients treated with LMWH, although the precise reason for this is not absolutely clear (117). In the United States, at the present time, two LMWH preparations are FDA-approved for use in patients presenting with DVT with or without acute PE. Enoxaparin is approved for both inpatient and outpatient use at a dose of 1.0 mg per kg subcutaneously every 12 hours or at 1.5 mg per kg once daily for inpatient use. The latter regimens were both proven effective in a large study of inpatients in which both doses proved as effective and as safe as unfractionated heparin (121). The second preparation, tinzaparin, is administered as 175 U once daily, with FDA approval being based on therapy of inpatients. The latter treatment indication is the only approved use for this drug in this country at present. Neither enoxaparin nor tinzaparin is approved for use in patients presenting with acute PE, although tinzaparin has proven effective in a large, randomized European trial of patients with PE (122). The FDA-approved indications for the three LMWHs approved for use in the United States are shown in Table 28.3. It should be noted that the prophylactic doses of these agents differ from the doses used for treating active disease.

	Low-molecular-weight heparin		
Indication[a]	Enoxaparin	Dalteparin	Tinzaparin
Patients presenting with acute DVT[b]	X		X
Prophylaxis for acute DVT in			
Total hip replacement	X	X	
Total knee replacement	X		
General abdominal surgery	X	X	
Hospitalized medical patients	X		
Acute coronary syndromes[c]	X	X	

DVT, deep venous thrombosis.
[a]It must be recognized that prophylactic doses differ from therapeutic doses.
[b]Enoxaparin is approved for use in both inpatients with DVT with or without pulmonary embolism at 1 mg/kg every 12 h or 1.5 mg/kg once daily and for outpatients (1 mg/kg every 12 h). The data supporting treatment with tinzaparin (175 units once daily) are based on studies of hospitalized patients. Neither drug is approved in patients presenting with acute pulmonary embolism.
[c]Unstable angina and non–ST-segment elevation myocardial infarction.

TABLE 28.3 U.S. FOOD AND DRUG ADMINISTRATION–APPROVED INDICATIONS FOR SPECIFIC LOW-MOLECULAR-WEIGHT HEPARINS

Novel Anticoagulants and Experimental Models of Thrombosis

Newer agents are being explored. Although heparin is the best studied antithrombotic agent, it works indirectly, requiring antithrombin III as a cofactor. Heparin's effects vary considerably between patients. Hirudin is a direct thrombin inhibitor that has several advantages over heparin, including efficacy against fibrin clot–bound thrombin. It does not require any cofactors and is not inactivated by platelet factor 4 or plasma proteins. This drug, derived from the saliva of the medicinal leach (*Hirudo medicinalis*), appears promising. Data from several clinical trials including the Global Use of Strategies to Open Occluded Coronary Arteries IIB trial suggested a small advantage of hirudin without increased bleeding when compared with heparin, in the setting of acute coronary syndromes (123). The results of the Thrombolysis In Myocardial Infarction 9B trial suggested that heparin and hirudin are equally effective and safe as adjunctive therapies for t-PA or streptokinase in preventing unsatisfactory thrombotic outcomes in acute myocardial infarction (124). Other agents such as the hirudin analogue bivalirudin await study. There are less data available for treatment of acute VTE. As with heparin, these direct thrombin inhibitors have very narrow therapeutic indices.

Inogatran, a new selective active-site inhibitor of thrombin was recently evaluated in a rat model of both arterial and venous thrombosis (125). This drug appears to be an effective antithrombotic agent in both models as well as an effective adjunct to t-PA in a thrombolysis model. Napsagatran, a new synthetic direct thrombin inhibitor, has been compared with heparin in a canine model of coronary thrombosis (126). In this model, arterial antithrombotic effects appeared similar to those of heparin. The direct thrombin inhibitor, argatroban, has been used during pulse-spray pharmacomechanical thrombolysis in a rabbit model of venous thrombosis (127). The use of intrathrombic argatroban together with t-PA significantly improved clot lysis when administered in this manner.

P>A selective factor X_a inhibitor, tick anticoagulant peptide, appears effective in restoring coronary blood flow and preventing reocclusion in a canine model of coronary thrombosis (128). Tissue factor pathway inhibitor (TFPI) controls activation of blood coagulation; antithrombin regulates the final stage (129). Both inhibitors inhibit the intermediate stage of activation. Heparin strongly accelerates antithrombin and releases TFPI in the blood. Thus, TFPI may contribute to the antithrombotic effect of heparin.

In summary, newer agents such as direct thrombin inhibitors, selective factor X_a inhibitors, and substances such as TFPI appear to merit further investigation in the prophylaxis and treatment of venous thrombosis.

Complications of Anticoagulation

Complications of heparin include bleeding and heparin-induced thrombocytopenia (HIT). The rates of major bleeding in recent trials using heparin by continuous infusion or high-dose subcutaneous injection are less than 5% (33). HIT (defined as a platelet count of less than 150,000 per µL) typically develops 5 or more days after the initiation of heparin therapy, occurring in 5% to 10% of patients. The syndrome is caused by heparin-dependent immunoglobulin G antibodies that activate platelets via their crystallizable fragment receptors (130). It has been demonstrated that these antibodies recognize heparin complexed with platelet factor 4 (131). Visentin and associates (132) have shown that such antibodies also react with endothelial cells coated with platelet factor 4, and such potential antibody-mediated vascular injury may help to explain the predisposition of patients with HIT to thromboembolism when challenged with heparin. Positive platelet aggregation tests for antibodies to heparin may be present in the absence of significant thrombocytopenia, and such tests may be negative despite a progressive decrease in platelet count (130). If a patient is placed on heparin for VTE and the platelet count progressively decreases to 100,000 per µLor less, heparin therapy should be discontinued. The formation of heparin-dependent immunoglobulin G antibodies and the risk of HIT appears to be lower with this form of heparin. HIT occurred in 9 of 332 patients receiving standard unfractionated heparin compared with none of 333 patients receiving enoxaparin (133). Eight of the nine patients receiving standard heparin developed one or more thrombotic events. However, it is important for clinicians to realize that HIT can occur with the use of either form of heparin. Newly developed

solid-phase assays that use complexes of heparin and platelet factor 4 as targets for the detection of heparin-induced antibodies are much more sensitive than the serotonin-release test used in the above study (133). Both argatroban and lepirudin are approved by the FDA for the treatment of VTE in the setting of HIT.

Heparin complication. Extensive purpura from heparin treatment.

Vena Cava Interruption

If heparin therapy cannot be continued, IVC filter placement can be undertaken to prevent lower extremity thrombus from embolizing to the lungs. These devices have been widely used for nearly two decades. The primary indications for filter placement include contraindications to anticoagulation, recurrent embolism while on adequate therapy, and significant bleeding complications during anticoagulation (134). Filters are sometimes placed in the setting of massive PE when it is believed that any further emboli might be lethal (135). A number of filter designs exist, but the Greenfield filter has been most widely used. Filters can be inserted via the jugular or femoral vein. These devices are effective and complications are unusual (135). Potential mechanisms of IVC filter failure include migration of the filter either distally or proximally to a point that no longer protects the vena cava, improper filter positioning allowing thrombi to bypass the filter, and formation of thrombosis proximal to the filter or on the proximal tip of the filter with subsequent embolization. Rare complications include clinically significant perforation of the IVC, cephalad migration, and displacement of the filter during insertion. IVC filters may rarely erode into the wall of the IVC. Occasionally, IVC obstruction due to thrombosis at the filter site may occur. Deaths due to filter placement are exceedingly uncommon. In general, anticoagulation is continued when a filter is placed unless it is contraindicated.

Thrombolytic Therapy

The National Institutes of Health consensus guidelines for PE thrombolysis issued in 1980 recommended thrombolytic therapy for patients with obstruction of blood flow to a lobe or multiple pulmonary segments and for patients with hemodynamic compromise, regardless of the size of the PE (136). The recommendations for use of lytic therapy in PE have recently been carefully reviewed (137). Current guidelines are presented in Table 28.4. We favor the use of thrombolytic therapy in patients with hemodynamic instability (hypotension) or severely compromised oxygenation (138). Stable patients with a significant embolic load are individualized, often receiving treatment in the absence of absolute or relative contraindications. For example, strong arguments for thrombolytic therapy can be made when the perfusion defect by lung scan or pulmonary arteriogram is extensive (defect approaching the equivalent of one-half of the pulmonary vascular bed) even without clear hemodynamic instability. Another setting in which thrombolytic therapy may be considered is when extensive DVT accompanies a submassive PE. There are no clinical studies suggesting a reduction in mortality in the latter settings, and perhaps future clinical trials will clarify appropriate guidelines.

Hypotension related to pulmonary embolism[a]
Severe hypoxemia
Lobar or greater perfusion defect[b]
Right ventricular dysfunction associated with pulmonary embolism
Extensive deep venous thrombosis

[a]This indication is widely accepted. All indications require careful review of contraindications to thrombolytic therapy.
[b]National Institutes of Health Consensus 1980 (136). This indication is not widely accepted.

TABLE 28.4 THROMBOLYTIC THERAPY IN VENOUS THROMBOEMBOLISM: POTENTIAL INDICATIONS

Acceleration of clot lysis in PE using thrombolytic therapy was first documented several decades ago (139,140 and 141). The multicenter, prospective, randomized Urokinase Pulmonary Embolism Trial evaluated 160 patients with arteriographically proven PE (55). Thrombolysis was accelerated in patients receiving urokinase compared with those on heparin when pulmonary arteriograms and lung perfusion scans were examined 24 hours after treatment. Thereafter, the difference between the two groups diminished, and by day 5 the improvement in each group was similar. There was no difference in the frequency of recurrent PE or mortality rate within 2 weeks of treatment. However, only 7% of the patients in the study were classified as having massive PE with shock. Although hemorrhagic complications in this trial were relatively high, further experience with thrombolytic therapy has suggested that adverse effects are reduced when venous cutdowns and unnecessary arterial phlebotomy are avoided. The second phase of this clinical trial also documented the efficacy of streptokinase administered over 24 hours. Finally, recombinant t-PA is approved for use in the treatment of PE and is administered as a 100-mg intravenous infusion delivered over 2 hours (142). Even shorter infusion durations have been evaluated, and future clinical trials may lead to wider acceptance of these regimens. At present, the above t-PA regimen is the most rapidly administered protocol that is currently approved for use.

Thrombolytic regimens approved by the FDA for the treatment of PE are presented in Table 28.5. Coagulation assays are unnecessary during thrombolysis because the approved regimens are administered as fixed doses. It is recommended that heparin be withheld until the thrombolytic infusion is completed. The aPTT is then determined, and heparin is initiated without a loading dose if this value is less than twice the upper limit of normal. If the aPTT exceeds this value, the test is repeated every 4 hours until it is safe to proceed with heparin. The method of delivery of thrombolytic agents has also been investigated. Although a number of investigators have used standard- or low-dose intrapulmonary arterial thrombolytic infusions to deliver a high concentration of drug in close proximity to the clot (143,144), intravenous therapy appears adequate in most cases (145). More direct techniques such as catheter-directed administration of intraembolic thrombolytic therapy are discussed below.

Streptokinase: 250,000 U i.v. (loading dose over 30 min), then 100,000 U/h for 24 h[a]
Urokinase: 2,000 U/lb i.v. (loading dose over 10 min), then 2,000 U/lb/h for 12 to 24 h[b]
Tissue-type plasminogen activator: 100 mg i.v. over 2 h

[a]Streptokinase administered over 24–72 h at this loading dose and rate has also been approved for use in patients with extensive deep venous thrombosis.
[b]Urokinase is not currently available in the United States.

TABLE 28.5 THROMBOLYTIC THERAPY FOR ACUTE PULMONARY EMBOLISM: APPROVED REGIMENS

The use of thrombolytic therapy for DVT is more controversial. A comprehensive review of the literature suggests that use of streptokinase may be associated with a reduction in postphlebitic syndrome when used for acute DVT, although bleeding is increased with thrombolytic therapy (146). Future studies may clarify the role of thrombolytic therapy for DVT. It is reasonable to consider systemic thrombolytic therapy in patients with proximal occlusive DVT associated with significant swelling and symptoms when there are no absolute or relative contraindications. Although agents other than streptokinase have been studied, there are no firm dosing recommendations for them. Catheter-directed techniques have been used for the treatment of acute DVT (see Pulmonary Embolectomy and Catheter-Extraction Techniques).

Hemorrhage is the primary adverse effect associated with thrombolytic therapy and generally occurs at sites of invasive procedures such as pulmonary arteriography or arterial line placement (147). Thus, when thrombolytic therapy is administered, invasive procedures should be minimized. The most devastating complication associated with this form of treatment is the development of intracranial hemorrhage (148). Clinical trials have suggested that this occurs in significantly less than 1% of patients. Contraindications to systemic thrombolytic therapy in VTE are listed in Table 28.6. Bleeding related to thrombolytic therapy requires immediate diagnosis and management. Bleeding from vascular puncture sites should be addressed with manual compression followed by a pressure dressing. Intracranial bleeding requires immediate discontinuation of thrombolytics or heparin, and emergent neurologic and neurosurgical consultation should be obtained. A noncontrasted brain CT scan should be performed. Retroperitoneal hemorrhage may result from a vascular puncture above the inguinal ligament and may be life-threatening. Patients with severe or refractory bleeding should be transfused with 10 U of cryoprecipitate and 2 U of fresh frozen plasma, and heparin can be reversed with protamine.

Absolute
Intracranial tumor or hemorrhagic stroke
Recent head trauma or cranial surgery
Active or recent internal bleeding
Relative
Thrombocytopenia or coagulopathy
Uncontrolled severe hypertension
Cardiopulmonary resuscitation
Surgery or biopsy within the previous 10 days

TABLE 28.6 THROMBOLYTIC THERAPY FOR ACUTE PULMONARY EMBOLISM: CONTRAINDICATIONS

Brachial artery hematoma. Hematoma complication after brachial artery catheterization and urokinase administration.

Pulmonary Embolectomy and Catheter-Extraction Techniques

Pulmonary embolectomy may be performed in the setting of acute massive PE. Although many patients die from PE before surgical embolectomy would be feasible, some deteriorate hours after the initial episode, suggesting that surgery may occasionally be appropriate. In one series of 71 embolectomies performed with cardiopulmonary bypass, hospital mortality was 29% (149). The mortality in those patients who had not sustained a cardiac arrest preoperatively was only 11%, however. Transvenous embolectomy via a suction-catheter device has been used by some (150,151) but has not received widespread acceptance. Timsit and associates (151) treated 18 patients over a 7-year period with massive PE using this technique. Clot extraction was successful in 11 of the patients. Thirteen survived their hospital stay, and five died.

Although the intravenous route has been the primary method of delivery, local thrombolytic therapy has been used in massive PE and may preclude the need for surgical embolectomy. Intrapulmonary arterial delivery of thrombolytic agents by bolus or prolonged infusion with or without concomitant heparin has been used for massive PE (see Thrombolytic Therapy) (152,153). These studies have generally been small and uncontrolled. Although intrapulmonary arterial delivery of thrombolytic agents appears to offer no advantage over the intravenous route (145), *intraembolic* thrombolytic infusions may offer advantages over merely infusing the agents into the pulmonary artery. Such techniques have been applied in both animal models of PE and in patients, with enhanced thrombolysis (152,153). Less than conventional doses of t-PA or urokinase are delivered via a catheter imbedded directly within massive emboli over 10 to 20 minutes (153). Combining thrombolytic therapy via direct delivery (at low doses) with the possible mechanical benefits of direct intraembolic infusion may have promise and could prove advantageous over the intravenous route, particularly in the setting of contraindications to thrombolytic therapy. Larger randomized studies are needed to demonstrate the efficacy, potential advantages, and safety of such techniques. The implementation of these techniques and the catheter-directed administration of intraembolic thrombolytic therapy described above depend on the experience of the medical team involved. Finally, catheter-directed techniques have been successfully used in the setting of acute iliofemoral DVT using urokinase doses ranging from 1,400,000 U to 16,000,000 U delivered over an average of 30 hours (154). Further investigation in this area is under way.

Hemodynamic Management of Massive Pulmonary Embolism

Massive PE should always be suspected in the setting of the sudden onset of hypotension or extreme hypoxemia. The presence of electromechanical dissociation or

sudden cardiac arrest should always make massive PE a consideration. If the patient is stable enough, V/Q scanning should be performed when possible. Although PE should be proven with either a high-probability V/Q scan (helical CT or MRI may also offer proof) and when necessary pulmonary arteriography, echocardiography may support the diagnosis of massive PE and may also suggest the need for aggressive intervention, including thrombolytic therapy (155). Once massive PE associated with hypotension and/or severe hypoxemia is suspected, supportive treatment is immediately initiated. Intravenous saline should be infused rapidly but cautiously because right ventricular function is often markedly compromised. Dopamine or norepinephrine appear to be the favored choices of vasoactive therapy in massive PE and should be administered if the blood pressure is not rapidly restored (155). General guidelines for the approach to massive PE are offered in Table 28.7. Because death in this setting results from right ventricular failure, dobutamine has been recommended by some as a means by which to augment right ventricular output (156,157). A vasopressor such as norepinephrine combined with dobutamine might offer optimal results, and further exploration of such combined therapy would prove enlightening. Oxygen therapy is administered, and thrombolytic therapy is considered as described above. Intubation and institution of mechanical ventilation are instituted as needed to support respiratory failure.

Oxygen therapy
Intubation and mechanical ventilation
Intravenous heparin
Fluid administration
Norepinephrine or dopamine
Thrombolytic therapy
Catheter or suction cup embolectomy
Surgical embolectomy
Vena caval filter placement

TABLE 28.7 ACUTE MASSIVE PULMONARY EMBOLISM: THERAPEUTIC CONSIDERATIONS

CHRONIC THROMBOEMBOLISM

Although the vast majority of acute PE cases resolves with treatment, occasionally a substantial residual thromboembolic burden remains (158,159). In this setting, the clot becomes organized and adherent and is not amenable to thrombolysis. If the obstruction becomes extensive, pulmonary hypertension develops. This syndrome most commonly occurs in patients 40 to 70 years of age but can occur at any age. At least 50% of patients who develop chronic thromboembolic pulmonary hypertension have no documented history of DVT or PE. This feature greatly impedes the diagnosis. Most patients have no identifiable coagulopathy. Fatigue and dyspnea with exertion are the most common complaints. The nonspecific nature of these findings may substantially delay the correct diagnosis. The physical examination generally reveals a right ventricular heave, a loud pulmonary component of the second heart sound, and tricuspid regurgitation consistent with pulmonary hypertension. In more severe cases, a right ventricular third heart sound may be present. In 20% of patients, one or more murmurs may be auscultated over the lung fields.

Once the diagnosis is suspected, the diagnostic evaluation is generally revealing. The chest radiograph usually reveals right ventricular enlargement and enlarged main pulmonary arteries. Electrocardiographic changes are consistent with pulmonary hypertension. Arterial blood gases generally reveal hypoxemia with a widened A-a difference, although some patients may only demonstrate exercise-induced hypoxemia. Echocardiography documents pulmonary hypertension and enlargement of the right ventricle. It is prudent to perform chest CT scanning, which may reveal other rare causes of pulmonary hypertension such as mediastinal fibrosis; it may, in fact, demonstrate evidence of chronic thrombi. Helical CT scanning may be particularly useful in this regard. The V/Q scan is nearly always high probability for PE but occasionally is less impressive. Right heart catheterization and pulmonary arteriography are performed, both to establish the diagnosis with certainty and to determine operability. Pulmonary angioscopy frequently has proven complementary to arteriography in assessing these patients (160).

Although anticoagulation should be instituted and IVC filters are recommended in patients with chronic thromboembolic pulmonary hypertension, the only means by which to alleviate symptoms and impact on survival is with surgery. The group from the University of California at San Diego has had tremendous experience with evaluation and surgical therapy of these patients. Pulmonary thromboendarterectomy is performed via median sternotomy on cardiopulmonary bypass, and the overall mortality, which has continued to improve, is now less than 5%. Lung transplantation can be performed in patients in whom thrombi are too distal to extract.

CONTROVERSIES AND PERSONAL PERSPECTIVES

VTE is difficult to study in large randomized trials because of the varying presentations of acute PE and DVT, the difficulty with diagnosis, and the many different settings and specialties involved. A number of questions remain unanswered. Cost-effective approaches to the diagnosis and therapy of DVT and PE remain unclear. In view of the numerous controversies currently facing us, several groups such as the American College of Chest Physicians and the American Thoracic Society have taken steps to form consensus guidelines for areas in which substantial data exist and opinion and position statements to address issues and plan research strategies for areas that remain less clear (111,161,162).

Diagnostic Approach to Venous Thromboembolism

There are no firm consensus guidelines for the diagnostic approach to VTE. Critical pathways have been constructed by experts in the field for the diagnostic approach to DVT, for example, but these approaches suffer from institutional variability, availability of certain diagnostic studies, and lack of incorporation of newer technologies such as MRI. The American Thoracic Society has recently formulated consensus guidelines for the diagnostic approach to VTE (162). These include algorithms and the role of new technologies and account for institution-specific differences in approach.

The International Cooperative Pulmonary Embolism Registry represents the largest prospective PE registry ever undertaken (163). This effort has helped to answer a number of clinical questions and contribute to future strategies in clinical investigation. It has already enhanced international communication, which should increase the number and quality of international randomized clinical trials and help to unify the approach to VTE.

The roles of newer methods to diagnose DVT and PE such as MRI and helical CT scanning need to be clarified, and recommendations may change as the technology continues to improve. How often are venography and pulmonary arteriography still necessary? When should MRI be used in addition to, or instead of, ultrasonography? Can all patients with a negative helical CT be safely followed without therapy?

Screening and Prophylaxis

Determining a practical means by which to identify patients with recently characterized thrombophilias such as activated protein C resistance and determining their significance will facilitate the implementation of more meaningful prophylaxis and treatment protocols. Who should be screened for activated protein C resistance? Do patients with this disorder require lifelong prophylaxis? When should combined mechanical and pharmacologic prophylaxis be applied? What is the appropriate duration of prophylaxis in different clinical settings? What *are* the differences between the different LMWH compounds? Although the American College of Chest Physicians guidelines are useful, more data are needed to enhance their usefulness. *At present, recommendations in specific settings must be made for specific agents that have been studied in that setting*.

Therapeutic Approaches

A number of anticoagulation issues require clarification. The duration of therapy in different subsets of patients with VTE needs to be determined. Should patients with PE and without residual DVT be treated for a shorter period of time than patients with extensive DVT? Is it beneficial to use MRI to document the extent of DVT in every patient? Is it appropriate to repeat lower extremity studies in patients with DVT to help determine treatment duration? We are treating increasing numbers of outpatients, and this is simplified with the LMWH preparations. Which agents (and doses) are appropriate? Where do the direct thrombin inhibitors, selective factor X_a inhibitors, and TFPI fit in?

What are appropriate guidelines for thrombolytic therapy in DVT and PE? Is one thrombolytic agent or regimen superior to others? When should acute pulmonary embolectomy be performed? Although some individuals believe that thrombolytic therapy should be reserved for patients with “hemodynamic compromise,” the latter term is not clearly defined. I believe that patients with PE, extreme hypotension, and evidence of end-organ dysfunction, or those with extreme hypoxemia refractory to

maximal oxygen therapy, should receive intravenous thrombolytic therapy even in the presence of certain “absolute contraindications” such as occult blood in the stool if other methods such as surgical embolectomy or catheter-based therapy are not immediately accessible. Even severe gastrointestinal bleeding can be controlled more easily than PE associated with shock. It is difficult to make blanket guidelines, and presence at the bedside may continue to be a prerequisite for rational decisions in such settings. Guidelines need to be investigated and clarified. The precise roles of systemic and local thrombolytic therapy and catheter-directed techniques, including indications, doses, duration of therapy, and delivery methods, all need clarification. The number of meaningful clinical trials planned and under way suggest that we may ultimately be able to resolve many of these controversies.

THE FUTURE

The future will be productive with regard to characterization of genetic risk factors, diagnosis, therapy, and prevention. The discovery of additional thrombophilic disorders appears inevitable, as does the development of standardized methods to screen patients for these. This, in turn, will undoubtedly affect current prophylaxis and treatment guidelines. Efforts currently under way include the PIOPED II, a prospective clinical trial evaluating the utility of helical CT scanning for suspected PE. Analysis of such data will assist in the delineation of appropriate algorithms for diagnosis. Nuclear imaging technology may improve, but the imaging of actual thromboses and emboli with MRI and CT appears to be much more promising. Our understanding of the utility of these techniques and the technology itself continue to evolve. The use of MRI, with its potential ability to distinguish acute from chronic thrombosis, may not only lead to more appropriate initiation of therapy but also may aid in the determination of the length and aggressiveness of therapy. CT scanning will become faster and undoubtedly more accurate. The latter techniques will likely replace arteriography and venography altogether. Hematologic studies such as the D-dimer may evolve into more useful techniques. The evolution of diagnostic technology will affect therapy. The ability to diagnose the presence and extent of acute DVT will permit refinement of treatment stratification. How issues such as extent of DVT, number of persisting risk factors, and specific therapeutic modality affect treatment duration should become more clearly defined. We are treating larger numbers of outpatients and using LMWHs. Newer agents such as direct thrombin inhibitors, selective factor X_a inhibitors, and TFPI, as well as more fibrin-specific thrombolytic agents, should have more clearly defined therapeutic roles. It is likely that we have an easier drug to use than warfarin. The means by which we monitor anticoagulation will improve. The roles of systemic and local thrombolytics, including indications, doses, duration of therapy, and delivery methods, need clarification. Guidelines for diagnostic and therapeutic approaches to VTE will become substantially more refined. It is very important to note that preventive efforts are of paramount importance. We are making strides in characterizing prolonged air travel as a risk factor for VTE. Paul Egermayer, a physician and VTE researcher, passed away in May 2001 in the midst of a very productive research career. This insightful and energetic individual wisely emphasized the importance of VTE prevention by stating that “the real problem is not the 10% of patients who survive long enough to receive treatment, but the 90% in the first hour after the event. For both groups, more systematic prophylaxis is clearly the way forward. Treatment is merely the ambulance waiting at the bottom of the cliff” (164).

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29

HYPERTROPHIC CARDIOMYOPATHY

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PERRY M. ELLIOTT

“ Indicates text or graphics that appear only in the electronic versions of this text.”

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OVERVIEW

Hypertrophic cardiomyopathy (HCM) is caused by mutations in genes that encode cardiac sarcomeric proteins. The disease is characterized by myocardial hypertrophy, most commonly affecting the interventricular septum, and disorganization (disarray) of cardiac myocytes and myofibrils. Myocardial fibrosis is common and may be associated with small-vessel disease. Twenty-five percent of patients have a dynamic left ventricular outflow tract gradient caused by the combined effects of rapid ventricular ejection, a narrowed outflow tract, and systolic anterior motion (SAM) of the mitral valve.

The characteristic pathology of HCM contributes to a spectrum of functional abnormalities that includes myocardial ischemia, diastolic dysfunction, ventricular and atrial arrhythmias, and congestive cardiac failure. Patients can present at any age with chest pain, dyspnea, palpitations, and syncope. The most important complication of the disease is sudden death, which occurs throughout life with an annual incidence (in referral populations) of 2% to 4% in children and adolescents and approximately 1% in adults. Other complications include thromboembolism, infective endocarditis, and conduction system disease. Clinical features associated with an increased risk of sudden death include nonsustained ventricular tachycardia (NSVT), syncope, a family history of sudden death, an abnormal exercise blood pressure response, and severe left ventricular hypertrophy.

The principal aims of management are the alleviation of symptoms and the prevention of sudden death. In patients with substantial left ventricular outflow tract obstruction, interventions that reduce the magnitude of the outflow tract gradient (e.g., disopyramide, beta-blockade, alcohol ablation of the interventricular septum, dual-chamber pacing, and surgery) often result in significant symptomatic improvement. Therapeutic options in patients without left ventricular outflow tract obstruction are more limited, but chest pain and, to a lesser extent, dyspnea may be alleviated by pharmacologic therapy. Clinical risk-stratification can identify the risk of sudden death in most adults and many adolescents, allowing effective prophylactic treatment with an implantable cardioverter-defibrillator (ICD) or reassurance where appropriate.

HISTORICAL PERSPECTIVE

HCM is currently defined by the presence of unexplained myocardial hypertrophy (1). Patients fulfilling this criterion have been described for more than 100 years (2,3,4,5,6,7,8,9,10 and 11), but it was not until the publication of Sir Russell Brock’s paper on “functional obstruction of the left ventricle” in 1957 (12) and Donald Teare’s description of asymmetric myocardial hypertrophy in 1958 (13) that HCM was established as a distinct clinical and pathologic entity. Since that time, clinical diagnostic criteria have evolved in parallel with the technology available to cardiologists. In the 1960s (14,15,16,17,18,19,20,21 and 22), reliance on stethoscope and cardiac catheterization meant that left ventricular outflow tract obstruction was considered to be the diagnostic hallmark of HCM. In the 1970s, the widespread use of M-mode echocardiography (23,24,25,26 and 27) emphasized the asymmetric nature of left ventricular hypertrophy and established asymmetric septal hypertrophy (ASH) as the sine qua non of the disease. However, with the advent of two-dimensional echocardiographic imaging, it became clear that the spectrum of ventricular involvement is much more heterogeneous and that virtually any pattern of unexplained myocardial hypertrophy is consistent with the diagnosis of HCM (28,29 and 30).

After reports described families in which a high incidence of premature sudden death, left ventricular hypertrophy, and subaortic stenosis was seen (10,11), early clinical studies suggested that HCM was inherited in 30% to 50% of patients (31). Subsequent M-mode echocardiographic studies reported higher figures but may have overestimated the prevalence of ASH (32,33). Prospective clinical genetic studies using two-dimensional echocardiography suggested that 50% to 60% of cases were inherited in an autosomal dominant fashion (34,35), but with more detailed pedigree analysis, this figure increased to more than 80%. The identification of numerous sarcomeric protein mutations in individuals with HCM (36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67 and 68) in the last decade has confirmed that sporadic disease is relatively uncommon. Genetic testing has also highlighted the phenomena of incomplete penetrance and age-related disease expression, and as a result diagnostic criteria are once again being revised (69).

ANATOMY

Macroscopic

HCM is defined by the presence of unexplained myocardial hypertrophy (1). In Teare’s original series (13), myocardial hypertrophy was asymmetric, involving the interventricular septum more than the posterior or free wall of the left ventricle (Fig. 29.1). Subsequent studies have shown that, although asymmetric septal hypertrophy is present in approximately two-thirds of patients (70,71), virtually any pattern can occur. Hypertrophy confined to the left ventricular apex is uncommon, except possibly in Japanese patients (72). Isolated right ventricular hypertrophy is unreported. Macroscopically, the cut surface of involved myocardium has a

characteristic appearance reminiscent of a uterine fibroid, with abnormally short and broad muscle fibers running in different directions. An additional feature occasionally seen during post mortem examination is a patch of subendocardial thickening on the septum caused by repeated contact with the anterior leaflet of the mitral valve.

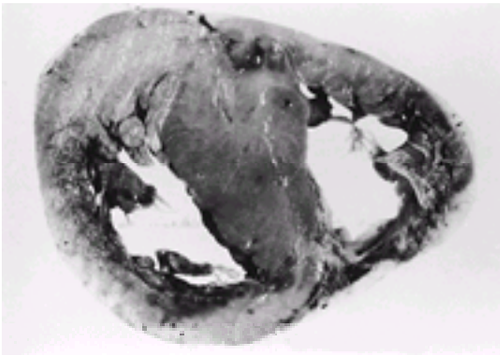


FIGURE 29.1 Myocardial section demonstrating the classical appearance of severe asymmetric septal hypertrophy in a patient with hypertrophic cardiomyopathy. (From Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958;20:1–8, with permission.)

Microscopic

The cardinal microscopic feature of HCM is myocyte disarray (70,71,73,74,75 and 76) (Fig. 29.2). This is recognized by a loss of the normal parallel arrangement of myocytes, with cells forming circles around foci of connective tissue. Individual myocytes may show marked variation in diameter and nuclear size and have abnormal intercellular connections. Myofibrillar architecture within cells is also disrupted—so-called myofibrillar disarray. Myocyte disarray is described in congenital heart disease, hypertension, and aortic stenosis, but in HCM it is typically more extensive, occupying 20% or more of at least one ventricular tissue block and more than 5% of total myocardium at post mortem examination. Disarray is often associated with myocardial fibrosis, ranging from extensive scarring in the interventricular septum, free wall of the left ventricle, and occasionally the left ventricular papillary muscles (77) to a more diffuse interstitial pattern (78). The demonstration of abnormal small intramural arteries (external diameter less than 1,500 mm) within fibrotic areas and in patients with ventricular dilatation and reduced systolic function (79,80) (Fig. 29.3) has suggested that contiguous myocardial scarring may be caused by myocardial ischemia. However, more recent data have shown that small-vessel disease may be just as widespread in patients without extensive fibrosis and may occur in the absence of myocardial hypertrophy (81).

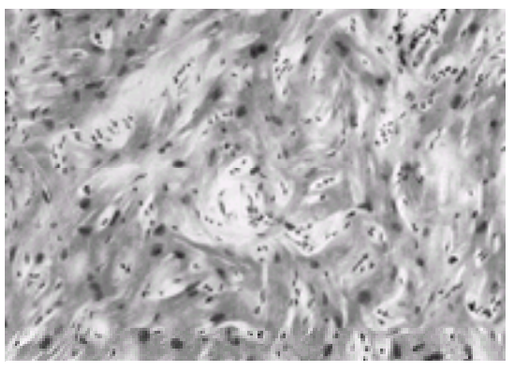


FIGURE 29.2 Myocyte disarray. Myocytes cross at right angles and display abnormal intercellular connections. Myocyte nuclei are large and of different sizes. Foci of fibrosis containing spindle-shaped connective-tissue cells are present. Evidence of marked disorganization of the intracellular myofibrillar structure is also seen (hematoxylin-eosin stain). (Courtesy of M. Davies, St. George's Hospital Medical School, London.)

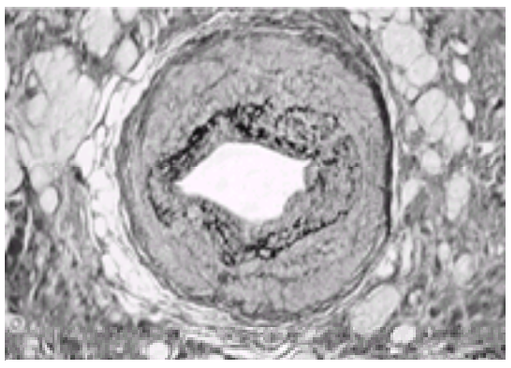


FIGURE 29.3 Section through a small artery demonstrating smooth-muscle disorganization in the intima and media, resulting in an abnormally high medial width–to-lumen ratio. In the adjacent myocardium, extensive replacement of myocytes by fibrous tissue can be seen (Elastica van Gieson stain). (Courtesy of M. Davies, St. George's Hospital Medical School, London.)

PATHOPHYSIOLOGY

Molecular Genetics

HCM is usually familial, with autosomal dominant inheritance. Early reports of autosomal recessive patterns of transmission (31) have not been confirmed. A cardiac phenotype similar to that seen in HCM is described in association with a number of rare genetically determined disorders, including Friedreich's ataxia (chromosome 9) (82,83), neurofibromatosis (chromosome 17) (84), hereditary spherocytosis (chromosome 14) (85), aniridia with catalase deficiency (chromosome 11) (86), and Noonan's syndrome (chromosome 12) (87,88 and 89). Because the clinical phenotype of these disorders differs considerably from that seen in most patients with familial HCM, and none of the genes associated with these disorders encode known cardiac proteins, the identification of candidate genes in familial HCM has until quite recently relied on linkage analysis and a positional candidate gene approach. The first disease locus to be identified was situated in the chromosome 14q1 region in a large French Canadian family (36). The genes encoding the two cardiac myosin heavy chains (a and b) are arranged in tandem on chromosome 14 band q11.2-13, and further analysis involving this Canadian family revealed that each affected member had a missense mutation in exon 13 of the b-myosin heavy-chain gene (38). Since this discovery, numerous mutations in seven other genes that encode thick and thin filament sarcomeric proteins have been reported (Fig. 29.4): cardiac troponin T (chromosome 1), cardiac troponin I (chromosome 19), a-tropomyosin (chromosome 15), cardiac myosin-binding protein C (chromosome 11), the essential and regulatory myosin light chains (chromosomes 3 and 12, respectively), and cardiac actin (chromosome 15) (36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66 and 67). In addition, a locus on chromosome 7 has been identified in a large Irish family with HCM and Wolff-Parkinson-White syndrome (90,91), and a further unconfirmed mutation in the gene encoding another sarcomeric protein, Titin (chromosome 2) (68), has been reported.

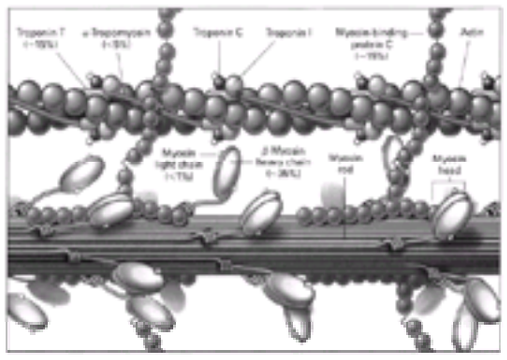


FIGURE 29.4 Structure of the human sarcomere. Cardiac contraction occurs as a consequence of actin-myosin interaction. This is initiated by the binding of calcium to the troponin complex (C, I, and T) and a-tropomyosin. Actin then stimulates adenosinetriphosphatase activity in the globular myosin head, resulting in the generation of contractile force. Cardiac myosin-binding protein C binds to myosin and modulates contraction. The estimated frequency of sarcomeric protein gene mutations that cause hypertrophic cardiomyopathy is shown. (From Spirito P, Seidman CE, McKenna WJ, et al. The management of hypertrophic cardiomyopathy. *N Engl J Med* 1997;336:775–785, with permission.)

Family studies have shown that disease-causing mutations are associated with considerable variation in disease penetrance and clinical expression. This is not surprising, given the extent of genetic heterogeneity in HCM and the different structural, regulatory, enzymatic, and force-generating properties of individual sarcomeric proteins. Preliminary data suggest that mutations in particular genes tend to be associated with a common phenotype—for example, patients with troponin-T gene mutations may experience sudden death with mild left ventricular hypertrophy, whereas most patients with b-myosin heavy-chain mutations that cause sudden death have at least moderate hypertrophy (92,93,94,95 and 96). However, considerable heterogeneity exists in the expression of different mutations within the same gene, and also between patients with identical mutations.

Allelic heterogeneity may be explained by the effect of a given mutation on the structure and function of the complete peptide. For example, b-myosin consists of a globular head, an a-helical rod and a hinge region. The globular head contains a catalytic adenosine triphosphatase-binding site, an actin-binding site, and interaction sites for regulatory and essential light chains in the head-rod region (47,97). Most mutations in the b-myosin gene are missense DNA nucleotide substitutions that change a single amino acid in the polypeptide sequence. The majority of disease-causing b-myosin heavy-chain mutations are found in one of four locations: the actin-binding site, the nucleotide-binding pocket, a region adjacent to the binding site for two reactive thiols in the hinge region, and the a-helix, close to the essential light-chain interaction site (47). Therefore, depending on the position of the mutation, changes might be expected in adenosine triphosphatase activity, actin-myosin interaction, and protein conformation during contraction.

The functional consequences of HCM mutations have been studied using isolated cardiac and skeletal muscle preparations, baculovirus-based systems, and transgenic animal models (97,98 and 99). Most data suggest that the majority of mutations have a dominant negative effect on sarcomere function, that is, the mutant protein may be sufficiently stable to be incorporated in the sarcomere, but its interaction with the normal wild-type protein may disrupt normal sarcomeric assembly and/or function. Studies of b-myosin heavy-chain mutations suggest that they reduce force generation and thus may cause compensatory hypertrophy—the so-called hypocontractile hypothesis. Mutations in the a-tropomyosin and possibly the essential and regulatory myosin light-chain genes, however, are reported to cause an increase in calcium sensitivity and hypercontractility. The effect of mutations in troponin T on contractility is more complex, but the overall effect seems to be a reduction in contractile performance and diastolic abnormalities. Recent work on a troponin T truncation mutation has shown that the functional effects of the mutation may be substantially altered by the ratio of wild-type to mutant protein expressed within the myocardium (100).

Variable expression of identical mutations indicates that other genetic and possibly environmental factors are important in disease expression. The effect of age is perhaps the best-characterized influence; most patients develop electrocardiographic (ECG) and echocardiographic manifestations of the disease after puberty and before the age of 30 years (101). Patients with mutations in the cardiac myosin-binding protein C gene may be an exception to this rule; in them, the prevalence of hypertrophy continues to rise beyond the third decade into old age (63,102). A single case of late disease expression has also been described in a patient with a troponin-T gene mutation (103).

Although no clinical study has demonstrated any convincing evidence for an effect of sex on disease expression, most large series show a predominance of male subjects. In one animal model (99), male mice with an a-myosin heavy-chain mutation developed more severe disease at an earlier age than their female counterparts. The relevance of this to human disease is unknown. Potential genetic modifiers of disease expression include renin-angiotensin-aldosterone system gene polymorphism (104,105,106,107,108,109 and 110) and the possibility of homozygosity and compound heterozygotes, both of which have now been described in HCM families (111,112 and 113).

Catecholamines

A role for excess catecholamine activity in HCM pathophysiology was first suggested by histologic studies describing the presence of increased myocardial sympathetic nerve fibers and norepinephrine content (73). Although these initial observations were subsequently found to be erroneous (114) and most studies in humans have failed to show convincing evidence for increased myocardial catecholamine concentration (115), the adrenergic hypothesis has persisted. Several studies have demonstrated evidence for decreased neuronal uptake and metabolism of norepinephrine, as well as reduced myocardial beta-adrenoceptor density (116,117 and 118). These abnormalities may simply reflect a loss of sympathetic nerve endings in areas of fibrosis or possible secondary disturbances in myocardial metabolism.

Myocardial Ischemia

Several studies have shown that patients with HCM have reduced coronary flow reserve and metabolic evidence for myocardial ischemia during pacing and pharmacologic stress (119,120,121,122,123,124 and 125). It is likely that myocardial ischemia is the cause of chest pain and dyspnea in many individuals, and limited data are available to suggest that myocardial ischemia may be a trigger for fatal ventricular arrhythmia (126,127). However, the clinical evaluation of patients with chest pain remains problematic. For example, whereas ST segment depression occurs in up to 40% of patients during exercise (118), lactate production during atrial pacing is seen in more than one-half of those with negative results of exercise tests. ST segment depression also occurs during ambulatory ECG monitoring in 25% of symptomatic young patients (128), but its metabolic significance in unknown. A number of pathophysiologic mechanisms have been suggested as causes of myocardial ischemia in patients with HCM (Table 29.1), but the predominant mechanism in individual patients is usually impossible to determine.

Increased myocardial oxygen demand
Myocardial hypertrophy
Diastolic dysfunction
Myocyte disarray
Left ventricular outflow obstruction
Arrhythmia
Reduced myocardial perfusion
Small-vessel disease
Abnormal vascular responses
Myocardial bridges
Increased coronary vascular resistance

TABLE 29.1 POTENTIAL MECHANISMS OF MYOCARDIAL ISCHEMIA IN HYPERTROPHIC CARDIOMYOPATHY

Diastolic Dysfunction

Several of the characteristic pathophysiologic features of HCM impair diastolic function, specifically, myocyte hypertrophy, myocyte and myofibrillar disarray, abnormal

intracellular calcium metabolism, myocardial fibrosis, abnormal ventricular geometry, and myocardial ischemia (129,130,131,132,133,134,135,136,137,138,139 and 140). In a minority of patients, a restrictive hemodynamic picture may predominate, with marked elevation of filling pressures, biatrial dilatation, and predominantly right-sided signs, often in the absence of substantial myocardial hypertrophy (137,138). In the majority of cases, a mixed picture with slow relaxation and elevated end diastolic pressures is observed. Invasive hemodynamic studies have demonstrated a flat pressure-volume relationship with a response to off-loading similar to that seen in patients with constrictive pericarditis, suggesting the presence of increased pericardial or possibly myocardial constraint (140).

CLINICAL PROFILE

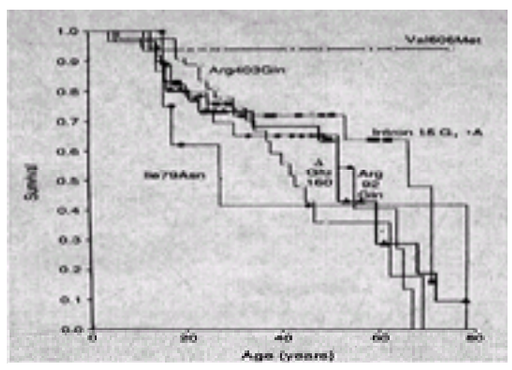
Epidemiology

Whereas HCM occurs in all racial groups, most of the published literature comes from populations in North America, Europe, and Japan. Of five studies that have examined the prevalence of HCM (141,142,143,144 and 145), all but one suggest a prevalence of 0.2% to 0.5% in the general population. The exception (144) was a disease surveillance study that examined the prevalence of HCM in a population of patients already suspected of having cardiac disease on clinical grounds.

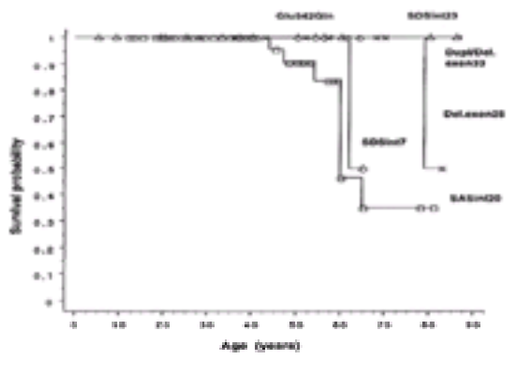
Natural History

Ventricular hypertrophy usually develops during periods of rapid somatic growth, sometimes during the first year of life, but more typically during adolescence (101). De novo myocardial hypertrophy in early middle age is not reported, but the diagnosis of idiopathic or inappropriate left ventricular hypertrophy in patients older than 60 years is well described (146,147,148,149 and 150). The pattern of disease in this age group is said to differ from that observed in younger patients with HCM, in that symptoms occur late in life, the prognosis for most patients is relatively good, and many have mild hypertension. A number of morphologic differences are also described, including restricted anterior excursion of the mitral valve, mitral annular calcification, and a crescent-shaped left ventricular cavity. Whether the majority of patients with this so-called elderly phenotype has a separate disease entity reflecting a polygenic response to hypertrophic stimuli remains uncertain, but recently gathered data from families with mutations in the cardiac myosin-binding protein C gene have shown that a phenotype identical to that of young patients can be seen in older patients (63,102).

In most patients with HCM, progression of symptoms is slow and age related and associated with a gradual deterioration in left ventricular function. This course may end at any point in sudden death. Early data from referral institutions reported annual mortality rates of approximately 2% per annum in adults and 2% to 4% during childhood and adolescence (151,152 and 153). More recent data from regional and tertiary adult populations (154,155,156,157,158 and 159) suggest a lower figure of approximately 1% per annum. Sudden death in the first decade of life is thought to be relatively uncommon, although only limited data about this age group are available (160). In fewer than 10% of patients, rapid symptomatic deterioration may occur in association with progressive myocardial wall thinning, a reduction in systolic performance, and an increase in left ventricular end systolic dimensions (161). Survival in patients with late-onset disease has been thought to be relatively benign in comparison with younger patients, but in some families with myosin-binding protein C mutations, the rate of death or adverse cardiovascular events can be similar to that of the most severe troponin-T or b-myosin heavy-chain mutations once disease is expressed (*e*Fig. 29.4.1 and *e*Fig. 29.4.2) (63,92,93,94,95 and 96,102).



***e*FIGURE 29.4.1** Kaplan-Meier survival curves in patients with hypertrophic cardiomyopathy caused by b-myosin heavy-chain and cardiac troponin-T mutations. The survival of patients with a “benign” b-myosin heavy-chain mutation Val606Met is much longer than patients with either troponin-T mutations (Intron 15 G1-A, Ile79Asn, D Glu160 and Arg92Gln) or a “malignant” b-myosin heavy-chain mutation Arg403Gln. (From Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* 1995;332:1058–1064.)



***e*FIGURE 29.4.2** Kaplan-Meier survival curves in patients with hypertrophic cardiomyopathy associated with six different mutations in the MYBPC3 gene. Del., deletion; Dupl, duplication. (From Charron P, Dubourg O, Desnos M, et al. Clinical features and prognostic implications of familial hypertrophic cardiomyopathy related to the cardiac myosin-binding protein C gene. *Circulation* 1998;97:2230–2236, with permission.)

Symptoms

Patients may present at any age with dyspnea, chest pain, unexplained syncope, or arrhythmia, or the disease may be identified after sudden death (13,14,20,28,151,152,153,154,155,156,157,158,159,160,161 and 162). Many patients have no or only minor symptoms, and in children and adolescents, the diagnosis is often made during family screening. Exertional chest pain occurs in up to 30% of adults, and many complain of atypical pain that is prolonged and occurs at rest and after meals (163). Dyspnea is common in adult patients, probably as a consequence of elevated pulmonary venous pressure resulting from impaired ventricular relaxation and filling. Patients less commonly present with paroxysmal nocturnal dyspnea and orthopnea, sometimes in the presence of apparently mild disease. The mechanism is uncertain, but myocardial ischemia or arrhythmia may be responsible.

Approximately 15% to 25% of patients experience syncope, and 20% complain of presyncope. In some, these symptoms are caused by paroxysmal arrhythmia, conduction system disease, or abnormal vascular responses during exercise, but in most cases, no underlying cause is identified even after extensive investigation. Recurrent unexplained syncope is associated with a higher incidence of sudden death when it occurs during adolescence (151,152 and 153,162). Palpitations are a frequent complaint. Symptomatic cardiac contractions and ventricular ectopy are not uncommon, but most sustained palpitation is caused by supraventricular arrhythmia (151,152).

Examination

In the majority of patients with HCM, physical examination is unremarkable. Patients may have a rapid upstroke to the arterial pulse, occasionally followed by a secondary peak, reflecting hyperdynamic left ventricular contraction (13,14 and 15,20). The left ventricular impulse may be forceful, and a palpable left-atrial beat may be present. In approximately one-third of patients, a prominent ‘a’ wave is seen in the jugular venous pressure wave caused by reduced right ventricular compliance. On auscultation, the first and second heart sounds are usually normal, but a fourth heart sound, reflecting atrial systole into a poorly compliant left ventricle, may be heard in patients who are in sinus rhythm. Occasionally, reverse splitting of the second heart sound may be heard in patients who have severe left ventricular outflow tract obstruction. In one-fourth of patients, a systolic murmur caused by left ventricular outflow obstruction can be heard at the left sternal edge, radiating to the aortic

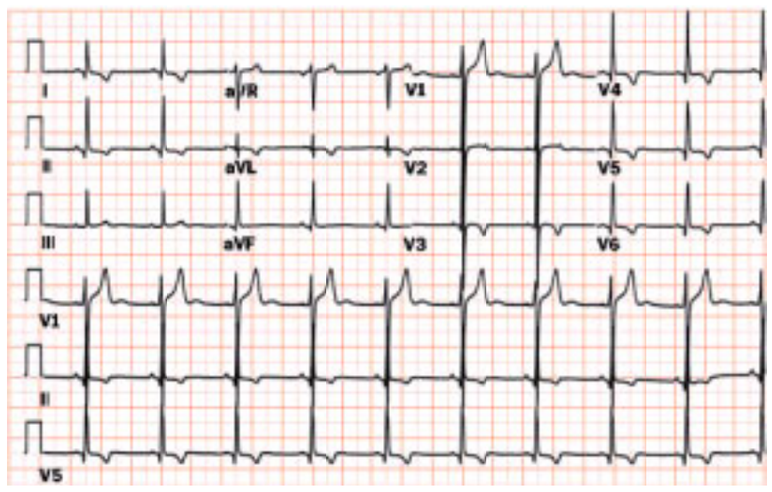
and mitral areas, but not into the neck or axilla. A characteristic feature of the murmur is its dependence on ventricular volume. Physiologic and pharmacologic maneuvers that decrease afterload or venous return (e.g., standing, Valsalva's maneuver, administration of amyl nitrate) increase the intensity of the murmur, whereas interventions that increase afterload and venous return (e.g., squatting and administration of phenylephrine) reduce it. The majority of patients with significant left ventricular outflow gradients also has mitral regurgitation. This can be difficult to distinguish clinically from the outflow gradient (13,14), but its presence is suggested by the length of the murmur (starting 30 to 40 ms before the onset of the outflow gradient), radiation to the axilla, and, in patients with severe regurgitation, a mid-diastolic rumble. Rarely, a systolic murmur may be heard in the pulmonary area as a consequence of right ventricular outflow obstruction.

HEART SOUNDS

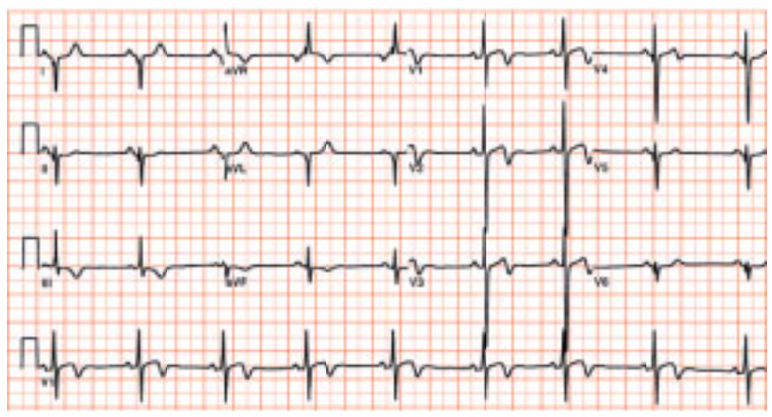
Audio 29.1 Hypertrophic cardiomyopathy. Auscultation performed in a 60-year-old male patient. The systolic gradient across the left ventricular outflow tract was 55 mm Hg at rest and increased to 121 mm Hg after amyl nitrate inhalation. The mid-systolic, crescendo-decrescendo ejection murmur is observed.Valsalva maneuver and sudden squatting are helpful in distinguishing this from fixed aortic valvular stenosis. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Electrocardiogram

Although ECG abnormalities occur in the majority of patients with HCM, no changes are specific to the disease (13,14 and 15,28,162,164,165,166,167,168,169,170 and 171). ECG evidence of right- and left-atrial enlargement is frequent. Voltage criteria for left ventricular hypertrophy in association with repolarization abnormalities are also common, but isolated increases in voltage without ST segment and T-wave changes are infrequent. Abnormal Q waves occur in 25% to 50% of patients (165,166 and 167), most commonly in the inferolateral leads and in young patients.



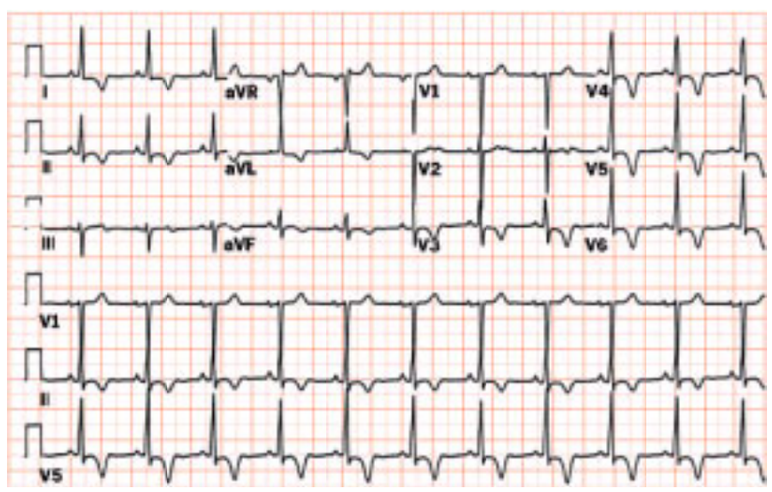
Hypertrophic cardiomyopathy. Inverted precordial T waves associated with hypertrophic cardiomyopathy.



A 28-year-old Caucasian male patient with hypertrophic obstructive cardiomyopathy.

Many mechanisms have been suggested for Q waves in HCM, including massive septal hypertrophy, abnormal septal activation, and myocardial ischemia. The presence and location of Q waves is predicted by the ratios of upper anterior–septal to mean right ventricular wall thickness and to upper posterior wall thickness (166).

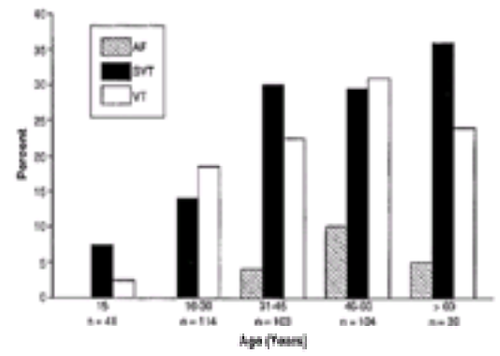
Giant negative T waves in the mid-precordial leads are said to be characteristic of Japanese patients with apical involvement (72), but they are also seen in Western patients with hypertrophy in other myocardial segments (169). Some patients have a short PR interval with a slurred QRS upstroke, which in a few patients is associated with Wolff-Parkinson-White syndrome (90,91,170,171). Personal experience suggests that the majority of individuals with this ECG abnormality do not have accessory pathways.



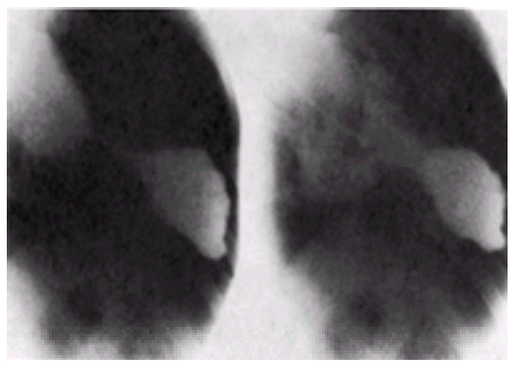
Yamaguchi's disease. Note anterior precordial T wave inversion in this Asian patient with apical hypertrophy.

In children and adolescents, the ECG may be a more sensitive marker of early disease than the echocardiogram (172,173). In adults, preliminary data indicate that a normal ECG and two-dimensional echocardiogram in adult patients with b-myosin mutations occur rarely, but minor ECG abnormalities with a normal echocardiogram may be more frequent in patients with mutations affecting other genes that are responsible for familial HCM, in particular, troponin T.

The frequency of detection of arrhythmias during 48-hour ambulatory ECG monitoring is age related (eFig. 29.4.3). NSVT occurs in 25% of adults with HCM during ambulatory ECG monitoring (174,175). Most episodes are relatively slow and asymptomatic and occur during periods of increased vagal tone (e.g., sleep). Clinical sustained ventricular tachycardia is uncommon and may occur in association with apical aneurysms (176) (eFig. 29.4.4). Paroxysmal supraventricular arrhythmias occur during ambulatory ECG monitoring in 30% to 50% of patients. Sustained atrial fibrillation (AF) is present in 5% of patients at diagnosis and develops in an additional 10% in the 5 years after diagnosis (177). Predisposing factors include left-atrial enlargement and marked left ventricular hypertrophy. AF is usually well tolerated, but loss of atrial systole can result in catastrophic hemodynamic collapse in some patients who have significant impairment of diastolic filling (178).



***e*FIGURE 29.4.3** Age-related incidence of supraventricular tachycardia (SVT), atrial fibrillation (AF), and nonsustained ventricular tachycardia (VT) in a referral population. (WJ McKenna and PM Elliott, *unpublished data*.)



***e*FIGURE 29.4.4** Diastolic and systolic frames during left ventricular angiography in an asymptomatic 40-year-old patient with asymmetric septal hypertrophy. Hyperdynamic contraction of the base of the left ventricle can be seen, with mid-systolic cavity obliteration and an apical aneurysm. (From Alfonso F, Frenneaux MP, McKenna WJ. Clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy: association with left ventricular apical aneurysm. *Br Heart J* 1989;61:178–181, with permission.)

Echocardiograph

The first echocardiographic diagnostic criteria in HCM were established using M-mode imaging (23,24,25,26,27,28,29 and 30,179). They include ASH of the interventricular septum, SAM of the mitral valve, a small left ventricular cavity, septal immobility, and premature closure of the aortic valve. With the experience of two-dimensional echocardiography, diagnostic criteria have been broadened to include virtually any pattern of hypertrophy (Fig. 29.5 and Fig. 29.6). The proportion of patients with asymmetric and concentric hypertrophy depends on what definitions are used. When a septal to free-wall thickness ratio of 1.3:1.0 is used to define asymmetry (29), concentric hypertrophy accounts for only 1% to 2% of cases. However, this proportion rises to approximately 31% when a septal to free-wall thickness ratio of 1.5:1.0 is used (180).

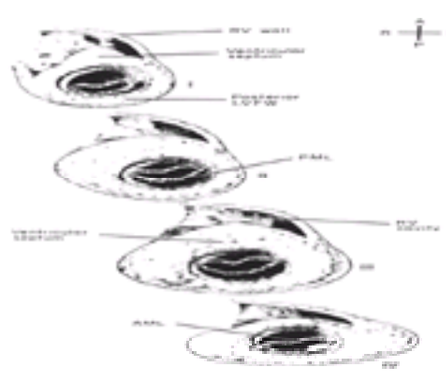


FIGURE 29.5 Maron classification. Artist's impression of four patterns of hypertrophy identified in 153 patients using two-dimensional echocardiography and shown on the short-axis plane at mitral valve level. **I:** Type I (10% of patients) hypertrophy confined to the anterior portion of the ventricular septum. **II:** Type II (20% of patients) hypertrophy involving the anterior and posterior septum. **III:** Type III (52% of patients) hypertrophy involving the anterior and posterior septum as well as the lateral free wall. **IV:** Type IV (18% of patients) hypertrophy involving left ventricular regions other than the anterior septum and the posterior free wall. A, anterior; AML, anterior mitral leaflet; L, patient's left; LVFW, left ventricular free wall; P, posterior; PML, posterior mitral leaflet; R, patient's right; RV, right ventricular. (From Maron BJ, Wolfson JK, Ciro E, et al. Relation of electrocardiographic abnormalities and patterns of left ventricular hypertrophy identified by 2-dimensional echocardiography in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 1983;51:189–194, with permission.)

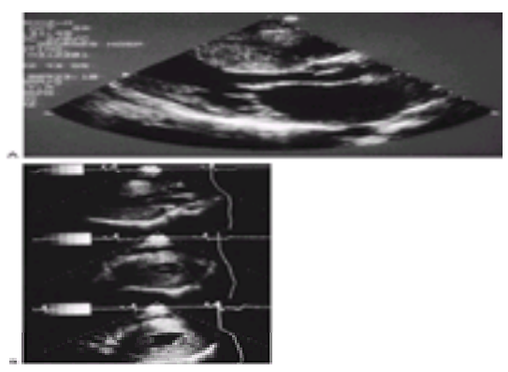
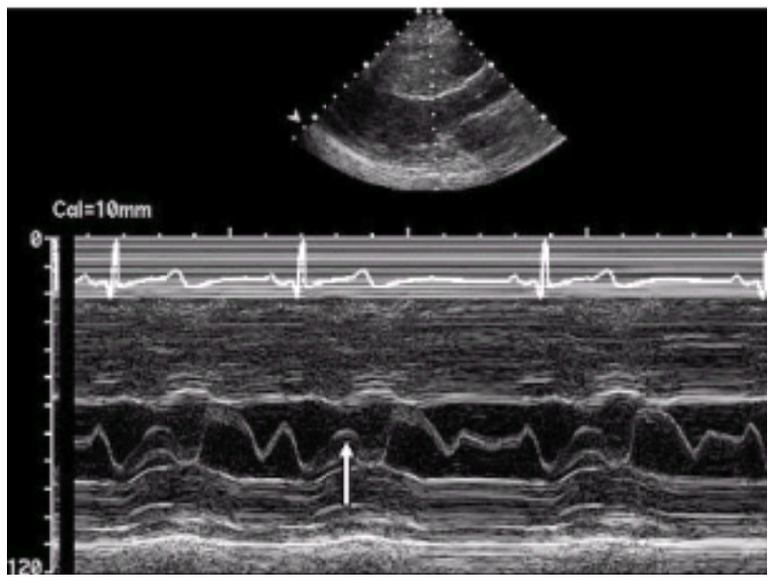


FIGURE 29.6 A: Two-dimensional echocardiogram in the parasternal long-axis view demonstrates asymmetric septal hypertrophy. **B:** Two-dimensional echocardiogram in the parasternal long- and short-axis view demonstrates severe concentric hypertrophy.



M-mode tracing of hypertrophic cardiomyopathy with severe septal hypertrophy seen at the top of the trace and systolic anterior motion (SAM) of the mitral valve in systole seen in the middle of the trace (designated by the arrow).

VIDEO

Video 29.2 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy (*first video*). Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy (*second video*) for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 29.3 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy (*first video*). Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy (*second video*) for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 29.4 Intraoperative transesophageal echo of a patient with hypertrophic obstructive cardiomyopathy and left ventricular outflow tract (LVOT) obstruction. The septum is hypertrophied, and the mitral leaflets show some systolic anterior motion of the mitral valve leaflets. An accessory mitral leaflet is located on the left ventricular septum. Note the independent motion of this leaflet in the LVOT. The pressure gradient across the LVOT/AV was greater than 100 mm Hg; however, the aortic valve opens freely. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 29.5 Ventriculography in a patient with Yamaguchi's apical hypertrophy. In this syndrome there is just proportionate hypertrophy near the apex, which produces a characteristic prolongation of the left ventricular silhouette during ventriculography (right anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 29.6 Parasternal long-axis view (*first video*) of a patient with apical hypertrophy. Note the marked increase in wall thickness apically. Parasternal short-axis (*second video*) view of the same patient with apical hypertrophy. Note the cavity obliteration at the mid–left ventricular level. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 29.7 Parasternal long-axis view (*first video*) of a patient with apical hypertrophy. Note the marked increase in wall thickness apically. Parasternal short-axis (*second video*) view of the same patient with apical hypertrophy. Note the cavity obliteration at the mid–left ventricular level. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Several scoring systems have been used to describe the severity of hypertrophy in HCM. One uses a point scoring system to grade the degree of septal thickness and the extension of hypertrophy to the left ventricular apex (30), using the apical four-chamber view to determine the extent of septal involvement and the parasternal short-axis view at the level of the mitral valve leaflet tips to assess anterolateral wall involvement (eTable 29.1.1). A simpler method defines the extent of hypertrophy as mild if only one left ventricular segment is involved, moderate if two segments are involved, and severe if three or more segments are involved.

***e*TABLE 29.1.1** WIGLE'S SCORING SYSTEM FOR LEFT VENTRICULAR HYPERTROPHY

Characteristic	Septal thickness (mm)	Point score
Extent of hypertrophy (basal one-third of septum)	15–19	1
	20–24	2
	25–29	3
	>30	4
Extension to papillary muscles (basal two-thirds of septum)		2

Extension to apex (total septal involvement)	2
Anterolateral wall extension	2
Total points possible	10

From Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy—the importance of the site and extent of hypertrophy: a review. *Prog Cardiovasc Dis* 1985;28:1–83.

Criteria for abnormal wall thickness vary, but a wall thickness more than 2 standard deviations from the mean, corrected for age, sex, and height (typically = 1.5 cm in an adult) is generally accepted as diagnostic. Right ventricular hypertrophy is diagnosed when at least two right ventricular wall measurements exceed 2 standard deviations from the mean recorded in healthy subjects. Using this criterion, right ventricular hypertrophy occurs in more than one-third of patients with HCM (181).

Approximately 25% of patients with HCM have a resting pressure gradient between the body and outflow tract of the left ventricle (13,14 and 15,23,24,25,26,27,28,29 and 30). This is almost always accompanied by SAM of the anterior mitral valve leaflet and ASH (Fig. 29.7). Some patients who show no evidence of outflow obstruction at rest have gradients that can be provoked by physiologic and pharmacologic interventions that diminish left ventricular end diastolic volume or augment left ventricular contractility. The clinical relevance of provokable obstruction is uncertain, but some workers advocate the use of such maneuvers in patients with ASH but no resting SAM, or whenever dynamic outflow tract obstruction is clinically suspected.

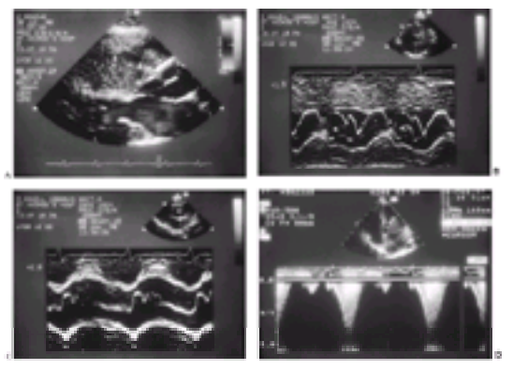


FIGURE 29.7 Sequence of four panels demonstrating **(A)** two-dimensional echocardiogram in the parasternal long-axis view that shows complete systolic anterior motion of the mitral valve and contact between the anterior mitral valve leaflet and the interventricular septum; **(B)** M-mode echocardiogram that shows asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, and contact between the anterior mitral valve leaflet and the interventricular septum; **(C)** M-mode echocardiogram that shows mid-systolic closure of the aortic valve in a patient with left ventricular outflow obstruction; and **(D)** continuous-wave Doppler image that shows characteristic “dynamic” left ventricular outflow tract obstruction.

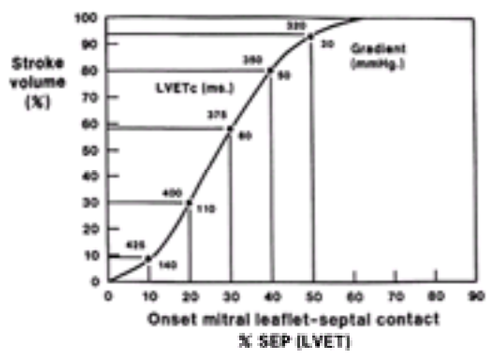
“True SAM” is characterized by an abrupt anterior movement of the mitral valve that reaches its maximum when approximately two-thirds of systole is completed and before maximum anterior movement of the posterior left ventricular wall. “Pseudo-SAM” is an exaggeration of the normal anterior movement of the mitral valve in systole that reaches its peak at the end of systole when the posterior left ventricular wall has fully contracted (182).

Until recently, the most commonly accepted theory for the cause of SAM was that septal hypertrophy and consequent outflow tract narrowing produced a high-velocity stream above the mitral valve that caused the tip of the anterior mitral valve leaflet to be sucked against the septum by the Venturi effect (28,30,183,184 and 185) (Fig. 29.7). However, this hypothesis does not explain a number of features seen in HCM, including the onset of SAM before aortic valve opening, the presence of SAM in patients who have primary mitral abnormalities and no septal hypertrophy, and the predominance of SAM at the center of the mitral valve. Experimental and observational data suggest that anterior papillary muscle displacement and primary mitral valve abnormalities create sufficient leaflet “slack” to allow SAM at low flows and in the absence of substantial septal hypertrophy (186,187,188,189,190,191 and 192).

The time of onset and the duration of mitral leaflet–septal contact in systole correlates with the magnitude of the outflow tract pressure gradient. M-mode recordings can be used to predict the severity of the outflow gradient by measuring the duration of septal contact (X) and the period from the onset of SAM to mitral leaflet–septal contact (Y) (30,193). The pressure gradient is then calculated using the regression equation: peak gradient = 25(X/Y) + 25. More commonly, Doppler echocardiography is used to calculate the gradient across the left ventricular outflow tract using the modified Bernoulli equation (194,195): peak gradient = $4Vmax^2$, where Vmax is the maximum velocity across the left ventricular outflow tract (Fig. 29.7).

The clinical significance of the outflow gradient in HCM has been hotly debated for many years (28,30,196,197,198,199 and 200). The hypothesis that the outflow gradient represents genuine and important obstruction to left ventricular ejection is based on several observations: the subaortic gradient develops simultaneously with mitral leaflet–septal contact; gradient severity correlates with the time of onset and the duration of mitral leaflet–septal apposition; a significant proportion of ventricular ejection can occur in the presence of the subaortic gradient and elevated intraventricular pressures; left ventricular ejection time is prolonged; and aortic flow profiles in patients with severe gradients demonstrate a characteristic mid-systolic deceleration coincident with mitral leaflet–septal contact. In addition, surgical or pharmacologic relief of obstruction is associated with clinical improvement in many patients. However, other studies have shown that in many patients with outflow gradients, more than 80% of ventricular ejection has been completed *before* the onset of mitral leaf–septal contact (197,198,199 and 200). Thus, some workers assert that the gradient does not represent true obstruction but is merely an inevitable consequence of rapid ventricular ejection. In addition, few studies have convincingly demonstrated any direct relation between left ventricular gradients and symptoms, arrhythmia, or sudden death.

The theoretical relationship between stroke volume and outflow gradient is shown in *e*Figure 29.7.1 (30). This predicts that in patients with modest gradients of less than 50 mm Hg, more than 80% of ventricular ejection occurs before the development of the outflow gradient. As the outflow gradient increases beyond 50 mm Hg, the percentage of ventricular ejection that occurs before mitral leaf–septal contact rapidly declines. The major clinical implication of this model is that the possibility of significant obstruction should only be considered when the outflow gradient is more than 50 mm Hg. Occasionally, outflow tract obstruction may be caused by contact between the interventricular septum and an anomalously inserted papillary muscle. This abnormality may be associated with SAM, but it is important to recognize, because conventional myectomy may not relieve the obstruction (201). Mid-cavity gradient may occur in association with cavity obliteration and is sometimes associated with paradoxical diastolic flow in the sequestered apical segments (202,203).



***e*FIGURE 29.7.1** Hypothetical relationship between the percentage of obstructed versus nonobstructed stroke volume (y axis), left ventricular outflow gradient, and left ventricular ejection time corrected for heart rate (LVETc). The LVET is equivalent to the systolic ejection period (SEP). (From Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy—the importance of the site and extent of hypertrophy: a review. *Prog Cardiovasc Dis* 1985;28:1–83, with permission.)

Mitral regurgitation occurs in almost all patients who have obstructive HCM, as a consequence of SAM and abnormal mitral leaflet coaptation (204). When no mitral valve abnormality other than SAM is present, a direct relationship exists between the pressure gradient and the severity of mitral regurgitation. In approximately 20% of patients with outflow gradients, mitral regurgitation is exacerbated by calcification of the mitral valve annulus, leaflet fibroelastosis caused by repeated traumatic septal contact, mitral valve prolapse, or rheumatic valve disease. Mitral regurgitation occurs in approximately 30% of patients with nonobstructive HCM but is usually mild and

may be associated with leaflet abnormalities.

Conventional M-mode and two-dimensional indices of systolic function are typically normal or supranormal in both obstructive and nonobstructive HCM. However, regional systolic function may be reduced, particularly in the interventricular septum, and indices of long-axis shortening are often abnormal (205,206,207,208 and 209). Thinning of hypertrophied myocardium and increases in end systolic dimensions occur in some adult patients as the disease progresses (161).

Early left ventricular filling velocities assessed using pulsed-wave Doppler imaging are, on average, very similar to control values, reflecting “pseudonormalization” of the transmitral Doppler filling pattern (210,211 and 212). E-wave deceleration time and isovolumic relaxation times are often increased. Pulmonary vein Doppler imaging often shows increased duration and peak velocity of the atrial reversal signal, reflecting increased left ventricular end diastolic pressure (210,211 and 212).

Cardiac Catheterization

Two-dimensional echocardiography has largely replaced cardiac catheterization in the diagnosis of HCM. Catheterization is indicated when the measurement of intracardiac pressures is likely to be useful in planning therapy (e.g., in patients who have severe mitral regurgitation), and for the exclusion of coronary atherosclerosis in older patients with chest pain. Left ventricular end diastolic pressure is often raised, secondary to increased stiffness and impaired relaxation. The characteristic left ventricular outflow gradient may be detected when careful pull-back across the aortic valve is performed (Fig. 29.8) or by measuring simultaneous aortic and left ventricular inflow pressures. An outflow gradient may be associated with an initial early spike in the aortic pressure wave, followed by a secondary dome-shaped tidal wave before the dichrotic notch (Fig. 29.8). In addition, the aortic pressure wave often fails to show post-extrasystolic potentiation and may actually reduce in amplitude after an extrasystole. This phenomenon may reflect worsening of the outflow gradient during the potentiated post-extrasystolic beat. Right atrial and right ventricular pressures are usually normal, except in patients with significant right ventricular outflow gradients or severe restrictive physiology. Pulmonary capillary wedge pressure may be elevated, particularly when mitral regurgitation is severe. An increased ‘v’ wave can also be seen in the pulmonary capillary wedge tracing in the absence of significant mitral regurgitation, when reduced left atrial compliance is present. Resting cardiac output is usually normal or increased, except in patients with advanced disease and systolic impairment. Left ventricular angiography may show a septal bulge encroaching on the left ventricular outflow tract during systole, together with SAM of the anterior mitral valve leaflet and mitral regurgitation. In patients with hypertrophy that is confined to the left ventricular apex, the ventricular angiogram may show a characteristic spade-shaped appearance in the right anterior oblique projection. Coronary arteriography is usually normal, but obliteration of epicardial vessels and a “sawfish” appearance during systole are described (213,214).

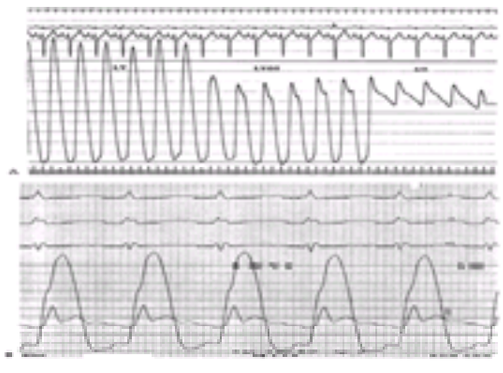
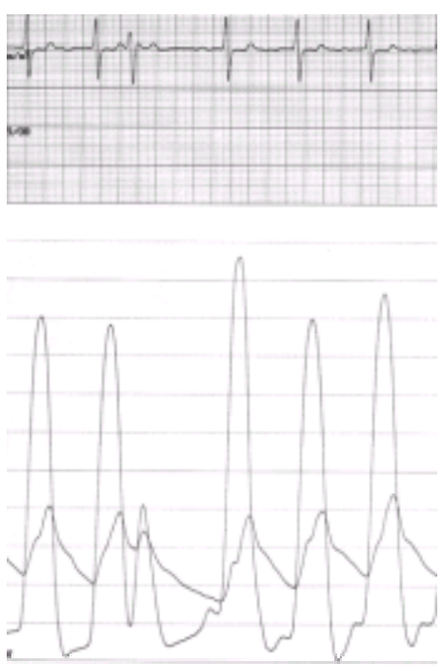
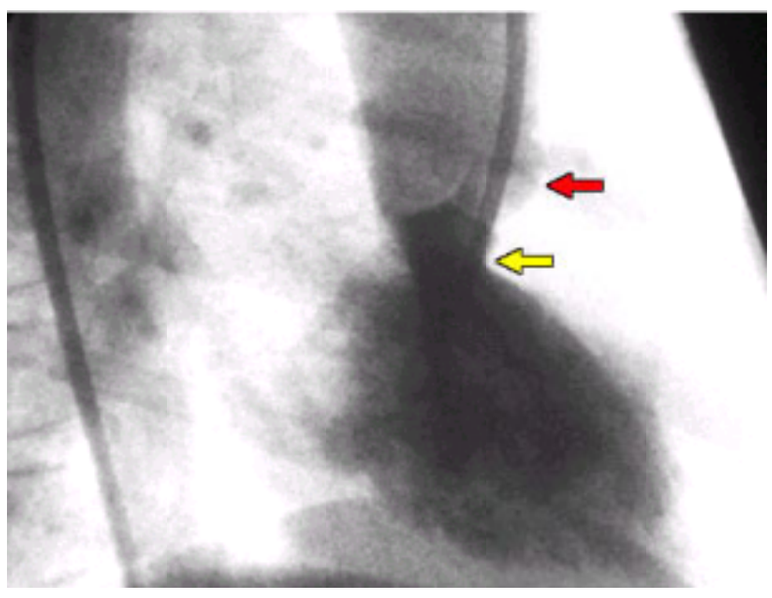


FIGURE 29.8 A: Pull-back pressure tracing shows sequential pressure pulses in the body of the left ventricle (LV), the left ventricular outflow tract (LVOT), and the aorta (AO). A pressure gradient exists between the body and outflow of the LV, and pulsus alternans is observed in the left ventricular pressure trace before the level of obstruction. **B:** Simultaneous LV (*upper trace*) and aortic (*lower trace*) pressure tracings in a patient with severe LV outflow obstruction. In the LV tracing, a prominent atrial contraction wave contributing to elevated LV end diastolic pressure can be seen. The aortic trace demonstrates a rapid upstroke with a second peak in late systole (“spike and dome”) before the incisura. The notch on the upstroke of the LV pressure tracing corresponds approximately with the time of mitral leaflet–septal contact.



A 57-year-old female patient with hypertrophic cardiomyopathy. This figure shows the Brockenbrough response after a ventricular premature beat. The Brockenbrough response includes an increase in left ventricular systolic pressure, a decrease in aortic systolic pressure, an increase in left ventricular–to-aortic gradient, and diminished aortic pulse pressure.



Subaortic stenosis. This right anterior oblique left ventriculogram demonstrates the presence of a stenosis in the left ventricular outflow tract (*yellow arrow*) just below the level of the aortic valve (*red arrow*).

Although anecdotal reports have been made of improved symptoms in patients who undergo surgery for myocardial “bridges,” the significance of systolic compression

of epicardial or intramural vessels is uncertain, because data showing an association between sudden death and myocardial bridging in a highly selected cohort of young patients have not been confirmed by more recent studies (215,216).

Radiography/Radionuclide Scanning

The chest radiograph of patients with HCM may be normal or show evidence of left or right heart enlargement, or both. Upper lobe blood diversion may be seen in patients with chronically raised left atrial pressures. Occasionally, mitral annular calcification is present.

Several studies have examined the relationship between stress-induced thallium-201 perfusion abnormalities and clinical features in patients with HCM. Fixed defects, thought to represent myocardial scars, are associated with increased left ventricular cavity dimensions, reduced shortening fraction, and impaired exercise capacity (119,217,218). Reversible regional thallium-201 defects occur in more than 25% of patients but correlate poorly with symptomatic status (119,121,124,127,219,220 and 221). Conflicting data also exist on the association between reversible defects and inducible myocardial ischemia (119,121). Some workers have described “apparent cavity dilatation” in patients (119,217) and have suggested that this represents subendocardial hypoperfusion. Radionuclide angiography has also been used to investigate global and regional left ventricular function. Several studies have demonstrated prolonged isovolumic relaxation; delayed peak filling; reduced relative volume during the rapid-filling period; and increased atrial contribution to filling and regional heterogeneity in the timing, rate, and degree of left ventricular relaxation and diastolic filling (129,134,136). A reduced peak filling rate has been shown to be associated with an increased disease-related mortality rate (136), but its predictive value is not high and adds little to conventional risk-stratification.

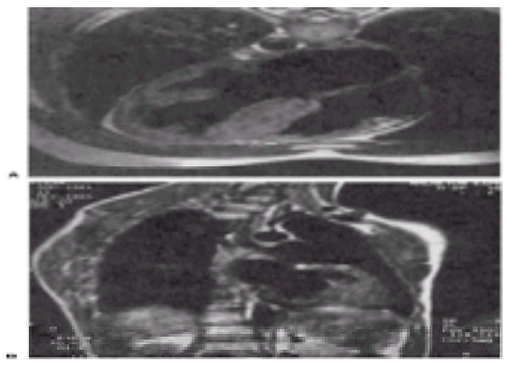
Studies using nitrogen-13 ammonia and positron emission tomography have shown that myocardial blood flow in the interventricular septum and in the left ventricular free wall are similar to normal controls at baseline but significantly less during dipyridamole-induced coronary vasodilatation (122). Positron emission tomography has also demonstrated subendocardial hypoperfusion across the septum of patients with asymmetric septal hypertrophy (222). The relation of flow abnormalities to myocardial metabolism has been investigated using fluorine-18–labeled deoxyglucose (FDG). Areas of mismatch between blood flow and FDG [thought to indicate the presence of ischemic myocardium (223)] have been described in patients at rest and during exercise (224). However, other studies have demonstrated only matched reductions in myocardial blood flow and FDG uptake in the septum (225), and more recent studies have suggested that heterogeneous FDG uptake may be related to regional systolic function and age (226,227).

Magnetic Resonance Imaging

In most patients with HCM, high-quality echocardiography suffices for diagnostic and therapeutic purposes, but magnetic resonance imaging may be useful in selected cases to assess right ventricular and apical involvement (eFig. 29.8.1). Technological advances have made it possible to use magnetic resonance imaging to assess structure, regional function, myocardial perfusion, and myocardial energetics in a single study (228,229,230,231 and 232).

VIDEO

Video 29.8 Subaortic poststenotic flow in hypertrophic cardiomyopathy (long-axis). Asymmetric hypertrophy is noted, resulting in dynamic narrowing of the left ventricular outflow tract with a signal-void jet in the subaortic region. In addition, a signal-void jet in the left atrium is also seen, representing mitral regurgitation due to systolic anterior motion of the anterior leaflet of the mitral valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 29.8.1** Spin-echo magnetic resonance images from different patients demonstrating asymmetric septal hypertrophy **(A)** and severe apical hypertrophy **(B)**. [Figure **(A)** courtesy of R Underwood, Royal Brompton Hospital, London.]

DIFFERENTIAL DIAGNOSIS

Existing diagnostic criteria for adults are based on the demonstration of unexplained left ventricular hypertrophy on echocardiography. That some individuals with HCM do not fulfill conventional echocardiographic criteria is, however, increasingly recognized. Because the probability of disease in a first-degree relative of a patient with HCM is 50%, minor ECG and echocardiographic abnormalities assume a far greater significance in the context of an affected family than in the general population. Based on this premise, new diagnostic criteria for HCM have been proposed (69) (Table 29.2). It is important to realize that these criteria only apply to unexplained ECG and echocardiographic abnormalities in first-degree adult relatives. Diagnosis in children and adolescents, athletes, and adults with hypertension and obesity can present problems and requires specific consideration in each circumstance. A number of rare clinical syndromes overlap with idiopathic HCM (Table 29.3) and should also be considered in the differential diagnosis.

Major criteria	Minor criteria
Echocardiography	
Left ventricular wall thickness ≥13 mm in the anterior septum or posterior wall or ≥15 mm in the posterior septum or free wall	Left ventricular wall thickness of 12 mm in the anterior septum or posterior wall or of 14 mm in the posterior septum or free wall
Severe SAM of the mitral valve (septal leaflet contact)	Moderate SAM of the mitral valve (no mitral leaflet-septal contact)
	Redundant mitral valve leaflets
Electrocardiography	
Left ventricular hypertrophy with repolarization changes (Romhilt-Estes)	Complete bundle branch block or (mild) intraventricular conduction defects (in left ventricular leads)
T-wave inversion in leads I and aVL (≥1 mm) (with QRS-T wave amplitude difference ≥500), leads V_3-V_6 (≥ 3 mm), or leads II and III and aVF (≥5 mm)	Minor repolarization changes in left ventricular leads
	Deep S wave in lead V_1 (≥25 mm)
Abnormal Q waves (≥40 ms or ≥25% R wave) in at least two leads from I, II, aVF (in the absence of left anterior hemiblock), and V_3-V_6, V_1-V_2, aVR, and V_3-V_6	Unexplained syncope, chest pain, dyspnea

aVF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead; SAM, systolic anterior motion.
Note: It is proposed that diagnosis of hypertrophic cardiomyopathy in first-degree relatives of patients with the disease be made based on the presence of one major criterion or two minor cardiographic criteria, or one minor echocardiographic and two minor electrocardiographic criteria.
From Willems IE, Spirito P, Devine W, et al. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. Heart 1995;77:138-142.

TABLE 29.2 PROPOSED NEW DIAGNOSTIC CRITERIA FOR HYPERTROPHIC CARDIOMYOPATHY IN FIRST-DEGREE RELATIVES OF AFFECTED PATIENTS

Primary genetic disorders characterized by LVH
Noonan's syndrome
Friedreich's ataxia
Lentiginosis
Exaggerated physiologic response
Renal and Afro-Caribbean hypertension
Athletic heart syndrome
Obesity
Metabolic disorders
Infants of diabetic mothers
Amyloid
Glycogen storage disease
Mitochondrial myopathy
Phaeochromocytoma
Inborn errors of fatty-acid metabolism
Fabry's disease

TABLE 29.3 DIFFERENTIAL DIAGNOSIS OF UNEXPLAINED LEFT VENTRICULAR HYPERTROPHY (LVH)

Friedreich's Ataxia

Friedreich's ataxia is an autosomal recessive disorder characterized by progressive degeneration of the corticospinal and posterior spinocerebellar tracts and the posterior columns. Coexistent cardiac involvement is described in 90% to 100% of patients during follow-up and is often the cause of death (82,83). Typically, progressive ataxia occurs before the development of overt cardiac disease, but initial presentation with heart disease is recognized. Concentric and asymmetric left ventricular hypertrophy are the commonest abnormalities, but progression to dilated cardiomyopathy and left ventricular outflow gradients are also described.

Noonan's Syndrome

Noonan's syndrome occurs with an estimated incidence of 1 in 1,000. Although some patients have a phenotype similar to Turner's syndrome, with short stature, neck webbing, and hypertelorism, the somatic manifestations may be very subtle and easily overlooked. Approximately 25% of affected individuals have left ventricular hypertrophy, predominantly affecting the upper ventricular septum (87,88 and 89). SAM and outflow obstruction are uncommon but, when present, are always associated with severe hypertrophy. Myocyte disarray is also described in Noonan's syndrome, but its significance in relation to familial HCM is uncertain. Of the other cardiac abnormalities described in Noonan's syndrome, pulmonary stenosis (24%) and secundum atrioseptal defects (10%) are the most frequent.

VIDEO

Video 29.9 Subaortic stenosis. A radiolucent membrane is visualized just below the aortic valve cusps (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Mitochondrial Cytopathies

It is increasingly recognized that mitochondrial DNA mutations are associated with HCM (233,234,235,236,237,238 and 239). One study (239) suggests that specific mitochondrial DNA mutations are associated with particular patterns of hypertrophy: asymmetric septal hypertrophy in patients with an adenine-to-guanine mutation at nucleotide position 8344, and symmetric hypertrophy in patients with an adenine-to-guanine mutation at nucleotide position 3243. However, most of the available clinical data in adults are derived from case reports and small pedigrees.

Lentiginosis

HCM is rarely associated with an autosomal dominant cardiocutaneous disorder, LEOPARD syndrome (L, lentigenes; E, ECG abnormalities; O, ocular hypertelorism; P, pulmonary stenosis; A, abnormal genitalia; R, retardation of growth; D, sensorineural deafness) (240,241,242 and 243). Some patients have left ventricular outflow and mid-cavity gradients, and at least one report exists of a patient with LEOPARD syndrome undergoing successful septal myotomy-myectomy (243).

Leopard's syndrome. Figure shows a patient with Leopard's syndrome characterized by multiple basal cell nevi and broad facies. There is an association with pulmonic stenosis.

The Athletic Heart Syndrome

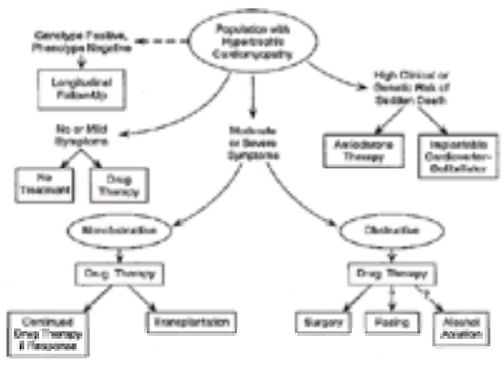
Although HCM is the commonest cause of death in young athletes (244,245), its diagnosis in individuals who regularly participate in competitive sports can be problematic (246,247,248,249 and 250), because the physiologic changes brought on by athletic training can mimic HCM. Athletes who participate in events that combine both isometric and isotonic activities are most at risk of developing increased left ventricular wall thickness. Pure strength training is associated with an increase in left ventricular mass and wall thickness relative to the left ventricular cavity size, but strength training is rarely associated with an increase in absolute wall thickness (251). In a study of more than 900 elite athletes (246), fewer than 2% had a wall thickness greater than 13 mm, and none had a wall thickness greater than 16 mm. In female athletes, maximum wall thickness was less than or equal to 14 mm. A diagnosis of HCM in an elite athlete is more likely when an individual has left ventricular wall thickness exceeding these values and/or when the athlete is symptomatic and has a family history of HCM and premature sudden death. The "athletic" ECG frequently displays voltage criteria for left ventricular hypertrophy, sinus bradycardia, and sinus arrhythmia. Although marked repolarization abnormalities are described in some elite athletes (252,253), they are uncommon and should always raise suspicion of myocardial disease. Echocardiographic features favoring HCM include small left ventricular cavity dimensions (athletes tend to have increased left ventricular end diastolic dimensions), left-atrial enlargement, left ventricular outflow gradients, and evidence on Doppler imaging of diastolic impairment. Recent data suggest that metabolic exercise testing may also be useful in differentiating athletic adaptation from HCM, with a peak oxygen consumption greater than 50 mL per minute per kg or more than 20% above the predicted maximum oxygen consumption that is highly suggestive of athletic adaptation (254).

PRINCIPLES OF CLINICAL MANAGEMENT

The main aims of clinical management in patients with HCM are to provide symptomatic relief and to prevent complications. In most cases, a relatively simple, noninvasive assessment that includes clinical history, echocardiography, ECG, 48-hour ambulatory ECG monitoring, and cardiopulmonary exercise testing is sufficient to identify patients who require specific treatments.

Symptomatic Therapy

Although pharmacologic therapy in patients with HCM is usually administered on an empirical basis, guided by subjective reporting of symptomatic improvement, the choice of therapy is influenced by left ventricular morphology and hemodynamics (eFig. 29.8.2). In patients with significant outflow obstruction, the principal aim of treatment is reduction of gradient using pharmacologic, surgical, or other means. Patients with outflow gradients or mitral regurgitation are also at increased risk of infective endocarditis, and standard antibiotic prophylaxis is recommended. Therapeutic options in patients without left ventricular outflow gradients are more limited, but pharmacologic therapy may improve chest pain and, to a lesser extent, dyspnea.



***e*FIGURE 29.8.2** Treatment algorithm for patients with hypertrophic cardiomyopathy. (Adapted from Spirito P, Seidman CE, McKenna WJ, et al. The management of hypertrophic cardiomyopathy. *N Engl J Med* 1997;336:775–785.)

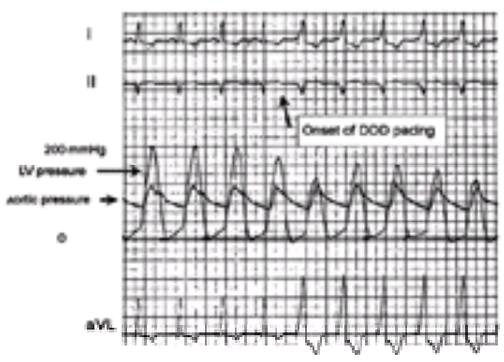
Obstructive Hypertrophic Cardiomyopathy

Patients who have moderate to severe left ventricular outflow tract obstruction may experience exertional chest pain, dyspnea, or syncope. Although some studies have suggested that up to 70% of patients improve with beta-blocker therapy, high doses are frequently required and side effects may be limiting (28,162). Furthermore, little convincing evidence exists that beta-blockers reduce the incidence of serious ventricular arrhythmias or sudden death (255). When beta-blockade alone is ineffective, the addition of disopyramide can be effective in reducing gradients and improving symptoms (256,257 and 258). Disopyramide should be titrated to patient's symptoms and the emergence of side effects, aiming for a maintenance dose of 400 to 600 mg daily. Data comparing beta-blockade and disopyramide are limited, but disopyramide may have a superior effect on exercise tolerance (258). In some patients, particularly elderly patients, anticholinergic side effects may preclude or limit the use of disopyramide. Recent data suggest that an alternative class I antiarrhythmic drug, cibenzoline, which has fewer anticholinergic side effects, may be equally effective (259). Verapamil is also used to treat symptoms in patients with outflow gradients, but its effect is unpredictable, and acute hemodynamic collapse is described in patients with substantial gradients or severe diastolic dysfunction.

Surgery should be considered in all patients with significant (i.e., greater than 50 mm Hg) outflow obstruction and symptoms refractory to medical therapy (260,261,262,263,264,265,266 and 267). The principal aim of surgical intervention is to eliminate SAM of the mitral valve and mitral leaflet–septal contact by widening the left ventricular outflow tract. The most commonly performed procedure is a ventricular septal myotomy-myectomy (Morrow procedure) performed using a transaortic approach. This procedure results in a significant reduction in outflow gradient in 95% of cases, reduced mitral regurgitation, and long-term symptomatic improvement in up to 70% of patients (260,261,262,263,264,265,266 and 267). Operative mortality rate figures in series reported elsewhere are of the order of 5% but are now probably less than 1% to 2% in centers with experienced surgeons. Complications such as atrioventricular block and ventricular septal defects do occur but have become less frequent with modification of surgical technique and the use of preoperative transesophageal echocardiography (268). Aortic regurgitation may occur in patients postoperatively but is not usually of hemodynamic significance (269).

Other techniques that have been advocated include myotomy alone (270) and mitral valve replacement (271). The latter option is controversial because of the subsequent risks of anticoagulation and prosthetic valve dysfunction, but mitral valve replacement may have a limited role in patients with other intrinsic mitral valve abnormalities. Mitral valve plication in conjunction with myotomy-myectomy has been advocated as an alternative to mitral valve replacement in patients who have elongation of the anterior mitral leaflet (272). More recently, elongation of the horizontal diameter of the mitral valve using a glutaraldehyde-preserved autologous pericardial patch has been advocated (273).

Although myotomy-myectomy remains the gold-standard interventional therapy for outflow tract obstruction, the procedure requires a level of expertise and support that are not universally available. Furthermore, additional comorbidities and patient reluctance may preclude this mode of therapy. Two novel approaches to gradient reduction have been recently evaluated. Several studies have suggested that dual-chamber pacing using a short programmed atrioventricular delay to ensure constant activation of the right ventricle from its apex improves symptoms in patients with left ventricular outflow tract gradients (eFig. 29.8.3) (274,275,276,277,278,279,280,281,282 and 283). Success depends on achieving an atrioventricular delay that gives maximum preexcitation while maintaining effective atrial transport. Although preliminary data indicated that pacing is capable of reducing gradients by approximately 50%, several multicenter trials have shown that pacemaker insertion is associated with a substantial placebo effect and little objective improvement in exercise capacity. Few comparative data are available for dual-chamber pacing and myectomy, but one small nonrandomized study has suggested that gradient reduction and exercise duration are greater after surgery (284). Nevertheless, a minority (10% to 20%) of patients do respond to pacing, and therefore pacemaker insertion remains an option in patients who have an unacceptable operative risk with myotomy-myectomy. Pacemaker insertion may also facilitate the use of higher doses of beta-blockers in some patients (280).



***e*FIGURE 29.8.3** Simultaneous left ventricular (LV) and aortic pressure traces in a patient with obstructive hypertrophic cardiomyopathy, demonstrating a reduction in the LV outflow tract gradient after the onset of synchronous atrioventricular pacing. aVL, augmented voltage unipolar left arm lead; DDD, dual-chamber.

The second novel intervention involves selective injection of alcohol into one or more septal perforator branches of the left anterior descending coronary artery to create of localized septal scar (285,286,287,288,289,290,291,292 and 293). Published data suggest that the procedure-related mortality rate is lower than 1% in centers with experienced clinicians, but deaths due to conduction system damage and inadvertent injection of alcohol into other myocardial segments have occurred. The latter problem is minimized by the injection of intracoronary echo contrast agents before injection of alcohol to ensure that only the septal bulge at the point of mitral leaflet–septal contact is opacified. Alcohol injection is contraindicated if opacification is present in other regions of the myocardium, such as the distal septum, the right ventricle, or the papillary muscles. In contrast to the results of surgery, most patients develop right and not left bundle branch block after alcohol ablation. Higher

degrees of AV block can occur transiently but persist in only 10% to 15% of patients. Prolonged or recurrent AV block after the procedure should prompt consideration of permanent dual-chamber pacing. Interim results suggest that left ventricular cavity dimensions increase slightly after alcohol ablation, but progressive ventricular dilatation and late arrhythmic complications have not yet been described. Results from the largest series show that gradients can be abolished or substantially reduced in 80% of patients. This reduction is paralleled by an improvement in symptom class and exercise tolerance.

Nonobstructive Hypertrophic Cardiomyopathy

Beta-blockade may improve chest pain and dyspnea, but patient response is usually suboptimal. Verapamil, often in high doses (240 to 480 mg per day), is a useful alternative, particularly in patients who experience exertional chest pain (294,295,296 and 297). The mechanism of action is uncertain, but verapamil can improve left ventricular relaxation and exercise tolerance. Data on its effect on myocardial perfusion are conflicting (297,298). Diltiazem (299) also has beneficial effects on symptoms and left ventricular function and provides a useful alternative to verapamil when side effects are problematic. Nifedipine (300) has been advocated, but the potential hazards of vasodilatation, particularly in patients with outflow gradients, preclude its general use. Although diuretics, sometimes in combination with beta-blockers or calcium antagonists, may alleviate symptoms caused by pulmonary congestion, their injudicious use can be dangerous, particularly in patients with severe diastolic impairment.

Supraventricular Arrhythmia

For the management of supraventricular arrhythmia, AF should be cardioverted; when this is not possible, control of the ventricular rate improves symptoms in most patients (177). AF in HCM is associated with a significant risk of thromboembolism, and anticoagulation therapy should be considered in all patients in whom AF is sustained or recurs frequently. Treatment is not usually indicated for other asymptomatic and self-limiting supraventricular arrhythmias, but if they are sustained or associated with symptoms, then specific medical therapy should be instituted. Treatment with low-dose amiodarone (1,000 to 1,400 mg weekly) is effective in maintaining sinus rhythm and in controlling the ventricular rate during breakthrough episodes. Beta-blockers with or without class III action may be useful, but class I agents are untested and potentially proarrhythmic.

Identification of High-Risk Patients

Patients who have HCM are prone to a number of potentially life-threatening complications, including sudden ventricular arrhythmia, thromboembolism, heart block, and congestive cardiac failure. Although the identification of patients who are at risk remains a clinical challenge, recent data show that high-risk patients can be identified and successfully treated.

Sudden death remains the greatest cause of premature death in patients with HCM (151,152,153,154,155,156,157,158,159 and 160). The underlying substrate for sudden death is complex and incompletely understood, but myocyte disarray and fibrosis—the microscopic hallmarks of the disease—provide the conditions for anisotropic conduction and reentry arrhythmia. Circumstantial evidence suggests that expression of this substrate is modified by factors such as myocardial ischemia, autonomic function, and abnormal vascular responses (119,120,121,122,123,124,125,126 and 127,301,302,303,304,305,306 and 307). Fortuitous ECG recordings made before sustained ventricular tachyarrhythmias in patients with HCM have shown that rapid AF may also act as a trigger to fatal arrhythmic events (178). In spite of this potent pathophysiologic substrate for sudden death, survival data in both regional and tertiary center populations indicate that only a minority of patients are at sufficiently high risk to warrant consideration for prophylactic therapy (151,152,153,154,155,156,157,158,159 and 160). Therefore, identifying readily applicable clinical risk markers that allow patients to be stratified into high- and low-risk cohorts is the clinical goal.

Clinical Markers of Risk of Sudden Death

Patients with HCM and a history of sustained ventricular arrhythmia have a risk of a fatal event of approximately 10% per annum (157,308,309). Although this is much lower than the risk seen with some other cardiac diseases (310), patients with HCM who survive a cardiac arrest are often young and are, therefore, at risk for a longer period than most patients with coronary artery disease or congestive cardiac failure. Many sudden deaths occur in patients who have minor symptoms. Children and adolescents who have two or more first-degree relatives with HCM who died prematurely are at risk of dying suddenly themselves (127,128 and 129). Recurrent unexplained syncope in the young is also a highly specific marker of risk (28,151,152 and 153,311). Pooled data from two studies (174,175) indicate that in patients with HCM, NSVT is associated with an increased risk of sudden death, with a sensitivity of 69% and a specificity of 80%. However, its value as a risk marker is limited by a modest positive predictive accuracy of 22%, reflecting the fact that most patients with NSVT do not die suddenly and that the incidence of NSVT in children is low. More recently, some workers have suggested that NSVT is significant only when it is repetitive or when it occurs in symptomatic patients (312), but few data support this. The onset of AF has, in the past, been considered to be an adverse prognostic event. However, at least one prospective study has shown that the 5-year survival rate in patients with AF is similar to that in age- and sex-matched patients who remain in sinus rhythm (177).

Approximately 25% of patients with HCM have abnormal blood pressure responses during exercise (305). This phenomenon is associated with a family history of sudden death, small left ventricular cavity dimensions, and, in patients younger than 40 years, a higher mortality rate (306,313,314). The underlying mechanism for the abnormal response remains speculative, but some evidence suggests that inappropriate vasodilatation in nonexercising muscles is responsible (307). The presence of a pressure-dependent vasodepressor response in patients with HCM may explain the poor tolerance of paroxysmal arrhythmia or sinus tachycardia seen in some patients. In patients who have a particular susceptibility, systemic hypotension may also cause a fall in myocardial perfusion pressure, with consequent metabolic changes that trigger ventricular arrhythmia.

Data from cross-sectional studies and more recent large prospectively followed cohorts in regional and tertiary centers have shown that patients with severe hypertrophy (i.e., a wall thickness ≥30 mm) have an increased risk of sudden death (154,315,316 and 317). However, this marker is of limited value, because the majority of patients who die suddenly has wall thickness values less than 30 mm. To date, there is no conclusive evidence that left ventricular outflow obstruction is associated with sudden death, but a recent series has suggested that substantial gradients may be associated with the overall cardiovascular mortality rate (155).

Electrophysiologic Markers of Risk

In patients with HCM, the QTc (QT corrected for heart rate) is longer, shows greater dispersion, and is correlated with the maximal left ventricular wall thickness (possibly owing to variable volumes of repolarizing tissue) in patients with HCM (318,319,320,321 and 322). In addition, the normal diurnal variation in QT interval is lost in some patients with HCM, suggesting the presence of abnormal autonomic function (319). The sensitivity of QT measurement can be improved by assessment of dynamic behavior and relationship to the preceding RR interval during ambulatory ECG monitoring. The QT/RR regression relationship is steeper when compared to normal controls, but neither the QTc nor the QT/RR slope discriminates between high- and low-risk patients (320).

An abnormal signal-averaged ECG (SAECG) is present in 10% to 20% of patients with HCM (323,324). Abnormal SAECGs are more common in patients with NSVT but are not associated with any other clinical risk factor. In addition, many patients who experience catastrophic cardiac events have normal SAECGs (324).

In patients with ischemic heart disease and heart failure, reduced parasympathetic and/or excess sympathetic activity is associated with sudden death and ventricular arrhythmias. Both global and specific vagal components of heart-rate variability (HRV) are reduced in patients with NSVT (301,302 and 303), but global HRV is increased in patients who have a family history of sudden death, and no differences in HRV are seen in patients who die or are successfully resuscitated from out-of-hospital ventricular fibrillation. The lack of a significant correlation with adverse prognostic indicators may reflect the sudden and short-lived nature of cardiovascular changes in HCM, making them difficult to detect when HRV is measured over long periods.

Several studies have investigated the role of programmed ventricular stimulation in the clinical assessment of patients with HCM. When up to three premature stimuli are delivered during three drive-pacing cycle lengths in the left or right ventricle, or both, 36% of patients have induced sustained ventricular tachycardia (325). Its presence is associated with a higher risk of cardiac events (defined as sudden death, cardiac arrest, or syncope accompanied by ICD discharge). However, this approach to risk-stratification in patients with HCM has important limitations. The response to ventricular stimulation in any patient depends in part on the protocol used. Aggressive protocols that involve three or more premature stimuli produce sustained polymorphic ventricular tachycardia in 30% to 40% of patients, with a low predictive accuracy for sudden death (326). Less aggressive protocols have a lower sensitivity. Furthermore, because ventricular arrhythmias are frequently associated with hemodynamic collapse in patients with HCM, the need to terminate such events rapidly can make it impossible to determine whether induced ventricular arrhythmias are sustained. The low positive and negative predictive accuracy of programmed stimulation in patients with HCM limits its role to use in patients who have sustained and clinically significant ventricular arrhythmias.

One of the consequences of myofibrillar and myocyte disarray is a dramatic variation in myocyte length and diameter. It has been hypothesized that this results in a spectrum of conduction velocities and refractory periods within the yocardium that, together with an increase in the number of potential conduction pathways, creates the necessary substrate for reentrant tachycardia (327). This putative arrhythmogenic substrate has been investigated by analyzing the changes in individual paced ECG transitions (“fractionation”) recorded at three sites in the right ventricle. Patients with a history of ventricular fibrillation have the greatest prolongation of the paced ECG, and prolongation occurs at longer extrastimulus coupling intervals than in other patients (327,328). Premature stimulation causes the least change in ECG

fractionation in control patients and patients with no clinical risk factors for sudden death. Patients with either a family history of premature sudden death or NSVT exhibit responses that span the range from high risk (ventricular fibrillation) to low risk (no adverse prognostic features). The spread of responses seen in patients with NSVT and a family history of sudden death provides a physiologic explanation for the relatively poor positive predictive accuracy of these observations. Although pooled data from two studies (327,328) demonstrate that patients with syncope also have a range of conduction responses, the incidence in patients with ventricular fibrillation is significantly higher. This suggests that the hemodynamic disturbance associated with syncope may act as a trigger for the cascade of events resulting in sudden death in patients with the appropriate electrical substrate.

Treatment of High-Risk Patients

There have been several obstacles to the construction of workable risk-stratification algorithms in patients who have HCM, most notably the low positive predictive accuracy of the majority of suggested risk markers for sudden death and the lack of data on the relative value of different risk markers. The latter problem has been difficult to study because of the relatively low incidence of HCM and the low annual event rates even within tertiary center populations. Some data suggest that a risk model based on a smaller number of easily assessed risk markers (specifically, NSVT, left ventricular wall thickness, abnormal blood pressure responses during exercise, family history of sudden death, and recurrent unexplained syncope) may allow identification of most high-risk patients with sufficient accuracy to permit rational decisions to be made about the necessity for prophylactic therapy (154) (Fig. 29.9). In this study, patients with two and three risk factors had an annual risk of sudden death of approximately 3% and 6%, respectively. Estimation of risk in patients with a single risk factor remains problematic, because the significance of a given risk factor may vary between individual patients, particularly in the context of a family history and syncope. Risk factors also have to be interpreted in the light of other features, such as patient age. Decision making in such patients inevitably has to be pragmatic and guided by physician experience and patient preference.

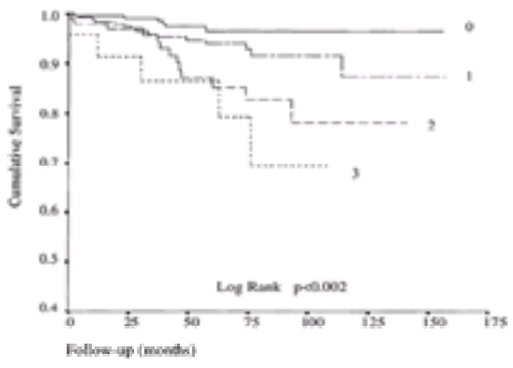


FIGURE 29.9 Kaplan-Meier survival curves in patients with zero, one, two, and three clinical risk factors. The risk factors used in this analysis were nonsustained ventricular tachycardia, family history of sudden death, recurrent unexplained syncope, and abnormal blood pressure during exercise (in patients younger than 40 years). (The original data set and the relationship between these risk factors and wall thickness are reported in Elliott PM, Gimeno Blanes JR, Mahon NG, et al. Relation between the severity of left ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;357:420–424.)

All patients who have spontaneous or exertional ventricular tachyarrhythmias should be considered for prophylactic ICD insertion (308,309 and 310,329,330). In patients who do not have a history of sustained ventricular tachycardia or cardiac arrest, the identification of two or more risk factors should also prompt consideration for prophylactic therapy. Low-dose amiodarone therapy has been shown to reduce sudden deaths in patients with NSVT (331) and in high-risk children (152), but evidence from multicenter ICD trials and reports of occasional deaths in patients with a history of ventricular tachycardia or ventricular fibrillation who were taking amiodarone has called into question its use as prophylactic therapy in patients considered to be at risk for sudden death. Because demographic and ethical considerations make a randomized study of ICD therapy in HCM extremely unlikely, patients should be offered the “best” therapy, which in most circumstances will be an ICD. Amiodarone continues to play a role in preventing potential triggers for sudden death or life-threatening arrhythmias, in particular paroxysmal AF and hemodynamically tolerated sustained monomorphic ventricular tachycardia. Other potential trigger factors, such as conduction system disease, accessory pathways, and myocardial ischemia, should also be treated when possible.

Exercise and Hypertrophic Cardiomyopathy

Although 40% of HCM-associated sudden deaths occur after moderate to severe exertion (244,332), the increase in the relative risk of sudden death incurred by regular participation in vigorous exercise is unknown. No systematic data are available to prove that abstention from vigorous physical activity prevents death, but most clinicians agree that young patients with HCM should not participate in competitive sports. The 29th Bethesda Conference (333) has produced guidelines on the eligibility of patients with HCM for participation in sports. It is suggested that athletes with unequivocal HCM should be advised not to take part in most competitive events, regardless of symptoms or the presence of left ventricular outflow obstruction. Because of the risk of sudden death is higher in younger patients, participation of individuals older than 30 years should be assessed on the basis of recognized or potential clinical risk factors, bearing in mind that these guidelines are conservative and based on a consensus view of best practice rather than definitive proof.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Over the past decade, considerable progress was made in unraveling the complex pathophysiology of HCM. We know now that most cases are caused by mutations in genes that encode sarcomeric proteins, and that the spectrum of disease is even more diverse than was previously thought. Nevertheless, many questions relating to pathophysiology remain unanswered, in particular, questions involving the mechanisms that determine disease expression and penetrance. Clinical management of HCM has also progressed, specifically in relation to the treatment options for outflow tract obstruction and the identification and treatment of patients at high risk of sudden death. These advances clearly are good news for patients, but for clinicians they make the management of patients with HCM more, rather than less, challenging. Physicians must now offer specialist genetic counseling, detailed assessment of symptoms and pathophysiology, and a wide range of surgical and invasive cardiologic expertise. This means that the care of patients requires involvement of many specialists and will probably result in centralization of resources in centers with a special interest in “HCMology.” The final result should be a major improvement in the outlook for patients with this capricious disease.

THE FUTURE

Over the past decade, we learned that familial HCM is a genetically heterogeneous disease of the cardiac sarcomere, with variable penetrance and disease expression. One of the major challenges for the next decade is to unravel the complex mechanisms that determine disease expression and thereby develop new therapies that could modify the natural history of the condition. Other therapeutic challenges include the management of the disease in symptomatic patients who do not have left ventricular outflow tract obstruction and the refinement of risk-stratification algorithms, particularly in young patients and in patients who have a single risk factor.

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CONGENITAL HEART DISEASE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

This chapter was organized to provide an introduction to congenital heart disease. Although the intent is to be complete, it is by no means exhaustive, and the reader ideally will be encouraged to pursue more extensive query into the literature in an effort to expand on the perspective provided. The section Historical Perspective outlines the historical landmarks in the relatively brief history of clinical pediatric cardiovascular medicine, beginning with pathologic recognition of the nature of congenitally malformed hearts and continuing with a description of the rapid evolution of diagnosis and management strategies. Prevalence, cardiac nomenclature, the segmental and sequential analysis of morphology and pathology, and an introduction to the genetics of congenital heart disease precede a description of the approach to the art of examining a neonate, infant, child, or adolescent with suspected congenital heart disease, including the issue of screening in children with trisomy 21. Naturally, the timing of presentation is important when considering congenital lesions, and in this light the roles of prostaglandin and persistent pulmonary artery hypertension of the newborn are discussed. Before considering individual conditions, the natural history of some of the more common lesions is outlined in an effort to provide a reference for the ensuing discussion. Whereas many systems exist, lesions are classified under the subgroups of those with a left-to-right shunt, obstructive lesions, cyanotic lesions, and those not easily assigned to any of the preceding categories. They are presented with reference to anatomic considerations, with an emphasis on issues important to diagnosis, subsequent treatment, and prognosis. The references listed are not intended to be exhaustive; rather, they should serve as a starting point for further investigation.

HISTORICAL PERSPECTIVE

As we begin the new millennium, we should not forget that it was just slightly more than 100 years ago when the systematic study of congenital heart malformations began in Montreal, Canada, under the aegis of Dr. Maude Abbott (1). In the 1930s, at The Johns Hopkins Hospital, Dr. Helen Taussig (2) used clinical examination, chest radiography, scalar electrocardiography, and cardiac fluoroscopy to catalog most forms of congenital heart disease. In 1937, at the Children's Hospital in Boston, the late Dr. Robert Gross (3) performed ligation of the arterial duct. The benchmark contribution of Taussig and Blalock (4) to the palliation of infants and children with cyanotic congenital heart disease in 1945 and repair of coarctation of the aorta by Crawford (5,6) also contributed to those exciting days of the birth of the study and treatment of congenital heart disease. By the late 1940s and early 1950s, contributions by Blalock and Hanlon to the atrial septectomy (7), Sir Russell Brock to the pulmonary valvotomy (8), and Muller and Dammann (9) to banding of the pulmonary trunk. This was followed by the repair of atrial septal defects and then ventricular septal defects (the latter using cardiopulmonary bypass), and the repair of tetralogy of Fallot all gave impetus to the medical and surgical therapy of the many forms of the congenitally malformed heart (10,11). By the late 1950s and the early 1960s, significant progress had been made in the treatment of complete transposition of the great arteries, with the exciting contributions by Senning (12) and then Mustard (13) with their atrial inversion repairs; but these surgical procedures for the repair of transposition of the great arteries in that era carried a substantial mortality and morbidity until the novel contribution of Rashkind and Miller (14) forever changed the once-dismal natural history of the patient with complete transposition of the great arteries, providing a nonsurgical methodology (balloon atrial septostomy) to enlarge the atrial septal defect, thus enhancing atrial mixing and improving systemic arterial oxygen saturation. In 1968, the use of a conduit to perform reparative surgery in a patient with pulmonary atresia and ventricular septal defect provided the possibility of repairing a wide range of congenitally malformed hearts in which there was no continuity between the ventricular mass and the pulmonary arteries. These surgical innovations were not carried out in isolation, however. Understanding the milieu for the neonate and the ability to regulate acid–base balance and ventilate the critically ill newborn and young infant provided the platform on which such surgical bravado could be conducted with increasingly satisfactory results. The clinical recognition that many forms of serious congenital heart disease presenting in the newborn and neonate were ductal dependent for either systemic or pulmonary blood flow stimulated the desire to define an agent to promote patency of the arterial duct beyond the time of its normal functional and anatomic closure. The recognition that an E-type prostaglandin could be used intravenously or even in an oral preparation to maintain ductal patency was an exciting "from-bench-to-bedside" development that dramatically altered the care of the often critically ill hypoxemic neonate (15).

The realization that blood could be conducted into the lungs without a pumping chamber set the stage for the now landmark contribution of Fontan and Baudet (16), whose signal operation originally was offered to the patient with tricuspid atresia. The Fontan operation, or one of its many surgical modifications, has been extended to a wide range of congenitally malformed hearts once deemed unsuitable for a biventricular repair. The ability to perform reparative heart surgery in the newborn and young infant using profound hypothermia with circulatory arrest gave impetus to primary repair of congenital heart malformations whenever possible. The Boston Children's cardiac surgical group (17) championed primary repair whenever possible, eschewing the two-staged approach of palliation followed by repair at an older age. This philosophy was dramatically demonstrated with the application of the arterial switch procedure to correct the heart anatomically with complete transposition of the great arteries, building on the accomplishment of Adib Jatene (18,19) of Sao Paulo, Brazil, who first performed this operation successfully. As to hypoplastic left-sided heart syndrome, infants with this constellation of varying degrees of severe hypoplasia of the inflow and outflow tract of the left side of the heart, considered by some to be the worst heart disease, were considered inoperable and usually died an early, predictable death. Predicated in large part on the surgical contribution of Fontan and Baudet (16) and data provided by the New England Regional Infant Cardiac Program (20) about babies with the hypoplastic left-sided heart syndrome, the late 1970s and early 1980s witnessed exciting surgical developments extended to these babies: a staged surgical approach initially to provide a stable source of systemic and pulmonary blood flow, eventually concluding in the Fontan operation (21,22 and 23). Most surgical centers in the early to mid-1980s, however, could not achieve the rates of salvage reported by Norwood. Interest in cardiac transplantation in the newborn was pioneered by Bailey and colleagues (24,25,26 and 27) initially with Baby Fae using a baboon's heart, then with same-species allografts, now used by many centers throughout the world.

These surgical accomplishments were not achieved in isolation. The many variations of the congenitally malformed heart were studied and reported in exquisite detail by Lev, Edwards, Van Praagh, Anderson, and their respective colleagues in a large number of publications (28,29,30,31 and 32). Richard Van Praagh and colleagues championed a “language” that could and would provide a segmental and sequential approach to congenital heart disease, an *Esperanto*. The heart was considered in terms of its fundamental building blocks: the atria, ventricles, and great arteries. In the early days of this language, the connections between the cardiac segments were deduced, but this was not acceptable to Robert H. Anderson of Great Britain, who emphasized the importance of connections between the cardiac segments (30). Through debate and publications, these two schools seemed quite polarized, but the implementation of a segmental and sequential nomenclature proved that these various nosologies were not mutually exclusive, but indeed complementary. As we learned more about the form and function of the congenitally malformed heart, through surgical practice and dissection of the specialized conduction tissue, the nature of the conduction tissue in the various forms of congenital heart disease became clearer. Through many forums, some form of a segmental and sequential approach to congenital heart disease was adopted by virtually every unit; whereas some adhered to the Boston/Van Praagh approach, others strongly advocated the European approach, but most developed an amalgam that suited the needs of the particular institution.

Imaging of the congenitally malformed heart has continued to evolve, from plain chest radiography, to cardiac fluoroscopy, then to cardiac angiography, and then with axial projections (historical aspects of cardiac angiography documented in reference 11). M-mode echocardiography added somewhat to the ability to study the form and function of the congenitally malformed heart; but cross-sectional echocardiography, with its subsequent applications of Doppler and color flow mapping and now three-dimensional (3-D) reconstruction, revolutionized the diagnostic algorithms applied to the patient with congenital heart disease. Indeed, the mid-1980s witnessed a dramatic decline in the number of so-designated diagnostic cardiac catheterizations, with imaging and physiologic information provided by cross-sectional imaging. The evolution from transthoracic to transesophageal imaging, and now transabdominal (fetal) imaging, provided even newer dimensions of cardiac imaging. The ability to provide 3-D imaging and tissue characterization has added yet further dimensions to this vital area.

Magnetic resonance imaging (MRI) is now established as an important tool in defining cardiovascular anatomy, physiology, and pathology (33,34 and 35). This technique is being applied in an ever wider spectrum of congenital heart abnormalities and is having a great impact on the management of children with these disorders. Compared with echocardiography, MRI has the advantage of being able to image distant structures, to image through air or bone, to have minimal artifact from most prosthetic materials, and to display images in exact reproducible planes with a wide field of view and 3-D reconstruction. It has several unique features that make it an attractive imaging modality: high natural contrast between flowing blood and the cardiovascular structures, allowing imaging without intravenous contrast, and the ability to display large fields of view in any angled plane without ionizing radiation. The main clinical application of MRI has been in morphologic diagnoses. The role of MRI in cardiac imaging, however, is evolving, with the evaluation of ventricular function, volumes, and mass proving to be highly accurate and reproducible (see Chapter 54). The areas in which MRI has been most useful in congenital cardiovascular disease include central pulmonary artery anomalies, aortic anomalies, complex disease, pulmonary venous anomalies, cardiac masses, and postoperative assessment.

Radionuclide techniques assume an important complementary role in the diagnosis and assessment of pediatric cardiac disorders (33). The major applications of radionuclide imaging in children with cardiac disease include gated blood pool ventriculography, first-pass radionuclide angiocardiography, myocardial perfusion imaging of coronary blood flow, pulmonary scintigraphy, myocardial infarction, and myocardial inflammation detection. Standardized techniques have been developed; with the increasing reliability of these techniques, defined roles in providing both diagnostic and prognostic information have been established. Finally, although we commented earlier on the historical aspects of cardiac angiography in the pediatric population, the introduction of axial angiocardiography virtually revolutionized the approach to the invasive imaging of children (36,37,38,39,40,41 and 42).

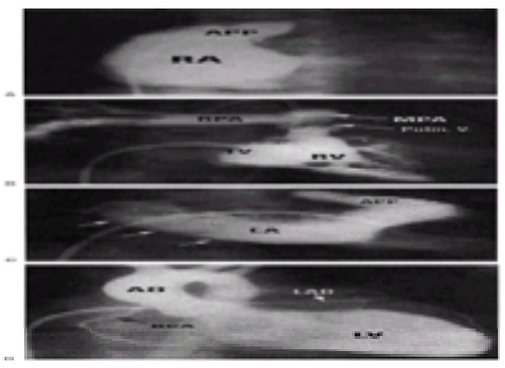
PREVALENCE OF CONGENITAL HEART DISEASE

Congenital heart malformations remain one of the most frequent birth defects, with a liveborn prevalence of approximately 8 per 1,000 liveborn infants in Western countries, where such prevalence data are tracked (43,44,45,46,47,48,49 and 50). Since the introduction of fetal echocardiography almost 20 years ago, fetal surveillance from numerous centers indicates that among some forms of congenitally malformed hearts, there is increased fetal death (50). Thus, for certain congenital heart malformations, the liveborn prevalence is lower than the fetal prevalence. Furthermore, prevalence data may be defined differently, depending on the methodology of recruitment, and data derived from an infant population may differ from a somewhat older population; in the latter, more minor forms of congenital heart disease are ascertained. The surveillance of a population beyond the infant group also may detect those abnormalities, often serious, that do not present invariably in the neonate or young infant, for example, the divided left atrium, so-called cor triatriatum, or coarctation of the aorta. A large number of studies have now been published addressing the prevalence of congenital heart disease from the United States, Canada, Great Britain, Europe, and Japan (literature annotated in references 43, 49, and 50). Clearly, differences between these studies exist, reflecting both the methods used to ascertain the specific type of heart disease and the ability to recruit all autopsy data.

Hoffman prepared a comprehensive overview of both the prenatal and postnatal incidence of congenital heart disease and those factors considered etiologic (49,50). Clearly, the incidence of congenital heart disease appears to be approximately 1 per 100 liveborn infants, but among infants dying before term, the incidence of congenital heart disease, particularly the more complex conditions, is considerably higher. The prenatal incidence ranges from 0.5% to 39.5% (median, approximately 7.9%). Many, but not all, of the fetuses dying of congenital heart disease have associated gross chromosomal abnormalities. Hook, cited in the Hoffman review, found that 39.9% of spontaneous abortions before 28 weeks’ gestation were associated with chromosomal abnormalities; for stillbirths after 28 weeks, the rate was 5.75%; and for all fetal deaths, the rate was 35.8% (50).

CARDIAC NOMENCLATURE: SEGMENTAL AND SEQUENTIAL APPROACH

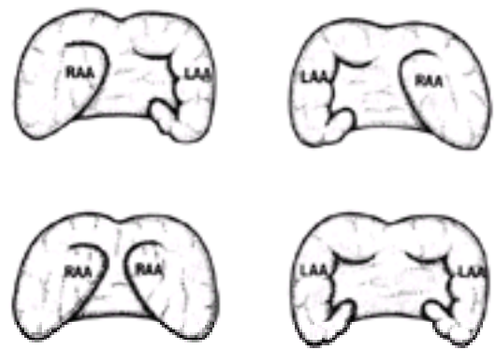
To bring an internal and external consistency to the nomenclature applied to the infinite variety of complex cardiac anomalies, it was self-evident that development of a nomenclature based on cardiac morphology and anatomy and cardiac connections was necessary. The development by Richard Van Praagh of a segmental and, indeed, sequential approach to understanding congenital heart disease, beginning more than 30 years ago, set the stage for a more universal language for persons caring for children who have congenitally malformed hearts (51,52,53,54,55,56,57,58 and 59). The major contribution of Van Praagh was to conceptualize the heart in terms of specific anatomic building blocks that could be connected into a single anatomic and functional unit (*e*Fig. 30.0.1). The building blocks were defined by their specific morphologic characteristics, not by their right or left orientation. Others using the same anatomic cardiac building blocks placed the emphasis of the nosology on the connections between the various segments. Instrumental in espousing the connections approach was Anderson of the United Kingdom (60,61 and 62).



***e*FIGURE 30.0.1** Segmental anatomy. **A:** Normal right atrial appendage (RA APP) with its blunt shape and wide ostium. **B:** Coarsely trabeculated morphologically right ventricle (RV). **C:** Typical morphologically left atrial appendage (LA APP). **D:** Smooth-walled morphologically left ventricle (LV). AO, aorta; LAD, left anterior descending; MPA, main pulmonary artery; Pulm. V., pulmonary vein; RCA, right coronary artery; RPA, right pulmonary artery; TV, tricuspid valve. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Cardiac Segments

The three cardiac segments are (a) the atria, (b) the ventricles, and (c) the great arteries (25,51,52 and 53,60,63,64,65 and 66) (*e*Fig. 30.0.1 and *e*Fig. 30.0.2). The atria and ventricles are connected by or at the atrioventricular junction, and the ventricles and great arteries are connected by the infundibulum, or conus.



***e*FIGURE 30.0.2** Segmental analysis: types of atrial situs. *Top left*: Atrial situs solitus; *top right*: atrial situs inversus; *bottom left*: so-called isomerism of right atrial appendage (RAA); *bottom right*: so-called isomerism of left atrial appendage (LAA). (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Atria

The normal atrial arrangement is characterized by a morphologically right atrium to the right and a morphologically left atrium to the left (51,52 and 53,60,63,64,65 and 66) (*e*Fig. 30.0.1). In the healthy heart, the right-sided morphologically right atrium has a broad, triangular atrial appendage with a wide connection at its junction with the smooth-walled atrium. The morphologically right atrium has a conspicuous crista terminalis, or terminal crest, and the right atrium normally receives the superior and inferior caval veins and the coronary sinus. In contrast, the left atrial appendage is thin, hooked, often crenelated, with a narrow junction with the morphologically left atrium. The normal right atrial appendage is remarkably consistent in position. The normal left-sided, morphologically left atrium receives the pulmonary veins, and its atrial appendage is not guarded by a terminal crest. Atrial situs inversus is the inverse arrangement of the aforementioned. Because of the many anomalies of systemic and pulmonary venous connections and because of the large defects of the atrial septum so common to many complex forms of congenital heart disease, most agree that the character of the atrial appendage is the best arbiter of the atrium as morphologically right or left, not atrial septal morphology or the specific systemic or pulmonary venous connections. In one group of hearts, often exhibiting complex anomalies, the atria are morphologically incompletely lateralized, or at least seemingly so (67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83 and 84). Such hearts with incompletely lateralized atria frequently coexist with splenic anomalies. Three types of atrial situs must be considered: (a) atrial situs solitus or the normal atrial relationship; (b) atrial situs inversus or the inverse normal or mirror image of the normal atrial relationship; or (c) ambiguous or isomeric atria, typically found in patients with visceral symmetry. Splenic anomalies, including asplenia or polysplenia as well as other splenic anomalies, are commonly, but not universally, found in patients with an ambiguous or isomeric atrial situs. The initial task in any segmental and sequential approach to the definition of congenital heart disease is definition of the atrial situs.

Without resorting to anatomic inspection, cardiac angiography, or cross-sectional echocardiography, both electrocardiography and the abdominal chest radiography provide some clues as to the determination of atrial situs (51,63,64,65 and 66,85,86,87,88,89,90,91,92,93,94,95,96,97,98 and 99). Normally lateralized atria, and, thus, by assumption, a normally positioned sinoatrial node, are suggested by a positive P wave in leads I, II, III, aV_L, and aV_F, but negative in aV_R in the standard surface electrocardiogram. Conversely, when the P-wave deflection is positive in leads I, II, III, aV_R, and aV_F, but negative in aV_L, this suggests inverted normal atria and would be consistent with inversus of the atria. A leftward and superior P-wave axis has been found in a substantial number of patients with left atrial isomerism, suggesting abnormal morphogenesis of the sinoatrial node. The hepatic and gastric shadows on the plain frontal chest radiograph also may provide evidence as to atrial localization. The presumption here is that viscerovenous right atrial concordance is present. A hepatic shadow lateralized to the right upper quadrant of the abdomen and a gastric air shadow or nasogastric tube in the left upper quadrant are consistent with solitus normal viscera and, by inference, a right-sided inferior cava vein and right-sided morphologically right atrium. There are, of course, exceptions, including isolated dextrocardia and the reality that the determination of visceral and, by deduction, atrial situs from the chest and abdominal radiograph is inaccurate and that hepatoatrial dissociation leads to an erroneous conclusion about situs. Isolated atrial inversion in either situs solitus or inversus is a rare congenital cardiac anomaly (99,100 and 101). In a healthy population with atrial situs solitus and levocardia, the left hemidiaphragm is at a lower position than the right hemidiaphragm. The widespread view is that the liver is responsible for the higher position of the right diaphragm, not the left-sided cardiac apex. Reddy and colleagues challenged this view and concluded that the cardiac mass determines the caudal displacement and lower position of the related hemidiaphragm (96). A midline horizontal liver in a patient with congenital heart disease is consistent with incompletely lateralized viscera and, by inference, nonlateralized atria as well. A midline horizontal liver in a cyanotic baby is considered ominous, raising the specter of complex cardiac disease associated with right atrial isomerism and asplenia (63,64,65 and 66,85,86 and 87) (*e*Fig. 30.0.3). Levocardia with apparent situs inversus of the abdominal viscera in a cyanotic neonate also should provoke concern about the gravity of congenital heart disease. Indirect determination of atrial situs can be inferred from the disposition of the tracheobronchial tree imaged from either the plain chest radiograph or high kilovoltage filtered films. The cross-sectional echocardiogram is certainly diagnostic of the venous connections to the atria, and even the character of the atrial appendages can be imaged, thus defining with some degree of accuracy the atrial situs. Recognition of azygous drainage of the inferior cava vein with connection of the hepatic veins directly to the atrium is highly suggestive of left atrial isomerism, often with multiple spleens (*e*Fig. 30.0.4 and *e*Fig. 30.0.5). Similarly, cross-sectional recognition of the unusual topography of the aorta and inferior caval vein with both on the same side of the vertebral column is highly suggestive of right atrial isomerism (98).

***e*FIGURE 30.0.3** Hepatic symmetry in a patient with visceroatrial heterotaxia. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

***e*FIGURE 30.0.4** Multiple spleens in a patient with left atrial isomerism. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing 1997, with permission.)

***e*FIGURE 30.0.5** Azygous continuation of the inferior caval vein in a patient with left atrial isomerism (*arrows*). (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Ventricles

Although there is unanimity of opinion as to what constitutes an atrium and a great artery, there is less agreement as to what constitutes a ventricle (52,54,60). The ventricular mass extends from the atrioventricular junction to the ventriculoarterial junction, and in the healthy heart, there are two distinct ventricles: the morphologically right and the morphologically left; about this, there is consensus. The disharmony, even today, concerns what constitutes a ventricle. Is the morphologically right ventricle a bipartite structure, composed of confluent sinus or body portion and an infundibular portion? Or is it tripartite, with confluent inlet, apical trabecular, and outlet components? Van Praagh advocates a bipartite perspective, whereas Anderson and others, advocating the position of Goor, support the view of the ventricle as a tripartite structure (52,54,60,102,103). What confers “rightness” or “leftness” to a ventricle is the character of the mural trabecular component, as there are so many variations of the ventricular inlets and outlets that it mutes their utility in ventricular designation. It is the coarse trabecular component that confers rightness to the ventricle, and the smooth mural myocardium confers leftness (10) (eFig. 30.0.1).

Great Arteries

The great arteries are rarely so malformed as to make identification difficult. The normal aorta is the arterial trunk that gives origin to the coronary and systemic arteries. The pulmonary trunk supports the right and left pulmonary arteries. Among some malformed hearts, a single common arterial trunk gives origin to coronary, pulmonary, and systemic arteries. Rarely, three great arteries have been identified originating from the base of the heart (104).

Types of Atrioventricular Connection

Anderson et al. differentiate the type of atrioventricular connection from the mode of connection (60,61). The type of atrioventricular connection indicates only how the atria are connected to the ventricles (i.e., concordant, discordant, or ambiguous) (60,61,64,65 and 66). The mode refers more specifically to the morphology of the valves at the atrioventricular junction. Three types of atrioventricular connections when the heart is biventricular can be defined: (a) concordant atrioventricular connection, (b) discordant atrioventricular connection, and (c) ambiguous atrioventricular connection. A concordant atrioventricular connection indicates that the morphologically right atrium connects to a morphologically right ventricle and the left atrium to a morphologically left ventricle. The atrioventricular connection is discordant when the morphologically right atrium connects to a morphologically left ventricle via a mitral valve and the left atrium to a morphologically right ventricle through a tricuspid valve. In hearts where the atria are not lateralized, the atrioventricular connection is by definition ambiguous. One of the areas in which Van Praagh and Anderson and their respective colleagues continue to differ is in the nomenclature applied to those hearts considered by Van Praagh et al. (59) as single ventricle. Anderson et al. (105) use the designation *univentricular atrioventricular connection* when one atrioventricular connection is absent; when both atria are connected to one ventricle, they advocate the designation *double-inlet ventricle*. Hearts with a univentricular atrioventricular connection may have a double-inlet connection or an absent right or left atrioventricular connection. The ventricular morphology receiving the atrioventricular connection may be that of a dominant left ventricle, a morphologically right ventricle, or a solitary ventricle, usually of indeterminate morphology. Abnormalities of the mode of atrioventricular connection include perforate versus imperforate atrioventricular valves, a common atrioventricular orifice, an unguarded atrioventricular orifice, and a straddling or overriding atrioventricular valve. A straddling atrioventricular valve designates one whose tension apparatus is attached to both sides of the interventricular septum. The extent of straddling can vary from mild to severe, and recognition of the presence and severity of straddling affects the choice of a biventricular repair versus atriopulmonary connection with atrial separation (Fontan operation).

Ventriculoarterial Connection

Using the same conventions as defining the type and mode of atrioventricular connection, the type and mode of ventriculoarterial connection can be characterized. The four types of ventriculoarterial connections include (a) concordant or normal ventriculoarterial connection, (b) discordant ventriculoarterial connection, (c) double-outlet ventriculoarterial connection, and (d) single-outlet ventriculoarterial connection. When the ventriculoarterial connection is concordant, the morphologically right ventricle supports the pulmonary trunk, and the morphologically left ventricle supports the aorta. A discordant ventriculoarterial connection defines that connection in which the aorta is supported by the morphologically right ventricle and the pulmonary trunk by the morphologically left ventricle. The more common designation for this type of ventriculoarterial connection is *transposition of the great arteries. Double-outlet ventricle* indicates that more than half of each great artery has its origin from one ventricle, be it right or left, dominant or rudimentary, or indeterminate. Examples of single outlet include hearts with truncus arteriosus, single pulmonary trunk with aortic atresia, and single aortic trunk with pulmonary atresia. In the nomenclature of single outlet of the heart, it is important to state the ventricular origin of the solitary trunk: left or right ventricle, indeterminate ventricle, or a biventricular origin.

Infundibular Anatomy

Four types of infundibular anatomy have been described: (a) subpulmonary infundibulum, (b) subaortic infundibulum, (c) bilaterally present infundibulum, and (d) bilaterally deficient infundibulum. The solitus normal heart has a well-defined subpulmonary infundibulum, whereas the subaortic infundibulum is severely attenuated (*e*Fig. 30.0.1). This attenuation of the left-sided infundibulum brings the aortic valve into fibrous continuity with the mitral valve. The neonate with complete transposition in isolation has a well-defined subaortic infundibulum that connects the transposed aorta to the morphologically right ventricle. Some patients with complex forms of transposition have a bilaterally well-expanded infundibulum, and in such hearts semilunar valves and atrioventricular valves are not in fibrous continuity. Rarely, some hearts with transposition of the great arteries have a bilaterally deficient infundibulum in which there is the potential for fibrous continuity between both semilunar and both atrioventricular valves. These morphologic observations illustrate the reality of differential conal growth and absorption and the spectrum of normal aortic-mitral fibrous continuity. The infundibulum of the heart is responsible in part for the anterior-posterior disposition of the great arteries relative to one another; also, infundibular development, or lack thereof, is responsible for discontinuity or continuity between semilunar valve and atrioventricular valve. Anderson and colleagues (105) reserve the term *crista supraventricularis* for healthy hearts or hearts with a normally connected and structured right ventricular outflow tract. For hearts with complex anatomy, it is useful to view the supraventricular crest in terms of its morphologic components: (a) the ventriculoinfundibular fold, (b) the infundibular septum, and (c) the septomarginal trabecula. The ventriculoinfundibular fold is derived from the inner curvature of the heart tube; this structure separates a semilunar valve from an atrioventricular valve. The infundibular septum is a muscular structure that separates the arterial outlets. It is this structure whose anterosuperior deviation is the essence of Fallot’s tetralogy; whose posterior malalignment or displacement produces in the patient with atrioventricular and ventriculoarterial concordance a particular type of muscular subaortic stenosis with the ventricular septal defect inferior to the malaligned infundibular septum. In the patient with atrioventricular concordance, but discordant ventriculoarterial connections, posterior displacement of the infundibular septum produces subpulmonary stenosis, whereas anterior displacement results in subaortic stenosis. The infundibular septum is usually a septal structure but not invariably. Finally, the septomarginal trabecula is an intrinsic component of the right ventricular septal surface, and this structure does not dissociate from the morphologically right ventricle.

Arterial Relationships

The spatial relationships between the aorta and pulmonary artery show a continuum of right-left and anteroposterior coordinates. An extensive literature demonstrates that spatial relationships between the great arteries, although important, are not predictive of the intracardiac anatomy.

Heart Positions

Levocardia indicates a heart predominantly in the left chest with the apex to the left. Dextrocardia indicates a right-sided heart with the cardiac apex pointing to the right. A midline heart is designated *mesocardia*. A rare type of cardiac malposition is ectopia cordis. Rarely, despite a heart predominantly in the left chest, the apex of

the ventricle points to the right (66).

Cardiac Malpositions

The cardiac malpositions include dextrocardia, isolated levocardia, mesocardia, thoracopagi, and ectopia cordis.

GENETICS OF CONGENITAL HEART DISEASE

Despite incredible advances in the diagnosis and treatment of congenital malformations of the heart, surprisingly little progress has been made in our understanding of the etiology of the defects presented at birth, perhaps in large part because of the severe penalty imposed on a person with congenital heart disease. In many instances, the malformation is lethal to the developing fetus because the cardiovascular system must remain functional during organogenesis, and, until relatively recently, persons born with significant defects of the heart have not attained a fitness to reproduce. This evolutionary disadvantage also seems to be evident across species, as evidenced by the paucity of animal models for many types of congenital heart diseases. It seems apparent that the embryology of the normal heart is under a genetic influence and reliability of its control preserved; however, our understanding of the mechanisms involved in normal cardiovascular embryology remains in its infancy. Decades of anatomic and physiologic information have resulted in classifications of congenital heart disease that are morphologically and pathophysiologically oriented rather than being focused on pathogenesis. Hence, when there is an error in the geometric morphology and topology of the heart, it is difficult to explain recurrence of not only the same lesion, but also of different lesions in subsequent generations. Perhaps in frustration we refer to a *multifactorial etiology* that bears a recurrence risk of 3% to 5%. New investigations may lead to more precise counseling (106,107).

Genetic investigation as it relates to clinical medicine can take several forms. Familiar to all is the epidemiologic observation of the syndrome that clusters individual persons with like features. Perhaps one of the best examples is that of Down syndrome, which was first described in terms of persons with like features. Our understanding grew with the acquisition of techniques to resolve gross abnormalities of chromosomes, which, when refined, allowed a better explanation of recurrence that depended on the type of chromosomal abnormality present in the affected child and parents. To further cloud the issue, familial clustering of related conditions suggesting a genetic influence is tempered by like sociologic influences.

Clinical genetic analysis uses the meticulous analysis of pedigree and mathematics to arrive at a model of inheritance (108,109,110 and 111). Chromosomal abnormalities describe a morphologic problem in genetic anatomy but do not describe pathogenetic mechanisms by which aneuploidy results in the associated cardiovascular features (eTable 30.0.1). Mendelian studies attempt to develop a mathematical model to relate single genes and clusters of genes to a condition. The lethality of malformations of the heart as described previously favors the presence of codominant, recessive, or deletion of genes owing to the reproductive disadvantage described previously.

***e*TABLE 30.0.1** GENETIC INFLUENCES IN CONGENITAL HEART DISEASE

Chromosomal abnormality	**Most common congenital heart lesion**
Aneuploidy	
Trisomy 21	Atrioventricular septal defect, VSD, ASD, PDA, TOF
Trisomy 18	VSD, PDA, double-outlet right ventricle
Trisomy 13	VSD, ASD, PDA
Trisomy 22	PS, VSD, ASD, PDA, TrAtr
Partial trisomy 22 (cat-eye syndrome)	TAPVD, TOF, VSD, TrAtr
4p- (Wolff's syndrome)	ASD, VSD, PDA, AoAtr
5p- (cri-du-chat)	VSD, ASD, PDA
XO (Turner's)	CoA, AS, HLHS
XXY (Klinefelter's)	TOF, VSD, PDA, MVP
13q-	VSD
18q-	VSD
XXXXY	PDA, ASD
Mendelian "recessive" conditions	
Alkaptonuria	Valvar disease
Carpenter's	PDA
Conradi's	VSD, PDA
Cockayne's	Atherosclerosis
Cutis laxa	PPS, pulmonary hypertension
Duchenne's and Dreifuss's muscular	Cardiomyopathy dystrophy (XLR)
Ellis-van Creveld	ASD and other coronary heart disease
Friedreich's ataxia	Cardiomyopathy
Glycogen storage disease (IIa, IIIa, and IV)	Cardiomyopathy
Homocystinuria	Coronary thrombosis
Hurler's (MPS I), also XLR	CAD, AI, MI
Jervell and Lange-Nielsen	Prolonged QT
Laurence-Moon-Biedl	VSD and others
Mucolipidosis III	Aortic valve disease
Scheie's (MPS IS), Morquio's (MPS IV), MPS VI	Aortic valve disease, CAD
Osteogenesis imperfecta	Aortic valve disease
Progeria	Atherosclerosis
Pseudoxanthoma elasticum	CAD, MI, systemic hypertension
Seckel's	VSD, PDA
Smith-Lemli-Opitz	VSD, PDA, others
Thrombocytopenia and absent radius (TAR)	ASD, TOF, dextrocardia
Mendelian dominant/gene monosomy syndromes	
Alpert's	VSD, TOF
Crouzon's	PDA
Catch 22 (deletion 22q11)	Conotruncal abnormalities, IAA, PA, VSD, truncus, DiGeorge
Ehlers-Danlos	Large vessel aneurysm, dissection, rupture
Holt-Oram	ASD, VSD
Hypertrophic cardiomyopathy	Subaortic muscular hypertrophy
Incontinentia pigmenti (XLD)	PDA
LEOPARD	PS, abnormal P waves, increased PR
Marfan (15q21.1)	Defective fibrillin-1: great artery aneurysms, AI, MI
Myotonic dystrophy	Cardiomyopathy
Neurofibromatosis	PS, CoA, pheochromocytoma with hypertension
Noonan's	PS, ASD, idiopathic hypertrophic subaortic stenosis
Osteogenesis imperfecta	AI
Osler-Weber-Rendu (9q33–34)	Abnormal gene product as yet unknown Hereditary telangiectasia
Romano-Ward	Long QT
Treacher Collins	VSD, PDA, ASD
Tuberous sclerosis	Rhabdomyomata
Williams syndrome, supravalvar aortic stenosis (7q11.23) single gene defect: heterozygous at locus	Defect in elastin synthesis: sporadic but likely related to single gene locus; supravalvar aortic stenosis, renovascular abnormalities

AI, aortic insufficiency; AoAtr, aortic atresia; AS, aortic stenosis; ASD, atrial septal defect; CAD, coronary artery disease; CoA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; MI, mitral insufficiency; MVP, mitral valve prolapse; PA, pulmonary atresia; PDA, patent ductus arteriosus; PPS, peripheral pulmonary stenosis; PS, pulmonary stenosis; TOF, tetralogy of Fallot; TrAtr, tricuspid atresia; VSD, ventricular septal defect.

With further understanding, the information contained in eTable 30.0.1 is presented with an organization that reflects an understanding of genetic influence on pathogenesis. In this light, special mention must be made of the condition known as *catch 22*. Clinicians are familiar with patients who have similar features, as described by DiGeorge, and velocardiofacial syndromes. Genetic investigation demonstrated that patients with catch features (*c*ardiac conotruncal abnormalities, *a*bnormal facies, *t*hymic abnormalities, *c*left palate, *h*ypocalcemia) also share monosomy of one region of chromosome 22 (22q11). The deletion must involve a variety

of genes. It has been noted in persons who do not have all features of the condition (20% to 30% of nonsyndromic patients). Pathogenesis is clouded by the observation that it has been noted in approximately 25% of patients without the syndromic features, and patients may be variably affected by learning disabilities, psychiatric conditions, ocular disorders, respiratory problems, and renal difficulties. The complexity of the language is expressed by the alphabet of the genome and our very basic understanding of its intricate nature. It heralds an exciting emerging cooperation of theoretic, basic, and clinical sciences in advancing our understanding of cardiovascular medicine.

PHYSICAL EXAMINATION OF THE PEDIATRIC PATIENT

Elsewhere in this text, the art of the general cardiac examination is detailed. Most of these general principles are, of course, applicable to the pediatric patient as well. It is perhaps more challenging to examine the very young patient, especially the newborn, neonate, and young infant (112,113). In examining the newborn, it is essential to be cognizant of the mother's pregnancy and medical history (e.g., her illnesses, drug history, history of substance abuse) and the infant's birth weight, gestational age, and Apgar scores. Is the infant's weight appropriate for gestational age? Was the baby a product of a precipitous vaginal delivery or urgent cesarian section because of fetal distress? Should the infant be considered for a disorder of the transitional circulation such as persistent pulmonary hypertension of the newborn or transient myocardial ischemia (114,115,116,117 and 118)?

The very young patient must be examined in a warm, comfortable environment. The examiner's hands and stethoscope should be warm, and the examiner must be patient and gentle. Trying to examine a fussy, crying infant will be frustrating for the examiner, and little will be gained by rushing and carrying out a superficial examination. As with the adult, the examination must be carried out with appropriate room illumination. The infant can be examined in a blanket so as not to become chilled or hypothermic, but the entire infant should be examined, with special attention to the general appearance of the patient because there are so many syndromes associated with congenital heart disease. Trisomy 21; Turner's, Noonan's, Williams, and Marfan syndromes; and trisomies 13 to 15 and 18 are but a few conditions in which the patient's appearance may provide strong clinical evidence of a syndrome or at least physiognomy associated with congenital heart disease. Examination of the skin for café au lait spots, multiple lentigines, multiple cutaneous hemangiomas, and cutis laxa are external clues to internal disorders.

As part of the neonatal cardiovascular examination, the infant's apparent sense of comfort or distress should be noted. Is the infant breathing quietly and in an unlabored way? Is the infant dyspneic, with alar flaring, grunting, or stridor? Does the chest move in a symmetric fashion or is one side less active? Both the pattern and number of respirations per minute are important in the overall evaluation. Are the extremities cool, even when the infant is being examined in an appropriately warm environment, such as the isolette? Is the infant pink or cyanotic? If cyanotic, is the infant generally cyanotic, or are just the extremities involved? It is important to assess the color of the mucous membranes in room air, and if the mucous membranes appear dusky or cyanotic, reexamination with an increase in ambient oxygen is important in establishing a respiratory or cardiac causality. After the physical and cardiac examination, this aspect of the physical examination will be complemented with blood gas analysis in room air and with hyperoxia. It is always important to remember that polycythemia with more than 5 g of reduced hemoglobin causes the infant to appear cyanotic, even in the absence of frank cardiac or respiratory disorders. Is there differential cyanosis? The appearance of a pink upper body and head with relatively "bluer" lower body and lower extremities should raise the specter of a heart with concordant atrioventricular and ventriculoarterial connections but with a severe aortic arch obstruction, such as interruption of the aortic arch. The upper body "sees" blood from the left ventricle, which is reflected in a pink upper body, whereas the lower body below the arterial duct "sees" bluer and less well-oxygenated blood because of right-to-left shunting at ductal level. The infant who has reversed differential cyanosis and a relatively bluer head and upper torso and pinker lower torso and lower extremities might have transposition of the great arteries and right-to-left ductal shunting with an obstructive anomaly of the aortic arch. The perception of differential cyanosis can be confirmed by measuring the oxygen saturation in the right hand and foot.

Careful attention must be paid to the caliber of the arterial pulses in the upper and lower extremities. The infant must be comfortable and lying quietly for the examiner to palpate carefully and consistently the brachial or axillary artery pulses and to assess their caliber or amplitude and symmetry. An important difference between the strength of the pulses in the right arm versus those in the left arm could reflect any of a number of important conditions, including the origin of the artery of the weaker pulse at or below an important obstructive anomaly of the aortic arch. Other reasons for asymmetry between the arterial pulses of the right and left arms include congenital stenosis or atresia or hypoplasia of one of the subclavian arteries or ductal origin of one of the subclavian arteries from the pulmonary artery. With constriction of the arterial duct connecting the pulmonary artery to the subclavian artery, the subclavian artery becomes isolated and the pulse weaker or imperceptible. Examination of the caliber of the femoral pulses in the infant or the pedal pulses in the older child or adult is absolutely essential. Palpation of the femoral pulses must be done gently, and it is important to assess simultaneously the caliber or amplitude of the brachial and femoral pulses. An important difference with weaker and delayed femoral pulses is consistent with an obstructive anomaly of the aortic arch. Diffusely weak and feeble arterial pulses may reflect severe impedance to systemic arterial blood flow, indicative of such conditions as the hypoplastic left heart syndrome, critical aortic stenosis, interruption of the aortic arch with severe subaortic stenosis with or without origin of both subclavian arteries below the level of the interruption, or severe obstruction. Diffusely weak and feeble upper and lower limb arterial pulses in the newborn also may be observed in the patient with overwhelming sepsis and shock, myocarditis, profound anemia reflecting blood loss or twin-to-twin transfusion, or cardiogenic shock. If an infant has had an umbilical artery line, diffusely weaker femoral pulses could indicate thrombosis of the aorta or iliofemoral arterial vessels. Spontaneous thrombosis of the ascending or descending aorta also could account for alterations in the caliber of the arterial pulses. Blood pressures must be recorded in all four limbs with an appropriately sized cuff, ideally using Doppler equipment. Bounding pulses are certainly uncommon in the newborn, but have been described in the conditions characterized by important aortic regurgitation.

Examination of the chest to define symmetry of breath sounds is germane to patients of any age. It is also important to auscultate over the head and gently over the eyes to define the presence of a cranial bruit. The absence of a cranial bruit certainly does not exclude a cerebral arteriovenous fistula, but the presence of a cranial bruit in a newborn with congestive heart failure certainly leads to that consideration. In some infants who have a large vein of Galen cerebral arteriovenous fistula, examination of the upper and lower extremity arterial pulses has suggested an obstructive anomaly of the aortic arch, reflecting the arterial steal to the cerebral circulation. Are the heart sounds best heard over the left or the right chest? Do not assume that a chest radiograph will always be labeled correctly. If the infant has a nasogastric tube in place, where can gastric sound be appreciated best: on the right or the left side of the abdomen? Braudo and Rowe and others (118,119,120 and 121) have discussed fully auscultation of the heart of the newborn and young infant.

Examination of the precordium with gentle palpation may provide important information. Remembering the precordial activity of a normal infant, a forceful left parasternal heave or thrust usually implies a volume- or pressure-loaded morphologically right ventricle (assuming normal cardiac relations). Special attention should be focused on the second heart sound: Is it split or single? Soft systolic heart murmurs are not uncommon in perfectly healthy babies; conversely, the absence of a heart murmur does not preclude life-threatening congenital heart disease. Blowing systolic heart murmurs radiating into both axillae and into the back may be consistent with physiologic pulmonary artery branch stenosis and with the normal remodeling of the contour and geometry of the bifurcation of the main pulmonary trunk into its branches; these murmurs usually disappear after the first weeks of life (119,120,121 and 122). Murmurs of grade 4 intensity are always pathologic; similarly, early diastolic murmurs emanating from the semilunar valves are abnormal. It is distinctly abnormal to appreciate a frankly continuous murmur in the newborn. Even a patent arterial duct is not characterized by a continuous murmur with a conspicuous diastolic component in the hour or 24 to 36 hours after birth. A continuous murmur attributed to a patent arterial duct in the first hours after birth must be differentiated from the to-and-fro murmurs of an absent pulmonary valve, as in the tetralogy of Fallot and absent pulmonary valve complex; the systolic and separate diastolic murmurs appreciated in an infant with a common arterial trunk and a regurgitant truncal valve; or the to-and-fro systolic and diastolic murmurs in the infant with an aorto–left ventricular tunnel. Occasionally, in the infant with complex pulmonary atresia and multiple aortopulmonary collaterals, continuous murmurs emanating from the collateral circulation may be noted. Murmurs of atrioventricular valve regurgitation may be transient, especially in infants who have transient myocardial ischemia of the newborn (117,118).

SCREENING IN DOWN SYNDROME

The association between Down syndrome and congenital heart disease is well known (123,124,125,126,127,128,129 and 130); thus, it is not surprising that the question would be raised of whether routine cardiac screening of children with Down syndrome should be done (131,132,133,134,135,136 and 137). The Committee on Genetics of the American Academy of Pediatrics recommends that patients with Down syndrome have a cardiac evaluation, and this task force has recommended an echocardiographic examination. What constitutes adequate screening for congenital heart disease remains the subject of controversy, however. Rosenberg et al. suggest that careful physical examination combined with an electrocardiogram may be adequate and appropriate cardiovascular screening of the infant or child with Down syndrome, referring the patient to a pediatric cardiologist if either is abnormal (11). In a number of situations, this approach could miss important congenital heart disease, at least important enough to warrant protection against endocarditis at the time invasive procedures that may produce bacteremia are done (129,130). Finally, Geggel et al. (138) documented development of valve dysfunction, mitral valve prolapse, and aortic regurgitation in a cohort of adolescents and young adults with Down syndrome and no known congenital heart disease. Because of these findings, they recommend screening adolescents and young adults with Down syndrome before dental or surgical procedures. Schneider and colleagues found cardiac care in infants with Down syndrome to be comparable with infants without Down syndrome. Down syndrome was present in 114 of 142 (80%) infants aged 1 year with the complete form of atrioventricular septal defect undergoing surgery in their institution (135). When viewed from the reverse perspective, 35% to 40% of patients with Down syndrome have an atrioventricular septal defect, and in most cases it is with a common rather than a partitioned atrioventricular orifice. De Biase and colleagues suggest that there is an increased prevalence of left-sided obstructive lesions in patients with atrioventricular septal defect without Down syndrome (139). Marino and colleagues assessed the prevalence of associated cardiac malformations in a large cohort of patients with atrioventricular septal defect compared with patients without Down syndrome (140,141,142 and 143). Among 220 patients with atrioventricular septal defect, 130 had a complete form of atrioventricular septal defect, 80 had Down syndrome (61.5%), and 50 were without Down syndrome (38.5%). Of the 90 patients who had a partial form of atrioventricular septal defect, 25 (28%) had Down syndrome and 65 (72%) were without Down syndrome. Thus, Down syndrome most commonly was associated with a complete form of atrioventricular septal defect (p <.01), and patients without Down syndrome tended to have the partial form of the defect. Addressing the entire spectrum of associated cardiac malformations in these 220 patients, 112 had a total of 137 associated malformations.

The associated cardiac malformations were found significantly more frequently in patients without Down syndrome. Among patients with Down syndrome and the complete form of atrioventricular septal defect, tetralogy of Fallot was more prevalent. In patients without Down syndrome, the hypoplastic left ventricle and coarctation were more common. Marino et al. (140,141,142,143 and 144) also found that patients without Down syndrome and atrioventricular septal defect have a higher risk of left-sided obstructive lesions. Interestingly, Marino and colleagues (140,141,142,143 and 144) documented the rarity of additional ventricular septal defects in the apical muscular septum of patients with atrioventricular septal defect and Down syndrome.

TIMING OF PRESENTATION OF CONGENITAL HEART DISEASE

Ductal-Dependent Congenital Heart Disease

In infants in whom the pulmonary blood flow is mediated in large part or entirely by a patent arterial duct, clinical presentation with an early appearance of cyanosis in the neonatal period can be expected (145,146). Indeed, for infants with critical pulmonary stenosis or pulmonary atresia, functional closure of the arterial duct results in progressive arterial hypoxemia; and if this condition is not treated, relentless metabolic acidosis, hyperkalemia, and death ensue (147). Similarly, in some infants the entirety of the systemic blood flow requires patency of the arterial duct; these infants have the hypoplastic left heart syndrome (148). Thus, it is not surprising that babies with the hypoplastic left heart syndrome usually present within the first hours or days after birth with features of low cardiac output and a progressive and intractable metabolic acidosis, resulting in death unless medical or surgical intervention occurs. Infants who have a profound aortic arch obstruction, including coarctation of the aorta, aortic arch atresia, or aortic arch interruption, also should be anticipated to have an early clinical presentation, again within hours or days after birth coincident with ductal closure (149). A similarly early clinical presentation is seen in infants with critical aortic stenosis, in whom much of the systemic circulation requires patency of the arterial duct (150).

Hearts with “Transposition” Physiology

A group of hearts is characterized by a discordant connection at either the atrioventricular or ventriculoarterial level (151). This single discordance results in cardiac physiology characterized by two parallel circulations (151,152 and 153). By far the most common of these so-called single discordance connections is the patient with complete transposition of the great arteries. The hearts of these patients are characterized by atrioventricular concordance and ventriculoarterial discordance. Approximately 66% to 70% of all patients with complete transposition of the great arteries have an intact ventricular septum, or nearly so (151), and 15% to 20% have a moderate to large ventricular septal defect; 10% have a large ventricular septal defect and important left ventricular outflow tract obstruction; and 5% have important left ventricular outflow tract obstruction and an intact ventricular septum. The hallmark of the circulation in the patient with complete transposition of the great arteries is the presence of two parallel circulations with a systemic and a pulmonary circulation (152,153). Survival for even a short time in infants who have an intact ventricular septum requires mixing between the two circulations at the atrial or ductal level. At the time of birth, and with the normal expansion of the lungs, the flap of the ovale foramen tends to limit any significant mixing at the atrial level, and with normal maturation of the arterial duct to functional and then anatomic closure, it is not surprising that most of these infants present within hours or a few days after birth with increasingly severe hypoxemia. In fact, we have seen infants with transposition of the great arteries dying within minutes of birth, some of whom were recognized antenatally as having premature constriction or closure of the arterial duct. The calculated pulmonary blood flow in an infant with transposition of the great arteries and an intact ventricular septum is high; thus, the chest radiograph of the baby with transposition of the great arteries shows normal to increased pulmonary blood flow, whereas in infants with a ductal-dependent pulmonary circulation, one would anticipate the chest radiograph to show frank pulmonary oligemia. From these clinical observations, it is evident that the systemic arterial oxygenation in an infant with transposition of the great arteries does not correlate with pulmonary blood flow, but rather with effective pulmonary blood flow. The effective pulmonary blood flow measures the amount of systemic venous return that is conducted into the pulmonary arteries and the pulmonary veins (152,153).

Hearts with Obstructed Pulmonary Venous Connections

The most common conditions primarily promoting severe obstruction of all the pulmonary veins are the conditions characterized by bilaterally total anomalous pulmonary venous connections (TAPVC) with severe obstruction (154,155). The usual morphologic expression of bilaterally TAPVCs is a confluence of all pulmonary veins behind the left atrium connecting to a systemic vein. The most common form occurs when confluence of the pulmonary veins is connected with a descending vein coursing through the diaphragm to join the ductus venosus, portal vein, hepatic vein, or left gastric vein. These babies all have severe hypoxemia with profoundly edematous lungs. The pulmonary venous obstruction is so egregious that many of these patients have pulmonary lymphangiectasia (154,155). Although infradiaphragmatic TAPVCs are invariably obstructed, severe obstruction also has been identified in patients with supracardiac connections to the left brachiocephalic vein, to the azygous vein, or to the right superior vena cava. A restrictive atrial septal defect also may promote obstruction in some patients when the actual connection to the systemic venous circulation is not particularly obstructed. A subdivided left atrium or cor triatriatum sinistrum may promote severe impedance to pulmonary venous blood flow, but rarely presents in the newborn period and, in fact, uncommonly presents in isolation at the end of the first month of life. Pulmonary venous obstruction may be particularly severe in infants with the hypoplastic left heart syndrome with a nearly intact atrial septum or premature closure of the foramen ovale. Indeed, it is in the setting of profound left-sided heart hypoplasia that a subdivided left atrium occasionally can be identified. Infants with right atrial isomerism also may have profoundly deranged pulmonary venous connections with severe obstruction (156,157). Not infrequently, the radiographic appearance of pulmonary venous obstruction is masked by the pulmonary outflow tract obstruction that so frequently coexists in these patients.

Miscellaneous Conditions Presenting in the Neonatal Period

Other conditions that certainly can present in the newborn and neonatal period are massive arteriovenous fistulae and severe atrioventricular valve regurgitation (e.g., Ebstein’s anomaly of the tricuspid valve and severe atrioventricular valve regurgitation in the patient with atrioventricular septal defect) (158,159). Common arterial trunk can certainly present early, and the subgroup with a particularly dysfunctional truncal valve (either obstructive or regurgitant) should be anticipated to have an even earlier presentation. Similarly, infants who have complete heart block and a low heart rate and those with supraventricular tachycardia, myocarditis, or other forms of myocardial disease may present in the first days after birth (160).

Presentation at 1 to 3 Months of Age

Infants with large pulmonary blood flow and pulmonary hypertension often present at the end of the first month of life, coincident with remodeling of the pulmonary arterial bed (158,159). Thus, one could anticipate the presentation of the infant with a large ventricular septal defect, atrioventricular septal defect, patent arterial duct, aortopulmonary window, nonobstructed total anomalous pulmonary venous return, common arterial trunk, single ventricle complex, and others. Some infants with obstructive lesions of the right or left side of the heart also present in this period.

Presentation beyond Infancy

Patients with mild to moderate stenosis of a semilunar valve, a bicuspid aortic valve, a restrictive ventricular septal defect, a partial form of atrioventricular septal defect or ostium primum atrial septal defect, a small patent arterial duct, a secundum atrial septal defect, or mild coarctation of the aorta may present with a heart murmur. Infants with these conditions would not be expected to present in heart failure. Rather, it is the presence of a heart murmur considered organic in an otherwise asymptomatic child that raises the specter of congenital heart disease.

ROLE OF AN E-TYPE PROSTAGLANDIN

In 1976, at the Toronto Hospital for Sick Children, Olley et al. (161) documented a unique and novel way to promote and maintain patency of the arterial duct: administration of an E-type prostaglandin. This application revolutionized care of the patient with ductal-dependent congenital heart disease. For infants who are dangerously hypoxemic and have a progressive metabolic acidosis, prostanoid therapy by dilating a severely narrowed or functionally closed arterial duct dramatically improves oxygenation, alleviating the metabolic acidosis as well. In infants with profound obstruction to systemic blood flow, prostanoid therapy improves cardiac output and oxygen delivery to the tissues.

The administration of prostaglandin, by dilating the arterial duct, augments blood flow to the left atrium and thereby increases mixing at that level in the patient with transposition of the great arteries. If the atrial defect is restrictive or intact, prostaglandin therapy may result in pulmonary edema by increasing pulmonary blood flow and left atrial return. In some conditions, of course, prostaglandin does not have its desired effect, as in infants in whom the arterial duct is congenitally absent or anatomically closed (162,163). By virtue of its pulmonary vasodilating effect, however, even when the arterial duct is congenitally absent or anatomically closed, some infants seemingly improve in the degree of hypoxemia (164,165). This effect is usually quite modest and transient. In some instances, a prostaglandin challenge is advisable to unmask obstructed TAPVCs in patients with right atrial isomerism (166).

Debate as to the histopathologic effect of prostanoids on the arterial duct has been ongoing (167,168,169,170 and 171). Hemorrhage and lacerations have been found in the arterial duct after prostanoid administration, but similar changes have been observed in the closing duct in the absence of prostanoid therapy. Cortical hyperostosis is a well-known complication of prolonged prostanoid administration. In addition, gastric outlet obstruction reflecting antral mucosal hyperplasia is a

complication of prolonged prostaglandin administration (172).

PULMONARY HTN IN THE NEWBORN

The fetal circulation is characterized by using the placenta as the organ of respiration. The ductus venosus allows half of the placental return to bypass the hepatic circulation and enter the inferior vena cava directly. This inferior caval flow then is directed to the left atrium via the foramen ovale. In contrast, blood returning to the heart via the superior vena cava is directed to the right ventricle, illustrating the physiologic phenomenon of advantageous streaming that can occur when blood is incompletely mixed. Blood exiting the right ventricle can enter either the systemic or pulmonary circulation as a result of the presence of the arterial duct. As the pulmonary circulation maintains a high resistance in the relative hypoxemia of the fetus and the systemic vascular resistance is low as a result of the low resistance of the placenta, approximately 90% of the blood leaving the right ventricle flows to the systemic circulation. The result from a systemic standpoint is that the postductal systemic circulation directed to the placenta receives blood that is less well oxygenated than the preductal circulation, including the coronary circulation.

The transition from intrauterine to extrauterine life represents a phenomenal example of adaptive physiology. Within minutes, the systemic vascular resistance increases because of loss of the placenta. As a result, baroreceptors decrease the heart rate. Newly inspired oxygen dilates the pulmonary vascular bed and results in increased pulmonary blood flow. The increased pulmonary venous return functionally closes the foramen ovale and also results in increased left ventricular output. With a decrease in the pulmonary vascular resistance and closure of the ductus arteriosus, right ventricular pressure also falls, within 2 to 3 days in most instances, but sometimes as long as 7 days. The neonatal circulation thus differs from that of the older infant in the ability to shunt right to left across the foramen ovale, in the ability to shunt across the ductus arteriosus, and in the presence of right ventricular hypertrophy. In addition, the pulmonary vascular bed is reactive to hypoxemia and acidemia. The neonate, however, is more tolerant of hypoxemia.

A useful clinical test is the hyperoxic test. Administration of 100% oxygen overcomes alveolar hypoventilation and to some degree offers improvement in the setting of ventilation-perfusion mismatch. The PO_2 is measured both preductally and postductally. Subsequently, 100% oxygen is administered and the PO_2 repeated. Both regions must have a PO_2 greater than 150 mm Hg to “pass” the test. The test is also useful for formally documenting differential cyanosis.

Persistent pulmonary hypertension of the newborn is a feature or consequence, not a specific diagnosis. It can result secondary to lesions of other systems or as a primary problem. Pulmonary venous hypertension due to venous atrial and mitral valve abnormalities and poor left ventricular diastolic function can be due to congenital heart lesions or transient in the setting of a healthy heart. Hyperviscosity associated with polycythemia represents a familiar cause of pulmonary hypertension. Primary and secondary pulmonary hypoplasia also may result in pulmonary hypertension. Lastly, cyanosis can be the result of pulmonary vasoconstriction due to the persistence of the ductus arteriosus with right-to-left shunt in the setting of persistent fetal circulation, secondary to pulmonary disease, and due to premature closure of the arterial duct.

PERSISTENT FETAL CIRCULATION

The condition of persistent fetal circulation describes a setting of persistent pulmonary hypertension of the newborn characterized, as the name suggests, by a maintenance of fetal hemodynamics. The pulmonary vascular bed remains vasoconstricted with profound cyanosis resulting from right-to-left shunts at the level of the foramen ovale and the ductus arteriosus. In most instances, the neonate is born at term, often with a history of perinatal hypoxia. The clinical examination may reveal only silent cyanosis; however, often a murmur of tricuspid insufficiency is present. The electrocardiogram reflects right ventricular hypertrophy, but is not diagnostic. Chest radiography reveals a normal heart size if ventricular function is preserved, and the vascular markings may be increased or decreased depending on the amount of blood flow and edema related to ventricular dysfunction and again is not diagnostic. In general, the patient fails the hyperoxic test and may exhibit differential cyanosis with decreased PO_2 noted in the lower extremities due to right-to-left shunt across the arterial duct. Patients must be distinguished from those with ventricular dysfunction and other silent causes of cyanosis, including transposition of the great vessels and total anomalous pulmonary venous return.

Treatment is generally supportive until the condition resolves by approximately 1 week of age. The neonate is kept well oxygenated and hyperventilated. Mechanical ventilation may include the use of high-frequency oscillation in an effort to decrease pulmonary barotrauma while removing CO_2 (173). Alkalemia is encouraged by administering bicarbonate in addition to the hyperventilation. Associated hypoglycemia and hypoxemia must be watched and treated carefully. Ventricular dysfunction may require inotropic support, recognizing that many agents also result in further pulmonary vasoconstriction. Selective pulmonary vasodilation is difficult to achieve because most also result in systemic hypotension due to systemic effects. The use of nitric oxide in this condition is being considered carefully by many investigators (174,175,176,177 and 178). In desperation, extracorporeal membrane oxygenation (179,180) can be used to support the young neonate while the problem resolves spontaneously.

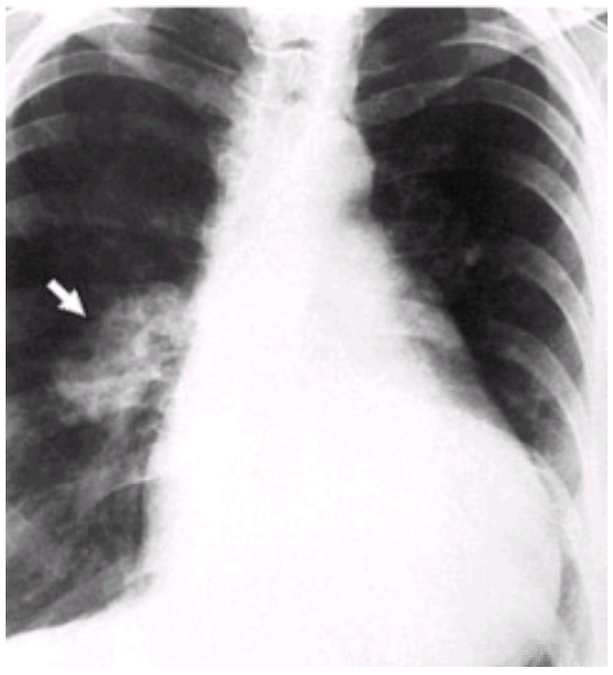
NATURAL HISTORY OF CONGENITAL HEART DISEASE

Ventricular Septal Defect

One of the difficulties and perhaps confounding aspects of the natural history studies of ventricular septal defect is that most do not distinguish between the various types of ventricular septal defects (181,182 and 183). Clearly, different events would be anticipated in patients with a perimembranous ventricular septal defect compared with a doubly committed or juxtaarterial defect or a midtrabecular muscular ventricular septal defect (184).

Acquisition of right ventricular outflow tract obstruction is a well-known phenomenon in the patient with a ventricular septal defect. The incidence of this occurrence has been reported to be 2% to 7%, and the inference of most of these studies is that the ventricular septal defect is perimembranous in position (183,184). Data on the incidence of acquired right ventricular outflow tract obstruction when the defect is muscular are limited. Most patients with a small or restrictive ventricular septal defect demonstrate spontaneous reduction in size of the defect or closure. In addition, spontaneous closure or significant diminution in size is so uncommon that surgical intervention is indicated for patients with a large ventricular septal defect, pulmonary artery hypertension, and an Rp/Rs (ratio of pulmonary to systemic vascular resistance) less than 0.7.

Probably 70% to 80% of all patients born with a ventricular septal defect have a restrictive or small defect, and most should be anticipated to become smaller or close (185,186 and 187). Of those identified in infancy with a moderate-sized ventricular septal defect, approximately 40% to 50% show some spontaneous reduction in size, with reduction of the often substantial left-to-right shunt and normalization of the modestly elevated pulmonary artery pressures. Patients with a large, nonrestrictive ventricular septal defect should not be expected to show spontaneous improvement on the basis of spontaneous reduction in size of the defect (181,182,183,184 and 185). Clinical improvement in such patients could reflect the development of pulmonary outflow tract obstruction, aortic valve prolapse with partial occlusion of the defect, or the development of pulmonary vascular obstruction.



Chest x-ray in patient with a congenital ventricular septal defect. There is fullness in the hilum secondary to an enlarged pulmonary artery (*white arrow*).

Pulmonary Stenosis

The mode of intervention for severe pulmonary valvular stenosis has changed from an operative one to a transcatheter methodology (181,182). Patients with mild or trivial pulmonary stenosis with a catheter gradient less than 25 mm Hg do not require surgery, and almost no significant progression is observed. Some patients with more moderate disease and who are initially treated medically do have a progression in severity, requiring intervention. The Joint Study on Natural History of Congenital Heart Defects recommends that patients with moderate disease do better in the long term with intervention, preferably valvuloplasty. Again, patients with severe obstruction require intervention.

Aortic Valve Stenosis

As with patients with isolated pulmonary valvular stenosis, those identified with severe disease are treated surgically, and those with mild to moderate obstruction tend to worsen (181,182,184,188). Of concern is the observation that many patients with initially mild or moderate obstruction who do not have regular cardiology follow-up are found on reexamination to have developed severe obstruction, not infrequently accompanied by myocardial ischemia (182).

Atrial Septal Defect

The natural history of the large secundum atrial septal defect has been defined, and there is little discussion that such a defect requires closure in childhood or later, assuming that there is no fixed pulmonary vascular obstructive disease. Certainly, fewer data are available on the necessity or advisability of repairing a small atrial septal defect with normal pulmonary artery pressures and a pulmonary to systemic flow ratio (Qp/Qs) less than 2, especially if the echocardiogram does not support significant volume loading of the right ventricle, and with normal or just flattened septal motion. It is still contentious as to whether there is an indication to consider transcatheter clamshell device closure of a patent foramen ovale. The argument put forward for intervention is that the patent foramen ovale presents a mechanism for a paradoxical thromboembolic event.

Infants with an atrial septal defect less than 3 mm need not have follow-up, as these defects close by age 18 months; those with a defect measuring 3 to 5 or 5 to 8 mm should be evaluated by the end of the twelfth and the fifteenth month, respectively, when 80% of these defects are closed. An atrial septal defect with a diameter greater than or equal to 8 mm may have little chance of closing spontaneously, and surgical correction should be considered. Defects less than 3 mm probably do not constitute a cardiac malformation in light of their natural evolution and gender distribution.

Fixed Forms of Subaortic Obstruction

The fixed forms of subaortic stenosis have been characterized as discrete, fibrous or membranous, fibromuscular, and tunnel forms, but clearly there is a continuum between these forms, and one form may progress from a less diffuse to a more diffuse and extensive form (189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212 and 213). Somerville et al. emphasized that the discrete form of so-called fibrous subaortic stenosis is rarely simple and discrete, and it is neither membranous nor diaphragmatic (201,202,203 and 204). Increasing clinical evidence, however, has accumulated suggesting that the fixed expressions of subaortic stenosis have both congenital and acquired features (192,193,194,195 and 196,202,203,204,205,206,207,208 and 209,212,213,214 and 215). It is more difficult to define the rate of progression of the fixed forms of left ventricular outflow tract obstruction. Many patients seem to have progression of severity, and there is an increasing incidence of aortic incompetence reflecting damage to and involvement of the aortic valve (10,11,12,13,14 and 15,18,19,20,21,22,23,24 and 25). Because the left ventricular outflow tract may be intrinsically abnormal, more narrow and elongated when compared with normal, it should not be surprising that recurrence of the obstruction is a well-documented phenomenon after surgical intervention (192,193,194,195 and 196,208,209,210 and 211).

Supravalvular Aortic Stenosis

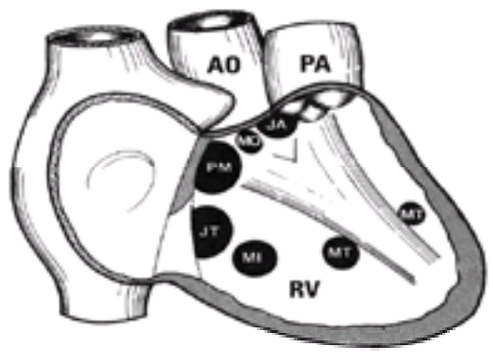
Although there is a spectrum of pathologies producing supravalvular aortic stenosis, the tendency is for progression or worsening of the obstruction over time (192,216,217,218 and 219). This disorder is frequently seen in patients with Williams syndrome, or in the nonsyndromic expression of this disorder (220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238 and 239). With the supraaortic narrowing of a sinotubular ridge, there is the potential of coronary ostial stenosis (239,240,241,242,243,244,245 and 246). In this regard, pathologic changes in the coronary arteries have received considerable attention in patients with supravalvular aortic stenosis, and the rare instance of sudden death may be related to coronary artery involvement (239,240,247). Of 80 patients with supravalvular aortic stenosis seen at the Mayo Clinic, dilatation of the right coronary artery was found in 29% of the patients and dilatation of the left coronary artery in 20% (245). Vascular lesions may progress in patients with the Williams-Beuren syndrome, sometimes malignantly (277). Ino and colleagues documented the progression of coarctation of the aorta in one patient and renal artery stenosis in another (233). Supravalvular aortic stenosis is a complex disorder with the potential for coronary artery involvement; stenoses in the major conducting arteries, including the cerebral vessels; aneurysms of the ascending aorta; and severe pulmonary arterial stenoses (67).

INDIVIDUAL CONDITIONS

Left-to-Right Shunt Conditions

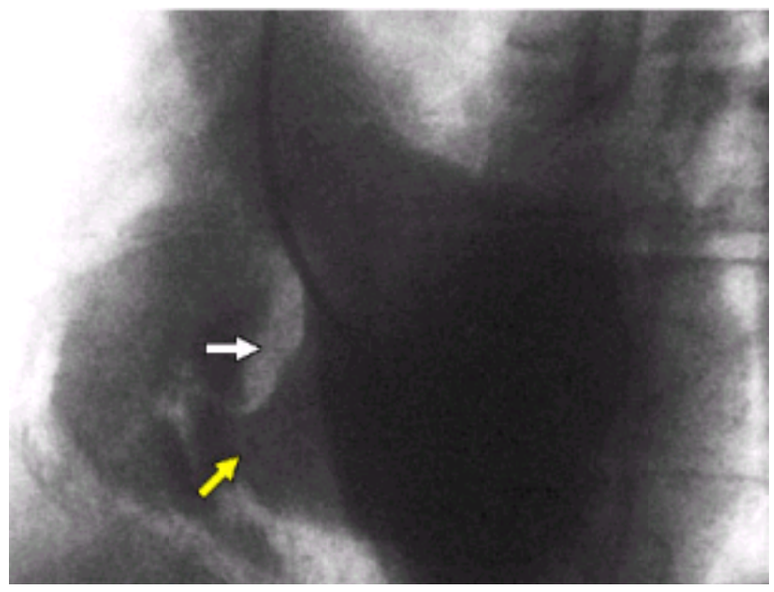
Ventricular Septal Defect

The ventricular septal defect is one of the most common lesions encountered in congenital heart disease, accounting for 25% to 30% of all patients (*e*Fig. 30.0.6). Perhaps more common are the bicuspid aortic valve and mitral valve prolapse; however, these conditions are rarely recognized in the neonate or young infant. Most defects are single and occur with an incidence of 1.2 per 1,000 live births. They can occur in isolation or in the setting of more complex congenital heart lesions, and extracardiac anomalies may be present in as many as 29% of infants. This section considers only the isolated condition, recognizing the dynamic nature of the lesion.



***e*FIGURE 30.0.6** Schematic diagram of ventricular septal defects. This diagram does not indicate that these defects may be confluent. AO, aorta; JA, juxtaarterial; JT, juxtatricuspid; MI, muscular inlet; MO, muscular outlet; MT, midtrabecular; PA, pulmonary artery; PM, perimembranous; RV, right ventricular. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

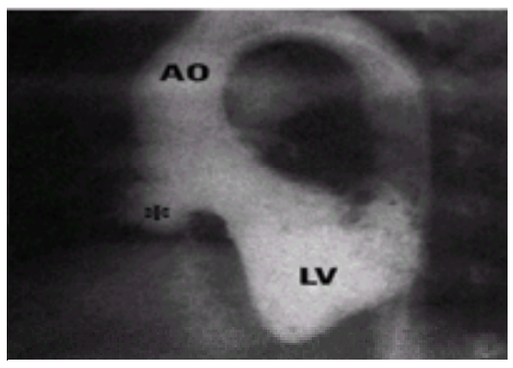
Currently, no consensus exists as to the nomenclature to describe a ventricular septal defect (248); however, the classifications generally agree on four locations of defects (*e*Fig. 30.0.6). The first describes defects of the inlet component of the ventricular septum described by terms such as *inlet septal*, *atrioventricular canal type*, or *muscular inlet*. The second occurs in the outlet septum and is termed *right ventricular outlet*, *conal septal*, or *juxtaarterial/doubly committed subarterial*. The third location is that of the *conoventricular* or *perimembranous septum*, recognizing that the defect is truly paramembranous and can extend to the inlet, trabecular, and outlet septum. Finally, the fourth location is that of the *trabecular* or *muscular septum*, which can be further divided into *inlet*, *apical*, and *anterior defects* (249,250 and 251).



Muscular ventricular septal defect. This left anterior oblique left ventriculogram demonstrates the presence of a muscular ventricular septal defect (*yellow arrow*) with opacification of the right ventricular cavity and pulmonary outflow tract. The ventricular septum (*white arrow*) is seen to divide the right and left ventricular chambers.

Video 30.1 Hepatoclavicular view (left anterior oblique 60, cranial 45) of a membranous ventricular septal defect in a 16-year-old male patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The size of the ventricular septal defect is also an important consideration. Large defects are larger than or equal to the size of the aorta, offer no resistance to flow, and result in equal ventricular pressures. The Qp/Qs is dependent on the pulmonary vascular resistance. Conversely, small defects restrict flow to the right ventricle and hence raise the right ventricular pressure beyond half systemic levels in the absence of right ventricular outflow tract obstruction and when the Qp/Qs is less than 1.75:1.00 (eFig. 30.0.7).



***e*FIGURE 30.0.7** A virtually closed perimembranous ventricular septal defect with adherent tricuspid valve producing a so-called aneurysm of the membranous septum (*asterisk*). AO, aorta; LV, left ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

The natural history of a patient with a ventricular septal defect is dynamic and often depends on the location and extent of the defect. Defects of the muscular or perimembranous septum may close spontaneously in 25% to 50% of patients or remain hemodynamically restrictive and asymptomatic as in the “maladie de Roger” defined in 1879 (252,253,254,255,256 and 257) (eFig. 30.0.7). The major complication associated with a small isolated ventricular septal defect is that of acquired bacterial endocarditis, stressing the importance of prophylactic antibiotic precautions. Large defects may contribute to pulmonary congestion and left ventricular volume load with dysfunction and heart failure. With time, pulmonary vascular obstructive disease develops and can become irreversible (Eisenmenger’s syndrome). Even small defects can be associated with the development of significant muscle bundles contributing to a two-chambered right ventricle, aortic insufficiency due to aortic cusp prolapse into the defect, or a fibrous subaortic ridge (258,259,260 and 261). Especially prone to aortic cusp prolapse with aortic valve deformity and eventual insufficiency is the conal (supracristal, doubly committed subarterial, or infundibular) defect (262,263). In this condition, the defect is effectively roofed by the aortic and pulmonary valve; thus, there is no support for the aortic valve cusps.

Clinical findings are often dynamic and reflect the natural history course of the defect. The patient with a small restrictive defect is asymptomatic with normal growth and development. In the first weeks of life, the neonate with a larger defect may be asymptomatic until the pulmonary vascular resistance falls, resulting in a greater left-to-right shunt. With increasing shunt, the infant becomes tachypneic and diaphoretic as a result of increased sympathetic tone, feeds poorly with poor weight gain and gastroesophageal reflux, and is susceptible to pulmonary infections, atelectasis, and wheezing. Physical examination depends on the size of the defect, the pulmonary vascular resistance, and the presence of associated anomalies. The infant or child with a small defect demonstrates a quiet precordium to palpation, with the exception of the presence of a thrill. The first and second heart sounds are normal with, importantly, respiratory physiologic variation of the second heart sound. The murmur produced by the defect is harsh and pansystolic. Late systolic accentuation is possible if there is tricuspid valve tissue associated with the defect. The murmur may cease before the second heart sound in the setting of a small muscular defect that is obliterated in late systole. In the moderate-sized defect in which the pulmonary to systemic flow ratios are approaching 2:1 or higher, the infant demonstrates a hyperdynamic precordium with a left precordial bulge. The pulmonary component of the second heart sound becomes accentuated, with narrowed splitting. In addition to the pansystolic murmur, a diastolic murmur also can be appreciated at the apex as a result of increased flow across the mitral valve. In the large defect, the second heart sound is loud and single due to pulmonary hypertension. A gallop rhythm may be present in congestive heart failure because of the volume load placed on the left ventricle.

Over time, one must be alert to changes that may signal the development of problems. The small defect with a pansystolic murmur that is spontaneously closing in the muscular septum may be progressing from pansystolic to a more abbreviated softer murmur. Conversely, the child with a large ventricular septal defect that is developing obstructive pulmonary vascular disease also may progress to a decrease in the duration of the murmur. Importantly, however, the second heart sound remains loud and single, and there may be evident cyanosis due to a right-to-left shunt. The pulmonary trunk may click with systole owing to dilation, and the diastolic flow rumble disappears as there is less flow across the mitral valve in the setting of increasing pulmonary vascular disease. A new decrescendo diastolic murmur should alert the clinician to the development of aortic insufficiency, whereas the change from pansystolic to a long ejection-type murmur may indicate right or left ventricular outflow tract obstruction.

The electrocardiogram is not specific for the ventricular septal defect. The QRS axis may be deviated leftward as in many defects of the inlet septum, or it may be normal to rightward. There may be left or combined ventricular hypertrophy; however, for small defects, the complexes appear normal. Changes in the ST-T wave also may be demonstrated. Progression or changes in electrocardiographic findings may herald changes in physiology or morphology. Chest radiography with larger defects demonstrates cardiomegaly with pulmonary plethora.

A 16-year-old male patient with biventricular hypertrophy secondary to ventricular septal defect and Eisenmenger's syndrome.

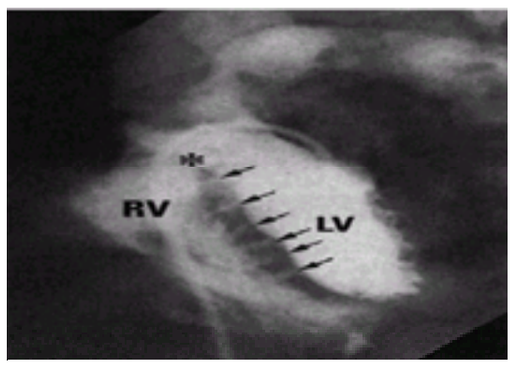
Echocardiographic imaging, particularly with the addition of Doppler-derived color flow mapping technology, is the mainstay of establishing the morphology of the defect (257,264,265,266,267,268,269,270 and 271). The ventricular septum is complex, necessitating multiple views from subcostal and precordial approaches in an effort to interrogate the entire septum thoroughly. The right ventricular and pulmonary artery pressures can be derived from color flow–directed Doppler indices, recognizing the limitations of the technique and the influence of associated lesions on the accuracy of the estimate (272,273,274,275 and 276). Although an estimation of the pulmonary to systemic flow ratio is possible (277), it is difficult in the small child because small errors in measurement have a profound effect on the calculated indices.

Many infants may proceed to surgical intervention in the setting of a straightforward defect assessed echocardiographically. If uncertainty exists as to the number of defects, the magnitude of the left-to-right shunt, the pulmonary vascular resistance, or the presence of associated anomalies, cardiac catheterization with angiography is necessary. Axial projections in angiography allow specific regions of the ventricular septum to be profiled, thus allowing precise localization of defects (278,279,280 and 281).

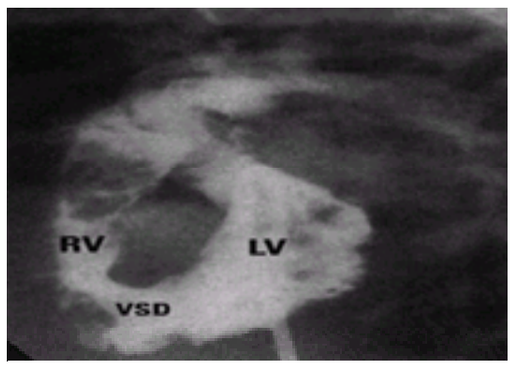
The medical management of ventricular septal defects in the symptomatic infant and child consists primarily of diuretic therapy with afterload reduction using an angiotensin-converting enzyme inhibitor. Although no large trials have been reported to support its use, digoxin also remains a medical mainstay of management. Small defects rarely require surgical intervention, and many defects undergo spontaneous closure. Indications for operative intervention include severe intractable heart failure and pulmonary congestion in the first 3 months of life or if the older infant fails to thrive with optimization of dietary needs and medical treatment. In general, the pulmonary vascular resistance is best below 8 Wood units if surgery is to be successful in the long term. Moderate-sized restrictive defects with a Qp/Qs greater than 2:1 and pulmonary congestion with cardiomegaly probably should be repaired. In addition, even the small subarterial defect can result in aortic cusp deformity with resultant insufficiency; hence, repair is recommended. The small defect that has also been subject to infective endocarditis is also repaired. Postoperative complications include the development of heart block, persistent ventricular dysfunction, surgically induced semilunar (especially aortic) or atrioventricular (especially tricuspid) incompetence, persistent shunt due to a postoperative residual patch leak or leak from a previously unrecognized defect, and pulmonary vascular disease.

Ventricular septal defects can be repaired from the right atrium or right ventricle and more rarely the left ventricle or pulmonary artery via a median sternotomy. The ventriculotomy is avoided where possible. Usually, the actual defect is repaired with a patch, with attention directed to avoiding the conduction tissue; however, smaller defects, particularly in the muscular septum, can be closed by using a direct suture technique. Pulmonary artery banding to limit flow to the lungs, hence protecting them from the development of obstructive pulmonary vascular changes, is undertaken only in unusual circumstances in the current surgical era (282,283,284,285,286,287,288 and 289).

Although surgery in the current era is associated with acceptable morbidity and mortality, multiple and apical ventricular septal defects are associated with higher surgical mortality than single defects, and severe deficiency of the muscular septum may preclude a biventricular repair (*e*Fig. 30.0.8 and *e*Fig. 30.0.9). In addition, postoperative residual defects also can contribute to persistent compromise to ventricular and respiratory function and remain a challenging surgical problem (282,290). Intervention is still directed to achieving primary closure when possible and reserving pulmonary artery banding for patients with more complex malformations.



***e*FIGURE 30.0.8** The so-called Swiss-cheese septum of a patient with many ventricular septal defects (*arrows*), producing a virtual sieve. The asterisk indicates the perimembranous defect. LV, left ventricle; RV, right ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)



***e*FIGURE 30.0.9** A large apical ventricular septal defect (VSD). LV, left ventricle; RV, right ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Transcatheter occlusion of ventricular septal defects using a double-umbrella device has been demonstrated to be a feasible strategy in the management of defects of the ventricular septum recognized preoperatively or as a postoperative residual problem (291,292,293 and 294). Although attractive as an alternative to surgery, considerable investigation must precede routine application of this new transcatheter technique.

Atrial Septal Defect

The atrial septal defect rarely presents in infancy and is more commonly a condition recognized in early childhood. It is rarely associated with symptoms unless it is very large or associated lesions or symptoms are present. Incidence of recognized defects ranges from 0.317 to 0.580 per 1,000 live births (295,296). It is the eleventh most frequent diagnosis in the New England Regional Infant Cardiac Program, with a prevalence of 2.9% in this study population (297). Although most cases are sporadic, familial occurrences are well documented. Defects of the atrial septum are also more frequent in patients with chromosomal abnormalities as well as

extracardiac midline defects, such as a cleft palate. Perhaps the most well-known association is that observed by Holt and Oram (298) in which the thumb is "digitalized"; however, other variations of the thumb, radius, and clavicles also have been described in association with a defect of the atrium that appears to be transmitted as an autosomal dominant syndrome. Atrial septal defects seem to occur more commonly in female infants, with a ratio that ranges from 1.5 to 3.5:1.0.

The atrial septum starts embryologically as septum primum grows from the roof of the atrium toward the endocardial cushion. As this occurs, septum primum becomes perforated, resulting in the ostium secundum. Septum secundum overlaps septum primum and forms the superior limb of the fossa ovalis. With increased venous return to the left atrium at birth, the septum primum is opposed to the left atrial side of septum secundum, resulting in fusion of the septae and closure of the foramen ovale by approximately 1 month of age. Up to 25% of persons continue to have a probe patent foramen ovale in autopsy series. Four basic defects of the atrial septum occur. The most common form of atrial defect is the secundum defect, which occurs in the region of the fossa ovalis. The defects may be single, multiple, central, or eccentric and may extend in any direction. Ostium primum defects are a form of atrioventricular (endocardial cushion) defects and are discussed with those defects. The coronary sinus may be "unroofed," particularly in association with a persistent left superior vena cava; however, multiple defects in the coronary sinus are known to occur in isolation. The so-called sinus venosus defect is commonly associated with anomalous drainage of the right upper pulmonary vein and is likely due to irregular absorption of the right pulmonary veins into the superior caval wall because of failure to isolate the appropriate part of the sinus venosus (299). This interatrial communication is really a defect of the sinus venosus and not of the atrium per se.

Video 30.2 Transesophageal echo with color Doppler flow demonstrating a secundum atrial septal defect with left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 30.3 Parasternal short-axis view (magnified) of an ostium primum atrial septal defect. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

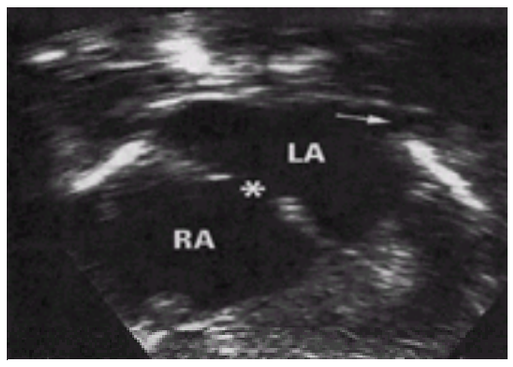
The left-to-right shunt that occurs across the atrial septum in late systole and during diastole is dependent on the size of the defect, the relative compliance of the ventricles, and the pulmonary relative to the systemic vascular resistance. If the defect is unrestrictive, there is no gradient between the atria. The shunt results in a diastolic volume load of the right ventricle, leading to enlargement as well as increased pulmonary blood flow, which can result in pulmonary hypertension and pulmonary vascular disease. Often, the magnitude of the shunt increases through infancy as a result of the decreasing compliance of the ventricle that occurs with age. In general, the volume load is well tolerated in childhood with low pulmonary pressures and vascular resistance.

Spontaneous closure of the defect in infancy is known to occur (300,301,302 and 303). Similarly, the magnitude of the left-to-right shunt may decrease if associated conditions that increase flow to the left atrium, such as the patent ductus or ventricular septal defect, become smaller or close spontaneously. Such defects likely represent a "stretched" foramen ovale rather than a true defect of the atrial septum. Although usually asymptomatic, the young child may present with decreased exercise tolerance and frequent respiratory infections (304). The defect may complicate concurrent respiratory conditions in the infant (e.g., bronchopulmonary dysplasia) because of the volume load to the lungs. Rarely, pulmonary hypertension complicates the presentation in the young infant (305). The association with mitral valve abnormalities (Lutembacher's syndrome and mitral valve prolapse) is well known. Adolescents and adults may develop atrial arrhythmias, pulmonary vascular disease, and symptoms of heart failure.

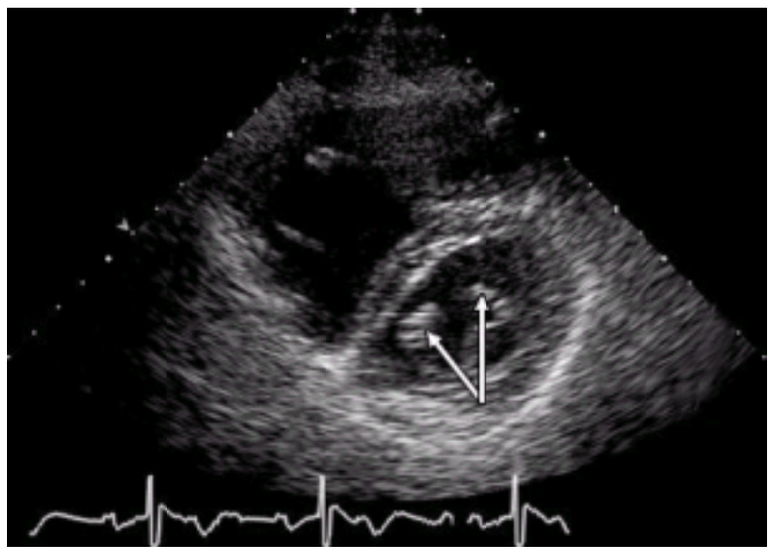
Typical findings on examination of a patient with an atrial septal defect include a prominent right ventricular impulse and, at times, a palpable pulmonary pulsation. The first heart sound is normal but may be followed by a click associated with mitral valve prolapse. The second heart sound is typically widely split and does not vary with respiration (306). One must be alerted to the possibility of pulmonary hypertension if the pulmonary component of the second heart sound is particularly loud, especially in the older patient. A systolic pulmonary flow murmur can be appreciated as well as a mid-diastolic rumble due to flow across the tricuspid valve if the left-to-right shunt is large. Cyanosis and clubbing are late findings if the patient develops significant pulmonary vascular disease.

The electrocardiogram typically demonstrates right-axis deviation (except in the ostium primum defects), right ventricular hypertrophy related to volume load, an rSR' or rsR' pattern in lead V_1, and prolongation of the PR interval. Left-axis deviation of the p wave manifests as an inverted complex in lead III and often is associated with the "sinus venosus" type of intraatrial connection. The chest radiograph typically demonstrates right atrial and ventricular hypertrophy, an enlarged pulmonary artery, and increased arterial markings.

The echocardiogram with Doppler evaluation of the atrial septum is the mainstay of diagnosis, particularly in the pediatric population (307,308,309,310,311,312 and 313) (eFig. 30.0.10). In the adult or pediatric patient with poor subcostal or parasternal windows, transesophageal imaging is often required and provides an excellent assessment of the atrial septum. In addition, 3-D ultrasound imaging techniques may serve to delineate the morphology of the septum further in planning some interventions (314,315 and 316). Imaging of the atrial septum is often optimally achieved using subcostal views, which allow visualization of the entire septum (317,318,319 and 320). Doppler echocardiography aids in the understanding of the physiology of the defect and confirms the presence of the defect noted by imaging. Indirect evidence includes the presence of a volume-loaded right ventricle with paradoxical septal motion. The right ventricular pressure may be assessed noninvasively using the tricuspid valve regurgitant jet in the evaluation for concurrent pulmonary hypertension.



***e*FIGURE 30.0.10** Secundum atrial defect: Subcostal echocardiographic image demonstrating a moderate-sized central secundum atrial septal defect (*asterisk*). Note the clear identification of right and left atria and normal left pulmonary venous drainage (*arrow*). LA, left atrium; RA, right atrium.



Parasternal short-axis view (transesophageal echo) of a cleft mitral valve. Notice the cleft in the center of the anterior mitral leaflet with its characteristic opening. (This patient also had a primum atrial septal defect, a commonly associated lesion). The double arrow demonstrates the two halves of the split anterior mitral leaflet.

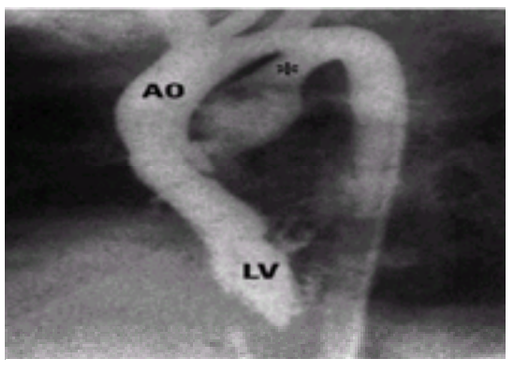
Video 30.4 Subcostal view of a primum atrial septal defect with color Doppler showing the left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Cardiac catheterization is undertaken when inconsistencies exist in noninvasive assessment or when significant pulmonary hypertension is present. The catheter course across the atrial defect, combined with angiography, outlines the location of the communication. Hemodynamic variables, including the pulmonary to systemic flow ratios and pulmonary vascular resistance, are measured, recognizing that flow ratios can be obtained using Doppler and nuclear medicine techniques. In addition, the pulmonary venous drainage can be demonstrated by selective injection in the pulmonary arteries.

In the asymptomatic child, surgical intervention is undertaken when the child is between 2 and 4 years of age with cardiopulmonary bypass by direct suture or patching of the defect. Results are excellent with low (less than 1%) mortality and morbidity. Closure is recommended for patients with pulmonary to systemic flow ratios greater than 1.5:1.0 in which the ratio of resistances is less than 0.7:1.0. Several surgical techniques were developed in an effort to minimize or avoid the median sternotomy approach to minimize the cosmetic effect of the resultant scar. With this in mind, transcatheter closure is becoming increasingly attractive as an alternative to surgery, with several devices currently in clinical trials (321,322,323,324,325,326 and 327). Whereas the shunt may be effectively reduced to that of being hemodynamically insignificant, large lesions have a higher prevalence of residual leak when rigorously assessed using current technology (328).

Patent Arterial Duct

The patent arterial duct (patent ductus arteriosus), representing persistence of the distal left sixth aortic arch, is usually a left-sided structure, but the arterial duct may be right-sided or bilateral (eFig. 30.0.11). The terms *persistent* and *patent* both have been used to describe the functional and anatomic integrity of the arterial duct. This section considers the arterial duct in isolation. One should remember that the arterial duct has an important role in conditions characterized by a ductal-mediated pulmonary blood flow (i.e., pulmonary atresia with or without ventricular septal defect) or in conditions in which patency of the arterial duct is fundamental to maintenance of part or the entirety of the systemic blood flow (i.e., aortic atresia complexes, interruption of the aortic arch, aortic arch atresia, or severe coarctation) (329,330,331 and 332).



***e*FIGURE 30.0.11** Large patent arterial duct (*asterisk*) demonstrated by long axial left ventriculogram. AO, aorta; LV, left ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Incidence

The estimated incidence of an isolated persistent arterial duct is subject to potential error, especially because of the inclusion of cases of prematurity or maternal rubella. Anderson (333) estimated the incidence to be between 1 in 2,500 and 1 in 5,000 births and to account for 12% of all congenital malformations. In a more extensive, relatively homogeneous population, Carlgren (334) found the overall incidence of all cardiac malformations to be 6.4 per 1,000, with persistent arterial duct the third most common lesion seen, or approximately 0.04% of live births. Mitchell et al. (335) reported the incidence at 0.06%, but may have included cases of prematurity or the influence of maternal rubella as well. The incidence in the general population may indeed be higher, however, as more sensitive imaging techniques are applied.

Clinical Findings

The arterial duct may remain patent in the preterm infant and promote the respiratory distress syndrome as well as persistent pulmonary hypertension of the newborn. The cardiac findings of the arterial duct in the newborn and neonate differ from those appreciated in the older infant and child (330,331,332,333,334,335 and 336). The precordium is usually overactive, and the murmur is usually systolic, sometimes breaching into early diastole, but it is not frankly continuous, reflecting the elevated pulmonary artery pressures. The pulses of all four limbs are bounding. When the diagnosis is confirmed by cross-sectional echocardiography and either duct-dependent congenital heart disease or a coarctation of the aorta is excluded, and the duct is considered hemodynamically important, pharmacologic intervention with indomethacin may promote ductal closure (330,331 and 332). When this is unsuccessful, then surgical ligation or division will be required (330,331 and 332).

In the older infant and child, the arterial duct, when small or moderate sized, is usually well tolerated. A dynamic left ventricle, a grade 3 or 4 continuous murmur in the left infraclavicular fossa, associated with multiple eddy sounds, and bounding arterial pulses are all findings typical of an arterial duct (336). When the duct is small, the chest radiograph and electrocardiogram results may be normal. When the duct is more moderate or large, this is reflected in the chest radiograph, which shows some degree of cardiac enlargement and pulmonary overcirculation.

The clinical diagnosis is rapidly confirmed with cross-sectional echocardiography. It is always important to scrutinize the aortic arch and isthmus to ensure that the arterial duct is not masking a coarctation of the aorta. Even the small arterial duct probably should be closed to prevent infective endarteritis or the chronic effects of left

ventricular volume loading. There is unanimity of opinion that the large arterial duct should be closed to prevent or treat congestive heart failure and to prevent the development of pulmonary vascular disease (336). The patient with clear-cut pulmonary vascular obstructive disease is not a candidate for duct closure, and lung transplantation eventually will be required (336).

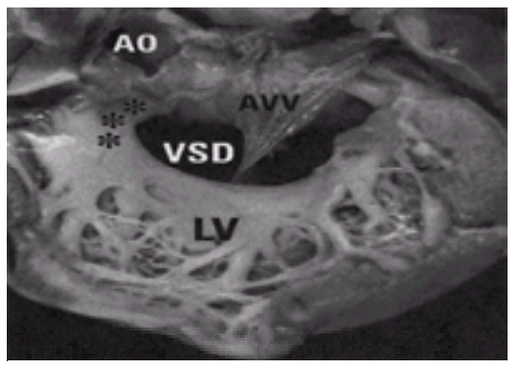
Ductal closure can be accomplished without a thoracotomy with the Rashkind ductal occluder or other systems (337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360 and 361) (see Chapter 87). The Rashkind system uses a catheter delivery system from either venous or arterial entry, although the use of a long sheath placed across the ductus from a transvenous route has become the technique of choice. Catheter closure is applicable in infants and young children but is restricted to an arterial duct no larger than 8 or 9 mm in diameter and is not applicable to the premature infant. Successful implantation can be accomplished in most (greater than 98%) with elimination of clinical signs of left-to-right shunting. Within the first 48 hours, few patients retain ductal murmurs despite correct placement, although some may have residual shunts without murmurs. Doppler evidence of residual shunting is often over the superior aspect of the device. Complications of this technique are few. Acute bacterial endarteritis has occurred after implantation when appropriate procedural coverage was not applied. Embolization to both systemic and pulmonary circulations has been encountered, with several patients requiring surgical referral. Severe hemolysis also has been reported (356,357 and 358). Protrusion of the Rashkind ductal device into the left pulmonary artery may be a cause of left pulmonary artery stenosis (345,346,355). Catheter retrieval has been accomplished in both situations, using snares, baskets, or grasping forceps.

Using pulsed and color flow Doppler techniques, occlusion rates have been evaluated. In a study by Hosking et al., 38% had Doppler evidence of shunting detected 1 year after the procedure, falling to 18% at 2 years and 8% at 40 months. Similar observations from several studies have been reported (351,353). A number of patients have undergone additional procedures with successful placement of a second device. The potential for long-term complications associated with a residual shunt, clinically silent, but detected by color flow Doppler mapping in the presence of a foreign body, remains unknown. A few patients have increased Doppler velocity shifts at the origin of the left pulmonary artery postimplantation, resulting from turbulence or encroachment into the ostium of the left pulmonary artery; incidence increased when placement was performed in children under 10 kg in weight.

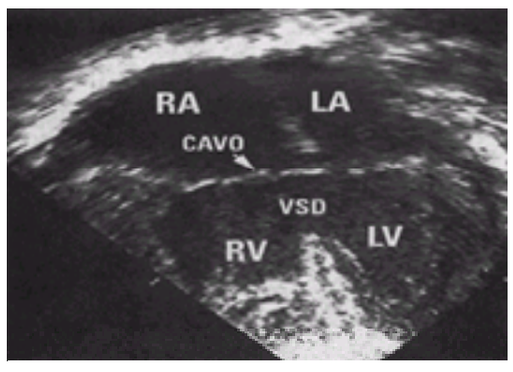
Using embolization spring coils (Gianturco, Cook Inc., Bloomington, IN), Cambier reported successful occlusion of small ductal communications (less than 2.5 mm) using a retrograde approach in three of four children. Lloyd and Moore expanded the early experience with this technique noting the approach to be effective and simple, and this technique can be performed in an outpatient setting. The use of the spring coil has gained popularity because of its significantly lower cost and ease of application. For the large arterial duct, however, surgical division, ligation, and thoracoscopic closure are techniques that can be used.

Atrioventricular Septal Defect

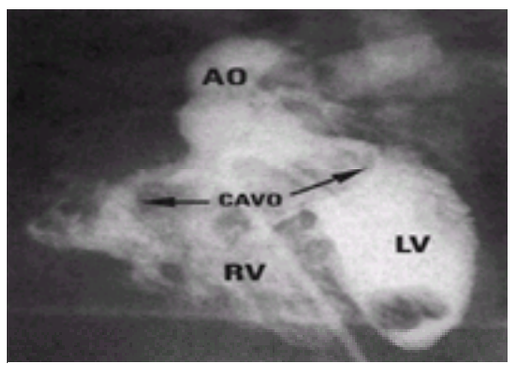
This is a heterogeneous group of cardiac malformations unified by the absence of the membranous and muscular atrioventricular septum (362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380 and 381) (*e*Fig. 30.0.12, *e*Fig. 30.0.13, and *e*Fig. 30.0.14). The absence of this component of the septum produces unique changes in the morphology of these hearts. The aorta is no longer wedged between the atrioventricular orifices; a characteristic disproportion between the left ventricular inlet and outlet results, and the morphology and disposition of the left-sided atrioventricular valve departs considerably from the normal mitral valve. These findings are germane to almost all hearts with a deficiency of the membranous and muscular atrioventricular septum. Yet there is a considerable variation by absence of the membranous and muscular atrioventricular septum (382,383). Some hearts are characterized by a large ostium primum atrial septal defect and a “cleft” mitral valve, but the clinical findings and hemodynamics are similar to the patient with a secundum atrial septal defect. Other hearts have large confluent atrial and ventricular septal defects and a common nonpartitioned atrioventricular valve. This type of malformation promotes large left-to-right shunts at the atrial and ventricular levels, and because of the large and nonrestrictive character of the ventricular septal component, pulmonary hypertension is at systemic levels. The left atrioventricular valve may or may not be competent in either of these situations, and severe incompetence is usually poorly tolerated. In other patients, deficiency of the atrial or ventricular septum may be relatively minor; rarely, both septa are intact or nearly so (375). In hearts with a complete form of atrioventricular septal defect, the attachments of the common atrioventricular valve, or lack thereof, to the ventricular septum or to the right side of the ventricular septum form the basis of the Rastelli classification (373,374). Designations such as *intermediate* or *transitional* forms of atrioventricular septal defect reflect the sizes of the various components of the defect (i.e., the size of the atrial septal defect; the size of the interventricular component; and the nature of the atrioventricular orifice, partitioned or common).



***e*FIGURE 30.0.12** Complete form of atrioventricular septal defect. Internal view of left ventricle showing the common atrioventricular valve (AVV), the large ventricular septal defect (VSD), and the typically elongated left ventricular (LV) outflow tract. The asterisks indicate the elongated outflow tract. AO, aorta. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)



***e*FIGURE 30.0.13** Apical four-chamber two-dimensional image of an atrioventricular septal defect. Note the deficiency of the inlet ventricular septum, the common atrioventricular valve orifice (CAVO), and the lack of the atrial septum primum. The defect is “balanced,” meaning that the atrioventricular orifice is committed equally to both ventricles. Doppler color-flow mapping of the common atrioventricular valve would assess for valve competency. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VSD, ventricular septal defect.

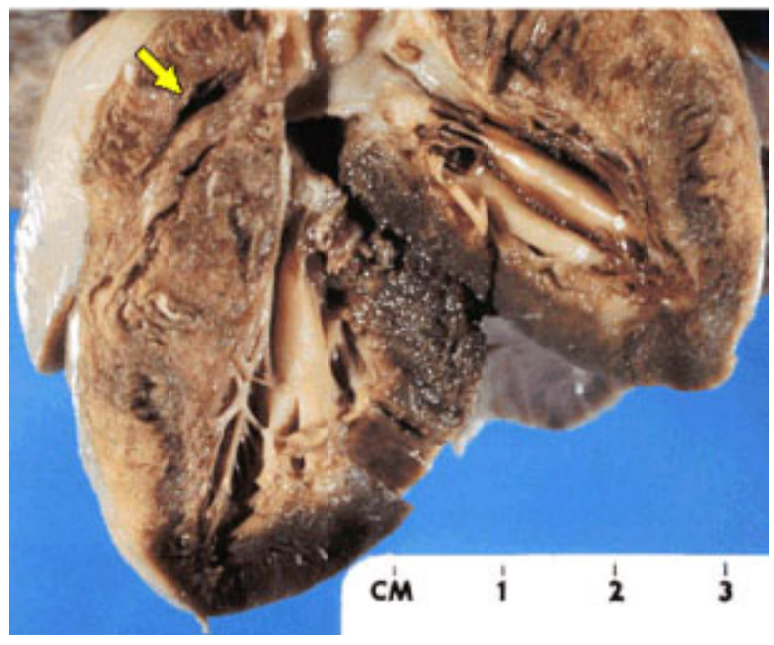


***e*FIGURE 30.0.14** Hepatoclavicular left ventriculogram shows the balanced form of the atrioventricular septal defect with the common orifice (CAVO) committed to both

ventricles. AO, aorta; LV, left ventricle; RV, right ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Patients with any form of atrioventricular septal defect may have specific anatomic risk factors that alter both the timing of surgery, mortality, and early and late outcomes (382,383,384,385 and 386):

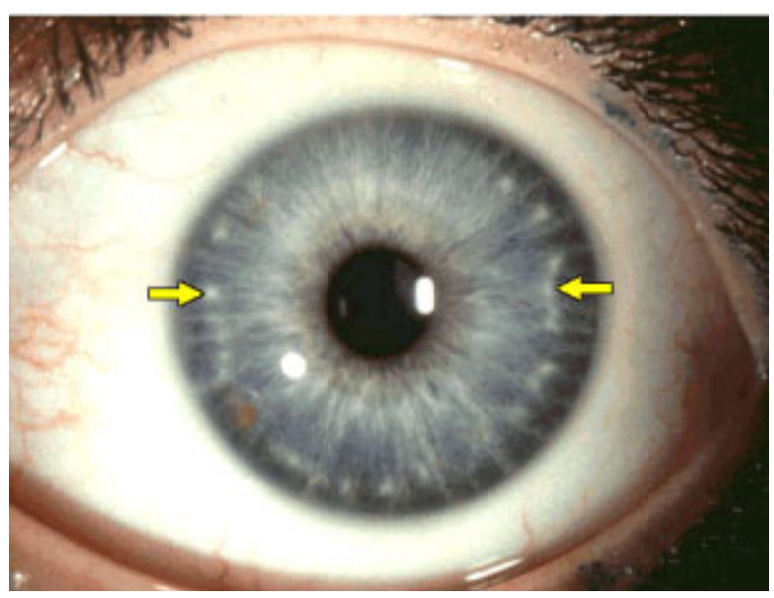
- Ventricular hypoplasia
- Left ventricular outflow tract obstruction
- Double-orifice left atrioventricular valve
- Parachute deformity of left atrioventricular valve
- Double-outlet atrium, right or left
- Association with other forms of congenital cardiac anomalies [tetralogy of Fallot, double-outlet right ventricle (DORV), hearts with right or left atrial isomerism, Ebstein's anomaly, and others]



Hypoplastic right heart in a neonate. The yellow arrow indicates a very small right ventricle chamber.

Relation to Down Syndrome

Beyond those issues of nomenclature, however, are the reality and management of patients, often further compromised by Down syndrome, with those cardiac lesions whose unifying feature is absence of the atrioventricular septum (384,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423 and 424). Down syndrome is present in approximately 80% of infants under 1 year of age, and those with the complete form of atrioventricular septal defect undergo surgery (400). When viewed from the reverse perspective, between 35% and 40% of patients with Down syndrome have an atrioventricular septal defect, and in most of these, it is with a common rather than a partitioned atrioventricular orifice. Down syndrome is most commonly associated with a complete form of atrioventricular septal defect, and the patients without Down syndrome tend to have the partial form of the defect. Among those patients with Down syndrome and the complete form of atrioventricular septal defect, tetralogy of Fallot is more prevalent. In patients without Down syndrome, the hypoplastic left ventricle left-sided obstructive lesions and coarctation are associated with more common anomalies.



Brush field spots in association with Down syndrome. The yellow arrows indicate grayish-white spots in the iris, which are associated with trisomy 21.

Surgical results for atrioventricular septal defect have been stratified against patients with and without Down syndrome (401,402,403,404,405 and 406). There is no unanimity of opinion that Down syndrome patients have disadvantageous surgical outcomes. Clearly, in many centers today, repair of the complete form of atrioventricular septal defect can be accomplished with a risk less than 5% (408).

Pulmonary Vascular Disease

The conclusion that patients with Down syndrome and the complete form of atrioventricular septal defect are at increased risk for the development of pulmonary vascular obstructive disease compared with otherwise healthy children with the same heart defect remains debatable (411,412,413,414,415,416,417,418,419,420,421,422,423 and 424). Clapp and colleagues showed that Down syndrome patients with complete atrioventricular septal defect have a greater degree of elevation of pulmonary vascular resistance in the first year of life and more rapid progression to fixed pulmonary vascular obstruction than patients without Down syndrome (406).

Accelerated pulmonary vascular disease in those patients with Down syndrome is well documented (419). Chronic upper airway obstruction with macroglossia and an inherently small hypopharynx, hypotonia, the predisposition to chronic infection, an abnormal capillary bed morphology, and the suggestion of pulmonary hypoplasia all can affect the pulmonary vascular bed (385,386,412). Surgical correction of the complete form of atrioventricular septal defect by 6 months of age is recommended.

Clinical Findings and Diagnosis

The clinical findings may be similar to those of an isolated secundum, atrial septal defect, or congestive heart failure, and pulmonary artery hypertension may reflect the complete form of the defect with a large nonrestrictive ventricular septal defect. Less commonly, the findings of florid "mitral" regurgitation dominate the clinical picture. The electrocardiogram in typical cases demonstrates a leftward and superior counterclockwise frontal QRS axis and not infrequently first arteriovenous block is evident. In the usual expression of the complete defect, one would anticipate right ventricular hypertrophy as well. The heart size and pulmonary vascular markings are, of course, quite variable, depending on the specific defects and age at presentation. Many of the specific risk factors in the patient with atrioventricular septal defect are also better sorted out with echocardiographic examination, including recognition of confounding conditions, including tetralogy of Fallot, DORV, and Ebstein's anomaly (*e*Fig. 30.0.13 and *e*Fig. 30.0.14). Of note, cardiac catheterization and angiography continue to have an important role in the evaluation of these patients, particularly in those with more complex forms of the malformation. Some evidence exists that patients with Down syndrome may be at risk for early development of pulmonary

vascular obstruction, and thus hemodynamics measured in room air, in increased FIO_2, or with the administration of nitric oxide may be important to define vascular reactivity and operability. The hemodynamic measurements may be confounded by the obligatory shunt from left ventricle to right atrium, which might suggest a large Qp and normal or only mildly elevated pulmonary vascular resistance despite severe pulmonary vascular disease. Similarly, in patients with an atrioventricular septal defect and cyanosis, malalignment of the atrial septum with shunting from right atrium to left ventricle must be excluded. In patients with Down syndrome, an effort should be made to obtain the history of mouth breathing and significant snoring. If present, the opinion of an otolaryngologist should be sought regarding tonsillectomy or adenoidectomy before cardiac catheterization. Also, if a cardiac catheterization is required to define the pulmonary vascular resistance, it is always important to sample the pulmonary veins and to obtain PO_2 in room air and in an FIO_2 of 100%, thus excluding any important pulmonary dysfunction. Rabinovitch and colleagues also advocate the role of pulmonary artery wedge angiography, with definition of the rate of vascular tapering and the assessment of the background capillary phase. In some patients, lung biopsy might be the final arbiter of operability.

Aortopulmonary Window, Fenestration, or Septal Defect

The aortopulmonary window septal defect or fenestration (425) is an uncommon cardiac anomaly with an incidence of only 0.1% to 0.2%, characterized by a communication, often large, between the ascending aorta and pulmonary trunk (426,427,428 and 429). Although considered clinically related to truncus arteriosus and located in the same area of the heart, evidence marshaled by Kutsche and Van Mierop suggests that these two anomalies are probably pathogenetically unrelated (427). The shape and size of the aortopulmonary window vary, but always are related to the aortic wall above the aortic sinuses containing the coronary arteries. The aortopulmonary window can occur in isolation, but it has been identified with a wide variety of other cardiac anomalies, including aortic arch interruption, isthmal hypoplasia, origin of the right pulmonary artery from the ascending aorta, transposition of the great arteries, tetralogy with or without pulmonary atresia, and origin of the right coronary artery from the pulmonary trunk (430,431,432,433,434,435,436,437,438,439,440,441,442,443 and 444).

Nonassociation with DiGeorge Syndrome

There is a well-known association between abnormalities of the third and fourth pharyngeal pouch and interruption of the aortic arch and common arterial trunk as well as with other conotruncal abnormalities. This association has not been documented with aortopulmonary septal defect.

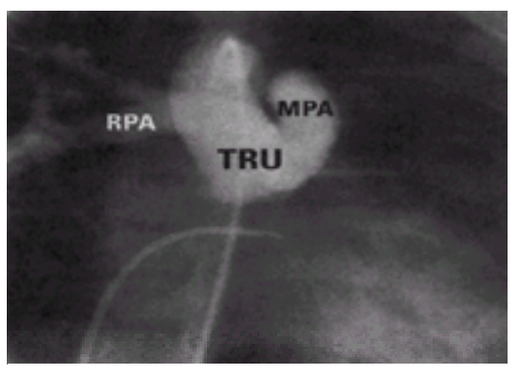
Diagnosis and Therapy

Neither the electrocardiogram nor the chest radiograph is specific for the diagnosis of aortopulmonary window. The echocardiogram is diagnostic of this condition with the following caveat (445,446,447,448 and 449): In the newborn period, while the pulmonary pressure is high, this lesion can be missed if the echocardiographer relies solely on Doppler echocardiography. It is, therefore, imperative that a thorough examination of the aortopulmonary septum is performed. It is also important to understand which lesions occur in association with aortopulmonary window. The diagnosis of aortopulmonary window is readily made by echocardiography; MRI may be helpful for interruption of the aortic arch or aortic origin of the right pulmonary artery (434).

Occasionally, a patient has a small aortopulmonary window, which can be closed in the catheter laboratory (450). For the remainder of patients, surgical intervention is necessary to prevent or treat congestive heart failure and pulmonary vascular obstruction. Repair of the aortopulmonary window in isolation carries a low operative risk (451), but the risk is increased if there are significant associated abnormalities.

Common Arterial Trunk or Truncus Arteriosus

Truncus arteriosus or common arterial trunk is characterized by a single arterial trunk supported by the ventricular mass giving origin to the coronary arteries, at least one pulmonary artery, and the brachiocephalic arteries (452) (eFig. 30.0.15). With rare exception, a ventricular septal defect is present (453,454,455,456,457 and 458). Classification (458) is first stratified by the presence or absence of a ventricular septal defect and by the presence of a main pulmonary trunk, separate origins of the right and left pulmonary arteries from the ascending portion of the arterial trunk, and nonconfluent pulmonary arteries with one pulmonary artery from the ascending portion of the arterial trunk and the other from an arterial duct or aortopulmonary collateral; the final form of common arterial trunk is that characterized by an obstructive anomaly of the aortic arch, coarctation of the aorta, aortic arch atresia, or interruption of the aortic arch. Hearts with truncus arteriosus are usually left sided, and the atrial situs is solitus. With rare exception, the hearts are biventricular, the atrioventricular connections are concordant, and there is often fibrous continuity between the mitral valve and the truncal valve. The right-sided ventriculoinfundibular fold may be attenuated, thus permitting continuity or nearly so between truncal valve and tricuspid valve. Occasionally, the single arterial root originates entirely above the right ventricle. Truncus arteriosus has been observed in the patient with right atrial isomerism and presumed asplenia. Truncus arteriosus also has been observed in the patient with tricuspid atresia as well as other forms of double-inlet ventricle. The truncal valve theoretically can possess one to six cusps, but the unicommissural, pentacuspid, and hexacuspid valves are uncommon (459,460,461,462,463 and 464). The truncal valve may guard the ventriculoarterial junction normally; the valve may be stenotic, regurgitant, or both. Severe truncal valve regurgitation has been reported as a serious complication. Most patients with persistent truncus arteriosus have excessive pulmonary blood flow and, when untreated, die in congestive heart failure. In approximately 10% of patients with truncus arteriosus, the pulmonary blood flow is restrictive. In most of these patients, the mechanism responsible for limiting the pulmonary blood flow is ostial stenosis resulting from an obstructive truncal leaflet.



***e*FIGURE 30.0.15** Common arterial trunk. This aortogram shows the most common form of common arterial trunk with a main pulmonary trunk originating from the base of the truncus (TRU) and dividing into branch pulmonary arteries. MPA, main pulmonary artery; RPA, right pulmonary artery. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

The coronary arteries exhibit a variable pattern of origin independent of the number of truncal valve leaflets (465,466,467 and 468). Abnormally high origin of a coronary artery, usually the right, has been observed in this disorder. Frank myocardial ischemia is usually the result of the disordered hemodynamics with a torrential pulmonary blood flow, a volume-loaded left ventricle, and a low aortic diastolic or coronary artery driving pressure. Rarely, a coronary ostium is congenitally stenotic and promotes an ischemic myocardium. Uncommonly, the coronary ostium is just superior to the truncal valve commissure, and a bulky, fleshy truncal valve leaflet obstructs the coronary ostium, resulting in coronary insufficiency.

Clinical Findings and Treatment

The incidence is between 0.7% and 1.4%, and the prevalence at live birth is 0.03 to 0.06 (469,470). Of 100 infants born with truncus who are surgically untreated, 20 will die in the first week, and at least 86 will have died by 1 year of age (471,472 and 473). A rare patient survives with pulmonary vascular obstructive disease into the fourth decade of life or beyond. Clinical experience also indicates that, uncommonly, some patients with truncus arteriosus survive past infancy without developing pulmonary vascular obstructive disease. Patients with common arterial trunk usually present within days or weeks after birth. The earliest presentation is in the group of infants who have either an obstructive anomaly of the aortic arch or severe truncal valve stenosis or regurgitation. This condition is characterized by the early appearance of congestive heart failure and progressive myocardial ischemia. Congestive heart failure reflects the tremendous increase in pulmonary blood flow, and myocardial ischemia reflects the frequent abnormalities of the coronary arteries and their ostia. Congestive heart failure and myocardial ischemia may be aggravated and accentuated by the presence of significant truncal valve stenosis or regurgitation. In infants with a common arterial trunk and aortic arch interruption, death is precipitated by functional and anatomic closure of the arterial duct. Abnormalities of the third and fourth pharyngeal pouch syndrome, DiGeorge syndrome, is common in these babies (474). The usual presentation is characterized by a mildly cyanotic infant with features of congestive heart failure. The left precordium is active; the second sound is single, and a systolic ejection click is audible at the lower left sternal edge. A grade 2 to 3/6 blowing systolic ejection murmur is heard along the left sternal edge. A soft murmur of aortic insufficiency may be heard along the left sternal edge. Except in infants with an obstructive anomaly of the aortic arch, all the pulses are brisk to frankly collapsing. Neither the electrocardiogram nor the chest radiograph is diagnostic of a common arterial trunk. It is common to see nonspecific

ST-T–wave changes in the limb leads and in the left precordial leads of the electrocardiogram; from the radiographs, a right-sided aortic arch is noted in approximately 20% to 25%.

The echocardiogram is usually diagnostic of common arterial trunk, and a systematic approach can answer most, if not all, questions about the associated anatomy. It is unusual to resort to cardiac catheterization unless questions arise about pulmonary artery nonconfluence or the status of the pulmonary vascular bed and operability in the older patient. Although digoxin and diuretics may improve the patient's well-being transiently, the only definitive therapy is surgery (475), usually performed within a few days of diagnosis. Surgery includes separation of the pulmonary arteries from the common arterial trunk; establishment of continuity between the right ventricle and pulmonary arteries with a valved conduit, usually a homograft; closure of the defect in the truncal wall; and patch closure of the ventricular septal defect. Complete repair can be accomplished with a mortality in the range of 10%, although this rate may be higher in patients with associated aortic arch interruption or those requiring truncal valve replacement (476,477).

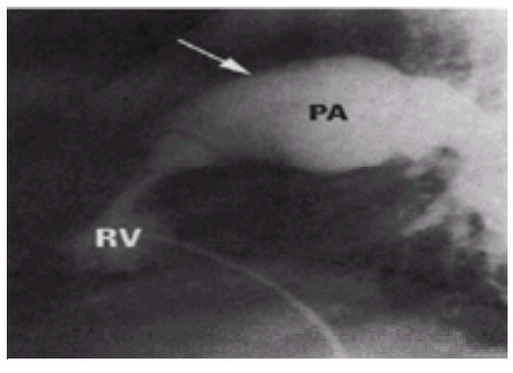
Obstructive Lesions

Pulmonary Valvular Stenosis

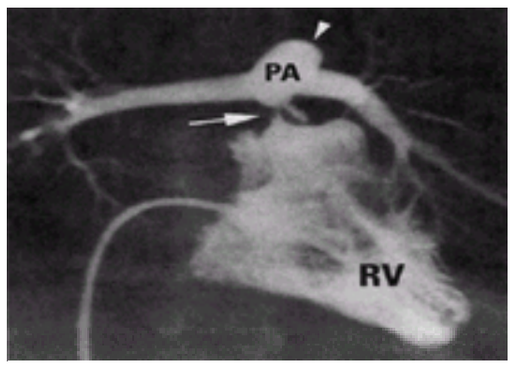
The terms *valvular* and *valvar* both refer to "a valve" and have been used interchangeably (478). Designations that have been used to define the stenosis as an isolated lesion include *pure* or *uncomplicated* valve stenosis and pulmonary stenosis with normal aortic root or with an intact septum. Isolated pulmonary valve stenosis is a form of an acyanotic cardiac malformation with normal or diminished pulmonary blood flow. The atrial septum is usually intact; if not, the defect is usually in the form of a patent foramen ovale, although an actual atrial septal defect may coexist.

Presentation

The prevalence range of 0.07 to 0.19 reflects the use of echocardiography and diagnosis of milder forms of valvular stenosis. Morphologically, in the neonatal expression of critical pulmonary stenosis, the fused raphes extend from a central opening to the pulmonary artery wall (acommissural), creating an eccentric (rarely circular) hemodynamic orifice of varying diameter, depending on the extent of commissural fusion. No separate leaflets are present, and although angiographically they may appear thin, histologically they appear as disorganized myxomatous tissue throughout (479,480,481 and 482). Secondary changes occur in the right ventricle and pulmonary artery as a result of the profoundly afterloaded ventricle. The right ventricle hypertrophies, particularly the infundibular region, with encroachment on the size of the cavity. This may be quite extensive and in the neonate gives the appearance of true hypoplasia of the chamber. Few newborns, however, after effective relief of the valve obstruction, require additional sources of pulmonary blood flow, as the chamber both enlarges and becomes more compliant with time (483,484 and 485). Some infants, despite a prolonged course of prostaglandin, require some surgical maneuver to augment pulmonary blood flow, despite what is seemingly adequate relief of the outflow tract obstruction. This problem may reflect a poorly compliant ventricle, at times aggravated by a slightly restrictive tricuspid valve annulus, with right-to-left atrial shunting. The outflow portion of the ventricle, the infundibulum, is not displaced anteriorly as in Fallot's tetralogy. The tricuspid valve is usually well formed and competent, although right atrial enlargement can develop with significant tricuspid insufficiency secondary to right ventricular hypertension. In the absence of an intrinsic tricuspid valve anomaly (dysplasia of the leaflets, clefts, abnormal chordal attachments) this, too, resolves with relief of the obstruction. The tricuspid valve may be congenitally abnormal, especially in the neonatal expression of the disorder, although perhaps less severely disordered than in the patient with pulmonary atresia and intact ventricular septum (486). Poststenotic dilation of the main pulmonary trunk is the rule (*e*Fig. 30.0.16). Such enlargement can be seen at all stages of disease expression, from newborn through adult and pulmonary artery aneurysms, although they have been described rarely (487,488). There is disproportionate dilatation of the left pulmonary artery branch, reflecting the leftward orientation of the right ventricular outflow tract and the parallel takeoff of the left pulmonary artery from the main trunk. Calcification may occur within the pulmonary valve, but is exceptional in any patient but the adult with long-standing disease (489). The aortic arch is usually, but not invariably, left sided when pulmonary valve stenosis is present with an intact ventricular septum, in contrast to the situation in Fallot's tetralogy, in which a right-sided aortic arch is present in 30% of cases. Although the expression of pulmonary valve stenosis is usually but not invariably an isolated malformation, in its "typical" presentation, when the mechanism of right ventricular outflow obstruction is due to valve dysplasia, there is a greater incidence of associated cardiac and noncardiac malformations (e.g., Noonan's syndrome, Williams syndrome, and Alagille syndrome), although peripheral pulmonary arterial stenosis is a more prominent feature (490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511, 512,513,514 and 515) (*e*Fig. 30.0.17).

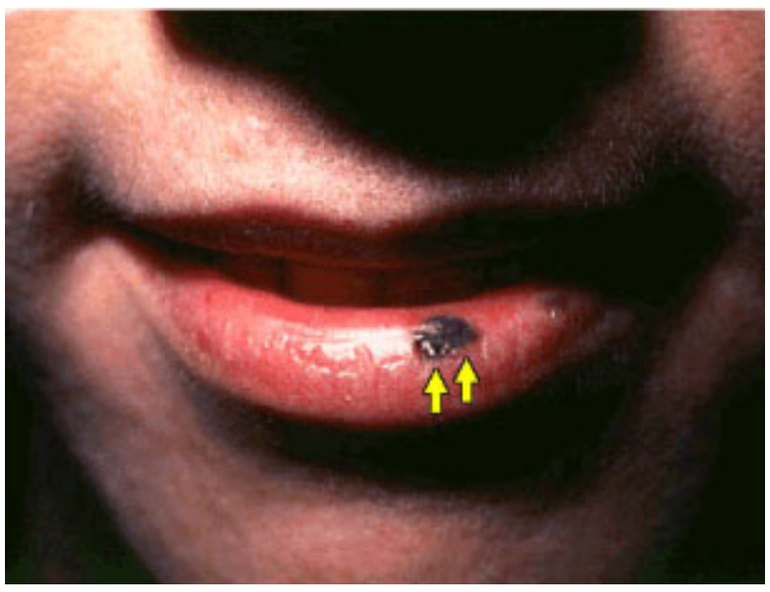


***e*FIGURE 30.0.16** Typical doming stenotic pulmonary valve with poststenotic dilation of main pulmonary artery (PA, *arrow*) demonstrated by this lateral right ventriculogram. RV, right ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)



***e*FIGURE 30.0.17** Severely dysplastic pulmonary valve (*arrow*) in a patient with Noonan's syndrome. The arrowhead points to the dilated main pulmonary artery (PA). RV, right ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Video 30.5 Coronary ectasia. These angiograms were obtained in a 40-year-old patient with Noonan's syndrome and no coronary risk factors. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Café au lait spot. There is a flat localized hyperpigmentation that is uniformly light brown in the lower lip (*arrows*) that may be associated with neurofibromatosis, Albright syndrome, or pulmonary stenosis.

Leopard's syndrome. Figure shows a patient with Leopard's syndrome characterized by multiple basal cell nevi and broad facies. There is an association with pulmonic stenosis.

The dysplastic form of pulmonary valve stenosis occurs much less frequently (in approximately 20% of cases with pulmonary valve stenosis) than typical valve stenosis (497) (eFig. 30.0.17). In this setting, obstruction to right ventricular outflow reflects the reduced mobility of the thickened valve leaflets with the often associated hypoplasia of the valve annulus, supravalve tethering, a small or short main pulmonary artery, and, frequently, peripheral pulmonary artery stenosis. The three leaflets are distinct, composed of disorganized myxomatous tissue, and generally have little or no commissural fusion. The response to balloon valvotomy would suggest that in some patients a commissural element exists (511,512 and 513). Valve thickening generally involves the entire leaflet through to the attachments to the annulus. The expression of pulmonary valve stenosis in the neonate has the appearance of such dysplasia angiographically; however, medium-term studies after successful balloon dilation documented that the valve becomes pliant and then with time or spontaneously normalizes, or nearly so.

Perloff (478) reviewed the typical clinical, radiographic, electrocardiographic, and chocardiographic findings of typical pulmonary valvular stenosis. The systolic ejection murmur maximally audible in the pulmonary area, an intermittent systolic ejection click along the left sternal border, variable splitting of the second heart sound, with a reduction in intensity of the pulmonary closure sound consistent with more disease, are the usual auscultatory findings. Indeed, with progressive severity, the systolic murmur becomes louder, peaking later in systole, and with very severe disease the click may be inaudible, as is the pulmonary closure sound. In patients with severe disease and an associated interatrial communication, right-to-left atrial shunting may result in hypoxemia. The electrocardiogram usually reflects the severity, except in infants who have right ventricular hypoplasia (478). There is unanimity of opinion that balloon valvuloplasty is the therapy of choice (516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538, 539,540,541,542,543 and 544), and a number of technical aspects have been addressed to cross the severely stenotic neonatal valve and the application of multiple balloons in those with a large pulmonary valve annulus. Most recommend this approach in patients with pressure gradients of at least 40 mm Hg, especially in those with typical pulmonary valvular stenosis. There is perhaps less enthusiasm for valvuloplasty in those with dysplastic pulmonary valves because of the variable result. Nonetheless, we still advocate this approach for the patient with pulmonary valve dysplasia requiring intervention. One should be reminded of the association between pulmonary valve dysplasia, eccentric cardiomyopathy, and Noonan's syndrome (501,502,503,504 and 505).

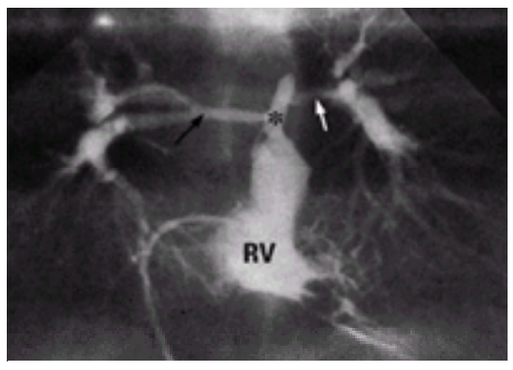
VIDEO

Video 30.6 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pulmonary Arterial Stenosis

Abnormalities of pulmonary artery branching, caliber, and origin can occur in relative isolation or may reflect a component of rubella embryopathy, an internal stigmata of generalized dysmorphism, the Silver-Russell syndrome, cutis laxa, and the Williams or Alagille syndromes (eFig. 30.0.18), among others; it may reflect a component of a widespread vasculopathy or be an integral component of congenital cardiac anomalies, including tetralogy of Fallot, pulmonary atresia and ventricular septal defect, the hypogenetic right lung syndrome, the complex heart malformations associated with right atrial isomerism, and many others (545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567, 568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585 and 586). Isolated pulmonary artery stenosis or that associated with similar systemic vascular lesions can occur in the main pulmonary artery, at its bifurcation, and at the secondary or even more distal branch points of the pulmonary artery, or such arterial stenoses may be very severe and extensive (560). Isolated stenosis of the main pulmonary artery alone is uncommon, however. Such obstruction is usually seen as part of a generalized pulmonary vascular dysplasia associated with obstruction to the pulmonary valve or the right ventricular infundibulum. The most common site of pulmonary artery stenosis is at the point of bifurcation of the main pulmonary artery and its right and left branches. The stenosis involves the distal main pulmonary artery and then extends a variable distance along the right or left pulmonary artery branch or both. Peripheral pulmonary artery stenosis involving the branch points of the right or left pulmonary artery may occur alone or associated with more proximal stenosis. Two basic forms of obstructive malformations of the pulmonary arteries can be identified: a focal and a diffuse form. The focal form of pulmonary arterial stenosis consists of a discrete obstruction preceded by a normal-sized artery and followed by poststenotic dilatation. The more diffuse type is characterized by a small vessel that remains small distally, resembling hypoplasia, and is not amenable to surgical reconstruction by local resection. Increasing experience has accumulated involving patients with bilateral severe pulmonary hypoplasia associated with jaundice and hepatic ductular hypoplasia, the so-called Alagille syndrome (560,561,562,563,564,565,566,567,568,569,570,571,572 and 573). This syndrome is an autosomal dominant disorder characterized by chronic cholestasis, reflecting a paucity of intrahepatic bile ducts, typical facies, peripheral pulmonary artery stenoses, skeletal abnormalities, and ocular posterior embryotoxon. Pulmonary arterial stenoses may be particularly severe and diffuse in patients with this syndrome, although at

least one follow-up study suggested that most such peripheral pulmonary arterial stenoses are relatively mild. In any patient, the recognition of pulmonary arterial stenosis should raise the possibility of a more widespread vasculopathy, such as that associated with rubella, infantile hypercalcemia, cutis laxa, and Ehlers-Danlos syndrome, among others. Rodriguez and Riggs (582) assessed so-called physiologic peripheral pulmonary arterial stenosis in infancy. They found that patients with physiologic peripheral pulmonary arterial stenosis have mild underdevelopment of the pulmonary artery branches, with consequent increased flow velocity and turbulent flow.

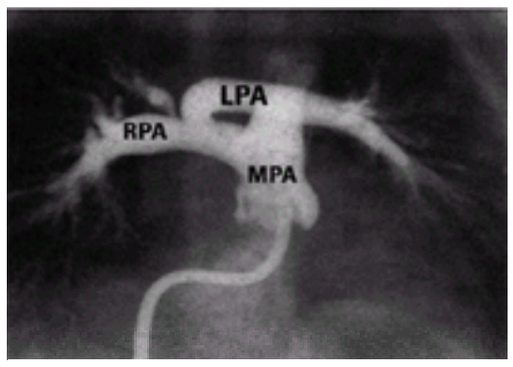


***e*FIGURE 30.0.18** Bilateral pulmonary arterial stenoses with a small main pulmonary trunk (*asterisk*). Left (*white arrow*) and right (*black arrow*) branch pulmonary artery stenoses are indicated. RV, right ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Aneurysms of the Pulmonary Arteries

Aneurysms of the pulmonary arteries have been identified in patients with a wide range of systemic disorders, from those with Marfan syndrome to Behçet's syndrome (560,587,588,589,590,591,592,593,594,595,596,597,598,599 and 600). Pulmonary artery involvement in Marfan syndrome is far less common than the well-known aortic involvement. Aneurysms of the pulmonary arteries have been identified in those with Behçet's syndrome (a nonspecific vasculitis of unknown etiology of large and small arteries, veins, arterioles, venules, and capillaries of both the systemic and pulmonary circulations) as well as in those with mucoid vasculopathy. Pulmonary artery stenoses and aneurysms have been observed in those with Takayasu's arteritis, rheumatoid arthritis, and other systemic disease processes. Mycotic aneurysms of the pulmonary arteries have been amply recorded in those with intravenous substance abuse.

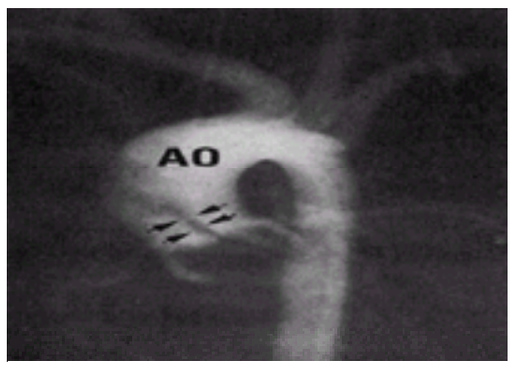
The clinical recognition of pulmonary arterial stenoses may be suggested by the presence of blowing systolic ejection murmurs conducting into the axillae and in the back. Neither the chest radiograph nor the electrocardiogram is specific for this diagnosis, although when arterial stenoses are severe, the electrocardiogram may show significant right ventricular hypertrophy. The echocardiogram may demonstrate a proximal arterial stenosis, and Doppler interrogation may provide some clue as to its or their hemodynamic significance. When the condition is unilateral, a pulmonary perfusion scan may demonstrate a significant perfusion imbalance. Selective pulmonary artery angiocardiography with craniocaudal tilt shows to advantage the pulmonary arteries, and such imaging defines whether the arterial stenosis or stenoses are diffuse, localized, and amenable to balloon angioplasty or intravascular stenting (559,560). Another important abnormality of the pulmonary arteries is the so-called pulmonary sling (*e*Fig. 30.0.19). In its errant course between the trachea and esophagus, it may cause severe bronchial compression and airway disease (559,560).



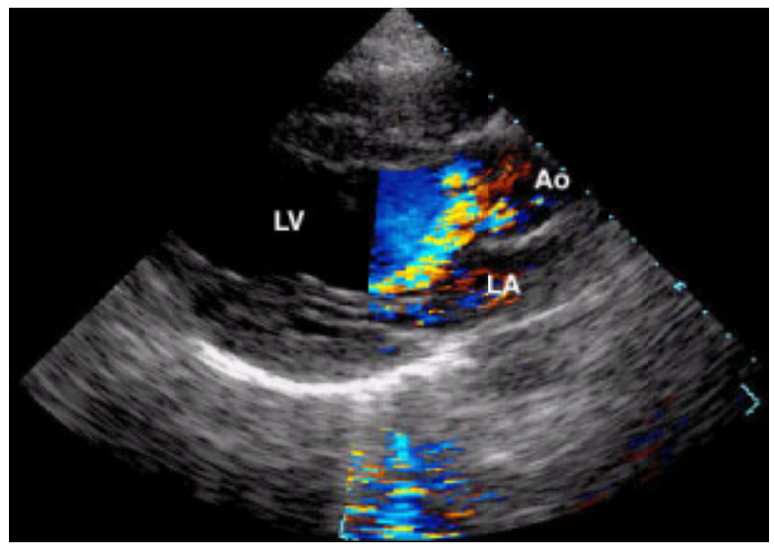
***e*FIGURE 30.0.19** The pulmonary sling results from the left pulmonary artery (LPA) originating from the right pulmonary artery (RPA), with an errant course between the trachea and the esophagus. MPA, main pulmonary artery. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Congenital Aortic Valve Stenosis

It is plausible that the true prevalence of a bicuspid aortic valve in the infant and child is underestimated because of an absence of signs and symptoms. Hence, it is likely that a bicuspid aortic valve is one of the most common congenital cardiac conditions (*e*Fig. 30.0.20). This discussion, however, focuses on the unique problem of aortic stenosis that presents primarily in the neonate. For more information regarding the adolescent or adult, please refer to Chapter 22.



***e*FIGURE 30.0.20** Critical aortic stenosis with a doming aortic valve and a narrow jet (*arrows*) of nonopacified blood. AO, aorta. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

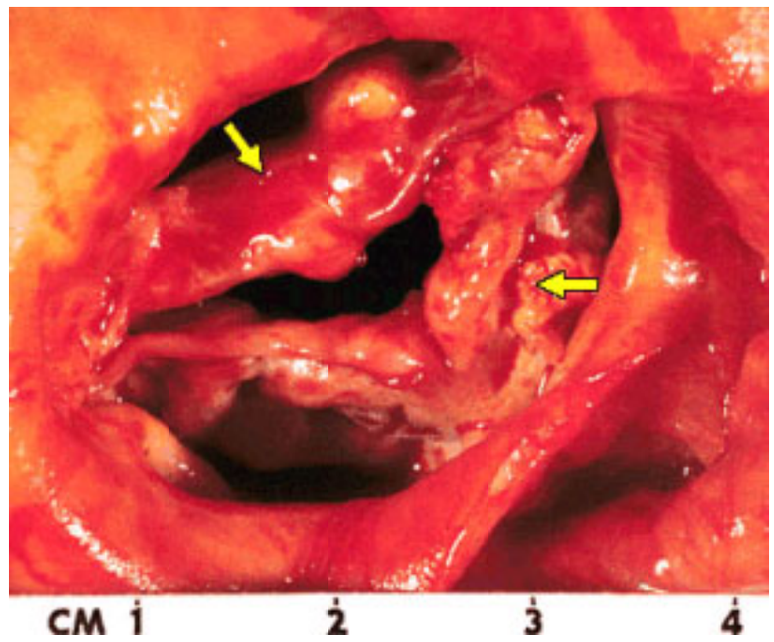


Parasternal long-axis view (transthoracic echo) with color Doppler demonstrating the posteriorly directed aortic insufficiency caused by prolapse of the anterior leaflet of a bicuspid aortic valve. Note that the jet hits the anterior mitral leaflet.

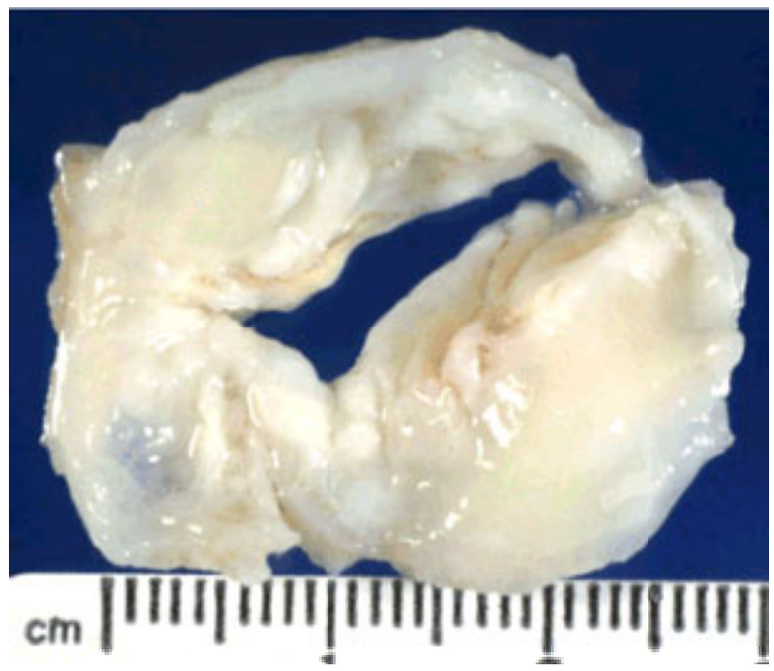
Parasternal long-axis view of a prolapsing anterior cusp (right coronary cusp + left coronary cusp fusion) of a bicuspid aortic valve (the prolapsing leaflet is demonstrated by the short arrow). The posteriorly directed aortic insufficiency that is produced causes the posterior deformation of the anterior mitral leaflet (designated by the long arrow) as the aortic insufficiency jet hits this leaflet.

Congenital aortic stenosis that presents in the first months of life is a rare lesion and accounts for only approximately 3% of neonates presenting with significant congenital heart lesions. In this group, approximately four times more male infants present than female infants, and approximately 20% have associated lesions, including endocardial fibroelastosis, persistent spongy myocardium, mitral valve stenosis (valve and supravalve), mitral regurgitation, coarctation of the aorta, patent ductus arteriosus, and hypoplasia of the left ventricle. There is indeed a spectrum of disease that encompasses the hypoplastic left heart syndrome with overlap of patients who cannot sustain a biventricular repair (601). The critically ill neonate may present with severe stenosis or atresia of the aortic valve, which renders patency of the arterial duct with right-to-left flow crucial for survival.

The neonate with “isolated” aortic valve stenosis generally exhibits a morphology consisting of a bicuspid valve with fused raphe, a unicuspid valve, or a valve with no discernible valve tissue. The valve may be myxomatous or dysplastic with annular hypoplasia. Calcification is exceedingly rare in childhood, unlike in adulthood. Associated endocardial fibroelastosis is not uncommon, and neonates are often subdivided into those with good functioning hypertrophied ventricles and those with poorly contractile, dilated ventricles. Subendocardial myocardial fibrosis is common, and there is often poststenotic dilatation of the ascending aorta.



Bicuspid aortic valve with calcific stenosis. The yellow arrows identify each of the valve leaflets.



Unicuspid aortic valve (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 30.7 A 60-degree intraoperative transesophageal echo of a patient with aortic stenosis due to a unicuspid valve (seen in short axis). Note the single commissure at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Most children with aortic valve stenosis are asymptomatic and present with a typical click and murmur in childhood, as previously described. The neonate with severe stenosis, however, presents early with cardiovascular collapse in the first days of life. In these neonates, poor feeding with tachypnea and diaphoresis precedes a rapid deterioration to medical or surgical emergency. There may be differential cyanosis with a lower saturation measured in the lower limbs as a result of the presence of right-to-left shunting at the ductal level, which may be further emphasized by the presence of a coarctation of the aorta or pulmonary hypertension. The liver is enlarged, and the peripheral pulses are poorly palpable. The precordium often demonstrates a right ventricular heave with no thrill. Auscultation typically finds a systolic ejection murmur at the right upper sternal border with a diminished aortic component. An aortic click is often not present in the neonate, depending on the severity of the valve leaflet dysplasia. In the desperately ill child who has an increasing metabolic acidosis as a result of poor systemic perfusion, a murmur may be absent, as there is little forward flow across the aortic valve in the situation of severe ventricular dysfunction.

HEART SOUNDS

Audio 30.8 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 30.9 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 30.10 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 30.11 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 30.12 Aortic ejection click. Auscultation in a 29-year-old female patient with congenital bicuspid aortic valve with no stenosis. Note the ejection click after the first heart sound and the single loud second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); apex, sitting (*fourth clip*); and apex, supine (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The chest radiograph demonstrates cardiomegaly with pulmonary venous congestion. Electrocardiographic findings are often consistent with left ventricular hypertrophy in most cases and also may be associated with strain and evidence of subendocardial ischemia. One must be alert to the presence of endocardial fibroelastosis or sclerosis in the setting of a concurrent left bundle branch block pattern. Right ventricular predominance or hypertrophy occurs in the setting of a hypoplastic left ventricle but also may be associated with pulmonary hypertension secondary to left atrial hypertension resulting from ventricular diastolic dysfunction or

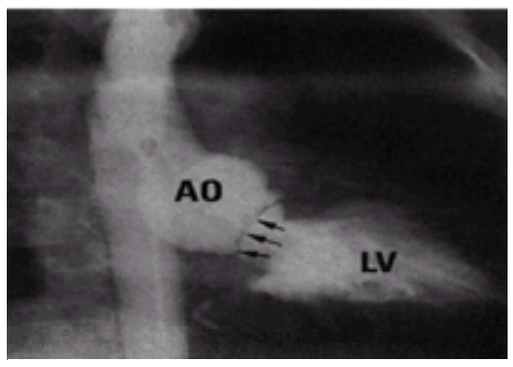
mitral valve disease.

The echocardiographic evaluation, including Doppler, reliably establishes the diagnosis (602,603,604,605,606,607,608 and 609). The aortic valve is often thickened and poorly mobile. Fusion of leaflets may be demonstrated, but this may be difficult in the severely dysplastic valve or unicommissural morphology. The annulus also may demonstrate hypoplasia. Increased echogenicity of the endocardium suggests the presence of fibroelastosis, and the global and segmental ventricular function can be assessed. Attention is often focused on distinguishing this entity from the hypoplastic left heart syndrome (60), especially when other anomalies of the left-sided structures coexist.

Prompt intervention is indicated in the neonate or child with symptomatic severe aortic valve stenosis, recognizing the difficulties in uniformly describing these patients. Patients who have less stenosis may have follow-up as outpatients, with the understanding that progression is usually the rule (610,611,612 and 613). It appears from studies of the natural history that the patient with a Doppler gradient greater than 80 mm Hg requires intervention, whereas the asymptomatic patient with a gradient less than 40 mm Hg can be safely observed. Indications for intervention in the group who is asymptomatic with a gradient between 50 and 80 mm Hg are less clear (613). The risk of sudden death in the population is usually related to severe disease; therefore, activity restriction is rarely indicated in the asymptomatic patient with a gradient less than 40 mm Hg. Naturally, antibiotic prophylaxis for potentially infective procedures is warranted. It is recognized that most patients with significant disease progress to aortic valve replacement later in life; however, palliation with open, closed, and transcatheter aortic valvuloplasty and valvotomy offers significant advantage to the growing infant and child. Surgical (604,614,615,616,617,618,619,620,621,622,623,624 and 625) and transcatheter (603,606,626,627,628,629,630,631,632,633,634,635 and 636) procedures result in similar relief of obstruction with equivalent incidence of postprocedure insufficiency and may delay the need for aortic valve replacement for several years. The method used to establish a reduction in the gradient is based more on institutional experience. Acute results in the neonate depend on associated conditions and the severity of ventricular dysfunction. Using the pulmonary valve to allow for growth of the aortic root is promising as an alternative, although long-term follow-up data are required in children and neonates before one considers this a primary option (625,637,638 and 639).

Left Ventricular Outflow Tract Obstruction

Obstruction to the left ventricular outlet can occur at a valvular level, a subvalvular or supravalvular level, or at more than one site (*e*Fig. 30.0.21). The fixed or discrete forms of subaortic obstruction have features of both congenital and acquired pathology, and many have some degrees of aortic-mitral separation, producing an intrinsically abnormal left ventricular outflow tract (640,641,642,643,644,645,646,647,648,649,650,651,652,653,654 and 655). This condition is rarely fibrous and discrete (646,647 and 648). The most commonly recognized complications of fixed subaortic stenosis include infective endocarditis, aortic regurgitation, and possible development of an inherent muscular obstruction. The incidence of aortic regurgitation is estimated to be as high as 50% in affected patients and is not static. Subaortic stenosis is a progressive condition, with worsening of the outflow tract pressure gradient over time (655); aortic regurgitation develops and progresses with time. At least two mechanisms have been implicated as causal to the aortic regurgitation. The probability of aortic incompetence at follow-up is significantly related to (a) older age at operation, (b) higher preoperative gradient, (c) cardiomegaly, and (d) surgical myomectomy. Early surgical intervention is likely to reduce acquired damage to the aortic valve, but this view is not universally supported (655). Aortic regurgitation may, in some patients, define the position of the obstructing subaortic fibromuscular tissue, a maneuver noted in cardiac angiography.



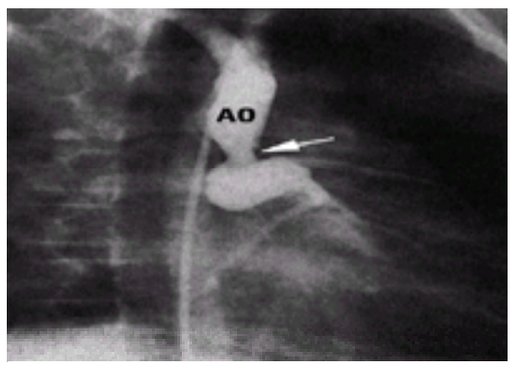
***e*FIGURE 30.0.21** So-called discrete, fixed-type, and short-segment subaortic stenosis (*arrows*) demonstrated by this right axial oblique left ventriculogram. AO, aorta; LV, left ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Video 30.13 Subaortic stenosis. A radiolucent membrane is visualized just below the aortic valve cusps (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Tissues derived from the membranous septum, tricuspid or mitral valve, accessory mitral valve, cysts of various composure, and cardiac tumor may produce left ventricular outflow tract obstruction. Posterior displacement of the infundibular septum is well recognized as perhaps the most frequent mechanism for subaortic stenosis in the patient with interruption of the aortic arch, and this produces a typical ventricular septal defect inferior to the displaced infundibular septum. An extensive literature documents the association between ventricular septal defect and subaortic stenosis (656,657,658,659,660,661 and 662). The morphologic bases for the subaortic stenosis are variable and may reflect posterior or caudal malalignment of the infundibular septum (as seen in the patient with interruption of the aortic arch or coarctation of the aorta); abnormal muscle bundles of the left ventricle in the patient with midtrabecular muscular ventricular septal defects; so-called fibrous type of subaortic stenosis associated with perimembranous ventricular septal defect and anomalous muscle bundle of the right ventricle; and subaortic stenosis reflecting tricuspid, mitral, or accessory tissue tags (656,657,658,659,660,661,662 and 663). It is often the ventricular septal defect or associated obstructive anomaly of the aortic arch that dominates the clinical picture in most of these patients. Indeed, in many patients, the subaortic stenosis seemingly develops on the substrate of a ventricular septal defect.

Ventricular Septal Defect, Subaortic Stenosis, and Divided Right Ventricle

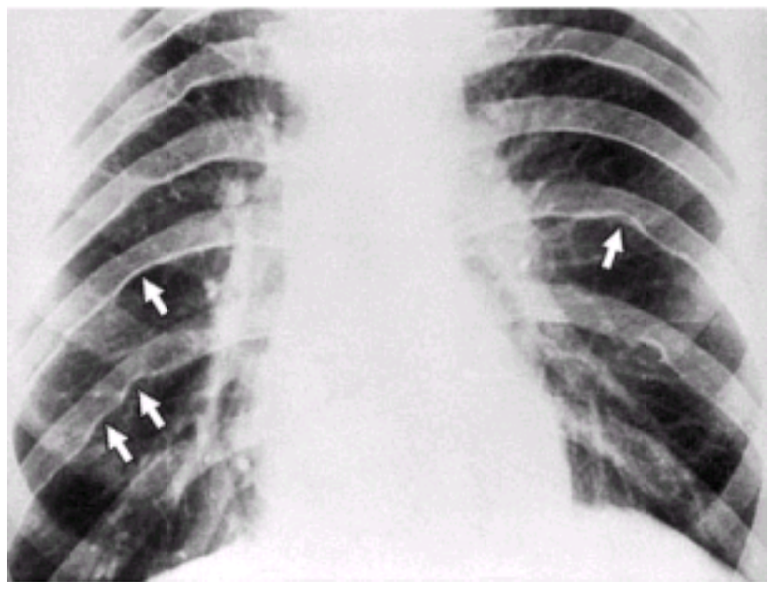
A well-known relationship in patients with a perimembranous ventricular septal defect, a right ventricular anomalous muscle bundle, and a fixed subaortic abnormality has been defined (664). In some patients, progression of a subaortic deformity initially produces no obstruction, and some years later causes severe left ventricular outflow tract obstruction after surgical closure of a ventricular septal defect with or without resection of anomalous muscle bundles of the right ventricle (664). For a discussion of supravalvular aortic stenosis (*e*Fig. 30.0.22), see the section Natural History of Congenital Heart Disease, earlier in this chapter.



***e*FIGURE 30.0.22** Supravalvular aortic stenosis in a patient with Williams syndrome. Note the important supravalvular narrowing (*arrow*). AO, aorta. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Coarctation of the Aorta

Coarctation of the aorta is defined by a narrowing of the descending thoracic aorta, usually in the region of the ductus (or ligamentum) arteriosus. This narrowing is due to the presence of a shelf composed of thickened intima with an increased media that typically contains collagen, smooth muscle cells, and varying amounts of elastic tissue. In the neonate or small infant, ductal tissue composed of smooth muscle fibers that constrict with ductal closure may be present (665,666). The ductus arteriosus plays a pivotal role in the clinical presentation of an isolated lesion. Prevalence at birth ranges from 0.239 to 0.430 per 1,000 live births (667,668). A coarctation of the aorta may occur in isolation; however, it is often associated with intracardiac congenital heart disease, often resulting in decreased aortic blood flow (*e*Table 30.0.2).

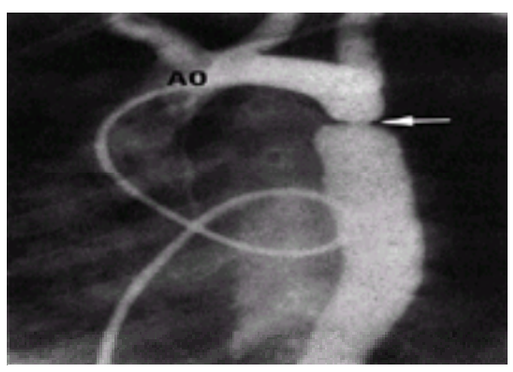


Chest x-ray in coarctation of the aorta. There is prominent rib notching (*white arrows*).

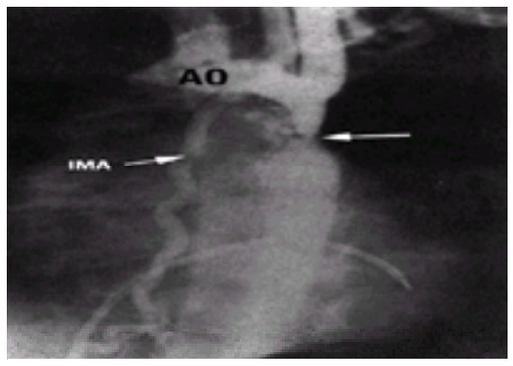
Video 30.14 Coarctation of aorta (oblique). A signal-void jet is visible in the proximal descending aorta due to a short-segment narrowing representing a coarctation. Left ventricular hypertrophy is also present. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

***e*TABLE 30.0.2** COARCTATION OF THE AORTA: ASSOCIATED ANOMALIES
Patent ductus arteriosus
Transverse aortic arch hypoplasia
Bicuspid aortic valve
Ventricular septal defect
Subaortic stenosis
Mitral valve anomalies
Positional anomalies of the great arteries (e.g., transposition)

The timing and type of clinical presentation vary in coarctation of the aorta, depending on the nature of the lesion with respect to the ductus arteriosus (*e*Fig. 30.0.23 and *e*Fig. 30.0.24). Consideration must be given to the possibility of Turner's syndrome in girls, as coarctation of the aorta represents the most common cardiovascular anomaly. In the so-called infantile-type isolated coarctation of the aorta, systemic blood flow is often dependent on the patency of the ductus arteriosus and may be affected by the status of the pulmonary vascular bed; thus, the presentation often evolves over the first week of life. Differential cyanosis may occur in the newborn as a result of the right-to-left flow of systemic venous blood from the right ventricle to the pulmonary artery and through the ductus arteriosus to supply the descending aorta (669). Restriction or closure of the ductus arteriosus can result in increased afterload, which, if severe, leads to profound left ventricular dysfunction, with circulatory collapse in the first week of life. Prostaglandin infusion to reestablish patency of the arterial duct can be life-saving. Typically, the affected neonate is pale and diaphoretic with a history of poor feeding and tachypnea. Pulses in the lower limbs are typically diminished or absent, and careful blood pressure measurements in all four limbs are mandatory, recognizing the care that must be taken in obtaining and interpreting neonatal blood pressure measurements (670,671 and 672). It is important to acknowledge that the femoral pulses may be normal early in the first week of life, as the ductus arteriosus usually is most restrictive at the pulmonary end, with diminished pulses present later as the aortic insertion of the ductus arteriosus becomes narrowed. In the setting of a persistently patent ductus arteriosus, diagnosis is indeed difficult. One must also be alerted to other more unusual causes of diminished femoral pulses in the neonate, including cerebral arteriovenous malformations, aortic thrombosis, or abdominal aortic coarctation. Auscultation often is related to associated defects; however, a gallop due to the presence of third and fourth heart sounds in the setting of a failing ventricle is not uncommon. Right ventricular hypertrophy results from the increased work in maintaining systemic flow and is evident on the scalar electrocardiogram with associated right-axis deviation and strain pattern. The chest radiograph may demonstrate cardiomegaly in the sick neonate, but is not diagnostic. Notably, the finding of rib notching is never present in the neonate.



***e*FIGURE 30.0.23** Severe coarctation of the aorta (AO) (*arrow*) demonstrated by aortography. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)



***e*FIGURE 30.0.24** Significant collaterals derived from the internal mammary artery (IMA) in a different patient with a severe coarctation of the aorta (AO) (*arrows*). (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

The older child or adult with a coarctation of the aorta presents differently. Often patients are asymptomatic with upper limb hypertension. Occasionally, some patients present with recurrent headache, nose bleeds, or lower limb claudication and weakness. Physical examination invariably includes differential blood pressure measurements, with diminished or absent femoral and pedal pulses underscoring the importance of palpating lower limb pulses in all patients with systemic hypertension (673). A short systolic murmur may be present over the anterior left precordium, radiating to the back, with continuous murmurs from collateral vessels in some patients over the superior left and right chest as well as the back. The electrocardiogram is often within normal limits for age but may demonstrate left ventricular hypertrophy. Rib notching due to collateral vessels may be noted in children most reliably over the age of 5 years with a characteristic “3” sign in many patients (674). It is possible to detect a coarctation of the aorta *in utero*, recognizing the need for meticulous serial aortic arch measurement and its known association with more complex congenital heart disease (21,675,676). First, laterality of the aortic arch is determined, followed by an assessment of the head and neck vessels and transverse arch. In the presence of a closed ductus arteriosus, there is a typical spectral pattern representing diastolic runoff with severe obstruction (677).

HEART SOUNDS

Audio 30.15 Left ventricular outflow tract obstruction in severe hypertensive heart disease. Auscultation in a 47-year-old female patient with severe concentric left ventricular hypertrophy with intracavitary velocity of 3.7 m/sec and pressure gradient across the left ventricular outflow tract of 50 mm Hg by catheterization. Note the systolic ejection murmur and normal second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 30.16 Left ventricular outflow tract obstruction in severe hypertensive heart disease. Auscultation in a 47-year-old female patient with severe concentric left ventricular hypertrophy with intracavitary velocity of 3.7 m/sec and pressure gradient across the left ventricular outflow tract of 50 mm Hg by catheterization. Note the systolic ejection murmur and normal second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be iewed with QuickTime. If you do not have QuickTime you may download it here.*

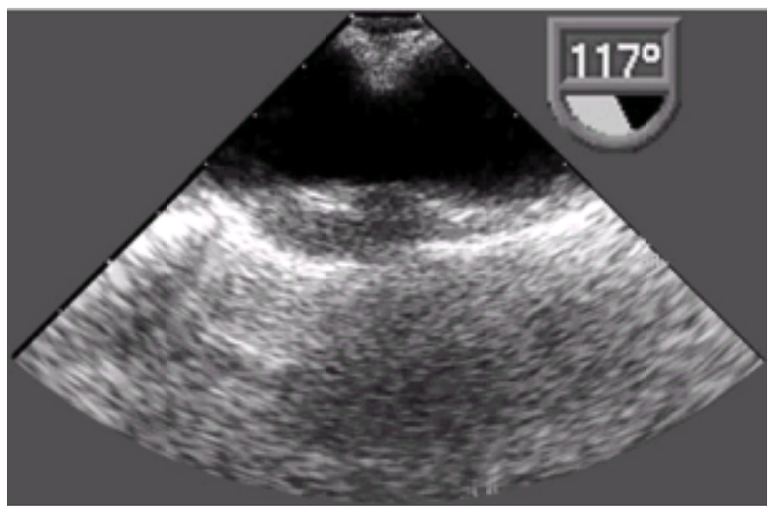
HEART SOUNDS

Audio 30.17 Left ventricular outflow tract obstruction in severe hypertensive heart disease. Auscultation in a 47-year-old female patient with severe concentric left ventricular hypertrophy with intracavitary velocity of 3.7 m/sec and pressure gradient across the left ventricular outflow tract of 50 mm Hg by catheterization. Note the systolic ejection murmur and normal second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 30.18 Left ventricular outflow tract obstruction in severe hypertensive heart disease. Auscultation in a 47-year-old female patient with severe concentric left ventricular hypertrophy with intracavitary velocity of 3.7 m/sec and pressure gradient across the left ventricular outflow tract of 50 mm Hg by catheterization. Note the systolic ejection murmur and normal second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

If echocardiography fails to delineate the anatomy completely, excellent images of the aortic arch can be obtained using MRI techniques (678,679). In general, invasive imaging using cineangiography or digital subtraction techniques as a diagnostic procedure is reserved for unusual situations. In addition to the coarctation, an assessment for the origin and course of the head and neck vessels, presence and extent of the collateral circulation, and the presence of aneurysmal dilatation of the aorta or subclavian vessels is important to planning intervention. A careful hemodynamic evaluation of the pressure gradient from proximal to distal descending thoracic aorta should distinguish the true lesion from a pseudocoarctation due to a tortuous course of the aorta distal to the transverse arch.



A still frame of a transesophageal echo demonstrating a coarctation of the aorta. Note the local narrowing of the aorta located at the junction of the distal arch and descending aorta. There was a 100–mm Hg pressure gradient across the coarctation as determined by continuous wave Doppler.

VIDEO

Video 30.19 Color Doppler interrogation of the coarctation demonstrating the high-velocity, turbulent flow across the focal narrowing in the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

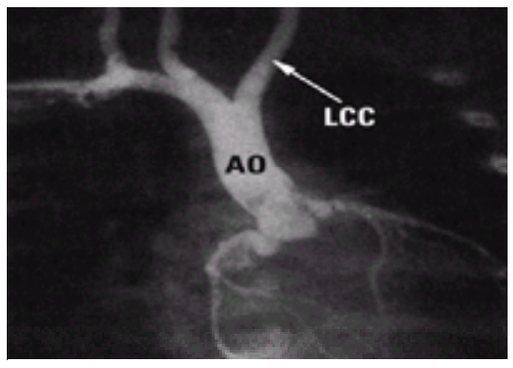
The outlook for neonates presenting with circulatory collapse is understandably dismal in the absence of intervention, initially with prostaglandin infusion to restore patency of the ductus arteriosus before more definitive therapy. Although surgical intervention has resulted in significant improvements in outcome, these patients remain at risk for premature atherosclerosis, late hypertension, and premature death, with age at operation reflecting an incremental risk factor (680,681,682 and 683).

Surgery for a “native” isolated coarctation of the aorta is directed to resecting the coarctation with either primary end-to-end anastomosis of the aorta or arch augmentation using a subclavian flap technique. An end-to-side augmentation of the transverse arch is used where significant hypoplasia is expected to compromise the postoperative course. In most situations, this is accomplished using a left posterolateral thoracotomy, but an anterior midline sternotomy may be used when associated lesions also are being addressed. Some surgeons prefer to augment the aorta with a Dacron patch arterioplasty, and rarely in long-segment lesions, an interposition graft is necessary. The hospital mortality in the current surgical era is low for neonates (2% to 10%), and results are even better for infants and older children (684,685,686,687,688,689,690 and 691). Postoperative problems include paradoxical systemic hypertension, abdominal pain, chylothorax, vocal cord paralysis, aneurysm formation, and rarely spinal cord ischemia, impaired left arm growth, or gangrene. Despite early intervention, there is some evidence of altered vascular reactivity, particularly in the upper limbs, which may predispose to hypertension, although the exact mechanism remains to be ascertained (680,683). Freedom from restenosis in early childhood in the current surgical era ranges from 81% to 96% for neonates and young infants (685,688); the risk of restenosis is less than 5% in the older patient (681).

Percutaneous transcatheter angioplasty of the so-called native or recurrent coarctation of the aorta also has been described, with acute results and long-term results similar to those of surgery (692,693,694,695,696,697,698,699,700,701,702,703 and 704). Concern arises with respect to the occurrence of aneurysms and the fate of the femoral artery used for the procedure. Results in neonates are not as encouraging as those in older children, with reintervention either in the catheterization laboratory or the surgical theater. Concern has been expressed regarding a potential for spinal cord compromise with surgery after angioplasty due to involution of protective collateral vessels, but this concern is not borne out by the literature (699). Complications include femoral artery thrombosis, aneurysm formation, thromboembolic cerebrovascular events, vessel perforation, and rarely aortic rupture. Life-long follow-up, ideally with periodic MRI, for growing aneurysms is mandatory, as is careful surveillance for restenosis. Whereas angioplasty remains most appropriate for the growing child, the development of extra-large stents offers an attractive alternative to surgery in selected patients (705,706,707 and 708).

Interruption of the Aortic Arch

Interruption of the aortic arch is an uncommon cardiovascular anomaly, accounting for less than 1.3% of critical congenital heart disease (709,710), characterized by the absence of anatomic continuity between the transverse aortic arch or isthmus and the descending thoracic aorta (711,712,713 and 714) (eFig. 30.0.25). This condition usually produces symptoms in the neonate coincident with constriction or closure of the arterial duct, although patients surviving to adulthood have been reported (715,716 and 717). Symptoms reflect a disordered circulation to that portion of the body supplied by the arterial duct before its functional closure. Interruption of the aortic arch should be distinguished anatomically from atresia of the aortic arch, where continuity between these segments is achieved by an imperforate fibrous strand of various lengths (although the hemodynamic and physiologic effects may be identical). This condition is usually not familial, but there is a well-known association between interruption of the aortic arch and DiGeorge syndrome; this syndrome is characterized by maldevelopment of the third and fourth pharyngeal pouches (i.e., the thymus and parathyroid glands) (718,719,720,721,722,723,724,725 and 726).



***e*FIGURE 30.0.25** Interruption of the aortic arch distal to the left common carotid artery (LCC) demonstrated by ascending aortography. AO, aorta. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

The initial classification for interruption of the aortic arch was proposed by Celoria and Patton (711) and was based on the site of the interruption: type A, distal to the left subclavian artery; type B, between the left common carotid artery and the left subclavian artery; and type C, between the innominate artery and the left common carotid artery. The last site of interruption is by far the least common. The classification of Celoria and Patton did not take into consideration patients with interruption and a right-sided aortic arch, nor did it mention the aberrant subclavian artery.

Commonly Associated Malformations

Interruption of the aortic arch rarely occurs in isolation. The most frequently associated cardiac lesions are a ventricular septal defect and a patent arterial duct. Considerable scrutiny has focused on the form of the ventricular septal defect. Although the ventricular septal defect may occupy any position within the ventricular septum, its morphology most commonly compromises flow to the ascending aorta during fetal life. The defect that so characterizes interruption of the aortic arch is the posterior malalignment of the infundibular septum, which occurs above the ventricular septal defect and below the aortic valve to encroach on the left ventricular outflow tract (714,715 and 716,727,728 and 729). The malalignment occurs as though the door of the infundibular septum is opened toward the left ventricular outflow tract. The so-called hinge of the door is along the ventriculoinfundibular fold when viewed from the right ventricle and along the aortic valve annulus when viewed from the left ventricle. The ventricular septal defect produced by this posterior malalignment of the infundibular septum is more commonly a muscular outlet defect and less frequently perimembranous. The ventricular septal defect in interruption of the aortic arch does not invariably involve posterior displacement of the infundibular septum. The doubly committed subarterial ventricular septal defect in the patient with interruption of the aortic arch can occur. In addition, a perimembranous confluent defect with aortic overriding and partial closure by tricuspid tissue was not uncommon in any large cohort of these patients. Tissue tags derived from the tricuspid valve and responsible for narrowing the ventricular septal defect may further compromise the left ventricular outflow tract, which is already reduced in size because of the aortic override.

Left Ventricular Outflow Tract Obstruction in Interruption of the Aortic Arch

Multiple mechanisms have been identified to produce left ventricular outflow tract obstruction in hearts with interruption of the aortic arch and concordant atrioventricular and ventriculoarterial connections (714,715 and 716,727,728,729,730 and 731). Those morphologic variables include the degree of development, malalignment, and deviation of the infundibular septum; the length of the subpulmonary infundibulum; overriding of one or the other of the arterial trunks; hypertrophy of the anterolateral muscle bundle; anteroseptal bulge or twist of the anterior interventricular septum; stenosis of the bicuspid aortic valve; or hypoplasia of the aortic valve annulus. The left ventricular outflow tract obstruction may be quite mild or severe, so severe in some patients that conventional biventricular repair is seemingly precluded.

Interruption of the Aortic Arch and DiGeorge Syndrome

There is a particular association between anomalies of the third and fourth pharyngeal pouch and interruption of the aortic arch, DiGeorge syndrome (718,719,720,721,722,723,724,725 and 726). Features typical of DiGeorge syndrome are hypocalcemia and defective thymic-mediated cellular immunity (725). Also common in these patients are anomalies of the face, palate, ears, and particular congenital heart malformations. The hypocalcemia and defective thymic-dependent cellular immunity reflect either absent or deficient thymic and parathyroid tissue. Interruption of the aortic arch, type B, is the major cardiac anomaly, and second in frequency is truncus arteriosus. When viewed from the perspective of interruption of the aortic arch, 68% had DiGeorge syndrome, as did 33% of the patients with truncus arteriosus. Microdeletion of chromosome 22 is quite common in patients with conotruncal abnormalities and between anomalies of the third and fourth pharyngeal pouch.

Clinical Features. With the normal postnatal changes in ductal structure and function, the portion of the systemic circulation requiring ductal patency becomes inadequate. Thus, in most instances, interruption of the aortic arch is a disorder of the neonate. The gravity of this disorder is illustrated by the observation that the

average age at death of these babies in Van Praagh's series was only 6 days; no sex predilection was found. Almost all these babies present with some respiratory distress, mild to severe cyanosis, varying degrees of congestive heart failure, and clinical evidence of low cardiac output. The amplitude of peripheral pulses may be reduced. In some infants in an agonal condition, all peripheral pulses are feeble. In others, the left brachial and radial pulses and the femoral pulses are substantially weaker in caliber than the right radial and brachial pulses, suggesting interruption proximal to the arch origin of the left subclavian artery. When both brachial pulses are relatively strong but the femoral pulses are weak or impalpable, one would suspect the level of obstruction to be distal to the left subclavian artery. In that situation, in which both arm and both leg pulses are weak while both carotid pulses are strong, one would suspect obstruction proximal to the left subclavian artery with aberrant origin of the right subclavian artery as the last arch branch. Strong right arm and right carotid pulses and weak left carotid, left arm, and both femoral pulses would localize the obstruction between the innominate artery and the left common carotid artery (type C interruption) with normal origin of the right subclavian artery. The cardiac examination often demonstrates a bulging left chest and a hyperdynamic left precordium with a prominent right ventricular impulse. The heart sounds are crisp, with the second sound closely split. A blowing systolic ejection murmur, grade 2 to 3/6, is audible along the left sternal edge. Conspicuous diastolic flow rumbles are uncommon in the neonate, but S_3 gallop rhythms are frequent. The liver shows a variable degree of enlargement, reflecting the severity of the congestive heart failure.

Diagnosis. Neither chest radiography nor electrocardiography is diagnostic of interruption of the aortic arch. The diagnosis of aortic arch obstruction has fallen into the care of the echocardiographers, and this diagnosis is usually easily established. Unlike aortic coarctation, interruption of the aortic arch is associated with significant intracardiac abnormalities in the form of ventricular septal defect(s), left ventricular outflow tract obstruction, and other complex malformations. Echocardiographic assessment should therefore address not only the morphology of the aortic arch but also the intracardiac anomalies that affect surgical management and outcome. Angiocardiography is rarely required to make the diagnosis of aortic arch interruption.

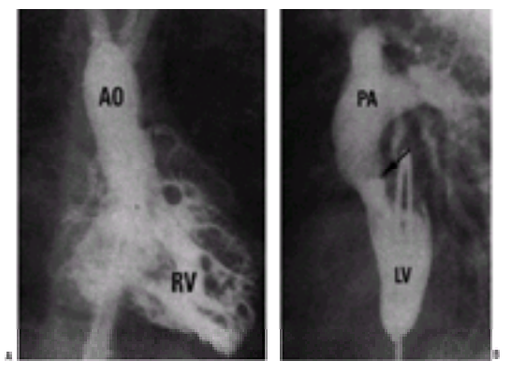
Medical Therapy. In any neonate in whom a severe obstructive anomaly of the aortic arch is considered likely, an E-type prostaglandin should be promptly administered intravenously (715,717,732). Attention should be paid to correcting any metabolic acidosis and to the maintenance of a satisfactory cardiac output. The judicious use of digoxin and potent diuretics is determined by the renal output and severity of congestive heart failure.

Surgical Therapy. Several major studies indicate that complete repair can be carried out with a mortality less than 10% to 15%, perhaps somewhat higher in those with severe subaortic stenosis (733,734,735,736,737 and 738). After repair, attention must be focused on the adequacy of the arch repair and on the development of left ventricular outflow tract obstruction (739).

Cyanotic Lesions

Transposition of the Great Arteries

The hallmark of transposition of the great arteries (740,741,742 and 743) is that the great arteries are placed across and originate from the inappropriate ventricle; thus, in the patient with atrial situs solitus or normal atrial arrangements and a concordant atrioventricular connection, the aorta originates from the morphologically right ventricle and the pulmonary artery from the morphologically left ventricle (744,745,746,747,748 and 749) (*e*Fig. 30.0.26). In the usual form of transposition of the great arteries, there is a well-formed subaortic infundibulum but no subpulmonary infundibulum, although other hearts with the abnormal or discordant ventriculoarterial connection of transposition have been described with bilateral infundibulum; bilaterally deficient infundibulum; or, rarely, just a subpulmonary infundibulum preventing mitral valve–pulmonary valve continuity (744,745,746,747,748,749,750 and 751). Whereas the most common spatial relationship between the great arteries in transposition is a rightward and anterior aorta, virtually any spatial relationship has been found, including the relatively uncommon posterior transposition (744,745,746,747,748,749,750,751,752,753,754 and 755).



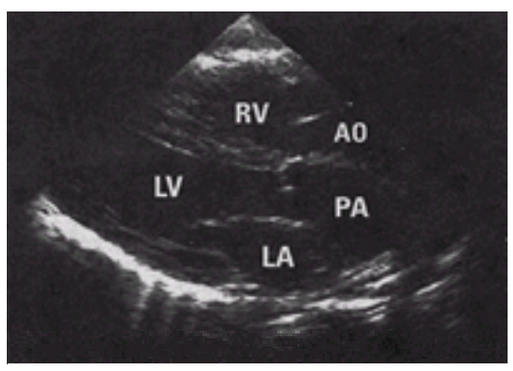
***e*FIGURE 30.0.26** Angiocardiography of complete transposition of the great arteries. **A:** The frontal right ventriculogram shows the discordantly connected transposed aorta (AO). **B:** The left ventriculogram shows the discordantly connected transposed pulmonary artery (PA) (*arrow*). LV, left ventricle; RV, right ventricle. (From Freedom RM, Mawson JB, Yoo S-J, et al. *Congenital heart disease: textbook of angiocardiography*. Armonk, NY: Futura Publishing, 1997, with permission.)

Prevalence

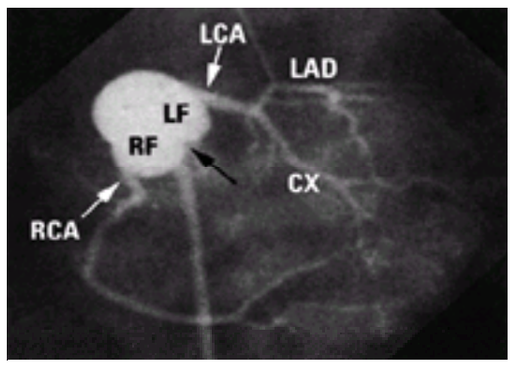
The prevalence of transposition of the great arteries is 0.2 per 1,000 live births, and approximately two-thirds are boys (756,757). Few major extracardiac anomalies are associated with transposition, and low birth weight is also uncommon.

Diagnosis

The clinical findings, chest radiographic findings, and electrocardiographic findings usually can make the diagnosis of complete transposition of the great arteries, but this diagnosis can be firmly established by two-dimensional echocardiography (740,743,758,759 and 760) (*e*Fig. 30.0.27). Diagnostic cardiac catheterization is rarely required in typical cases, although many institutions still perform aortography to define the anatomy of the coronary circulation (760,761) (*e*Fig. 30.0.28). The sites for mixing in transposition of the great arteries include the atrial septum, arterial duct, and ventricular septum. Because 65% to 75% of babies with transposition of the great arteries have an intact ventricular septum, it is not surprising that shortly after birth these babies become profoundly hypoxemic, coincident with ductal constriction and closure of the ovale foramen. For profoundly hypoxemic babies, institution of an E-type prostaglandin followed by balloon atrial septostomy should improve the state of arterial oxygenation (762,763,764,765,766 and 767).



***e*FIGURE 30.0.27** Transposition of the great arteries. Parasternal long-axis echocardiographic image of the great vessels in transposition of the great arteries. In contrast to the normal ventriculoarterial arrangement, the pulmonary and aortic roots align in the same two-dimensional plane, resulting in the typical appearance above in the setting of a discordant connection. Note that the aortic root lies anterior to the pulmonary valve. AO, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RV, right ventricle.

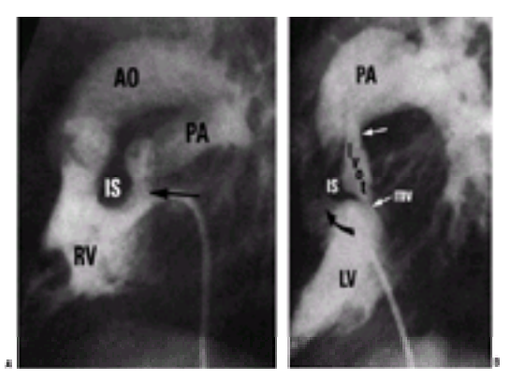


***e*FIGURE 30.0.28** The down-the-orifice view of the coronary arteries in complete transposition using the techniques of balloon occlusion. CX, circumflex artery; LAD, left anterior descending; LCA, left coronary artery; LF, left-facing sinus; RCA, right coronary artery; RF, right-facing sinus.

Surgical Therapy

A remarkable evolution in surgical therapy has occurred for the patient with complete transposition of the great arteries. In the long-term follow-up of large cohorts of patients who had undergone the atrial repair (after Senning or Mustard) for transposition, late right ventricular dysfunction, atrial rhythm disturbances reflecting damage to the sinoatrial node or its artery, and sudden death caused continuing concern because of ongoing attrition and morbidity (768,769,770,771,772,773,774,775,776 and 777). By the mid-1980s, the arterial switch procedure with coronary relocation was extended to the neonate (777,778,779,780,781,782 and 783). Today, in centers of excellence, the arterial switch operation can be carried out with a mortality less than 5% whether the ventricular septum is intact or in infants with an associated ventricular septal defect. Perhaps the risk for the arterial switch procedure is increased in infants with an intramural coronary artery or other uncommon coronary artery pattern. Thus, there has been increasing scrutiny on the echocardiographic and angiographic definition of the coronary artery anatomy in patients considered for the arterial switch repair. For infants presenting after the first month of life or in those with central nervous system hemorrhage or necrotizing enterocolitis or other medical or surgical conditions necessitating delay in the performance of the arterial switch procedure, Jonas and colleagues, of the Boston Children's group, championed the rapid two-stage arterial switch for transposition of the great arteries and intact ventricular septum beyond the neonatal period (784), which includes banding the pulmonary artery and placement of an arterial shunt to prepare the left ventricle by increasing its mass; the shunt is necessary to maintain a "reasonable" systemic arterial oxygen level. In the mid- and long-term follow-up of infants who undergo the arterial switch repair, some experience pulmonary artery stenoses, although this number has been reduced subsequent to the implementation of LeCompte's maneuver (785). Important supraaortic obstruction after the arterial switch operation has been uncommon. Although there have been comforting data supporting the growth of the coronary arterial anastomoses, more recent data provoke some concern in this regard.

In some patients with complex transposition, anatomy does not permit an arterial switch procedure. The most common of these is the group with a large malalignment ventricular septal defect and important left ventricular outflow tract obstruction (786,787,788,789,790 and 791) (*e*Fig. 30.0.29). In these patients, Rastelli's operation or the *reparation à l'étage ventriculaire* procedure can be used to achieve an anatomic repair. The left ventricle is tunneled through the ventricular septal defect to the aorta (the Rastelli concept); the main pulmonary trunk is divided or ligated as it exits the left ventricle, and continuity is achieved with a valved conduit. The *reparation à l'étage ventriculaire* procedure is similar, but the outlet septum is widely resected to permit a more direct pathway to the aorta from the left ventricle, and the main pulmonary trunk is connected directly to the right ventricle, thus avoiding the ongoing morbidity and need for reoperation when a conduit is used. These procedures usually are performed beyond infancy, and such patients may require palliation with balloon atrial septostomy and an arterial shunt.



***e*FIGURE 30.0.29** Transposition of the great arteries, ventricular septal defect, and left ventricular outflow tract obstruction (lvot). **A:** This lateral right ventriculogram shows the anterior aorta (AO), the smaller posterior pulmonary artery (PA), and the caudal displacement of the infundibular septum (IS), producing the lvot (*arrow*). **B:** This long axial left ventriculogram also demonstrates the posteriorly displaced IS, the ventricular septal defect (*black arrow*), and the long tunnel between the mitral valve (mv) and pulmonary valve (*white arrows*). LV, left ventricle; RV, right ventricle.

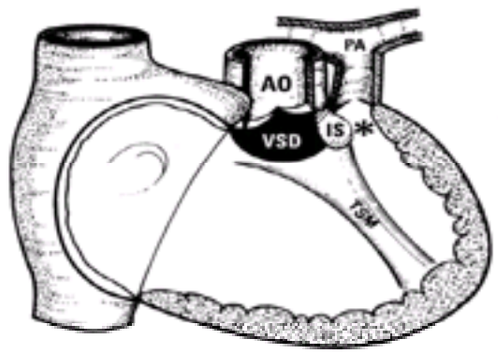
The Mustard or Senning forms of atrial repair still may be required for patients with a small ventricular septal defect and important pulmonary valvar stenosis. In both operations, the systemic venous return is diverted or baffled through the mitral valve into the left ventricle and then the pulmonary arteries, with the pulmonary venous return diverted to the tricuspid valve, the right ventricle, and the aorta. The long-term complications of these atrial repairs have been amply catalogued and reflect rhythm disturbances secondary to injury to the sinoatrial node or its artery, sudden death, and failure of the systemic ventricle, often accompanied by tricuspid regurgitation. In patients with a failing right ventricle, there has been some experience in converting them to anatomic repair (792,793,794 and 795). Most patients require preparation of the left ventricle by banding of the pulmonary trunk to increase the left ventricular mass. A few patients with a failing right ventricle have prepared the left ventricle by virtue of pulmonary hypertension (from pulmonary venous baffle obstruction) or from dynamic left ventricular outflow tract obstruction. In some patients with a failing right ventricle and important tricuspid regurgitation, banding of the pulmonary trunk to prepare the left ventricle by changing the geometry of the ventricular septum improves the tricuspid regurgitation (795).

Tetralogy of Fallot

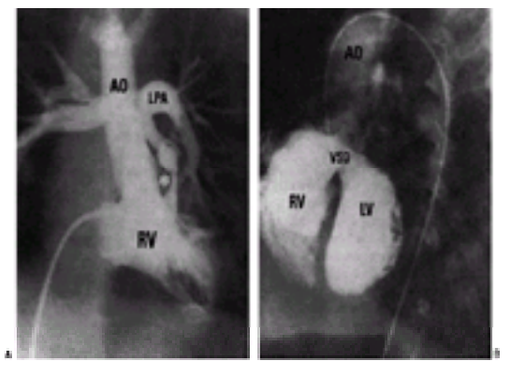
Considerable evolution has occurred in our understanding of what constitutes tetralogy of Fallot. Fallot, and those who translated his work, considered tetralogy as consisting of a ventricular septal defect, stenosis of the pulmonary outflow tract, an overriding aorta, and right ventricular myocardial hypertrophy, this last feature a natural consequence of the pulmonary outflow tract obstruction (796,797,798 and 799). The evolution in our understanding of the morphology is paralleled by those achievements in therapy: from palliation as the only form of therapy 50 years ago, to repair of this malformation at almost any age today (800,801,802,803,804,805,806,807,808,809,810,811 and 812). The most frequent segmental anatomy of tetralogy of Fallot is levocardia, atrial situs solitus, and concordant atrioventricular and ventriculoarterial connections. Tetralogy of Fallot in situs inversus totalis is uncommon (less than 5%), as is tetralogy of Fallot with isolated dextrocardia.

The morphologic findings of tetralogy of Fallot include pulmonary stenosis of a specific infundibular character, a ventricular septal defect located between the anterior and posterior limbs of the trabecular septal band overriding the aorta, and right ventricular hypertrophy (800,801,812,813,814 and 815). Right ventricular hypertrophy is progressive, reflecting the myocardial response to both right ventricular outflow tract obstruction and to the large nonrestrictive ventricular septal defect. Uniting these features is anterocephalad deviation of the infundibular outlet septum, and this malalignment or displacement of the infundibular septum is now considered the essence of tetralogy of Fallot (*e*Fig. 30.0.30). Indeed, in 1970, Van Praagh and colleagues suggested that tetralogy of Fallot is really a "monology" of Fallot resulting from this displaced infundibular or outlet septum and that in tetralogy the outlet septum is "too short, too narrow, and too shallow" (816,817 and 818). The leftward or septal end of the infundibular septum is displaced anteriorly, inserting in front of the left anterior division of the septal band rather than between its two divisions as in the normal heart. The rightward aspect of the infundibular septum is rotated anteriorly and passed anteriorly and inferiorly to reach the free wall of the right ventricle so that the infundibular septum and its parietal extension lie almost in a sagittal plane rather than the usual frontal plane (806). Others, although agreeing that tetralogy reflects this malalignment of the outlet septum, do not agree that invariably the outlet septum is hypoplastic (813). In many patients, this infundibular obstruction is aggravated by a hypoplastic pulmonary valvular annulus, pulmonary valve stenosis with a bicuspid valve with thickened cusps and fused commissures, anomalous muscle bundles, and varying degrees of hypoplasia of the main pulmonary trunk and its branches (*e*Fig. 30.0.31). The pulmonary arteries can exhibit considerable variability in caliber; they may be nonconfluent with one pulmonary artery originating from an arterial duct (819). Rarely, one pulmonary artery, usually the left, may originate from the ascending

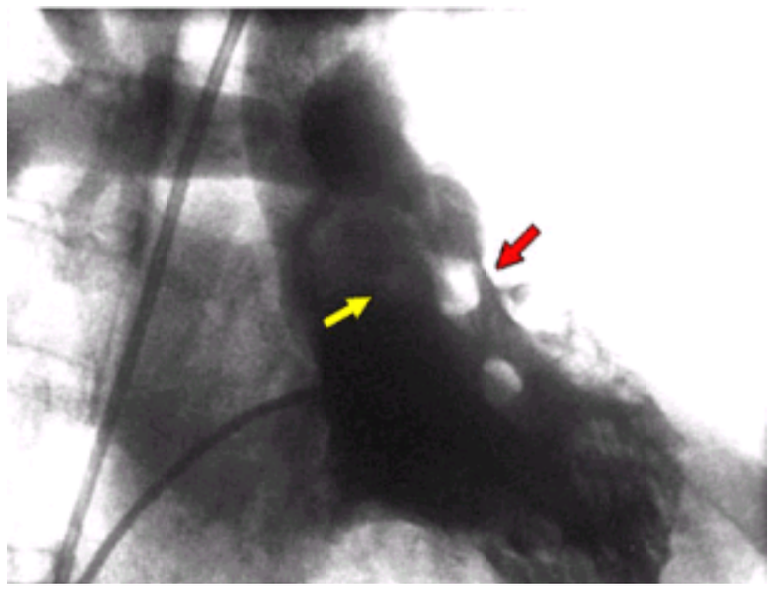
aorta. The coronary arteries also may exhibit variation in aortic origin and epicardial course. The most important abnormality is origin of the anterior descending coronary artery from the right coronary artery (819). The left anterior descending coronary artery crosses the right ventricular outflow tract to descend in the anterior interventricular sulcus. In approximately 25% to 30%, the aortic arch is right-sided. Five to seven percent have multiple ventricular septal defects. A few patients with typical infundibular anatomy of tetralogy of Fallot have important ventricular hypoplasia.



***e*FIGURE 30.0.30** Diagram showing the essential "monology" of Fallot, posterior displacement of the infundibular septum (IS) producing a typical ventricular septal defect (VSD), and a narrowed pulmonary outflow tract (*asterisk*). AO, aorta; PA, pulmonary artery; TSM, trabecula septomarginalis.



***e*FIGURE 30.0.31** Tetralogy of Fallot. **A:** Right ventriculogram with cranial caudal angulation demonstrates right-to-left shunting to the aorta (AO) via the ventricular septal defect (VSD) and the narrowed (*asterisk*) right ventricular outflow tract. **B:** The VSD and overriding AO are demonstrated by this long axial oblique left ventriculogram. LPA, left pulmonary artery; LV, left ventricle; RV, right ventricle.



Tetralogy of Fallot. This right anterior oblique right ventriculogram demonstrates some of the findings of tetralogy of Fallot with subpulmonic or infundibular stenosis (*red arrow*) and overriding aorta (*yellow arrow*) and prominent trabeculation of the right ventricle consistent with right ventricular hypertrophy.

VIDEO

Video 30.20 Parasternal short-axis view of tetralogy of Fallot. Note the ventricular septal defect just beneath the right coronary cusp of the aortic valve. The infundibular pulmonic stenosis can be seen superiorly while the pulmonary valve with its vegetation can be seen to the upper right of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 30.21 Parasternal long-axis view of tetralogy of Fallot. Note the ventricular septal defect and the aorta and aortic valve overriding the interventricular septum. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 30.22 Color Doppler in the apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect by color flow and the overriding aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 30.23 Apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect, the overriding aorta, and the right ventricular hypertrophy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Prevalence

The diagnostic frequency for tetralogy of Fallot of 0.214 per 1,000 live births was provided by the New England Regional Infant Cardiac Program (820), and data from the more recently completed Baltimore-Washington Infant Study provided a prevalence of 0.262 per 1,000 live births (821). The Alberta Heritage Study indicated a liveborn prevalence of 0.184 per 1,000 live births (822) for tetralogy of Fallot.

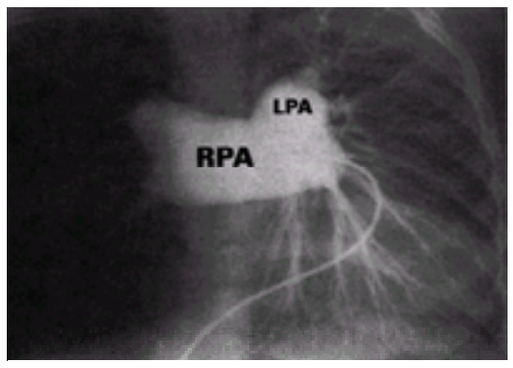
Clinical Course and Surgical Intervention

Untreated, only 10% of patients with tetralogy of Fallot survive to 10 years of age (823). Today, many centers prefer to carry out complete repair at any age, even in very young patients with small pulmonary arteries (805,806,807,808,809 and 810). The pulmonary arteries are small and thin-walled because they are underfilled (824). Most patients undergoing repair of tetralogy of Fallot require a transannular patch and thus have significant pulmonary regurgitation, which may have a long-term effect on the size and function of the right ventricle, and some may require pulmonary valve replacement. In these patients, it is always important to exclude important stenoses within the pulmonary arteries, whether acquired from a previously constructed surgical shunt or from ductal tissue in the wall of the pulmonary artery (825). Of the many morphologic considerations in the preoperative investigation of the patient with tetralogy of Fallot, it is imperative to define the epicardial course of the coronary arteries, showing whether a major coronary artery crosses the right ventricular outflow tract (819,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840 and 841). Surgical repair of uncomplicated tetralogy of Fallot can be accomplished with a mortality less than 3% (804,806,807,809,820). Medical treatment with a beta-blocker should be considered only a short-term maneuver to treat a hypercyanotic spell, but should not forestall surgical therapy, whether primary repair or a palliative shunt.

In follow-up, these patients should be surveyed for the effect of chronic pulmonary regurgitation, residual pulmonary artery branch stenosis, a residual left-to-right shunt, rhythm disturbance, and aortic insufficiency. As for any cardiac condition with residual morphologic abnormalities, the patient must be protected against infective endocarditis at times of risk.

Variant of Tetralogy of Fallot with Absent Pulmonary Valve

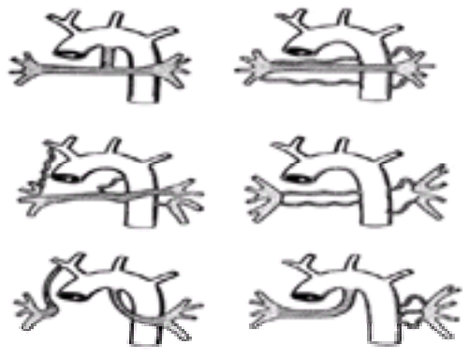
Variant of tetralogy of Fallot with absent pulmonary valve is rare, with a prevalence of approximately 0.0065 per 1,000 live births (842). Like other conotruncal abnormalities, there is an association with DiGeorge syndrome and deletion within chromosome 22, and most affected patients have the velocardial facial syndrome (843,844,845,846,847,848 and 849). Tetralogy of Fallot with absent pulmonary valve produces the substrate for varying degrees of right ventricular outflow tract obstruction, pulmonary regurgitation because of a pulmonary valve annulus completely devoid or nearly so of valvar issue, and right-to-left ventricular shunting at ventricular level because of a large ventricular septal defect resulting from anterior displacement of the infundibular septum, a finding considered characteristic of tetralogy of Fallot (850,851,852,853,854,855,856 and 857). What is so unusual about patients with tetralogy of Fallot and absent pulmonary valve is the aneurysmally dilated pulmonary arteries with their potential for compression of the major bronchi (*e*Fig. 30.0.32), potentially resulting in massively hyperinflated lungs and spontaneous pneumothorax. Patients with this syndrome also may have nonconfluent pulmonary arteries, with either a ductal origin or origin from the ascending aorta (858,859). Primary repair of the symptomatic infant with plication of the aneurysmal pulmonary arteries is preferred (860,861,862,863 and 864). Some of these infants may require lobectomy or subtotal lobectomy because of profound air trapping. In the preoperative management of the very ill infant with profound respiratory distress, it might be appropriate to keep the infant on his or her stomach (865).



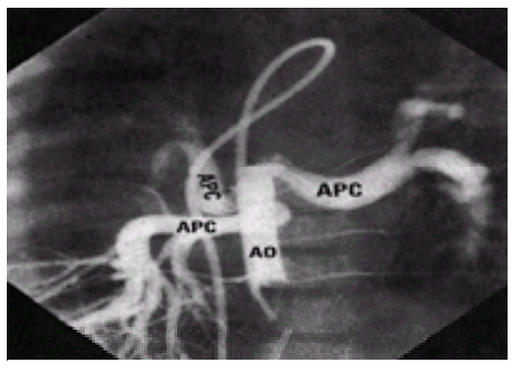
***e*FIGURE 30.0.32** The pulmonary arteries in the tetralogy of Fallot and absent pulmonary valve syndrome. Note the aneurysmally dilated pulmonary arteries. LPA, left pulmonary artery; RPA, right pulmonary artery.

Tetralogy of Fallot with Pulmonary Atresia

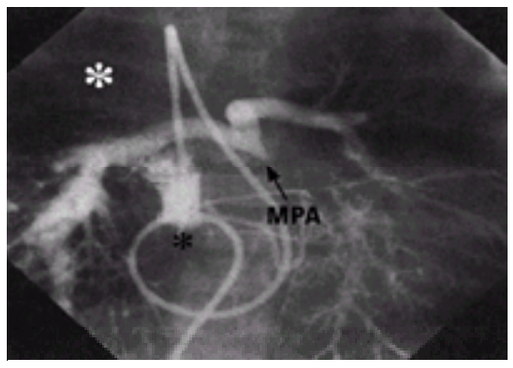
In hearts with tetralogy of Fallot and pulmonary atresia or pulmonary atresia and ventricular septal defect, fundamental to management and prognosis is the definition of pulmonary arterial supply (*e*Fig. 30.0.33, *e*Fig. 30.0.34, and *e*Fig. 30.0.35). For the most part, this is via the arterial duct or from collateral arteries originating directly or indirectly from the aorta (866,867,868,869,870,871,872,873,874,875,876 and 877). The surgical challenge rests with the ability to define, recruit, and rehabilitate the pulmonary arteries (877,878,879,880,881,882,883,884,885,886,887,888,889,890,891 and 892), achieved in part by resolution of the following questions: How is blood conducted into the lungs, and how does one define those sources of pulmonary blood supply to each of the bronchopulmonary segments (877,878,879,880 and 881) (*e*Fig. 30.0.34)? At this time, surgery should be eschewed because of the potential and reality for compromising the often fragile pulmonary circulation (893,894,895 and 896).



***e*FIGURE 30.0.33** Schematic diagram demonstrating some of the myriad variations in pulmonary arterial supply in the patient with pulmonary atresia and ventricular septal defect.



***e*FIGURE 30.0.34** Multiple large direct aortopulmonary collateral arteries (APCs) in a patient with pulmonary atresia and ventricular septal defect demonstrated by balloon occlusion aortography. AO, aorta.



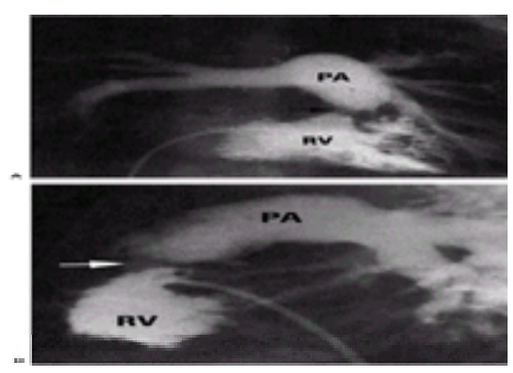
***e*FIGURE 30.0.35** Small confluent pulmonary arteries with the so-called seagull configuration demonstrated by balloon occlusion aortography. Note that the right upper lung field (*asterisk*) is not supplied from the true lung arteries. MPA, main pulmonary artery.

For the patient with tetralogy and pulmonary atresia, there is no “easy” surgical algorithm. Even the surgical management with confluent pulmonary arteries mediated by a solitary arterial duct remains contentious. Some would palliate the neonate or young infant with a modified Blalock-Taussig shunt until the patient reaches the age of 1 or 2 years and then carry out a complete repair. Others advocate a complete repair even in the neonate. The situation is even more complex for the patient with multiple sources of pulmonary blood flow. Many of these patients require unifocalization of the various sources of pulmonary blood flow, and the timing and methodologies remain both debatable and complex. Among any cohort of babies with complex pulmonary atresia and multiple sources of pulmonary blood supply, some sources will be precarious because of severe stenosis within the collateral, whereas in others the absence of any obstruction may promote pulmonary vascular obstruction in that segment of lung perfused by the “unprotected” collateral. Thus, in any given patient, some bronchopulmonary segments may be profoundly underperfused, and others are at risk for pulmonary vascular obstruction (878,879,881,897,898).

Clearly, however, for neonates presenting with profound hypoxemia, administration of an E-type prostanoid should by virtue of dilating a constricted arterial duct afford considerable improvement until the nature of the pulmonary blood supply is clarified by echocardiography or angiocardiography (878,879,881,899). Even in infants without an arterial duct, the prostanoid may provide improvement because of its pulmonary vasodilating effect.

Divided Right Ventricle and Ventricular Septal Defect

The most common etiology for division of the right ventricle is the so-called anomalous right ventricular muscle bundles (900,901,902,903,904,905 and 906) (*e*Fig. 30.0.36). There are, however, a variety of structures that may divide the right ventricle, including from tissue derived from perimembranous septum or septal leaflet of the tricuspid valve, the obstructive or imperforate form of Ebstein’s tricuspid valve deformity, accessory tricuspid valve, a windsock deformity of the tricuspid valve and contiguous tissue, muscular division within the right ventricle, neoplastic obstruction to the right ventricular outlet, hypertrophic obstructive cardiomyopathy, neurofibromatosis, or combinations of these (905,906).



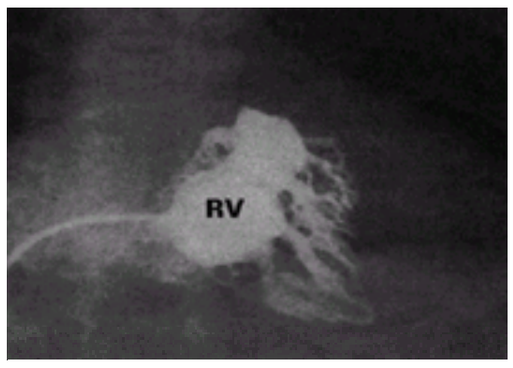
***e*FIGURE 30.0.36** Frontal **(A)** and lateral **(B)** right ventriculogram in a patient with anomalous muscle bundles (*arrow*) dividing the right ventricle (RV). PA, pulmonary artery.

The so-called double-chambered or divided right ventricle describes the conditions in which the morphologically right ventricle is divided or septated by muscular or fibrous structures (903). Most reported cases of the divided right ventricle are characterized by muscular obstruction, which usually but not invariably produces some degree of obstruction within and between the component parts of the right ventricle. Division of the right ventricle can occur at the junction between the inlet and trabecular components of the right ventricle or more distal at the level of the infundibulum. In a large cohort of patients with muscular division of the right ventricle, the most frequent associated abnormality is the perimembranous ventricular septal defect (900,903,907). When the ventricular septal defect is large and the right ventricular obstruction severe, the findings should be similar to the patient with tetralogy of Fallot. In some patients, however, the ventricular septal defect is only moderate in size, and spontaneous diminution in size of the defect may occur (905). If the muscular division of the right ventricle is particularly severe, profound right ventricular hypertrophy is a consequence of progressive diminution in the size of the ventricular septal defect and progression of the anomalous right ventricular muscles. It is important to remember the association between the perimembranous ventricular septal defect, muscular division of the right ventricle, and left ventricular outflow tract obstruction (905,906,907,908,909 and 910). In most patients, surgery can be accomplished with low risk (911).

Pulmonary Atresia and Intact Ventricular Septum

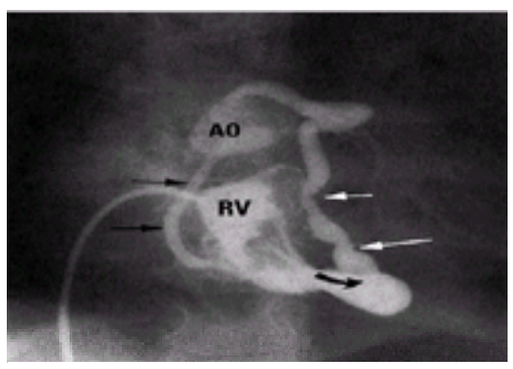
In its simplest definition, pulmonary atresia and intact ventricular septum constitute a disorder characterized by complete membranous and, in many patients, muscular obstruction to the right ventricular outlet (912,913,914,915,916,917,918,919,920,921,922 and 923). The pulmonary valve is imperforate, and in many patients right ventricular infundibular muscular atresia of variable extent or length is also present. The ventricular septum is intact (*e*Fig. 30.0.37). With rare exception, pulmonary blood flow in these patients is mediated by a patent arterial duct, and there is an obligatory right-to-left shunt at the atrial level (912). Rarely, the pulmonary arteries are nonconfluent, each mediated by its own arterial duct (924). Rarely, the only sources for pulmonary blood flow are direct aortopulmonary collaterals (925). Because the right ventricular outlet is blind, there is an obligatory right-to-left shunt at atrial level. As in the patient with tricuspid atresia, an atrial septal defect of some form is invariably present because of the obligatory right-to-left shunt at atrial level. In some infants, the atrial septal defect is restrictive at birth, and a balloon atrial septostomy

is necessary (912). In other patients, a seemingly adequate interatrial communication becomes restrictive with time.

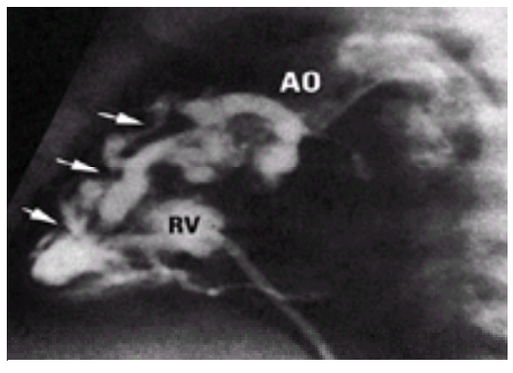


***e*FIGURE 30.0.37** Pulmonary atresia and intact ventricular septum with a well-formed tripartite right ventricle (RV).

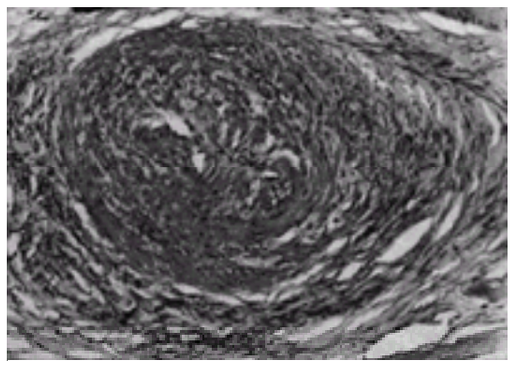
There is considerable heterogeneity. Some patients have a nearly normal-sized right ventricle and a blind pulmonary valve with only mild infundibular narrowing (*e*Fig. 30.0.37). Such patients are amenable to surgical pulmonary valvotomy or to radiofrequency catheter perforation of the valve (926). In other patients with pulmonary atresia and an intact ventricular septum, massive tricuspid regurgitation reflecting displacement or dysplasia of the tricuspid valve or even an unguarded tricuspid orifice results in extreme cardiomegaly and lung underdevelopment (927,928 and 929). These infants have a grossly disadvantaged right ventricle that is thinned, virtually devoid of normal myocardium that cannot generate systemic pressures (927,928). At the other end of the spectrum of this disorder are those patients with extreme tricuspid valve stenosis and hypoplasia, a hypertrophied and diminutive right ventricle that can generate systemic or suprasystemic right ventricular pressures (912) (*e*Fig. 30.0.38 and *e*Fig. 30.0.39). Many of these infants have ventriculocoronary connections with the potential for coronary arterial stenosis or interruption (930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949 and 950). Some infants in this group have a coronary circulation that is right ventricular dependent (*e*Fig. 30.0.40) (i.e., because of coronary arterial stenosis or interruption, coronary blood flow is mediated by right ventricular systole and blood entering the right ventricle) (930,934,935,937,938,939,940 and 941,943,944,945,946 and 947,949,950). In this situation, any maneuver that reduces the right ventricular systolic pressure or prevents blood from entering the right ventricle (thromboexclusion of the right ventricle) can unmask the egregious nature of the coronary circulation, resulting in myocardial ischemia, infarction, or death (951).



***e*FIGURE 30.0.38** Pulmonary atresia and intact ventricular septum with a unipartite right ventricle (RV), extensive ventriculocoronary connections (*curved black arrow*) to both ventricles with luminal irregularities. Note the retrograde flow from the coronary arteries to the aorta (AO). The straight black arrows point to the right coronary artery; the white arrows note the anterior descending coronary artery.



***e*FIGURE 30.0.39** Multiple levels of coronary artery stenosis and interruption (*arrows*) in this patient with pulmonary atresia and intact ventricular septum and a right ventricular (RV)–dependent coronary circulation. AO, aorta.



***e*FIGURE 30.0.40** The nearly complete occlusive coronary artery pathology in a patient with pulmonary atresia, intact ventricular septum, and a right ventricular–dependent coronary circulation.

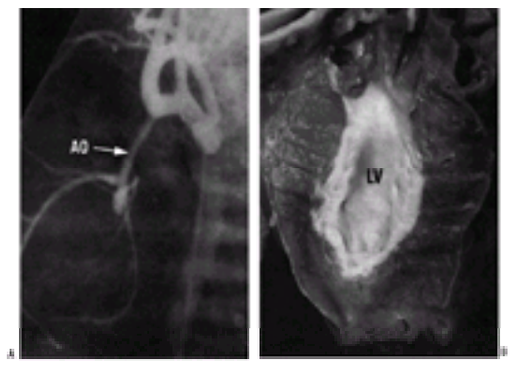
Pulmonary atresia and intact ventricular septum constitute an uncommon form of congenitally malformed heart, accounting for only approximately 3% of newborns with serious congenital heart disease (952) and a prevalence of 0.083 per 1,000 live births (953). In a survey of cyanotic neonates with congenital heart disease, this disorder ranks third after transposition of the great arteries and pulmonary atresia and ventricular septal defect (954). Fetal echocardiography provides a unique window to study the later phases of the fetal heart and to define specific types of heart predisposed to fetal death. There is increasing evidence that fetuses with florid tricuspid regurgitation may not fare well (955,956,957,958,959 and 960). Such fetuses are known to develop right-sided heart failure with pleural and pericardial effusions, ascites, pulmonary hypoplasia, and fetal death. Thus, fetal loss might be anticipated in a specific subset of patients with pulmonary atresia, intact ventricular septum, extremely severe tricuspid regurgitation, and a low-pressure right ventricle.

With the profound heterogeneity in the form of hearts with pulmonary atresia and intact ventricular septum, many of whom have a profoundly abnormal coronary

circulation, the surgical algorithms are complex. Because pulmonary blood flow is duct dependent, until a stable source of pulmonary blood flow is established, an E-type prostaglandin must be given. The diagnosis of pulmonary atresia and intact ventricular septum is usually easily established by cross-sectional echocardiography (961,962 and 963), but in those with the hypertensive and hypertrophied right ventricle, it is usually necessary to perform a cardiac catheterization to define the nature of the coronary circulation (912,920,922,923,930,935,936,937,938 and 939,964,965 and 966). Thus, some infants are amenable to right ventricular outflow tract reconstruction; others are amenable to some form of pulmonary valvotomy, but an arterial shunt is necessary to maintain a satisfactory systemic arterial oxygenation. Only 30% to 35% were alive at 15 to 20 years (967,968 and 969). We reported the results of the Fontan operation in these patients, including a group with a right ventricular–dependent coronary circulation (970). For infants with massive tricuspid regurgitation and a grossly disadvantaged right ventricle, the novel approach of Starnes of converting these patients to tricuspid atresia might salvage some (971).

Hypoplastic Left Heart Syndrome

Hearts with the usual forms of hypoplastic left heart syndrome are usually left-sided; the usual atrial arrangement (solitus) is present, and the atrioventricular and ventriculoarterial connections are concordant, although various expressions of the hypoplastic left heart syndrome have been identified in patients with right or left atrial isomerism. Hearts with the usual forms of hypoplastic left heart syndrome exhibit aortic atresia or severe stenosis, mitral atresia or severe stenosis, and often profound left ventricular hypoplasia with variable left ventricular endocardial fibroelastosis (eFig. 30.0.41). The interatrial communication is represented by a flap of the foramen ovale, but in 20% of patients with the hypoplastic left heart syndrome, the foramen ovale is prematurely sealed. Such infants are extremely hypoxemic, and many exhibit some degree of pulmonary lymphangiectasia. Once considered uncommon, a coarctation of the aorta is probably identified in 70% to 80%. Rarely, aortic arch interruption coexists with aortic atresia. In these uncommon patients, blood to the ascending aorta is conducted either from a right-sided arterial duct, an aortopulmonary fenestration, or via fifth aortic arch. The aortic arch is usually left-sided, and an arterial duct supports the entire systemic circulation in those infants with the usual expression of the hypoplastic left heart syndrome. With ductal closure, systemic output, including coronary blood flow, rapidly becomes inadequate, and a relentless metabolic acidosis results, culminating in death. Prevalence ranges from 0.164 to 0.267 per 1,000 live births (972,973).



***e*FIGURE 30.0.41 A:** Diminutive aorta (AO) and aortic atresia demonstrated by retrograde aortography in this duct-dependent condition. **B:** Small left ventricle (LV) with severe endocardial sclerosis.

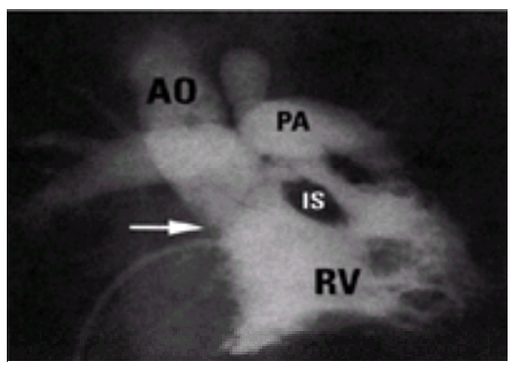
Treatment

The mainstay of medical therapy for hypoplastic left heart syndrome is the administration of an E-type prostaglandin to promote and maintain patency of the arterial duct and correction of metabolic acidosis (971,972,973,974,975 and 976). Many of these infants are better cared for ventilated and paralyzed. Supplemental oxygen should be administered judiciously because of the precarious balance between the systemic and pulmonary circulations. Enhancement of pulmonary blood flow could promote a “steal” from the systemic circulation, leading to myocardial insufficiency and death. Diagnosis is rapidly established by cross-sectional echocardiography, and cardiac catheterization is rarely required. Some infants with the hypoplastic left heart syndrome are extremely hypoxemic, reflecting premature closure of the ovale foramen (974,975).

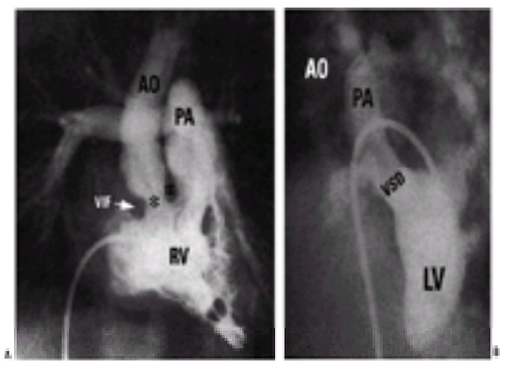
Hypoplastic left heart syndrome was once considered inoperable, but now two major forms of active intervention are available: staged surgical therapy as pioneered by Norwood, concluding in a Fontan operation (977,978,979,980,981,982,983,984,985 and 986), and cardiac transplantation (987,988,989,990 and 991). The initial operation consists of a wide atrial septectomy, reconstruction of the often diminutive ascending aorta with connection from the main pulmonary trunk and augmentation of the aortic isthmus to treat the often present coarctation of the aorta, and a 3.0- to 3.5-mm modified Blalock-Taussig shunt to the distal confluent pulmonary arteries. The point of disconnection of the distal pulmonary arteries is widely patched to avoid unilateral obstruction. Although in some centers this initial form of palliation can be achieved with a mortality of between 10% and 15%, the mortality in most centers is considerably higher. Between the first and second stage, unfortunately, some infants die; the causes of death include shunt occlusion, infection, adverse central nervous system events, and presumed dysrhythmia. The second stage usually is carried out when the infant is 3 to 9 months of age, which takes the form of a bidirectional cavopulmonary shunt with repair of any pulmonary artery stenosis and an atrial septectomy if necessary. Some patients also may require a tricuspid valve annuloplasty at this time. The “final” operation is a Fontan-type operation, usually a fenestrated lateral tunnel or extracardiac Fontan. The bidirectional cavopulmonary connection has a mortality of approximately 5%, and for patients meeting Fontan’s criteria, a Fontan-type operation can be carried out with a mortality less than or equal to 5%. The Loma Linda group has had extensive experience with transplantation as primary therapy for the hypoplastic left heart syndrome (987,988,989,990 and 991). They report a 25% pretransplant mortality, a 10% operative mortality, and 1- and 7-year survivals of 84% and 72%, respectively (42,43).

Double-Outlet Right Ventricle

DORV is a condition in which more than one-half of each great artery is connected to the morphologically right ventricle (992,993,994,995,996,997,998,999,1000,1001,1002 and 1003) (*e*Fig. 30.0.42 and *e*Fig. 30.0.43). In the uncommon situations in which the ventricular septum is intact, there is no difficulty in determining that both great arteries originate from the morphologically right ventricle; but usually there is a ventricular septal defect, and there may be difficulty in assigning the ventriculoarterial connection. DORV reflects considerable heterogeneity, with a wide range of spatial relationships between the great arteries; considerable variation in the location of the ventricular septal defect; pulmonary or aortic outflow tract obstruction; varying degrees of ventricular hypoplasia; and important abnormalities of the atrioventricular junction. Indeed, for some patients with significant ventricular hypoplasia or major straddling of an atrioventricular valve or a ventricular septal defect that is remote from either great artery, a one-ventricle or Fontan-type repair is considered. For those patients with a subaortic ventricular septal defect and no pulmonary outflow tract obstruction, presentation is similar to a patient with a large and nonrestrictive ventricular septal defect, and most are amenable to primary repair. The patient with the tetralogy type of DORV has a clinical presentation and course similar to that of the patient with tetralogy of Fallot (*e*Fig. 30.0.42). Most patients are amenable to primary repair, although some prefer palliation with a systemic-to-pulmonary artery shunt for small infants. The arterial switch operation with coronary artery relocation is the preferred operation for the patient with DORV with subpulmonary ventricular septal defect or the Taussig-Bing form of DORV, although some are treated by an intraventricular repair (*e*Fig. 30.0.43). Patients with DORV and subpulmonary ventricular septal defect or the Taussig-Bing form of DORV are likely to have right ventricular subaortic obstruction; some may have an associated obstructive anomaly of the aortic arch.



***e*FIGURE 30.0.42** Double-outlet right ventricle (RV) of the tetralogy-type with side-by-side great arteries and a narrowed subpulmonary outflow tract demonstrated by this frontal right ventriculogram. Arrow points to the level of the aortic valve. AO, aorta; IS, infundibular septum; PA, pulmonary artery.



***e*FIGURE 30.0.43 A:** Double-outlet right ventricle (RV) of the Taussig-Bing form with side-by-side great arteries and a narrowed subaortic outflow tract (*asterisk*) demonstrated by this frontal right ventriculogram. **B:** This left long axial oblique left ventriculogram demonstrates the subpulmonary ventricular septal defect (VSD) in this patient previously palliated by pulmonary artery (PA) banding. AO, aorta; LV, left ventricle; RV, right ventricle; VIF, ventricular infundibular fold.

Diagnosis and Treatment

Prevalence of DORV is low: 0.03 to 0.06 per 1,000 live births (1004,1005). The considerable heterogeneity in cardiac morphology embraced by the designation *DORV* is reflected in various clinical presentations as well. Thus, no single clinical feature, electrocardiogram, or chest radiograph is diagnostic of this condition. The echocardiogram certainly can establish the diagnosis of DORV and can define the important associated abnormalities as well. For most patients considered for either a biventricular repair and for all considered for a one-ventricle or Fontan-type repair, cardiac catheterization with angiocardiography is required (1006). The categorization of DORV by the relative position of the ventricular septal defect has been integrated into common usage, but this approach is physiologic, not anatomic (*e*Table 30.0.3).

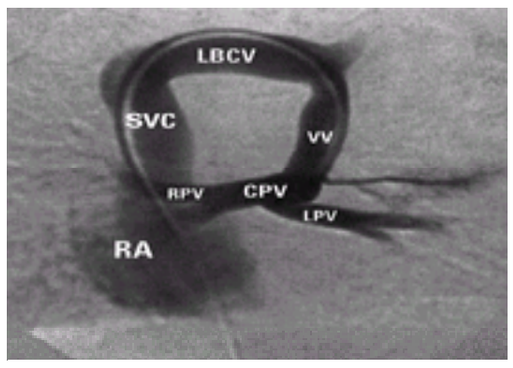
***e*TABLE 30.0.3** TYPES OF DOUBLE-OUTLET RIGHT VENTRICLE
Subaortic ventricular septal defect
Subpulmonary ventricular septal defect
Juxtaarterial or subarterial ventricular septal defect
Remote ventricular septal defect

One can provide general guidelines for the treatment of patients with the generic type of DORV as follows (996,997,998,999,1000,1001,1002 and 1003,1006):

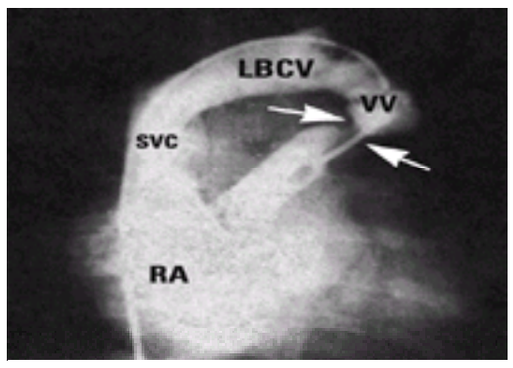
- DORV, large ventricular septal defect, and no pulmonary outflow tract obstruction: primary repair.
- DORV of the tetralogy type: Some would palliate in infancy, with repair beyond age 1 to 2 years; others would carry out a primary repair when the patient is symptomatic.
- DORV with subpulmonary ventricular septal defect, or DORV of the Taussig-Bing form: The two primary surgical considerations are (a) the arterial switch operation with coronary artery relocation with closure of the ventricular septal defect and (b) an intraventricular repair.
- DORV with so-called remote ventricular septal defect or complex DORV with ventricular hypoplasia or major straddling of an atrioventricular valve: Consider a one-ventricle-type repair.

Total Anomalous Pulmonary Venous Connections

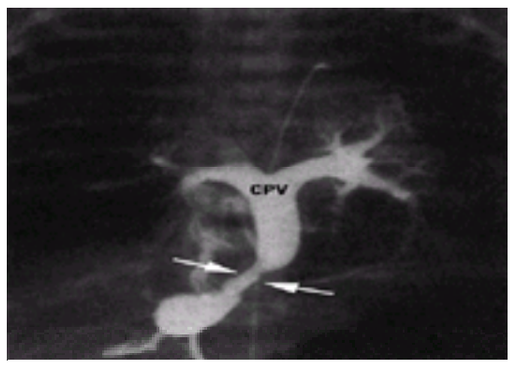
TAPVC is characterized by connection of all the pulmonary veins to one or more systemic veins and the right atrium or to the coronary sinus (1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017 and 1018) (*e*Fig. 30.0.44, *e*Fig. 30.0.45, and *e*Fig. 30.0.46). *e*Table 30.0.4 provides a commonly used classification of TAPVC.



***e*FIGURE 30.0.44** Total anomalous pulmonary venous return, supracardiac type, with a vertical vein (VV) connecting to the left brachiocephalic vein (LBCV). CPV, common pulmonary vein; LPV, left pulmonary vein; RA, right atrium; RPV, right pulmonary vein; SVC, superior vena cava.



***e*FIGURE 30.0.45** The vertical vein (VV) is narrowed (*arrows*) in its course through the anatomic vise. LBCV, left brachiocephalic vein; RA, right atrium; SVC, superior vena cava.



***e*FIGURE 30.0.46** Infradiaphragmatic total anomalous pulmonary venous connections to the portal system, with narrowing in its course (*arrows*). CPV, common pulmonary vein.

***e*TABLE 30.0.4** CLASSIFICATION OF TOTAL ANOMALOUS PULMONARY VENOUS CONNECTIONS
Supracardiac type
Right superior vena cava
Left superior vena cava
Left brachiocephalic vein via a vertical vein
Azygous vein
Cardiac
Right atrium
Coronary sinus
Left atrium (failure of complete incorporation of common pulmonary vein)
Infradiaphragmatic
Inferior vena cava
Ductus venosus
Portal vein
Left gastric vein
Mixed
To more than one site

The most serious clinical manifestation of TAPVC is severe obstruction (1011,1012,1014,1016,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030, 1031,1032,1033 and 1034), which results when the common pulmonary vein connects below the diaphragm to the ductus venosus or to the portal vein (*e*Fig. 30.0.46). Severe obstruction also has been documented with the supracardiac type, especially the form connecting to the brachiocephalic vein via a vertical vein. In this form, the ascending common pulmonary vein is obstructed in its course in the anatomic vise: the left pulmonary artery and the left mainstem bronchus (1014,1016,1017) (*e*Fig. 30.0.45). Rarely, pulmonary venous connections are obstructed in their connection to the coronary sinus. Perhaps the most severe form of obstructed TAPVC occurs when both right- and left-sided pulmonary veins form a confluence behind the heart, but an ascending or descending pulmonary vein has not formed or is atretic (1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033 and 1034). The obstructed form of TAPVC is characterized by progressive hypoxemia, a small heart, and intense pulmonary edema, sometimes accompanied by pulmonary lymphangiectasia (1024). In patients with so-called unobstructed TAPVC, most patients present in the first months of life, occasionally earlier, with findings of congestive heart failure and mild hypoxemia. Rarely, the patient with unobstructed TAPVC presents late, such as the patient with a large secundum atrial septal defect. The so-called “snowman” appearance in the supracardiac form of TAPVC to the brachiocephalic vein mediated by a vertical vein is rarely appreciated in the first months of life (1009,1010,1011 and 1012,1014,1016).

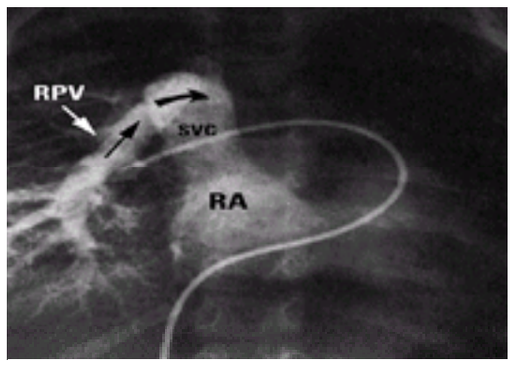
Diagnosis and Therapy

The diagnosis is readily made clinically and from cross-sectional echocardiography. Cardiac angiography is rarely required in typical forms of TAPVC, but it may be required in those patients with complex mixed or double drainage. Judicious use of digoxin and diuretics with ventilation are important preoperative maneuvers, with mechanical ventilation often being important in infants with severely obstructed total anomalous pulmonary venous return.

The treatment of choice is surgical repair; there is little to be gained by delay. The confluence of pulmonary veins behind the left atrium is the surgeon’s friend, and reanastomosis of the confluence to the posterior wall of the left atrium can be accomplished with a low surgical mortality (1014,1018). Some patients have come back with postoperative pulmonary venous obstruction, and surgical salvage in these patients has been disappointing (1014).

Partial Anomalous Pulmonary Venous Connections

One or more pulmonary veins may connect anomalously to a systemic vein, right atrium, or coronary sinus, with most pulmonary veins connecting to the left atrium (1035,1036,1037,1038,1039,1040,1041 and 1042) (*e*Fig. 30.0.47). The clinical findings, especially when there is an associated atrioventricular septal defect, are similar to the patient with a large uncomplicated atrioventricular septal defect, and repair usually can be deferred until the patient is 1 year of age or older. Occasionally, partial anomalous pulmonary venous return is identified in the patient with an intact atrial septum. The second heart sound may split and move normally, and the decision to intervene surgically is predicated on how many veins connect to the right side of the heart.



***e*FIGURE 30.0.47** Partial anomalous pulmonary venous connections of the right middle pulmonary vein (RPV) to the right superior caval vein (SVC). RA, right atrium.

Cor Triatriatum or Subdivided Left Atrium

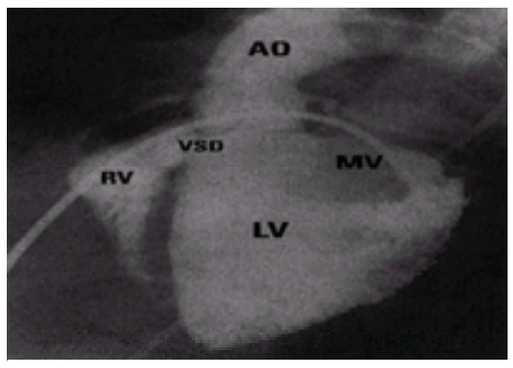
This uncommon congenital abnormality is characterized by a membrane dividing the left atrium into a superior chamber receiving the pulmonary veins and an inferior chamber receiving the left atrial appendage and mitral inflow (1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054 and 1055). The atrial septum may be intact, or an interatrial communication may be identified between the superior chamber and the right atrium, or inferior chamber and the right atrium. Rarely presenting in isolation in the newborn, cor triatriatum may present with pulmonary hypertension and pulmonary edema in infants as young as 1 to 2 months, and this disorder has been recognized in the adult as well. The clinical presentation depends on the size of the orifice of the dividing membrane and on any associated cardiac malformation. The severity of the pulmonary venous obstruction may be masked by the presence of associated complex congenital heart disease with important pulmonary outflow tract obstruction. The diagnosis is readily established by cross-sectional echocardiography, and surgical excision is the therapy of choice. Most data support the finding that reoperation is rarely necessary.

Congenital Pulmonary Vein Stenosis or Atresia

Congenital pulmonary vein stenosis and atresia are uncommon conditions. Congenital stenosis of all four pulmonary veins is considerably more complex than its designation implies, and often the process of pulmonary vein stenosis is diffuse with hypoplasia of the pulmonary veins (1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069 and 1070). This condition only rarely involves a discrete obstruction at the left atrial pulmonary vein connection; thus, surgical results for most patients are disappointing, with early initial improvement followed by recurrence of the stenosis, progressive pulmonary venous obstruction, pulmonary hypertension, and death. Congenital pulmonary vein atresia is usually unilateral (1071,1072,1073,1074 and 1075). By redistributing pulmonary blood flow to the unaffected side, unilateral pulmonary vein atresia may be reasonably well tolerated considering the ventilation-perfusion mismatch.

Tricuspid Atresia

The classic expression of tricuspid atresia is an absent right-sided atrioventricular connection (1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090 and 1091). Atrioventricular sulcus tissue is interposed between the floor of the right atrium and the ventricular mass, preventing any potential connection with the rudimentary right ventricle. Indeed, the floor of the right atrium is potentially in communication with the left ventricle, not the right (1085,1086). The right ventricle is usually quite small, lacking its inlet component (*e*Fig. 30.0.48). An atrial septal defect of some form is invariably present because of the obligatory right-to-left shunt at the atrial level. In some infants the atrial septal defect is very restrictive at birth, and a balloon atrial septostomy is necessary. In other patients, a seemingly adequate interatrial communication becomes restrictive with time. The ventriculoarterial connection may be concordant or normal, discordant or transposed. Rarely, there is a double outlet from the rudimentary right ventricle or left ventricle; a common arterial trunk has also been described. The original classification of tricuspid atresia is further subdivided in these patients by the character of the pulmonary blood flow: reduced, normal, or increased (1090,1091).



***e*FIGURE 30.0.48** Typical right ventricular hypoplasia in a patient with tricuspid atresia. AO, aorta; LV, left ventricle; MV, mitral valve; RV, right ventricle; VSD, ventricular septal defect.

Tricuspid atresia is an uncommon form of congenital heart disease, clearly less frequent than transposition of the great arteries, tetralogy of Fallot, or truncus arteriosus. Prevalence ranges between 0.039 and 0.051 per 1,000 live births (1092,1093 and 1094). Familial instances of tricuspid atresia have been reported (1095,1096). Seven percent of babies with tricuspid atresia in the New England Regional Infant Cardiac Program had birth weights less than 2.0 kg, and 13% were considered to have severe extracardiac anomalies (1095).

The diagnosis of typical tricuspid atresia can be suspected in a cyanotic infant with reduced pulmonary markings on the chest radiograph and a systolic ejection murmur whose electrocardiogram demonstrates left-axis deviation, right atrial enlargement, and left ventricular hypertrophy with a paucity of right ventricular forces (1097). Beyond echocardiography, cardiac catheterization is rarely required, but such investigation may be required before the performance of a bidirectional cavopulmonary connection and then again before the Fontan procedure.

The life history of patients with tricuspid atresia and indeed a wide range of congenitally malformed hearts was forever altered by the signal contribution of Fontan and Baudet, when they partitioned and thus separated the atria and constructed an atriopulmonary connection (1098). These maneuvers effectively separated the systemic venous from the pulmonary venous circulations, and blood is conducted into the lungs without the benefit of ventricular contribution. The Fontan operation or one of its many modifications can be performed today in patients with tricuspid atresia meeting certain criteria, with a surgical mortality less than 5%; effective long-term palliation is achieved in many patients (1099,1100,1101 and 1102). An occasional patient with tricuspid atresia may survive into the third or fourth decade of life with a palliative shunt, but most are not so fortunate (1103,1104 and 1105). In long-term series before the Fontan operation, creation of a surgical shunt greatly improved (to 50%) the chance of survival to 15 years (1106). In the current era, 45% meet and successfully undergo the Fontan operation, with most deaths occurring in patients with tricuspid atresia and pulmonary atresia, and thus diminutive pulmonary arteries, or in patients with tricuspid atresia and transposition of the great arteries, with many in this latter group particularly predisposed to developing subaortic stenosis (1107,1108). Of the patients who survived to a Fontan procedure but were excluded from consideration, the more common factors leading to exclusion included ventricular dysfunction, severe distortion of pulmonary arteries from previous shunts, mitral regurgitation, and severe myocardial hypertrophy (1095,1107,1108,1109,1110,1111,1112,1113,1114,1115 and 1116). The classic Fontan criteria are listed in *e*Table 30.0.5 (1117).

***e*TABLE 30.0.5** CRITERIA FOR THE FONTAN OPERATION
Normal sinus rhythm
Normal caval and pulmonary venous connections
Normal pulmonary vascular resistance, with a mean pulmonary artery pressure <15–20 mm Hg
No significant pulmonary artery branch stenosis that would preclude surgical repair
Pulmonary artery to aortic ratio >0.75
“Normal” ventricular function
No regurgitation of the systemic atrioventricular valve
Normal diastolic ventricular function
Optimal minimal age: uncertain, but when anatomy and hemodynamics are ideal, probably 2–4 yr; until relatively recently, a minimum age of 4 yr was advocated

These criteria continue to evolve and today the Fontan operation is often performed in children aged 2 to 3 years or younger (1118,1119,1120,1121,1122 and 1123). Variations in caval anatomy can be addressed by the staging maneuver of a bidirectional cavopulmonary connection or bilateral bidirectional cavopulmonary connections. It is less important that the Fontan operation be carried out in patients with normal sinus rhythm, although one would not want to carry this out or indeed any operation if the patient is in a tachycardia. We have learned that myocardial hypertrophy is a risk factor for a poor outcome at Fontan’s operation (1095,1109,1110,1111,1112,1113,1114,1115 and 1116). Such myocardial hypertrophy was identified frequently in patients with a discordant ventriculoarterial connection and increased pulmonary blood flow treated by banding of the pulmonary trunk. Today, palliative pulmonary artery banding is eschewed, and these patients are treated with a Norwood-like approach. At 3 to 9 months of age, these patients are staged with a bidirectional cavopulmonary connection (1124,1125,1126,1127,1128,1129,1130,1131,1132 and 1133). Any pulmonary arterial stenosis or restrictive atrial septal defect also can be addressed at this time with the Fontan operation, whether a lateral tunnel or extracardiac, with or without a fenestration, at approximately 2 years of age.

The strategy for any patient with tricuspid atresia is to preserve the myocardial matrix, its structure and function, as well as the integrity of the pulmonary arteries and to optimize the pulmonary hemodynamics to allow patients to survive to and meet the criteria for a Fontan-type operation with a favorable outcome. Thus, for the patient with tricuspid atresia, concordant ventriculoarterial connections, and severe pulmonary outflow tract obstruction requiring palliation in the first days or weeks of life, we would perform a modified right-sided Blalock-Taussig shunt. When the patient is 3 to 9 months old, the right-sided Blalock-Taussig shunt would be closed and a bidirectional cavopulmonary connection performed, with completion of the Fontan operation at 18 to 24 months of age. Today, in most centers, a Fontan operation can be accomplished with a surgical mortality less than 5%.

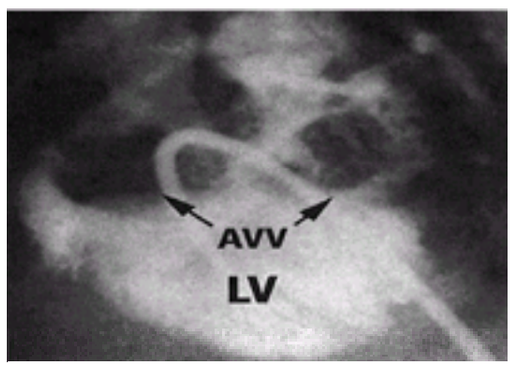
Finally, most life tables constructed from patients surviving a Fontan operation demonstrate ongoing attrition with morbidity as well (1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151, 1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164 and 1165). *e*Table 30.0.6 lists some of the sequelae of the Fontan operation.

***e*TABLE 30.0.6** SEQUELAE OF THE FONTAN OPERATION
Right atrial enlargement for those treated with a right atrium–pulmonary artery connection

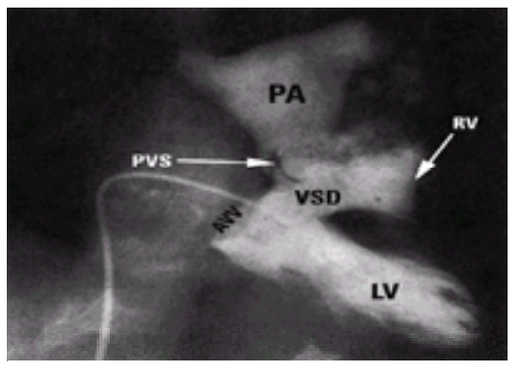
Enlargement of the coronary sinus for those in whom the coronary sinus was left on the systemic venous side of the circulation
Distention of the hepatic veins
Cirrhosis
Thrombosis of the right atrium or lateral tunnel
Obstruction of foreign material contributing to atriopulmonary, lateral tunnel, or extracardiac connection
Development of systemic venous collaterals with the potential for systemic vein–pulmonary vein or left atrial connection
Atrial arrhythmias
Surgically created Wolff-Parkinson-White syndrome
Right-to-left shunting at atrial level
Cerebrovascular accidents
Systemic ventricular outlet obstruction
Atrioventricular valve regurgitation
Ventricular dysfunction
Development of pulmonary arteriovenous fistulae
Protein-losing enteropathy
Plastic bronchitis

Double-Inlet Ventricle

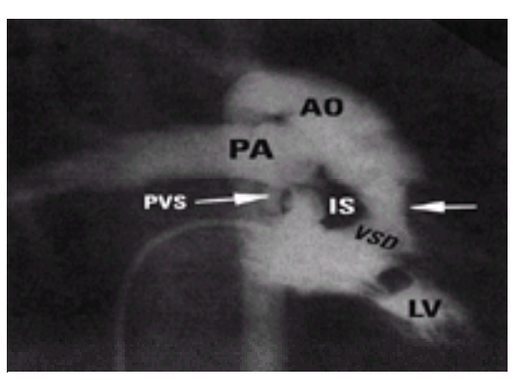
A group of complex congenital heart malformations characterized by connection of both atrioventricular valves to one ventricle are often designated as a double-inlet ventricle or single ventricle (1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177 and 1178) (*e*Fig. 30.0.49, *e*Fig. 30.0.50, and *e*Fig. 30.0.51). Most patients with a double-inlet left ventricle, all patients with a double inlet to a morphologically right or indeterminate ventricle, and all those with an absent atrioventricular connection are not candidates for a biventricular repair, but they are potential candidates for a one-ventricle or Fontan-type repair. This challenge is “tested” by the change in form and function known to occur in these hearts and vascular systems (1176,1179,1180,1181,1182,1183,1184 and 1185).



***e*FIGURE 30.0.49** Double-inlet left ventricle (LV) in a patient demonstrated by hepatoclavicular left ventriculogram. Both atrioventricular valves (AVVs) connect to the dominant LV.

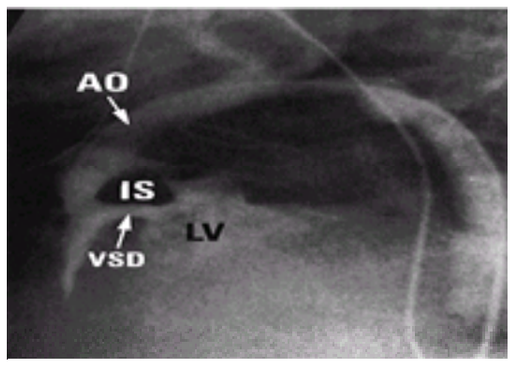


***e*FIGURE 30.0.50** Double-inlet left ventricle (LV), a left-sided rudimentary right ventricle (RV), and discordant ventriculoarterial connections. Note the excellent-caliber main pulmonary artery (PA) and pulmonary valve stenosis (PVS). AVV, atrioventricular valve; VSD, ventricular septal defect.



***e*FIGURE 30.0.51** Another patient with double-inlet left ventricle (LV), a left-sided rudimentary right ventricle, discordant ventriculoarterial connections, and pulmonary valve stenosis (PVS). The subaortic infundibulum is mildly narrowed as well (*arrow*). AO, aorta; IS, infundibular septum; PA, pulmonary artery; VSD, ventricular septal defect.

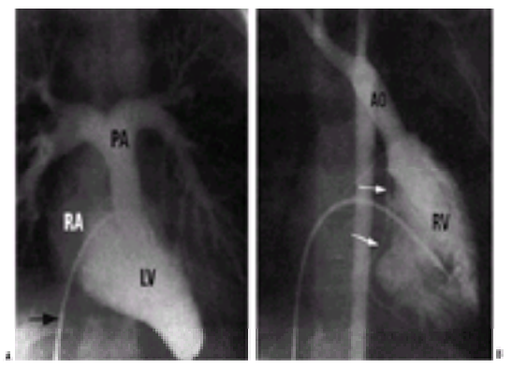
Most patients with a double-inlet ventricle have a dominant ventricle of left ventricular morphology receiving both atrioventricular valves, a left-sided rudimentary right ventricle, and transposed or discordantly connected great arteries (*e*Fig. 30.0.50, *e*Fig. 30.0.51, and *e*Fig. 30.0.52). Many have valvar or subvalvar pulmonary stenosis, but some have torrential pulmonary blood flow and pulmonary artery hypertension. The strategies to preserve the functional integrity of the myocardium, to avoid ventricular hypertrophy, and to preserve the anatomy and hemodynamics of the pulmonary vascular bed are fully discussed elsewhere. Indeed, the once common strategy of banding the pulmonary trunk in patients with no pulmonary outflow tract obstruction and excessive pulmonary blood flow and pulmonary artery hypertension is largely eschewed to avoid myocardial hypertrophy, a risk factor for those considered for the Fontan operation (1186,1187,1188,1189,1190 and 1191), although some still advocate banding with a rapid conversion to a bidirectional cavopulmonary connection and a proximal pulmonary artery aortic connection (1192,1193). The current surgical results for the Fontan procedure for most patients with double-inlet ventricle or for those patients with more complex anomalies of the atrioventricular junction, although quite good, do not reflect the reality that many patients do not survive to a Fontan procedure or are excluded from consideration because they do not meet the criteria (1194,1195,1196,1197 and 1198).



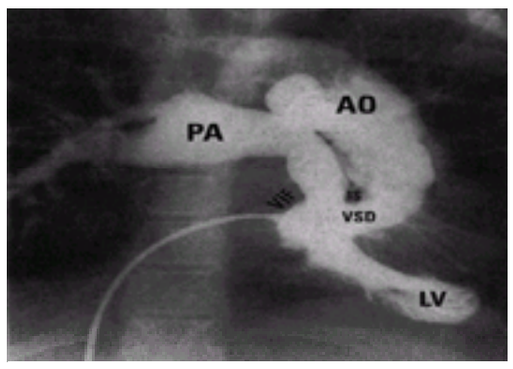
***e*FIGURE 30.0.52** Severe subaortic stenosis in this patient with a univentricular atrioventricular connection, discordant ventriculoarterial connections, and a small ventricular septal defect (VSD). Note the enlarged infundibular septum (IS). AO, aorta; LV, left ventricle.

Congenitally Corrected Transposition of the Great Arteries

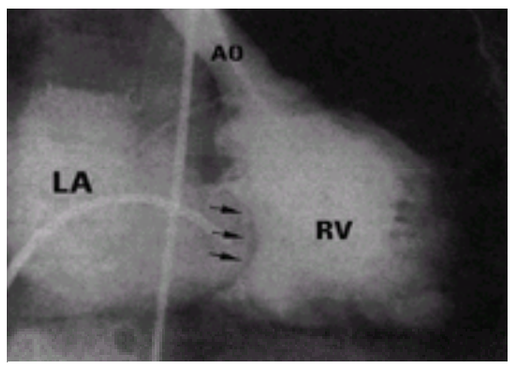
Congenitally corrected transposition of the great arteries is an uncommon cardiac anomaly that, despite its designation as congenitally corrected, rarely occurs in isolation and thus should not be considered "corrected" (1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210 and 1211). This condition is characterized by atrioventricular and ventriculoarterial discordance (*e*Fig. 30.0.53). In the patient with normal or solitus atrial arrangement, the systemic venous return connects with the morphologically right atrium. This atrium is connected by a mitral valve with the morphologically left ventricle, which in turn supports a discordantly connected transposed pulmonary artery (*e*Fig. 30.0.53). There is mitral valve–pulmonary valve fibrous continuity, indicative of a poorly defined subpulmonary infundibulum. The left atrium receiving the pulmonary veins connects through a tricuspid valve with its normal septal attachments with the morphologically right ventricle, which in turn supports a transposed aorta. The aortic valve is anterior and to the left of the pulmonary valve; a subaortic infundibulum is well developed, promoting discontinuity between the tricuspid and aortic valves. The effects of ventricular inversion are potentially corrected by the associated transposition of the great arteries, but in reality, most patients with so-called congenitally corrected transposition of the great arteries have abnormalities singularly or in combination involving the ventricular septum, the left ventricular or pulmonary outflow tract, and the morphologically tricuspid valve (1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210 and 1211) (*e*Fig. 30.0.54 and *e*Fig. 30.0.55). The specialized conduction tissue in the patient with atrioventricular and ventriculoarterial discordance has received considerable and appropriate attention because of the striking difference in the position of the atrioventricular node and penetrating bundle, with the important surgical and natural history implications (1212,1213,1214,1215,1216,1217,1218,1219 and 1220). The prevalence of this condition ranges from 0.60% to 0.95% (1221,1222,1223,1224 and 1225).



***e*FIGURE 30.0.53** Atrioventricular and ventriculoarterial discordance. **A:** This frontal left ventriculogram shows the double discordance with the right artery (RA) connected to the left ventricle (LV) and LV-to–pulmonary artery (PA) connection. The arrow points to the catheter in the inferior vena cava. **B:** This frontal right ventriculogram shows the levopositioned discordantly connected aorta (AO). Arrows note the coronary artery in the left-sided atrioventricular groove. RV, right ventricle.



***e*FIGURE 30.0.54** Double discordance, ventricular septal defect (VSD), and left ventricular outflow tract obstruction shown in this frontal left ventriculogram. AO, aorta; IS, infundibular septum; LV, left ventricle; PA, pulmonary artery; VIF, ventricular infundibular fold.



***e*FIGURE 30.0.55** Double discordance and severe left atrioventricular valve (*arrows*) regurgitation shown by this frontal right ventriculogram. AO, aorta; LA, left atrium; RV, right ventricle.

The heart position and its apex may be normal (levocardia) or in the midline (mesocardia), but in approximately 20% of patients with congenitally corrected transposition of the great arteries, the cardiac apex is predominantly right-sided (i.e., dextrocardia). The atrial situs is solitus in approximately 92% to 95% of patients; an inverse atrial situs was recorded in 5% to 8%. The most commonly associated anomalies in patients with congenitally corrected transposition of the great arteries include (a) ventricular septal defect, (b) pulmonary outflow tract obstruction, (c) dysplasia and displacement of the left or systemic atrioventricular valve, or (d) combinations of these associated lesions (1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210 and 1211) (*e*Table 30.0.7). Furthermore, intrinsic to hearts exhibiting atrioventricular discordance is a particularly fragile specialized conduction system. It is the unusual disposition of the conduction tissue that predisposes patients with atrioventricular discordance to spontaneous heart block, occurring in approximately 4% of patients with this condition per year (1226).

***e*TABLE 30.0.7** COMMONLY ASSOCIATED MALFORMATIONS IN HEARTS WITH CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES
Systemic (tricuspid) atrioventricular valve regurgitation
Abnormal atrioventricular conduction tissue
Left ventricular outflow tract obstruction
Ventricular septal defect

Even in patients with congenitally corrected transposition of the great arteries without major associated abnormalities, spontaneous onset complete heart block is always a hazard.

Diagnosis and Therapy

The clinical findings in patients with congenitally corrected transposition of the great arteries have been amply reviewed elsewhere (1199,1200,1201,1202,1203,1204 and 1205,1209,1210 and 1211,1225). For many patients with this disorder, the clinical suspicion of this diagnosis is readily confirmed by cross-sectional echocardiography and angiocardiography (1201,1202,1204,1209,1210 and 1211).

Congenitally malformed hearts are well known to change in form and function, particularly patients with congenitally corrected transposition of the great arteries. There are considerable data showing that progressive regurgitation of the morphologically tricuspid valve, the systemic atrioventricular valve, is well known in these patients (1201,1202,1204,1209,1210,1227,1228,1229 and 1230). This change in the function of the morphologically tricuspid valve has been observed before reparative surgery, after repair. In addition, the function of the morphologically right ventricle, the systemic ventricle, demonstrates in many of these patients progressive deterioration regardless of whether major associated anomalies are present (1229,1230,1231,1232 and 1233). Thus, it is not surprising that many ask, Can the morphologically right ventricle function as the systemic right ventricle in the long term? Although some individuals with congenitally corrected transposition of the great arteries survive into the seventh or eighth decades of life, the natural or modified history of many patients is clouded by the reality of progressive regurgitation of the systemic atrioventricular valve, deterioration of the systemic and morphologically right ventricle, or both (1201,1202,1204,1209,1210,1227,1228,1229,1230,1231,1232,1233,1234,1235 and 1236).

Surgical Intervention

Until the past few years, conventional surgery included (a) closure of the ventricular septal defect, (b) closure of the ventricular septal defect and interposition of a conduit between the morphologically left ventricle and pulmonary artery in those with ventricular septal defect and tunnel-form left ventricular outflow tract obstruction, (c) replacement of the severely regurgitant tricuspid valve, or (d) some combination of these (1208). Concerns about the function and progressive deterioration of both the morphologically tricuspid valve and right ventricle led to the novel surgical approach of a double-switch procedure (1237,1238,1239,1240,1241,1242 and 1243). When this extensive surgery is successful, the morphologically right ventricle faces a lower afterload, the pulmonary circulation, and improvement in both the function of the tricuspid valve and right ventricle may be anticipated. The double-switch operation takes two major forms: (a) In patients who do not have important pulmonary outflow tract obstruction, an atrial switch of the Senning or Mustard type and a classic arterial switch are performed; (b) in patients with important pulmonary outflow tract obstruction and a perimembranous outlet ventricular septal defect, an atrial switch of the Senning or Mustard type and a “ventricular” switch are performed. The morphologically left ventricle is tunneled through the ventricular septal defect to the aorta (the Rastelli concept); the main pulmonary trunk is divided or ligated, and continuity between the morphologically right ventricle and pulmonary artery is usually achieved with a valved conduit. Finally, because of the significant heterogeneity in hearts with atrioventricular and ventriculoarterial discordance, surgical intervention must be individualized.

Right Atrial Isomerism

A group of patients exists in whom it is difficult, if not impossible, to assign visceral situs because the abdominal viscera are not lateralized, or at least are incompletely lateralized (1244,1245,1246,1247,1248,1249,1250,1251,1252,1253,1254,1255,1256,1257,1258,1259,1260,1261, 1262,1263 and 1264) (*e*Fig. 30.0.3, *e*Fig. 30.0.4, and *e*Fig. 30.0.5). Such patients are considered to have visceral heterotaxia (from the Greek words *heteros*, other than, and *taxis*, arrangement; i.e., other than the normal arrangement). The liver is more symmetric than normal, and the bowel is not fixed in the normal way (1250,1251,1252 and 1253). In these same patients, the thoracic contents also often have a degree of symmetry, with both major bronchi having the appearance of a right mainstem bronchus (so-called bilateral eparterial bronchi) or left mainstem bronchus (so-called hyparterial bronchi) (1245,1247,1253,1255). Frequently, each of the lungs is trilobed in patients with bilateral eparterial bronchi, resembling the right lung, and bilobed and like the left lung in patients with hyparterial bronchi, although lobation is considerably more variable in this setting than the character of the bronchi. In patients with incomplete lateralization of visceral and thoracic contents, the atrial appendages are also not clearly lateralized, and in many of these patients both atrial appendages look like a morphologically right atrial appendage or a morphologically left atrial appendage, thus the designation by some of *atrial isomerism* to characterize these hearts. In 1955, Ivemark (1244) helped to define those complex cardiac malformations associated with splenic agenesis, indeed establishing the concept of the splenic agenesis or asplenia syndrome (1249).

It has also long been appreciated that the syndrome of so-called visceral heterotaxia includes severe and characteristic malformations of the heart, frequently but not invariably associated with malformations of the spleen (i.e., asplenia and polysplenia among others) (1244,1245,1246,1247,1248,1249,1250,1251,1252,1253,1254,1255,1256,1257,1258,1259,1260,1261, 1262,1263 and 1264). In patients with either right or left atrial isomerism, but particularly right, visceral heterotaxy or abnormal lateralization has been and still is a clinical marker of the splenic syndromes. Common to most of these patients is nonfixation of the gastrointestinal tract, varying degrees of malrotation, and not uncommonly an annular pancreas. In a survey of patients with asplenia, one-fourth had anomalies of the genitourinary system. A major concern to patients with polysplenia is the known association with extrahepatic biliary atresia and a short pancreas as well (1265,1266,1267,1268,1269,1270,1271,1272 and 1273). Indeed, up to 25% of babies with biliary atresia bear associated malformations that most often cluster in the polysplenia syndrome. Among patients with visceroatrial heterotaxia, definition of splenic function or hypofunction must be ascertained so that prophylaxis against overwhelming infection can be instituted (1274,1275,1276 and 1277).

Complex cardiac malformations should be anticipated in patients with visceroatrial heterotaxia, especially those with right atrial isomerism and asplenia. There is considerable literature defining the range of the cardiac malformations in the cardiosplenic isomerism syndromes and in the noncardiac malformations as well (1244,1246,1248,1249,1253,1256,1260,1262,1263,1278). The prostaglandin challenge is particularly helpful in this assessment. Abnormalities of systemic venous connections are particularly frequent.

Diagnosis and Treatment

One can suspect the diagnosis of visceroatrial heterotaxia and complex heart malformations in any cyanotic infant in whom the visceral situs is uncertain from a plain chest radiograph, in a cyanotic infant with discordancy between heart position and apparent visceral situs, in an infant whose echocardiogram suggests abnormal juxtaposition of the abdominal inferior caval vein and aorta, in an infant with azygous continuation of the inferior caval vein, or in any infant who has complex congenital heart disease in which the echocardiogram defines the spectrum of heart malformations listed previously, or in whom the echocardiogram suggests atrial appendages of like morphology and appearance (1278,1279,1280,1281,1282,1283,1284,1285,1286,1287,1288,1289,1290,1291,1292,1293,1294,1295, 1296 and 1297). The appearance of normal visceral lateralization on a chest radiograph (i.e., left-sided gastric bubble and right-sided hepatic shadow) does not exclude the consideration of right or left atrial isomerism. A leftward and superior P-wave axis is particularly common in patients who have left atrial isomerism and abnormal formation of the sinoatrial node.

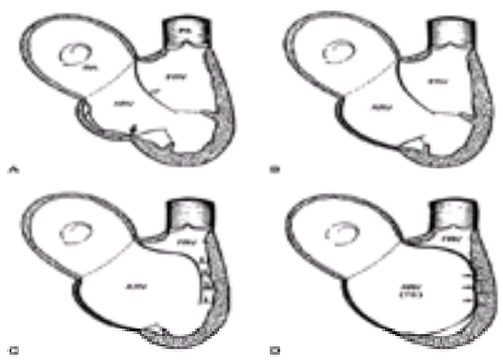
Whereas an increasing number of reports have documented surgical successes in patients with right atrial isomerism, most address only patients undergoing a one-ventricle type of repair. Long-term survival in this group is improved, with 44% alive at 5 years (1298,1299). Thus, despite some surgical successes with a Fontan-type repair or, less commonly, a biventricular repair, overall survival is poor, reflecting the egregious nature of the complex heart malformations.

Other Conditions

Ebstein’s Anomaly of the Tricuspid Valve

This is an uncommon (prevalence of 0.5% to 1.0% of congenital heart disease) congenital abnormality of the tricuspid valve that is characterized by variable degrees of displacement and dysplasia of the mural and septal leaflets of the tricuspid valve (1300,1301,1302,1303,1304,1305,1306,1307,1308,1309,1310,1311,1312,1313,1314,1315,1316,1317, 1318,1319,1320,1321,1322,1323,1324 and 1325). Such displacement and dysplasia of the tricuspid valve may be mild, and patients have survived to the seventh and eight decades of life. At the other end of the spectrum are the fetuses with florid tricuspid regurgitation developing severe hydrops with an intrauterine death. Some newborns with extreme tricuspid regurgitation may present with profound hypoxemia and no forward flow from the right ventricle to the pulmonary artery, and the clinical dilemma posed by these newborns is to determine whether the pulmonary atresia is functional or organic. These infants often have gigantic hearts virtually obscuring both lung fields. The right ventricle of this particular group of infants is severely disadvantaged, being profoundly thinned and devoid of right ventricular musculature, especially in the so-called atrialized zone of the right ventricle, that portion of the right ventricle between the right atrioventricular valve and the displaced tricuspid valve. Other expressions of Ebstein’s anomaly of the

tricuspid valve include those with so-called linear distal attachments posing obstruction to pulmonary blood flow (eFig. 30.0.56). The most severe expression of distal attachments is the imperforate form of Ebstein's anomaly, producing an uncommon form of tricuspid atresia.

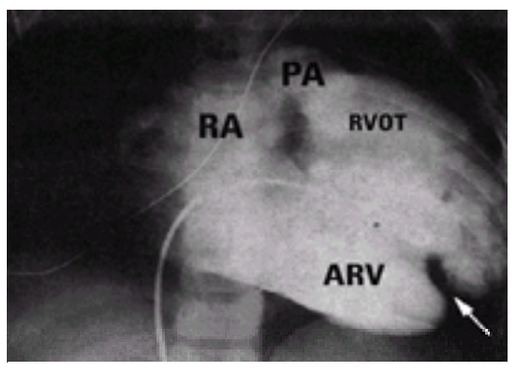


***e*FIGURE 30.0.56** Diagram showing Ebstein's anomaly of the tricuspid valve and distal linear attachments. **A:** Moderate displacement of septal and posterior leaflets (*closed arrow*) with mobile anterior leaflet (*open arrow*). **B:** Marked displacement of septal and posterior leaflets with mobile anterior leaflet. **C:** Nonmobile anterior leaflet with chordal tethering (*arrows*) to ventricle. **D:** Severely stenotic or imperforate Ebstein's anomaly (*arrows*). ARV, atrialized right ventricle; FRV, functional right ventricle; PA, pulmonary artery; RA, right atrium; TS, tricuspid sac.

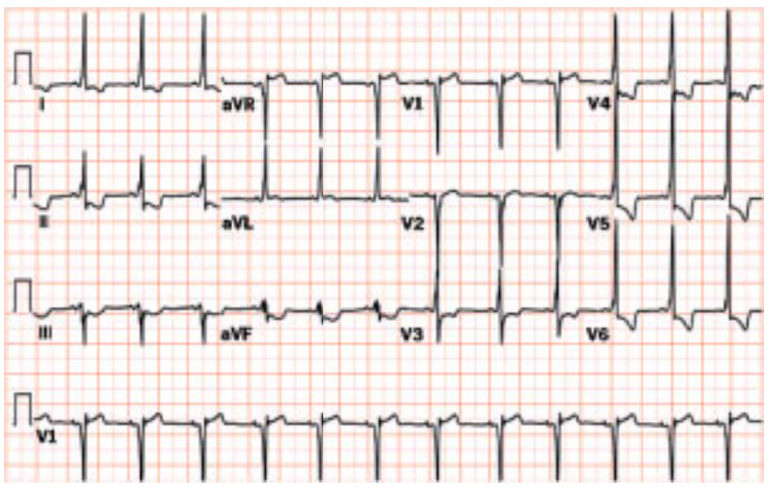
The most common associated anomaly in patients with Ebstein's anomaly is the secundum atrial septal defect, although many forms of congenitally malformed hearts have been found in association with Ebstein's anomaly, including tetralogy of Fallot, atrioventricular septal defect, ventricular septal defect, pulmonary stenosis, and atresia (1315,1316 and 1317). In addition, left ventricular myocardial abnormalities and mitral valve prolapse may confound the clinical course and management of patients with this disorder (1316,1317).

Diagnosis

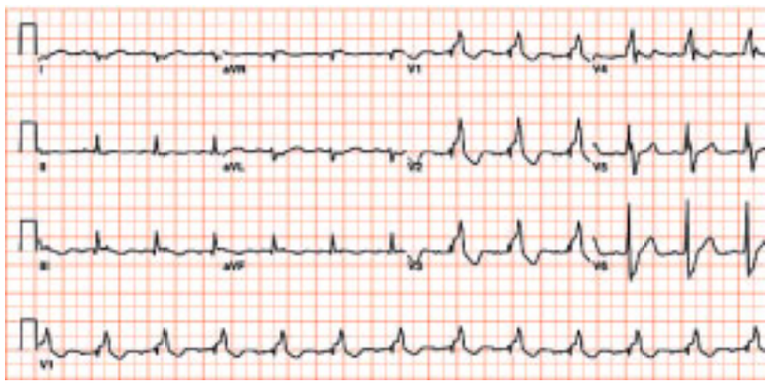
The diagnosis of Ebstein's anomaly of the tricuspid valve should be considered in any patient with tricuspid regurgitation, and especially those with evidence of preexcitation (1326). The findings of a patient with a murmur of tricuspid regurgitation, a triple or quadruple rhythm with multiple clicks, with or without cyanosis, is presumptive of this diagnosis. The heart size varies from only mildly enlarged to severe heart enlargement (eFig. 30.0.57). Echocardiography is nearly always definitive.



***e*FIGURE 30.0.57** Right ventricular angiogram showing a notch of the displaced tricuspid valve (*arrow*) on the diaphragmatic surface of the right ventricle, typical of Ebstein's anomaly of the tricuspid valve. ARV, atrialized right ventricle; PA, pulmonary artery; RA, right atrium; RVOT, right ventricular outflow tract.

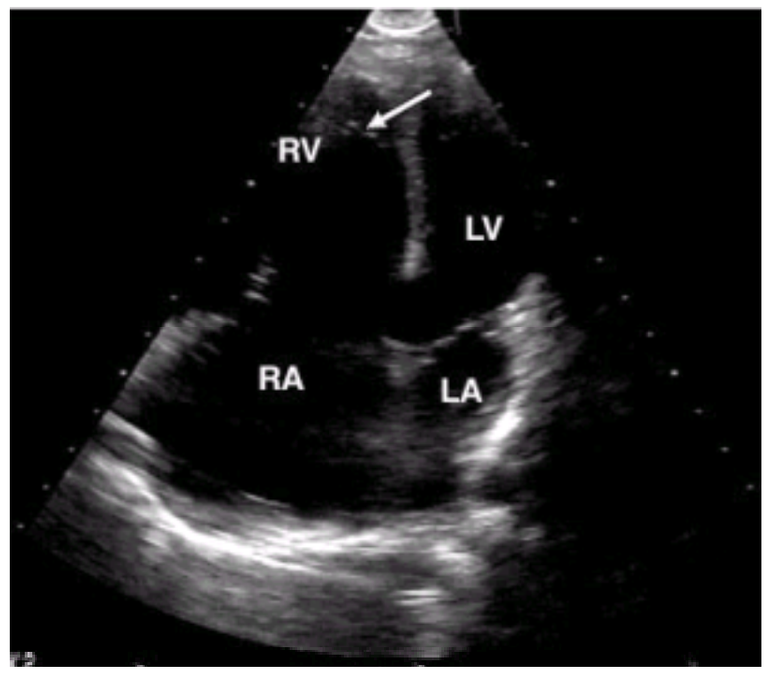


Wolff-Parkinson-White syndrome. Eleven-year-old patient with manifest preexcitation consistent with Wolff-Parkinson-White.

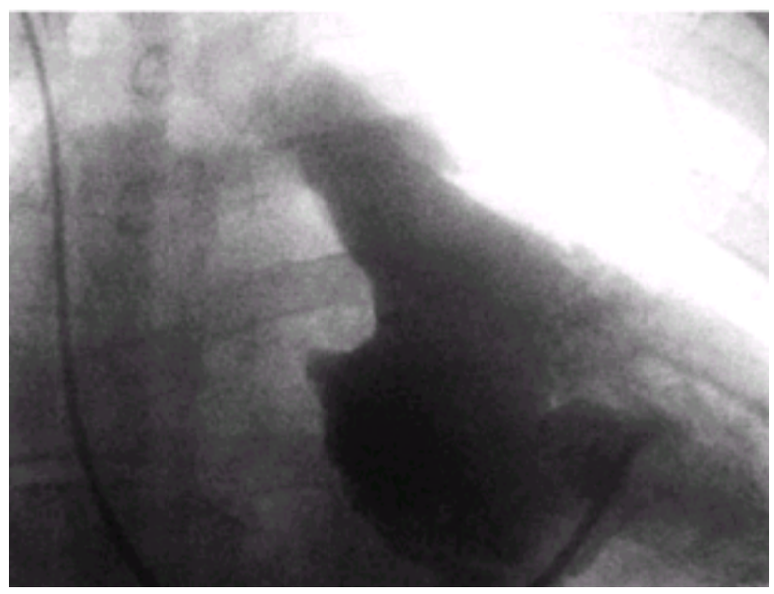


A 47-year-old male patient with Ebstein's anomaly.

A 19-year-old male patient with Ebstein's anomaly.



Ebstein's anomaly of the tricuspid valve. Note marked apical displacement of the tricuspid leaflets, especially the septal leaflet. The arrow designates the septal leaflet of the tricuspid valve.

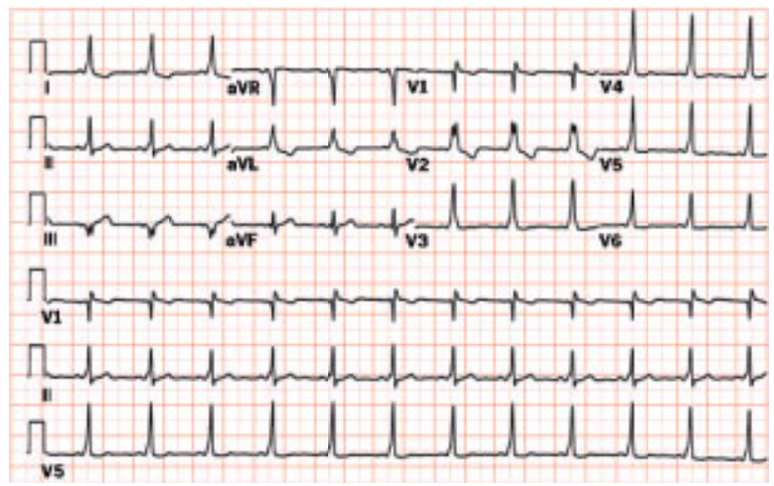


Epstein's anomaly. Right anterior oblique projection of a right ventriculogram demonstrating Epstein's anomaly.

Prognosis

For infants with gigantic hearts and functional or organic pulmonary atresia, the outlook is poor (1327), although some demonstrate spontaneous improvement coincident with maturation of the pulmonary vascular bed. The significant predictors of mortality in a bivariate analysis include the presence of functional or organic pulmonary atresia, increased displacement of the tricuspid valve and more severe tricuspid regurgitation, larger atrioventricular septal defect, and reduced left ventricular function (1327).

Wolff-Parkinson-White syndrome, type B, is particularly well known to be associated with Ebstein's anomaly of the tricuspid valve and to complicate its course (1326). For infants who die in the newborn or neonatal period with hypoxemia and congestive heart failure, results of either tricuspid valvuloplasty or tricuspid valve replacement have been dismal, likely reflecting the severe impact of this disorder on the right ventricular myocardium (1311,1316,1317). Cardiac replacement is certainly one alternative, as is the novel approach taken by Starnes and associates of closing the tricuspid valve, placing an arterial shunt and thus putting the patient on a one-ventricle repair tract (1328). Fortunately, probably less than 20% to 30% of patients with Ebstein's malformation of the tricuspid valve require surgery in the first decade of life; surgery is well tolerated in older patients (1329).



Wolff-Parkinson-White syndrome. Note short PR interval with classic delta wave due to accessory pathway conduction.

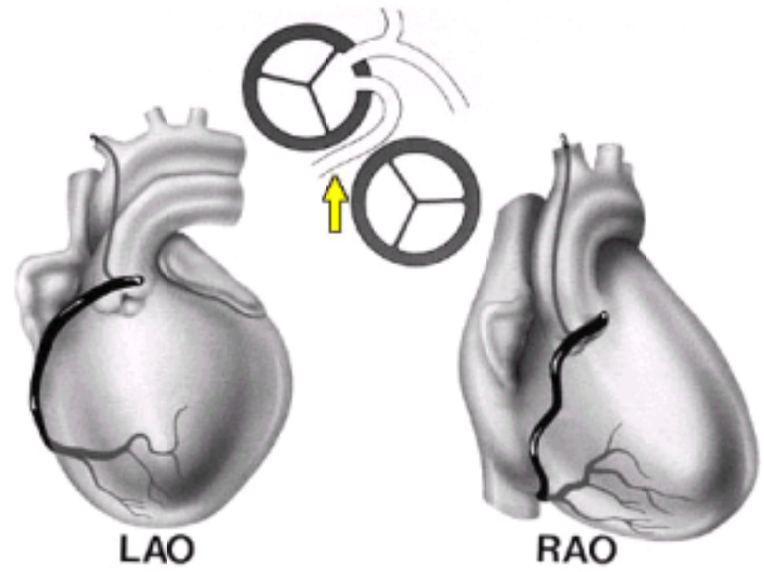
Congenital Anomalies of the Coronary Arteries

It is important to recognize that anomalies of the coronary arterial circulation may coexist with other congenital heart anomalies and may have significant implications in planning surgical intervention (*e*Table 30.0.8). Therefore, a complete evaluation of the preoperative patient includes an assessment of the origin and distribution of the coronary arteries. Because of its usual presentation in infancy, anomalous origin of the left coronary artery from the main pulmonary artery deserves more extensive comment.

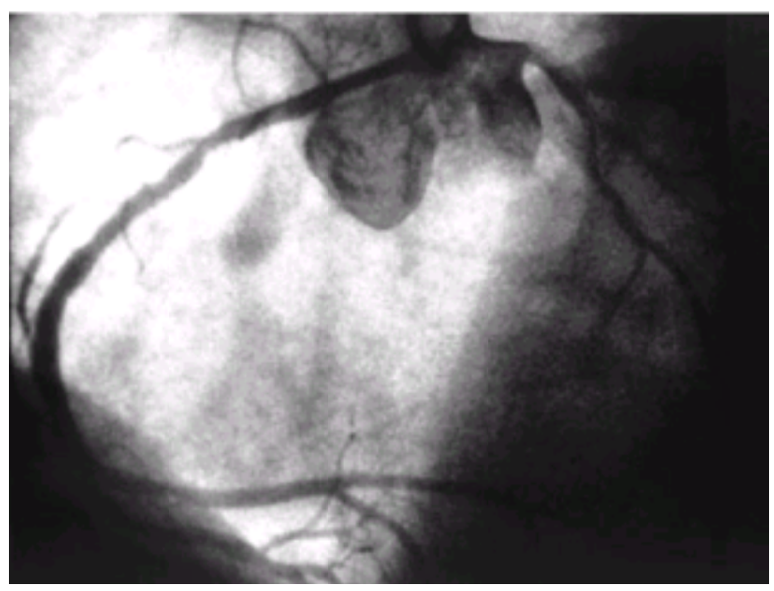
***e*TABLE 30.0.8** CONGENITAL ANOMALIES OF THE CORONARY ARTERIES

Coronary arterial ostia	High origin of coronary artery
Position	Both coronaries arise from the same sinus of Valsalva
	Common ostial origin, closely related above a commissure
	Acute angular origin of a coronary artery
	Single coronary artery
	Absent proximal connection of the coronary artery
Number	Separate origin of the artery to the conus
	Separate origin of the circumflex
Single coronary artery	Several variations in origin, course, and distribution exist

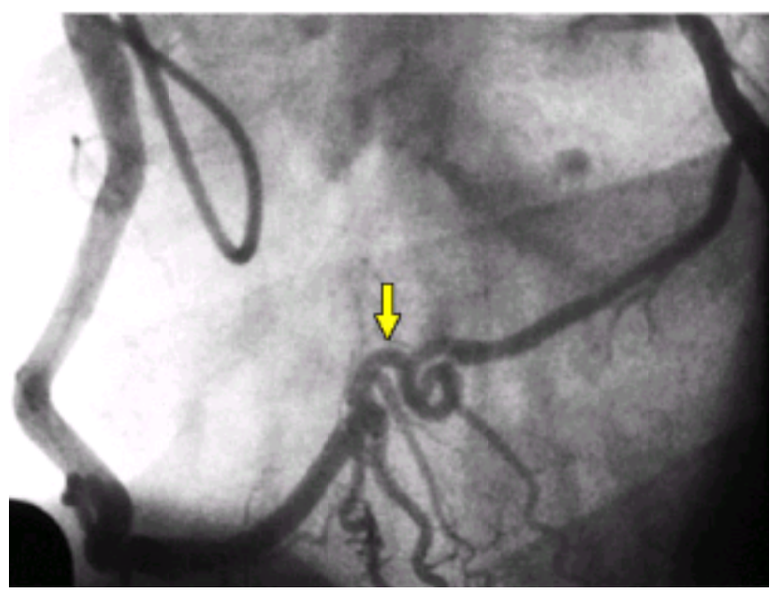
Stenosis or atresia of the ostium	
Anomalous origin of the coronary arteries from the main pulmonary artery	Left or, more rarely, right system
Abnormal origin and distribution of epicardial branches	For example, origin of the circumflex from the right coronary artery Left coronary artery coursing between the great vessels
Coronary artery fistulae	To the cardiac chambers, coronary sinus, superior vena cava, or pulmonary arteries Most connect to right-sided chambers
Obstructive lesions	Mural left anterior descending coronary artery associated with sudden death Obstructive lesions seen in association with pulmonary atresia and intact ventricular septum with fistulous connections
Aneurysms	Congenital aneurysms occur; however, Kawasaki's disease most common acquired condition



Anomalous origin of the right coronary artery. In the left panel, the left anterior oblique projection shows the right coronary artery originating from the left sinus of Valsalva. The course of the right coronary artery passes between the aorta and pulmonary artery (*yellow arrow*). In the right panel the right anterior oblique projection of this same anomalous coronary artery is illustrated.



Angiogram showing anomalous origin of the right coronary artery. In this left anterior oblique cranial projection the right coronary artery originates from the left sinus of Valsalva and passes between the aorta and pulmonary artery.



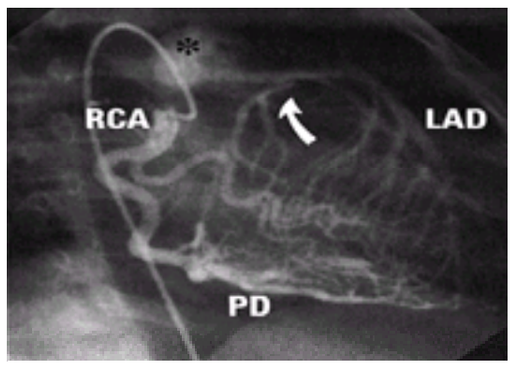
Anomalous connection of right coronary artery to left circumflex artery. This anomaly is known as the Miller connection, as shown in this shallow left anterior oblique projection (*yellow arrow*).

Video 30.24 Anomalous origin of the right coronary artery from the left coronary sinus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery

Anomalous origin of a coronary artery from the pulmonary artery, a rare anomaly, usually involves the left coronary artery, but it also has been noted to occur with the right system, rarely both (eFig. 30.0.58). Early in neonatal life the distribution of the anomalous vessel is perfused with the lower saturated blood of the mixed venous (pulmonary artery) return; however, this occurs at relatively higher pressures as a result of the higher pulmonary pressures in the newborn period. As the pressure in the pulmonary arterial system falls, the perfusion pressure to the anomalous coronary artery also falls, and myocardial perfusion relies heavily on collateral vessels from the right coronary artery system. If extensive, the collateral flow can result in steal from the coronary to the pulmonary circulation and a left-to-right shunt. The effect of this process on myocardial perfusion and function is varied and can result in one of several clinical presentations. Usually, the infant is brought to medical attention within the first 4 months of life with angina-like symptoms [ashen color (especially after feeding), tachypnea, diaphoresis, failure to thrive] or severe ischemic cardiomyopathy. A murmur of mitral insufficiency may also be present because of ischemic papillary muscle dysfunction and annular dilatation. The chest radiograph typically demonstrates pulmonary venous congestion with cardiomegaly, and the electrocardiogram suggests anterolateral myocardial infarction (1330). It can be

difficult to distinguish this presentation from that of acute myocarditis or cardiomyopathy from another cause. Echocardiography with pulsed and color flow Doppler establishes the diagnosis in most instances; however, transesophageal echocardiography and cardiac catheterization with aortography and selective coronary angiography can be of assistance (1331,1332,1333,1334,1335 and 1336). A careful assessment of the origin of the coronary arteries must accompany the complete investigation of any patient presenting, particularly in infancy, with dilated myocardial dysfunction. Selective angiography also serves to assess the nature of the collateral circulation as well as the status of myocardial perfusion.



***e*FIGURE 30.0.58** Anomalous left coronary artery originating from the main pulmonary trunk. Selective right coronary artery (RCA) injection with filling of the posterior descending coronary artery (PD) and then the left anterior descending coronary artery (LAD), which connects to the pulmonary trunk (*asterisk*). The arrow points to the collateral connection to the LAD.

Older infants and children may present with a murmur of mitral insufficiency, and those with well-developed collateral circulation may present late with a continuous murmur (1337). Some instances have been detected unexpectedly at postmortem examination in an adult with no history of coronary anomaly who suddenly collapsed.

Surgical treatment of this condition has evolved over time. Most institutions favor the maintenance of a two-coronary system for myocardial perfusion, and so the previously popular ligation of the coronary artery at the origin from the pulmonary artery to minimize the steal phenomenon has fallen out of favor (1338,1339). A two-coronary system is preserved by a variety of techniques, including the creation of an aortopulmonary tunnel, reimplantation, and ligation with saphenous or arterial coronary bypass (1340,1341,1342,1343,1344 and 1345). Although results of this approach have been gratifying, concern remains with respect to persistent problems in myocardial perfusion in follow-up (1346,1347).

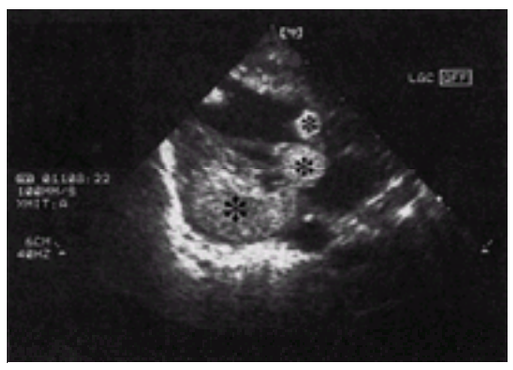
The diagnosis of anomalous left coronary artery from the pulmonary artery often can be made on the basis of typical clinical, electrocardiographic, and radiographic findings and confirmed by echocardiography (1348). Retrograde aortography or selective right coronary arteriography may be needed in some cases to establish this diagnosis firmly (1349,1350).

Cardiac Tumors

Cardiac tumors in the pediatric population are extremely uncommon, and the most common type of tumor in the neonate and young infant is extremely uncommon in the adult and vice versa (1351,1352,1353,1354,1355,1356,1357,1358,1359,1360,1361,1362,1363,1364,1365,1366,1367,1368, 1369,1370,1371,1372,1373,1374,1375,1376,1377,1378,1379,1380,1381,1382,1383,1384,1385,1386, 1387,1388,1389,1390,1391,1392,1393,1394,1395,1396,1397,1398,1399,1400, 1401,1402,1403,1404 and 1405).

Rhabdomyoma

The most common intracardiac tumor of the neonate is the rhabdomyoma, followed by the cardiac fibroma (1351,1356,1358,1360,1382,1384,1389,1390,1391,1392,1393,1394,1395,1396,1397,1398,1399,1400, 1401,1402 and 1403). Cardiac rhabdomyoma is often associated with tuberous sclerosis (1351,1353,1355,1356,1357 and 1358,1361,1362,1367,1371,1378,1380,1383,1392,1395,1403) (*e*Fig. 30.0.59). The tuberous sclerosis complex is an autosomal dominant disorder with a high mutation rate, affecting the brain, heart, skin, kidneys, and other organs. These histologically benign tumors consist of vacuolated cells resembling spider cells and contain glycogen. The cardiac rhabdomyoma tends to be multiple and to involve the intraventricular septum and the walls of the heart; it appears to be filling defects in the cavities of both ventricles, with a special predilection to involving the left ventricular outflow tract. These tumors may be strategically placed to interfere with cardiac filling, and tumors approximating the right atrioventricular junction have simulated tricuspid atresia, and those obstructing the mitral valve have simulated mitral atresia and the hypoplastic left heart syndrome and have produced severe myocardial ischemia. Subaortic stenosis has been a fairly common finding in the infant with cardiac rhabdomyomata, with pedunculated tumors in the subaortic vestibule. Superior or inferior caval vein obstruction is well recognized in the infant with cardiac rhabdomyoma. Patients with cardiac rhabdomyomas may present with almost any type of atrial or ventricular dysrhythmia, including preexcitation (1372,1378,1391,1392). Fetal dysrhythmias or hydrops may be the presenting features in some patients with cardiac rhabdomyoma. Cardiac rhabdomyomas are often diagnosed in the first year of life, and there is increasing experience with fetal diagnosis of these tumors. Another association of the cardiac rhabdomyoma is with the basal cell nevus syndrome (1404).



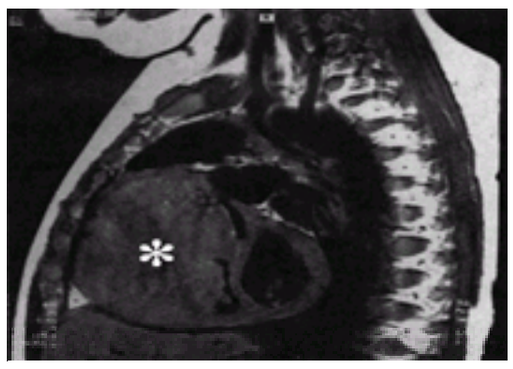
***e*FIGURE 30.0.59** Multiple cardiac rhabdomyoma (*asterisks*) in a newborn with tuberous sclerosis.

One of the peculiar aspects of these tumors is the observation of spontaneous regression (1353,1355,1364,1368,1374,1375 and 1376,1379,1380 and 1381,1395,1396,1400,1401,1403). Thus, surgery is recommended only for patients with severe hemodynamic compromise or refractory dysrhythmias. Even with regression of cardiac rhabdomyomas, a substantial number of patients are still disadvantaged by cerebral involvement.

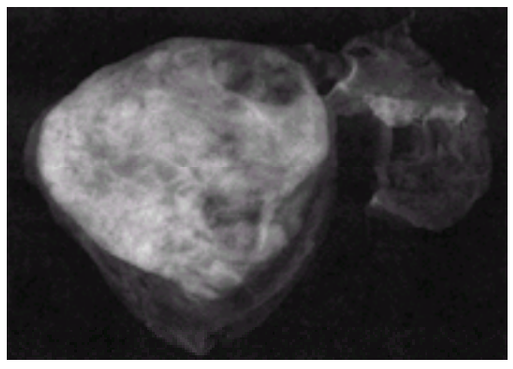
Cardiac Fibroma

The cardiac fibroma is second in frequency after the cardiac rhabdomyoma in infancy and childhood (1406,1407,1408,1409,1410,1411,1412,1413,1414,1415,1416,1417,1418,1419,1420,1421,1422, 1423,1424,1425,1426 and 1427) (*e*Fig. 30.0.60 and *e*Fig. 30.0.61). The mean age at diagnosis is 13 years, ranging from 1 day to 56 years. More than one-third of the patients were younger than 1 year at diagnosis. This tumor, usually solitary, most often involves the left ventricular free wall or septum. Involvement of the right ventricular free wall and cavity is less frequent. The cardiac fibroma is not encapsulated, and its tissue blends or merges with normal myocardium. Noninvasive assessment by MRI usually can differentiate between fibroma and rhabdomyoma. This tumor is benign, but continued slow growth may cause conduction defects, may spread to the ventricular free wall, and may result in atrioventricular valve inflow or arterial outflow tract obstruction. Cardiac fibroma has presented in the neonate as severe congestive heart failure. Rarely, this tumor may simulate cyanotic heart disease in the newborn because of septal and right ventricular involvement, promoting right-to-left shunting at atrial level. Spontaneous regression of the type seen in the patient with cardiac rhabdomyoma has not been observed in the patient with cardiac fibroma, and operative intervention is usually required. Ventricular tachycardia and an abnormal cardiac silhouette on chest radiography in the infant and child may be considered presumptive evidence of a cardiac fibroma (1412). Even less

common are intrapericardial teratoma (1428,1429,1430,1431 and 1432) and myxoma (1433,1434,1435,1436,1437,1438,1439,1440,1441 and 1442).



***e*FIGURE 30.0.60** A huge cardiac fibroma (*asterisk*) is demonstrated by this magnetic resonance imaging study.



***e*FIGURE 30.0.61** Huge cardiac fibroma from an infant who successfully underwent cardiac transplantation.

Congenital Abnormalities of the Mitral Valve Producing Stenosis or Regurgitation

Previous sections have described the mitral valve abnormalities associated with rheumatic heart disease and prolapse, with and without associated disease states involving connective tissues. This section focuses primarily on congenital mitral valve conditions, excluding prolapse.

Congenital Mitral Stenosis

Obstruction to mitral valve flow can occur at the supravalvar level, annular level, free valve margin, and at the tensor apparatus or papillary muscle level. Typically, the mitral valve demonstrates thickened rolled-valve leaflet edges with short thick chordae and papillary muscles that are hypoplastic and close to one another. When the papillary muscles fuse, the so-called parachute mitral valve is formed. Typically, the abnormalities coexist with other left-sided lesions, including obstructive abnormalities of the left ventricular outflow tract and coarctation of the aorta. Leaflet and chordae dysplasia also may result in coaptation abnormalities that lead to valvar regurgitation. Approximately 40% of patients in an autopsy series had truly hypoplastic valves with little leaflet and chordal dysplasia. This type of abnormality was most commonly associated with severe left ventricular outflow tract abnormalities (1443). At the other end of the spectrum is the perforate but severely dysplastic valve associated with the hypoplastic left heart syndrome with a diminutive annulus and leaflets, diminutive or absent chordae, and papillary muscles that are incorporated into the fibroelastic scar of the ventricle.

The supramitral ring consists of a fibrous tissue that arises above the leaflets of the mitral valve but, in contrast to the membrane of cor triatriatum, remains below the level of the orifice of the left atrial appendage. The classic description by Shone et al. (1444) of the ring occurred as a complex with a parachute mitral valve, subaortic stenosis, and coarctation of the aorta. In the parachute mitral valve, the anterolateral papillary muscle is usually absent and has a common insertion of thick shortened chordae.

The timing of clinical presentation depends on the presence of associated lesions and the degree of obstruction to left ventricular inflow. This condition may have a profound effect on the nutritional status and growth of the patient. Other congestive symptoms include tachypnea, diaphoresis, poor feeding, cough, and frequent respiratory infections. Severe obstruction manifests with poor systemic perfusion and an active right ventricular heave resulting from elevated pulmonary artery pressures secondary to left atrial hypertension. An opening snap is rarely heard, as the leaflets are often severely dysplastic. Frequently, the pulmonary component of the second heart sound is more intense, and there is a mid-diastolic murmur with presystolic accentuation in the setting of sinus rhythm.

In all instances, the electrocardiogram usually exhibits left atrial enlargement, with right ventricular hypertrophy indicating significant pulmonary hypertension. The left ventricular voltages may be reduced as a result of concurrent left ventricular hypoplasia. Echocardiography often provides the mainstay of diagnosis both in two-dimensional assessment of the anatomy and in the functional assessment of severity, recognizing that many previously described indices have not been validated in children (1445,1446,1447,1448 and 1449).

Medical management consists of decreasing pulmonary congestion and attention given to nutrition, infection, atrial arrhythmias, and embolic phenomena. If unresponsive to medical management, surgery is directed at primarily preserving native valve function while preserving its integrity. Repair of the native valve often is focused on modifying the annulus, leaflets, or chordae (1450,1451,1452,1453,1454,1455,1456,1457 and 1458). Papillary muscles are subject to commissurotomy and fenestration. If a double orifice exists that is adequate, it is best not to incise the bridging tissues. Supramitral rings are generally excised, taking care to avoid the circumflex coronary artery. The role of balloon valvotomy in the child with congenital stenosis is controversial, with some centers reporting good palliation; however, the results are less satisfying than procedures undertaken for rheumatic disease (1459,1460,1461,1462 and 1463). Transesophageal echocardiography is mandatory before proceeding with left atrial catheterization (1464). Mitral valve replacement is best undertaken after the age of 3 years with a mechanical valve as opposed to a bioprosthetic appliance (1465,1466). Difficulties exist in anticoagulation, especially in the setting of a changing diet with varying amounts of vitamin K.

Congenital Mitral Valve Regurgitation

Congenital mitral regurgitation is particularly uncommon (1467). In the morphologic assessment of the congenitally regurgitant mitral valve, virtually all aspects of the mitral valve, including abnormalities of the free valve margin, chordal apparatus, and papillary muscles, have been identified in the etiology of the regurgitation (1468,1469,1470,1471,1472,1473,1474,1475,1476,1477,1478,1479,1480,1481,1482,1483,1484,1485,1486,1487,1488,1489,1490,1491,1492,1493,1494,1495,1496,1497,1498,1499,1500,1501,1502,1503,1504,1505,1506,1507,1508,1509,1510,1511,1512,1513,1514,1515,1516,1517,1518,1519,1520 and 1521). Such abnormalities include dysplasia of the valve, double-orifice deficient leaflet tissue, isolated anterior cleft of the mitral valve, polyvalvular disease, displacement of the mitral valve of the Ebstein type, and the so-called anomalous mitral arcade. Mitral regurgitation can occur in the newborn period, reflecting a disordered transitional circulation (i.e., transient myocardial ischemia of the newborn) (1503,1504 and 1505). Papillary muscle ischemia and infarction in the infant with critically severe aortic stenosis have been well described (1521). Mitral regurgitation also has been identified in the newborn infant with myocarditis as well as other primary endomyocardial disorders. Usually, beyond the newborn period, infants with anomalous left coronary artery originating from the pulmonary artery or with atresia of the left coronary artery ostium and inadequate coronary artery collateralization develop papillary muscle ischemia or frank infarction with resultant mitral regurgitation. Mitral regurgitation has been observed in patients with coarctation of the aorta, representing either functional impairment of the left ventricle or congenital abnormalities of the mitral valve. In the infantile presentation of Marfan syndrome and severe mitral regurgitation, the mitral valve may exhibit features of dysplasia as well as prolapse. Mitral regurgitation can occur in the patient with Kawasaki's disorder, infective endocarditis, following trauma, and in the patient with chronic anemia.

The so-called anomalous mitral arcade (1484), which is responsible for this lesion, is characterized by connection of left ventricular papillary muscles to the anterior mitral leaflet, either directly or through the interposition of unusually short chordae (1485,1486,1487,1488,1489 and 1490). Enlarged thickened papillary muscles in

close approximation to the free valve margin of the mitral valve contribute to subvalvular obstruction. Although the anomalous mitral arcade is considered a disorder of the pediatric age group, it has been recognized in the adult (1488).

Among the causes of the congenital mitral regurgitation is the isolated cleft of the anterior leaflet of the mitral valve (1491,1492,1493,1494,1495,1496,1497,1498,1499,1500 and 1501). This disorder is quite different from the so-called cleft left atrioventricular valve in the patient with an atrioventricular septal defect (1499). The isolated cleft of the anterior mitral leaflet is characterized by a cleft dividing the anterior leaflet of the mitral valve into two portions with a normally positioned mitral annulus and intact atrioventricular muscular and membranous septum. This deformity of the mitral valve is an uncommon cause of congenital mitral regurgitation, but it has been identified in patients with ventricular septal defect, tetralogy of Fallot, tricuspid atresia, and others.

Double-orifice mitral valve is a condition in which two complete orifices are supported by their own tension apparatus (1502) and should be distinguished from a simple fenestration of a valve leaflet not supported by its own tension apparatus. The basic morphology is either central division into two orifices of equal size by a bridge of leaflet tissue or presence of an accessory orifice at a commissure or in a leaflet. The double-orifice mitral valve is a well-known morphologic finding in the patient with an atrioventricular septal defect, but a number of cases of double-orifice mitral valve have been documented in patients with normal atrioventricular septa. This condition does not invariably result in a regurgitant valve, although severe regurgitation in the setting of a double-orifice mitral valve has been observed in the pediatric patient as well as in the adult in the seventh decade of life.

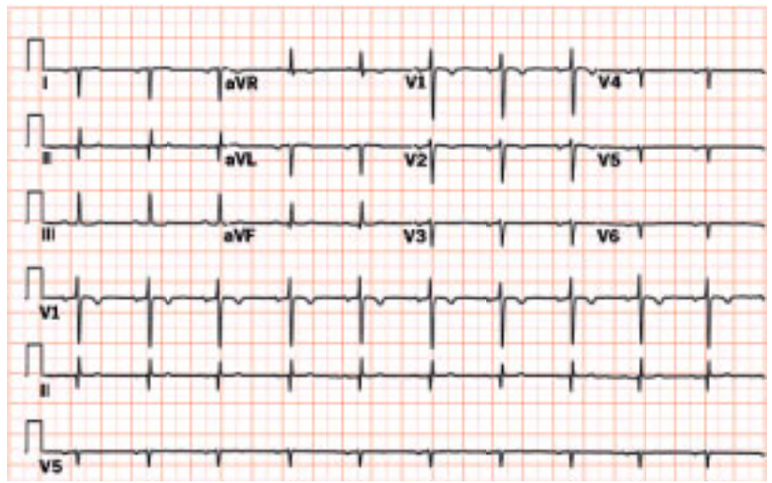
Congenital Pericardial Defect

A congenital defect of the pericardium represents defective formation of the pleuropericardial membrane and may involve the entire pericardium, the left-sided aspect of the pericardium, or the right pericardium (1522,1523,1524,1525,1526,1527,1528,1529,1530,1531,1532,1533,1534,1535,1536,1537,1538,1539, 1540 and 1541). Defects of the left pericardium are most commonly involved, but complete and small right-sided defects are well described (1529,1535). Incomplete formation of the septum transversum is believed to be responsible for a diaphragmatic defect. Partial absence of the left pericardium may be suspected clinically in the child or adult because of chest pain and an unusual cardiac silhouette observed on the plain chest radiograph. In patients with partial absence of the left pericardium, either the cardiac ventricles or the left atrial appendage may protrude or herniate through the pleuropericardial defect, leading in some patients to chest pain or syncope; in others, strangulation of the ventricles or left atrial appendage may lead to death. Herniation or protrusion of the right lung into the pericardial cavity may obstruct the right superior cava vein. Herniation of the omentum into the pericardial cavity occurs when there is a diaphragmatic pericardial defect and a defect in the diaphragm.

All these defects are uncommon, and we are aware of only a few instances of symptomatic right- or left-sided pericardial defect being recognized in the neonate. The chest radiograph in the older child may provide a clue as to the presence of a left-sided defect, and diagnosis may be confirmed by cross-sectional echocardiography and contrast-enhanced computed tomography or MRI (1524,1526,1532,1534,1535 and 1536,1538,1540,1541). In symptomatic patients, surgical attention, including treatment by thoracoscopic pericardiectomy, is required to close or widely open the pleuropericardial defect.

Dextrocardia, Situs Inversus, and Kartagener's Syndrome

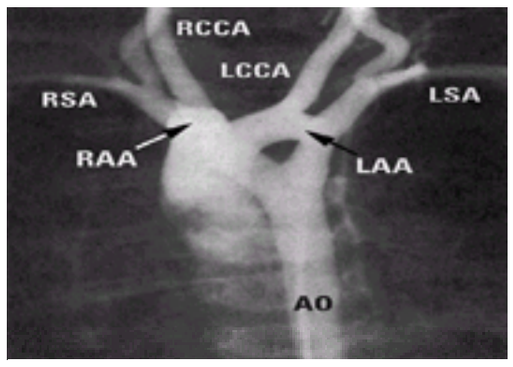
Kartagener's syndrome is the syndrome of dextrocardia with situs inversus totalis, sinusitis, and bronchiectasis (1542,1543,1544,1545,1546,1547,1548,1549,1550,1551,1552,1553,1554,1555,1556 and 1557). The respiratory difficulties, including recurrent middle ear infections, in this syndrome result from hypomotility or immotility of the tracheobronchial cilia. The basic defect is lack of ciliary dynein (1544,1545,1546,1547,1548,1549,1550 and 1551). Male subjects with this disorder are usually infertile, and the absence of dynein in the sperm tails accounts for spermatic immotility (1547,1553). Although it is uncommon to establish this diagnosis in the neonate, in at least one neonate the diagnosis of primary ciliary dyskinesia was confirmed by both ultrastructural and functional investigations (1553). The immotile cilia syndrome was suspected in this patient because of respiratory distress, situs inversus, abnormal nasal discharge, and hyperinflated chest radiograph. Others also have made this diagnosis in the neonate and young infant. In the older patient with Kartagener's syndrome, end-stage bronchiectasis has been treated by heart-lung or double-lung transplantation (1555,1556 and 1557).



Dextrocardia. Notable findings include a positive R wave in aVR and counterclockwise rotation in the precordial leads.

Vascular Rings

There are a wide variety of aortic arch anomalies and related conditions, some of which cause vascular rings (*e*Fig. 30.0.62). Vascular rings and slings usually present with respiratory distress in the neonate or infant. Because of respiratory distress, difficulty swallowing, and wheezing, they may present in older children or remain clinically silent, being discovered only as an incidental finding. The true vascular ring comprises a complete encirclement of the trachea and esophagus. A number of entities cause incomplete encirclement, including the pulmonary sling. When sufficient compression of the trachea and esophagus exists, symptoms are present; however, when the compression is mild, symptoms may be absent. Dysphagia tends to be a problem only after solid foods are introduced. The most common of these anomalies are well documented in the literature (1558,1559,1560,1561,1562,1563,1564,1565,1566,1567,1568 and 1569), as are the imaging findings. Cross-sectional imaging, particularly MRI and echocardiography, have supplanted cardiac catheterization and angiography as the modalities of choice to supplement the chest radiograph and esophagogram in the investigation of uncomplicated patients. Vascular rings represent approximately 1% to 2% of cases of isolated congenital heart malformations (1566,1567 and 1568). Additionally, they may be found in association with other malformations, particularly tetralogy of Fallot, in which some 10% of those having a right aortic arch have an aberrant left subclavian artery with a patent arterial duct or ligamentum completing the ring (1568,1569).

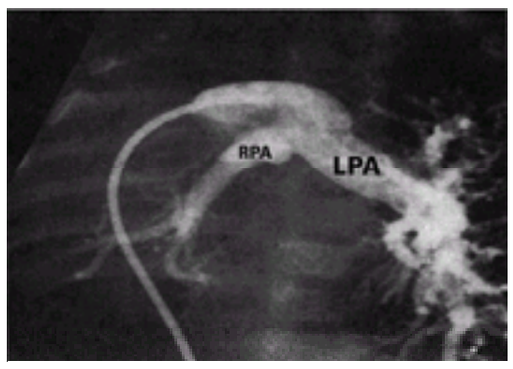


***e*FIGURE 30.0.62** Vascular ring in patient with both right and left arches widely patent. AO, aorta; LAA, left aortic arch; LCCA, left common carotid artery; LSA, left subclavian artery; RAA, right aortic arch; RCCA, right common carotid artery; RSA, right subclavian artery.

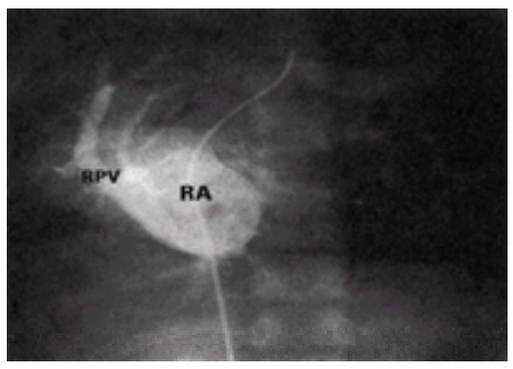
Scimitar Syndrome

Scimitar syndrome derives its name from the radiographic appearance of the anomalously draining right pulmonary veins, which, in their connection to and intraparenchymal course to the inferior vena cava, suggest the appearance of a scimitar (1570,1571,1572 and 1573) (*e*Fig. 30.0.63, *e*Fig. 30.0.64, and *e*Fig. 30.0.65).

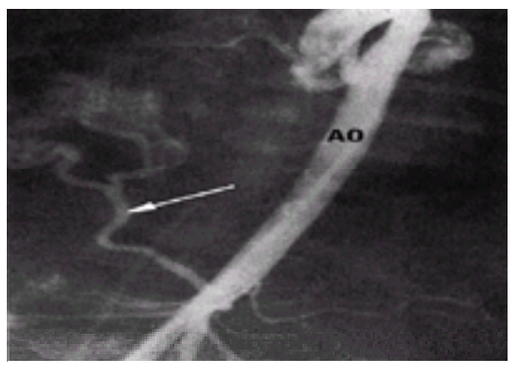
Also termed the *hypogenetic right lung syndrome*, these patients usually have some degree of hypoplasia of the right pulmonary artery and right lung, anomalous connection of the right pulmonary veins to the inferior vena cava or the caval-atrial junction, and an aberrant systemic artery from the descending thoracic aorta supplying a portion of the right lung (1570,1571,1572,1573,1574,1575,1576,1577,1578,1579,1580,1581,1582,1583,1584,1585,1586,1587 and 1588) (*e*Fig. 30.0.63, *e*Fig. 30.0.64, and *e*Fig. 30.0.65). Not infrequently, there is sequestration as well. The heart is often in the right chest, reflecting the right pulmonary artery hypoplasia. Some patients who have this syndrome may present in infancy, reflecting a large anomalous systemic artery or severe anomalies of the pulmonary veins (1573,1578,1580,1582,1583,1584,1585,1586,1587 and 1588). Other patients present in childhood with recurrent chest infection, sometimes progressing to bronchiectasis. Surgical repair seldom results in normal blood flow to the right lung, but should abolish the left-to-right shunt. We have found that postoperative pulmonary venous obstruction is prevalent, especially in the infant (1571).



***e*FIGURE 30.0.63** Hypogenetic right lung or scimitar syndrome. Note the smaller right pulmonary artery (RPA). LPA, left pulmonary artery.



***e*FIGURE 30.0.64** In this patient with the scimitar syndrome, note the anomalously connected right pulmonary veins (RPV). RA, right atrium.



***e*FIGURE 30.0.65** In this patient with the scimitar syndrome, note the anomalous systemic artery (*arrow*) originating from the descending aorta (AO) and coursing into the right lung.

CONTROVERSIES AND PERSONAL PERSPECTIVES

To look into the future for the diagnosis and treatment of congenital heart disease, one must observe the lessons from the past. The themes and variations present in the anatomy and physiology are subject to interpretation analogous to that of the conductor expressing the nuances of a symphony. Added to this is the influence of local experience and expertise as they relate to peer-reviewed evidence. Indeed, perusal of the published literature in clinical congenital heart disease rarely exceeds the levels of case report, case series (either retrospective or prospective), or retrospective case controls. The terms *double-blind*, *placebo-controlled*, and *randomized* do not find their way into the titles and methods of the clinical literature. The lack of large cohorts of patients in general does not allow the power for most investigators to suggest more than a trend in the difference between observations to support an argument. Acceptance of the null hypothesis is rarely valid given the limitations of sample size inherent in most publications. We are often compelled, therefore, to manage problems based on consensus or expert opinion, neither of which is particularly stringent in this era of attempting to define evidenced-based plans for care. A valid argument is not the equivalent of truth. As management protocols move through the continuum described by the nouvelle to that of the established or the discarded, one must be ever vigilant in assessing the nature of the evidence, whether by induction or deduction.

One does not have to look much beyond the present to find controversies in management. Many of our own current perspectives have been presented in the preceding pages. Contrary opinion can be found repeatedly in many aspects of diagnosis and management. We have witnessed a trend to neonatal correction of congenital heart problems. Whereas mortality statistics are often compared, the challenge will be to answer the questions of morbidity. For instance, there is a paucity of literature comparing the neurodevelopmental outcome of neonatal patients undergoing elective bypass repair with those repaired later, after years of cyanosis; however, few would consider a randomized trial today in this setting. We made a major move to designating the arterial switch as the operation of choice for patients with transposed great vessels and an intact ventricular septum, and yet there is no long-term follow-up of the arterial switch patient to suggest that there is not a steep increase in hazard function due to problems with the coronary circulation over time. Once beta-blockers were considered absolutely contraindicated in the patient with ventricular dysfunction, but are now receiving attention as a powerful addition to the pharmacologic management of patients with end-stage ventricular dysfunction and congenital heart disease. Acute myocarditis is still the subject of ongoing controversy in establishing the diagnosis and determining optimal treatment. Natural and unnatural history data continue to be debated when considering the optimal timing of cardiac replacement therapy. A well-known example is the patient with the hypoplastic left heart syndrome. Some believe that cardiac transplantation is the best palliative strategy, whereas others contend that the best option is that of palliative surgery in staged sequences in an effort to defer transplantation to later years. The relative shortage of donor grafts and improvements in immunotherapy foreshadow the ongoing debate regarding the merits of xenograft transplantation, and opportunities of fetal diagnosis spark further discussion of outcomes and challenge us to be consistent in our consideration of the potential for differences in standards of care. The list goes on.

The patient and family are not only interested in whether the child will survive, but increasingly we are called on to comment on the child's future. Practical issues dictate that we must strive to reach decisions with patients and families to use the best of incomplete information and experience in an uncompromising ethic of truly caring for the child. We have journeyed a long way this century and clearly have a long way to go as we travel through the next millennium.

FUTURE DIRECTIONS

The discipline of clinical pediatric cardiovascular medicine has evolved in less than a century from a meticulous pathologic description of morphology to a dynamic interaction of molecular biology, embryology, clinical application of anatomy and physiology, diagnostic imaging, and medical and surgical intervention. The advent of

advances in ultrasound technology and the development of computerized tomography and MRI have resulted in a move toward less invasive preoperative imaging and hemodynamic assessment. The catheterization laboratory has evolved from being primarily a diagnostic to an ever-increasing therapeutic resource. Issues in genetics and fetal medicine have resulted in new considerations and challenges in embryology and its application to the developing fetus. Indeed, fetal therapeutic intervention using the skills of surgeons, obstetricians, and cardiologists is no longer a dream of the future; instead, it is a present reality. Importantly, a description of the natural history of congenital heart diseases now should reflect the prenatal development as well as the postnatal progression and should include the outcome of intervention.

As already noted, the importance of a recognizable and practically applicable denominator remains one of the great challenges in the description of the management and progress of patients with congenital heart disease that occurs in isolation and with other defects in growth and development. Given the diversity of lesions, the challenge is in finding meaningful cohorts of patients for description, as few patients have identical disease. The result is an exciting creative application of a changing technology. This technologic imperative, however, must be guided by a responsibility for critical evaluation of its clinical utility. Malformations can be repaired and palliated with increasing success, as evidenced by the growing and changing face of the practice of adult congenital heart disease. In cases in which this is not possible, the heart can be mechanically supported and replaced, again with increasing success. Although we strive to define evidence to guide our practice, experience remains central to management, particularly in the setting of complex issues. To be truly successful, we must continue to care for and define not only where the child has been, but also what the child will become.

THE FUTURE

The challenges are many for the patient with congenital heart disease and those caring for these patients. From maximizing care for the child and adult with congenital heart disease, to defining insurability for the adult with congenital heart disease, to defining care givers for the adult with congenital heart disease or the “aftermath” of congenital heart surgery, these are but some of the obvious challenges. For many patients with complex heart malformations, much has been accomplished, but there are still patients who die before, or fail to meet the criteria for, the Fontan operation or other surgical interventions. Patients undergoing the Fontan operation, double switch, or others are probably just the “tip of the iceberg.” Considerable emphasis should focus on the denominator, not just the numerator. Outcomes must be measured in more sophisticated, meaningful ways. Neurodevelopmental outcome and strategies—both peri- and postoperative—must be designed and used to preserve the integrity of cerebral function. To address the root of the problem, there must be reallocation of resources—human as well as fiscal—to define the causation of congenital heart disease. The application of molecular genetics and ongoing definition of the human genome will likely redefine the issues of those caring for the patient with congenital heart disease.

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ADULT CONGENITAL HEART DISEASE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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Chapter References

OVERVIEW

At the time of adulthood, native anatomy, physiology, and operative status converge to determine prognosis and surgical and medical management considerations. For common simple shunt lesions or single obstructive lesions of the right or left ventricular outflow tracts, early intervention for significant disease leads to optimal long-term results. When patients with complex lesions unoperated or palliated reach adulthood, physiologic repair may be feasible. The decision to proceed depends on the reversibility of deleterious physiology and the possibility of preventing further deterioration. The long-term complications of palliative shunts are pertinent, particularly for the first generation of patients who have undergone surgery. When physiologic repair has taken place, issues of concern in long-term follow-up include hemodynamic and arrhythmic complications and reoperation.

Adolescents and adults with congenital heart disease (CHD) are optimally cared for in specialized centers staffed by medical and pediatric cardiologists or cardiologists trained and committed to the care of adults with CHD as well as cardiac surgeons with skill in congenital heart surgery. These facilities should have easy access to specialists including those in cardiac anesthesia, obstetrics and gynecology, pulmonary disease, hematology, neurology, psychiatry, and genetic counseling.

The purpose of this chapter is to provide an overview of the issues that will be of major concern for physicians who are given the responsibility of following these patients as adults. We discuss a framework for clinical assessment and management at the time of presentation in adulthood. The role of invasive and noninvasive diagnostic modalities is reviewed. A problem-oriented discussion of the unoperated and operated lesions most likely to be encountered in this patient population is provided. Specialized issues pertinent to this population as a whole, such as Eisenmenger's syndrome, the medical management of cyanosis, endocarditis prophylaxis, exercise recommendations, pregnancy, and psychosocial issues, are summarized.

GLOSSARY

Complex lesions: A combination of lesions, the most common patterns of which, seen in adults, are described in this chapter.

Cyanosis: A blue discoloration of the mucous membranes resulting from an increase in the amount of reduced hemoglobin. Central cyanosis occurs when the circulation is mixed secondary to a right-to-left shunting. Cyanosis can be observed in unoperated and palliated patients with native cyanotic lesions.

Eisenmenger's complex: A term referring to flow reversal across a ventricular septal defect when pulmonary vascular resistance exceeds systemic levels.

Eisenmenger's physiology: A term used to designate the physiologic response in a broader category of lesions in which a right-to-left shunt occurs in response to an elevation in pulmonary vascular resistance.

Eisenmenger's syndrome: A term applied to common clinical features shared by patients with Eisenmenger's physiology. These findings in combination with the absence of left-to-right shunting make the patient inoperable.

Native lesions: The anatomic lesions at birth.

Palliative interventions: Increase or decrease pulmonary blood flow while a mixed circulation and cyanosis persist. Palliative surgical shunts aimed at increasing pulmonary blood flow are summarized in Table 31.1.

Palliative surgical shunts	
Systemic venous-to-pulmonary artery shunts	
Classic Glenn	SVC to right PA
Bidirectional Glenn	SVC to right and left PA
Bilateral Glenn	Right and left SVC to right and left PA
Systemic arterial-to-pulmonary artery shunts	
Classic Blalock-Taussig	Subclavian artery to PA
Modified Blalock-Taussig	Subclavian artery to PA (prosthetic graft)
Pott's anastomosis	Descending aorta to left PA
Waterston's shunt	Ascending aorta to right PA

PA, pulmonary artery; SVC, superior vena cava.
Adapted from Marelli AJ, Mullen M. Congenital heart disease onward into adulthood. *Baillieres Pediatr* 1996;4:192.

TABLE 31.1 SURGICAL PALLIATION OF CONGENITAL HEART LESIONS

Physiologic repair: A term applied to procedures that result in total or near total anatomic and physiologic separation of the pulmonary and systemic circulations in complex cyanotic lesions. These patients are typically acyanotic.

Simple lesions: Shunt lesions or obstructive lesions of the right or left ventricular outflow tract that occur in isolation.

HISTORICAL PERSPECTIVE AND EPIDEMIOLOGY

Over the past four decades, the convergence of major advances in pediatric and medical cardiology as well as cardiovascular surgery has resulted in the survival of an increasingly large number of patients with complex structural heart lesions. Table 31.2 provides a historical perspective of primary operations for major disease categories. This chronologic listing of surgical interventions and their dates of introduction provides a basis for predicting the sequential rise in expected survival for patients with specific diseases.

1955	Tetralogy of Fallot
1959	Senning atrial baffle in TGA
1964	Mustard atrial baffle in TGA
1969	Rastelli right ventricle to pulmonary artery conduit
1971	Fontan anastomosis in tricuspid atresia
1975	Jatene arterial switch in TGA with ventricular septal defect
1983	Norwood reconstruction in hypoplastic left-sided heart syndrome
1984	Neonatal arterial switch in TGA with intact ventricular septum

TGA, transposition of the great arteries.
Adapted from Marelli AJ, Mullen M. Congenital heart disease onward into adulthood. *Baillière's Pediatr* 1996;4:189.

TABLE 31.2 SURGICAL REPAIR OF COMPLEX CONGENITAL HEART LESIONS

Congenital cardiac malformations occur at a rate of 8 per 1,000 live births, corresponding to approximately 32,000 infants with newly diagnosed CHD each year in the United States. An estimated 20% die within the first year from life-threatening conditions, a substantial decrease from the reported 40% in the late 1960s (1). An approximate 80% of the first-year survivors live to reach adulthood in the current era (2,3 and 4). Coincident with improved survival in the neonatal and early childhood years, these numbers continue to grow with prevalence rates of adults with CHD in the United States estimated to be an approximate 800,000 (5).

PRESENTATION IN ADULTHOOD

The management of the young adult with CHD requires the clinician, at the end of his or her assessment, to determine the native anatomy, the surgical anatomy, the patient's physiology, and operative candidacy (Fig. 31.1) (6).

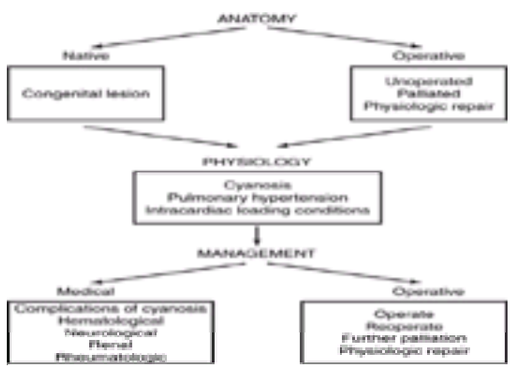


FIGURE 31.1 The goals of complete clinical assessment are to define anatomy and physiology to determine appropriate management. (From Marelli AJ. Congenital heart disease in adults. In: Goldman L, Bennett J. *Cecil's textbook of medicine*. Philadelphia: WB Saunders, 1999, with permission.)

Understanding the details of the native and surgical anatomy is the cornerstone of appropriate management. Information obtained from objective diagnostic tests should complement that obtained from review of all previous available records. Reconsideration of the findings is imperative in delivering proper care, as the management of CHD has changed significantly over the last thirty years.

Determination of the *physiology* includes two components. The first relates to the presence or absence of cyanosis, the medical complications that ensue, and the assessment of the pulmonary vascular bed. The second relates to the loading conditions of the cardiac chambers. Congenital heart lesions are classified as cyanotic or acyanotic (7). The presence or absence of pulmonary hypertension, with or without an increase in pulmonary vascular resistance, depends on the quantity and source of pulmonary blood flow. If forward flow from the right side of the heart is insufficient, native collaterals, surgical shunts, or both provide alternate sources of pulmonary blood flow. An increased volume load to the heart can result from intracardiac shunting or valvular regurgitation. An increase in pressure afterload can result from native or acquired stenosis of either outflow tracts or high pulmonary or systemic vascular resistance. It is the interaction between the pulmonary vascular bed and the heart that determines the patient's physiology.

Palliative interventions are defined as those operations that serve to either increase or decrease pulmonary blood flow while allowing a mixed circulation and cyanosis to persist. Palliative surgical shunts aimed at increasing pulmonary blood flow are summarized in Table 31.1. Systemic arterial-to-pulmonary artery shunts may result in a significant improvement in saturation levels but at the price of high levels of pulmonary blood flow and direct exposure of the pulmonary vascular bed to the high pressures of the systemic circulation (8). The possible long-term complications of these shunts include pulmonary hypertension, pulmonary artery stenosis, and volume overload of the ventricle receiving pulmonary venous return, making further surgical intervention more difficult or impossible. This is particularly true of large central shunts, the Pott's shunt, and Waterston's anastomosis. Well-sized Blalock-Taussig shunts can result in more controlled pulmonary flow, but may stenose over time and distort the pulmonary artery anatomy (9). These considerations provide the rationale for the current widespread use of systemic venous-to-pulmonary arterial shunts resulting in acceptable saturations with more balanced pulmonary blood flow and a lower transpulmonary pressure gradient (10). Surgical *pulmonary artery banding* is a palliative measure aimed at decreasing pulmonary blood flow and protecting the pulmonary vascular bed against direct exposure to systemic pressures. The pulmonary band is usually placed above the valve and below the pulmonary artery bifurcation. This procedure has been performed in patients with a ventricular septal defect (VSD) large enough to significantly increase pulmonary blood flow in the presence or absence of other complex lesions. In long-term follow-up, two issues are of concern. The first relates to distortion of the pulmonary artery trunk or at the bifurcation, with or without migration of the band. This can preclude or complicate adequate late repair, requiring reconstruction of the proximal pulmonary vascular bed. The second complication of the band has been observed in a subgroup of patients having a univentricular heart and transposition of the great arteries with a potentially or truly restrictive VSD. It has been suggested that banding the pulmonary trunk stimulates myocardial hypertrophy, promoting spontaneous reduction in the size of the bulboventricular foramen, leading to secondary subaortic stenosis. The surgical management of this is associated with a high mortality (11).

Physiologic repair is a term applied to procedures that result in total or near total anatomic, physiologic, or both anatomic and physiologic separation of the pulmonary and systemic circulations. Examples include repair of tetralogy of Fallot (TOF), the Senning's or Mustard's operation for transposition of the great arteries, and the Fontan operation for the single ventricle. Although an attempt is made to approximate normal physiology, long-term complications relating to prosthetic materials, valves, and conduits, as well as ventricular dysfunction, require careful and continued follow-up. These are discussed, where applicable, in the context of specific

lesions.

DIAGNOSTIC TECHNIQUES: APPROACH, STRENGTHS, AND LIMITATIONS

Adequate use of the diagnostic tools assists in the determination of the anatomy, physiology, and operative status of the adult patient. A complete clinical assessment is essential and includes 12-lead electrocardiography, chest radiography, and baseline oxygen saturation. Serial use of these tests, Holter monitoring, and cardiorespiratory exercise testing are tailored to the individual patient. In this section, we describe the use of noninvasive imaging and cardiac catheterization as it pertains to adults with CHD.

Transthoracic Echocardiography

Two-dimensional and Doppler echocardiography is the cornerstone of imaging for diagnosis and follow-up of congenital lesions. The principle of segmental analysis of anatomy and hemodynamics underlies the echocardiographic examination of CHD in patients of all ages. The segmental approach to congenital cardiac disease (12) refers to sequential diagnosis of the major cardiac segments in a venous-to-arterial sequence, consistent with the development of the heart. Native and surgical anatomy is therefore described from inflow to outflow in keeping with the concept of a circulation in series.

The three major cardiac segments consist of the visceroatrial segment, the ventricles, and the great arteries. The two major connecting segments are the atrioventricular junction and the ventriculoarterial junction. Because the visceral and atrial situs are usually concordant with one another, the viscera and the atria are considered as one segment. A segmental approach in echocardiographic diagnosis is performed by examining the viscera, systemic and pulmonary venous return, atria, atrioventricular junction, ventricular arrangement, and great arteries. Starting with extracardiac structures and going to intracardiac structures, and within the heart, going from chamber and great vessel arrangement to valvular function, a complete diagnostic examination is performed. The diagnosis of complex disease is derived from the information obtained at each segment. Each segment is therefore a building block. The sum of these parts constitutes the final diagnosis. For complete assessment of the patient with CHD, this principle should be respected if not in the sequence of image acquisition, then in the analysis and synthesis of information.

The number of ventricles, their relative size, and arrangement influence two key factors of the patient's natural history: (a) whether the patient is a candidate for biventricular repair, and (b) which of the two morphologic ventricles is subaortic and therefore performs systemic work. Assessment of ventricular function is crucial and yet difficult. Geometric assumptions necessary to quantitate ventricular function limit the ability to accurately measure morphologic right ventricular and distorted single-ventricular contractility. Right ventricular pressure inferred from the velocity of a tricuspid regurgitation should be cross-checked from a measured pressure gradient between both ventricles in the event of a restrictive VSD and with knowledge of systemic blood pressure measured simultaneously. In the absence of obstruction to right ventricular outflow, this pressure reflects that in the pulmonary vascular bed. On the other hand, a gradient across the right ventricular outflow tract can be used to approximate pulmonary artery pressure when the right ventricular pressure has otherwise been estimated based on a tricuspid regurgitation or properly aligned VSD jet. When conotruncal anatomy is difficult to image from standard parasternal views, off-axis views can be used in experienced laboratories to maximize determination of pressure gradients in native outflow or conduit stenosis. Distal pulmonary anatomy beyond the pulmonary artery branches is a notoriously difficult area. In the absence of pulmonary hypertension, when right ventricular pressure is elevated, and there is no stenosis of the proximal right ventricular outflow tract, other diagnostic modalities should be used to examine the distal pulmonary artery branches. The aortic arch, isthmus, and descending aorta can also be difficult to image in the adult. Erroneous pressure-gradient measurements in patients with coarctation of the aorta can result from stenosis in series or from pressure recovery secondary to long tubular segments (13). Native and surgical pulmonary artery shunts can be interrogated to determine patency. When the systemic pressure is known, it may be possible to infer pulmonary artery pressure from a pressure gradient measurement aligned with a systemic arterial to pulmonary artery shunt.

Accurate assessment of complex congenital anatomy results from a careful interactive diagnostic search, which becomes progressively more specific and focused as the examination proceeds. This is particularly important during a patient's first examination, as echocardiography becomes the key to the future clinical and surgical management. In adults and older children in whom acoustic windows are more challenging, information can be maximized by adhering to three precautions: referring the patient to an echocardiographer who is familiar with congenital heart lesions and technically versatile with adults, providing as much information on the patient's history ahead of time, and referring the patient to the same laboratory for sequential examinations.

Complete spatial understanding of complex congenital lesions can be challenged by the limitations of two-dimensional echocardiography. Three-dimensional reconstruction of images acquired transthoracically offers unique imaging perspectives, more closely approximating surgical anatomy and optimizing surgical planning (14,15). Improved accuracy and spatial resolution of suboptimal data sets as well as the ability to quantitate cardiac function (16) are broadening the application of three-dimensional echocardiography (17).

Transesophageal Echocardiography

The transesophageal echocardiographic (TEE) examination is particularly useful in adults to maximize image acquisition when transthoracic acoustic windows are poor (18). TEE is routinely used to clarify and detail intracardiac anatomy when transthoracic echocardiography is problematic. By comparison with transthoracic imaging, TEE provides additional anatomic information for specific posterior and anterior congenital lesions. Anomalous pulmonary venous connections (19) and atrial septal defects (ASDs), in particular those of the sinus venosus type (20), and atrial septal aneurysms can be detected transthoracically but are best imaged using a combination of horizontal and vertical transesophageal planes. Integrity of atrial baffles and Fontan connections can sometimes only be inferred from abnormal flow patterns, using transthoracic imaging in adolescents and adults. Obstruction due to thrombus or progressive narrowing can clearly be seen using TEE. Assessment of complex atrioventricular anatomy and function can be enhanced using posterior acoustic windows. For central pulmonary vascular architecture, subaortic and supraaortic lesions, as well as ventriculoarterial conduit function, specific sites of obstruction can be clearly delineated with vertical transesophageal views. Proximal coronary artery anomalies and coronary fistulas at their point of exit and entry can be easily imaged using transesophageal views. Using transthoracic echocardiography, a patent ductus arteriosus (PDA) can be inferred from a turbulent flow pattern seen at the origin of the left pulmonary artery. In adolescents and adults, however, often the duct cannot be directly visualized. TEE can be used to confirm the diagnosis and exclude the presence of endarteritis (21). Palliative shunt anastomosis can be imaged and interrogated using a combination of transesophageal views. Difficulty in properly aligning the Doppler signal parallel to the shunt can hinder the ability to make a definitive diagnosis of an obstructed shunt. Aortic coarctation can be diagnosed using multiple transesophageal views, but accurate multilevel measurements of the arch and descending aorta often require the use of other complementary examinations.

Intraprocedural TEE has become increasingly important. Intraoperative TEE is used as an adjunct to complex intracardiac repair. In pediatric series, intraoperative TEE has been shown to affect surgical management of complex congenital lesions in up to 20% of cases (22,23). TEE is being routinely used during interventional catheter-guided atrial septal device closure (24) and coarctoplasty. Atrial baffle dilations can be guided using TEE. In addition, the electrophysiologist can be helped in guiding ablation catheters through the heart when abnormal native or surgical anatomy results in a distortion of the usual landmarks. This can be particularly useful for ablation therapy in patients with right-sided Ebstein's anomaly and congenitally corrected transposition of the great arteries, after Mustard's procedure for complete transposition of the great vessels and after the Fontan operation (18).

Magnetic Resonance Imaging and Computed Tomography

These imaging modalities are available in specialized centers and can be used as adjuncts to cardiac ultrasound and angiography. Magnetic resonance imaging (MRI) and ultrafast computed tomography (CT) can be particularly useful for detailed assessment of the aorta, branch pulmonary arteries, systemic-to-pulmonary artery shunts, and anomalous systemic venous connections (25,26). For patients with TOF repair, MRI is particularly useful to clarify anatomy and function of the pulmonary arteries and right ventricle (27). Judicious use of complementary noninvasive tools to elucidate anatomy allows a more focused application of cardiac catheterization.

Diagnostic Cardiac Catheterization

There are three principal indications for diagnostic studies most commonly performed before surgical or catheter-based intervention. These include assessment of pulmonary vascular bed, clarification of anatomy, and coronary angiography in patients over the age of 40 years. The study usually includes a aturation run for shunt calculations, right and left pressure measurements as needed, cardiac output measurements, and appropriate biplane cine angiographic views. Shunt quantification can usually be inferred from secondary chamber enlargement using noninvasive imaging. In instances in which an atrial or ventricular level shunt is of borderline significance or in which chamber enlargement is secondary to concomitant primary regurgitant lesions, pulmonary to systemic flow ratios should be directly measured. In assessing the pulmonary vascular bed, cardiac catheterization is indicated when there exists doubt as to the etiology and potential reversibility of pulmonary vascular disease (28). Morphometric analysis of lung biopsy specimens and pulmonary wedge angiography can be used to quantify pulmonary vascular obstructive correlating obliterative vascular changes with hemodynamic abnormalities in the pulmonary circulation (29).

The etiology of unexplained pulmonary hypertension in patients with complex CHD can vary. Patients with repaired TOF may have right ventricular hypertension due to proximal or distal pulmonary artery stenosis. Pulmonary hypertension itself is rare. Pulmonary vascular disease can be seen in the setting of a previous large arterial-to-pulmonary artery shunt. Unoperated patients with complex tetralogy (pulmonary atresia with VSD) have extensive aortopulmonary collaterals. Determination

of resistance and delineation of the exact source of collaterals is indicated when unifocalization procedures are contemplated. In patients who have undergone Mustard's or Senning's repair for complete transposition of the great arteries, pulmonary venous baffle obstruction should be sought as a reversible cause of unexplained pulmonary hypertension. In the unoperated patient with single ventricle physiology, Fontan candidacy necessitates a detailed assessment of pulmonary vascular resistance and proximal and distal pulmonary artery anatomy. After Fontan repair, systemic venous congestion may indicate obstruction or thrombosis at the pulmonary artery anastomotic site. In the absence of an atrial level residual shunt across the cavopulmonary anastomosis in a patient with Fontan repair or Glenn's shunt, increasing cyanosis may be secondary to pulmonary arterial venous fistulae. After the Fontan procedure, the occurrence of a new harsh mid-systolic murmur in a patient with previous pulmonary artery banding should prompt a search for the latent development of bulboventricular subaortic obstruction.

INTERVENTIONAL CARDIAC CATHETERIZATION

Intercirculatory Shunts

The Rashkind foam-covered, double-umbrella device, the Bard clamshell septal umbrella, button devices, coil embolization, and the Amplatzer device have all been used for nonsurgical closure of PDAs measuring 7.0 to 12.5 mm (30,31,32,33 and 34).

A large experience has been gained using the Rashkind PDA occluder device. In a multicenter series, there were no procedure-related mortalities in over 600 cases in the trials conducted in the early 1990s. Complications including device embolization were seen in 2% of patients, and residual shunts occurred in less than 8% of the patients. Most residual shunts were detected only by echocardiography with no audible murmur (35,36). Using the Rashkind device, closure of the ductus arteriosus can be accomplished safely and effectively in adult patients with or without calcification of the duct (37). Coil embolization of a duct can be accomplished using one or more coils, particularly for PDAs measuring less than 7 mm. Residual shunts occur in less than 3% of patients and at 3-year follow-up there is no evidence of delayed coil migration, thromboembolism, or endocarditis (38). The use of the Amplatzer duct occluder has made it possible to close larger ducts measuring up to 12.5 mm in adults with a less than 0.5% residual shunt rate at 12 months (39). In the largest series, there was no evidence of thromboembolism, and spontaneous device embolization was seen in 2 of a total of 252 patients (39,40).

Successful device closure of ASDs and patent foramen ovale (41) can be performed using transcatheter techniques with a variety of devices with data reported on over 1,000 patients. Experience has been obtained with the ASDOS device (42), the buttoned device (43), the Angel Wings Das device (44), the Cardio-Seal implant (48), and, most recently, the Amplatzer device (45,46,47 and 48), which has been used to close ASDs measuring up to 3.5 cm in stretched diameter.

Complete occlusion rates for ASDs are variable from one device to another and improve over time with follow-up of individual devices. Residual shunt rates have been reported in as little as 10% of patients at 24 hours (48) or as much as 30% of patients at 1 year (42). Complete occlusion rates have been achieved in 98% of patients by 3 months using the Amplatzer device (46,47). Structural and clinical complication rates are variable and reported with all devices. Embolization, entrapment of adjacent structures, arm fracture necessitating transcatheter or surgical removal of the device, thromboembolic complications (49), and heart block have been observed in less than 10% of patients in most series. Direct comparison of transcatheter and surgical ASD closure reported with the Amplatzer device (50) underscores that in centers where expertise is available, adequate patient selection for interventional closure of ASDs (51) can lead to good results with less morbidity and a decreased hospital stay.

There are reports of catheter closure of VSDs in adults (52,53). Success rates are higher for congenital VSDs than for post–myocardial infarct VSDs, in which damaged tissue does not lend itself to secure device closure. Coil embolization has been used to occlude bronchial collateral arteries before and after repair of TOF with pulmonary atresia (54) and to occlude Blalock-Taussig shunts (55). Transcatheter closure has also been used to close residual postoperative interatrial communications after the Fontan procedure (56), atrial baffle leak after Mustard's procedure (57), and coronary artery fistulas (58,59).

Right and Left Ventricular Outflow Tract Obstruction

Pulmonary angioplasty is the procedure of choice for adults with congenital pulmonary valve stenosis (60). Long-term follow-up data of nearly 10 years demonstrates persistent resolution of the dynamic component of sub–pulmonary stenosis and no restenosis at the valvar level even for severe pulmonary stenosis (61,62). Pulmonary regurgitation is noted in an approximate 10% of patients and improves over time. Stents have been used in adults to relieve right ventricular pulmonary artery conduit obstruction (63) and peripheral pulmonary artery stenosis (64). The clinical usefulness of stents in the pulmonary arteries is particularly important in postoperative patients with TOF and truncus arteriosus with small pulmonary arteries. These patients may have peripheral pulmonary stenosis with severe pulmonary regurgitation after surgical repair. Stent placement with reduction in pulmonary artery pressure may reduce the amount of pulmonary regurgitation, decrease right ventricular dilatation and tricuspid regurgitation, and improve right ventricular function.

Balloon aortic valvuloplasty is recognized as the treatment of choice for children with congenital nonrheumatic stenosis in whom delaying the need for aortic valve replacement confers a therapeutic advantage. Aortic valvuloplasty has been described in adolescents and young adult patients. Reported success rates are as high as 89% with a 55% reduction in the mean peak-to-peak gradient after dilation, follow-up residual gradients of less than 55 mm Hg, and only mild to moderate aortic regurgitation after the procedure (65). This experience contrasts with that in older patients in whom the high incidence of early restenosis in the presence of acquired calcification of the aortic valve makes surgical intervention the procedure of choice.

Aortic coarctation can safely and effectively be treated with balloon dilation with or without stent implantation, particularly for adult patients with recoarctation after surgical repair (66,67). Incomplete relief is observed in 25% of patients with recoarctation versus 19% of patients with native coarctation (66). Restenosis remains a concern and appears to occur more frequently in children with native coarctation. The incidence of incomplete relief and restenosis is decreased in adolescents and adults with endovascular stent implantation (68). Aortic aneurysm formation is reported in 7% to 17% of adult patients (68,69), and aortic rupture occurs rarely. Percutaneous coarctoplasty is contraindicated in those with transverse arch hypoplasia.

LONG-TERM FOLLOW-UP AND MANAGEMENT OF THE MOST COMMON SPECIFIC LESIONS

A problem-oriented approach to the lesions most commonly encountered in this patient population, based on observations across the age groups (70), is provided. The patients presenting to adult cardiologists are a mixed population of operated and unoperated patients, the relative proportion of which will continue to vary, based on evolving therapeutic trends in pediatric cardiology. The discussion pertinent to each lesion is divided into three parts. Prevalence and Anatomy provides epidemiologic information and reviews the anatomy necessary to understand diagnostic categories. Outcome describes the clinical course and complications of the operated or unoperated patients, based on the pathophysiology of the lesion. Management provides a problem-oriented discussion of issues related to choice of medical or surgical therapy and surveillance of the patient presenting as an adult.

Isolated Shunt Lesions

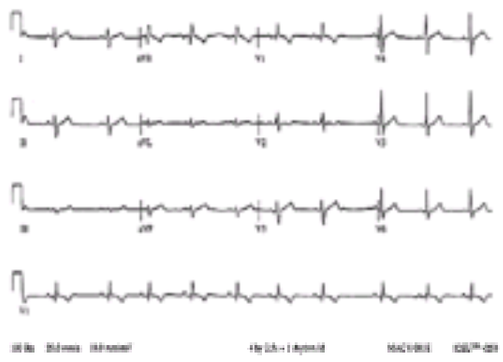
Shunts at the atrial, ventricular, and great artery levels are some of the most commonly encountered lesions in children and adults. Hemodynamic complications of significant shunts relate to volume overload and chamber dilation of the primary chambers receiving the excess left-to-right shunt: the right side of the heart for patients with ASD and the left side of the heart for patients with VSD and PDA. Secondary complications result from valvular dysfunction and damage to the pulmonary vascular bed. The size and duration of the shunt determine the natural history and therefore the indications for closure. The degree of shunting is always a function not only of the size of the communication, but also a function of its location on biventricular compliance, the pulmonary and systemic vascular resistances, or both. Hemodynamic sequelae of shunts are typically clinically apparent or can be expected to occur when pulmonary-to-systemic flow ratios exceed 1.5 to 1.0; hence, the designation of a "significant shunt." It should be noted, however, that the diagnostic method used influences the clinical detectability of abnormal findings. For example, assessment of a mildly enlarged right ventricle may be variable between the physical examination, chest roentgenology, and cardiac ultrasound. Uncertainty about the physiologic significance of a borderline shunt can be minimized by integrating serial determinations from multiple clinically relevant diagnostic sources, rather than making management decisions based strictly on a calculated shunt value. Clinical decision making takes into consideration the patient's age, symptoms, and direct and indirect diagnostic information reflecting intracardiac and pulmonary hemodynamics.

Atrial Septal Defects

Prevalence and Anatomy

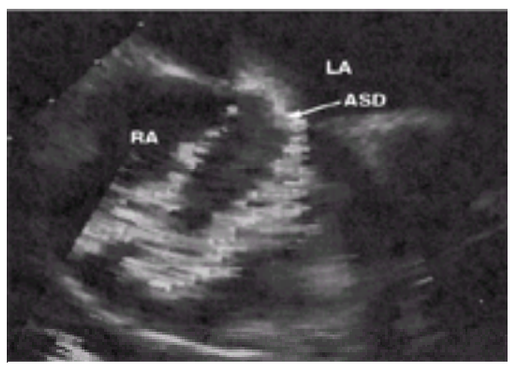
The ostium secundum ASD is reported to account for 7% of all congenital lesions and is twice as prevalent in female patients (71) (*e*Fig. 31.1.1 and *e*Fig. 31.1.2). Defects of the atrial septum constitute 30% to 40% of CHD seen in adults (70). The secundum ASD occurs as a result of an enlarged foramen ovale, an excessive resorption of the septum primum, or inadequate growth of the septum secundum (*e*Fig. 31.1.3). Abnormal development of the endocardial cushions results in a variety of atrioventricular canal defects, the most common of which consists of an atrial defect in the ostium primum location, typically accompanied by a cleft mitral valve (*e*Fig. 31.1.4). The sinus venosus defect of the superior vena caval type accounts for 2% to 3% of all interatrial communications. It is located posterior to the fossa

ovalis at the junction of the superior vena cava and right atrium and is generally associated with an anomalous connection of the right-sided pulmonary veins. Less commonly, interatrial communications can be seen at the site of the coronary sinus, typically associated with an anomalous left superior vena cava (72). Although most cases of ASD occur sporadically, there is a reported genetic anomaly associated with a range of skeletal anomalies of the upper extremities (73).

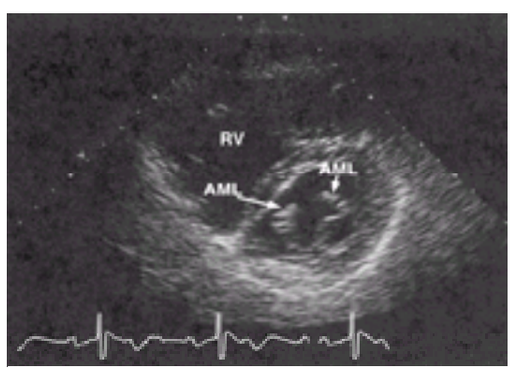


***e*FIGURE 31.1.1** Twelve-lead electrocardiogram of a 37-year-old patient with secundum atrial septal defect showing incomplete right bundle branch block.

***e*FIGURE 31.1.2** Chest radiograph of adult patient with secundum atrial septal defect showing increase in pulmonary artery size and shunt vascularity in both lung fields.



***e*FIGURE 31.1.3** Transesophageal echocardiogram demonstrating a left-to-right shunt across a secundum atrial septal defect (ASD). LA, left atrium; RA, right atrium.



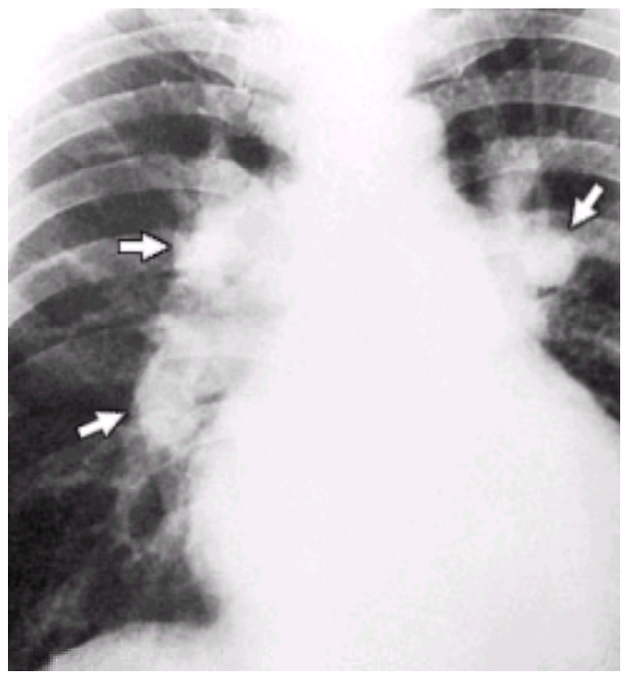
***e*FIGURE 31.1.4** Parasternal short-axis view of a transthoracic echocardiogram demonstrating a cleft anterior mitral leaflet (AML) in a patient with an atrioventricular canal defect. RV, right ventricle.

Video 31.1 Transesophageal echo with color Doppler flow demonstrating a secundum atrial septal defect with left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 31.2 Subcostal view of a primum atrial septal defect with color Doppler showing the left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 31.3 A modified transthoracic view demonstrating the tricuspid valve of a patient with an endocardial cushion defect including a primum atrial septal defect and cleft mitral valve. The septal leaflet of the tricuspid valve is characteristically tethered, forming a septal aneurysm, decreasing the size of a ventricular septal defect or completely closing the ventricular septal defect, which is part of the endocardial cushion defect. (The septal leaflet of the tricuspid valve is located towards the left of the

screen.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Chest x-ray in atrial septal defect. There is plethora of the pulmonary vasculature with prominent main pulmonary arteries (*white arrows*).

Outcome

Right atrial and right ventricular dilatation occurs as a function of shunt size and may become accelerated as systemic hypertension and coronary artery disease modify left ventricular compliance, favoring left-to-right shunting. The unoperated history of secundum atrial defects has been well studied. Although most patients are minimally symptomatic in the first three decades, more than 70% become impaired by the fifth decade, and annual mortality increases to 10% in the sixth decade (74). Complications include pulmonary hypertension, right-sided heart failure, atrial fibrillation or flutter, and stroke (75). Symptoms include exercise intolerance, dyspnea on exertion, fatigue, palpitations, and syncope. Mitral valve disease and left ventricular dysfunction are unusual in the young, but the incidence is as high as 15% in patients over age 50 (76).

The overall incidence of pulmonary hypertension, defined either as a mean pulmonary artery pressure greater than 20 mm Hg or a systolic pulmonary artery pressure greater than 50 mm Hg, occurs in 15% to 20% of patients with ASD (77,78). Pulmonary hypertension is unusual before age 20 but is seen in 50% of patients above age 40 (78,79). The elevation in pulmonary pressure occurs on account of increased pulmonary blood flow. Eisenmenger's disease with pulmonary vascular obstructive disease and reverse shunting is a late and rare complication of isolated secundum ASD, reported in 5% to 10% of patients, and more commonly in female subjects (77,80).

Management

The goal of management in patients with ASD is to prevent death, right-sided heart failure, atrial arrhythmia, and pulmonary hypertension (see the section Outcome for a description of complications). ASD closure may be achieved percutaneously (see previous discussion) or surgically. Uncomplicated secundum ASDs may be closed surgically in children and adults with minimal operative mortality, in the range of 1% to 3% (75) or less. The long-term prevention of death and complications is best achieved when ASD is closed before age 25 and when the systolic pressure in the main pulmonary artery measured at cardiac catheterization is less than 40 mm Hg. This results in a long-term mortality that is similar to age- and sex-matched control populations (75). Closure after age 40 in symptomatic patients with significant shunts improves survival, prevents deterioration in functional capacity (81), and improves exercise tolerance (82) when compared with patients treated medically. In contrast, surgical closure after age 40 does not reduce the risk of nonfatal cardiovascular complications, including supraventricular arrhythmias and cerebrovascular events (75,81). Age greater than 60 is not a contraindication to ASD closure in the presence of a significant shunt because up to 80% of patients show evidence of symptomatic improvement (83). ASD closure in asymptomatic patients with significant shunts between age 25 and 40 years is controversial (84), but is associated with a reduced incidence of atrial arrhythmia (85) and is undertaken in many centers with the expectation that long-term symptomatic deterioration is preventable (86).

Preoperative pulmonary artery pressure and the presence or absence of pulmonary vascular disease are important predictors of successful surgical outcome (75,80). Patients with a total pulmonary vascular resistance of less than 7 Wood units show improvement in New York Heart Association (NYHA) class, regression of symptoms, radiographic evidence of pulmonary artery enlargement, and electrocardiographic evidence of right ventricular hypertrophy, while a pulmonary vascular resistance greater than 15 Wood units is associated with a high surgical mortality (80). If pulmonary artery pressure, pulmonary vascular resistance, or both are greater than two-thirds systemic, there should be a net left-to-right shunt of at least 1.5:1.0 or evidence of reversibility during reactive pulmonary vascular reactivity studies before proceeding to surgical repair (87).

Patients who have had surgical closure of an uncomplicated ASD before age 25 have a favorable prognosis. Patients who are older at the time of repair require variable supervision depending on the presence and degree of preoperative and postoperative medical complications. Atrial fibrillation or flutter is more prevalent as the age of operation increases (85) and is present in up to 50% to 60% of patients over the age of 40, regardless of surgical status. In 60% to 70% of patients with preoperative arrhythmias, the rhythm persists postoperatively (75), particularly if surgery is undertaken after the age of 40 years (85). Ten percent to 25% of patients may develop new-onset atrial arrhythmias in spite of operation (75,81). Thromboembolic events including transient ischemic attacks or stroke are also observed in 5% to 10% of patients on long-term follow-up, regardless of surgical status (75,81). Atrial arrhythmias may be better tolerated postoperatively and should be managed with conventional therapy, including anticoagulants. Depending on the preoperative status, continued surveillance and conventional medical management of pulmonary hypertension and ventricular dysfunction in addition to acquired cardiac disease are necessary.

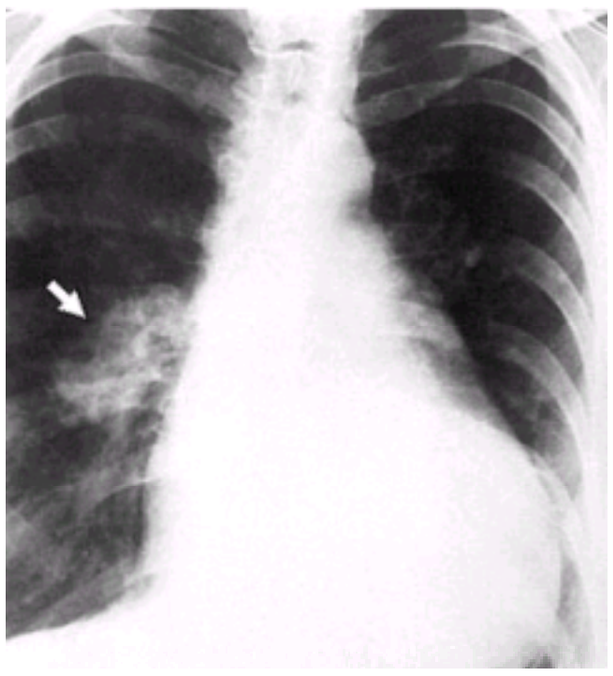
Ventricular Septal Defect

P> **Prevalence and Anatomy**

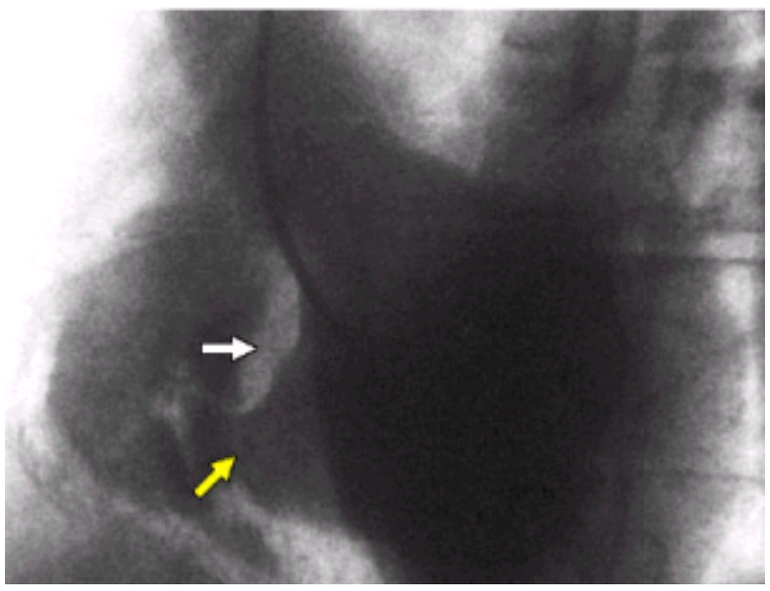
The isolated VSD is the most common congenital defect seen in the pediatric population (88). For anatomic classification (89), the interventricular septum can be divided into four regions. Defects of the membranous septum or infracristal VSDs, located in the left ventricular outflow beneath the aortic valve, account for up to 80% of VSDs. The membranous septum itself is small and is located posterior to the conal septum, below the crista supraventricularis. These VSDs typically show a variable degree of extension into the inlet or outlet septum, hence their designation as *perimembranous*. Infundibular defects or supracristal outlet VSDs occur in the conal septum above the crista supraventricularis and below the pulmonary valve. Inlet defects are identified at the crux of the heart between the tricuspid and mitral valves and are usually associated with other anomalies of the atrioventricular canal. Defects of the trabecular or muscular septum can be multiple and occur distal to the septal attachment of the tricuspid valve and toward the apex.

VIDEO

Video 31.4 Hepatoclavicular view (left anterior oblique, 60; cranial, 45) of a membranous ventricular septal defect in a 16-year-old male patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Chest x-ray in patient with a congenital ventricular septal defect. There is fullness in the hilum secondary to an enlarged pulmonary artery (*white arrow*).



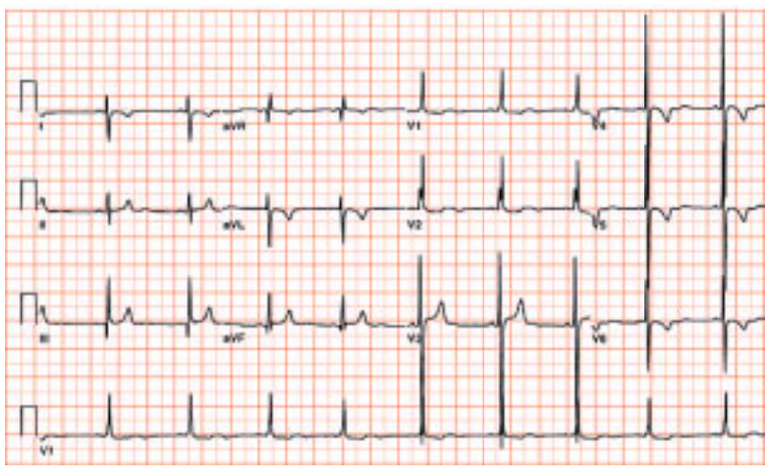
Muscular ventricular septal defect. This left anterior oblique left ventriculogram demonstrates the presence of a muscular ventricular septal defect (*yellow arrow*) with opacification of the right ventricular cavity and pulmonary outflow tract. The ventricular septum (*white arrow*) is seen to divide the right and left ventricular chambers.

Outcome

The clinical course of VSDs depends on the size of the defect and the pulmonary vascular bed, both of which can change with time. Unlike ASDs, spontaneous closure of VSDs can occur and do so as a function of native defect size, anatomy, and patient age. Approximately one-half of all VSDs are small (90) and up to 75% of those close spontaneously (89). Five percent to 10% of moderate or even large VSDs may also undergo some degree of spontaneous closure (91). Trabecular muscular septal defects may close more frequently than perimembranous defects, whereas closure of outlet defects is least common (92,93). The highest closure rates are observed in the first year of life. Ninety percent of VSDs destined to close have done so by age 10, whereas spontaneous closure in adult life is unusual but reported (91).

The physiologic severity of VSDs takes into account the pulmonary-to-systemic flow ratios (Qp:Qs), the main pulmonary artery pressure (MPAP), and the ratio of pulmonary-to-systemic vascular resistance (Rp:Rs). VSDs can be classified based on the criteria used in the First Natural History Study of Congenital Heart Defects (NHS-1) (90). Patients in group I have trivial or mild shunts with a Qp:Qs ratio of less than 1.5 and a mean MPAP of less than 20 mm Hg. Patients in group II have moderate defects with a Qp:Qs ratio of greater than 1.2, a mean MPAP greater than or equal to 20 mm Hg but an Rp:Rs ratio of less than 0.2. Patients in group III have severe defects with an MPAP greater than or equal to 20 mm Hg and an Rp:Rs ratio between 0.2 and 0.7. Patients in group IV have Eisenmenger's physiology with a systemic or near systemic MPAP, a pulmonary vascular resistance that is greater than two-thirds systemic resistance, and a right-to-left shunt or a left-to-right shunt with a Qp:Qs of less than 1.2.

Minimal or mild defects can be expected to cause no significant physiologic abnormality. A moderate or severe defect causes volume loading of the left side of the heart. Left atrial and ventricular dilatation occurs as a function of the degree of left-to-right shunting. Shunting across the ventricular septum occurs predominantly during systole when left ventricular pressure exceeds that on the right. The first intracardiac chamber to sustain a significant diastolic filling abnormality is the left atrium. With moderate or severe defects, the right side of the heart becomes secondarily affected as a function of the increase in pulmonary pressure. Note that this is in contrast to shunting at the atrial level where the right atrium and ventricle tolerate both primary volume and secondary pressure loading. An approximate 10% (90) of patients with VSDs develop Eisenmenger's complex (94), typically during the first decade (95), when pulmonary vascular resistance rises progressively to exceed systemic levels, resulting in shunt reversal. The majority of patients with Eisenmenger's physiology are said to have nonrestrictive defects. By definition this means that there is no resistance to flow at the level of the defect per se. Typically, the defect is as large as the aorta, pressures in both ventricles are equal, and the degree of shunting is determined by the ratio of pulmonary to vascular resistances. This has two major implications: The first is that the pulmonary vascular bed is exposed directly to systemic pressures in the left ventricle, resulting in an accelerated increase in pulmonary pressure and resistance; the second is that, likewise, the right ventricle is directly exposed to pressure overload early in life. In the simplest terms, a *restrictive* VSD is one through which there exists a systolic pressure gradient between both ventricles in the absence of right ventricular outflow tract obstruction. In physiologic terms this is useful insofar as it indicates that there is a resistance to left-to-right shunting at the ventricular septal level and that the size of the defect is less than that of the aorta. It follows that in terms of physiologic severity a "restrictive" defect is often trivial, mild, or moderate, but can also be severe as long as the pressure between both ventricles has not equalized.



A 16-year-old male patient with biventricular hypertrophy secondary to ventricular septal defect and Eisenmenger's syndrome.

Management

For patients with VSD, management issues vary depending on the shunt size as manifested by volume overload of the left side of the heart and the presence or absence of pulmonary hypertension (see the section Outcome for a description of complications). The NHS-1 enrolled 1,280 patients with VSD from 1958 to 1969 (91). The overall 25-year survival rate for all patients managed with medical or surgical therapy is 87%, with mortality increasing with the severity of the VSD (90). Adult presentation is most frequently that of a small restrictive VSD, native or postsurgical, or that of a large unoperated VSD with Eisenmenger's complex (70).

Patients with Eisenmenger's complex can survive into the fourth decade (91). The focus of management for patients with Eisenmenger's complex centers around the medical complications of cyanosis. These include death due to intracardiac or pulmonary complications, prevention of infective endocarditis, and systemic complications related to the neurologic, hematologic, and renal systems. These issues are discussed in this chapter as part of a discussion of the medical complications of cyanosis applicable to all patients with Eisenmenger's syndrome.

Excluding those with Eisenmenger's physiology, the majority of unoperated patients have a small VSD and therefore have a favorable long-term prognosis (90). Late results after operative closure of isolated VSDs show residual patency in up to 20% of cases (96) but with only a 5% incidence of need for reoperation, indicating that most residual surgical defects are small (90). For patients with small residual defects, native or surgical management revolves around endocarditis prophylaxis and complications related to secondary valvular anomalies. Perimembranous defects may regress in size through aneurysm formation by engaging part of the septal tricuspid leaflet, resulting in secondary tricuspid insufficiency (97). Prolapse of the right or noncoronary cusp results in acquired aortic valve disease in approximately 2% of patients, regardless of surgical status (90). This occurs most frequently with subarterial outlet VSDs, but also with perimembranous and inlet defects (98). The surgical management of this group of patients is controversial and needs to take into account the location of the VSD, the degree of aortic regurgitation, and the patient's age (99,100). Hence, for a substrate of patients with small VSDs, the potential for progressive valvular insufficiency necessitates careful consideration and follow-up even after the defect is closed.

Patients with moderate pulmonary hypertension and operated or unoperated VSD require particular consideration. Fifteen percent of patients who had a large VSD in infancy or childhood, surgically closed when pulmonary vascular resistance was normal, are found to have indirect evidence of pulmonary hypertension on long-term follow-up, even in the absence of a residual shunt (90). These may represent a substrate of patients in whom factors responsible for triggering the development of pulmonary vascular disease are already engaged at time of VSD closure. When a VSD is present and appears small but the pulmonary pressure is moderately elevated, the left heart is enlarged, or both, there may have been partial closure of the VSD, either through a spontaneous reduction in size or through surgical intervention. One of two hemodynamic scenarios is possible: Either the pulmonary hypertension is "residual" from a previous large shunt and is not related to current shunt size or there is a significant moderate residual shunt, the closure of which may be beneficial (87,90). If surgical closure is contemplated and pulmonary artery pressure, pulmonary vascular resistance, or both are greater than two-thirds systemic, there should be a net left-to-right shunt of at least 1.5:1.0 or evidence of reversibility during pulmonary vascular reactivity studies before proceeding to surgical repair (87).

Sudden cardiac death after surgical repair of VSD occurs in 2% of patients (90,96). The etiology is unclear, and it remains surprising that even patients with small VSDs may be at risk for sudden cardiac death (90). It is reasonable, however, to consider age at operation and the presence of pulmonary hypertension as possible contributing factors. Abnormal myocardium long exposed to volume or pressure overload or both, with or without surgical scar, is likely to provide the substrate for arrhythmias and heart block. Rhythm disturbances after surgical closure of VSDs include tachyarrhythmias and conduction disturbances (90,96,101). Right bundle branch block is reported to occur in 30% to 60% of patients and appears independent of whether the VSD was repaired through an atrial or ventricular incision (90,96,101). Right bundle branch block with left-axis deviation is seen in 3% to 15% of patients (96,101). First-degree atrioventricular block occurs in approximately 10% of patients and the incidence of complete heart block on long-term follow-up is 1% to 3% (96,101). On 12-lead electrocardiography, couplets are observed in 18% of patients, while nonsustained ventricular tachycardia occurs in 5% of patients. Arrhythmia management should be symptom directed, with particular attention paid to reversible hemodynamic factors. Unexplained syncope is usually an indication for an electrophysiology study when Holter monitoring is unrevealing, and there are no exercise-induced arrhythmias.

Patent Ductus Arteriosus

Prevalence and Anatomy

The estimated incidence of the isolated PDA is 1 in 2,000 or approximately 10% of all congenital cardiac lesions at birth, with a female predominance (102). The ductus arteriosus connects the descending aorta to the main pulmonary trunk with the pulmonary arterial end found immediately to the left of the bifurcation of the pulmonary trunk near the origin of the left pulmonary artery. The aortic end is found just distal to the origin of the left subclavian artery. Normal postnatal closure results in fibrosis and degenerative changes in the ductal lumen, leaving in its place the residual ligamentum arteriosus, which can become part of a vascular ring (103,104).

Constriction of the ductus arteriosus starts at the pulmonary end of the ductus and proceeds toward the aorta. Hence, the observed conical shape of a patent duct with narrowing at the pulmonary arterial end and a dilated ampulla at the aortic end is seen in 65% of cases (105). Other ductal shapes include a short duct with narrowing at its aortic insertion, a tubular duct without constriction, a channel with multiple constrictions, or a long duct with an unusual shape (105). Progressive dilatation of the aortic end with aneurysm formation has also been observed (106).

The fetal ductus is derived from the sixth aortic arch as are the right and left pulmonary arteries. The fetal duct is therefore a direct extension of the pulmonary artery but enters the aortic isthmus at a sharp angle. Not surprisingly, when the duct persists, significant calcification of the aortic ductal end can be observed (102,107).

Outcome

A small PDA is one in which there is continuous flow throughout the cardiac cycle without left-sided heart dilatation and without pulmonary hypertension. Patients with a small PDA, although protected from hemodynamic complications of a significant left-to-right shunt, remain at risk for infectious endarteritis, which usually occurs on the pulmonary side of the duct. Early natural history studies in patients with clinically detectable shunts document a risk of endocarditis of 0.45% per year after the second decade and death from endocarditis accounting for up to one-third of total reported mortality (108). These ominous figures have led to widespread acceptance of ductal closure as a safe therapeutic alternative, even in patients with small shunts. The advent of echocardiography, highly sensitive for the detection of small shunts, has led to the concept of the clinically "silent duct," that is to say, a shunt that is not audible on clinical examination but is present on Doppler interrogation of the pulmonary artery (109,110). Although this remains controversial, these patients do not appear to be at risk for endocarditis (110).

A patent duct is of moderate or large size but still restrictive when there is a left-to-right shunt throughout systole and a variable duration of diastole. Left atrial or ventricular dilatation, or both, as well as pulmonary hypertension, varies with the quantity of left-to-right shunting as well as with the secondary effects on the pulmonary vascular bed. An unoperated moderate or large persistent ductus is associated with a high morbidity and mortality in the first year of life (108). If unoperated after the first year, most children become asymptomatic for the first two decades (108). In the second and third decades symptoms include the onset of dyspnea secondary to enlargement of the left side of the heart (108), palpitations secondary to atrial arrhythmias, and exercise intolerance (107). Morbidity occurs on account of heart failure, pulmonary hypertension, and endarteritis. By the fourth decade, mortality rises to 3% to 4% per year (108). One-third of patients die by age 40 and two-thirds by age 60 (108).

Five percent of patients with an isolated PDA develop Eisenmenger's physiology with systemic or suprasystemic pulmonary pressures (102). The resulting right-to-left shunt from pulmonary artery to descending aorta can result in oxygen saturations, which are decreased in the lower extremities compared with those in the upper extremities.

Management

Most of the patients with moderate or large PDA have undergone ductal ligation in infancy (see the section Outcome for a description of complications). Typically, these patients have had the lesion repaired early enough that few sequelae can be expected to occur. If the clinical examination, electrocardiography, and chest radiography results are normal, surveillance requirements are minimal.

Adult patients with a PDA but without an audible murmur may come from one of two groups: those with Eisenmenger's physiology and irreversible pulmonary vascular obstructive disease, or those with a fortuitously discovered PDA on echocardiography. The management of patients with Eisenmenger's disease is as outlined for patients with VSD and Eisenmenger's physiology and is described later in this chapter (see Eisenmenger's Syndrome). Based on the observation that endocarditis has been documented in conjunction with an audible murmur, the current consensus is that the presence of a silent duct does not warrant closure unless endarteritis has occurred (87).

In all other patients, in the presence of a PDA with an audible murmur, the combined risk of endarteritis, left-sided heart failure, and late mortality provides the rationale for shunt closure (87). Between 1951 and 1984, 117 patients were seen at The Cleveland Clinic with a diagnosis of isolated PDA (107). Although the majority of patients was in NYHA class I or II on initial presentation, significantly higher mortality was found in the nonsurgical patient group. After a mean follow-up of 18 years,

mortality occurred in 39% of the nonsurgical compared with 7% of the surgical group. Sixty percent of the patients who underwent ductal ligation reported symptomatic improvement compared with 19% of patients without ductal closure (107). These findings underscore the poor outcome of unoperated patients, even in the absence of significant symptoms at the time of presentation. If pulmonary artery pressure, pulmonary vascular resistance, or both are greater than two-thirds systemic, there should be a net left-to-right shunt of at least 1.5:1.0 or evidence of reversibility during pulmonary vascular reactivity studies before proceeding with PDA occlusion (87).

Options for ductal repair include surgical closure and transcatheter methods. Reported operative mortality varies from 0% to 8% (111,112,113 and 114). Calcification of the aortic end of the ductus and excessive bleeding if pulmonary hypertension is present may complicate the surgical approach and lead to incomplete ductal closure in adults (111,113). As described previously, transcatheter device closure or coil occlusion is considered the procedure of choice for PDA closure in adults (30,32,33 and 34,40,87).

Obstructive Lesions of the Right and Left Ventricular Outflow Tracts

The focus of the discussion that follows is on the most common single obstructive lesions of the pulmonary and aortic valves and aortic coarctation. Other anatomic variants are defined and referenced in the Prevalence and Anatomy section for each lesion. Obstructive lesions of the outflow tract are complicated by the secondary effects of pressure overload in the chamber proximal to the obstruction. In the presence of significant lesions, the inability to increase systemic or pulmonary blood flow in the face of a fixed obstruction, exercise intolerance, inadequate myocardial perfusion, ventricular arrhythmias, and sudden death requires monitoring, activity restriction, and timely intervention. Although recommendations for intervention are based on peak-to-peak gradients measured at cardiac catheterization, serial echocardiographic Doppler measurements can be used to assess initial disease and screen for significant changes in severity with the knowledge that cardiac catheterization–derived peak gradients correlate best with mean gradients obtained by echo-Doppler (115).

Pulmonary Stenosis

Prevalence and Anatomy

Obstruction of the right ventricular outflow tract can occur at the level of the pulmonary valve, below, or above it, either in the main pulmonary artery trunk or at one or both of its branches. These lesions as a group represent a spectrum of unoperated and postoperative anomalies and are some of the most commonly encountered in the adult with congenital disease.

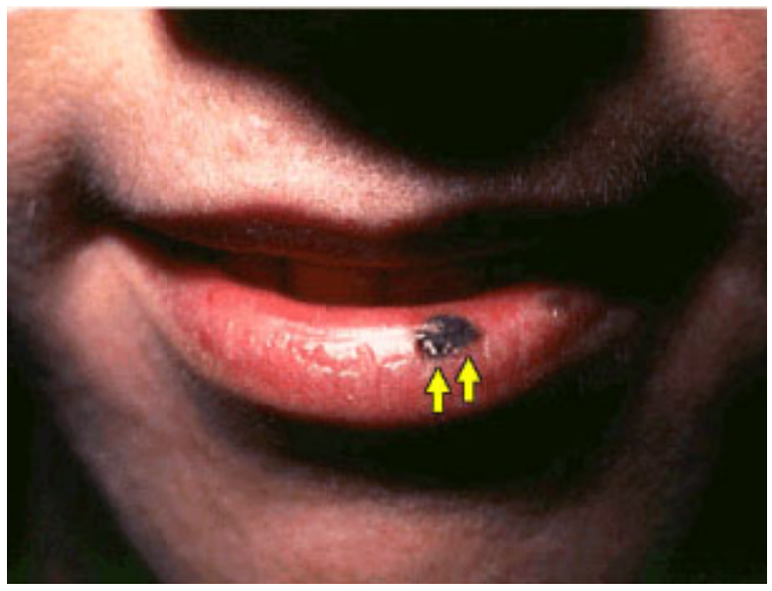
VIDEO

Video 31.5 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Isolated congenital valvar pulmonary stenosis is a common lesion reported to occur in 10% of all patients with CHD (116). The normal adult pulmonary orifice is approximately 2 cm per m^2. When stenosis of the valve occurs, fusion of the leaflets results in a narrow orifice seen at the top of a doming valve. There is a variable degree of thickening and calcification in older patients. A bicuspid pulmonary valve is seen in 20% of autopsied cases of pulmonary stenosis. In the majority of remaining cases, the valve is trileaflet. In 10% of these, the valve is dysplastic. The obstruction is not due to fusion but rather to myxomatous changes and severe thickening (117).

Pulmonary atresia with intact ventricular septum is a complex cyanotic lesion seen in newborns and infants, the physiology of which is governed by the variable degree of right ventricular hypoplasia and the presence of an abnormal coronary circulation (118). At the current time, these patients, operated on or not, are rarely encountered as adults. Pulmonary atresia with nonrestrictive VSD is a complex cyanotic lesion that can be seen in unoperated or operated adult patients. This is discussed in this chapter in conjunction with the TOF.

Supravalvar and branch pulmonary artery stenoses constitute important and common complications of the patient with TOF and are discussed with other complex lesions (see Complex Lesions). Residual supravalvar pulmonary stenosis can be encountered in patients who have had palliative pulmonary artery banding to decrease pulmonary blood flow in the presence of an isolated large VSD or other complex cyanotic lesions discussed in this chapter. Distortion of the main pulmonary artery trunk or the origins of the right and left pulmonary arteries can occur in up to 25% of cases (119). Congenital branch pulmonary artery stenosis can occur in isolation, in association with valvar pulmonary stenosis, with shunt lesions, or in association with a variety of syndromes. Patients with Noonan's syndrome—in addition to having a characteristic phenotypic facial appearance, short stature, and webbed neck—may have a dysplastic pulmonary valve and hypertrophic cardiomyopathy of the left ventricle in addition to peripheral pulmonary artery stenosis (116). Supravalvar pulmonary stenosis can occur with supravalvar aortic stenosis in association with the William's elfin facies syndrome (120).



Café au lait spot. There is a flat localized hyperpigmentation that is uniformly light brown in the lower lip (*arrows*) that may be associated with neurofibromatosis, Albright syndrome, or pulmonary stenosis.

Leopard's syndrome. Figure shows a patient with Leopard's syndrome characterized by multiple basal cell nevi and broad facies. There is an association with pulmonic stenosis.

Primary infundibular stenosis with intact ventricular septum can result from a fibrous band at the infundibulum (117). Right ventricular obstruction can also be due to the presence of anomalous muscle bundles that divide the right ventricle into two chambers; a high-pressure chamber below the hypertrophied muscle bundles and a low-pressure chamber above the bundles and below the valve. Hence the designation *double-chambered right ventricle*. The clinical features vary depending on the presence or absence of concomitant valvar pulmonary stenosis or a VSD, which typically communicates with the high-pressure chamber (121).

Outcome

Twenty-five-year survival is 96% of 586 patients with valvar pulmonary stenosis enrolled in the NHS-1 (122). Of the original cohort, 331 patients were followed for 16 to 29 years and enrolled in the NHS-2 (122). Poorest survival occurred in patients who had severe pulmonary stenosis on admission to the study. In patients with moderate pulmonary stenosis, with peak systolic gradients between 50 and 80 mm Hg at catheterization, survival was excellent, regardless of the choice of medical or surgical management. One-third to two-thirds of patients had echo-Doppler or clinical evidence of pulmonary insufficiency, the incidence of which was higher in surgically treated patients. Bacterial endocarditis, complex ventricular arrhythmias, and progression of the severity of the gradient was rare in those managed medically. Overall, the majority of patients had an excellent clinical status.

Management

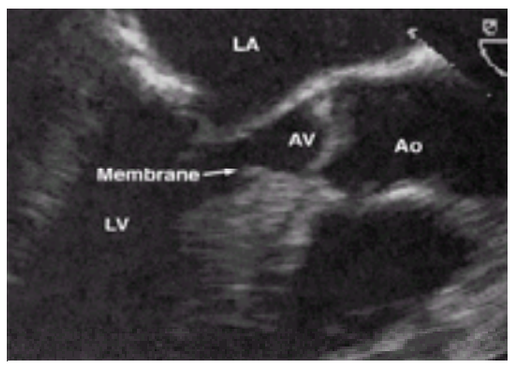
For patients with pulmonary stenosis, indications for intervention should be tailored to symptoms, subjective and objective exercise tolerance, and the presence or absence of syncope and arrhythmias (see the section Outcome for a description of complications). Data from the NHS-1 and NHS-2 have been used to support recommendations for the management of valvar pulmonary stenosis (87,122). Intervention is usually indicated for severe lesions, defined as peak pulmonary gradients of greater than 80 mm Hg obtained on cardiac catheterization. Intervention is also indicated in patients with gradients greater than or equal to 50 mm Hg and symptoms. Conservative management is indicated for mild stenosis, defined as a gradient of less than 40 mm Hg. Unlimited athletic participation is allowed for asymptomatic patients with a peak echo-Doppler gradient of less than 50 mm Hg in patients with pulmonary stenosis (123).

The advent of balloon valvuloplasty for pulmonary valve obstruction has facilitated the decision to intervene in young patients, in whom the prospect of delaying or avoiding surgery with or without valve replacement is attractive (see previous discussion). Surgical valvulotomy remains a viable and safe alternative when valvuloplasty is not possible (124).

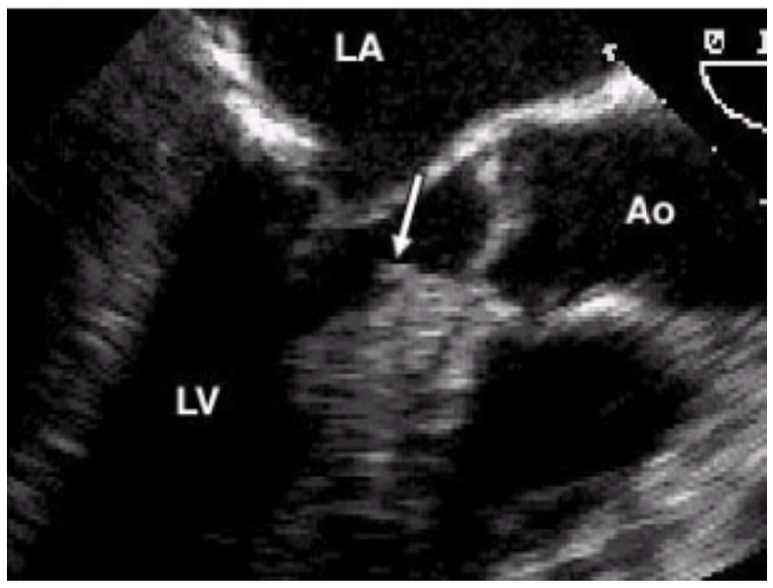
Aortic Stenosis

Prevalence and Anatomy

Stenosis of the left ventricular outflow tract can occur at, below, or above the aortic valve. Aortic coarctation is discussed later in this chapter (see Aortic Coarctation). Other forms of supravalvar aortic stenosis are seen in the context of William's elfin facies syndrome (120). Discrete subaortic stenosis accounts for 10% of all cases of congenital aortic stenosis and typically consists of a diaphragm or fibrous ring around the left ventricular outflow tract (eFig. 31.1.5) (125,126 and 127).



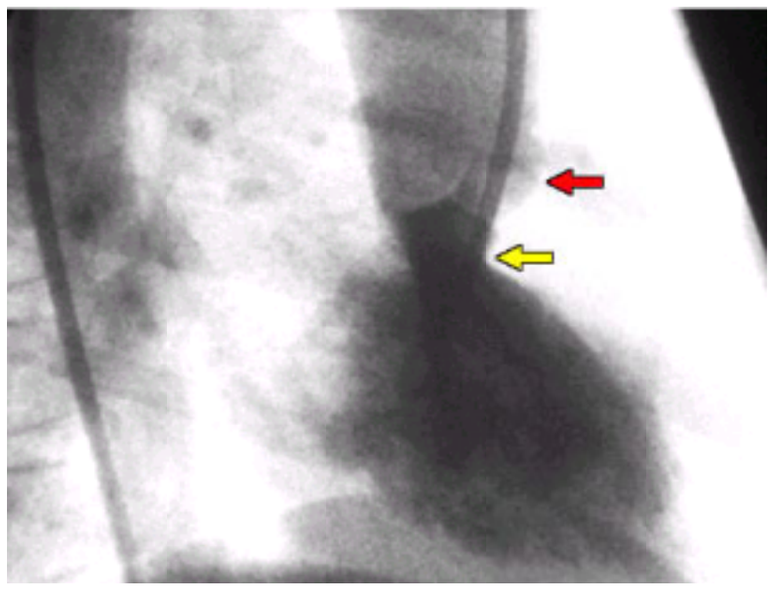
***e*FIGURE 31.1.5** Transesophageal echocardiogram demonstrating a subaortic membrane best seen in a longitudinal plane. Ao, aorta; AV, aortic valve; LA, left atrium; LV, left ventricle.



Transesophageal echo at 120 degrees of the aortic valve with a subaortic membrane in the left ventricular outflow tract (designated by the arrow).

Video 31.6 Subaortic stenosis. A radiolucent membrane is visualized just below the aortic valve cusps (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

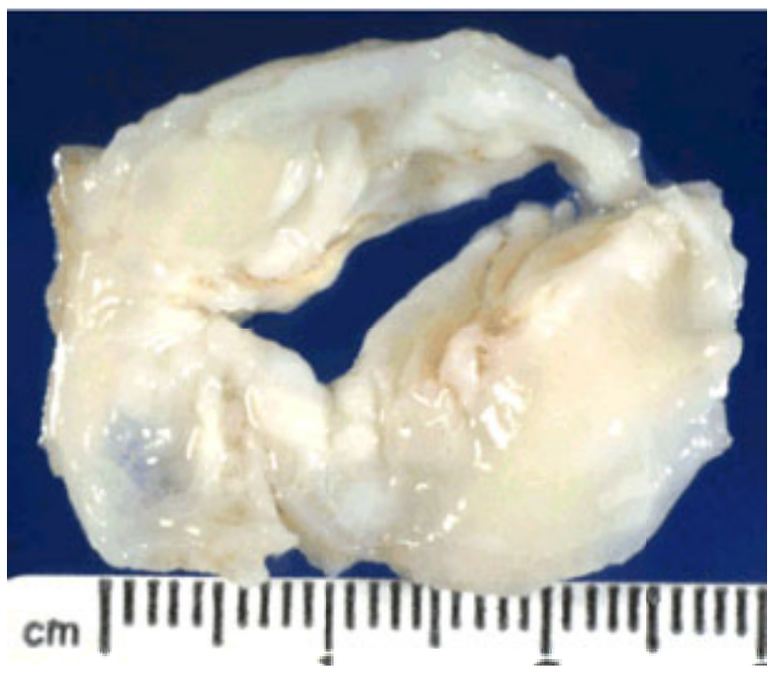
Video 31.7 Transesophageal echo in a patient with a subvalvular membrane in the left ventricular outflow tract. Note the normal mobility of the aortic valve. This patient had a significant pressure gradient across the left ventricular outflow tract/AV. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Subaortic stenosis. This right anterior oblique left ventriculogram demonstrates the presence of a stenosis in the left ventricular outflow tract (*yellow arrow*) just below the level of the aortic valve (*red arrow*).

The normal aortic valve has three cusps and commissures. Variations in the number and size of aortic cusps are well described (128). When the aortic valve is unicuspid, a single commissure is most commonly observed. The commissural unicuspid aortic valve accounts for the majority of cases of severe aortic stenosis in infants. Quadricuspid valves can be functionally normal or insufficient as is observed in truncus arteriosus. These valves are rarely stenotic. Congenital valvar aortic stenosis due to a bicuspid aortic valve is one of the most common congenital anomalies and accounts for up to one-half of all operated cases of aortic stenosis in adults (128) (eFig. 31.1.6). In patients with bicuspid aortic valve, associated dilatation of the aortic root with or without aneurysm occurs secondary to changes in the media of the aortic wall (129) and can occur out of proportion to the hemodynamic lesion (130,131).

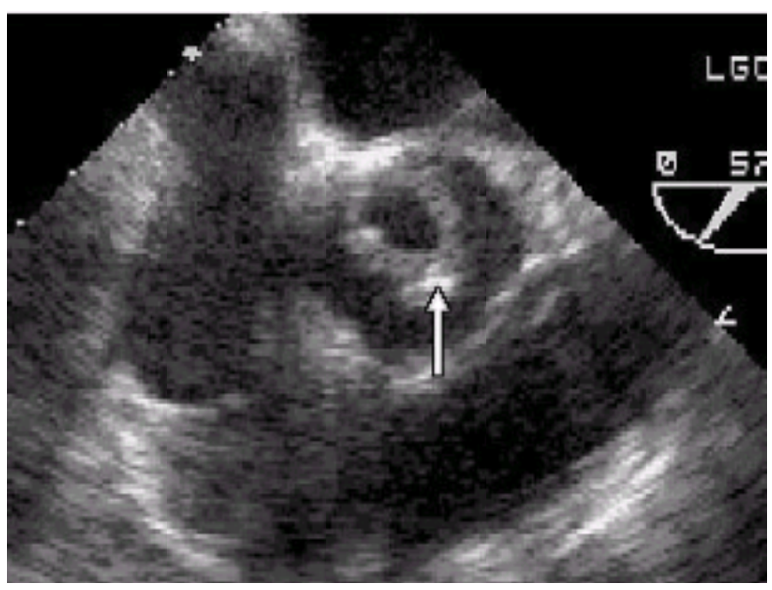
***e*FIGURE 31.1.6** Transesophageal echocardiogram showing a bicuspid aortic valve.



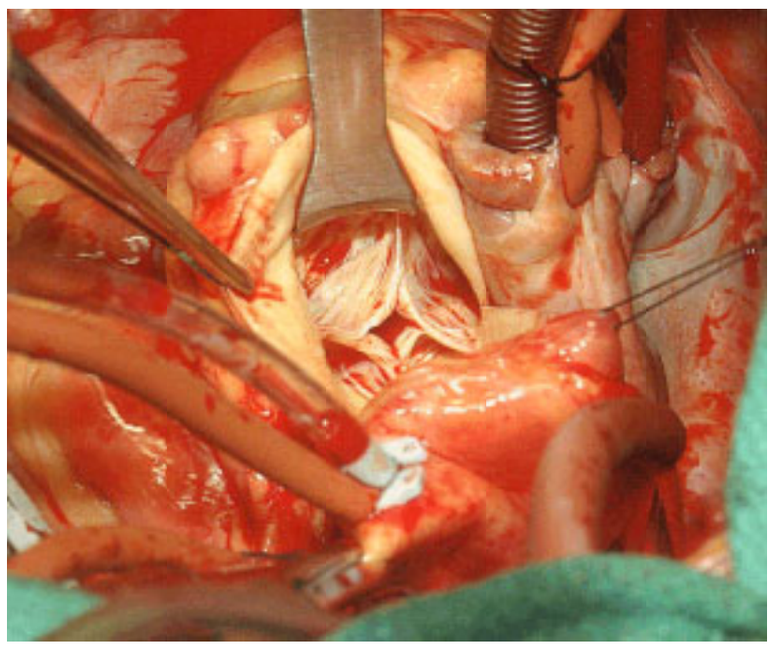
Unicuspid aortic valve (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 31.8 A 60-degree intraoperative transesophageal echo of a patient with aortic stenosis due to a unicuspid valve (seen in short axis). Note the single commissure at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Short-axis transesophageal view of a unicuspid aortic valve with aortic stenosis. The arrow designates the single commissure present in this aortic valve. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)



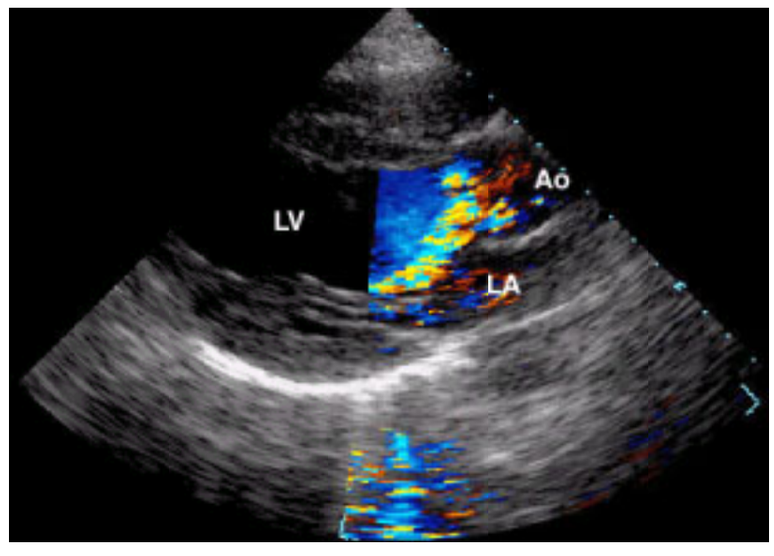
Intraoperative view of a quadricuspid aortic valve in the center of the field. This corresponds to the echocardiographic short-axis view.

VIDEO

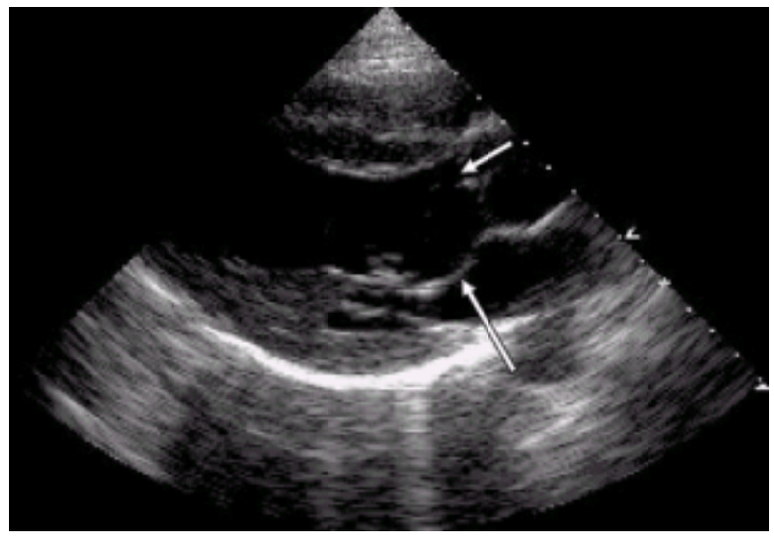
Video 31.9 A 60-degree transesophageal short-axis view **(A)** of the aortic valve demonstrating a quadricuspid (as opposed to the typical trileaflet) valve. Note the presence of four leaflets and four commissures. The second video shows a 60-degree transesophageal short-axis view of quadricuspid aortic valve with color Doppler demonstrating moderate central aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

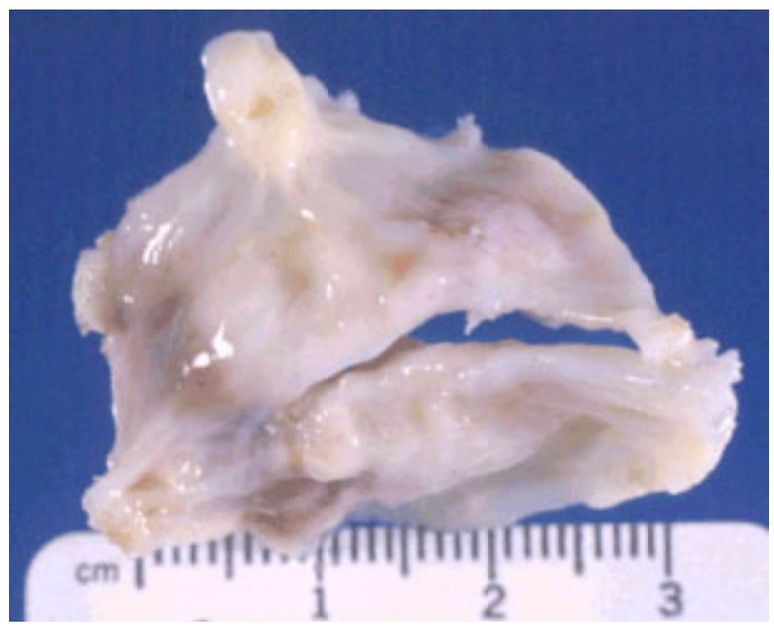
Video 31.10 A 60-degree transesophageal short-axis view **(A)** of the aortic valve demonstrating a quadricuspid (as opposed to the typical trileaflet) valve. Note the presence of four leaflets and four commissures. The second video shows a 60-degree transesophageal short-axis view of quadricuspid aortic valve with color Doppler demonstrating moderate central aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Parasternal long-axis view (transthoracic echo) with color Doppler demonstrating the posteriorly directed aortic insufficiency caused by prolapse of the anterior leaflet of a bicuspid aortic valve. Note that the jet hits the anterior mitral leaflet.



Parasternal long-axis view of a prolapsing anterior cusp (right coronary cusp + left coronary cusp fusion) of a bicuspid aortic valve. (The prolapsing leaflet is demonstrated by the short arrow). The posteriorly directed aortic insufficiency that is produced causes the posterior deformation of the anterior mitral leaflet (designated by the long arrow) as the aortic insufficiency jet hits this leaflet.



Bicuspid aortic valve with calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 31.11 Congenital bicuspid aortic valve with mild aortic regurgitation (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Outcome

The estimated overall 25-year survival for patients with valvar aortic stenosis is 85% (132). Based on data obtained in 457 patients from the NHS-1 and NHS-2, those patients with initial peak cardiac catheterization gradients of less than 50 mm Hg at entry have a long-term survival of over 90% compared with those with gradients of greater than or equal to 50 mm Hg whose equivalent survival rates are 80%. Over one-half the deaths were sudden or unexpected. Forty percent of the patients required a reintervention or a first intervention if the initial decision was medical management. Twelve percent of patients treated surgically had complex ventricular arrhythmia on follow-up. Three percent of the original cohort had bacterial endocarditis. Only one-third of patients were in excellent clinical status on long-term follow-up (132). These findings are in sharp contrast to the favorable operated and unoperated history of patients with pulmonary stenosis; hence the difference in recommended threshold for intervention.

Management

For patients with aortic stenosis acquired as children, indications for intervention should be tailored to absolute gradients as well as symptoms (see the section Outcome for a description of complications). Data from the NHS-1 and NHS-2 can be used to support recommendations for the management of valvar aortic stenosis (87,132,133). Conservative management is generally indicated only for mild stenosis, defined as a peak cardiac catheterization gradient of less than 25 mm Hg, although close supervision is required because 20% of these patients are expected to require an intervention during long-term follow-up. The significant incidence of death during exercise in patients with severe aortic stenosis (134) underscores the need for close supervision and serial assessment for progression of disease. This is well reflected in the contrast between recommended exercise parameters for patients with pulmonic and aortic valve disease (123). Unlimited athletic participation is only allowed for asymptomatic patients with a peak echo-Doppler gradient of less than 20 mm Hg, and for patients with aortic stenosis, only if there are normal electrocardiogram and exercise test results. For patients in whom moderate or severe aortic stenosis is acquired during adulthood, indications for intervention are similar to those described for patients with other forms of acquired aortic valve disease described in Chapter 22.

In the absence of significant aortic insufficiency, transcatheter aortic valvotomy can be achieved successfully in children, although results are less uniform and less predictable than with pulmonary valvotomy (135). In young adults, aortic valvuloplasty can be considered as described previously. Calcification limits the procedural

success, prompting consideration of well-established surgical alternatives described elsewhere in this text.

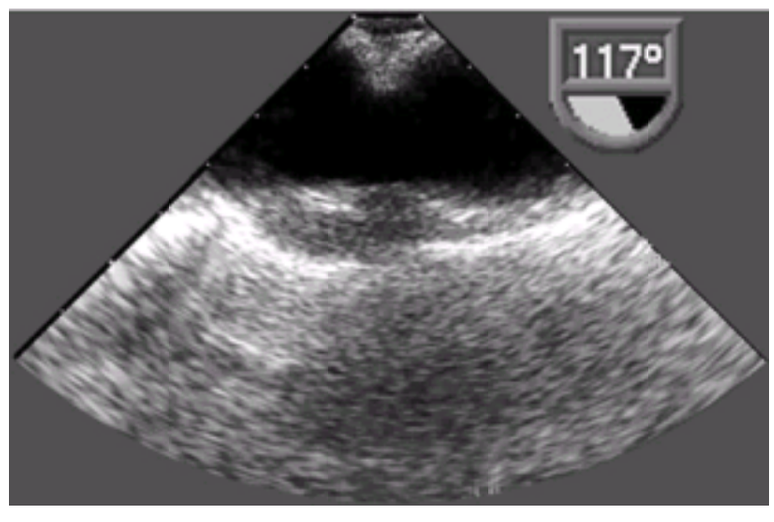
In patients with fixed fibromuscular subaortic stenosis, aortic regurgitation occurs in over 50% of cases (126) as the jet damages one or more of the leaflets of an otherwise normal valve. For these patients, surgical closure is indicated with resting gradients greater than 50 mm Hg, particularly in the presence of more than mild aortic insufficiency to prevent further deterioration of the valve (87,136).

Aortic Coarctation

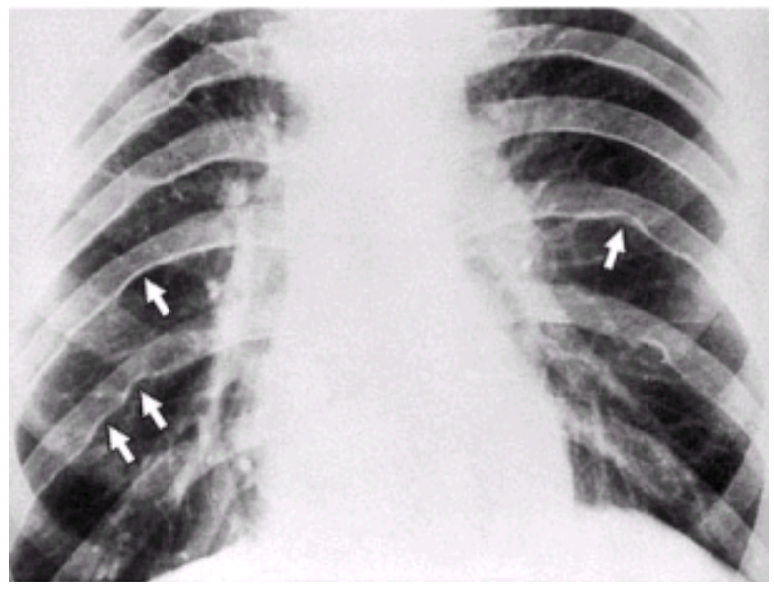
Prevalence and Anatomy

Aortic coarctation is a common congenital lesion in the infant population (137) in whom the presentation can be that of a severe low output state. In adolescents and adults, the diagnosis should always be sought in the event of unexplained hypertension of the upper extremities. The anatomy of coarctation (138) typically consists of a constriction just distal to the left subclavian at the site of the aortic ductal attachment or its residual ligamentum arteriosum. Less commonly, the coarctation ridge lies proximal to the left subclavian, giving rise to a differential blood pressure in the upper extremities. When aortic coarctation is diagnosed, careful assessment is made of the mitral inflow and the aortic outflow in its entirety for assessment of associated lesions. A bicuspid aortic valve is the most common coexisting anomaly, but obstruction above or below the valve as well as malformations of the mitral valve apparatus should not be missed. The coexistence of a VSD or a PDA is well documented (138). The transverse arch should be carefully examined for tubular hypoplasia. *Pseudocoarctation* refers to buckling or kinking of the aortic arch without the presence of a significant gradient (138,139).

Video 31.12 Coarctation of aorta (oblique). A signal-void jet is visible in the proximal descending aorta due to a short-segment narrowing representing a coarctation. Left ventricular hypertrophy is also present. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



A still frame of a transesophageal echo demonstrating a coarctation of the aorta. Note the local narrowing of the aorta located at the junction of the distal arch and descending aorta. There was a 100–mm Hg pressure gradient across the coarctation as determined by continuous wave Doppler.



Chest x-ray in coarctation of the aorta. There is prominent rib notching (*white arrows*).

Outcome

Complications of aortic coarctation include secondary left ventricular hypertrophy, systemic hypertension, heart failure, aortic dissection, premature coronary disease, and cerebrovascular complications (138,140). With untreated coarctation a mean survival of 35 years with a 75% mortality by age 50 years can be expected (140).

In a long-term study from the Mayo Clinic of over 500 patients who underwent coarctation repair, estimated survival at 30 years is 76 (141). Outcome after repair is closely related to the age at operation, with long-term survivorship maximized when surgery is performed before age 10 (141,142). Fifty percent of patients who received repairs after age 40 have residual hypertension, whereas those who underwent surgery between the ages of 1 and 5 have a less than 10% prevalence of hypertension on long-term follow-up (142). Not surprisingly, for those who have required surgery before the age of 1, the incidence of residual systemic hypertension is higher, reflecting the severity of neonatal coarctation syndrome (142). Even in the absence of systolic hypertension at rest after successful coarctectomy, an abnormal hypertensive response to exercise and a persistently elevated left ventricular mass have been documented (143,144). Cerebral vascular complications, myocardial infarction, and aortic dissection can occur in 2% to 6% of patients (142). After the age of 40, heart failure becomes increasingly frequent in the presence of unoperated coarctation and may persist after coarctation repair (142).

Management

Intervention in patients with coarctation or recoarctation should be performed with gradients greater than 50 mm Hg documented by cardiac catheterization (145) (see the section Outcome for a description of complications). For patients with gradients above 20 mm Hg, the occurrence of symptoms, systemic hypertension, or both warrant consideration for intervention (87).

Surgical intervention is well established (141). Surgery is more hazardous in adults than in children. When patients of all ages are considered, perioperative death rates are 3% (141) or less. The incidence of paraplegia due to spinal cord injury is less than 1% and the preferred surgical approach is resection with end-to-end anastomosis of the descending aorta (119). This approach has the advantage of removing the site of cystic medial necrosis, which has been observed at the site of coarctation, thereby decreasing susceptibility to aneurysm formation and dissection (146). Recoarctation is least common when an end-to-end anastomosis is performed, but the prevalence varies from 11% requiring a reoperation (141) to as high as 30%, depending on the age of repair and the surgical approach used (147). Latent development of coronary artery disease (141) and systemic hypertension (147) require lifelong monitoring (142).

Percutaneous coarctoplasty is being increasingly used as an alternative to surgical intervention (see Interventional Cardiac Catheterization). It is the treatment of

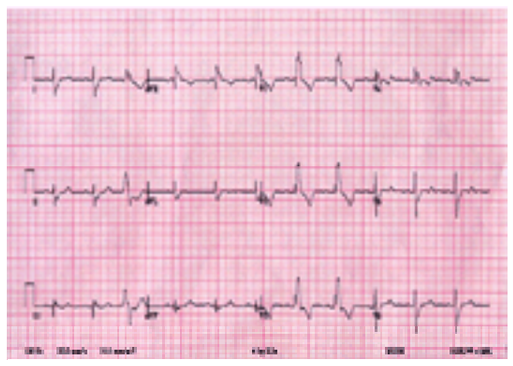
choice for focal recoarctation in adult patients who are previously operated. For adults with native coarctation, the choice of surgery or percutaneous coarctoplasty depends on the coarctation anatomy, the presence or absence of associated anomalies, as well as local expertise (87,148).

Complex Lesions

Tetralogy of Fallot

Prevalence and Anatomy

TOF is the most common cyanotic malformation (137) and was the first complex cyanotic lesion to be surgically repaired, as reported by Lillehei in 1955 (149). Hence, it is not surprising that repaired TOF accounts for one the most common lesions seen in adults with congenital cardiac anomalies (eFig. 31.1.7 and eFig. 31.1.8).



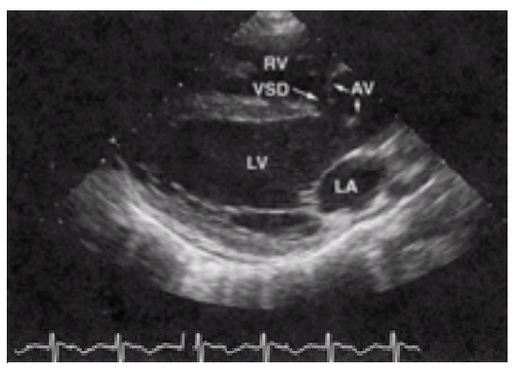
***e*FIGURE 31.1.7** Twelve-lead electrocardiogram of an adult patient with tetralogy of Fallot repair. Note the complete right bundle branch block and the ventricular ectopic beat.

***e*FIGURE 31.1.8** Chest radiograph of an adult patient with tetralogy of Fallot repair showing midline surgical clips, the persistent upturned right ventricular apex, the small main pulmonary artery segment, and the right-sided aortic arch.

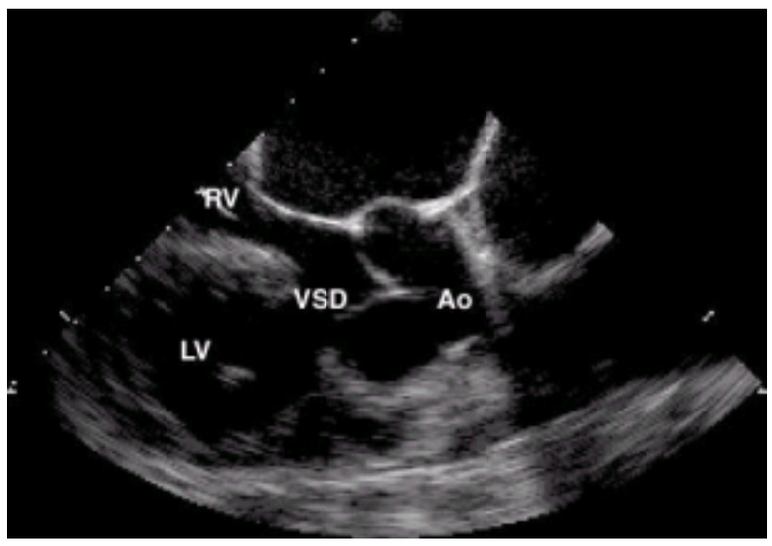
HEART SOUNDS

Audio 31.13 Tetralogy of Fallot. Auscultation performed in a 25-year-old male with newly diagnosed tetralogy of Fallot. Note the mid-systolic ejection murmur probably related to right ventricular outflow tract obstruction. Left lower sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

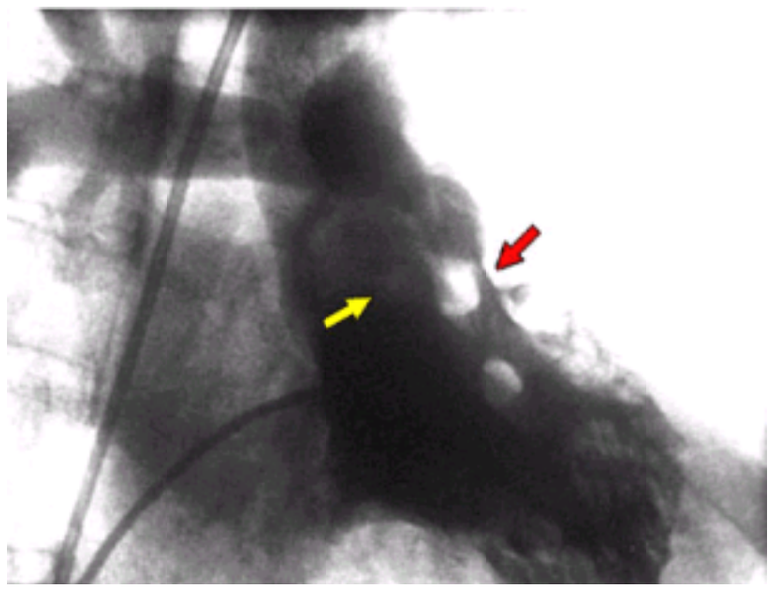
The core lesion is an underdeveloped subpulmonary infundibulum (150), which is superiorly and anteriorly displaced, resulting in the well-known tetrad: pulmonary stenosis, VSD, aortic override, and right ventricular hypertrophy (eFig. 31.1.9). The term *pulmonary stenosis* in this context seems deceptively benign. The nature, degree, and site of right ventricular outflow obstruction represents the spectrum of severity seen with this lesion. This includes malformations of the subvalvar and valvar areas, distal pulmonary artery stenosis, and pulmonary artery hypoplasia. Hence, the right ventricular outflow tract is the seat of the most difficult preoperative and postoperative management issues. The following remarks are confined to TOF without pulmonary atresia.



***e*FIGURE 31.1.9** Parasternal long-axis echocardiographic view of an unoperated patient with tetralogy of Fallot showing the overriding aorta and perimembranous ventricular septal defect (VSD). AV, aortic valve; LA, left atrium; LV, left ventricle; RV, right ventricle.



Parasternal long-axis view of Tetralogy of Fallot. Note the aortic valve overriding the ventricular septum and the ventricular septal defect (VSD).



Tetralogy of Fallot. This right anterior oblique right ventriculogram demonstrates some of the findings of tetralogy of Fallot with subpulmonic or infundibular stenosis (*red arrow*) and overriding aorta (*yellow arrow*) and prominent trabeculation of the right ventricle consistent with right ventricular hypertrophy.

VIDEO

Video 31.14 Parasternal short-axis view of tetralogy of Fallot. Note the ventricular septal defect just beneath the right coronary cusp of the aortic valve. The infundibular pulmonic stenosis can be seen superiorly, and the pulmonary valve with its vegetation can be seen to the upper right of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 31.15 Parasternal long-axis view of tetralogy of Fallot. Note the ventricular septal defect and the aorta and aortic valve overriding the interventricular septum. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 31.16 Color Doppler in the apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect by color flow and the overriding aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 31.17 Apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect, the overriding aorta and the right ventricular hypertrophy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 31.18 Parasternal short-axis view of a cleft mitral valve. Note the characteristic opening (split appearance) of the cleft anterior mitral leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Outcome

Published data, on approximately 1,500 patients with complete TOF repair followed for at least 10 years, show 90% to 95% survivorship with good functional results (151,152,153 and 154). Overall 35-year survival rates are maintained at 85% (154,155), but mortality increases after 25-year follow-up (155). The best results are obtained when repair is performed before age 5 (154), thereby providing the rationale for current trends in complete early repair, avoiding the use of palliative surgical shunts (155,156). In patients who have not benefited from early repair, total correction in adulthood is possible with a low mortality and a favorable long-term follow-up (155,157). Residual pulmonary stenosis, proximal or distal, with a right ventricular pressure greater than half systemic has been reported in up to 25% of patients (152,158). Some degree of pulmonary insufficiency is common, particularly if a patch has been inserted at the level of the pulmonary valve or if there has been a pulmonary valvotomy. An approximate 12% of patients undergo pulmonary valve replacement (159). Residual VSDs can be found in up to 20% of patients, but significant shunts are less common (154,158). The most common electrocardiographic finding after TOF repair appears to be the most benign: the complete right bundle branch block. This is seen on follow-up 12-lead electrocardiography in 80% to 90% (152). Even in the presence of a left anterior hemiblock, the prognosis for

these patients is favorable (152,160). Sinus node dysfunction, atrial fibrillation or flutter, and nonsustained ventricular tachycardia are seen in approximately 20% to 40% of patients (161). The reported incidence of sudden death in patients after TOF repair is approximately 5% (162), with an increase in yearly incidence with duration of follow-up (155).

Management

Long-term management in the patient with TOF is focused on maximizing right ventricular function, the need for surgical or percutaneous intervention, and arrhythmia therapy (see the section Outcome for a description of complications). An unoperated or palliated adult with TOF should be considered for full repair. Candidacy for repair depends on the pulmonary vascular bed in a patient who has been palliated and on biventricular function in a patient who is unoperated. Indications for reoperation in a patient who has undergone physiologic repair most commonly include recurrent stenosis in the right ventricular outflow tract if the right ventricular pressure is greater than two-thirds systemic or if residual pulmonary stenosis occurs in combination with significant pulmonary regurgitation (87). Other indications include the presence of a significant residual VSD or significant aortic regurgitation. The indication for pulmonary valve replacement in a patient with asymptomatic significant pulmonary insufficiency remains controversial (159), but surgery is recommended when progressive right ventricular dilatation and dysfunction occur, particularly in the presence of significant arrhythmia.

Hemodynamic complications coexist with arrhythmias. The most contentious is the well-named *ectopic* ventricular beat, poorly understood and difficult to manage. Ventricular arrhythmias can be detected on a 12-lead electrocardiogram in 10% of patients, during an exercise test in 40% of patients, and during 24-hour Holter monitoring in 40% to 60% of patients (160,163). Although symptomatic patients with atrial or ventricular arrhythmia should be treated with antiarrhythmic therapy, it is not recommended to attempt suppression of ventricular ectopy in those who are without symptoms (164).

On 12-lead electrocardiography, a QRS duration of more than 180 ms correlates with right ventricular size, sustained monomorphic ventricular tachycardia, and sudden cardiac death (165,166). In addition to sustained ventricular tachycardia, severe right ventricular systolic hypertension (152,163) and significant pulmonary regurgitation (165) have both been implicated in sudden cardiac death, which is reported in up to 5% of patients after TOF repair (162). The presence of ventricular arrhythmia in combination with right ventricular pressure or volume overload conspires to increase the risk of sudden death more than either one alone, and therefore in the presence of either, the other should always be sought.

Monitoring of arrhythmias may be undertaken using 24-hour Holter monitoring and exercise testing every 1 to 2 years. Underlying hemodynamics, using two-dimensional and Doppler echocardiography, should be carefully and serially reassessed, particularly in the event of a change in frequency or complexity of ventricular ectopy. A reversible cause for a new-onset ventricular arrhythmia such as a rise in right ventricular pressure or a change in right ventricular function should not be missed. There is no role for routine electrophysiologic testing in the prevention of sudden death, but patients with unexplained syncope should be referred for detailed assessment in specialized centers. In addition to surgical or percutaneous intervention aimed at improving significant hemodynamic lesions, antiarrhythmic therapy, pacemakers, and implantable defibrillators may be indicated.

Pulmonary Atresia with Ventricular Septal Defect

Prevalence and Anatomy

TOF with pulmonary atresia or pulmonary atresia with ventricular septal defect (PA-VSD) is a complex form of TOF. As the name indicates, the right ventricular outflow tract is completely atretic, with pulmonary blood flow being derived from aortic-to-pulmonary collaterals. This group of patients is of interest to the adult cardiologist because unoperated adult survival is well documented (167).

Outcome

Survival depends on the adequacy of pulmonary blood flow derived from systemic collaterals. Unoperated PA-VSD exhibits a bimodal mortality pattern. The majority of unoperated patients with inadequate aortic-to-pulmonary blood flow dies in infancy or childhood. A small percentage survive to adulthood because of adequate but not excessive aortic-to-pulmonary circulation, but one-third of all unoperated adult survivors and close to one-half of those who remain unoperated die at a mean age of 33 (167). Morbidity in the unoperated adult survivor relates mainly to heart failure and aortic regurgitation (167).

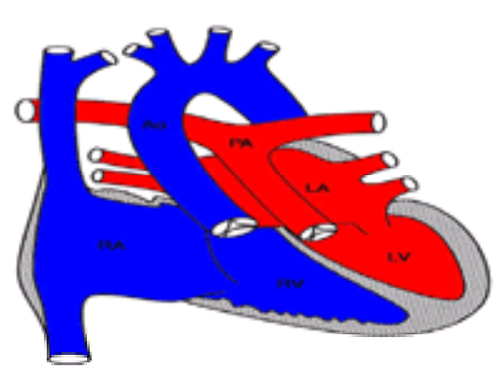
Management

Staged reconstructive operations are now performed on a broad range of patients with PA-VSD, but long-term results of complex surgical management remain uncertain. Of adult survivors, two-thirds may be eligible for physiologic repair with low postoperative mortality and seemingly favorable outcome (167). Whether complex unifocalization techniques are destined to provide the best long-term follow-up remains to be seen, but consideration should be given to surgical management in specialized centers where expertise is available.

Complete Transposition of the Great Arteries

Prevalence and Anatomy

The following remarks are confined to simple complete transposition of the great arteries, defined anatomically as atrioventricular concordance with ventriculoarterial discordance, in the absence of tricuspid or mitral atresia or univentricular heart. In this variant of the transposition complexes, the aorta is most often anterior and rightward (dextroposed), with respect to the pulmonary artery. Hence the designation D-*transposition* of the great arteries (eFig. 31.1.10). This lesion constitutes the second most common cyanotic lesion (137) and, in its surgically corrected form, accounts for an important group of operated adult survivors.



***e*FIGURE 31.1.10** Schematic illustration of complete transposition of the great arteries with S,D,D segmental anatomy. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

The chronologic evolution of surgical treatment for D-transposition of the great arteries is shown in Table 31.2. This exemplifies the progress achieved in congenital cardiac surgery and demonstrates how surgical strategies determine anticipated clinical profiles. The current issues of major concern in the late follow-up of these patients reflect the application of repair at the atrial (Senning's and Mustard's atrial baffles as described below) and ventricular levels (168). Over the course of the next two decades we will see a different set of complications related to the primary neonatal arterial switch operation with its formidable coronary translocations (169).

Outcome

The native physiology is such that at birth, the pulmonary and systemic circulations occur in parallel instead of in series, with effective pulmonary blood flow being dependent on intracardiac shunting. Not surprisingly, without treatment mortality is 90% in the first year of life (170). At the present time the problems of major concern are the ones associated with the atrial switch. These procedures are designed to reroute systemic and pulmonary venous return so that deoxygenated blood can be directed to the pulmonary artery and oxygenated blood to the aorta. This is accomplished by using native atrial tissue in Senning's operation (171) or pericardial tissue

with or without prosthetic material in Mustard's operation (172) to create an intraatrial baffle. "Repair" is accomplished, but at the cost of the morphologic right ventricle remaining in the subaortic position to perform lifelong systemic work.

Of an approximate 1,200 patients followed, on whom long-term published data are available, survival estimates average 75% at 15 years and 67% to 76% at 20 years (173,174 and 175). Although 90% of patients deny subjective limitation in daily life (175), right ventricular dysfunction can be documented in asymptomatic patients, at rest in over 30%, and during exercise in up to 60% of those tested at approximately 10 years' follow-up (176,177). Tricuspid regurgitation is present in 40% of patients with or without right ventricular dysfunction (178). Compounding the hemodynamic complications of systemic right ventricular dysfunction, the extensive atrial surgery results in a progressive decline in the prevalence of sinus rhythm with sinus bradycardia, nodal rhythms, and heart block occurring with increased frequency (173,175). At 20-year follow-up, less than one-half the patients are in sinus rhythm (175). Late atrial flutter or fibrillation occurs in 20% of patients (179). The late occurrence of atrial flutter is an important predictor of poor outcome and may precede the accelerated decline in right ventricular dysfunction (175,180). The incidence of sudden cardiac death varies from 2% to 3% (173) to as high as 16% (175). The etiology of sudden death is poorly understood, but it is likely to be multifactorial and related to poor right ventricular hemodynamics in combination with bradyarrhythmias and tachyarrhythmias (175).

Management

In patients who have undergone Senning's or Mustard's operation arrhythmia management, systemic right ventricular dysfunction, and the need for reoperation constitute the key issues in long-term follow-up (see the section Outcome for a description of complications). Reoperation is performed in an approximate 20% of patients (181). The indications relate to baffle leak or obstruction, significant systemic tricuspid regurgitation, progressive left ventricular outflow tract obstruction, or rarely pulmonary venous obstruction (181).

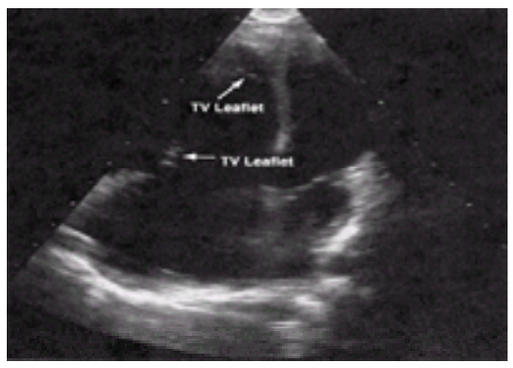
Long-term follow-up reveals an increasing incidence of bradyarrhythmias and supraventricular tachyarrhythmias. Surveillance of arrhythmias should include Holter monitoring and exercise testing at regular intervals. Every attempt should be made to maintain the patient in sinus rhythm, using electrical cardioversion, medical therapy, or both. Pacemaker insertion should be considered in patients with symptomatic bradyarrhythmias. Transvenous pacing with fixation in the morphologic left ventricle (subpulmonary) may be required with or without antitachycardia pacing. Baffle integrity should always be verified to rule out obstruction or leak possibly giving rise to paradoxical emboli. Epicardial pacing is an alternative when ventricular access is hampered by small venous baffle channels. Referral for electrophysiologic studies should be considered in the event of unexplained syncope or arrhythmias unresponsive to medical therapy. Radiofrequency catheter ablation of supraventricular tachycardias can be performed in experienced specialized centers (182). The concurrent monitoring of hemodynamics is crucial. New arrhythmias should always prompt a search for a change in ventricular function or progressive atrioventricular valvar regurgitation requiring tricuspid valve replacement or repair. Trials are ongoing to examine if afterload reduction with angiotensin-converting enzyme inhibitors or receptor blockers may improve systemic right ventricular dysfunction.

For patients with unmanageable systemic right ventricular failure, atrial baffle takedown with a late arterial switch operation has been attempted as an alternative to heart transplantation (183,184,185 and 186). At the current time, mortality for this procedure is high, and much remains to be learned before this can be recommended. The problems delineated previously provide the rationale for the widespread application of the arterial switch operation whereby the left ventricle is reinstated to perform its destined systemic function, and the mismatch between morphology and function is restored. For the arterial switch operation, center-specific series are now emerging with encouraging results (187). Cumulative 15-year survival is over 85% and is expected to increase as improved early mortality makes an impact. The most common complication is neopulmonary stenosis, and thus far, arrhythmias and coronary complications are infrequent (187).

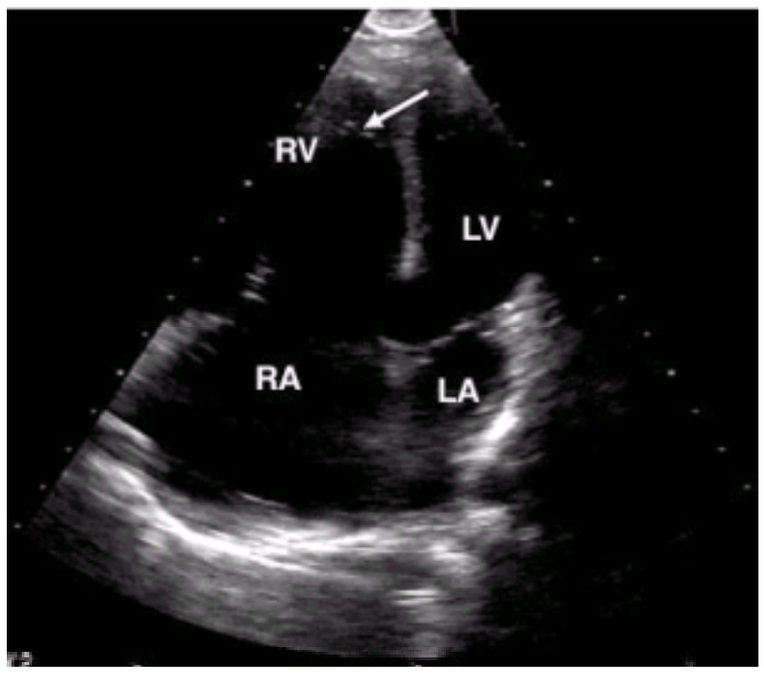
Right-Sided Ebstein's Anomaly

Prevalence and Anatomy

Transthoracic two-dimensional echocardiography has become the method of choice for diagnosing Ebstein's anomaly. The most sensitive echocardiographic feature is distal septal tricuspid leaflet displacement of greater than 8 mm per m^2 (indexed to body surface area). Measurements can be made from the tricuspid valve annulus at the crux (*e*Fig. 31.1.11) (188). In right-sided Ebstein's anomaly of the tricuspid valve, the right side of the heart consists of three anatomic components including the right atrium proper, the functional right ventricle (true right ventricle), and the atrialized portion of the right ventricle between the two. The displaced tricuspid valve lies between the atrialized right ventricle and the true right ventricle. The atrialized right ventricle is anatomically and electrically right ventricle, but functionally right atrium. It generates a ventricular QRS but an atrial pressure pulse (189). Hence, it fills while it contracts. There is a wide spectrum of severity of the lesion, based on degree of tricuspid leaflet tethering, the relative proportion of atrialized and true right ventricle, and the presence or absence of right ventricular outflow tract obstruction. These variations account for differences in clinical presentation. The most common associated cardiac defect is a secundum ASD or patent foramen ovale reported in over 50% of patients (190).



***e*FIGURE 31.1.11** Four-chamber echocardiographic view showing apical displacement of septal tricuspid (TV) leaflet in a patient with Ebstein's anomaly.

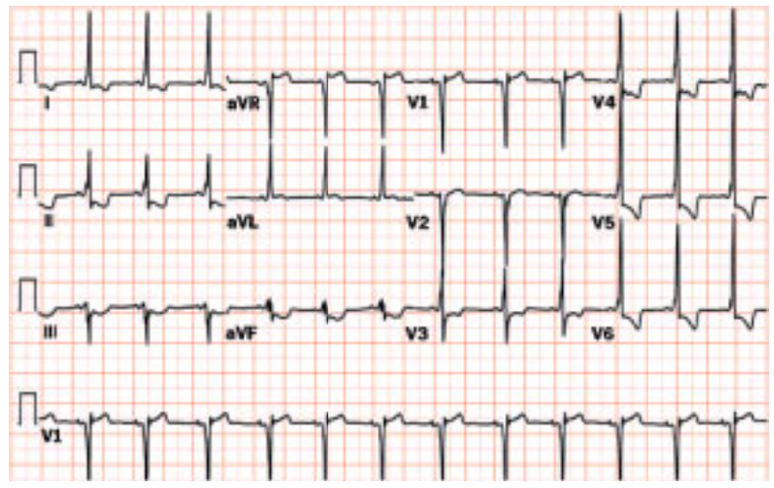


Ebstein's anomaly of the tricuspid valve. Note marked apical displacement of the tricuspid leaflets, especially the septal leaflet. The arrow designates the septal leaflet of the tricuspid valve.

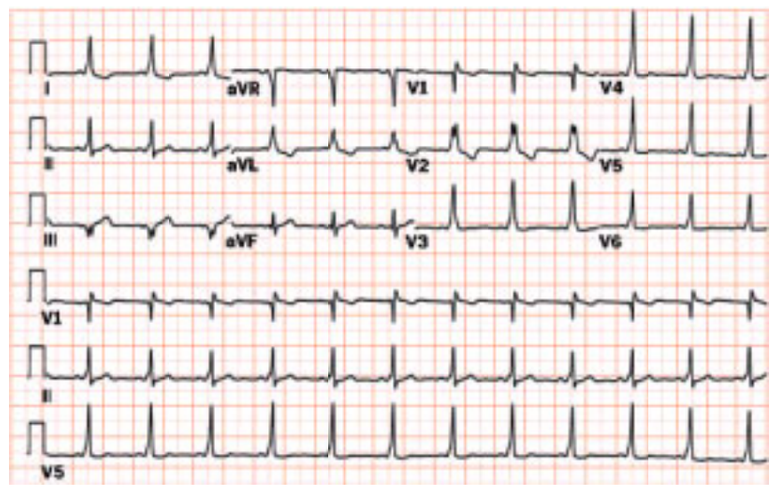
Outcome

Ebstein's anomaly diagnosed in the neonatal period and in infancy has a poor prognosis, with mortality of 30% to 40% in the first decade. When patients of all ages are

taken together, the predicted mortality is approximately 50% by the fourth or fifth decade (191,192). Clinical factors that have been shown to predict poor outcome include infancy at the time of diagnosis, NYHA class III or IV, oxygen saturation of less than 90%, and cardiothoracic index of greater than or equal to 0.65 (191,192 and 193). Cardiomegaly at the expense of the right atrium and atrialized right ventricle are indicators of poor outcome (191). Preexcitation by 12-lead electrocardiography occurs in 20% of patients (191). Supraventricular tachyarrhythmias, including reentrant supraventricular tachycardia, atrial fibrillation, and atrial flutter, occur in 30% to 40% of patients and constitute the most common presentation in adolescents and adults (191,192). The role of arrhythmias in the etiology of sudden death, reported in 3% to 4% of patients (191), remains unclear.



Wolff-Parkinson-White syndrome. Eleven-year-old patient with manifest preexcitation consistent with Wolff-Parkinson-White.



Wolff-Parkinson-White syndrome. Note short PR interval with classic delta wave due to accessory pathway conduction.

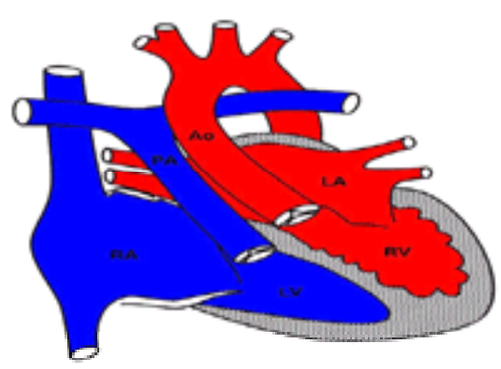
Management

In patients with Ebstein's anomaly, the indications for surgery are deterioration in functional class, progressive cardiomegaly or tricuspid regurgitation, and worsening cyanosis (87) (see the section Outcome for a description of complications). For surgical purposes, Carpentier has distinguished four types of Ebstein's anomalies emphasizing the mobility of the anterior leaflet of the tricuspid valve (type A and B) or its restricted motion (type B and C) as well as the variable degree of the septal leaflet displacement and the variable size and function of the atrialized right ventricle and the true right ventricle (194). Surgical options used in patients with Ebstein's anomaly include tricuspid valve replacement (195) or repair (194,196,197 and 198) of the tricuspid valve and closure of the atrial septal defect. Preservation of the native tricuspid valve and feasibility of tricuspid valvuloplasty depend on the size and mobility of the tricuspid leaflet used to construct a unicuspid right atrioventricular valve (194,196,197 and 198). Although early reports were associated with a mortality of 25% (193), more recent reports have shown early and late mortality of 3% to 14% with (195) or without (194,199) tricuspid valve replacement. In patients with high-risk preoperative anatomy the inclusion of a bidirectional cavopulmonary shunt decreases operative mortality (200). Addition of the Maze procedure in experienced centers is expected to reduce the incidence of atrial arrhythmias (201).

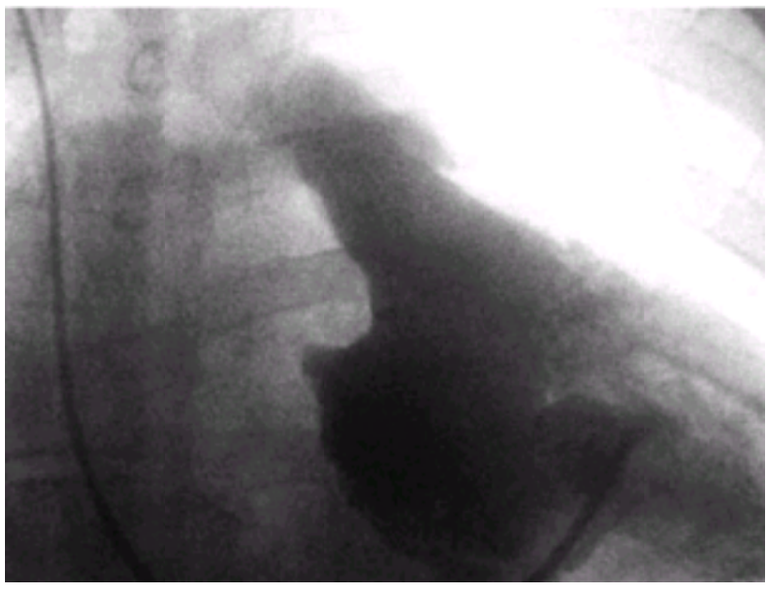
Congenitally Corrected Transposition of the Great Arteries

Prevalence and Anatomy

Congenitally corrected transposition of the great arteries is a condition in which, although the great arteries are transposed, the ventricles are also inverted. There is visceral situs solitus, atrial situs solitus, ventricular inversion (L ventricular loop), and most commonly the aorta is anterior and leftward, hence the designation S,L,L segmental anatomy (*e*Fig. 31.1.12). There is atrioventricular discordance as well as ventriculoarterial discordance. The occurrence of this double discordance has two important implications. First, the systemic and pulmonary circulations are in series, as is the case in the normal cardiopulmonary circulation, and therefore, in the absence of a shunt, the patient is acyanotic; the condition is thus "congenitally corrected." Second, the morphologic right ventricle and tricuspid valve are aligned with the aorta and perform lifelong systemic work. It follows that, although this lesion has been reported in only 1% to 2% of pathologic series of congenital lesions, the presentation of a seemingly well unoperated adult is not uncommon for adult cardiologists. The physiology is determined by the presence of accompanying lesions, which occur in isolation or in various combinations in 20% to 90% of patients. These include a perimembranous VSD, pulmonary stenosis, and Ebstein's malformation of the tricuspid valve (202,203). The presence of left-sided Ebstein's anomaly can occur with or without left-sided accessory bypass tracts between the left atrium and systemic right ventricle, thereby predisposing the patient to preexcitation and reentrant tachycardias (202). The coronary anatomy tends to be uniform, with the left coronary artery supplying the morphologic left ventricle and the dominant right coronary artery arising from the left sinus, supplying the morphologic right ventricle (204).



***e*FIGURE 31.1.12** Schematic illustration of congenitally corrected transposition of the great arteries with S,L,L segmental anatomy. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.



Epstein's anomaly. Right anterior oblique projection of a right ventriculogram demonstrating Epstein's anomaly.

Outcome

The patient's presentation and clinical outcome are determined by the presence or absence of associated lesions, systemic morphologic right ventricle dysfunction, atrioventricular valve regurgitation, and rhythm disturbances. Patients with congenitally corrected transposition of the great arteries and no other associated defects can remain free of symptoms until the sixth decade, at which time significant atrioventricular valve regurgitation, heart failure, and supraventricular arrhythmias occur in over 50% of patients (205). Survival rates at 20 years are strongly influenced by the presence of significant (systemic) tricuspid regurgitation, which affects the course of right ventricular function (206). Complete heart block is reported in 10% to 40% of patients (203,205,207) and develops at a rate of 2% per year. In the presence of associated lesions requiring palliative or definitive surgical repair, mortality increases and survivorship diminishes significantly (203). When adults are considered as a group, at least 30% to 50% of patients are likely to require surgery over the course of follow-up (203,207).

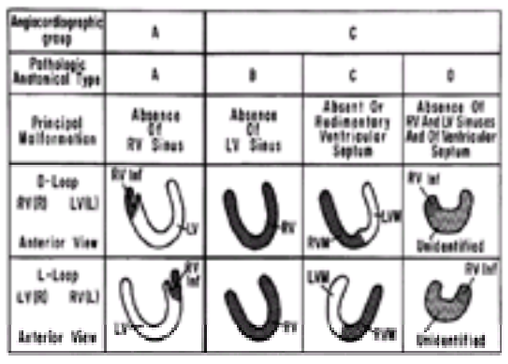
Management

In patients with congenitally corrected transposition of the great arteries, management issues relate to maintenance of systemic right ventricular function, treatment of heart block, and surgical correction of residual or associated lesions (see the section Outcome for a description of complications). Trials are ongoing to determine the effectiveness of afterload reduction in improving ventricular performance. Indications for surgery fall into one of three categories: pacemaker insertion, correction of associated VSD or pulmonary stenosis, and atrioventricular valve replacement or repair. Permanent pacing is usually required in the presence of complete heart block. DDD pacing is preferable to maximize ventricular filling in a systemic morphologic right ventricle. Surgical ablation of accessory pathways sometimes occurs fortuitously or with surgical intervention on the tricuspid valve. In the presence of a shunt, transvenous pacing is contraindicated because of the risk of paradoxical emboli. A VSD should be closed when the shunt is significant. Intervention or reintervention for pulmonary stenosis should be considered when the left ventricular outflow tract gradient exceeds 60 to 70 mm Hg. For uncomplicated congenitally corrected transposition of the great arteries, the timing of surgical intervention for atrioventricular valvular regurgitation remains controversial but should be considered in patients with moderate atrioventricular valve regurgitation in the face of worsening systemic right ventricular function. Early and late surgical mortality appears related to progressive ventricular failure. Postoperative survivorship correlates with a preoperative ventricular ejection fraction (208). A poor outcome occurs when preoperative ejection fraction is less than 40% to 45% (208).

Univentricular Heart and Tricuspid Atresia

Prevalence and Anatomy

Complex lesions such as single ventricle and tricuspid atresia account for less than 2.5% of all CHD (240), but operated adult survivors are becoming increasingly common (5). The terms *single ventricle*, *common ventricle*, and *univentricular heart* have been used interchangeably to indicate a condition in which one ventricular chamber receives both the tricuspid and mitral valves, hence the accurate designation *double-inlet ventricle*. Patients with a single ventricle can be categorized based on two principal findings: the morphology of the ventricle and the presence or absence of an outlet chamber giving rise to one or both great arteries. In the majority of cases, the single ventricle is of the morphologic left ventricular type with a univentricular heart of the right ventricular type accounting for 10% to 25% of all cases (210). Least commonly, the ventricular morphology is indeterminate. Most commonly, an outlet chamber is present and is found in the anterosuperior position, either to the right (D-loop or noninverted) or left (L-loop or inverted) (eFig. 31.1.13, type A). In the majority of cases, the ventriculoarterial connection is discordant, with the aorta arising from the outflow chamber (eFig. 31.1.14). Obstruction of one of the great arteries is frequent (210).



***e*FIGURE 31.1.13** Classification of univentricular heart. LV, left ventricle; LVM, left ventricular muscle; RV, right ventricle; RVM, right ventricular muscle.

***e*FIGURE 31.1.14** Angiogram of univentricular heart.

Tricuspid atresia has been classified into eight basic categories (eTable 31.2.1) (211). Patients with associated pulmonary atresia (types 1A and 2A) rarely survive infancy unless they have a persistent PDA or have a palliative surgical shunt. Patients with pulmonic stenosis (types 1B, 2B, and 3A) account for 70% of all patients with tricuspid atresia and constitute the most common anatomy associated with adult survival (212).

***e*TABLE 31.2.1** CLASSIFICATION OF TRICUSPID ATRESIA
Type 1: Normally related great arteries (69%)
Pulmonary atresia
Pulmonary stenosis and ventricular septal defect
Large ventricular septal defect without pulmonary stenosis
Type 2: D-Transposition of the great arteries (27%)
Pulmonary atresia
Pulmonary stenosis and ventricular septal defect
Large ventricular septal defect without pulmonary stenosis
Type 3: L-Transposition of the great arteries (3%)
Pulmonary stenosis
Subaortic stenosis

Outcome

Long-term follow-up of unoperated and palliated patients with univentricular heart has been studied (213,214). Of 83 unoperated patients (242), type A single ventricle anatomy was observed in 81% and type C in 19%. Fourteen years after diagnosis, when most patients were in their late teens and late twenties, 50% of the patients with type A univentricular heart had died at an approximate annual death rate of 5%. Sixteen years after diagnosis, only 30% of the patients with type A anatomy were alive. Type C anatomy had a poorer prognosis. Only 50% of these patients were alive 4 years after diagnosis. Long-term follow-up of 84 palliated patients with univentricular heart was also examined (214). Mean age at diagnosis was 10 years, with a mean follow-up of 5 years. Palliative procedures included systemic-to-pulmonary-artery shunts alone in 43, pulmonary artery banding in 15, and a combination of procedures in 26. At the end of the observed follow-up period at a mean age of only 15 years, close to one-third of patients had died. The outcome of patients who have undergone the Fontan operation is described in the next section.

Management

Patients with univentricular heart and tricuspid atresia require a detailed evaluation with noninvasive and invasive imaging techniques. Two-dimensional echocardiography and Doppler interrogation as well as MRI are used to determine ventricular and atrioventricular valve function, pulmonary artery pressure and resistance, and pulmonary anatomy. When biventricular repair is not feasible, patients may benefit from further palliation with a Glenn's shunt or may be eligible for the Fontan operation.

In both instances, a direct anastomosis is performed between the systemic venous and pulmonary circulations. The Glenn's anastomosis diverts part of the systemic venous return to the lungs, whereas the Fontan procedure and its variants divert the entire systemic venous circulation to the pulmonary vascular bed. Both are done with the goal of improving oxygenation and loading conditions of the systemic ventricle. Partial volume unloading of the single ventricle can be achieved with a bidirectional Glenn's anastomosis (215). Cavopulmonary shunts confer long-term benefit to ventricular function when compared with aortopulmonary shunts (216). Actuarial survival with Glenn's shunt is 84% and 66% at 10 and 20 years, respectively (10).

Fontan Operation

Since its first application in patients with tricuspid atresia in 1972, the Fontan procedure has undergone multiple modifications, resulting in improved surgical technique and expanded criteria for surgical candidacy. In its most recent anatomic variants, direct anastomosis between the systemic venous and the pulmonary circulations is achieved by bypassing the systemic venous ventricle (modified Fontan) or both the systemic venous atrium and ventricle (total cavopulmonary anastomosis) with or without a fenestration (217,218). In the absence of a pulsatile subpulmonary chamber, pulmonary pressures must necessarily be low. In the presence of a fenestration, the established communication between the Fontan conduit and the atrial cavity allows "decompression" of the pulmonary pressures maximizing flow through the pulmonary vascular bed. The goals of the Fontan operation are threefold: relief of cyanosis, maximal reduction of volume loading of the systemic ventricle, and maintenance of appropriate cardiac output. For optimal results, a successful Fontan operation requires preserved ventricular function, minimal atrioventricular valve regurgitation, unobstructed anastomosis between the systemic veins and the pulmonary arteries, as well as a low pulmonary vascular resistance.

The Fontan operation can be successfully performed in selected adults with a low operative mortality and favorable intermediate-term results (219,220). The Mayo Clinic reported a large series of 121 patients over 18 years who had the Fontan procedure (219). This included 34 patients with tricuspid atresia, 38 patients with double-inlet left ventricle, and 49 patients with complex malformation, such as double-inlet right ventricle, associated with asplenia and heterotaxy syndromes. The operative mortality in adults from 1988 to 1992 was 10%. During the same time period, the operative mortality for children less than 17 years of age was not significantly different at 7%, confirming that older age at the time of intervention is not an independent marker of poor outcome (219,220 and 221). When patients of all ages are considered together, examining a cohort of subjects operated before 1985, 5- to 10-year survival varies from 60% to 70%. Late deaths are due to reoperation (220), arrhythmia, ventricular failure, and protein-losing enteropathy.

At 5- to 10-year follow-up, 80% or more of Fontan survivors are in NYHA functional class I or II (220,221 and 222). Successful pregnancy has been reported in a small number of patients after the Fontan operation (223). Despite the fact that most patients report good subjective aerobic functional capacity, objective measures of exercise tolerance are impaired. The heart-rate response to exercise is blunted (221), and ventricular ejection fraction increases little in response to exercise (221). Other parameters of abnormal cardiopulmonary response include lower maximum workload, lower aerobic threshold (221), a decreased maximum oxygen uptake, and a restrictive pattern in lung function when compared with normal (224). In addition, decreased ventilatory threshold, increased physiologic dead space, and ventilation-perfusion mismatch have been reported (221,225).

The incidence of atrial arrhythmia varies between 20% and 40% of patients 10 years after the Fontan operation (226). The occurrence of new atrial arrhythmias should motivate a search for hemodynamic complications such as worsening of atrioventricular valvular function or obstruction of Fontan anastomosis with or without thrombus (227). Important predictors of supraventricular tachyarrhythmias after surgery are related more to abnormalities of the atrioventricular valve and age at operation rather than to the anatomic variant of Fontan procedure (228). Atrial flutter and fibrillation are poorly tolerated and should be treated aggressively with overdrive pacing or DC cardioversion combined with appropriate antiarrhythmic medication (226). When atrial arrhythmias are refractory to medical therapy, Fontan revision with cryoablation may be considered (229). Long-term anticoagulation with coumadin should be instituted. There are a significant number of adult patients who develop late sinus bradycardia. For symptomatic bradycardia, permanent atrial pacing is required. As many as 10% of long-term survivors may require permanent pacing for sinus node dysfunction or atrioventricular block (226).

Protein-losing enteropathy is a serious complication of the Fontan procedure occurring in 4% to 10% of Fontan patients during early or late follow-up (230,231). In conditions predisposing to systemic venous congestion, it is postulated that chronic elevation in superior vena cava pressures may lead to impaired lymphatic drainage with enteric protein loss and secondary hypoproteinemia. Clinical findings include peripheral edema, ascites, pleural effusions, and elevated right atrial pressures. When other causes of hypoproteinemia have been excluded, the diagnosis is made by quantifying gastrointestinal protein loss using $alpha_1$-antitrypsin clearance or ^{51}chromium-labeled albumin. Medical therapy includes the use of diuretics, afterload reduction, and protein infusions. Surgical or interventional therapy uses a wide variety of procedures aimed at optimizing Fontan hemodynamics. Conversion of the Fontan operation to a bidirectional Glenn's shunt or heart transplantation may be necessary. Overall prognosis is poor, with an approximate 50% survival at 5 years (230).

The prevention and management of thromboembolic complications of the Fontan procedure remain controversial (232). The prevalence of intracardiac thrombosis is as high as 30% when transesophageal echocardiography is used for diagnosis (233). Patients may or may not be symptomatic, and the risk of thromboembolism does not appear to be clearly modified by the type of Fontan anastomosis (234). At the current time anticoagulation with coumadin is recommended in the presence of arrhythmias in patients with a Fontan fenestration and when evidence of stasis is seen on echocardiographic examination.

The Fontan operation and its evolution illustrate some fascinating surgical concepts that have challenged our understanding of the subpulmonary circulation. Because palliated survival with single-ventricle physiology is possible, performing the Fontan operation in adult life may be appropriate and should be considered in individual cases. The two issues to be determined are, first, is it feasible, and, second, is it beneficial? As described in this chapter, the Fontan operation can be performed in properly selected adults with acceptable operative mortality and encouraging results. The question as to whether the Fontan operation *should* be performed on an adult is more controversial. The rationale for doing so is twofold: prevention of progressive ventricular deterioration and the alleviation of cyanosis. On the other hand, what more do we achieve with the Fontan procedure in an adult? Is quality of life improved? Which complications are easier to live with? The answers to these questions are still controversial, but when appropriate, they should always be asked with respect to the individual patient. The final decision should be made in centers of expertise where experience, knowledge, and skill maximize the clinical outcome.

EISENMENGER'S SYNDROME

Definition

The designation *Eisenmenger's syndrome* is not synonymous with pulmonary hypertension in a cyanotic patient with CHD. The term is reserved for patients in whom, in the presence of pulmonary vascular obstructive disease, pulmonary vascular resistance is fixed and irreversible. These findings in combination with the absence of left-to-right shunting make the patient inoperable in terms of physiologic repair or further palliation. It then becomes useful to designate the patient's physiology and its consequences as Eisenmenger's syndrome. The focus of management and therapy of chronic cyanotic heart disease is described.

Outcome and Cardiovascular Management

Survival into the seventh decade is rare but has been documented in Eisenmenger's patients (235,236) and is determined by the underlying cardiac condition and the medical complications of cyanosis. Mortality is high, and up to two-thirds of the deaths are sudden and unexpected. The etiology of sudden cardiac death remains poorly defined (235,236 and 237). Multiple factors including arrhythmias have been described. Symptomatic arrhythmia should be treated with individualized antiarrhythmic therapy depending on the presence or absence of ventricular dysfunction. An implantable defibrillator should be considered in patients with syncope and documented concurrent ventricular arrhythmia. The decision to use anticoagulants in patients with cyanosis is complicated by the presence of bleeding diathesis. Patients with atrial fibrillation should receive warfarin therapy with judicious monitoring of international normalized ratio levels.

MANAGEMENT OF CYANOTIC PATIENTS

Cyanosis is seen when persistent venous-to-arterial mixing results in hypoxemia. When cyanosis is not relieved, chronic hypoxemia and erythrocytosis result in systemic complications that require continued surveillance. Medical complications of cyanosis (238) are observed in unoperated or palliated adult patients with CHD. Hematologic, neurologic, renal, and rheumatic complications (236) and their management (239) are well described. Hematologic management is described here.

Hematologic complications (240) of chronic hypoxemia include erythrocytosis, iron deficiency, and bleeding diathesis. Erythrocytosis is different from polycythemia, which is the result of an increase in cellular mass not only of red cells, but also of white cells and platelets. Symptoms of hyperviscosity include headaches, faintness, dizziness, fatigue, altered mentation, visual disturbances, paresthesias, tinnitus, and myalgias. Patients with compensated erythrocytosis establish equilibrium hematocrit at higher levels in an iron-replete state with minimal symptoms. Patients with decompensated erythrocytosis manifest unstable rising hematocrit levels and experience severe hyperviscosity symptoms. In the iron-replete state, moderate to severe hyperviscosity symptoms may occur, typically when hematocrit levels are in excess of 65%.

Iron deficiency (241) is a common finding in cyanotic adult patients occurring because of inappropriate phlebotomy or excessive bleeding. Although normochromic erythrocytosis is not usually symptomatic at hematocrit levels of less than 65%, iron deficiency may manifest as symptoms similar to hyperviscosity at hematocrits well below 65%. If iron deficiency anemia is confirmed, careful iron replacement with 325 mg of ferrous sulfate or 65 mg of supplemental iron should be prescribed until an increase in hematocrit is detected, typically within 1 week. A significant and rapid increase in hematocrit is undesirable as it may exacerbate hyperviscosity symptoms, leading to phlebotomy, which can in turn worsen the iron deficiency (240).

Hemostatic abnormalities (240) have been documented in cyanotic patients with erythrocytosis and can occur in up to 20% of patients. In a minority of patients, hemoptysis or postoperative bleeding can be life-threatening. An elevated prothrombin and partial thromboplastin time, decreased levels of various coagulation factors, in addition to thrombocytopenia, and platelet disorders have been described (242,243). The management of bleeding diathesis is determined by the clinical circumstance, the severity, and the abnormal hemostatic parameters. Aspirin, heparin, and coumadin should be avoided unless indicated for chronic atrial fibrillation or in the presence of a mechanical prosthetic valve. Platelet transfusions, fresh frozen plasma, vitamin K, and cryoprecipitate and desmopressin can be used to treat severe bleeding.

Pulmonary thrombosis *in situ* and pulmonary hemorrhage have been described in up to 30% of patients with Eisenmenger's VSD who have CT scans of the chest (236,244). Typically, *in situ* thrombosis presents in a patient with a rapid clinical decline associated with progressive hypoxemia, marking the terminal stage of the disease. The tendency to form laminated thrombus in calcified, aneurysmal proximal pulmonary arteries is poorly understood. Currently, no benefit has been observed with the use of oral, intravenous, or intrapulmonary anticoagulants or from an attempt at pulmonary endarterectomy. The risk of bleeding and the potential for massive pulmonary hemorrhage continue to appear to outweigh the benefits of anticoagulation.

Neurologic complications (245), including cerebral hemorrhage, can occur secondary to hemostatic defects and can be seen after inappropriate use of anticoagulant therapy. Patients with right-to-left shunts may be at risk for paradoxical cerebral emboli. Focal brain injury may provide a nidus for brain abscess if bacteremia supervenes. Attention should be paid to the use of air filters in peripheral intravenous lines to avoid paradoxical emboli through a right-to-left shunt. Cyanotic adults are not at risk for cerebral arterial thrombosis (245). The occurrence of cerebrovascular accidents secondary to cerebral venous thrombosis in children (246,247) does not justify the presumed risk of cerebral arterial thrombosis in adults.

Phlebotomy is indicated under two sets of circumstances: for patients symptomatic of hyperviscosity in a nondehydrated state, most commonly when hematocrit levels exceed 65; and in asymptomatic patients with hematocrit levels greater than 65 before surgery to minimize postoperative bleeding. If symptoms occur with hematocrits of less than 65, evidence of iron deficiency should be sought. When indicated, removal of 500 mL of blood over 30 to 45 minutes followed by quantitative volume replacement with normal saline or dextran can be performed. Symptom control can be achieved with the removal of less than 2 L of blood and sometimes with as little as 250 mL. The procedure may be repeated every 24 hours until improvement occurs. An attempt should be made to achieve symptom control with the smallest quantity of blood removal to avoid iron deficiency. Prophylactic phlebotomy has no place in the prevention of cerebral arterial thrombosis (245,248).

Renal dysfunction (236,249) can manifest as proteinuria, hyperuricemia, or renal failure. Increased blood viscosity from erythrocytosis with or without iron deficiency in combination with arteriolar vasoconstriction can lead to renal hypoperfusion with progressive glomerulosclerosis. Hyperuricemia is common and is thought to be due mainly to the decreased reabsorption of uric acid rather than to overproduction from erythrocytosis. Urate nephropathy, uric acid nephrolithiasis, and gouty arthritis are rare but may occur. Gallstones composed of calcium bilirubinate and consequent cholecystitis occur with increased frequency in adults, adolescents, and children (244). Hydration before procedures involving contrast media should be prescribed to avoid renal dysfunction.

Rheumatologic complications include gout and hypertrophic osteoarthropathy, which is thought to be responsible for the arthralgias affecting up to one-third of patients (236,244). In patients with right-to-left shunting, megakaryocytes released from the bone marrow bypass the lung, escaping fragmentation. Their entrapment in systemic arterioles and capillaries induces the release of platelet-derived growth factor, promoting local cell proliferation. Digital clubbing and new osseous formation with periostitis occur, giving rise to symptoms of arthralgia. Asymptomatic hyperuricemia should not be treated. Long-term therapy aimed at lowering uric acid levels has not been shown to prevent renal disease or gout. Symptomatic hyperuricemia and gouty arthritis can be treated as necessary with colchicine, probenecid, sulfinpyrazone, or allopurinol. Nonsteroidal antiinflammatory drugs should be avoided to prevent hemostatic anomalies (244).

The use of angiotensin-converting enzyme inhibitors in patients with cyanotic CHD (250) is controversial and should therefore not be routinely used in cyanotic patients. Afterload reduction may, on the one hand, increase cardiac output and improve oxygen delivery, but on the other hand, lower systemic vascular resistance may increase right-to-left shunting with worsening cyanosis.

The results of cardiac transplantation in properly selected patients with CHD, with and without previous palliative surgery, have improved both in terms of hospital and medium-term mortality (251). Lung transplantation (single or double) (252) with intracardiac repair can be effective in reducing pulmonary hypertension. Long-term complications relate to those of obliterative bronchiolitis and to a variable course in right ventricular recovery, with or without the development of dynamic subpulmonary obstruction after the procedure.

SPECIALIZED ISSUES

Issues Pertinent to Patients Undergoing Noncardiac Surgery

Patients with acyanotic congenital lesions require routine intraoperative and postoperative care for noncardiac procedures. The intracardiac hemodynamics and arrhythmic complications are determined by the native and surgical anatomy. In patients with intracardiac shunts who are cyanotic or acyanotic, the risk of paradoxical embolization is increased (253). To avoid the introduction of air or particles into peripheral or central venous catheters, filters should be placed in intravenous lines, with care taken to avoid the introduction of air or bubbles (256). Other issues of concern include difficulties in venous and arterial access, appropriate volume and airway management, prevention of hemostatic anomalies as described previously, and precautionary measures in the administration of anesthesia (254,256,257 and 258). Because hemostatic defects correlate with the severity of hypoxemia and the degree of erythrocytosis, reduction in erythrocyte mass results in improved hemostasis

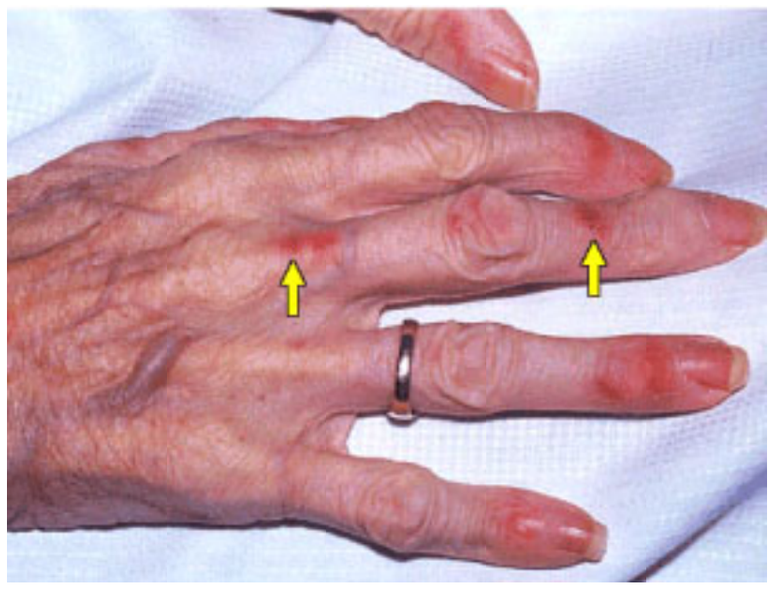
(255). Cyanotic patients undergoing surgery should have prophylactic phlebotomy if the hematocrit is greater than 65 to minimize bleeding.

Noncardiac surgery in patients with Eisenmenger's syndrome is associated with a 5% to 10% mortality even for minor procedures (259). In patients with pulmonary vascular disease (256) management includes the prevention of dehydration and hypovolemia. Large fluctuations in systemic vascular resistance should be avoided. Systemic hypotension can lead to an increase in the right-to-left shunt with a decrease in pulmonary blood flow. Hypercapnia and hypoxia are also hazardous, in that they stimulate an increase in pulmonary vascular resistance. Close monitoring of intravascular blood volume and cautious use of systemic vasodilators, including regional anesthesia, are mandatory. The usefulness and risks of using a pulmonary artery catheter during and after the procedure in patients with pulmonary hypertension are controversial (257). Airway management can be complicated by an enlarged pulmonary artery with resulting chronic compression of the left main stem bronchus or the right middle lobe bronchus and recurrent atelectasis, pneumonia, or localized emphysema (258). An enlarged hypertensive pulmonary artery trunk can also compress the recurrent laryngeal nerve, resulting in chronic hoarseness (258). Previous surgery may have resulted in injury to the phrenic nerve with subsequent development of diaphragmatic palsy (256). Patients with cyanotic CHD tend to have increased ventilation with normal P_{CO_2}. Scoliosis occurs with a frequency reported to be as high as 19% (258). Although the degree of scoliosis is not always severe enough to impair pulmonary function, restrictive airway obstruction is well recognized (258).

Anesthesia care of patients with congenital disease requires precautionary measures (256,257). Epidural anesthesia has been used successfully in patients with pulmonary vascular disease, but local anesthetic needs to be given slowly. Of major concern is the period of anesthetic induction. It is critical in patients with elevated pulmonary artery pressure that they not become hypotensive during induction. Volume expanders and drugs such as epinephrine and levarterenol (Levophed) need to be available to be sure that systemic vascular resistance and arterial pressure are maintained.

Endocarditis

Prolonged survival of patients with complex CHD has resulted in a population at increased risk for developing infective endocarditis in unoperated and operated patients (260). Infection most commonly affects sites of turbulent blood flow (260) on the low-pressure side of gradients. Such sites include restrictive VSDs, PDA, the cleft mitral valve, aortic coarctation (most often at the site of an associated bicuspid aortic valve), and prosthetic shunts, valves, and conduits in the postoperative patient (261). These lesions may occur in combination in complex operated cyanotic heart disease. The risk of endocarditis associated with isolated low-pressure lesions in the right side of the heart is low in both simple and complex lesions (260).



Septic emboli from infective endocarditis (*arrows*).

Janeway lesions of endocarditis. There are hemorrhages with nodular character at the fingertips (*arrows*).

Osler nodes. There are tender nodules on the toe pads (*arrows*) secondary to infective endocarditis.

Splinter hemorrhages. Linear hemorrhages on the fingertips of a patient with infective endocarditis.

Current recommendations for the prevention of bacterial endocarditis apply to most congenital heart lesions with the exception of the isolated secundum ASD, the surgically repaired atrial and ventricular or ductal shunt without residual shunt beyond 6 months after repair. These guidelines should be used for dental, oral, or respiratory procedures (262).

Pregnancy

The reported genetic transmission of maternal CHD to offspring varies from 4% (264) to as high as 16% (267). The conditions that result in the greatest risk to the mother and fetus include Eisenmenger's syndrome, severe pulmonary hypertension, severe left ventricular outflow tract obstruction, Marfan's syndrome with an enlarged aortic root, and heart failure resulting in NYHA class III or IV. Pregnancy in patients with Eisenmenger's syndrome is associated with mortality of up to 50% (268,269). Pregnancy in cyanotic CHD that excludes Eisenmenger's reaction results in a 3% incidence of maternal cardiovascular complications and a near 40% incidence of prematurity (264). These data support the recommendation that pregnancy should be avoided in patients with Eisenmenger's syndrome (87). When women with operated or unoperated CHD are studied as a group, live birth rates are 80% (270). In women after successful coarctation repair, in the presence of an arm-to-leg blood pressure gradient of less than 20 mm Hg, the incidence of preeclampsia is not increased (271). For patients with complex lesions, individual series have reported a total of nearly 250 pregnancies with no maternal mortality (272,273,274 and 275). Successful pregnancies have been reported in patients following surgically repaired transposition of the great arteries (265,272); congenitally corrected transposition of the great arteries (273); Ebstein's anomaly (266,274); and the Fontan operation (275). Although small individual series are encouraging, complication rates remain significant even when close follow-up is undertaken in specialized centers. These patients should always be referred to experienced facilities when pregnancy is being considered.

Prepartum assessment includes a thorough cardiovascular evaluation of the mother and the fetus (277). The efficacy and ease of each method of contraception will need to be weighed against risks to the mother, the efficacy and ease of the method itself, and the risk of pregnancy, should it occur (276). The more pregnancy is contraindicated, the more fail-safe the method chosen should be. Barrier methods are usually safe to the woman, but have pregnancy prevention failure rates in the range of 10% to 20%. The intrauterine device has a failure rate of approximately 4%, but is a potential source of infection. Hormonal suppression of ovulation is associated with failure rates of less than 3%, but may lead to thromboembolism and should be avoided in patients with right-to-left shunts. Male or female sterilizations are most efficacious, with failure rates of less than 1%, but they are also more definitive and difficult psychologically. Intrapartum and postpartum management of the mother requires surveillance of changes in cardiac status, including the development of hypertension, heart failure, or arrhythmias; aggravation of the underlying condition; management of anticoagulation therapy; and endocarditis prophylaxis at the time of delivery. Anticoagulant therapy is an important part of stroke prevention in patients with mechanical valves and needs to be carefully continued during pregnancy. Warfarin embryopathy can be a serious complication of therapy to the offspring, particularly during the first trimester (278). Anticoagulation can be achieved with heparin, which does not cross the placenta. Recommendations with respect to specific anticoagulation during pregnancy are controversial (279) and are based on the regional experience and discussions with the patient. Although antibiotics are frequently administered, the American Heart Association guidelines do not recommend endocarditis prophylaxis for uncomplicated vaginal delivery (262).

Exercise

The goals of exercise evaluation are to assess functional results of therapeutic interventions and provide guidelines for athletic participation. Patients with residual hemodynamic lesions or unrepaired congenital cardiac anomalies should be evaluated on an annual basis with physical examination, electrocardiography, and cardiac ultrasound if indicated. Pertinent additional tests may include Holter monitoring and exercise testing. Attention should be directed to the detection of pulmonary hypertension, arrhythmias, myocardial dysfunction, and symptoms including exercise-induced syncope, chest pain, or dizziness. A series of guidelines have been proposed for major groups of congenital heart defects, including shunt lesions, obstructive lesions, and unrepaired and repaired defects (123). These are summarized in Table 31.3.

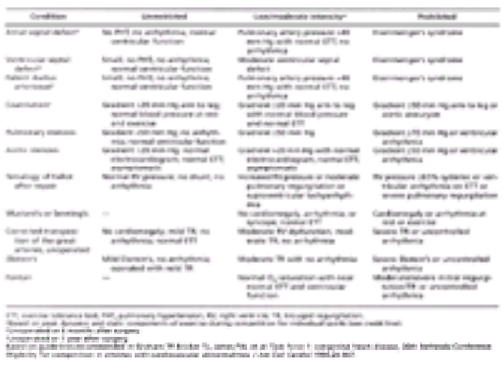


TABLE 31.3 EXERCISE RECOMMENDATIONS IN ADULTS WITH CONGENITAL HEART DISEASE

Psychosocial Issues

In addition to physical defects, mental retardation syndromes and long-term neurologic consequences of cyanotic heart disease or cardiac surgery may be present in the young adult with CHD (263). In comparison with peers, young adults with CHD may choose a more dependent lifestyle with significant involvement of parents or other family members (280).

CONTROVERSIES AND PERSONAL PERSPECTIVES

This subspecialty of cardiology is in its infancy. There are more questions than answers. To date, for an individual patient, the most controversial question has been to operate or not to operate? As surgical data accumulate, the consensus favors surgery. However, the same procedure in an infant and in an adult results in an operation with a different outcome, and can we use data generated in high-volume centers to make decisions about individual patients around the world? In the neonate and infant, current surgical strategy aims at intervening early enough to prevent exposure to deleterious physiology. In the adult, lifelong exposure to abnormal hemodynamics may offset the benefits of anatomic correction. On the other hand, a firm understanding of patient's anatomy may permit interventions that were previously not feasible. For both infants and adults, when physiologic repair has taken place, many issues of concern in long-term follow-up continue to exist, as described in this chapter. Right ventricular function and dysfunction take many forms in the numerous variants of CHD. Response to right ventricular remodeling and its prevention is undetermined. The right ventricle as a culprit for sudden cardiac death is atypical for adult cardiologists. The prevention of thromboembolic complications in a right-sided cardiopulmonary circulation without a subpulmonary ventricle is difficult. The organization of health care delivery for this group of patients remains our biggest challenge. Recommendations have been thoroughly laid out at the 32nd Bethesda conference (281,282). Their implementation remains variable. The

importance of appropriate referral cannot be overemphasized. Even in patients with simple lesions, the decisions can be complex. Those with adequate training and experience are best suited to make management decisions that take into account the patient's needs and the reality of the medical environment where these needs can be met.

THE FUTURE

A new landscape in CHD care has been created in a way that would have been difficult to envisage a mere 50 years ago. The concepts of surgical palliation and repair evolved sequentially in progressively younger and younger patients. At the current time, our youngest patients are rapidly growing in numbers. They are most likely to have been operated and reoperated. The first intervention may have occurred as early as 24 hours of age. The efforts of pediatric cardiologists and congenital heart surgeons have resulted in one of the most rewarding achievements of twentieth-century medicine. The trends witnessed since the 1950s are shaping our direction as we engage the twenty-first century. We want these patients to stay alive as long and as *well* as possible, defying anatomy and physiology as we know it. They continuously bring us back to the reality of persistent, changing, and growing medical and surgical problems. Ultimately, these adults should be framing the pediatric perspective. What we need for this young specialty are data. We need to quantify where we are, rather than describe it. We need national and international databases. We need randomized trials. This should be given priority in parallel with the molecular biology that will enable prevention in the fetus and perhaps the embryo. We encourage our readers to understand the principles that govern current thinking so as to be equipped to follow the direction of a specialty in evolution. The big picture appears promising. We are watching. The color of the future is coming to light as it unfolds.

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32

THE HEART AND PREGNANCY

KENNETH L. BAUGHMAN

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OVERVIEW

Pregnancy normally induces significant physiologic adaptation in the cardiovascular system, including increases in heart rate, left ventricular size, stroke volume, and left ventricular mass. Systemic vascular resistance decreases during pregnancy. The maximal increase in hemodynamic burden for the pregnant patient is achieved at the end of the second trimester. Uterine contractions and the sympathetic discharge associated with delivery further increase cardiovascular demands on the pregnant patient, with the greatest increase in cardiac output achieved in the final stages of delivery. These alterations are resolved approximately 6 weeks after delivery. Moderate aerobic exercise during pregnancy is safe, increasing maximal aerobic power and the capacity for sustained submaximal exercise, as well as preserving aerobic capacity in late gestation.

Hypertension complicates 10% of pregnancies, is rarely due to secondary causes, and is classified as chronic hypertension, gestational hypertension, or preeclampsia. Preeclampsia, the most worrisome of these disorders, involves hypertension, proteinuria, edema, and possibly coagulopathy and liver dysfunction. If preeclampsia is severe, the condition may lead to eclampsia, a seizure disorder associated with high morbidity and mortality. The HELLP syndrome (*h*emolysis, *e*levated *l*iver function tests, and *l*ow *p*latelet levels) is a preeclampsia variant that has the same potential for malignant degeneration to eclampsia.

Peripartum cardiomyopathy is the presence of a new cardiomyopathy, without any other cause of congestive heart failure or preexisting heart muscle disorder, that appears in the final month of the pregnancy or in the first 5 months postpartum. Older patients, patients experiencing multibirth pregnancies, patients with toxemia, and patients carrying a first child are somewhat more likely to experience this condition. Most patients with this condition present within 1 to 2 months of delivery. Myocarditis is frequently found in patients who undergo endomyocardial biopsy early after presentation.

All forms of chronic anticoagulation may result in bleeding between the uterus and placenta and subsequent pregnancy loss. Heparin may cause osteoporosis if it is administered at a high dosage for long periods, and warfarin (Coumadin) may be associated with an embryopathy or central nervous system abnormality. Patients who require anticoagulants should receive heparin in the first trimester and in the terminal stages of pregnancy. Coumadin can usually be safely administered through the remainder of pregnancy until just before delivery.

Bioprosthetic heart valves frequently degenerate in and around the time of pregnancy and may require replacement. Pregnant patients who have mechanical prostheses have a lower live birth rate and higher incidence of thromboembolic complications.

Myocardial infarctions associated with pregnancy are unusual; however, pregnancy is associated with an increased incidence of vasospasm and coronary dissection. Pregnant patients are also predisposed to aortic dissection, particularly if they have aortic disease, including Marfan syndrome or Takayasu's syndrome.

Patients who have congenital heart disease, even if it is corrected, must be screened carefully before they become pregnant to ensure that their pulmonary vascular resistance, ventricular function, valvular insufficiency, prosthetic devices, and aortopathy will be able to tolerate the cardiovascular strains of pregnancy.

Tocolytic therapy consists of the use of b-sympathomimetic agents to decrease uterine contraction and allow fetal lung maturation. Approximately 5% of exposed fetuses develop pulmonary edema, which appears to be a capillary leak syndrome.

Because antiarrhythmic agents pose a significant risk to the patient and fetus, they must be chosen carefully.

GLOSSARY

Bioprosthesis: An artificial valve made of biologic material, including either homograft (human) or heterograft (pig) tissue.

Embryopathy: Damage to the embryo, usually as a result of maternal exposure, typically in the first trimester of pregnancy.

HELLP syndrome: Hemolysis, elevated liver function tests, and low platelet levels in pregnant patients. Considered to be a variant of preeclampsia.

Myocarditis: Inflammation of the myocardium, characterized by a significant inflammatory infiltrate associated with myocyte necrosis.

Peripartum cardiomyopathy: Cardiomyopathy appearing in the final month of pregnancy or the first 5 months postpartum, with no preexisting heart muscle disorder and absence of any other cause of congestive heart failure.

Preeclampsia: The appearance of hypertension, proteinuria, and edema in a patient of more than 20 weeks' gestation.

Teratogenic risk: Risk of an induced fetal abnormality, usually caused by maternal exposure in the first trimester of pregnancy.

Tocolytic therapy: Sympathomimetic therapy used to decrease uterine contractions; usually initiated to prolong gestation and increase fetal lung maturation.

INTRODUCTION

Cardiologists and internists are more and more often consulted in the management of cardiovascular complications associated with pregnancy. A greater number of women with known or potential cardiovascular disease are becoming pregnant, and cardiovascular complications in pregnant women are increasingly recognized.

This chapter discusses the normal morphologic and physiologic changes that occur during pregnancy, as well as the pathophysiology and management of hypertension associated with pregnancy and peripartum cardiomyopathy. Treatment of pregnant patients who have congenital heart disease or artificial heart valves and of those who require anticoagulation during pregnancy is outlined. Detection and management of coronary artery disease and coronary dissection, as well as the use of a cardiopulmonary bypass during pregnancy, is reviewed. Avoidance of fetal risk factors during pregnancy, including toxic drinking water, is addressed, as are the potential cardiac dangers of the use of tocolytic therapy to retard uterine contraction. Finally, management of both supraventricular and ventricular tachycardia in pregnancy is reviewed.

NORMAL PHYSIOLOGIC AND MORPHOLOGIC CHANGES IN PREGNANCY

Striking adaptations occur in the maternal cardiovascular system in response to pregnancy. An appreciation of these changes is mandatory to allow appropriate treatment of pregnant patients who have cardiovascular disease. Relatively accurate noninvasive techniques for measurement of maternal physiologic changes, including echocardiographic evaluation of the heart structure and function and respiratory gas exchange assessment of functional status, have improved our understanding of these alterations.

In 1992, Hunter and Robson (1) summarized hemodynamic and structural changes in maternal subjects based on many years of echocardiographic studies performed in their laboratory. Longitudinal studies of cardiac output began before conception and continued into the postnatal period. Cardiac output increases as early as 5 weeks after the last menstrual period and rises to 45% above baseline at 24 weeks' gestation. Increased cardiac output is achieved by an increase in heart rate, which rises progressively until 32 weeks' gestation, and in stroke volume, which begins to increase by 8 weeks and peaks as early as 20 weeks (Fig. 32.1). Twin pregnancies result in an additional 15% rise in cardiac output in mothers. The cardiovascular system is taxed further by stage 1 of labor, which is associated with an additional 12% increase in demand for cardiac output. This demand increases to a mean of 34% above the already increased baseline value as labor progresses to its final stages (Fig. 32.2). After-delivery stroke volume decreases by 2 weeks postpartum, but a small further reduction occurs up to 6 months after delivery. Notably, the stroke volume remains at pregnancy levels for the first 2 days postpartum and then falls dramatically. Heart rate remains elevated for 2 days postpartum and returns to baseline by 10 days after delivery. Cardiac output similarly decreases from pregnancy levels to normal levels between 24 hours and 10 days postpartum.

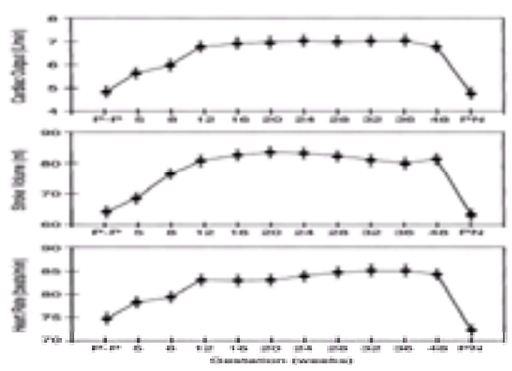


FIGURE 32.1 Serial echocardiographically determined changes in heart rate, stroke volume, and cardiac output during pregnancy and the early postpartum period. P-P, peripartum; PN, postnatal. (From Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992;68:540–543, with permission.)

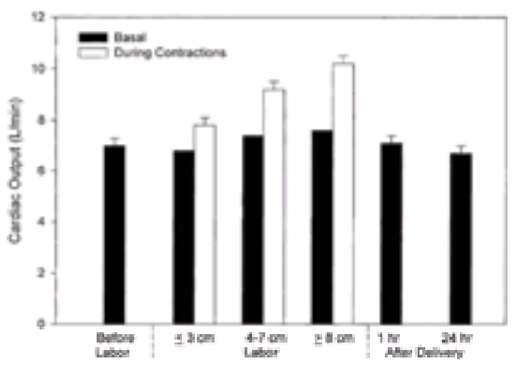


FIGURE 32.2 Normal labor-associated contractions increase cardiac output demands 12% to 34% above an already increased baseline cardiac output. (From Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. *Br Heart J* 1992;68:540–543, with permission.)

The magnitude of these echocardiographic changes was documented by Mabie and associates (2), who repeated echocardiograms monthly for 18 pregnant patients from 8 to 11 weeks' gestation to 6 to 12 weeks postpartum. Cardiac output, as measured by pulsed Doppler studies, increased from 6.7 L per minute to 8.7 L per minute by 36 to 39 weeks and fell to 5.7 L per minute 2 weeks postpartum. Increases in heart rate and stroke volume of 29% and 18%, respectively, were documented. Additionally, left ventricular mass increased in association with an increased thickness of the left ventricular wall, which was maximal at 24 to 27 weeks. Vered and colleagues (3), in a similar echocardiographic analysis of 15 patients, noted that left ventricular mass increased from 172 to 186 g in association with increased body weight.

The structural changes noted by echocardiography are secondary to the alterations in intravascular volume and neurohumoral stimulation that are associated with pregnancy. Hess and Hess (4) summarized the physiologic fluid changes associated with pregnancy. Plasma volume increases approximately 40% and red blood cell volume 30% above baseline prepregnancy levels, resulting in mild relative anemia. Estrogen-mediated stimulation of the renin angiotensin axis results in increased renal tubular absorption of sodium and an increase in total body salt and water, contributing to the increased plasma volume. Systemic vascular resistance and diastolic blood pressure decrease as a result of changes in aortic compliance and arterial venous shunting in the uterus.

The normal physiologic changes associated with pregnancy result in alterations in the physical examination of the pregnant patient (Table 32.1). It is important to understand findings that are physiologic so that pathologic changes can be distinguished. Because of the increase in total body salt and water, as well as plasma volume, the jugular veins are often full, and the central venous pressure may be slightly increased. Similarly, the pregnant patient may have 1 to 2+ lower-extremity edema. As pregnancy progresses, increased uterus size forces both diaphragms upward, which may decrease pulmonary vital capacity and total lung volume. These mechanical changes may increase the work required for breathing. The previously documented changes in left ventricular size and mass, which are associated with increased volume, result in a mildly displaced and diffuse point of maximal impulse of the left ventricle and increased atrioventricular and aortic as well as pulmonic valve closure sounds. Because of the insulation of the atrioventricular sounds by the abdomen, only the aortic and pulmonic closure sounds are characteristically louder on examination. Increased flow through the pulmonic valve causes a characteristic "functional" early systolic murmur and slight widening of the physiologic variation of closure of the pulmonic component of the second heart sound. Ventricular gallop rhythms and diastolic murmurs are unexpected and serve as clues to anatomic or functional cardiac abnormalities. Occasionally, a normal physiologic diastolic murmur can be heard at the left sternal border in pregnant patients. This physiologic murmur is usually generated by increased diastolic flow through the internal mammary artery, located in the peristernal area and engorged with increased flow to the breasts of pregnant patients. This mammary souffle may persist in lactating mothers, even after delivery. The expected decrease in aortic diastolic pressure during pregnancy that is associated with the decreased systemic vascular resistance results in a widened pulse pressure (systolic pressure minus diastolic pressure) and pulsatile fingertips, warm hands, and occasional Quincke's sign in the extremity nail beds. These findings are also suggestive of aortic regurgitation that may be confused by the diastolic murmur of the mammary souffle at the sternal border. Echocardiography may be required to distinguish the presence or absence of aortic

valve disease.

Mild jugular venous distention
1–2+ Lower-extremity edema
Decreased breath sounds at bases
Upward and leftward deviation of point of maximal impulse
Volume-loaded ventricle (active precordium)
Increased valve closure sounds
"Flow" murmurs (pulmonic and aortic)
Mammary souffle (left sternal border)
Wide pulse pressure
Increased heart rate

TABLE 32.1 PHYSICAL FINDINGS DURING NORMAL PREGNANCY

The physiologic changes associated with pregnancy may also alter the results of noninvasive evaluations of the heart (Table 32.2). The increase in size and left ventricular mass seen by echocardiography has already been described in detail. The electrocardiogram may also be altered. Upward movement of the diaphragm is expected to result in a leftward shift of the electrical axis of ventricular depolarization, and increased ventricular mass may result in increased ventricular voltage. Although changes are altered relative to the subject's baseline values, most changes are not outside the normal limits of variability. Heart rate may be increased, particularly late in pregnancy, and atrial as well as ventricular arrhythmias may increase in frequency in patients predisposed to such events. Chest radiographic studies, which are rarely performed because of radiation risk to mother and fetus, reveal a mild increase in cardiac size, a horizontal shift of the heart that increases with the duration of pregnancy, and fullness of the left cardiac border and pulmonary vascular supply (5).

Test	Change
Electrocardiography	Leftward axis deviation
	Increased ventricular voltage
	Increased rate
	Repolarization changes
Chest x-ray film	Upward diaphragm displacement
	Horizontal heart placement
	Enlarged pulmonary silhouette
Echocardiography	Increased left ventricular diastolic dimension
	Increased left ventricular wall thickness
	Mild increase in contractility

TABLE 32.2 CHANGES IN NONINVASIVE TEST RESULTS THAT OCCUR DURING PREGNANCY

Sophisticated measurements of the cardiovascular response to exercise are now possible, using measurement of respiratory gas exchange during exertion. Sady and coworkers (6) studied nine women at 25 weeks of pregnancy and again at 2 and 7 months postpartum. Their data revealed that the augmented cardiovascular response to exercise associated with pregnancy was reduced by 2 months postpartum but was not completely normal until 7 months after delivery. Lotgering and colleagues (7) studied 33 pregnant women at 16, 25, and 35 weeks of pregnancy as well as at 7 weeks postpartum and proved that pregnant women could exercise maximally without jeopardizing fetal health, and that previous estimates of maximal oxygen exercise capacity, using submaximal exercise values and estimating $\dot{V}O_2$max, were inaccurate. This inaccuracy is due to the altered slope of the relationship between maximal heart rate and percentage $\dot{V}O_2$max in pregnancy. The same investigators later demonstrated that the lower-than-expected peak exercise carbon dioxide production during pregnancy is likely caused by decreased buffering capacity of bicarbonate or increased use of lactic acid by the fetoplacental structures or pregnant liver (8). Wolfe and associates (9) conditioned 18 previously sedentary women during pregnancy with three 25-minute sessions per week, performed exercise stress tests at 17, 27, and 37 weeks' gestation and 20 weeks postpartum, and compared these results with those from a nonexercising control group of pregnant women. Exercise increased oxygen pulse by 17% at peak exercise in the third trimester, with a reduced respiratory exchange ratio. Moderate aerobic exercise during pregnancy is safe; it increases maximal aerobic power and the capacity for sustained submaximal exercise and preserves aerobic capacity in late gestation. Therefore, pregnancy need not limit exercise, and exercise may result in improved conditioning in the pregnant subject.

RADIATION AND PREGNANCY

X-rays produce direct and indirect damage to cells. Direct damage results from the effect of the high-energy radiation beam on cellular and molecular structure. Indirect damage is the result of ionized water and free radical generation. The strength and potential damage of x-rays are measured by the amount of ionic charge created per unit mass of air. One R (roentgen) creates more than 2 billion ion pairs per cm^3 of exposures to air. The absorbed dose of radiation is measured in rad, calculated by the energy imparted to tissue per unit mass of tissue. One rad is equivalent to the deposition of .01 J of energy per kg of tissue. One R of radiation usually produces 1 rad in tissue. Roentgen-equivalent-man (REM) is a measure of absorbed radiation modified by local tissue characteristics, which better delineate the risk of radiation damage to a given organ.

Radiation is harmful to all living tissue and particularly to the conceptus. Increasing radiation exposure is associated with a range of tissue defects, beginning with isolated cellular damage and progressing to growth impairment, structural deformity, neoplasia, and gonadal damage. Environmental radiation results in 50 to 100 mREM exposure during the 9 months of childbearing. The amount of radiation considered to be "safe" is unclear; however, virtually no data have demonstrated significant fetal damage after exposure to less than 1 rad (10).

Several features alter the amount of radiation exposure that occurs during radiologic procedures, including the nature of the radiation source, the equipment used, the size of the patient, the depth of the uterus and conceptus, and the distance from the area being investigated, as well as the extent of the radiologic study. The dose of radiation received by the uterus may vary by 50-fold, depending on these features and whether appropriate uterus shielding is performed.

The increased risk of development of a subsequent malignancy by children receiving radiation *in utero* was reported by the Childhood Cancer Research Group in 1956 and confirmed in 1975 (11). Bithell and Stewart (11) demonstrated a relative risk of 1.47 for the development of subsequent malignancy in children whose mothers underwent radiographs during pregnancy. Furthermore, the relative risk increased progressively from 1.26 for one film exposure to 2.32 for five or more x-rays, indicating a dose response. A first-trimester exposure resulted in a relative risk of malignancy of 8.95, falling to 1.25 and 1.41 in the second and third trimesters, respectively. The risk of childhood cancer from radiation exposure is displayed in *e*Table 32.2.1 (10).

***e*TABLE 32.2.1** PERCENTAGE LIKELIHOOD THAT CHILDHOOD CANCER WILL NOT DEVELOP AFTER PRENATAL IRRADIATION

Gestational age	None	1 rad	5 rad	10 rad
First trimester	99.93	99.75	99.12	98.25
Second and third trimesters	99.93	99.88	99.70	99.48

The risk of radiation must be evaluated relative to the benefit to the mother. It is imperative that the clinician define (a) the dose of radiation to the conceptus, (b) the age and development of the conceptus, (c) the radiation risk from the radiation source, (d) the risk associated with delaying or not performing the test, and (e) the potential for alternative means of answering the question with nonradiation studies.

Standard X-Ray

The estimated exposure to the uterus from standard radiologic examinations is shown in *e*Table 32.2.2 (12).

***e*TABLE 32.2.2** AVERAGE DOSE (MRAD) TO UTERUS BASED ON 1,000-MR EXPOSURE

	Beam quality half-value laser (MMA1)	
Exposed area, position	**1.5**	**4.0**
Chest		
PA	0.3	4.5
Lateral	0.1	1.8
Pelvis		
AP	142.0	486.0
Lateral	13.0	97.0
Thoracic spine		
AP	0.2	3.0
Lateral	0.04	0.8
Intravenous pyelogram or barium enema, AP	133.0	451.0
Renal angiogram, lateral	13.0	91.0

AP, anteroposterior; PA, posteroanterior.
From Rosenstein M. Organ doses in diagnostic radiology. US Department of Health, Education, and Welfare, May 1976, with permission.

Cardiac Catheterization

Using the same assumptions noted in this chapter, cardiac catheterization results in exposure of approximately 500 mrad to a shielded uterus, compared with an estimated exposure of 50 mrad for a standard chest x-ray (10). Obviously, the radiation exposure may vary depending on the complexity and duration of the examination. If cardiac catheterization is necessary, brachial as opposed to femoral arterial access should be used, and, where appropriate, noninvasive studies such as echocardiography, transesophageal echocardiography, and contrast echocardiography (13) should be used to define left and right ventricular performance and regurgitant valvular disease, to limit radiation exposure.

Right heart catheterization is occasionally used to monitor cardiac hemodynamics, particularly during delivery and immediately postpartum in patients who have advanced or unstable cardiac disease. This technique can almost always be accomplished without fluoroscopy at the patient's bedside, using an internal jugular approach. Only if the catheter cannot be advanced into the pulmonary artery or if significant atrial or ventricular ectopy occurs with attempted placement should fluoroscopy be used. If fluoroscopy is needed, very limited fluoroscopic visualization is usually necessary.

Computed Tomographic Scanning

Computed tomographic scanning uses circumferential radiation exposure, usually in 1-cm slices. The exposure of the uterus to radiation "leakage" distal to the areas of interest is small but may vary according to (a) the area scanned, (b) proximity of the area scanned to the uterus, (c) the number of images obtained, and (d) the type of machine used. The average skin exposure associated with computed tomographic scanning is 4 rad, with approximately 70% of skin dose still measurable in the midbody. It is estimated that uterine exposure is 1.6 to 4.0 rad and is usually less than 1 rad if examination is confined to the chest cavity.

Radionuclides

Radionuclides are radiation-emitting substances that are injected intravenously and used to image the blood pool or organs of interest. The degree of exposure is correlated with (a) the dose of radionuclide given, (b) the uptake of the radionuclide by organs, (c) the proximity of concentrating organs to the developing child, (d) the type of radiation (g- versus b-emitting), (e) the amount of placental transfer associated with the radionuclide agent, and (f) the length of time that the radionuclide remains in the mother. Several examples are listed in *e*Table 32.2.3 (10).

***e*TABLE 32.2.3** CONCEPTUS DOSE ESTIMATES FROM RADIONUCLIDE EXPOSURE

Radionuclide	Conceptus age (wk)	**Organ**	Dose per unit maternally administered activity (rad/mCi)
^{99m}Tc sodium pertechnetate	1.5–6.0	Whole	0.0027–0.048
^{99m}Tc polyphosphate	1.5–6.0	Whole	0.025
^{67}Ga citrate	1.5–6.0	Whole	0.25
^{131}I	1.5–6.0	Whole	0.1–3.0

^{67}Ga, gallium 67; ^{131}I, iodine 131; ^{99m}Tc, technetium 99m.
From Wegnerckileser RG, Saldana LR. *Exposure of the pregnant patient to diagnostic radiation: a guide to medical management.* Philadelphia: JB Lippincott, 1985, with permission.

Magnetic Resonance Imaging

Magnetic resonance imaging uses strong and weak magnetic fields and radiofrequency waves to image human tissue. This is a relatively new method, and no short- or long-term ill effects of this technology on the fetus or mother are clearly recognized. Until appropriately performed prospective trials are completed, use of the technique should be approached with caution. It is hoped that the lack of radiation exposure will make this technique widely applicable in the future.

It is evident that radiation should be avoided throughout pregnancy and particularly in the early months after conception. Occasionally, medical illness in the mother will mandate investigations using radiation, and it is important for the clinician to have an understanding of the radiation risk involved. The interested reader is referred to Wagner, Leser, and Saldana and their excellent book entitled *Exposure of the Pregnant Patient to Diagnostic Radiation: A Guide to Medical Management* (10).

HYPERTENSION DURING PREGNANCY

High blood pressure may complicate as many as 10% of all pregnancies and remains a major cause of maternal and fetal morbidity and mortality (14,15). In normal pregnancy, diastolic blood pressure falls, often by as much as 10 mm Hg in the first and second trimesters as a result of decreased systemic vascular resistance and increased cardiac output. Blood pressure then increases gradually at or near term and may transiently rise higher than nonpregnant values in the immediate puerperium. Rarely is high blood pressure in pregnancy the result of secondary causes such as intrinsic renal disease, endocrinopathies, or renal vascular obstruction. The currently accepted categories for high blood pressure in pregnancy are (a) chronic hypertension, (b) gestational hypertension, and (c) preeclampsia, with or without preexisting high blood pressure.

Chronic high blood pressure is categorized as preexistent hypertension or a blood pressure of at least 140/90 mm Hg before 20 weeks' gestation. If the diastolic blood pressure is 110 mm Hg or greater, severe hypertension is diagnosed. Pregnant women with a diastolic blood pressure higher than 75 mm Hg in the second trimester and 95 mm Hg in the third trimester should be observed carefully (16). The maternal and fetal outcomes are good unless preeclampsia or abruptio placentae complicates the final stages of gestation. Clear evidence exists (17) that treatment of blood pressure of greater than 110 mm Hg (diastolic) during pregnancy lowers the risk of stroke and cardiovascular complications, although the benefit of lowering blood pressure in mild chronic hypertension during pregnancy is less clearly defined.

Gestational hypertension is defined as asymptomatic blood pressure elevation after 20 weeks' gestation. Unless this elevation of pressure reflects early preeclampsia or unrecognized chronic hypertension, the maternal and fetal outcomes are usually very good, even without treatment.

Preeclampsia is the most feared hypertensive disorder of pregnancy and may lead to life-threatening eclampsia, a convulsive disorder. Preeclampsia is characterized by hypertension, proteinuria (levels greater than 300 mg in 24 hours), and edema but may include coagulopathy and altered liver function in pregnant patients after 20 weeks' gestation (Table 32.3). Preeclampsia may be mild or severe, depending on the degree of blood pressure elevation and proteinuria. In preeclampsia, plasma volume and cardiac output fail to rise, and systemic resistance does not fall. This appears to be related to failure of the uterine spiral arteries to develop, preventing the anticipated arteriovenous shunting. Some researchers believe the primary abnormality causing preeclampsia is the result of prostaglandin deficiency; endothelial cell dysfunction; or immune, genetic, or sodium/calcium membrane disorders. Schobel and colleagues (18) recently demonstrated that preeclampsia is associated with a dramatic increase in sympathetic nervous system activity. This conclusion was reached by evaluation of postganglionic sympathetic nerve activity in the blood vessels of skeletal muscles of preeclamptic patients, compared with those in pregnant and nonpregnant control subjects. Recently, investigators have demonstrated an increased level of platelet-activating factor (19) and plasma levels of prostaglandin isoforms (20) in preeclampsia subjects compared with levels in pregnant and nonpregnant control subjects. Dechend and coworkers (21) demonstrated angiotensin-1 receptor autoantibodies in preeclamptic patients and that these

immunoglobulins may cause vascular smooth muscle cells to express tissue factor that may be responsible for placental infarction (often associated with preeclampsia). These observations may have ramifications for treatment. The maternal risks of preeclampsia include cerebral hemorrhage, pulmonary edema, disseminated intravascular coagulopathy, liver failure, renal failure, convulsions, and death. These risks are correlated with the severity of the complications and level of gestation at the onset of the condition. The fetus may suffer hypoxemia, acidosis, growth retardation, and death.

Definition
Hypertension
Proteinuria
Edema
Coagulopathy
Liver dysfunction
After 20 wk gestation
Categories
Mild
Severe

TABLE 32.3 TYPICAL FINDINGS IN PATIENTS WITH PREECLAMPSIA

Mild preeclampsia may be managed at home; however, development of progressive symptoms such as headache, visual disturbances, and abdominal pain requires hospitalization (*e*Table 32.3.1). The use of antihypertensive or anticonvulsant therapy to treat mild preeclampsia remains questionable. Treatment of severe preeclampsia, on the other hand, may require termination of the pregnancy, regardless of fetal viability, if the mother's life is in jeopardy. Antihypertensive therapy should be initiated with hydralazine, labetalol, or nifedipine to lower mean blood pressure and diastolic blood pressure to 126 and 90 mm Hg, respectively. Because these patients are already volume-depleted, use of diuretics should be avoided. Intravenous magnesium should be given during labor and delivery and for 24 hours postpartum for patients who have severe preeclampsia to avoid convulsions.

***e*TABLE 32.3.1** OMINOUS SIGNS AND SYMPTOMS IN WOMEN WITH PREECLAMPSIA

Blood pressure ³ 160 mm Hg systolic or ³ 110 mm Hg diastolic
Proteinuria of new onset at a rate of ³ 2 g per 24 h or ³ 100 mg/dL in a randomly collected specimen
Increasing serum creatinine levels [especially >177 mmol/L (2 mg/dL) unless the level was known to be elevated previously]
Platelet count <10 × 10^9 cells/L or evidence of microangiopathic hemolytic anemia (e.g., schistocytes or increase in lactic acid dehydrogenase and direct bilirubin levels)
Upper abdominal pain, especially epigastric and right-upper-quadrant pain
Headache, vision disturbances, or other cerebral signs
Cardiac decompensation (e.g., pulmonary edema, usually associated with underlying heart disease or chronic hypertension)
Retinal hemorrhage, exudates, or papilledema (these signs are extremely rare in the absence of other indicators of severity and, when present, almost always indicate underlying chronic hypertension)
Fetal growth retardation

From Cunningham FG, Lindheimer MD. Hypertension in pregnancy. *N Engl J Med* 1992;326:927–932, with permission.

There is no known mechanism for avoidance of preeclampsia, although sodium chloride restriction, diuretics, low-dose aspirin, and increased dietary calcium have been attempted.

A variant of preeclampsia, the HELLP syndrome, is characterized by minimal or no elevation of blood pressure, mild decreases in platelet levels, hemolysis, mild liver function abnormalities, and absence of renal impairment at the onset (*e*Table 32.3.2) (15,17). This syndrome may progress rapidly, resulting in hemolysis, thrombocytopenia, and liver failure. Recognition of this syndrome prepartum should prompt immediate delivery. O'Brien and coworkers (22) have suggested that corticosteroids may be of some benefit in this unusual disorder; however, recommendation of corticosteroid therapy is dependent on the outcome of prospective randomized trials in affected patients. Both the HELLP syndrome and preeclampsia may occur up to 10 days postpartum.

***e*TABLE 32.3.2** CHARACTERISTICS OF THE HELLP SYNDROME[a]

Preeclampsia variant
Minimal blood pressure elevation
Low platelet count
Mild liver function abnormalities
Malignant potential

[a]The HELLP syndrome is a variant of preeclampsia with the same potential for deterioration.
HELLP, hemolysis, elevated liver function tests, and low platelets.

Preeclampsia, the most devastating form of hypertension to affect the pregnant patient, has a unique pathophysiology and requires prompt and appropriate management for avoidance of serious complications to the mother and fetus. Use of antihypertension agents in pregnant women requires special consideration of the effect on the fetus and the uteroplacental unit, as well as on the mother. Cardiologists will likely increasingly be called on to assist in the management of this condition in a usually older, multigravida population.

TREATMENT OF HYPERTENSION DURING PREGNANCY

Medications commonly used to treat chronic, gestational, and preeclamptic hypertension are listed in Table 32.4 and Table 32.5. Appropriate medical management of pregnancy-related hypertension depends on an understanding of the pathophysiology outlined in the previous sections. Some changes are unique to alterations in kidney handling of sodium and water.

Regulation of blood pressure
The degree to which blood pressure should be decreased is disputed; we recommend maintaining diastolic levels between 90 and 110 mm Hg.
Drug therapy
Hydralazine administered intravenously is the drug of choice. Start with low doses (5 mg as an intravenous bolus), then administer 5 to 10 mg every 20 to 30 min to avoid precipitous decreases in pressure. Side effects include tachycardia and headache.
Diazoxide is recommended for women whose hypertension is refractory to hydralazine. Use 30-mg minibolusses, because precipitous hypotension may result if higher doses are used. Side effects include arrest of labor and neonatal hypoglycemia.
The experience with labetalol is growing, and some physicians use this agent, instead of diazoxide, as a second-line drug.
Favorable results have been reported with calcium channel blockers. If magnesium sulfate is being infused, magnesium may potentiate the effects of calcium channel blockers, resulting in precipitous and severe hypotension.
Refrain from using sodium nitroprusside, because fetal cyanide poisoning has been reported in animals. However, maternal well-being should dictate the choice of therapy.
Prevention of convulsions
Parenteral magnesium sulfate is the drug of choice for preventing eclamptic convulsions. Therapy should be continued for 12 to 24 h postpartum, because one-third of women with eclampsia have convulsions during this period.

From Cunningham FG, Lindheimer MD. Hypertension in pregnancy. *N Engl J Med* 1992;326:927–932, with permission.

TABLE 32.4 GUIDELINES FOR TREATING SEVERE HYPERTENSION NEAR TERM OR DURING LABOR

TABLE 32.5 ANTIHYPERTENSIVE DRUGS USED TO TREAT CHRONIC HYPERTENSION IN PREGNANT WOMEN

The mean increase in total body water and sodium during pregnancy is 6 to 8 L and 500 to 900 mEq, respectively, approximately one-half of which is extracellular (23). Many factors alter sodium excretion in pregnancy, of which a 50% increase in the glomerular filtration rate and elevated levels of progesterone and aldosterone are most important. The result is that more than 80% of all healthy pregnant women develop physiologic-dependent or generalized edema.

Edema may be a normal physiologic response; hypertension and preeclampsia are not. Hypertension in pregnancy is associated with increased rates of preterm delivery, perinatal mortality, and probably small-for-date babies and fetal neurologic impairment (16). Preeclampsia is a vascular abnormality, and the earliest manifestation, which occurs well before other manifestations of disease, can be demonstrated as an abnormal pressor response to infused angiotensin. Despite the increase in interstitial volume that occurs with preeclampsia, the intervascular volume is reduced, and oliguria and hemoconcentration are typically present. There is no evidence that sodium restriction or diuretics prevent preeclampsia or other hypertensive complications of pregnancy, and use of such agents may cause additional volume contraction, alkalosis, electrolyte abnormalities, pancreatitis, and bleeding or hyponatremia in the neonate (16,23). Use of diuretics in women with preeclampsia should be avoided, and these agents are of limited benefit for treatment of pregnancy-related hypertension. Patients who have taken diuretics chronically before pregnancy or who are extremely sensitive to salt may derive some benefit from them (23).

Among agents used to treat chronic hypertension in pregnancy, Aldomet (methyldopa) is safe and preferable to other drugs. Randomized trials have demonstrated that Aldomet improves fetal survival significantly, and it is the only drug with long-term follow-up (7.5 years), in which no difference in health, physical, or intellectual outcomes was seen between patients who received treatment with this agent and those who did not (24,25). The use of beta-receptor–blocking agents, including oxprenolol, atenolol, and acebutolol, during pregnancy has been studied. Growth retardation, acute fetal distress, high perinatal mortality, and hypoglycemia, all early concerns, have been found to be nearly nonexistent in controlled trials, and use of these agents is now considered nearly as safe as administration of Aldomet (25,26). Type II calcium channel blockers, including nifedipine, nicardipine, and nitrindipine, are potent vasodilators and have been used to treat hypertension during pregnancy. Nifedipine may induce a rapid fall in blood pressure if given in high dose or sublingually, which may result in reflex tachycardia. Uterine blood flow is minimally affected by nitrindipine and nifedipine, and the drug may decrease uterine contractions as a result of its smooth muscle relaxant properties; therefore, it may serve as a successful tocolytic agent (27).

Angiotensin-converting enzyme (ACE) inhibitors are currently the agents of choice for use in nonpregnant patients who have cardiomyopathy or congestive heart failure and after myocardial infarction, but this class of antihypertensive drugs should *never* be used during pregnancy. Animal and human studies have demonstrated a high degree of morbidity and mortality in infants exposed to ACE inhibitors during pregnancy (28). Complications include growth retardation, renal failure, bone malformations, oligohydramnios, patent ductus arteriosis, pulmonary hypoplasia, respiratory distress syndrome, and neonatal death. The U.S. Food and Drug Administration has issued a warning against the use of ACE inhibitors during pregnancy after the first trimester (29). Most authorities favor avoiding these agents even in patients who are merely contemplating pregnancy.

Preeclampsia requires prompt control of accelerated hypertension. Because of its long history of use for preeclampsia, hydralazine remains the drug of choice for most physicians. The drug can be given intravenously, intramuscularly, or orally and titrated to achieve maximal effect (16). Labetalol combines alpha- and beta-blocking properties, can be given intravenously, and incurs a prompt response. Nifedipine has been used sublingually and, when compared with hydralazine in a small, controlled trial, resulted in improved blood pressure control (27). Type II calcium channel blockers are tocolytic, which may be advantageous for treatment of patients who have premature contractions but deleterious for patients in whom delivery should be hastened. Nitroprusside probably should be avoided because of the potential for thiocyanate accumulation. Magnesium sulfate has been demonstrated to be beneficial during preeclampsia and for up to 24 hours after delivery.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy, a relatively infrequent dilated cardiomyopathy that occurs in women of reproductive age, is defined as “a disorder of heart muscle, which presents clinically with the onset of heart failure in the last month of pregnancy or the first 5 postpartum months” (30,31). Established diagnostic criteria include (a) absence of a determinable cause for cardiac failure, (b) absence of preexisting heart muscle disease, and (c) time limitations of onset of illness. Other causes of congestive heart failure in pregnancy should be ruled out, including congenital, valvular, infectious, metabolic, and toxic etiologies, as well as preeclampsia and pulmonary emboli, which may complicate late pregnancy and delivery. Some recent literature on this topic is tainted by the inclusion of patients who were in the last trimester of gestation rather than the final month. This expansion of the definition encompasses the response of patients with preexistent heart disease to the volume load imposed by pregnancy, which clouds the clinical observations about this unique disorder. Such patients should be excluded.

Peripartum cardiomyopathy complicates 1 in 1,300 to 1 in 4,000 deliveries in the United States (32,33). This condition may affect women of any race, age, or number of prior deliveries; however, pregnancies in older age, multigravida pregnancies, African-American race, and twin pregnancies are thought to represent predisposing features (Fig. 32.3).

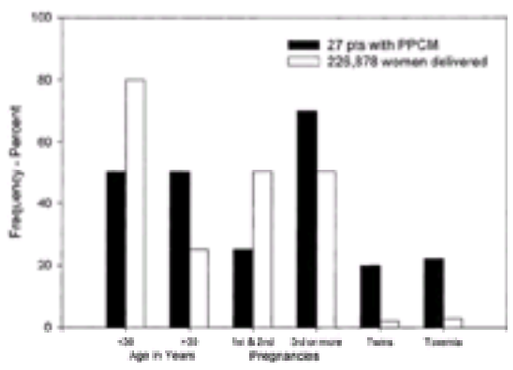


FIGURE 32.3 Risk factors for the development of peripartum cardiomyopathy (PPCM). pts, patients. (From Demakis JG, Rahimtoola SH. Peripartum cardiomyopathy. *Circulation* 1971;44:964–968, with permission.)

The etiology of peripartum cardiomyopathy is unknown (*e*Table 32.5.1). Melvin and associates (34) in 1982 demonstrated myocarditis by endomyocardial biopsy in three of three patients presenting with peripartum cardiomyopathy. All three patients were treated with immunosuppressive therapy, and ventricular function improved in all three. Sanderson and associates (35) performed biopsies on 11 African women with peripartum cardiomyopathy in Nairobi and found healing myocarditis in five. Four patients with myocarditis during follow-up failed to improve, and no immunosuppressive treatment was given. O’Connell and coworkers (36) evaluated 14 consecutive patients with peripartum cardiomyopathy using endomyocardial biopsy, which revealed myocarditis in four (29%); all patients in whom the diagnosis of myocarditis was made underwent biopsy within 1 week of the onset of symptoms. Two of the four patients with myocarditis died, the condition of one stabilized, and the condition of one improved; none was treated with immunosuppressive therapy. Eight of these 14 patients presented before delivery, and these authors extended the window for diagnosis of peripartum cardiomyopathy to the last trimester of pregnancy, rather than to the last month, making their data difficult to interpret.

***e*TABLE 32.5.1** STUDIES OF PERIPARTUM CARDIOMYOPATHY MYOCARDITIS

Reference	Incidence	Immunosuppression	Outcome
Melvin et al. (34)	3/3	Yes	3/3 improved
Sanderson et al. (35)	5/11	No	3/4 experienced congestive heart failure
O'Connell et al. (36)	4/14	No	3/4 experienced congestive heart failure
Midei et al. (37)	14/18	Yes/no	13/14 improved

Midei and coauthors (37) at The Johns Hopkins Hospital reported that 14 (78%) of 18 consecutive patients with peripartum cardiomyopathy had myocarditis found on endomyocardial biopsy. Felker and colleagues (38) expanded their study to include 42 women with peripartum cardiomyopathy who underwent biopsy. Despite a delay in biopsy of 1 to 2 weeks after presentation, the incidence of myocarditis remained high (62%). Additionally, the Johns Hopkins group demonstrated that the prognosis for mothers with peripartum cardiomyopathy is good relative to patients with idiopathic dilated cardiomyopathy (39) (Fig. 32.4). Of 42 patients included in that study, only three died (7%), and three underwent orthotopic heart transplantation (7%) (38). Ventricular function improved in most patients. In our experience, patients presenting early after delivery had more profound congestive heart failure and dramatic myocarditis found by endomyocardial biopsy, but they also had a greater chance of spontaneous resolution, even if they did not receive immunosuppressive therapy. These studies suggest that peripartum cardiomyopathy is immunologic in origin. Whether the inciting agent is an inapparent viral infection or an aberrant immunologic response to a placental or fetal antigen is unknown. As is true of the other cardiomyopathies that present with heart failure, patients with peripartum cardiomyopathy display elevated levels of tumor necrosis factor-a, interleukins, and apoptosis-signaling receptors (40).

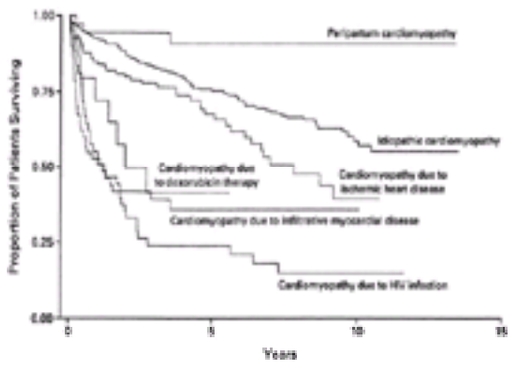


FIGURE 32.4 Adjusted Kaplan-Meier estimates of survival, according to the underlying cause of cardiomyopathy. Only idiopathic cardiomyopathy and cardiomyopathy resulting from causes for which survival was significantly different from that among patients with idiopathic cardiomyopathy are shown. HIV, human immunodeficiency virus. (From Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;342:1077–1084, with permission.)

Patients who have peripartum cardiomyopathy typically present with heart failure, which in our experience has been more profound near the time of delivery and more subtle in presentation when it occurs months later. Approximately 80% of patients present within the first 3 months postpartum (Fig. 32.5). Symptoms of heart failure may be particularly difficult to diagnose for patients in the last month of pregnancy and very early postpartum, when dyspnea, edema, and fatigue may be the result of normal pregnancy and delivery. The physical findings of congestive heart failure are manifest, including jugular venous distention, rales, hepatic congestion, and edema. Patients presenting early may not have cardiomegaly, and the point of maximal impulse is frequently superiorly placed, in our experience.

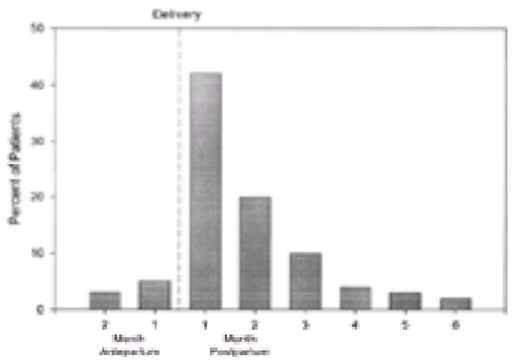
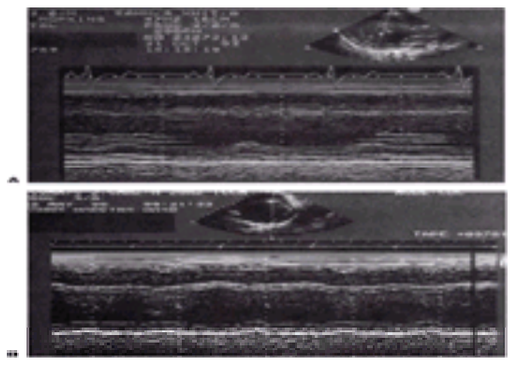


FIGURE 32.5 Peripartum cardiomyopathy. Most patients present with peripartum cardiomyopathy within 2 months of delivery. By definition, those presenting earlier than the last month of pregnancy do not have peripartum cardiomyopathy. (From Homans DC. Current concepts: peripartum cardiomyopathy. *N Engl J Med* 1985;312:1432–1437, with permission.)

The chest x-ray confirms the presence of pulmonary congestion and usually cardiomegaly. Echocardiography, which is mandatory in the evaluation of these patients, demonstrates markedly decreased contractility with variable degrees of cardiac enlargement (eFig. 32.5.1). The results of electrocardiography are almost always abnormal and show nonspecific ST-T–wave changes. Right heart catheterization (if performed) reveals high filling pressures and decreased cardiac output that are compatible with cardiomyopathy. Only if the patient has multiple risk factors for coronary artery disease or is suspected of having a coronary dissection should coronary angiography be performed.



***e*FIGURE 32.5.1** Echocardiographic appearance of peripartum cardiomyopathy. **A:** Nondilated. Often, in the acute setting, patients present with severe heart failure and nondilated, thickened left ventricles with severe hypofunction. The diastolic dimension of the left ventricle is 5.2 cm, and the systolic dimension 4.8 cm. Left ventricle thickness is 1.5 cm. **B:** Dilated. More traditionally, the left ventricle is modestly dilated, thin walled, and hypofunctional. The diastolic dimension is 6.0 cm, systolic dimension is 4.8 cm, and wall thickness is 1.1 cm.

We do not perform endomyocardial biopsy or right heart catheterization on patients with peripartum cardiomyopathy unless they fail to show improvement in signs and symptoms of congestive heart failure and in echocardiographic ventricular function after 2 weeks of standard management therapy for congestive heart failure. Although endomyocardial biopsy can define the presence and severity of myocarditis in patients who have peripartum cardiomyopathy, it is unclear that this offers any therapeutic advantage, because immunosuppressive therapy is likely ineffective in influencing long-term left ventricular function (K. L. Baughman, *unpublished data*).

Standard management of heart failure should be applied to these patients postpartum, with careful attention to the potential influence of drugs on the uterus and, for patients in the last month of pregnancy, the fetus. Standard treatment includes afterload reduction therapy, diuresis, administration of digoxin (if signs or symptoms of

congestive heart failure persist despite preload and afterload reduction therapy), and anticoagulation therapy (if ventricular compromise persists).

In Demackus and coworkers' initial series (30,31), two groups of patient outcomes were categorized. Approximately one-half of the affected patients recovered normal heart size, and one-half still had cardiomegaly at 6 months' follow-up. Patients with persistent cardiomegaly had the same poor prognosis as patients with dilated cardiomyopathy; 80% died, with an average survival of 4.7 years after presentation. Of patients whose hearts returned to normal size, 14% died, none from cardiovascular disease. This pattern of survival has persisted in all subsequent studies, and, until recently, the prognosis for such patients was poor. Earlier recognition of peripartum cardiomyopathy due to the availability of echocardiography, more sophisticated standard therapy for congestive heart failure, and referral for full cardiac evaluation for patients who fail to respond to early heart failure management have likely improved the prognosis. Cole and associates (41) reported the echocardiographic evolution of peripartum cardiomyopathy compared with peripartum control subjects in 14 patients who presented with this entity. The left ventricular end diastolic volume index was 95 versus 67 mL per m^2, respectively; the end systolic volume index was 66 versus 27 mL per m^2, respectively; and left ventricular wall mass was 139 versus 96 g per m^2, with an ejection fraction of 29% versus 67%, respectively. Despite these findings, 13 of 14 patients improved early and rapidly with standard therapy, despite the fact that none of the five who underwent to endomyocardial biopsy had histologic myocarditis.

We routinely follow patients closely after presentation with peripartum cardiomyopathy. Most patients require hospitalization on presentation because of the severity of congestive heart failure symptoms. Appropriate therapy is administered until the patient's condition is stabilized. This can usually be accomplished with standard medical therapy, but occasionally extraordinary therapy is needed, including intraaortic balloon counterpulsation or use of a left ventricular assist device. Because the degree of reversibility of left ventricular dysfunction associated with peripartum cardiomyopathy is high, and because the patients are young, all means necessary should be applied to ensure the mother's survival. Once discharged from the hospital, patients are followed every 2 weeks with clinical evaluation and an echocardiogram until left ventricular function is stabilized and no longer improving. Echocardiograms are repeated at 3 months and 6 months postpartum. The ventricular function at 6 months will likely be the ventricular performance that the patient maintains. Vigorous activity and nursing are discouraged during this interval to avoid left ventricular stress, which might alter ventricular remodeling during recovery. No other noninvasive tests are helpful in follow-up, in our experience.

Recurrent pregnancies in patients who have experiences peripartum cardiomyopathy remain problematic. Demakis and Rahimtoola (31) reported that in 14 patients whose hearts returned to normal, eight patients attempted 21 subsequent pregnancies. Of these eight patients, three experienced transient cardiac decompensation responsive to heart failure management. Of the 13 patients whose hearts failed to recover, six attempted repeat pregnancy with three experiencing deterioration and death. Through a survey mechanism, Elkayam et al. (42) identified 44 patients who attempted 60 subsequent pregnancies after documented peripartum cardiomyopathy. Patients presenting in the last trimester—as opposed to the last month of pregnancy—were included. Of the 28 patients who normalized ventricular function at rest, there was a significant decrease in ejection fraction (from 56% to 49%), whereas 21% experienced congestive heart failure with subsequent pregnancies. Of the 16 patients with abnormal resting ventricular function, ejection fraction decreased (from 36% to 32%), and 44% developed symptomatic congestive heart failure with repeat pregnancy. Mortality was not noted in those with normalized ventricular function but was 19% in those with persistent dysfunction. Lampert (42a) studied ventricular reserve in patients with peripartum cardiomyopathy who normalized ventricular function. Ten patients were evaluated approximately 9 months after ventricular recovery from peripartum cardiomyopathy. These authors used an echocardiographic load and heart rate–independent mechanism to assess ventricular contractility and reserve in response to methoxamine and dobutamine infusion. Contractile reserve, even in patients with ventricular recovery, was impaired.

There are, therefore, three categories of patients after peripartum cardiomyopathy: those with persistent abnormal cardiac function, those with normal resting but abnormal cardiac reserve with stress, and those with normal resting and stress ventricular performance. For patients who do not recover left ventricular function, standard long-term management for congestive heart failure should be undertaken. For those whose congestive heart failure is unresponsive to treatment, cardiac transplantation can be done (42a,44) with a favorable long-term survival and morbidity comparable to that in age-matched control subjects. For patients with normal resting but abnormal stress ventricular response, pregnancy can be undertaken; however, cardiac decompensation may occur. Fortunately, this decompensation is usually responsive to medical management, and maternal mortality is not expected. In patients with normal resting and stress ventricular response after peripartum cardiomyopathy, repeat pregnancy can be undertaken with less risk of decompensation.

For patients who do not recover left ventricular function, standard long-term management for congestive heart failure should be undertaken. Cardiac transplantation can be done (43,44) for those whose congestive heart failure is unresponsive to treatment, with a favorable long-term survival and morbidity comparable to that in age-matched control subjects.

TRANSPLANTATION

The transplanted heart is denervated and may have limitations in ventricular dilatation, making the hemodynamic burden of pregnancy more difficult to manage (45). Cardiac transplant patients are usually hypertensive and hypercholesterolemic, and they face the potential that accelerated atherosclerosis will develop in the transplanted heart's coronary arteries, increasing the risk of cardiovascular compromise. Pregnancy may interrupt routine surveillance endomyocardial biopsy procedures because of the risk of fetal radiation exposure, thereby limiting the transplant cardiologist's ability to diagnose and treat rejection successfully before hemodynamic compromise develops. Immunosuppressive agents pose a potential risk to the fetus of genetic alterations and to the mother's renal function (cyclosporine) and bone, skin, and adrenal integrity (prednisone). Scott and colleagues (46) reviewed the literature and the University of Utah experience and polled other cardiac transplant centers to gather the experience of 30 posttransplant patients who became pregnant. Overall, 48% had chronic hypertension, 24% had preeclampsia, and 28% had preterm labor. Six episodes of rejection required increased immunosuppressive therapy, and nine required increased cyclosporine dosage to maintain therapeutic levels. Of 27 live births, ten infants were preterm (less than 36 weeks), five infants were small for gestational age, and four infants had neonatal complications. No congenital abnormalities were reported. Data from the National Transplantation Pregnancy Registry compiled by Branch and coworkers (47) confirmed a high incidence of premature and low-birth-weight infants born to 35 transplant recipients with 47 pregnancies. The risks appear to be similar in heart-lung transplant recipients (48). Pregnancy in cardiac transplant recipients must be considered high risk for mother and fetus and is discouraged.

BACTERIAL ENDOCARDITIS PROPHYLAXIS

Vaginal delivery in the presence of infection is thought to increase the risk of bacterial endocarditis in patients who have (a) prosthetic valves; (b) previous bacterial endocarditis, even without organic heart disease; (c) most congenital abnormalities; (d) rheumatic and other acquired valvular abnormalities, even after repair; (e) hypertrophic cardiomyopathy; and (f) mitral valve prolapse with valvular regurgitation. Insufficient data exist that describe the risk of bacterial endocarditis after cardiac transplantation; however, most clinicians favor treatment with antibiotics. No adequate controlled trials have been performed that examine the use of antibiotic regimens for the prevention of bacterial endocarditis in humans, and recommendations are based on animal models and *in vitro* studies (49).The regimens proposed are outlined in *e*Table 32.5.2.

***e*TABLE 32.5.2** DRUG REGIMENS FOR GENITOURINARY AND GASTROINTESTINAL PROCEDURES

Drug	Dosage regimen
Standard regimen	
Ampicillin, gentamicin, and amoxicillin	Intravenous or intramuscular administration of ampicillin, 2.0 g, plus gentamicin, 1.5 mg/kg (not to exceed 80 mg), 30 min before procedure; followed by amoxicillin, 1.5 g, orally 6 h after initial dose; alternatively, the parenteral regimen may be repeated once 8 h after initial dose
Regimen for patients allergic to ampicillin, amoxicillin, and penicillin	
Vancomycin and gentamicin	Intravenous administration of vancomycin, 1.0 g, over the course of 1 h plus intravenous or intramuscular administration of gentamicin, 1.5 mg/kg (not to exceed 80 mg), 1 h before procedure; may be repeated once 8 h after initial dose
Alternate low-risk patient regimen	
Amoxicillin	3.0 g orally 1 h before procedure; then 1.5 g 6 h after initial dose

Note: Initial pediatric doses are as follows: ampicillin, 50 mg/kg; amoxicillin, 50 mg/kg; gentamicin, 2.0 mg/kg; and vancomycin, 20 mg/kg. Follow-up doses should be one-half the initial dose. Total pediatric dose should not exceed total adult dose.

From Dajani AS, Bisno AL, Chung JK, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1990;264:2919–2922, with permission.

ANTICOAGULATION AND PREGNANCY

Occasionally, pregnant patients require systemic anticoagulation for prophylaxis and treatment of venous or arterial thromboembolic disease or because of the presence of an artificial heart valve. Systemic anticoagulation exposes the mother and fetus to significant risks. Both heparin and warfarin may cause *in utero*placental bleeding, resulting in spontaneous abortion. Long-term systemic heparinization may cause osteoporosis. Heparin does not cross the placental barrier and has no effect on the fetus. Warfarin, on the other hand, does cross the placental membrane and causes fetal anticoagulation. More important, administration of warfarin during the first trimester may cause an embryopathy, and exposure at any time in gestation may cause central nervous system abnormalities in the fetus. Weeks 6 to 12 of gestation appear to be the critical time interval for embryopathy caused by warfarin exposure, resulting in nasal hypoplasia or stippled epiphysis. Central nervous system abnormalities caused by warfarin exposure include hemorrhage and dorsal or ventral midline dysplasia. Data concerning low-molecular-weight heparin are limited. Ellison and coauthors (50) reported a retrospective series of 57 pregnancies in 50 women and found a low incidence of complications with use of 40 mg of

low-molecular-weight heparin once per day. Satisfactory antifactor X_a levels and prevention of thromboembolism were achieved (50).

Systemic heparinization during pregnancy traditionally has been thought to result in high risk to the fetus and mother. Ginsberg and Hirsh (51) reviewed the published literature in 1989 and reported a summary of 106 studies that evaluated 1,325 pregnancies in women who were receiving anticoagulation therapy. After excluding comorbid conditions, the risk of maternal death was 2.5% (7 of 278 patients) for women receiving heparin and 16.8% (95 of 567 patients) for patients treated with oral anticoagulants. These authors and colleagues (52) also carried out a prospective study of 77 women with 100 pregnancies, among whom heparin was given for prevention or treatment of venous thromboembolism in 98 pregnancies and because of a prosthetic valve replacement in two. The rates of prematurity, abortion, stillbirths, neonatal deaths, and congenital abnormalities are similar to those in normal populations. In addition, no symptomatic thromboembolisms and only two episodes of bleeding were seen after a mean of 18 weeks of treatment per pregnancy. As noted, few of these authors' patients received anticoagulation therapy for valvular disease or prosthesis. Osteoporosis is a potential complication of heparin therapy. Barbour and associates (53) performed a prospective study of heparin use in pregnant patients, using bone densitometry to evaluate osteoporosis. Of the 14 pregnant patients given heparin, 36% experienced a greater than 10% decrease in femur bone density measurements from baseline to immediately postpartum, compared with none of 14 pregnant control subjects who were not receiving heparin. The difference in bone density remained statistically significant at 6 months postpartum. These data confirm that one-third of pregnant patients treated with prolonged heparin are likely to develop osteoporosis, even at doses as low as 15,000 units per day. Additionally, patients rarely may develop heparin-associated antibodies during pregnancy, resulting in thrombosis and thrombocytopenia (54).

In their literature review, Ginsberg and Hirsh (51) reported warfarin embryopathy in 45 of 970 exposed fetuses and central nervous system abnormalities in 26 of 970 patients. Of 22 cases of heparin osteoporosis that have been reported, seven have occurred in pregnant patients. Development of osteoporosis may be related to total exposure and has been reported in patients receiving 15,000 to 20,000 units daily for more than 6 months.

Based on these data, most authors recommend systemic heparinization during the critical weeks 6 to 12 of gestation and in the last 2 weeks of pregnancy to allow rapid reversal for delivery. A dosage of 10,000 units twice per day subcutaneously is the recommended treatment. Activated partial thromboplastin time should be measured 6 hours after administration of heparin and should be 1.5 to 2.0 times control. Warfarin can be administered during the remainder of gestation with little risk of embryopathy.

PREGNANCY IN WOMEN WITH VALVE PROSTHESES

Cardiologists are often asked to evaluate and manage the condition of patients with prosthetic heart valves during pregnancy or to advise young women on the selection of an appropriate artificial valve, designed to maximize the potential for a future successful and uncomplicated pregnancy. However, limited data are available to assist in these tasks (*e*Table 32.5.3).

***e*TABLE 32.5.3** STUDIES OF THE USE OF VALVE PROSTHESES IN PREGNANT uwomen

				Thromboembolic complications, %		
Reference	Type of prosthesis	Pregnancies, no.	Live births, %	Valve thrombi	Emboli	Valve degeneration, %
Hanania et al. (55)	Mechanical	95	53	11	9	0
Sbarouni et al. (56)	Mechanical	151	73	9	5	0
Born et al. (57)	Mechanical	35	63	8	3	0
Hanania et al. (55)	Bioprosthesis	60	80	0	0	18
Sbarouni et al. (56)	Bioprosthesis	63	83	0	0	35
Born et al. (57)	Bioprosthesis	25	100	0	5	16

Note: Valve-related risk factors during pregnancy. Both thromboembolic and valve degeneration problems may appear.

Hanania and associates (55) reported a French cooperative study involving 155 pregnancies in 103 women with 182 prosthetic heart valves. Of the 108 pregnant patients with mechanical prostheses, thromboembolic events occurred in 16 patients (14.8%), and 12 of the 16 patients were undergoing subcutaneous heparin treatment. The thromboembolic risk was higher for patients who had undergone mechanical mitral valve replacement (21%) than for those who had undergone mechanical aortic (4.5%) valve replacement. Of the 16 patients who experienced thromboembolic complications, ten were associated with mechanical valves, again affecting mitral (11%) more frequently than aortic (4.5%) prostheses. Four patients with valve thrombosis died, three required cardiovascular surgery, and the remainder were treated with fibrinolytic therapy or heparin. Only 53% of patients with mechanical prostheses delivered healthy fetuses. Eighty percent of patients with bioprostheses had normal deliveries, and the birth weight was significantly higher than in the mechanical prosthesis group. However, 16.7% (13 of 74) of bioprosthesis valves degenerated during pregnancy, an average of 5.9 years (2.5 to 8.0 years) from the time of initial implantation. The risk of premature valve failure attributed to pregnancy was estimated to be 5%. These authors recommended systemic warfarinization, except during the final 2 weeks of pregnancy and during weeks 6 to 12 of gestation, when heparin therapy was thought to be advantageous, to avoid warfarin embryopathy.

Sbarouni and Oakley (56) reported on the outcome of 214 pregnancies in 178 women with prosthetic heart valves who were seen in major European centers. Of these patients, 133 women with mechanical valves sustained 151 pregnancies, and 45 women with bioprostheses had 63 pregnancies. Only 17% of the patients with bioprostheses were receiving anticoagulation therapy, as opposed to all but one patient with mechanical prostheses (one patient with an aortic valve refused anticoagulation therapy). Including spontaneous and therapeutic abortions, 73% of pregnancies in patients with mechanical prostheses and 83% of pregnancies in patients with bioprostheses resulted in healthy babies, born either at full term or prematurely, who ultimately did well. Between the mechanical prostheses and bioprostheses groups, stillbirths (7% vs. 4%) and spontaneous abortions (12% vs. 10%) did not differ significantly. One woman refused anticoagulation therapy and experienced an aortic valve thrombosis. Five additional maternal deaths occurred in the mechanical prosthesis group; four were related to valve thrombosis, and one was related to a fatal cardiovascular embolism. Nine other pregnancies in women with mechanical prostheses were complicated by nonfatal valve thrombosis; five patients required emergency valve replacement, and the conditions of four patients were managed medically. Notably, 10 of the 13 patients with valve thromboses were receiving heparin for systemic anticoagulation, two were receiving warfarin, and one received no anticoagulation therapy. Additionally, 12 of 13 thrombosed valves were in the mitral position. Of seven patients who had major bleeding complications (defined as complications requiring two units of blood for transfusion), five patients were being treated with heparin. In total, complications occurred in 48% of the 34 pregnancies in 29 women who were treated with heparin anticoagulation therapy: valve thrombosis occurred in 24%, bleeding in 12%, and systemic embolic events in 12%. Of the 49 bioprosthetic valves, 17 (35%) deteriorated markedly during or shortly after pregnancy, requiring two emergency valve replacements during pregnancy and 13 electively after delivery. These authors speculated that the increased calcium turnover associated with pregnancy may accelerate bioprosthesis deterioration and wrote that "because of accelerated valve degeneration and the need for early re-operation, bioprostheses should not be recommended to young women who intend to become pregnant" (56).

The outcome of pregnancy in the European study was best for mothers who had prosthetic heart valves and were given heparin for the first trimester, followed by warfarin until delivery. Because pregnancy is a hypercoagulable state, and because of the frequent thrombotic complications of heparin, its use cannot be recommended throughout pregnancy.

Born and associates (57) reported a Brazilian study involving 60 consecutive pregnancies in 49 patients with prosthetic heart valves who were prospectively evaluated. These authors confirm the high risk of valve thrombosis (3 of 35 patients) and cerebral embolism (1 of 35 patients) among patients who have mechanical prostheses and the increased risk of valve degeneration (4 of 25 patients) among those with bioprostheses. In total, four women with artificial heart prostheses died during gestation. Additionally, these authors emphasized the increased incidence of low birth weight and prematurity in infants of mothers receiving warfarin anticoagulation. Mothers with class III or IV congestive heart failure at the time of pregnancy had a 16% rate of spontaneous abortion, 22% rate of prematurity, and 28% risk of bearing low-birth-weight infants. Five of 45 neonatal deaths and four of 45 birth defects occurred in this group of patients. These data clearly demonstrate the fetal and neonatal risks of attempted pregnancy in mothers who have poorly controlled congestive heart failure and valvular prostheses.

Chan and coworkers (58) performed a literature review that compared the use of oral anticoagulation therapy throughout pregnancy, the use of oral anticoagulation therapy throughout pregnancy with the exception of administration of heparin in the first trimester (weeks 6 to 12), and administration of heparin throughout the pregnancy in patients with heart valve replacements. Oral anticoagulation resulted in an embryopathy incidence of 6.4% but the lowest risk of valve thrombosis (3.9%). Heparin administration eliminated the risk of embryopathy but increased the risk of valve thrombosis to 9.2%. The risk of fetal wastage was similar with all approaches, and overall maternal mortality was 2.9%. Use of low-molecular-weight heparin has been limited but does not, even in this small experience, protect against valve thrombosis (59). The use of homographs and newer pericardial prostheses may lower the risk of complications and valve degeneration during pregnancy and delivery (60,61). Finally, percutaneous mitral valvuloplasty is a successful mechanism for relieving critical mitral stenosis in the pregnant patient who would otherwise be unable to complete the pregnancy because of congestive heart failure or arrhythmias (62).

Recently, Vongpatanasin and colleagues (63) recommended that administration of warfarin be discontinued in patients attempting pregnancy and that administration of subcutaneous heparin be substituted, twice per day at a dose that prolongs the activated partial thromboplastin time by more than two times control 6 hours after administration. After week 12 of gestation, warfarin can be safely substituted until "the middle of the third trimester, after which warfarin should be discontinued and heparin resumed until delivery."

In summary, (a) pregnancy in a woman with an artificial valve prosthesis poses significant risks to the mother and fetus; (b) pregnancy is a hypercoagulable state, and valve thrombosis or thromboembolic complications are not rare, particularly in women with mechanical prostheses and especially in women with mitral valve replacement; (c) bioprostheses may degenerate in an accelerated fashion during or shortly after delivery; (d) maternal and fetal risks are increased by the presence of advanced congestive heart failure, and pregnancy is inadvisable for women with artificial heart valves and symptoms of significant heart failure; and (e) heparin cannot be recommended for use as the sole anticoagulating agent during pregnancy and should be combined with warfarin after week 12 of gestation for women with mechanical heart prostheses who require anticoagulation therapy.

CARDIOPULMONARY BYPASS DURING PREGNANCY

Severe native or prosthetic valvular heart disease and, rarely, symptomatic coronary atherosclerosis may require cardiac surgical intervention in pregnant women. A mortality rate as high as 20% may be seen among pregnant patients with native valvular heart disease and class III to IV congestive heart failure (64). Although balloon commissurotomy of mitral stenosis or percutaneous transluminal coronary angioplasty of coronary atherosclerosis may be beneficial for pregnant women who have appropriate mitral or coronary anatomy, most other valve and coronary disease patients require more than medical treatment and should undergo cardiopulmonary bypass.

Pomini and associates (65) examined 59 reports of cardiac surgery performed with the aid of cardiopulmonary bypass from 1958 through 1992. Cardiopulmonary bypass may compromise the placenta and fetus as a result of hypothermia, decreased arterial perfusion, and alterations in coagulation as well as acid-base balance. The reported fetal and maternal mortality rates were, respectively, 2.9% and 20.2% overall, but 0% and 12%, respectively, for the 40 most recently reported subjects (1975–1991). Hypothermia alters placental oxygen exchange and has been demonstrated to initiate uterine contractions. Embryo fetal mortality associated with hypothermic cardiopulmonary bypass was 24%, and mortality associated with normothermic perfusion was 0. Increased rates of pump flow diminished evidence of fetal cardiac distress, and higher-volume cardiopulmonary bypass flow is recommended, with the appropriate fetal monitoring to ensure adequacy. Therefore, normothermic bypass at high-flow volumes is recommended.

Additionally, it is recommended that patients whose pregnancies are past 20 weeks' gestation be positioned in the left lateral decubitus position during surgery to ensure that the uterus does not obstruct venous return as a result of direct inferior vena cava compression. Hyperkalemic arrest solutions may reach the fetal circulation and should be avoided, if possible. Finally, the duration of cardiopulmonary bypass should be minimized, and the operating room must be prepared for emergency cesarean section (65).

In summary, cardiopulmonary bypass may be necessary during pregnancy. To avoid maternal and particularly fetal complications, cardiopulmonary support should be high flow, normothermic, and initiated without hyperkalemic arrest. Surgery should be performed with the patient in the left lateral decubitus position if the pregnancy is past 20 weeks' gestation, and the operating room must be prepared for a potential emergency cesarean delivery.

MYOCARDIAL INFARCTION ASSOCIATED WITH PREGNANCY

Symptomatic coronary artery disease and myocardial infarction occur infrequently during pregnancy (66,67). Nevertheless, because pregnant patients may display spontaneous coronary artery dissection, and because the population of women attempting pregnancy is progressively older, cardiologists must be familiar with this potential problem.

The estimated incidence of myocardial infarction in pregnancy is 0.01%; 125 documented cases were reported in 1996 by Roth and Elkayam (68). The incidence is higher in multigravida, older (>33 years) women (68). The maternal mortality rate is 21%, and the highest rates are reported closer to delivery. Assuming that the patient does not have a hypercoagulable state (such as the antiphospholipid syndrome), Kawasaki disease, or congenital coronary abnormalities and does not use cocaine, the most likely etiologies for myocardial infarction in pregnancy are coronary artery vasospasm (29%), fixed coronary artery disease (43%), coronary dissection (16%), and thrombosis (21%).

Management of an acute myocardial infarction during pregnancy is complicated. Little experience with thrombolytic therapy is available (68); maternal hemorrhage is likely. Aspirin, beta-blockers, and nitrates can be used with caution (69). Although it is of questionable benefit in standard myocardial infarction management, nifedipine may relieve coronary spasm and decrease uterine contractility. Magnesium may decrease myocardial damage and avoid hypertension and uterus hypercontractility. High-dose aspirin may prematurely close the ductus arteriosus, beta-blockers may cause fetal growth retardation and bradycardia, calcium channel blockers (such as verapamil) may cause excessive depression of cardiac function, and diltiazem may be teratogenic (68). Coronary angioplasty has been performed during pregnancy; however, no reports of primary angioplasty for acute myocardial infarction are available (70).

Only 13 cases of postpartum coronary artery dissection were reported until 1994 (71,72 and 73). This represents approximately one-third of the experience with spontaneous coronary artery dissection in women, which may occur up to 120 days after delivery. One, two, or all three major epicardial vessels may be dissected at the time of presentation (74). It is believed that the neurohormonal milieu predisposes the coronary artery tree to mechanical degeneration and vasospasm, which contribute to the artery disruption. There is no accepted form of treatment, although controlling blood pressure and preventing coronary vasospasm seem most appropriate; surgery should be avoided.

Patients who have vasospasm but no fixed coronary artery disease can now be managed successfully with use of nitrates, calcium channel blocking agents, or other therapies directed at reversal of the increased coronary vasoreactivity. Adequate levels of blood pressure must be maintained to ensure placental perfusion, and attention must be directed at ensuring that medical management does not jeopardize fetal growth. Radiographic or scintigraphic investigation should be avoided until after the first trimester, unless it is absolutely necessary. Stress echocardiography or dobutamine echocardiography may be substituted to detect coronary artery disease in the pregnant patient.

VIDEO

Video 32.1 Severe diffuse spasm of the right coronary artery after administration of ergonovine. In this example, the right coronary artery is significantly reduced in caliber with several areas of focal "stenosis." *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 32.2 Resolve spasm of the right coronary artery. This cineangiogram was obtained after administration of intracoronary nitroglycerin and shows resolution of the spasm. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The condition of patients with fixed coronary artery disease or prior myocardial infarction who are undergoing pregnancy can usually be managed with medical therapy. Pombar and coworkers (75) reported the cases of 19 women who experienced myocardial infarction before pregnancy and underwent successful completion of gestation without maternal loss and with good fetal outcome. Three patients who had undergone bypass survived subsequent pregnancy and delivery without apparent compromise. Clearly, however, patients with known coronary artery disease should be advised against pregnancy. If these patients do become pregnant, their condition must be managed carefully to adjust for the anticipated increased cardiovascular demands of gestation.

In summary, cardiologists must be aware of the potential for fixed or vasospastic coronary artery disease during pregnancy, as well as the risks of spontaneous coronary artery dissection.

PREGNANCY IN WOMEN WITH CONGENITAL OR ACQUIRED CARDIAC DISEASE

Women who have congenital or acquired cardiac disease with or without surgical correction should approach an obstetrician and a cardiologist for assistance in management of their condition during pregnancy. Siu and colleagues (76) examined prospectively the maternal and neonatal risks associated with pregnancy in

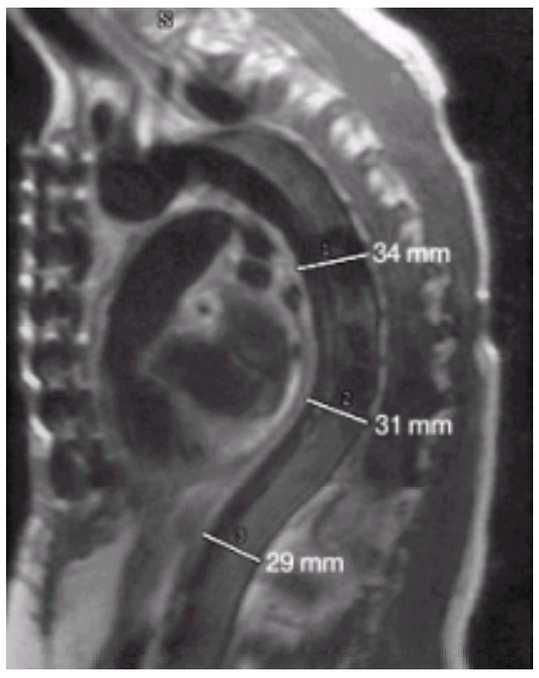
women with known heart disease. Investigators at 13 Canadian cardiac and obstetric hospitals enrolled 562 consecutive patients and determined outcome in 599 pregnancies. Maternal cardiac complications (pulmonary edema, arrhythmia, stroke, or cardiac death) complicated 13% of pregnancies and were predicted by prior cardiac events or arrhythmia, poor functional class or cyanosis, left heart obstruction, and left ventricular systolic function. Patients experienced a 4%, 31%, or 68% risk of primary or secondary cardiac events with 0, 1, and more than 1 predictors. Neonatal complications occurred in 20% of pregnancies and were associated with poor functional class or cyanosis, left heart obstruction, anticoagulation, smoking, and multiple gestations. At the Royal Infirmary of Edenberg University, 50 years of experiences were reviewed; a decreasing incidence of rheumatic heart disease in pregnant women was seen (94% from 1928 through 1947 and 36% from 1968 through 1977). In the same time interval, the incidence of pregnant women presenting with congenital heart disease increased from 3.6% to 70.0% (77). Wooley and Sparks (78) summarized five clinical studies published between 1963 and 1977 that included a total of 490 patients who had congenital heart disease and were undergoing pregnancy, and reported a maternal mortality of 0.53% and a fetal mortality of 18.90%. Certain congenital defects were considered to place patients at a higher risk by these authors, including Eisenmenger's complex, pulmonary hypertension, and cyanotic cardiac defects. Aortopathy associated with Marfan syndrome and coarctation increased risks. Perloff (79) identified potential residual changes after congenital surgical correction that increased concern about maternal and fetal outcomes, including (a) residual elevation of pulmonary vascular resistance, (b) residual aortic stenosis or regurgitation, (c) persistent right or left ventricular dysfunction, (d) aortopathy after aorta or aortic valve repair or replacement, (e) uncertain capability of prosthetic material, and (f) cleft mitral valve residual defects after endocardial cushion repair (eTable 32.5.4).

***e*TABLE 32.5.4** AREAS OF POTENTIAL CONCERN FOR PATIENTS WITH "CORRECTED" CONGENITAL HEART DISEASE WHO ARE CONTEMPLATING PREGNANCY
Residual elevation of pulmonary vascular resistance
Persistent ventricular dysfunction
Residual valvular insufficiency
Prosthetic devices or material
Aortopathy

During pregnancy, Eisenmenger's complex is associated with a maternal death rate of approximately 40%. Coarctation of the aorta, even after repair, may still be associated with aortic valve disease, thoracic aortopathy, adverse affects of long-standing hypertension, and potential aneurysms of the circle of Willis, which may further complicate pregnancy.

Aortic dissection may occur in pregnancy, particularly during the third trimester or the early postpartum interval. Marfan syndrome is associated with increased risks of aortic dissection (eFig. 32.5.2). Pyeritz (80), at The Johns Hopkins Hospital, reviewed this subject, including a retrospective medical literature analysis of 32 patients with Marfan syndrome who were undergoing pregnancy and the course of 26 pregnant patients with Marfan syndrome at The Johns Hopkins Genetics Clinic. Among the retrospective group, one-half of the women died during or shortly after pregnancy; only one of 26 expired in the Genetics Clinic series. Pyeritz recommended that patients with Marfan syndrome and mitral regurgitation who have any degree of left ventricular decompensation and patients with aortic regurgitation or aortic root dilatation greater than 40 mm be advised against pregnancy because of the high risk. Pregnancy appears to predispose other patients with connective tissue disorders to aortic rupture.

***e*FIGURE 32.5.2** Aortic dissection in patient with Marfan syndrome. Massive dissection of the ascending aorta.



Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

VIDEO

Video 32.3 Aortic insufficiency associated with annuloaortic ectasia of aortic root (oblique-coronal). An "onion-bulb" dilatation of the proximal ascending aorta and the sinuses of Valsalva is observed. A signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricular cavity during diastole. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

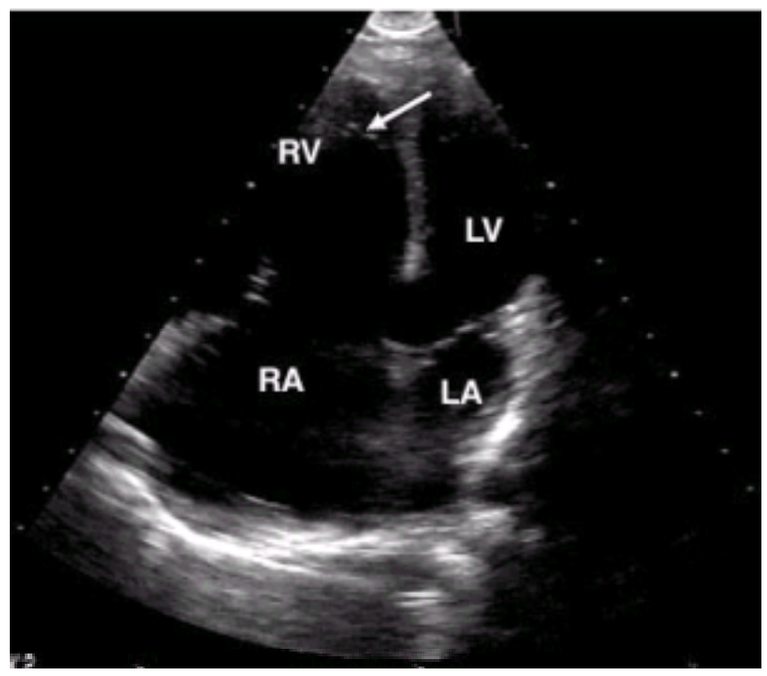
With regard to inheritable myocardial disorders, patients with hypertrophic cardiomyopathy usually fare well, although one sudden death has been reported at 28 weeks' gestation (81). The enhanced volume load associated with pregnancy decreases the symptoms of outflow obstruction and is well tolerated unless myocardial fibrosis has developed, with resultant altered myocardial compliance and high filling pressures. Postpartum blood loss and myocardial hypercontractility of pregnancy may exacerbate the dynamic obstructive characteristics of this disorder, and careful attention must be paid to preload, particularly in the peripartum interval. Oakley and associates (82) reviewed 54 pregnancies in 23 patients with hypertrophic cardiomyopathy; no mother or infant died in the prenatal period. Beta-blockers, diuretics, or both were used as needed for symptoms. Tang and associates (83) reported the outcomes of 37 pregnancies in women who had mitral valve prolapse. No cardiac complications occurred, and only three cesarean deliveries were required for obstetrical complications. There was no maternal mortality, and no congenital defects were noted in the offspring. Pregnant women with these two common inheritable syndromes have relatively good prognoses.

VIDEO

Video 32.4 Aortic dissection (left anterior oblique). Type A dissection of the aorta is manifested on the cine image loop by a mobile intimal flap extending from the mid-ascending aorta to the descending thoracic aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

A number of authors have evaluated specific congenital disorders. Presbitero and coworkers (84) reviewed 96 pregnancies in 44 patients with cyanotic congenital heart disease (excluding Eisenmenger's complex). Maternal cardiovascular complications occurred in 32%, with one death; only 43% of pregnancies resulted in live births. Univariate analysis suggested that maternal disease, hemoglobin, and prenatal oxygen saturation were helpful in discriminating patients who were likely to experience difficulties during pregnancy. Multivariate analysis showed that the prenatal maternal arterial oxygen saturation was the strongest predictor of a live birth.

Connolly and Warnes (85) analyzed the cases of 44 women with Ebstein's anomaly who had 111 pregnancies. Eighteen of these patients experienced cyanosis. No serious pregnancy-related maternal complications were seen, but only 76% of gestations resulted in a live birth, and 23 of 111 deliveries were premature. Patients who have residual atrial septal defects or patent foramen ovale must be monitored for venous thrombosis to avoid paradoxic embolism to the arterial circuit.



Ebstein's anomaly of the tricuspid valve. Note marked apical displacement of the tricuspid leaflets, especially the septal leaflet. The arrow designates the septal leaflet of the tricuspid valve.

Clarkson and associates (86) describe the cases of 23 late survivors of the Mustard operation for transposition of the great arteries. Nine women experienced 15 pregnancies and were asymptomatic before and after the pregnancies. Among these 15 pregnancies, 12 live births, two spontaneous abortions, and one intrauterine death occurred. The greatest risks were right ventricular (systemic ventricle) volume overload or failure, atrial arrhythmias, or both. Patients who are compensated despite corrective congenital heart disease usually fare well during the cardiac challenge presented by pregnancy.

Connolly and coauthors (87) reported the outcomes of pregnancy in 22 patients who had congenitally corrected transposition of the great arteries. Among 60 pregnancies, 50 (83%) resulted in live births, and one patient sustained 12 pregnancies despite toxemia, congestive heart failure, myocardial infarction, and subacute bacterial endocarditis. Another patient required valve replacement for mitral regurgitation and congestive heart failure. Therefore, maternal morbidity is potentially increased for pregnant women who have corrected transposition.

Lao and associates (88) reviewed 25 pregnancies in 13 patients with congenital aortic stenosis and 106 pregnancies in 65 patients (inclusive of their patients) from 11 series in the medical literature with this disorder. In the entire series, a maternal mortality rate of 7 (11%) of 65 patients, 24 therapeutic or spontaneous abortions (23%) of 106 pregnancies, and a perinatal mortality of 3 (4%) of 8 were seen. The risk of fetal congenital heart disease is 5% to 26% in this group, and performance of fetal echocardiography at 20 weeks' gestation to evaluate its presence is justified. An associated coarctation of the aorta was found in 31% of the original 13 patients and may be associated with a high risk of aortic or cerebral vascular complications.

Among patients with rheumatic heart disease, those with mitral stenosis are likely to become symptomatic during the increased volume load and heart rate of pregnancy. There is evidence that management with beta-receptor blocking agents may control heart rate and result in symptomatic improvement and successful term delivery in most patients (89).

Patients with congenital or heritable disorders may attempt pregnancy. The patients at highest risk are those who have residual pulmonary hypertension, right or left ventricular dysfunction, aortopathy, or persistent valvular or intracardiac chamber communication with cyanosis. The potential for miscarriage or premature birth is high, and the potential for fetal congenital heart or vascular disease is increased. A comprehensive noninvasive structural and functional analysis by history, physical examination, and Doppler echocardiography, with or without exercise or dobutamine, should be performed for all women with congenital or heritable cardiovascular disorders who wish to become pregnant to determine their suitability to undergo this challenge.

CARDIOVASCULAR COMPLICATIONS OF TOCOLYTIC THERAPY

Tocolytic agents decrease uterine contractility and are used to prolong gestation, usually beyond week 34, to allow fetal lung maturation. These agents are used in up to 5% of all pregnancies. Drugs used include b-sympathetic agents such as terbutaline, isoxsuprine, ritodrine, salbutamol, and, recently, nifedipine (90). Physiologic effects from this class of agents include tachycardia and antidiuresis. In one study, as many as 4.4% of the female patients exposed to tocolytic drugs developed pulmonary edema (72). The peculiar nature of this life-threatening complication must be understood by the cardiologist for him or her to assist the obstetrician in intelligent management.

Pisani and Rosenow (91) reviewed 22 years of medical literature to report on 58 cases. Thirty-six percent of affected women were primigravida. The most commonly used agent was terbutaline (41%), followed by isoxsuprine (33%), ritodrine (17%), and salbutamol (10%). Corticosteroids were used in two-thirds of the patients to accelerate fetal lung maturation. The average duration of treatment was 54 hours, but the syndrome can appear after less than 24 hours' exposure, and in a few cases, symptoms began after drug discontinuation, although never more than 12 hours after administration of the drug was stopped. Patients complained of dyspnea (76%), chest pain (24%), and cough (17%). Affected women sometimes had fever (temperature higher than 38°C; 14%), were rarely hypotensive, and uniformly had pulmonary rales. Chest x-rays showed bilateral pulmonary infiltrates (81%) and rarely showed effusion. The mean P_{O_2} was only 50 mm Hg in patients in whom it was measured. Echocardiography revealed normal left ventricular function in only seven patients. Right heart catheterization demonstrated elevated filling pressures in only two of nine cases, and the cardiac index was greater than 61 minutes per m^2, on average.

Treatment includes discontinuation of tocolytic therapy and administration of supplemental oxygen and intravenous diuretics. Response is usually gratifying and rapid, within 12 hours. Maternal and fetal mortality is rare, unless the woman's condition is complicated by sepsis or full-blown acute respiratory distress syndrome. The etiology of tocolytic pulmonary edema remains unknown but does not appear to be related to myocardial failure and associated pulmonary congestion.

Other entities that may present similarly include peripartum cardiomyopathy, pulmonary embolism, aspiration with acute respiratory distress syndrome, pneumomediastinum, and amniotic fluid embolization. Amniotic fluid embolization, although rare (incidence of one in 8,000 to one in 80,000 deliveries), is associated with cardiovascular collapse, respiratory distress, disseminated intravascular coagulopathy, and coma and is rapidly fatal in more than 80% of patients (92).

The risks for development of tocolytic therapy pulmonary edema appear to be related in part to the dose, the number of agents used, and the form of delivery (intravenous vs. subcutaneous). Perry and colleagues (93) studied 8,709 women who were given continuous subcutaneous infusions of terbutaline to arrest preterm labor. Patients were followed daily in the hospital or at home. Pulmonary edema developed in only 0.32% (28 of 8,709 patients). Of the 28 patients affected, 17 were receiving one to three tocolytic agents and aggressive intravenous hydration. It appears that tocolytic therapy can be administered relatively safely; however, patients

receiving certain dosages, multiple drug infusions, and supplemental intravenous hydration must be watched carefully.

ARRHYTHMIAS IN PREGNANT WOMEN

Page (94), Cox and Gardner (26), and Rutherford (95) have recently reviewed the treatment of arrhythmias during pregnancy. The hemodynamic stress of pregnancy may exacerbate arrhythmias, and treatment of rhythm disorders poses a risk to the mother as well as to the fetus (96).

Pregnancy significantly alters drug absorption and metabolism as a result of (a) altered gastrointestinal motility, (b) expanded plasma volume, (c) decreased plasma protein, (d) progesterone-induced alterations of hepatic metabolism, and (e) increased renal blood flow. Therefore, frequent measurement of drug levels may be necessary. The teratogenic risk of drug exposure is greatest in the first trimester of pregnancy; use of drugs should be avoided during this time if possible.

*e*Table 32.5.5 lists commonly used antiarrhythmic agents and their adverse effects, teratogenic risks, presence in breast milk, and overall risks. In the Vaughan-Williams classification of antiarrhythmic agents, among the class I agents, the longest experience is with procainamide, quinidine, and lidocaine, and these are at least as safe for use in pregnant women as in the nonpregnant population. Although the pregnant patient is usually younger, with less organic heart disease, it must be assumed that the disappointing results of antiarrhythmic drug trials extend to this population. Little is known about flecainide and propafenone in pregnancy, and dilantin is contraindicated because of its high risk for birth defects.

***e*TABLE 32.5.5** PHARMACODYNAMICS AND ADVERSE EFFECTS OF CARDIOVASCULAR DRUGS IN PREGNANCY

Drug	Classification (Vaughan-Williams)	Therapeutic concentration, mg/mL	Protein binding, %	Fetal/maternal ratio	Breast milk/plasma ratio	FDA pregnancy category	Adverse effects
Digoxin		0.5–2.0 ng/mL	20–25	~1	0.6–0.9	C	Low birth weight
Adenosine		NA	NA	ND	ND	C	None
Quinidine	1A	3–6 µg/mL	70–80	0.24–1.40	0.71	C	Low platelet levels
Procainamide	1A	4–8 µg/mL	15–20	0.28–132	~1	C	None
Disopyramide	1A	2–4 µg/mL	35–90	0.39	0.9	C	Uterine contraction
Lidocaine	1B	1.5–5.0 µg/mL	60–80	0.5–0.6	~1	B	Cardiovascular system side effects
Mexiletine	1B	0.5–2.0 µg/mL	60–75	1.0	0.78–1.89	C	Decreased heart rate, low birth weight, low APGAR score
Tocainide	1B	4–10 µg/mL	10–15	ND	ND	C	ND
Phenytoin	1B	10–20 µg/mL	90	0.65–1.00	0.12–0.45	C	Mental and growth retardation
Flecainide	1C	<0.2–1.0 µg/mL	40	0.70–0.83	1.57–2.18	C	None
Encainide	1C	0.5–1.0 µg/mL	75–85	ND	ND	B	None
Propafenone	1C	0.2–3.0 µg/mL	~95	0.14–0.20	0.14–0.20	C	None
Beta-blockers	2	Variable	Variable	Variable	Variable	C	Possible low heart rate, hypoglycemia
Amiodarone	3	1.0–2.5 µg/mL	96	0.09–0.14	2.25–9.00	C	Low thyroid, growth retardation, premature birth
Sotalol	3	ND	ND	ND	ND	B	Beta-blocker effect
Bretylium	3	0.5–1.0 µg/mL	0–8	ND	ND	—	ND
Verapamil	4	15–30 ng/mL	90	0.17–0.40	0.23–0.94	C	Heart block, hypotension
Diltiazem	4	50–300 ng/mL	80–90	ND	ND	C	Teratogenic?
Furosemide		NA	NA	Placental transfer		C	Low Na^+, K^+, glucose levels
Heparin		NA	NA	No placental transfer		C	Abortion
Coumadin		NA	NA	Placental transfer		D	Abortion hemorrhage

APGAR, activity, pulse, grimace, appearance, respiration; FDA, U.S. Food and Drug Administration; NA, not applicable; ND, not determined.
From Rutherford JD. Management of cardiovascular disease during pregnancy. In: Smith TW, ed. Cardiovascular therapeutics. Philadelphia: WB Saunders, 1996:695–701; and Cox JL, Gardner MJ. Treatment of cardiac arrhythmias during pregnancy. *Prog Cardiovasc Dis* 1993;36:137–178.

Class II Vaughan-Williams agents, the beta-blocking drugs, may cause growth retardation, fetal bradycardia, hypoglycemia, and elevated bilirubin. Beta-1 selective agents have been recommended; they appear to alter vasodilatation and uterine contraction less than nonselective beta-blocking drugs.

Among the class III Vaughan-Williams agents, sotalol is associated with fewer potential long-term fetal and maternal complications, including thyroid deficiency, than amiodarone. None of the agents in this category should be used for treatment of pregnant women, except in the case of severe, life-threatening rhythm disorders.

Class IV agents, the calcium channel blocking agents, may cause hypotension, maternal and fetal bradycardia, and decreased uterine contractility and are used infrequently in pregnancy.

Digoxin is relatively safe in pregnancy, but avoidance of toxicity is important. Adenosine may cause the expected short-term flushing, chest pain, and dyspnea as a result of peripheral and coronary vasodilatation but is effective in terminating supraventricular tachycardia in pregnant women (97).

Nonpharmacologic methods of arrhythmia management may be used, including endocardial pacing and direct current electrocardioversion, without significantly increased risk. Ablation therapy of arrhythmias is best delayed until after pregnancy unless the supraventricular or ventricular tachycardia is incessant and not adequately suppressed by medical management.

Ventricular tachycardia may appear in pregnant women who do not have structural heart disease. Brodsky and associates (98) reviewed reports of 26 patients with ventricular tachycardia during pregnancy, 22 of whom had no apparent ventricular dysfunction or known cardiac disease. Stress and physical exercise exacerbated arrhythmias in 15 patients, anterior myocardial infarction in two, QT prolongation in two, and hypokalemia or mitral regurgitation in one each. Antiarrhythmic agents, including beta-blockers (in 12 patients), class I agents (in 16 patients), and amiodarone (in one patient), were used, and only two maternal deaths were reported. It is presumed that the cardiovascular alterations and enhanced sympathetic tone associated with pregnancy may stimulate repetitive monomorphic ventricular tachycardia or idiopathic left ventricular tachycardia. Diagnosis of early peripartum cardiomyopathy should be considered for patients who develop ventricular tachycardia in the last month or within 5 months of delivery and present with new ventricular arrhythmias.

Wide complex tachycardia. Atrioventricular dissociation confirms ventricular origin.

Arrhythmias that appear during pregnancy may be the result of exacerbation of preexisting, underlying cardiovascular disease or stimulation of de novo arrhythmia as a result of the cardiovascular stress of the condition and the increased sympathetic tone or sensitivity, rather than of organic heart disease. Because of the potential risk to the fetus and mother, use of antiarrhythmic therapy must be carefully weighed, and care must be exercised in the selection of an antiarrhythmic agent.

MATERNAL RISK AND ASSOCIATED FETAL ABNORMALITIES

Cardiologists must be aware of some of the potential dangers of fetal birth defects associated with maternal consumption of toxins. Any medication is most likely to cause fetal malformation if exposure occurs during the first trimester, when embryogenesis and fetal formation are occurring. Cardiac medication risks have already been reviewed.

Physicians should be aware of the potential harm of exposure to the common agents alcohol, aspirin, and drinking water. It has been commonly held that excessive alcohol consumption during pregnancy results in congenital defects stemming from the cranial neural crest cell population, resulting in malformations of the ear, face, neck, and upper heart (ventricular septal defect, transposition of the great vessels, tetralogy of Fallot, truncus arteriosus, and pulmonic stenosis). Werler and associates (99) compared 1,464 infants with these abnormalities to 1,427 infants with other fetal abnormalities using the case-control method and demonstrated a higher-than-predicted risk of cleft lip with or without cleft palate in association with the mother's consumption of five or more alcoholic drinks per day. Aspirin had similarly been thought to increase the risk of certain congenital defects that affect the heart. Werler and coworkers (100) evaluated first-trimester aspirin use by 2,646 mothers whose infants had any structural cardiac defect compared with that in a control group of 6,966 mothers whose infants had other malformations. Interestingly, the prevalence of aspirin use was the same among those with congenital cardiac defects and control subjects. The authors concluded that "aspirin use during the first trimester of pregnancy does not increase the risk of congenital heart defects in relation to that of other structural malformations."

Finally, Goldberg and colleagues (101) reported on the association between congenital cardiac malformations and drinking water contaminants. In an informal survey in 1973, it was noted that a large proportion of the population with congenital heart disease in Arizona lived in the Tucson Valley area. Well water contaminated with trichloroethylene was documented nearby. Using a case registry and a random dialing technique, the authors demonstrated an odds ratio of 3 for congenital heart disease for children of parents who had contact with an area with contaminated water. Therefore, although our focus has been on protecting infants and mothers from medication exposure risks, over which we have some control, it is clear that other contaminants of daily living or over-the-counter medications may influence fetal structural and cardiac abnormalities.

ANTIPHOSPHOLIPID SYNDROME

The antiphospholipid syndrome should be suspected in mothers with arterial or venous thrombosis, thrombocytopenia, neurologic disease, or recurrent abortion. Fetal loss is associated with thrombosis of the uteroplacental vasculature. Antiphospholipid antibodies recognize a plasma cofactor on the trophoblast and/or endothelial cell surface that produces a procoagulant state (102). Women with systemic lupus erythematosus who have the lupus anticoagulant or antiphospholipid antibodies have a greater than 60% chance of pregnancy loss, compared with a 15% loss among women with systemic lupus erythematosus who do not have these antibodies. It is believed that the antiphospholipid antibody results in placental infarction or thromboses, with subsequent pregnancy loss.

Silveria and coauthors (103) treated 11 consecutive patients who had positive anticardiolipin (antiphospholipid) assays and had experienced at least one pregnancy loss with prednisone and aspirin. This resulted in an improved live birth rate, from 15.6% before treatment to 100% after treatment, without significant adverse effects to the mother or fetus. Heparin, low-dose aspirin, and intravenous immunoglobulin have been proposed as treatment options for the antiphospholipid syndrome. In a prospective, double-blind, placebo-controlled trial involving only 50 patients who had antiphospholipid antibodies and three or more fetal losses, 75 mg per day of aspirin had no influence on the live birth rate compared with placebo (80% vs. 85%, respectively) (104). Similarly, Branch and colleagues (105) found no difference in maternal or fetal outcomes when intravenous immunoglobulin was added to a regimen including aspirin and heparin for patients who had antiphospholipid antibodies. Interruption of the anticardiolipin cycle of thrombosis may be important, because patients with this syndrome may develop ventricular diastolic dysfunction over the course of time (106).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Peripartum cardiomyopathy remains a controversial area in the management of the pregnant or peripartum patient. Some authors have inappropriately reported patients in their series who showed evidence of congestive heart failure and cardiomyopathy earlier than the last month of pregnancy or later than 5 months after delivery. Inclusion of patients outside these parameters has tainted some of the data concerning the incidence of myocarditis, response to immunosuppressive agents, and outcome of individuals with this disorder. Not all authors agree that peripartum cardiomyopathy is associated with myocardial inflammation. Even those who believe that myocarditis is a component of peripartum cardiomyopathy have failed to recognize inflammation in all patients who underwent endomyocardial biopsy. Therefore, the etiology of the syndrome remains unknown. Assuming that the condition is associated with myocardial inflammation, the antigen to which the immune response is directed remains unknown. Even more controversial is the potential use of immunosuppressive agents. No prospective randomized trial involving patients with peripartum cardiomyopathy has been carried out on treatment with immunosuppressive therapy of patients with myocarditis proven by endomyocardial biopsy. It is also evident that in a high proportion of patients, peripartum cardiomyopathy, with or without myocarditis, resolves spontaneously. We have, therefore, taken the stance that once peripartum cardiomyopathy is recognized, patients should be treated with standard heart failure therapy for 2 weeks. If clear echocardiographic evidence of improvement in the myopathic state is seen, patients need not undergo endomyocardial biopsy. If the myopathic state does not improve or deteriorates, the patients undergo endomyocardial biopsy, and those with myocarditis are treated with immunosuppressive agents in hopes of improving left ventricular function. Patients with ejection fractions in the exceedingly low range (less than 15%) and those who are more than 4 months from delivery are unlikely to respond, even if myocarditis is demonstrated. Only patients in whom ventricular function does not return to normal after peripartum cardiomyopathy should be should be discouraged from additional pregnancies.

A second controversial area is the use of anticoagulants in pregnant patients. Some authors use heparin throughout the pregnancy to avoid any warfarin-related embryopathy or central nervous system abnormality. Other authors have observed such a low rate of embryopathy and central nervous system disorders with use of warfarin that the agent is used throughout the pregnancy, until delivery. Unless the patient declares her desire for a pregnancy and switches from warfarin to heparin before conceiving, most patients receiving chronic anticoagulants present to their physician already pregnant. These patients have already sustained most of the potential risk for embryopathy by the time the physician is aware of the pregnancy. On balance, the risk to the patient and fetus seems least if warfarin is discontinued before pregnancy is initiated and if heparin is used through at least the first 12 weeks of gestation. Thereafter, warfarin can be used until just before delivery, when heparin must be substituted to allow delivery without substantial bleeding.

The choice of artificial heart valves is a third controversial area of management in pregnant patients. Patients with bioprostheses have a much higher live birth rate and usually do not require chronic anticoagulation. However, the potential for degeneration of bioprostheses is associated with pregnancy and delivery. Mechanical prostheses do not degenerate but are associated with a higher rate of thromboembolic complications, including valve thrombosis and embolic phenomena in the central nervous system and periphery. Most of these thromboembolic complications have occurred in patients receiving inadequate heparin therapy. I favor the implantation of a mechanical prosthesis, even for the patient who desires a subsequent pregnancy. On the patient's declaration of the intention for pregnancy, conversion from warfarin to adequate heparin anticoagulation until after the first trimester, and then careful management of warfarin therapy, should diminish the potential for thromboembolic complications.

Not all clinicians are willing to follow patients who have undergone corrected congenital or acquired heart disease through pregnancy. These patients have often sustained life-threatening complications before surgery, and the surgery itself is usually high risk. Once patients have survived these risks, many clinicians are wary of the patient's decision to incur what some would consider an unnecessary additional risk. There is also the potential that the mother's genetic disorder may be passed on to any children. Other clinicians empathize with the patient's desire to bear and raise children despite the risk to the patient. We ensure that the patient is informed of the potential risk that her cardiac disorder could be transmitted to her offspring. If a patient is willing to accept this risk and we concur, a full cardiovascular evaluation is undertaken to evaluate the patient's cardiopulmonary capability to sustain the cardiovascular stress of normal pregnancy and delivery. Occasionally, the risk is determined to be too great, based on elevated pulmonary vascular resistance, high filling pressures, left or right ventricular dysfunction, or inadequate correction of congenital abnormalities. Most patients are willing to accept the decision to avoid pregnancy after a thorough evaluation.

Little controversy exists about the risks of use of antiarrhythmic agents, regardless of the state of pregnancy. Drugs are infrequently used and when used are carefully chosen to avoid teratogenic and maternal problems.

FUTURE DIRECTIONS

It is likely that an increasing proportion of high-risk pregnancies will be undertaken by older women or women with preexisting heart disease. These factors will result in continued growth and development of the already strong relationships between physicians in cardiology and in high-risk obstetrics.

Because exercise in pregnancy has clear-cut advantages, it is appropriate for a larger proportion of pregnant patients to be involved in aerobic exercise.

It is likely that the etiology of preeclampsia will be discovered in the near future. An increased understanding of vascular biology and alterations of vascular biology that occur in pregnant women will allow an appropriate recognition of the underlying abnormality associated with this potentially fatal complication of pregnancy. Once the

pathophysiology is understood, it is almost certain that an effective therapy can be introduced, significantly reducing maternal and fetal morbidity and mortality.

We are only beginning to understand the pathophysiology of peripartum cardiomyopathy. If the condition is associated with myocarditis, it seems logical that the etiology is immunologic. It is unlikely that the causative agent is viral and more likely that it is related to an altered placental antigen. Understanding the pathophysiology of the condition will allow better recognition and treatment of patients with this disorder. Once the pathophysiology is understood, it is anticipated that almost all patients who have peripartum cardiomyopathy will recover, as opposed to the approximately 50% recovery rate that is currently achieved.

Although new forms of anticoagulants are available, including low-molecular-weight heparin, antiplatelet agents, and platelet IIb/IIIa glycoprotein inhibitors, it is unlikely that any significant improvement will be made in the risk to patients who are pregnant and require anticoagulant therapy. Progress in this regard is again dependent on advances in vascular biology. Estrogen, progesterone, and other pregnancy-related hormone alterations that affect vascular and platelet reactivity may serve as a nidus for thrombus formation. Effective anticoagulant therapy depends on the physician understanding these alterations and providing appropriate interruption of pregnancy-related changes. Once these thrombogenic abnormalities are recognized and understood, it is expected that pregnancy can be more safely undertaken by women with mechanical valve prostheses. There is likely nothing that can alter the increased metabolic and calcium turnover in bioprostheses that are associated with pregnancy, and therefore the degeneration of these prostheses that is associated with pregnancy is likely to continue.

Although earlier correction of congenital and acquired heart disease is possible, it is unlikely that the early repair of these disorders will significantly alter the risk to the patient associated with pregnancy and delivery. More thorough prepregnancy cardiovascular evaluations, including stress or dobutamine echocardiography, and magnetic resonance imaging with or without exercise will likely better identify patients who are capable of proceeding safely with pregnancy and delivery.

Safer doses and durations of tocolytic therapy are already being used. The lack of understanding of pulmonary edema related to tocolytic therapy is the result primarily of inadequate investigation into the condition of these relatively rare patients. Despite the small number of patients who experience this disorder, the nature of the disorder can be ascertained, and appropriate treatment regimens can be designed.

The increased risk associated with use of antiarrhythmic agents has been recognized in nonpregnant patients. This risk is increased further with the pregnant state, because drug absorption and metabolism both alter in association with pregnancy. Therefore, drug therapy should be avoided if possible during pregnancy, and if it is used, agents without teratogenic risk or proarrhythmic potential are favored.

THE FUTURE

An increased understanding of the pathophysiology of disorders such as preeclampsia and peripartum cardiomyopathy will lead to more effective therapies. With advances in vascular biology, more effective anticoagulation regimens can be used in patients who have thrombogenic abnormalities. More thorough prepregnancy cardiovascular evaluations, including stress or dobutamine echocardiography and magnetic resonance imaging, will better identify patients with acquired or corrected congenital heart disease who are able to proceed safely with pregnancy and delivery.

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AGING AND THE HEART

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The extraordinary increase in the number of older persons and the frequency of cardiovascular disease, coupled with inevitable age-related changes in the cardiovascular system, make the study and understanding of cardiovascular disease in the elderly one of the most important and intriguing scientific endeavors in medicine. The high, and increasing, costs of cardiovascular care also demand a better appreciation of the appropriate use of the many treatments and interventions available for the elderly.

The interaction between age-related changes in the cardiovascular system and cardiovascular disease substantially modifies the presentations and outcomes of diseases in the elderly. The enormous heterogeneity of the aging process complicates the issues and requires a more deliberative approach. Biologic age, not chronologic age, should be the basis for assessment. Lifestyle changes in the elderly further complicate all issues, because lack of exercise, depression, and poor nutrition (among other issues) can masquerade as the aging process or disease. The interaction among disease, age, and lifestyle requires careful analysis when interpreting a patient's complaints and altered functional capacity.

Changes in the pharmacokinetics and pharmacodynamics of many cardiovascular drugs related to the patient's age demand careful monitoring for side effects and the differentiation of side effects from symptoms of new or worsening disease.

For multiple reasons, therapies known to be effective (and sometimes inexpensive and relatively safe), such as aspirin and beta-blockers, are underused in the elderly. Others, such as catheter-based interventions, require additional systematic study, especially because their use is increasing rapidly and they are expensive.

Randomized controlled trials, so useful in gaining knowledge about treatments in younger cohorts, are likely to be of limited value in older patients with cardiovascular disease because of the heterogeneity of this population. Critical data prospectively entered into databases and analyzed with sophisticated approaches should provide the most valuable insights about the most effective use of medical, financial, and other resources in older patients.

Older patients require a comprehensive, highly individualized approach to clinical decision making, because of the heterogeneity of this group and the many complex interactions that exist. In many situations, older patients should be given an active role in clinical decision making, because management decisions often involve a complex set of variables and no clearcut preferred choice is apparent. This requires considerable time and insight on the physician's part and a knowledge of the patient's values and expectations, issues not of such critical importance in younger patients. The older the patients, the more important is this aspect of their care, but data indicate that heterogeneity of the patient group becomes the major issue in patients older than 75 years.

Systematically collected data about outcomes, especially functional status for the several years after a major management decision, are critical to the understanding of the widely disparate practices and costs in caring for elderly patients with cardiovascular disease.

Cost-effective, evidence-based medicine may be seriously explored in the elderly because cardiovascular diseases are so common, the enormous costs for care are paid by public funds (which makes accountability more urgent), and the options for management are multiple. Studies involving prospective formulation of important outcomes can be effective instruments (randomized clinical trials are not practical) for assessing care and costs, which makes the study of practice an appealing approach to improving practice.

HISTORICAL PERSPECTIVE

The number of older Americans—those older than 65 years of age—is increasing at a remarkable rate, both in absolute terms and as a proportion of the population. Since the beginning of the twentieth century, longevity has increased by an average of 28 years (1). In 1994, 33.2 million Americans were at least 65 years old; this number is expected to more than double (to 70.2 million) by 2030 (1,2 and 3). Furthermore, the proportion of the population aged 75 years or older may triple from 1.6% to 4.8% between 2000 and 2050 (4). Due to a significant reduction in the death rate among people older than the age of 85, the greatest rate of increase in the population will continue to occur in this "oldest-old" group (5). Thus, the proportion of very elderly in the population is expected to increase dramatically, whereas that of the young will remain relatively stable over the next 50 years (6) (eFig. 33.0.1).

***e*FIGURE 33.0.1** Distribution of the U.S. population by 5-year age categories for 1900 and 1990 and projections for 2050 (6). The distribution becomes rectangular as the proportion of the population achieving old age increases and (projected) birth rates stabilize. (From US Census Bureau. *J NIH Res* 1995;7:29.)

This increase has been achieved primarily because more people are living to old age, not because the age at which the oldest people die has been greatly extended. In 1900, the life expectancy from birth was 47 years in the United States; today it is 72 years for men and 79 years for women (7). The average maximum length of life during this period has not increased significantly and remains at 85 to 90 years (6,7 and 8). This is an important consideration with regard to the use of resources and expectations in patients older than the age of 80 who have cardiovascular disease, because longevity in many patients is quite limited independent of the outcome of the treatment of their cardiovascular disease.

Never has a society had as many old people and as many who are frail, and never has there been so great a commitment of society's resources to their well-being. Over 40% of noninterest U.S. federal spending is committed to the elderly, especially in Medicare and Medicaid. In 1997, $26.9 billion was paid for hospital care to Medicare beneficiaries with cardiovascular problems (9). Cardiovascular disease is the most common cause of morbidity and mortality among the elderly (10). In 1997, 25.8% of elderly nursing home residents age 65 and older had a primary diagnosis of cardiovascular disease at admission. This was the highest disease category for these residents (11). The 20-year follow-up of participants in the Framingham Heart Study of the National Heart, Lung, and Blood Institute revealed that the average annual rate of a first major cardiovascular event rises from 7 per 1,000 in men between the ages of 35 and 44 to 60 per 1,000 in men between the ages of 85 and 94, nearly a tenfold increase in the risk for cardiovascular events. Comparable rates were seen in women but were achieved 10 years later (12,13). Despite these data, few cardiovascular therapies have been studied systematically in trials in this group. Until recently, older patients were excluded from therapeutic trials, perhaps out of concern that they would skew the outcomes or make complication rates unacceptably high (*e*Table 33.0.1). In large heart failure trials, the average age was 59 to 64 with few elderly patients, yet congestive heart failure (CHF) is the most common diagnosis-related group (DRG) in the Medicare population (14,15,16,17,18,19 and 20). More than 60% of cases of acute myocardial infarction (AMI) occur in patients older than the age of 65, but older patients are underrepresented in clinical trials and average age is usually relatively young, 57 to 62 years (21,22,23,24,25,26,27 and 28). A similar situation has occurred with regard to atrial fibrillation, a condition for which the median age is 75 years (29). This situation is improving, but the medical system commits limited money and energy to the study of the patients who account for most cardiovascular disease and for whom health-care expenditures are growing the fastest. Of great importance, Bayes theorem dictates that data from clinical trials in younger cohorts may not be generalizable to the large heterogeneous elderly diseased population.

***e*TABLE 33.0.1** AVERAGE AGE OF PATIENTS ENROLLED IN RECENT CLINICAL TRIALS

Trial	Average age (yr)	Elderly patients in study population (%)
Congestive heart failure trials		
GESICA (10)	59	
SAVE (11)	59	15 (>75 yr)
PRAISE (12)	64	54.8 (³65 yr)
V-HeFT–II (13)	60	
SOLVD (14)	61	
CHF STAT (15)	66	
U.S. Carvedilol (16)	58	50.6 (³59 yr)
Australia/New Zealand Carvedilol (17)	67	
Myocardial infarction trials		
CAST	61	
WARIS	61	
DUCCS-1	62	
TAMI I-IX	57	
TIMI III	58	
GUSTO-1	62	
GUST-2	65	
CARS	59	
CARE	59	

In this chapter, three key issues regarding the problems of cardiovascular disease in the elderly are repeatedly cited. First, age-related cardiovascular changes, including degenerative changes in the conduction system (resulting in rhythm abnormalities), alterations in the myocardium and left ventricular function (resulting in diastolic dysfunction), and senile calcification of the aortic valve (with eventual stenosis) are described. These and other changes are the consequences of aging, which occur at a highly variable rate and can substantially alter the clinical presentation and course of cardiovascular disease in the elderly. Management is further altered by changes in the pharmacokinetics and pharmacodynamics of drugs related to patient age. Second, how these age-related changes modify the clinical management and outcomes of therapy is emphasized. The third issue is that heterogeneity is the attribute of aging that has greatest importance in clinical decision making. It is heterogeneity that dictates the need for highly individualized decisions in the elderly, particularly for those older than the age of 75 or 80. This heterogeneity, overtly manifest in the physical and physiologic variation among elderly patients, is especially important when considering patients' preferences and expectations. For many older persons, quality of life rather than longevity, remaining functionally independent (hospitalization results in a total loss of control), and more subtle aspects of their value systems are of key importance, unlike in clinical decision making in the younger population. To evaluate these issues requires major physician involvement and precious time. In addition, these outcomes, generally classified as quality-of-life outcomes, are not easily measured but may be most important from the elderly patient's perspective.

CARDIOVASCULAR CHANGES RELATED TO AGING

Age-related changes in the cardiovascular system occur in parallel with age-related changes elsewhere in the body, but all organ systems do not develop age-related changes at the same rate. Age-related changes in a single organ or group of organs, such as the brain, lungs, or kidneys, may be responsible for the limitations and deterioration of aging, whereas all other organs may remain functionally intact. Age-related alterations in the cardiovascular system tend to be selective; some of the major anatomic and physiologic changes are listed in *e*Table 33.0.2 and *e*Table 33.0.3. Age-related changes must be differentiated from changes that result from alteration in lifestyle. Many older patients become inactive, both physically and mentally, and show major deterioration and loss of function that can be reversed by rehabilitation efforts and treatment of depression, regardless of the patient's chronologic age (30,31 and 32a).

*e*TABLE 33.0.2 NORMAL AGE-RELATED CHANGES IN CARDIAC ANATOMY

Myocardium
Increased heart weight, left ventricular (LV) mass, LV wall thickness
Mild hypertrophy
Fibrosis, collagen accumulation
Chambers
Decreased LV cavity size, shortened long axis
Rightward shift and dilatation of the aorta
Dilatation of left atrium, senile septum
Valves
Calcific and fatty degeneration of valve leaflets and annuli
Coronary arteries
Dilation, tortuosity, and Mockeberg medial calcification (arteriosclerosis)
Conduction system

Fibrosis and loss of specialized cells and fibers
Loss of 75% of pacemaker cells in sinoatrial node
Fibrosis of atrioventricular node and left anterior fascicle

From Kitzman DW, O'Connor CM. Acute myocardial infarction in the elderly. In: Gersh BJ, Rahimtoola SH, eds. *Acute myocardial infarction*, 2nd ed. New York: Chapman & Hall, 1997;602–634, with permission.

*e*TABLE 33.0.3 NORMAL AGE-RELATED CHANGES IN CARDIOVASCULAR PHYSIOLOGY
Aortic elasticity decreases; aortic impedance increases.
Myocardial relaxation decreases; diastolic dysfunction develops.
Peak exercise heart rate declines.
Peak exercise ejection fraction is maintained by a larger diastolic volume.
Cardiac output and stroke volume are not diminished.
Systolic blood pressure increases.
Valvular regurgitation develops.
PR, QRS, QT are prolonged; left-axis deviation develops.
Reactivity to chemoreceptors and baroreceptors is diminished.
Sensitivity to beta-agonists is decreased.
Pharmacokinetics and pharmacodynamics are altered.

From Kitzman DW, O'Connor CM. Acute myocardial infarction in the elderly. In: Gersh BJ, Rahimtoola SH, eds. *Acute myocardial infarction*, 2nd ed. New York: Chapman & Hall, 1997;602–634, with permission.

Consensus is lacking regarding the gross and microscopic findings in the senescent heart, but some general statements can be made. The weight of the heart increases by 1.0 g to 1.5 g per year between 30 and 90 years of age (33,33a). Ventricular septal thickness increases between the third and tenth decades of life, whereas the base-to-apex dimension decreases, which creates a smaller ventricular chamber. Another morphologic change in the senescent heart is the "sigmoid septum," which probably results from the reduction in the ventricular size and the rightward shift of the dilated ascending aorta (34). The curved ventricular septum has no hemodynamic significance, although echocardiographically it may simulate asymmetric hypertrophic cardiomyopathy. Elderly hearts reveal relative myocyte hypertrophy, most marked in the middle myocardium, and a distinct increase in connective tissue matrix, particularly in the posterior left ventricle (35).

With aging, a progressive reduction of the more distensible form of collagen with an augmentation of the more rigid type may occur. Such an alteration in the connective tissue matrix may cause the greater stiffness of the senescent heart, which requires greater filling pressures to adapt to an increased preload by the Frank-Starling mechanism (36).

Age-related changes in the arteries begin in midlife and accelerate in old age, resulting in alteration in elasticity, distensibility, and dilatation. These changes are believed to be independent of atherosclerosis and hypertension (although exacerbated by those processes) (37,31,32,33,34,35,36,37,38,39 and 40). Histologic changes include irregularity in the size and shape of aortic and endothelial cells and increases in multinucleated endothelial giant cells. The subendothelial layer becomes thick and includes more smooth muscle cells, elastic lamella lipids, and foci of calcification. The media, besides showing the fragmentation of elastic lamellae, reveals increased amounts of collagen and mucopolysaccharides and thus appears thick despite the concomitant dilatation.

Reduced prostacyclin synthesis by endothelial cells may play a role in the development of thrombosis and atherosclerosis (41). Functional changes in small vessels are more difficult to study, but endothelial-derived relaxation factor may not be elaborated as effectively in the old as in the young. Endothelial-dependent responses to agonists such as acetylcholine are reduced (42,43 and 44). Such alterations have important clinical implications for response to stresses and disease. Changes of the aging endothelium per se are difficult to separate from the same alteration (reduced endothelial-dependent relaxation) resulting from hypertension, atherosclerosis, and hypercholesterolemia. In a variety of studies, however, age has been found to be an independent risk factor for loss of endothelial-dependent relaxation.

These processes are probably caused by concomitant disease and possibly by genetics. They generally result in less elasticity and distensibility and progressive dilatation and elongation of the aorta, which reduces its diastolic contraction (the "secondary pump" in the young) and results in higher systolic pressure and a greater pulse pressure. The left ventricle has a greater afterload, which results in mild but definite thickening and increased left ventricular muscle mass in active older patients (45,46,47 and 48).

Myocardial function with aging has been studied extensively. In a wide variety of species, as well as in humans, systolic myocardial function (the ability of heart muscle to shorten, develop tension, or both) remains essentially normal. Extensive investigations have been conducted of age-related changes in systolic and diastolic myocardial function at the cellular and subcellular level, including study of the availability and use of energy stores, intracellular calcium handling, and evaluation of the transmembrane action potential (49).

Some intriguing features of direct clinical pertinence are provided by studies in isolated cardiac muscle. Muscles from older animals show a reduction in inotropic response to catecholamines and digitalis (which require a receptor) but an unchanged response of myofibrils to direct exposure to calcium (after chemical removal of the cell membrane). In addition, postextrasystolic potentiation is maintained in senescent animals, a response that would be predicted by the calcium observations. A diminished response to digitalis is seen in both old rats and old dogs (50). Observational and anecdotal evidence suggests that such changes occur with human aging. Older persons have higher levels of catecholamines and greater release of catecholamines with stress but reduced chronotropic and inotropic responses.

In contrast to systolic function, which overall is preserved (although modified in its response to various agonists), diastolic function is impaired. The changes are usually not dramatic but may be clinically important. Based on study of a variety of senescent animal models, the most striking and predictable change in the function of cardiac muscle is the longer duration of relaxation. This inherent property of senescent myocardium is likely attributable both to the slower intracellular handling of calcium and to the longer action potential that occurs with aging. Diastolic dysfunction in the intact heart is also a result of the age-related left ventricular chamber alterations described earlier and possibly of structural changes in the mitral valve. Age-specific infiltration of amyloid (discussed later) occurs in some patients, producing additional diastolic dysfunction. Echocardiographic Doppler studies have confirmed a slower relaxation phase and diastolic dysfunction in normal old persons compared to young persons (51,52 and 53).

The changes in the myocardium and ventricular performance with aging can be summarized. Peak contractile force and the ability of heart muscle to shorten is not impaired; systolic function is preserved. Agonists such as digitalis and beta-adrenergic stimuli that require a receptor have diminished effect, whereas direct stimulation of the muscle with calcium does not result in diminution. The most consistent change in the aging heart due to myocardial as well as left ventricular chamber alterations is a diminution in myocardial relaxation producing diastolic dysfunction. These changes have major implications in reference to all cardiovascular diseases in which left ventricular filling pressure may be altered substantially due to disease (AMI, hypertension) or to drugs (diuretics).

Overall Integrated Cardiovascular Performance

The age-related changes in the heart and peripheral vasculature alter considerably the integrated response to stress, including that from daily activities such as exercising, standing, and eating. These matters are important in considering the consequences of and response to disease entities such as myocardial infarction (MI) and CHF, as well as responses to drugs.

Differentiation of the effects of aging on integrated cardiovascular performance from those related to disease and lifestyle changes is not always possible. Early studies found a steady decline in overall cardiovascular performance, as judged from exercise training, with aging (54). All studies show a decline in maximum oxygen consumption, but this could be the result of a decrease in muscle mass with aging, rather than being related to reduced overall cardiovascular performance or cardiac output (55).

Afterload increases due to age-related changes in the aorta, and contractility and heart rate response during stress and exercise become reduced due to the reduced myocardial response to beta-adrenergic stimulation.

Rodeheffer (56) evaluated this issue by studying 61 highly motivated, healthy participants, aged 25 to 79 (fewer than ten were older than age 70) with no evidence of cardiovascular disease. The group engaged in vigorous exercise at 125 W and to the point of exhaustion, which indicated that they were well conditioned. Maximum cardiac output did not decrease with advancing age, but data on healthy people older than age 75 are sparse. Measurement of ventricular volumes with radionuclide methods provided insights into the mechanism for maintenance of cardiac output. Increasing age correlated with a decreased heart rate, decreased contractility, and increased impedance to ejection (afterload), which was offset by an increased end diastolic volume (preload). The larger diastolic volume in the older subjects resulted in an increase in stroke volume to maintain cardiac output, according to the Frank-Starling mechanism, in the face of reduced peak heart rate. Acute beta-blockage in young individuals blunts the heart rate response and results in an increase in end diastolic volume with exercise, which simulates what happens in elderly healthy

people and suggests that the exercise-related differences in cardiac performance are due to age-related reduction in beta-adrenergic responsiveness (57).

Hence, motivated fit normal older persons achieve the same peak cardiac output as younger cohorts but do so by different mechanisms. Longitudinal studies of aging are needed to confirm these concepts in a rigorous fashion. Of great importance, older individuals can derive benefit from successful physical training in the same ways as younger persons in terms of increased exercise tolerance, muscle mass, and improved ventricular performance, probably related to reduction in age-related arterial stiffness (58,59,60,61,62,63 and 64).

Age-related changes in cardiac valves and the conduction system are discussed in a later section describing valvular and conduction system diseases in the elderly.

Drug Use in the Elderly

Age-related alterations in both pharmacokinetics (what the patient does to the drug) and pharmacodynamics (what the drug does to the patient) are discussed in Chapter 40. *e*Table 33.0.4 summarizes many of the changes important in treating patients with cardiovascular disease. The general axiom in reference to drug dosing of “Start low and go slow” is a sensible approach. Drug use in the elderly cardiovascular patient, however, is complicated not only by age-related changes in drug kinetics and dynamics but also by the common occurrence of drug interactions because older patients take many drugs, often as many as eight to fifteen (65,66). Age-related changes in the gastrointestinal tract and frequently used drugs such as antacids or anticholinergic agents can reduce the absorption of many drugs. Studies of drug absorption in the elderly are limited, but several alterations might be expected. Estimates are that the absorptive surface of the mucosa of the small bowel is reduced by 30% due to flattening of the intestinal villi. Also, gastric pH decreases as a result of diminished acid-secretory capacity, gastrointestinal motility decreases, and blood flow to the small intestine is reduced by 40% (66,67 and 68).

*e*TABLE 33.0.4 AGE-RELATED PHARMACOLOGIC CHANGES IN THE ELDERLY
General considerations
Three times as many drugs prescribed over age 65
Multiple drugs usual, drug interactions common
Memory problems and confusion (or lack of patient education) a major issue
Pharmacokinetics (bioavailability)
Absorption (usually not important)
Reduced gastric emptying time and gastrointestinal motility
Reduced splanchnic blood flow
Decreased mucosal absorptive surface (small bowel)
Drug distribution
Less lean body mass and decreased blood volume
Changes in volume of distribution depending on lipid solubility (increased for lipophilic drugs, reduced for hydrophilic drugs)
Metabolism (biotransformation)
Less liver mass, reduced blood flow
Reduced cellular enzyme activity (primarily affects oxidation)
Elimination
Glomerular filtration rate and tubular secretion reduced
Protein binding
Higher alpha acid glycoprotein
Reduced albumin levels in elderly with poor nutrition
Pharmacodynamics (altered sensitivity to drugs)
Receptor change(s)
Reduced $beta_1$-adrenergic responsiveness
Blunted reflex responses
Reduced baroreceptor response

The alterations in drug distribution related to changes in body composition and plasma proteins that occur with age have many implications for response to a wide variety of drugs. Age-associated changes include an increase in adipose tissue, a decrease in total body water, and a decrease in lean body mass. This may result in a more extensive distribution of lipid-soluble drugs resulting in a longer half-life, and a reduced volume of distribution of water-soluble drugs leading to a higher serum concentration (65,66). Alterations in binding to plasma proteins may be expected as well. A reduction in serum albumin has been observed with age; however, the effect of age on $alpha_1$-acid glycoprotein is less clear (65,66,69,70). Although alterations in protein binding may occur, these changes are not as clinically significant as the effects of pathophysiologic changes (reduced renal and hepatic function, reduced cardiac output) on drug disposition. Alterations in hepatic blood flow and metabolism (particularly the cytochrome P-450 enzyme system) and the well-known changes in renal function with aging are major considerations in selecting drug dosage and are important determinants of the half-life of drugs. Important age-related changes in drug clearance would be attributed to liver size, liver blood flow, liver uptake, and the activities of specific hepatic enzymes. That a reduction in the activity of hepatic enzymes would account for most of the reduction in hepatic clearance of drugs may seem likely, but information indicates that reduction in liver size and blood flow account for most changes in drug metabolism that occur with age (71,72,73 and 74).

Although studies are somewhat fragmentary, glomerular filtration rate at age 70 may be only 60% of that at age 20. Renal blood flow may be decreased by 40%, and maximum sodium and water conservation in older persons is impaired. Because of the reduced muscle mass, calculated creatinine clearance does not indicate the same glomerular filtration rate in the old as in the young. The true glomerular filtration rate, however, may remain within the normal range in the *healthy* elderly individual and could be underestimated by creatinine clearance values, especially creatinine clearance calculated by the Cockroft-Gault formula (73).

Age-related changes in the conduction system and altered baroreceptor responses make bradycardia, hypotension, and orthostatic responses more frequent when antihypertensive agents, calcium channel blockers, or nitroglycerin are used.

Pharmacologic age-related changes can be summarized. Drugs can improve function and make elderly patients more comfortable, but adverse reactions and drug interactions are so common that constant vigilance is essential. Overall, a propensity is seen for increased drug concentrations in the blood as a result of reduced metabolism, decreased tissue and protein binding, and slower elimination. This, coupled with alterations in end-organ response, reduced blood volume, and altered reflex responses, emphasizes the need to give lower dosages of drugs, monitor the patient critically, alert the patient to side effects and the possible need for dosage adjustment, and minimize the use of multiple drugs. Finally, confusing drug effects with manifestations of disease is problematic in the aged. Further clinical investigations specifically studying the elderly, especially those older than age 75, are urgently needed.

CARDIOVASCULAR RISK FACTORS IN THE ELDERLY

The role of conventional cardiovascular risk factors in the elderly is incompletely understood because only fragmentary and inadequate data are available in most instances. The hypothesis that conventional risk factors are not important in the aged, because age itself is such a powerful risk factor, is no longer tenable as more and better data concerning conventional risk factors, particularly smoking, hypertension, and lipid levels, are obtained.

Hypertension

Hypertension is the most important modifiable cardiovascular risk factor in the elderly (see Chapter 5). *Hypertension*, defined as systolic pressure greater than 140 mm Hg as an isolated finding or in association with a diastolic pressure of greater than 90 mm, occurs in more than one-half of the elderly (60 years or older) (75,76,77,78 and 79).

Isolated systolic hypertension (ISH) presents problems in definition related to what is normal, inevitable, and innocent aging. The morphologic changes in the aorta and the peripheral vessels make systolic hypertension inevitable and, at least partly, a consequence of aging per se (80,81), as discussed in an earlier section. In addition, the choice of drugs is an issue because the incidence of adverse effects is common and costs can be great.

Epidemiologic data, especially during the last decade, persuasively demonstrate the major risks for cardiovascular events in the elderly with ISH (79,82,83,84,85 and 86). Wide pulse pressure has been identified as a specific risk (86,87,88,89,90,91 and 92).

In several studies, wide pulse pressure is more strongly associated with risk than either systolic blood pressure or diastolic blood pressure (86,89,91). After adjusting for demographics, morbidity, and coronary heart disease (CHD) risk factors, 10–mm Hg increments in pulse pressure were associated with a 12% increase in CHD death. The risk of CHD rose 2% to 22% and the risk of CHF increased 14% with each 10–mm Hg increment. Although systolic blood pressure and mean arterial blood

pressure showed positive association with these end points, pulse pressure yielded the highest likelihood ratio. When pulse pressures were entered into a model in conjunction with other blood pressure parameters, the association remained positive for pulse pressure but became negative for the other blood pressure variables. These data strongly support the hypothesis that pulse pressure is a powerful independent predictor of cardiovascular end points in the elderly (86,87). Possibly the principal reason to measure diastolic blood pressure carefully in the elderly is to determine the pulse pressure to assess risk. Treatment trials have not used pulse pressure per se as an entry criterion, so pulse pressure should not be used in place of elevated systolic blood pressure as an indication to treat. Clearly a lower diastolic blood pressure should encourage rather than discourage the treatment of high systolic blood pressure (85).

Multiple studies have assessed the risks of elevated systolic blood pressure in the elderly. The Framingham study demonstrated that elevation of systolic or diastolic pressure or both was associated with major increased risk of CHD in both men and women. In the Framingham study, participants aged 65 to 94 years with a systolic pressure greater than 180 mm Hg had a three- to fourfold increased risk of CHD compared to patients with a systolic pressure less than 120 mm Hg (80,82). The risk curve in this population does appear to be J shaped, especially in patients older than age 85 (79,88). The postulation is that the lower diastolic perfusion pressure may be proischemic, although interpretation is complicated by possible comorbidity resulting in lower pressure and increased mortality and morbidity. Nonetheless, treatment of diastolic hypertension in older patients has been shown to reduce morbidity and mortality.

Nonpharmacologic Treatment

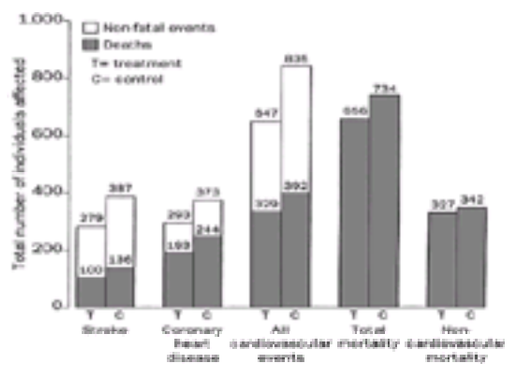
Nonpharmacologic treatment should be pursued in all patients and includes salt restriction, exercise, abstinence from alcohol, and weight reduction when appropriate. The Trial of Nonpharmacologic Interventions in the Elderly (TONE) enrolled 975 hypertensive patients between the ages of 60 and 80. Patients were randomly assigned to undergo a reduction in dietary sodium intake, weight reduction, both interventions, or neither. Each intervention individually reduced blood pressure significantly, but the combination reduced blood pressure the most (93).

Drug Therapy

The first randomized, controlled trial of the treatment of ISH was the Systolic Hypertension in the Elderly Program (SHEP) (94). Nearly 450,000 patients older than age 60 were screened, and 4,736 were randomly assigned to receive treatment or placebo and followed for approximately 5 years. An unequivocal benefit was seen for the primary end point (stroke) and the secondary end point (MI) with treatment. A strong trend toward improved overall and cardiovascular survival with treatment was also seen. Results of other studies indicate that blood pressure reduction affects occurrence of cerebrovascular events more than occurrence of cardiovascular events or total mortality. Adverse drug effects were not an important problem in these trials, likely related to the low dosages of drugs used (thiazide diuretic or beta-blocker or both in those showing inadequate response). This supports the points emphasized in the pharmacology discussion.

Additional random controlled trials confirm this favorable benefit with acceptable adverse drug effects (82,83). The principal drugs used in these trials, particularly the diuretics, are inexpensive; however, newer but more expensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers, are widely used. The Syst-Euro study used a calcium channel blocker (82). The health policy implications of using such drugs to treat all older patients with ISH needs careful study. Because of the favorable effects of ACE inhibitors on renal function, however, elderly hypertensive patients with renal disease should be treated with that class of drugs (79,80,81,82,83,84 and 85).

A metaanalysis of eight trials involving patients aged 60 years or older with ISH and enrolling a total of more than 16,000 patients in their sixties and seventies has been reported (84). The weighted average age was 70.3 years. The risk of death was directly correlated with systolic blood pressure and inversely related to diastolic pressure, which suggests that pulse pressure perhaps is a marker for arterial stiffness and is a new risk factor for cardiovascular complications. When results of all trials were combined, treatment was found to lower systolic blood pressure by 10 mm Hg and diastolic blood pressure by 4 mm Hg. Total mortality was decreased by 13% in the treatment group, with a 26% reduction in all fatal and nonfatal cardiovascular events, a 30% reduction in stroke, and a 23% reduction in coronary events. Active treatment was particularly effective in men, in patients 70 years or older, and in patients with cardiovascular complications. For seven clinical trials addressing treatment of hypertension, data from patients who were 80 years of age or older were selectively analyzed. A total of 1,640 patients were evaluated in the metaanalysis, ranging in age from 80 to 99 years (weighed mean age, 83 years). The analysis showed that treatment significantly reduced the risk of stroke by 34% and also significantly reduced the risk of cardiovascular events and heart failure (eFig. 33.0.2) (84).



***e*FIGURE 33.0.2** Metaanalysis-isolated systolic hypertension. Total number of individuals affected in this metaanalysis of more than 16,000 patients with mean age of 70.3 years. (From Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000;355:865–872, with permission.)

Although this analysis had limitations, a placebo-controlled trial, Hypertension in the Very Elderly Trial, provided more data indicating that treatment is useful in patients older than age 80 unless they have specific contraindications or conditions that would significantly limit their life expectancy (95,96).

In summary, studies over the past few years have focused on the importance of systolic hypertension and pulse pressure as risk factors for cardiovascular and cerebrovascular complications in the elderly. New clinical trials indicate that systolic hypertension can be treated safely and effectively by means of lifestyle changes. When drugs are used, the choices are as broad as for younger patients. Although some controversy remains regarding long-acting dihydropyridine, calcium channel blockers appear to be safe and effective in the elderly; however, they do not displace diuretics as the first-line therapy, nor ACE inhibitors or beta-blockers as appropriate treatment for CHD and heart failure. ACE inhibitors remain the first choice in patients with renal disease, especially those with diabetes (79,95).

Dyslipidemia

The importance of dyslipidemia (see Chapter 3) as a risk factor in the elderly, particularly those older than age 75, has been a subject of increasing interest and continuing controversy. Because CHD is the leading cause of death in older people, even a modest relative effect of lipid lowering would represent a substantial absolute mortality and morbidity benefit. Hence, although the relative risk benefit may be less in older people when lipids are favorably influenced, the absolute benefit and number of lives saved could be greater. A particularly contentious aspect has been the role of screening, which is exceedingly popular in younger persons. This relates, in part, to the fact that epidemiologic studies suggesting that hypercholesterolemia is a risk factor in the elderly are confounded by the inclusion of frail, ill, older people, who have low cholesterol levels because of poor health and wasting and whose survival is shortened by noncardiac diseases (97,98). Further, whether lipid-lowering treatment would benefit patients whose dyslipidemia is detected only by routine screening (primary prevention) is not clear (87,88). This emphasizes the issue repeatedly discussed in this chapter: that is, a highly individualized approach to treatment of cardiovascular disease in old age, including the decision to measure blood lipid levels and consider lipid-lowering therapy, is essential. Lipid levels should be evaluated in vigorous elderly patients who are biologically young, and if they meet conventional indications (in younger patients) for treatment, they should be treated; this is particularly true in reference to secondary prevention, which has been shown to have a highly favorable effect (99,100,101,102,103 and 104).

The Rotterdam study—a population-based cohort study of 6,006 individuals older than the age of 55 years—is instructive (105). In both men and women 70 years of age and older, total cholesterol level remained an important risk factor for MI. Relative risk for the top quartile compared to the bottom quartile was 3.2 for men (confidence interval, 1.3 to 7.7) and 2.9 for women (confidence interval, 1.3 to 6.6). For high-density lipoprotein (HDL), the relative risk in the highest quartile compared to that in the lowest quartile was 0.5 for men (confidence interval, 0.3 to 0.9) and 0.4 for women (confidence interval, 0.2 to 0.9). HDL cholesterol was a weaker predictor in men after the age of 70 with wide confidence intervals (quartile 4 vs. quartile 1, 0.8; confidence interval, 0.3 to 2.1). In women of 70 years and older, the relative risk also was not significant (quartile 4 vs. quartile 1, 0.6; confidence interval, 0.3 to 1.3), although the trend over the quartiles was significant. The convincing findings in this study tended to be confirmed by a variety of other studies that were less well designed or included few older people or both.

The information can be summarized as follows. Epidemiologic studies have been inconsistent and somewhat confusing, but the body of evidence now indicates that dyslipidemia remains a risk factor in elderly people, although data for those older than age 75 are sparse. Randomized controlled trials of treatment of dyslipidemia in the elderly, and particularly in patients older than the age of 75, are sparse. A metaanalysis of five trials (30,817 participants) of statin therapy (104) revealed an overall 31% reduction in major coronary events and 21% reduction in mortality of all causes in the treatment arm. Reduction in risk of major cardiac events was similar in persons older than 65 years (32% reduction) and in the younger cohort (31% reduction). Hence, this metaanalysis suggests a risk reduction that is similar for elderly and middle-aged persons. In vigorous elderly patients (biologically young), age should not be considered a contraindication for therapy. Secondary prevention should be instituted along the same lines as for younger patients. Comorbidity, particularly diabetes, which is common, must be taken into consideration. The choice of drugs is discussed in detail in Chapter 3, and the same considerations for drug selection are appropriate to the elderly. The easiest group for which to make decisions is the young old, those between 65 and 70 years of age, for whom the algorithms applied to the young, including screening, should pertain. In addition to obtaining more and better data on who should be screened in the elderly population and for whom treatment is effective, many more data on cost effectiveness must be obtained. Studies on cost effectiveness show an enormous variation with regard to cost-benefit analyses, depending on the subset of patients undergoing treatment (106).

Diabetes Mellitus

Studies of the epidemiology and pathophysiology of glucose intolerance in the elderly and the availability of new drugs has heightened awareness and interest in the importance of diabetes mellitus in the elderly (see Chapter 7). Diabetes mellitus is common in older persons, occurs in nearly 1% to 15% of people older than the age of 70, and is overwhelmingly type 2 diabetes (non–insulin-dependent diabetes mellitus) (107,108). Hereditary associations are found, and the condition may be aggravated by obesity and several commonly used drugs as well as dietary intake. Age-related deterioration in glucose tolerance enhances the propensity to develop type 2 diabetes because of the lack of multiple reserve mechanisms to control hyperglycemia. Late-onset diabetes has pathophysiologic mechanisms different from diabetes in the young, in whom autoimmune mechanisms are important and insulin lack is a key abnormality. Impairment in glucose-induced insulin release and resistance to insulin-mediated glucose disposition (particularly in the obese) are important mechanisms in the elderly (109,110). The diagnosis of non–insulin-dependent diabetes mellitus is assuming increasing importance at a time when establishing the diagnosis is more problematic (see Chapter 7).

Epidemiologic surveys of the elderly show that impaired glucose tolerance is underdiagnosed, but known diabetes correlates with risk factors for adverse cardiovascular events, including death (even in patients older than 75 years). The elderly, especially among ethnic minorities, also have more complications of diabetes (111). The elderly are particularly susceptible to drug-induced hypoglycemia because of reduced awareness of hypoglycemic warning. The frequent use of beta-blockers and the age-related reduction in the levels of regulatory hormones, particularly glucagon, and other hormones, including growth hormone, add to the need for careful monitoring (109).

Although data from randomized trials such as have been performed in younger cohorts (112,113) are lacking, abundant epidemiologic evidence suggests that good blood glucose control can reduce the risk of long-term cardiovascular complications in the elderly. The options for treatment have expanded in recent years and involve enhancement of glucose secretion, alteration of absorption, and gluconeogenesis. Lack of insulin is usually not the primary cause of hyperglycemia, as is the case for diabetes in the young, but insulin therapy is sometimes needed (114). Fastidious dietary regulation with emphasis on weight reduction for obese elderly patients, as well as exercise, are critical aspects of treatment (see Chapter 7).

Left Ventricular Hypertrophy

An important but poorly appreciated risk factor in the elderly is left ventricular hypertrophy (LVH). LVH often reflects arterial hypertension and (to a lesser extent) obesity but is an important independent risk factor for cardiac events. Echocardiographic studies have shown that increased left ventricular mass is independently associated with higher risk of cardiovascular events (115,116 and 117). Because hypertension and obesity increase with age, the prevalence of LVH may be 50% in people older than 65 years.

Initially, LVH is a compensatory response, but as it progresses, it is associated with serious morbidity and mortality. Some but not all antihypertensive agents can slow the progression of or reverse the course of LVH, and whether regression of LVH reduces cardiovascular morbidity and mortality is currently being evaluated in several large studies (118,119,120,121 and 122).

Smoking

Twenty percent to 30% of the elderly are smokers. Smoking is a much stronger predictor of cardiovascular events in the young than in the elderly, and studies of smoking as a risk in the elderly have yielded mixed results (123,124).

An observational study of the Coronary Artery Surgical Study Registry (125) encompassed 1,800 patients divided into two groups reasonably well matched except for smoking. All patients were older than 55 years but the mean age was only 60 years and few were older than the age of 75. A statistically significant reduction in the risk of MI or death occurred in patients with advanced CHD if they quit smoking. When the patients were divided into risk quartiles, the benefits of smoking cessation were demonstrated to be greatest in those with a moderate risk (of infarction or death) and barely discernible for the two quartiles with minimal and highest risk. More data are needed, but smoking cessation likely will benefit patients at risk in all age groups.

Psychosocial Risk Factors

Not only are social isolation and depression more common in elderly patients after MI, but emerging data indicate that they may represent independent risk factors for recurrent events and death (126,127). In the Cardiovascular Health Study, depression in the elderly was an independent risk factor for cardiac events (128). Emerging evidence indicates that the treatment of these risk factors results in improved outcomes. Clinical trials are very difficult to perform in the elderly, even more so in the psychosocial area, but data, including trial results, are accumulating (129).

Estrogen and Cardiovascular Risk (Postmenopausal State)

The very complicated, interesting, and important topic of estrogen levels and cardiovascular risk is reviewed extensively in Chapter 8. The estrogen deprivation that occurs with menopause results in an increase in low-density lipoprotein cholesterol, a small decrease in HDL, and possibly changes in lipid uptake in the vessel wall, as well as altered glucose and insulin levels. Regardless of the mechanisms, postmenopausal women have increased risk for CHD, so that by the time women reach their seventies, their risk is equal of that of men. Early menopause and bilateral oophorectomy increase risk at an earlier age. In addition to having the potential to reduce cardiovascular disease in postmenopausal women, hormone replacement therapy (HRT) also offers the advantage of reducing osteoporosis and hip fracture. Dosage levels and drug formulations have been sources of great debate and many studies. The benefits of HRT come at the cost of an increased risk of uterine cancer (which probably can be prevented by the concomitant use of progestins) and a possible small increase in breast cancer risk (130,131,132 and 133).

Many mechanistic studies of the effects of estrogen on hemostasis, carbohydrates, and lipoproteins, as well as vessel wall reactivity, support a cardioprotective role for estrogen. In addition, observational studies have found that estrogen replacement therapy, with or without progesterone, significantly reduces the risk of CHD. These mechanistic and observational studies can only establish association, however, not a cause-and-effect relationship; bias and patient selection may influence the risk estimates in observational trials.

The Heart and Estrogen/Progestin Replacement Study (134) was the first large randomized, controlled trial to evaluate the efficacy of estrogen/progesterone replacement therapy. This was a secondary prevention trial. Women with established CHD were selected for the trial and followed an average of 4.1 years. The average age was 66.7 years. Overall, the study found that HRT did not reduce cardiovascular risk, and an early increase in the risk of thromboembolic events was seen. Hence, this large randomized, controlled trial for secondary prevention (the only randomized, controlled trial available) failed to confirm the value of HRT despite the appealing underlying hypothesis and the results of observational trials. Additional analyses and follow-up will be forthcoming, but health-care providers must carefully consider whether to prescribe HRT solely for secondary prevention.

HRT to reduce cardiovascular risk and osteoporosis remains a very attractive hypothesis, and as an approach to primary prevention can still be strongly supported. Issues related to patients with established CHD and other cardiovascular syndromes require further study and clarification almost certainly requiring randomized, controlled trials.

Exercise

That exercise has value in reducing the risk of CHD mortality and morbidity is intuitively appealing but has been very difficult to investigate. The Honolulu Heart Program studied 2,678 physically capable elderly men, aged 71 to 93 (135). The study demonstrated a relationship between a reduction in the risk of CHD and an increase in the distance walked. Men who walked less than 0.25 miles a day had a twofold higher risk of CHD than those who walked more than 1.5 miles per day

(5.1% vs. 2.5%). Combined with the evidence indicating that an active lifestyle reduces the risk of CHD in younger and more diverse groups, these data suggest that walking has value for elderly men (and, by extrapolation, women). A realistic walking exercise program in the elderly can be assumed to have a beneficial effect and should be recommended.

Potential and Emerging Risk Factors

Ankle to Brachial Blood Pressure

Low ankle to brachial blood pressure index (ABI) is a marker of generalized atherosclerosis in the elderly. The Honolulu Heart Program evaluated ABI level as a risk factor in 2,863 Japanese American men (71 to 93 years of age) who were followed for 3 to 6 years (136). One hundred eighty-six coronary events occurred. Age-adjusted benefit related to ABI persisted even after adjustment for other risk factors. Men with an ABI of less than 0.8 had an event incidence of 15.3%, whereas those with an ABI of 1.0 or more had a 5.4% event incidence. This potentially significant risk factor needs further study to confirm and clarify its importance in the elderly.

Hyperhomocystinemia

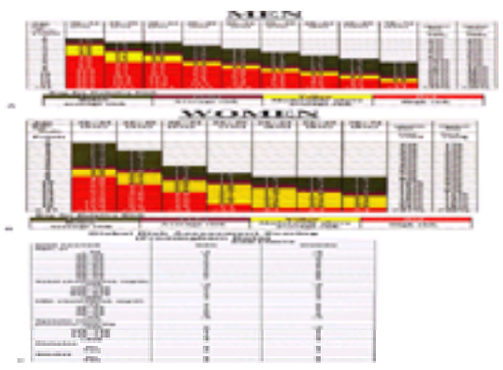
The data are persuasive that hyperhomocystinemia increases the risk of CHD. The prevalence of hyperhomocystinemia in the general population is between 5% and 15% and may be as high as 35% to 40% in the elderly population (137,138). Although evidence is insufficient to recommend routine screening in the elderly at the present time, consumption of the recommended daily allowance of folate, vitamin B_{12}, and vitamin B_6 from dietary sources should be strongly encouraged.

Infection and Inflammatory Markers

Additional emerging risk factors include levels of C-reactive protein (CRP) (which must be measured with special techniques) and fibrinogen, and *Chlamydia pneumoniae* antibody titers. These and other factors are under intense investigation as potential markers of disease activity and targets for therapeutic intervention (139,140). High-sensitivity CRP has the potential to predict events in the short term and to help define the unstable phase. *C. pneumoniae* may be involved in the development of atherosclerosis.

Assessment of Total Risk

In the elderly, as in the young, it is the total risk that is most important. Hypertension, smoking, dyslipidemia, diabetes mellitus, as well as extent of target organ damage (heart, cerebral, or peripheral vascular disease; retinopathy; nephropathy) must all be assessed to determine total risk. Grids developed from epidemiologic data are available to help estimate risks in specific patients (*e*Fig. 33.0.3) (141).



***e*FIGURE 33.0.3** Multiple risk factor estimates for men **(A)** and women **(B)**. Relative risk corresponds to color: green, below-average risk; violet, average risk; yellow, moderately above-average risk; red, high risk. Low absolute risk (*) level = 10-year risk for total coronary heart disease (CHD) end points for a person of the same age with blood pressure <120/<80 mm Hg, total cholesterol 160–199 mg/dL, high-density lipoprotein cholesterol ³45 mg/dL, no smoking, no diabetes. Percentages show 10-year absolute risk for total CHD end points. †Points can be calculated from table in **C**. ‡Includes all forms of CHD. ¶Hard CHD end points are death and myocardial infarction. **C:** Global risk score is the sum of the six variables and is used to estimate total risk from **A** and **B**. HDL, high-density lipoprotein. [From Grundy S, Pasternak R, Greenland P, et al. Assessment of cardiovascular risk by use of multiple risk factor assessment equations. *Circulation* 1999;100(13):1481–1492, with permission.]

CORONARY HEART DISEASE

General Principles

The precise relationship between coronary atherosclerosis and aging is difficult to define, but atherosclerosis is universally present and increasingly severe in the elderly, although not inevitable. At autopsy, more than 50% of people older than the age of 50 were found to have significant stenosis of at least one coronary artery, and the severity and number of stenoses increase with each age decile (142). The incidences of all cardiovascular disease, including stroke, peripheral arterial disease, and particularly CHF, increase markedly with age (see Chapter 1). In the case of CHD, the relationship to aging may reflect the cumulative effects of exposure to the risk factors discussed in the previous section.

The important gender-age relationship in CHD has been cited earlier. Event rates are much lower in women than in men at age 35 (ratio of 1:5); however, the frequency of events steadily increases in women, so that by age 75 the ratio is 1:1 (143).

Presentation

Textbooks have traditionally described CHD from the perspective of young white men (younger than 65 to 70 years of age). With the dramatic aging of the population, more than 60% of AMIs—and all other manifestations of CHD—occur in patient older than 65 years of age. Hence, although clinical presentations are often described as “atypical” for cardiovascular syndromes in the elderly, the fact is becoming increasingly apparent that the “atypical presentation” should be folded into a broader definition of the norm. For CHD, the diagnosis depends less on the presence of chest pain, because other symptoms, particularly dyspnea, and other vague complaints are often present as “ischemic equivalents.” Inactivity in the elderly may prevent effort-related symptoms from occurring, and comorbidity—especially pulmonary, renal, and musculoskeletal—can greatly modify symptoms. In addition, as the nation has become more diverse culturally, it has become apparent that the clinical presentation and course of CHD are different in minority populations than in young white males.

The electrocardiogram (ECG) of an elderly patient frequently shows nonspecific changes or consequences of aging, such as bundle branch block or other intraventricular conduction delays. ST-segment depression, rather than ST-segment elevation with typical Q-wave changes, is often the manifestation of AMI. Physical examination and basic laboratory screening can identify conditions that predispose to myocardial ischemia, such as thyroid dysfunction, anemia, and any cause for LVH (especially increased blood pressure and aortic stenosis), all common in the elderly. A variety of noncardiovascular comorbid conditions are regularly manifest on the physical examination, and their presence modifies the workup and clinical decision making.

Diagnostic Testing

Older patients often cannot increase the heart rate to the desired 85% of the predicted maximum on exercise, which makes nuclear and pharmacologic stress testing useful and popular. Exercise testing is preferred, however, because valuable data in addition to diagnosis, including prognosis, can be obtained. Echocardiographic findings with stress testing have been studied to a limited degree in elderly people, and a variety of abnormalities occurring in the elderly (including diastolic dysfunction) can confound interpretation of echocardiographically monitored stress testing. These issues are discussed in the sections on specific clinical syndromes.

When the diagnosis of CHD remains questionable and establishing the diagnosis is important to the patient, angiography should be considered. As with all other modes of evaluation in the elderly, however, interpretation of angiographic findings presents special complexities, because atherosclerosis is apt to be present and may be

severe with no manifestations of CHD. Hence, the coronary arteriogram can represent a false positive in reference to diagnosis, although the information may be useful. Important comorbidity, including renal disease, is often present, and complications are modestly increased with diagnostic arteriography.

Interventions

Randomized clinical trials of interventions have included few elderly patients. Analyses of retrospective studies and some prospectively collected data form the basis for much of the current knowledge, providing valuable descriptive information and some outcome data (144,145,146,147,148,149,150,151,152,153,154,155,156 and 157). Revascularization is an important strategy in the management of CHD in the elderly, and these procedures, especially catheter-based interventions, are becoming increasingly popular. The elderly may be more refractory to medical therapy, possibly because of the far-advanced atherosclerotic disease and ventricular dysfunction (particularly diastolic dysfunction). The elderly are less tolerant of drug therapy, as discussed in the section on pharmacology, which makes relief of symptoms by percutaneous catheter-based intervention attractive. Details regarding patient selection and discussion of outcomes in the stable angina pectoris and acute coronary syndromes are discussed in subsequent paragraphs.

The goals of revascularization in the elderly depend on the physiologic age of the patients. For patients who are “old-old” and have important comorbidities, the objective is relief of symptoms; percutaneous revascularization is the strategy of choice, but it may not be feasible due to diffuse disease.

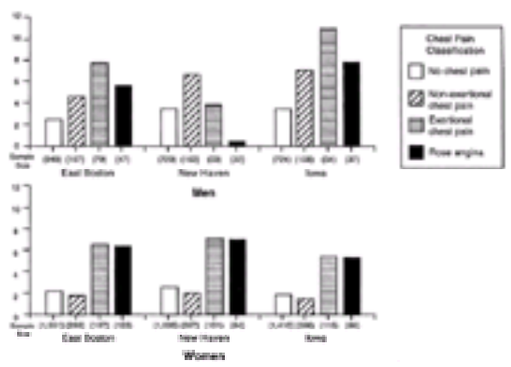
The heterogeneity of the aging process makes assessment of the total patient, not primarily the extent of cardiovascular disease, the key to successful clinical decision making and successful outcomes of treatment (pharmaceutical or otherwise) in the elderly patient. This assessment should be prospective and ongoing, because such assessment is not possible in the acute situation. Intentionally incomplete revascularization (targeting of the culprit lesion) has appeal (158). The “long-term” (3-to 5-year) outcome is primarily dependent on the overall status of the patient, not on the details or extent of CHD (32,32a,159). Competing risks are a major issue in clinical decision making (160). If the patients are “young-old” or have a good comorbidity profile, then the extent of disease, degree of left ventricular dysfunction, and patient preference should dictate the type of revascularization procedure.

Finally, the patients’ values and preferences should be a major consideration. Determination of these requires considerable physician time and is difficult under any circumstances, but it is particularly complicated when rapid management decisions are required, such as during acute MI or life-threatening arrhythmias. Psychosocial problems are also more prevalent and more challenging to deal with in elderly patients. Depression, dementia, noncompliance, isolation, inadequate social support, and dependency are all issues that can complicate care of the elderly and shorten survival independent of disease severity. These factors emphasize that one must consider the entire clinical and personal situation in the elderly and make highly individualized clinical decisions, particularly for patients older than age 75, and especially for patients older than age 80.

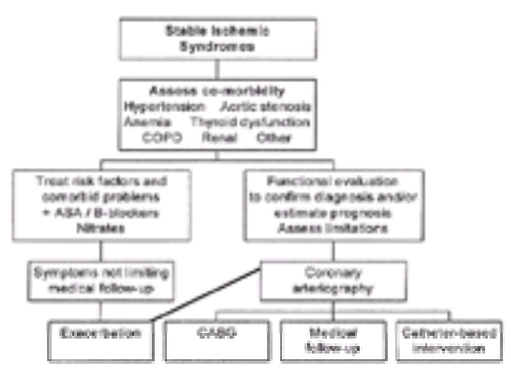
Stable Angina Pectoris

Clinical Recognition and Diagnosis

Stable angina pectoris (SAP) is a common presentation for CHD with a prevalence of 10% in people older than age 65. The diagnosis can be difficult because atypical, vague symptoms, dyspnea, weakness, and silent ischemia are common. In three large community cohort studies, individuals with typical and atypical complaints had a similar 3-year mortality (161) (eFig. 33.0.4). Comorbidity, which is frequently present, may produce complaints that mimic SAP. A particular problem in elderly patients with angina is the lack of vigorous physical activity, so that angina may rarely occur even though severe ischemia is present. Communication and memory problems make the recall of symptoms vague, incomplete, and inconsistent from one interview session to the next. All of these difficulties require additional time and careful attention to multiple lines of inquiry if a proper interpretation is to be made. Detailed information concerning functional capacity in reference to activities of daily living is of particular importance in deciding how to proceed. Symptoms are a critical element in the decision to pursue further investigation and represent the principal reason for interventions with increasing age (eFig. 33.0.5).



***e*FIGURE 33.0.4** Three-year mortality data for 8,359 people aged 65 and older in reference to chest pain evaluated by questionnaire. All members of three diverse communities were studied. All patients with a history of myocardial infarction (“heart attack”) were excluded from the sample. Atypical complaints (any exertional chest pain or nonexertional chest pain) were associated with a mortality rate similar to that for typical angina (Rose angina). (From LaCroix AZ, Guralnik JM, Curb JD, et al. Chest pain and coronary heart disease mortality among older men and women in three communities. *Circulation* 1990;81:437–446, with permission.)



***e*FIGURE 33.0.5** Stable ischemic syndromes. The algorithm illustrates the need for a broader but more individualized approach in the elderly (details discussed in the text). ASA, acetylsalicylic acid (aspirin); B-blockers, beta-blockers; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease.

Noninvasive Testing

In the elderly, noninvasive testing is rarely justified as a screening tool in the asymptomatic individual, particularly those older than age 75, although silent ischemia increases with age in asymptomatic individuals (162,163). Testing can be useful in symptomatic patients in whom the diagnosis is not established by clinical evaluation or when prognostic information is needed. Because the presence of associated cardiac diseases, inability to exercise, and resting ECG abnormalities complicates test performance and interpretation, noninvasive testing is less helpful and predictive in elderly patients than in younger cohorts. Systematic data from large numbers of older patients undergoing functional tests with meaningful long-term (3- to 5-year) follow-up do not exist. Small studies of highly selected patients fail to provide information about the incremental value of the tests (164,165,166 and 167).

Exercise ECG testing (see Chapter 48) remains the simplest, most widely available, and least expensive approach, and provides valuable information (168,169,170,171,172 and 173). Exercise protocols must often be modified with regard to speed and rate of incline of the treadmill. Exercise duration and workload can usually be safely increased to achieve a satisfactory heart rate pressure product. Heart rate may not reach 85% of the predicted value, but the marked increases in systolic blood pressure that frequently occur result in a major increase in myocardial oxygen consumption and a high heart rate pressure product. The high incidence of resting ECG abnormalities in this age group lowers the sensitivity and specificity of ST-segment depression. Multiple studies demonstrate that the ability to exercise and the duration of exercise are much more important in assessing prognosis than any single feature, such as ST-segment depression. Conversely, the inability of an

older patient to exercise, regardless of the reason, carries a poor prognosis (171,172 and 173).

Nuclear imaging and echocardiographic techniques (see Chapter 51 and Chapter 53) have become popular because of the desire to increase the diagnostic yield (sensitivity) and prognostic capability of noninvasive testing. Pharmacologic agents (dipyridamole, adenosine, and dobutamine hydrochloride) are frequently used to produce the stress, which further enhances the appeal of the test for the elderly, who are frequently unable to perform dynamic exercise because of underlying medical conditions, particularly orthopedic conditions. Data for elderly patients with stable ischemic syndromes are sparse and fragmentary, and include retrospective analyses of relatively small numbers of highly selected elderly patients. Studies are consistent in demonstrating that completely normal studies predict a very low incidence of MI and death. The data on long-term outcomes with positive test findings are sparse and give conflicting results with reference to prognosis (173,174,175,176 and 177).

Coronary Arteriography

The role of coronary arteriography in the diagnosis and management of stable ischemic syndromes in the elderly is an interesting, complex, and important issue. Coronary arteriography is the standard for establishing the presence and extent of coronary atherosclerosis during life. The belief is widespread that defining the atherosclerosis anatomically must be of value in any patient known or suspected of having CHD, but such is not true in the elderly. The decision to use coronary arteriography is complicated by the high prevalence of significant coronary atherosclerosis, which makes it problematic to attribute functional significance to the anatomic abnormalities defined. Hence, in elderly patients, coronary arteriography may be of little help in establishing the diagnosis of CHD or assessing prognosis in the absence of unequivocal clinical manifestations or functional studies demonstrating ischemia in stable patients.

In light of its limited usefulness as a diagnostic test in elderly patients, angiography should be undertaken primarily to assess the suitability of the coronary circulation for revascularization; that is, arteriography is usually performed as an aid in planning therapy. Despite the fact that older patients tend to have more severe symptoms of longer duration with a greater extent of left ventricular dysfunction, the complication rate for arteriography is not much increased, provided that the patient is stable and does not have major complicating comorbidity in the heart or elsewhere (177,178).

Revascularization

The frequency of revascularization procedures in the elderly is increasing dramatically. Morbidity and mortality from procedures is significantly higher in the elderly and highly dependent on case selection. Diabetes, prior MI, reduced ventricular function, renal insufficiency, and frailty substantially increase the risk. In a single-center study (768 patients older than 65 years of age seen at the Mayo Clinic) (179), 3.4% of patients undergoing revascularization experienced in-hospital MI or death. In a registry evaluation of 301 patients older than the age of 80 undergoing stenting procedures (157), death or MI occurred in 11%, but mortality was only 1.3% (compared to 0.1% mortality in patients younger than the age of 80). Most of the infarcts (9.3%) were non–Q-wave MIs. In a large database in New York State including 68,088 cases (Hannan EL, *personal communication*, December 15, 2000), in-hospital mortality for stent-placement procedures was 2.28% in patients older than age 75 compared to 0.46% for patients younger than age 65, with an intermediate 0.9% mortality rate for patients aged 65 to 74. For percutaneous transluminal coronary angioplasty (PTCA), mortality was 2.62%, 0.51%, and 1.04% for the respective age groups. In another portion of the database (180) comparing single-vessel stent placement (8,075 patients) with PTCA (33,077 patients), the mortality rates were minimally lower for stent procedures but the age gradients remained unchanged; for example, for those 75 years or older, mortality was 1.6% for stents and 2.6% for PTCA. In another large registry of nearly 110,000 patients (151), the 7,472 octogenarians had an in-hospital mortality of 3.8% compared to 1.1% in the younger patients in the cohort, and showed a slightly higher rate of Q-wave MI, stroke, renal failure, and vascular complications. In this study, the mortality for octogenarians varied tenfold depending on the presence of comorbidities (0.79% to 7.20%).

Coronary artery bypass grafting (CABG) in the elderly has a highly variable mortality and morbidity depending on the number of patients in the various reports and on case selection. In a study of the Medicare database (144), 24,461 octogenarians who underwent isolated CAGB had a 30-day mortality of 10.5% compared to 4.3% in the cohort 65 to 80 years old. A report of a voluntary registry (155) of 22 centers that enrolled 64,467 patients (4,306 of whom were older than 80 years) found that mortality was 8.1% among octogenarians and 3% among others for isolated CABG. Mortality for aortic valve replacement (10.1%) and mitral valve replacement (19.6%) with CABG was much higher in the octogenarians. In addition to having a greater frequency of far advanced coronary atherosclerosis, the octogenarians also more frequently had comorbid conditions, including peripheral vascular disease, pulmonary disease, and renal disease.

Although improved case selection and technical advances will undoubtedly alter mortality and morbidity, substantially higher risks seem certain to persist in the elderly. With a highly individualized approach to case selection, revascularization is the preferred approach in many stable patients. Further, as more experience is gained, the long-term (3-year) outcome will become increasingly important in selecting patients for revascularization procedures, because 3-year mortality in octogenarians, when reported, remain high—usually in excess of 30% regardless of the in-hospital mortality for CABG; this finding again emphasizes the phenomenon of competitive risk (160).

Acute Coronary Syndromes: Unstable Angina Pectoris and Acute Myocardial Infarction

More and better prospectively collected data are needed to understand acute coronary syndromes in the elderly (see Chapter 17, Chapter 18, Chapter 19, and Chapter 20). Data from randomized, controlled trials usually involve relatively small numbers of the elderly, and those participating tend to represent “healthy” older persons. Diagnostic problems arise, as alluded to in the earlier section, because clinical presentations are atypical, the ECG is much less likely to show an elevated ST segment in AMI (and a variety of ECG changes related to past coronary and other cardiovascular disease may be present), and only minimal enzyme elevations may occur. Hence, differentiating unstable angina pectoris (UAP) from AMI is difficult. Management is often similar in patients who present this diagnostic dilemma. Definite AMI carries a higher mortality and greater risk of complications, but with UAP, advanced age is an independent risk factor for complication and death. Elderly patients who present with acute coronary syndromes are more likely to be female and to have a history of hypertension, diabetes, previous MI, angina pectoris, or CHF than their younger counterparts. Delay in presenting to the hospital is a feature of acute coronary syndromes in the elderly. Forty percent of patients older than age 75 may die before arrival at the hospital, in part due to a delayed response to symptoms and psychosocial factors (181,182,183,184 and 185).

Clinical Presentation

Clinical presentation in AMI can be classified as typical, painless or atypical, or silent. Silent MI (absolutely no symptoms and detection exclusively by serial ECG changes or unmistakable evidence of myocardial scar or both) occurs in 40% of elderly patients (186,187,188 and 189). Complaints other than pain, particularly dyspnea (30% to 50% of patients) but also syncope, acute confusion, vague constitutional symptoms, or signs and symptoms of stroke or peripheral embolism, are as common as typical ischemic discomfort, particularly in the over-80 age group (190,191).

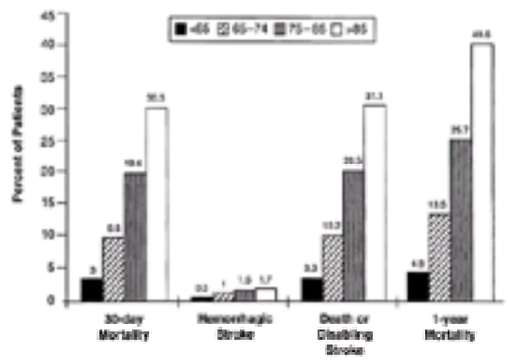
Dyspnea in the elderly MI patient may be more common due partly to age-related diastolic dysfunction, age-related lung changes, or associated independent pulmonary disease (145,192). Neurologic symptoms, syncope, stroke, and acute confusion are related to an acute reduction in cardiac output and age-related central nervous system (CNS) changes or independent cerebrovascular disease. Concurrent hypoxemia, changes in glucose tolerance, or delayed medication clearance may be contributors. Delirium may accompany any illness in the elderly and may be the presenting complaint in the very elderly with AMI.

When pain is the principal presenting complaint, it may be atypical in character and location, and sometimes appears as an upper abdomen pain rather than a crushing or squeezing substernal sensation. Elderly patients have changes in opiate receptor affinity and an altered pain threshold, but the explanation for frequent atypical and confusing pain syndromes is not known.

Diagnosis and Clinical Course

The elderly have a higher rate of non–Q-wave MI (184,192) and much higher mortality. Complications are more frequent among the elderly despite their having lower total creatine kinase levels. This paradox cannot be explained on the basis of past disease, because patients with their first MI (with or without ST-segment elevation) also show these phenomena (193,194). Their occurrence may be related to a different pathophysiology with less frequent total coronary artery obstruction.

Age is by far the single strongest predictor of 30-day mortality in many different models and for study sample sizes varying from a few hundred to 41,000 patients (146,193,194 and 195,242) (*e*Fig. 33.0.6). This extraordinarily high mortality with increasing age must be related in large part to changes of aging per se (which reduce the elderly patients’ physiologic reserve and ability to respond to the stress of AMI); these include diastolic dysfunction, altered baroreceptor and beta-receptor responses (diminishing heart rate and increasing blood pressure), and reduced lung compliance and renal function (which make these organs prone to complications due to reduced cardiac output and pressure changes). Electrocardiographically determined infarct location does not predict risk in the elderly as well as in the young. Inferior infarcts carry risks similar to anterior ones, which is probably related to a high incidence of right ventricular infarction or age-related changes or both.



***e*FIGURE 33.0.6** Profound effects of age on mortality and stroke in a very large sample of 41,021 patients from the GUSTO-I trial (95). Of the total, 24,708 were younger than 65; 11,201 were 65 to 74; 4,625 were 75 to 85; and 412 were older than 85 years. All patients had ST-segment elevation and were treated with thrombolytic agents. Postdischarge 1-year mortality remained high in the oldest group (6.1% and 10.3%) and continued to be low (1.5%) in the under-65 group. (From White HD, Barbash GI, Califf RM, et al. Age and outcome with contemporary thrombolytic therapy: results from the GUSTO-I trial. *Circulation* 1996;94:1826–1833, with permission.)

A single-institution study of 198 patients with inferior MI who were older than 75 years (195) found an overall mortality of 23%. In patients who had right ventricular MI (41% of the sample), mortality was 47%. A graded mortality from 5% to 30% was seen in patients without right ventricular MI related to the degree of reduction in left ventricular ejection fraction. No relationship was seen between left ventricular ejection fraction and mortality in patients with right ventricular MI. Death was primarily related to cardiogenic shock. A higher incidence of complete atrioventricular block (33% vs.9%) and interventricular septal rupture (9% vs.0%) was present in the patients with right ventricular MI. This was the first MI for all patients studied.

The nonspecific ECG changes that are often present with AMI and bundle branch block deserve special comment. Right or left bundle branch block occurs in 5% to 10% of AMI cases. In an extraordinary sample of 29,585 patients with AMI and left bundle branch block in the Second National Registry of Myocardial Infarction, the mean age was 76.4 years and mortality was 22% (145). Only 8.4% of this sample had any form of reperfusion therapy. This low use of a powerfully effective therapy in such a high-risk group of AMI patients must be related to the lack of typical symptoms (only 50% of this sample had chest pain) and “nonspecific” ECG (left bundle branch block) abnormalities.

The risk of cardiac rupture greatly increases in the elderly, reflecting age-related fundamental changes in cardiac anatomy (193). Thrombolytic therapy increases the risk of cardiac rupture (197), adding to the age-related hazard of rupture.

Management and Reperfusion Therapy

Management decisions during the first several hours have the greatest effect on survival in the elderly (147,196,197,198 and 199), as is true for all age groups. The pivotal decision is whether to proceed to reperfusion therapy (thrombolytic therapy or percutaneous catheter-based intervention). The overall care available and the expertise and experience of the hospital and its staff may be the most important factors determining outcome for the majority of elderly AMI patients (148,149). Therapeutic interventions carry added risks in the elderly, so the potential benefits must be carefully considered and judged to be clearly present. In younger patients, the prevailing philosophy in the United States is to undertake many therapies and interventions in AMI almost as a routine despite the lack of convincing evidence of benefit with regard to mortality and recurrence of MI in some subsets (200). This approach is clearly not justified in the elderly. An additional important factor in treating the elderly, particularly those older than 80 years of age or those who are frail, is the need to consider the patients’ values and wishes—a matter that is extremely difficult to address in view of the drama and urgency that surround AMI and often include transfer to physicians at facilities with no background information concerning the patient. For many elderly patients, life will not be prolonged (or quality of life improved) despite effective therapy for their acute coronary syndromes (160). Thoughtful, refined clinical judgment with a highly individualized approach to each patient is the key to optimal management with emphasis on the use of treatments that are known to be helpful and have a low propensity for major complications.

Thrombolytic Therapy

Elderly patients are underrepresented in all thrombolytic trials (147,196,197,198 and 199) because of concern about the risk of complications, particularly cerebral hemorrhage. Although most major hemorrhages occur at vascular puncture sites, intracranial hemorrhage rates are increased in the elderly. Spontaneous ischemic strokes related to AMI increase in frequency with age.

The increased risk of stroke in patients older than age 70 is thought to result from the reduced integrity of the cerebrovascular system, previous silent cerebral ischemic events, or cerebral amyloid angiopathy. Large randomized, controlled trials and case-control studies all demonstrate a higher risk of cerebral hemorrhage in the elderly with tissue-type plasminogen activator (t-PA) than with streptokinase treatment (201,202 and 203). An algorithm to estimate the probability of hemorrhagic stroke after thrombolysis indicated that age and the use of t-PA are two of the most important variables, along with female gender, low body weight, and hypertension (33,33a).

Heparin sodium use requires special attention in the elderly. In addition to age, small body size and female gender alter metabolism and dosing requirements. Lower dosages, a 3,000-U bolus (instead of 5,000) and 500 U per hour rather than 1,000 should be considered for 50-kg elderly patients, and partial thromboplastin time should be followed fastidiously. Low-molecular-weight heparin is increasingly popular and does not require monitoring. Comparative safety data for the elderly are not available.

Given the profound effect of age on mortality, the increased rate of hemorrhagic events must be weighed against the substantial mortality reduction that is felt possible with thrombolytic therapy. Efficacy was demonstrated in multiple randomized, controlled trials. In the Fibrinolytic Therapy Trialists’ overview, the greatest absolute benefit of thrombolytic therapy was seen in patients older than age 75 (147), but the number of elderly in randomized, controlled trials is relatively small. Studies of effectiveness now question this finding. The data compiled by the Health Care Financing Administration for its Cooperative Cardiovascular Project during the years 1994 to 1995 have been studied by two different groups of investigators in retrospective studies. Patient selection was different and methodologies were not identical. In the study by Berger et al., 15,940 patients older than the age of 65 had thrombolytic therapy or primary angioplasty (1,599) (204). They concluded that patients who underwent reperfusion had a lower mortality at 1 year than those who did not undergo reperfusion. Interestingly, only primary angioplasty was associated with a better survival at 30 days (see subsequent paragraph). Using the same database, Thiemann et al. evaluated 7,864 Medicare patients who had fee-for-service treatment (205). In evaluating thrombolytic therapy in this group, they concluded that a survival benefit was seen in patients 65 to 75 years old, but in the group aged 76 to 86 years, thrombolytic therapy was associated with survival disadvantage. Hence, data are conflicting, and a serious concern exists that patients older than the age of 75 may not benefit from thrombolytic therapy. If adverse outcomes in the over-75 group are confirmed, pharmacologic differences in the handling of drugs (and the interaction among drugs) as well as changes related to the aging process per se may explain the lack of benefit.

These confusing and inconsistent findings coupled with the atypical clinical presentations and ECG findings, as well as the delay in seeking care, make the use of thrombolytic therapy problematic in older patients, especially those older than the age of 75. In addition, a disappointingly small number of elderly patients meet conventional eligibility criteria for thrombolytic therapy: ST-segment elevation, arrival within 6 hours of the event, and no contraindication. In one study, only approximately 10% of patients older than age 75 met eligibility criteria because of the absence of ST-segment elevation, late arrival, and comorbidity (184).

Primary Percutaneous Catheter-Based Interventions

Issues related to logistics and the treatment of low-risk patients are still debated, but the extremely high mortality and features discussed earlier make PCI particularly appealing for the elderly because it can be used in patients without ST-segment elevation and the major CNS morbidity risks of thrombolytic therapy can be largely avoided.

Some of the issues related to the use of PCI have been discussed under “thrombolysis” (see also Chapter 18). Pooled analyses of the results of randomized, controlled trials of PTCA versus thrombolytic therapy (primarily in younger patients) found a mortality advantage and reduced in-hospital reinfarction rates in patients randomly assigned to undergo to angioplasty (206,207). These results were not confirmed in an important observational study of patients of all ages (more than 3,000 patients) performed in Seattle, Washington, and in a French study, which showed no benefit for angioplasty (208,209).

Another observational trial of the Second National Registry of Myocardial Infarction suggests that primary PTCA and fibrinolytic therapy result in similar outcomes (154). Patients with ST-segment elevation underwent primary PTCA (4,939) or were given t-PA (24,705). Fifteen percent of the patients in both groups were older than

75 years of age, and mortality among these patients was 16.5% in the group receiving t-PA and 14.4% in those undergoing PTCA. For total mortality and disabling strokes, the rates were 18.4% for those given t-PA and 14.6% for those undergoing PTCA.

Two registry studies add substantial observational data but do not resolve some of the major issues. Berger et al. (204) studied the Health Care Financing Administration's Cooperative Cardiovascular Project database, which contains information on 140 clinical variables collected prospectively. They studied the 20,683 patients who received reperfusion therapy out of 80,356 who were judged eligible for reperfusion. The total cohort contained 234,769 patients older than 65 years. The data analyses are extensive, complex, and sophisticated, and incorporated baseline patient cardiac risk factors, hospital characteristics, and (to a limited degree) qualitative general patient characteristics, including presence of chronic obstructive pulmonary disease or dementia, and degree of mobility limitation. The conclusion from this study is that primary PTCA is associated with a modest short-term and long-term mortality benefit compared to fibrinolytic therapy. Thirty-day mortality was 8.7% versus 11.9% and 1-year mortality was 14.4% versus 17.6%. In the smaller subgroup of patients who were classified as ideal for reperfusion therapy, the observed benefit of primary PTCA was not seen. The relatively low mortalities indicate considerable bias in case selection in favor of healthier old people.

In summary, the precise role of PCI in elderly patients with AMI remains to be defined. Additional registry data will be useful, but the decision to use PCI, fibrinolytic therapy, or neither—particularly in patients older than the age of 75—is likely to remain inherently a highly individualized clinical decision. In addition, the logistics and expertise required for timely catheter-based interventions provide major obstacles to the widespread and routine use of this approach. The presence of multivessel disease, which is regularly found in the elderly, makes it imperative to identify the infarct-related vessels in these patients, most of whom have ST-segment depression.

Adjunctive Therapy

Adjunctive therapy has not been evaluated as intensely in the elderly as in the young, but clearly several adjunctive agents are very effective in the elderly and tend to be underused.

Aspirin use was investigated in the Second International Study of Infarct Survival (198). Patients older than age 70 achieved particular benefit, with a 21% relative reduction in mortality (from 22.3% to 17.6%). As doses increased from 80 mg to 325 mg in this study, the rate of gastrointestinal complications increased twofold, particularly in the elderly. No data are available on gastrointestinal bleeding in the elderly with the use of cyclooxygenase-2 inhibitors. Aspirin is underused in treating acute MI in the elderly, with reported usage rates of 55% in patients older than age 75 versus 65% in those younger than age 75 (210,211,212 and 213).

Early studies of intravenous glycoprotein II_b/III_areceptor blockers have shown promise in treating acute coronary syndromes but primarily in patients undergoing PCI. Data specifically pertinent to older patients are fragmentary. If PCI is not performed, no mortality benefit has been seen in randomized, controlled trials. Trials combining II_b/III_a agents and thrombolytic agents for reperfusion are under way (see Chapter 17 and Chapter 18).

Beta-blocker therapy has a greater effect on survival after MI in the elderly than in younger patients (214,215), with a 34% reduction in mortality in patients between the ages of 60 and 69 but only a 19% reduction in patients aged 30 to 59 years who received propranolol 5 to 21 days after MI. Early intravenous administration has been studied in three randomized, controlled trials (216,217,218 and 219). In 8,513 patients older than 60 (the majority was older than 65), mortality was reduced from 8.9% to 6.9%, so that 20 lives were saved per 1,000 patients treated. In the 14,687 patients younger than age 65, the mortality reduction, from 2.6% to 2.5%, was insignificant. These studies were performed before the fibrinolysis era, but the use of early intravenous beta-blockade as an adjunct to thrombolysis suggests that the agent is useful in that setting.

The use of long-term beta-blocker therapy for secondary prevention after AMI is of value in elderly patients. Three large randomized, controlled trials using propranolol hydrochloride, atenolol, or metoprolol show convincing reduction in mortality in both young and old patients after MI (217,220,221). Mortality reduction was much greater in the 2,462 older patients (14.9% to 8.9%) than in the 4,654 younger patients (7.6% to 5.5%). For every 1,000 patients treated, 60 lives were saved among the older patients compared with 21 lives among the younger patients. Despite these clear benefits, clinicians underprescribe beta-blockers in elderly patients (212,213), perhaps because they fear the side effects that are more frequent in the elderly, including heart block, CHF, bronchospasm, depression, and impaired glucose metabolism. Beta-blocker therapy can benefit even those with mild CHF, diabetes, or both. The substantial benefit of these drugs makes it important that they be used liberally, with careful observation for adverse effects in patients who have relative contraindications, such as bradycardia, low systolic blood pressure, and propensity to heart block.

The survival benefit of treatment with ACE inhibitors after AMI is greater in the elderly than in younger groups. In one trial, the reduction in the risk of death was greatest (25%) in patients older than 65 years who received captopril, whereas it was lower in those younger than 55 years (8%); the reduction in recurrent, fatal, or nonfatal MI was also greater in those older than 65 years (213). Among patients older than 70 in the third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio study (GISSI-3), a 12% reduction was seen in the combined end point of mortality and severe ventricular dysfunction (222,223). Details concerning the timing of initiation of therapy and implications of left ventricular dysfunction are discussed in Chapter 18.

The role of intravenous antithrombin agents in the elderly is complicated. Intensive anticoagulation poses particular bleeding risks in the elderly. The use of low-molecular-weight heparin has not been compared with the use of fractionated heparin in the elderly. Combinations of fibrinolytic, antiplatelet (glycoprotein II_b/III_c), and antithrombin agents are being evaluated, which adds to the uncertainty. Heparin is required with t-PA therapy but offers no advantage with streptokinase treatment (224). The use of heparin is always associated with increased bleeding risks.

Calcium channel blockers are favored in many situations when beta-blockers are contraindicated, but multiple clinical studies have shown no benefit of this treatment for AMI (225,226). Although their use remains popular, the lack of efficacy of these agents appears to be a class effect, and independent of age, at least for the first-generation calcium channel blockers. Second-generation agents may have a role in certain subsets (see Chapter 18 and Chapter 20).

Glucose-Insulin Infusions

Diabetes is commonly present in elderly MI patients and is a predictor of adverse outcomes. The hypothesis that glucose-insulin-potassium infusions can alter the metabolic substrate and improve the outcome of AMI has been evaluated for 40 years (227,228). Swedish investigators (229,230) have used insulin-glucose infusions to treat diabetic patients. The short-term and long-term outcomes obtained in a well-designed randomized, controlled trial involving 600 patients (mean age, 68 years) demonstrated convincing benefit. After a 24-hour infusion, subcutaneous insulin was given four times daily for at least 3 months in the treatment group. Mortality was lower in the treatment group than in the control group (9.1% vs. 11.2%). By the end of 1 year, the reduction in mortality was 18.6% versus 26.1%. This mortality benefit was still present 3.5 years after infarction. Of particular importance is the fact that the mortality reduction was most evident in patients who had a low cardiovascular risk profile and who had received no insulin treatment before the AMI. Among this subset of patients, the 3-year mortality was 6.5% in the infusion group and 13.5% in the control group. Fastidious control of hyperglycemia during the course of AMI should be seriously considered in all elderly patients.

Complications and Cardiogenic Shock

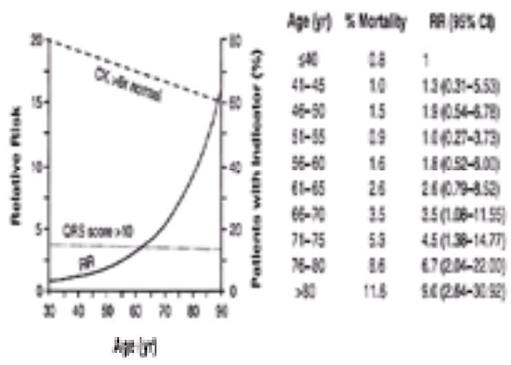
The complications of AMI are, overall, more frequent and the consequences of the complications more catastrophic in the elderly. Primary ventricular fibrillation is the probable exception to that rule because it is less frequent with increasing age. Complications are discussed in detail in Chapter 18, Chapter 19, and Chapter 20. The approach to complications is no different in the elderly than in younger cohorts, when allowances are made for comorbidity and the implications of competing risks.

Cardiogenic shock (see Chapter 19) deserves special comment because it is relatively common (7% to 10% of all AMI cases), is the leading cause of death in AMI, occurs overwhelmingly in the elderly, and continues to carry a high mortality. The studies of Hochman and her colleagues (231,232 and 233) have provided important insight into the issues involved, including the problems in establishing the diagnosis, that is, verifying that the shock is related to myocardial dysfunction. In addition to confirming that the patient's hypotension and hypoperfusion are not related to decreased left ventricular filling pressure or arrhythmias, one must look for mechanical complications (ruptured ventricular septum, ruptured papillary muscle with mitral regurgitation, and free wall ventricular rupture) (233,234,235 and 236). All of these complications are more frequent in the elderly and, of course, require a different management approach. Hochman and her colleagues have studied cardiogenic shock in a sample of 302 patients in a randomized, controlled trial and have extensive data on a registry of an additional 1,109 patients.

These studies provide an extraordinary body of data, but problems related to transfer bias and the fact that these studies were performed at highly experienced centers that can provide optimum care for complicated cases make it probable that their results cannot be directly transferred to the usual practice setting. The outcome for patients age 75 or older, however, is probably correct. In that subset of patients, revascularization had an adverse effect compared to optimum medical therapy. Of the many subsets analyzed, this was the only subset in which an adverse outcome occurred with revascularization. In multiple subsets, the benefit of revascularization was small and often statistically insignificant (see Chapter 19 for further information). The complexities of cardiogenic shock, including the use of intraaortic balloon pumping, revascularization therapies, and a variety of pharmacologic agents, require the ultimate in clinical judgment in treating the elderly and especially patients older than age 75 (237). A highly individualized, thoughtful approach will provide the optimum outcome and most humanistic alternative in treating this relatively common and extremely lethal complication, which probably carries a mortality of at least 50% despite optimum therapy (231,232,233,234,235,236 and 237).

Risk Stratification after Myocardial Infarction

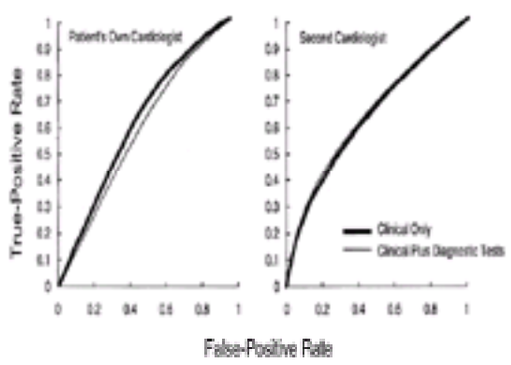
Elderly hospital survivors of AMI have an extremely high overall 1-year mortality, in the range of 30% to 40%, including hospital mortality. This rate is highly variable depending on a number of factors, particularly left ventricular dysfunction, residual myocardial ischemia, and major ventricular arrhythmias (*e*Fig. 33.0.7). Half of these deaths occur within the first 3 months (238,239). (See also Chapter 20.)



***e*FIGURE 33.0.7** Six-month mortality for 9,720 patients surviving their first myocardial infarction. All patients had ST-segment elevation on electrocardiogram, presented within 6 hours of the onset of chest pain, and were given thrombolytic agents. The creatinine kinase (CK) release and QRS scores with acute myocardial infarction were lower in older patients. The postdischarge 6-month mortality was quite low in patients younger than age 65 and increased markedly with age. CI, confidence interval; RR, relative risk. (From Maggioni AP, Maseri A, Fresco C, et al. Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. *N Engl J Med* 1993;329:1442–1448, with permission.)

A useful approach is to divide the survivors of AMI into high- and low-risk groups and use revascularization procedures in the high-risk groups (240,241). Intensive medical therapy for left ventricular dysfunction and prevention of progression of atherosclerosis is indicated in all survivors, as discussed in the section Cardiovascular Risk Factors in the Elderly. Very high 1-year mortality (up to 50%) is seen for some elderly AMI survivors who have significant ventricular dysfunction, major comorbidities, and limited ability to ambulate. The inability to perform an exercise test, regardless of the reason, is associated with a high short-term mortality (171,172). However, this group also has a high rate of mortality and complications after interventions. Again, a highly individualized approach must be taken through risk stratification after AMI in the elderly, with emphasis on noncardiac disease features—evidence of aging and comorbidity. Overall exercise tolerance is the single most predictive feature.

Clinical exercise test variables that correlate with adverse long-term outcome in the elderly include an inability to increase systolic blood pressure by more than 30 mm Hg, an exercise duration of less than 5 minutes, and poor increase in the rate pressure product. In one study, the prediction of 1-year outcome for older patients after MI on clinical grounds only (by experienced clinicians) was not improved by knowledge of the results of exercise testing, radionuclide angiography, or 24-hour Holter ECG recording (241) (*e*Fig. 33.0.8). All these studies emphasize the importance of the overall evaluation of the elderly patient after MI, not only the assessment of CHD severity.



***e*FIGURE 33.0.8** Attempt to determine the incremental value of post–myocardial infarction noninvasive testing in 147 older patients (mean age, 75 years). Clinical evaluation included history, physical examination, routine laboratory studies, electrocardiographic data, and chest radiograph. Noninvasive diagnostic tests included an exercise test, 24-hour ambulatory electrocardiographic monitoring, and radionuclide-based estimate of ejection fraction. The postdischarge 1-year mortality was 16% for the group. Using receiver operating characteristic (ROC) curves, clinical estimates by the patients' own cardiologists and by a second independent cardiologist were compared with estimates that also incorporated the noninvasive diagnostic testing. In this study, the addition of the noninvasive diagnostic test selected did not add incremental value to estimates of 1-year mortality, perhaps because ventricular function—the most powerful predictor of outcome—has been recently estimated by clinical data. Disappointingly, the ROC curve areas were in a relatively low range (0.60 to 0.65). (From Myers MG, Baigrie RS, Charlat ML, et al. Are routine non-invasive tests useful in prediction of outcome after myocardial infarction in elderly people? *Lancet* 1993;342:1069–1072, with permission.)

Because many elderly patients cannot exercise (40% in some studies), stress has been induced pharmacologically to assess perfusion and ventricular performance. Dipyridamole, adenosine or dobutamine in conjunction with thallium or echocardiography can be used; dobutamine is particularly useful in older patients with obstructive lung disease for whom dipyridamole and adenosine are relatively contraindicated. Although these approaches are appealing, reports ordinarily do not give information about the incremental value of these approaches. An urgent need exists to determine the incremental value of post-MI testing in the elderly.

The use of coronary arteriography is another debated issue. Valuable information can be obtained, including information on systolic and diastolic function, cardiac hemodynamics, and extent, severity, location, and characteristics of lesions (including residual thrombosis of coronary lesions). In addition, valvular disease, particularly calcific aortic stenosis, is frequently present and can be evaluated. For these reasons, some argue that angiography should be a routine part of risk stratification (240,241) in the elderly. Multivessel disease is present in a high percentage of elderly patients, however, and the incremental value of coronary arteriography for assessing prognosis (in contrast to planning treatment) is problematic. In a large observational study of post-MI angiography in the United States and Canada, the greater use of angiography in the United States (35% vs. 10%) was not associated with a reduction in 1-year mortality (35% in both cohorts) (150).

Video 33.1 A 76-year-old female patient with bicuspid aortic valve, aortic stenosis, and coarctation of aorta. Left anterior oblique aortogram revealed coarctation of the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In the absence of outcome data, highly individualized decisions are required with regard to the use of post-MI arteriography in the heterogeneous population of elderly post-MI patients.

Cardiac Rehabilitation

Normal aging is accompanied by reduced exercise capacity or alterations in lifestyle, or both, which reduce physiologic reserve. Hence, rehabilitation involving exercise is particularly important in the elderly (243,244,245,246 and 247). Healthy elderly patients can significantly increase their exercise capacity through exercise training,

which need not occur within a structured group program but is feasible at home (although fewer outcome data are available using this design). An important component of cardiac rehabilitation programs is individual and group counseling, including focused diet, risk-factor modification, and social adjustment interventions. A British study of 166 consecutively treated patients aged 70 to 97 years randomly assigned to attendance at a special outpatient counseling clinic or to the usual medical follow-up showed reduced hospital readmissions, less depression and anxiety, and increased mobility and physical function with outpatient counseling (244). Comprehensive cardiac rehabilitation in some form should be strongly considered after MI in elderly patients.

CONGESTIVE HEART FAILURE

Incidence, Risk Factors, and Implications

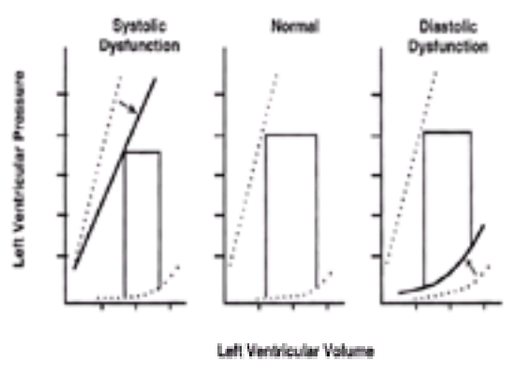
CHF (see Chapter 88, Chapter 89, Chapter 90, Chapter 91, and Chapter 92) is the most common reason for admission of Medicare recipients to an acute care hospital, and readmission rates are extremely high (30% to 50%) within 3 to 6 months of the initial discharge. CHF is one of the most important chronic conditions contributing to limitations in mobility and activities of daily living (248,249,250 and 251).

Age is a powerful risk factor for development of CHF. The risk of developing heart failure was nearly twice as high in persons 75 to 85 years of age than in those 65 to 74 years of age. The incidence of CHF further increased in both men and women from 13% and 8% per 1,000 person-years, respectively, at age 65 to 74 years to 29% and 18% per 1,000 person-years, respectively, at age 85 and older. Other strong risk factors are left ventricular hypertrophy, coronary artery disease, cardiomegaly, reduced vital capacity, valvular heart disease, elevated baseline body mass index, elevated pulse pressure, MI, and diabetes mellitus (250).

Randomized controlled trials have provided a huge volume of data that help characterize patients with CHF and define treatment (14,15,16,17,18,19 and 20). Unfortunately, such trials provide limited insight with regard to older patients. Older patients included in trials do not reflect the typical older patient with CHF. The Study of Left Ventricular Dysfunction (SOLVD) trials developed a registry of patients with CHF or left ventricular dysfunction to understand this issue better (252,253). The 6,273 patients in this registry demonstrated important differences from the 7,897 SOLVD trial patients; the most important was that the registry contained a much higher proportion of patients aged 71 years or older (23.8% vs. 11.0% of trial patients). The 1-year mortality and hospitalization rates were higher in the registry group. This emphasizes the problems in interpreting the results of many randomized controlled trials, in which relatively healthy and low-risk elderly patients are selected, and in which a relatively small number of elderly patients are included.

Pathophysiology

CHF is a syndrome of diverse causes and well-known signs and symptoms, which results in the inability of the heart to adequately supply the oxygen and metabolic needs of the body, sometimes at rest but especially with exercise, at normal intracardiac filling pressures (254,255 and 256) (*e*Fig. 33.0.9). The syndrome may be due to myocardial dysfunction of systolic or diastolic origin, but myocardial function may be normal and abnormal loading conditions (valvular disease and hypertension, common conditions in the elderly) may be responsible for the syndrome. Rarely, a restrictive process (such as pericarditis) is responsible. In any situation congestion may not be present, so the term *heart failure* is more appropriate than *congestive heart failure*.

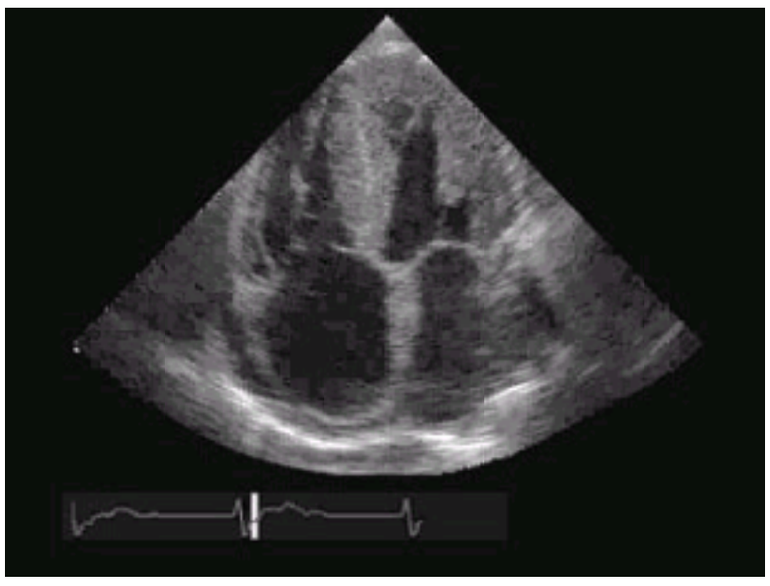


***e*FIGURE 33.0.9** Diagram of left ventricular pressure-volume loops illustrating systolic and diastolic dysfunction. In systolic dysfunction, the end systolic pressure-volume relationship (ESPVR, *dotted line*), an estimate of contractility, is displaced downward and to the right, and the stroke volume (SV) and ejection fraction (EF) are reduced. In diastolic dysfunction, which can occur as a consequence of aging, hypertrophy, or diabetes, the diastolic pressure-volume relationship is shifted upward and to the left, but the SV and EF are normal. Contractility is preserved (ESPVR is unchanged). In this setting, use of diuretics will reduce SV and EF if left ventricular filling pressure is lowered to a normal range. Inotropic agents are not useful (discussed in text). (From Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. *JAMA* 1994;271:1276–1280, with permission.)

Regardless of the cause or pathophysiology of CHF, age-related changes in the cardiovascular system contribute to its development and complicate its diagnosis and treatment (257). This is particularly true for older patients with CHF and preserved systolic function (258,259,260,261,262,263 and 264). Many elderly patients with CHF, possibly a majority older than the age of 80, have preserved systolic function. Age-related diastolic dysfunction results from both the altered myocardial properties and left ventricular chamber characteristics described earlier in this chapter. In addition, in patients older than the age of 75, amyloid deposits may be sufficient to worsen diastolic dysfunction (discussed in subsequent paragraphs). Diastolic dysfunction coupled with CHD, so prevalent in the elderly, is particularly devastating because myocardial ischemia also produces diastolic dysfunction. Precipitation of myocardial ischemia can produce sudden, dramatic increases in left ventricular filling pressure and pulmonary venous pressure, which results in dyspnea and “flash pulmonary edema.” The etiology of CHF in the elderly is frequently multifactorial. Atrial fibrillation, common in the elderly, results in loss of “atrial kick”; this produces a substantial increase in left ventricular filling pressure, which may result in pulmonary congestion and heart failure (222). The contribution of atrial contraction in maintaining a relatively low left ventricular filling pressure is especially important when diastolic dysfunction is present (254,260,263).

Clinical Presentation and Diagnostic Assessment

Diagnosis of heart failure in elderly patients can be challenging, as is true for all cardiovascular syndromes in the elderly. The usual symptoms of dyspnea, cough, paroxysmal nocturnal dyspnea, and orthopnea may be present, but noncardiac symptoms often predominate or may be the only presenting complaint (255), in part because of patients’ sedentary lifestyle. Nonspecific complaints such as weakness, fatigue, and anorexia may be the primary features, or subtle deterioration in CNS function with resultant somnolence, confusion, and disorientation (on occasion related to azotemia secondary to reduced renal perfusion) may confuse the diagnosis. Objective data are particularly valuable because multiple causes are frequently present, and the pathophysiology of heart failure in the elderly is complex. Electrocardiogram and chest radiograph are always useful, but the echocardiogram is the most valuable imaging technique in the elderly. Determining left ventricular ejection fraction is essential. Doppler echocardiography is of particular value because of the high incidence of diastolic heart failure. Heart failure with preserved systolic function occurs in at least 30% to 40% of elderly patients, and at even higher rates in the oldest old (258). Establishing the pathophysiology of CHF with echocardiography is critical in selecting therapy. In addition, the echocardiogram can precisely define valvular abnormalities, which are common, and give clues to rare but important abnormalities that occur in the elderly, such as amyloid infiltration.



Apical four-chamber view of amyloid heart disease. Note the significant thickening of the left ventricle and right ventricle walls due to infiltration. There is also characteristic thickening of the valves and biatrial enlargement. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)

Video 33.2 Transthoracic apical four-chamber view of a patient with amyloidosis. Note the thickened “sparkling” walls of the right and left ventricles. Both the mitral and tricuspid valves are mildly thickened and there is biatrial enlargement and a trivial pericardial effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 33.3 Transthoracic subcostal view of a patient with amyloidosis showing markedly thickened right and left ventricular walls, showing the characteristic “sparkle.” The right ventricle is towards the top of the screen and the right ventricle free wall is 1.5 cm thick. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The difficulties in diagnosing heart failure in the elderly even with sophisticated and expert echocardiography have led to an interest in the use of neurohormonal markers to diagnose heart failure as well as to assess prognosis (see Chapter 88). One of the more widely studied markers is brain neuropeptide (266,267).

Prognosis

The prognosis for elderly patients with CHF varies extensively (1-year mortality rates from less than 10% to well over 50%), depending on the cause of CHF, the patient’s age, the presence of atrial fibrillation, and the presence of comorbidity (258,259,264,265,268,269). Patients with primarily diastolic dysfunction tend to fare better than those with principally systolic dysfunction or a combination of the two. Female gender and diabetes worsen prognosis (270). In randomized trials, the oldest patients tend to benefit most from therapy because their mortality rate is much higher (269), but mortality and morbidity remain at high levels despite this therapy benefit.

Management

Careful assessment of the pathophysiology is the key to appropriate management. Calcific aortic stenosis, CHD, hypertension, or diastolic dysfunction—or some combination of these entities—is often present in a single patient. This emphasizes the importance of echocardiographic evaluation and the complexity of treatment. Sodium restriction is as effective in the elderly as in the young and should be recommended.

Systolic Heart Failure

Systolic dysfunction is treated as in younger cohorts, with allowances made for the comorbidity and altered pharmacology in the elderly. Diuretics are the cornerstone of therapy for controlling congestive symptoms and preventing heart failure in hypertensive patients. Digoxin continues to be used to control heart failure symptoms but has no advantage with respect to survival and must be dosed carefully in the elderly (15). ACE inhibitor therapy is the cornerstone of treatment, although dosage remains controversial. In ACE-intolerant patients, angiotensin II receptor blockers have been used, and two studies (ELITE-1 and ELITE-2) have evaluated their use in the elderly with conflicting results (16,20). The more recently completed ELITE-2 study showed a trend for the angiotensin II receptor blocker losartan potassium to be inferior to captopril, results that reversed the earlier findings of the ELITE-1 study. The situation is complicated further by the view that a combination of ACE inhibitor and angiotensin II receptor blocker may be superior because the agents work by different mechanisms. Clinical trials of carvedilol and metoprolol have shown a morbidity and mortality advantage in treating systolic heart failure independent of age. Calcium channel blockers have not demonstrated effectiveness in treating patients with left ventricular systolic dysfunction, including the elderly population. The PRAISE-II study, in which the calcium blocker amlodipine besylate was used, did not confirm the early advantage seen in PRAISE-I (17,271). Control of hypertension is an important aspect of preventing heart failure in the elderly (272).

The role of anticoagulant therapy for CHF in the absence of specific complications or atrial fibrillation is uncertain (273,274). Trials are under way to answer these questions. In fragile people, the benefit from anticoagulation therapy must be weighed against the risks of falls, gastrointestinal bleeding, and drug interactions. Nonsteroidal antiinflammatory agents are frequently used in the elderly because of the high prevalence of musculoskeletal disorders. Nonsteroidal antiinflammatory agents not only can attenuate the benefits of diuretic therapy or ACE inhibitors but may actually contribute to worsening renal function, hyperkalemia, and other abnormalities (275,276).

Diastolic Heart Failure

When diastolic heart failure is the primary problem, pulmonary congestion can be relieved by diuresis, but the very steep diastolic pressure-volume relationship (eFig. 33.0.9) indicates that even a modest decrease in circulating blood volume can markedly reduce left ventricular filling pressure, which results in hypotension, fatigue, and reduced renal perfusion. Hence, the use of diuretics requires individualized decisions with regard to dosage and duration of treatment as well as careful monitoring (eFig. 33.0.9). Judicious use of nitrates may be helpful, but avoidance of undue reduction in preload is critical.

The paucity of well-done control studies involving elderly patients with heart failure and preserved systolic function makes the choice of drugs problematic. Diastolic dysfunction with impaired left ventricular filling may be improved, however, by the use of beta-blockers and calcium channel blockers, which may enhance compliance and also reduce atrioventricular node conduction and slow the ventricular response, prolonging filling. ACE inhibitors are probably valuable for most patients with diastolic dysfunction because the nonhemodynamic effects of these drugs may be useful in reducing the collagen deposition of diastolic heart disease and because most elderly patients have an element of systolic, as well as diastolic, dysfunction related to systolic hypertension.

Digitalis preparations are of limited value in both systolic and diastolic heart failure (15) (see Chapter 91, Chapter 92, Chapter 93, Chapter 94, and Chapter 95). No inotropic agent (and digitalis is a weak one) can be expected to provide any benefit to diastolic dysfunction. Although debate exists on this point, digitalis preparations may produce more toxicity in the elderly because of myocardial alterations and because of age-related myocardial and renal changes. Digitalis preparations may be useful in controlling the ventricular rate in patients with atrial fibrillation, but age-related atrioventricular nodal dysfunction often prevents a rapid ventricular response to

atrial fibrillation.

VALVULAR HEART DISEASE

Systolic murmurs are extremely common in elderly patients, with a prevalence of 60% or greater. Most murmurs do not carry important clinical implications and are the result of age-related aortic valve thickening and sclerosis or minor mitral regurgitation secondary to papillary muscle dysfunction caused by CHD, hypertensive or idiopathic cardiomyopathy, or age-related mitral valve changes (277).

Senile Calcific Aortic Stenosis

The most frequent cause of potentially serious valvular heart disease in older persons is calcific aortic stenosis. A Finnish epidemiologic study in a population older than the age of 55 demonstrated a steady increase in the degree of aortic valve calcification and stenosis (278). In the group aged 55 to 71 years, only 7% had severe calcification and 72% had no calcification, whereas in the group older than age 85 years, 19% had severe calcification and only 25% had no calcification. In the 75- to 79-year-old group, 4.1% had an aortic valve area of less than 1 cm^2; this number had risen to 13.7% in the over-85 age group, with 4% having a valve area of less than 0.6 cm^2 (eTable 33.0.5).

*e*TABLE 33.0.5 HELSINKI AGING STUDY: AORTIC VALVE AREA AND AGE

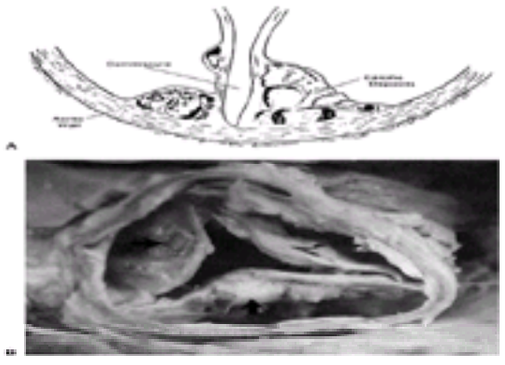
	Age group (yr)		
Aortic valve area (cm^2)	**75–76 (n = 197)**	**80–81 (n = 155)**	**85–86 (n = 124)**
£1.2	2.5%	3.9%	8.1%
<1.0	2.6%	2.6%	8.1%
<0.8	0.5%	2.6%	5.6%
<0.6	None	1.9%	3.2%
<0.4	None	None	0.8%

Note: Critical as +2.9; moderate as +4.8.
From Lindroos M, Kupari M, Heikkila J, et al. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 1993;21:1220–1225.

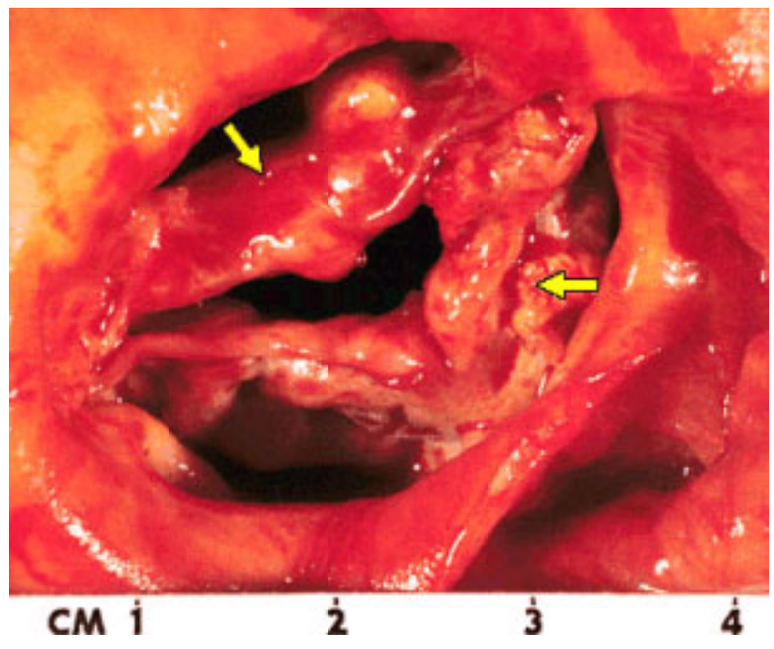
Early changes are characterized by fibrosis followed by calcium deposition, first within the fibrosa at the base of the cusps, which results in cuspal stiffness (279). Calcium deposits do not extend beyond the linea alba and do not involve or compromise the commissures, which is distinctly different from the case with rheumatic or congenital lesions. Mild or even moderate calcific deposits may reduce cuspal mobility but impose minimal hemodynamic alterations; however, heavy deposits may immobilize all three cusps with resultant stenosis. Age-related changes in the aortic ring may produce a systolic murmur that must be differentiated from aortic valve stenosis. The loss of parallel orientation of collagen fibrils, development of fatty changes, and eventually calcification may result in annuloaortic ectasia and sometimes mild or moderate aortic regurgitation. The histopathology of these changes may be an inflammatory process with macrophage and T-cell infiltration, lipid deposition, and basement membrane disruption.

Aortic valve calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

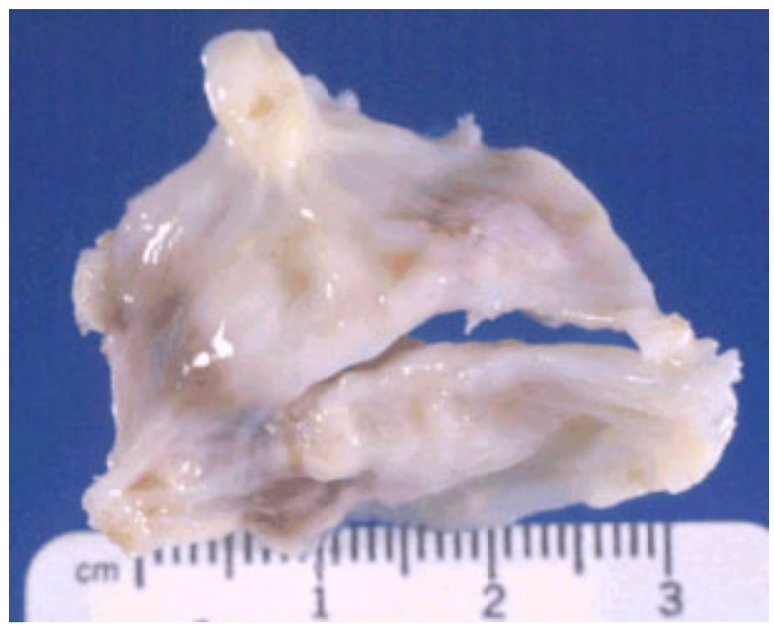
A congenitally bicuspid aortic valve with acquired calcification and stenosis is the most frequent cause of calcific aortic stenosis into the sixth decade (280); by age 70, however, age-related changes in the normal tricuspid aortic valve are usually responsible for stenosis (*e*Fig. 33.0.10). Rheumatic aortic stenosis (now extremely rare in the United States) does not occur as an isolated finding and mitral involvement is always present.



***e*FIGURE 33.0.10 A:** Schematic presentation of early calcific deposits at the junction of the cusps with the aortic wall. Note that the process does not induce commissural adhesions. **B:** Photograph of senile calcific aortic stenosis from above the valve. Heavy calcific deposits are seen at the depths of the sinuses (*arrows*), and no commissural fusion is present. (From Friesinger GC, Gravanis ME. Aging and the cardiovascular system. In Gravanis ME, ed. *Health and disease in cardiovascular disorders*. St. Louis: Mosby, 1993, with permission.)



Bicuspid aortic valve with calcific stenosis. The yellow arrows identify each of the valve leaflets.



Bicuspid aortic valve with calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Clinical Evaluation

The murmur of significant senile calcific aortic stenosis may not be prominent and often is no greater than grade 2. The associated findings, including left ventricular hypertrophy, delayed carotid upstroke, narrow pulse pressure, and basal thrill, are often absent in older patients because of comorbid conditions such as hypertension or pulmonary disease. A diminished aortic second sound is virtually always present, however, because of the restricted valve movement with heavy calcification.

Doppler echocardiography is the ideal approach to assess the significance of basal systolic murmurs and follow the course of senile calcific aortic stenosis. Whenever the condition is suspected, this study provides the diagnosis and assesses its severity.

Compensatory hypertrophy may not be as great in elderly patients, especially in women; at least, hypertrophy has been shown to be age dependent in the rat model (281). The clinical diagnosis of senile calcific aortic stenosis can be difficult. A high level of suspicion and a careful search for physical findings is needed. It should be considered in all elderly patients with angina, dyspnea, or subtle CNS symptoms, and echocardiography should be performed if doubt exists.

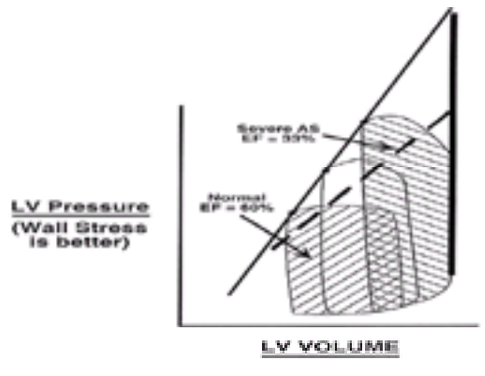
Management

Management of senile calcific aortic stenosis is similar to management of calcific aortic stenosis in younger patients (see Chapter 22) but is more complicated because of the frequent presence of associated important coronary atherosclerotic disease and other cardiac and noncardiac comorbidities. In addition, operative mortality and morbidity are considerably higher. Hence, the timing of aortic valve replacement must be highly individualized in older patients with severe obstruction.

As in younger patients, postponing valve replacement until the appearance of major symptoms of aortic stenosis—CHF, angina, and syncope (or equivalent symptoms)—is usually appropriate, but interpreting symptoms in elderly patients can be very difficult because of confounding factors. Angina can be related to CHD, CHF to past hypertensive disease or old infarction, and syncope (or CNS symptoms) to degenerative conduction-system disease, arrhythmias, and carotid or cerebral vascular disease. When convincing symptoms and a major mean gradient (50 mm Hg) are present, the decision to proceed with valve replacement is straightforward. Even if associated CHD and important comorbidity are present, the decision is justified *if the patient wishes to proceed*, with the understanding that mortality is high (up to 50% in the oldest patients) during the following 3 or 4 years (282).

Two clinical situations constitute special and relatively common problems in elderly patients with calcific aortic stenosis. First, patients with a reduced ejection fraction and a moderate gradient (mean of 25 to 30 mm Hg) whose symptoms are likely to be multifactorial in origin (dyspnea from pulmonary disease, angina because of major coronary arteriosclerosis, etc.) present a particularly difficult treatment problem even when the aortic valve area is markedly diminished (less than 1 cm^2). Highly individualized decisions are needed that consider the patients' desires and reflect the understanding that operative risk is high, complications frequent, convalescence often prolonged, and long-term benefit less likely than in patients in whom symptoms can be clearly attributable to severe aortic stenosis. A variety of provocative tests designed to assess the ability of these dysfunctional ventricles to "recruit contractility" and increase the gradient have been proposed. Most popular has been the use of dobutamine echocardiography (283,284). Although some studies report that this approach can be useful, no agreement has been reached on the issue, and the decision to replace the aortic valve remains inherently a clinical one.

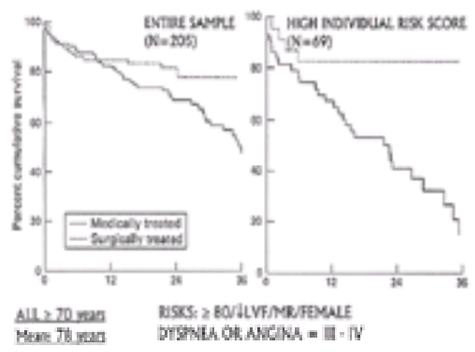
The end systolic pressure-volume relationship provides a powerful conceptual framework to assess the effect of afterload and contractility on reduced ejection fraction (285) (eFig. 33.0.11). If the left ventricular systolic peak pressure is no greater than 130 to 140 mm Hg, severe contractile dysfunction is usually present despite severe aortic stenosis and markedly reduced aortic valve area. In patients with low left ventricular systolic peak pressure, operative mortality is high and a very significant number of patients experience no benefit even if they survive surgery. Perhaps as many as one-third of the patients undergoing surgery experience substantial benefit. Preoperative selection of these patients remains problematic (286).



***e*FIGURE 33.0.11** End systolic pressure-volume relationship in aortic stenosis (AS). The solid line represents normal contractility for the end systolic pressure volume relationship. The dashed line represents reduced contractility. For the same degree of aortic stenosis and same reduction in ejection fraction (EF), the left ventricular (LV) systolic pressure is greatly reduced with diminished contractility (discussed further in the text).

The second difficult clinical situation involves patients with severe angina whose extensive coronary atherosclerosis requires CABG and who have associated mild to moderate calcific aortic stenosis; that is, aortic valve replacement would not be recommended in the absence of the need for CABG. The ability to predict the rate of progression of calcific aortic stenosis is needed to make the best judgment in this situation. Despite multiple reports studying the progression of aortic stenosis and reasonable agreement about progression in various groups of patients, variability in individual patients is very high. In a carefully done prospective study including patients with an average age of approximately 65 years, the increase in the mean left ventricular aortic gradient was approximately 7 mm per year and the decrease in the aortic valve area was approximately 0.1 cm^2 per year (287). Individual variability in such studies is too wide for the results to be useful in predicting progression in a specific patient. Other investigators have performed retrospective studies involving patients with mild to moderate aortic stenosis who underwent CABG without aortic valve replacement (288). In short-term follow-up of such patients (less than 5 years in most cases), the need for reoperation for aortic valve replacement was high (25%). Although whether or not to replace the aortic valve when mild to moderate stenosis is present at the time of CABG remains an inherent clinical problem, strong consideration should be given to replacement if surgical mortality can be kept low. Avoiding a second operation in the short term (less than 5 years) is highly desirable. Issues such as aortic valve area (range of 1 cm^2), gradient (20 to 25 mm Hg or more), velocity of the jet (3 to 4 m per second), and probably the extent of aortic valve calcification should enter into the decision.

Operative mortality ranges from under 5% to over 20% (289,290,291,292 and 293). Risk factors increasing operative mortality include low functional class, lack of sinus rhythm, preoperative left ventricular systolic dysfunction, aortic regurgitation, performance of concomitant surgical procedures, previous bypass surgery, need for emergency surgery, coronary artery disease, female gender, concurrent mitral valve surgery, hypertension, and left ventricular systolic dysfunction (*e*Fig. 33.0.12). Perioperative complications are common, and the incidence of stroke varies from under 2% to more than 10%. As has been emphasized, not only the extent of cardiovascular disease but also the overall preoperative status of the patient is of particular importance in assessing operative risk and especially long-term outcome. Assessment of biologic age rather than chronologic age is the important issue.



***e*FIGURE 33.0.12** Surgical versus medical treatment for aortic stenosis in the elderly with 36-month outcomes. ↓LVF, decreased left ventricular ejection fraction; MR, mitral regurgitation. [From Bouma BJ, van Den Brink RB, van Der Meulen JH, et al. To operate or not on elderly patients with aortic stenosis: the decision and its consequences. *Heart* 1999;82(2):143–148.]

Percutaneous balloon dilatation of the aortic valve has been explored as an alternative to valve replacement. Although the procedure may benefit a few highly selected patients, the risks of the procedure and lack of a long-term benefit in the overwhelming majority of patients has led to its abandonment (294,295) (see Chapter 91).

Aortic Regurgitation

Aortic regurgitation, much less common than aortic stenosis in the elderly, is usually trivial and results from hypertension, age-related valvular deformity, or changes in the aortic root including dissection. Occasionally it results from infectious endocarditis and a variety of rare causes, including Marfan syndrome, ankylosing spondylitis, and collagen vascular diseases (296). For aortic regurgitation in the elderly to be severe enough to justify surgery is unusual. Aortic regurgitation secondary to dissection and endocarditis are exceptions and are discussed in Chapter 25 and Chapter 107. Aortic regurgitation related to dissection or endocarditis usually has a sudden onset and is relatively easily diagnosed.

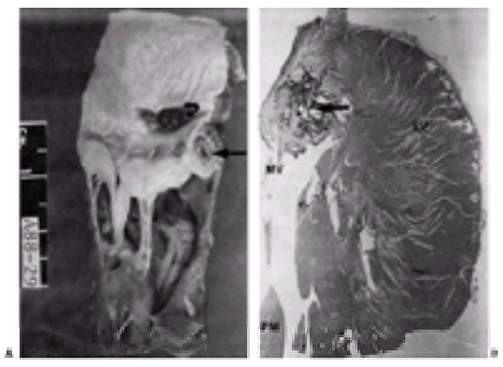
As with all valvular disease, echocardiography usually allows a precise determination of cause and evaluation of the severity of the lesion, as well as an estimate of left ventricular function, the latter of which is of critical importance in estimating prognosis and surgical outcomes. Patients with severe aortic regurgitation can usually be easily diagnosed by clinical examination using the pulse pressure, classic peripheral findings, evidence of left ventricular hypertrophy, and the diastolic murmur. These findings may be modified in the elderly because of associated peripheral atherosclerosis, which results in wide pulse pressure and modification of peripheral signs, and in particular produces systolic hypertension. In addition, only a short or difficult-to-hear regurgitant murmur may be present because of associated pulmonary disease or high left ventricular end diastolic pressure or both.

Because left ventricular dysfunction can occur in the absence of symptoms, the practice of operating to correct severe aortic regurgitation in younger patients before the development of symptoms has become understandably and appropriately popular. A variety of clinical prediction rules related to echocardiographic abnormalities have been developed to aid the decision to perform surgery. These include a variety of measurements but generally some estimate of left ventricular ejection fraction and end systolic dimension (297). The 55-55 rule is often cited: When the ejection fraction is under 55% or the left ventricular end systolic dimension is greater than 55 mm or both, aortic valve surgery should be undertaken, because waiting longer may result in increased operative mortality and a poorer outcome with regard to left ventricular function. Conceptually, this approach stems from application of the principle of the left ventricular end systolic pressure-volume relationship. In elderly patients, particularly those older than the age of 75, postponing surgery even in this situation seems reasonable, because the risk of surgery and long-term outcomes are not well characterized and medical therapy using afterload reduction is a reasonable alternative. In younger patients, nifedipine therapy has been shown to postpone and reduce the need for surgery in a randomized, controlled trial (298). Afterload reduction with ACE inhibitors is strongly suspected to be the treatment of choice in elderly patients.

Mitral Regurgitation

Mitral regurgitation is extremely common in the elderly and is usually mild. Minor mitral regurgitation from papillary muscle dysfunction is common. Mitral regurgitation often represents an incidental finding that is unlikely ever to require any medical or surgical therapy. However, in a substantial minority of the elderly with mitral regurgitation, the degree of regurgitation poses a major dilemma in assessing its importance in reference to the patient's syndrome. This problem is particularly important when coronary bypass surgery is under consideration. This matter is discussed in subsequent paragraphs.

Age-related changes in the mitral valve are more striking in the anterior leaflet, where they are characterized by fragmentation and disorganization of elastic and collagen fibers, and deposition of lipids and calcium. Similar degenerative changes in the fibrous ring of the mitral valve lead to calcification. Severe calcification abolishes the sphincteric function of the mitral ring, may immobilize the posterior mitral leaflet, and results in moderate mitral regurgitation. Extensive calcific deposits in the mitral ring may affect the conduction system and produce heart block, ulcerate and embolize, or become the site of infectious endocarditis (*e*Fig. 33.0.13).



***e*FIGURE 33.0.13** Age-related changes in the mitral valve (MV) apparatus. **A:** Photograph of a longitudinal section of the posterior wall of the left atrium, posterior mitral leaflet, and posterior left ventricular wall. Note massive calcification of the mitral annulus (*straight arrow*) and the ulceration through the atrial endocardium. The latter is covered by a thrombus (*curved arrow*). **B:** Microscopic longitudinal section of posterior left ventricular wall, posterior mitral leaflet, and posteromedial papillary muscle (PM). Massive calcification of the mitral annulus (*arrow*) is apparent, extending also into the adjacent myocardium. [From Kitzman DW, Scholz DG, Hagen PT, et al. Age-related changes in normal human hearts during the first 10 decades of life. Part II (maturity): a quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. *Mayo Clin Proc* 1988;63:137–146.with permission.]

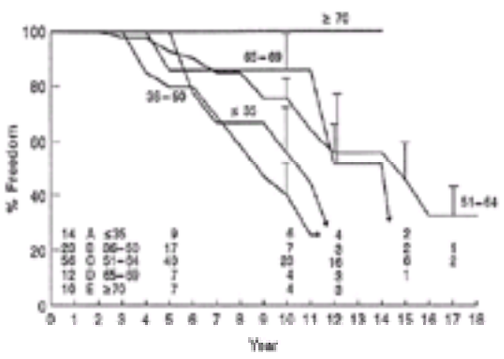
Mitral annular calcification, usually associated with only mild or moderate regurgitation, occurs almost exclusively among the elderly. (It may occur in young patients with specific diseases, such as Marfan syndrome.) It can be seen easily on chest radiography, is always diagnosed by echocardiography, and should be considered in a differential diagnosis of a systolic murmur in older persons, particularly women (299). Rarely, the regurgitation can be marked, and occasionally calcification is so extensive that mitral inflow is impeded and functional mitral stenosis is present.

The regurgitation that occurs with mitral valve prolapse (MVP), which is common in the young (more frequently in women) but seems less frequent in older persons, is of increasing interest and importance. A minority of patients with MVP have progressive regurgitation, and in older age a few experience spontaneous chordal rupture with marked mitral regurgitation and associated CHF (300,301). MVP with myxomatous degeneration of the mitral valve is an increasingly common indication for mitral valve replacement or repair in older patients (302). In a report of 266 patients undergoing mitral valve surgery for severe mitral regurgitation (mean age, 64 years), slightly over 60% had MVP. The underlying morphologic changes (expansion of the leaflets, stretching and thinning of the chordae tendineae, and increased mucopolysaccharides in the spongiosa layer of the leaflets) are similar to those observed in younger patients but are more extensive, which makes mitral valve repair less likely (302).

Management and Surgical Considerations

The threshold for the use of afterload-reducing agents, particularly ACE inhibitors, should be low in elderly patients with regurgitant lesions, particularly because of associated hypertension and CHD. In well-compensated moderate to severe mitral regurgitation, the left ventricular ejection fraction should be above normal, but a well-maintained left ventricular ejection fraction should not be considered a contraindication to the use of afterload-reducing agents, even though no convincing data exist to indicate that the progression of the disease is slowed. Watchful waiting, judicious use of vasodilator therapy, and careful serial echocardiography are key issues in decision making regarding surgical intervention.

The indications for mitral valve surgery in the elderly are similar to those in the young, with greater emphasis on relieving symptoms rather than on preserving ventricular function (in the absence of symptoms). Myocardial dysfunction can progress despite maintenance of overall pump function (absence of symptoms and a normal ejection fraction), and this has led to earlier surgery (in which valve repair is often possible) in younger cohorts. In mitral regurgitation, the increase in preload can obscure the fact that left ventricular dysfunction is occurring; that is, left ventricular ejection fraction can be maintained in the normal range (pump function is preserved) while contractility is being compromised (muscle function is deteriorating). The left ventricular end systolic pressure-volume relationship provides a conceptual framework to allow differentiation of muscle dysfunction and pump function. A variety of indices have been developed relating preoperative left ventricular end systolic volume (or echocardiographic dimension) with ejection fraction to allow prediction of postoperative ejection fraction, which is the most important determinant of long-term outcome. One popular algorithm calls for operating when the left ventricular end systolic dimension is less than 45 mm and the ejection fraction is in the normal range (285,302). Due to the shortened life expectancy, increased mortality, and increased complication rate after valve surgery, however, decisions must be must be highly individualized. An exception to this approach is older patients who are in general good health and who have developed acute or subacute symptoms due to rupture of major chordae tendineae, for whom prompt operation is desirable. Biologic valves, subject to degeneration and calcification in younger patients, are frequently the valves of choice in older individuals, in whom prosthesis longevity is increased (303) (*e*Fig. 33.0.14).



***e*FIGURE 33.0.14** Freedom from structural deterioration of Carpentier-Edwards porcine bioprosthesis, stratified by age group, for all valve positions. (From Jamieson WRE, Munro AI, Miyagishima RT, et al. Carpentier-Edward standard porcine bioprosthesis: clinical performance to seventeen years. *Ann Thorac Surg* 1995;60:999–1007, with permission.)

Mitral valve repair instead of replacement has become increasingly effective and popular, and is always desirable when feasible. Preserving the valve, and particularly the valvular apparatus including the papillary muscles, lessens postoperative complications and greatly improves long-term outcome, and should always be encouraged; however, it is not always possible in the elderly (303) (see Chapter 21).

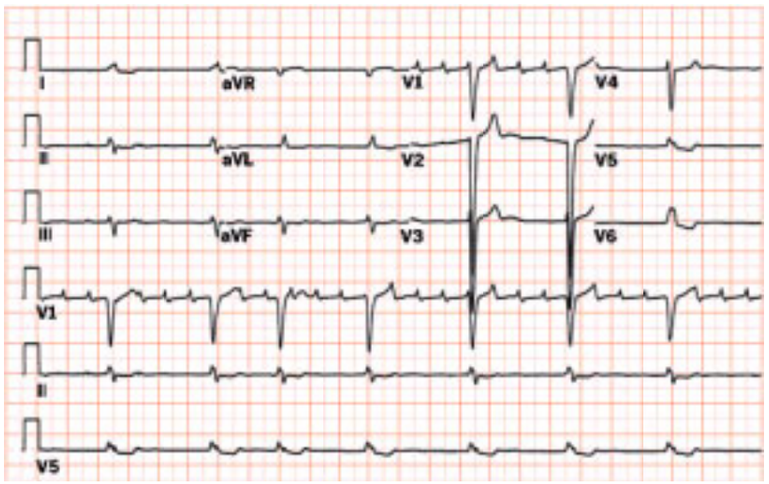
As with aortic stenosis, a large proportion of elderly patients with important mitral regurgitation have accompanying advanced coronary heart disease with past infarction or active myocardial ischemia or both. This constitutes a special problem in clinical decision making. Most of these elderly patients are in a situation in which the conventional measures predicting a good outcome have been exceeded, ejection fraction is substantially reduced (often 35% or less), and the end systolic dimension exceeds the desirable limit (304,305,306,307 and 308). In patients in whom CABG is clearly indicated because of important ischemia, the preferred approach usually is to perform the bypass and not to include mitral valve repair if the regurgitation is only mild or moderate and particularly if it is not associated with pulmonary hypertension. In many such patients the mitral regurgitation may improve postoperatively, which is probably related to ventricular remodeling due to the improved myocardial blood flow. In this setting, a highly individualized decision must be made and is guided not only by clinical judgment but by the experience of each center. In those patients in whom the clinical problem is primarily or exclusively CHF with severe mitral regurgitation related to CHD, anecdotal experience and reports of small series indicated that patients can undergo operation with a relatively low surgical mortality (range of 10% to 15%) and that in some instances the ejection fraction, surprisingly, is improved with mitral valve repair. Long-term follow-up information is limited, however, and postoperative mortality remains high. In all patients with valvular disease, fastidious attention to prophylaxis for subacute bacterial endocarditis is a very important part of management.

Arrhythmias

Arrhythmias are a major problem in the elderly but are discussed only briefly here. Chapter 58, Chapter 59, Chapter 60, Chapter 61, Chapter 62, Chapter 63, Chapter 64, Chapter 65, Chapter 66, Chapter 67, Chapter 68, Chapter 69, Chapter 70, Chapter 71, Chapter 72, Chapter 73, Chapter 74, Chapter 75, Chapter 76, and Chapter 77 comprehensively and extensively summarize the data on mechanisms, diagnosis, prognosis, and treatment. Age-related changes in the heart and autonomic

nervous system discussed in earlier sections of this chapter, especially those involving the conduction system, are important in arrhythmias.

Age-related electrocardiographic and electrophysiologic abnormalities are common in the elderly. Degenerative changes in the conduction system (309,310,311,312,313,314,315 and 316) produce important clinical manifestations. Sinus pauses, sinus bradycardia, atrial fibrillation, and other varieties of atrial ectopy and arrhythmias result. The number of sinus node cells decreases with age, and a greater irregularity is seen in their shape. An increase in fat, elastic fibers, and collagen within the nodal tissue is also seen with aging. Despite the significant cellular reduction, particularly after the age of 75, sinus node activity may be normal. Vascular disease in the sinus node artery is not considered to be the cause of the histologic changes in the sinus node (312).



High-grade atrioventricular block. Note marked discrepancy between atrial and ventricular heart rates.

Trifascicular block. Note right bundle branch block, left anterior hemiblock, and associated first-degree atrioventricular block.

An 83-year-old patient with complete heart block, junctional escape rhythm, left anterior hemiblock, and complete right bundle branch block.

“Sick sinus syndrome” is a misnomer because other manifestations of degenerative conduction system disease can usually be uncovered when specifically sought. In many instances, the ECG also shows additional infranodal conduction defects such as left anterior hemiblock and right or left bundle branch block. These changes in the His-Purkinje system are sometimes, but not always, predictors of progressive degeneration of the conduction system and the development of heart block, frequently with syncope. However, electrophysiologic studies undertaken to predict progressive changes and important clinical manifestations have been disappointing (310).

A 93-year-old male patient with trifascicular block.

A 75-year-old male patient with trifascicular block.

In cases of complete heart block, and in some cases of supraventricular tachycardia, the arrhythmia per se is responsible for symptoms and dictates the management approach. More frequently, the extent of associated cardiac disease, primarily CHD with ischemia or left ventricular dysfunction or both, are key features in producing symptoms. The total picture—not the presence of ECG abnormalities caused by degenerative conduction system disease and the arrhythmias (especially if atrial)—should dictate therapy.

Drugs commonly used in older patients, including beta-blockers, calcium channel blockers, digitalis, and antihypertensives (such as alpha-methyldopa), can produce some of the same ECG changes as degenerative conduction system disease. This further illustrates the need to carefully differentiate abnormalities and findings caused by adverse drug reactions from those related to disease in the elderly.

Atrial Fibrillation

Atrial fibrillation (see Chapter 64) is extremely common in the elderly. It is responsible for considerable morbidity and mortality, especially stroke and CHF (29,265,317,318,319 and 320), and is a marker for increased in-hospital mortality in Medicare patients. Often, it is asymptomatic. Its prevalence may be 10% in persons older than 70 and may increase to 15% by the mid-eighties. The median age for atrial fibrillation is 75 years. The range for 1-year mortality is extremely wide, from less than 1% to 15%. Patients at highest risk for stroke are those older than age 75 and those with impaired ventricular function and a history of thromboembolism and associated conditions, particularly hypertension and diabetes. Left atrial size as judged by echocardiography is another independent predictor but has not been well studied in the elderly population.

A careful general clinical evaluation searching for subtle hyperthyroidism, chronic pulmonary disease, the use of beta-agonists, hypokalemia (from drugs), and alcoholism is important. These and other diseases and conditions can precipitate atrial fibrillation and can be very subtle in their clinical manifestations in the elderly. Cold remedies, antihistaminics, and all varieties of stress (especially infections and surgery) may precipitate atrial fibrillation.

Management

Management of atrial fibrillation is complex in the elderly, but as in the young, the goals are prevention of thromboembolytic complications and treatment of arrhythmia-related symptoms, especially CHF. Transthoracic and, on occasion, transesophageal echocardiography have an important role in the evaluation and management of patients with atrial fibrillation. Details about ventricular function, size of the left atrium, and presence of valvular disease, and a search for intraatrial thrombi (usually requiring transesophageal echocardiography) are of great value in assessing the cause, potential for sustained sinus rhythm after cardioversion, and the risk of thromboembolism (321,322a). All patients should receive anticoagulation therapy unless specific and strong contraindications exist. Data are convincing that warfarin should be used. In patients presenting with acute symptoms, initial treatment aimed at slowing the rate is essential, and a variety of approaches are available (see Chapter 64). For treatment after the acute phase has been addressed, two strategies are debated: control of the ventricular rate and restoration of sinus rhythm.

The decision to convert atrial fibrillation to sinus rhythm in the elderly is complex and problematic. The frequency of side effects of commonly used antiarrhythmic medications and the relatively low rate of maintenance of sinus rhythm (30% to 60% revert to atrial fibrillation within a year) diminish the attractiveness of cardioversion unless the atrial transport function can be shown to be of major benefit in improving symptoms of CHF. Age-related diastolic dysfunction makes it desirable to restore normal sinus rhythm with the expectation that left ventricular filling pressure will be reduced and symptoms of pulmonary congestion alleviated. In many elderly patients, however, sinus bradycardia with ineffective atrial contraction follows restoration of sinus rhythm. Other approaches to maintain sinus rhythm, particularly the use of amiodarone hydrochloride and, more recently, nonpharmacologic approaches such as atrioventricular nodal modifications or ablation with use of rate-responsive pacemakers, implantable atrial defibrillators, or even surgical interventions (maze procedure), are increasingly used, but these are apt to be helpful in only a limited number of highly specialized situations in the elderly. In many patients, maintenance of an optimum antithrombotic regimen and control of ventricular response are the preferred approaches. The National Institutes of Health Atrial Fibrillation Following Investigation of Rhythm Management (AFFIRM) study is a large randomized, controlled trial that is investigating the feasibility, desirability, and implications of restoration of sinus rhythm versus control of ventricular rate. Results of a small randomized, controlled trial have been reported, and restoration of sinus rhythm has not been shown to be superior to rate control and anticoagulation therapy (352).

The use of pacemakers in atrial fibrillation due to sick sinus syndrome is very popular and is often invoked because of drug-induced bradycardia or the desire or need to use antiarrhythmic agents that may interfere with atrioventricular conduction in elderly patients who have age-related atrioventricular nodal dysfunction. Ambulatory electrocardiographic monitoring is frequently performed in these patients, and pauses of 2 to 4 seconds (sometimes longer), particularly during nighttime, are commonly found. Elderly patients tend to have cerebral symptoms, fatigue, and other symptoms that might be related to pauses, but unless the symptoms and pauses correlate, the use of a pacemaker is difficult to justify. This common practice has not been evaluated in any systematic way, although the belief that pacemakers should be used to abolish symptoms, possibly pause related, or prevent long pauses, even though asymptomatic, or both is intuitively appealing.

Ventricular Arrhythmias

The risk of ventricular arrhythmias is related to the structural heart disease and other comorbidities. CHD and ventricular dysfunction are the most important structural heart diseases that increase the risk of sudden cardiac death, but smoking, systolic hypertension, hypercholesterolemia, and left ventricular hypertrophy are additional risk factors.

Monitoring and electrophysiologic testing are key elements in evaluation of patients who have or are suspected of having ventricular arrhythmias. These matters are discussed in detail in Chapter 60, Chapter 62, and Chapter 67. Treatment for sustained ventricular arrhythmias has increasingly involved the use of implantable cardioverter-defibrillators (ICDs; see Chapter 67 and Chapter 75). The benefit of ICDs in patients older than the age of 70 is similar to that in younger patients (perhaps greater), but the number of elderly studied in controlled trials has been small, and such patients are undoubtedly highly selected (323,324 and 325). As has been repeatedly emphasized, the evaluation of the total patient—particularly with reference to comorbidity and competing risks—should dictate treatment when an ICD is being considered (326,327,328,329 and 330). In patients who are physiologically young and are judged to have the opportunity to benefit for a number of years, ICD placement should be considered according to criteria similar to those used for younger cohorts, as has been demonstrated to be useful in randomized, controlled trials. [Clearly, the indications for ICD placement in practice do not follow those adopted in randomized, controlled trials (326,328).] In many older patients, however, particularly those older than age 75 and especially those older than age 80, death from noncardiac disease or nonarrhythmic death becomes increasingly likely (160,327). In a single-center observational study, among 74 patients older than the age of 75 who underwent ICD implantation, mortality was 33% at 4 years. Appropriate shocks were infrequent (35%). No sudden deaths occurred. This high non–sudden cardiac death mortality in the elderly again emphasizes that caution is needed in extrapolating outcomes found in younger cohorts, because benefit in the elderly will most certainly be overestimated. Antiarrhythmic drug therapy, particularly the use of beta-blockers, has an important role in the treatment of sustained ventricular tachycardia in the elderly (331), although drug selection is always complicated and problematic (see Chapter 67).

The large group of patients with asymptomatic nonsustained ventricular arrhythmias represents a major clinical dilemma, because data for this group of the elderly are totally inadequate to direct clinical decision making. The principles discussed in Chapter 67 and Chapter 75 apply but must be used in a much more precise and highly individualized fashion. In particular, attention to comorbidity, frailty, and ventricular function is important. Although the range of available devices is becoming broader and devices are becoming more sophisticated, this only adds to the complexity in making clinical decisions for the elderly without greatly simplifying the issues.

Complete Heart Block

Complete heart block occurs overwhelmingly in the elderly population. Chapter 63, Chapter 71, and Chapter 74 discuss the issues involved, including indications for the use of pacemakers in heart block and the rationale for selection of a specific type of pacemaker. Assessing the cause of symptoms can be very difficult in the elderly because conduction system disease is frequently present in the absence of symptoms, and a variety of disease processes, particularly carotid and cerebrovascular disease, may be responsible for the patient's complaints of dizziness or syncope. Therefore, a fastidious workup is required. On occasion, an empiric clinical decision must be made in the absence of any supporting documentation regarding the cause of complaints (332). Debate is ongoing as to whether more sophisticated and expensive atrioventricular universal (DDD) pacemakers provide additional benefit over atrioventricular sequential pacing (DVI) pacemakers in the elderly (333,334 and 335).

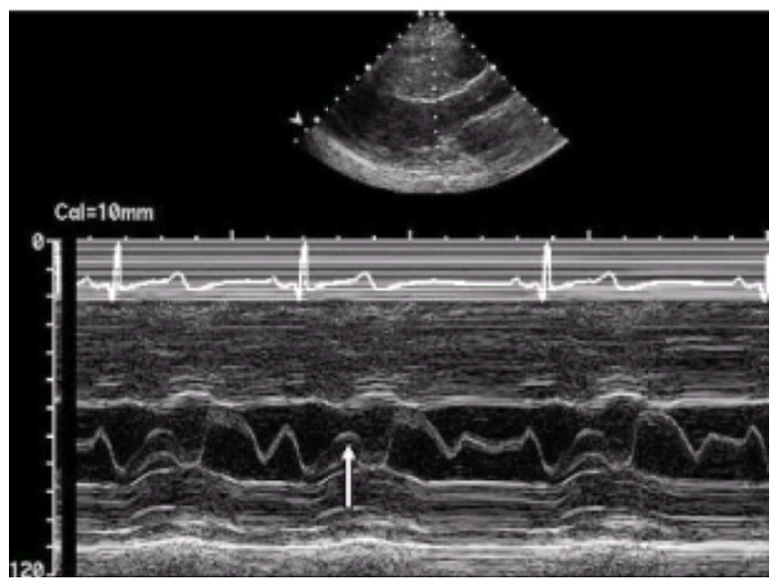
Electrophysiologic and Ablation Treatments

The indications for electrophysiologic testing are evolving and for some patient groups are controversial, so the fact that no consensus exists about the use of these approaches in elderly patients is not surprising. However, EPS clearly is feasible, can provide valuable information, and is specifically helpful in directing therapy in elderly patients. Patient selection remains the issue. Similarly, catheter ablation treatments at the atrioventricular node for selected cases of atrial fibrillation and for supraventricular tachycardia in elderly patients not responding to simple drug therapy is feasible, carries relatively low risk, and is effective.

Hypertrophic Cardiomyopathy and Hypertensive Hypertrophic Cardiomyopathy

That hypertrophic cardiomyopathy (see Chapter 29) has a different genetic basis and a different prognosis in the elderly than in young patients is increasingly evident. The condition is not rare in the elderly, and several studies have found that more than 50% of patients are older than the age of 50 and as many as 40% are older than the age of 60 (336). Morphology is also different.

Echocardiographic studies have shown similar asymmetric hypertrophy of the septum, systolic anterior motion of the mitral valve, and severity of an outflow tract gradient, in young and elderly patients, although younger patients have more severe hypertrophy (337,338). Ventricular cavity contours differ; the septum in the young is more hypertrophied, has reversed curvature, and thus creates a crescent-shaped left ventricular cavity, whereas elderly patients have normally shaped left and right ventricles and less severe hypertrophy overall.



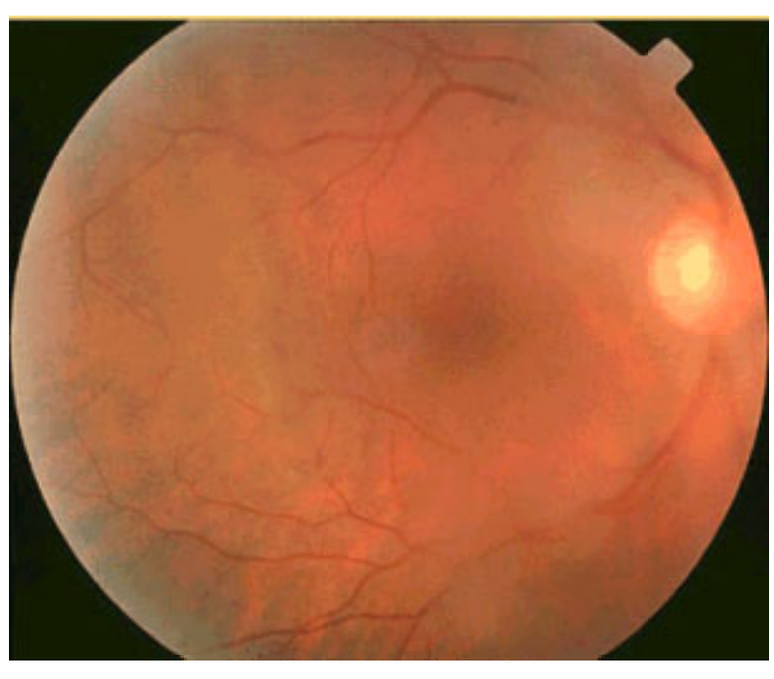
M-mode tracing of hypertrophic cardiomyopathy with severe septal hypertrophy seen at the top of the trace and systolic anterior motion (SAM) of the mitral valve in systole seen in the middle of the trace (designated by the arrow).

A subgroup of elderly patients with obstructive hypertrophic cardiomyopathy, 87% of whom were women, revealed an atypical systolic contact between the mitral valve and the intraventricular septum, which produced a dynamic subaortic obstruction (338). This contact can also result from a posterior excursion of the ventricular septum toward the mitral valve. Sizable calcium deposits in the mitral valve annulus in these patients probably contributed to the outflow tract narrowing. Another subset of patients, most of whom were African-American, showed severe concentric hypertrophy with a small left ventricular cavity, an increased ejection fraction (80%), and diastolic dysfunction (339). Most of these patients had hypertension; the increased blood pressure may somehow serve as the stimulus to unusual and severe hypertrophy. The association of hypertrophic cardiomyopathy with systemic hypertension in a subgroup of elderly patients has prompted some to suggest an etiologic link between these two entities. Others, although recognizing that hypertension may aggravate the underlying cardiomyopathy (leading to an increase in myocardial mass), have stressed that hypertension is not the primary cause of hypertrophic cardiomyopathy. These observations indicate the complexity of the spectrum of hypertrophic cardiomyopathic disease in the elderly.

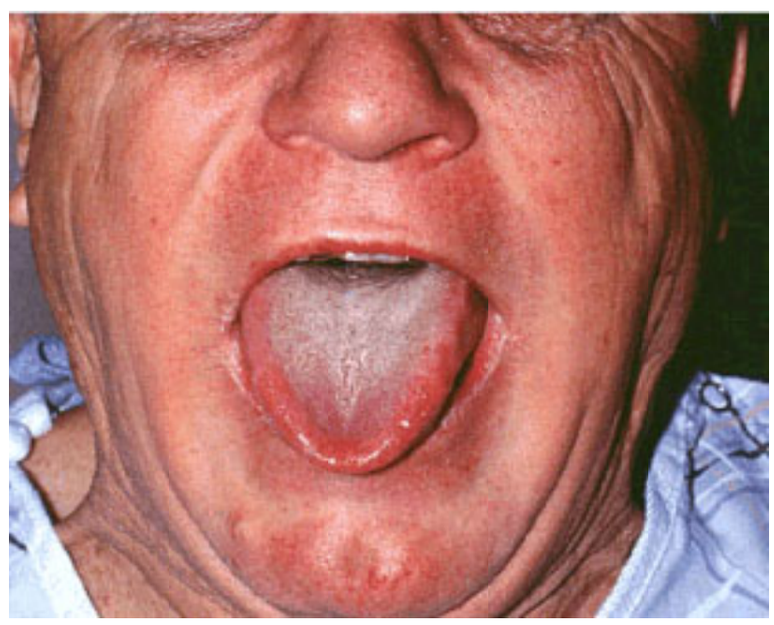
The long-term survival rate of elderly patients with hypertrophic cardiomyopathy is very similar to that of an age- and sex-matched control group (336,337,338,339 and 340). Although adequate studies on the genetic transmission of hypertrophic cardiomyopathy in the elderly are lacking, the genotypes are different from those that occur in the more malignant syndrome seen in younger patients (341,342), especially patients with a family history of disease (and, most important, when the family history involves sudden cardiac death) (341,342,343,344 and 345).

Senile Amyloidosis

Autopsy studies indicate that amyloid is commonly present in patients older than the age of 75, and up to two-thirds of patients older than age 85 may show evidence of amyloidosis (346). Among these patients, approximately one-third may show extensive ventricular involvement; CHF is present in approximately half the patients and may be attributable primarily to the amyloidosis (347). Amyloidosis was judged to be an important contributor to death (perhaps the primary cause) in one group of patients (348). Amyloid deposits were first described in elderly patients in 1876, but their potential importance with regard to pathophysiology in most patients is not clear. In addition, the biochemical properties of amyloid in old hearts and its relationship to the amyloid in familial amyloidosis and that associated with multiple myeloma need further clarification (336). Although it is rarely diagnosed clinically, definitive diagnosis has been made by biopsy (349).

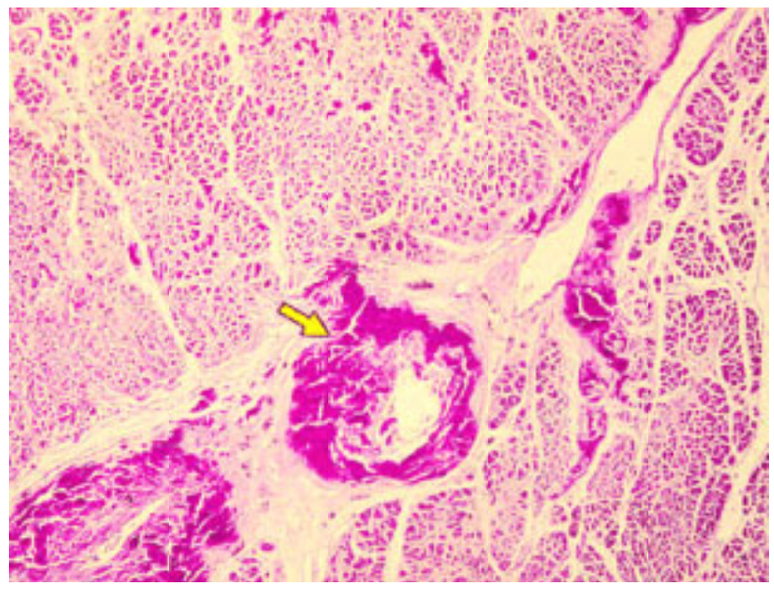


Vitreous opacities in association with amyloidosis.

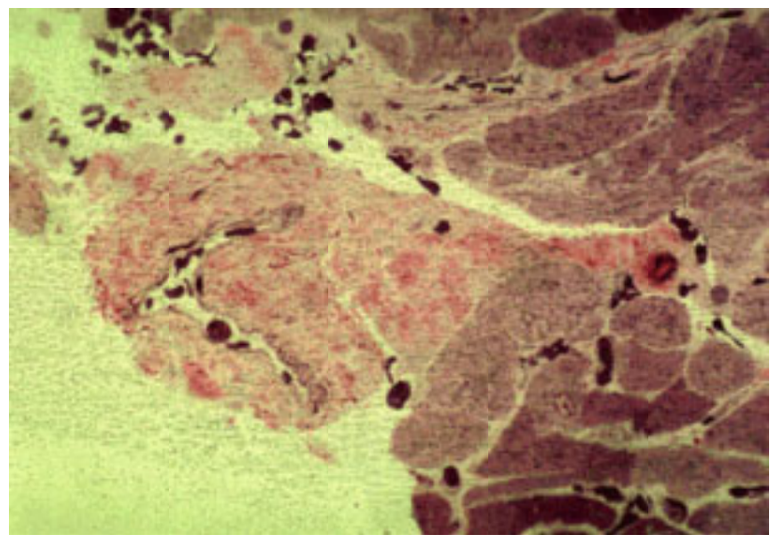


Amyloidosis. Infiltration of the tongue occasionally leads to macroglossia. Cardiac manifestations include cardiomegaly, congestive heart failure, and arrhythmias.

Amyloidosis. Infiltration of the skin results in raised waxy papules or plaques that are usually in clusters.



Amyloidosis of the heart. This is cresyl violet stain of the left ventricular myocardium. The yellow arrow indicates a metachromatic red-violet homogenous deposit around an intramyocardial arteriole with similar interstitial deposits.



Amyloid deposition. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

In recent years, immunohistochemical studies have recognized three distinct types of senile cardiovascular amyloidosis: isolated atrial amyloidosis, senile aortic amyloidosis, and senile systemic amyloidosis, in which organs such as lungs, liver, and kidneys are involved (in addition to the heart) (350). The latter, although rare, may cause significant cardiovascular morbidity. Distinguishing between nonsecretory, immunoglobulin-derived primary amyloidosis with cardiac involvement and senile systemic amyloidosis is possible only with immunohistochemical techniques.

Diastolic dysfunction increases as amyloid deposits increase, which results in pulmonary congestion and eventual right heart failure with edema. Conduction defects and atrial fibrillation, although common in older patients with amyloid deposits, do not seem related to amyloid infiltration into the conducting system. This must not be confused with the conduction system disease that occurs because of deposits in patients who have familial amyloidosis with polyneuropathy (351). Echocardiographic study can be useful and may be relatively specific in diagnosis (see Chapter 49).

Patients with senile amyloidosis may be more sensitive to the effects of digitalis and have more episodes of digitalis toxicity, but this is not well established (351,352). The outcome of patients with senile amyloidosis is grave, and such patients have a mortality of 50% by 6 months from the time of endomyocardial biopsy diagnosis. Not surprisingly, the CHF responds poorly to all interventions. Much remains to be learned about the characteristics, occurrence, and pathophysiologic effects of senile amyloidosis. Whether its occurrence is somehow genetically determined or is only related to the immunologic changes associated with aging is also unclear.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The amount and cost of cardiovascular care provided to the elderly will continue to increase because of the growing number of elderly patients, the larger number of services and procedures provided per patient, and the increased cost of the sophisticated care given. The pressure to control cost will continue (Medicare expenditures are now at $200 billion annually). Although the rate of rise will ameliorate, the absolute expenditures will continue to increase appreciably. This will be particularly true in the over-75 age group, because cardiovascular disease tends to have a more complicated course in this group and the physiologic changes, both in the cardiovascular system and throughout the rest of the body, make all management strategies different and more complicated than in the younger old (65 to 75 years).

Physicians will feel obligated to use the considerable fiscal resources available for elderly care most appropriately. They will require more and better outcome data for all major cardiovascular syndromes, which will lead to an understanding (or disappearance) of the widely disparate practice patterns, especially in the use of procedures in the elderly. Data on such outcomes must include “long-term” information, because these older patient subsets have a high 3- to 5-year mortality even with successful therapeutic interventions. These “long-term” outcome studies will highlight the need for a philosophical approach that emphasizes quality of life and the patient’s choice (incorporating the patient’s individual value system). These issues may be more important than short-term mortality data and longevity per se.

Randomized, controlled trials are unlikely to play a major role in resolution of management dilemmas in the elderly because of the extraordinary heterogeneity in this population. Registries (databases) involving carefully prospectively collected key variables are likely to be a more effective approach. Critical characterization of complications of procedures and adverse drug reactions, and collection of follow-up data on functional status are among the critical issues, and these can be addressed by registry studies. Algorithms and clinical rules developed for younger cohorts are not directly transferable to elderly cardiovascular patients, which further emphasizes the need for prospectively collected, syndrome-specific data.

The heterogeneity of aging will serve as a stimulus for physicians to characterize elderly patients more objectively in relation to their ability to withstand the stress of procedures and complications of disease, with emphasis on physiologic reserve and biologic age rather than chronologic age. With better characterization of biologic age and physiologic reserve, more precise estimates of outcomes of therapies and interventions can be made, patients can be given better information, and, with their families, they will have more realistic expectations. Better-informed decisions will result. Biologic age is multifactorial, involving cognitive, emotional, physical, and nutritional attributes as well as function of specific organs (lung, kidney, liver), because no single feature can characterize the total elderly patient. The concept of competing risks will evolve, since even the most successful therapy will have limited effect on longevity in the very old.

Although important research at the cellular and molecular level will characterize and provide better understanding of the aging process, this basic information is not likely to be immediately useful in the management of the large number of elderly patients with major cardiovascular disease. Preventive measures, including physical exercise, mental stimulation, avoidance of depression, good nutrition, and abstinence from tobacco use, are helpful approaches to postpone or ameliorate the consequences of aging and allow patients to tolerate cardiovascular diseases better when these become manifest.

THE FUTURE

Advances in medicine will result in a larger elderly population. These patients will require a more philosophical approach with emphasis on quality of life and the patient's choice, as well as cost considerations. Data from "long-term" outcome studies will guide the physician in making appropriate choices and providing realistic expectations for the elderly patient. Prevention and postponement of cardiovascular disease will be emphasized as the most effective approaches.

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END-OF-LIFE CARE

GARY S. FRANCIS

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OVERVIEW

Life in the coronary care unit (CCU) is changing. Once a comfortable “laboratory” for conducting studies of physiology and pharmacology, as well as a bastion of medical education, the modern CCU has become a vastly different place over the course of the last 15 to 20 years. This is particularly true in large, tertiary teaching hospitals. The patients are older and sicker, and they have more multiorgan dysfunction than before. They frequently require multiple-team, interdisciplinary management. Patients who have routine, uncomplicated myocardial infarction continue to be admitted, but many such patients are now well cared for in large suburban hospitals by highly qualified cardiologists. Tertiary teaching hospitals more often receive elderly patients with highly complex conditions who are transferred on day 2 or 3 of acute myocardial infarction complicated by acute pulmonary edema, stroke, refractory ventricular tachycardia, cardiogenic shock, severe mitral regurgitation, ruptured interventricular septum, critical aortic stenosis, acute renal failure, sepsis, or some combination of the above. Such patients can usually be stabilized and their conditions managed, but they not uncommonly languish for days in the CCU, obtunded, unable to be easily weaned from the ventilator. Anxious families understandably become frustrated, and uncertainty about prognosis only serves to further fracture the bond between physicians and family members.

The dilemma is made worse by the inability of many patients to participate in the decision-making process. Families may be absent. Occasionally, competing interests and desires may emerge among family members. Decisions about the end of life are seemingly more complex in today’s world. Resources are often constrained, and economic pressures exist to reduce the length of stay in the CCU. The overall daily charges for the CCU range from $2,000 to $10,000 per day. To put the economic burden into perspective, it is estimated that critical care costs in the United States are more than $80 billion per year, or approximately 1% of the gross domestic product (1). Of course, the high cost of care is a global problem, certainly not unique to the United States.

The aging CCU patient population, complexity of disease, high prevalence of multiorgan dysfunction, unrealistic expectations of patients and families, and persistence of taboos regarding discussions of the end of life in most cultures mean that physicians who work in the CCU must be familiar with certain guiding principles regarding the withholding and withdrawal of life-support systems. The decision to withhold or withdraw life-sustaining support from a critically ill patient is an increasingly difficult but necessary part of providing care in the CCU. The preciousness of human life is embedded in nearly every religion and culture. The natural tendency of every physician is to nurture the patient back to health, and therefore to preserve life without regard to age, cost, or other culturally imposed boundaries. It is clear that in a small number of cases, death is inescapable. In such cases, the wise physician turns attention to the family, while ensuring that the patient is made comfortable. But mostly there are gray zones, in which outcomes are uncertain and decisions about continued aggressive treatments are extremely difficult. Uncertainty becomes champion.

How are these decisions made? Who makes these decisions? What are the ethical principles that underlie these decisions? How does a physician actually withdraw life support? The goal of this chapter is to provide CCU physicians with practical advice that will help guide them through this difficult process.

HISTORICAL PERSPECTIVE

For many years, the ethical and legal consensus in the United States has been that patients and their surrogates have the right to refuse life-prolonging therapy. This stems from the common-law right of self-determination (the principles of autonomy), which was upheld by the U.S. Supreme Court in 1891 (2). Despite agreement on this general principle, dying patients in the United States frequently receive unwanted interventions (3,4). The patient’s right to autonomy, though sacred and carefully guarded, sometimes competes with the staff member’s skill in providing aggressive life-extending treatment. Physicians and nurses are often poorly trained in withholding or withdrawing intensive life support. It is sometimes easier for them to continue aggressive care than to struggle with the difficult decision to withdraw life support. This issue came to a head in the landmark case of Karen Ann Quinlan (1976), and the courts ultimately forged a legal consensus based on the principle of patient autonomy. This principle establishes the right of patients (or their surrogates) to determine which medical interventions to accept or refuse, even when the absence of treatment results in death. It was affirmed by the U.S. Supreme Court in the case of Nancy Cruzan in 1990. The court acknowledged that patients who die after life support is withheld or withdrawn die of the underlying disease process. Such deaths are not assisted suicides or euthanasia. The courts have also reasoned that the spouse and children are the most appropriate surrogates because they are best positioned to know the patient’s feelings and desires about treatment.

In fact, next of kin are no better than physicians in estimating what the patient would want with regard to end-of-life care (5). Therefore, the physician, acting on behalf of the patient, must assess the validity of the surrogates’ preferences and the commonality of belief structure. Friends or family members may hold power of attorney to make decisions for the patient, as directed by a living will or advanced directive. However, living wills have not had a major impact on decision-making or costs associated with end-of-life care, because they are so nonspecific. Patients frequently express different beliefs when they are healthy than when they face decisions about withdrawal of life-support measures (6). The U.S. Supreme Court has unanimously ruled that there is no constitutional right to physician-assisted suicide but has also effectively required all states to ensure that their laws do not obstruct the provision of palliative care—including the administration of drugs as needed to avoid pain at the end of life (7). The provision of morphine or other medications at the end of life to control pain and suffering has the full force of the judiciary behind it.

From a historical context, these rulings have come at a time when modern technology can sustain organ function for prolonged periods, and thus they are of great importance to physicians working in the CCU. Lay people, through the print media and television, have come to expect full recovery after illness. Families and patients often seem mystified when informed of the details of an illness and become alarmed when they realize that meaningful recovery may not be possible. The gap between family expectations and medical reality can only be closed by frequent empathetic and effective communication between the medical team, the family, and, when appropriate, the patient.

ETHICAL PRINCIPLES

Some fundamental principles of medical ethics have evolved over centuries and are generally accepted (Table 34.1).

Autonomy
Preservation of life
Alleviation of suffering
First do no harm
Justice: ensure that medical resources are allocated fairly
Telling the truth
The rule of double effect

TABLE 34.1 FUNDAMENTAL PRINCIPLES OF MEDICAL ETHICS

Autonomy

The term *autonomy* is derived from the Greek words *auto* (self) and *nomos* (rule or law). The principle is the source of the common-law right of self-determination and lies behind the constitutional right of privacy. No right is held more sacred, and the U.S. Supreme Court has used this principle in asserting the right of patients to refuse life-saving treatment. If an adult patient is heavily sedated or unconscious, a surrogate decision-maker (usually a spouse or family member) should authorize decisions about care. Health care providers need to realize that decisions about care are in the hands of the patient, not the medical team. The attending physician and other members of the medical team determine treatment strategy on the basis of scientific principles and then decide on the best course of action based on discussion with the patient or the families. The patient (or the surrogate decision-maker) almost always accepts the team's advice, but the relationship is one of partnership, not paternalism. The ethical principle of autonomy states that the patient has a right to self-determination that supersedes the desires of the medical team—even if it means that death of the patient will result. In the United States, minors do not have autonomy under the law, and parents become the decision-makers.

The CCU environment doesn't always allow for the luxury of time, and lengthy discussions with multiple family members are sometimes not possible. Management of cardiogenic shock, recurrent ventricular fibrillation, acute pulmonary edema, or acute aortic dissection requires quick, reasoned actions. In such emergencies, the principle of preservation of life guides the physician, provided there are no antecedent instructions from the patient or family to withhold life support.

Although end-of-life issues are best discussed in the privacy of the outpatient clinic when the patient is medically stable, many patients misunderstand the process of advanced life support or are apprehensive about discussing death. This may be related to the nearly universal taboo against discussing death, which is particularly common among the older generation. A significant number of people prefer a less dominant autonomous role in end-of-life decisions and put their trust in their doctors and the health care system (8). To approach a critically ill patient in the CCU with heartless questions about cardiopulmonary resuscitation and intubation is a grotesque distortion of what should be a very private, reasoned dialogue. Trying to berate a sick patient into being autonomous near end of life is a tragic mistake. My practice is always to discuss end of life in the outpatient setting when possible. When this is not possible, which is often the case, it is helpful to talk to the patient alone at the bedside and attempt to have them understand and make distinctions between short-term aggressive care and prolonged life support.

In the end, the informed patient can usually make an autonomous decision. Physicians must guard against imposing their own values and should not slant the discussion in such a way as to mirror their own feelings about the end of life. It must be recognized that some cultures object to informing patients of a terminal diagnosis. It may be believed that the family, not the patient, should make life-support decisions. Violating a patient's cultural values should be avoided. This is a serious problem that defies a simple solution. It is often useful to have serious dialogue with the family and then the patient as soon as possible—usually within 48 hours of admission to the CCU.

Preservation of Life

All physicians are aware of this ethical principle, and it requires no explanation. Problems may arise when preservation of life competes with beneficence or alleviation of suffering. For a dying patient, alleviation of suffering may be more important than prolonging the end of life. However, the sanctity of life is of great importance and has its roots in most religions of the world. Many believe that every second of life is sacred and must be preserved at all cost.

Alleviation of Suffering (Beneficence)

To restore health and relieve suffering is one of the most time-honored goals of physicians. It is the fundamental duty of all doctors. Beneficence supersedes the perceived beliefs of society or the personal values of the physician. Relief of suffering may supersede preservation of life (see the section Rule of Double Effect), particularly when death is inescapable.

First Do No Harm (Nonmaleficence)

Primum non nocere is an ancient principle of medicine and is embedded in the Hippocratic oath: "I will use treatment to help the sick according to my ability and judgment, but I will never use it to injure or wrong them." This principle underlies the physician's decision to recognize that death is inescapable and to proceed with comfort care. However, the Hippocratic oath's injunction to "do no harm" seldom applies in today's environment. It is unethical to continue aggressive care for patients who have no hope for recovery; the physician's goal is to provide comfort, not to prolong dying. Likewise, inappropriate drug use and the ordering of diagnostic tests that are potentially risky but not likely to help the patient are unethical under certain circumstances. On the other hand, there may be pressure from families to "keep going." Such a dilemma requires frequent and careful dialogue with the family. It may take days for some family members to realize that death is imminent. In the CCU, it isn't always possible to know when death is inescapable, and it is important for the physician to convey a sense of hope, when appropriate. Families and patients sometimes have unrealistic expectations and will request that "everything be done," even though the patient has little or no hope for meaningful recovery. Some families will put a highly spiritual spin on the problem and insist that the medical team should hold out for a "miracle." Often, the patient wants more aggressive care than the family (9). Physicians may be inaccurately overly pessimistic, whereas patients tend to be inaccurately overly optimistic (8). Frequent, careful assessment of the patient and the prognosis coupled with frequent communication with family becomes even more important.

An experienced CCU physician can often sense when multiorgan failure is beginning to emerge and is keenly aware of this when each day brings a new struggle to keep the patient alive. Such patients are often intubated, sedated, and unable to carry on meaningful dialogue. It is the physician who has specialized knowledge of the natural history of disease, not the family, and it is the physician who must use this powerful knowledge to help guide families when making decisions about withdrawal of life support. Families often want certainty, but there is no certainty in most instances, only judgments. Physicians should clearly describe what will likely happen if aggressive treatments are continued and contrast this information with what will likely happen if comfort care only is begun. A combination of objective quantitative information and the physician's judgment about outcome is better than either alone (8).

Justice: Ensure That Medical Resources Are Allocated Fairly

It is clear that some economically deprived populations are underserved and as a consequence may have higher morbidity and mortality rates. Decisions regarding care should be blind to economic circumstances, ethnicity, perceived societal views, political persuasion, gender, and age. As care becomes more rationed in our society, the principle of justice takes on more practical importance. Heart transplantation, for example, is a highly rationed form of treatment with generally accepted medical indications and contraindications. If a heart is transplanted into a patient who does not comply with treatment and who dies quickly of rejection, two people die: the noncompliant patient, and the anonymous patient on the transplant list who dies while waiting for a heart transplant. In our society, end-stage heart failure and the need for heart transplants occurs in cocaine dealers, prisoners, pedophiles, and wealthy elderly people who are beyond the usual age limit for heart transplantation. The principle of justice would assume that only medical need determines care. However, outcomes for heart transplantation are affected by social issues, medical compliance, age, family support, and underlying general health. If there were a surplus of donor hearts, decisions about who should receive a heart transplant would be less difficult. As all therapy becomes more rationed in an era of harsh cost-containment, the principle of justice becomes more applicable in the CCU. The principle of justice will become more difficult to apply as competition for scarce resources intensifies. Some evidence exists that justice has been ignored and that racial bias has entered the decision-making process (9).

Telling the Truth

Honest communication between physician and patient is very important and is a major principle of ethics in Western society (10). In some Asian societies, it is

considered inappropriate to tell a patient that he or she has cancer; the stigma and fear associated with knowing one has cancer outweigh the active withholding of information about diagnosis and prognosis. In the United States, it is assumed that patients and families want to understand the diagnosis, prognosis, and risks and benefits of various diagnostic and therapeutic procedures, but the level of understanding desired by patients and families is highly variable (5). This principle is particularly important to uphold in the CCU, where the presence of many different teams and fellows can greatly fragment the care of the patient. It is important to try to personally explain to the patient the risks and benefits of cardiac catheterization, percutaneous coronary interventions, and cardiac surgery, fully understanding that someone else will obtain direct informed consent and will further expound on the risks and benefits of these procedures. Patients tend to view the CCU team and the attending physician as “their” doctors. This is who they see on rounds daily and know and trust most explicitly, and this is who should explain to the patient and family what diagnostic and therapeutic plans are evolving—what the strategy will be for the next 24 to 72 hours. Consultants may be asked to discuss the case with families on occasion. For example, when complex noncardiac complications occur, such as intracerebral hemorrhage or severe hypoxic encephalopathy, it is reasonable for the neurology team to have a discussion with the family. If an internist or family doctor has a long-standing relationship with the patient, that person should be consulted and engaged with the decision when possible.

Rule of Double Effect

The rule of double effect may be the ethical principle least understood by medical personnel and lay people. Many are not even aware of the principle. According to the rule of double effect, outcomes that would be morally wrong if intentionally provoked are permissible if foreseen but unintended (11,12 and 13). Specifically, administering opioids to treat a terminally ill patient’s dyspnea or pain may be acceptable even if the medication contributes to or causes the patient’s death. A harmful effect of treatment, even death, is permissible if death is not intended but occurs only as a side effect of a beneficial action. It is not uncommon for dying or terminally ill patients in the CCU to receive morphine as part of comfort care. It is usually given in small doses (an initial drip of 1 to 2 mg per hour or repeated boluses ranging from 10 to 30 mg per hour) to alleviate air hunger or dyspnea, supplemented by benzodiazepines to treat anxiety or agitation. Appropriate use of opioids for symptom control does not usually shorten life, and there is generally little or no need to invoke the rule of double effect (14).

The rule of double effect was developed by moral theologians of the Roman Catholic Church in the Middle Ages (15,16). The underlying logic is that it is impossible for a person to avoid all harmful actions. Failure to intervene to comfort a dying patient harms the patient by allowing treatable discomfort to continue. If the intent of treatment is to relieve suffering, the foreseen but unintended risk of earlier death is permissible. The U.S. Supreme Court has demonstrated support for this principle by requiring all states to ensure that their laws do not obstruct the provision of adequate palliative care, especially for alleviation of the physical discomfort of patients who are facing death (17,18). The physician’s goal under these circumstances is to relieve the patient’s discomfort (in this case, air hunger or dyspnea). Neither the physician nor the patient intends for the patient to die. If death occurs from the opioids (rare), it is foreseen but unintended. The rule of double effect and subsequent legal rulings supporting the principle have served to reassure physicians that prescribing morphine drips for terminally ill patients is morally and legally permissible and is the proper thing to do (19).

FAMILY CONFLICTS

The decision to withdraw advanced life-support measures is one of the most difficult decisions that clinicians and families must make. Often the prognosis is not absolutely certain. The patient’s judgment should be involved when possible, although most patients who are on advanced life support are not mentally competent. Only a small minority are able to participate in the initial decision to limit treatment [4% in a surgical intensive care unit (ICU) vs. 27% in an oncology service] (20). It is important to provide hope to families, but hope is a double-edged sword. Hard questions need to be asked of families: What has been the family’s experience with other dying patients? What do they consider “suffering”? What is their concept of “meaningful recovery”? The medical team should avoid offering guarantees and certainties regarding death or recovery. The worst thing a physician can do is give mixed messages or abdicate responsibility. Families need time to deal with the devastating thought of withdrawal of life-support systems and death. A useful tactic is to get the family together in a quiet, private room and discuss the issue at length. Give them room to vent. Allow the family to verbalize their grief. Make sure their spiritual needs are attended to by a hospital chaplain. Warring siblings with polarized desires for aggressive care versus comfort care are a particularly difficult problem, and an ethics consultation is usually in order. When our CCU team is first contemplating withdrawal of advanced life support, we take the following steps:

1. Determine the prognosis as carefully as possible. Unfortunately, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) scores do not apply to CCU patients. One must be able to deal with the uncertainty of dying.
2. Assess the patient’s competence; engage them when possible. Patients receiving advanced life support are generally not mentally competent.
3. Discuss the case with the whole team and reach consensus about a decision. Nurses often have a more expansive knowledge of the family and the patient’s needs and wants.
4. Do not rush the families! A useful strategy is to tell them that if things do not improve over the next 48 to 72 hours, withdrawal of life support may be appropriate. It should be stressed that repeated procedures and diagnostic tests can be uncomfortable and can be a form of suffering. Emphasize that comfort care may allow the patient to have a more peaceful and dignified death. The time-limited goal often allows the family time to contemplate a most difficult decision.
5. Families need assurances that comfort care will be maintained and that the CCU team will not abandon them. However, in some cases, transferring the patient out of the CCU after withdrawal of life support is appropriate, and this should be explained to the family in anticipation of such a move.

When family members or legal surrogates want “everything done,” the medical team should comply with this request. A direct challenge by the medical team usually fails to convince the family of the futility of further treatment, but repeated, compassionate discussions can result in ethical decisions that will benefit the patient.

FUTILITY

The concept of medical futility has been controversial and remains vague. It attempts to establish the principle that physicians may use their judgment and skills to determine when treatment is futile. Once such a determination has been made, the physician can unilaterally withhold or withdraw treatment, even if the patient or family objects. The principle of autonomy is thus essentially expunged. Futility is not an objective entity but embraces many judgment-based values (21). There is no clear definition of medical futility (22). Such decisions, other than about physiologic futility (e.g., treating hypertension with an antibiotic) or an absolute inability to prevent death, always involve judging value. Whose value counts?

In reality, physicians can only frame choices for the patient; they cannot make unilateral decisions. Moreover, the courts have not recognized the right of physicians to act unilaterally in cases in which they believe further care would be futile (23). This is not to say that physicians do not recognize clinical situations in which care is futile. It simply means they cannot act unilaterally. Their obligation is to speak with the patient or the family, frame the issue, and have the patient or the family participate fully in the decision regarding further care. Judgments about anything other than physiologic futility are vague; imposed value judgments, imprecise definitions, a lack of concrete data, and great uncertainty about the definition of “futility” intervene. Communication of information to the family such as the success rate of resuscitation, long-term meaningful recovery, and likelihood of discharge from the hospital must be clear and consistent.

WITHHOLDING OR WITHDRAWAL OF LIFE-SUSTAINING THERAPY

Once the medical team and the patient or family has decided that the patient is dying and that further aggressive care is unwarranted, there is precious little guidance about how the process should be implemented. Physicians seem poorly trained in managing the transition from aggressive care to comfort care. The following steps should be considered:

- A final decision should be made after careful discussion with the patient (if appropriate), the family, and the nursing staff.
- Such patients are frequently intubated, and therefore a do-not-resuscitate order should also be written. If the patient is not intubated, a do-not-intubate order should be written.
- A morphine drip should be started. Patients in the CCU often suffer dyspnea as the primary discomfort, and morphine, 1 mg per hour, will usually alleviate this symptom. Presumed respiratory distress can be treated with a 5- to 10-mg bolus of morphine, followed by an increase in the infusion to 2 to 5 mg per hour.
- Conscious patients who manifest anxiety should be treated with intravenous lorazepam (1 to 4 mg every 30 minutes), and patients with delirium should be treated with intravenous haloperidol if necessary. If tolerance to these medications has developed, the hypnotic drug propofol may be used.
- Ventilation: in most cases, I prefer to leave the endotracheal tube in place while gradually decreasing the ventilator rate, positive end-expiratory pressure, oxygen therapy, and tidal volume until the patient is spontaneously breathing room air through the endotracheal tube. This way, secretions can be suctioned to prevent rattling, which may be perceived as suffering by the family. The gradual turning off of the ventilator (30 minutes to 3 hours) allows the family to spend time at the bedside if desired, but there is no merit in prolonging the dying process by very slow weaning over the course of many hours. Patients who are receiving neuromuscular blocking drugs should cease receiving such treatment before the ventilator is withdrawn. Such agents should not be introduced when the ventilator is being withdrawn, and neuromuscular function should be restored before life support is withdrawn (24). It is believed that withdrawal of life support can ethically occur in the presence of pharmacologic neuromuscular blockade when death is expected to be rapid, but it is usually safest to stop neuromuscular blockade before withdrawing the ventilator, because assessment of comfort is impossible. When discontinuation of neuromuscular blockade is not possible because the burden on the family of waiting for neuromuscular blockade to wane exceeds the benefits of allowing better assessment of the patient’s comfort level, sedatives and analgesics can be skillfully administered.
- Some patients or families will specifically request that the endotracheal tube be removed. This can be done after appropriate suctioning. Humidified air can be

given to prevent drying of the airway.
- Pressors should be stopped.
- Intraaortic balloon pumps should be turned off.
- Antibiotic therapy should be stopped.
- Artificial nutrition should be stopped.
- Blood draws should be stopped.
- Intravenous fluids should be reduced and used to facilitate analgesics and sedation.
- Restraints should be removed, monitors discontinued, and alarms silenced.
- Excess secretions should be suctioned.

The median time between withdrawal of life support and death was 3.5 hours in one study but varied from 5 minutes to 5.5 days (25). Families should be told that death may not be instantaneous, and that patients are sometimes transferred to a palliative care ward where they will be kept comfortable. Rarely, patients may even spontaneously recover.

Withdrawal of artificial nutrition and hydration is often very difficult for health care workers and families to accept (26). However, both ethical guidelines and court decisions support the practice (27,28). Recent information supports the conclusion that tube feeding seldom achieves the intended medical aims and that it may cause, rather than prevent, suffering (29). Continued nutrition and hydration may lead to considerable volume overload and pulmonary edema in a patient who is not otherwise being monitored carefully (30). Emerging consensus now suggests that dying patients experience little or no discomfort on withdrawal of tube feedings, parenteral nutrition, and intravenous hydration (31).

There is a growing recognition that nephrologists should maintain a low threshold for initiating dialysis on a trial basis, and a similarly low threshold for discontinuing dialysis that fails to appreciably improve the quality of life. Death occurs, on average, 9.6 days after discontinuation of chronic dialysis treatment (32).

Lastly, it must be emphasized that forgoing life-sustaining treatment is usually not a single-point decision but one that evolves over the course of several days (20). In two large academic surgical ICUs (Moffitt-Long Hospital, San Francisco, and San Francisco General Hospital), the median time from ICU admission to death in patients undergoing withholding or withdrawal of life support varied from 4 to 8 days (median time period at Moffitt-Long Hospital and San Francisco General Hospital, respectively) (33). This suggests that it takes time for the decision to evolve and for the patient to die after the decision is made. However, surgical ICUs are quite different from CCUs. No such data are yet available from CCUs. At the Cleveland Clinic Foundation, the CCU mortality rate is 7.5%. Approximately one-half of the deaths result from withholding or withdrawing of life support, and one-half result from “natural” causes. Current prognostic models have limitations (Table 34.2) but should be used as an adjunct to the process of shared decision-making.

Prognostic models give probabilities of survival or death rather than a "yes" or "no" answer; because of 95% confidence intervals, no model can statistically exclude survival even in the most severely ill patients.
Individual accuracy of these predictions depends on whether a specific patient's medical condition was reasonably well represented in the population from which the model was derived.
Most models derive their predictions from factors present at or shortly after admission to the intensive care unit and do not provide updated mortality estimates as the patient's condition changes.
Some patients have inherently unpredictable courses.
Conventional models of patients in the intensive care unit predict only hospital survival, not long-term survival, functional status, or quality of life after hospital discharge.

Modified from Faber-Langendoen K, Lanken PN. Dying patients in the intensive care unit: foregoing treatment, maintaining care. *Ann Intern Med* 2000;133:886–893, with permission.

TABLE 34.2 LIMITATIONS OF PROGNOSTIC MODELS FOR END-OF-LIFE DECISION-MAKING IN THE CORONARY CARE UNIT

The withholding or withdrawal of life support is a difficult, often agonizing process. It requires careful scrutiny and rests on important ethical and legal principles that are continually evolving (34). There are no absolute guidelines for deciding when to withdraw advanced life support. Each patient and clinical situation must be considered in their own contexts. Frequent communication with patients, families, or legal surrogates; open sharing of data; and careful assessment of the changing prognosis are critical to the process.

EUTHANASIA

Euthanasia is the act of putting to death without pain a person suffering from an incurable and painful condition. It is a vague and emotionally provocative term and best describes an act such as giving a lethal injection. It is not to be confused with withholding or withdrawing life support in a dying patient. The U.S. Supreme Court has unanimously ruled that there is no constitutional right to physician-assisted suicide (euthanasia) (17,18). There is no constitutional right to suicide, and there is no legal or historical support for such a right. The right to abortion or the right to refuse treatment is different from the right to assisted suicide. Limiting physician-assisted suicide to terminally ill patients also has no basis in constitutional principles. Only 6% of medical students, house staff, or faculty physicians surveyed in one study were willing to terminate the life of a patient deliberately by administering medication to cause respiratory arrest, and only 1.1% of those surveyed were willing to do so if it causes a cardiac arrest (35). Of course, it is possible that these numbers might increase if legal restraints were removed. However, there is a long and impressive list, starting with Hippocrates and including leading physicians, philosophers, and biomedical ethicists, of professionals who are opposed to euthanasia. One humane alternative is to simulate a home environment for dying patients in the ICU (Table 34.3).

Transportable aspects of a patient's home	Ways to provide these aspects in the intensive care unit
Privacy	Provide a private room Close doors and curtains
Ready access to family	Suspend restrictive visiting hours Provide comfortable chairs, recliners, and cots for family members in the patient's room
Access to patient's own possessions and amenities	Allow family to bring in favorite music, clothes, religious icons, food, and pets
Family serving as personal caregivers	When appropriate, allow family to assist with patient care
Access to religious rituals and spiritual support	Provide religious and spiritual resources Encourage religious and other family rituals at the bedside before and after death

Modified from Faber-Langendoen K, Lanken PN. Dying patients in the intensive care unit: foregoing treatment, maintaining care. *Ann Intern Med* 2000;133:886–893, with permission.

TABLE 34.3 WAYS IN WHICH INTENSIVE CARE UNITS CAN SIMULATE A HOME ENVIRONMENT FOR DYING PATIENTS

Strong popular support for euthanasia exists in Holland, which legalized euthanasia in 2000 (36). It is estimated that 5,000 to 10,000 Dutch citizens die each year after administration of a barbiturate followed by a lethal injection of a paralytic agent. In 1994, Oregon voters passed the Death with Dignity Act. This act does not permit euthanasia, but it allows state residents to receive prescriptions for self-administered lethal medications from their physicians. A 1-year follow-up indicated that only 23 patients received such prescriptions, 15 patients died after taking them, six died from underlying illness, and two patients who received such prescriptions were still alive (37). Some good has come out of the euthanasia movement—it has forced physicians to deal with death and dying.

SUMMARY

People in the United States are uncomfortable discussing death. They do not know how to start the conversation and in some cases do not want to discuss it at all. People remain confused about what constitutes a “good death” (Table 34.4). A good death includes management of pain and symptoms, clear decision-making, preparation for death, and completion. The language is not always precise—a feeding tube is not the same as food and water. Only frequent, clear, and open dialogue will overcome this hurdle. Eventually, society needs to understand end-of-life issues in a more realistic light and to realize that what they see on the television series *ER* does not mimic the real world. Patients will die despite our best efforts. Our job as physicians is to help patients and their families through the dying process, just as

we help them achieve meaningful recovery.

To know when death is coming, and to understand what can be expected
To be able to retain control of what happens
To be afforded dignity and privacy
To have control over pain relief and other symptom control
To have a choice and control over where death occurs (at home or elsewhere)
To have access to information and expertise as necessary
To have access to any spiritual or emotional support required
To have access to hospice care in any location, not only in the hospital
To have control over who is present and who shares the end
To be able to issue advance directives that ensure wishes are respected
To have time to say goodbye and control over other aspects of timing
To be able to leave when it is time to go, and not to have life prolonged pointlessly

Modified from Brown M. A good death. Principles of palliative care are yet to be applied in acute hospitals. BMJ 2000;320:1266, with permission.

TABLE 34.4 PRINCIPLES OF A GOOD DEATH

CONTROVERSIES AND PERSONAL PERSPECTIVES

The concept of futility is controversial (21). It is supported by neither scientific principle nor the justice system. When continued aggressive life-support seems futile, it is best to discuss the likely outcome of continued support versus comfort care with the family. The final outcome—death—may be the same, but how the patient dies may be quite different. It is best that the family not perceive that the team is giving up, but rather that passive comfort care may be preferable to the potential suffering associated with continued life support. It must be stressed that such a decision is based on experience and judgment, not on the certainty of death. The family needs to understand and agree that the patient's best interests are served by such a strategy. Medical futility cannot be easily defined and is value-laden.

It has also been my personal experience that partial withdrawal of life support or "slow codes" confuse the issue and can prolong suffering. Decisions to withdraw or withhold life support should be complete. Only those measures that offer comfort should be continued.

THE FUTURE

We do a poor job of training our residents and fellows in end-of-life issues. Dying is part of living, and to ignore the management of dying is as grievous an error as ignoring methods of managing a major illness. We need to do a better job of educating our trainees and ourselves about these uncomfortable issues. At our institution, we have end-of-life small-group seminars as part of our didactic curriculum in the CCU. Bioethicists, pharmacists, and cardiologists assigned to the CCU participate in these lectures, which are often centered around a specific case history. We need to educate the public about death and dying. Expectations for individual patients must be framed carefully and repeatedly. Above all, families must be drawn into these important dialogues. Hope for meaningful recovery must in some cases be replaced with hope for comfort and caring.

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35

THE HEART AND OTHER ORGAN SYSTEMS

ROBERT M. CALIFF

Introduction

INTRODUCTION

Cardiovascular specialists are often consulted to evaluate patients with diseases that emanate from organ systems remote from the heart, but with substantial cardiac manifestations. At some point the cardiovascular system becomes a factor in most major systemic diseases. In this section, commonly encountered problems involving an interaction of the heart and other organ systems are reviewed. The goal is to focus on the cardiovascular manifestations of these problems without providing a comprehensive review of the illnesses per se.

Increasing attention is being focused on the interaction between the cardiovascular system and the central nervous system. Ranging from genetic diseases associated with neuromuscular degeneration to atherosclerotic disease of the cerebrovascular circulation, considerable knowledge about cardiovascular manifestations is required to understand the manifestations of neurologic disorders.

Myocarditis, endocarditis, and pericarditis are covered in detail in other portions of the book, but the enormous number of infectious causes of these problems, each with specific implications for treatment, requires discussion here. In addition, the rapidly growing knowledge base concerning the effects of the human immunodeficiency virus on the cardiovascular system will increasingly require the attention of cardiovascular specialists.

Although cardiovascular manifestations of rheumatic diseases are not common compared with atherosclerosis, some of the most striking cardiovascular problems arise from rheumatic diseases. The management of vasculitis, pericarditis, or aortic valve difficulties associated with rheumatic diseases requires a thorough understanding of both areas.

As with cerebrovascular disease, the basic approaches to atherosclerosis (medical management, percutaneous intervention, and surgical intervention) create a close tie between the most common type of renal disease and the cardiovascular system. In addition, the rapid growth of angiography with its associated problem of contrast nephropathy creates an iatrogenic condition requiring careful evaluation and treatment by the angiographer.

Finally, in many respects, cardiovascular disease is an endocrine disease in the sense that a major contributor to disease progression and outcome in cardiovascular diseases is the neuroendocrine status. In particular, diabetes has become the focus of activity in understanding factors associated with increased risk.

We hope that these sections in combination with specific disease-oriented chapters throughout the book will provide the reader with a comprehensive view of the interaction of the cardiovascular system with other organ systems in the development and progression of human disease.

35A

ENDOCRINE SYSTEMS

MARCO ROFFI

"Indicates text or graphics that appear only in the electronic versions of this text."

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The Thyroid
Thyrotoxicosis
Hypothyroidism
Amiodarone and Thyroid Dysfunction
Investigational Thyroid Hormone Therapies
The Adrenal Gland
Cushing's Syndrome
Primary Aldosteronism
Pheochromocytoma
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Acromegaly
Growth Hormone Deficiency
Growth Hormone Abuse
Growth Hormone Therapy in Heart Failure
Hyperparathyroidism
Cardiovascular Involvement
Diagnosis and Therapy
Androgens and the Cardiovascular System
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INTRODUCTION

Cardiovascular involvement is frequent in endocrine disturbances. Clinical suspicion remains the most important step in diagnosing endocrine disorders—in particular, their cardiovascular manifestations, as they can be subtle and nonspecific. The purpose of this chapter is to summarize relevant interactions between endocrinologic diseases and the cardiovascular system to facilitate diagnostic recognition and to highlight management options.

THE THYROID

A relation between the thyroid and the heart has long been recognized (1). In the late 1700s, a patient with clinical features of thyrotoxicosis including palpitations, irregular pulse, and dyspnea was described (2). In the early 1900s, a patient with "myxedema heart" was reported: The critical findings were enlarged cardiac silhouette, low electrocardiographic voltage, and bradycardia (3).

Thyroxine (T_4), a relatively inactive hormone, is the major secretory product of the thyroid gland. Triiodothyronine (T_3), the biologically active compound, is in large part derived from peripheral conversion of T_4 by the 5'-monodeiodinase enzyme. Therefore, alteration in T_3 plasma level may occur independently from thyroid function. Cardiovascular manifestations are frequent in thyroid dysfunction and may be the result of direct hormone effects at the cellular level, interactions with the sympathetic nervous system, or alterations of peripheral circulation and metabolism (4). At the cellular level, thyroid hormones act mainly through binding to specific nuclear receptors and activation of gene transcription (5). Additionally, they activate extranuclear sites as mitochondrial and membrane-bound enzymes (6). Women are more likely to develop thyroid dysfunction, with an estimated 2.7% prevalence of hyperthyroidism and 1.9% prevalence of hypothyroidism in an unselected population (7).

Thyrotoxicosis

The terms *hyperthyroidism* and *thyrotoxicosis* can be differentiated but are frequently used interchangeably. Hyperthyroidism is defined as increased formation and release of thyroid hormones from the thyroid gland, whereas thyrotoxicosis describes the clinical syndrome that results from the thyroid hormone excess. The most frequent cause of thyrotoxicosis is Graves' disease, which accounts for 60% to 90% of cases and occurs among women ten times more frequently than men. This disorder is characterized by autoantibodies activating the thyroid-stimulating hormone (TSH) receptor. Other causes of thyrotoxicosis include toxic adenoma (Plummer's disease), toxic multinodular goiter, thyroiditis, and thyroid autonomy. Common symptoms of thyrotoxicosis are nervousness, emotional lability, sleep disturbances, tremor, diarrhea, heat intolerance, and weight loss. Clinical findings include goiter, exophthalmos, proximal muscle weakness, hyperreflexia, and occasionally pretibial myxedema. Thyrotoxicosis in the elderly might be particularly subtle and present with nonspecific symptoms such as weakness, weight loss, and apathy.

Amyloidosis. Infiltration of the skin results in raised waxy papules or plaques that are usually in clusters (*arrow*).

In subjects with preexisting thyroid autonomy, iodine administration (i.e., in the form of amiodarone or contrast agents) can result in iodine-induced thyrotoxicosis. Iodine deficiency, the presence of a goiter, and baseline low TSH levels have been considered risk factors for iodine-induced thyrotoxicosis. Accordingly, this disease is more frequently observed in areas with low iodine intake. An investigation in almost 800 patients from an iodine-deficient area undergoing coronary angiography showed that the risk of developing thyrotoxicosis was low (<0.3%) despite significant prevalence of low TSH levels (4%) and goiter (23%) (8). In contrast, amiodarone may induce thyrotoxicosis in up to 10% of iodine-deficient patients (9).

Cardiovascular Involvement

Thyrotoxic patients have increased mortality, primarily because of cardiovascular complications (10). Cardiovascular symptoms in this setting are frequently nonspecific. Palpitations are usually caused by sinus tachycardia and, occasionally, by atrial fibrillation. Exercise intolerance and dyspnea on exertion may be caused by a combination of inability to raise cardiac output and skeletal and respiratory muscle weakness. Cardiovascular involvement in the elderly may be limited to arrhythmias such as sinus tachycardia or atrial fibrillation, which occasionally trigger heart failure, angina, or both. The hemodynamic changes occurring in thyrotoxicosis are summarized in Table 35A.1 and include tachycardia, increased cardiac output and stroke volume, and decreased systemic vascular resistance (11,12). In contrast to hypothyroidism, which is characterized by diastolic hypertension, hyperthyroidism is associated with systolic hypertension in the presence of normal or low diastolic blood pressure. It is speculated that isolated systolic hypertension is secondary to the inability of the vasculature to accommodate increased cardiac output and stroke volume (1).

	Thyrotoxicosis	Hypothyroidism
Systemic vascular resistance	↓	↑
Cardiac output	↑	↓
Systolic blood pressure	↑	↓ or →
Diastolic blood pressure	↓	↑ or →
Heart rate	↑	↓
Systolic function	↑	↓
Diastolic function	↑	↓
Blood volume	↑	↓

↑, increased; ↓, decreased; →, unchanged.

TABLE 35A.1 CARDIOVASCULAR HEMODYNAMICS IN THYROID DYSFUNCTION

Sympathetic Nervous System

Many of the cardiovascular signs and symptoms of thyrotoxicosis mimic those occurring in states of increased beta-adrenergic activity and respond to beta-blockade (13), suggesting an underlying dysfunction of the catecholamine metabolism or, alternatively, an increased sensitivity to catecholamines. However, patients with thyrotoxicosis have low or normal plasma catecholamine levels and normal urinary catecholamine excretion (14). Moreover, these patients have normal responses to catecholamine infusion (13). Finally, there is no conclusive evidence of increased beta-adrenergic receptor density in the myocardium, increased catecholamine turnover at neural synapses, or increased affinity of adrenergic receptor for catecholamines (15).

Ventricular Function

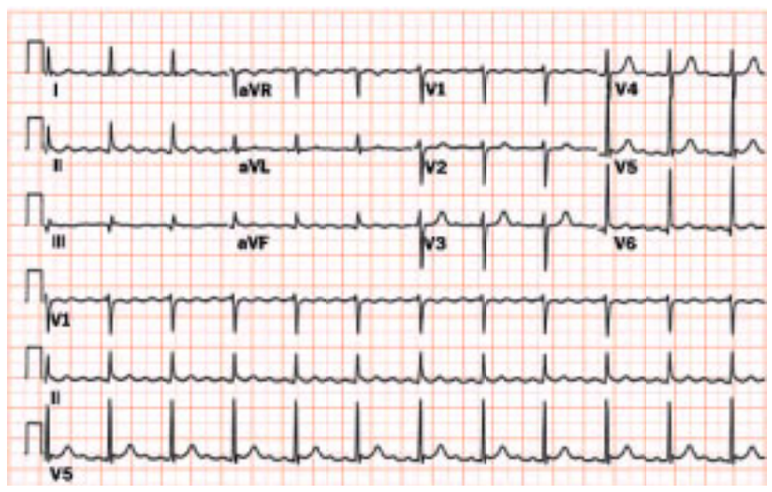
Short-term hyperthyroidism is associated with increased cardiac contractility and improved diastolic function (16,17) (Table 35A.1), which may be caused, at least in part, by augmented activity of the sarcoplasmic reticulum calcium ATPase pump (18). Both in humans (19) and animals (20), chronic thyrotoxicosis causes variable degrees of left ventricular hypertrophy (LVH). Thyroid hormones have been shown to induce cardiac protein synthesis, leading to the hypothesis that this is the trigger of LVH (21). However, beta-adrenergic blockade has been shown to block or reverse hypertrophy, suggesting that increased cardiac workload is the mediator of hypertrophy (22,23 and 24). In addition to the effects on the myocardium, thyroid hormones, specifically T_3, show vasodilator properties by acting directly on vascular smooth muscle cells, potentially explaining the decreased systemic vascular resistance observed in hyperthyroidism (25,26).

It remains a source of debate whether thyrotoxicosis per se may lead to heart failure. In the vast majority of cases, heart failure can be explained by the combination of underlying heart disease, arrhythmias, and/or chronically increased cardiac output. However, myocardial dysfunction has been described also in absence of underlying cardiac disease (27), even in children (28), and improvement in myocardial contractility after restoration of euthyroidism has been reported (29,30). Several factors may potentially contribute to heart failure in thyrotoxicosis. Diastolic function deteriorates in the course of the disease because of LVH and progressive LV stiffness, leading to filling impairment, particularly in the setting of tachycardia or atrial fibrillation (4). Additionally, thyrotoxicosis is associated with increased total blood volume and plasma volume (31). Occasionally, the decreased systemic resistance may overwhelm the cardiac capacity and cause high output failure. More frequently, however, the high-output state may unmask coronary artery disease, and heart failure is precipitated by ischemia. Myocardial ischemia in thyrotoxic patients has been described even in the absence of significant coronary artery disease, secondary to coronary vasospasms (32,33 and 34).

Arrhythmias

Sinus tachycardia at rest, during sleep, and during exercise is the most common arrhythmia in thyrotoxicosis (35,36). It is speculated that thyroid hormones have direct effects on the conduction system, possibly via cellular changes in cation transport, including a decrease of atrial excitation threshold, an increase of sinoatrial node firing, and a shortening of conduction tissue refractory time (11,37). Other common arrhythmias include atrial premature contractions and atrial fibrillation. Less frequently, patients present with paroxysmal atrial tachycardia and atrial flutter. Ventricular premature contractions and ventricular arrhythmias are rare.

Acute inferior myocardial infarction complicated by atrial fibrillation. Note ST-segment elevation in the inferior leads with reciprocal changes laterally. Atrial fibrillation has complicated this acute infarct.



Atrial flutter. Atrial rate of 300 beats/min with upright P waves inferiorly. This is consistent with atypical atrial flutter.

Although thyrotoxicosis accounts for less than 5% of all cases of atrial fibrillation, this arrhythmia occurs in up to 15% of hyperthyroid patients (15). The ventricular rate response is frequently rapid because of increased atrioventricular node conduction. Atrial fibrillation related to thyrotoxicosis is more frequent in the elderly and in male subjects, probably reflecting their increased prevalence of intrinsic heart disease (38). Because this arrhythmia, particularly in the elderly, may be the only manifestation of thyrotoxicosis, thyroid hormone excess should always be excluded in patients with atrial fibrillation. Accordingly, one report showed subtle hyperthyroidism in 12.5% of elderly patients with atrial fibrillation previously considered idiopathic (39). One study, performed in patients 60 years of age or older, demonstrated that even patients with subclinical hyperthyroidism (i.e., asymptomatic but with low TSH) had a threefold higher risk of developing atrial fibrillation in the subsequent decade (40) (Fig. 35A.1). Major complications of thyrotoxic atrial fibrillation include heart failure and embolic events. In the absence of chronic atrial fibrillation or underlying heart disease, most patients convert spontaneously to sinus rhythm within 8 to 12 weeks of antithyroid treatment (41). Conversely, reversion into atrial fibrillation is likely in persistently thyrotoxic patients. Anticoagulation is indicated and cardioversion should be deferred until euthyroidism is restored.

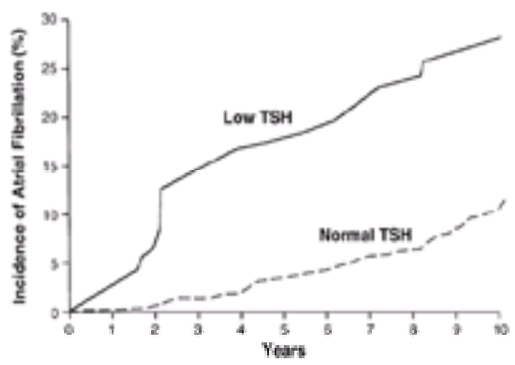


FIGURE 35A.1 Cumulative incidence of atrial fibrillation among subjects 60 years of age or older, according to serum thyroid-stimulating hormone (TSH) levels at baseline. Low TSH defined as £0.1 mU per L; normal TSH defined as >0.4 to 5.0 mU per L. (Adapted from Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 1994;331:1249–1252.)

Diagnosis and Therapy

Measurement of serum TSH is the most sensitive screening test for hyperthyroidism. An undetectable value is the hallmark of this thyroid dysfunction, whereas normal TSH levels virtually exclude the disease (42). Confirmation is usually sought measuring elevated serum free T_4 and free T_3. Beta-adrenergic blockers provide relief of symptoms such as tachycardia, tremor, anxiety, and heat intolerance. The nonselective agent propranolol has been traditionally used for this purpose but selective $beta_1$-adrenergic antagonists such as atenolol appear equally effective. If beta-blockers are contraindicated, calcium channel blockers such as verapamil or diltiazem can be administered as negative chronotropic agents (43). However, caution is warranted, as these agents may lead to hemodynamic instability by further reducing systemic vascular resistance and contractility. The thionamide derivatives propylthiouracil and methimazole are effective in decreasing thyroid hormone synthesis. Radioactive iodine is a valid alternative, particularly for older patients with moderate hyperthyroidism and goiter, for patients with prior allergic or toxic reaction to the antithyroid medication, and when frequent medication intake cannot be guaranteed. The disadvantages of radioactive iodine include a long latency of action and the fact that this therapy is ineffective in iodine-induced hyperthyroidism. Surgery is indicated in patients with large goiters causing airway obstruction or with malignant or equivocal nodules on fine-needle aspiration. Occasionally, surgery is necessary in severely hyperthyroid patients not responding to conservative treatment.

Hypothyroidism

Hypothyroidism is the clinical syndrome associated with decreased secretion of thyroid hormones. This condition reflects in over 90% of cases a disease of the gland itself (primary hypothyroidism). Rarely, hypothyroidism can be caused by pituitary disease (secondary hypothyroidism) or hypothalamic disease (tertiary hypothyroidism). The most frequent cause of hypothyroidism in adults is autoimmune thyroiditis, or Hashimoto's disease. Accordingly, women are more frequently affected. The slow and progressive nature of hypothyroidism often makes the diagnosis difficult. This is particularly true in elderly patients whose clinical manifestations may be limited to dry skin, weight gain, fatigue, and forgetfulness—all of which are easily explained by the aging process. Other complaints of hypothyroid patients include increased tiredness and sleep requirement, depressed mood, cold intolerance, constipation, and decreased exercise tolerance. Pleural effusions and pitting edema may occur in absence of heart failure.

Cardiovascular Involvement

Most hypothyroid patients present with nonspecific symptoms caused by psychological or skeletal muscle dysfunction. However, long-standing hypothyroidism may affect the cardiovascular system in several ways (Table 35A.1). Bradycardia is common, and pericardial effusion may occur in up to one-half of patients but rarely causes hemodynamic compromise (44). Both diastolic and systolic LV performance may be decreased (45), presumably because of alterations in calcium uptake and release by cardiac myocytes (18). Additionally, an increase in systemic vascular resistance is observed, possibly as the result of the lack of direct vasodilatory effect of thyroid hormones (25,26). Despite the fact that hypothyroid patients have symptoms suggesting a decreased sympathetic tone, plasma catecholamines are increased (46). The resulting hemodynamic changes are opposite but less marked than with thyrotoxicosis. Characteristic features include low cardiac output; decreased stroke volume, diastolic function, intravascular volume, and peripheral oxygen consumption; and increased systemic vascular resistance (47,48 and 49). Heart failure may occur when the metabolic demand cannot be matched by adequate cardiac output. As in patients with thyrotoxicosis, overt heart failure in hypothyroidism generally represents exacerbation of intrinsic cardiac disease. Rarely, however, hypothyroidism alone may cause cardiomyopathy (50). Therefore, unexplained heart failure should prompt determination of thyroid hormones. In the absence of underlying heart disease, the decreased myocardial contractility observed in hypothyroidism is generally reversible after hormone replacement (45,47), probably as a result of improved calcium handling in cardiac myocytes (18) and decreased systemic vascular resistance (47).

Risk Factors

Total cholesterol, low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, lipoprotein(a), and apolipoprotein B concentrations are often elevated in hypothyroidism; some patients have high serum triglyceride levels (1). It has been demonstrated that patients with hypothyroidism have an intrinsic LDL catabolism dysfunction, which is reversible after hormone replacement (51). Therefore, screening for this condition is mandatory when assessing patients with hyperlipidemia. The powerful interaction between thyroid hormones and lipid metabolism is highlighted by the fact that thyroid hormones have been used in the past as lipid-lowering agents. However, this strategy was associated with increased morbidity and mortality in patients after myocardial infarction (52).

Hypothyroidism is associated with increased prevalence of hypertension. In a review of 12 studies, the overall prevalence of hypertension was 21% (1). In large series of hypertensive patients, hypothyroidism accounted for 3% to 5% of the cases (53,54). Hypothyroid patients have a low-renin form of hypertension, and the mechanism remains unknown (54). The causal link between thyroid hormone deficiency and hypertension is confirmed by the fact that hormone replacement may lead to improvement of hypertension (54).

Coronary Artery Disease

Patients with hypothyroidism frequently have risk factors for coronary artery disease, but data to support the direct association between hypothyroidism and coronary artery disease are lacking (55). The suggestion that hypothyroidism may indeed represent an independent risk factor for coronary disease comes from a population-based cross-sectional study. In this analysis, women with subclinical hypothyroidism—defined as asymptomatic, with normal serum free T_4 and elevated TSH—had a higher prevalence of aortic atherosclerosis and myocardial infarction than euthyroid women (56). These observations are in agreement with previous case-control studies showing an association between subclinical hypothyroidism and coronary heart disease in elderly women (57,58). In contrast, a Finnish study addressing latent thyroid failure in both men and women found no association with coronary disease (59).

Diagnosis and Therapy

An elevated TSH combined with a low free T_4 is diagnostic of primary hypothyroidism. Antimicrosomal and antithyroglobulin antibodies are characteristic of Hashimoto's disease. Hypothyroidism is preferentially treated with thyroxine because of its long half-life. In the elderly, as well as in patients with known or suspected coronary disease, it is prudent to start hormone substitution at a lower dosage. However, exacerbation of angina because of hormone replacement is rare (60) and responds well to beta-adrenergic blockade.

Amiodarone and Thyroid Dysfunction

Amiodarone is an iodine-rich benzofuran derivative with similar molecular structure to thyroid hormones. Organic iodine represents almost 40% of the molecular weight of amiodarone. A daily dose of 200 mg of amiodarone corresponds to an intake of 75 mg of organic iodide and generates approximately 7 mg of free iodine (61). Given the fact that the normal dietary requirement of iodine is 100 to 200 µg per day, amiodarone therapy is associated with an enormous iodide load, reflected in a 40-fold increase in plasma and urinary iodide levels (61). Because iodine is a necessary substrate for thyroid hormone synthesis but, at the same time, directly influences intrathyroidal processes, it is not surprising that over 50% of the patients on amiodarone have abnormal thyroid function test results, although most of them remain euthyroid (62). The predominant peripheral action of amiodarone on thyroid hormones is the inhibition of the deiodination of T_4 to T_3. As a result, the serum levels of T_4 increase and the levels of T_3 decrease (61,63) (Table 35A.2). In addition, high iodide availability initially inhibits thyroid hormone synthesis (the Wolff-Chaikoff effect) (64). During the first 3 months of therapy, TSH levels are commonly slightly elevated because of lack of feedback inhibition, due to the lowered T_3 levels, but they tend to normalize during long-term administration. Amiodarone-induced thyrotoxicosis (AIT) prevails in areas with low iodine intake, and hypothyroidism is more frequent in areas with high iodine intake. Whereas thyrotoxicosis can occur throughout the treatment period and even several months after treatment, hypothyroidism rarely develops beyond 18 months of initiation of therapy (65). Monitoring of thyroid function in this setting relies on TSH. If TSH is abnormal, free T_4 and free T_3 levels should be assessed to detect underlying gland dysfunction that may predispose to amiodarone-induced hyperthyroidism or hypothyroidism. Additional assessments are recommended at approximately 3 months and yearly thereafter.

Test	Treatment <3 mo	Treatment >3 mo
Thyroxine	Increased	Remains increased by up to 40% above baseline; may be in high reference range or modestly raised
Triiodothyronine	Decreased, usually to low reference range	Remains in low reference range or slightly low
Thyroid-stimulating hormone	Transient increase (up to 20 mU/L)	Normal, but may fluctuate with periods of high and low values

From Newman CM, Price A, Davies DW, et al. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart 1998;79:121–127, with permission.

TABLE 35A.2 EFFECTS OF AMIODARONE ON THYROID FUNCTION IN PATIENTS REMAINING EUTHYROID

A noniodinated analog of amiodarone, dronedarone, has been synthesized. Preliminary animal data show that this compound has similar electrophysiologic effects to amiodarone (66). The development of dronedarone or a similar compound will be followed with interest, because iodine deletion is expected to overcome endocrine side effects of amiodarone. However, extensive safety and efficacy data in animals are required before human testing.

Amiodarone-Induced Hypothyroidism

Hypothyroidism is a frequent sequela of amiodarone therapy, with a reported incidence ranging from 13% in iodine-replete countries to 6% in countries with low or intermediate iodine intake (63). Its occurrence is not related to the daily or cumulative dose of the drug. The risk of developing hypothyroidism is increased in the elderly and women, particularly in the setting of autoimmune thyroiditis. Accordingly, women on amiodarone with microsomal, thyroglobulin, or both autoantibodies have been shown to have more than a tenfold higher risk for subsequent hypothyroidism (65). Possible mechanisms leading to hypothyroidism in this setting include failure to escape the Wolff-Chaikoff effect and iodine-mediated exacerbation of preexisting autoimmune thyroid disease. TSH levels above 10 to 15 mU per L in patients on chronic amiodarone usually represent hypothyroidism. The diagnosis is confirmed by low T_4 or free T_4. The assessment of T_3 or free T_3 adds little information, because these parameters may be diminished in euthyroid patients on amiodarone. Once the diagnosis of hypothyroidism is established, the drug can be safely continued, if needed, and thyroxine replacement added in increasing doses at 4- to 6-week intervals until TSH returns within normal limits and symptoms resolve (63). If amiodarone is discontinued, recovery of thyroid function is influenced by the presence of thyroid antibodies. In fact, the absence of antibodies is associated with frequent recovery, mostly within a few months, whereas patients with thyroid antibodies usually do not recover normal thyroid function (63).

Amiodarone-Induced Thyrotoxicosis

In countries with high iodine intake, AIT is less frequent than hypothyroidism, with an estimated incidence of approximately 2%. In contrast, in the presence of iodine deficiency, AIT may occur in up to 10% (9). Antiadrenergic effects of amiodarone may partially conceal thyrotoxic symptoms. AIT should be suspected in the presence of new or recurrent atrial arrhythmias or unexplained weight loss. Three pathophysiologic mechanisms have been associated with thyrotoxicosis in the setting of chronic amiodarone therapy (61). First, iodine may affect thyroid autoregulatory mechanisms and may lead, particularly in patients with underlying thyroid disease, to excessive hormone synthesis. Second, inflammatory destructive histologic changes and increased cytokines (e.g., interleukin-6) and thyroglobulin levels have been demonstrated in this setting, suggesting a direct cytotoxic effect of amiodarone (67). Third, it has been postulated that amiodarone may trigger an autoimmune response to the thyroid gland. Amiodarone should be discontinued whenever possible. The choice of treatment can be guided by distinction of two forms of AIT (68). In type I AIT patients have a goiter, positive thyroid antibodies, and abnormal (i.e., measurable or even high) 24-hour radioiodine uptake. Treatment consists of a combination of thionamides, propylthiouracil or methimazole, which inhibit hormone biosynthesis, and potassium perchlorate, which blocks thyroid iodide uptake (69,70). Patients with type II AIT have a normal thyroid and low radioiodine uptake. The efficacy of corticosteroids, alone or in combination with thionamides, has been convincingly demonstrated in this setting (68,71,72). However, because a mixed form of AIT is frequent, patients can be approached pragmatically with an initial combination of thionamides and potassium perchlorate, with corticosteroids being added after 2 weeks if no improvement occurs (Fig. 35A.2). In patients not responding to this therapy, lithium may be a valid alternative (73).

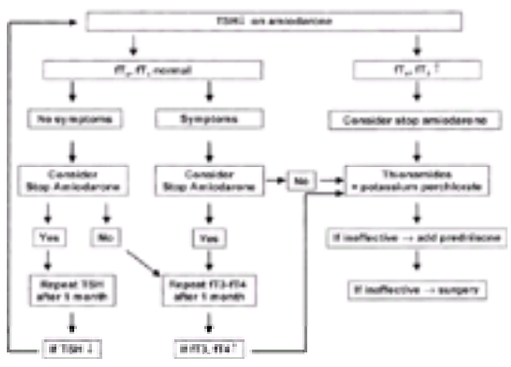


FIGURE 35A.2 Management algorithm for amiodarone-induced thyrotoxicosis. fT_3, free triiodothyronine; fT_4, free thyroxine; TSH, thyroid-stimulating hormone. (Courtesy of F. Cattaneo, MD, Lugano, Switzerland.)

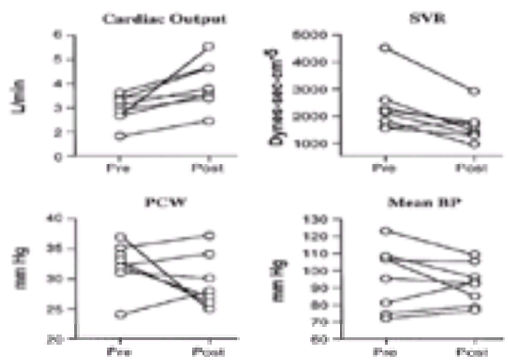
The cardiovascular risk associated with continuing amiodarone therapy is unknown, but the rate of remission following antithyroid drugs is decreased. However, discontinuation of the drug can be hazardous, particularly if the indications were ventricular arrhythmias, and thyrotoxicosis may take up to 8 months to subside (74). In addition, because of the extremely long terminal half-life of amiodarone, the use of beta-adrenergic antagonists is limited by the additive chronotropic and dromotropic effects, potentially leading to severe bradycardia, conduction abnormalities, or both. Because the high iodide plasma concentrations typically suppress iodine uptake in

the thyroid, radioactive iodine treatment is not effective in this particular form of thyrotoxicosis. Subtotal thyroidectomy is the treatment of choice if pharmacologic regimens are ineffective (75,76). Surgery has been associated with low perioperative morbidity and mortality, even in the presence of thyroid storm, heart failure, and therapy-refractory arrhythmias (63,75,76).

Investigational Thyroid Hormone Therapies

Heart Failure

Because low thyroid hormone levels have been associated with poor prognosis in heart failure (77), hormone supplementation has been attempted in this setting. Bolus and infusion of T_3 in a small group of euthyroid patients with advanced heart failure have been shown to increase cardiac output and lower systemic vascular resistance, with no change in LV ejection fraction or filling pressures (78) (*e*Fig. 35A.2.1). A small randomized study showed improved exercise capacity with 100 µg per day of thyroxine for 1 week in 20 patients with idiopathic dilated cardiomyopathy (79). Benefits in terms of LV ejection fraction, LV diastolic dimension, and functional capacity were observed in another small placebo-controlled trial after administration of the same dose for 3 months (80). Although these initial reports are intriguing, there are currently no data to support routine thyroid hormone supplementation in euthyroid patients with heart failure.



***e*FIGURE 35A.2.1** Hemodynamic parameters at baseline (Pre) and 2 hours after (Post) 0.7 µg per kg triiodothyronine (T_3) bolus and 0.17 µg per kg per hour infusion in seven patients with severe heart failure. BP, arterial blood pressure; PCW, pulmonary capillary wedge pressure; SVR, systemic vascular resistance. (From Hamilton MA, Stevenson LW, Fonarow GC, et al. Safety and hemodynamic effects of intravenous triiodothyronine in advanced congestive heart failure. *Am J Cardiol* 1998;81:443–447, with permission.)

Bypass Surgery

Patients undergoing cardiac surgery frequently have low thyroid hormone levels in the postoperative phase (81). Based on this observation and on initial encouraging data (82), two trials have randomized patients undergoing cardiopulmonary bypass surgery to perioperative administration of large doses of T_3 or placebo (83,84). Thyroid hormone therapy was not associated with improved outcome or diminished inotropic requirement.

Organ Donors

Brain death is associated with rapid loss of pituitary functions and low levels of cortisol and TSH. Preliminary data suggest that administration of T_3 to brain-dead organ donors may be beneficial in maintaining organ viability by increasing hemodynamic stability, reducing inotropic agent requirement, decreasing filling pressures, and improving metabolic status (85). Further studies are needed to validate this interesting observation.

THE ADRENAL GLAND

The cortex of the adrenal gland produces corticosteroid hormones, and the medulla—functionally a sympathetic ganglion—produces catecholamines. Clinical syndromes associated with adrenal hypersecretion and cardiovascular involvement include Cushing's syndrome and primary aldosteronism (Conn's syndrome) and result from excessive secretion of cortisol and mineralocorticoid, respectively. Cardiovascular involvement in adrenal insufficiency is mainly limited to its acute form (Addison's crisis) and is characterized by volume depletion, refractory hypotension, arrhythmias, and conduction abnormalities secondary to electrolyte disturbances.

Cushing's Syndrome

Cortisol, a central modulator of carbohydrate and protein metabolism, is synthesized in the adrenal cortex in response to pituitary adrenocorticotropic hormone (ACTH). The term *Cushing's syndrome* denotes glucocorticoid excess, which can be either endogenous or exogenous. ACTH-secreting pituitary tumor (Cushing's disease) accounts for approximately 80% of the cases of endogenous hypercorticism. In 10% of cases, an ectopic ACTH-producing tumor is identified (ectopic ACTH syndrome). Glucocorticoid excess is caused in another 10% of cases by adrenal pathologies such as adenoma, carcinoma, or bilateral hyperplasia.

Clinical Findings and Cardiovascular Risk

The characteristic findings in Cushing's syndrome include truncal obesity, abdominal striae, hypertension, osteoporosis, proximal muscle weakness, fatigue, and hyperglycemia. Concomitant androgen excess may lead to hirsutism and amenorrhea, and mineralocorticoid effect may cause hypokalemia. Early studies performed when no treatment was available showed that glucocorticoid excess is associated with premature atherosclerosis and increased cardiovascular morbidity and mortality (86). The risk profile of this population is characterized by a high prevalence of glucose intolerance or overt diabetes mellitus and hypertension (87). Additional cardiovascular risk factors include truncal obesity and hyperlipidemia. Hypertension has been related to volume expansion, increased production of vasoactive substances, and increased reactivity of vascular smooth muscle cells (88,89 and 90). LVH may be more frequent, more severe, or both in patients with Cushing's syndrome when compared with patients with essential hypertension (91). Despite surgical treatment, cardiovascular morbidity and mortality remain higher than in the general population (92), possibly because of residual obesity, insulin resistance, or both (93).

Cushing's syndrome. Deposition of adipose tissue in the face and in the interscapular area causes "moon facies" and "buffalo hump." This is seen in hypercortisolism.

Diagnosis and Therapy

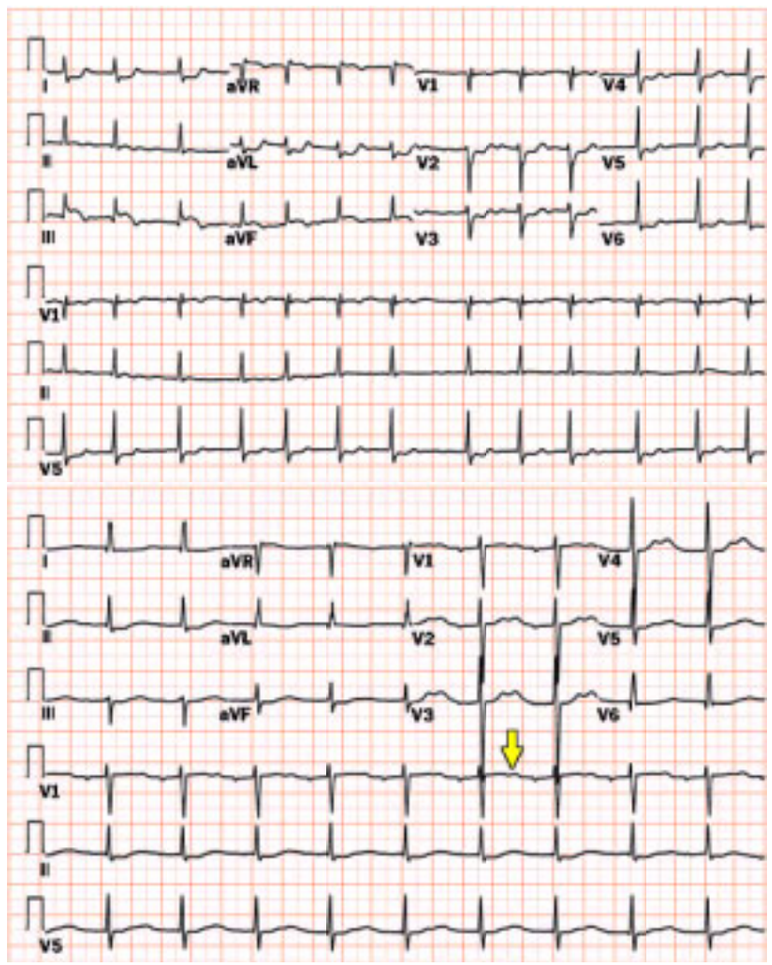
Diagnosis and treatment of Cushing's syndrome are complex and go beyond the scope of this textbook. In patients with clinical features suggestive of hypercorticism, screening can be performed with, among others, a 24-hour urine collection for free cortisol. Confirmatory tests include, among others, the dexamethasone suppression test or a second elevated free cortisol in a 24-hour urine sample (94). Specific treatment, which may include surgical removal or pharmacologic or radiation therapy, is chosen depending on the underlying process.

Primary Aldosteronism

Primary aldosteronism was first described in 1955 by Conn in a patient with an aldosterone-producing adrenal adenoma (95). This benign tumor is the most common cause of primary aldosteronism, accounting for approximately 65% of cases, whereas bilateral adrenal hyperplasia, also called *idiopathic hyperaldosteronism*, accounts for another 30% of cases. Primary aldosteronism has been considered the cause of hypertension in a minority of unselected hypertensive patients, with an incidence ranging between 0.05% and 2.20% (96). However, recent data suggest a higher prevalence of primary aldosteronism in the hypertensive population (97,98). Symptoms of primary aldosteronism are nonspecific and mainly result from potassium depletion. Neuromuscular involvement includes weakness, paralysis, cramps, tetany, and paresthesias.

Cardiovascular Manifestations

Primary aldosteronism is associated with moderate to severe hypertension (99). Acute mineralocorticoid administration induces renal sodium retention and potassium and hydrogen excretion, resulting in vascular volume expansion, hypokalemia, and metabolic alkalosis. Although hypertension is presumably related to sodium retention and volume expansion, chronic mineralocorticoid excess is associated with only mild hypervolemia due to escape mechanisms (99). Accordingly, peripheral edema is rare. Primary aldosteronism is associated with cardiac and vascular remodeling. Characteristic features include perivascular fibrosis, excessive LVH, and myocardial fibrosis (100,101).



Hypokalemia. Prominent U waves are seen.

Diagnosis and Therapy

Because mineralocorticoid excess does not produce specific symptoms, primary aldosteronism is a biochemical diagnosis. Diagnostic tests of choice include plasma renin activity, plasma aldosterone levels, aldosterone-to-renin ratio, and dexamethasone suppression test (102). The association of hypertension and hypokalemia, if not diuretic induced, is characteristic of primary aldosteronism and should prompt appropriate analyses. However, mineralocorticoid excess may be present also in normokalemic subjects (97,98). Surgery is the treatment of choice in aldosterone-producing adenomas, but hypertension resolves only in approximately 35% to 50% of cases (96). As the rate of hypertension regression following bilateral adrenalectomy in idiopathic hyperplasia is even lower, therapy in this setting relies on the aldosterone antagonist spironolactone and a sodium-restricted diet.

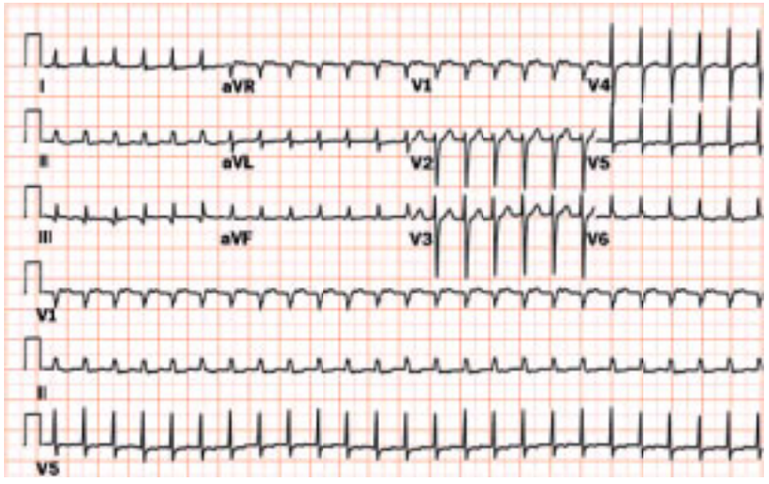
Pheochromocytoma

The clinical presentation of pheochromocytoma is characterized by episodic catecholamine release. In approximately 90% of cases, pheochromocytomas are located in the adrenal glands (in less than 10% the process is bilateral), whereas extraadrenal tumors, originating from chromaffin tissue of any sympathetic paraganglion (paragangliomas), account for the remaining 10% of cases. Over 90% of pheochromocytomas are benign and cured by surgery with low operative mortality (103). After surgical resection, up to 25% of patients may remain hypertensive. Life-long follow-up is mandatory because the disease may show late recurrence (104). Familial forms are rare and associated with bilateral or extraadrenal involvement and occasionally with multiple endocrine neoplasia type II.

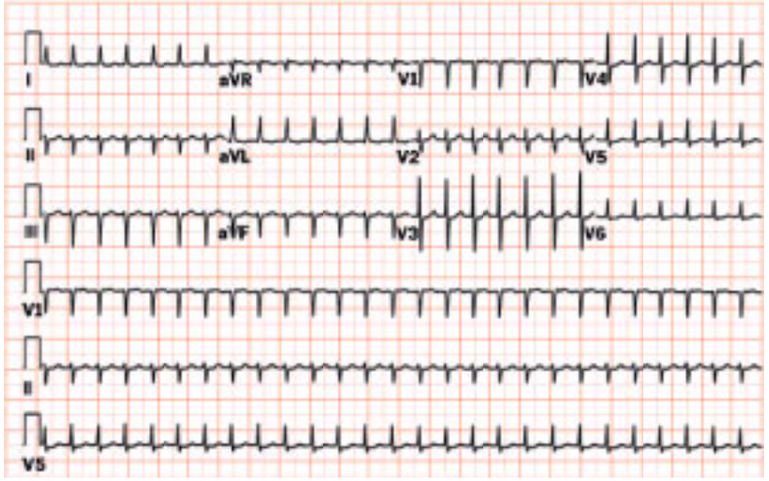
The classic presentation of pheochromocytoma consists of a paroxysm of the triad of palpitations, diaphoresis, and headache. These episodes begin abruptly, may last for minutes to hours, and subside gradually. Less common symptoms include orthostatic hypotension, anxiety, tremor, chest pain or abdominal pain, weakness, and weight loss. Because only a minority of patients presents with characteristic paroxysmal symptoms, the diagnosis is easily missed.

Cardiovascular Manifestations

Hypertension, one of the hallmarks of pheochromocytoma, is paroxysmal only in approximately one-half of the cases (105). Heart rate is frequently elevated during hypertensive episodes but may decrease because of reflex bradycardia, and usually no factors precipitating hypertensive episodes can be elicited. Prolonged exposure to high levels of catecholamines results in arterial and venous vasoconstriction and plasma volume contraction. Orthostatic hypotension may occur; possible mechanisms include plasma volume contraction and autonomous nervous system dysfunction (106). Electrocardiographic abnormalities are frequent but nonspecific and include T-wave abnormalities, signs of LVH, sinus tachycardia, and occasionally supraventricular ectopy and paroxysmal supraventricular tachycardia. In addition, particularly during hypertensive episodes, patients may show ischemic electrocardiographic changes. It has been postulated that pheochromocytoma affects the myocardium in the form of catecholamine-induced myocarditis, cardiomyopathy, or both (107,108). Tumor removal has been associated with regression of both LV dilatation and LVH (109,110 and 111).



Supraventricular tachycardia. Note narrow QRS complex with short RP interval.



Supraventricular tachycardia. P wave is not visible in this example, suggesting atrioventricular nodal reentry tachycardia.

Diagnosis

Because pheochromocytoma is the cause of hypertension in only approximately 0.1% of unselected patients (96), routine screening is not warranted. There is no gold standard to diagnose pheochromocytoma. Assessments of 24-hour urinary metanephrines and plasma metanephrines have shown comparable diagnostic sensitivity and specificity (112). Alternatively, plasma and urine metanephrines can be obtained during hypertensive paroxysm. Because only extreme elevations of plasma catecholamines affect blood pressure, normal levels in the setting of a hypertensive episode make pheochromocytoma highly unlikely. The great majority of pheochromocytomas are located in the abdomen and can be imaged by computed tomography or magnetic resonance imaging. Metaiodobenzylguanidine or octreotide scintigraphy may be useful for localization of metastatic, recurrent, or extraadrenal tumors.

Therapy

Surgery frequently represents the cure for pheochromocytoma. Adrenergic blockade for a few weeks is indicated before tumor resection, although on rare occasions urgent surgery may be necessary (Fig. 35A.3). The goal of preoperative treatment is adequate blood pressure control without inducing intolerable orthostatic hypotension. The alpha-blocker phenoxybenzamine, an irreversible noncompetitive antagonist predominantly of the $alpha_1$-receptors, has been the mainstay of preoperative and perioperative antihypertensive therapy (103,113). In patients intolerant to phenoxybenzamine, the $alpha_1$-selective antagonists prazosin, terazosin, or doxazosin have been used (103,113). To achieve optimal control of hypertension, tachyarrhythmias, and sinus tachycardia, beta-blockers can be added. However, beta-blockade should not be started if the patients are not pretreated with alpha-blockers. In fact, in the setting of high catecholamine levels, blockade of $beta_2$-mediated vasodilation can potentially lead to unopposed $alpha_1$-mediated vasoconstriction and exacerbation of hypertension. Frequently used drugs include the nonselective antagonist propranolol, $beta_1$-selective antagonists such as metoprolol or atenolol, and the mixed alpha/beta-blocker labetalol. However, because labetalol has a predominantly beta effect, additional alpha-blockade is usually required. In subjects with contraindications to beta-blockade, amiodarone can be used for tachyarrhythmia control. Severe hypertensive crisis may be acutely managed with intravenous nitroprusside or the $alpha_1$/$alpha_2$-blocker phentolamine. Several drugs can potentially trigger hypertension in pheochromocytoma and should, therefore, be avoided, including opiates, cocaine, tricyclic antidepressants, and metoclopramide (114).

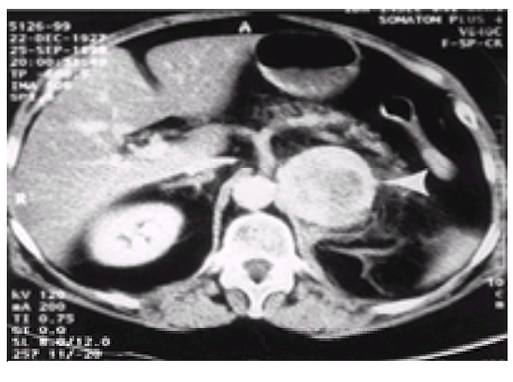


FIGURE 35A.3 Abdominal computed tomographic scan with contrast showing hemorrhagic transformation of a pheochromocytoma (*arrowhead*). The patient presented with lower back pain and extreme hemodynamic instability requiring emergency surgery. (Courtesy of E. Lipp, MD, Swiss Cardiovascular Center, Bern, Switzerland.)

Perioperative and Postoperative Management

Hypertensive episodes are more likely to occur during anesthetic induction, intubation, tumor palpation, and ligation of tumor veins (103). Intraoperative or postoperative hypotension is first approached with aggressive intravascular volume expansion. Only after euvolemia is restored, norepinephrine infusion may be indicated. Hypertensive responses are frequently controlled with intravenous nitroprusside, or alternatively, with phentolamine (113). Persistent hypotension is the main complication following surgery, possibly caused by tumor-induced suppression of catecholamine secretion of the contralateral adrenal gland and/or downregulation of adrenergic receptors (103). Less frequently, patients may be hypertensive postoperatively, because plasma catecholamines may remain elevated for several days after tumor removal. If hypertension persists several weeks after surgery, 24-hour urinary metanephrines should be assessed in order to exclude residual unresected tumor. In addition, hypoglycemia may be encountered in the perioperative or postoperative period.

ACROMEGALY AND GROWTH HORMONE DEFICIENCY

Growth hormone (GH) is produced and stored in large amounts in the pituitary gland. Direct GH effects include stimulation of lipolysis and gluconeogenesis. Indirect GH actions are mediated by insulin-like growth factor (IGF)-1. IGF-1, synthesized in hepatocytes and fibroblasts following GH stimulation, inhibits GH secretion in a classic feedback loop mechanism and acts as mediator of GH effects at the tissue level (i.e., it promotes chondrocytes proliferation and stimulates protein synthesis and glucose uptake in muscle cells). Stress, exercise, and a variety of neurogenic stimuli increase GH secretion. GH secretion persists throughout life, reaching the

maximum during puberty and then gradually declining in adulthood. In this book, the focus is exclusively on pituitary gland dysfunctions in the adult.

Acromegaly

Acromegaly is a rare disorder caused by a GH-secreting pituitary tumor, with an estimated incidence of approximately three per million (115). Excess GH secretion occurring during childhood leads to gigantismus. GH-producing tumors account for 10% to 15% of all pituitary neoplasms. Signs and symptoms are either caused by tumor mass effect (e.g., headaches, visual field defects, and hypopituitarism) or by GH excess (e.g., acral overgrowth, excessive sweating, and soft tissue swelling). Changes in facial appearance include enlargement of the lower jaw (prognathism), leading to malocclusion and increased spacing between the teeth and enlargement of the lips, tongue, nose, and sinuses. Progressive increase in shoe size and inability to wear rings are typical. Other features include sleep apnea, arthropathy, neuropathy, and cancer. Specifically, acromegalic patients have a three- to eightfold excess risk of colon cancer or premalignant polyps (116). Therefore, in these patients, screening with colonoscopy is recommended over the age of 50 years.

Acromegaly. The soft tissue and bone enlargement caused by growth hormone excess result in increased hand size as shown here. This condition may be associated with hypertension, cardiomegaly, and left ventricular hypertrophy.

Cardiovascular Involvement

Despite the fact that cardiovascular symptoms are the leading feature at presentation in less than 5% of the patients, overt cardiac disease may occurs in as many as 20% of acromegalic patients (117). GH excess is associated with a two- to threefold increase in mortality, mainly due to cardiovascular disease (118,119 and 120). Other causes include neoplastic and respiratory disorders. Hypertension is present in 25% to 35% of acromegalic patients, a three- to fourfold increase over the general population (117,121). The pathophysiology remains unknown, but its salt-sensitive nature suggests that, at least in part, it may be caused by a direct GH effect on the renal sodium pump leading to sodium retention (117,121). Glucose intolerance is present in up to 50% of the patients and overt diabetes mellitus in 10% to 25% (117). Diabetes resolves in two-thirds of patients after successful surgery (122). The lipid metabolism in acromegaly is characterized by hypertriglyceridemia (123), whereas no consistent findings on cholesterol abnormalities have been reported.

Electrocardiographic abnormalities are frequent and include ST-segment and T-wave depression, other signs of LVH, and, occasionally, conduction defects. Echocardiographic abnormalities, found in up to 80% of patients, include LVH and decreased systolic function (124,125). It has long been postulated that GH has trophic properties on the myocardium, but to date it remains a source of debate whether acromegalic cardiomyopathy exists. The assessment is complicated by frequent concomitant hypertension and/or coronary artery disease. However, echocardiographic studies in patients with acromegaly of recent onset and no associated cardiovascular abnormalities have demonstrated LVH, with or without associated diastolic dysfunction (126,127). These observations are in accordance with previous reports showing that less than 10% of patients with LVH and impaired LV function may have no evidence of hypertension or coronary artery disease (122,128). Additional arguments in favor of an acromegalic cardiomyopathy include the observation that LVH, LV dysfunction, or both may improve with treatment of GH excess (129,130). Moreover, both *in vitro* and *in vivo* animal models of GH excess have consistently demonstrated LV hypertrophic response and enhanced cardiac function (131,132). Finally, one autopsy series of acromegalic patients showed frequent myocardial interstitial fibrosis and inflammatory infiltrates (133). These observations suggest that, although most cardiac disease in acromegaly is explained by coexisting hypertension and/or coronary artery disease, a small proportion of patients may have a cardiomyopathy. It is speculated that elevated GH and/or IGF-1 levels may initially lead to LVH, followed by fibrosis, diastolic dysfunction, and later in the process, systolic dysfunction and overt heart failure (134).

A 71-year-old patient with left ventricular hypertrophy and negative U waves.

Diagnosis and Therapy

Because GH is secreted in a pulsatile manner, random GH plasma levels are not useful in diagnosing acromegaly. IGF-1 levels correlate with GH production and disease activity and represent the screening test of choice. Definitive diagnosis is made with the glucose tolerance test, showing no decrease of serum GH level following oral glucose load.

The goals of therapy are to reverse or prevent tumor mass effects and to reduce the long-term morbidity and mortality without incurring hypopituitarism. The current treatments for acromegaly include surgery, radiation therapy, and pharmacologic management. Among patients treated surgically, only 60% overall and less than one-half of those with large tumors can be cured (135,136). These low rates are explained by the fact that frequently, because of its extension and infiltrative nature, the tumor cannot be completely resected. Radiation therapy is characterized by delayed effect, poor efficacy, and a high incidence of panhypopituitarism (137). Preliminary data on stereotactic radiotherapy (gamma knife) appear promising, but its role in the treatment of acromegaly has yet to be demonstrated. Dopamine agonists, such as bromocriptine, cabergoline, or quinagolide (not available in the United States), adequately lower GH levels in only a minority of patients, and their adverse effects limit compliance (138). The somatostatin analogs octreotide and lanreotide inhibit the secretion of GH and are regarded by many authors as the first-line treatment of acromegaly. However, this drug class also leads to normalization of GH and IGF-1 levels only in approximately one-half of patients (139,140).

Pegvisomant is a recently developed, genetically engineered GH receptor antagonist. In the short run, this compound has been shown to be effective and well tolerated in over 100 patients with acromegaly (141). Should these promising results be confirmed in a large patient population with longer follow-up, GH receptor antagonism may become a useful tool for the medical management of acromegaly.

Growth Hormone Deficiency

GH deficiency (GHD) in the adult is primarily caused by hypothalamic or pituitary disorders, often leading to multiple pituitary hormone deficiencies (hypopituitarism). Neoplastic lesions, particularly pituitary adenomas, are the most common cause of acquired hypopituitarism. Other causes include radiation, trauma, pregnancy

(pituitary apoplexy, Sheehan's syndrome), anticoagulation-related pituitary hemorrhage, sickle cell anemia, and sarcoidosis.

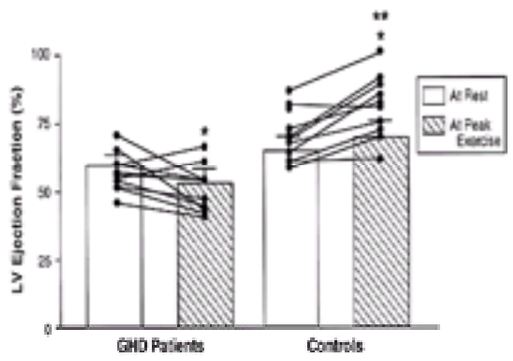
Clinical Presentation and Cardiovascular Risk Factors

GHD is a common finding in adults with hypothalamic or pituitary diseases. The deficiency is clinically characterized by changes in body composition including increase in adipose tissue mass and reduction in lean body mass, bone density, muscular strength, and exercise capacity (142,143). The psychosocial constellation of adult-onset hypopituitarism includes fatigue, emotional lability, sex life disturbances, and social isolation (144).

Several studies have shown that life expectancy in hypopituitary patients is decreased, mainly because of excess cardiovascular mortality, even after correct replacement of thyroid, adrenal, and sexual hormones (145,146). Serum total and LDL cholesterol, apolipoprotein B, and triglycerides are elevated in GH-deficient adults, whereas high-density lipoprotein (HDL) cholesterol is decreased (147,148). GH is believed to play a role in the regulation of hepatic LDL receptor activity, a major pathway of plasma LDL cholesterol removal (149). Hypertension is not a major feature of hypopituitarism, and the increased prevalence found in some studies compared with the normal population may be the result of more intense medical care (150).

Cardiovascular Involvement

There have been conflicting reports on LV wall thickness, LV mass, and systolic function in hypopituitary patients. On the contrary, diastolic dysfunction has been a consistent finding (150). Diminished exercise capacity compared with control subjects has been shown in a limited number of studies (151). In addition, abnormal LV systolic function during peak exercise has been reported (152,153) (eFig. 35A.3.1). One single study has so far addressed carotid artery morphology in patients with adult-onset hypopituitarism, showing a greater intima-media thickness ultrasound compared with controls (154). Studies on coronary arteries are lacking.



***e*FIGURE 35A.3.1** Left ventricular (LV) ejection fraction at rest and at peak exercise in growth hormone–deficient (GHD) patients and controls measured by radionuclide angiography. The bars represents the mean ± standard error of the mean. *, p <.05 compared with LV ejection fraction at rest; **, p <.001 with LV ejection fraction in GHD patients. (From Colao A, Cuocolo A, Di Somma C, et al. Impaired cardiac performance in elderly patients with growth hormone deficiency. *J Clin Endocrinol Metab* 1999;84:3950–3955, with permission.)

Diagnosis and Therapy

Insulin tolerance test, which assesses GH response to hypoglycemic stress following intravenous administration of insulin, is the diagnostic tool of choice for GHD (155). Alternatively, GH secretion can be assessed following stimulation with arginine or arginine and GH-releasing hormone. Despite being expensive, the administration of recombinant human GH has been approved in several countries for treatments of adults with GHD. Short-term studies show that GH replacement increases lean body mass, decreases adipose tissue mass, and improves the sense of well-being in adults with documented GHD, but long-term safety and efficacy data are limited. Benefits of long-term administration of GH in 12 patients was confined to body composition, with no effects on lipid levels or exercise tolerance (156). In particular, it remains unknown whether GH treatment affects mortality, and specifically cardiovascular mortality, associated with the disease.

In conclusion, although increased cardiovascular mortality has been attributed to GHD, the exact mechanisms have not been established. Chronic under- or overreplacement of other hormones may potentially contribute to the cardiovascular risk of hypopituitary patients.

Growth Hormone Abuse

The role of GH as performance enhancer in athletes has been reviewed (157). Over the last 10 years, GH abuse by athletes and body builders has been increasingly reported, facilitated by the fact that it remains undetected. Although the number of controlled trials is small, there is no scientific evidence that GH, even in supraphysiologic doses, enhances exercise performance or strength (157). In athletes undergoing regular training, the administration of supraphysiologic doses of GH for up to 3 months was not beneficial in terms of muscle strength or body composition (158,159). However, dose and duration of GH administration were different from those taken by athletes or body builders.

Chronic abuse of GH is likely to be associated with significant side effects, and potentially with the increased morbidity and mortality observed in acromegaly. In addition, it has been reported that, because of the high costs of recombinant GH, athletes may be purchasing cheaper cadaveric GH extracted from human pituitary glands (157). This product has been associated with Creutzfeldt-Jakob disease, and despite being banned in most western countries, it remains available (160).

Growth Hormone Therapy in Heart Failure

Several animal studies have indicated that GH and IGF-1 induce favorable early postinfarction remodeling, characterized by additional hypertrophy of the noninfarcted myocardium, reduction of LV dilatation, and decrease in systemic vascular resistance (161,162). Interestingly, GH-induced hypertrophy appears to be physiologic, as indicated by lack of fibrosis and by improved diastolic function (162,163). GH axis stimulation has been reported in patients with myocardial infarction (164), although the significance of this observation remains uncertain. GH has received attention as a potential adjunctive treatment for heart failure. In this setting, chronic administration of GH has been shown to induce concentric LVH (165,166). Initial small and uncontrolled trials have shown beneficial effects of GH therapy in heart failure (165,167). However, these results could not be reproduced in a larger placebo-controlled trial (166).

HYPERPARATHYROIDISM

In primary hyperparathyroidism (PHPT), inappropriate secretion of parathormone (PTH) causes excessive renal calcium reabsorption, phosphaturia, $1,25(OH)_2D$ synthesis, and increased bone reabsorption. Hypercalcemia, hypercalciuria, hypophosphatemia, and loss of cortical bone are typical associated findings. Based on surveys, a prevalence of PHPT between 0.1% and 0.5% has been estimated (168). Women are affected approximately twice as much as men, and after the age of 40 years the incidence of the disease sharply increases (168). The underlying pathology is in over 80% of cases parathyroid adenoma, in 10% to 20% hyperplasia of all parathyroid glands, and in fewer than 2% parathyroid carcinoma (169). Hyperplasia of parathyroid glands is most often familial and found in the context of inherited diseases, such as multiple endocrine neoplasia types I and II and familial hypocalciuric hypercalcemia.

PHPT is most frequently diagnosed following incidental plasma calcium measurements. Therefore, nowadays, most patients with PHPT are either asymptomatic or have vague, nonspecific symptoms such as fatigue, weakness, and mental disturbances. Other manifestations include proximal muscle weakness and pseudogout. Subperiosteal bone reabsorption and kidney stones are rare.

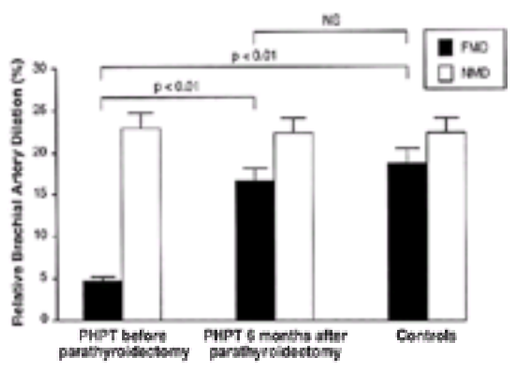
Cardiovascular Involvement

The relationship between PHPT and cardiovascular disease has not been conclusively defined. Previous epidemiologic studies (170,171) linking PHPT with increased mortality, and specifically, increased cardiovascular mortality, have been questioned by other large-scale observations (172,173). This discrepancy may be at least in part explained by different patient selection. Older studies frequently enrolled symptomatic patients with markedly elevated plasma calcium levels, whereas patients in

more recent studies were more likely to be asymptomatic and have mild hypercalcemia.

Approximately 30% to 40% of PHPT patients are hypertensive, which represents an approximately twofold increased incidence compared with the general population of the same age and sex (168). In an unselected population of hypertensive patients, approximately 1% may have PHPT (96). Because no direct correlation between hypertension and elevated PTH or calcium levels has been found, the pathophysiology of hypertension in this setting remains unclear. It is controversial whether PHPT in the absence of hypertension causes LVH. Mild LVH was documented in one small echocardiographic series (174), but this observation could not be reproduced (175). More convincing data on a link between high PTH levels and LVH are derived from patients with end-stage renal disease. End-stage renal disease is characterized by, among others, secondary hyperparathyroidism—a condition that produces much higher PTH levels than PHPT. The incidence of LVH is higher in this patient population if compared with controls matched for age, sex, and blood pressure (176,177). Additionally, a regression of LVH after parathyroidectomy in hemodialysis patients has been described (178,179).

Endothelial dysfunction in otherwise healthy patients with PHPT has been reported (180). Interestingly, the same authors found that endothelial dysfunction was reversible after parathyroidectomy (181) (eFig. 35A.3.2). Similar findings were documented in another small series (182). In addition, initial data show that mild PHPT might be associated with decreased vascular compliance (183).



***e*FIGURE 35A.3.2** Relative flow-mediated (endothelium-dependent) vasodilation (FMD) and nitroglycerine-induced (endothelium-independent) vasodilation (NMD) of the brachial artery of patients with primary hyperparathyroidism (PHPT, n = 19) before and after parathyroidectomy and of control subjects (n = 20). There was no significant difference in NMD with time or between groups. FMD was significantly reduced in PHPT compared with controls at baseline and improved significantly after parathyroidectomy with time. (From Kosch M, Hausberg M, Vormbrock K, et al. Impaired flow-mediated vasodilation of the brachial artery in patients with primary hyperparathyroidism improves after parathyroidectomy. *Cardiovasc Res* 2000;47:813–818, with permission.)

Diagnosis and Therapy

The finding of hypercalcemia in the presence of an elevated or nonsuppressed intact PTH level is the key to diagnosis. Parathyroidectomy remains the therapy of choice for patients with severe hypercalcemia, recurrent kidney stones, nephrocalcinosis, renal failure thought to be related with the disease, reduced bone mass, and probably for asymptomatic patients younger than 50 years (184). Patients older than 50 years with mild PHPT may not need surgery (184). This approach is supported by long-term studies showing a remarkable stability of the disease over the years, but prospective randomized trials are lacking. Because hypertension remission after surgery is variable, hypertension is considered a minor criterion for recommending parathyroidectomy (185). Cure rates, extremely operator-dependent, range between 90% and 95% (186,187).

A 54-year-old male patient with hypercalcemia.

ANDROGENS AND THE CARDIOVASCULAR SYSTEM

Androgens in general, and testosterone in particular, are widely believed to be associated with a higher cardiovascular risk in men, probably because male gender itself is an established independent risk factor for cardiovascular disease. Additionally, the abuse of synthetic androgens in high doses by athletes and body builders has been associated with hypertension, cardiomyopathy, myocardial ischemia, and sudden death (188). However, a number of more recent reports challenge the assumption that androgen is detrimental for the cardiovascular system. Animal studies *in vitro* have shown that testosterone is a coronary vasodilator (189). This observation was reproduced in humans in a study showing that intracoronary administration of physiologic doses of testosterone increased coronary blood flow in men with ischemic heart disease (190). Accordingly, significant improvements in angina threshold have been demonstrated in patients given supplemental intramuscular, oral, or intravenous testosterone (191,192). However, the doses used in these trials were supraphysiologic, raising concerns about potential side effects. The daily administration of small doses of testosterone to men with chronic stable angina was shown to prolong time to myocardial ischemia compared with placebo, and the magnitude of the benefit was comparable with the previous studies using higher testosterone doses (193). Additionally, castration resulted in a significant increase in aortic atherosclerosis in cholesterol-fed rabbits—a process that was markedly inhibited by testosterone replacement (194). In men without prior myocardial infarction referred for coronary angiography, a significant inverse correlation was found between plasma testosterone levels and extent of coronary disease, suggesting that low testosterone may represent a risk factor for coronary atherosclerosis (195). However, a number of prospective epidemiologic studies have failed to show a relationship between baseline testosterone levels and the subsequent development of coronary disease (196,197 and 198). The influence of androgens on serum lipids and glucose metabolism in men remains controversial (195,199,200). Currently no data exist on the effects of testosterone therapy on cardiovascular morbidity and mortality and on potential side effects such as growth in prostatic hyperplasia or prostatic cancer.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Cardiovascular involvement is frequent in endocrine disease. However, it is often controversial whether hormonal imbalance has direct deleterious effects on the cardiovascular system or if cardiovascular involvement is caused by the increased prevalence of associated cardiovascular risk factors. Little is known about how hormones directly interact with the cardiovascular tissue and how they influence risk factors such as hypertension or hyperlipidemia.

In addition, it remains unproven whether therapy reduces cardiovascular morbidity and mortality in endocrine diseases other than diabetes mellitus. The fact that many endocrine disturbances are uncommon makes clinical research in this field difficult.

The potential for thyroid hormone and GH supplements in heart failure has been recognized. Data are limited; therefore, these therapies should be considered investigational. Equally controversial is the interaction between androgens, and specifically testosterone, and the cardiovascular system in men.

Notwithstanding the interest of these topics, we have to realize that frequently the most challenging step in endocrine disorders remains the diagnosis. Clinical suspicion is essential, as endocrine diseases and, in particular, their cardiovascular manifestations may present in a subtle and nonspecific way.

THE FUTURE

Amiodarone remains a cornerstone of antiarrhythmic therapy. However, its use is limited by side effects and, in particular, by frequent thyroid dysfunction. Preliminary animal data on a noniodinated analog of amiodarone have been encouraging. An iodine-free “amiodarone-like” compound without the disturbing endocrinologic side effects would be a major advance in cardiovascular medicine.

In the near future, newer innovative therapeutic modalities, including applications of pharmacogenomics, may modulate endocrinologic diseases before cardiovascular involvement. In addition, targeted therapy based on a patient’s individual genetic profile may allow more selective and specific treatment of cardiovascular manifestations of endocrine diseases.

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35B

HEMATOLOGIC AND ONCOLOGIC DISORDERS

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"Indicates text or graphics that appear only in the electronic versions of this text."

Anemia
Pathophysiology
Treatment
Thalassemia
Sickle Cell Disease
Hemolysis and Heart Disease
Disorders with Increased Blood Viscosity
Polycythemia
Essential Thrombocythemia
Hematologic Effects of Cardiac Drugs
Heparin-Induced Thrombocytopenia
Oncologic Disorders and the Heart
Metastatic Disease Involving the Heart
Direct Effects of Tumors
Indirect Effects of Tumors
Cardiac Effects of Radiation Therapy for Cancer
Effects of Chemotherapy on the Heart
Controversies and Personal Perspectives
Anemia
Heparin-Induced Thrombocytopenia
Malignant Pericardial Effusion
Chemotherapy and Cardiac Toxicity
Chapter References

ANEMIA

Pathophysiology

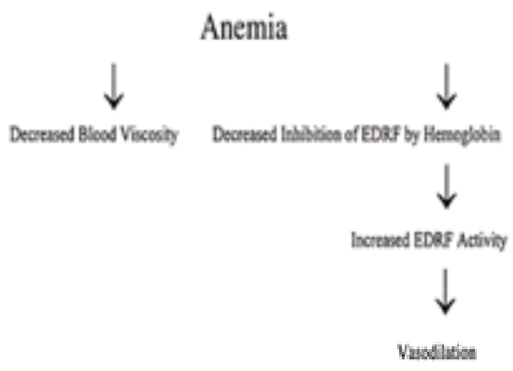
Severe anemia (hemoglobin less than 7.0) results in profound hemodynamic and neurohormonal changes aimed at maintaining adequate oxygen delivery to vital organs (eTable 35B.0.1 and eFig. 35B.0.1). Hemodynamic changes observed in patients with severe anemia include increased cardiac output, heart rate, and stroke volume and decreased systemic vascular resistance, mean arterial pressure, and circulatory transit time (1). Neurohormonal changes include activation of the renin-angiotensin-aldosterone system and increases in vasopressin and norepinephrine release. Elevated levels of 2,3-diphosphoglycerate result in lower oxygen affinity for hemoglobin and hence greater tissue extraction of oxygen (2). All these adaptations correct with reversal of the anemia. Although healthy adults can sustain hemoglobin concentrations as low as 5 mg per dL without detrimental effects on tissue oxygenation (1), symptoms of fatigue may occur in anemia and resolve with transfusion (3). Although clinically significant myocardial ischemia is rare in otherwise healthy people, cardiac reserve is impaired (4).

***e*TABLE 35B.0.1** CARDIOVASCULAR EFFECTS OF SPECIFIC HEMATOLOGIC DISORDERS

Anemias
Thalassemia
Cardiac hemosiderosis secondary to multiple transfusions
Restrictive cardiomyopathy
Systolic dysfunction
Arrhythmia
Pericarditis
Sickle cell disease
Nonspecific electrocardiographic changes
Cardiomegaly
Right and left ventricular hypertrophy
Diastolic dysfunction
Possible systolic dysfunction
Stroke
Increased blood viscosity
Polycythemia vera
Myocardial infarction
Transient ischemic attacks
Stroke
Deep venous thrombosis and pulmonary emboli
Peripheral arterial thromboemboli
Hemorrhage
Secondary absolute polycythemia
Myocardial infarction
Hemorrhage
Essential thrombocythemia
Myocardial infarction
Transient ischemic attacks
Stroke
Venous thrombosis
Hemorrhage

***e*FIGURE 35B.0.1** Compensatory physiologic changes associated with anemia. ADH, antidiuretic hormone; CO, cardiac output.

The high cardiac output found in anemia results from decreased systemic vascular resistance and increased heart rate. Heart rate is increased as a result of lower basal parasympathetic tone (5). The mechanisms by which systemic vascular resistance is decreased in anemia include both decreased blood viscosity and vasodilation (eFig. 35B.0.2). Experiments in anemic dogs, in which hematocrit is held constant but blood viscosity is varied using dextrans of varying molecular weights, have shown that decreased blood viscosity contributes to, but does not fully explain, the decreased resistance and increased cardiac output found in anemia.



***e*FIGURE 35B.0.2** Mechanisms by which anemia reduces vascular resistance. EDRF, endothelium-derived relaxing factor.

One hypothesis for the mechanism by which the vasodilation component of decreased systemic vascular resistance is produced is that endothelium-derived relaxing factor (EDRF) activity is enhanced by anemia. Anand and colleagues studied forearm blood flow in eight patients with chronic severe anemia and found that N^G-monomethyl-L-arginine, a specific inhibitor of EDRF, decreased forearm blood flow three times more than for controls or anemic patients after treatment, suggesting that EDRF is indeed a major contributor to the vasodilatation found in anemia (6). Hemoglobin, a known potent inhibitor of EDRF, may enhance EDRF activity in anemia because of reduced inhibitory effect.

In the most severe cases of anemia, congestive heart failure may develop and can resolve by simply correcting the anemia. *Congestive heart failure* is actually something of a misnomer in this case because most patients usually have normal or increased myocardial contractility. However, in some cases of protracted anemia, left ventricular systolic dysfunction can develop, and this, too, is reversed by correcting the anemia (7). When ventricular function remains preserved, the fluid retention in severe anemia appears to be caused by the neurohormonal activity (induction of the renin-angiotensin-aldosterone system and increased vasopressin release) that is caused by the decreased renal blood flow that occurs when low systemic arterial pressures result in a reflexive increase in renal vascular resistance.

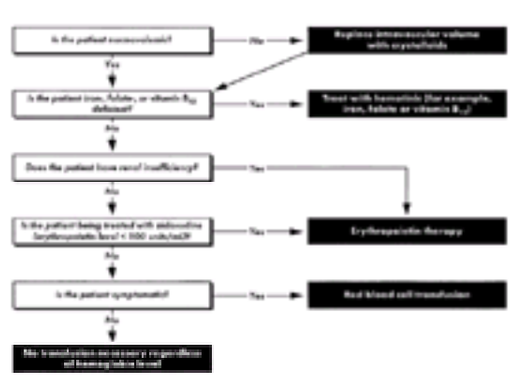
Treatment

All of the hemodynamic and neurohormonal changes described previously readily correct with reversal of the anemia. The risks of blood transfusion, although low, are not zero. The risks of transmission of the potentially deadly viruses hepatitis C, hepatitis B, and human immunodeficiency virus have been estimated at 1:300 to 1:900, 1:200 to 1:300, and 1:40,000 to 1:1,000,000, respectively, with current screening practices (2). The risks of the noninfectious complications of minor immunologic reaction (fever, chills, urticaria), hemolytic transfusion reaction, and fatal hemolytic transfusion reaction have been estimated at 1:50 to 1:100, 1:6,000, and 1:100,000, respectively. Transfusion-related graft-versus-host disease has also been reported in immunocompetent recipients, but the quantitative risk is unknown (2). Because of these potential complications, red cell transfusions should be performed only when the benefit is judged to outweigh these risks.

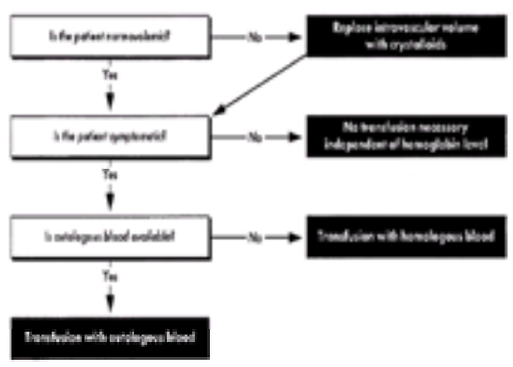
Guidelines have increasingly advised that routine transfusion using the *10/30 rule*(hemoglobin of 10 mg per dL or hematocrit of 30%) as a trigger should be avoided. Both to reduce the risk to transfusion recipients and to conserve blood products, the overall status of the patient should be considered in addition to the specific measurements of hemoglobin or hematocrit. The primary reasons usually given for transfusion are to increase myocardial oxygen supply and to diminish the increased demand caused by the physiologic adaptations described previously. However, most evidence supports the concept that myocardial oxygen supply is maintained above a hemoglobin of 6 to 7 mg per dL (2) and that, at least in otherwise healthy individuals, administration of stored blood in mild anemia does not improve hemodynamics or tissue oxygenation. In a randomized clinical trial of critical care patients, those kept at a hemoglobin level of 7 to 9 mg per dL had a lower in-hospital mortality (p = .05) and a nonsignificantly (statistically) lower 30-day mortality compared with those kept at a hemoglobin of 10 to 12 mg per dL (8).

In anemia from acute blood loss, blood volume should be replaced first with crystalloid before determining if red cell transfusion is necessary, based on signs or symptoms. If blood loss can be anticipated, such as in elective surgery, arrangements should be made, if possible, for autologous blood donation. Finally, in chronic anemia, homologous blood transfusion should be the treatment of last resort: All other avenues, such as iron replacement or erythropoietin, should be tried before consideration of homologous transfusion, and then transfusion should only be performed for symptoms or signs attributable to the anemia. These symptoms include syncope, dyspnea, orthostatic hypotension, tachycardia, angina, or transient ischemic attacks (2).

The absence of definitive evidence concerning the point at which the increased myocardial oxygen demand creates a problem for patients with coronary artery disease makes practical criteria for cardiac patients difficult. No evidence exists that anemia in these patients predisposes to adverse cardiovascular events. Deleterious consequences of sending patients home after cardiopulmonary bypass or percutaneous intervention with hematocrit values between 21% and 30% have not been documented. One study suggests that, among patients with angina and anemia, low exercise capacity is caused more by anemia than by coronary disease when the hematocrit is below 25% (9). Therefore, the general guidelines of the American College of Physicians are recommended (eFig. 35B.0.3 and Fig. 35B.0.4); only severe symptomatic anemia should be corrected with red cell transfusions, and only after nontransfusion therapy has been exhausted (2). In the setting of persistent refractory ischemia, packed red blood cells should be given to correct the anemia until the acute situation is stabilized.



***e*FIGURE 35B.0.3** Elective red blood cell transfusion in patients with persistent anemia: management strategy. (From Welch HG, Mechan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med* 1992;116:393–402, with permission.)



***e*FIGURE 35B.0.4** Elective red blood cell transfusion in patients with transient anemia from acute blood loss: management strategy. (From Welch HG, Mechan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med* 1992;116:393–402, with permission.)

Among patients with chronic heart failure, anemia is common and increases in frequency with severity of heart disease, such that nearly 80% of patients with New York Heart Association class IV symptoms were anemic in one study (10). This prospective study found that raising the hemoglobin from a mean of 10 mg per dL to 12 mg per dL with iron and erythropoietin in a group of heart failure patients was associated with improved ejection fraction (EF) and functional class and reduction in hospitalization and diuretic dose (10). Another study found that patients with ischemic cardiomyopathy had a lower cardiac index when anemic, and that correcting the anemia increased the cardiac index (11).

Patients with end-stage renal disease represent a separate entity. The link between anemia and heart failure in these patients is strong, and anemia in this population is also associated with cardiac mortality (12). Heart failure in these patients can develop as a result of the stress of long-standing anemia on the heart leading to myocyte hypertrophy. These hypertrophic changes have been shown to regress after reversal of anemia (13). Improvement in myocardial ischemia has not been shown (14).

A few specific causes of anemia merit special consideration from the cardiologist because of their relationship to cardiac disease. These include the hemoglobinopathies, including the thalassemias and sickle cell anemia, and hemolytic anemia related to heart disease.

Thalassemia

The thalassemias are diseases of the red blood cell resulting from decreased amounts of either the a (a-thalassemia) or b (b-thalassemia) chain components of hemoglobin, because of either absent or defective genes. The relative excess of the normal globin component leads to hemolysis and ineffective erythropoiesis. The thalassemic syndromes range from subclinical to life-threatening depending on the number and severity of the genetic defects. b-Thalassemia major, characterized by defects in both copies of the beta-globin gene, has been the best studied with regard to cardiac problems.

Cardiac disease, the most common cause of death in b-thalassemia major, develops because of multiple blood transfusions (which become necessary beginning at 4 to 6 months of age when beta-chain production supplants g-chain production) rather than the disease itself. These blood transfusions, plus increased gastrointestinal absorption of iron, result in an iron-overload state, which leads to myocardial iron deposition, causing a restrictive cardiomyopathy, cardiac enlargement, ventricular dysfunction, and congestive heart failure. Both systolic and diastolic left ventricular dysfunction can occur (15). Arrhythmias (atrial and ventricular tachyarrhythmias and bradyarrhythmias, particularly involving atrioventricular block) may result from this cardiomyopathy or from hemosiderosis-related damage to the conduction system. Pericarditis is also commonly seen (16).

The advent of the iron-chelating agent deferoxamine in the mid-1970s resulted in an overall reduction in cardiac complications (17) and improvement in survival (18). Thus, deferoxamine, generally administered by continuous subcutaneous injection by a pump device, is a mainstay of medical treatment of b-thalassemia major. Allogeneic bone marrow transplant has been used as an alternative to long-term transfusion and iron chelation therapy (19).

Sickle Cell Disease

Sickle cell anemia is caused by a point mutation in the beta-globin gene, resulting in the substitution of valine for glutamate in the sixth amino acid of the protein. This change, in homozygous form, results in deoxygenated HbS polymerizing, distorting the shape of the red blood cell (sickling) and leading to occlusion of capillaries and end-organ damage. In addition, the abnormal hemoglobin results in a shortened life span of the erythrocyte, resulting in an anemia with reticulocytosis.

Sickle cell ulcer. Chronic skin ulcer in the leg commonly occurs in sickle cell disease. The chronic severe anemia and hypoxemia impose a burden on the heart that may elicit a hyperdynamic response.

In contrast to b-thalassemia, cardiac complications of sickle cell anemia are not among the major causes of morbidity or mortality, although the heart is affected. Several studies using noninvasive imaging techniques have demonstrated abnormalities in sickle cell patients. Diastolic dysfunction, increased left ventricular mass and wall thickness, and enlargement of the cardiac chambers and aortic root are all common by echocardiography (20). Although resting EF is almost always normal (21,22), subtle abnormalities in load-independent parameters suggest underlying systolic dysfunction (21), and impaired EF response to exercise has been described (23). Right ventricular abnormalities and significant pulmonary hypertension are uncommon (21,24). Primary valvular disease is uncommon as well (24). Treatment involves addressing the underlying disease, including supportive therapy consisting of hydration, analgesics, oxygen, and transfusions when indicated. Newer therapies include hydroxyurea and allogeneic bone marrow transplant.

Changes associated with anemia in general, as described previously, are present in sickle cell disease, especially when the hemoglobin falls below 7 mg per dL. Most of the physical examination findings relate to compensatory adjustments to the anemia, rather than intrinsic cardiac abnormalities. Thus, a widened pulse pressure, prominent precordial impulse, and systolic and diastolic flow murmurs may be present, all reflecting a hyperdynamic state. The electrocardiographic (ECG) results are frequently abnormal, although there is no specific finding indicative of sickle cell disease. One study by Uzsoy found ECG abnormalities in 78% of 148 patients, including left ventricular hypertrophy, first-degree atrioventricular block, right ventricular hypertrophy, and nonspecific ST changes (25). Increased voltage, even when meeting the Sokolow-Lyon criteria, is not specific for left ventricular wall thickening, but instead represents ventricular dilatation and eccentric remodeling. Abnormal septal Q waves are reflective of septal hypertrophy and correlate with anemia. Chest radiography generally reveals an enlarged cardiac silhouette (25) and enlarged pulmonary artery segments.

Evidence is sparse for a specific cardiomyopathy directly related to the sickle cell anemia. Most autopsy studies reveal no myocardial infarction or narrowing of

epicardial vessels (26). However, one study did find pathologic evidence of myocardial necrosis in 7 of 72 patients, and microthrombi in two of these, with clinical correlates of chest pain, typical ECG abnormalities, and one sudden death (27). Among 531 patients with acute chest syndrome in a multicenter study, the most common specific causes were pulmonary fat embolism and infection. Serious in-hospital complications involved pulmonary emboli, pneumonia, and neurologic catastrophe and rarely related to cardiac events. None of the 18 deaths was cardiac in nature (28). Echocardiographic findings remain constant during a sickle crisis (26), and many of the chronic echocardiographic abnormalities described previously correlate with the degree of anemia. Thus, acute cardiac events are rare, and chronic abnormalities are most often caused by the stress of chronic anemia.

Hemolysis and Heart Disease

Hemolysis following valve replacement occurs mainly because of turbulence of blood flow and, in patients with mechanical valves, direct trauma to erythrocytes (29) (see Chapter 24). It is common, occurring in up to 50% of patients, although severe hemolysis is rare (30). Significant hemolysis is strongly indicative of valve dysfunction or a paravalvular leak (30) and may even be the presenting sign (31). The degree of hemolysis is directly related to severity of regurgitation. However, severe hemolysis necessitating repeat surgery in the absence of paravalvular leak or valve dysfunction has been reported (32). Risk factors for hemolysis include smaller prosthesis, mechanical valve versus bioprosthesis (29), double- versus single-valve replacement (30), suture type (33), and annular calcification (33). In addition to prosthetic valve disease, hemolysis has been reported following mitral valve repair, with native valve disease, and in patients following repair of ventricular septal defect (34). Diagnosis of hemolysis requires elevated lactate dehydrogenase, which is the most sensitive test and correlates well with severity (35). Other laboratory evidence includes elevated reticulocytes, low haptoglobin, hemosiderinuria, anemia, and schistocytes seen on peripheral smear (30). Treatment is usually conservative, consisting of observation and iron and folate supplementation as needed. Beta-blockers may help by ameliorating shear stress (34). Transfusions may be required. Severe refractory anemia may necessitate repeat surgery.

DISORDERS WITH INCREASED BLOOD VISCOSITY

Polycythemia

Polycythemia is characterized by an increased concentration of circulating red blood cells. Absolute polycythemia represents an increase in red cell mass, whereas relative polycythemia denotes increased red cell concentration with normal red cell mass, due to reduced plasma volume. Absolute polycythemias may be characterized as primary (polycythemia vera) or secondary, caused by an increase in erythropoietin.

Polycythemia vera, caused by a neoplastic, clonal proliferation of hematopoietic stem cells, results in excess bleeding as well as thromboembolic complications in up to 60% of patients (36). These events include stroke, myocardial infarction, deep venous thrombosis, pulmonary embolism, and arterial embolism (36,37). Neurologic symptoms such as headache, dizziness, vision changes, and confusion may result from chronic decreased cerebral perfusion caused by elevated blood viscosity, rather than an acute event. Although thromboembolism tends to occur mainly in small vessels, aortic and cardiac intraventricular thrombi have been reported (38). Valvular lesions by echocardiography, usually thickening but occasionally distinct vegetations, occur commonly and are associated with thromboembolic events (39). Acute events are treated with phlebotomy and aspirin at a dose of approximately 300 mg per day (40). Chronic therapy includes phlebotomy (41), hydroxyurea (42), and interferon-a (43). Prophylaxis against thromboembolism with low-dose aspirin (75 mg per day) could be considered, although no randomized prospective trials of this have yet been conducted, and a higher risk for bleeding is incurred (40).

Secondary polycythemias may be caused by either an appropriate increase in erythropoietin secondary to hypoxia (such as in chronic obstructive pulmonary disease or congenital heart disease with right-to-left shunt; see Chapter 31) or an inappropriate increase in erythropoietin production due to an erythropoietin-producing tumor such as a renal cell carcinoma. Hematocrits tend to vary inversely with arterial oxygen saturation and in congenital heart disease have been reported to be as high as 85%. Clinical manifestations of secondary polycythemia are similar to those of polycythemia vera and can include thrombotic episodes and bleeding.

Polycythemia associated with smoking and chronic obstructive pulmonary disease is associated with a lower frequency of thromboembolic events compared with polycythemia vera, but events may occur in up to 40% of patients (36). The benefit of phlebotomy to reduce such events has not been conclusively proven (44). Exercise tolerance, however, has been shown to improve with phlebotomy to achieve a hematocrit in the range of 50%, but no further benefit seems to accrue by keeping hematocrit in the normal range (45). The mechanism may be caused by improved right ventricular performance due to decreased preload. Patients in clinical congestive heart failure receive more benefit than mildly symptomatic patients. To avoid significant hypovolemia, simultaneous volume expansion with normal saline may be required (41).

Relative, or spurious, polycythemia is defined by increased hematocrit with normal red cell mass, generally caused by either reduced plasma volume or the combination of high normal red cell volume and low normal plasma volume. Morbidity is not directly related to this condition; thus, phlebotomy is not warranted.

Essential Thrombocythemia

Essential thrombocythemia is a myeloproliferative disorder similar to polycythemia vera with clonal overexpression of a multipotent stem cell, but resulting predominantly in thrombocytosis rather than erythrocytosis (46). As in polycythemia, this condition results in both bleeding and thromboembolic complications, with 9% to 40% of patients experiencing one or more thrombotic events (47,48). Large vessel thrombosis is most common, but myocardial thrombosis has been reported (48). Because a history of a thrombotic event is a risk factor for future recurrence, patients suffering such events are usually started on cytoreductive therapy, which may include radiophosphorus, hydroxyurea, busulfan, or interferon-a (46,47). Platelet count does not correlate with thrombosis in most studies, and even young patients may have serious or even fatal thrombotic events (48). The benefit of prophylactic therapy, however, currently remains controversial (46,49).

HEMATOLOGIC EFFECTS OF CARDIAC DRUGS

Occasionally, drugs used to treat cardiovascular disorders may cause hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia (*e*Table 35B.0.2). Antihypertensive drugs associated with rare untoward hematologic effects include captopril, which has been associated with leukopenia, neutropenia, and fatal pancytopenia (50). Thiazides have been associated with thrombocytopenia (51). Hemolytic anemia (51) and thrombocytopenia (52) have been seen with use of alpha-methyldopa. Agranulocytosis has been reported after propranolol administration (53). Antiarrhythmic drugs have also been associated with hematologic abnormalities. Thrombocytopenia has been seen with digoxin use (52). Quinidine has been associated with hemolytic anemia and thrombocytopenia (52), and neutropenia and agranulocytosis have been reported with use of procainamide and tocainide (54). Use of the antiplatelet agent ticlopidine after coronary stent procedures has been associated with neutropenia, aplastic anemia, thrombocytopenia, and an incidence of thrombotic thrombocytopenic purpura of 1 in 1,600 to 5,000, resulting in over 250 deaths (55) and prompting recommendation of screening hematologic profiles while the patient remains on the drug (56). Clopidogrel is an alternative that has a safer hematologic profile, but nonetheless has been associated with thrombotic thrombocytopenic purpura (57). Hematologic abnormalities generally reverse with discontinuation of the offending agent.

***e*TABLE 35B.0.2** HEMATOLOGIC EFFECTS OF SOME COMMONLY USED CARDIOVASCULAR DRUGS

	Anemia	**Neutropenia**	**Thrombocytopenia**
Antihypertensives			
Captopril	Yes	Yes	Yes
Thiazides	No	No	Yes
Methyldopa	Yes	Yes	Yes
Propranolol	No	Yes	No
Antiarrhythmics			
Digoxin	No	No	Yes
Quinidine	Yes	Yes	Yes
Procainamide	No	Yes	No
Tocainide	Yes	Yes	No
Inotropes			
Milrinone	No	No	Yes
Amrinone	No	No	Yes
Antiplatelet agents			
Ticlopidine	Yes	Yes	Yes
Anticoagulants			
Heparin	No	No	Yes

Heparin-Induced Thrombocytopenia

Frequency

Perhaps one of the most commonly seen hematologic abnormalities caused by a cardiac drug in clinical practice is heparin-induced thrombocytopenia (HIT). Two types of HIT have been observed. Type I HIT is the more common, milder form, rarely resulting in platelet counts below 100,000. It occurs with a frequency of 10% to 25%, usually during the first 4 days of therapy, and resolves without serious sequelae despite continuation of heparin (58). A proaggregatory effect on platelets by heparin has been proposed as the mechanism for type I HIT. In contrast, type II HIT, a much more serious complication that is the subject of the remainder of this section, occurs with a frequency of approximately 1% to 5% of patients receiving heparin, usually 4 to 8 days after the start of heparin therapy (58). If there has been previous exposure to heparin, however, especially within the previous 3 months, onset may be much sooner, and therefore timing of thrombocytopenia alone cannot distinguish between HIT types I and II. The frequency with low-molecular-weight heparin is less than 1% (58).

Pathophysiology

The prevailing mechanistic theory is that binding of platelet factor 4 to heparin causes expression of an epitope that induces production of an immunoglobulin (Ig) G antibody, which then binds to platelets via the Fc receptor, in turn causing platelet activation and aggregation (59,60). Thrombosis is caused by aggregation and activation of platelets, including platelet production of microparticles inducing procoagulant activity, leading to induction of the coagulation cascade and thrombin generation (61). The platelets coated with antibody are removed from circulation by the reticuloendothelial system, thereby producing thrombocytopenia. Other negatively charged, polysulfated saccharides such as dextran sulfate may also induce an antibody response. The tendency to induce this response is likely related to a molecule's molecular weight and degree of sulfation (58). In some cases the antibody may recognize chemokines such as interleukin-8 and neutrophil-activating peptide-2, both of which are similar in structure to platelet factor 4. Moreover, in some patients type II HIT has been documented with induction of antibodies of the IgM and IgA, but not IgG, subtype, implying that the Fc receptor is not always involved in pathogenesis.

Genetic predisposition to HIT may occur. Specifically, the Fc-RIIA subclass may commonly exhibit a mutation at position 131, substituting histidine for arginine. The mutated protein binds strongly to HIT antibodies of the IgG_1 subclass. Accordingly, patients with HIT have a disproportionately high frequency of this genetic polymorphism (62).

Clinical Presentation

Thrombocytopenia occurs 4 to 8 days after the start of heparin and almost always drops to below 100,000, usually to a nadir of 30,000 to 50,000 (58,63). The platelet count decreases to less than 15,000 in only 5% of patients, in contrast to other drug-induced thrombocytopenias, in which nadirs are typically around 15,000 (64). Timing of thrombocytopenia has been documented to start as early as 2 days after initiation of therapy if recent previous exposure has occurred.

Thrombosis occurs with a high frequency, anywhere from 25% to 80%, depending on the patient population and treatment initiated (58,65). Importantly, up to 50% of thrombotic events occur before HIT can be recognized by low platelet counts, and patients remain at increased risk for events up to 30 days after the syndrome has been identified, despite cessation of heparin (58,65) (Fig. 35B.1).

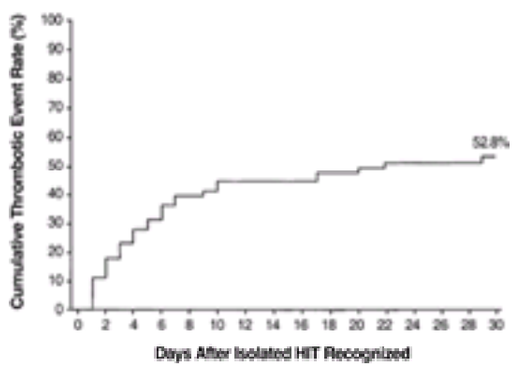


FIGURE 35B.1 Cumulative frequency of thrombotic events in patients with heparin-induced thrombocytopenia (HIT) presenting with isolated thrombocytopenia. (From Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med* 1996;101:502–507, with permission.)

The types of thrombotic events that occur are almost always severe. Pulmonary embolism accounts for up to one-fourth of the events (65), followed by proximal deep venous thromboses, stroke, myocardial infarction, and otherwise rare events such as bilateral adrenal vein thrombosis, cavernous sinus thrombosis, and extremity or visceral arterial thrombosis (64,65). Death occurs in up to 10% to 20% of patients, despite cessation of heparin and initiation of appropriate treatment (63,66). Despite sometimes severe thrombocytopenia, hemorrhage is relatively rare in HIT, occurring in under 10% of patients (58,63).

Attempts at predicting thrombotic events have not met with success. Although lower platelet count nadir and an earlier decrease in platelets are strongly associated with new thrombotic events, thromboses have been documented in patients with platelet counts above 150,000 (58), although in all these patients the counts had dropped by at least 30%. Although therapeutic doses result in HIT more often than prophylactic doses, even small amounts of heparin associated with flush solutions can cause the syndrome. Heparin resistance, likely caused by release of platelet-factor 4 into the circulation binding to and inhibiting heparin (60), tends to occur before thromboses, but not reliably so.

Diagnosis

Because the HIT antibody may be found in the absence of any clinical sequelae (58), HIT remains a clinical diagnosis, requiring the following conditions: (1) occurrence of thrombocytopenia during heparin administration, (2) resolution of thrombocytopenia after heparin is discontinued, and (3) exclusion of other causes. Heparin resistance, a new thrombotic event, and laboratory evidence all help support the diagnosis.

Among the laboratory assays, the ^{14}C-serotonin release assay is the most sensitive and remains the current standard for laboratory diagnosis, although it is difficult to perform and time-consuming. It relies on detection of ^{14}C-serotonin when radiolabeled donor platelets are incubated with serum from a patient with HIT and heparin and has a sensitivity of approximately 94%, with a specificity of 90% to 100% (67). The platelet aggregation test uses platelet-rich plasma from both normal donors and patients incubated together. The test result is positive when platelet aggregation occurs when heparin but not buffer is added. This test is the easiest to perform, but usually has a sensitivity of only 50% (60). The sensitivity may approach that of the ^{14}C-serotonin release assay, however, when washed platelets from multiple donors are used, and different concentrations of heparin are used as well (60). The enzyme-linked immunosorbent assay test to detect IgG antibody is sensitive but not very specific because weak antibodies may be detected (60).

Functional laboratory assay results become negative an average of 3 months after resolution of the clinical syndrome, but may remain positive for as long as 14 months (63,68). Platelet counts return to normal after a mean of 4 to 6 days, but this may take as long as 2 weeks (63,64).

Treatment

Cessation of heparin is critical when the diagnosis of HIT is reasonably suspect. Because thrombotic complications may occur even after stopping heparin (58), additional anticoagulation should be strongly considered. Lepirudin, a recombinant derivative of hirudin, an anticoagulant originating from leeches, is currently the only drug approved by the U.S. Food and Drug Administration for treatment of HIT. It directly inhibits thrombin and is renally excreted. Two clinical trials have shown improvement compared with historical controls with respect to death (9% vs. 22%) and new thromboembolism (18% vs. 32%) (66,69). During the trials, new events were reduced from 5.1% per patient-day before treatment to 1.5% per patient-day during treatment. Bleeding was higher (44% vs. 27%), but there was no statistically significant increase in the requirement for transfusion (13% vs. 9%). Other agents that have been used include danaparoid, argatroban, and anacrod (59). Of note, argatroban is excreted normally in patients with renal failure. Low-molecular-weight heparin should not be used to treat HIT because of a high rate (up to 85%) of cross-reactivity with the antibody.

ONCOLOGIC DISORDERS AND THE HEART

Metastatic Disease Involving the Heart

Metastatic disease involving the heart is uncommon, but not rare. In contrast, primary tumors of the heart are exceedingly rare, with an incidence of less than 0.002% of all autopsies (70). Of 58,600 autopsies done between 1936 and 1960 as described in ten reports, the incidence of metastases to the heart was 1.1% of all cases (range, 0.2% to 6.0%) and 6.4% of all patients with malignancy (range, 2% to 21%) (71). In a study of 3,314 consecutive autopsies over a 14-year period at a single center, Abraham and colleagues reported a 2.9% incidence of metastatic malignancy involving the heart (70). Of the 3,314 cases, 24.3% revealed evidence of cancer, and of these cancer cases, 11.8% revealed evidence of metastatic cardiac involvement. The most common area of involvement was the myocardium (53.9%), followed by pericardium (28.4%), epicardium plus pericardium (13.7%), and endocardium (3.9%). However, other autopsy studies have indicated that the pericardium and epicardium are more common sites of metastasis than the myocardium (72).

The primary tumors resulting in cardiac metastases, in order of decreasing frequency, were lung (31.6%), lymphoma (15.8%), breast (13.7%), leukemia (13.7%), stomach (5.3%), melanoma (3.2%), liver (3.2%), colon (3.2%), and other tumors (10.5%) (70). These rates were dependent on the varying incidences of the primary tumors. To determine the propensity of a given tumor to metastasize to the heart, one large series examined the rate of cardiac metastases in autopsies showing evidence of each tumor. Malignancies with a high propensity for metastasis included leukemia (46% of all autopsies with leukemia showed cardiac involvement), melanoma (37%), thyroid (30%), lung (28%), sarcoma (26%), esophagus (23%), kidney (22%), lymphoma (22%), and breast (21%) (72).

Video 35B.1 Apical four-chamber view (transthoracic) in a patient with metastatic lung cancer demonstrating a moderate to large pericardial effusion and a very large, highly organized pleural effusion encasing the heart. (Pleural effusion is towards the right of the screen.) Note the extensive fibrinous network in the pleural effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35B.2 Transesophageal echo of a large mobile mass seen in the right atrium, entering from the inferior vena cava. This patient had renal cell cancer that invaded the inferior vena cava. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Direct Effects of Tumors

Noncardiac tumors may either affect the heart directly, by actual infiltration of cardiac structures, or indirectly by thrombotic effects or secretion of mediators with cardiovascular effects (eTable 35B.0.3). Malignancy can involve the heart (including the pericardium) by a retrograde lymphatic route (carcinomas), hematogenously (carcinomas, sarcomas, lymphoma, leukemia, or melanoma), or by direct extension from contiguous structures (lung, breast, or esophageal carcinoma). Cardiac complications from direct effects of the tumor may occur by myocardial infiltration of tumor, pericardial infiltration causing effusion and tamponade, obstruction of the superior or inferior vena cava or right atrium, and pulmonary tumor emboli leading to elevated right-sided pressures and consequently right-sided heart failure (73). Cardiac complications are rarely the first signs of the malignancy; usually, the diagnosis of the primary tumor is well established before manifestation of cardiac involvement. It is also rare for cardiac metastases to occur without evidence of other metastases.

***e*TABLE 35B.0.3** CLINICAL CONSEQUENCES OF EFFECTS OF CANCER ON THE HEART
Direct effects
Myocardial infiltration
Arrhythmia
Myocardial infarction
Congestive heart failure
Pericardial infiltration
Symptomatic effusion
Tamponade
Venous infiltration or compression
Superior vena cava syndrome
Inferior vena cava obstruction
Myocardial infarction
Stroke
Pulmonary tumor emboli
Dyspnea
Cor pulmonale
Indirect effects
Nonbacterial thrombotic (marantic) endocarditis
Systemic emboli
Hormone-producing tumors
Pheochromocytoma
Hypertension
Arrhythmia
Angina
Myocardial infarction
Carcinoid
Diarrhea
Bronchospasm
Hypotension
Right-sided valvular disease
Secondary amyloidosis (myeloma)
Restrictive cardiomyopathy
Arrhythmia
Congestive heart failure

Video 35B.3 Transgastric 90-degree long-axis transesophageal echo view of a patient with a sarcoma metastatic to his left ventricular anterior wall. Note the invasion of the myocardium by this large mass. Additionally, there is severe hypokinesis of the anterior wall. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Myocardial Infiltration

Myocardial infiltration by metastases may be diagnosed by two-dimensional echocardiography or endomyocardial biopsy (74) (Fig. 35B.2), although most often it is discovered incidentally at autopsy. ECG findings are usually nonspecific. Multiple reports exist, however, of persistent ST-segment elevation changes resembling those

of myocardial infarction without other clinical evidence of myocardial infarction in patients with malignant myocardial infiltration, particularly if the epicardium is involved (75).

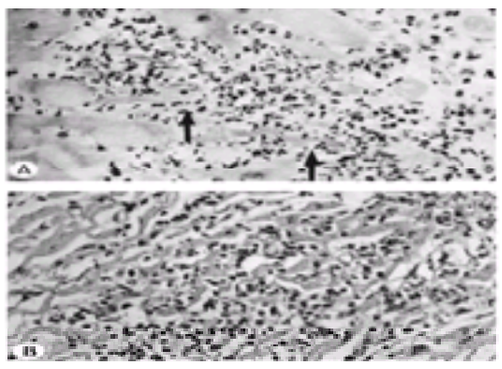


FIGURE 35B.2 A: Endomyocardial biopsy specimen in acute myelogenous leukemia showing myocardial infiltration by atypical hematopoietic cells and myocyte necrosis (*arrows*) (hematoxylin-eosin; ×400). **B:** Presence of immature myelogenous precursor cells is ascertained by chloroacetate esterase stain (×400). (From Flipse TR, Tazelaar HD, Holmes DR Jr. Diagnosis of malignant cardiac disease by endomyocardial biopsy. *Mayo Clin Proc* 1990;65:1415–1422, with permission.)

Myocardial infiltration by tumor is often clinically silent even when large amounts of myocardium are replaced by tumor, as in *charcoal heart* caused by metastatic malignant melanoma. However, clinical manifestations can include congestive heart failure (76), myocardial infarction (caused by tumor emboli, extrinsic compression, or ostial obstruction of coronary arteries) (77), and conduction disturbances (77,78). The pericardium is frequently also involved, and in these cases the clinical manifestations of pericardial disease predominate.

Treatment consists of addressing the underlying tumor; however, myocardial infiltration often represents an advanced state of the disease, in which treatment is ineffective. In cases of solitary cardiac metastases, surgical resection may be curative if the primary tumor has been controlled (79).

Pericardial Infiltration

Metastatic pericardial involvement, like myocardial involvement, is often asymptomatic and discovered as an incidental finding at autopsy. When clinically evident, pericardial disease is most often manifested by symptomatic pericardial effusion including tamponade. In rare cases pericardial tumor may encase the heart, leading to constriction. Initial diagnosis of pericardial disease is generally made by echocardiography, although occasionally computed tomographic scan may show disease when the echocardiography result was negative or may be necessary because of technically inadequate echocardiography (80).

When pericardial disease is discovered antemortem in cancer patients, malignant disease must be differentiated from idiopathic pericarditis and radiation-induced pericardial disease, both common in cancer patients. Clinical features helping to differentiate them include facial swelling in malignant pericardial disease; fever, pericardial friction rub, and improvement with nonsteroidal antiinflammatory drugs in idiopathic pericarditis; and constrictive pericarditis in radiation-induced disease. Cytologic examination of fluid is positive for malignant cells in 50% to 85% of cases (81). Bloody pericardial fluid with specific gravity greater than 1.016 and total protein greater than 3 mg per dL is also suggestive of malignant effusion.

Treatment of malignant pericardial effusions is only indicated in symptomatic patients. One retrospective, observational study of 93 consecutive patients revealed no difference in survival, duration of hospital stay, or hospital charges in less symptomatic patients managed conservatively initially compared with more symptomatic patients managed invasively. Furthermore, only 20% of the conservatively treated patients eventually required pericardiocentesis (82). Median survival after treatment is on the order of 3 to 4 months (81).

Treatment methods for malignant pericardial effusion include pericardiocentesis, pericardial sclerosis, systemic chemotherapy, radiotherapy, and surgery. Pericardiocentesis should be performed to relieve symptoms. Extended catheter drainage is associated with reduced recurrences compared with simple pericardiocentesis (81). Although pericardiocentesis alone can provide prolonged relief, symptomatic recurrence is frequent, up to 20% in one large series (81). Pericardial sclerosis may be performed using tetracycline.

Case series of patients undergoing pericardial sclerosis suggest that it is generally successful, with low recurrence rates (0% to 5%) and only minor complications such as fever or transient atrial arrhythmia, although an average of three instillations of tetracycline are required (83,84). Tetracycline sclerotherapy is an option for patients whose tumors are neither chemotherapy nor radiation sensitive, and who are poor surgical candidates. However, because of the potential complications and frequent discomfort, and since simple drainage is safe and effective, sclerotherapy may deserve second-line status after repeated failure of pericardiocentesis (81).

As reported in small case series, systemic chemotherapy has been effective in treating malignant pericardial effusions in conjunction with pericardiocentesis for tumors highly sensitive to chemotherapy, such as lymphoma, leukemia, and breast cancer. Other studies in patients with breast cancer, however, have shown a high rate of progression of pericardial disease in nonsurgically treated patients (85).

External radiation has also been used to treat malignant pericardial effusion and appears to be most effective in treating effusions from tumors known to be radiosensitive, such as Hodgkin's and non-Hodgkin's lymphoma, leukemia, and breast carcinoma. It can be used in patients who are refractory to chemotherapy, have radiosensitive tumors, and are poor candidates for surgical therapy.

Surgical therapy is commonly used to treat malignant pericardial effusion, usually by formation of a pericardial window. Multiple case series of patients undergoing pericardial window procedures have been reported. All show a high percentage of patients experiencing improvement in symptoms (range, 72% to 100%). Recurrence rates range from 0% to 33%, and death within 30 days due to the underlying malignancy is not uncommon (range, 0% to 67%), illustrating the importance of taking into account the prognosis of the underlying illness in patient selection for the procedure.

Conventional surgical approaches include the subxyphoid, left anterior thoracotomy, or median sternotomy. The advantage of the subxyphoid approach is that it can be done under local anesthesia, appears to be effective, and generally results in low morbidity and mortality. The theoretical advantages of the thoracotomy or median sternotomy approaches are that they allow greater exposure of the pericardium and hence larger amounts of pericardium to be removed. However, they have not clearly been shown to be more effective than the subxyphoid approach. One retrospective, nonrandomized comparison study of the subxyphoid approach with the anterior thoracotomy technique in 28 consecutive patients showed that although there was no difference in survival between the two groups, there was a much higher incidence of postoperative morbidity in the thoracotomy group (67% vs. 10%), including major complications in 50% of patients treated with thoracotomy, and none in those treated with the subxyphoid approach (86). However, for constrictive disease, a simple pericardial window is inadequate and extensive pericardial resection is required, generally through a median sternotomy approach (87).

Newer techniques for treatment of pericardial disease include video thoracoscopic surgical techniques and percutaneous approaches with balloon catheters. A report on 22 patients with pericardial effusion (9 malignant, 13 benign) who underwent video thoracoscopic pericardiectomy was promising, with no recurrences and no significant morbidity (88), but since the technique still requires general anesthesia, direct comparison studies with the subxyphoid approach would be required to demonstrate its equivalent or superior efficacy and safety. Results from percutaneous balloon catheter techniques for creation of pericardial windows have been reported and appear promising (89), but also require direct comparison studies with surgical approaches to determine their efficacy and safety.

Obstruction of Venous Inflow

Tumors may obstruct venous inflow into the heart, either by extrinsic compression or by direct invasion. Obstruction of the superior vena cava may result in the superior vena cava syndrome, which is caused in approximately 85% of cases by bronchogenic carcinoma, 10% by lymphomas, and the rest miscellaneous causes including benign etiologies (90). Extrinsic compression of the vein causes approximately 60% of cases and thrombosis the remainder.

In a retrospective review of 84 patients at a single center with superior vena cava syndrome, Perez and colleagues found that the most common presenting symptoms were shortness of breath (greater than 50%), facial swelling (43%), and swelling of the trunk or arms (40%). Chest pain, cough, and difficulty swallowing were also

common and each occurred in approximately 20% of patients. Physical findings in decreasing order of frequency were trunk vein distention (67%), jugular vein distention (59%), facial edema (56%), tachypnea (40%), facial plethora (19%), cyanosis (15%), arm edema (9.5%), vocal cord paralysis (3.5%), and Horner's syndrome (2.3%) (90).

Treatment generally involves chemotherapy or radiation therapy or both. In this series, chemotherapy, radiation therapy, or both resulted in excellent or good symptomatic improvement in 70% of patients with bronchogenic carcinoma and 95% of patients with lymphoma. Percutaneous stenting has also been used to relieve symptoms of superior vena cava syndrome (91).

Other conduits of venous inflow to the heart may also be obstructed. The inferior vena cava is most often obstructed by liver or renal tumors. Renal cell carcinoma may grow into the renal vein, and then continue on into the inferior vena cava and even the right atrium. Surgery to remove the tumor may be beneficial. Bronchogenic carcinoma may similarly invade the pulmonary veins and extend into the left atrium, impeding left-sided filling or potentially embolizing and causing myocardial infarction and cerebral infarction (73).

A final means of direct effects of malignancy on the heart is through pulmonary tumor emboli. In a review of 1,085 autopsies with evidence of malignancy, 2.4% had evidence of pulmonary tumor emboli, often with associated pulmonary thromboemboli. Of the patients with pulmonary tumor emboli, 31% had unexplained dyspnea and cor pulmonale and 15% had right ventricular hypertrophy. The tumors responsible included gastrointestinal carcinomas, breast carcinoma, and hepatoma (92).

Indirect Effects of Tumors

Nonbacterial Thrombotic (Marantic) Endocarditis

Nonbacterial thrombotic endocarditis (NBTE) is a condition in which sterile vegetations, consisting of mostly fibrin and platelets but not inflammatory cells, develop on valve leaflets. In contrast to infectious endocarditis, there is no disruption of the underlying valve architecture. This condition is frequently, but not exclusively, associated with malignancy and may be seen in other debilitating conditions (73). One case report of NBTE of the mitral valve documents resolution of the vegetation 4 weeks after resection of a hepatic tumor (Fig. 35B.3).

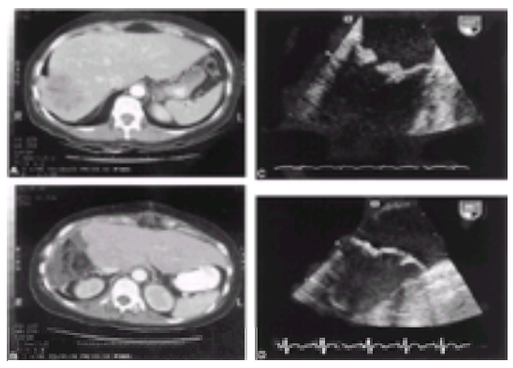
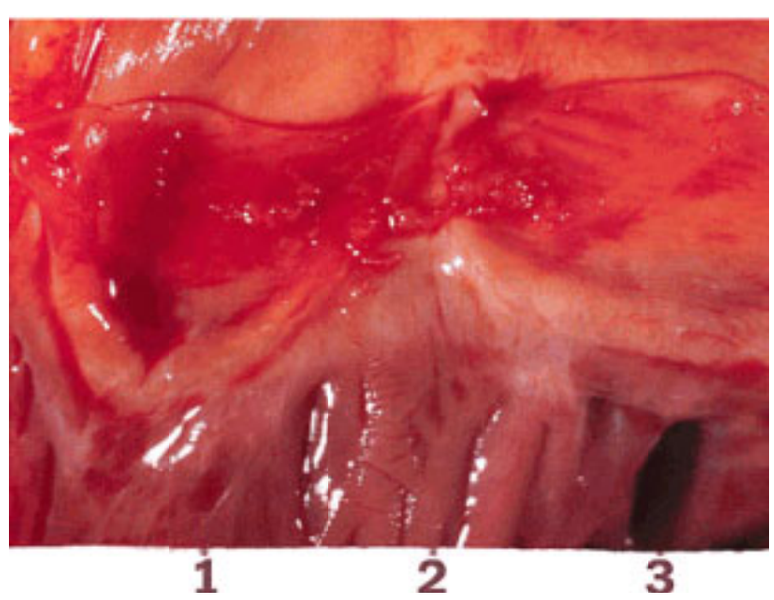


FIGURE 35B.3 Computed tomography scans of a hepatic tumor before **(A)** and after **(B)** resection. Transesophageal echocardiography demonstrating echodensities on the mitral valve consistent with vegetations **(C)**, and resolution of the abnormality 4 weeks after surgery **(D)**. (From Cockburn M, Swafford J, Mazur W, et al. Resolution of nonbacterial endocarditis after surgical resection of a malignant liver tumor. *Circulation* 2000;102:2671–2672, with permission.)



Marantic (nonbacterial) endocarditis of the pulmonic valve. Multiple vegetations are seen on the pulmonic valve in this patient with no bacterial growth from multiple blood cultures.

In one autopsy study of 3,404 patients reported by Chino and colleagues, 2.4% were found to have nonbacterial thrombotic endocarditis (93). Of these patients, 62% had associated malignancy, and 38% did not. Vegetations were present exclusively on the aortic or mitral valves or both. Other studies have shown that the right-sided valves may rarely be affected, although the presence of indwelling right-sided catheters may increase the likelihood of their involvement (94). In Chino and colleagues' study, NBTE was seen most frequently in patients with carcinoma of the colon, rectum, and female genital organs (93). Some other studies have found a greater degree of association between pancreatic and stomach cancer and NBTE, whereas others have shown higher rates in bronchiolar and adenocarcinoma of the lung (95). Although NBTE may not be clearly associated with one particular type of tumor, it does seem to be predominately associated with adenocarcinoma, probably because of a hypercoagulable state associated with these tumors. Although the exact underlying etiology of NBTE is unknown, immune complexes due to the underlying malignancy may play a role, as may a hypercoagulable state (73).

NBTE is usually clinically silent and can be diagnosed by transthoracic echocardiography, although transesophageal echocardiography is more sensitive (96). However, embolism of vegetations can occur and have been shown to cause infarctions in the brain, myocardium, kidney, spleen, and thyroid gland (93,95).

Pheochromocytoma

Pheochromocytomas are neoplasms that arise from the adrenal medulla or preganglion cells and secrete norepinephrine and epinephrine. Clinical manifestations include hypertension (present in most, but not all, patients), which may be sustained (approximately 60% of cases) or episodic (approximately 40% of cases) (97).

Paroxysms or crises occur in more than 50% of patients and are characterized by headache, diaphoresis, palpitations, pallor or flushing, and elevated blood pressure, at times to severe levels. Effects on the heart can include arrhythmias, angina, and even myocardial infarction. In addition, focal areas of myocardial necrosis with contraction bands may occur, probably because of the toxic effects of catecholamines on myocytes, and may with time lead to cardiomyopathy and congestive heart failure (98). Reduced myocardial ^{123}I-metaiodobenzylguanidine uptake has been noted with pheochromocytoma, suggesting that the high circulating catecholamines may damage cardiac sympathetic nerve function (99).

The disorder may be suspected when hypertension is present in conjunction with symptoms or signs of a hyperadrenergic state, such as tachycardia, palpitations, sweating, paroxysmal anxiety attacks, or headache (100). However, because these signs are nonspecific and the disease is rare, many patients who are evaluated for the disease end up not having it. Diagnosis is by determination of urinary levels of vanillylmandelic acid, metanephrines, and unconjugated catecholamines. Treatment involves surgery if possible to remove the tumor. Before surgery, cardiovascular effects can be managed with alpha-adrenergic receptor blockers such as phenoxybenzamine or prazosin and beta-adrenergic blockers. Alpha-receptor blockade should be fully established before beta-blockade, because beta-blockade alone

could lead to alpha-receptor–mediated vasoconstriction unopposed by beta$_2$-receptor–mediated vasodilation.

Carcinoid

Carcinoid tumors originate from amine precursor uptake and decarboxylase cells, and most commonly arise from the gastrointestinal tract. The tumors may secrete circulating chemical mediators such as serotonin and bradykinin, causing the carcinoid syndrome, which is characterized by flushing, diarrhea, wheezing, and episodic hypotension. Because these mediators are inactivated by the liver, carcinoid syndrome generally only develops if liver metastases are present or if the tumor is extraintestinal.

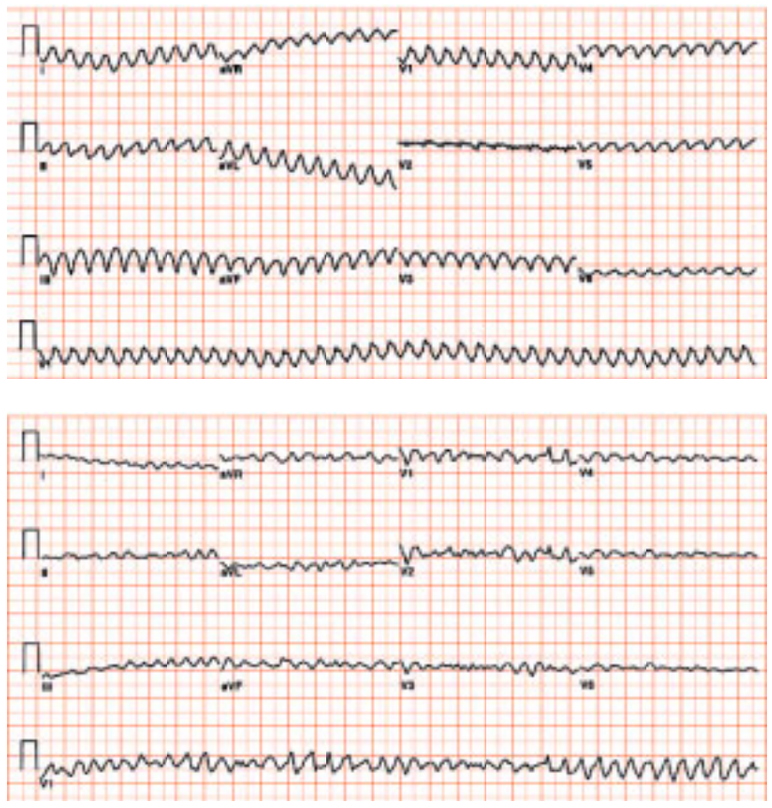
Cardiac abnormalities occur in approximately one-half of carcinoid syndrome cases. The cardiac lesion consists of a fibrous plaque made up of smooth muscle cells and collagen fibers in an acid mucopolysaccharide matrix (101). The lesions usually affect the right side of the heart only and may cause tricuspid valve and pulmonic valve dysfunction, typically tricuspid insufficiency and pulmonic stenosis. Although tricuspid valve surgery seems to result in symptomatic improvement in survivors of surgery, perioperative mortality is high (35% and 63% in two series) (102,103).

Although the etiology of the plaque is uncertain, it is probably caused by healing from multiple episodes of endothelial damage brought on by circulating mediators secreted by the tumor (73). Studies have shown that cardiac involvement with carcinoid correlates with higher levels of serotonin (104) and progression of cardiac disease (detected echocardiographically) correlates with posttreatment urinary 5-hydroxyindoleacetic acid levels (105), supporting the hypothesis that mediators released by the tumor cause the cardiac damage.

Cardiac Amyloidosis Secondary to Multiple Myeloma

Systemic amyloidosis occurs in approximately 10% of patients with multiple myeloma. When present, there is a high rate of cardiac involvement. One series reported amyloid-related cardiac failure in 40% of patients with systemic amyloidosis associated with myeloma (106). Clinical manifestations include congestive heart failure, arrhythmia, and restrictive cardiomyopathy. Definitive diagnosis must be made by endomyocardial biopsy, although the myeloma-involved heart has a characteristic, hyperrefractile appearance on echocardiography, which may assist in diagnosis. Other echocardiographic features include thickened ventricular walls, pericardial effusion, and thickening of multiple valves with regurgitation. Magnetic resonance imaging has also demonstrated promise in establishing the diagnosis noninvasively (107). Treatment is aimed at the underlying disease, in addition to using diuretics. There is anecdotal evidence that digoxin may be harmful because of heightened binding by amyloid fibrils in the heart, but systematic studies have failed to confirm this hypothesis (108). Coumadin may be beneficial, because intracardiac thrombi are frequently noted (108).

Apical four-chamber view of amyloid heart disease. Note the significant thickening of the left ventricle and right ventricle walls due to infiltration. There is also characteristic thickening of the valves and biatrial enlargement. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)



Ventricular flutter (A). Same patient with degeneration into ventricular fibrillation (B).

VIDEO

Video 35B.4 Transthoracic apical four-chamber view of a patient with amyloidosis. Note the thickened “sparkling” walls of the right and left ventricles. Both the mitral and tricuspid valves are mildly thickened and there is biatrial enlargement and a trivial pericardial effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Cardiac Effects of Radiation Therapy for Cancer

Radiation therapy is used to treat many thoracic cancers and may cause injury to the heart and surrounding tissues (eTable 35B.0.4). The majority of patients with such radiation-induced heart disease (RIHD) have had Hodgkin’s disease. Because they tend to be young at the time of treatment and are curable, they live long enough to develop the clinical sequelae of RIHD, many of which are delayed (109,110). However, patients irradiated for non-Hodgkin’s lymphoma, esophageal

carcinoma, thymoma, lung, and breast cancer have also developed RIHD.

***e*TABLE 35B.0.4** RADIATION-INDUCED HEART DISEASE
Pericardial disease
Acute
Pericarditis
Chronic
Delayed onset “acute” pericarditis
Chronic effusion
Constriction
Myocardial disease
Fibrosis and restrictive cardiomyopathy
Left ventricular and right ventricular dysfunction
Valvular heart disease
Aortic > mitral > right-sided
Coronary artery disease
Ostial right coronary artery and left main disease
Conduction system disease
Bundle branch block
Atrioventricular block
Pacemaker malfunction

The likelihood of RIHD depends on the dose and method of administration of the radiation. The larger the total dose of radiation, the shorter the time period over which it is given, and the greater the volume of heart exposed, the higher the probability of RIHD (110,111). Using anterior and posterior fields instead of anterior fields alone decreases the dose of radiation to the heart and thereby lowers the incidence of RIHD. Cardiac exposure can be further reduced by subcarinal blocking with lead shields. Carmel and Kaplan found that the incidence of RIHD decreased from 20.0% to 2.5% when such blocking was used in patients with Hodgkin’s disease.

The most common form of RIHD is pericardial disease. Radiation-induced pericardial disease may be either of acute, or more commonly, delayed onset. The clinical presentation of acute radiation-induced pericarditis is similar to that of acute pericarditis of other etiologies. It is characterized by pleuritic chest pain, fever, friction rub, and ST-segment and T-wave abnormalities (111). It occurs most frequently in patients with a large mediastinal tumor burden next to the heart, probably resulting from inflammation related to tumor destruction rather than a toxic effect on the pericardium, and does not increase the likelihood of late cardiac complications (112). The incidence is uncommon, with one series of 635 patients showing an incidence of 1.2% for acute pericarditis, compared with 6.9% for delayed pericardial complications (113).

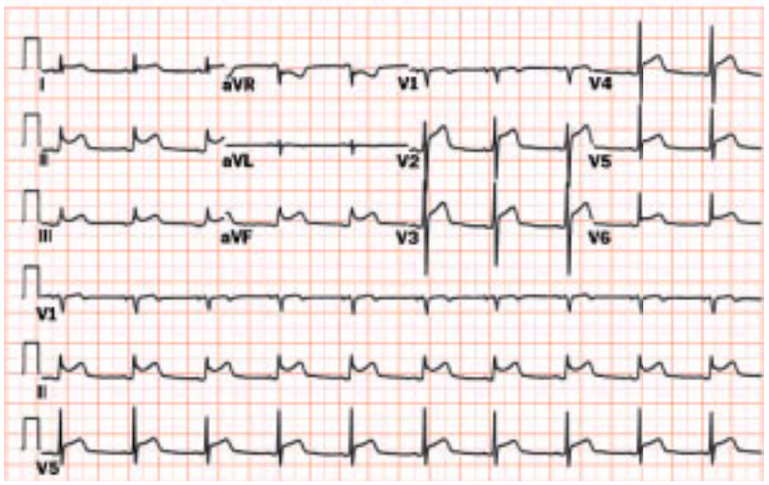
Delayed onset pericardial disease is the most common form of RIHD. It may occur months to years after treatment, but often occurs within 12 months of therapy (114). One manifestation of disease may be a delayed acute pericarditis, with symptoms and findings typical of pericarditis including pleuritic chest pain, fever, pericardial rub, and ST-segment and T-wave abnormalities. Pericardial effusion is common and may result in tamponade (112). Case reports have suggested that corticosteroids may be helpful, although withdrawal of the corticosteroids may lead to recurrence (112). However, randomized controlled trials of corticosteroids in RIHD have not been performed to confirm this benefit.

VIDEO

Video 35B.5 Apical four-chamber view demonstrating a large pericardial effusion causing tamponade. Note the inability of the right side to fill. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 35B.6 Subcostal short-axis view of a large pericardial effusion causing tamponade. Note that the right side is small and under filled. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Acute pericarditis. Note diffuse, marked ST-segment elevation with PR-segment elevation in lead aVR.

The other form of delayed onset pericardial disease is chronic, consisting of either chronic effusion or constrictive pericarditis. Risk of constrictive pericarditis ranges from 4% to 20% in different series and depends on the amount of radiation given and the method of administration (112,113). The risk of constriction appears to be increased in patients in whom delayed acute pericarditis develops, especially if an effusion is present, with as many as 20% of such patients eventually developing constriction (112). Furthermore, a majority of patients with constriction previously had pericardial effusions. Treatment is pericardiectomy, although patients with constrictive disease caused by radiation therapy tend to do worse after pericardiectomy than those with constriction from other causes, with one series reporting a 12% 30-day mortality for patients undergoing pericardiectomy for any reason, but a 21% mortality in those who had the procedure for radiation-induced constriction (115).

VIDEO

Video 35B.7 Transesophageal echo (four-chamber view) demonstrating constrictive pericarditis. Note the abnormal septal bounce and the tethering of the right atrium and right ventricle by the thickened pericardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Radiation therapy only rarely causes injury to the myocardium itself, which is of clinical importance. Pathologically, myocardial fibrosis may occur (116). Clinical sequelae are usually mild or absent (109). However, subtle impairment of left ventricular function at rest and especially with exercise may be seen with radionuclide techniques or echocardiography (117). The right ventricle may also be abnormally dilated or have wall motion abnormalities (118). Most patients do not have overt congestive heart failure; however, a restrictive cardiomyopathy may be present and in the worst cases lead to actual heart failure (112). Restrictive cardiomyopathy and

constrictive pericarditis may both be present and may result in less than expected improvement after pericardiectomy, and may account for the poorer prognosis of radiation-treated patients after pericardiectomy (119). Chemotherapeutic agents, particularly anthracyclines, may potentiate the myocardial damage caused by radiation therapy (120).

Valvular heart disease may occur secondary to radiation therapy, probably secondary to endocardial fibrosis, causing valvular thickening and deformity (116,121). In a series of 129 patients treated with radiation for Hodgkin's disease, examined 5 to 13 years after treatment, Lund and colleagues found that 24% had valvular regurgitation, with the aortic valve involved most often, the mitral valve less often, and no cases of right-sided valvular abnormalities (122). Right-sided valvular disease, however, has been reported after radiation therapy (117,123). Although echocardiographic abnormalities are relatively common, clinically significant valvular heart disease is rare, with only three deaths occurring from valvular disease out of 635 patients in one series (113).

The risk of coronary artery disease is increased after radiation therapy to the chest, as shown by an autopsy study (116) and several case reports of coronary artery disease in irradiated patients who were young and without other risk factors (124,125). Angiographic assessment of the coronary arteries in such patients reveals frequent high-degree ostial stenosis of the right coronary artery and left main involvement (126). Boivin and colleagues reported a relative risk of death from myocardial infarction after mediastinal irradiation but not after chemotherapy, based on analysis of 4,665 patients treated for Hodgkin's disease with a mean of 7 years of follow-up (127). Coronary artery disease tends to appear late after radiation therapy and can be treated with coronary artery bypass surgery if necessary. However, because the left internal mammary artery is exposed to radiation, it may be difficult to dissect and may have a tendency to occlude prematurely (128).

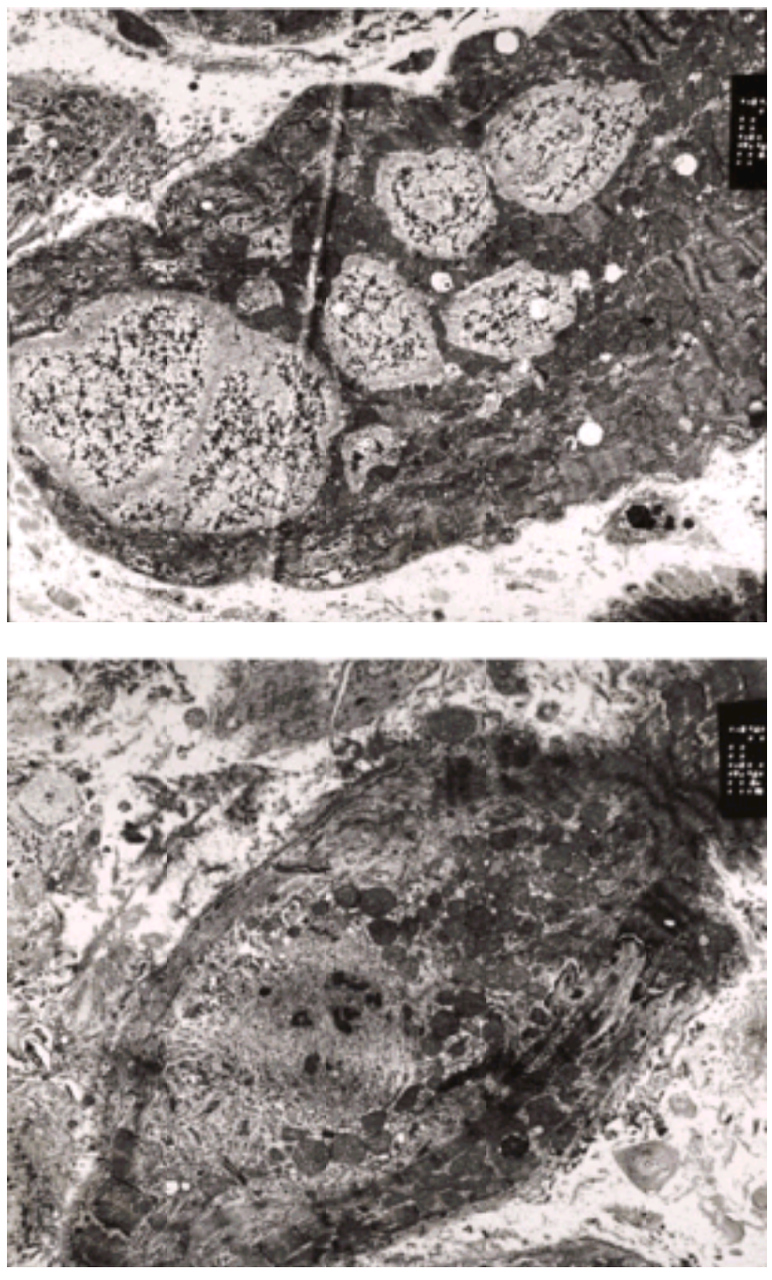
Pathogenesis of the ischemic heart disease associated with radiation appears to occur via damage to the microcirculation and epicardial arteries. Light and electron microscopy of irradiated rabbits has revealed cytoplasmic endothelial cell swelling followed by loss of capillaries and a decrease in capillary-to-myocyte ratio with the end result of progressive fibrosis (109). With regard to epicardial coronary artery disease, autopsy studies of humans have shown lesions that are largely fibrotic with a relative lack of lipids. Studies of irradiated animals have also shown adventitial fibrosis (109). In addition, studies of irradiated animals fed a high cholesterol diet have noted more large vessel changes than with the high cholesterol diet alone, suggesting that radiation damage may act synergistically with other factors to promote atherosclerosis (111).

Finally, radiation therapy to the chest may lead to conduction system abnormalities, including bundle branch block, and varying degrees of atrioventricular block, including complete heart block (111,129). Radiation may also affect pacemaker function, and therefore patients with pacemakers undergoing therapy should be closely monitored (130,131).

Effects of Chemotherapy on the Heart

Multiple chemotherapeutic agents cause cardiac toxicity (Table 35B.1), but the most widely recognized are the anthracyclines (e.g., doxorubicin and daunorubicin) used in treating leukemias, lymphomas, and solid tumors, because their main dose-limiting side effect is cardiac toxicity. Clinical manifestations of anthracycline-induced cardiac toxicity may be acute or chronic (132). Acute toxicity (occurring during or just after a single dose) is rare. Transient nonspecific ECG abnormalities are the most common manifestation, but arrhythmias such as supraventricular tachyarrhythmia or increased ventricular ectopy may be seen (133). These rarely are of clinical importance. Rare cases of acute left ventricular failure, pericarditis, fatal myocarditis, and sudden death have been reported (134,135). Chronic anthracycline-induced cardiac toxicity is more common and usually appears within 1 year of exposure (120). However, it may also become apparent after a prolonged, sometimes several-year, asymptomatic latent period. This has been particularly apparent in childhood survivors of cancer who are cured of their malignancy and live for long periods of time after treatment (136).

TABLE 35B.1 CHEMOTHERAPEUTIC AGENTS AFFECTING THE HEART



Electron microgram of 3+ doxorubicin (Adriamycin) toxicity (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic

Foundation.)

The exact mechanisms by which anthracyclines cause myocardial damage are not fully established, but evidence points to free radical–induced myocyte damage as being an important factor. Effects on intracellular calcium homeostasis, adrenergic function, and damage caused by vasoactive amines and release of inflammatory cytokines such as interleukin-2 and tumor necrosis factor-a have also been proposed as mechanisms for anthracycline-induced myocardial injury (137,138). The most important predictor of cardiac toxicity is total cumulative dose, with probability of congestive heart failure increasing for doses above 400 mg per m^2 body surface area, and particularly above 500 mg per m^2 (120). However, toxic thresholds are variable, with doses above 1,000 mg per m^2 being tolerated by some patients, and doses less than 200 mg per m^2 causing cardiac damage in others. As described previously, concomitant or previous mediastinal irradiation also increases the likelihood of cardiac damage. Other proposed risk factors for cardiac toxicity include age greater than 70, combination chemotherapy, previous cardiac disease, hypertension, liver disease, and hyperthermia (139).

Clinically, cardiotoxicity can result in deterioration of systolic and diastolic left ventricular function as determined either by radionuclide techniques or echocardiography, which progresses to overt congestive heart failure in some patients (132,140). When overt congestive heart failure occurs, risk of mortality may be substantial, with reported mortality in patients with congestive heart failure ranging from 2.2% (141) to 43.0% (120). Clinical recovery with conventional heart failure therapy may occur in those who survive (141), including rare cases of complete reversal of left ventricular dysfunction (142). Prolonged infusions of drug (143), or more frequent dosing (144), may decrease toxicity for a given dose.

VIDEO

Video 35B.8 Standard anterior view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating global hypokinesis and a reduced left ventricular ejection fraction of 25% in a patient with nonischemic dilated cardiomyopathy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 35B.9 Standard lateral view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating global hypokinesis and a reduced left ventricular ejection fraction of 25% in a patient with nonischemic dilated cardiomyopathy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Prevention of anthracycline-induced cardiac toxicity is accomplished by monitoring for signs of myocardial damage using radionuclide angiocardiography, echocardiography, or both (*e*Table 35B.1.1). Schwartz and colleagues proposed guidelines for monitoring the EF of patients receiving doxorubicin, which were retrospectively validated by showing a lower incidence of clinical congestive heart failure in patients whose management was consistent with the guidelines (141). According to these guidelines, EF is determined by radionuclide angiocardiography at baseline. If the baseline EF is normal, then the second study should be at a cumulative dose level of 250 to 300 mg per m^2. If risk factors are present, the study is repeated at 400 mg per m^2, otherwise at 450 mg per m^2, and before all subsequent doses thereafter. If EF declines more than 10% during treatment to an absolute value less than 50%, then treatment is stopped. If baseline EF is greater than 30% but less than 50%, studies should be obtained before each dose, and treatment should be discontinued for a decrease in EF greater than 10% or an absolute EF less than 30%. If the baseline EF is less than 30%, anthracycline therapy should not be used (141).

***e*TABLE 35B.1.1** GUIDELINES FOR MONITORING PATIENTS RECEIVING DOXORUBICIN

Perform baseline radionuclide angiocardiography at rest for calculation of LVEF before administration of 100 mg/m^2 doxorubicin. Subsequent studies are performed at least 3 weeks after the indicated total cumulative doses have been given, before consideration of the next dose

Patients with normal baseline LVEF (³50%)

Perform the second study after 250–300 mg/m^2

Repeat study after 400 mg/m^2 in patients with known heart disease, radiation exposure, abnormal electrocardiographic results, or cyclophosphamide therapy; or after 450 mg/m^2 in the absence of any of these risk factors

Perform sequential studies thereafter before each dose

Discontinue doxorubicin therapy once functional criteria for cardiotoxicity develop [i.e., absolute decrease in LVEF ³10% (EF units) associated with a decline to a level £50% (EF units)]

Patients with abnormal baseline LVEF (<50%)

Doxorubicin therapy should not be initiated with baseline LVEF £30%

In patients with LVEF >30% and <50%, sequential studies should be obtained before each dose

Discontinue doxorubicin with cardiotoxicity; absolute decrease in LVEF ³10% (EF units), final LVEF £30%, or both

LVEF, left ventricular ejection fraction.

From Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. *Am J Med* 1987;82:1109–1118, with permission.

Additional measures to prevent anthracycline-induced cardiotoxicity include incorporating measurement of the peak filling rate (a measure of diastolic function) by radionuclide angiography into such guidelines for earlier detection of anthracycline toxicity. Systolic and diastolic function can also be assessed by echocardiography as a guide to development of cardiotoxicity (132). Echocardiographic parameters showing deleterious effects of anthracyclines on diastolic function have included automatic border detection calculation of peak filling rate (145) and Doppler measures of mitral valve inflow (146). In addition, the degree of uptake of indium-111–labeled antimyosin monoclonal antibodies has been shown to correlate with the degree of depression of the EF during anthracycline therapy. Both increased indium-111 antimyosin uptake and decreased iodine-123-metaiodobenzylguanidine uptake (indicating denervation of the heart) have also been shown to occur before deterioration of systolic dysfunction (147). Although these methods are highly sensitive, their relative lack of specificity for predicting clinical events may limit their usefulness. Elevation of troponin I after high-dose chemotherapy has been shown to predict more profound and prolonged decreases in left ventricular EF (148). At this point, however, the mainstay of monitoring for cardiac toxicity remains the radionuclide angiographically determined EF.

Pharmacologic agents have been investigated for use as cardioprotectants during anthracycline therapy. Currently, only dexrazoxane (ICRF-187), an iron-chelating agent that reduces free radicals produced by anthracyclines, has been approved in the United States for use during doxorubicin therapy (132,149). It is approved for use in metastatic breast cancer in patients who have received more than 300 mg per m^2 of doxorubicin. Probucol, calcium antagonists, and beta-blockers have also been proposed as cardioprotective agents, but more work must be done in human prospective studies to determine if they are truly efficacious (132,150).

Several other anticancer drugs have been associated with cardiac toxicity. There appears to be an increased risk of cardiomyopathy with doxorubicin when given in combination with paclitaxel (for metastatic breast cancer). Such adverse synergy does not appear to occur with doxorubicin and docetaxel. One possible explanation is that paclitaxel may interfere with the elimination of doxorubicin (151). Rhythm disturbances such as sinus bradycardia and atrioventricular block have also been seen with paclitaxel administration; however, ischemic manifestations seen during treatment largely occurred in patients with preexisting cardiac disease (152). Trastuzumab, a monoclonal antibody against the HER2 receptor, also used to treat metastatic breast cancer, has led to a high incidence of congestive heart failure (up to 28%) when used in combination with anthracyclines (153). The mechanism of cardiac toxicity with trastuzumab is uncertain, but it has been demonstrated that the HER2 receptor is involved in myocyte survival pathways. Cardiac complications with 5-fluorouracil have been reported with an incidence of 1.6% to 3.0% (154). Adverse effects have included angina, myocardial infarction, arrhythmia, and reversible left ventricular dysfunction (154). Cyclophosphamide, when given in high doses such as those used for pre–bone marrow transplant regimens, may cause a hemorrhagic myopericarditis characterized by left ventricular dysfunction, congestive heart failure, and pericardial effusion that is often fatal (155). In those who survive, left ventricular function appears to recover (155). The closely related drug ifosfamide has also been shown, in high doses, to cause severe, reversible myocardial dysfunction (156). Myocardial ischemia and myocardial infarction have been attributed to cisplatinum and etoposide (157). Amsacrine has been associated with cardiac abnormalities such as nonspecific ECG changes, atrial and ventricular arrhythmias, and congestive heart failure in approximately 1.2% of patients administered the drug (158). Finally, pre–bone marrow transplant regimens involving high doses of combination chemotherapy, including cyclophosphamide and cytosine arabinoside, plus total body irradiation, have been associated with a high incidence of cardiac complications including arrhythmia, congestive heart failure, and pericarditis (159).

Biologic anticancer agents such as the interferons and interleukin-2 have also been associated with cardiac toxicity. A review of 44 known cases of

interferon-associated cardiotoxicity (interferon-a or interferon-a_2 used in 36, interferon-g in 8) revealed arrhythmia as the most common manifestation, followed by myocardial infarction or ischemia, cardiomyopathy, sudden death, atrioventricular block, and congestive heart failure. Although some of the patients experiencing arrhythmia or myocardial ischemia had preexisting heart disease, this was not true for any of the five patients who developed cardiomyopathy (160). Interleukin-2 has been approved for use in renal cell carcinoma. It may cause a capillary leak syndrome resulting in hypotension, tachycardia, increased cardiac output, and decreased systemic vascular resistance. Arrhythmias, myocardial ischemia and infarction, left ventricular dysfunction, and a reversible lymphocytic and eosinophilic myocarditis have been reported with interleukin-2 administration (161).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Anemia

Whether patients with heart disease and mild anemia derive significant benefit from treating the anemia deserves further study. We believe that nontransfusion therapy, such as iron and folate, should be given to increase cardiac reserve, both for patients with obstructive coronary artery disease and particularly for patients with heart failure, because such a strategy in these patients is supported by prospective intervention data (161). The use of erythropoietin is likely to be cost effective only in patients with at least moderate anemia and severe heart failure requiring frequent hospitalization.

Heparin-Induced Thrombocytopenia

Laboratory testing for HIT remains controversial, because none of the tests is perfectly accurate. We recommend that the platelet aggregation test be performed first, because it is available in most laboratories and can be performed quickly and easily. When HIT is suspected, all heparin should be stopped even if the test result is pending or negative, given the potential devastating consequences of continuing heparin in the face of ongoing HIT. For patients with a negative platelet aggregation test result and a clinically high likelihood of the disease, the ^{14}C-serotonin release assay or enzyme-linked immunosorbent assay test should be performed to confirm the diagnosis.

Whether alternative anticoagulation should be given to patients with HIT in the absence of thromboembolic complications is considered by some an issue of controversy. We believe that these patients should receive a direct thrombin inhibitor in addition to discontinuation of heparin, because of ongoing thrombin generation imparting risk of developing serious events. This therapy may be discontinued once platelet count returns to baseline. Further therapy with warfarin should be strongly considered, because some patients may develop thrombotic complications even after the platelet count returns to normal. In the presence of an established thrombotic event, warfarin should be given in the absence of contraindications. Warfarin therapy should always initially overlap with direct thrombin inhibition by several days to avoid paradoxical limb gangrene. Clinicians should be aware that lepirudin increases the prothrombin time. Direct factor X assays could be used to monitor warfarin therapy while the patient remains on lepirudin.

Malignant Pericardial Effusion

The optimal invasive treatment for malignant pericardial effusion is not well defined. We recommend initial treatment in symptomatic patients with a percutaneous approach, including use of extended catheter drainage. Sclerotherapy should be tried next if pericardiocentesis fails or becomes frequently required. Surgery should be offered after failure of the first two approaches, depending on the overall status of the patient, and if the patient is willing to accept the perioperative risk.

Chemotherapy and Cardiac Toxicity

Areas for continuing investigation include optimizing methods for early detection and prevention of cardiac toxicity, such as cardioprotective agents or particular dosing strategies. Although use of the cardioprotective agent dexrazoxane has been controversial because of concerns that it may reduce antitumor activity, this has not been a consistent finding in trials of this agent. Therefore, we think it is reasonable to use dexrazoxane in patients receiving high doses of doxorubicin or with borderline left ventricular function before therapy.

THE FUTURE

Future studies will better delineate the potential benefits of treating anemia in patients with heart disease. The prevalence of HIT may decline with increasing use of low-molecular-weight heparins in lieu of unfractionated heparin. Genetic advances will allow clinicians to better define an individual patient's susceptibility to HIT and to cardiac damage from radiation therapy and chemotherapy. Additional agents that protect the heart from damage by chemotherapeutic agents will be developed.

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35C

RENAL SYSTEM

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Patients with renal impairment experience a disproportionate burden of cardiovascular morbidity and mortality, largely the result of accelerated atherogenesis, a hallmark characteristic of significant renal dysfunction (1,2 and 3). The increased risk associated with renal impairment has a pervasive influence on outcomes across all aspects of cardiac disease including acute coronary syndromes, cardiac failure, coronary revascularization, and valvular heart disease. Furthermore, renal insufficiency is associated with adverse outcomes, with the magnitude of risk positively correlated with the degree of renal impairment (1,4). Consequently, among patients with end-stage renal disease (ESRD), cardiac mortality accounts for approximately one-half of all deaths, and of these, more than 50% occur as a result of acute myocardial infarction, with an incidence three to five times higher than the general population (5,6). Salient data from the 34,189 patient U.S. registry of long-term dialysis demonstrate that myocardial infarction was associated with a 59% 1-year, 73% 2-year, and 90% 5-year mortality (7). Further contributing to symptomatic myocardial ischemia is small vessel disease, reduced capillary density, volume overload, and altered myocyte bioenergetics. Hence, up to 27% of patients have myocardial ischemia without obstructive coronary artery disease. A greater prevalence and consequence of traditional coronary risk factors such as diabetes, lipid abnormalities, and hypertension underlie this increased risk (8,9,10,11 and 12). These risk factors are often coexistent and therefore synergistic in their potentiation of atherosclerosis in addition to their effect on renal dysfunction (2). Whether dialytic therapy directly contributes to the increased risk of coronary artery disease remains contentious (13).

Renal dysfunction contributes to perturbation in all components of vascular integrity, culminating in both an elevated bleeding risk and a thromboinflammatory state (14,15). Uremia is associated with chronic endothelial injury with increased tissue plasminogen activator and von Willebrand's factor release (16,17); elevated plasma levels of F1+2, thrombin–antithrombin complex, fibrinopeptide A, and D-dimer, implicating increased thrombin generation (18); and heightened factor VII coagulant activity that correlates with the increased cholesterol levels, triglyceride levels, and thrombin generation (17). Finally, chronic renal failure (CRF) is associated with a proinflammatory state, evidenced by elevated interleukin-1, tumor necrosis factor, and fibrinogen levels; monocyte activation; and increased tissue factor and metalloprotease expression (19,20). As a clinical marker of this inflammatory process, elevated C-reactive protein among end-stage renal patients is associated with up to a 5.5-fold risk of coronary artery disease and 4.5-fold risk of cardiovascular death (21).

Left ventricular (LV) hypertrophy and cardiac failure are also more prevalent among patients with significant renal impairment and are observed in approximately 35% to 40% of the renal dialysis population (9,22,23). Reports observe an increasing prevalence of cardiac failure among hemodialysis patients, corresponding to a similar increase in the prevalence of coronary artery disease (24). High-output states associated with arteriovenous fistulas, salt and water overload, and anemia further contribute to ventricular overload and LV hypertrophy, whereas chronic ischemia and increased myocardial oxygen demand, hyperparathyroidism, uremia, and malnutrition augment cardiomyocyte loss, fibrosis, and systolic dysfunction (25,26,27,28 and 29).

This chapter focuses on the effect of the numerous metabolic derangements associated with chronic renal insufficiency and ESRD including secondary hyperparathyroidism; vitamin D deficiency; and phosphorus, calcium, and lipid abnormalities. These disturbances may be causal in changes of cardiac structure and function responsible for the high cardiovascular morbidity and mortality within this population. Given the biochemical uniqueness of these patients, the diagnosis and treatment of cardiac disease among patients with renal insufficiency present issues of interpretation and management. These issues, along with a description of the cardiovascular effects of renal replacement therapies, are also discussed.

METABOLIC CHANGES ASSOCIATED WITH CHRONIC RENAL FAILURE

Hyperparathyroidism

Secondary hyperparathyroidism is a multifaceted process and is highly prevalent among CRF patients. Decreased renal mass lowers 1,25-$(OH)_2D_3$ production, leading to hypocalcemia, while phosphorus retention also occurs. Other factors involved include impaired calcemic response to parathyroid hormone (PTH), altered degradation of PTH by the kidney, abnormal regulation of calcium-controlled PTH release, abnormalities in the calcium-sensor receptor, autonomous proliferation of the parathyroid gland, and increased levels of calcitonin, acidosis, sex steroids, cytokines, and growth factors (30,31 and 32). Experimental models have associated PTH with several changes in cardiovascular structure and function among patients with renal insufficiency. These include increased cardiomyocyte contractile force and frequency, increased blood pressure by increasing intravascular smooth muscle cell calcium, increased intracellular cardiomyocyte calcium concentration, increased LV mass via cardiomyocyte hypertrophy and interstitial fibrosis, increased atherosclerosis via increases in insulin resistance, calcium and phosphorus deposition in vessel walls, disturbed lipoprotein metabolism, hypertension, and increased intravascular smooth muscle cell calcium concentration (33,34,35 and 36). Treatment with

calcium channel blocker has been shown to block PTH-induced calcium entry and to restore normal cytosolic calcium levels, thus suggesting that these changes may be reversible (37,38).

Among patients with CRF, the presence of secondary hyperparathyroidism, or its markers, has been associated with increased myocardial calcium content and impaired ventricular systolic and diastolic function (39). LV function is inversely related to plasma PTH concentration; this is not universally reversed with parathyroidectomy, suggesting that either the PTH-induced changes became irreversible over time or that other factors are more important than PTH excess (33). Current treatment guidelines set a goal PTH level of 100 to 200 pg per mL in order to balance bone disease and cardiovascular effects.

Vitamin D

Vitamin D deficiency is also common among ESRD patients. With advanced CRF the increased serum phosphorus complexes with serum calcium, producing hypocalcemia, and also downregulates the a_1-hydroxylase that is responsible for the renal conversion of 25-(OH)D_3 to 1,25-$(OH)_2D_3$. The resultant deficiency of active vitamin D leads to deranged calcium and phosphate metabolism and accompanying increases in PTH levels.

The effects of vitamin D on cardiovascular structure and function seem to be related to opposing the effects of PTH. These include regression of LV hypertrophy (40) and decreased coronary artery calcification (41). Moreover, 26% of patients with congestive heart failure, New York Heart Association class III or IV, were found to have low serum concentrations of 1,25-$(OH)_2D_3$ (42), and the administration of vitamin D to patients with CRF has improved cardiac function either indirectly by suppression of PTH synthesis and secretion or directly via a vitamin D–dependent process in cardiac muscle (43). Intravenous calcitriol is commonly used to help control secondary hyperparathyroidism among ESRD patients. Subsequently, they are at risk of excess vitamin D that can lead to hypercalcemia, hyperphosphatemia, systemic calcinosis (including calcium-phosphorus deposits in vessel walls and heart valves), and hypertension (33). Vitamin D therapy among ESRD patients is limited by the calcium-phosphorus product with the risk of metastatic calcification increased when the product exceeds 60 to 70 $(mg/dL)^2$. The use of phosphate binders (either calcium- or non–calcium-containing) is mandatory. Vitamin D analogs and calcimimetic agents, which purportedly have a lower incidence of hypercalcemia and hyperphosphatemia, are currently being studied.

Calcium and Phosphorus

Hypocalcemia occurs commonly among ESRD patients and has been strongly associated with ischemic heart disease (26). It has also been shown to be independently associated with mortality in a large cross-section of dialysis patients (44). Treatment is with supplemental calcium and vitamin D and, if necessary, use of a dialysis solution containing at least 3.5 mEq per L calcium. Hypercalcemia also occurs and is most often associated with calcium administration, vitamin D therapy, or both. Hypercalcemia increases myocardial contractility and shortens ventricular systole. It can also cause characteristic electrocardiographic (ECG) changes, including a shortened QTc interval, T-wave broadening, and first-degree heart block. Treatment is directed toward correcting the underlying cause, i.e., decreasing calcium or vitamin D supplementation, dialysate calcium, and so forth.

A 54-year-old male patient with hypercalcemia.

Hypophosphatemia is associated with serious cardiac arrhythmias or respiratory arrest due to respiratory muscle weakness. Predisposing factors include poor nutritional intake, excessive phosphate-binding therapy, or overaggressive dialysis. Treatment is supplements and supportive therapy. Hyperphosphatemia results from decreased urinary elimination of phosphorus and is a consequence of vitamin D administration, limited clearance of conventional dialysis, limitations of phosphate binders (hypercalcemia, gastrointestinal side effects, improper dosing, and so forth), tissue breakdown, and dietary and medication noncompliance. Hyperphosphatemia and high calcium-phosphorus ion product has been associated with an approximately 30% increase in mortality among patients with ESRD (45) and is independent of PTH levels (46). Hyperphosphatemia has also been associated with progression of secondary hyperparathyroidism, elevated calcium-phosphorus product, coronary artery calcification, conduction defects, hypertriglyceridemia, hypercholesterolemia, myocardial fibrosis, and systemic calcification (including mitral and aortic valves, peripheral vessels, pulmonary, and periarticular). Importantly, an increased incidence of progression of coronary artery calcification is detectable by electron beam computed tomography among young patients (20 to 30 years old) with ESRD, correlating with serum phosphate levels, the calcium-phosphorus product, and the duration of dialysis. The relationship between this finding and clinically significant coronary lesions remains to be defined (47). Two different modalities have been used in an attempt to reverse hyperphosphatemia: restricting dietary phosphate intake and prevention of gastrointestinal absorption with the use of phosphate binders. Longer dialysis sessions and daily nocturnal dialysis can also improve clearance of phosphate (48).

Lipid Abnormalities

Abnormal lipid metabolism is common among patients with CRF (49) and contributes to the increase in cardiovascular events. These abnormalities are most prominent in the nephrotic syndrome in which marked elevations in the plasma levels of cholesterol, triglycerides, and lipoprotein(a) are common.

The two most common lipid abnormalities in the nephrotic syndrome are hypercholesterolemia and hypertriglyceridemia (50), possibly the result of increased hepatic synthesis of lipoproteins containing apolipoprotein B and cholesterol in response to the reduced plasma oncotic pressure (50,51). The severity of the hyperlipidemia is inversely related to the decrease in oncotic pressure (51), and albumin or dextran administration produces a rapid reduction in lipid levels (52). Alternate evidence suggests that reduced catabolism is primarily responsible for hypercholesterolemia among patients with the nephrotic syndrome (53) and is also a cause of the elevated triglyceride levels (49,50). The delipidation cascade in which very-low-density lipoproteins are converted to intermediate-density lipoproteins and then to low-density lipoproteins (LDL) by lipoprotein lipases is slowed in the nephrotic syndrome and with a trend toward reduced LDL receptor–mediated clearance of LDL and intermediate-density lipoproteins (54).

In concert with renal impairment, hyperlipidemia is a potent risk factor for cardiovascular disease (49,55). Compared with age-matched controls, a relative risk of 5.5 for death from coronary artery disease, 5.2 for myocardial infarction, and 2.8 for coronary death has been reported for nondiabetic nephrotic patients (56). The lipid abnormalities induced by the nephrotic syndrome reverse with resolution of the disease. The optimal treatment of patients with long-standing persistent nephrotic syndrome is uncertain because randomized trials have not been performed (49,50). The most successful lipid-lowering agents have been the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the bile acid sequestrants (49,50,57). Treatment with these agents should also extend to renal insufficiency patients with hyperlipidemia in the absence of nephrotic syndrome. Angiotensin-converting enzyme (ACE) inhibitors are another potential adjunctive therapy for hyperlipidemia since they lower 24-hour urine protein excretion (58,59) and are associated with a 10% to 20% decline in the plasma levels of total and LDL cholesterol and lipoprotein(a) (60). Similar findings have been shown with losartan, an angiotensin II receptor antagonist (61).

Hyperhomocystinemia

Homocysteine levels have been shown to be elevated two- to fourfold among patients with CRF (62,63,64 and 65). Moderate hyperhomocystinemia is a recognized independent risk factor for coronary artery disease and is a strong predictor of mortality among patients with established coronary artery disease (66,67,68,69 and 70). From prospective observational data, hyperhomocystinemia remains an independent risk factor for cardiovascular morbidity and mortality among the ESRD population, conferring a relative risk of 1% per µmol per L increase in total homocysteine concentration or a relative risk ratio of 1.5 for levels greater than 5 µmol per L (2,71).

Homocysteine metabolism is dependent on vitamin B_6, vitamin B_{12}, and folic acid. In renal failure, poor nutrition coupled with removal of water-soluble vitamins by dialysis may partially explain a tendency to deficiencies of these vitamins and the high prevalence of hyperhomocystinemia. In non-ESRD populations, treatment with folic acid alone or in combination with vitamins B_{12} and B_6 has been shown to lower homocysteine levels. Low doses of folic acid have been shown to lower homocysteine levels in non-ESRD patients; however, the effects have not been as pronounced in ESRD patients (72,73). To date, no prospective studies have

reported the effect of lowering homocysteine levels on cardiovascular events, and this question requires further investigation.

Uremic Cardiomyopathy

Uremic syndrome is a multisystem deterioration including the cardiovascular, neurologic, hematologic, and immunologic systems. The pathophysiology of uremic syndrome is not completely understood but results from the retention of substances that are ordinarily removed by the kidneys, intake of dietary precursors, and derangements of hormonal and enzymatic homeostasis. The putative substance(s) or uremic toxins have not been clearly identified; however, several substances have been studied, including urea, PTH, beta$_2$-microglobulin, and middle molecules. Several factors may predispose or contribute to myocardial dysfunction in uremia, including hypertension, anemia, electrolyte disturbances, acidosis, hyperlipidemia, accelerated atherosclerosis, glucose intolerance, and malnutrition.

Abnormalities of LV structure and function are common among patients starting renal replacement therapy. Concentric LV hypertrophy is present in approximately 40% of ESRD patients starting dialysis (22,25,74). Twenty-seven percent of patients had LV dilatation and 18% had systolic dysfunction. These abnormalities occur early in CRF and progress rapidly as renal function deteriorates (75). Twenty-seven percent of patients with creatinine clearance greater than 50 mL per minute had LV hypertrophy and this increased to 31% and 45% for clearances between 25 and 50 mL per minute and less than 25 mL per minute, respectively.

VIDEO

Video 35C.1 Apical long-axis view of a patient with severe left ventricular dysfunction and annular dilatation causing 4+, centrally directed mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Clinical cardiac failure is also common in ESRD patients with almost 50% having a history of cardiac failure before initiating dialysis (74). Congestive heart failure at the beginning of dialysis is an important predictor of cardiovascular and overall mortality in the ESRD population (median survival rate of 32 vs. 62 months) (74). Among ESRD patients, the incidence of valvular dysfunction is also elevated. Some studies note mitral or aortic valvular abnormalities in almost one-half of all patients with CRF. The most common reported abnormalities are mild to moderate mitral regurgitation secondary to LV dilatation and calcification. However, the prevalence of hemodynamically important valvular dysfunction is not well described in the literature thus far.

Uremic Pericarditis

Pericarditis associated with CRF was first described by Bright in 1836. It accounts for 3% to 4% of all deaths in dialysis patients, as a result of tamponade, cardiac arrhythmias, or heart failure. Initially, it was believed that uremic pericarditis would disappear with adequate dialysis because the presumed cause of pericarditis was the retention of nitrogenous waste products (76). The majority of nondialyzed patients with uremic pericarditis did improve rapidly after the initiation of dialysis; however, pericarditis occurred in up to 20% of patients on maintenance dialysis (77,78). Moreover, the pericarditis among patients on maintenance dialysis failed to resolve despite intensified dialysis treatments (79), thereby suggesting a different etiology. Pericarditis associated with CRF has been divided into two categories: uremic- and dialysis-associated pericarditis.

VIDEO

Video 35C.2 Apical four-chamber view demonstrating a large pericardial effusion causing tamponade. Note the inability of the right side to fill. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 35C.3 Subcostal short-axis view of a large pericardial effusion causing tamponade. Note that the right side is small and underfilled. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Uremic pericarditis is observed in 6% to 10% of patients with advanced renal failure (acute or chronic) before or shortly after dialysis is initiated (80). It results from inflammation of the visceral and parietal membranes of the pericardial sac. The pathogenesis is poorly understood, but among others, fluid overload, the hemorrhagic tendency of uremia, serositis, decreased fibrinolytic activity, and hyperparathyroidism have been implicated.

Dialysis-associated pericarditis occurs in approximately 13% of patients on maintenance hemodialysis (81) and may occasionally be seen with chronic peritoneal dialysis. Among patients undergoing dialysis, pericarditis may be the result of several factors, including inadequate dialysis, volume overload, accumulation of middle molecules, malnutrition, hyperparathyroidism, heparin therapy, viral infection, and, possibly, immune mechanisms (82).

Clinically, these two entities are similar. There is one relatively characteristic feature of uremic pericarditis: The ECG does not usually show the typical diffuse ST- and T-wave elevations, presumably because epicardial injury is uncommon (83).

The development of uremic pericarditis is an indication to institute dialysis, providing there is no circulatory compromise or evidence of impending tamponade. The majority of these patients responds quickly to dialysis with resolution of signs and symptoms. Either hemodialysis or peritoneal dialysis can be used; however, each has corresponding advantages and disadvantages. Heparin can increase hemorrhage into the pericardial space and therefore heparin-free hemodialysis should be used. Acute fluid removal with hemodialysis can lead to cardiovascular collapse among patients with tamponade or pretamponade. Alternatively, peritoneal dialysis can compromise respiratory function because of intraperitoneal fluid accumulation.

Dialysis-associated pericarditis requires more complicated management. The dialysis schedule is usually intensified by increasing the frequency of dialysis treatments in hemodynamically stable patients with no or small to medium-sized effusions. However, increased dialysis may result in intravascular volume depletion and electrolyte disturbances such as hypokalemia or hypophosphatemia (84). Intensified dialysis therapy usually leads to resolution of the pericarditis within 1 to 2 weeks. Surgical drainage, however, may be necessary before the initiation of dialysis if the effusion is significantly large (estimated to exceed 250 mL by echocardiography) or mandatory when overt tamponade appears (85). Antiinflammatory medications and systemic corticosteroids are associated with limited success in refractory pericarditis. Therefore, drainage is the treatment of choice if the effusion enlarges or fails to resolve after a trial of intensified dialysis (86).

Surgical drainage can be accomplished by any of four ways: pericardiocentesis, pericardial window, subxyphoid pericardiostomy, or anterior pericardiectomy. Pericardiocentesis using a blindly inserted needle is dangerous and never indicated except as emergency therapy. Hemorrhagic effusions are poorly drained using this technique, and the risk of coronary artery or cardiac puncture and arrhythmia are substantial. Subxyphoid pericardiostomy is the procedure of choice. The tube is left in place to closed drainage for several days until drainage ceases. Anterior pericardiectomy requires general anesthesia and thoracotomy and carries a significantly greater associated morbidity. Therefore, it is usually recommended only when pericardiotomy cannot be performed or has been unsuccessful.

RENAL INSUFFICIENCY AND END-STAGE RENAL DISEASE

Diagnosis

Clinical history remains the cornerstone of diagnosis in stable and unstable coronary artery disease among patients with renal insufficiency. However, the prevalence of reduced physical capacity and significant comorbidities among these patients may somewhat obscure clinical manifestations of coronary artery disease. Similarly,

specific interpretation of ECG changes is often limited by changes related to the presence of long-standing hypertension, LV hypertrophy, and electrolyte abnormalities. These factors may either falsely suggest or conceal the diagnosis of myocardial ischemia. These issues limit the diagnostic utility of the resting or exercise ECG in excluding significant myocardial ischemia among renal failure patients. The value of ambulatory ECG monitoring among patients on long-term dialysis also remains in question (87).

Video 35C.4 Parasternal long-axis view **(A)** of a patient with apical hypertrophy. Note the marked increase in wall thickness apically. Parasternal short-axis **(B)** view of the same patient with apical hypertrophy. Note the cavity obliteration at the mid–left ventricular level. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35C.5 Parasternal long-axis view **(A)** of a patient with apical hypertrophy. Note the marked increase in wall thickness apically. Parasternal short-axis **(B)** view of the same patient with apical hypertrophy. Note the cavity obliteration at the mid–left ventricular level. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

A 71-year-old patient with left ventricular hypertrophy and negative U waves.

Cardiac Markers

Among patients with significant renal insufficiency, transient elevations in cardiac enzymes are commonly observed in the absence of clinical myocardial ischemia and are reported in up 72% of patients over long-term follow-up. The source of these enzyme elevations remains uncertain, but appears unrelated to the type of dialysis (peritoneal vs. hemodialysis) or the level of uremia. Elevations of these enzymes may be persistent, although often at low concentrations, with creatine kinase-MB (CKMB) fractions rarely exceeding 8%. Isolated elevation of the CKMB subfraction in the absence of demonstrable myocardial necrosis has also been observed. Nonspecific elevations of CK and CKMB contribute to a reduced diagnostic utility of these assays for confirming clinically significant ischemia (88). Similarly, serum myoglobin levels have limited diagnostic utility within this population because of the presence of these enzymes in skeletal muscle and its reduced renal clearance.

Cardiac troponin elevation is frequently observed among dialysis-dependent patients (30% to 50%), and less commonly, among patients with chronic renal impairment not requiring renal replacement (10% to 20%) (89). Troponin levels may also be directly influenced by hemodialysis. Consequently, reduced specificity and possibly sensitivity for myocardial ischemia has been reported within this population (90,91,92 and 93). Mild elevations in troponin T appear more common than in troponin I, suggesting that this assay may have greater specificity. Cross-reactivity with skeletal muscle enzymes may explain the high prevalence of troponin T elevation (89,93,94 and 95), although this is less of an issue with more recent assays (96). Nevertheless, troponin I or T among patients with symptomatic myocardial ischemia remains predictive of in-hospital mortality, whereas patients without troponin elevation appear to be at low risk (97,98). Increased troponin T on routine serial measurements of asymptomatic dialysis patients may also predict long-term adverse events, but this has not been consistently demonstrated (89,99,100 and 101). Among stable hemodialysis patients with and without known atherosclerosis, troponin T greater than 0.1 ng per mL has been associated with a sevenfold increase in long-term mortality (102). These studies demonstrate an acceptable sensitivity and improved specificity by adopting a higher threshold level. Conversely, among asymptomatic patients with renal insufficiency not requiring dialysis, the predictive utility of either troponin I or T remains low (89). Therefore, among patients with renal impairment, troponin elevation should be interpreted within the context of the clinical presentation, treatment with dialysis and the assay used, although adopting a higher threshold level may improve diagnostic specificity (Table 35C.1).

		Troponin I >0.5 ng/mL	Troponin T >0.04 ng/mL	Troponin T >0.1 ng/mL	Troponin T >0.2 ng/mL
Roppolo	Sensitivity (%)	50	–	100	83
	Specificity (%)	100	–	56	91
	Positive predictive value (%)	100	–	24	56
	Negative predictive value (%)	54	–	100	98
Dierkes	Sensitivity (%)	–	45	83	–
	Specificity (%)	–	100	100	–

TABLE 35C.1 TROPONIN: IMPROVED SENSITIVITY FOR PREDICTING LONG-TERM ISCHEMIC EVENTS AMONG PATIENTS UNDERGOING RENAL DIALYSIS WITH HIGHER THRESHOLD TROPONIN LEVELS

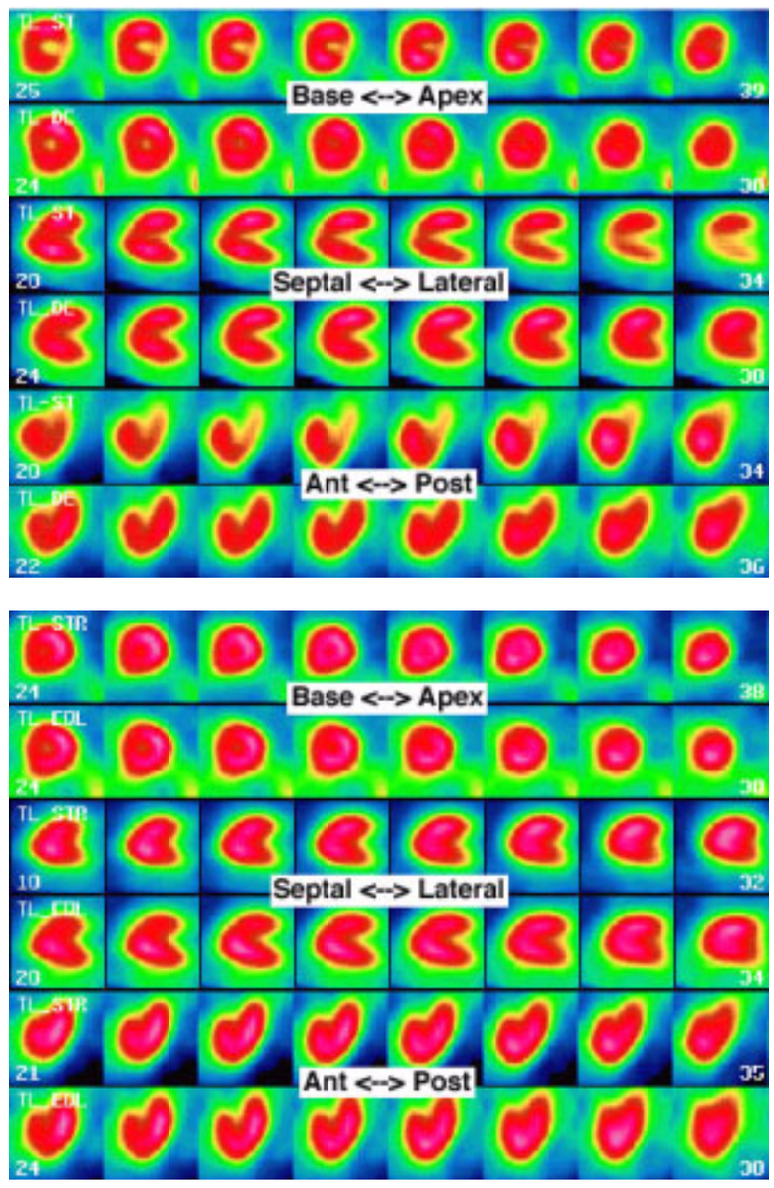
Exercise Electrocardiography

Among patients with CRF, exercise ECG testing for the diagnosis of coronary artery disease has demonstrated a sensitivity 50% to 60% of the diagnosis of single-vessel coronary artery disease and over 85% for triple-vessel disease (103). However, baseline ECG abnormalities and reduced exercise capacity are frequent in this patient population, limiting the diagnostic utility of this study. The sensitivity of exercise testing is dependent on adequate heart rate responses (85% of the age-predicted maximum heart rate), with this level being achieved in only 8% to 20% of patients undergoing treadmill testing (104,105).

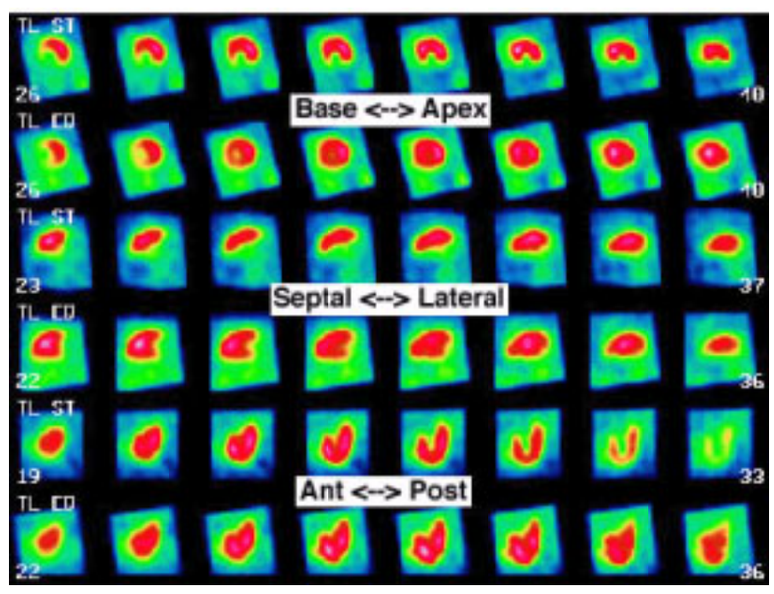
Thallium Scintigraphy

The uses of diagnostic imaging studies overcome the issues of LV hypertrophy and repolarization abnormalities that confound the diagnosis of ischemia by ECG alone. However, the diagnostic utility of these noninvasive studies for coronary artery disease remains dependent on the cardiac work induced by either exercise or pharmacologic means. Consequently, among patients with renal failure, earlier studies have documented reduced utility of thallium scans for the diagnosis of coronary artery disease with a sensitivity and specificity as low as 37% and 75%, respectively (106). Furthermore, a low clinical value of thallium scans in predicting coronary artery disease and perioperative events in diabetic patients undergoing renal transplantation was initially observed. These results were attributable to a high prevalence of inadequate tests resulting from reduced exercise tolerance, inadequate heart rate response, concurrent beta-blockade, and the presence of LV hypertrophy (107,108

and 109).



Thallium-201 single-photon emission computed tomography stress and delayed images (A). Transverse, sagittal, and coronal plane images demonstrating lateral wall ischemia in a patient with severe proximal left circumflex artery stenosis. Thallium-201 single-photon emission computed tomography stress and equilibrium images (B). Transverse, sagittal, and coronal plane images obtained from the same patient as in A after successful intervention for severe proximal left circumflex artery stenosis (normal study).



Thallium-201 single-photon emission computed tomography stress and equilibrium images. Transverse, sagittal, and coronal plane images demonstrating inferior and posterior wall ischemia in a patient with a severe proximal stenosis in a dominant right coronary artery.

More recent reports document substantially improved sensitivity and specificity of thallium-201 scans for the diagnosis of coronary artery disease and prediction of subsequent cardiac events. This improved diagnostic utility has been associated with the use of dipyridamole or combined dipyridamole and exercise testing in some studies, overcoming the issue of limited exercise capacity of these patients (110,111 and 112). Of note, Dahan et al. demonstrated a 92% sensitivity, 89% specificity, and 71% positive predictive value with dipyridamole and exercise thallium scanning in patients undergoing hemodialysis. Within this study, the negative predictive value of a normal scan was 91% during 2.8 years of follow-up (113).

Dobutamine Stress Echocardiography

Stress echocardiography may also be a useful means of diagnosing coronary artery disease among patients with end-stage renal failure and stratifying risk for candidates for renal transplantation (114,115). The use of dobutamine serves to overcome the limited exercise capacity frequently encountered within this population. Initial studies have documented sensitivity and specificity in the range of 75% to 95% and 70% to 90%, respectively, for the detection of coronary artery disease among renal transplant candidates, with a normal study predicting a 97% 12-month event-free survival (116). The cost-effectiveness of dobutamine stress echocardiography in pretransplant risk stratification has also been demonstrated (117,118). Utility for predicting late cardiac events has also been documented among patients with ESRF. Compared with an 84% event-free survival observed among patients without ischemia, a 66% event-free survival over a mean of 38 months' follow-up was documented in ischemia on dobutamine stress echocardiography. Importantly, this study observed a prominent increase in events after 2 years in those without initial ischemia, potentially highlighting the duration of prognostic information provided by diagnostic testing in these patients with aggressive coronary artery disease (119).

VIDEO

Video 35C.6 Dobutamine echo. Parasternal long-axis view of a patient with left anterior descending artery scar and peri-infarct ischemia. No obvious ischemia is seen in this view (see apical two- and four-chamber views). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 35C.7 Parasternal short-axis view of a dobutamine stress echo of a patient with peri-infarct ischemia in the left anterior descending coronary artery territory. No ischemia seen in this view (see ischemia in apical two- and four-chamber views). *This video must be viewed with QuickTime. If you do not have QuickTime you may*

download it here.

Video 35C.8 Apical four-chamber view of a dobutamine stress echo of a patient with peri-infarct ischemia in the left anterior descending coronary artery territory. Note the distal septal resting wall motion abnormality that fails to augment with peak dobutamine infusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35C.9 Apical two-chamber view of a dobutamine stress echo of a patient with peri-infarct ischemia in the distal anterior and distal inferior walls. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Angiography and Contrast-Induced Nephropathy

The indications for coronary angiography within this population remain similar to the general population. However, in the patient with significant renal impairment not managed with renal replacement therapy, the additional risk of contrast-induced nephropathy bears careful consideration and preparation. Moreover, renal impairment is associated with a 3.3-fold increase in the overall complication rate during coronary angiography (120). Therefore, coronary angiography should be undertaken only when the anatomic information provided is essential to the planning of future management. Furthermore, technical considerations, such as the site of vascular access, bear careful consideration.

Contrast-induced nephropathy is a leading cause of in-hospital acute renal failure, occurring in less than 0.5% of patients undergoing coronary angiography. However, among patients with renal insufficiency, deterioration in renal function is reported to be between 10% and 40% of patients, depending on associated comorbidities (121,122,123,124 and 125). Of these patients, 75% experience complete recovery, whereas 10% require permanent dialysis. Factors clearly associated with worsening renal function are elevated baseline creatinine, volume depletion, diabetes, cardiac failure associated with a low output state, functioning renal allografts, the dose of contrast agent, and repeat contrast studies within 72 hours (126,127 and 128). Other potential contributing factors include hyperuricemia, anemia hypertension, and proteinuria (129). Age alone does not appear to increase the risk of contrast nephropathy (122).

Diabetes mellitus is a potent risk factor for the development of contrast-induced nephropathy, although most of this risk relates to the presence of associated diabetic nephropathy (130). In the diabetic patients with concurrent renal dysfunction, the risk is approximately fourfold that of diabetics without documented renal dysfunction, with an incidence of approximately 30%. In addition, the risk in diabetic patients appears greater for those with insulin-requiring diabetes than in those managed with oral therapy, although this may simply reflect the increased prevalence of diabetic nephropathy in the latter group. A strong correlation between dose and repeat administration of contrast and renal deterioration has been observed (123), although an independent relationship has not been universally demonstrated (122). Nevertheless, limiting the dose of contrast in these patients remains an important clinical practice. Low-osmolar agents are associated with less nephrotoxicity in animal models and fewer side effects clinically. However, a substantial difference between the low- and high-osmolality agents among relatively low-risk patients has not been consistently observed (131,132 and 133). Conversely, among high-risk patients, low-osmolar agents are associated with significantly lower rates of contrast-induced nephropathy (131). As with osmolarity, ionicity also appears to affect the development of contrast-induced nephropathy, again predominantly among patients with renal insufficiency (130). Therefore, the use of low-osmolar nonionic agents is advocated among those at substantial risk of contrast-induced nephropathy.

The precise mechanism of contrast-induced nephropathy has not been clearly defined. Direct toxic effects on proximal renal tubular epithelium and mitochondrial function have been observed (131). Intraluminal precipitation of protein has also been suggested (134). Glomerular hyperfiltration with mismatch between perfusion and filtration, particularly in the renal medulla observed with diabetes, may increase the susceptibility of these patients to contrast-induced nephropathy (135,136 and 137). Contrast agents may also induce a shift in the oxygen-dissociation curve, therefore reducing the availability of oxygen to the renal medulla (138). Heightened endothelial release of endothelin-1 may have a role in this response, with endothelin release increased with ionic compared with nonionic contrast media (139). Other potential contributing mechanisms include increased red cell rigidity and white cell margination, potentially affecting blood viscosity and rheology within the renal vasculature (140).

Clinically, contrast nephropathy manifests as an increase in serum creatinine, occurring 24 to 48 hours after angiography, peaking over 3 to 5 days, with slow resolution over 7 to 10 days. Oliguria is common among patients with reduced baseline renal function, with up to 50% of these patients requiring permanent dialysis. In addition, urinary sodium excretion is low, as is the fractional excretion of sodium (less than 1%). A persistent nephrogram on abdominal radiography and renal cortical attenuation on computed tomography are also frequently observed for more than 24 hours.

Maintenance of adequate intravascular volume status remains central in the prevention and management of contrast-induced nephropathy. Enhanced diuresis with either furosemide or mannitol has been shown to be of no greater efficacy compared with saline administration alone among patients with significant renal impairment (mean creatinine, 2.1 mg per dL) (141). Administration of 0.45% saline (1 mL per kg per hour) begun 12 hours before coronary angiography was associated with the lowest risk of renal insufficiency (11%) compared with either saline plus mannitol, 25 g (28%), or saline plus furosemide, 80 mg (40%) (141). Reports suggest that use of isotonic saline may be more efficacious (138). While improving urine output, the addition of diuretic agents may induce relative volume depletion and exacerbate nephrotoxicity (136,142). Forced diuresis with intravenous crystalloid infusion, furosemide, or mannitol, with or without dopamine, may also reduce the risk of contrast-induced nephropathy if a high level of urinary volume can be achieved (143). However, caution must be exercised in those with reduced cardiac function. Routine use of dopamine is not associated with a lower risk of contrast-induced nephropathy in high-risk populations (144). Vasodilation with endothelin-receptor antagonists appears to exacerbate contrast-induced nephropathy (139). By preventing renal vasoconstriction, calcium antagonists are a logical approach and have been shown to protect against reductions in glomerular filtration rate (GFR) and proteinuria. Similarly, the efficacy of alternate vasodilatory agents, such as atrial natriuretic peptide, adenosine, and theophylline, has been suggested in experimental models and some small human studies. A reduced rate of contrast-induced nephropathy has also been observed with ACE inhibition, but confirmation with larger studies is required for all of these agents (145). Interestingly, the preventive efficacy of acetylcysteine, an antioxidant administered together with intravenous saline, has been demonstrated. Among 83 patients with a mean creatine of 2.4 mg per dL, acetylcysteine, 600 mg twice daily administered for 1 day before and on the day of investigation, was associated with a small improvement in serum creatinine (0.4 mg per dL) compared with a small deterioration in renal function among controls (0.2 mg per dL; p <.001) (146).

Pharmacotherapy of Ischemic Heart Disease and Cardiac Failure

Reflecting general recommendations, risk-factor modification including smoking cessation, tight glucose control among diabetics, a goal blood pressure of less than 120/80 in predialysis patients and less than 140/90 in dialysis patients, total serum cholesterol less than 200 mg per dL, and LDL cholesterol less than 140 mg per dL remain important among patients with both renal insufficiency and cardiac disease. Other empiric recommendations unique to ESRD patients include hemoglobin 10 ± 0.5 g per dL, Kt/V greater than 1.2 in hemodialysis patients, weekly Kt/V greater than 2 in peritoneal dialysis patients, serum albumin greater than 3.8 g per dL, serum calcium greater than 2.2 mmol per L, and PTH less than 200 ng per L. Importantly, anemia decreases oxygen delivery, increases cardiac work by volume overload, and reduces coronary filling times and vasodilator reserve. Correction of uremic anemia with erythropoietin improves cardiac performance (147) and reduces angina, although no reduction in fatal or nonfatal cardiac events has been documented (148). Although hyperparathyroidism also results in increased cardiomyocyte calcium content, affecting myocardial oxidative metabolism and increasing the susceptibility of myocytes to injury (149), the value of rigorous control of calcium metabolism on cardiac end points requires prospective study.

When considering the choice of pharmacotherapy for patients with renal insufficiency, several issues bear consideration. These include the relative efficacy of the specific agent within this population and the implications of reduced renal function on dosing regimens. Dose modifications for most therapies among patients with renal insufficiency have been described. Furthermore, among preuremic patients the effect of therapy on renal function in those not yet requiring renal replacement therapy and the prevention of deterioration in renal function should also be considered. However, most randomized trials assessing the long-term efficacy of therapies used in the management of cardiac conditions have excluded patients with moderate to severe renal insufficiency (creatinine greater than 2.5 mg per dL). Thus, in the absence of specific data, recommendations for the management of cardiac indications among patients with renal insufficiency follow the guidelines set forth for the general

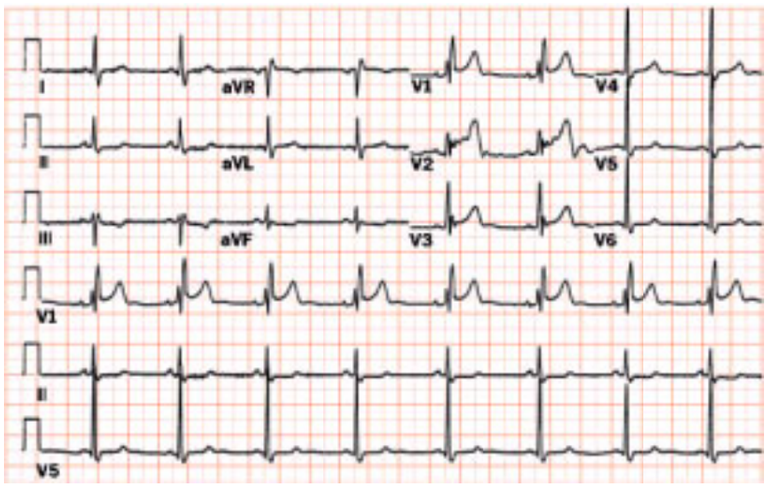
population. Nevertheless, the presence of renal impairment defines the high-risk nature of these patients, often warranting aggressive optimization of therapy.

Management of Hypertension

Control of hypertension is an important therapeutic goal for the prevention of LV failure and impeding the deterioration of function. Few data are available for guiding the choice of therapies among patients with renal insufficiency. Coexistent clinical indications may help guide therapy (e.g., beta-blockers among patients with ischemic heart disease). ACE inhibitors are of proven efficacy in the control of hypertension, may improve vascular distensibility (150), and also slow the progression of renal disease. Independent of their effects on blood pressure, these agents improve glomerular hemodynamics, reduce proteinuria, and antagonize the development of glomerular hypertrophy in patients with and without diabetes mellitus (151,152,153,154,155,156 and 157). Whether ACE inhibitors provide superior protection from renal deterioration in comparison with other agents is uncertain, but has also been suggested (158). Although calcium antagonists are also effective in the treatment of hypertension, the amlodipine arm of the African American Study of Kidney Disease and Hypertension Pilot Study (159) has been stopped. In this study, the use of this drug compared with ramipril and metoprolol was found to be relatively ineffective in preventing progression to dialysis and death among patients with severe proteinuria (L. Agodoa, *personal communication*, October 2000). Furthermore, renal-protective effects have also been documented among diabetic patients, mediated by improved renal blood flow, reduced glomerular hypertrophy, reduced proteinuria, and altered calcium metabolism with the kidney (160,161,162 and 163). Diuretic therapy is effective among patients with hypertension and fluid overload. Use of potassium-sparing diuretics in combination with ACE inhibitors should be avoided because of the risk of hyperkalemia. Thiazides may be ineffective among patients with a GFR less than 30 mL per minute.

Management of Acute Coronary Syndromes

In the absence of specific data within this high-risk patient subset, the management of acute coronary syndromes follows the guidelines developed for the general population. Mortality among patients presenting with acute coronary syndromes remains high, and underuse of therapies may account for some of this excess risk. Importantly, renal insufficiency is not a contraindication to the use of fibrinolytic therapy among patients presenting with ST-elevation myocardial infarction, but remains underused (164). No dose adjustment of any of the thrombolytic agents is required, and a marked increase in bleeding has not been observed in clinical trials. Nevertheless, attention to the established predictors of hemorrhagic risk should be maintained. Aspirin therapy is also indicated among patients presenting with acute coronary syndromes.



Anterior myocardial infarction in setting of right bundle branch block. ST-segment elevation in the anterior precordial leads and primary T-wave changes support acute anteroseptal myocardial infarction.

Because renal failure is considered a prothrombotic state, treatment with antithrombin therapy seems logical in the absence of specific data. With unfractionated heparin, titration of infusion doses to target activated partial thromboplastin time levels as defined within the general population is recommended. In contrast, despite the equivalent and possibly superior efficacy of low-molecular-weight heparins compared with unfractionated heparin within acute coronary syndrome patients, these trials have excluded those with significant renal impairment. Therefore, specific benefit among these patients has not been defined. The half-life of elimination for the low-molecular-weight heparins is significantly prolonged in the presence of renal impairment. Consequently, decreased frequency of dosing and monitoring of antifactor Xa levels are advocated, although specific dose-attenuation scales have not been defined. Although currently available direct thrombin inhibitors (bivalirudin) provide a useful alternative in those with heparin sensitivity, these agents also undergo renal elimination, and experience among patients with renal impairment is limited.

Trials evaluating glycoprotein IIb/IIIa inhibitors have excluded patients with significant renal impairment (creatinine greater than 2.0 to 2.5 mg per dL). Given the lack of randomized data in patients with significant renal impairment coupled with known underlying platelet dysfunction, use of these agents should be undertaken with caution and weighed carefully in the setting of acute coronary syndromes. Close attention to bleeding risk should be maintained. Both currently available small molecule antagonists (eptifibatide and tirofiban) undergo significant renal excretion and appear to be removed by dialysis. The adenosine diphosphate receptor antagonists are a useful alternative to aspirin, or in combination with aspirin among those receiving coronary stents. The degree of platelet inhibition provided by these agents among dialysis patients appears to be similar to that of the general population (165). Elimination of the adenosine diphosphate receptor antagonists clopidogrel and ticlopidine are by hepatic excretion, and dose attenuation is not required.

Management of Stable Coronary Artery Disease

Few randomized data are available to guide the choice of antianginal therapy among patients with renal insufficiency. Aspirin appears to increase skin bleeding time and reduce platelet aggregation by a greater degree in dialysis patients compared with healthy patients. Because of the known platelet defect associated with renal disease, the intermittent need for anticoagulation, and the high prevalence of clinical conditions known to be associated with adverse events following aspirin therapy, patients with renal disease receiving aspirin therapy as primary prevention should be monitored closely. In contrast, despite the lack of specific data, aspirin therapy is advocated as secondary prevention in all patients with coronary artery disease, based on compelling data within the general population. Among patients with renal impairment, beta-blockers are both safe and effective. As long-term therapy following myocardial infarction, treatment with beta-blockers is associated with mortality reductions among patients with renal insufficiency comparable with the general population. Chronic beta-blockade is associated with reduced renal blood flow and GFR, although these alterations in renal hemodynamics are usually minor and subclinical. Calcium antagonists are also effective in ischemic heart disease and can generally be administered without dose adjustment. Advantages with respect to the preservation of renal function have been suggested but require prospective validation. Nitrate preparations are also useful among patients with angina and renal insufficiency. However, given the prevalence of LV hypertrophy, these patients may be sensitive to preload reduction, which may be further exacerbated by dialysis. Ample evidence supports the aggressive treatment of hyperlipidemia, especially with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, among patients with coronary artery disease within the general population. These recommendations have been extended to patients with renal insufficiency.

Management of Cardiac Failure

Within the general population, the benefit of ACE inhibition for the treatment of cardiac failure is well established. These agents are also advocated among patients with renal insufficiency. Specifically within the renal failure patient, ACE inhibitors have been shown to reduce LV hypertrophy and may improve vascular distensibility (150). Furthermore, among patients with a diverse array of cardiovascular indications treated with ACE inhibition, mild to moderate renal impairment (creatinine 1.4 to 2.3 mg per dL) is associated with a greater mortality reduction compared with patients with normal renal function. Nevertheless, among patients at risk of acute renal insufficiency such as the elderly; patients who are substantially volume depleted; and those with bilateral renal artery stenosis, diabetes mellitus, hypertensive nephrosclerosis, and cardiac failure associated with renal impairment, ACE inhibitor therapy should be instituted with caution. In these conditions, GFR is often maintained in the face of reduced renal perfusion by afferent arteriolar vasodilation and efferent arteriolar vasoconstriction mediated by angiotensin II. By reducing systemic pressure and limiting this compensatory response, these agents may induce a marked decline in GFR. Deterioration in renal function is usually reversible, with dose reduction or cessation of therapy. Effects on renal hemodynamics and proteinuria are also similar to those observed with ACE inhibitors, suggesting the effect on the kidney is mediated by antagonizing the effect of angiotensin II rather than potentiation of bradykinin (166,167,168,169 and 170). However, specific evidence of renoprotective and cardioprotective effects remains to be demonstrated.

Beta-blockers are also indicated among patients with cardiac failure, although data specific to patients with renal insufficiency are limited. Extending beta-blockers to patients with end-stage cardiac failure awaiting cardiac transplantation does not appear to be associated with a significant deterioration in renal function (170). Caution should be exercised with the use of digoxin among patients undergoing hemodialysis because rapid reductions in plasma potassium, magnesium, and hydrogen ions lead to elevated ionized calcium concentrations potentially exposing patients to digoxin-induced arrhythmias. Although digoxin Fab fragments are useful in the treatment of digoxin-induced arrhythmias, renal elimination of the digoxin Fab fragment remains prolonged, requiring extended monitoring in these patients. Both digoxin and the Fab immune fragment are removed by continuous arteriovenous hemodialysis. Among the inotropic agents, specific benefits of dopamine with respect

to renal function have been suggested but not substantiated by randomized studies.

Coronary Revascularization

The principles of revascularization among patients with renal impairment are similar to nonrenal patients, though the effect of renal disease on both short- and long-term outcomes bears careful consideration (Table 35C.2). Frequently, mechanical revascularization is essential for the management of acute coronary syndromes and to control angina resistant to medical therapy and should follow guidelines set forth within the general population in the absence of specific data. In particular, patients with cardiac failure or hemodynamic compromise as manifestations of myocardial ischemia warrant more aggressive investigation and management.

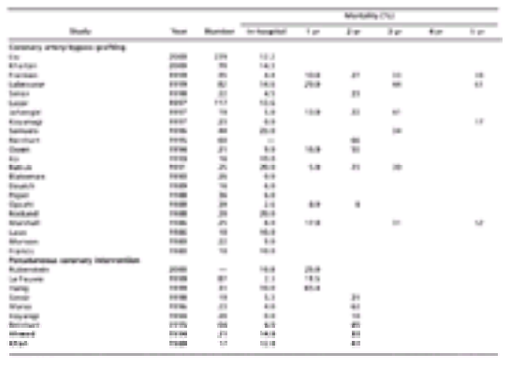


TABLE 35C.2 IN-HOSPITAL AND LATE MORTALITY AFTER CORONARY REVASCULARIZATION

Although the choice between revascularization strategies remains contentious within the general population, the poor long-term results associated with percutaneous coronary intervention has led many to recommend coronary artery bypass grafting as the preferred strategy for patients with significant renal impairment (171,172 and 173). However, with the continued evolution in mechanical revascularization strategies, of particular note coronary stenting, comparison of the relative benefits of each strategy among patients with ESRD requires prospective evaluation.

RENAL TRANSPLANTATION

Among patients undergoing renal transplantation, the incidence of coronary artery disease is increased and associated with a greater mortality, especially in high-risk groups (174,175). Risk stratification (176) and subsequent revascularization appear to reduce long-term cardiac events (174). Therefore, a diagnostic strategy among these patients is warranted. Coronary angiography has commonly been advocated for the screening of coronary artery disease given its prevalence within this population. However, strategies among asymptomatic patients identifying intermediate- and low-risk groups may allow some patients to proceed to transplantation without invasive testing. Patients considered at intermediate risk include those older than 50 years or with diabetes in the absence of clinical cardiac disease and may warrant initial noninvasive investigations. Patients younger than 45 years, with no history of smoking, without diabetes for more than 25 years, and no ST-T–wave changes on ECG, again without clinical cardiac disease, appear to be at low risk of coronary artery disease, and transplantation without prior cardiac investigation may be safe (177). These recommendations have been set forth in the American Society of Transplant Physicians Guidelines for risk stratification before renal transplantation (Fig. 35C.1).

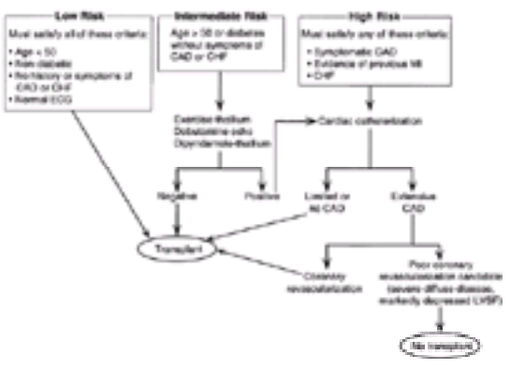


FIGURE 35C.1 American Society of Transplant Physicians Guidelines for risk stratification before renal transplant. CAD, coronary artery disease; CHF, congestive heart failure; ECG, electrocardiography; LVSF, left ventricular shortening fraction; MI, myocardial infarction.

Similarly, parameters of LV function also correlate with long-term mortality after renal transplantation. In a study of 141 patients undergoing echocardiography before transplantation, ejection fraction, end systolic and diastolic diameter, LV mass index, fractional shortening, and age were independent predictors of mortality. Not surprisingly, age and end systolic diameter were the strongest predictors of mortality (end systolic diameter risk ratio, 2.16; 95% confidence interval, 1.27 to 3.66, p <.01), whereas an association between LV mass index and mortality was also observed (178). However, whether targeting echocardiographic abnormalities provides improved survival in these cases requires validation.

Percutaneous Coronary Intervention

In comparison with the general population, earlier studies of coronary angioplasty among end-stage renal failure patients have reported reduced procedural and clinical success rates because of a substantial increase in ascular complications, long-term recurrent angina, myocardial infarction, restenosis, as well as in-hospital and long-term mortality (179,180 and 181). This excess in late adverse outcome extends to patients with chronic renal insufficiency, not requiring renal replacement therapy.

VIDEO

Video 35C.10 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 35C.11 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Developments in interventional practice, namely coronary stenting and novel adjunctive therapies, have led to some attenuation in the excess risk associated with renal impairment (182). Within a series of 362 patients, newer interventional techniques (coronary stenting in most patients) appear to be associated with an improved

procedural success rate and reduced long-term death, myocardial infarction, or revascularization rates compared with balloon angioplasty, among patients with baseline creatinine greater than 1.5 mg per dL. However, coronary stenting has also been associated with an increased rate of in-hospital cardiac events compared with balloon angioplasty (stents 11% vs. percutaneous transluminal coronary angioplasty 5%) among dialysis patients. Within this study, target vessel revascularization at 1 year was required in 22% of dialysis-dependent patients receiving stents, a rate that was comparable with a contemporaneous non–renal failure population. Nevertheless, late mortality and disease progression resulted in a poor late event-free survival (183), whereas angiographic restenosis after coronary stenting remains elevated even among patients with mild to moderate renal impairment (184). Evidence supporting alternate interventional techniques such as rotational atherectomy is promising but limited to small observational studies.

Data supporting the use of glycoprotein IIb/IIIa inhibition specifically in the renal insufficiency patient are limited. Given the substantial benefit within the context of percutaneous coronary intervention, extrapolation of the results seen within the general population to those with significant renal impairment appears reasonable, although an increased risk of bleeding has been observed (185). Bedside tests of platelet aggregation may also prove useful in guiding therapy with these agents, although appropriate therapeutic targets for platelet inhibition within this population have yet to be defined.

With the continued evolution of interventional strategies, more recent evidence indicates an improvement in acute procedural results (186,187), although still inferior to the general population, and an increased rate of in-hospital major adverse events (10.8% rate of death, Q-wave myocardial infarction, and urgent coronary artery bypass grafting) persists. Long-term recurrent angina, myocardial infarction, and target vessel revascularization remain a problem with target vessel revascularization rates and mortality remaining in the range of 50% and 30%, respectively. Factors contributing to these adverse events include a higher degree of calcification, greater residual stenosis, and smaller vessel size, reflecting the diffuse atheromatous disease process (188,189). An increased intensity of prothrombotic and proinflammatory mechanisms as evidenced by increased fibrinogen levels has also been linked to the restenotic process and late events (189). Thus, whether contemporary catheter-based revascularization offers results comparable with coronary artery bypass grafting remains to be examined prospectively (190).

Coronary Artery Bypass Grafting

The adverse prognostic effect of renal insufficiency on the outcomes after coronary artery bypass grafting is well established and extends to include those with moderate renal dysfunction (creatinine greater than 2.5 mg per dL). In addition to an increased prevalence of risk factors such as extensive coronary artery disease, LV dysfunction, diabetes, and prior myocardial infarction, elevated blood urea nitrogen appears to impart increased risk of perioperative mortality and a low cardiac output postoperative state. The mortality risk associated with blood urea nitrogen may be partly attributable to the presence of associated comorbid conditions, such as uremia-induced platelet dysfunction and fluid, electrolyte, and acid–base disturbances contributing to perioperative cardiac failure and arrhythmias. Depressed immune function also increases the rate of infection. Therefore, patients with renal insufficiency experience an increased incidence of prolonged ventilation, mediastinitis, and stroke, contributing to increased intensive care and in-hospital stays as well as an in-hospital mortality ranging from 4% to 14% or approximately three times the rate observed among the general population. Furthermore, combined coronary artery bypass grafting and valvular surgery appears to be associated with an even greater risk of in-hospital mortality (191).

Even within the general population, the incidence of renal failure after cardiac surgery ranges between 1% and 8% but is associated with a striking increase in operative mortality (63.7% vs. 4.3%, p <.001) (192). Similarly, myocardial infarction, mediastinitis, and reoperation for bleeding are also increased. Preexisting renal impairment, age, diabetes, and cardiac failure are important predictors of deterioration in renal function with approximately 25% of patients with preexisting mild or moderate renal insufficiency requiring permanent dialysis after cardiopulmonary bypass (192,193 and 194). Among renal transplant patients, a relatively small deterioration in renal function is also observed (195).

The use of peritoneal dialysis or hemodialysis on the day before surgery and after the operation is practiced in some centers. Minimizing fluid shifts and electrolyte disturbance during the procedure with intraoperative dialysis has also been suggested. Similarly, developments in operative technique and increased use of arterial conduits (196) may benefit these high-risk patients, while the minimally invasive surgery may prove a particular advance in renal failure patients, but this remains to be documented.

Although randomized comparisons are lacking, coronary artery bypass grafting appears to be associated with lower long-term mortality compared with patients receiving coronary stents or balloon angioplasty as observed in the United States Renal Data System database (61.2%, 70.6%, and 71.4%, respectively) (190). Nevertheless, the 22% mortality per year reported in more recent studies remains high (190,197,198,199 and 200). More recent reports of long-term survival do not differ substantially from earlier series. Furthermore, the presence of cardiac failure before coronary artery bypass grafting is associated with a three- to fourfold risk of increased late mortality (191,201). Thus, long-term survival after coronary artery bypass grafting is similar to the overall survival rates observed among dialysis patients regardless of revascularization (191,201,202 and 203). Whether revascularization provides a mortality benefit is uncertain and appears to depend not only on the extent of coronary artery disease, but also on the coexistent medical conditions within the individual patient.

OUTCOMES

Long-term morbidity and mortality from cardiac disease among patients with significant renal impairment remain high. Mortality is observed at a rate of approximately 1% per year among patients with renal insufficiency not treated with dialysis. After renal transplantation, annual mortality of 0.54% or approximately twofold greater than the general population is evident. Among patients receiving renal replacement therapy, cardiac mortality accounts for greater than 40% of all deaths, with an annual cardiovascular mortality 10- to 30-fold higher than the general population. This increased mortality extends across gender, race, and the presence of diabetes. An annual incidence of myocardial infarction among hemodialysis patients is reported to be approximately 8%, with a similar annual incidence of developing pulmonary edema or requirement for extra hemofiltration. Within this population, myocardial infarction is associated with a mortality of 59% and 90% at 1 year and 5 years, respectively (7). LV function remains an important determinant of survival. Among patients starting dialysis therapy, systolic dysfunction portends a median survival of approximately 3 years, whereas outcomes in those with LV dilation or concentric LV hypertrophy are slightly better (23). Patients with clinical cardiac failure commencing dialysis experience a near doubling of mortality compared with their counterparts without cardiac failure, whereas the development of new onset cardiac failure when on hemodialysis therapy is associated with a median survival of 18 months (23).

RENAL REPLACEMENT THERAPY IN A PATIENT WITH CARDIAC DISEASE

Hemodialysis

The term *hemodialysis* is applied to all renal replacement modalities that involve clearance of water and solutes across a synthetic semipermeable membrane. Clearance of solutes and water occurs by two processes, diffusion and convection, and although conceptually different, both processes occur contemporaneously. In chronic ESRD, hemodialysis is usually performed on a thrice-weekly basis for 3 to 4 hours. In critically ill, hemodynamically unstable patients, a more continuous dialysis or continuous renal replacement therapy can be used. Although conceptually identical to hemodialysis, continuous renal replacement therapy allows a wider variation in diffusive and convective clearance.

The acute hemodynamic consequences of renal replacement therapy and the long-term effects of renal replacement therapy both have an effect on cardiovascular disease. This discussion focuses primarily on the intradialytic element of the interaction between renal replacement therapy and cardiovascular disease, highlighting the special considerations of renal replacement therapy to patients with cardiovascular disease.

Hemodynamic Concerns

Hemodialysis alters both intracellular and extracellular composition and volume. These alterations may have the hemodynamic effects of hypotension, dysrhythmias, and ischemia that are particularly important among patients with cardiovascular disease. Hypotension is the most common complication of hemodialytic therapy. Cardiac output and systemic vascular resistance are the major components of blood pressure. Cardiac output is a function of heart rate and stroke volume, and stroke volume is affected by plasma volume. Ultrafiltration of intravascular fluid during hemodialysis reduces plasma volume subsequently, resulting in a decline in cardiac output and blood pressure. Hypotension, however, is not merely a reflection of ultrafiltration and its rate of removal. There are a number of other factors and processes relevant to dialysis-associated hypotension including plasma refill rate, dialysate-related factors, dialysis membrane factors, and autonomic and cardiac function.

Plasma refill rate is defined as the rate at which plasma volume removed by ultrafiltration is restored from intracellular and interstitial fluid compartments. Although there is wide patient variation, the size of the interstitial component has a direct relationship with refill rates (204). One mechanism driving plasma refill rate is the increase in intravascular oncotic pressure secondary to hypotonic fluid removal by ultrafiltration (205). Patients with low plasma protein levels are predisposed to intradialytic hypotension (206) related perhaps to reduced plasma oncotic pressure and consequently reduced plasma refill rate. As an elevated ultrafiltration rate can quickly overcome plasma refill rate, greater weight gain between dialysis treatments requires a faster ultrafiltration rate to achieve prescribed dry weights and therefore predisposes to hypotension. Removal of a high solute load from the intravascular space may cause an intracellular fluid shift and contribute to hypotension.

Dialysate may also play a role in dialysis hypotension. The inclusion of acetate as a buffer in dialysate lowers plasma refill rate and may have a negative inotropic effect (207,208 and 209). The widespread replacement of acetate with bicarbonate, however, has largely obviated this concern. Other electrolytes including sodium and calcium in the dialysate may also contribute to blood pressure modulation. As low sodium concentration in dialysate is associated with hypotension (210,211), elevated dialysate sodium is used therapeutically for intradialytic hypotension (212). Modeling of sodium concentration in the dialysate, usually programmed as a progressive decline from somewhat elevated to more physiologic concentrations over the course of a dialysis treatment, has been used to intervene or prevent hypotension. The long-term benefits of such interventions are not clear (212,213), as most studies report positive sodium balance, temporary decreases in intradialytic hypotension, less blood volume reduction, and a subsequent increase in thirst and body weight.

The use of an increased calcium concentration in the dialysate generally results in an increased serum ionized calcium concentration and improved LV contractility (214). This may contribute to the higher blood pressures seen with the use of low bicarbonate dialysate with higher ionized calcium concentration (215). Serum magnesium levels are frequently elevated among patients with ESRD; therefore, dialysate magnesium is kept at a low concentration. Intradialytic hypotension is less common with low dialysate magnesium (216). The variations in dialysate potassium concentrations have not been shown to significantly alter blood pressure during dialysis, although hypokalemia does have a theoretical inotropic effect.

Other factors that influence blood pressure include anemia, membrane interactions, and dialysate temperature. Intradialytic hypotensive episodes are significantly reduced in anemic patients after transfusion (217). Although the issue of biocompatibility and hypotension is controversial, it arose from the observation that hemofiltration is associated with a greater hemodynamic stability than hemodialysis (218). Although data suggest that the use of dialysis membranes that are considered biocompatible may be associated with less hypotension (219), this finding is not consistent across all studies (220). Dialysate temperature influences hemodynamic response by allowing dissipation of body heat without cutaneous vasodilatation. Maintenance of core temperature during isolated ultrafiltration and hemodialysis optimizes hemodynamic stability during dialysis (221).

The autonomic nervous system should provide an increase in systemic vascular resistance during ultrafiltration (222). Patients with cardiovascular disease may be more prone to hypotension if their sympathetic compensatory mechanisms are already maximized or if the use of certain medications, such as beta-blockers or ACE inhibitors, further compromises compensatory mechanisms.

Hypotension among patients with ESRD may also be an early sign of pericarditis or pericardial effusions. These disorders heighten the sensitivity of blood pressure to ultrafiltration and volume shifts. The treatment for pericarditis usually involves increasing dialysis dose; however, patients with large effusions may benefit from drainage or surgical therapy (223). Dialysis should be performed without heparin to minimize the risk of bleeding into the pericardial space. Aggressive ultrafiltration may reduce intradialytic right ventricular volume and may further predispose these patients to hypotension and cardiovascular collapse.

Seventy percent of incident hemodialysis patients have LV hypertrophy (22). V hypertrophy is associated with reduced LV compliance. Small increases in intraventricular volume may, therefore, result in disproportionate increases in diastolic pressure. Conversely, rapid lowering of preload impairs systolic function. Among patients who have narrow volume ranges because of these factors, modalities using longer durations such as continuous renal replacement therapy or peritoneal dialysis have been suggested (224).

Dysrhythmias

Dysrhythmias are seen frequently among patients during hemodialysis (225). The etiology of intradialytic dysrhythmias may be related to fluid, acid–base, or electrolyte shifts. Patients with ESRD and LV hypertrophy have significantly increased risks of sudden death (226), with up to 75% of such deaths attributable to ventricular fibrillation (227). Bicarbonate dialysate is associated with less frequent dysrhythmia than acetate dialysate (228). Hypokalemia precipitates dysrhythmias, and patients taking digoxin are more susceptible (229). Prevention of hypomagnesemia may also reduce intradialytic ventricular ectopy.

Ischemia and High Output Cardiac Failure

Fluctuations in blood pressure and heart rate during dialysis may lead to alterations in coronary perfusion. Hypoxemia is a common intradialytic problem compounding ischemia (230). The presence of LV hypertrophy and coronary artery disease among patients undergoing hemodialysis may further undermine coronary reserve. Intradialytic ischemia can be complicated by the sudden release of adenosine, which further compounds hypotension (231). Chest pain on dialysis should be treated with supplemental oxygen and by minimizing ultrafiltration rate. Patients with recurrent ischemia should be prescribed a tight fluid restriction to minimize ultrafiltration requirements. Intradialytic ST depression on ECG is predictive of future cardiac morbidity (232), and continuous blood volume monitoring has theoretic benefits in minimizing ischemia by reducing the amplitude of fluid shifts (233). Increasing the length of dialysis sessions to achieve adequate volume removal at a slower rate may minimize these clinical problems.

Arteriovenous fistulas are associated with cardiac enlargement and hypertrophy among patients with ESRD (234). The extent to which they contribute to high output failure is unclear as the occurrence of failure is unusual (235).

Peritoneal Dialysis

Peritoneal dialysis involves the same principles of ultrafiltration and diffusion. Ultrafiltration is achieved through the instillation of hypertonic fluid containing high concentrations of dextrose into the peritoneal cavity. Diffusion subsequently occurs across the semipermeable peritoneal membrane. The removal of solutes depends on a concentration gradient between blood and intraperitoneal fluid. The gradient is greatest at the beginning of dialysis and diminishes as dialysis progresses. Among patients susceptible to volume shifts, lower osmolarity PD fluid and longer dwell times can attenuate the rate of ultrafiltration.

Among patients with advanced LV systolic failure, peritoneal dialysis has been advocated as the therapy of choice. Because fluid shifts occur gradually, a more constant volume status is maintained. In addition, the need for an arteriovenous fistula with its consequent high output state is obviated (234). Whereas the intermittent nature of hemodialysis may contribute to an increased rate of sudden and cardiac deaths early in the week, sudden cardiac deaths are more evenly distributed among patients on peritoneal dialysis, suggesting a more benign effect of therapy (236). Peritoneal dialysis may lead to regression of LV hypertrophy (237), and although it has been associated with greater long-term mortality, this increase in mortality is not attributable to an increase in clinical and echocardiographic cardiac disease (13).

Peritoneal dialysis is associated with a large absorption of glucose across the peritoneal membrane, which may contribute to a number of metabolic abnormalities, including abnormal glucose and insulin metabolism, glucose intolerance, hyperinsulinemia, reduced peripheral sensitivity to insulin (238), and hyperlipidemia (239). Both hyperinsulinemia and hyperlipidemia are of concern for patients with ESRD, as they may constitute increased risk for development and progression of atherogenesis. Hyperinsulinemia and hyperlipidemia are thus important factors to consider among patients with preexisting atherosclerotic disease on peritoneal dialysis and should play at least some role in modality selection (240).

Nonenzymatic glycation of proteins in the peritoneal cavity with the resultant formation of advanced glycation end products may play a role in the genesis and progression of cardiovascular disease (241). Such concerns with glucose have contributed to the advent of alternative peritoneal dialysis solutions such as amino acid–containing solutions.

Transplantation

Although transplantation is considered the treatment of choice for management of ESRD and has been associated with regression of cardiovascular disease and particularly LV hypertrophy (242), atherosclerotic disease is the major cause of morbidity and mortality in transplant recipients (243,244). Two-year mortality after myocardial infarction for transplant recipients has been reported at 33.6% (245). The increasing prevalence of atherosclerotic disease in the transplant population may be related to the increase in age and increasing proportion of diabetics currently undergoing transplantation. There are, however, a number of factors specifically related to immunosuppressive therapies that predispose toward development and progression of atherosclerotic heart disease.

Therapy with calcineurin inhibitors is associated with the development of hypertension (246) and has been linked to accelerated atherosclerotic disease through mechanisms including the induction of heat shock proteins (247), enhancing endothelial sensitivity (248), and alteration of cardiac vascular remodeling (249). These drugs have been shown to potentiate the atherosclerotic effects of hyperlipidemia in mice (250) and to increase LDL oxidation in humans (251). Calcineurin inhibitors cause hypertension through a decrease in renal blood flow and an increase in systemic vascular resistance (252). Through these mechanisms, these drugs may predispose toward development of LV hypertrophy and uremic cardiomyopathy.

Electrolyte abnormalities are also associated with immunosuppressive agents. The use of cyclosporin is associated with hypomagnesemia (253), whereas both cyclosporin (254,255) and tacrolimus (256) can cause hyperkalemia. The development of diabetes mellitus posttransplant is associated with the use of corticosteroids,

cyclosporin, and tacrolimus (257) and may contribute significantly to increased cardiovascular risk. Tacrolimus suppresses insulin production in the pancreatic beta cells (258), and the introduction of tacrolimus has been associated with a significantly higher incidence of this problem (259).

THE FUTURE

Patients with both cardiac disease and renal insufficiency are increasing in prevalence, associated with an increase in the incidence of diabetes coupled with an aging population. Consequently, randomized trials of current and novel therapies addressing this high-risk population will provide specific clinical data to guide the management of these patients. Recognition of the heightened inflammatory, thrombotic, and metabolic processes contributing to cardiovascular disease within patients with renal insufficiency promises to provide important pathophysiologic information. Further, an understanding of the role of these mechanisms in the increased prevalence of cardiovascular disease among the population of patients with renal disease will provide insight into differential benefit from therapies such as revascularization procedures and pharmacologic management.

It has long been established that patients with ESRD have a tremendous burden of coronary artery and other cardiovascular disease. Increasing focus, however, is now being placed on the period in a patient's clinical course before the development of ESRD. The epidemiology of cardiovascular disease among patients with early renal insufficiency has not been fully explored. This population of patients has greater comorbidity and a unique pathobiology of disease that will require dedicated and focused study. A better understanding of the distribution and determinants of disease as well as the development of therapeutic strategies targeting the unique mechanisms is essential toward affecting the burden of cardiovascular disease in this population.

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35D

THE HEART AND OTHER ORGAN SYSTEMS:

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"Indicates text or graphics that appear only in the electronic versions of this text."

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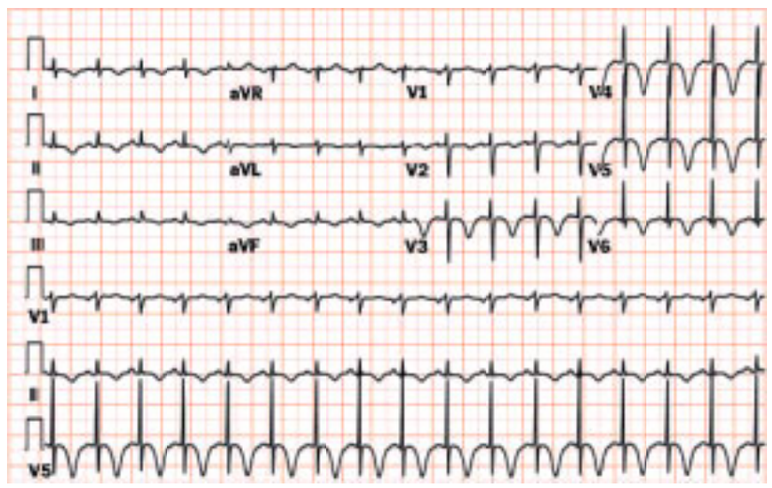
OVERVIEW

Cardiac manifestations of neurologic disorders are common and diverse. Understanding the pathophysiology of cardiac and neurologic disorders is critical for physicians caring for patients with cardiovascular and neurologic disease states and investigators attempting to develop therapies and management strategies for disorders that have both central nervous system (CNS) and cardiovascular components. The importance of interactions between cardiology and neurology is exemplified by ongoing collaborative efforts between cardiologists and neurologists in several key clinical areas, including stroke prevention in atrial fibrillation, percutaneous intervention in cerebrovascular occlusive disease, and the use of thrombolytic and antiplatelet therapies in nonhemorrhagic stroke. Many of these specific issues are discussed in other chapters. In this chapter, the focus is on cardiac manifestations of specific CNS events and the cardiac anomalies associated with hereditary and acquired neuromuscular disorders.

CARDIAC MANIFESTATIONS OF CENTRAL NERVOUS SYSTEM EVENTS

It was more than 60 years ago that Beattie and colleagues recognized that the CNS had neurogenic input in cardiac arrhythmias (1). Soon after, Aschenbrenner and Bodechtel reported electrocardiographic (ECG) abnormalities in young patients with brain lesions and presumed normal cardiac structure (2). It is now commonly known that ECG abnormalities can occur in the setting of CNS abnormalities such as ischemic stroke, intracranial hemorrhage, seizure, headache, meningitis, encephalitis, and cranial trauma. Generally, these ECG features can be interpreted correctly in the setting of known or suspected neurologic disease. However, the erroneous diagnosis of primary cardiac disease can occur and, more importantly, result in inappropriate therapy or delay in proper treatment. Substantial work has been done to attempt to understand the pathophysiology of these cardiac manifestations.



Neurogenic T waves. These deep, symmetric T-wave inversions developed after intracranial hemorrhage.

Acute Ischemic Stroke

Cardiovascular complications are extremely common following stroke and represent a major form of morbidity. These complications may be caused by focal cerebral injury or may be a manifestation of preexisting cardiac disease, which is common in this patient population.

Several studies have documented a high prevalence of ECG changes and arrhythmias in patients presenting with acute ischemic stroke. Common ECG changes include QT prolongation, T-wave abnormalities, prominent U waves, and ST-segment abnormalities (eTable 35D.0.1) (3,4,5,6 and 7). Although ECG changes are common with ischemic stroke, interpretation of these studies is difficult, as the prevalence of asymptomatic coronary artery disease in patients with symptomatic cerebrovascular disease has been reported to be as high as 28% to 65% (8,9). Thus, cerebrovascular disease may be a marker for coronary artery disease that becomes clinically apparent during the physiologic stress of acute ischemic stroke. Few studies have systematically examined old tracings to establish if the ECG changes were new (10). There has been no definitive correlation between the presence of ECG changes and cerebral infarct location.

***e*TABLE 35D.0.1** REPORTED ELECTROCARDIOGRAPHIC CHANGES AND ARRHYTHMIAS IN PATIENTS WITH INTRACRANIAL HEMORRHAGE OR ISCHEMIC STROKE

Electrocardiographic changes
QT prolongation
T-wave inversion
Increased T-wave amplitude
Prominent U waves
ST-segment elevation
ST-segment depression
Premature atrial complexes
Premature ventricular complexes
Atrioventricular block (first-, second-, and third-degree)
Fascicular block
Bundle branch blocks
Arrhythmias
Sinus tachycardia

Sinus bradycardia
Sinus arrest
Asystole
Supraventricular tachycardia
Wandering atrial pacemaker
Atrial fibrillation
Atrial flutter
Ventricular tachycardia
Ventricular flutter
Ventricular fibrillation
Idioventricular rhythm
Torsades de pointes

Arrhythmias are also common after acute ischemic stroke (*e*Table 35D.0.1). Atrial fibrillation has been most frequently described, although it is often unclear whether the atrial fibrillation was the cause of a cardioembolic event or secondary to cerebral infarction (3,10,11). Ventricular ectopy has also been frequently reported, although episodes of sustained ventricular tachycardia are distinctly uncommon. Atrioventricular (AV) block has been reported and has been attributed to excessive vagal stimulation (12). Intensive monitoring of patients presenting with acute stroke has increased the recognition of these arrhythmias, but this practice has not been shown to reduce morbidity or mortality. Because life-threatening arrhythmias in these patients are uncommon, it may be difficult to show a clear benefit. Prolonged cardiac monitoring, however, may be a useful diagnostic tool to help define the stroke etiology.

As many as 15% of patients with acute ischemic stroke may suffer a myocardial infarction (13,14). With the high coexistence between coronary artery and cerebrovascular disease, it is difficult to imply causality, although it is clear that there is a significantly increased morbidity in ischemic stroke patients who have a concurrent myocardial infarction.

Intracranial Hemorrhage

Byer et al. in 1947 first reported large T waves and QT prolongation in a patient with subarachnoid hemorrhage (15). The first systematic review of ECGs in patients with intracerebral or subarachnoid hemorrhage was done in 1954 and reported that QT prolongation, increased T-wave amplitude, and abnormal U waves were the most common abnormalities (16). Others have reported similar changes in small groups (*e*Table 35D.0.1) (17,18).

The precise incidence of specific ECG abnormalities is not known because reports have included patients with diverse baseline clinical characteristics and lesion types. The level of sophistication of ECG analysis has also varied. Reported rates for abnormalities on the ECG in patients with intracranial hemorrhage vary from 50% to 98% (3,10,17,19). Several larger series provide the best estimate of the frequency of ECG abnormalities. In 100 consecutive patients with acute stroke, 91% of patients with intracerebral or subarachnoid hemorrhage had abnormal ECG results (3). QT prolongation, increased T-wave amplitude, or prominent U waves were seen in 50% of patients. In another series of 45 patients with intracranial hemorrhage, ECG tracings from this group were compared with ECGs from a group of patients with ischemic stroke and a third group of age- and sex-matched general surgery patients who did not have a history of cerebrovascular or cardiovascular disease (19). Only 18% of the patients with intracranial hemorrhage had a normal ECG result compared with 46% in the ischemic stroke group and 75% in the control group. QTc prolongation occurred in 62% of the patients with hemorrhagic stroke, 18% of patients with ischemic stroke, and 11% of controls. Quantitative analysis of the QTc revealed that prolongation was particularly more frequent in the patients with intracerebral or intraventricular hemorrhage. Although there has been no definitive correlation between hemorrhage location and the ECG changes, several studies have noted an association between frontal lobe hemorrhage and QT prolongation (5,20).

The largest comparative series documenting specific ECG abnormalities in stroke patients included 150 stroke patients and 150 age- and sex-matched controls: 92% of stroke patients and 65% of controls had abnormal ECG results. Abnormal ECGs were found in 43 (98%) patients with intracranial hemorrhage. The most common ECG changes were QT prolongation, T-wave inversion, and prominent U waves. Few ECG findings characterized a particular stroke type. Atrial fibrillation was significantly more common in patients with cerebral embolus (47% vs. 9% for other stroke type), and QT prolongation was most common in patients with subarachnoid hemorrhage (71% vs. 39% for other stroke types). U waves were more common in patients with intracranial hemorrhage than in patients with other stroke types (25% vs. 8%). Prior ECG abnormalities were seen in 91% of stroke patients and 71% of controls. New ECG abnormalities at the time of stroke were identified in 74% of stroke patients and 14% of controls.

Supraventricular and ventricular arrhythmias as well as conduction abnormalities have been well documented in patients with intracranial hemorrhage (*e*Table 35D.0.1). Several observational series have reported arrhythmias in 47% to 90% of patients (10,11,21,22) and serious or life-threatening arrhythmias in 20% to 50% of patients with intracranial hemorrhage (21,23,24 and 25). However, because of diverse patient populations, the level of cardiac monitoring, and the severity of the disease state, the true incidence of specific arrhythmias is unknown.

The best data for the incidence of arrhythmias in stroke patients are from a large series reported by Di Pasquale and colleagues (21). Twenty-four-hour Holter monitor recordings were performed on 120 patients with subarachnoid hemorrhage: 96 of 107 patients (90%) with adequate recordings had arrhythmias. The most common arrhythmias were premature ventricular contractions (46%), sinus bradycardia (39%), sinus tachycardia (30%), sinus arrhythmia (30%), supraventricular premature complexes (27%), and sinoatrial block (21%) (*e*Table 35D.0.2).

***e*TABLE 35D.0.2** CARDIAC ARRHYTHMIAS AND TRANSIENT ST-SEGMENT CHANGES IN 107 PATIENTS WITH SUBARACHNOID HEMORRHAGE AND TECHNICALLY ADEQUATE HOLTER RECORDING

Holter findings	**Early stage (n = 62)**	**Late stage (n = 45)**	***p* value**
Ventricular premature complex	34	15	<.05
Nonsustained ventricular tachycardia	5	0	NS
Supraventricular premature complex	14	15	NS
Paroxysmal atrial fibrillation	2	0	NS
Paroxysmal supraventricular tachycardia	4	3	NS
Sinus bradycardia <50/min	19	23	NS
Sinus tachycardia >120/min	29	3	<.05
Sinus arrhythmia	18	14	NS
Wandering pacemaker	5	2	NS
Sinoatrial block	14	9	NS
Sinoatrial arrest >3 sec	4	2	NS
Atrioventricular dissociation	4	0	NS
Second-degree atrioventricular block	1[a]	0	NS
Idioventricular rhythm	2	0	NS
Torsades de pointes	4	0	NS
Ventricular flutter	1	0	NS
Ventricular fibrillation	1	0	NS
Asystole	5	0	NS
ST-segment depression[a]	4	3	NS
ST-segment elevation[b]	1	0	NS
Negative recording	3	8	NS

NS, not significant.
[a]Decreased ST ³1.5 mm.
[b]Increased ST, 1.5 mm.
From Di Pasquale G, Pinelli G, Andreoli A, et al. Holter detection of cardiac arrhythmias in intracranial subarachnoid hemorrhage. *Am J Cardiol* 1987;59:596–600, with permission.

Arrhythmias tended to be more frequent and severe in patients with recordings in the first 48 hours after onset of bleeding. The QTc interval was significantly prolonged in patients with malignant ventricular arrhythmias. Nearly one-half of the patients had hypokalemia on admission, and potassium levels were significantly lower in patients with ventricular arrhythmias in the first 48 hours. The site or extent of intracranial hemorrhage did not correlate with the presence or type of arrhythmia.

Severe life-threatening arrhythmias in patients with subarachnoid hemorrhage including torsades de pointes in the setting of marked QT prolongation have been reported (26,27,28,29,30 and 31).

The implications of arrhythmias are important because they can cause hemodynamic compromise that may have adverse effects on cerebral perfusion or may increase

the risk of further cerebral insult such as with atrial fibrillation. The presence of malignant ventricular arrhythmias or asystole has been reported as a univariable predictor of mortality after intracranial hemorrhage (10).

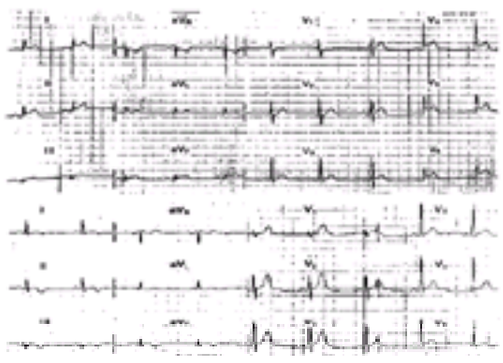
Management of Arrhythmias in Patients with Intracranial Hemorrhage or Ischemic Stroke

Management of patients with arrhythmias in the setting of intracranial hemorrhage has not been studied rigorously. Because of the high incidence of arrhythmias, continuous ECG monitoring is recommended, but there is no consensus about its required duration. Patients with QT prolongation should be monitored closely, and possible causative factors such as medications or electrolyte abnormalities should be identified and corrected. Patients with torsades de pointes have been treated with atrial or ventricular overdrive pacing or isoproterenol. Left stellate ganglion block has also been proposed in patients with recurrent arrhythmias (32).

Intracranial Hemorrhage and Electrocardiographic Changes Consistent with Acute Myocardial Infarction

Multiple cases of patients with intracranial hemorrhage and ECG changes consistent with acute myocardial infarction and normal coronary anatomy by cardiac catheterization or at autopsy have been reported (33,34,35,36,37 and 38). Although a rare clinical entity, physicians need to be aware that ECG changes and symptoms consistent with myocardial ischemia or acute infarction coexist with intracranial hemorrhage.

*e*Figure 35D.0.1 shows an ECG consistent with an acute myocardial infarction from a 30-year-old man with a several-day history of recurrent headache associated with nausea, vomiting, and chest pain. The patient was treated with streptokinase. The following day the headache recurred and computed tomography of the head revealed a large, left cerebellar hemorrhage. Coronary angiography revealed normal coronary arteries. An ECG 13 days later showed resolution of the ST-segment elevation (*e*Fig. 35D.0.1).



***e*FIGURE 35D.0.1** Electrocardiogram of a 30-year-old man with cranial trauma at admission and 13 days after admission. (From Kitching AD, Bernstein M, O'Kelly BF. Primary intracranial hemorrhage simulating acute myocardial infarction: a contraindication to thrombolytic therapy. *CMAJ* 1994;150:519–522, with permission.)

Intracranial hemorrhage associated with ECG evidence of acute myocardial infarction is uncommon. However, patients should undergo a thorough history and physical examination to avoid the catastrophic consequences of administering thrombolytic, anticoagulant, or antiplatelet therapy. Physicians should consider beta-blocker therapy in these patients, although there are no definitive supporting data.

Mechanisms of Electrocardiographic Changes and Arrhythmias in Patients with Intracranial Hemorrhage or Ischemic Stroke

Substantial work in experimental models and humans has been done to try to understand the pathogenesis of the ECG changes seen in patients with cerebrovascular events. The first comprehensive report of CNS control of cardiovascular function was proposed more than a century ago by Jackson (39). The most widely accepted mechanism by which lesions in the CNS result in changes in the ECG is a direct result of alterations in the autonomic nervous system control on cardiac electrophysiology. Several other processes are considered contributory, including a direct effect on the myocardium, consequences of the associated hemodynamic derangements, electrolyte abnormalities, alterations in circulating catecholamine levels, or concurrent coronary artery disease.

Experimental animal studies have strongly supported the belief that ECG changes associated with neurologic lesions are caused, at least in part, by altered sympathetic tone. Stimulation of various brain structures has resulted in specific ECG changes similar to those seen in patients with ischemic stroke and intracranial hemorrhage. Stimulation of the cortical surface of the frontal lobe (area 13) and the cingulate gyrus (area 24) caused increases or decreases in the blood pressure and changes in the heart rate (40). In cats, stimulation of the basal ganglia produced premature ventricular contractions, and stimulation of the posterior hypothalamus produced premature ventricular contractions and T-wave abnormalities (41). Many others have also reported ECG changes and arrhythmias with cortical, hypothalamic, and basal ganglia stimulation (42,43,44,45 and 46). The insula may also be an arrhythmogenic center based on several animal studies (47,48 and 49). ST-segment changes have also been associated with ablation or stimulation of sympathetic nerve fibers at the level of the stellate ganglion in dogs (50). Stimulation of the ganglion resulted in shortening of the ventricular recovery time, and ablation resulted in prolongation of the recovery time. This is particularly important because unilateral sympathetic stimulation and ablation resulted in localized effects on cardiac recovery. Unilateral stimulation or ablation of the right stellate ganglion resulted in effects in the anterior and superior ventricular walls, whereas left stellate ganglion manipulation resulted in changes in recovery time in the posterior and inferior walls. These changes resulted in specific abnormalities with ST elevation and inverted T waves during right stellate ganglion stimulation, and ST depression and peaked T waves during left stellate ganglion stimulation. Others have found more diverse ECG changes (51). These changes may be the substrate for ventricular arrhythmias.

A few studies performed during neurosurgery have investigated the cardiac effects of cortical stimulation. The cingulate gyrus, areas of the temporal lobes, and the frontal cortex have all been shown to have cardiovascular effects when stimulated (52,53,54 and 55). In addition, stimulation of the insula, because of its connections with other deep brain structures such as the limbic system and hypothalamus, may be associated with similar cardiovascular responses as seen in animal models (56,57). Specifically, stimulation of the left insular cortex can cause bradycardia and a vasodepressor response, whereas stimulation of the right insular cortex results in tachycardia and increased vasomotor tone (56). In reports based on human models, ECG changes similar to those seen in acute CNS events have been reported after right radical neck dissection (58) and during manipulation of the carotid body and stimulation of area 13 of the frontal cortex during aneurysm repair after subarachnoid hemorrhage (20). Sympathetic trunk ablation during surgery or stimulation of known vagal centers supports the hypothesis that centrally mediated alterations in sympathetic or vagal tone result in the observed ECG changes.

These observations led others to try to determine the neuroanatomic substrate for the ECG changes seen during provocative stimulation of cerebral structures. The ECG abnormalities in cats caused by cortical stimulation were reversed with transection of the spinal cord above the level of the sympathetic outflow tracts, suggesting that alterations in autonomic outflow may cause the cardiac findings (59). Others have proposed that changes in sympathetic and vagal tone and noradrenaline were all contributing factors for the ECG changes seen in an elaborate set of studies involving hypothalamic stimulation in cats (60).

Increased circulating catecholamine levels have been proposed by some to be a potential cause of the ECG abnormalities observed in patients with an acute neurologic event (61). ECG abnormalities in dogs after brain stimulation have been reversed by propranolol administration (46). In addition, increased levels of catecholamines in hearts of animals after brain stimulation have been documented (61). Others believe that ECG abnormalities are independent of elevated plasma norepinephrine levels (62), and measurements of urinary catecholamines in humans after cerebrovascular events have been inconclusive (63).

The ECG changes seen in patients with CNS disorders are not completely explained by alterations in catecholamine levels or changes in sympathetic or vagal tone. Patients with cerebrovascular disease are also at risk for cardiovascular disease. Hertzer and colleagues performed cardiac catheterization on 1,000 patients undergoing vascular surgery (64). In the subgroup of 295 patients with a primary diagnosis of cerebrovascular disease, 59% of the patients had significant coronary artery disease, and almost one-half (44%) of the patients without symptoms of coronary disease had significant stenosis, severe operable, or severe inoperable coronary atherosclerotic disease. Patients with coronary disease may manifest symptoms of cardiac ischemia and associated ECG changes during acute CNS processes. Transient coronary vasospasm may also contribute to the ECG changes. Abnormal electrolyte concentrations, particularly hypokalemia, may also contribute to some of the ECG findings seen in patients with intracranial hemorrhage. Vomiting is common in patients with increased intracranial pressure and elevated levels of circulating catecholamines, and cortisol may be responsible for the electrolyte abnormalities.

The pathogenic mechanism for arrhythmias has not been determined clearly. Experimental studies have demonstrated that injection of blood into the subarachnoid space is associated with the rapid onset of arrhythmias. Chronic elevations of intracranial pressure, however, typically cause bradyarrhythmias (65,66 and 67). Others have observed premature ventricular contractions and ventricular arrhythmias in anesthetized cats during stimulation of the hypothalamus, particularly the posterior

hypothalamus (1). Based on these animal models and clinical observations, several mechanisms for the arrhythmias have been proposed. Sudden increases in intracranial pressure cause compression on the brainstem and diencephalic structures, which results in increased sympathetic or vagal stimulation of the heart. Alterations in cerebral vascular tone may cause changes in systemic hemodynamics. Underlying coronary artery disease and hypertensive heart disease, which are common in patients with cerebrovascular disease, may be contributing factors in some patients (11). Hypoxia caused by respiratory compromise, elevated catecholamines, and electrolyte imbalances, particularly hypokalemia, may also contribute to the arrhythmias (21).

Myocardial Damage in Patients with Intracranial Hemorrhage and Ischemic Stroke

Some controversy remains as to whether ECG abnormalities observed in patients with acute ischemic stroke or intracranial hemorrhage are caused solely by alterations in autonomic control or whether they represent primary myocardial changes. Experimental studies have shown pathologic myocardial changes after intracranial blood injection in mice (68,69). Focal myocardial lesions consisting of infiltrates of lymphocytes or histiocytes, which displaced or replaced short segments of myocardium, were seen in 45% of rats with experimentally induced intracranial hemorrhage (70). Subendocardial hemorrhages have been reported after subarachnoid hemorrhage and stellate ganglion stimulation in animals (71,72). The incidence of these myocardial changes was dramatically reduced in rats treated with propranolol. Others have reported similar findings (73,74). Several investigators have shown focal necrosis, myofibrillar degeneration, and inflammatory cell infiltration in animals after catecholamine infusions or hypothalamic stimulation (73,75,76,77,78,79,80 and 81).

Despite numerous reports of patients with normal myocardium after stroke even in the presence of ECG changes (18,20,35,82), data from human autopsy series suggest that a subgroup of patients with acute ischemic stroke or intracranial hemorrhage may have abnormal myocardial pathology. In two autopsy series, 8% to 12% of patients with intracranial hemorrhage, tumor, infection, or head injury had foci of myocytolysis predominantly in the left ventricle, without evidence of infarction (63,83). Focal myocytolysis is often seen with myocardial infarction, but is a distinctive lesion. It was first reported by Schlesinger and Reiner (84). The characteristic features of myocytolysis are loss of sarcoplasm from focal areas of myocardium with retention of the cellular nuclei and sarcolemma.

Others have also reported myocardial damage in patients with cerebrovascular events, ranging from the changes consistent with myocytolysis to foci of necrosis (85,86 and 87). The cause of these myocardial findings is unknown but may be sympathetic cardiac stimulation or excessive catecholamine levels. The significance is also unclear, and it is unknown if they contribute to the ECG changes or the arrhythmias seen in patients with neurologic lesions.

Catecholamine elevations are well known to be a nonspecific response to stress and have been shown to be elevated in some patients with intracranial hemorrhage (61). Myocardial lesions, similar to those in animal studies, have been reported in patients with pheochromocytoma (88). In addition, corticosteroids may potentiate the catecholamine effects on the myocardium and have been shown to be elevated in the majority of patients with subarachnoid hemorrhage (89).

Epilepsy

Cardiac arrhythmias are common during partial and generalized seizure activity and may be associated with significant morbidity and mortality. In several series, sinus tachycardia was the most common arrhythmia and was present during 97% of ictal episodes. By contrast, severe or life-threatening arrhythmias were present in only 5% of patients (90,91,92 and 93). There have been numerous reports of cardiac arrest and asystole associated with seizure activity, and undiagnosed seizure disorders have presented as unexplained syncope (94,95,96,97 and 98).

Even when accidental deaths that might be associated with seizure activity are discounted, epileptic patients are at significantly higher risk of sudden death than the general population (99,100). Several epidemiologic studies have suggested that sudden unexplained death may account for more than 10% of deaths in an epileptic population (99,100). Sudden death is usually attributed to neurogenic cardiac arrhythmias, although it is possible that neurogenic pulmonary edema may play a role in this phenomenon (101). There is no evidence that patients with epilepsy have a higher rate of occult cardiac disease than the general population, and many of the patients experiencing sudden death do not have known cardiac risk factors. Several series have suggested that risk factors include the presence of a structural CNS lesion, noncompliance with anticonvulsant medication, young age, and poorly controlled generalized seizures (99). As opposed to nonepileptic patients with sudden cardiac death, the cardiac pathology is usually unremarkable, although one series has reported evidence of focal areas of subendocardial fibrosis (101,102,103 and 104). These lesions could have many etiologies, although a sustained increase in sympathetic tone may cause a similar pattern of injury.

The possibility that temporal lobe discharges may produce cardiac arrhythmias is supported by animal and clinical studies. In a rat model, the stimulation of the insular cortex caused changes in cardiac rhythm. Oppenheimer and Cechetto have demonstrated chronotropic organization in this model, with the stimulation of the rostral insula causing tachyarrhythmias, and the stimulation of the caudal insula resulting in bradyarrhythmias (49). This work was extended in a clinical study examining the effects of intraoperative stimulation before temporal lobectomy for seizure control. Although there was variability between individuals, tachycardia and pressor responses were more often elicited from the stimulation of the right insular cortex, whereas bradycardia and vasodepressor responses were more common with stimulation of the left insular cortex (56). In clinical practice, however, a close correlation between type of arrhythmia and seizure focus has never been established, although some studies have suggested that temporal lobe seizures may be more arrhythmogenic (105,106).

Migraine Headache

The precise etiology of migraine headaches is unknown. Migraine headaches are generally thought to be associated with arterial vasomotor and autonomic nervous system abnormalities. There are reports of typical angina-like chest pain and myocardial infarction in patients during the acute phase of a migraine headache. A generalized vasospastic disorder has been suggested to explain these findings (107,108). Ischemic ECG changes have been reported with normal coronary angiography, supporting coronary spasm as the cause of ischemia (107,108). Sympathetic function is impaired in some patients with migraine headaches (109). Several studies of ambulatory ECG monitoring have shown altered autonomic innervation of the heart in patients with migraine compared with controls (110,111 and 112).

Common medications used to treat migraine headaches can also have cardiac effects. Ergot compounds and sumatriptan are the two most common therapies used in aborting migraine headache. Dihydroergotamine has a high affinity for 5-HT_1, 5-HT_2, dopamine, and other catecholamine receptors (113). Ergotamine has been shown to precipitate coronary spasm and chest pain in patients with migraine (114). Sumatriptan has a more specific agonist of the presynaptic and postsynaptic 5-$HT_{1B/D}$ receptor and works by constricting large intracranial vessels and blocking neurogenic inflammation (115). Sumatriptan has produced chest pain syndromes (116), and although it may affect blood pressure, the symptoms are generally not associated with ECG changes (117,118). Both agents have the potential for coronary vasoconstriction and are contraindicated in patients with ischemic heart disease or variant angina. Patients with multiple risk factors for ischemic heart disease should undergo evaluation for coronary artery disease, including ECG and stress testing before initiating therapy. Based on the success of sumatriptan, several oral second-generation triptans have also been developed, including zolmitriptan, rizatriptan, and naratriptan. Although experience with these newer agents is more limited and there are conflicting reports regarding their potential for coronary vasoconstriction, all of these drugs maintain the same precautions and contraindications as sumatriptan regarding administration to patients with coronary artery disease.

Meningitis and Encephalitis

Cardiac abnormalities may occur in patients with meningitis and encephalitis. Alterations in CNS function caused by increased intracranial pressure or involvement of specific neurologic centers known to be key in autonomic control of the heart can result in ECG abnormalities or arrhythmias.

Meningitis has been associated with several nonspecific ECG changes. Prominent P waves and U waves have been reported in 30% to 40% of patients with meningitis in one series (82). ST elevation and sinus arrhythmias were noted in one-third of the patients. QTc prolongation was not observed, and T-wave inversion was seen in only 15% of patients. Another series including echocardiographic analysis noted systolic filling abnormalities in more than 50% of patients with meningitis, but only 10% had ST-T–wave changes or QTc prolongation (119). In addition, ECG changes and arrhythmias, including sick sinus syndrome, sinus node dysfunction, complete heart block, and premature supraventricular and ventricular complexes, have been reported (82,120,121).

Encephalitis can cause severe neurologic sequelae, resulting in cardiac arrhythmias caused by compromise of respiratory or other organ dysfunction. In a systematic review of 26 noncomatose patients with encephalitis, 10 patients (38%) had abnormalities on the ECG, including sinus arrhythmia, sinus tachycardia, sinus bradycardia, sinus arrest, ST-segment changes, premature ventricular complexes, and T-wave changes (122). No QT prolongation was noted. Others have reported torsades de pointes (123) and bifascicular block (124) in patients with encephalitis.

Cranial Trauma

Patients with cranial trauma can have ECG changes and arrhythmias similar to patients with intracranial hemorrhage. In an extensive review, ECG tracings from 164 patients younger than 40 years and without a history of cardiovascular disorder were compared with those from 100 patients with limb injury, and 164 healthy age- and

sex-matched controls. Patients with head injury had an increased frequency of QTc prolongation (15% vs. 0% to 1% in other groups), increased P-wave amplitude (24% vs. 2% to 14% in the other groups), and T-wave inversion (10% vs. 0% to 6% in other groups). The incidence of ECG abnormalities increased with worsening level of consciousness. ST elevation and prominent U waves occurred in 14% to 21% of patients with limb or head trauma, without increased frequency in the head trauma group (125). Others have reported sequential ECG changes in a patient with severe cranial trauma suggestive of acute myocardial infarction, but no evidence of structural heart disease at autopsy (126).

Experimental models of head trauma in mice revealed that all mice developed increased T-wave amplitude and multiple arrhythmias, including sinus arrhythmia, premature ventricular contractions, and sinus and atrioventricular nodal block. A second group of mice pretreated with atropine did not develop significant arrhythmias. The authors proposed that these findings supported the role of vagal stimulation in the genesis of arrhythmias in the setting of head trauma (127).

NEUROMUSCULAR DISORDERS WITH CARDIAC MANIFESTATIONS

Cardiac disease may be associated with the major types of diseases of the peripheral nerves, the neuromuscular junction, and the muscles with varying characteristics and severity. The cardiac manifestations and the clinical features of the neuromuscular disorders are heterogeneous. In some disorders, the most distinguishing feature is a cardiomyopathy, whereas in other disorders, conduction abnormalities are prominent (eTable 35D.0.3). The cardiac involvement can be minimal or life threatening. Several of the more common and clinically important diseases are reviewed here.

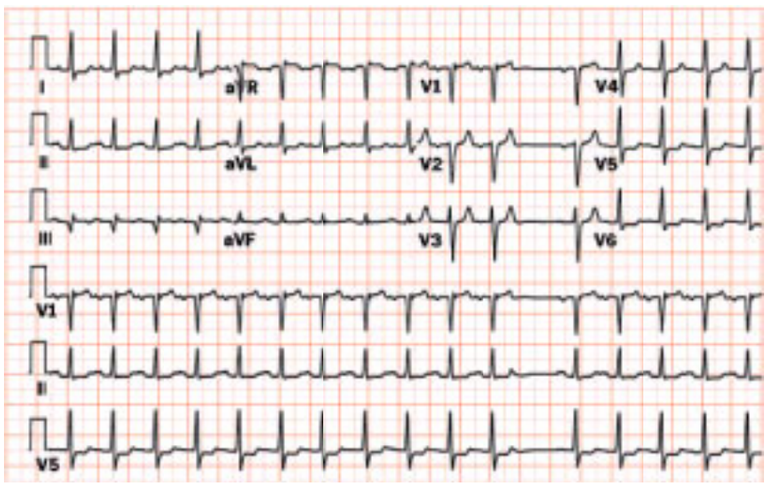
***e*TABLE 35D.0.3** CARDIAC MANIFESTATIONS OF NEUROMUSCULAR DISORDERS
Neuromuscular disorders commonly associated with electrocardiographic abnormalities
Guillain-Barré syndrome
Duchenne's muscular dystrophy
Becker's muscular dystrophy
Kearns-Sayre syndrome
Myotonic muscular dystrophy
Scapuloperoneal syndrome
Periodic paralysis
Myasthenia gravis
Peroneal muscular atrophy
Neuromuscular disorders commonly associated with cardiomyopathy
Duchenne's muscular dystrophy
Becker's muscular dystrophy
Centronuclear myopathy
Myasthenia gravis

Disorders of Peripheral Nerves

Guillain-Barré Syndrome

Guillain-Barré syndrome is an acute autoimmune polyneuropathy that involves inflammation and demyelination of nerves and is classically characterized by ascending motor weakness and areflexia. The diagnosis is supported by a compatible clinical presentation, cerebral spinal fluid findings of albuminocytologic dissociation, and electrodiagnostic evidence of acute demyelination. Autonomic and cardiac complications in patients with Guillain-Barré syndrome are more common than generally recognized and may significantly complicate medical management.

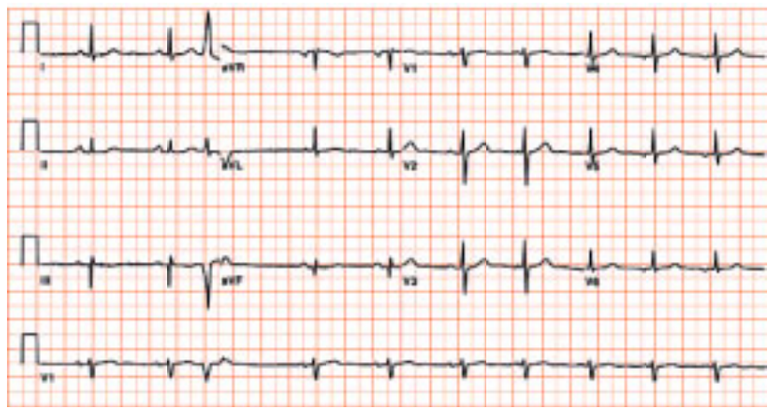
Cardiac involvement in Guillain-Barré syndrome was initially described by Sir William Osler in 1892, who made the observation that some patients with "acute febrile neuritis" succumbed to "paralysis of the heart" (128). Cardiac arrhythmias are also common. Sinus tachycardia has been reported in 45% to 79% of patients (129). Bradyarrhythmias, sinus pauses, and asystole are also common and may portend cardiac arrest (130). Some authors recommend prophylactic pacemaker insertion for patients with clinically significant bradycardias or sinus pauses (131,132 and 133). Although bradyarrhythmias may occur spontaneously, patients often exhibit vagal hypersensitivity to suctioning, and care should be taken to preoxygenate adequately, suction gently, and administer atropine when appropriate.



Sinus tachycardia with blocked premature atrial contraction. Premature atrial beat fails to conduct, producing a pause.

Other arrhythmias and conduction abnormalities, although less common, have been described: atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, and ventricular tachycardia (130,131,134). Cardiac involvement usually parallels severity of disease, and patients at the highest risk for malignant arrhythmias are often ventilator dependent and have more fulminant disease progression. ECG abnormalities have also been described in Guillain-Barré syndrome, with nonspecific ST-T–wave changes observed most commonly (130).

Acute inferior myocardial infarction complicated by atrial fibrillation. Note ST-segment elevation in the inferior leads with reciprocal changes laterally. Atrial fibrillation has complicated this acute infarct.



A 76-year-old male patient with paroxysmal ectopic atrial rhythm.

A 59-year-old female patient with atrial flutter with 4:1 atrioventricular conduction.

Autonomic neuropathy is commonly associated with Guillain-Barré syndrome and may be associated with cardiac dysfunction. Early evidence of autonomic dysfunction may become clinically manifest as abnormalities of bladder function, gastroparesis, abnormal pseudomotor activity, or blood pressure lability. Formal autonomic testing has revealed subclinical evidence of neuropathy in two-thirds of patients with Guillain-Barré syndrome. It is difficult to get a true measure of the clinically relevant autonomic neuropathy in Guillain-Barré syndrome, as most of the published observations are case reports or small series. Hypertension is common, with a reported incidence of 5% to 79%. Clinically significant hypotension may also occur and is often exacerbated by impaired venous return to the heart caused by positive pressure ventilation and paralysis of the calf and abdominal musculature. The occurrence of dysautonomia in Guillain-Barré syndrome is most likely caused by a failure of baroreflex buffering mechanisms due to deafferentation of baroreceptor impulses.

Recognition of the features of early dysautonomia in the setting of Guillain-Barré syndrome is important. Patients with these symptoms are at increased risk for developing cardiac arrhythmias, especially AV block. Identification of this population with autonomic screening tests has met with limited success (135,136). It is probable that fulminant autonomic neuropathy with inflammation of the small intramyocardial nerves is responsible for the focal myocarditis described in Guillain-Barré syndrome (137). A dysautonomia-induced hypersympathetic state may also be responsible for acute reversible left ventricular dysfunction in these patients (138).

Friedreich's Ataxia

Friedreich's ataxia is an autosomal recessive neurodegenerative disease characterized by progressive ataxia, areflexia, proprioceptive loss, and upper motor neuron findings. When strict neurologic and genetic criteria for this disorder were met, cardiac involvement was reported in more than 90% of the patients (139,140). No correlation between severity of neurologic and cardiac disease has been confirmed.

The most common cardiac abnormality in patients with Friedreich's ataxia is concentric left ventricular hypertrophy (141,142). The cardiac pathology in this disorder is differentiated from genetic hypertrophic cardiomyopathy by the lack of cellular disorganization in the ventricular septum. Echocardiographic assessment of systolic and diastolic function is usually normal. The concentric hypertrophy associated with Friedreich's ataxia also tends to have a more benign course than hypertrophic cardiomyopathy, and malignant arrhythmias are distinctly uncommon (143).

A minority of patients with Friedreich's ataxia may develop a dilated cardiomyopathy associated with global hypokinesis. Although much less common than concentric left ventricular hypertrophy, this carries a worse prognosis, and patients usually experience progressive deterioration of cardiac function (144). Symptomatic atrial and ventricular arrhythmias are more common in this subgroup (139).

Peroneal Muscular Atrophy

Peroneal muscular atrophy includes two autosomal dominant genetic disorders collectively called *Charcot-Marie-Tooth neuropathy*. The clinical features include progressive distal lower extremity muscle weakness that begins in the second or third decade of life. Peroneal muscular atrophy does not normally involve the heart. Atrial flutter has been reported (145), but more common findings are conduction disturbances with complete heart block and right bundle branch block, which have been reported in several members of a family (146,147 and 148).

Disorders of the Neuromuscular Junction

Myasthenia Gravis

Myasthenia gravis is caused by an autoimmune process that results in a decrease in the number of acetylcholine receptors at the neuromuscular junction. It affects women more frequently than men and can appear at any age, with increased frequency in the third and fourth decades in women and the sixth and seventh decades in men. Weakness and fatigue are the classic symptoms, with weakness worsening after repeated use and improving after periods of rest.

Substantial data support the association with myocardial disease, particularly with malignant thymoma, although the nature and pathology of this process are unresolved. The cardiac abnormalities may represent a progressive autoimmune process or coincidental findings from other disease processes. Typical cardiac manifestations include nonspecific ECG changes, arrhythmias, and heart failure. The ECG changes have been reversed with neostigmine treatment. Drugs used to treat arrhythmias and cardiac disease, such as quinidine, procainamide, lidocaine, and calcium channel blockers, should be used with caution as they can exacerbate symptoms of myasthenia gravis (149,150).

Disorders of Muscle

Cardiac dysfunction is relatively common with primary disorders of muscle. In some circumstances, these cardiac abnormalities are potentially life-threatening, and cardiac evaluation is an important aspect of the clinical management of these patients. In Duchenne's muscular dystrophy, a dilated cardiomyopathy is present in virtually all patients by the age of 18 years, and management of associated heart failure is an important component of care. In other conditions, such as myotonic dystrophy and polymyositis, the conduction system is preferentially affected and may lead to clinically important arrhythmias or sudden cardiac death. Table 35D.1 summarizes the key neurologic features and cardiac manifestations of these primary muscle disorders.

TABLE 35D.1 DISORDERS OF MUSCLE ASSOCIATED WITH CARDIAC MANIFESTATIONS

Duchenne's and Becker's Muscular Dystrophy

Duchenne's muscular dystrophy is an X-linked recessive disorder with an incidence of 1:3,300 male births (151). This disorder, which is caused by a mutation in the dystrophin gene, usually presents in early childhood with severe and progressive muscle wasting. Death usually occurs by the third decade of life and is caused by respiratory and cardiac compromise.

Cardiac abnormalities are common in Duchenne's muscular dystrophy and include ECG changes, dilated cardiomyopathy, and arrhythmias. Up to 90% of patients with Duchenne's muscular dystrophy have characteristic electrographic abnormalities, which include the presence of tall precordial R waves, an increase in R/S ratio in V_1, and deep, narrow Q waves in the left precordial leads (152,153). Rhythm disturbances are also quite common. The majority of patients have sinus tachycardia, which may be either sustained or labile (14). AV block is less common but has been reported. Accelerated AV conduction may lead to a decrement in the PR interval (154). Dilated cardiomyopathy is also common in Duchenne's muscular dystrophy, and heart failure may be the terminal event in 10% of patients (155). Pathologically, patients with Duchenne's muscular dystrophy demonstrate extensive myocardial fibrosis, most prominently in the posterobasal left ventricular wall (154,156,157). There is usually selective sparing of the septum, right ventricle, and atrium. Degenerative changes of the conduction system have also been described (152). Given the absence of dystrophin in all cells, it is unclear why this pattern of selective myocardial involvement occurs.

Clinical management of cardiac complications in patients with Duchenne's muscular dystrophy is an important aspect of their care. In a large, longitudinal study of more than 300 patients, preclinical evidence of cardiac involvement was present in approximately one-fourth of patients younger than 6 years. Clinically apparent cardiomyopathy typically appeared by age 10 years and was present in virtually all patients by age 18 years (158). Surprisingly, given the prevalence and severity of these cardiac abnormalities, most patients usually remain relatively asymptomatic until late in the course of their disease. This may be because of the disproportionate involvement of the muscles of respiration and because these cardiac abnormalities develop slowly enough to allow some degree of compensation (159). In approximately 10% of patients, the proximal cause of death is directly referable to a cardiac cause (155). Female carriers are not usually symptomatic, although ECG abnormalities have been reported (160).

Becker's muscular dystrophy is a milder variant of Duchenne's muscular dystrophy, which is also caused by a mutation of the dystrophin gene. Becker's dystrophy is characterized by a much later onset of weakness and less fulminant progression. Only 10% of patients are wheelchair bound by the fifth decade of life (161). Cardiac abnormalities are similar to those seen in Duchenne's muscular dystrophy, although usually not as severe. Up to 75% of patients with Becker's muscular dystrophy develop cardiac abnormalities, although the majority of these are subclinical. A subset of patients may develop severe cardiomyopathy, often disproportionate to the degree of skeletal muscle weakness (162,163). It is usual for congestive heart failure to be a presenting symptom (164). Thus, longitudinal noninvasive assessment of cardiac function is warranted in patients with Becker's muscular dystrophy. When cardiac failure occurs, symptoms may develop precipitously. Initial management should include diuretics and afterload reduction. Because Becker's muscular dystrophy is associated with a near normal life expectancy, cardiac transplantation has been performed in these circumstances (165).

Myotonic Dystrophy

Myotonic dystrophy is characterized by myotonia, muscle weakness, frontal balding, cataracts, and gonadal dysfunction. It is an autosomal dominant disease, which is caused by an unstable triple repeat expansion in chromosome 19. A variety of cardiac disturbances have been associated with myotonic dystrophy, including conduction abnormalities, mitral valve prolapse, and cardiomyopathy. These usually become clinically symptomatic several years after the onset of other symptoms associated with myotonic dystrophy.

Conduction disturbances account for the most common abnormality in this condition. Approximately 90% of patients with myotonic dystrophy eventually have ECG abnormalities (166). The most frequent abnormalities are first-degree AV block and intraventricular conduction delay (167,168). In one series, first-degree AV block was seen in approximately two-thirds of patients, and one-third had right bundle branch block or left anterior hemiblock. Left bundle branch block was less common (169). These conduction disturbances are probably progressive, but only a few small longitudinal studies have evaluated the natural history.

Approximately one-fourth of patients have evidence of mitral valve prolapse, although the significance of this is unclear given the high prevalence of this condition in the general population (170,171). In one of the few series examining the cardiac pathology of patients with myotonic dystrophy, fibrosis and fatty infiltrate of the sinoatrial and AV nodes, conduction system, and ventricular walls were noted (172). Recognition of the high incidence of cardiac pathology plays an important role in the management of patients with myotonic dystrophy. In general, the cardiac abnormalities associated with myotonic dystrophy are relatively well tolerated, although 7% of patients have clinical evidence of heart failure, and sudden cardiac death has been reported (173,174).

Periodic Paralysis

There are several forms of familial, or primary, periodic paralysis (175). Hypokalemic periodic paralysis is associated with low potassium at the onset of the paralytic attack. Hyperkalemic periodic paralysis is characterized by increased potassium concentrations at the initiation of the episodes, but normal serum potassium concentrations are common (176). These primary periodic paralyses have some common features. They are generally inherited as autosomal dominant traits with symptoms first recognized early in life and uncommonly after the third decade. Attacks of paralysis are characterized by weakness of the limbs, proximal more than distal, with respiratory muscles rarely involved. Other common features include susceptibility after strenuous exercise, termination of attacks with mild exercise, normal function between attacks (although persistent weakness may develop after years of repeated episodes), and precipitation of attacks with cold.

Cardiac manifestations include the classic ECG abnormalities associated with alterations in serum potassium concentrations. Ventricular electrical instability can occur with premature ventricular complexes, fusion beats, multiple ventricular complexes, and ventricular tachycardias, including bidirectional ventricular tachycardia, which can be treated with potassium supplementation in the hypokalemic variety and epinephrine or glucose and insulin for the hyperkalemic or normokalemic types (177,178,179 and 180).

Limb-Girdle Dystrophies

The limb-girdle dystrophies include several disorders. Autosomal recessive and autosomal dominant inheritance has been reported in different families. Muscle weakness begins in the first to fourth decades, generally in the proximal lower extremity first and the upper extremities later, with variable progression (181). Cardiac involvement is uncommon but can include nonspecific ECG changes, arrhythmias, and conduction system disturbances. Rarely, a cardiomyopathy can occur with heart failure (182,183).

Facioscapulohumeral Dystrophy

Facioscapulohumeral dystrophy is an autosomal dominant disorder characterized by onset of weakness in the first or second decade. Facial muscle weakness is generally the initial manifestation. Subsequent involvement of the upper extremities is followed by proximal lower extremity weakness. Cardiac involvement is extremely uncommon. There are sporadic cases of cardiomyopathy and conduction abnormalities. The rare entity of atrial paralysis or standstill has been reported with a familial occurrence associated with facioscapulohumeral dystrophy (184,185,186 and 187).

X-Linked Humeroperoneal Dystrophy

Typical clinical presentation is proximal upper extremity and distal lower extremity weakness beginning in the first decade of life. Progression is slow and often stabilizes by the second decade, but contractures may develop. Cardiac involvement is common and appears to exclusively affect the atrium (188). Atrial fibrosis and myocyte degeneration may occur. ECG abnormalities include small P waves, atrial fibrillation, atrial flutter, atrial paralysis, and varying degrees of AV block. Permanent ventricular pacing is recommended.

Scapuloperoneal Syndrome

Scapuloperoneal syndrome is an X-linked myopathy characterized by weakness of the shoulder girdle and distal lower extremities. Cardiac abnormalities appear to be isolated to the conduction system, and complete heart block and sudden cardiac death have been reported, generally in the third or fourth decade (189,190).

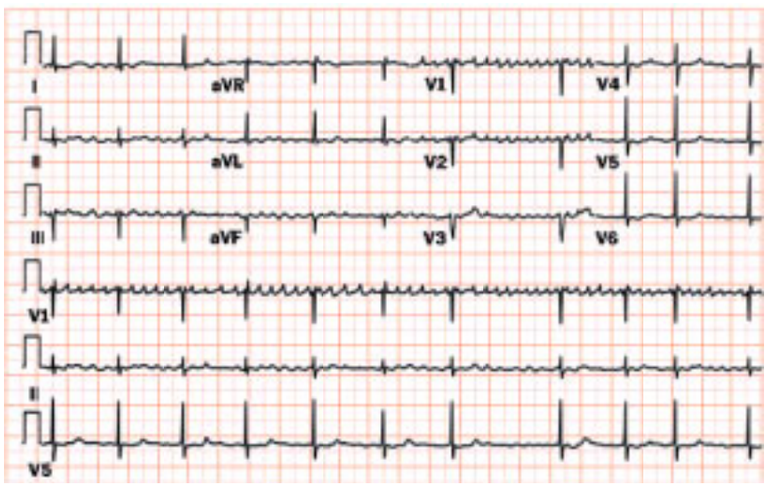
Centronuclear Myopathy

Centronuclear myopathy is a slowly progressive disease characterized by skeletal muscle wasting and characteristic central nuclei on histologic examination (191). There are several forms of the disease with onsets at birth, early childhood, or later in early adulthood. Familial occurrence is reported, but there is no definitive inheritance pattern established. Ptosis of the eyelids is almost universal, as well as hyporeflexia or areflexia. A cardiomyopathy has been described with extensive fibrosis, dilatation, and focal compensatory hypertrophy (192,193 and 194). Progressive heart failure and death can occur at an early age (192).

Polymyositis

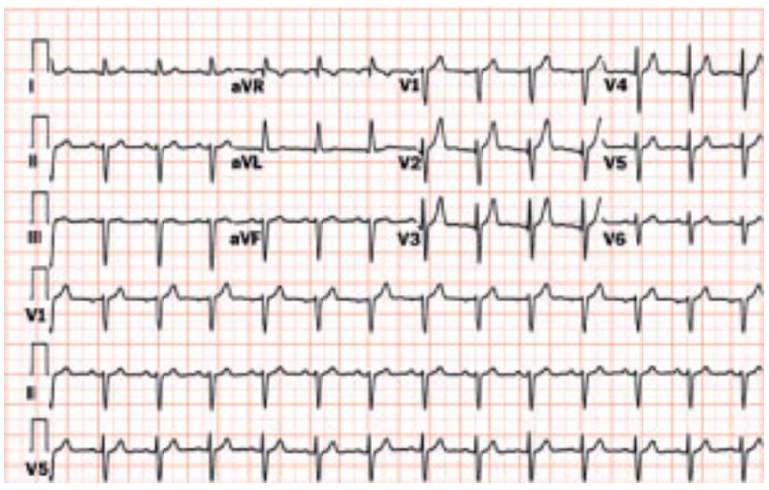
Polymyositis is a nonsuppurative inflammatory process of skeletal muscle and thought to be caused by genetic factors, viral infections, and autoimmune mechanisms. The heart is infrequently involved. The myocardium can have diffuse interstitial and perivascular mononuclear infiltrates, muscle fiber degeneration, and fibrosis (195,196). The conduction system, including the sinoatrial node, bundle of His, and left and right bundle branches, can be involved with similar histologic changes (197,198). Several series have found ECG changes and arrhythmias in more than one-half of the patients (199,200).

ECG abnormalities include atrial fibrillation, atrial flutter, atrial and ventricular premature complexes, AV conduction delay, and bundle branch blocks. Echocardiographic or cardiac catheterization findings include mitral valve prolapse and enhanced cardiac function (200,201). Contrary to these data, a cardiomyopathy with congestive heart failure also has been reported (196,202). It has not been clearly demonstrated that the cardiac abnormalities observed in polymyositis are caused by the same process involving the skeletal muscle disease or whether they represent a coincidental finding or are caused by treatment of the primary disease by agents such as corticosteroids. The high frequency rate of the findings suggests a common pathology.



Atrial fibrillation. Narrow complex QRS with irregular RR intervals. Ventricular rate is controlled.

Atrial flutter. Inverted "saw-tooth" waves in the inferior leads suggest typical atrial flutter.



Left anterior fascicular block. Note left-axis deviation and small Q waves in leads I and aVL. Small Q wave in lead V_4 strongly suggests anterior myocardial infarction.

Left bundle branch block. Wide QRS complex, negative in lead V_1, is associated with secondary T-wave inversions.

Trifascicular block. Note right bundle branch block, left anterior hemiblock, and associated first-degree atrioventricular block.

Kearns-Sayre Syndrome

The mitochondrial myopathies are a heterogeneous collection of diseases characterized by abnormal muscle fibers. Cardiac involvement is rare. The Kearns-Sayre syndrome, however, is characterized by the triad of progressive external ophthalmoplegia, retinal pigmentary degeneration, and heart block (203). The syndrome is generally thought to be acquired, afflicting both sexes equally, with onset before the age of 20. Common features include ataxia, hearing loss, dementia, short stature, delayed secondary sexual characteristics, peripheral neuropathy, and endocrine abnormalities.

Cardiac abnormalities almost exclusively involve the conduction system. Characteristic conduction abnormalities are right bundle branch block, left anterior fascicular block, and atrioventricular block (204,205 and 206). A normal PR is common because of the selective infranodal involvement. Sudden death has been recognized, and pacemaker insertion is recommended (207).

CARDIOVASCULAR ABNORMALITIES IN NEURODEGENERATIVE DISEASES

Parkinson's Disease

Cardiovascular abnormalities are common in Parkinson's disease and may be challenging to manage. In particular, autonomic dysfunction is prevalent, and orthostatic hypotension often exacerbates postural instability, one of the hallmarks of this neurodegenerative disorder. Lewy bodies, the eosinophilic cytoplasmic inclusions characteristic of Parkinson's disease pathology, have been identified throughout the autonomic nervous system, including the hypothalamus, sympathetic system (thoracic intermediolateral nucleus and sympathetic ganglia), and parasympathetic system (dorsal vagal nucleus and parasympathetic nuclei). Of note, there is also evidence of cardiac sympathetic denervation, and Lewy bodies have been identified in the cardiac plexus (208). Myocardial imaging with ^{123}I-metaiodobenzylguanidine has demonstrated functional loss of cardiac sympathetic tone associated with these anatomic abnormalities (209). Interestingly, the marked decrease in myocardial ^{123}I-metaiodobenzylguanidine uptake appears to be specific for Parkinson's disease and may have some diagnostic value in differentiating atypical Parkinson's disease from other neurodegenerative disorders associated with extrapyramidal features (209). These abnormalities in cardiac autonomic tone seen in Parkinson's disease may also have contributed to several sporadic cases of sudden cardiac death associated with a prolonged QTc interval (210).

Alzheimer's Disease

Although less systematically studied, dysautonomia has also been described in Alzheimer's disease (211). Vascular disease is also associated with dementia and is often difficult to clinically distinguish from Alzheimer's disease. A large population-based study in Rotterdam explored the relationship between atherosclerosis and dementia. Evaluation of 284 demented patients and 1,698 healthy controls revealed that the odds ratio for Alzheimer's disease in those with severe disseminated atherosclerosis compared with those with normal vasculature was 3.0 (212). Although the biology for the association between atherosclerosis and Alzheimer's disease remains undefined, presence of the APOE4 allele appears to be a risk factor. Patients with atherosclerotic cerebrovascular disease and Alzheimer's disease have a higher prevalence of the apolipoprotein E_4 genotype.

CONTROVERSIES AND PERSONAL PERSPECTIVES

A large clinical interface between the practices of cardiology and neurology is becoming increasingly apparent. As cardiac and neurologic intensivists, we see this in a number of situations. The advent of specialized neurocritical care units in parallel with coronary care units is but one example. Another is the American Heart Association emphasis on diagnosis and treatment of "brain attack." We continue to focus on the breakdown of subspecialty barriers because with this approach we will optimize the clinical management of these patient populations.

THE FUTURE

Intensive collaboration between cardiologists and neurologists is ongoing and will result in incredible advances in our understanding of disease mechanisms and therapeutic interventions. Studies evaluating the ability of the brain to withstand ischemic insults, exploration of the use of glycoprotein IIb/IIIa inhibitors and other anticoagulants in patients with both cardiovascular and cerebrovascular disease, and investigation of diagnostic strategies with various biomarkers to diagnose stroke and myocardial infarction are being conducted. Furthermore, as the genetic basis of diseases continues to be unraveled, there will be tremendous opportunities to gain further understanding of the relationships between neuromuscular disorders and associated cardiac manifestations. Work in the basic sciences, clinical trials, and the important translation of scientific discoveries to the bedside will provide ample opportunity in the coming years for cardiologists and neurologists to work together on exciting projects.

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35E

THE HEART AND OTHER ORGAN SYSTEMS:

DAVID H. LEWIS

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The rheumatic diseases are a heterogeneous group of illnesses with protean manifestations and multisystem organ involvement. Although each individual disorder is relatively rare, together they represent important causes of morbidity and mortality worldwide. It is not at all unusual for specialists in cardiovascular medicine to encounter patients with these disorders in the office setting, hospital, or emergency department. Cardiac manifestations range from unusual to prominent (Table 35E.1) and from mild to dramatic. Occult cardiovascular involvement is common, is frequently detectable on noninvasive studies, and has important prognostic implications. Cardiovascular death is common, may be due to disease-specific cardiac involvement or secondary effects of disease on the heart, and underscores the importance of primary and secondary preventive strategies in this patient population (Table 35E.2).

Disorder	Pericardial	Valvular	Myocardial	Coronary	Arrhythmic
Systemic lupus erythematosus	25%	Rare	5%–10%	Rare	Rare
Rheumatoid arthritis	10%	Rare	Rare	Rare	Rare
Systemic sclerosis	7–10%	–	10%	–	10%
Kawasaki disease	Rare	1%	30%	20%,[a] 8%[b]	rare
Takayasu's disease	2%	1–20%	Rare	5–10%	1%
Ankylosing spondylitis	Rare	10–20%	Rare	Rare	10%
Churg-Strauss syndrome	20–32%	–	13–48%	Rare	Rare
Polyarteritis nodosa	2–3%	–	10%	5%	Rare
Giant cell arteritis/temporal arteritis	Rare	5–10%[c]	Rare	Rare	–
Wegener's granulomatosis	6–10%	Rare	2%	1%	1–2%
Polymyositis/dermatomyositis	1%	Rare	5%	–	6%

[a]Untreated.
[b]Treated.
[c]Valvular involvement secondary to aortic disease.

TABLE 35E.1 INCIDENCE OF CLINICAL CARDIAC MANIFESTATIONS OF SELECT RHEUMATIC DISORDERS

Disorder	Annual incidence per million population	Clinical cardiac involvement	Cardiac involvement on autopsy	Most common causes of death
Systemic lupus erythematosus	40–80	50%	>60%	Renal, infection, cardiac
Rheumatoid arthritis	250–500	10–15%	>30%	Cardiac, infection, cancer
Systemic sclerosis	18	10%	>30%	Renal, cardiac, pulmonary
Kawasaki disease	105 (Japan); 5–15 (United States)	1–5%	>80%[a]	Cardiac
Takayasu's disease	2.6	20–30%	20–30%	Cardiac, stroke
Ankylosing spondylitis	70	10–20%	20%	Cardiac, stroke, pulmonary
Churg-Strauss syndrome	2.4	40–60%	>60%	Cardiac, renal, stroke
Polyarteritis nodosa	7	10–30%	>60%	Renal, stroke, cardiac
Giant cell arteritis	170[b]	5–10%[c]	5–10%[c]	Cardiac, stroke, renal
Wegener's granulomatosis	8.5	10–40%	>60%	Infection, cardiac, renal
Polymyositis/dermatomyositis	10	6–10%	>25%	Infection, cancer, cardiac

[a]Among those dying during the acute phase of the disease.
[b]In individuals older than 50 years.
[c]Valvular involvement secondary to aortic disease.

TABLE 35E.2 DISEASE INCIDENCE, FREQUENCY OF CARDIAC INVOLVEMENT, AND CAUSES OF DEATH IN PATIENTS WITH SELECT RHEUMATIC DISORDERS

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by antibodies against a variety of cellular antigens, resulting in multisystem organ dysfunction. Biett (1) first described the dermatologic manifestations of SLE in 1828. Nearly a half-century passed before it was recognized that SLE involved organs other than the skin, and not until a half-century after that was histopathologic proof of cardiac involvement systematically described by Libman and Sacks (2). Because of the protean manifestations of the disease, a diagnosis of SLE relies on the fulfillment, over time, of four criteria from a list of specific laboratory, histologic, and clinical findings (3). The most common presenting signs and symptoms are polyarthritis and dermatitis (4).

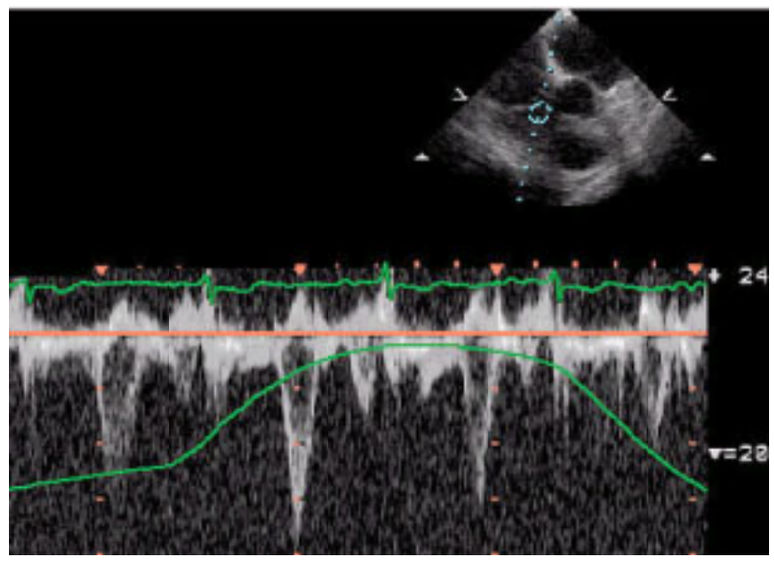
Discoid lupus. The skin lesion shown is raised and scaly, with an erythematous rim, and associated with follicular plugging and telangiectasia (*arrows*).

SLE affects 40 to 50 per 100,000 individuals (5) and has an annual incidence of 4 to 8 in 100,000 worldwide. Survival rates among patients with SLE have improved dramatically with the introduction of corticosteroid therapy and advances in supportive care. The most common causes of death in patients with SLE are active SLE (particularly nephritis), infection, and cardiovascular events (6,7). Current 5-, 10-, and 20-year survival rates are estimated to be 93%, 85%, and 68%, respectively (7). Mortality analyses have shown a reduction in the percentage of deaths due to active SLE and an increase in the percentage of deaths due to infection and cardiovascular disease.

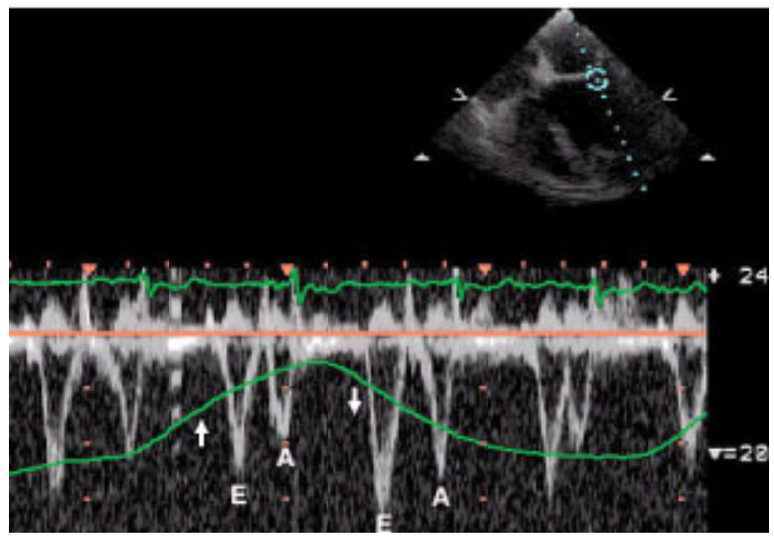
SLE is a pancarditis in which morbidity and mortality are the result of pericarditis, myocarditis, endocarditis, and coronary arteritis. More than 50% of patients with SLE experience clinical cardiovascular involvement during the course of the illness (8). Asymptomatic cardiac involvement is detected in a number of additional patients at autopsy. Cardiac involvement is rarely the initial presenting symptom of SLE (5).

Pericardial Involvement

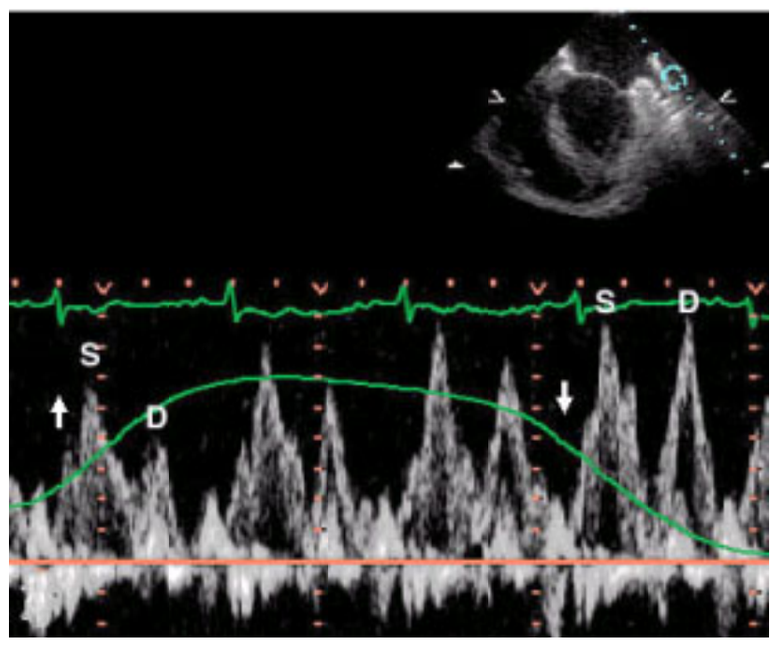
Pericarditis is the most common cardiovascular manifestation of SLE. It has an estimated clinical frequency of 25% and autopsy frequency of 62% (9). Echocardiographically, pericardial abnormalities are present in 7% to 54% of asymptomatic individuals (10,11,12 and 13). Acute pericarditis is the only cardiovascular manifestation of SLE that is included in the diagnostic criteria for the disease (3), and it commonly occurs as part of a generalized serositis. It is also the only cardiovascular manifestation strongly related to disease activity, as assessed by clinical and laboratory variables (10). Histopathology of pericardial tissue reveals proliferation of the pericardial vessels, vasculitis, fibrosis, and fibrin stranding (14).



Pulsed wave Doppler through the tricuspid valve of a patient with constrictive pericarditis. Note the decrease of the E wave with inspiration due to interventricular dependence.

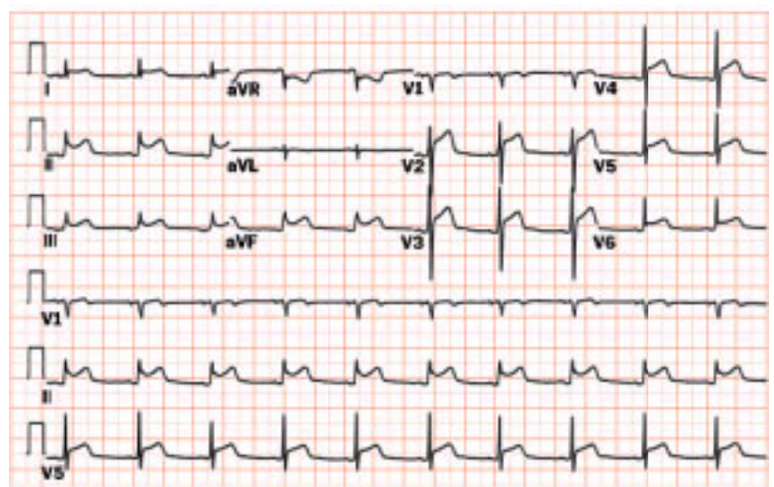


Pulsed wave Doppler of the mitral valve inflows of a patient with constrictive pericarditis. Note the decrease of the E wave during inspiration (*upward arrow*) due to interventricular dependence, and the increase in the E wave during expiration (*downward arrow*) for the same reason.



Pulsed wave Doppler of the pulmonary veins of a patient with constrictive pericarditis. Note the inspiratory decrease of the S and P waves and the expiratory increase due to interventricular dependence. (Inspiration is denoted by the upward arrow and expiration by the downward arrow).

Pericarditis associated with SLE manifests clinically as chest discomfort that is frequently pleuritic and worse in the recumbent position. Examination may reveal fever, tachycardia, a pericardial friction rub, and diminished breath sounds as a result of concomitant pleuritis with effusion. Laboratory features include leukocytosis, elevated sedimentation rate, and elevated titers of anti–double-stranded DNA, which are indicative of active SLE. Chest radiography may reveal an enlarged cardiac silhouette and pleural effusion. Electrocardiography (ECG) typically reveals diffuse ST-segment elevation and PR-segment depression, except in lead aVR, where these findings are reversed. Pericardial fluid is exudative and characterized by high protein levels, normal glucose levels, a predominance of polymorphonuclear cells, low complement levels, and the ability to fix complement (15). The presence of LE cells and immune complexes in the pericardial fluid is not diagnostic, but it supports an immune-mediated cause of pericardial disease in patients with SLE (16).



Acute pericarditis. Note diffuse, marked ST-segment elevation with PR-segment elevation in lead aVR.

Complications of pericarditis include pericardial tamponade, purulent pericarditis, and constrictive pericarditis. These entities are uncommon, but not rare, in SLE-induced pericarditis. Pericardial tamponade occurs in 0.25% to 2.50% of patients (6,9,14). It may be due to exuberant inflammation with translocation of fluid, hemorrhage, or, rarely, aortic dissection. Pericardiocentesis may be lifesaving in the critically ill patient, but a high rate of complications has been reported in this population. Pericardial window is the definitive procedure for treatment of patients with recurrence. SLE is an oft-quoted risk factor for purulent pericarditis, even though it occurs in only 0.250% to 0.375% of patients (6,9). Purulent pericarditis may be caused by hematologic seeding of an existing pericardial effusion or by direct extension from a penetrating endocardial abscess or empyema. *Staphylococcus aureus* is the most frequently encountered pathogen. Treatment includes surgical drainage and antibiotics. Constrictive pericarditis typically presents with signs and symptoms of right-sided heart failure, such as fatigue, dyspnea with exertion, jugular

venous distention, hepatomegaly, ascites, and edema. Constrictive pericarditis, when severe, is best managed with pericardiectomy.

Video 35E.1 Apical four-chamber view demonstrating a large pericardial effusion causing tamponade. Note the inability of the right side to fill. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35E.2 Subcostal short-axis view of a large pericardial effusion causing tamponade. Note that the right side is small and underfilled. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pericardial tamponade. Low QRS voltage and electrical alternans are characteristic findings of tamponade.

Video 35E.3 Transesophageal echo (four-chamber view) demonstrating constrictive pericarditis. Note the abnormal septal bounce and the tethering of the right atrium and right ventricle by the thickened pericardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35E.4 Aortic dissection (left anterior oblique). Type A dissection of the aorta is manifested on the cine image loop by a mobile intimal flap extending from the mid–ascending aorta to the descending thoracic aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35E.5 Aortic dissection (left anterior oblique). Type B dissection of the aorta extending distally from the isthmus, just after the left subclavian artery, to the abdominal aorta. A communication between the true and false lumen is seen in the proximal portion of the descending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Valvular Involvement

Valvular pathology that is attributable to SLE is seen in nearly one-half of all patients in whom SLE is found at autopsy (9,17,18). Libman and Sacks (2) were the first to describe the pathognomonic valvular lesion of SLE. Gross (19) later described them as gray-pink and flat or raised clusters that may be found on either side of the valves, in the valve pockets, or adherent to the chordae or myocardium (Fig. 35E.1). Antiphospholipid antibodies have also been demonstrated within valvular lesions, leading some to suggest that endocardial damage and thrombosis may initiate lesion formation (20).

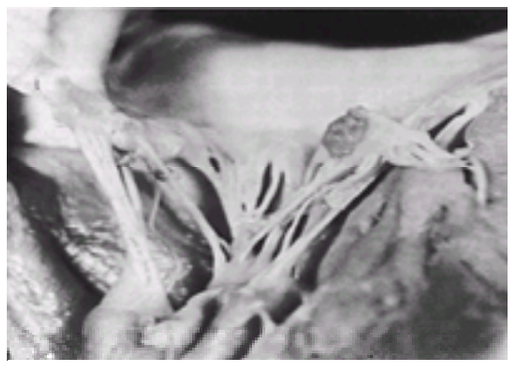
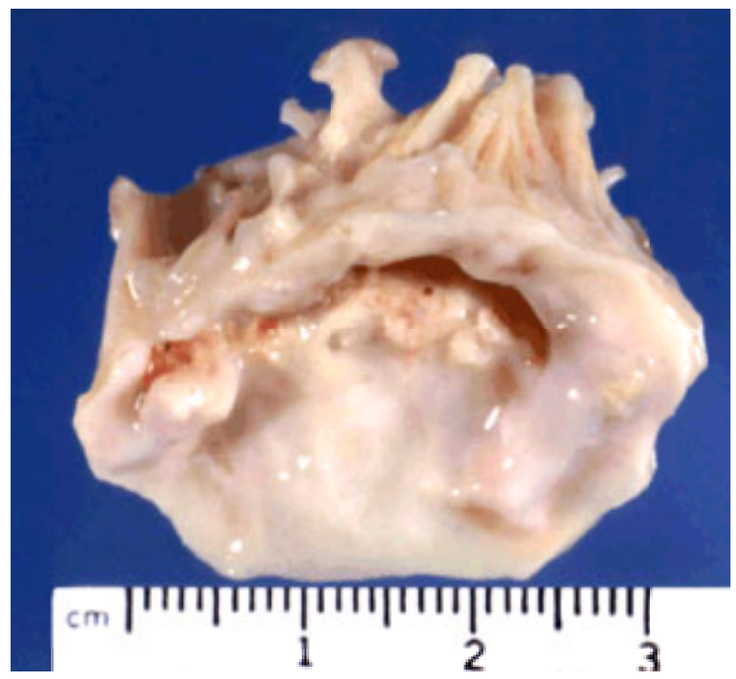


FIGURE 35E.1 Characteristic Libman-Sacks vegetation on the posterior cusp of the mitral valve. (From Cosh JA, Lever JV. *Rheumatic diseases and the heart*. Berlin: Springer-Verlag, 1988, with permission.)

Video 35E.6 Ventricular noncompaction. Apical four-chamber view without **(A)** and with **(B)** intravenous contrast of a patient with ventricular noncompaction. Note the characteristic trabeculations and recesses that result from arrest on intrauterine development. *This video must be viewed with QuickTime. If you do not have*

QuickTime you may download it here.

Video 35E.7 Ventricular noncompaction. Apical four-chamber view without **(A)** and with **(B)** intravenous contrast of a patient with ventricular noncompaction. Note the characteristic trabeculations and recesses that result from arrest on intrauterine development. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Rheumatic mitral valve. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

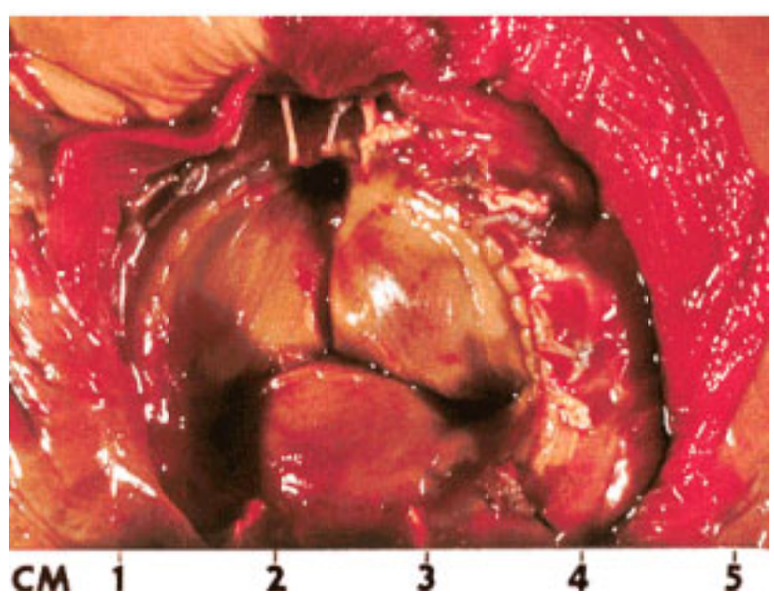
Microscopically, Shapiro identified three main zones within a valvular lesion. The zone of neovascularization is located near the normal valvular structure and consists of maturing fibroblasts, connective tissue, and inflammatory cells. The zone of organization is in the middle of the lesion and consists of proliferating blood vessels. The zone of exudation is the outermost zone and consists of fibrin, proteinaceous material, and hematoxylin-stained bodies. Shapiro (21) also identified immune complexes within the zone of neovascularization, which suggests that a pathogenic role is probable.

Improvements in survival rates and the use of corticosteroids have changed the face of valvular heart disease for patients with SLE. Roberts (22) elegantly compared valvular pathology in the pre- and postcorticosteroid eras. Early autopsy studies in the precorticosteroid era reported equal involvement of left- and right-sided heart valves and a predominance of “fresh” vegetations consisting of inflammatory cells, neovascularization, and fibrin deposition (2,17). Recent studies have found more left-sided valvular lesions and a predominance of “healed” vegetations with organization and fibrosis (18). “Healing” and fibrosis may predispose the valve to impaired mobility of the valve apparatus and thus to regurgitation.

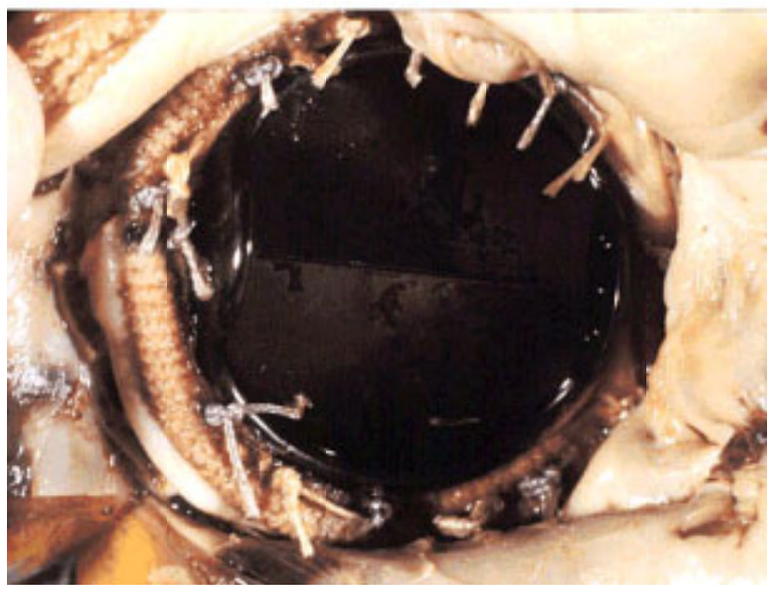
Patients with SLE who have antiphospholipid antibodies are more likely to manifest valvular abnormalities than those without these antibodies. Khamashta and colleagues (23) and Nihoyannopoulos and associates (12) independently reported an approximately threefold increase in the incidence of valvular abnormalities among unselected patients with SLE who had antiphospholipid antibodies, compared with the incidence among SLE patients who did not have antiphospholipid antibodies. In a smaller study, Roldan and colleagues (24) did not confirm this association. Whether or not antiphospholipid antibodies increase the frequency of *clinically important* valvular disease is unknown.

Clinically important valvular disease is much less common than asymptomatic disease detected by echocardiography or autopsy. Hemodynamically significant valvular disease may be caused by any combination of the following: valvulitis, fibrosis, infective or noninfective endocarditis, ischemic cardiomyopathy, papillary muscle dysfunction, and aortic dissection. Clinically important aortic regurgitation appears to be more frequent than mitral regurgitation, but the true incidence of each is unknown (9). Mitral stenosis, aortic stenosis, and right-sided valvular disease are all rare. Early reports of valve replacement in patients with SLE found an extremely high associated mortality, approaching 25% (25); however, recent reports have been more encouraging (26). Mechanical prostheses, bioprosthetic valves, and homografts have all been used to treat this condition. Patients with SLE are at high risk for hemorrhagic complications from anticoagulation therapy, because of the frequency of intracranial and pericardial disease in this population. However, they often have other indications for anticoagulation therapy, such as the antiphospholipid antibody syndrome with clinical thrombosis. Clearly, the choice of valvular prosthesis must be individualized.

Video 35E.8 Long-axis 120-degree transesophageal view of a rheumatic aortic valve with central aortic insufficiency due to furled, restricted leaflets. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Porcine prosthetic mitral valve. In this example, the valve is normal and the suture line is intact.



Normal St. Jude valve in the mitral position.

Aortic thrombus in a patient with lupus anticoagulant. A probe is placed behind the thrombus within the lumen of the aorta (*yellow arrow*).

The lesions of Libman-Sacks endocarditis act as a nidus for infective endocarditis. Clinical infective endocarditis occurs in 1% to 2% of SLE patients. At autopsy, it is found in nearly 5% (9). Patients with SLE and significant valvular dysfunction who are undergoing invasive medical or dental procedures are at moderate risk for infective endocarditis and should receive antibiotic prophylaxis, according to published guidelines (27).

Myocardial Involvement

Myocarditis is found commonly at autopsy of patients who had SLE. In the precorticosteroid era, myocarditis was found in nearly one-half of all SLE patients at autopsy (9). More recent autopsy series have shown a prevalence of less than 10% (18). When myocarditis is found, however, it typically involves only small patches of myocardium, and only 5% to 10% of SLE patients experience clinical myocarditis (9). Histopathology reveals perivascular and interstitial inflammation characterized by plasma cells, mononuclear cells, myocardial degeneration and regeneration, and, occasionally, necrosis. SLE is generally a corticosteroid-responsive disorder, but no randomized trials of the use of immunosuppressive therapy for myocarditis in patients with SLE have been performed. Trials of the use of immunosuppressive agents to treat other types of myocarditis have been disappointing. Endomyocardial biopsy should be considered when a patient with SLE develops severe myocarditis, to guide immunosuppressive therapy.

Congestive heart failure (CHF) is common and usually multifactorial in patients with SLE. It is the cause of death in 1% to 5% of patients with SLE (6,7). Ischemia, valvular heart disease, hypertension, and myocarditis may produce either systolic or diastolic dysfunction. Mild global left ventricular systolic dysfunction is present in 5% to 15% of patients with SLE (10,28). Echocardiography has detected abnormalities of myocardial relaxation in young, asymptomatic SLE patients (29,30). Other studies, however, have not reproduced this in normotensive SLE patients (31).

Coronary Involvement

Coronary artery disease (CAD) has become an increasingly important cause of morbidity and mortality among patients with SLE. Ischemic heart disease in patients with SLE presents, in order of decreasing frequency, as acute myocardial infarction (MI), CHF, sudden cardiac death, and angina pectoris. It is estimated that 3% to 15% of patients with SLE die from acute MI (7,32,33). Ischemic coronary events are attributed most frequently to coronary atherosclerosis, less frequently to coronary arteritis, and rarely to embolic phenomena involving the coronary circulation.

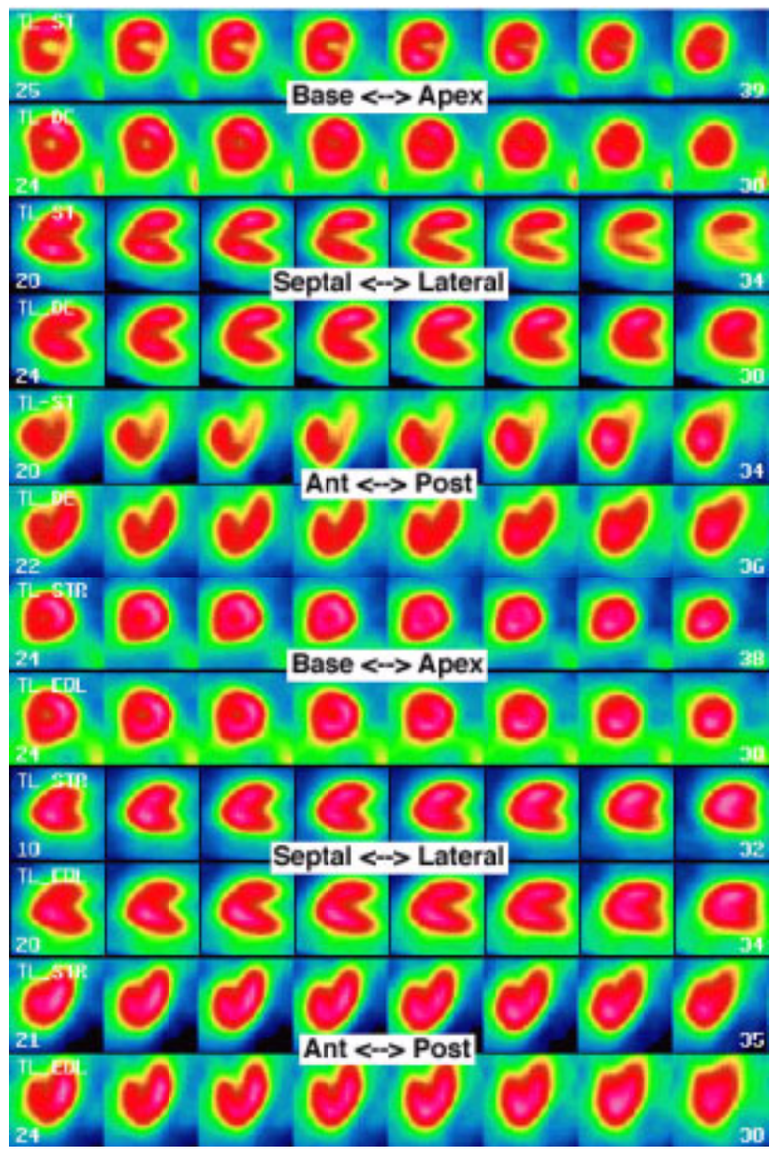
Video 35E.9 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35E.10 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

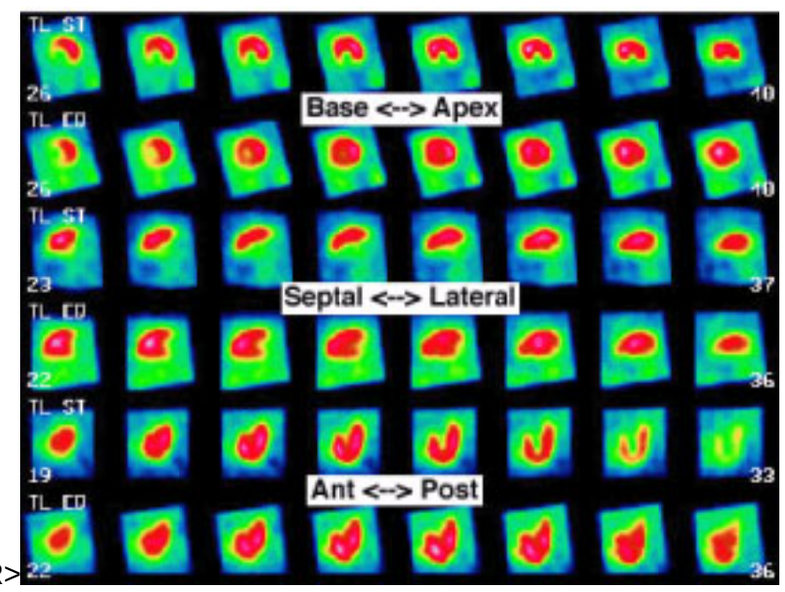
Video 35E.11 Anomalous origin of the left main trunk from the right coronary sinus with a course anterior to the pulmonary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Coronary atherosclerosis is accelerated in patients with SLE. This likely is related to the effects of corticosteroids, the prevalence of traditional risk factors among patients with SLE, and coronary inflammation. The role of antiphospholipid antibodies in the pathogenesis of CAD and the occurrence of subsequent coronary events is controversial. Patients with SLE have a fivefold risk of acute MI, compared with age-matched control subjects (34). Women 35 to 44 years of age were found to have a relative risk of 52 (95% confidence interval, 21.6 to 98.5) for MI, compared with matched controls (32). Two groups have found a 40% prevalence of asymptomatic

CAD in patients by nuclear stress testing (28,35). Autopsy studies have demonstrated a 50% prevalence of moderate to severe CAD both in general SLE populations (7) and in SLE patients less than 37 years of age (36).



Thallium-201 single-photon emission computed tomography stress and delayed images (A). Transverse, sagittal, and coronal plane images demonstrating lateral wall ischemia in a patient with severe proximal left circumflex artery stenosis. Thallium-201 single-photon emission computed tomography stress and equilibrium images (B). Transverse, sagittal, and coronal plane images obtained from the same patient as in A after successful intervention for severe proximal left circumflex artery stenosis (normal study).

CENTER> 

Thallium-201 single-photon emission computed tomography stress and equilibrium images. Transverse, sagittal, and coronal plane images demonstrating inferior and posterior wall ischemia in a patient with a severe proximal stenosis in a dominant right coronary artery.

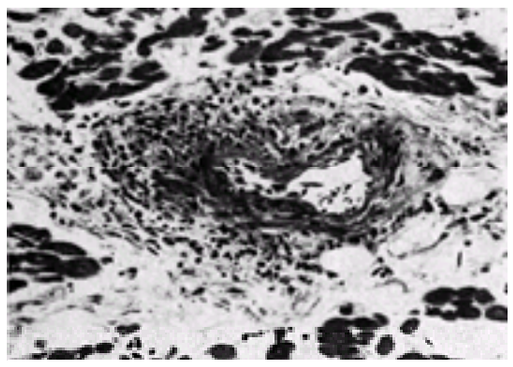
Traditional risk factors for CAD are present in most patients with SLE. Hypertension is present in 38% to 66%, hyperlipidemia in 5% to 50%, tobacco abuse in 38% to 50%, and diabetes mellitus in nearly 10% (32,35,37). Corticosteroid therapy may contribute to hypertension, hyperlipidemia, and diabetes.

Coronary arteritis accounts for less than one-half of the cases of ischemic heart disease that occur in individuals with SLE. The diagnosis of coronary arteritis is made histopathologically, but it may be suggested during coronary angiography by aneurysmal dilation of a coronary segment or an abrupt change in lesion severity, although these changes can also be seen in the absence of arteritis. Discrepancies between angiographic and histopathologic diagnosis of coronary arteritis occur commonly. Improvements in lesion severity have been observed in coronary arteritis after high-dose corticosteroid therapy (38). A trial of corticosteroid therapy may be justified for stable patients whose clinical course is strongly suggestive of coronary arteritis, but long-term administration likely will further accelerate the atherosclerotic process.

Corticosteroid therapy and improvements in patient survival rates have also changed the face of CAD in patients with SLE (22). In the precorticosteroid era, epicardial CAD was infrequent. Small-vessel arteritis and small-vessel occlusion by fibrinous material were more prominent (17). More recent autopsy series reveal severe epicardial atherosclerosis in nearly 50% of patients (7,18,36). Important coronary events resulting from embolization of valvular vegetations have been reported (18), but these are considered rare.

Conduction System Involvement

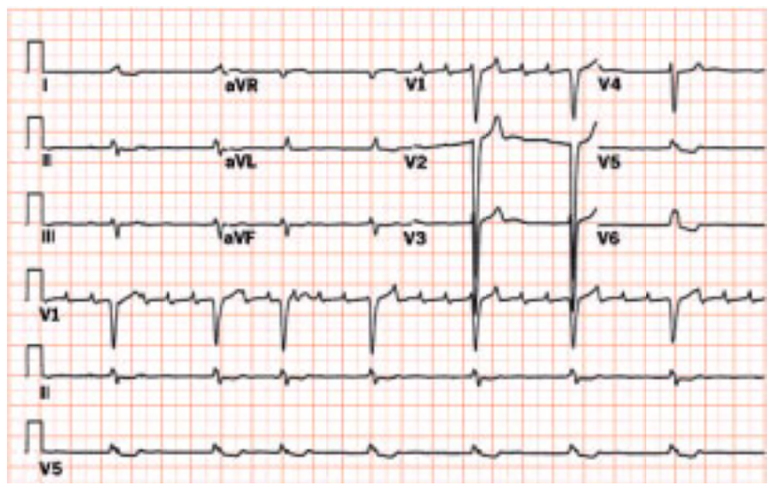
SLE infrequently causes clinical arrhythmias in adults. Histopathologic correlation of SLE-related destruction of the conduction system with cases of clinical arrhythmia has, however, been documented (39). Arteritis of the sinoatrial (SA) nodal and atrioventricular (AV) nodal arteries has been observed (*e*Fig. 35E.1.1), as has fibrosis of the SA and AV nodes.



***e*FIGURE 35E.1.1** Sinus node artery inflammation. No clinical arrhythmia was reported in this case. (Reprinted from Straaton KV, Chatham WW, Reveille JD, et al. Clinically significant valvular heart disease in systemic lupus erythematosus. *Am J Med* 1988;85:645–650, with permission.)

Evidence also exists for the occurrence of autoimmune injury to the conductive tissue. Adults with SLE and anti-Ro antibodies are more likely to have evidence of heart block on ECG than are adults with SLE and no anti-Ro antibodies (40). No recent prospective studies have addressed the prevalence of symptomatic or asymptomatic conduction system abnormalities in adult patients with SLE.

Neonatal SLE occurs in newborns of mothers with SLE, typically lasts 3 to 6 months, and resolves on clearance of maternal immunoglobulin G from the infant's circulation. Transient symptoms such as photosensitivity, cytopenias, and hepatitis may occur. Unlike these transient manifestations of neonatal SLE, congenital complete heart block (CHB) is usually permanent. The presence of anti-Ro antibodies in maternal serum was first recognized by Scott and colleagues (41) as a risk factor for congenital CHB. Anti-La antibodies are also associated with congenital CHB. The antigen against which anti-Ro antibodies are directed has been demonstrated in the nuclei of myocardial cells and conduction tissue cells (42). Immunoglobulin and complement deposition has been demonstrated in all cardiac tissues of affected infants at autopsy. Approximately 3% of infants whose mothers are antibody positive develop CHB (22).



High-grade atrioventricular block. Note marked discrepancy between atrial and ventricular heart rates.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology. It is characterized primarily by an erosive arthritis with progressive joint destruction, deformation, and immobility. RA has a prevalence of 1% worldwide and an annual incidence of 250 to 500 cases per 1 million individuals (43). The diagnosis relies on a variety of clinical, laboratory, and radiographic findings. Extraarticular manifestations are common but usually are overshadowed by joint involvement.

Four of the following criteria must be met for a diagnosis of RA to be indicated: morning stiffness that lasts at least 1 hour; arthritis affecting three or more joints; arthritis affecting the proximal interphalangeal, metacarpophalangeal, or wrist joints; symmetric arthritis; rheumatoid nodules; the presence of rheumatoid factor; and radiographic evidence of joint erosion or periarticular osteopenia (44). Symptoms should be present for 6 weeks before a diagnosis is made.

Caring for individuals with RA requires a multidisciplinary approach that includes the efforts of physicians, nurses, and physical and occupational therapists. Non–weight-bearing exercise, joint orthotics, and joint replacements may significantly improve patient function.

Steroids and nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase-2 inhibitors, are the backbone of symptomatic therapy. Disease-modifying antirheumatic drugs include hydroxychloroquine, penicillamine, azathioprine, leflunomide, sulfasalazine, gold preparations, and methotrexate. Newer biologic response modulators, including etanercept and infliximab, which inhibit the activity of tumor necrosis factor-a, have been beneficial in patients who are resistant or intolerant to disease-modifying antirheumatic drugs. The use of etanercept in the treatment of heart failure is being investigated in the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines trial. Conversely, concern has been raised regarding the safety of using cyclooxygenase-2 inhibitors in patients with cardiovascular disease. Anecdotal reports and initial clinical trial results suggest that these drugs have a potential prothrombotic effect, including an increased incidence of MI. Further study is required.

The profound morbidity associated with RA is undisputed. However, only recently has the substantial increase in mortality associated with the disease come to be appreciated. Standardized mortality ratios, which compare observed to expected event ratios in a population, reveal a greater than twofold increase in mortality among RA patients compared to that among epidemiologic controls (45). Cardiovascular disease is the most common cause of death in patients with RA (45,46 and 47).

Pericardial Involvement

Cardiac involvement in RA was first reported in 1881 by Charcot, who described a patient with clinical and autopsy evidence of pericarditis (48). Autopsy evidence of pericarditis is now recognized in nearly one-third of patients who have RA (49). Clinical pericarditis is much less common, occurring in fewer than 10% of patients who have RA in most series (49,50). Echocardiographic evidence of pericardial disease occurs in 8% to 50% of asymptomatic RA patients (51,52 and 53) and may be more common among those with subcutaneous rheumatoid nodules (52).

The pericardial fluid of patients who have RA with cardiac involvement is typically exudative and characterized by elevated leukocyte, protein, and lactate dehydrogenase levels. Glucose and complement levels are low, with undetectable glucose levels being reported in some instances. Histopathologic examination of removed pericardium may reveal nonspecific fibrosis or may, rarely, reveal fibrinoid necrosis, palisaded inflammatory cells, and plasma cells, changes similar to those seen in rheumatoid nodules (*e*Fig. 35E.1.2).

***e*FIGURE 35E.1.2** Chronic pericarditis in a patient with rheumatoid arthritis demonstrating rheumatoid nodules (*arrows*) with central necrosis (N) and surrounding inflammation. P, parietal pericardium; V, visceral pericardium. (Reprinted from Burney DP, Martin CE, Thomas CS, et al. Rheumatoid pericarditis. *J Thorac Cardiovasc Surg* 1979;77:513, with permission.)

Pericarditis may be asymptomatic and detected by physical examination, echocardiogram, or ECG. When symptoms are present, positional chest pain is most common, followed by dyspnea and swelling. NSAIDs or corticosteroids may be used for treatment, but trials comparing treatment strategies are lacking. Constrictive pericarditis has been reported in 0.64% of men and 0.06% of women (54). Tamponade is less common. Management of tamponade in patients with RA is complicated by a poor response to medical therapy and by frequent loculations. Pericardiocentesis may be attempted in patients with tamponade, but most patients with either tamponade or constrictive pericarditis eventually require pericardiectomy (55). Clinical predictors of poor outcome in patients with pericardial disease include advanced age, jugular venous distension, hypotension, and other extraarticular RA manifestations (50).

Valvular Involvement

Hemodynamically significant, histologically proven valvular involvement in RA is rare. Many of such patients reported in the literature showed evidence of superimposed rheumatic valvular heart disease. In 1941, Baggenstoss and Rosenberg (56) were the first to describe valvular disease in patients with RA. Roberts and coworkers (57) went on to describe in more detail the gross findings, noting firm, smooth, yellow deposits with a predilection for left-sided heart valves. Histologic changes may consist of bland fibrosis or may reveal inflammatory changes similar to rheumatoid nodules (57). Concurrent involvement of more than one valve is common among patients with valvular disease.

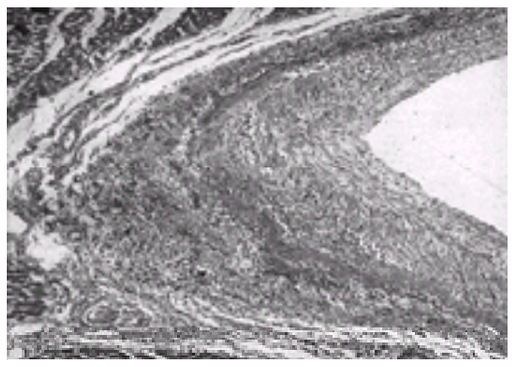
Myocardial Involvement

Rheumatoid nodules have been found within the myocardium of patients with RA. Sensitive echocardiographic techniques used to measure diastolic function have revealed abnormalities of myocardial relaxation in nearly 25% of patients with RA (53). However, clinical CHF and systolic dysfunction that can be attributed to RA are rare.

Coronary Involvement

Acute MI is common in patients with RA. This seems to reflect the high risk of MI in all adults, rather than a profound disease-specific increase in risk due to RA. A 51% excess in death due to ischemic heart disease was noted in one retrospective study (47), but another retrospective case-control series found an increase in MI only among RA patients who tested positive for rheumatoid factor (58), and other studies have found no increase in incidence of MI (46). In fact, autopsy series have actually suggested that patients with RA have a lower risk of MI than do control subjects, despite similar incidence of coronary atherosclerosis (59). The authors hypothesized that aspirin use may protect RA patients from coronary thrombosis.

Coronary atherosclerosis is an inflammatory process. Therefore, care must be taken when coronary lesions in patients with RA are ascribed to arteritis. Few reports of acute MI due to coronary arteritis, with histologic confirmation, have been published (eFig. 35E.1.3) (60,61). Coronary lesions in these patients resemble rheumatoid nodules, consisting of palisaded inflammatory cells, fibrinoid necrosis, and plasma-cell infiltration. Atheromatous changes, such as foam cells, cholesterol clefts, and calcification, were lacking.



***e*FIGURE 35E.1.3** Subacute coronary arteritis with mononuclear cell infiltration and fibrinoid necrosis in a patient with rheumatoid arthritis. (Reprinted from Karten I. Arteritis, myocardial infarction, and rheumatoid arthritis. *JAMA* 1969;210:1717–1720, with permission.)

Conduction System Involvement

CHB due to RA is rare, but it has been reported. Autopsy studies have confirmed involvement of the cardiac conduction system by rheumatoid nodules (62). Other potential mechanisms for heart block in patients with RA include vasculitis of the arterial supply to conductive tissue, hemorrhage into a rheumatoid nodule, extension of an inflammatory lesion from the aortic or mitral valve, and associated amyloid deposition. Ahern and colleagues (62) found CHB in 0.1% of RA patients and noted that it was more common among female patients, tended to be sudden in onset, and was more prevalent among patients who had subcutaneous nodules (62).

SYSTEMIC SCLEROSIS

Background

Systemic sclerosis (SSc) is a rare connective-tissue disorder of unknown etiology, characterized by abnormal collagen deposition and fibrosis of the skin, viscera, and vasculature. Five- and 10-year survival rates are 70% and 50%, respectively (63,64), although wide ranges have been reported at different centers. Variables predicting a poor prognosis include male gender, advanced age at the time of diagnosis, and visceral involvement. Renal involvement portends the worst prognosis (5-year survival rate of 10%), followed by cardiac involvement (5-year survival rate of 40%) (64).

Scleroderma. In scleroderma, there is swelling of the fingers and hands, later becoming firm, thick, and tight with flexion contractures. In the second panel, digital ulcers are shown (*arrows*). Cardiac manifestations include cardiac fibrosis, abnormality of the conduction system, and pericarditis.

Scleroderma. Calcific deposit in subcutaneous tissue in the olecranon bursa (*arrows*).

SSc is diagnosed clinically, relying mainly on the prominent dermal changes characteristic of the disease. The sole major criterion for diagnosis is proximal scleroderma. Minor criteria include sclerodactyly, digital pitting scars or loss of distal finger pads, and bibasilar pulmonary fibrosis. The presence of one major or two minor criteria has greater than 95% sensitivity and specificity for diagnosis (65). Cold-induced digital pallor, followed by cyanosis and, later, reactive hyperemic rubor (Raynaud's phenomenon), is nearly universally present. Similar pathophysiology may contribute to pulmonary, cardiac, and renal damage. Limited SSc is characterized by a more indolent course with calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasias, and, rarely, severe pulmonary hypertension.

Cardiac dysfunction is common in patients with SSc. Symptomatic cardiac involvement occurs in approximately 10% of these patients, ECG and echocardiography detect abnormalities in 50%, and autopsy evidence of cardiac involvement is present in up to 80% (66,67 and 68). The presence of either occult or symptomatic evidence of cardiac involvement portends a poor prognosis. Clements and associates constructed a "cardiac score," based solely on the presence of left-axis deviation on ECG and the size of pericardial effusion, and found that this score was a strong independent predictor of survival in patients with SSc (69). Chest pain and shortness of breath are often ascribed to noncardiac causes, but their occurrence should prompt investigation into the possibility of cardiac involvement.

Pericardial Involvement

Pericardial disease is common in SSc; autopsy evidence of acute or chronic pericarditis is seen in 50% to 80% of patients (68,70,71), echocardiographic evidence in 10% to 40% of patients (72,73 and 74), and clinical evidence in 7% to 16% of patients (68,70). Pericardial effusion tends to be of little clinical importance, but it carries a poor prognosis if the effusion is large (greater than 200 mL). For reasons that are unclear, patients with large pericardial effusions frequently have progression to renal failure within 1 year (73,75). Pericardial fluid analysis typically reveals a bland exudate with high protein levels, high lactate dehydrogenase, normal immunoglobulin and complement levels, and a paucity of leukocytes (75,76). Patients may present with typical findings of acute pericarditis or may have nonspecific symptoms. Constrictive pericarditis is rare (67). Tamponade has been reported (77). Treatment of acute pericarditis consists of administration of NSAIDs and corticosteroids, but renal function should be closely monitored during therapy. Large effusions may require percutaneous or surgical drainage.

Valvular Involvement

Clinically important valvular heart disease is not a feature of SSc. Individual cases of severe valve dysfunction in patients with SSc have been reported, but without firm evidence of causation (78). Two echocardiographic studies involving unselected SSc patients have suggested that the prevalence of mild mitral regurgitation in this group is high, which may be related to papillary muscle fibrosis and dysfunction (74). Autopsy studies have demonstrated thickening of the mitral leaflets and chordae tendineae, but at levels no different than those in control subjects (68).

Myocardial Involvement

In 1943, Weiss (79) observed patchy myocardial fibrosis in patients with SSc, establishing sclerodermal heart disease as a clinical entity. Myocardial fibrosis has been found at autopsy in 37% to 81% of patients (67,68,80). Pathologic specimens reveal patchy areas of transmural fibrosis, which are not confined to epicardial coronary artery distributions. Areas of contraction-band necrosis, typical of myocardial ischemic injury followed by reperfusion, are well described. Myocardial injury may have a pathogenesis similar to that of the vasospasm-induced digital gangrene produced by Raynaud's phenomenon. This patchy fibrosis has, therefore, been termed the *myocardial Raynaud's phenomenon* (67). Support for this theory has been provided by investigators who have shown that cold-induced myocardial ischemia occurs in patients with SSc. This has been demonstrated by cold-induced echocardiographic wall motion abnormalities and abnormalities of thallium uptake (74,81). Interestingly, nondihydropyridine calcium channel antagonists and angiotensin-converting enzyme (ACE) inhibitors have been shown to blunt this response (82,83). Although such therapy is theoretically attractive, primary prevention of myocardial fibrosis and cardiac death with ACE inhibitors has not been studied in patients with SSc.

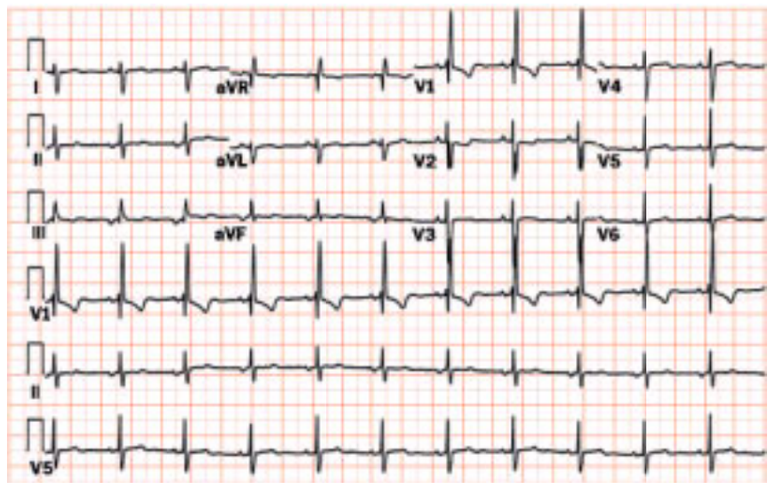
Diastolic dysfunction accompanied by echocardiographic evidence of impaired ventricular filling is common in patients with SSc (84,85). Myocardial fibrosis sufficient to produce systolic left ventricular dysfunction is uncommon but not rare and is mainly observed in autopsy studies. The prevalence of clinically apparent CHF has been reported to be 10% (86), but large series are lacking. Once thought to be contraindicated in patients with Raynaud's phenomenon, beta-blockers are now believed to be safe (87). Immunosuppressive treatment with corticosteroids is unlikely to be beneficial, because inflammation is rarely a major feature of this disease, and such treatment generally should be used only with the guidance of endomyocardial biopsy results.

Many patients who display normal systolic function at rest may demonstrate abnormal systolic responses during exercise. Follansbee and coauthors (88) found abnormal systolic response to exercise in 45% of patients with limited SSc and normal baseline ventricular function, with 14% of patients exhibiting a fall in ejection

fraction to less than 50%.

Patients with SSc and myositis of skeletal muscle appear to be at high risk of severe myocardial dysfunction and death (89). Indirect evidence points to myocarditis as the cause of death, because many of these patients have tachycardia, ST-segment abnormalities, clinical CHF, conduction delays, arrhythmias, or elevated CK-MB fractions. No records of endomyocardial biopsy are available, but one 12-year-old, whose case was reported by Follansbee and associates (89), showed evidence of contraction-band necrosis of 30% of the left ventricle at autopsy.

Right ventricular systolic and diastolic dysfunction are uncommon among patients with diffuse SSc. However, patients with CREST (*c*alcinosis cutis, *R*aynaud's phenomenon, *e*sophageal dysfunction, *s*clerodactyly, and *t*elangiectasia) syndrome may develop severe pulmonary hypertension due to primary vascular changes in the lungs, with secondary pulmonary hypertension and right ventricular dysfunction. Nondihydropyridine calcium channel antagonists and prostacyclin may reduce pulmonary artery pressure and improve symptoms, but the prognosis in these patients is grim.



Right ventricular hypertrophy. Note incomplete right bundle branch block pattern, right axis deviation, and ST-T–wave changes secondary to right ventricular hypertrophy.

Mitral stenosis. Left atrial enlargement and right ventricular hypertrophy have developed secondary to mitral stenosis, causing fixed pulmonary hypertension.

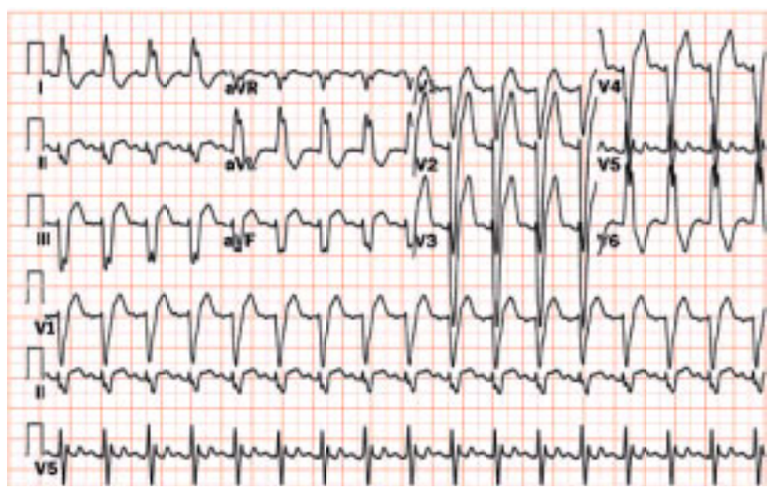
Coronary Involvement

Accelerated coronary atherosclerosis is not a feature of SSc. Chest pain, however, is a common symptom among patients with SSc and may be the result of esophageal dysfunction, lung involvement, or pulmonary hypertension. Typical angina pectoris is not characteristic of SSc, and its presence should prompt evaluation for coincidental epicardial coronary disease. As noted, many SSc patients have abnormalities of wall motion and radionuclide uptake, despite normal coronary arteries, which means that noninvasive testing has a low positive predictive value for the detection of CAD. If the index of suspicion for CAD is high, then cardiac catheterization should be considered.

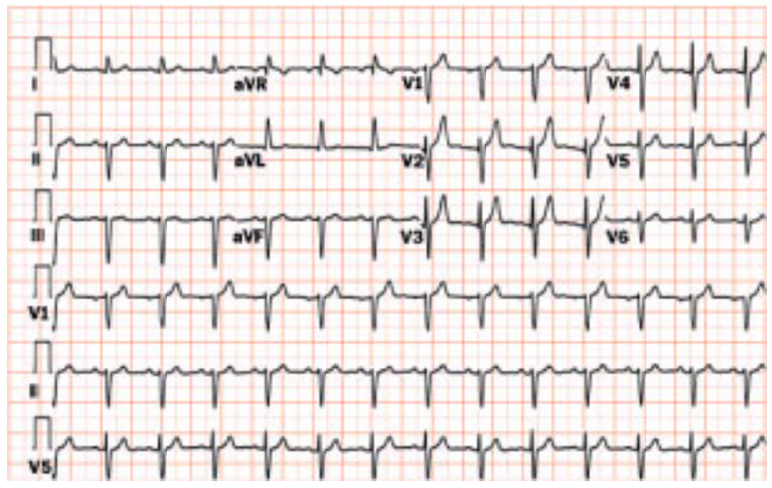
Abnormalities of small intramural coronary arteries have been reported in some studies (68,90), but not in others (67,80). James (90) described such abnormalities as "mural fibrosis, intimal proliferation and widespread fibrinoid necrosis, with occasional platelet-fibrin occlusions," and correlated the presence of small-vessel disease with the areas of myocardial fibrosis.

Conduction System Involvement

Abnormal ECG results are found in 50% of patients with SSc (91) and are an independent predictor of mortality in these patients (64,69). Nonspecific ST-T–wave abnormalities and conduction delays are most common. Autopsy studies suggest that conduction delays, such as left anterior fascicular block, left bundle branch block, and right bundle branch block, are more likely to be caused by slow conduction through fibrotic myocardium than by intrinsic disease of the conduction tissue (92). However, cases of clinical arrhythmia with pathologic evidence of direct involvement of the cardiac conduction tissue (93) and its arterial blood supply (90) have been reported.



Left bundle branch block. Wide QRS complex, negative in lead V_1, is associated with secondary T-wave inversions.



Left anterior fascicular block. Note left axis deviation and small Q waves n leads I and aVL. Small Q wave in lead V_4 strongly suggests anterior myocardial infarction.

Trifascicular block. Note right bundle branch block, left anterior hemiblock, and associated first-degree atrioventricular block.

Atrial and ventricular arrhythmias are common among asymptomatic patients with SSc and are associated with a poor prognosis. Their occurrence exemplifies the importance of detecting asymptomatic cardiac involvement in SSc. Nonsustained ventricular tachycardia (VT) has been demonstrated by 24-hour Holter monitoring in 7% to 13% of unselected patients with SSc (72,94). Supraventricular arrhythmias, such as transient atrial fibrillation, flutter, or paroxysmal supraventricular tachycardia, may be present in 20% to 30% of SSc patients (94). Patients with frequent ventricular ectopy had a 50% mortality during 33 months of follow-up. This compares with 8% mortality among patients without frequent ectopy (94). These data have led some authors to recommend use of Holter monitoring in the routine evaluation of patients with SSc (72). Patchy myocardial fibrosis provides an ideal substrate for tachyarrhythmias that are dependent on reentrant circuits, a phenomenon that has been demonstrated with electrophysiologic studies (95). Life-threatening ventricular arrhythmias have been successfully treated with implantable cardioverter-defibrillator (96) and ablative therapy (95).

KAWASAKI DISEASE

Dr. Tomisaku Kawasaki first examined a patient with what he called “mucocutaneous lymph node syndrome” in 1961, published a series of 50 cases in 1967, and reported it in English in 1974 (97). Kawasaki disease is an arteritis involving large, medium-sized, and small arteries and is associated with a mucocutaneous lymph-node syndrome (98). It is a disease of unknown etiology, with recognized perturbations of the cellular and humoral immune systems, and speculation of a viral or superantigen-driven pathologic inflammatory response (99).

The annual incidence of Kawasaki disease is 105 cases per 100,000 children in Japan (100) and approximately 10 cases per 100,000 children in the United States (101). The disease primarily affects children younger than 5 years of age. Diagnosis is based on clinical criteria. Laboratory abnormalities are nonspecific. In addition to fever of at least 5 days’ duration, four of the following criteria must be met: polymorphic exanthem, oropharyngeal erythema (including “strawberry tongue”) or fissuring, erythema and indurated edema of the palms or soles of the feet, bilateral conjunctival injection without exudate, and cervical lymphadenopathy (102).

Physical features in Kawasaki’s disease. These are capillary hemangiomas (*yellow arrow*).

Based on autopsy findings, the disease has been divided into four stages (103). Stage 1 occurs from days 0 to 9 and includes perivasculitis of small arteries and pancarditis. Stage 2 occurs from days 12 to 25 and is characterized by panvasculitis of medium-sized arteries with aneurysm formation. Stage 3 occurs from days 28 to 31 and involves intimal proliferation and resolving inflammation. Stage 4 occurs after 40 days and is characterized by arterial scarring and stenosis formation.

Kawasaki disease is the number one cause of acquired heart disease in children in Japan and in North America. Although it is primarily a disease of children, arterial damage incurred during the acute phase of the illness may result in a high prevalence of early coronary events in affected adults. Advances in early treatment have allowed more patients with Kawasaki disease to survive into adulthood.

Pericardial Involvement

Autopsy series report pericarditis in 90% of patients who have died because of Kawasaki disease (103). Pericarditis is uncommonly reported in clinical series of patients with Kawasaki disease, suggesting that it is either commonly asymptomatic or underreported or that the autopsy series are not representative of the majority of patients. Echocardiographic studies report effusions in 30% of patients during the acute phase of the illness (104).

Valvular Involvement

Clinically evident valvular heart disease develops in the acute phase of Kawasaki disease in slightly more than 1% of patients (104,105 and 106). Valvulitis is detected at autopsy in 20% of patients (103). Ischemic papillary muscle dysfunction may also contribute to valvular dysfunction. Mitral regurgitation is most commonly seen,

followed by aortic regurgitation. Severe valvular dysfunction requiring valve replacement has occurred, but most patients recover spontaneously. Valve dysfunction is more common among patients who have either prolonged fever or coronary aneurysm formation (106). The impact of intravenous immunoglobulin (IVIG) on valvular dysfunction in the acute phase of the illness has not been described.

Myocardial Involvement

Myocarditis, characterized by myocardial edema and polymorphonuclear leukocyte infiltration, is common in autopsy studies of patients with Kawasaki disease; it has an overall incidence of 45% and an incidence of 88% when death occurs between days 12 and 25 of the disease (103). Patients with myocarditis have tachycardia out of proportion to fever, a gallop rhythm, pulmonary congestion, and arrhythmia. The severity of myocarditis is not associated with the presence of coronary artery aneurysms (107). Left ventricle dimensions are increased and systolic function is abnormal in patients with Kawasaki disease in comparison with control subjects. Complete recovery is the rule, with normalization of ventricular function within 6 months in most patients (107,108). IVIG speeds recovery of myocardial function (108). CHF due to ischemia, infarction, or valvular heart disease may also occur. Heart transplantation has been required in some patients.

Coronary Involvement

Coronary artery aneurysm formation with subsequent myocardial ischemia and infarction is the most recognized and important cardiac complication of Kawasaki disease. MI is the leading cause of death in these patients. In untreated patients, 25% will develop coronary aneurysms in the acute phase of the illness (105). Within 2 years of detection, 50% of these patients will have complete angiographic resolution of the aneurysms. Giant aneurysms, those greater than 8 mm or more than four times the normal size of the vessel, occur in nearly 5% of patients and have special prognostic implications. As opposed to smaller aneurysms, giant aneurysms do not regress; frequently cause arterial remodeling, resulting in stenosis; and are prone to thrombosis, resulting in acute MI (Fig. 35E.2). More than one-third of infarctions may be silent, and more than two-thirds occur within the first year after the acute phase of the illness. Despite their young age, children with Kawasaki disease and acute MI have a 22% mortality rate (109).

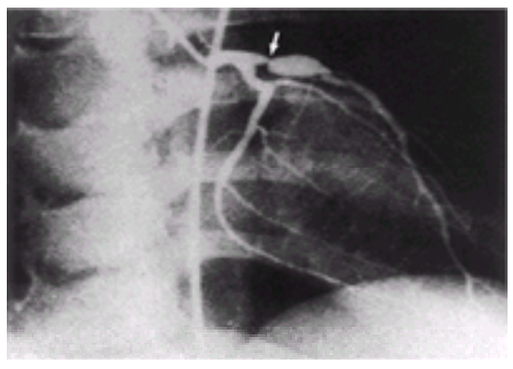


FIGURE 35E.2 Coronary angiogram revealing aneurysmal dilatation of the left anterior descending coronary artery with preceding focal stenosis (*arrow*). (Reprinted from Ino T, Akimoto K, Ohkubo M, et al. Application of percutaneous transluminal coronary angioplasty to coronary arterial stenosis in Kawasaki disease. *Circulation* 1996;93:1709–1715, with permission.)

Video 35E.12 Aneurysmal atherosclerotic disease involving the left main trunk, proximal left anterior descending artery, and proximal left circumflex artery in a 72-year-old male patient with a long history of smoking. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

IVIG has dramatically reduced the incidence of coronary aneurysms among patients with Kawasaki disease, from 23% to approximately 8% (110). High-dose aspirin administration is used until the febrile illness has passed, at which point the dose is reduced. In patients without coronary abnormalities, the aspirin may be discontinued 6 to 8 weeks after the acute phase of the illness. Patients with giant aneurysms or numerous smaller aneurysms should receive lifelong aspirin therapy, with or without coumadin. Frequency of clinical follow-up, ECG, echocardiography, and stress testing depends on the estimated risk of the patient. Patients with giant aneurysms, especially those with known coronary obstruction, require the most frequent follow-up (111).

Given the high cost and potential morbidity associated with coronary angiography, as well as the low incidence of coronary aneurysms since IVIG treatment came into use, routine angiography is not recommended in the acute illness, convalescent phase, or long-term follow-up of patients with Kawasaki disease. In the acute and convalescent phases, echocardiography has been validated as the procedure of choice in detecting coronary aneurysms, with sensitivity of nearly 100% and specificity of 97% (112). Echocardiography performed by an experienced pediatric sonographer is recommended at the time of diagnosis, at 6 to 8 weeks, at 6 to 12 months, and when symptoms of ischemia are seen (111). Changes in patient size and artery characteristics limit the use of echocardiography beyond the first decade of life. Long-term follow-up with stress imaging procedures done at yearly intervals is recommended for patients with known stenoses and should be considered for patients with giant or multiple aneurysms. Dipyridamole-thallium testing is well validated and outperformed angiography in predicting future coronary events in one trial (113). Heart catheterization is indicated when noninvasive studies suggest the presence of flow-limiting coronary stenoses.

A number of therapeutic modalities have been used when patients with Kawasaki disease develop acute coronary syndromes or chronic ischemic heart disease. Thrombolysis has been used with good results to treat pediatric patients who have acute MI, unstable angina, and documented thrombosis in aneurysms (105). Coronary artery bypass graft surgery (CABG) is the procedure of choice for patients who require revascularization, but it is less effective in the very young patient. A recent series from Japan described surgical results in 100 patients who underwent CABG surgery, with 6.7 ± 4.5 years' follow-up. No intraoperative deaths occurred. Recurrent ischemia developed in 15% of patients, and 2% of patients died during the follow-up period. One-year, 5-year, and 10-year graft patency rates were 94%, 82%, and 78% for arterial grafts and 82%, 63%, and 36% for venous grafts, respectively (114). The use of percutaneous coronary intervention (PCI) in this setting has been somewhat disappointing, characterized by high procedural mortality rates, frequent procedural failure, formation of new aneurysms, and high restenosis rates (115). There are no series that used state-of-the-art PCI with stents and glycoprotein IIb/IIIa antagonists.

Conduction System Involvement

Nonspecific ECG abnormalities are present in one-third of patients in the acute phase of the illness. Inflammation of the AV node, bundle of His, and bundle branches are present in 25% of patients at autopsy (103). Bradyarrhythmias and CHB may occur. Ventricular arrhythmias are more likely to be mediated by ischemia or infarction than by inflammation.

TAKAYASU'S DISEASE

Takayasu's disease is a chronic arteritis of the aorta, its major branches, pulmonary arteries, and coronary arteries. Takayasu, an ophthalmologist, first reported the ischemic retinal findings of the disorder in 1908. It is a rare disorder of unknown etiology with an annual incidence of 2.6 cases per 1 million individuals. It typically affects women of childbearing age, although cases affecting men are increasingly reported. Survival rates at 5 and 10 years are 91% and 84%, respectively. Clinical variables associated with poor outcome include hypertension, cardiac involvement, and poor functional capacity (116). Cardiac failure is the most common cause of death (116,117).

Diagnosis of Takayasu's disease relies on clinical, laboratory, and angiographic variables (118). Vascular bruits are the most common examination finding, followed by diminished or absent pulse. Claudication is the most common symptom, with upper extremity symptoms being more common than lower extremity symptoms (119). Arterial involvement includes, in order of decreasing frequency, the innominate and subclavian arteries, aorta, common carotid arteries, and renal arteries (120). Arterial lesions are occlusions or long, smooth stenoses more commonly than they are aneurysms or areas of ectasia.

Immunosuppression using corticosteroids and cytotoxic agents is the mainstay of medical therapy. A stepwise approach to medical therapy is advised, with initial corticosteroid therapy followed by the addition of cytotoxic agents, until clinical remission is achieved (119). No randomized, controlled trials of medical therapy have

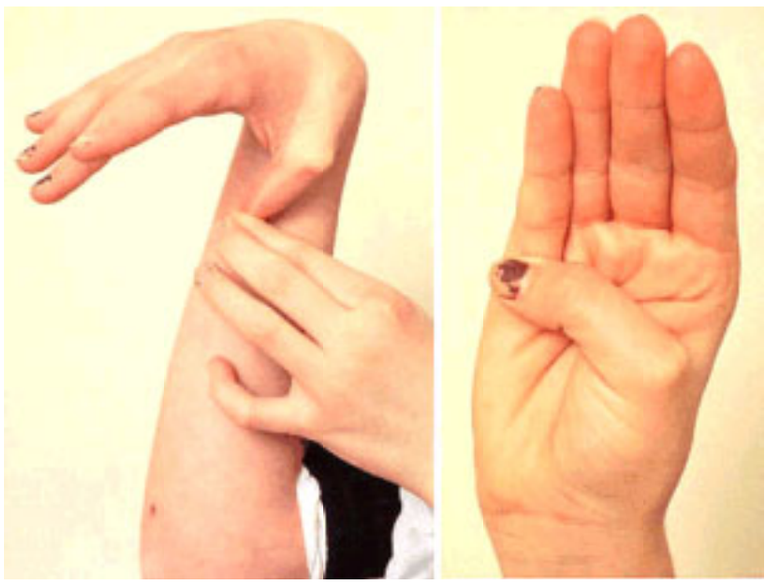
been performed, but observational data suggest that immunosuppression improves symptoms and may be associated with arterial lesion regression (119,121). Surgical and percutaneous revascularization of coronary and peripheral arteries has been described. In general, medical therapy may be pursued when symptoms are chronic and stable, but revascularization should be pursued when ischemia threatens life or limb.

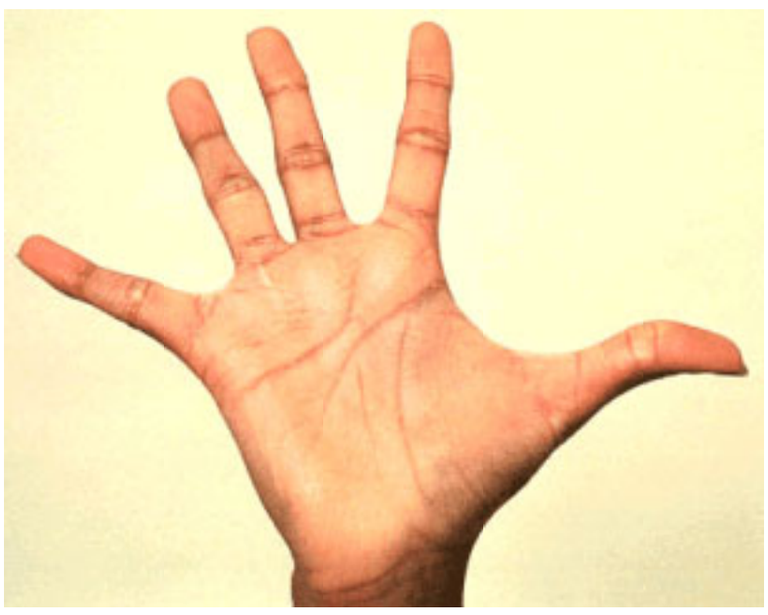
Pericardial Involvement

During phases of clinical disease activity, patients may experience systemic findings such as fever, malaise, new arterial lesion formation, arterial tenderness, erythema nodosum, myalgias, arthralgias, weight loss, and night sweats. Pericarditis may occur as part of this symptom complex. Overall, however, pericarditis is uncommon in Takayasu's disease and has an estimated clinical frequency of only 2% (117). Cases of patients presenting with large effusions have been reported, and steroids have been used, with anecdotal success (122).

Valvular Involvement

Aortic regurgitation is common among patients with Takayasu's disease, is frequently severe, and is an independent predictor of mortality in these patients. Clinically detectable aortic regurgitation is present in 7% to 20% of patients (116,117,119,123). Aortic valve replacement is necessary in approximately 1% of patients. Regurgitation is usually the result of aortic root dilation and requires combined valve and root replacement. Leaflet thickening due to inflammation and subsequent fibrosis may contribute to valvular dysfunction (124).





Ehlers-Danlos syndrome. There is severe joint laxity and hypermobility that may produce joint dislocations (A–C).

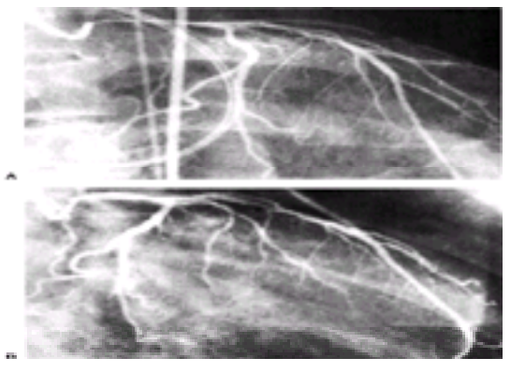
Video 35E.13 Intraoperative transesophageal echo (120-degree view) with color Doppler demonstrating aortic insufficiency due to aortic dilatation (sinuses measure 5.0 cm) causing failure of leaflet coaptation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Myocardial Involvement

CHF is the most common cause of death among patients with Takayasu's disease (116,117). CHF in these patients is usually multifactorial, with contributions from aortic regurgitation, hypertension, coronary involvement, and pulmonary artery involvement. Two-thirds of juvenile patients present in CHF, and one-third of adults experience heart failure (117). CHF with global left ventricular systolic dysfunction has been reported in the absence of hypertension or aortic regurgitation. When other markers of systemic inflammation are present, most of these patients exhibit myocarditis on endomyocardial biopsy, characterized by mononuclear cell infiltrate, necrosis, myocytolysis, and edema (125). Dramatic but anecdotal improvement has been noted after administration of corticosteroid therapy. Treatment with steroids must be done, with careful clinical follow-up, because of the capacity of steroids to increase sodium retention and raise blood pressure.

Coronary Involvement

Clinically important coronary artery involvement associated with Takayasu's disease occurs in 5% to 10% of patients (116,117). Three patterns of coronary involvement have been described: ostial stenosis; long, smooth stenoses; and aneurysm formation. The first two patterns predominate, and patients usually present with recent-onset exertional angina or non–ST-segment elevation MI (eFig. 35E.2.1). Thrombosis of a coronary aneurysm resulting in abrupt vessel occlusion that presents as an ST-segment elevation MI is distinctly rare. Because of the frequency of occurrence of ostial stenosis, CABG has been the treatment of choice. However, graft survival is poor, which is likely a reflection of aortic disease at the proximal graft anastomosis. The high likelihood of subclavian artery disease precludes the use of internal thoracic artery grafts (126). When possible, surgery is delayed for these patients until medical therapy has induced remission of active aortic inflammation. PCI has been used with increasing frequency, but no large series are available that would allow the risk of procedural failure or restenosis to be estimated. Unprotected angioplasty of the left main coronary artery was undertaken in an 11-year-old girl in one case report. This is unconventional therapy, and the authors acknowledge that "acute obstruction is an inherent risk of PTCA [percutaneous transluminal coronary angioplasty] and can be deleterious in left coronary artery main stem lesions" (127).



***e*FIGURE 35E.2.1** Severe left main coronary artery stenosis in a patient with Takayasu's arteritis **(A)**. The stenosis improved after immunosuppressive therapy **(B)**. An internal mammary artery bypass graft to the LAD can be seen in **B**. (Reprinted from Iga K, Gohma I, Hori K. Regression of the left main trunk lesion by corticosteroid administration in Takayasu's aortitis. *Chest* 1991;99:509, with permission.)

Conduction System Involvement

ECG results are abnormal in 78% of patients with Takayasu's disease (117). The most common abnormality is left ventricular hypertrophy, followed by left atrial enlargement. These changes are frequently secondary to hypertension and aortic regurgitation, rather than to primary involvement of the conductive tissue. Holter monitoring of patients with Takayasu's disease reveals frequent ventricular ectopy in one-third and nonsustained ventricular tachycardia in 5%. The appearance of frequent ventricular ectopy during Holter monitoring is associated with echocardiographic evidence of aortic regurgitation and with the appearance of perfusion defects on thallium imaging. Patients who have Takayasu's disease and frequent ventricular ectopy have an increased risk of sudden cardiac death (128).

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis is a seronegative spondyloarthropathy characterized by ankylosis and sacroiliitis, peripheral arthritis, iritis, and aortitis. It is a relatively common disorder, with a prevalence of 1% in white individuals (129). The pathogenesis is thought to have both heritable and environmental components. HLA-B27 is thought to be not only a marker of the disease, but pathologically involved. The diagnosis of ankylosing spondylitis is made on the basis of clinical and radiographic features. Cardiac involvement is associated with the presence of peripheral arthritis and with disease duration; it usually occurs after 10 to 20 years of disease (130). Heart disease is the most common cause of death among patients with ankylosing spondylitis (131). Reiter's syndrome, psoriatic arthritis, and inflammatory bowel disease have similar cardiac manifestations and are not discussed separately.

Pericardial Involvement

Pericarditis is rarely reported among patients with ankylosing spondylitis. Bulkley and coworkers, in a small autopsy series, found the pericardium to be normal in patients who had not had prior open heart surgery. Echocardiographic studies in unselected patients, however, have revealed a 5% to 10% incidence of pericardial thickening and effusion (132). Complicated pericardial disease would be reportable.

Valvular Involvement

Valvular heart disease occurs in approximately 10% of patients with ankylosing spondylitis (132,133 and 134). Pathology reveals fibrous thickening 1 to 2 cm superiorly and inferiorly from the aortic valve. Histopathology reveals adventitial scar, intimal proliferation, and inflammation of the vasa vasorum with lymphocytes and plasma cells (135). A "ridge" or "bump" of fibrous tissue may accumulate below the aortic valve on the membranous portion of the interventricular septum. Aortic regurgitation caused by fibrotic shortening of the aortic valve leaflets and aortic root dilatation occurs in approximately 8% of patients and may be severe. Mitral regurgitation due to extension of the fibrotic process to the anterior mitral leaflet has been reported (136). Mitral valve prolapse has been reported in as many as 10% of patients (132). Disease duration, advanced patient age, and the presence of peripheral arthritis predict valvular involvement. Echocardiography is a sensitive method for detection of preclinical valvular involvement, but whether early detection will affect late outcomes is unclear. Patients in whom careful clinical examination detects murmurs of aortic regurgitation should undergo echocardiography.

Myocardial Involvement

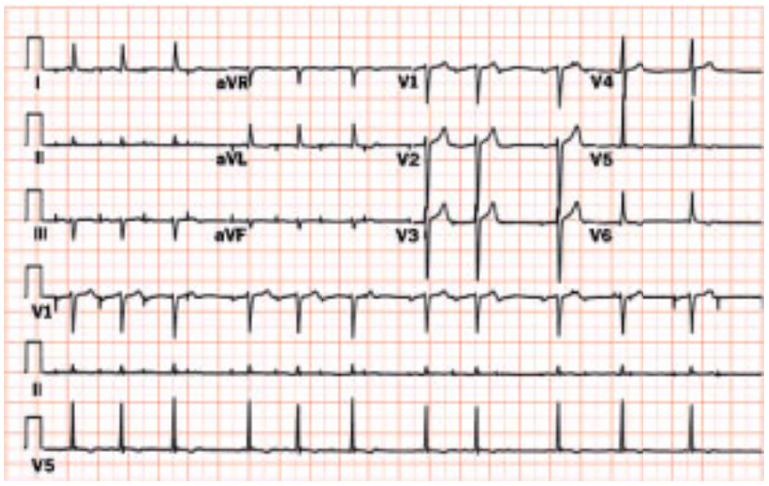
CHF is rarely reported among patients with ankylosing spondylitis, and systolic ventricular dysfunction is rare in the absence of ischemia, valvular heart disease, or hypertension. Diastolic dysfunction, however, has been found in up to 55% of patients (137). Diffuse myocardial connective tissue deposition in the absence of valvular heart disease, CAD, or hypertension has been observed histologically (137).

Coronary Involvement

Patients with ankylosing spondylitis do not appear to be at an increased risk for atheromatous CAD, and significant inflammation of the epicardial coronary arteries has not been reported. Despite this, MI is an important cause of death in these patients, because of its high incidence in the general population (130). Extension of aortic pathology with ostial coronary artery narrowing presenting as stable angina has been reported in one patient with Reiter's syndrome (138).

Conduction System Involvement

Abnormalities of cardiac impulse formation or conduction are common among patients with ankylosing spondylitis and occur in 10% of patients (133). Sinus node dysfunction may be manifest as asymptomatic sinus pauses or sinus bradycardia (132,134). AV block is common, ranging from first-degree block to CHB. It is more common among patients with aortic regurgitation and occurs in as many as 44% of these patients (139). This is consistent with the known pathology of the disease, in which the fibrotic process extends into the interventricular septum, through which the conduction system traverses. Aortic regurgitation usually precedes heart block in the course of the disease (130). Bergfeldt and coauthors (140) studied a group of 223 consecutive men referred for pacemaker implantation and found 15 cases of ankylosing spondylitis, many of which were undiagnosed, suggesting that spondyloarthropathies may be an underappreciated cause of bradycardia.



Mobitz I second-degree atrioventricular block. Note electronic atrial pacemaker with progressive PR segment prolongation before dropped QRS complex.

CHURG-STRAUSS SYNDROME

Churg-Strauss syndrome (CSS) is characterized by eosinophil-rich and granulomatous inflammation that involves the respiratory tract and necrotizing vasculitis that affects small to medium-sized vessels, associated with asthma and eosinophilia (98). It is a rare disorder of unknown etiology, with an estimated annual incidence of less than one case per 100,000 individuals (141). Current therapy consists of administration of corticosteroids and cytotoxic agents, and the survival rate is 72% at 7 years (142). Cardiac involvement is a prominent feature of CSS; it occurs in 60% of patients in some studies and is the most common cause of death in most studies (142,143,144 and 145). Heart disease in patients with CSS is predictive of a poor outcome.

Pericardial Involvement

Clinically diagnosed pericarditis occurs in 20% to 32% of patients with CSS (142,145,146). Constrictive pericarditis and tamponade are rare but reported complications. Pericardial fluid may be bland or rich in eosinophils (147,148). Pericardial histopathology can be diagnostic and may reveal necrotizing granulomata, fibrosis, and prominent eosinophils. Acute management includes administration of corticosteroids and cytotoxic agents and drainage of the effusion when it causes hemodynamic compromise. Surgical creation of a pericardial window may be required for patients with recurrent disease and provides tissue for pathologic evaluation when the diagnosis is in doubt.

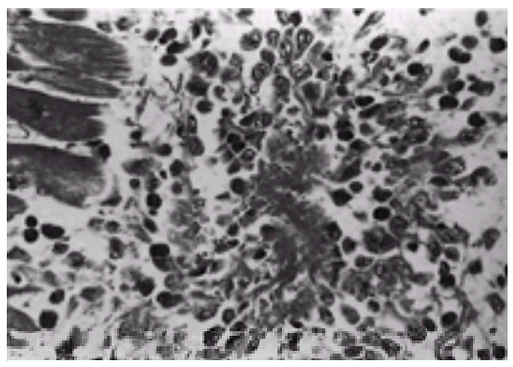
Valvular Involvement

Valvular heart disease is not a consequence of CSS.

Myocardial Involvement

Patients with CSS suffer considerable morbidity and mortality from CHF. Clinical evidence of CHF is present in 13% to 48% of patients (142,145). As noted earlier, cardiovascular disease is the most common cause of death among patients with CSS, and CHF is the most common cause of cardiovascular death. CHF that results from systolic dysfunction, diastolic dysfunction, and restrictive physiology may all be important. Ventricular thrombosis and thromboembolism resulting from underlying myocardial involvement have been reported (149).

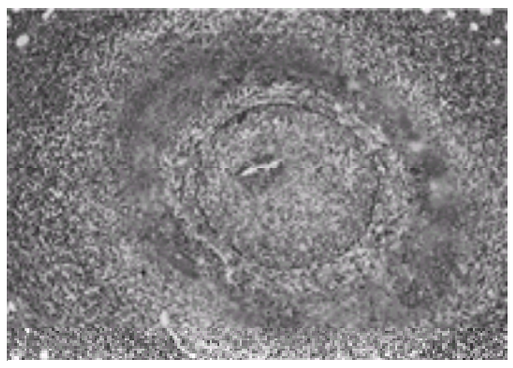
Unlike many of the other connective tissue disorders and vasculitic syndromes, left ventricular dysfunction in association with CSS is frequently the result of primary myocardial involvement by the inflammatory process. Endomyocardial biopsy may show necrotizing granulomata and, frequently, eosinophils during the acute phase of the illness (*e*Fig. 35E.2.2) (150). Anecdotal reports are available of dramatic improvement in left ventricular function after immunosuppressive therapy is begun (150,151). Heart transplantation has been performed in a patient with CSS and fulminant myocarditis (152). Immunosuppression should be guided by endomyocardial biopsy, when possible, because fibrotic changes alone may be present if patients present late in the course of the illness (151).



***e*FIGURE 35E.2.2** Myocarditis in a patient with Churg-Strauss syndrome, revealing granulomatous and eosinophilic inflammation. (Reprinted from Sasaki A, Hasegawa M, Nakazato Y, et al. Allergic granulomatosis and angiitis. *Acta Pathol Jpn* 1988;38:781–788, with permission.)

Coronary Involvement

Autopsy evidence of coronary arteritis is present in more than one-half of patients with CSS (144). Acute MI is responsible for up to 20% of deaths in some series (143) (*e*Fig. 35E.2.3). Angiographic improvement of coronary arteritis after the start of medical therapy has been documented (153). Because of the difficulty in distinguishing between coronary arteritis and atherosclerotic CAD by angiography, corticosteroid therapy may be added to conventional therapy in select patients whose clinical course is stable and is strongly suggestive of arteritis.



***e*FIGURE 35E.2.3** Arteritis of the left anterior descending coronary artery in a patient with Churg-Strauss syndrome. Fibrinoid necrosis of the media and eosinophilic infiltration can be seen. (Reprinted from Sasaki A, Hasegawa M, Nakazato Y, et al. Allergic granulomatosis and angiitis. *Acta Pathol Jpn* 1988;38:781–788, with permission.)

Conduction System Involvement

Although ECG abnormalities are present in up to 50% of patients who have CSS, arrhythmias are uncommon. Those that have been reported are conduction abnormalities that appear in the setting of myocardial disease and respond to medical therapy (142).

POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) is a rare (154), nongranulomatous, necrotizing vasculitis of medium-sized and small arteries that is not accompanied by glomerulonephritis or microscopic angiitis (98). It is diagnosed by a combination of clinical and laboratory features, including weight loss, livedo reticularis, testicular pain, myalgias, neuropathy, diastolic hypertension, renal insufficiency, abnormal results of serologic testing for hepatitis B virus, and arteriographic or biopsy evidence of arteritis (155). Historically, survival rates have been only 13% 5 years after diagnosis (156). Advances in supportive care and medical treatment with corticosteroids and cyclophosphamide have improved the survival rate to 82% at 5 years (157). Death is usually the result of renal failure or infection. Cardiac involvement occurs in more than one-half of patients but is symptomatic in only 10% to 30% (154). The heart may be a direct target of the disease process, or it may be secondarily affected by hypertension, renal insufficiency, and corticosteroid use.

Livedo reticularis. Mottled reddish discoloration of the lower extremities with accompanying multiple ulcerations associated with atheroemboli.

Pericardial Involvement

Clinically apparent pericarditis is uncommon in PAN and occurs in 2% to 5% of patients (154). At autopsy, however, pericarditis is observed in 27% of patients with PAN (158). It may be fibrous or fibrinous. Pericardial involvement complicated by purulent pericarditis, tamponade, or constrictive pericarditis would be worth reporting.

Valvular Involvement

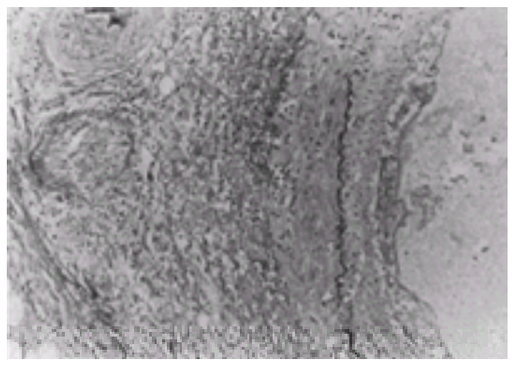
PAN does not appear to be associated with valvular heart disease.

Myocardial Involvement

CHF is common among patients with PAN, occurring in 10% to 15%, but is usually secondary to associated hypertension, renal failure, or coronary involvement. Limited myocarditis has been reported in approximately 15% of patients with PAN at autopsy and is more common among patients with active arteritis (158). It is usually mild and of little clinical significance.

Coronary Involvement

Symptoms of coronary insufficiency occur in 4% to 15% of patients with PAN (154). Acute MI due to epicardial coronary artery necrotizing inflammation has been documented (*e*Fig. 35E.2.4) (159), but its exact incidence is unknown. Hypertension, corticosteroid use, and renal failure contribute to the high prevalence of atheromatous CAD among patients with PAN. Retrospective cohort series of patients with PAN report the occurrence of MI in 1% to 5% (154). MI in patients with PAN may be silent, or CHF may be the presenting symptom. PAN patients who present with chest pain and ST-segment elevation should be treated with either thrombolysis or primary coronary angioplasty, because occlusive lesions are typically caused by thrombus overlying areas of inflammation.

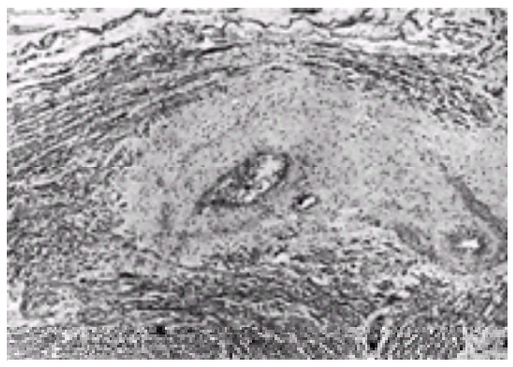


***e*FIGURE 35E.2.4** Necrotizing arteritis of the left anterior descending coronary artery in a patient with polyarteritis nodosa. [Reprinted from Odhav S, McKown K, Lohr KM. Polyarteritis nodosa presenting as recurrent myocardial infarction (letter). *Chest* 1994;105:1615, with permission.]

Pathologic evidence of coronary arteritis is more common than symptomatic disease and is found in one-half of all patients at autopsy (158). Arteritis begins with granulocytic infiltration of the vessel wall, followed by mononuclear cell predominance and then by fibrotic healing. Inflammation of epicardial coronary arteries may occur, but PAN more typically causes inflammatory lesions in intramyocardial coronary arteries (158). The clinical importance of this inflammation is unknown.

Conduction System Involvement

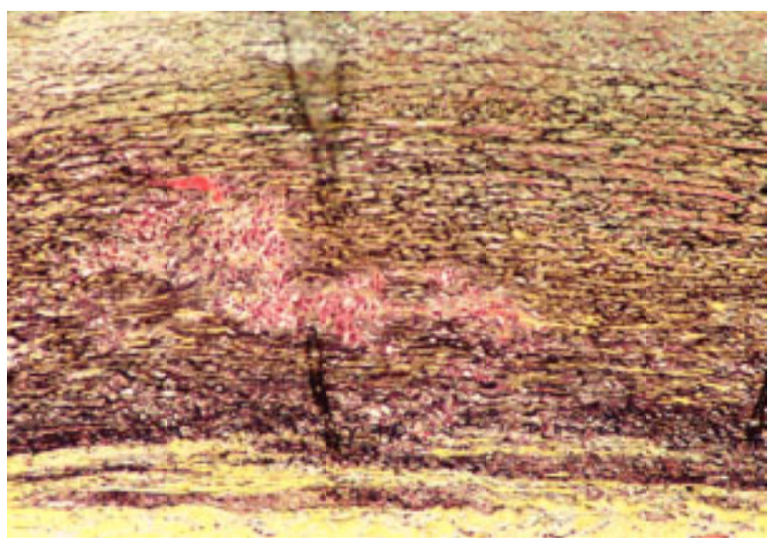
Autopsy evidence of involvement of the cardiac conduction system is commonly found in patients with PAN; however, clinically important arrhythmias are uncommon. Schrader and associates (158) reported sudden cardiac death to be the cause of death in 11% of their autopsy subjects, although detailed descriptions of the conductive tissue were not provided. Pathology of the AV nodal and SA nodal arteries, due to both ischemia and inflammation extending from the vessel into the conductive tissue, has also been implicated in clinical arrhythmias (*e*Fig. 35E.2.5) (160).



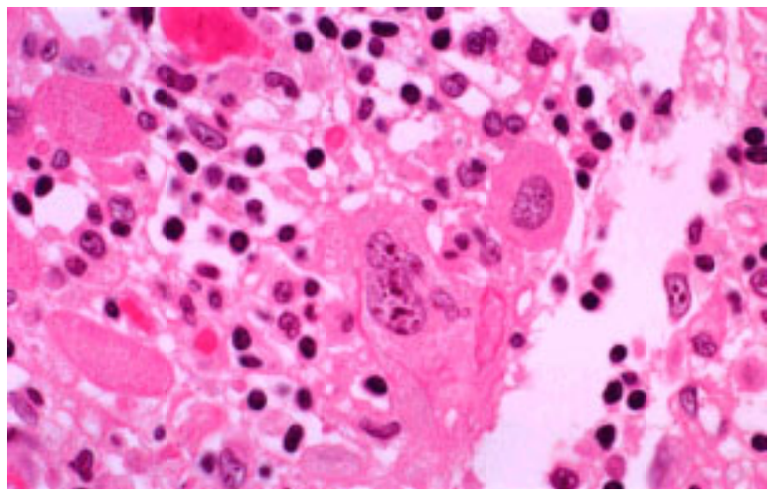
***e*FIGURE 35E.2.5** Healed arteritis in the atrioventricular nodal artery with residual intraluminal thrombus and perivascular fibrosis in a patient with polyarteritis nodosa. (Reprinted from Thiene G, Valente M, Rossi L. Involvement of the cardiac conducting system in panarteritis nodosa. *Am Heart J* 1978;95:716–724, with permission.)

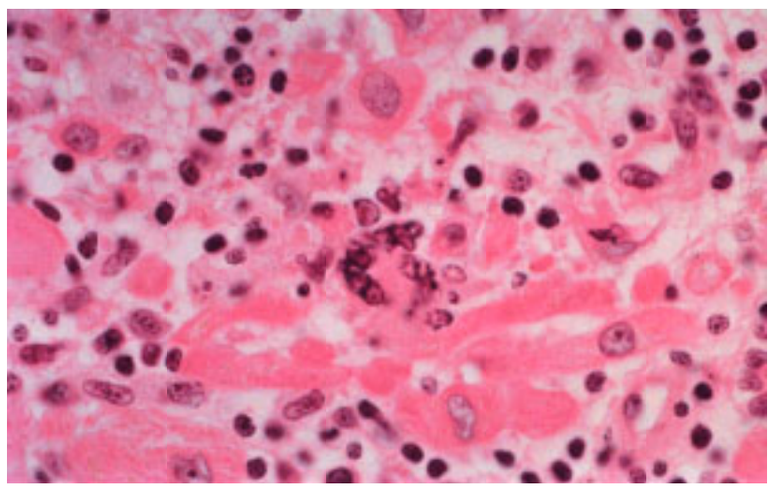
GIANT CELL (TEMPORAL) ARTERITIS

Giant cell arteritis (GCA) is a granulomatous arteritis of the aorta and its major branches that has a predilection for the extracranial branches of the carotid artery, often involves the temporal artery, and usually occurs in patients older than 50 years (98). The first case description is attributed to Hutchinson, in 1890 (161). The cause of GCA is not known, but it appears to be pathologic inflammation driven by a specific antigen and mediated by CD4+ lymphocytes, resulting in cytokine release and macrophage-induced oxidative damage (162). Diagnosis is based on clinical and pathologic criteria, including three of the following: age older than 50 years, new-onset headache, clinical abnormality of the temporal artery, elevated erythrocyte sedimentation rate, and diagnostic temporal artery biopsy (163). Its annual incidence in a predominantly white population is 17.8 in 100,000, but may reach 50.0 in 100,000 among elderly patients (164). Cardiac dysfunction occurs in 5% to 10% of patients with GCA (165). It is usually secondary to disease of the ascending aorta, rather than to primary cardiac involvement. Cardiac disease is the most common cause of death among patients with GCA (166).

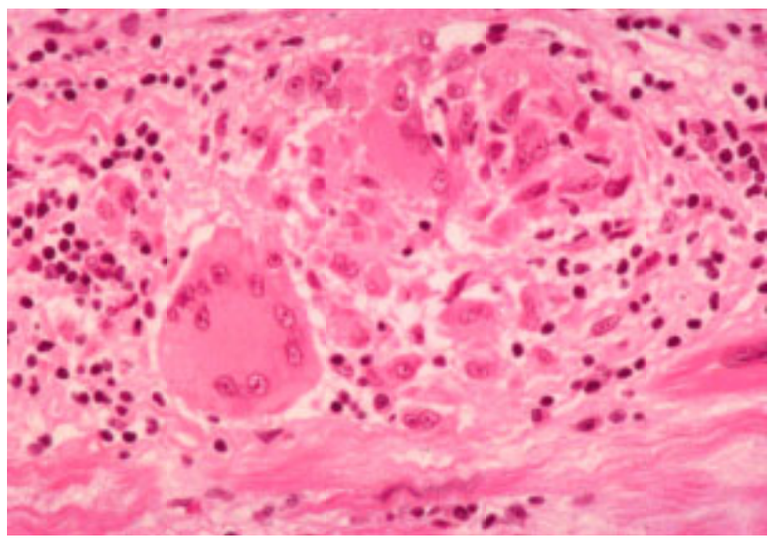


Section of aortic wall demonstrating giant cell arteritis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)





Giant cell myocarditis with apoptosis (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Giant cell myocarditis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Coronary Involvement

Coronary involvement in GCA appears to be rare, but it may be underreported. A number of case reports of histopathologically confirmed GCA of the coronary arteries have been published and summarized by Paulley (167), but the true incidence of coronary involvement is unknown. Acute MI has been reported (168). General angiographic predictors of arterial involvement by GCA include the presence of long, smooth stenoses; involvement of arch vessels; tapered occlusions; and the presence of skip lesions with diseased segments interspersed with normal segments (169). Traditional risk factors for the development of CAD are prevalent in patients with GCA. Hypertension has been noted in 43% of these patients, tobacco use in 14%, diabetes mellitus in 6%, and a positive family history of CAD in 31% (170). Risk factors should be aggressively treated, as should established CAD.

Aortic Involvement

Large arteries are involved in the cases of almost 15% of patients with GCA (171). The incidence of thoracic aortic aneurysms among these patients is 17.3-fold higher than that in the general population. On average, more than 5 years passes between diagnosis of GCA and diagnosis of aortic aneurysm. No clinical predictors of aneurysm development have been identified (165). Aortic dissection or rupture may occur. Despite this, life expectancy for patients with GCA is similar to that in the general population (165,166). Therefore, radiographic screening for aortic aneurysm in patients with GCA is not advocated. However, careful clinical examination may reveal evidence of aortic aneurysm or large-vessel involvement, and further evaluation in these patients is warranted.

Video 35E.14 Intraoperative transesophageal echo with color Doppler of an ascending aortic dissection. Note the mobile flap with the color flow separation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35E.15 Short-axis transesophageal echo view of a type I aortic dissection. Note the flap originating within the noncoronary cusp (leaflet upper left screen) and extending towards the ostium of the left main trunk. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Ascending aortic dissection extending into the left main. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Valvular Involvement

Aortic regurgitation has been described in 5% to 10% of patients with GCA. Histologic examination has shown that the valve itself is an innocent bystander. Aortic valve regurgitation is due to ascending aortic aneurysm formation with aortic root dilatation (Fig. 35E.3). Aortic valve replacement with aortic root reconstruction should be undertaken when patients develop large ascending aortic aneurysms or severe aortic regurgitation with either symptoms of CHF or signs of ventricular dysfunction.

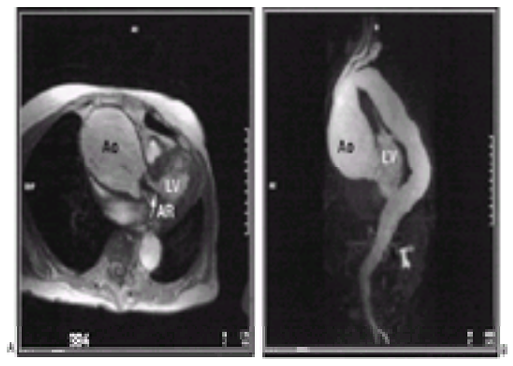


FIGURE 35E.3 Cross-sectional **(A)** and left anterior oblique **(B)** cardiac magnetic resonance images of a 72-year-old woman with giant cell arteritis/temporal arteritis, revealing an 8-cm ascending aortic aneurysm (Ao) and aortic regurgitant jet (AR, *arrow*). LV, left ventricle.

Pericardial involvement, myocardial involvement, or conduction system involvement in GCA with pathologic confirmation would be reportable.

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis (WG) is a rare systemic disorder of unknown etiology that is characterized by granulomatous inflammation involving the respiratory tract, necrotizing vasculitis of small and medium-sized vessels, and, commonly, necrotizing glomerulonephritis (98). Diagnosis relies on fulfillment of clinical criteria, including two or more of the following: nasal or oral inflammation, abnormal results of chest radiography, hematuria or red blood cell casts in urine, and granulomatous inflammation on examination of biopsy specimens. The presence of cytoplasmic patterned antineutrophil cytoplasmic antibody aids in diagnosis, but its pathologic role is uncertain. Once WG was almost uniformly fatal within months of diagnosis, but medical therapy with corticosteroids and cytotoxic agents has improved survival rates to 87% at 8 years (172). Despite this, patients with WG have standardized mortality ratios of more than 4, compared with the general population (173). Causes of death in these patients, in order of decreasing frequency, include infection, cardiovascular disease, renal failure, cancer, unknown causes, pulmonary disease, and stroke

(173). Pulmonary and renal disease accounts for the majority of disease-related deaths. As the life expectancy for WG patients increases, cardiovascular disease is emerging as an important cause of morbidity and mortality. Cardiac involvement occurs in 12% to 14% of patients with WG (173,174).

Pericardial Involvement

Pericarditis is the most common cardiac manifestation of WG, occurring in one-half of patients with cardiac involvement (175) and in 6% to 10% of the overall patient population (172,173 and 174). It presents most commonly as acute pericarditis, but tamponade and constrictive pericarditis have been rarely reported (176,177). Histopathologic examination reveals fibrinous pericarditis with occasional pericardial granulomata (176,178). When pericarditis associated with WG is part of a systemic flare, it should be treated with initiation or intensification of steroid and cyclophosphamide therapy.

Valvular Involvement

Hemodynamically significant valvular dysfunction is uncommon, although not rare, in patients with WG. Clinical or autopsy evidence of valvulitis is found in 21% of patients with WG and cardiac involvement (175). Numerous case reports of severe aortic regurgitation with echocardiographic and histopathologic evidence of involvement by WG are available in the literature (176,179,180). Aortic valve leaflet perforation seems to have been reported with disproportionate frequency, relative to aortic regurgitation from other causes (181,182). Mitral valve regurgitation and stenosis appear to be less common than aortic regurgitation. When tissue is available from intraoperative or autopsy specimens, bland fibrosis with degeneration of collagen has been found more commonly than has active inflammation.

HEART SOUNDS

Audio 35E.16 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border, sitting (*first clip*); Right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 35E.17 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border, sitting (*first clip*); Right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 35E.18 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border, sitting (*first clip*); Right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 35E.19 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border, sitting (*first clip*); Right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Myocardial Involvement

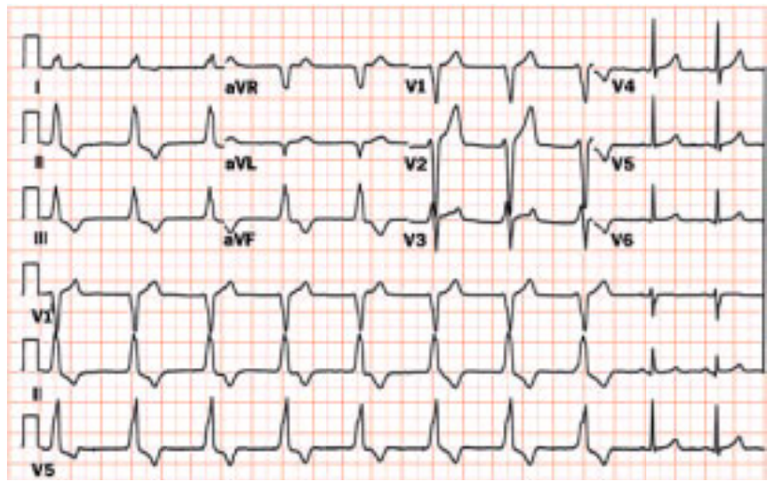
Myocarditis occurs in approximately 2% of patients with WG (174). Myocarditis may present as diffuse myocarditis, myocardial mass, or arrhythmia. Severe left ventricular systolic dysfunction due to myocarditis may respond to treatment with prednisone and cyclophosphamide, with resolution of symptoms and normalization of ventricular function (183). Kosovsky and associates (184) reported the case of a patient with a well-defined right ventricular mass, presenting as ventricular tachycardia, that was revealed on resection to be composed of granulomatous inflammatory tissue. Fauci and coauthors (174) also reported cases in which cardiomyopathy in patients with WG presented as ventricular tachycardia. On the basis of anecdotal improvements in left ventricular function that have been reported in patients with WG, it is reasonable to initiate or intensify immunosuppressive therapy in patients who present with new left ventricular systolic dysfunction, while standard heart failure therapy is started concurrently. This is particularly true if myocarditis occurs in conjunction with other signs or symptoms of active vasculitis.

Coronary Involvement

Coronary arteritis presenting as acute MI is rare but has been reported in patients with WG (185). Coronary arteritis at autopsy is present in one-half and evidence of MI in 11% of patients who have WG and known cardiac involvement (175). Histopathologic examination reveals epicardial arteritis with fibrinoid necrosis of the media and small-vessel fibrinoid occlusion (178). Patients with WG may, of course, have atheromatous CAD, and MI is a common cause of death in these patients (173).

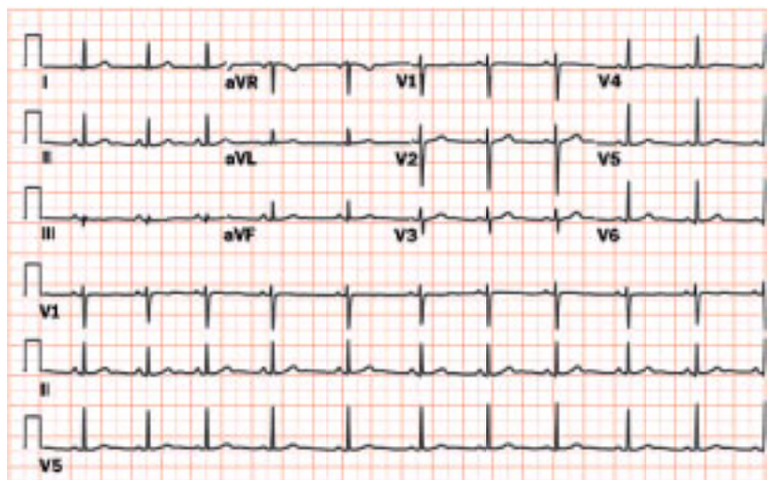
Conduction System Involvement

A variety of arrhythmias have been described in patients with WG. CHB may be caused by granulomatous inflammation of the AV node, bundle of His, or bundle branches, or by inflammation of the artery to the AV node (175,178). Immunosuppressive therapy allowed pacemaker insertion to be avoided for one patient with CHB who had a stable ventricular response (177), and extraction of a pacemaker was possible for another patient (175). Sinus node dysfunction and atrial arrhythmias may be caused by inflammation of the sinus node artery or by extension of inflammation from overlying pericarditis. As noted, patients with WG and myocardial involvement may also present with ventricular tachycardia. A short trial of temporary pacing may be considered for patients who have symptomatic bradycardia, while immunosuppressive therapy is initiated.



Isorhythmic dissociation. In the rhythm strip there is no relationship between the P waves and QRS complexes for the first eight beats. Subsequently, the QRS complex narrows and a P wave is well seen. This is consistent with isorhythmic dissociation.

Ashman's phenomenon. Underlying rhythm is atrial fibrillation. QRS complex with right bundle branch block morphology after long-short coupling interval is diagnostic of Ashman's phenomenon.



Sinus arrhythmia. Young female patient with sinus rhythm characterized by irregular RR intervals.

POLYMYOSITIS AND DERMATOMYOSITIS

Background

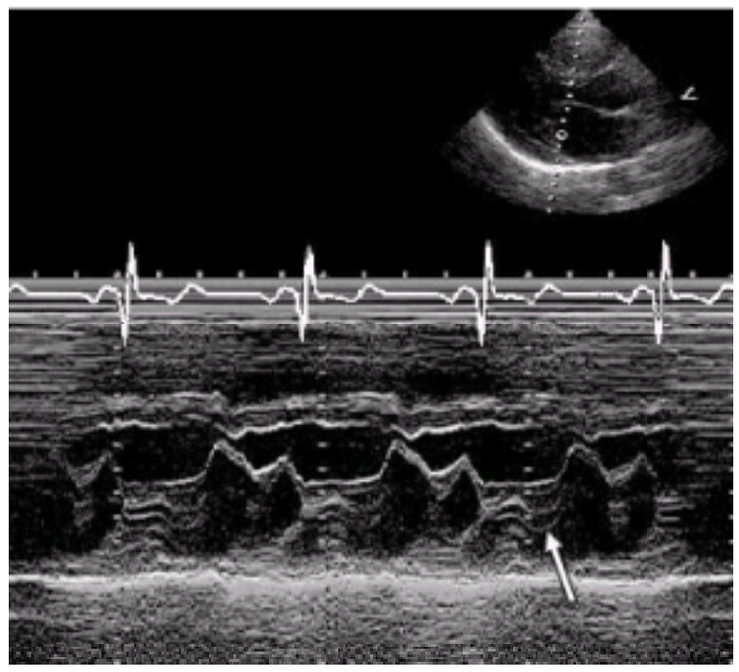
Polymyositis (PM) and dermatomyositis (DM) are inflammatory myopathies of unknown etiology. Diagnosis is based on fulfillment of clinical criteria put forth by Bohan and colleagues (186), which include proximal muscle weakness, serum enzyme abnormalities, abnormal results of electromyography, abnormal results on examination of muscle biopsy specimens, and, for diagnosis of DM, typical cutaneous manifestations. The survival rate is 73% at 8 years. The major causes of death are sepsis, malignancy, and cardiovascular disease (187). Cardiac involvement is the worst prognostic sign that may be found in patients with PM and DM (187). Symptoms suggesting cardiac involvement occur in 6% to 10% of patients.

Pericardial Involvement

Pericarditis is an uncommon but reported feature of PM and DM. Hochberg and colleagues (187) reported that 7% of the patients they followed for a mean time period of 8 years developed pericarditis. Echocardiography of unselected patients who have PM/DM reveals pericardial effusion in 8% (188). Complicated pericardial disease, such as purulent pericarditis, constrictive pericarditis, or tamponade, would be reportable.

Valvular Involvement

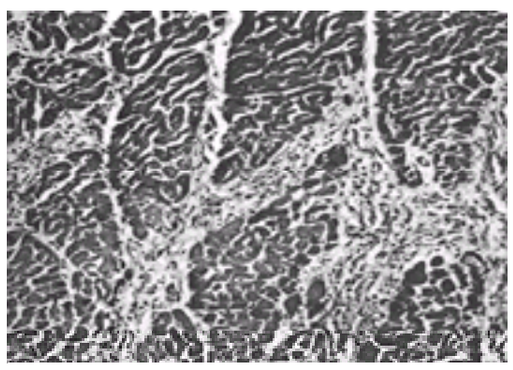
Clinically important valvular dysfunction is exceedingly rare in patients with PM/DM.One report suggests that the prevalence of mitral valve prolapse is 65%, diagnosed by both echocardiography and the presence of an audible mid-systolic click (189). None of those patients had hemodynamically significant regurgitation, and subsequent autopsy and echocardiographic studies have not supported so prominent an association (188,190).



M-mode tracing of posterior leaflet mitral valve prolapse. Note the posterior displacement of the posterior mitral leaflet after the leaflets close in systole.

Myocardial Involvement

A number of clinical, echocardiographic, biopsy, and autopsy studies have confirmed the occurrence of myocardial involvement in patients with PM/DM. Systolic dysfunction, diastolic dysfunction, and hyperdynamic states have all been described. Large retrospective studies report an incidence of symptomatic CHF that is lower than 5% (186). Autopsy studies find clinical CHF in nearly 50% of patients with PM/DM. At autopsy, approximately one-half of these patients are found to have myocarditis (*e*Fig. 35E.3.1) (190,191). Diastolic dysfunction has been reported in 42% of patients with PM/DM (188). The relative contributions of myocarditis, chronic corticosteroid use, and hypertension are unknown. PM and DM generally are steroid-responsive diseases. A trial of high-dose corticosteroids may be warranted in patients with PM/DM who present with fulminant heart failure due to systolic left ventricular dysfunction; however, because of the rarity of the condition, no trials have been performed.



***e*FIGURE 35E.3.1** Interstitial myocarditis in a patient with polymyositis. (Reprinted from Denbow CE, Lie JT, Tancredi RG, et al. Cardiac involvement in polymyositis: a clinicopathologic study of 20 autopsied patients. *Arthritis Rheum* 1979;22:1088–1092, with permission.)

A small percentage of patients with PM/DM have hyperdynamic cardiac function characterized by left ventricular ejection fractions of greater than 75% and an elevated cardiac index. This has been demonstrated in the absence of anemia, infection, hyperthyroidism, and hepatic or renal disease (188,189).

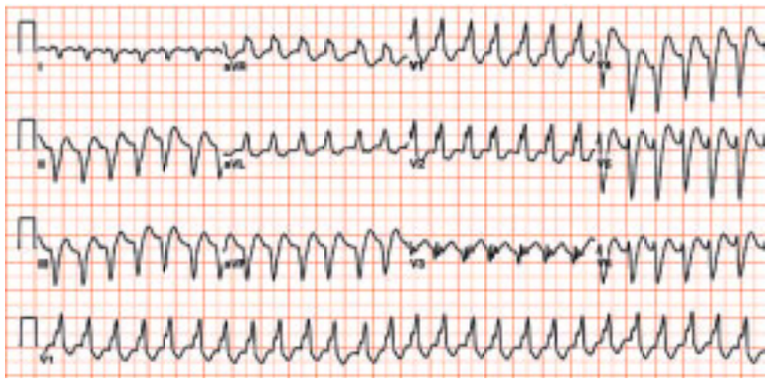
Coronary Involvement

Patients with PM/DM are not prone to accelerated atherosclerosis or to inflammation of the epicardial coronary arteries. Small-vessel disease, which is characterized by medial hypertrophy and hyperplasia, may be present in up to 20% of patients (191). Occasionally, this is associated with myocardial scar in the absence of epicardial CAD or myocarditis. Its clinical importance, however, is unknown. Patients with PM/DM may have an elevated CK-MB level and an elevated CK-MB index in the absence of myocardial necrosis induced by myocarditis or MI. This may be caused by injury-induced regression to a more juvenile skeletal muscle composition (192) and may result in diagnostic confusion when patients present with chest pain.

Conduction System Involvement

Conduction system involvement in association with myocardial involvement may be a prominent feature in patients with PM/DM. ECG abnormalities occur in one-half of all patients and consist mainly of conduction delays and chamber hypertrophy (188,189). Holter monitoring detects abnormalities in more than 75% of patients, and important atrial and ventricular arrhythmias are found in 26% of patients. CHB is the most clinically important electrophysiologic manifestation of PM/DM. High-grade AV block occurs in 2% of patients (186), and autopsy studies reveal lymphocytic infiltration and fibrosis of the conduction system (190).

A 71-year-old patient with left ventricular hypertrophy and negative U waves.



An 81-year-old male patient with ventricular tachycardia.

OTHER DISEASES

Behçet's disease is a rheumatic disease of unknown etiology that is characterized by orogenital ulcers, chronic uveitis, skin lesions, and, frequently, arthritis. Patients with the disease are prone to aortic aneurysms and venous and arterial thrombosis. MI due to thrombosis of an epicardial coronary artery may occur (193). Aortitis with resultant aortic regurgitation, myocarditis, pericarditis, and noninfective endocarditis has also been reported. Echocardiographic studies done on asymptomatic patients, however, reveal no differences from control subjects (194).

Relapsing polychondritis is a disorder characterized by nasal, auricular, and laryngeal cartilage inflammation and peripheral arthritis. Cardiac involvement affects 6% to 12% of patients. Aortic regurgitation is most common, with aortitis, coronary arteritis, and heart block also described (195).

Adult-onset Still's disease is a variant of juvenile RA characterized by maculopapular rash, fever, arthritis, leukocytosis, and myalgias. Pericarditis is common in this disease, affecting as many as one-fourth of patients (196,197). Myocarditis has rarely been described but may be fulminant when it occurs (197). Treatment consists of administration of NSAIDs, corticosteroids, and cytotoxic agents, depending on disease severity.

THERAPY

Primary prevention for patients with rheumatic diseases includes not only traditional risk-factor modification, but also minimization of cardiotoxic and atherogenic medications. Nonpharmacologic methods of prevention include smoking cessation, dietary changes, and exercise. Pharmacologic methods to prevent coronary events include 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors for hyperlipidemic patients, antihypertensive therapy for patients with hypertension, and aspirin and ramipril for high-risk patient groups. Newer immunomodulating therapies and cytotoxic agents may allow reduction of steroid doses, which may translate into a reduction in the incidence of manifest cardiac disease.

Patients with established CAD and heart failure are candidates for secondary prevention strategies. These include nonpharmacologic methods such as sodium restriction, dietary changes, exercise, and smoking cessation. Secondary prevention for patients with CAD includes administration of aspirin and ACE inhibitors for all patients, beta-blockers for patients with a history of MI, and include 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors for patients with hyperlipidemia. Patients with chronic heart failure who have systolic left ventricular dysfunction benefit from ACE inhibitors, beta-blockers, digoxin, and diuretics. The optimal treatment of heart failure due to diastolic dysfunction is less well characterized; control of hypertension is paramount. Standard recommendations for use of revascularization, valvular surgery, pacemakers, and implantable cardioverter-defibrillators apply. No randomized controlled trials have evaluated any of these therapies specifically for use in patients with rheumatologic disease, and therefore therapy should be tailored to the individual patient.

The use of immunosuppressive therapy for patients with pericarditis, myocarditis, valvulitis, or coronary arteritis should be guided by adjunctive clinical, histologic, or laboratory evidence of inflammation, when possible. The treatment of myocarditis demands special attention, because trials addressing immunosuppressive therapy for "idiopathic" myocarditis have been disappointing. Endomyocardial biopsy may allow the clinician to distinguish between active inflammation and the subsequent fibrotic response that occurs in many of these illnesses. The rheumatic diseases, with few exceptions, are generally steroid-responsive. Immunosuppressive therapy should be considered when these patients present with biopsy-proven, symptomatic myocarditis.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The rarity and clinical heterogeneity of both the cardiac and noncardiac manifestations of the rheumatic diseases have precluded prospective, randomized, controlled trials of therapeutic strategies. The clinician, therefore, is called on to draw from general principles of physiology and pharmacology, as well as the observational experience of the medical community, to guide individual patient care. This frequently involves a team approach, with internist, rheumatologist, cardiologist, and surgeon collaborating to benefit the patient.

The cardiac manifestations of the rheumatic diseases may be dramatic but more frequently are subtle, or patients may even be asymptomatic. The presence of these manifestations below the level of clinical detection belies their prognostic importance. The proper vigor with which to seek out cardiac involvement in these disorders remains to be defined. Careful attention should be paid to the cardiovascular system during physical examination and on any incidentally obtained studies.

THE FUTURE

Progress in the treatment of the cardiac manifestations of the rheumatic diseases will require continued diligence, both at the bench and at the bedside. Basic research in immunology and the infectious diseases will, hopefully, provide insight into disease etiology and guide development of disease-specific therapies. Clinical research in rheumatology and cardiology may provide better treatment of established disease. Multicenter randomized controlled trials will be required to accrue adequate numbers of patients to draw firm conclusions with regard to detection and treatment of cardiovascular involvement in the rheumatic diseases.

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35F

THE HEART AND OTHER ORGAN SYSTEMS:

ANDREW JAMES BOYLE

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Infections of the heart are increasingly more prevalent and more serious causes of morbidity and mortality. Infective endocarditis is the most common clinically important entity and is occurring more frequently as greater numbers of prosthetic devices are being implanted into patients, predominantly in the form of valves, leads for pacemakers and defibrillators, and patches to repair various anatomic abnormalities (see Chapter 25). Although infectious myocarditis occurs less frequently than infectious endocarditis, it remains an important cause of both fulminant and chronic heart failure. Systemic infections, such as infection with the human immunodeficiency virus (HIV) and Chagas' disease, are common causes of profound heart failure, particularly in developing countries. A method for accurately diagnosing infectious myocarditis premortem remains elusive, and diagnosis currently relies largely on circumstantial evidence, such as increases in serum antibody titers. Newer techniques, such as gene amplification by reverse transcription polymerase chain reaction (rt-PCR) and nucleic acid hybridization of right ventricular endomyocardial biopsy (EMB) tissue, suffer from a lack of sensitivity. Furthermore, once the diagnosis of infectious myocarditis is made, treatment is mainly focused on providing hemodynamic support and symptom relief, as opposed to counteracting the pathogenic organism. Nevertheless, full recovery of cardiac function is common, although not uniform. Infectious pericarditis is also a common clinical cardiac infection (see Chapter 26).

Infectious pathogens have also been implicated as potential etiologic agents for the development of coronary atherosclerosis or restenosis after percutaneous coronary interventions. Although a causal relationship has yet to be established, this idea has given rise to several large prospective trials, which are currently ongoing.

CLINICAL PRESENTATION IN INFECTIOUS MYOCARDITIS

There is a wide spectrum of clinical presentations associated with infectious myocarditis, ranging from a clinically silent syndrome that ends in complete recovery to acutely or chronically decompensated irreversible heart failure that leads either to death or to heart transplantation. The symptoms of mild to moderate infectious myocarditis are relatively nonspecific, consisting of fever, sweats, or chills associated with mild dyspnea and palpitations. In severe cases of infectious myocarditis, symptoms relate to hypoperfusion and cardiac congestion, for example, mental status changes, limb or gut ischemia, and shortness of breath. Chest pain is relatively infrequent and usually results from accompanying pericarditis. The signs of infectious myocarditis are also nonspecific, and they include frequent atrial and ventricular extrasystoles, sinus tachycardia that is out of proportion to the degree of hyperthermia, and, in severe cases, more significant arrhythmias, a soft first heart sound, a third heart sound, and pulmonary edema. Varying degrees of atrioventricular heart block may develop transiently and usually resolve spontaneously and completely (1). In the majority of cases, the initial infection remains completely unrecognized, and full recovery of cardiac function ensues. However, for unclear reasons, the infectious insult leads in a minority of patients to progressive myocardial dysfunction either acutely or, more commonly, many years after the original insult. This is felt to be one of the more common etiologies for dilated cardiomyopathy (DCM), and it accounted for 12.8% of all cases in a recent study (2). Most commonly (in 51.2% of all cases), no etiology is discovered, and the cardiomyopathy is thus called *idiopathic*.

DIAGNOSIS OF INFECTIOUS MYOCARDITIS

In light of the lack of specific signs and symptoms for infectious myocarditis, accurate and early diagnosis of this condition relies on a high level of clinical suspicion in the practitioner. Often the earliest evidence of active myocarditis is nonspecific changes seen on the resting electrocardiogram. These changes usually involve the ST segment and the T wave, but, in severe cases, significant intraventricular conduction delays can develop, either transiently or permanently. A pseudoinfarction electrocardiographic pattern with Q waves and ST-segment elevation indicates a particularly poor prognosis and is often associated with a rapidly fatal course of the disease (3). Abnormal QRS morphology and left bundle branch block are also indicative of a worse prognosis, although clinical deterioration usually is the result of progressive congestive heart failure that occurs over a protracted time course (1). These electrocardiographic changes are more helpful when a baseline electrocardiogram is available for comparison.

Left bundle branch block. Wide QRS complex, negative in lead V_1, is associated with secondary T-wave inversions.

Serum creatinine kinase levels, particularly the MB fraction (4), as well as both serum troponin I (5) and T levels (6), can be elevated as a reflection of ongoing myocardial necrosis resulting from the inflammatory process. The degree of elevation, and indeed whether these levels are elevated at all, is a function of the severity of the inflammatory insult and its acuity. Both the sensitivity and specificity of these markers of myonecrosis are particularly poor.

A documented fourfold rise in serum viral antibody titers from the acute to the convalescent stage of the infection is reasonable, but delayed, indirect evidence of viral infection does not assist in the management of the patient in the acute phase of the illness (7). A significant rise in virus-specific immunoglobulin M (IgM) antibody titers is an earlier serologic finding, although it is still not rapid enough to have therapeutic implications.

Various imaging modalities can also be used, with varying degrees of success, to assist in the diagnosis of acute infectious myocarditis. Echocardiography is of limited

use and serves mainly to confirm left ventricular systolic dysfunction and to eliminate other potential etiologies, particularly valvular cardiomyopathies and anatomic abnormalities, such as atrial and ventricular septal defects. In antimyosin scintigraphy, a radiolabeled antimyosin antibody is infused and binds to cardiac myosin heavy chains that are exposed to the circulation. In highly selected patient populations, this diagnostic tool is reasonably specific, but it is less sensitive than EMB with immunohistologic analysis (8). However, the specificity of antimyosin scintigraphy is dramatically reduced in less selective populations, because a positive study is a reflection of active myonecrosis, regardless of its etiology, including myonecrosis that occurs after a myocardial infarction. For these reasons, this method has not been widely implemented. Similarly, gadolinium-enhanced magnetic resonance imaging has proven to be relatively sensitive in the detection of acute myocarditis (9). However, it lacks specificity, because abnormal myocardial enhancement reflects only active inflammation, regardless of the etiology, including inflammation that occurs after myocardial infarction and various other cardiomyopathic processes (10). Magnetic resonance imaging may play a more important role in the future, once effective and specific therapies have been discovered and serial assessments can be used to determine the adequacy of therapy.

Video 35F.1 Normal parasternal short-axis view of the left ventricle by transthoracic echo. The anterior wall is located at the top and the inferior and posterior walls are located towards the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

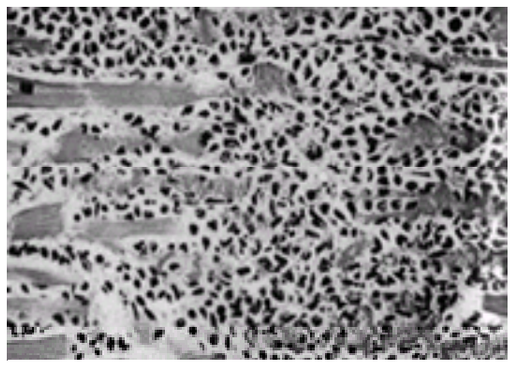
Video 35F.2 Normal parasternal long-axis view in a transthoracic echocardiogram. The mitral and aortic valves are well seen, as are the anteroseptal and posterior walls of the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35F.3 Normal apical five-chamber view in a transthoracic echo obtained by angling the transducer anteriorly from the four-chamber view to bring the aortic valve into view (see the center of screen). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35F.4 Normal apical four-chamber view of a transthoracic echo. Note that the left ventricle is on the right of the screen showing the septum and lateral walls, and the right ventricle is to the left. The left atrium is in the lower right of the screen and the right atrium to the lower left. The mitral and tricuspid valves can be seen in this view. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35F.5 Normal apical two-chamber view of a transthoracic echocardiogram. The anterior wall of the left ventricle is on the right of the screen and the inferior wall is to the left. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The EMB remains the gold standard for diagnosis of acute viral myocarditis, despite its many imperfections. The Dallas criteria were created by a panel of cardiac pathologists in 1986 to standardize the pathologic requirements for a diagnosis of myocarditis (11). In brief, a diagnosis of myocarditis in this classification system requires the simultaneous finding of lymphocyte infiltration and myocyte necrosis (eFig. 35F.0.1). Biopsy samples in which one criterion is met but not the other indicate borderline myocarditis. Despite this attempt to create worldwide uniformity in histologic diagnosis, there remains significant interobserver variability (12). Furthermore, lymphocytic myocarditis is a patchy disease that is unevenly distributed throughout the myocardium (13). In some patients, the pathologic myocardium is not easily accessible by the bioptome, which, by definition, is limited to sampling subendocardial tissue. Even when the inflammatory process involves the subendocardium, a tremendous sampling error may be present when only three to five biopsies are obtained (14). The rate of false-negative results of EMB is as high as 83% for individual biopsies and as high as 55% when five biopsy samples are obtained in a single patient with autopsy-proven myocarditis (13). In addition, there is a high rate of false-positive results of EMB because of the small numbers of lymphocytes that are normally present in the interstitium and because of the difficulty in distinguishing between lymphocytes and interstitial macrophages, fibroblasts, endothelial cells, and pericytes using light microscopy (15). Efforts to improve on this histologic classification system by adding a clinical perspective have not been widely accepted or implemented (16). Newer techniques developed to detect intramyocardial viral genome products in EMB samples using cloned DNA fragments that are complementary to the viral genome (*in situ* DNA hybridization) and rt-PCR have generally been successful (17,18). However, these techniques require adequate biopsy samples and thus suffer from significant sampling errors. Furthermore, they have yet to be implemented in the clinical setting, because few virus-specific therapies exist that could be initiated should a specific etiology be identified.



***e*FIGURE 35F.0.1** Example of severe diffuse lymphocytic myocarditis in a human right ventricular endomyocardial biopsy sample. An extensive interstitial lymphocytic infiltrate and myocyte necrosis are readily seen. (Reprinted from Hauck AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. *Mayo Clin Proc* 1989;64:1235–1245, with permission.)

Because of the relatively low sensitivity and specificity of all of the aforementioned diagnostic studies, the diagnosis of myocarditis at this time and for the foreseeable future remains mainly a clinical one.

ETIOLOGIC AGENTS OF INFECTIONS IN THE HEART

Table 35F.1 lists pathogenic causes of acute infectious myocarditis.

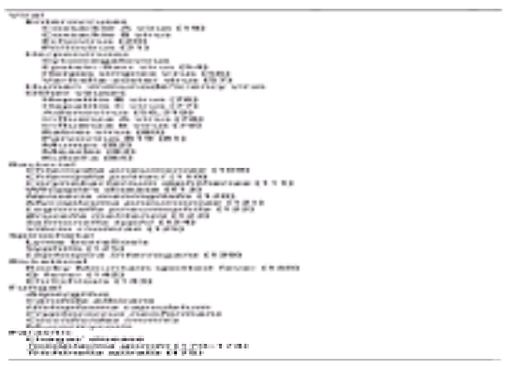


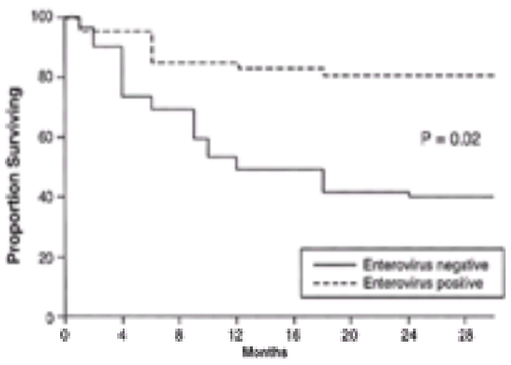
TABLE 35F.1 PATHOGENIC CAUSES OF ACUTE INFECTIOUS MYOCARDITIS

Viruses

Enteroviruses

The enteroviruses, as their name implies, are a group of single-stranded RNA viruses pathogenic to the gastrointestinal and upper respiratory tracts. Individual species in this group, such as coxsackie A and B viruses, echovirus, and polioviruses, have been implicated as etiologic agents of viral myocarditis (19,20 and 21). Coxsackie B viruses (CBV) appear to be the most common pathogens. Serologic studies have revealed that 36% of all adults with acute myocarditis have demonstrable rises in either serum anti-CBV antibody titers or IgM (22,23). The full epidemiologic impact of CBV-induced myocarditis is difficult to assess because of the ubiquitous nature of this organism, as evidenced by the high rate of similar findings in control populations (22,23). Elements of the CBV genome have also been detected using rt-PCR in EMB of patients that met the Dallas criteria for diagnosis of acute myocarditis (17,24,25). The specificity of this finding is questionable, however, because of the unexpectedly high finding of enteroviral RNA on autopsy of patients who did not have cardiac disease (24). Furthermore, delineation of the exact viral species using this method is difficult, because significant nucleic acid sequence homology exists at the 5'-untranslated region of the RNA of all enteroviruses (26). However, probes do exist to species-specific regions of the RNA that are thus able to differentiate among various species using *in situ* hybridization.

In the majority of patients infected with CBV, cardiac manifestations are not found, although cardiac involvement has been estimated to be as high as 5.3% (27). Findings most frequently consist of asymptomatic and nonspecific electrocardiographic changes (28). In most cases, the signs and symptoms of infection are benign and resolve spontaneously. Some investigators have nevertheless proposed that some cases of nonischemic DCM may represent the end stage of either a previously detected (29) or undetected (30) enteroviral infection. Much of this speculation has arisen as a result of the frequent, although not uniform, detection of enteroviral RNA in EMB from patients who have nonischemic DCM without clinical evidence of myocarditis (18,24,30). In addition, recent studies have suggested that patients with DCM in whom persistent enteroviral RNA can be detected on EMB have a much poorer clinical prognosis (eFig. 35F.0.2) (25,31). However, because of the high prevalence of enteroviral infections in the community, these studies provide only circumstantial evidence of a link between enteroviral myocarditis and DCM without offering definitive proof. In fact, in one study, enteroviral RNA was detected more frequently in control patients undergoing either heart or lung transplantation for ischemic heart disease or primary lung disease than in patients with nonischemic DCM (30). This finding has been confirmed by another, similar study (32). The clinical association between enteroviral myocarditis and DCM, therefore, remains controversial and is yet to be proven.



***e*FIGURE 35F.0.2** Survival curves for patients for whom results of right ventricular endomyocardial biopsies, using *in situ* DNA hybridization, were enterovirus positive or enterovirus negative. (Reprinted from Why HJ, Meany BT, Richardson PJ, et al. Clinical and prognostic significance of detection of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy. *Circulation* 1994;89:2582–2589, with permission.)

Some investigators have suggested that enteroviruses have a potential role in the genesis of coronary atherosclerosis (33). However, the evidence is not very compelling, and the current focus of investigational attention has shifted toward more promising organisms.

Herpesviruses

Cytomegalovirus (CMV) is a double-stranded DNA herpesvirus readily identified in infected cells by its characteristic microscopic nuclear and paranuclear inclusion bodies. CMV is a ubiquitous organism that, in the immunocompetent host, commonly produces an asymptomatic primary infection, demonstrated by the presence of circulating anti-CMV antibodies in the majority of the population (34). Even in immunocompetent patients, CMV has been shown to cause myocarditis (35), albeit rarely. More commonly, however, as with all herpesviruses, CMV may remain latent intracellularly indefinitely in the host, until it is reactivated and leads to a systemic infection when the patient becomes immunocompromised, usually as a result of HIV infection, neoplasia, immunosuppression for rheumatologic or pulmonary disease, or after transplantation (34,36). One component of this generalized infection may be acute CMV myocarditis, which can be adequately treated with ganciclovir (37,38). Systemic CMV infection has been associated with a higher rate of acute allograft rejection in the first 3 months after heart transplantation (39), although other studies have failed to confirm this finding (40,41). Furthermore, CMV has been associated with accelerated cardiac allograft vasculopathy, which is generally believed to be reflective of chronic allograft rejection (39,42). This hypothesis also remains controversial; other investigators have not been able to confirm the findings (43,44). Even more intriguingly, however, treatment of heart transplant recipients immediately postoperatively with ganciclovir appears to lower the incidence of allograft vasculopathy, regardless of whether the recipients developed a systemic CMV illness (45).

Of greater importance epidemiologically is the link between CMV seropositivity and development of primary coronary atherosclerosis (46), although the majority of studies have not confirmed this result (47,48 and 49). Pre-procedural CMV seropositivity has even been linked to restenosis after percutaneous transluminal coronary atherectomy (50,51) but not to restenosis after percutaneous transluminal coronary balloon angioplasty (52,53). The reason underlying this apparent discrepancy is unclear and is the focus of current investigation. At this time, the best that can be said with regard to the potential association between coronary atherosclerosis and CMV is that it is circumstantial and rather tenuous.

Epstein-Barr virus, the organism responsible for infectious mononucleosis, is a double-stranded DNA herpesvirus that can rarely cause symptomatic myocarditis (54). Epstein-Barr virus has also been implicated in the development of lymphoproliferative disease after heart transplantation (55), a life-threatening complication that is often treated by lowering of the patient's immunosuppression with or without antiviral therapy.

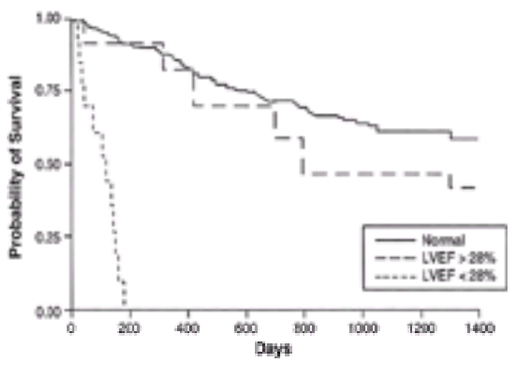
Herpes simplex virus (HSV) is a double-stranded DNA herpesvirus that has been implicated as a rare etiologic agent of acute myocarditis (56). Current data do not support an etiologic role for HSV in the development of coronary atherosclerosis; evidence from studies of patients who have HSV seropositivity is conflicting (46,47,49).

Varicella-zoster virus, another herpesvirus, has also been infrequently associated with acute myocarditis (57).

Human Immunodeficiency Virus

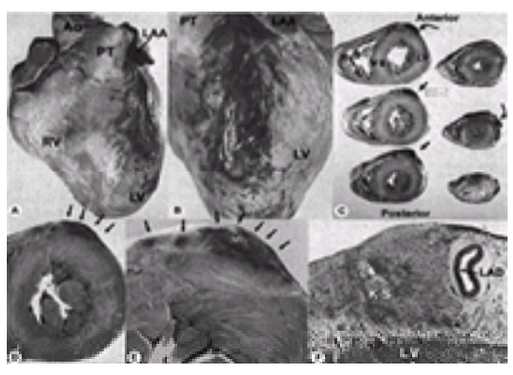
Acquired immunodeficiency syndrome (AIDS) is the end stage of HIV infection. As the number of worldwide HIV infections has reached epidemic proportions, and because advances in medical therapies have prolonged survival of patients with AIDS and various opportunistic infections, the cardiac manifestations of this disease have become more apparent. These cardiac manifestations include the direct effects of HIV itself and effects resulting from opportunistic infections that arise as a consequence of a profoundly immunosuppressed state.

EMB-proven acute or chronic lymphocytic myocarditis is a frequent finding in patients with AIDS (58,59). Most frequently, this is a consequence of a superimposed opportunistic infection (36,58). HIV RNA and DNA have been detected in such biopsies but are usually very sparse, most often appearing in areas of myocardium where there is no inflammatory infiltrate or ongoing myonecrosis, and are frequently associated with other opportunistic pathogens (60,61). A causal relationship between HIV and myocarditis has therefore not been firmly established. It must be noted, however, that no pathogen is identified in a large percentage of cases of AIDS-associated cardiomyopathy (36), a finding not dissimilar to that among patients whose cardiomyopathy is not related to AIDS. Some investigators have proposed that AIDS-associated cardiomyopathy may result from antiretroviral therapy, specifically from administration of the nucleoside analogue azidothymidine (62,63). Multiple cytokines, vascular changes, nutritional deficiencies, and illicit drug use have also been implicated (64). However, regardless of the etiology of the cardiomyopathic process associated with AIDS, the diagnosis is a harbinger of an extremely poor clinical prognosis, irrespective of the adequacy of the anti-HIV therapy itself (*e*Fig. 35F.0.3) (65).



***e*FIGURE 35F.0.3** Survival curves for 296 human immunodeficiency virus–positive patients who had structurally normal hearts or cardiac dysfunction. LVEF, left ventricular ejection fraction. (Modified from Currie PF, Jacob AJ, Foreman AR, et al. A review of endocarditis in acquired immunodeficiency syndrome and human immunodeficiency virus infection. *Eur Heart J* 1994;309:1606, with permission.)

Marantic endocarditis (66), infective endocarditis (usually found in intravenous drug users) (66), pericardial effusions (67), infective pericarditis (particularly that caused by *Mycobacterium tuberculosis* in Africa) (68), and pulmonary hypertension with cor pulmonale (69) are all infrequent findings in patients with HIV. Cardiac neoplasms also develop in these patients. Cardiac Kaposi's sarcomas are not usually isolated to the heart but rather are part of a widely metastatic process (70). They are usually asymptomatic and involve the subepicardium (*e*Fig. 35F.0.4) (70) or the pericardium, where they can lead to effusions (71). Most cases are discovered unexpectedly at autopsy. Cardiac non-Hodgkin's B-cell lymphoma is also usually associated with a widely disseminated malignant process in HIV patients, but it can be a primary lesion as well (72).



***e*FIGURE 35F.0.4 A–F:** Gross appearance of cardiac Kaposi's sarcoma (KS) (*arrows*) in a 44-year-old man with acquired immunodeficiency syndrome. LAA, left atrial appendage; LAD, left anterior descending coronary artery; LV, left ventricle; PT, pulmonary trunk; RV, right ventricle. [Reprinted from Silver MA, Macher AM, Reichert CM, et al. Cardiac involvement by Kaposi's sarcoma in acquired immune deficiency syndrome (AIDS). *Am J Cardiol* 1984;53:983–985, with permission.]

Accelerated coronary atherosclerosis has also been observed on autopsy of relatively young HIV patients, although a causal relationship has yet to be established (73). Recent studies have also implicated protease inhibitors, antiretroviral agents used to treat patients with HIV, in the development of coronary atherosclerosis (74,75); a profound deleterious effect on the serum lipid profile is the likely mechanism.

Other Viruses

Several other viruses have also been proven to rarely cause acute myocarditis, including hepatitis B virus (76), hepatitis C virus (77), adenoviruses (56), influenza A (78) and B (79) viruses, rabies virus (80), and parvovirus B19 (81). Cases of mumps (82), measles (83), and rubella (84) myocarditis have all been reported, and fetal rubella infection, resulting from early gestational maternal transmission, can lead to multiple congenital heart defects. However, mumps, measles, and rubella have largely been eradicated as a result of widespread childhood immunization programs.

Bacteria

Rheumatic Fever

Acute rheumatic fever is characterized by a systemic inflammatory response that occurs approximately 3 weeks after an untreated group A streptococcal pharyngeal infection but never after a cutaneous infection. The incidence of acute rheumatic fever in the developed world is on the decline as a result of widespread use of antistreptococcal antibiotic therapy for upper respiratory tract infections and general improvements in living conditions. The same is not true in the developing world. Administration of appropriate antibiotic therapy during pharyngeal infection essentially eliminates the future risk of developing rheumatic fever (85).

The diagnosis of acute rheumatic fever is mainly a clinical one, using the revised Jones criteria of 1992 (86) (Table 35F.2). Evidence of two major criteria or one major criterion and at least two minor criteria is required for a presumptive diagnosis of acute rheumatic fever and is enhanced by either a history of a recent upper respiratory tract infection, a positive throat culture, or a positive antistreptococcal antibody test.

Major criteria
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules
Minor criteria
Arthralgia
Fever
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein levels
First-degree atrioventricular block

Adapted from Guidelines for the diagnosis of rheumatic fever: Jones criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. JAMA 1992;268:2069–2073, with permission.

TABLE 35F.2 REVISED JONES CRITERIA FOR THE DIAGNOSIS OF ACUTE RHEUMATIC FEVER, 1992

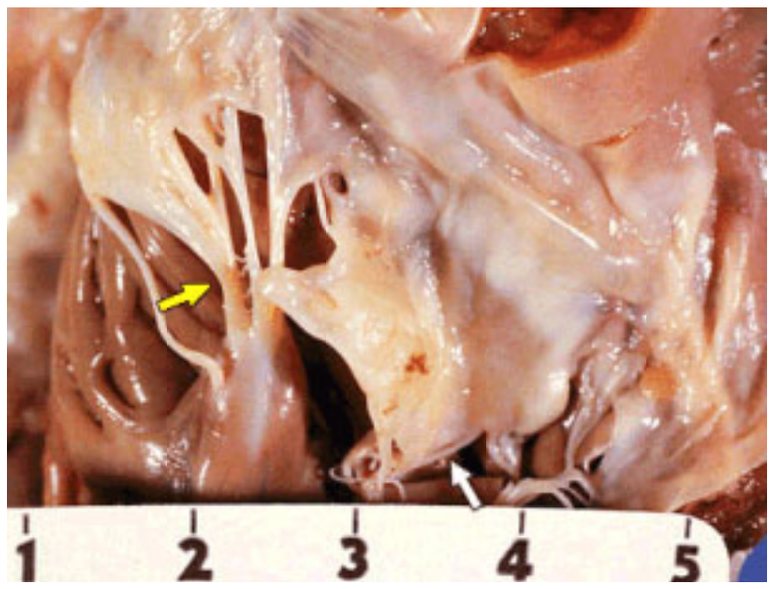
Rheumatic carditis can involve the endocardium, myocardium, or pericardium. Most commonly, there is variable involvement of the cardiac valves, particularly the mitral valve and its subvalvular apparatus, including papillary muscles and their attached chordae tendineae. Severe clinical decompensation is the exception rather than the rule. The most feared consequence of this pathologic process is chronic scarring that leads to mitral, and potentially aortic, valvular stenosis and/or regurgitation.

Video 35F.6 Parasternal long-axis view of a rheumatic mitral valve with thickened, restricted, doming leaflets. Severe mitral regurgitation is the primary functional problem with this valve with only mild mitral stenosis. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35F.7 Parasternal long-axis view of a rheumatic mitral valve with color Doppler. Mitral regurgitation is the primary problem seen by color Doppler, with only mild mitral stenosis due to the thickened and doming leaflets. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35F.8 Apical four-chamber view of a patient with severe rheumatic mitral stenosis with marked thickening and doming of the mitral leaflets, with severe ALE and spontaneous echo contrast within the left atrium. Note the left ventricle remains small. Because of long-standing severe mitral stenosis, the patient has severe pulmonary hypertension with right ventricular hypertrophy and right ventricular failure and severe right atrial enlargement. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35F.9 Long-axis 120-degree transesophageal view of a rheumatic aortic valve with central aortic insufficiency due to furled, restricted leaflets. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Rheumatic disease of the tricuspid valve. Note the shortened cordae (*yellow arrow*) and thickened valve leaflet (*white arrow*).

Treatment of mild cases is usually administration of high doses of aspirin (87). Corticosteroids can be added to this regimen for severe cases. To prevent recurrences of carditis and acute rheumatic fever, long-term, perhaps even lifelong, antibiotic prophylaxis involving administration of benzathine penicillin G intramuscularly every 3 weeks is recommended, although the duration of therapy should be individualized, depending on the patient's risk of recurrence (88).

Chlamydia pneumoniae

The chlamydiae are ubiquitous obligate intracellular gram-negative bacteria that have generated tremendous interest recently as a result of the purported association between *C. pneumoniae* and the development of coronary atherosclerosis. Seroepidemiologic studies initially demonstrated increased anti–*C. pneumoniae* antibody titers in patients who had acute myocardial infarctions (68%) or chronic angina (50%) as compared to control subjects (17%) (89). This concept, however, remains controversial—several studies have since confirmed this finding (90,91 and 92), but others have refuted it (93,94 and 95), mainly because of a prevalence of high seropositivity in the control groups of the latter studies. Nevertheless, the potential evidence supporting this association is strengthened by the vast majority of studies, which have readily demonstrated the presence of *C. pneumoniae* organisms in atherosclerotic plaques (96,97 and 98) but rarely in normal coronary arteries. This evidence is weakened, however, by the finding that although *C. pneumoniae* DNA could be detected in the presence of coronary atherosclerosis, it did not reflect either the extent or severity of the disease (99). In this study, *C. pneumoniae* DNA could be detected only at one site in one patient with severe diffuse atherosclerosis, whereas another patient with only mild coronary atherosclerosis had detectable DNA in every arterial segment examined. Furthermore, in contrast to CMV, no evidence exists to support an association between *C. pneumoniae* and the occurrence of restenosis after percutaneous coronary atherectomy (100).

The ability to detect *C. pneumoniae* in coronary atherosclerotic plaques does not prove that the organism plays a role in the genesis of the disease. The evidence would be more convincing if a reduction in cardiovascular events could be shown after eradication of the organism using antibiotic therapy. Thus far, one small study has demonstrated a fivefold reduction in cardiovascular events after short-term therapy with azithromycin in patients who had experienced a myocardial infarction (101). In the ROXIS study (Randomized Trial of Roxithromycin in Non–Q-Wave Coronary Syndromes), a small but statistically significant reduction in cardiovascular events at 30 days was found in patients who had unstable angina and were treated with roxithromycin, although this effect was not sustained to 90 days (102). The ACADEMIC study (Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with *Chlamydia*) failed to show any benefit at 6 months in a lower-risk population of individuals with stable coronary disease who were treated with azithromycin, although the primary end point of cardiovascular events at 2 years has yet to be completed (103). Nevertheless, two large randomized, placebo-controlled trials using prolonged treatment courses of azithromycin are currently under way (WIZARD [Weekly Intervention with Zithromax (Azithromycin) for Atherosclerosis and Its Related Disorders] [104] and ACES [Azithromycin and Coronary Events Study] [105]). However, because antibiotics such as azithromycin produce key antiinflammatory effects by virtue of matrix metalloproteinase inhibition, it will not be possible to assert fully the role of *C. pneumoniae* in the atherosclerotic process on the basis of the aforementioned studies alone. At this juncture, therefore, insufficient data exist to justify the widespread use of antibiotic treatment in patients with coronary atherosclerosis.

Intriguingly, it has recently been hypothesized that the early lesions found in nonrheumatic aortic stenosis have striking similarities to the early lesions of coronary atherosclerosis, including the predominance of inflammatory cells, the accumulation of lipid, and the thickening of the fibrosa (106). In recent data very reminiscent of those collected for coronary atherosclerosis, several small studies have found evidence of *C. pneumoniae* in aortic valve lesions in patients who have nonrheumatic aortic stenosis (107,108), although a causal link has yet to be established.

C. pneumoniae (109) and *Chlamydia psittaci* (110) have also both been implicated in cases of acute myocarditis, albeit rarely.

Other Bacteria

Corynebacterium diphtheriae infection can commonly lead to myocarditis by virtue of the associated exotoxin, which has a high affinity for the cardiac conduction system. Once myocardial involvement occurs, the patient has a much poorer prognosis, and the mortality rate is higher than 50% (111). This disease has largely been eradicated in the developed world as a result of widespread childhood immunization programs, but it persists in the developing world, where such programs have not been implemented. Treatment of this life-threatening condition consists of both antitoxin towards the exotoxin and antibiotics effective against the infecting organism.

Whipple's disease, or intestinal lipodystrophy, is a rare chronic systemic bacterial infection caused by *Tropheryma whippelii*. Cardiac involvement in Whipple's disease is common, with histologic evidence in up to 78% of patients including the pericardium (112), myocardium (113), valves (114), and coronary arteries (115). Patients are rarely symptomatic.

Initially, *Helicobacter pylori* was serologically linked to coronary atherosclerosis in several small studies (116,117). However, the results of several larger studies have since contradicted this finding (118,119), and further investigation of this organism has largely been abandoned.

Many other bacteria have also been associated with myocarditis, including *Neisseria meningitidis* (meningococcus) (120), *Mycoplasma pneumoniae* (121), *Legionella pneumophila* (122), *Brucella melitensis* (123), *Salmonella typhi* (124), and *Vibrio cholerae,* by way of its cholera toxin (125).

Spirochetes

Lyme Disease

Lyme disease is a systemic illness caused by the spirochete *Borrelia burgdorferi,* whose primary vector is the ixodid tick. Carditis is a common manifestation thought to occur in approximately 10% of all patients in the disseminated phase of the illness, often weeks to months after the initial infection (126,127). Because it can take as long as 8 weeks for serologic conversion to occur, signs and symptoms of Lyme borreliosis frequently precede positive serologic tests, and many false-negative results may be seen before seroconversion. The most common cardiac finding in patients with Lyme disease is varying degrees of atrioventricular heart block, which can fluctuate from normal to first-degree atrioventricular block to complete heart block in the same patient within minutes (126,127). Although patients are often asymptomatic, some may become syncopal during periods of high-degree atrioventricular block and may benefit from temporary transvenous pacing (127,128). Permanent pacing is rarely indicated, and complete resolution of the conduction disturbance usually occurs within 1 to 2 weeks (126,127).

Less commonly, Lyme borreliosis can also cause acute myopericarditis (126,128,129), and *B. burgdorferi* has been isolated from EMB from patients with acute (128,130) and chronic (131) cardiomyopathies. Furthermore, patients with chronic DCM are more likely to have positive results of serologic testing for *B. burgdorferi* than are control subjects (132), although the association seems to be weak and has not been confirmed by other studies (133). This hypothesis is enhanced by the finding in one study that ceftriaxone reversed the cardiomyopathic process in 9 of 42 patients who were seropositive for *B. burgdorferi* (134), although other studies have been unable to demonstrate such a reversal (131,132). Suffice it to say, the evidence supporting an epidemiologic role for *B. burgdorferi* in DCM is very circumstantial, fails to prove causation, and is not currently the subject of major investigative efforts.

Current recommendations for treatment of Lyme disease carditis are listed in Table 35F.3 (135). Treatment during the early phase of the disease seems to eliminate the potential for development of future disseminated disease, including carditis (136). No evidence exists, however, demonstrating administration of appropriate antibiotic therapy after carditis has developed leads to more rapid resolution of the carditis, since Lyme disease carditis is usually self-limited, with complete recovery in most cases. Nevertheless, administration of antibiotic therapy is now common clinical practice, used mainly to prevent further dissemination of the disease, including avoidance of neurologic sequelae. Others have advocated the use of corticosteroids and salicylates for patients with severe cases (126,127), but this approach has not been proven by prospective studies to confer any therapeutic advantage.

Early Lyme disease
Doxycycline, 100 mg twice daily for 10–21 d; amoxicillin, 500 mg three times daily for 10–21 d
Lyme carditis
Ceftriaxone, 2 g i.v daily for 14 d
Penicillin G, 20 million U i.v. daily for 14 d
Alternatives, for mild cases of Lyme carditis only
Doxycycline, 100 mg orally twice daily for 14–21 d
Amoxicillin, 500 mg three times daily for 14–21 d

Adapted from Rahn DW, Malawista SE. Lyme disease: recommendations for diagnosis and treatment. *Ann Intern Med* 1991;114:472–481, with permission.

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TABLE 35F.3 RECOMMENDATIONS FOR THE TREATMENT OF LYME CARDITIS

Other Spirochetes

In the early part of the twentieth century, syphilitic aortitis, caused by the spirochete *Treponema pallidum,* was relatively common and resulted in aortic aneurysms, aortic valvular insufficiency, and coronary ostial stenoses (137). However, this condition has largely been eradicated by widespread public health measures put in place to stop the spread of sexually transmitted diseases and by the development of effective antibiotic therapy (see Chapter 109). Localized gummatous myocarditis was exceedingly rare even before the eradication of this disease (137).

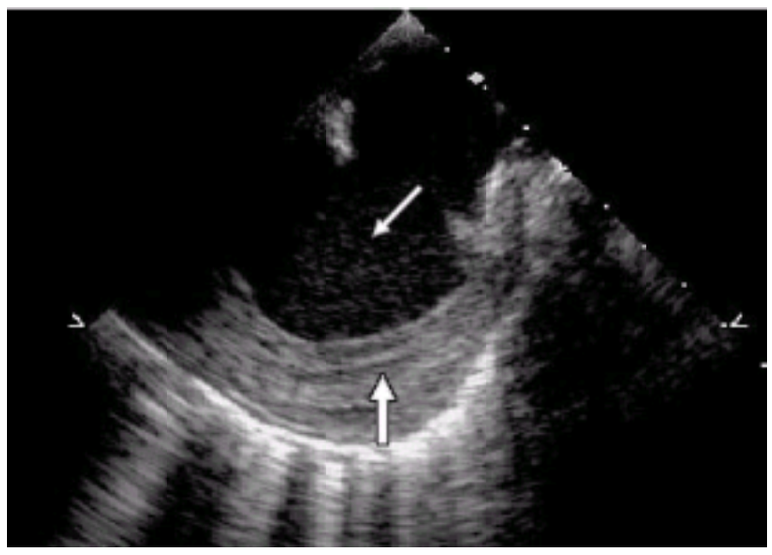
VIDEO

Video 35F.10 Transgastric view (transesophageal echo) of the mitral valve in a patient with severe aortic insufficiency. Note the fluttering of the anterior mitral leaflet (*left*) due to the jet of aortic insufficiency hitting it (color flow seen on the left). (Reproduced with permission from the Adult Clinical Cardiology Self Assessment

Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35F.11 Aortography showing an aneurysm of the ascending aorta with 3+ aortic regurgitation. The aortogram in this patient with cystic medial necrosis shows a maximum dimension of 5.4 cm. The dilation is confined to the ascending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 35F.12 Transesophageal echo view of a patient after a large left anterior descending coronary artery territory infarction with an apical aneurysm. Note the spontaneous echo contrast seen within the left ventricular cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Transesophageal view of the aortic arch demonstrating an arch aneurysm (*thin arrow*) with layering of thrombus inferiorly (*thick arrow*).

Patients with severe leptospirosis, caused by the spirochete *Leptospira interrogans,* often have transient electrocardiographic changes (138) and can develop acute myocarditis (139). Acute coronary arteritis and aortitis are also common postmortem findings in patients with severe leptospirosis (139).

Rickettsiae

Rocky Mountain spotted fever is a tick-transmitted systemic illness caused by *Rickettsia rickettsii* that is characterized by a generalized vasculitis. Acute myopericarditis and atrioventricular conduction disturbances are relatively common and can be fatal (140) but are usually not clinically significant (141).

Q fever is a systemic rickettsial illness caused by *Coxiella burnetii*, usually inhaled by humans after aerosolization from the placenta of farm animals. Valvular endocarditis is by far the most common clinical presentation of chronic Q fever infection (142). Conversely, acute myopericarditis is a rare phenomenon, although it portends a much worse prognosis (142).

Ehrlichiosis is caused by *Ehrlichia*, a tick-borne rickettsial organism that infects circulating monocytes and granulocytes. It can also rarely cause acute myocarditis (143).

Fungi

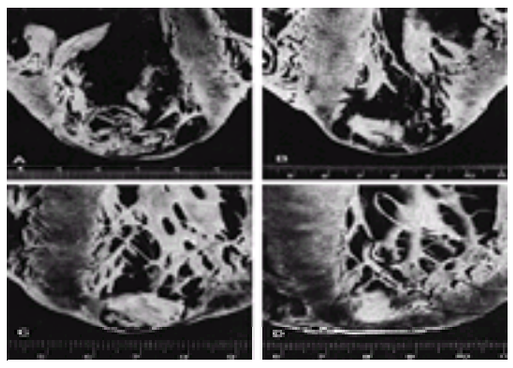
Fungal infections of the heart are uncommon and generally occur only in patients who are immunosuppressed after chemotherapy, after organ transplantation, or because of HIV (36,144). Fungal endocarditis can also occur after cardiac surgery, intravenous drug abuse, or prolonged central venous access (145,146). Although disseminated *Aspergillus* and *Candida* infections are common after heart transplantation (147), involvement of the myocardium is exceedingly rare. Fungal myocarditis has been reported as a result of infection with *Aspergillus* (144,145,148), *Candida albicans* (145,149), *Histoplasma capsulatum* (36), *Cryptococcus neoformans* (36,150), *Coccidioides immitis* (151), and mucormycosis (152). In postmortem studies, myocardial fungal involvement is characterized by diffuse myocardial abscesses and coronary artery occlusion by fungal mycelia and thrombus (145,149,152). However, direct invasion via the mediastinum has also been observed (153).

Parasites

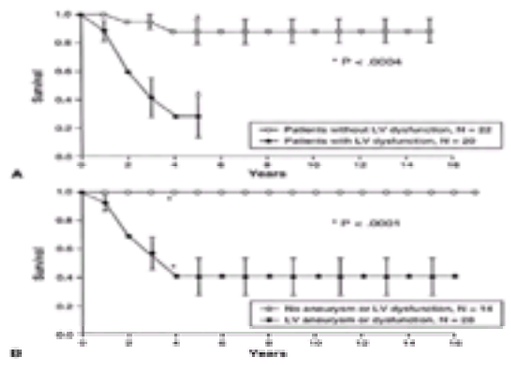
Chagas' Disease (Trypanosomiasis)

Chagas' disease is a protozoal infestation caused by *Trypanosoma cruzi* and is transmitted to humans in the feces of the reduviid bug as it bites. Chagas' disease is endemic to Central and South America, where more than 20 million people are currently estimated to be infected (154). More rarely, it may be transmitted by blood transfusions from a previously infected donor (155). The acute phase of the human disease is usually benign and clinically asymptomatic, with the exception of a mild fever, although acute myocarditis can be demonstrated by EMB in most patients and can be fatal (156). More commonly, a slowly progressive cardiomyopathic process ensues that may remain clinically unrecognized for more than 20 years (154). During this indeterminate phase, 30% to 40% of infected patients (and more than 80% of those who go on to develop a cardiomyopathy) develop cardiac conduction abnormalities due to extensive myocardial fibrosis. Right bundle branch block and left anterior hemiblock are the most frequently seen abnormalities and can progress to higher degrees of atrioventricular heart block (157).

Chronic Chagasic cardiomyopathy develops in approximately 10% to 30% of all infected patients. The pathogenesis of this disease remains highly controversial, but it is likely multifactorial, including a continued direct parasitic effect on the myocardium (158), autoimmune-mediated myocyte injury (159), and parasite-mediated microvascular endothelial injury resulting in compromised myocardial perfusion (159). Anatomically, Chagas' disease can be distinguished from other cardiomyopathies by the classical finding of apical thinning and aneurysm formation (eFig. 35F.0.5) (154,157). Functionally, multiple segmental wall motion abnormalities are common, as is global systolic dysfunction (157), highlighting the need to rule out a coronary etiology for the cardiomyopathy. These apical aneurysms and their accompanying left ventricular systolic dysfunction place patients at risk for thromboembolism (160) and potentially lethal ventricular arrhythmias (161,162). Alternatively, the cardiomyopathic process may progress unrelentingly until the patient develops overt congestive heart failure, a harbinger of a very poor prognosis (eFig. 35F.0.6) (163).



***e*FIGURE 35F.0.5 A–D:** Examples of left ventricular apical aneurysms in patients with Chagas' disease. [Reprinted from Samuel J, Oliveira M, Correa De Araujo RR, et al. Cardiac thrombosis and thromboembolism in chronic Chagas' heart disease. *Am J Cardiol* 1983;52(1):147–151, with permission.]



***e*FIGURE 35F.0.6 A:** Survival curves for patients who have Chagas' disease with and without left ventricular (LV) dysfunction. (Reprinted from Hagar JM, Rahimtoola SH. Chagas' heart disease. *Curr Probl Cardiol* 1995;20:825–924, with permission.) **B:** Survival curves for patients who have Chagas' disease with LV dysfunction or aneurysm or with neither. (Reprinted from Hagar JM, Rahimtoola SH. Chagas' heart disease in the United States. *N Engl J Med* 1991;325:763–768, with permission.)

Antiparasitic therapy at this stage is generally thought to be ineffective, although recent studies have suggested that treatment may prevent disease progression in a minority of patients (164,165). Because the prognosis for these patients is relatively poor, it would seem appropriate to attempt one course of antiparasitic therapy in virtually all patients, although this is controversial. Despite the inflammatory nature of this disorder, immunosuppression is not advised because of the potential for reactivation of otherwise latent organisms (166). Because iatrogenic immunosuppression is routinely used to prevent rejection after heart transplantation, concerns have arisen with regard to the candidacy of patients with end-stage Chagasic cardiomyopathy for transplantation. However, successful heart transplantation can be performed if it is accompanied by careful follow-up with serologic testing to detect and treat any reactivation of the disease, which occurs at some point in nearly all patients (167,168). However, the higher incidence of malignant neoplasms that has been observed in these patients in comparison with control subjects is of great concern and may be related to parasite reactivation or to the specific antiparasitic therapy they received (169). Further follow-up studies are required to examine this issue.

Other Parasites

Acute myocarditis resulting from parasitic infestation is a rare phenomenon, although multiple parasites have been implicated. *Toxoplasma gondii* may cause acute myocarditis in the immunocompetent (170) as well as the immunocompromised patient, including patients with HIV (171), patients who have undergone chemotherapy (172), and after transplantation (173). *T. gondii* can be transmitted to a heart transplant recipient through the donor allograft (174), which indicates that there is a need for careful preoperative serologic screening of both the donor and recipient.

Trichinella spiralis may also cause acute myocarditis (175). Acute cardiac decompensation can also rarely occur with *Plasmodium falciparum* infection (malaria), as a result of parasitic coronary occlusion (176). Patients with hepatosplenic schistosomiasis can develop portal hypertension and, consequently, via collateral circulation, *Schistosoma mansoni* eggs can embolize and occlude the pulmonary arteries, leading to pulmonary hypertension and cor pulmonale (177). Hydatid cysts can form within the myocardium, can compress or obstruct the adjacent chamber (178), and can be safely treated with surgical excision.

MECHANISM OF INJURY IN VIRAL MYOCARDITIS

Current knowledge about the pathogenesis of viral myocarditis is derived almost exclusively from animal studies and remains controversial and incomplete (Fig. 35F.1). There are at least three phases of injury: (a) a direct effect of the viral pathogen on the myocyte, (b) an acute inflammatory response resulting in viral clearance and myocytolysis of infected cells, and (c) a chronic phase that occurs in animals that are unable to eradicate the virus. Although the time sequence in the murine viral myocarditis model is more rapid, it is generally thought to accurately reflect the sequence of events in humans.

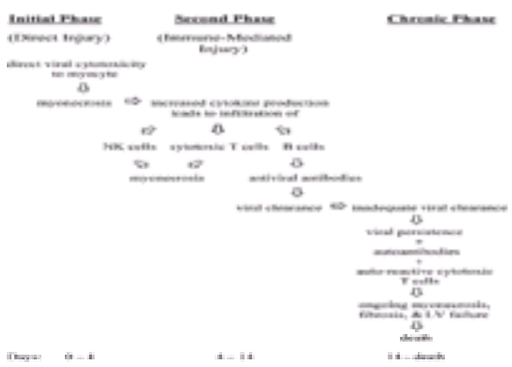
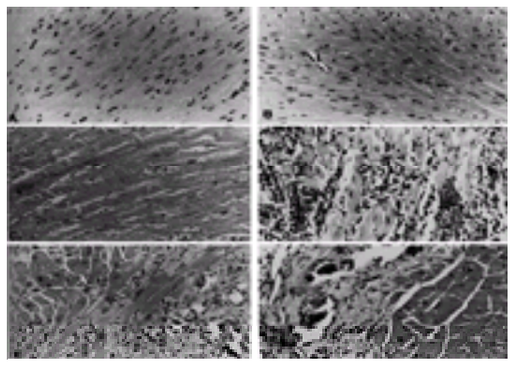


FIGURE 35F.1 Pathogenesis of acute infectious myocarditis. LV, left ventricular; NK, natural killer.

The initial phase in this murine model is characterized by the direct cytotoxic effect of the virus on the myocyte during the first 4 days after inoculation. At this time, no inflammatory infiltrate is visualized histologically (179,180), yet myocyte necrosis is seen (*e*Fig. 35F.1.1) (179,181). This hypothesis is strongly supported by the finding that mice with severe combined immunodeficiency syndrome, which therefore have no B- or T-cell immunologic response, have widespread myonecrosis without accompanying inflammatory cells (182).



***e*FIGURE 35F.1.1** Typical histopathologic findings in the murine experimental myocarditis model. **A:** Control subject. **B:** One day after inoculation, no histologic changes are seen. **C:** Three days after inoculation, small foci of degenerated myocytes can be seen. **D:** Seven days after inoculation, extensive cellular infiltration and myonecrosis are visible. **E:** Fourteen days after inoculation, reduced mononuclear cell infiltration and fibrosis around necrotic zones are present. **F:** Eighty days after inoculation, dense fibrosis surrounding calcification is visible. (Modified from Shioi T, Matsumori A, Sasayama S. Persistent expression of cytokine in the chronic stage of viral myocarditis in mice. *Circulation* 1996;94:2930–2937, with permission.)

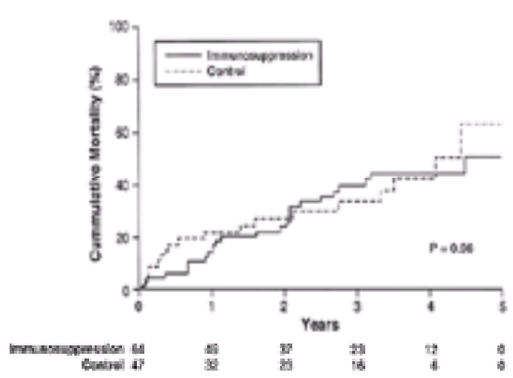
The second phase, which usually occurs from days 4 through 14, is characterized by a large increase in cytokine production that leads to severe inflammatory cell infiltration and myocyte necrosis (*e*Fig. 35F.1.1) (179). Similar cytokine elevations have also been observed in humans who have acute myocarditis (183). Natural killer cells appear in this inflammatory milieu on approximately day 4 and inhibit viral replication, which is also peaking at this time (184), resulting in cytolysis of infected cardiac myocytes (185). Viruses are also cleared via B lymphocyte–derived antiviral antibodies, which appear after day 4 with a rapidly rising titer (186,187). T lymphocytes are also crucial in this phase, and concentration of these cells peaks on days 7 through 14, resulting in widespread myonecrosis of infected cells (188). The importance of lymphocytes to the process of virus load clearance has been confirmed in mice with severe combined immunodeficiency syndrome, in which viremia persisted throughout the duration of the study (182). T lymphocytes recognize viral proteins expressed on the surface of infected myocytes, resulting in further myocytolysis (189). However, T lymphocytes are not critical for virus load clearance and seem to play a role that is more harmful than helpful by increasing the severity of the resulting myonecrosis (180,190) and perhaps also by killing uninfected myocytes through autoimmune mechanisms (190,191). Therefore, in this model, humoral immunity is responsible for virus clearance, and cellular immunity inflicts much of the pathologic damage to the myocardium.

The chronic phase is characterized by progressive myocardial dysfunction and left ventricular dilation. Several different mechanisms have been proposed to explain this deterioration, but, in all likelihood, the process is multifactorial. With more sensitive diagnostic tools such as rt-PCR and *in situ* DNA hybridization, persistence of viral RNA has been demonstrated in the hearts of patients with chronic cardiomyopathy, raising the possibility that virus-specific immune-mediated damage is ongoing (18,24,192). Alternatively, ongoing myonecrosis may be caused either by autoantibodies, which cross-react between viral antigens and cardiac myocyte antigens (193,194 and 195), or by autoreactive cytotoxic T lymphocytes, which cross-react in a similar manner (191). In this scenario, uninfected cells are also irreversibly injured.

TREATMENT OF INFECTIOUS MYOCARDITIS

Treatment for both acute and chronic infectious myocarditis is generally aimed at reducing congestion, improving cardiac hemodynamics, and prolonging survival, irrespective of the etiology of the disease. Several guidelines exist and are updated regularly to assist in this endeavor (196,197). This topic is covered in greater detail in Chapter 91 and Chapter 92. However, it is important to note that, in murine models of acute myocarditis, high doses of digoxin increased mortality, presumably by increasing the production of various cytokines, in contrast to congestive heart failure from other etiologies (198).

Immunosuppression by means of corticosteroids, cyclosporine, azathioprine, or a combination was once advocated for the treatment of new-onset myocarditis. However, the Myocarditis Treatment Trial showed no survival benefit or improved myocardial recovery among patients who received immunosuppression (*e*Fig. 35F.1.2) (199). Nevertheless, no harmful effect from immunosuppression could be demonstrated, raising the possibility that patients with infectious myocarditis may have a poorer prognosis when they receive immunosuppression as a result of increased virus proliferation, whereas patients with a purely inflammatory or autoimmune etiology may in fact improve with such therapy. The ongoing European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases is addressing this issue by treating patients for whom viral etiologies have been identified with a specific antiviral agent, whereas patients in whom no viral etiology has been found are treated with corticosteroids (200). Immunosuppression has also been shown to be clinically ineffective when used to treat patients with DCM (201,202), although a more recent nonrandomized study has contradicted this finding (203).



***e*FIGURE 35F.1.2** Actuarial mortality in the Myocarditis Treatment Trial. The numbers of patients at risk are listed at the bottom of the graph. (Reprinted from Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med* 1995;333:269–275, with permission.)

Intravenous immunoglobulin therapy had also recently been advocated for patients with acute myocarditis, including pathogen-specific immunoglobulin (such as for CMV) (204) and nonspecific high-dose immunoglobulin (205,206 and 207). A recently completed randomized trial—Intervention in Myocarditis and Acute Cardiomyopathy—failed to demonstrate any therapeutic effect of intravenous immunoglobulin therapy (207a). Treatment of patients with acute myocarditis with immunomodulating agents such as interferon-a or thymomodulin, which reduces viral replication and myocardial inflammation, has been proposed (208,209). Although this suggestion is supported by results of a study using a murine model (210), larger randomized human studies are necessary before such treatment is widely implemented.

Specific antimicrobial therapy should always be tried when it is available. This is particularly true for patients infected with CMV, bacteria, spirochetes, rickettsiae, or parasites. However, the most common viral species have no specific antiviral therapy. Ribavirin, a nucleoside analog with potent nonspecific antiviral activity, has been shown to prevent the development of viral myocarditis in a murine model (211,212). Ribavirin was only effective, however, when it was administered before or at the same time that inoculation with the viral pathogen occurred. Any delay in the administration of the ribavirin rendered it useless, which may explain its apparent ineffectiveness in humans (212).

Infrequently, acute myocarditis may become fulminant and lead to circulatory collapse and cardiogenic shock. Such patients can be hemodynamically supported with extracorporeal membrane oxygenation (213) or ventricular-assist devices (214). Most patients can be successfully weaned from these devices within a few days, as ventricular function improves. If ventricular function does not improve, these devices can serve as a bridge to transplantation. Initial concerns about decreased survival after heart transplantation in the setting of active myocarditis (215) have been recently contradicted by a large retrospective analysis (216). However, a greater frequency of episodes of acute rejection, particularly in the first 4 months after transplantation, is observed in patients who have preoperative myocarditis (215,217), which may predispose them to an increased risk of transplant vasculopathy (218). At this juncture, it seems prudent to attempt to stabilize patients medically for as long as possible, to allow them a chance to recover ventricular function, or, at the very least, to perform transplantation in a less inflammatory or infectious milieu (214).

CONTROVERSIES AND PERSONAL PERSPECTIVES

A clinician's ability to accurately diagnose and specifically treat patients with acute infectious myocarditis has not progressed at the same rate as it has with other cardiac ailments. This stems from four fundamental difficulties associated with this disease process: (a) patients do not present to a physician before most of the damage is already done, (b) clinicians have a low index of suspicion for this disorder, (c) identifying the exact causative pathogen in a time-efficient manner is difficult, and (d) few specific therapies are available once a pathogen has been identified. Although the EMB remains the current gold standard for the diagnosis of acute infectious myocarditis, it will always suffer from a lack of sensitivity and specificity. The addition of rt-PCR and *in situ* DNA hybridization has enhanced this diagnostic modality, but they are targeted at identification of specific DNA sequences and thus require knowledge of which organisms should be sought. In light of the plethora of potential pathogens, such testing could become an expensive and time-consuming endeavor, like searching for the proverbial needle in a haystack. Furthermore, the lack of specific antimicrobial therapies renders the identification of the pathogen mainly an academic exercise. Therefore, it seems to me that any advancement in this field must begin with the development of either specific effective therapies against the offending pathogen or immunomodulatory therapies that would reduce the extent and severity of the immune-mediated injury. Only then will improvements in diagnostics become clinically meaningful.

THE FUTURE

The greatest worldwide epidemiologic impact on infectious myocarditis could be achieved via improved living and health standards in the Third World, including methods for prevention of sexually transmitted diseases. Clearly, the incidence and prevalence of HIV and Chagasic cardiomyopathies could be significantly reduced with such measures.

Further investigations are currently under way to determine whether coronary atherosclerosis is truly an infectious disease. These results should be available within a few years and may alter the way in which this disease process is perceived. At the very least, it is likely that infectious diseases serve a facilitative role in promoting vascular inflammation and, in some patients, may represent the principal pathway to decompensation of vulnerable atherosclerotic plaque.

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36

SUBSTANCE ABUSE AND THE HEART

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SHEREIF REZKALLA

“ Indicates text or graphics that appear only in the electronic versions of this text.”

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OVERVIEW

Cocaine may be associated with myocardial ischemia and myocardial infarction (MI). A physician who sees a young person with an unexplained MI should consider cocaine use to be a possible cause. Cocaine may also cause hypertension, cardiomyopathy, arrhythmias, and sudden death. Whether coffee is associated with cardiovascular disease remains highly controversial. Anabolic steroids and amphetamines have been associated with cases of MI. Excessive alcohol consumption causes dilated cardiomyopathy and hypertension, although small doses of alcohol may reduce coronary disease. Tobacco use is unquestionably a strong risk factor for coronary artery disease.

COCAINE CARDIOTOXICITY

Of the various substances of abuse that may affect the heart, cocaine has received the most attention over the last 10 years (1,2,3,4,5,6,7,8 and 9). This is largely a result of its widespread use, especially in large urban areas of the United States; the relative ease with which the substance can be obtained; and the occurrence of sudden death among athletes who have used cocaine. In this section, we review the history of cocaine use, describe the basic science of the effect of cocaine use on the heart, detail the results of clinical and autopsy reports of cocaine use in humans, and describe the clinical approach to and therapy for patients who have cocaine cardiotoxicity.

History

Cocaine is an alkaloid from the *Erythroxylon coca* plant, which grows primarily in South America (10). The Indians of South America have chewed coca leaves for thousands of years. During the Inca empire, coca leaves were used as part of religious ceremonies and given as gifts for special services. In the eleventh century, coca leaves lost their religious significance, and chewing of the leaves spread across all social classes; the leaves were often used as payment for labor in the fields. Writings tell of the restorative powers of coca leaves, including their ability to satisfy hunger and provide a sense of strength and power to the weary. Albert Nieman identified cocaine as the active substance in coca leaves in the late 1850s, and as early as 1880, experimental studies in dogs showed that cocaine had a cardiac-accelerating effect. Sigmund Freud advocated the use of cocaine for a host of ailments, and Carl Koller and William Halstead demonstrated that cocaine had local anesthetic properties.

In the 1860s, a wine known as Vin Mariani, which contained cocaine as a stimulant, was introduced to the market, and in 1886, the drink Coca-Cola was introduced, with cocaine as the active ingredient in the original preparation. Cocaine has since been removed from Coca-Cola, but in the late 1800s, a number of wines and tonics contained cocaine. The first death associated with cocaine use was reported in the 1890s, and numerous reports of addiction and death—including death from use of cocaine as a local anesthetic—occurred in the early 1900s.

That cocaine could affect the human heart was suggested by an article by Lewin, in 1931, which stated, “Experiments carried out years ago in Europe roved that drinking of an infusion of 12 g of coca leaves, occasioned—besides a greater frequency of pulse, palpitations of the heart, faintness, seeing of sparks and tinnitus aurium—a feeling of augmented power and a greater desire for activity” (11,12).

By the early 1900s, cocaine was regarded as a dangerous and addictive substance. President William Howard Taft, in an address to Congress in 1910, said that “cocaine posed the most dangerous drug problem that the United States ever faced.” The Pure Food and Drug Act of 1906 required that cocaine be listed as an ingredient whenever it was included, and the Harrison Narcotic Act of 1914 permitted sale of cocaine by prescription only and banned the use of cocaine in patented remedies. Public sentiment was in favor of these regulations, and medical problems caused by cocaine use were relatively infrequent until the 1970s, when cocaine gained prominence as a recreational drug. In the mid-1980s, several highly publicized cases of deaths in athletes who used cocaine and various reports (13) that linked the recreational use of cocaine to cardiac events stimulated renewed interest in the medical consequences of cocaine abuse. (The chewing of coca leaves is still common in South America, where, in general, serious medical consequences have not been reported; this may be because a lower dose of the substance is extracted when the plant leaves are chewed, because cocaine is degraded by gastric acid, and because only a small amount of gastrointestinal absorption occurs when cocaine

is taken in this fashion.)

It is estimated that approximately 5 to 6 million people in the United States use cocaine on a regular basis, that approximately 1 million are addicted, and that 25 to 30 million Americans have tried cocaine at least once (2,3).

Forms of Cocaine

Cocaine hydrochloride is a water-soluble form of cocaine in which the alkaloid extract of the *E. coca* plant is dissolved in hydrochloric acid to form a white crystalline powder (14,15). Because the white powder can be absorbed by the mucous membranes, intranasal insufflation (snorting) of this white powder is the most common route of administration. The powder also can be injected intravenously. Cocaine is not readily absorbed gastrointestinally, and the low pH of the gastric mucosa may inactivate the alkaloid (14,15).

Crack cocaine is produced by mixing cocaine powder with baking soda and water and then heating the results. The alkaloid base precipitates into a soft mass that hardens and is then smoked. The term “crack” derives from the cracking or popping sound heard when the cocaine crystals are prepared in this fashion.

Freebase cocaine is made by mixing the cocaine powder with a base (such as ammonia) and a solvent (such as ether). The alkaloid base or “free base” is extracted from the ether by evaporation. Like crack, freebase cocaine is smoked. The flammability of ether poses yet another danger in the preparation of this form of cocaine. Freebase use has declined as crack has become more available, and because crack does not pose the problem of flammability.

An estimated 90% of cocaine use in the United States is carried out through nasal snorting. In addition, approximately one-third of cocaine users have smoked crack. Less than 10% have injected the drug intravenously. Because cocaine is rapidly absorbed through the respiratory tract, smoking of either crack or freebase cocaine rapidly delivers cocaine to the circulation. Cocaine enters the brain within 6 to 8 seconds by the respiratory route (smoking) and within 10 to 15 seconds by an intravenous route. Snorting cocaine results in eak cocaine concentrations in 30 to 60 minutes (15). The amount of cocaine that can be absorbed through the nasal route may be self-limited to some extent because of vasoconstriction of the nasal mucosa induced by cocaine itself.

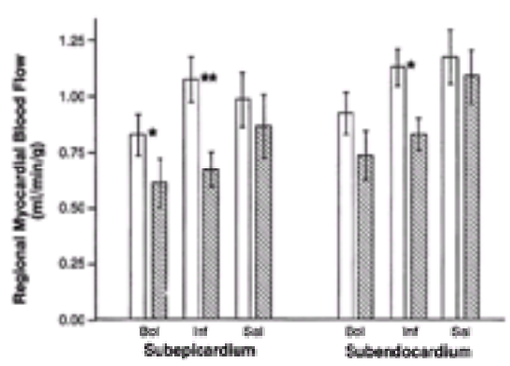
Cocaine is often combined with other substances, most commonly ethanol. An estimated 9 to 12 million individuals use this combination on a recreational basis (16,17). Cocaethylene is the cocaine metabolite formed in the presence of ethyl alcohol and may be more potent than cocaine itself (see Cocaethylene).

Pharmacology

The pharmacology of cocaine is complex and has been the subject of a vast amount of basic science research during the last 10 years. First, cocaine is a local anesthetic. It blocks sodium and potassium channels (6) and thus blocks initiation and conduction of electrical impulses. This effect accounts for prolongation of electrocardiographic (ECG) intervals and decreases in cardiac contractility and may lead to a proarrhythmic effect (18). Second, cocaine blocks the reuptake of neurotransmitters at the presynaptic endings of nerves. As a result, neurotransmitters such as dopamine and norepinephrine accumulate in the synaptic cleft, which results in an intense sympathomimetic effect (6). This second major action of cocaine accounts for increases in heart rate, blood pressure, and contractility and, by stimulation of alpha receptors in the vasculature, contributes to vasoconstriction. A third pharmacologic action of cocaine that affects the cardiovascular system is a decrease in vagal tone, which also contributes to an increase in heart rate (19). Thus, on the one hand, cocaine may have a cardiodepressive effect resulting from its effect on sodium and potassium channels. On the other hand, it has a stimulatory effect because of its sympathomimetic properties. These opposing forces may result in very complex outcomes (20).

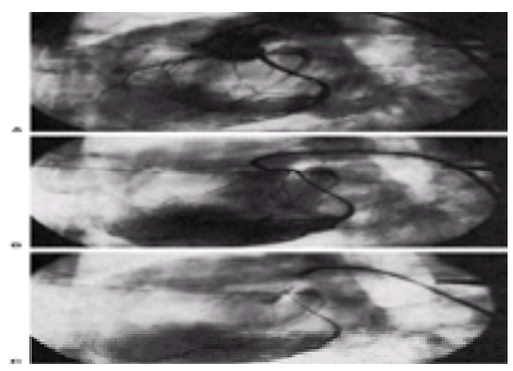
Effects of an Acute Dose of Cocaine on the Heart in Experimental Studies

A number of studies have investigated the acute effects of cocaine on the heart. In one study involving canines anesthetized with sodium pentobarbital (21), the hemodynamics, regional myocardial blood flow, and echocardiographic effects of an intravenous dose of cocaine, 10 mg per kg—a dose that simulates the use of either intravenous cocaine or inhalation of crack smoke—was assessed. Cocaine caused no significant effect on heart rate or blood pressure in this model, probably because the animals were already influenced by the sympathomimetic effect of sodium pentobarbital. In awake, conscious preparations, cocaine typically produces an increase in both heart rate and blood pressure (22,23). Cocaine caused a significant depression in the change of ventricular pressure over time (dP/dT) and an acute dilatation of the left ventricle seen on echocardiography, with increases in both end systolic and end diastolic left ventricular (LV) cross-sectional area (21). Regional myocardial blood flow, assessed by radioactive microspheres, showed an acute reduction in global flow, most impressive in the subepicardium (eFig. 36.0.1).

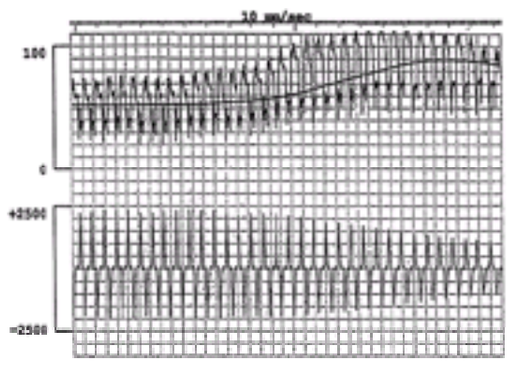


***e*FIGURE 36.0.1** Regional myocardial blood flow in the subepicardium and subendocardium of anesthetized dogs before (*open bars*) and 15 minutes after (*hatched bars*) administration of cocaine or saline. Bol, bolus cocaine administration; Inf, cocaine infusion; Sal, saline; **p* <.04; ***p* <.004. (From Hale SL, Alker KJ, Rezkalla S, et al. Adverse effects of cocaine on cardiovascular dynamics, myocardial blood flow, and coronary artery diameter in an experimental model. *Am Heart J* 1989;118:927–933.)

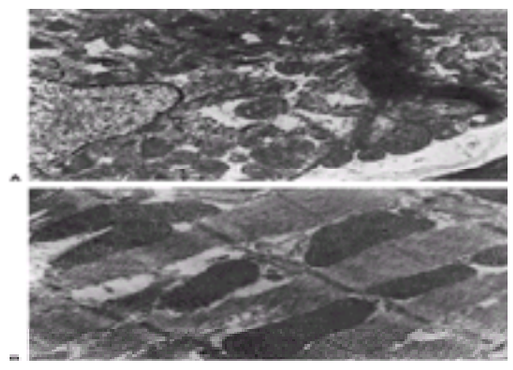
Coronary angiography in dogs receiving an acute bolus of cocaine showed diffuse coronary vasospasm in all epicardial coronary arteries (eFig. 36.0.2). An assessment of timing of acute depression of ventricular function versus blood flow revealed a fall in dP/dT before a fall in coronary blood flow (eFig. 36.0.3), suggesting that depression of ventricular function was a primary effect of cocaine, followed by a further secondary fall in ventricular function caused by subsequent reduction in coronary flow (24). Other investigators have described an acute fall in LV function with administration of cocaine. Sequential intravenous boluses of cocaine administered to dogs resulted in a progressive deterioration of both positive and negative dP/dT (25). Cocaine administration to anesthetized rabbits resulted in acute regional wall motion abnormalities seen on two-dimensional echocardiography (26). In some animals, ultrastructural abnormalities were identified, including contraction-band necrosis and sarcoplasmic reticular edema (eFig. 36.0.4).



***e*FIGURE 36.0.2** Cineangiograms of coronary arteries of a dog before **(A)**, during **(B)**, and after **(C)** cocaine administration. The circumflex artery is to the right. Note the considerable reduction in circumflex artery and left anterior descending diameter after cocaine administration. (From Hale SL, Alker KJ, Rezkalla S, et al. Adverse effects of cocaine on cardiovascular dynamics, myocardial blood flow, and coronary artery diameter in an experimental model. *Am Heart J* 1989;118:927–933.)



***e*FIGURE 36.0.3** Recording showing changes in coronary blood flow (mL/min, *top channel*) and left ventricular dP/dT (change of ventricular pressure over time; mm Hg/sec, *bottom channel*) that occur shortly after cocaine bolus in anesthetized dog. Note that flow increases concurrent to a decrease in contractility, suggesting that the reduced dP/dT at this phase is unrelated to any fall in blood flow. (From Hale SL, Alker KJ, Rezkalla SH, et al. Nifedipine protects the heart from the acute deleterious effects of cocaine if administered before but not after cocaine. *Circulation* 1991;83:1437–1443, with permission of the American Heart Association.)

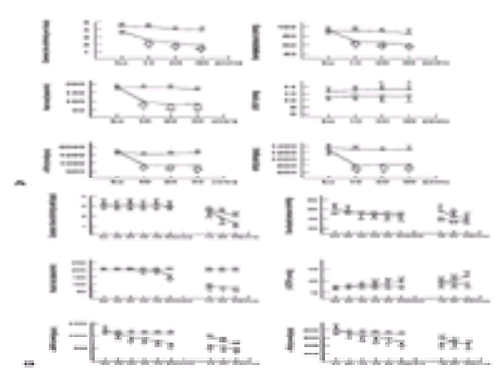


***e*FIGURE 36.0.4 A:** Electron micrographs of biopsy specimens of rabbit ventricular myocardium from rabbits that received acute doses of cocaine. A dark contraction band is observed in the upper right. **B:** Mild intermyofibrillar edema (*clear spaces*) and swollen sarcoplasmic reticulum in a rabbit that received an acute dose of cocaine. (From Gardin JM, Wong N, Alker K, et al. Acute cocaine administration induces ventricular regional wall motion and ultrastructural abnormalities in an anesthetized rabbit model. *Am Heart J* 1994;128:1117–1129.)

Because cocaine can increase blood pressure, its effect on cardiac contraction may be clouded by changes in afterload. Several studies, therefore, have investigated the effect of cocaine either in models in which loading conditions could be accounted for or in isolated heart models or cultured myocytes to determine more directly its effect on contractility.

In one study, cocaine depressed contractility in conscious dogs, independent of loading conditions (27). In another, cocaine was administered to isolated perfused rabbit ventricular septal preparations while coronary flow of oxygenated Kreb's solution and constant heart rate were maintained by pacing the septa (28). Cocaine at various concentrations caused a reduction in developed tension, maximum contraction velocity, and maximum relaxation velocity. LV function recovered completely after washout of the cocaine. The authors concluded that cocaine has an acute direct, though reversible, depressant effect on the myocardium, independent of coronary flow.

The effects of an acute dose of cocaine in the Langendorff-perfused isolated rabbit heart have been reported (29). In nonpaced hearts, 10-, 25-, and 50-µM concentrations of cocaine caused a dose-dependent deterioration in cardiac contractility, manifest by reductions in positive and negative dP/dT (*e*Fig. 36.0.5). At 50-µM doses, the decrease in cardiac contractility during the first 60 seconds of infusion preceded a fall in coronary flow or a change in heart rate. Thus, a rapid decrease in contractility was the first manifestation of the direct cardiotoxic effects of cocaine in this isolated heart model. Experiments carried out in isolated cardiomyocytes in culture have confirmed a direct negative inotropic effect of cocaine (30).



***e*FIGURE 36.0.5** Early and late effects of cocaine, 50 µM versus control, on hemodynamic variables in isolated nonpaced retrogradely perfused rabbit hearts **(A)** and in isolated paced retrogradely perfused rabbit hearts **(B)**. Ordinate: hemodynamic variables. Abscissa: Time in protocol. Values are mean ± standard error of the mean. *Open circles,* control group (n = 6); *open triangles,* cocaine-treated group (n = 6). bs, baseline; HR, heart rate; LVEDP, left ventricular end diastolic pressure, +dP/dT, positive change in ventricular developed pressure over time; –dP/dT, negative change in developed pressure over time; **p* <.05 versus control group; ***p* <.05 versus bs. (From Simkhovich BZ, Kloner RA, Alker KJ, et al. Time course of direct cardiotoxic effects of high cocaine concentration in isolated rabbit heart. *J Cardiovasc Pharmacol* 1994;23:509–516.)

In chronically instrumented conscious dogs, the effect of cocaine on cardiac hemodynamics differs from that observed in anesthetized animal models (22). In the awake state, 1 mg per kg of cocaine caused a transient reduction in LV dP/dT, followed by a 25% increase at 15 minutes. Beta-blockers prevented the positive inotropic effects. The authors concluded that acute intravenous cocaine (0.1 to 2.0 mg per kg) results in a "biphasic effect on myocardial and left ventricular function with a transient depression followed by a significant sustained increase in left ventricular contractility" (22). These observations are consistent with an initial local anesthetic or sodium channel blocking effect (cardiodepressive) followed by sympathetic stimulation.

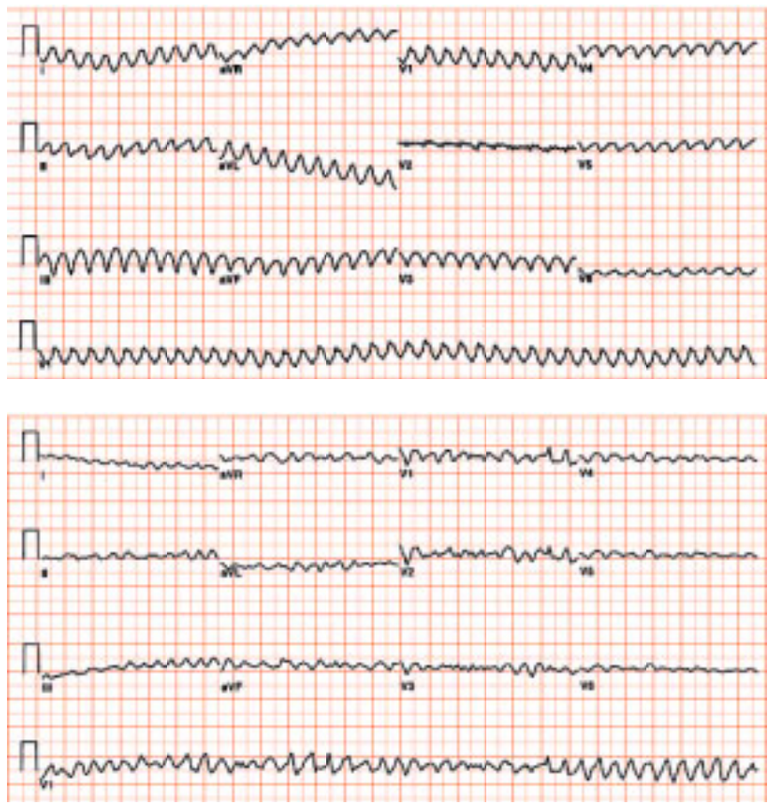
Not only did cocaine reduce coronary blood flow in the canine model with an associated diffuse coronary vasospasm of the epicardial arteries (21,31), but it also induced coronary vasospasm within arterioles (32). Several investigations have observed that isolated vascular rings constrict when exposed to cocaine (1) or the cocaine metabolite norcocaine.

Effects of an Acute Dose of Cocaine on Cardiac Rhythm

As shown in experimental animal studies, cocaine can affect cardiac rhythm by several mechanisms: (a) a sympathomimetic effect with stimulation of alpha and beta receptors may increase ventricular excitability, (b) an increase in intracellular calcium may be linked to alpha-receptor stimulation and result in oscillatory after-depolarizations, (c) vagolytic effects may be present, and (d) the local anesthetic effect (blocking sodium channels) inhibits the generation and conduction of

action-potential generation in nerve and heart tissue.

Cocaine induced ventricular tachycardia and fibrillation during catecholamine injections in anesthetized animals and ventricular fibrillation during exercise-induced ischemia in conscious animals (10). The accentuation of the sympathetic nervous system by cocaine may contribute to these lethal arrhythmias.



Ventricular flutter (A). Same patient with degeneration into ventricular fibrillation (B).

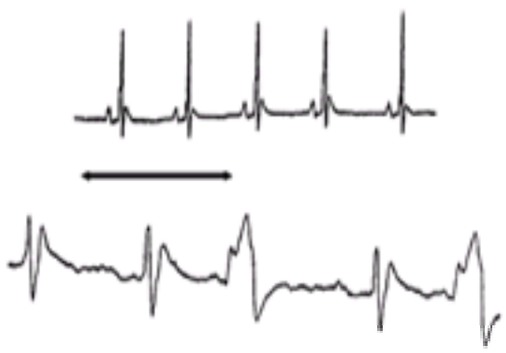
An 81-year-old male patient with ventricular tachycardia.

It has been suggested that, although stimulation of both beta and alpha receptors may play a role in cocaine-induced arrhythmias, alpha-adrenergic stimulation may be especially crucial (10). By increasing catecholamine levels, cocaine may stimulate alpha adrenergic receptors in the myocardium, resulting in an increase in intracellular calcium concentrations that can trigger delayed after-depolarizations and arrhythmias. Prazosin (an alpha-blocker) reduced the incidence of ventricular arrhythmias when administered to animals stressed by cocaine and exercise-induced ischemia. It prevented ventricular fibrillation in most cases. Propranolol was effective but lost its efficacy when its negative chronotropic effect was counteracted by pacing.

Studies have shown that cocaine increases intercellular calcium levels (33,34). Calcium channel blockers, which would reduce intracellular calcium concentrations, have been shown to be beneficial in cocaine-induced arrhythmias. This observation would also support the alpha receptor–calcium influx theory of cocaine-induced arrhythmias. Verapamil, nifedipine, and other calcium channel blockers reduce ventricular arrhythmias induced by cocaine in experimental models (10).

Recent reports have suggested that not only does cocaine increase cardiac sympathetic activity, which could predispose the heart to ventricular arrhythmias, but it also reduces vagal activity, manifested by a significant reduction in heart-rate variability (18,19,35). This withdrawal of vagal tone is very prominent when cocaine is administered during an episode of myocardial ischemia.

In a study of the effects of a 3-hour infusion of cocaine compared with saline in anesthetized rats, cocaine increased both heart rate and blood pressure during the first hour of administration, but by the second and third hour, these parameters were no longer increased (36). In cocaine-treated hearts, a significant increase in PR, QRS, QT, and corrected QT intervals on the ECG persisted for 3 hours. In four of six cocaine-treated rats, frequent atrial extrasystoles or atrial tachycardia was observed, and one rat demonstrated ventricular extrasystoles (eFig. 36.0.6). The lengthening of both intraventricular conduction and repolarization time (QT interval) may have been related to cocaine's depressant effect on action potential upstroke (local anesthetic effect) or to "quinidine-like properties of the drug." A marked prolongation of the effective refractory period in paced isolated rabbit hearts exposed to cocaine was also described (37). Several other reports have documented electrophysiologic abnormalities induced by cocaine in intact animals, including prolonged PR, QRS, and QT duration and increase in the bundle of His–ventricular HV interval (38,39,40 and 41). High doses of cocaine have induced asystole and conduction block (42,43). These effects probably result from cocaine's ability to reduce the automaticity of Purkinje cells and depress phase O of the action potential (44). Cocaine also results in delayed repolarization because of its blocking action on the calcium-dependent potassium channel (45).



***e*FIGURE 36.0.6** Electrocardiogram from a rat before (*top*) and 3 hours after (*bottom*) administration of cocaine. After cocaine, PR interval and QRS duration are markedly lengthened and there are ventricular premature beats. Distance between arrows is 1 second. (From Hale SL, Lehmann MH, Kloner RA. Electrocardiographic abnormalities after acute administration of cocaine in the rat. *Am J Cardiol* 1989;63:1529–1530.)

Conduction delays and heterogeneity of repolarization may also lead to serious ventricular arrhythmias. Thus, the local anesthetic effect of cocaine contributes to life-threatening rhythm disturbances. Bauman and associates stated that the nature of cocaine-induced sudden death in humans suggested a proarrhythmic effect of the drug similar to that of agents such as flecainide (18).

In summary, studies analyzing the effects of acute doses of cocaine in animals suggest that cocaine has both cardiodepressive and cardiostimulatory effects on the

heart. The cardiodepressive effects include reductions in contractility, blood flow, and conduction abnormalities, probably related to its local anesthetic effects. The cardiostimulatory effects are increases in heart rate, blood pressure, contractility, and ventricular excitability, and coronary vasoconstriction related to cocaine's sympathomimetic and vagolytic effects.

Another action of cocaine that can affect the cardiovascular system includes an increase in platelet aggregation, which has been documented in a rabbit model (46) as well as *in vitro* in human blood (47). his is likely caused by platelet activation and the release of alpha granules (48).

Effects of Chronic Cocaine Administration in Experimental Models

Fewer data are available on the effects of chronic cocaine use in animal models. Rats (49) given 10 mg per kg of intraperitoneal cocaine every 12 hours for 10 days developed several histochemical abnormalities, including reduction in cardiac enzymes (glucose-6-phosphate dehydrogenase, lactate dehydrogenase, and myosin-adenosinetriphosphatase). Rats receiving 8 days of cocaine administration developed electron microscopical abnormalities, including contraction bands and mitochondrial swelling (50). Rabbits kept on high-cholesterol diets developed acceleration of atherosclerosis when cocaine was administered daily (51,52). These experiments and observations made at autopsy in young patients who died of cardiovascular complications of cocaine (see below) have led some investigators to suggest that chronic cocaine use damages the endothelium, resulting in acceleration of atherosclerosis (53).

Controlled Studies of Administration of Cocaine in Humans

Cocaine is known to increase both heart rate and blood pressure in awake individuals. Fischman and coworkers (54) demonstrated a dose-related increase in these parameters when patients received intravenous cocaine. Although small doses did not have a significant effect, an intravenous injection of cocaine, 16 and 32 mg, resulted in a significant rise in both heart rate and blood pressure in human volunteers. The changes peaked at 10 minutes after administration and returned to baseline in approximately 1 hour.

To examine the acute effects of cocaine in humans, investigators administered low doses (2 mg per kg) of intranasal cocaine to patients in the cardiac catheterization laboratory (3,55,56 and 57). They observed increases in heart rate and blood pressure but only mild, diffuse reductions in coronary caliber (8% to 12% of normal), a 33% increase in coronary vascular resistance, and a 17% reduction in coronary sinus blood flow. Thus, even though myocardial oxygen demand increased—with an increase in double-product—these patients exhibited a decrease in coronary blood flow. It is likely that in cocaine abusers, who often use much higher doses than those administered in this controlled study, the imbalance in oxygen supply and demand is even worse. It was shown that the cocaine-induced coronary vasoconstriction could be reversed with the alpha adrenergic blocking agent phentolamine, suggesting that alpha-receptor stimulation by cocaine is a crucial aspect of the vasoconstriction. The vasoconstriction was worse at sites of atherosclerosis and could be relieved by nitroglycerin (58). The beta-blocker propranolol potentiated the cocaine-induced vasoconstriction, presumably because the beta receptors were blocked, leaving the alpha receptors unopposed. Investigators showed (59) that accumulation of cocaine metabolites may also contribute to coronary vasospasm. Addition of ethanol to intranasal cocaine did not worsen coronary vasospasm (16). Isolated human coronary arteries from patients undergoing cardiac transplantation have also been shown to undergo vasospasm when exposed to cocaine.

Administration of cocaine as a local anesthetic agent for use in laryngoscopy increased the frequency of ventricular premature beats (60). There have been occasional case reports of acute MI when intranasal cocaine was used as a topical anesthetic for nasal operative procedures. The effects of cocaine on human fetal left ventricles were studied (61). Cocaine reduced action potential amplitude, depressed the force of ventricular contraction, and then, at 90 minutes of exposure, resulted in electrical and mechanical arrest, which also suggests that cocaine has a direct cardiodepressant effect on cardiac muscle. And finally, we observed that when human blood is exposed to cocaine, in approximately one-half of the samples, platelet aggregation to adenosine diphosphate but not collagen or epinephrine is increased (Fig. 36.1) (47).

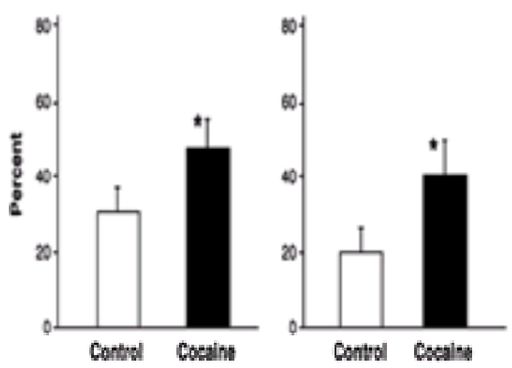


FIGURE 36.1 Platelet aggregation from humans (1 µg, adenosine diphosphate) after incubation with saline or cocaine. Peak aggregation (*left*) and aggregation at 15 minutes (*right*). Data are expressed as mean ± standard error of the mean; *p <.02. (From Rezkalla SH, Mazza JJ, Kloner RA, et al. Effects of cocaine on human platelets in healthy subjects. *Am J Cardiol* 1993;72:243–246.)

In summary, controlled studies in humans receiving low doses of intranasal cocaine showed that cocaine increases heart rate and blood pressure but causes coronary vasoconstriction at the same time. Thus, the potential for ischemia through an imbalance between oxygen supply and demand may occur, especially when even higher doses of cocaine are used.

Cardiovascular Disease Associated with Cocaine Use

Most of our knowledge regarding the clinical complications of cocaine use in patients comes from clinical reports and autopsy studies. A number of cardiovascular diseases associated with cocaine use have been reported in the literature. These are summarized in Table 36.1, and mechanisms of cocaine action are illustrated in Fig. 36.2.

Myocardial infarction and myocardial ischemia
Myocarditis
Cardiomyopathy: dilated and hypertrophic
Arrhythmias: tachy- and bradyarrhythmias
Hypertension
Aortic dissection
Endocarditis
Acceleration of atherosclerosis?

TABLE 36.1 CARDIOVASCULAR COMPLICATIONS OF COCAINE USE

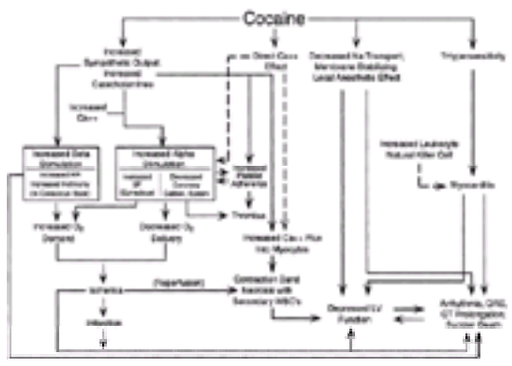
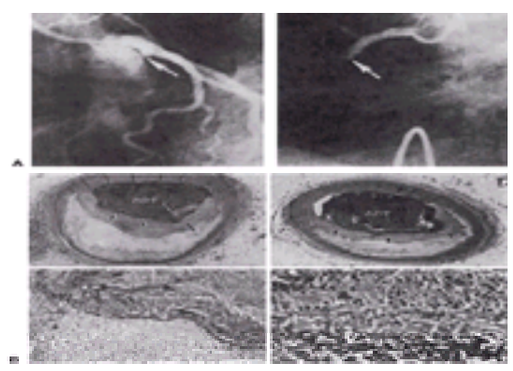


FIGURE 36.2 Schematic diagram describing potential mechanisms of the cardiotoxic effects of cocaine. Two primary mechanisms are suggested. First, cocaine inhibits presynaptic reuptake of catecholamines, resulting in a potentiation of the sympathetic nervous system and an increase in catecholamine levels. Second, cocaine inhibits sodium transport across the sarcolemmal membrane, leading to a membrane-stabilizing or local anesthetic effect that has been likened to a type I antiarrhythmic effect. In conscious preparations, increased sympathetic output and catecholamine levels result in an increase in heart rate and, in some studies, inotrophy, which can increase oxygen demand. a-Stimulation of blood vessels causes a vasoconstrictor response with increase in blood pressure in conscious preparations, also resulting in increased oxygen demand. a-Sympathetic stimulation decreases coronary artery caliber, increases coronary vascular resistance, and may lead to coronary spasm in both conscious and anesthetized preparations, thus reducing oxygen supply. Repetitive bouts of coronary spasm might alter or damage the endothelium, contributing to accelerated atherosclerosis, which has been reported with use of cocaine. Increased platelet aggregability has been reported with use of cocaine (and may be related to increased catecholamine levels), which can contribute to thrombus formation. All of these factors contribute to an imbalance between oxygen supply and demand and may thus lead to myocardial ischemia with subsequent infarction and associated left ventricular dysfunction and arrhythmias. Increased sympathetic output may also contribute to tachyarrhythmias. Catecholamine excess is known to lead to contraction-band formation, and this is thought to be related to calcium overload. Isner and Chokshi (1) postulated that cocaine may have a direct effect on calcium flux into blood vessels (and perhaps myocytes), leading to vasoconstriction that may be independent of the sympathetic nervous system (*dashed lines*). The local anesthetic effect of cocaine may cause direct depression of inotrophy (which in some studies surpasses any indirect positive inotropic response caused by sympathetic simulation) and can lead to a transient cardiomyopathic presentation. This local anesthetic effect can also lead to prolongation of electrocardiographic intervals, including QRS and QT duration, perhaps resulting in arrhythmias and sudden death, much like the proarrhythmic effects of agents such as quinidine. Hypersensitivity to cocaine has been postulated but not absolutely proved to be a cause of myocarditis. In addition, an increase in natural killer cell activity (which may be related to increased catecholamines) has been reported with cocaine and could lead to myocarditis. Scattered foci of myocarditis could lead to a cardiomyopathic presentation and form the nidus for arrhythmias. BP, blood pressure; HR, heart rate; LV, left ventricular; WBC's, white blood cells. (From Kloner RA, Hale S, Alker K, et al. The effects of acute and chronic cocaine use on the heart. *Circulation* 1992;85:407–419, with permission of the American Heart Association.)

Acute Myocardial Infarction

Four possible causes of MI are related to cocaine use. (a) Coronary artery spasm is caused by the intense alpha-sympathetic stimulation associated with use of cocaine. (b) Thrombus formation was observed in 24% of patients in whom coronary artery disease was absent (62). Thrombus may have occurred on top of an area of vasospasm that was then relieved, and increased platelet aggregability may contribute (47). Thrombus formation may also occur on top of atherosclerotic narrowing (eFig. 36.2.1). Plaque fracture or rupture, which is common in most Q-wave MIs, is usually not observed in cocaine-related infarcts (53,63). (c) Increased myocardial oxygen demand may occur in the presence of a fixed lesion. Chronic use of cocaine may cause an acceleration of atherosclerosis, resulting in atherosclerotic narrowing in young patients (53). The sympathomimetic responses of increased heart rate and blood pressure, in addition to the stenosis, may contribute to infarction. (d) Some combination of the above three may cause MI.



***e*FIGURE 36.2.1 A:** *Left,* Selective injection into left coronary artery in left anterior oblique projection, demonstrating proximal occlusion of left anterior descending artery (*arrow*). *Right,* Injection into right coronary artery in left anterior projection, demonstrating proximal occlusion of right coronary artery (*arrow*) from a 38-year-old man with acute myocardial infarction and history of both chronic and acute use of cocaine. **B:** Histopathologic features of coronary arteries from the same patient. *Top left,* Low-magnification photomicrograph of proximal left anterior descending coronary artery shows atherosclerotic plaque, thin layer of organizing mural thrombus (MT) (*arrowheads*), and large acute occlusive thrombus (AOT). Note presence of thrombus within focally disrupted plaque (*arrow*). *Top right,* Right coronary artery shows features virtually identical to those of left anterior descending coronary artery. Arrowheads indicate thin layer of organizing MT. *Bottom left,* Higher-magnification view of left anterior descending coronary artery shows loose, edematous connective tissue in a superficial portion of plaque (*bottom*) and a thin layer of organizing MT (*middle*), partially lined by flat, endothelial-like cells; the AOT is composed of large mass of granular platelets with entrapped leukocytes [hematoxylin and eosin; ×14 (*top left* and *top right*) ×70 (*bottom left*), and ×280 (*bottom right*). (From Stenberg RG, Winniford MD, Hillis LD, et al. Simultaneous acute thrombosis of two major coronary arteries following intravenous cocaine use. *Arch Pathol Lab Med* 1989;113:521–524.)

At least 114 cases of cocaine-related MI have been reported in the literature (64). Many more probably occur but are never reported. Clinical, angiographic, and autopsy features reveal some unique properties of cocaine-related infarction. MI after cocaine use typically occurs within 3 hours of use of cocaine, but this period ranges from minutes to a few days. The median time of onset of chest pain in the infarct patient depends on the route of administration (62). Onset of chest pain occurred at a median time of 30 minutes with intravenous use, 90 minutes with use of crack cocaine, and 135 minutes with nasal insufflation. In a study of 3,946 patients with acute MI (65), 38 patients reported cocaine use before the clinical presentation. The risk appears to be higher in the 60 minutes after cocaine administration, and it rapidly decreases after the first hour. In one study, the description of chest pain was typical: "pressure, crushing, squeezing, tightness, discomfort, heaviness, and in one case, sharp." Forty-four percent of patients had a history of chest pain (62). There may be a vasospastic component to some of these cases, as suggested by Holter monitoring studies of cocaine use (66). In 1988, at Montefiore Medical Center in Bronx, New York, 35 patients were admitted for chest pain associated with cocaine use. Of these, 11 developed infarction (67). Chest pain after the use of cocaine is not always caused by MI and may indicate the presence of angina or be noncardiac in nature.

In one report, the mean age of patients with acute MI associated with cocaine was 33 years, and 92% of patients were male (67). The most common associated risk factor was cigarette smoking. There does not appear to be any clear-cut dose relationship between the use of cocaine and development of MI. Chronic, occasional, and first-time users may develop infarction. The ECG was abnormal in 90% or more of patients in the emergency department. ECG abnormalities included ST segment elevation, T-wave inversion, and Q waves. Both Q- and non–Q-wave infarcts have been reported after cocaine use. High creatine kinase (CK) levels may be present as a result of trauma or rhabdomyolysis. Therefore, CK–MB elevation is needed to document damage to the myocardium (68). Cocaine users who develop coronary artery disease and MI tend to be older and to have multiple risk factors, such as smoking, compared with users who do not have evidence of coronary disease (69).

Coronary vasospasm has been well documented in only a few cocaine-related infarct patients. Coronary stenosis is present in 29%. Thrombosis is present in approximately one-fourth of the cases. In an analysis of 92 cases in which either coronary angiographic or coronary anatomic data were collected at autopsy (64), 38% of patients had normal coronary anatomy. Of these, 77% had infarcts of the anterior wall.

In a review of the literature (62), 22 of 91 cases of cocaine-induced infarction had some complication: six had congestive heart failure, three had cardiogenic shock, 11 had potentially life-threatening arrhythmias, three had ventricular fibrillation, six had ventricular tachycardia, and two had cardiac arrests. Three deaths occurred. In the series from Montefiore Hospital (67), among 22 patients with cocaine-related acute MI, no in-hospital deaths occurred, and only one episode of heart failure and

ventricular tachycardia was seen. A case report of a patient who developed an intraventricular thrombus after cocaine-induced MI was recently described (70).

Management of Cocaine-Induced Myocardial Ischemia and Myocardial Infarction

No controlled, randomized, prospective trials clarify the best way to manage cocaine-induced ischemia or infarction. As stated earlier, not all episodes of chest pain associated with cocaine are necessarily MIs. The incidence of MIs associated with cocaine-induced chest pain was 0% to 31% in retrospective analysis and approximately 6% in prospective analyses (71). In addition, not all cocaine-related chest pain is necessarily ischemic; pleuritic pain has been reported. Chest radiographs should be obtained to rule out pneumothorax and pneumomediastinum, which have both been reported with cocaine use. Initiation of thrombolytic therapy should not be delayed while chest radiographs are awaited, however, unless physical examination strongly suggests conditions other than MI.

Patients who enter the emergency department with pain that suggests ischemia (but do not have evidence of infarction) after cocaine use should be observed (71,72 and 73). One report (71) favors a 12-hour observation period during which ECG and serial CK-MB measurements are obtained to rule out MI. Total creatine phosphokinase level elevation appears to occur in a significant number of cocaine users. This is an unreliable screening test for the detection of myocardial injury (74). Myoglobin level is not reliable in detecting MI secondary to cocaine use, but troponin-1 and CK-MB appear to have a good specificity (75). If possible, previous ECGs should be obtained, because cocaine users not infrequently also have early repolarization variants on their ECG or LV hypertrophy.

Medical therapies for cocaine-related chest pain that is ischemic (anginal) but is not infarction include nitroglycerin, oxygen, aspirin, and benzodiazepines (71,72 and 73). Verapamil or other calcium channel blockers and phentolamine may be considered if pain continues (71). If the ECG suggests MI, administration of thrombolytic agents (intravenous or intracoronary) (76) and aspirin should be considered. Some investigators (73) suggest the use of two-dimensional echocardiography to confirm regional wall motion abnormalities before thrombolysis is instituted in patients in whom ST segment elevation is not clearly present. Thrombolytic therapy has, in fact, been used successfully, but no contraindications, such as severe hypertension, intracerebral hemorrhage, or seizures, all of which may occur with cocaine, should be present. A few case reports have raised some safety issues regarding thrombolytic agents in the setting of cocaine. One death has occurred from intracerebral hemorrhage. Thus, primary angioplasty may be another approach. A recent case report described the efficacy of platelet glycoprotein IIb/IIIa inhibitor, given intravenously, with complete resolution of a thrombus in the coronary artery that was temporally related to use of crack cocaine (77). Primary coronary intervention has been tried in cocaine users with success (78). One 36-year-old cocaine user presented to the emergency department with acute MI and ventricular fibrillation. During emergency catheterization, a significant stenosis of the circumflex artery was found, and a coronary stent was successfully deployed. The authors noted that before the stent deployment, intense and frequent coronary spasms were seen.

Because beta-blockers may exacerbate coronary vasospasm in cocaine-induced coronary ischemia secondary to unopposed alpha-receptor stimulation, they should be used with extreme caution, if at all, in the acute setting. The available data are from scattered case reports, and no final conclusion has been drawn (79). At the time of the patient's discharge, however, beta-blockers should be considered part of routine postinfarction therapy. The benefits of beta-blockers may outweigh the potential risk of increasing the vasomotor tone, particularly because the cocaine effect should be gone by the time of discharge. If, however, the patient begins to use cocaine again after discharge, beta-blockers could worsen vasospasm. Labetalol might be a safer choice, but its primary effect is beta-blockade, not alpha-blockade, and therefore even this agent is controversial.

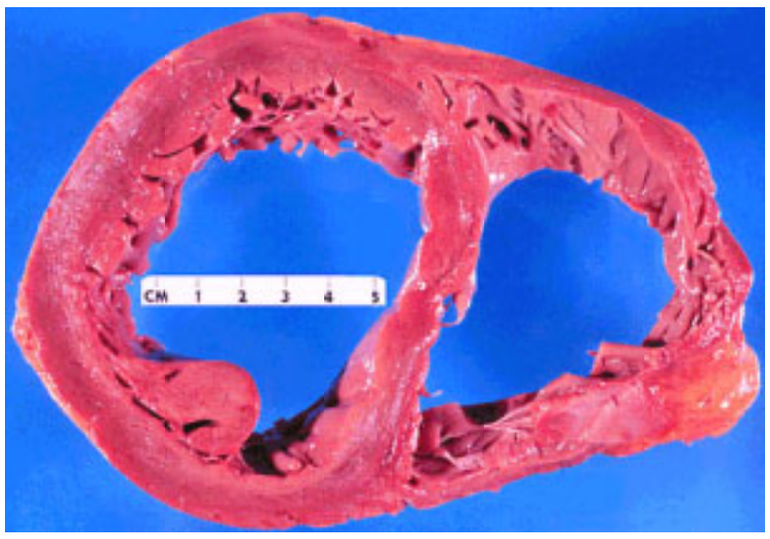
The best therapy for cocaine-induced ventricular arrhythmias remains to be determined. In experimental studies, sodium bicarbonate reverses QRS prolongation caused by cocaine (80). The use of lidocaine is debated, because lidocaine, a sodium channel blocker and local anesthetic, could theoretically worsen the proarrhythmic effect of cocaine. Some studies, however, suggest that lidocaine is safe when it is administered several hours after the use of cocaine.

Obviously, it is crucial that patients stop using cocaine and that they be educated about the dangers of this substance. Concern that cocaine may accelerate atherosclerosis is an additional reason to recommend drug rehabilitation programs.

Our own experience in an inner-city hospital was that acute MI occurring in an otherwise healthy young person may be related to cocaine, and a history of cocaine use and urine testing for cocaine should be considered. Urine testing may detect cocaine or its metabolites as long as 3 weeks after use. Various methods are used, including enzyme-multiplied immunoassay technique, gas chromatography, and mass spectrometry. A skin patch has recently been tested as an easy-to-use screening tool. When a young person has an MI, the physician should remember to ask whether the patient has been using cocaine (81).

Cocaine-Induced Cardiomyopathy and Myocarditis

Cases of transient congestive heart failure have occurred after use of cocaine (82). In some cases, this has involved global hypokinesis, typical of a cardiomyopathy, that may be accompanied by normal coronary angiograms (83,84). Clinically unrecognized reduction in LV function was reported in 7% of chronic cocaine users in one study (85). A case of recurrent dilated cardiomyopathy in a patient who quit and then began reusing cocaine was also reported (86).



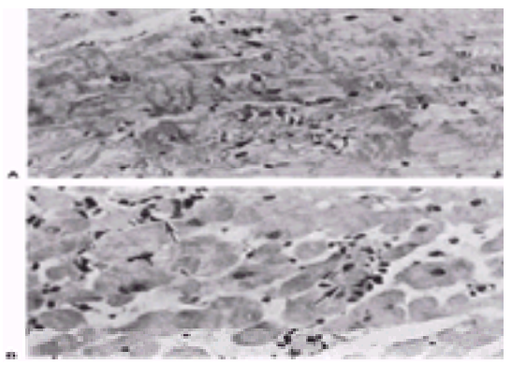
Dilated congestive cardiomyopathy. Both the left and right ventricles are significantly enlarged. In this example, the left ventricular wall thickness falls within normal limits.

Video 36.1 Apical two-chamber view of a dobutamine stress echo of a patient with three-vessel coronary artery disease. Note the deterioration of the inferior wall (*left*) and the anterior wall (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 36.2 Standard anterior view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating global hypokinesis and a reduced left ventricular ejection fraction of 25% in a patient with nonischemic dilated cardiomyopathy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In a controlled, randomized study, intracoronary cocaine or saline was administered to 20 patients during cardiac catheterization. Cocaine, but not saline infusion, led to an increase in LV end diastolic pressure and a decrease in LV ejection fraction (87). These findings suggest that cocaine can induce a global toxic effect on myocytes. Autopsy reports have described a mononuclear cell–type myocarditis in chronic cocaine users (88). Lymphocytes and macrophages were observed in the region of myocyte necrosis (eFig. 36.2.2). A second common morphologic finding among chronic cocaine users is the presence of contraction bands. Myocardial

contraction-band necrosis occurs with catecholamine excess and calcium overload, as well as after reperfusion of ischemic tissue. In an experimental study involving rabbits, we observed that an acute infusion of cocaine caused foci of contraction-band necrosis in some of the animals (26).



***e*FIGURE 36.2.2 A:** Endomyocardial biopsy of a 24-year-old woman with a history of cocaine abuse and chest pain shows multifocal myocyte necrosis (*arrows*). Necrotic myocytes with contraction bands are smudgy with disruption of membranes, granulation, and vacuolization and stain purple-blue on Mallory trichrome staining (×100). **B:** Endomyocardial biopsy from a 33-year-old woman with a history of cocaine abuse and congestive heart failure and ventricular fibrillation shows multifocal myocyte necrosis (*arrows*). Necrotic myocytes are smudgy, vacuolated, and surrounded by lymphocytes (×100). (From Peng SK, French WJ, Pelikan PC. Direct cocaine cardiotoxicity demonstrated by endomyocardial biopsy. *Arch Pathol Lab Med* 1989;113:842–845.)

As is true for MI, no controlled studies are available that clarify the best therapy for cocaine-induced cardiomyopathy. Limited data suggest that this condition may be reversible after cessation of cocaine use for 2 to 7 months. Administration of diuretics and angiotensin-converting enzyme inhibitors certainly should be considered.

In addition to dilated cardiomyopathy, LV hypertrophy has been reported with chronic cocaine use. It is presumably caused at least in part by the elevations in blood pressure that occur with cocaine (89).

Cocaine-Induced Hypertension

The hypertension induced by cocaine use is most likely secondary to the drug's sympathomimetic effect (90). Labetalol has been suggested as therapy because it blocks both alpha and beta receptors. This agent is primarily a beta-receptor blocker, however, and therefore unopposed alpha-receptor stimulation could increase both peripheral vascular and coronary vascular resistance. Calcium channel blockers and alpha-blocking agents such as prazosin and phentolamine might be a better choice.

Cocaine-Induced Arrhythmias

Case reports have described a variety of arrhythmias associated with cocaine use, including ventricular tachycardia, ventricular fibrillation and sudden death (2,91), and supraventricular arrhythmias (42). Ventricular arrhythmias may be associated with MI. One case report described a patient who developed ventricular tachycardia and fibrillation after using cocaine but who had no infarct and had normal coronary arteries at catheterization. After defibrillation, the ECG showed ST segment elevation in leads V_1 and V_2, suggesting that the arrhythmia may have been related to transmural ischemia (possibly caused by transient vasospasm). A case report of torsades de pointes in a patient with cocaine-related prolongation of the QT interval was described. On the basis of these and other case reports, six potential types of cocaine-induced arrhythmias in humans are thought to be likely: (a) those associated with structural damage (i.e., cocaine-induced MI or cardiomyopathy); (b) those caused by QT prolongation, the direct effect of cocaine on the myocardium; (c) those resulting from cocaine's sympathomimetic and vagolytic effects; (d) those resulting from cocaine-induced ischemia; (e) those caused by reperfusion after resolution of coronary artery vasospasm; and (f) those resulting from the systemic effects of cocaine, such as hyperthermia, seizures, and acidosis.

On rare occasions, bradyarrhythmias and sinus arrest have been described in cocaine users (92). This could be related to cocaine-induced myocardial ischemia. No controlled studies in humans have determined the best approach to cocaine-induced arrhythmia. In animal studies, sodium bicarbonate has been shown to reverse cocaine's prolongation of the QRS interval. Concerns about the use of beta-blockers have been described. Antiarrhythmic agents, such as lidocaine, procainamide, and quinidine, have the potential to compound cocaine's depressant effects on the conduction system and prolongation of the QT interval. Calcium channel blockers, such as nitrendipine and verapamil, have shown promise in experimental animal studies. If the arrhythmia is thought to be caused by ischemia or infarction, then the antiischemic and antiinfarction agents described earlier should be used to relieve ischemia.

Acceleration of Atherosclerosis Associated with Cocaine Use

Severe atherosclerosis of the coronary arteries has been described in young patients who died from cocaine (53). In one study (52), the average age of patients who developed cocaine-induced thrombus was only 29 years. It is important to remember, when interpreting these studies, that cocaine users tend also to be cigarette smokers, which might contribute to acceleration of atherosclerosis. An increase in adventitial mast cells within the atherosclerotic coronary arteries of cocaine users has been described (52). It was suggested that release of vasoactive substances by the mast cells could explain the acceleration of atherosclerosis in cocaine users (88). Elevation of catecholamine levels can increase low-density lipoprotein (LDL) uptake by the arterial wall. Hence, increases in catecholamine levels in cocaine users might also help explain this acceleration of atherosclerosis. Jones and colleagues (93) observed that cocaine had a direct toxic effect on coronary endothelium, resulting in endothelial denudation. Repetitive episodes of coronary vasospasm might also eventually lead to endothelial damage.

In addition to an acceleration of atherosclerosis, a few cases of intimal hyperplasia have been described as a cause for coronary narrowing (94,95). Another study (96) described thickening of intramural coronary arteries in young men who had ischemic chest pain related to cocaine use and had epicardial coronary arteries of normal appearance.

Miscellaneous Cardiac Conditions Reported with Cocaine Use

Cocaine use has been associated with aortic dissection, presumably because of the associated acute elevation of blood pressure (4), and intravenous cocaine use has been associated with bacterial endocarditis. It has been suggested that left-sided endocarditis is more common than right-sided endocarditis in this setting (4). Cocaine users are also prone to developing paravalvular abscesses.

The best way of avoiding cocaine-induced cardiovascular diseases is total abstinence. Various methods for treatment of cocaine addiction exist, including aversion therapy and narcotherapy. No long-term comparative studies on the usefulness of various programs are available, and the most optimistic success rate at 1 year is approximately 60%. It seems that greater efforts should be directed at preventing substance abuse before it starts, particularly in adolescents and in young adults.

Cocaine has also been shown to have a deleterious effect on other blood vessels, including peripheral (97,98), intestinal (99), and cerebral vessels (100,101). A summary of the effects of cocaine on the heart is shown in Fig. 36.2.

COCAETHYLENE

Cocaethylene is a pharmacologically active cocaine metabolite that has been detected in patients who simultaneously abuse cocaine and ethanol. It has been estimated that 9 to 12 million people in the United States use a combination of cocaine and ethanol (16,17), which accounts for more than 1,000 yearly deaths. The combination may be more toxic than either agent alone. Studies have suggested that their simultaneous use markedly increases the rate of sudden death (102), and that patients dying from the combination had cocaine blood concentrations lower (900 mg per mL) than those in patients dying of cocaine abuse alone (2,800 mg per mL), suggesting a synergistic effect (103). Other studies (104), however, have suggested that blood cocaine concentrations become elevated when oral ethanol is given to people snorting cocaine. Cocaethylene was more potent in killing mice than cocaine alone (105).

The mechanism whereby cocaethylene has such deleterious effects has been the subject of recent research. Combinations of cocaine and alcohol result in greater increases in heart rate, cardiac output, diastolic blood pressure, and myocardial depression than either agent alone (106,107 and 108). Although both cocaine and

cocaethylene produced direct negative inotropic effects on isolated cardiac myocytes by decreasing the availability of calcium, the negative inotropic effect was more potent with cocaethylene, and this was related to an additional action, reduction of myofilament responsiveness to calcium (30).

Cocaethylene is more potent than cocaine in depressing contraction of myocardial cells in culture (17). In a study comparing cocaine, ethanol, and a combination of both, cocaine alone increased heart rate and blood pressure and, as previously observed, decreased coronary artery diameter (16). In patients receiving both substances, rate-pressure product increased, but coronary diameter increased as well. Therefore, ethanol did not potentiate the vasoconstrictor effect of cocaine; in fact, it appeared to counteract it. This study suggested that the combination of cocaine and alcohol probably does not exacerbate ischemia. However, the doses of cocaine used were low.

Although the exact mechanism whereby the combination of cocaine and ethanol causes increased rates of sudden death in humans remains to be elucidated, it is a deadly combination with which physicians should be familiar.

CAFFEINE AND COFFEE

Few areas in the medical literature are as confusing as the question of whether coffee and caffeine have deleterious effects on the cardiovascular system. Numerous studies describe data that conflict with others, and, in the end, it is difficult to draw conclusions. Recent reviews have described some of the difficulties in the papers published to date on this issue (109,110). Often, animal studies have used doses of caffeine that are “hundreds to thousands of times those achieved by normal human consumption.” In addition, tolerance to caffeine is common in humans who regularly drink coffee, and most animal studies do not include conditioning protocols. Coffee and caffeine consumption is often associated with other variables and risk factors for coronary artery disease that are not always taken into account. For example, coffee consumption is more common among people with higher education levels and incomes, more common among white people, and more common among Catholics. It is less common among Mormons and Seventh Day Adventists, for religious reasons. Coffee is more commonly consumed among patients who are depressed and are experiencing anxiety and is commonly used by people who also smoke cigarettes. Most physiological studies in humans and animals test the effects of caffeine and relate this to coffee use. However, coffee may have compounds other than caffeine that can affect the cardiovascular system. Nevertheless, caffeine is an important compound in coffee that has been implicated in cardiovascular events.

Physiology of Caffeine Use

Caffeine is a methylxanthine found in a variety of products, including coffee, tea, chocolate, soft drinks, and many over-the-counter medications. Coffee is the predominant source of caffeine in the Western Hemisphere, and tea is the most common source in the rest of the world. Ninety-nine percent of caffeine from beverages is absorbed by the gastrointestinal tract and peaks in the serum within 30 to 60 minutes of ingestion. Caffeine is metabolized by the liver, and a very small percent is excreted unchanged by the kidneys.

Caffeine’s major mechanism of action is to antagonize adenosine receptors. A second, less important action at the usual levels of consumption is phosphodiesterase inhibition. By antagonizing adenosine, caffeine blocks the vasodilatory effect of adenosine and adenosine’s inhibitory effects on platelet aggregation, catecholamine levels, and renin release, as well as lipolysis. Thus, acute caffeine administration may increase blood pressure and increase levels of plasma catecholamine, renin (111), and free fatty acid. Tolerance develops within hours to days of caffeine use, and the effect of caffeine on any individual is highly dependent on the individual and the pattern of consumption.

In general, the effects of caffeine on heart rate and blood pressure in humans are quite variable, and contradicting statements about those effects can be found in the literature. In people who do not regularly drink caffeinated beverages, caffeine may initially increase blood pressure, but the effect is lessened or absent in those who regularly consume caffeine. In one study, a 10 mm Hg increase in blood pressure was seen after consumption of 3 to 5 mg per kg of caffeine. There was an initial *decrease* in heart rate during the first hour after consumption, followed by an *increase* from 2 to 3 hours after consumption (111). Prolonged exposure to caffeine results in tolerance, but chronic drinkers of caffeinated coffee may still exhibit small long-term increases in blood pressure, which seems to be worse among drinkers of boiled rather than filtered coffee (112,113). The increase in both systolic and diastolic blood pressure is more consistent in hypertensive patients, particularly in older men and women (114,115). In one study of 499 hypertensive men, the risk of thromboembolic stroke increased significantly in coffee drinkers (116). However, this finding requires confirmation in larger-scale epidemiologic studies.

Coffee and Coronary Heart Disease

Debate about whether coffee consumption and coronary heart disease are associated continues. Some epidemiologic studies suggest that they are, and that the prevalence of coronary disease increases among coffee drinkers, especially with intake of five or more cups of coffee per day. In a study of 1,130 male medical students older than 25 years, daily consumption of one to two cups of coffee resulted in a relative risk of coronary heart disease of 1.3; more than five cups of coffee daily increased the risk to 2.5 (117). The investigation did not fully control for all risk factors, but it did control for smoking. Other studies also suggested a relationship between increased coffee consumption and coronary events (118). Many studies (usually with a shorter period of follow-up), however, have been entirely negative. In a study of 45,589 men, daily consumption of four or more cups of coffee increased the risk of a cardiovascular event to only 1.04 (119). The study concluded that consumption of caffeinated coffee is in most cases unlikely to be a risk factor for cardiovascular disease.

A recent epidemiologic study suggested that tea drinking may reduce the risk of MI (120). In the Rotterdam study, tea drinking was associated with less atherosclerosis, as determined by radiographic examination of the abdominal aorta (121). This beneficial effect likely is secondary to the flavonoids present in tea and perhaps to other unknown products. Until the controversy regarding the effect of caffeinated coffee on coronary heart disease events is resolved, it might be prudent to limit patients with ischemic heart disease to fewer than four cups of coffee per day (122). Tea drinking, however, appears to be safe and may even be beneficial.

Coffee and Lipid Alterations

There is also ongoing debate about whether coffee increases serum cholesterol levels. Many of the studies that have shown a correlation between coffee consumption and increases in serum cholesterol levels have been performed outside the United States, whereas some of the studies that showed no association were performed in the United States.

It has been suggested that the method of brewing the coffee may be important. In some of the European studies, coffee was prepared by boiling, whereas in the United States, coffee is brewed mainly by filtering. Boiled coffee appears to have a greater adverse effect than filtered coffee on total serum cholesterol, LDL cholesterol, and apoprotein B levels. It has been postulated that the caffeine in coffee plays a minimal role in altering lipid levels, and that a surfactant in coffee (which is removed by filtration) is responsible for the elevation in lipid levels observed in some of the European studies (110,123). Other factors associated with boiled coffee that have been implicated in increasing serum lipids include cafestol and kahweal, two subfractions that can be found within the lipid fraction of coffee.

Studies in the United States did not report any increase in total or LDL cholesterol levels in patients who consumed filtered coffee (124,125). Thus, at least in the United States, the use of filtered coffee does not seem to cause an increase in cholesterol levels, and in European studies in which boiled coffee did seem to have this effect, a component other than caffeine appeared to be the culprit.

Coffee and Homocysteine Levels

Several studies have demonstrated a positive correlation between heavy coffee consumption and elevated homocysteine levels. These studies included drinking of filtered and unfiltered coffee (126,127 and 128). In a controlled crossover study, 64 healthy volunteers were randomly assigned to receive 1 L of unfiltered coffee daily for 2 weeks or to ingest a coffee-free diet (129). In the heavy coffee-drinking group, plasma fasting homocysteine levels were elevated by 10%. These studies were short-term studies and did not investigate whether a concomitant increase in cardiovascular events occurred. The results may, however, explain the reported increase in cardiovascular events among people who consume large amounts of coffee, particularly unfiltered coffee, in some studies.

Coffee and Arrhythmias

Although a common belief exists that caffeine can exacerbate arrhythmias, the evidence supporting this in humans is limited. Animal studies have examined this question, but studies demonstrating an association between caffeine and arrhythmia have usually involved doses that were several times higher than those ingested by humans.

One study demonstrated that caffeine had little or no effect on cardiac conduction in humans but might exacerbate underlying susceptibilities to arrhythmias (130). Although earlier studies found an increase in ventricular premature beats on the ECGs of patients who drank nine or more cups of coffee or the equivalent amount of

tea (131), more recent studies have been negative.

In a study that examined the effect of caffeine on 50 patients with histories of symptomatic ventricular arrhythmias, continuous ECG recordings at rest and during exercise revealed no increase in ventricular arrhythmias after caffeine consumption, despite an increase in plasma norepinephrine and epinephrine levels (132). During programmed ventricular stimulation, the effect of caffeine varied among the patients. Some patients required an increase, others a decrease, and others no change in the extra stimuli needed to induce arrhythmias during exposure to caffeine (133). Although moderate caffeine ingestion produces a slight prolongation of QRS complexes seen on signal-averaged ECG (134), many studies suggest that moderate ingestion of caffeine does not exacerbate arrhythmias (135,136 and 137).

ANABOLIC STEROIDS AND CARDIOVASCULAR DISEASE

It is estimated that approximately 1 million Americans use anabolic steroids (138). Recent case reports suggest that anabolic steroids used primarily among bodybuilders may be associated with MI. Kennedy (139) described a 24-year-old bodybuilder who presented with 3 days of dull chest pain. He had been taking anabolic steroids, including oral stanozolol, intramuscular nandrolone, and intramuscular sustanon. He also had a history of smoking. The patient developed a lateral-wall MI, demonstrated by ECG and enzyme criteria. He was found to be hypertensive, his total serum cholesterol level was observed to be high, and his high-density lipoprotein (HDL) levels were observed to be low.

Acute MI was also reported in a young power lifter who was taking androgenic steroids (140). This patient had hypercholesterolemia, hyperaggregable platelets, and normal appearance of coronary arteries on angiography. Other cases have been documented in which MI, thrombotic occlusion of the coronary artery, and strokes were associated with use of anabolic steroids (140).

In a literature review on the link between anabolic steroids and atherogenic changes, anabolic steroids caused a 52% decrease in HDL levels, a 78% decrease in HDL b levels, and a 36% increase in LDL levels (141). Some studies reported depression of apolipoprotein A-1 and increases in apolipoprotein B. Commonly used anabolic steroids were stanozolol, oxandrolone, testosterone, methandrostenolone, nandrolone decanoate, and oxymetholone—usually in various combinations.

Changes in serum lipid levels after administration of anabolic steroids are rapid, occurring within days to a week. Lipid levels return to baseline approximately 3 to 5 weeks after cessation of anabolic steroid use, according to some reports, whereas other reports suggest that a prolonged residual effect may be seen, with lipid levels abnormal even at 6 months after steroid use has ended.

It has been estimated that the deleterious effects of anabolic steroid use on serum lipid levels might increase the risk of coronary heart disease to three to six times normal (141). The actual incidence of cardiovascular events among anabolic steroid users is probably underreported, however, and is limited to occasional case reports. Moreover, many young patients likely conceal their use of anabolic steroids when questioned. It is important to point out that physiologic doses of testosterone do not seem to adversely affect lipid levels. No effect on HDL levels was seen after administration of such doses in older men, and epidemiologic studies actually suggest a positive correlation between endogenous testosterone and HDL levels (142).

Exogenous steroids can also increase blood pressure (143) and hence cause LV hypertrophy and possibly increase thrombosis. A link between androgen use and thrombus formation is largely derived from experimental animal studies. In experimental thrombosis models, administration of exogenous androgens resulted in development of a larger experimental thrombus and reduced time to blood vessel occlusion (144,145,146 and 147). Use of exogenous androgens has also been reported to enhance platelet aggregation (148).

QT dispersion is increased in athletes who take anabolic steroids (149). QT dispersion reflects the heterogeneity of ventricular repolarization and is known to be associated with increased risk of ventricular arrhythmias. Atrial fibrillation was also reported in young athletes who abuse anabolic steroids (150).

AMPHETAMINES

Amphetamines are stimulants that are noncatecholamine sympathomimetic agents. Use of amphetamine and its derivatives may increase blood pressure and has been associated with lethal arrhythmias and MI (151,152,153,154,155 and 156). A 27-year-old man who developed an acute MI and ventricular fibrillation after intravenous amphetamine and was successfully cardioverted was shown to have normal coronary arteries during angiography (152). It was suggested that amphetamines might cause coronary artery vasospasm followed by thrombus formation (157). Cases of cardiomyopathy have also been reported with use of amphetamines (158,159), including smoking of crystal amphetamine, or “ice” (159).

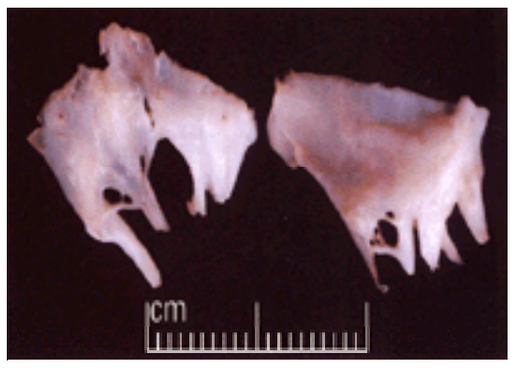
ECSTASY

Ecstasy is 3,4-methylendioxymethyamphetamine, a very popular designer drug that is gaining popularity among young adults. The drug has potent sympathomimetic properties and has been linked to a variety of vascular emergencies. Intracerebral hemorrhage, stroke, hypertension, ventricular arrhythmias, and even death have been described with use of the drug (160,161 and 162). The deaths reported after ecstasy use were related to massive cerebral hemorrhage and, less often, ventricular fibrillation.

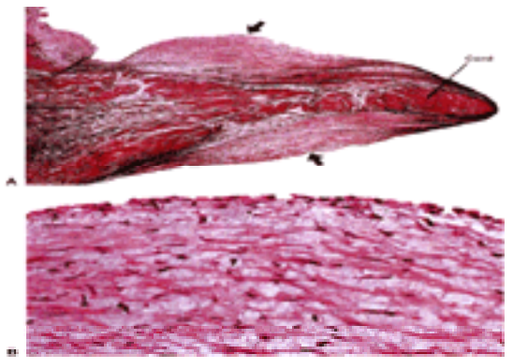
PHENTERMINE-FENFLURAMINE (PHEN-FEN)

Phentermine is a nonsympathomimetic stimulant that inhibits the clearance of serotonin in the lungs. Fenfluramine is a sympathomimetic amine that promotes the release of serotonin (163). Both drugs in combination were widely used as anorexigenic agents for management of obesity. Shortly after their release, a variety of side effects were reported, including valvular regurgitation, primary pulmonary hypertension, endomyocardial fibrosis, and retroperitoneal hemorrhages.

In 1997, the cases of a group of 24 women who developed valvular heart disease after phentermine-fenfluramine therapy were reported (164). Twenty patients presented with various cardiovascular symptoms, and a new murmur was discovered in four patients during physical examination. The most common valvular abnormalities were mitral regurgitation and aortic regurgitation. The valves showed a glistening appearance on inspection (*e*Fig. 36.2.3). On histopathologic examination, proliferation of fibroblasts and an increase in extracellular matrix were found (*e*Fig. 36.2.4). These patients were young and had no previous histories of heart disease. Surgical intervention was performed in five patients.



***e*FIGURE 36.2.3** Explanted mitral valve from a patient reveals valve thickening and glistening white leaflet appearance. (From Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;337:581–588.)



***e*FIGURE 36.2.4** Histopathology of a mitral valve in a patient who was receiving fenfluramine-phentermine, stained with hematoxylin and eosin, under low-power **(A)** and high-power **(B)** views. Arrows point to valve thickening. (From Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;337:581–588.)

Further epidemiologic studies confirmed a relationship between phentermine and fenfluramine and valvular regurgitant lesions, but to a much lesser extent (165,166,167 and 168). The incidence of valvular abnormalities ranges between 6% and 30% among patients who are taking phentermine-fenfluramine, with the most common lesion being aortic regurgitation. The incidence appears to be higher among patients who have undergone longer treatment with the drugs (169) and may regress after the cessation of therapy (170). The United States Department of Health and Human Services recommends that patients exposed to these medications undergo cardiovascular and echocardiographic examination, and that antibiotic prophylaxis be administered when appropriate (171).

A less common but more serious complication of phentermine-fenfluramine therapy is primary pulmonary hypertension (172). This occurs after exposure of at least a few months and has a 3-year survival rate of 50% (173). In one study, histologic examination at autopsy revealed intimal hyperplasia, medical hypertrophy, intimal fibroelastosis, and plexogenic arteriopathy of the pulmonary arteries (174).

Another rare complication of phentermine-fenfluramine therapy is restrictive cardiomyopathy secondary to endomyocardial fibrosis (175). A case report of ruptured retroperitoneal aneurysm had been described (176) and was felt to be secondary to enhanced sympathetic activity.

ALCOHOL

It is estimated that alcohol is consumed by two-thirds of the adult population in the United States, which makes alcohol one of the most widely used addictive drugs. It is also a unique substance in that a small amount may have some benefit on cardiovascular morbidity and mortality rates, but consumption of larger amounts can have devastating effects. The toxic effect of alcohol extends to the brain, liver, skeletal muscle, and many other organs. In this section, we focus on its cardiovascular effects.

Epidemiology

Approximately two-thirds of the adult population in the United States report alcohol consumption, and 10% of these are heavy drinkers. Men drink more than women, but women are more sensitive to the cardiac effects of alcohol. In one study, even though women drank only 60% of the lifetime alcohol dose consumed by men, they had a higher incidence of alcoholic cardiomyopathy (177). Alcohol consumption is also prevalent among adolescents, with rates ranging from 10% to 35% (178). It is more prevalent among young men than young women and among white students than black students; white male adolescents have the highest rate of consumption. Alcohol abuse is present in approximately 15% of the geriatric population. Depression, anxiety, and loneliness are some of the precipitating factors, and patients in that age group are more susceptible to the side effects of alcohol use (179).

Metabolism

Alcohol is absorbed from the stomach and small intestine. It is then distributed to tissues rich in water content and blood flow. Thus, the heart, liver, and brain are prime targets for alcohol's effects (180). In the liver, ethylalcohol is metabolized first to acetaldehyde and then to acetate. Acetate leaves the liver and is metabolized in extrahepatic tissues.

Cardiovascular Effects of Alcohol

Alcoholic Cardiomyopathy

Chronic ingestion of alcohol produces a decrease in both systolic and diastolic function of the myocardium. The condition is clinically indistinguishable from idiopathic dilated cardiomyopathy. Grossly, the myocardium is dilated and flabby, with diffuse areas of fatty degeneration and fibrosis (181). The condition is also histologically similar to idiopathic dilated cardiomyopathy, but the degree of myocyte hypertrophy and the extent of fibrosis are less pronounced (182). Ethanol and its metabolites, acetaldehyde and acetate, exert direct cardiac toxic effects. Although the nutritional deficiencies associated with alcoholism may play some role in alcoholic cardiomyopathy, they probably are not the only source; dietary supplementation fails to prevent the condition.

VIDEO

Video 36.3 Apical long-axis view of a patient with severe left ventricular dysfunction and annular dilatation causing 4+, centrally directed mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Initially, loss of the integrity of the sarcolemmal membrane occurs, resulting in loss of its function. This leads to an increase in the concentration of intracellular calcium. Animal studies showed that alcohol administration for 12 weeks led to a threefold increase in intracellular calcium (183). Furthermore, investigators found that administration of verapamil prevents alcohol-induced LV dysfunction (184). Ethanol also affects the sarcoplasmic reticulum, the mitochondria, and contractile protein synthesis and may produce oxygen free radicals (185,186). All of these adversely affect the structure and function of the myocardium.

The symptoms of alcoholic heart disease include dyspnea on exertion, orthopnea, fatigue, and peripheral edema. On examination, signs of right-sided and left-sided heart failure may be present. In addition, signs of chronic alcoholism, such as telangiectasia, spider angioma, and hepatic enlargement are a clue to the diagnosis. Chest radiography shows cardiomegaly and pulmonary congestion. A 12-lead ECG may show LV hypertrophy, nonspecific ST- and T-wave abnormality, and various cardiac arrhythmias.

One clue to the diagnosis of alcoholic myopathy is the presence of skeletal myopathy presenting as muscle weakness. Because the direct toxic effect of alcohol is usually exerted on the striated muscle, the effects are typically present in both heart and skeletal muscle. In a cross-sectional study (187), 24 patients with alcoholic cardiomyopathy were compared to chronic alcohol drinkers with normal heart function and to patients with idiopathic and ischemic cardiomyopathy. Only patients with alcoholic cardiomyopathy had significant skeletal myopathy as determined by muscle biopsy.

Individuals who drink alcohol may have various nutritional deficiencies, among them thiamine deficiency. Thiamine deficiency may lead to beriberi, which may also present with dilated cardiomyopathy. It is, however, distinct from pure alcoholic myopathy in that it is a form of high cardiac output failure (188). The two conditions may coexist.

The most sensitive and clinically useful tool in management and diagnosis of alcoholic cardiomyopathy is echocardiography. This technique usually reveals dilation of all chambers of the heart, and Doppler echocardiography shows valvular regurgitation, particularly of the mitral and tricuspid valves. Alcohol affects both systolic and diastolic function. Studies have shown a decrease in ejection fraction and stroke index (189). Doppler echocardiography is quite sensitive in evaluating diastolic dysfunction, even before the development of clinically evident dysfunction. Thirty-two alcohol users with no clinical evidence of cardiomyopathy were studied by

Doppler echocardiography (190). Patients had a prolonged relaxation time, a decrease in peak early diastolic velocity, and a slower acceleration of early diastolic flow. Diastolic dysfunction, as detected by Doppler studies, may precede systolic dysfunction and may be the only manifestation seen in some patients with chronic alcoholism (191).

The hearts of alcoholic cardiomyopathy patients may have an increased uptake of antimyosin antibody, which may decrease after alcohol withdrawal (192). The natural history of alcoholic cardiomyopathy depends largely on the patient's drinking habits. If treatment is started early and the patient stops drinking, it may be partially reversible (193). Well-developed disease, however, is usually fatal if the patient continues to consume alcohol.

Treatment of alcoholic cardiomyopathy usually follows several paths. Treatment of the manifestation of congestive heart failure with angiotensin-converting enzyme inhibitors and diuretics is helpful. Nutritional deficiency, such as thiamine deficiency, and various electrolyte abnormalities, such as hypophosphatemia (194), hypomagnesemia, and hypokalemia, should be corrected. The mainstay of therapy is cessation of alcohol use. The earlier abstinence occurs in the course of the disease, the more pronounced is the benefit. In a group of patients with pure alcoholic cardiomyopathy (195), patients who abstained had a marked improvement in their ejection fraction, as measured by radionuclide angiography, and in their cardiothoracic ratio, as seen by chest radiography. Most of the improvement occurred in the first 6 months of abstinence, but improvement continued through up to 2 years of observation. Patients who did not abstain showed no improvement. In alcoholic cardiomyopathy, the benefit of abstinence from alcohol exceeds the benefits of medical therapy alone (196). The prognosis of alcoholic myopathy is similar to that of idiopathic dilated myopathy (197).

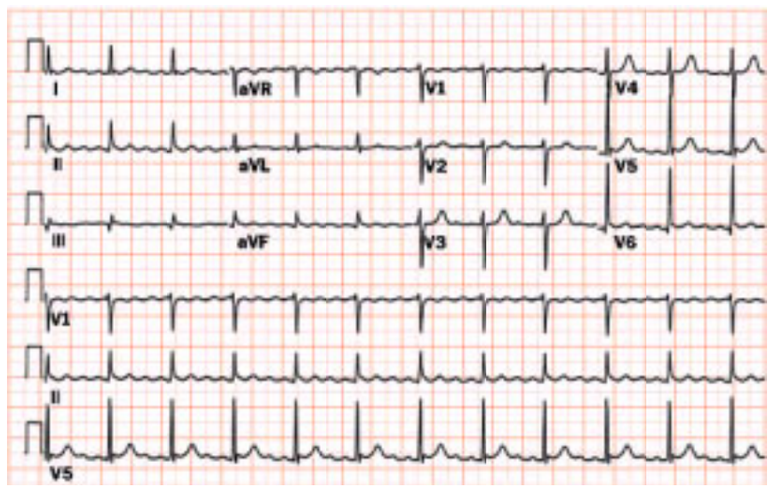
Hypertension

A link between alcohol use and high blood pressure has long been suspected (198). Social drinking is associated with a mild rise in systolic pressure, whereas those who drink heavily may have a substantial rise (199,200). Several mechanisms have been proposed. However, the exact mechanism is not clear. This may, at least in part, explain the increase in LV mass. However, even alcoholic individuals who are normotensive may have an increase in LV mass (201). Blood pressure may normalize after a short period of abstinence.

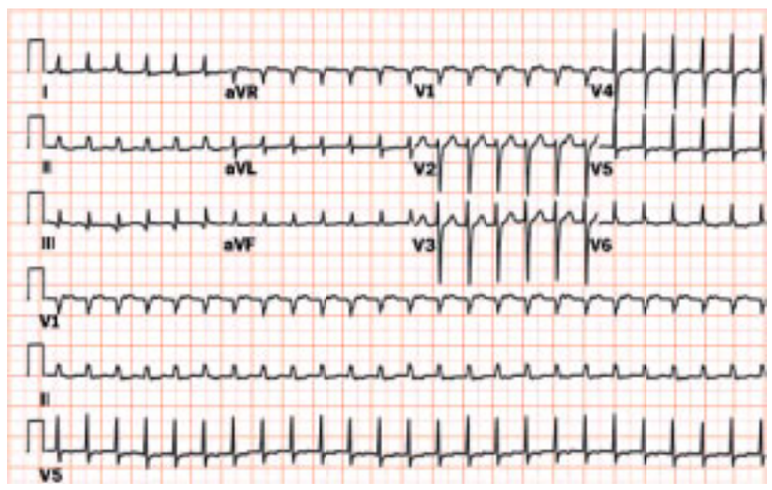
Cardiac Arrhythmias

Alcohol use is associated with a variety of atrial and ventricular arrhythmias, regardless of whether the patient has overt alcoholic heart disease. Possible mechanisms include electrolyte imbalance, the hypercatecholamine states often seen during alcohol withdrawal, and a patchy delay in conduction that results in increased reentry (202). The QT-interval prolongation seen in alcoholic patients may be implicated in the genesis of ventricular arrhythmias (203). Atrial arrhythmias include premature atrial contractions, supraventricular tachycardia, and atrial flutter and fibrillation. Ventricular arrhythmias include premature ventricular depolarization and ventricular tachycardia or fibrillation. The most common arrhythmia, however, appears to be atrial fibrillation.

Acute inferior myocardial infarction complicated by atrial fibrillation. Note ST-segment elevation in the inferior leads with reciprocal changes laterally. Atrial fibrillation has complicated this acute infarct.



Atrial flutter. Atrial rate of 300 beats/min with upright P waves inferiorly. This is consistent with atypical atrial flutter.



Supraventricular tachycardia. Note narrow QRS complex with short RP interval.

In a study of 32 episodes of cardiac arrhythmias in 24 patients who used alcohol, patients reported consuming alcohol every day for an extended period of time, yet had a marked increase in alcohol consumption on weekends or near holidays. No overt signs of alcoholic heart disease were seen. The most common arrhythmia noted was atrial fibrillation. The majority of episodes was seen in the hospital at the beginning of the week or after holidays; hence the term "holiday heart" (204).

In patients with new onset of atrial fibrillation, alcohol was responsible for 35% of the cases and up to two-thirds of the cases in patients younger than 65 years (205). It was also found to be an independent risk factor for recurrence of atrial fibrillation (206). Electrophysiologic testing in humans showed that alcohol enhances the vulnerability of normal hearts to induction of atrial flutter and fibrillation (207). The treatment is cessation of alcohol consumption; most rhythm disturbances disappear with little or no intervention.

Sudden Death

Heavy alcohol drinking is associated with an increase in sudden death. In one study, the increased incidence of sudden death was reported regardless of whether patients had coronary artery disease (208). The increase was also more pronounced in older age groups, regardless of social class. For nonsudden death, alcohol drinking had a biphasic effect, depending on the amount of alcohol consumed. Heavy drinkers were at a greater risk for death from noncardiovascular causes, particularly cirrhosis, accidents, and tobacco-related cancer. This increased risk was higher among women and among younger persons (209). Lighter drinkers, however, were at a lower risk for death from cardiovascular diseases, particularly coronary artery disease. In a prospective 13-year follow-up of 12,321 male British doctors, the consumption of one or two drinks each day was associated with a significantly lower mortality rate than that seen among heavy drinkers or nondrinkers (210). The mechanism of this benefit was not apparent in that study, yet it was postulated that a beneficial effect on coronary artery disease might be responsible.

Coronary Artery Disease

Heavy alcohol drinking is associated with an increased incidence of coronary artery disease and cardiovascular death. This is not surprising—such patients have an increased tendency for hypertension with increased cardiac muscle mass and hypertriglyceridemia, and they also tend to be smokers. Alcohol use is paradoxical; mild to moderate alcohol intake is associated with a decreased risk of MI and cardiovascular death. Various mechanisms contribute to that result, including the effect of alcohol consumption on HDL.

Investigators examined the relationship between alcohol ingestion and MI among 340 patients with MI, compared with an age- and sex-matched control group (211). Alcohol intake was inversely related to the risk of MI. Furthermore, a substantial component of that benefit resulted from an increase in HDL and its subfractions. It also appeared that this benefit derived from the alcohol itself and was not specific to any particular alcoholic drink (212). Most of this benefit is achieved by consumption of as little as half a drink per day (213,214). Other mechanisms that may play a role in this effect on coronary artery disease are the effects of alcohol on endogenous tissue–type plasminogen activator and on platelet function. In a study of 631 healthy male doctors, moderate drinking increased plasma levels of endogenous tissue plasminogen activator antigen (215). In addition, alcohol consumption resulted in the inhibition of platelet aggregation and prolongation of blocking time (216). These effects likely decrease the occurrence of coronary thrombosis in moderate alcohol drinkers.

What advice should physicians give their patients with regard to alcohol consumption? We must remember that alcohol is an addictive drug, and it may be difficult for some people to control their drinking. Heavy drinking increases overall mortality rates (217). Other risk factor modifications should be the priority in patients who have coronary artery disease. Mild alcohol drinking may, however, have a role in the subgroup of patients who have low HDL levels as the sole risk factor for coronary artery disease and in whom other measures to improve HDL levels have failed.

Alcohol Withdrawal

Alcohol withdrawal is usually managed in a quiet, supportive environment. The importance of close supervision cannot be understated. Benzodiazepines are the mainstay of therapy. Two cardiovascular effects commonly occur during alcohol withdrawal: significant hypertension and cardiac arrhythmias. They are likely related to the activation of the autonomic nervous system and usually subside spontaneously but may require a temporary pharmacologic intervention. In patients who have acute ischemic syndromes and are also experiencing alcohol withdrawal, control of blood pressure and heart rate is crucial. Liberal use of beta-blockers and intravenous nitroglycerin is recommended.

Prevention of Alcohol Addiction

Attempts to cure alcohol addiction are not always successful and often begin after many years of drinking, when significant health problems have already developed. Thus, efforts toward prevention of drinking should be the goal. Various programs are already in place that have had some success (218).

TOBACCO

A cigarette is a controlled device that delivers nicotine and many other substances to the human body. With each puff, approximately 100 µg of nicotine is absorbed through the lungs, with an average drug delivery of 1 to 2 mg of nicotine per cigarette. With the widespread use of smoking and its significant effects on the cardiovascular system, cigarette smoking has a major impact on public health.

Epidemiology

The number of tobacco smokers in the world exceeds 1.1 billion. Approximately 300 million smokers live in developed countries, and more than 800 million smokers live in developing countries. Globally, smoking is responsible for 3 million deaths per year, and this number is expected to reach 10 million per year in the year 2020, if current trends continue. It is estimated that 50 million Americans smoke on a regular basis. Although the overall number of adult smokers has decreased in the United States, smoking among teenage girls is on the rise. The prevalence of smoking among the African-American and Hispanic populations has surpassed that in the white population, but white smokers smoke more cigarettes per day, seem to be more addicted to smoking, and report more smoking-related illnesses than African-American and Hispanic smokers (219). Although some decline has been seen in the overall incidence of cigarette smoking in the United States, cigar smoking is on the rise, and smoking in general is not showing any significant decline in developing countries.

Tobacco Addiction

Drug addiction or dependency is described as “a behavioral pattern in which the use of a given psychoactive drug is given a sharply higher priority over other behaviors which once had a significantly higher value” (220). In other words, addiction is defined as loss of control over use of the drug and an inability to quit despite obvious risks associated with drug use. In the case of cigarette smoking, the drug is nicotine. Smokers report pleasure, relaxation, reduction of anxiety and stress, and improved attention after cigarette smoking (221). Within seconds of smoking a cigarette, nicotine is absorbed through the lung alveoli and taken up by the bloodstream to the brain and other tissues. In the brain, it acts at the nicotinic receptors, which are known to be increased in the brain tissues of smokers. As a result, dopamine, norepinephrine, acetylcholine, and endorphins are released. This results in the reported feelings of decreased anxiety and tension, pleasure and relaxation, and increased performance. Cigarette smoking may also be associated with a decrease in the enzyme monoamine oxidase, which is responsible for the breakdown of dopamine, in the brain (222). Thus, cigarette smoking not only increases the secretion of dopamine, but it also slows its metabolism.

With each cigarette smoked, tolerance to the effects of nicotine develops. But with abstinence at night, the effects are renewed, so that the first cigarette of the day produces the maximal psychological effect. When smoking ceases, symptoms of restlessness, irritability, impatience, and increased anxiety occur. Most symptoms gradually disappear in 1 to 2 weeks, but the desire to smoke may persist for a very long time.

Despite a recent controversy regarding whether cigarettes should be considered addictive, the balance of the arguments strongly suggests that they are (223). It has also been suggested that an individual’s genetic composition may influence smoking behavior (224).

Cardiovascular Effects

The main components of cigarettes that exert cardiovascular effects are nicotine and carbon monoxide. The former may lead to the release of norepinephrine, which increases pulse rate, blood pressure, and platelet aggregability. It may also cause endothelial injury and adversely affect events that occur during atherosclerotic plaque rupture (225). Carbon monoxide displaces the oxygen from hemoglobin, interfering with oxygen delivery to cardiac tissue. Cigarette smoking has also been associated with hyperfibrinogenemia and low levels of HDL (226). These mechanisms lead to the devastating effects of smoking, regardless of the method used.

In a major epidemiologic study, 10,914 subjects were followed to assess the progression of atherosclerotic disease (227). Carotid ultrasounds were performed on the subjects, and the intimal medial thickness was measured at baseline and at 3 years of follow-up. Current smokers had a 50% increase in the rate of progression of atherosclerosis compared to nonsmokers. Past smokers had a 25% increase in atherosclerosis. Even passive smokers who had never smoked had more progression than control subjects. The increase in the rate of atherosclerosis progression associated with smoking was more marked in diabetic and hypertensive patients.

Smoking results in an increase in heart rate and blood pressure. In a study of 135 healthy subjects, 24-hour ambulatory blood pressure monitoring revealed an increase in both heart rate and blood pressure (228). In addition to an increased cardiovascular risk profile, this increase in myocardial oxygen demand may increase, at least theoretically, anginal episodes in patients who already have coronary artery disease.

Active Smoking

Although cigarette smoking had long been suspected to increase the risk of cardiovascular diseases, the two were formally linked in 1958 (229). Subsequently, pathologic studies showed more-advanced coronary artery disease among heavy smokers than among light smokers (230). Smoking is associated with a two- to fourfold increase in coronary artery disease and an increased risk of MI and sudden death (231). Furthermore, if patients with MI continue to smoke, the rate of reinfarction and death also increases. The risk appears to be related to the duration of smoking and the number of cigarettes smoked per day. Smoking also has a synergistic effect with other coronary risk factors, particularly hypercholesterolemia.

Passive Smoking

Passive smoking is the involuntary inhalation of air contaminated by cigarette smoke. It affects both smokers and nonsmokers. Smokers have an increased risk of developing various cardiovascular effects, whereas nonsmokers may have an increased incidence of MI with chronic exposure and impaired cardiac performance with acute exposure. Investigators exposed patients who survived a first heart attack to passive smoking during an exercise stress test. During passive-smoking exposure, exercise tolerance decreased, time to recovery to baseline heart rate was prolonged, and the occurrence of cardiac arrhythmias increased (232).

Passive environmental smoking results in a 25% increase in the risk of coronary artery disease (233) and death (234) and is now estimated to be the third leading preventable cause of death after active smoking and alcohol abuse (235). Controlled studies showed that passive smoking impairs endothelial-dependent coronary vasodilation (236), and this is only partially reversible after exposure has ended (237). Passive smoking also leads to accelerated lipid peroxidation and accumulation of LDL cholesterol in human macrophages (238). These effects contribute to accelerated atherosclerosis (227) and subsequently to increased mortality rates (235). Educating smokers about the risk of passive smoking appears to be more important than ever in the face of these data.

Cigar and Pipe Smoking

Although cigarette smoking overall is on the decline in the United States, cigar smoking is rising. Regular cigar smokers who inhale smoke or are heavy smokers have an increased risk of coronary artery disease (239). One prospective study, however, suggested that the cardiovascular risk associated with cigars is less than that associated with cigarettes (240).

Smokeless Tobacco

Smokeless tobacco refers to tobacco snuff, chewing tobacco, and the recently introduced smokeless cigarette. Smokeless tobacco delivers an average amount of nicotine similar to smoking and may produce similar cardiovascular effects. In addition, chewing tobacco leads to a variety of cancerous and precancerous conditions, commonly oral leukoplakia (241). An epidemiologic study from Sweden, however, failed to show an increased risk of MI in people who use tobacco snuff (242).

Smoking Cessation

Smoking cessation includes three phases (243): preparation, intervention, and maintenance. The preparation phase primarily includes motivation of the patient. The intervention phase involves initiation of a specific method of smoking cessation, which ordinarily includes the daily use of nicotine gum or a patch and a gradual decrease in the dose of nicotine delivered. Other methods used alone or in combination are behavioral therapy, acupuncture, and hypnosis. The maintenance phase ensures that the patient continues to not smoke and includes stress reduction as an integral part of management, because the urge to return to smoking is accentuated by stressful conditions.

Nicotine patches are probably the most commonly used method of smoking cessation. Nicotine patches are safe, particularly because they deliver less nicotine in a slow, steady state, as opposed to the pulsatile nature of cigarette delivery. Investigators compared the effects of cigarette smoking, nicotine patches, and placebo patches on platelet aggregation in a crossover design (244). Smoking was associated with an increase in platelet activation, but nicotine patches were not. Use of nicotine patches should be limited to patients who have stable cardiovascular disease and avoided in patients who have unstable ischemic syndromes, because cases of MI during the use of such patches have been reported (245,246). The antidepressant drug bupropion is also effective in smoking cessation and may even be more effective than nicotine-containing products (247).

Smoking Prevention

Despite the widespread availability of high-quality programs for smoking cessation, the rate of success is lower than desired. This low rate may result in part from the strongly addictive nature of tobacco use and the ease of obtaining cigarettes. Smoking prevention appears to be the best way to decrease the number of smokers and the incidence and prevalence of smoking-related illness (248). Every day, approximately 3,000 young people start smoking (249); individuals who do not smoke their first cigarettes as teenagers are less likely to start smoking as adults (250). School-based programs need to be initiated at an early phase in a child's education (251) to have an impact on the number of adult smokers.

INFECTIVE ENDOCARDITIS IN DRUG ADDICTS

Infective endocarditis (IE) is an infection of the endocardial surface of the heart. Although it primarily affects heart valves, it may also involve mural endocardium, cause septal defects, and extend into the subendocardial region. This section focuses on IE in drug addicts.

The term "infective endocarditis" was first suggested by Thayer in 1931 (252) and was later popularized by Lerner and Weinstein in 1966 (253). Lerner and Weinstein found that the incidence of reported cases of IE was dropping with the emergence of antibiotics. The rise in intravenous drug abusers, however, was accompanied by a surge in cases of IE, and its presentation was somewhat different from the classic form of the disease.

Epidemiology

A population-based study of IE was conducted in Olmsted County, Minnesota, between 1950 and 1981. An incidence of 3.8 cases per 100,000 residents was reported (254). The most common underlying cause was rheumatic heart disease, and no intravenous drug abusers were identified in that study. In a second, recent study of the epidemiology of IE in an urban community, the incidence was 6.2 cases per 100,000 individuals (255). That study included intravenous drug users and showed a higher incidence among women and older patients. Further studies have suggested that the increased incidence of IE is likely to be explained by a progressive increase in the number of drug addicts who contract the disease (256).

Bacteriology

In a 2-year review of cases of IE among drug addicts, *Staphylococcus aureus* was the most commonly identified causative organism, accounting for 50% of cases. Enterococci accounted for 26% of cases, and *Pseudomonas aeruginosa* accounted for 10% (257). Methicillin-resistant and methicillin-tolerant *S. aureus* are isolated with increasing frequency from patients with IE in some areas of the United States, particularly in the Midwest. These microorganisms tend to be present in older patients who are addicted to intravenous drugs, in patients who were hospitalized in the past, and in patients who used nonprescribed antibiotics.

Clinical Presentation

Symptoms

The symptoms of endocarditis in drug addicts vary widely. These patients may present at the emergency department with vague, nonspecific complaints of symptoms that resemble those of a viral syndrome, or they may present with full-blown classic endocarditis that culminates in neurologic or cardiovascular catastrophe (258). Thus, IE should be suspected in drug addicts who present with fever and no obvious source of infection.

In a study of 55 episodes of IE in drug addicts, the most common symptoms were fever and chills, chest pain, and cough. Other symptoms were headache, nausea, vomiting, diarrhea, and arthritic pain (259). The duration of symptoms before admission averaged 8.1 days, with a range of 1 to 30 days. Temperature is almost always elevated and tends to be much higher in IE patients than in patients addicted to drugs who present with only bacteremia. Fever may persist for longer than 1 week, even after a regimen of appropriate antibiotics has been started. The chest pain associated with IE is usually pleuritic in nature and, if accompanied with a cough, is

likely an indication of pulmonary septic emboli. Shortness of breath may occur, either from pulmonary involvement or from the development of valvular regurgitation. Occasionally, symptoms may be nonspecific, and the diagnosis may first be made at autopsy (260).

Signs

In a study of drug addicts in Detroit Medical Center, cardiac murmurs were found in 35% of patients on admission (261). In right-sided endocarditis, the murmur is often that of tricuspid regurgitation and less often of pulmonic stenosis. In left-sided endocarditis, the murmur is usually that of mitral regurgitation and less frequently of aortic regurgitation. Patients may develop new murmurs during therapy. Pulmonary rales and rhonchi may be found and are likely an indication of pulmonary septic emboli or of the development of congestive heart failure. As congestive heart failure progresses, jugular venous distention, liver congestion, and peripheral edema may be observed. Roth's spots and Osler's nodes may be present; Janeway lesions are less often seen. Splinter hemorrhages are not uncommon.

Laboratory Findings

Leukocyte counts are usually elevated in these patients. Anemia is often present and is likely a nonspecific finding because it is present in most addicts who do not have IE (intravenous drug addicts usually lose blood each time they inject). Sedimentation rate may be elevated. Mild hyponatremia may be seen and is usually an indication of the severity of the disease. Elevation of blood urea nitrogen or serum creatinine levels may be seen if congestive heart failure or glomerulonephritis develops.

Causative Microorganisms and Clinical Presentation

S. aureus affects primarily the right side of the heart, causing the development of tricuspid vegetations and tricuspid regurgitation. Complications of infection with *S. aureus* include pulmonary septic emboli and congestive heart failure. Streptococci infect left-sided valves, particularly the mitral valve, which can lead to systemic emboli and pulmonary edema. In *Pseudomonas* endocarditis, multivalvular involvement is common. Polymicrobial endocarditis tends to run an aggressive course with an increased possibility of valve destruction and the need for surgical intervention.

Left-Sided Endocarditis

Although IE in drug addicts is more commonly seen on the right side of the heart, left-sided endocarditis is not uncommon, and it is associated with a significantly worse prognosis. In a study of 67 patients with IE, left-sided endocarditis was more common in women, and 8% of the cases ended with valve replacement or death (262).

Infectious Endocarditis in Acquired Immunodeficiency Syndrome

Autopsy studies may show thrombotic nonbacterial endocarditis in patients who have acquired immunodeficiency syndrome (AIDS). In AIDS patients, however, IE occurs almost exclusively in intravenous drug users (263). Human immunodeficiency virus (HIV) infection, regardless of whether AIDS has developed, does not seem to affect the incidence or the clinical course of IE in these patients (264). However, rate of death from IE is increased among HIV patients who have severe immunosuppression (265).

Diagnosis

IE should be suspected in any intravenous drug user who presents with fever, cardiac murmur, and absence of any other source of infection. Blood cultures are almost always positive. In clinical practice, however, establishing a diagnosis may be difficult (266), although various attempts have been made to establish diagnostic criteria for IE. The von Reyn criteria were published in 1981 (267). They include categories for definite, probable, and possible endocarditis. "Definite" endocarditis should have direct evidence based on histologic studies done at surgery or autopsy. "Probable" endocarditis includes cases in patients who have persistently positive blood cultures, new cardiac regurgitant murmur, or predisposing cardiac disease, and a vascular phenomenon such as Osler's nodes or splinter hemorrhages. "Possible" endocarditis includes cases in patients who have positive blood cultures with predisposing heart disease or a vascular phenomenon. With the emergence of echocardiography, Durack and associates (268) proposed a classification that includes two major and six minor criteria. Major criteria include typical blood cultures and positive signs on echocardiograms. Minor criteria are predisposition to IE, fever, vascular phenomena, immunologic phenomena, suggestive results of echocardiography, and suggestive results of microbiologic testing. Diagnosis requires two major criteria, one major and three minor criteria, or five minor criteria. A more practical method was proposed by Levine and coauthors (261), who found that persistent positive blood culture with no apparent extracardiac source and two or more of the following suggests endocarditis: significant cardiac murmur, pulmonary or peripheral septic emboli, positive echocardiogram, and elevated teichoic acid antibody.

Echocardiography has emerged as one of the most important tools in diagnosis and management of IE. It may show various valvular abnormalities, vegetations, and evidence of perivalvular abscess or fistula. It is also useful in assessing the effects of therapy. An enlarging vegetation, extension of infection outside the valve, or increase in valvular regurgitation may be an indication of failure of medical treatment and the need for surgical intervention. Transthoracic echocardiography often is limited by the inability to obtain adequate imaging, and this has led to the more recent use of transesophageal echocardiography (TEE).

VIDEO

Video 36.4 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis **(A)** showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. *B:* intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 36.5 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis **(A)** showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. *B:* intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 36.6 Transesophageal echo of a large tricuspid valve vegetation in a patient with infectious endocarditis. This patient was an intravenous drug user, which is common in patients with right-sided endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In experienced hands, TEE should be considered in patients in whom endocarditis is suspected. Negative results of a technically adequate TEE study usually mean that the probability of infection is low (269). TEE shows abscesses in 5% to 30% of patients with IE (270). It also has prognostic value, because aortic involvement, growth in the size of the vegetation, and presence of spontaneous echocardiographic contrast are indicators of high-risk endocarditis (270). In 121 patients with IE, TEE added additional information in 32% of patients, resulting in appropriate surgical intervention in 22 instances (271). To clearly assess the value of TEE in IE, 118 consecutive patients were studied prospectively with two-dimensional transthoracic echocardiography and with TEE. Results were correlated with direct inspection of

the valve at surgery or at autopsy. Compared to transthoracic echocardiography (28.3%), TEE was more sensitive and more specific for abscess detection (98.6%). Abscesses were detected in 40 instances, were commonly located in the aortic valve region, and were frequently secondary to *S. aureus* infection (272).

Cardiac catheterization may have an important role in some cases, particularly before surgical intervention. Catheterization is of greater value when more than one left-sided valve lesion is present and when an extravalvular infection is suspected. It should not be performed routinely in all cases before surgical intervention, because it has a somewhat increased morbidity (273).

Gallium-67 myocardial imaging detects increased activity in patients with IE, and positive scans may be seen if imaging is done 3 to 8 days after injection (274). Imaging with technetium-99m–labeled antibacterial antibody was successful in the experimental setting (275). Advances in echocardiography have meant that nuclear studies are rarely used.

Management

The mainstay of therapy for IE is sterilization of the vegetation. Details of therapy for endocarditis are covered elsewhere in this book. The general principles are to identify the causative organism, make an *in vitro* determination of its susceptibility, and select a bactericidal antibiotic (276). Patients infected with methicillin-sensitive *Staphylococcus* may be treated with nafcillin. Patients with methicillin-resistant *Staphylococcus* endocarditis may be treated with vancomycin with or without rifampin. Recent randomized studies have suggested that in uncomplicated, right-sided endocarditis caused by methicillin-sensitive *S. aureus*, a 2-week course of therapy may be sufficient to eradicate the disease (277). Outpatient therapy for IE has been attempted in some countries (278), and although inpatient therapy is still recommended, some hospitals have begun to adopt outpatient treatment protocols.

Surgical treatment for IE should be considered in patients who have congestive heart failure, recurrent embolic phenomena, and persistent sepsis despite administration of appropriate antibiotic therapy (279,280 and 281). Other conditions that favor surgical intervention include IE with echocardiographic evidence of definite abscesses or mycotic aneurysms, embolic complication with persistent mobile vegetation, aortic valve endocarditis with significant regurgitation, and possibly polymicrobial endocarditis. Surgical correction includes valvulectomy with a prosthetic valve replacement, valvulectomy without valve replacement in right-sided valve endocarditis, vegetectomy with or without valve reconstruction surgery, and drainage of abscesses.

Valve replacement is associated with high mortality rate, which is the result of early prosthetic valve endocarditis, the return of approximately 50% of drug users to drug injection with subsequent development of severe prosthetic valve endocarditis and poor compliance with anticoagulant regimens, and the development of fatal complications.

In right-sided endocarditis, Arbulu and colleagues performed tricuspid valvulectomy without valve replacement (282). Since the initial description of this procedure, Arbulu has performed the operation on at least 53 patients. At 22 years after surgery, the actuarial survival rate was 64% (283). Patients who survive are expected to lead a normal life, provided they abstain from intravenous drug injection, even though they may have variable degrees of systemic congestion. This operation appears to be the operation of choice for right-sided intractable endocarditis in patients who are addicted to injection drug use. Vegetectomy is another option, in which the vegetation is excised with full preservation of the valve and its supporting structures (284), but experience with and usefulness of this technique are quite limited.

Prognosis

Mortality rates among patients with IE are high in the initial phase. The risk decreases significantly 1 year after infection. In follow-up of 330 patients with IE, survival was 75% at 6 months and 57% at 5 years (285). The most important prognostic factor is age at onset of infection.

CONTROVERSIES AND PERSONAL PERSPECTIVES

A few controversies still persist regarding substance abuse and the heart. Some of the controversy regarding how an acute dose of cocaine affects the heart depends on the model being studied. When cocaine is administered to awake, conscious animals and humans, the sympathomimetic effects predominate, with increases in heart rate and blood pressure. When the drug is administered to pentobarbital-anesthetized animals, the sympathomimetic effects appear to be masked and the cardiodepressive effects predominate. This has caused some confusion in the literature regarding the acute effects of cocaine on the heart. Some debate exists as to whether cocaine actually accelerates atherosclerosis, because many of the clinical reports suggesting such an effect involved patients who also have other risk factors, especially tobacco smoking. No general agreement exists regarding the best way to treat acute cocaine cardiotoxicity, and virtually no controlled studies have addressed this issue. The use of beta-blockers remains controversial. Although they decrease the heart rate and blood pressure, they block the beta receptors, leaving the alpha receptors unopposed, with the potential to worsen coronary artery vasospasm.

My personal observation (R.A.K.), in a large inner-city county hospital, is that cocaine cardiotoxicity is probably more common than we realize, especially in that type of environment. When a younger person presents with an acute MI, especially if other risk factors are not present, it is very important to remember to ask about a history of substance abuse, especially cocaine. Initially, patients may be reluctant to divulge this information. However, eventually, with compassionate persistence, the story often emerges. Patients then need to be educated about the hazards of substance abuse. Most will not be aware that cocaine can affect the heart.

It is likely that the controversy regarding whether coffee and caffeine are deleterious to the cardiovascular system will continue for some time. Until the controversy is resolved, coffee should be consumed in moderation, especially by individuals with a history of coronary artery disease.

SUMMARY

Substance abuse remains an ongoing public health problem in the United States. Several common agents of abuse contribute to heart disease. The types and frequency of heart disease related to substance abuse probably vary depending on the prevalence and frequency of the type of drug being used. An acute dose of cocaine can have several adverse effects on the heart, including cardiodepressor effects, reductions in contractility and coronary artery blood flow, and conduction abnormalities, which are probably related to its local anesthetic properties. At the same time, cocaine has cardiostimulatory effects, increasing heart rate, blood pressure, contractility, ventricular excitability, and coronary vasoconstriction, related to its sympathomimetic and vagolytic effects. Cocaine has the potential for exacerbating ischemia in patients by increasing heart rate and blood pressure at the same time that it causes coronary vasoconstriction. The following common cardiovascular diseases have been associated with cocaine abuse in patients: acute MI and myocardial ischemia, dilated and hypertrophic cardiomyopathy, myocarditis, hypertension, arrhythmias, and possibly acceleration of atherosclerosis. Aortic dissection has been reported (286).

Controversy regarding the safety of caffeine and coffee use among coronary artery disease patients is ongoing. The consumption of filtered coffee does not cause an increase in cholesterol levels, whereas boiled coffee may negatively affect lipid levels. Moderate consumption of coffee probably is safe for most patients who have coronary artery disease. Anabolic steroid abuse has been associated with acute MI and lipid abnormalities. There are case reports of MI and cardiomyopathy after use of amphetamines. Small amounts of alcohol may have some benefit on cardiovascular morbidity and mortality rates, but excess use is associated with alcoholic cardiomyopathy, hypertension, arrhythmias, and sudden death.

Tobacco use is a risk factor for coronary artery disease. Both active smoking and exposure to passive smoke increase the risk of coronary artery disease events. Substance abuse associated with injection of intravenous material results in a risk of IE.

The best approach to long-term therapy for heart disease related to substance abuse is to avoid the deleterious substances. Rehabilitation programs play an important role in this regard. Specific therapies for cardiotoxicity in general are lacking. Anecdotal reports regarding therapy for acute ischemic cocaine cardiotoxicity favor nitrates, oxygen, aspirin, benzodiazepines, alpha-blockers, and possibly calcium channel blockers. If acute MI is present, use of thrombolytic agents and aspirin may be considered, unless contraindications such as severe hypertension, intracerebral hemorrhage, or seizures are present. Future studies are necessary to help clarify the best therapy for cocaine cardiotoxicity.

Primary prevention of substance abuse is clearly the most important goal for our society—although a formidable one, it is worth striving for. The cardiotoxicity of substance abuse is generally serious and potentially life-threatening, and treatment is far less optimal than preventing the behavior that causes disease in the first place.

THE FUTURE

The association between substance abuse and heart disease is one that has received increased attention, largely as a result of publicity surrounding the deaths of athletes and stars who have used drugs such as cocaine. Given the prevalence of drug abuse in this country, it is a topic that likely will remain important over the next decade. Its importance may vary, depending on which drugs are most used at a given point in time.

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37

ATHLETE'S HEART

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N. A. MARK ESTES III

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OVERVIEW

Athlete's heart was first described by Henschen in 1899 and is now recognized as a constellation of clinical findings known as *the athletic heart syndrome*. These findings include sinus bradycardia, atrioventricular (AV) conduction delay, systolic flow murmurs, and cardiac chamber enlargement with normal or augmented function. All four cardiac chambers may be enlarged. Chamber enlargement may rarely exceed the upper limits of normal, but marked enlargement of the right ventricle or either atrium suggests a pathologic process. Clinical findings of the athletic heart syndrome are limited to athletes whose sports and training require a large aerobic or endurance exercise component. Left ventricular (LV) wall thickness can be slightly thickened, but this thickening is generally restricted to athletes with LV chamber enlargement and rarely reaches the thickness of pathological states such as hypertrophic cardiomyopathy (HCM). Physicians often are required to evaluate asymptomatic athletes before participation and to evaluate symptomatic athletes before permitting their return to vigorous exercise training. In these situations, the athletic heart syndrome must be differentiated from pathological conditions associated with cardiac complications during exercise, including HCM, coronary artery anomalies, aortic stenosis, right ventricular or LV cardiomyopathy in young athletes, and coronary artery disease in adults.

GLOSSARY

Athlete's heart or athletic heart syndrome: a constellation of clinical, electrocardiographic, and echocardiographic variants of normal found in well-trained athletes who participate in sports requiring prolonged aerobic exercise training.

Endurance or isotonic exercise: generally rhythmic, physical exertion (e.g., running, swimming, and bicycling) that requires significant, sustained increases in oxygen uptake.

External workrate: the amount of work an individual can perform on the environment. External workrate can be measured by oxygen uptake.

Internal workrate: the myocardial oxygen consumption during exertion. Internal workrate can be estimated by the triple product (heart rate × systolic blood pressure × LV ejection time) or double product (heart rate × systolic blood pressure).

Maximal oxygen uptake ($\dot{V}O_2max$): the physiologic and highly reproducible upper limit of an individual's ability to extract and use oxygen during progressive isotonic exercise.

Onset of blood lactate accumulation (OBLA): the point during exercise at which the accumulation of lactate can be detected in blood samples. This point corresponds to an abrupt increase in the respiratory rate and often is referred to as the *anaerobic threshold*.

Relative workrate: the percentage of maximal oxygen uptake required to perform a certain physical task.

Strength exercise: physical exertion that requires lifting or moving objects against resistance. Strength exercises can result in motion against resistance (e.g., weightlifting) or require exertion against a fixed object, referred to as isometric exercise.

HISTORICAL PERSPECTIVE

The history of the athlete's heart is as clouded by myth and misinformation as the condition itself. Take, for example, the legend of Pheidippides, who reportedly ran 40 km (24 miles) from the battlefield at Marathon to Athens to announce the Athenians' victory over the Persians. After announcing the victory, he collapsed and died. This story provides a marvelous introduction to the risks of exercise, but it is probably not true. Pheidippides was more likely named Philippids or Phidippus. His run was not from Marathon to Athens to announce victory but from Athens to Sparta to solicit military aid, then back to Athens with the bad news that the Spartans were not coming. This distance was not 40 km but closer to 500 km (300 miles). Most distressing of all to those who cite this event, our runner, name uncertain, probably survived. Herodotus, the major historian of the event, never mentioned the runner's demise (1).

Similar confusion has plagued the concept of the athlete's heart—what we prefer to label *the athletic heart syndrome*—because this condition is often a constellation of findings. Indeed, as with the story of Pheidippides, the first telling was probably the most correct. Subsequent versions only distorted or embellished the truth.

The first description of the athletic heart syndrome was provided more than 100 years ago. Henschen used percussion of the chest to determine heart size in cross-country skiers before and after a ski race (2). His report in 1899 concluded that skiing produces a physiologic cardiac enlargement that enables the athlete's heart to perform more work than the heart of an untrained individual. He also noted that the right and left sides of the heart were enlarged. He concluded that this enlargement is due to athletic activity, and he called the condition "the athlete's heart." Subsequent studies by a plethora of others using roentgenographic, echocardiographic, computerized tomographic, and magnetic resonance imaging techniques have confirmed Henschen's conclusion that exercise training produces a generalized cardiac enlargement.

Henschen also noted acute cardiac dilation after exhaustive exercise, and he attributed this dilation to cardiac failure. This conclusion has long been considered incorrect, although more recent echocardiographic studies have resurrected the possibility that prolonged, exhausting, competitive events such as triathlons may produce a cardiac fatigue typified by temporarily decreased LV contractility (3). Perhaps Henschen was not as wrong as previously thought.

How could Henschen, over 100 years ago and using a technique as crude as chest percussion, have reached such accurate conclusions? The answer is that he picked the right athletes, but this simple response obscures several principles critical to understanding the athletic heart syndrome. First, Henschen studied endurance-trained athletes. Strength-trained athletes such as weightlifters have increased cardiac dimensions, but their hearts' enlargement is related to body size and muscle mass (4).

Only endurance-trained athletes or athletes training with endurance and strength modalities develop the athletic heart syndrome. Second, Henschen selected cross-country skiers—endurance athletes whose exercise uses arm and leg muscles. Cardiac dimensions and stroke volume are greatest in athletes whose training requires use of the most muscle mass.

NORMAL RESPONSE TO EXERCISE AND EXERCISE TRAINING

A basic understanding of the acute response to endurance exercise and of the exercise training response is useful in evaluating athletes with possible athletic heart syndrome.

Acute Response to Exercise

Compared to the general population, endurance athletes are characterized by a higher ability to perform maximal dynamic exercise. This ability can be measured as $\dot{V}O_2$max. $\dot{V}O_2$max is expressed as liters of oxygen per minute or is "normalized" for body weight as milliliters of oxygen per minute per kg of body weight. $\dot{V}O_2$max is physiologically limited by the ability of the cardiopulmonary system to deliver oxygen and the ability of the exercising muscles to use oxygen. Rearranging the Fick equation for cardiac output [cardiac output = volume of oxygen/arteriovenous oxygen difference ($\dot{V}O_2$/A-V O_2)] demonstrates that $\dot{V}O_2$max is the product of maximal cardiac output and the maximal A-V O_2 difference. Maximal cardiac output is the product of maximal heart rate and stroke volume. Because maximal heart rate among healthy individuals varies primarily by age, and because the ability to increase the A-V O_2 difference is limited, the major factor responsible for the higher $\dot{V}O_2$max among endurance athletes is an increased stroke volume. The clinical findings typical of the athletic heart syndrome are generally manifestations of this increased stroke volume.

Although higher $\dot{V}O_2$max values distinguish endurance athletes from sedentary individuals, $\dot{V}O_2$max is not a good discriminator of superior athletic performance among endurance athletes. This is because $\dot{V}O_2$max does not measure an individual's ability to maintain exertion over a long period of time. Other factors, including the athlete's mechanical efficiency and "anaerobic threshold," or OBLA, contribute to submaximal work capacity and are better discriminators of competitive exercise performance among athletes. Enhanced mechanical efficiency means that an athlete can perform a physical task while consuming less oxygen than a less efficient athlete. A higher OBLA means that the athlete can perform more mechanical work without producing lactate. OBLA indicates the onset of several factors that eventually reduce exercise capacity. OBLA is associated with a higher respiratory rate stimulated by the production of carbon dioxide from buffering lactic acid ($HLactate + HCO_3^- \rightarrow H_2CO_3 + lactate^- \rightarrow H_2O + CO_2$). In addition, the lactate production indicates a level of exertion requiring glycogen catabolism, and glycogen depletion is one potential limiting factor in endurance performance. Finally, lactic acid itself contributes to fatigue.

Acute cardiovascular adaptations to exercise in young, healthy subjects are mediated by several mechanisms. The increase in heart rate initially is due primarily to withdrawal of resting vagal tone. At approximately 50% of maximal heart rate, additional acceleration of heart rate is associated with increased sympathetic nerve activity and norepinephrine spillover into the circulation (5). Peak heart rate is estimated as 220 – age, but the standard deviation of this estimate is ± 11 to 22 beats/min (6). Therefore, the 95% confidence limits are ± 22 to 43 beats/min, and the range of normal can be 44 to 86 beats/min. These limits underscore the problem of estimating heart rate by age. Changes in stroke volume during exertion are influenced by body position. During supine exercise, the increase in stroke volume is due primarily to increases in end diastolic volume. During upright exercise, increases in stroke volume are produced by increases in end diastolic volume and decreases in end systolic volume (5). The increase in the A-V O_2 difference is produced by redistribution of blood from nonexercising tissue to the exercising musculature, increased extraction of oxygen over the exercising muscle bed, and hemoconcentration (5). Sweat loss is not required for this hemoconcentration, because plasma fluid moves into exercising muscle to produce the muscle swelling obvious in recently exercised muscle. These changes and the mediating mechanisms apply to young, healthy subjects such as those most likely to present with clinical findings of the athletic heart syndrome. Altered responses and different mechanisms are observed in elderly subjects and in patients with disease.

It is important for clinicians to recognize that any change in any component of this system can affect maximal exercise capacity. Cardiologists tend to focus on changes in maximum heart rate and stroke volume, but changes in hemoglobin concentration, the ability to fully oxygenate red blood cells, the capacity to shunt blood to exercising muscle, or the ability of the muscles to extract the available oxygen can affect exercise performance. These factors should be considered in evaluating athletes for problems with exercise performance.

As mentioned above, there are differences in mechanical efficiency among different athletes performing identical exercise tasks. Nevertheless, in general, a specific physical task requires approximately the same oxygen uptake when performed by different individuals. Consequently, knowing the workrate of exercise permits a general estimation of the $\dot{V}O_2$ required, even when the $\dot{V}O_2$ is not measured. The oxygen consumption required by a physical task is referred to as the *external workrate* (7). The external workrate also determines the cardiac output response to the exercise task. In general, a 1-L increase in oxygen consumption produces a 6-L increase in cardiac output (8). The external workrate is also referred to as the *absolute workrate* or the *absolute* $\dot{V}O_2$. The *relative workrate* refers to the percent of an individual's $\dot{V}O_2$max that is required for that person to perform a certain physical task. In other words, relative workrate is the required $\dot{V}O_2$ relative to the individual's maximum. Individuals differ in their maximal exercise capacity, primarily because maximal stroke volume and maximal cardiac output vary among individuals. Because of differences in individual exercise capacity, the same physical task usually requires approximately the same absolute workrate for different individuals, but the task often requires markedly different relative workrates.

Identical external workrates can produce markedly different myocardial oxygen demand. Myocardial oxygen demand has been referred to as the *internal workrate* (7). Myocardial oxygen demand increases with increasing heart rate and systolic blood pressure (9). The product of heart rate and systolic blood pressure or rate pressure product is used clinically to estimate the myocardial oxygen demand of exertion (9). Heart rate and systolic blood pressure increase linearly with the relative workrate. Consequently, identical external workrates can produce markedly different internal workrates or myocardial oxygen demands, depending on the individual's $\dot{V}O_2$max. The implication of this observation is that a physical task requires less myocardial oxygen supply for an individual with a high $\dot{V}O_2$max than for a less fit individual.

Effect of Exercise Training on Exercise Performance

The increase in $\dot{V}O_2$max produced by 2 to 3 months of exercise training in young subjects is produced by increases in maximal stroke volume and the maximal A-V O_2 difference. It is generally stated that approximately 50% of the increase in $\dot{V}O_2$max is due to increases in stroke volume and 50% to changes in the A-V O_2 difference (10), but these amounts vary greatly among studies (11). Increases in $\dot{V}O_2$max are greater with increasing duration and intensity of the exercise training program and with the amount of muscle mass used in training (5). Also, with prolonged training, more of the increase in exercise capacity is due to increased stroke volume. Apparently, the increase in the A-V O_2 difference is an early adaptation to habitual exercise, whereas large increases in stroke volume require cardiac adaptations over a longer, albeit undefined, period of time. The average increase in $\dot{V}O_2$max in healthy subjects after jogging or cycling for 3 to 12 months is approximately 20% (12), but it is less in more fit and older individuals. Increments in $\dot{V}O_2$max can be considerably larger if training is prolonged over years rather than months.

The increase in absolute work capacity produced by exercise training means that the same external workload after training represents less of the individual's relative workload. Because exercise-induced increases in heart rate and systolic blood pressure are related to the relative, as opposed to the absolute, exercise workload, the same external workload after training elicits smaller increments in heart rate, blood pressure, and myocardial oxygen demand.

CLINICAL COMPONENTS OF THE ATHLETIC HEART SYNDROME

Variants Attributed to Enhanced Parasympathetic Tone

Several of the findings of the athletic heart syndrome (e.g., resting bradycardia, sinus arrhythmia, and AV conduction delay) are generally attributed to changes in the sympathetic nervous system with enhanced parasympathetic tone and reduced sympathetic tone. Of these two factors, enhanced parasympathetic tone is most important (13). These alterations in the sympathetic nervous system control are unlikely to be the entire explanation, however. The resting heart rates of endurance athletes remain lower than those of sedentary subjects, even after sympathetic nervous system control is theoretically eliminated in both groups with large doses of atropine and beta-adrenergic blockade; these circumstances suggest that other factors such as larger cardiac dimensions also contribute to the reduced heart rate (14,15). Similarly, athletes may demonstrate ST–T-wave changes of early repolarization and T inversions, which are also attributed to sympathetic nervous system alterations (Fig. 37.1 and Fig. 37.2). Some of the T-wave changes can be quite bizarre and may be similar to changes seen with conditions known to affect the parasympathetic nervous system, such as subarachnoid hemorrhage.

FIGURE 37.1 Electrocardiogram from a 53-year-old physician who has run a minimum of 60 km weekly for 40 years. The axis is 70 degrees—somewhat unusual in a healthy individual in this age group—and there is ST elevation of early repolarization in leads V_3–V_6.

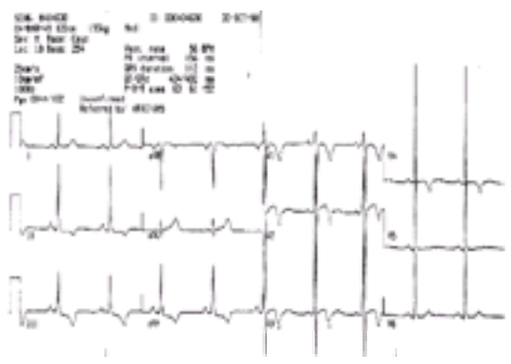


FIGURE 37.2 Electrocardiogram (ECG) from a 49-year-old white physician showing diffuse T-wave inversions. He had run 58 to 108 km weekly and ridden a bicycle 32 km weekly for 20 years. The ECG was obtained when he volunteered for a study of healthy subjects. An echocardiogram showed left ventricular (LV) internal dimensions at end diastole and systole of 50 mm and 20 mm, respectively, and LV posterior and septal wall thickness of 12 mm each. He was not restricted from athletic competition.

Nevertheless, not all extreme T-wave abnormalities in athletes are due to athletic heart syndrome. For example, among 26 Spanish athletes evaluated for negative T waves ³2 mm, four were found to have HCM (16) (eFig. 37.2.1). Many of the changes typical of athletic heart syndrome (e.g., sinus arrhythmia and the ST changes of early repolarization) are also characteristic of young, healthy individuals, but they are more marked or more frequent in athletes and may persist into middle age among physically active subjects. All of these abnormalities in sinus rate, AV conduction, and the ST changes of early repolarization should resolve with exercise with its attendant withdrawal of vagal tone and increased sympathetic activity. This is not always true for marked T-wave inversions (16), however, so their failure to resolve does not necessarily imply a pathologic process.

***e*FIGURE 37.2.1** Electrocardiogram from a 45-year-old African-American man who experienced cardiac arrest while playing basketball. The tracing shows a prolonged PR interval, impressive left atrial enlargement, anterior T abnormalities, and an abnormal QRS pattern. These findings are not typical of the athletic heart syndrome. Echocardiography showed findings of hypertrophic cardiomyopathy, including an enlarged septum (17 mm), a reduced ejection fraction, and no resting outflow tract gradient.

Sinus Bradycardia

$\dot{V}O_2$max and maximal cardiac output are increased in endurance athletes, but there is little change in resting oxygen consumption or cardiac output. Consequently, the larger resting stroke volume characteristic of endurance athletes permits a reduction in resting heart rate. Sinus bradycardia, generally defined as a heart rate <60 beats/min, is typical of athletic heart syndrome and reported in up to 91% of endurance athletes (17). Bradycardia in athletes can be profound, and a rate of 25 beats/min has been reported in one distance runner (18). In addition to sinus bradycardia, sinus pauses or “sinus arrest” of >2 seconds have been documented during sleep in endurance athletes (17) (Fig. 37.3).

FIGURE 37.3 Electrocardiogram from a 36-year-old physician showing marked bradycardia of 46 beats/min, voltage criteria for left ventricular (LV) hypertrophy (note the 1/2 standard calibration), and a prolonged QT interval in lead V3. He was 180 cm (5'10") tall and weighed 67 kg (147 lb). He had played college lightweight American football and rowed in lightweight crew. Over the past 5 years, he had run 100 to 130 km weekly and competed in 42-km foot races. He was asymptomatic and had no family history of cardiac complications. His echocardiogram showed LV internal dimensions at end diastole and systole to be 54 and 37 mm, respectively. The LV posterior wall thickness was 10 mm, and the septal thickness was 11 mm. He was not restricted from athletic participation, despite the QT interval, because he was totally asymptomatic.

Sinus Arrhythmia

Sinus arrhythmia refers to variation in sinus rate with respiration. Specifically, the sinus rate decreases slightly at the start of the expiratory phase of the respiratory cycle. Sinus arrhythmia is common in young, healthy subjects, but it is more marked in endurance athletes.

Atrioventricular Conduction Delay

First degree AV block, defined as a PR interval of >0.20 seconds, is reported in 10% to 33% of endurance athletes (19). Second degree AV block of the Mobitz I or Wenckebach pattern is characterized by progressive prolongation of the PR interval before a nonconducted P wave and is also seen more commonly in the athletic heart syndrome (19). Second degree AV block with Mobitz II appearance is characterized by a nonconducted P wave without preceding PR prolongation, but it is not typical of the athletic heart syndrome. Mobitz II block typically occurs at the level of the His-Purkinje system, whereas Mobitz I block is due to progressive slowing of conduction in the AV node. An AV block with Mobitz II appearance may occur in well-trained athletes due to enhanced vagal tone, but this is rare (17) (Fig. 37.4 and *e*Fig. 37.4.1). The presence of Mobitz II block should prompt a search for other causes and should be attributed to athletic training only if the athlete is asymptomatic and no other abnormalities are detected.

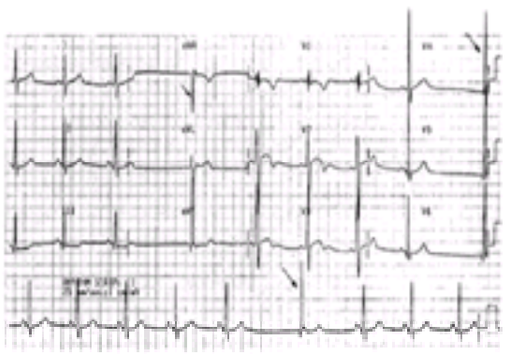
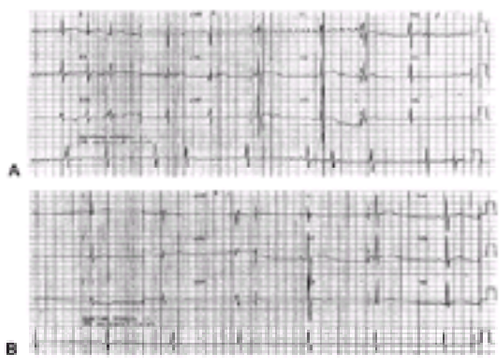


FIGURE 37.4 Electrocardiogram (ECG) from a 28-year-old man who had run 42 km in 2 hours and 17 minutes. He was evaluated for momentary chest discomfort felt in 1984, several days after the death of James Fixx, the author of *The Complete Book of Running*. The ECG shows an axis of 110 degrees, incomplete right bundle branch block, sinus pauses with junction "escape" beats (*arrows*), slight P-wave enlargement in lead II, increased precordial voltage, and biphasic T waves in V_2 and V_3. He was otherwise asymptomatic, had a normal echocardiogram, and was treated with reassurance. (Reproduced from Thompson PD. Cardiac evaluation of the young or old, competitive or recreational athlete. In: Strauss RH. *Sports medicine*, 2nd ed. Philadelphia: WB Saunders, 1991, with permission.)



***e*FIGURE 37.4.1** Electrocardiograms during **(A)** and after **(B)** an episode of atrial fibrillation in a 42-year-old man who ran 70 km weekly. The ventricular rate was only 100 beats/min during atrial fibrillation despite no medication and only 43 beats/min after cardioversion, illustrating the slow heart rate of endurance-trained individuals. The tracings also show incomplete right bundle branch block, precordial ST elevations, and T inversions in V_3—all of which can be normal in endurance-trained patients. (Reproduced from Thompson PD. Cardiac evaluation of the young or old, competitive or recreational athlete. In: Strauss RH. *Sports medicine*, 2nd ed. Philadelphia: WB Saunders, 1991, with permission.)

The prolongation of the AV interval and decrease in AV conduction velocity previously described may also unmask ventricular preexcitation—also known as Wolff-Parkinson-White (WPW) syndrome—when accompanied by symptomatic arrhythmia. Indeed, a WPW conduction pattern is more common in endurance athletes (19). Cardiologists should be cognizant of this fact when evaluating athletes for an asymptomatic WPW conduction pattern, because the risk of sudden death in asymptomatic subjects with this abnormality is low.

Vasovagal Syncope

Vasovagal syncope appears to occur more frequently in endurance-trained individuals because it is related, in part, to these athletes' enhanced vagal tone. Lower-body negative pressure is a research technique used to examine blood pressure control and an individual's response to orthostatic stress. Compared to nonathletes and strength-trained athletes, endurance-trained individuals have a reduced ability to maintain blood pressure during lower-body negative pressure (20). The clinical implications of this reduced ability are that endurance-trained individuals are more vulnerable to vasovagal syncope or simple fainting and that positive tilt-table responses are almost the norm in well-trained endurance athletes. These athletes have a large venous capacity, enhanced vagal tone, and reduced sympathetic tone—all of which make them vulnerable to postural hypotension and a positive tilt-table response. Tilt-table results should not be interpreted as an adequate explanation for syncope in athletes, therefore, unless the clinical situation also strongly supports this explanation.

Electrocardiographic ST–T-Wave Changes

ST elevation of the early repolarization pattern is so common in endurance-trained athletes that it should be considered the norm rather than the exception. Persistent training into advanced age can preserve this pattern in older athletes. ST depression, in contrast, is rare and should prompt a search for other causes. Peaked, biphasic, and inverted T waves in the precordial leads are frequently seen in endurance athletes. The biphasic T waves typically occur in the precordial "transition" leads, where the QRS complex is changing from a primarily negative deflection in the right precordial leads to a primarily positive deflection in the left-sided leads. Deeply inverted T waves can also be normal in athletes, but they are rare and require the exclusion of significant disease (16). Of 952 healthy, Italian, national-caliber athletes, only 27 had marked T-wave inversions. Three-hundred seventy-five had abnormal or mildly abnormal electrocardiograms (ECGs), suggesting HCM in 11 and arrhythmogenic right ventricular cardiomyopathy in 16. Only one of these athletes actually had HCM, however (21).

Evidence of Cardiac Enlargement

Habitual endurance exercise produces a global cardiac enlargement that may affect the atria and ventricles. The most consistent enlargement is seen in the LV chambers, where intracavity dimensions and, rarely, wall thickness, can be large enough to raise the suspicion of cardiac disease. Mild enlargement of both atria and the right ventricle can occur, but marked enlargement of these structures is suggestive of a disease process and is not observed in the athletic heart syndrome.

Electrocardiographic Evidence of Chamber Enlargement

The ECG in well-trained athletes may show mildly increased P-wave amplitude that suggests right atrial enlargement, P-wave notching that suggests left atrial enlargement, incomplete right bundle branch block (IRBBB), and voltage criteria for right ventricular and LV hypertrophy (17) (Fig. 37.5).

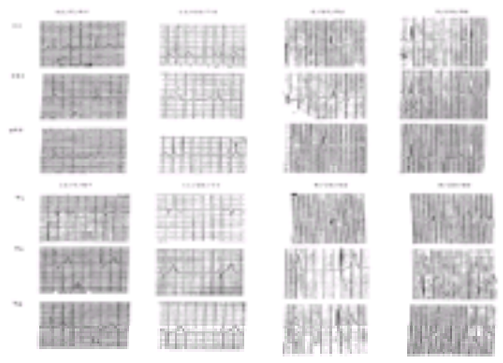
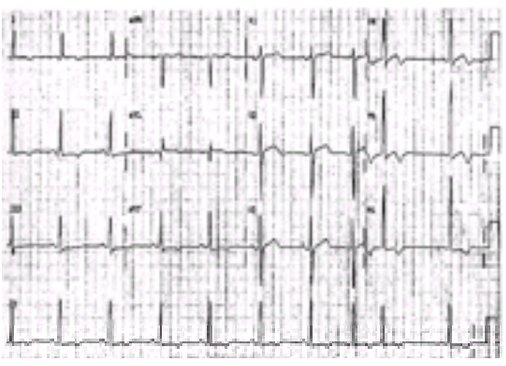


FIGURE 37.5 Selected leads from the serial electrocardiograms (ECGs) of a 42-year-old physician who began running in the late 1960s and progressed to running multiple 42-km foot races. The tracings show the development of the classic ECG of the athletic heart syndrome, including increased P-wave height (lead II), increased P-wave negativity (V_1), increased right-sided R wave (V_1), increased precordial voltage (V_5 and V_6). These developments suggest right and left atrial and ventricular enlargement, respectively. There are also progressive T-wave changes with increased precordial T waves (V_5 and V_6) and increasing negative T waves in the inferior leads (III and aVF). The presence of all of these findings in a single ECG is unusual, even among well-trained, elite athletes. This individual remains healthy in his mid-50s.

Among endurance athletes, voltage criteria for right ventricular hypertrophy are noted in 18% to 69% of subjects (19). This ECG evidence for atrial and right ventricular enlargement does not usually suggest extreme enlargement, so marked evidence of atrial or right ventricular enlargement should prompt a search for pathologic causes. Similarly, although IRBBB is common, complete heart block generally is not accepted as part of the athletic heart syndrome (17).

In contrast to ECG evidence of atrial and right ventricular enlargement, the voltage criteria for LV hypertrophy can be extreme in endurance athletes (*e*Fig. 37.5.1). QRS voltage is greater in endurance athletes than in other subjects, even after adjusting for LV mass, suggesting that some of the extreme voltage seen in endurance-trained subjects is due to thinner chest walls (4).



***e*FIGURE 37.5.1** Electrocardiogram showing left ventricular hypertrophy and premature atrial contractions in an asymptomatic, healthy, 31-year-old, nonhypertensive athlete.

Echocardiographic Evidence of Cardiac Enlargement

Echocardiography frequently is performed in evaluating symptoms in athletes, so it is important for clinicians to know the limits of cardiac enlargement produced by exercise training.

Thomas and Douglas have recently summarized the topic of echocardiographic dimensions in athletes (3). At least 59 studies have used echocardiography to examine cardiac dimensions in athletes (3). These studies consistently documented increased LV dimensions. Thirteen studies comparing right ventricular dimensions in athletes and controls demonstrated that the right ventricular transverse dimension was increased an average of 24% in the athletes (22 mm vs. 17 mm) (3). Fourteen studies comparing the left atria of athletes and controls demonstrated that the transverse dimension was 16% larger in the athletes. To our knowledge, only one study has documented a larger right atrial size in the athletes (3).

Pelliccia and colleagues have explored the upper limits of echocardiographic dimensions in athletes using data obtained in studies of Italian national athletes at the Institute of Sports Science in Rome. These authors examined LV wall thickness in 947 athletes, 209 of whom were women (22). Only 16 athletes (1.7%) had an LV wall thickness >12 mm, the upper limit of normal. Fifteen of these athletes participated in rowing or canoeing, sports that require isotonic and isometric effort and involve a large muscle mass. These 15 athletes represented 7% of the rowers and canoeists studied. The only other athlete with increased wall thickness was a cyclist. All athletes with increased wall dimensions had won medals in international competition. The largest wall thickness in any athlete was 16 mm. All of the female athletes had wall thicknesses less than 11 mm.

Six of the athletes with marked LV wall enlargement discontinued exercise training and were restudied after 40 to 240 (average = 90) days of reduced activity. Average wall thickness decreased from 12.8 ± 0.9 mm to 10.5 ± 0.4 mm, $p < .05$. Three of the athletes—none of whom had increased wall thickness—had localized apical hypertrophy suggestive of apical HCM, but none of these subjects had the marked apical T-wave abnormalities characteristic of this condition. All of the athletes with increased wall thickness also had increased cavity dimensions, which suggests that the increase in wall thickness in these subjects is an adaptation to maintain normal wall stress.

These results are extremely useful in differentiating the athletic heart syndrome from HCM. LV wall thickness >12 mm was unusual, even in elite athletes. Consequently, the presence of increased wall thickness in recreational or elite athletes should prompt a search for pathologic causes. No athlete had an LV wall thickness >16 mm, and values above this range should raise the possibility of HCM. Wall hypertrophy above the normal range was not observed in female athletes. All athletes with wall hypertrophy also demonstrated increased cavity dimensions, which are not seen in HCM or in other diseases with pathologic wall thickening. Finally, wall thickening in high-caliber athletes should regress with detraining.

In another study, Pelliccia et al. examined LV cavity dimensions in 1,300 elite athletes participating in 38 different sports (23). The LV end-diastolic diameter (LVEDD) was greater in male (55 mm) than in female (48 mm) athletes. The LVEDD was >55 mm (i.e., the upper limits of normal) in 45% of the athletes and exceeded 60 mm in 14% of the subjects. The largest cardiac dimensions by gender were 66 mm for a female athlete and 70 mm for a male athlete. Regression analysis demonstrated that body surface area (r = 0.76), heart rate (r = –0.37), and age (r = 0.29) correlated with the LVEDD, indicating that these three variables accounted for 60% of the variability in the LVEDD. Adding gender and the type of sport to these factors accounted for 72% of the variability. Age may function in this group as a surrogate for the duration of training, but this is not certain because age did not differ between athletes whose LVEDD was >60 mm or <60 mm. The sports that were most associated with an LVEDD ³60 mm were cycling (49% of cycling athletes), ice hockey (42%), basketball (40%), rugby (39%), canoeing (39%), and rowing (34%). All are sports that require a large endurance component or a combination of moderate endurance training and increased body size. Systolic and diastolic function were normal in the athletes. Once again, few athletes had evidence of LV wall hypertrophy. Only 14 of the athletes (1.1%) had a septal thickness >12 mm, and only four athletes (0.3%) exceeded this posterior wall thickness. Wall thickness among all of the athletes correlated with cavity dimensions. Athletes with increased cavity dimensions also tended to have larger left atrial and aortic root dimensions.

Throughout this chapter we have emphasized that the largest changes in cardiac dimensions occur with endurance exercise training or the combination of endurance and strength training in large individuals. Nevertheless, the concept that endurance and strength exercise training produce different cardiac adaptations is widely accepted by many clinicians. Habitual, high-dynamic exercise training is presumed to increase primarily LV volume, whereas exercise with a high static component is presumed to increase LV wall thickness. This concept has been challenged by investigators who could find no significant differences between strength-trained athletes and controls (24). In the most comprehensive examination of this issue, Pluim and colleagues performed a metaanalysis on all 59

echocardiographic studies of athletes published from 1975 to 1998 (25). They divided the 1,451 subjects into endurance-trained athletes (e.g., long-distance runners), strength-trained athletes (e.g., weight lifters), and combined static- and dynamic-trained athletes (e.g., rowers and cyclists). These reports included 31 studies of endurance athletes, 24 studies of strength athletes, and 23 studies of combination athletes. Septal thickness in endurance athletes (10.5 mm) was significantly greater than that in controls (8.8 mm) but less than that in strength-trained subjects (11.8 mm) and combination athletes (11.3 mm). Posterior wall thickness, in contrast, was actually greater in endurance athletes (10.3 mm) than in controls (8.8 mm), but it was not different from combination (11 mm) or strength-trained (11 mm) subjects. Pluim et al. concluded that the differences in the cardiac dimensions of endurance- and strength-trained athletes are relatively minor and that there is no clear dichotomy in the cardiac adaptations to endurance or strength training. None of the cardiac dimensions are adjusted for body size, nor are any of the included studies prospective, so it is possible that some of the septal thickness in strength-trained and combination-trained athletes results from body size and not the training modality.

The clinical significance of these findings is that clinicians should avoid ascribing cardiac wall hypertrophy to the effects of exercise training—even among strength-trained athletes—because the effects of such activity alone on cardiac wall thickness is minor.

Functional Cardiac Murmurs in Athletes

Both young and old endurance athletes often have functional cardiac murmurs created by cardiac adaptations to exercise training. Blood flow is laminar and without turbulence until a critical Reynolds number (Re) is exceeded. Re is determined by the following formula:

$$\text{Re} = \frac{\text{average velocity} \times \text{tube diameter} \times \text{fluid density}}{\text{fluid viscosity}}$$

Laminar flow is disrupted above an Re of 2,000, creating turbulence and murmurs. As previously discussed, endurance exercise training reduces resting heart rate, increases resting stroke volume, and enhances cardiac performance. Training does not change resting cardiac output, which is delivered via a slower heart rate and a larger stroke volume. Much of the larger stroke volume is delivered more vigorously in early systole by a more dynamic ventricle. This delivery increases blood velocity. The pulmonic and aortic valve orifices do not increase with exercise training, so the increased blood velocity produces early systolic “flow murmurs.” Such flow murmurs in young athletes are due to flow across the pulmonic valve and often vary with respiration. Athletes aged 50 years and older may have mild sclerosis of the aortic valve leaflets, and their flow murmurs are often due to aortic valve sclerosis and the turbulence mentioned above. These murmurs are less “innocent” because they may progress to important aortic stenosis, especially in athletes with other risk factors for atherosclerosis such as hypercholesterolemia (26,27). Treatment of these risk factors may reduce the development of important aortic stenosis, but this has not been studied. Nevertheless, we often recommend 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors in adult patients with noncritical aortic stenosis in the hope of preventing such progression.

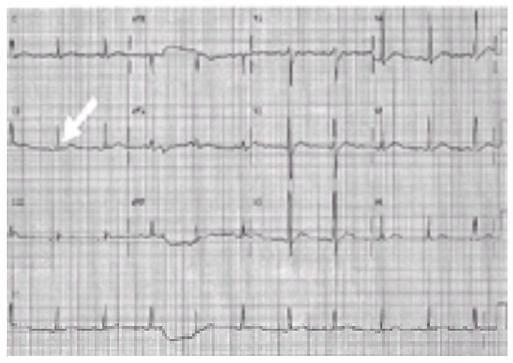
EXERCISE-RELATED CARDIAC EVENTS

Clinicians are often required to differentiate the athletic heart syndrome from life-threatening cardiac disease and to make recommendations about the risks of exercise in individuals with diagnosed abnormalities. This section discusses the risks of exercise and the conditions associated with exercise-related cardiac events. There is little doubt that vigorous physical exertion increases the risk of cardiac events in children and adults with cardiovascular abnormalities. This increased risk of exertion has been quantified and documented conclusively only in adults in whom the risk of sudden death (28,29) and acute myocardial infarction (30,31 and 32) is increased by exercise. The data are less definitive in children, but the clinical association of exertion and sudden death in children with a variety of congenital and acquired cardiac diseases leaves little doubt that exercise has a provocative role in these events.

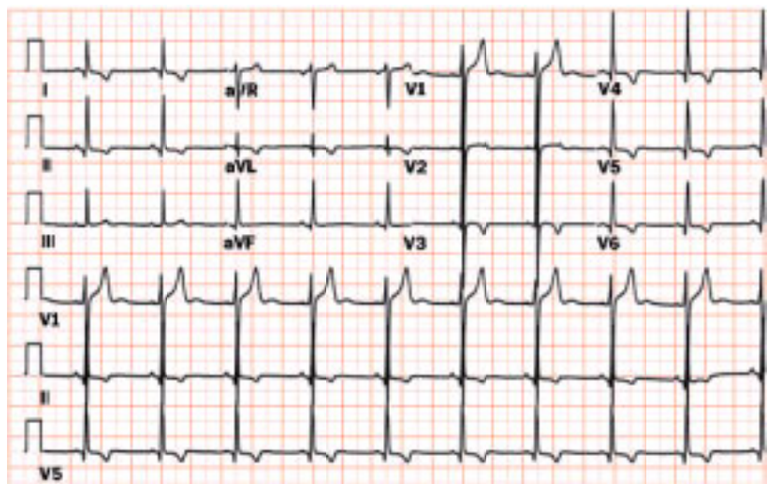
Pathology of Exertion-Related Cardiac Events

The causes of exertion-related cardiac events varies by the age of the subject. Among adults older than 29 or 39 years, atherosclerotic vascular disease is the cause of almost all exercise-related cardiac complications (32,33). A rare exercise-related death in an adult is due to other causes such as HCM, infiltrative diseases such as amyloidosis (34), and intramyocardial coronary arteries (35). Among younger subjects, the causes of death are usually congenital cardiac abnormalities or acquired myocarditis or cardiomyopathy. The prevalence of various causes of exercise-related events may vary by geographic distribution. HCM repeatedly has been shown to be the dominant cause of exercise-related deaths in young American athletes (36,37), whereas right ventricular dysplasia is the primary cause of such events in Italian athletes, especially in the Veneto region of Italy (38). The reasons for this discrepancy are unclear, but it has been attributed to a required national screening program for Italian athletes that has identified and excluded athletes with HCM (39). Other factors such as a regional interest in the disease, an increased prevalence of the condition in the Mediterranean area (40), or recent international recognition of right ventricular dysplasia may also contribute to the discrepancy (*e*Fig. 37.5.2 and *e*Fig. 37.5.3).

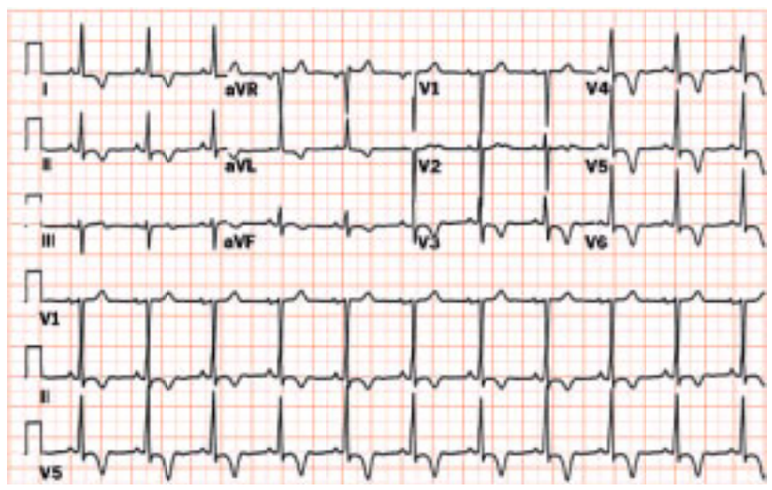
***e*FIGURE 37.5.2** Electrocardiogram (ECG) from a 22-year-old woman who experienced cardiac arrest while playing soccer. Echocardiography demonstrated right ventricular cardiomyopathy. The ECG shows T-wave inversions in leads V_1–V_3. She was treated with an implantable defibrillator.



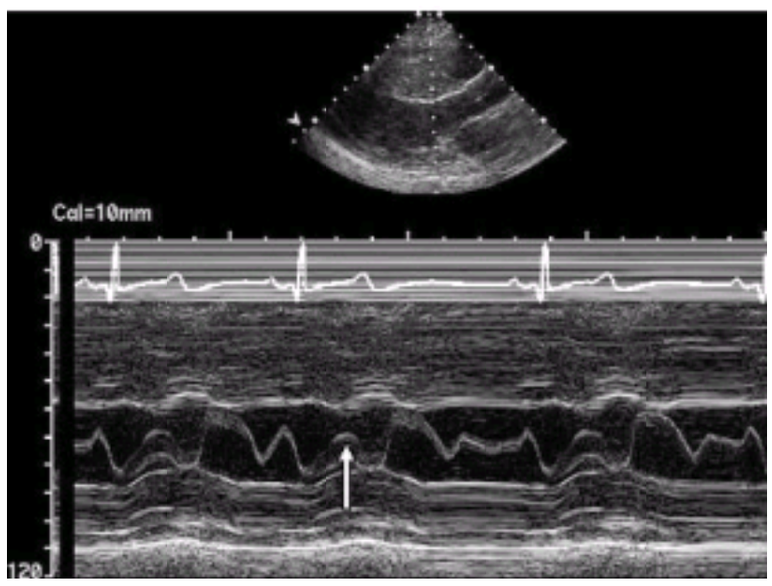
***e*FIGURE 37.5.3** Electrocardiogram from a 28-year-old African-American man who experienced cardiac arrest during basketball. Echocardiography and angiography confirmed right ventricular cardiomyopathy. Note the epsilon waves in lead II (*arrow*), lead III, and the augmented voltage unipolar left foot lead (aVF). Epsilon waves represent delayed depolarization of the right ventricle.



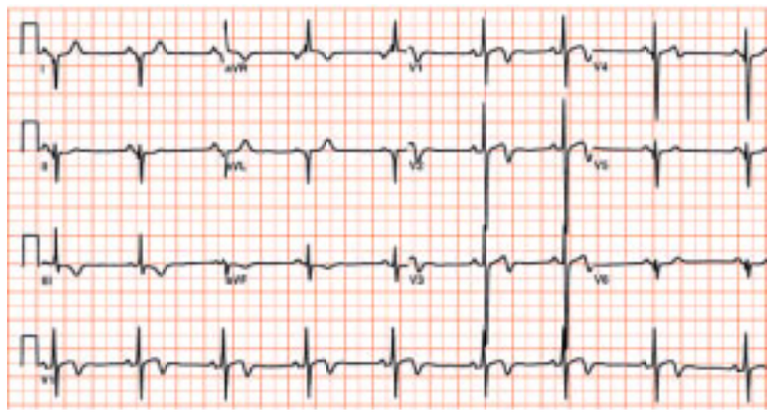
Hypertrophic cardiomyopathy. Inverted precordial T waves associated with hypertrophic cardiomyopathy.



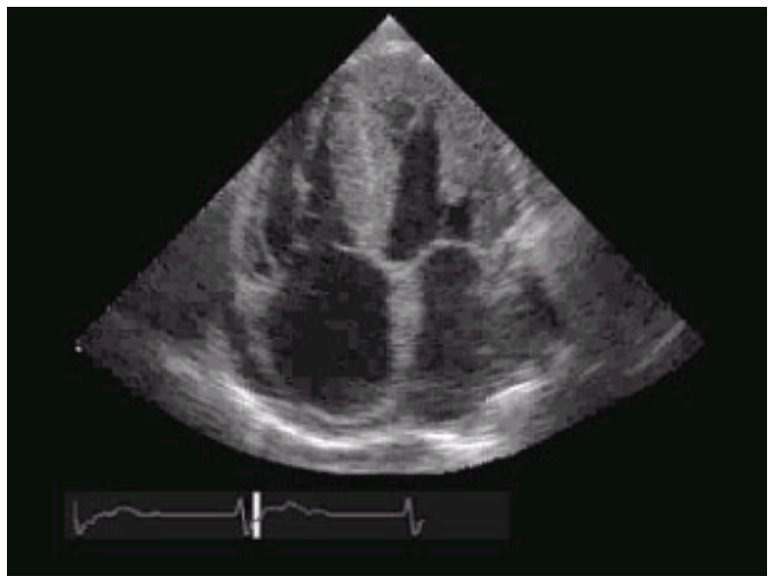
Yamaguchi's disease. Note anterior precordial T-wave inversion in this Asian patient with apical hypertrophy.



M-mode tracing of hypertrophic cardiomyopathy with severe septal hypertrophy seen at the top of the trace and systolic anterior motion (SAM) of the mitral valve in systole seen in the middle of the trace (designated by the arrow).



A 28-year-old Caucasian male patient with hypertrophic obstructive cardiomyopathy.



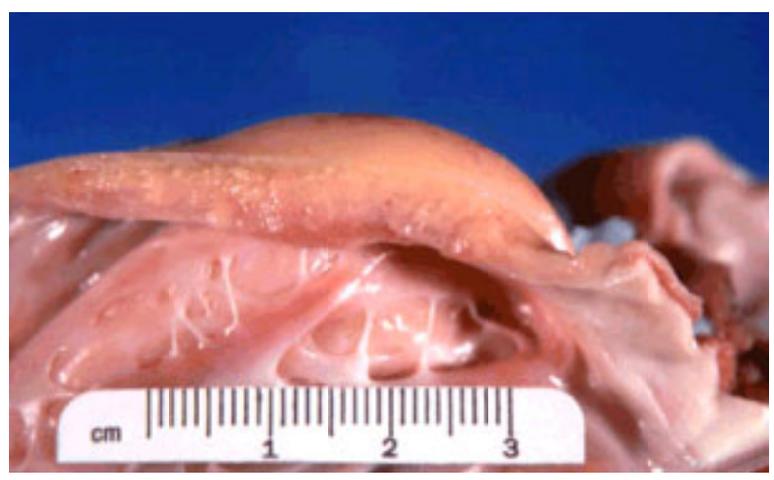
Apical four-chamber view of amyloid heart disease. Note the significant thickening of the left ventricle and right ventricle walls due to infiltration. There is also characteristic thickening of the valves and biatrial enlargement. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)

VIDEO

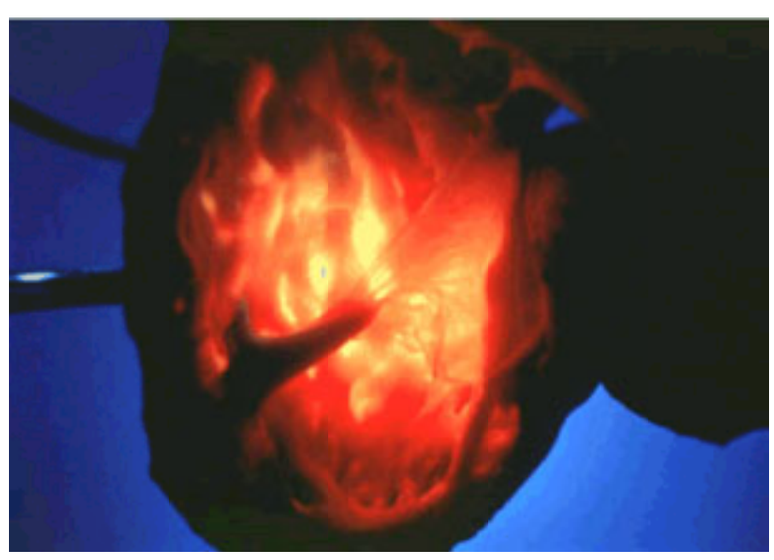
Video 37.1 Transthoracic apical four-chamber view of a patient with amyloidosis. Note the thickened “sparkling” walls of the right and left ventricles. Both the mitral and tricuspid valves are mildly thickened and there is biatrial enlargement and a trivial pericardial effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 37.2 Transthoracic subcostal view of a patient with amyloidosis showing markedly thickened right and left ventricular walls, showing the characteristic “sparkle.” The right ventricle is towards the top of the screen and the right ventricle free wall is 1.5 cm thick. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Muscular hypertrophy of the arterial wall in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Right ventricle completely replaced by fat in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Arrhythmogenic right ventricular dysplasia. Illumination reveals thinned right ventricular wall. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)

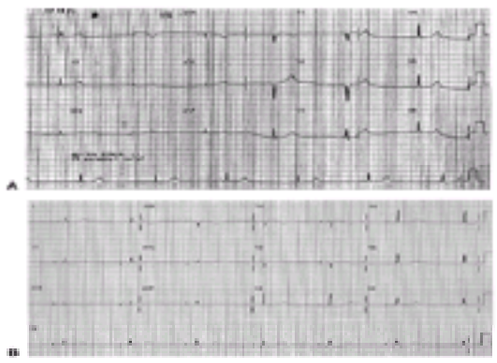
In contrast to the findings in adults, atherosclerotic coronary artery disease is a rare cause of exercise-related deaths in younger subjects. The conditions associated with exercise-related sudden death in young athletes has been presented by Van Camp et al. with data from the National Center for Catastrophic Sports Injury Research (37). These authors examined 136 deaths in American athletes that occurred during or within 1 hour of sports participation. Cardiac conditions were associated with 100 deaths, including HCM (50% of the cases), coronary artery anomalies (13%), myocarditis (7%), aortic stenosis (6%), and dilated cardiomyopathy (6%) (Table 37.1). The coronary artery anomalies included anomalous origin, intramyocardial course, and an ostial ridge at the coronary origin. Some coronary anomalies, such as an acute take-off of the artery from the aorta (41), may be overlooked or unappreciated during autopsy. Only one case was attributed to right ventricular dysplasia, contrasting with the findings in Italian subjects, as previously discussed. Other investigators have presented similar data for American athletes (42).

	Men	Women
Hypertrophic cardiomyopathy[a]	50	1
Probable hypertrophic cardiomyopathy	5	0
Coronary artery anomalies[c]	11	2
Myocarditis	7	—
Aortic stenosis	6	—
Cardiomyopathy	6	—
Atherosclerotic coronary disease	2	1
Aortic rupture	2	—
Subaortic stenosis	2	—
Coronary aneurysm	—	1
Mitral prolapse	1	—
Right ventricular dysplasia	—	1
Cerebral arteriovenous malformation	—	1
Subarachnoid hemorrhage	—	1

[a]Adapted from Van Camp SP, Bloor CM, Mueller FO, et al. Nontraumatic sports death in high school and college athletes. Med Sci Sports Exerc 1995;27:641-647, and reproduced from Thompson PD. The cardiovascular risks of exercise. In: Thompson PD, ed. Exercise and sports cardiology. New York: McGraw-Hill, 2000, with permission.
[b]Three subjects also had coronary anomalies, one subject had Wolff-Parkinson-White syndrome.
[c]This category includes anomalous left coronary artery (LCA) from right sinus of Valsalva (n = 6), intramural left anterior descending (n = 6), anomalous LCA from pulmonary artery (n = 2), anomalous right coronary artery (RCA) from left sinus (n = 2), hypoplastic RCA (n = 2), and ostial ridge of the LCA (n = 2). Three subjects with coronary anomalies also had hypertrophic cardiomyopathy and are tabulated with that group.

TABLE 37.1 CARDIAC CAUSES OF DEATH IN HIGH SCHOOL AND COLLEGE ATHLETES[a] (n = 100)

These reports do not include all of the cardiac conditions for which exercise increases the risk of sudden death and should not be used to decide to permit an individual with a diagnosed cardiac condition to participate in vigorous exercise and competitive sports. Cardiac arrhythmia and sudden death in the long-QT syndromes, for example, are often associated with physical activity (43), especially swimming (44) (eFig. 37.5.4 and eFig. 37.5.5). Long-QT syndrome was not identified as a cause of death in these studies (37,42), because the diagnosis can only be made with a surface ECG antemortem or postmortem by molecular genetic testing of autopsy material (44). Recommendations for athletic participation for various cardiac conditions are available elsewhere (45).



***e*FIGURE 37.5.4 A,B:** Electrocardiogram from a 40-year-old woman showing QT prolongation. She presented with presyncope and syncope due to torsades de pointes during running and swimming. Her symptoms responded to beta-blockade, but marked sinus bradycardia required pacemaker placement with atrial pacing **(B)**.

***e*FIGURE 37.5.5 A,B:** Electrocardiogram from a 27-year-old man who experienced cardiac arrest. **(A)** shows unusual repolarization abnormalities in leads V_1–V_3 not typical of those seen with the athletic heart syndrome. Challenge with flecainide 150 mg by mouth produced right bundle branch block and repolarization changes consistent with Brugada's syndrome **(B)**. Brugada's syndrome usually produces syncope or sudden death unassociated with physical exertion.

There are several clinically important lessons to learn from these pathologic studies of exercise-related events. Several of the conditions identified at autopsy could have been detected before death. These conditions include valvular and subvalvular aortic stenosis, Marfan syndrome as a cause of aortic rupture, and possibly HCM, although a murmur in the later condition is detected in only 25% of cases. Few of the victims were women, which is consistent with other observations that women are protected, to some extent, from sudden death (46).

Incidence of Exercise-Related Cardiac Event

Although vigorous exertion acutely increases the risk of sudden death during exercise for individuals with known or occult cardiac disease, it is important for clinicians to remember that the absolute risk of a cardiac event during exercise is extremely low. The estimated annual incidence of exercise-related deaths among high school and college athletes is only one death per 133,000 men and 769,000 women, respectively (37). These estimates include 36 noncardiac deaths and thereby overestimate the cardiac risks of athletic competition. The death rate is higher among college men than high school men (1.45 vs. 0.66 events per 100,000) for unclear reasons, but it may be related to cardiac size because cardiac size itself is a risk factor for cardiac death (47,48), and more mature athletes should have larger hearts. These reports do not provide any information on how many individuals with cardiac conditions were prohibited from participating in sports and thereby escaped an exercise-related complication.

The risk of exercise-related sudden death is considerably higher in adults because of the increased prevalence of coronary disease, but it has been estimated that there is only one death per year for every 15,000 to 18,000 asymptomatic middle-aged men (28,29). Published studies on adults have wide confidence limits, however, because they are based on few subjects. Using the 95% confidence limits from a study done in Rhode Island, the death rate may vary from one death per year for every 4,000 to 26,000 asymptomatic men (28).

PREPARTICIPATION SCREENING OF COMPETITIVE ATHLETES

There is ongoing debate about the value of screening competitive athletes and the extent to which such screening should go. It is critically important that cardiologists know the issues involved, because they are frequently asked to evaluate athletes with possible abnormalities detected during screening. Often, these abnormalities are bradycardia or functional murmurs and are of no significance, but on rare occasions, a completely asymptomatic athlete with a major cardiac abnormality is identified.

The American Heart Association has issued a medical and scientific statement on the cardiovascular preparticipation screening of competitive athletes (49). This document recommends a personal and family history and a physical examination before high school participation in sports, with the examination repeated at least every 4 years. This statement does not advocate routine echo- or electrocardiography.

Others maintain that routine electrocardiography should be required for all young athletes (50). Fuller and colleagues obtained a medical history, had a cardiologist perform cardiac auscultation, and recorded a resting ECG on 5,615 athletes. Cardiovascular abnormalities were detected in 582 of the athletes (10.4%). These abnormalities included an abnormal cardiac history in 2.0%, abnormal auscultatory findings in 3.0%, hypertension in 0.3%, and an abnormal ECG in 2.6% of the athletes. Only 22 athletes were ultimately denied participation in sports due to severe aortic insufficiency (AI) (n = 1), severe hypertension (n = 5), WPW ECG pattern (n = 6), premature ventricular contractions (n = 5), RBBB (n = 4), and supraventricular tachycardia (n = 1). The reasons for excluding the athletes with WPW pattern, premature ventricular contractions, and RBBB were not provided. Among the 22 excluded athletes, the patient with severe AI underwent valve replacement, the hypertensive patients were treated, and the patient with supraventricular tachycardia underwent therapeutic ablation. Fifteen of the excluded subjects were lost to follow-up, greatly reducing the value of the study. Over the 3 years of the study, there was one cardiac arrest in an athlete. This occurred in an athlete with an anomalous right coronary artery who had successfully passed screening. Fuller et al. reason that including electrocardiography in the evaluation of high school athletes increases the detection of cardiac abnormalities. An alternative interpretation is that sphygmomanometry and auscultation alone could have detected most important abnormalities, and that the ECG only increases the detection of asymptomatic abnormalities unlikely to be of major significance.

Because HCM is the predominant cause of exercise-related sudden death in young athletes, other physicians have reasoned that echocardiography should be included routinely in the preparticipation screening of all young athletes (51). Italian investigators have been among the more enthusiastic supporters of this approach (39). Italy has had a national law since 1971 requiring athletes to undergo an examination that includes a medical history, physical examination, ECG, and step test. Athletes with abnormal findings are referred for other testing, including a 24-hour ECG recording, an echocardiogram, and a formal exercise test. This program has screened 33,735

athletes and referred 3,016 for echocardiography. Of the referred athletes, 621 were disqualified from competition—58.7% because of cardiac issues, including 22 athletes with HCM. Four disqualified athletes died over 8.2 ± 5.0 years (mean ± standard deviation) of follow-up. None of the 22 athletes with HCM died. A total of 49 nondisqualified athletes died, yielding an annual death rate of 1 per 62,500 athletes. The authors compared the frequency of HCM as a cause of exercise deaths in the United States and in Italy and concluded that the low prevalence of HCM among their athletes who died was most likely a result of the screening program.

Several problems limit the widespread application of these results. The prevalence of HCM in the Italian athletes is low. Only 0.06% of the athletes had this diagnosis, whereas the expected prevalence in a sample of healthy young Americans is 0.20% (52). Only 4 of 365 athletes who were excluded from participation in sports died of a cardiac condition. We do not know how these excluded athletes were medically managed, but the death rate is extremely low, which raises the possibility that screening prohibited the sports participation of individuals who were not at great risk for exercise-related sudden death. The annual death rate of 1 per 62,500 athletes is similar to, if not higher than, the death rate of 1 per 133,000 American male athletes who presumably underwent far less screening (37). Consequently, instead of supporting extensive screening, these results actually raise questions about its effectiveness.

Cardiac Examination of Competitive Athletes

The components of the cardiovascular examination are detailed elsewhere in this text, and a consensus statement on the components of the preparticipation cardiac examination has been published (49). The following section emphasizes clinical principles useful when examining athletes as part of a preparticipation examination or when evaluating athletes for suspected cardiac abnormalities.

Preparticipation Screening of Athletes

The preparticipation screening of athletes should include an inquiry about (a) exertional symptoms including chest discomfort, syncope, dyspnea, and fatigue; (b) a history of cardiac murmurs, hypertension or cardiac diagnoses; and (c) a family history of sudden death or of any of the conditions known to be associated with sudden death (49). The physical examination should include brachial artery blood pressure measurement, precordial auscultation with the athlete supine and standing, simultaneous palpation of the radial and femoral pulses to exclude coarctation, and an assessment for stigmata of Marfan syndrome.

Examining Athletes for Suspected Disease

The examination of athletes for suspected cardiac disease should be considerably more detailed than the preparticipation examination. Even with modern diagnostic techniques, the cardiac evaluation remains an important part of evaluating athletes. The severity of valvular lesions, for example, can be over- or underestimated by echocardiography, cardiac catheterization, and the physical examination. The best decisions are made when the results of several examination techniques are compared for agreement or discrepancies and the cardiologist does not rely on clinical, echocardiographic, or catheterization data alone. We have seen multiple athletes with clinical symptoms and physical examination findings of severe aortic stenosis that were not repaired because the catheterization data did not indicate a “critical” valve area. Mild, moderate, and severe aortic stenosis are classified as a calculated aortic valve area >1.5 cm^2, 1.0 to 1.5 cm^2, and <1.0 cm^2, respectively, but these values are not normalized for body surface area (53) and may severely underestimate the severity of the stenosis in large individuals.

Someone trained to avoid the digit selection and rounding to tens that are common in most blood pressure “determinations” should measure blood pressure in both arms. The average systolic pressure is several millimeters higher in the right arm, probably because of the more direct course of the pulse wave to the innominate and right subclavian arteries. A systolic pressure >15 mm higher in the right arm, if associated with a systolic ejection murmur, suggests supravalvular aortic stenosis (54). A widened pulse pressure >40 mm Hg suggests a regurgitant murmur and should prompt auscultation for AI.

Elevated blood pressure in a young athlete requires simultaneous palpation of the radial and femoral pulses to exclude a radial/femoral pulse delay suggestive of aortic coarctation. It is often incorrectly assumed that the mere presence of a femoral pulse excludes coarctation, but some patients can reconstitute a palpable femoral pulse via collaterals. In these patients, it is the delayed impulse between the radial or brachial and femoral pulse that suggests the diagnosis (54).

Palpating the carotid pulse is an important maneuver in athletes because aortic stenosis remains a frequent, easily identified cause of sudden cardiac death. A carotid pulse that is low volume, has a slow upstroke, or is difficult to locate should increase suspicion of important aortic stenosis.

During cardiac auscultation, the examiner should ignore any obvious murmur and proceed with a sequential systematic examination of the heart sounds, possible gallops and clicks, diastolic murmurs, and, finally, systolic murmurs. The intensity of the first heart sound (S_1) is partly determined by the degree of mitral and tricuspid leaflet separation at the onset of ventricular contraction. S_1 is generally soft in well-trained athletes because heart rate is slow, lengthening diastole and allowing approximation of the mitral leaflets. If the mitral leaflets are widely separated to accommodate delayed ventricular filling, such as with mitral stenosis, the valve leaflets travel farther at the onset of systole and S_1 is loud. If the leaflets have been partially closed by the regurgitant jet of AI, S_1 is soft. AI and isolated mitral stenosis are notoriously difficult to hear and often require special maneuvers. The intensity of S_1 helps indicate when these additional maneuvers are required.

The second heart sound (S_2) is produced by closure of the aortic valves followed by the pulmonic valves. During inspiration, filling of the right ventricle is augmented. The larger volume of blood in the right ventricle shifts the intraventricular septum leftward, compromises LV filling, and reduces the LV stroke volume (55). This process hastens aortic closure so that the aortic valve closes earlier in the cardiac cycle during inspiration. On the right side, the larger right ventricular volume delays pulmonic valve closure. The earlier aortic closure and the delayed pulmonic closure increase the splitting of S_2 during inspiration. This process is best appreciated when the patient is in the seated position. In the supine position, venous return from the legs can nearly maximize right ventricular filling so that any additional increase in the splitting of S_2 is difficult to detect. This is especially true in endurance athletes, whose plasma volume can average 800 mL larger than comparison subjects (56). In the supine position, part of this increased plasma volume shifts to the central circulation. During the expiratory phase of the cardiac cycle, aortic and pulmonic closure occurs almost simultaneously, and S_2 should be single or nearly so. If there is an intracardiac connection between the right and left sides of the heart, such as an atrial septal defect (ASD), there is no or little differential in right and left cardiac filling during respiration. Right ventricular filling is also increased from left to right intracardiac shunting, which increases the right ventricular stroke volume. S_2, therefore, is often widely split, does not move during respiration, and fails to close during expiration. Several clinical characteristics of ASDs are also found in the athletic heart syndrome, including a systolic murmur similar to the benign pulmonic flow murmur common in athletes and right ventricular conduction delay on the ECG. The behavior of S_2 is useful for distinguishing an ASD from the athletic heart syndrome.

The gallops of the third and fourth heart sounds are common in athletes and are of no importance unless the gallops are loud or associated with other abnormalities.

The initial auscultatory examination of the athlete is performed with the athlete seated. This reduces the chance of producing a flow murmur, facilitates hearing AI, and maximizes the splitting of S_2. The upright position reduces ventricular volume and increases the chance of detecting a murmur in obstructive HCM. Auscultation should be repeated with the athlete in the supine and left-lateral positions. If there is any suspicion of HCM, the athlete should also be examined standing and squatting. Squatting increases ventricular afterload, which decreases the murmur of obstructive HCM, whereas standing often increases the murmur if obstruction is present.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Our perspective on the athletic heart syndrome is indeed personal. One of us (P. D. T.) started training for competitive distance running events at age 12 and ultimately qualified for the 1972 U.S. Olympic Marathon Trials as a medical student. However, during the first year of medical school, he had a murmur detected during a demonstration of cardiac auscultation. His subsequent ECG showed marked LV hypertrophy and early repolarization changes, prompting an interest in cardiology and the medical problems of endurance athletes. The other author (N. A. M. E. III) developed his interest in athletic heart syndrome in part from his experiences as a secondary school and collegiate athlete. We have had the privilege of providing advice and medical care to hundreds of competitive athletes, including two medalists in the Olympic Marathon. The opportunity to combine our personal interest in athletics with our professions as cardiologists has enriched our academic careers.

In evaluating athletes for cardiac abnormalities, we make a strong distinction between abnormalities discovered during screening examinations and those discovered during the evaluation of symptoms. Most screening examinations do not detect real disease, but they do detect a high frequency of normal variants common in young, healthy subjects and part of the athletic heart syndrome. In our experience, physicians frequently overreact to mild abnormalities detected during screening because of legal concerns and the lack of appreciation for the magnitude of changes that can be produced by extreme endurance exercise.

On the other hand, symptomatic athletes require a thorough examination. We are repeatedly impressed with the number of well-known athletes who die during exercise after having presented with symptoms that were ignored or inadequately evaluated. Excluding important cardiac disease in symptomatic athletes may be the most efficient way to prevent exercise-related complications.

In evaluating symptoms, it is extremely important to evaluate any possible cardiovascular disease in the context of the athlete’s total physical and psychological

situation. Many young, competitive athletes face enormous pressure from coaches, parents, and peers. Failure to achieve the desired level of success is extremely stressful on competitors at any age. Young athletes who present with fainting, for example, may be simply seeking a medical way out of a difficult, stressful situation. It is easier to claim a medical reason for failure than to simply not be good enough. We refer to this condition as *the athletic swoon syndrome*. Typically, this condition occurs in a young athlete in an individual sport who competes well when winning but collapses dramatically when losing, often within sight of the finish line. We do not mean to minimize the importance of this problem. The athlete often needs reassurance, both medically and personally, to place winning and losing in a more healthy perspective. Athletic swoon syndrome must be differentiated from true exercise-induced syncope and long-QT syndrome. True exercise-induced syncope is a threatening symptom associated with important cardiac disease, and patients with long-QT syndrome are occasionally misdiagnosed as having hysterical syncope (57).

We strongly recommend that individuals who serve as trainers and coaches or who officiate at sporting events should learn and update yearly their cardiopulmonary resuscitation skills. We also recommend that automatic defibrillators be available in areas where athletes train and compete. Coaches and officials are often present when athletes collapse. If properly trained in resuscitation and the use of automatic defibrillators, coaches and trainers may be able to resuscitate potential victims of exercise-related sudden death. We believe that competency in these skills should be a prerequisite for physical educators, coaches, and sports officials.

THE FUTURE

The future of research and treatment of athletic heart syndrome, as with many aspects of medicine, will be greatly influenced by the revolution in genetic medicine. Molecular biologic approaches have already led to an understanding of the genetic basis for a number of cardiovascular conditions associated with cardiovascular complications during exercise. The genetic basis for HCM, arrhythmogenic right ventricular cardiomyopathy and the closely related Naxos disease, congenital long-QT syndromes, idiopathic ventricular fibrillation, familial atrial fibrillation, and familial dilated cardiomyopathy have all been partially elucidated. There will be an ongoing evolution of molecular biologic techniques and their application to the prediction, prevention, and treatment of cardiovascular disease. We foresee at least three ways in which this evolution may influence the cardiac care of athletes.

First, genetics will likely be used to predict which individuals with a disease phenotype are at risk for an exercise-related complication. HCM is the leading cause of exercise-related deaths among American athletes, and those with this condition are routinely restricted from athletic competition. There are reports, however, of athletes who have had successful athletic careers despite presence of the disease (58). Among the nonathletic population with HCM, those genetic mutations associated with a change in the electrical charge of their encoded amino acid in the myosin heavy chain appear to be associated with the greatest cardiac risk (59). Consequently, it may eventually be possible to predict by genetic analysis which athletes are or are not at risk of exercise-related events. Before such techniques can be used clinically, however, there will need to be widespread availability of the testing methods that are now available only for research, as well as careful clinical studies to determine the ability of genetic analysis to predict prognosis.

Second, genetics will be increasingly used to diagnose disease and may ultimately have a role in the preparticipation screening of athletes. This possibility is illustrated by the case report of a physically active 19-year-old woman who died after a near drowning. Molecular genetic screening of a sample of the deceased's myocardium demonstrated a novel genetic mutation of the long-QT 1 locus. The woman's 18-year-old sister had a similar mutation and was counseled about the risks of strenuous exercise, as well as the potential benefits of beta-adrenergic blockage (44).

Third, genetic analysis may help differentiate disease from normal physiologic adaptations to physical training. Some athletes appear to experience especially large changes in cardiac dimensions with endurance training. This response is influenced by genetic variants. The angiotensin-converting enzyme gene has two common variants. One variant, referred to as the *D*, or *deletion allele*, has a 287–base pair deletion and is associated with higher angiotensin-converting enzyme blood levels than the I or insertion allele. Among military recruits subjected to 10 weeks of intense physical training, echocardiographic changes in LV mass and ECG evidence of LV hypertrophy were greatest in individuals with the D allele (60). Additional genetic factors influencing the cardiac response to exercise training will undoubtedly be found. Knowledge of such variants may ultimately help in separating athletes with an excessive physiologic response to training from individuals with HCM.

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38

CARDIAC TRAUMA

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“ Indicates text or graphics that appear only in the electronic versions of this text.”

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OVERVIEW

Among young people, trauma is the most common cause of death, with cardiovascular mortality being the major contributor. Patients with injury to the thorax, blunt or penetrating, should be transferred rapidly to a trauma center for fast and expert surgical evaluation. In unstable patients, echocardiography helps to identify critical injury and facilitates early surgical exploration, which can be lifesaving. In more stable patients, the goal of evaluation is to rule out significant occult cardiac and thoracic great vessel injury. Echocardiography, computed tomographic (CT) scan, thoracoscopy, and magnetic resonance imaging (MRI) can make accurate diagnosis of these injuries. Although normal electrocardiography (ECG) helps to identify low-risk patients with blunt cardiac injuries, the significance of abnormal ECG and cardiac enzyme elevation in this setting remains unclear.

INTRODUCTION

Trauma is a leading cause of death for young adults in the United States (1), with thoracic trauma accounting for 30% to 50% of 150,000 total deaths from trauma occurring annually (2,3 and 4). The heart and thoracic great vessels are commonly involved in blunt and penetrating trauma. Most serious injuries to these vital organs are rapidly fatal. Therefore, fast transport of the patients to trauma centers, rapid recognition of injury, and expeditious expert treatment are essential for better survival.

INJURY TO THE HEART

Classification of Cardiac Injury

Physical trauma to the heart can be penetrating or blunt. A penetrating injury results when a foreign object enters the body and pierces the heart. Blunt injury, on the other hand, results from physical forces acting externally on the body. Iatrogenic injuries to the heart and great vessels from invasive procedures are not uncommon. Electrical and radiation injury are other uncommon mechanisms of cardiovascular trauma.

Penetrating Cardiac Injury

Historical Perspective

Penetrating cardiac injury has been well-recognized for centuries, with earliest descriptions by Homer in *The Iliad* (5). Beck has aptly divided the history of cardiac trauma into three historical periods (6). First is the period of mysticism, when cardiac wounds were thought to be necessarily fatal. In this period, even scholars such as Aristotle thought that “[t]he heart alone of all the viscera cannot withstand serious injury. This is to be expected because when the main source of strength (the heart) is destroyed there is no aid that can be brought to the other organs which depend on it.” This era of pessimism extended to the seventeenth century, followed by a period of observation and experimentation. In 1761, Morgagni (7) noted that blood in the pericardial sac could lead to compression of the heart. In 1810, Larrey (8) performed the first drainage of pericardium, but the patient died of suppurative pericarditis. Fischer (9), in 1868, reported pericardial drainage after injury in 452 cases, with 10% survival. But, even in this era, there was serious skepticism about the therapy. One of the prominent surgeons of this time, Billroth, stated, “The surgeon who should attempt to suture a wound of heart would lose respect of his colleagues” and “Let no man dare to operate on the heart” (10). The third era started when Block, in 1882, showed in the rabbit model of heart injury that successful suturing of cardiac wound was feasible (6). In 1896, for the first time in a human, Cappelen repaired the left ventricle and left anterior descending artery, but the patient did not survive. Rehn (11), at approximately the same time, is credited with the first right ventricular repair in which the patient survived. In 1902, Hill (12), of Montgomery, Alabama, became the first American surgeon to suture a myocardial injury, in a 13-year-old boy by the flickering lights of kerosene lamps on a kitchen table. Two other surgeons had first repaired the pericardium in the United States approximately 10 years before Hill, but their work was not recognized until later (13,14).

Anatomic Considerations

The classic precordium is defined as an area of chest bounded by sternal notch superiorly, xyphoid process inferiorly, and nipples laterally. Most stab wounds injuring the heart enter through the classic precordium. The majority of gunshot wounds strike the heart without entering this zone. The relative frequency of cardiac chamber involvement depends on the anatomic location of the chamber as well as the type of penetration. The right ventricle, with its maximum anterior exposure, is at the greatest risk for injury. In a series of penetrating wounds to the heart, the right ventricle was involved 42% of the time, left ventricle 33%, left atrium 6%, and right atrium 15% (15). Pericardial reflections are important to recognize, as they are positioned on portions of ascending aorta, portions of main pulmonary artery, portions of right and left pulmonary arteries, portions of pulmonary veins, and portions of superior and inferior vena cava. This is important because even trivial injuries to the intrapericardial portions of these vessels can result in cardiac tamponade. Typically, wounds to the base of the heart are rapidly fatal due to involvement of the aortic root and coronary arteries. However, stab wounds to the root of the aorta are extremely uncommon, as the sternum protects this portion.

Etiology

Penetrating wounds to the heart commonly result from puncture wounds, knife wounds, and gunshot wounds (16). Puncture wounds are caused by ice picks, needles, or pellets from an air gun or a distant shotgun, typically involving a single chamber. Knife injuries also frequently involve a single chamber, producing a slit-like defect. Small-caliber gunshot wounds can cause multiple-chamber perforations along with injuries to the great vessels. In contrast, large-caliber gunshot wounds result in fatal gaping cardiac defects.

Pathophysiology

The size of pericardial defect and the severity of cardiac injury determine the clinical presentation and subsequent outcome. If the defect in the pericardium is small,

blood clot may seal this defect. If the bleeding from the heart or proximal vessels continues in the closed pericardial sac, intrapericardial pressure rapidly increases. Rapid accumulation of blood, even when small (100 mL or less), leads to sufficient rise in intrapericardial pressure to cause tamponade. On the other hand, if the defect in the pericardium is large, there is rapid exsanguination and death. The number of cardiac structures involved determines the severity of cardiac injury. Multiple-chamber injury is usually fatal. Involvement of one or more cardiac valves with damage to the leaflets, annulus, chordae, or papillary muscle can lead to hemodynamic compromise (17). Conduction system damage (18) and coronary artery injury, although less common than in blunt trauma, has been reported with penetrating injury (19).

Clinical Profile

Patients presenting to the emergency room (ER) with penetrating cardiac injury may be dead on arrival, alive but hemodynamically compromised, or hemodynamically stable. A few patients that are dead on arrival can be revived with resuscitative thoracotomy in the ER. Identifying this small subgroup of patients is important to conserve resources because the yield of indiscriminate resuscitative thoracotomy is very low (less than 5%). Patients who show some signs of life on transport have up to a 30% chance of successful resuscitation (20). Patients with stab wounds compared with gunshot wounds and patients presenting with cardiac tamponade have a better chance of survival.

In the second group of patients with hemodynamic compromise, it is important to recognize cardiac tamponade. Dyspnea, diaphoresis, agitation, confusion, apathy, or a feeling of strangling oppression should alert the physician to look for cardiac tamponade (21). Only 10% to 40% of trauma victims with tamponade present with the Beck's triad of hypotension, jugular distention, and muffled heart sounds (22). Neck vein distention may be absent due to accompanying hypovolemia. Pulsus paradoxus is neither sensitive nor specific for tamponade in this situation.

The third, more stable group should be examined in detail after primary assessment of airway, breathing, and circulation. The entry site is especially important with stab wounds. An entrance wound high on the right side is likely to involve the aorta and right atrium. Lower right and left parasternal wounds involve the right ventricle, whereas inferolateral left parasternal wounds typically signify left ventricle involvement (23). In a gunshot wound, the entry site may be deceptive. If the entry site involves the "danger zone" of Suer and Mordax, which includes the precordium, epigastrium, and superior mediastinum, cardiac injury is typically present (15). Trajectory of the gunshot should also be determined. If the trajectory suggests juxtacardiac passage, the physician should keep a high index of suspicion for cardiac injury.

Management

Rapid transport of the patient to the trauma center is essential for better outcome. The so-called scoop and run policy, without an attempt to stabilize the patient in the field, is the best approach (24). Even roadside thoracotomy done by medical teams flown to the scene is without benefit (25). Intubation is beneficial for patients with cardiac arrest or hemodynamic instability (26). Closed-chest cardiopulmonary resuscitation (CPR) is not only ineffective but also contraindicated if an impaling weapon is present. An intravenous line can be started en route to the hospital, although the role of intravenous fluids is controversial (27).

For patients who are dead on arrival, a diagnostic and therapeutic procedure is an ER thoracotomy with a goal to relieve tamponade, control hemorrhage, and restore cardiac function (28). After resuscitation, the patient should be rapidly transferred to the operating room for definitive surgery.

In patients with hemodynamic compromise, rapid operating room thoracotomy by a cardiothoracic trauma surgeon appears to be the most effective. The role of ER thoracotomy has been a constant source of debate but it should be restricted to patients who arrive in a moribund state or who rapidly deteriorate after arrival (29,30,31 and 32). ER thoracotomy with use of staples to control cardiac bleeding and to minimize risk of personal contamination from a needle stick remains controversial (33). Staples to the heart can enlarge the wound and at times are difficult to remove during definitive surgery. Definitive surgical treatment is detailed elsewhere, but the general principles are as follows (34). Myocardial rupture is repaired in all cases. With distal coronary artery injury, ligation is sufficient. Definitive valve or shunt surgery is usually deferred until later. Approach to a foreign body is variable, but most commonly only those projecting into cavities or involving the left ventricle are removed.

In hemodynamically stable patients or those stabilized with volume, transthoracic echocardiography (TTE) should be performed rapidly to diagnose pericardial effusion (PE). PE, however small, serves as a marker for cardiac penetration (35). When compared prospectively with a surgical gold standard (subxyphoid window), echocardiography has high specificity and sensitivity in diagnosing PE (36). It has rapidly become a modality of choice to assess patients with thoracic trauma (37). However, in the presence of hemothorax, its sensitivity is significantly decreased (38). Transesophageal echocardiography (TEE) can overcome this limitation of TTE, but in many patients it either is not feasible due to other injuries or is not expeditiously available and hence is of limited usefulness (39,40). Subxyphoid pericardial window was the traditional way to rule out PE in patients with suspected penetrating wound to the heart. It is best performed in the operating room under light general anesthesia. Although it is a safe procedure and provides a definitive diagnosis of hemopericardium (41,42,43 and 44), it is a surgical procedure that typically results in 75% to 80% negative explorations (43). The availability of TTE in the ER has significantly reduced the frequency of this operation, which is now used only in few difficult situations to complement echocardiography (45). Thoracoscopic pericardial window is another alternative that has been shown to be safe and effective in diagnosing cardiac injury (46). However, echocardiography has other advantages in that it is a reliable tool to localize foreign bodies (Fig. 38.1) (47,48) and helps in diagnosing and monitoring structural abnormalities such as valvular regurgitations and shunts (Fig. 38.2, Fig. 38.3, Fig. 38.4, Fig. 38.5, Fig. 38.6, and Fig. 38.7) (49). Therefore, availability of TTE in the ER is shown to decrease time to definitive therapy, leading to a better outcome (50,51).

FIGURE 38.1 A transthoracic echocardiogram, a parasternal long-axis view, demonstrating a shotgun pellet (*white arrow*) in the distal posterior wall of the left ventricle. The pellet was identified years after the injury, and the patient was asymptomatic. Note how the pellet casts an acoustic shadow (*black arrow*). AO, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (Courtesy of Dr. Carlos Antonio Da Mota Silveira and Dr. Roberto Pereira, Pernambuco University, Brazil.)

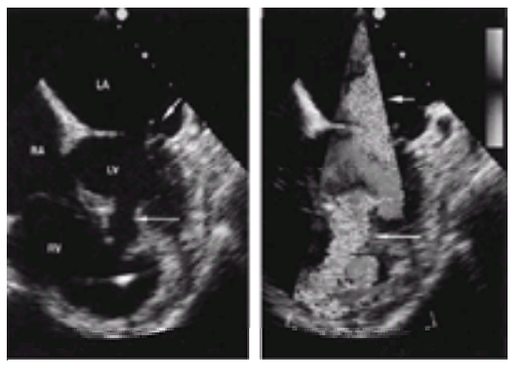


FIGURE 38.2 A transesophageal echocardiogram demonstrating a traumatic ventricular septal defect (*long arrow*) and mitral regurgitation (*short arrow*) from a gunshot wound. Swan-Ganz catheter is seen in the right ventricle (RV). LA, left atrium; LV, left ventricle; RA, right atrium. (From the DICOM demonstration DISC 96.)

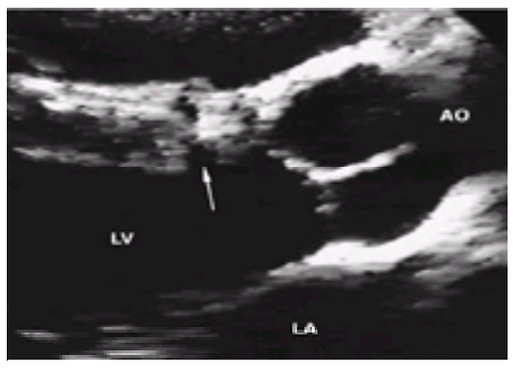


FIGURE 38.3 A transthoracic echocardiogram, a parasternal long-axis view, showing an interventricular septal defect (*arrow*) from a stab wound. This was successfully repaired. AO, aorta; LA, left atrium; LV, left ventricle. (Courtesy of Dr. Carlos Antonio Da Mota Silveira and Dr. Roberto Pereira, Pernambuco University, Brazil.)

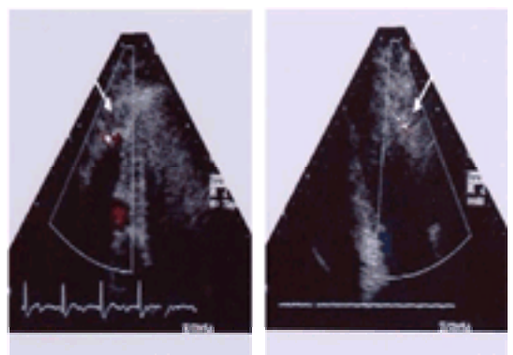


FIGURE 38.4 Patient with stab wound to the chest and right ventricle perforation. Perforation was repaired but on follow-up echocardiogram there was a very small pseudoaneurysm with some flow (*arrows*). Patient was conservatively managed without any complications.

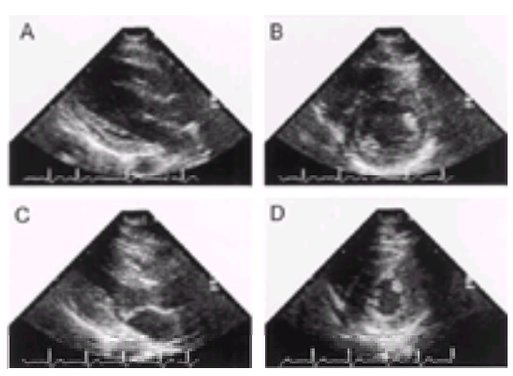


FIGURE 38.5 Patient with pneumatic staple gun injury to chest. Emergent echo in the emergency room initially did not demonstrate any pericardial effusion **(A,B)**, but while echocardiography was being performed (within 5 minutes), pericardial fluid accumulated **(C,D)**. (Courtesy of Dr. Riyad Karmy-Jones and Eric Sisk, University of Washington, Seattle.)

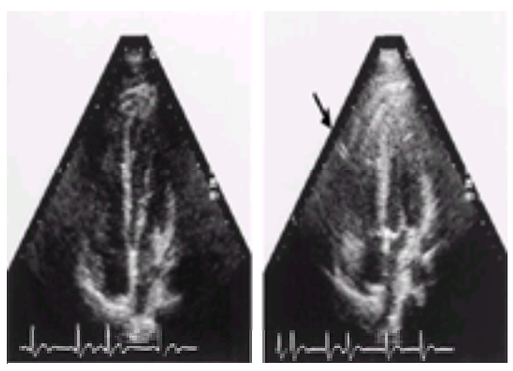


FIGURE 38.6 In the same patient, apical view showing increasing blood in the pericardium with a presence of staple in pericardium (*arrow*). Patient underwent emergent surgery. The needle was removed, and the right ventricle was successfully repaired.

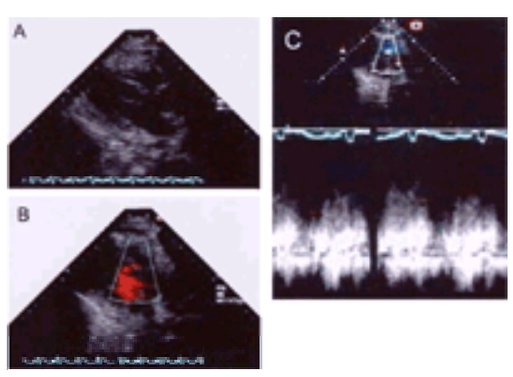


FIGURE 38.7 Patient with stab wound to chest with transsection of mid–left anterior descending artery (LAD) at the bifurcation and injury to the left ventricle. The patient had an emergency-room thoracotomy with ligation of LAD and diagonal branch. The left ventricle was successfully repaired in the operating room, and an intraaortic balloon pump was placed. There was mid and distal anteroseptal wall motion abnormality **(A)**. Abnormal flow was detected from the interventricular septum into the right ventricle **(B,C)**, which was diagnosed to be a coronary fistula (via a septal perforator) to right ventricular fistula by coronary angiography. (Courtesy of Dr. Riyad Karmy-Jones and Eric Sisk, University of Washington, Seattle.)

It is important to note that the ECG is not helpful in evaluating penetrating injury. It inconsistently shows injury pattern and if negative does not rule out significant injury (38,52). The chest x-ray may help by identifying patients with hemothorax who are difficult to image with ultrasound. But, other findings, such as an enlarged cardiac shadow or pneumopericardium, are infrequently present (53). Pericardiocentesis is not indicated for diagnosis in stable patients and can actually be harmful (54).

Prognosis

Various indices to categorize patients with penetrating cardiac trauma are available. Trauma indices describing anatomic severity, such as the Penetrating Cardiac Trauma Index, the Penetrating Thoracic Trauma Index, the Penetrating Trauma Index, the Cardiovascular-Respiratory Score component of trauma score, and the Injury Severity Score, are good predictors of outcome. However, the general condition of the patient plays a significant role in determining the prognosis of cardiac trauma. For this reason, a general condition index such as the Physiologic Index can be combined with anatomic indices to better categorize a patient. One such method is shown in *e*Table 38.0.1 (55). A unified index to objectively compare results among different institutions is not available (56).

***e*TABLE 38.0.1** INJURY SEVERITY OF PENETRATING CARDIAC INJURY

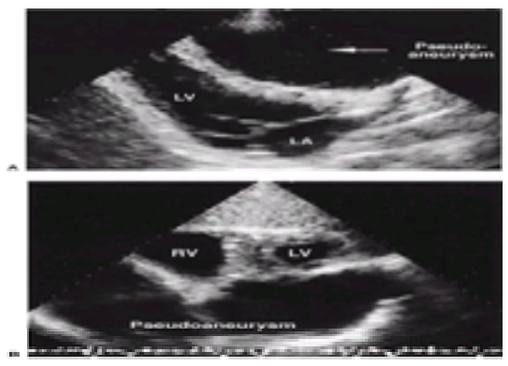
Anatomic: organ risk factor × injury severity estimate	
Organ risk factor	5
Injury severity estimate	
Tangential, involving pericardium or wall up to but not through the endocardium	1
Single right-sided chamber	2
Comminuted tears of a single chamber	3
Multiple chambers, isolated left atrial, or ventricular injury	4
Coronary vessel injury or major intracardiac defects	5
Physiologic (physiologic index)	
Stable	5
Systolic blood pressure <80 mm Hg, conscious	10
Semiconscious, thready pulse, gasping respiration, no measurable blood pressure	15
Unconscious, no vital signs, no respiratory efforts, no physical activity but had signs of life on transit to hospital	20

Patients who reach the operating room without requiring ER thoracotomy have a favorable outcome (57,58). Overall, patients with stab wounds have a better prognosis than those with gunshot wounds (59). Single-chamber injury to the heart with hemodynamic stability, shorter duration of CPR before arriving at the hospital, successful intubation, and younger age are all factors associated with better outcome (60). Presence of pericardial tamponade is thought to be a favorable predictor, as it possibly prevents exsanguination (61). Various late sequelae have been reported, including aneurysm formation, shunts, fistulas, and valvular regurgitation (*e*Table 38.0.2) (62,63). Surveillance for these anatomic sequelae with echocardiography is recommended (*e*Fig. 38.7.1) (18,64).

Video 38.1 Aortography showing an aneurysm of the ascending aorta with 3+ aortic regurgitation. The aortogram in this patient with cystic medial necrosis shows a maximum dimension of 5.4 cm. The dilation is confined to the ascending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

***e*TABLE 38.0.2** LATE SEQUELAE OF PENETRATING CARDIAC INJURY

Pericardium	Constrictive pericarditis
Myocardium	Aneurysm
	Pseudoaneurysm
	Shunts (arterial septal defect, ventricular septal defect)
Coronary arteries	Fistula
	Aneurysm
	Pseudoaneurysm
Valves	Regurgitation
Conduction system	Conduction block
	Arrhythmia



***e*FIGURE 38.7.1** Pseudoaneurysm, a delayed sequela of stab wound. Patient had a large, chronic pseudoaneurysm that is well seen on the echocardiogram. **A:** Parasternal long-axis view. **B:** Subxyphoid short-axis view of this large pseudoaneurysm. (LA, left atrium; LV, left ventricle; RV, right ventricle.) (Courtesy of Dr. Carlos Antonio Da Mota Silveira and Dr. Roberto Pereira, Pernambuco University, Brazil.)

Blunt Cardiac Injury

In civilian life, the most common cause of blunt cardiac injury is a motor vehicular collision. Falls from heights, falling objects, direct trauma from assault, and blast injury are other less common causes. Injury patterns in motor vehicular collision are governed by the location of the individual in the vehicle and the direction of impact. In a front impact, abrupt deceleration against the steering wheel is the most common cause of cardiovascular trauma. Side impact generates a high shearing force, more commonly causing an aortic injury. Seat belts and air bags also play a major role in determining the injury patterns. For unrestrained drivers, cardiac and aortic injury each occurs in approximately 20% of cases (65). Even in restrained drivers, significant thoracic injuries can still occur from contact with the steering wheel and from deceleration, but the number of deaths from thoracic injuries is significantly lower (66). The air bag has been associated with rupture of the right atrium (67).

Myocardial Contusion

Historical Perspective

Myocardial contusion was first noted by Burch in 1676 in an 8-year-old boy. In 1859, Schnabel noted hematoma with right atrial tear in a 49-year-old man who died several hours after the blunt injury. In 1954 Burchell aptly observed “and always with heart contusion, arise both doubt and much confusion” (68). The confusion is still prevalent in literature, as myocardial contusion is a pathologic diagnosis without an accurate clinical counterpart (69). It implies a bruise to a segment of myocardium that reveals subepicardial and intramyocardial hemorrhage, disruption of myocardial fibers, cellular infiltration, and interstitial edema on histologic examination. The definition by some includes the presence of myocardial necrosis with or without bleeding into the myocardium (70). In strict pathologic terms, contusion should not include necrosis as its integral part. Therefore, *myocardial contusion* is considered a less favorable term to describe this injury pattern (71). *Commotio cordis* is a term used to describe fatal cardiac arrest without detectable structural damage to the heart as a result of blunt impact to chest (72). Various mechanisms, including ventricular fibrillation, have been proposed to explain this phenomenon (73).

Anatomic Considerations

The anterior right ventricular wall is most commonly involved in myocardial contusion. The anterior interventricular septum and anterior-apical left ventricle are next in

frequency. Blunt injury can also damage the conduction system of the heart, manifesting as a right bundle branch block (74).

Pathophysiology

Autopsy studies of patients who died of blunt cardiac injury show subendocardial and interstitial hemorrhage, large surrounding areas of focal myocardial edema, myofibrillar degeneration, myocytolysis, and infiltration with polymorphonuclear cells. In essence, it resembles myocardial infarction (MI). The few distinguishing features of blunt injury are the more abrupt demarcation between normal and abnormal, more hemorrhage, and more frequent cellular laceration (75,76). Functionally, these changes present with a decrease in myocardial contractility and cardiac output (77). Right ventricular ejection fraction is more commonly decreased, probably due to its anterior location and the acutely altered loading condition of the ventricle (78). At times, patients with mild injury present with regional wall motion abnormalities but negative chemical markers of myocardial necrosis. The term *cardiac concussion* has been used to describe this. The mechanism is not known, but local factors that impair cardiac contractility, such as hematoma and focal inflammation, are considered to be responsible. These patients have excellent short-and long-term prognoses.

Clinical Profile

Cardiac contusion presents with a wide spectrum of severity. Patients with contusion can be hemodynamically unstable or stable. Pericardial tamponade and valvular regurgitation are important cardiac reasons for decompensation. Coronary artery injury, most typically right coronary artery injury, can present with acute MI. Arrhythmias are not infrequent, but their significance remains unclear. Atrial fibrillation, but not premature ventricular contractions and nonsustained ventricular tachycardia, has been associated with a worse outcome (77).

Hemodynamically unstable patients should be evaluated for the cardiac and noncardiac causes of hypotension. Noncardiac causes include hypovolemia and associated vascular injuries. Fluid challenge helps to identify significant hypovolemia. For vascular injuries, blood pressure and pulses in both upper and lower extremities should be carefully checked for discrepancies. The cardiac cause of hypotension in this group is pericardial tamponade. Clinical signs of pericardial tamponade should be evaluated carefully. Muffled heart sounds and pulsus paradoxus are not specific for tamponade and are absent in a significant number of patients. Neck veins may not be distended due to associated bleeding and hypovolemia. Other mechanical causes of cardiac decompensation are valvular regurgitation and shunts. Any murmur, especially pansystolic or continuous, should point to one of these complications. Left or right ventricular failure can lead to hypotension and would manifest with a third heart sound, rales, and increased jugular venous pressure. Coronary artery injury presents with chest pain similar to MI, but in the presence of trauma it may be difficult to ascertain the quality of chest pain. In hemodynamically stable patients, special attention should be given to complaints of chest pain, new murmur, early signs of pericardial tamponade, and heart failure.

Management

For hemodynamically unstable patients arriving after blunt chest trauma, echocardiography should be performed quickly. If echocardiography suggests a mechanical cause for hypotension, rapid appropriate surgical correction is mandatory. If there is severe ventricular dysfunction without myocardial rupture or PE, right heart catheterization may be useful to manage fluids and inotropes. Intraaortic balloon pump counterpulsation, after ruling out aortic injury, has been effectively used in this situation (79). For the more stable group, various diagnostic tests, including ECG, cardiac enzymes, and other imaging modalities, are available to quantify cardiac damage. The goal of these investigations is to identify patients at risk of immediate and future cardiac complications, but no test is considered a “gold standard.” A normal ECG helps to identify a very low-risk population, but ECG changes are neither specific nor sensitive to identify presence of wall motion abnormalities. Although echocardiography can identify these wall motion abnormalities, its role in management of stable patients after chest trauma has been questioned because the presence of wall motion abnormality does not signify a worse outcome in patients with normal ECG and enzymes (80). Cardiac enzymes, especially creatine kinase (CK) and isoenzyme of creatine kinase with muscle and brain subunits (CK-MB), are difficult to interpret in the presence of other injuries. Elevated levels of troponin T and I, although more specific, do not predict worse late clinical outcomes. The need to measure these enzymes in blunt injury patients is controversial (81,82).

Electrocardiogram. Approximately two-thirds of patients presenting with significant chest trauma have an abnormal ECG (83). Approximately half of these patients have specific ECG changes suggestive of cardiac contusion, which include conduction abnormalities, ST depression or elevation of 1 mm, and T-wave inversion in two consecutive leads (84). However, these criteria are only 47% sensitive and 79% specific in identifying the presence of wall motion abnormalities (85). Even adding right-sided ECG leads does not improve the sensitivity (86). Despite this lack of sensitivity, ECG has a very high negative predictive value for cardiac complications (87,88).

Cardiac Enzymes. Levels of CK and CK-MB are elevated in patients with blunt cardiac trauma. Elevation of CK level in blunt injury is commonly caused by skeletal muscle damage and does not help in diagnosing cardiac injury. Normal CK levels, on the other hand, do not eliminate cardiac damage, as wall motion abnormalities may still be present in two-thirds of patients with normal CK levels (89,90). The small amount of CK-MB released from the heart is diluted in the large amount of CK from other tissues. This can be overcome by use of absolute CK-MB. As CK-MB isoenzyme is found in skeletal muscle, pancreas, lung, colon, liver, stomach, and small bowel, injury to these organs can also cause some elevation of the CK-MB level (91). To improve the specificity of CK-MB, a concentration of more than 200 mg per dL has been used (87). With this high cutoff, sensitivity decreases considerably. Even different CK–to–CK-MB ratios (3% to 8%) for determining myocardial damage have not been very useful (70,92,93). This makes routine use of cardiac enzymes questionable (94).

Cardiac troponin T and I (cTn-T and cTn-I) are contractile proteins unique to cardiac muscle and can be differentiated by immunologic methods from their skeletal-muscle isoforms. These enzyme levels are elevated in a few hours after the onset of myocardial damage and remain increased for several days. There is some experimental evidence that the accuracy of cTn-I in detecting the extent of myocardial injury with contusion is higher compared with cTn-T and CK (95). Although improved specificity of cTn-I and cTn-T compared with conventional markers, the main problem with cTn-I and cTn-T is low sensitivity as well as low predictive values in diagnosing myocardial contusion. cTn-I and cTn-T measurement is currently not an improved method in diagnosing blunt cardiac injury in hemodynamically stable patients. Moreover, there is no association of postmyocardial contusion cell injury and late outcome in these patients when cTn-I and cTn-T and other conventional markers are considered (96,97).

Radionuclear Studies. Technetium pyrophosphate scan can label hydroxyapatite in the infarcted myocardium and can be useful for diagnosis of myocardial necrosis in blunt trauma. Sensitivity to identify nontransmural damage and right ventricular damage is low due to the masking effect of the large left ventricle. Specificity suffers because it cannot distinguish sternal fracture or chest wall injury from right ventricular contusion (98). First-pass biventricular radionuclide angiography with segmental wall motion analysis performed at the bedside can accurately estimate right and left ventricular ejection fraction. This is a sensitive way to diagnose cardiac abnormalities, but the positive predictive value for cardiac events is still low (77). Thallium with single-photon emission CT scan has been used for the diagnosis of myocardial damage, but the right ventricle cannot be adequately studied with this technique (99). Although presence of single-photon emission CT abnormalities is associated with a higher incidence of arrhythmia (100), it is clinically of limited use because abnormal ECG can identify this group of patients (101).

Echocardiography. Contused myocardium is identified by its increased echogenicity, increased end diastolic thickness, and impaired systolic function (102). The most common echocardiographic finding is right ventricular wall motion abnormality with some dilatation (103). However, the presence of wall motion abnormality does not signify a worse outcome if the patient has a normal ECG and enzymes (80). In patients with thoracic wall trauma, TEE is preferred over TTE because it allows a detailed study of the great vessels (84,104,105). However, safety of this procedure in trauma victims is still not well-established (106). Contrast echocardiography has been reported to help in making accurate diagnosis in some difficult cases (107).

Approach to patients with blunt trauma has to be individualized according to hemodynamic stability and other injuries. In a hemodynamically stable patient, if no abnormalities are detected on initial detailed physical examination, ECG, and chest x-ray, the patient can be observed in the ER for 12 hours and then discharged. If the ECG shows nonspecific changes, 24 hours of observation with serial enzyme assay is advisable. If enzymes are negative after the period of observation the patient can be discharged without further investigations. If, on initial ECG, there are specific abnormalities or if the chest x-ray is abnormal, echocardiography should be performed to further assess cardiac injury. If the patient with suspected cardiac contusion has to be operated on for other injuries under general anesthesia, preoperative echocardiography and/or intraoperative invasive monitoring are recommended.

Prognosis

Late complications such as arrhythmia, aneurysm, pseudoaneurysm, heart failure, valvular regurgitation, and shunts have been reported but are rare. Although similarities are drawn between MI and cardiac contusion, there are significant differences that affect the outcome. Typically the trauma victims are younger and in good general health. Also, the underlying cause of myocardial damage (trauma) is episodic and not an ongoing process (atherosclerosis). So, the prognosis in these patients is much better than in those with MI (108).

Myocardial Rupture

Rupture of the cardiac chamber, the most severe form of blunt cardiac injury, is a common finding in the patients with fatal nonpenetrating cardiac trauma (76). The right-sided chambers rupture more frequently than the left-sided chambers. Atria are more commonly involved than the ventricles (76,109). Interventricular septal rupture, an uncommon event, involves the apical part of the muscular septum more than the membranous interventricular septum (110). Interatrial septal rupture occurs rarely (111). Rarely, patients with isolated interventricular septal defect can present late with heart failure and a holosystolic murmur (112). A small muscular interventricular septal defect can be treated expectantly and repaired after 6 to 8 weeks, depending on the size of the shunt and intracardiac pressures. Myocardial rupture results in sudden cardiovascular collapse in most patients (113). On physical examination of rare survivors of free wall rupture, a sound resembling a splashing mill wheel (*bruit de moulin*) has been described. Rapid recognition of cardiac rupture with immediate thoracotomy can be lifesaving (114).

Pericardial Injury

Blunt trauma can lead to pericardial tears along with myocardial tears. These tears occur most commonly on the left side, parallel to the phrenic nerve. Other sites include the diaphragmatic surface of the pericardium, the right pleuropericardium, and the anterior pericardium (112). Irrespective of the site of the tear, cardiac herniation and strangulation can occur (115). With diaphragmatic tear, abdominal viscera can herniate into the pericardial space (116).

With pericardial tear, patients are unstable due to concomitant myocardial tear. Diagnosis is made at the time of thoracotomy. Intrapericardial diaphragmatic hernia presents with epigastric pain, gastric distention, palpitations, and shortness of breath. Gurgling sounds in the chest with muffled heart sounds and air bubbles in the pericardium on chest x-ray help in the diagnosis. Blunt trauma can lead to pericarditis without a tear. Depending on the size of the effusion, cardiac tamponade can develop. Some patients can develop late PE due to the “postpericardiotomy syndrome.”

Pericardial tamponade. Low QRS voltage and electrical alternans are characteristic findings of tamponade.

Patients with hemodynamic instability should undergo thoracotomy. Myocardial tears are repaired, leaving the pericardium open. In the presence of significant hemopericardium, surgical drainage is recommended. With a small effusion, conservative management with echocardiographic follow-up is recommended. Rarely, constrictive pericarditis may develop within 6 months to a year.

Valve Injury

Valves are involved less commonly with blunt injury. Commonly involved valves are the aortic, mitral, and tricuspid, in that order. The pulmonary valve is rarely involved. Many patients have an underlying valvular pathology that predisposes them to rupture. The aortic valve is most vulnerable in the isovolumetric relaxation phase and the mitral valve in the isovolumetric contraction phase. Injury to the tricuspid valve occurs due to a sudden increase in hydrostatic pressure on the right side of the heart from venous compression (117). With blunt trauma, the aortic valve tears at the leading edge of the cusp, more commonly near the commissures (Fig. 38.8). Bioprosthetic valves are particularly at risk (118). Mitral valve injury includes rupture or avulsion of a papillary muscle (most common), rupture of chordae, or, rarely, a tear of the valve leaflets. Tricuspid injury leads to regurgitation from rupture of the anterior papillary muscle, tear in the anterior leaflet, or, rarely, tear of the septal leaflet (119,120 and 121).

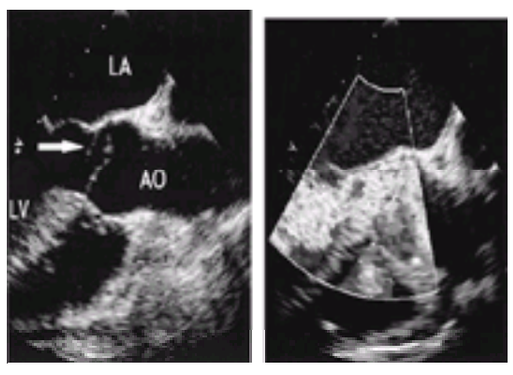
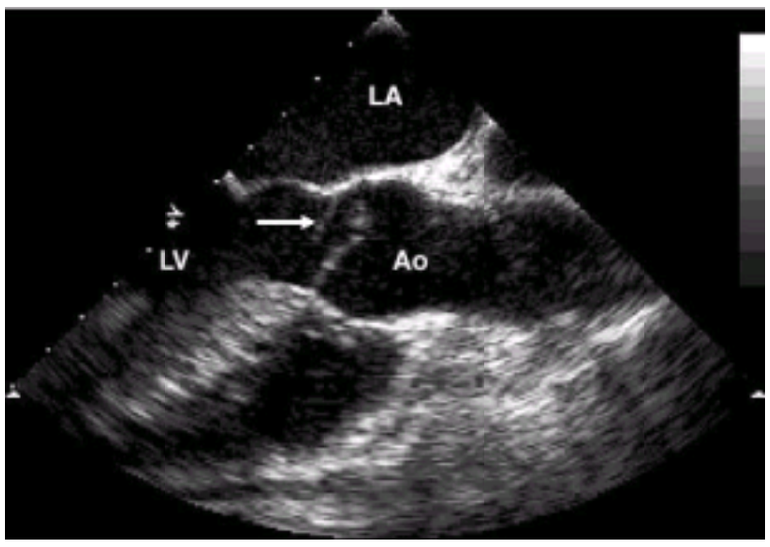
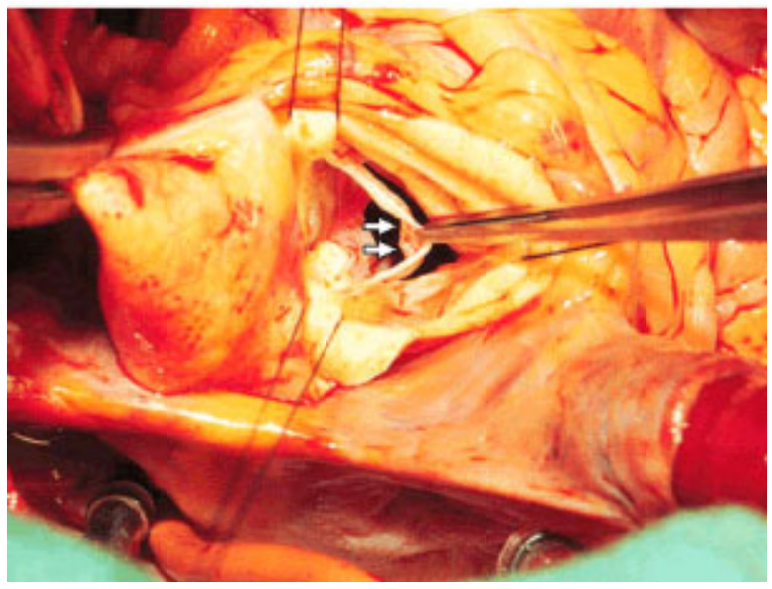


FIGURE 38.8 Aortic valve rupture from blunt injury due to a motor vehicle collision. The intraoperative transthoracic echocardiogram in long axis shows the flail left coronary cusp (*white arrow*) resulting in severe acute aortic regurgitation. AO, aorta; LA, left atrium; LV, left ventricle. (Courtesy of Dr. Ellen Mayer and Dr. Joseph Sabik, The Cleveland Clinic Foundation.)



Traumatic left coronary cusp flail (*arrow*) of the aortic valve due to blunt trauma. There was resulting 4+ anteriorly directed aortic insufficiency.



Surgical field demonstrating a ruptured left coronary cusp of an aortic valve (ruptured at leaflet base) in a patient who sustained blunt trauma to the chest wall. The free edge of the left cusp is unharmed. The arrows demarcate the tear.

Valvular injuries present with acute regurgitation. Acute aortic regurgitation can present with left ventricular failure without signs of wide pulse pressure. In mitral regurgitation, harsh pansystolic murmur radiating to the base rather than the axilla with an apical systolic thrill can be present (122). Tricuspid regurgitation presents with hypotension and signs of right heart failure. TEE helps to delineate the mechanism and severity of valvular regurgitation. Acute severe valvular regurgitation requires surgical reconstruction (119). For mild to moderate regurgitation, follow-up with rest or stress echocardiography is recommended (123). Endocarditis prophylaxis is recommended in all cases.

VIDEO

Video 38.2 A 120-degree intraoperative transesophageal echo of a patient with aortic insufficiency due to blunt trauma causing a flail left coronary cusp. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Coronary Artery Injury

Coronary artery injury is rare in patients who die of blunt injury (76,124). If a patient presents with clinical signs of acute MI, cardiac catheterization should be considered (125,126). If coronary artery thrombosis is identified, percutaneous intervention or surgery should be considered depending on the clinical situation (127). Posttraumatic arteriovenous and arteriocameral fistulae have been reported.

Electrical Injury

Historical Perspective

In 1750, Benjamin Franklin showed by flying a wired kite during a thunderstorm that electric charge could be passed from the cloud to the primitive accumulator, the Leyden jar. This led to the discovery of the Franklin rod, a device designed to safely conduct atmospheric electricity to earth. Every day, 50,000 lightning bolts are estimated to hit the earth. The flash lasts 0.2 to 1.0 seconds, with an amplitude of 25,000 to 500,000 amp and voltage of more than 1,000 kV. Most of these enter the earth without destruction, and only unprotected people or structures are sometimes involved. In the United States, lightning injuries are more common on the Eastern Seaboard than on the West. Wyoming, due to heavy outdoor activity, has the highest incidence of fatal lightning strikes in the country. Men are more involved with lightning strikes than women (4:1). But, interestingly, when a bolt comes through the telephone system, women are more likely to be the victims (128,129). In the United States, 100 to 300 persons die annually due to lightning injury. Accidental exposure to household alternating current (AC) leads to approximately 1,000 deaths annually in the country (130).

Pathophysiology

There are major differences between injuries from AC and direct current (DC). AC changes the polarity of cells and depolarizes them. This results in acetylcholine release at the neuromuscular junction and subsequently tetanic spasm of the muscles. This leads to prolonged contact with the source, as the flexors of the hand are more powerful than the extensors. The current also causes tetanic spasms of the blood vessels, leading to ischemia in the distal bed. In the heart it causes direct tissue damage with contraction band necrosis. Conduction abnormalities are common, as conduction tissue is sensitive to the AC. The lower domestic frequency (50 Hz in Europe and 60 Hz in the United States) of AC induces ventricular fibrillation. Higher-frequency AC, as used in diathermy, is thought to be relatively safe and causes only local tissue damage. DC causes less direct tissue damage compared with similar-energy AC. DC, as in lightning stroke, can lead to ventricular fibrillation or uniform depolarization of the left ventricle, causing asystole. Sometimes cardiac automaticity can be restored spontaneously after asystole. However, concomitant respiratory arrest may continue, and hypoxic cardiac arrest may occur. The path of AC or DC through the body is also important in determining the severity of injury. Transthoracic current flow (e.g., hand-to-hand pathway) is more likely to be fatal from respiratory and cardiac arrest than a vertical- or straddle-current path (131). However, vertical path can also cause significant myocardial injury due to the direct effect of the current on the heart and due to coronary vasospasm (132,133).

Clinical Profile

Electrical injuries present with ventricular fibrillation, ventricular asystole, conduction system disturbances, transient myocardial ischemia, and myocardial damage. Cardiac arrest can be a primary ventricular fibrillation or secondary to prolonged respiratory center arrest or muscle paralysis. Electrical injury has a predilection for the conduction system for unclear reasons. It presents with sinoatrial or atrioventricular node dysfunction. MI can result from coronary artery spasm because angiography is frequently normal in these patients (130). It presents with increased enzyme levels and wall motion abnormalities. The ECG may show typical ST elevations, and Q waves can develop with evolution. QT prolongation has been noted in patients with electrical injury. This may be due to the direct effect of the current on myocardium or due to indirect effect from injury to the central nervous system.

Management

If the patient is in cardiopulmonary arrest, he or she should be resuscitated with standard advanced cardiac life support protocol. Due to low metabolic rate, survival after prolonged arrest is better in patients with electrical injury, especially from lightning, than from other causes (134). Lightning victims who do not suffer cardiac arrest have an excellent chance of recovery because subsequent arrest is uncommon. Therefore, when multiple victims are struck simultaneously with lightning, usual triage priorities should be reversed. Rescuers should give highest priority to patients in respiratory or cardiac arrest. Patients who regain their vitals after resuscitation have high survival rates (135).

After resuscitation, patients should be monitored for arrhythmia. They may develop significant tachycardia and hypertension due to catecholamine surge that may require beta-blocker therapy. Serial enzymes and echocardiography may help to estimate the extent of myocardial injury. Patients with significant myocardial damage should be monitored closely for complications. Treatment of post-MI complications is similar to that from other causes (136).

After AC shock, if the patients are stable and have a normal ECG, cardiac monitoring is not necessary (137). However, for patients struck by lightning, overnight monitoring is recommended, even if they are stable and have a normal ECG. If admission ECG is not normal (one-third of victims of electrical injury), irrespective of the cause of injury, echocardiographic assessment of left ventricular function and serial CK estimation are indicated (138).

Prognosis

The mortality with lightning injury is 20% to 30% (135). The mortality with domestic AC electrocution is difficult to estimate due to variability in severity of the shock. For every three significant injuries there is approximately one death (139). This amounts to 1,000 annual deaths in the United States (130). ECG abnormalities usually resolve in a few weeks (140). Ventricular dysfunction also improves in most patients (141). Patients tend to have a good long-term prognosis, but they should be monitored periodically for at least 1 year (137).

Radiation Injury

The heart was thought to be resistant to radiation injury in the first half of the twentieth century (142). High-dose radiation was delivered without proper cardiac shielding. Many reports of radiation-induced cardiac abnormalities changed the perception of safety of radiation to the heart. Radiation, when used in the treatment of mediastinal tumors, primarily Hodgkin's and non–Hodgkin's lymphoma, and spinal irradiation can cause cardiac abnormality in as many as 40% of patients (143). This awareness and the availability of better radiation techniques in the last decade have led to careful use of high-dose radiation to the chest with proper cardiac shielding. More than 30 Gy to the chest is usually not used. Therefore, the long-term effects of modern radiation may be less severe than before (144). However, due to better long-term survival of patients who received radiation in the past and delayed manifestation of cardiac effects, we are likely to continue to encounter these problems (145). The injuries due to radiation involve various cardiac structures and can cause acute or delayed manifestations.

Pericardium

Acute pericarditis due to radiation is rare (approximately 2% of total population undergoing chest radiation). Over the years, approximately one-half of the patients develop echocardiographically demonstrable abnormalities, and approximately 5% develop clinically significant pericardial disease (146,147). Clinical manifestations and management of radiation pericarditis are discussed in detail in Chapter 26.

Myocardium

Radiation causes progressive fibrin deposition and capillary destruction, leading to fibrosis in the myocardium (148). This leads to mild left ventricular dysfunction not requiring specific treatment (147,149). Coronary artery disease should be ruled out when significant systolic dysfunction of the left ventricle is identified. Restrictive cardiomyopathy has also been described from radiation treatment (150,151).

Valves

Valvular thickening is present in many patients after radiation treatment, but significant valvular disease is an infrequent sequela (147). The mean time from radiation to clinically recognizable valvular disease is approximately 10 years, and the symptoms develop approximately 5 years after that. Aortic and mitral replacement from radiation-induced sclerosis with significant aortic stenosis or mitral regurgitation has been reported (152). Pulmonary and tricuspid valve disease is even less common (153,154 and 155).

Conduction System

Nodal and infranodal conduction abnormalities occur with radiation injury. Although right bundle branch block is most common, complete heart block has been reported (150,154,156). Management of these abnormalities is similar to that from other causes.

Coronary Arteries

External radiation injury involves the proximal portion of coronary arteries (157,158,159 and 160). Left and right coronary ostia and proximal left anterior descending and left circumflex are involved in most cases. The lesions have an increased number of plasma cells with paucity of lipids (161). Large, bizarre fibroblasts are also present (162). Coronary disease commonly presents approximately 5 years after radiation but can present as late as 29 years (160). Predisposing factors other than the total dose of radiation are not clearly identified. Patients can present with any ischemic complication, such as angina, MI, arrhythmia, or heart failure. Children treated with chest radiation have a higher risk of MI (163). For significant left main stenosis, coronary artery bypass grafting with left internal mammary artery conduit is recommended, although surgery can be technically difficult due to excessive scarring. For other focal lesions, percutaneous transluminal coronary angioplasty can be useful. Intracoronary radiation is now used to treat recurring in-stent restenosis. The long-term effects of this type of therapy remain unknown (164,165).

Iatrogenic Cardiac Injury

With rapid increase in percutaneous interventions and devices, many procedural complications that lead to cardiac injury have been recognized. CPR can infrequently lead to cardiac trauma.

Procedural Complications

Procedural complications are described in detail with individual procedures. In the catheterization lab, with myocardial biopsy or diagnostic catheterizations, significant vascular injuries, valve injuries, and myocardial injuries have been reported (166,167). With percutaneous coronary interventions, coronary artery perforation and accompanied complications have been well-recognized (168,169). Cardiac perforation is a recognized complication of transseptal valvuloplasty (170). Central line–related cardiac injuries have been frequently reported (171,172 and 173). Pericardiocentesis can be complicated by ventricular perforation (174). In the electrophysiology lab, with transvenous pacemakers, defibrillators, and radiofrequency ablation catheters, ventricular perforation is encountered (175). Timely recognition of these complications is the key to appropriate management and better outcome.

Injuries during Cardiopulmonary Resuscitation

Closed-chest cardiac resuscitation is safe and not commonly associated with significant physical trauma to the heart. Rib fractures can occur despite proper CPR technique. Complications such as fracture of the sternum, separation of the ribs from the sternum, pneumothorax, hemothorax, lung contusions, laceration of the liver and spleen, and fat emboli can be avoided with careful attention to the details (176). CPR can cause mild elevation of CK and CK-MB levels, even in patients with normal coronary arteries (177). In rare instances, right ventricular papillary muscle rupture, rupture of atria, rupture of aorta, and coronary artery dissection have been reported (178,179). In some patients with MI who had CPR, left ventricular rupture can be found on autopsy. This is more likely to be the cause rather than the effect of CPR.

INJURY TO THE GREAT VESSELS

Penetrating Injury

Thoracic great vessel injuries cause immediate death in a significant number of patients with penetrating injury. Gunshot wounds and knife wounds are the common causes of injury (180). Iatrogenic injuries to intrathoracic vessels can result from percutaneous placement of jugular venous lines, overinflation of Swan-Ganz catheter balloon, or intraaortic balloon pump (181). These injuries can manifest with simple lacerations, pseudoaneurysm, or an arteriovenous fistula. A high suspicion for injury is warranted while evaluating all penetrating thoracic wounds, as clinical signs of pulse deficit or murmur may be absent despite significant vascular injury (182). The chest x-ray may show hemothorax, widened mediastinum, and cervical or supraclavicular widening. In stable patients, aortography and CT scan may help to decide further management. In unstable patients, surgical exploration with thoracotomy is indicated. Follow-up of these patients is recommended, as some of them may develop late complications such as distal ischemia, edema, and pseudoaneurysms.

Blunt Injury

Anatomic Considerations

Motor vehicular accidents are responsible for the majority of cases of aortic rupture (178). As the blood vessels are fixed by their branches to the chest wall, the

direction of the pull determines the site of the tear. Aorta is fixed superiorly to the thoracic outlet and posteriorly to the chest wall. Vertical deceleration pulls the heart down and to the left, which causes shear on the right side, leading to a tear at the origin of the innominate artery. Horizontal deceleration causes shear at the aortic isthmus, the junction between the relatively mobile arch and the fixed descending aorta (183). Aortic injury can result in rupture, medial tear, and intramural hematoma or only intimal disruption. Rupture of the thoracic aorta causes immediate death in 75% to 90% of patients. Patients with contained ruptures have an unpredictable course, with up to 30% mortality in the first 24 hours (76,184). Patients with intimal flap or mural hematomas have a benign course.

Clinical Profile

Aortic rupture alone does not cause shock, as it quickly leads to exsanguination and death. Patients who arrive at the ER have sealed their defect with a clot. These patients may have reverse coarctation due to injury to the origin of subclavian artery, acute pseudocoarctation with upper-extremity hypertension, and increased pulse amplitude (182). Injury to the branches of the aortic arch can cause cerebral ischemia, but limb ischemia is rare due to a rich collateral supply (see Chapter 109) (185).

Management

In unstable patients with suspected aortic injury, the cause of bleeding should be ascertained and treated before aortic surgery (184,186). In stable patients with aortic rupture, chest x-ray can show mediastinal widening (8 cm or more), blurred aortic knob, shift of trachea or nasogastric tube when present, depressed left main bronchus of more than 40 degrees, presence of apical cap sign, obliteration of aortopulmonary window, and multiple rib or sternal fractures (187). These signs are present in 70% to 95% of cases (188). If the chest x-ray is abnormal, TEE is performed to confirm the diagnosis. TEE is sensitive and specific for the diagnosis of aortic intimal disruption, medial tear, and perivascular hematoma. The advantages over aortography are the bedside availability, the noninvasive nature of the study, and the ability to simultaneously evaluate the heart. However, its limitations are an occasional inability to pass the probe in patients with cervical injury, “blind spot” (this is the 3- to 5-cm portion of upper ascending aorta that is blinded by trachea) of ascending aorta, and operator variability (189). If TEE shows no abnormality, the patient should be observed, and chest x-ray should be repeated in 6 hours. If TEE shows rupture of the aorta, surgery is indicated. In patients with a small intramural hematoma or a small intimal flap, conservative medical management with close follow-up is justified. If TEE is nondiagnostic, other imaging modalities are used. Magnetic resonance imaging is useful in this situation, as it gives an excellent definition of anatomy, including the arch vessels. Biplane aortogram is no longer considered to be the gold standard, as, depending on the plane of projection, tears and perivascular hematomas can be missed. It is an invasive procedure with occasional serious complications. CT scan has a high sensitivity for screening purposes and is a very useful imaging tool that is complementary to TEE (190,191 and 192). If the initial chest x-ray does not show any signs of aortic injury, further management should be guided by clinical judgment (193). TEE should be performed in patients older than 65 years with significant other injuries and comorbid factors.

In stable patients, nonoperative management of an intimal tear of the thoracic aorta or delayed operative management of full-thickness tear in patients with multiple injuries is favored. Use of beta-blockers to medically control shear stress by controlling heart rate and blood pressure appears to be effective in these patients.

Prognosis

Patients treated for thoracic aortic rupture with surgery have risk for paraplegia (4% to 10%) (194,195 and 196). Brain ischemia, MI, and other end-organ damage have been reported. Overall mortality is 10% to 25% when patients reach the hospital alive.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The role of echocardiography is becoming clearer in the management of stable patients with penetrating cardiac injuries. TEE has proven to be useful in management of suspected great vessel injuries and is also useful in difficult situations to complement TTE. In the management of blunt trauma with stable hemodynamics, the role of echocardiography remains less clear, but it is extremely useful when structural problems need to be ruled out. Percutaneous interventions with stent grafts may find its role in management of a subgroup of patients with thoracic great vessel injuries. Coronary interventions have been successfully used in some cases of blunt trauma–related coronary thrombosis and closure. Thoracoscopy is also being more frequently used to assess the extent of injury in stable patients.

THE FUTURE

Improvement in emergency services with a special effort for rapid patient transport to a well-equipped trauma center can save patients with serious cardiovascular trauma. TEE has significantly changed some of the protocols for evaluation of stable patients with thoracic injury, but more prospective studies are needed to better define its role. A consensus for the clinical definition of cardiac contusion is needed to avoid discrepancies in literature. Similarly, for better comparison of data from various institutions, a unified injury index should be used. Endovascular stent grafts may help in management of some injuries to thoracic great vessels.

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39

CARDIAC NEOPLASMS

WILLIAM C. ROBERTS

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OVERVIEW

Primary cardiac tumors involving the heart may be either benign or malignant. Most of the benign tumors are myxomas, which are most commonly located in the left atrium. Primary malignant neoplasms usually involve the myocardium and the interior of the cardiac cavities, whereas metastatic neoplasms to the heart most commonly involve the pericardium, and pericardial effusion and constriction are the most common consequences. Computed tomography (CT) and magnetic resonance imaging (MRI) are becoming the most useful instruments of precision to diagnose cardiac tumors. A number of nonneoplastic conditions in the heart or pericardium are frequently mistaken for cardiac neoplasms, including pericardial cysts, teratoma, lipomatous hypertrophy of the atrial septum, papillary fibroelastoma, thrombi, and sarcoid. There are a number of cardiac consequences of malignancy, including radiation heart disease, cardiac hemorrhages, cardiac infection, and cardiac adiposity of the corticosteroid-treated heart, cardiac hemosiderosis, and anthracycline chemotherapy. Carcinoid heart disease is a unique type of heart disease associated with a unique type of cancer.

HISTORICAL PERSPECTIVE

In the last 40 years, cardiac neoplasms have progressed from clinical curiosities described primarily in numerous case reports, with diagnosis mainly at autopsy, to fairly rapid antemortem diagnosis and frequent curative operative therapy. Diagnosis has been greatly facilitated by two-dimensional echocardiography and, in select cases, the use of MRI or CT.

CLASSIFICATION

There is no perfect classification for cardiac neoplasms. Like any organ or tissue, neoplasms involving the heart may be primary or secondary. The primary ones may be benign or malignant, and the secondary or metastatic ones are, by definition, malignant. The metastatic neoplasms are far more frequent than are the primary neoplasms by at least a 30:1 ratio (1,2). The various frequencies of the primary benign and primary malignant tumors vary from report to report, approximately 0.1% to 0.3% in most autopsy series. A list of primary benign neoplasms gathered by investigators at the Armed Forces Institute of Pathology is presented in Table 39.1; primary malignant tumors encountered are listed in Table 39.2 (3). The frequencies of the metastatic neoplasms also vary from report to report, but nearly all studies have listed carcinoma of the lung as the most commonly encountered metastatic tumor at autopsy, with cancer of the breast, followed by lymphoma and leukemia, as the next leading causes (Table 39.3). The order of frequency of metastases is different, however, if the frequency of each different type of tumor with metastasis to the heart is determined. For example, Table 39.4 lists the frequencies of metastases to the heart in each of 100 cases of 20 separate tumors: Melanoma has the highest frequency of metastases to the heart followed by malignant germ cell tumor, leukemia, lymphoma, cancer of the lung, and then the various sarcomas (3).

Tumor*	Total	Surgical	Autopsy	Age (%) at diagnosis
Myxoma	114	102	12	4
Rhabdomyoma	20	6	14	20
Fibroma	20	18	2	10
Hemangioma	17	10	7	2
Atrioventricular nodal	10	0	10	2
Granular cell	4	0	4	0
Lipoma	2	2	0	0
Paraganglioma	2	2	0	0
Myocyte hamartoma	2	2	0	0
Histiocytoid cardiomyopathy	2	0	2	2
Inflammatory pseudotumor	2	2	0	1
Fibrous histiocytoma	1	0	1	0
Epithelioid hemangioendothelioma	1	1	0	0
Bronchogenic cyst	1	1	0	0
Teratoma	1	0	1	1
Totals	199	146 (73%)	53 (27%)	45 (23%)

*Excludes papillary fibroelastoma and lipomatous hypertrophy of the atrial septum.
Modified from Burke A, Virmani R. Atlas of tumor pathology: Tumors of the heart and great vessels. Washington, DC: Armed Forces Institute of Pathology, 1996:231.

TABLE 39.1 PRIMARY BENIGN NEOPLASMS OF THE HEART (1976–1993)

Tumor	Total	Surgical	Autopsy	Age (Y) at diagnosis
Sarcoma	137 (91%)	116	21	11 (8%)
Angiosarcoma	33	22	11	1
Unclassified	33	30	3	3
Fibrous histiocytoma	16	16	0	1
Osteosarcoma	13	13	0	0
Leiomyosarcoma	12	11	1	1
Fibrosarcoma	9	9	0	1
Myxosarcoma	8	8	0	1
Rhabdomyosarcoma	6	2	4	3
Synovial	4	4	0	0
Liposarcoma	2	0	2	0
Schwannoma	1	1	0	0
Lymphoma	7 (5%)	1	6	0
Totals	144 (100%)	133 (91%)	27 (19%)	11 (8%)

Modified from Burke A, Virmani R. Atlas of tumor pathology. Tumors of the heart and great vessels. Washington, DC: Armed Forces Institute of Pathology; 1996:231.

TABLE 39.2 PRIMARY MALIGNANT TUMORS OF THE HEART (1976–1993)

Primary tumor	Total autopsies	Metastases to heart
1. Lung	1,082	180 (17)
2. Breast	685	70 (10)
3. Lymphoma	392	67 (17)
4. Leukemia	202	66 (33)
5. Esophagus	294	37 (13)
6. Uterus	451	36 (8)
7. Melanoma	80	32 (40)
8. Stomach	603	28 (5)
9. Sarcoma	159	24 (15)
10. Oral cavity and tongue	235	22 (9)
11. Colon and rectum	440	22 (5)
12. Kidney	114	12 (11)
13. Thyroid gland	97	9 (9)
14. Larynx	100	9 (9)
15. Germ cell	21	8 (38)
16. Urinary bladder	126	8 (6)
17. Liver and biliary tract	325	7 (2)
18. Prostate gland	121	6 (5)
19. Pancreas	185	6 (3)
20. Ovary	188	2 (1)
21. Nose (interior)	32	1 (3)
22. Pharynx	67	1 (1)
23. Miscellaneous	245	0
Totals	6,240	653 (10)

Numbers in parentheses are percentages.
Modified from Burke and Virmani, who combined studies of McAllister HA and Fenoglio JJ Jr. Tumors of the cardiovascular system. Atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology; 1978:111–119; and Mikuni K, Shimizu T, Tomonaga K, et al. The incidence of secondary tumors of the heart and pericardium: a 10-year study. Jpn J Clin Oncol 1988;18:195–201.

TABLE 39.3 METASTATIC NEOPLASMS IN THE HEART AT NECROPSY IN THE ORDER OF FREQUENCY OF CANCERS ENCOUNTERED

Primary tumor	Number of autopsies	Percent with metastases to heart
1. Melanoma	100	46
2. Germ cell	100	38
3. Leukemia	100	33
4. Lymphoma	100	17
5. Lung	100	17
6. Sarcoma	100	15
7. Esophagus	100	13
8. Kidney	100	11
9. Breast	100	10
10. Mouth and tongue	100	9
11. Thyroid gland	100	9
12. Uterus	100	8
13. Urinary bladder	100	6
14. Stomach	100	5
15. Colon and rectum	100	5
16. Prostate gland	100	4
17. Pancreas	100	3
18. Nose (interior)	100	3
19. Ovary	100	1
20. Pharynx	100	1
21. Miscellaneous	100	0

These percentages were obtained by combining studies by McAllister HA and Fenoglio JJ Jr. Tumors of the cardiovascular system. Atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology; 1978:111–119; and Mikuni K, Shimizu T, Tomonaga K, et al. The incidence of secondary tumors of the heart and pericardium: a 10-year study. Jpn J Clin Oncol 1988;18:195–201.

TABLE 39.4 METASTATIC NEOPLASMS IN THE HEART AT NECROPSY: ORDER OF FREQUENCY OF METASTASES OF EACH DIFFERENT PRIMARY TUMOR

LOCATION OF CARDIAC NEOPLASMS

Cardiac neoplasms may involve only the endocardium, only the myocardium, only the epicardium, or various combinations (Fig. 39.1). By far, the most common location of metastatic cardiac neoplasm is the epicardium. Neoplasms limited to parietal pericardium without extension into the epicardium are not considered cardiac neoplasms. The epicardial tumor deposits may be multifocal or single, or they may be extensive and essentially diffuse or nearly so. Likewise, the intramyocardial masses may be focal or multifocal. The most common locations for intramyocardial masses are the left ventricular free wall and the ventricular septum, the portions of the heart, of course, with the greatest myocardial mass. The endocardial neoplasms are the intracavitary ones. They may involve a single cardiac cavity or more than one. They may be limited to either the right or left side of the heart, or they may involve both. Intracavitary tumors produce obstruction to inflow into the heart or into a ventricular cavity or outflow from a ventricular cavity. The intracavitary neoplasms are the ones that may partially dislodge and produce either pulmonary or systemic emboli or both. The intracavitary deposits have the potential of producing the triad of obstruction, embolization, and constitutional symptoms.

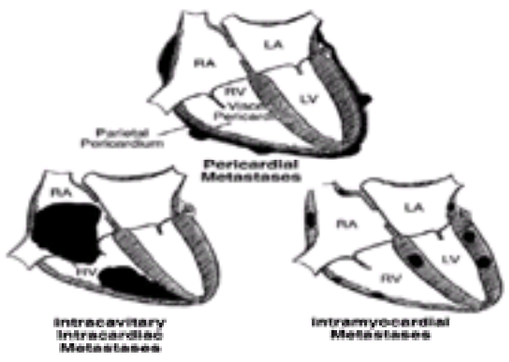


FIGURE 39.1 Diagram showing various locations of cardiac neoplasms involving the heart. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

TECHNIQUES FOR DIAGNOSING CARDIAC NEOPLASMS

Symptoms and Physical Signs

The signs and symptoms produced by the various cardiac neoplasms are determined primarily by the tumor's location in the heart. Physical examination is rarely diagnostic (4,5,6 and 7). Pericardial (specifically epicardial) involvement is the most common type of involvement by metastatic neoplasms to the heart (7). Neoplastic pericardial disease is usually asymptomatic and detected only as an incidental finding at autopsy. Signs of cardiac tamponade may be the initial or later manifestation of neoplastic pericardial disease. In patients with epicardial constriction by neoplasm, dyspnea is most commonly followed by chest pain, cough, orthopnea, and hepatomegaly. Distal cardiac sounds and a pericardial friction rub are infrequent.

Intramyocardial neoplasms are usually clinically silent. Occasionally, there are disturbances of conduction or rhythm, and both of these disturbances are determined primarily by the actual location of the tumor. The sudden development of complete heart block or high degrees of atrioventricular block or asystole are suggestive of myocardial involvement. A wide range of arrhythmias may be produced, including atrial fibrillation or flutter, paroxysmal atrial tachycardia with or without block, nodal rhythm, ventricular premature complexes, ventricular tachycardia, and ventricular fibrillation. On occasion, intramyocardial tumors impair ventricular function, resulting in confusion with restrictive cardiomyopathy or hypertrophic cardiomyopathy.

Left atrial cavitary neoplasms may produce signs and symptoms often mimicking those of mitral valve disease, especially mitral stenosis, including dyspnea, orthopnea,

paroxysmal nocturnal dyspnea, pulmonary edema, cough, hemoptysis, chest pain, peripheral edema, and fatigue. Additionally, some patients—particularly those with left atrial myxoma—may lose weight, become pale, faint, and have cardiac arrest. Left atrial tumors may produce symptoms suddenly or intermittently; sometimes, they come and go depending on body position. Although most symptoms produced by left atrial tumors are nonspecific, the occurrence of paroxysmal symptoms that occur characteristically in a particular body position and are out of proportion to the clinical findings should raise suspicion of a left atrial myxoma.

Right atrial cavitary neoplasms, if large enough, produce signs and symptoms of right-sided heart failure, including peripheral edema, ascites, hepatomegaly, and prominent ‘a’ waves in the jugular venous pulse. It may take years from the symptomatic presentation to the correct diagnosis. The development of right-sided heart failure may be rapidly progressive and is often associated with new systolic or diastolic precordial murmurs or both. The murmurs generally are the result of obstruction to the tricuspid valve orifice by the neoplasm, tricuspid regurgitation caused by the tumor’s interference with valve closure, or direct destruction of the tricuspid valve leaflets by the tumor’s movement in the tricuspid valve orifice. Signs of pulmonary embolism and pulmonary hypertension may occur. If the right atrial pressure increases to levels greater than that of the left atrium and if the foramen ovale is patent (15% of population), a right-to-left shunt may be the consequence, and systemic hypoxia, cyanosis, clubbing, and polycythemia may result. Evidence of superior or inferior vena caval obstruction, hepatomegaly, and ascites may be found. An early diastolic rumbling murmur alone or in combination with a holosystolic murmur, which increases with inspiration, usually indicates tricuspid regurgitation. A protodiastolic “tumor plop” also may occur with right atrial tumors. The jugular venous pressure may be elevated, and the ‘a’ wave within the venous system may be quite prominent.

Right ventricular cavitary neoplasms often present with right-sided heart failure as a result of an obstruction to right ventricular filling or outflow, and the consequences include peripheral edema, hepatomegaly, ascites, dyspnea, syncope, and cardiac arrest. A systolic ejection murmur at the left sternal border is usually present. Neoplastic emboli to peripheral pulmonary arteries may cause pulmonary hypertension. If the neoplasm extends into the pulmonary trunk, it may interfere with pulmonic valve closure, resulting in pulmonic regurgitation. The jugular veins are frequently distended with a prominent ‘a’ wave and a Kussmaul’s sign.

Left ventricular cavitary neoplasms are probably most frequently located at the apex of this chamber and, as a consequence, are usually clinically silent. Those in the left ventricular outflow tract may lead to obstruction to outflow, producing syncope or evidence of heart failure. Chest pain also may occur. A neoplasm in the left ventricular outflow tract may cause a precordial systolic murmur. The intensity of the murmur and the level of the blood pressure may vary with position.

Electrocardiography

The electrocardiogram (ECG) result is usually nonspecific (8,9), but it could be far more useful than has been appreciated in the past. The problem has been that the ECG may be recorded when diagnosis is first considered, but subsequent ECGs are not taken frequently toward the end of the patient’s life. One study (8) compared findings on ECG in patients with malignant lymphoma who had cardiac lymphoma to another group of patients with lymphoma who did not have cardiac involvement. The percentage with abnormal tracings (62%) was similar in each of the two groups. Fewer than one-half of the patients had more than one ECG during the entire illness. Findings included sinus tachycardia, low-voltage, ectopic tachycardia (including atrial fibrillation), atrial flutter, atrial tachycardia, atrial ventricular block (including prolonged PR interval), second- and third-degree block, premature ventricular complexes, right- or left-axis deviation, right bundle branch block, T-wave abnormalities, and ST-T–wave changes of usually nonspecific nature. The sudden development of some of these ECG findings in a patient who previously lacked these changes suggests cardiac involvement.

Radiography

The chest radiograph may be helpful, particularly when an epicardial neoplasm is present (10). Enlargement of the cardiac silhouette, mediastinal widening, a hilar mass, or an irregular contour of the cardiac silhouette may suggest pericardial involvement. Calcium within an intracardiac neoplasm can be seen, on occasion, by chest radiography or fluoroscopy. The lung fields may have a paucity of pulmonary markings in patients with large right atrial or right ventricular neoplasms. Patients with neoplasms in the left atrium may have pulmonary changes similar to those in mitral stenosis. Likewise, left ventricular neoplasms causing obstruction to left ventricular inflow or outflow may produce similar pulmonary arterial vascular changes.

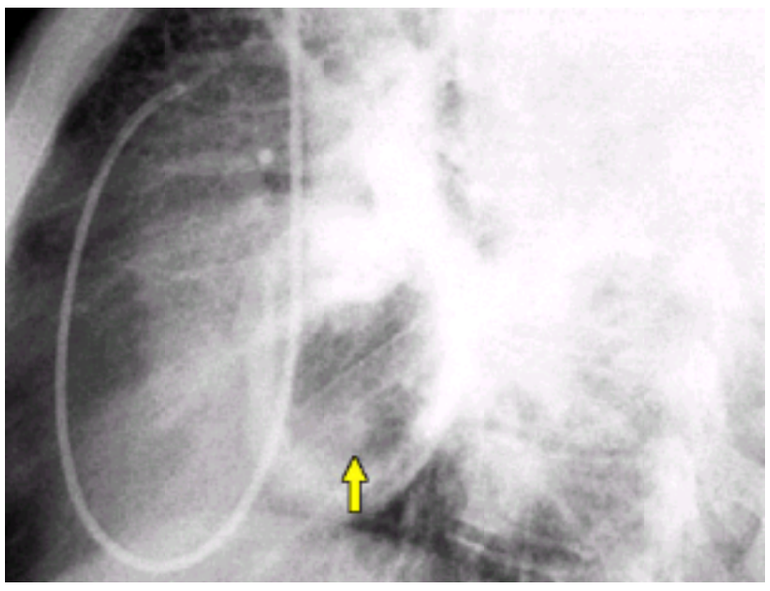
Echocardiography

More cardiac tumors today are diagnosed by echocardiography (Table 39.5), at least initially, than by any other instrument of precision. Diagnosis of left atrial myxoma has been one of the principal uses of echocardiography since the introduction of the technique (11,12,13,14 and 15). The classic left atrial myxoma is a mobile echogenic mass that is in the body of the left atrium in ventricular systole and passes into the mitral orifice in ventricular diastole. Occasionally, echocardiography detects a left atrial myxoma that is small or not close to the mitral orifice; therefore, it is clinically silent. Although it is usually possible to detect intracardiac tumors with transthoracic echocardiography, the transesophageal examination produces, as a rule, spectacular images and makes diagnosis, particularly of atrial masses, relatively easy (16,17). The transesophageal examination not only offers a higher sensitivity for detecting left atrial tumors, for example, but also permits a clearer picture of the attachment or stalk of the tumor and more precise characterization of the size, shape, and location of the mass. A major advantage of echocardiography is its ability to provide serial studies. Thus, by this technique, one may see progressive increase in size of a neoplasm or detect recurrence once the initial tumor is excised. The echocardiogram also has been useful in detecting intracardiac tumors other than myxomas, including rhabdomyomas and rhabdomyosarcomas, neoplasms that occur primarily in infants and are located usually in the ventricles. The echocardiogram is also helpful in detecting metastases to the heart. This is particularly true in neoplasms that migrate up the inferior vena cava into the right side of the heart, such as renal cell carcinoma or adrenal cell carcinoma. Echocardiography, particularly transesophageal, has been extremely helpful in detecting mediastinal or extracardiac masses, which may compress the cardiac structure.

	Radiography	Computed tomography	Angiography	Magnetic resonance imaging	Echocardiography
Primary benign tumors					
Myxoma	+	++	+++	++++	+++++
Pericardial cyst	++	+++	0	+++++	+
Lipoma	+	+++	+	+++++	+++
Fibroelastoma	0	0	0	+++	+++++
Rhabdomyoma	0	+	+	++++	+++++
Fibroma	0	+		++++	++++
Primary malignant tumors					
Sarcoma	+	++	++	+++++	+++
Mesothelioma	+	+++	+	+++++	++
Lymphoma	++	+++	+	+++++	++
Secondary tumors					
Direct extension	+	+++	++	+++++	+++
Venous extension	0	+	+++	++++	++++
Metastatic spread	+	++	+	++++	++

0, of no use; +, of limited use; ++, may be of use; +++, useful; ++++, very useful; +++++, preferred diagnostic tool.
From Valente FJ, Cohen GI, Wilson RD, et al. Cardiac tumors: diagnosis and management. Curr Prob Cardiol 1992;17:75–137, with permission.

TABLE 39.5 IMAGING TECHNIQUES FOR THE DIAGNOSIS OF CARDIAC TUMORS



Left atrial myxoma. This left anterior oblique projection depicts the left atrial filling phase of a pulmonary angiogram performed via a pulmonary artery catheter inserted into the right jugular vein. A large contrast free space (*yellow arrow*) depicts a space occupying mass within the left atrial cavity, which

surgical pathology confirmed to be a myxoma.

Atrial myxoma. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Computed Tomography

CT is useful in diagnosing cardiac tumors (18,19); it may be especially useful in defining the degree of intramyocardial extension or the lack thereof and whether the tumor is present in adjacent extracardiac structures. Ultrafast CT appears to be particularly well suited for assessing intracardiac masses.

Magnetic Resonance Imaging

Compared with CT, MRI appears to be of greater value in delineating cardiac tumors (20). It may be able to depict the size, shape, and surface characteristics of the tumor more clearly than CT. This technique also can provide information regarding tissue composition that can help to differentiate neoplasms from thrombi.

Video 39.1 Atrial myxoma (long-axis). A myxoma attached to the interatrial septum is seen. During diastole, the myxoma moves through the mitral orifice into the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Angiography

A cardiac catheterization and selective angiography are no longer necessary in all patients with cardiac neoplasms because adequate preoperative information can usually be obtained by echocardiography, CT, or MRI. For cases in which the latter three techniques have not fully defined the location and attachment of the neoplasm, in which all four chambers of the heart have not been well delineated, or in which another type of cardiac condition is suspected (such as coronary arterial narrowing), then cardiac catheterization with angiography might be necessary. Angiography in patients with cardiac neoplasms is particularly useful in detecting compression or displacement of cardiac cavities or large masses and the magnitude of the intracavitary filling defects. The most frequent angiographic findings are intracavitary filling defects, which may be either fixed or mobile, lobulated or smooth, and attached over a broad base or by a narrow stalk. Coronary angiography is sometimes helpful in visualizing the vascular supply of the neoplasm and the relation of the neoplasm to the coronary arteries. The vascular pattern is not helpful, however, in differentiating benign from malignant tumors. In contrast to the other diagnostic techniques, cardiac catheterization can be a bit risky in patients with intracardiac neoplasms, because the catheter may dislodge a fragment of the tumor with resulting embolus. Thus, the noninvasive techniques are preferred before cardiac catheterization in a patient suspected of having an intracardiac mass. The transseptal approach to the left atrium is not advised if a left atrial tumor is suspected, because the stalk of the left atrial myxoma is usually attached to the fossa ovale membrane, where the transseptal catheter courses.

Video 39.2 Identification of intercardiac mass by negative contrast effect. Left atrium contrast injection showing negative contrast of tumor. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 39.3 An 80-year-old male patient with weight loss, fever, and dyspnea for 2 months. Angiography revealed vascular tumor, which received blood supply from the right coronary artery. Echocardiograph confirmed location of the tumor in the left atrium with appearance consistent with myxoma. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

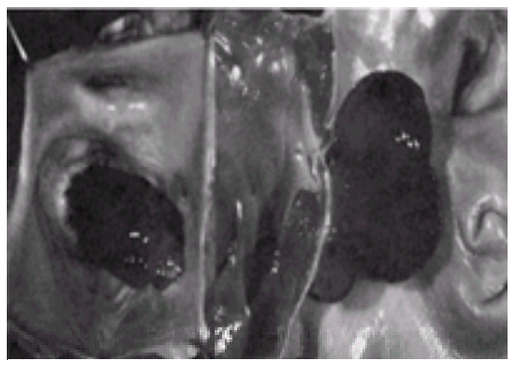
SPECIFIC BENIGN PRIMARY CARDIAC NEOPLASMS

Myxoma

Myxomas are by far the most common type of primary cardiac tumor; 75% of them are located in the left atrial cavity (eFig. 39.1.1), approximately 23% in the right atrial cavity (Fig. 39.2), and approximately 2% in a ventricular cavity (21,22,23,24,25,26,27,28,29,30,31,32 and 33). On rare occasion, the tumor is present in more than one cavity. Generally, when located in the left atrium, the neoplasm produces symptoms when it reaches approximately 7 cm in size. Those in the right atrium that produce symptoms are usually approximately twice as large and sometimes several-fold larger. The cell of origin of the myxoma is still unclear (22,34,35 and 36). How fast atrial myxomas grow has never been clarified. An attempt to answer this question was provided by a study that examined the size of recurrent myxomas and divided that size in grams by the interval between the first and second operations (37). It was estimated that recurrent left atrial myxomas grow an average of 0.15 cm per month or 1.80 cm per year, or an average of 1.2 g per month or 14.0 g per year. Whatever the exact growth rate may be, both recurrent and initial left atrial myxomas appear to grow rather rapidly (38,39). Morphologic diagnosis of myxoma is readily made by gross inspection, and their appearance is clearly different from thrombi. The surface is smooth but irregular, shiny, and usually multicolored. Although there are exceptions (29,30,31 and 32,40,41,42 and 43), attachment is nearly always to the atrial septum if the tumor is in the left atrium, and the stalk is most commonly much smaller than the maximal diameter of the mass. On occasion, the site of attachment to the atrial septum is broad. The mean age of patients with sporadic myxoma is 56 years, and at least 75% are women. During the last 10 years at Baylor University Medical Center in Dallas, 15 left atrial myxomas have been excised—14 were in women.

Video 39.4 Myxoma tumor blush from left circumflex artery. Contrast injection of left coronary showing perfusion of the tumor. *This video must be viewed with*

QuickTime. If you do not have QuickTime you may download it here.



***e*FIGURE 39.1.1** Left atrial myxoma in a 60-year-old woman (A69-275) who died of metastatic carcinoid and never had clinical evidence of heart disease. The myxoma was not large enough to prolapse through the mitral orifice during ventricular diastole. *Left*: View of left atrium cephalad. *Right*: Longitudinal view showing attachment of the myxoma to the atrial septum by a relatively broad base.

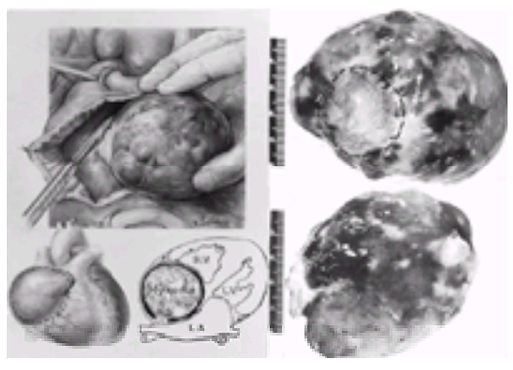


FIGURE 39.2 Myxoma excised from the right atrium of a 46-year-old man (S61-980) who had had evidence of cardiac dysfunction for 12 years. The tumor was attached to the atrial septum by a relatively small stalk (surrounded by dashed circle, *upper right*). The myxoma weighed 142 g, and its largest diameter was 8 cm. A view of the cut section of the tumor is shown in the lower right. LA, left atrium; LV, left ventricle; RV, right ventricle.

Familial cardiac myxomas constitute approximately 10% of all myxomas, and they appear to have an autosomal dominant transmission (44). These occur in younger patients (mean age, 25) and have less female gender predominance. The myxomas in the familial syndrome are much more liable (50% of the time) to be multiple and to have a ventricular cavity location (13% as compared with <1% in the nonfamilial or sporadic patients with myxomas). These patients typically have exterior facial freckling; they have noncardiac myxomas (breast or skin) and also endocrine neoplasms. Both the NAME (nevi, atrial myxoma, neurofibromata, ephelides) and the LAMB (lentigines, atrial myxoma, and balloon nevi) syndromes are associated with the familial variety of cardiac myxoma. Chromosomal abnormalities for atrial myxoma on chromosome 2 (Carney's) and chromosome 12 (*Ki-ras* genes) have been described.

Myxomas probably present the most varied clinical picture of all primary cardiac neoplasms (4,5 and 6,23,25,26,45). Several major syndromes have been observed, including presentation with signs of emboli, obstruction to blood flow, and various constitutional syndromes. Fragments of tumor located in the right side of the heart may embolize to the lungs, and of those in the left side of the heart, of course, to various systemic organs. Diagnosis may be made, on occasion, by finding typical myxomatous endothelial-like cells, which are elongated and spindle shaped with round or oval nuclei and prominent nucleoli, in surgically removed emboli.

Obstruction to blood flow may occur at the orifice of any valve, most commonly of course, the mitral valve. Interference with flow through the mitral orifice may mimic signs of mitral stenosis, including signs of pulmonary congestion, diastolic apical rumble, opening snap, and accentuated first heart sounds. A murmur of mitral regurgitation may also be present as a result of chronic damage to the valve leaflets or to interference with proper closure of the valve by tumor. Differentiation between left atrial tumor and primary mitral stenosis is suggested by the influence of position on symptoms and on the intensity of the precordial murmurs and the opening snap.

HEART SOUNDS

Audio 39.5 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 39.6 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 39.7 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 39.8 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 39.9 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 39.10 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 39.11 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The constitutional symptoms associated with atrial myxomas include fever, weight loss, Raynaud's phenomenon, digital clubbing, anemia, elevated erythrocyte sedimentation rate, elevated leukocyte count, decreased platelet count, positive seroreactive protein, and abnormal serum proteins (usually increased gamma globulins). These constitutional symptoms may mimic infective endocarditis, collagen vascular disease, or occult malignancy. A myxoma also may become infected (46).

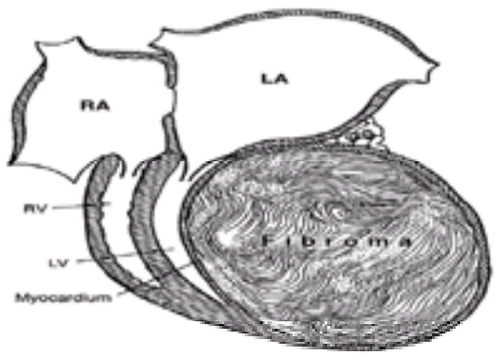
The proper treatment of myxoma in any cavity of the heart is operative resection, because no medicine is known to shrink myxomas or to prevent their continued growth (21,27,33). Some surgeons advise a biatrial approach for full visualization of both sides of the heart and then complete removal of a left or right atrial myxoma, excising the full thickness of the atrial septum if the neoplasm is attached to the region of the fossa ovalis. If a large portion of the atrial septum is removed, a patch must be used to close the defect. Because fragmentation and embolization of the tumor are ever-present threats, vigorous palpation and other manipulations of the heart should be avoided until cardiopulmonary bypass is initiated. Most surgeons induce ventricular standstill with cardioplegia solution before manipulating the heart to reduce the possibility of fragmentation of portions of the tumor. Left atrial myxomas have been removed successfully during pregnancy. On occasion, an atrioventricular valve has been so traumatized by the tumor prolapsing through it during ventricular diastole that valve excision and replacement are necessary. Fortunately, recurrences of atrial myxomas are rare, and if they do recur, it is usually within a 4-year period (38,39).

Rhabdomyoma

The most common cardiac neoplasm in infants and children is rhabdomyoma (47). There is some question about whether this particular tumor is a true neoplasm or a hamartoma. These neoplasms are usually multiple, most often involve the ventricular myocardium, and project into the cavity or move freely as a pedunculated mass (48,49 and 50). Associated tuberous sclerosis is present in approximately one-third of the patients. The diagnosis is suggested by the presence of yellow-brown angiofibromas (adenoma sebaceum) on the face, sublingual fibromas around the fingernails, café au lait spots, and subcutaneous nodules. Presenting symptoms may be caused by obstruction to inflow to or outflow from the ventricles, arrhythmias, atrioventricular block, pericardial effusion, and even sudden death (51). These neoplasms may mimic pulmonic valve stenosis and produce hypoxic spells, resembling those seen in tetralogy of Fallot. These neoplasms are usually readily diagnosed by echocardiography, angiography, or MRI. Prenatal detection of intracardiac rhabdomyoma by intrauterine echocardiography has been reported. The occurrence of more than one tumor does not prevent operative intervention. On rare occasions, these tumors have produced ventricular tachycardia in infants, and this arrhythmia has disappeared following successful operative removal.

Fibroma

Fibromas are usually within a ventricular wall (intramural) (3,52) (*e*Fig. 39.2.1). Most also occur in infants and children. Calcific deposits may be present within the neoplasm. Sudden death has occurred in approximately one-third of the patients, presumably the result of a conduction defect, arrhythmia, or obstruction to outflow from a ventricle. Left axis deviation has been seen on ECG. Total or partial resection of the neoplasm may relieve obstruction with an excellent probability of long-term survival.



***e*FIGURE 39.2.1** Diagram of an intramyocardial fibroma seen at necropsy in a 5-month-old boy (A07-92) who was found dead in his crib. The neoplasm had been diagnosed by biopsy during the child's first few days of life. It was considered nonresectable. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Lipoma

Lipomas involving the heart may be extremely small and represent incidental necropsy findings or they may be massive (53,54,55 and 56). The largest cardiac

neoplasm ever reported apparently was an intrapericardial lipoma. They may be mistaken for pericardial cysts, cause pericardial effusion, or they may be asymptomatic and suggested by a widened mediastinum on chest radiography. Intramyocardial lipomas are encapsulated and usually small. Lipomas also have been located on cardiac valves, where they may simulate vegetations or myxomas (55). MRI permits preoperative identification of these fatty tumors.

Hemangioma

Hemangiomas are best diagnosed by coronary angiography, which yields a characteristic “tumor blush.” Spontaneous resolution without treatment has been reported. Total excision usually is not possible.

Video 39.12 Transesophageal view demonstrating the right atrium with the inferior vena cava off to the left of the screens, the superior vena cava to the right, and the left atrium at the top, with the interatrial septum in the middle. This view shows a hemangioma in the interatrial septum found incidentally at the time of preoperative transesophageal echo for mitral valve replacement for severe mitral regurgitation. Intraoperatively, the mass was highly vascular as expected and was resected. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 39.13 Transesophageal four-chamber view showing an encapsulated mass in the interatrial septum that has a heterogenous appearance centrally. This was a hemangioma of the septum. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

SPECIFIC MALIGNANT PRIMARY CARDIAC NEOPLASMS

Angiosarcoma

Nearly all primary malignant cardiac neoplasms are sarcomas; the most frequent is angiosarcoma (57,58,59,60,61 and 62), which characteristically originates from the right atrium or from the epicardium of the right atrium. The large quantity of vascular channels within these tumors and the subsequent large quantity of blood flowing through them may produce a continuous precordial murmur. Approximately 25% of all angiosarcomas are, at least in part, intracavitary with valvular obstruction and cause right-sided heart failure and pericardial tamponade with a hemorrhagic-type fluid. The course is rapid, with widespread metastases, and operative intervention is usually unsuccessful.

Rhabdomyosarcoma

Rhabdomyosarcoma is the second most frequent primary sarcoma of the heart, and, like angiosarcoma, it is most common in male subjects (63,64 and 65). In contrast to angiosarcoma, however, no single cardiac chamber has a predilection for this neoplasm. Indeed, the neoplasm may be in all four cardiac chambers, or at least in more than one, and obstruction may occur in one or more valve orifices. Again, prognosis is poor, survival is short, and operative intervention is usually futile.

Miscellaneous Neoplasms

Fibrosarcoma, liposarcoma, primary malignant lymphoma, and occasional sarcomas of other cell types constitute the remaining but infrequent primary malignant coronary neoplasms (66,67,68 and 69) (Fig. 39.3, *e*Fig. 39.3.1, and Fig. 39.4). All of these neoplasms may obstruct valvular orifices or obliterate chambers, produce peripheral emboli, or both (70). Hypertrophic cardiomyopathy has been suggested by heavy tumorous infiltrations of the ventricular septum (71).

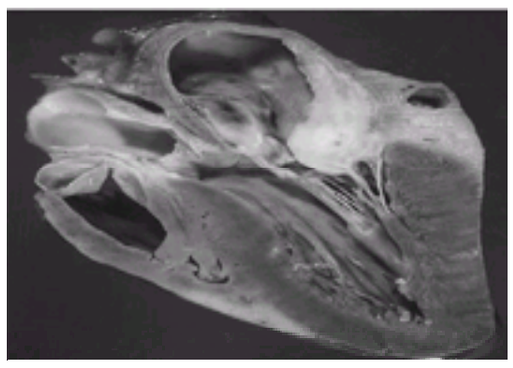
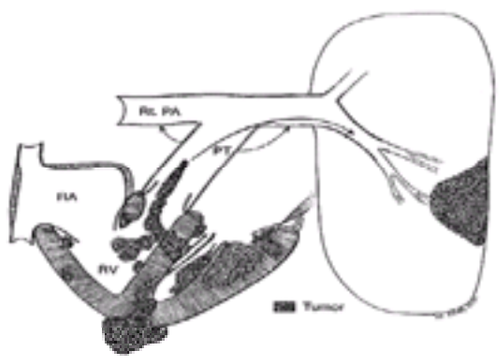


FIGURE 39.3 Primary cardiac sarcoma, undifferentiated type, causing mitral stenosis in a 46-year-old woman (A90-2) who had been well until 8 months before death. Cardiac catheterization disclosed a 20 mm Hg mean diastolic gradient between the pulmonary artery wedge position and the left ventricle. The right ventricular pressure was 105/18 mm Hg. The neoplasm was located in the walls of the left atrium and in both arteries and posterior mitral leaflets. (From Domanski MJ, Delaney TF, Kleiner DE Jr, et al. Primary sarcoma of the heart causing mitral stenosis. *Am J Cardiol* 1990;66:893–895, with permission.)



***e*FIGURE 39.3.1** Primary cardiac sarcoma, undifferentiated type, with neoplastic emboli to lung and other organs in a 26-year-old man (A69-149) who had been well until 3 months before death. PA, pulmonary artery; PT, pulmonary trunk; RA, right atrium; RV, right ventricle.

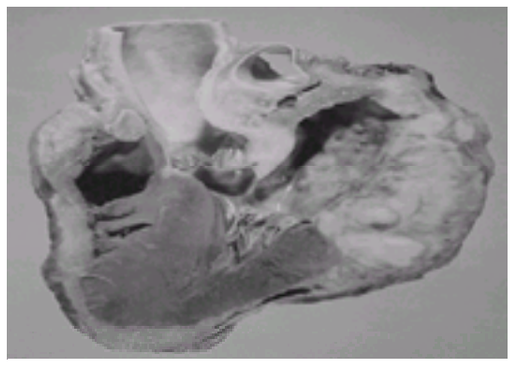
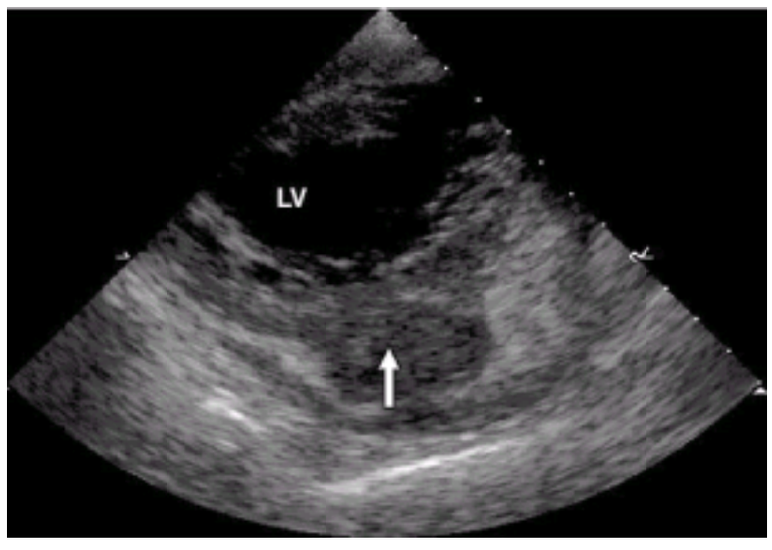


FIGURE 39.4 Cardiac histiocytic lymphoma in a 64-year-old woman (A77-172) who had had evidence of congestive heart failure for 7 months. The cause of the heart failure was not apparent until necropsy. The wall of the left atrium is massively thickened by the neoplasm. (From Roberts CS, Gottdiener JS, Roberts WC. Clinically undetected cardiac lymphoma causing congestive heart failure. *Am Heart J* 1990;120:1239–1242, with permission.)



Transgastric long-axis view of a metastatic sarcoma within the anterior wall of the left ventricle at the bottom of the screen (designated by the arrow).

VIDEO

Video 39.14 Transgastric 90-degree long-axis transesophageal echo view of a patient with a sarcoma metastatic to his left ventricular anterior wall. Note the invasion of the myocardium by this large mass. Additionally, there is severe hypokinesis of the anterior wall. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

METASTATIC NEOPLASMS TO THE HEART

Metastatic or secondary tumors of the heart with a primary in another body organ or tissue are far more frequent than are primary tumors of the heart (72). The secondary tumors are far more commonly carcinomas than sarcomas, simply because carcinomas are far more common. Diagnosis can be suspected whenever cardiac manifestations occur in a patient diagnosed with a primary tumor in an organ or tissue other than the heart. The development of cardiac enlargement, tachycardia, arrhythmias, or heart failure in the presence of neoplasm elsewhere in the body is highly suggestive of cardiac metastases. Only rarely is metastatic tumor limited to the heart. Thus, the presence of metastatic tumor in the heart usually indicates widespread metastases in a number of body organs. On rare occasion, cardiac involvement may be the first or only expression of a noncardiac primary neoplasm. The most common sign is tamponade (73). Direct invasion of the heart via the vena cava or pulmonary veins may lead to obstruction of an atrioventricular valve, as well as to pulmonary or systemic emboli or both (74,75 and 76).

VIDEO

Video 39.15 Transesophageal echo of a large mobile mass seen in the right atrium, entering from the inferior vena cava. This patient had renal cell cancer that invaded the inferior vena cava. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

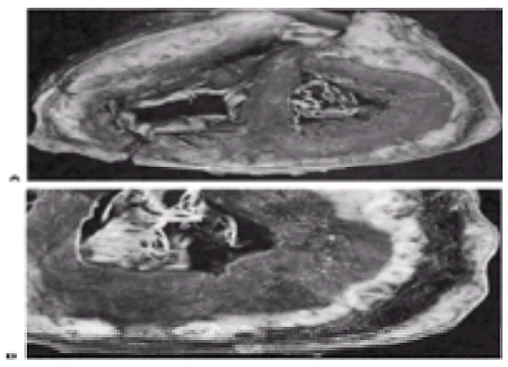
Carcinoma of the lung and carcinoma of the breast tend to invade the parietal pericardium and then the visceral pericardium, leading to myocardial constriction, pericardial effusion, or both (eFig. 39.4.1). Another common presentation of cancer of the lung is invasion of the pulmonary veins within the lung, with spread of the cancer within the lumen of the pulmonary veins into the left atrium. From there, the cancer in turn can continue into the mitral orifice, sometimes causing obstruction of that orifice (77,78) (Fig. 39.5). Metastatic cancer from the lung to the adrenal gland also may extend into the inferior vena cava and then into the right side of the heart (Fig. 39.6), just as primary adrenal gland or renal cancer can (79). Cancer of the lung or breast surrounding the main right or left pulmonary artery can lead to pulmonary arterial obstruction (80).

VIDEO

Video 39.16 Subcostal short-axis view demonstrating the left ventricle surrounded by an organized pericardial effusion, which is adjacent to highly organized pleural effusion in a patient with metastatic lung cancer. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 39.17 Apical four-chamber view (transthoracic) in a patient with metastatic lung cancer demonstrating a moderate to large pericardial effusion and a very large, highly organized pleural effusion encasing the heart. (Pleural effusion is towards the right of the screen.) Note the extensive fibrinous network in the pleural effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 39.4.1** Metastatic squamous cell carcinoma of the lung in a 61-year-old man (67A-531). Cardiac tamponade was the immediate cause of death. The entire heart and great vessels were encased in tumor as shown in **(A)**. A close-up view of the tumor encasing the left ventricle is shown in **(B)**. (From Roberts WC, Spray TL. Pericardial heart disease. *Curr Prob Cardiol* 1977;2:1–71, with permission.)

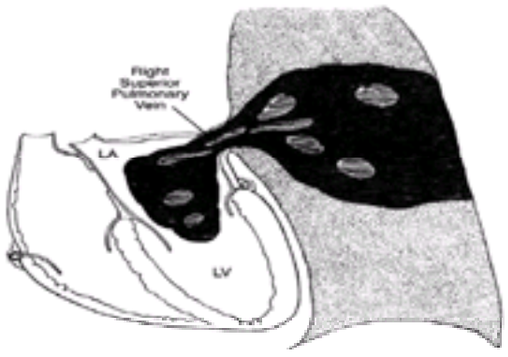


FIGURE 39.5 Sarcoma, undifferentiated type, in lung (primary uncertain, possibly in pulmonary vein) in a 29-year-old woman (A21-83) in whom echocardiography disclosed the tumor in the left atrium moving about “like a yo-yo.” The left lung and its left atrial extension were operatively excised. LA, left atrium; LV, left ventricle.

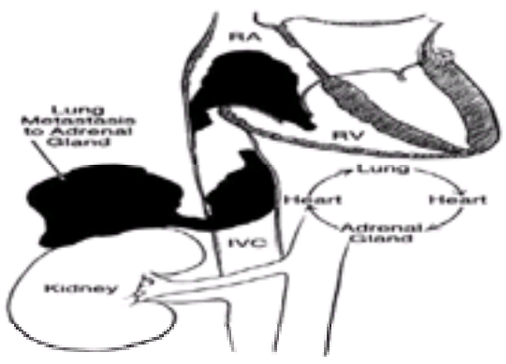
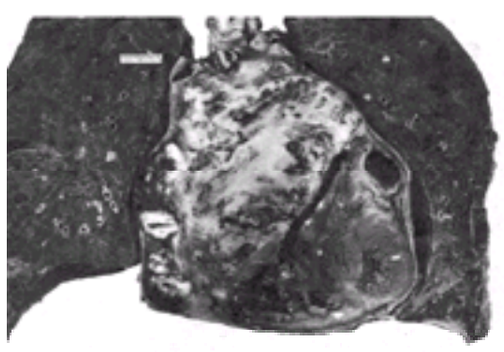
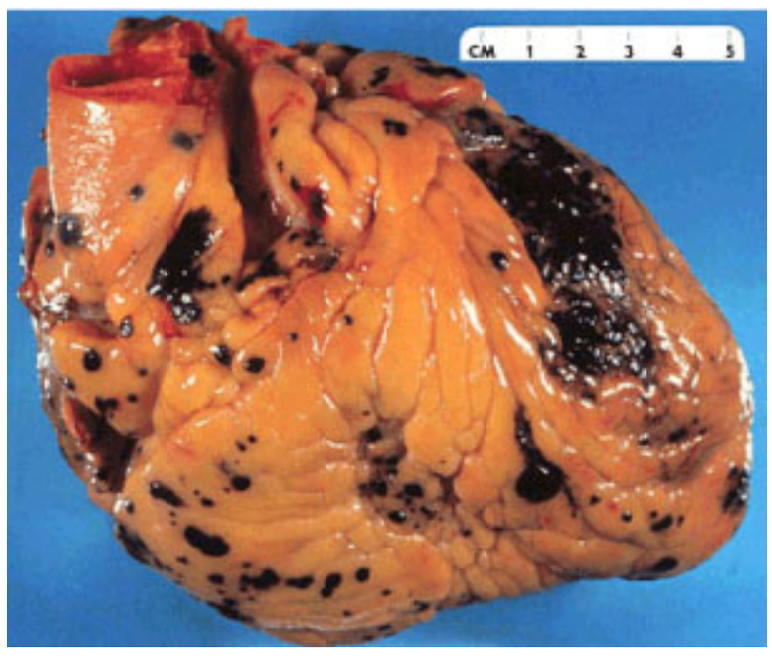


FIGURE 39.6 Diagram of metastatic cancer of the lung to the right adrenal gland with extension into the inferior vena cava (IVC) and then into the right side of the heart in a 57-year-old man (DCVAH 84A-121). Echocardiography showed the right atrial mass, which prolapsed through the tricuspid valve in atrial systole. RA, right atrium; RV, right ventricle.

Melanoma has the highest frequency of metastases to the heart per 100 cases of any neoplasm (81,82). The metastases may be anywhere in the heart; usually, melanotic metastases invade the walls of all four cardiac chambers, the epicardium, and the endocardium (*e*Fig. 39.6.1). The cancers in these patients are in so many organs that the presence of the neoplasm in the heart is almost incidental. Resection of an intracardiac melanoma has been accomplished (83).



***e*FIGURE 39.6.1** Metastatic melanoma to the heart in a 53-year-old man (A75-41). During life, a pericardial friction rub was audible, and the neck veins were quite distended. The parietal pericardium is everywhere adherent to the epicardium. The superior vena cava, right atrium, right ventricle, and pulmonary trunk are severely compressed by the tumor. (From Roberts WC, Spray TL. Pericardial heart disease. *Curr Prob Cardiol* 1977;2:1–71, with permission.)

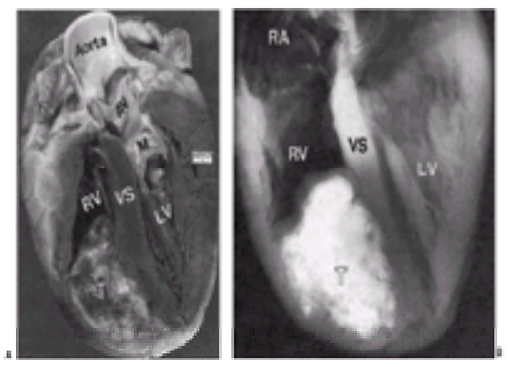


Metastatic malignant melanoma on the epicardial surface. The black deposits represent metastatic melanoma deposits.

Leukemia commonly invades the heart (84). In the days before platelet transfusions, extensive hemorrhages into the myocardial walls and into the endocardium and epicardium were commonly found in patients with fatal leukemia of various types. Histologically, leukemic infiltration between myocardial cells is quite common, and sometimes gross deposits of leukemic cells are visible within the heart. A few patients with leukemia present with pericardial effusion, which is usually hemorrhagic. Large calcific deposits in the right side of the heart have been reported (85).

Lymphoma also has a high frequency of metastases to the heart (86,87,88 and 89). Nearly 25% of patients with lymphomas of various types have lymphoma involving the epicardium, myocardium, or endocardium, or combinations. In contrast to leukemic involvement, the lymphomatous deposits are usually grossly discernible.

Some cancers, like osteogenic sarcoma, may have calcium within them (90,91 and 92) (eFig. 39.6.2).



***e*FIGURE 39.6.2** Osteogenic sarcoma to the heart in a 39-year-old woman (A80-81) with a large calcified tumor (T) in the right ventricle (RV). This patient, who was ill for 20 months, had episodic ventricular tachycardia during her last 10 months. **A:** View of both ventricles showing the tumor in the right ventricle. **B:** Radiograph of the heart at autopsy showing calcium in the right ventricular neoplasm. AV, aortic valve; LV, left ventricle; M, mitral leaflet; RA, right atrium; VS, ventricular septum. (From Seibert KA, Rettenmier CW, Waller BF, et al. Osteogenic sarcoma metastatic to the heart. *Am J Med* 1982;73:136–141, with permission.)

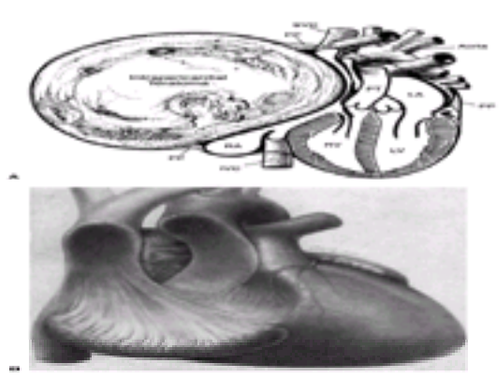
CONDITIONS MISTAKEN FOR CARDIAC NEOPLASMS

Pericardial Cyst

Pericardial or mesothelial cysts are the most frequent benign “tumors” of the pericardium. These cysts are generally asymptomatic and found on routine chest radiography (93). Approximately one-fourth of the patients, however, develop various symptoms including chest pain, dyspnea, cough, and tachycardia, as a consequence of a pericardial cyst. The cysts are usually outside the pericardial cavity and, therefore, they really should not be considered cardiac tumors.

Teratoma

Teratomas are actually extracardiac in at least 99% of the cases but still within the pericardial cavity (94,95 and 96) (eFig. 39.6.3). They arise and receive their blood supply from the ascending aorta or pulmonary trunk, presumably through the vasa vasorum. Most are found in infants and children and primarily in female subjects. Recurrent serous pericardial effusion in children should suggest intrapericardial teratoma. Because these tumors may become quite large, they may cause compression of various cardiac chambers and resulting symptoms.



***e*FIGURE 39.6.3** Intrapericardial teratoma in a stillborn. The infant’s heart weighed 8 g, and the tumor, which greatly compressed the heart, weighed 20 g. **A:** Diagram showing comparative size of the intrapericardial teratoma and the heart. **B:** Drawing showing compression of the superior vena cava, right atrium (RA), and aorta by the tumor. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; M, mitral leaflet; PP, parietal pericardium; PT, pulmonary trunk; RV, right ventricle; SVC, superior vena cava. (From Brabham KR, Roberts WC. Cardiac-compressing intrapericardial teratoma at birth. *Am J Cardiol* 1989;63:386–387, with permission.)

Lipomatous Hypertrophy of the Atrial Septum

Massive fatty infiltration of the atrial septum is an extremely common condition occurring almost exclusively in persons over 50 years of age and usually over 65 years of age (97) (Fig. 39.7). These lesions are essentially limited to obese people, and they are always associated with enormous quantities of subepicardial adipose tissue, particularly enormous amounts of adipose tissue in the atrioventricular sulci. These hearts are almost always so fat that they float in water (98). Normally, the atrial septum is less than 1 cm in thickness. In patients with lipomatous hypertrophy of the atrial septum, the atrial septum cephalad to the fossa ovale may be as thick as 7 cm, and the portion of atrial septum caudal to the fossa ovale may be as thick as 4 cm. Enormous infiltration of fat into the atrial septum may be associated with atrial arrhythmias. The importance of lipomatous hypertrophy of the atrial septum in the context of cardiac tumors is that these patients should not be operated on to remove fat from the atrial septum. The treatment is simply weight loss. These fatty deposits may be diagnosed by echocardiography, CT, or MRI (99,100). Fat in the subepicardial adipose tissue has been confused by echocardiography with pericardial effusion (101).

FIGURE 39.7 Lipomatous hypertrophy of the atrial septum in a 74-year-old woman (GT 77A-42) with huge fatty deposits in the atrial septum (except for the fossa ovale area). [From Shirani J, Roberts WC. Clinical, electrocardiographic and morphologic features of massive fatty deposits (“lipomatous hypertrophy”) in the atrial septum. *J*

Am Coll Cardiol 1993;22:226–238, with permission.]

Papillary Fibroelastomas

Papillary fibroelastomas are small avascular growths with multiple papillary fronds usually limited to cardiac valves (mainly the aortic and mitral valves), and they are common in older persons (102). They consist of fibrous tissue covered by an elastic membrane, which in turn is covered by endocardium. Occasionally (approximately 15% of cases), they also occur on left ventricular or ventricular septal mural endocardium (103,104,105,106,107,108,109,110,111 and 112), particularly in patients with small or relatively small ventricular cavities, such as in patients with hypertrophic cardiomyopathy (103,109) or mitral stenosis with or without aortic valve stenosis (107,110,111). When located on the aortic valve, papillary fibroelastomas are usually found on the ventricular aspects of the cusps in the more central portions. They also occur on the aortic aspects of these cusps, usually near the margins (113,114,115 and 116). On the mitral valve leaflets, they are usually on the atrial aspects near the margins (117,118,119,120,121,122,123 and 124). In patients with hypertrophic cardiomyopathy or mitral stenosis, they may be on the ventricular aspects of the anterior mitral leaflet and sometimes on mural endocardium, particularly over the papillary muscles. These lesions may be the result of contact of one valve leaflet with another or one mural endocardial surface with another.

Papillary fibroelastoma removed from the aortic valve. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

A number of patients have been reported with papillary fibroelastomas and stroke (115,116,117 and 118,122,123,125,126,127,128 and 129). Whether the stroke was truly connected with the cardiac fibroelastomas is debatable. Some patients have been in their 20s or 30s without other predisposing features or findings commonly associated with cerebral infarction, and the occurrence of stroke in the younger age group is suggestive of a connection. In contrast to myxoma, in which myxomatous material has been seen in systemic emboli, however, histologic findings of papillary fibroelastomas have not been observed in a cerebral artery in a patient with stroke and cardiac papillary fibroelastomas. Furthermore, the papillary fibroelastomas are firmly attached to valvular or mural endocardium, and dislodgement of a fibroelastoma therefore would appear unlikely. Thrombus, however, is occasionally superimposed on papillary fibroelastomas, and it may be that the thrombus is the material that is dislodged and responsible for the stroke.

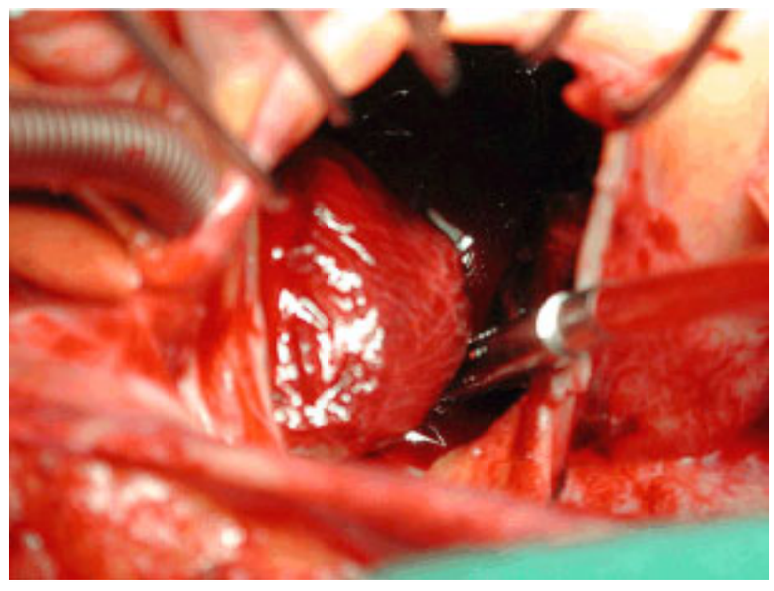
Additionally, angina pectoris (129), acute myocardial infarction (130,131,132,133 and 134), and sudden death (130,135) have been observed in patients with cardiac papillary fibroelastomas, mainly on the aortic valve. These papillary growths may obstruct an aortic ostium of a coronary artery (136,137). On rare occasion, papillary fibroelastomas have been observed on the right side of the heart, mainly the tricuspid valve (138,139,140 and 141).

Papillary fibroelastomas have been operatively excised from the cardiac valve, mural endocardium, or both in patients with evidence of stroke or other peripheral events, and a few patients have had cardiac valve replacement (107,109,111,112,115,116,118,119 and 120,125,126,133,137,139,141). When papillary fibroelastomas are detected by echocardiography in asymptomatic patients, operative excision rarely appears warranted.

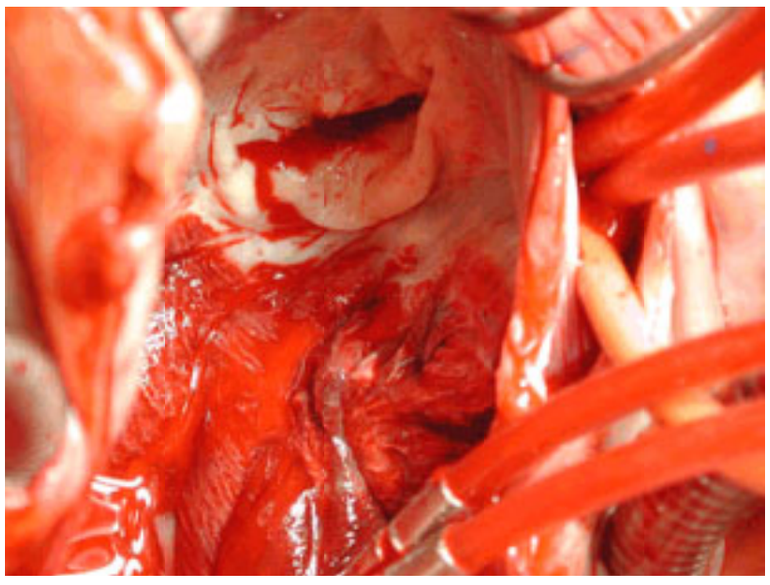
Thrombi

Thrombi within an intracardiac cavity may be indistinguishable from neoplasm by echocardiography or radiography. Grossly, however, they are very different.

Video 39.18 Subcostal view of a patient with severe left ventricular dysfunction and multiple mobile thrombi within the left ventricular cavity. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Intraoperative field looking into the left atrium of a patient with severe mitral stenosis who developed extensive clot within the left atrium. Notice the large mass in the center of the field, to the left of the opening within the left atrium. This is the largest portion of the left atrial thrombosis.



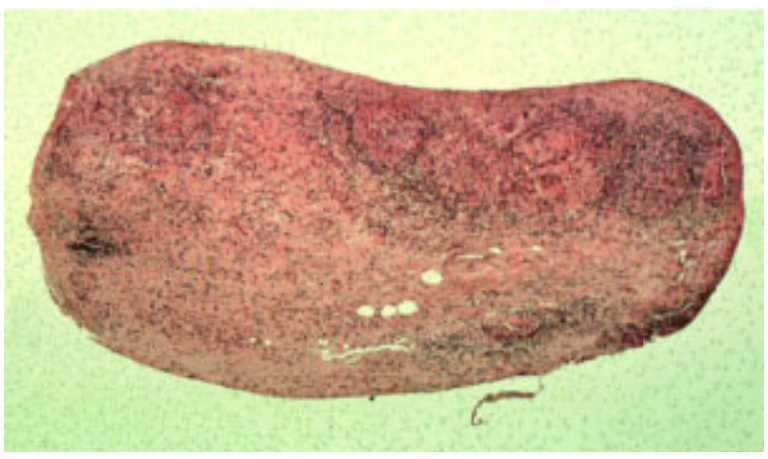
Intraoperative field looking into the left atrium after the large left atrial thrombus was resected demonstrating the rheumatic mitral valve at the top of the screen. Note the scarred, thickened, restricted mitral leaflets. This patient had severe mitral stenosis with a mean pressure gradient of 20 mm Hg across the valve and a mitral valve area of 0.7 cm^2.

Surgical specimen of the large left atrial mass explanted at the time of surgery. Note its somewhat pale, glistening surface, suggesting that the thrombus is not fresh and possibly endothelialized.

Sarcoid

When located in myocardium, sarcoid granuloma may grossly resemble neoplasm (142,143 and 144).

Sarcoidosis. Skin plaques with purple, raised lesions seen in sarcoidosis (*arrows*).



Endomyocardial biopsy demonstrating multiple granulomas in a case of sarcoidosis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

CONSEQUENCES OF THERAPY FOR NEOPLASMS IN THE HEART OR MEDIASTINUM

Radiation Heart Disease

Radiation heart disease was first recognized after radiation therapy for Hodgkin's disease (145,146,147 and 148). Some of the earlier patients with Hodgkin's disease

received 8,000 rad, which adversely affected the pericardium, myocardium, and endocardium. The most common manifestation of radiation heart disease is pericardial effusion. Fibrin deposits occur on both the visceral and parietal aspects of the pericardia. Because coronary arteries are located in subepicardial adipose tissue, they often receive the effects of radiation. Many patients have been reported to have coronary arterial narrowing at a very young age after radiation therapy, particularly patients with Hodgkin's disease. The intimal plaques resulting from radiation heart disease cannot be distinguished from plaques occurring from typical atherosclerosis. The distinguishing feature of radiation heart disease involving the coronary arteries is extensive fibrous thickening of the adventitia, and also loss, focally or diffusely, of internal and external elastic membranes, particularly the latter. Narrowing of coronary ostia also is common in radiation heart disease. In addition, radiation can cause considerable scarring within the subepicardial adipose tissue. The second most common manifestation of radiation heart disease is mural endocardial thickening, most commonly of the right atrium and ventricle, but focally also in the left ventricle. The third most common manifestation of radiation heart disease is interstitial fibrosis; depending on the portal of entry, it usually involves the anterior wall of the right ventricle more than any other portion of the heart.

Cardiac Hemorrhages

Thrombocytopenia, particularly if persistent, often results in focal epicardial, myocardial, and mural endocardial hemorrhages. If the hemorrhages are located in conduction tissue, various degrees of heart block or arrhythmias may be the consequence.

Cardiac Infection

The most common cardiac infections today in cancer patients are myocardial abscesses and mural endocardial and epicardial abscesses. These are particularly prevalent in patients with prolonged leukopenia (149,150). Patients having unsuccessful bone marrow transplantation are particularly prone to these infections, which usually are produced by fungi, not bacteria. Gas gangrene may involve the heart as well as most other body organs and tissues (151).

Cardiac Adiposity or the Corticosteroid-Treated Heart

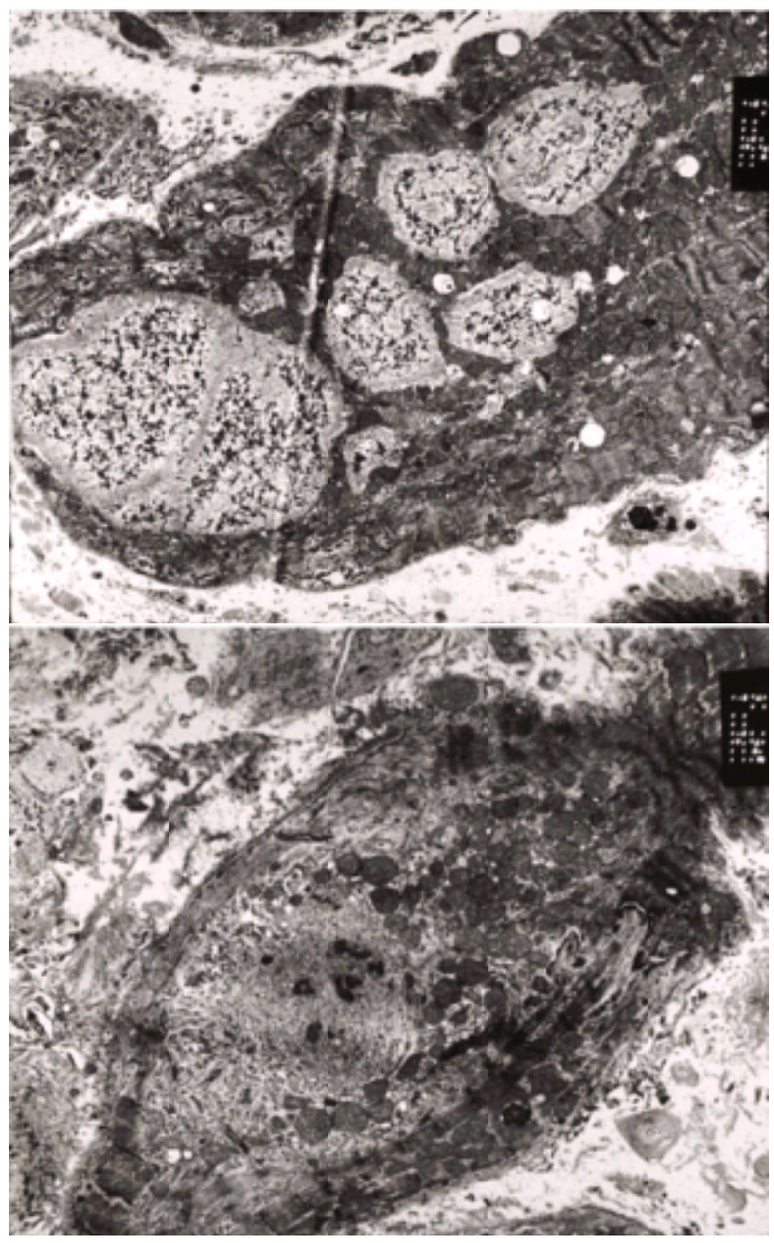
Patients with various types of cancers, particularly those with leukemia and lymphoma, and those developing cancer after transplantation of one or more body organs, usually receive corticosteroid therapy for prolonged periods. The consequence is excessive deposition of fat in the heart, mainly in the subepicardial areas (152). These hearts may become so fatty that they float in water (buffalo hump of the heart), and this excessive subepicardial adipose tissue may simulate pericardial effusion.

Cardiac Hemosiderosis

Normally, the human body contains approximately 4 g of iron. If the deposits increase to approximately 25 g, iron deposits are then usually found within myocardial cells. Patients who receive 100 units of blood without associated bleeding diatheses can acquire approximately 25 g of iron within the body organs and tissues. This situation may exist in some patients with cancer, particularly leukemia, and the result is cardiac hemosiderosis (153). These patients may be asymptomatic, or they may develop features of dilated cardiomyopathy with heart failure. At times, ventricular arrhythmias may be a consequence. Myocardial restriction as a result of myocardial ironic deposits has occurred, but dilatation is far more common (154).

Anthracycline Chemotherapy (Doxorubicin and Daunorubicin)

Cardiac toxicity is a well-recognized complication of doxorubicin and daunorubicin therapy and is frequently the dose-limiting factor in their administration (155,156 and 157). Clinical toxicity is usually manifested by evidence of impaired left ventricular systolic function. Morphologic signs of toxicity may be present when clinical signs of toxicity are absent.



Electron microgram of 3+ doxorubicin (Adriamycin) toxicity (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

A UNIQUE HEART DISEASE ASSOCIATED WITH A UNIQUE CANCER: CARCINOID HEART DISEASE

Carcinoid tumors are never primary in the heart, and they rarely metastasize to the heart (158). Nevertheless, patients with ileal, bronchial, or ovarian carcinoid, when hepatic metastases are present, often develop distinctive lesions in the heart, particularly in the right side (159,160,161,162 and 163) (Fig. 39.8). The distinctive lesions consist of deposits of fibrous tissue devoid of elastic fibers on the ventricular aspect of the tricuspid valve leaflets and on the arterial aspect of the pulmonic valve leaflets. Occasionally, deposits also are seen on the ventricular aspects of the mitral leaflets and, rarely and usually to a small extent, on the aortic aspects of the aortic valve cusps. These lesions may result in tricuspid regurgitation and stenosis and pulmonic valve stenosis and regurgitation. Surprisingly, patients with carcinoid heart disease, compared with patients with metastatic carcinoid disease without carcinoid heart disease, have similar life spans after diagnosis of the carcinoid syndrome. The syndrome is diagnosed primarily by the presence of facial flushing and diarrhea.

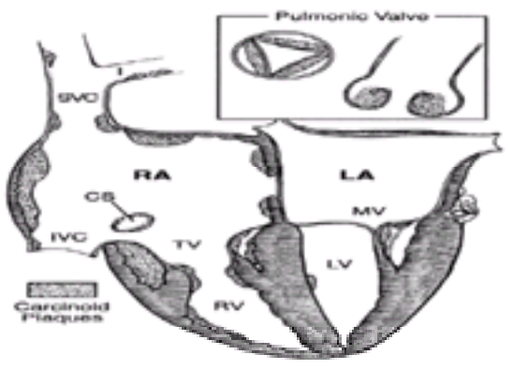


FIGURE 39.8 Diagram showing location of carcinoid fibrous plaques in carcinoid heart disease. CS, coronary sinus ostium; I, innominate vein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve. (From Ross EM, Roberts WC. The carcinoid syndrome: comparison of 21 necropsy subjects with carcinoid heart disease to 15 necropsy subjects without carcinoid heart disease. *Am J Med* 1986;79:339–354, with permission.)

Ross and Roberts (162) studied at necropsy 36 patients with metastatic carcinoid: 21 (57%) with and 15 (43%) without carcinoid heart disease. The two groups were similar in mean age (54 vs. 55 years), duration of clinical illness (4.7 vs. 6.3 years), body weight (50 vs. 52 kg), systemic blood pressure (117/77 vs. 128/77 mm Hg), blood hematocrit levels (37% vs. 36%), total serum protein levels (6.0 g per dL), and serum albumin levels (2.2 vs. 2.6 g per dL). The two groups differed in the frequency of the presence of precordial murmurs consistent with tricuspid regurgitation, pulmonic stenosis, or both (95% vs. 13%); cardiomegaly by chest radiography (38% vs. 0%); low voltage on ECG (47% vs. 0%); and location of the primary site of the carcinoid tumor. Total ECG 12-lead QRS voltage was similar in each group (105 vs. 132 mm; 10 mm = 1 mV). Of the patients with carcinoid heart disease, 43% died of cardiac causes; none of those without carcinoid heart disease died of cardiac causes. Of the 21 subjects with carcinoid heart disease, seven had left-sided cardiac involvement, but in none was it of functional significance. Thus, although carcinoid heart disease frequently is the cause of death in patients with the carcinoid syndrome, the development of carcinoid heart disease is not related to the duration of symptoms of the carcinoid syndrome.

All of the 21 patients with carcinoid heart disease studied by Ross and Roberts (162) had involvement of both tricuspid and pulmonic valves by carcinoid plaques, and 19 also had carcinoid plaques on the mural endocardium of the right atrium and usually also on the mural endocardium of the right ventricle. The number of subjects with right-sided valvular dysfunction as a consequence of the carcinoid plaques on the valvular leaflets is less certain because of the relative difficulty in diagnosing by auscultation mild degrees of tricuspid and pulmonic valve dysfunction. In 2 of the 21 subjects with right-sided carcinoid heart disease, the degree of morphologic involvement of both valves was minimal, and valvular function clearly was not affected. Of the remaining 19 subjects, 18 had precordial systolic, diastolic, or both kinds of murmurs of grade 2/6 or greater intensity.

Although the composition and location of the carcinoid plaques on both right-sided cardiac valves are similar, the functional consequences of the carcinoid plaques are different. The deposits occur nearly entirely on the downstream side of the valvular leaflets (i.e., on the ventricular aspects of the septal and posterior tricuspid leaflets and on the pulmonary arterial side of the pulmonic valve cusps). On the anterior tricuspid valve leaflet, the deposits can be on both sides. The consequence of the “downstream” deposition is an adherence of the leaflet to the underlying mural endocardium (tricuspid septal and posterior leaflets) or to the underlying pulmonary arterial endothelium (pulmonic valve) via the carcinoid plaques. The fibrous tissue of the carcinoid plaque acts as a constricting substance such that the “ring” of both right-sided cardiac valves is made smaller than normal; at the same time, leaflet mobility is diminished. The consequence is tricuspid regurgitation with or without some degree of stenosis. Nearly all patients with pure tricuspid regurgitation (no element of stenosis) have dilated valve rings, but patients with some degree of stenosis in addition to regurgitation do not have dilated annuli. Patients with carcinoid heart disease follow this principle. Thus, patients with carcinoid heart disease have much more tricuspid regurgitation than stenosis, but usually there is some degree of stenosis, albeit small.

In contrast to the tricuspid valve, the dominant functional pulmonic valve lesion is stenosis, although all patients with stenosis have some degree of pulmonic regurgitation. The reason for the difference from the tricuspid valve is that the orifice of the normal pulmonic valve is much smaller initially than the orifice of the tricuspid valve. Thus, the constriction by deposition of carcinoid plaques within the pulmonic sinuses causes constriction of the pulmonic root with the production of pulmonic stenosis. Because the distal portions of the pulmonic cusps are inverted toward the sinuses and the mobility of the cusps is lost, some degree of regurgitation is inevitable in patients who have any degree of pulmonic stenosis.

Although combined lesions of both mitral and aortic valves are fairly common as a consequence of rheumatic heart disease, infective endocarditis, or both, combined lesions of tricuspid and pulmonic valves are rare, and carcinoid heart disease is the only condition in which uniformly both right-sided valves are involved, not just one. The two dominant functional consequences of right-sided carcinoid heart disease are pulmonic stenosis and tricuspid regurgitation. These two lesions in the same patient are particularly unfavorable because pulmonic stenosis increases the degree of tricuspid regurgitation. A commonly employed method of producing chronic congestive heart failure in experimental animals is by banding the pulmonary trunk to create pulmonic stenosis and excising or destroying one or more tricuspid valve cusps to make the valve purely regurgitant. Thus, right-sided carcinoid heart disease, in essence, creates this experimental model. If a patient with carcinoid heart disease had only dysfunction of the pulmonic or the tricuspid valve, the functional consequence probably would be insignificant. The combination of both right-sided valvular lesions, namely pulmonic stenosis and tricuspid regurgitation, has the potential of being devastating.

Clinical diagnosis of carcinoid heart disease can usually be established by noninvasive means. Auscultation, of course, is the first clue. In Ross and Roberts’ study (162), 20 (95%) of 21 subjects with carcinoid heart disease and 5 (33%) of 15 subjects without carcinoid heart disease had one or more precordial murmurs. Of the 20 subjects with precordial murmurs and carcinoid heart disease, 8 had both systolic and diastolic murmurs and 12 had only systolic murmurs; of the 5 subjects with precordial murmurs but without carcinoid heart disease, all the murmurs were systolic only. Thus, nearly all patients with carcinoid heart disease have precordial murmurs, and when the murmur has a diastolic component, diagnosis of carcinoid heart disease can be made with confidence.

The systemic arterial blood pressure is not helpful in either diagnosing carcinoid syndrome or distinguishing those with from those without carcinoid heart disease. Only 3 of the 36 subjects studied by Ross and Roberts (162) had indirect systolic systemic arterial pressures of more than 140 mm Hg, diastolic arterial pressures of more than 90 mm Hg, or both: 1 of the 21 with carcinoid heart disease and 2 of the 15 without it. The average peak systolic pressure was 117 mm Hg in the 21 subjects with carcinoid heart disease and 128 mm Hg in the 15 subjects without it. The average diastolic pressure in both groups was 77 mm Hg.

Chest radiography is helpful in diagnosing carcinoid heart disease. The cardiothoracic ratio was more than 0.50 in 8 (38%) of the 21 subjects with carcinoid heart disease and in none of 15 subjects without it. Thus, the cardiothoracic ratio is not a very sensitive test for carcinoid heart disease, but it is specific.

The resting ECG is somewhat useful in distinguishing subjects with and without carcinoid heart disease. In Ross and Roberts’ study (162), the sum of the QRS voltage in leads 1, 2, and 3 was 15 mm or less in 9 of the 21 subjects with carcinoid heart disease and in none of the 15 subjects without the disease. The sum of the total 12-lead QRS voltages ranged from 58 to 227 mm in 34 subjects, and the mean values did not differ significantly between the two groups (105 vs. 132 mm). Evidence of right ventricular hypertrophy was rare. The R wave was greater than the S wave in either lead V_1 or V_2 in only 4 of the 21 subjects with carcinoid heart disease and in none of the 15 subjects without it. Despite right atrial dilatation in most of the subjects with carcinoid heart disease, all 21 with and all 15 without carcinoid heart disease had sinus rhythm. The RR interval was normal (0.20 sec or less) in 18 of 21 subjects with the disease and in 14 of 15 subjects without it. The width of the QRS complex was normal (0.12 sec or less) in all subjects, irrespective of whether they had carcinoid heart disease. Thus, other than the higher frequency of low voltage in the subjects with carcinoid heart disease, ECG was not helpful in distinguishing between subjects with and without carcinoid heart disease.

Echocardiography, particularly cross-sectional, is helpful in diagnosing carcinoid heart disease (164,165). Callahan and associates (164) described retrospectively echocardiographic features in 20 patients with the carcinoid syndrome. By physical examination, 15 patients had a diagnosis of carcinoid heart disease and the other five did not. Both M-mode and cross-sectional examinations in the latter five patients disclosed no abnormal findings. Of the 15 patients with auscultatory evidence of carcinoid heart disease, five had normal M-mode and cross-sectional echocardiographic findings. The other ten, all of whom had tricuspid regurgitation by physical examination, had dilated right ventricular cavities, abnormal motion of the ventricular septum, and of the nine in whom the tricuspid valve leaflets were visualized by cross-sectional echocardiography, strikingly abnormal tricuspid leaflets (thickened and retracted with fixed orifice). The pulmonic valve cusps were not visualized in any patient by M-mode echocardiography, but in the four in whom they were visualized by cross-sectional echocardiography, the pulmonic valve cusps were abnormal in each.

Howard and associates (165) prospectively examined by cross-sectional echocardiography 14 patients with the carcinoid syndrome, and eight had definite abnormalities of one or both right-sided cardiac valves. Clinically, five had auscultatory evidence of tricuspid regurgitation, and all five had diffusely thickened and retracted tricuspid valve leaflets; the other nine patients had normal tricuspid valves by echocardiography. Four patients by auscultation had evidence of pulmonic

stenosis with or without pulmonic regurgitation. The pulmonic valve cusps were visualized by echocardiography in seven patients: Two had retracted pulmonic cusps with decreased systolic motion (one of whom had pulmonic stenosis by auscultation), and five had normal cusps (none of whom had auscultatory evidence of pulmonic stenosis).

Right-sided cardiac valve excision with or without valve replacement or valve commissurotomy or annuloplasty has been carried out in some patients with carcinoid heart disease. The interval from onset of symptoms and signs of congestive heart failure to cardiac valve operation in 15 patients collected from published reports by Ross and Roberts (162) ranged from 3 to 60 months (mean, 14) and the interval from onset of symptoms of the carcinoid syndrome to cardiac valve operation ranged from 0.5 to 33.0 years (mean, 10). Preoperatively, at least 12 of the 15 patients had hemodynamic evidence of tricuspid valve stenosis with mean diastolic pressure gradients between right atrium and right ventricle ranging from 4 to 24 mm Hg (mean, 9). Of 15 patients, 14 had tricuspid regurgitation, which was graded as severe at angiography in at least seven patients. Pullback pressures between pulmonary artery and right ventricle were recorded in 14 patients, 12 of whom had peak systolic pressure gradients ranging from 3 to 50 mm Hg (average, 29). The presence or absence of pulmonic regurgitation as determined by pulmonary angiography was noted in 12 patients, and only two apparently had regurgitation into the right ventricle during ventricular diastole. Of the 15 patients, 14 had tricuspid valve procedures: replacement in 13 and annuloplasty in one. Ten patients had pulmonic valve procedures: commissurotomy in six, replacement in three, and excision only in one. Of the 15 patients, eight had died at the time of the report: four within 2 months of operation, and one each 4, 8, 24, and 72 months after the operation. The other seven patients were alive 4 to 132 months (median, 23) after the operation.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Benign cardiac tumors should constantly be kept in mind because so many of them are entirely curable by operative therapy. It is not bad to overlook metastatic cancer to the heart, because virtually no cancers metastasize to the heart without metastasizing to other body organs and usually multiple other body organs. Cardiac tumors, whether primary or secondary, can simulate more common types of cardiac disease, and this fact should always be kept in mind.

THE FUTURE

Improvement of chemotherapy will almost certainly improve outcome of primary and metastatic cancer involving the heart.

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CARDIOVASCULAR CLINICAL PHARMACOLOGY

RAYMOND L. WOOSLEY

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Currently available cardiovascular agents are often limited by side effects and the potential for exacerbating the condition being treated. In addition, therapy is complicated by altered disposition of drugs as a result of concomitant disease processes, active metabolites, drug interactions, and poorly defined therapeutic ranges with great interpatient variability. The considerations presented here can serve only as a first approximation in determining a suitable drug or dosage regimen. Clinical observation then allows at least some appreciation of how a particular patient responds to a drug. With an understanding of basic pharmacologic principles, the patient's response to and disposition of drug at other doses can then be predicted. A grasp of such principles is invaluable in the choice of drug, its dosage, and the establishment of an optimal risk-benefit ratio for the patient.

DRUG ACTION

Receptors

At the beginning of the twentieth century, it was generally accepted that the response to a drug is mediated by interaction of the drug with specific cellular-binding sites called *receptors*. Technologic advances, notably affinity chromatography, photoaffinity labeling, and modern molecular biologic techniques, have allowed characterization of the receptor macromolecules themselves and the steps involved from initial recognition and interaction between a ligand and receptor (drug or endogenous substance) to the expression of effect. Ligand-binding studies have also aided our current understanding of receptor localization, specificity, structure–activity relationships, and receptor dynamics. Drug–receptor interactions may alter a process directly or act by an allosteric mechanism to produce graded increases or decreases in sensitivity to endogenous ligands.

Receptors are heterogeneous, ranging from enzymes (digitalis glycosides bind to Na^+-K^+-adenosine triphosphatase) to nucleic acids (with which many antineoplastic agents interact). Ligand–receptor interactions, however, generally result in changes either in ion permeability or in some biochemical function (second messengers) such as activation of a cyclic nucleotide-dependent protein kinase, or both.

Signal Transduction

The ligand–receptor activation process can be modeled to various degrees of sophistication; the simplest model is an equilibrium between two receptor states: resting and activated. One theory proposes that the relative affinity of a ligand for these two receptor states determines its biologic activity. For example, agonists (agents that elicit a response) shift the equilibrium in favor of the activated state (i.e., they promote the interaction of the receptor with the coupling protein), whereas antagonists (agents that prevent a response to the agonist) show equal affinity for both receptor states and do not alter their equilibrium. The formation of the antagonist–receptor complex prevents agonists from binding that would normally have the ability to shift the equilibrium and increase the amount of receptor in the activated states. A partial antagonist (e.g., a beta-blocker with intrinsic sympathomimetic activity) may be thought of as having an only somewhat greater affinity for the activated state. Thus, it causes only a slight shift of the equilibrium in favor of the activated state.

An important concept is that the receptor population is not fixed, and the number of receptors self-regulates in response to the degree of stimulation. Thus, phenomena related to an attenuated or augmented response (tolerance, tachyphylaxis, desensitization, or increased sensitivity to the drug) can be wholly or in part due to changes in receptor density. For example, beta-adrenergic receptor density increases (upregulation) during chronic treatment with propranolol. The effect appears to persist as long as propranolol is administered and for some time after discontinuation, providing a possible explanation for the delayed supersensitivity to beta-adrenergic stimulation seen after stopping propranolol therapy (1). Clinically, this may be manifest as increased heart rate, increased blood pressure, worsened angina, or arrhythmias. Chronic receptor stimulation (e.g., the use of sympathomimetics in the treatment of asthma) may lead to a reduction (downregulation) in receptor density and therefore to a loss of efficacy.

Another mechanism of receptor sensitivity control may be modification of receptor coupling to a regulatory protein, so that ligand–receptor binding is divorced from the sequence of events leading to effect. Such a mechanism may be important in instances of acute desensitization to the agonist. In more recent years, it has become apparent that inherited differences in the amino acid sequences of receptors (i.e., receptor polymorphisms) are responsible for some medical disorders (e.g., asthma, obesity) and are probably responsible for variability in response to drugs. This exciting new area of molecular pharmacology holds the potential of much more specific and targeted drug therapy. In many cases, specificity of action extends to steric requirements. Thus, only the L-optical isomer of norepinephrine, and not the D-isomer, elevates blood pressure; the L-enantiomer of verapamil has more potent hypotensive and negative chronotropic effects than the D-verapamil (2).

Not all drugs interact with specific receptors, however. For example, by generating a nitric oxide free radical, nitrate vasodilators may initiate vascular smooth muscle

relaxation mediated by increases in cyclic guanosine monophosphate (3). Osmotic diuretics depend on their physical properties for therapeutic benefit.

Structure-Activity Relationships

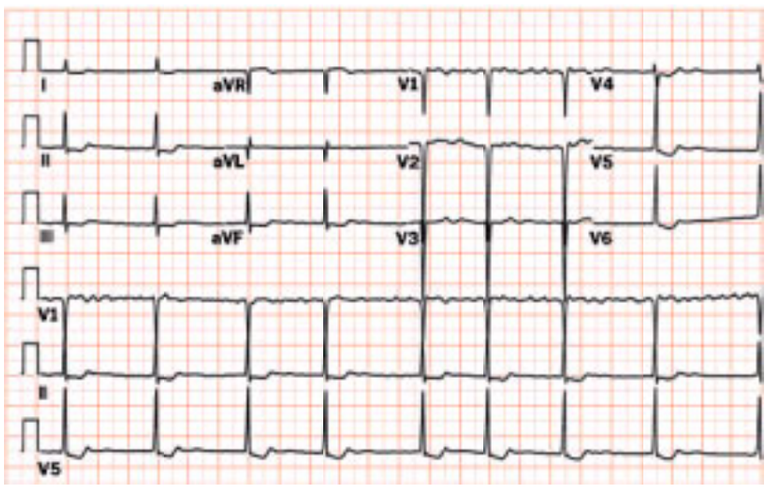
The therapeutic usefulness of most drugs depends on their specificity, which in turn implies interaction with a receptor. The ability of a drug to interact with a receptor depends on its having the correct physical, chemical, and spatial configuration. Minor modifications in structure can yield compounds with widely differing potencies or loss of efficacy. The screening of a series of chemical compounds related in structure to a known active compound not only can produce information on chemical relationships crucial to pharmacologic activity, but also can provide clues to receptor configuration.

The specificity of a drug for a particular receptor also determines the scope of its biologic activity. For example, terfenadine and its active metabolite, fexofenadine, are commercially available antihistamines. Although fexofenadine differs only slightly in structure, the drugs have very different pharmacologic actions. Both drugs block histamine receptors, but only terfenadine blocks cardiac potassium ion channels (55). The extent to which these two agents interact with the receptors involved in transducing these effects determines their relative potencies and, in this case, their safety. Terfenadine's ability to block cardiac potassium channels has been associated with rare but serious reports of torsades de pointes, a potentially life-threatening ventricular arrhythmia. Fexofenadine, although differing only slightly in structure, lacks this risk.

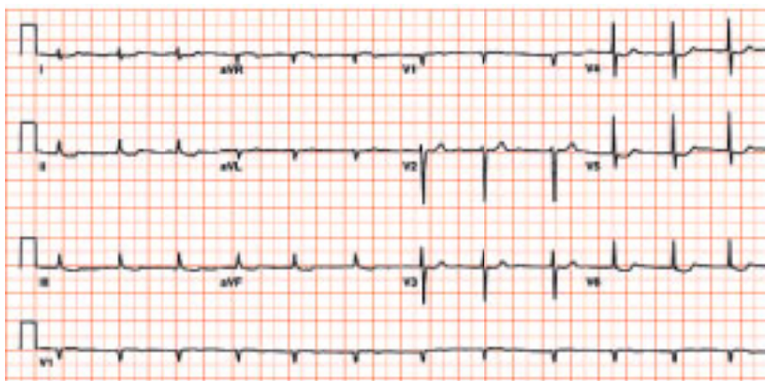
Dose Response Relationships and the Therapeutic Window

The therapeutic window for a drug encompasses the range of doses (or plasma concentrations when there is a reliable correlation with pharmacologic effect) that elicits a therapeutic effect in the majority of patients, with adverse effects occurring in only a few. At some appropriately chosen low dose, most patients do not respond at all. Increasing doses result in more and more patients showing a desired therapeutic response, and this is most likely paralleled by an increasing number of patients who develop unwanted adverse effects. The wider the margin between the concentrations that produce efficacy and those associated with side effects, the more leeway there is in dosing, and the wider the therapeutic window. Conversely, a narrow therapeutic window requires careful dose adjustment to avoid toxic effects. The therapeutic window also depends on the definition of efficacy. For example, the therapeutic window for slowing of atrial fibrillation with digoxin is probably wider than that for improving heart failure.

Heparin complication. Extensive purpura from heparin treatment.



Digitalis effect. Note controlled ventricular rate with short, scooped ST segments in the lateral leads.



A 74-year-old male patient with accelerated junctional rhythm secondary to digitalis toxicity and retrograde P waves.

One aim of understanding pharmacokinetics is to assist in the achievement and maintenance of plasma concentrations within the therapeutic window. This is especially important when dealing with cardiovascular agents because their *therapeutic ratio* (the plasma concentration that produces a desired therapeutic effect compared with the concentration that elicits toxic effects) is usually low.

Active Drug Metabolites

In numerous cases, the drug administered is a prodrug (i.e., it is converted in the body to a metabolite that is responsible for the pharmacologic actions of the drug). In many cases, the action is the desired action. The 5-hydroxy metabolite of propafenone is active and likely contributes to the antiarrhythmic activity of the parent drug (4). The *O*-desmethyl metabolite of the potent sodium channel blocking drug, encainide, is more active than encainide and is most likely responsible for excess conduction delay and induction of new arrhythmias in some individuals (5). In addition, the metabolites of drugs can be chemically reactive and bind to tissues, causing damage, as in the case of acetaminophen.

PHARMACOKINETIC PRINCIPLES

Absorption

Following administration of most drugs (aside from intravenous injection), the agent first must be absorbed from the gut, oral mucosa, muscle, skin, or subcutaneous tissue and must enter the systemic circulation before it can reach its site of action. Several factors influence the rate and extent of absorption from these sites, including the physicochemical properties of the drug, the surface area available for absorption, and regional blood flow. In general, lipid-soluble drugs penetrate cell membranes more readily than hydrophilic agents; a nonionized drug permeates more readily than an ionized drug. Because many drugs are either weak acids or weak bases, differences in the pH of the gastrointestinal tract (strongly acid stomach, nearly neutral small intestine) determine the extent of ionization and thus the rate of absorption following oral administration. For practical purposes, however, the greatest amount of absorption occurs in the small intestine by virtue of the large surface area available.

Gastrointestinal pathology can influence the amount of drug absorbed. Diarrhea or extensive small bowel resection, both of which reduce intestinal transit time, can result in markedly diminished absorption, especially of sustained release preparations that are designed to allow prolonged absorption.

The same principles apply to other routes of administration. For example, following intramuscular injection, absorption is more rapid from deltoid rather than gluteal muscle because the former has a higher blood flow. Drugs that are insoluble at tissue pH, or those in an oily vehicle or microcrystalline suspension, form a depot, releasing the drug slowly, which may allow less frequent injections.

Bioavailability

Bioavailability is the proportion of an administered dose that reaches the systemic circulation. By definition, following intravenous injection, a drug is 100% bioavailable. Thus, bioavailability after oral administration is determined by comparison of the area under the plasma concentration–time curves following oral and intravenous dosing. Bioavailability can be lowered by incomplete absorption because of problems in the drug's formulation or the presence or absence of food, or by concomitant administration of agents that alter gastric pH (e.g., antacids) or motility (e.g., narcotic analgesics and atropine-like drugs that slow gastric emptying, or metoclopramide, which speeds it). Efficient presystemic extraction by the gut wall or the liver (first-pass effect) also lowers systemic availability.

The time course of absorption may also be important in instances in which rapid attainment of a therapeutic plasma concentration is desirable following the initial (or single) dose. Although either rapid absorption or slow absorption can result in the same amount of drug becoming available systemically (equal areas under the concentration-time curves), therapeutic concentrations are achieved sooner if absorption is rapid. It has become apparent that the bioavailability of many drugs can be influenced by the food or drink accompanying their oral administration. Likewise, the time of day at which the drug is administered can influence the bioavailability of some drugs (e.g., theophylline).

Volume of Distribution Estimates

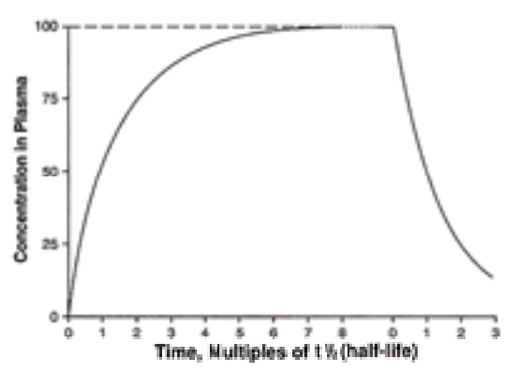
Having entered the systemic circulation, the drug distributes throughout the body, carried by the extracellular (vascular and interstitial) water in which it is dissolved. As in the case of absorption from the site of administration, the drug's passage into various body tissues depends on the lipid solubility of the drug, its degree of ionization, the vascularity of the tissue, and the size of the drug molecule, or drug–protein complex when the drug is bound to plasma protein. Lipid-soluble drugs readily diffuse across capillaries and all biologic membranes (including the blood–brain and blood–cerebrospinal fluid barriers), whereas hydrophilic drugs depend on the permeability characteristics of the capillaries to allow access to extravascular sites. The capillaries in the liver and kidney are particularly permeable to all but highly protein-bound drugs, whereas those of the brain are virtually impermeable to water-soluble molecules of any size. In more recent years it has become apparent that access to the brain and some intracellular spaces is tightly regulated by the activity of membrane pumps that exclude many drugs (6). Because quantification of the amount of drug in the various body spaces is not readily feasible, the plasma concentration usually serves as a surrogate and a guide to the rate of drug disposition.

The *volume of distribution* (V_D) is a parameter often used to describe what happens to a drug once it is in the body. It is a useful but often misunderstood term. It is obtained by measuring the plasma concentration after a dose of known magnitude has been given; if one assumes instantaneous mixing and extrapolates the measured concentrations back to the time of drug injection, that concentration is determined by the volume into which the drug is dissolved. At any time following administration, the drug concentration in plasma is defined by the amount of drug in the body and all of the volumes in which it is distributed. If we place 100 g of drug into the body and it distributes in 100 L of fluid, the concentration in that fluid will be 1 g per L. However, this rarely is the plasma concentration. Intracellular protein binding or tissue sequestration results in only a small amount of drug being left in the extracellular water. Thus, the plasma concentration is low. On the other hand, the calculated variable, the (apparent) volume of distribution, will be large, because estimation of the volume of distribution is by comparison of the amount of drug administered with the plasma concentration. Obviously, the smaller the fraction in plasma, the larger the calculated volume of distribution. Thus, the apparent volume of distribution should not be ascribed to actual anatomic volumes. For instance, the volume of distribution of mexiletine is approximately 600 to 700 L (7), far in excess of total body water. The usual reason for such a large value is extensive tissue binding, leaving little drug in the plasma.

Some substances, however, are confined to certain physiologic volumes and may be used as reference materials in pharmacokinetic studies. For example, certain dyes such as methylene blue remain confined to plasma, inulin distributes throughout the extracellular water, and antipyrine distributes throughout total body water. Their apparent volumes of distribution for a 70-kg individual are 3, 13 to 16, and 40 to 46 L, respectively. In general, however, the calculated volume of distribution of most drugs relates to the extent of tissue localization or metabolism of a drug rather than to any actual physiologic volume.

Metabolism and Elimination

Even before a drug enters the circulation, it is available for elimination. Enzymes in the intestinal wall rapidly destroy many drugs. Once in the plasma, elimination usually occurs either by metabolic modification of the drug or by excretion via the kidneys. The rate of removal of a drug is termed *clearance* and is expressed as the volume of plasma from which a drug is completely removed per unit time (e.g., milliliters per minute). *Total body clearance* is the sum of clearance at all sites of elimination. Another important term, *half-life*, is the time for any process to change to one-half of its original value. It can be used to describe a decrease or increase in the amount of drug in the body. A half-life of *elimination* is the time required for one-half of the drug in the body to be eliminated or for the plasma concentration to fall to one-half of its original level (eFig. 40.0.1).



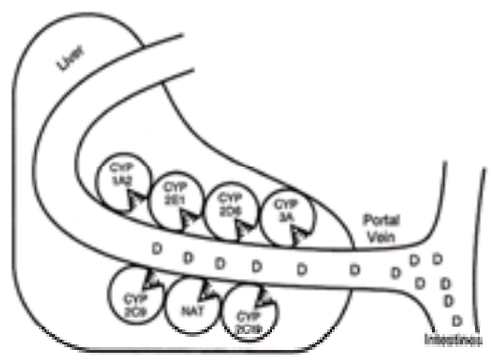
***e*FIGURE 40.0.1** Accumulation and elimination as a function of half-life.

Metabolic Pathways: Pharmacogenetics of P450 Enzymes

Most lipophilic drugs are extensively metabolized by oxidative enzyme products that can then be conjugated with acetate, glucuronic acid, or mercapturate, forming highly water- soluble compounds that are almost always pharmacologically inactive and readily excreted in the bile or urine. The oxidative step in this process is performed by enzymes belonging to a superfamily called *cytochrome P450* (CYP). The name cytochrome comes from the bright red color that the enzymes impart to the tissue and the characteristic wavelength (450 ^{l}) for absorption of ultraviolet light when exposed to carbon monoxide. A standardized designation has been developed for specific genes and enzymes in this superfamily based on their DNA homology. For example, *CYP2D6* specifies that the enzyme is in the cytochrome P450 superfamily, 2 family, D subfamily, and 6 gene.

As shown in eFigure 40.0.2, these enzymes form a potential barrier to protect the individual from foreign substances in the environment. These enzymes are found in

especially high amounts in the appropriate sites to prevent entry into the body (i.e., the gastrointestinal mucosa, liver, and lungs). They are also found in many other tissues, such as the brain, where their function is less clear. Some research indicates that they may function to regulate the levels of intracellular substances responsible for controlling ion channel permeability. In the gastrointestinal mucosa and liver, they are a formidable barrier to many of the orally administered drugs. As shown in *e*Table 40.0.1, many families of P450 have different but sometimes overlapping specificity for metabolism of certain cardiovascular drugs. *e*Table 40.0.1 lists the drugs for which a specific P450 is the major enzyme responsible for its metabolism, and it also lists drugs or agents that induce the synthesis of the P450s and agents that are inhibitors of the enzymes. Notice that some agents have relative selectivity for a given P450, whereas others are more general in their ability to inhibit or induce P450s. The cardiovascular drugs are predominantly metabolized by CYP3A and CYP2D6. Knowledge of the specific P450 involved in the metabolism of drugs has become of clinical value in more recent years. For example, if it is known which P450 is responsible, it is possible to predict the extent of variability of metabolism in the population at large. It will also be possible to predict which drugs are likely to inhibit or induce the metabolic clearance of the drug. In the relatively near future, it is likely that knowledge of the genetic inheritance of an individual will allow the physician to predict the degree of P450 enzyme expression in an individual and adjust therapy appropriately.



***e*FIGURE 40.0.2** A drug (D) absorbed from the intestines passes to the liver via the hepatica vein. As it passes through the liver, the drug may be metabolized by one or more of the phase 1 P450 enzymes (e.g., CYP3A, 2C19, 2D6, 2E1, 1A2, 2C9). The oxidized product may then be conjugated by phase 2 enzymes such as *N*-acetyltransferase (NAT), glutathione-*S*-transferase, or others before being excreted into the bile or passing into the hepatic vein and ultimately into the systemic circulation.

***e*TABLE 40.0.1** OXIDATIVE DRUG METABOLISM

CYP1A2	2C19	2C9	2D6	2E1y	3A3,4,5
Drugs					
Theophylline	S-mephenytoin	Tolbutamide	Propafenone	Acetaminophen	Erythromycin
R-warfarin	Phenytoin	Phenytoin Y4-OH	Flecainide	Theophylline	Clarithromycin
Caffeine	Diazepam	S-warfarin	S-mexiletine	Ethanol	Quinidine
Acetaminophen	Omeprazole	Losartan	Lidocaine (in part)	Ondansetron	Lidocaine
Amiodarone	Lansoprazole	Fluconazole	S-metoprolol	Halothane	Cyclosporine
Cimetidine	R-warfarin	Isoniazid	Propranolol	Enflurane	FK506
Mexiletine	Propranolol (in part)	Amiodarone	Timolol	Sevoflurane	Terfenadine
Propranolol	Imipramine		Carvedilol	Methoxyflurane	Astemizole
Estradiol	Amitriptyline (in part)		Phenytoin	Isoflurane	Verapamil
Verapamil	Indomethacin		Guanoxan		Nifedipine
			Clomipramine		Diltiazem
			Imipramine		Felodipine/nisoldipine
			Haloperidol		Lovastatin
			Dexfenfluramine		
Inhibitors					
Cimetidine	Ketoconazole	Fluconazole	Haloperidol	Disulfiram	Ketoconazole
Amiodarone	Cimetidine	Isoniazid	Quinidine		Itraconazole
Fluoroquinolones	Omeprazole	Amiodarone	Fluoxetine		Fluconazole
	Lansoprazole		Cimetidine		Erythromycin
	Fluoxetine		Ranitidine		Clarithromycin
	Fluvoxamine		Paroxetine		Cimetidine
	Paroxetine		Amiodarone		Amiodarone
					Ciprofloxacin
					Fluvoxamine
					Nor-fluoxetine
Inducers					
Omeprazole	Rifampin	Rifampin	Rifampin	Isoniazid	Rifampin
Tobacco	Prednisone			Ethanol	Phenytoin
					Carbamazepine
					Barbiturates
					Glucocorticoids

Adapted from http://www.drug-interactions.com/, by David A. Flockhart, MD, PhD, Indiana University, Indianapolis, IN.

Hepatic Clearance

For many drugs, the liver is the major site of drug-metabolizing activity in the body. Hepatic extraction may include biotransformation (metabolism), biliary excretion, and drug binding to intracellular proteins. Hepatic clearance is influenced by two independent variables: the activity of drug-metabolizing enzymes and liver blood flow. The relative importance of these two factors depends on the particular drug. For a drug with a low hepatic extraction ratio, increases in enzyme activity result in important changes in pharmacokinetic variables (increases in clearance and a shortened elimination half-life). On the other hand, for a drug with a high extraction ratio, increased metabolizing activity has little effect. Conversely, changes in hepatic blood flow affect high-extraction drugs, but not low-extraction drugs. Thus, changes in liver blood flow do not alter the disposition of phenytoin (a low-extraction drug), whereas enzyme induction does not have a large effect on the disposition of lidocaine or propranolol (high-extraction drugs).

Some drugs are so extensively cleared by the liver after absorption by the gut and before entering the general circulation (the first-pass effect) that oral use is not feasible. One example is lidocaine, which is well absorbed, but only approximately 35% is systemically bioavailable after oral administration. Increasing the oral dose to attain therapeutic plasma levels results in a corresponding increase in the levels of lidocaine's metabolites. These metabolites, however, result in unacceptable central nervous system (CNS) side effects, precluding the use of large oral doses of lidocaine.

Enzyme Induction and Inhibition

Certain agents (enzyme inducers) can promote synthesis of microsomal enzymes, resulting in increased drug-metabolizing activity. In some cases, the increased activity results in more rapid destruction of the drug itself, and tolerance to the drug develops as a consequence. Some drugs, however, are able to induce enzymes for which they themselves are not substrates. Concomitantly administered agents, which happen to be substrates for the induced enzyme, then may be subject to increased hepatic metabolism. Enzyme induction is most likely to have important consequences for the disposition of drugs with a normally low hepatic extraction ratio.

A number of agents can inhibit drug-metabolizing enzymes, increasing the systemic availability of drugs normally highly extracted by the liver. For instance, cimetidine increases the availability and prolongs the half-life of lidocaine (8) and propranolol (9). Propranolol, both by reducing hepatic blood flow and by inhibiting microsomal enzymes, decreases the clearance of lidocaine (10).

Obviously, careful patient observation is necessary whenever multiple medications are prescribed, but especially when stopping or starting a drug that alters the metabolism of other agents. Some drugs with known or proposed enzyme induction or inhibition effects in humans are listed in *e*Table 40.0.1.

Such changes in drug metabolism can result in unexpected toxicity or loss of therapeutic effect and may not be immediately apparent. For example, amiodarone covalently binds to several cytochrome P450s and noncompetitively inhibits the hepatic clearance of many drugs (11). Because the elimination half-life of amiodarone ranges from 2 weeks to 15 weeks, it may take months before the effect becomes manifest or months before normal hepatic clearance of other drugs is restored after stopping amiodarone.

Renal Clearance

Products of drug metabolism are usually more polar, and thus more water soluble, than the parent compound, facilitating excretion via the kidneys by either passive glomerular filtration or active tubular secretion. The kidneys are by far the most important routes of excretion of unchanged drug or drug metabolites. In some cases, excretion by the kidneys is the major route of elimination and the means of terminating a drug's effect. In other cases, the kidneys simply excrete a drug's inactive metabolites.

Elimination by glomerular filtration is a passive process, dependent on the extent of plasma protein binding. Because only free drug can pass the glomerular membrane, a highly protein-bound drug that is not actively secreted into the urine is eliminated slowly. If this is the main route of elimination and the volume of distribution is large (i.e., little drug in plasma), a prolonged half-life can result. For example, diazoxide is 90% bound to albumin and eliminated by glomerular filtration with a half-life of approximately 30 hours. Changes in protein binding that result in an increase in free drug concentration also increase renal elimination and shorten the elimination half-life.

Although glomerular filtration is a passive process, tubular secretion is an active process and may or may not occur, depending on the particular drug. When renal clearance exceeds clearance by filtration, tubular secretion can be inferred. As free drug is carried into the tubular lumen, more free drug dissociates from the protein–drug complex to replace the "lost" drug. Protein binding, therefore, does not limit tubular secretion as it does glomerular filtration.

Tubular reabsorption can also be important in reducing the renal clearance of drugs. Because the nonionized form of a weak acid or base can diffuse readily from the tubular urine back across the tubule cells into plasma, an alkaline urine promotes excretion and prevents reabsorption of a weak acid, whereas an acidic urine diminishes excretion and favors reabsorption. The opposite relationship is true for weak bases. For example, the half-life of mexiletine, a weak base, is approximately 9 hours when the urine is alkaline, and 3 hours when the urine is acidic (12).

Protein Binding

In plasma, most drugs are reversibly bound to plasma proteins, including albumin, alpha-1-acid glycoprotein (AAG), lipoproteins, and gamma globulins. Although the most abundant protein, albumin, avidly binds acidic drugs, many cardiovascular agents are basic and bind to AAG (13). AAG is an acute-phase protein whose concentration increases dramatically in response to stresses such as myocardial infarction, burns, or surgery. Increased levels have also been reported in chronic inflammatory diseases such as rheumatoid arthritis, inflammatory diseases, and Crohn's disease.

The degree of protein binding has implications for both drug disposition and drug effect. Only the unbound free drug is able to cross cell membranes or bind to receptor sites, thereby eliciting a pharmacologic effect. A decrease in protein binding, as a result of disease or displacement by another drug, increases the free fraction, which in turn increases the amount of drug available for equilibration with extravascular sites. This increases the volume of distribution and may alter clearance as described here.

Changes in protein binding are most likely to be clinically important for drugs that are highly protein bound. For example, for a drug that is 98% bound to plasma protein, a decrease in binding to 96% doubles the free fraction from 2% to 4%. For a drug that is 60% bound, a similar decrease in binding results in only an increase of one-twentieth (from 40% to 42%) in the free fraction. In the latter case, clinically important consequences of the change in protein binding are unlikely. In the former case, the clinical significance depends on the total amount of drug present in the plasma and whether the increase in free fraction results in a corresponding increase in free drug concentration. This, in turn, depends on whether the increase in free fraction is accompanied by an increase in clearance. For most protein-binding displacement interactions, so-called bumping reactions, the *transient* increase in free drug is not clinically relevant because the drug rapidly distributes into tissues, is metabolized, or both. In the rare cases in which displacement of drug from plasma proteins is clinically relevant, a concomitant inhibition of drug metabolism is usually responsible for accumulation of excess drug (14).

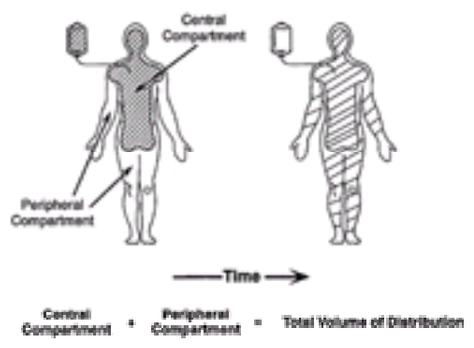
Plasma protein binding can serve as a drug storage site, "protecting" drug from passive elimination processes in the liver and kidneys, or it can act as a delivery system for drugs that are highly cleared by the liver or kidneys as a result of active transfer processes.

For most drugs, the fraction of drug bound to protein, at least for doses in the therapeutic range and well beyond, remains constant. Some drugs (e.g., disopyramide), however, show nonlinear saturable protein binding in the range of concentrations attained during routine clinical use. Thus, as the total plasma concentration increases, so does the free fraction. For example, doubling the total disopyramide concentration from 2 to 4 µg per mL may increase the free disopyramide concentration by as much as sixfold (15). The use of a slow-release formulation of disopyramide causes downward peaks on the impact of saturable protein binding.

CLINICAL PHARMACOKINETICS

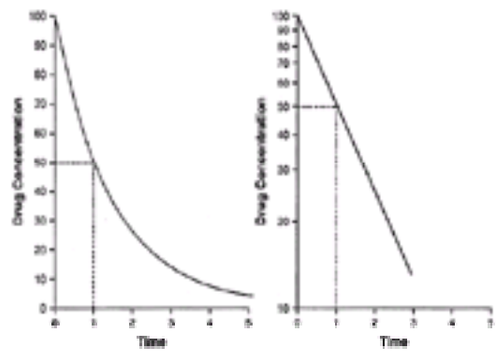
Pharmacokinetics describes the relationship of the processes of absorption, distribution, and elimination of a drug with time. The application of pharmacokinetics principles in the practice of medicine can improve dosage selection, resulting in improved clinical benefits and reduced toxicity (16,17). The fate of a drug in the body can be approximated by mathematical models fit to plasma concentration data that, in turn, allow prediction of dosing schedules.

The various spaces into which the drug distributes can be viewed as theoretical "compartments" or volumes containing a certain mass of drug, with rate constants for entry and exit of drug from each of these compartments. Entry and exit of drug occur from a central compartment, which in practical terms may be thought of as the plasma (and perhaps highly perfused tissues such as brain, lung, heart, and kidneys, depending on the rapidity of distribution to these tissues relative to others). The drug may distribute more slowly into various tissues that can then be regarded as peripheral compartments, with rate constants of entry to and exit from the central compartment (*e*Fig. 40.0.3). Although the postulated compartments may correspond to drug distribution and elimination from discrete tissue groups, such physiologic processes cannot be reliably inferred from the model. It is important to recognize that the purpose of partitioning a drug into compartments is simply to allow convenient mathematical description of the time course of drug disposition and to use knowledge of this time course to determine optional dosing regimens.



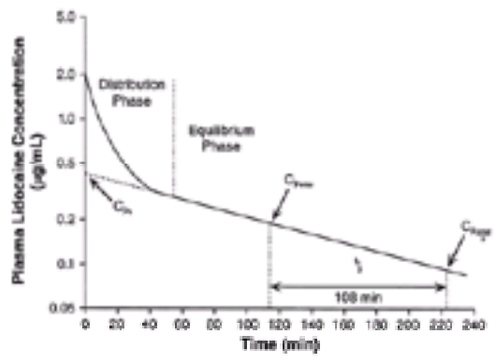
***e*FIGURE 40.0.3** Two-compartment model of drug distribution. A drug administered intravenously produces a high concentration in the central compartment; this concentration dilutes as the drug distributes into a larger peripheral compartment.

The simplest case is that of rapid, intravenous injection of a drug that is not distributed to other compartments. In this case, a semilogarithmic plot of plasma concentration against time yields a straight line (*e*Fig. 40.0.4). Such a linear relationship describes a first-order process (i.e., a process dependent on only one parameter). The amount of drug cleared from the plasma depends, at any instant, on one parameter, the amount of drug remaining in the plasma. Thus, plasma concentration decreases by a constant fraction with each unit of time. The most useful unit of time is that required for the plasma concentration to decrease by half and is the *elimination half-life*.



***e*FIGURE 40.0.4** Drug concentration with time during first-order elimination for a single compartment plotted on an arithmetic scale **(left)** and on a semilog scale **(right)**.

Following intravenous administration of a drug such as lidocaine, a plot of log plasma concentration against time (semilog plot) often shows an initial curvature. This departure from linearity represents the initial dilution of drug within the plasma and its distribution to other tissues. Once distribution is complete, drug in both the central and peripheral compartments is in equilibrium. The curve can be dissected into two straight lines rather than one; the first represents the *distribution* half-life (8 minutes for lidocaine), and the second already is familiar as describing the *terminal elimination* half-life (108 minutes for lidocaine) (eFig. 40.0.5).

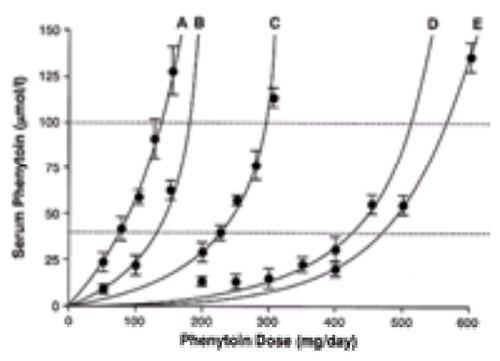


***e*FIGURE 40.0.5** Semilogarithmic plot of drug concentration against time, two-compartment model. The initial rapid decrease in plasma concentration (C_p) primarily reflects distribution.

This concept of mass action compartments wherein drug is distributed can be extended to multicompartment models. The semilog plot of plasma concentration with time following a single intravenous dose may then be described by a polyexponential equation, with rate constants for entry to and exit from each compartment. With the aid of computers to fit the data to an equation, however, most drugs can be modeled to one or two compartments. It is unusual to require more complex considerations such as a three-compartment model. A prominent example of such complexity is amiodarone, which usually requires three or more exponents to describe its disposition.

A drug administered by a route other than an intravenous one first must be absorbed into the circulation. A semilog plot of plasma concentration against time shows an initial increase in concentration as drug is absorbed, followed by equilibration of drug between central and peripheral compartments, and a linear elimination phase with a slope identical to that evidenced with intravenous administration. Absorption, like elimination, is usually a first-order process; a constant fraction of the total drug present is absorbed per unit of time. As the amount of drug remaining to be absorbed diminishes, so does the rate of absorption. Sustained release preparations, in which drug slowly dissolves out of a wax or polymer matrix, are designed to be roughly analogous to a constant-rate infusion. This may be zero-order (independent of the total amount of drug) absorption (i.e., a constant amount of drug is absorbed per unit of time). Zero-order absorption is the case whenever a reservoir of drug is available to replace the amount absorbed.

Pathways of elimination (e.g., biotransformation, renal tubular secretion) may become saturated at high doses of drug, and elimination may change from a first-order to a zero-order process. This is the case for elimination of propranolol (18), phenytoin (19), and possibly diltiazem (20), which exhibit first-order elimination at low doses and zero-order elimination at high doses, leading to disproportionately large increases in plasma concentration with increasing dose (eFig. 40.0.6).

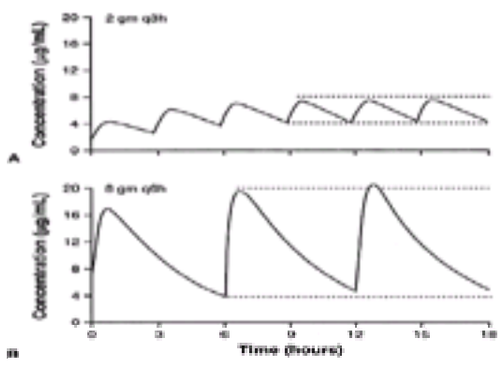


***e*FIGURE 40.0.6** Effect of increasing phenytoin dose on plasma phenytoin concentration. Dashed lines indicate therapeutic window. At low doses, increasing the dosage produces a proportional increase in plasma concentration. At high doses, as elimination pathways become saturated, increased dosage produces a disproportionately large increase in plasma concentration. (From Richens A, Dunlop A. Serum phenytoin levels in the management of epilepsy. *Lancet* 1975;2:247, with permission.)

The mathematical relationships describing the previously mentioned processes provide the basis for constructing dosing schedules and are of practical utility in understanding and interpreting plasma drug concentration information (21,22).

Drug Accumulation

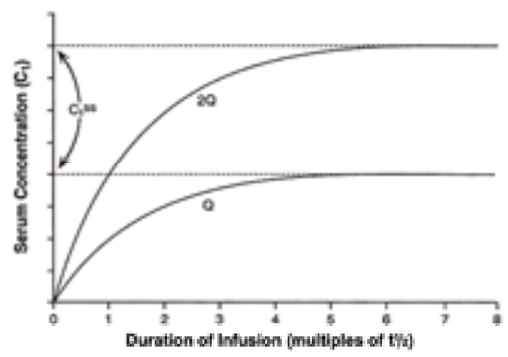
Most drugs are given as multiple doses to maintain an effective plasma concentration. In practice, there is fluctuation about a mean plasma concentration between doses. The degree of thefluctuation depends on the length of the dosing interval relative to the elimination half-life. If the dosing interval is short relative to the half-life, the fluctuation will be small, but the degree of accumulation will be large. Conversely, a long dosing interval combined with a short half-life results in wide fluctuation but little accumulation. By definition, the plasma concentration of a drug administered at intervals corresponding to its half-life shows a twofold fluctuation between minimum and maximum plasma concentration. The acceptability of a dosage regimen depends more on the width of the therapeutic window than on the half-life (eFig. 40.0.7); in fact, few drugs are administered every half-life (23).



***e*FIGURE 40.0.7** Relationship among the elimination half-life, the width of the therapeutic window, and the frequency of dosing for a rapidly absorbed and eliminated drug (in this case, procainamide). These computer simulations of plasma concentrations show that frequent dosing is required when the therapeutic window is narrowing (4 to 8 µg per mL) **(A)** to avoid excessively high or low values. If the therapeutic window were wider (e.g., 4 to 20 µg per mL) **(B)**, larger doses could be given less frequently. Because the elimination half-life (139 minutes) is not changed, the time to reach steady-state conditions is the same. (From Roden DM, Woosley RL. Application of pharmacologic principles in the evaluation of new antiarrhythmic agents. In: Morganroth J, Moore EN, eds. *Sudden cardiac death and congestive heart failure: diagnosis and treatment*. Amsterdam: Martinus Nijhoff, 1983:13, with permission.)

Steady State

By definition, following multiple dosing or continuous infusion, a drug reaches *steady state* when the rate of entry into the body equals the rate of elimination (i.e., true equilibrium). An important concept is that the time taken to reach steady state or to eliminate the drug completely depends only on the elimination half-life of the drug or active metabolites, if these accumulate. *e*Figure 40.0.1 illustrates the relationship between half-life and drug accumulation or elimination. It is evident that after approximately five half-lives, either process is virtually complete. Neither increasing the dose nor increasing the rate of administration hastens the achievement of the plasma concentration plateau; such maneuvers simply increase the final plasma concentration achieved (*e*Fig. 40.0.8). Loading doses (see Loading Dose Calculations, later in this chapter) may allow one to reach an effective concentration sooner, but do not alter the time ultimately required to reach true steady state.



***e*FIGURE 40.0.8** Plasma concentration against time for constant infusion at rates Q and 2Q. Note that plateau concentration is reached at the same time, independent of Q, but that the plateau concentration achieved depends on Q. C_1^{SS} is the concentration at steady state for each of the two infusion rates.

It also follows that factors influencing the elimination half-life also affect the time taken to reach steady state. For instance, a reduction in liver blood flow due to diminished cardiac output or treatment with beta-blockers or cimetidine can prolong the half-life of drugs that are extensively metabolized in the liver. Renal dysfunction can slow clearance and thus prolong the half-life of drugs eliminated by the kidneys. In either case, it will take correspondingly longer to reach steady state, so that premature dose escalation based on the usual time taken to achieve plateau plasma levels would lead to excessive accumulation of drug. Chronic administration of drug can also be associated with changes in elimination kinetics, especially for drugs eliminated mainly by the liver and for those with hemodynamic effects that reduce splanchnic blood flow. For example, the elimination half-life of verapamil is approximately twice as long during long-term oral therapy (24), so that less frequent dosing is required to prevent toxicity.

Initial Dose Calculations

The selection of an initial dose of a drug must take into account the pharmacokinetics of the drug and the clinical objectives of therapy. In most cases, the drug accumulates to some degree during chronic therapy. Unless the patient requires urgent treatment, it is often preferable to allow the drug to accumulate to steady state without the use of a loading dose (see following section). The initial dose should be one that is likely to be safe and well tolerated when steady state is reached. If one has an estimate of the volume of distribution of the drug and a target plasma concentration, it is a simple matter to estimate the initial dosage that will produce that concentration. As shown in *e*Figure 40.0.7, it is essentially the definition of the word *concentration*. Concentration = mass/volume or, stated more appropriately,

$$\text{Target concentration} = \frac{\text{Dosage of drug}}{\text{Volume of distribution}}$$

Loading Dose Calculations

In many instances, it is not feasible to wait four to five half-lives before effective plasma concentrations are attained. In such cases, a loading dose can be employed to attain an initial rapid increase in plasma concentration followed by maintenance doses to keep the plasma concentration within the therapeutic range. It always takes five half-lives to achieve steady-state concentration, but an effective plasma concentration may be attained sooner. The price paid is an increased risk of attaining toxic plasma levels after an initial large dose. Loading doses may not be feasible if a drug has an active metabolite that accumulates slowly and is required for optimal clinical response. In addition, should the maintenance dose be too high or too low, side effects or loss of efficacy, respectively, will develop after an apparently calculated beneficial response to the loading dose. For these reasons, reassessment of a patient's response at true steady state is always essential.

In cardiology, one of the most common applications of loading dosages is in the treatment of ventricular arrhythmias with drugs such as lidocaine. In this clinical situation, it is desirable to produce an antiarrhythmic effect rapidly. The relatively long half-life of lidocaine (approximately 2 hours) means that it will be several hours before lidocaine accumulates to effective concentrations if a patient were simply placed on a maintenance infusion. The following is a general discussion of how the principles of a loading dosage can be applied to the use of lidocaine.

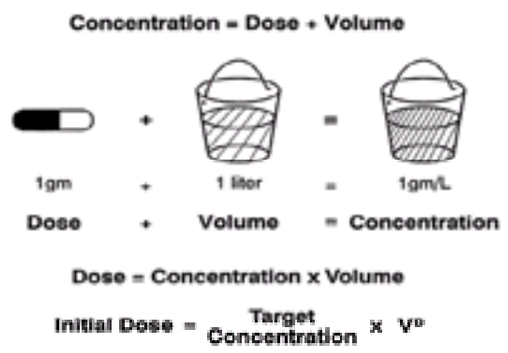
A loading dose ideally would be adequate to produce a concentration in the middle of the therapeutic window (3 µg per mL) when the drug has totally distributed throughout the body. For a 75-kg person with normal hemodynamics and organ function, however, the total volume of distribution of lidocaine at steady state averages 100 L. *e*Table 40.0.2 and *e*Figure 40.0.9 describe the concepts and the equation to calculate the magnitude of a loading dose when the volume of distribution and the desired concentration are known. However, calculation of the loading dose for the volume of distribution at steady state would result in a loading dose of 300 mg of lidocaine, a dose that would be extremely toxic if given at one time. We know that lidocaine, when administered intravenously, behaves according to the kinetics of a linear two-compartment model system. Initial concentrations after a rapid injection indicate that the volume of the central compartment is approximately 33 L, approximately one-third of the total volume of distribution. Administering one-third of the total loading dose should produce a plasma level of 3 µg per mL in the central compartment, which then declines with a distribution half-life of 8 minutes. After 8 minutes, the level should fall to 1.5 µg per mL because half of the initial dose (50 mg) has distributed into the peripheral compartment and replacement with a 50-mg injection should return the concentration to 3 µg per mL. If no additional loading dose is given at this time, the plasma concentration continues to fall below the usual therapeutic range. The maintenance dose should accumulate to reach the therapeutic range in several hours. During this period, however, the patient's arrhythmia may recur, and the patient may be mistakenly labeled "refractory" to lidocaine. As shown in *e*Figure 40.0.10, a series of loading injections every 8 minutes prevents the plasma concentration from falling below the therapeutic window and thereby prevents the

patient from becoming vulnerable to the development of lethal arrhythmias. eTable 40.0.3 displays a simplified version that is easy to remember and appropriate for most male or female patients of average size (approximately 70 kg). Both tables list the reduction in loading doses necessary for patients with heart failure in whom the volume of distribution is usually reduced to 50% of normal.

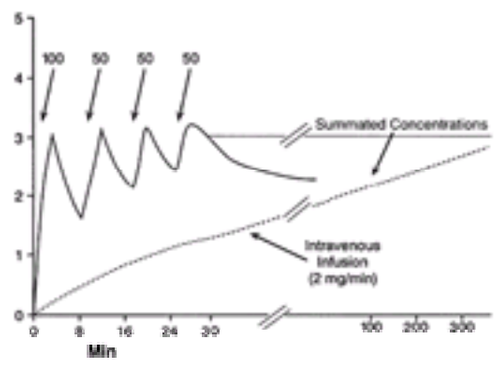
***e*TABLE 40.0.2** PROTOCOL FOR RAPIDLY PROVIDING PLASMA LIDOCAINE CONCENTRATIONS OF 3 µG PER ML[a]

			Load by body weight (mg/kg)	
Time	**Dose**		**Healthy patient**	**Patient with heart failure**
0	First bolus	Loads central compartment	1.5	0.9
8 min	Second bolus	Replaces loss in first half-life	0.8	0.4
16 min	Third bolus	Replaces loss in second half-life	0.8	0.4
24 min	Fourth bolus	Replaces loss in third half-life	0.8	0.4
		Total body load	3.9	2.1

[a]Protocol is based on loading dose = volume of distribution × desired plasma concentration = 1.32 L/kg × 3 µg/mL = 3.9 mg/kg. The patient should be monitored carefully and evaluated before each bolus injection (see text).



***e*FIGURE 40.0.9** The volume of distribution is based on the definition of the term *concentration*. Knowledge of the dose and the final concentration allows one to calculate the theoretical volume of distribution. Also, the initial dose can be calculated by multiplying the target concentration by the volume of distribution (V^D).



***e*FIGURE 40.0.10** Lidocaine loading regimen. An intravenous bolus of 100 mg reached 3 mg per mL (the target) but rapidly distributed to subtherapeutic levels (less than 1.5 mg per mL). To maintain concentrations in the therapeutic range, a series of replacement boluses should be given unless the patient has side effects (e.g., persistent tinnitus, heart block, hypotension, lethargy, slurred speech, seizures).

***e*TABLE 40.0.3** LIDOCAINE LOAD FOR AVERAGE PATIENT (MG)[a]

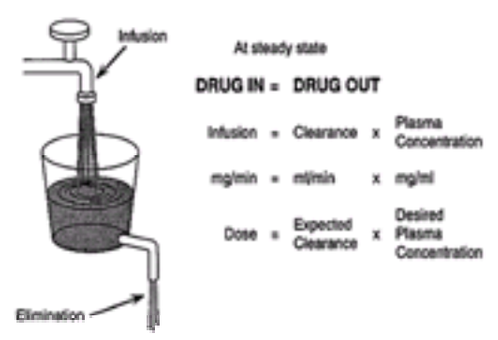
	Time (min)			
Patient type	**0**	**8**	**16**	**24**
Normal	100	50	50	50
With congestive heart failure	50	25	25	25

[a]Stop load for central nervous system symptoms, hypotension, heart block, and bradycardia (see text).

It must be emphasized that these guidelines are based on average values, and there is a large variance in the pharmacokinetic data for lidocaine. For example, the volume of the central compartment has been found to vary from 33 to 60 L. This means that the peak plasma concentration after a bolus injection varies up to twofold in healthy individuals. For this reason, one should choose the lower value of 33 L to calculate the initial loading bolus dose. Awareness of this variability is essential and requires that the patient be evaluated continuously while receiving lidocaine. During the loading process, the patient's electrocardiogram, blood pressure, and mental status should be monitored; at the first sign of excessive lidocaine administration, the loading process should be stopped.

Maintenance Dose Calculations

The selection of a maintenance dose is based on the concept that at steady state the amount of drug cleared from the body must be replaced. If the volume of plasma cleared of drug per unit of time (clearance) and the target concentration are known, multiplying these values yields the mass of drug cleared per unit of volume. eFigure 40.0.11 and eTable 40.0.4 and eTable 40.0.5 demonstrate how this calculation can guide the selection of an infusion rate that can be individualized for patients with heart failure or liver disease. eTable 40.0.4 lists the calculated dosages based on body weight in kilograms, and eTable 40.0.5 gives a simplified dosing regimen estimated for an average 75-kg adult.



***e*FIGURE 40.0.11** Calculation of a maintenance dose based on the principle that, at steady-state equilibrium, the amount of drug administered must equal what is eliminated.

***e*TABLE 40.0.4** PROTOCOL FOR MAINTAINING PLASMA LIDOCAINE CONCENTRATION OF 3 µG PER ML[a]

Patient	**Infusion rate (µg/kg/min)**
Normal (clearance = 10 mL/min/kg)	30
Heart failure (clearance = 6 mL/min/kg)	18

[a]Protocol based on dose = desired plasma concentration × clearance (e.g., = 3 µg/mL × 10 mL/min/kg = 30 µg/kg/min).

***e*TABLE 40.0.5** LIDOCAINE MAINTENANCE THERAPY FOR AVERAGE PATIENTS

Healthy patients	2–3 mg/min or 30 µg/kg/min
Heart failure	1–3 mg/min or 19 µg/kg/min
Liver disease	0.5–1.0 mg/min or 10 µg/kg/min

Again, it must be emphasized that these are first approximations of dosage, and all patients must be monitored to detect individuals who fall at the extremes of the normal distribution. Because some patients have a half-life of elimination of 4 to 5 hours, accumulation may occur for up to 24 hours. Late development of CNS side effects, disorientation, or lethargy should prompt the suspicion of lidocaine toxicity, which can be easily verified with a lidocaine plasma assay. Any patient who develops late CNS symptoms while receiving lidocaine is a likely candidate for lidocaine toxicity. The utility of plasma concentration monitoring in this and other situations is discussed in the following sections.

CAUSES OF VARIABILITY IN DRUG RESPONSE

Liver Disease

Chronic liver disease has the greatest effect on drugs that are normally highly cleared by the liver. Both drug-metabolizing activity and hepatic blood flow may be reduced, with portosystemic shunting diverting portal blood (and unchanged drug) directly to the systemic circulation. These changes reduce hepatic clearance and thus raise plasma concentrations of unchanged drug. For most drugs, reduction in dosage or dosage interval is necessary to avoid toxicity. For a drug with active metabolites, the net effect would depend on the pharmacokinetics and pharmacodynamics of the metabolites compared with the parent drug. In cases in which therapeutic benefit is largely derived from active metabolites, another agent, not subject to hepatic metabolism, should be considered. Aside from changes in drug disposition, there is some evidence of pharmacodynamic change for certain drugs in patients with hepatic disease. For example, the CNS effects of benzodiazepines are exaggerated in such patients, particularly in the presence of hepatic encephalopathy.

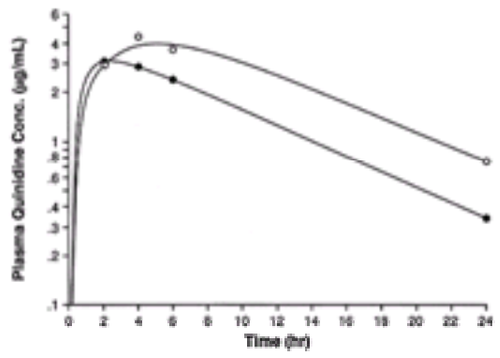
Renal Disease

Obviously, renal disease has the greatest effect on those drugs eliminated mainly by the kidneys. Renal disease can also affect protein binding (25) (hypoalbuminemia; presence of binding inhibitors or altered affinity of protein for drug), drug metabolism (diminished activity of some enzyme systems including *N*-acetyltransferase), and urinary pH (alkalinization can alter tubular reabsorption of drugs and the degree of ionization of weak bases, resulting in diminished excretion).

It is difficult to predict the interplay and relative contribution of these various effects to changes in drug disposition. For drugs that are mainly eliminated by renal excretion, one can expect decreased clearance and prolongation of elimination half-life, often in direct proportion to the decrease in creatinine clearance. For example, the half-life of digitoxin, elimination of which involves mainly extrarenal pathways, does not change in renal failure, whereas the half-life of digoxin, which is largely eliminated by the kidneys, increases with severe renal failure from 36 hours to approximately 4 days. Sotalol and the active metabolite of procainamide, *N*-acetylprocainamide (NAPA), are eliminated by the kidneys and can accumulate to toxic levels in renal failure (26,27). Obviously, if accumulation to toxic levels is to be avoided, less drug must be administered, by either increasing the dosing interval or decreasing the dose administered.

Cardiac Failure

Decreased cardiac output and increased sympathetic tone in patients with congestive heart failure result in diminished blood supply to the gut, liver, and kidneys, and in poor peripheral perfusion. These changes have implications for drug absorption, distribution, and elimination. Delayed and incomplete absorption of drugs in patients with cardiac failure can be expected. For instance, cardiac patients may absorb approximately half as much quinidine as healthy subjects and take twice as long to reach peak plasma concentration (28). Because of the reduced volume of distribution, however, plasma concentrations attained by cardiac patients may be higher than those in control subjects (*e*Fig. 40.0.12).



***e*FIGURE 40.0.12** Plasma quinidine concentrations in healthy subjects (*closed circles*) and in congestive heart failure patients (*open circles*) following oral administration of 600 mg of quinidine sulfate. The data points are the mean levels in ten subjects. (From Crouthamel WG. The effect of congestive heart failure on quinidine pharmacokinetics. *Am Heart J* 1975;90:335, with permission.)

A decreased volume of distribution in cardiac failure has also been described for disopyramide (29) and lidocaine (30). It is important to recognize that, even in patients with fluid retention and “volume excess,” the volume of drug distribution can be *reduced*, increasing plasma concentrations and resulting in excess drug action. Cardiac failure may also result in significant changes in drug clearance, both for drugs with a clearance dependent mainly on organ blood flow and for those with a clearance determined by drug-metabolizing enzyme activity. Cardiac failure decreases perfusion of the liver and kidneys, and a decrease in drug-metabolizing enzyme activity has been found in liver biopsy specimens from patients with congestive cardiomyopathy. A direct relationship between plasma clearance of lidocaine and cardiac output has been described, with a mean 39% decrease in lidocaine clearance among heart failure patients compared with healthy subjects (30).

Depending on the relative magnitude of changes in clearance and volume of distribution, the elimination half-life may be unaffected or prolonged. Despite changes in clearance, the mean elimination half-life of lidocaine (30), procainamide (31), and quinidine (28) appear similar in patients with and without heart failure, whereas those of disopyramide (29) and mexiletine (32) appear to be prolonged in patients with heart failure and require a proportionately longer time to reach steady state. It is important to recognize that, although half-life may not be prolonged in congestive heart failure, clearance is usually reduced and total dosage must be reduced proportionately.

Clearly, drug therapy in patients with cardiac failure requires initial low doses with escalation under careful supervision. Prolongation of elimination half-life may also warrant less frequent dosing and less frequent changes of dose because the length of time to reach steady-state plasma concentration is increased.

Acute Myocardial Infarction

The patient with acute myocardial infarction presents a special challenge with respect to drug therapy. Altered hemodynamics and increased levels of AAG can markedly affect the disposition of any drug administered following myocardial infarction.

Lidocaine is one of the most frequently administered and probably the most extensively studied drug in the setting of acute myocardial infarction. Administration of lidocaine to patients suspected of having sustained an infarction results in a broad range of plasma levels with accumulation of lidocaine in plasma during a constant infusion in patients with confirmed infarction. These changes can be largely explained by an increase in plasma protein binding as a result of increased levels of AAG (33). Although the total plasma concentration increases in parallel to AAG concentration, the free fraction declines, and free lidocaine concentration remains fairly constant. Therefore, higher than usual plasma concentrations may be well tolerated in acute myocardial infarction (concentrations of 6 to 12 µg per mL, normally considered toxic, have been reported to be well tolerated several days after myocardial infarction) and indeed may be necessary to maintain adequate free lidocaine levels for antiarrhythmic effect. Similarly high plasma concentrations of drug when administered to patients with myocardial infarction have been reported for quinidine (34) and disopyramide (35). In addition to increased total plasma concentration of drugs binding to AAG, the changes in drug disposition described for lowered cardiac

output and renal impairment may also apply following myocardial infarction.

A further consideration in drug therapy following myocardial infarction is that the usual temporal relationship between drug administration and effect may be altered. The heart is normally a highly perfused organ so that most drugs in plasma rapidly equilibrate with myocardial tissue. In infarction, however, the areas of poorly perfused myocardium appear to accumulate (and eliminate) drug far more slowly than does the rest of the heart (36). Thus, such areas function as peripheral, rather than central, pharmacokinetic compartments and, depending on the drug's effector site, there may be a corresponding delay between drug administration and pharmacologic effect.

Age

Drug disposition in both the elderly and the very young can vary widely from that in the young adult population in which it is usually defined during drug development. Deterioration or immaturity of renal and hepatic function can result in significant changes in the pharmacokinetic variables. For example, elderly patients have a reduced response to beta-receptor agonists and antagonists, probably because the number of beta-receptors declines with age (37). On the other hand, elderly patients show an increased sensitivity to benzodiazepines (38) and coumarin anticoagulants (39). However, many drugs have not been systematically evaluated in either the very young or the elderly, and information has often been gained through anecdotes or adverse clinical experiences, sometimes at considerable human expense.

Biologic Sex

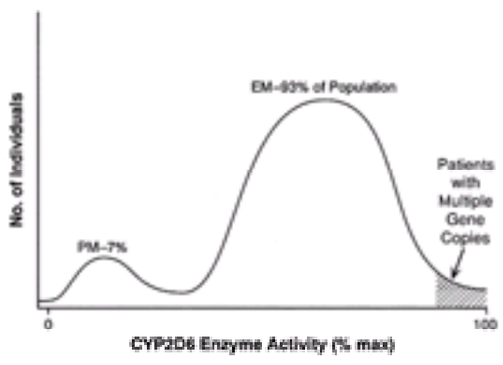
In more recent years, we have become aware of the importance of examining the importance of sex in determining drug response. However, there are still limited data comparing drug response in men and women. Numerous studies have demonstrated pharmacokinetic differences between men and women, mainly for drugs metabolized by CYP3A4. However, none of the differences is large enough to be clinically relevant.

On the other hand, Makkar et al. (52) called attention to the greater risk of torsades de pointes in women treated with antiarrhythmic drugs. This retrospective metaanalysis was supported by two clinical studies in which the investigators demonstrated a greater sensitivity of the QT interval in female than male subjects to ibutilide (52a) or quinidine (53). Drici et al. (54) have observed that treatment with dihydrotestosterone can reduce the QT response to quinidine in isolated perfused rabbit hearts. These studies have demonstrated, for the first time, clear sex differences in myocardial response to drugs and point out the need for further studies with other drugs, especially those affecting cardiac repolarization.

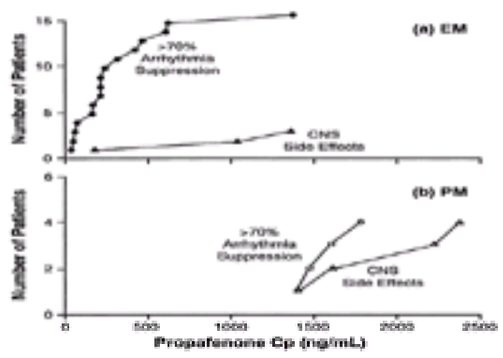
Metabolic Polymorphism

Although in most cases drugs are metabolized to compounds with little or clinically inconsequential pharmacologic activity, in some instances metabolites can contribute significantly to the efficacy or toxicity observed after administration of the parent drug. For instance, the monoethylglycine xylidide metabolite (MEGX) of lidocaine possesses some antiarrhythmic activity, and the glycine xylidide metabolite potentiates the convulsant properties of both lidocaine and MEGX (40). Certain metabolites of quinidine may be antiarrhythmic and may contribute to QT prolongation seen during therapy (41). NAPA, the major metabolite of procainamide, can be antiarrhythmic in its own right, with electrophysiologic and clinical effects distinct from procainamide. Therefore, NAPA may or may not contribute to the antiarrhythmic actions of procainamide. However, high concentrations of NAPA can certainly contribute to toxicity, including torsades de pointes, a syndrome of polymorphic ventricular tachycardia occurring in a setting of marked prolongation of the QT interval. Acetylator phenotype, which markedly influences the response to drugs that are substrates for *N*-acetyltransferase, is genetically determined and bimodally distributed. In white and black populations, the distribution between slow and fast acetylators is approximately equal, whereas Asian populations are predominantly (90%) rapid acetylators. Procainamide-induced lupus occurs more frequently and earlier in slow acetylators. However, there is no readily available way of predicting acetylator phenotype without administering a drug. Therefore, one should monitor both parent drug and metabolite levels on at least one sample in patients receiving these drugs. A NAPA to procainamide ratio greater than unity when dosing is at steady state (and renal failure is absent) indicates a rapid acetylator phenotype (42). The clinician should be aware that the patient may be responding to parent drug, metabolite, or both.

Bimodal distribution of enzymes involved in oxidative metabolism has been described for debrisoquine (43), propranolol (44), flecainide, timolol, metoprolol (45), carvedilol (46), and propafenone (*e*Fig. 40.0.13) (4). As described previously, 7% of the population lack the major enzyme responsible for biotransformation of these drugs, CYP2D6. The clinical implications in these poor metabolizers depend on the relative potencies and pharmacokinetics of the arent drug and metabolites. For example, in CYP2D6 extensive metabolizers, the oral bioavailability of propafenone (a drug with sodium channel and beta-blocking actions) is approximately 25% to 35% as a result of extensive presystemic metabolism; the elimination half-life of propafenone in these individuals is approximately 5.5 ± 2.0 hours (range, 2 to 10 hours) (4). Apparent elimination half-lives of 5-hydroxy propafenone, a metabolite with sodium channel blocking activity but little potency as a beta-blocker, on the other hand, are considerably longer (9.0 ± 1.5 hours) (47). In contrast, in poor metabolizers (7% of the population), oral bioavailability is approximately 90% to 95%, with a propafenone elimination half-life of 17 ± 8 hours. These differences result in a distinct plasma drug-concentration profile and pharmacodynamic consequences in poor metabolizers (eFig. 40.0.14), because certain metabolites of propafenone have antiarrhythmic activity equal to that of propafenone.



***e*FIGURE 40.0.13** The graph displays the distribution pattern for the activity of the CYP2D6 enzyme activity in a white population. Most patients are either homozygous for the normal (wild-type) alleles or are heterozygous and have one mutant allele. These are termed *extensive metabolizers* (EM). Ninety-three percent of the population are extensive metabolizers with two wild-type alleles, but 7% express the highest activity because they have multiple copies of the CYP2D6 gene. Seven percent of the population inherit two alleles for one or more of the seven known mutations that result in low or absent levels of enzyme activity and are termed *poor metabolizers* (PM). In African-American or Asian populations, the PM incidence is 1% to 2%.



***e*FIGURE 40.0.14** Predose plasma concentration (Cp) of propafenone versus cumulative frequency of antiarrhythmic response and central nervous system (CNS) side effects in patients with the CYP2D6 extensive metabolizer (EM) phenotype **(a)** and poor metabolizer (PM) phenotype **(b)**.

Receptor Polymorphism

In more recent years, it has become apparent that some of the variability in response to drugs is caused by inherited differences in the structure of the receptors for drugs. Polymorphisms in the beta-receptor have been associated with the development of tolerance to beta-agonists in asthma (54a). Mutations in the serotonin transporter are thought to be responsible for depression in Parkinson's patients (54b). In these cases, the response to a given drug depends on whether it has the same action at the mutated receptor as at the wild-type receptor. This is an active area of research and one that has a great deal of potential to reduce much of the empiricism now such a great part of therapeutics.

Drug Interactions

Drug interactions can generally be classified as either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions are the result of processes that lead to a change in the disposition of one or more drugs and result in a change in clinical response. The most common form of a pharmacokinetic interaction is when one drug induces or inhibits the metabolism, elimination, or both of another, and the steady-state concentration of a drug is lowered or raised. Pharmacodynamic interactions result when drugs have separate actions that are either augmented or antagonized when the drugs are used together. A common example is when drugs that block beta-receptors and calcium channels are given together and produce excessive slowing of atrioventricular nodal conduction and heart block. It is important to note, however, that not all drug interactions are detrimental. Many times in medicine, pharmacokinetic interactions are used to reap a therapeutic advantage. The best example again involves beta-blockers and calcium channel blockers used synergistically to treat angina pectoris or hypertension.

ROLE OF THERAPEUTIC DRUG MONITORING

The usefulness of drug plasma concentrations as a means of guiding therapy presupposes a correlation between pharmacologic effect and plasma concentration of a drug. Although there generally is a correlation, plasma concentration can be misleading in some instances. For example, a pharmacologic effect may persist even after drug has been eliminated from plasma. Often, this may be accounted for by the presence of an active metabolite (e.g., NAPA) or some irreversible action of the drug that requires physiologic regeneration for termination of effect (e.g., depletion of catecholamine stores by reserpine). In some cases, a temporal delay between plasma concentration and effect may be the result of the drug's receptor site residing in a poorly perfused tissue or in a tissue into which drug diffuses slowly.

Further complications are poorly defined therapeutic ranges [the usually quoted therapeutic range for quinidine is derived using a nonspecific assay and is based mainly on 30-year-old data on conversion of atrial fibrillation (48)] and great interpatient variability in response. Part of this variability is explained by the fact that the free unbound drug is considered pharmacologically active, whereas most therapeutic ranges are based on total plasma concentration of the drug (free drug plus that quantity bound to plasma protein). The extent of binding to plasma protein varies considerably. A range of 51% to 87% among healthy subjects has been quoted for quinidine (49); it is likely that variability among patients is greater. The situation could be improved by monitoring free drug rather than total plasma drug concentration, because the amount of free drug should correlate better with pharmacologic effect. For example, acute electrocardiographic changes caused by intravenous quinidine (50) and disopyramide (51) correlated well with free, but not total, drug levels. However, free levels of drug are rarely measured, partly because they are often too low for accurate measurement by conventional methods. It also should be mentioned that drug concentrations in whole blood or serum are not equivalent to plasma concentration. The ratio of blood to plasma concentration is related to the hematocrit, the affinity of the drug for blood cells, and the protein binding. Determination in serum carries the potential of loss of drug adsorbed to clots.

The specificity of the drug assay also should be taken into consideration when interpreting drug-level data. Is the assay specific for unchanged drug, or does it also include metabolites that may themselves possess pharmacologic activity and distinct pharmacokinetics Newer, more specific assays that measure parent drug alone may not correlate well with a therapeutic range based on older nonspecific assays.

Drug-level data can be useful only if accompanied by some knowledge of the dosing history, when the sample was obtained relative to the time of dosing, concomitant medication, and other disease processes. Only then can the measured concentration be evaluated in a meaningful way. Finally, drug levels are no substitute for clinical judgment. Some patients respond (or even develop side effects) at low concentrations, whereas others may require high concentrations or tolerate them without side effects.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Therapeutic clinical trials have led to major advances in the treatment of cardiovascular disease, but none has had a more dramatic influence on the overall practice of medicine and the science of clinical trial methodology than the Cardiac Arrhythmia Suppression Trial (CAST). CAST demonstrated the potential error of extrapolating results in one population to another without confirmation of overall clinical benefit (i.e., drugs effective in suppression of life-threatening ventricular arrhythmias were found to increase mortality in a lower risk population). The results of CAST have made regulatory agencies reluctant to assume drugs are safe and effective unless tested in the relevant population. For example, aspirin prevents recurrent strokes and heart attacks, but is it safe and effective for primary prevention? The other obvious message from CAST emphasizes the value of having a placebo group. A therapy may not be effective even if the results are better than historical controls. Subsequently, the negative results seen with potassium channel blockers in the Survival with Oral d-Sotalol Study and the modest response, at best, to amiodarone in large clinical trials, have reinforced the lessons we learned in CAST. Another lesson from these trials is that drugs should not be developed to block normal ion channels. The targets for drug development should be selected based on an understanding of the mechanism of the disease. We do not yet understand the mechanism of sudden cardiac death at the cellular or metabolic level. Only with that knowledge will we be successful in designing new effective therapies.

But are therapeutics being practiced optimally? Fewer than one-half of the patients with heart failure who are candidates for beta-blockers or ACE inhibitors are prescribed these potentially life-saving drugs. Over 50% of post–myocardial infarction patients fail to receive potentially life-saving beta-blocker therapy, but an equal number receive potentially harmful calcium channel blockers. Twenty-three percent of prescriptions for the elderly have been judged inappropriate or dangerous. The second most common cause of malpractice suits is a prescription error. The data indicate that there is a serious need for better understanding of the drugs being prescribed, yet the changes in medical care today discourage this. Managed care organizations and insurers confront physicians with formularies that demand that their patients receive the lowest-bid drugs in each class. Physicians trying to prescribe the drug that they know best in a class are coerced to change their patients to the drug preferred by their insurers because it costs less. Physicians must master the needed information about therapeutics and stand firm as advocates for their patients.

THE FUTURE

The ability to determine the genetic basis of disease and genetic predictors of response to drugs is beginning to yield strategies that will reduce the current level of empiricism that complicates therapeutics. Today, we treat hypertension by empirically suggesting salt restriction and diuretic therapy. The only logic in the decision-making process is that certain populations (e.g., the elderly, African-Americans, whites) respond to a given class of drug. With improved understanding about the molecular mechanism for hypertension, it should be feasible to target therapy more specifically. As the molecular mechanisms of diseases are determined, more specific therapy will surely result.

It is currently possible to use polymerase chain reaction–based techniques to identify mutations responsible for common polymorphisms of cytochrome P450, CYP2D6, and CYP2C19. This knowledge can predict individuals at risk for flecainide toxicity; excessive beta-blockade with timolol, propranolol, or metoprolol; and unexpected responses to many other potent cardiac and neurologic drugs. The routine availability of P450 genotyping should enable physicians to choose drugs and dosages more intelligently, reducing the number of titrations necessary to obtain an optimal response and reducing the incidence of excessive drug effects. This will undoubtedly become routine in future therapeutics.

The basic principles of pharmacology will change dramatically as we are able to identify the genetic factors responsible for the variability in response to drugs. Genetic polymorphisms will be identified and drugs will be selected to act on genetically defined components of physiology or pathology.

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ROLE OF THE CARDIOLOGY CONSULTANT

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The relationship between generalists and specialists and the role that each has in the overall care of patients has become an increasingly important issue in health care delivery and is undergoing dramatic changes. *Consultation* is the act of seeking advice regarding diagnosis and management, and *referral* is transferal of the patient to another physician for a specific therapy or management of a particular medical problem while the primary (or referring physician) provides general care. Consultation may be a major component of a cardiologist's practice, but a consultant's good clinical judgment only has an impact on a patient's care if recommendations are communicated effectively.

During consultation, ideally, there should be an exchange of information between the primary physician and the cardiology consultant, as well as coordination of care that ensures that patients receive care from the physician who is most likely to be able to provide a favorable outcome at the lowest cost. The consultant should determine whether the clinical situation is an emergency or whether it is urgent or elective. Emergency or urgent consultations should be discussed with the primary physician. It is important for the consultant to verify all information communicated by the physician. The most important component of successful cardiology consultation is effective communication with patients and primary physicians. The consultant should provide contingency plans and remember that follow-up increases compliance with recommendations.

Preoperative risk assessment is a frequent reason for cardiac consultation. As morbidity and mortality related to noncardiac surgery steadily decrease, cardiovascular management strategies that are known to improve long-term outcomes should guide decision making in the perioperative setting. Several factors may limit the predictive value of the clinical indices. There is extensive published data on the role of radionuclide perfusion imaging for preoperative risk stratification. Stress echocardiography is also evolving as a valuable tool for identifying high-risk patients. Risk reduction is the cornerstone of preoperative evaluation and management. Medical treatment and coronary revascularization procedures, when used appropriately, may significantly reduce perioperative cardiac events.

The preoperative cardiac consultation also represents an opportunity to initiate or modify cardiac care, including primary and secondary preventive measures. A stepwise approach to perioperative cardiac risk assessment, as set forth by recent joint American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, should be used.

HISTORICAL PERSPECTIVE

Physicians have collaborated in the care of patients since antiquity. Hippocratic writings dating back to 400 BC refer to the importance of consultation in challenging medical cases (1). In 1927 (for the first edition of his textbook), Cecil explained why the work required more than one author:

"The rapid growth of medical science during the last few years has made it almost impossible for a single individual to master the entire field. In Internal Medicine, as in other branches of human knowledge, the age of specialism has of necessity arrived, and some of our ablest practitioners even devote themselves in great measure to one disease . . ." (2)

In 1940, approximately 1,000 American physicians considered themselves to be heart specialists, but few of them had received formal training in cardiology (3). Earlier in the twentieth century, possession of an electrocardiograph (ECG) defined a physician as a cardiovascular specialist. With the trend toward specialization, the number of cardiovascular specialists has increased substantially. Today, cardiologists still fill the traditional roles of teachers, researchers, and care providers, but the field has diversified to include endeavors from molecular biology to disease prevention to cardiac imaging to coronary intervention (3). In 1965, the number of self-designated cardiologists was 1,901. The ACC on its fiftieth anniversary reported 25,214 members, including 34 masters and 20,525 fellows (4). In 1999 and 2000, there were 190 cardiology training programs and 2,164 trainees (5). Burgeoning numbers of cardiovascular specialists have contributed to substantial advances in cardiovascular knowledge and patient care.

Foot and associates (6) studied the effects of the changing demographics of the U.S. population on the cardiology workforce. They estimated that the U.S. population would reach 275 million in 2000, 297 million in 2010, and 397 million in 2030. As a result of the World War II baby boom, the population is aging, and the number of senior citizens (age >65 years) will increase from 12.6% to 20.0% of the population between 2000 and 2030. Due to the increasing prevalence of heart disease, deaths from heart disease are projected to increase by 128% between 2000 and 2050 (6). This suggests that demand for cardiovascular specialists in the future will increase. Unless a revolutionary breakthrough in the management of cardiovascular diseases occurs, this demand will be evident in the next 5 to 10 years and will continue until at least 2030.

Although consultation can be a major component of a cardiologist's practice, the skills necessary to provide coordinated patient care are generally learned by trial and error. Primary care providers may seek some consultants, but other consultants may have difficulty converting knowledge gained through years of specialty training and practice into cost-effective cardiovascular consultation (7). The hallmark of successful cardiology consultation is effective communication with referring physicians. A consultant's good clinical judgment only has an impact on a patient's care if recommendations are communicated effectively (8). This chapter focuses on the goals and components of clinical assessment, the context in which such assessment occurs, and the function and elements of effective consultation.

RELATIONSHIP TO REFERRING PHYSICIANS

Generalists and surgeons usually have some knowledge and experience in treating patients with cardiovascular diseases, and therefore thresholds for referral to a cardiologist will vary. Referral may be influenced by a practitioner's level of diagnostic certainty (9), the availability of consultants (10), and the accessibility of diagnostic tests (11). Ongoing changes in the American health care system are likely to influence the route by which patients reach the care of a cardiovascular specialist, and self-referral by patients likely will be dramatically reduced if development of managed care continues to its logical conclusion. The Physician Workforce Advisory Committee of the ACC performed a membership survey to quantify the amount of cardiovascular care provided by noncardiologist primary care physicians. Figure 41.1 summarizes the type of cardiovascular procedures performed by the primary care physicians. The most commonly performed procedure was ECG; 44% of internists performed exercise stress tests, compared with less than 18% of family practitioners. Primary care physicians indicated that 29% to 52% of their patients with cardiovascular disease or cardiovascular risk factors also saw a cardiologist (*e*Fig. 41.1.1). On the other hand, cardiologists perform a significant amount of the primary care. Cardiologists indicated that they were the primary care source for 30% of their patients and primary care providers for 13% of patients not seen for cardiac diagnoses (12).

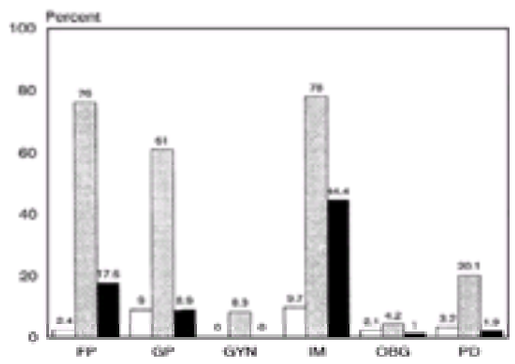
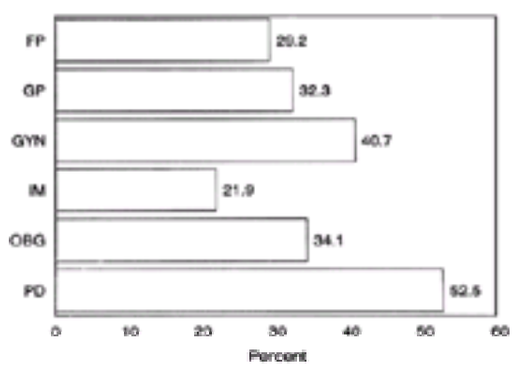


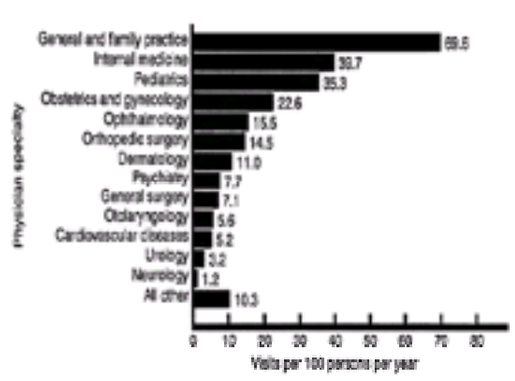
FIGURE 41.1 Frequency with which noninvasive cardiovascular procedures are performed by primary care specialists. Crosshatched bars, electrocardiography; solid bars, exercise stress tests; open bars, echocardiography. FP, family practitioner; GP, general practitioner; GYN, gynecologist; IM, internal medicine; OBG, obstetrician-gynecologist; PD, pediatrician. (From Vetrovec GW, Gardin JM, Gregory JJ, et al. Adult cardiovascular physician resources and needs assessment. *J Am Coll Cardiol* 1995;26:1125–1132, with permission.)



***e*FIGURE 41.1.1** Percentage of patients with cardiovascular disease who see a cardiovascular specialist, as reported by indicated practitioners. FP, family practitioner; GP, general practitioner; GYN, gynecologist; IM, internal medicine; OBG, obstetrician-gynecologist; PD, pediatrician. (From Vetrovec GW, Gardin JM, Gregory JJ, et al. Adult cardiovascular physician resources and needs assessment. *J Am Coll Cardiol* 1995;26:1125–1132, with permission.)

The ACC defines a cardiologist as a "physician with special training and skills in finding, treating, and preventing diseases of the heart and blood vessels in adults." A board-certified cardiologist is a physician who has completed training and certification in cardiovascular medicine after completion of training in internal medicine. Thus, the cardiologist has general competence in general internal medicine, in addition to the skills required to perform and interpret cardiovascular tests and procedures. Cardiologists have expertise in diagnostic and therapeutic procedures including echocardiography, nuclear cardiology, electrophysiology, angiography, and cardiovascular interventions (13).

According to the National Ambulatory Medical Care Survey (1995–1996), 2.1% of office visits (5.2 visits per 100 persons per year) are to specialists in cardiovascular diseases (13). The distribution of visits to cardiologists, general and family practitioners, internists, and other physicians is shown in eFigure 41.1.2. In another survey (1989–1990), cardiologists provided 35.3% of all physician visits for angina, 32.8% for cardiac dysrhythmias, 23.9% for other forms of chronic ischemic heart diseases, and 5.2% for essential hypertension. Consultation accounts for approximately 40% of a cardiologist's work week, whereas diagnostic tests and procedures account for less than 20% (14).



***e*FIGURE 41.1.2** Annual rate for office visits by physician specialty, United States, 1995–1996. (From Schappert SM, Nelson C. National ambulatory medical survey. *Vital Health Stat 13* 1999;142:1–14, with permission.)

Although it may be in society's best interest for generalists to provide cardiologic care to whatever extent safety and effectiveness allow, the optimal divisions of care between cardiologists and noncardiologists are unclear. The ability of residents in internal medicine to recognize common heart murmurs is less than expected (15,16). Less is known about the abilities and clinical judgment of general practitioners. Based on the content of certifying examinations of the American Board of Internal Medicine, internists are expected to have sufficient knowledge to manage a wide range of common cardiologic problems in hospitalized patients. However, subspecialists do significantly better than general internists on items pertaining to their area of specialization on examination for recertification (17), and in a survey of perceived causes of family physicians' errors, 49% of participating physicians reported lack of knowledge about the medical aspects of a case and reaching beyond capabilities as contributing to errors (18).

Whether the additional training and experience of cardiologists translate to improved cardiovascular outcomes has not been firmly established. We know that for a controlled population, specialists use more resources than do primary care providers (19). An important question is whether the increased cost of care incurred by specialists translates into improved outcomes. Schreiber and colleagues (20) reviewed a prospective cohort of 890 consecutive patients discharged with a diagnosis-related group diagnosis of unstable angina from William Beaumont Hospital (Royal Oak, Michigan). They compared 225 patients treated by internists with

665 patients treated by cardiologists with regard to patterns of use of established pharmacotherapies for unstable angina, diagnostic testing, and clinical outcome. Patients treated by internists had a prior cardiac history less frequently (53% vs. 80%, $p < .001$). Cardiologists were more likely to use aspirin (78% vs. 68%, $p = .032$), heparin (84% vs. 67%, $p < .001$), and beta-adrenergic blocking agents (30% vs. 18%, $p < .004$) in initial management. Exercise tests were undergone less frequently by cardiologist-treated patients (22% vs. 37%, $p < .001$), but catheterization (61% vs. 27%, $p < .0001$) and angioplasty (40% vs. 7%, $p < .0001$) were undergone more frequently. Patients with unstable angina whose care was directed by internists experienced a trend toward increased hospital mortality (4.0% vs. 1.8%, $p = .06$), although the incidence of myocardial infarction (MI), length of stay, and hospital charges were similar (20).

These observations support a previous study by Greenfield and coworkers (19) that indicated that cardiologists tend to use more expensive diagnostic techniques. Interestingly, patients of cardiologists were older, had worse functional status and well-being scores, and had more chronic diagnoses than patients of general internists (21). In another investigation, Greenfield and colleagues (22) found no evidence that specialists achieved better long-term outcomes than generalists for patients with non–insulin-dependent diabetes mellitus or hypertension. It is possible that this may be the result of the very common nature of these illnesses and of good dissemination of information related to optimal care of these conditions.

Improved dissemination of information from clinical trials was advocated by Ayanian and coauthors (23), based on the finding that internists and family practitioners are less aware of or less certain about important advances in the treatment of MI. They surveyed 1,211 cardiologists, internists, and family practitioners in two states about four treatments demonstrated by randomized clinical trials to improve survival after MI (thrombolytic therapy, immediate and long-term use of aspirin, and long-term use of beta-blockers) and two treatments for which such evidence is lacking (diltiazem for patients with pulmonary congestion and prophylactic lidocaine). They asked physicians about the effect of each treatment on survival and the likelihood that they would prescribe each class of drugs. Cardiologists believed more strongly than internists and family physicians that survival was improved by the four beneficial treatments and were more likely to prescribe these drugs ($p < .001$). With regard to thrombolytic agents, for example, 94% of cardiologists said they were very likely to use these medications to treat an acute MI, compared with 82% of internists and 77% of family practitioners. On the other hand, cardiologists were less likely than internists and family practitioners to believe there was benefit associated with the two treatments for which the trials showed no survival benefit. Cardiologists were significantly less likely to prescribe these drugs ($p < .001$); only approximately 5% of cardiologists reported that they were very likely to use prophylactic lidocaine, compared with 13% of internists and more than 16% of family practitioners.

These findings may help to explain those of Jollis and associates (24), who examined mortality according to admitting physician specialty among 8,241 Medicare patients admitted for acute MI in four states during a 7-month interval in 1992. Patients admitted by cardiologists were more likely to have had a previous MI or coronary artery bypass graft surgery (CABG), to have an anterior MI, and to have lower blood pressure on admission, whereas patients admitted by primary care physicians had lower rates of inferior MI and presentation as Killip class I. Primary care physicians' patients also had higher rates of diabetes mellitus and cerebrovascular disease. The investigators found that cardiologists had higher rates of use of cardiac procedures and medications associated with improved survival, such as thrombolytic agents and beta-blockers. They also found that patients who were admitted to the hospital by a cardiologist for treatment of acute MI were 12% less likely to die within 1 year than those admitted by a primary care physician ($p < .001$). Thus, although health care strategies that shift the care of patients with acute MI from cardiologists to primary care physicians may result in lower resource use at potentially lower costs, such a shift may cause decreased survival (24).

In a retrospective study of 327 patients with MI, management of hyperlipidemia for secondary prevention of coronary disease was shown to vary by physician specialty. Only 30% of patients with LDL levels greater than 130 mg per dL who were followed in a general internal medicine clinic received a cholesterol-lowering agent, compared with 55% of patients who were followed in a cardiology clinic ($p < .008$). This Veterans Affairs Health Care System–based study, in which access to drug treatment was equal among all patients, implies that patients observed by cardiologists are likely to have better outcomes, in part as a result of better secondary prevention (25). More recently, Stafford and Blumenthal (26) examined specialty differences in cardiovascular disease prevention practices. Using a national survey of office visits, they analyzed 30,929 adult visits to 1,521 physicians selected at random. When analysis was controlled for patient and visit characteristics, the likelihood that preventive services would be provided was higher for cardiologists than for general internists [adjusted odds ratio (OR), 1.65; 95% confidence interval (CI), 1.44 to 1.89].

Currently, there is a paucity of empirical evidence to support guidelines with regard to indications for and timing of cardiovascular consultations. This suggests that more research is needed that documents outcomes for patients with many types of medical problems who are treated by generalists and specialists in various systems of care. Cardiologists should take an active role in fostering research that evaluates patient outcomes for a variety of cardiovascular conditions. Cardiologists can also educate referring physicians and should make themselves available to discuss clinical situations with referring physicians. Such a process may facilitate patient care and allow primary care physicians to appreciate nuances of patient presentations that justify referral, even in the presence of guidelines that suggest that the role of the cardiologist in patient care is limited.

Conversely, the cardiologist is a subspecialist with training in internal medicine. The cardiologist might seek the assistance of a generalist or other specialist for care beyond the cardiologist's usual practice. This interchange may be an important educational opportunity for both physicians: The generalist or other medical specialist may gain insight into cardiologic problems and management, and the cardiologist has an opportunity to learn about new approaches in other specialties (8).

REASONS FOR REFERRAL AND CONSULTATION

Although the terms "consultation" and "referral" are often used interchangeably, their definitions are distinct. *Consultation* is the act of seeking advice regarding diagnosis and/or management (14). Such an exchange between the primary physician and the consultant may be formal (an appointment for an outpatient visit is made or an order for an inpatient consultation is written in the medical record) or informal (the "curbside consult," consisting of conversation regarding a patient between two physicians either in the hallway or by phone). A patient, a patient's family, or an insurance company may also seek a "second opinion." These are usually alluded to as "confirmatory consults." *Referral* represents transferal of the patient to another physician for a specific therapy or management of a particular medical problem while the primary (or referring physician) provides general care (14).

In cardiology practice, it is quite common for primary physicians to cede the care of the patient to the cardiologist when cardiovascular problems predominate. This represents *transferal of care*, which makes the cardiologist responsible for a patient's overall care during that hospitalization. In this situation, it is prudent for the primary care physician to continue observing the patient to remain abreast of clinical developments during the hospitalization. This maintains continuity of care and helps provide guidance regarding noncardiac problems and complex medicosocial decisions such as end-of-life issues. Finally, on discharge, the cardiologist should ideally send a letter to the primary care provider describing the patient's hospital course and a cardiac management plan as well as outstanding medical issues.

Referral and consultation rates vary widely, even for family physicians and nurse practitioners within the same practice. The rate at which a practitioner orders consultation in a specialty area increases in relation to the diagnostic certainty at the time of the consultation (9). Diagnostic certainty may be related to a referring practitioner's knowledge in a specialty field (implying that greater knowledge in a specialty leads to more consultations in that field). Studies have shown that referral rates range from 1.5% to 11% of patient visits in the family practice setting (27,28,29 and 30). In the managed care era, we can expect an increase in research evaluating the costs and effectiveness of calling on different types of physicians, with special focus on comparisons between generalists and specialists (31). Kaiser Permanente, a large health maintenance organization that provides health care services to 25% of the total population in northern California, has reported declines in consultation request rates with the introduction of the hospitalist system (32). Little information is available regarding referral to specific specialties. However, 10% of referrals from the University of Missouri–Columbia Department of Family and Community Medicine (14) and 6.8% of referrals from general internal medicine at University Hospital in Boston (33) were for cardiology services, and 11.9% of patients at Family Medical Center at the University Hospital in Seattle were referred to cardiology (34).

Consultation with a cardiologist may be sought to establish or confirm a diagnosis, to review or suggest specific management options for a known medical problem, to perform or interpret diagnostic tests, to perform a therapeutic procedure, or to clarify prognosis or cardiovascular risk associated with noncardiac tests and procedures. Depending on the severity of the patient's of illness and the urgency of the questions being asked of the consultant, patients may be evaluated in the outpatient setting (e.g., office, preadmission testing clinic, emergency department, or free-standing diagnostic imaging center) or inpatient setting (e.g., ward or specialized care or intensive care unit). The expectation is that the patient-physician relationship will terminate when the service requested by the primary care physician is complete. However, consultation may require multiple patient visits over an extended period of time, depending on the nature of the medical problem (35). Alternatively, a primary care physician may not feel that formal consultation is required and may desire only to confirm impressions or plans that have already been formulated. This type of informal consultation occurs frequently and involves a brief telephone call, e-mail, or hallway conversation.

ROLE OF THE CARDIOLOGY CONSULTANT

The opinions and reports of the Judicial Council of the American Medical Association, published in 1960 (36), contain one of the most comprehensive lists of the responsibilities of a consultant. This document lists nine ethical principles of consultation, six pertaining to the role of the consultant:

- The attending physician has the overall responsibility for the patient's treatment.
- The consultant should not assume the primary care of the patient without consent of the referring physician.
- The consultation should be done punctually.
- Discussions during consultation should be with the referring physician and only with the patient by prior consent of the referring physician.

- Conflicts of opinion should be resolved by second consultation or withdrawal of the consultant; however, the consultant has the right to render an opinion to the patient in the presence of the referring physician.

More than 40 years later, these tenets remain the guiding principles for the conduct of a successful consultant.

Evaluation

The first tasks for the cardiology consultant are to establish what question the primary physician would like to have answered and to establish the urgency of the consultation (37). Frequently, the question has not been clearly communicated by the primary care physician, and at other times, the consultant may overlook the question. If the issue prompting consultation is not clear, direct contact with the primary care physician can help to avoid consultations that do not meet the primary care physician's needs. Whether a scheduled patient is to be seen in the office or in the hospital, the consultant should determine whether the clinical situation is an emergency or whether it is urgent or elective.

The consultant's evaluation of a patient begins with a detailed medical history, physical examination, and review of data that may have already been obtained by the referring physician. It is important to "look for yourself" (37). Consultations are rarely requested to obtain assistance in interpreting already available data (38), but a careful review of the patient's chart is imperative for a complete consultation. This review should include obtaining outside records, pursuing unreturned laboratory workups, and personally reviewing ECGs, echocardiograms, and radiographs. Previous angiographic and hemodynamic data should also be reviewed personally. The New York Heart Association has classified the components of a complete cardiovascular evaluation and diagnosis of disease into the following categories: etiology, anatomy, physiology, cardiac status and prognosis, and specific recommendations (39). A complete cardiac diagnosis will likely include one or more of these categories. Based on this evaluation, tests may occasionally be repeated or new tests recommended.

Not every patient requires every test. The consultant should be mindful of test characteristics and the influence of pretest likelihood (prior probability) on posttest likelihood (predictive value). *Sensitivity* is the frequency of a positive test result in a population of patients with a particular disease. *Specificity* is the frequency of a negative test result in a cohort of patients without a certain disease. The *positive predictive value* of a test is the proportion of patients with a specific disease in a group of patients with a positive test result. The *negative predictive value* is the proportion of patients without a specific disease in a group of patients with a negative test result. The overall *diagnostic accuracy* of a test is the percentage of patients correctly classified by the test. *Bayes' theorem* states that the predictive value of a test result is a function of the prevalence of disease in the population being evaluated. The *posttest likelihood* of a disease is equal to the pretest likelihood multiplied by the probability that the test result is a true one. Therefore, a false-negative test is most likely to occur when the test is applied to a member of a patient group in which the particular disease is very common; conversely, a false-positive test is most likely to occur when the test is applied to a member of a patient group in which the particular disease is very uncommon. Posttest probability can be calculated from the disease prevalence and diagnostic test sensitivity and specificity (eTable 41.0.1). With these principles in mind, Patterson and Horowitz (40) have suggested a clinical approach to the use of diagnostic tests (eTable 41.0.2).

***e*TABLE 41.0.1** CHARACTERISTICS OF DIAGNOSTIC TESTS
Sensitivity: $TP/(TP + FN)$
Specificity: $TN/(TN + FP)$
Positive predictive value: $TP/(TP + FP)$
Negative predictive value: $TN/(TN + FN)$
Overall accuracy: $TP + TN$/total number of tests
Bayes' theorem:
Probability of disease with a positive test =

$$\frac{\text{sensitivity} \times \text{prevalence}}{(\text{sensitivity} \times \text{prevalence}) + [(1 - \text{specificity}) \times (1 - \text{prevalence})]}$$

Probability of disease with a negative test =

$$\frac{(1 - \text{sensitivity}) \times \text{prevalence}}{(1 - \text{sensitivity} \times \text{prevalence})\ [\text{specificity} \times (1 - \text{prevalence})]}$$

FN, false negative (negative result in a patient with disease); FP, false positive (positive result in a patient without disease); TN, true negative (negative result in a patient without disease); TP, true positive (positive result in a patient with disease).

From O'Rourke R. Introduction to the general evaluation of the patient. In: Schlant RC, Alexander RW, eds. *The heart,* 8th ed. New York: McGraw-Hill, 1994:202, with permission.

***e*TABLE 41.0.2** CLINICAL APPROACH TO USE OF DIAGNOSTIC TESTS
1. Make a clinical estimate of the probability of disease based on the patient's history, physical examination, and preliminary laboratory tests.
2. Formulate options in further management.
3. Define the specific question that needs to be answered to decide among management options.
4. Define performance of tests available to answer the specific question (sensitivity and specificity).
5. Synthesize test results with preliminary clinical estimate to give the best answer to the specific question (predictive value and error).
6. Determine which further tests or therapies are needed on the basis of clinical data and initial test results.
7. Review whether the testing strategy used was optimal for each individual patient.

From Patterson RE, Horowitz SF. Importance of epidemiology and biostatistics in deciding clinical strategies for using diagnostic tests: a simplified approach using examples from coronary artery disease. *J Am Coll Cardiol* 1989;13:1653–1665, with permission.

Another important application of cardiovascular testing is in establishing prognosis. Knowledge of prognosis potentially affects decisions regarding medical management of a wide range of cardiovascular and noncardiovascular problems, as well as patient decisions regarding lifestyle and medical therapy. For example, physicians frequently use exercise testing to establish a prognosis in patients with stable coronary artery disease (CAD) or recent MI (41). Results may assist the physician in selecting patients who may be treated medically or should undergo further noninvasive or invasive evaluation (42).

Communication

A patient may be confused about the various doctors involved in his or her care. The following information should be discussed with the patient at the beginning of the consultant's visit: the consultant's name, the fact that the consultant is providing a service at the request of the patient's primary physician, the specialty that consultant represents, and the reason for consultation (37). If more than one person from the consulting service is involved (e.g., a student or a fellow), this should be explained to the patient, as should each person's role (36).

After the initial patient evaluation and the formulation of a management plan, the cardiology consultant must record his or her findings in the medical chart and communicate an assessment and recommendations to the primary physician who requested the consultation or referred the patient to the cardiologist. Opinions should be expressed in as brief a manner as appropriate. When writing in the hospital chart, it may be sufficient to merely note the history already provided and add components not already documented (38). This preliminary note may serve to communicate the initial assessment and recommendations to the medical team and to supplement a conversation between the consultant and primary physician. However, this brief note may be inadequate from the standpoint of medicolegal documentation and for documentation reimbursement purposes (see Documentation Compliance with Federal Health Programs). Although a long list of possible diagnoses with references to the medical literature may be of academic interest, lengthy intellectual discussions are unlikely to be read. Nevertheless, a copy of one or two key references, preferably from top-tier subspecialty journals, left at the front of the chart may be greatly appreciated. The cardiology consultant should share expertise with brevity, clarity, and lack of condescension (eFig. 41.1.3). Also, whether the consultant or the primary physician will execute the recommendations or arrange the pertinent tests should be either clearly stated in the note or verbally communicated. Specific recommendations should be made, with contingency plans (37). The primary physician should be able to copy recommendations directly to the order sheet if he or she is in agreement. By anticipating potential problems, contingencies allow for brief management strategies to be in place if a patient's status changes (8).

***e*FIGURE 41.1.3** Sample inpatient preoperative cardiology consultation. BP, blood pressure; CHF, congestive heart failure; CXR, chest x-ray; ECG, electrocardiogram; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

The consultative process represents an exchange of information between the primary physician, who may be a generalist, surgeon, or other medical subspecialist, and the cardiology consultant. As such, consultation provides a unique opportunity for the consultant to learn about state-of-the-art therapies provided by other medical specialties (8).

Documentation Compliance with Federal Health Programs

In its February 1999 Comprehensive Plan for Program Integrity, the federal agency that administers Medicare and Medicaid, the Health Care Financing Administration (HCFA), stated that “Our program integrity goal is straightforward . . . to pay the right amount, to a legitimate provider, for covered, reasonable and necessary services, provided to an eligible beneficiary . . .” (43). Accurate and complete medical records are absolutely essential to ensure high-quality patient care and an efficient and smooth process for the submission and reimbursement of claims. One of the most important principles is to verify that the current procedure terminology codes indicating the services provided match the services rendered and that *ICD-9* (*International Classification of Diseases, Ninth Revision*) codes indicating diagnosis support the services provided. The consultant must also be able to prove the scope of medical history covered, the extent of the physical examination, and the complexity of the decision making. HCFA’s evaluation and management documentation guidelines define exactly how much documentation must be provided for each type of encounter. Detailed description of these guidelines is beyond the scope of this text and is available through the American College of Physicians or can be found as part of Medicare billing rules (44).

Extensive documentation is also supposed to improve patient care. However, HCFA’s complex evaluation and management requirements may also result in omission of critical information from the patient’s chart while the physician attempts to document trivial details (45). However, the reality is that a consultant must comply with HCFA’s burdensome evaluation and management rules or risk the consequences.

Effective Consultation

Certain aspects of a consultant’s role may influence whether recommendations are carried out by the requesting physician. Literature on this subject is limited and is available primarily from academic institutions. One measure of consultative quality is compliance with the consultant’s recommendations. In one study, compliance with the consultant’s advice ranged from 54% to 77% in academic centers (36). A study in a military teaching center reported that 90% of the recommendations were followed, implying higher compliance in nonacademic institutions (46).

Most research on the consultative process confirms the importance of good communication. In one study, disagreement occurred between the primary physician and the consultant on the issues of a consultation in 14% of cases (37). No specific question may be asked in 24% of preoperative consultations, and consultants may ignore explicit questions in 12% of cases (47). Direct contact between the consultant and the physician ordering the consultation can clarify misperceptions and has been associated with increased compliance with recommendations (46).

Compliance with recommendations decreases as the number of suggestions increases. Sears and Charlson (48) found that compliance was highest in their series of 202 general medicine consultations when five or fewer recommendations were made, regardless of the severity of the illness. The inverse relationship between number of recommendations and compliance has been observed in other studies (46,49). Identifying essential recommendations leads to greater compliance. Pupa and colleagues (46) found that labeling recommendations as “crucial” led to more than 90% compliance, even when the recommendations were contained in a long list of other suggestions. Verbal communication of high-priority recommendations is extremely effective. Recommendations should be as specific as possible so that physicians less familiar with cardiovascular tests and medications can copy suggestions directly to the order sheet in the chart (37). Horwitz and associates (50) found 100% compliance with recommendations for pharmacologic therapy when dose and duration were included in the consultant’s note; compliance fell to 85% when only dose or duration was specified and to 65% when neither was stated ($p < .001$).

Thus, when composing a consultative note in the chart, one might consider listing the impression and plan at the top to gain greater attention. Brief bullets are often more effective than long sentences. Recommendations may be divided into those aimed at making a diagnosis and those used for further management or therapy.

An effective consultant may also benefit from an organized referral evaluation team. The structure of this team greatly varies according to the size of the referral base and the consultant’s practice. For example, a single cardiologist in a multispecialty group may have nurse practitioners and physician assistants as a part of his referral team compared to multiple cardiologists in a single specialty group. Another variation in the practice of cardiology pertains to physicians being on staff at an academic medical center where medical housestaff and cardiology fellows may play an important role in accepting, evaluating, and treating a patient. One of the most important elements of providing consultative services, regardless of the structure of the team, is appropriate acceptance followed by expedited evaluation and cohesive management. This can be achieved by providing easy access to the referring physician and delegating responsibility among the members of the referral evaluation team.

Follow-Up and Prevention

Many cardiovascular conditions require follow-up, which allows the cardiologist to adjust medications and assess response to therapy. Examples include management of severe hypertension and hyperlipidemia, cardiomyopathy, and inoperable CAD. Several studies have shown the importance of follow-up in gaining greater compliance with recommendations (47,51). Horwitz and colleagues (50) found that when more than one follow-up note was written, consultation had an effect on diagnosis in 92% of cases and an effect on management in 84% of cases. When one or no follow-up note was written, effects on diagnosis were noted in only 74% of cases ($p < .001$), and effects on management were observed in only 56% of cases ($p < .001$). A final job for the consultant is to ensure continuity of the patient’s care for cardiac problems after discharge. A letter to the primary physician is often indicated to better coordinate the long-term management plan (36).

Just as follow-up improves compliance with recommendations in the hospital, continued communication with a referring physician facilitates fine-tuning and monitoring of medical therapy by the primary physician between patient visits to the cardiologist. Conversely, after treatment for acute cardiovascular disease, follow-up in some circumstances is best performed by the primary physician, and the patient should be promptly sent back to the referring physician. Greenfield and colleagues (52) investigated “reverse referrals” (i.e., referrals from subspecialists to generalists) and found that such patients had more diagnoses, complaints outside of the subspecialty, and total clinic visits, including increased visits to different types of clinics, than retained patients. The referring generalist may best manage patients with complex psychosocial issues or those who have a long-standing relationship with the primary care physician. However, referral back to the primary physician should occur only after a clear management plan has been established.

PREOPERATIVE EVALUATION

Advances in surgical and anesthetic techniques and an aging patient population have resulted in more complex procedures being performed in greater numbers of patients with higher likelihood of significant cardiovascular disease. Consultation may be sought for a history of cardiovascular disease, hypertension, or chest pain, or in the presence of a murmur, arrhythmia, or abnormal ECG results (51,52 and 53). Preoperative cardiac consultations are also frequently obtained for patients who have high pretest likelihood of CAD or in patients undergoing a high-risk noncardiac surgery.

Although consultation may occur in the office, on the ward, or in the postanesthesia care unit, recent greater emphasis on outpatient surgery or admission of patients on the morning of the planned surgical procedure has led to more frequent evaluations in a preadmission testing clinic (53). After noncardiac surgery, patients with

cardiovascular disease require surveillance for cardiac complications, particularly for the first 48 hours after surgery, although the risk of MI may persist for at least 5 to 6 days after surgery (54). Particular attention to good consultative techniques is warranted, because it has been suggested that compliance with consultant recommendations is lower for preoperative consultation than for consultations performed in other settings (55).

Cardiology consultants have sought to identify the patients at highest risk for perioperative cardiac complications and to intervene to reduce risk. Risk stratification has been achieved with clinical criteria (56,57), screening ECG (58), results of cardiac evaluations using exercise testing (59,60 and 61), thallium scanning (62,63 and 64), stress echocardiography (65,66), and coronary angiography (67,68), as well as the combination of clinical criteria and noninvasive testing (69). Coronary revascularization in selected patients may reduce the risk of noncardiac surgery (70,71), but bypass surgery and coronary angioplasty also have risks. The evidence on which decisions are made regarding use of these tests and procedures comes largely from retrospective studies, because the necessary clinical trials require large numbers of patients and have not been performed (72).

Perhaps partially due to the lack of results of clinical trials to guide decision making, there is significant variation in practice with regard to risk stratification (73). Furthermore, stress testing all patients who undergo high-risk procedures may not be effective (74), and therefore selective screening of high-risk patients is preferable. The process of risk assessment is costly, estimated to be $3.7 billion annually (73), and the vast majority of patients will not die or sustain a postoperative MI.

Epidemiology of Postoperative Myocardial Infarction

Of the 27 million men and women who have surgery each year in the United States, 1 million have perioperative cardiac complications, which result in approximately $20 billion in costs of in-hospital and long-term care (75). Over the course of the next 25 years, it is estimated that 37 million patients will undergo an operation, and 12 million of those will be older than 65 years. As a result, perioperative mortality will increase substantially, resulting in an approximate cost of $40 billion by the year 2018 (76).

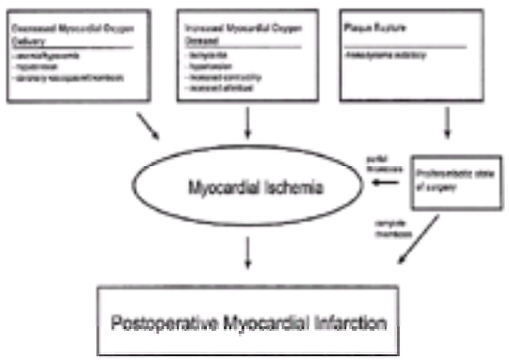
The overall risk of postoperative MI is low overall (<1%) (77,78). A history of MI increases the chance of sustaining a recurrent perioperative MI to approximately 6% (79). The risk of MI peaks within the first 3 postoperative days. Von Knorring (80) prospectively analyzed a cohort of surgical patients and found that 87% of perioperative MIs occur within the first 3 postoperative days, with peak incidence on postoperative day 2. Most postoperative MIs are non–Q-wave MIs and are usually detected in the first 24 hours after the operation, probably as a result of increased surveillance using frequent ECG and measurement of cardiac enzymes (81,82 and 83).

Because atherosclerosis is a diffuse process, patients with peripheral vascular disease often have CAD. In a study seeking to define the relationship between CAD and peripheral vascular disease, 1,000 patients undergoing peripheral vascular reconstruction at The Cleveland Clinic underwent preoperative coronary angiography; only 14% had normal coronary arteries (68). Several other studies have correlated coronary angiographic findings with different types of vascular diseases. The incidence of severe CAD among patients with abdominal aortic aneurysms is 52% to 82%, and the incidence among patients with peripheral occlusive disease is 47% to 60% (84). In a random sample of 6,895 Medicare patients undergoing major vascular surgery, perioperative mortality was 7.3% for aortic surgery and 5.8% for infrainguinal vascular surgery (85). Eagle and coworkers (86) identified 3,368 patients from the Coronary Artery Survival Study (CASS) registry who underwent noncardiac surgery, after a mean follow-up of 4.1 years. In patients with CAD who have not undergone revascularization, abdominal, vascular, thoracic, and head and neck surgery each had a combined rate of death and MI of more than 4%, with the highest event rate in vascular surgery patients (rate of perioperative MI, 8.5%; mortality rate, 2.8%). Therefore, the substantially higher cardiac morbidity and mortality among patients with nonrevascularized CAD who are undergoing vascular surgery mandates the need for an aggressive risk stratification strategy.

The presentation of postoperative MI is often silent or subtle because of residual effects of anesthesia or the presence of narcotics and sedatives. Nonspecific symptoms, such as new or worsening congestive heart failure (CHF), hypotension, nausea, altered mental status, or arrhythmias, may be the only clinical indications of infarction (87). For these reasons, and because the average mortality associated with postoperative MI may be as high as 50% (57,77,78,87), close perioperative surveillance with prompt initiation of therapy if infarction is suspected is warranted. Some procedures incur a higher risk because of associated blood loss, higher risk of hypotension, intravascular fluid shifts, or tendency for older, debilitated patients to require the procedure. Conversely, procedures performed under local anesthesia are usually associated with very low risk. For example, ophthalmologic procedures and herniorrhaphies have been performed soon after MI (88,89).

Pathophysiology

Alterations in the balance of clotting and fibrinolytic systems, varying as a function of the magnitude of the surgery, create a “prothrombotic milieu” (*e*Fig. 41.1.4) in the postoperative period that predisposes the patient to thrombotic complications such as deep vein thrombosis, stroke, and MI (91). The stress response is a physiologic measure of the magnitude of the surgery and surgical factors such as urgency, blood loss, and perioperative fluid shifts, which have been shown to influence perioperative cardiac events (90).



***e*FIGURE 41.1.4** Pathophysiology of perioperative myocardial infarction. In the setting of a coronary stenosis, the normal ability of vasculature to adjust flow and meet an increase in myocardial oxygen demand is limited. Even if demand is steady, acute decreases in oxygen supply can occur. The combination of these conditions may lead to myocardial ischemia, although an alternative hypothesis implicates plaque rupture and thrombus formation at a noncritical stenosis. (From Beattie C, Fleisher LA. Perioperative myocardial ischemia and infarction. *Int Anesth Clin* 1992;30, with permission.)

To date, very few studies have attempted to elucidate the pathophysiologic mechanism of postoperative MI. Traditionally, oxygen supply–demand mismatch has been invoked as the pathophysiologic mechanism of postoperative MI. However, plaque rupture followed by intracoronary thrombosis may also be a causative mechanism in patients who experience fatal MI. Cohen and Aretz (91) identified 26 patients who had sustained a fatal postoperative MI out of a total of 1,841 autopsies. They found that plaque rupture was present in almost one-half (46%) of the patients. In another study, Dawood and associates (92) found evidence of plaque rupture in 23 (55%) of 42 patients who died after noncardiac surgery. Therefore, in addition to oxygen supply-demand mismatch, plaque rupture followed by coronary thrombosis may also be an important pathophysiologic mechanism, and multiple strategies likely are required to lower the risk of postoperative MI.

Clinical Prediction

Several groups have stratified surgical risk based on patient characteristics. First, Dripps and colleagues (93) assigned a physical status class to patients, before administration of anesthesia, over a 10-year period (1947–1957). This physical status index is still used by the American Society of Anesthesiologists (ASA; *e*Table 41.0.3) (94) and has been validated in a large cohort of patients (95). However, the index is subjective and may be less predictive in some subsets of patients, such as elderly patients, obese patients, and patients with prior MI or mild systemic disease (96). Goldman and coworkers (57) developed a multifactorial index to assess the cardiac risk of noncardiac surgery in 1,001 consecutive general surgery patients (57) (*e*Table 41.0.4). To adjust risk estimates for a specific planned surgical procedure, Detsky and colleagues (97) developed a modified index of perioperative cardiac risk. They altered several features of Goldman’s original index, based on the authors’ clinical experiences (*e*Table 41.0.5).

***e*TABLE 41.0.3** DRIPPS’ MODIFICATION OF THE INDEX OF PHYSICAL STATUS, AMERICAN SOCIETY OF ANESTHESIOLOGISTS
1. A healthy patient.
2. A patient with mild systemic disease.
3. A patient with a severe systemic disease that limits activity, but is not incapacitating.
4. A patient with an incapacitating systemic disease that is a constant threat to life.

5. A moribund patient who is not expected to survive 24 hours with or without an operation.

Note: In the event of an emergency operation, precede the number with an E.

From American Society of Anesthesiologists. I. New classification of physical status. *Anesthesiology* 1963;24:111, with permission.

***e*TABLE 41.0.4** THE GOLDMAN MULTIFACTORIAL CARDIAC RISK INDEX

Criterion	Points
History	
Age >70 yr	5
Myocardial infarction in previous 6 mo	10
Physical examination	
Third heart sound gallop or jugular venous distention	11
Important valvular aortic stenosis	3
Electrocardiography	
Rhythm other than sinus or premature atrial contractions on last preoperative electrocardiogram	7
>5 premature ventricular contractions/min documented at any time preoperatively	7
General status	
PO_2 <60 or PCO_2 >50 mm Hg; K <3.0 or HCO_3 <20 mEq/L; blood urea nitrogen >50 or serum creatinine >3.0 mg/dL; abnormal level of serum glutamic oxaloacetic transaminase, signs of chronic liver disease, or patient bedridden from noncardiac causes	3
Operation	
Intraperitoneal, intrathoracic, or aortic operation	3
Emergency operation	4
Total	53

From Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;297:845–850, with permission.

***e*TABLE 41.0.5** THE MODIFIED MULTIFACTORIAL CARDIAC RISK INDEX

Variable	Points
Coronary artery disease	
Myocardial infarction within past 6 mo	10
Myocardial infarction >6 mo ago	5
Canadian Cardiovascular Society angina	
Class 3	10
Class 4	20
Unstable angina within past 3 mo	10
Alveolar pulmonary edema	
Within 1 wk	10
Ever	5
Valvular disease	
Suspected critical aortic stenosis	20
Arrhythmias	
Sinus plus APDs or rhythm other than sinus on last preoperative ECG	5
>5 ventricular premature depolarizations at any time before surgery	5
Poor general medical status[a]	5
Age >70 yr	5
Emergency operation	10

APDs, action potential durations; ECG, electrocardiogram.

[a]PO_2 <60 mm Hg; PCO_2 >50 mm Hg; serum K^+ <3.0 mmol/L; serum $^-HCO_3$ <20 mmol/L; blood urea nitrogen ³18 mmol/L; serum creatinine >260 mmol/L; abnormal aspartate aminotransferase level; signs of chronic liver disease; and/or patient bedridden because of noncardiac causes.

Reprinted from Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing noncardiac surgery. *J Gen Intern Med* 1986;1:211–219, with permission.

The Goldman risk index has been tested prospectively (98) and demonstrated an incremental increase in cardiac risk according to preoperative classification in a broad group of patients presenting for a variety of surgical procedures. The applicability of the Goldman index for more specific patient subsets and types of surgery has been questioned. For example, Gerson and coworkers (99) evaluated the predictive value of patient history, physical examination, and rest and exercise radionuclide ventriculography (RVG) to risk-stratify 155 geriatric patients presenting for nonemergency abdominal, thoracic, or aortic surgical procedures. No clinical predictor, including the Dripps-ASA and Goldman indices, provided any additional independent predictive information. In another study, Jeffrey and colleagues (100) prospectively evaluated the Goldman risk index for 99 consecutive patients who presented for elective abdominal aortic surgery. The risk of serious cardiovascular complications was significantly higher than predicted among Goldman class I patients (7%) and insignificantly higher among class II and class III patients. The authors concluded that the Goldman risk index was not as accurate in predicting cardiac risk among patients undergoing elective aortic surgery. More recently, Gilbert and coauthors (101) prospectively compared the ASA index, Goldman's index, Detsky's index, and the Canadian Cardiovascular Society index for angina level in 2,035 patients scheduled for urgent or elective surgery. To determine the overall accuracy of the stratification systems, they calculated the area under the receiver operating characteristic curve for each index. All the cardiac risk indices provided a significant degree of risk stratification (p <.001); however, the difference among areas under the receiver operating characteristic curves for various indices was not statistically significant (p >.05).

Several factors may limit the predictive value of these clinical indices. When estimating surgical risk, relevant factors (patient-specific, institution-specific, and procedure-specific) must be considered. These considerations, as well as the desire to increase predictive accuracy, have led to investigation of noninvasive tests to help assess preoperative risk to the patients in an incremental fashion.

Stress Testing and Assessment of Left Ventricular Function

One of the first noninvasive technologies used in preoperative cardiac risk stratification was exercise treadmill testing, because poor functional capacity in patients with CAD is associated with an increased incidence of subsequent cardiac events. The positive predictive value for postoperative death and MI of abnormal results of an exercise stress test ranges from 5% to 25%. The negative predictive value of normal results of a maximal study exceeds 90% (102). An important limitation of exercise testing in preoperative evaluation of noncardiac surgery is patients' inability to perform optimal level of exercise in 30% to 50% of cases (102). This does not preclude obtaining important functional information, and estimates of perioperative risk can be determined in patients who can exercise. Numerous studies have examined the usefulness of exercise stress testing as a preoperative diagnostic tool in men, and the results may not be reliable when applied to women (75). Exercise stress testing has a lower overall accuracy among women compared with that among men because of the higher prevalence of ECG changes with hyperventilation or position change among women. Table 41.1, from the ACC/AHA guidelines, illustrates selected studies of preoperative exercise testing before major noncardiac surgery (103).

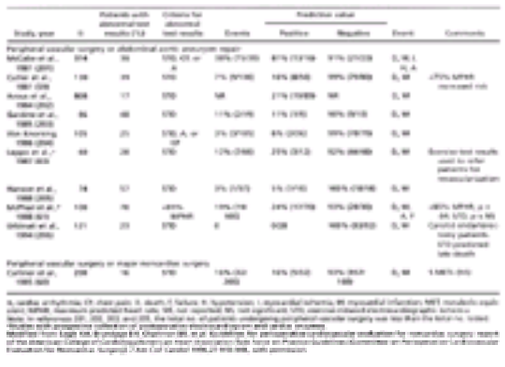


TABLE 41.1 SUMMARY OF STUDIES EXAMINING THE VALUE OF PREOPERATIVE EXERCISE TESTING BEFORE MAJOR NONCARDIAC SURGERY

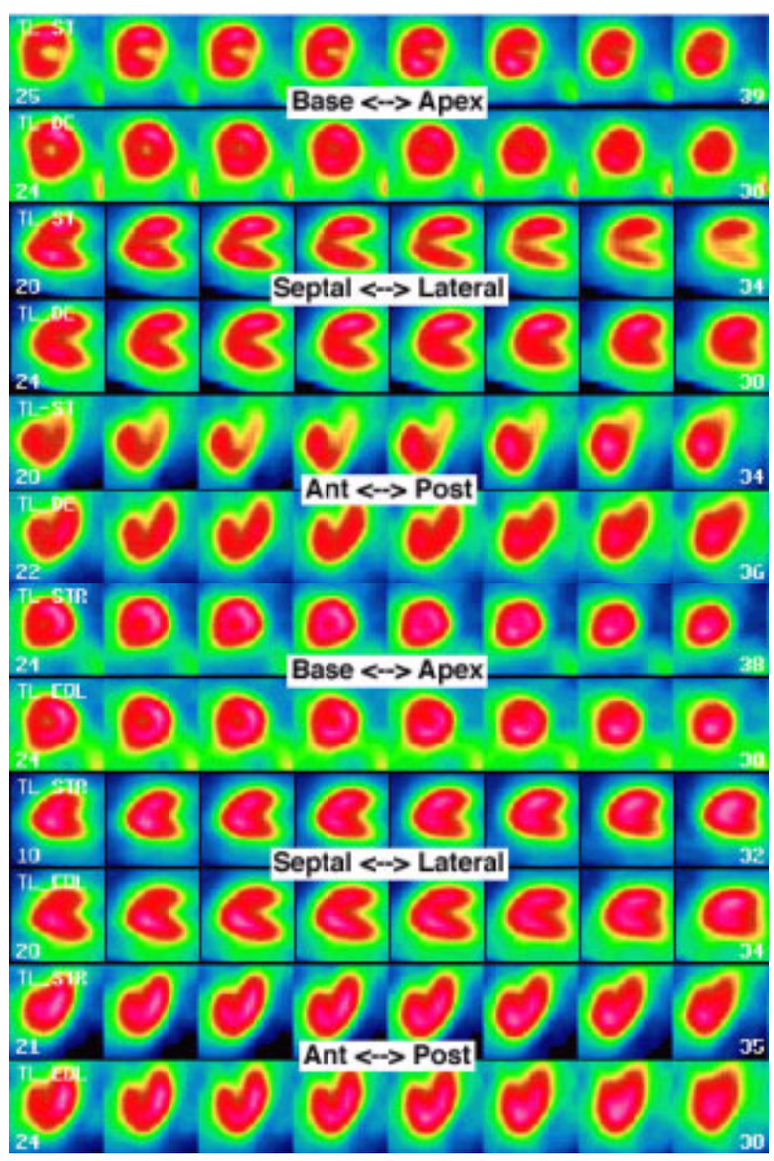
Several studies suggest that inability to perform even modest levels of exercise identifies a high-risk subset of patients (61,101,102). McPhail and associates (61) demonstrated that patients who achieved greater than 85% predicted maximal heart rate during exercise testing had a postoperative cardiac complication rate (cardiac death, MI, CHF, malignant ventricular ectopic activity) of 6%, whereas patients who achieved less than 85% of their predicted maximal heart rate had a complication rate of 24%. In addition, Gerson and colleagues (104) showed that inability to perform 2 minutes of supine bicycle exercise to raise the heart rate above 99 beats/min was a good predictor of perioperative pulmonary, cardiac, and combined cardiopulmonary complications (104).

Investigators have also assessed resting and exercise left ventricular function using RVG and echocardiography. Initial studies showed a relationship between decreased left ventricular systolic function and adverse cardiac events (105,106,107,108,109,110 and 111). However, subsequent studies (112,113,114,115 and 116) failed to show a statistically significant relationship between resting left ventricular ejection fraction (LVEF) and the development of perioperative adverse cardiac events. Thus, taken together, the data indicate that resting LVEF is a relatively insensitive and nonspecific marker for postoperative MI and cardiac death, however poorly left ventricular systolic function or diastolic dysfunction may predict postoperative CHF. Similar findings have been reported with echocardiography, although results have not been uniform across studies (117). More recently, Rhode and coauthors (118) studied the incremental value of transthoracic echocardiography after consideration of clinical data for prediction of cardiac complications after a major noncardiac surgery in 570 patients. In univariate analyses, preoperative systolic function was associated with postoperative MIs (OR, 2.8; 95% CI, 1.1 to 7.0). In logistic regression analysis, models with echocardiographic variables predicted major cardiac complications much better than those that included only clinical variables. Studies of exercise LVEF (104,119) also have indicated that resting LVEF and exercise-induced wall motion abnormalities are insensitive predictors of postoperative MI and cardiac death.

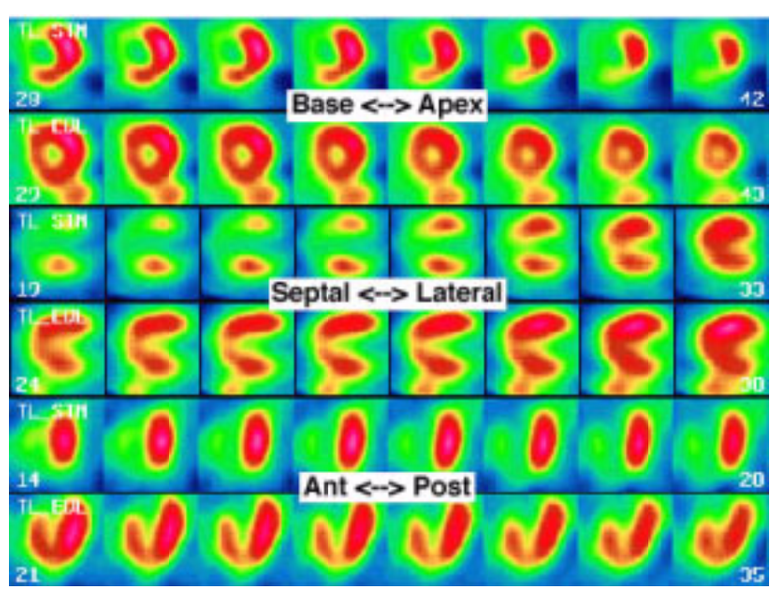
Perfusion Imaging

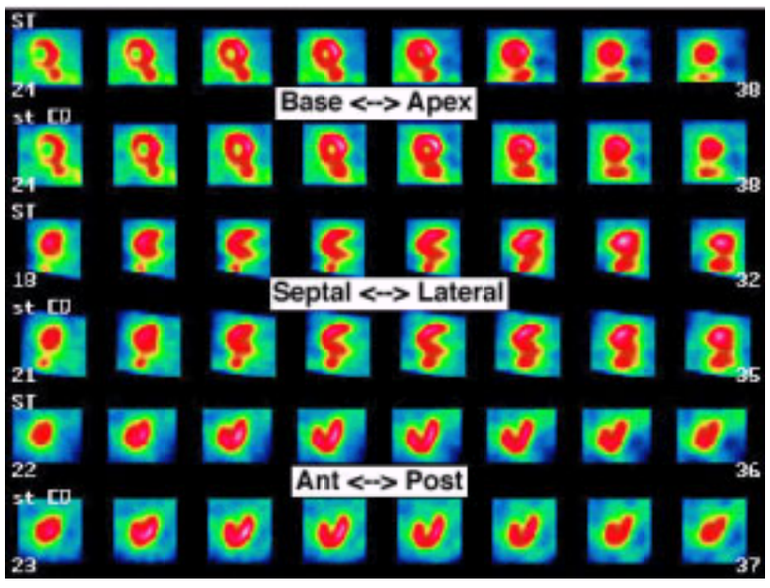
Although functional capacity appears to be a strong determinant of overall prognosis, as well as a significant predictor of perioperative cardiac risk, there are many patients who have a limited ability to exercise. Thus, exercise testing has limited prognostic value (120,121 and 122) in many patients who are scheduled to undergo vascular, orthopedic, or neurosurgical procedures. Preoperative patients with amputation, claudication, morbid obesity, or advanced age are frequently studied under pharmacologic stress, using agents such as dipyridamole, adenosine, or dobutamine (102).

The first study to demonstrate the usefulness of dipyridamole-thallium scanning for preoperative cardiac risk assessment in patients who are unable to exercise was carried out by Boucher and coworkers (62). Of the 48 patients (89%) who underwent vascular surgery without coronary angiography, 16 patients had thallium redistribution on preoperative dipyridamole-thallium scintigraphy. Eight perioperative ischemic cardiac events (unstable angina, MI, or cardiac death) occurred. All eight events occurred in the group of 16 patients who had preoperative thallium redistribution. No adverse postoperative cardiac events were seen in the 20 patients for whom results of dipyridamole-thallium scanning were normal or in the 12 patients who had persistent thallium defects only. All six patients who underwent coronary angiography before surgery had multivessel coronary disease; four patients underwent CABG, followed by peripheral vascular surgery, without postoperative cardiac ischemic events. The results of this landmark study have been confirmed by many subsequent studies (61,62 and 63,68). Leppo and colleagues (63) progressed to the next logical step by comparing dipyridamole stress with exercise stress ECG. Multivariate analysis revealed that thallium redistribution was the best predictor of perioperative cardiac events; 14 (33%) of 42 patients with thallium redistribution defects suffered MI or perioperative death (63). Waters and colleagues (123) demonstrated a significant correlation between reversible perfusion defects and intraoperative development of new wall motion abnormalities, confirming the relationship between jeopardized myocardium and preoperative perfusion abnormalities during noncardiac surgery.

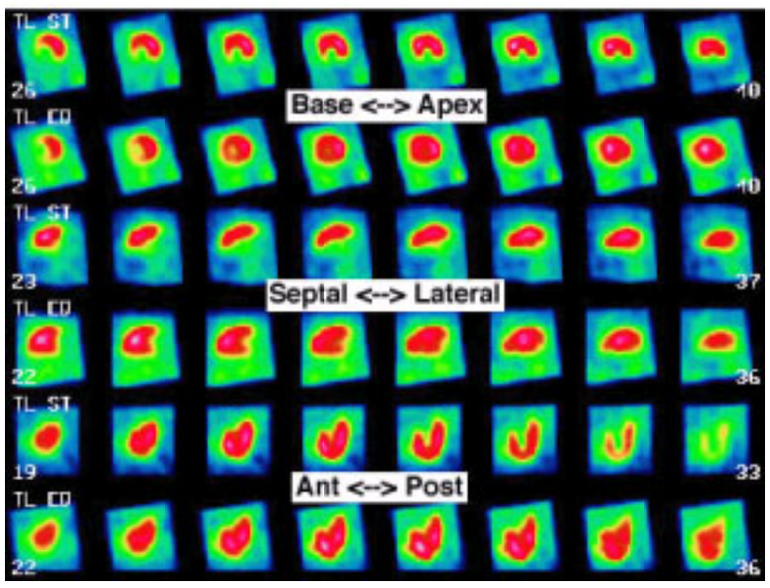


Thallium-201 single-photon emission computed tomography stress and delayed images (A). Transverse, sagittal, and coronal plane images demonstrating lateral wall ischemia in a patient with severe proximal left circumflex artery stenosis. Thallium-201 single-photon emission computed tomography stress and equilibrium images (B). Transverse, sagittal, and coronal plane images obtained from a patient after successful intervention for severe proximal left circumflex artery stenosis (normal study).



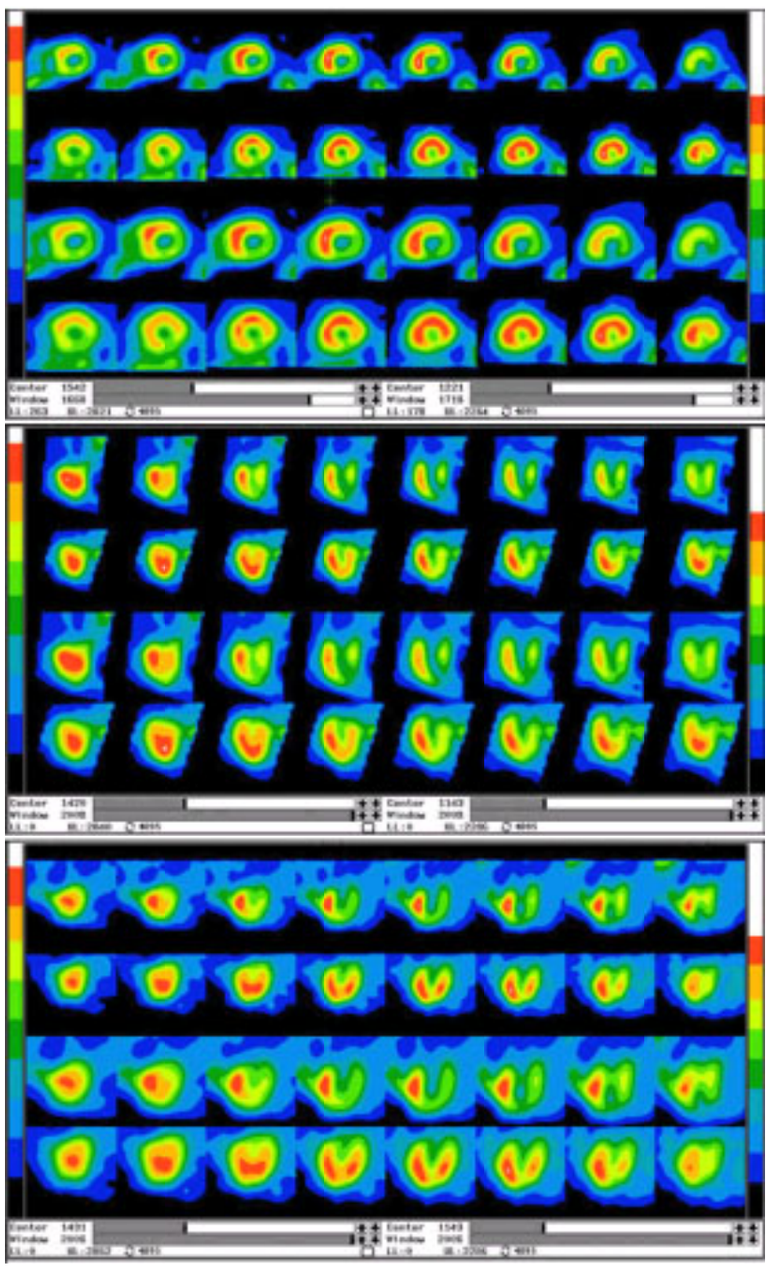


Thallium-201 single-photon emission computed tomography stress and equilibrium images. A: Transverse, sagittal, and coronal plane images demonstrating anterior, septal, apical, and distal inferior ischemia in a patient with a severe proximal left anterior descending (LAD) artery stenosis in whom the LAD wraps around the left ventricular apex. B: Transverse, sagittal, and coronal plane images from the same patient as A after intervention for severe proximal LAD artery stenosis (normal study).



Thallium-201 single-photon emission computed tomography stress and equilibrium images. Transverse, sagittal, and coronal plane images demonstrating inferior and posterior wall ischemia in a patient with a severe proximal stenosis in a dominant right coronary artery.

The concept that risk of cardiac events is not simply related to the presence or absence of jeopardized viable myocardium and is directly proportional to the extent of myocardium at risk has also been demonstrated (124). Lane and colleagues (64) found that perioperative cardiac risk was related to the number of reversible thallium defects on planar imaging; five or more transient defects were associated with 44% probability of a cardiac event, compared with 14% among patients with one or more transient defects (p <.01). Lette and coworkers (125) defined semiquantitative indices of the extent and severity of reversible thallium abnormalities. There was a strong correlation between the indices of severity and extent of thallium redistribution and postoperative cardiac death or MI. Reversible left ventricular cavity dilation was also a significant predictor of postoperative cardiac complications. Similarly, Levinson and coauthors (126) showed that patients with redistribution in four or more myocardial segments were more likely to experience a perioperative ischemic cardiac event than patients with three or fewer such segments (38% vs. 12%; p = .03). Patients with dipyridamole-thallium redistribution in two or three coronary artery territories were significantly more likely than patients with redistribution in only one coronary artery territory to have a perioperative cardiac complication (43% vs. 13%; p = .007). Multivariate analysis identified thallium redistribution in more than one view (p <.001) as the strongest predictor of perioperative cardiac complications. Therefore, assessment of perioperative risk must take into consideration the extent of ischemia. Patients who have only a small amount of jeopardized viable myocardium appear to be at low risk for cardiac events and probably do not need preoperative coronary revascularization (124).

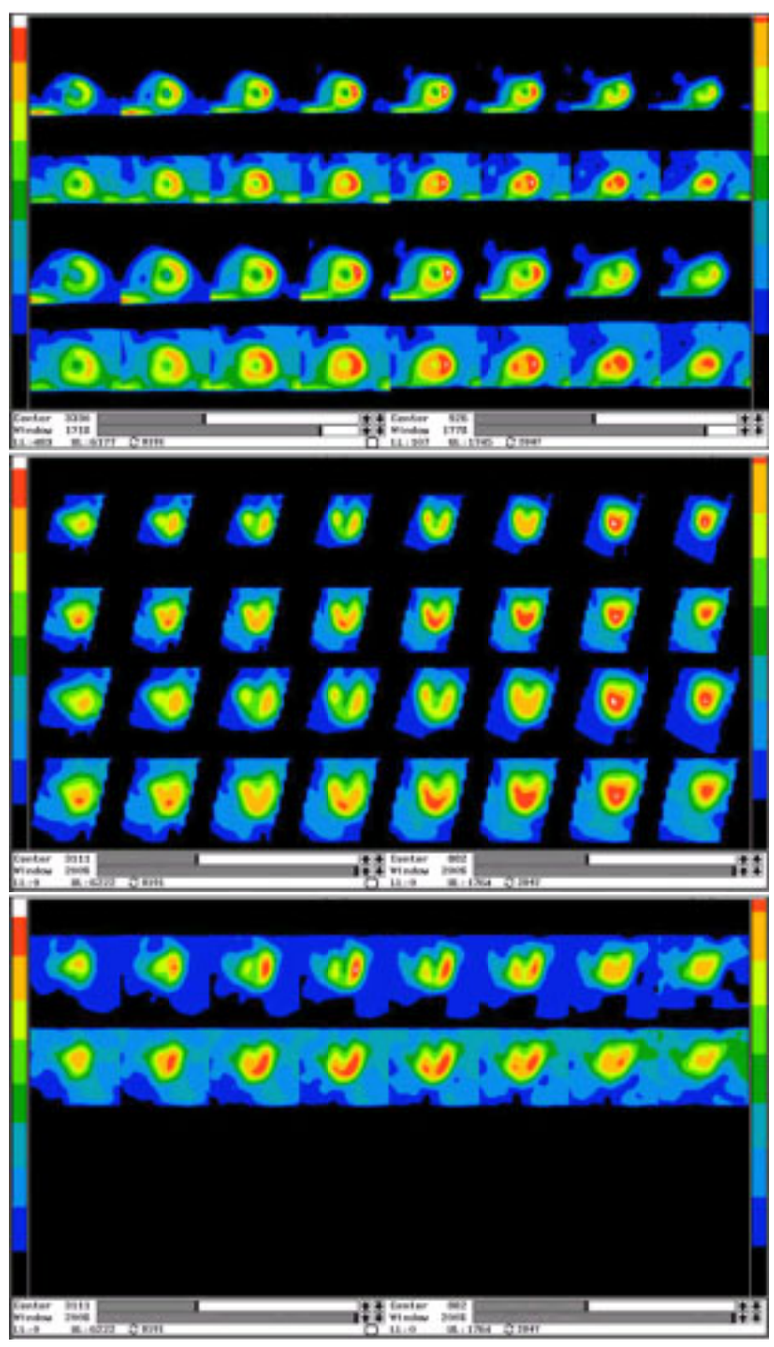


**Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second*

***image*), and coronal (*third image)* plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery.**

Video 41.1 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image)* plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 41.2 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image)* plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

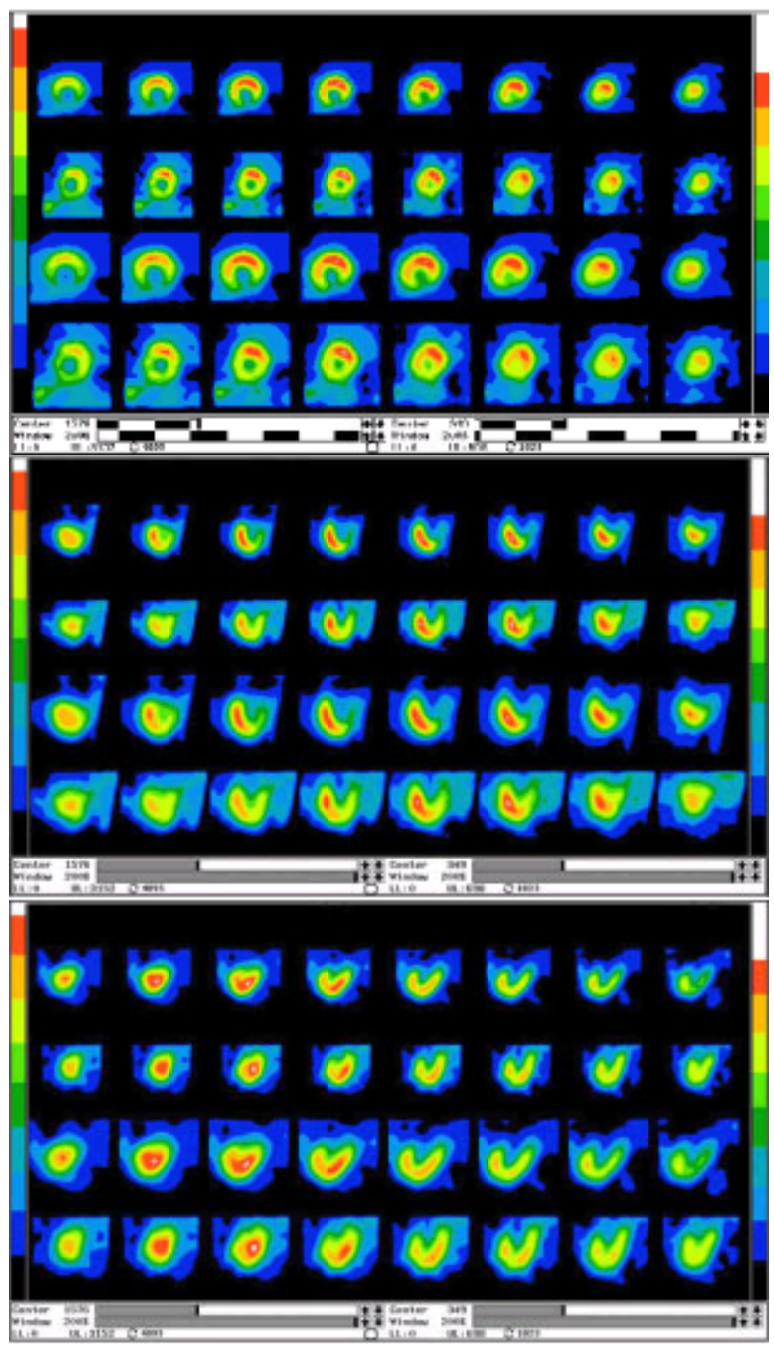


Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the mid and distal anteroseptal, distal septal, distal anterior, and apical walls. The left anterior oblique cranial view (*first video*) of the left coronary artery in the same patient shows severe proximal stenosis of the left anterior descending artery. The right anterior oblique view (*second video*) shows a widely patent right coronary artery with extensive septal collateralization to the severely diseased left anterior descending coronary artery.

Video 41.3 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the mid and distal anteroseptal, distal septal, distal anterior, and apical walls. The left anterior oblique cranial view (*first video*) of the left coronary artery in the same patient shows severe proximal stenosis of the left anterior descending artery. The right anterior oblique view (*second video*) shows a widely patent right coronary artery with extensive septal collateralization to the severely diseased left anterior descending coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 41.4 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the mid and distal anteroseptal, distal septal, distal anterior, and apical walls. The left anterior oblique cranial view (*first video*) of the left coronary artery in the same patient shows severe proximal stenosis of the left anterior descending artery. The right anterior oblique view (*second video*) shows a widely patent right coronary artery with extensive septal collateralization to the severely diseased left anterior descending

coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



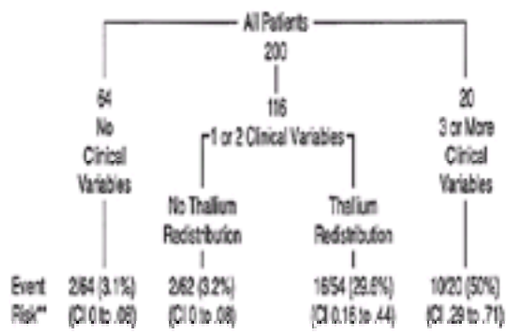
Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the inferolateral, inferior, and proximal to mid inferoseptal walls. The left anterior oblique cranially angulated view (*video*) shows severe stenosis of the distal right coronary artery before the posterior descending and posterolateral arteries in the same patient.

Video 41.5 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the inferolateral, inferior, and proximal to mid inferoseptal walls. The left anterior oblique cranially angulated view (*video*) shows severe stenosis of the distal right coronary artery before the posterior descending and posterolateral arteries in the same patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Although thallium redistribution appears to be quite sensitive for predicting postoperative ischemic cardiac events, specificity is low. However, applying the test in a higher-risk cohort and not performing the test in low-risk subsets could improve specificity. Stratification of patients into groups of those who should and should not have further noninvasive cardiac assessment was the focus of two studies by Eagle and colleagues (69,127). In the first study, the authors evaluated the predictive value of dipyridamole-thallium imaging for postoperative cardiac events in 61 patients referred for elective aortic surgery (abdominal aortic aneurysm resection or aorto-iliac reconstruction) (69). Thallium redistribution predicted postoperative ischemic events (unstable angina, ischemic pulmonary edema, MI, or cardiac death). Several clinical variables, including Q waves on ECG, history of CHF, and possibly presence of diabetes, also had predictive value. The absence of these variables was considered, along with the history of MI or angina, to attempt to identify a clinically low-risk subset of patients who could proceed directly to vascular surgery without further noninvasive testing. Only 1 (3.4%) of 29 low-risk patients (defined by absence of all five clinical markers) experienced a perioperative ischemic event (unstable angina), whereas seven (22%) higher-risk patients (defined by the presence of one or more of the five clinical markers) experienced a perioperative ischemic event. The stratification instrument was then prospectively validated in 50 patients undergoing vascular procedures. There were 23 low-risk patients, among whom no ischemic events occurred. Among the 27 patients with one or more clinical markers, the event rate was 37%, including three cardiac deaths. Thallium redistribution had been seen on preoperative dipyridamole-thallium scintigraphy for each patient who died.

These investigators later extended their observations by retrospectively analyzing 200 consecutive patients referred for vascular surgery (aorto-iliac or aortofemoral bypass grafting in 67 patients, abdominal aortic aneurysm resection in 71 patients, and peripheral vascular procedures such as femoral popliteal bypass or carotid endarterectomy in 62 patients) (69). In multivariate analysis, Q waves on the preoperative ECG, history of angina, history of ventricular ectopic activity requiring treatment, diabetes requiring pharmacologic therapy, and age older than 70 years were independent clinical predictors of postoperative ischemic events. The two independent dipyridamole-thallium scanning predictors of ischemic events were thallium redistribution and ischemic ECG changes during or after dipyridamole infusion (p <.01). Three logistic regression models were created to predict postoperative cardiac ischemic events: (a) clinical variables alone, (b) dipyridamole-thallium scanning results alone, and (c) both clinical and dipyridamole-thallium test variables. The sensitivities and specificities of these three models were compared.

Thallium redistribution was the most sensitive predictor, but it was less specific than several of the clinical variables, particularly the appearance of Q waves on the preoperative ECG. The model in which both clinical markers and dipyridamole-thallium test results were used achieved significantly higher specificity, at equivalent sensitivity levels, than models using either clinical variables alone or dipyridamole-thallium test results alone (eFig. 41.1.5). Of 64 patients with none of the five clinical variables, only two patients (3.1%; 95% CI, 0% to 8%) suffered postoperative cardiac ischemic events, compared to 10 (50%; 95% CI, 29% to 71%) of 20 patients who had three or more clinical markers. Patients with either one or two clinical variables had an intermediate risk; 18 ischemic events were seen in 116 patients (15.5%; 95% CI, 7% to 21%). The presence or absence of thallium redistribution further delineated the intermediate-risk group into low- and high-risk categories; only 2 (3.2%; 95% CI, 0% to 8%) of the 62 patients in the intermediate-risk subgroup without thallium redistribution experienced events, compared to 16 events (29.6%; 95% CI, 16% to 44%) among the 54 patients with thallium redistribution. Collectively, these studies indicate that the specificity of preoperative dipyridamole-thallium scintigraphy is improved by considering clinical variables. Such variables may be used to identify clinically low- and high-risk subsets of vascular surgery patients, while reserving dipyridamole-thallium imaging for further risk stratification of intermediate-risk patients.



***e*FIGURE 41.1.5** Clinical markers of risk (Q waves on electrocardiography, age >70 years, history of angina, history of ventricular ectopic activity requiring treatment, and diabetes requiring treatment) and thallium redistribution. **Unstable angina, ischemic pulmonary edema, myocardial infarction, or death. CI, confidence interval. (From Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. *Ann Intern Med* 1989;110:859–866, with permission.)

Baron and coworkers (74) prospectively evaluated 457 consecutive patients undergoing elective abdominal aortic aneurysm surgery with dipyridamole-thallium single-photon emission computed tomography (SPECT) and RVG. The cardiac event rate was 19% (prolonged myocardial ischemia in 61 patients, MI in 22, CHF in 20, severe ventricular tachyarrhythmia in two, and death from any cause in 20). Clinical evidence of CAD (OR, 2.6; 95% CI, 1.6 to 4.3) and age older than 65 years (OR, 2.3; 95% CI, 1.4 to 3.6) were better predictors of adverse outcome than thallium redistribution (OR, 1.1; 95% CI, 0.6 to 2.0). LVEF measured by RVG predicted only postoperative CHF. The authors concluded that the routine use of dipyridamole-thallium SPECT and RVG for preoperative cardiac risk assessment before abdominal aortic surgery might not be justified. Zarich and colleagues (128) prospectively evaluated 93 diabetic patients with quantitative planar thallium scintigraphy before noncardiac surgery. They divided the patient population into two groups: those with and those without clinical markers of significant CAD. Overall, adverse cardiac events occurred in nine patients, with MI in six patients and death in three patients. No adverse cardiac event occurred in diabetic patients who did not have the clinical markers (angina, CHF, MI, or pathologic Q waves), despite a 58% prevalence of abnormal thallium scans, signifying a low positive predictive value. They concluded that preoperative myocardial perfusion imaging might add little to cardiovascular risk assessment in asymptomatic diabetic patients who did not have other markers of significant CAD.

In a multicenter study that sought to develop and validate a Bayesian risk prediction model for vascular surgery candidates, L'Italien and coworkers (129) developed a prediction model involving 567 patients from two centers based on clinical variables (age older than 70 years, angina, history of MI, diabetes mellitus, history of CHF, and prior coronary revascularization). A second model was developed from dipyridamole-thallium scanning results (i.e., perfusion abnormalities and ST-segment changes). Model performance, alone and in combination, was evaluated using ROC analysis. The models were then validated in a separate cohort of 514 patients from three centers. The observed and predicted cardiac event rates were comparable for both sets. The addition of dipyridamole-thallium scan data reclassified more than 80% of intermediate-risk patients into low-risk (3% event rate) and high-risk (19% event rate) categories (p <.0001) but provided no stratification for patients classified as low risk or high risk by the clinical model. The authors concluded that clinical markers, weighted according to prognostic impact, reliably stratify risk for patients who are candidates for dipyridamole-thallium scintigraphy, obviating the need for more expensive testing.

Because of the association between CAD and peripheral vascular disease and a higher event rate in this population, most investigations have evaluated noninvasive testing in the population of patients undergoing vascular surgery. However, preoperative noninvasive cardiac risk assessment has also been evaluated in patients undergoing other noncardiac surgery, with similar results. Patients undergoing renal allograft surgery, like those in the vascular surgery cohort, are at an increased risk of coronary disease and ischemic complications. Brown and colleagues (130) studied this cohort preoperatively, using dipyridamole-thallium scintigraphy and RVG. Multivariate regression analysis revealed that a reversible thallium defect and LVEF were the only significant predictors of death or MI. Studies involving other groups of patients have demonstrated a positive predictive value of 8% to 27% and a negative predictive value of 98% to 100% for MI or death (131,132,133,134,135 and 136). Two general principles apply to risk stratification for nonvascular noncardiac surgery. First, risk stratification should be considered when the surgical procedure being undertaken is associated with substantial perioperative cardiac complications. Second, myocardial perfusion imaging is more helpful when it is applied in a population with a high prevalence of CAD (e.g., prior MI or history of angina). Because the prevalence of significant CAD is much lower among patients who do not have vascular disease, it may be more appropriate to use clinical evidence of coronary disease to determine whether to proceed with myocardial perfusion imaging for further risk stratification (124).

Newer imaging agents and modalities are now in common use. Technetium-99m sestamibi (MIBI), an agent with higher energy than thallium, produces superior image quality and may also have utility in preoperative coronary risk assessment (133,134,137). Two studies (138,139) described the value of dobutamine stress myocardial perfusion imaging in assessing cardiac risk associated with vascular surgery. Both studies (involving 126 and 142 patients) found a significantly increased risk of perioperative cardiac events among patients with reversible perfusion defects (50% vs. 5% and 19% vs. 3%, respectively) (140).

The ACC and the AHA task force summarized current knowledge regarding preoperative myocardial perfusion imaging methods (eTable 41.1.1) (103). The task force report noted that the predictive value of thallium redistribution for MI or death ranged from 4% to 20% in selected reports that included more than 100 patients. The positive predictive value has decreased over the course of time, a change that likely is related to use of thallium imaging results for therapeutic interventions such as coronary revascularization or intensive medical therapy before noncardiac surgery. Furthermore, the results of myocardial perfusion imaging may lead to the performance of less extensive procedures or cancellation of surgery. Nevertheless, the negative predictive value has remained high (approximately 99%), and the prognosis associated with normal results of scanning is excellent (103).

***e*TABLE 41.1.1** SUMMARY OF STUDIES EXAMINING THE VALUE OF DIPYRIDAMOLE-THALLIUM IMAGING FOR PREOPERATIVE ASSESSMENT OF CARDIAC RISK

Study, year	*N*[a]	No. (%) of patients with ischemia by TI-RD imaging	Events,[b] no.	Perioperative events: RD scan Positive predictive value	Perioperative events: Normal scan Negative predictive value	Comments
Vascular surgery						
Boucher et al., 1985 (62)	48	16 (33)	3 (6)	19% (3/16)	100% (32/32)	First study to define risk of thallium redistribution
Cutler et al., 1987 (207)	116	54 (47)	11 (10)	20% (11/54)	100% (60/60)	Only aortic surgery
Fletcher et al., 1988 (208)	67	15 (22)	3 (4)	20% (3/15)	100% (56/56)	
Sachs et al., 1988 (209)	46	14 (31)	2 (4)	14% (2/14)	100% (24/24)	
Eagle et al., 1989 (69)	200	82 (41)	15 (8)	16% (13/82)	98% (61/62)	Defined clinical risk
McEnroe et al., 1990 (114)	95	34 (36)	7 (7)	9% (3/34)	96% (44/46)	Fixed defects predict events
Younis et al., 1990 (142)	111	40 (36)	8 (7)	15% (6/40)	100% (51/51)	Included long-term follow-up
Mangano et al., 1991 (210)	60	22 (37)	3 (5)	5% (1/22)	95% (19/20)	Managing physicians blinded to results of scan
Strawn et al., 1991 (211)	68	NA	4 (6)	NA	100% (21/21)	
Watters et al., 1991 (212)	26	15 (58)	3 (12)	20% (3/15)	100% (11/11)	Included echocardiographic (TEE) studies
Hendel et al., 1992 (141)	327	167 (51)	28 (9)	14% (23/167)	99% (97/98)	Included long-term follow-up
Lette et al., 1992 (213)	355	161 (45)	30 (8)	17% (28/161)	99% (160/162)	Used quantitative index for scans
Madsen et al., 1992 (214)	65	45 (69)	5 (8)	11% (5/45)	100% (20/20)	

Brown et al., 1993 (215)	231	77 (33)	12 (5)	13% (10/77)	99% (120/121)	Prognostic utility enhanced by combination of scanning and clinical factors
Kresowik et al., 1993 (216)	170	67 (39)	5 (3)	4% (3/67)	98% (64/65)	Did not analyze for cardiac death; no independent value of scanning
Baron et al., 1994 (74)	457	160 (35)	22 (5)	4% (7/160)	96% (195/203), NFMI only	Cost-effectiveness data included
Bry et al., 1994 (138)	237	110 (46)	17 (7)	11% (12/110)	100% (97/97)	
Nonvascular surgery[c]						
Camp et al., 1990 (131)	40	9 (23)	6 (15)	67% (6/9)	100% (23/23)	Diabetes mellitus, renal transplant
Iqbal et al., 1991 (132)	31	11 (41)	3 (11)	27% (3/11)	100% (20/20)	Exercise thallium study, 86%; diabetes mellitus; pancreas transplant
Coley et al., 1992 (133)	100	36 (36)	4 (4)	8% (3/36)	98% (63/64)	Defined clinical risk factors for patients with known or suspected CAD
Shaw et al., 1992 (134)	60	28 (47)	6 (10)	21% (6/28)	100% (19/19)	Used adenosine
Takase et al., 1993 (135)	53	15 (28)	6 (11)	27% (4/15)	100% (32/32)	Patients with documented or suspected CAD underwent resting echocardiography
Younis et al., 1994 (136)	161	50 (31)	15 (9)	18% (9/50)	98% (87/89)	Intermediate- to high-risk CAD

CAD, coronary artery disease; NA, not applicable; NFMI, nonfatal myocardial infarction; Tl-RD, thallium redistribution; TEE, transesophageal echocardiography.

Note: Patient information was acquired prospectively in all studies except those by Coley and colleagues (133) and Shaw and associates (134). Only in reports by Mangano and coworkers (210) and Baron and colleagues (74) were the results of scanning blinded from attending physicians. Patients with fixed defects were omitted from calculations of positive and negative predictive value.

[a]No. of patients who underwent surgery.

[b]Myocardial infarction or death.

[c]Studies used pharmacologic and/or exercise thallium testing.

Reprinted from Eagle KA, Brundage BH, Chaitman BR, et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery: report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 1996;27:910–948, with permission.

Long-Term Prognostic Value of Perfusion Imaging

Because the prevalence of CAD is high among patients with peripheral vascular disease, patients undergoing peripheral vascular surgery remain at increased risk of cardiac events in subsequent years, even if they remain event-free during the immediate postoperative period (127). Hendel and colleagues (141) evaluated 360 patients, of whom 327 patients underwent vascular surgery. Operative death and nonfatal MI occurred in 4.9% and 6.7%, respectively. A cardiac event (nonfatal MI or cardiac death) occurred in 14.4% of patients with a transient thallium defect, compared to 1% among patients with normal results of scanning (p <.001). Multivariate analysis revealed that the best predictor of perioperative events was the presence of a reversible thallium defect. Late cardiac events occurred in 53 (15.2%) surgical survivors or nonsurgically treated patients who were followed for a mean of 31 months. Patients with a fixed perfusion abnormality had a 24% late-event rate, compared with 4.9% among patients with normal results of the dipyridamole-thallium study (p <.01). Cox regression analysis showed that a fixed thallium defect was the most powerful predictor of late events and increased the relative risk by almost fivefold. A history of CHF was the only significant clinical variable that contributed additional value to knowledge of the presence of a fixed defect. Life-table analysis confirmed the strong relationship between fixed defects and cardiac event–free survival (p <.0001).

Younis and coworkers (142) also evaluated late outcomes among 131 patients scheduled for peripheral vascular surgery. Two years after surgery, the actuarial event-free survival rate for patients with thallium redistribution was approximately 50%. Urbinati and colleagues (207) evaluated early and late cardiac events among 106 patients with neither history nor symptoms of CAD who underwent exercise thallium myocardial perfusion imaging before carotid endarterectomy. No cardiac deaths or MIs occurred within 30 days of surgery. However, actuarial survival without coronary events was 51% among patients with positive results of stress test and thallium redistribution, compared with 98% among patients without such results (p <.01) by 7 years (Fig. 41.2).

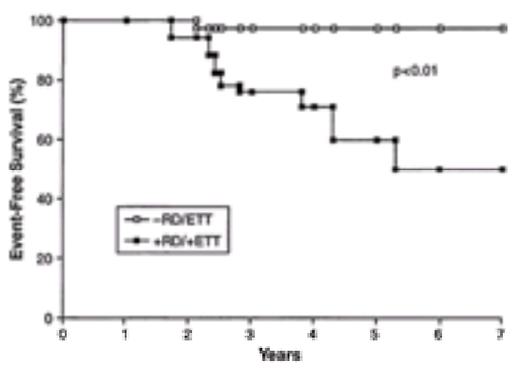


FIGURE 41.2 Long-term follow-up in patients undergoing exercise thallium-201 imaging before carotid endarterectomy. p <.01. ETT, positive stress electrocardiogram; RD, reversible defects.

Among 172 patients who were followed for a mean of 21 ± 14 months after elective vascular surgery, event-free survival was significantly less for patients with abnormal MIBI scans than for those with normal scan results (74% vs. 96%; p <.0001). After controlling for other clinical factors using Cox proportional hazards models, abnormal results of an MIBI study (relative risk, 3.7; 95% CI, 1.2 to 11.4) and MIBI-detected ischemia (relative risk, 2.7; 95% CI, 1.2 to 6.1) remained significant predictors of increased risk of late cardiac events (143). More recently, Cohen and associates (144) reported long-term prognostic significance of preoperative dipyridamole technetium-99m MIBI scanning in vascular surgery patients. They followed 153 patients for as long as 4 years after the dipyridamole MIBI scan to determine nuclear imaging predictors of death and MI. The only statistically significant predictor of death and MI visible on dipyridamole MIBI scanning was abnormality in the left anterior descending artery territory (adjusted relative risk, 2.9; 95% CI, 1.2 to 7.3).

Stress Echocardiography

Several reports have evaluated the accuracy of pharmacologic stress echocardiography in identifying patients who are at risk for postoperative cardiac events (65,66,145,146,147,148,149 and 150) (Table 41.2). Most studies have used dobutamine, although dipyridamole has also been used. The populations examined predominantly have been patients undergoing vascular surgery. Only one study has blinded clinicians to the echocardiographic results (147). In the other studies, results affected management, including decisions about whether to perform preoperative coronary angiography and coronary revascularization. Among the studies of preoperative dobutamine echocardiography, the positive predictive value for MI and death ranged from 7% to 23%; the negative predictive value was 100% in all but one study. The severity of wall motion changes at low-dose dobutamine infusion may be especially important. Furthermore, Poldermans and coworkers (151) have shown that stress-induced ischemia on dobutamine echocardiography is predictive of late cardiac events after vascular surgery. Recently, Ballal and coauthors (152) reported long-term cardiac outcome in 233 vascular surgery patients who underwent preoperative dobutamine stress echocardiography. Late events occurred in 36 patients after a mean follow-up of 28 months. New or worsening regional wall motion abnormality was predictive of these events, even after the analysis was adjusted for clinical variables and left ventricular dysfunction (relative risk, 3.3; p = .001).

Video 41.6 Dobutamine echo. Parasternal long-axis view of a patient with left anterior descending artery scar and peri-infarct ischemia. No obvious ischemia is seen in this view (see apical two- and four-chamber views). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 41.7 Stress echo of a patient with left anterior descending coronary artery ischemia, parasternal long-axis and short-axis views. Note the deterioration of the anteroseptal wall (upper right panel) and the anteroseptum and anterior walls (*lower right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 41.8 Stress echo (apical views) of a patient with left anterior descending coronary artery ischemia. Note the worsening of the distal septum and entire anterior wall. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 41.9 Parasternal long-axis view of a dobutamine stress echo demonstrating viability and ischemia in the left anterior descending coronary artery territory. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 41.10 Parasternal short-axis view of a dobutamine stress echo demonstrating a biphasic response (viability and ischemia) in the left anterior descending coronary artery territory. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 41.11 Stress echo of a patient with right coronary artery ischemia: **Upper panels:** Apical four-chamber view showing worsening of basal septum (rest images to left, stress images to right). **Lower panels:** Apical two-chamber view demonstrating deterioration of the basal and mid inferior wall. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 41.12 Parasternal long-axis view of a dobutamine stress echo of a patient with three-vessel coronary artery disease. Note the deterioration of the anteroseptal and posterior walls in this view and the chamber dilatation. The images are arranged from upper left image = rest, to upper right and lower left = low-dose infusion, to lower right = peak infusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Study, year	Patients with ischemia who underwent surgery, no. (%)	Events,* no. (%)	Criteria for abnormal test results	Predictive value†		Comments
				Positive†	Negative	
Lane et al., 1991 (60)	28 (60)	2 (8%)	New WMA	14% (2/14)	100% (19/19)	Vascular and general surgery
LeBlanc et al., 1992 (145)	60 (60)	9 (15%)	New or worsening WMA	23% (7/30)	93% (28/30)	Multivariate analysis
Eichelberger et al., 1992 (146)	75 (30)	2 (3%)	New or worsening WMA	7% (2/27)	100% (48/48)	Managing physicians blinded to DSE results
Langer et al., 1993 (147)	74 (24)	3 (4%)	New WMA or ICC/dilatation	11% (2/18)	100% (56/56)	
Poldermans et al., 1993 (148)	131 (27)	5 (4%)	New or worsening WMA	14% (5/35)	100% (96/96)	Multivariate analysis, managing physicians blinded to DSE results
Davila-Roman et al., 1995 (149)	86 (23)	2 (2%)	New or worsening WMA	10% (2/20)	100% (66/66)	Included long-term follow-up

DSE, dobutamine stress echocardiogram; WMA, wall motion abnormality.
*Myocardial infarction or death.
†Numbers in parentheses are no. of patients/total no. in each group.
Reprinted from Eagle KA, Brundage BH, Chaitman BR, et al: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery: report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 1996;27:910-948, with permission.

TABLE 41.2 SUMMARY OF STUDIES EXAMINING THE VALUE OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY (ECG) FOR PREOPERATIVE RISK ASSESSMENT

A metaanalysis of published reports on preoperative pharmacologic stress risk stratification identified ten reports on dipyridamole–thallium-201 scintigraphy and five on dobutamine stress echocardiography (153). Random effect models were used to calculate the summary OR and 95% CIs. The summary OR for death or MI and secondary cardiac end points were greater for dobutamine-induced echocardiographic dyssynergy (14-to 24-fold) than for dipyridamole-thallium defect redistribution (fourfold). However, wide CIs were noted with dobutamine echocardiography (Fig. 41.3). Therefore, the published experience with stress echocardiography is not as extensive as that with radionuclide perfusion imaging, but the literature to date suggests that dobutamine stress echocardiography is a valuable risk stratification modality.

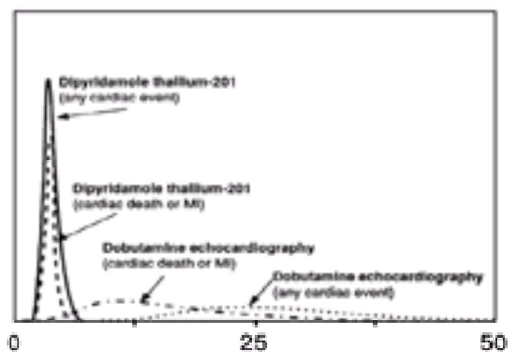


FIGURE 41.3 Summary odds ratio and 95% confidence intervals for risk stratification of patients undergoing pharmacologic stress perfusion and echocardiographic imaging, as determined by metaanalytic confidence profile method. Because of larger sample sizes, narrower confidence profiles are seen for dipyridamole–thallium-201 perfusion imaging than for dobutamine stress echocardiography, although point estimates for the summary odds ratio are greater using echocardiography. MI, myocardial infarction. [From Shaw LJ, Eagle KA, Gersh BJ, et al. Meta-analysis of intravenous dipyridamole–thallium-201 (1985–1994) for risk stratification before vascular surgical candidates. *J Am Coll Cardiol* 1996;27:787–798, with permission.]

Alternative Methods of Risk Stratification

The predictive value of ambulatory ECG monitoring for 24 to 48 hours preoperatively has been reported by several investigators who studied patients undergoing vascular and other types of noncardiac surgeries (81,107,154,155,156,157,158 and 159). Although some of these reports have suggested favorable utility, preoperative ST-segment monitoring has several significant limitations, including a low positive predictive value (10%) (102). Finally, other imaging modalities may have limited utility. Coronary calcification on computed tomographic scans performed before noncardiac thoracic surgery has been shown to be predictive of postoperative cardiac morbidity (160). Stress magnetic resonance imaging or ultrafast cine computed tomography theoretically should identify patients at risk. However, less expensive and more widely available technologies exist.

Perioperative Evaluation of Other Cardiac Conditions

To this point, we have considered the evaluation of the patient only in terms of the presence or absence of significant CAD and the implications for prognosis. However, preoperative cardiac consultation is sought for a variety of indications, including CHF, murmurs, and arrhythmias (51,52 and 53).

CHF is an important harbinger of poor postoperative outcome (64,65,161). Therefore, great effort should be made to identify and treat unsuspected heart failure by performing a careful history and physical examination. It is important to identify the mechanism of CHF, because systolic dysfunction, diastolic dysfunction, and valvular abnormalities all can cause this syndrome, and management of each of these disease entities is significantly different. Determination of etiology may have prognostic implications (103).

Cardiac murmurs are common. The cardiology consultant must determine etiology and distinguish significant murmurs from those that are not clinically important. Severe aortic stenosis conveys high risk (57) and may justify postponement or cancellation of surgery. Rarely, percutaneous balloon aortic valvuloplasty may be justified in a patient who is not a candidate for aortic valve replacement, which is the preferred treatment before noncardiac surgery (103). Mild or moderate mitral stenosis requires monitoring to maintain reasonable control of heart rate to reduce the risk of pulmonary congestion associated with a decreased diastolic filling period. Patients with severe mitral stenosis may benefit from balloon mitral valvuloplasty or open surgical repair before high-risk noncardiac surgery (103). Patients with regurgitant lesions may benefit from heart-rate control, antibiotic prophylaxis, or afterload reduction, depending on the etiology and severity of the lesions. Patients with prosthetic valves should receive appropriate antibiotic prophylaxis for endocarditis (162). In addition, patients with mechanical prosthetic valves require careful management of coagulation and may need a short course of intravenous heparin therapy.

Cardiac arrhythmias and conduction disturbances are common in the perioperative period (56,86,163). Although both supraventricular and ventricular arrhythmias have been associated with increased risk of adverse postoperative cardiac events, they are probably markers for underlying cardiopulmonary disease that places a patient at higher risk. Perioperative atrial fibrillation is a common arrhythmia, especially after intrathoracic surgical procedures; direct atrial irritation may be the operative mechanism. Because of the increased catecholamine state that occurs in the immediate postoperative period, it may not be possible to maintain sinus rhythm, and therapy should be directed at heart-rate control and anticoagulation, if indicated (164). Cardioversion is usually reserved for hemodynamically compromising atrial fibrillation. Most arrhythmias are not malignant, but their presence can expose underlying disease that may compromise the patient (e.g., new atrial fibrillation with rapid ventricular response that precipitates ischemia and subsequent CHF). Patients with conduction disease and no history of high-grade atrioventricular block generally do well. However, high-grade atrioventricular block may require insertion of a temporary pacing wire. Transcutaneous pacing allows rapid response to sudden and hemodynamically significant heart block (106).

For patients with pulmonary vascular disease, the risk associated with noncardiac surgery is higher. Abnormal pulmonary vasoreactivity may make these patients prone to further increases in pulmonary vascular resistance during periods of perioperative hypoxia (164). Corrected and uncorrected congenital heart disease, sometimes associated with pulmonary vascular disease, may be accompanied by lower cardiac reserve, increasing perioperative risk (164). However, pulmonary hypertension has not been extensively studied as an independent perioperative risk factor for noncardiac surgery.

The cardiology consultant may also play an important role in patient care during recovery from surgery. Postoperative arrhythmias, hypotension, and hypertension may occur in the postanesthesia care unit. The consultant should evaluate the patient's volume status to prevent hypotension and CHF in the first 48 hours (54). Because of the risk of ischemic events in patients with CAD, the cardiology consultant should check the ECG immediately after surgery. The consultant should also check the ECG daily and follow the patient for at least 3 days after the operation if the patient remains in the hospital.

Risk Reduction

Risk reduction is the cornerstone of preoperative evaluation and management. Generally, interventions aimed at reducing perioperative cardiac risk can be classified as perioperative monitoring, medical therapy, or preoperative revascularization. In preoperative monitoring, the role of pulmonary artery catheters has been studied, although not extensively. The effect of various medical therapies, including beta-blockers, alpha-adrenergic agents, and calcium channel blockers has been reported. Preoperative coronary revascularization to decrease cardiac risk has also been studied, but most of the data have been observational.

There is some evidence that optimization of preoperative hemodynamics may be beneficial (165), and careful perioperative hemodynamic monitoring may decrease cardiac morbidity (166). However, Bender and associates (167) randomly assigned 104 patients to one of two groups: a group in which all patients received a pulmonary artery catheter and a group in which only patients with accepted indications for pulmonary artery catheterization received such a catheter. The authors demonstrated no significant difference in rates of intraoperative and postoperative complications or mortality between the two groups. Valentine and colleagues (168) reported a randomized trial studying the routine use of pulmonary artery catheters in 120 patients undergoing aortic surgery. They found no significant reduction in morbidity and a higher rate of intraoperative cardiac events among patients who had a pulmonary artery catheter. Overall, the routine use of pulmonary arterial catheters in the initial care of surgical patients has been discouraged (167,168,169 and 170). Consultants should be aware that insertion of a pulmonary artery catheter, by itself, does not constitute a cure. It is only by obtaining vital information that is used to guide therapy and interpreting that information correctly that the pulmonary artery catheter may prove useful (170). Furthermore, a retrospective analysis of data for patients who underwent abdominal aortic surgery revealed that risk of cardiac arrest was higher when no daily rounds were made by an intensive care unit physician (OR, 2.9; 95% CI, 1.2 to 7.0) (171). Therefore, careful postoperative management of critical patients by an intensivist and sound decision making based on clinical and procedural data are the only monitoring strategies that may be recommended.

Several studies suggest that beta-blockade may be beneficial in the perioperative period and long term in patients who have undergone noncardiac surgery (172,173 and 174). The first well-designed trial randomly assigned 200 patients undergoing noncardiac surgery to receive atenolol or placebo. Atenolol was used intravenously before and immediately after surgery and orally thereafter for the duration of the hospitalization. No difference was noted in the perioperative MI or death, but the overall mortality after discharge from the hospital was significantly reduced among patients who received atenolol (0% vs. 8% at 6 months; p <.001; 3% vs. 14% at 1 year; p = .005; 10% vs. 21% at 2 years) (172). However, the placebo group had a higher risk profile as a result of unequally distributed risk factors. More recently, Poldermans and coworkers (174) performed a randomized trial involving 173 high-risk patients in whom inducible regional wall motion abnormalities were seen on dobutamine stress echocardiography to assess the effect of perioperative bisoprolol on the incidence of cardiac events within 30 days after a major vascular surgery. The primary end point of cardiac death and MI occurred in two patients (3.4%) in the bisoprolol group versus 18 patients (34%) in the group of patients who received standard care without beta-blockers (p <.001). This dramatic reduction in events may be partly attributed to selection bias; the study was performed in a high-risk cohort in which an exceptionally high event rate was seen in the placebo group.

Administration of nitroglycerin in the perioperative period may decrease the incidence of intraoperative myocardial ischemia, but reduction in the incidence of MI or cardiac death has not been demonstrated (175,176). One small study evaluated the efficacy of use of intravenous diltiazem in patients undergoing vascular surgery. A lower incidence of myocardial ischemia was noted among patients who were receiving diltiazem. However, the study was too small for it to be possible to draw conclusions about the effect of diltiazem on MI or death (177). Perioperative use of $alpha_2$-agonists has also been studied in few small randomized trials that failed to demonstrate a significant reduction in postoperative events (178,179). In a European multicenter trial, 2,801 patients with known CAD who were undergoing noncardiac surgery were assigned to receive intravenous mivazerol (an $alpha_2$-agonist that reduces postganglionic noradrenaline availability and sympathetic efferent output) or placebo. Mivazerol failed to reduce the overall rate of death and MI. However, among a preselected cohort of patients with known CAD who were undergoing vascular

surgery, a reduced risk of death and MI was seen in the mivazerol group (relative risk, 0.67; 95% CI, 0.45 to 0.98) (180). Further study of the alpha-adrenergic agents may, therefore, be warranted. Presumably, these medical interventions could prevent postoperative adverse cardiac events that are preceded by tachycardia and ECG evidence of ischemia (181,182).

Interventions aimed at increasing oxygen supply through increased oxygen delivery (183) or improved blood flow via intraaortic balloon counterpulsation (IABP) may reduce postoperative cardiac morbidity and mortality (183,184 and 185). Arafa and associates (186) analyzed 344 patients undergoing cardiac operations who required perioperative use of IABP, with a mean follow-up of 7.45 years. On regression analysis, timing of IABP insertion was identified as an independent predictor of early (30-day) mortality (p <.05) and late death (p <.05). Survival analysis demonstrated significantly improved survival among patients who received an IABP preoperatively (p <.02). These studies may justify allowing preoperative IABP a more liberal role in treatment of high-risk patients undergoing cardiac surgery.

There are no randomized trials to evaluate the protective role of percutaneous coronary revascularization before noncardiac surgery. Studies by Golden and colleagues (187) and Younis and coworkers (136) suggest that coronary intervention in patients identified as high risk by myocardial perfusion scintigraphy may improve cardiac outcomes. Retrospective analysis of data regarding the role of use of percutaneous transluminal coronary angioplasty (PTCA) for preoperative revascularization has been reported (188,189 and 190). All three studies reported a low incidence of perioperative cardiac events after noncardiac surgery. However, these studies did not define a clear indication for PTCA, and they also lacked a control arm, making interpretation of the results difficult. A recent study that used an administrative database of patients who underwent noncardiac surgery revealed that PTCA was associated with significant reduction in perioperative cardiac events (191). Interestingly, the percutaneous revascularization procedure reduced risk only if it was performed more than 90 days before surgery. This finding suggests that PTCA immediately before surgery may not confer protection against perioperative cardiac events, and that the immediate postprocedure period is probably not the optimal time for noncardiac surgery. Coronary stenting before noncardiac surgery presents a unique clinical dilemma because of the risk of acute stent thrombosis and bleeding complications associated with postprocedure anticoagulation. Kaluza and colleagues (192) studied 40 patients who underwent noncardiac surgery less than 6 weeks after coronary stent placement. Seven MIs and eight deaths occurred, all in patients who underwent surgery fewer than 14 days after coronary stenting. Judging by ECG and by enzymatic and angiographic evidence, stent thrombosis accounted for most of the fatal events. Therefore, postponing elective noncardiac surgery for at least 4 weeks after coronary stenting should allow completion of a mandatory antiplatelet regimen, thereby reducing the risk of postoperative cardiac events.

Studies have shown that patients who have undergone recent CABG before noncardiac surgery have postoperative cardiac morbidity and mortality rates that are similar to those among patients who have no clinical evidence of CAD (193,194 and 195). Manske and colleagues (196) performed a randomized trial in which patients with coronary disease who were scheduled to undergo renal transplantation were assigned to receive medical therapy or CABG. Although a 57% reduction in cumulative probability of unstable angina, MI, or death at 12 months was observed among patients who underwent revascularization compared with that among medically treated patients and the study was terminated early, loss to follow-up and small size limit the study's usefulness. A similar randomized trial involving patients who had peripheral vascular disease has not been performed. However, the CASS registry provided a unique opportunity to evaluate the outcome of patients with CAD who were either medically managed or had undergone CABG and subsequently underwent noncardiac surgery. Eagle and colleagues (86) evaluated 3,368 patients, of whom 1,546 were undergoing abdominal, vascular, or head and neck surgeries. Among the patients who underwent these high-risk procedures, a dramatic reduction in event rates and fewer deaths (1.7% vs. 3.3%; p = .03) and MI (0.8% vs. 2.7%; p = .002) were seen in the CABG group than in the medically treated group. Rihal and associates (197) analyzed data from the CASS registry to examine the long-term outcomes of 1,834 patients undergoing noncardiac surgery. For patients treated with CABG, the Kaplan-Meier 8-year and 16-year survival rates were 72% and 41%, respectively; for the medically treated group, the corresponding survival rates were 57% and 34%, respectively (p <.0001). However, the benefits were limited to patients with three-vessel CAD and inversely related to LVEF. These data may suggest that the relatively high short-term risks of CABG may be outweighed by the long-term benefits, even though the overall long-term survival rates among patients with peripheral vascular disease remain poor. Finally, in a recently published analysis of the Bypass Angioplasty Revascularization Investigation trial, patients randomly assigned to undergo CABG or PTCA who underwent noncardiac surgery during the follow-up period were evaluated for perioperative cardiac events (198). After an average of 29 months of follow-up, low perioperative event rates were associated with both of the revascularization procedures (1.6% in each group), suggesting that coronary revascularization of either type may reduce the event rate of cardiac complications after noncardiac surgery (199).

Certain issues regarding risk reduction remain unresolved: (a) the lack of randomized trials that evaluate preoperative coronary revascularization and the optimal timing for the revascularization procedure, (b) the optimal timing and duration of perioperative beta-blocker therapy and the usefulness of beta-blockers to treat patients undergoing nonvascular surgery and low-risk patients, and (c) the role of alpha-adrenergic agents and the usefulness of their addition to perioperative beta-blocker therapy.

Stepwise Approach to Preoperative Cardiac Risk Assessment

Preoperative cardiac testing achieves both short-term and long-term risk assessment. With use of current anesthetic, surgical, and medical care techniques, it is rare for the clinician to encounter a patient in whom the noncardiac surgical risk exceeds that associated with CABG. Therefore, strategies that are known to improve long-term outcomes should guide decision making, and in this regard, the preoperative setting represents for many patients the first opportunity for coronary evaluation. Additionally, preoperative evaluation may have value other than the detection of significant CAD, including the identification of asymptomatic or minimally symptomatic valvular or myocardial disease that requires long-term management. Costs and quality of testing modalities vary locally and regionally. The cost-effectiveness of alternative modalities, such as preoperative stress echocardiography, has not been evaluated to date. Therefore, the clinician must weigh these factors in determining a risk assessment strategy that is appropriate for a specific patient.

The ACC and the AHA have jointly produced guidelines, based on current knowledge, for cardiac evaluation before noncardiac surgery. A general strategy for preoperative cardiac risk assessment is summarized in Figure 41.4. Ideally, this strategy should be applied in the outpatient setting for elective surgery. A stepwise approach to risk stratification includes the following (103):

FIGURE 41.4 American College of Cardiology/American Heart Association Guidelines flow diagram. *Subsequent care may include cancellation or delay of surgery, coronary revascularization followed by noncardiac surgery, or intensified care. **Major clinical predictors: unstable coronary syndromes, decompensated congestive heart failure, significant arrhythmias, severe valvular disease. †Intermediate clinical predictors: mild angina pectoris, previous myocardial infarction (MI), compensated or previous congestive heart failure (CHF), diabetes mellitus. ‡Minor clinical predictors: advanced age, abnormal results of electrocardiography (ECG), rhythm other than sinus, low functional capacity, history of stroke, uncontrolled systemic hypertension. MET, metabolic equivalent.

1. Determine whether the patient has undergone coronary revascularization in the past 5 years. Prior coronary revascularization probably reduces the cardiac risk associated with noncardiac surgery (70,71).
2. Determine whether the patient has had an adequate, favorable prior cardiac evaluation in the past 2 years. If there have been no new intercurrent symptoms, it may not be necessary to repeat costly testing.
3. Determine whether the patient has an unstable coronary syndrome or a major clinical predictor of risk (e.g., decompensated heart failure, significant arrhythmias, severe valvular disease), which usually leads to cancellation or delay of surgery until the problem has been diagnosed and treated.
4. Determine whether the patient has intermediate clinical predictors of risk (e.g., prior MI recognized by history or by ECG, angina pectoris, compensated or prior heart failure, and diabetes mellitus). Consider the patient's functional capacity and surgery-specific risk.
5. Patients who have no major predictors but who have intermediate predictors of clinical risk and at least moderate functional capacity generally may undergo intermediate risk surgery with low probability of perioperative MI or death. Conversely, patients with poor functional capacity (inability to exercise at 4 metabolic equivalents) or who have multiple markers of risk and who are undergoing higher-risk surgery should undergo noninvasive evaluation to further stratify risk. If the anticipated risk of surgery is high and results of noninvasive testing show abnormalities that suggest significant CAD, coronary angiography, followed by coronary revascularization if appropriate, should be considered.
6. Noncardiac surgery is generally safe for patients with neither major nor intermediate predictors of clinical risk and at least moderate functional capacity.
7. Use results of the preoperative evaluation, including noninvasive testing in selected patients, to determine further preoperative management. Use information

gained during preoperative evaluation and careful postoperative surveillance to tailor long-term therapy and follow-up.

To date there have been no large prospective studies of preoperative cardiac risk reduction, in part because of the difficulties associated with designing and carrying out such investigations (74). Because of the lack of sufficient sound evidence, the decision to perform coronary angiography based on preoperative noninvasive cardiac testing remains difficult, controversial, and costly. The ACC/AHA guidelines for perioperative cardiovascular evaluation before noncardiac surgery do not address whether coronary angiography should be performed in response to specific test results (103). Therefore, using a modification of the *Delphi method* (a term sometimes used to describe a reiterative process by which consensus panels make recommendations), Cohen and Eagle (200) offered an expert opinion regarding the indications for preoperative coronary angiography when results of noninvasive tests are known. There was agreement that catheterization should be performed for (a) ischemia seen on exercise ECG in a patient with a blood pressure drop greater than 10 mm Hg; (b) stress perfusion scan reversibility in greater than or equal to one-half of SPECT slices; and (c) ischemia seen on stress echocardiography in more than five segments, more than two coronary artery zones, or four left anterior descending coronary artery segments. Therefore, in general, coronary angiography should be performed in the appropriate clinical context, based on results of noninvasive tests that indicate large zones of myocardial ischemia, and should not be performed for patients who have limited ischemia without other significant clinical findings.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Cardiology consultants frequently provide perioperative cardiac care. Evidence supports selective screening and efforts at cardiac risk reduction. “Universal precautions,” including intensified antiischemic medical regimens and close hemodynamic monitoring, combined with constantly improving surgical and anesthetic techniques, may make preoperative cardiac risk assessment less cost-effective. In this context, surgery may be considered just one of many potential triggers of cardiac morbidity and mortality with which a person may come in contact during daily life. The preoperative cardiac consultation may, therefore, represent an opportunity to initiate or modify cardiac care, including primary and secondary preventive measures. The consultant should assess and suggest management for risk factors for CAD (e.g., hypertension and hyperlipidemia) and heart failure. Further evaluation may be appropriate after the patient has recovered from surgery. The physician responsible for the long-term care of the patient should receive pertinent information obtained during the perioperative consultation (103). One of the most important aspects of a consultation is referral back to the primary care provider. This ensures that the physician responsible for the overall medical needs of the patient remains involved in the individual’s care. Also, the primary care provider may have the benefit of long-term follow-up, providing more insight into the social and psychological aspects of patient care. Lastly, referral back to the primary care provider helps strengthen the relationship between the consultant and the referring physician, which may result in continued referrals to the consultant’s practice.

THE FUTURE

Regardless of the political and economic environment in which medicine is practiced, successful cardiology consultation requires more than proficiency in taking histories, examination, and test interpretation. The ideal consultant “informs without patronizing, educates without lecturing, and directs without ordering. . . .” (36). Cardiology consultants might gain from the adage: “Successful consultation depends on the ‘3 A’s’: affability, availability, and ability—in that order!”

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MEDICAL ECONOMICS IN CARDIOVASCULAR MEDICINE

DANIEL B. MARK

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

During the late 1960s and 1970s (an era that has been euphemistically termed the *open checkbook era* in health care), hospitals and doctors in the United States were paid essentially what they charged. Competition on price was nonexistent, but competition among hospitals to have the most modern, technologically up-to-date facilities was fierce. The resulting double-digit annual escalation in health care costs alarmed policy makers and private businesses and led to the first concerted efforts to control the growth of medical spending (1).

The failure of modest efforts at medical cost control during the 1970s and 1980s convinced many payers that the medical establishment would not voluntarily become fiscally accountable. In the late 1980s, the business and insurance communities began an aggressive bid for control of health care costs and increased accountability in medicine, catching the profession largely by surprise (2). Many physicians had assumed that the value of the U.S. health care system was self-evident and hence that their dominant role in it was assured. Others believed that pathophysiologic reasoning or personal experience and judgment were sufficient to justify a course of action, regardless of the cost. Still others regarded any discussion of costs as demeaning to the profession. These attitudes largely became untenable when multiple outcome studies in the 1980s demonstrated that physicians practicing in different areas of the country made remarkably different management decisions for similar patients (3,4). Other studies from this period reported that doctors across the country performed significant numbers of unnecessary surgical procedures, particularly coronary bypass surgery. Together, variability of practice and appropriateness of care studies suggested the presence of substantial waste in the medical care system and demonstrated that physicians and hospitals by themselves had no incentives to develop a more standardized and efficient mode of practice.

Managed care can trace its origins back to the 1930s, but it first gained serious national attention during the 1970s as a method of controlling escalating health care costs. It was not until the late 1980s, with costs continuing to rise unabated and the medical establishment's prestige and credibility in tatters, that managed care began its exponential growth phase. Two major factors have driven this expansion: (a) the failure of health care reform efforts during the first term of the Clinton administration and (b) the demand by large employers for their employee health care costs to start shrinking rather than growing. For a brief period in the 1990s, managed care became the *de facto* national health care reform policy in the United States. However, because it is driven by market interests rather than carefully crafted policy, it does not address many key issues (such as access to care and funding of medical research and education). Furthermore, managed care will not be successful in the long-term control of medical spending. Between 1999 and 2006, medical costs in the United States are expected to double. The pressure from payers to resist these increases is therefore likely to intensify in the next 5 years. For clinicians to be partners in shaping the future of medicine during the critical period to come, they must understand the outcomes of medical care and its costs. The purpose of this chapter is to provide a general introduction to the key concepts of medical cost analysis and to review current knowledge about the economic consequences of cardiovascular diagnostic and therapeutic technologies.

MAJOR MEDICAL COST CONCEPTS

Medical cost analysis is a hybrid field that owes as much to the discipline of accounting as to economics. Economics provides much of the theoretical framework, whereas cost accounting deals with issues of empiric measurement. This section provides an introduction to the major economic and accounting concepts of medical cost and an overview of cost terminology that clinicians are likely to encounter and then examines the issue of empiric cost measurement. The section concludes with an examination of selected methodologic issues that are relevant to studying costs in the medical arena.

Medical Cost: General Considerations

To the average person, "cost" means money. The accountant has a more detailed notion of the resources required to produce the good or service that underlies any given monetary payment (5,6). The economist, however, operates from a more theoretical position (7,8). A major economic axiom is that any societal decision to use resources in the production of goods or services is accompanied by foregone opportunities to do something else with those resources (9,10). Because each health service or program uses up some societal resources that could have been used for some other purpose, it thereby involves a cost. Economists refer to this as *opportunity cost*. When economists talk about cost, they usually have opportunity cost rather than dollars in mind.

Economics also holds as axiomatic that society's resources are finite. Hence, choices must be made among the competing goals that society has for its resources, and not all goals can be fulfilled (9,10). Economics provides a set of tools to help define alternatives and make choices. In this context, the health economist is concerned with answering three basic questions (7,8):

1. How much should be spent on health care and what health care goods and services should be produced?
2. How shall these goods and services be produced?
3. For whom shall they be produced?

Resources are typically divided into large generic categories, such as labor, land, and capital (e.g., machines, factories, and stores of materials). The application of technology allows society to convert these raw resource inputs into desired goods and services, such as medical care. To compare societal choices for potential alternative uses of resources, it is necessary to assess the opportunity cost of health care, weapons, public education, and other societal priorities in some common metric. Some societies use barter, the transformation of one good into another of equivalent value through physical exchange, to match goods and services to individual needs. In industrialized societies, however, markets are used to match buyers and sellers, and money is used as the exchange intermediary. The market price in these societies then represents the amount of money equivalent in value to the total resource inputs used in the production of each good or service. (Market prices also include a profit component that ideally is equivalent to a fair rate of return on investment.) The key concept to the economist is consumption of resources. The dollar cost is merely a convenient way of valuing all the disparate resources involved on a common scale.

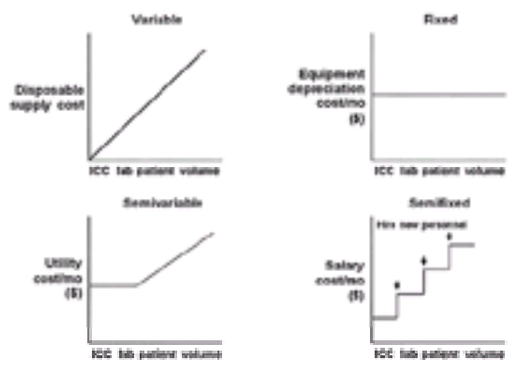
Medical Cost: Terminology

Several types of cost terms are used in the medical economics literature (*e*Table 42.0.1). One set of terms describes the behavior of cost as production volume

changes (1,5,9,10) (eFig. 42.0.1). *Variable costs* are those that change with unit changes in service volume; *fixed costs* remain unchanged as production of health care services (e.g., tests or treatments) is increased or decreased. For example, each extra balloon angioplasty catheter or coronary stent that is used in a revascularization procedure increases the cost of the procedure in a predictable fashion. These items would be counted as variable costs in a cost analysis. In contrast, the catheterization laboratory itself is a fixed cost. Whether two or ten cases are done a day in that facility has no effect on the costs that are attributable to the facility (such as depreciation of the building and the major equipment in it). (It should be noted also that a cost is fixed in relation to a finite defined period of time. With a long enough time horizon, virtually all costs become variable.)

***e*TABLE 42.0.1** MAJOR COST CONCEPTS AND TERMINOLOGY

Behavior of cost relative to health care service production
Variable costs
Fixed costs
Semifixed costs
Traceability to the production of health care services
Direct costs
Indirect costs (overhead)
Cost changes with shifts in the use of health service
Marginal costs
Incremental cost
Future cost consequent to initial health care provided
Induced costs (and savings)
Societal costs due to lost productivity
Indirect costs (productivity costs)



***e*FIGURE 42.0.1** Graphic representation of terms relating behavior of cost to production volume changes. ICC, intensive coronary care.

Many costs do not behave as either completely variable or fixed. Hence, two additional cost behavior terms are occasionally used to describe hybrid categories (1). *Semifixed costs* change with changes in output but in a step fashion rather than continuously (eFig. 42.0.1). Catheterization laboratory personnel often represent fixed costs because they are paid a certain salary per month regardless of the caseload. However, if the laboratory volume goes up past a certain threshold, the director may need to hire additional staff. The costs of running the facility would then increment up by the amount of these additional salaries. Alternatively, persistently low volume may persuade the laboratory director to downsize by reducing the staff of the facility. This would step the fixed costs down accordingly.

The other hybrid cost behavior category is *semivariable*. This type of cost typically starts with a fixed component and then becomes variable past a certain threshold (eFig. 42.0.1). For example, the electricity cost in the catheterization laboratory would be greater than zero even if no cases were done at all. Each case increases the electricity cost of the laboratory beyond this fixed threshold in a proportional or variable manner. Other utility costs tend to behave in the same fashion. Personnel costs may also behave this way if the laboratory uses a core of salaried employees and supplements them with temporary help who are paid on an hourly basis.

Another set of cost terms describes the traceability of individual costs to the production of health care services (eTable 42.0.1). *Direct costs* can be unambiguously linked to the production of a given product or service. They are also generally under the control of the health care providers. In a cardiac care unit, examples of direct costs include personnel (such as nursing time), disposable supplies (such as electrocardiographic electrodes), and medications administered. *Indirect costs*, in contrast, cannot be traced to the production of specific medical goods and services and are instead allocated arbitrarily, using one of several accounting methods available, among all goods and services produced. These costs are generally not controllable by the physicians and nurses who care for patients (although there are some exceptions). Hospital administration, depreciation on the hospital building and the major equipment in it, medical billing, and medical records are all considered indirect costs. For accountants, indirect costs are synonymous with overhead; economists use “indirect costs” differently, as discussed below. One caveat: The distinction between what is considered direct versus indirect is dependent in part on the perspective of the analyst and the sophistication of the cost-accounting data that are available. Some costs may be assigned to the overhead category for the convenience of the analyst rather than because of conceptual difficulty in tracing their relationship to the production of health care services.

In general, the direct versus indirect cost distinction has primarily been used for accounting purposes within a given health care institution to ensure that expenditures match revenues. The distinction can also be useful in a cost-finding study that is trying to define and cost out all the medical resources consumed in the production of a particular medical service. This distinction has also become relevant for clinicians who are under great pressure (often from hospital administrators—who are part of the overhead costs) to reduce the direct cost of patient care. A detailed analysis of medical services to identify all the major cost components, direct and indirect, is the first step in responsible cost reduction.

Marginal cost is a concept that is frequently referred to by economists. It is defined as the extra cost involved in producing one extra unit of good or service. For all practical purposes, it is identical to the variable costs of production described earlier. For example, if a patient with uncomplicated myocardial infarction (MI) is discharged on day 4 instead of day 5, the hospital saves the variable costs associated with the extra hospital day. If that hospital bed cannot be filled by another patient, however, the hospital still has fixed costs associated with that bed that must be paid (electricity, heating, depreciation, and possibly even idle hospital staff).

The concept of one more (or less) test or procedure is a useful construct for economic analysis. In clinical practice, however, a more pragmatic question is the cost of shifting a group of patients from one diagnostic or therapeutic strategy to an alternative. In this latter setting, many economic analysts substitute the term *incremental cost* for marginal cost (11). Incremental cost analysis addresses a key issue in health care: How much savings are available (or costs are added) by shifting from one clinical strategy to an alternative? Incremental cost analysis is a fundamental aspect of (see Cost-Effectiveness Analysis). It should be noted that some analysts use the terms *marginal* and *incremental* interchangeably (12).

Two additional cost terms are frequently used in medical economic analyses. *Induced costs* (*savings*) refers to the costs of tests or therapies added (or averted) as a consequence of some initial management decision. For example, the use of angiotensin-converting enzyme (ACE) inhibitors in patients with heart failure reduces the need for future hospitalizations. In this case, the therapy is said to have induced a cost savings equal to the cost of the hospital days avoided. In another familiar example, performance of an initial percutaneous transluminal coronary angioplasty (PTCA) is associated with a need for repeat revascularization in 20% to 25% of patients to treat restenosis. These follow-up procedures are an induced cost of the initial PTCA procedures.

Finally, the term *indirect cost* is used by economists to refer to the societal costs associated with loss of productivity due to morbidity. The term *productivity costs* has been proposed to avoid confusion with the accounting meaning of indirect costs (9). The productivity costs associated with morbidity include time lost from work or (more controversially) leisure activities. Changes in productivity due to shortened life expectancy are by convention counted as negative health benefits rather than productivity costs.

Medical Cost: Measurement

As mentioned at the outset of this chapter, “cost” means different things to different analysts and consumers of cost data. To measure cost, one must have a clear operational definition of what is to be measured. The economist’s concept of opportunity cost represents the purest definition of “true cost.” However, opportunity cost is a theoretical construct that does not have a practical measurement analog.

Accountants are more concerned with measurement than are economists and consequently make a number of important simplifications. To measure true accounting

costs all the individual resources consumed in the production of a particular medical good or service must be determined and market prices assigned to each. Although measurement of true accounting costs is possible in some restricted situations, most cost analyses incorporate a number of approximations to increase ease of measurement. Because collecting cost information itself has a cost, the cost analyst must decide how much detail is necessary to satisfy a particular cost-accounting goal.

Two general approaches can be used to assess the cost of medical care services and products, “bottom-up” and “top-down” (1) (*e*Table 42.0.2). They differ in the level of detail used to describe resource consumption and in the quality of the cost weights collected. The bottom-up methods all involve enumeration of individual resources consumed in an episode of medical care and the corresponding cost weights. The gold standard bottom-up approach (also known as *microcosting*) involves a detailed enumeration of all the resources consumed by the medical care in question, detailed cost-accounting estimates of individual resource cost weights, and assignment of appropriate cost weights to each resource (5). The sum of the resources multiplied by their unit cost yields the total cost. However, this methodology can be quite laborious and expensive and is therefore infrequently used. For a relatively simple service, such as the administration of an antibiotic or performance of a laboratory test, this type of analysis may be feasible. A microcosting analysis of a more complex hospital procedure, such as a coronary angioplasty, or an episode of hospital care, such as an admission for acute MI, is a substantially greater challenge, in part because of the greater number and variability of resource inputs involved in the analysis.

***e*TABLE 42.0.2** OPTIONS FOR COST MEASUREMENT
Bottom-up methods
Microcosting analysis (gold standard)
Hospital cost-accounting system
“Big ticket” cost analysis
Top-down methods
Charge to cost conversion (hospital bill–based, United States only)
Diagnosis-related group standard costs

In the United States, some hospitals have installed computer-based cost-accounting systems that provide a bottom-up estimate of cost for each identifiable product that the institution produces. The level of detail and accuracy of such systems can approach that of a true microcosting analysis; however, substantial variability among vendors and even among hospitals using the product of an individual vendor likely occurs, partly because these systems typically allow the user to control the level of detail and the accuracy of the cost and resource data contained in the system. At present, many institutions still do not have electronic cost-accounting systems. Furthermore, such detailed cost-accounting systems are rare outside the United States.

A simplified version of the bottom-up approach involves enumeration and costing of “big ticket items.” This method requires the identification of the subset of resources consumed that are considered the most important cost components (“the big tickets”). Use of this approach allows the analyst to concentrate on costing out only a subset of the entire resources consumed. The principal advantage of this approach is that it is less expensive. However, this approach also has several important potential limitations (*e*Table 42.0.3).

***e*TABLE 42.0.3** STRENGTHS AND LIMITATIONS OF COST MEASUREMENT METHODS

Method	Strengths	Limitations
Full microcosting analysis	Most accurate	Most expensive and time consuming
Hospital cost-accounting system	Accuracy approaches that of microcosting	Variable levels of detail used Many key assumptions invisible to end user
Big ticket cost analysis	Efficient Less expensive	Estimates average (not marginal) cost May oversimplify, miss important cost differences Presumes uniform cost weights
Hospital bill charge to cost conversion	Efficient Based on detailed resource use data Can be used for most U.S. hospitals	Estimates average cost (not marginal cost) Variable methodologies used by different hospitals
DRG reimbursement rates	Efficient Least expensive	Not sensitive to resource use variations within a DRG category Health Care Financing Administration reimbursement rates may be lower than true costs

DRG, diagnosis-related group.

The other major approach to cost estimation is the top-down approach. At least two variants of this method can be used, one based on detailed hospital billing data and the other on summary episode-of-care descriptors. The method that uses hospital billing records is suitable for use only in U.S. institutions that generate hospital bills (and analyses that involve hospitalizations). The medical charges that appear on U.S. hospital bills represent a tremendously inflated statement of the underlying true costs for the care in question (13). In the earlier (preprospective payment) era of Medicare, hospitals were reimbursed on the basis of their “reasonable and necessary” costs of providing care to patients. To define what proportion of hospital charges these reasonable costs were, Medicare developed an elaborate reporting system that required each hospital to file a cost report each year with the Health Care Financing Administration (HCFA). This report provides a set of correction factors, known as the *Medicare ratios of cost to charges*. These are used with an HCFA-defined summary billing form, the Uniform Billing Form of 1992 (UB-92), to generate an estimate of hospital costs from hospital charge data for any hospital admission at an institution that participates in the Medicare program. The major U.S. hospitals that do not generate the data necessary for these calculations include the Veterans Administration System, some other military hospitals, and some fully capitated health maintenance organizations. The strengths of this approach are severalfold (14) (*e*Table 42.0.3). Most important, it is based on a detailed enumeration of resource consumption and thus tends to provide a sensitive measure of variations in resource use. In addition, this method is suitable for use in large-scale multicenter studies involving U.S. hospitals. The top-down charge-to-cost conversion also has several limitations that should be kept in mind (15) (*e*Table 42.0.3).

Medicare diagnosis-related group (DRG) reimbursement rates provide an alternative top-down cost estimation method that does not depend on conversion of hospital charge data (1). Once the patient’s DRG is defined, it becomes a straightforward matter to assign the “hospital costs.” This methodology has a number of important limitations (*e*Table 42.0.3). Most important, it is not sensitive to variations in resource use intensity within a given type of hospitalization. Furthermore, the reimbursement rates that are set by HCFA or that are provided by private insurers are only very loosely related to the true hospital costs of providing care. For these reasons, DRG reimbursement rates are primarily used for economic analyses done from the HCFA or other payer’s perspective. They are used for other cost analyses only when more accurate and appropriate cost weights cannot be obtained or the accuracy of such estimates is not particularly important to the overall analysis. Analogous DRG-based methods are available for use in some European countries.

Assignment of costs to physician services is typically done in one of three ways (1). In the past, physician fees (charges) were used. These numbers are determined by what the physician was historically able to bill for his or her services in the fee-for-service sector rather than the true cost of the resource inputs. Thus, physician fees are a distorted and inflated measure of physician service costs analogous to hospital charges. However, unlike the situation with hospital charges, no Medicare conversion factors have been established to translate these numbers into true physician costs. Alternatively, physician services can be included in a microcosting analysis (discussed earlier), although assigning costs remains problematic with this approach.

For this reason, we prefer to use the Medicare Fee Schedule, which is based in part on a resource-based relative value scale developed by Hsiao and colleagues at Harvard (16). The underlying concept of this scale is that the price of a physician service should reflect the long-term cost of providing that service. Thus, the resulting physician fees include the variable costs of the service in question as well as a component of fixed costs reflecting practice overhead expenses (such as office staff and malpractice insurance). Medicare fees under this system are tied to the physician’s *Current Procedural Terminology* classification system developed by the American Medical Association. Thus, use of the system in a cost analysis starts with assignment of appropriate *Current Procedural Terminology* codes to the relevant physician services.

For cost analyses outside the United States, a variety of estimates of physician service cost may be available. In Canada, for example, the Provincial Health Authorities each generate their own Physician Fee Schedule that is similar in general outlines to the Medicare Fee Schedule.

Medical Cost: Methodology of Cost Studies

The performance of a medical cost study requires that consideration be given to five issues (*e*Table 42.0.4): (a) the structural framework for the cost analysis, (b) the perspective(s) of the analysis, (c) the approach to cost measurement, (d) the importance of time and the need for discounting costs in the analysis, and (e) issues related to generalizability of the findings (1).

***e*TABLE 42.0.4** METHODOLOGIC ISSUES IN MEDICAL COST STUDIES

Structural framework of the study
Observational study
Randomized controlled trial
Cost-effectiveness model
Perspective(s) of the study
Societal
Medicare, managed care organization, other third-party payers
State or local government
Integrated health care system
Hospitals, clinics, other providers
Patients
Approach to cost measurement
Bottom-up
Top-down
Time effects
Discounting
Inflation
Generalizability
Practice setting(s)
Geographic relevance

Structural Framework

Cost studies generally fall into three major domains: observational studies, randomized controlled trials, and cost-effectiveness models. Cost effectiveness is discussed in a separate section. *Observational cost studies* include descriptive series (which are sometimes referred to as *cost-finding* or *cost-identification studies*) and more complex analyses using regression models in nonrandomized comparisons. Descriptive cost series are primarily useful in areas in which there are still few published data on costs. More complex observational studies are used to identify the major determinants of a particular treatment cost (cost drivers) or to make comparisons among providers or strategies for a particular condition. To identify the independent cost drivers in a data set, statistical multivariable models are used (see next section). In scorecarding or benchmarking applications, appropriate use of statistical adjustment techniques is critical to “level the playing field.” Understanding the major cost drivers allows the analyst to ensure that the factors most important to creating a level playing field have been accounted for.

Over the last decade, an increasing number of randomized trials have incorporated cost measurement into their design (17,18). Cost data are collected in a randomized trial primarily to answer the question, “If the intervention under study is found to be effective, as hypothesized, then what are its economic implications?” Because effectiveness is almost always the primary issue for the trial, cost is typically evaluated as a secondary end point or in an ancillary study. The method of economic data collection for a clinical trial is chosen from the options described under the previous section on cost measurement. The Duke Outcomes Group has been involved in more than a dozen multicenter randomized trials in which cost data were collected on up to 4,000 patients per trial. Our approach has been to use the top-down method with hospital billing data to estimate hospital costs and the Medicare Fee Schedule to estimate physician and outpatient care costs. Medical resource use data are ideally collected on the medical case report form, but if this is not feasible, the economic substudy must make provisions to collect the appropriate data. Whenever possible, the economic portion of the trial should be planned and conducted prospectively along with the clinical part of the trial (19). This ensures that the proper economic variables are incorporated into the case report form and that additional economic data required can be collected efficiently.

Not all randomized trials are suitable for economic analysis. In our experience, the sample size requirements to obtain a precise estimate of the difference in costs between two treatment strategies may be surprisingly large. Even in a large clinical trial, economic analysis may be problematic if the clinical protocol specifies important additional testing or treatment that distorts standard patterns of care. Generally, the best trials for economic analysis are the large simple randomized trials that attempt to mimic as closely as possible good clinical practice as it occurs in the medical community at large (20).

An intention-to-treat analysis in a randomized trial protects from unaccounted-for treatment selection biases but not other types of potential biases. Some economic analysts have been critical of the use of economic analysis in randomized trials because these analyses do not provide a picture of the economic effects of the new therapy as it will be used in the community at large. The providers and institutions in a trial are almost never representative of the medical communities in which they practice. Trial investigators may systematically steer certain eligible patients away from enrollment in the trial because they feel certain that they already know what is best for these individuals. Demographic and educational factors have been shown to affect patient willingness to be randomized in a trial. Although these biases may affect the generalizability of the economic substudy of a randomized trial, they also affect the generalizability of clinical results of that trial (21). These issues are discussed further in the section Generalizability.

Perspectives of Cost Analysis

A cost analysis always entails a perspective that is defined by who the buyers and sellers (or consumers or producers) of the medical care in question are (9). *e*Table 42.0.4 lists the most common perspectives used for cost studies. The importance of perspective (also referred to by some as the *viewpoint* for the analysis) is pragmatic: A particular medical care, good, or service may be a cost from one perspective but not from another. For example, the use of a statin agent to lower cholesterol after an MI is a cost in an analysis using the societal viewpoint but is not a cost in an analysis using a fee-for-service hospital viewpoint, because the care takes place in the outpatient setting and the drug is not provided by the hospital. Most health economists and health policy analysts recommend the routine use of the societal perspective (9). This is the broadest viewpoint, and it provides for comparability with other societal perspective cost analyses. If other viewpoints are relevant to the analyst, they can be used in addition to the societal perspective.

Resource Use and Cost Measurement

After the structure and objectives of the study have been defined and the perspective(s) has been agreed on, decisions must be made about what resources to include in the analysis and the method to be used for assigning costs to those resources. The details of cost measurement using bottom-up or top-down approaches have already been discussed.

Time Effects on Cost

Time has an important influence on medical costs that must be considered in economic studies. When medical care or its consequences take place over a period of years, there is broad agreement in the economic community that all future costs (as well as future health outcomes) should be expressed in terms of their “present value” to the decision maker (9). The mathematical procedure for calculating present value costs from a stream of costs that occur over a period of years is called *discounting*. The rationale for discounting costs can be easily illustrated. Given the choice between having $100 now and $100 five years from now, the decision maker always chooses the former option. This reflects the decision maker’s time preference for present value relative to future value. The time preference is logical because if the decision maker has the $100 now, he or she can invest it and have significantly more than $100 five years from now. Conversely, receiving $100 five years from now would be equivalent to receiving a sum of less than $100 today.

Inflation is a separate issue from discounting (9). Inflation causes the value of money to diminish over time. As a simplifying step, most medical economists tend to ignore the effects of inflation. The implicit assumption is that inflation affects all components of the costs being studied or compared equivalently. However, inflation must be taken into account when comparing the results of (historical) cost studies from different years. For example, a study done in 1985 on the cost of coronary bypass surgery would need to be adjusted for inflation to provide properly calibrated cost estimates that are relevant to 2002. The most common method for achieving this kind of inflation correction is through the use of the medical care component of the Consumer Price Index or a relevant subcomponent.

Generalizability

The methodology that we have reviewed so far relates to the assessment of the costs of medical care for a defined cohort of patients in the context of an observational study or a randomized trial. In either case, it is possible to collect empiric resource use and cost data on the patients in question and to draw conclusions about the economic effects of the given medical care from the empiric data that are available. Sometimes, however, the economic analyst is interested in a broader question: What is the economic impact of the therapy in question on an entire health system? For example, we were able to calculate the incremental costs of substituting accelerated tissue plasminogen activator (t-PA) for streptokinase in the treatment of eligible MI patients in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) I trial using the empiric data collected from that trial (22). However, the GUSTO trial does not address the question of what the economic impact would be of adopting a policy of substitution of t-PA for streptokinase nationwide. Many policy makers and other health care decision makers are more interested in the systemwide impact of a new therapy on costs than they are in the detailed cost analysis that is typically obtained in a given clinical study. The system

in question may be a country, a state or province, a managed health care organization, or a chain of hospitals.

Clear trade-offs must be made in moving from the empiric arena to the health system or policy arena. In particular, policy or systemwide projections typically involve far greater uncertainty and consequent imprecision. We can calculate quite precisely the incremental costs of t-PA in the GUSTO study, but extrapolating to the national use of thrombolytic therapy requires detailed empiric data about how many MI patients a year in the United States are eligible and are treated with thrombolytic therapy along with relevant demographic and clinical characteristics of those patients. Such data are usually not available. Typically, one of a number of surrogate sources is used to estimate the relevant information, such as claims data or even expert opinion. When several such estimates of uncertain accuracy are used together, the result may be little more than an elegant “back of the envelope” projection.

Medical Cost: Cost Drivers

Cost drivers can be considered conceptually to fall into four major categories (Table 42.1): patient-related factors, treatment-related factors, provider-related factors, and geographic/economic factors (1). *Patient-related factors* affect cost primarily by influencing the likelihood of complications of various types and severity due to variations in the severity in the underlying disease process and the extent of comorbidity. *Treatment-related cost determinants* fall into two major categories. The first involves costs incident to management decisions made by the medical providers. Thus, an aggressive interventional management strategy for a patient with an acute coronary syndrome is associated with higher medical costs (over the short run at least) than a conservative strategy. Second, there is a more complex interaction between the management strategy selected and the patient characteristics, which may result in an increase or decrease in treatment-related complications and consequent cost. For example, timely aggressive intervention may prevent a serious complication that would have otherwise occurred as a result of disease progression. Alternatively, use of an aggressive strategy may result in a previously unsuspected comorbidity becoming clinically manifest and inducing extra medical care costs.

Patient-related factors
Age
Sex
Cardiac disease severity (e.g., ejection fraction, extent of coronary artery disease)
Cardiac comorbidity (cardiac disease other than the principal condition under study)
Noncardiac comorbidity
Treatment-related factors
Aggressive versus conservative management
Complications
Provider-related factors
Quality of care
Efficiency of care
Preferred management styles
Geographic/economic factors
Labor costs
Supply costs

TABLE 42.1 MAJOR CATEGORIES OF MEDICAL COST DRIVERS

Provider-related factors refer to quality and efficiency of care issues as well as overall preferred management styles for a particular clinical problem. Complications associated with medical care cannot be eliminated, but care that is of a very high technical quality can minimize those complications relative to care of lesser quality. Efficiency of care as it relates to a provider refers to the provision of the required care with a minimum set of necessary medical resources and, thus, the minimum amount of waste achievable. Multiple studies have shown that some practitioners have a more resource-intensive style of practice than do others; how these different styles relate to quality and efficiency of care remains controversial (23,24,25,26,27 and 28).

Even after all the preceding characteristics are accounted for, costs will still vary from one provider to the next because of *geographic/economic factors* that create true variations in the costs of the component resources required to provide the care in question. Variations in the cost of medical care labor in different geographic markets and variations in the purchase price of supplies can both affect cost in important ways. For example, low unemployment rates and a shortage of skilled registered nurses may drive up the salary rate for nurses in a particular region. Very large hospital chains or payers can negotiate discounts with medical suppliers and pharmaceutical companies that are not available to small independent providers.

Cost-Effectiveness Analysis

Cost-effectiveness analysis is a form of economic efficiency analysis (1,9,10,12). As described earlier in this chapter, economists are concerned with making decisions about the most efficient use of scarce societal resources. The principal agenda of the analysis is to define for the policy maker how to allocate finite health care dollars among the possible alternative programs. In its most general form, economic efficiency analysis attempts to help solve problems of allocation of resources across major sectors of the economy, such as education, defense, public works, and health care. It is assumed in such analyses that the decision maker desires to maximize the benefits produced for society for a given investment of resources. Consequently, these techniques are insensitive to considerations about who gains and who loses as such trade-offs are made.

Types of Analyses

Economic efficiency analysis includes three related analytic techniques: cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis (11) (*e*Table 42.1.1). These methods have several important features in common. First, all three explicitly evaluate the following decision maker’s dilemma: “In moving from a reference therapy (strategy) to a new therapy (strategy), how much will be gained in additional benefits, how much additional cost will be incurred, and will the resource (monetary) investment required to produce an extra unit of benefit with this new therapy fall into an acceptable or worthwhile range judged according to past experience or other precedents?” The general formula for all three techniques is

$$\frac{C_{\text{new}} - C_{\text{usual care}}}{E_{\text{new}} - E_{\text{usual care}}}$$

where *C* = costs and *E* = effectiveness. Second, they all use the same calculation for the incremental costs of the new strategy or therapy (*e*Table 42.1.1).

***e*TABLE 42.1.1** COST-EFFECTIVENESS, COST-UTILITY, AND COST-BENEFIT RATIOS: SAMPLE CALCULATIONS

Strategy	Treatment costs	Effectiveness (life expectancy)	Utility (QOL)	QOL-adjusted life expectancy	Benefits[a]
Rx A	$20,000	4.5 yr	0.80	3.60 QALYs	$4,000
Rx B	$10,000	3.5 yr	0.90	3.15 QALYs	$2,000

$$\text{Incremental cost-effectiveness ratio} = \frac{\$20{,}000 - \$10{,}000}{4.5\text{ yr} - 3.5\text{ yr}} = \$10{,}000 \text{ per life-yr saved}$$

$$\text{Incremental cost-utility ratio} = \frac{\$20{,}000 - \$10{,}000}{3.6\text{ QALYs} - 3.15\text{ QALYs}} = \$22{,}222 \text{ per QALY saved}$$

$$\text{Incremental cost-benefit ratio} = \frac{\$20{,}000 - \$10{,}000}{\$4{,}000 - \$2{,}000} = 5$$

QALY, quality-adjusted life-year; QOL, quality of life; Rx, treatment.

[a]Shows health benefits valued in dollars.

From Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990;113:147–154, with permission.

The three modes of economic efficiency analysis differ in the way that they evaluate incremental health benefits (11) (eTable 42.1.1). *Cost-effectiveness analysis* expresses incremental benefits in terms of natural units. Most commonly, incremental life-years are used. It is this form of the cost-effectiveness ratio for which most of the available benchmarks exist (eTable 42.1.2). However, it is legitimate to calculate cost-effectiveness ratios using other medical end points. For example, a cost-effectiveness ratio of incremental dollars required to save an additional life or to produce an additional 30-day survivor or to discover one additional patient with left main coronary disease could be calculated if such outcomes were deemed relevant to decision making. The difficulty is not in calculating such ratios but in interpreting them. The consensus is that cost-effectiveness ratios of less than $50,000 per added life-year are "economically attractive," whereas ratios above $100,000 per added life-year are "economically unattractive" (1,9). The middle zone represents an uncertain area. Some have proposed setting the economically attractive threshold as low as $20,000 per added life-year (29). No such benchmarks exist for cost-effectiveness ratios constructed with other effectiveness measures such as were cited previously. Thus, these alternative cost-effectiveness ratios cannot be used for making broad-based trade-offs among alternatives for societal investment, and they can be problematic to interpret as isolated measures of value within a given health care system.

***e*TABLE 42.1.2** EXAMPLE LEAGUE TABLE OF COST-EFFECTIVENESS RATIOS

New therapy	Comparison therapy	Patient group	Cost-effectiveness ratio
CABG	Medicine	Left main disease, severe angina	$7,000
Medical Rx	No Rx	Severe HBP	$20,000
Hemodialysis	No hemodialysis	Chronic renal failure	$35,000
Medical Rx	No Rx	Moderate HBP	$40,000
Cholesterolemia	No Rx	Cholesterol >265 in asymptomatic men aged 45–60 yr	$180,000

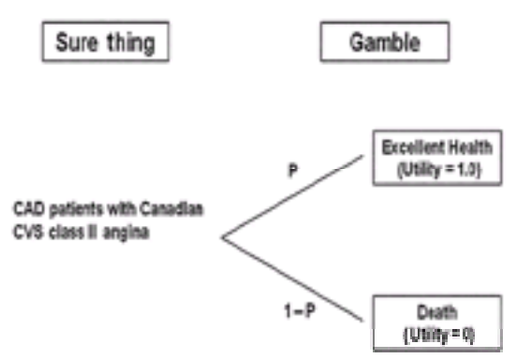
CABG, coronary artery bypass graft surgery; HBP, hypertension; Rx, treatment.

Data from Goldman L. Cost-effective strategies in cardiology. In: Braunwald E, ed. *Heart disease: a textbook of cardiovascular medicine*. Philadelphia: WB Saunders, 1992:1694–1707.

It is important for medical consumers of economic analyses to recognize that cost-effectiveness ratios are not the precise figures that they appear to be (30). Rather, they are estimates with varying (often large) degrees of uncertainty incorporated in their calculation. Furthermore, there is no single cost-effectiveness threshold that separates the "worthwhile" from the "worthless" interventions. The figures discussed in the previous paragraph for dollars per added life-year are general guidelines, not absolute benchmarks. A cost-effectiveness analysis addresses a particular decision scenario for a particular time. Its results are not absolute for all scenarios at all times. A particular intervention may be judged economically attractive in the United States but not in the United Kingdom. Similar disparities may arise in the fee-for-service versus managed-care segments of the U.S. health care system. These differences relate in part to variations in the costs of care in these different systems as well as to the different levels of willingness to spend additional dollars to buy more health care benefits.

Cost-utility analysis is a special case of cost-effectiveness analysis in which the benefit is expressed most often as a quality-adjusted life-year (QALY) (11) (eTable 42.1.1). Calculation of such a quantity assumes that patients would be willing to give up extra survival to improve quality of life. The process of equating various quality of life states to their equivalent survival durations is known as *utility assessment*. Although conceptually attractive, there are a number of important pragmatic problems in assessing utilities and incorporating them into an economic analysis. Utilities or utility weights are quantitative measures of the relative desirability of different health states. By convention, they are scored from 0 (death) to 1 (excellent health), although values of less than 0 can be used to represent health states judged worse than death. Utilities for use in economic analysis are derived by two major methods, direct assessment and use of a health utility index. Direct assessment typically involves interview- or questionnaire-based measurements using patients in a given health state of interest or, less commonly, other subjects who are asked to imagine (with the help of certain descriptive aids) being in the health state in question.

The most commonly used direct assessment methods are the standard gamble and the time trade-off (9,31). The standard gamble asks the subject to consider choosing (hypothetically) between remaining in his or her current (suboptimal) health state (the "sure thing") and a gamble. The gamble is constructed with two possible outcomes, one better than the sure thing (such as excellent health) and one worse (such as death). The probabilities of the gamble are varied systematically until the patient reports being indifferent between the sure thing and the gamble. The simple example in eFigure 42.0.2 shows the process for assessing the utility of Canadian Cardiovascular Society class II angina. The patient with this condition (or a nonpatient assessor who is provided a comprehensive description of the health state being evaluated) is asked about his or her willingness to gamble on a chance of excellent health (given the probability, p) versus immediate death (with a probability of $1 - p$). If the patient reports being indifferent, for example, between a 90% chance of excellent health (with a 10% chance of immediate death) versus class II angina, then class II angina would be assigned a utility weight of 0.9. The more unfavorable the patient's view of the sure thing, the more he or she will likely be willing to consider riskier gambles (yielding lower utility values).



***e*FIGURE 42.0.2** Simple standard gamble for assessing the utility of Canadian Cardiovascular Society (CVS) class II angina. CAD, coronary artery disease.

On theoretical grounds, many economists and decision scientists favor the standard gamble for assessment of utilities because it is most consistent with the axioms of game theory (the Von Neumann–Morgenstern axioms) that collectively define how decision makers should act in situations of uncertainty. A central premise of decision theory is that decision makers should select the option with the highest expected utility. Whether decision makers actually act in this fashion and whether empirically observed violations of the principle of utility maximization pose a threat to the validity of the standard gamble remain controversial (32,33). Investigations have shown that many individuals are inconsistent in their attitude toward risk (the gamble); specifically, they tend to overvalue a loss of certain magnitude relative to a gain of equal magnitude.

Most researchers have found the standard gamble complex to use and impractical for large-scale studies. A popular alternative is the time trade-off (34,35). In this method, the patient (rater) is asked in a series of questions how much of his (or her) life expectancy he (or she) would be willing to give up to live the remaining years in excellent health. Although simpler than the standard gamble, the time trade-off is still difficult for many patients to understand. This method also has the potentially undesirable property of valuing all future survival uniformly. In contrast, most patients tend to value their next year of life significantly higher than one that they will experience 10 years from now.

The major alternatives to the direct utility assessment techniques described previously are the health utility indexes. Each index consists of a set of discrete health states, typically defined in relatively simple generic terms, for which utility weights have been derived. Most often utility weights are obtained from the general (nondiseased) population. Seven health utility indexes are currently in use, although none has achieved widespread use in the United States (9,36).

Cost-benefit analysis requires that health benefits be converted to their monetary equivalent (11) (eTable 42.1.1). Because physicians and patients are often uncomfortable with these conversions, and because the methodology for making such equations is vulnerable to important technical and ethical criticisms, this method of analysis is infrequently used in medicine. Its principal advantage over the other forms of economic analysis is that it can be used across the entire spectrum of societal decision making, whereas cost-effectiveness and cost-utility analysis are useful only for health policy decisions in which the goal is to maximize the added life-years (or added QALYs) produced. Cost-benefit analysis directly calculates the gain or loss for society of a particular program expressed in terms of dollars invested versus the monetary value of the return on investment. The results can be expressed as a ratio (as shown in eTable 42.1.1) or (more preferably) as the net benefits of the program (the incremental benefits minus the incremental costs). If the cost-benefit ratio is greater than 1, or the net benefits are positive, the program is judged "worthwhile" from a societal perspective.

One confusing issue to many noneconomists is the distinction between incremental cost effectiveness and average cost effectiveness (11). As noted earlier, all

cost-effectiveness analysis compares a new strategy with some alternative, typically “usual care.” In incremental cost-effectiveness analysis, the new strategy and the comparison strategy are defined explicitly by the analyst. Some researchers have proposed calculating an average cost-effectiveness ratio by dividing the average effectiveness of a particular therapy or strategy into the average cost. Although this might appear to be a reasonable measure of “value” or “average bang for the buck,” this calculation actually provides an unrealistic incremental cost-effectiveness ratio in which the comparison strategy has no effectiveness (i.e., all patients die immediately) and no cost. In almost no clinical situation in medicine are these circumstances fulfilled, because even with no medical therapy there are downstream costs (such as hospitalization to treat complications) and positive health outcomes (i.e., in most cases, some of the patients survive even in the absence of any effective therapy). Thus, average cost-effectiveness ratios are misleading and should be avoided.

Standards for Economic Analysis

Economic efficiency analysis has as one of its principal goals the provision of information that is necessary to maximize the health benefits for a given population using a specific (fixed) budget. Despite the importance of this goal and the absence of competing quantitative methodologies for achieving it, cost effectiveness has never been used to make policy and allocation decisions explicitly in a health care system. Oregon attempted to use cost-effectiveness rankings to prioritize medical benefits in its Medicaid program, but after the initial effort proved extremely controversial and, in a number of cases, counterintuitive, cost effectiveness was eliminated as a ranking method in favor of effectiveness alone (37,38 and 39).

Several factors have been identified as limits on the practical use of cost effectiveness in policy making. First, many policy makers (and members of the public at large) do not accept the underlying economic model involving efficient allocation of scarce resources as the most desirable method of making health care decisions at a societal or health-system level. In particular, it has been shown that many potential decision makers place greater importance on equity considerations than is done with traditional economic analytic techniques (40). Second, there are many medical strategies for which no adequate cost-effectiveness data exist, making it difficult to use these methods for system-level allocation decisions even if desired. (The absence of adequate data is one major reason given for the failure of the Oregon Medicaid experiment with cost effectiveness.) Finally, the methodology used by different analysts to generate cost-effectiveness estimates can be so variable that even where data on cost effectiveness of different strategies exist, they may not be comparable due to methodologic differences. In addition, the absence of standard methodologies creates the impression that economic analysis is very *ad hoc* and thus quite susceptible to investigator bias.

Several national groups and one *ad hoc* group have proposed standards for cost-effectiveness analysis (9,41,42 and 43). The Panel on Cost Effectiveness in Health and Medicine convened by the U.S. Public Health Service published standards for U.S. cost-effectiveness analysis (9,44,45 and 46). Most of the standards proposed are not new. The fact that they are only intermittently used at present reflects more the limitations of the available data and the resources available to support these types of analyses than explicit decisions on the part of the analyst.

ECONOMIC STUDIES OF CARDIOVASCULAR DISEASE

Acute Coronary Syndromes

General Considerations

Acute coronary syndromes (acute MI, unstable angina) share a common pathophysiology, similar clinical manifestations, a need for hospital-based management in the vast majority of cases, and a self-limited course that typically extends 30 to 60 days from presentation (47,48). After this period, most (surviving) patients cycle back to a stabler phase of coronary disease. The economic analysis of acute coronary syndromes and their treatments therefore is primarily focused on the events during the critical initial phase of presentation and care, particularly those that occur during the initial hospitalization.

Conceptually, the cost of hospitalization for an acute coronary syndrome can be divided into four major resource/cost components (Fig. 42.1). In patients who are eligible for reperfusion therapy, the reperfusion strategy selected (i.e., either thrombolytic therapy or direct coronary angioplasty) is a major cost component. Although streptokinase is relatively inexpensive (at approximately $300 per dose), t-PA, recombinant tissue plasminogen activator (rt-PA), and TNK all cost more than $2,000 per dose, and the procedural costs of direct PTCA are even higher. A second component is the routine hospital stay that is required for the patient with an uncomplicated course. For acute MI patients in the United States, this typically includes 1 or 2 days in the intensive care unit and 3 or 4 days more in a step-down or regular hospital floor setting. For unstable angina, the course is typically shorter. The primary cost components for this type of care are the hospital room costs and the associated ancillary care costs (such as laboratory testing, medications administered, consultations obtained, radiology testing performed, and so on). A third major component is the risk stratification strategy selected. For many patients in the United States with acute coronary syndromes, diagnostic coronary angiography is the principal mode of risk stratification. Use of coronary revascularization techniques has been shown to track the use of coronary angiography with a fair degree of predictability (49). The need for revascularization is a major predictor of higher hospital costs (50). For some patients, one of several noninvasive testing strategies can be used. These may eventually lead to coronary angiography and revascularization or may permit the patient to be discharged without such testing being performed.

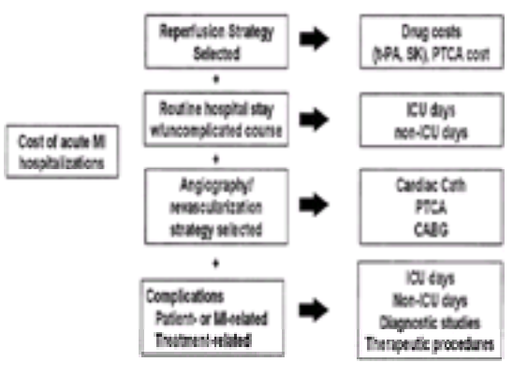


FIGURE 42.1 Cost components for an acute coronary syndrome hospitalization. CABG, coronary artery bypass graft surgery; ICU, intensive care unit; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; SK, streptokinase; t-PA, tissue plasminogen activator.

The last category of cost components for patients with acute coronary syndrome is complications. These are of several different types and have varying cost implications. The reperfusion strategy selected, for example, can induce a variety of complications, including minor bleeding (which may have no discernible cost effects) and major bleeding (which may induce a significant extra cost). Coronary angiography in the anticoagulated patient may lead to a major groin hematoma or other vascular complications, which in turn require additional days of care, testing, and consultation. Thrombolytic and anticoagulant drugs may induce gastrointestinal bleeding, sometimes because of previously undiagnosed gastrointestinal comorbidity. The acute coronary syndrome itself may produce complications (e.g., heart failure, arrhythmias, and recurrent ischemia). Costs related to complications can be substantial and are difficult to predict.

Thrombolytic Therapy

The benefits of thrombolytic therapy in acute MI are firmly established (51). Of the approximately 16 studies that have been published on the cost effectiveness of thrombolytic therapy, most are now of historical interest because of their age or because of changes in the standard of practice, or both (52). Four thrombolytic strategy comparisons are of current relevance: streptokinase versus no reperfusion therapy, t-PA versus streptokinase, t-PA versus rt-PA or TNK, and rt-PA versus rt-PA with abciximab. As of 2001, the U.S. market share for streptokinase was only approximately 4%, that for t-PA was approximately 44%, and rt-PA and TNK were equivalent at approximately 25% each. Outside of the United States, streptokinase remains the most widely used thrombolytic agent (53).

However, none of the large-scale randomized trials of streptokinase versus conservative (i.e., no reperfusion) therapy collected the empiric data on resource use or cost that are necessary to estimate the direct costs of these two strategies. Given inadequate data, we are forced to take a conservative position and assume that the improved medical outcomes (particularly survival) seen in the randomized trials of streptokinase are associated with an increased net cost relative to no reperfusion therapy, making it necessary to evaluate the drug’s cost effectiveness. One of the most useful studies in this area was conducted by Naylor et al. (54). They estimated that substitution of intravenous streptokinase for no reperfusion therapy had a cost-effectiveness ratio of approximately $2,000 to $4,000 per added life-year, assuming that each additional survivor due to streptokinase therapy had a life expectancy of approximately 10 years. These figures make streptokinase therapy an extremely economically attractive intervention, probably falling into the category of “best buy.”

Krumholz and colleagues (55) estimated the cost effectiveness of intravenous streptokinase in elderly patients (age 75 years or older). The effectiveness portion of

their analysis was based on the Gruppo Italiano Per lo Studio Della Streptokinase Nell'Infarto Miocardio (GISSI) and International Study of Infarct Survival-2 (ISIS-2) data, which indicated a 13% relative reduction in short-term mortality. The base case cost-effectiveness ratio for an 80-year-old with a projected (undiscounted) life expectancy of 2.7 years was $21,200 per added life-year (1990 dollars). For a 70-year-old with a projected life expectancy of 5.5 years, the cost-effectiveness ratio was $21,600 per added life-year.

GUSTO I clearly established that t-PA was superior to intravenous streptokinase in establishing Thrombolysis in Myocardial Infarction flow grade 3 (TIMI-3) coronary flow and in saving lives (56). Because the cost of t-PA is substantially higher than that of streptokinase, the question that directly emerged from the clinical results of GUSTO I was whether the added benefits of accelerated t-PA were sufficient to justify the added costs of this regimen. It is important to note that from a patient perspective (assuming that the patient does not bear the added cost of t-PA), the choice of thrombolytic regimen virtually always favors t-PA on medical grounds alone (i.e., additional survivors minus additional disabling strokes). On the other hand, from the fee-for-service hospital perspective, t-PA is usually a losing financial proposition, because the added costs of the therapy are often not reflected in the reimbursement received. The one added survivor per 100 generated by t-PA is a statistical survivor, and the individual patient who is actually "lost" when streptokinase is used in lieu of t-PA cannot be identified clinically and is therefore invisible to the hospital. Furthermore, most of the added life-years generated by t-PA, as is discussed below, occur after patients are discharged from the hospital.

In a detailed prospective economic analysis, the GUSTO I trial estimated that cumulative medical costs (hospital costs plus physician fees) at 1 year averaged $24,575 for streptokinase patients and $24,990 for t-PA patients exclusive of the costs of the thrombolytic agent (22). When the average wholesale drug costs for the two agents were added in, the incremental lifetime (undiscounted) costs for each patient who received t-PA was $2,845. Using the empiric 1-year GUSTO survival data, additional data from the Duke Cardiovascular Database, and statistical modeling, we projected a life expectancy for t-PA patients of 15.41 years versus 15.27 for the streptokinase patients, an undiscounted increase in life expectancy for t-PA of 0.14 years per patient. This result can be more intuitively restated as follows: The one extra patient per 100 saved with accelerated t-PA lives an average of 14 additional years.

With an increased life expectancy of 0.14 years of life per patient for t-PA patients and an increased cost of $2,845 per patient, the incremental cost-effectiveness ratio for t-PA (discounted at 5%) was $32,678 per year of life saved (22). Because the average thrombolytic drug cost to hospitals is lower than the average wholesale prices for the two drugs, we substituted a cost of $270 for the streptokinase and $2,216 for the 100 mg t-PA and repeated the calculations. These lower drug costs yielded a cost-effectiveness ratio of $27,115 per year of life saved (22).

The GUSTO III trial compared rt-PA with t-PA and found no difference in major cardiovascular events (including death, stroke, and bleeding) out to 1 year (57). The costs of these two agents are the same, and although the nursing time and ancillary costs associated with a double-bolus regimen are likely smaller than with a bolus and 90-minute infusion, inefficiencies in the care process would likely eliminate these small theoretical savings.

TNK-tPA was compared with rt-PA in 16,999 patients in the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT) 2 Study (58). Mortality was identical in the two arms as was intracranial hemorrhage. Bleeding complications and need for blood transfusion were modestly reduced by TNK. The cost of TNK is the same as that of t-PA, and the single-bolus administration regimen is attractive to a busy emergency department, if not cost saving. A formal economic analysis of ASSENT 2 has not been performed.

The GUSTO V trial compared rt-PA with half-dose rt-PA plus full-dose abciximab in 16,588 patients (59). The combination regimen reduced nonfatal reinfarction but did not alter 30-day mortality. The rt-PA plus abciximab regimen also reduced urgent revascularization but increased bleeding, although strokes and intracranial hemorrhage rates were equivalent. A cost analysis of this trial is currently under way.

Primary Percutaneous Coronary Reperfusion

A quantitative overview of all the randomized trials conducted through 1996 showed that there was a strong possibility that direct angioplasty was superior to thrombolytic therapy in saving lives (60). Furthermore, comparison of hospital charges in the Primary Angioplasty in Myocardial Infarction I (PAMI I) study and estimated hospital costs in the Mayo Clinic Randomized Trial both suggested that direct angioplasty might also be a less expensive reperfusion strategy (61,62 and 63). However, of the ten trials included in the overview, nine were quite small. The largest, by far, was GUSTO II.

Although the small randomized trials had established that dedicated experienced operators could achieve excellent results with primary angioplasty, the GUSTO II study was meant to evaluate whether the technique was practically suited for larger-scale implementation in the cardiovascular community. GUSTO II compared accelerated t-PA and primary angioplasty. A total of 1,138 patients were enrolled (1994–1995) in the trial from 57 hospitals in nine countries (64). The 30-day results of this trial showed a statistically significant 33% reduction in the primary outcome event (the combination of death, nonfatal MI, and disabling stroke) for primary angioplasty. However, at the end of 6 months of follow-up, the 30-day benefit had attenuated by approximately 50%, and the intention-to-treat comparison was no longer statistically significant. The small differences observed in mortality and nonfatal MI, both favoring direct angioplasty, were not statistically significant. However, the study was not powered to detect such differences.

The principal resource use data from the U.S. portion of the trial showed the expected extra procedures in the direct angioplasty group (65). Importantly, the rate of diagnostic angiography was approximately 70% in the accelerated t-PA group. This is consistent with the rates observed in GUSTO I and reflects the predominant choice among U.S. GUSTO investigators in the use of angiography as a primary risk stratification tool after MI. At the end of the initial hospitalization, direct angioplasty showed a $900 cost advantage in the use of hospital resources, whereas accelerated t-PA had a $600 cost advantage in the use of physician resources, leaving a net cost advantage for direct angioplasty of approximately $300 ($p$ >.05) (65). At the end of the 6-month follow-up period, the net cost advantage of direct angioplasty had fallen to approximately $100.

One of the main limitations of the direct angioplasty reperfusion strategy is that only approximately 20% of U.S. hospitals have catheterization facilities, and many of these are not staffed 24 hours a day (66). Building new interventional catheterization laboratories, training new personnel to staff them, and providing 24-hour coverage would substantially increase the long-term per-case cost of the procedure over that calculated in the GUSTO II analysis (67).

The Myocardial Infarction Triage Intervention registry performed an observational comparison of 1,050 patients who received direct angioplasty with 2,095 patients who received thrombolytic therapy (65% t-PA, 32% streptokinase, 3% other) (68). This community-based study found no mortality benefit for angioplasty, but, in contrast to the GUSTO II economic analysis, it found that the thrombolytic group had 13% lower costs at 3 years.

More recently, the percutaneous approach to acute MI patients has been modified to include stenting and the use of glycoprotein (GP) IIb/IIIa inhibitors. Stenting versus PTCA has been compared in six randomized trials, five of which were quite small (see Chapter 18). The largest, STENT PAMI, randomized 900 patients to stent over balloon PTCA (69). Only approximately 5% of patients received a GP IIb/IIIa inhibitor. At 1 month, the stent group had a nonsignificant increase in mortality and a nonsignificant decrease in reinfarction. The major difference in outcome was a lower rate of target vessel repeat revascularization seen in the stent arm (10 per 100 fewer at 6 months). Cohen and colleagues (70) performed an economic analysis of STENT PAMI. The index hospital costs in the stent arm were approximately $2,000 higher, due primarily to the extra costs of the stents used. The decreased need for follow-up procedures saved approximately half that amount over the first year of follow-up. In addition, the avoidance of recurrent angina and repeat procedures was associated with a small utility benefit for the stent patients. Thus, with a net cost of approximately $1,000 per patient and a utility advantage of 0.02, the cost per QALY added with stenting was $65,000 using the technology available during the trial. With the current repertoire of longer stents that allow a reduction in the total number of stents placed, the equipment cost of the stent arm in STENT PAMI would have been lower and the cost per QALY would have been less than $30,000, using the assumptions of the investigators.

The benefits of adding abciximab to primary PTCA were evaluated in 483 MI patients enrolled in the ReoPro and Primary PTCA Organization and Randomized Trial (71). No significant benefit was seen for the addition of abciximab to PTCA on death or reinfarction out to 6 months. Urgent target vessel repeat revascularization was significantly reduced, but any target vessel revascularization was not. In addition, major bleeding and the need for transfusion were increased by abciximab.

The benefits of adding abciximab to primary stenting in acute MI were tested in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. This trial enrolled 2,665 acute MI patients who were within 12 hours of symptom onset and who were deemed eligible for stenting. Randomization used a factorial design: balloon PTCA versus stent and abciximab versus no abciximab. In contrast to STENT PAMI, this trial showed a nonsignificant mortality benefit for stenting over PTCA. The addition of abciximab reduced ischemia and ischemia-driven target revascularization for stent and for PTCA patients. The Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL) trial randomized 300 acute MI patients who were undergoing acute coronary intervention with stenting to abciximab or placebo (72). At 30 days, the abciximab arm had a 49% lower mortality, a 49% lower incidence of reinfarction, and a 58% reduction in target vessel revascularization. Major bleeding was not increased by abciximab, although minor bleeding was. At 6 months, the abciximab arm had a 5.4% absolute decrease in the need for revascularization.

Neither CADILLAC nor ADMIRAL has yet reported economic data (73). Given that bolus plus 12-hour infusion therapy with abciximab adds approximately $1,400 to the cost of care, examination of resource use patterns and associated costs will be an important aspect of final interpretation of these data. At present, it appears that percutaneous revascularization is a clinically acceptable but less available and more expensive alternative to thrombolytic therapy.

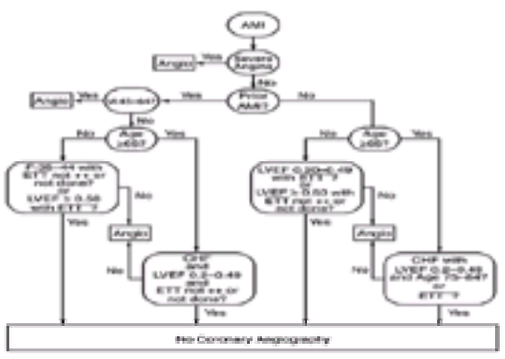
Coronary Angiography and Predischarge Risk Stratification

Several randomized trials have now compared different forms of invasive and conservative management strategies for patients with acute coronary syndromes. The TIMI IIIB trial compared these two strategies in 1,473 patients (74). Early invasive management involved routine angiography at 18 to 48 hours after presentation. Early conservative management used angiography only if certain high-risk indicators were present. At 6 weeks, the two strategies had identical rates of death and MI. Hospital stay was shortened for the invasive arm, and rehospitalization for recurrent unstable angina was also reduced in this arm. Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH), in contrast, found that early conservative management in 920 patients with non–Q-wave MI was associated with lower mortality at hospital discharge and at 12 months (75). In the conservative arm of TIMI IIIB and of VANQWISH, catheterization was used in approximately half of the assigned patients. In contrast, in Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II, only 10% of patients from the conservative arm received catheterization (76). If such an extreme conservative strategy is the comparator, invasive therapy has clearly demonstrable benefits in patients with acute coronary syndrome. What is less clear is whether a policy that uses angiography approximately half the time is inferior to one that uses it almost all the time. The most recent clinical trial to address this issue is the TACTICS-TIMI 18 study (77). At 6 months, death was equivalent in the two arms and there was an approximately 2 per 100 reduction in the rate of MI in the invasive arm. A cost analysis of this trial found that the invasive arm was modestly more expensive during the index hospitalization ($14,660 vs. $12,667) but less expensive during the first 6 months of follow-up ($6,063 vs. $7,203) (78). Thus, cumulative costs at 6 months were equivalent.

Despite the absence of conclusive evidence from randomized trials favoring routine angiography in acute coronary syndromes, data from the GUSTO trials show that 70% to 80% of such patients in the United States routinely undergo coronary angiography before discharge (26,64). In 16 managed-care Kaiser hospitals, angiography rates between 1990 and 1992 were somewhat lower, ranging from 30% to 77% (79). Because coronary angiography is a diagnostic technology, it produces no direct health benefits (aside from the rare negative health benefit of a procedure-related complication). Consequently, to evaluate the cost effectiveness of this form of risk stratification relative to potential alternatives such as the use of various noninvasive tests or even clinical screening alone, a linkage must be made between the likely information provided by the tests and the subsequent management decisions by physicians that would ultimately be likely to yield improved survival or quality of life, or both. Given the difficulty in making such linkages and the lack of good empiric data with which to do so, it is not surprising that very few attempts have been made to produce a cost-effectiveness analysis of this problem.

Kuntz and colleagues (80) examined the cost effectiveness of routine coronary angiography in the convalescent phase of acute MI versus an exercise tolerance test and selective referral to angiography. Their decision model examined long-term costs and survival along with angina class and heart failure. Clinical data for the model came from pooled analyses of the literature. Where no adequate data were available, such as in estimating post-MI coronary artery bypass graft (CABG)–related survival, data were used from other patients with coronary artery disease (CAD), and the assumption was made that these results were pertinent to acute MI patients as well. Long-term survival after MI in patients who were given medical therapy was derived from the Coronary Heart Disease Policy Model, which uses data from U.S. life tables and various epidemiologic studies to simulate the long-term survival pattern of patients with coronary heart disease (CHD). Cost data were obtained from the Medicare files for 1987, with costs adjusted to 1994 dollars using the Consumer Price Index.

The base case analysis of this model showed that routine coronary angiography increased quality-adjusted life expectancy in all post-MI patient subgroups except women aged 35 to 44 years old with normal left ventricular function, no postinfarction angina, and a negative exercise treadmill test (80). When costs were considered, two factors were especially influential in creating favorable cost-effectiveness ratios for coronary angiography: inducible myocardial ischemia (either spontaneous or during a stress test) and a history of prior MI. When both these factors were present, the cost-effectiveness ratios ranged between $17,000 and $44,000 per QALY. In contrast, most patient subgroups with a negative exercise test had incremental cost-effectiveness ratios for coronary angiography in excess of $50,000 per QALY added. Some of the results of this model were counterintuitive. For example, favorable cost-effectiveness ratios were found for men aged 45 to 74 with a negative exercise treadmill test and an ejection fraction of 50% or greater but a history of prior MI. A summary flow diagram for the use of routine coronary angiography in post-MI patients based on a cost-effectiveness threshold of $50,000 per QALY added is shown in eFigure 42.1.1.



***e*FIGURE 42.1.1** Cost-effective use of diagnostic coronary angiography in acute myocardial infarction (AMI) survivors. CHF, congestive heart failure; ETT, exercise tolerance test; LVEF, left ventricular ejection fraction. (From Kuntz KM, Tsevat J, Goldman L, et al. Cost-effectiveness of routine coronary angiography after acute myocardial infarction. *Circulation* 1996;94:957–965, with permission.)

Antithrombin Therapy

Small randomized trials of heparin versus no heparin in patients with unstable angina or non–Q-wave MI have shown a reduction in short-term death and nonfatal MI. Consequently, heparin has been adopted as a standard of care for these patients in the early phase of their presentation (47).

Recent work has centered on identifying more potent antithrombin agents that would improve on the results obtained with heparin. The most promising new antithrombin at present is bivalirudin. Kong and colleagues (81) performed a metaanalysis of six trials that compared this agent with standard heparin therapy in elective percutaneous revascularization (4,603 patients) and in acute coronary syndrome (1,071 patients). Overall, at 30 days, bivalirudin reduced the risk of death or MI by 27% (p = .02). In addition, bivalirudin was associated with a 59% decrease in major bleeding. These data suggest at least equivalent effectiveness with heparin and better safety. Two ongoing large phase III trials are testing bivalirudin in percutaneous coronary revascularization and acute coronary syndromes, respectively. Both trials are including prospective economic analyses.

Several studies have been conducted using low-molecular-weight heparins in patients with acute coronary syndromes. The first such study, FRISC, reported a benefit for dalteparin but had some important design limitations that made it difficult to interpret the study for current cardiovascular practice. In the FRISC II trial, patients with acute coronary syndrome were randomized to dalteparin plus aspirin versus aspirin alone for approximately 1 month (82). At 6 days, the dalteparin arm had a significant reduction in death or MI, but these differences did not persist at the 6-month follow-up.

A second agent, enoxaparin, has been compared with unfractionated heparin in more than 7,000 patients in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) (3,171 patients) and TIMI IIB (3,910 patients) trials. Metaanalysis of these two trials showed a 23% reduction in death or MI at 8 days that persisted at 6 weeks (83). In the ESSENCE trial, these benefits lasted out to 1 year. The economic analysis of ESSENCE showed that the low-molecular-weight heparin strategy was associated with a drug cost of $155 per patient (2.5 days of therapy) in the United States. After taking this cost into account, the enoxaparin strategy was associated with a cost savings of $760 to $1,170 per patient shifted from standard unfractionated heparin therapy because of a reduction in use of invasive procedures and length of stay (84).

Antiplatelet Therapy

As reviewed elsewhere in this text, a number of new compounds have been developed that block the platelet GP IIb/IIIa receptor, thereby providing potent inhibition of platelet aggregation. Three compounds have been approved for clinical use in the United States: abciximab (in patients undergoing or planned for percutaneous revascularization), eptifibatide, and tirofiban. The GUSTO IV trial surprisingly failed to show a benefit of abciximab therapy in patients with non–ST-elevation acute coronary syndrome (85). Tirofiban has been tested in two trials, Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS).

The PRISM trial tested tirofiban without heparin and found a significant mortality reduction but no effect on MI or refractory ischemia at 30 days (86). However, the same tirofiban plus aspirin with no heparin regimen had the highest mortality in PRISM-PLUS, and this arm was stopped prematurely (87). Thus, many believe that the

mortality benefit in PRISM was not a real finding. With no mortality benefit and also no effect on MI, there is little effectiveness in PRISM to use as the basis for a cost-effectiveness analysis.

In PRISM-PLUS, investigators were “encouraged” to refer patients to coronary angiography between 48 and 96 hours after enrollment, and 90% of patients underwent catheterization. This protocol-guided care represented a substantial shift from usual practice for most of the participating sites and creates difficulties in assessing the economic impact of the tirofiban plus heparin regimen. To date, no formal cost-effectiveness analysis of the entire PRISM-PLUS trial has been performed. Based on the 1.8% absolute reduction in mortality and 2.9% absolute reduction in MI at 6 months for the tirofiban plus heparin arm and a mean infusion duration of 71 hours (total cost of tirofiban infusion is approximately $1,000 to $1,100), it is likely that a formal cost-effectiveness analysis would find this therapy to be economically attractive.

The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), with 10,948 patients, is the largest trial of an intravenous GP IIb/IIIa inhibitor in patients with non–ST-segment elevation acute coronary syndrome. At 30 days, the eptifibatide arm had a 1.5% absolute reduction in death or MI compared with placebo (p = .04) (88). A detailed prospective economic substudy in the 3,522 U.S. patients enrolled in PURSUIT showed two major findings (89). First, with a diagnostic catheterization rate of 85% as background, the addition of eptifibatide did not alter the use of invasive cardiac procedures or hospital length of stay. Second, with a cost for the eptifibatide regimen ranging from $1,217 (average wholesale price) to $1,014 (hospital discounted price) and an incremental increase in life expectancy of 0.11 years attributable to eptifibatide therapy in U.S. patients, the cost per year of life added was between $13,700 and $16,500. This fulfills criteria cited earlier for an economically attractive therapy.

Coronary Revascularization

In the United States, it is estimated that approximately 1.3 million diagnostic cardiac catheterizations, approximately 553,000 coronary artery bypass surgeries, and 926,000 percutaneous interventional procedures (on 528,000 patients) are performed annually (based on 1998 figures) (90). Thus, defining the clinical effectiveness, costs, and appropriate roles for these technologies has been a paramount research problem in clinical medicine over the last decade. Early outcomes research studies in cardiology found a surprising and substantial degree of variability in the use of these procedures in different geographic areas in the United States (91). More recent investigations have at least partially explained the sources of these variations. Two of the paramount determinants are the availability of cardiovascular specialists in the geographic area and the availability of angiographic and revascularization facilities (27,49). Strong correlations are also found between the use of noninvasive diagnostic testing and subsequent use of coronary angiography on the one hand and between the use of coronary angiography and subsequent revascularization procedures on the other (92). Early responses from health policy analysts to the observations about geographic variability in cardiac procedure use centered on the presumption that the high-use areas had a higher rate of inappropriate care (93). However, a number of studies using rigorous expert panel consensus guidelines for appropriate and necessary care have failed to confirm this supposition. In fact, the rate of unnecessary procedures in New York State is virtually equivalent to that in Ontario, Canada, a geographic area with approximately half the overall procedure rate of New York (94). Work by Hux and colleagues (95) in Canada has suggested that in areas of Ontario where the use of angiography and revascularization is higher, a greater proportion of patients who receive the procedures have small predicted marginal health benefits in terms of survival or angina relief. Thus, the debate about the appropriate use of invasive cardiac procedures is shifting from a focus on wasteful and unnecessary care to the balance between incremental benefits and incremental costs. However, although a number of studies have described the costs of different interventional strategies for coronary disease, very few have attempted to address their cost effectiveness. A comprehensive cost-effectiveness analysis in this area would, in fact, be quite difficult due to the complexity of the underlying clinical decisions, the difficulty in obtaining adequate outcome data, and the rapidly evolving technologies that comprise the set of currently used invasive cardiac procedures. Wong and colleagues (96) made the most recent attempt, in 1990, but their model does not include more recent data or changes in current evidence or practice patterns.

Percutaneous Coronary Revascularization

In the Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GPIIb/IIIa Receptor Blockade (EPILOG) multicenter randomized trial, which involved 2,792 patients undergoing nonemergent balloon PTCA in 1995 and 1996, mean length of stay was 3.3 days; mean hospital costs were $7,600 with physician fees (from the Medicare Fee Schedule) of $1,400, yielding a total initial medical cost of $9,000 (97). Costs for follow-up hospitalizations and procedures to 6 months were $3,400, so that cumulative 6-month medical costs totaled $12,400. As noted earlier, PTCA costs can be systematically examined by separating them into four categories (Table 42.1). Patient characteristics can alter the costs of coronary angioplasty through their effects on the complexity of the procedure, the likelihood of success, and the rate of complications, early (e.g., abrupt closure) and late (e.g., restenosis). Patients with American College of Cardiology/American Heart Association type B2 or C lesions, for example, tend to have higher procedure-related costs because the procedure is less often successful, and, even when it is initially successful, the results are less often durable (98). In the Duke database, costs for angioplasty were lowest for one-vessel disease, intermediate for two-vessel disease, and highest for three-vessel disease (99). The Bypass Angioplasty Revascularization Investigation (BARI) study confirmed these findings and also reported that costs associated with an angioplasty strategy in diabetic patients were substantially higher than those for nondiabetics ($9,500 more for diabetics with 2-vessel disease vs. nondiabetics, more than $40,000 more for 3-vessel disease after 5 years of follow-up) (100). In a consecutive series of 1,258 patients who underwent percutaneous revascularization at The Cleveland Clinic between November 1992 and June 1993, the strongest clinical predictors of increased cost were admission for acute MI (91% increase), recent MI (17% increase), more complex lesion morphology based on the American College of Cardiology/American Heart Association classification (³12% increase), diabetes (12% increase), and the number of diseased vessels (9% increase per vessel) (101).

In a private insurance claims database, Topol and coworkers (102) found that hospital charges for PTCA were higher in older patients, in women, and in individuals with a history of prior MI. In summary, the most consistent patient-related predictors of higher initial hospital costs for percutaneous coronary intervention (PCI) are acuity of presentation, complexity of treated lesions, presence of diabetes, more extensive coronary disease, and older age. Some of these predictors, in turn (e.g., age, diabetes), may be surrogates for unmeasured aspects of disease severity or lesion complexity.

Treatment-related factors can also have a large effect on PCI costs. Ellis and colleagues (101) found that decision delay (delay between admission and diagnostic angiography or between diagnostic angiography and revascularization) was associated with an 86% increase in hospital costs and that weekend delay (postponed procedure due to a weekend) was related to a 61% increase. In a separate analysis, combined angiography and PTCA increased hospital costs by $850 versus separate procedures (98). Reeder and coworkers at the Mayo Clinic found that failed PTCA more than doubled hospital charges (due primarily to referral for CABG) relative to initially successful procedures (103,104). Use of adjunctive procedures and pharmacologic agents has a substantial influence on the cost picture of PTCA. In The Cleveland Clinic study, urgent CABG increased costs 83% and intraaortic balloon pump use increased costs by 42% (101). Costs were also increased with the use of transluminal extraction catheter atherectomy (40% increase), Rotablator (25% increase), stents (25% increase), perfusion balloons (12% increase), directional coronary angioplasty (10% increase), and laser (7% increase). In the EPILOG randomized trial, use of abciximab (with low-dose heparin) increased index hospital costs by a net of approximately $600 (97). Average cost for the drug itself was approximately $1,450 per patient, and reduced complications offset some, but not all, of that initial cost. In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT), the cost of stenting added approximately $2,200 to the hospital costs (not counting professional fees), and stenting with abciximab added $3,600 (105). Thus, the main procedural determinants of PCI costs are related primarily to extra therapies that are used to prevent or treat complications.

With regard to provider-related factors, care at a teaching hospital was associated with lower charges for PCI in one study (102). The physician who performed the procedure was a major cost driver in 250 consecutive patients treated at the University of California at San Francisco, with a $4,400 cost increase from lowest-cost to highest-cost physician (98). This difference appeared to reflect a behavioral pattern by the more expensive operators of using more catheterization laboratory resources. No differences were found with lower-cost operators in patient characteristics, lesion characteristics, success rate, or complications. Shook and colleagues (106) found that high-volume operators (³50 cases/year) averaged slightly lower hospital costs compared with low-volume operators ($7,977 vs. $8,278, p = .07) despite greater complexity and risk of procedures done by the high-volume operators. Geographic factors have also been identified as an important source of cost variability, with the western region of the United States having the highest charges and the Midwest having the lowest for balloon PTCA (102).

Coronary Artery Bypass Graft Surgery

The costs of CABG surgery have been studied for approximately two decades. During this time, the technical aspects of the procedure as well the postprocedure care and the long-term outcomes have changed substantially. Therefore, only the more recent literature is of relevance to current practice. The most recent national cost figures for bypass surgery come from an analysis by Cowper and coworkers (107) at Duke Medical Center of the 1990 Medicare database. At that time, the average hospital costs for an admission for bypass surgery were $23,000. With an additional $10,000 in physician fees (i.e., charges), the total cost of an isolated bypass surgery was approximately $30,000. In 2001 figures, this equates to a cost of approximately $41,000. The distribution of costs for the initial hospitalization included 37% for intensive care unit and regular care rooms, 21% for operating room, and 42% for laboratory/supply/pharmacy and other departments.

A number of studies have evaluated the determinants of the cost of CABG. Patient characteristics typically account for no more than 25% of the total variance in hospital costs for this procedure. In an analysis of 604 patients treated at Duke, factors identified as predictive of higher costs included older age (p <.0001), female gender (p <.005), black race (p <.19), lower ejection fraction (p <.0001), prior bypass surgery (p <.0001), more extensive coronary disease (p <.01), prior CABG (p <.0001), and diabetes (p <.03) (108). In 807 patients treated at Emory University, patient predictors of higher cost included higher angina class (p = .02), previous MI (p = .03), older age (p = .0001), heart failure (p = .001), and a higher number of diseased vessels (p = .0001) (109). Diabetes was a marginally significant predictor of higher costs (p = .07). However, in the BARI study, diabetic patients who underwent CABG had 5-year costs that were $15,000 higher than those of their nondiabetic

counterparts (100). In contrast, there was no difference in cost between patients with two- and three-vessel disease who were undergoing CABG in BARI.

Two procedural factors have been associated with higher CABG costs: need for additional invasive procedures, such as valvular surgery or coronary angiography, and use of internal mammary artery grafts (107). Perioperative complications are a major source of increased hospital costs for CABG. Complications identified as important cost drivers in the Emory study included adult respiratory distress syndrome, pneumonia, septicemia, major arrhythmias, neurologic events, and bleeding that required reexploration (109). Patients with no complications had a mean hospital cost of $16,776 (1990 dollars). Patients with one of the above complications had hospital costs of $17,794, patients with three complications had costs of $23,624, and patients with five complications had costs of $50,609.

Analysis of the national Medicare data has indicated that hospital-level provider-related factors account for approximately 17% of the total variation in bypass surgery costs, independent of patient-level factors (107). Analysis of determinants of CABG costs at Duke Medical Center showed that the attending surgeon was the single most important determinant of cost (108). Median hospital cost for the most expensive surgeon was $15,000, whereas the corresponding figure for the least expensive surgeon was $10,800.

As with coronary angioplasty, the costs for coronary bypass surgery are a moving target. Nationally, length of stay for this procedure has decreased substantially over the last decade, in part because of the pressures of managed care. Progress with minimally invasive coronary artery bypass surgery (MICAB) has raised the possibility of further reductions in cost (110). Investigators from Johns Hopkins University reported length-of-stay and cost figures for MICAB that are comparable to those of percutaneous interventional procedures ($7,803 for PTCA, $13,415 for stent, $11,623 for MICAB) (111). However, the technology is still in its developmental phase, and its true role in the panoply of revascularization options will likely not be defined for at least several more years.

Two trials have compared medical therapy with percutaneous revascularization. The Angioplasty Compared to Medical Therapy (ACME) trial found a very modest improvement among 212 patients with single-vessel disease in exercise treadmill time and physical functioning in the PTCA arm (112). A preliminary economic analysis of ACME was conducted but has not yet been published. The second Randomized Intervention Treatment of Angina (RITA-2) trial found that PTCA improved angina and exercise test performance but had a slight excess of procedure-related MIs. Quality of life was significantly better for the PTCA arm at 1 year, but these benefits attenuated by 3 years (113). At least part of this attenuation appears due to late revascularization procedures in the medical arm. An economic analysis of RITA-2 has not yet been published.

The Asymptomatic Ischemia Pilot randomized 558 patients with clinically stable coronary disease and documented ischemia to one of three treatment strategies: angina-guided medical care, ischemia-guided medical care, and revascularization. The ischemia-guided therapy was adjusted on the basis of repeated ambulatory monitoring studies. The principal medical regimens used in this pilot study were either atenolol-nifedipine or diltiazem-isosorbide. Patients who were randomized to revascularization received either PTCA or CABG at the discretion of the principal investigator. Although an economic analysis was not initially planned for this study, we performed a *post hoc* analysis using the available resource use data along with cost estimates taken from the GUSTO I analysis (114). At the end of 3 months, the average costs for the revascularization patients were $13,400, compared with $1,500 for the angina-guided patients and $900 for the ischemia-guided patients. However, between 3 months and 2 years, the costs for the medical arms significantly exceeded those for the revascularization arm, primarily because of an increased need for revascularization procedures and rehospitalizations. At the end of 2 years, the cumulative costs for the angina-guided strategy were $7,735, those for the ischemia-guided strategy were $8,575, and those for the revascularization strategy were $16,782. No empiric data were collected past 2 years in the Asymptomatic Ischemia Pilot. However, taking the second-year costs as the best estimate of annual costs for each treatment arm, a simple linear extrapolation (discounting future costs at a 3% rate) suggested that at 10 years the medical arms would have cumulative costs of approximately $23,500 and the revascularization arm would average $25,300. However, good empiric data on resource use patterns after 5 years in a modern cohort of CAD patients does not exist.

Two randomized trials have compared the costs of coronary angioplasty and coronary bypass surgery in patients with multivessel coronary disease in the United States. The clinical outcomes from these trials are reviewed in Chapter 16. The Emory Angioplasty Surgery Trial (EAST) enrolled 392 patients between 1987 and 1990 (115). Patients were followed every 6 months for 3 years. Hospital costs were estimated from hospital bills, with charges converted to costs using department-level cost-charge ratios (116). Physician fees for care at Emory were obtained from physician bills (i.e., charges). Hospital cost data were not collected for outside (i.e., non-Emory) hospitalization. Instead, Emory costs were applied to the follow-up hospitalizations reported on follow-up contacts. Costs were all deflated to 1987 dollars. For the initial hospitalization, hospital costs were $11,684 (median, $10,290) for PTCA and $14,579 (median, $13,991) for CABG ($p$ <.0001) (116). With physician fees added in, total initial costs were $16,223 for PTCA and $24,005 for CABG ($p$ <.0001) (Fig. 42.2). At the end of 3 years, cumulative costs for the PTCA arm were $23,734 versus $25,310 for CABG ($p$ <.0001) (Fig. 42.3). Thus, PTCA costs initially constituted 68% of CABG costs but after 3 years had risen to 94% of these costs (116). In multiple regression analysis, the major correlates of initial medical costs were randomization to CABG, heart failure, and male gender (Table 42.2). Regression analysis of 3-year costs identified ejection fraction, hypertension, and male gender as the major cost correlates. Assignment to CABG was no longer an independent predictor. Between 3 and 8 years, the CABG patients had $2,700 of extra medical costs versus $4,700 for the PTCA arm. With 8 years of follow-up, total costs were $46,348 for the CABG arm and $44,491 for the PTCA arm (p = .37) (117).

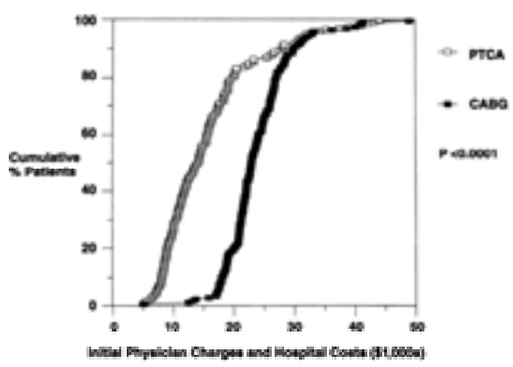


FIGURE 42.2 Cumulative distribution plot of total initial costs (hospital and physician) by treatment group in the Emory Angioplasty versus Surgery Trial. CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty. [From Weintraub WS, Mauldin PD, Becker E, et al. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary disease: results from the Emory Angioplasty versus Surgery Trial (EAST). *Circulation* 1995;92:2831–2840, with permission.]

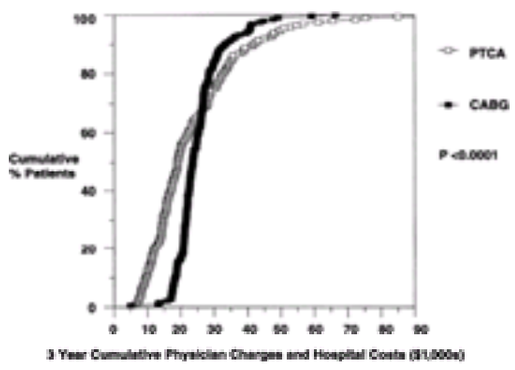


FIGURE 42.3 Cumulative distribution plot of 3 years of costs by treatment group in the Emory Angioplasty versus Surgery Trial. CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty. [From Weintraub WS, Mauldin PD, Becker E, et al. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary disease: results from the Emory Angioplasty versus Surgery Trial (EAST). *Circulation* 1995;92:2831–2840, with permission.]

Variable	Cost	p
Correlates of initial hospital and physician costs		
Surgical group	$7,725	<.01
Heart failure	$6,766	.01
Older age (per yr)	$122	.01
Male	$2,777	.01
Hypertension	$1,934	.04
Angina class	$622	.08
Correlates of 3-yr cumulative costs*		
Ejection fraction (per %)	−$115	.01
Hypertension	$3,289	.01
Male	$3,465	.02
Angina class	$834	.08

*Surgical group no longer significant independent correlate.
From Weintraub WS, Mauldin PD, Becker E, et al. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary disease: results from the Emory Angioplasty versus Surgery Trial (EAST). Circulation 1995;92:2831–2840, with permission.

TABLE 42.2 MAJOR COST CORRELATES IN EMORY ANGIOPLASTY SURGERY TRIAL

BARI enrolled 1,829 patients with multivessel CAD between 1988 and 1991 in 18 centers (118). The BARI Substudy of Economics and Quality of Life was conducted in 7 of the 18 enrolling sites and collected cost data on 934 of the 1,829 total patients randomized in the trial (100). Detailed cost data were collected on all hospitalizations (regardless of diagnosis) as well as outpatient visits to ten different types of health care providers and outpatient cardiac tests and procedures. Medication use was also collected in this trial. Initial length of stay was 9 days for the PTCA arm and 13.3 days for the CABG arm. Hospital costs were $14,415 versus $21,534, and physician fees were $6,698 versus $10,813 (100) (Fig. 42.4). In follow-up, PTCA patients averaged 3.1 readmissions versus 2.7 for CABG patients. Total inpatient follow-up costs (hospital plus physician) were $27,439 for PTCA and $19,529 for CABG. Number of outpatient visits was equivalent for the two therapies, as were outpatient costs ($1,656 vs. $1,617). The PTCA patients took an average of 4.1 cardiac medicines at a cumulative 5-year cost of $4,948. The CABG patients averaged 4.0 cardiac medicines at a cost of $3,670. Outpatient diagnostic testing was equivalent in the two treatments, but CABG patients had a slightly higher rate of nursing home admission (3.2% vs. 2.6%) with higher associated costs ($1,027 vs. $265). After 5 years of follow-up, total discounted costs in the CABG arm were 5% greater than those for PTCA ($58,889 vs. $56,225) (Fig. 42.4). In subgroup analyses, patients with two-vessel disease had significantly lower costs with angioplasty ($52,390 vs. $58,498 for CABG), whereas angioplasty costs were actually higher than those of bypass surgery in patients with three-vessel disease ($60,918 vs. $59,430).

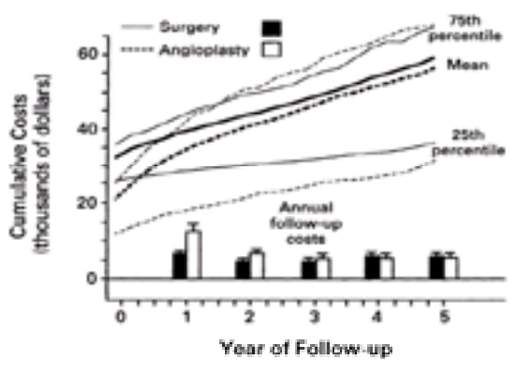


FIGURE 42.4 Cumulative cost at quarterly intervals for patients in Bypass Angioplasty Revascularization Investigation Substudy of Economics and Quality of Life. The thick lines indicate mean cumulative costs. The lighter lines represent twenty-fifth and seventy-fifth percentiles of the cumulative costs. The bars at the bottom show the mean (±2 standard error) follow-up costs accrued over the prior year. (From Hlatky MA, Rogers WJ, Johnstone I, et al. Medical care costs and quality of life after randomization to coronary angioplasty or coronary bypass surgery. *N Engl J Med* 1997;336:92–99, with permission.)

Cost analysis of the British Randomized Intervention Treatment of Angina trial of 1,011 patients confirmed the findings of EAST and BARI (119). The initial costs (estimated in British pounds) of treating with PTCA were approximately 52% those of CABG, but at the end of 2 years PTCA costs were 80% those of CABG. Follow-up in this trial out to 10 years is planned.

Coronary Stents

Coronary artery stents have undergone an exponential increase in usage since 1994. Data from 18 high-volume interventional programs participating in the National Cardiovascular Network showed that 6% of interventional cases at these institutions involved stents in 1994; by 1996, that proportion had risen to 39%, and current usage averages more than 70% (120).

To date, five randomized trials have compared a strategy of primary stenting versus conventional balloon PTCA (with stent backup if necessary) in stable patients with lesions of 20 mm or less in large target vessels (³3.0 mm): the Stent Restenosis Study I (STRESS I), Belgian Netherlands Stent Study (BENESTENT) I, BENESTENT II, the Optimum Percutaneous Transluminal Coronary Angioplasty Compared with Routine Stent Strategy (OPUS) trial, and the Doppler Endpoint Stenting International Investigation (121,122,123,124 and 125). The clinical data from these trials are reviewed in Chapter 80. Most important, these trials did not show any significant differences between initial stent and initial PTCA strategies in mortality, nonfatal MI, stroke, or anginal symptoms. The principal benefit of stenting that emerged from these trials was a reduction in repeat revascularization rates. In BENESTENT II, which used a heparin-coated Palmaz-Schatz stent and a ticlopidine-aspirin antithrombotic regimen in lieu of the earlier aspirin-warfarin regimen, 14% of PTCA patients and 9% of stent patients required a repeat revascularization procedure out to 6 months (125). These results are important not only because of the substantial reduction in clinical restenoses achieved in the stent arm but also because of the very substantial improvement in outcomes reflected in the PTCA arm statistics relative to earlier trial results.

Sukin and coworkers (126) compared 1995 practice in 78 patients who underwent coronary stenting at the Beth Israel Hospital with earlier data from the STRESS I trial (1991–1993). The major temporal trends observed in the use of coronary stenting included use of more stents and more adjunctive balloons per patient to achieve “optimal stent deployment.” The associated catheterization laboratory costs rose from $3,012 in STRESS I to $5,209, a $2,197 increase. Stenting of large lesions or multiple lesions increased catheterization laboratory costs by an additional $2,000 relative to single-lesion stenting.

Peterson and colleagues (127) compared hospital costs of stenting with those of balloon PTCA at Duke Hospital from 1995 to 1996 (Table 42.3). Compared with PTCA, stenting costs were $3,600 more per case in catheterization laboratory resources and $3,300 higher in total hospital costs (127). Over the next 6 months, however, stent patients were rehospitalized less often (22% vs. 34%) and had less frequent need for repeat revascularization (9% vs. 26%). Thus, at 6 months, the costs for the two strategies were equal ($19,600 vs. $19,800), and this economic parity was maintained out to 1 year.

Cost category	Stent, 5/95–6/96 (n = 384)	PTCA, 5/95–6/96 (n = 159)	p Value
Catheter laboratory			
Balloons	$1,759	$1,479	<.001
Stents	$3,629	$199	<.001
Abciximab	$661	$817	.15
Guide catheter/wire	$481	$490	.54
Dye	$516	$504	.34
Other costs	$2,694	$2,765	.82
Total	$8,780	$6,224	<.001
Rooms			
Routine	$1,309	$1,479	.88
Step-down/intensive care unit	$1,368	$1,402	.79
Pharmacy	$302	$289	.89
Laboratory	$285	$345	.31
Emergency room	$287	$756	.35
Catheter laboratory	$8,780	$6,224	<.001
Other	$871	$1,100	.30
In-hospital costs	$14,802	$11,534	<.001
Professional fee	$1,863	$1,816	<.001
Total in-hospital costs	$16,665	$13,350	<.001

From Peterson ED, Cowper PA, Delong ER, et al. Acute and long-term cost implications of coronary stenting. J Am Coll Cardiol 1999;33:1510–1518, with permission.

TABLE 42.3 COMPARISON OF STENT AND PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) COSTS AT DUKE HOSPITAL

The OPUS-1 trial tested whether routine coronary stenting was superior to optimum PTCA with provisional stenting in 479 patients with one-vessel disease (123). In the routine stenting arm, patients averaged 1.2 stents, whereas in the optimum PTCA arm they averaged 0.5 stents, and 37% of patients in this arm required stent implantation. Use of abciximab was low in both arms (13% to 14%). Index hospital length of stay was similar in the two arms (2.5 to 2.6 days). The procedural costs were higher for routine stenting ($5,455 vs. $4,219, p <.001), and total initial hospital costs were correspondingly higher for the stent arm: $9,234 versus $8,434 ($p$ <.001). Follow-up cardiac events out to 6 months were higher in the PTCA arm (123). In particular, target vessel repeat revascularization occurred in 10% for the PTCA arm versus 3% for stenting and any repeat revascularization procedure in 15% of the PTCA arm versus 5% of the stent arm. Hospital readmissions were twice as frequent for PTCA-arm patients. These follow-up costs offset the extra initial costs of routine stenting so that at 6 months, the stent group had slightly lower cumulative costs ($10,206 vs. $10,490 for PTCA). A bootstrap simulation yielded a net 6-month cost savings for routine stenting in 69% of 1,000 replications, with a mean savings of $268.

Comparisons of PTCA with stenting must also be interpreted in the larger context of a comparison of percutaneous revascularization (including stenting and PTCA) versus CABG and medicine. Several trials have compared a percutaneous revascularization strategy with routine stenting to CABG. The Arterial Revascularization Therapies Study randomized 1,205 patients with multivessel CAD to stent versus CABG (128). At 1 year, there was no significant difference in mortality, stroke, or MI. Repeat revascularization occurred in 16.8% of stent patients versus 3.5% of CABG patients. Initial procedural costs (based on European practices and prices and converted to U.S. dollars) were lower in the stent arm ($6,400 vs. $10,700). At 1 year, these differences had narrowed somewhat because of the extra repeat procedures in the stent arm: $10,700 for the stent arm versus $13,600 for the CABG arm (p <.001). The relevance of these cost data for U.S. practice is uncertain given the unexpectedly low cost estimates for CABG. The Canadian/European Surgery or Stent study has been reported in abstract form, and an economic analysis of this trial is anticipated. The ongoing Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial is comparing optimal medical therapy with a strategy of PCI, and an economic analysis of this trial is planned.

Heart Failure

Approximately 4.7 million Americans carry a diagnosis of heart failure, and more than 550,000 new cases are identified each year (90). Approximately 70% of cases are due to coronary disease, with hypertension the next most common underlying disorder (129). The annual hospitalization volume for heart failure now approaches 1 million (1998 figure), with an associated annual cost in excess of $3.7 billion. The prevalence of heart failure rises with increasing age, and it is the single most frequent cause of hospitalization in the Medicare population (age ³65) (90). After a first admission for heart failure, Medicare patients have a 44% chance of being readmitted at least once within 6 months (130).

Costs of Medical Care of Heart Failure

To analyze the costs of heart failure and their determinants, it is useful to look at three cost components (Fig. 42.5): maintenance care, care for episodes of decompensation, and procedures to reverse the heart failure state. Maintenance care includes the use of medications and routine medical follow-up for the patient with a stable, well-compensated course. The goals of maintenance therapy are to reduce symptoms and improve functional status to the extent possible, to improve survival, and to decrease the need for repeat hospitalizations. Periodically, patients with heart failure enter a state of decompensation; this may occur gradually as a result of progressive myocardial dysfunction or more abruptly (e.g., because of complicating arrhythmias, excess intake of dietary sodium, infection, or inappropriate cessation or reduction of medical therapy). The three most common causes of need for hospitalization in patients with congestive heart failure (CHF) are uncontrolled ischemia, uncontrolled atrial fibrillation, and increasing pulmonary or peripheral edema. Although not all hospitalizations for CHF can be eliminated without reversing the underlying heart failure state, some interventions have been proven to reduce the need for such admissions. Whether the efficiency of admissions for heart failure can also be improved (with a consequent reduction in costs) remains largely undefined. Finally, there are a growing number of nonpharmacologic interventions whose goal is to stabilize or even reverse the heart failure state. These include cardiac transplantation, use of various mechanical assistive devices, and CABG (with or without left ventricular reconstruction).

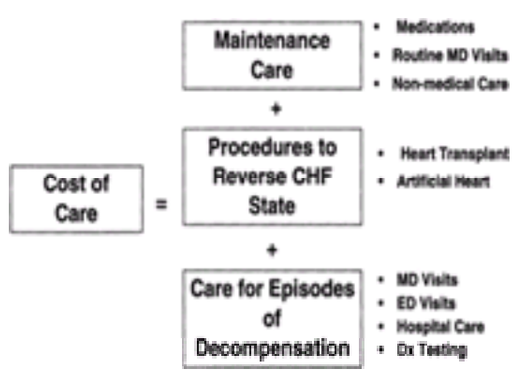


FIGURE 42.5 Cost components for heart failure care. CHF, congestive heart failure; Dx, diagnosis; ED, emergency department; MD, doctor of medicine.

The costs of care for a typical group of patients with heart failure consist of a mix of costs due to maintenance care and costs for treatment of decompensation. Only very small numbers of patients (2,360 in 2000) undergo cardiac transplantation (90). No “natural history” cost studies of heart failure have been done, and therefore it is difficult to define the cost of the disorder independently of the interventions used to treat it. Overall annual costs for patients with advanced heart failure, including inpatient and outpatient care and outpatient medications (including ACE inhibitor therapy), averaged $22,500 in the Fosinopril Efficacy/Safety Trial (FIRST) study and $21,100 in the Washington University trial (131,132). Patients with New York Heart Association (NYHA) class IV had higher costs than those with class III; costs were also increased for patients with renal insufficiency and with diabetes (131).

Digoxin

Digoxin is one of the oldest pharmacologic interventions in cardiovascular medicine, but its clinical effectiveness remains controversial. The National Institutes of Health DIG trial found no survival benefit for digoxin but a significant 6% reduction in the need for hospitalization (133). Using DRG-based Medicare reimbursement rates, Eisenstein and colleagues (133) performed a cost analysis of the DIG trial. Digoxin patients averaged fewer all-cause (1.9 vs. 2.0, p = .01) and heart-failure (0.6 vs. 0.8, p = .001) hospitalizations. Digoxin patients had higher total medical costs ($12,648 vs. $12,362, p = .001). Heart-failure costs were lower ($3,122 vs. $4,130, p = .001), but non–heart-failure costs were higher. PTCAs were more frequent in the digoxin arm, suggesting that these patients improved enough clinically to be treated more aggressively for their CAD. The average cost of the digoxin therapy over a mean of 37 months was $163. A cost-effectiveness analysis of this trial is planned.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitor therapy is recognized as one of the foundations of modern medical therapy for heart failure (134). A number of large-scale clinical trials have clearly demonstrated that ACE inhibitors prolong survival in patients with heart failure due to systolic dysfunction. However, none of these trials included prospective measurement of costs. Two U.S. studies have used decision analysis models to estimate the cost effectiveness of this form of therapy (135,136).

Glick and colleagues (135) used primary data to form the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial (mild to moderate heart failure and ejection fraction <35%) to model the cost effectiveness of enalapril therapy. The model evaluated 48-month outcomes (from the available empiric data) and projected lifetime outcomes. Analysis was done from a societal perspective, and costs were expressed in 1992 U.S. dollars. On the health-benefit side, this study estimated that patients who were randomized to enalapril gained 0.14 discounted years of life and 0.11 discounted quality-adjusted years of life during the 4-year follow-up of the trial. The life expectancy of these patients was estimated at 6.5 to 7.0 years, and over this period enalapril was projected to add 0.30 discounted years and 0.21 discounted QALYs.

On the cost side, enalapril patients averaged $11,840 in discounted costs of hospitalization, enalapril therapy, and outpatient visits during the 4 years of the study. The corresponding cost for the placebo patients was $12,560. Thus, during the trial period, enalapril saved $720 per patient (135). Importantly, these savings occurred during the first 18 months of the trial, and costs after this point were similar. Over the projected life expectancy of the study cohort, enalapril patients had discounted costs of $22,000 and placebo patients had costs of $21,975. The lifetime incremental cost of enalapril therapy was therefore projected to be $25 per patient.

During the 4 years of the trial, enalapril improved survival and reduced medical costs. Projecting these data out to a lifetime cost-effectiveness perspective, enalapril saved an added life-year for $80 and an added QALY for $115 (135). These data demonstrate that, at a minimum, ACE inhibitor therapy with enalapril in mild to

moderate CHF is in the “best buy” category of cost effectiveness. For several reasons, it is likely that in this population ACE inhibitor therapy is actually cost saving over the patient’s lifetime. First, sensitivity analysis on the long-term effects of enalapril shows that if the drug continued to reduce hospitalizations after 18 months it would be cost saving (135). Second, the average wholesale price for a year’s supply of enalapril, 20 mg per day, is $475. The advent of generic captopril makes an ACE inhibitor available for a substantially lower cost and would, therefore, make the therapy cost saving over a lifetime. Finally, the cost assigned to follow-up hospitalizations was based on HCFA DRG reimbursement rates and may have, therefore, underestimated the fair cost of such an event (and, hence, the value of preventing it).

Paul and colleagues (136) created a decision model of ACE inhibitor therapy using published data from SOLVD treatment and Veterans Administration Heart Failure Trials I and II. Because they did not have access to primary patient-level data, they were not able to evaluate the cost-saving potential of enalapril. This analysis assigned a cost of $6,750 (1992 U.S. dollars) to each heart failure hospitalization and a cost of $959 for a year of 20 mg per day enalapril therapy (based on a telephone survey of ten retail pharmacies in Boston). In this analysis, enalapril was projected to increase life expectancy from 4.36 years to 4.65 years at an incremental cost of $2,569. The cost-effectiveness ratio for enalapril was $9,700 per life-year. Although less favorable than the SOLVD analysis, this study confirms that ACE inhibitor therapy is economically in the “best buy” category of therapies. Several economic analyses of ACE inhibitor therapy for heart failure have been conducted in Europe (137). Using data from the Munich Mild Heart Failure Trial, Kleber (138) found that ACE inhibitor therapy recouped approximately 75% of the cost of medication by reducing the need for hospitalization in patients with progressive heart failure. The Institute for Medical Technology Assessment in the Netherlands found that survival was increased and costs were decreased by first-line ACE inhibitor use in heart failure (139). A third model was based on published SOLVD treatment trial outcomes and U.K. costs (140). This model evaluated the importance of different modes of initiation of ACE inhibitors (hospitalization for various durations vs. outpatient initiation). Hospital initiation (3-day hospital stay) was cost effective, and outpatient initiation made the therapy cost saving overall.

Beta-Blocking Agents

Two important randomized trials reported that beta-blocker therapy in heart failure produces a clinically important and statistically significant reduction in mortality and hospitalization. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) randomized 3,991 patients with class II or greater heart failure and an ejection fraction of 0.40 or less to metoprolol CR/XL or placebo (141). With an average follow-up of 1 year, metoprolol reduced death or heart transplantation by 32%. All-cause hospitalization was reduced from 33% to 29% (p = .004), and days in hospital were reduced from 6.1 to 5.1 per patient (p = .004). The discounted retail cost of metoprolol XL/CR therapy ranges from $20 per month for the 50-mg dosage ($240 per year) to $54 per month for the 200-mg dosage ($650 per year). Although a formal cost analysis of MERIT-HF has not yet been reported, the cost of metoprolol therapy should be largely offset by the approximate 1-day average reduction in hospital stay.

The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) enrolled 2,647 patients with heart failure in class III or IV with an ejection fraction of 35% or less (142). All-cause mortality was reduced 34% by bisoprolol (p <.001). All-cause hospitalization was reduced 20% from 34% to 33% (p <.001). An economic analysis of CIBIS II is planned. In contrast, the Beta-Blocker Evaluation of Survival Trial randomized 2,708 class III or IV heart failure patients to bucindolol or placebo (143). At an average of 2 years, there was no significant effect on mortality overall, although nonblack patients had a survival advantage. Hospitalization was reduced by 8% in the bucindolol group (p = .08).

Economic analysis of the smaller U.S. Carvedilol Heart Failure Trials Program was performed using a Markov decision model, clinical data from the trials, and published cost data (144). Trial data were projected out to a lifetime perspective. Projected lifetime costs of conventional CHF care in this model were $28,750. Costs for the carvedilol strategy were $36,420, or $7,600 more than conventional therapy. Carvedilol was projected to extend life expectancy by 0.31 to 0.95 years per patient over the life expectancy without such therapy (6.7 years). This range reflects different assumptions about the persistence of therapeutic benefit. The corresponding cost effectiveness of carvedilol therapy ranged from $30,000 per life-year added to $13,000 per life-year added. Current (2001) discounted retail price for carvedilol is approximately $90 per month, or $1,080 per year.

Other Pharmacologic Agents

The evidence base for the survival benefits of hydralazine and isosorbide in combination is substantially less than for ACE inhibitor therapy (134). Based on the published results of Veterans Administration Heart Failure Trial I, Paul and colleagues (136) estimated an incremental cost-effectiveness ratio for this regimen of $5,600 per added life-year.

Surgical Approaches to Heart Failure

Invasive approaches that have been used to reduce or reverse the heart failure state include CABG (with or without ventricular reconstruction), heart transplantation, and left ventricular assist devices (LVADs).

For patients with ischemic cardiomyopathy, CABG has offered a theoretically attractive but controversial approach. Although registry data suggest a more favorable survival with CABG than with medical therapy, no randomized trial has validated these observations (145). Randomized trial and registry data from the 1970s comparing CABG and medicine demonstrated a magnification in absolute terms of the survival benefits of surgery in patients with impaired left ventricular function (146). Whether these observations extend to patients with advanced heart failure (NYHA class III) and a severely impaired left ventricle (ejection fraction <35%) remains uncertain. In recent years, clinicians at some centers have begun using “viability” radiologic studies such as positron emission tomography or perfusion imaging to identify the subset with substantial ischemic viable myocardium who are presumed most likely to benefit from a high-risk CABG. The Surgical Treatment for Ischemic Heart Failure (STICH) trial will be the first large-scale randomized trial of modern surgical versus optimal modern medical therapy in these difficult patients and will include an economic evaluation as well as substudies to define whether preoperative viability screening is of benefit (145).

Heart transplantation offers a radical but effective therapy for a small subset of patients with advanced heart failure. Although it has been estimated that there are more than 40,000 patients a year with advanced heart failure who could benefit from cardiac replacement therapy, only approximately 2,300 donor hearts are available each year for transplantation. This shortage of available organs relative to organs needed creates some major inefficiencies in the care of patients on the heart transplant list. The availability of a suitable heart for a given patient is, of course, unpredictable, and because available organs are allocated on an illness severity-based priority scale, doctors face an incentive to keep their candidate patients hospitalized in the intensive care unit with intravenous inotropes and a balloon pump to preserve their position at the top of the list. As a consequence, patients may wait for months in the hospital.

No high-quality modern cost data on transplantation have been published, but claims (charge) data are available (147). In 1999, charges per transplant patient averaged $303,000 through the end of the first year (corresponding costs are likely to be approximately half that amount). Hospital charges were $181,000, physician charges $23,000, and organ procurement $24,000. Follow-up care averaged $40,000, and immunosuppressive therapy charges were $11,400. The average medical charges for care after the first year (including angiography, biopsies, and drug therapy) are approximately $24,000. Thus, cumulative 5-year charges for heart transplantation are currently approximately $400,000 (representing probably approximately $200,000 in medical costs). Although no modern cost-effectiveness analysis of heart transplantation has been done, heart transplantation currently has a 1-year survival rate of more than 90% and a posttransplant life expectancy of approximately 9 to 11 years. This represents a huge increment in life-years over medical treatment of advanced heart failure, and the cost per added life-year is therefore likely to fall securely in the economically attractive zone.

Several LVADs have been approved by the U.S. Food and Drug Administration as a bridge to transplant. The acquisition cost of these devices is high, currently $50,000 to $75,000 (not counting costs of implantation or follow-up care). One small observational study suggests that, when used as a bridge to transplant, these devices pay for themselves (148). Of 90 consecutive patients on the heart transplant list who received LVAD, 44 were discharged to home to await their transplant. The cost for pretransplant care at home was $13,200, versus $165,200 for inpatient care. In addition, 30% of the outpatients resumed working, and all were independent in activities of daily living.

The more controversial aspects of LVAD use is as “destination therapy.” As noted earlier, more than 40,000 patients a year could be candidates for this form of therapy if it is approved by the U.S. Food and Drug Administration. The Randomized Evaluation of Mechanical Assistance Therapy for Congestive Heart Failure (REMATCH) trial randomized class IV patients who were ineligible for transplantation to the HeartMate vented electric LVAD or optimal medical therapy (149). If this study shows a survival advantage for the LVAD, a wider indication for these devices could add more than $5 billion to the annual health care budget in the United States. For reference, the total annual cost for heart transplantation in the United States is approximately $700 million, but this figure is constrained by the lack of more donor hearts. An economic analysis of REMATCH is planned.

Disease Management Approaches

Disease management is a composite strategy that seeks to reconfigure the medical care process to provide equal or better outcomes relative to conventional care at a lower net cost. It is based on the use of national peer-reviewed practice guidelines and locally created critical pathways to define standard care goals and the most efficient means of reaching them. Nonphysician medical staff is used to follow patients carefully (in clinic or over the telephone), encourage compliance with prescribed

therapies, and solve problems before they reach a crisis stage. Often, problem solving requires formulating a fresh view of how the medical care system should operate (sometimes referred to as *reengineering*). Outcome measurement and continuous quality improvement are other integral aspects of disease management.

Three randomized trials of disease management strategies involving heart failure patients have been published. Rich and colleagues (132) at Jewish Hospital in St. Louis enrolled 182 hospitalized elderly heart failure patients (mean age, 79 years; mean NYHA class, 2.4) at high risk for readmission into a disease management trial. Enrollment occurred over a 4-year period. The intervention arm consisted of patient and family education by a registered nurse, dietary consultation by a registered dietitian, review and simplification of the medical regimen by a geriatric cardiologist, and intensive follow-up by telephone and home visits. The control arm consisted of standard care. Over the 90-day follow-up period, intervention patients had a 44% reduction in all-cause rehospitalization (p = .035) and a significant improvement in quality of life. Economic assessment showed that the intervention arm was associated with a net $460 cost saving per patient. The cost of the program itself was $216 per patient. More than $1,000 per patient was saved by the reduced need for follow-up hospitalization (132). Compliance with prescribed medical therapy (as assessed by pill counts) was 88% in the intervention arm and 81% in the control arm (p = .003) (150).

A second trial of disease management was conducted among 1,296 veterans who were hospitalized with diabetes, chronic obstructive lung disease, or CHF at nine Veterans Administration Medical Centers (151). CHF was the primary diagnosis in 504 patients. The test strategy in this trial was an intensive primary care intervention delivered by a physician and a nurse that started before discharge and continued for 6 months. Contrary to expectations, patients in the intervention group had significantly higher rates of readmission than did the controls (p = .005). No medical benefits were observed for this intervention, but intervention patients were significantly more satisfied with their care.

The third trial randomized ten community hospitals to a quality improvement intervention versus usual care (152). This intervention had a nonsignificant effect in the beneficial direction on mortality, readmission, and quality of life. The economic effects included a 1.1-day reduction in length of stay (p = .18) and an $817 reduction in hospital charges (p = .31).

These trials point out some of the opportunities and challenges posed by disease management. First, in some situations the opportunities to improve outcomes and reduce costs using disease management strategies appear substantial. Second, opportunities for improvement may well be greater in some segments of the heart failure population than in others. Third, not all disease management interventions will be equally effective. Finally, the effectiveness and favorable economic consequences of any new disease management program need to be proven before general implementation. The Veterans Administration study shows how a seemingly positive intervention can have unintended consequences.

The investigators at Stanford have reported pilot data on their physician-supervised, nurse-mediated, home-based system for heart failure management (MULTIFIT). The key elements of the program were use of the Agency for Health Care Policy and Research Heart Failure Guidelines to direct pharmacotherapy and diet therapy and a nurse manager using frequent telephone contacts to monitor clinical status and enhance patient compliance. Compared with the 6-month period preceding the start of the pilot, patient dietary sodium fell by 38% and mean dose of ACE inhibitor increased significantly. Functional status improved significantly, whereas hospitalization rates declined by 74% and outpatient visits declined by 23% (153).

Prevention of Coronary Heart Disease and Its Complications

Clinically overt CHD has a prevalence of approximately 7 million persons in the United States and is the most common cause of death in this and other industrialized countries (90). It is also a major cause of morbidity and resulting disability. Approximately 2.0 to 2.3 million individuals with CHD in the United States have limitations in their daily activities as a result of the disease. CHD accounts for more than 2.2 million hospital admissions per year and over 10 million outpatient medical visits. The direct medical costs of caring for coronary disease patients in the United States have been estimated at $47.5 billion, and the cost to society of the loss in productivity due to morbidity and premature mortality has been assessed at $43 billion (90). For many years, it has been hypothesized that prevention might be a more cost-effective way of reducing the clinical and economic sequelae of CHD than treatment of symptomatic or decompensated disease. As discussed elsewhere in this text, epidemiologic studies have identified a set of major modifiable risk factors for CHD, and clinical trials have been conducted to define the relationship between modification of these risk factors and subsequent outcome. *Primary prevention* is usually defined as prevention in individuals at risk for the disease but without any clinical evidence that the disease has actually developed. *Secondary prevention* is prevention in patients with clinically manifest disease. In primary prevention, the risk factors that have been most often targeted are hypercholesterolemia, smoking, hypertension, diabetes, and physical inactivity. In secondary prevention programs, in addition to these risk factors, major emphasis is given to the use of aspirin, beta-blockers, and ACE inhibitors in appropriate patients. The medical effectiveness of these interventions is discussed in detail elsewhere. In this section, we review the available work on their economic implications.

In general, effective prevention programs for CHD improve outcomes at a net increased cost (154). Secondary prevention programs usually have more favorable cost-effectiveness ratios than do primary programs. Some clinicians find this counterintuitive because, they argue, prevention programs are usually less expensive on a per-patient basis than is treatment with expensive high-technology therapies. Although this may be true, the total economic picture is very substantially influenced by the number of individuals who must be treated to prevent a single death or major complication. Because risk factors for CHD only define a propensity for future disease, many individuals who are enrolled in primary prevention programs never develop the disease and consequently cannot benefit from the interventions being applied. In contrast, secondary prevention programs target individuals with an established propensity to development of disease-related complications. Consequently, the number needed to treat to prevent one adverse event is small. For example, using data from the West of Scotland trial (largely a primary prevention population), prevention of one additional death by cholesterol reduction with a statin agent would require treating 166 patients for 5 years (155). Using data from the Cholesterol and Recurrent Events (CARE) study of patients with established CHD and modestly elevated cholesterol, prevention of one death would require treating 91 patients for 5 years (156). Using the Scandinavian Simvastatin Survival Study (4S) results in patients with CHD and very elevated cholesterol levels, only 29 patients would have required 5 years of statin therapy to prevent one death (157). Because the direct costs of statin therapy would be similar in the preceding three examples, it is clear that the largest “bang for the buck” (and the most favorable cost-effectiveness ratio) would be obtained in treating the highest-risk patients.

Hypercholesterolemia

Numerous observational studies have established a strong dose-response relationship between total cholesterol levels and CHD risk. The National Cholesterol Education Program has established a target desirable level of less than 220 mg per dL for adults without evidence of clinical CHD. The corresponding low-density lipoprotein (LDL) cholesterol level is less than 130 mg per dL. Earlier primary prevention trials tested diet and pharmacologic regimens that were able to achieve reductions in total cholesterol of approximately 10%. Associated reductions in all-cause mortality were small and largely nonsignificant. Consequently, early cost-effectiveness analysis based on these clinical data generally concluded that cholesterol reduction as a primary prevention strategy was not economically attractive (158).

The West of Scotland Coronary Prevention Study (WOSCOPS) found that primary prevention with pravastatin at 40 mg per day reduced total cholesterol by 20% relative to placebo in 4,159 men older than age 45 years with LDL cholesterol levels of 155 mg per dL or greater. Pravastatin patients experienced a 22% reduction in all-cause mortality (p = .051) (155). Over 4.9 years of follow-up, for every 1,000 patients shifted to the pravastatin arm, there were five fewer deaths, 19 fewer MIs, 14 fewer diagnostic catheterizations, and eight fewer revascularization procedures. An economic analysis using British costs and the WOSCOPS data has been published (159). This analysis estimated that treating 10,000 men such as those in the trial would prevent the development of CHD in approximately 300. The pravastatin therapy cost $3,700 per patient for 5 years and saved approximately $100 per patient as a result of reduced procedures and complications. Life expectancy was increased by pravastatin by 0.10 years, and the cost per year of life added was $32,600.

A cost-effectiveness model of cholesterol-lowering strategies in the United States reported that primary prevention with a statin compared with diet therapy has a cost-effectiveness ratio ranging from $54,000 per QALY to $1.4 million per QALY depending on patient risk level (160). Importantly, the WOSCOPS economic model did not assume a preexisting secondary prevention program (i.e., wait to treat patients once they manifest clinical CAD), which may explain part of the difference with this U.S. model.

The Air Force/Texas Coronary Atherosclerosis Prevention Study randomized 6,605 subjects without clinical CAD and with average cholesterol levels to lovastatin or placebo (161). Over 5 years of therapy, lovastatin reduced acute coronary events by 37% (p <.001). In absolute terms, for every 1,000 patients shifted to lovastatin therapy there were four fewer cardiovascular deaths, 26 fewer MIs, 16 fewer unstable angina admissions, and 31 fewer revascularization procedures. The cumulative 5-year cost of lovastatin therapy was $4,654 per patient, and there was a $524 cost offset due to reduced cardiac events and procedures (net cost of drug therapy $4,130). A cost-effectiveness analysis of this trial has not yet been reported.

The National Cholesterol Education Program has identified an LDL cholesterol of less than 100 mg per dL as optimal in patients with evidence of CHD. Although a number of important secondary prevention trials have been published, two of the most useful for assessing economic impact are the 4S and the CARE trial. The 4S randomized 4,444 patients of both sexes aged 35 to 60 years with a history of angina or prior MI and total cholesterol of 210 to 310 mg per dL to adjusted-dose simvastatin or placebo (157). The majority of patients received 20 mg simvastatin, and 37% required 40 mg per day. Over a median of 5.4 years, simvastatin decreased total cholesterol by 25% and LDL cholesterol by 35% and decreased total mortality by 30% (p = .0003) (157). The study also observed a 37% reduction in the need for revascularization in the simvastatin arm (p <.0001). In a subsequent analysis, the 4S investigators reported that simvastatin therapy reduced hospitalizations for acute cardiovascular disease, including revascularization (81% of which were CABG), by 26% (p <.0001). Over the course of the study, total

hospital days due to cardiovascular disease were reduced by 5,138 days in the simvastatin arm (p <.0001). The beneficial effect of simvastatin on hospitalization first became evident after 10 months of therapy and became statistically significant after 22 months. No effect was seen on the use of antianginal or other cardiovascular drugs.

Using U.S.-derived reimbursement rates as cost weights, the 4S investigators estimated that the observed reduction in hospitalizations would equal a $3,872 reduction in average cost per patient treated with simvastatin (162). With a wholesale price for simvastatin over the trial averaging $4,400 per patient ($4,879 undiscounted), the net cost of simvastatin therapy was estimated to be $528 per patient over the trial or $0.28 per day (an offset of 88% of the drug's cost). The cost of repeat laboratory measurement of lipids and transaminases (three to four in the first year, annually after year 1) added a discounted cost of $250 per patient or an additional $0.13 per day. Thus, the total net cost of the simvastatin strategy was estimated at $778 per patient over a mean of 1,915 days of follow-up (approximately $148 per year). As noted earlier, the benefits of simvastatin on follow-up medical care take 10 months to become clinically detectable and appear to increase progressively as treatment is continued.

Three separate cost-effectiveness analyses have been conducted using the data from the 4S trial. One was done from a Swedish perspective (163); two others were conducted from a U.S. perspective. Schwartz (164) estimated a cost per year of life saved of $18,100 with a cost per QALY saved of $15,100, assuming that costs and benefits only occurred for the duration of the trial. Extrapolating to a lifetime perspective yielded a cost per year of life saved of $5,800, with a cost per QALY saved of $6,100. The most recently published analysis used the empiric data from 4S in a Markov model to evaluate cost effectiveness of therapy for different subgroups (165). In this analysis, costs were derived from four hospitals in Sweden that had patient-based cost-accounting systems. Swedish costs were converted to U.S. dollars. The patient's work status, measured every 6 months, was used to estimate productivity costs saved by simvastatin. This analysis estimated that for 59-year-old men, the cost effectiveness of 5 years of simvastatin therapy was $5,400 per year of life saved; the corresponding figure for 59-year-old women was $10,500. Adding in the productivity costs related to time lost from work saved by simvastatin improved the cost-effectiveness ratios to $1,600 for men and $5,100 for women (165). Extensive sensitivity analyses showed that statin therapy was very economically attractive under a wide range of assumptions.

The CARE study evaluated pravastatin versus placebo in 4,159 patients who were 3 to 20 months post-MI and who had a total cholesterol of less than 240 mg per dL and an LDL cholesterol of 115 to 174 mg per dL (156). Like in other statin trials, pravastatin reduced total cholesterol by 20% and LDL cholesterol by 28%. Death and nonfatal MI were reduced by 24%. The mean cost for 6 years of pravastatin therapy in CARE was $5,500, which was partially offset by a $1,660 savings from reduced cardiac events and procedures (166). A cost-effectiveness model using the CARE data estimated that to add a life-year with pravastatin therapy would cost between $16,000 and $31,000.

Cigarette Smoking

Smoking has repeatedly been identified in observational studies as one of the major reversible risk factors for atherosclerotic disease. No randomized trials have tested continued smoking versus complete cessation, but observational data comparing quitters versus continued smokers have suggested that quitting is associated with reductions in mortality due to cardiovascular disease and lung cancer. Using such data, Tsevat (167) estimated that smoking cessation could add 2 to 5 years to a patient's life expectancy.

Office advice to quit smoking in a primary prevention situation is very modestly effective but also very inexpensive, yielding a cost-effectiveness ratio of $2,000 or less per year of life added (168). Use of nicotine replacement therapies as an adjunct to physician advice has been reported to have cost-effectiveness ratios of less than $10,000 per year of life added (169).

Effectiveness of smoking cessation interventions appears to be somewhat higher in the secondary prevention settings, such as after acute MI or CABG, with cessation rates of approximately 50% to 75% (170,171). One randomized trial of a smoking cessation and relapse program in postoperative CABG patients found that validated continuous nonsmoking status was achieved by 44% of intervention and of control patients at 5.5 years (171). Regression analysis identified two independent predictors of maintained nonsmoking status at 5.5 years, fewer than three previous attempts to quit and definite intention to quit.

In a cohort of 173 smokers with a recent MI, Taylor and colleagues (172) tested a nurse-managed intervention begun in the hospital and continued largely by telephone for 4 months. At 1 year, the intervention group had a smoking cessation rate of 71%, compared with 45% in the usual-care group (p = .003). In logistic regression analysis, two factors predicted 1-year smoking status, smoking status 3 weeks after MI and self-efficacy. The former was strongly related to intention to quit. In this study, the intervention program required 3.5 hours per patient on average.

Krumholz and coworkers (170) created a decision model to estimate the cost effectiveness of the Taylor et al. smoking cessation intervention. The estimated direct costs of the program in this model were $100 (3.5 hours of nurse time at $30 per hour). On the benefit side, the model projected an incremental life expectancy of 1.7 years per quitter. For the base case, the program was assumed to create 26 extra quitters per 100 patients enrolled, yielding a cost-effectiveness ratio of $220 per year of life saved. In sensitivity analysis, even if the program only yielded three extra quitters per 1,000 subjects enrolled, the cost-effectiveness ratio was less than $20,000. Thus, many forms of stop-smoking interventions are very economically attractive.

Hypertension

One in four U.S. adults has hypertension (90). Numerous studies have shown that hypertension is a major risk factor for CHD. Randomized trials have clearly shown that effective treatment of hypertension reduces the risk of stroke and CHF (173). However, the evidence for prevention of CHD has been less persuasive. Metaanalysis of large trials evaluating treatment for mild to moderate hypertension demonstrated a 16% reduction in CHD death and a 21% reduction in all-cause death (174,175). An overview of placebo-controlled trials of ACE inhibitor therapy showed a 30% reduction in stroke and 20% reduction in CHD (176). An overview of calcium antagonists showed a 39% reduction in stroke. Comparisons among agents have not yielded clear evidence of major differences in outcomes. However, another overview of nine trials concluded that calcium antagonists were inferior to other major antihypertensives despite providing a similar level of blood pressure control (177).

Weinstein and Stason's (178) classic analysis from the 1970s found that screening to detect and treat hypertension as a primary prevention had cost-effectiveness ratios of less than $50,000 per QALY saved for a broad range of patient subgroups. Treatment of moderate or worse hypertension was substantially more economically attractive than treatment of mild hypertension (179).

Another important determinant of the cost effectiveness of hypertension treatment as primary prevention is the antihypertensive regimen chosen. In the study of Edelson et al. (180), the cost effectiveness of propranolol for monotherapy of mild to moderate hypertension was $10,900; for hydrochlorothiazide, it was $16,400; and for captopril, it was $72,100 per year of life added. The less favorable cost-effectiveness ratio for captopril in this model was due to the higher cost of this agent and to the pooled literature estimates that suggested a smaller effect on diastolic blood pressure than either propranolol or hydrochlorothiazide. Littenberg (181) also found that cost effectiveness was most favorable when the least expensive antihypertensive regimen was chosen. Results of studies comparing different agents are quite dependent on starting assumptions (182).

The extrapolation of the benefits of blood pressure control from asymptomatic persons with mild to moderate hypertension to hypertensive patients with manifest CHD (i.e., secondary prevention) seems logical and is accepted in medical practice but has not been demonstrated empirically in large-scale clinical trials. Similarly, there have not been any cost-effectiveness models created to evaluate hypertension control in CHD patients.

Physical Inactivity and Cardiac Rehabilitation

A wealth of epidemiologic evidence supports the concept that individuals who exercise regularly have less CHD and longer life expectancies than individuals who do not. It is reasonable to suppose, but less well established, that habitually inactive subjects who begin to exercise regularly will live longer and have less CHD than their persistently inactive counterparts. On the other hand, most exercise programs are quite inexpensive, and exercise does have readily measurable benefits on weight, blood pressure, and serum lipid levels. One study has evaluated the cost effectiveness of exercise to prevent CHD (183). In a cohort of 1,000 hypothetical 35-year-old men, regular exercise in the form of jogging 20 miles per week was assumed to reduce the risk of CHD by 50% (based on published epidemiologic data). The direct costs of the program consisted of exercise equipment ($100 per year) and a portion of an annual physician visit. The productivity costs were estimated as $9 per hour for subjects who disliked exercise, $4.50 per hour for neutral subjects, and $0 for subjects who enjoyed exercise. The resulting cost-effectiveness ratios for regular exercise versus no exercise were $1,359 per QALY added when considering only direct costs and $11,313 per QALY added when productivity costs were also included. This analysis presumes that even subjects who do not like exercise continue in the program. Alternatively, if the program is made voluntary, it saves lives and money, even when productivity costs are included.

Almost all the data about the benefits of regular exercise in patients with CHD come from studies of structured cardiac rehabilitation, primarily involving patients who are recovering from an MI. Exercise training has not been definitively shown to reduce deaths or other cardiac events in patients with established CHD. Most of the studies in this area have been too small or had other methodologic limitations. Two metaanalyses of the available randomized trial data have found a 20% to 25%

reduction in death plus nonfatal MI with exercise (184,185). Dennis and colleagues reported favorable effects of cardiac rehabilitation on earlier return to work after MI, and economic analysis suggests that these programs may reduce morbidity costs and productivity costs (due to lost time from work) (186,187). Oldridge and coworkers (188) have estimated that structured cardiac rehabilitation is cost effective in the post-MI population. The major limitations of structured cardiac rehabilitation are its cost and the fact that only a minority of eligible patients choose to participate.

Multiple Risk Factor Interventions

Although in this section we have so far evaluated risk factor modification as isolated activities, in clinical practice patients often require multiple coordinated interventions. The Stanford Coronary Risk Intervention Program randomized 300 patients with angiographically proven CAD to usual care or multifactor risk reduction (189). The risk reduction intervention consisted of individual programs involving diet, exercise, weight loss, smoking cessation, and cholesterol reduction pharmacotherapy. After 4 years, the intervention patients had a 22% reduction in LDL cholesterol, a 4% decrease in body weight, a 20% increase in exercise capacity, and significant improvement in the Framingham CHD risk score (189). Follow-up angiography showed that this intervention program was associated with a statistically significant attenuation in the progression of coronary atherosclerosis. Clinically, there was a drop in the composite end point of death, hospitalization for nonfatal MI, CABG, or PTCA in the intervention group (p = .05). Furthermore, most of the events that occurred in this group took place in the first year of the study, suggesting that the benefits of these interventions may take up to a year to become clinically evident and may increase progressively over time. Using simple projections based on the published data from the Stanford Coronary Risk Intervention Program, Superko (190) projected that the program would cost approximately $1,500 per patient per year (including medication) but that these costs would be partially offset by reduced hospitalizations for cardiac events. He estimated the net cost of the program as $630 per patient per year.

DeBusk and colleagues (191) tested a nurse-based case management model of home-based cardiac rehabilitation (MULTIFIT) in 585 post-MI patients at three Kaiser Permanente hospitals. The special intervention group received assessment, education, risk factor counseling, goal setting, and telephone follow-up by a nurse case manager. At the end of 12 months, the intervention group had an 11% greater improvement in functional capacity, a 32% higher smoking cessation rate, and a 19% reduction in LDL cholesterol (all three differences were statistically significant). During 1 year of the MULTIFIT program, each patient received up to four face-to-face visits, 11 telephone contacts, and four mailings. Nurses spent an average of 9 hours per patient over the year. The per-patient charge for nursing salary, office space, and equipment was approximately $550 (192). This model of post-MI cardiac rehabilitation is clearly more economically efficient than traditional hospital-based or community-based cardiac rehabilitation centers, which may charge $1,800 to $3,000 for a 3-month program. Although formal cost-effectiveness analysis of this program has not been conducted, its lower cost along with its competitive effects on cardiac risk factors (summarized previously) should make it more economically attractive than traditional cardiac rehabilitation programs.

Other Pharmacologic Secondary Preventions

Long-term aspirin therapy is the mainstay of secondary prevention efforts in patients with manifest coronary disease (193). The clinical effectiveness is substantial, and the cost is minimal. Therefore, although aspirin use has not been the subject of a formal economic analysis, this therapy clearly belongs in the “best buy” category of medical intervention. Despite these attractive characteristics, much evidence exists that aspirin is underused in patients with coronary disease (194). Long-term use of beta-blockers after MI was modeled by Goldman and colleagues (195). Based on the earlier (prethrombolytic) beta-blocker trials, they estimated cost-effectiveness ratios of less than $15,000 per life-year added, with ratios less than $5,000 for moderate- or high-risk patients. Their model projected a 6-year course of therapy, with 25% mortality reductions by beta-blockers in years 1 to 3, 7% reduction in years 4 to 6, and gradual attenuation of treatment benefit over a subsequent 9-year period. Based on the data from the Survival and Ventricular Enlargement trial, Tsevat and colleagues (196) developed a decision model to assess the cost effectiveness of captopril therapy in 50-to 80-year-old survivors of acute MI with an ejection fraction of 40% or less. Under the assumption that survival benefits of captopril persisted for more than 4 years, these investigators estimated cost-effectiveness ratios of $10,400 per QALY or less (1991 dollars), depending on age. Analysis of the cost effectiveness of early lisinopril use in acute MI based on GISSI-3 data yielded a cost-effectiveness ratio of $2,300 (U.S.) per 6-week death avoided (197). Assuming that the clinical benefits observed in GISSI-3 were sustained over a 10- to 15-year life expectancy, these data suggest that 6 weeks of ACE inhibitor therapy for all post-MI patients may fall into a “best buy” category of economic attractiveness.

CONTROVERSIES AND PERSONAL PERSPECTIVES

As recently as the early 1990s, medical economics was viewed as a scholarly academic discipline that was largely irrelevant to the practice of medicine. Cost is now one of the dominant issues in almost all medical decisions, although it is the controlling issue in only a minority. Demands by payers that medicine demonstrate its value (benefits produced for dollars spent) have thrust economists into the mainstream of the revolution that is currently reshaping medical practice. However, just as clinicians found themselves woefully unprepared to prove the medical benefits of their decisions, economists were unprepared to provide the pragmatic sorts of data that are now required of them. As was discussed earlier, medical economics is principally concerned with matters related to the efficient societal allocation of scarce resources. Economists have paid little attention to measuring the cost of health care, preferring to discuss the abstract notion of “opportunity cost” while leaving the more pragmatic measurement issues to the accountants. Payers and policy makers, however, are not interested in theories or abstract problems of resource allocation. Instead, they wish to understand the costs of care and how they can be reduced or at least controlled. Clinicians are also not interested in theoretical economic exercises. They want to be able to prove that the care they provide their patients is worth the money it costs. Cost-effectiveness ratios are the economists’ measure of value and have some important strengths. However, the need to frame all cost-effectiveness ratios in terms of dollars required to add an extra QALY (9) often stretches the available clinical and cost data beyond credibility.

THE FUTURE

New approaches are needed in this area to meet the demands for information and for relevant measures of medical value. Three major areas need intensive work over the next few years. The first is to improve methods for costing out medical care accurately but efficiently (i.e., with a relatively low cost of data collection). The second is to develop new measures of value that do not require extrapolation out to a lifetime perspective. These measures would not preclude traditional cost-effectiveness analysis but could be used to supplement it. The third area is education of medical practitioners about medical economics. It is only by getting practitioners to use cost data on a daily basis, asking questions about it and challenging it, that we will get better data and ultimately better value-based medical decision making.

In the final analysis, no economic model can dictate how many resources society should expend on health care and what types of health care should be given priority. These are political and ethical questions that transcend medicine. However, the medical profession must constantly strive to achieve better outcomes at an acceptable cost and to continue the dramatic pace of technological advances set over the last century.

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DESIGN AND CONDUCT OF CLINICAL TRIALS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

As medicine enters the era of evidence-based medicine, the need to understand appropriate quantitative methods is becoming more clear. The hierarchy of clinical evidence, ranging from the randomized clinical trial to the individual case report, provides a variety of approaches that can be used to make inferences about diagnostic and therapeutic strategies. Although a comparative experiment was described in the Bible, randomized clinical trials are a product of the twentieth century; the ability to approach complex medical problems quantitatively has only been possible with the advent of the powerful computing capabilities in the last decade.

When reading or planning a clinical study, the concepts of validity and generalizability provide the broad conceptual framework. Clinical research is only meaningful when it is internally valid and when the results can be applied beyond the population from which they were derived. The results of clinical outcome studies should be expressed in terms of relative differences and absolute differences. Practitioners' perceptions of the appropriate clinical strategy vary considerably when results are depicted in relative and absolute terms, because relative differences can be large with only small absolute differences when the events being treated occur infrequently.

Common principles underlying the behavior of clinical therapeutics include the following: Treatment effects are usually modest, qualitative interactions are common, quantitative interactions are uncommon, unintended biologic effects are more common than previously believed, interactions are unpredictable, and long-term effects frequently differ from short-term effects. Given these principles, it is necessary to separate explanatory trials (designed to elucidate biologic principles) from pragmatic trials (designed to determine which therapeutic approaches should be used in practice). Explanatory trials can often use small sample sizes, complex data collection instruments and detailed protocols, whereas the imperative for large sample sizes in pragmatic trials necessitates simple data collection and trial designs with minimal interference with clinical practice. Although type I statistical errors are commonly accounted for in study design, too often multiple comparison problems and type II errors plague the interpretation of clinical research.

Organizing clinical trials with a recognition of the need for checks and balances involving the sponsor, investigators, management of data, and oversight can lead to more successful and meaningful research.

INTRODUCTION

Medical practice has entered an era of "evidence-based medicine," characterized by an increasing societal belief that clinical practice should be based on a combination of scientific information and expert judgment, rather than relying on intuition, memory, or opinion. As our society has exhausted its tolerance for increasing

the proportion of financial resources spent on medical care, the only rational way to allocate resources is to understand whether competing diagnostic and therapeutic approaches provide clinical benefit and, if so, the cost required to achieve that benefit. Simultaneous with the realization that financial support for medical care has limits, the huge investment in biotechnology is beginning to pay off with many new approaches to treating disease. Similarly, genomics, combinatorial chemistry, proteomics (1), and advanced biomedical engineering are leading to a desirable, but challenging, proliferation of diagnostic and therapeutic opportunities. Thus, the need for evidence is increasing faster than resources are being made available to perform the studies that produce the evidence.

This accelerating pace of quantitative research creates a need for practicing physicians to understand the methods of evaluating clinical evidence well beyond the level they learned in most medical schools. The plethora of new studies and the increasing questioning of medical decision making point to the benefits of practitioners better understanding the critical issues in clinical research design. Because of the high visibility and quantitative nature of cardiology, the priority to develop these skills among cardiologists is paramount.

HISTORY

The first chapter of the Book of Daniel in the Bible describes a comparative experiment in which Daniel urged a servant to experiment with refraining from eating the king's food, and indeed, the healthier diet was associated with the finding that "at the end of ten days their countenances appeared fairer and they were fatter in flesh, than all the youths that did eat of the king's food." The modern human clinical trial, however, was not pioneered until 1747, when Lind tried six different treatments for scurvy in 12 sailors (2); despite the small sample size, the virtues of oranges and lemons became evident. Partly because of an inadequate sample size, however, Lind failed to recognize the primary beneficial effect of oranges and lemons, considering "pure dry air" to be the most beneficial intervention.

P. C. A. Louis (3) has been credited with developing the concept of comparative observational studies in the nineteenth century, which he delineated in a treatise entitled "La Méthode Numérique" (4). In casting doubt on the common practice of bloodletting, he clearly identified the concept of confounding and emphasized the need to have comparable groups when making comparisons. In the 1840s, Semmelweis (5) noted that maternal mortality was higher in women giving birth in hospitals in which deliveries were attended by physicians than in hospitals in which deliveries were attended by midwives. He showed that the excess mortality was related to contamination from autopsies, and he succeeded in separating autopsy teaching from attending childbirth by physicians, with a resultant decrease in maternal mortality.

The first randomization was performed by Fisher and Mackensie in 1926 in an agricultural study (6). In developing analysis of variance, they recognized that experimental observations must be independent and not confounded to allow full acceptance of the statistical methodology. They therefore randomized different plots to different approaches to the application of fertilizer. Amberson has been credited with the first randomization of patients, using a coin toss to make treatment assignments in a 1931 trial of tuberculosis therapy in 24 patients (2). The British Medical Research Council trial of streptomycin in the treatment of tuberculosis marked the modern era of clinical trials in 1948 (7). This trial established the principles of randomization for large numbers of patients and set guidelines for administering the experimental therapy and objectively evaluating outcomes.

Modern outcomes research was presaged by important observations from Florence Nightingale, who observed a higher mortality in hospitals than out of hospitals in the treatment of amputation. Her notes provide a detailed accounting of observational study methodology in the adjustment for differences in outcome as a function of baseline characteristics.

In 1914, Codman (8) wrote a treatise about measurement of outcomes that provides a classic discussion of the need for hospitals to evaluate outcomes. He proposed that reimbursement be based on demonstration of results. However, his message was not popular, and his hospital went bankrupt.

In the last decade, computers have enabled rapid accumulation of data in thousands of patients in studies conducted throughout the world. Peto, Yusuf, Sleight, and Collins developed the concept of the large, simple trial in ISIS-1 (9), beginning with the concept that only by randomizing 10,000 patients could the beneficial effects of beta-blockers be understood. The development of client–server architecture provided a mechanism for aggregating large numbers of data and distributing them quickly to multiple users. Finally, advances in the development of the World Wide Web provide an opportunity to share information instantaneously in multiple locations around the world, and the personal digital assistant provides new opportunities for point-of-care data acquisition and retrieval. Innovative approaches to using the Internet are creating communities of practitioners interested in contributing to a body of knowledge about the diagnosis and treatment of patient groups.

PHASES OF EVALUATION OF THERAPIES

Evaluating therapies and interpreting the results as they are presented require an understanding of the goals of the investigation; these goals can be conveniently categorized in a similar manner to the nomenclature used by the U.S. Food and Drug Administration (FDA) (10) to characterize the phase of investigation in clinical trials (*e*Table 43.0.1). Conclusions drawn from a small pilot study of a therapy never before given to humans should be quite different from conclusions drawn from a study measuring clinical outcomes of two therapies used in current practice; thus, regulatory authorities have developed a nomenclature for discussing these phases of investigation.

***e*TABLE 43.0.1** PHASES OF EVALUATION OF NEW THERAPIES

Phase	Features	Purpose
I	First administration of a new therapy to patients	Exploratory clinical research to determine if further investigation is appropriate
II	Early trials of new therapy in patients	To acquire information on dose-response relationship, estimate incidence of adverse reactions, and provide additional insight into pathophysiology of disease and potential impact of new therapy
III	Large-scale comparative trial of new therapy versus standard of practice	Definitive evaluation of new therapy to determine if it should replace current standard of practice; randomized controlled trials required by regulatory agencies for registration of new therapeutic modalities
IV	Monitoring of use of therapy in clinical practice	Postmarketing surveillance to gather additional information on effect of new therapy on treatment of disease, rate of use of new therapy, and more robust estimate of incidence of adverse reactions established from registries

Adapted from Antman EM, Califf RM. Clinical trials and meta-analysis. In: Smith TW, ed. *Cardiovascular therapeutics*. Philadelphia: WB Saunders, 1996:679.

When a new therapy is devised, it must first be studied in normal, healthy volunteers to ensure that no unexpected side effects occur. This type of study is commonly referred to as *phase I*. In some cases, when concern exists that the therapy may be highly toxic, patients in an advanced stage of the disease (with little to lose and much to gain if the treatment was successful) are evaluated instead. Many novel therapies affecting the coagulation system in which the risk of bleeding would not be acceptable for a normal volunteer fall into this category. The most extreme example of this approach was the use of recently deceased subjects (neomorts) in the initial studies of glycoprotein IIb/IIIa inhibitors (11). Although phase I trials may generate substantial enthusiasm, they should not be used to make recommendations for routine clinical practice.

After the new therapy demonstrates some physiologic effect in phase I, it must, in phase II, demonstrate both desired physiologic activity and evidence of clinical benefit in the clinically relevant disease, at least from the perspective of "surrogate" pathophysiologic end points. Because most measures do not reach the established criteria for a surrogate (12), the term *biomarker* is preferred. For example, in a phase II trial, a heart failure therapy would need to demonstrate improvement in cardiac output, left ventricular function, or neurohormonal status. Often investigators are tempted to use these biomarker end points to recommend major changes in practice, but multiple experiences have demonstrated the danger of this approach to recommending changes in clinical practice. Often, even if the biomarkers appear to be improved, large enough trials may show that clinical outcomes are adversely affected. One of the major unresolved conceptual issues in modern cardiovascular research is how to use phase II data to make wise choices about proceeding to the next phase.

The third phase, commonly referred to as the *pivotal phase*, evaluates the therapy in the relevant clinical context, with the goal of determining whether the therapy should be used in clinical practice. For phase III, the relevant end points include measures that can be recognized by patients as important: survival time, major clinical events, quality of life, and cost. A well-designed clinical trial with a positive effect on clinical outcomes justifies serious consideration for a change in clinical practice and certainly provides grounds for regulatory approval for sales and marketing. Although this categorization into phases I, II, and III is convenient in concept, in reality, it may be best to blend the research phases in order to move quickly and efficiently through the development process (13). By law in the United States, regulatory approval is based on evidence that use of the medical product is safe and effective compared with no treatment. Because effective treatments exist for many diseases today, this standard frequently leaves a medical product in an uncertain category relative to other available therapies at the end of phase III. To generate this needed information, directly comparative trials need to be done.

After a therapy is in use and approved by regulatory authorities, phase IV begins. Traditionally, phase IV has had the responsibility of developing more effective protocols for the use of therapies in clinical practice based on inferences gained from monitoring observations and reporting adverse events. The importance of this phase has evolved from recognizing that randomized trials completed by the time of regulatory approval often will not have encountered many circumstances experienced in clinical practice. Examples of phase IV studies include the evaluation of new dosing regimens, as in several ongoing comparisons of low-dose versus

high-dose angiotensin-converting enzyme inhibition in patients with heart failure, and prospective registries of therapeutic usage, such as the National Registry of Myocardial Infarction (14).

With an increasing array of effective therapies, phase IV has been viewed as a time to compare one effective marketed therapy against another. In some cases, this need arises because of changing doses or expanding indications for a therapy, whereas in other cases, the phase III trials did not provide the relevant comparisons for a particular therapeutic choice. Global Utilization of Streptokinase and rt-PA for Occluded Coronary Arteries I (GUSTO-I) was an example of a phase III trial in which a new (accelerated) dosing regimen of alteplase was compared with a standard dose of streptokinase (15). The GUSTO-III trial was an example of a phase IV study initiated because reteplase was approved by regulatory authorities based on a comparison with streptokinase, but it was not compared with accelerated alteplase; thus, GUSTO-III performed that comparison because accelerated alteplase was the reference standard for practice in the United States (16).

A rash of product recalls have focused national attention on phase IV trials. Cisapride was recalled because it caused sudden death due to QT prolongation (17); mibefradil had multiple drug interactions that were known but much more severe than expected (18); and a prosthetic aortic valve was recalled when a comparative trial showed a higher rate of valve leak than expected (19). More direct comparative trials will be done and a more comprehensive system of postmarketing surveillance will be developed to deal with these issues (19,20).

CRITICAL GENERAL CONCEPTS

With rare exceptions, the purpose of a phase III or IV clinical trial or outcome study is to estimate what is likely to happen to the next patient given one treatment or the other. To assess the degree to which the proposed study enhances the ability to understand what will happen to the next patient, the investigator must be aware of an array of methodologic and clinical issues. Although this task requires substantial expertise and experience, the issues can be considered in a broad framework. The broadest but most essential concepts to understanding the relevance of a clinical study to practice are the concepts of validity and generalizability. *e*Table 43.0.2 illustrates an approach to these issues, developed by the McMaster group, to be used when reading the literature (21).

***e*TABLE 43.0.2** QUESTIONS TO ASK WHEN READING AND INTERPRETING THE RESULTS OF A CLINICAL TRIAL
Are the results of the study valid?
Primary guides
Was the assignment of patients to treatment randomized?
Were all patients who entered the study properly accounted for at its conclusion?
Was follow-up complete?
Were patients analyzed in the groups to which they were randomized?
Secondary guides
Were patients, their clinicians, and study personnel blinded to treatment?
Were the groups similar at the start of the trial?
Aside from the experimental intervention, were the groups treated equally?
What were the results?
How large was the treatment effect?
How precise was the treatment effect (confidence intervals)?
Will the results help me in caring for my patients?
Does my patient fulfill the enrollment criteria for the trial? If not, how close is the patient to the enrollment criteria?
Does my patient fit the features of a subgroup in the trial report? If so, are the results of the subgroup analysis in the trial valid?
Were all the clinically important outcomes considered?
Are the likely treatment benefits worth the potential harm and costs?

Validity

The most fundamental question about a clinical trial is whether the result is valid. Are the results of the trial internally consistent? Would the same result be obtained if the trial was repeated? Was the trial design adequate, including blinding, endpoint assessment, and statistical analyses? Of course, the most compelling evidence of validity in science is replication. If the results of a trial or study remain the same when the study is repeated, especially in a different clinical environment by different investigators, the results are likely to be valid.

The Evaluation of Losartan in the Elderly Study and Prospective Randomized Amlodipine Survival Evaluation trials provide excellent examples of the quest for validity. In both cases, an initial trial (22,23) showed a surprising apparent effect of a treatment on mortality; in both cases, follow-up trials—essentially attempting to replicate the surprise finding—showed no such benefit. With similar patient populations and identical drug-dosing regimens used, these findings exemplify the need to have a second trial for cross-validation (24,25).

Generalizability

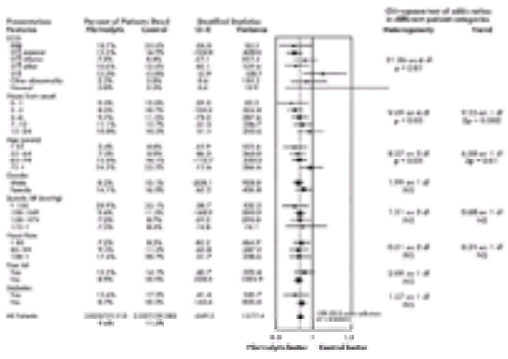
Given a valid clinical trial result, it is equally important to determine whether the findings are generalizable. Unless the findings can be replicated and applied in multiple practice settings, little has been gained by the trial. Because it is impossible to replicate every clinical study in practice, it is especially important to understand the inclusion and exclusion criteria for patients entered into the study and to have an explicit understanding of additional therapies that the patients received. For example, studies done in “ideal” patients without comorbid conditions or young patients without severe illness can be misleading when the results are applied to clinical practice. Failure to perform generalizable trials before marketing approval led to a surprising rate of serious drug interactions with the calcium channel blocker mibefradil (18), leading to its withdrawal from the market.

EXPRESSING CLINICAL TRIAL RESULTS

The manner in which the results of clinical research are reported can profoundly influence the perception of practitioners using the information to decide which therapies to use. A clinical trial produces a different degree of enthusiasm about the tested therapy when the results are presented in the most favorable light, even when the exact results are provided in addition to the risk reduction so that the practitioner can reconstruct the results in different ways (26). Multiple studies (27,28) have demonstrated that physicians are much more likely to recommend a therapy when the results are presented as a relative risk reduction rather than as an absolute difference in outcomes.

An example of a trial that has evoked considerable interest based on a predominant depiction of relative treatment effect is the Scandinavian Simvastatin Survival Study trial comparing simvastatin with placebo in patients with elevated low-density lipoprotein cholesterol and a history of ischemic heart disease (29). The results have usually been depicted as a 30% reduction in overall mortality and a 42% reduction in coronary mortality. Rarely have the results been presented in terms of absolute differences (approximately 0.6% reduction in mortality per year). This difference was highly significant because over 4,000 patients were randomized; the cost-effectiveness data support use of simvastatin in this situation (30). In contrast, the Bypass Angioplasty Revascularization Investigation found almost exactly the same difference between coronary artery bypass grafting and percutaneous revascularization, but with just over 1,800 patients randomized, this difference was not statistically significant, and the conclusion was reached that no major differences in outcome exist between the two technologies in patients with coronary anatomy suitable for either procedure (31). If the same result had been achieved in 4,000 patients, would the same conclusion have been drawn as for simvastatin?

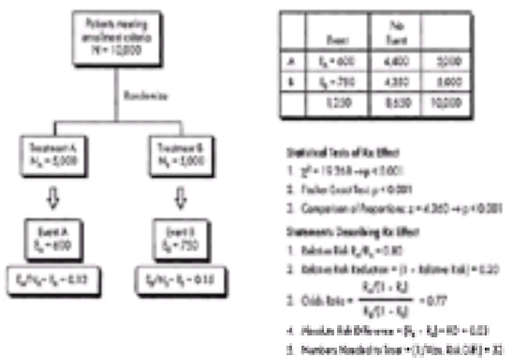
The results of pragmatic clinical trials are most appropriately expressed in terms of the number of poor outcomes prevented by the more effective treatment per 100 or 1,000 patients treated. This measure, representing the absolute benefit of therapy, the number needed to treat, translates the results for specific populations studied into public health terms by quantifying how many patients would need to be treated to create a specific health benefit. The absolute difference can be used to assess quantitative interactions (i.e., significant differences in the number of patients needed to treat to achieve a degree of benefit with a therapy as a function of the type of patient treated). An example is the use of thrombolytic therapy; the Fibrinolytic Therapy Trialists’ collaboration demonstrated that 37 lives per 1,000 patients treated are saved when thrombolytic therapy is used in patients with anterior ST-segment elevation, whereas only 8 lives per 1,000 are saved when patients with inferior ST-segment elevation are treated (*e*Fig. 43.0.1) (32). The direction of the treatment effect is the same, but the magnitude of the effect is different.



***e*FIGURE 43.0.1** Proportional effects of fibrinolytic therapy on mortality. BBB, bundle branch block; BP, blood pressure; df, degrees of freedom; ECG, electrocardiography; MI, myocardial infarction; NS, not significant; O-E, observed – expected; SD, standard deviation.

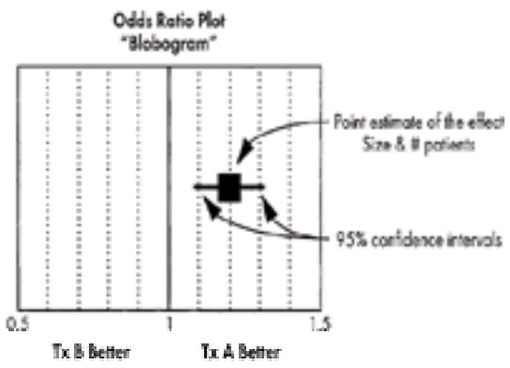
This approach becomes more complex with end points that are not discrete, such as exercise time. One approach to expressing trial results when the end point is a continuous measurement is to define the minimal clinically important difference (the smallest difference that would lead practitioners to change their practices) and to express the results in terms of the number needed to treat to achieve that difference.

The relative benefit of therapy, on the other hand, is the best measure of the treatment effect in biologic terms. This concept is defined as the proportional reduction in risk resulting from the more effective treatment and is generally expressed in terms of an odds ratio or relative risk reduction. The relative treatment effect can be used to assess qualitative interactions, which represent statistically significant differences in the direction of the treatment effect as a function of the type of patient treated. In the Fibrinolytic Therapy Trialists' analysis, the treatment effect in patients without ST-segment elevation is heterogeneous compared with patients with ST-segment elevation (32). *e*Figure 43.0.2 gives the calculations for commonly used measures of treatment effect.



***e*FIGURE 43.0.2** Summary measures of treatment effect. Rx, therapy.

A particularly useful display of data is the odds ratio plot, as shown in *e*Figure 43.0.3. Both absolute and relative differences in outcome should be expressed in terms of point estimates and confidence intervals. This type of display gives the reader a balanced perspective, since both the relative and absolute differences are important, as well as the confidence in the estimate. Without the confidence intervals, the reader has difficulty knowing the precision of the estimate of the treatment effect.



***e*FIGURE 43.0.3** Odds ratio plot. Tx, treatment.

CONCEPTS UNDERLYING TRIAL DESIGN

As experience with multiple clinical trials is accumulating, some general concepts seem worth emphasizing. These generalities do not always pertain, but they serve as useful guides to the design or interpretation of trials.

Treatment Effects Are Modest

The most common mistake in designing clinical trials is overestimation of the expected treatment effect. Most individuals heavily involved in therapeutic development cannot resist the assumption that the pathway being targeted is the most important contributor to patient outcome. Unfortunately, relative reductions in adverse clinical outcomes exceeding 25% are extremely uncommon.

When treatments affecting outcome in acute myocardial infarction (MI) have been assessed, small trials have typically greatly overestimated the effect observed in subsequent larger trials. The reasons for this observation are not entirely clear. One important factor is negative publication bias. Of the many small studies done, the positive ones tend to be published and the negative ones do not (33). A second factor could be analogous to regression to the mean in observational studies: When a variety of small trials are done, only those with a substantial treatment effect are likely to be continued into larger trials. Of course, in most cases, the small trials have so much uncertainty in the estimate of the treatment effect that the true effect of many of the promising therapies is overestimated, whereas the effect of some of the therapies showing little promise based on point estimates from small studies is underestimated. Thus, when larger studies are completed, giving a more reliable estimate of treatment effect, the estimate of benefit tends to regress toward average.

Qualitative Interactions Are Uncommon

A reversal of treatment effect as a function of baseline characteristics is unusual. Many training programs have taught clinicians that many therapies are effective only in select subsets of the population, yet there are few examples demonstrating such a targeted effect. One exception in cardiovascular trials is the probable harm of thrombolytic therapy for patients without ST-segment elevation, although this finding lacks adequate statistical power, and the Late Assessment of Thrombolytic Efficacy trial found thrombolytic therapy to be beneficial in these patients (34). One issue that is underappreciated is the sample size required to prove that such a qualitative interaction actually exists: Given a treatment with an overall 20% reduction in event rates, to detect a subpopulation with a treatment effect of 40% compared with no treatment effect in another subset requires sample sizes more than twice as large as the sample required for the primary comparison.

Quantitative Interactions Are Common

When therapies are beneficial for specific patients with a given diagnosis, they are generally beneficial to most patients with that diagnosis. However, therapies commonly provide a differential absolute benefit as a function of the severity of the patient's illness. Given the same relative treatment effect, the number of lives saved or events prevented will be greater when the therapy is applied to patients with a greater underlying risk. Examples of this concept include the greater benefit of angiotensin-converting enzyme inhibitors in patients with markedly diminished left ventricular function (35), the larger benefit of thrombolytic therapy in patients with anterior infarction, and the greater benefit of bypass surgery in older patients compared with younger patients.

Unintended Targets Are Common

Therapies are appropriately developed by finding a pathophysiologic pathway or target that can be altered and by exploiting that concept using a model that does not involve the intact human. Despite all good intentions, proposed therapies frequently either work via a different mechanism than the one for which the therapy was devised, or they affect an entirely different system. Examples include thrombolytic therapy for MI, which was developed using coronary thrombosis models; unfortunately, this therapy also affects the intracranial vessels. Inotropic therapies for heart failure were developed using measures of cardiac function, but many of these agents, which clearly improve cardiac function acutely, also cause an increase in mortality, perhaps because of a detrimental effect on the neurohormonal system. Most recently, the orally administered glycoprotein IIb/IIIa inhibitors were developed with the concept that blocking platelet aggregation would prevent thrombotic events; surprisingly, excess mortality was observed in a series of trials evaluating this therapy (36). Only after the trials of oral IIb/IIIa inhibitors were completed did new data from cell culture and receptor biology studies demonstrate paradoxical activation of platelets and apoptosis of cardiac myocytes (37,38).

Interactions Are Not Predictable

Clinical trials tend to evaluate only one treatment at a time, yet most cardiovascular diseases are treated with a complex combination of therapies. The typical patient with coronary heart disease or heart failure is now taking more than four different medications at the same time. Unfortunately, predicting whether a combination of therapies would be synergistic, additive, neutral, or negative has proven to be treacherous. In the development of abciximab, the initial trial showed a substantial reduction in ischemic events but an excess of bleeding (39). When the amount of heparin was reduced in subsequent trials, there was concern that the benefit would be lost as the bleeding diminished. The lower doses of heparin indeed produced less bleeding, but surprisingly, the efficacy at preventing ischemic events increased. In retrospect, the added efficacy with less bleeding was a fortuitous and unpredictable finding.

Long-Term Effects Cannot Be Assumed from Short-Term Results

Many cardiovascular therapies produce an early hazard followed by a later benefit. Bypass surgery initially increases the risk of death, and in clinical trials, the survival curves have not crossed for a year. Fibrinolytic therapy produces an excess hazard in the first day. Hormone replacement therapy causes an excess risk of thrombotic events in the first year, and then the curves appear to come together (40). Perhaps no example has generated as much public awareness as the diet combination fenfluramine (fen-phen), which in short-term studies generated weight loss with little apparent toxicity, but in longer-term studies caused both pulmonary hypertension and valvular regurgitation (41,42).

GENERAL DESIGN CONSIDERATIONS

When reading the results of a clinical study or designing a study, the purpose of the investigation is critical to placing the outcome in context. Those who design the investigation have the responsibility of constructing the project and presenting the results in a manner that reflects the intent of the study. In a small phase II study, an improvement in a surrogate pathophysiologic outcome is exciting and could easily lead the investigator to overstate the clinical implications of the finding. Similarly, megatrials with little data collection seldom give useful information about disease mechanisms unless carefully planned substudies are performed. The structural characteristics of trials can be characterized as a function of the following attributes.

Pragmatic versus Explanatory

Most clinical trials are designed to demonstrate a physiologic principle as part of a chain of causality of a particular disease. Such trials, termed *explanatory trials*, need only be large enough to prove or disprove the hypothesis being tested. Major problems have arisen because of the tendency of those doing explanatory trials to generalize the findings into recommendations about clinical therapeutics.

Trials designed to answer questions about which therapies should be used are called *pragmatic trials*. These trials should have clinical outcomes as the primary end point, so that when the trial is complete, the result will inform the practitioner and the public whether using the therapy in the manner tested will result in better clinical outcomes than alternative approaches. These trials generally require much larger sample sizes and a more heterogeneous population.

The decision about whether to perform an explanatory trial or a pragmatic trial has major implications for the design of the study. When the study is published, the reader must also take into account the intent of the investigators, because the implications for practice or knowledge will vary considerably depending on the type of study.

Entry Criteria

In an explanatory trial, the entry criteria should be carefully controlled so that the measurements of interest will not be confounded. For example, a trial designed to determine whether a treatment for heart failure improves cardiac output should study patients who are stable enough for elective hemodynamic monitoring. In contrast, in a pragmatic trial, the general goal is to include patients representative of the population seen in clinical practice, and who the organizers of the study believe can make a plausible case for benefit in outcome. From this perspective, the number of entry and exclusion criteria should be minimized, because the rate of enrollment will be inversely proportional to the number of criteria.

Data Collection Form

The data collection form provides the information on which the results of the trial are built; if an item is not included on the data collection form, it will obviously not be available at the end of the trial. On the other hand, the likelihood of collecting accurate information is inversely proportional to the numbers of data collected. In an explanatory trial, patient enrollment is generally not an issue because small sample sizes are needed. In a pragmatic trial, however, there is almost always an imperative to enroll patients as quickly as possible. Thus, a fundamental concept in pragmatic trials is to keep the data collection form as brief as possible.

The ultimate example of this concept is the ISIS approach of collecting only the front of a single page in a clinical trial (9). This approach has allowed the enrollment of tens of thousands of patients in mortality trials with no reimbursement to the health care providers enrolling patients. Regardless of the ultimate length of the data collection instrument, it is critical to include only information that will be useful in analyzing the trial outcome or understanding why the result occurred.

Ancillary Therapy

Decisions about the use of nonstudy therapies in a clinical trial are critical to its validity and generalizability. Including therapies that will interact in a negative way with the experimental agent could ruin the chance to detect a clinically important treatment advance. Especially in a physiologic experiment, interfering with the primary question by including another therapy would be a serious problem.

Alternatively, in a pragmatic trial, the goal is to evaluate the therapy in the context in which it will be used. Because clinical practice is not managed by a prespecified algorithm, evaluation of the experimental therapy in the context of such an approach is likely to give an unrealistic approximation of the likely effect of the therapy in clinical practice.

Multiple Randomizations

Until relatively recently, enrolling a patient in multiple simultaneous clinical trials was considered to be ethically questionable. The origin of this ethical concern is unclear, but it seems to have arisen from a general impression that clinical research encroaches on clinical practice; thus, more clinical research would be detrimental. More recently, the concept has been proposed that when the best treatment is not known, randomization is desirable (the uncertainty principle). Stimulated by the apparent need to develop multiple therapies simultaneously in the treatment of acquired immunodeficiency syndrome, the concept of multiple randomizations has been

reconsidered.

Factorial trial designs represent a specific approach to multiple randomizations with advantages from the statistical and the clinical perspectives. Because most patients are now treated with multiple therapies, the factorial design represents a clear method to determine whether therapies add to each other, work synergistically, or nullify the effects of one or both therapies being tested. As long as a significant interaction does not exist between the two therapies being tested, both can be tested in a factorial design with a sample size close to the size needed to test one therapy.

LEGAL AND ETHICAL ISSUES

Multiple considerations pertain to the question of whether a clinical trial should be done and how the results of the trial should be disseminated. Perhaps too little thought is given to critical ethical issues before trials are done. Three general principles should be considered when clinical investigation is considered (43). *Respect for persons* embodies the concept that the investigator recognizes that patients are not simply sources of data; they are individuals deserving of the opportunity to provide informed consent, and they should be considered as collaborators in the investigation. *Beneficence* refers to the concept that the research will be done to improve the state of knowledge and that the risks assumed by the subjects in the study are not out of proportion to the potential benefits. This concept has particular relevance to failure to publish negative clinical trials; when a patient has consented to participate in an experiment, failure to use the information gained to advance the state of knowledge raises a concern. *Justice* refers to the concept that the benefits, risks, and inconvenience should be distributed fairly; because volunteering for a study implies a risk is taken to benefit others, efforts must be made to avoid subjecting some groups to risk so as to benefit other groups.

Medical Justification

Each of the proposed treatments in the trial must be within the realm of currently acceptable medical practice for the specific medical condition of the patient. Difficulties with consideration of medical justification typically arise in two areas: Studies are generally initiated because there is a reason to believe that one therapeutic approach is better than another, and many currently accepted therapies have never been subjected to the type of scrutiny being applied to new therapies. These factors create a dilemma for the practitioner, who may be uncomfortable with protocols asking for a change in standard practice. An approach to this dilemma, called the *uncertainty principle*, has been proposed. In this scheme, clinicians should be comfortable offering entry into a study at any time they are substantially uncertain about whether one of the treatments is better than the other. The patient, of course, is given the opportunity to review the situation and make a decision, but for most patients the physician's recommendation will be a critical factor in deciding whether to participate in a study.

An interesting twist on this theme occurs when a treatment has been shown to be effective but is not used as a routine part of practice because of cost. The ESPRIT trial proposed to evaluate a new dosing regimen of eptifibatide compared with placebo in patients undergoing percutaneous coronary intervention (44). Although abciximab had been shown to reduce serious events in this setting, the majority of patients in the United States were not being treated with it because of the cost. The FDA initially rejected the protocol on ethical grounds, but after considerable discussion, a controversial decision was made to proceed in centers not currently using abciximab routinely (45). Clinical equipoise based on assessment of cost effectiveness will increasingly become a critical issue.

Groups of Patients versus Individuals

The ethical balance typically depends on the good of large numbers of patients versus the good of individuals involved in the trial. Examples are accumulating in which a therapy appeared to be better based on preliminary results or small studies, and then was shown to be inferior based on adequately sized studies. These experiences have led some authorities to argue that clinical practice should not change until a highly statistically significant difference in outcome is demonstrated (46). Indeed, the standard for acceptance of a drug for labeling by the cardiorenal group at the FDA is two adequate and well-controlled trials, each independently reaching statistical significance. If the alpha for each trial is 0.05, an alpha value of 0.0025 (0.05×0.05) would be needed for both to be positive. The counterargument is that the physician advising the individual patient should let the patient know which treatment is most likely to lead to the best outcome. In fact, Bayesian calculations could be used to provide running estimates of the likelihood that one treatment is better than the other.

Informed Consent

The U.S. Department of Health and Human Services and the International Guidelines for Biomedical Research Involving Human Subjects provide standards for the process of informed consent. Elements common to informed consent have been defined and should pertain regardless of the exact nature of the investigation. The research project, including the names of the investigators, should be described to the patients. The procedures that will be involved, including follow-up information, should be described in enough detail that patients can envision what participation will entail. The potential risks and benefits of participation should be described, including a description of alternatives to participation in the study. Patients should be reassured that participation in the study is voluntary and that their confidentiality will be protected. Finally, they should be given the chance to ask questions.

An area of increasing confusion is the distinction between clinical investigation and measures undertaken to improve the quality of care as an administrative matter. The argument has been made that the former requires individual patient informed consent, whereas the latter falls under the purview of the process of medical care and does not require individual consent.

Several special situations must be considered in cardiovascular studies. In a cardiac emergency, there is often insufficient time to explain the research project in exact detail and obtain informed consent. When therapies for treatment of acute MI are compared, the time to administration of therapy is a critical determinant of outcome, and time spent considering participation in a protocol could increase the risk of death. Accordingly, an abbreviated consent to participate followed by a more detailed explanation later in the hospitalization has been sanctioned. An even more complex situation occurs in research concerning treatment of cardiac arrest. Clinical investigation in this field almost came to a halt because of the impossibility of obtaining informed consent. After considerable national debate, such research is now being done only after careful consideration by the community of providers and citizens about the potential merits of the proposed research.

Blinding

Blinding is essential in most explanatory trials, because the opportunity for bias is so substantial. In most pragmatic trials, blinding is also greatly preferred to reduce bias in the assessment of outcome. *Single-blinding* refers to blinding of the patient, but not the investigator, to the therapy being given. *Double-blinding* refers to blinding of both the patient and the investigator, whereas *triple-blinding* refers to a double-blinded study in which the committee monitoring the trial is also blinded to which group is receiving which treatment. Despite the rarity of deceit in clinical research, examples of incorrect results caused by bias in trials without blinding (47) and in trials with single-blinding reinforce the value of blinding (48).

When blinding would prevent a true test of a treatment strategy, other methods must be used to ensure objectivity. The clearest example is a trial of surgical versus medical therapy; in this situation, neither the patient nor the primary physician can be blinded. A similar situation exists when one therapy is given in a markedly different manner than another. In some cases a *double-dummy* technique (in which the comparative therapies each have a placebo) can be used, but often this approach leads to too much complexity. An example of the futility of blinding in some cases arose in the GUSTO-III trial, which evaluated emergency administration of thrombolytic therapies (16). The potential advantage of reteplase over alteplase depended on its administration as a bolus with no time delays, and administering a double-dummy therapy rapidly in an emergency situation proved to be an unreasonable expectation.

Given the large number of effective therapies in cardiovascular disease, an increasing problem will be the lack of availability of placebo. It is both complex and expensive to manufacture a placebo that cannot be distinguished from the active therapy and could not affect outcome. Often when a new therapy is compared with an old therapy, or two available therapies are compared, the manufacturer of the established therapy often will not cooperate because it has nothing to gain by participating in a comparative trial with a new therapy. Because a placebo needs to mimic the active therapy enough that the blind cannot be broken, the success of a placebo-controlled trial depends on the cooperation and participation of the manufacturers of both therapies.

Endpoint Adjudication

Most important end points in cardiovascular trials (other than death) require a judgment. When the study is blinded, the decision about whether an end point occurred usually does not require an independent review. However, in trials without treatment blinding, unbiased assessment of end points is essential. This point has been made vividly in trials of cardiovascular devices. In the initial CAVEAT trial comparing directional coronary atherectomy with balloon angioplasty, the majority of MIs during the follow-up period were not noted on the case report form, despite electrocardiographic and enzymatic evidence of these events (49). Even in a blinded trial, the end points of MI, recurrent ischemia, and new or recurrent heart failure are subjectively enough recorded that an independent judgment is thought to be helpful in most cases (50).

INTENSITY OF INTERVENTION

When a therapeutic intervention is tested, one must always consider whether its intensity is appropriate. This issue is quite obvious in the dosing of drugs. In three trials of direct thrombin inhibitors, a twofold error in the dosing of hirudin resulted in a significant increase in the risk of intracranial hemorrhage (51,52 and 53). Perhaps even more important, when the target range for the activated partial thromboplastin time (aPTT) was modestly increased for heparin therapy, the actual observed aPTT increased by only 8 seconds, but the intracranial hemorrhage rate increased to an unacceptable range. Correction of the dosages of hirudin and heparin brought clinical outcomes for both agents within the acceptable range (54,55).

This same issue also exists in behavioral or policy interventions. A trial using prognostic and normative information to assist in end-of-life decision making failed to change behavior, perhaps because the strength of the intervention was not adequate to truly affect the practitioners (56). The major strategic question is how to design appropriate explanatory studies to define the most likely effective strength of the intervention before embarking on a large pragmatic trial.

Surrogate End Points (Biomarkers)

In cardiovascular disease, because of the ready availability of biologic measurements reflecting disease severity or progression, small studies have used pathophysiologic constructs to determine the strength of the intervention for definitive evaluation. Unfortunately, this approach has led to a number of therapeutic misadventures (*e*Table 43.0.3). Antiarrhythmic drugs were developed based on their ability to reduce ventricular arrhythmias recorded on ambulatory monitoring. When the Cardiac Arrhythmia Suppression Trial was terminated prematurely because of a higher mortality with therapies that had been shown to reduce ventricular arrhythmias on monitoring, it became clear that ambulatory monitoring was an inappropriate surrogate marker (57). Similarly, studies developing dosing for therapies for heart failure have used improvement in cardiac output as a surrogate marker. A succession of inotropic (milrinone, ibopamine) and vasodilator (flosequinan, prostacyclin) compounds has been shown to improve hemodynamics in the short term, but the results of chronic therapeutic trials have been disastrous (58). Concern has been raised about blood pressure–lowering drugs; two compounds (diuretics and alpha-adrenergic blockers) that were almost equally effective in lowering the blood pressure had very different effects on mortality and other major clinical outcomes (59).

***e*TABLE 43.0.3** SPECULATION ON REASONS FOR FAILURE OF SURROGATE END POINTS

	End points		**Reason for failure**[a]			
Disease and intervention	**Surrogate**	**Clinical**	**A**	**B**	**C**	**D**
Cardiologic disorder						
Arrhythmia						
Encainide; flecainide	Ventricular arrhythmias	Survival		+		++
Quinidine; lidocaine	Atrial fibrillation	Survival		+		++
Congestive heart failure						
Milrinone; flosequinan	Cardiac output; ejection fraction	Survival		+		++
Elevated lipid levels						
Fibrates; hormones; diet; lovastatin	Cholesterol levels	Survival		+		++
Elevated blood pressure						
Calcium channel blockers	Blood pressure	Myocardial infarction; survival		+		++
Cancer						
Prevention						
Finasteride	Prostate biopsy	Symptoms; survival	++[b]			
Advanced disease						
Fluorouracil plus leucovorin	Tumor shrinkage	Survival		+		++
Other diseases						
HIV infection or AIDS						
Antiretroviral agents	CD4 levels; viral load	AIDS events; survival		+	+	+
Osteoporosis						
Sodium fluoride	Bone mineral density	Bone fractures	+			+
Chronic granulomatous disease						
Interferon-a	Bacterial killing; superoxide production	Serious infection				++

+, likely or plausible; ++, very likely; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

[a]A, surrogate end point not in causal pathway of the disease process; B, of several causal pathways of the disease, the intervention only affects the pathway mediated through the surrogate; C, the surrogate is not in the pathway of the intervention's effect or is insensitive to its effect; D, the intervention has mechanisms of action that are independent of the disease process.

[b]In settings in which only latent disease is prevented.

Adapted from Fleming TR, DeMets DL. Surrogate endpoints in clinical trials: are we being misled? *Ann Intern Med* 1996;125:607.

Because of these lessons, it is no longer reasonable to accept a proposed surrogate end point unless it has met stringent criteria. For a biologic measure (called a *biomarker*) to truly stand in as a surrogate, it must not only be correlated with the true outcome of interest, but the change in the biomarker measure induced by the treatment must explain a high proportion of the treatment benefit. To be used prospectively, the biomarker must have been validated as a surrogate with more than one treatment.

These lessons about surrogate markers have important implications for clinicians treating cardiac patients. Titrating therapy to a physiologic end point may or may not be the correct approach to improving the outcome of the patient. In the administration of oral beta-blocking agents to patients with heart failure, hemodynamics commonly deteriorate before they improve. Thus, physiologic surrogates as therapeutic targets in individual patients should be validated in populations before they are accepted as standard practice.

CONFLICT OF INTEREST

The concept of an investigator completely free of bias is a theoretical ideal that is not achievable. The degree of bias or conflict of interest can be considered in a graded fashion. Investigators should not have a direct financial interest in an industry sponsor of a clinical trial. Paid consultancies are also considered to be beyond the scope of acceptable relationships with industry. Compensation for work done on a clinical research project should be reasonable for the work performed and should be handled through an explicit contract. Perhaps the most universal and common conflict in clinical investigation is the bias of the investigator because of belief in a particular concept. Blinding greatly reduces this risk, but the vast majority of clinical studies cannot be blinded. Failure to keep an open mind about the basic results of the investigation can cause the researcher to miss critical discoveries.

Several documents have explicitly laid out guidelines for governing conflict of interest (*e*Table 43.0.4). In addition, attention has been focused on the responsibility of those who write editorials to be free of any conflict of interest (60,61). Perhaps most importantly, the inventor/investigator/manufacturer is at special risk of serious conflict. The individual who has invented a new therapeutic approach and proposes to both manufacture the substance or device for early human studies and to conduct those studies must develop a highly proactive approach to safeguarding against conflict. Studies by Lo et al. and McCrary et al. have underscored the need to prohibit any equity holding by investigators involved in the conduct of clinical trials, as well as the fact that simple disclosure of equity interest to an institution is not sufficient protection for individuals engaged in human experiments (62,63).

***e*TABLE 43.0.4** CONFLICT-OF-INTEREST GUIDELINES IN CARDIOVASCULAR CLINICAL TRIALS AND MEDICAL ORGANIZATIONS

	Stock, equity, interest	**Consultancy**	**Honoraria, educational program payments**	**Travel expenses**	**Financial time window**
Multicenter cardiovascular trials					
Post–coronary artery bypass graft	No	No	Not addressed	Not addressed	Until date of publication
Bypass Angioplasty Revascularization Investigation	No	No	Not addressed	Not addressed	Not addressed
Thrombolysis in Myocardial Infarction phases III–IV	No	No	Not addressed	Not addressed	1 yr after presentation

Global Utilization of Streptokinase and rt-PA for Occluded Coronary Arteries	No	No	No	No	1 yr after publication
Medical organizations					
American Medical Association	No	Disclosure	Disclosure	Not addressed	
National Institutes of Health and Alcohol, Drug Abuse, and Mental Health Administration (rejected)[a]	No	No	No	Not addressed	
ACC	Disclosure to ACC if >$10,000	Disclosure to ACC if >$10,000	Disclosure to ACC if >$10,000	Not addressed	
Harvard Medical School	No	No	Not addressed	Not addressed	
British Cardiac Society	Disclosure with publication	Disclosure with publication	Disclosure with publication	Not addressed	
American Federation for Clinical Research	No	Disclosure with lectures	Disclosure with lectures	Not addressed	
American Heart Association	Disclosure if invited speaker, committee	Disclosure if invited speaker, committee	Not permitted when representing American Heart Association	Not addressed	

ACC, American College of Cardiology; rt-PA, recombinant tissue-type plasminogen activator.

[a]Proposed guidelines September 1989.

Adapted from Topol EJ, Armstrong P, Van de Werf F, et al. Patient safety and conflict of interest in clinical trials. *J Am Coll Cardiol* 1992;19:1123–1128.

SPECIAL ISSUES WITH DEVICE TRIALS

Trials of cardiovascular devices raise special issues that deserve careful consideration. In comparisons of devices with other devices or with medical therapy, the orientation of clinicians implanting the devices is often complicated by the fact that their technical skills are an integral component of the success or failure of the therapy. Therefore, failure of therapy can be interpreted as a failure of the physician as well as of the device. Obviously, in most device trials blinding is also impossible. For these reasons, particular focus on methodology is required in the assessment of clinical outcomes in device trials. Ideally, clinical outcomes should be assessed by a blinded review mechanism, and studies should be designed by groups including investigators who do not have a particular interest in the device-related outcomes but who have expertise in the disease-specific outcomes or clinical research methodology.

HYPOTHESIS FORMULATION

Primary Hypothesis

Every clinical study should have a primary hypothesis. The goal of the study design is to develop a hypothesis that allows the most important question from the viewpoint of the investigators to be answered without ambiguity. This issue is obvious in clinical trials, but in observational studies the appropriate approach to the problem is much less clear. Too often, the investigator is tempted to “dredge” the data; no method of tracking multiple analyses exists to develop considerations related to multiple hypothesis testing.

Secondary and Tertiary Hypotheses

The data collection form provides an information infrastructure for organizing questions to be answered by the trial. A number of secondary hypotheses will be of interest to investigators, including analyses of the relationship between patient characteristics and treatment effect.

In addition to answering questions about the therapy being evaluated, the study can address questions concerning other aspects of the diagnosis, treatment, or outcomes of the disease. Constructing pathophysiologic substudies embedded in larger clinical outcome studies has been especially rewarding. The GUSTO-I trial convincingly demonstrated the relationship between coronary perfusion, left ventricular function, and mortality in a systematic substudy (64).

Finally, many interesting issues about medical practice can be addressed through ancillary studies of clinical trials. Comparisons of outcomes in Canada and the United States (65,66) and regional variations in the United States (67) have provided insight into medical practice.

Intention to Treat

One of the most important concepts in the interpretation of clinical trials is that of intention to treat. Exclusion of patients who were randomized into a trial leads to bias that cannot be quantified; therefore, the results of the trial cannot be interpreted with confidence.

The purpose of randomization is to ensure the random distribution of any factors, both known and unknown, that might affect the outcomes of the patients randomly allocated to one treatment or the other. Any postrandomization deletion of patients weakens the assurance that the randomized groups are at equal risk before treatment. Nevertheless, there are several common situations in which it may be reasonable to drop patients from analysis.

In blinded trials, when patients are randomized but do not receive the treatment, it is reasonable to have a study plan that would drop these patients from the primary analysis. The plan can call for substitution of additional patients to fulfill the planned sample size. When this happens, extensive analyses must be done to ensure that there was no bias in determining who was not treated. In unblinded trials, dropping patients who do not receive the treatment is treacherous and should not be allowed. Similarly, withdrawing patients from analysis after treatment has started cannot be permitted in trials designed to determine whether a therapy should be used in practice, because the opportunity to “drop out without being counted” does not exist when a therapy is given in practice.

Publication Bias

Clinical trials with negative findings are much less likely to be published than those with positive results. Approximately 85% of reports in medical journals report positive results (68). In a sobering analysis, Simes found that a review of published literature showed combination chemotherapy for advanced ovarian cancer to be beneficial, whereas a review of published and unpublished trials together showed that the therapy had no significant effect (69). Dickerson and Min found substantial evidence of negative reporting bias in a review of clinical trial protocols submitted to Oxford University and Johns Hopkins University (33). In particular, industry-sponsored research with negative results was unlikely to be published.

Observational studies are probably even more subject to publication bias than randomized trials. Because of the planning and the need for informed consent with randomized trials, the clinical and ethical imperatives to publish the results are substantial. There is no way to estimate the number of observational analyses done. If an interesting result is found, it is likely to be published, whereas mundane results or results counter to the expectation of the investigator are much less likely to be published.

Awareness of this publication bias should lead to several actions by researchers and practitioners. First, researchers must strive to make clinical research results available to the scientific community through publication, regardless of whether those results are consistent with preconceived notions. Second, the reader must be cautious in interpreting studies showing positive results out of the context of independent confirmation; certainty that unpublished negative results from another investigation do not exist cannot be ensured in most cases. Finally, researchers working on systematic overviews are compelled to search through all means for both published and unpublished findings; because positive results are much more likely to be published, combining only published findings can lead to the wrong conclusion.

STATISTICAL CONSIDERATIONS

Type I Error and Multiple Comparisons

The hypothesis testing in a clinical study may be thought of as setting up a “straw man” that the effects of the two treatments being compared are identical. The goal of statistical testing is to determine whether this straw man hypothesis should be accepted or rejected based on probabilities. The type I error (alpha) is the probability of rejecting the null hypothesis when it is correct. Since clinicians have been trained in a simple, dichotomous mode of thinking, as if the *p* value was the only measure of

probability, the type I error is generally designated at an alpha level of .05. However, if the same question is asked repeatedly, or if multiple subgroups within a trial are evaluated, the likelihood of finding a *nominal p* value of less than .05 increases substantially (70). When evaluating the meaning of a *p* value, the clinician should be aware of the number of tests of significance performed and the importance placed on the *p* value by the investigator as a function of multiple comparisons.

Type II Error and Sample Size

The type II error (beta) is the probability of inappropriately accepting the null hypothesis (no difference in treatment effect) when a true difference in outcome exists. The power of a study (1 – beta) is the probability of rejecting the null hypothesis appropriately. This probability is critically dependent on two items: the difference in outcomes observed between the treatments and the number of primary end points. A common error in thinking about statistical power is to assume that the number of patients determines the power; rather, it is the number of end points that determines the power.

The precision with which the primary end point can be measured also affects the power of the study; end points that can be measured precisely require fewer patients. An example of this issue is the use of sestamibi-estimated myocardial infarct size. Measuring the area at risk before reperfusion and then measuring final infarct size can dramatically reduce the variance of the end point measure by providing an estimate of salvage rather than simply infarct size (71). As is often the case, however, the more precise measure is more difficult to obtain, leading to great difficulty with finding sites that can perform the study; in many cases, the time taken to complete the study is as important as the number of patients needed.

For studies using physiologic end points, using the continuous measure generally increases the power to detect a difference. In restenosis trials, the number of patients needed to detect a reduction in diameter stenosis below 50% is greater than the number of patients needed to detect a difference in the mean or median diameter stenosis or minimal luminal diameter.

A review of the *New England Journal of Medicine* in 1978 determined that 67 of 71 studies with negative results had made a significant (more than 10% chance of missing a 25% treatment effect) type II error, and that 50 of the 71 trials had more than a 10% chance of missing a 50% treatment effect (72). The situation has not improved enough since that time. The most common reasons for failing to complete studies with inadequate power include inadequate funding for the project and loss of enthusiasm by the investigators.

It is highly desirable to have a power of at least 80% when conducting a clinical trial; 90% power is preferable. Discarding a good idea or a good therapy because of a study that had little chance of detecting a true difference is obviously an unfortunate circumstance. An inadequately powered study not only has little chance of demonstrating a significant difference in favor of the better treatment, but also because of random variation with small samples, in which the direction of the observed treatment effect is highly unpredictable. There is an overwhelming tendency to assume that if the observed effect is in the wrong direction in a small study, the therapy is not promising, whereas if the observed effect is in the expected direction, but the *p* value is insignificant, the reason for the insignificant *p* value was a sample size that was too small.

Observational comparisons are at least as likely as randomized trials to include too few patients. Yet rarely do observational studies include power calculations. The same type of calculations commonly used in randomized trials can be used to place an observed effect with a *p* value greater than .05 in perspective. By discussing the minimal clinically important difference and providing the reader with an estimate of the probability of finding such a difference if it existed, the author of an observational study can place the study in much sharper perspective.

Equivalence and Noninferiority

The concept of equivalence will become increasingly important in today's cost-conscious environment. When an effective therapy already exists, the substitution of a less expensive (but clinically equivalent) therapy is attractive. By definition, the studies done to establish this ranking of effective therapies must be positive control studies, and substantial effort is required to define equivalence. Sample size estimates require the designation of a difference below which the therapies would be considered equivalent and above which one therapy would be considered superior to the other. Sample sizes are often larger than the requirements to demonstrate if one therapy is clearly superior to the other. Another important element of this issue occurs when a new therapy is thought to be only slightly better than current therapy but may have an advantage in terms of cost, ease of administration, or side effects. In this situation, trials are done to ensure the community that the new therapy is not inferior to the current standard. Sample sizes are lower with such noninferiority testing than either superiority or equivalence testing.

A common example of an issue that will increasingly arise concerns the substitution of a less expensive treatment for MI patients. Given the 10% underlying risk of death at 30 days with contemporary therapies, *e*Table 43.0.5 gives the sample sizes for ensuring that a new treatment does not increase the risk of death by 1%, 2%, or 3%.

***e*TABLE 43.0.5** EQUIVALENCE SAME SIZE ESTIMATES[a]

Old treatment no worse than	Number of patients
1% increase in mortality	32,582
2% increase in mortality	8,575
3% increase in mortality	3,998

[a]Standard treatment mortality estimated at 10%. A new, less expensive therapy is developed: How many patients will it take to prove "equivalence" (alpha = .05; beta = .10)?

Clinicians must beware of studies that are designed with a substantial type II error resulting from an inadequate number of end points and conclusions that the two treatments are equivalent because the *p* value is greater than .05. This approach could lead to a gradual loss of the current level of effectiveness of therapy for cardiovascular conditions. If we were willing to accept that a therapy for acute MI with a 1% higher mortality in an absolute sense was "equivalent," and we examined four new, less expensive therapies that met those criteria, we could cause a significant erosion of the decline that has occurred in acute MI mortality.

Several major cardiovascular trials have been based on the concept of equivalence. The Bypass Angioplasty Revascularization Investigation study was predicated on the hypothesis that percutaneous intervention would not increase the 5-year mortality beyond 2% (31). The International Joint Efficacy Comparison of Thrombolytics study examined the hypothesis that reteplase retained at least one-half the benefit of streptokinase in reducing mortality compared with conservative therapy, and the Assessment of the Safety and Efficacy of a New Thrombolytic 2 trial demonstrated that lanetoplase, given as a bolus, was equivalent to alteplase in terms of both mortality and intracranial hemorrhage (73,74).

Sample Size Calculations

The critical step in a sample size calculation, whether for a trial to determine a difference or to test for equivalence, is the estimate of the minimally important clinical difference. By reviewing the proposed therapy in comparison with currently available therapy, the investigators should endeavor to determine the smallest difference in the primary end point that would change clinical practice. Practical considerations may not allow a sample size large enough to evaluate the minimally important clinical difference, but the number should be known. In some cases, the disease may be too rare to enroll enough patients, whereas in other cases, the treatment may be too expensive or the sponsor may not have enough money. Once the minimally important clinical difference and the financial status of the trial are established, the sample size can be determined easily from a variety of published computer algorithms or tables. We have found it useful to produce plots or tables to enable the investigators to see the effects of small variations in event rates or treatment effects on the needed sample size. In the GUSTO-I trial, the sample size was set after a series of international meetings determined that saving an additional one life per 100 patients treated with a new thrombolytic regimen would be a clinically meaningful advance (15). With this knowledge and a range of possible underlying mortalities in the control group, a table was produced demonstrating that an absolute reduction of 1% (difference of one life per 100 treated) or a relative reduction of 15% could be detected with 90% certainty with inclusion of 10,000 patients per arm.

METAANALYSES AND SYSTEMATIC OVERVIEWS

Regardless of the goal of doing adequately sized clinical trials, clinicians are often faced with therapeutic dilemmas in which there is not enough evidence to be certain of the best treatment. The basic principle of combining medical data from multiple sources seems intuitively appealing, because this approach results in greater statistical power. However, the tradeoff is the assumption that the studies being combined are similar enough that the combined result will be valid. Inevitably, this assumption rests on expert opinion.

*e*Table 43.0.6 provides an approach to reading metaanalyses. The most common problems with metaanalyses are combining studies that have different designs or outcomes and failing to find negative studies that have not been published. There is no question about the critical importance of a full literature search, as well as involving experts in the field of interest to ensure that all relevant information is included. Statistical methods have been developed to help assess systematic publication bias (75). Another complex issue involves determining the quality of individual studies within a systematic overview. Statistical methods have been proposed

for differential weighting as a function of quality (76), but these have not been adopted on a wide scale.

***e*TABLE 43.0.6** HOW TO READ AND INTERPRET A METAANALYSIS
Are the results of the study valid?
Primary guides
Does the overview address a focused clinical question?
Are the criteria used to select articles for inclusion appropriate?
Secondary guides
Is it unlikely that important, relevant studies were missed?
Is the validity of the included studies appraised?
Are the assessments of studies reproducible?
Are the results similar from study to study?
What are the results?
What are the overall results of the review?
How precise are the results?
Will the results help me in caring for my patients?
Can the results be applied to my patient?
Are all clinically important outcomes considered?
Are the benefits worth the risks and costs?

The methodology of the statistical evaluation of pooled information has been a source of tremendous interest. The fixed effects model assumes that the trials being evaluated are homogeneous with regard to estimate of the outcome; given the uncertainties expressed previously, the assumption of homogeneity seems unlikely. Accordingly, a random effects model has been developed that considers not only the variation within trials, but also the random error between trials (77).

An interesting approach to metaanalyses, termed *cumulative metaanalysis*, has been developed. With this approach, as data become available from new trials, they are combined with findings of previous trials with the calculation of a cumulative test of significance. In theory, this approach should allow the medical community to determine the point at which the new therapy should be adopted into practice. Another variation on the theme of metaanalysis is metaregression, a method allowing the evaluation of covariate effects within multiple trials to explain heterogeneity in observed results.

The apparent lack of congruence between the results of metaanalyses of small trials and subsequent results of large trials has been a source of substantial confusion. Metaanalyses of small trials found that both magnesium therapy and nitrates provided a substantial (>25%) reduction in the mortality of patients with MI (78). The large ISIS-4 trial (79) found no significant effect of either treatment on mortality. Although many discussions have been posited for these discrepancies, a definitive explanation does not exist. The major message seems to be that large numbers of patients are needed to be certain of the effect of a therapy in cardiovascular disease. Guidelines for reading metaanalyses are given in eTable 43.0.6.

Systematic overviews followed by direct comparative trials have raised the question of determining when the effect of a treatment can be considered a class effect and when it should be attributed to a specific molecular entity. When a biologic target is identified, multiple ways of altering the biology of that target can be devised; almost certainly, different approaches to altering the target will share some common attributes but will differ with regard to others. Until relatively recently, the tendency has been to assume a class effect until proven otherwise. However, trials have demonstrated differences within the class of platelet inhibitors (80,81), while significant questions have been raised about cholesterol-lowering drugs (82), beta-blockers, low-molecular-weight heparins (83,84), and calcium channel blockers. Thus, lumping all members of a “class” into a systematic overview may ignore important differences within the class, and indirect comparisons of treatment effect within systematic overviews are treacherous.

UNDERSTANDING COVARIATES AND SUBGROUPS

Because of the insatiable curiosity of clinicians and patients about whether different responses to treatment may be seen in different types of patients, an analysis of trial results as a function of baseline characteristics is inevitable. Traditionally, this analysis has been performed using a subgroup analysis, in which the treatment effect is estimated as a function of baseline characteristics taken one at a time (e.g., age, sex, and weight). This approach has been called a *false-positive result machine*, but might just as well be referred to as a *false-negative result machine*. The false-positive results are generated because of the problem of multiple comparisons: By chance alone, a significant difference will be apparent in at least 1 in 20 subgroups, even if there is absolutely no treatment effect (70). In 1980, Lee et al. randomly split a population of 1,073 into two hypothetical treatment groups (the treatments were actually identical) and found a difference in survival in a subgroup of patients, with a p value of <.05.

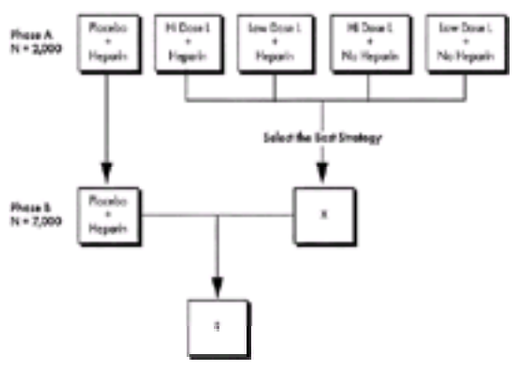
At the same time, given the large number of patients needed to demonstrate an important treatment effect, dividing the population into subgroups markedly reduces the power to detect differences when they are real. Consider a treatment that reduces mortality 15% in a population equally divided between men and women, with a p value for the treatment effect of .03. If the treatment effect is identical for men and women, the approximate p value will be .06 within each subgroup, since each group is half as large. It would obviously be foolish to conclude that the treatment was effective in the overall population, but not in men or women.

A more appropriate and conservative method would be to develop a statistical model predicting outcome with regard to the primary end point for the trial, then evaluate the effect of the treatment as an effect of each covariate after adjusting for the effects of the general prognostic model. This type of analysis, known as a treatment by *covariate interaction analysis*, assumes that the treatment effect is homogeneous in subgroups unless a definitive difference is observed.

An example of this approach occurred in the Prospective Randomized Amlodipine Survival Evaluation trial (23), which observed a reduction in mortality with amlodipine in patients with idiopathic dilated cardiomyopathy, but not in patients with ischemic cardiomyopathy. When an effort was made to validate the finding in the Prospective Randomized Amlodipine Survival Evaluation 2 trial, no mortality benefit was seen in patients with idiopathic dilated cardiomyopathy (25). In the Bypass Angioplasty Revascularization Investigation trial (31), a post hoc analysis showed a significant benefit of bypass surgery in patients with treated diabetes, but not in other patients. The test for interaction has been said to have limited power so that a borderline significant result should attract clinical interest, although there is inadequate experience with this test to be comfortable about interpretation.

PICK THE WINNER

There is no other effective way to develop therapies than measuring intermediate physiologic end points in the early phases of study. Based on favorable physiologic responses, some therapies are brought forward for more extensive studies and others are dropped. However, other approaches to winnowing the possible doses or intensities of therapy must be developed, because these physiologic end points are unreliable. One such approach is termed *pick the winner*. In this design (eFig. 43.0.4), several doses or intensities of the therapy are devised, and at regular intervals during the trial an independent Data and Safety Monitoring Committee evaluates clinical outcomes with the goal of dropping arms of the study according to prespecified criteria.



***e*FIGURE 43.0.4** “Pick the winner” strategy.

THERAPEUTIC TRUISMS

A review of clinical trials points out that many commonly held beliefs about clinical practice need to be challenged. If these assumptions are shown to be less solid than previously believed, a substantial change in the pace of clinical investigation will be needed.

Frequently, medical trainees have been taught that variations in practice patterns are inconsequential. The common observation that different practitioners treat the same problem in different ways has been tolerated because of the general belief that these differences did not matter. Clinical trials have demonstrated, however, that small changes in practice patterns for epidemic diseases can have a sizable impact. An example is the extreme variation in recommendations regarding the preferred aPTT for patients treated with unfractionated heparin. Based on the pathophysiologic surrogate of arterial patency (85,86), the GUSTO investigators adjusted the recommended aPTT upward in the transition from GUSTO-I to GUSTO-IIa. The average 8-second increase in aPTT resulted in a doubling of the rate of intracranial hemorrhage in patients treated with thrombolytic therapy and heparin (51). When the heparin dose was reduced in GUSTO-IIb, the intracranial hemorrhage rate reproduced that observed in GUSTO-I (54).

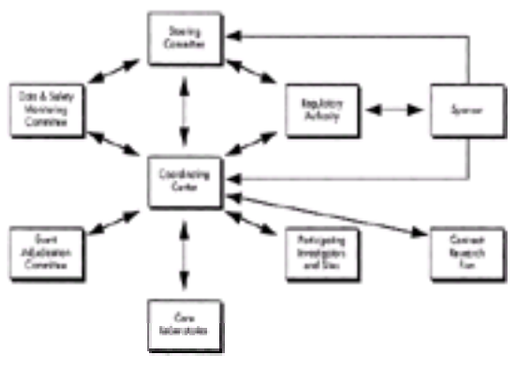
Another ingrained belief of medical training is that observation of the patient provides evidence for changing treatment. Although no one would dispute the importance of following symptoms, many acute therapies have effects that cannot be judged in a short time, and many therapies for chronic illness prevent adverse outcomes in patients with few symptoms. For example, in treating acute congestive heart failure, inotropic agents improve cardiac output early after initiation of therapy but lead to a higher risk of death. Beta-blockers cause symptomatic deterioration acutely but appear to improve long-term outcome.

Similarly, the standard method of determining the dose of a drug has been to measure physiologic end points. In a sense, this technique represents a surrogate end point approach. No field has more impressively demonstrated the futility of this approach than the treatment of heart failure. A variety of vasodilator and inotropic therapies have been shown to improve hemodynamics in the acute phase but subsequently were shown to increase mortality.

Finally, the maxim “do no harm” has been a fundamental tenet of medical practice. However, most biologically potent therapies cause harm in some patients while helping others. The emphasis on the neurologic complications of bypass surgery (87,88) amply demonstrates that a therapy that saves lives can also lead to complications in individuals. Intracranial hemorrhage resulting from thrombolytic therapy exemplifies a therapy that is beneficial for populations but has devastating effects on some individuals. The patients who are harmed can be detected easily, but those whose lives are saved cannot be detected.

STUDY ORGANIZATION

Whether the investigator is contemplating a large or small trial, the general principles of organization of the study should be the same (eFig. 43.0.5). A balance of interest and power must be created to ensure that after the trial is designed, the experiment can be performed without bias and the interpretation will be generalizable.



***e*FIGURE 43.0.5** General principles of study organization.

Steering Committee

In a large trial, the steering committee is a critical component of the study organization. This group designs, executes, and disseminates the study. A diverse steering committee, providing multiple points of view representing biology, biostatistics, and clinical medicine, will more likely organize a trial that will withstand external scrutiny. This same principle holds for small trials; an individual investigator, by organizing a committee of peers, can avoid egocentric thinking about a clinical trial.

Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) is constructed to oversee the safety of the trial from the point of view of the patients being enrolled. The DSMC should include clinical experts, biostatisticians, and sometimes medical ethicists; these individuals should have no financial interest, emotional attachment, or other investment in the therapies being studied. Committee members have access to otherwise confidential data during the course of the trial, allowing decisions to be made in a way that could compromise the objectivity of those conducting the study. Similarly, in a small trial, a smaller group of external reviewers keeping watch over the study can be helpful.

Not only should the DSMC be appointed before the initiation of a clinical trial, but its charter should be agreed on by the sponsor, the steering committee, and the DSMC itself (89,90,91,92,93,94,95 and 96).

Institutional Review Board

The institutional review board (IRB) continues to play a critical role in the conduct of all types of clinical research. Approval by the IRB is generally required for any type of research, even if it is not funded by an external source. The IRB should consist of physicians with expertise in clinical trials, as well as representatives with expertise in medical ethics and representatives of society in the community in which the research is being conducted. Several types of studies are typically exempted from the IRB process, including studies of public behavior, research on educational practices, and studies of existing data in which the research data cannot be linked to individual subjects. Surveys and interviews also may be exempted when the subjects are not identified and the data have a low likelihood of leading to a lawsuit, financial loss, or reduced employability of the subject. Attention has been focused on the need for systematic review of research by IRBs rather than the creation of large amounts of unnecessary paperwork (97).

Major concern has been raised about the level at which IRBs function. A major government report claimed that IRBs do not have the resources or expertise needed to protect human subjects; substantial IRB reform is under way.

Regulatory Authorities

Government regulatory authorities have played a major role in the conduct of clinical research. Requirements by the FDA and other national health authorities define the way industry-sponsored clinical trials are conducted. In general, regulatory requirements include interpretation of fundamental guidelines to ensure adherence to human rights and ethical standards. The FDA and equivalent international authorities are charged with ensuring that drugs and devices that are marketed are safe and effective (a charge with broad leeway for interpretation). Importantly, in the United States, there is no mandate to assess comparative effectiveness or cost effectiveness.

Industry or Government Sponsors

Having provided funding for the study, the sponsor of a clinical trial understandably wishes to be heavily involved in the conduct of the study. Worldwide, the majority of clinical investigation is now done either directly by the pharmaceutical or medical device industry, or indirectly by for-profit clinical research organizations. This approach seems reasonable and desirable for explanatory trials, but pragmatic trials, if not performed by an independent steering committee, run a greater risk of bias, as the sponsor of a study has a large financial stake in the success of the therapy being tested. Even in the case of government sponsorship, trials frequently arise out

of political agendas, with much to be gained or lost for individuals within the scientific community depending on the result.

INTEGRATION INTO CARDIOVASCULAR PRACTICE

Because the goal of clinical investigation is to improve the care of patients, findings of a clinical investigation must be integrated into practice carefully. The old method of each practitioner reading the literature and making individual decisions is inadequate. Recognition of this deficit has led to a variety of efforts to synthesize empirical information into practice guidelines. These guidelines may be considered as different paths to the top of the mountain, with several routes acceptable as long as the difficulty and likelihood of success are known. In addition, large efforts such as the Cochrane Collaboration (98) are attempting to make available systematic overviews of clinical trials in most major therapeutic areas.

A series of reports has demonstrated that adhering to clinical practice guidelines results in better patient outcome (99,100). In the United States, a system has been developed in which professional societies develop the guidelines, and the government provides support for evidence-based practice centers, which provide empirical overviews of the risks and benefits of diagnostic or therapeutic approaches.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Governmental Regulation

Over the past decade, as the U.S. health care system has evolved into a business model, controversy has arisen over the role of government regulation in clinical research. Regulation comes in two forms: regulatory authorities charged with ensuring the safety and efficacy of products sold for medical purposes, and ethical regulation of investigation done for the public good. Although the usual business approach is to assume that the marketplace will sort out beneficial therapies from those that do not work, history belies this belief in terms of medical therapies. Determining medical benefit is complex, and simple observation is inadequate; without requirements for controlled trials, many detrimental therapies in cardiology would likely still be in use. The initial formation of the FDA occurred because of the sale of pharmaceutical products that were lethally contaminated, and every new regulation has resulted from a similar tragedy. The mandate of the FDA extends only to the point of determining that a therapy is safe and effective compared with *no* therapy, however, and does not include the determination of which therapies are more effective when two effective therapies are available. Additionally, the mandate with regard to pharmaceuticals is more stringent with a general requirement for substantial evidence of clinical benefit from randomized, controlled trials, whereas device regulations allow less definitive evidence of clinical benefit. Once a product is on the market, the FDA rigorously controls the advertising and promotion that can be done with that product, but the FDA can deal only with errors of commission rather than errors of omission. Thus, a therapy that lowers blood pressure and has been shown in adequate controlled trials to lower mortality and stroke rates can advertise that benefit. A comparative therapy that lowers blood pressure but never has been shown to reduce mortality and stroke can be advertised as being effective in lowering blood pressure without mentioning the absence of clinical outcome trials.

We believe that the onus is on the medical profession to ensure that adequate clinical trials are done to demonstrate which therapies are most effective. The industry that develops new therapies is obligated only to meet the regulations for being marketed. Managed care organizations are focused on cost rather than outcome; in many cases, incentives exist to impede new therapies from clinical use when they increase expense. Only with the active involvement of health care providers will the needed studies be done to allow the best information to be available to make choices among active therapies.

Composite and Surrogate End Points

The number of important clinical questions far exceeds our ability to address them. For this reason, there is a great temptation to perform clinical trials using composite and surrogate end points. Composite end points have the advantage of creating an outcome scale that allows for categorical or continuous measures that add power to the study. However, the problem arises that less important end points can drive the difference, when small differences in a more important end point (such as mortality) could not possibly be detected. Similarly, surrogate end points are hampered by constant uncertainty about whether the surrogate will work, particularly because the difference between therapies might relate to an outcome dictated by an unexpected effect of the therapy. For these reasons, surrogates and composites should be regarded as intermediate approaches to determining which therapies need to be tested definitively. One exception is when a minor modification is made to a drug or device, and a consensus exists that the modification will not fundamentally alter the effect of the treatment. Practitioners and investigators need to eschew the temptation to substitute surrogates for adequate measures of health outcomes in large enough populations. Instead, the clinical community should focus on more efficient methods of aggregating large amounts of information at a lower cost.

Randomized Trials versus Observational Studies

Randomized trials and observational studies represent different approaches to answering questions. Traditionally, the randomized trial has been hampered by two factors: enrollment of selected patients perhaps not representing clinical practice and concern about human experimentation. It is simply a fact that given the current organization of medicine, the number of therapeutic questions will far exceed the number of randomized trials that can be performed. Having been involved in numerous randomized trials and observational treatment comparisons, it is our belief that much more effort is needed to expand the ability to perform randomized trials. Until the technology revolution allowing the rapid accumulation of information from multiple sites and the introduction of the large, simple trial methodology, it seemed that observational studies were needed to fill in the huge gaps in clinical therapeutics (101). With current capabilities, the major role of observational studies should be to generate hypotheses, fill in information about small variations in practice, and deal with the extrapolations necessary to inform decisions about chronic disease management. Another important use of observational databases is to provide audit and feedback to practitioners about whether they are adhering to guidelines for practice. Given the fact that most patients live for years with cardiovascular disease, the long-term implications of therapies such as choice of prosthetic valve, choice of revascularization method in stable angina, and risk factor modification require extrapolations beyond the time frame that can reasonably be measured. The technology half-life is now so short that long-term randomized trials have the risk of being historical artifacts.

Sharing of Information

Given the for-profit nature of the medical products and pharmaceutical industry and the increasingly financial orientation of the health care delivery system, a risk exists that important medical information will not be available. The financial incentive in the medical products industry has stimulated tremendous creativity and should be preserved. A potential conflict exists, however, between the professional ethic of the health care provider to share information to improve the delivery of health care in broader terms, and the need of financially driven delivery systems to maintain a competitive edge. This potential conflict ironically arises at a time when the ability to rapidly share data and their interpretation has improved in an exponential fashion. Patients expect that when medical research is done, the information will be shared; one could argue that information sharing to advance health in general is a critical part of the ethical contract between provider and patient when informed consent is obtained.

THE FUTURE

Because of the continuing explosion of knowledge about the biology of heart disease and society's inability to increase the financial outlay for the unfettered use of biology and technology, the future of clinical investigation is bright. Without quantitative information, there is no rational method to make decisions about what will be supported in medical practice and what will be discarded.

Over the next several years, cardiovascular practitioners will be increasingly using computerized databases to capture information at the point of care. Early efforts in this area, focusing on procedure reports to meet mandates from payers and quality reviewers, will be replaced by systems aimed at capturing information about the entire course of the patient's encounter with heart disease. Although the impetus for this approach will come from those who pay for health care, practitioners will find the information to be useful for justifying rational medical care and improving the overall efficiency with which it is delivered. Multimedia presentations will allow the clinician to view medical records and imaging studies simultaneously in the clinic or in the hospital. To efficiently exchange information, the nomenclature of cardiovascular diagnosis, treatments, and outcomes will progressively become standardized.

The computerized management of information will be part of an inevitable coalescence of practitioners into integrated health systems. To efficiently care for populations of patients at a reasonable cost, practitioners will work in large, geographically linked, and economically interdependent groups. This integration of health systems will propel outcomes research into a new era in which strategies of care can be tested over time and refined in continuous learning processes for health care providers.

Although integrated health care systems will provide the structure for medical practice, global communications will provide mechanisms to quickly answer questions about the diagnosis, treatment, and prognosis of heart disease. The ability to aggregate information about thousands of patients in multiple health systems will change the critical issues facing clinical researchers. Increasingly, attention will be diverted from efforts to obtain data, and much effort will be required to develop efficient means of analyzing and interpreting the types of information that will be available.

Ultimately, leading practitioners will band together in global networks oriented toward treating illnesses of common interest. When a specific question is identified requiring randomization, the studies will be much simpler because the randomization can simply be added to the computerized database, and information that currently requires construction of a clinical trials database will be immediately accessible without additional work. Information systems will be designed to provide continuous feedback of information to clinicians, supporting rational decisions about therapy. In essence, a continuous series of observational studies will be in progress, managed by a community of practitioners linked via the Internet, assessing outcomes as a function of diagnostic processes and therapeutic strategies.

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44

DATABASES IN CARDIOLOGY

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

A clinical database is a systematic collection of observations related to patients and/or clinical processes. With the advent of relatively inexpensive and sophisticated computer technology, databases can be used for information retrieval, case finding, description of cohorts, and predictive modeling of outcomes and risks. Databases are increasingly being used for a process known as *outcomes management*, or technology of experience. According to outcomes management, predefined standards and coding systems are used to describe systematically all patients and outcomes encountered. Large databases are then used to identify variances in outcome that may be related to processes in patient care. Although this process is potentially very powerful for identifying and improving deficiencies in patient care, it suffers from a number of inherent methodologic difficulties.

Databases in cardiology have been developed and described in five major settings: (a) population-based studies, such as the Framingham Heart Study, which are used to describe risk factors for and the natural history of cardiovascular disease in the community; (b) disease-oriented registries, which describe care processes for and outcomes of patients with specific problems, such as acute myocardial infarction; (c) procedure- or technology-oriented registries; (d) government-mandated and administrational databases; and (e) registries derived from randomized clinical trials. Newer database technologies, including the development of object-oriented databases, along with the computerized medical record, represent means by which clinical database methods can be incorporated into routine clinical care.

GLOSSARY

American Standard Code for Information Interchange (ASCII): A code representing English characters and numbers with each letter assigned a number from 0 to 127 (7-bit ASCII) or 0 to 255 (8-bit ASCII) that is independent of machine (computer) and operating systems. A more universal standard is ISO Latin-1, used on the World Wide Web.

Attributional validity: Whether an apparent association between a variable and an outcome reflects reality as opposed to confounding by an unknown or unconsidered covariate.

Case-control study: A study design in which patients with and without a certain outcome are identified and then compared with respect to an exposure variable of interest.

Case-mix adjustment: Identifying and controlling for patient-specific factors over which physicians and health care institutions have no control and that may explain variances in outcome.

Categorical variable: A variable that can have only a finite set of values.

Clinical model concept: A model whereby outcomes are related to patients factors, physician plan factors, and hospital execution factors.

Coding system: A system for describing outcomes, clinical findings, and therapies according to a standardized format (e.g., Current Procedural Terminology; International Classification of Diseases, Ninth Revision, Clinical Modification; Systemized Nomenclature of Medicine).

Cohort study: A study design in which a population cohort is prospectively defined and divided according to the presence or absence of an exposure variable of interest and then followed over time for the occurrence of prespecified outcomes.

Colinearity: Spurious associations or lack of associations in a multivariable model due to excessive correlation of covariates with one another.

Computerized patient record: A type of clinical database in which an electronic medium is used to capture, process, analyze, and retrieve values for variables representing the entire clinical process.

Content validity: Appropriate and complete selection of covariates in a predictive model.

Continuous variable: A variable that can have an infinite set of values.

Cox proportional hazards model: A multivariable model that relates the log of the unspecified hazard function ratio between groups of patients to a linear equation.

Data dictionary: A set of uniform definitions for data elements.

Data element: A specific piece of organized information about a person or event.

Database design: A model according to which data elements are linked logically to one another.

Database management system: A set of computer programs that manage access to, modification of, and analyses of a database.

Database standards: Agreed-on methods for defining terms and interfaces, thus allowing cross-communication between databases.

Extensible Markup Language (XML): A formal, concise, human-legible machine (computer)- and operating system–independent language that describes both data entities (objects) and the behavior of computer programs (XML Processor) to understand and present them. This is achieved through markup, which encodes (tags) a description of the entity's storage layout and logical structure.

External Data Representation (XDR): A standard for describing and encoding data in a fashion that is machine (computer)- and operating system–independent. It uses a language to describe data formats (structure) and has been particularly useful in exchange of so-called binary data (data, such as real numbers, that are not human-readable).

Face validity: The clinical sense of a prediction model—that is, the model makes sense given current understanding.

Field: A placeholder for a specific value regarding a person or event; synonymous with *variable*.

Flatfile: A single data table that contains columns representing variables and rows representing bases of observations, for example, individuals. The table has no structural information about the data values themselves.

Hazard function: The instantaneous risk of a time-related event.

Hierarchical database: A database model based on a nested root-subordinate segment structure.

Interaction: Also known as *effect modification* or *modulation*; a situation in which the strength of association between one variable and an outcome is affected by another variable; to be distinguished from confounding, in which an association between a variable and an outcome is only a reflection of the association between another variable with the index variable and with outcome.

Internet: A complex system of worldwide interacting computer networks.

Logistic regression model: A multivariable prediction model in which the log of the odds of a time-fixed outcome event is related to a linear equation.

Metadata: Data about data—that is, information describing other data. Metadata in one context may be data in another, in effect metadata describing metadata. In a database context, metadata is usually considered the structural information associated with both data and the database organization.

Object-oriented database: A database model in which complex data structures (objects) are used that consist of both values for variables and instructions for operations to be performed on the data.

Outcomes management: A process by which clinical processes and outcomes are recorded systematically in large databases and then analyzed to detect variances in outcome that can be improved by altering those processes.

Overfitting: Using too many covariates for the number of outcome events in a multivariable predictive model; can lead to spurious or incorrect associations.

Predictive modeling: A process by which a clinical database is used to describe mathematically the likelihood of outcome events, given a set of values for variables of a new patient.

Predictive validity: How well a multivariable predictive model predicts outcome in a database separate from the one from which the model was derived.

Relational database: A database model that consists of multiple cross-referenced tables that can be linked together by set(s) of user-defined "linking variables" and queried using Structured Query Language.

Reliability: Reproducibility or stability of data measures.

Semistructured data: Complex data elements whose contextual structures are embedded along with the values for variables, rather than being dependent on an external data structure. As such, the data elements are simultaneously independent self-defining entities and self-organizing given a specific query.

Spreadsheet: A table of values arranged in rows and columns in which values at row-column intersections (called *cells*) can have predefined relationships with other cells. Data structure accompanies the spreadsheet.

Time-oriented database: A database model in which time is the organizing theme to facilitate temporal reasoning based on temporal attributes (duration) and temporal relations to other data (temporal order).

Validity: How well a data element or predictive model reflects what is really supposed to be measured or predicted.

World Wide Web: A technology by which access to the Internet is made easy by use of graphical hypertext-linked interfaces.

INTRODUCTION

In the late 1940s and early 1950s, epidemiologists from the U.S. Public Health Service and academic cardiologists and internists in the Boston area collaborated to develop a population-based database of cardiovascular disease in Framingham, Mass. (1,2). The early development of the Framingham Heart Study database was fraught with difficulties (3): Methods of population sampling were not well developed, the natural history of coronary artery disease (CAD) was poorly understood, the clinical manifestations of CAD were known to only partially reflect pathologic events, the modern "computer era" had not yet begun, and modern biostatistical science was in its infancy. Nonetheless, the investigators successfully assembled a cohort of more than 5,000 adults who have now been systematically followed for nearly 50 years (1); later in the 1970s, a new cohort based on the offspring and spouses of offspring of the original cohort was assembled and continues to be followed (4). Numerous analyses of the characteristics and outcomes of the participants in the Framingham Heart and Offspring studies have yielded invaluable insights into the risk factors, pathogenesis, and natural history of cardiovascular disease (5); the Framingham and other population-based databases continue to be fruitful sources for cardiovascular investigators today (6,7,8,9,10,11,12,13 and 14).

The Framingham Heart Study is illustrative of many of the attributes of a successful database (15). The database was assembled and continues to be maintained by a large, multidisciplinary team with involvement of clinicians, classic epidemiologists, computer engineers, and biostatisticians; they have been able to depend on adequate and stable funding. The goals of the database were well-defined, leading to high-quality, focused data collection. Efforts have been consistently made to keep

the database relevant, with appropriate addition, alteration, and deletion of data fields as new technologies and understanding of disease processes change the questions that investigators wish to answer. Finally, and perhaps most important, dynamic and strong leaders have championed the development, implementation, use, and analyses of the database as well as publicly advocated its benefits.

With the advent of the computer, large databases became possible in clinical environments as well. Early examples of clinical databases included the Duke Databank for Cardiovascular Disease (16), which was established in 1969, and the Coronary Artery Surgery Study database (17). Today, clinical databases have expanded into multiple areas of practice and investigation, presenting tremendous opportunities for improving knowledge about and care of patients with cardiovascular disease but also frustrating developers and users with numerous technical and inherent design problems.

This chapter reviews population-based and clinical databases, with particular attention to their applications in cardiology. The use of these databases for clinical investigation, quality assessment, and outcomes analyses are explored.

WHAT IS A DATABASE? DATABASE TECHNOLOGY, TERMS, AND DEFINITIONS

A clinical database is a systematic collection of facts about individual patients or clinical events (Table 44.1). Facts about a person or event might include, for example, last name, patient identifier, birth date, heart rate at the time of admission, or medications used.

Concept	Description	Types
Fields (variables)	Factor information about a particular subject or patient; resumes data definitions (metadata)	Discrete (categorical) Dichotomous (yes/no) Ordinal (e.g., New York Heart Association functional class) Polytomous (lists) Continuous
Management system	Computer programs that manage access to and use of databases	Multiple services required: Data sharing Consistency, error checks Security Protection and backup Timeliness Standards for entry Query engine Temporal attributes Extensibility
Design	Model by which variables are logically linked to one another	Flatfile Spreadsheet Relational Object-oriented Time-oriented Semistructured
Focus	Orientation of developers and questions of interest	Disease Population Procedure/therapy/device Computerized patient record Values for variables of all health care-related data

TABLE 44.1 BASIC CONCEPTS OF DATABASE CONSTRUCTION

Computer-based databases divide these facts into (a) what the fact is, which can be termed a *variable* or in specific contexts a *field* or *column name*; (b) the specific *value* for the variable for an individual patient; and (c) *structural* information, including the name of the data element, unique identifier for the data element, version, authorization information, language, definition, obligation (whether the data element is required or not), data type (e.g., numerical or character), limits (e.g., age cannot be less than 0 or more than 120), author (who or what obtained and recorded the information), time stamp, temporal attributes, and many other attributes of the variable and value. All these properties of a clinical fact constitute a data element either implicitly in most traditional databases or explicitly in semistructured data.

A collection of data elements that relate to one specific person or clinical event constitutes a *patient record*. Thus, a clinical database can be thought of as a potentially limitless collection of patient records consisting of data elements. In the simplest database designs, the patient record may constitute a single row in a table, with one or more columns of variables containing data for that patient.

Focuses of Clinical Databases

Clinical databases can have one of two primary focus types: (a) disease- or population-oriented or (b) procedure-, therapy-, or device-specific (15). Both of these types of databases are used in cardiology. The Framingham Heart Study, the Nurses' Health Study (18), the Cardiovascular Health Study (19), and a hospital-based computerized patient record are examples of population-oriented databases. The Duke Databank for Cardiovascular Disease (16) is a disease-oriented database that is focused primarily on CAD. The National Heart, Lung, and Blood Institute angioplasty registry (20) and the Cardiac Transplant Research Database (21) are examples of procedure-oriented databases.

Types of Database Elements

Possible values for clinical database variables can be either *categorical* or *continuous*. Categorical variables may be limited to only two possible values and thus be *dichotomous*; examples include yes or no, 0 or 1, male or female, and presence or absence of chronic heart failure. Alternatively, categorical variables may be *ordinal*—that is, have a limited list of possible values that bear an ordered relation to one another; examples include the Canadian angina class, the New York Heart Association functional class, severity of mitral valve regurgitation, and pain scales. These types of measures have been termed by Feinstein as *clinimetrics* (22). Finally, categorical variables may be *polytomous*—that is, have an unordered but finite list of possible values, such as etiology of subacute bacterial endocarditis or names of bones in the body.

Continuous variables have a theoretically infinite number of possible values. Examples of continuous elements are age, blood pressure at admission, peak creatine kinase level after an index myocardial infarction, or number of hours between symptom onset and performance of emergent primary percutaneous coronary intervention.

Data Dictionaries and Metadata

If data are to be understood, valid, and reliable, it is essential that all data elements be defined precisely. A common means of handling this is to create a separate computer file that contains the list of all files in the database, a list of all variables, definitions and data type of each variable, and lists along with definitions of all possible values with each variable. Such a file is known as a *data dictionary* (23). Certainly, simple-to-follow yet precise definitions allow for high-quality entry of data by multiple personnel and guard against unneeded redundancies (24).

With the advent of worldwide exchange of information, attention has focused on data definition and formatting *that are independent of specific machine types and operating systems* and using internationally agreed-on standards. Data definitions are now more fully expressed in terms of *metadata*. Metadata are data about data that contain all structural attributes of the data and database. Until recently, metadata have been exploited mainly in presenting a single user image of multiple, disparate databases, possibly in multiple locations, as if they were one. More recently, it has been suggested that all input and output of data could, in theory, be managed through a metadata "layer." The metadata may be separated from the data to form part of the structure of the database, in which case, data elements are simple, consisting of just the value, or they may be directly associated with each data element, in which case data elements may be complex.

Structure and Content of Clinical Databases

Determination of the size, structure, and content of clinical databases has been a major source of frustration, in part because no standards for these existed before the modern computer age. Dolin points out that any database that is to be used for assessment of outcomes must contain information in three key areas: input, intervention, and outcome (25). Input data include demographics, family history, reproductive history, social history, types of episodes and encounters (e.g., ambulatory, emergency, critical care), signs and symptoms, diagnoses, and test results. Intervention data include information on medications, immunizations, operations, procedures, functional assessment, and socioeconomic assessment. Outcomes data include death, disability, discomfort, drug toxicity, and dollar costs; the last includes service costs, hospital days, and days of missed work. Some validated data already exist for assessing outcomes in specific situations; an example would be the Acute Physiology, Age, Chronic Health Evaluation III for analyses of outcomes in noncoronary critical care units (26).

Ellwood describes certain rules that should be followed if a large clinical database is to remain robust over time (27). The goals of assembling the database have to be prospectively determined to define appropriate data elements. The size of the database must be carefully considered; large databases contain more information, but excessively large numbers of data elements can lead to significant deterioration of data quality. Although data may be collected in many geographic locales, a

mechanism for centralizing data is essential. Finally, the ideal clinical database is not confined to hospital events.

Database Standards

For clinical data obtained outside the confines of a clinical trial or registry to be considered reliable for analyses, it is absolutely essential for standards to be developed to allow for data fields to be validly compared between different databases and to allow data to be transferred between systems. As stated by McDonald and Hammond (28), “standards let us mix and match components, create large assemblies from many parts, and communicate efficiently.”

Coding Systems

Coding systems for clinical databases can be divided into clinical classifications and nomenclatures (29,30). A clinical classification system is designed to group patients for specific reasons, such as analyzing clinical or financial outcomes, whereas a nomenclature system seeks to specifically represent clinical findings, therapies, and outcomes in an accepted, standardized format. In reality, there is considerable overlap between classification and nomenclature coding systems. Examples of currently popular coding systems include the *International Classification of Diseases, Ninth Revision, Clinical Modification* of the U.S. Government Printing Office (31), *International Classification of Diseases, Tenth Revision* of the World Health Organization (32), Systemized Nomenclature of Medicine of the College of American Pathologists (33), Unified Medical Language System of the National Library of Medicine (34), Current Procedural Terminology of the American Medical Association (35), and the North American Nursing Diagnosis Association (36).

Data Exchange

Exchange of data in a universal format according to internationally agreed upon standards is much more important now than in the past. Older standards included the ASCII English character set. This has been replaced for the World Wide Web by a more universal standard (ISO-8859-1 Latin-1) that represents non-English characters. For exchange of data that cannot be represented by characters or real numbers, an external data representation standard (XDR) has been introduced. XDR is a language that describes both data structure (metadata) and the data themselves. In the domain of clinical medicine, universal standards have been developed such as Health Level 7 (HL7) that define complex data elements, including not only values for laboratory tests, but also extensive process information. As of this writing, however, the standard that is ermeating the world most rapidly, because of its tie to the World Wide Web, is XML, which was initially envisioned as a universal language for documents but later became recognized as a medium of data exchange. Thus, the new HL7 (version 3.0) will be cast into an XML format. As a result of the U.S. Food and Drug Administration Modernization Act of November 1997, more than 5,000 clinical research trials have been represented in a publicly accessible system (see http://www.clinicaltrials.gov/), with data being provided primarily by National Institutes of Health in XML format.

Database Management Systems

For databases to be useful, they have to be accompanied by a database management system (37), which is a set of computerized programs or algorithms that manage access to the database (38); a user interface by which data entry and retrieval efforts occur; an “analysis module” by which specific patterns for data fields are sought or rejected; and a query engine such as Structured Query Language, which enables users to retrieve, modify, and analyze subsets of data with the aid of standard statistical programs. The ways in which these elements of databases are organized characterize their technical and data architecture.

Kahn (24) outlined seven essential services provided by database management and related systems: (a) data sharing, by which multiple users can have simultaneous access to data over a computer network; (b) data consistency, ensured by error checking and calculated constraints (e.g., no person can have an age of more than 100 or 120 without verification from the user); (c) data security with authorization controls; (d) data protection with backup and retrieval functions in case of software or hardware catastrophes; (e) data timeliness, by which data become immediately available to all those who have access privileges; (f) data standards with data definitions for database entry; and (g) as mentioned above, data use with programs for producing queries, retrievals, and reports.

For clinical data, several additional specialized services are important. Because clinical data and events are nearly universally time-related, use of a query language that recognizes temporal attributes is critical (39). Examples include queries as to how many myocardial infarctions a patient may have had, when the first or last one occurred, and the duration of hospitalization for each; temporal changes in blood pressure; or the severity of the most recent episode of rejection in a heart transplant patient.

Another service of growing importance is database extensibility. Adding new facts—variables—to most existing databases requires change in the structure of the database itself. This imposes at times monumental database maintenance problems, as advances in medical knowledge increase and as the need for cross-disciplinary databases is demanded. A response to this has been academic work in the area of extensible object models and semistructured data (40). These approaches envision “packaging” metadata (structural information about the new data) directly with the values for variables and are described in more detail below.

Database Designs

A *database design* refers to the model that describes which data fields are logically linked to one another (41); the most commonly cited database designs are flatfile, spreadsheet, hierarchical, relational, and object-oriented. The simplest design is a single table of values called a *flatfile*. A flatfile is non–self-documenting, requiring a separate data dictionary to accompany the data file. The next simplest design is the spreadsheet. It is superior to the flatfile in containing not only self-documentation, such as column headings, but also in allowing in-place associations to be established among the data cells themselves. A major limitation of flatfiles and spreadsheets is that they have primarily been proprietary products requiring either export in a more universal form or the definition of a software driver that permits direct communication.

One of the earliest database designs was the *hierarchical* model. This consisted of linkage of multiple collections of similar information into a tree structure, with a root and child nodes like branches and ending with leaf nodes. In effect this model acts as a collection of index cards in which each card has a small number of variables (e.g., demographics) about one patient. A major disadvantage of this database design is that hierarchies are rather arbitrary. For example, one might think of the heart as the root of a hierarchy of the cardiovascular system. However, one could imagine it also in the domains of infectious disease (bacterial endocarditis), developmental disorders, neuroendocrine function, a hierarchy of surgical procedures, and many others. Thus, use of a single hierarchy rapidly becomes limiting. Today, hierarchical database models have been extended to polyhierarchical models, which are of interest in medical nomenclature.

A database model that ties together multiple tables of information provides more flexibility and is called a *relational model*. Relational databases allow for very efficient and powerful storage of large quantities of information (38,42). The multiple tables in a relational database are linked together by user-defined cross-references, or “linking variables” (Fig. 44.1). As an example, a database might be designed to contain a patient’s name and the name of the primary physician. In a hierarchical or flatfile design, the name of the primary physician would have to be individually entered for each patient; thus, the names of physicians who care for more than one patient might have to be entered multiple times. A relational database would have a separate table with the names and characteristics of all primary physicians; thus, when it comes time for the user to enter the name of the primary physician, he or she can simply refer to the primary physician table and, using a “pick list,” click the appropriate name. Data entry is therefore easier and of better quality. The relational database also allows one to modify a data element in one table with assurance that the same data element in other tables will be automatically updated without a need to alter programs that use the data.

ID#	Lastname	Age	Gender	Physician
22005	Jones	45	M	Lauer
22006	Smith	52	F	Fortin

ID#	PCW	PAS	PAD
22005	23	62	27
22006	12	25	13

Physician	Gender	Institution
Lauer	M	Cleveland Clinic
Fortin	M	Duke University

FIGURE 44.1 Schematic of a relational database. Tables are linked to one another by linking variables (in this case, ID# and Physician). Data entry of “Physician” into the first table is made easy by linking to data available in the third table.

Relational databases are, however, static repositories of data. Imagine a database that could note that an entered value for a glucose tolerance test was well above the normal range and therefore set into motion a predetermined sequence of activities, such as paging the physician, printing a diabetic diet based on patient characteristics, discovering a clinical trial of pancreatic islet transplantation, or a host of other functions. This is possible in *object-oriented* databases. Objects contain not only data, but also *instructions* as to what might be done with them given that certain data values are present. A major modern challenge in clinical database technology has been to define an object model of medicine and all its accompanying behaviors.

Although the relational model is the most pervasive in clinical databases today, two other challengers deserve mention: an old technology, *time-oriented* databases, and a new technology, *semistructured* databases. Time-oriented database models have been of interest since at least the early 1980s, particularly in cardiology (43,44). Over the last 10 years, new query tools have been developed, particularly at Stanford University, for exploiting the power of such databases (45).

The other model represents a complete departure from traditional database design: semistructured databases. Semistructured databases permit the self-assembly of an *ad hoc* structured database at the time of an analysis using information embedded in the data elements themselves. This is the exact opposite of the traditional approach to structured databases, in which the database is first assembled and only then is an analysis performed. The semistructured database model provides the most flexibility available today in database design because hierarchical, relational, object-oriented, or time-oriented structured databases can be assembled at the time of selection of variables for analysis or query, depending on the specific needs of that time. Ideas about semistructured databases sprung up simultaneously in several disciplines in the early 1990s, such as that in medicine by Dr. John Kirklin and his colleagues at the University of Alabama at Birmingham and the computer science department of Stanford University (40,46). A query language known as *Lore* for a semistructured database has been developed at which time it was recognized that much of the information on the World Wide Web could be considered semistructured data. In particular, the special extensible object language developed for storing and retrieving semistructured data was discovered to have extensive homology to XML (47).

Data Quality

Missing Data

Rigorously run prospective randomized clinical trials and some multicenter registries have specific mechanisms in place to ensure comprehensive data collection. In most cases, specific people are assigned to collect and document data and others to enter them into the computer, with both of these processes occurring independently of routine clinical care. Observational clinical databases in which data are obtained as part of clinical care are often plagued, however, by missing data, which can seriously affect accurate analyses and development of prediction models (eTable 44.1.1) (27,48).

***e*TABLE 44.1.1** LIMITATIONS OF OBSERVATIONAL DATA

Type of limitation	Description and causes
Missing data	Clerical errors
	Busy practitioners enter data hurriedly
	Patients seek care from outside providers
	Tests and procedures not ordered
	Coding restrictions
	Concept recorded in different field
Inaccurate data	Reliability: inter- and intraobserver consistency
	Validity: data truly represent what they are supposed to measure
Bias	Systemic causes of missing data
	Appropriate covariates not captured
	Definitions of, and therapies for, disease change over time
	Different measurement methods
	Gaming: coding to maximize reimbursement or optimize risk-adjusted outcomes rather than to best reflect clinical reality

Data may be missing for a number of reasons. Subjective data, such as diagnoses, that need to be recorded by a clinician may be missed because of inadequate documentation by busy practitioners (27). Some data may be missed because patients often seek care from multiple providers, who do not enter all data into the same database. One area where this can lead to serious inaccuracies is in the documentation of medications (49). Data that are recorded initially on paper and then entered into the computer as a separate act may be lost for clerical reasons. If a patient's condition does not lead to the collection of certain data, this can lead to missing fields; a common example of this might be coronary anatomy data in patients with chest pain and normal stress tests. In real clinical practice, most of these patients are not referred for coronary angiography. Thus, attempts to analyze the clinical effectiveness of stress testing are inherently limited by a bias related to systematically missing data (50).

Missing data elements can lead to very serious misinterpretations. For example, Iezzoni et al. analyzed an administrative database and found that among patients hospitalized with stroke, myocardial infarction, pneumonia, or congestive heart failure, the presence of comorbidities such as hypertension, angina, diabetes, or valvular disease was associated with a paradoxically lower mortality rate (51). The reason for this finding is that only five diagnoses were permitted on the discharge abstract, and thus the patients with many principal diagnoses were more likely to have less serious comorbid conditions recorded. Others have confirmed this type of problem as well (52).

Data may appear to be missing when in fact a certain concept may be recorded in more than one field. For example, Iezzoni found that the concept of "chest pain" could be found under one of three Medicare Diagnosis Related Groups in an administrative database: chest pain, angina, or atherosclerosis (53).

Methods of Dealing with Missing Data

In any large database, missing data are almost always a problem. Variables with a large amount of missing data may be considered poor-quality variables and should be eliminated from consideration in analyses. For example, some cardiologists may doubt the value of the ejection fraction, preferring an integrative, qualitative assessment of systolic ventricular function. In such an institution, measurements of ejection fraction may be unavailable for a large number of patients. Despite its consistent association with survival, the ejection fraction in these institutions should simply not be considered a variable that can be used with any degree of credibility.

As described by Little and Rubin (54) missing data can be classified into three specific types: (a) *missing completely at random*, in which patients with missing data cannot be in any way distinguished from those without missing data; (b) *missing at random*, in which the pattern of missing data is due to some external cause unrelated to the variable with missing data; or (c) *not missing at random*, in which the mechanism by which data are missing is directly linked to the variable itself. An example of the last case is lack of stress testing data in a patient with cardiogenic shock.

A number of methodologies have been developed for the management of missing data. However, developments in this field have largely involved survey data, where large amounts of missing data are the norm. This is a quite different situation from that pertaining to high-quality cardiologic databases, where investigators are typically faced with a large number of scattered individual holes in the data. Any given variable may have a rather small amount of data missing. However, a large percentage of the patients, sometimes all, may have at least one piece of information missing. It has been argued by some that missing-data strategies must be entirely different in this situation than in the situation in which large volumes of data are missing (55).

As a general rule, entire records of patients or subjects with any missing data should not be automatically deleted. The deletion strategy may be reasonable with survey data but is not reasonable with sporadic scattered missing data, such as occurs in cardiologic databases. The exception to this rule may be missingness of the specific outcome variable of interest—that is, *incomplete follow-up*. Incomplete follow-up, particularly less than 80%, presents serious bias problems, as patients who are lost to follow-up tend to be very different from those who are easily followed—for example, they often turn out to be dead!

Several strategies for dealing with missing data are commonly used. The simplest is mean value imputation, in which the mean value of a particular variable for the entire nonmissing population is substituted for the missing value. Although statisticians often decry this approach, it may well be reasonable when less than 5% of the values for any given variable is missing. A more sophisticated approach is informed mean value imputation. For example, if it is known that a patient with a missing blood glucose value is diabetic, that missing value could be imputed by using the mean blood glucose value of diabetic patients who do not have missing data.

Other more complex imputation schemes include nearest-neighbor matching, imputation from regression equations, and propensity analysis. In nearest-neighbor matching, a missing value is imputed by taking the same nonmissing value from another patient who is otherwise very similar. In propensity analysis a logistic regression model is created that defines the probability that a particular dichotomous variable has a value of yes (or 1) compared with no (or 0); for patients with

missing data, a value of 1 may be imputed if the propensity model finds that the probability that that patient would have had a value of 1 is more than 50%.

Finally, a number of very complex, computer-intensive methods have been developed to account for missing data, either with or without explicit data imputation; these methods may or may not be clearly applicable to the cardiologic database setting. These include Rubin's multiple imputation methodology, which was developed specifically for surveys (56,57) and a companion technique that uses the bootstrap (58). These methods address an important issue in missing-value imputation and management, namely, the preservation of the distributional structure of variables that is disturbed when a large amount of imputation is made using a single value.

Most of these imputation methods implicitly assume the data are missing at random. It may well be true that, instead, there is a systematic pattern in the randomness that may be present. One technique that may be used to determine this is to generate a missing-value indicator that identifies patients or subjects for which data have been imputed for a specific variable. This indicator can be incorporated into multivariable models, both to test the association of missingness with outcome, such as when certain tests cannot be performed because of the dire condition of the patient, and in some sense, to adjust for that systematic missingness. Use of this strategy requires that missingness is associated with at least a few events of interest (five to ten); otherwise no estimate can be made.

Data Credibility

When considering the accuracy of data, one must assess both reliability and validity. *Reliability* refers to how stable or reproducible measurements are. If several independent reviewers code a certain set of measurements or abstract information from a chart in very similar ways, the data can be considered to be reliable. *Validity*, on the other hand, refers to the issue of whether the data represent what they are really supposed to measure. For example, in one database the diagnosis of "myocardial infarction" turned out to be incorrect in 57% of recorded cases (59).

The relative accuracy, in terms of both reliability and validity, of data depends on a number of factors (60). One must consider how and by whom the data are actually collected, codified, and recorded. An ideal situation would be on-line recording of information by clinical providers, but this is often not practical. If data are collected or entered by people unfamiliar with clinical issues, the likelihood of error is increased. The location where measurements are made is important—for example, blood pressure readings would be expected to be more accurate if obtained from a hypertension clinic rather than an orthopedics ward (27). If data are collected from discharge abstract information, validity may be compromised because the severity of diagnoses or conditions is often not coded, coding of clinical events may be clouded by physicians' concerns regarding the recording of complications that may later be held against them in court or by peer review organizations, and data are often based on attestation sheets that are compiled by clerks who do not have physicians' knowledge or have access to a dictated narrative summary of a hospitalization (61).

Good-quality databases require frequent and systematic checks of reliability. Investigators often measure intrarater, and, more important, interrater, reproducibility. A random set of records might be chosen for independent review by two different data collectors/abstractors who are blinded to each other's views and identities. Data are more likely to be reliable when they are collected prospectively by well-trained abstractors who are using standardized definitions and who routinely undergo interrater quality checks (60). Furthermore, computer programs can be written to minimize errors by identifying inconsistencies—for example, a person cannot have a test performed on a date that occurs before his or her birth date. Thus, should a date be entered in error, the database management system can alert the user of a likely data quality problem.

In the construction of databases that assist in obtaining high-quality information, three common mistakes and their remedies should be mentioned. First, to the uninitiated, it is not uncommon for a data field to be populated by more than one atomic value. The remedy is to ensure that every data element consists of only one variable-value pair. Typical examples are spreadsheets in which the investigator has recorded the date of birth and age in the same field, multiple attributes of a mitral valve repair in a single field, or catheter type and size in the same field. Second, investigators may code a variable inconsistently, such as with uppercase versus lowercase letters, abbreviations, misspellings, and the like. To ensure consistency, insofar as possible, pick lists of mutually exclusive and exhaustive values for variables should be constructed from which the investigator chooses the appropriate answer. Among those appropriate answers should be one or more indicators for missing values: The answer may be truly unknown, the information to determine the answer may be unavailable, or information may be insufficient to answer the question with credibility. The third common problem is the practice of physicians to code by exception. This leads to a database design of lists of responses that are not mutually exclusive. Typical examples are so-called multiple pick lists, in which one to several of the responses may be chosen. This practice leads to systematic errors, particularly errors of omission (62). The solution to this problem rests with database design, in which all responses for all variables are mutually exclusive.

WHAT ARE THE USES OF CLINICAL DATABASES?

Fundamental Uses of Clinical Databases

As described by Safran (63), there are four fundamental uses of clinical databases: (a) results reporting, (b) case finding, (c) cohort description, and (d) predictive modeling. *Results reporting* refers to the ability to retrieve information about a specific patient or procedure; this is the type of activity by which practicing clinicians would most often interact with, or at least "seek rewards" from, a clinical data repository. Case finding involves looking for patients with similar problems or outcomes as a patient of interest, often to direct management based on prior individual experiences. Cohort description seeks to simply describe a group of patients or procedures based on a common set of attributes. Finally, prediction modeling involves applying sophisticated analytical methods to describe changes or associations that can lend insight into the natural history of disease processes, the effects of different clinical interventions, and/or quality of care within given institutions or by specific providers. It is this use of databases that presents the most powerful, and perhaps also the most controversial, benefit of computerized clinical information technology.

Case for Outcomes Management

In the 1988 Shattuck Lecture to the Annual Meeting of the Massachusetts Medical Society, Paul Ellwood advocated the nationwide adoption of outcomes management, which he described as a new "technology of patient experience" (27). Work by Wennberg and others (64,65 and 66), which showed tremendous variation of practice patterns without clear differences in patient outcome, has caused the public and third-party payers to demand better-quality information by which the clinical effectiveness of various interventions and providers can be systematically studied. Practice variation is a ubiquitous problem in medicine; within cardiology, recent evaluations of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries database, for example, have revealed marked geographic variation of management of postinfarct patients within the United States and among countries (67,68 and 69), with varying differences in clinical outcomes. In addition to patients and payers, physicians too are frustrated by their inability to accurately and quantitatively predict the impact of their care on patient outcomes, as good-quality data from randomized controlled trials simply do not exist for many common clinical scenarios (70). To help solve these problems, the process of outcomes management would seek to use high-quality data based on real patient experiences to help physicians, payers, and patients make the most rational choices.

Ellwood described four processes by which outcomes management occurs (*e*Table 44.1.2): (a) adoption of database standards and clinical guidelines; (b) routine systematic measurements of patient outcomes at appropriate times (or follow-up); (c) pooling of clinical, outcome, and financial data into enormous databases; and (d) careful analyses and dissemination of results of these analyses to appropriate parties.

***e*TABLE 44.1.2** THE PROCESS OF OUTCOMES MANAGEMENT

Process	Description	Examples
Adoption of standards and guidelines	Standards: allow for comparisons between databases	Standards: *International Classification of Diseases, Ninth Revision, Clinical Modification*; Health Level 7; Systemized Nomenclature of Medicine
	Guidelines: allow for meaningful measurements of impacts of interventions	Guidelines: American College of Cardiology/American Heart Association guidelines on management of acute myocardial infarction
Measurement of outcomes	Uniform follow-up for clinically relevant, objective, unbiased, predefined end points	All-cause mortality
		Quality of life
		Costs of care
Pooling into databases	Data fields determined and defined based on standards, guidelines, likely risk-determining characteristics, and outcomes	See Table 44.3
Analyses and dissemination	Provide for publication and/or appropriate parties along with feedback	Risk-associated mortality
		Assessment of patient risk prior to procedures
		Postmarketing drug surveillance
		Assessment of practice variation in process and outcomes

Type of database	Examples
Population-based studies	Framingham Heart Study Physicians' Health Study Nurses' Health Study Cardiovascular Health Study
Disease-oriented registries	National Registries of Myocardial Infarction Minnesota Heart Survey Duke Databank for Cardiovascular Disease
Technology- and procedure-oriented registries	Cardiac Transplant Research Database United Network for Organ Sharing database National Heart, Lung, and Blood Institute registries on percutaneous transluminal angioplasty and new technologies Northern New England Cardiovascular Disease Study Group Surgeons' National Database Veterans' Affairs Cardiac Surgery Database The Cleveland Clinic Foundation Exercise Stress Laboratory Database
Administrative and abstracted based on administrative databases	New York State Cardiac Surgery database Health Care Financing Administration Cardiovascular Care Project American College of Cardiology
Randomized clinical trial registries	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trials Thrombolysis in Myocardial Infarction trials Coronary Artery Surgery Study Beta-Blocker Immediate Survival Study

TABLE 44.3 EXAMPLES OF DATABASES IN CARDIOLOGY

The enormous databases to be used in the outcomes management process may be organized according to the *clinical model concept* (Fig. 44.2), as described by Steen (71). This model divides clinical encounters into four sets of data elements: (a) patient factors, (b) physician plan, (c) hospital execution, and (d) outcome measures. Patient factors are extremely important to recognize and codify properly, as they represent variables that are related to outcome but over which providers have little or no control. These include specific disease entities, comorbidities, socioeconomic background, compliance, and satisfaction. The physician plan has two major components, namely, an assessment of diagnostic probabilities and an assessment of the urgency of action needed to address them. Between the physician plan and outcomes are hospital execution factors; no matter how excellent a physician's assessment and plan are, if hospital systems fail to respond to them in an efficient and timely way, adverse outcomes may result. For example, an emergency room physician may quickly and accurately diagnose acute myocardial infarction and appropriately prescribe thrombolysis, but if pharmacy, transport, and clerical staff are not properly organized, there may still be significant delays in implementing therapy. Outcome measures include not only standard mortality and morbidity measures, but also "softer" end points such as quality of life and costs of care.

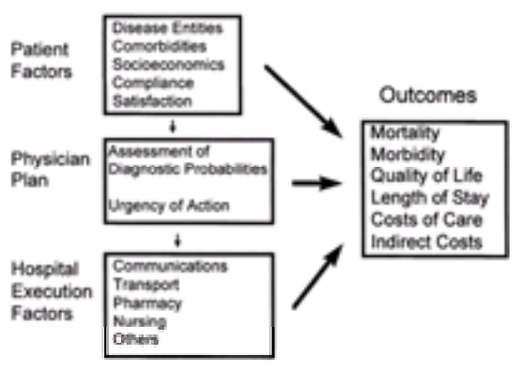

FIGURE 44.2 The clinical concept model. Patient factors, physician plan, and hospital execution factors all play a role in determining patient outcomes.

Analyses of enormous databases can be used to achieve a number of objectives (72). These include assessment of patient risk based on clinical characteristics and medical test results, risk-adjustment assessment of quality of care, postmarketing drug surveillance, assessment of resource consumption, analyzing and improving clinical decision making, identifying and correcting variations in physician practice, and aiding in collaborative clinical research projects.

Why Not Just Use Randomized Controlled Trials to Determine Clinical Effectiveness? Bias and Unexplained Confounders

A major component of outcomes management is determination, based on analyses of large observational clinical databases, of how outcomes are associated with physician plan and hospital execution factors after "adjusting for" patient factors. Some have argued, though, that using observational databases to assess the impacts of therapies or behaviors under physician or patient control is inherently flawed and that randomized trials can appropriately answer these questions (73). This belief is held so strongly that one major textbook on clinical epidemiology (74) recently stated, "If you find that a study was not randomized, we'd suggest that you stop reading it and go on to the next article." Indeed, today the randomized controlled trial is considered by many to be the gold standard method of assessing the relative impact of different therapies.

The main strengths of randomized controlled trials are reviewed by Moses (75): (a) assembly of a single, well-defined inception cohort; (b) elimination of potential biases and confounding, particularly those caused by unknown or unmeasurable factors; and (c) adherence to well-defined clinical care and data collection protocols with vigorous quality assurance and safety mechanisms in place. However, as reviewed by Califf (76), clinical trials suffer from several inherent limitations: (a) they are expensive and sometimes very time-consuming; (b) therapies change such that by the time trial results are reported, new technologies become available that may replace the methods used; (c) many patients, particularly those with comorbidities or the elderly, are excluded; (d) trials are performed more often in patients at tertiary referral centers, raising generalizability questions; and (e) the benefits of a therapy as noted in the ideal conditions of a clinical trial may not necessarily apply to the "real world" of clinical care. Furthermore, some clinical treatment questions simply cannot be answered with randomized trials. For example, a study found that a prolonged door-to-balloon time was associated with a higher mortality among patients undergoing primary angioplasty for acute myocardial infarction (77). It is difficult to imagine that the validity of this finding could be tested by a controlled trial in which patients would be randomized to an immediate versus a delayed angioplasty (70).

Causes of Bias

Although some have found that analyses of clinical databases can lead to conclusions that are consistent with those from presumably unbiased randomized clinical trials (78,79 and 80), the presence of bias remains a major impediment to the widespread acceptance of clinical databases as a valid source of insights on clinical effectiveness (73,75,81). There are many potential reasons for bias. Data that are systematically missing because of patient or condition-specific reasons can lead to serious misinterpretations, as described above. Patients who visit a given health facility less frequently because they are less ill or because they "shop around" for care may have fewer data available (27). Patients may be selected for treatment or interventions for reasons that, no matter how ostensibly comprehensive a database is, are simply not adequately captured. For example, some patients may not receive therapies because they are "too sick," making it appear that healthier patients do worse than they really do after undergoing those therapies. Definitions of disease and the nature of therapies are often unstable over time, making comparisons between time eras difficult (82). For example, both medical and surgical therapies for CAD have changed dramatically over the past 15 to 20 years, making comparisons between them problematic if assessed over long periods. Because of more intensive screening and treatment of coronary risk factors, some patients with milder forms of disease may be identified now, whereas they may have been missed in years past. Measurement bias may occur because patients in different groups have certain variables measured in different ways (83).

Other types of bias are more germane to administrative databases such as Medicare. The federal government asks hospitals to record additional diagnoses that "affect patient care in terms of requiring clinical evaluation, therapeutic treatment, diagnostic procedures, extended length of hospital stay, or increased nursing care and/or monitoring"(84). Such a statement is subject to broad interpretation, especially when considering that hospitals have an incentive to record diagnoses in such a way as to maximize reimbursement. Other administrative or government databases that are used to assess quality of care may suffer from a form of bias known as "gaming," in which the severity and presence of comorbidities that may have an adverse impact on outcome are exaggerated, leading to a form of "clinical inflation" (85). Individual providers would have an incentive to do this to improve their "risk-adjusted" outcomes, but in the aggregate, this practice leads to decreased power of the database.

Risk Adjustment and Measurement of Case Mix

One important method of overcoming bias in observational databases involves developing and applying prognostic risk models to control for severity of illness. Examples of such risk prediction models include the Acute Physiology, Age, Chronic Health Evaluation score (86), the Severity of Illness Index (87), the Charlson comorbidity score (88), the risk prediction model derived from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries study (89), and a measure of prognosis among patients with CAD derived from the Duke Databank for Cardiovascular Disease (90). Using this approach, Duke

investigators have found that conclusions drawn from an observational database compare well with those obtained from randomized controlled clinical trials (91).

Case-mix adjustment (92) specifically refers to identifying patient-specific factors that may explain differences in outcomes among patients cared for by different providers or institutions. The validity of case-mix adjustment has been questioned because of a number of unresolved methodologic issues. The use of diagnoses to describe patient illness may fail to adequately describe risk (93). There is considerable controversy over whether data obtained or measured after a clinical intervention should be included as part of risk adjustment. Some patients are evaluated with more sophisticated technology, which could bias comparisons in that those patients not selected for certain imaging techniques may have major comorbidities missed. The source of data abstraction is also key: Administrative or financial databases, although readily available and large, often do not have the richness of clinical detail needed to make a valid assessment of illness severity or comorbidities (72,93,94). Small numbers of patients with specific diagnoses in individual hospitals may also cloud case-mix adjustments (95).

Overcoming Bias

To correct for systematic (biased) differences between groups, Moses argues that three objectives must be met (75): (a) the sources of bias—that is, the relevant covariates—must be known; (b) those variables must be systematically and uniformly measured; and (c) appropriate statistical techniques must be used to overcome misleading conclusions. A statistical method known as *propensity analysis* (see Modern Multivariable Techniques) has been proposed as a method of assessing unbiased treatment effects in observational studies (96,97 and 98). Nonetheless, the inability to fully identify and describe unknown, unmeasured covariates that may play a major role in why patients or their physicians behave in certain ways is considered by some to doom even the most sophisticated statistical analyses (73). This argument has been used to criticize observational studies with troubling conclusions, as in, for example, reported higher myocardial infarction rates among hypertensive patients taking calcium channel blockers (99), worse outcomes in critically ill patients monitored with pulmonary artery catheters (100), and possibly adverse interactions between aspirin and angiotensin-converting enzyme (ACE) inhibitors in patients with and without heart failure (101). Other reports have suggested that standard adjustment techniques may lead to misleading conclusions about, for example, the quality of care of patients being treated for heart failure (102) or identification of outlier surgeons performing coronary bypass surgery (103).

Randomized Trials and Observational Studies: Empirical Evidence

Even setting aside all the arguments that biases and confounding can be overcome, critics of treatment assessments based on observational analyses point to studies in which observational data inflated positive treatment effects when compared with randomized trials (79,104,105,106,107 and 108). These comparisons were based on studies done in the 1970s and 1980s, when database technology and analytical methods were less developed than they are today. Benson and Hartz performed a systematic comparison of results of randomized trials and observational studies that were published between 1985 and 1998 (79). Figure 44.3 shows their analyses of cardiac treatments based on eight articles; in nearly all cases, randomized trials and observational studies yielded remarkably similar results. The one discrepant comparison involved low-risk patients undergoing bypass surgery or angioplasty; the authors suggested that the unusually low bypass surgery mortality rate in the randomized trial might have explained the difference.

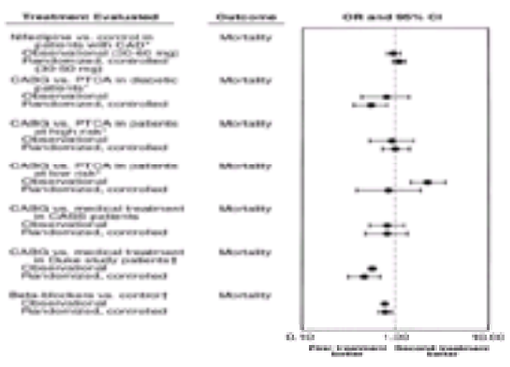

FIGURE 44.3 Results of observational studies and randomized, controlled trials of cardiologic treatments. The figure is based on data from eight articles. *, studies that reported relative risks rather than odds ratios; †, studies that reported neither a confidence interval nor a *p* value for the odds ratio; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CASS, Coronary Artery Surgery Study; CI, confidence interval; Duke, Duke Databank for Cardiovascular Disease; OR, odds ratio; PTCA, percutaneous transluminal coronary angioplasty. (From Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials [see comments]. *N Engl J Med* 2000;342:1878–1886, with permission.)

A similar comparison of randomized trials and observational studies was also reported by Concato and colleagues (80). Based on published metaanalyses, they compared the results of 14 randomized trials and nine cohort observational studies that assessed the impact of treatment of hypertension on occurrence of coronary heart disease events. The randomized trials, which enrolled a total of 36,894 patients, found a positive treatment effect (risk ratio, 0.86; 95% confidence interval, 0.78 to 0.96). The cohort studies, which described a much larger patient sample of 418,343 patients, found a remarkably similar positive treatment effect (risk ratio, 0.77; 95% confidence interval, 0.75 to 0.80). Another comparison of 14 randomized trials and seven cohort studies that evaluated the impact of antihypertensives treatment on stroke again found remarkably similar positive treatment effects; for the randomized trials the risk ratio was 0.58 (95% confidence interval, 0.50 to 0.67), whereas for the cohort studies the risk ratio was 0.62 (95% confidence interval, 0.60 to 0.65).

Incorporating Guidelines into Clinical Databases

Object-oriented database technology presents a whole new potential function for clinical databases, namely, computer-assisted interventions. As previously mentioned, object-oriented databases not only contain data but also instructions of how certain types of data combinations are to be handled; these instructions could well be clinical guidelines, such as those published by the American College of Cardiology and the American Heart Association, on a variety of topics (109,110,111,112,113 and 114). Recent reports on the frequency and dangers of medical errors (115,116,117,118,119 and 120), most of which are primarily due to systems errors rather than individual human failings or negligence, highlight the potential value of using object-oriented databases for providing clinicians with point-of-care information and practical advice. A number of reports have already demonstrated the clinical benefits of incorporating clinical guidelines into computerized clinical databases to generate physician reminders (121,122,123,124,125,126,127 and 128); nonetheless, this process is uncommonly practiced in most institutions.

ANALYTICAL METHODS

Univariable Methods

The fundamental goal of any data analysis is to describe an association between an exposure and an outcome. An exposure could be a treatment or a characteristic, such as cholesterol level, whereas an outcome could be mortality or morbidity or the result of a blood test.

Three analytical approaches are commonly used to establish associations between exposures and outcomes. In a *cohort study,* a group of patients is prospectively assembled and then classified according to the presence or absence of an exposure variable of interest, after which time the patients are followed for the occurrence of an outcome event. In a *case-control* study, patients are selected according to whether or not the outcome occurred and are then compared for the presence or absence of an exposure variable. In a *clinical trial*, a group of patients is assembled and then treatments assigned, typically by random allocation, after which patients are followed for the occurrence of outcome events. In reality, a clinical trial is a kind of cohort study.

When comparing continuous variables between two groups (e.g., blood pressure with and without treatment), commonly used statistical tests include the Student's *t* test when the variables are normally distributed (i.e., follow a gaussian bell-shape curve) and the Wilcoxon rank sum test when an assumption of normal distribution cannot be made. When three or more groups are being compared, the analogous tests are analysis of variance and the Kruskal-Wallis test. The purpose of these statistical tests is to determine whether any apparent association between the exposure and outcome are merely due to chance; the probability that the association is merely due to chance is expressed as the *p* value.

When comparing categoric variables, the commonly used statistical test is the chi-square test, which again determines whether an apparent association between an exposure and an outcome are due to chance. Often it is more helpful to describe the magnitude of difference between groups. This is done by calculating relative risk

differences, absolute risk differences, number needed to treat to prevent one outcome event, and their confidence intervals (see Chapter 43).

Survival Analyses

In survival analyses, the outcome of interest is not only whether a particular patient died or suffered from an adverse event but also the *length of time* until that event did or did not occur. Three mathematical descriptions are often given regarding survival, namely the *survival function*, the *probability density function*, and the *hazard function*. The survival function S(t) is the probability that a person has lived longer than any given time T. The probability density function f(t) is the negative derivative of the survival function. The hazard function is the ratio of f(t) to S(t) [i.e., f(t)/S(t)] and can be thought of as the instantaneous risk of an event, such as death, given that a person is still alive and free of the event at time T.

An important concept regarding survival analyses is that of *censoring*. In a chronic care study, patients are enrolled over a long period, while follow-up must by necessity end on a certain day. Thus, even among patients who survive, the length of follow-up will be variable: Those patients who were enrolled early in the study will have had a long period of follow-up, whereas those enrolled later will only have been followed for a short period. Patients who do not experience an outcome event before the end of follow-up are considered to be censored. Robust survival methods take censoring into account when attempting to link certain exposures to length of time free of an outcome event. Readers who are interested in learning more about censoring and survival analysis methods are encouraged to read elsewhere (129,130 and 131).

Multivariable Methods

Analyses of large clinical databases usually involve multivariable regression techniques. Multivariable regressions are used to develop models by which outcomes can be predicted or to evaluate the impact of particular variables of interest on outcome after considering potential confounding or interaction from other variables. The development of regression models includes four key steps (71): (a) population selection, (b) outcome selection, (c) type of regression, and (d) variable selection. Other critical aspects of model development include formal testing for goodness of fit and validity as well as assessment for possible interactions (132).

The type of regression model chosen depends in large part on the outcome variable of interest. Many analyses are interested in binary outcomes such as death, occurrence of a major nonfatal cardiac event, or readmission to the hospital within a given time. If the outcome is time-independent (e.g., in-hospital mortality, readmission any time within 30 days), then logistic regression is the most common type of model chosen (133). The logistic model seeks to predict outcomes according to a linear equation:

$$\log \text{Odds}_{event} = a + b_1x_1 + b_2x_2 + b_3x_3 + \ldots + b_ix_i$$

where

- Odds = $(\text{probability}_{event})/(1 - \text{probability}_{event})$,
- a = y-intercept,
- $x_1, x_2, x_3, \ldots, x_i$ are variables chosen for the model (e.g., age, gender, number of diseased coronary arteries), and
- $b_1, b_2, b_3, \ldots, b_i$ are "parameter coefficients," which are estimates based on examination of the data relating each variable to the log Odds_{event} after adjusting for all other covariates.

Logistic regression modeling consists of estimating values and standard errors of parameter coefficients based on observed outcomes in a selected data set. Although much of the work of modeling is performed by computers using powerful statistics packages (e.g., PROC LOGISTIC of the SAS System, Cary, NC), the validity of the models developed depend largely on appropriate model specification and variable selection by the investigators. Models can be built in a number of ways, including simple inclusion of all variables, forward or backward selection, and cluster analyses; the method of model building used can have a significant impact on results (134).

When the outcome is time-dependent, such as time free of death or major nonfatal cardiac events, survival analyses are used. The most popularly used multivariable model for survival outcomes is the Cox proportional hazards regression (135). The hazard function of an event describes the instantaneous risk of its occurrence. Cox proposed that if the ratio of the hazard functions between different groups (known as the *hazard ratio* or *relative risk*) can be assumed to remain constant over time, then the hazard ratio can be modeled:

$$\log [\text{Hazard}_{event}(x,t)/\text{Hazard}_{event}(0)] = a + b_1x_1 + b_ix_i + b_3x_3 + \ldots + b_ix_i$$

where $\text{Hazard}_{event}(x,t)$ refers to the hazard function at time t given circumstances $(x_1, x_2, x_3, \ldots, x_i)$ and $\text{Hazard}_{event}(0)$ is the hazard function for a hypothetical patient where all $x_1, x_2, x_3, \ldots, x_i$ are equal to 0. Analogous to the logistic regression model, each parameter coefficient estimates the association between its associated variable and the log of the hazard ratio after adjusting for all other covariates considered. Also, models can be built according to forward and backward selection techniques.

Many situations in clinical cardiology are characterized by rapidly changing hazard functions over time. For example, after myocardial infarction the hazard of death is exceedingly high during the first few days and then rapidly falls (136). Risk factors for death may be also be time-dependent—that is, those characteristics that predict death during the first 30 days after acute myocardial infarction may be quite different than those that predict death from months 2 through 12. One way of dealing with this is to use logistic regression techniques to analyze risk during the early period and Cox regression techniques for late events. However, this approach suffers from establishing an arbitrary cutoff time. Blackstone and colleagues have described a parametric modeling system for describing time-varying hazard functions by decomposing patterns of risk into phases and then systematically assessing risk factors that apply to each of these phases (137). Thus, after myocardial infarction, the first phase would be one of an initially very high hazard with a rapid decline, followed by a prolonged phase of relatively constant hazard. The use of this type of multivariable analysis in the hazard function domain has been used extensively, for example, to describe risk of death (21) and rejection after cardiac transplantation (138).

When the outcome of interest is a continuous variable, such as length of stay or cost of care, linear regression techniques are often used for predictive modeling:

$$\text{Outcome} = a + b_1x_1 + b_2x_2 + b_3x_3 + \ldots + b_ix_i$$

Linear regression models are derived using the "least squares technique," by which parameter estimates are derived that minimize the squares of the differences between actual and predicted outcome values.

Problems with Multivariable Models

Multivariable regression, when properly performed, allows for powerful analyses of large datasets. However, failure to consider inherent limitations and assumptions on which the models are built can lead to serious misinterpretation or invalid results (Table 44.2). Serious error can result from a number of problems: (a) model overfitting, (b) inappropriate use of a linear model, (c) violation of proportional hazards, (d) failure to test for interaction, (e) inappropriate variable selection techniques, (f) colinearity of variables, and (g) excessively influential observations (139).

Type of limitation	Description and possible solutions
Model overfitting	Too few outcome events for number of covariates Use no more than one covariate per ten events
Inappropriate linear assumption	Linear model incorrect Test with goodness-of-fit or examination of residuals Use nonlinear techniques or transformations
Violation of proportional hazards assumption	Ratio of hazard function between groups fails to remain constant over time Use hazards analyses Time interaction terms Divide into arbitrary time periods
Failure to account for interaction	One or more variables may modify the strength of association between outcome and another variable Incorporate interaction terms in analyses
Inappropriate variable selection	Forward and backward analyses may not reflect clinical reality Important covariates missing Consider sequential models, principal components/cluster analyses
Colinearity	Covariates closely associated with one another Test with variance inflation factors or cross correlation matrices
Excessively influential observations	Formally test

TABLE 44.2 LIMITATIONS OF MULTIVARIABLE ANALYSES

Model overfitting is a common error in which the number of outcome events is too few for the number of covariates considered (132). If there are very few events, the parameter coefficients derived from a regression model are inherently untrustworthy, with the risk for poor precision of estimation or, worse, detection of outright spurious associations. It has been proposed that there must be at least 10 outcome events for each covariate considered for a model to be considered valid (132,140).

Most multivariate regressions use linear models to estimate outcome, but often the risk of events does not follow a linear gradient. For example, a change in ejection fraction from 60% to 50% does not have the same prognostic significance as a change from 40% to 30%. Formal methods exist for confirming the appropriateness of linear models (133); nonlinearity can be examined by performing logarithmic transformations on independent and/or dependent variables or by incorporating quadratic or other exponential terms in the model.

The proportional hazards model of Cox is dependent on the assumption that the hazard ratio remains constant over time. This assumption is sometimes not valid. For example, a comparison of medical and surgical therapies for coronary disease might find that during the first month of follow-up, surgical therapy carries a worse survival because of perioperative complications. However, after the end of the first month, surgical therapy might be associated with a better survival. A Cox model that includes both periods of time would be invalid because the hazard ratio relating surgical to medical therapies changes markedly during the first few months of follow-up. Formal methods have been derived to test the proportional hazards assumption (129,130 and 131,141,142).

Interaction is an exceedingly important phenomenon that is often ignored. When the strength of association between an outcome and one particular variable is affected, the level of another variable, “effect modification,” or interaction is present. For example, heparin dose is associated with risk of bleeding in most patients, but this association is much stronger in lower-weight patients than in obese patients. In this case, there is an interaction of body weight with heparin dose regarding the outcome of bleeding risk. Unlike confounding or bias, which potentially can invalidate an apparent association, interaction is of great clinical interest and should be actively sought by investigators when developing multivariate models.

Statistical software packages offer investigators forward or backward variable selection techniques by which the computer inserts or deletes variables from models based on the relative strengths of association between them and the outcome. Although attractive on the surface, forward and backward selection often do not take into account biologic sensibility in constructing models and thus may lead to misleading results. “Principal components” and cluster analyses are approaches by which stepwise approaches can be made to better approximate biologic reality (143).

Regression models are all based on the assumption that all covariates exist independently of one another; in real life, this is almost never the case. Models can yield highly imprecise or even nonsensical parameter estimates when high degrees of correlation, or “multicolinearity,” exist between covariates. For example, measures of ejection fraction and cardiac output may be highly correlated.

Regression models are sometimes heavily influenced by a small number of observations that have extreme values for certain variables. Subjects with extreme values, such as exceedingly long lengths of stay after surgery, are known as *outliers*. It is often not clear how best to handle outliers, as sometimes they are reflective of clinically important events. Outliers may be excluded from analyses, but it is not enough to just use statistical techniques to show that a particular observation is an outlier; appropriate biologic justification is essential. For example, an analysis of blood pressure and left ventricular mass may be excessively influenced by one patient with hypertrophic obstructive cardiomyopathy. Because we understand this disorder to be biologically distinct from hypertensive heart disease, it may well be appropriate to exclude such an outlier. Another related problem, important to analyses of quality of care, is that multivariable models tend to overestimate risk among low-risk patients and underestimate risk among high-risk ones (144).

Model Validation Techniques

Even when the above problems are appropriately avoided or dealt with, multivariable models may still not be valid predictors of outcome. Several different types of validity need to be considered (60). *Face validity* refers to the clinical sense that a model has. For example, many models of risk of valve surgery do not include endocarditis as a covariate because in many series this is a relatively uncommon occurrence. Nonetheless, most surgeons would argue that endocarditis is an important predictor of outcome. *Content validity* depends on the appropriate and complete selection of covariates that are related to outcome. Closely related to this is *attributional validity*, which relates to whether an apparent independent association between a variable and an outcome is really true or whether it is confounded by a covariate that was not considered in the model. Thus, different “risk-adjusted” outcomes among different operators may be real or may exist because not enough variables were considered for adequate risk adjustment.

Predictive validity refers to how well a model actually predicts outcome. Within the database studied, there are formal methods for testing the ability of a multivariate model to accurately discriminate high-risk subjects from low-risk subjects. For example, for a binary, time-independent outcome in a logistic regression model, the c-index, or area under the receiver operating characteristic curve, is often reported: A value of 1.0 implies perfect discrimination, whereas one of 0.5 is consistent with nothing better than random chance. Hosmer and Lemeshow (133) have derived a “goodness-of-fit” statistic that tests the validity of logistic models. The predictive validity of linear regression models can be measured using the model R^2 statistic: This reflects what proportion of the variance of the outcome variable can be explained by the variables included in the model. For example, many models of left ventricular mass in populations report R^2 values of well under 0.5, suggesting that many of the important determinants of this variable are either not known or not yet accurately measured.

Another dimension of predictive validity is how well a regression model predicts outcomes in datasets different from that upon which it was derived. For example, one can study a series of coronary interventions and come up with a prediction model of adverse events. To test the validity of the model, it can be used to predict the likelihood of events in a different set of patients. Some investigators will formally report results from “test sets” and “validation sets,” which are two entirely different groups of patients from which multivariate predictive models are derived and then tested. There are also methods, such as the “jackknife” and “bootstrap,” by which model derivation and validation can be performed on the same dataset (145).

Modern Multivariable Techniques

Because of the recognized limitations of standard multivariable techniques, several newer methods have gained popularity among clinical investigators and biostatisticians. *Propensity analysis* is a technique by which a new variable, called the *propensity score*, is derived from a logistic regression model where the exposure variable becomes the dependent variable (96,97 and 98). As an example, in a study relating delayed door-to-balloon time to increased mortality among patients undergoing primary angioplasty for acute myocardial infarction, the investigators modeled the likelihood of having longer than a 2-hour delay (77). The result of this modeling is that for each patient a probability of having a delayed door-to-balloon time could be calculated and incorporated into multivariable models. Propensity analysis has been shown to analyze and adjust for baseline differences much more effectively than standard multivariable methods (98).

Information theory attempts to identify optimal models by considering both the number of variables considered in a model and the model’s goodness of fit to a particular data set (146). For any given data set, the more variables a model has, the closer the model will fit the data, but this comes at the expense of modeling peculiarities of the specific data set that are unlikely to be true of data sets elsewhere. When information theory is used, multiple candidate models are considered based on prespecified biologic knowledge and then a calculated value, such as the Akaike Information Criterion (147), is used to identify the best model (146).

In a number of settings, the search for insight into mechanisms and outcomes of disease by explicit biomathematical or biostatistical modeling may be subservient to the need to classify. Should the patient be catheterized, be operated on, be withdrawn from therapy, be expected to have a prolonged stay, or be managed as if convalescence were proceeding normally after operation? Classification problems such as these have been approached by biostatistical methods, such as optimal classification tree methods (148,149,150 and 151). However, alternative analytical methods have been developed in the disciplines of computer science and applied mathematics that may perform better or at least equivalently. One such method is *artificial neural networks*.

An artificial neural network can be thought of as a potentially time-varying, adaptive, complex, nonlinear mapping from the input variable space (patient characteristics, measurements, attributes) to the output class space. The mapping is often termed the *transfer function*. This transfer function is generally, although not necessarily, a “black box” consisting of hidden layers of weighted combinations of variables (152). In direct comparisons of traditional statistical modeling versus artificial neural networks, classification results have tended to be similar (153,154 and 155).

DATABASES IN CARDIOLOGY

Many cardiology-oriented clinical databases have been developed and are actively used today. This section is not meant to be exhaustive; it provides a brief summary of how some of these databases have been developed and are being applied. Cardiology databases can be roughly divided into five major types: (a) population-based epidemiologic studies; (b) disease-oriented registries; (c) technology- and procedure-focused registries; (d) administrative, financial, and government-sanctioned databases that relate to cardiac issues; and (e) databases derived from randomized clinical trials (Table 44.3).

Population-Based Studies

Framingham Heart Study

The Framingham Heart and Offspring studies are prototypic population-based cardiovascular epidemiologic databases (1,2,3,4 and 5,156). The original cohort consisted of 5,209 adults between ages 18 and 62 years. Since the late 1940s this group has been invited back every 2 years for serial examinations that have consisted of a detailed medical history, physical examination, electrocardiogram, laboratory studies, and imaging studies. In the 1970s, offspring and spouses of the offspring of the original cohort formed a second group of approximately 7,000 adults for the Framingham Offspring Study. This group has been invited for follow-up examinations every 4 years. One of the major strengths of the study has been the nearly complete follow-up with high-quality descriptions of outcome events. Over the past few decades new technologies have been incorporated into the study, including echocardiography, exercise testing, Holter monitoring, heart rate variability analyses, carotid Doppler studies, and sophisticated genetic tests.

The concepts of risk factors, or characteristics that define high-risk subsets of populations initially free of disease, and multivariate risk formulation, according to which risk could be attributed to multiple risk factors, were first coined by Dawber and Kannel (156) and have been extensively developed over several decades. Despite criticism of the epidemiologic method (157,158), work derived from the Framingham Heart Study database has formed the foundation for much of our understanding of the nature of atherosclerotic cardiovascular disease. The epidemiologic method continues to be a valid source of valuable insights in the 1990s, as evidenced, for example, by recent Framingham Heart Study work in the areas of lipid abnormalities (159), homocysteine metabolism (160), risk factor clustering (161), echocardiographic left ventricular mass (162), coronary heart disease risk prediction instruments (163), and mortality risks associated with atrial fibrillation (9,164). As an example of the ongoing power and relevance of the Framingham Heart Study, independent investigators recently found that the Framingham risk prediction instrument accurately identified absolute coronary heart disease risk in a cohort of British hypertensive men (165).

Physicians' and Nurses' Health Studies

The Physicians' Health Study was originally conceived as a randomized trial of aspirin and b-carotene for prevention of coronary heart disease events and cancer among 22,071 male physicians aged 40 to 84 years (164). The aspirin part of the trial was stopped prematurely due to a marked reduction in coronary events among those participants randomized to aspirin (166). However, the database derived from the Physicians' Health Study has been quite comprehensive and has been used to examine a number of issues, including the prognostic importance of endogenous tissue-type plasminogen activator (167), homocysteine (167), C-reactive protein (168), fibrinogen (169), ACE gene polymorphisms (170), adhesion molecules (171,172), and lipoprotein(a) (173).

The Nurses' Health Study was started in 1976 as a prospective study of 121,700 female registered nurses aged 30 to 55 years (174). A questionnaire was sent to the nurses covering information about age, weight, height, smoking, cardiac history, reproductive history, drug use, dietary and other lifestyle habits, and other factors. Every 2 years, subjects were sent a repeat questionnaire to update their data. The Nurses' Health Study database represents a very large population sample of women; very good quality follow-up, careful verification of outcome events, and large numbers of outcome events have allowed for a number of powerful analyses. The database has been used to examine the importance of obesity (175), smoking (176), and lack of postmenopausal hormone replacement (18) as cardiovascular risk factors in women (19,177). Recent work from the Nurses' Health Study has included reports on the prognostic significance of whole grain, saturated fat, nut, dietary fiber, and egg consumption (178,179,180,181,182 and 183); weight cycling (184); abdominal adiposity (185); use of calcium channel blockers for hypertension (186); intake of folate and vitamin B_6 from dietary sources and supplements (187); and physical activity (188,189).

Cardiovascular Health Study

The Cardiovascular Health Study is a population-based study of coronary heart disease and stroke among adults aged 65 years or older. This database has been developed because of the well-documented aging of the U.S. population and the fact that much of the morbidity and mortality associated with cardiovascular disease occur among older adults. By routinely performing diagnostic studies among asymptomatic elder adults, the database is designed to learn more about "subclinical" cardiovascular disease and its association with overt clinical events, as well as to learn more about conventional and hypothesized risk factors for cardiovascular disease. The cohort includes 5,201 ambulatory subjects who were recruited in 1989 and 1990 from four field centers: Forsyth County, North Carolina; Sacramento County, California; Allegheny County, Pennsylvania; and Washington County, Maryland, with the coordinating center located at the University of Washington, Seattle. Cohorts were assembled by random sampling from Medicare eligibility lists. Examinations included detailed home health, dietary, and psychosocial interviews as well as measurement of blood pressure, height, weight, physical activity, functional status, and neurologic function; spirometry; electrocardiography; echocardiography (190); carotid ultrasonography; and blood laboratory studies. Early reports from this study yielded valuable insights on cardiovascular in the elderly, with, for example, reports on the population prevalence of atrial fibrillation (191) and on determinants of left ventricular mass (192). Recent reports have addressed the prognostic importance of aspirin use (193), silent myocardial infarction (194), ankle-arm index (195), daytime sleepiness (196), and carotid artery intima and media thickening as detected by ultrasound (197).

Disease-Oriented Registries

Myocardial Infarction Registries

The National Registry of Myocardial Infarction was organized in 1990 as a postmarketing survey of the treatment of myocardial infarction in 1,073 U.S. hospitals (198). Participation in the study is voluntary, although hospitals are encouraged to enter data on consecutive patients irrespective of presentation or treatment. For each patient, a simple one-page form is filled out and sent to a central data coordinating center; the form covers demographics, presentation of illness, electrocardiographic findings, treatment, clinical course, including complications, and status at time of hospital discharge. To ensure data quality, all data abstractors undergo training, and internal computer audits are present to check for inconsistencies, missing data, and out-of-range values. In the first 3 years of activity, the registry recorded data on 240,989 patients with acute myocardial infarction. The database was first used to examine treatment patterns in clinical practice outside the settings of clinical trials (175), use of thrombolytic drugs in elderly patients (199), and the association between thrombolytic therapy and myocardial rupture (200). Recent work from this registry and from its successor, National Registry of Myocardial Infarction 2, which now includes close to 1 million patients, has included reports on prevalence of primary angioplasty (201,202), door-to-needle time (203,204), door-to-balloon time (77), bundle branch block (205,206), myocardial infarction without chest pain (207), procedural volume and outcome (208), economics of myocardial care (209,210), risks for intracranial hemorrhage (211), early use of ACE inhibitors (212), seasonal distribution of myocardial infarction (213), and outcomes in blacks (214) and women (215).

Duke Databank for Cardiovascular Disease

A prospective database on patients referred for diagnostic and therapeutic cardiovascular procedures has been in place at Duke University since the early 1970s (16,126). One of the original goals of the database was to help physicians better care for patients by examining prior experience in a systematic manner. The database eventually broadened to include information on patients with suspected coronary disease as well as to incorporate a medical record system used for routine clinical care (16). Currently, the database functions in administrative, research, and clinical care arenas. Reports from the Duke Databank for Cardiovascular Disease cover a vast array of topics, including exercise treadmill testing (216) and prognosis of CAD patients treated with different modalities (217,218 and 219). One important study compared survival rates with medical therapy, coronary angioplasty, and coronary artery bypass grafting in 9,263 patients who were followed for a mean of 5.3 years, during which there were 1,665 deaths (220). The large number of outcome events allowed for detailed Cox proportional hazards analyses, which identified that only nine baseline characteristics were predictive of death. Ejection fraction, age, and coronary anatomy were the three most predictive factors. After considering these characteristics, the authors then identified patient subsets that had better outcomes with angioplasty and other subsets with better outcomes with coronary artery bypass grafting.

Technology- and Procedure-Oriented Registries

Cardiac Transplantation Databases

The Cardiac Transplant Research Database was initiated in 1990 when 25 major cardiac transplant centers agreed to share data on the clinical characteristics and

outcomes of patients undergoing cardiac transplantation. Each center was responsible for completing coded forms and sending them to a central data processing center at the University of Alabama at Birmingham. During computer entry, all data were checked for validity with range and inconsistency checks, and all missing or "suspicious" data elements were forwarded back to the original centers for correction and completion. During the first 18 months of operation, data on 911 patients were collected and used to identify risk factors for death after heart transplantation (21). This database has subsequently been used to rigorously study a number of issues related to outcome after heart transplantation, including donor-specific characteristics associated with outcome (221), pretransplantation risk factors (138), influence of human leukocyte antigen mismatching (222), risks for late recurrent rejection (223), and impact of trends in practice on outcome after transplantation (224). The Cardiac Transplant Research Database has been used to develop predictive software by which clinicians can very quickly compare potential transplant recipients to previous recipients to predict long-term outcome and thereby use the database to make more efficacious point-of-care decisions (225). Recent reports have addressed cardiac allograft vasculopathy (226) and the prognostic importance of pretransplantation body mass (227).

Angioplasty and Percutaneous Revascularization Registries

The first percutaneous transluminal coronary angioplasty was performed by Gruntzig et al. (228) in Zurich, Switzerland, September 16, 1977, with data on four patients presented at the American Heart Association meeting in November of that year. Less than 2 years later, in March 1979, the National Heart, Lung, and Blood Institute established a percutaneous transluminal coronary angioplasty registry through which a centralized accumulation of data obtained from multiple centers would allow for a rapid and systematic assessment of procedure-related outcomes (20). The registry collected data on 3,248 patients who underwent angioplasty at 105 different centers between 1977 and 1981; after September 1981, consecutive cases were no longer recorded. In 1985, 15 centers that contributed to the original registry cooperated to form a second registry that recorded data on all patients undergoing angioplasty between August 1985 and May 1986.

The structure of the original registry has been described by Mullin et al. (20) and is illustrative of the multidisciplinary team approach required for a database to be successful. The overall administration and policy making for the registry came from the Cardiac Diseases Branch of the National Heart, Lung, and Blood Institute Program Office. A steering committee, made up of both elected and appointed investigators, met several times a year to review policy and scientific direction. Collection, verification, storage, and analysis of all data were performed at a central data-coordinating center at the University of Pittsburgh.

Because of the increasing use of new devices, particularly coronary stents, a new registry known as *New Approaches to Coronary Intervention* was established with the aid of the National Heart, Lung, and Blood Institute in the early 1990s (229,230). This database has been used to study a number of important issues, including the association of use of new technologies with outcome (229), coronary artery size (231), and the impact of race (232).

Cardiac Surgery Databases

In 1986, the Health Care Financing Administration encouraged public release of crude mortality statistics for coronary bypass grafting (233). Because of concern that administrative and financial databases that were being used to assess mortality after coronary artery bypass grafting did not have the richness of clinical detail to provide fair, risk-adjusted measures of outcome, a number of groups assembled clinically oriented databases. The Northern New England Cardiovascular Disease Study Group collected data since 1987 on more than 60,000 patients undergoing coronary bypass surgery in the five northern New England hospitals performing the procedure (234,235 and 236). Data were collected on demographic data, cardiac and angiographic variables, priority of surgery, and comorbidities using the Charlson comorbidity index (88). Results of interim data reports are given to participating centers and surgeons in the hope that feedback will result in changes of processes that can lead to better outcome. The study group has noted improvements in risk-adjusted mortality and in reducing costs, improving patient satisfaction, and matching patient expectations with outcomes (237,238 and 239). Recent publications from this database have included reports on operator volumes and outcomes (240), obesity (241), preoperative aspirin use (242), and mediastinitis (243).

In 1989, the Society of Thoracic Surgeons established a national database for cardiac surgery (244). It may well be the largest cooperative database of its kind in medicine, with more than 500 participating sites and more than 1.5 million patients. The national data warehouse and analysis center are located in the Duke Clinical Research Institute. The database is voluntary, and in the first 10 years of its existence, data have largely been acquired from community-based cardiac surgery practices and only a few university-based academic practices. Because of its political clout and the adoption of its data elements for statewide and payor quality initiatives, its generalizability has become greater as academic institutions have joined its ranks.

The major strength of the Society of Thoracic Surgery database is in very high numbers. However, to attract continuing participation, the number of data elements collected from participants has been reduced to a core number that appear to influence outcome, and for the most common operations. Recent major publications have focused on risk adjustment, logistic regression models of early risk after coronary artery bypass grafting (245), and cardiac valve replacement (246).

The Cleveland Clinic Foundation Stress Laboratory Database

Beginning in September 1990, all patients undergoing stress testing at The Cleveland Clinic Foundation had their medical histories, medication lists, and exercise test results entered prospectively and immediately on-line into a computerized database (247,248). An early application of the database was to assess whether an association exists between exercise hypertension and angiographic severity of coronary disease (249). By linking stress test results with the Social Security Death Index (250,251), the database has been used to describe the prognostic importance of a number of exercise test findings, including exercise capacity (248), chronotropic incompetence (252), and an attenuated heart rate recovery (253,254).

Administrative, Financial, and Government Databases

New York State Cardiac Surgery Database

Beginning in 1989, all centers performing coronary artery bypass grafting in the state of New York were required by the New York State Department of Health to provide data on a quarterly basis on all patients undergoing the procedure; with these data, risk factors for death and the calculation of hospital-based adjusted mortality rates were reported (255). Each hospital was provided feedback regarding its own actual and expected mortality rates. After 4 years, a significant reduction in risk-adjusted mortality was noted (256), with subset analyses suggesting that the improvement in outcome may have been related to centers responding to data reports by making positive changes in personnel and processes (257). At one cardiac surgery program with a very high reported risk-adjusted mortality, initial frustration with the database gave way to a careful, systematic evaluation of outcome at that center (258). The program directors were able to identify the primary source of their high mortality rates, namely, emergency cases, especially those with recent acute myocardial infarction. They deliberately worked to change the processes by which these patients were managed, with many more patients receiving intraaortic balloon pumps before going to the operating room. Since making these changes, this program has noted a marked decline in its risk-adjusted mortality. Other investigators have suggested, however, that the apparent improvements in outcome since the establishment of the database reporting system may be more due to rejection of high-risk patients, with some of them being referred out-of-state to other centers (257,259).

The story of the New York State Cardiac Surgery Database took an interesting twist in 1991, when *Newsday*, invoking the Freedom of Information Act, successfully sued the New York State Department of Health for surgeon-specific mortality data (260). Since then, operator-specific mortality data have been publicly released yearly, with each surgeon assigned a risk-adjusted mortality rate and a notation as to whether that mortality rate is statistically better, the same, or worse than average. Interestingly, the public release of surgeon-specific mortality data has had little impact on cardiologists' referral patterns (261). Topol and Califf (262) point out that the extension of traditional risk-adjustment data modeling methods to individual operators, or "scorecard medicine," raises a number of concerns, including (a) failure to account for outcomes other than mortality; (b) difficulty establishing an appropriate reference group; (c) limited sample sizes with small numbers of outcome events for each surgeon; (d) difficulty with risk adjustment and appropriate weighting of variables, as well as "rewarding" operators for taking on very high-risk patients; and (e) logistical problems with proper collection and maintenance of costly data. The American College of Cardiology has already taken steps to address these problems not only through the publication of guidelines but also through the establishment and maintenance of a national database of cardiac procedures (263).

Medicare, the Health Care Financing Administration, and the Cardiovascular Care Project

The process by which Medicare monitors and attempts to improve quality of care among its beneficiaries has undergone a marked change during the past 5 to 15 years, with less emphasis on identifying and removing "bad apples" and more on affecting mainstream care processes (61,264). The Cardiovascular Care Project represents an effort by many different physicians, health service researchers, and professional societies to identify and measure a variety of "quality of care indicators" for patients presenting with acute myocardial infarction and for those undergoing myocardial revascularization. Examples of quality indicators for acute myocardial infarction include percentage of eligible patients receiving therapies such as aspirin, thrombolysis, ACE inhibitors, and beta-blockers; percentage of smoking patients who receive smoking cessation counseling; and percentage of patients who undergo or are scheduled to undergo some form of stress testing or cardiovascular imaging at the time of discharge. A four-state pilot study from this project reported multiple opportunities for improvement among Medicare myocardial infarction patients (265). A number of important reports about quality of myocardial infarction care (266,267) have more recently appeared based on this database, including publications about why "America's best hospitals" have lower myocardial infarction mortality rates (268), the importance of physician specialty (269), the use of

beta-blockers (270,271), and the impact of mental illness on the use of cardiovascular procedures (272).

Databases Derived from Randomized Clinical Trials

Although randomized clinical trials are designed to answer specific therapeutic questions, investigators often use them to assemble large observational databases that can be used to study natural history, prognosis, diagnostic questions, and outcomes related to interventions other than those tested. A prototypical example of this is the Coronary Artery Surgery Study, from which a large database was created of 24,959 patients with suspected or known coronary disease who were admitted to one of 15 clinical centers between 1974 and 1979 (273). Although the study results regarding the impact of coronary bypass surgery were published nearly 15 years ago (274), the database emanating from that study continues to provide insight regarding the prognosis of patients with coronary heart disease (275). Some clinical trial registries, such as that of the Studies of Left Ventricular Dysfunction, include patients who were not included in the trial itself (276). Other examples of clinical trial registries being used as observational databases for answering questions unrelated to the trial itself include an analysis of gender and management of acute myocardial infarction from the Myocardial Infarction Triage and Intervention Registry (277); an analysis of the impact of race, age, and sex on management of unstable angina from the Thrombolysis in Myocardial Ischemia III Registry (278); and an analysis on the impact of elevated blood pressure on presentation mortality and stroke outcomes after acute myocardial infarction from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Registry (279). More recent observational studies based on clinical trial databases include reports on the combination of aspirin and ACE inhibitors in patients with coronary disease (101) and on the impact of diabetes and lesion characteristics among patients undergoing myocardial revascularization (280).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Formally organized databases have existed in cardiology for more than 50 years, even predating the modern computer age. The last 5 to 10 years have witnessed an explosion in database numbers and sizes, such that very large databases now exist in virtually all areas of clinical cardiology. The use of these databases to analyze the importance of patient characteristics and clinical test results for predicting long- and short-term risks is well-established. In the realm of therapeutics, however, there remains considerable controversy, with some strongly believing that the real-world effects of drugs and procedures can be validly assessed by careful analyses of observational databases, whereas others argue that therapeutic effectiveness and safety can only be measured with randomized, controlled trials. There will always be skepticism of database models that describe risk-adjusted outcome, especially for those individuals and institutions where the outcomes appear to be poor. Clinical science is very complex, and clinical knowledge continues to explode; thus, one can always argue that case mix can never be wholly adequately adjusted for. Improvement of analytical methods and ways to identify and adjust for bias and confounding must remain a high priority within the clinical database and research communities.

Once it is widely accepted that, when properly analyzed, observational databases can be used to assess the impacts of treatments on outcomes, it will then become, we believe, incumbent on the cardiology community to implement Ellwood's technology of experience into routine clinical care. This means careful design and universal use of computerized patient records as well as computerized recording of the nature and outcomes of all cardiac procedures. Considerable investment will be required to purchase hardware and software; employ support personnel; and train and support clinical researchers who will have the skills, enthusiasm, time, and resources needed to appropriately analyze observational databases and disseminate their results. The existence of large databases, along with the rapidly improving technologies to develop, store, manipulate, and analyze them, means that we owe our future patients nothing less.

THE FUTURE

The future of clinical databases in clinical cardiology is uncertain. Academic cardiologists will likely continue to nurture and develop population-based, disease-oriented, and procedure-oriented registries, and these will continue to provide new and valuable insights into the nature and optimal management of cardiovascular disease. Some of these databases are growing to truly humongous sizes, allowing for previously unimagined statistical power. Professional societies, such as the American College of Cardiology, are also actively developing databases for outcomes assessment. However, it is very unclear how computerized databases will be used at the level of routine clinical care. It is hoped that academic and clinical leaders will successfully champion the enormous benefits of the "power of information." One cardiac surgeon who has successfully used a clinical database to improve his outcomes may have seen the future: "'Playing by the numbers' has radically changed the way people involved think about their jobs. We have moved from feeling out of control to feeling in control, from being reactive to being proactive, and from not knowing to beginning to know" (237).

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MEDICAL ERRORS AND QUALITY OF CARE IN CARDIOVASCULAR MEDICINE

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OVERVIEW

Quality of care is linked with achieving the best outcomes for patients, but the term is a complex one that can mean access to care, the appropriateness of procedures or tests, absence of errors, or patient satisfaction level. It is difficult to measure, particularly when one deviates from using mortality as the principal outcome, because of the intrinsic difficulties of risk-adjustment modeling. Despite some of these limitations, the use of “report cards” or “scorecards” is more commonplace than ever for evaluating managed care organizations, individual hospitals, and, in some cases, even the physicians themselves.

Much is being done to improve the methodology of assessing quality, and this will help make the process more acceptable and meaningful. One of the major issues that has emerged is the remarkable expense required to collect data at community and academic centers for such analytical work to be performed. For several cardiovascular procedures and diagnoses—including coronary artery bypass grafting (CABG), percutaneous transluminal coronary intervention (PCI), and acute myocardial infarction (MI)—the relationship of volume to operator or hospital has turned out to be a pivotal index for outcomes. Consistently, across the procedures and diagnoses, low volume reflects suboptimal quality. Although one solution is to regionalize centers (“centers of excellence”), an alternative is to have risk-adjusted modeling data available to secure the level of care provided by low-volume operators. Mortality is only one outcome that needs to be considered and, although easier to measure, should not override key morbidity outcomes such as stroke, MI, or functional status. On the other hand, the best measurement of overall quality related to outcomes may be considered the total mortality of the population seen in a health system rather than the mortality for a particular segment such as bypass surgery or acute MI. The focus on medical errors by the Institute of Medicine (IOM) report in 1999 brought these issues to the forefront (1,2,3,4 and 5). For the field to further evolve, report cards of the report cards will need to be assessed on a frequent basis. A major objective in the field is to drive quality to an unprecedented high level.

HISTORICAL PERSPECTIVE

Although the quality of medical care has been considered since the beginning of the medical profession, Florence Nightingale is generally credited with the fundamental insights in her book *Notes on Hospitals*, published in 1863 (6). In this review of hospitals in London and the United Kingdom, she noted a 91% death rate in the 24 hospitals in London as compared with 40% in 55 county and regional facilities. She recommended sweeping changes in operation and location of the London hospitals and was a veritable pioneer to advance the quality of medical care (6,7). Her vision of the field is well exemplified by her writing:

> Accurate hospital statistics are much more rare than is generally imagined, and at best they only give the mortality which has taken place in the hospitals, and take no cognizance of those cases which are discharged in a hopeless condition, to die immediately afterwards, a practice which is followed to a much greater extent by some hospitals than others.
> We have known incurable cases discharged from one hospital, to which the deaths ought to have been accounted and received into another hospital, to die there in a day or two after admission, thereby lowering the mortality rate of the first at the expense of the second” (6).

Ironically, nearly 135 years later, we are still coping with many of the same issues—suboptimal data collection, lack of adequate follow-up, interhospital transfer of high-risk patients who do not “show” on report card instruments, and less-than-expected accountability.

In 1914, Ernest Amory Codman, a surgeon in Boston, formed his own hospital known as End-Result Hospital, based on the philosophy that hospitals should study their mortality rates and that hospitals with the lowest adjusted mortality should be able to charge the highest rates (8,9). He told the Philadelphia Medical Society the following:

> We must formulate some method of hospital report showing as nearly as possible what are the results of the treatment obtained at different institutions. This report must be made out and published by each hospital in a uniform manner, so that comparison will be possible. With such a report as a starting point, those interested can begin to ask questions as to the management and efficiency” (8).

Despite these pioneering concepts, Codman’s hospital went bankrupt, and the idea was not adopted. This may be telling, as the cost of collecting data for report cards is a significant burden.

Intuitively, the need for risk adjustment of relevant patient demographic features is essential for comparison of outcomes. However, it was Roemer and colleagues (10) in 1968, and later Iezzoni and others (9,11), who demonstrated the critical need of adjustment for severity of illness.

Substantial national attention was drawn to quality assessment when the U.S. Health Care Financing Administration (HCFA) began publishing hospital mortality rates in 1986 (12,13). There was substantial concern over the risk adjustment used in this project, given the limited data in the Medicare administrative billing database (9,14); ultimately, HCFA stopped the release of hospital mortality reports (12). This, too, is a telling historical anecdote. The difficulties in risk adjustment are significant, and this indeed represents a formidable challenge for the future of quality assessment. In the early 1990s, Chelimsky (15) noted that there was much more interest in the cost of health care than in quality. Clearly, the lay press, as represented by *The New York Times*, focused on cost and access rather than quality indicators. But in recent years, although cost continues to be a central factor, there has been considerable research dedicated to the quality of medical care (16,17,18,19 and 20). In some instances, there has been application of relatively crude assessment tools in clinical practice; as a result, the field has been quite controversial. Some cardiologists and internists have the sense that quality assessment is simply a means of camouflage to reduce costs; others feel they are being harassed by such efforts. Nevertheless, if quality assessment is properly done in cardiovascular medicine, there is significant potential improvement in patient care (21).

DEFINITION OF QUALITY OF CARE

General

Despite the fact that quality of care became a standard phrase in the late 1990s, the operational definition of *quality* has been a source of confusion and difference of opinion. The IOM (22,23,24 and 25) defined *quality* as the "degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." The technical excellence of the care that is provided, with special emphasis on the physician-patient relationship, is a common theme for most definitions of *quality of care*. Two factors drive the technical quality—the appropriateness of the services provided and the skill with which the appropriate care is performed.

One reason why cardiovascular medicine has been a major focus of quality efforts is that the most obvious health outcome—death—is common in patients with identified cardiac disease. This ease of measurement coupled with the high cost of cardiovascular care has made cardiology a focal point for quality measurement activities.

The determination of quality depends to some extent on the perspective of the person for whom the assessment is done. Patients, health care providers, and policy makers tend to have somewhat different, though considerably overlapping, concepts regarding quality. Patients tend to focus on the nature of the interactions with providers, including personal attention, courteous behavior, and prompt service, elements of what has been termed *patient satisfaction*. A major issue is the view that patients, as consumers, should have all of the information necessary to make judgments about the value of medical services, the concept of "patient-centered care" (22).

In contrast, providers tend to emphasize the technical aspects of quality, including whether correct decisions regarding diagnostic or therapeutic strategies have been made and whether those strategies have been executed with proper skill and knowledge. Policy makers and managers of health plans or health benefits organizations are most interested in measures of health and satisfaction of the overall population rather than a single measure of health. Integrating these different perspectives can be a daunting task, and most quality assessments tend to emphasize one of the three perspectives. Ultimately, quality of care is evaluated at three different levels—structure, process, and outcome (26).

Clinical practice guidelines are a pivotal part of defining quality on an evidence basis, with a list of class IA, IB, II, and III recommendations. By simply counting the number of times such recommendations are followed as a proportion of the number of opportunities, one can derive a quality measure which should relate quite nicely to outcomes.

Structure

The *structure* of a health care system refers to the characteristics of physicians, other health care providers, and the facilities in which they deliver health care. For cardiology practice, the critical structural characteristics comprise the specialty status, practice organization, availability of facilities for noninvasive and invasive testing and therapeutic intervention, and the types of disease management programs. Recent information has demonstrated that both specialty status (27) and environment, such as teaching or financial status of hospitals (28,29), have an influence on mortality. These studies reinforce the component of structure for determining quality of care.

Process

The "time-honored" method of peer review has been the morbidity and mortality conference. In this approach, when a poor outcome occurred, the patient's care was reviewed in front of a peer group. This approach suffered from lack of consistency and frequently did not provide the type of information that could lead to systematic improvement in the delivery of care. In a sense, quality assessment has followed the same course as clinical investigation: from anecdote to systematic quantitative assessment.

An appealing approach to measurement of quality is to determine when it is known that one diagnostic or therapeutic strategy is superior to an alternative and to measure how often the preferred strategy is used rather than the inferior strategy (26). "Doing the right thing at the right time" in concept can be measured relatively easily, and because multiple patient encounters occur, this sort of process measurement has a frequency of events high enough to allow for meaningful quantitative measures. Thus, measurement of the proportion of post-MI patients treated with aspirin and beta-blocker drugs has become a standard method of assessing quality.

The use of statins in patients with atherosclerosis and low-density lipoprotein of more than 100 mg per dL is a useful index. A recent report by Bradley and colleagues (30) on beta-blockers after acute MI highlights the process issues. Eight representative hospitals across the United States were selected to prospectively study the use of beta-blockers (Table 45.1). The range of improvement varied between 30% and –21%. The key factors characterizing improvement were administrative support, support and leadership among clinicians, use of data, explicit goals, and the proper design and execution of initiatives to affect change (30).

State	Staffed beds	Beta-blocker use rate, patients, %		Absolute change in beta-blocker use (% points)	Beta-blocker use rating	
		Baseline	Follow-up		Improvement	Follow-up
California	277	43	70	+30	High	High
Ohio	438	47	69	+22	High	High
Florida	628	56	68	+12	High	High
California	353	39	46	+7	Average	Medium
New York	237	61	67	+6	Average	High
Arkansas	275	29	35	+6	Average	Low
Missouri	708	63	47	-16	Low	Medium
Minnesota	110	66	45	-21	Low	Medium

*Beta-blocker use rates were calculated as the number of patients who received beta-blockers at discharge divided by the total number of patients discharged from each hospital during the relevant (baseline or follow-up) period.

TABLE 45.1 LISTING OF STUDY HOSPITALS

Another increasingly used measure is the time from admission to the emergency department to the administration of thrombolytic therapy. In patients with congestive heart failure, the proportion of patients with left ventricular function measurements and the proportion of patients receiving angiotensin-converting enzyme inhibitors among those with reduced systolic function comprise data-derived explicit process measures.

This approach of using explicit process-based criteria derived from results of randomized trials has increasingly supplanted traditional peer review, which consisted of a review of the chart by an independent expert to assess the degree to which care of the patient seemed to reflect community standards with nonquantitative feedback to individual practitioners. The weaknesses of this nonquantitative, implicit assessment are obvious. The lack of consistency increases the chance of arbitrary use of the

information for negative feedback rather than providing standards by which self-improvement can be made.

Brook and colleagues (26) described the rationale for the subjective approach. An expert or a “peer” reviews the documentation in the medical record. The first question asked in the examination is whether the basic approach to patient care was adequate by community standards. The second question is whether a different approach to care would have improved the outcome. Finally, these two elements are put together to determine whether the overall quality of care was “acceptable.” Multiple problems have been encountered with this approach, including difficulty identifying peers or experts to perform the review (excellent practitioners spend their time caring for patients and not reviewing others’ charts) and inadequacies in the typical medical record in terms of providing the best information for quality assessment.

An appealing method that combines process and intermediate measures of outcomes is to identify a physiologic outcome that would fall within an excellent, acceptable, or unacceptable range based on what is known about the disease pathophysiology and its management (26). An example of this type of measure is the assessment of hemoglobin A_{1C} in patients with diabetes. It is assumed that excellent care for diabetes will result in low hemoglobin A_{1C} levels, although multiple methods of achieving these levels might be acceptable practice (diet, exercise, insulin, oral hypoglycemic agents). Therefore, a quality assessment might simply consist of measuring the proportion of patients seen by a practitioner for longitudinal care with acceptable hemoglobin A_{1C} measures.

This approach can be extrapolated to populations of patients by evaluating the proportion of patients meeting the physiologic target. Variation in compliance would be expected in a population, and therefore an acceptable range of uncontrolled diabetic patients could be defined based on community data. The proportion of patients with adequately controlled blood pressure or stable weight could also be quantified and compared using benchmarking methods. Of course, these measures are subject to gaming in the same way as complex outcome measures, by steering high-risk patients for poor outcomes or poor compliance away from the practice (21).

Appropriateness

A more formal means of assessing whether the “right thing was done at the right time” is to evaluate its appropriateness. Whether a diagnostic or interventional procedure was properly indicated and needed is an alternative assessment of process. To determine the “appropriateness” of a medical procedure, it is necessary to have the circumstances judged by an independent group of health care professionals, with access to the medical records and relevant laboratory information. Ratings of appropriateness have been used for CABG, PCI, coronary angiography, and other cardiovascular procedures (31,32,33 and 34). However, it is cumbersome to review the patients on a case-by-case basis. The qualitative and subjective aspects, in trying to assess whether the accepted criteria or indications have been met, can be difficult to resolve. Accordingly, a considerable proportion of the procedures performed for patients wind up being scored as “uncertain.” Still, the level of appropriateness of a given procedure may be used as an index of quality of a given hospital, health care system, or even operator.

Medical Errors

One of the most controversial areas to have been highlighted in recent years is that of medical errors. The IOM report issued in 2000 (initially issued in 1999) (1) set off considerable debate in the medical community and peer-reviewed medical literature (2,3,4 and 5). The report claims that at least 44,000 to 98,000 deaths occur in American hospitals each year that are attributable to medical errors. The IOM notes a “cycle of inaction” and calls for prevention of errors and resultant injuries, along with better accountability and dedicated research. In review of the literature surrounding the report, it is clear that medical errors constitute a problem. But what remains unclear is whether the magnitude of the problem has been exaggerated. On one hand, noted authorities such as Brennan (2) and McDonald et al. (3) have questioned the report’s accuracy and potential for harm itself. Others such as Leape (4) and Meyer et al. (5) stand firm behind the report. Of note, Meyer et al. represent the Agency for Healthcare Research and Quality, which stands to gain considerable federal funding for research in this area. Much of the debate is related to the data from which the potential error death toll is extrapolated, such as a 1984 study of New York hospitals, and a 1991 to 1992 study in Colorado and Utah hospitals (2). For example, postoperative hemorrhages are classified as “errors” when most physicians would not consider this as an appropriate categorization. Another example of potential miscalculation was that of medication errors that were attributable to drug abuse rather than an iatrogenic cause (3). The IOM report calls for a future 50% reduction in the incidence of errors, but there is no accurate incidence available in a general medical population. Some data suggest that safety has already improved from the 4% to 5% rate of injury reported in California in 1976 to the 2.9% in Colorado and Utah in 1992 (2).

Recently, Hayward and Hofer (34a) estimated the number of deaths from medical errors in the United States to be 5,000 to 15,000 per year. The gross discrepancy (one-tenth of the IOM estimate) was attributed to inaccurate definitions of what constitutes a medical error. Hayward and Hofer looked at 111 in-hospital deaths at seven Veterans Administration hospitals between 1995 and 1996 and concluded that a very small proportion (0.5%) of patients would have lived at least 3 months in good health if optimal care was delivered.

Despite the media attention and headline-grabbing nature of the IOM report and the flurry of additional editorials, the positive side is more focus and attention to the issue of quality of care. Many examples have been developed in cardiovascular medicine. MI, which has the greatest profile of conditions in the field, has been the subject of several recent papers on errors in medication (35,36,37,38,39,40,41 and 41a) and of media coverage. The alarming newspaper coverage of one of the first reports of errors in fibrinolytic dosing in acute MI read “up to 25% of heart attack patients who are given the two most widely used clot-busting drugs during heart attacks get the wrong doses, doubling their death rates.”

It is particularly confounding to analyze medication errors in the treatment of acute MI, because patients die before they can receive the complete dose, and this could be wrongly classified as an “error.” In Figure 45.1, a report from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) III trial by Goodman et al. highlights the association between deviation in planned dosing and mortality, both for alteplase and reteplase (35). The difficult issue, however, is to establish cause and effect, and none of the studies to date was prospectively defined to address this pivotal question. It seems logical that bolus fibrinolytic agents such as reteplase or tenecteplase may reduce errors in dosing, as compared with the complex regimen of accelerated alteplase, which required a 90-minute infusion and different doses of the drug in three discrete phases (bolus, initial 30 minutes, next 60 minutes). Similarly, excessive dosing could result in intracranial hemorrhage or other life-threatening bleeding complications. As with the overall problem of medical errors, we can be assured that there is indeed a problem, but the precise quantification is quite difficult with fibrinolytics in acute MI.

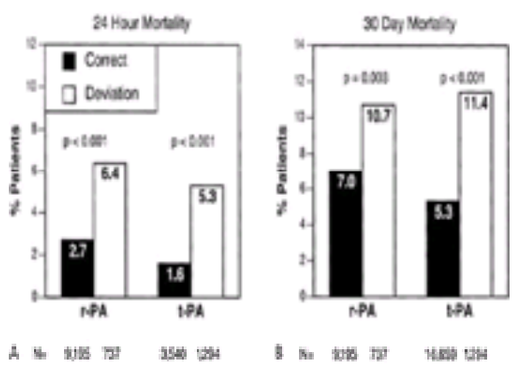


FIGURE 45.1 Mortality at 24 hours **(A)** and 30 days **(B)** in the GUSTO III trial by correct or incorrect fibrinolytic dosing. r-PA, reteplase; t-PA, alteplase. (From Goodman S, et al. Presented at the American College of Cardiology, March 2001, with permission.)

It should be noted that the IOM report and related studies have focused only on in-patient medical errors. Although these are relatively easier to measure (despite controversy over definitions), important errors also occur in the outpatient arena, and those represent a major challenge for our health care system.

Outcomes

The concept that medical outcomes should be the gold standard of quality assessment is not difficult. However, a number of problems with collection and assessment of the relevant data severely limit the degree to which outcomes can be used in the current environment. Several studies found that when both process and outcomes are measured with adequate power, the two indicators point in the same direction (26). The list of potential key outcomes include mortality, morbidity, cost, and patient satisfaction.

Mortality

Mortality is the most appealing outcome to use in the assessment of quality in cardiovascular disease. It is easy to measure and difficult to manipulate. Additionally, as compared with many other medical problems, mortality is the critical outcome in the treatment of most cardiovascular problems.

Only certain cardiovascular diagnoses or procedures have an appreciable risk of mortality to make them suitable for a parameter of quality assessment. In patients who present with either acute MI or congestive heart failure or who undergo cardiac transplantation or coronary artery bypass surgery, the proportion of expected deaths may be adequate to use this as a benchmark of the quality of care. But for the common diagnoses such as unstable angina, evaluation of chest discomfort, or procedures such as percutaneous coronary revascularization, the fatality rates are too low for meaningful assessment. Thus, despite its importance, death is rare enough that in most circumstances adequate numbers of deaths cannot be accumulated to develop statistically robust estimates.

Furthermore, although statistical models to predict mortality have been developed more extensively for cardiovascular procedures and problems than for other medical conditions, the majority of the variance in mortality cannot be explained by known factors. Accordingly, considerable debate remains about whether differences observed in mortality outcomes between systems, practices, or practitioners represent differences in quality, differences in risk status of the population before treatment, or random variation.

Beyond the problem of low incidence and potential of random variance, mortality may not be the most important outcome to assess for a given diagnosis or procedure. For example, with percutaneous revascularization, the occurrence of periprocedural MI and the need for emergency bypass surgery or repeat PCI are much more common adverse outcomes than mortality. Furthermore, the durability of the procedure is reflected by the avoidance of the need for repeat procedures during extended follow-up, along with the patient being symptom-free. In such patients, an assessment of mortality does not indicate the important outcomes that one needs to know to adjudicate the quality of a particular center or even operator.

There are certain instances in which mortality and morbidity may not track. For example, in a center where patients undergo CABG with a low mortality but with a heightened risk of perioperative stroke or mediastinitis, one could be misled by the low occurrence of fatal outcomes. Indeed, Silber and colleagues (42) identified a poor correlation between nonfatal and fatal complications of CABG in 57 hospitals and nearly 17,000 patients. Of note, this study also suggested that sites that record details of medical care may be the ones with the lowest operative mortality.

Major Morbidity

Major morbidity has advantages as a measure of quality in that it is more common and it is usually detectable in the medical record. However, the imperfections of major morbidity result from variability in definition, degree of documentation, and adjustment models. Although the general concept of MI or stroke is intuitively obvious, the actual classification of individual cases is highly variable. The diagnosis of MI is dependent on timely measurement of enzymes and electrocardiograms, the type of enzyme assay used (creatinine kinase-MB, troponin), and appropriate interpretation of the data with recording in the medical record. Particularly with cardiovascular procedures, there is a well-described bias of the person performing the procedure to minimize procedure-related difficulties; in clinical trials of percutaneous interventional procedures, detection of nonfatal MI by the practitioner occurs at much lower rates than does detection by a clinical events committee (43). Additionally, uncertainty concerning the accuracy of statistical models to adjust for differences in baseline risk for death is multiply compounded in the prediction of nonfatal events.

Cost

The use of cost as a measure of quality is controversial. In the in-patient setting, costs are increasingly measured for administrative reasons to ensure the financial viability of hospitals. Because patients are also concerned about cost, it is reasonable to consider that high-quality physicians or practices might be defined as providing excellent outcomes or evidence of excellent process at a reasonable cost. Outpatient costs are more difficult to obtain and have not become a commonly used measure for comparative data.

With the availability of extensive financial data in some centers, it is often easier to measure hospital and professional costs rather than clinical outcomes. Such indices as length of stay or cost per case have been increasingly used in recent years but may not accurately reflect quality of care. Ideally, the best outcomes can be achieved at the lowest cumulative cost. Interestingly, the state of Pennsylvania technology assessment program showed an inverse correlation between hospital costs and outcomes for coronary artery bypass surgery (44) that was not expected. The centers with the lowest cost tended to also achieve the best outcomes. Whether this will occur with other diagnoses, procedures, and even for this particular operation in other health care systems remains to be seen. The economy of scale with high volume may be a principal driving factor when there is a direct relationship between quality and cost. At times, use of “big ticket” items such as stents or abciximab may be linked to much higher costs but would be expected to provide reduced risk of ischemic complications.

Patient Satisfaction

Patient satisfaction, like cost, has become a standard administrative measure to ensure that practices remain economically viable. It can be measured quickly and efficiently, just as satisfaction with other services can be measured in our society. Large numbers can be aggregated to allow accurate statistical comparisons to be made.

However, little relationship exists between the satisfaction of the patient with the encounter and the technical quality of care delivered. A patient undergoing an uncomplicated percutaneous intervention that was not indicated in the first place may have felt that the care was excellent, but the judgment about whether the procedure was indicated requires substantial medical knowledge. Patient satisfaction is typically rated via questionnaires and may be difficult to interpret. The parameter that seems to drive this in a favorable direction is time with the physician and the sense that the physician is giving the patient undivided attention and utmost priority. However, factors such as parking at the hospital, the cafeteria, accommodations, reading materials in the waiting room, the service orientation of ancillary personnel, and many others play a role in the composite experience. Therefore, patient satisfaction is an important parameter to survey, but its relationship with clinical outcomes is not established. It is possible that the three different indices of clinical outcomes, cost, and patient satisfaction may go in different directions. For the low-volume center that is characterized by exquisite customer service and long physician and physician extender visits, for example, there may be excellent patient satisfaction but excessive costs and suboptimal outcomes. Nevertheless, with health care plans that rely on patient subscription, this may be one of the most important indices to evaluate a program’s success.

METHODS OF MEASUREMENT

The validity of proposed measures of quality cannot be understood without a thorough knowledge of the source of data. A major problem with interpretation of much of the data made available to the public has been the reliance on inaccurate sources of data and extrapolation beyond the limits of the data. Because most of the medical record consists of handwritten notes, there is no available method of aggregating information that captures the interaction between the health care provider and the patient in most systems. Consequently, administrative databases or medical record reviews have formed the basis for most quality assessments.

Administrative Databases

Administrative databases designed to allow patient billing and tracking for financial reasons provide excellent information concerning demographics, procedures, and survival. However, this information does not reflect the modifying medical information concerning severity of illness, complications, or medical outcomes other than death. Multiple studies have demonstrated that the clinical information contained in administrative databases is incomplete and often erroneous and misleading. Comparisons of insurance claims information with clinical databases have demonstrated poor concordance rates in classifying patient diagnosis, ranging from 0.09 for unstable angina to 0.83 for diabetes (45).

Administrative databases such as Medicare or those at state departments of health are especially attractive to use because they contain large data sets with the sufficient outcomes needed to analyze the relationship of a hospital or clinician to outcomes. However, these databases were frequently not designed to perform such an analysis and may be quite insufficient with respect to missing data. Often, only mortality data are available with limited demographic information. These typically represent retrospective ad hoc assessments. Many of the data, if not all that have been entered, have not, ironically, been quality-assured except for the financial component. More recently, using an administrative database to prospectively capture relevant data, such as is ongoing in New York for PCI procedures, is a powerful means of combining large numbers of patients, outcomes, and establishing the relationship.

Medical Record Review

Although administrative or claims databases certainly have problems, the medical record itself has many deficiencies that make chart audit a suboptimal exercise. The nomenclature used to describe similar phenomena varies from practitioner to practitioner. Pertinent negatives are frequently not mentioned so that the reviewer must assume that if a finding or procedure is not mentioned in the medical record, it was not evaluated or done. In an adverse event reporting study, a chart audit missed

more than half of adverse events related to medications (46). On the other hand, physician reporting of adverse events in the same study was equally remiss for identifying the outcomes but twice as likely to detect the important, preventable events. The physician-reporting mechanism was considered less costly: $15,000 compared with $54,000 (46). This study emphasizes some of the pivotal shortcomings of chart review—its lack of accuracy and high cost.

Clinical Databases

Very few clinical databases are used in concurrent patient care. Such databases tend to have considerably more information that is relevant, with data having more likely been verified by source medical record or other documentation, and are easier to work with. A clinical database can take the form of a single center's results, a clinical trial, or a consortium of sites. Prospective randomized clinical trials are emerging as a powerful tool to provide information on outcomes between different health care systems or regions (47,48).

Risk Adjustment

Although it seems that determining the severity of illness for patient groups and performing risk adjustment might be straightforward, this has not proved to be the case (49,50 and 51). There is considerable debate about what constitutes the clinical vital facts; whether to use administrative data alone or incorporate relevant laboratory data; and the value of further clinical data that can be obtained only via the time-consuming, labor-intensive, and expensive abstraction of medical records. Several proprietary commercial severity measures have been used (*e*Table 45.1.1). Of these, the MedisGroups has been adopted by Pennsylvania for the "consumer guide" for CABG; the Acute Physiology and Chronic Health Evaluation III "physiology score" has been widely used to assess quality of care for intensive care units. Of note, direct comparisons of these four severity measures showed considerable variance, with only about 80% of patients receiving similar rankings between severity tools (49).

***e*TABLE 45.1.1** FOUR SEVERITY MEASURES

Severity measure	Source	Data used and definition of severity[a]	Classification approach	Derivation[b]
MedisGroups (Westborough, MA)	MediQual Systems, Inc. death; score calculated within 64 disease groups	Clinical data; in-hospital	Probability ranging from 0 to 1 modeling	Empirical
Physiology score	Patterned after acute physiology score of APACHE III	Clinical data; in-hospital death for patients in intensive care unit	Integer score starting with 0; APACHE III's Acute Physiology Score ranges from 0 to 252	Empirical modeling with clinical guidance
Disease staging	SysteMetrics/MEDSTAT Group (Santa Barbara, CA)	Discharge abstract; probability of in-hospital death	Probability ranging from 0 to 1	Empirical modeling
All patient refined diagnosis-related groups	3M Health Information Systems (Wallingford, CT)	Discharge abstract; total hospital charges	Four severity classes (A, B, C, and D) within adjacent diagnosis-related groups[c]	Empirical modeling with clinical guidance

APACHE III, Acute Physiology and Chronic Health Evaluation III.

[a] Discharge abstract: standard hospital-discharge data elements, such as basic demographics and diagnosis and procedure codes. Clinical data: clinical information, such as vital signs and test results, abstracted from the medical record.

[b] *Derivation* indicates the principal method used to create the severity scoring method. *Clinical guidance* reflects primarily the use of expert physician guidance; *empirical modeling* indicates primarily the use of statistical techniques.

[c] Adjacent diagnosis-related groups were formed by grouping individual diagnosis-related groups previously split by complications and comorbidities.

From Iezzoni LI, Ash AS, Shwartz M, et al. Predicting who dies depends on how severity is measured: implications for evaluating patient outcomes. *Ann Intern Med* 1995;123:763–770, with permission.

The discriminatory power of a particular model for risk adjustment can be assessed by comparing c-statistics, which are equivalent to area under receiver-operating characteristic curves (50). Pine and colleagues (51) showed that a model that relies solely on administrative data compares favorably (good concordance) to one that incorporates administrative, laboratory, and clinically extracted data, with an area under receiver-operating characteristic curves of approximately 0.85. This remains controversial, as many studies have demonstrated the added value of the laboratory and additional clinical data. Nevertheless, review of these data is instructive to highlight some of the difficulties encountered in performing risk adjustment of patients, even for mortality outcomes.

WHO IS MEASURING QUALITY?

Because participants in health care ranging from the patient to the practitioner to the health care administrator are interested in quality, considerable overlap exists in the assignment of responsibility of its assessment. An understanding of the roles currently assumed by various organizations could allow the practitioner to develop an approach to responding to the demands and needs of the various constituents.

H4>Centers for Medicare and Medicaid Services

As the largest single payer for health care delivery in the United States, the government has been concerned with the quality of medical care since its beginning. The evolution of thinking about how to assess quality has been propelled by the initiative that the Centers for Medicare and Medicaid Services (formerly HCFA) has taken in making risk-adjusted data for such procedures as CABG or cardiac transplantation available to the public. The public availability of this information has also allowed for ascertainment of outcome data for various constituents to use for benchmarking and advertising. Given that the clinical information contained in the Centers for Medicare and Medicaid Services database reflects diagnoses recorded for billing purposes, this approach has been highly controversial (14,52) and, ultimately, for in-hospital mortality data the practice was abandoned in 1993.

National Committee on Quality Assurance

The National Committee on Quality Assurance (NCQA) was founded in 1979 as an effort to establish a system of quality assessment by national managed care organizations (35). In addition to a primary interest in the importance of quality assessment, this organization was provided as an alternative to government intervention. With grant funding, the NCQA became independent of the national managed care organizations and its board was altered to provide a societal perspective on quality. One perspective on the NCQA is that it represents the most powerful single organization through which employers can participate in the assessment and the improvement of large health plans.

The method by which the NCQA accredits health plans includes a review of operations and an assessment using the Health Plan Employer Data and Information Set (HEDIS). HEDIS is a continually evolving set of measures designed to assess quality, access, and satisfaction in addition to critical issues in finances and administration. The measures are simple, and the HEDIS measures in use in 1996 included only whether cholesterol screening was used as a cardiovascular outcome measure. In *e*Table 45.1.2, a version of HEDIS is provided. More disease-specific measures are currently being added to the system. In a review of the NCQA, Iglehart (53) reported that the organization is growing and making a difference despite the rudimentary nature of the instruments being used and concern about the cost by managed care organization administrators.

***e*TABLE 45.1.2** COMPONENTS OF HEALTH PLAN EMPLOYER DATA AND INFORMATION SET 2.5

Quality (9 measures)

Preventive medicine
- Childhood immunization
- Cholesterol screening
- Mammographic screening
- Pap smears for cervical cancer

Prenatal care
- Low birth weight
- Prenatal care in first trimester

Acute and chronic disease
- Hospital admissions for asthma
- Retinal examination for diabetes

Mental health and substance abuse
- Ambulatory follow-up after hospital treatment of major affective disorders

Access and patient satisfaction (5 measures)

Access
- Percentage of members 42 to 64 yr old with visit to the plan in previous 2 yr

Number and percentage of primary care physicians accepting new patients
Existence of access standards for various types of visits and telephone responses
Satisfaction
Percentage of members who are “very satisfied” with the plan
Provision of plan satisfaction surveys
Membership and use (approximately 20 measures)
Indicators providing data on membership and the use of services in various categories, including frequency of selected surgical procedures, rates of hospitalization, nonacute in-patient care and ambulatory care, maternity and obstetrical care, drug utilization, and care for mental health and chemical dependency
Finance (approximately 15 measures)
Indicators of performance (income and loss rates), liquidity (cash on hand), efficiency (measures of uncollected funds due), and compliance with statutory requirements (e.g., financial reserves)
Plan management (approximately 15 measures)
Indicators providing descriptive information on the network of providers (board certification of physicians, turnover, and compensation) and on clinical management, including management of quality, preventive care, case management, utilization review, and risk management

From Epstein A. Performance reports on quality—prototypes, problems, and prospects. *N Engl J Med* 1995;333:57–61, with permission.

State agencies (peer review organizations) have focused on quality assurance in the practice of medicine but have generally not collected large data sets on particular diagnoses or procedures. Some exceptions are highlighted in the subsequent section on outcome assessment by procedure.

Agency for Healthcare Research and Quality

In the United States, the new federal agency responsible for quality health care is the Agency for Healthcare Research and Quality, formerly the Agency for Health Care Policy and Research. The agency has solid government funding and an ambitious agenda to improve the country’s health care delivery.

State Agencies

In the late 1980s, New York State instituted mandatory reporting of baseline characteristics and outcomes in patients undergoing CABG. Since then, percutaneous interventional procedures have been added to the mandatory reporting scheme. This approach has caused substantial controversy both because of the public disclosure of this information and because of uncertainty about whether this system has actually improved care. Pennsylvania and California have instituted similar programs for producing outcome report cards for acute myocardial infarction and revascularization procedures.

Regional Efforts

The Northern New England Group has organized major hospitals performing coronary revascularization in the New England region, with a goal of improving quality through the collection and dissemination of process and outcome data. A common database has been developed and used to provide scorecards for outcomes, and serial measures of process have been used to document improvement in the quality of care.

Cities

A number of metropolitan areas have now developed business coalitions interested in assessing the quality of medical care. This approach was quite visible in Cleveland with the organization known as the Cleveland Health Quality Choice. Formed in the early 1990s by the Cleveland Metropolitan Business Coalition to facilitate selection of hospitals, the 30 centers were ranked on a quarterly basis for risk-adjusted mortality for five different diagnoses (50), including acute MI and congestive heart failure. The data were published in the newspaper along with other indices such as patient satisfaction and length of stay. Ultimately, the rating system was terminated when the costs of accruing the data specific to the project became unacceptable to some of the large hospital providers.

Managed Care Organizations

Individual managed care organizations typically provide individual assessments of quality and satisfaction, but the major method of ensuring accountability is external accreditation. The HEDIS measures (eTable 45.1.2) administered by the NCQA have become the standard, although these measures have almost no relevance to the care of patients with cardiovascular disease.

Professional Societies

Although professional societies can provide standards for quality assessment, the responsibility of professional societies to guard the welfare of their members makes actual assessment of the quality of individual practitioners difficult. An approach adopted by the American College of Cardiology focuses on the development of standards for data collection that will allow the assessment of structure, process, and outcome measures (54). The Society of Thoracic and Cardiovascular Surgeons is far ahead of the American College of Cardiology, and output from their database has been linked to driving better quality at institutions throughout the United States.

Individual Hospitals

The interest of individual hospitals in quality measures has been primarily to promote excellence in the quest for managed care contracts or public attention. However, in this process substantial progress has been made at the local level in the ascertainment and aggregation of major procedural outcomes. The major mechanism of quality assessment in this manner has been the use of clinical databases. The American College of Cardiology is playing a major role in focusing commercial database sponsors on common nomenclature and collection of baseline clinical data that will allow for adjustment according to baseline risk.

The National Hospital Network provides one example of a large group of hospitals that have organized for contracting purposes and to that end have developed common standards for data capture. This database provides reports to individual institutions, benchmarking them against other institutions in the network with regard to patient characteristics, choices of procedures, and outcomes. The database has provided substantial documentation of a wide variation in practice patterns related to choice of devices, even in high-volume institutions.

QUALITY OUTCOMES FOR PARTICULAR CARDIOVASCULAR PROCEDURES AND DIAGNOSES

Coronary Artery Bypass Surgery

The most extensively studied medical procedure for relationship of volume to outcome is bypass surgery. The procedure is ideal for scorecard analysis because it is frequently performed, it carries an appreciable risk of mortality, and there has been extensive refinement of the features that are important for risk adjustment. Luft and coworkers (55,56 and 57) pioneered much of this effort and were among the first to document the inverse relationship between hospitals with low volume and high mortality in the late 1970s. In the mid-1980s, the HCFA and Veterans Affairs hospitals began reporting hospital CABG activity and risk-adjusted mortality on an annual basis to the public (9,12,13,21,58). As early as 1989, Hannan and colleagues (59) from New York State noted that the surgeon’s annual volume was even more critical a determinant than the hospital volume of CABG for risk-adjusted mortality. In 1991, two influential studies from the Northeast demonstrated the extensive interhospital, interoperator, and geographic variability for CABG risk-adjusted mortality outcomes (60,61). There has been considerable effort and clinical investigation in the Northeast on this topic, especially in New York, Pennsylvania, and northern New England (59,60 and 61).

In New York, a pivotal study in 1990 described the statewide Cardiac Surgery Reporting System and tracking of the 28 hospitals performing CABG, with four hospitals demonstrating mortality rates that were significantly higher than expected—one with a death rate of 14.3% and only 63 cases during a 6-month period in 1989 (62). These data attracted considerable attention in December 1991, when a newspaper sued the State Department of Public Health for access to the operator- and hospital-specific data. A supreme court in New York ruled that the citizens of the state have a right to know these data and granted the newspaper access, setting a national precedent for public disclosure of not only hospital-specific but also physician-specific crude and risk-adjusted mortality data (21,63).

The findings in New York of certain hospital outliers were replicated in other parts of the country (62,64). Pooling seven studies that examined the relationship between hospital volume and mortality outcome for CABG, Sowden and coworkers (65) showed that the adjusted relative risk of dying was between 0.44 and 0.83 for surgery in a high-volume hospital (cutoff of high volume ranging from 150 to 223 cases per year). Of interest, in Ontario, Canada, where there are no low-volume hospitals (all performed more than 300 cases per year in 1992 and 1993), there were no outliers and the in-hospital mortality was consistently low in all nine hospitals (66). These findings certainly provide a foundation for the call for “regionalization” that many of the studies have beckoned (57,64,66,67). Of note, in contrast to California there is

considerable lack of a regionalized approach. In California, 91% of patients are within 25 miles of a center that offers bypass surgery, as compared with 82% in New York and 60% in Canada (67). Along with this, in 1987 to 1989, 31% of California hospitals performed fewer than 100 CABGs per year, as compared with 10% in New York and 0% in Canada (67).

The tracking of hospital- and operator-specific risk-adjusted mortality has been associated with a reduction in mortality not only in New York and northern New England but also in Massachusetts, where there is no centralized tracking (68,69,70 and 71). Hannan and colleagues (68) reported a New York statewide 41% decrease in risk-adjusted CABG mortality (from 4.2% to 2.5%) from 1989 to 1992. This mortality decline could not be explained by shifts of patients from low-volume to high-volume surgeons, changes in patient mix, or improvement of performance of surgeons with low volumes (69). Rather, it was suggested the improvement was related to the influx of new cardiac surgeons with better results and the exodus of some low-volume surgeons with high risk-adjusted mortality (69). As with New York, O'Connor and colleagues (70) reported a 24% reduction in mortality from 1987 to 1993 for patients undergoing surgery in Maine, New Hampshire, and Vermont. Quite comparable to the improved cardiac mortality observed in New York, in Massachusetts the observed mortality rates decreased from 4.7% to 3.3% from 1990 to 1994 (71), despite the absence of statewide reporting of outcomes.

The relationship of surveillance reporting systems and improvement of outcomes has fueled considerable controversy and has important implications on regional and national health care policy (72,73 and 74). It remains unclear that a statewide report card directly influences outcomes because the CABG mortality rate has decreased on a national level (72). Green and Wintfeld (74) harshly criticized the claims of the New York State Department of Health's first physician-specific mortality report by objecting to the validity of the risk-adjusted mortality model, changing of definitions from any in-hospital death to in-hospital death within 30 days, and changing in coding of key risk factors (renal failure, congestive heart failure, chronic obstructive pulmonary disease, and low ejection fraction). Examples that they cited were a 350% to 600% increase in coding of renal failure (with a change in definition to creatinine of more than 2.5 mg per dL instead of dialysis) and increase in coding of chronic lung disease from 2% to 53% (74).

Chassin and members of the New York State Department of Health (75,76) strongly objected to these critique points and quantitatively assert that the reduction of CABG is real and attributable to the reporting system. Omoigui and coworkers (77) from The Cleveland Clinic Foundation showed that patients from New York State outmigrated to The Cleveland Clinic with increased frequency during the period of the statewide reporting system, and these patients were distinctly higher risk. However, the number of patients who were shown to outmigrate from New York could not have accounted for the marked reduction in CABG-related mortality during the period under study (75,76 and 77); perhaps it accounted for a small contribution (75,76,77 and 78).

The statewide reporting mechanism of CABG results has also been available in Pennsylvania since 1990 with hospital and professional charge data, in addition to hospital- and physician-specific outcome data (Fig. 45.2) (44). Recently, Schneider and Epstein (79) surveyed Pennsylvanian cardiologists and cardiac surgeons and claimed that the state's *Consumer Guide to Coronary Artery Bypass Surgery* has limited credibility and raised concern that such a guide could have an unfavorable effect on access to CABG for the most severely ill patients who need surgery the most.

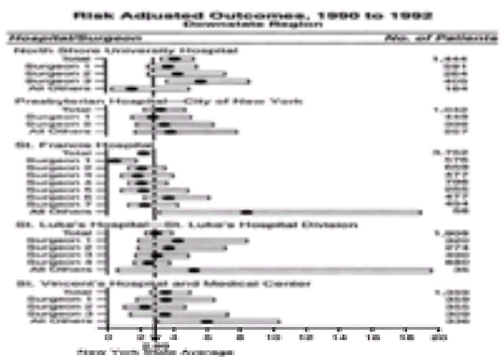


FIGURE 45.2 Risk-adjusted coronary artery bypass surgery mortality data (black dots are point estimates) with 95% confidence intervals (*horizontal bars*) for representative hospitals in Downstate New York. (From Topol EJ, Block PC, Holmes DR, et al. Readiness for the scorecard era in cardiovascular medicine. *Am J Cardiol* 1995;75:1170–1173, with permission.)

The New York CABG database has offered a window to the effect of managed care insurance (80). Recently, Peterson et al. used the New York CABG database to analyze access to care and elderly patient outcome (81). This group of investigators also examined the difficulties of risk adjustment for comparing CABG mortality results (82). The refinement of risk-adjusted indices for CABG has continued with work by Ivanov et al. (83).

In summary, report cards on CABG have been extensively used in many parts of the country, but their true effects on favorably modulating mortality are not completely accepted. This particular operation has been the "front-runner" in the field for hospital- and physician-specific outcomes and the testing grounds for public disclosure. Surely the lessons learned from the experience and controversies will be instructive in other procedures and diagnoses in cardiovascular medicine.

Percutaneous Coronary Intervention

PCI has been more difficult to study and produce scorecards for because, although the procedure is very frequently performed, the mortality is quite low (approximately 1% or less) and the morbidities of emergency bypass surgery or MI are difficult to define, especially in a post hoc analysis of a large administrative database (84). Nevertheless, the studies that have been reported parallel the findings of CABG, with a clear-cut inverse relationship of hospital and operator volume and adverse outcomes. Hannan and associates (85) studied more than 5,800 patients in New York State to delineate a multivariate risk-adjusted model. One of the first activity-to-volume relationship studies was performed by Ritchie and colleagues (86), who showed, using nearly 25,000 procedures in the state of California during 1989, that urgent CABG was progressively more likely as hospital percutaneous transluminal coronary angioplasty (PTCA) volumes fell below 200 per year. Further, in patients having PTCA related to a principal diagnosis of acute MI, the relationship of hospital volume to adverse outcomes was exaggerated in hospitals with an annual volume of fewer than 200; the death or urgent CABG rate was 12.4%.

The Society for Cardiac Angiography and Interventions reported on more than 19,500 consecutive patients in 48 hospitals in North America. Most of the hospitals performed more than 200 PTCAs per year, and the major finding was fewer major complications in centers performing more than 400 procedures per year (a 44% risk reduction, risk-adjusted) (87). Of note, if the threshold of 400 cases is used, these data suggest a 2-fold reduction in mortality, a 10-fold reduction in emergency CABG, and an 18-fold reduction in periprocedural MI (87).

The relationship of hospital volume to major complications was studied by Jollis and colleagues (88) using the Medicare database of more than 217,000 patients. As shown in Figure 45.3, there was a definite relationship of hospital volume and mortality as well as the rate of CABG during the index hospitalization. Of note, the patients undergoing PTCA in hospitals without surgical backup had the highest mortality (9.9%), which may be attributed in part to a higher proportion of primary PTCA for acute MI.

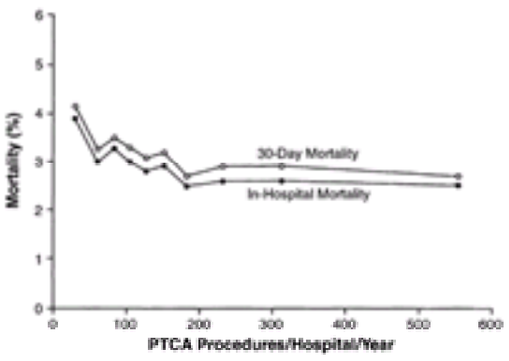


FIGURE 45.3 Mortality among Medicare beneficiaries who underwent percutaneous transluminal coronary angioplasty (PTCA) from 1987 through 1990, according to the volume of PTCA procedures at the hospitals where they were treated. The points on the curves correspond to the mortality rates among patients treated at hospitals with volumes of 1 to 46, 47 to 70, 71 to 93, 94 to 114, 115 to 137, 138 to 166, 167 to 206, 207 to 261, 262 to 371, and 372 to 987 procedures per year. (From

Jollis JG, Peterson ED, DeLong ER, et al. The relation between the volume of coronary angioplasty procedures at hospitals treating Medicare beneficiaries and short-term mortality. *N Engl J Med* 1994;331:1625–1629, with permission.)

Operator-specific results in PCI have been studied by many groups, and parallel trends of a volume to outcome relationship have been shown (87,88,89,90,91,92 and 93). Ellis and associates (90) pointed out some of the difficulties in categorizing a “poor” operator or outliers with a database of nearly 5,000 procedures. By using a 50 cases per year dichotomization for low- and high-volume operators, Shook and colleagues (92) demonstrated a near doubling of emergency bypass surgery (2.1% vs. 3.9% for low-volume operators) and significant differences in length of stay as well as hospital costs. The 2001 guidelines for the American College of Cardiology/American Heart Association call for a minimum of 75 cases per year (94). Still, it is estimated that in the United States, 55% of physicians perform fewer than 75 procedures per year and 46% of hospitals perform fewer than the recommended 400 per year (95).

The data set from New York State for all 62,670 patients undergoing PCI between 1991 and 1994 is illuminating and further corroborates the volume relationship (96). As shown in Figure 45.4, patients undergoing PCI by cardiologists with annual volumes of fewer than 75 cases had a substantial rise in same-day bypass surgery need. Risk-adjusted mortality was unfavorably affected in hospitals with annual PTCA volumes of fewer than 600. Although not as striking, the relationship of activity and mortality outcomes by hospital and operator was similar. The New York State data have been made available to the public (97). These data provide independent verification of the critical relationship of major complications and PTCA hospital and physician volume.

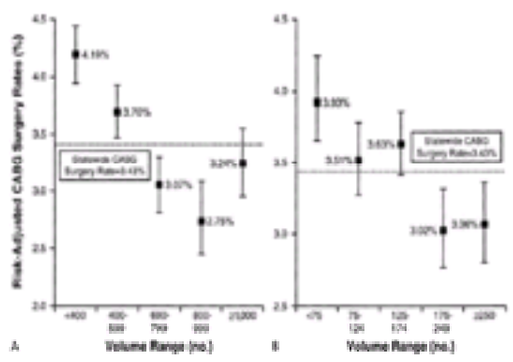


FIGURE 45.4 A: Risk-adjusted coronary artery bypass grafting (CABG) surgery rates for different hospital percutaneous transluminal coronary angioplasty volume ranges. Data presented as mean, with 95% confidence intervals indicated by the vertical bars. **B:** Risk-adjusted CABG surgery rates for different cardiologists’ percutaneous transluminal coronary angioplasty volume ranges. Data presented as mean, with 95% confidence intervals indicated by the vertical bars. (From Hannan EL, Racz M, Ryan TJ, et al. Coronary angioplasty volume-outcome relationships for hospitals and cardiologists. *JAMA* 1997;277:892–898, with permission.)

Much recent work has reinforced the operator-volume and outcome correlation in PCI (98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118 and 119). A prototypic example of the relationship was reported by McGrath et al. (119) involving 167,208 Medicare patients in 1,003 hospitals and 6,534 operator-physicians. The need for CABG by operator volume and the hospital volume–mortality relationships are presented in Figure 45.5. Although the operator volume did not affect mortality and the hospital volume was not associated with urgent CABG use, the relationships that were found appear to be quite convincing and reinforced by the bulk of the other parallel studies.

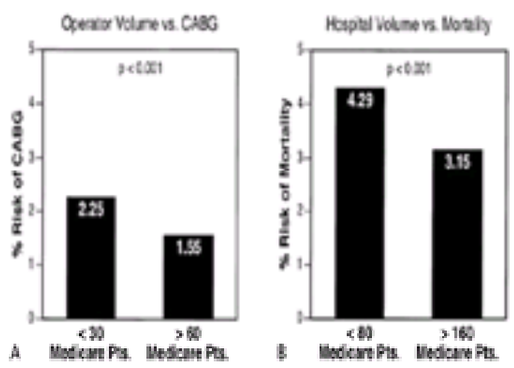


FIGURE 45.5 Rates of coronary artery bypass grafting (CABG) **(A)** or 30-day mortality **(B)** after percutaneous transluminal coronary intervention according to annual physician percutaneous coronary intervention volume among Medicare beneficiaries. (Data from McGrath PD, Wennberg DE, Dickens JD Jr, et al. Relation between operator and hospital volume and outcomes following percutaneous coronary interventions in the era of the coronary stent. *JAMA* 2000;284:3139–3144.)

Acute Myocardial Infarction

The risk-adjusted modeling for acute MI in the reperfusion era was addressed by Lee and colleagues (120) and in a large Medicare cohort by Normand and associates (121). Many states and regions have begun to analyze outcomes for acute MI by hospital. In December 1993, the state of California published the California Hospital Outcome Project, which provided extensive data for the diagnosis and outcome for patients presenting with acute MI for every hospital in the state. Representative data are summarized in eTable 45.1.3 (122,123). Beyond the outcome of mortality, important parameters such as the time to treatment, the use of thrombolytic therapy or catheter-based reperfusion, and the use of aspirin and other adjunctive medications are reflective of the quality of care for MI patients (121). Significant regional and global variability exists in the use of angiography, PTCA, adjunct medications, and outcomes (46,47). Interestingly, the availability or age of the patient appears to be driving most of the coronary angiography performed after MI in the United States, rather than the expected medical indication of recurrent ischemia (124). The care pattern is affected by not only whether a primary care physician is involved but also improved when a noninvasive or invasive cardiologist is involved (27,125,126 and 127) and is affected by the type of hospital (128,129). The tremendous variability in practice patterns, even in the United States, with limited long-term data for large populations, underscores the uncertainty as to the appropriate level of aggressiveness.

***e*TABLE 45.1.3** CALIFORNIA DATA FOR ACUTE MYOCARDIAL INFARCTION IN REPRESENTATIVE HOSPITALS IN SAN FRANCISCO AND LOS ANGELES

Hospital name	Rating	No.	Observed (%)	Risk adjusted (%)	Expected (%)	95% Confidence interval	*p* Value
Queen of Angels, Los Angeles	❑	120	26.7	22.3	15.9	17.2, 27.5	<.001
St. John’s Hospital and Health Center, Los Angeles	✪	150	8.7	7.5	15.3	2.8, 12.2	.008
University of California, Los Angeles	☆	96	10.4	8.9	15.5	2.9, 14.9	.006
Cedars Sinai, Los Angeles	✪	418	9.8	8.7	15.0	5.8, 11.5	<.001
Kaiser Foundation Hospital, San Francisco	✪	168	8.9	7.7	15.5	3.2, 12.1	.006
St. Mary’s Hospital and Medical Center, San Francisco	❑	98	12.2	11.7	13.9	5.5, 17.9	.376
Chinese Hospital, San Francisco	❑	24	16.7	8.9	25.0	0.1, 17.5	.234
San Pedro Peninsula Hospital, Los Angeles	❑	72	22.2	20.0	14.8	13.1, 27.0	.047

✪, significantly better than expected, models A and B; ☆, significantly better than expected, model A or B; ❑, not significantly better than expected in either model. The two risk-adjusted statistical regression models (A and B) used different variables and coefficients.

From Topol EJ, Block PC, Holmes DR, et al. Readiness for the scorecard era in cardiovascular medicine. *Am J Cardiol* 1995;75:1170–1173, with permission.

Two studies suggested that involvement of a cardiologist in the care of a patient with acute MI may have a particularly beneficial impact on survival (27,130,131,132,133 and 134). In the Medicare study performed by Jollis and coworkers, involving 8,241 patients in four states in 1992, a significant relationship of risk-adjusted mortality reduction was demonstrated according to the specialty of the admitting physician. The odds reduction of mortality of approximately 12% to 15% for a cardiologist versus a primary care physician (Fig. 45.6) is noteworthy, as this represents at least as much of a benefit that has been targeted in several large-scale

MI intervention trials (135,136,137 and 138). Willison et al. and others provide data and insight to reinforce Jollis' report (139,140 and 141). Consistent with the mortality effects was the use of evidence-based medications such as beta-blockade, aspirin, and angiotensin-converting enzyme inhibitors. A similar pattern of physician specialty and outcome was found for patients with unstable angina (142). An analysis of superior outcomes for MI in the 40 "top" heart hospitals reinforced the use of evidence-based treatment (lytics, aspirin, beta-blockade) as a marker for improved quality of care (143). Like the critique of scorecards, a point of vulnerability is the validity of the risk-adjusted modeling for making key comparisons in these large administrative data sets. Of interest, if the gradient of mortality reduction of 10% to 15% (or more) can be achieved through improvement of process, such as the reduction of time to thrombolytic treatment by 1 hour on average associated with a 15% reduction of 30-day mortality, then meaningful improvement in outcomes can be derived and anticipated in the most common killer of patients in Western society today.

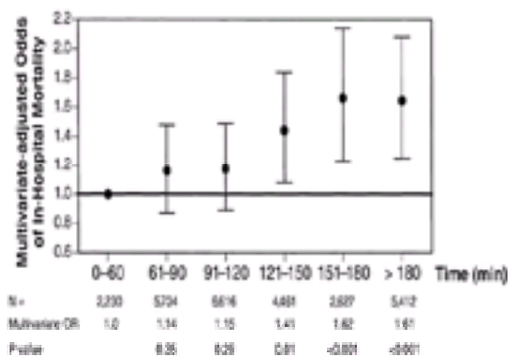


FIGURE 45.6 Multivariate-adjusted relationship between door-to-balloon time and mortality (c^2 trend = 99.5; p <.01). Error bars indicate 95% confidence intervals. *Door time* refers to arrival at the hospital; *balloon time* refers to the time of first balloon inflation of the primary angioplasty procedure. OR, odds ratio. (From Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000;283:2941–2947, with permission.)

Outcomes research in acute MI reperfusion has been very helpful in demonstrating the importance of door-to-balloon time, hospital volume, and mortality. Using the National Registry of Myocardial Infarction data in 27,080 patients and multivariate adjustment, Cannon et al. showed the striking direct relationship of door-to-balloon and the odds ratio of mortality (Fig. 45.6) (144). Furthermore, these investigators went on to show the hospital volume–mortality relationship with primary angioplasty (Fig. 45.7) (144). Using the National Registry database from 1994 to 1999 in 62,299 patients, Magid et al. provided a comprehensive analysis of both thrombolytic therapy and primary angioplasty (145). As summarized in Figure 45.8, low-volume hospitals (fewer than 16 patients per year) had the longest door-to-balloon time and achieved similar in-hospital mortality for lytics or catheter-based reperfusion. On the other hand, the high-volume MI centers had better door-to-balloon times and better results for PCI compared with lytics (p <.001 for a strategy-hospital volume interaction) (145). Tu and colleagues have taken the field a step further by analyzing MI outcomes in 98,194 patients treated by 5,374 physicians in Canada (146). A strong inverse relationship between average annual volume of MI cases treated by the admitting physician and mortality rate was demonstrated (Fig. 45.9) (146).

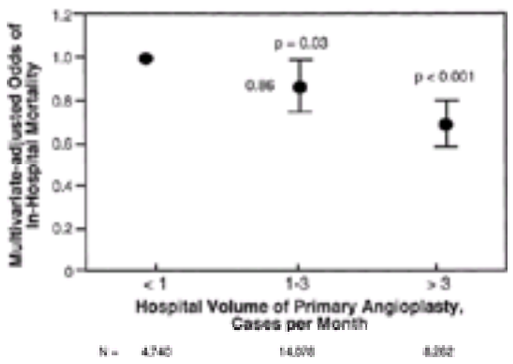
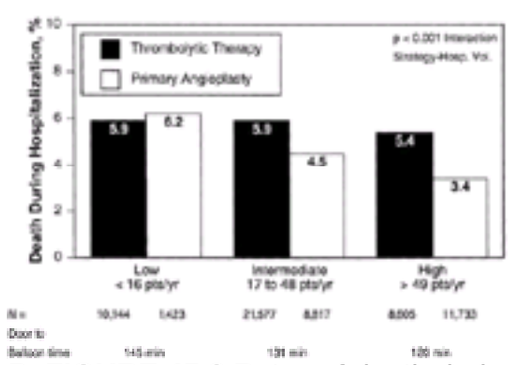


FIGURE 45.7 Multivariate-adjusted relationship between institutional volume of primary angioplasty cases and mortality. (From Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000;283:2941–2947, with permission.)



P>**FIGURE 45.8** Rates of death during hospitalization for patients with acute myocardial infarction treated with thrombolytic therapy versus primary angioplasty, stratified by hospital primary angioplasty volume. *Door time* refers to arrival at the hospital; *balloon time* refers to the time of first balloon inflation of the primary angioplasty procedure. (From Magid DJ, Calonge BN, Rumsfeld JS, et al., for the National Registry of Myocardial Infarction 2 and 3 Investigators. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA* 2000;284:3131–3138, with permission.)

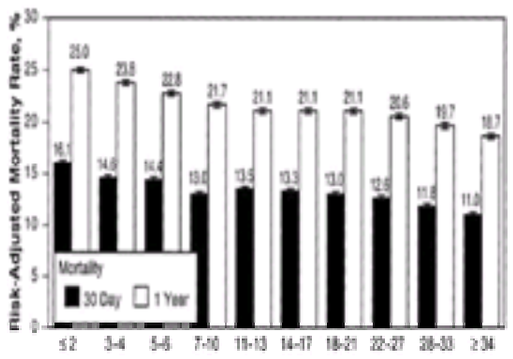


FIGURE 45.9 Risk-adjusted acute myocardial infarction mortality rates at 30 days and 1 year by deciles of annual volume of acute myocardial infarction patients treated by admitting physician. Error bars indicate 95% confidence intervals for mortality rates. (Adapted from Tu JV, Austin PC, Chan BTB. Relationship between annual volume of patients treated by admitting physician and mortality after acute myocardial infarction. *JAMA* 2001;285:3116–3122, with permission.)

The health care system and type of hospital have also been the subject of study for MI outcome research. The advantages of teaching and academic centers

(147,148), those that have on-site revascularization (149) and Medicare compared with the Veterans Health Administration (150,151), have all been explored.

COMMON THEMES AND PROBLEMS

Process versus Outcome

The debate about whether quality of care measurements should focus on the process of care or outcomes remains highly controversial. Advocates of measuring process point to the near impossibility of being certain that outcomes can be risk-adjusted and to the huge costs of measuring outcomes other than death. Furthermore, difficulty with common definitions and the ease of gaming the system with regard to nonfatal outcomes continue to produce substantial difficulty in the assessment of outcomes. Finally, the large number of outcomes that must be identified to discern differences in quality produces a fundamental limitation for the system.

Some have advocated that clinical trials should be used to establish efficacy and that outcome research should be used to determine the most effective way of delivering a diagnostic therapy or strategy. When these components have been evaluated in adequately sized studies, measurement of how often appropriate practices are used provides a method of measuring quality that is firmly based in empirical methodology and does not require adjustment for differences in baseline characteristics of patients seen by one practice compared with another.

Volume versus Outcome

The relationship between volume and outcome has been at the center of discussion because it is an easy structural measure to record and to assess in an aggregate manner. The fundamental observation that “practice makes perfect” seems to be a verifiable observation across multiple medical practices and procedures. This relationship seems to hold not only for individual practitioners, but also for institutions.

However, volume is not the only determinant of quality, and empirically, differences in volume account for only a modest amount of differences in outcomes observed. Nevertheless, almost all adequately sized studies indicate that focus on a particular medical problem or procedure as evidenced by high volume tends to be associated with better outcome; therefore, when all other factors are equal with regard to medical outcomes, one would prefer to be cared for by a high-volume clinician in a high-volume facility.

A particularly interesting issue in the volume-outcome relationship is the extent to which the proper environment can allow the low-volume clinician to achieve adequate or excellent outcomes. For example, interventional laboratories in which a high-volume operator is physically present may allow many low-volume operators to thrive with oversight and help from a more experienced person. Similarly, although cardiologists provide care for acute MI, which has a more consistent evidence base for appropriate use of therapies and better outcomes than what internists or family practitioners provide, it is also likely that a coronary care unit supervised by a cardiology intensivist can allow equal or better quality of care with multiple lower-volume generalists admitting patients.

Individual versus Institutional Assessment

Arguments can be made that oversight agencies should concern themselves with aggregate measures of performance of practice groups or institutions, allowing internal assessments to govern the behavior of individual practitioners. This approach has the advantage of providing adequate sample size to discern differences and of allowing for high-quality, low-volume operators to perform within groups that can monitor quality in groups of patients. It also seems apparent that holding groups responsible for outcomes will allow the natural selection process to occur, as groups will not want poor performers to drag down the overall group effort, and it is likely that gravitation toward development of shared expertise would occur. This approach is already being used in the assessment of managed care organizations by the NCQA and in the assessment of institutions by managed care organizations in the determination of which practices are awarded contracts.

Multifactorial Understanding of Outcomes

The science of determining the reasons for the variability in underlying risk that can affect outcome is in an early stage of development. In the past, this science was mostly limited by the inability to aggregate large amounts of data, but this restriction is no longer a problem. The most fundamental limitation remains difficulty accessing true clinical information, because little of it is recorded in a computerized format. Statistical methodology, including multivariable regression analysis and neural networking, continues to develop, but for the most part, an understanding of the empirical basis for reaching a conclusion remains elusive to most practitioners, and statistical concepts are even more foreign to most administrators and patients. Finally, an understanding of the biologic and clinical constructs that are critical to the prediction of outcomes generally falls far short of desired accuracy, even with the best statistical methodology and careful prospective data collection.

Low-Volume Operator

The low-volume operator or low-volume provider presents a special problem with regard to statistical assessment. In the absence of a sufficient number of cases, a few bad outcomes will give unreliably high point estimates of event rates. Additionally, practitioners with low volume may have the appearance of excellent outcomes due to chance. A useful rule of thumb is that when no complications have been observed, an approximation for the upper ninety-fifth percentile of the confidence interval is $3/N$, where N is the number of patients treated.

Fundamentally, the numbers demonstrate that determining complication rates or outcomes with confidence is nearly impossible in the low-volume situation. This conclusion limits the number of options. Because it is known that low-volume operators have worse outcomes, they could simply be banned; this approach is not likely to succeed in the current environment. A second option would be to allow low-volume operators to avoid statistical assessment until an adequate number of cases had been recorded. An alternate option would set up a “buddy,” or pairing, configuration of operators as long as the group volume was adequate for statistical assessment. This approach would promote peer review as the main method of controlling quality in the low-volume operator, with substantial motivation through peer pressure.

New Operator

In an environment focused on assessment of quality, the training of new operators requires special consideration. The lack of experience and volume would be expected to lead to less sufficient process and outcome measures. Teachers and teaching institutions put themselves at risk in this situation. An evaluation of this problem leads to the inevitable conclusion that special allowances need to be made for teaching institutions, but the measurement of process and outcomes provides a motivation for providing top-notch teaching rather than “laissez-faire” training programs.

Difficulty of Data Collection

Substantial information exists to validate the concept that a hierarchy of accuracy of clinical data exists. Prospective clinical databases provide the highest level of data reliability, followed by chart review, administrative reports, and self-audit. Several studies provide substantial insight into the difficulties with self-audit. A review of the literature on reported complications of carotid endarterectomy revealed that studies with only individual surgeon assessment of the patient found only a 2.3% rate of death or major complications, whereas multiauthored reports showed a 5.5% rate and reports with specific assessments by internists or neurologists revealed a 7.7% rate of death or major complications (152). Similarly, when cardiologists report rates of nonfatal MI after percutaneous intervention, much lower rates are observed with self-report than with individual assessment (43). Extensive data are available comparing self-report with core laboratory assessment of procedural anatomic results indicating a similar phenomenon: Practitioners have difficulty of bias when reporting on their own care (153). Administrative databases provide low-quality, but comprehensive data. In one report (45), agreement rates between clinical and claims databases varied from 0.83 for diabetes diagnosis to 0.09 for unstable angina, with a wide variety of values in between. All of these findings point to the fact that the ideal data system does not currently exist. The limitations of these systems should be acknowledged in quality reports, but too often this issue is forgotten.

Cost

The cost of collecting data specific for quality assessment is much higher than anticipated. For hospitals that are responsible to provide their data to multiple payers, this burden can be overwhelming. In Pennsylvania, where extensive data are required to submit for patients, the cost per case for specific data collection was estimated to be $17.43, or representing approximately $100,000 per year (51). In comparison, to participate in the Cleveland Health Quality Choice program of rating risk-adjusted mortality for five diagnoses, it costs The Cleveland Clinic Foundation more than $450,000 per year for chart abstractors, data management, and quality assurance. Thus, the cost of the collection of the data can be quite imposing and represents a major obstacle to the widespread use and acceptance of serial quality assessments. Efforts to reduce the costs by using electronic means of capturing the data, from both the administrative database and the laboratory, with avoidance of chart review, are under way (51).

Auditing

The difficulties with statistical modeling to adjust for differences in baseline characteristics have been reviewed elsewhere. Regardless of the method used, when the results in one practice differ from the results in another practice, whether the different outcomes resulted from differences in medical care, the play of chance, or a greater severity of underlying illness from one practice to another cannot be determined with certainty. Fortunately, it has been the experience of most outcome assessors that when major differences in outcomes occur, the differences in quality are measurable on multiple levels. Even when high-quality statistical models are available, the ability to game the system can be substantial. As reviewed for bypass surgery in New York State, concern exists about practices ensuring that maximum severity of illness is coded so that the observed versus expected numbers will be as favorable as possible (74).

Rewarding High Risk

Another special problem is the frequent inability of statistical models to account adequately for those who care for specially high-risk populations. Inner-city or extremely rural populations may have worse outcomes due to difficulty with compliance or resources. These sorts of variables are frequently not collected or accounted for. It has been proposed that special consideration should be given to practices voluntarily caring for identifiable high-risk populations. In the context of gaming the system, this approach would reduce the current incentive to steer high-risk patients away from practices undergoing substantial outcome scrutiny or financial pressures. Outcome models frequently neglect recording critical information about patients transferred from one institution to another.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The public entitlement for complete information on hospitals and physicians has been validated by the supreme court in New York, but the most important concern is that the public accesses quality information about the quality of care. Many clinical, statistical, and logistic problems, summarized in *e*Table 45.1.4, largely remain unresolved. Although public release of meaningful data can be supported, the most critical obstacle is whether and how such data can be generated. The public expectations of assessing the quality of care have been raised in the last few years. In a State of the Union address, former President Bill Clinton stated the following:

***e*TABLE 45.1.4** CLINICAL, STATISTICAL, AND LOGISTIC PROBLEMS OF RELEASING OPERATOR-SPECIFIC DATA TO THE PUBLIC

Clinical problems
Mortality, although easiest to track, may not be the most meaningful index (e.g., length of stay, readmission, functional status, recurrence of symptoms)
Difficult to establish the appropriate reference group for comparison
Incomplete data (e.g., lack of ejection fraction)
Statistical problems
Limited sample, with respect to number of patients, event rates, and time of assessment
Risk adjustment is difficult
Proper weighing of variables
Small differences that are not statistically significant on an individual basis can have a meaningful cumulative impact
“Reward” for high-risk patients
Cluster phenomenon and periodicity of release
Logistic problems
Collection and proper maintenance of the data, preserving authenticity
Cost of data management

From Topol EJ, Califf RM. Scorecard cardiovascular medicine. *Ann Intern Med* 1994;120:65–70, with permission.

> We have evidence that more efficient delivery of health care doesn’t decrease quality. . . . Pennsylvania discovered that patients who were charged $21,000 for coronary artery bypass surgery received as good or better care as patients who were charged $84,000 for the same procedure in the same state. High prices simply don’t always equal good quality” (49).

Clearly, the amalgamation of cost and quality into the “value” of health care has become a principal competitive concept, for one health care system to prevail against another. However, the data for the quality component are too often “soft,” with such components as patient satisfaction indices heavily relied on. Even for comparing cardiac services between hospitals or health care systems, it is very difficult to get an authentic quantitative evaluation of interventional cardiology, bypass surgery, electrophysiology and pacing, management of acute MI and heart failure, and all the other facets of a heart center. Paradoxically, in this world of a high density of information that is immediately electronically available for business, sports, and news, we are still lacking the critical data that would be necessary for decisions on health care.

Assuming that one can strive to generate worthwhile data, there is also the controversy about whether the data have an impact on improving the quality of care. With CABG the best-case scenario for measuring outcomes and assessing and adjusting risk, the debate continues as to whether the 40% reduction in mortality in CABG throughout New York State was a direct result of detailed quality assessment. Transfer of high-risk patients outside a particular medical system continues to be studied (154).

Operator- or physician-specific outcome data are perhaps most controversial of all because the inadequacies of sample size magnify the problems of interpreting these data. Nonetheless, such data have been used for cardiac surgeons in New York State and in Pennsylvania. Ultimately, for low-volume operators to assert their capabilities to deliver excellent care, it will be essential to demonstrate lack of complications on a risk-adjusted basis.

FUTURE DIRECTIONS

As was expressed by Nightingale more than a century ago, there is a need for better accountability in medicine. Via the study of quality parameters, it is hoped that health care systems, hospitals, and physicians will accept more responsibility for maintaining data and disclosing the data in suitable circumstances. Surely checks on process, such as monitoring the proportion of patients with proven coronary disease and hypercholesterolemia who are not getting secondary prevention therapy or the number of patients with heart failure not on an angiotensin-converting enzyme inhibitor, will be worthwhile. Internally, medical centers should consider developing risk-adjusted models for such procedures as CABG and percutaneous revascularization to monitor groups of physicians over an extended period, such that the number of operations or procedures is suitable for analysis.

Many factors suggest that the future of quality assessment will continue to be mired with controversy (155,156,157,158,159,160 and 161). The cost of information about quality care (162,163) and the cost of not delivering quality care (164) will remain contentious. The risks of risk adjustment (165,166 and 167) and release to the public of such data (168,169,170,171 and 172) remain unsettled issues. Fundamental issues such as defining the optimal way to measure quality (173,174,175,176,177 and 178), appropriateness of procedures (179,180), and physician competence (181,182) lie at the heart of debate and will continue to evolve over time. Without question, the effect of simply studying quality can have a salutary outcome (183), and as clinical trials continue to address major, unanswered dilemmas it becomes easier to judge whether evidence-based medicine is being practiced (184). A major, penetrating issue is individual physician and institution accountability. Kassirer, a former editor of the *New England Journal of Medicine*, claims we remain in a state of “pseudoaccountability” (185) and that hospitals need to heal themselves (186). Much of Iglehart’s review of the American health care system (187) and the insight of Shine, who directs the IOM (188) and the International Practitioners Data Bank (189), reinforce this perspective. The recent British Royal Infirmary Inquiry and Report underscored the nature of pseudoaccountability recounting the deaths of brain-damaged children (in 167 of 1,827 children undergoing cardiac surgery in a 12-year period) and the media characterized the “club” atmosphere with reluctance to accept criticism that allowed poor surgical standards to continue undetected for years (190,191 and 192). Certainly, in our quest to improve the quality of care and to avoid medical errors in cardiovascular medicine, there will need to be deep commitment for not only improving the data accountability and measurement instruments, but also the “teeth,” or active steps towards privileging, credentializing, and close surveillance of hospital and physicians.

THE FUTURE

Electronic data retrieval, ultimately via Internet entry, will greatly facilitate collection and analysis of data. There will be steady refinement of risk adjustment for each of the major diagnoses and procedures in cardiovascular medicine (e.g., acute MI, heart failure, atrial fibrillation, CABG, PCI). Ultimately, the goal of measuring quality and stepwise reduction of medical errors will be increasingly achieved over time.

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PRINCIPLES OF IMAGING

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Accurate imaging is essential to assess cardiac anatomy, function, perfusion, and metabolism, and revolutionary advances have been seen in the past 20 years, primarily because of improvements in computer technology and digital signal processing. The heart may be imaged using x-rays [radiography, angiography, computed tomography (CT)], gamma rays (radionuclide imaging, positron emission technology), sound waves (Doppler echocardiography), and the magnetic properties of the hydrogen nucleus [magnetic resonance imaging (MRI)]. Tests may be compared by their ability to detect and exclude disease (sensitivity and specificity, respectively), but the predictive value of the test depends largely on the prevalence of the disorder in the population being tested (Bayesian analysis). Computer processing is important both in generating images and in enhancing the images for display (smoothing and edge enhancement); Fourier transformation is commonly used to analyze the frequency content of images and data in Doppler echocardiography, MRI, and radionuclide ventriculography. Digital image storage is becoming feasible with reductions in computer costs and agreement on the Digital Imaging and Communications in Medicine (DICOM) Standard for medical image exchange. The massive storage requirements may be reduced by careful clinical editing of studies and with digital compression algorithms. All-digital storage and transmission will greatly enhance the value of cardiac studies and facilitate telemedicine.

GLOSSARY

Convolution: Altering a pixel based on the values of surrounding pixels.

DICOM: Digital Imaging and Communications in Medicine, a formatting standard to allow the exchange of medical images.

Digital compression: Recording an image to require less storage. *Lossless* compression does not change the appearance at all (but yields little compression), whereas *lossy* compression yields greater savings (but with some alteration of the image).

Doppler principle: Ultrasound signals have their frequency shifted in proportion to the blood velocity.

Fourier analysis: Analysis of the frequency content of an image or signal.

Gamma ray: High-energy photon produced by nuclear decay.

Nuclear magnetic resonance: Spinning or precessing of certain nuclei (typically the hydrogen proton) in the presence of a magnetic field.

Photons: "Particles" of electromagnetic radiation.

Piezoelectric: A property of matter that converts electricity into vibration and vice versa.

Point processing: Altering an image gray scale, pixel by pixel.

Positron: Positive electron (antimatter); when it encounters an electron, both are annihilated and two 511-keV photons are emitted in opposite directions, forming the

physical basis for positron emission tomography.

X-ray: High-energy photon produced by rearrangement of an atom's electron cloud.

INTRODUCTION

High-fidelity imaging is required to understand cardiovascular anatomy, function, metabolism, and blood flow more than any other organ system in the body. The fine structure and complex motion of the heart demand imaging modalities with high temporal and spatial resolution. Fortunately, intensive research in physics, pharmacology, and computer processing over the past 50 years has led to dramatic improvements in our ability to characterize and quantify disorders of the cardiovascular system. The next 11 chapters describe in greater detail the clinical aspects of the major cardiovascular imaging modalities: radiography, echocardiography, angiography, nuclear cardiology, and MRI. As a prelude, this chapter describes many of the concepts common to each of these techniques, including image generation, computer processing, assessment of diagnostic accuracy, and the emerging area of digital storage and transmission. An understanding of the physical background of these methods will help the reader to understand better the clinical applications described in later chapters.

Here we consider four broad ways to acquire images of the heart: x-ray transmission, radionuclide emission, ultrasonic reflection, and nuclear magnetic resonance. Although these techniques share many features, together they span virtually all of classical and quantum physics. This chapter can only touch on these topics, and the reader is referred to a number of excellent texts for greater detail (1,2,3,4,5,6,7,8 and 9).

What Is Imaging?

In a broad sense, imaging displays the differential interaction of energy with matter to discern structure or function. For instance, the printed page reflects fewer photons from dark letters, allowing them to be seen against the photon-rich white page. Similarly, radiography exploits the fact that more x-rays are absorbed by bone than by soft tissue, and echocardiography displays the reflection of ultrasonic energy from the border of two tissues with different acoustic impedances. Radionuclide techniques are slightly different in that they deliver an energy source (the radioactive compound) to the body, where it is concentrated in structures of interest and then localized by external detectors. MRI defines the differential distribution of weak magnetic characteristics within the body.

Basic Concepts

A number of terms and concepts are common to all imaging modalities.

Resolution

Resolution can have several meanings in imaging. *Spatial resolution* reflects the smallest separation that two objects can be distinguished. For example, in radiography, spatial resolution is measured with a grid of finely spaced lines. The densest packing of lines that can be distinguished is reported as the number of line pairs per centimeter. For radiography, resolution is relatively constant across the field of view. This is not true for echocardiography, which typically has greater resolution in the near field than in the far field, because of the divergence of the ultrasound beam. Furthermore, in echocardiography, resolution is *anisotropic*, that is, better in the axial direction (along a scan line) than in the lateral direction (across scan lines). One must also take care to distinguish the physical resolution of the imaging modality from the resolution of a video or computer display (commonly used in nuclear imaging, echocardiography, MRI, and digital angiography). The spacing of the picture elements (*pixels*) on the screen may be greater or lesser than the physical resolution. This screen resolution typically is stated in the number of pixels across the screen in the horizontal and vertical direction (640 × 480 is typical for low-end computer monitors; 1,024 × 1,024 for high-resolution digital angiography; and 2,048 × 2,048 or even higher for digital radiographic and mammographic images). The functional spatial resolution is always the lesser of the physical and screen resolutions.

Temporal resolution reflects the frequency with which an image is generated, usually stated in frames per second. Plain film radiographs are typically taken as single images, but temporal resolution may still be relevant because the *shutter speed* (the time the film is actually exposed to x-rays) determines whether rapid movements (such as prosthetic valve motion) can be "frozen" in the image. There often is a trade-off between temporal and spatial resolution. Echocardiograms can be generated more frequently, but this usually requires that the density of scan lines per image be reduced. The data for a multigated nuclear scan can be divided into shorter temporal "bins," but this reduces the amount of data available for each image, reducing the signal-to-noise ratio and spatial resolution.

Resolution issues are also important in the calculation of cardiac blood velocity (by Doppler echocardiography or MRI). Velocity resolution reflects the smallest difference in velocity that can be discerned, whereas temporal resolution is the frequency with which the velocity data are updated. Just as with images, there usually is a trade-off between velocity and temporal resolution. Increasing the frequency of display reduces the velocity resolution and vice versa.

Dimensionality

The heart is a four-dimensional structure, possessing three spatial dimensions of shape and one temporal dimension of motion. Most imaging modalities have two spatial dimensions (i.e., a picture, such as a radiograph or an echocardiographic image). M-mode echocardiography displays structures along a single line in the heart (like an ice pick), and so is a one-dimensional display. Magnetic resonance, CT, and some nuclear and echocardiographic studies are intrinsically three-dimensional (3-D), although the display may be on a two-dimensional (2-D) screen. Because motion is critical to many cardiac diagnoses, most modalities include the temporal dimension, typically with a series of 2-D or 3-D images. Plain film radiographs and some nuclear studies do not show motion.

Transmission versus Tomographic Imaging

Two-dimensional images of the heart can be generated by either *transmission* or *tomographic* techniques. In transmission imaging, the full thickness of the heart is projected onto a screen, whereas a tomogram displays structures lying within a single plane of the heart. For most applications, tomographic imaging (used in MRI, CT, echocardiography, and many nuclear tests) is preferable, because there is no interference from overlying structures. For angiography, however, transmission imaging is actually an advantage, because the full course of the vessel can be visualized, something no single tomographic plane could do. Indeed, in magnetic resonance angiography, the 3-D data set is projected onto a plane to generate a transmission image for easier diagnosis.

IMAGING WITH ELECTROMAGNETIC RADIATION: X-RAYS AND GAMMA RAYS

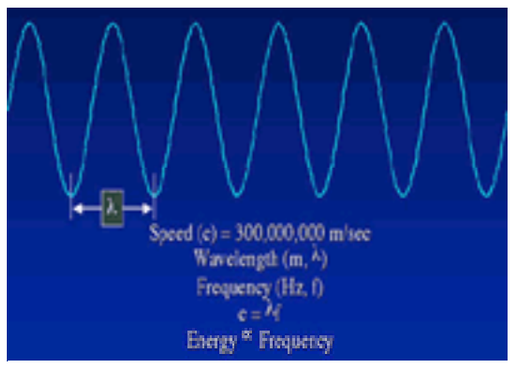
Radiography uses x-rays delivered externally to image the body, whereas nuclear imaging uses gamma rays produced inside the body. There is in fact no physical difference between x-rays and gamma rays, both being forms of high-energy electromagnetic radiation. The only distinctions are historic and etiologic: Gamma rays by definition are produced by radioactive decay within the atomic nucleus, whereas x-rays are produced by processes in the electron cloud surrounding the nucleus. As detailed in the CD-ROM and online versions of this chapter, electromagnetic radiation is characterized by frequency and wavelength, the product of which is equal to the speed of light (299,792 km per second) and an energy, which is proportional to the frequency. Table 46.1 shows typical values for a range of electromagnetic radiation.

Radiation	Frequency (Hz)	Wavelength (m)	Energy (eV)
AM radio	1.00×10^{6}	300	4.14×10^{-9}
^{1}H in 1T field	4.26×10^{7}	7.04	1.76×10^{-7}
FM radio	1.00×10^{8}	3.00	4.14×10^{-7}
Microwave oven	2.45×10^{9}	1.22×10^{-1}	1.01×10^{-5}
Infrared	4.29×10^{14}	7.00×10^{-7}	1.78
Green light	6.00×10^{14}	5.00×10^{-7}	2.48
Ultraviolet	1.00×10^{15}	3.00×10^{-7}	4.13
Diagnostic x-ray	1.45×10^{19}	2.07×10^{-11}	6.00×10^{4}
Technetium-99m gamma ray	3.38×10^{19}	8.87×10^{-12}	1.40×10^{5}
β+ β− gamma ray	1.23×10^{20}	2.43×10^{-12}	5.11×10^{5}
Therapeutic gamma ray	4.80×10^{21}	6.25×10^{-14}	2.00×10^{7}
Cosmic rays	6.00×10^{23}	5.00×10^{-16}	2.49×10^{9}

TABLE 46.1 ELECTROMAGNETIC RADIATION

Nature of Electromagnetic Radiation

Quantum mechanics has taught us that electromagnetic radiation can be thought of as eing made up of either waves or particles (10). Before the twentieth century, the classical perception was that of electrical and magnetic waves, propagating at the speed of light c, 299,792 km per second. Viewed this way (eFig. 46.0.1), electromagnetic radiation is characterized by a wavelength l and a frequency *f* related to c as



***e*FIGURE 46.0.1** Parameters of electromagnetic radiation. In the wave representation of electromagnetic radiation, key parameters are the wavelength and frequency, the product of which is the speed of light. In the particle representation, the key parameter is photon energy, which is proportional to frequency.

$$\lambda f = c$$

Table 46.1 displays the wavelength and frequency for some familiar forms of electromagnetic radiation. As can be seen, there is over a 10^{15}-fold range between AM radio waves and the highest frequency radiotherapeutic gamma rays, with visible light lying roughly in the middle.

The second representation of electromagnetic radiation, discovered in the early part of this century, is of discrete particles (*photons*), massless "billiard balls" propagating at the speed of light. These photons have an energy, *E*, associated with them given by the product of frequency multiplied by Planck's constant h, 6.625 × 10^{-27} erg-second (g-cm^2/s):

$$E = hf$$

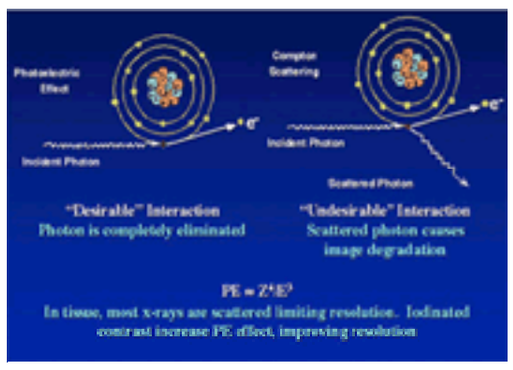
Because the erg is so large compared with typical photon energies, *E* frequently is expressed by the electron volt (eV), the energy acquired by an electron being accelerated by a 1-V electrical field: 1 eV = 1.602 × 10^{-12} erg. As Table 46.1 shows, photons of light have an energy of approximately 2 eV with typical x-rays in the 50- to 100-keV range.

It is important to remember that neither the particle nor wave nature of electromagnetic radiation is the "correct" representation. Both are correct all of the time, but in practice, one aspect or the other typically is more evident. Indeed, quantum mechanics has further taught us that particles such as the electron can sometimes have wavelike properties.

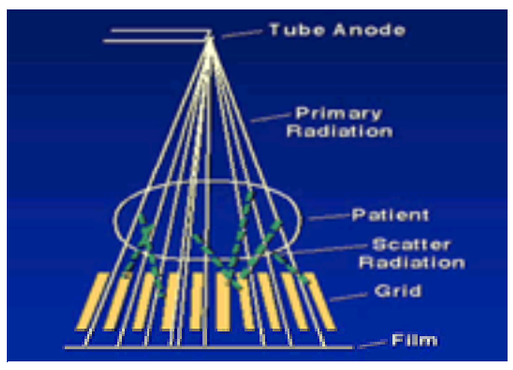
Interaction of X-Rays and Gamma Rays with Matter

Radiography depends on the differential absorption and scattering of photons by various types of tissue. In nuclear imaging, by contrast, nuclide distribution in the body is the primary determinant, although photon scattering is a major cause of image degradation.

Thus, understanding how x-rays and gamma rays interact with tissue yields insight into how both types of images are formed. For photons in the 50- to 500-keV range (those of principal diagnostic importance), there are two major interactions with matter to consider: the *photoelectric effect* and *Compton scattering* (eFig. 46.0.2). In the photoelectric effect, a photon is completely absorbed by an atom, which then emits a high-speed electron that is quickly stopped in the surrounding tissue, thus removing the photon completely from the image. In Compton scattering, a high-speed electron is also emitted, but the original photon is not completely absorbed but rather scattered at a lower energy and at a different angle from the original direction. This scattering can significantly degrade the image, since these photons may escape the body and strike the x-ray film in a random location. This scattering can be partially ameliorated by a collimating grid in front of the film to admit only photons traveling in a straight line from the x-ray source (*e*Fig. 46.0.3). In nuclear medicine, it is harder to exclude these scattered photons, leading to worse image degradation than in radiography.



***e*FIGURE 46.0.2** Interaction of x-rays and gamma rays with matter: the photoelectric effect (PE) and Compton scattering. In each case, a shell electron is emitted that quickly loses energy by ionizing adjacent atoms. With Compton scattering, however, a lower energy photon is also emitted, traveling in a different direction from the incident one, which leads to image degradation. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:627, with permission.)



***e*FIGURE 46.0.3** Exclusion of Compton-scattered photons by a collimating grid.

It would be better if all photons interacting with the tissue did so by the photoelectric effect, since photons are completely absorbed rather than scattered. Unfortunately, the likelihood of the photoelectric effect is inversely proportional to the third power of the photon energy *E* and directly proportional to the fourth power of the atomic number *Z* (number of protons) of the interacting atom: photoelectric effect $\approx Z^4/E^3$. For tissue (average $Z \approx 5$), virtually all attenuation is caused by Compton scattering above an energy of 80 keV (typical for a diagnostic x-ray or thallium decay). By comparison, the *Z*-dependence is exploited in iodinated contrast agents and sodium iodide detectors for nuclear medicine; because iodine has a *Z* of 53, the photoelectric effect is dominant up to photon energies of 300 keV.

Photon Attenuation

The net effect of Compton scattering and the photoelectric effect is to remove a certain percentage of the incident photons for each centimeter of tissue they pass through. This percentage is determined by the linear attenuation coefficient μ (cm^{-1}), which causes the intensity of an x-ray beam to decrease exponentially with distance traveled through the body. The critical factor for x-ray imaging is that the attenuation coefficient μ varies for different tissues in the body, being low for lung, intermediate for soft tissue, and high for bone and radiographic contrast media such as barium and iodine. The coefficient μ further varies inversely with photon energy (generally), yielding deeper penetration for higher energy photons.

As a beam of photons passes through the body, the rate of attenuation changes as they pass through tissue with variable attenuation coefficient μ. Figure 46.1 shows the photon intensity as a function of depth of travel into the tissue, which decays most rapidly when μ = 5 (arbitrary units). The 2-D image that results from the passage of x-rays thus has lost all information about the distribution of matter along the x-ray path. CT techniques (see Computed Tomography) must be used to reconstruct the 3-D distribution of μ.

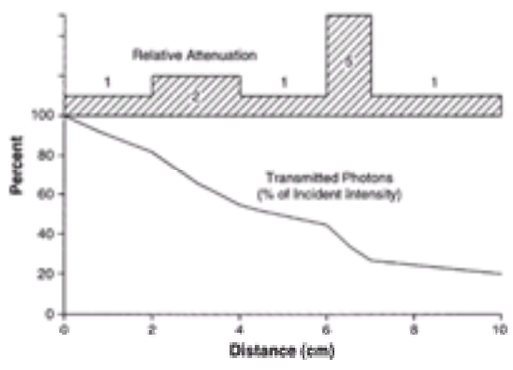


FIGURE 46.1 Impact of linear attenuation coefficient (μ) on the rate of photon intensity decay. A beam of photons (with 100% intensity) enters the tissue at 0 cm, losing intensity in proportion to μ (upper bar graph, units arbitrary). Only 21% of the incident photons traverse the entire tissue without absorption or scattering. Each of the segments is an exponential curve with a decay constant proportional to μ. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:628, with permission.)

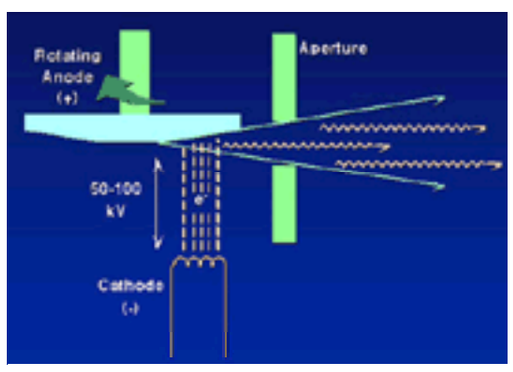
Note that attenuation has different implications for x-ray and nuclear imaging. In radiography, all diagnostic information results from differential attenuation of the x-ray beams passing through the body. In nuclear medicine, by contrast, the photons themselves are similar to x-rays, but it is their distribution *within* the body that is of interest. Ideally, there should be no attenuation at all to maximize the diagnostic information available at the surface, but short of this, attenuation should be as uniform as possible.

The distinctive features of radiography and nuclear medicine are discussed.

Imaging with X-Rays

Production of X-Rays

The basic method for generating energetic x-rays has changed little since the early part of this century (11,12). The cathode (negative electrode) of a vacuum tube is heated white hot, allowing electrons to “boil” from its surface (*e*Fig. 46.1.1). The electrons are then accelerated to roughly half the speed of light by a 50- to 150-kV gradient before they collide with the anode (positive electrode) made of tungsten or similar heavy metal. Most of these electrons collide with the shell electrons of the anode metal, dissipating their energy as heat. A small proportion of incident electrons actually pass close enough to an atomic nucleus in the target to “feel” the intense electric field surrounding the protons. This electric field abruptly decelerates the electron, bending its course and causing release of an x-ray, a process termed *bremsstrahlung* radiation, which occurs only approximately 0.5% of the time for 100-keV electrons striking tungsten, the remaining energy being wasted in heat. Because only a small percentage of x-rays will be emitted in the direction of the patient, the efficiency of the x-ray tube is further reduced by at least another factor of 10.



***e*FIGURE 46.1.1** Schematic diagram of x-ray production. Within a vacuum tube, electrons “boil” off of the heated cathode and are accelerated by the 50- to 150-kV potential difference before striking the rotating tungsten anode. There, a tiny fraction of the electrons interact with the tungsten nuclei and produce x-rays by the *bremsstrahlung* effect. These x-rays are collimated to produce a small cone of radiation. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:628, with permission.)

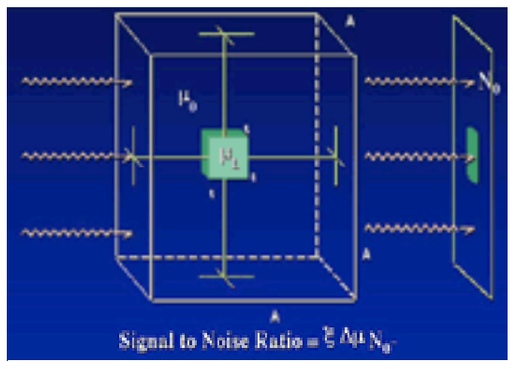
For instance, a typical x-ray tube used in cineangiography might have 100-kV potential and 500-mA current (50,000 W) and fire for 3 ms per pulse (150 J). If 0.5% of this (0.8 J or 8×10^6 ergs) is converted into 100-keV x-rays (1.6×10^{-7} erg each) then approximately 5×10^{13} x-rays will be produced, of which, perhaps 2%, or 1 trillion, ultimately strike the patient.

Statistical Limitations to X-Ray Image Resolution

Two major factors have an effect on overall x-ray image resolution: system noise and the geometry of the imaging system. System noise is related to the random variation in the number of photons striking any given area of the patient. Because the x-ray production obeys Poisson’s statistics, the standard deviation s in the number of photons striking any given area (noise) is approximately equal to the square root of the number of photons expected (signal). For the previous example, if the 1 trillion x-rays per pulse irradiate a 32 × 32-cm area on the patient (1,000 cm^2), this yields an x-ray density of approximately 1 billion photons per square centimeter, with a standard deviation of approximately 32,000, leading to a signal-to-noise ratio of 32,000:1. A 1-mm^2 patch will have one-hundredth of this number of

photons but one-tenth the variability, a reduction in signal to noise by a factor of 10 to 3,200:1.

For a structure to appear distinct from the background, it must attenuate the x-ray beam differently enough so that the change in the number of transmitted photons (D*N*) exceeds the natural variability s expected for a region of that size. eFigure 46.1.2 illustrates a cubic nodule, z cm on a side, nested inside an otherwise homogeneous cube of tissue from which it differs in attenuation coefficient by Dμ; the signal-to-noise ratio then is given (approximately) by |D*N*|/s:



***e*FIGURE 46.1.2** Diagram to illustrate statistical aspects of x-ray resolution. A uniform block of tissue A cm on each side has uniform linear attenuation coefficient = μ_1 except for a small x × x × x-cm block with $\mu = \mu_2$. Incident photon flux is F/cm^2 with N_0 striking an n × n patch on the surface and N_1 and N_2 exiting the tissue having passed and not passed, respectively, through the small block. The signal-to-noise ratio is given by the difference between N_1 and N_2 (D*N*) compared with the expected statistical variation in N_1, which is s = $(N_1)^{1/2}$. See text for details. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:628, with permission.)

$$\text{Signal-to-noise ratio} = \zeta\, \Delta\mu\, N_0^{1/2}$$

where N_0 is the number of photons that would pass through the tissue if the nodule were not there. Thus, the signal-to-noise ratio is reduced when small nodules are sought and when there is little contrast between the tissues. N_0 exerts a profound influence on signal-to-noise ratio; it relates directly to the intensity of the x-ray beam and inversely to the attenuation coefficient of the background tissue. If the x-ray beam is highly attenuated by the surrounding tissue, then signal-to-noise ratio will be poor regardless of the other factors. This explains why it is much easier to image a piece of lead suspended in air than to see a bubble of air inside a block of lead, even though the difference in attenuation, Dμ, is the same in each case.

The signal-to-noise ratio in an image is related to the difference in attenuation coefficient between the object of interest and the background, as well as the number of photons passing through the body. How may resolution be improved? An obvious solution is to do something to increase Dμ. If the nodule is actually a small vessel, infusing iodinated contrast medium dramatically improves resolution. Increasing the density of the incident photons (by increasing the current in the x-ray tube or lengthening the pulse) will help some but not much; it takes approximately a 16-fold increase in photon density to improve the resolution by a factor of 2. As an alternative method to improve photon transmission number, some catheterization laboratories may require obese patients to undergo weight reduction before study. One may also reduce attenuation by increasing the energy of the incident x-rays by raising the x-ray tube voltage. However, this effect must be balanced against the reduction in Dμ, which also typically occurs with increasing photon energy.

Geometric Limits to X-Ray Image Resolution

The second major determinant of x-ray image quality relates to the finite size of the x-ray source. Within the x-ray tube, the anode is beveled at a small angle (7 to 13 degrees), so that the x-rays, emitted at right angles to the electron beam, appear to arise from a small focal spot, perhaps 1 mm^2 in area. As shown in Figure 46.2, even this small spot may blur the image. For a focal spot *a* cm in diameter, positioned *A* cm from the patient with the film *B* cm from the patient, the width of blurring will be *aB*/*A*. To minimize this, one seeks as small a focal spot as possible, limited principally by anode heat. Similarly, *B* should be as small as possible, but this is usually dictated by patient size. Finally, resolution can be improved by positioning the focal spot as far from the patient as possible (large *A*), but since x-ray density declines as 1/*A*^{2}, a trade-off exists between signal-to-noise ratio and blurring.

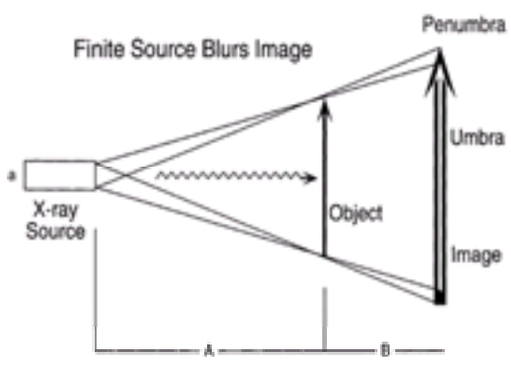


FIGURE 46.2 Geometric limits to x-ray resolution. The finite size of the x-ray source (a) leads to a penumbra around solid objects of *aB*/*A*. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:630, with permission.)

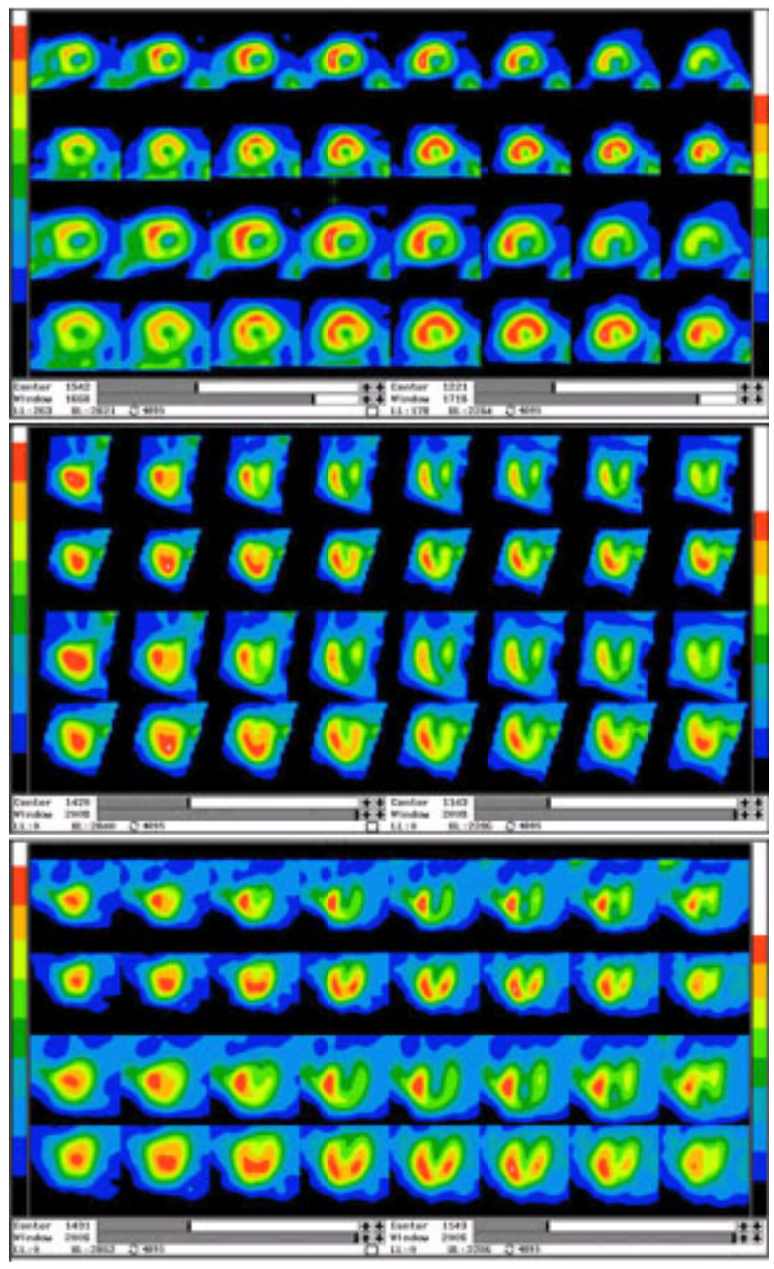
Recording X-Ray Images

In conventional radiography, images are recorded by exposing photographic film to the transmitted photons. To exclude Compton-scattered photons, a lead collimating grid is placed in front of the film to absorb all photons arriving more than approximately 5 degrees out of line with the x-ray source (eFig. 46.0.3). The relationship between film exposure and darkening is complex, but there generally is only a rather narrow exposure range over which the film responds linearly; at very low and high exposures, the film response is flat and shows little contrast.

Alternatively, the x-ray image may be intensified by video techniques and then recorded on light-sensitive film or on videotape, or digitized for computer storage and analysis, a method used in cineangiography and digital radiography. Key to this is the *image intensifier*, which converts a weak x-ray image into a bright visual image. In this device, transmitted x-rays (after collimation) strike a cesium iodide screen from which visible photons impinge on a negatively charged photocathode, which in turn emits electrons; these electrons are focused and accelerated to approximately 30 keV and cause a second, smaller output phosphor to display a much brightened visible version of the original x-ray image. This image can then be directed either to a cinefilm camera (typically 35 mm) or to a TV camera for display, video recording, or digitization. Because the details of digitization and image processing have much in common with the other imaging techniques of the chapter, these are discussed below.

Nuclear Imaging

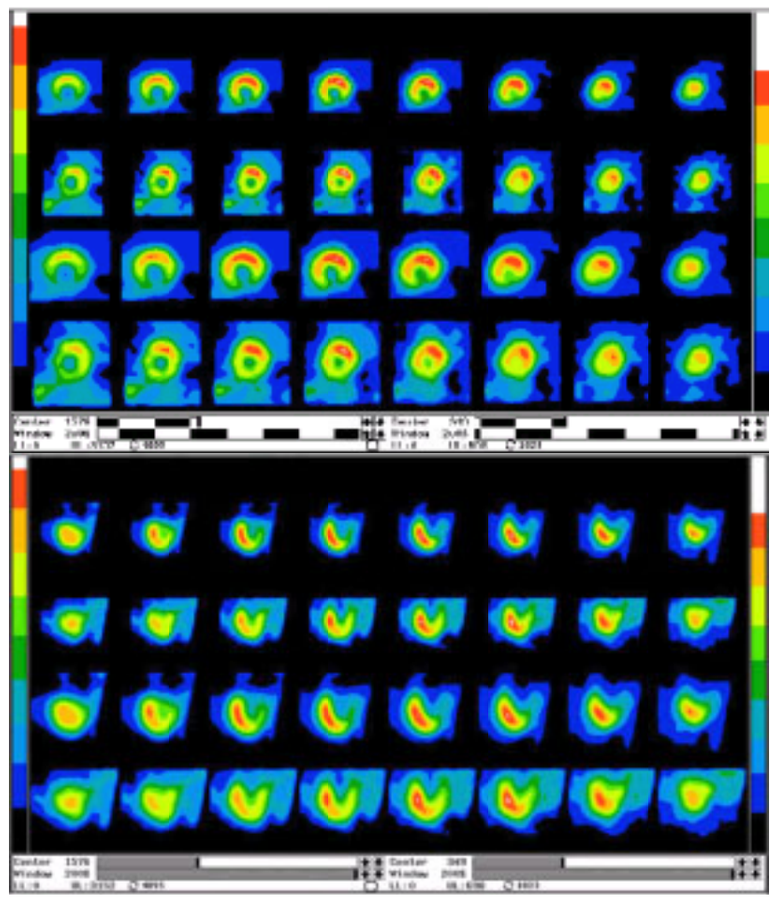
Nuclear imaging uses trace quantities of radioactive isotopes to produce high-energy photons inside the body. The internal distribution of the radioactive compound is based on its *chemical* properties, giving it affinity for specific anatomic or pathologic structures (bone, blood, myocardium, for example). Localization and quantification of photon production gives diagnostic information about these structures.

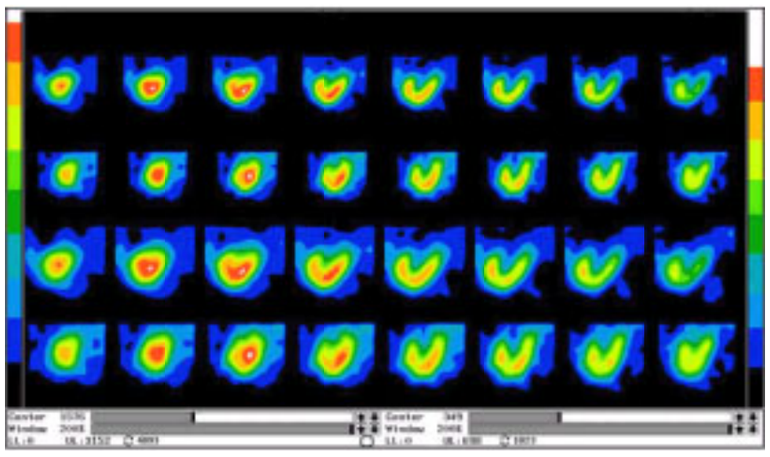


Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery.

Video 46.1 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 46.2 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*





Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the inferolateral, inferior, and proximal to mid inferoseptal walls. The left anterior oblique cranially angulated view (*fourth image*) shows severe stenosis of the distal right coronary artery before the posterior descending and posterolateral arteries in the same patient.

Video 46.3 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the inferolateral, inferior, and proximal to mid inferoseptal walls. The left anterior oblique cranially angulated view (*fourth image*) shows severe stenosis of the distal right coronary artery before the posterior descending and posterolateral arteries in the same patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In general, the isotopes of nuclear medicine can be divided into two broad types, those that produce single photons when they disintegrate and those that produce pairs of oppositely directed photons. Table 46.2 lists the decay mechanism and photon energy of several important isotopes, the details of which are provided on the CD-ROM and online versions of this chapter.

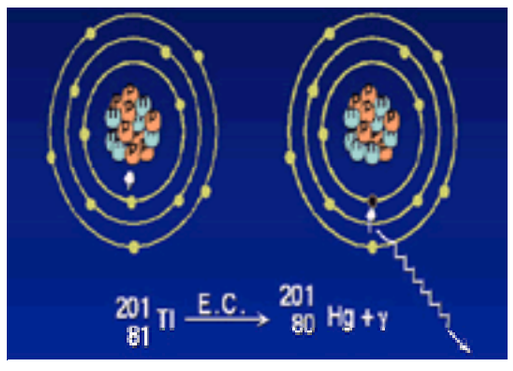
Isotope	Decay mode	Half-life	Photon energy (keV)*
^{99m}Tc	Isomeric transition	6.0 h	140
^{201}Tl	Electron capture	73.0 h	69–83
^{133}Xe	β–	5.3 d	81
^{82}Rb	β+	1.25 min	511 (2)
^{11}C	β+	20.5 min	511 (2)
^{15}O	β+	2.0 min	511 (2)
^{18}F	β+	1.8 h	511 (2)

β–, beta-emission; β+, positron emission; (2), 2 photons of 511 keV are emitted.
*Photon energies are for the principal decay mode. There usually are other emissions of lesser frequency.

TABLE 46.2 CHARACTERISTICS OF DIAGNOSTIC RADIOISOTOPES

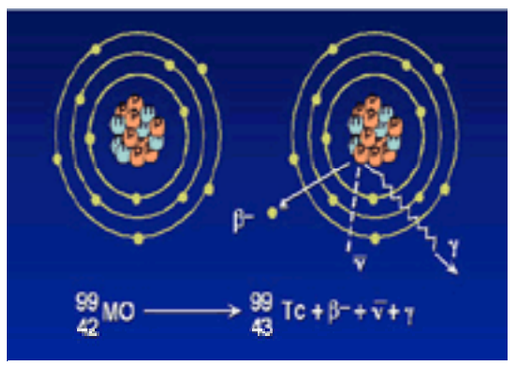
Single Photon Production

One common process by which single photons are produced is electron capture (eFig. 46.2.1), whereby a nuclear proton captures an inner shell electron, converting the proton to a neutron and reducing the atomic number by one, while leaving the atomic mass unchanged. Typical of this class of decay is thallium, $^{201}_{81}$Tl, which captures an electron to become mercury, $^{201}_{80}$Hg. As an outer electron falls to fill the vacancy in the lower energy inner shell, it releases the difference in energy as a characteristic x-ray, usually one of 80 keV.



***e*FIGURE 46.2.1** Photon emission by electron capture (E.C.). See text for details. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:632, with permission.)

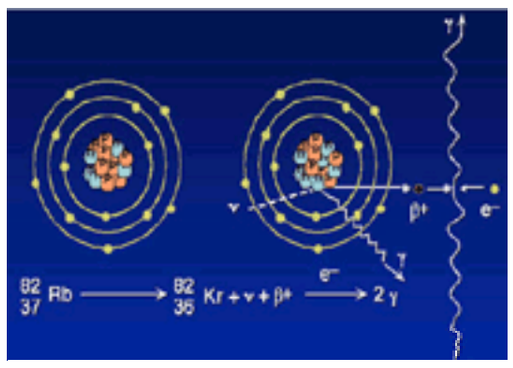
Another single photon scheme is beta decay (eFig. 46.2.2), in which a nuclear neutron becomes a proton with the emission of an electron (beta particle) and an antineutrino. This leaves the nucleus in an excited state, and when the nucleons "reshuffle," a gamma ray is emitted. The nucleus may remain in a metastable state, however, releasing its gamma ray after some time. This *isomeric transition* is the decay process for the important cardiac imaging isotope technetium-99m where the *m* stands for metastable.



***e*FIGURE 46.2.2** Photon emission by beta decay. See text for details. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:632, with permission.)

Dual-Photon Production

All dual gamma-ray isotopes decay by a process called *positron emission*. In this transition, a nuclear proton turns into a neutron with the emission of a positive electron (positron) plus a neutrino (eFig. 46.2.3). This positron travels only a short distance before it collides with an electron, leading to the annihilation of both. The mass of the two particles is completely converted into energy (by $E = mc^2$) and results in two 511-keV photons being emitted in opposite directions.



***e*FIGURE 46.2.3** Positron emission, which is similar to beta decay except that a positively charged electron is emitted, which is rapidly annihilated, producing two high-energy (511 keV) photons directed in opposite directions. See text for details. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:632, with permission.)

Radioactive Decay Rates

The number of disintegrations per second in an isotope is proportional to the amount of the isotope and to a decay constant l, which expresses the likelihood of a given atom decaying per second. Another common way to characterize the decay rate is the half-time $t_{1/2}$, the time required for half of the isotope to decay. It is related to l by

$$t_{1/2} = 0.693/\lambda$$

The half-time of an isotope has important practical and safety impacts. If $t_{1/2}$ is too long, then a large dose of the isotope will have to be given to the patient to get adequate images, leading to excessive long-term exposure unless the compound is cleared from the body chemically (e.g., via the kidneys). If $t_{1/2}$ is too short, however, the isotope may be impossible to transport: Many positron emitters have a $t_{1/2}$ measured in minutes and must be generated by an on-site cyclotron.

Imaging the Emitted Gamma Rays

The Anger gamma camera uses a large sodium iodide (NaI) crystal that emits light by the photoelectric effect in proportion to the energy of an impinging high-energy photon. This provides a means of not only counting the photons, but also of identifying the isotopes from which they arise. When a scintillation event occurs, it is “seen” by several photomultiplier tubes behind the NaI crystal, triangulating the position of the discharge before computer storage (Fig. 46.3).

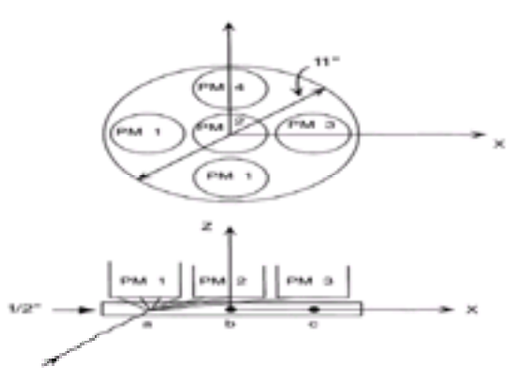


FIGURE 46.3 Schematic diagram of the Anger camera. The different output magnitudes from the photomultiplier (PM) tubes allow localization of the impinging gamma ray.

Unfortunately, reconstructing the internal distribution of the nuclide is hampered by several factors, the first of which is attenuation. Unlike radiography, in which photon attenuation is essential to diagnosis, in nuclear imaging it only causes image degradation. This problem is compounded by photon divergence, which causes photon flux to fall (in the absence of attenuation) as $1/r^2$ where r is the distance from the source. In x-ray imaging, the source is far enough from the patient that this divergence is slight over the width of the body. For a gamma-ray source producing N_0 photons per second at the center of a sphere with radius R and linear attenuation coefficient μ, the photon flux F decreases dramatically:

$$\Phi = \frac{N_0 e^{-\mu R}}{4\pi R^2}$$

Photon Scatter

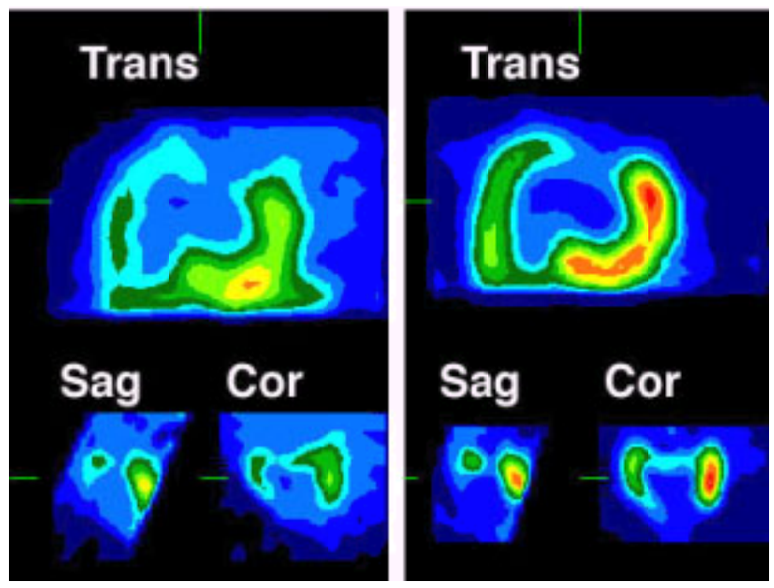
As with x-ray imaging, photon scattering significantly degrades nuclear images. Because diagnostic gamma rays are in the 80- to 500-keV diagnostic range, most photon interactions are by Compton scattering, which changes the energy and direction of the photon. As many as half of the photons escaping the body may be scattered and thus give false localizing data. One way to exclude these scattered photons is with a collimator, the simplest of which is just a small hole drilled in a sheet of lead, which causes an inverted image of the heart to be projected on the gamma camera. While giving reasonable image resolution, such a collimator is extremely inefficient and may image only 1 photon in 10,000 produced in the heart. Multihole collimators address this problem to some degree, although there is usually a trade-off between resolution and sensitivity in nuclear imaging.

Scattered photons may also be excluded on the basis of their energy. If the primary photon radiation from an isotope is in a narrow range, it should be possible to ignore lower energy Compton photons because they produce a dimmer scintillation in the NaI crystal. Unfortunately, in the 80- to 150-keV range, there is little energy change even for significant scattering. For example, a 100-keV photon scattered by 30 degrees loses only 1.5% of its energy. The 511-keV photons of positron

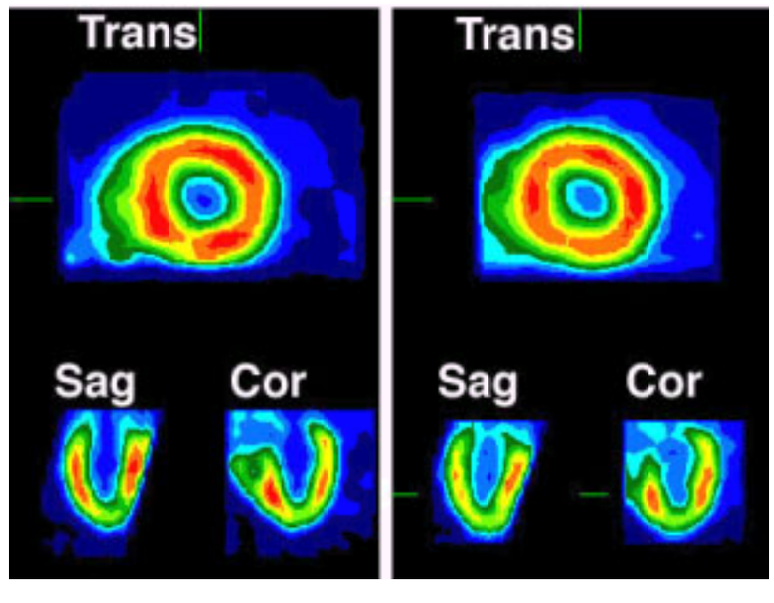
annihilation have a narrow spectrum and also transfer much more energy on scattering, so this method is more useful for them.

Positron Emission Tomography

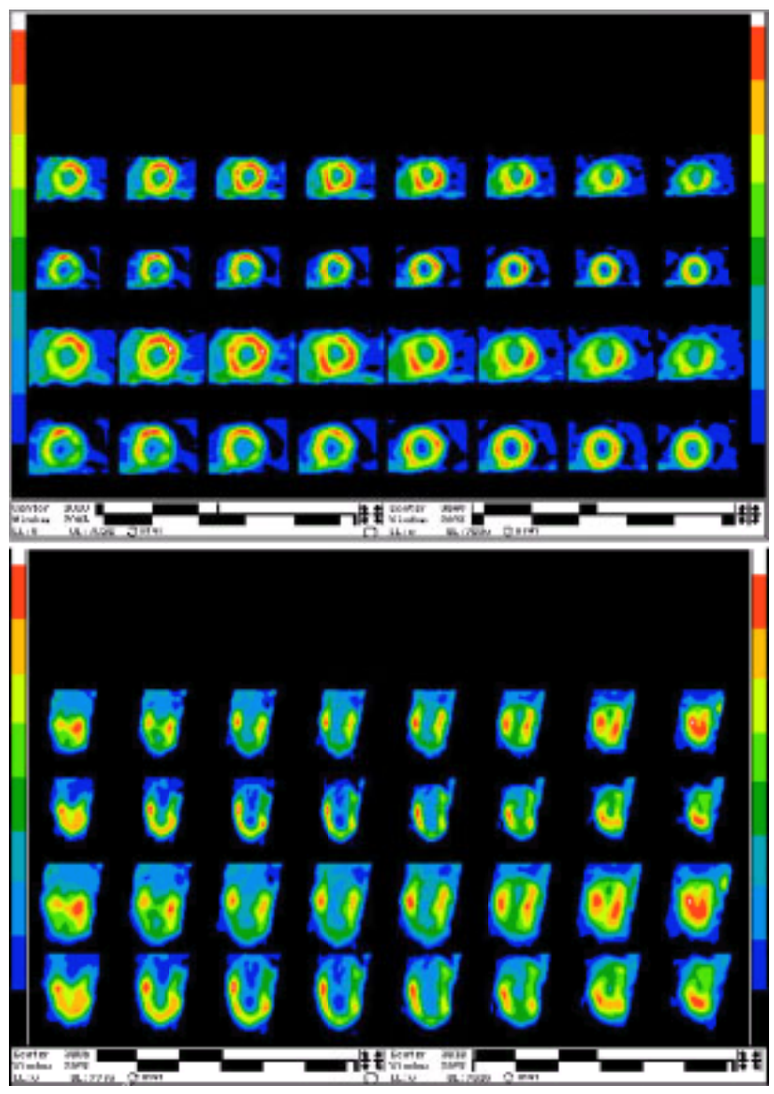
Imaging with positron emitters offers both advantages and disadvantages over single-photon imaging. The major disadvantage is that most positron sources have very short half-lives and thus must be made at the imaging site by a nearby cyclotron. An exception to this is rubidium-82, which can be eluted from a generator similar to technetium-99m and thus stored for some time.

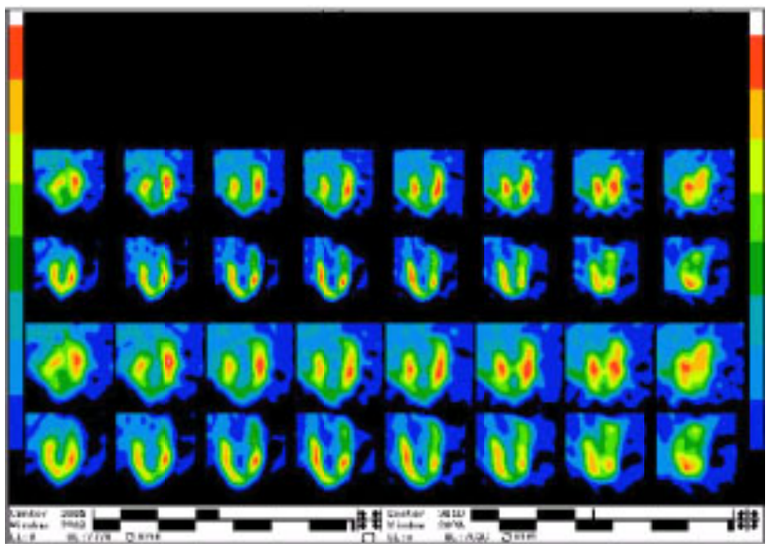


Matched resting rubidium (*left*) and radiolabeled fluoro-deoxyglucose (*right*) positron emission tomographic images. Transverse, sagittal, and coronal positron emission tomographic images demonstrating extensive scar in the left anterior descending and right coronary artery territories with evidence of myocardial hibernation in the left circumflex artery territory and right artery territory (including the right ventricle).



No fixed or transient changes in between stress (*left*) and resting (*right*) rubidium-82 positron emission tomographic images on transverse, sagittal, and coronal slices, demonstrating a dilated left ventricular cavity and a lack of myocardial scar or ischemia in a patient with nonischemic dilated cardiomyopathy.





Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image),* and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery.

VIDEO

Video 46.4 Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image),* and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 46.5 Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image),* and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The major advantage of positron imaging is that each decay event generates two high-energy photons (511 keV) directed 180 degrees from each other (Fig. 46.4). Using a ring of gamma cameras surrounding the patient, these photons will be detected simultaneously by two cameras, and the disintegration must have occurred on a line between them, allowing truly tomographic images to be obtained (13). Further refinement is possible by measuring the tiny difference in reception time for the two "simultaneous" photons, localizing the disintegration event along the line connecting the detectors. Unfortunately, the incredible speed of light (30 cm per nanosecond) and the finite temporal resolution of the simultaneity circuits (approximately 300 picosecond) limits localization to approximately 5 cm. Although this alone is not sufficiently accurate, it does aid in the statistical reconstruction from multiple events (14). Further refinement in electronic hardware may improve this performance in the future.

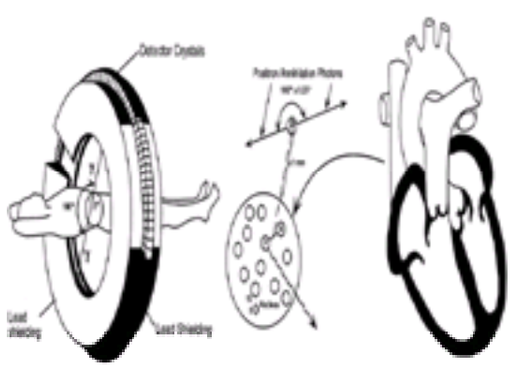


FIGURE 46.4 Positron emission tomography. The simultaneous detection of two photons localizes the disintegration to a line connecting the two detectors.

IMAGING WITH ULTRASOUND

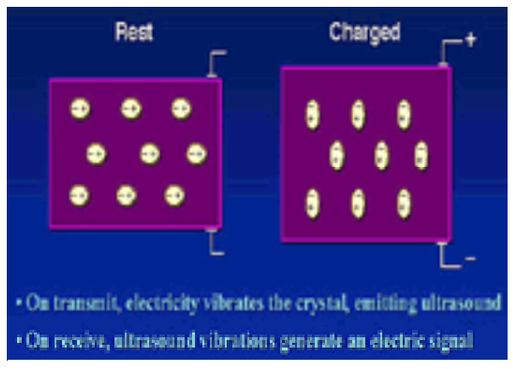
We now turn from imaging modalities that use high-energy photons to the use of high-frequency sound waves, which have a much longer wavelength and slower propagation than the photons considered previously. In addition, the speed of sound *c* is not constant like the speed of light, but rather varies with the medium through which it is passing. For typical soft tissue, this speed is approximately 1,540 m per second or 1.54 mm per μs (Table 46.3), and, as with electromagnetic radiation, there is an inverse relationship between wavelength l and frequency *f*: l = *c*/*f*.

Tissue	Velocity (m/sec)	Attenuation (cm^{-1})	Impedance (10^4 kg/m^2 sec)
Blood	1,580	0.0198	1.6
Bone	2,240	3.01	3.8–7.4
Fat	1,450	0.100	1.4
Muscle	1,580	0.193	1.7
Lung	—	—	0.26
Plasma	—	0.0069	1.5
Water	1,480	—	—

TABLE 46.3 ULTRASONIC PARAMETERS

Production of Ultrasound

Typical ultrasonic transducers have frequencies from 2.5 to 15.0 MHz, corresponding to wavelengths from 0.6 to 0.1 mm, respectively. They produce ultrasonic vibrations by the piezoelectric effect, in which a ceramic crystal vibrates when a high voltage is applied across it (eFig. 46.4.1). The size of the crystal largely determines the frequency of the vibrations, which propagate through the body as a longitudinal traveling wave, displacing the tissue to and fro by microscopic amounts in the direction parallel to the sound propagation. Wave energy exists as kinetic energy of particle motion and potential energy of tissue compression and rarefaction, which generally are 90 degrees out of phase with each other.



***e*FIGURE 46.4.1** Piezoelectric crystal. When a voltage is applied across the crystal, the highly polarized ovoid structures rotate, causing the crystal to thicken and produce ultrasound. Conversely, when ultrasound is received, the mechanical vibration of these structures produces an output voltage. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:635, with permission.)

Interaction of Ultrasound with Matter

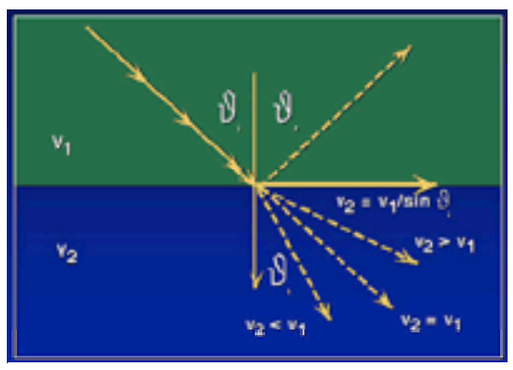
The important interactions to consider are attenuation, reflection, refraction, and scattering. Like electromagnetic radiation, ultrasound suffers an exponential decrease in amplitude as it passes through homogeneous tissue. Attenuation varies with tissue type (Table 46.3) and is faster at higher frequencies, limiting the frequency that can be used clinically in echocardiography (15).

Whenever a sound wave encounters a boundary between two types of tissue, the energy partially reflected with the remainder transmitted into the second tissue, the proportion being determined by the difference in acoustic impedance Z of the two tissues, defined as the product of sound velocity and tissue density, $Z = rc$. For relatively large, flat boundaries, the amount of reflected energy I_R is given by

$$I_R = I_i\,[(Z_2 - Z_1)/(Z_2 + Z_1)]^2$$

where I_i is the incident intensity and Z_1 and Z_2 are the impedances for the two tissues (16) (Table 46.3). Boundaries with a large difference in impedance reflect much more energy than those between tissues with similar acoustic properties. For instance, the heart–lung interface reflects 54% of the incident ultrasound, whereas the blood–myocardium boundary reflects less than 0.1%.

The unreflected portion of the wave passes into the second tissue but is refracted to travel in a different direction if the velocity of sound differs in the two media (eFig. 46.4.2). Since blood and most tissue have similar sound velocity, this is not a prominent effect in echocardiography.



***e*FIGURE 46.4.2** Snell's law. Ultrasound is reflected at the angle of incidence ($q_r = q_i$). The transmitted wave is bent to an angle q_t such that $\sin q_t = (v_2/v_1) \sin q_1$. If $(v_2/v_1) \sin q_1$ is greater than 1, then no transmission can occur. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:636, with permission.)

For interactions with structures that are smaller than the wavelength of sound, *scattering* occurs, the small object radiating sound outward as 3-D spherical waves. Scattering intensity varies approximately with the sixth power of particle radius and the fourth power of ultrasound frequency, strongly favoring larger particles and higher frequency. Scattering occurs within tissue at inhomogeneities between cellular and matrix elements that are not simple point scatterers. Further, these sources are so close to each other that the reflected waves interfere with each other producing a complex ultrasound pattern, *speckle*.

Echocardiographic Imaging

In echocardiography, short pulses of ultrasound are attenuated, scattered, and refracted as they pass through tissue, with a small amount of energy reflected from deep structures to the transducer. Assuming the velocity of sound c to be constant in soft tissue (1,540 m per second), the depth d of a reflector is given by the time

delay D*t* between transmission of the ultrasound pulse and receipt of the echo: $d = c\mathrm{D}t/2$, the factor of 2 entering because D*t* includes time *to* and *from* the object, approximately 13 µs per cm of depth (Fig. 46.5).

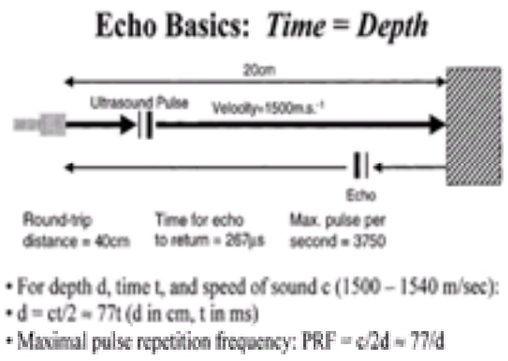
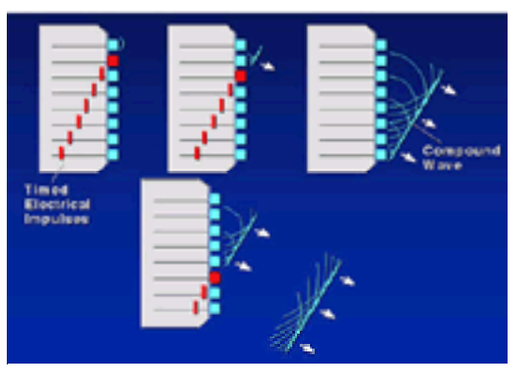


FIGURE 46.5 Basics of echocardiographic imaging. Because of the relatively fixed speed of sound in tissue, the delay in echo return can be translated into the distance to the reflection.

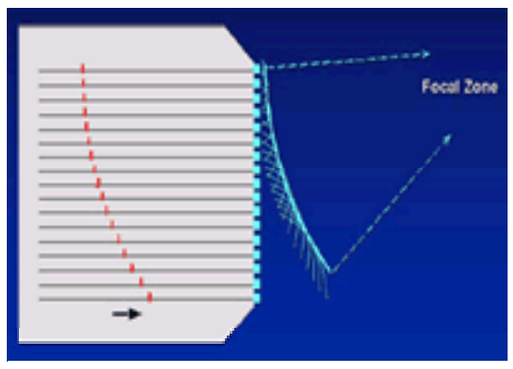
Echocardiographic Transducers

The original ultrasound transducers were single, flat crystals that produced approximately planar waves. For circular crystals, the wave front initially converges to approximately half its original width at a focal distance r^2/l from the transducer (*r* is crystal radius and l the wavelength), thereafter diverging to its original width at twice the focal depth. Acoustic lenses or curved crystals may give tighter focus in the near field at the expense of more rapid divergence in the far field.

Most current transducers are linear arrays of 64 to 256 narrow piezoelectric crystals. By precisely timing their firing, it is possible to direct the ultrasound in any direction within a wide sector coplanar with the array (eFig. 46.5.1) and to adjust the focal zone both on transmission and receiving (eFig. 46.5.2). Furthermore, by the principle of superposition of sound waves, it is possible to stimulate the array to send out multiple ultrasound pulses simultaneously in different directions, dramatically improving ultrasound frame rate by processing multiple scan lines in parallel. Finally, transducer technology has been expanded to 2-D arrays of crystals, allowing ultrasound pulses to be directed anywhere in a pyramid-shaped volume below the transducer, facilitating real-time 3-D imaging.



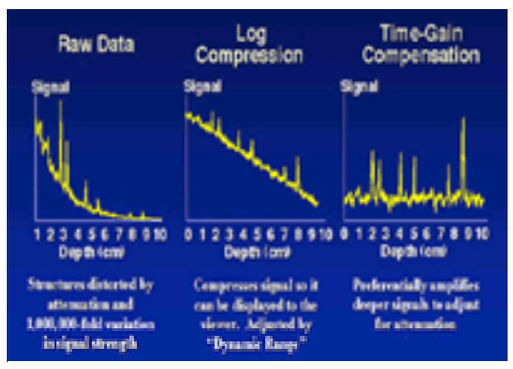
***e*FIGURE 46.5.1** Phased array echo transducer. By changing the timing of transmission from a linear array of crystals, it is possible to steer a planar ultrasound wave in different directions.



***e*FIGURE 46.5.2** Focused phased array echo transducer. If the time delay between adjacent crystals is not constant, it is possible to focus the wavefront at a specific depth.

Ultrasound Reception

When a reflected echo strikes the transducer, the piezoelectric crystal produces a minuscule voltage in response to the vibrations from the returning ultrasound. Because of attenuation within the tissue, the returning echoes from shallow structures are much stronger than those from deeper layers. To adjust for the significantly weaker echoes from deep structures, *time-gain compensation* applies greater amplification to echoes returning at longer intervals from the echo pulse. This may be adjusted by the user for individual variation in attenuation. Even with this depth compensation, echo signals may vary in intensity by a factor of 10^9 or more, while the human eye can only appreciate approximately 500 gray levels on a television screen. Thus, the echo signal must be compressed to this smaller dynamic range by *logarithmic amplification*, which amplifies weak input signals much more than strong ones, in effect converting an exponential distribution of voltages into a linear one (eFig. 46.5.3).



***e*FIGURE 46.5.3** Scan-line processing. To normalize the billion-fold variation in signal strength with depth, logarithmic compression and time-gain compensation must

be applied to the returning echoes.

The amplified signal now consists of the radiofrequency wave of the transducer, modulated in time by the reflective structures in the body. In most echo instruments, these lower frequency (100 to 500 kHz) modulations are extracted from the multimegahertz carrier by full-wave rectification and low-pass filtration, leaving only the *amplitude* of the ultrasonic reflections. More recently, however, it has become possible to use the *phase* information to improve the lateral resolution of the ultrasonic image, allowing objects to be localized, even if they fall between scan lines.

Display Modes

As discussed in Chapter 49, echo signals can be displayed in various formats. In M-mode echocardiography, repeated echo pulses are made along a single scan line, and the processed envelope is drawn vertically on the output video with subsequent envelopes displaced rightward, so that the horizontal axis of the display corresponds to time while the vertical axis relates to distance from the chest wall (Fig. 46.6).

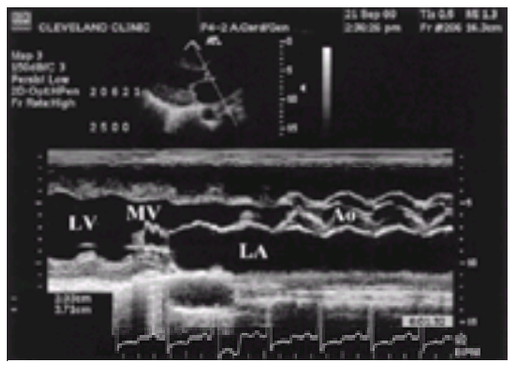
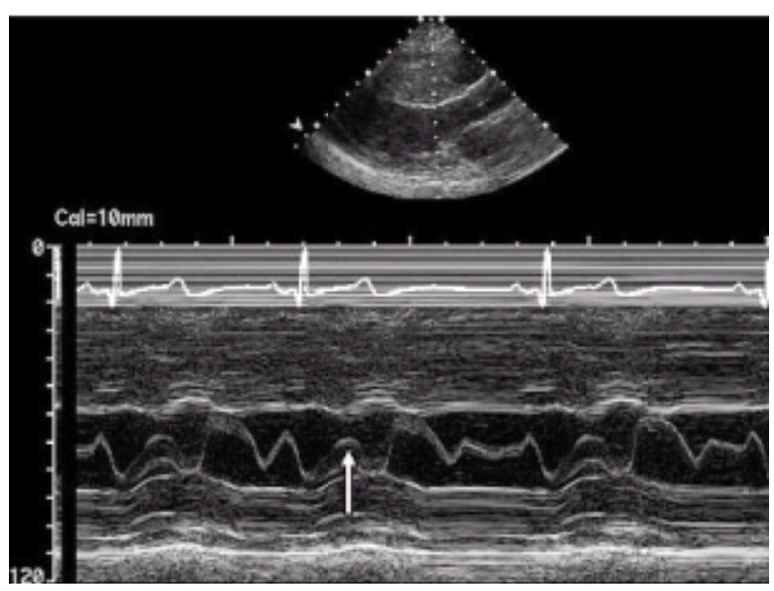


FIGURE 46.6 M-mode echocardiographic imaging. The M-mode display shows depth vertically and time horizontally. Ao, aorta; LA, left atrium; LV, left ventricle; MV, mitral valve.



M-mode tracing of hypertrophic cardiomyopathy with severe septal hypertrophy seen at the top of the trace and systolic anterior motion (SAM) of the mitral valve in systole seen in the middle of the trace (designated by the arrow).

In 2-D or sector scanning, echo interrogations are made sequentially throughout a 60- to 90-degree sector, fanning out from the transducer, typically approximately 100 scan lines per frame. For a 20-cm imaging depth, pulses can be emitted every 260 µs, allowing a 100–scan-line frame to be formed in 26 ms, and a display rate of over 38 frames per second. With parallel processing, up to four scan lines can be displayed simultaneously, allowing frame rates over 150 per second (Fig. 46.7).

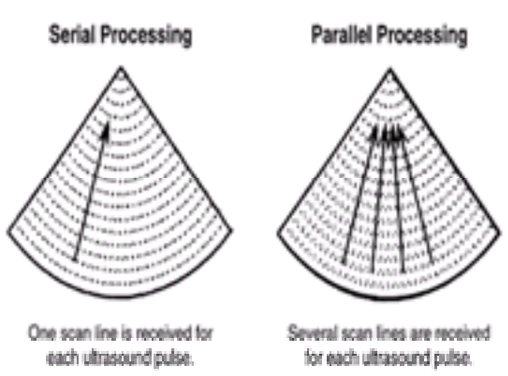
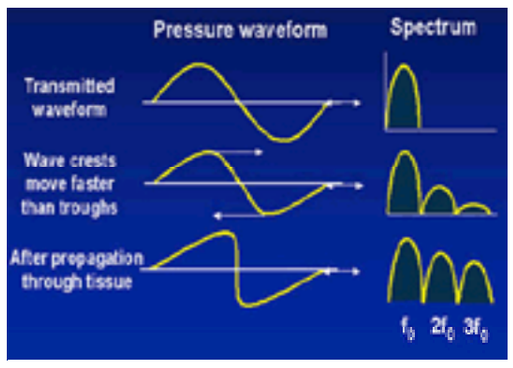


FIGURE 46.7 Serial versus parallel processing. By analyzing several scan lines simultaneously through parallel processing, frame rate can be significantly improved.

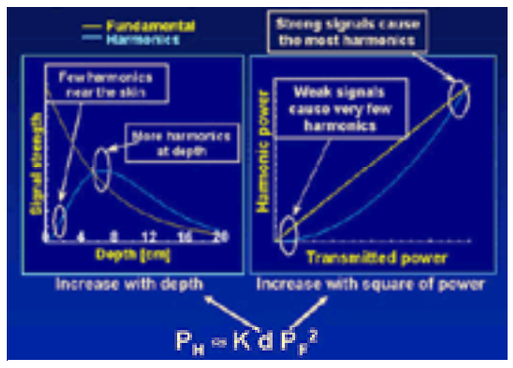
Tissue Harmonic Imaging

One of the greatest advances in echocardiographic image quality in the past years has been the development of tissue harmonic imaging. When ultrasound waves propagate through tissue, their frequency content does not remain constant, but rather shifts to increasing amounts of higher frequencies (17).

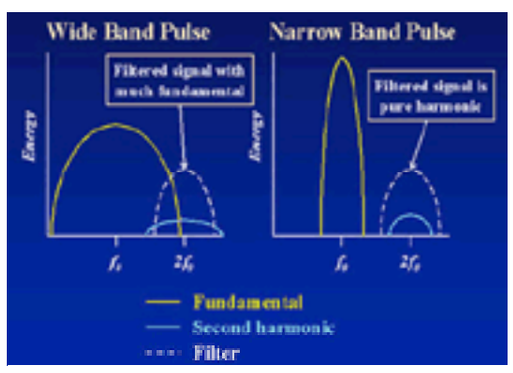
*e*Figure 46.7.1 illustrates how this happens: Because the peaks of the sound waves propagate a little faster than the troughs, with distance the waveforms transform from simple sinusoids (pure frequency content) to asymmetric waves containing a significant quantity of energy at multiples of the original frequency, termed *harmonics*. An approximate formula for the development of these harmonics is $P_H \approx K\, d\, P_F^2$, illustrating that harmonic power (P_H) grows linearly with the distance of propagation (d) and nonlinearly with the square of the power in the original fundamental wave (P_F). As shown in *e*Figure 46.7.2, these two features determine the key utility of harmonics: (a) There are few harmonics in the near field, so distortion from the chest wall is eliminated; and (b) only the strongest fundamental echoes (resulting from the central beam of the transducer) are likely to generate harmonics, whereas artifactual signals (reverberations and beam width and side lobe artifacts) generate few harmonics. To take advantage of these harmonic echoes, an instrument needs three key features: (a) a wide dynamic range so that the weak harmonic echoes can be detected with adequate signal-to-noise ratio, (b) a narrow output spectrum so that the dominant fundamental energy falls outside the second harmonic band, and (c) a sharp receive filter so that only the harmonic signal is passed through to the amplifier. *e*Figure 46.7.3 (left panel) shows the impact of too wide a transmit spectrum that cannot be separated from the harmonic signals, while the narrow spectrum in the right panel can be separated by use of a sharp receive filter.



***e*FIGURE 46.7.1** Nonlinear acoustic propagation. Because blood and tissue are not completely incompressible, the peaks of ultrasound waves propagate slightly faster than the troughs, leading to a gradual change in the shape of the wave with distance due to the shift of energy to second and higher order harmonics.



***e*FIGURE 46.7.2** Determinants of harmonic generation. As shown by the equation, harmonic energy (P_H) grows with distance *d* from the skin surface (*left panel*) and varies with the square of the incident fundamental energy (P_F). This means that the most common echo artifacts (near field distortion and scattering, side lobe, or beam width artifacts) do not produce significant harmonic signals, resulting in a cleaner image at the harmonic frequency.



***e*FIGURE 46.7.3** Instrument requirements for tissue harmonic imaging. If the transmitted pulse has too broad a frequency spectrum (*left panel*), it will be impossible to separate it from the much weaker harmonic signal. In contrast, a narrow transmit signal can be separated from the harmonics with a sharp receive filter, provided the other instrument has very high signal-to-noise ratio (*right panel*).

Figure 46.8 shows the impact of harmonic imaging in a patient with mitral stenosis, demonstrating improved endocardial definition and imaging of the subvalvular apparatus. Clinical tests on this modality have shown improved contrast between the wall and cavity (18) without adverse effect on valve thickness (19).

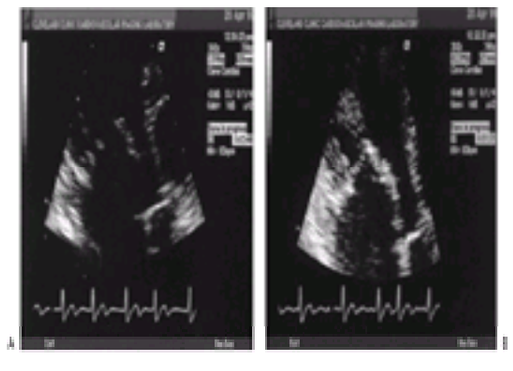


FIGURE 46.8 Impact of harmonic imaging in a patient with mitral stenosis. **A:** Fundamental. **B:** Harmonic.

Doppler Echocardiography

Exploitation of the Doppler principle to define intracardiac blood velocity adds enormous value to echocardiographic imaging (20,21). It is based on the observation that sound reflected from moving objects is frequency shifted in proportion to the ratio of object velocity *v* and sound velocity *c*: $f_d = 2vf_0/c$, where f_0 is the transducer frequency and f_d is the amount of the Doppler shift. The factor 2 occurs because the frequency is shifted when the sound hits the moving particle and again when it is reradiated by scattering. Only the component of particle velocity parallel to the ultrasound beam affects the Doppler shift (Fig. 46.9). For a particle moving at an angle q to the scan line, the Doppler shift is proportional to the cosine of q: 30-degree misalignment leads to a 13% velocity underestimation.

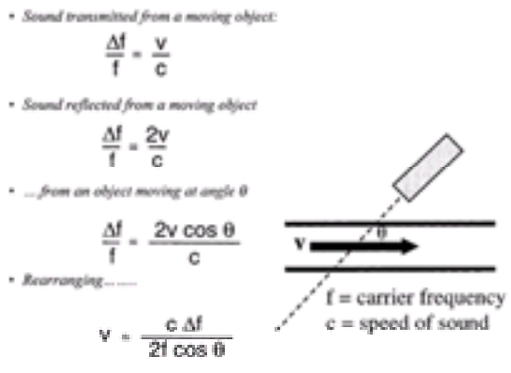
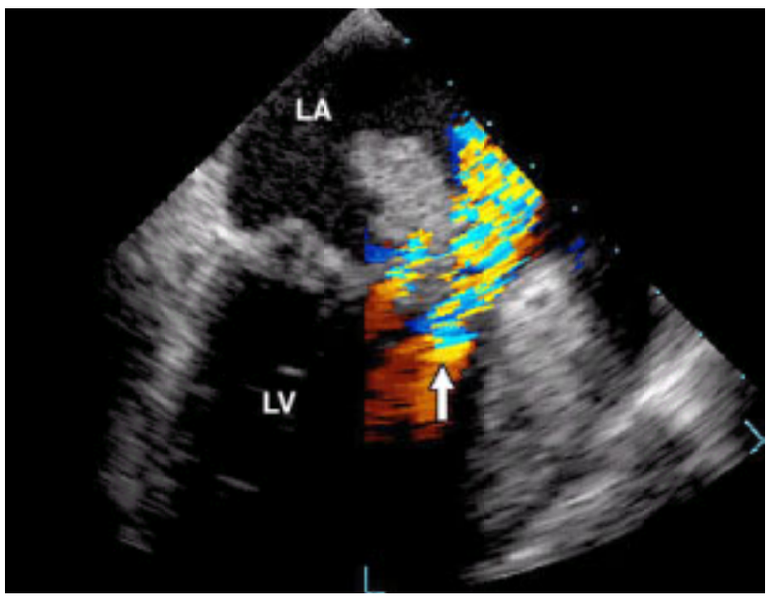
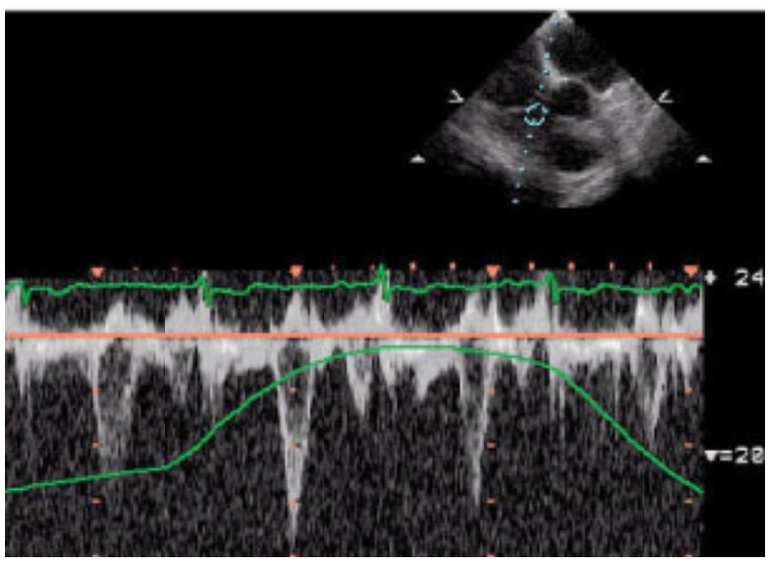


FIGURE 46.9 Determinants of the Doppler shift. When sound is emitted from a moving object, the frequency is shifted in proportion to the velocity. For reflected sound, the factor 2 occurs because this shift occurs on absorption and reflection. Only the component of velocity parallel to the sound wave contributes to the Doppler shift.

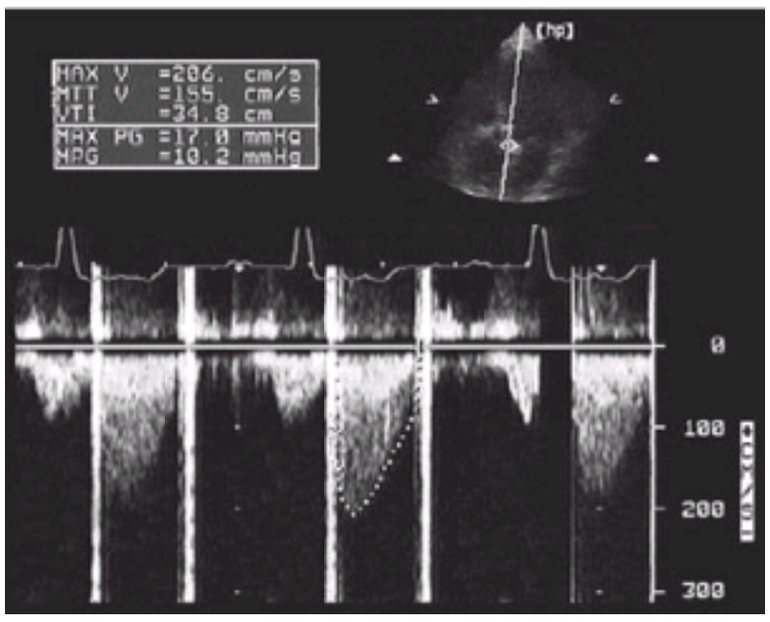


Color Doppler showing a perforation of the base of the anterior mitral leaflet from *Streptococcus* endocarditis. The patient's underlying pathology was myxomatous mitral valve disease with mitral valve prolapse. The proximal flow convergence of the mitral regurgitation jet is demonstrated by the arrow at the orifice of the large perforation.

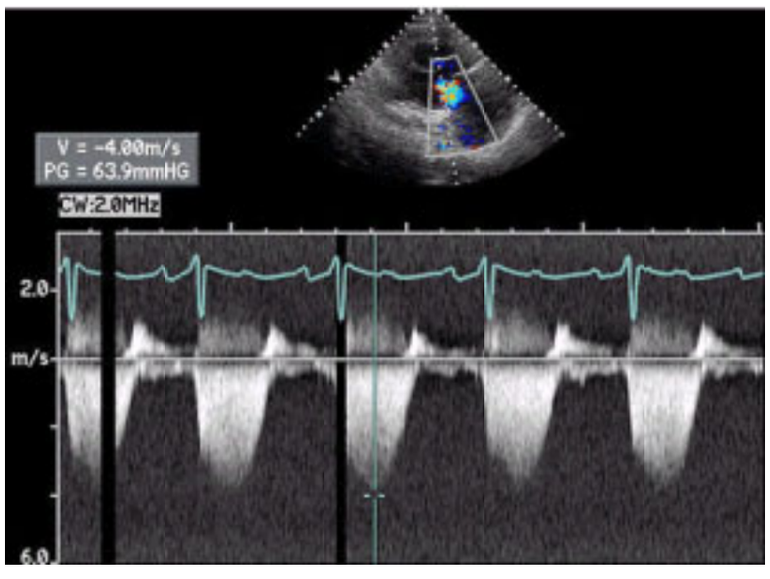


Pulsed wave Doppler through the tricuspid valve of a patient with constrictive pericarditis. Note the decrease of the E wave with inspiration due to interventricular dependence.

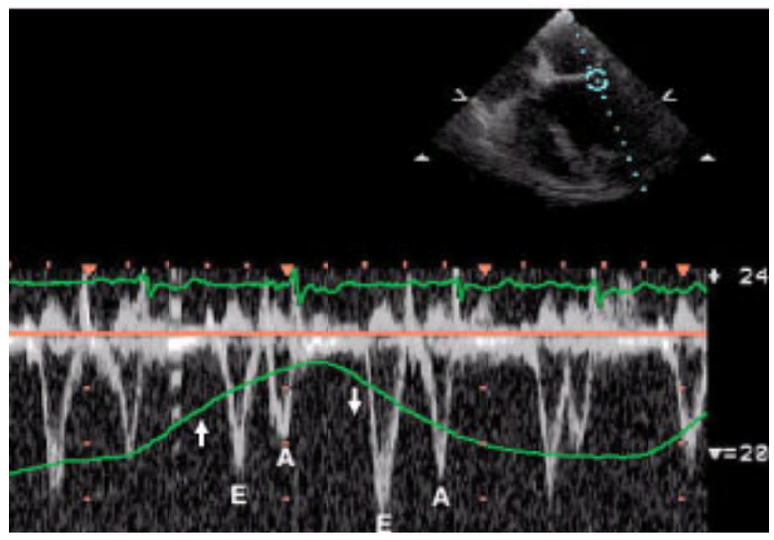
In general, three different types of Doppler processing are available on contemporary echocardiographic equipment: continuous wave Doppler, pulsed Doppler, and Doppler flow mapping ("color Doppler"). Each is processed differently and discussed in detail on the CD-ROM and online versions of this chapter.



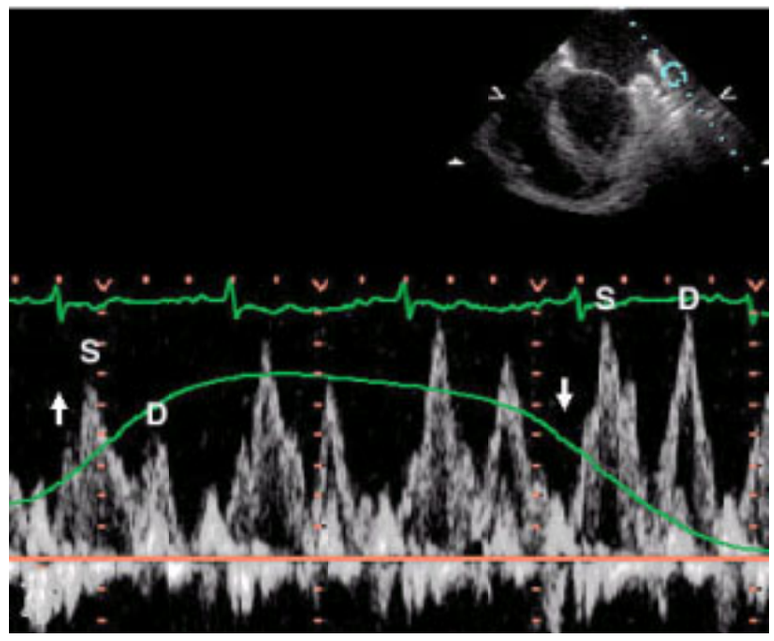
Continuous wave Doppler spectrum of mechanical prosthesis in the aortic position. Note opening and closing clicks and calculation of mean and maximal pressure gradients.



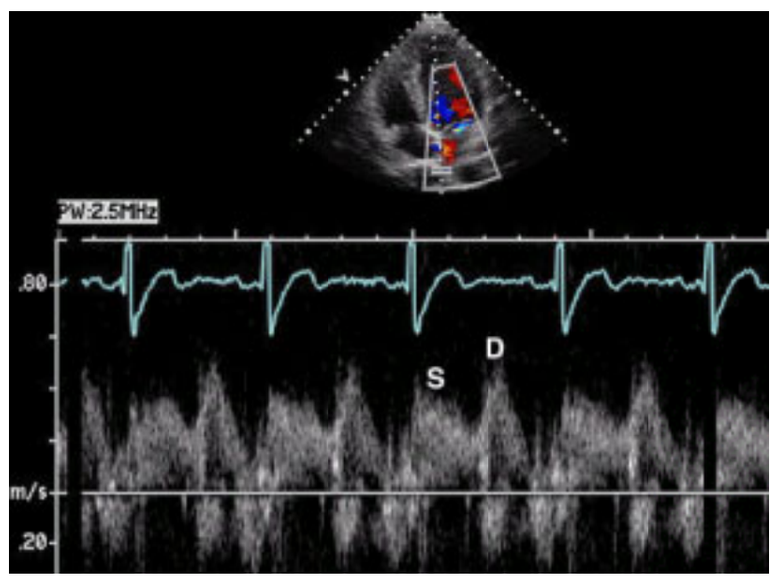
Continuous wave Doppler trace through the tricuspid valve of a patient with pulmonary hypertension. The maximal jet velocity of 4 m/sec corresponds to a pressure gradient of 64 mm Hg or a PA pressure of approximately 80 mm Hg.



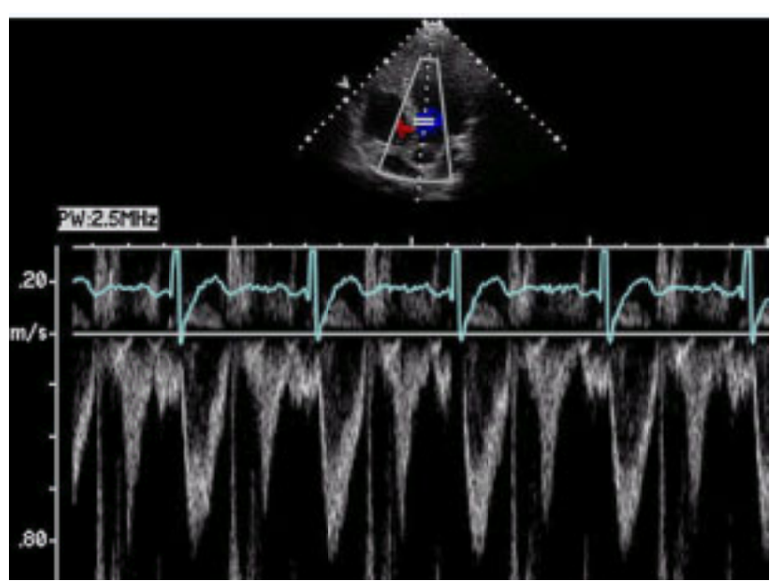
Pulsed wave Doppler of the mitral valve inflows of a patient with constrictive pericarditis. Note the decrease of the E wave during inspiration (*upward arrow*) due to interventricular dependence, and the increase in the E wave during expiration (*downward arrow*) for the same reason.



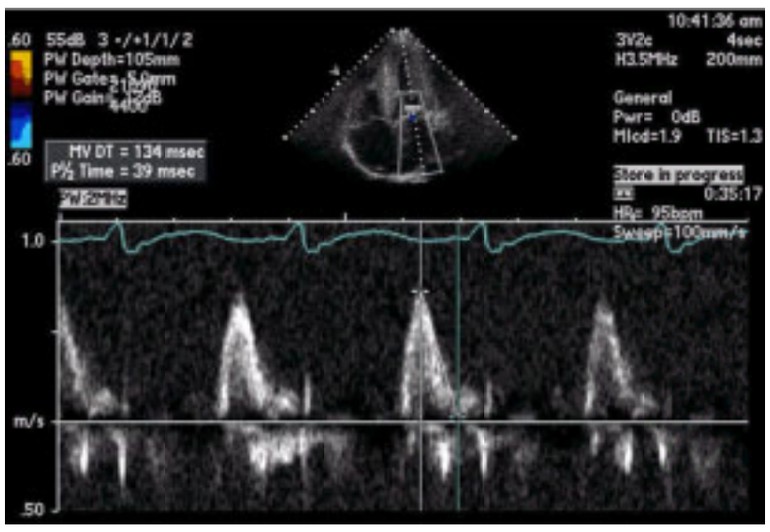
Pulsed wave Doppler of the pulmonary veins of a patient with constrictive pericarditis. Note the inspiratory decrease of the S and P waves and the expiratory increase due to interventricular dependence. (Inspiration is denoted by the upward arrow and expiration by the downward arrow).



Pulmonary vein pulsed wave Doppler flow. Note the S (systolic) wave and the D (diastolic) wave.



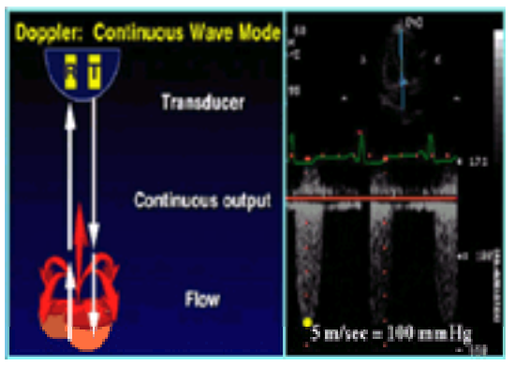
Normal pulsed wave Doppler signal from the left ventricular outflow tract. Note the maximal velocity is only 80 cm per second.



Pulsed wave Doppler of the mitral valve inflow in a patient with amyloidosis demonstrating a short deceleration time (134 ms) consistent with restrictive physiology.

Continuous Wave Doppler

In continuous wave Doppler, the transducer contains two crystals, one to send and the other to receive ultrasound continuously (eFig. 46.9.1). The returning signal is compared with the original carrier frequency by quadrature demodulation, and the frequency-shifted echoes are quantified by Fourier analysis. Because Fourier analysis plays a pivotal role in many types of cardiac imaging, a section of this chapter describes it in greater detail, particularly its role in Doppler processing (see Application of Fourier Analysis in Cardiac Imaging, later in this chapter).

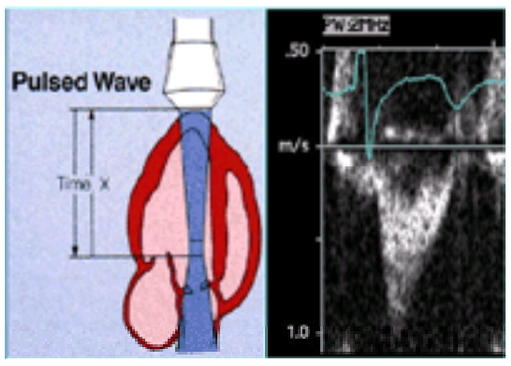


***e*FIGURE 46.9.1** Continuous wave Doppler. By continuously transmitting and receiving Doppler-shifted echoes, it is possible to quantify velocities of any magnitude, although at the cost of not having range information as to the specific depth of that velocity. A common application is quantification of aortic stenosis (*right panel*), using the simplified Bernoulli equation, $Dp = 4v^2$.

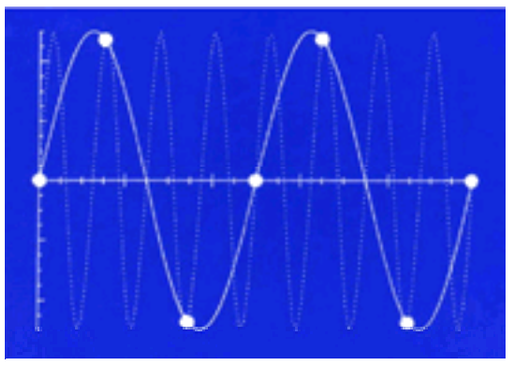
A limitation of continuous wave Doppler is its lack of range information about the signals it displays. Because the ultrasound is continuously emitted and received, the detected Doppler shifts may have arisen from any depth along the scan line. This disadvantage is countered by the ability of continuous wave Doppler to quantify high intracardiac velocities as might be encountered in stenotic or regurgitant lesions.

Pulsed Doppler

In pulsed Doppler echocardiography, brief (1 to 4 µs) bursts of ultrasound are transmitted into the patient, with the receiver timed to “listen” to the returning signal at a specific time delay, Dt, after the pulse transmission, corresponding to reflections from depth $d = cDt/2$, where c is the velocity of sound (eFig. 46.9.2). The advantage of recording blood velocity from a specific location within the heart is balanced by limitations on the maximal velocity that can be unambiguously displayed. This limitation arises because, to fully reconstruct a Doppler shift frequency f_d, it must be sampled by pulses at twice this rate, $2f_d$, and signals that are undersampled will appear misdirected much as wagon wheels may appear to turn backward in motion pictures, an effect termed velocity *aliasing* (eFig. 46.9.3). To record signals at a depth d, pulses can be emitted at a maximal pulse repetition frequency (PRF) of $c/2d$, so the maximal resolvable Doppler shift is half this, or $c/4d$. Applying the fundamental Doppler equation shows that the peak recordable velocity is $c^2/8df_0$, inversely related to both transducer frequency and sample volume depth. For example, the maximal unambiguous velocity from a 3-MHz transducer at 10-cm depth is approximately 100 cm per second (if flow is known to be in one direction, this velocity can be doubled by shifting the baseline of the display). To reconstruct the Doppler spectrum in detail, the instrument typically sends out 128 or 256 pulses, then analyzes them by a fast Fourier transform, updating the velocity information approximately every 10 ms.



***e*FIGURE 46.9.2** Pulsed wave Doppler. By transmitting a brief pulse of ultrasound and “listening” for returning echoes from a specific depth, it is possible to localize velocities within the heart, though at the cost of not being able to quantify very high velocities.



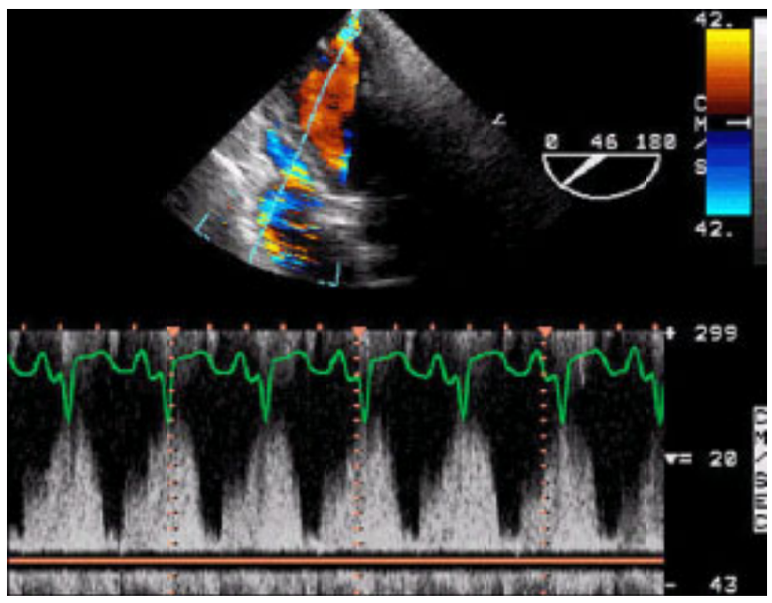
***e*FIGURE 46.9.3** Impact of aliasing in Doppler echocardiography. If the actual Doppler waveform (*dotted line*) is undersampled (*white dots*), the reconstructed

waveform (*solid line*) will be at a falsely low frequency (and thereby velocity).

Doppler Velocity Mapping

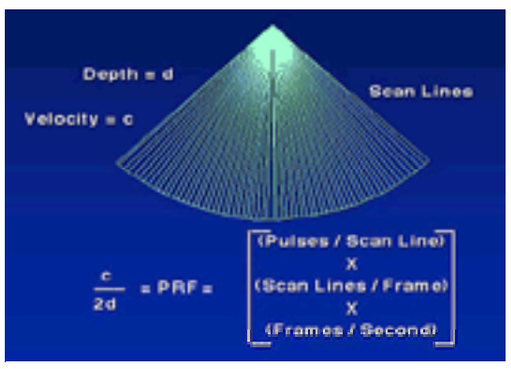
Doppler velocity mapping superimposes color on an echo sector scan to show the distribution of blood velocity throughout the heart, allowing the dynamic display of normal flow patterns and those associated with valvular regurgitation, stenosis, and various shunt lesions (eFig. 46.9.4). Color Doppler shares many limitations with pulsed Doppler such as limited PRF (to allow pulses from the deepest part of the sector to return before another is emitted) and velocity aliasing, but differs in that all the returning echoes from the entire scan line are analyzed, not just those from a specific depth. Furthermore, whereas in pulsed Doppler a given point may be interrogated over 100 times before velocity is calculated, in color Doppler the complete sector must be swept many times a second to capture the dynamic nature of intracardiac blood flow (22), imposing fundamental limits on the spatial, temporal, and velocity resolution of the system.

***e*FIGURE 46.9.4** Color Doppler echocardiography. By processing successive ultrasound pulses with autocorrelation techniques, it is possible to map velocity throughout the imaging sector.



Doppler recording of flow through an ischemic ventricular septal defect before surgical repair.

To understand how these resolutions relate to each other, recall that the fundamental data limitation in Doppler is the PRF, fixed (inversely) by the depth of the sector. This limits the displayable velocity range and the detail with which the velocity map can be reconstructed and updated (eFig. 46.9.5). Three key parameters enter into this trade-off, the product of which cannot exceed the PRF: the number of interrogations per scan line N_i, the number of scan lines per frame N_s, and the number of frames per second N_f. The N_f should be at least 15 frames per second for a smooth display, and for brief intracardiac events or fast heart rates, a more frequent update is desirable. The second factor, N_s, is determined by the width of the color sector and the density of interrogation within the sector, so that reducing the sector width to concentrate on the region of interest (such as a regurgitant jet) allows higher frame rates. The final factor, the number of interrogations per scan line, largely determines the accuracy with which the velocity is measured, since the more a scan line is interrogated, the finer the velocity resolution. For example, a scan depth of 10 cm translates into a PRF of approximately 7,700 Hz. If eight bursts are used per scan line (a typical value, in contrast to the 128 used in pulsed Doppler) and the sector is narrowed to 50 scan lines, then just over 19 frames per second can be reconstructed. The emerging technology of parallel processing allows this frame rate to be increased considerably (Fig. 46.7).

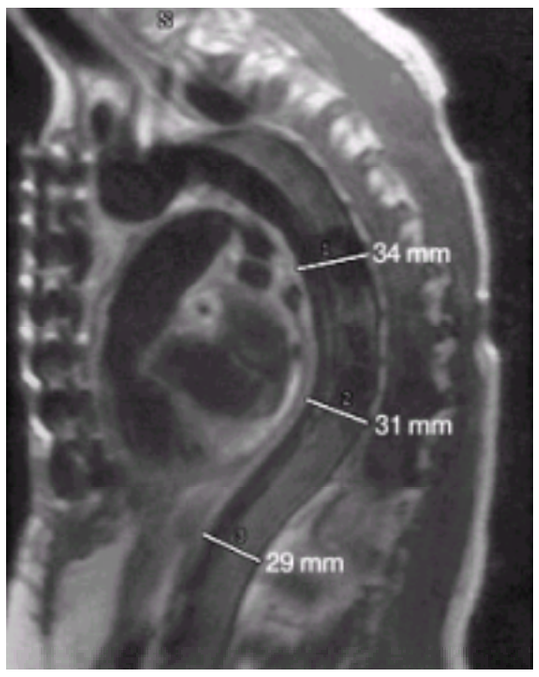


***e*FIGURE 46.9.5** Temporal, spatial, and velocity trade-offs in Doppler flow mapping. The pulse repetition frequency (PRF, number of interrogations per second) is fixed by the depth of imaging and the velocity of sound: PRF = $c/2d$. This PRF must be divided between the number of pulses per scan line (which determines velocity resolution), the number of scan lines per frame (which determines spatial extent and resolution of the flow map), and the number of frames per second (which is temporal resolution). (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:638, with permission.)

To show velocity, blood moving toward the transducer is typically displayed in red, whereas reverse flow is colored blue. Additionally, velocity variability may be estimated from the scatter in individual velocity measurements from the multiple scan line interrogations. This velocity “variance” is typically coded in green, although its physical connection with true turbulence is not precise.

MAGNETIC RESONANCE IMAGING

The third physical principle used in cardiac imaging, nuclear magnetic resonance, is less familiar than electromagnetic and sonic radiation, but its physical basis has been well defined in the last half-century, an understanding of which helps in the appreciation of clinical MRI. Pauli first suggested the existence of microscopic magnetic moments within atomic nuclei in 1924. Studies of this phenomenon in the presence of external magnetic and electromagnetic fields by Purcell and Bloch in 1946 were landmarks and led to the two sharing the Nobel Prize for physics in 1952.



Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

Video 46.6 Post–myocardial infarction apical thrombus (long-axis). Akinesia of thin apical wall with adjacent thrombus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 46.7 Post–myocardial infarction true aneurysm (long-axis). Dyskinesia and thinning of the left ventricular apex due to an occlusion of left anterior descending artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 46.8 Aortic stenosis and insufficiency (long-axis). A systolic signal-void jet of aortic stenosis is visible extending from the aortic valve into the ascending aorta. In addition, a diastolic signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricular cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 46.9 Aortic insufficiency associated with annuloaortic ectasia of aortic root (oblique-coronal). An “onion-bulb” dilatation of the proximal ascending aorta and the sinuses of Valsalva is observed. A signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricular cavity during diastole. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 46.10 Subaortic poststenotic flow in hypertrophic cardiomyopathy (long-axis). Asymmetric hypertrophy is noted, resulting in dynamic narrowing of the left ventricular outflow tract with a signal-void jet in the subaortic region. In addition, a signal-void jet in the left atrium is also seen, representing mitral regurgitation due to systolic anterior motion of the anterior leaflet of the mitral valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 46.11 Arrhythmogenic right ventricular dysplasia (transaxial). Thinning the right ventricular wall with dyskinesia of the right ventricular free wall during systole is due to fibrous replacement of the myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Physical Principles

Although many nuclei are magnetic, by far the most important to medical imaging is the single hydrogen proton (^{1}H), both because of its abundance and its high sensitivity to external influences. An individual proton in an external magnetic field of strength B_0 spins or *precesses* about the magnetic field at the *Larmor frequency*, f, proportional to the strength of the external field B_0 and the magnetogyric ratio g, a constant specific to each nuclear species: $f = gB_0/2p$. For the hydrogen proton, g/2p is 42.58 MHz per Tesla (Fig. 46.10), where Tesla is a standard unit of magnetic field strength, equivalent to 10,000 Gauss, an older unit. Typical MRI magnets have field strengths from 0.5 to 4.0 T. By way of comparison, the earth’s magnetic field strength is approximately 0.3 Gauss or 3×10^{-5} T, and thus a proton in the Earth’s magnetic field will precess at approximately 1,280 Hz.

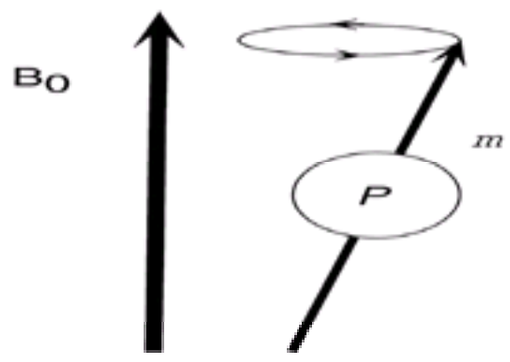


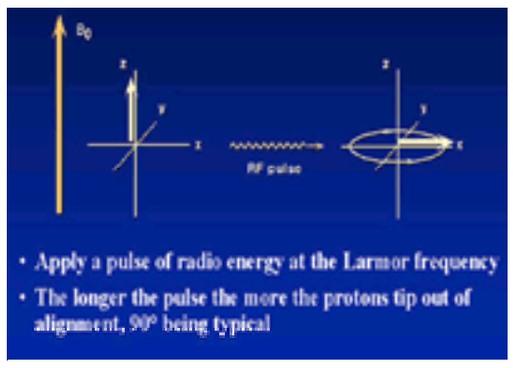
FIGURE 46.10 Precession. Nuclei with odd numbers of protons and neutrons are weakly magnetic with magnetic moment μ, ^{1}H being most important. In a strong magnetic field (strength B_0), a few protons line up; in a 1T field (3,000 × earth), <0.001% are aligned. If these "aligned" protons are tipped out of alignment, they will precess like a wobbling top at 42.6 MHz per Tesla. This Larmor frequency is proportional to the magnetic field, critical to magnetic resonance imaging. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:639, with permission.)

Production and Control of the Magnetic Moment

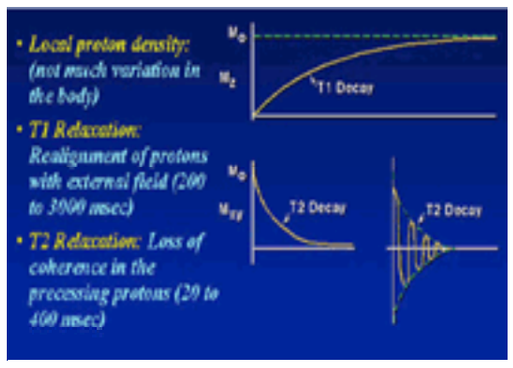
Any magnetic field that changes its strength or direction in time radiates electromagnetic radiation outward at the precessional frequency, which can be received by an antenna and amplified electronically. This radiated signal forms the basis for MRI. Normally, however, the proton moments in the body are oriented randomly in space, and the radiation from their precession cancels out. Only if these magnetic moments can be made to line up, by application of a strong external magnetic field, will there be a net magnetization vector whose precession will cause radiation of energy to the outside. Actually, only a tiny fraction of the protons will be aligned by the magnetic field, fewer than 0.001% in a 1-T field, as a result of thermal energy randomizing atomic orientation. Nevertheless, this is enough to give a net magnetization vector to the substance as a whole, which can be exploited by MRI.

Tissue Relaxation Parameters

Producing a net magnetization vector is only the first step in MRI. This vector must next be tipped away from the direction of the main magnetic field so that it will precess within that field, emitting radiation that can be detected. This is done with a pulse of electromagnetic radiation at the precessional frequency [termed a *radiofrequency* (RF) *pulse*], which exerts a torque on the magnetization vector. The longer the duration of the RF pulse, the more the magnetization vector is tipped away from the main magnetic field, say 90 degrees. When the RF pulse is removed, the tipped magnetic moment precesses about the main magnetic vector, emitting electromagnetic radiation at the Larmor frequency, which can be detected externally (eFig. 46.10.1). The initial strength of this signal depends primarily on the local proton density, but this does not vary enough within the body to give sufficient contrast to distinguish tissues. Fortunately, there are several other magnetic properties that can be exploited to enhance contrast (eFig. 46.10.2), the first of which is the rapidity with which the tipped magnetization vector realigns itself with the external magnetic field. This time constant, termed *T1*, the longitudinal relaxation time, or the spin-lattice relaxation time, typically is of the order of 200 ms to 3 seconds (eTable 46.3.1). The second time constant, T2, refers to the rapidity with which the precessing vector loses coherence in the transverse plane because of the interaction of adjacent magnetic moments. For this reason, it is also called the transverse or spin-spin relaxation time. It usually is shorter than corresponding T1 values, typically 20 to 400 ms. By delaying the signal reception for a certain period after the RF pulse, it is possible to highlight either T1 or T2 differences between tissues of interest. The subject of pulse sequencing to contrast magnetic properties is highly complex and is discussed in detail elsewhere (23,24). Cardiac imaging involves several additional difficulties because of the periodic contraction of the heart and the motion of blood within it. Gated nuclear magnetic resonance (to avoid motion artifact) and pulse sequencing to highlight blood flow are discussed in Chapter 54.



***e*FIGURE 46.10.1** Tipping the magnetic moment. Delivery of radio-frequency (RF) energy at the Larmor frequency causes the mean magnetization vector to tip away from the *z*-axis. Precise timing of the pulse tips the vector by precisely 90 degrees into the *x-y* plane where it will precess about B_0, emitting electromagnetic radiation (again at the Larmor frequency), which can be detected externally. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:640, with permission.)



***e*FIGURE 46.10.2** Relaxation parameters used in magnetic resonance imaging. T1 represents the realignment of the magnetic moment with the external field (directed along the *z*-axis), whereas T2 reflects the loss of coherence in the *x-y* plane of the precessing protons.

***e*TABLE 46.3.1** MAGNETIC RESONANCE IMAGING PARAMETERS

Tissue	^{1}H density (% H_2O)	T1 (ms)	T2 (ms)
Muscle	100	600	40
Liver	91	270	50
Renal cortex	95	360	70
Renal medulla	95	680	140
Spleen	92	480	80
Fat	98	180	90
White matter	100	390	90
Gray matter	94	520	100

Blood	90	800	180
Cerebrospinal fluid	96	2,000	300
Water	100	2,500	2,500

Adapted from Bushong SC. *Magnetic resonance imaging*. St. Louis: Mosby, 1988.

Localizing the Signal

The final issue to contend with is localizing a particular magnetic signal within the body. Because all protons in a magnetic field B_0 will precess with the same frequency $f = gB_0/2p$ (except for minuscule variations related to the local chemical environment and exploited in magnetic resonance spectroscopy), there is no way for an external receiver to distinguish where the signals are arising. It is possible, however, to make the precessional frequency a function of position by varying the magnetic field across the patient during the readout period. If a magnetic gradient G_x is applied across the region of interest in the *x*-direction, the precessional frequency will be $f = g(B_0 + xG_x)/2p$, and protons at high *x* values will ring at a higher frequency than those at low *x* values. By analyzing the frequency content of the received signal, it is possible to distinguish regions with different *x*-coordinates (in much the same way that it is possible to tell whether the right or left end of the piano keyboard has been struck simply by listening to the pitch of the emitted note; Fig. 46.11). This process is intimately involved with Fourier transform theory (see Application of Fourier Analysis in Cardiac Imaging, later in this chapter).

FIGURE 46.11 Localizing the magnetic resonance imaging signal. By varying the strength of the magnetic field across the image, the proton precessional frequency varies, allowing them to be localized by Fourier analysis, much like a piano note can be localized.

COMPARISON OF TECHNIQUES

The preceding physical descriptions and the subsequent chapters show there are a host of diagnostic tests available for most cardiovascular disorders. To choose among them in the workup of a given patient, one may apply any of several criteria, such as cost, safety, accuracy, and availability of the test. Also of critical importance is the likelihood that a particular disease is actually present in the patient.

Sensitivity and Specificity

Two key parameters for the accuracy of a test are its sensitivity and specificity. In general, *sensitivity* refers to the likelihood that a patient with a given disease will have a positive test result, whereas *specificity* is the likelihood that a patient without that disease will have a negative test result. We can divide patients into four general classes: true-positive results (TP, patient with disease has a positive test result), true-negative results (TN, patient without disease has a negative test result), false-positive results (FP, patient without disease has a positive test result), and false-negative results (FN, patient with disease has a negative test result). Sensitivity then is defined as TP/(TP + FN), whereas specificity is TN/(TN + FP). Closely related to these concepts are the positive and negative predictive values for a test. The positive predictive value is the proportion of patients with positive test results who, in fact, have the disease: TP/(TP + FP), whereas the negative predictive value reflects patients with a negative test result who are free of the disease: TN/(TN + FN). Overall accuracy of the test is given by the percentage of patients who have the proper test result: (TP + TN)/(TP + TN + FP + FN).

Critical to rational use of sensitivity and specificity figures is knowing the prevalence of disease in the test population. For example, a test with a specificity of 95% sounds very accurate, but in a population whose prevalence is only 1:1,000, there will be 50 false-positive test results for every patient who actually has the disease.

Bayesian Analysis

To determine the true value of a test in a given patient population, one uses Bayesian analysis. If the prevalence of a finding in a given population is *p*, then the likelihood of being free of that disease is 1 – *p*. Sensitivity and specificity data can then be used to derive the positive and negative predictive value for a given *p*:

$$\text{Positive predictive value} = Se \cdot p/[Se \cdot p + (1 - Sp)(1 - p)]$$

$$\text{Negative predictive value} = Sp \cdot p/[Sp \cdot p + (1 - Se)(1 - p)]$$

Thus, when the prevalence of a disease is low, a test must have extraordinarily good specificity for most of the positive test results not to represent false-positive results. Alternatively, one may solve for the prevalence of disease at which the predictive value positive for a test is 0.5 (equal odds of disease vs. false-positive result), given by $p = (1 - Sp)/(1 + Se - Sp)$. Thus, for a test with equal sensitivity and specificity, this break-even point for predictive value positive is given by a prevalence of $1 - Sp$. It is often unwise to perform tests in populations with either a very low prevalence of disease (high proportion of false-positive test results) or a very high prevalence (most negative test results are false negative).

Receiver-Operator Curve Analysis

Often a test may produce a continuum of parameter values, and it is unclear what threshold should be used to determine whether a disease is present. If the threshold is set too low, this results in an unacceptable number of false-positive readings, whereas a threshold set too high will miss many patients with disease. A receiver-operator curve is useful for determining the optimal test threshold as well as judging the overall value of the test. In receiver-operator curve analysis (Fig. 46.12), one specificity is plotted along the *x*-axis, while sensitivity is plotted along the *y*-axis with various points plotted corresponding to alternative test thresholds. A test that is entirely without value (such as flipping a coin) produces a diagonal line between (0,0) and (1,1). There is always a trade-off between sensitivity and specificity of a test as the threshold is altered, but generally the optimal point is the one that is closest to the upper left-hand corner of the receiver-operator box (0,1). The area under the receiver-operator curve (or between the receiver-operator curve and the line of identity) is a measure of the overall worth of the test, and tests that approach the ideal are those that are skewed strongly to the upper left-hand corner.

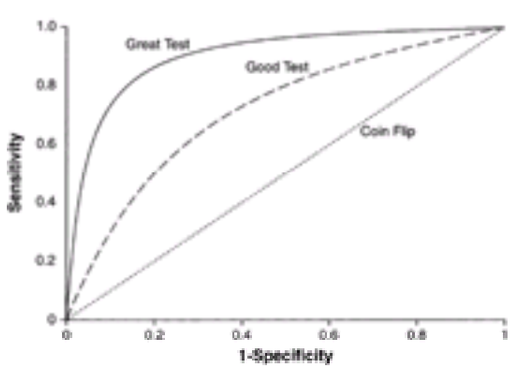


FIGURE 46.12 Receiver-operator curve analysis. For tests with continuous output parameters, there is a trade-off between sensitivity and specificity based on the choice of the cutoff to declare a test result positive. The closer a test result approaches the ideal of 100% sensitivity and specificity (*upper left corner*), the better the test.

Economic Analysis

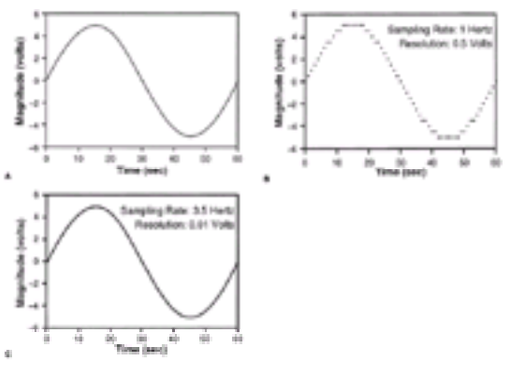
With the current restraints on health care expenditures, the cost of a diagnostic test must be considered in judging its overall worth. Unfortunately, determining the cost-effectiveness of a diagnostic test (in terms such as the cost per additional quality year of life) is more difficult than a therapeutic maneuver (25). With a therapeutic intervention, there is a discrete encounter with a well-defined cost and an outcome that can be tracked from that point forward. With a diagnostic test, however, a physician must act on the test, putting a cloud of therapeutic uncertainty between the diagnostic test and the outcome. Furthermore, this evaluation does not in any way account for the significant reassurance that a patient may feel by having a negative test outcome.

DIGITAL DATA PROCESSING

We now discuss digital imaging and image processing, the hallmark of which is that parameters of interest (such as x-ray attenuation or Doppler shift) are measured at discrete time or space intervals and quantized into a limited number of values. This contrasts with *analog processing*, in which these parameters are handled as continuous functions of space or time. Digitized signals are easier to process, because digital amplifiers need only distinguish whether a voltage is on (i.e., above a certain level) or off (i.e., below this voltage threshold). Furthermore, to change the analysis requires only a modification of the computer program, not a change in the physical components of the system, a flexibility that has allowed the development of complex CT and MRI algorithms, which could not even be attempted on an analog system.

Analog versus Digital Representation of Signals

*e*Figure 46.12.1A displays a sine wave in analog format, varying smoothly between +5 volts and –5 volts. Since this is a *continuous* function, every point in time (*x*-axis) has a corresponding voltage (*y*-axis), without intrinsic resolution limitation: The signal is 2.5 V at 5 seconds and 2.500037 V at 5.0001 seconds. In practice, however, analog equipment seldom has this accuracy.



***e*FIGURE 46.12.1** Analog versus digital representation of data. The same physical signal (a slowly varying voltage ranging between ±5 volts and described mathematically as 5 sin p*t*/30) is represented in analog fashion in **A** and digital format in **B**. **A:** Both time and voltage are *continuous* quantities, the quality of the data determined by the intrinsic accuracy of the measuring equipment. **B:** The data are sampled only once per second (1 Hz), and no information is available between these points. Furthermore, the magnitude of the voltage is stored in 0.5-V increments, leading to a less accurate representation than the analog signal. **C:** There is improved digital representation of the signal, with a sampling rate of 3.5 Hz and a resolution of 0.01 V, leading to a much more faithful rendering of the data, indistinguishable in this reproduction from the original analog representation. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:653, with permission.)

In contrast, a digital representation of the same voltage wave is shown in *e*Figure 46.12.1B, differing from *e*Figure 46.12.1A in that the signal is measured and displayed only at *discrete* 1-second time intervals; the measured voltage can take on values that are multiples of 0.5 V. *e*Figure 46.12.1C, however, shows that digital signals may be as accurate as needed by measuring the voltage more frequently and storing it more precisely.

Digital signals are stored as a series of binary bits, which can represent only 0 or 1. The more bits stored per value, the more precisely it is represented and the wider the dynamic range. Four-bit numbers have only 16 levels, whereas 6-bit may represent 64, 8-bit 256, 10-bit 1,024, 12-bit 4,096, 16-bit 65,536, and 24-bit may take on 16,777,216 values. Compared with the data in *e*Figure 46.12.1B, the data in *e*Figure 46.12.1C has 3.5 times as many numbers to store (because of the more frequent sampling), and each number requires 10 bits rather than 4 to get the 50-fold finer resolution, and thus almost nine times as many data must be stored. In general, it pays to use a digital representation of a signal with a precision roughly equivalent to the accuracy of the original analog signal from which it was derived.

Image-Processing Hardware

Analog-to-Digital Conversion

The interface between the computer and the outside world is the analog-to-digital converter, which converts the analog value of a signal (e.g., the magnitude of a reflected echo) into a binary representation. Two figures of merit characterize the performance of analog-to-digital converters: *resolution* (the number of bits per datum discussed previously) and *throughput* (the number of samples digitized per second). The resolution should be carefully matched to the intrinsic accuracy of the signal being digitized: 6 to 8 bits for visual gray-scale data and 12 to 16 bits for pressure or flow data. Throughput should be at approximately twice the maximal frequency component of interest.

Digital-to-Analog Converters

The human eye is a fundamentally analog system, so the processed, digitized signal must be converted back to analog format for displaying on a monitor or plotting on a graph. This digital-to-analog conversion is characterized by the same resolution and throughput concerns of the analog-to-digital converter.

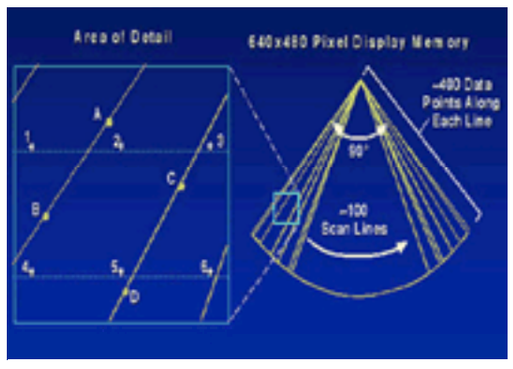
Analog and Digital Representation of Video

The analog television image is formed by sweeping an electron beam across and down the screen 30 times a second to form a video *frame*. In actuality, each frame is composed of two *fields*, containing (respectively) the even- and odd-numbered scan lines (called *raster lines*), interlaced to form 60 video fields per second, which reduces image flicker. The video standard in the United States, National Television Standards Committee (NTSC) has 525 raster lines in a frame (26). Computer monitors typically use *progressive* scanning (noninterlaced) and may have true frame rates over 80 Hz and resolution from 640 × 480 pixels to over 2,000 × 2,000 pixels. Color on such monitors may be represented by 8 bits (256 colors), 16 bits (thousands of colors), or 24 bits (8 bits for each primary color, red, blue, and green), producing photographic quality of millions of colors.

Digital Scan Conversion

The digital scan converter (DSC) changes the image data from its internal representation (in this example, the polar representation of ultrasound) to the rectangular video format (*e*Fig. 46.12.2) (27). A typical sector has approximately 100 scan lines, each of which has approximately 400 discrete echo amplitude points. The DSC

maps the ultrasonic intensity at each of these sampled points onto the video memory *buffer* (storage area), which is arranged in Cartesian (rectangular) format. Near the top, several scan lines overlap each pixel, and the DSC uses the polar point falling closest to the center of the pixel. At the periphery, many pixels are not crossed by a scan line, and interpolation from adjacent data points is therefore necessary (28). Because the data are in digital format, it is simple to shift images on the screen to show Doppler or M-mode information and to insert calibration marks and patient identification. Finally, every 16.7 ms, the memory buffer is scanned, and analog signals are calculated corresponding to the horizontal raster lines, first the odd lines, then the even ones for NTSC output. These writing and reading tasks need not be synchronized; thus, the transducer scan rate may be different from the video output rate. Commonly the video buffer may have many frames from which cardiac motion from echocardiographic, MRI, and nuclear data may be displayed as a cine loop.



***e*FIGURE 46.12.2** Digital scan converter. The data from each sector sweep consist of approximately 100 scan lines, each of which is digitized at several hundred points. These data form a fan radiating out from the scan head. The digital scan converter maps these data, which are in a *polar* geometry, onto a rectangular array of memory pixels. This output buffer is then scanned 60 times a second to generate the analog video output signal. In the close-up, it is evident that the rectangular grid points do not in general line up with the polar data points. Simple algorithms assign the value of the nearest polar point to a given rectangular point, whereas more sophisticated techniques interpolate among the four nearest neighbors to yield a smoother video output. (Adapted from Weyman AE, et al. *Principles and practice of echocardiography*, 2nd ed. Philadelphia: Lea & Febiger, 1994:60, with permission.)

On-Screen Data Analysis

The digital memory buffer allows on-screen analysis since placing a cursor on the screen simply requires writing the value for bright white (usually 255) to form a cross in video memory, which is displayed on the screen. Knowing the location in video memory and the calibration for the screen, the computer may compute dimensions, circumferences, and areas for various structures identified by the operator on the screen.

Image Processing

Although the mathematics of image processing may be daunting for the average reader, even a cursory knowledge of this technique will facilitate understanding of the edge-enhancing techniques of angiography, echocardiography, and others. A more detailed description of the mathematics of image processing may be found in standard texts (29).

Overview

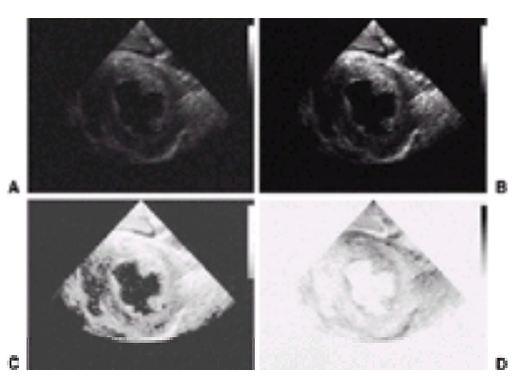
Image processing can be loosely divided into low-level and high-level components. Low-level processing deals with the individual points or pixels that make up an image, which are smoothed, sharpened, and edge-enhanced to yield a collection of *features* on which high-level processing operates to render an interpretation. By analogy, the retina and optic nerve act like a low-level processor, reducing the billions of photons per second impinging on the rods and cones to a smaller list of edges, corners, movement, and texture, which are passing to the high-level processor, the occipital cortex. Low-level processing may be subdivided into four steps: (a) *analog-to-digital conversion*; (b) *reduction of noise*, both within (spatial noise) and between (temporal noise) video frames; (c) *enhancement of edges* and other key features of the image; and (d) *extraction* of the location and characteristics of these features, which may then be passed along to a high-level processor for interpretation by template matching and pattern recognition. Despite intense research in artificial intelligence, the high-level processor usually remains the interpreting physician.

Low-Level Processing

Once a sequence of images has been digitized, processing algorithms can be applied to individual points (point processing), to single image frames (*spatial convolution*), and to a sequence of frames (spatiotemporal convolution).

Point Processing

Point processing alters each pixel value individually and is typically used to optimize image brightness and contrast. For example, *e*Figure 46.12.3 shows the effect of several pixel remappings on a B-mode echocardiogram. The ultimate contrast stretch is thresholding, in which pixels above a certain value become white, and those below that value become black.

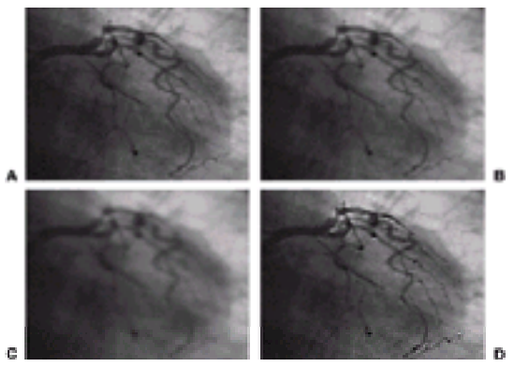


***e*FIGURE 46.12.3** Remapping of pixel values within an image. **A:** The original parasternal short-axis echocardiographic image is shown. **B:** The image is brightened and the contrast enhanced. **C:** The contrast is optimized by histogram equalization (spreading pixel values across all 256 potential values). **D:** Image inversion (white becomes black and vice versa).

Spatial Convolution

In spatial convolution, the output value of a pixel is determined by its own input value and those of its neighbors within a single frame. If these pixels are averaged together, random noise is reduced (30,31), although at the expense of some blurring of edges and other sharp features (32,33). *e*Figure 46.12.4 shows the effect of slight (B) and severe (C) noise reduction. In contrast, if the difference of pixel values is calculated, then edges are highlighted. *e*Figure 46.12.4D shows the effect of unsharp masking, which increases the contrast at edges. The simplest convolution requires nine multiplications and one addition, so that processing a 512 × 512 image at 30 frames per second requires almost 80,000,000 operations per second, previously requiring dedicated computer hardware to convolve video in real-time. With the dramatic increase in computer speed, however, such processing can now be implemented in software. More complex convolutions may apply an asymmetric mask to the image, recognizing that axial and lateral resolution may differ (34). In addition, different filtration masks may be applied on a pixel-by-pixel basis to smooth *along* the

edges but not *across* them. Such filters are nonlinear in character and thus computationally more intense.



***e*FIGURE 46.12.4** By adjusting a pixel based on the value of its neighbors, noise reduction and edge enhancement can be accomplished. **A:** The unprocessed angiogram. **B,C:** Moderate and severe smoothing using a Gaussian (bell-shaped) averaging scheme. **D:** The effect of unsharp masking that increases contrast at edges.

Temporal Noise Reduction

Because there is some randomness in the data arising from a single point over time, *temporal noise* is introduced, which must be minimized for subsequent edge and motion analysis to be accurate. Two general approaches to temporal noise reduction have been described. First, a given pixel may be averaged with the same location on previous and subsequent frames (12,35), which may blur out rapidly moving valve structures, but appears acceptable for the slower endocardial motion. The second general approach is *gated averaging* of corresponding video fields from successive cardiac cycles, taking advantage of the natural periodicity of cardiac movement, commonly done in nuclear cardiology and MRI (36,37). Averaging *N* images together should decrease the random noise by a factor of $(N)^{1/2}$, though image misalignment and ultrasonic “speckle” noise limit its use in echocardiography.

It is also possible to combine spatial and temporal operations into a single 3-D convolution encompassing three (or more) video fields. With faster hardware, it should be possible to use nonlinear filters, such as those described in this chapter, to preserve and highlight moving as well as static edges.

Edge Extraction

To actually extract the edges themselves from an image, one may threshold a gradient image to select points with strong edge characteristics. These candidate edges may be serially thickened and thinned to form a single closed contour and eliminate extraneous “edge” pixels. Once in this form, the boundaries may be output, for example, to a computer for automated quantification of regional wall motion or quantitative coronary angiography. Motion analysis may follow edge enhancement. The optical flow algorithm tracks edges on successive frames to quantify their perpendicular motion (38); one group has used this technique with echocardiographic images (39,40) to identify regions of convergence (contraction), divergence (dyskinesis), translation, and distortion. If one has an accurate sequence of edge maps, the convected activation algorithm can calculate perpendicular edge motion at the video frame rate (41). However, such a technique is critically dependent on the continuity and accuracy of the input edge maps.

Practical Experience with Edge Detection

Critical to the success of any edge-detection scheme is the quality of the raw data. Data with high signal-to-noise ratio and highly defined edges, such as contrast ventriculography, are most amenable to automated border detection (42). Image enhancement by digital subtraction of a noncontrast image further improves this process (43). Automated and semiautomated methods for tracking contrast-filled coronary arteries have been used to assess hydrodynamic severity of stenosis (44,45).

Nuclear Imaging

In nuclear cardiology, despite the low signal-to-noise ratio, it has been possible to enhance endocardial borders by a combination of thresholding with first and second spatial derivative operators (46,47). An advantage of radioventriculography is the ability to measure ventricular volume directly from the photon count without geometric assumptions, from which rates of filling and ejection can be measured. Because these calculations require temporal differentiation, which amplifies noise, Fourier analysis is commonly used to reconstruct the ventricular volume curve using only the low-frequency harmonics (48). By mapping the phase and amplitude of the first harmonic for all the pixels in the image, it is possible to assess regional function (from the amplitude image) and time and location of ventricular activation (from the phase image) (49,50).

Magnetic Resonance Imaging

Because magnetic resonance images are of such high quality, they are good candidates for image processing and automated edge detection. This is especially so because edges may be detected within one plane and tracked to adjacent planes at the same point in time, or projected forward and backward in time to yield a full four-dimensional data set of cardiac anatomy. Such a reconstruction presents formidable challenges for surface modeling and display (51).

Echocardiography

An early approach to echocardiographic edge extraction used either the Sobel or Laplacian operators applied to an entire ventricular image, with either a user-specified (9) or automated (52) threshold declaring a pixel to be an edge, but it is difficult to exclude extraneous edge points and fill in regions of echo dropout. A fundamentally different approach assumes a priori that the short-axis left ventricular endocardium is a closed, nearly circular, curve (53). After the user specifies a point within the ventricular cavity, the ventricular centroid is defined and a radial search performed for points of maximal gradient, presumed to represent the endocardium and epicardium, with points rejected if they cause too sharp a discontinuity in the border. Efforts have also been made to use the position of the endocardium in one frame to guide the subsequent border search (54). Like the earlier serial methods (17), these search radially from the ventricular centroid but use pixel intensity, spatial gradient, and local variance in combination to assign a probability that a pixel is on an edge. Some methods have also allowed the user to correct computer errors on a single frame (for instance, to include or exclude the papillary muscles) and then extrapolate this correction throughout the cardiac cycle (55).

Artificial Intelligence Techniques

Many analytic methods are quite specific in their application: They require data from specific imaging views in a particular format. The long-term goal is a much more robust system, one that could accept data from the low-level processor from a variety of views (perhaps nonstandard) and fit this information into a 3-D model of how a normal heart should appear, judging abnormality as a discrepancy from this normal model. Ideally such a system should interact with the low-level processing algorithms to optimize the features extracted and perhaps cue the examiner for additional views. Although such a system is far in the future, the use of artificial intelligence modeling has been described to guide ultrasonic data acquisition (56). In this preliminary work, the size and shape of a balloon were reconstructed by sequential input of border information together with 3-D positioning data from sonic spark gaps mounted on the transducer. The computer used previously provided information concerning the typical appearance of a balloon to build a 3-D model of the object being imaged and request additional views as needed.

APPLICATION OF FOURIER ANALYSIS IN CARDIAC IMAGING

Fourier analysis is a technique for extracting the frequency components from a signal or image (57,58 and 59), a powerful mathematical tool that has achieved a prominent role in diagnostic cardiology. Most familiar is its use in Doppler echocardiography to convert the frequency-shifted signal into blood velocity. Fourier analysis is also integral to image formation in nuclear magnetic resonance and CT and is gaining utility in wall motion analysis in nuclear cardiology and echocardiography. Although the mathematical details are daunting, it is hoped that the graphic description here will give all readers insight into the principles and limitations of Fourier

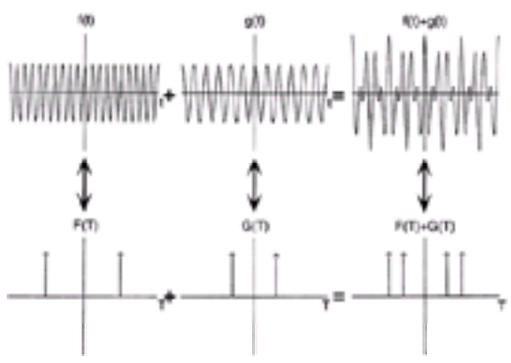
analysis.

Notational Conventions

Functions of time, space, or both have lowercase names and variables, $y(t)$, $f(x)$, $s(q)$, and so forth, while the corresponding Fourier transforms will be capitalized, $Y(T)$, $F(X)$, $S(Q)$, and so forth, related by $\leftrightarrow$: $y(t) \leftrightarrow Y(T)$. The variables $t \leftrightarrow T$ are reciprocal to each other: if t is time in seconds, then T is temporal frequency in sec^{-1} or Hertz. It is critical to appreciate that $y(t)$ and $Y(T)$ are simply different representations of the same thing, with a flexible interrelationship. Sometimes it is more convenient to consider the individual values of a signal [use $y(t)$], whereas at other times it is more informative to display its component frequencies [use $Y(T)$].

Fourier Transform Properties

The Fourier transform theorem states that any function of time, $f(t)$, can be duplicated by adding together sine and cosine waves of different frequencies. eFigure 46.12.5 shows how two cosine waves of different frequencies can be added together to produce a complex waveform (top row). The corresponding Fourier transforms on the lower row demonstrate several features. First, the higher frequency signal (10 Hz, left) has the broader Fourier transform with data present at ±10 Hz (the presence of negative frequencies is a mathematical artifact); second, just as the waveforms can be added together, the two transforms can be added together (right panels). This linearity property is critical for the utility of the Fourier transform. We can either add two signals together and take the transform of the result or take the transform of the two signals separately and add these together. The result is the same.

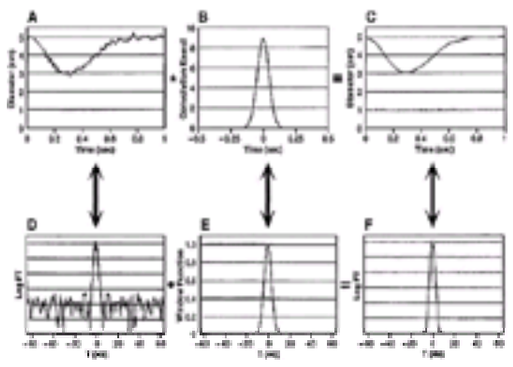


***e*FIGURE 46.12.5** Fourier transformation is a linear process. $f(t)$ is a cosine wave with frequency 10 Hz, whereas its transform $F(T)$ is nonzero only at 10 Hz; similarly, $g(t)$ is a lower frequency wave, with $G(T)$ positive at 6 Hz. The Fourier transform of the sum $f(t) + g(t)$ is simply the sum of the two component transforms $F(T) + G(T)$ (*right*). (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:643, with permission.)

Applications

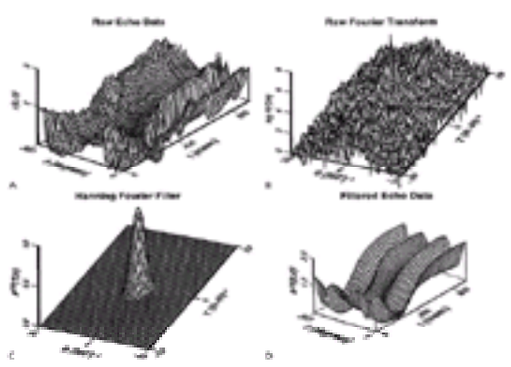
Data Smoothing

eFigure 46.12.6 illustrates an important application of Fourier analysis, smoothing a noisy signal. In A, a ventricular diameter curve is seen with random measurement error of approximately ±0.2 mm superimposed. The transform below shows that this noise is mostly contained in the higher frequencies of the signal, with the true signal concentrated below 10 Hz. By multiplying the transform in D by the windowing curve in E, we can eliminate all frequencies over 10 Hz (F), and when this is inverse transformed, we obtained a smoother rendition of ventricular contraction in C. Note that exactly the same result would result from computing the moving average of the signal in A with the smoothing curve in B, using a complex process termed *convolution*. It is often more efficient to smooth a signal by the Fourier filtration approach (A→D→E→F→C) than to do the computationally more difficult convolution (A→B→C).



***e*FIGURE 46.12.6** Fourier filtration to smooth a noisy signal. The noisy signal in **A** (analogous to an M-mode left ventricular diameter) is Fourier transformed in **D**, showing that most of the noise is in higher frequencies. Multiplying this by the windowing curve in **E** eliminates these high frequencies **(F)**, which, on inverse transformation, reveals the smoothed curve in **C**. Alternatively, the noisy signal can be convolved with the Gaussian function in **B** to yield the smoothed curve in **C**, but this is often more computationally difficult than using the Fourier transform. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:646, with permission.)

This efficiency is even more obvious as one moves beyond the one-dimensional data set of eFigure 46.12.6 to a 2-D data set as shown in eFigure 46.12.7, showing the traced endocardial borders from a short-axis echocardiogram throughout a complete cardiac cycle (60). This data set has both a temporal dimension (the t-axis) and a spatial one (the q-axis, representing the angular distance around the border). The radial distance of the endocardium from the ventricular centroid is shown as a height, $r(t,q)$. Although one can discern in A gross systolic contraction (between 0 and 300 ms) and the location of the papillary muscles (at approximately 45 and 300 degrees), much is lost in the random noise of the traced contours. The 2-D Fourier transform of these data (eFig. 46.12.7B) shows physiologic information at low frequencies (center of the graph) with a noise spectrum in the high frequencies. These noisy frequencies are eliminated by multiplying eFigure 46.12.7B by the filter function in eFigure 46.12.7C. Performing the inverse Fourier transform on these filtered data yields the smoothed profile in eFigure 46.12.7D in which cardiac structure and function are much more evident.

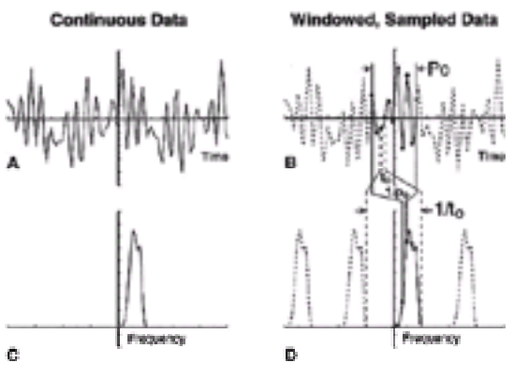


***e*FIGURE 46.12.7** Spatiotemporal Fourier filtration. The noisy data in **A** (traced endocardial borders) is Fourier transformed in **B**, which is multiplied by the filter function in **C**, and then inverse transformed to yield the smoothed data set in **D**. See text for discussion. (Reprinted from Thomas JD, Hagege AA, Choong CY, et al. Improved

accuracy of echocardiographic endocardial borders by spatiotemporal filtered Fourier reconstruction: description of the method and optimization of the cutoffs. *Circulation* 1988;77:415–428, with permission.)

Doppler Processing

Fourier analysis helps to appreciate the limitations of pulsed Doppler echocardiography. Consider eFigure 46.12.8 showing the actual Doppler-shifted signal from a region of the heart, whose transform is shown in C. Pulsed Doppler processing imposes two fundamental changes on this picture (right panels). First, since blood velocity changes throughout the cardiac cycle, the Doppler signal must be analyzed in discrete windows of duration p_0 (typically 2 to 20 ms). Alternatively, analysis of the whole cycle would simply yield the mean velocity without any phasic information. The second limitation is imposed by the pulsed nature of the interrogation: The Doppler signal is not sampled continuously but rather at the PRF, represented by intervals of t_0 (typically 0.1 to 0.5 ms). These impose limitations on both the maximal and minimal velocities resolvable by Doppler. The discrete sampling interval dictates that the maximal resolvable frequency is $1/2t_0$ (actually, twice this, $1/t_0$, if the Doppler baseline is shifted maximally), manifested physically as Nyquist's velocity. The window period p_0 dictates the *minimal* resolvable frequency, $1/p_0$, leading ultimately to the velocity resolution. This kind of trade-off is ubiquitous throughout Fourier analysis: Longer observation periods lead to finer frequency resolution but worsen the temporal resolution of phasic velocity changes. Such changes in velocity can be tracked more closely by decreasing the window internal p_0, but only at the expense of worsened velocity resolution. eFigure 46.12.8 shows this graphically, where t_0 is related inversely to the width of the resolvable frequency spectrum and p_0 is related inversely to the minimal resolution of the spectrum.



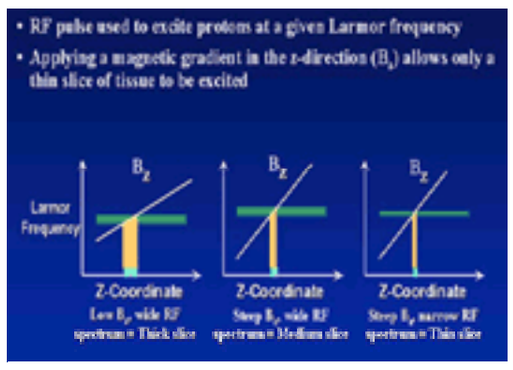
***e*FIGURE 46.12.8** Effect of sampling and windowing of the Doppler waveform on its frequency representation. The "true" Doppler signal in time **(A)** and frequency (Fourier) domains **(C)** are shown on the left. The continuous temporal data are sampled at intervals of t_0 for a period of p_0 (a total of p_0/t_0 readings, **B**); in effect, it is multiplied by d($t_0 \pm nt$) and convolved with d($t \pm np_0$). In the frequency (velocity) domain **(D)**, these effects are reversed and inverted: The data sampling leads to repetition of the velocity waveform at frequencies $1/t_0$ (i.e., convolving it with d[$T \pm n/t_0$]), whereas convolving the window leads to multiplication of the velocity profile by the repeating delta function, d($T \pm n/p_0$). Thus, unambiguous frequency data are available only for p_0/t_0 frequencies between $\pm 1/2t_0$ at intervals of $1/p_0$. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:648, with permission.)

Magnetic Resonance Imaging

Fourier processing has a critical effect on the initial magnetization and subsequent extraction of spatial information from magnetic resonance signals (61). Recall that delivery of an RF pulse at the Larmor frequency will tip the mean magnetization vector out of alignment with the external magnetic field, after which it rotates, emitting radiation at the Larmor frequency. MRI exploits this frequency dependence both to excite part of the imaging field selectively and to separate signals from different locations within that field.

Slice Selection

Before a magnetic resonance image can be formed, a slice of tissue must be localized by changing the orientation of the magnetic moment. This is done by applying an RF pulse at the Larmor frequency, given by $gB_0/2p$, where g is the gyromagnetic ratio and B_0 is the strength of the external magnetic field. If the sample is irradiated by RF at anything other than the Larmor frequency, nothing occurs, a frequency dependence that allows selection of a specific slice by varying the strength of B_0 along the axis of the body. The more rapidly B_0 varies along the body, the thinner the excited slice will be, as shown in the left and middle panels of eFigure 46.12.9. Also affecting slice thickness is how well defined the frequency of the RF is, and here Fourier theory enforces a trade-off between this frequency definition and the speed with which the magnetization can occur. The shorter the RF pulse, the more rapidly images can be obtained, but short pulses have more spectral broadening and thus excite a slice of tissue less precisely. The right panel of eFigure 46.12.9 shows how a longer, weaker RF pulse excites a thinner slice but at the price of slower data acquisition.



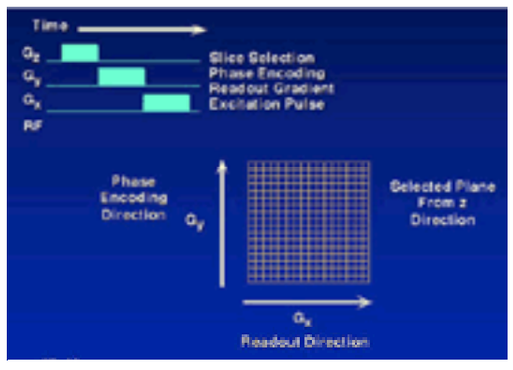
***e*FIGURE 46.12.9** Slice selection in magnetic resonance imaging by selective excitation. The thickness of the plane excited by a radiofrequency (RF) pulse (*yellow bar*) depends on the steepness of the magnetic gradient (*diagonal line*) and the spectral width of the RF pulse (*green bar*). (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:649, with permission.)

Spatial Resolution within the X-Y Plane

Following selective excitation of a slice of tissue, features within the plane are localized by varying the strength of the magnetic field across the plane to make the protons "ring" at a frequency specific to their location. Fourier analysis is then used to recover position from these frequencies. If the only challenge were to localize a structure in one direction (say the *x*-direction), one could simply change B_0 linearly along that direction, yielding a spectrum at which frequency is directly related to position (not unlike the keyboard of a piano; Fig. 6.11). The faster the rate of change in B_0, the finer the potential resolution along that axis, but the greater the risk that frequency shifts on the periphery of the image may exceed the capacity of the instrument, leading to the MRI equivalent of aliasing, folding over of structures into the incorrect location.

To resolve features in the perpendicular (*y*) direction requires processing a series of signals that are frequency encoded in the *x*-direction, each of which is additionally encoded by a brief gradient of varying duration or strength applied in the *y*-direction (eFig. 46.12.10) (62). These phase-encoding steps highlight different spatial

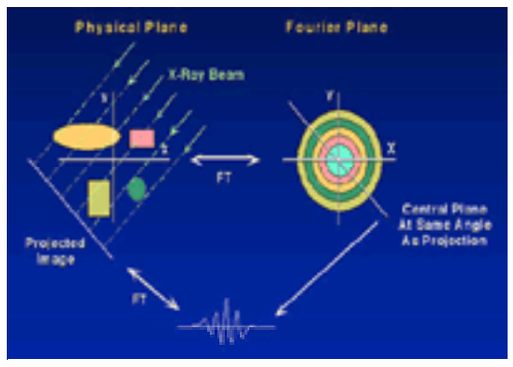
frequencies in the *y*-direction. The net effect of this is to perform a 2-D inverse Fourier transform on the structural anatomy within the plane (an inverse transform because position in the slice is equivalent to frequency, which is converted into a temporal signal). To recover the positional data, the many digitized induction signals are arranged mathematically into an array, where time within each signal is along one axis and degree of *y*-phase encoding is along the other axis. A 2-D Fourier transform then yields the desired anatomic data. The number of phase-encoding sequences applied along the *y*-axis determines the resolution of the image in this direction. A more detailed description of the pulsing necessary for cardiac gating and multislice imaging is included in Chapter 54.



***e*FIGURE 46.12.10** Nuclear magnetic resonance Fourier zeugmatography. After selectively exciting a single slice of tissue (with the *z* gradient), a phase-encoding gradient is applied in the *y*-direction followed by a frequency-encoding *x* gradient during the signal readout period. By combining data from multiple phase-encoding steps (which highlight specific Fourier components in the *y*-direction) one is left with a two-dimensional Fourier transform of the tissue slice from which one can reconstruct the original anatomy. RF, radiofrequency. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:650, with permission.)

Computed Tomography

Fourier analysis also plays a pivotal role in the theoretical underpinnings and practical implementation of computed x-ray tomography (63,64 and 65). Similar to MRI, a CT scan is built from a series of slices, but in contrast, each slice is generated from a number of x-ray projections across the slice. The difficulty is obtaining information across the depth of the slice from these projections, which (as in standard radiography) blur all details along the path of the beam. If it were possible to derive the 2-D Fourier transform of the anatomy of the slice, $F(X,Y)$, inverse transformation would yield the actual structure, $f(x,y)$. Fortunately, the 2-D Fourier transform can be built up a slice at a time as shown in eFigure 46.12.11. This is because the Fourier transform of a projection at angle q is precisely the same as the 2-D transform sampled along a line passing through the origin of the 2-D Fourier plane and inclined at an angle q. Thus, by gathering projections from a variety of qs, the complete 2-D transform $F(X,Y)$ can be filled in by interpolation. In actual implementation, a related numeric approach of filtered back projection is used, but the overall principle is the same, illustrating again how much of contemporary cardiac imaging depends on facile movement of data from real space to Fourier space and back again to simplify complex calculations.



***e*FIGURE 46.12.11** Physical and Fourier representations of an image: application to computed tomography. The projected image is obtained by integrating image density along the direction of the x-ray beam (just as a standard x-ray does). The central slice theorem states that the Fourier transform (FT) of the projection is precisely the same as the plane of the full FT passing through the Fourier origin at the same angle as the image projection. (Adapted from Fozzard HA, et al. *The heart and cardiovascular system*, 2nd ed. New York: Raven, 1992:651, with permission.)

PRACTICAL ASPECTS OF DIGITAL IMAGING

The foregoing indicates that much of contemporary cardiac imaging relies on digital acquisition and processing, but until relatively recently, the final image was usually stored in analog format: 35-mm film for angiography, videotape for echocardiography, and cut film for radiography and nuclear cardiology. Increasingly, however, images are being stored in digital format for review, analysis, and archiving. Among the advantages of digital storage are the following (66,67): (a) individual components of an examination (e.g., cine runs in angiography, echocardiographic views) can be quickly reviewed without needing to search through the entire study; (b) prior examinations are available for side-by-side comparison with the current study; (c) studies can be reviewed by clinicians throughout the hospital; (d) images can be transferred instantaneously to other institutions for consultation or referral (68,69); (e) spatial, temporal, and other calibration data can be stored with the study, facilitating quantitative off-line analysis; (f) sophisticated image-processing algorithms can be readily applied to the original data; (g) images can be duplicated without degradation; (h) long-term archiving can be accomplished without loss of quality; and (i) costs may be lower than with analog techniques. To accomplish this goal has required agreement on formatting standards, dramatic improvement in the cost-effectiveness of computers and networks, and agreement within the clinical community as to the degree of data compression that will be allowable.

Digital Imaging and Communications in Medicine Image Format Standard

Until fairly recently, commercial digital archiving systems for medical applications typically used proprietary, closed technology for image storage, so a study recorded using one manufacturer's system could not be viewed on another vendor's equipment. To head off this coming "tower of Babel" in medical imaging (70), the American College of Radiology and the National Electrical Manufacturers' Association organized in the early 1980s to standardize the exchange of digital images. Initial versions were published in 1985 and 1988 but had little effect on cardiology because angiography and echocardiography (beyond single-frame gray-scale images) were not addressed. The scope was further limited to point-to-point communications, meant to allow American College of Radiology/National Electrical Manufacturers' Association–compliant radiographic machines to exchange images, with no provision for storage of these images on exchange media, whether floppy disk, hard disk, or magnetic tape. Furthermore, the protocol was extremely limited, requiring the use of a unique 50-pin connector, which did not conform to any emerging networking standards in the computer industry. By contrast, version 3 of the American College of Radiology/National Electrical Manufacturers' Association Standard, now specified as DICOM, to emphasize its role in the general field of medical imaging as well as the inclusion of many other professional organizations (including the American College of Cardiology, the American Society of Echocardiography, and the Society for Nuclear Cardiology) in its formulation, has addressed many of the prior limitations. It now specifies a much wider range of image types, including ultrasound, MRI, CT, and x-ray angiography. In particular, color images are now enabled as are moving images and physiologic data. It specifies both network exchange of images as well as media storage, and the network interface is now an industry standard.

Overall Structure of Digital Imaging and Communications in Medicine

DICOM is simply a set of rules to specify how images and other data should be exchanged between compliant pieces of equipment. Individual image files are stored with information on the patient, the purpose and technique of the examination, interpretation of the image, and, of course, the pixel data themselves. Each modality (echo, CT, MRI, nuclear, angiography) has specified which data elements are required and which are optional in the file and the exact nature of the pixel storage, including any possible digital compression. Images may be exchanged either by network or by disk. For network communications, a process of negotiation goes on

between equipment to determine the most efficient format for the image data to be exchanged (as a lowest common denominator, all must be able send and receive uncompressed images). For disk exchange, the format must be agreed to in advance (termed *application profiles*, specific to each modality); this made up the bulk of the DICOM efforts from 1994 to 1996. It should be emphasized that DICOM is not an archival standard, but rather a communication and exchange standard. Within an institution, images may be stored on whatever media are most appropriate.

Digital Imaging and Communications in Medicine for X-Ray Angiography

The initial application profile approved for angiography specifies the writable CD-ROM (CD-R, 680 MB in capacity) as the storage medium. Studies are to be stored as 512 × 512 pixel images with 8 bits used for the gray-scale information. Lossless compression must be obtained with the Joint Photographic Expert Group (JPEG) algorithm, which reduces storage needs by 50% to 60% (see Digital Compression of Images, later in this chapter). With these rules, approximately 4,800 cine frames can be stored on a disk, sufficient for over 95% of the diagnostic and interventional studies performed in the United States. The recent progress in CD player speed allows images to be reviewed at full speed (15 frames per second). A large trial demonstrated that *lossy* compression will not be acceptable for angiographic storage, as even minor degrees of degradation resulted in a quantifiable loss in interobserver agreement (71).

Digital Imaging and Communications in Medicine for Echocardiography

In echocardiography, the needs for image interchange are more diverse. Accordingly, several interchange media are supported by the standard. Gray-scale, color, and spectral Doppler images can be exchanged over a network or stored on 1.44-MB floppy disks, 3.5-and 5.25-in. magneto-optical drives, and CD-R disks. Calibration factors may be stored for linear, temporal, and velocity measurements and 3-D registration. Images may be stored either uncompressed or with lossless or lossy compression (72).

Digital Imaging and Communications in Medicine for Nuclear Cardiology

The DICOM nuclear standard has been updated to encode the complex studies of nuclear cardiology. Truly multidimensional data sets may be stored, reflecting the four-dimensional, multistage, multinuclide nature of contemporary protocols. Because the size of the actual data sets is small in comparison with echocardiography and angiography, nuclear studies are stored without any compression.

Digital Compression of Images

Cardiac images are voracious consumers of disk storage and network bandwidth. Even a relatively low-resolution angiographic run (512 × 512 × 8 bits × 30 frames per second) will consume 7.5 MB per second, as much as 1 GB in a complex study. Full-color echocardiography (640 × 480 × 24 bits × 30 frames per second) requires 30 MB per second, up to 20 GB for a typical 10-minute study. Such requirements outstrip contemporary, affordable computer systems, highlighting the need for data reduction in cardiac imaging.

Clinical Compression

Much efficiency can be obtained through judicious editing of images on clinical grounds. In echocardiography, for example, single cardiac cycle loops can be stored for repetitive display rather than long acquisitions, a 20- to 30-fold saving. In stress echocardiography, images have been stored in quad screen format, saving only the systolic frames, a further eightfold savings. However, for both echocardiography and angiography, in which such clinical editing is not advocated, there remains a need for digital compression of the images themselves, both for storage efficiency and for speed in network and telemedicine transmission.

Digital Compression

Digital compression of images falls into two broad categories, *lossless* and *lossy*. As the name implies, lossless algorithms allow the original image to be recovered in every detail, removing all concern that such compression might affect the clinical content of the image. For lossless encoding, the echocardiographic DICOM standard uses a scheme called *packbits*, in which repetitive blocks of same-valued pixels are coded efficiently (termed *run-length encoding*). The angiographic standard currently allows only lossless encoding, using the lossless version of the JPEG algorithm. A disadvantage of all lossless techniques is relatively poor compression ratios, typically 2:1 or 3:1.

To gain more efficient compression (often beyond 100:1) *lossy* algorithms must be used, which distort the recovered image in a slight (and inapparent, it is hoped) fashion. The DICOM echocardiography standard allows the use of the lossy JPEG algorithm in which 8 × 8 pixel blocks are in essence Fourier-transformed and only the significant, mostly low-, frequency components are stored. Quantitative image analysis has shown little degradation of echocardiographic images at compression ratios as high as 20:1, whereas images stored on super VHS (SVHS) videotape show degradation equivalent to 26 to 30:1 compression (73,74). In a blind comparison, a large group of observers overwhelmingly selected digital echocardiograms over videotape equivalents, with no impact of 20:1 JPEG compression (75). Other studies have shown that 20:1 JPEG compression has no adverse effect on edge-detection algorithms and allows accurate extraction of velocity from color Doppler maps. Thus, 20:1 JPEG compression appears acceptable in clinical echocardiography; a major trial is under way to determine the effect of 7 to 14:1 JPEG compression on angiographic images. Other trials have shown the acceptability of lossy compression for CT (76) and nuclear medicine (77).

Higher degrees of compression are available from other algorithms, although these have not yet been standardized within DICOM. The Motion Pictures Expert Group (MPEG) approach extends JPEG by exploiting redundancies between frames, achieving compression ratios beyond 100:1 with excellent fidelity. MPEG is attractive because it is emerging as the standard for multimedia computing and entertainment, and prior concerns that it was more difficult to encode than decode and did not allow crisp stop frames appear to have been alleviated. It has been demonstrated that MPEG encoding has diagnostic content equivalent to videotape (78), while even higher quality can be obtained by transmitting echoes over high-speed digital networks (5 MB per second) using MPEG-2 encoding (79). Among other algorithms being evaluated are wavelet compression, which uses a continuum of frequencies to compress the image rather than the discrete frequencies of the Fourier transform (80), and H.261, a multiframe precursor of MPEG widely used in videoconferencing.

Digital Imaging at The Cleveland Clinic Foundation

The year 2000 marked the time that digital storage became a reality in the echocardiography and catheterization laboratories. Figure 46.13 shows the current architecture in use for digital echocardiography in our laboratory. All echo machines in the inpatient and outpatient laboratories, operating rooms, and regional satellite facilities are capable of digital output of still images and loops in the DICOM format using a standard TCP/IP network (100 MB per second for the local machines, 1.54-MB per second T1 lines for the regional facilities). For portable studies performed outside the high-speed network, studies can be stored temporarily on the machine's hard disk for later network export or stored on a magneto-optical disk for "sneaker netting" onto the archive. Within the echo laboratory, all image traffic is handled over a network that is isolated by switches so as not to degrade performance of the remainder of the cardiology network. A typical study in our laboratory contains 30 to 80 single-cycle cine loops with an additional 10 to 20 still frames of spectral Doppler and M-mode tracings, yielding an average study size of approximately 60 MB. With 160 studies performed daily, this requires 10 GB of storage daily or approximately 2.5 TB of storage annually. To handle this enormous storage need while providing rapid review of recent studies (access times less than 30 seconds), data sets are initially stored on a local hard drive with almost 1 TB of storage, where they remain for 30 to 60 days. Simultaneously, data are also copied to a long-term digital tape archive providing 160-TB storage with 2- to 3-minute access time. All of this is controlled by a dedicated software program running on several viewing stations in the laboratory. A similar architecture is used in the catheterization laboratory with a dedicated network providing access to up to 60 angiographic studies performed daily and stored using the DICOM standard and lossless JPEG encoding.

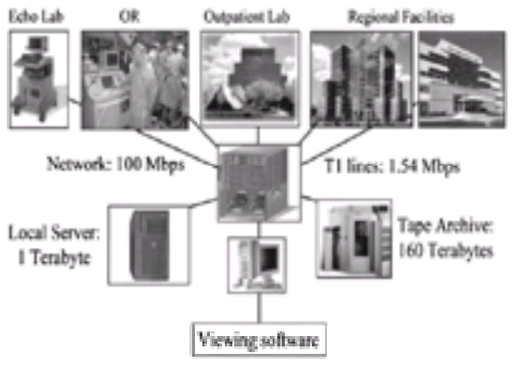


FIGURE 46.13 Implementation of digital echocardiography at The Cleveland Clinic Foundation in 2001. High-speed networks connect more than 30 echocardiographs to a central server and archive. See text for details. OR, operating room.

SUMMARY

The theory underlying cardiac imaging techniques spans a wide range of physical principles, from low-energy photons (magnetic resonance) to high-energy photons (radiography and nuclear medicine) to acoustic energy (ultrasound). With each of these methods, there are fundamental trade-offs to be made in terms of spatial resolution, temporal resolution, acquisition time, and radiation exposure, trade-offs that often become clearer when studied in terms of the spectral content of signals using Fourier analysis. Finally, combining data from any of these imaging modalities with techniques of digital image processing may provide new ways for automated image analysis and understanding.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Each year brings dramatic new developments in cardiac imaging. Since the physical interaction of photons, ultrasound, and magnetism with matter has changed little, most of these improvements result from enhancement in the computer processing of these data. Extrapolating to the future, we can only expect this to continue. Moore's law states that, over the past 50 years, computer processing power (per unit cost) doubled every 18 months. Had the auto industry shown similar productivity gains, the cost of a new car would be less than 1 cent. Since the mid-1990s, the trend toward all-digital acquisition and storage for radiography, angiography, and echocardiography has become reality, with practical solutions available from several vendors. For the most part, however, these solutions are isolated from each other and are not generally available throughout the hospital. If we are to achieve true intervendor, intermodality utility, the medical community must insist on adherence to both the letter and spirit of DICOM: DICOM should be output (by disk, network, or both) by each imaging machine and read by all information management systems. In this way, the end-user can choose components based solely on quality and price performance without concern for interoperability. In the next 5 years, we can expect solutions to emerge that can read multiple modalities and deliver these quickly to the practitioner's screen, allowing the easy integration of echo, nuclear, catheterization, and MRI data to guide management of the patient.

Digital storage and transmission should also make health care more economical by reducing the need for duplicate studies. Patients will carry their medical records and images with them, initially on compact disk but perhaps soon on a small holographic card. Images will be transmittable via telephone, satellite, or the Internet, allowing remote consultation and timely referral. Equally important is extracting as much data as we can from any given study. In this regard, several modalities (ultrasound, MRI, and nuclear imaging) are touting themselves as "one-stop shopping" for cardiac structure, function, and perfusion. Of the three, ultrasound permits the least expensive assessment of chamber size, global and regional ventricular function, and valvular stenosis and regurgitation. With the development of stress echocardiography and novel contrast agents, myocardial perfusion may similarly be measurable. Unfortunately, echocardiography has been used traditionally in a largely qualitative fashion; it is hoped that the trend toward quantitative processing of color Doppler velocities and regional wall motion will continue. Nuclear imaging has seen great improvement in the last two decades and represents the current gold standard for myocardial perfusion and metabolism. Positron emission tomographic scanning is uniquely informative, but so expensive as to be confined to a few large medical centers. In this era of cost containment, it is hard to imagine widespread dissemination of this technology. MRI provides high-resolution isotropic 3-D data throughout the body without the restriction of echocardiographic windows. With improvements, the large epicardial coronary arteries may be routinely imaged, contrast may assess myocardial perfusion, and spectrographic techniques may detect ischemia. Like positron emission tomography, though, the large capital investment and operating expense of MRI will likely limit it to specialized applications in major medical centers. More recently, computed tomography with spiral scanning techniques has allowed rapid acquisition of gated cardiac images, allowing excellent visualization of the aorta and proximal coronaries at considerably lower cost and complexity than MRI.

THE FUTURE

The next decade will see continued technical progress in all cardiac imaging modalities, but economic forces will increasingly force clinicians to choose between examinations. Those tests that provide the most comprehensive assessment of the heart at the least cost will prosper, whereas others may see diminished use. A great challenge is the routine exchange of digital studies both within and between institutions. Vendors and professional societies have agreed on the DICOM standard for this exchange, but implementation remains incomplete. The medical community must insist on adherence to standards if global interoperability is ever to be achieved.

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47

PLAIN FILM EXAMINATION OF THE CHEST

LAWRENCE M. BOXT

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The value of plain film examination of the heart and lungs lies in its availability, long history of clinical utility, and ability to display acute and chronic changes in a safe and convenient manner. Diagnosis is based on identification and characterization of variance in the appearance of structures on chest film from their expected normal appearance. Interpretation of the chest radiograph involves systematic evaluation of the quality of the examination, the position of the patient undergoing examination, as well as the radiographic changes encountered in the examination. The validity and significance of observed abnormalities depend on a belief in the physiologic or technical basis for their presence. Attention to these factors allows extraction of pertinent, reliable evidence of pathophysiologic mechanisms that allows the observer to make cardiovascular diagnoses, as well as to assess the instant physiologic status of the patient at the time of examination.

GLOSSARY

Cardiac contour: The borders of the cardiac silhouette are formed by portions of the cardiac chambers and aorta and pulmonary artery; in oblique view, different border-forming chambers are accentuated or brought into view. Analysis of chamber and great artery abnormality is based on systematic estimation of the appearance of these contours. Evaluation begins by dividing the cardiac silhouette into the left and right heart borders. The left heart border is composed of the aortic arch, main pulmonary artery, left atrial appendage, and left ventricular portion. The right heart border is composed of the superior vena cava, ascending aorta, and right atrial portion.

Cardiac position: This describes the position of the heart within the chest. In general, it is determined by estimating where the bulk of the cardiac silhouette resides. We expect the cardiac apex and bulk of the ventricular myocardium to lie just slightly off the midline, toward the left (levocardia). Thus, *mesocardia* and *dextrocardia* describe the heart as straddling over toward the right with respect to an imaginary line drawn in the chest midline. *Dextrocardia* refers to the presence of a heart in the right chest resulting from an abnormality of embryologic cardiac rotation. It is frequently associated with congenital heart disease. *Dextroposition* describes a heart in the right chest, caused by noncardiac abnormalities that affect the normally formed heart.

Cardiac rotation: The heart and proximal great arteries are contained by the pericardium and fixed in the superior mediastinum and at the diaphragm. Right atrial, ventricular, or both atrial and ventricular dilatation produces (looking from below) clockwise rotation of the heart and great vessels, so that the appearance of the left heart border in postero-anterior view is altered. The superior mediastinal silhouette is narrow as the superior vena cava rotates toward the midline, and the mid-left heart border becomes more convex as the dilated right ventricular outflow forms the left heart border.

Left ventricular configuration: Hearts that appear unusual may be morphologically normal. However, many abnormal hearts share a common appearance: The contour of the left ventricular portion of the left heart border appears greater in curvature than expected. This appearance of the left-sided heart contour is found in a variety of congenital and acquired forms of heart disease. It is a sensitive "case finder" or indicator of cardiac abnormality. However, it is nonspecific and requires appreciation of other radiographic or clinical findings for more precise cardiac diagnosis.

Pulmonary edema: This term refers to the characteristic inhomogeneous appearing infiltrates found with alveolar edema. It represents the severe end of the spectrum of the radiographic changes of pulmonary venous hypertension. The earliest radiographic finding in elevated left atrial pressure is indistinct lower lobe pulmonary vessels.

Pulmonary vascularity: The radiographic appearance of the pulmonary arteries and veins closely correlates with left atrial pressure and the regional distribution of water in the lungs. This general term refers to the caliber of the larger pulmonary arteries and veins in a chest radiograph. Comparison of left-sided vessels with those on the right, upper with lower vessels, and central with peripheral vessels is commonly used to differentiate failure from pneumonia and shunt from pulmonary hypertension.

Shunt vascularity: This subcategory of pulmonary vascularity refers to the status of the pulmonary arteries in individuals with left-to-right shunts. In particular, it refers to increase in the caliber of the entire pulmonary arterial tree, from main pulmonary artery segment, to peripheral subsegmental pulmonary arterial branches. Vessels are sharp, demonstrate normal peripheral branching, and extend further toward the pleura.

INTRODUCTION

Plain film examination of the chest is nearly always employed to determine the presence of heart disease and to help establish its etiology and severity. The development and use of angiographic, nuclear, and tomographic cardiac imaging technologies (echocardiography, computed tomography, and magnetic resonance imaging) have changed but not excluded the role of plain film radiography in the management of these patients. Characteristic changes in the atrial and ventricular portions of the cardiac contour reflect change in their chamber volume and myocardial mass. Similarly, changes in the contours formed by the great arteries and veins of the chest reflect altered pressure and blood flow. Evaluation of these changes provides the substrate for constructing a differential diagnosis or to assess the severity and often etiology of the cardiac dysfunction.

This chapter is designed to assist clinicians in the use of plain film examination of adult patients with acquired and congenital heart disease. Conventionally, chapters describe radiographic abnormalities in an organized list of cardiovascular conditions. This format can be excellent if the reader knows the answer before asking the question (i.e., if you know the patient has mitral stenosis, then reference to such a chapter provides a source for review of the literature concerning radiographic diagnosis and so on). However, as is more often the case, one does not know the plain film diagnosis; rather, one has acquired a list of positive (and negative) radiographic findings and is in need of an outline of differential diagnoses. In other words, the role of the chest film examination has changed in the management of patients with cardiovascular disease. The examination is performed more to evaluate the instant physiologic status of the patient. This change in use is not surprising, considering the rapid advance in noninvasive cardiovascular imaging. On the other hand, there remains a great deal of diagnostic information contained in plain film examination that can and does benefit the clinician.

This chapter is organized based on radiographic abnormality [i.e., the cardiac silhouette in the postero-anterior (PA) chest film is divided into left and right heart borders and the pulmonary vascularity]. The left heart border contains the aortic arch, pulmonary artery, left atrial appendage, and left ventricular contours. The right heart border contains the superior vena cava, ascending aorta, and right atrial contours. The parenchymal pulmonary vascularity is described in terms of the appearance of the pulmonary vessels. Thus, entrée into cardiovascular diagnosis and differential diagnosis is based on identification of an abnormality or constellation of abnormalities. This approach is useful, especially if one does not know the diagnosis before interpretation of the examination.

After describing the normal appearance of the cardiopulmonary structures, the range of abnormalities of that portion of the chest film is characterized and the differential diagnosis of congenital and acquired cardiovascular disease based on those specific changes is presented. That is, many different diseases may produce individual specific changes in the chest film, but more specific diagnosis may be made or a differential diagnosis ordered by evaluation of the particular constellation of findings present. In other words, rather than review the radiographic findings of a series of cardiovascular lesions, I describe particular radiographic abnormalities, explain how these changes may represent the effect of a congenital abnormality or acquired pathophysiologic mechanism, and then use these findings to construct a differential diagnosis. This is a clinically relevant approach, and it more effectively demonstrates the utility and limitations of chest film examination.

As the reader will appreciate, the utility of plain film examination in the evaluation of adult patients with congenital heart disease is emphasized. This is an important area of rapid growth. This chapter should aid clinicians who encounter such a patient or have an established practice containing many such individuals. Few non–plain film images are included in this chapter; only a few relevant images are included to reinforce mechanisms of radiographic changes in the plain film. One final note on the interpretation of plain chest films. In many cases, one may observe major “obvious” findings that form the basis for an anatomic diagnosis. Further careful analysis of the image, however, often reveals other subtler observations that correlate with the major findings. The constellation of all findings allows the observer to assess not only the disease and its severity, but also to assess the confidence the individual has in that diagnosis.

HISTORY OF CHEST RADIOGRAPHY IN CARDIAC DISEASE

Wilhelm Conrad Roentgen discovered x-rays on November 8, 1895 (1). Immediately after his discovery, physicians around the world began using this new tool in the evaluation of bone fractures and abnormalities of the gastrointestinal tract. Within months of the discovery, application of the “new photography” to chest examination was reported. Williams (2) reported fluoroscopic examination of a patient with cardiomegaly and described the findings for pericardial effusion. Early examinations were crude and dangerous by today’s standards. For example, Walsh (3) published a text that included a chest film demonstrating the position and dimensions of the heart. The exposure required 20 minutes and was obtained using a 30-in. focus-film (x-ray tube–to-film) distance.

A report of heart size in healthy individuals (4) was published in 1902; by 1909 (5), a review of the normal appearance of the heart, the size and appearance of the heart in patients with aortic and mitral valvular disease, and a thoracic aortic aneurysm was published. The measurement of the cardiothoracic ratio (the quotient of the transverse diameter of the heart divided by the greatest transverse chest diameter) was introduced by Danzer (6) in 1919. In his paper, he also noted that the normal ratio is probably greater in children. Radiographic demonstration of pericardial calcification (7) and rheumatic valvular calcification (8) were reported in the early 1920s. Evaluation of changes in cardiac size, as determined by computation of the area of the cardiac silhouette in PA chest film examinations of patients with valvular heart disease, myocarditis, systemic hypertension, and hyperthyroidism (9,10) became routine during the latter half of the decade.

Seeking to gain improved insight into the sensitivity of chest film examination for detecting cardiac disease, Ungerleider and Gubner (11) reviewed the PA chest films of 1,460 healthy individuals and published nomograms for normal transverse diameter and radiographic area of the heart, an indicator of cardiac volume.

The clinical value of plain film examination of the heart was pointed out by Paul Dudley White in an address to the American Roentgen Ray Society in 1929 (12). He emphasized that radiographic examination of the heart provided the most accurate available means of estimating cardiac size and detecting unsuspected pericardial calcification and aortic aneurysms. Furthermore, he praised the technique for its ability to estimate atrial and ventricular chamber enlargement and to provide clinical information in patients too obese or emphysematous for accurate physical examination of the heart. Although there are other imaging modalities, the value of plain chest film examination remains high, and in terms of clinically relevant information obtained, the cost to perform, and patient risk, it remains an integral means of cardiac diagnosis.

THE CHEST FILM ITSELF: IMAGE QUALITY

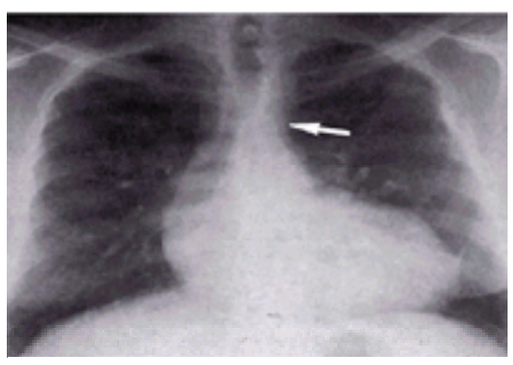
Estimation of the radiographic technique helps the observer to assess the severity of pulmonary vascular changes. A properly penetrated chest examination should allow differentiation of the four basic radiographic densities: air, bone, soft tissue, and fat. Radiographic exposure factors should be chosen so that the resultant examination permits faint visualization of the thoracic spine and the intervertebral disks so that the lung markings behind the heart are clearly visible. Proper radiographic technique allows evaluation of the sharpness of the pulmonary vascular markings and fluid status of the parenchyma. Standard high kilovoltage technique (13,14) radiographs are obtained with a fixed 145 kVp, varying mA between 400 and 600; exposure is controlled by phototimer. Exposure times of between 10 and 60 ms establish an exposure range of between 5 and 30 mA. This method produces clearer visualization of the pulmonary vasculature and better penetration of the mediastinum. However, this technique produces diminished visibility of intrathoracic calcium. Ideally, the lungs should appear gray. Radiographic underexposure (“light films”) generally result in overestimation of the unsharpness of vessels, leading to overinterpretation of pulmonary vascular congestion. Conversely, overpenetration (“dark films”) may produce better visualization of the mediastinal structures, but it prevents detailed observation of the pulmonary parenchyma, leading to underestimation of congestion or the belief that pulmonary blood flow is diminished.

Conventional chest film examination of the heart and lungs is performed using a 6-ft PA beam (i.e., the upright patient faces the film screen combination), and the radiographic exposure comes from behind (the view is named by the course of the beam, hence *PA*). Using this method, the x-ray beam is nearly parallel (nondiverging). The ventrally located heart is close to the film screen and is therefore not (minimally) magnified. Emergency room or intensive care chest radiography is typically performed from in front of the patient who leans against the film cassette. Thus, in this antero-posterior radiograph, the heart is away from the film screen combination, and the x-ray beam is not parallel and therefore diverges. These factors result in magnification of the heart.

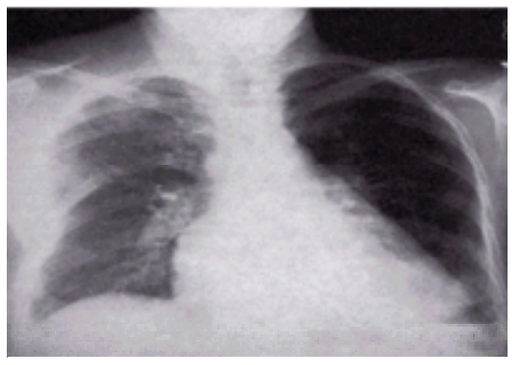
If chest radiographs are obtained with the patient upright, we see a reasonable representation of the distribution of interstitial lung water and pulmonary blood flow. When supine, the lower lobe pulmonary vessels lose their gravity dependence, and the upper lobe pulmonary veins become dependent. In the supine chest radiograph, the lungs usually show some degree of pulmonary redistribution, even in an individual with normal cardiac function.

Minor degrees of patient rotation may result in distortion of normal cardiac structures. The degree of film rotation can be judged by evaluation of the trachea, the clavicular heads, and anterior ends of the ribs with the thoracic spine. The trachea is a midline structure, and in a straight PA view, it should be projected over the spinous processes of the cervical and upper thoracic vertebrae. In this view, the lengths of the two clavicles are equal. Furthermore, the distance between the ends of the anterior ribs and the lateral margins of the thoracic spine is equal. Displacement of these landmarks is a sensitive indicator of patient rotation.

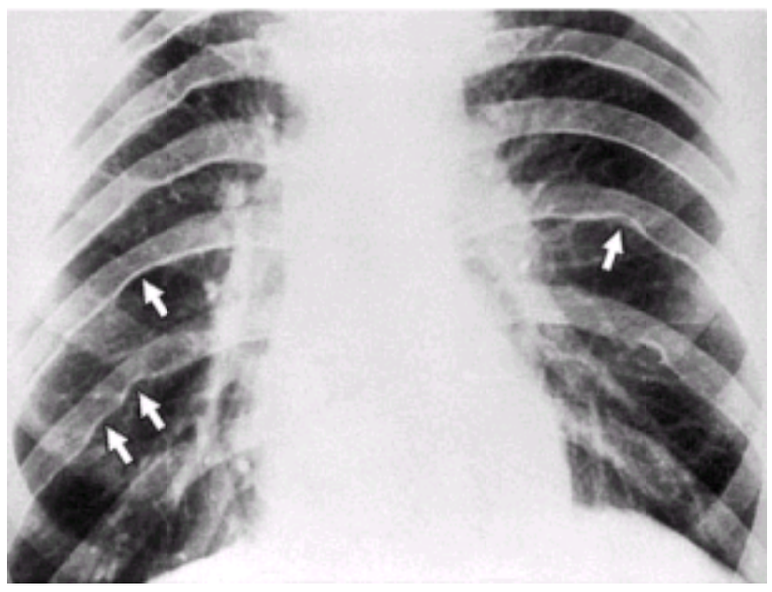
Radiographic signs of previous chest surgery include the obvious placement of midline sternal sutures and mediastinal clips or valvular prostheses as well as subtler findings such as the absence of a posterior rib or asymmetry of the intercostal spaces. Surgery in the more distant past may be evident by the appearance of a regenerating rib (eFig. 47.0.1). More recent surgery may be deduced by asymmetric chest wall edema (eFig. 47.0.2). In a manner analogous to rotation of the entire chest, scoliosis and chest wall deformity may distort cardiac structures, giving the impression of cardiac rotation or chamber enlargement. When scoliosis is present, changes of pulmonary hypertension and cor pulmonale (15,16) correlate with increasing angle of the scoliosis and patient age (17). Assessment of the size of the heart and state of pulmonary vasculature in these circumstances is difficult. Pectus excavatum (“funnel chest”) is a common deformity consisting of depression of the sternum such that the anterior ribs on each side protrude more anteriorly than the sternum itself. Some investigators have suggested (18) that the primary defect in this lesion is an anomalous position of the heart to the left of midline, leaving the retrosternal space “empty,” allowing the sternum and costal cartilages to fall posteriorly. In the PA projection the heart is rotated and displaced to the left (19). The parasternal soft tissues of the anterior chest wall are viewed in profile rather than *en face*, increasing their radiographic density, resulting in the appearance of a right middle lobe infiltrate.



***e*FIGURE 47.0.1** A 32-year-old man with a previously repaired coarctation of the aorta (the regenerating left fourth rib is irregular and faintly seen). The aortic arch segment (*arrow*) is inconspicuous. Left ventricular dilatation and mild pulmonary vascular congestion are caused by infection and subsequent insufficiency of his congenitally bicuspid aortic valve.



***e*FIGURE 47.0.2** A 48-year-old man with rheumatic mitral stenosis 4 days after right thoracotomy. The right sixth rib has been resected. Asymmetry between density of the right and left chest is caused by posttraumatic edema on the operated side. Note the mild pulmonary vascular congestion and straightening of the left atrial contour on the left heart border.



Chest x-ray in coarctation of the aorta. There is prominent rib notching (*white arrows*).

THE HEART AND GREAT ARTERIES

Cardiac Position

The heart lies just to the left of midline, and the bulk of the ventricular myocardium is in the left chest (Fig. 47.1). The position of the heart within the chest depends on cardiac looping and intrathoracic rotation, as well as the presence of skeletal, pulmonary, and diaphragmatic lesions. In situs solitus, a right-sided heart secondary to a noncardiac abnormality is called *dextroposition* (eFig. 47.1.1). This term implies an abnormal position of the heart in the absence of an intrinsic cardiac abnormality. Dextroposition may be caused by abnormalities of the bony thorax (scoliosis, deformities of the sternum or ribs), the lungs (pulmonary agenesis, pneumonectomy, right pneumothorax, chronic volume loss, scimitar syndrome), eventration, or diaphragmatic hernia.

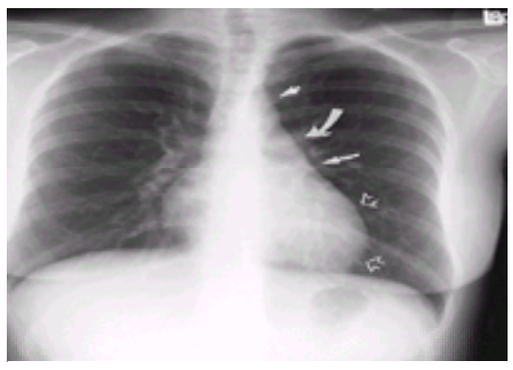
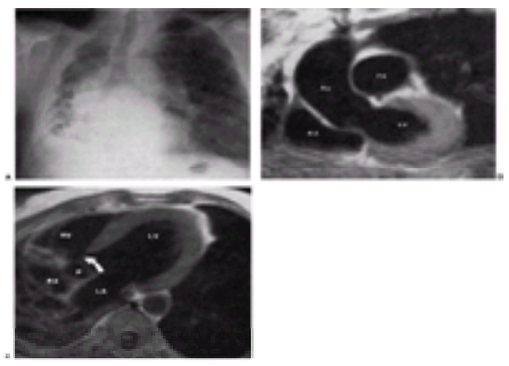


FIGURE 47.1 Normal postero-anterior chest film from a 35-year-old woman. The contours of the left heart border include the aortic arch (*short arrow*), the pulmonary artery segment (*curved arrow*), the concave left atrial appendage segment (*long arrow*), and the gentle curvature of the left ventricular segment (*open arrows*). The lower right heart border is derived from the lateral border of the right atrium.



***e*FIGURE 47.1.1** A 63-year-old man with chronic tuberculosis. **A:** Postero-anterior chest film. The heart and mediastinal structures are displaced into the right chest. Notice the pleural thickening and right lower lobe pulmonary changes. **B:** Coronal spin-echo magnetic resonance image through the aortic root. The chronic pulmonary changes, volume loss, and displacement of the heart into the left chest are evident. The ascending aorta (Ao), main pulmonary artery (PA), right atrium (RA), and left ventricle (LV) are labeled. **C:** Axial spin-echo magnetic resonance image through the posterior right sinus of Valsalva (p). The heart is intrinsically normal but rotated slightly to the left. The thin, membranous interventricular septum (*curved arrow*) is seen. RV, right ventricle.

The diagnosis of pneumothorax is made by identification of the visceral pleural line. Only large pneumothoraces produce complete lung collapse and significant mediastinal shift. The roentgenographic density of the ipsilateral collapsing lung changes little until lung volume is greatly reduced (20). In a pneumothorax of any size, shift away from that side is inevitable because pressure in the normal hemithorax remains relatively more negative. Such a circumstance must be differentiated from a tension pneumothorax, in which there is a check valve mechanism, which allows air into the pleural space during inspiration, but prevents its egress during expiration. In tension pneumothorax, one finds inspiratory shift of the heart and mediastinum away from the side of the pneumothorax associated with ipsilateral diaphragmatic depression (Fig. 47.2). Eventration of the diaphragm is a congenital failure of the muscular development of one or both diaphragms (21). Unless occurring in neonates (21,22), this condition does not cause symptoms.

FIGURE 47.2 Tension pneumothorax in a 30-year-old man. The left ventricular contour is medial (*black arrows*) to the line of the pleura (*white arrows*) against the air-filled left chest. The heart and mediastinal structures are shifted toward the right. Notice the flattened left diaphragm.

The scimitar syndrome (23,24 and 25) is an unusual malformation consisting of partial or total anomalous pulmonary venous return of the right lung veins to the inferior vena cava just above or below the diaphragm. It is frequently associated with hypoplasia of the right lung and right pulmonary artery. Frequently, bronchial anomalies and anomalous arterial blood supply to the right lung from the aorta are found (26). PA chest films demonstrate a slight decrease in the size of the right bony thorax and a shift of the heart and mediastinal structures to the right. The characteristic anomalous vein, or scimitar (after the Turkish curved sword), shows a vertical course toward the right cardiophrenic angle, closely paralleling the right atrial border (eFig. 47.2.1). Depending on the degree of right lung hypoplasia, the scimitar may project through the heart or in the right pericardial area.

***e*FIGURE 47.2.1** Two patients with scimitar syndrome. **A:** A 26-year-old woman. The heart is displaced into the smaller right chest. The scimitar may be faintly visualized (*white arrows*) crossing the right atrial border. **B:** A 35-year-old woman. The scimitar (*black arrows*) increases in caliber as it curves inferiorly to cross the diaphragm and enter the inferior vena cava (not demonstrated).

Cardiac Situs

Cardiac atrial situs is assumed to be solitus in the presence of thoracoabdominal situs concordance and abdominal situs solitus. Thus, identification of a right-sided liver and left-sided gastric air bubble establishes normal abdominal situs (Fig. 47.1). Thoracic situs is reliably determined by analysis of the trachea and lungs (27). That is, the morphologic left lung has two lobes (and therefore no minor fissure) and a longer left main bronchus over which the morphologic left pulmonary artery passes proximal to the origin of the left upper lobe bronchus. The morphologic right lung has three lobes (and thus a minor fissure). The right bronchus travels a short course before the origin of the right upper lobe bronchus. The morphologic right pulmonary artery lies anterior and slightly inferior to the right bronchus. Under these circumstances, atrial situs solitus (i.e., morphologic right atrium on the right and morphologic left atrium on the left) can be assumed. The position of the aortic arch or cardiac apex cannot be used to ascertain thoracic situs. Patients with atrial situs solitus may have an isolated right aortic arch or the bulk of their myocardial mass in the right chest (situs solitus with dextrocardia, isolated dextrocardia) in the absence of any other abnormality (Fig. 47.3). Atrial situs inversus is deduced by concordance between inverted abdominal viscera and lung morphology (Fig. 47.4).

FIGURE 47.3 A 21-year-old man with isolated dextrocardia. The heart and lungs are normal. The cardiac apex is in the right chest. The trachea (*arrows*) is midline.

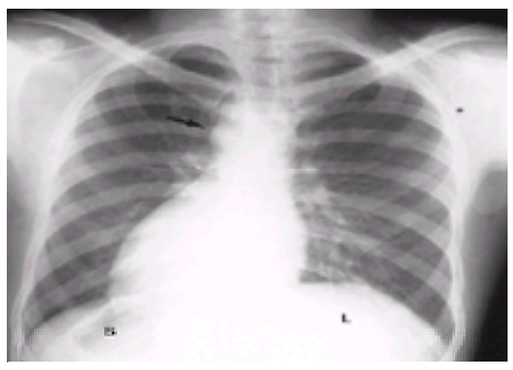


FIGURE 47.4 A 30-year-old man with complete situs inversus. The liver (L) is on the left, and the stomach bubble (S) is on the right. The aortic arch (*arrow*) and cardiac

apex are on the right.

Aortic Arch and Ascending Aorta

The normal aortic arch passes to the left, displacing the trachea toward the right (Fig. 47.1). Measurement of the true caliber of the aorta is difficult on plain chest examination because both contours are not visualized in frontal projection. The left border of the descending thoracic aorta is visualized in the PA radiograph, but the right border is not. The contour of the ascending aorta should not extend to the right beyond the vascular pedicle of the right hilum or shadow of the superior vena cava. Enlargement of the ascending aorta is characterized by increased curvature of the middle third of the mid-right heart border or by a forward bulge of the anterior border of the aorta, as viewed on lateral examination (Fig. 47.5). The aortic arch diameter (28) is the sum of the distances measured between the midline and the right-most ascending aortic contour and left-most aortic shadow, measured above the base of the heart. The diameter of the aortic arch may vary in healthy individuals between 1.8 and 3.8 cm but must not exceed 4.0 cm. However, the ascending aorta, for which there are no “normal” values, is most frequently enlarged in disease.

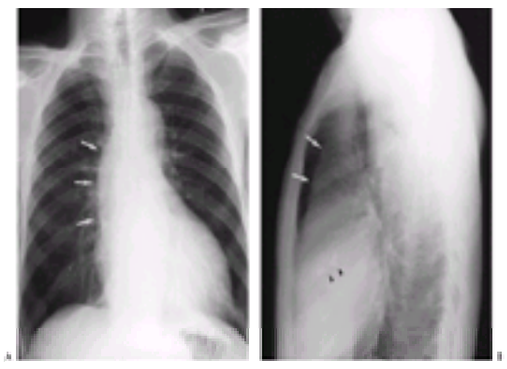
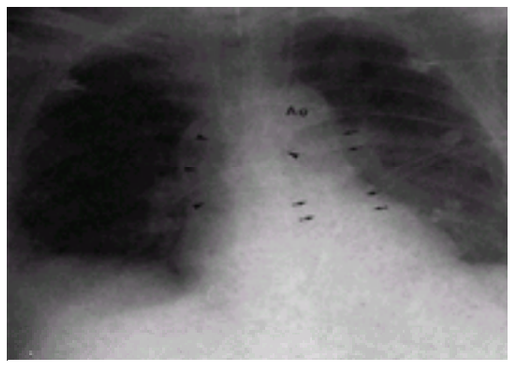


FIGURE 47.5 A 60-year-old man with degenerative calcific aortic stenosis. **A:** Postero-anterior examination shows increased rounding of the left ventricular portion of the left heart border and dilatation of the ascending aorta (*arrows*). **B:** Lateral examination shows aortic valvular calcification (*arrowheads*) in the center of the cardiac silhouette and filling of the retrosternal air space by the dilated, calcified (*arrows*) ascending aorta. The left ventricle is not dilated.

The proximal descending thoracic aorta may be identified as a straight line seen through the cardiac silhouette running parallel to the spine in continuity with the inferior, medial aspect of the aortic arch. Usually this line is to the left of the spine, but the proximal portion may be right-sided in cases of right aortic arch. Unless situs inversus is present, the aorta in cases of left and right aortic arch enters the abdomen through the left-sided aortic hiatus.

Discrete, rim-like calcification of the aorta and aortic arch is usually a sign of degenerative intimal change, most often resulting from atherosclerosis (eFig. 47.5.1). The distance between visualized calcification and the outer aortic contour is an estimation of aortic wall thickness; its measurement may be helpful in evaluating acute and chronic changes. If care is taken to consider the effects of supine versus upright examination, and the effects of tangential visualization of the heart and aorta in oblique or antero-posterior versus PA examination, then the distance between intimal calcification and the outer wall of the aorta should be no greater than 10 mm (29). This sign is valuable in the descending aorta but may be of limited value in analysis of the more proximal aortic arch as a result of technical problems described previously.



***e*FIGURE 47.5.1** A 60-year-old man with mild congestive heart failure. Antero-posterior intensive care unit examination shows an endotracheal tube in good position with its tip above the carina, and a Swan-Ganz catheter whose tip is in the right pulmonary artery. There is extensive calcification of the ascending aorta (*arrowheads*), the aortic arch (Ao), and descending aorta (*arrows*).

When there is a right aortic arch, the convex shadow of the aortic arch lies on the right side of the superior mediastinum, displacing the tracheal air column to the left (Fig. 47.6). Right aortic arches may be classified (30,31 and 32) by whether the arch is anterior or posterior to the esophagus. This distinction is important, because the heart is characteristically normal when a posterior arch is present. The presence of an anterior arch is almost universally associated with congenital heart disease. This distinction is made by evaluation of the lateral chest radiograph. In the posterior right aortic arch, found in approximately 0.1% of the population (33,34), there is a large retroesophageal defect produced by the junction of the posterior right aortic arch with the descending aorta, causing anterior bowing of the tracheal air shadow. This form of right aortic arch is usually asymptomatic and frequently associated with an aberrant left subclavian artery.

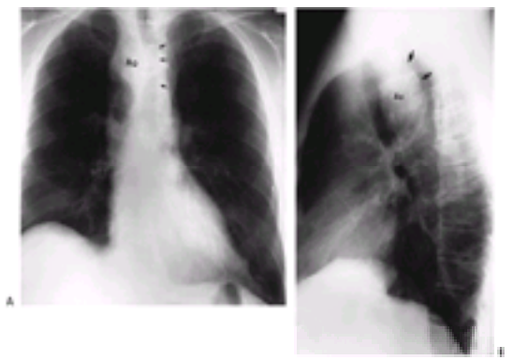
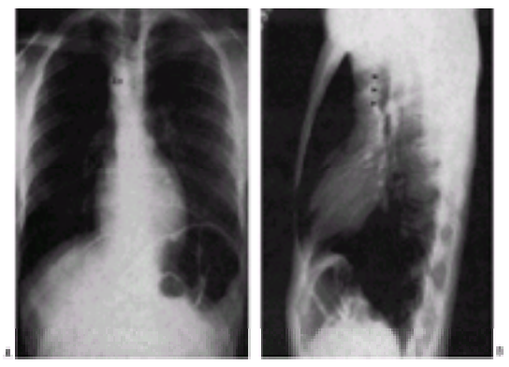


FIGURE 47.6 A 78-year-old man without cardiovascular complaints. **A:** Postero-anterior chest examination shows the convexity of the right aortic arch (Ao) displacing the trachea to the left (*arrows*). **B:** In lateral view, the trachea is bowed anteriorly by the calcified (*arrows*) arch (Ao).

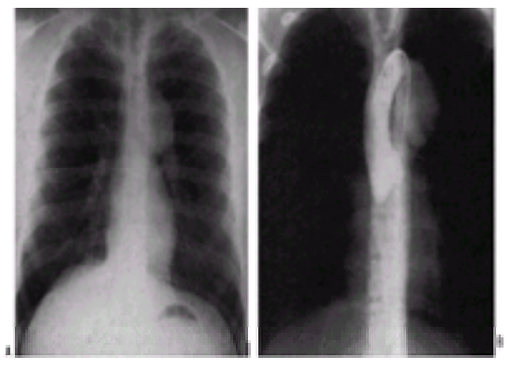
The anterior aortic arch is frequently associated with mirror-image branching. That is, the first branch from the aortic arch is a left-sided innominate trunk, followed by the right common carotid and right subclavian arteries. In this case, there is no retroesophageal component, and thus, no anterior bowing of the tracheal air column (*e*Fig. 47.6.1). There is a significant association between this form of right aortic arch and congenital heart disease. Between 18% (35) and 34% (33) of patients with tetralogy of Fallot (TOF), 33% (36) and 60% (33) of patients with truncus arteriosus, and 4.9% (24) and 6.7% (33,37) of patients with D-transposition of the great arteries have this form of right aortic arch. Unoperated survival of individuals with these lesions into adulthood is uncommon. However, differentiation among these lesions can be made based on the appearance of the superior mediastinum, the pulmonary artery segment, and the pulmonary vasculature. In patients with TOF one

finds a small pulmonary artery segment and decreased pulmonary vascularity; in D-transposition and persistent truncus arteriosus, the pulmonary artery segment is not found on the left heart border, and there is increased pulmonary vascularity.



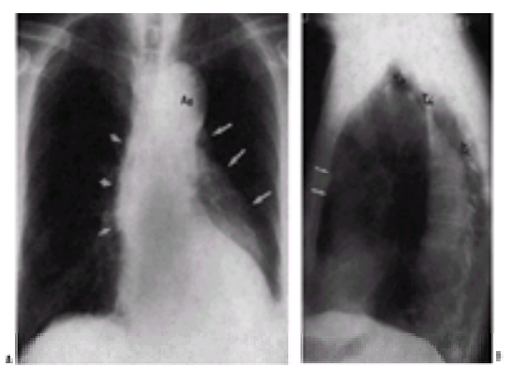
***e*FIGURE 47.6.1** A 32-year-old man with isolated anterior right aortic arch. **A:** Postero-anterior examination shows the aortic arch (Ao) on the right displacing the tracheal air column toward the left. **B:** Lateral view shows no anterior displacement of the tracheal air column (*arrowheads*).

Increase in the caliber of the aortic arch segment may be caused by changes in the aortic wall, often associated with more generalized changes in the aorta or by localized increase in vessel caliber. The former class of diseases includes atherosclerosis and systemic hypertension. They often result in a “prominent” appearing aortic arch, but one not necessarily dilated to pathologic size. Focal atherosclerotic aneurysms of the distal aortic arch or proximal descending aorta may present in association with other localized areas of increase in aortic caliber. Diseases resulting in focal dilatation of the aortic arch include aortic dissection and posttraumatic aortic pseudoaneurysm formation (*e*Fig. 47.6.2).

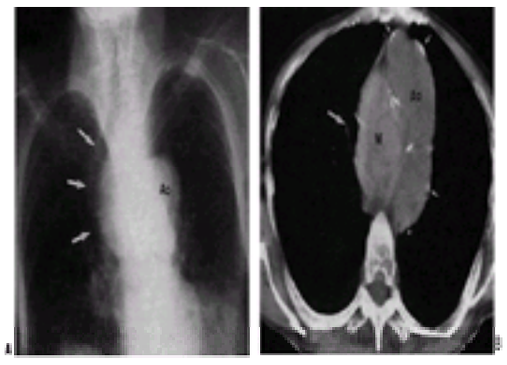


***e*FIGURE 47.6.2** A 26-year-old man with a history of an automobile accident 7 years ago. **A:** Postero-anterior chest examination shows marked dilatation of the aortic arch segment of the left heart border. The remainder of the examination is unremarkable. **B:** Antero-posterior image from an ascending aortogram demonstrates opacification of the dilated distal aortic arch segment.

Atherosclerosis is the most common cause of descending aortic aneurysm (38,39 and 40). These aneurysms are typically located just distal to the origin of the left subclavian artery and appear as fusiform enlargement of the aortic contour (*e*Fig. 47.6.3). Focal aneurysmal enlargement of the aorta may be difficult to differentiate from diffuse aortic ectasia or from focal mediastinal or pulmonary masses. Most often, however, these aneurysms project into the left chest. Displacement of the distal trachea is most often caused by increased caliber of the proximal portion of the aortic arch as well as by masses within the superior mediastinum, medially located with respect to the aortic arch (*e*Fig. 47.6.4).



***e*FIGURE 47.6.3** A 78-year-old man with an aneurysm of the entire thoracic aorta. **A:** The left ventricular contour is enlarged due to chronic aortic regurgitation. Dilatation of the ascending aorta (*short arrows*) and the aortic arch (Ao), as well as the descending thoracic aorta (*long arrows*), is significant. **B:** In lateral view, calcification of the ascending aorta (*closed arrows*) and the irregular contour of the proximal descending aorta (*open arrows*) are viewed.



***e*FIGURE 47.6.4** An 80-year-old man with lymphoma and a tortuous, calcified aorta. **A:** Postero-anterior chest examination shows the dilated aortic arch (Ao) and marked bowing of the trachea to the right (*arrows*). **B:** Computed tomography of the chest obtained at the level of the aortic arch. The trachea (*large arrow*) is displaced far to the right by the mediastinal lymph node mass (M) interposed between the left-sided aortic arch (Ao) and the trachea. Note the diffuse, mild aortic calcification (*small arrows*).

A high index of suspicion is the most important factor in diagnosing aortic dissection (29). In the appropriate clinical setting, an abnormal chest radiograph lends support to this diagnosis. However, the aortic arch, and in fact the entire chest film examination itself, may appear normal in the presence of an aortic dissection (41). When the aortic arch is involved, one frequently finds widening of the distal portion of the arch, beyond the origin of the left subclavian artery; the aortic arch is abnormal in 80%

to 90% of patients with dissection involving the arch (42). Intimal aortic calcification separated by more than 6 (29,43) to 10 (44,45 and 46) mm from the outer contour of the arch shadow is an excellent indicator of intramural hemorrhage and dissection. One must keep in mind, however, that calcification in a more proximal portion of the aortic arch may be projected medial to the outer contour of the distal arch, and that calcification of mural thrombus or inflammatory thickening of the aortic wall may produce a false-positive diagnosis. Any subtle or questionable finding becomes significant when a change in appearance from a previous examination is demonstrated (Fig. 47.7).

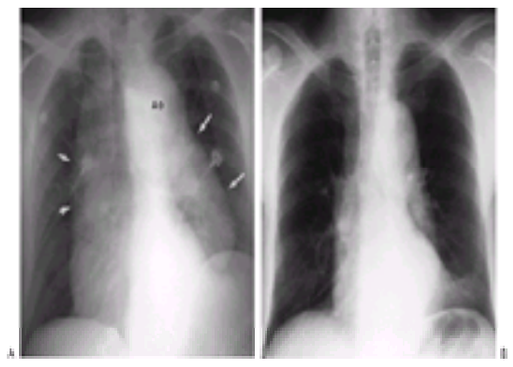
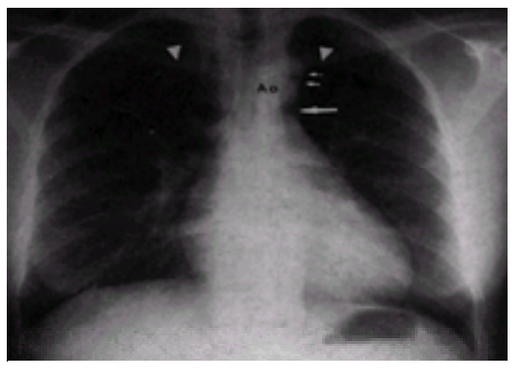
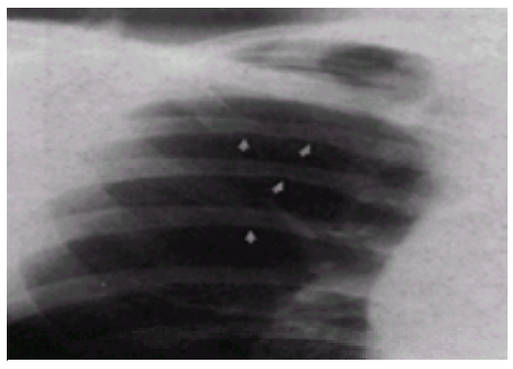


FIGURE 47.7 A 71-year-old hypertensive man awakened from sleep with midscapular back pain. **A:** Postero-anterior chest examination shows marked widening of the mediastinum, particularly involving the ascending aorta (*short arrows*), the aortic arch (Ao), and descending aorta (*long arrows*). **B:** Postero-anterior examination from 18 months earlier.

Diminution of the aortic arch segment may be real, as seen in patients with coarctation of the aorta, or apparent, as in the case of individuals with increased pulmonary blood flow in left-to-right shunts. In the former circumstance, there is tubular hypoplasia of the distal aortic arch proximal to the actual area of focal coarctation. The resulting narrow aorta presents as a small, inapparent aortic arch segment (eFig. 47.7.1). The focal coarctation presents as a concave (to the right) notch in the proximal descending aorta, immediately below the aortic arch. The descending aortic shadow can usually be followed from below in a cephalad direction just to the left of the spine, continuous with the aortic arch shadow. In patients with coarctation, the shadow of the descending aorta is interrupted caudad to its continuity with the aortic arch. Rib notching (eFig. 47.7.1 and eFig. 47.7.2) is a reliable sign of retrograde collateral flow to the postcoarctation aorta by dilated intercostal arteries.



***e*FIGURE 47.7.1** A 25-year-old woman with coarctation of the aorta. There is increased curvature of the left ventricular contour of the left heart border. The aortic arch (Ao) is inconspicuous, and the left subclavian artery (*small arrows*) is dilated. Note the break in the shadow of the descending aorta (*large arrow*) just inferior to the aortic arch at the site of the aortic narrowing. Irregular erosions (*arrowheads*) on the underside of the left and right fourth ribs (rib notching) are seen.

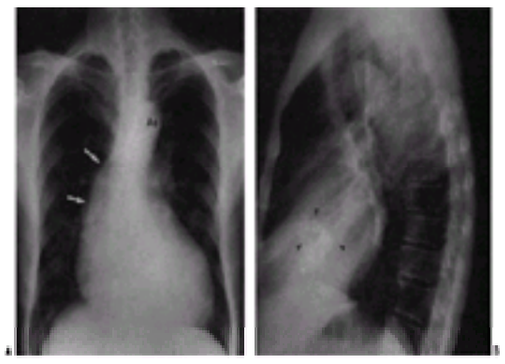


***e*FIGURE 47.7.2** Close-up from the postero-anterior examination of a 24-year-old man with coarctation of the aorta. The sclerotic margin along the superior border of the scalloped inferior erosions (*arrows*) characterizes rib notching.

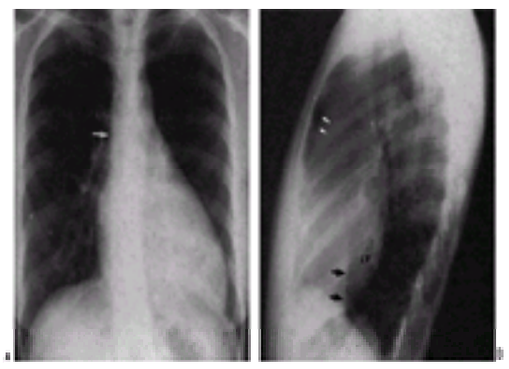
The hearts of patients with corrected transposition of the great arteries have discordant atrioventricular and ventriculoarterial relations. The systemic venous return is as expected, to the right-sided morphologic right atrium. Blood drains across a right-sided mitral valve to the right-sided morphologic left ventricle, which supports a right-sided main pulmonary artery. Pulmonary venous blood returns to the left-sided left atrium, across a left-sided tricuspid valve, and into the left-sided morphologic right ventricle, which supports a left-sided aortic valve and ascending aorta. The left-sided ascending aorta in these patients produces an aortic arch segment that is typically longer and more convex than that found in the normal segment (47,48 and 49). Furthermore, although the hilar pulmonary arteries may appear normal, the main pulmonary artery segment of the left heart border is not seen (eFig. 47.7.3). Mesocardia and dextrocardia are relatively common in corrected transposition of the great arteries. Mirror-image patterns of this anomaly occur in situs inversus (in which the convex upper right cardiac contour is produced by the ascending aorta).

***e*FIGURE 47.7.3** Two patients with corrected transposition of the great arteries. **A:** A 48-year-old woman. There is a left aortic arch (Ao). The superior left heart border (which extends down to the left ventricular portion of the contour) is formed by the left-sided ascending aorta. The left pulmonary artery (L) is seen passing over the left bronchus. However, no pulmonary artery segment is seen along the left heart border. **B:** A 32-year-old man. The liver (L) is on the right, the stomach (S) is on the left, and the cardiac apex is toward the right; situs solitus with dextrocardia. Although not nearly as pronounced as in **(A)**, the upper left heart border is formed by the left-sided ascending aorta, which obscures the pulmonary artery segment.

Increase in the prominence of the ascending aortic segment on frontal examination may be a sign of increase in aortic caliber or tortuosity of the aorta itself. Poststenotic dilatation of the aorta may be found in aortic stenosis (50) (eFig. 47.7.4). More generalized dilatation of the ascending aorta may be found in aortic insufficiency or in dissection of the aorta. In systemic hypertension, or in long-standing atherosclerosis, the aorta may become mildly dilated and “meander” through the mediastinum, causing increase in the curvature of the ascending aorta on frontal examination. Whether the aorta is dilated or tortuous, these changes may not always be readily apparent on the frontal examination. If the predominant direction of the aortic curve is anteriorly into the anterior mediastinum, then the retrosternal space on the lateral examination will become filled and reveal this abnormality (eFig. 47.7.5).



***e*FIGURE 47.7.4** A 64-year-old man with degenerative calcific aortic stenosis. **A:** Postero-anterior view. Notice the typical concavity of the pulmonary artery and left atrial appendage segments of the left heart border sandwiched between the convexities of the aortic arch (Ao) and the prominent left ventricular contour. The mid-right heart border contains the convexity (*arrows*) of the dilated ascending aorta. **B:** Lateral view. The aortic valve (*arrowheads*) is calcified. Despite the prominence of the left ventricular contour in the postero-anterior view, there is no left ventricular dilatation.



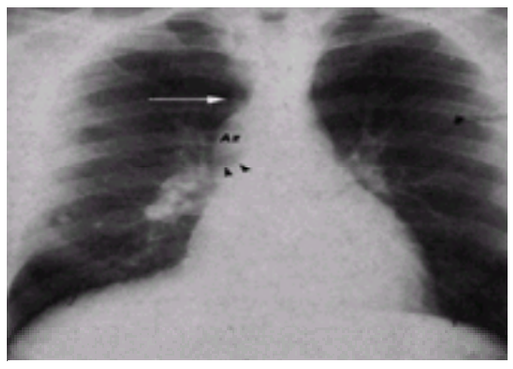
***e*FIGURE 47.7.5** A 39-year-old woman with aortic regurgitation. **A:** In postero-anterior view, the left ventricle contour is increased in curvature, extending toward the left chest wall. The ascending aorta is barely seen along the mid-right heart border (*arrow*). **B:** In lateral view, the retrosternal space is nearly filled by the dilated ascending aorta (*white arrows*). The shadow of the dilated left ventricle (LV) extends more than 18 mm behind the inferior vena cava (*black arrows*).

Superior Vena Cava

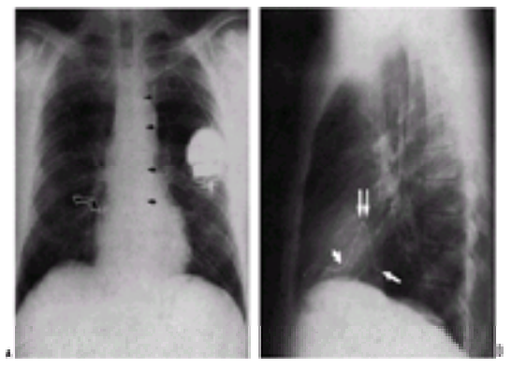
The superior vena cava is formed by the junction of the left and right brachiocephalic veins dorsal to the right first sternochondral articulation, behind the right border of the sternum. As it descends in the anterior mediastinum, it makes a slight curve convex to the right and dorsalward before emptying into the right atrium at the level of the third costal cartilage ventrally and the seventh thoracic vertebra dorsally. The superior vena cava forms the upper half of the right heart border on the frontal radiograph. The caval shadow is fairly straight and lies parallel to and to the right of the tracheal air column. It extends from the inferior edge of the clavicle to its insertion into the right atrium. At its inferior extension, its insertion into the right atrium, there is a break in the contour of the right heart border, representing the superior aspect of the curve of the right atrium.

The superior vena cava may be displaced to the right by a dilated or tortuous ascending aorta, giving the observer the impression of a widened superior mediastinum. Masses in the superior mediastinum cause extrinsic compression of the cava, resulting in the superior vena cava syndrome. In this circumstance, the cava may actually be displaced medially (to the left) by the mass. More distal caval obstruction (secondary to lymphadenopathy or mediastinal fibrosis) may result in dilatation of the cava and innominate veins, resulting in widening of the mediastinum with prominent curvature of the superior right heart border. Similarly, the functional obstruction and resulting elevation of caval pressure caused by pericardial constriction may present with a dilated superior vena cava. Because there is no obstructing valve in the superior vena cava, elevation of right atrial pressure—such as that found in severe tricuspid regurgitation or right ventricular failure of any etiology—is transmitted back, resulting in dilatation of the azygos vein, and if severe enough, the cava itself.

Dilatation of the azygos vein is found in patients with interruption of the inferior vena cava with azygos continuation. PA chest examination reveals a prominent rounded contour adjacent to the right hilum, at the junction of the distal trachea and origin of the right mainstem bronchus (eFig. 47.7.6). In individuals with isolated lesions, the chest film is otherwise unremarkable. This condition (27,51,52) is frequently associated with polysplenia and left isomerism (bilateral left-sidedness), but may be found as an isolated lesion in adults. Failure of development of the intrahepatic portion of the inferior vena cava results in passage of lower extremity and abdominal venous return to the heart via the dilated azygos vein. Persistence of the superior vena cava (eFig. 47.7.7) results from failure of the obliteration of the left anterior cardinal vein. It most frequently drains to the coronary sinus and right atrium, resulting in no hemodynamic insult. In approximately 15% of cases, the right superior vena cava may be absent.

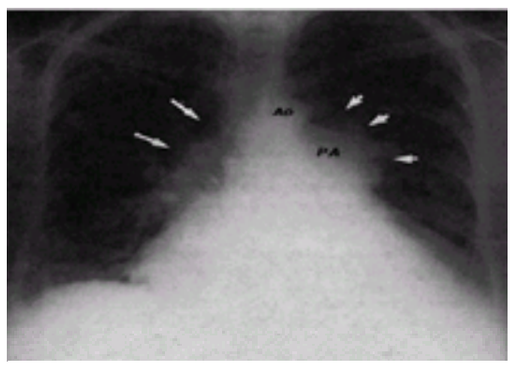


***e*FIGURE 47.7.6** A 36-year-old man with interruption of the inferior vena cava and azygos continuation. The abnormally convex, dilated azygos vein (Az) crosses above the right bronchus (*arrowheads*) and extends beyond the shadow of the superior vena cava (*arrow*).



***e*FIGURE 47.7.7** A 62-year-old man with persistence of the left superior vena cava draining to the coronary sinus. **A:** Postero-anterior examination shows the pacing wire descending to the left of the spine (*arrows*) and looping in the right atrium (*curved arrow*). **B:** Lateral view shows the descent of the wire through the left-sided superior vena cava and coronary sinus to enter the posterior aspect of the right atrium (*arrow*), looping in the right atrium (*double arrow*), and passing across the tricuspid valve (*curved arrow*). The tip of the wire is in the right ventricle.

Increased blood flow through the superior vena cava results in its dilatation and increase in the curvature of the superior right cardiomediastinal silhouette. This may be found in children with intracerebral arteriovenous malformations, or in individuals with total anomalous pulmonary venous connection above the heart. In the latter entity, both the left and right superior mediastinal contours are convex; the left contour is dilated by the draining vertical vein and the right by the dilated superior vena cava (*e*Fig. 47.7.8). These individuals have a characteristic “snowman” configuration of the heart and mediastinum and increased caliber of their pulmonary artery segment and parenchymal pulmonary arteries, evidence of left-to-right shunt.



***e*FIGURE 47.7.8** A 64-year-old woman with total anomalous pulmonary venous return. There is dilatation of the main pulmonary artery segment (PA) and the parenchymal pulmonary arteries. The vertical vein, draining pulmonary venous blood from both lungs (*short arrows*), extends to just inferior to the small appearing aortic arch (Ao). The convex, dilated superior vena cava (*arrows*) makes the superior right heart border.

In individuals with right-sided heart dilatation, the heart rotates (looking from below) in a clockwise manner, bringing the bulk of the cardiac mass into the left chest and causing the superior vena cava to come to lie over the spine, resulting in a narrow-appearing superior mediastinum. This is common in patients with atrial septal defect (ASD) or in patients with pulmonary hypertension and secondary tricuspid regurgitation.

Main and Central Pulmonary Arteries

The main pulmonary artery and pulmonary valve are supported by the right ventricular infundibulum and thus lie cephalad and to the left of the aortic valve. The pulmonary artery segment of the left heart border is composed of the main pulmonary and proximal portion of the left pulmonary artery (Fig. 47.1). The right pulmonary artery originates from the main pulmonary artery, passing over the roof of the left atrium to enter the right lung. The right hilum is slightly caudad with respect to the left hilum. The main pulmonary artery then passes over the left mainstem bronchus to become the left pulmonary artery. Because, in PA projection, a portion of the main pulmonary artery segment is derived from the proximal left pulmonary artery, accurate measurement of the caliber of the main pulmonary artery in this view is inaccurate. The main pulmonary artery is best viewed in shallow right anterior oblique projection (Fig. 47.8), which has the effect of rotating the proximal left pulmonary artery posteriorly, away from the cardiac contour. The pulmonary artery appears as a smooth convexity above the upper portion of the right ventricular contour, paralleling the distal trachea and left main bronchus. In individuals with normal pulmonary artery pressure and no left-to-right or right-to-left shunt [i.e., left ventricular output equals right ventricular output (Qp:Qs = 1.0)], the size of the pulmonary artery segment should be nearly the same side as the aortic arch segment on the PA radiograph. As the main pulmonary artery ascends and curves to become the left pulmonary artery, it runs away from the sternum to leave a retrosternal clear space behind (Fig. 47.9).

FIGURE 47.8 Normal right anterior oblique chest film of the same woman in Figure 47.1. The pulmonary artery (*arrow*) lies beneath the aortic arch (Ao). Left pulmonary artery branches (*arrowheads*) are seen projected through the heart.

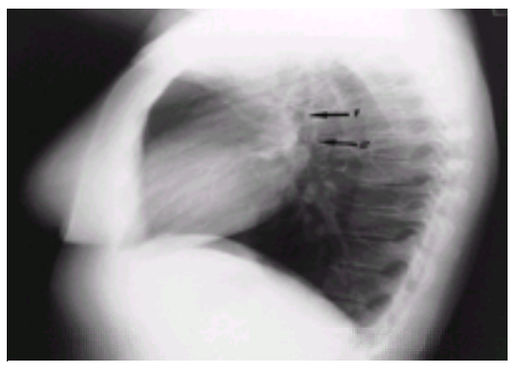


FIGURE 47.9 Normal lateral chest film of the same woman shown in Figure 47.1 and Figure 47.8. The retrosternal space is air filled. The right pulmonary artery lies anterior to the trachea. The right upper lobe bronchus (*arrow 1*) and left upper lobe bronchus (*arrow 2*) are labeled.

Often, both lateral and medial borders of the left pulmonary artery may be visualized through the heart, descending in the left chest. The right pulmonary artery shadow on lateral examination is identified as a round density anterior to the tracheal air column at the level of the carina. The left pulmonary artery is visualized in cross-section just as it passes over the left bronchus, behind and slightly superior to the right pulmonary artery.

On PA view, the right descending pulmonary artery is found running from the right hilum parallel to the right heart border. Its widest point is distal to the origin of the right middle lobe artery. At this level, the contour of the artery is sharply outlined against the air-filled lung on its right and by the air-filled right mainstem bronchus along its left border. In patients with pulmonary hypertension, the caliber of the artery is greater than 16 mm in men and 15 mm in women (53).

Pulmonary Vasculature

The majority of right and left hilar opacities is formed by the right and left pulmonary arteries, respectively. In the infant and adolescent, the left hilum may be obscured by the superimposed thymus and pulmonary trunk. Beyond each hilum, the intrapulmonary arteries extend in a tree-like branching pattern, gradually tapering with each division. It is abnormal for a pulmonary vessel to change caliber abruptly. The branching pulmonary arteries and veins should be identified nearly two-thirds the distance from the hilum to the pleural surface. Beyond this region, the spatial resolution of the chest film technique is inadequate to resolve individual vessels.

The distribution of the pulmonary vessels is uniform in both the left and right lungs, as well as between upper and lower lung zones. In general, the pulmonary arteries appear to converge at the hila, and the pulmonary veins course toward the left atrium to enter the cardiac silhouette at a level lower than the arteries. In healthy individuals, there is a normal, gravity-dependent perfusion gradient from pulmonary apex to base. Furthermore, alveolar air pressure in the upper lung segments narrows and collapses upper lobe capillaries and pulmonary veins, increasing upper lobe pulmonary resistance. In the upright position, therefore, lower lobe perfusion is four times that of the upper lobes. Thus, the intrapulmonary vessels of the lower lobes carry greater pulmonary blood flow and appear larger radiographically. When in the supine position, the normal apex-to-base gravitational gradient is lost; in its place, a similar gravitational anterior-to-posterior lung segment gradient develops. Therefore, when supine, the radiographic appearance of the pulmonary vessels is altered; one observes an increase in the caliber of the upper lobe pulmonary arteries (which lie relatively posterior) with respect to the lower lobe vessels (which are now relatively anterior).

The intrapulmonary arteries are sharply outlined by the air-filled lung and appear to branch in a relatively regular pattern as they extend toward the chest wall. The interstitial connective tissues of the lung invest the pulmonary arteries and veins, lymphatics, bronchi and bronchioles, and nerves. Connective tissue supports the alveolar spaces and forms the interlobar septa that delineate the pulmonary lobules. The pulmonary interstitium does not produce identifiable shadows on plain chest film examination but may be identified by an overall, faint homogeneous density to the space between parenchymal pulmonary arteries and veins. The normal pulmonary interstitium should not appear “busy” or filled with radiographic density not conforming to any vascular structure.

Increased Pulmonary Blood Flow

Because left ventricular output should equal right ventricular output, the main pulmonary artery and aortic arch segments of the left heart border should be approximately the same size. Patients experiencing hypermetabolic states, including fever, pregnancy (54,55), and hyperthyroidism (56,57) or those experiencing hyperkinetic, nonhypermetabolic conditions such as anemia (58,59), arteriovenous fistula (60,61), and beriberi (62,63) all exhibit increased preload with a reduction in afterload, resulting in cardiac chamber dilatation with increased caliber of the pulmonary vascular markings (*e*Fig. 47.9.1). If the increase in ventricular filling pressure is great enough, symptoms of congestive failure occur even though myocardial contractility is normal. Maintenance of increased cardiac output in the face of congestive heart failure is referred to as *high output cardiac failure*.

***e*FIGURE 47.9.1** A 29-year-old man with sickle cell anemia in high output failure. The lower left cardiac border is rounder in contour and extends toward the lateral chest wall. The central pulmonary arteries are increased in caliber, and the upper lobe veins (*arrows*) are as great in caliber as the lower lobe vessels, indicating increased pulmonary blood flow. The edges of the upper lobe vessels are sharper than vessels in the lower lungs, and the central hilar vessels are not sharp, all resulting from pulmonary interstitial edema caused by left atrial hypertension.

In circumstances of increased pulmonary artery blood flow, pressure, or both, the main pulmonary artery segment appears increased in size with respect to the aortic arch. In patients with left-to-right shunts, the difference in size is a function of the difference in blood flow carried by the two vessels. Therefore, small left-to-right shunts may not be identified by plain film examination. In patients with increased pulmonary artery pressure, the greater pulmonary artery caliber may be the result of increased distension. Differentiation between increased pressure and increased flow may be difficult, but in general, the two may be identified by further analysis of the pulmonary vascular tree (53).

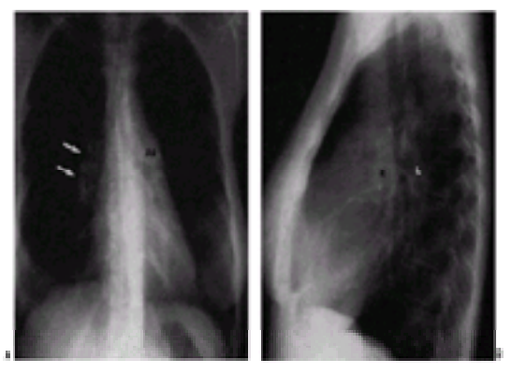
Shunt vascularity may be characterized by increase in the size of the entire roentgenographically visualized pulmonary tree (Fig. 47.10). That is, not only are the central main and proximal hilar left and right pulmonary arteries dilated, but the branch parenchymal vessels are increased in size. Furthermore, the pulmonary artery branches appear sharp and are visualized far beyond the usual two-thirds of the way between hilum and chest wall. The vessels in both the upper and lower lobes appear to be dilated to the same degree as well. Depending on the adequacy of roentgenologic technique, and the depth of the individual’s inspiratory effort, dilated, sharp, branching vessels may be seen far into the posterior pulmonary sulci and out to the lateral chest wall pleura on PA and lateral views. The increased arterial flow in shunt lesions is matched by an increase in the size of the draining pulmonary veins.

FIGURE 47.10 A 46-year-old woman with secundum atrial septal defect. Mean pulmonary artery pressure is 20 mm Hg. **A:** The heart lies in the left chest. The pulmonary artery segment (PA) is greater in caliber than the aortic arch (Ao). The pulmonary artery branches of both lungs are all dilated, sharp edged, and extend nearly to the pleura. The narrow superior mediastinum and decreased concavity in the middle of the left heart contour are caused by cardiac rotation secondary to right heart dilatation. Furthermore, as the heart rotates, the left bronchus no longer crosses the left heart border. **B:** In lateral view, the retrosternal space is filled by the dilated right ventricle and proximal pulmonary artery. The orifices of the right upper lobe bronchus (*arrow 1*) and left upper lobe bronchus (*arrow 2*) are in line with the tracheal air column (T), a sign of normal left atrial volume. The right (*long arrows*) and left (*arrowheads*) pulmonary arteries are dilated. Analysis of the relation between the inferior vena cava (*short arrows*) and the posterior left ventricular border reveals no left ventricular enlargement.

The differential diagnosis of increase in the caliber of the main pulmonary artery segment depends on associated cardiac and pulmonary vascular changes. Adolescents and young adults (especially women) under 30 years of age commonly have an isolated *prominence* or increase in caliber of the main pulmonary artery segment (eFig. 47.10.1) without any abnormality of the central or parenchymal pulmonary arteries, and without any cardiac chamber abnormality. These individuals, in fact, have no cardiac or pulmonary abnormality and thus represent a normal anatomic variant.

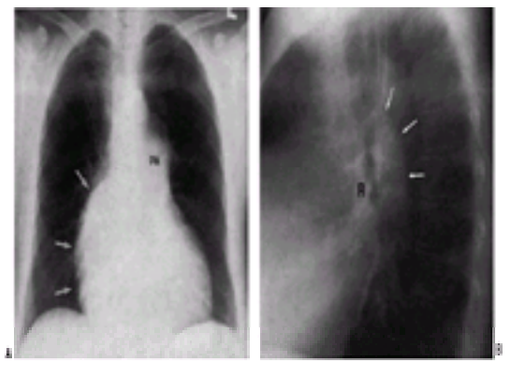
***e*FIGURE 47.10.1** A 26-year-old woman being treated for lymphoma. Postero-anterior examination reveals apparent enlargement of the pulmonary artery segment. The central pulmonary artery segments are normal, and there is no evidence of pulmonary vascular change.

Idiopathic dilatation of the pulmonary artery (64,65) (eFig. 47.10.2) is a benign condition that does not affect cardiac function. It is characterized by prominence of the pulmonary artery segment and proximal pulmonary arteries with normal or slightly increased heart size. In this lesion, pulmonary insufficiency is frequently associated, resulting in a typical murmur and dilatation of the right ventricle.



***e*FIGURE 47.10.2** A 39-year-old woman with idiopathic dilatation of the pulmonary arteries. **A:** Postero-anterior view of the chest reveals dilatation of the pulmonary artery segment (PA) of the left heart border as well as dilatation of the hilar right pulmonary artery (*arrows*). **B:** On lateral view, the dilated right (R) and left (L) pulmonary arteries are viewed.

If enlargement of the pulmonary artery segment is associated with shunt vascularity, then a left-to-right shunt should be considered. Disparity between the caliber of the central pulmonary arteries and the peripheral branches indicates pulmonary hypertension. Dilatation of the pulmonary artery in the face of normal pulmonary vascular markings should raise the possibility of valvular pulmonic stenosis. Valvar pulmonic stenosis is usually congenital in origin and frequently bicuspid in nature (66). It is a common congenital cardiac malformation in adult patients. In these patients, there is dilatation of the pulmonary artery segment and classically that of the proximal left pulmonary artery as well (eFig. 47.10.3). The caliber of the pulmonary artery segment does not correlate with the gradient across the valve. If right ventricular hypertension results in tricuspid regurgitation, then right atrial and ventricular dilatation occurs, and the heart rotates into the left chest. Otherwise, the heart usually appears normal in size. Long-standing turbulence in the main and left pulmonary artery may result in aneurysmal pulmonary arterial dilatation (Fig. 47.11). Identifying normal appearing parenchymal pulmonary arterial branches (the consequence of the normal pulmonary blood flow) helps differentiate the appearance of valvular pulmonic stenosis from pulmonary hypertension.



***e*FIGURE 47.10.3** A 49-year-old woman with valvular pulmonic stenosis. **A:** Postero-anterior view shows the dilated pulmonary artery segment (PA). The right atrial contour (*arrows*) is markedly convex, and the superior mediastinum is narrow, resulting from right atrial and right ventricular dilatation caused by tricuspid regurgitation. **B:** In lateral view, the retrosternal clear space is partially filled. Notice the dilatation of the left (*arrows*) and the normal appearance of the right (R) pulmonary artery.

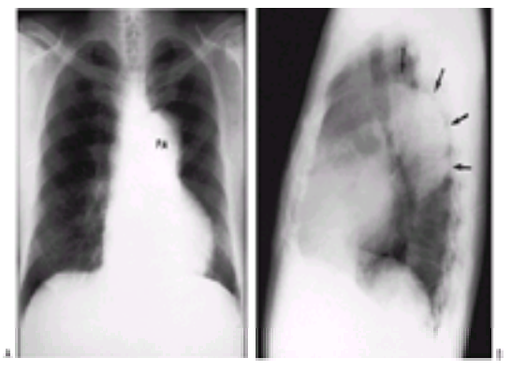
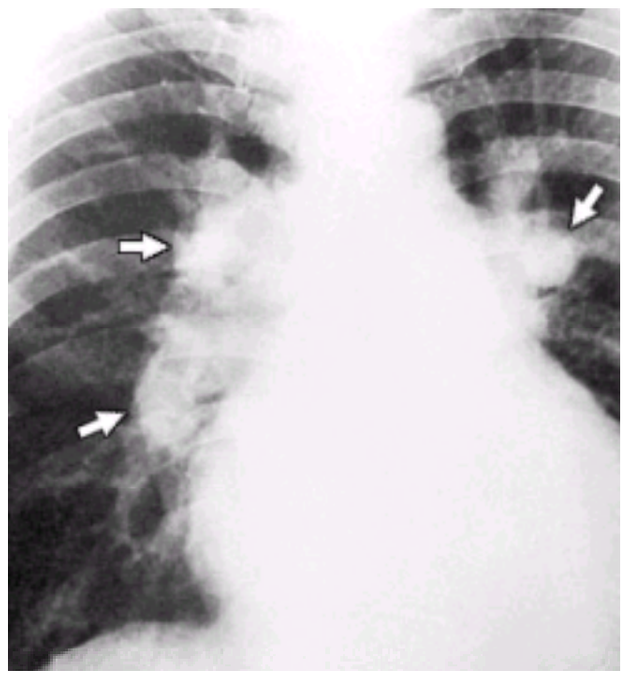


FIGURE 47.11 A 61-year-old man with valvular pulmonic stenosis. **A:** In postero-anterior view, the dilated pulmonary artery segment (PA) is apparent and obscures the proximal left pulmonary artery. The contour of the right atrium is normal. **B:** In lateral view, the aneurysmal dilation of the main and left pulmonary artery (*arrows*) is better viewed.

Shunt Lesions in Adults

Adult survival with secundum ASD is the rule. Secundum ASD is the most common congenital cardiac lesion diagnosed in adult patients. In a review of 412 patients with ASD, 45% were more than 20 years old at the time of diagnosis (67). Sixty-five percent of these patients were female; 35% were male. The radiographic appearance of uncomplicated secundum ASD is characterized by normal or near normal overall cardiac size, changes in the heart contours secondary to cardiac rotation, and pulmonary arterial changes caused by the increased pulmonary blood flow. In these patients, right atrial and ventricular dilatation rotates the heart and shifts it into the left chest. The superior mediastinum is relatively narrow, and the lucency of the left bronchus runs parallel to the convex curve of the mid-left heart border. The pulmonary artery segment and both central left and right pulmonary arteries are dilated. Furthermore, the parenchymal branch pulmonary arteries are sharply defined, dilated, and visualized further toward the pleura than in normal individuals. Both the left ventricle and left atrium are typically normal in size.



Chest x-ray in atrial septal defect. There is plethora of the pulmonary vasculature with prominent main pulmonary arteries (*white arrows*).

Changes in myocardial compliance and pulmonary vascular resistance play an important role in the radiographic appearance of adults with ASD. The decreased compliance of older ventricular myocardium, especially if further reduced by superimposed myocardial ischemia, results in decreased myocardial compliance, resulting in elevation of left atrial pressure, further increasing the left-to-right shunt across the atrial septum. This causes progressive elevation of pulmonary arteriolar tone, resulting in increased pulmonary vascular resistance and the radiographic appearance of pulmonary hypertension. In a review of 311 patients with ASD who underwent cardiac catheterization (67), 31% had pulmonary hypertension (mean PA pressure greater than 20 mm Hg). Pulmonary hypertension was found to increase in incidence with increasing age; from 14% of patients under 20 years of age to 53% of patients greater than 30 years of age had pulmonary hypertension.

The chest radiograph of patients with ASD and pulmonary hypertension displays relative paucity of peripheral pulmonary artery branches and abrupt change in caliber of the central pulmonary arteries, typical of the generalized changes of pulmonary hypertension. However, careful inspection reveals that although sparse, upper lobe as well as lower lobe vessels are enlarged, and that branching vessels often may be identified farther out toward the pleura than in other patients with non–shunt-related causes of pulmonary hypertension. The size of these vessels reflects the sequelae of the increased blood flow of the shunt. Their number is an indication of the reduced cross-sectional area of the pulmonary bed (*e*Fig. 47.11.1).

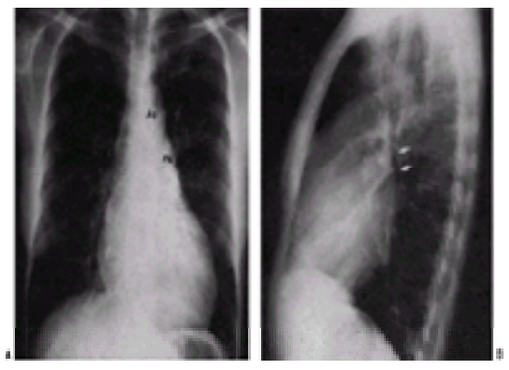
***e*FIGURE 47.11.1** A 55-year-old woman with atrial septal defect and pulmonary hypertension. The pulmonary artery is dilated. The dramatic difference between the caliber of the hilar and lobar pulmonary arteries and the segmental branches is typical of pulmonary hypertension. However, these segmental arteries branch and extend toward the pleura, which is typical of shunt vessels.

Progressive, severe mitral regurgitation is found in 15% of patients with ASD (68,69 and 70). In these patients, left atrial (and left ventricular) dilatation (71) confuses the picture, making it difficult to radiographically differentiate ASD from other shunts. An unusual cause of left atrial enlargement in adult patients with ASD is Lutembacher's syndrome (ASD with coexisting rheumatic mitral stenosis). The picture may be complicated further in cases in which left atrial pressure is elevated, resulting in radiographic changes of pulmonary venous hypertension and left atrial enlargement superimposed on shunt vascularity (*e*Fig. 47.11.2).

***e*FIGURE 47.11.2** A 45-year-old woman with secundum atrial septal defect and rheumatic mitral stenosis, postero-anterior view. Findings of marked pulmonary hypertension and left atrial outflow obstruction characterize the picture. The marked dilatation of the pulmonary artery segment (PA) and central PAs is striking against the small aortic segment (Ao). There is abrupt change in the caliber of the segmental and subsegmental pulmonary artery, but branching vessels may be seen out toward the pleural edge (*arrows*).

Most patients with patent ductus arteriosus (PDA) present early in childhood. Those who survive their first year of life are generally asymptomatic. Among 804 patients with PDA seen in one series (72), 37 (4.6%) reached 50 years of age. Of these, 35 had exclusively left-to-right shunts, and 28 of the 35 (80%) were women. The mean

age at diagnosis in this group was 49 years (range, 19 to 73 years). PDA may rarely be diagnosed in patients more than 50 years old (73,74). If the shunt is small, the heart may appear normal. The right ventricle dilates if there is pulmonary hypertension or heart failure. The central pulmonary arteries are dilated, and occasionally, one may see aneurysmal dilatation of one pulmonary artery or another (75). In adult patients with shunt vascularity, the radiographs of individuals with PDA often exhibit dilatation of the ascending aorta (*e*Fig. 47.11.3), an indication of the extracardiac shunt. Calcification of the ductus arteriosus itself is of limited value; it does not necessarily indicate whether the duct is patent or occluded (75). Calcification of the ligamentum arteriosus, however, implies closure of the duct.



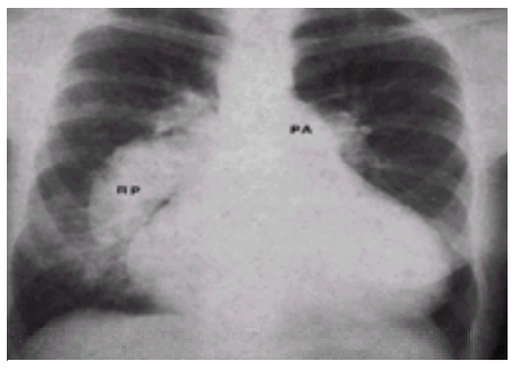
***e*FIGURE 47.11.3** A 48-year-old man with a patent ductus arteriosus and moderate pulmonary hypertension. **A:** The aortic arch (Ao) and pulmonary artery segment (PA) are both enlarged. However, the parenchymal pulmonary arteries are decreased in caliber and barely visible. The left ventricular contour is enlarged. **B:** In lateral view, the left bronchus is posteriorly displaced (*arrows*), indicating left atrial enlargement, and the retrosternal space is filling by the dilated ascending aorta and main pulmonary arteries.

If pulmonary hypertension persists, the chest film reflects changes in the appearance of the heart. Signs of right ventricular hypertrophy and pulmonary hypertension (dilatation of the central pulmonary arteries with diminished caliber of the peripheral vessels) dominate the film. Reversal of the shunt results in a decrease in cardiomegaly.

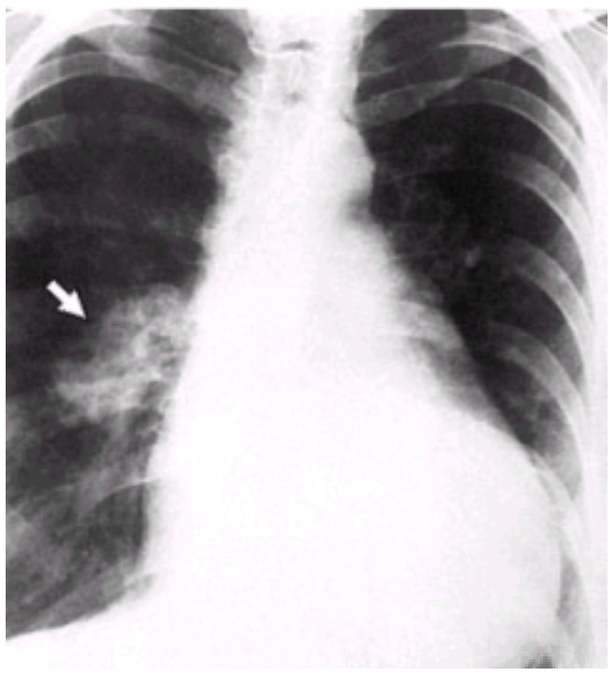
Spontaneous closure or surgical repair in childhood both decrease the prevalence of ventricular septal defect (VSD) in the adult population. VSD is found in 0.5% of adults (76,77) and 10.0% of adult patients with congenital heart disease (78). Adult patients with VSD may be classified (79) based on the size of their defects. Patients with small defects (with mean pulmonary arterial pressure less than 20 mm Hg) are usually treated medically and appear not to develop progressive pulmonary vascular changes. Patients with larger defects (mean PA pressure greater than or equal to 20 mm Hg) are more likely to undergo surgical repair, as well as develop Eisenmenger's syndrome (79). Patients with Eisenmenger's syndrome have four times the risk of death compared with patients with normal pulmonary artery pressure (80).

There is marked variation in the chest film appearance of individuals with VSD, depending on the size of the defect and the pulmonary resistance. An adult with a small VSD may have a nearly normal examination, with only a suggestion of dilatation of the pulmonary artery segment (*e*Fig. 47.11.4). Individuals with larger defects have the typical appearance of shunt vascularity, with dilatation of the left atrium and both right and left ventricles. In the face of cardiac rotation secondary to right ventricular enlargement, left ventricular dilatation may be difficult to assess. The right atrial contour should appear normal as it is not dilated. The aorta should appear normal or slightly decreased in size (*e*Fig. 47.11.5). If pulmonary resistance exceeds systemic resistance and the shunt reverses, then the heart may appear normal or small or demonstrate rotation resulting from right atrial and ventricular dilatation. The typical appearance of pulmonary hypertension—dilated central pulmonary arteries and constricted peripheral vessels—is expected.

***e*FIGURE 47.11.4** A 26-year-old man with a small membranous ventricular septal defect. The heart is slightly rotated to the left. The pulmonary artery segment is just barely greater in caliber than the aortic arch, and the left atrial appendage portion of the left heart border is straightened. All visualized pulmonary artery branches have sharp edges, are dilated, and extend far out toward the pleura.



***e*FIGURE 47.11.5** A 32-year-old woman with a moderate-sized ventricular septal defect. The heart is markedly enlarged. Dilatation of the pulmonary artery segment (PA) and descending right pulmonary artery (RP) is marked. Abrupt change in caliber of the parenchymal pulmonary artery branches indicates pulmonary hypertension.



Chest x-ray in patient with a congenital ventricular septal defect. There is fullness in the hilum secondary to an enlarged pulmonary artery (*white arrow*).

Pulmonary Hypertension

In patients with pulmonary arterial hypertension, the more distal pulmonary artery branches are vasoconstricted. Therefore, not only are the visualized parenchymal pulmonary artery branches smaller in caliber than normal, but fewer (of the more peripheral pulmonary artery branches) are visualized. There is an apparent disparity between the appearance of the dilated central and hilar pulmonary arteries and the more peripheral vessels (Fig. 47.12). Not only is the appearance of gradual taper in caliber between the central and peripheral vessels lost, but the space between peripheral vessels appears to be increased. Thus, the “ratio” of central pulmonary artery to peripheral branch pulmonary artery caliber is greatly increased, and the lungs appear “blacker.”

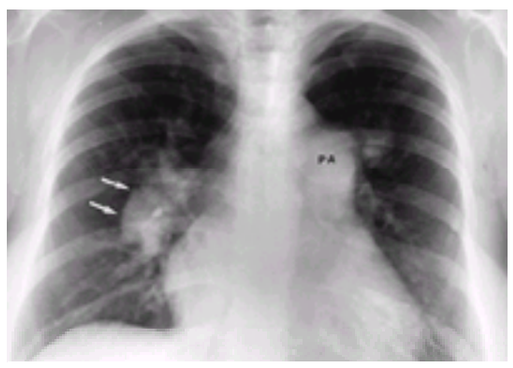


FIGURE 47.12 A 45-year-old woman with unexplained pulmonary hypertension. The pulmonary artery segment (PA) and descending right pulmonary artery (*arrows*) are markedly enlarged. Note the abrupt change in caliber of the peripheral pulmonary arterial branches beyond the right hilum. Right atrial and ventricular dilatation are indicated by the pronounced contour of the lower right heart border and rotation of the heart into the left chest.

The chest films of patients with pulmonary hypertension secondary to left-to-right shunts present an interesting hybrid picture. Their predominant vascular appearance is that of central pulmonary arterial enlargement with constricted peripheral vessels (i.e., that of pulmonary hypertension). However, close inspection of the vasoconstricted peripheral parenchymal pulmonary artery branches reveals that sharply defined branches are identified going far out into the periphery of the lung (i.e., findings of both shunt and hypertensive constricted vessels are evident).

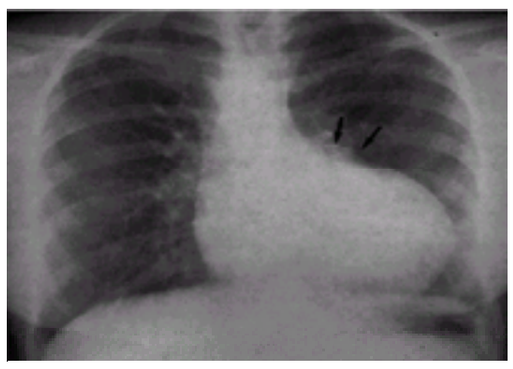
Decreased Pulmonary Blood Flow

Diagnosing decreased pulmonary blood flow may be difficult. When right ventricular cardiac output is decreased, the size of the main pulmonary artery and the pulmonary arterial segment of the left heart border appear decreased in caliber. The caliber of the central and hilar pulmonary arterial branches, as well as the parenchymal pulmonary arterial segments, is decreased. The parenchymal pulmonary arterial segments appear normal, but the overall appearance of the lung is that of greater spacing among the arterial segments, and increased “blackness” of the pulmonary parenchyma. Regions of the lung distal to a focal branch pulmonary artery stenosis may appear focally darker, resulting from the focal perfusion defect. Without good data describing the normal caliber of pulmonary arterial branches, objective plain film changes may be hard to detect and differentiation between normal caliber and mild to moderately decreased blood may not be reliable.

The limited differential diagnosis of adult patients with decreased pulmonary blood flow includes TOF, pulmonary atresia with VSD (PAVSD), Ebstein’s anomaly, and tricuspid atresia.

Most patients with TOF die before the end of their second decade. Only 11% are alive at 20 years, 6% at 30 years, and 3% at 40 years (81,82). Survival to adulthood in patients without prior surgical palliation or repair appears to be associated with early development of collateral circulation to the lungs and progressive narrowing of an initially mild infundibular stenosis with age (83). Decreased pulmonary blood flow results in a small main pulmonary artery segment with commensurate decrease to normal caliber of all visualized pulmonary arterial branches (*e*Fig. 47.12.1). Systemic-to-pulmonary arterial collaterals appear as unusually shaped radiographic densities among the normally distributed arterial branches. Not uncommonly, collateralization is asymmetric, so that the pulmonary arterial branches in one lung are greater in caliber than in the other. Generalized cardiomegaly is frequently found in adult patients with TOF. Cardiomegaly was found in 25% (83) of adult patients without previous surgical intervention. Among patients followed after surgical repair, postoperative cardiomegaly was reported in 85% (84) and 42% (85). Aneurysm of the right ventricular outflow after patch repair is uncommon, but may be associated with residual distal obstruction (86) or pulmonary insufficiency leading to right ventricular enlargement (*e*Fig. 47.12.2). Right aortic arch was the most frequently reported anomaly (83,84). PAVSD may be regarded as a severe variant of TOF. However, in PAVSD, pulmonary blood flow is maintained via systemic-to-pulmonary artery collaterals. Thus, radiographically, these patients may differ from those with TOF (Fig. 47.13). In the former, the main pulmonary artery segment of the left heart border is smaller and often concave, as opposed to only diminished in caliber in patients with TOF. Furthermore, collateralization to the lungs in patients with TOF is usually only from the bronchial arteries, and that in PAVSD is via larger systemic-to-pulmonary artery collaterals (87,88 and 89). Hence, asymmetry in pulmonary blood flow as well as the radiographic appearance of larger collateral vessels is usually found in patients with PAVSD. The incidence of right aortic arch is approximately 40% in these patients (90), greater than the expected 33% in patients with TOF.

***e*FIGURE 47.12.1** A 35-year-old woman with unrepaired tetralogy of Fallot. Kyphoscoliosis causes the unusual orientation of the ribs and asymmetric density between the right and left chest. The pulmonary artery segment is small, and the pulmonary vascular markings are decreased in caliber. The apical curvature of the left heart border is elevated (*coeur en sabot*).



***e*FIGURE 47.12.2** A 28-year-old woman with repaired tetralogy of Fallot. The heart is enlarged and rotated into the left chest. The main pulmonary artery remains concave, but the pulmonary vascular markings are nearly normal. Note the thin calcified rim (*arrows*) along the aneurysmal right ventricular outflow patch.

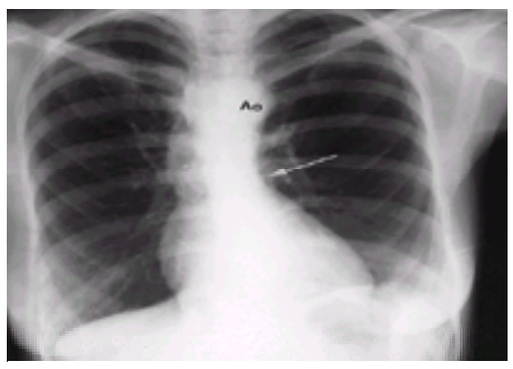


FIGURE 47.13 A 28-year-old woman with pulmonary atresia with ventricular septal defect. There is a left aortic arch (Ao). The pulmonary artery segment is concave (*arrow*), and the parenchymal pulmonary artery segments are decreased in caliber.

In patients with Ebstein's malformation, the tricuspid valve is displaced into the right ventricle, resulting in "atrialization" of a portion of the right ventricle (91,92 and 93). Tricuspid regurgitation dilates the "true" right atrium as well as the "atrialized" right ventricle, causing right-sided enlargement and cardiac rotation (*e*Fig. 47.13.1). The right atrium may become markedly enlarged, filling the retrosternal space on lateral examination. The main pulmonary artery segment is normal to small, and the parenchymal pulmonary artery segments are normal to decreased in caliber (94). Left atrial size is generally normal, but, depending on the amount of right-to-left shunting across the atrial septum, there may be evidence of mild pulmonary vascular congestion.

***e*FIGURE 47.13.1** A 22-year-old woman with Ebstein's malformation. **A:** Postero-anterior examination shows the concave pulmonary artery segment (*long arrow*) and cardiac rotation. The superior mediastinum is narrow, and the left cardiac border (*short arrows*) is filled by the remaining functional right ventricular chamber. Notice how the left bronchus (*arrowheads*) parallels the left heart border of the rotated heart. **B:** In lateral view, severe right atrial dilatation results in posterior displacement of the inferior vena caval shadow (*arrows*).

The chest film appearance of the heart in patients with tricuspid atresia depends on the relationship of the great arteries, the presence or absence of a VSD, and the state of the pulmonary valve (95,96). In patients with normally related great arteries with associated pulmonic stenosis, the main pulmonary artery segment appears small, and parenchymal pulmonary artery branches are decreased in caliber (*e*Fig. 47.13.2). In the presence of transposition of the great arteries or in patients with normally related great arteries and a large VSD without pulmonic stenosis, pulmonary blood flow may appear increased. Right-to-left shunting across the interatrial septum causes left atrial dilatation with or without evidence of left atrial hypertension. Left ventricular enlargement is characteristic in these patients.

***e*FIGURE 47.13.2** A 40-year-old woman with tricuspid atresia, normally related great arteries, and no ventricular septal defect, after Potts and Glenn shunts. Postero-anterior view of the chest demonstrates the small pulmonary artery segment (*arrowhead*) over which the markedly dilated left pulmonary artery is superimposed (*long arrows*). The superior vena cava (*short arrows*) is mildly dilated. The right atrial contour is increased in curvature, there is left atrial and left ventricular enlargement, and the pulmonary arteries in the right lung are small in caliber.

Left Atrium and Left Atrial Appendage

The left atrial appendage is a long, finger-like extension of the left atrium. It wraps around the left side of the base of the heart to form the left heart border between the main pulmonary artery segment and the superior portion of the left ventricular contour. When left atrial pressure and volume are normal, this segment of the left heart border is concave.

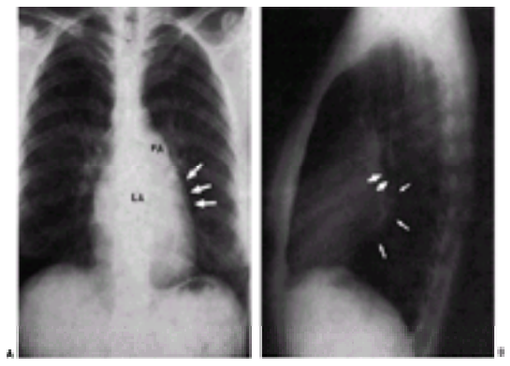
The body of the left atrium lies in the midline, superior and posterior to the left ventricle, and beneath the tracheal bifurcation. In lateral view, the superior posterior border of the heart is formed by the left atrium. Early or mild enlargement of the left atrium may be detected as enlargement of the left atrial appendage (i.e., straightening of this segment of the left heart border). Subsequent enlargement of the atrium results in convexity of the left atrial appendage portion of the left heart border and development of a double density in the midportion of the cardiac silhouette (representing the dilated, blood-filled left atrium). The double density is characterized by identification of its right lateral border medial to the right atrial portion of the right cardiac border. Displacement of the left bronchus can be recognized by analysis of the lateral examination. The right upper lobe bronchus originates just after the tracheal bifurcation. The left main bronchus travels for several centimeters before the origin of the left upper lobe bronchus. The plane of the tracheal bifurcation is nearly parallel to the coronal, so that when viewed in lateral, the ostia of the right and left upper lobe bronchi have a directly superior-inferior relationship. Thus, if one can draw a straight line passing through the distal tracheal air column and the centers of the right and left upper lobe bronchi, then the left atrium is not enlarged.

Left Atrial Enlargement

Analogous to the left ventricle, the left atrium is a muscular cardiac chamber, albeit thinner. Therefore, smaller increases in volume and pressure manifest as changes in the shape of the left atrium and, therefore, its radiographic appearance. Increased left atrial pressure or volume increases the size of the left atrium. Radiographically, this is manifested by change in the contour of the left atrium, extrinsic compression of adjacent structures, and change in the radiographic appearance of the chamber. Furthermore, depending on the severity and chronicity of the disease processes resulting in the elevation of left atrial pressure and volume, characteristic pulmonary vascular findings may exist.

Straightening of the left atrial appendage segment between the level of the main pulmonary artery and left ventricular segments on the left border of the heart is the earliest and most sensitive radiographic sign of elevated left atrial pressure or volume (Fig. 47.14). Continued left atrial enlargement results in convexity of this segment beyond the lower, left ventricular contour, and then identification of a double density to the right of the spine on the PA examination (*e*Fig. 47.14.1). This represents displacement of the right inferior border of the left atrium caused by enlargement of the left atrial body. This is associated with a discrete convex bulge to the superior posterior cardiac contour below the carina on the lateral examination. The distance between the midpoint of the double density and the midpoint of the left mainstem bronchus (the left atrial dimension) is less than 7.5 cm in the adult man and less than 7.0 cm in the adult woman. Enlargement is a good sign of previous rheumatic disease. Enlargement of the left atrium results in posterior displacement of the left bronchial tree (97), and in chronic cases of left atrial enlargement, elevation of the left main bronchus (98). On the frontal radiograph, the normally observed carinal angle of approximately 75 degrees may be increased to 90 degrees or more. However, care must be taken in considering this observation. Without a previous PA chest examination for comparison, it is difficult to judge small differences from normal. In the lateral view, a sensitive marker of left atrial enlargement is posterior displacement of the left bronchus. Normally, a straight line constructed by connecting the centers of the right and left upper lobe bronchi, when extended superiorly, should pass within the main tracheal air column. In cases of left atrial enlargement, this line extends outside of the trachea. Care must be taken to make this observation only in true lateral radiographs. When the left atrium is enlarged, it produces a superior, posterior mass behind the heart and under the tracheal carina. Often the mass extends inferiorly, producing a second contour along the posterior aspect of the heart. Although no longer in common practice, barium esophagography is a sensitive technique for demonstrating the extrinsic compression of the esophagus by the dilated left atrium. Severe left atrial enlargement results in merging of the left atrial contour with the right atrial contour on the right border of the heart on PA examination.

FIGURE 47.14 A 37-year-old woman with rheumatic mitral stenosis. **A:** Postero-anterior examination demonstrates straightening of the left atrial appendage portion of the left heart border (*arrows*). The right border of the left atrium (*arrowheads*) appears to approach the right cardiac contour. There is indistinctness of the pulmonary vessels, including the descending right pulmonary artery. The caliber of the upper lobe vessels is greater than that in the lower lung zones. The pulmonary artery segment (PA) is larger than the aortic arch segment. The left ventricle is normal. **B:** There is fullness in the superior posterior cardiac space, but no displacement of the left bronchus.



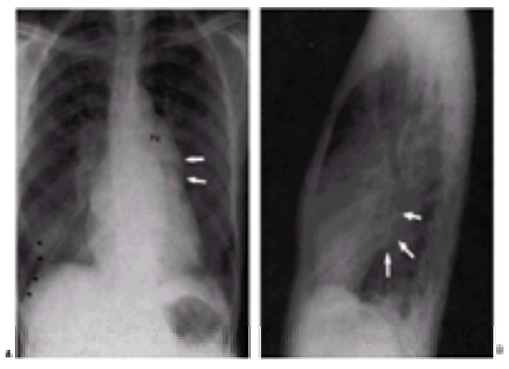
***e*FIGURE 47.14.1** A 41-year-old woman with rheumatic mitral stenosis. **A:** The left atrial appendage segment is convex (*arrows*). The double density of the left atrium (LA) extends to the right cardiac border. Dilatation of the pulmonary artery segment (PA) and decreased caliber of the peripheral vessels indicates pulmonary hypertension. **B:** Lateral view demonstrates fullness of the superior posterior cardiac space (*thin arrows*) and posterior displacement of the left bronchus (*thick arrows*).

Pulmonary Venous Hypertension

In the normal lung, there is a gravity-dependent perfusion gradient between the apex and base (99,100). In the upright position, upper lobe alveolar pressure narrows the upper lobe capillaries and pulmonary veins, causing their collapse and therefore relatively poor visualization on chest films. Furthermore, the lower lobe veins contain a hydrostatic pressure gradient, distending them and increasing their radiographic caliber. This decreases lower lobe pulmonary resistance, resulting in increased lower lobe blood flow. There is nearly four times as much blood flow to the lower than to the upper lobes.

The pulmonary veins are valveless. Therefore, increased left atrial pressure is freely transmitted through the pulmonary veins to the pulmonary bed, resulting in chest film changes in the appearance of the parenchyma and pulmonary vascular markings. Mild elevation of left atrial pressure stretches the intracellular pores of the capillary endothelium, allowing leakage of large molecules from the vascular compartment into the pulmonary interstitium. Migration of edema fluid into the interstitium is mediated, in part, by the pulmonary lymphatics. The lymphatics remove large (protein) molecules as well as provide a route for return of excess fluid to the mediastinal veins, helping to maintain low interstitial fluid pressure. Capillary leakage in prolonged left atrial hypertension may overwhelm these lymphatics, causing increased interstitial fluid volume and an increase in interstitial pressure. Eventually, fluid begins to collect away from the thin alveolar septa, separating the capillary from alveolar endothelium. Continued passage of fluid from the pulmonary parenchyma into the pulmonary lymphatics results in lymphatic engorgement, further

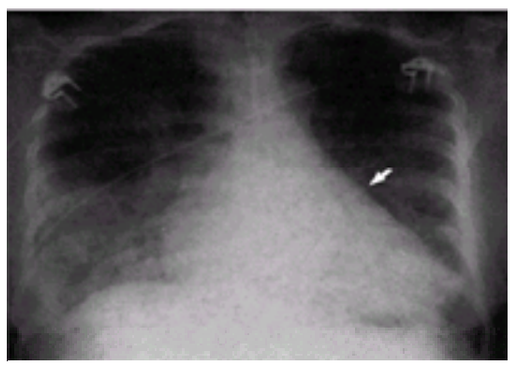
resulting in fluid accumulation in peribronchial sheaths, edema of bronchial walls, and thickening of the subpleural interlobular septa. The interstitial fluid volume may increase by nearly sixfold before development of clinical symptoms or radiographic changes (101). Eventually, the summation of the thickened, edematous interstitial tissues overlaps, blurring the shadows of the lower lobe pulmonary vessels, making them appear indistinct (102) (Fig. 47.14, eFig. 47.14.1 and eFig. 47.14.2). Similarly, edematous swelling of the bronchial walls and peribronchial connective tissues results in peribronchial cuffing (103) and Kerley B lines (104,105), distinct, parallel opacities in the lung bases, oriented perpendicular to the pleural surface (eFig. 47.14.2). B lines are often followed by A and C lines, as the pulmonary lymphatic system increases in caliber to handle the increased parenchymal edema. A and C lines are the radiographic manifestation of more deeply situated lymphatic segments and appear as randomly distributed linear densities found in the mid-lung fields.



***e*FIGURE 47.14.2** A 45-year-old woman with rheumatic mitral stenosis. **A:** Postero-anterior examination shows convexity of the left atrial appendage (*arrows*), which appears to blend into the dilated pulmonary artery segment (PA). The central right pulmonary artery is indistinct. Kerley lines are visible in the right lower lung zone (*arrowheads*). **B:** In lateral view, the dilated left atrium extends inferiorly (*arrows*), the left ventricle is normal, and the retrosternal clear space is filled by the dilated right ventricle.

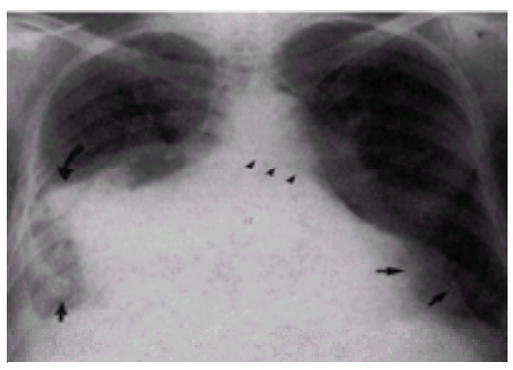
Edema fluid passing from the vascular compartment into the lung parenchyma first obscures the edges and then causes silhouetting of the lower lobe pulmonary vascular markings, making them more difficult to identify on the plain chest. The continued migration of water increases the space between the pulmonary capillary bed and the alveolar compartment of the lung, causing local arteriolar hypoxemia, a potent vasoconstrictive stimulus. This and the decreased compliance of the mildly edematous lung parenchyma cause local increase in the lower lobe pulmonary resistance (106), which induces an intrapulmonary shunt of pulmonary arterial blood flow from the lower lobes to the upper lobes. Normally, the upper lobe pulmonary veins are collapsed (alveolar pressure is greater than pulmonary venous pressure). The intrapulmonary change in blood flow causes increased upper lobe blood flow, and thus increased venous return from the upper lobe segments. These changes result in further impairment in the ability to identify lower lobe vessels as well as increase in the caliber of the upper lobe vessels, referred to as redistribution or “cephalization” of blood flow. In these cases, the caliber of an upper lobe pulmonary vessel is greater than that of another vessel measured an equal distance from the pulmonary hilus in the lower lobe. The pulmonary hila in these individuals may become dense and appear enlarged, similar to findings in shunt lesions. Convergence of the shadows of engorged pulmonary septa in the region of the pulmonary hila causes accentuation of background density, producing an indistinct and fuzzy hila and an especially indistinct descending right pulmonary artery (“perihilar haze”) (107). The hila and central pulmonary arteries in patients with shunt lesions, on the other hand, are sharp and distinct.

Elevation in left atrial pressure to greater than 25 mm Hg (thus exceeding colloid oncotic pressure) results in eventual flooding of the alveolar space, producing frank pulmonary edema. Radiographically, this has an appearance similar to but differentiable from other air space consolidation or infiltrates. In pulmonary edema, the alveolar air is replaced by edema fluid. It is uncommon for all alveoli in a geographic region to be filled with fluid. Therefore, the average radiographic density of the lung is composed of the increased density of the filled alveoli mixed with the low-density regions of air-filled alveoli. Thus, the infiltrates of pulmonary edema are generally less dense in appearance than the more uniformly dense infiltrates of many forms of pneumonia (eFig. 47.14.3). Furthermore, in pulmonary edema the infiltrates are more often bilateral, change in geographic distribution over short periods of time (“fleeting infiltrates”), and are associated with rapid changes in severity associated with changes in the patient’s functional cardiac status. The confluent, patchy infiltrates of pulmonary edema usually involve the medial two-thirds of the lungs and expand outward from the mediastinum, giving the appearance of wings (108). The most frequent presentation of acute pulmonary edema is that of bilateral, fluffy pulmonary infiltrates. Occasionally, the pulmonary edema may be unilateral (109), but within a day or so, the other lung is found to be involved. In patients with acute or chronic mitral regurgitation, focal right upper lobe pulmonary edema may be found (110). This finding may be the result of the jet of regurgitant blood directed toward the right upper lobe pulmonary vein, accentuating the forces for edema formation in the right upper lobe. The known diagnosis or suspicion of mitral valvular disease, as well as the presence of interstitial edema in the remainder of the lung, is helpful in differentiating this condition from pneumonia.



***e*FIGURE 47.14.3** A 72-year-old woman in pulmonary edema. The left ventricle is enlarged. The left atrial appendage portion of the left heart border is nearly convex (*arrow*). The upper lobe vessels are dilated and indistinct. The diffuse and inhomogeneous infiltrates involve the lower lungs, sparing the upper lobes.

Chronic left atrial hypertension is associated with elevated pulmonary vascular resistance and the radiographic changes of pulmonary hypertension, including enlargement of the pulmonary artery segment as well as central left and right pulmonary arteries with marked decrease in peripheral pulmonary arterial caliber. Eventually, chronic left atrial hypertension results in right ventricular dilatation and failure. In long-standing and severe left atrial hypertension, hemosiderosis and pulmonary ossification may be observed. The latter processes are the sequelae of microvascular bleeding and passage of formed blood products into the alveolar space and pulmonary interstitium (eFig. 47.14.4).



***e*FIGURE 47.14.4** A 55-year-old man with chronic rheumatic mitral stenosis. The left atrium is markedly enlarged. It splays the tracheal bifurcation, elevating the left bronchus (*arrowheads*), and forms part of the lower right heart border. The central pulmonary arteries are enlarged. However, upper lobe vessels are greater in caliber than the lower lobe vessels, an indication of chronic left atrial hypertension rather than shunt. Numerous small and punctate calcified nodules (*arrows*) are distributed mostly to the lower lobes. Fluid loculated in the minor fissure (*curved arrow*) appears as a pseudotumor.

Differential Diagnosis of Left Atrial Enlargement

Left atrial enlargement is most frequently caused by left atrial obstruction in chronic rheumatic mitral stenosis. Early roentgenologic changes in these patients may be limited to left atrial enlargement. With time and progressive increase in the mitral valvular gradient, signs of pulmonary venous hypertension and eventually pulmonary hypertension are seen. Untreated, mitral stenosis may cause chronic parenchymal pulmonary hemorrhage, resulting in hemosiderosis, nodular calcific (predominately lower lung zone) densities. The pulmonary hypertension associated with mitral stenosis may eventually result in right ventricular failure. Left atrial and left atrial appendage calcification is frequently associated with chronic mitral stenosis. Calcium deposits are most often found within the endocardial or subendocardial layers of the myocardium, but may also be found in organized thrombus adherent to the atrial wall (111), appearing as a curvilinear circumferential calcific shell (112,113). Left atrial enlargement may also be found in other forms of left atrial obstruction, including left atrial myxoma and congenital mitral stenosis.

Increased left atrial volume results in left atrial enlargement. Chronic mitral valvular regurgitation often results in massive left atrial enlargement. Increased pulmonary blood flow, as seen in VSD and PDA, results in left atrial dilatation. It is important to remember that increased pulmonary blood flow does not necessarily result in left atrial enlargement. The left atrium is of normal size in patients with ASD. In these individuals, the increased pulmonary blood flow reaching the left atrium divides between flow across both the mitral valve and atrial defect, resulting in increased blood flow through the left atrium, but normal atrial volume.

The etiology of left atrial enlargement can be distinguished by analysis of associated findings in the chest examination. Left atrial enlargement associated with left atrial outflow obstruction is associated with a normal-appearing left ventricle and findings associated with chronic pulmonary venous hypertension (i.e., interstitial edema, redistribution, and evidence of pulmonary hypertension). Atrial tumors often calcify. Left atrial enlargement resulting from mitral regurgitation is associated with left ventricular enlargement and a conspicuous absence of significant pulmonary venous changes. Most notably absent is any sign of pulmonary hypertension, nearly always found in patients with chronic mitral stenosis. Shunt lesions resulting in left atrial enlargement present most notably with shunt vascularity and enlargement of the central and peripheral pulmonary arterial segments.

Left Ventricular Free Wall and Left Ventricle

In a normal heart (situs solitus, D-loop, normally related great arteries), the left ventricle lies posterior to and slightly to the left of the right ventricle. The plane of the tricuspid valve (and thus, the right ventricular inflow) lies to the right of the plane of the mitral valve (the left ventricular inflow). The shape of the left ventricle is best approximated by a prolate ellipsoid (114,115) or football. The ventricular long axis is rotated approximately 25 to 30 degrees clockwise from the coronal plane, and 10 to 20 degrees caudal to the axial. The apex of the normal left ventricle points down, anteriorly, and to the left. Thus, in PA, the inferior portion of the left heart border is formed by the anterolateral wall of the left ventricle, the portion of the left ventricular myocardium lateral to the interventricular sulcus. In lateral view (Fig. 47.9), the lower one-half of the posterior border of the heart is formed by the free wall of the left ventricle. When the right ventricle is not enlarged, the shadows of the inferior vena cava and the posterior border of the heart intersect approximately 2 cm above the level of the diaphragm (Fig. 47.9 and Fig. 47.14B) (116).

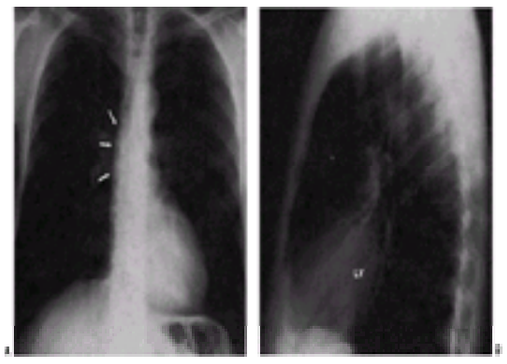
Left Ventricular Enlargement and the Left Ventricular Configuration

In adults, the appearance of the left heart border may change in the absence of left ventricular dilatation. In this circumstance, the heart assumes in the PA view a so-called left ventricular configuration (117); i.e., there is an increase in the curvature of the left ventricular contour and aortic arch segment of the left heart border, between which are sandwiched normal (and thus relatively concave appearing) left atrial appendage and pulmonary artery segments (eFig. 47.14.5). Although this configuration may be found in individuals with healthy hearts, its recognition may be helpful in identifying patients with subtle and significant heart disease.

***e*FIGURE 47.14.5** A 59-year-old man with chronic stable angina. The contour of the left ventricular portion of the left heart border is enlarged. The left atrial appendage and pulmonary artery segments are concave and normal in appearance. The upper lobe pulmonary veins are greater in caliber than vessels in the lower lung zone.

The left ventricular configuration is associated with increased left ventricular wall stress, including volume-loaded, pressure-loaded, ischemic, and cardiomyopathic left ventricular myocardium. In the absence of a lateral chest examination, identification of the left ventricular contour is useful as a case finder or entry point into a differential diagnosis. Left ventricular obstruction, whether caused by asymmetric subaortic septal hypertrophy, congenital or acquired aortic stenosis, coarctation of the aorta, or essential hypertension (Fig. 47.15), may present with this configuration. Associated other observations will help to differentiate among these lesions. For example, the ventricular appearance associated with a small aortic arch segment, with or without the presence of rib notching, may be diagnostic of coarctation of the aorta. If the aortic arch segment appears prominent or enlarged, one might consider the diagnosis of systemic hypertension. When the ascending aorta is volume loaded, its lateral contour is directed toward the right. When this is associated with a left ventricular configuration, then aortic regurgitation (eFig. 47.15.1) is a likely diagnosis. Calcification of the aortic valve (118) is almost always found on plain chest film examination in patients with clinically significant degenerative calcific aortic stenosis. In patients with congenitally bicuspid aortic valve, calcification is almost universally present but may not be apparent on plain chest films. Patients with rheumatic aortic stenosis may not have the calcification found in cases of nonrheumatic disease.

FIGURE 47.15 A 69-year-old man with essential hypertension. In postero-anterior view, the left ventricular contour is rounder and extends farther toward the left chest wall than is normal. Visualization of more than half the circumference of the aortic arch segment (Ao) increases its apparent size, accentuating the concavity of the pulmonary artery and left atrial appendage segments. The lateral view (not shown) demonstrates normal left ventricular volume.

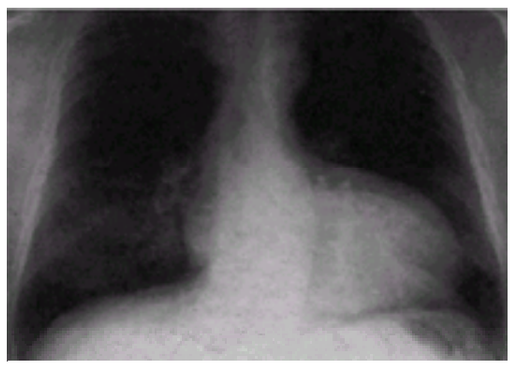


***e*FIGURE 47.15.1** A 40-year-old man with aortic regurgitation. **A:** Postero-anterior view. The left ventricular contour is prominent, and the left atrial appendage and pulmonary artery segments are concave. The ascending aorta (*arrows*) forms the mid-right heart border. **B:** In lateral view, the left ventricle (LV) is dilated.

In some patients with ischemic heart disease, the only morphologic abnormality identifiable on PA chest examination may be the left ventricular configuration. However, in most of these individuals, elevated left ventricular filling pressure manifests radiographically as elevation of pulmonary venous pressure. Depending on the severity and chronicity of the ischemia, one may find only subtle signs of indistinctness of lower lobe vessels or mild redistribution. The left atrium may be normal in size, allowing the chest film to retain a typical convex-concave-convex appearance. Similarly, patients with other abnormalities that result in abnormal left ventricular diastolic compliance, including cardiomyopathy, may present with the left ventricular configuration, with or without evidence of pulmonary venous hypertension.

The addition of the lateral view aids in differentiation between a dilated and nondilated (and potentially hypertrophied) left ventricle and adds information about the presence or absence of intracardiac (aortic) valvular calcification. The left ventricular configuration with a normal-sized heart may be found in patients with aortic stenosis. If calcification of the aortic valve is found in the presence of a left ventricular configuration and a normal-sized heart, then the diagnosis of valvular aortic stenosis is assured. The left ventricular configuration with left ventricular dilatation, as determined from the lateral view, is often associated with aortic regurgitation. The ascending aorta usually dilates toward the right in PA view. However, if the aorta dilates in an anterior direction, then the ascending aortic segment of the right heart border on PA view may appear normal, but on lateral view, the retrosternal air space fills, confirming the presence of a dilated aorta.

Left ventricular dilatation increases the roundness of the lower left cardiac border (eFig. 47.15.2). The apex of the heart may appear to be displaced in a downward direction. In films obtained during deep inspiration, the left ventricular apex may not be separated from the left diaphragm. In both oblique and lateral examination, the inferior posterior cardiac border extends posterior to the inferior vena caval shadow filling the retrocardiac space, and the heart appears to increase in size inferiorly, causing extrinsic compression of the superior aspect of the gastric air bubble. Hoffman and Rigler (116) found that the relationship between inferior vena cava and left ventricle on lateral chest film may provide important information concerning left ventricular size. If the posterior border of the left ventricle extends more than 1.8 cm posteriorly to the border of the inferior vena cava when measured at 2 cm cephalad to the crossing of the right hemidiaphragm and inferior vena cava, then one may presume with certainty that the left ventricle is enlarged. Care must be taken, however, to perform this measurement in true lateral views; measurement in oblique chest examinations results in erroneous interpretation (119).



***e*FIGURE 47.15.2** A 53-year-old man with dilated cardiomyopathy. The curvature of the left ventricular portion of the left heart border is exaggerated, and the overall heart size is increased. However, the left atrial appendage and pulmonary artery segments are concave and normal.

Global left ventricular enlargement is commonly found in patients with left ventricular ischemia, aortic or mitral regurgitation, or cardiomyopathy. This appearance may be mimicked by a pericardial effusion. In patients with ventricular ischemia, the left ventricle dilates to maintain wall stress, and left atrial pressure increases to maintain ventricular filling at increased end diastolic pressure. Depending on the duration and severity of the ventricular ischemia and the compliance of the left atrial myocardium, one might expect to find patients with myocardial ischemia in whom there is left ventricular dilatation with left atrial hypertension in the absence of left atrial dilatation. Chronic left ventricular ischemia results in dilatation of the left atrium as well as the left ventricle.

In patients with chronic aortic regurgitation, left ventricular dilatation becomes pronounced and progressive (120). In these individuals, the volume-loaded left ventricle unloads into the ascending aorta, resulting in the typical picture of left ventricular and ascending aortic dilatation (eFig. 47.15.1). The dilatation of the ascending aorta may appear as an increase in the curvature of the ascending aortic segment of the mid-right heart border, or in the lateral view, present as filling of the retrosternal air space by the dilated ascending aorta (Fig. 47.5B). Generally, these individuals have normal left ventricular filling pressures and, therefore, present with a normal-sized left atrium and no evidence of left atrial hypertension.

In acute mitral regurgitation, the left ventricle and left atrium do not dilate in the face of the rapid increase in volume. Rather, these individuals present radiographically with normal-sized hearts and marked left atrial hypertension, caused by the systolic emptying of the left ventricle through the left atrium and into the pulmonary veins, with the resultant dramatic increase in pulmonary venous pressure (Fig. 47.16). However, in chronic mitral regurgitation, both the left atrium and left ventricle adapt to the increased volume load and dilate. Increased left atrial volume results in near normal left atrial and thus pulmonary venous pressure. The chest radiographs of patients with chronic mitral regurgitation demonstrate dilatation of both the left atrium and left ventricle in the absence of significant pulmonary venous hypertension (Fig. 47.17). In fact, although the left atrium in chronic mitral regurgitation is generally the largest encountered radiographically [greater in size than that found in mitral stenosis (120)], the disparity between the size of the left atrium and the paucity of pulmonary venous change is most pronounced.

FIGURE 47.16 A 52-year-old woman experiencing an acute myocardial infarction. **A:** The heart is not enlarged. The left atrial appendage segment of the left heart contour (*arrows*) is straightened. Notice the moderate to severe bilateral interstitial edema obscuring the pulmonary vascular markings and the increase in caliber of upper lobe vessels. **B:** In lateral view, all vascular markings are indistinct, and the interlobar fissures are thickened (*arrowheads*), containing edema fluid. The left ventricle is not dilated. Although the left atrial appendage segment is straightened on the postero-anterior view, the left bronchus is not posteriorly displaced in lateral, indicating the mildness of left atrial enlargement.

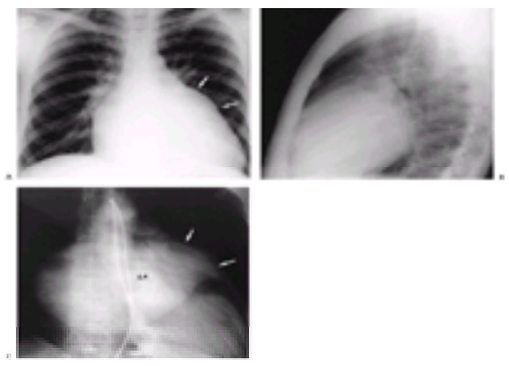
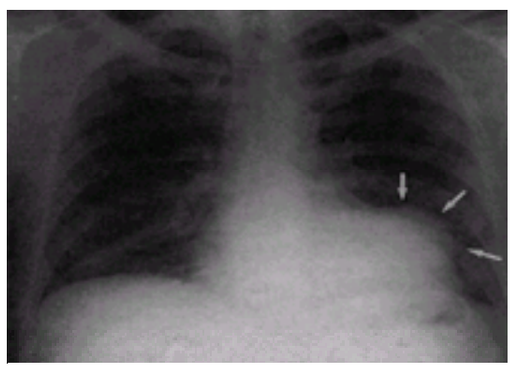


FIGURE 47.17 A 34-year-old man with rheumatic mitral regurgitation. **A:** Postero-anterior examination shows convexity of the dilated left atrial appendage segment (*arrows*) and displacement of the left ventricular contour toward the left chest wall. The pulmonary vascular markings are only mildly indistinct. **B:** Lateral view shows filling of the retrocardiac space by the dilated left atrium and ventricle. **C:** Postero-anterior image from a retrograde left ventriculogram demonstrates the dilated opacified left atrium (LA) and left atrial appendage (*arrows*).

Left Ventricular Aneurysm

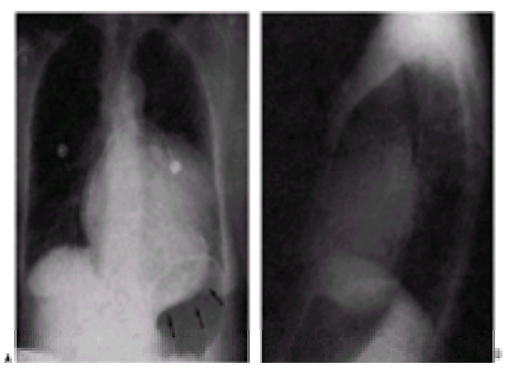
Focal aneurysmal dilatation of a portion of the ventricular wall is found in between 8% and 12% of patients who sustain an acute myocardial infarction (121). The overwhelming majority of left ventricular aneurysms is caused by ischemic heart disease (*e*Fig. 47.17.1). Ventricular aneurysms are localized, permanent, blood-filled dilatations of the left ventricle (122). Gradual bulging (expansion) of the involved (thinned) portion of the LV wall (123,124 and 125) results in a true aneurysm with a wide mouth. Nearly all anterolateral and apical aneurysms are true aneurysms (126) (*e*Fig. 47.17.2). False aneurysms (pseudoaneurysms) are the result of contained cardiac rupture. The wall of a false aneurysm is fibrous, containing blood clot, but without myocardium present. Nearly 50% of false aneurysms are posterior in location.



***e*FIGURE 47.17.1** A 44-year-old man 4 years after acute myocardial infarction with left ventricular aneurysm. Postero-anterior examination shows a focal convexity (*arrows*) along the mid-portion of the left ventricular contour, which itself is pronounced. The lower lobe vessels are indistinct, indicating mild left atrial hypertension.

***e*FIGURE 47.17.2** A 58-year-old man with a complex anterior left ventricular aneurysm. **A:** Postero-anterior view of the chest shows left ventricular enlargement and mild pulmonary vascular congestion. A focal convexity (*arrows*) formed by a portion of the aneurysm is seen protruding from the mid-left ventricular contour. In addition, faint calcification of an inferior portion of the aneurysm (*arrowheads*) is seen medial to the left ventricular contour. **B:** On lateral view, the superior portion of the aneurysm is superimposed on the heart (*arrows*). Calcification (*arrowheads*) takes the course of the distal interventricular septum.

Occasionally, the inferior border of the heart appears abnormal (*e*Fig. 47.17.3). When the aneurysm is large, it can be identified in more than one projection. Whether they appear as focal or global contour abnormalities, left ventricular aneurysms frequently have curvilinear, rim-like calcifications (*e*Fig. 47.17.2, *e*Fig. 47.17.3, and Fig. 47.18) immediately subjacent to their abnormal curvature, resulting from dystrophic calcification of the underlying infarcted ventricular myocardium (111). On occasion, a ventricular aneurysm may be detected on the lateral radiograph (127) as a retrosternal or superior soft tissue border (*e*Fig. 47.17.2B) produced by the wall of the aneurysm silhouetting against the midline cardiac shadow. False ventricular aneurysms may not be directly differentiated from true aneurysms on plain film examination. Location is not an absolute means of differentiating between true and false aneurysms.



***e*FIGURE 47.17.3** A 34-year-old woman with a huge inferior left ventricular aneurysm. **A:** In antero-posterior view, the left ventricle and left atrium are markedly enlarged. The calcified inferior aneurysm extrinsically compressed the gastric cardia (*arrows*). Note the near normal pulmonary vascular markings. **B:** Lateral view further defines the size of the aneurysm and compression of the stomach.

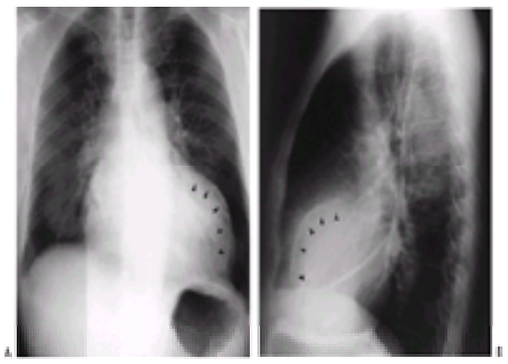
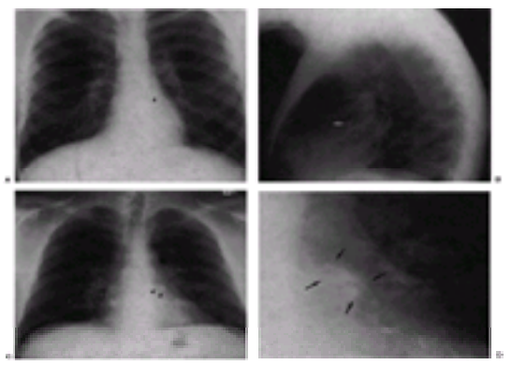


FIGURE 47.18 A 53-year-old man with chronic stable angina. **A:** Postero-anterior view of the chest shows mild pulmonary venous hypertension and enlargement of the left ventricular contour. Curvilinear calcification of the distal interventricular septum (*arrowheads*) defines the extent of a previous myocardial infarction. **B:** In lateral view, the calcification (*arrowheads*) is superimposed on the cardiac mass.

A close relationship between the presence and extent of coronary arterial calcification and the presence and severity of coronary atherosclerosis (128,129,132,133) has been known for years. However, the only reasonably sensitive means of detection of coronary calcification had been cardiac fluoroscopy (130,131,134), a decidedly operator-dependent technique. Thus, investigation of coronary calcification as a detector of coronary atherosclerosis and quantitation of the degree and distribution of calcification as a function of clinical status and prognosis were severely limited. Although limited in its sensitivity, coronary calcification may be detected on plain chest film examination by evaluation of a triangular area located on the left mid-heart border, bordered medially by the vertebral column, inferiorly by a horizontal line drawn from the vertebral column to the top of the left ventricular portion of the left heart border, and diagonally by connecting the former two borders (135). These authors found coronary calcification or a strong suspicion of coronary calcification within this triangle in 42% of patients with fluoroscopically detected coronary calcification (*e*Fig. 47.18.1).



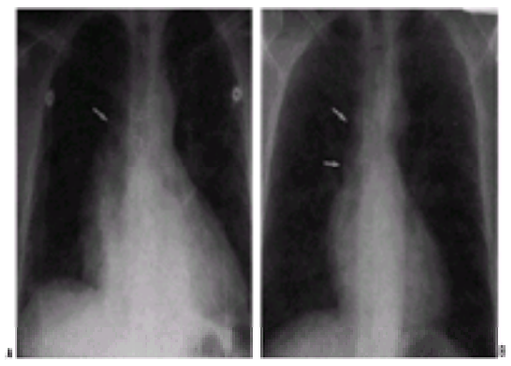
***e*FIGURE 47.18.1** Two patients with coronary arterial calcification. **A:** An 18-year-old man with a history of Kawasaki's disease, postero-anterior view. Calcification is faintly seen (*arrowhead*) medial to the mid-left heart border. **B:** In lateral view, the ring calcification of a coronary artery aneurysm (*arrow*) is seen. **C:** A 59-year-old man with coronary atherosclerosis and chronic stable angina, postero-anterior view. Irregular calcification of the proximal anterior descending coronary artery (*arrowheads*) is found just beneath the lucency of the left bronchus. **D:** Enlargement of the mid-portion of the left heart border, better displaying the calcification (*arrows*).

Pericardial Effusion

Nonspecific change in the appearance of the lower left heart contour may be an indication of pericardial disease, most commonly pericardial effusion. Small pericardial effusions may not be detected by plain film examination. The greater the accumulation of fluid, the more apparent the change in cardiac contour, and the greater the confidence one has in making the diagnosis. The pericardium is an Erlenmeyer flask–shaped fibrous bag consisting of the visceral pericardium, the parietal pericardium, and the normally occurring 20 to 60 mL of fluid collection between them. The normal visceral pericardium (or epicardium) covers the external surface of the heart. Beneath the visceral pericardium is either myocardium or epicardial fat. This layer extends for short distances along the pulmonary veins, the superior vena cava below the azygos vein, the inferior vena cava, the ascending aorta to a point 20 to 30 mm above the root, and the main pulmonary artery as far as its bifurcation. It then reflects on itself to become the parietal pericardium, which is a 1-mm-thick outer fibrous layer composed of dense collagen lined on the inside by a monolayer of mesothelial cells.

On the lateral chest radiograph, the normal pericardium may occasionally be seen as a 1- to 2-mm-thick curved stripe anterior to the heart set between more radiolucent mediastinal fat anteriorly and epicardial fat posteriorly. The visceral pericardium is normally thin and is therefore not visualized separately by any imaging modality.

An abrupt asymmetric increase in the dimension of the cardiac silhouette without specific chamber enlargement suggests the diagnosis of pericardial effusion. Frequently, the asymmetric change in configuration occurs along the right atrial contour of the right heart border (*e*Fig. 47.18.2), suggesting loculation of fluid about the right atrium. Filling of the retrosternal space, effacement of the normal cardiac borders, development of a "flask" or "water-bottle" cardiac configuration, and bilateral hilar overlay are characteristic of a larger pericardial collection (Fig. 47.19). The epicardial fat pad "sign" is positive when, visualized in the lateral projection, an anterior pericardial stripe (bordered by epicardial fat posteriorly and mediastinal fat anteriorly) is thicker than 2 mm. This sign is diagnostic of pericardial disease (136) (Fig. 47.20). Because there is abundant fat between the pericardium and the pleura at the cardiac apex, a positive epicardial fat pad may also be seen in the frontal projection. This is usually seen as an elliptical stripe internal to and paralleling the lower left heart border. This radiolucent line may migrate toward or away from the cardiac border with changes in the amount of pericardial fluid (137,138). Although diagnostically valuable in many patients, reliance on the plain film diagnosis of pericardial effusion has been largely supplanted by echocardiography and other cross-sectional imaging techniques.



***e*FIGURE 47.18.2** A 38-year-old woman recently reoperated to replace an aortic valve prosthesis. **A:** Postero-anterior examination shows a broad lower right heart contour extending cephalad to the carina (*arrow*). **B:** Postero-anterior examination obtained immediately before the recent surgery. Although the right heart border appears prominent, the curvature does not extend as far cephalad and does not obscure the curve of the ascending aorta (*arrows*).

FIGURE 47.19 An 87-year-old woman with chronic renal failure. The silhouette of the heart is globular in shape. The density of the fluid collection is defined by the attachments of the pericardium to the ascending aorta (*thick arrows*) above the azygos vein (a) and to the top of the pulmonary artery (*thin arrows*). The pulmonary hila are hidden.

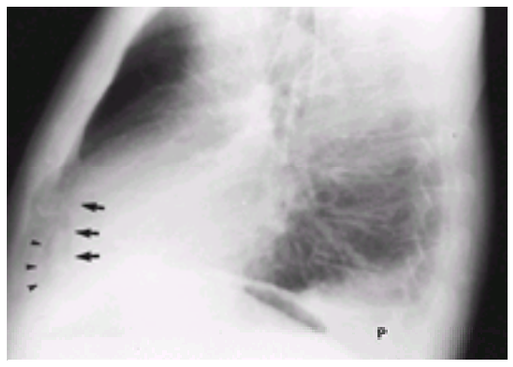


FIGURE 47.20 A 52-year-old man with pericardial and pleural effusion, lateral view. The lucency of the epicardial fat (*arrows*) is separated from the lucency of the pericardial fat (*arrowheads*) by the density of fluid in the pericardial space. A small left pleural effusion (P) silhouettes the posterior left hemidiaphragm.

Pericardial Calcification

Constrictive pericarditis is usually the result of a chronic pericardial insult. The greatest number of cases are of unknown etiology, presumably secondary to an inapparent viral pericarditis (139). Outside the United States, the most common cause is probably tuberculosis or fungal etiology (140). Other causes of nontuberculous disease include connective tissue disorders such as rheumatoid arthritis (141) and systemic lupus erythematosus (142), hemodialysis-treated chronic renal failure (143,144), and neoplastic infiltration of the pericardium, most commonly secondary to carcinoma of the lung or breast, lymphoproliferative malignancies, and melanoma (145). Pericardial constriction may occur months to years after mediastinal irradiation, usually performed to treat Hodgkin's disease (127) or breast carcinoma. Constrictive pericarditis had been considered a rare complication of cardiac surgery (146), especially in those cases in which the pericardium was left open. However, more recent experience (147) has shown a 0.2% incidence of constrictive pericarditis following cardiac surgery (148).

Pericardial calcification is not pathognomonic for pericardial constriction. However, extensive calcification is found in nearly one-half of patients and strongly suggests pericardial constriction of infectious etiology (149,150) (*e*Fig. 47.20.1). Pericardial calcification appears as irregular, large loci, distributed on both the left and right of the midline, reflecting the distribution of the pericardial space (151). Although the heart in most patients with constrictive pericarditis is usually enlarged, it is not unusual for the heart size to be normal (152). Coexisting pericardial effusion may increase the apparent heart size, but indirect findings associated with increased right-sided pressure (i.e., dilatation of the superior vena cava and azygos vein) help suggest the diagnosis. These radiographic findings are common to both constrictive pericarditis and restrictive cardiomyopathy.

***e*FIGURE 47.20.1** A 76-year-old woman with progressive shortness of breath. Thick, irregular calcification is seen along the right atrial contour of the right heart border (*arrows*) and the anterior interventricular groove (*arrowheads*).

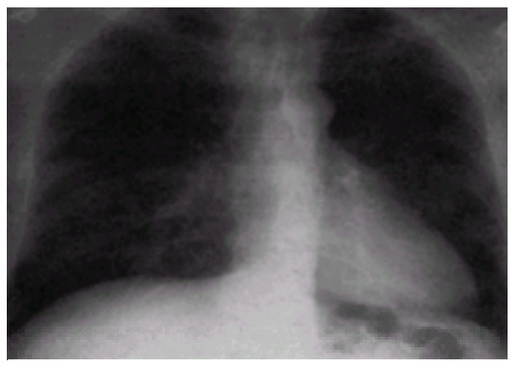
Pericardial Cyst

Most pericardial cysts appear as sharply demarcated masses near the right cardiophrenic angle (*e*Fig. 47.20.2). They may be found in other mediastinal locations, including at the left cardiophrenic angle. The borders of the cysts are usually round, but a pointed upper border may also be seen. This is thought to be due to drooping of the cysts originating higher in the mediastinum into the cardiophrenic region (153). Pericardial diverticula can be suggested on plain films and fluoroscopy by their change in contour and size during deep inspiration (154,155).

***e*FIGURE 47.20.2** Asymptomatic 77-year-old woman with a pericardial cyst. The left ventricle is enlarged. Pericardial effusion obscures the lower left heart border. A large pericardial cyst increases the curvature in the right atrial contour of the right heart border (*arrows*).

Congenital Partial Absence of the Pericardium

As described previously, the heart is fixed within the middle mediastinum by the pericardial attachments. Any interruption of this fixation results in distortion of the normal cardiac silhouette. The characteristic plain film findings (156) are usually present in complete absence of the left pericardium and include displacement of the left ventricle and pulmonary arteries toward the left side (*e*Fig. 47.20.3). The individual cardiac segments that make up the left heart border may be more clearly defined and separated than usual. Both the medial and lateral borders of the main pulmonary artery may be visualized more clearly because of an absence of the anterior pericardial reflection between the aorta and the pulmonary artery. In partial pericardial defects, varying degrees of prominence of the pulmonary artery or left atrial appendage or both may be seen, whereas the heart retains its normal position in the thorax (156).



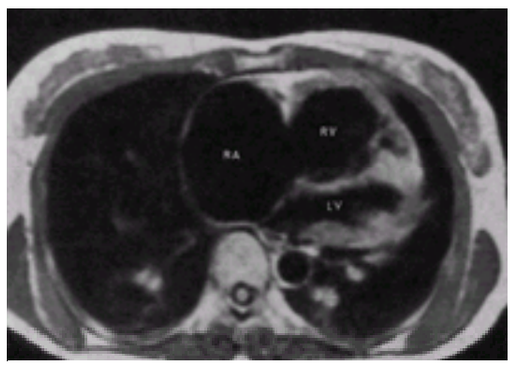
***e*FIGURE 47.20.3** Asymptomatic 59-year-old man with partial absence of the left side of the pericardium. The heart is rotated and shifted into the left chest. The right heart border is displaced toward the left and is projected over the spine. The pulmonary vascularity is normal.

In an asymptomatic patient the characteristic plain film findings may be sufficient to make the diagnosis. However, because plain film findings are frequently subtle and nonspecific, the condition often goes unrecognized (157). In a series of six patients only two had the diagnosis suggested on plain chest radiography (157). None of the 15 patients diagnosed with congenital absence of the pericardium during unrelated cardiac or thoracic surgery reported in the Mayo Clinic series had the diagnosis suggested on preoperative chest radiography (158).

Right Ventricle

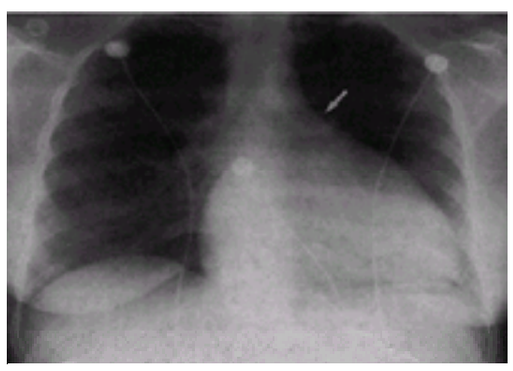
The right ventricle is an anterior, midline structure. The right medial border is limited by the anterior atrioventricular ring containing the tricuspid valve. To the left, the ventricle is limited by the anterior interventricular sulcus containing the left anterior descending coronary artery. Thus, in PA projection, the right ventricle does not form a cardiac border. In lateral projection, the right ventricle fills the inferior retrosternal air space; the free wall of the right ventricle lies directly subjacent to the inferior half of the sternum (Fig. 47.9).

Right ventricular hypertrophy may alter the appearance of the lower left cardiac contour and cardiac apex on PA view. The cardiac apex may be lifted from the diaphragm, and the curvature of the left ventricular contour may become more rounded. In the absence of another associated lesion (such as induced tricuspid regurgitation), right ventricular hypertrophy does not cause right ventricular dilatation. In PA projection, right ventricular dilatation causes (as viewed from below) clockwise rotation of the heart (*e*Fig. 47.20.4). This has the effect of altering the superior portion of the lower third of the left heart contour. As the heart rotates, the relative concavity of the left atrial appendage segment is rotated posteriorly and medially, and the right ventricular outflow tract and anterior interventricular sulcus are displaced laterally and come to form that portion of the left heart border. This portion of the left heart border appears fuller than in the healthy heart. This change can be differentiated from left ventricular and left atrial enlargement by recognition of the increased distance between the left main bronchus (which itself does not appear elevated on frontal examination or displaced on lateral examination) and the left heart border itself. In addition, in cases of right ventricular dilatation, other signs of heart and mediastinal rotation usually occur. The most important of these is medial displacement of the superior vena caval shadow; this results in disappearance of the vertical line of the superior vena cava over the spine. In lateral view, changes in the size of the right ventricular chamber manifest as filling of the retrosternal clear space and posterior displacement of the left ventricle, as manifested by posterior displacement of the inferior posterior heart border toward the spine.



***e*FIGURE 47.20.4** A 26-year-old man with cystic fibrosis, pulmonary hypertension, and secondary tricuspid regurgitation. Axial spin-echo magnetic resonance image demonstrates the clockwise rotation of the heart into the left chest. The right ventricle (RV) is dilated and moderately hypertrophied. Notice that the left ventricle (LV) is rotated into a posterior position and that the lateral border of the heart is formed by the right ventricle. The right atrium (RA) is dilated as well.

Right ventricular dilatation may be observed in patients with left-to-right shunts or malformations of the tricuspid valve or primary abnormalities of the right ventricular myocardium (159,160) (*e*Fig. 47.20.5). More commonly, however, they result from right ventricular dysfunction caused by left-sided heart problems, pulmonary disease, and primary or secondary right ventricular myocardial disease. The most common cause of right-sided heart failure is chronic left-sided heart failure (161). The common denominator of this and other left-sided heart problems causing right ventricular dysfunction is chronic left atrial hypertension transmitted back to the pulmonary veins, capillaries, and arteries. Similar cardiac changes may be found in cor pulmonale, the syndrome of right ventricular hypertrophy, dilatation, and failure resulting from pulmonary hypertension secondary to lung disease (162). Although the condition may be acute, as seen in sudden massive pulmonary thromboembolism (163,164), it most often develops chronically, resulting from hypoxia-induced pulmonary arteriolar vasoconstriction or fibrosis of the pulmonary vascular bed (165,166).



***e*FIGURE 47.20.5** A 24-year-old woman with Uhl's anomaly. The heart is rotated into the left chest. The dilated left heart contour is formed by the dilated right ventricle.

Notice the small pulmonary artery segment (*arrow*), indicating the decreased pulmonary blood flow in this lesion.

Right Atrium

The convexity of the lower right heart border on PA examination is formed by the lateral wall of the right atrium. Estimation of right atrial enlargement is difficult on plain films of the chest. Few linear measurements of the radiographic size of the right atrium have clinical significance. There is no good way to reliably differentiate patients with right atrial enlargement from those without (167). The chamber overlaps the right ventricle, and when the right ventricle is enlarged (which is the case in most conditions causing right atrial enlargement), determination of right atrial size can be difficult. On lateral examination, posterior displacement of the inferior vena caval shadow is a very specific finding.

Isolated enlargement of the right atrium is uncommon. Enlargement secondary to volume loading is most often the case, usually caused by tricuspid regurgitation (eFig. 47.20.4 and Fig. 47.21). The most common cause of tricuspid regurgitation is pulmonary hypertension of any etiology. In these cases, the diagnosis is made by observation of associated evidence of changes in the central and peripheral pulmonary arteries. Until right ventricular failure supervenes, right atrial dilatation in the absence of right ventricular dilatation is found. By the time the right ventricle has failed, clockwise rotation of the heart has occurred, and other findings associated with right atrial hypertension are found, including dilatation of the azygos vein and the presence of pleural or pericardial effusion or ascites.

FIGURE 47.21 A 56-year-old woman with rheumatic mitral stenosis and secondary tricuspid regurgitation. The pulmonary artery segment is enlarged. The right atrial contour of the right heart border is increased in convexity. Convexity of the left atrial appendage section of the left heart border and pulmonary vascular redistribution are evident. Visualized lower lobe vessels are acutely smaller in caliber than the hilar pulmonary arteries. The left ventricle is normal.

Marked dilatation of the right atrium may be found in congenital tricuspid regurgitation or Ebstein's anomaly. More severe tricuspid regurgitation is found in individuals with more severe tricuspid valvular malformations. Depending on how much of systemic cardiac output is derived from right-to-left shunting across the interatrial septum, varying degrees of left ventricular enlargement may be found.

In patients with tricuspid atresia, there is no antegrade filling of the right ventricle from the right atrium. Furthermore, in nearly 75% of patients there is pulmonic stenosis or a restrictive VSD, resulting in decreased pulmonary blood flow and an overall normal-sized heart (eFig. 47.21.1). The tricuspid valve obstruction and obligatory right-to-left shunt across the atrial septum results in right atrial dilatation (increased curvature of the right atrial border) and a normal-appearing to slightly enlarged left atrium. Depending on the size of the shunt and left atrial compliance, mild pulmonary venous hypertension may be evident. The left ventricle in these patients is dilated (it receives both systemic and pulmonary blood flow). The dilated ascending aorta increases the curvature of the right upper cardiac border directly and by lateral displacement of the superior vena cava. In approximately 25% of patients with tricuspid atresia, there is associated transposition of the great arteries, resulting in a less specific radiographic picture of increased pulmonary circulation and left atrial and ventricular enlargement without the characteristic increase in right atrial convexity.

***e*FIGURE 47.21.1** A 44-year-old man with tricuspid atresia and Pott's anastomosis. The left pulmonary artery is dilated, although the pulmonary artery segment (PA) is small. The right pulmonary artery branches are diminutive. The right atrial portion of the right heart border is increased in contour.

CONTROVERSIES AND PERSONAL PERSPECTIVES

There is little that is controversial about chest film examination of the heart. The role of the chest film has shifted in the past half century from a central role in cardiac diagnosis and patient management to more of a barometer of patient physiologic status. This reflects the increase of more sensitive and accurate imaging modalities, rather than the limited accuracy of plain film examination. In an era of advancing invasive means of monitoring physiologic status, the role of the chest film for assessment of cardiac chamber pressure will wane. However, there is still no better means than the plain chest film for displaying the presence and location of the myriad devices used for the monitoring of an intensive care unit or recovery room patient.

The form of image obtained from chest examination has begun to change. The evolution in electronic imaging that began in the 1970s and 1980s has produced reliable means of acquiring high-resolution imagery, high-volume means of archiving these images, and tools for distributing the data to sites around the hospital and community. As institutions have felt the pinch for space, the cumbersome radiology film library has evolved into an electronic library for examinations obtained with filmless systems. These studies arrive at the library via network and are archived for the short- or long-term on magnetic or optical disc. The file room now serves as the distribution center for direction of collected imagery to reading terminals, where algorithms may be applied to manipulate image data, and for the purpose of enhancing the appearance of the heart and pulmonary vascularity. The era of the 14-in. × 17-in. plain film is nearly over. Although the electronic revolution in radiologic imaging and archiving always raises the issue of automated image evaluation, we still have not reached that level of sophistication. The wide variation in physiologic statuses of individuals, as well as the potential artifacts and overlying hardware in and around an acutely ill individual in an intensive care unit, has confounded attempts to automate image evaluation. For the foreseeable future, humans will probably continue to interpret and report the results of these examinations.

THE FUTURE

This is the future. Over the past 25 years, a revolution in the practice of cardiac imaging has occurred. It is becoming mainstream practice for chest radiography to be acquired and archived in digital format and displayed electronically on a video monitor. In a post-future era, we can expect to see better interconnectivity among imaging devices and their networks, as well as among cardiac imagers themselves. This will increase the availability of previous examinations and allow easier comparison of current examinations with other imaging modalities. Along with a more sophisticated approach to the issues of privacy and broad public access, access to diagnostic imagery will be broadened, increasing network volume and maintaining pressure for network growth and evolution. Credit card–based access to all medical imagery and the means of transferring image studies, supporting the availability of rapid second opinions, will change the manner in which we manage patients with cardiovascular disease. As society becomes wired for broadband cable as well as ground-based and satellite-based Internet services, expect to see rapid growth in the use of distant reviewing stations for interpretation of centrally obtained diagnostic imagery. The film library will continue its evolution from storage facility to networking hub for distribution of electronic imagery.

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48

EXERCISE ELECTROCARDIOGRAPHY

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Exercise electrocardiography (ECG) is the most widely used method for assessment of the presence and severity of coronary artery disease. Clinical confidence in the exercise ECG has been eroded by the limited sensitivity and predictive value of standard ST-segment depression criteria and by the overapplication of Bayesian principles to interpretation of the exercise ECG in comparison with other noninvasive modalities. However, the development of new approaches to analysis of the ST-segment response to exercise, including the heart rate (HR)–adjusted indices of ST-segment depression (the ST/HR slope and ST/HR index) and treadmill exercise scores, has led to a resurgence of clinical and research interest in the exercise ECG. These methods improve the accuracy of the exercise ECG for the identification and quantification of coronary artery disease and improve risk stratification in both asymptomatic low-risk subjects and symptomatic patients with coronary artery disease. Application of HR-adjusted techniques has been supported by theoretical and experimental evidence that relates the magnitude of ischemic ST depression at peak exercise to both the area of ischemic territory and the degree of myocardial oxygen supply-demand mismatch as reflected by changing HR. Novel approaches to analysis of the ECG during exercise, including changes in QRS complex duration and high-frequency content and assessment of HR responses during both exercise and recovery, hold promise for future improvements in test performance.

GLOSSARY

Bayesian analysis: Relation of test performance to the prevalence of disease in a population.

Chronotropic response index: Fraction of HR reserve achieved with exercise, adjusted by the fraction of metabolic reserve achieved.

ETT: Exercise tolerance test or exercise electrocardiogram.

J-point: Junction of the end of the QRS complex and the beginning of the ST segment.

Rate-recovery loop: Plots of ST-segment depression as a function of HR during both exercise and recovery.

ST/HR index: Maximal change in ST-segment depression with exercise, divided by the total change in HR.

ST/HR slope: Linear regression–based calculation of maximal rate of change in ST-segment depression as a function of change in HR during exercise.

INTRODUCTION

Exercise ECG, or the exercise tolerance test (ETT), is the most widely used and widely available technique for the investigation of known or suspected coronary artery disease. It has been estimated that 6 to 8 million treadmill tests are performed annually in the United States. Nonetheless, clinical confidence in the simple ETT has been eroded by the limited sensitivity and predictive value of standard ECG criteria. However, new approaches to analysis of the ETT have been developed over the past 15 years that improve the accuracy of the exercise ECG to levels found with use of more expensive and less widely available imaging methods. This chapter reviews the development of exercise ECG; gives a brief review of the pathophysiologic basis for exercise-induced ST-segment depression; provides detailed information on the performance, interpretation, and applications of the ETT; and addresses the controversies and future directions in exercise ECG.

HISTORICAL PERSPECTIVE

The development of exercise ECG was based on the empiric observation that ST-segment depression occurs after exercise in patients with coronary artery disease. In 1928, Feil and Siegel (1) reported ST-segment depression after exercise in patients with angina. They demonstrated that the ECG changes resolved after the pain subsided or after administration of nitroglycerin and ascribed the ST-segment depression to a decrease in blood flow to the heart. These observations and conclusions were supported by the subsequent studies of Hellerstein and Katz (2) that described the direction of the vector associated with subendocardial injury in various regions of the left ventricle and, using direct current electrograms, demonstrated that ST-segment depression is primarily a diastolic injury current.

In 1929, Master and Oppenheimer (3) published their first description of an exercise test, the standardized step method that was to become popular for several decades. However, they did not recognize the value of the ECG for the identification of ischemia until 1941, when Master and Jaffe (4) proposed that an ECG could be performed before and after the exercise test to detect coronary insufficiency. Before this, Wood and Wolferth (5) and Katz and Landt (6) had demonstrated the value of ST-segment changes after exercise for the diagnosis of angina and reported that the precordial leads were more useful than the standard limb leads for the identification of ischemic changes. In 1940, Riseman and colleagues (7) first described the use of continuous monitoring during exercise and reported that ST-segment depression usually appeared before the onset of angina and persisted for some time after the symptoms resolved. In 1952, Yu and Soffer (8) reported that the appearance of 1 mm (0.1 mV) of ST-segment depression on the ECG after Master's stair test was consistent with ischemia, and by 1955, the Master's test had

become widely accepted as a result of its simplicity and presumed accuracy.

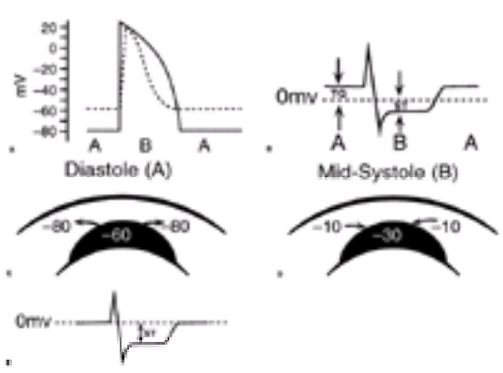
Modern stress testing can be dated from the mid-1950s, when Bruce (9) described a treadmill exercise protocol that provided a more adequate stress than the Master's test and allowed stratification of patients according to the New York Heart Association classification. Although numerous additional treadmill exercise protocols have subsequently been developed, many, if not most, of the protocols currently in use clinically are modifications of the original protocol of Bruce. The next two decades were marked by continued refinement of ST-segment depression criteria (10), with particular attention paid to the number and types of leads used for exercise testing (11), and by the application of exercise ECG for risk stratification (12,13). This period also marked the introduction of computers for the processing of exercise ECGs and measurement of ST-segment changes (14,15) and the subsequent development of quantitative scores based on computer-measured ST-segment depression in combination with other exercise test variables (16).

During the late 1970s and early 1980s, the relation of test performance to the pretest likelihood of disease, or "Bayesian analysis" (17,18 and 19), was brought to bear on the ETT, leading to an era for the exercise ECG that could best be called the "period of Bayesian paralysis" (17). Numerous studies were published that examined the predictive value of the ETT according to population probability of coronary artery disease (18,19), demonstrating the low positive predictive accuracy of the method when it was used for patients who had a low pretest likelihood of disease and the high positive predictive accuracy of the test when it was used for patients who had a high clinical likelihood of having disease. Even though the same principles apply to other noninvasive methods for the detection of coronary artery disease, these effects were particularly emphasized with respect to the ETT. Partly as a consequence of these findings, clinicians lost faith in the routine ETT, leading to more widespread use of newly available imaging modalities during exercise testing.

The past decade has seen a resurgence of interest in the exercise ECG. ETT research has focused on new ECG markers for ischemia, such as the HR-adjusted indices of ST-segment depression [the ST/HR slope, ST/HR index, rate-recovery loop, and ST/HR hysteresis (20,21,22 and 23a)] that significantly improve the accuracy of the exercise ECG. Additional work has led to a greater appreciation of the importance of an attenuated HR response both during and after exercise in the recognition of coronary artery disease in patients and in risk stratification (24 and 25a), brought about the incorporation of ST depression and other exercise parameters into treadmill scores that can improve performance of the ETT (26), and examined changes in QRS prolongation and QT dispersion during exercise as a marker for myocardial ischemia (27,27a).

PATHOPHYSIOLOGY OF ST DEPRESSION

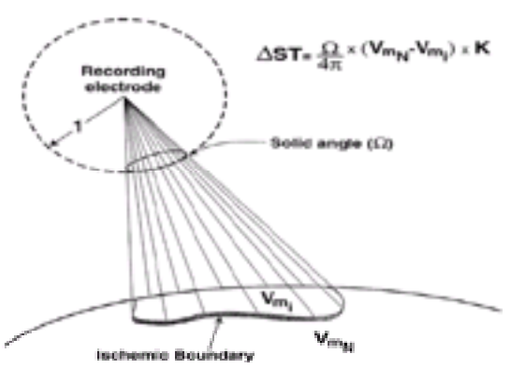
Diagnostic exercise ECG is predicated on the concept that the resulting tachycardia produces subendocardial ischemia, which in turn reverses the normal transmural gradient of ventricular repolarization properties to produce ST-segment depression on the surface ECG (28). The putative mechanism for ST-segment depression that is seen during subendocardial ischemia and the primary electrophysiologic events thought to occur in normal and ischemic myocardium underlying a surface electrode are illustrated in *e*Fig. 48.0.1 (29,30). As is shown in *e*Fig. 48.0.1A, during ischemia, the transmembrane potential of the ischemic cells is altered in comparison with that of normal cells. During diastole, ischemic cells have a lower (less negative) transmembrane potential than do normal cells; as a result, current flows from ischemic tissue to normal tissue (*e*Fig. 48.0.1C). During systole, the transmembrane potentials of the ischemic cells become negative earlier than those of the normal cells, and as a consequence, current flows from the normal to the ischemic tissue (*e*Fig. 48.0.1D). Thus, the current flow during diastole produces TQ-segment elevation in leads overlying the ischemic area, and the current flow during systole produces ST-segment depression in the same leads (*e*Fig. 48.0.1B). As a result, the phenomenon commonly referred to as *ST-segment depression* reflects the sum of TQ-segment elevation and true ST-segment depression. However, because of the manner in which clinical ECGs are recorded, the sum of the true TQ-segment elevation and ST-segment depression (*e*Fig. 48.0.1B) is displayed only as ST-segment depression (*e*Fig. 48.0.1E).



***e*FIGURE 48.0.1 A:** Transmembrane potentials of ischemic (*broken line*) and normal (*solid line*) tissue. **B:** Electrocardiogram recorded by an electrode overlying the ischemic tissue. The TQ segment is located above the isoelectric line (*broken line*), and the ST segment is located below the isoelectric line. **C:** Potential gradients existing at the boundary between normal and ischemic tissue during electrical diastole. **D:** Potential gradients existing at the boundary between normal and ischemic myocardium at mid-systole. **E:** The electrocardiogram shown in **B**, when recorded on a typical electrocardiograph, shows the sum of TQ elevation and ST-segment depression seen in **B** as only ST depression. Arrows in **C** and **D** indicate the direction of current flow (positive to negative) at the boundary. A, diastole; B, mid-systole. (Adapted from Holland RP, Brooks H. Precordial and epicardial surface potentials during myocardial ischemia in the pig: a theoretical and experimental analysis of the TQ and ST segments. *Circ Res* 1975;37:471, with the permission of the American Heart Association.)

The relationship between reduced subendocardial blood flow and consequent subendocardial ischemia, and ST-segment depression in the presence of coronary artery stenoses has been well documented (28,31). Numerous studies have demonstrated that tachycardia in the presence of coronary artery obstruction produces a decrease in subendocardial blood flow with essentially no change in epicardial flow, and a resulting decrease in the endocardial/epicardial flow ratio. If HR and the area (extent) of the tissue that is becoming ischemic are held relatively constant, a linear relationship between the decrease in subendocardial blood flow and the magnitude of ST-segment depression can be shown (28). Further evidence for the relationship of ST-segment depression to subendocardial ischemia is found in the study of Wilson and associates (32), which demonstrated a strong correlation between reduced coronary flow reserve and both the ST segment and HR response to exercise in patients with angiographically proven coronary artery disease. The similar linear relationship between changing HR and endocardial/epicardial flow ratio and resultant direct linear relationship between HR and the magnitude of subendocardial ischemia has important implications for the development of HR-adjusted ST-segment depression criteria (20,21,22 and 23,33).

Theoretical and experimental evidence (28,29,30,31,32 and 33) demonstrates that the determinants of the ST-segment response to exercise can also be mathematically modeled based on solid-angle theory (*e*Fig. 48.0.2). Based on a distributed dipole model of electrical activation of the heart, solid-angle theory indicates that the magnitude of ST-segment depression recorded at a surface (DST) can be related to the product of spatial and nonspatial determinants as defined by the relationship



***e*FIGURE 48.0.2** Mathematical and pictorial representation of solid-angle theory**.** The TQ-ST–segment voltage (DST) recorded at the electrode is given by the equation. The solid angle (W) is defined as the area of spherical surface cut off a unit sphere (inscribed about the recording electrode) by a cone formed by straight lines extending between the recording electrode and every point along the ischemic boundary. The ischemic boundary is a source of current flow established by differences in the transmembrane potentials of the normal (V_{mN}) and ischemic (V_{mi}) cells during diastole and systole. *K* is a term correcting for differences in intra- and extracellular conductivity and the occupancy of much of the heart muscle by interstitial tissue and space. (Adapted from Holland RP, Brooks H. TQ-ST segment

mapping: critical review and analysis of current concepts. *Am J Cardiol* 1977;40:110, with the permission of Excerpta Medica, Inc.)

$$\Delta ST = (\Omega/4\pi)\ (\Delta V_m)K$$

where W is the solid angle subtending the boundary of the ischemic territory, DV_m is the difference in transmembrane voltage between the ischemic and the adjacent nonischemic regions, and *K* is a term correcting for the differences in intracellular and extracellular conductivity and changes in gap junctional conductance. As a consequence, during the transient ischemia associated with exercise, the magnitude of ST-segment depression recorded by a surface electrode is proportional both to the area of ischemic territory subtended by the recording electrode and to the local transmembrane potential difference, which reflects the electrical consequences of the metabolic severity of ischemia at the level of the myocardial cell. This relationship remains proportional under conditions in which major changes in gap junctional conductance do not occur.

It is clear that during exercise the severity of ischemia is directly proportional to changes in myocardial oxygen demand and the ratio of endocardial/epicardial blood flow (31), which in turn can be linearly related to increasing HR (DHR) in experimental studies (31,34). As an arithmetic consequence of this relationship, the ratio DV_m/DHR should remain constant as ischemia develops (33). Dividing the solid-angle relationship in Equation 1 by DHR and making the appropriate substitution for a constant DV_m/DHR reveals that, under conditions in which changes in conductance are proportional or small,

$$\Delta ST/\Delta HR = (\Omega/4\pi)(c)$$

where *c* is a new constant of proportionality. Thus, during exercise-induced transient subendocardial ischemia caused by increased workload, the instantaneous ratio of changing ST-segment depression to changing HR should be directly proportional to the area of ischemic boundary. Furthermore, this ratio should remain independent of the metabolic effects of ischemic severity on transmembrane potential differences across the ischemic boundary. The relationships inherent in Equation 2 provide a strong theoretical basis for the practical application of HR adjustment to analysis of the ST-segment response to exercise, whereas Equation 1 offers further insight into the poor performance of traditional exercise test criteria that are based solely on the magnitude and configuration of ST-segment depression (10,11).

As seen in Equation 1, the ability of standard exercise test criteria to detect coronary artery disease is dependent on the product of both spatial and nonspatial factors reaching a threshold magnitude of ST-segment depression. However, this threshold may not be met when the voltage difference across the ischemic boundary is small, even when disease is anatomically extensive. Thus, sensitivity of standard criteria for the detection of coronary artery disease (= 0.1 mV horizontal or downsloping ST depression) depends on the achievement of a sufficiently high augmentation of myocardial oxygen demand by means of exercise-induced change in HR to produce a threshold amplitude of ST-segment depression (10,11,33). As a consequence, the high prevalence of false-negative standard test responses that can occur during submaximal testing can be both physiologically and mathematically related to reduced ST-segment depression associated with lower HRs and the lower voltage difference that results at the ischemic boundary. HR correction can overcome this fundamental limitation of standard test criteria by adjusting smaller amounts of ST-segment depression for the smaller increases in myocardial oxygen demand that are associated with submaximal exercise.

It is important to recognize that several factors may potentially limit application of this theoretical construct (33,35,36,37 and 38). The traditional view that exercise-induced myocardial ischemia primarily reflects fixed supply and varying demand inadequately describes a more complex pathophysiology. Variability in the functional significance of obstructive coronary artery disease, caused by variable collateral supply, variable differential transmural perfusion, and variable loading conditions in patients who have compromised flow reserve, should make correlation of the anatomic extent of disease with the rate-related change in ST-segment depression imperfect (35). The effects of variable luminal obstruction due to changes in coronary vasomotor tone, the effects of abnormalities of vasodilator reserve, and the effects of serial lesions in diseased vessels should also reduce this correlation (36). In patients who have normal coronary arteries, both exercise- and pacing-induced tachycardia may produce dilatation of epicardial vessels with a concomitant increase in coronary blood flow seen with pacing (37,38). Patients who have nonstenotic atherosclerotic vessels may fail to dilate or to increase coronary blood flow under similar circumstances, whereas patients with stenotic coronary arteries may exhibit epicardial coronary artery vasoconstriction that can be associated with a reduction in coronary blood flow (37,38).

Although these findings may alter the relation of this model of exercise-induced ST-segment depression to all types of ischemic responses, they do not appear to significantly affect the clinical utility of HR-adjusted methods in most cases of typical effort-related ischemia, in which the end-exercise ST-segment and HR responses are indeed quite strongly linear. Moreover, these findings may offer insight into the lower specificity of both the standard and HR-adjusted ST-segment depression criteria in patients who have “nonsignificant” coronary obstructions, in whom exercise-mediated failure to vasodilate (37) could play a role in the development of apparently ischemic ST-segment responses. The findings may also shed light on the relatively incomplete correlation of ST-segment depression criteria with the extent and severity of coronary artery disease, in which varying degrees of exercise-provoked epicardial coronary artery vasoconstriction might be expected to alter the severity of ischemia (37,38).

PERFORMING AN EXERCISE ELECTROCARDIOGRAM

Indications and Contraindications

The most widely accepted indications for ETT are in patients with known or suspected coronary artery disease, in whom ETT is used to determine the likelihood of coronary artery disease, to assess the likelihood of anatomic or functionally severe disease that may be of prognostic importance, to determine functional capacity, and to assess the effects of therapy (39,40). Although indications for the exercise ECG continue to evolve, a joint committee of the American College of Cardiology and American Heart Association has published categories of indications for the ETT based on published literature (39). Their classification includes conditions that are generally accepted as indications for exercise testing, conditions for which the test may be indicated, and conditions for which the ETT is generally considered to have marginal value (Table 48.1). Clinical contraindications to performing diagnostic exercise ECG include acute myocardial infarction, unstable angina before a period of stabilization, uncompensated severe congestive heart failure, advanced atrioventricular (AV) block or life-threatening arrhythmias, acute myocarditis or pericarditis, severe aortic stenosis, severe resting hypertension, and any medical condition that precludes the patient’s walking safely on the treadmill. The presence of left bundle branch block, left ventricular hypertrophy with strain, ventricular preexcitation (Wolf-Parkinson-White syndrome), or permanent ventricular pacing on the ECG is a contraindication to use of the exercise ECG for diagnostic purposes, because of the uncertain diagnostic value of additional ST-segment changes in these settings, but these factors do not preclude use of the ETT to assess exercise performance or to evaluate the risk of arrhythmia, when indicated.

Clearly indicated
Diagnosis of CAD in men with atypical symptoms
Patient has known CAD; assess prognosis and functional capacity
Symptomatic, recurrent, exercise-induced arrhythmias
Patient has experienced an uncomplicated myocardial infarction; evaluate prognosis and functional capacity
Patient has undergone coronary artery revascularization; evaluation recommended
Possibly indicated
Diagnosis of CAD in woman with typical or atypical angina
Diagnosis of CAD in patient taking digitalis
Diagnosis of CAD in patient with complete right bundle branch block
Patient has CAD or heart failure; evaluate functional capacity and response to therapy
Patient has variant angina; evaluation recommended
Patient has known CAD; serial evaluation recommended
Asymptomatic man who is older than 40 yr and in a high-risk occupation, who has two or more risk factors for CAD, or who is sedentary and plans to begin a vigorous exercise program; evaluation recommended
Asymptomatic patient after coronary revascularization; annual evaluation recommended
Selected patients with valvular heart disease; evaluate functional capacity
Probably not indicated
Asymptomatic patient with isolated ventricular ectopy; evaluation recommended
Patient is enrolled in a cardiac rehabilitation program; serial evaluation recommended
Diagnosis of CAD in patient with left bundle branch block or ventricular preexcitation (Wolff-Parkinson-White) syndrome on resting electrocardiography
Asymptomatic man or woman; evaluation recommended
Man or woman with chest pain of noncardiac etiology; evaluation recommended

CAD, coronary artery disease.
Adapted from Schlant RC, Blomqvist CG, Brandenburg RO, et al. Guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Exercise Testing). *J Am Coll Cardiol* 1986;8:725, with the permission of Elsevier Science, Inc.

TABLE 48.1 INDICATIONS FOR EXERCISE ELECTROCARDIOGRAPHY

Patient Preparation and Technique

The American Heart Association has published guidelines for clinical exercise testing laboratories that provide recommendations regarding the performance of clinical ETTs (41). All patients should be instructed not to eat, drink caffeinated beverages, or smoke for at least 3 hours before the test and to wear comfortable clothes and rubber-soled shoes or sneakers. Physicians should instruct patients on whether to continue or discontinue cardioactive medications before the ETT, depending on the indication for the test and the relative safety for the patient of exercising while not receiving medications. In a patient referred for testing, a brief history should be obtained to confirm the indication for the test and to determine cardiac risk factors and whether cardioactive medications are being taken. A directed physical

examination should be performed to exclude the presence of significant valvular or myopathic disease that might preclude exercise evaluation. The risks and benefits of the procedure should be carefully explained, and informed consent should be obtained before the study is begun.

Attention to adequate skin preparation before electrode placement is the most important technical aspect in obtaining high-quality ECG recordings. The areas where electrodes are to be placed should first be cleaned with alcohol to remove surface oils and then abraded with a scouring pad or other rough material to remove the most superficial layer of skin. Abrasion should be performed to reduce resistance at the skin-electrode interface to 5,000 ohms or less. Silver–silver chloride electrodes should be used to produce high-quality tracings.

Before exercise, a supine 12-lead ECG should be obtained with the limb electrodes on the extremities in the normal positions; this tracing should be carefully examined for any signs of active ischemia, for interval myocardial infarction, and for abnormalities that would prohibit performance of the ETT. Limb electrodes should then be shifted to the more proximal positions recommended by Mason and Likar (42) to reduce motion artifact during exercise, and additional ECG tracings should be obtained while the patient is in the supine and standing positions. Notably, because the Mason-Likar modification results in significant changes in QRS axis and amplitudes, the modified lead positions should not be used for interpretation of the resting ECG. Blood pressure should be measured while the patient is in the standing position, the patient should be instructed on how to perform the test, and walking on the treadmill should be demonstrated before the ETT is begun.

A 12-lead ECG should be obtained each minute during exercise, at peak exercise, and every minute during the postexercise recovery period. Rhythm strips and additional 12-lead ECGs should be recorded as needed. Blood pressure should be measured immediately before exercise while the patient is in the standing position, immediately before the end of each stage of exercise, and for each minute of recovery until the blood pressure has returned to baseline. Patient position in the postexercise recovery phase varies between laboratories. Many labs have the patient assume the supine position immediately after peak exercise; this will increase venous return and increase end diastolic volume and may augment ST-segment changes that are present at end-exercise. In our laboratory, we have the patient remain in the upright position, if possible, and have used a cool-down phase of 3 minutes immediately after peak exercise, during which the patient continues to walk at 1.7 miles per hour at a 0% grade. This allows patients a more gradual decrease in HR after exercise and appears to decrease the incidence of postexercise vagally mediated hypotension. In other laboratories, the patient remains in an upright seated position immediately after exercise.

Equipment and Personnel

Although excellent-quality stress tests can be obtained using standard 12-lead cardiographs that conform to the recommendations of the American Heart Association, most ETTs currently performed use equipment specifically designed for exercise testing. These computerized systems combine a cardiograph with a display monitor for continuous rhythm analysis and are capable of controlling treadmills and bicycle ergometers according to specific exercise protocols. The lead systems should be lightweight but strong and well shielded. In case of emergency, the stress lab should be equipped with a defibrillator that has the ability to perform synchronous cardioversion, an Ambu-bag and oxygen supply, and a cardiac arrest cart.

Exercise tests should be performed under the supervision of a physician who has been trained to conduct exercise tests. The degree of supervision required is primarily dependent on the type of patient being tested and can range from direct performance of the test for patients who are at higher risk of complications (e.g., those who have unstable angina after stabilization, who have congestive heart failure, or who have a high risk of arrhythmias) to assigning the performance of the test to an appropriately trained exercise physiologist or a specialist in patients at lower risk. In all cases, a physician should be immediately available during the exercise test.

Treadmill Protocol

Most exercise ECG laboratories in the United States use a treadmill rather than a bicycle ergometer for stress testing. The advantages of the treadmill lie in the greater familiarity of most people in this country with walking and the ability to increase both speed and grade of the treadmill to increase workload. Although a number of excellent treadmill protocols are available for use, by far the most commonly used protocols are the original protocol of Bruce (43) and modifications of this protocol. The Cornell protocol, originally developed in our laboratory to produce the smaller HR increments between stages that are necessary for calculation of the ST/HR slope (44), is a more graded modification of the Bruce protocol that divides each standard stage into 2-minute half-stages. To allow adequate warm-up time and to allow more patients to be able to exercise for a period of time adequate for calculating the ST/HR slope, the protocol begins with a 2-minute stage 0 at 1.7 miles per hour and 0% grade, with a 2-minute stage 0.5 at 1.7 miles per hour at a 5% grade, before reaching the usual starting point of the Bruce protocol (1.7 miles per hour and a 10% grade) (*e*Table 48.1.1).

***e*TABLE 48.1.1** COMPARISON OF STANDARD BRUCE PROTOCOL AND THE CORNELL PROTOCOL

		Bruce protocol		Cornell protocol	
Walking speed (mph)	**Grade (%)**	**Stage**	**Elapsed time (min)**	**Stage**	**Elapsed time (min)**
1.7	0			0	2
1.7	5			0.5	4
1.7	10	1	3	1.0	6
2.1	11			1.5	8
2.5	12	2	6	2.0	10
3.0	13			2.5	12
3.4	14	3	9	3.0	14
3.8	15			3.5	16
4.2	16	4	12	4.0	18
4.6	17			4.5	20
5.0	18	5	15	5.0	22

Lead Systems

The number and types of leads used in exercise ECG vary widely, but with the advent of modern recording devices, most stress laboratories monitor and record at least three leads during the test. Although the use of all 12 conventional leads is becoming more common, almost all of the useful diagnostic ST-segment information from these leads is present in limb leads II, III, and aVF and precordial leads V_3 to V_6. Bipolar lead systems that include one electrode in the V_5 position provide additional diagnostic information; bipolar lead CM_5 is the most sensitive for ST-segment changes (11) and is particularly important in optimal recording of the ST/HR slope (45). Orthogonal XYZ leads or Frank vector leads have also been widely used and analyzed, and there is general agreement that lead X (equivalent to a bipolar lead from right to left axilla) provides the most useful information. This lead set continues to be widely used in Europe. Preliminary results in 245 patients suggest that incorporation of ST-segment depression and elevation in right precordial leads may improve sensitivity of the ETT with no apparent decrease in specificity (45a). Further validation of these findings will be necessary before routine use of right precordial leads can be recommended.

Indications for Test Termination

The general indications for terminating an exercise test are outlined in Table 48.2. In the absence of symptoms or signs that warrant termination of the exercise ECG, patients should exercise with 100% of age-predicted target HR as the goal. Although use of 100% of the age-predicted target HR as an indication for terminating an exercise test may prevent the accurate assessment of functional exercise capacity in patients able to exercise beyond this point, in general, achievement of greater than 85% of target HR provides an adequate level of stress for diagnostic exercise ECG (10). Various equations have been used to relate target HR to age, but the simplest and most commonly used are 220 – age and 200 – (age/2). Although angina alone is not an absolute indication for test termination, progressively worsening typical anginal symptoms are a reason to stop the test, as are any other symptoms that limit further walking on the treadmill.

Achievement of target heart rate (see text for definitions)
Progressive angina
Other limiting symptoms (dyspnea, fatigue, lightheadedness, claudication)
ST-segment elevation >2 mm (in leads without a resting Q wave)
Severe ST-segment depression (see text)
Nonsustained ventricular tachycardia (three or more sequential ventricular premature contractions)
New onset of atrial fibrillation, atrial flutter, or of a supraventricular tachycardia
Development of second- or third-degree atrioventricular block
Development of a new left bundle branch block
A 10-mm Hg drop in systolic blood pressure
Extreme elevation of systolic or diastolic blood pressure
A progressive drop in heart rate with continued exercise
Equipment problems, such as loss of electrocardiographic signal

TABLE 48.2 GENERAL INDICATIONS FOR TERMINATING AN EXERCISE TEST

ST-segment elevation in the absence of Q waves is consistent with possible transmural injury and a reason for immediate termination of the ETT. In contrast, ST-segment depression alone is rarely an indication for cessation of the exercise test. Indeed, only marked ST depression (>3 mm of additional ST depression compared with baseline) would warrant test termination in the absence of other findings. New sustained tachyarrhythmias are clearly an indication for stopping the test, as is the development of second- or third-degree heart block. Routine diagnostic stress tests should also be halted if nonsustained ventricular tachycardia is seen, unless the patient is undergoing the test expressly for evaluation of the possibility of exercise-induced ventricular tachycardia with the extra precautions taken of having a second physician in attendance, intravenous access, and additional leads to a synchronous cardiodefibrillator. Other relative indications for terminating the ETT include development of a new left bundle branch block that precludes further evaluation of ST-segment changes, a 10–mm Hg or greater drop in systolic blood pressure, an extreme elevation of systolic or diastolic blood pressure, a progressive decrease in HR with exercise, or significant equipment problems, such as loss of the ECG signal.

Other Applications of Stress Testing

Performance of an exercise test for indications other than routine assessment of the presence or severity of coronary artery disease or evaluation of functional capacity deserves comment. After uncomplicated myocardial infarction, exercise testing is frequently performed to assess functional capacity and to help stratify risk (46). When exercise testing is performed early after myocardial infarction (i.e., before discharge or within 2 to 3 weeks of the infarction), submaximal symptom-limited testing is recommended (40), to a target HR of 140 beats/min or a metabolic equivalent of 7 in patients younger than 40 years and to a maximum HR of 130 beats/min or a metabolic equivalent of 5 in patients 40 years and older. A full symptom-limited maximal test is appropriate more than 3 weeks after myocardial infarction. Exercise ECGs are also commonly performed to evaluate the risk of exercise-induced tachyarrhythmias in patients who have exercise-related presyncope or syncope. Because of the risk of inducing a hemodynamically significant arrhythmia in these settings, the ETT should be performed with at least one (and preferably two) physicians present, with intravenous access, and with leads connected to a defibrillator.

Exercise ECG is also frequently used after percutaneous transluminal angioplasty to stratify risk and aid in the assessment of restenosis and appears to be well tolerated (47,48). However, reports of acute stent thrombosis associated with exercise testing soon after stent placement (49) raise the question of whether exercise testing should be performed in the immediate post-stent period. Until further data become available, caution should be used in the performance of exercise testing soon after the placement of intracoronary stents, with strong consideration given to the use of pharmacologic stress if early noninvasive assessment is indicated (49).

INTERPRETATION OF THE EXERCISE ELECTROCARDIOGRAM

ST-Segment Depression Criteria

To fully appreciate the ST-segment excursions that occur during the transient ischemia associated with exercise in patients with coronary artery disease requires some understanding of the ST-segment changes that occur during exercise in healthy subjects (Fig. 48.1). At baseline, most healthy subjects will have ST segments that are either at the isoelectric level or slightly elevated as a result of physiologic early repolarization of the J-point. As HR increases, progressive J-point or junctional depression occurs, with resultant rapidly upsloping ST segment (50,51). After exercise is terminated, the J-point depression tends to resolve quickly (usually within the first 2 minutes), as does the rapidly upsloping ST-segment depression. In contrast, the ST-segment depression associated with subendocardial ischemia is more likely to be horizontal or downsloping but may also be slowly upsloping (Fig. 48.2) (10,51). With progressive exercise, increasing HR, and the resulting increasing myocardial oxygen demand, the magnitude of ischemic ST-segment depression will increase, and the ST depression is more likely to be horizontal or downsloping. Placing the patient in the supine position immediately after exercise may accentuate ischemic ST-segment depression. However, ischemic ST depression may occur during exercise only, emphasizing the importance of adequate skin preparation before electrode placement. In a small percentage of cases, ischemic ST-segment depression will be seen during recovery only (52), especially when the patient is placed in the supine position, but isolated recovery-phase ischemic ST-segment depression is less common when patients remain in the upright position after exercise. In rare instances of exercise-induced transmural ischemia or injury, ST-segment elevation similar to that seen during the acute injury of myocardial infarction may also occur.

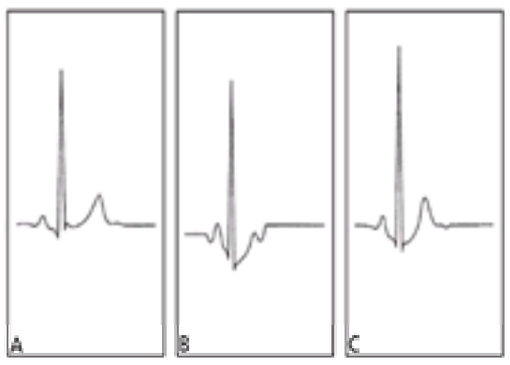


FIGURE 48.1 Progression of ST-segment changes that occur in healthy subjects from isoelectric at baseline **(A)** to J-point depression with rapidly upsloping ST-segment depression at peak exercise **(B)** and rapid resolution of the ST changes in recovery **(C)**.

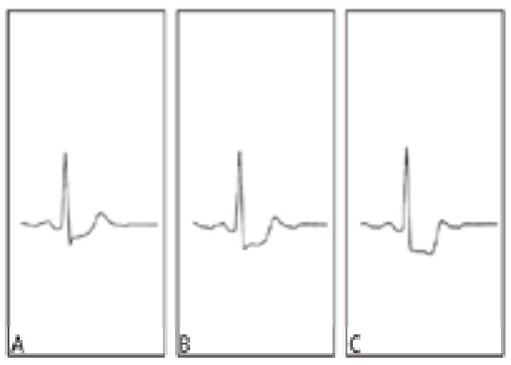


FIGURE 48.2 Comparison of the different patterns of ST depression. **A:** Slowly upsloping ST-segment depression. **B:** Horizontal ST-segment depression. **C:** Downsloping ST-segment depression.

Differences in the patterns of ST-segment depression in healthy subjects and in patients with coronary artery disease highlight the importance of choosing the correct point on the ST segment at which to measure the magnitude of ST-segment depression (15,50,51). Recommendations for the measurement of ST-segment depression have varied from the J-point (53) to between 60 and 80 ms after the J-point (10,39). Performance of standard ST-segment depression criteria varies with the timing of ST-segment measurement relative to the J-point, but measurements made at 60 ms after the J-point have generally outperformed J-point measurements for the identification of coronary artery disease (15,50,51). We have previously found that performance characteristics of HR-adjusted ST depression criteria are optimized when ST-segment depression is measured at 60 ms after the J-point, whereas use of J-point depression reduces performance of HR-adjusted criteria to the level of standard criteria (51). Thus, we currently recommend that ST-segment depression be measured at 60 ms after the J-point (45).

The actual measurement of ST-segment deviation on the exercise ECG is most accurately performed by the computerized systems that are widely in use today, but accurate ST-segment measurements can be performed by hand if careful attention is paid to proper selection of the correct measurement points. In measurement of

ST deviation, the PQ segment is usually chosen as the isoelectric point, which some computerized systems choose by scanning before the QRS complex for the 10-ms interval with the lowest slope, and ST-segment depression should be measured at 60 ms after the J-point. Computer systems are capable of accurately measuring ST deviation to the nearest 10 µV, and careful hand measurements using calipers or a magnifying graticule can readily achieve a precision of 25 µV for ST measurements (54). However, when computer measurements are used, it is important to recognize that motion artifact, electrical interference, and changes in QRS or atrioventricular conduction can interfere with PQ segment and J-point determinations and introduce error into the computerized ST measurements. Therefore, physicians should routinely compare the raw ECG signal with the computer-averaged or median beats used to perform ST measurements before accepting the computer measurements as accurate.

Standard Test Criteria

Assessment of the magnitude and configuration of ST-segment depression on the exercise ECG provides the basis for the standard ST depression criteria that are commonly in use. A positive test result based on standard ST depression criteria has been routinely defined as the achievement of 0.1 mV (100 µV) or more of horizontal or downsloping ST-segment depression at peak exercise or in early recovery compared with the baseline pre-exercise ECG (10,39,40). However, as is discussed later, these criteria have only limited test sensitivity for the presence of coronary artery disease and variable performance for identification of anatomically severe disease and for risk stratification (10,11,12,13,14,15 and 16,20,21,22 and 23,45,55). Additional factors that can affect the likelihood that coronary artery disease or multivessel disease will be detected in the presence of traditional criteria include the magnitude, time of onset, duration, and number of leads with ST depression. Although inclusion of upsloping ST depression of greater than or equal to 0.1 mV or 0.15 mV has been suggested as an additional component of standard criteria, to increase sensitivity for the detection of coronary artery disease (56,57), the incorporation of upsloping ST depression also lowers test specificity (10,20,55,56). As a consequence, we consider the presence of upsloping ST-segment depression of 1 mm (0.1 mV) or more to be an “equivocal” test response by standard criteria.

Heart Rate–Adjusted Criteria

HR adjustment of the magnitude of ST-segment depression is a rational, physiologic approach to interpretation of the ETT. Two related but distinct methods of HR adjustment of ST-segment depression seen during exercise have evolved: the linear regression–based ST/HR slope and the simpler ST/HR index. The ST/HR slope method was originally developed in England (58) and Hungary (59) and has subsequently been applied to treadmill exercise, using computerized ST-segment measurements, and further refined in our laboratory at Cornell (20,21,22 and 23,25,44,45,51,54). The ST/HR slope is calculated from the maximal rate of change of ST depression relative to HR during the period of active ischemia that accompanies end-exercise (Fig. 48.3). The ST/HR index, originally described by Detrano and coworkers (60), represents the average change of ST depression relative to HR change over the entire course of exercise, which underestimates the maximal ST/HR slope because it includes a large change in HR before any ischemia occurs (Fig. 48.3). Both of these methods specifically do not consider any ST depression that occurs during the postexercise recovery period.

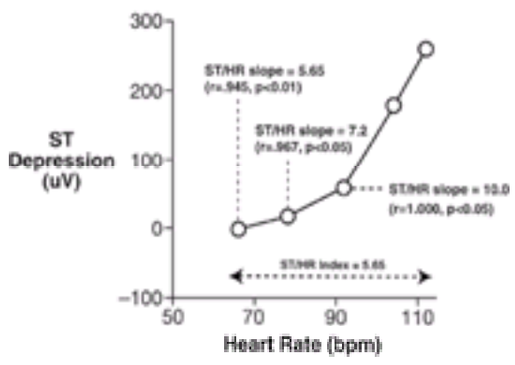


FIGURE 48.3 Calculation of the ST/heart rate (HR) slope. Progressive ST-segment depression in lead CM5 (shown as a positive magnitude on the vertical axis) is plotted against exercise HR in a patient with three-vessel coronary artery disease. This case illustrates the linear relation of ST-segment depression to HR as peak exercise is approached. As a result, the slope of the line relating the final three data points by linear regression is higher than the slope of lines incorporating earlier data points. When more than one linear correlation is statistically significant, the greatest value (in this case, 10.0) is taken as the test result for that patient. Note that the value obtained by simply dividing the total change in ST-segment depression by the total change in HR (the ST/HR index) markedly underestimates the true ST/HR slope. (Reprinted from Okin PM, Kligfield P. Heart rate adjustment of ST depression and performance of the exercise electrocardiogram: a critical evaluation. *J Am Coll Cardiol* 1995;25:1726, with the permission of Elsevier Science, Inc.)

Calculations of the ST/HR slope and ST/HR index are illustrated in Figure 48.3. Measurement of the ST/HR slope is determined by linear regression analysis to relate the measured amount of ST-segment depression in each lead to the HR at the end of each stage of exercise and at peak exercise. Because the maximal rather than the average rate of change is sought, linear regression analysis is performed from the end of exercise to progressively earlier intermediate stage data points, using HR as the independent variable and ST depression as the dependent variable. The highest ST/HR slope with a statistically significant correlation coefficient is taken as the test finding for that lead (in µV per beat per minute). After calculation of the maximal ST/HR slope for each lead, the highest ST/HR slope among all the leads (including bipolar lead CM_5, but excluding aVR, aVL, and V_1) is taken as the final test result (45,54). The ST/HR index is derived by dividing the maximal change in ST-segment depression during exercise by the total change in HR from rest to peak effort (45,60). Initial studies from our laboratory (20) established partition values, with specificities of 95% in healthy subjects, of more than 2.40 µV per beat per minute for the ST/HR slope and more than 1.60 µV per beat per minute for the ST/HR index for the identification of coronary artery disease. Partition values of more than 6.0 µV per beat per minute (ST/HR slope) and more than 3.3 µV per beat per minute (ST/HR index) have been established for the identification of three-vessel, left main, and functionally severe coronary artery disease (45).

Analysis of the behavior of ST-segment depression as a function of HR during both exercise and recovery using the rate-recovery loop (21,22,45) can elicit additional diagnostic and prognostic information from the ETT. Physiologic correlates of rate-recovery loop patterns can be found in the initial observations of Detry and Bruce and associates (61,62), which compare myocardial ischemia during exercise and recovery. They found a close linear relation of ST-segment depression during exercise to myocardial oxygen demand, as reflected by the tension-time index, among patients with coronary artery disease. During recovery, however, this relation was nonlinear, with similar ST-segment depressions observed at lower tension-time indexes than those seen during exercise. Additional support for this approach is found in reports of cases of subendocardial ischemia that continue into the recovery period with persistent ST-segment depression that remains greater relative to HR during early recovery than during the development of ischemia (63,64). Rate-recovery loops are constructed by plotting ST-segment deviation, with reference to changing HR, throughout treadmill exercise and recovery (Fig. 48.4). Healthy subjects typically exhibit a clockwise loop of ST-segment depression as a function of HR during exercise and recovery, whereas patients with coronary artery disease commonly exhibit a counterclockwise loop. Quantification of the degree of abnormal rate-recovery loop behavior by integrating the difference in ST depression between exercise and recovery phases from peak-exercise to the end of 3 minutes of the recovery phase can further stratify the presence and severity of coronary artery disease (23a).

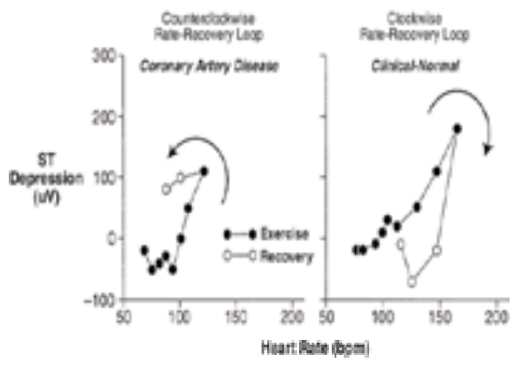


FIGURE 48.4 ST-segment deviation as a function of heart rate during exercise and recovery, with ST-segment depression shown in the upward direction and ST-segment elevation shown in the downward direction. Typical rate-recovery loops are shown for a clinically normal subject (*right*) and a patient with coronary artery disease (*left*). Despite a greater magnitude of ST-segment depression at peak exercise in the clinically normal subject, there is a clockwise pattern of ST-segment depression relative to heart rate during recovery; the patient with coronary artery disease has the opposite, counterclockwise pattern. (Reprinted from Okin PM, Kligfield P. Heart rate adjustment of ST depression and performance of the exercise electrocardiogram: A critical evaluation. *J Am Coll Cardiol* 1995;25:1726, with permission of Elsevier Science, Inc.)

Treadmill Exercise Scores

Numerous investigators have used either multivariate analyses or Bayesian theory to produce clinical scores in an attempt to improve the accuracy of the ETT (16,26,65,66,67 and 68). However, many of these methods incorporated clinical and catheterization data that make the contribution of the exercise test unclear. Two methods that have used data only from the ETT are the Hollenberg exercise score (16) and the Duke treadmill score (Table 48.3) (26,65). The Hollenberg exercise score quantifies the ECG response to exercise by measuring the cumulative area of ST depression and ST slope in leads V_5 and aVF during exercise and recovery, which is then normalized for R-wave height and workload (exercise duration and HR). The Duke treadmill score is a simple quantitative score, derived using a Cox regression model in a training sample of more than 1,400 patients, that includes exercise duration and weighted measures of ST-segment deviation and an angina score. The prognostic value of this score has been validated for ambulatory patients (26) and for patients undergoing angiography (65).

Hollenberg exercise score (16)
$\text{Exercise score} = \dfrac{\text{area (J-point + ST slope) } V_5 \times 12 \cdot RV_5 + \text{area (J-point + ST slope) aVF}}{\text{exercise duration} \times \text{fraction of maximal predicted heart rate}}$
(where exercise duration is in min and R-wave amplitudes are in mm)
Duke treadmill score (26)
Treadmill score = exercise duration − (5 × ST deviation) − (4 × TM angina index)
(where exercise duration is in min; ST deviation is in mm; and TM (treadmill) angina index = 0 for no angina, 1 for nonlimiting angina, or 2 for exercise-limiting angina)

TABLE 48.3 TREADMILL EXERCISE SCORES

ST Integral

Originally proposed by Sheffield and colleagues (14), the time-voltage integral of ST-segment depression (the ST integral) examines the total area of repolarization abnormality from the J-point to a terminal point late in the ST segment at which the ST segment crosses the isoelectric baseline. This method has primarily been applied in a series of population-based studies to assess risk (69,70), but the need for computer measurements and the lower accuracy of this method relative to standard ST-segment depression criteria (71) have limited its general applicability.

QRS Complex Criteria

An increase in R-wave amplitude that is seem during exercise has been proposed as a possible marker of myocardial ischemia and left ventricular dysfunction in patients with coronary artery disease (72). However, subsequent studies have demonstrated that R-wave amplitude changes associated with exercise are highly correlated with HR and that much of the discrimination between healthy subjects and patients with coronary artery disease thought to be due to R-wave amplitude changes actually reflects differences in the HRs achieved during exercise (73).

Changes in QRS complex duration and in intra-QRS amplitudes have also been suggested as possible markers of ischemia (27,74). Michaelides and company (27) demonstrated that QRS duration was more likely to shorten during exercise in healthy subjects than in patients with coronary artery disease, in whom, on average, QRS duration was more likely to increase. They further found that the magnitude of QRS duration prolongation in patients who had coronary artery disease was directly related to the number of obstructed coronary arteries and to the number of segmental wall motion abnormalities. Investigation of a more experimental nature, using signal-averaging of high-frequency ECGs during myocardial ischemia produced by balloon-catheter inflation in the catheterization laboratory, has demonstrated a reversible reduction in mid-QRS high-frequency signal strength during ischemia, with a sensitivity of 88% for acute coronary occlusion, which is significantly greater than the 71% sensitivity of standard ST elevation changes (74). These findings offer promise for increased use of QRS complex changes during exercise to improve the recognition of myocardial ischemia, but further work using computer measurements based on digital data recorded at high acquisition rates (500 to 1,000 Hz) during exercise will be necessary to clarify the role of these approaches in the diagnosis of coronary artery disease.

Chronotropic Response to Exercise

Independent of evidence of myocardial ischemia, an attenuated HR response to exercise, a measure of chronotropic incompetence, has been associated with the presence and severity of coronary artery disease (25,75) and has been shown to be a predictor of both coronary heart disease events and of total mortality (24,76,76a). Different measures of chronotropic response to exercise have been used to assess the adequacy of HR response, including simple measures such as peak exercise HR, percentage of target HR achieved, and change in HR during exercise. In addition, simple and HR-adjusted ST-segment depression criteria can be corrected for an attenuated HR response to exercise by adjustment of these measurements for the fraction of HR reserve achieved during exercise, which is the change in HR during exercise divided by the difference between 100% of age-predicted target HR and the HR at standing rest (25). A more complex measure is the chronotropic response index (24,25), which adjusts the fraction of HR reserve achieved for workload as measured by the fraction of metabolic reserve. HR changes during the recovery phase of the exercise test have also been demonstrated to provide prognostic information. A delayed decrease in HR after exercise, or abnormal HR recovery, predicts all-cause mortality among healthy adults and in patients referred for exercise testing, independent of evidence of inducible ischemia and beyond the predictive value of exercise-phase changes in HR (25a,76b,76c).

Blood Pressure Changes

Among patients with coronary artery disease, failure to increase systolic blood pressure to 120 mm Hg or higher and a sustained decrease in systolic blood pressure of 10 mm Hg or more both have been associated with an increased likelihood of anatomically extensive disease. However, other conditions can produce a blunted blood pressure response to exercise, such as obstruction of left ventricular outflow, hypovolemia, left or right ventricular dysfunction, cardioactive medications, and vigorous exercise. In contrast, although an exaggerated blood pressure response to exercise has been clearly associated with an increased risk of developing hypertension at rest and with a greater prevalence of left ventricular hypertrophy (77), the prevalence of coronary artery disease appears to be similar among patients who do and those who do not have exercise hypertension (210 mm Hg or higher in men and 190 mm Hg or higher in women) (78). Moreover, an exaggerated systolic blood pressure response to exercise appears to be associated with a lower likelihood of anatomically severe disease and with a lower 2-year overall mortality rate (78).

In the postexercise recovery phase, a progressive decline in systolic blood pressure is usually seen. Failure of systolic blood pressure to decline normally during early recovery, as measured by an increased ratio (greater than 0.90) of systolic blood pressure during the first 3 minutes of recovery to peak exercise systolic blood pressure, has been reported to be useful in the diagnosis of coronary artery disease (79). However, an increased ratio is also seen in patients who have hypertension and no significant coronary obstructions (79), and additional studies have not substantiated a high sensitivity of this ratio for coronary artery disease (80). Further study of the utility of blood pressure changes in improving the accuracy of the diagnosis of coronary artery disease by ETT is necessary before the routine application of these criteria can be recommended.

Rhythm and Conduction Changes

The ETT can be used to evaluate the risk for significant abnormalities of cardiac rhythm and conduction under appropriate conditions. Exercise-induced ventricular premature contractions (VPCs) are common, increase in prevalence with age, are more frequent, and may be associated with a somewhat worse prognosis in patients with coronary artery disease (81). In contrast, neither the abolition of VPCs with increasing exercise nor development of VPCs only during the postexercise recovery period appear to be of clinical significance, and the appearance of nonsustained ventricular tachycardia during exercise testing does not appear to convey an increased short-term risk (82). The development of sustained ventricular tachycardia during exercise testing in patients who have coronary artery disease is most commonly the result of myocardial ischemia and can be prevented by treatment of the underlying ischemia. Exercise testing can play an important adjunctive role to electrophysiologic studies in the evaluation of patients with exercise-induced ventricular tachycardia in whom the presumptive mechanisms are after-depolarizations or enhanced automaticity and who have no obvious structural heart disease. A left bundle branch block morphology and termination of ventricular tachycardia with vagal maneuvers or adenosine strongly suggest that delayed after-depolarizations are the cause of the tachycardia. Exercise-induced supraventricular arrhythmias occur in

4% to 8% of patients, increase in frequency with age, and do not reflect the presence of coronary artery disease.

Changes in AV and intraventricular conduction may occur during exercise. Rarely, exercise testing can elicit second-degree AV block in patients with exertional fatigue or dyspnea, but more commonly, AV conduction is enhanced with exercise as a result of increased sympathetic tone and increased circulating catecholamines. Exercise-induced, rate-related development of right or left bundle branch block is relatively rare; it is not associated with an increased incidence of underlying coronary artery disease in younger subjects (younger than 40 years), but it appears to be associated with coronary artery disease in older subjects. When right bundle branch block is seen on resting ECG, exercise-induced ST-segment depression in leads V_1 to V_4 commonly occurs and is not diagnostic for coronary artery disease; ST-segment depression in the inferior leads and leads V_5 and V_6 is consistent with ischemia. ST-segment changes in the presence of a left bundle branch block are best considered nondiagnostic for coronary artery disease.

The presence of preexcitation on the ECG invalidates the use of ST-segment depression criteria for the diagnosis of coronary artery disease, because abnormal repolarization frequently is associated with aberrant depolarization accompanying anterograde conduction over an accessory pathway. Exercise ECG may play a useful adjunctive role in the assessment of accessory pathway physiology in patients in whom preexcitation is seen at rest. The abrupt disappearance of a delta wave during exercise reflects a longer effective refractory period during anterograde conduction over the bypass tract and may be associated with a lower risk of ventricular fibrillation. Although a more gradual disappearance of preexcitation can occur when the enhancement in AV nodal conduction that accompanies increased sympathetic stimulation is greater than the increased conduction in the accessory pathway, this finding does not exclude the possibility that a shortening of an accessory pathway refractory period may be present that is associated with an increased risk of ventricular fibrillation when atrial fibrillation is manifest. Therefore, caution should be used before therapeutic decisions involving patients who have preexcitation are made solely on the basis of the results of exercise evaluation, and electrophysiologic testing should be used as indicated (see Chapter 62).

Drugs and Hormonal Effects

Cardioactive drugs and sex hormones can significantly affect interpretation of the ETT. Drugs that blunt the HR and blood pressure response to exercise, such as beta-blockers, diltiazem, and verapamil, may delay or diminish ST-segment depression during exercise and reduce the sensitivity of standard test criteria. Although the sensitivity of HR-adjusted criteria appears to be less affected by these medications (45), failure to produce ischemia during exercise that is the result of medication limits the diagnostic accuracy of any noninvasive modality. Conversely, digitalis preparations can produce ST-segment changes in the absence of heart disease, significantly decreasing the specificity of ETT criteria that are based on ST-segment changes. Similarly, both endogenous and exogenous estrogens and progesterones have been implicated in abnormal ST-segment responses that are seen in healthy women (83,84). Moreover, the administration of estrogens can increase the magnitude of ST-segment depression in men and women with ischemic disease (23,83,84), and consideration of estrogen status significantly improves the overall accuracy of the ETT in women (85). Although numerous investigators have reported lower accuracy when standard ST-segment depression criteria are used for women than when these criteria are used for men, whether these differences are better explained by lower test sensitivity or lower specificity in women remains controversial (23). Although the mechanisms of ST-segment changes in response to cyclic hormonal variations remain to be determined (23,83,84), notably, both the ST/HR index and ST/HR slope provide diagnostic accuracy that is similar in men and women, despite these potential limitations (23).

APPLICATIONS AND TEST PERFORMANCE OF THE EXERCISE ELECTROCARDIOGRAM

Identification of Coronary Artery Disease

The diagnosis of coronary artery disease remains the most frequent indication for exercise testing with standard ST depression criteria; achievement of at least 0.1 mV of additional horizontal or downsloping ST-segment depression is the most common diagnostic criterion. However, utility of the standard ETT for this purpose has been limited by the relatively low sensitivity and poor predictive accuracy of standard criteria (10,11,20,45,55). Although the exact performance of any test is difficult to determine because of the influence of study design, population selection, and referral bias (45,55,86,87 and 88), a metaanalysis assessing the sensitivity and specificity of the ETT in 24,074 patients evaluated in 147 consecutively published reports provides some important insights into the performance of standard ST depression criteria (55). Using 50% luminal obstruction at angiography as the diagnostic standard for coronary artery disease, the weighted mean sensitivity was 68% (range, 23% to 100%), and mean specificity was 77% (range, 17% to 100%); when upsloping ST depression was considered to be abnormal, test specificity was significantly reduced (from 80% to 73%), but sensitivity increased by a similar amount (8%). Predictably, use of these criteria for the identification of multivessel disease or left-main or triple-vessel disease was associated with higher sensitivity (mean, 81% and 86%, respectively) but also was associated with lower test specificity (mean, 66% and 53%) (89).

The results of this metaanalysis highlight the effects that differences in patient population can have on the sensitivity and specificity of standard ST depression criteria. Whereas sensitivity has been found to vary in accordance with the severity of coronary artery disease in the study population, specificity varies in accordance with the admixture of patients who have noncoronary heart disease that can produce ST-segment changes in the study population; both measures of test performance are affected by the degree of workup or referral bias (18,19,66,86,87 and 88). The combined effects of population selection are reflected in the results of one study from our laboratory (88), in which the 54% sensitivity of standard ST depression criteria when used to diagnose patients with clinical angina who had not undergone angiography was significantly lower than the 70% sensitivity seen when the criteria were used to diagnose patients with disease defined by angiography. Similar effects of population selection were observed on standard test specificity: the 97% specificity seen when the test was used for clinically normal subjects was significantly greater than the 74% specificity seen when the test was used for patients referred to angiography and found to have no significant coronary luminal obstruction greater than 50% (88).

Although some controversy persists over the value of HR-adjusted criteria (see the section Controversies and Personal Perspectives), the great majority of published studies that have adhered to proscribed requirements for ST-segment depression measurements have demonstrated that the ST/HR slope and the simple ST/HR index improve performance of the ETT as a tool for recognizing coronary artery disease. Early studies of the ST/HR slope by Elamin and colleagues (58), using an individually tailored bicycle ergometry protocol, demonstrated 100% specificity and 100% sensitivity for the detection of coronary artery disease; however, subsequent investigators have failed to reproduce this perfect test performance. Initial studies from our laboratory, using computerized ST measurements at 60 ms after the J-point and the Cornell modification of the Bruce protocol, derived criteria for the ST/HR slope and the ST/HR index that yielded a 95% specificity when used for clinically normal subjects, similar to the specificity of standard test criteria used for the same subjects (20). Test sensitivity of these criteria in separate groups of patients with clinical angina and with angiographically proven coronary artery disease were 94% and 95%, respectively, for the ST/HR slope and 88% and 93%, respectively, for the ST/HR index, all of which are significantly greater than the 68% sensitivity of use of standard ST-segment depression criteria for these populations (20). Moreover, these new criteria maintained similar specificity to standard criteria among patients in whom no significant obstruction was demonstrated by angiography (ST/HR slope, 72%; ST/HR index, 61%; standard criteria, 56%). Compared with standard test criteria, rate-recovery loops have demonstrated similarly high specificity in healthy subjects (95% vs. 93%), similar specificity in patients in whom no significant coronary obstruction was demonstrated by angiography (71% vs. 71%), and better sensitivity for the detection of coronary artery disease (93% vs. 74%) (21). Additional studies of the ST/HR slope from our laboratory and from investigators in Japan, Europe, and the United States have confirmed that the performance of this method in detecting coronary artery disease is superior (45). Improved accuracy for the detection of coronary artery disease has also been found in association with the simple ST/HR index in most but not all studies from other centers (45,53,60,68).

Detection of Anatomically and Functionally Severe Coronary Artery Disease

The poorer prognosis of patients with multivessel, and in particular three-vessel or left-main, coronary artery disease has made recognition of these patients a clinical priority. A metaanalysis of the cases of 12,030 patients that involved 60 consecutively published reports, comparing the ETT with findings at coronary angiography, found a weighted mean sensitivity of 81% (range, 40% to 100%) and mean specificity of 66% (range, 17% to 100%) for multivessel disease and mean sensitivity of 86% and specificity of 53% for three-vessel or left-main disease (89). In this metaanalysis, use of HR adjustment of ST depression was independently associated with improved specificity of the ETT for identification of three-vessel or left-main coronary artery disease (89). Factors that have been found to improve the performance of standard test criteria for these purposes include use of 2 mm or greater horizontal or downsloping ST-segment depression, early test positivity (Bruce stage 2 or earlier), and persistence of test positivity 8 minutes or more into recovery, all of which improve test specificity. In addition, both the Duke treadmill score and a consensus score that includes clinical variables have been shown to provide useful information for the recognition of anatomically severe coronary artery disease (89a,89b).

Studies from multiple investigators have demonstrated that both the ST/HR slope and the ST/HR index improve performance of the ETT for the identification of multivessel coronary artery disease. In early studies from our laboratory, standard test criteria identified multivessel coronary artery disease with a sensitivity of 76%, which is significantly lower than the 97% sensitivity associated with an ST/HR slope greater than 2.4 and than the 94% sensitivity associated with an ST/HR index greater than 1.6, with similar differences in test sensitivity for three-vessel disease (20). Similarly, when criteria that are specifically designed for the identification of three-vessel disease are used, the ST/HR slope significantly improves performance of the ETT for diagnosis of anatomically or functionally severe coronary artery disease, compared with standard test criteria. An ST/HR slope of more than 6.0 µV per beat per minute significantly improves ETT identification of three-vessel or left-main coronary artery disease and has been shown to be more accurate than standard criteria for assessment of the anatomic extent of coronary obstruction, as alternatively defined by high Duke jeopardy scores or Gensini scores (45,90,91 and 92). Further, as a functional consequence of extensive coronary obstruction, high ST/HR slopes have been found to correlate with large decreases in left ventricular ejection fraction during exercise and with abnormal results of thallium imaging

(91,92). However, the simple ST/HR index does not appear to consistently improve performance of the exercise ECG for identification of extensive coronary artery disease, compared with standard test criteria (45).

Risk Stratification and Assessment of Prognosis

Although the value of screening asymptomatic subjects for coronary artery disease remains controversial because of the poor predictive value of positive test findings in populations in which the prevalences of disease is low (18,19,22,93,94), numerous studies have documented the ability of the ETT to stratify risk in low-risk populations (12,13,22,69,70,95). An ischemic ST-segment response to exercise as judged by standard criteria was a significant predictor of cardiac morbidity and mortality in the overall population of the Seattle Heart Watch (13) and in a referred group of clinically normal male Air Force personnel (12). However, standard test criteria did not significantly concentrate risk among the large subset of asymptomatic healthy subjects in Seattle (13), did not concentrate risk in a nonreferred subset of healthy pilots and astronauts undergoing exercise testing as part of routine preflight assessment (12), was not predictive of coronary events in more than 3,000 asymptomatic men and women in the Framingham Offspring Study (Fig. 48.5) (22), and was not predictive of coronary heart disease mortality in 5,940 asymptomatic men from the usual-care arm of the Multiple Risk Factor Intervention Trial (MRFIT) (Fig. 48.6) (95).

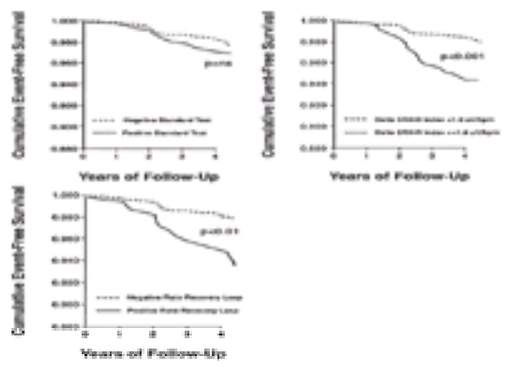


FIGURE 48.5 Kaplan-Meier plots of survival free of angina, nonfatal myocardial infarction, or coronary heart disease death according to exercise test criteria in the Framingham Offspring Study. Both the ST/heart rate (HR) index and the rate-recovery loop were predictive of outcome, with significantly lower event-free survival rates among subjects with positive than those with negative test outcomes. In contrast, no significant difference was seen in event-free survival between subjects with positive and with negative standard exercise tests, as defined according to traditional electrocardiographic criteria. ns, not significant. (Reprinted from Okin PM, Anderson KM, Levy D, et al. Heart rate adjustment of exercise-induced ST segment depression: improved risk stratification in the Framingham Offspring Study. *Circulation* 1991;83:866, with the permission of the American Heart Association.)

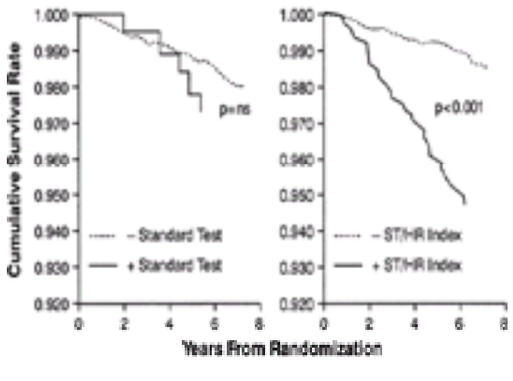


FIGURE 48.6 Kaplan-Meier plots of cumulative survival according to exercise test criteria in 5,940 asymptomatic men from the usual-care arm of the Multiple Risk Factor Intervention Trial. An abnormal ST/heart rate (HR) index identified a group of men with a significantly lower 7-year survival rate. In contrast, no significant difference was seen in survival rates between men with positive and with negative standard exercise test responses. ns, not significant. (Reprinted from Okin PM, Grandits G, Rautaharju P, et al. Prognostic value of heart rate adjustment of exercise-induced ST segment depression in the Multiple Risk Factor Intervention Trial. *J Am Coll Cardiol* 1996;27:1437, with the permission of Elsevier Science, Inc.)

In contrast, an ST/HR index greater than 1.60 µV per beat per minute significantly concentrated the risk of primarily nonfatal coronary events in asymptomatic men and women in the Framingham Offspring Study (Fig. 48.5) and stratified the risk of coronary heart disease death in MRFIT (Fig. 48.6) (22,95). In both studies, risk concentration by the ST/HR index was independent of age and additional cardiac risk factors and, in the Framingham Offspring Study, was similar in men and in women. An ST/HR index of more than 3.3 µV per beat per minute, previously demonstrated to be associated with anatomically extensive coronary artery disease (90,92), was associated with a nearly tenfold increase in risk of coronary death in MRFIT (95). In addition, an abnormal rate-recovery loop, both alone and in combination with the ST/HR index, and a blunted HR response to exercise, independent of ST depression findings, improved risk stratification by the ETT in the Framingham Offspring Trial (22,24). Perhaps most important, the decreased 7-year coronary mortality associated with an abnormal ST/HR index that was seen in the special-intervention group of MRFIT, compared with that in the usual-care group, suggests that this methodology can be used to identify men who are at increased risk of coronary death and will benefit from an aggressive risk factor–reduction program (95a).

The ETT can also be used to stratify risk among symptomatic patients who have known or presumed coronary artery disease (26,65,76,76c,96). In 4,083 medically treated patients from the Coronary Artery Survival Study registry, a high-risk subset with an annual mortality rate greater than 5% was identified when patients had positive results of standard testing and an exercise workload less than Bruce stage 1; a low-risk subset with an annual mortality rate less than 1% was identified by the ability to exercise to at least stage 3 of the Bruce protocol with a negative ST-segment response (96). The Duke treadmill exercise score (26,65,76c,96a) provides additional risk stratification to supplement that provided by ST-segment depression criteria among inpatients who have undergone angiography, outpatients who have suspected coronary artery disease, and patients who have resting ST-T–wave abnormalities. Further, among 1,300 symptomatic patients in whom coronary artery disease was demonstrated by angiography, the ST/HR index improved risk stratification by the Duke treadmill score and clinical variables and was an independent predictor of cardiac death in both men and women (97).

The prognostic value of standard ST-segment depression criteria after myocardial infarction has been well studied. In a metaanalysis of post–myocardial infarction exercise testing, Froelicher and coauthors (46) found exercise-induced ST-segment depression, poor effort tolerance, and an abnormal systolic blood pressure response to exercise to be associated with an increased risk of adverse outcome. The prognostic value of ST-segment changes after myocardial infarction in an era in which thrombolytic medications are available remains uncertain, because outcomes are similar in patients with and those without ischemic ST-segment changes (98). However, an inability to perform a predischarge low-level exercise test appears to be associated with a poor prognosis after myocardial infarction, independent of the use of thrombolytic agents (46,98). Independent of ECG, thallium imaging, or echocardiographic evidence of myocardial ischemia, attenuated HR changes, both during exercise and in the postexercise recovery phase, have been demonstrated to stratify the risk of all-cause mortality in asymptomatic subjects and in patients undergoing diagnostic exercise testing (24,24a,25a,76a,76b and 76c). An impaired chronotropic response to exercise, defined as failure to achieve 85% of target HR or a low chronotropic index, is associated with a 1.8- to 2.2-fold increased risk of all-cause mortality, after the analysis has been adjusted for confounding variables (24a). A delayed decrease in HR during the first minute of recovery provides similar risk concentration for overall mortality, even when exercise-phase HR responses were taken into account (25a).

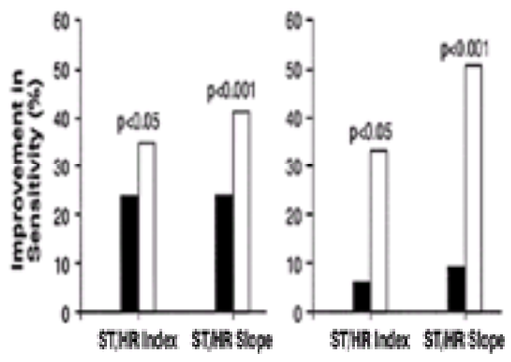
Test Performance in Women

Among the problems associated with use of the standard ETT is the lower overall test accuracy for the identification of coronary artery disease in women compared with that in men. However, it remains unclear whether the decreased test performance among women is a result of lower test sensitivity or of lower specificity. In a large subgroup of men and women from the Coronary Artery Survival Study who were matched for age, prevalence, and severity of coronary artery disease (99), no significant difference was seen in test sensitivity between women and men (76% vs. 78%), but specificity was significantly lower among women (64% vs. 73%). Barolsky and associates (100) reported similarly lower specificities when the test was used for women compared with its use for men (68% vs. 89%), with no significant gender differences in sensitivity (60% vs. 65%). However, when patients taking digitalis preparations were excluded from these analyses, standard ST-segment depression criteria had identical 95% specificity but lower sensitivity with use for women than with use for men (50% vs. 64%). We have found similar differences in

sensitivity of standard test criteria between women and men (51% vs. 67%), with matched specificities of 96% (23). Morise and colleagues (85) found lower overall test accuracy among women, which was the result of a combination of lower sensitivity and specificity associated with use for women than that associated with use for men.

It has been suggested that differences in the magnitude of ST depression between otherwise healthy men and women are a possible explanation for gender differences in test specificity. However, we found no significant difference in either standard test specificity or in the mean values or frequency distributions of ST-segment depression between clinically normal men and women (23). In contrast, the lower sensitivity of standard ST-segment depression criteria when they were used for women in our study (23) could be directly attributed to the lower magnitude of ST-segment depression found among women with coronary artery disease. Gender differences in the magnitude of ST-segment depression may be due in part to the effects of either estrogens or progesterones on the ST-segment response to exercise in women (83,84 and 85). The observation that consideration of estrogen status significantly improves the accuracy of the ETT in women (85) further supports this possibility. Last, solid-angle theory provides a basis for the theory that gender differences in ST-segment depression may in part reflect the effects of gender differences in left ventricular mass or chamber size on the projection of ST-segment changes to the body surface (29,30,33). However, this concept remains speculative.

Independent of these findings, adjustment or correction of ST depression by HR clearly improves test performance in women (23,68,101). In a study of 620 patients (23), we found that, compared with use of non-gender-specific test criteria in both sexes, use of gender-specific test criteria with high specificity improved sensitivity of the ST/HR slope for the identification of coronary artery disease in women from 84% to 91%, with no decrease in sensitivity in men. Compared with standard criteria, the increase in sensitivity provided by HR adjustment was significantly greater among women than among men, both for the detection of any coronary obstruction (40% vs. 21%) and for the identification of three-vessel coronary artery disease (50% vs. 9%) (*e*Fig. 48.6.1). Thus, at the present time, we recommend use of HR-adjusted criteria for improved test accuracy in women.



***e*FIGURE 48.6.1** Bar graphs showing sex differences in the improvement in sensitivity obtained using the ST/heart rate (HR) index and ST/HR slope compared with standard test criteria for the identification of coronary artery disease (*left*) and for the identification of three-vessel coronary artery disease (*right*). Solid bars represent men; white bars represent women. (Reprinted from Okin PM, Kligfield P. Gender-specific criteria and performance of the exercise electrocardiogram. *Circulation* 1995;92:1209, with the permission of the American Heart Association.)

CONTROVERSIES AND PERSONAL PERSPECTIVES

Although most studies performed to date suggest that HR adjustment improves performance of ST-segment depression criteria in diagnosis of coronary artery disease, some controversy remains (45,53). Initial reports from England reporting perfect test accuracy for the ST/HR slope (58) were met with well-deserved skepticism. These studies and other early reports documenting the expected imperfect performance of this technique severely hindered acceptance of HR adjustment of ST-segment depression, as did more recent studies that reported no improvement in sensitivity with use of the simple ST/HR index (53). However, these studies did not reproduce the methods previously used, and it has subsequently been shown that improved accuracy of HR-adjusted methods is strongly dependent on exercise protocol, number of ECG leads, the time of ST-segment measurement relative to the J-point, and the precision and accuracy of ST-segment measurement (44,45,51,54,71). Recent reports have demonstrated that HR adjustment improves risk stratification compared with standard test criteria in many different studies from various other centers (22,95,97), further highlighting the utility of these methods. Although final acceptance of these methods will require even further study in clinically more diverse populations, it should be emphasized that no study has demonstrated *lower* sensitivity of HR-adjusted ST depression criteria compared with standard test criteria, and numerous manufacturers have incorporated ST/HR slope calculation into their clinical ETT systems (54).

The diagnostic utility of the ETT in patients who have some resting ECG abnormalities and in patients who are receiving digoxin is variable, so caution must be used in applying ST-segment depression criteria under these circumstances. We have found that the high sensitivity and specificity of the HR-adjusted ST-segment depression criteria appear to be maintained in patients who have isolated ST-segment depression and in whom minor intraventricular conduction delays are seen on the resting ECG. In contrast, we have observed that administration of digoxin can produce marked ST-segment depression during exercise, even in healthy subjects with normal results of resting ECGs who have normal results of ETTs during exercise while they are not receiving digoxin. However, we do not have enough data to assess the performance of these criteria in patients with left ventricular hypertrophy (demonstrated by ECG or echocardiography); ongoing studies will help to address this gap in our knowledge. As a consequence, at the present time I would advocate the use of imaging modalities in conjunction with ECG criteria in diagnosis for patients who have left ventricular hypertrophy and patients who are receiving digitalis preparations.

My own perspective is that exercise ECG is not optimally used in current practice. In large part because of limited confidence in the accuracy of the simple ETT, the number of nuclear and echocardiographic imaging stress tests performed in the United States has increased dramatically. Although these methods provide important localizing information and are clearly indicated in situations in which performance of the exercise ECG is known to be poor, I believe that imaging stress tests are overused for the routine assessment of patients who have known or suspected coronary artery disease. It is also clear that exercise testing in general is inappropriately applied in large numbers of low-risk patients who undergo screening stress tests as part of annual physical examinations. The appropriate application of Bayesian analysis to these populations demonstrates that the large number of false-positive test responses (regardless of the test used) is a consequence of the extremely low pretest likelihood of disease and leads to further noninvasive and invasive testing at substantial cost and some risk to these patients. A better understanding of the limitations and indications of exercise testing and application of the more accurate HR-adjusted ST-segment depression criteria hold promise for improvement of the use and accuracy of the exercise ECG in clinical practice.

THE FUTURE

The development of new ECG criteria that have increased sensitivity at high specificity based on precise computer-based measurements is essential to improving the performance of the ETT. The increased accuracy seen with incorporation of measures of chronotropic incompetence in analysis of the ETT (24,25) suggests that further improvements in test performance may be achievable with better adjustment of ST-segment depression for HR changes that occur with exercise. Additional refinements in the ETT may be achieved by the combination of HR-adjusted ST-segment depression criteria with less-expensive imaging modalities, such as stress echocardiography, to increase accuracy and localize ischemia. Novel and interesting approaches to ETT analysis, based on examination of ECG findings that are distinct from the ST segment itself, also hold promise. These include measures of amplitude, duration, and frequency content of the QRS complex and measures of duration and dispersion of repolarization during exercise. Development and further refinement of computerized methods are needed before many of these new approaches can be adequately evaluated and used in clinical practice.

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TRANSTHORACIC ECHOCARDIOGRAPHY

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JAMES D. THOMAS

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OVERVIEW

Since its development in the early 1950s to assess mitral valve (MV) motion, echocardiography has become the most commonly performed cardiac imaging test. It provides data with high spatial and temporal resolution while being noninvasive, portable, and inexpensive relative to competing technologies. Ultrasound images can be obtained along a single scan line (M mode) or swept along a two-dimensional sector through the heart, and extensions to three-dimensional imaging are in development. An echocardiographic examination should consist of a structured interrogation of all cardiac chambers and valves, with the quantitative data providing chamber size, stroke volume, and transvalvular flow. Systematic examination of the left ventricle localizes regional wall motion abnormalities and characterizes hypertrophic, dilated, and restrictive cardiomyopathies. Valve morphology is readily seen, although Doppler interrogation and often transesophageal imaging are necessary for quantifying stenosis and regurgitation. Cardiac tumors, thrombi, and vegetations are commonly diagnosed by transthoracic echocardiogram, although the transesophageal approach has a higher sensitivity. Evolving echocardiographic techniques include three-dimensional imaging, parallel computer processing to improve frame rate and resolution, contrast echocardiography for myocardial perfusion, and all-digital storage and transmission.

INTRODUCTION AND HISTORY

Echocardiography (cardiac ultrasound) is the most powerful diagnostic tool in cardiology. Although technically demanding, its diagnostic accuracy, cost effectiveness, availability, and noninvasive nature have made it the largest cardiovascular expense item in the Medicare budget.

As summarized by Feigenbaum (1), interest in sonic testing of materials spurred Hertz (an engineer) (2) and Edler (a clinical cardiologist) (3) to collaborate on the echocardiographic identification of normal and pathologic cardiac structures. The major initial contribution was identifying changes of the anterior mitral leaflet in rheumatic mitral stenosis (MS) (4,5), independently confirmed by Joyner et al. (6) and Feigenbaum (7), who did the most to popularize the technique in the United States (8).

An echocardiographic examination consists of three elements: M-mode and two-dimensional imaging (the subjects of this chapter) and Doppler interrogation (see Chapter 51). Echocardiography provides functional and anatomic information, with virtually no macroscopic feature of the heart inaccessible to visualization and quantitation. The physical and instrumentation principles of echocardiography are summarized in Chapter 46 and elsewhere (9,10 and 11).

MODALITIES OF ECHOCARDIOGRAPHY

M-mode echocardiography was the first form of cardiac ultrasound (Fig. 49.1), in which a single beam is directed toward the heart and reflected signals are displayed on a strip chart or oscillograph at high data rates (>1,000 Hz in early machines, 200 Hz in most contemporary machines). Two-dimensional echocardiography (Fig. 49.2) is created by sweeping an ultrasound beam back and forth through an arc either mechanically or by phased-array transducer. Minimizing the depth of interrogation or the width of the sector scan can enhance the frame rate. Structural resolution is dependent on imaging depth and transducer frequency. Transducer focus improves resolution in the focal zone, at the expense of greater divergence for deeper structures.

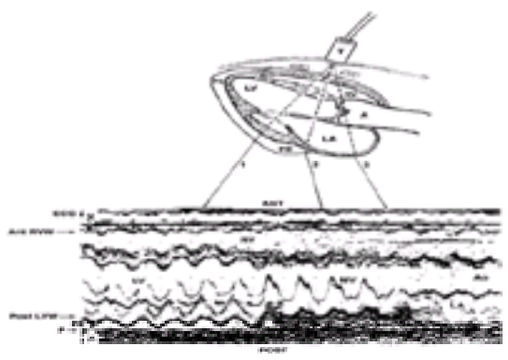


FIGURE 49.1 M-mode echocardiogram displaying motion along a single scan line within the heart. Here, the transducer (T) is swept from the left ventricular level (*left side of scan*) to the mitral valve level (*middle*) and up to the left atrial level (*right*). A, aorta; Ao, aorta; ANT, anterior; ECG, electrocardiogram; LA, left atrium; LV, left ventricle; MV, mitral valve; P, pericardium; PE, pericardial effusion; POST, posterior; RV, right ventricle; RVW, right ventricular wall. (From Cheitlin MD, Sokolow M, McIlroy MB. *Clinical cardiology*, 6th ed. Norwalk, CT: Appleton & Lange, 1993, with permission.)

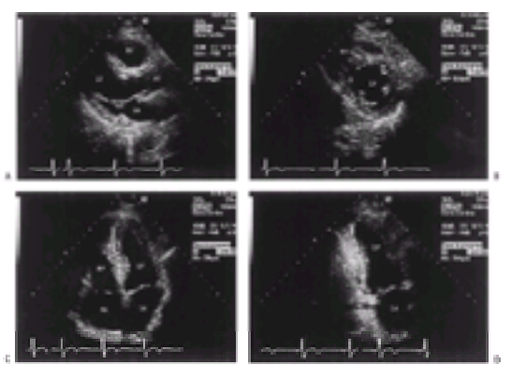
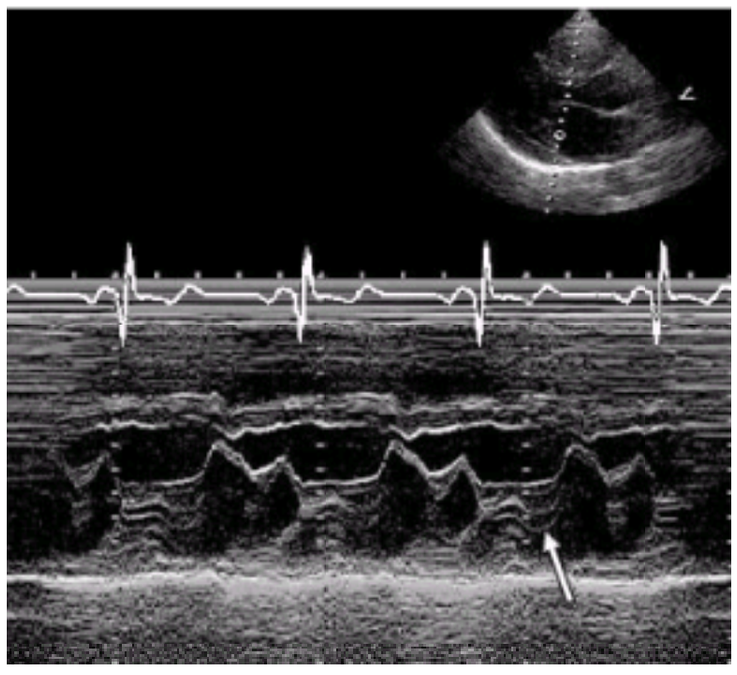


FIGURE 49.2 Two-dimensional echocardiography. Four standard views. **A:** Parasternal long axis. **B:** Parasternal short axis. **C:** Apical four chamber. **D:** Apical two chamber. AO, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.



M-mode tracing of posterior leaflet mitral valve prolapse. Note the posterior displacement of the posterior mitral leaflet after the leaflets close in systole.

ECHOCARDIOGRAPHIC EVALUATION OF THE CARDIAC CHAMBERS

Left Ventricle

Left ventricular (LV) evaluation is probably the single most important clinical application of echocardiography. A combined M-mode, two-dimensional, and Doppler evaluation of the LV can provide reliable information about overall systolic function, regional wall motion, and ventricular mass and geometry.

Evaluation of Global Systolic Function of the Left Ventricle

Reliable determinations of LV function require the qualitative and quantitative evaluation of images taken from several standard windows. Typically, the LV is first viewed in the parasternal long-axis and short-axis planes (Fig. 49.2). From these, M-mode tracings are generated. If quantitation of M-mode tracings is used clinically, the American Society of Echocardiography recommends obtaining these from the parasternal short axis in the two-dimensional M mode (12,13) (Fig. 49.3).

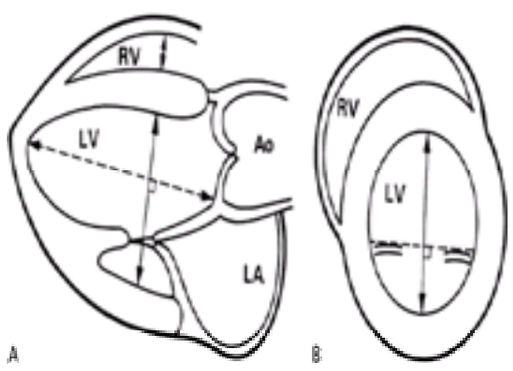


FIGURE 49.3 Quantitation of left ventricular size. Measurement sites recommended by the American Society of Echocardiography (12). **A:** Parasternal long-axis view. **B:** Parasternal short-axis view. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (Reproduced with permission of the American Society of Echocardiography.)

M-Mode Evaluation

Standard M-mode measurements are shown in Figure 49.4. Fractional shortening by M mode is given by left ventricular diameter at end diastole ($LVED_d$) – left ventricular diameter at end systole ($LVES_d$)/$LVED_d$ where ED_d is the LV minor axis in diastole and ES_d in systole. Normally, fractional shortening is approximately 50% and is considered clearly abnormal when it falls below 30% (8,14). Another M-mode measurement is the E-point septal separation (15,16) (a marker of LV dysfunction when it exceeds 7 mm).

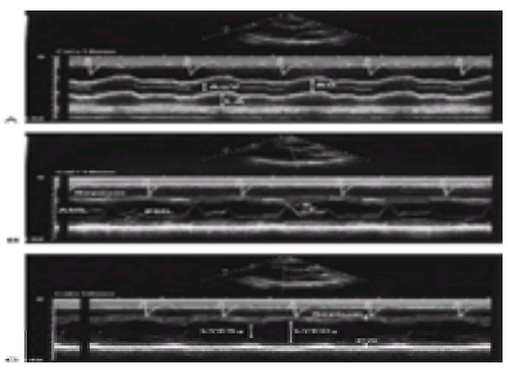
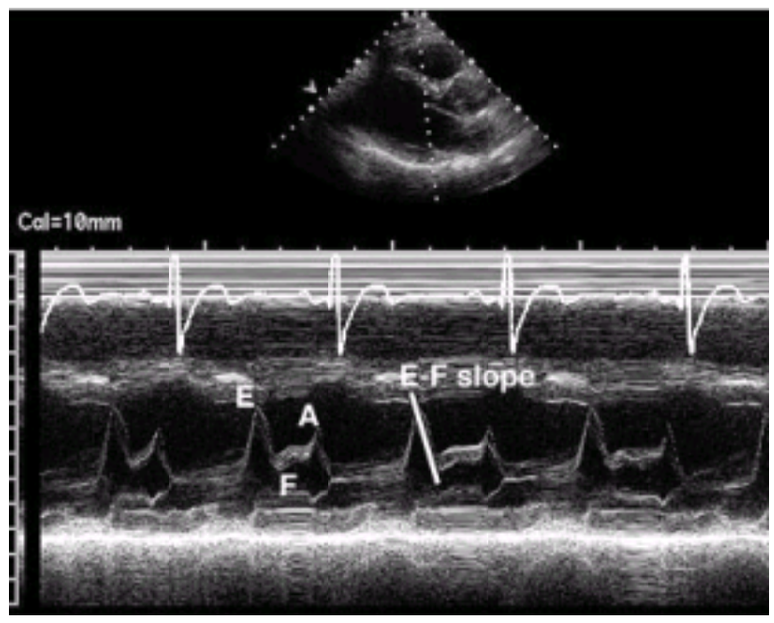
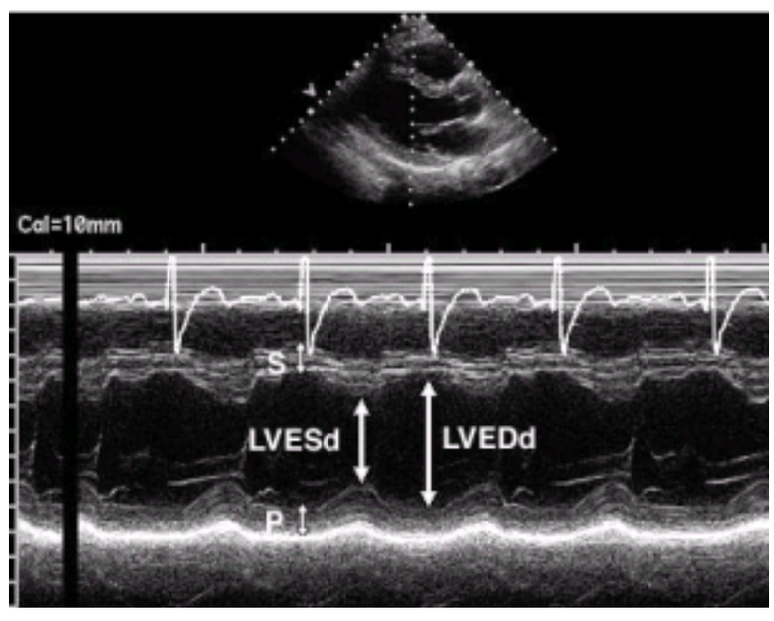


FIGURE 49.4 Standard measurements from M mode. Shown are sweeps at the aortic level **(A)**, mitral valve level **(B)**, and left ventricular level **(C)**. AML, anterior mitral leaflet; Ao, aortic root diameter; AoV, opening of aortic valve; EF, E to F slope (rate of closure of mitral valve); LA, end systolic left atrial diameter; $LVED_d$, left ventricular diameter at end diastole; $LVES_d$, left ventricular diameter at end systole; PML, posterior mitral leaflet; PW, posterior wall thickness; SEPTUM, septal thickness.

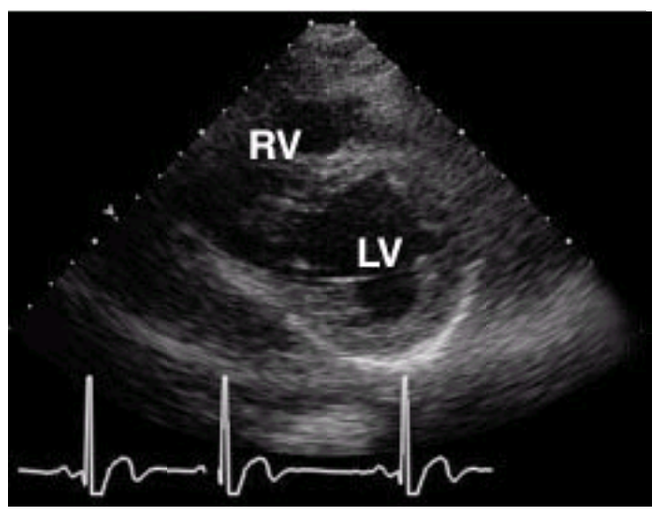


M-mode trace through the level of the mitral valve from the parasternal long-axis view. Note the E point, F point, A point, and the E-to-F slope.



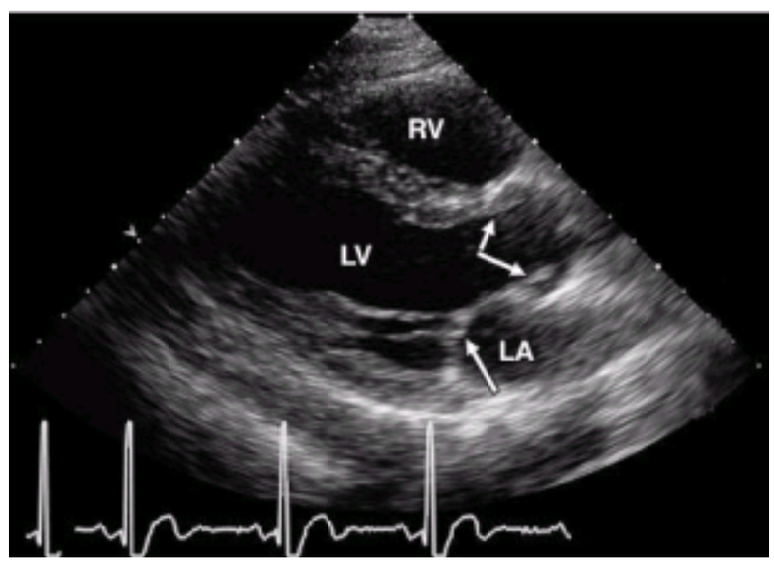
M-mode at the left ventricular (LV) level from the parasternal long-axis view. Note the location of the various measurements. LVEDd, LV end-diastolic dimension; LVESd, LV end-systolic dimension; P, posterior wall thickness; S, interventricular septal wall thickness.

A further M-mode guide to overall LV function is aortic root motion, largely reflecting the atrial filling curve (17,18). With normal cardiac output, change in atrial volume moves the aorta anteriorly approximately 14 mm, but with low stroke volume, the aorta barely moves (19). This also yields information about diastolic function. In youth, most atrial emptying occurs early in diastole, with atrial contraction accounting for less than 30% of the total. Hypertrophy and aging slow early passive relaxation, and therefore the majority (up to 70%) of emptying occurs late in diastole at the time of atrial contraction. Finally, aortic valve (AV) opening yields useful information about LV function, opening fully when stroke volume is normal but incompletely when stroke volume falls.

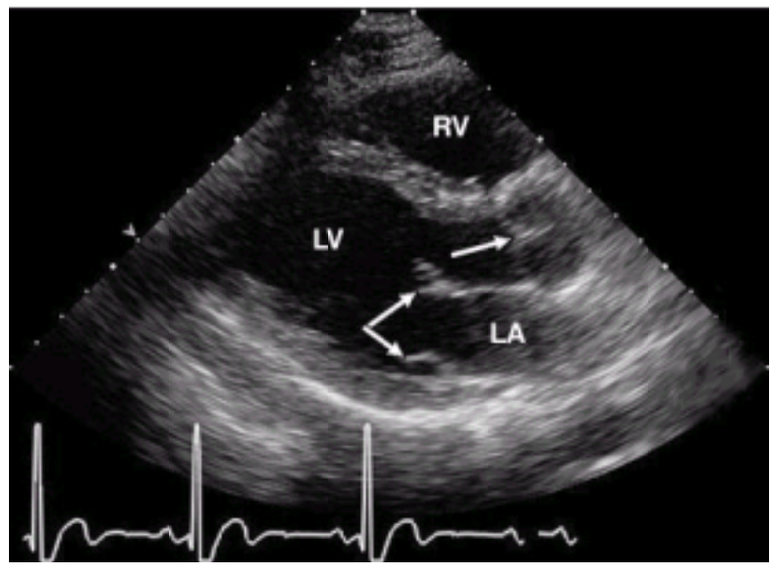


Short-axis view of the left ventricle (LV) from the parasternal window of a transesophageal echo. RV, right ventricle.

Magnified view of the short-axis of an aortic valve from the parasternal window as seen in diastole. Note the position of the LCC (left coronary cusp), RCC (right coronary cusp) and NCC (noncoronary cusp).



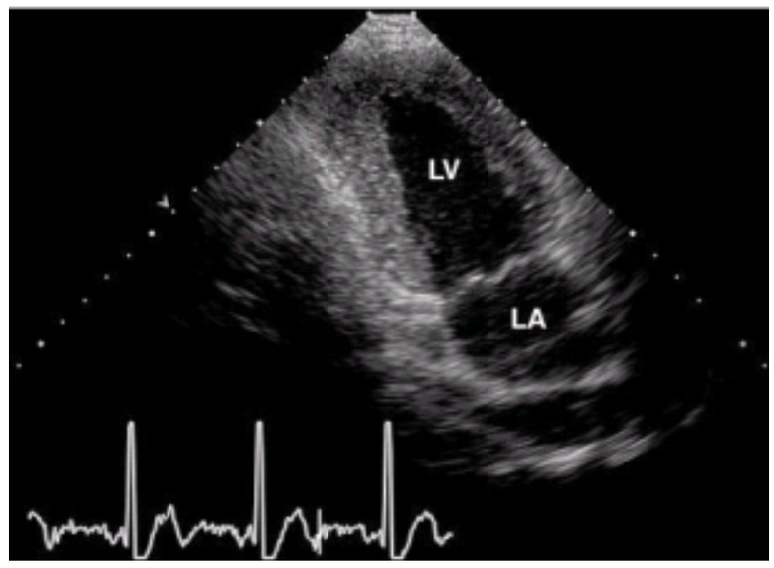
Normal parasternal long-axis view by transthoracic echo (in systole). Note the closed mitral valve (*single arrow*) and opened aortic valve (*double arrow*).



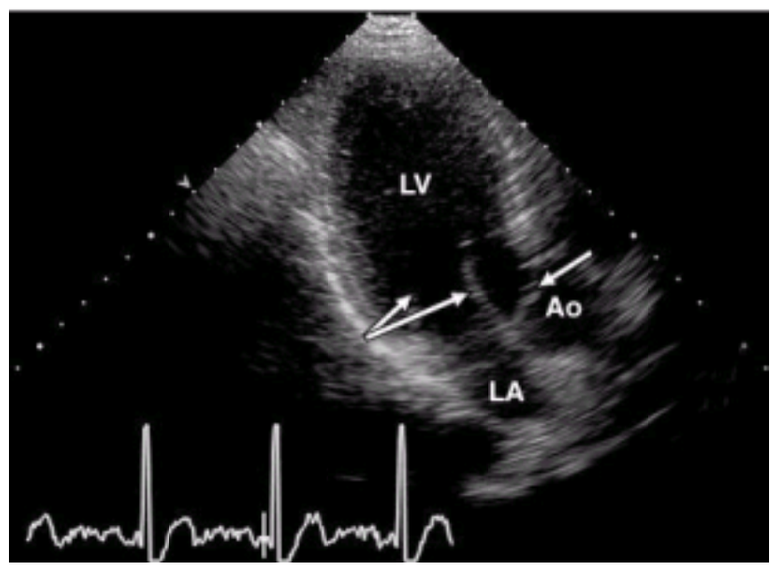
Parasternal long-axis view of a transthoracic echo in diastole. Note the left atrium, left ventricle, and right ventricle. The mitral valve (*double arrow*) is open, and aortic valve (*single arrow*) is closed.

Apical Window Imaging

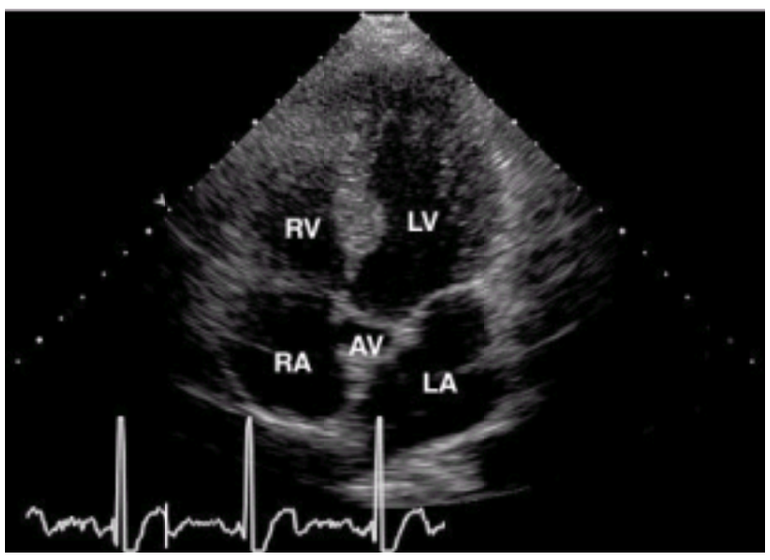
After the parasternal images, the left ventricle is displayed along its long axis from the apical impulse location, with axial rotation of the transducer producing any number of long-axis views. However, the standard examination typically includes the apical four- and two-chamber views (orthogonal to each other, Fig. 49.2) and the apical long-axis view (20,21).



Normal apical two-chamber view by transthoracic echo. Note the location of the anterior wall of the left ventricle (to the right) and the inferior wall (to the left).



Normal apical long-axis view by transthoracic echo in diastole. Note the open mitral valve designated by the double arrow and the closed aortic valve designated by the single arrow. The posterior wall of the left ventricle is to the left of the screen and the anteroseptum is to the right.



Normal apical five-chamber view by transthoracic echo. View is obtained by angling the transducer anteriorly from the apical four-chamber view, thus bringing the aortic valve (AV) into view. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

VIDEO

Video 49.1 Normal apical five-chamber view in a transthoracic echo obtained by angling the transducer anteriorly from the four-chamber view to bring the aortic valve into view (see the center of screen). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

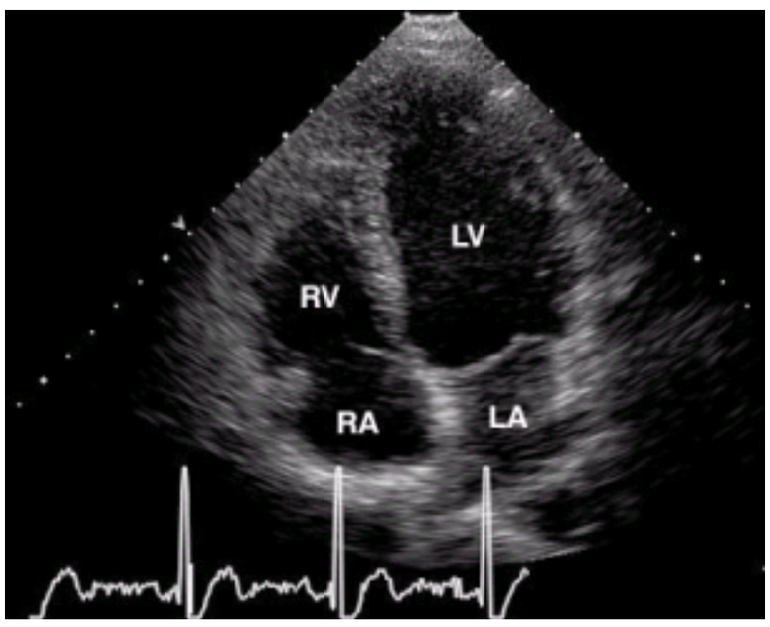
VIDEO

Video 49.2 Normal apical four-chamber view of a transthoracic echo. Note that the left ventricle is on the right of the screen showing the septum and lateral walls, and the right ventricle is to the left. The left atrium is in the lower right of the screen and the right atrium to the lower left. The mitral and tricuspid valves can be seen in this view. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

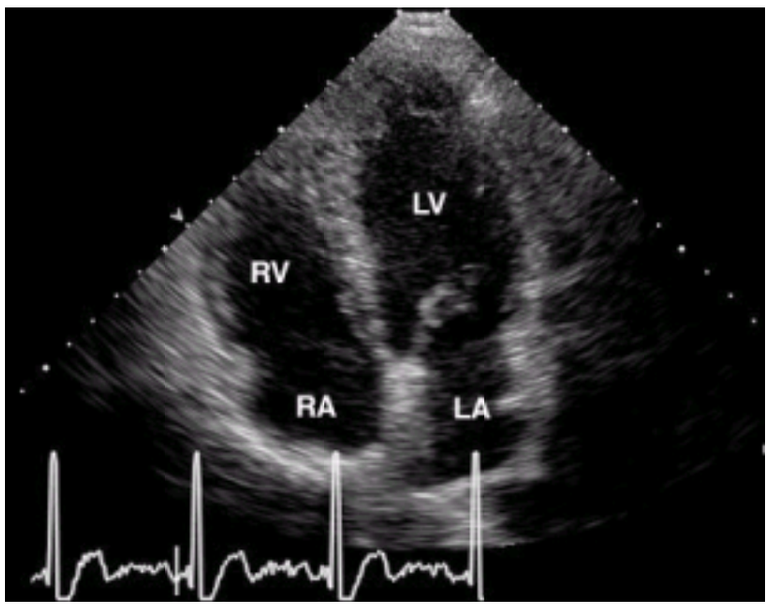
VIDEO

Video 49.3 Normal apical two-chamber view of a transthoracic echocardiogram. The anterior wall of the left ventricle is on the right of the screen and the inferior wall is to the left. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The four-chamber view (20) displays the midseptum and inferolateral LV wall and shows the right ventricle (RV) at its widest point, including the moderator band. At the cardiac base, the mitral and tricuspid valves (TVs) are shown, with the TV being displaced approximately 1 cm more apically than the MV by the membranous septum. The atria are shown partitioned by the interatrial septum. Posterior transducer angulation reveals the coronary sinus and papillary muscles. Anterior angulation shows the LV outflow tract. To enhance endocardial definition, ultrasonic contrast agents that cross the lungs intact (unlike agitated saline contrast) can be used. Because ultrasound energy can destroy these bubbles, intermittent insonification (e.g., once per cardiac cycle) permits the development of greater contrast effects in the myocardium and the cavity. Further contrast augmentation is gained by displaying the second harmonic of the transmitted ultrasound carrier frequency.

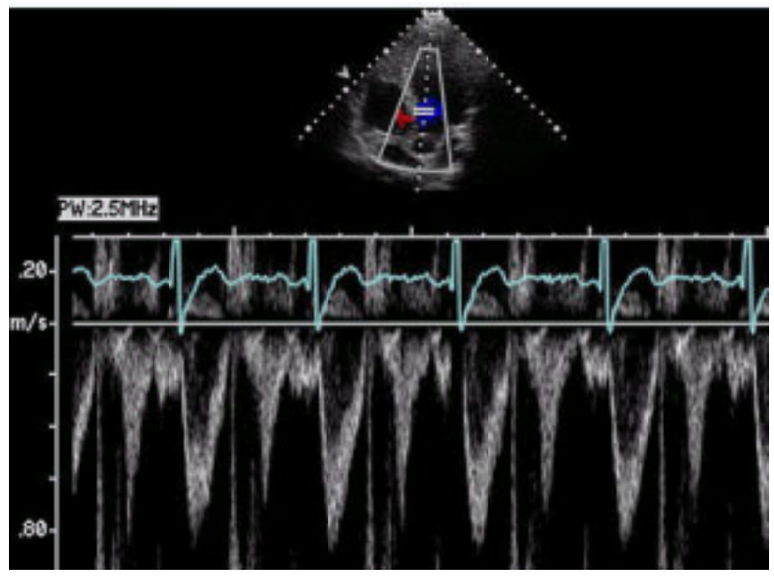


Normal apical four-chamber view by transthoracic echo (in systole). Closed mitral (*right*) and tricuspid (*left*) valves.



Normal apical four-chamber view (in diastole) by transthoracic echocardiography. Note location of left ventricle (LV), right ventricle (RV), open mitral valve

(right), and open tricuspid valve (*left*) and corresponding atria. LA, left atrium. RA, right atrium.

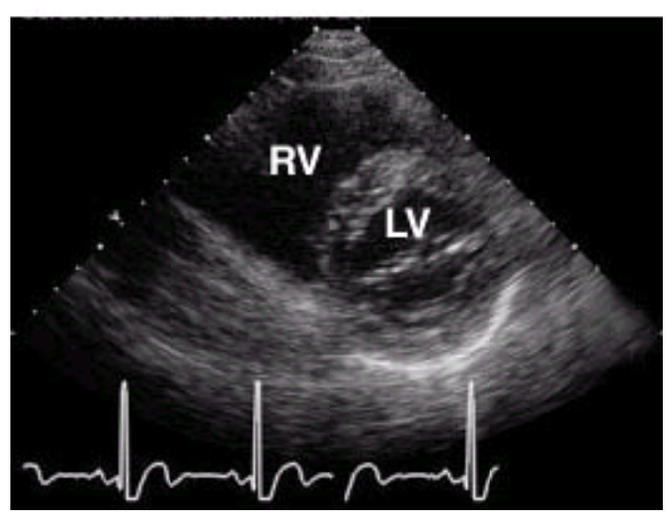


Normal pulsed wave Doppler signal from the left ventricular outflow tract. Note the maximal velocity is only 80 cm/second.

The shape of a healthy left ventricle is a truncated ellipsoid with the long axis roughly twice the length of the short axis. As the heart decompensates, it assumes a more globular shape (22) (eFig. 49.4.1). Diastolic wall thickness is viewed in absolute terms (approximately 1 cm is normal, >1.2 cm is considered hypertrophied) and relative to LV cavity size, with a radius-thickness ratio that is typically about 2:1. The distribution of hypertrophy is important. In secondary hypertrophy (e.g., from hypertension or outflow obstruction), the increase in wall thickness is uniform or concentric, whereas it is typically confined to the septum in asymmetric hypertrophy. Regional LV function is assessed by looking for inward motion of the endocardium and, more importantly, segmental thickening. Myocardial texture is also informative. Scar formation results in a thin bright segment, and infiltrative disease yields increased reflectance in approximately half of such cases. Geometric uniformity is another useful feature and becomes important after infarction. LV remodeling in its extreme form involves an entire region in an aneurysm (eFig. 49.4.2), which is distinguished from simple dysfunction by deformity throughout the cardiac cycle. Generally, all endocardial segments should move inward synchronously, with incoordinate contraction suggesting at least moderate LV dysfunction. However, it can also be seen with left bundle branch block (23) or RV pacing. Finally, the longitudinal motion of the heart can be observed by the descent of the cardiac base (annular plane) toward the nearly fixed cardiac apex (24). A decrease in this parameter is often the first sign of nascent cardiomyopathy.

***e*FIGURE 49.4.1** Dilated cardiomyopathy. Parasternal long-axis view demonstrating an enlarged left ventricle with incomplete closure of the mitral valve and left atrial enlargement.

***e*FIGURE 49.4.2** Lateral left ventricular aneurysm. Apical four-chamber view of a patient with a recent lateral wall infarct. Note that the neck of the aneurysm is quite broad, indicating that this is a true aneurysm and not a pseudoaneurysm.



Parasternal short-axis view of the mitral valve and left ventricle (LV). RV, right ventricle.

Video 49.4 Normal parasternal short-axis view of the left ventricle by transthoracic echo. The anterior wall is located at the top and the inferior and posterior walls are located towards the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.5 Normal parasternal long-axis view in a transthoracic echocardiogram. The mitral and aortic valves are well seen, as are the anteroseptal and posterior walls of the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Left bundle branch block. Wide QRS complex, negative in lead V_1, is associated with secondary T-wave inversions.

Quantitation of Left Ventricular Function

Although automated methods of measurement have been developed for assessing LV function (25), the standard method remains manual border tracing (26,27 and 28). Although ejection fraction (EF) is commonly estimated by visual inspection, this is prone to error and interobserver variability.

M-mode measurements of LV function (29,30,31 and 32) are limited because they use a single LV short-axis dimension, generally assuming a long-axis–short-axis ratio of 2:1 to extrapolate information to three dimensions. Unfortunately, many pathologic states introduce regional asymmetry or alter the ratio toward unity. Because volume is a cube function of dimension, errors are compounded (26,33,34). In contrast, two-dimensional volumes and mass compare favorably to those that are obtained from angiography and autopsy, but only if care is taken to optimize data acquisition and analysis (12).

The best apical images are usually obtained with the patient lying in the left recumbent position. Image enhancement can be accomplished by using a mattress with a removable panel and positioning the sonographer to the patient's left. A foreshortened ventricle can be avoided by maximizing the visualized long axis. Because the heart moves with respiration, images should be obtained during unforced suspended expiration. Digital acquisition enhances accuracy and ease of review, with systolic frames stored from four views in a quad screen format. Routine digital storage also allows easy comparison with prior studies. Finally, on-line sonographer measurement is preferred to off-line measurement for accuracy and for improved workflow.

Electronic calipers are used to measure distances and areas. To quantify LV volume, the endocardium is traced in systole and in diastole, using the highest frequency transducer to enhance endocardial definition. *End systole* is defined as the last frame before mitral opening with end diastole just before valve closure.

The biplane method of disks (referred to less precisely as *modified Simpson's rule*) most closely predicts angiographic volumes (21,26,27 and 28). The single-plane area length is also suitable, provided that the ventricle is symmetric (35) (Fig. 49.5). These algorithms are applied to orthogonal apical two- and four-chamber views. The apical four-chamber view (21) should display the true LV apex, showing neither the aorta nor the coronary sinus while maximizing RV size. The two-chamber view should not include any portion of the RV, aorta, or right atrium (RA) (Fig. 49.2).

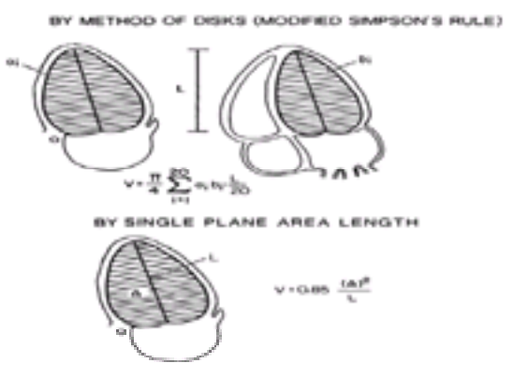


FIGURE 49.5 Left ventricular (LV) volume determination. The biplane method of disks (*upper panels*) requires orthogonal two- and four-chamber apical views and is more accurate in asymmetric hearts than the single-plane method shown below. In symmetric ventricles, the single-plane method is almost as accurate as the biplane one. [Reproduced with permission from the American Society of Echocardiography (26).

LV mass computed from two-dimensional images is more reproducible and anatomically rational than M-mode values but is still limited by relatively wide standard deviations (±35 g for 95% confidence intervals) (36,37). The truncated ellipsoid and area-length methods are both recommended by the American Society of Echocardiology for mass determination (12,38).

Clinical Use

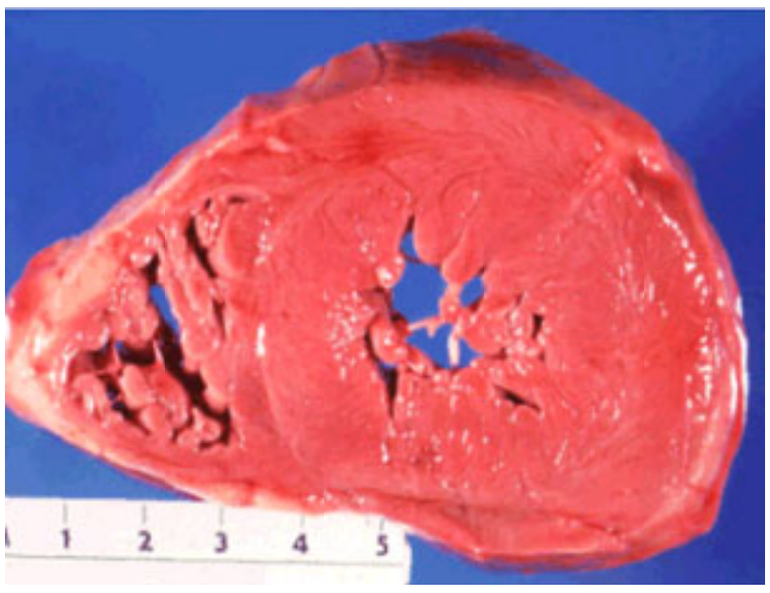
End systolic volume is a powerful measurement. Sagawa et al. (35) have noted that the end systolic pressure-volume ratio is relatively insensitive to loading conditions and is a good marker for contractility. Fortunately, it is one of the easiest and most reproducible echo volume measurements to make (39). Borow et al. (40) have shown that complications following aortic and mitral surgery were confined to patients with end systolic volume indexes greater than 66 mL per m^2. Hammermeister et al. (41) showed that an end systolic volume index of 45 mL per m^2 led to a threefold increase in mortality in patients with coronary artery disease (50 vs. 150 deaths per 1,000 patient-years). White et al. (42) confirmed these data with ventriculography in 600 patients following myocardial infarction. After accounting for end systolic volume, the other variables showed no additional predictive value. The Study of Survival and Ventricular Enlargement (43) showed that the end systolic size (area) was the most powerful predictor of survival. In summary, if an echocardiography laboratory were to choose one simple measurement to report, end systolic volume index would be a strong candidate parameter.

End diastolic volume is important, although less predictive of cardiac events. Endocardial definition is often problematic, especially of the lateral wall (95% confidence intervals of ±25 mL) (37). EF is probably the most commonly cited clinical index of LV function, which should be measured (stroke volume/end diastolic volume, 95% confidence interval of ±6%) rather than visually estimated. Although not as predictive as end systolic volume, EF provides highly useful prognostic data, as shown by a large-scale thrombolytic trial (44) and White et al.'s study (42).

Video 49.6 Apical long-axis view of a patient with severe left ventricular dysfunction and annular dilatation causing 4+, centrally directed mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Wall Thickness and Left Ventricular Mass

Hypertrophy is defined anatomically as an increase in the mass of the ventricular myocardium, but wall thickness often serves as its surrogate. Initially obtained from M mode (45), wall thickness is usually determined from two-dimensional images with normal values from 0.6 to 1.1 cm. Wall thickness should be measured at the onset of the QRS (rather than in diastasis), because atrial contraction may thin the wall considerably. Analogously, if filling volume is greatly reduced (e.g., in cardiac tamponade), the wall becomes thickened despite normal mass and a dilated ventricle may have increased mass with normal thickness. To overcome the shortcomings of simple wall thickness, actual mass can be estimated. However, M-mode formulas (29,46,47 and 48) suffer the same theoretical limitation as the cube method of estimating LV volume, especially in hearts with asymmetric thickening (49). Despite this, the Framingham Study has used M-mode methods to yield valuable insight into the electrocardiographic (ECG) criteria for hypertrophy (47,50,51) and the adverse prognosis of ventricular hypertrophy (52).

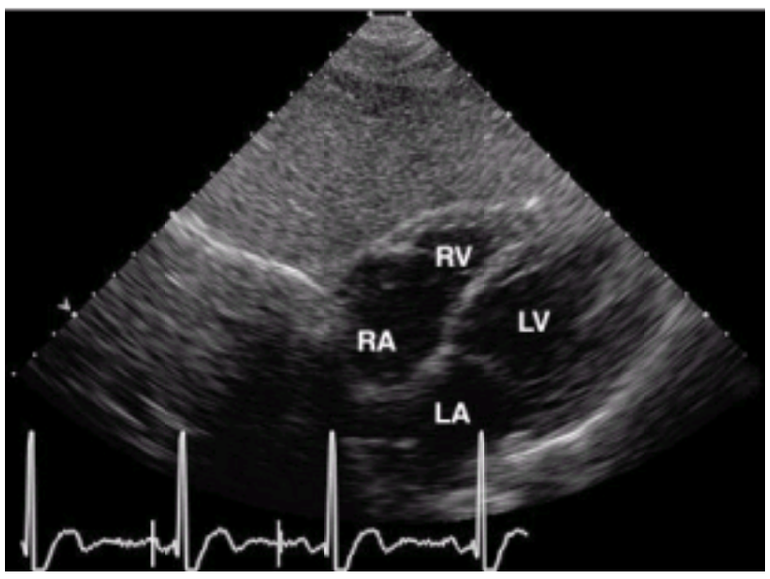


Massive left ventricular hypertrophy as well as concentric hypertrophic cardiomyopathy. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

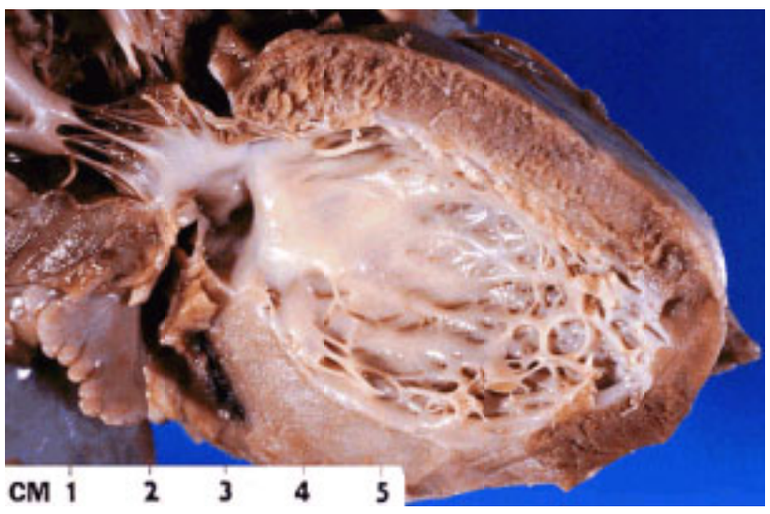
Video 49.7 Transthoracic apical four-chamber view of a patient with amyloidosis. Note the thickened “sparkling” walls of the right and left ventricles. Both the mitral and tricuspid valves are mildly thickened and there is biatrial enlargement and a trivial pericardial effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.8 Transthoracic subcostal view of a patient with amyloidosis showing markedly thickened right and left ventricular walls, showing the characteristic “sparkle.” The right ventricle is towards the top of the screen and the right ventricle free wall is 1.5 cm thick. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Most two-dimensional methods for determining LV mass (12,36,37 and 38) are similar because they combine a short-axis estimation of wall thickness with an estimation of ventricular length. The difference between the endocardial and epicardial volumes multiplied by the specific gravity of myocardium (1.05 g per mL) yields myocardial mass. Even two-dimensional methods have relatively wide 95% confidence bounds (±25 g) (34,36,37).



Long-axis view from the subcostal window of a transesophageal echo showing the left and right ventricles (LV and RV) and the left and right atria (LA and RA).



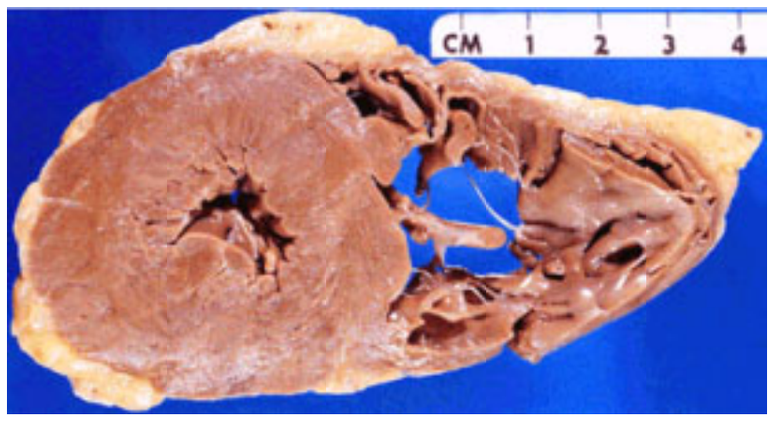
Fibroelastosis and hypertrophy of the left ventricle. This specimen was obtained from a 3-month-old child with incomplete closure of the foramen ovale.

Three-dimensional imaging techniques may improve the reproducibility of volume and mass measurements, with preliminary studies demonstrating accuracy comparable to that of magnetic resonance imaging and computed tomographic echocardiography (53,54,55,56,57,58,59,60 and 61). If these techniques could be obtained with standard instruments, and the requirement for hand tracing eliminated by automation, echocardiographic mass could be routinely determined.

eTable 49.0.1 lists normal values for LV volume and mass. Left atrial volumes are derived from several studies (12,21,62,63,64,65,66,67,68,69 and 70) and may serve as a reference for clinically measured studies.

***e*TABLE 49.0.1** NORMAL VALUES FOR LEFT AND RIGHT VENTRICULAR VOLUME, LEFT VENTRICULAR MASS, AND LEFT AND RIGHT ATRIAL VOLUME DERIVED FROM SEVERAL STUDIES

End diastolic volume left ventricle (two-and four-chamber apical views/biplane method of disks)
Male: 111 mL index 58 mL/m^2 (80)
Female: 80 mL index 50 mL/m^2 (66)
End systolic volume left ventricle (two- and four-chamber apical views/biplane method of disks)
Male: 34 index 18 mL/m^2 (30)
Female: 29 index 18 mL/m^2 (32)
Ejection fraction
61 ± 10%
End diastolic volume right ventricle (based on normal ratio of left ventricle–right ventricle of 0.6)
Male: 67 mL
Female: 48 mL
Left ventricular mass (truncated ellipsoid)
Male: 135 g index 71 g/m^2 (96)
Female: 99 g index 62 g/m^2 (89)
Volume-mass ratio: 83
Left atrial volume (two- and four-chamber apical views/biplane method of disks)
Male: 38 mL index 21 mL/m^2
Female: 32 mL index 21 mL/m^2
Left atrial volume four-chamber view (single-plane area-length)
Male: 38 mL
Female: 34 mL
Left atrial volume two-chamber view (single-plane area-length)
Male: 46 mL
Female: 36 mL
Right atrial volume four-chamber view (single-plane area-length)
Male: 39 mL
Female: 27 mL



Left ventricular hypertrophy secondary to chronic hypertension with secondary ectasia of the right ventricle.

Two-Dimensional Echocardiography in Ischemic Heart Disease

Myocardial infarction produces regional akinesis within seconds of coronary occlusion. The presence of scarring (thinning and increased brightness) indicates an old infarction. The interface between contracting and akinetic tissue forms a visually distinctive “hinge point.” The diffuse hypokinesis of ischemic cardiomyopathy can be difficult to distinguish from primary myocardial disease.

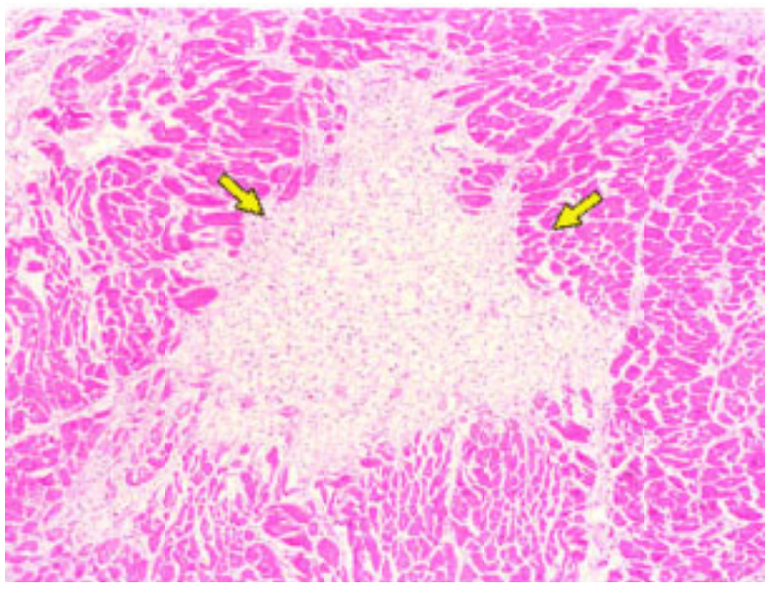
To localize segmental wall motion abnormalities in a standardized format, the American Society of Echocardiography has recommended dividing the ventricle into 16 segments (12). Grading of these segments generates a wall motion score index that has been shown to have prognostic value (71). A diastolic deformity, sharply demarcated, indicates aneurysm formation. Hypokinesis without wall thinning suggests ischemia rather than completed infarction, but the specificity of this is not high. Echocardiography is valuable in the assessment of chest pain (72,73,74,75 and 76), because a normal echocardiogram makes cardiac ischemia unlikely. The reliability and speed in detecting ischemic hypokinesis have led to the use of echocardiography in conjunction with exercise and pharmacologic stress testing (see Chapter 50).

VIDEO

Video 49.9 Apical four-chamber view of a very large, highly loculated pleural effusion. Note the extensive network of fibrinous stranding. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.10 Apical long-axis view demonstrating an anteroseptal myocardial infarction. Note the akinetic anteroseptum to the right of the picture. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

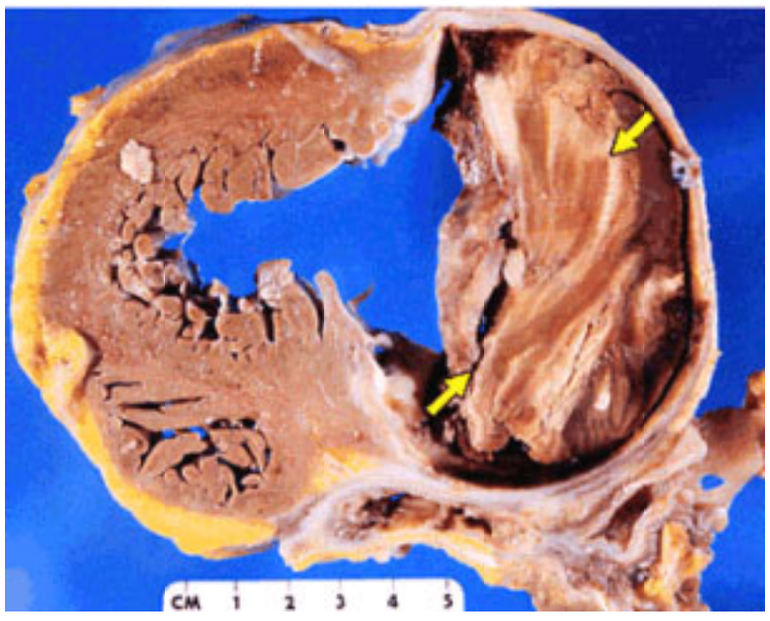


Histology showing the early stages of healing following myocardial infarction. These changes are typical in the second week after the acute event. This is a hematoxylin-eosin stain showing removal of the necrotic myocytes and early ingrowth of vascular tissue and fibroblasts, particularly evident at the edges of the lesion (*yellow arrows*).

Complications of Myocardial Infarction: Recognition by Echocardiography

Many of the complications of myocardial infarction can be diagnosed by a bedside echocardiogram. LV thrombi occur frequently in the setting of extensive anteroapical infarction and rarely in inferior infarction. They can appear within days of the infarction and typically are highly mobile. Older thrombi tend to have smooth surfaces and a texture like liver and may have a layered appearance (eFig. 49.5.1). The more mobile and irregular the surface of the thrombus, the higher the risk of embolization (77,78,79 and 80). Thrombi can be difficult to differentiate from apical trabeculations, which may be pronounced in cardiomyopathy (81).

***e*FIGURE 49.5.1** Apical thrombus in the apical two-chamber view. This patient had recently experienced a large anteroapical myocardial infarction, and this apical thrombus, approximately 2.5 cm in greatest dimension, subsequently developed. LV, left ventricle.



Healed, atrophic posterolateral infarct and ventricular aneurysm containing a mural thrombosis (*yellow arrows*).

Video 49.11 A 54-year-old male patient with filling defect of the left ventricular apex consistent with left ventricular apical thrombus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

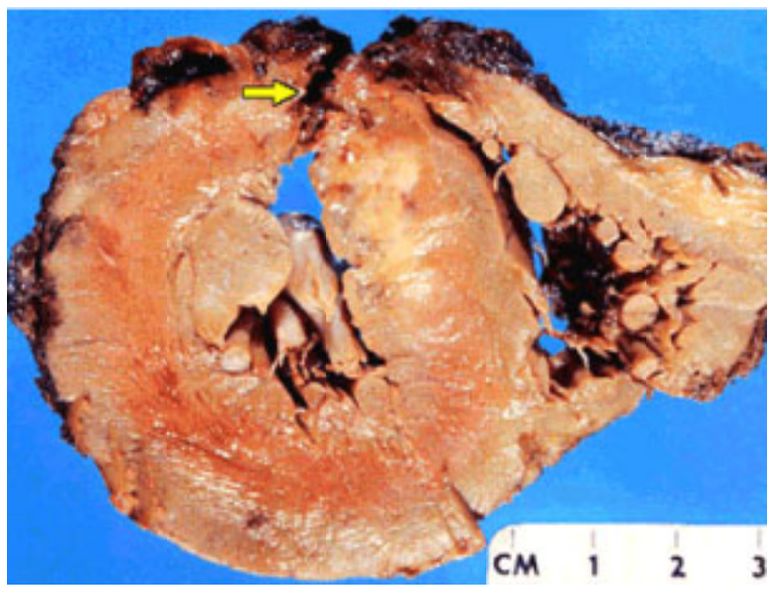
Video 49.12 Post–myocardial infarction apical thrombus (long-axis). Akinesia of thin apical wall with adjacent thrombus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Embolus. Dislodged thrombus that embolized to the toes and caused gangrene (*arrows*).

Postinfarction aneurysms are characterized by a wall motion abnormality with a diastolic deformity. The ability of echocardiography to delineate aneurysm is emphasized (82,83 and 84) (*e*Fig. 49.4.2).

Video 49.13 Post–myocardial infarction true aneurysm (long-axis). Dyskinesia and thinning of the left ventricular apex due to an occlusion of left anterior descending artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pseudoaneurysms, which result from frank wall rupture or cardiorrhexis, are actually composed of pericardium, which confines the rupture. Because only small ruptures in the wall are compatible with survival, pseudoaneurysms tend to have narrow necks, in contrast to the more open neck of true aneurysms (see Chapter 19). Pseudoaneurysms typically form at the inferoposterior base of the heart, are usually accompanied by pericardial effusion (85), and carry a poor prognosis if unrepaired.



Cardiac rupture after acute transmural anteroseptal myocardial infarction. The yellow arrow indicates the site of rupture.

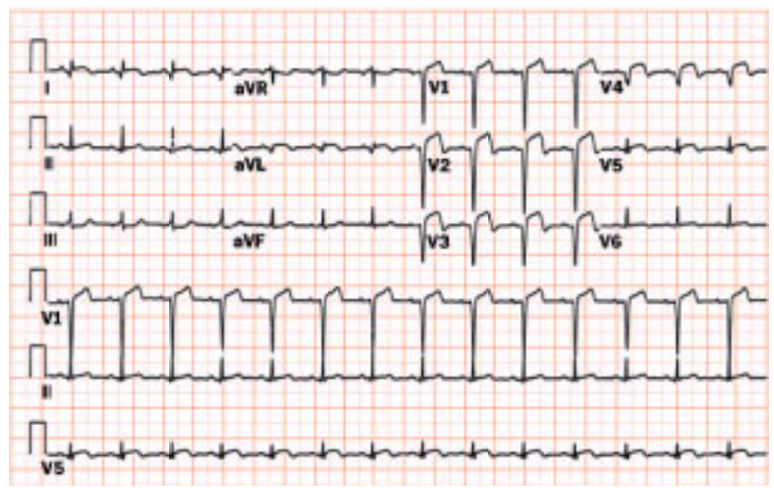
Video 49.14 Aortography showing an aneurysm of the ascending aorta with 3+ aortic regurgitation. The aortogram in this patient with cystic medial necrosis shows a maximum dimension of 5.4 cm. The dilation is confined to the ascending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.15 Post–myocardial infarction pseudoaneurysm (short-axis). Rupture of the inferolateral wall of the left ventricle due to circumflex artery occlusion. The pseudoaneurysm cavity is contained by pericardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

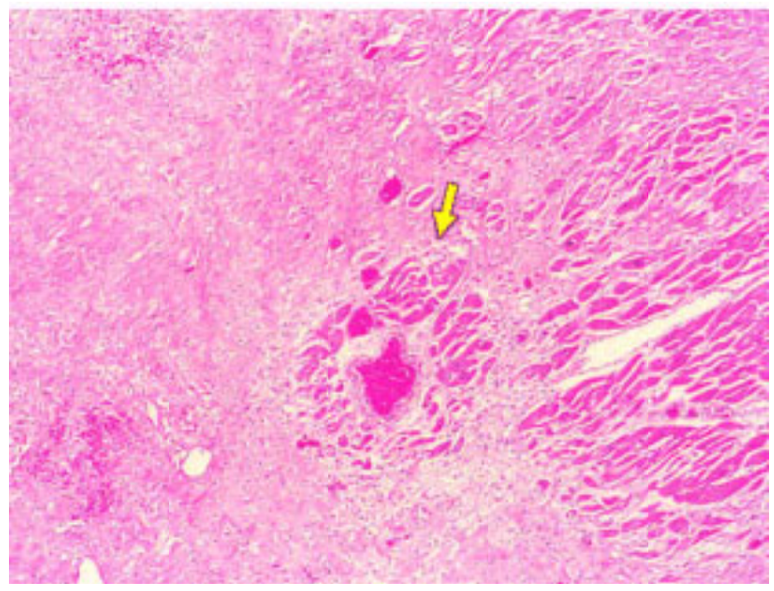
Recent myocardial infarction with free wall rupture of the anterior wall of the left ventricle. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 49.16 A 61-year-old male patient with left ventricular pseudoaneurysm after acute anterolateral myocardial infarction. Patient underwent successful surgical repair. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

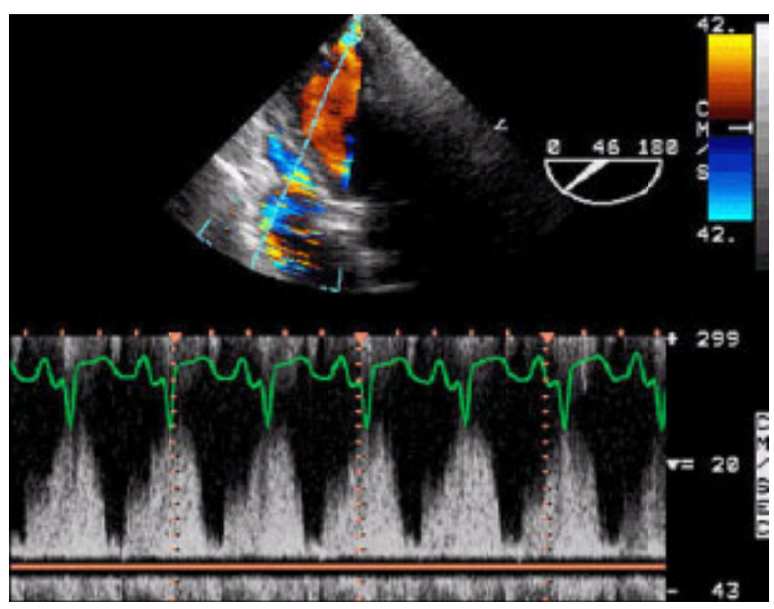
Abrupt myocardial rupture into the pericardial sac is rapidly fatal, although slower accumulations can allow time for surgery. Most postinfarction pericardial effusions are either due to local inflammation (early) or Dressler's syndrome (late). The incidence of pericardial effusions has ranged from 6% (86) to 37% (87) after infarction, and there is poor correlation with physical signs of pericarditis. Ventricular septal defect is a contained cardiorrhexis (88,89,90,91 and 92), typically at the anteroapex for left coronary infarction and the inferior base for right coronary infarction.



Evolution of acute anterolateral myocardial infarction at 72 hours. Q-wave pattern in the anterolateral leads is well established. Persistent ST-segment elevation suggests complication by aneurysm or pericarditis.



Healed patchy myocardial infarction. The arrow demonstrates an island of "trapped" myocytes.

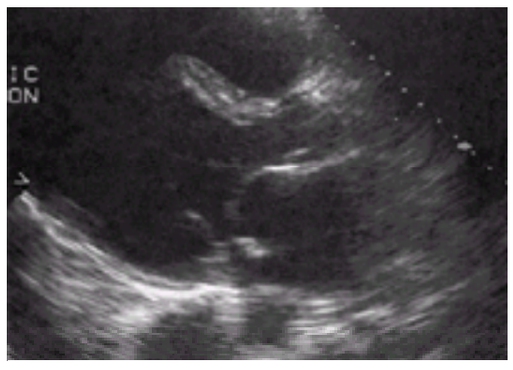


Doppler recording of flow through an ischemic ventricular septal defect before surgical repair.

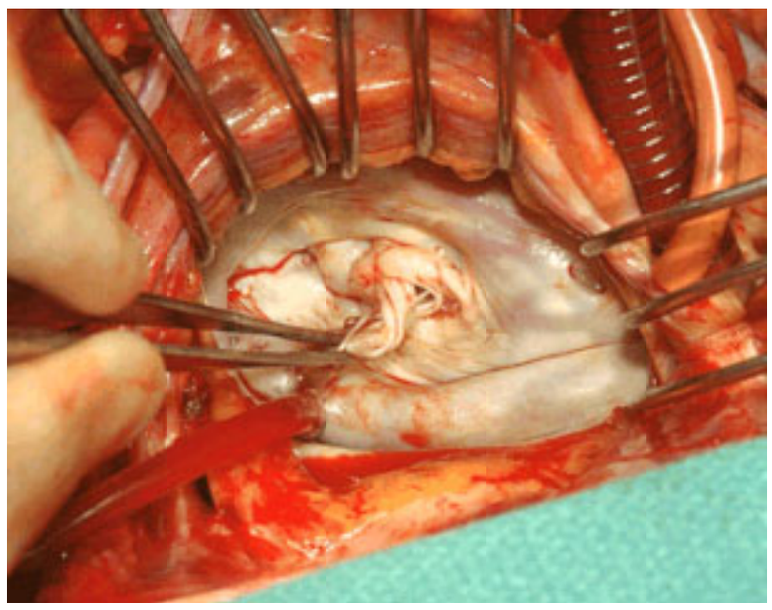
Video 49.17 Color Doppler view of a post infarct ventricular septal defect in the inferior septum. Note the color flow thru the large defect. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.18 This is an intraoperative transgastric transesophageal view of an ischemic ventricular septal defect after an acute inferior myocardial infarction. Note the location of the large defect in the inferior septum. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Mitral regurgitation (MR) is regularly encountered as a periinfarction complication (22,88). Papillary muscle rupture is always disabling and may be rapidly fatal (93,94) (*e*Fig. 49.5.2). Because of cross support of the chordae, free motion of the liberated papillary muscle can sometimes be inapparent. Therefore, any patient with severe heart failure and unexpectedly good ventricular function after infarction should have papillary muscle rupture considered. Less severe MR is also commonly seen after myocardial infarction, typically due to the abnormal wall motion displacing or undermining the papillary muscle (see Chapter 51).



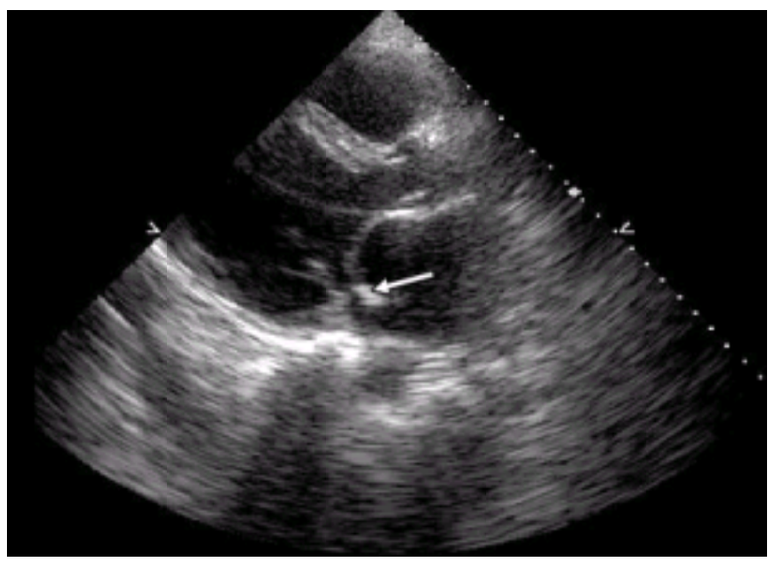
***e*FIGURE 49.5.2** Ruptured papillary muscle. In this parasternal long-axis view, a ruptured posteromedial papillary muscle is seen flailing into the left atrium. This rupture resulted from a recent inferior myocardial infarction.



Intraoperative field demonstrating a mitral valve with a torn papillary muscle prolapsing across the mitral valve into the left atrium. The surgeon has the papillary muscle in forceps demonstrating the chordae attached to the posteromedial commissure, predominantly attached to the anterior mitral leaflet. (The patient's head is to the left of the screen and feet to the right.)

Surgical pathology specimen demonstrating a torn papillary muscle seen to the lower right of the screen, attached via chordae to a portion of the anterior mitral leaflet. Note the torn "ragged edges" at the bottom of the papillary muscle head.

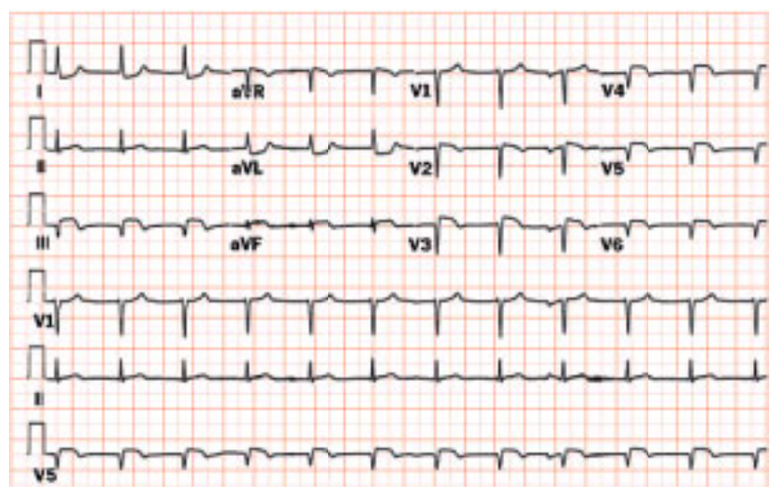
Video 49.19 Parasternal long-axis view of a ruptured papillary muscle after myocardial infarction. Note the bright mass (papillary muscle) attached to the tip of the anterior mitral leaflet as it flails into the left atrium. This resulted in severe mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Parasternal long-axis view of a papillary muscle rupture after myocardial infarction. Note the piece of papillary muscle attached to the tip of the anterior mitral leaflet as it flails into the left atrium (demonstrated by the arrow).

RV infarction can be seen in approximately 40% of inferior infarctions (95,96), with injury ranging from subclinical depression to severe RV dysfunction causing a low-output state with high mortality. RV infarction is characterized by ventricular enlargement, decreased descent of the base, and inferior vena cava (IVC) plethora (95,96). Elevation of right-sided filling pressures can cause right-to-left shunting through a patent foramen ovale and can be easily documented by the passage of saline microbubbles across the interatrial septum.

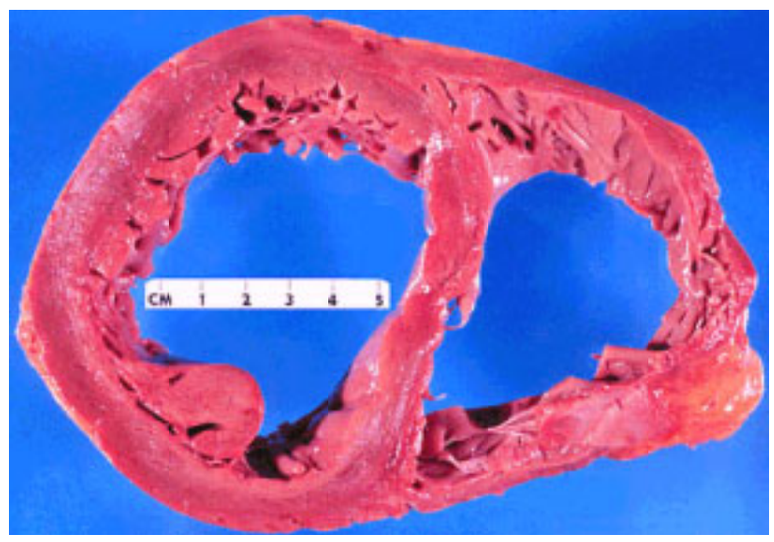
Right ventricular infarct. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Right ventricular infarction. ST-segment elevation in leads V_4R and V_5R reveals right ventricular involvement complicating the inferior infarct.

Cardiomyopathies: Their Recognition by Echocardiography

Dilated, hypertrophic, and restrictive cardiomyopathies can be characterized by two-dimensional echocardiography. Congestive cardiomyopathy shows spherical cavitary dilatation (LV volume often >250 mL), normal wall thickness, and poor wall thickening and endocardial motion (eFig. 49.4.1).M-mode echocardiography displays mitral-septal E-point separation, poor mitral and AV opening, and decreased systolic aortic root motion. Involvement of the right heart is important because it implies pulmonary hypertension and RV cardiomyopathy, which independently worsen prognosis (97,98). In spite of an EF of less than 30%, cardiac output (stroke volume × heart rate) may be normal due to tachycardia and the large end diastolic volume.



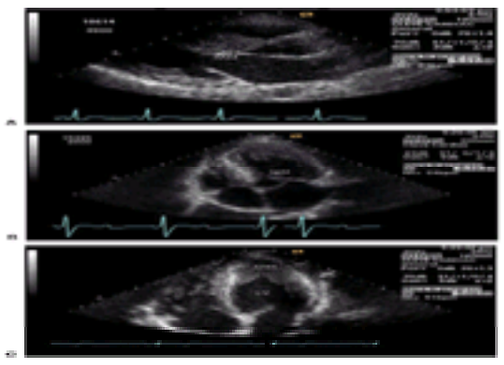
Dilated congestive cardiomyopathy. Both the left and right ventricles are significantly enlarged. In this example, the left ventricular wall thickness falls within normal limits.

Early signs of cardiomyopathy are a decrease in the descent of the cardiac base (24), an increase in sphericity (24), and a rise in end systolic volume index (40,42). This latter value is highly useful in detecting early cardiomyopathy because the end systolic volume tends to be more sensitive to contractility than the preload volume (35). An end systolic volume index that exceeds 30 mL per m^2 indicates significant global dysfunction. In valve disease, patients whose end systolic volume index exceeded 60 mL per m^2 (40) had a much poorer outcome than did other patients. Similarly, in ischemic cardiomyopathy the value of 45 mL per m^2 segregates patients with poor outcome.

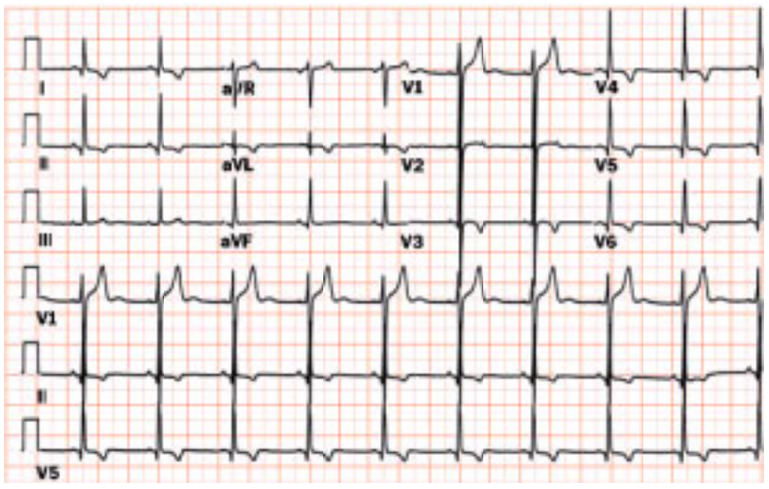
In South America, a congestive or a segmental cardiomyopathy raises the possibility of Chagas' disease (99), in which insect-borne *Trypanosoma cruzi* eventually leads to damage of the myocardium. It may appear as global dysfunction or as an apical aneurysm that, unlike coronary disease, spares the interventricular septum. Less commonly, the inferior base can be the site of segmentally isolated thinning and scar formation.

Hypertrophic Cardiomyopathies

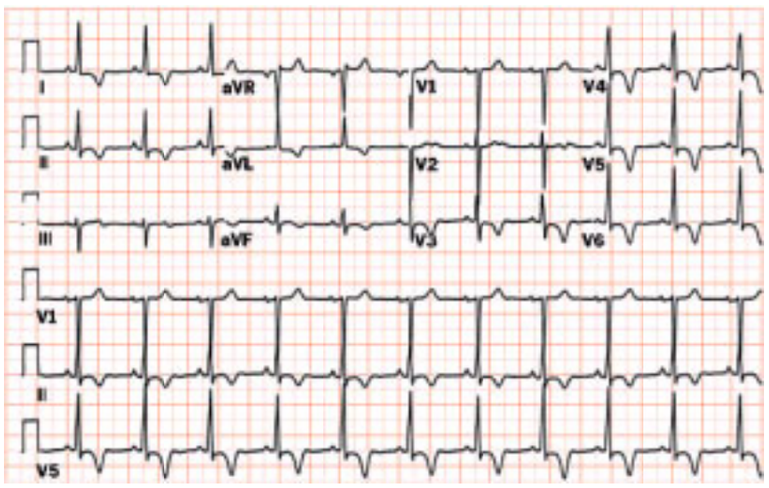
Primary hypertrophic cardiomyopathies are characterized by increased LV mass without apparent etiology, such as hypertension or aortic stenosis, and can be asymmetric or symmetric (100,101,102 and 103). In asymmetric septal hypertrophy (ASH), the increased wall thickness is typically localized in the basal septum (101) (eFig. 49.5.3A and eFig. 49.5.3B), and, although it is clearly heritable, there is variable expressivity among affected family members. An unusual variation of ASH is apical hypertrophy (so-called Yamaguchi's disease) (104,105) (eFig. 49.5.3C). When dynamic outflow tract obstruction accompanies ASH, hypertrophic obstructive cardiomyopathy is present (106,107 and 108). Findings that are consistent with obstruction may be noted echocardiographically at rest or with provocation by amyl nitrite, exercise, or inotropic stimulation (100). Fully developed hypertrophic obstructive cardiomyopathy consists of ASH, systolic anterior motion of the MV, crowding of the LV outflow tract by the mitral apparatus and septum, partial mid-systolic closure or notching of the AV, and mitral annular calcification.



***e*FIGURE 49.5.3** Hypertrophic cardiomyopathy. Parasternal long-axis view **(A)** and apical four-chamber view **(B)** of two patients with hypertrophic cardiomyopathy, demonstrating asymmetric septal thickening with systolic anterior motion (SAM) of the mitral valve. **C:** Apical four-chamber view of a patient with apical hypertrophy or Yamaguchi's disease. LV, left ventricle.



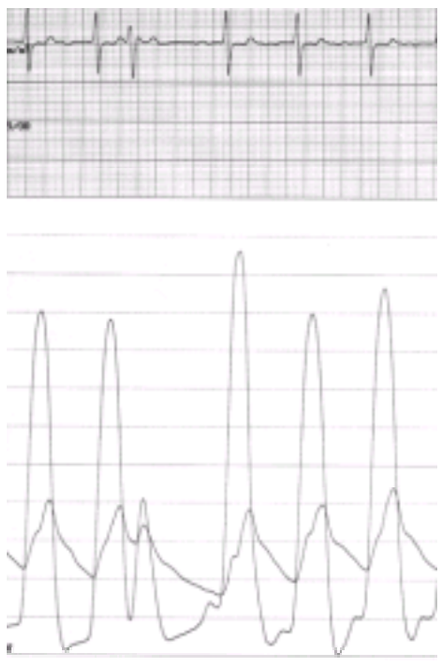
Hypertrophic cardiomyopathy. Inverted precordial T waves associated with hypertrophic cardiomyopathy.



Yamaguchi's disease. Note anterior precordial T wave inversion in this Asian patient with apical hypertrophy.

VIDEO

Video 49.20 Ventriculography in a patient with Yamaguchi's apical hypertrophy. In this syndrome there is just proportionate hypertrophy near the apex, which produces a characteristic prolongation of the left ventricular silhouette during ventriculography (right anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



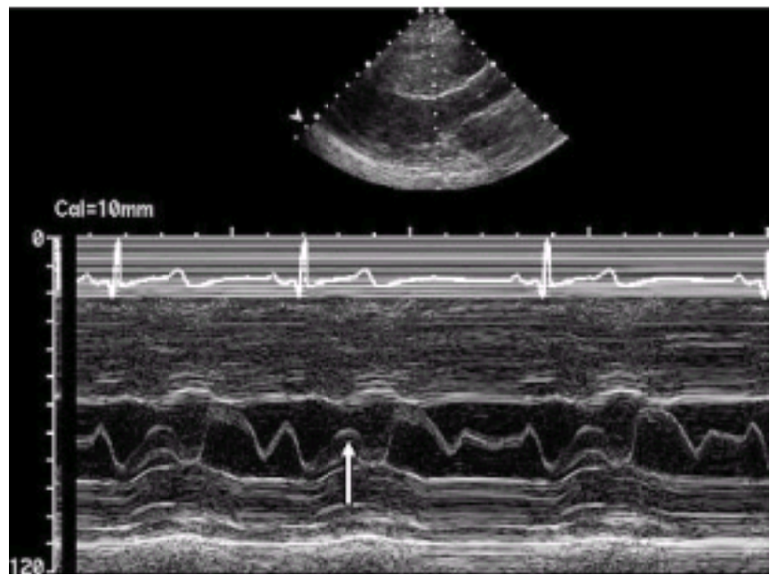
A 57-year-old female patient with hypertrophic cardiomyopathy. This figure shows the Brockenbrough response after a ventricular premature beat. The Brockenbrough response includes an increase in left ventricular systolic pressure, a decrease in aortic systolic pressure, an increase in left ventricular–to-aortic gradient, and diminished aortic pulse pressure.

VIDEO

Video 49.21 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy **(A)**. Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy **(B)** for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.22 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy **(A)**. Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy **(B)** for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Secondary LV hypertrophy (LVH) is most commonly due to hypertension and conveys a poor prognosis (52). The sensitivity of M-mode echocardiography for detecting LVH is clearly superior to ECG (50), but two-dimensional echocardiography has superior reproducibility.

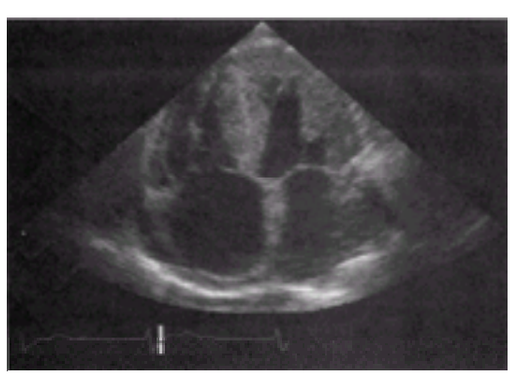


M-mode tracing of hypertrophic cardiomyopathy with severe septal hypertrophy seen at the top of the trace and systolic anterior motion (SAM) of the mitral valve in systole seen in the middle of the trace (designated by the arrow).

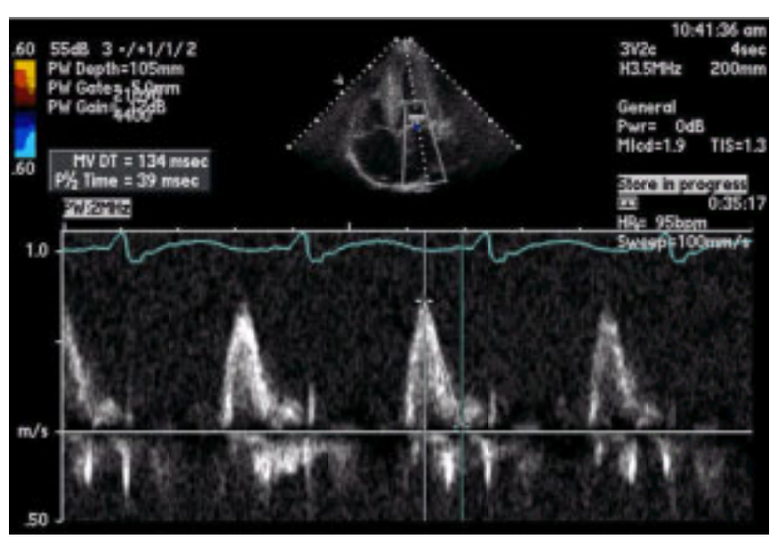
Restrictive Cardiomyopathy

Restrictive cardiomyopathies are more difficult to diagnose than hypertrophic or congestive states, but echocardiography remains the most effective diagnostic test. The most common restrictive state is the small stiff heart of diabetes (109). It is clinically inapparent in the majority of diabetics but may lead to pulmonary congestion in association with regional ischemia.

Amyloid heart disease is rare (110,111 and 112) and carries a poor prognosis (113). Amyloid infiltration is characterized echocardiographically by increased LV wall thickness and a peculiar glittering or scintillating appearance of the myocardium (eFig. 49.5.4). Superficially, amyloid heart disease can resemble typical LVH (110). Contractile function is nearly normal or mildly depressed, and the left atrium (LA) is usually enlarged. The presence of these findings along with typical clinical signs or symptoms (e.g., low ECG voltage, neuropathy) should prompt a gingival or rectal biopsy.



***e*FIGURE 49.5.4** Amyloidosis. Apical four-chamber view showing typical appearance of amyloidosis, including wall thickening with highly reflective myocardium (speckling). The interatrial septum is also thickened, helping to distinguish this from left ventricular hypertrophy.



Pulsed wave Doppler of the mitral valve inflow in a patient with amyloidosis demonstrating a short deceleration time (134 ms) consistent with restrictive physiology.

Unclassified Cardiomyopathy

Ventricular noncompaction is a rare form of ventricular dysplasia that results from intrauterine arrest in endomyocardial morphogenesis (114,115). It involves the LV or the LV and RV, most commonly in association with other congenital malformations, but occasionally in isolation (116). The myocardium is characterized by numerous prominent, excessive trabeculations with deep intertrabecular recesses. Noncompaction most commonly affects the apical, mid-inferior, and mid-lateral segments (117).

Video 49.23 Ventricular noncompaction. Apical four-chamber view without **(A)** and with **(B)** intravenous contrast of a patient with ventricular noncompaction. Note the characteristic trabeculations and recesses that result from arrest on intrauterine development. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.24 Ventricular noncompaction. Apical four-chamber view without **(A)** and with **(B)** intravenous contrast of a patient with ventricular noncompaction. Note the characteristic trabeculations and recesses that result from arrest on intrauterine development. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

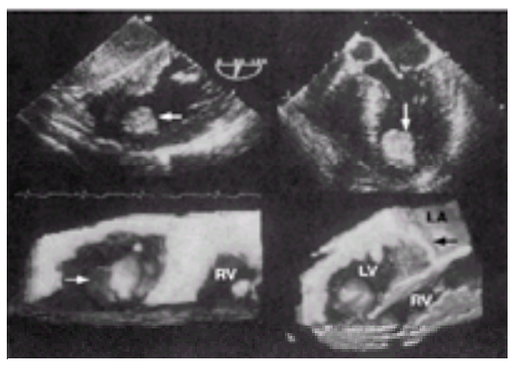
Video 49.25 Apical two-chamber view of a patient with noncompaction with the inferior wall to the left of the screen and the anterior wall to the right. Again, note the thickened, heavily trabeculated myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.26 Apical four-chamber view of a patient with noncompaction with the right ventricle to the left of the field and the left ventricle to the right. Note the thickened, heavily trabeculated myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

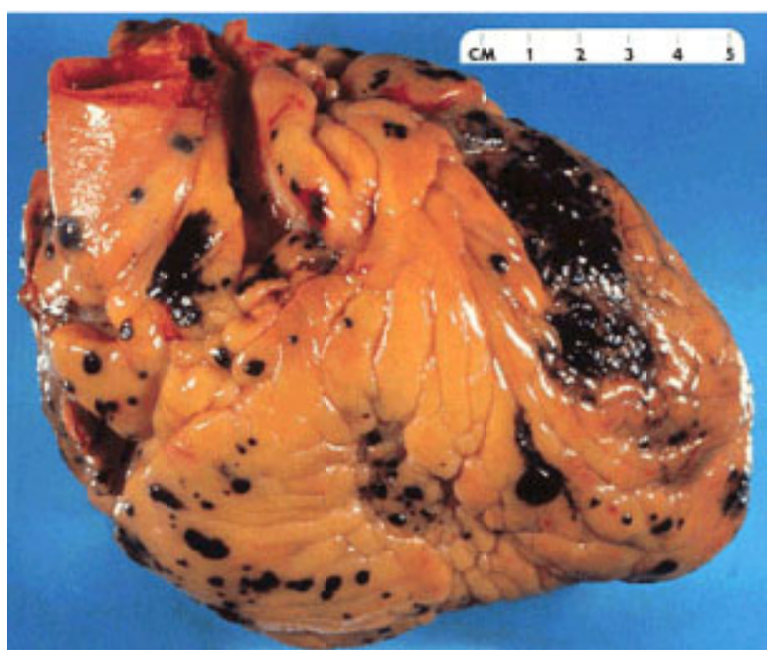
Video 49.27 Apical long-axis view of a patient with noncompaction. Isolated ventricular noncompaction is a rare idiopathic cardiomyopathy characterized by abnormal structure of the myocardium caused by intrauterine arrest of compaction of the myocardial fibers without any coexisting congenital lesions. The typical echocardiographic appearance includes segmental thickening of the myocardium consisting of two layers: a thin compacted epicardial and an extremely thickened endocardial layer with prominent trabeculations and deep recesses. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Left Ventricular Masses

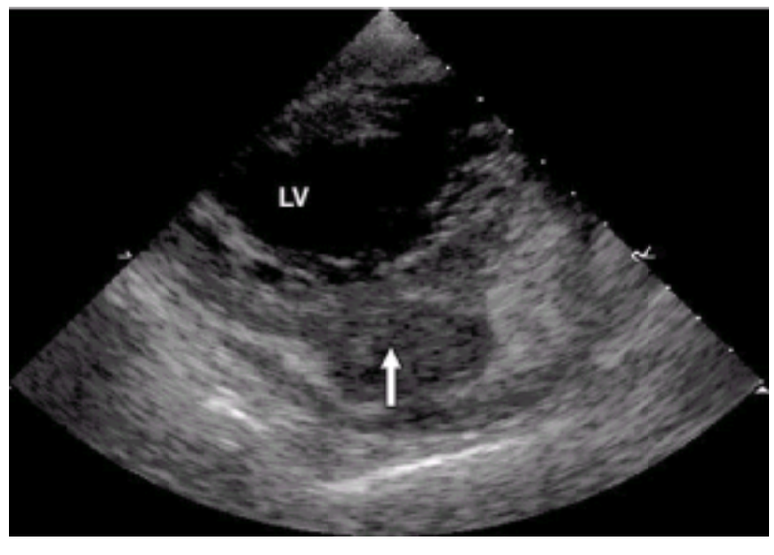
Nonthrombotic masses of the left ventricle are quite rare, but approximately 25% are malignant (33% angiosarcomas, 20% rhabdomyosarcomas, 10% mesotheliomas, and 11% fibrosarcomas with melanomas reported) (118). In the pediatric population, the most common tumors are rhabdomyomas associated with tuberous sclerosis. *e*Figure 49.5.5 shows a three-dimensional image of an apical mass, found to be a benign lipoma at surgery. Nonmalignant lesions include myxomas and fibroelastomas, and both have considerable embolic potential. Myxomas can occur anywhere in the left ventricular cavity, whereas fibroelastomas usually occur on the MV or valvular apparatus.



***e*FIGURE 49.5.5** Left ventricular lipoma. Transgastric (*upper left*) and transesophageal (*upper right*) two-dimensional echocardiograms demonstrating a highly reflective mass in the left ventricular apex. The lower panel shows three-dimensional reconstruction of this mass, demonstrating its relationship to the surrounding myocardial wall. LA, left atrium; LV, left ventricle; RV, right ventricle. (Images courtesy of Dr. Raymond Stainback.)



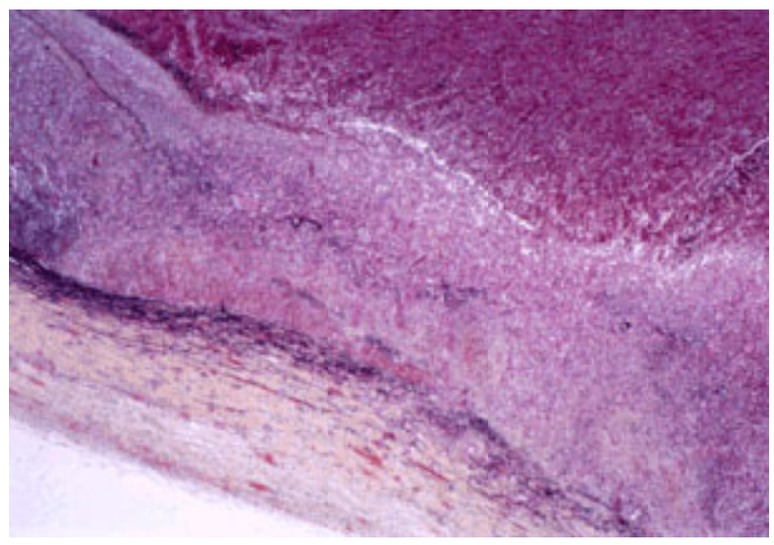
Metastatic malignant melanoma on the epicardial surface. The black deposits represent metastatic melanoma deposits.



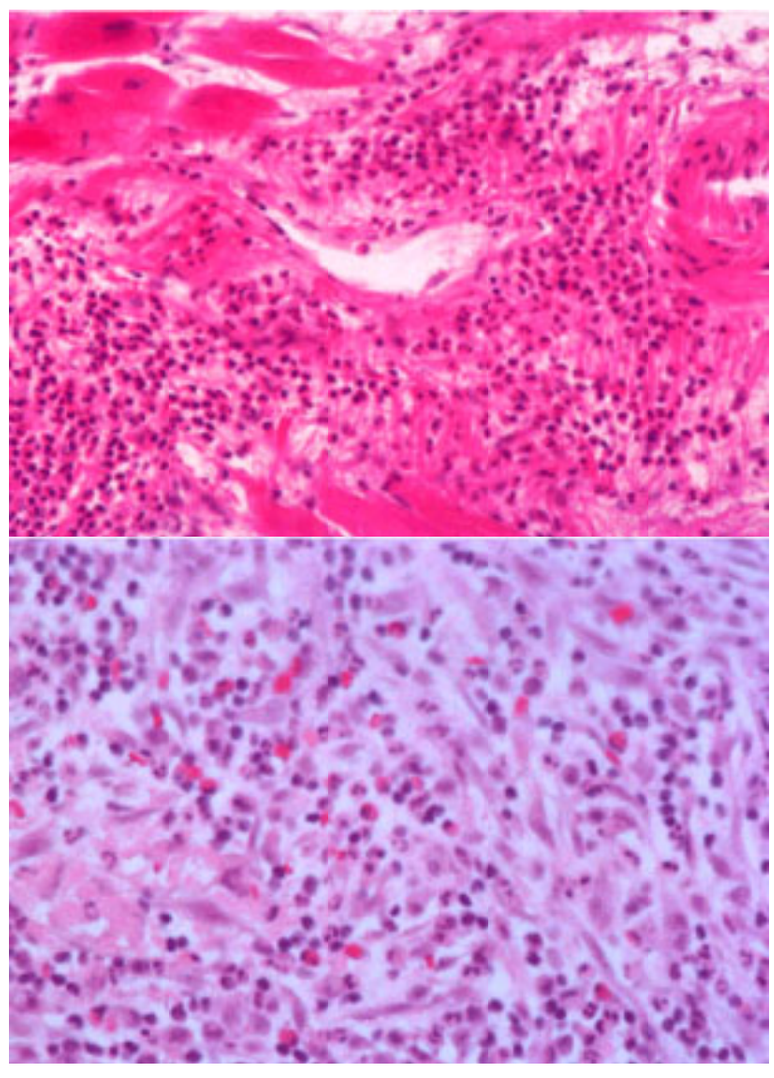
Transgastric long-axis view of a metastatic sarcoma within the anterior wall of the left ventricle at the bottom of the screen (designated by the arrow).

Video 49.28 Transgastric 90-degree long-axis transesophageal echo view of a patient with a sarcoma metastatic to his left ventricular anterior wall. Note the invasion of the myocardium by this large mass. Additionally, there is severe hypokinesis of the anterior wall. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Endomyocardial fibrosis is a disease of the impoverished living in North Africa and South America. It is associated with restriction of LV and RV filling by obliteration of one or both cardiac apices by a thrombotic fibrocalcific process (119). The disease can also occur in relation to eosinophilia (Loeffler's or Davies' disease) and eosinophilic leukemia. In addition to the unique appearance of the apices, the atria are strikingly enlarged, with mitral and tricuspid regurgitation (TR) complicating the picture. Its recognition depends on a high degree of clinical suspicion and a characteristic echocardiographic appearance. In South America, a surgical approach has been developed that debulks fibrotic material from the apex and restores LV compliance.



Löffler's syndrome. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



A case of Löffler's syndrome demonstrating extensive infiltration of the myocardium by eosinophils (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Right Ventricle

Imaging the RV is an essential portion of a comprehensive echocardiographic evaluation, as occult right heart disease may occur as a result of left-sided pathology.

Right Ventricular Wall Thickness, Contractile Function, and Size

RV wall thickness, assessed from the parasternal or subcostal windows, should be only 3 to 4 mm thick, with 5 mm considered hypertrophied (13,45,120). In contrast to the elliptical LV, the shape of the RV frustrates volumetric measurement. It has been described as a pyramid with a triangular base or as a teapot. The tomographic nature of echocardiography makes imaging this irregular-shaped organ in a single plane impractical (56,120,121,122,123 and 124). One simple analog is the parasternal M-mode diameter of the RV, although a more accurate dimension can be obtained from a two-dimensional image. The size of the normal RV is considerably less than the left ventricle, whether imaged from the parasternal long axis, the parasternal short axis, or the apical four-chamber view (Fig. 49.2). In the latter view, the LV should form the cardiac apex. If the RV even shares the apex, RV dilatation should be suspected.

A 42-year-old female patient with right ventricular hypertrophy.

Muscular hypertrophy of the arterial wall in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)

To assess RV contractility visually, careful adjustments of instrument settings may be needed to detect RV inward systolic motion or wall thickening accurately. Most M-mode images are of the RV outflow tract region, which may not be representative of the whole chamber.

RV volume and EF can be estimated by the area-length algorithm applied from the apical four-chamber or subcostal views (122,123 and 124). This correlates reasonably well (r = 0.83) with radionuclide scanning for EF (121), although absolute volumes are significantly underestimated. The four-chamber area-length RV-LV volume ratio should be approximately 0.6, but it increases to greater than 1.1 in cor pulmonale (125).

Descent of the RV base toward the fixed apex is easily seen in the subcostal and four-chamber views and, if depressed, is a sensitive indicator of RV systolic dysfunction (124). Descent of the RV base was 0.7 ± 0.2 cm in patients with hemodynamically significant RV infarction, 1.3 ± 0.4 cm in those with ECG evidence but without hemodynamic compromise, and 2.0 ± 0.2 cm in a group of 20 normal control patients (p <.001). Doppler tissue imaging has yielded similar results in normal subjects (126).

Segmental Abnormalities of the Right Ventricle

The most common segmental RV abnormality results from RV infarction, usually in the setting of inferior wall myocardial infarction (95), and may lead to a lethal low-output syndrome even when LV damage is not extensive. In RV infarction, there is cavity enlargement (96) with mid-anterior and inferior wall akinesis or even aneurysm by two-dimensional imaging. A hinge point may differentiate infarcted from normal segments, and the descent of the RV base is impaired (95). The degree of RV dilatation and IVC plethora provides clues to the hemodynamic severity of RV infarction (95).

Endocardial fibrosis (with or without eosinophilia) can also segmentally affect the RV. The apex fills with fibrothrombotic matter, resulting in RV restriction, TR, and atrial enlargement (99,119).

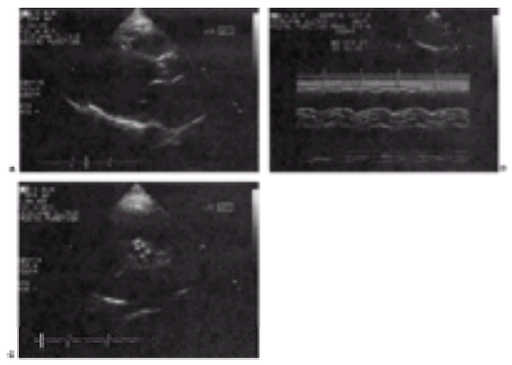
Right Ventricular Tumors and Masses

RV masses can be primary, metastatic, or embolic in nature (127,128). Generally, the same masses that affect the LV can also involve the RV. Myxomas are the most common benign RV tumors and tend to be larger because they are detected later. Primary malignant tumors are very rare and are usually angiosarcomas. Metastatic melanoma can occur, but usually very late in the course of the disease. More commonly, tumors reach the right heart by propagating through the venae cavae. Hepatic, renal, and adrenal tumors can present in this manner, and a malignant thymoma that obstructs RV inflow has been observed. Such masses can be surgically palliated.

The most important propagating masses are embolic thrombi from the lower extremities (129). These thrombi, which may present as a localized mobile RV mass, are generally less reflective than malignant masses. RV enlargement and pulmonary hypertension suggest multiple pulmonary emboli. These masses may remain in the right heart, embolize to the lungs, or rarely cross a patent foramen ovale (130). These thrombi generally have an ominous prognosis and require aggressive medical or surgical intervention.

Conditions Associated with Right Ventricular Dilatation

RV volume overload without pulmonary hypertension is seen in atrial septal defect (ASD), tricuspid insufficiency, and pulmonary insufficiency, in which cases the RV enlarges to form the cardiac apex. RV contractile function is usually preserved, and wall thickness remains normal. In ASD, the pulmonary artery is also enlarged. *e*Figure 49.5.6 shows a suprasternal view of the aortic arch and pulmonary artery bifurcation. If the right pulmonary artery is of normal caliber, pulmonary hypertension and left-to-right shunts of any magnitude are unlikely. Similarly, the short-axis basal precordial view is the best window for evaluating the size of the main pulmonary artery.



***e*FIGURE 49.5.6** Pulmonary artery bifurcation. Parasternal image demonstrating the right ventricular outflow tract (RVOT), pulmonary valve (PV), and bifurcation of the pulmonary artery (PA) into the right (RPA) and left (LPA) pulmonary arteries. AO, aorta.

An ASD can be further confirmed by saline contrast injection, showing a negative contrast jet in the RA or right-to-left shunt flow in the LA. Sometimes the defect itself can be seen, especially with color Doppler, which may also show discrepant flow through the RV and LV outflow tracts (121). Congenital absence of the pericardium may cause RV enlargement (131) due to rotation of the heart, but with a small pulmonary artery, low pulmonary pressure, and a normal contrast study. RV enlargement may also be caused by severe TR, most commonly due to LV dysfunction, rheumatic disease, endocarditis, and primary pulmonary hypertension. Two-dimensional signs of TR include leaflet flail or malcoaptation, although color Doppler is the most reliable modality.

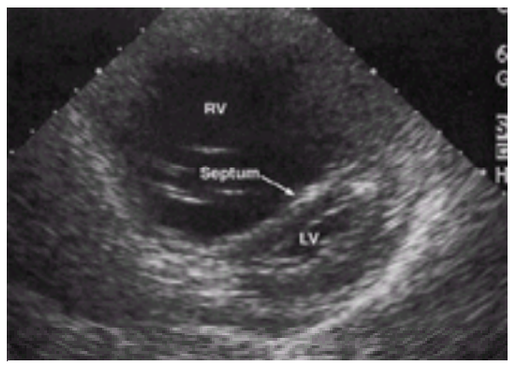
Chronically elevated pulmonary vascular resistance leads to cor pulmonale with a dilated apex-forming RV (125), mild to moderate RV hypertrophy, and a dilated IVC that is unresponsive to respiration. A patent foramen ovale (20–30% of patients) may show right-to-left shunting with contrast injection. The etiology usually is chronic obstructive lung disease but may be chronic pulmonary embolism, cystic fibrosis, bronchiectasis, connective tissue disease, adult respiratory distress syndrome, asthma, sarcoid, obesity with sleep apnea, or chronic pulmonary infection.

Severe right ventricular hypertrophy resulting from pulmonary hypertension. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 49.29 Apical four-chamber transthoracic view demonstrating a patient with severe pulmonary hypertension with a markedly dilated right ventricle with right ventricular dysfunction and a dilated tricuspid annulus. This annular dilatation causes severe tricuspid regurgitation. Because of the severe tricuspid regurgitation, there is significant right atrial dilatation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.30 Apical four-chamber view with color Doppler demonstrating severe tricuspid regurgitation due to annular dilatation. There is right ventricular dilatation and significant right ventricular dysfunction. Note the large zone of proximal flow convergence on the right ventricular side of the tricuspid valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Echocardiographic features of primary pulmonary hypertension are similar to those of cor pulmonale but with greater RV hypertrophy and septal flattening (eFig. 49.5.7), often preceding IVC plethora. Pulmonary hypertension from congenital heart disease (atrial or ventricular septal defect) may cause severe RVH, but right heart failure may be minimal early on. In the end stage, it may be difficult to distinguish ASD/Eisenmenger complex from primary pulmonary hypertension with a patent foramen ovale.

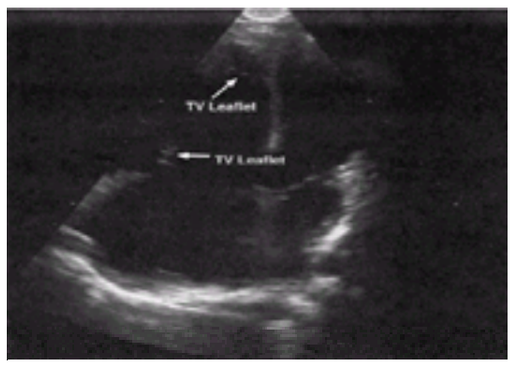


***e*FIGURE 49.5.7** Pulmonary hypertension. Parasternal short-axis view showing a massively enlarged right ventricle (RV) causing marked septal flattening and a small left ventricular (LV) cavity.

Isolated RV dilatation may be seen in arrhythmogenic RV dysplasia (parchment ventricle or Uhl's disease) (132). Features of RV dysplasia include a thin RV wall, increased epicardial fat, aneurysms of the RV free wall, and a prominent moderator band with complex attachment to the septum and RV free wall. Spontaneous fatal ventricular arrhythmias may be seen with this condition.

In Ebstein's anomaly, the septal leaflet of the TV is displaced toward the RV apex, leaving an "atrialized ventricle" behind the valve (eFig. 49.5.8). Contraction during

systole may cause right-to-left shunting across a patent foramen and cyanosis (133,134).

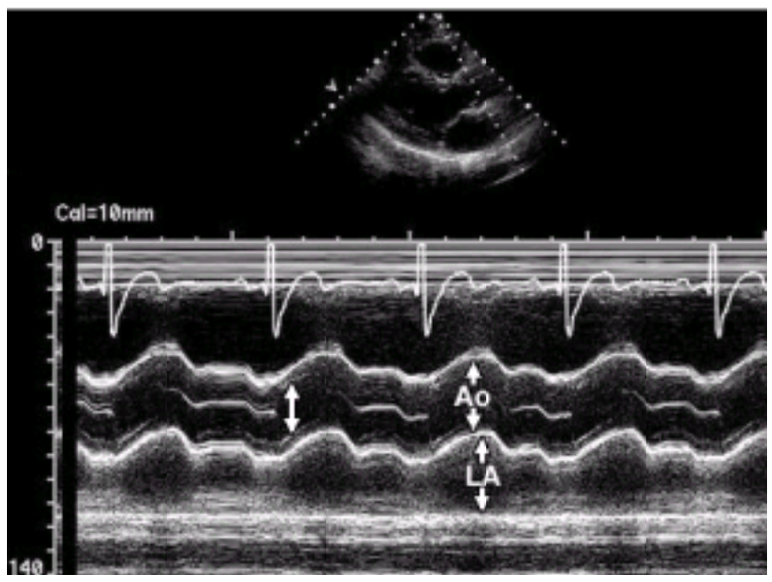


***e*FIGURE 49.5.8** Ebstein's anomaly. Apical four-chamber view of a patient with Ebstein's anomaly. The septal leaflet of the tricuspid valve (TV) is misplaced apically, leaving an atrialized portion of the right ventricle.

ECHOCARDIOGRAPHY OF THE ATRIA

Left Atrium

The LA serves reservoir, conduit, and booster pump functions for blood that enters the LV. It is commonly involved in pathologic processes, including dilation, thromboembolic and neoplastic disease, extrinsic compression, and fibrillation, each of which is well assessed by echocardiography.



Normal M-mode through the aortic valve and left atrium (LA) in the parasternal long-axis view by transthoracic echo. (The unlabeled arrow represents the opening of the aortic valve.) Ao, aorta.

Surgical specimen of the large left atrial mass explanted at the time of surgery. Note its somewhat pale, glistening surface, suggesting that the thrombus is not fresh and possibly endothelialized.

Echocardiographic Assessment of Left Atrial Volume and Function

The standard parasternal M-mode image yields the anterior-to-posterior dimension of the LA (Fig. 49.4), typically the smallest, perhaps because of confinement between the sternum and the spine (135). This dimension is the least sensitive to enlargement but, when increased, is highly specific.

Because this single anterior-to-posterior dimension may underestimate overall LA size, volume estimates are preferred, requiring two sector scans, preferably orthogonal apical planes. The area-length formula has shown good correlation (r = 0.82–0.98) with angiography and contrast computed tomographic scanning (66,135), with some underestimation (up to 23%) but good reproducibility (95% confidence interval = 10 mL). Normal values throughout the cardiac cycle are shown in *e*Table 49.0.1 (65,68). Maximal volume occurs at end systole and averages 40 mL, falling to 25 mL after passive and active emptying. For a normal LV stroke volume of 65 mL, approximately 25 mL is reservoir emptying and 40 mL is conduit flow from the pulmonary veins. In the healthy young heart, only 10 mL atrial transport occurs with atrial contraction, the rest entering by passive flow early in diastole. With aging, the amount of active atrial transport more than doubles.

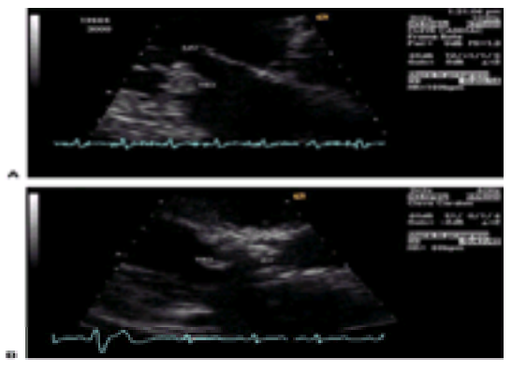
Atrial fibrillation causes progressive LA enlargement (136), which may be prevented by cardioversion (137). In rheumatic disease, LA diameter is predictive of atrial fibrillation (138) and the restoration of atrial function after cardioversion (139). However, the recurrence of lone atrial fibrillation appears to be independent of atrial diameter (140). Atrial volume has not been used in these studies.

Left Atrial Thrombi, Masses, and Tumors

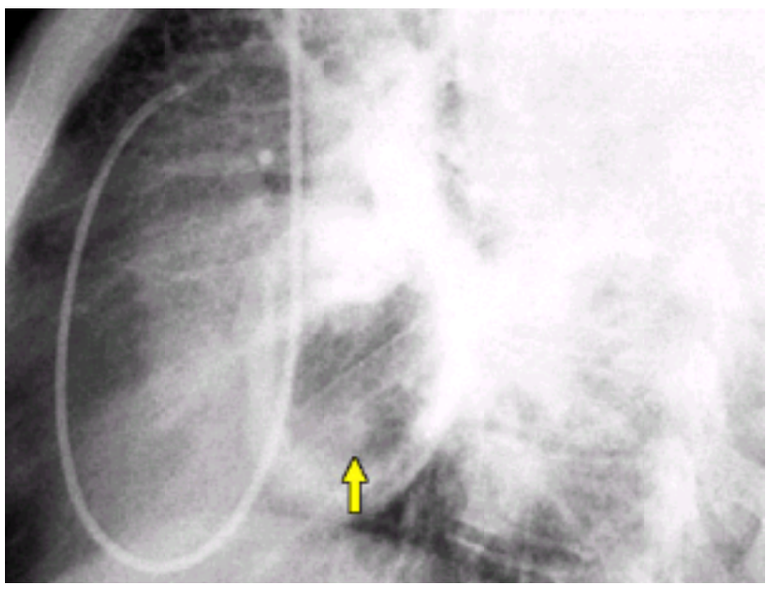
Left atrial thrombi are common but must be large to be identified by transthoracic echocardiography (TTE). This is especially true of the left atrial appendage, which usually requires transesophageal interrogation (141).

The most common LA tumor is myxoma (*e*Fig. 49.5.9), a benign mass that most commonly arises from the inferior limb of the fossa ovalis. It can present with

embolism or obstruction to mitral inflow. Myxomas may be encapsulated or highly mobile and amorphous, with the latter at highest risk for peripheral emboli. Encapsulated myxomas may have clear spaces (cysts) and highly reflective patches (bone). Attachment is typically by a stalk to the interatrial septum and may be biatrial. The attachment of amorphous myxomas is broader based, with a highly mobile, less reflective tip. Malignant LA tumors include fibrosarcoma, liposarcoma, and osteogenic sarcoma that may metastasize through the pulmonary vein.



***e*FIGURE 49.5.9** Left atrial (LA) myxoma (Myx). Apical four-chamber view showing a left atrial myxoma attached to the lower portion of the interatrial septum. RA, right atrium; RV, right ventricle.



Left atrial myxoma. This left anterior oblique projection depicts the left atrial filling phase of a pulmonary angiogram performed via a pulmonary artery catheter inserted into the right jugular vein. A large contrast free space (*yellow arrow*) depicts a space occupying mass within the left atrial cavity, which surgical pathology confirmed to be a myxoma.

Atrial myxoma. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 49.31 Atrial myxoma (long-axis). A myxoma attached to the interatrial septum is seen. During diastole, the myxoma moves through the mitral orifice into the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Right Atrium

M-mode techniques for measuring the RA have not been developed. However, area and volume can be assessed by two-dimensional imaging from the four-chamber and subcostal views. Viewed qualitatively, the two atria normally appear similar in size and smaller than the respective ventricle. Using true RA size as a standard, the best ECG criteria for RA enlargement (142) are a P-wave height of greater than 1.5 mm in lead V_2, a QRS axis of greater than 90 degrees, and an R/S ratio of greater than 1 in lead V_1 (without right bundle branch block; combined sensitivity 49% with 100% specificity). P-pulmonale detected only 6% of patients with right atrial enlargement. Tumors and thrombi (143,144) are discussed in the section Right Ventricular Tumors and Masses. Rarely, biatrial myxomas are observed (*e*Fig. 49.5.10).

***e*FIGURE 49.5.10** Biatrial myxoma. Apical four-chamber view demonstrating myxomas in the right and the left atria.

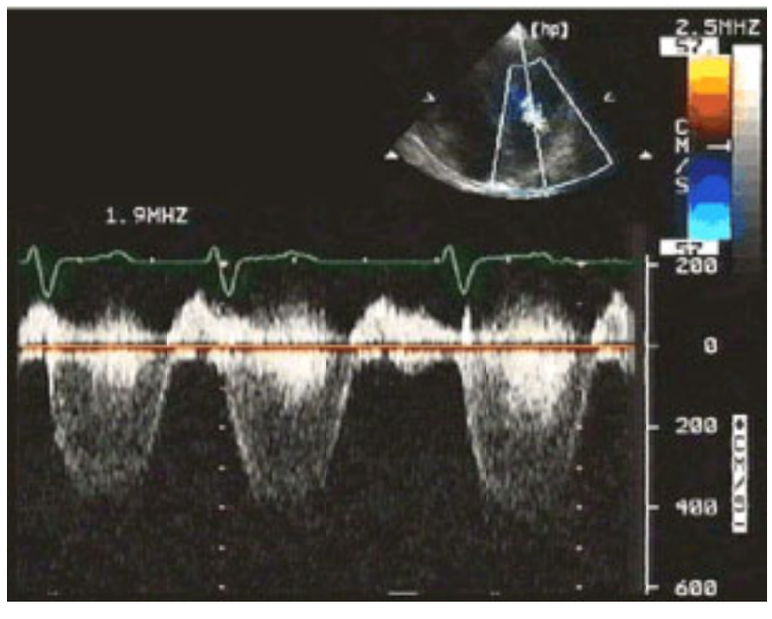
Video 49.32 Apical four-chamber view with the dilated right ventricle and right atrium to the left of the screen. Note the doming appearance of the rheumatic tricuspid valve. (The small left ventricle and left atrium are to the right of the screen.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

ECHOCARDIOGRAPHY OF THE CARDIAC VALVES

Echocardiography images the cardiac valves as does no other modality, providing high temporal and spatial resolution while relating valve structure to surrounding structures. Doppler is also critical to valve interrogation. It is discussed in detail in Chapter 51.

Evaluation of the Mitral Valve

Historically, the mitral valve was the first structure to be identified by echocardiography (3,4 and 5,145). An integrated investigation of the MV includes an M-mode tracing, several two-dimensional views, a Doppler evaluation, and, if needed, transesophageal imaging (141).



Apical continuous wave spectral Doppler recording of mitral regurgitation (systolic parabolic downward velocities). Note beat-to-beat variation due to atrial fibrillation.

The anterior mitral leaflet is highly mobile and quite echogenic, whereas the posterior leaflet is somewhat less apparent (Fig. 49.2). Images are acquired from the parasternal, apical, and subcostal regions. By M mode, an M-shaped pattern of MV motion is seen, reflecting first passive rapid filling and second atrial contraction, with near closure during diastasis, although blood may still pass from pulmonary veins to LV using the atrium as a conduit (65). Final closure results from atrial inflow deceleration and isovolumic LV contraction (Fig. 49.4).

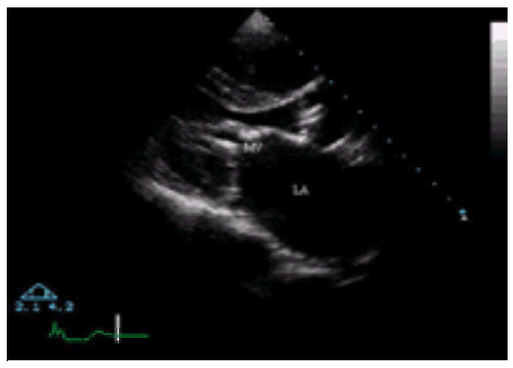
By two-dimensional imaging in the short-axis plane (Fig. 49.2), the MV is an ovoid orifice. In the long-axis plane, it resembles clapping hands moving freely in diastole, but forming a stable coaptation plane in systole. The MV and annulus descend with the cardiac base to assist left atrial filling.

Normal mitral leaflets are thin (<2 mm), although somewhat thicker at points of chordal attachment to the free margin (primary chordae) and leaflet body (secondary chordae). Transducer frequencies of greater than 2.5 MHz are required for adequate resolution. The papillary muscles can be seen in the short-axis view at four and eight o'clock with highly variable anatomy. From the apical four-chamber view, posterior angulation (typically showing the coronary sinus) is necessary to show the papillary muscles and chordae. Normal chordae appear fragmented unless they are thickened and fused by fibrosis or calcification. The mitral annulus has been shown to be nonplanar (saddle-shaped) and highly dynamic by three-dimensional imaging. On two-dimensional imaging annular diameter and calcification can be noted.

Mitral Pathology

Mitral Stenosis

From the earliest days of echocardiography (4), MS has been recognized by altered motion of the valve due to commissural fusion and chordal shortening. MS severity can be assessed on M mode by measuring the delay in diastolic closure (E-F slope). A normal value is greater than 60 mm per second; a slope of less than 10 mm per second indicates severe MS (146). By two-dimensional echocardiography, the leaflets dome into the ventricle throughout diastole (eFig. 49.5.11). In short axis, the mitral orifice can be reliably measured by direct planimetry (146,147), with an area of less than 1 cm^2 defining severe MS. Doppler quantitation methods are discussed in Chapter 51.



***e*FIGURE 49.5.11** Mitral stenosis. Parasternal long-axis view showing doming of the mitral valve (MV) in diastole with restricted opening and an enlarged left atrium (LA).

Video 49.33 Apical four-chamber view of a patient with severe rheumatic mitral stenosis with marked thickening and doming of the mitral leaflets, with severe ALE and spontaneous echo contrast within the left atrium. Note the left ventricle remains small. Because of long-standing severe mitral stenosis, the patient has severe pulmonary hypertension with right ventricular hypertrophy and right ventricular failure and severe right atrial enlargement. *This video must be viewed with QuickTime. If*

you do not have QuickTime you may download it here.

HEART SOUNDS

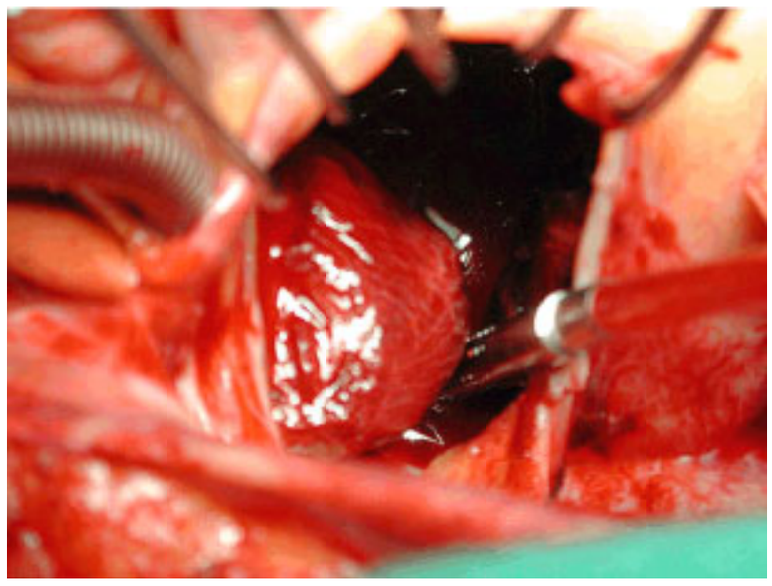
Audio 49.34 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm^2. Note the loud S_1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border **(A)** and apex **(B)**. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

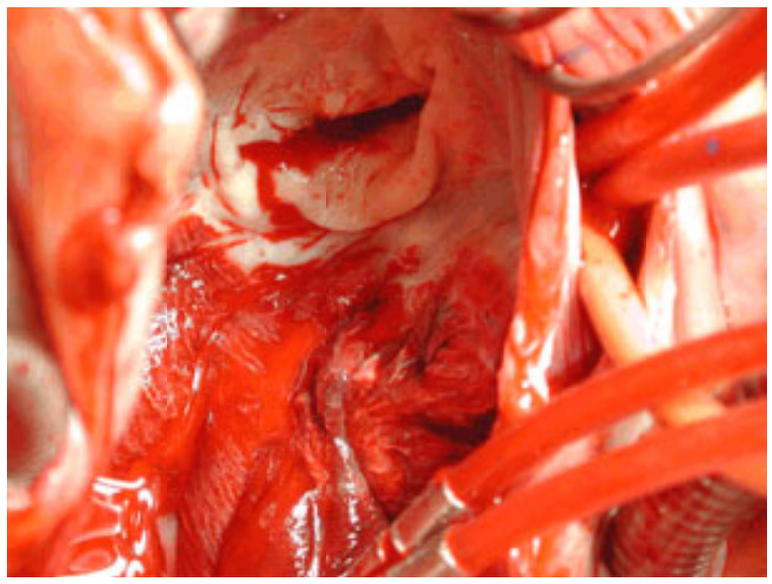
Audio 49.35 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm^2. Note the loud S_1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border **(A)** and apex **(B)**. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Indirect signs of MS severity include chordal shortening, leaflet calcification, LA enlargement, LV underloading, and right heart involvement (pulmonary hypertension). Progression cannot be accurately predicted, although those with mild MS and aortic insufficiency progress slightly faster (148).

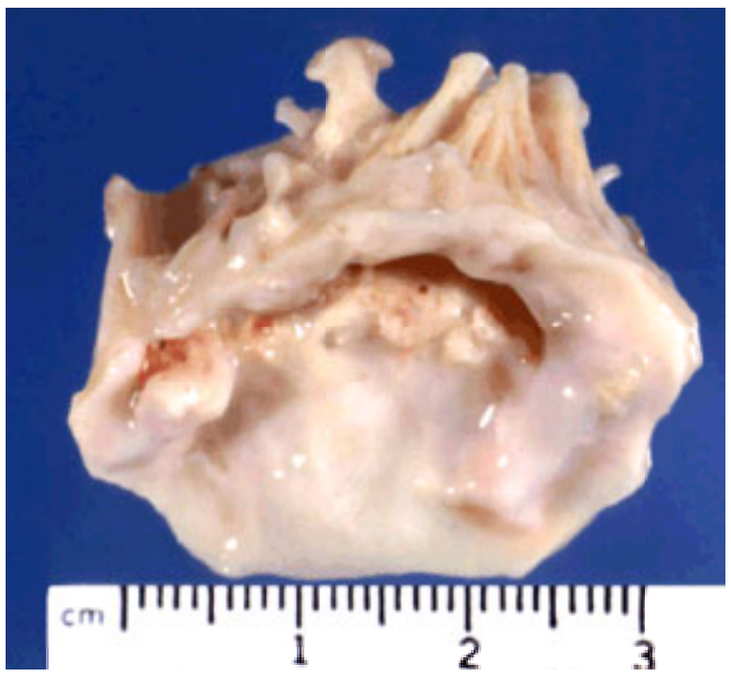
A 62-year-old female patient with mitral stenosis.



Intraoperative field looking into the left atrium of a patient with severe mitral stenosis who developed extensive clot within the left atrium. Notice the large mass in the center of the field, to the left of the opening within the left atrium. This is the largest portion of the left atrial thrombosis.



Intraoperative field looking into the left atrium after the large left atrial thrombus was resected demonstrating the rheumatic mitral valve at the top of the screen. Note the scarred, thickened, restricted mitral leaflets. This patient had severe mitral stenosis with a mean pressure gradient of 20 mm Hg across the valve and a mitral valve area of 0.7 cm^2.



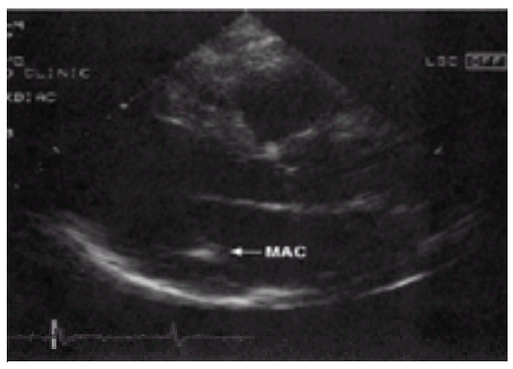
Rheumatic mitral valve. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Echocardiography in Balloon Valvuloplasty

Echocardiography is useful in guiding the transseptal puncture in balloon valvuloplasty and identifying appropriate candidates for this procedure. A “splitability score” grades four morphologic features of the MV—mobility, thickness, calcification of the anterior leaflet, and severity of subvalvular disease—each on a four-point scale (149,150). A total score of less than 7 indicates a high probability of success. An alternate score is based on the distribution of calcium around the stenotic orifice (151). More than mild insufficiency usually disqualifies patients from this procedure. This topic is covered in Chapter 86.

Other Causes of Inflow Obstruction

Mitral annular calcification is easily recognized in the long-axis view as a bright reflector in the atrioventricular groove, shadowing objects behind it (152,153 and 154). It may grow into the surrounding myocardium and inflow tract and should be distinguished from posterior leaflet calcification. In the short-axis view, it is C-shaped, lying between the papillary muscles, and is rarely associated with hemodynamically important mitral insufficiency, stenosis, or endocarditis (155,156) (eFig. 49.5.12). Annular calcification is mostly associated with age but is seen with hypertrophic cardiomyopathy (103), embolic stroke (156), secondary hyperparathyroidism (157), and atrioventricular conduction defects. Rarely, inflow obstruction becomes severe enough to warrant surgery (158).



***e*FIGURE 49.5.12** Mitral annular calcification (MAC). Parasternal long-axis view demonstrating hyperreflective material in the posterior mitral annulus.

Mitral stenosis. Left atrial enlargement and right ventricular hypertrophy have developed secondary to mitral stenosis, causing fixed pulmonary hypertension.

Congenital causes of MS include parachute MV (single papillary muscle), supravalvular mitral ring (between the left atrial appendage and MV), and cor triatriatum (a linear LA structure above the appendage). When detected in adults, they usually are not severely obstructive. Left atrial myxomas may rarely cause inflow obstruction by their bulk. Carcinoid syndrome (usually confined to right-sided valves) and ergot use may rarely cause MS (159). When bronchial carcinoid occurs alone, it can result in isolated MS.

Mitral Regurgitation

Regurgitant lesions may be structurally more subtle than stenotic ones, with Doppler (see Chapter 51) playing an even more dominant role. Nevertheless, careful structural interrogation is critical to evaluating MR.

HEART SOUNDS

Audio 49.36 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S_1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.37 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S_1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.38 Mitral regurgitation. Auscultation performed in a 52-year-old male patient with severe bileaflet mitral prolapse and regurgitation. Note the muffled S_1 and the holosystolic blowing murmur that radiates to the axilla at the apical position. A musical, squeaky quality is heard over the left sternal border. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.39 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.40 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.41 Mitral regurgitation. Auscultation performed in a 37-year-old male patient with bileaflet mitral valve prolapse and severe regurgitation. Note the soft S_1, nonejection click, mid-systolic blowing murmur, and the prominent S_3. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.42 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.43 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.44 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.45 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.46 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip*); left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.47 Parasternal long-axis view of a rheumatic mitral valve with color Doppler. Mitral regurgitation is the primary problem seen by color Doppler, with only mild mitral stenosis due to the thickened and doming leaflets. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.48 Left ventriculography with severe mitral regurgitation. After contrast injection in the left ventricle, the left atrium achieves the equal opacity to the left ventricular cavity indicative of severe (4+) mitral regurgitation. Before contrast injection, calcification in the mitral annulus and descending aorta is evident. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Rheumatic Mitral Regurgitation

In rheumatic disease, the posterior leaflet is fixed and shortened, allowing the anterior leaflet to override it on closure and resulting in posteriorly directed MR. The degree of malcoaptation is predictive of MR severity (160).

VIDEO

Video 49.49 Parasternal long-axis view of a rheumatic mitral valve with thickened, restricted, doming leaflets. Severe mitral regurgitation is the primary functional problem with this valve with only mild mitral stenosis. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

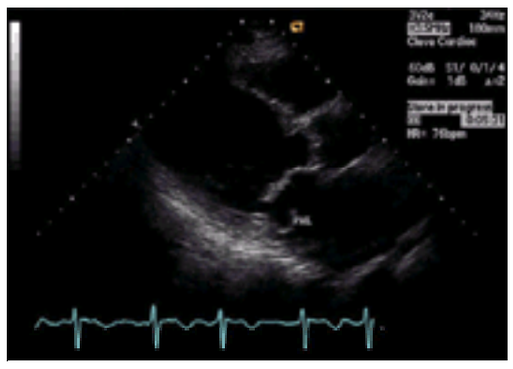
Mitral Valve Prolapse

The original clinical, auscultatory, and angiographic descriptions of mitral valve prolapse (MVP) (161,162) were rapidly supplemented by echocardiographic studies (163,164 and 165), which contributed to an “epidemic” of MVP by overly liberal diagnostic criteria.

VIDEO

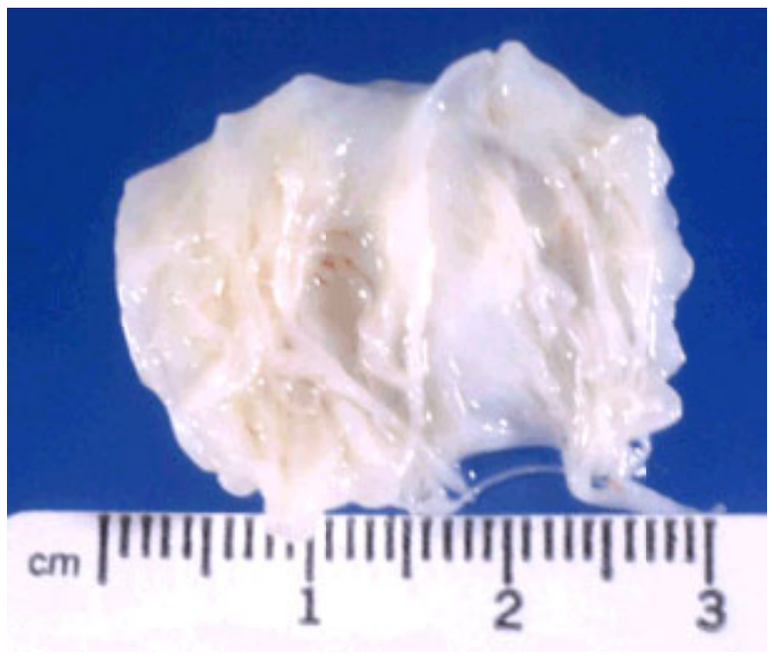
Video 49.50 Severe angiographic mitral valve prolapse with mitral regurgitation. In the angiogram there is a prolapse of the posterior leaflet accompanied by severe mitral regurgitation (4+). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Although MVP has a classic appearance by M mode (mid- or pansystolic posterior motion), up to 23% of healthy asymptomatic women may be diagnosed by these criteria (165). Two-dimensional echocardiography yielded a similar diagnostic prevalence until Levine et al. (166) demonstrated that the mitral annulus was saddle-shaped (nonplanar). Thus, leaflets may appear to close above the annulus in the apical four-chamber view (cutting through the low points of the annulus), while being normally oriented in a long-axis view (through the high points of the annulus). Current diagnosis of MVP rests on this long-axis displacement, although anatomic variability dictates that the full anterior leaflet and each of the three posterior scallops be thoroughly interrogated (eFig. 49.5.13).



***e*FIGURE 49.5.13** Mitral valve prolapse. Parasternal long-axis view of myxomatous mitral valve disease with prolapse and flail of the posterior mitral leaflet (PML).

MVP is also associated with myxomatous leaflet thickening and redundancy, with the tips sometimes being club-like, with a ground-glass appearance extending onto the chordae. The degree of MV deformity has been related to chest pain, arrhythmias, endocarditis, systemic emboli, and chordal rupture (167). Extreme prolapse may be difficult to differentiate from frank chordal rupture or endocarditis.



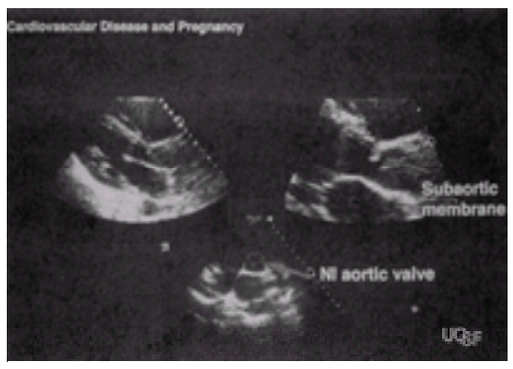
Myxoid mitral valve. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

ECHOCARDIOGRAPHY OF THE AORTIC VALVE

Aortic Valve

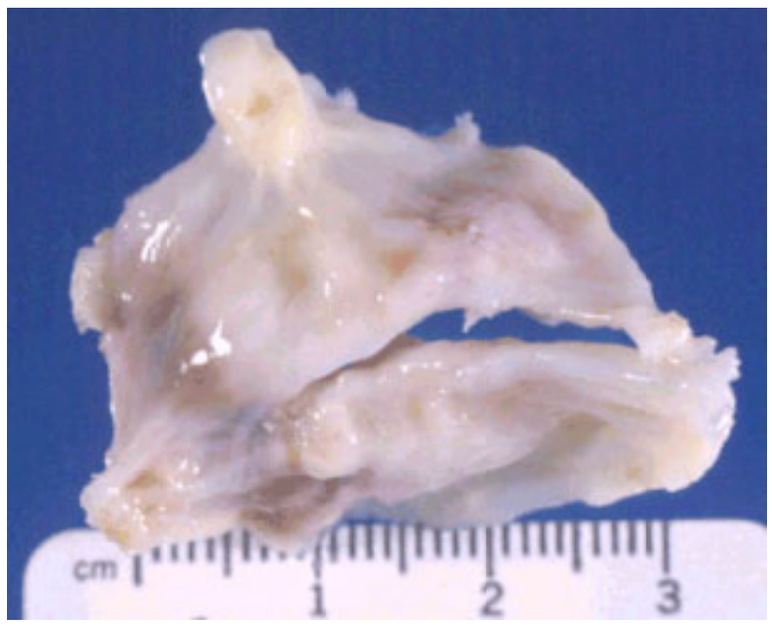
Normal Aortic Valve

M-mode echocardiography of the AV and root demonstrates leaflet closure at the midpoint of the aortic root and opening throughout systole to the walls of the aortic root, producing a “box-like” M-mode waveform. Fine systolic vibrations can be seen and correspond to a normal flow murmur. Failure to achieve or sustain full opening implies decreased stroke volume. Abrupt early closure may be caused by fixed subvalvular stenosis (*e*Fig. 49.5.14), and subsequent reopening in later systole may imply dynamic subvalvular obstruction. The coapted leaflets move parallel to the aortic root in diastole, with vibrations suggesting valve disruption or endocarditis. Eccentricity on closure typically indicates a congenital bicuspid valve (*e*Fig. 49.5.15).



***e*FIGURE 49.5.14** Subvalvular membrane. Parasternal long-axis view (*upper left with zoomed image in upper right*) of a discrete subvalvular membrane within the left ventricular outflow tract. The short-axis view of the aortic valve (*lower panel*) shows it to be a normal trileaflet valve. NI, normal. (Courtesy of Dr. Elyse Foster.)

***e*FIGURE 49.5.15** Bicuspid aortic valve. Transesophageal echocardiogram showing a functionally bicuspid aortic valve with fusion between the right (*bottommost*) and left (*right-sided*) coronary cusps. The valve opens with an oval orifice but may appear nearly normal when closed in diastole.



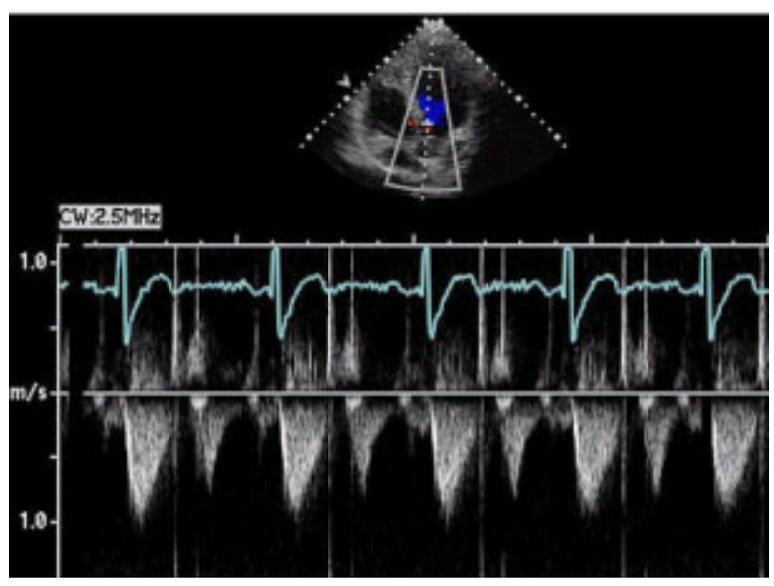
Bicuspid aortic valve with calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Unicuspid aortic valve (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 49.51 Congenital bicuspid aortic valve with mild aortic regurgitation (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

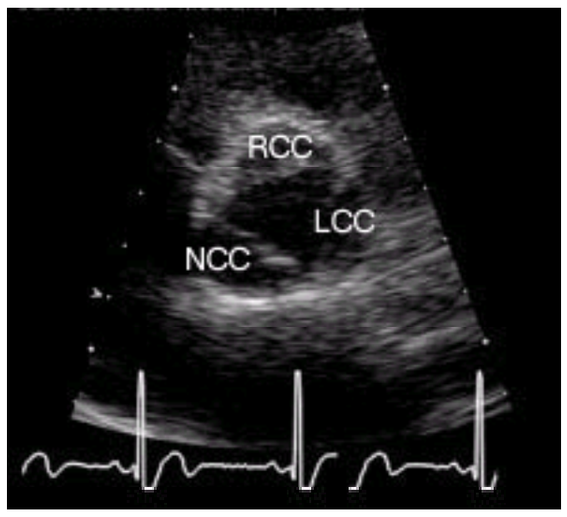
Video 49.52 A 76-year-old female patient with bicuspid aortic valve, aortic stenosis, and coarctation of aorta. Left anterior oblique aortogram revealed coarctation of the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Normally, the aortic root moves more than 7 mm anteriorly in systole, with fair concordance to stroke volume independent of LV EF (e.g., an underfilled LV with normal EF causes decreased root motion). Augmented motion of the root despite reduced aortic leaflet separation is typical of mitral insufficiency. Slowed posterior motion of the root in early diastole with augmented presystolic movement is analogous to the delayed relaxation pattern of mitral inflow. In restrictive states, root motion is flat, reflecting reduced stroke volume.

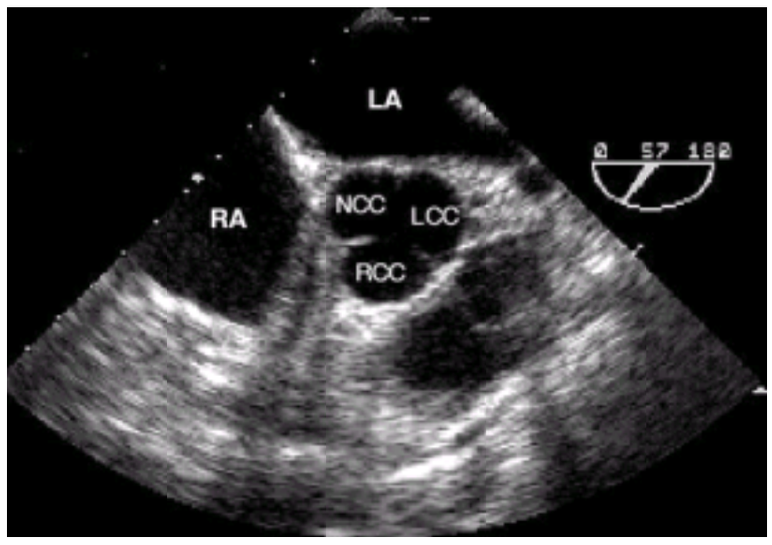


Normal continuous wave Doppler through the aortic valve by transthoracic echo. Note that the maximal velocity is approximately 1 m/sec (capillary wedge pressure gradient = 4 mm Hg).

Two-dimensional imaging of the normal AV demonstrates three thin leaflets, opening as a circular orifice and closing as a three-pointed star with slight central thickening. The left coronary cusp is adjacent to the left atrial appendage, the left main coronary artery, and the pulmonary valve and artery. The right lies just posterior to the RV outflow tract, close to the septal attachment of the TV. The noncoronary cusp sits above the RA and the interatrial septum. Aortic diameter is largest at the sinuses of Valsalva and should not exceed 3.5 cm.



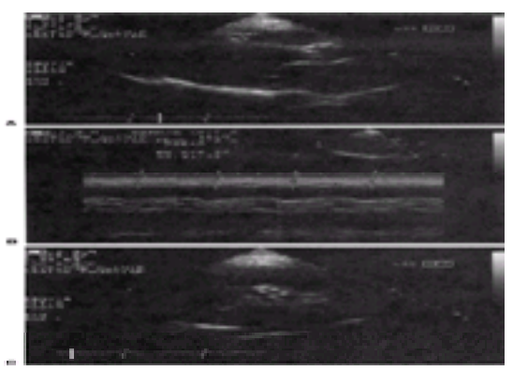
Magnified view of the aortic valve in short axis as seen from the parasternal window in systole. All three leaflets are opened. LCC, left coronary cusp; NCC, noncoronary cusp; RCC, right coronary cusp.



Short-axis transesophageal echo view of the aortic valve seen in diastole. Note the closed leaflets of the aortic valve.

Aortic Stenosis

In severe AS, the M mode shows dense persistent echoes with little systolic separation (168) (eFig. 49.5.16). Aortic sclerosis without stenosis shows dense echoes, but at least one leaflet will move rapidly or will vibrate, indicating a peak systolic gradient below 50 mm Hg. M mode also shows secondary features of AS such as LVH and LA enlargement.



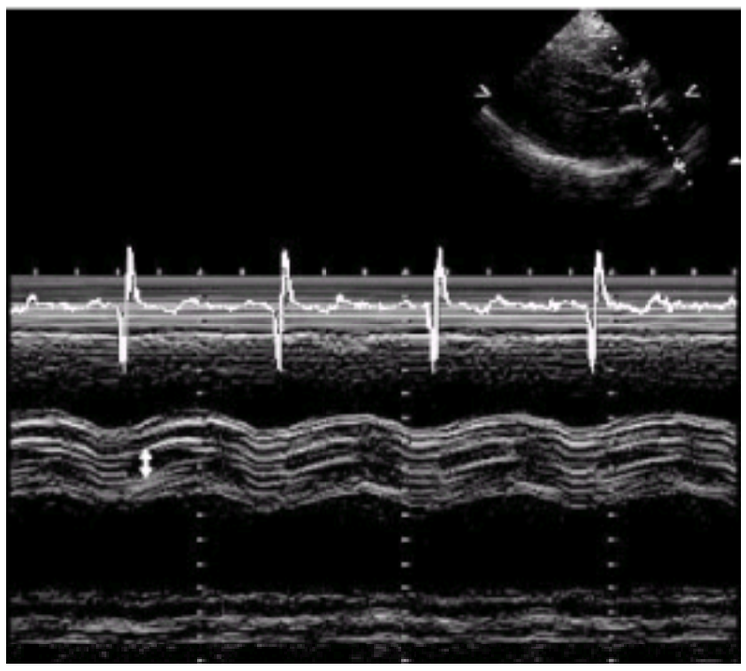
***e*FIGURE 49.5.16** Calcific aortic stenosis. **A:** Parasternal long-axis view showing thickened hyperreflective mitral leaflets with restricted opening. **B:** M mode through aortic valve showing multiple echogenic structures with limited leaflet separation in systole. **C:** Parasternal short-axis view showing calcific deposits within the cusps of the aortic valve.

HEART SOUNDS

Audio 49.53 Severe valvular aortic stenosis. Auscultation at the right upper sternal border performed in a 70-year-old male patient with a calcified and degenerated aortic valve. The peak and mean systolic gradients across the aortic valve were 100 and 55 mm Hg, respectively. The valve area calculated by the continuity equation was 0.5 cm^2. Note the soft A_2 and the high-pitched mid-systolic crescendo-decrescendo murmur. Right upper sternal border (*first clip*) and left upper sternal border (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.54 Severe valvular aortic stenosis. Auscultation at the right upper sternal border performed in a 70-year-old male patient with a calcified and degenerated aortic valve. The peak and mean systolic gradients across the aortic valve were 100 and 55 mm Hg, respectively. The valve area calculated by the continuity equation was 0.5 cm^2. Note the soft A_2 and the high-pitched mid-systolic crescendo-decrescendo murmur. Right upper sternal border (*first clip*) and left upper sternal border (*second clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



M-mode through a stenotic aortic valve. Note the thickened aortic leaflets with decreased excursion. (The small arrow designates the limited excursion of the aortic leaflets.)

HEART SOUNDS

Audio 49.55 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.56 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.57 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.58 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.59 Moderately severe valvular aortic stenosis. Auscultation at the right upper sternal border (sitting) in a 72-year-old male patient with moderately severe aortic valve stenosis (peak gradient of 58 mm Hg and mean gradient of 32 mm Hg with calculated aortic valve area by continuity equation of 0.8 cm^2). Note the systolic ejection murmur and the soft second heart sound. Right upper sternal border, sitting (*first clip*); right upper sternal border, supine (*second clip*); left upper sternal border (*third clip*); left lower sternal border (*fourth clip*); and apex (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.60 Parasternal long-axis view of a stenotic aortic valve. Note the thickened, calcific aortic leaflets with markedly reduced excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.61 Aortic stenosis and insufficiency (long-axis). A systolic signal-void jet of aortic stenosis is visible extending from the aortic valve into the ascending aorta. In addition, a diastolic signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricular cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.62 Moderate valvular aortic stenosis. Auscultation in a 79-year-old female patient with moderate aortic valve stenosis (peak gradient of 41 mm Hg, mean gradient of 23 mm Hg, and aortic valve area of 0.9 cm^2. Note the systolic ejection murmur with crescendo-decrescendo pattern and distinct second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.63 Moderate valvular aortic stenosis. Auscultation in a 79-year-old female patient with moderate aortic valve stenosis (peak gradient of 41 mm Hg, mean gradient of 23 mm Hg, and aortic valve area of 0.9 cm^2. Note the systolic ejection murmur with crescendo-decrescendo pattern and distinct second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

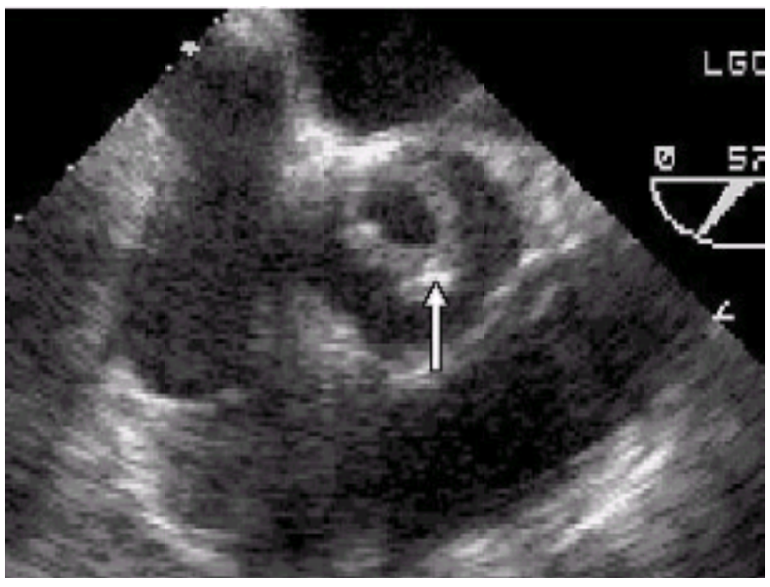
HEART SOUNDS

Audio 49.64 Moderate valvular aortic stenosis. Auscultation in a 79-year-old female patient with moderate aortic valve stenosis (peak gradient of 41 mm Hg, mean gradient of 23 mm Hg, and aortic valve area of 0.9 cm^2. Note the systolic ejection murmur with crescendo-decrescendo pattern and distinct second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

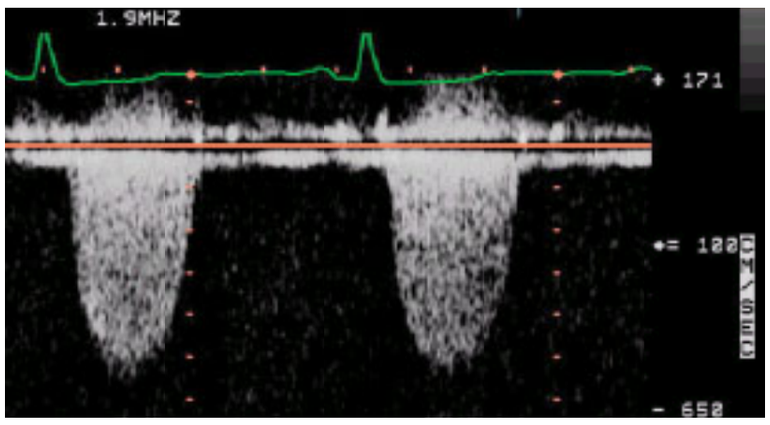
HEART SOUNDS

Audio 49.65 Moderate valvular aortic stenosis. Auscultation in a 79-year-old female patient with moderate aortic valve stenosis (peak gradient of 41 mm Hg, mean gradient of 23 mm Hg, and aortic valve area of 0.9 cm^2. Note the systolic ejection murmur with crescendo-decrescendo pattern and distinct second heart sound. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Cusp separation by two-dimensional imaging is helpful if it is less than 8 mm or more than 12 mm but poorly predictive between 8 and 12 mm (169). Leaflet doming, poststenotic aortic dilatation, and LVH are predictive of significant AS, although none approaches the utility of Doppler-derived pressure gradient and valve area (169,170,171 and 172).

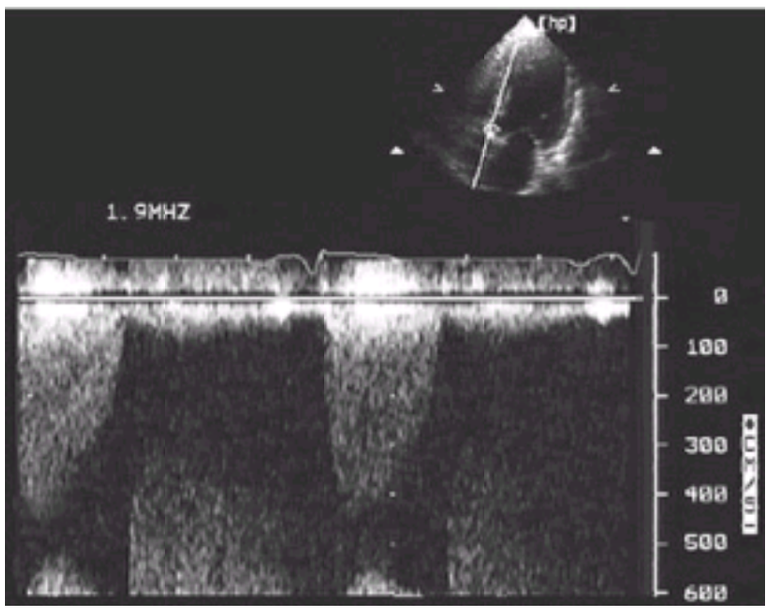


Short axis transesophageal view of a unicuspid aortic valve with aortic stenosis. The arrow designates the single commissure present in this aortic valve. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)



Continuous wave Doppler through a stenotic aortic valve. The maximal velocity is 5.5 m/sec, consistent with a peak pressure gradient of 121 mm Hg.

The severe calcification of senile AS is nonspecific as to underlying pathology. In younger patients, bicuspid valves show eccentric opening and only two moving leaflets. On closure of the valve, three commissures may be seen due to raphe formation between two leaflets, usually the left and right. Rheumatic AS shows commissural fusion and leaflet retraction and is generally associated with rheumatic mitral disease. Senile calcification typically begins in the aortic annulus, spreading centrally into the leaflets.



Apical continuous-wave Doppler spectrum of aortic valve disease. Note high forward velocities in systole (V_{max} 4.5 m/sec) and early peak of aortic stenosis. At the bottom, wrapped-around diastolic flow velocities from aortic regurgitation are seen.

Subvalvular and Supravalvular Stenosis

Fixed subvalvular stenosis is occasionally encountered in the adult population (173,174 and 175), often with prior ventricular septal defect. The subvalvular membrane is a narrow ridge in the distal septum (eFig. 49.5.14). Because the narrowing may be difficult to appreciate by inspection, Doppler remains the definitive quantitative modality. Dynamic subvalvular stenosis is discussed above under Normal Aortic Valve. Supravalvular AS is rarely seen in adults. Features include narrowing above and affixed to the valve leaflets, aortic insufficiency, enlarged coronary arteries (sometimes obstructed), and severe hypertrophy (176).

VIDEO

Video 49.66 Subaortic stenosis. A radiolucent membrane is visualized just below the aortic valve cusps (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.67 Transesophageal echo in a patient with a subvalvular membrane in the left ventricular outflow tract. Note the normal mobility of the aortic valve. This patient had a significant pressure gradient across the left ventricular outflow tract/AV. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Aortic Regurgitation

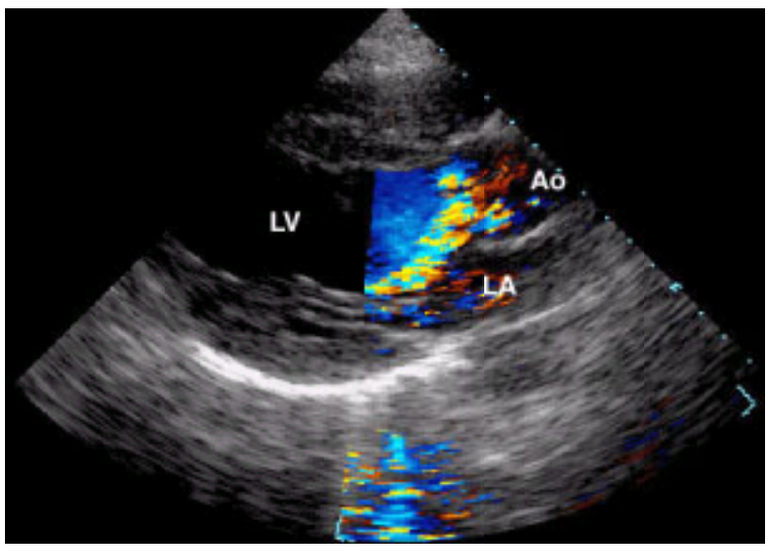
Aortic regurgitation (AR) can be seen with diastolic fluttering of the anterior mitral leaflet by M mode (177), a sign largely supplanted by Doppler. With severe acute AR, M mode may show early closure of the MV (178), indicating precarious hemodynamics and a need for urgent pharmacologic or surgical intervention (178). Henry et al. (179) have suggested that an LV end systolic dimension of greater than 55 mm predicts poor operative results—a concept challenged by Fioretti et al. (180), perhaps due to improvements in myocardial preservation at surgery. Assessment of AR severity by two-dimensional echocardiography has not been adequately studied (181). Posteriorly directed AR may reverse the diastolic curvature of the anterior mitral leaflet (182), but no two-dimensional sign replaces a quantitative Doppler examination (177,183) (see Chapter 51).

VIDEO

Video 49.68 Parasternal long-axis view (transthoracic echo) of a bicuspid aortic valve with prolapse of the anterior leaflet causing posteriorly directed aortic insufficiency. The aortic insufficiency hits the anterior mitral leaflet, causing deformation of this leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.69 Parasternal long-axis view (transthoracic echo) of a bicuspid aortic valve with prolapse of the anterior cusp (right and left coronary cusps fused) causing posteriorly directed aortic insufficiency. Note the posterior displacement of the anterior mitral leaflet (AML) caused by the aortic insufficiency jet hitting this leaflet. The left ventricular cavity is dilated. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Parasternal long-axis view (transthoracic echo) with color Doppler demonstrating the posteriorly directed aortic insufficiency caused by prolapse of the anterior leaflet of a bicuspid aortic valve. Note that the jet hits the anterior mitral leaflet.

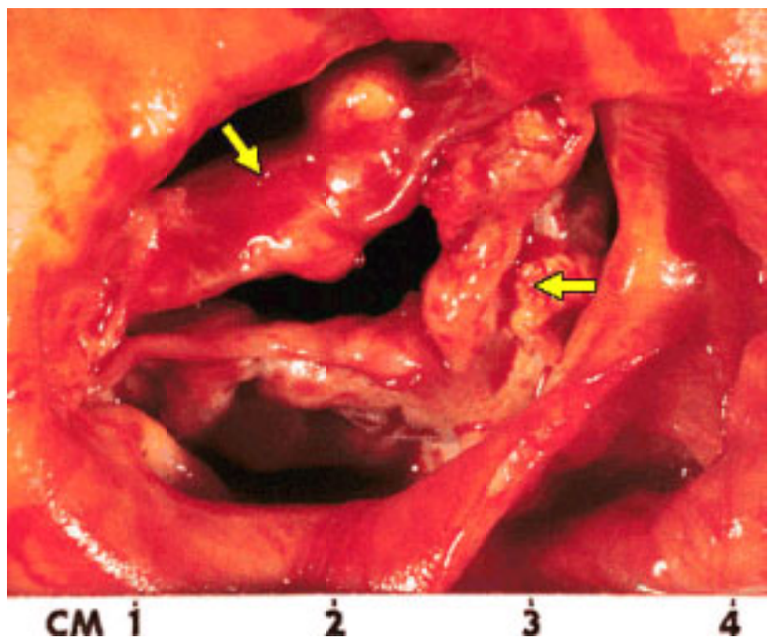
Video 49.70 A 49-year-old male patient with bicuspid aortic valve and severe aortic regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.71 Multiple gated acquisition scan of a patient with aortic insufficiency, ascending aortic aneurysm, and congestive heart failure. The ascending aorta is dilated, and there is moderate to severe left ventricular dilatation (ejection fraction approximately 30%). There is a prominent septal separation suggesting left ventricular hypertrophy. Analysis of regional wall motion reveals mild septal and posterolateral hypokinesis, moderate anterolateral and anterior hypokinesis, and inferoapical and apical dyskinesis in the anterior (*first video*) and left anterior oblique (*second video*) projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.72 Multiple gated acquisition scan of a patient with aortic insufficiency, ascending aortic aneurysm, and congestive heart failure. The ascending aorta is dilated, and there is moderate to severe left ventricular dilatation (ejection fraction approximately 30%). There is a prominent septal separation suggesting left ventricular hypertrophy. Analysis of regional wall motion reveals mild septal and posterolateral hypokinesis, moderate anterolateral and anterior hypokinesis, and inferoapical and apical dyskinesis in the anterior (*first video*) and left anterior oblique (*second video*) projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Senile calcification typically results in mild AR. Rheumatic disease causes leaflet retraction and a central AR jet. Bicuspid aortic valves may have significant AR due to leaflet prolapse, usually of a conjoined anterior leaflet. Endocarditis may cause acute severe AR, recognized as mobile echoes prolapsing into the LV outflow tract. Transesophageal echocardiography (TEE) has greatly improved detection of aortic vegetations (184). AR can arise from subaortic membrane jets that undermine valve integrity. Myxomatous disease can cause AV prolapse. In Marfan disease (eFig. 49.5.17), isolated dilation of the sinuses of Valsalva causes traction on the aortic commissures and a central jet of AR (185). Other aortic diseases that are associated with AR include dissection, sinus of Valsalva aneurysms, aortoannular ectasia, and aneurysms due to atherosclerosis, syphilis, and ankylosing spondylitis. As discussed in Chapter 52, TEE is preferred for emergent diagnosis (186). Small perimembranous ventricular septal defects may close in childhood but leave behind AR. Doubly committed subarterial ventricular septal defect is also associated with aortic regurgitation.

***e*FIGURE 49.5.17** Aortic aneurysm. Parasternal long-axis view of a patient with Marfan syndrome showing dilatation of the aortic root and ascending aorta (AO), with effacement of the sinotubular junction.



Bicuspid aortic valve with calcific stenosis. The yellow arrows identify each of the valve leaflets.

Aortic valve calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 49.73 Parasternal short-axis view of a patient with senile calcific aortic stenosis. Note the heavily calcified, distorted leaflets with restricted motion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.74 Transgastric view (transesophageal echo) of the mitral valve in a patient with severe aortic insufficiency. Note the fluttering of the anterior mitral leaflet (*left*) due to the jet of aortic insufficiency hitting it (color flow seen on the left). (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Ectopia lentis. This lens dislocation is associated with Marfan syndrome.

Arachnodactylia in Marfan syndrome. The ratio of finger length to hand size is markedly increased.

VIDEO

Video 49.75 Intraoperative transesophageal echo (120-degree view) with color Doppler demonstrating aortic insufficiency due to aortic dilatation (sinuses measure 5.0 cm) causing failure of leaflet coaptation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Tricuspid Valve

The TV has anterior, septal, and posterior leaflets; the latter two are somewhat variable in size and position. M mode from the parasternal window with rightward and

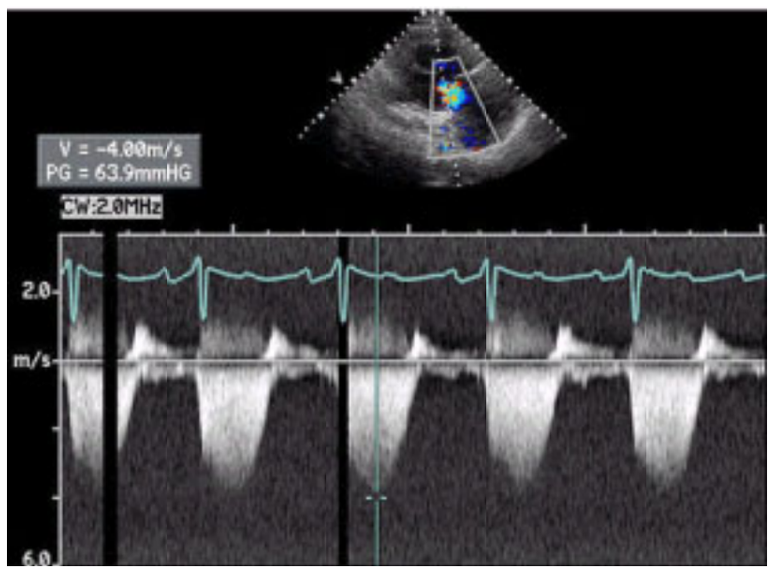
inferior angulation is useful for timing. Two-dimensional imaging can be recorded from the parasternal long- and short-axis and apical four-chamber views for anatomic and Doppler evaluation. The TV is apically displaced by the membranous septum, which is useful in identifying the TV in congenital heart disease. Transesophageal imaging offers relatively little advantage, especially for measuring TR velocity (187).

Tricuspid Insufficiency

Contemporary echocardiography confirms Sir James Mackenzie's claim, made in 1908, that TR is ubiquitous. Present in 80% of normal subjects and nearly all cardiac patients, this "abnormality" usually is just a convenient means to estimate pulmonary artery pressure (188). Pathologic TR causes RV and RA enlargement, paradoxical septal motion, and systolic IVC pulsation from retrograde flow. M mode shows paradoxical septal motion, with anterior systolic motion of the septum related to the exaggerated RV stroke volume. M mode can also record systolic IVC expansion, which should not be confused with respiratory fluctuations. By two-dimensional imaging, RV dilatation can be seen, although quantitation is imprecise (125) and hyperdynamic function can be seen due to the augmented stroke volume (24,236). RA enlargement is common and is related to TR duration and severity and the presence of atrial fibrillation. With severe TR, the normal leftward bulging of the interatrial septum is reversed (189).

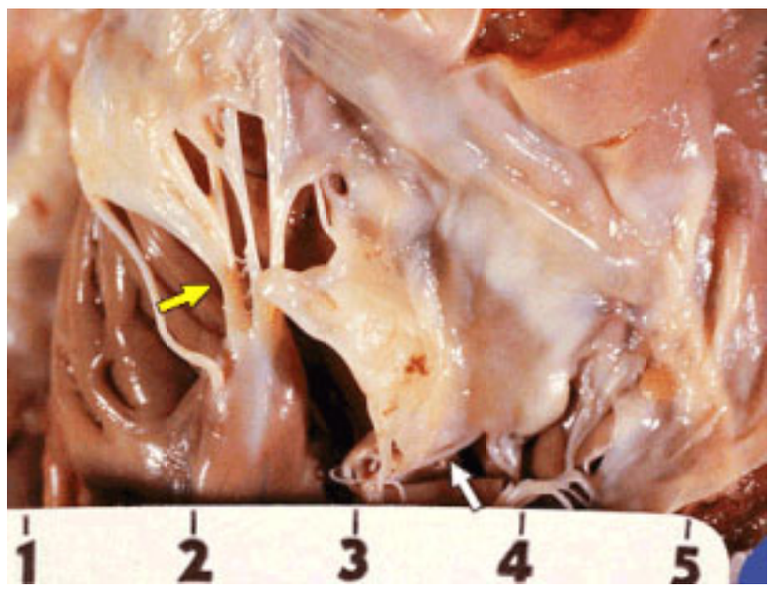
The most common cause of significant TR is RV failure from high LV filling pressures, with annular dilatation and failure of leaflet coaptation (190). Rheumatic TR rarely exists without MV involvement. It is characterized by leaflet thickening, commissural fusion and calcification, and chordal shortening. Myxomatous MV disease may be accompanied by tricuspid prolapse (191), but severe TR is uncommon unless there is chordal rupture (192). RV biopsy may rarely cause iatrogenic chordal rupture (193). Endocarditis (usually due to intravenous drug use) causes bulky prolapsing vegetations and flail leaflets (194) (*e*Fig. 49.5.18). Metastatic liver carcinoid causes TV leaflet shortening with more regurgitation than stenosis (159). Ebstein's anomaly commonly causes severe TR (133) (*e*Fig. 49.5.8).

***e*FIGURE 49.5.18** Tricuspid valve endocarditis. Apical four-chamber view showing multiple bulky vegetations on the tricuspid valve with an enlarged right atrium and the interatrial septum bowing to the left, consistent with elevated right atrial pressure. (Images courtesy of Advanced Technology Laboratories, Bothel, WA.)



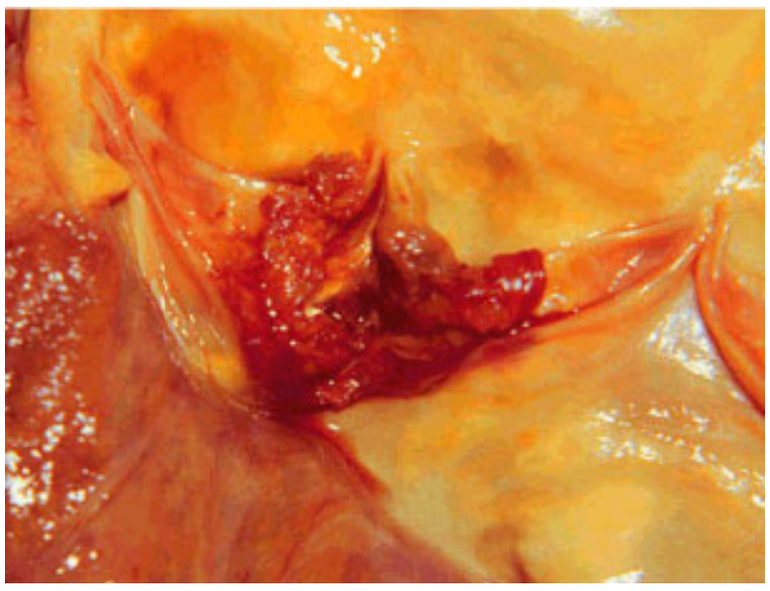
Continuous wave Doppler trace through the tricuspid valve of a patient with pulmonary hypertension. The maximal jet velocity of 4 m/sec corresponds to a pressure gradient of 64 mm Hg or a PA pressure of approximately 80 mm Hg.

Video 49.76 Transesophageal four-chamber view focusing on the tricuspid valve showing myxomatous tricuspid valve disease with severe prolapse causing severe tricuspid regurgitation (pre-operative). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

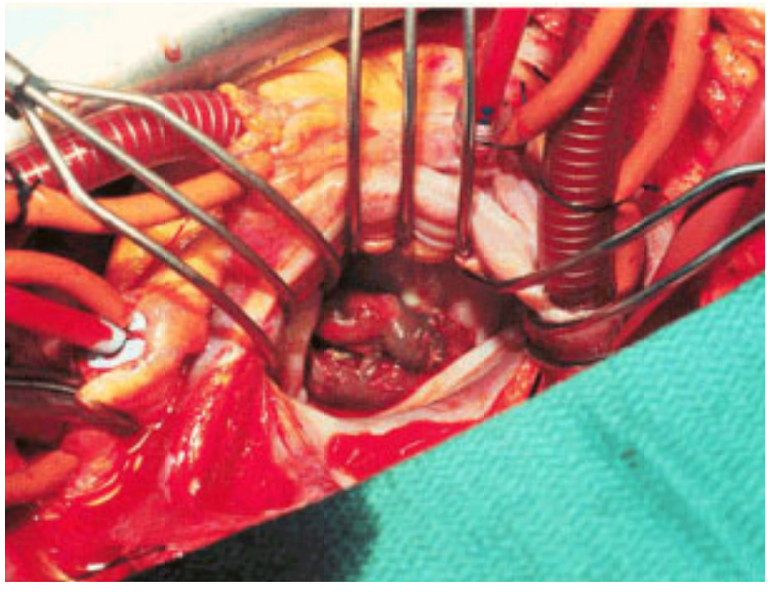


Rheumatic disease of the tricuspid valve. Note the shortened cordae (*yellow arrow*) and thickened valve leaflet (*white arrow*).

Video 49.77 Transthoracic right ventricular inflow view demonstrating rheumatic tricuspid valve disease. Note the doming of the tricuspid valve leaflets as well as their restricted closure causing both tricuspid stenosis and regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Verrucal endocarditis of the aortic valve. Multiple vegetations are seen on the aortic valve cusps in this patient with subacute bacterial endocarditis.



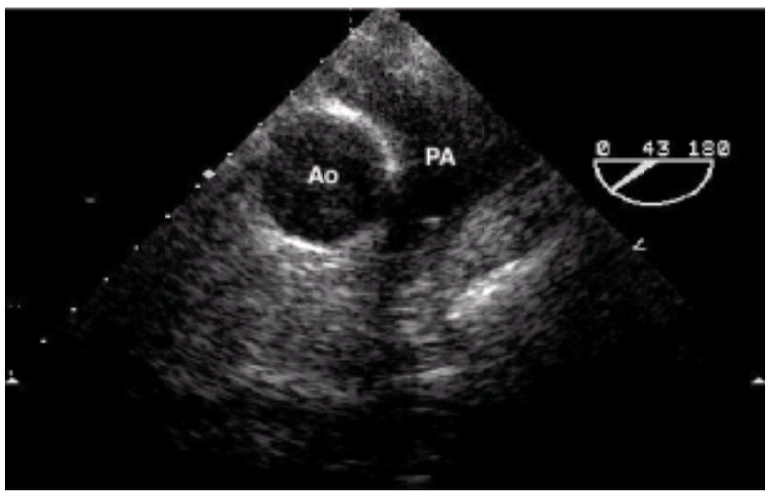
Surgical field of a patient with infectious endocarditis and a large vegetation with perforation of the anterior mitral leaflet. The entire surgical view is filled with the large vegetation.

Tricuspid Stenosis

Tricuspid stenosis may be due to rheumatic disease, carcinoid syndrome, or prolapsing RA tumors. Two-dimensional planimetry is not reliable, making Doppler the mainstay of quantitation.

Pulmonary Valve and Artery

Pulmonary valve pathology is common in congenital disease but is rarely acquired. M-mode and two-dimensional imaging are limited to leaflet inspection (often difficult) and pulmonary artery dilatation. The M mode in pulmonary stenosis (PS) shows an exaggerated diastolic "'a' wave" caused by powerful RA contraction opening or doming the pulmonary valve. By two-dimensional imaging, PS shows systolic leaflet doming, variable leaflet thickening, poststenotic dilation of the main PA with decreased pulsations, and variable RV hypertrophy. PS must be distinguished from subpulmonic stenosis and double-chamber RV that results from prior ventricular septal defect.



Transesophageal echo view demonstrating the pulmonary artery bifurcation at the center of the screen and the aorta in short axis to the left. This view is useful to look for a large, saddle embolus to the pulmonary artery bifurcation, although smaller, more distal emboli will be missed.

HEART SOUNDS

Audio 49.78 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.79 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 49.80 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Leopard's syndrome. Figure shows a patient with Leopard's syndrome characterized by multiple basal cell nevi and broad facies. There is an association with pulmonic stenosis.

VIDEO

Video 49.81 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Trivial pulmonary regurgitation (PR) is present in most healthy persons. Severe PR rarely occurs from prior tetralogy of Fallot repair, endocarditis (195), or carcinoid (159). Moderate PR can result from pulmonary hypertension (Graham Steell's murmur).

Infective Endocarditis

Echocardiography is essential to the diagnosis and management of patients with infective endocarditis (IE). Early studies of echocardiography and IE used the criteria of Von Reyn et al. (196) for diagnosis. New echocardiographic criteria for diagnosing IE have been prospectively tested by the Duke Endocarditis Service (197,198). In these studies, echocardiography increased the sensitivity for detecting IE from 51% to 80%, although TEE was required to visualize the vegetations in 41% of cases.

VIDEO

Video 49.82 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis **(A)** showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. **B:** intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

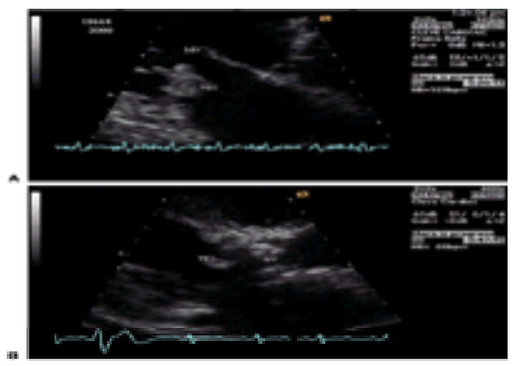
Video 49.83 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis **(A)** showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. **B:** intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 49.84 Complicated prosthetic aortic valve endocarditis. Transesophageal echocardiography demonstrates fistulous tracts communicating the left ventricular outflow tract (LVOT) with left (LA) and right atria (RA). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Vegetations

The hallmark of IE is the vegetation. Identification depends on a variety of patient and technical factors (eFig. 49.5.19). Images should be obtained with the highest transducer frequency (>2.5 MHz) that is capable of penetrating the chest for optimal resolution. Dynamic range should be optimized and the highest frame rate used. Color encoding ("B color") may enhance the appearance of vegetations. Echocardiographic visualization of vegetations is hampered by obesity, chronic lung disease, valvular calcification, and prostheses and may require TEE. A high degree of pretest suspicion promotes sensitivity for small vegetations, but it should be recognized that all valves normally have small nodules and that overvigilance may lead to false-positive findings.



***e*FIGURE 49.5.19** Mitral and aortic endocarditis. Parasternal long-axis views of **(A)** mitral (MV) and **(B)** aortic (AV) valve vegetations (VEG).

M-Mode Echocardiography

M mode may detect vegetations as small as 5 mm (199). Its key advantage (at least historically) is the very high sampling rates (>1,000 Hz) that can detect vegetative vibrations from the AV (diastole) and MV (systole) (200). These signs are less helpful currently, as M-mode rates are only approximately 200 Hz with contemporary equipment.

Two-Dimensional Imaging

In a metaanalysis of 16 early studies (641 patients), O'Brien and Geiser (201) reported a mean sensitivity of 79% for two-dimensional detection of vegetations and 52% for M mode, with vegetations as small as 3 mm reported by two-dimensional imaging (200). More recently, however, the reported sensitivity of TTE has dropped to 62% despite equipment improvement (184,202,203,204,205,206 and 207), reflecting less biased case selection and the fact that these studies used TEE (sensitivity of 92%).

Sanfilippo et al. (208) retrospectively studied 204 patients with IE, showing that larger (>10 mm) mobile noncalcified vegetations were predictive of antibiotic failure, congestive heart failure, embolization, surgery, and death. Size was highly predictive of complications: 10% for 6-mm vegetations, 50% at 11 mm, and almost 100% at 16 mm.

Explanted Carpentier-Edwards mitral valve regurgitation in a patient with severe infective prosthetic valve endocarditis. The patient had severe mitral stenosis due to the large vegetations on the prosthesis.

Transesophageal Echocardiography

Just as two dimensional supplanted M mode as the imaging mode of choice (209), TEE (210) brings even better sensitivity in IE (184), although at the cost of a semiinvasive procedure (190,206,207,208 and 209,211). Diagnostic features of vegetations (208) include texture (like myocardium), location (upstream side of valves), motion (chaotic, prolapsing), shape (lobulated, amorphous), and accompanying abnormalities (abscesses, fistulae). A negative TEE renders endocarditis very unlikely but not impossible. False positives may occur as a result of minor valve irregularities (184), such as Lambl's excrescences, suture material, redundant chordae, false tendons, and Chiari networks. Prosthetic valve endocarditis, in particular, requires TEE because of shadowing from the chest wall, with sensitivities reported from 82% to 100% versus 25% to 43% for transthoracic imaging (212,213 and 214).

VIDEO

Video 49.85 Intraoperative transesophageal echo of a mitral valve with multiple, large, highly mobile vegetations from endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

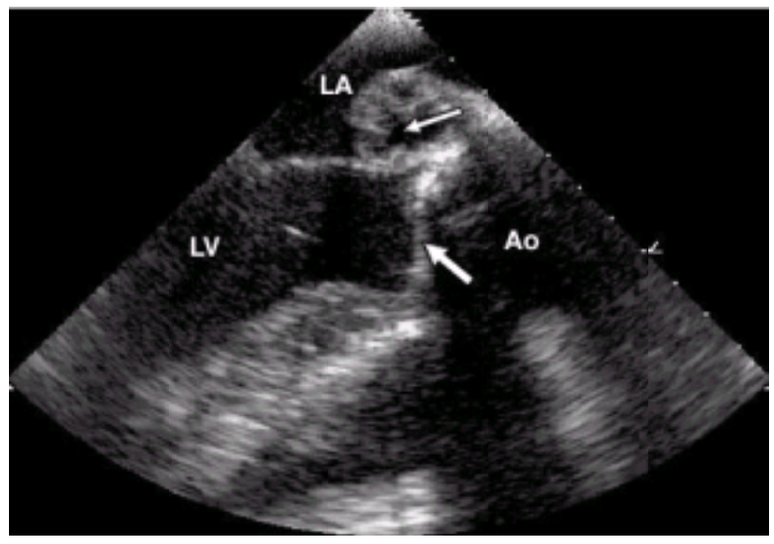
Prognosis in Infective Endocarditis

Echocardiography has proved useful in predicting complications of IE, although the data are somewhat discrepant (202,208,215,216 and 217). Heinle et al. (217) found high interobserver agreement on location, but not size, of vegetations and little prognostic value for complications. Mugge et al. (202) found that vegetations of greater than 10 mm had an embolic rate of 46% versus 20% for smaller ones (p <.001). Rohmann et al. (215) observed an adverse prognosis if vegetations failed to regress with therapy: valve replacement (45% vs. 2%), emboli (45% vs. 17%), abscess (13% vs. 2%), and mortality (10% vs. 0%; all p <.05).

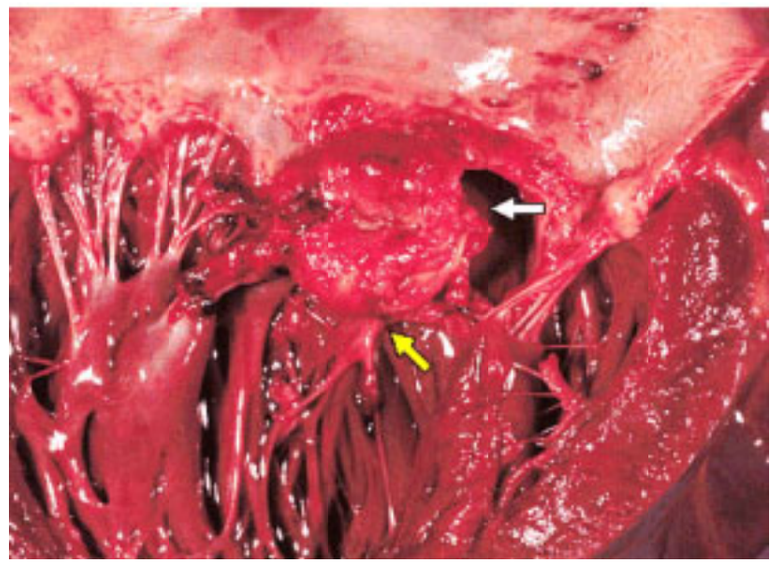
A negative TEE has 98% negative predictive value for IE (184), although vegetations may be missed with monoplane examination (206), especially on an aortic prosthesis.

Complications of Infective Endocarditis

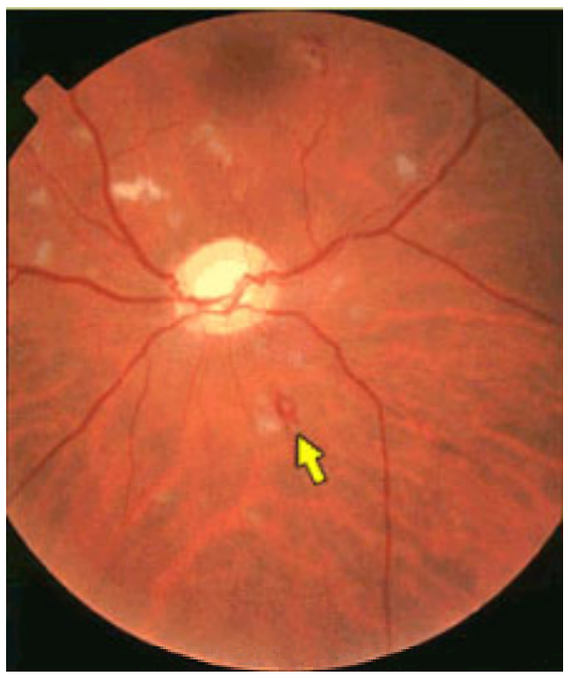
Infection may invade the surrounding myocardium and fibrous tissue, causing cellulitis and, ultimately, an abscess that can rupture into another cavity as a fistula (218). A septal abscess can cause arteriovenous block (219). Daniel et al. (205) found an abscess in 37% of 118 cases, with a sensitivity of 87% by TEE versus 26% by TTE, which was subsequently confirmed by others (219,220).



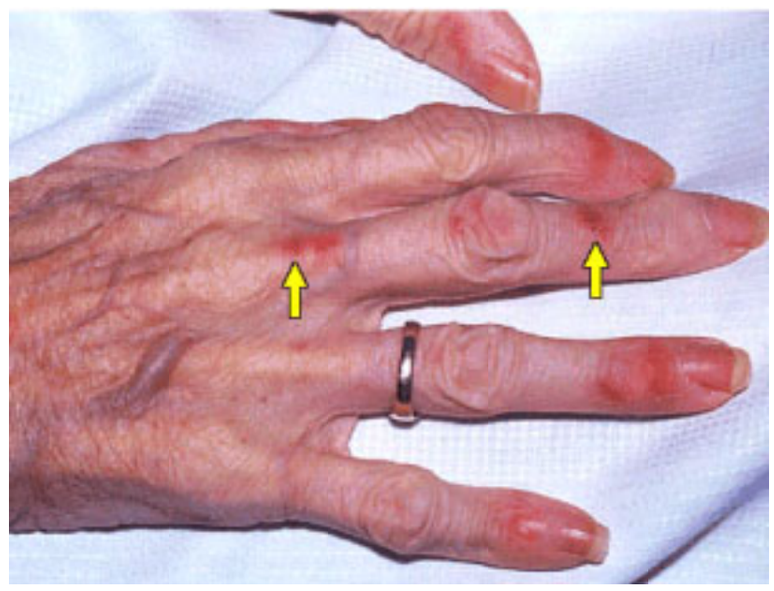
A 120-degree transesophageal echo of an aortic valve abscess seen in the inner annular fibrosa. The thin arrow designates the abscess cavity, while the thicker arrow demonstrates the aortic valve.



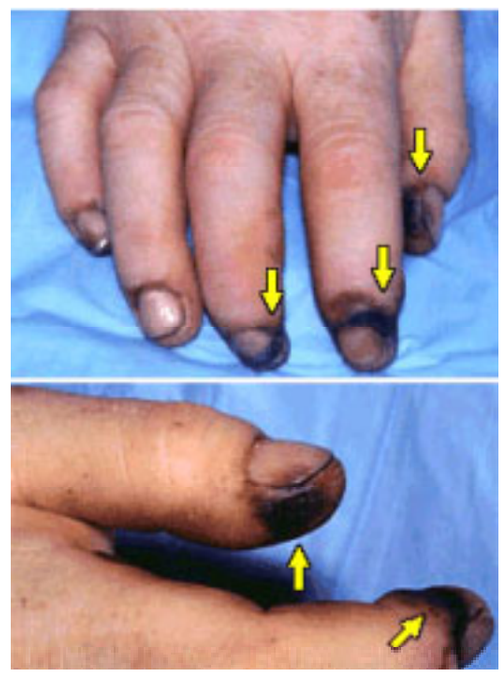
Infectious endocarditis of the mitral valve with cordal rupture. The infected leaflet is indicated by the yellow arrow. The usual cordal attachment to the leaflet is absent (*white arrow*).



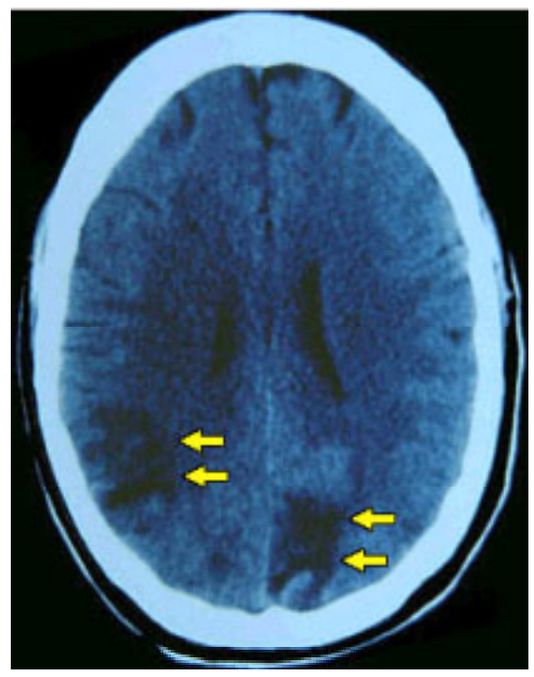
Roth's spot. The yellow arrow indicates a hemorrhage with a white central spot typical of subacute bacterial endocarditis.



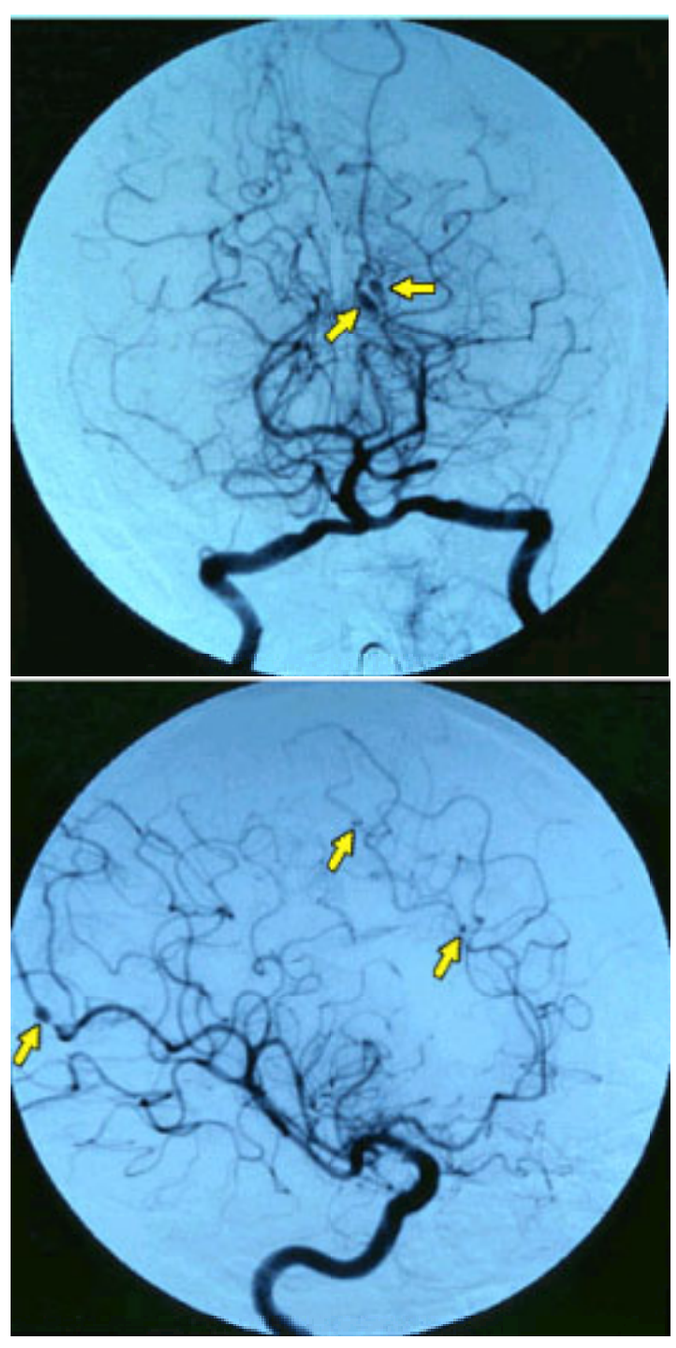
Septic emboli from infective endocarditis (*arrows*).



Janeway lesions of endocarditis. There are hemorrhages with nodular character at the fingertips (*arrows*).



Ruptures mycotic aneurysms. Several areas of hypodensity representing ruptured mycotic aneurysms as a result of endocarditis (*arrows*).



Mycotic aneurysms from infective endocarditis. Localized aneurysmal dilatation of cerebral vessels as a result of endocarditis (*arrows*, A,B).

Osler nodes. There are tender nodules on the toe pads (*arrows*) secondary to infective endocarditis.

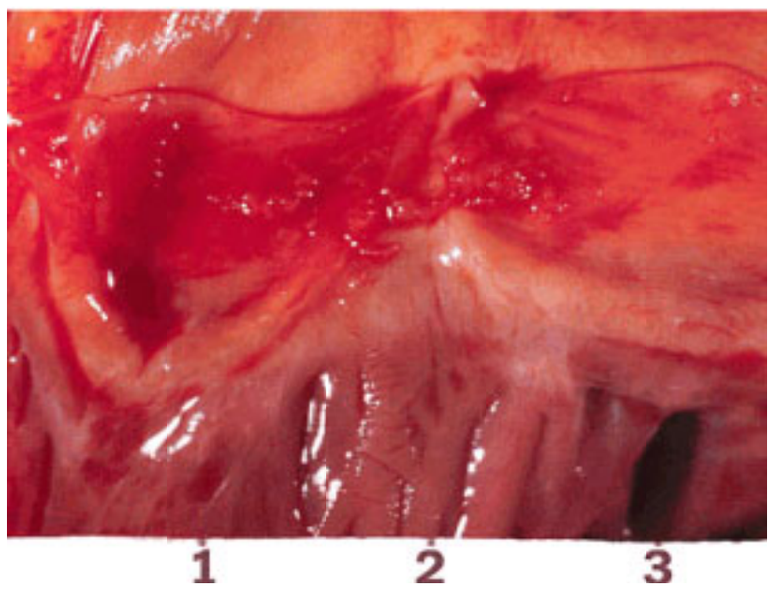
Septic emboli. Raised nodules from septic embolization from infective endocarditis.

Splinter hemorrhages. Linear hemorrhages on the fingertips of a patient with infective endocarditis.

Video 49.86 A 120-degree transesophageal echo demonstrating an abscess cavity in a patient with endocarditis of an aortic valve. Note the systolic expansion of the cavity located between the aortic and mitral valved in the inner annular fibrosa. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Right-Sided Infective Endocarditis

Tricuspid IE (usually *Staphylococcus aureus*) typically occurs in intravenous drug users (221) and causes large vegetations that are equally well detected by TTE and TEE (187). Multiplane TEE may be of value for the very rare pulmonic vegetations (195).



Marantic (nonbacterial) endocarditis of the pulmonic valve. Multiple vegetations are seen on the pulmonic valve in this patient with no bacterial growth from multiple blood cultures.

Video 49.87 Transesophageal echo of a large tricuspid valve vegetation in a patient with infectious endocarditis. This patient was an intravenous drug user, which is common in patients with right-sided endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

PERICARDIAL DISORDERS

Echocardiography detects virtually all pericardial effusions (222,223) and is the diagnostic test of choice (224), providing important hemodynamic data as well. Normally, there is less than 20 mL pericardial fluid (225), barely detected during systole by M mode. The high temporal resolution of M mode is valuable in assessing pericardial motion and RA and RV dynamics. The parietal pericardium is highly echogenic.

Two-Dimensional Echocardiography

Two-dimensional echocardiography and Doppler are key in assessing pericardial disease, with small effusions first seen above the RA. The normal systolic torsion of the heart is lost when inflammation causes adhesions between the pericardial layers. Pericardial fat may mimic effusion (226), typically seen anterior to the heart. D'Cruz and Hoffman (227) have described an ellipsoidal formula for estimating effusion size, although effusions typically are graded as small (separation seen throughout the cardiac cycle), medium, and large (typically >2 cm circumferentially). Although transudates, exudates, and blood appear similar, septations suggest chronicity.

Tamponade

Tamponade is a continuum of hemodynamic embarrassment, often associated with large effusions (228,229,230,231,232,233,234 and 235), although small rapid accumulation can be life threatening. Characteristic echocardiographic features are listed in Table 49.1. The heart is usually small, unless previously enlarged (229), and respirophasic ventricular interdependence is seen. The RV enlarges with inspiration and the LV with expiration, the echocardiographic equivalent of pulsus paradoxus (229,236). RV diastolic collapse and RA invagination (>one-third of cardiac cycle) are seen (229,230,232,233) (eFig. 49.5.20). Central venous pressure (CVP) can be estimated from IVC dynamics (231). If CVP is normal, the IVC is greater than 17 mm and decreases by more than 5 mm during inspiration. With elevated CVP, typical of tamponade, the IVC exceeds 20 mm and respiratory change is blunted (231,237) (eFig. 49.5.21), a sign that is less useful with mechanical ventilation (238).

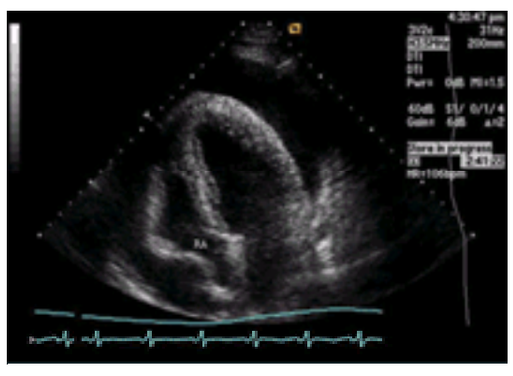
Large effusion
Right atrial (RA) expiratory collapse
Right ventricular (RV) expiratory compression or collapse
IVC plethora with diminished respiratory response
Left atrial compression
Small chamber volumes
Reciprocal size changes between RV and LV and excursion between MV and TV

Sensitivity, specificity, and positive and negative predictive values

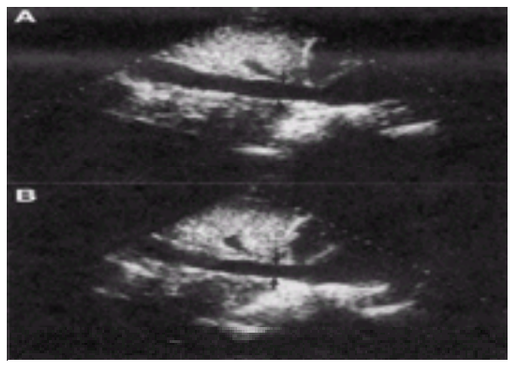
	Sen	Spec	PPV	NPV
Size (large vs. moderate)	—	97	45	96
RV compression	48	95	38	96
RA compression	55	88	10	99
IVC plethora	97	66	7	96

IVC, inferior vena cava; LV, left ventricular; MV, mitral valve; NPV, negative predictive value; PPV, positive predictive value; TV, tricuspid valve.

TABLE 49.1 TWO-DIMENSIONAL ECHOCARDIOGRAPHIC FINDINGS IN TAMPONADE



***e*FIGURE 49.5.20** Pericardial tamponade. Apical four-chamber view showing large circumferential pericardial effusion with invagination of the right atrial (RA) free wall, consistent with tamponade.



***e*FIGURE 49.5.21** Inferior vena cava (IVC) plethora. Subcostal views of the IVC during expiration **(A)**. The IVC is distended and fails to collapse with inspiration **(B)**. Arrows denote the width of the IVC.

Video 49.88 Apical four-chamber view demonstrating a large pericardial effusion causing tamponade. Note the inability of the right side to fill. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download*

it here.

Loculated Effusion

Following pericardiotomy, effusions may be loculated, making the diagnosis of tamponade and differentiation from pleural effusions difficult. Many two-dimensional signs of tamponade (such as RA invagination) may be absent if the hematoma is not localized to that area. Postcardiotomy (Dressler's) syndrome may develop days to weeks after surgery and requires a high degree of clinical suspicion to diagnose.

Pleural versus Pericardial Effusion

Left pleural effusions can be distinguished by their posterior location, passing behind the descending aorta. Large bilateral pleural effusions may occasionally cause tamponade that is responsive to drainage (239).

Video 49.89 Subcostal short-axis view of a large pericardial effusion causing tamponade. Note that the right side is small and under filled. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.90 Apical four-chamber view (transthoracic) in a patient with metastatic lung cancer demonstrating a moderate to large pericardial effusion and a very large, highly organized pleural effusion encasing the heart. (Pleural effusion is towards the right of the screen.) Note the extensive fibrinous network in the pleural effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.91 Subcostal short-axis view demonstrating the left ventricle surrounded by an organized pericardial effusion, which is adjacent to highly organized pleural effusion in a patient with metastatic lung cancer. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pericardial Thickening and Constriction

Pericardial thickening is common, although constriction is rare. Thickening and adhesion are distinguished from simple effusion by the parallel (rather than damped) motion of the epicardium and visceral pericardium with the parietal pericardium. Pericardial constriction is a continuum of hemodynamic impairment, which may overlap with tamponade and (when the visceral layer is primarily involved) may have a component of restriction. By M mode, a septal notch may be seen in early diastole around the time of the pericardial knock (between S_2 and S_3) (240,241). Two-dimensional echocardiography may show extensive adhesion and a diastolic septal bounce (237), which may resemble left bundle branch block or RV pacing. IVC plethora is usually seen (231,237) unless the patient is severely dehydrated. In the four-chamber view, the ventricles appear elongated, and the atria are globally enlarged. Brief constrictive phases may be seen with resolution of simple effusions. Table 49.2 lists two-dimensional signs of constriction, distinct from restrictive cardiomyopathy. Malignancy often causes pericardial effusions and pericardial studding, and frank-mass effect may be seen.

Pericardial thickening and adhesion: lack of "sliding"; heart motion transmitted to other organs ("tugging")
Septal bounce: abrupt transient rightward movement
Inferior vena cava plethoric and unresponsive; hepatic veins dilated
Left and right ventricle size decreased; heart tubular in shape
Mild biatrial enlargement

TABLE 49.2 PERICARDIAL CONSTRICTION FINDINGS ON TWO-DIMENSIONAL ECHOCARDIOGRAPHY

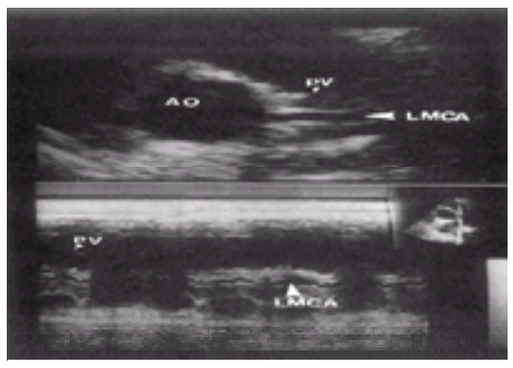
Video 49.92 Transesophageal echo (four-chamber view) demonstrating constrictive pericarditis. Note the abnormal septal bounce and the tethering of the right atrium and right ventricle by the thickened pericardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Congenital Abnormalities

Complete absence of the pericardium causes RV enlargement and paradoxical septal motion (144). Partial absence may cause LV herniation through the defect with coronary compression and myocardial infarction. Pericardial cysts are difficult to localize by echocardiography due to their lateral position (242).

Aorta and Great Vessels

Despite the primacy of TEE, TTE is useful in assessing the great vessels. The aortic root and ascending aorta are well seen in the parasternal long- and short-axis views. Coronary artery ostia can be visualized (eFig. 49.5.22), sometimes allowing for diagnosis of coronary anomalies and Kawasaki's disease.

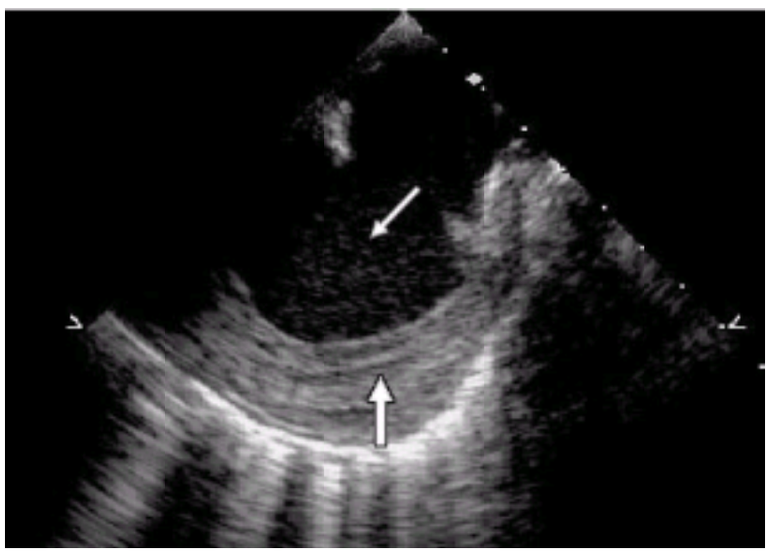


***e*FIGURE 49.5.22** Coronary artery visualization. Parasternal short-axis view showing the left main coronary artery (LMCA) arising from the aorta (AO). PV, pulmonary valve.

Aortic Aneurysm

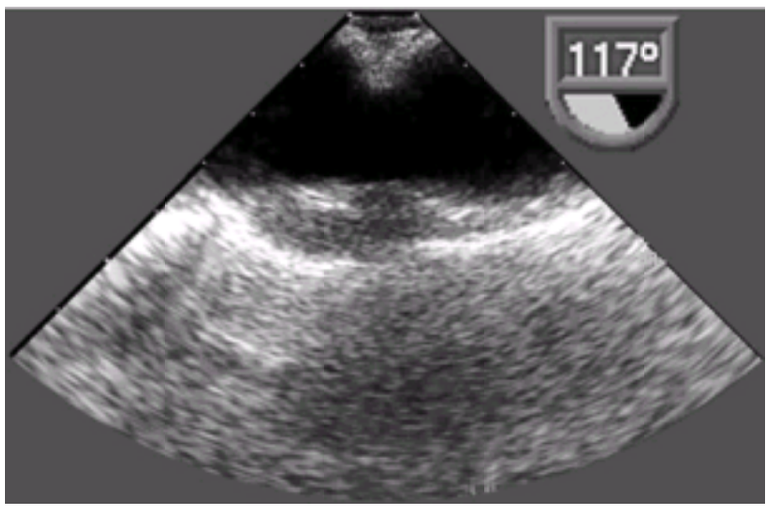
Symmetric sinus of Valsalva aneurysms (243,244) may be seen in Marfan syndrome. Echocardiographic enlargement of the root beyond 55 mm should generally prompt surgery. Ascending aortic dilatation may be poststenotic or atherosclerotic in origin, requiring high parasternal and right parasternal imaging to observe. The descending thoracic aorta can be seen in the long- and short-axis parasternal views posterior to the AV groove. The left and right pulmonary arteries may be seen in the short-axis view. The suprasternal notch allows visualization of the transverse and descending aorta as well as the origins of the innominate, left common carotid, and left subclavian vessels. In the apical views, posterior angulation often produces long- (two-chamber) and short- (four-chamber) axis views of the thoracic aorta. Atheroma and aneurysms of the abdominal aorta may be seen subcostally to the left of and deep to the IVC (245). Thoracic aortic dissection with effusion can also be imaged from the left paraspinal window, although TEE is the preferred method to assess the aorta (246).

Ascending aortic dissection extending into the left main. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Transesophageal view of the aortic arch demonstrating an arch aneurysm (*thin arrow*) with layering of thrombus inferiorly (*thick arrow*).

Transesophageal echo view of the descending aorta in short axis demonstrating significant atheromatous plaque.



A still frame of a transesophageal echo demonstrating a coarctation of the aorta. Note the local narrowing of the aorta located at the junction of the distal arch and descending aorta. There was a 100–mm Hg pressure gradient across the coarctation as determined by continuous wave Doppler.

Video 49.93 Short-axis transesophageal echo view of a type I aortic dissection. Note the flap originating within the noncoronary cusp (leaflet upper left screen) and extending towards the ostium of the left main trunk. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 49.94 Intraoperative 120-degree transesophageal echo of an ascending aortic dissection. Note the large, complex flap in the ascending aorta seen originating near the origin of the right coronary artery. There is a small amount of aortic insufficiency. Flow is seen in the true lumen (*left*) whereas no flow is seen in the false lumen (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Great Veins

The IVC is seen subcostally, crossing the diaphragm just after receiving the confluence of the hepatic veins. Its size and response to respiration predict RA pressure (247,248). If the vessel loses 50% of its initial expiratory diameter during deep inspiration (while lying supine with the knees bent), RA pressure is considered normal. The superior vena cava can be seen from a suprasternal notch plane orthogonal to the aortic arch view, allowing Doppler interrogation of its flow.

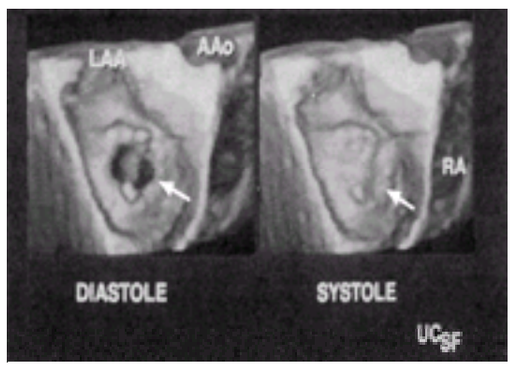
ADVANCES IN INSTRUMENTATION

Advances in instrumentation are occurring in many areas. Included in these are automatic border detection, Doppler tissue imaging, ultrasonic tissue characterization, video densitometry, and three-dimensional echocardiography.

Automatic border detection can track the LV endocardium (249,250,251 and 252), although it requires technically excellent images and has wide standard deviation among measurements. Another promising approach to endocardial border detection is Doppler display of low-velocity myocardial movement (so-called Doppler tissue imaging) (253,254). Enhancement of the LV blood pool and myocardium using ultrasonic contrast may allow these methods to become the standards.

Ultrasonic tissue characterization has shown slow progress, with cyclic variation in backscatter used as a marker for segmental ventricular function (255,256). Although many studies have sought to identify histologic changes (257,258,259,260 and 261), none has as yet entered common practice. Video densitometry can plot instantaneous changes in backscatter intensity as a bolus of contrast passes through the vasculature of the myocardium. Because it provides an analog of local flow, it should become useful when improved intravenous agents that can cross the pulmonary circulation intact and behave as surrogate red cells (262) become available.

Three-dimensional echocardiography can be accomplished by spatially registering each tomographic slice relative to the other (263,264,265 and 266). Quantitation of a three-dimensional data set can be done by selecting two-dimensional slices and tracing an outline of each slice (57,58,59,60 and 61,267). The slices are then added together to yield a volume or mass, a process that is independent of geometry yielding measurements that are accurate and reproducible. Unfortunately, this approach is time consuming and tedious; however, it may be improved by automated edge tracing and contrast enhancement of the myocardium and blood pool. Once it has been collected, a three-dimensional data set can place a virtual imaging window in any position (eFig. 49.5.23). Three-dimensional imaging remains in its formative stages. Two commercially available systems acquire spatially registered data sets over many cardiac cycles by using ECG and respiratory gating (264,268). These are limited by prolonged acquisition time between slice artifacts and long reconstruction times.



***e*FIGURE 49.5.23** Three-dimensional echocardiography. Three-dimensional reconstruction of a St. Jude valve (*arrow*) in the mitral position. The images are in diastole (*left*) and systole (*right*). LAA, left atrial appendage; AAo, ascending aorta; RA, right atrium.

CONTROVERSIES AND PERSONAL PERSPECTIVES

TTE is the single most useful imaging test in cardiology. Its use has grown tremendously over the last 10 years. However, this examination is not performed and interpreted uniformly—a fact that has attracted unfavorable attention to the potential overuse of echocardiography in the United States. Particularly appalling is the lack of quantitation in many echocardiographic reports. Echocardiography is quantitative in nature—calibration marks are included on every screen, and the Digital Imaging and Communications in Medicine (DICOM) standard allows them to be stored digitally; yet, echocardiograms too often are interpreted in general categoric terms.

Of the emerging echocardiographic (distinct from Doppler) technologies, three are most noteworthy: three-dimensional imaging, contrast echocardiography, and harmonic imaging. Three-dimensional reconstruction has been available commercially for several years and is a valuable tool in quantifying chamber size and visualizing cardiac structures. Nevertheless, it has failed to penetrate the clinical arena completely, primarily because of the prolonged acquisition and display times. With the development of real-time three-dimensional acquisition, however, examination time could become shorter, as all structural data could be captured in a data set

from a single cardiac cycle. True three-dimensional display remains problematic, but even scanning the data with properly oriented two-dimensional planes would be of great value.

Recent advances in echocardiography have resulted in improvements in image quality, especially for patients whose echocardiographic examination was previously suboptimal. Intravenous contrast agents are now available for LV opacification and endocardial border detection. Guidelines for the use of ultrasonic contrast in echocardiography have been published (269). Intravenous contrast agents should be used to provide additional diagnostic information for the detection of cardiac disease in difficult-to-image patients. They have been shown to be especially beneficial in obese patients, those with lung disease, and individuals who are receiving mechanical ventilation.

Use of harmonic frequencies to image tissue and contrast agents can further enhance image quality. In contrast harmonics, the harmonic frequency energy is generated on reflection of the ultrasound wave from the microbubble contrast agent. In tissue harmonics, the energy is gradually generated as the ultrasound wave propagates through the tissue. Essential to the utility of tissue-generated harmonic frequencies is their origin beyond the chest wall and their nonlinear relation to the fundamental frequency energy strength. These characteristics ensure that the echocardiograms that are most likely to produce artifact are least likely to produce harmonic waves (270). It is anticipated that harmonic imaging will become the standard for assessment of regional and global LV function in difficult-to-image patients.

Contrast agents that cross the lungs to opacify the LV cavity and myocardium combined with novel imaging techniques (e.g., transmitting at 2 MHz but receiving at 4 MHz) allow myocardial perfusion to at least be assessed in a binary sense (presence of coronary occlusion, occurrence of reperfusion). This may greatly assist in the detection and management of acute coronary syndromes. Even more exciting is the possibility of quantifying regional perfusion and flow reserve, an achievement that would bring echocardiography close to the holy grail of “one-stop shopping” that is claimed by other modalities.

THE FUTURE

Over the next 10 years, the field of echocardiography will be under intense pressure as cost containment leads to decreased reimbursement. This is ironic, because the value of the test should grow enormously as contrast, three-dimensional, and digital technologies mature. Although videotape will still be used, digital storage would allow retrieval throughout the hospital and transmission anywhere in the world, eliminating repetition of tests. Adherence to international formatting standards is critical. Attesting to the value of echocardiography are plans for a permanent ultrasound machine aboard the International Space Station for scientific research and for medical diagnosis.

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50

STRESS ECHOCARDIOGRAPHY

THOMAS H. MARWICK

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Stress echocardiography provides a means of identifying myocardial ischemia by detection of stress-induced wall motion abnormalities on comparison of pre-stress and post-stress images. The technological revolution of ultrasound and digital technology has driven the development of this modality from a research to a clinical tool. However, interpretation of these studies remains subjective, and the learning curve of skills required to use this modality must be considered.

Echocardiography may be combined with various stressors and used in a variety of environments. The test is patient friendly because it is rapidly performed and inexpensive. The accuracy of stress echocardiography in detecting significant coronary stenoses ranges from 80% to 90%, depending on the population studied, and the specificity is high. The accuracy exceeds that of exercise electrocardiography (ECG), especially in subgroups among whom the latter is unreliable (e.g., women and patients with left ventricular hypertrophy), and the accuracy is comparable with that of stress myocardial perfusion scintigraphy. The need to induce ischemia limits the accuracy of stress echocardiography in detecting coronary artery disease (CAD) in patients who exercise submaximally or who are on antianginal therapy. However, the detection of ischemia may prove to be of value in using this test for prognostic evaluation or for monitoring the efficacy of therapy. Use of dobutamine echocardiography for identification of viable myocardium following myocardial infarction is another application that has moved this modality into the arena of assisting decision making in the management of CAD. Similarly, this test may provide useful data for the management of valvular and primary myocardial disease.

Stress echocardiography has been refined significantly over the last 3 years, and progress is likely to continue at a rapid pace. Endocardial border detection has been facilitated by harmonic imaging and contrast echocardiography. Tissue Doppler imaging and acoustic quantification techniques have been used to develop a quantitative approach to interpretation that is likely to become more sophisticated. The next major step is likely to be routine or selective use of echo-contrast agents to permit acquisition of both left ventricular (LV) function and perfusion data at rest and after stress.

GLOSSARY

Coronary steal: A situation in which a vasodilator increases runoff to a normal branch, thus reducing the driving pressure in an artery proximal to a stenosis and causing ischemia because of reduced blood flow across the stenosis.

Echocardiographic contrast agents: Injectable compounds comprising gas-filled microbubbles approximately the size of or smaller than erythrocytes that increase the reflected signal of the cardiac structures in which they are located.

Myocardial tissue Doppler imaging: Use of Doppler principle to examine myocardial rather than blood flow velocity.

Sensitivity: Proportion of patients with CAD correctly identified as abnormal.

Single-photon emission computed tomography (SPECT): A means of acquiring and portraying scintigraphic data in a tomographic fashion.

Specificity: Proportion of patients without CAD correctly identified as normal.

Viable myocardium: Myocardial segments characterized by reduced function at rest but potentially recoverable either spontaneously (*stunned*) or with revascularization [usually associated with reduced myocardial perfusion (i.e., *hibernating myocardium*)].

INTRODUCTION

The use of exercise testing to provoke ischemic symptoms, ECG changes, and assess exercise capacity for the purpose of evaluating CAD dates back to the 1950s (1). However, while the exercise ECG is the most commonly accepted functional test for the diagnosis of CAD, there are situations in which it is inappropriate. First, patients who either cannot exercise or exercise submaximally account for 30% to 40% of patients presenting for functional testing (2). These patients are best studied using the combination of pharmacologic stress with various imaging techniques for the diagnosis of coronary disease. Second, even if the patient is able to exercise, the ECG may be uninterpretable because of repolarization abnormalities. In these circumstances, the ability of the patient to exercise is exploited by the combination of exercise testing with an imaging modality.

The use of stress imaging tests is not restricted to the diagnosis of coronary disease. As the ability to perform revascularization has improved, there has been a need to evaluate coronary disease on a functional basis, both to understand the site of ischemic tissue (and hence the likely culprit lesion) and to distinguish between ischemic,

infarcted, and viable myocardium. Exercise ECG testing is unable to provide these data, which mandate the use of imaging. Similarly, the management of non–coronary heart disease, including valvular heart disease, primary myocardial disease, and some obstructive lesions may be facilitated by an appreciation of functional responses to stress.

Imaging modalities that may be used to examine regional and global LV function include contrast ventriculography, nuclear ventriculography, echocardiography, magnetic resonance imaging (MRI), and fast computed tomographic scanning. Contrast ventriculography is invasive, and although serial measurements may be performed in the course of pressure volume loop analysis, this is of little clinical value. The use of the MRI in combination with exercise has been constrained by the need to use nonmagnetic materials in this environment, so that most studies have been performed with pharmacologic stress (3,4 and 5). The cost and availability of both MRI and fast computed tomography are also important limitations. Thus, nuclear ventriculography and echocardiography are the most commonly used techniques for the assessment regional and global LV function in combination with stress. These techniques are compared in the section Comparison with Other Techniques.

DEVELOPMENT OF STRESS ECHOCARDIOGRAPHY

In the 1970s, the clinical role of echocardiography became established in the diagnosis and management of predominantly valvular and congenital heart disease. The use of M-mode echocardiography for the analysis of ventricular function was constrained by the need to assume that the ventricle had a geometric shape (6)—an assumption that is often inappropriate in a setting of ischemic heart disease. Nonetheless, M-mode echocardiography was combined with exercise stress for the detection of ischemia-induced wall motion abnormalities in the late 1970s (7).

The development of two-dimensional echocardiography in the 1980s permitted echocardiography to become a truly tomographic technique for the analysis of ventricular function. The calculation of global ventricular function became less limited by geometric assumptions (6). Not surprisingly, cross-sectional echocardiography was combined with stress (8), although the narrow (30-degree) sector angle of the early scanners, combined with poor imaging quality and the need to compare segmental function in different segments of videotape, posed important technical limitations on the new approach. As the technology became more sophisticated and image quality improved, successful image acquisition became possible in over 90% of patients using a wide angle (90-degree) sector (9,10). It was soon recognized that the most feasible approach was the comparison of pretreadmill and immediate posttreadmill images (10) as peak exercise imaging on the treadmill was difficult (11), although peak bicycle stress imaging using the subcostal approach was used in the same era (12). Even with the technical limitations of exercise echocardiography at that time, it was found to be comparable in accuracy with nuclear ventriculography (13,14 and 15) and planar thallium imaging (16).

The major impetus to the development of stress echocardiography as a routine clinical tool came with the development of digital image processing in the late mid-1980s (17). The use of digital frame grabbers enabled the rapid acquisition of postexercise cine loops, gated in systole, and independent of respiratory artifact. Moreover, the digital approach allowed the side-by-side analysis of images that facilitated the recognition of regional wall motion abnormalities. Future advances in stress echocardiography are likely to be in the realm of quantitation and obtaining data regarding myocardial perfusion.

PATHOPHYSIOLOGY

Effects of Ischemia on Left Ventricular Function

Ischemia develops after a mismatch occurs between nutrient supply and the demands of the cardiac myocyte. Most commonly, this mismatch occurs because of fixed stenoses in epicardial coronary vessels, and less commonly due to vasoconstriction or small vessel disease. The vasodilator reserve of the coronary vasculature is such that ischemia occurs at rest only in the setting of critical (greater than 90% coronary diameter) narrowings (18). During stress, limitation of the ability to generate a hyperemic response may reduce maximal hyperemic coronary flow in the presence of stenoses of greater than 50% diameter, although the anatomic severity of stenosis and the physiologic consequences are poorly related (19). Clearly, the ability to provoke ischemia in the setting of relatively mild coronary stenoses is dependent on the performance of maximal stress.

Detection of schemia by Echocardiography

The normal response of the left ventricle to increasing workload is a uniform increase of regional wall motion, thickening, and a reduction of end-systolic LV cavity size, with minimal changes of diastolic size during exercise or vasodilation (20). These changes return to baseline usually within minutes of the conclusion of the stress (21).

The distinction between resting and stress-induced wall motion abnormalities (Table 50.1) fundamentally differentiates prior myocardial infarction, identified by resting akinesis or dyskinesis, from induced ischemia, characterized by either new or worsening wall motion abnormalities. This effect of ischemia on regional ventricular function has been well defined with microcrystals (22), as well as with echocardiography (23,24). A more subtle index of myocardial ischemia is delayed contraction (25). The presence of LV enlargement following stress identifies severe ischemia or other serious heart muscle diseases. The time course of offset of regional myocardial dysfunction is variable and probably reflects the severity and duration of ischemia. Wall motion abnormalities may rapidly recover following the cessation of stress (26,27) but may also persist for 30 minutes or longer (9), especially if stunning is induced.

Characterization of tissue	Resting function	Low-dose	Peak/poststress function
Normal	Normal	Normal	Hyperkinetic
Ischemic	Normal	Normal (ischemic with severe coronary artery disease)	Reduction vs. rest Reduction vs. adjacent segments Delayed contraction
Viable, nonischemic	Rest WMA	Improvement	Sustained improvement
Viable, ischemic	Rest WMA	Improvement	Reduction (compared with low-dose)
Infarction	Rest WMA	No change	No change

WMA, wall motion abnormalities (severe hypokinesis, akinesis, dyskinesis).

TABLE 50.1 INTERPRETATION OF EXERCISE AND PHARMACOLOGIC STRESS ECHOCARDIOGRAPHY

VIDEO

Video 50.1 Appearance of myocardial scar at exercise echocardiography. The resting images (*left*) show thinning and akinesis of the anteroseptal wall. Even though this wall is not resolved after exercise, the diagnosis of left anterior descending territory scar is clear. The posterior wall is initially normal and deteriorates after exercise, consistent with left circumflex territory ischemia. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

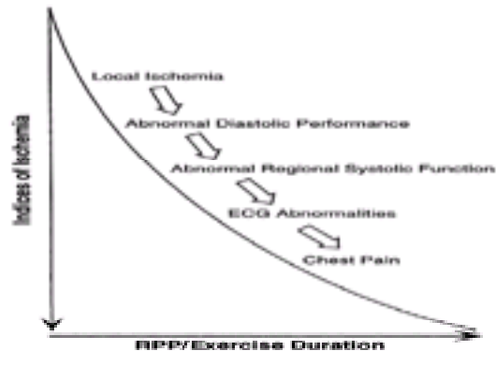
Video 50.2 Diagnostic information from changes in left ventricular shape and size at exercise echocardiography in a patient with left anterior descending coronary artery and left circumflex coronary artery disease. The apical four-chamber view shows development of akinesis in the mid and apical septum after stress; this causes the left ventricular cavity to assume an “hourglass” shape in systole due to an apical bulge. The development of left ventricular cavity enlargement draws attention to a lateral wall motion abnormality after stress. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The presence of regional systolic dysfunction is usually caused by CAD, although cardiomyopathic processes may be regional rather than global. Resting wall motion abnormalities may not necessarily indicate the presence of transmural infarction; hypokinetic segments may be partially infarcted (especially the subendocardium) or

viable (28). Viable segments may recover spontaneously (if the tissue is stunned) or following revascularization (if the myocardium is hibernating) (29,30). The presence of residual viable tissue is more common in hypokinetic than akinetic segments and least common in dyskinetic segments (31). Viable myocardium augments function in response to inotropic stimulation, and this response may be detected using echocardiography, as discussed in the section Identification of Myocardial Viability. Probably, both stunned and hibernating tissue contribute to chronic LV dysfunction due to CAD, and the conventional stress echo interpretation algorithm has been modified by the application of these findings to the clinical arena (Table 50.1).

Ischemic Cascade

The ischemic cascade describes a temporal sequence of physiologic disturbances that occur sequentially in the context of ischemia (*e*Fig. 50.0.1). These were initially described in the setting of supply-based ischemia (32). Following the initial development of regional malperfusion, the development of regional systolic dysfunction was preceded by abnormalities of diastolic function (33) with global changes of systolic function occurring later, and finally the development of ST-segment changes and chest pain. The sequence of these changes might be expected to lead to a superiority of myocardial perfusion imaging (which identifies regional flow heterogeneity) over stress echocardiography (which identifies regional systolic dysfunction). However, this supposition ignores the characteristics of these diagnostic modalities, and the description of such a sequence does not necessarily indicate a substantial delay between these phenomena. In particular, the development of ventricular dysfunction occurs rapidly following coronary occlusion (34). Moreover, there is a relationship between the severity of reduction of flow and the presence and extent of wall motion abnormalities; for detectable regional wall motion abnormalities to occur, flow needs to be reduced by at least 50% in at least 5% of the myocardium (35). Finally, it should be made clear that the classical description of the ischemic cascade, based on “supply side” ischemia, may not necessarily be applicable to stress-induced ischemia, which is due to increased myocardial oxygen demand.



***e*FIGURE 50.0.1** Ischemic cascade. The development of chest pain and electrocardiographic (ECG) changes of ischemia occur at a greater level of cardiovascular stress than wall motion or perfusion abnormalities. RPP, rate-pressure product.

VIDEO

Video 50.3 Dobutamine echo. Parasternal long-axis view of a patient with left anterior descending artery scar and peri-infarct ischemia. No obvious ischemia is seen in this view (see apical two- and four-chamber views). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.4 Parasternal short-axis view of a dobutamine stress echo of a patient with peri-infarct ischemia in the left anterior descending coronary artery territory. No ischemia seen in this view (see ischemia in apical two- and four-chamber views). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.5 Apical four-chamber view of a dobutamine stress echo of a patient with peri-infarct ischemia in the left anterior descending coronary artery territory. Note the distal septal resting wall motion abnormality that fails to augment with peak dobutamine infusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.6 Dobutamine stress echocardiogram showing a biphasic response. The quad-screen display shows resting images in the upper left, low-dose (5 and 10 µg/kg/min) in upper right and lower left, and peak stress images in the lower right in the apical two-chamber view. A resting wall motion abnormality of the basal and mid inferior segments improves to normal at 10 µg/kg/min but deteriorates at peak stress. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

METHODOLOGY OF STRESS ECHOCARDIOGRAPHY

Stress Testing Modalities

Exercise Stress

The use of stress echocardiography in patients with known or suspected CAD *who are able to exercise* usually incorporates exercise stress. The choice of modalities in this respect is between the treadmill and cycle ergometry, which may be upright or supine. During exercise, heart rate, blood pressure, and inotropic state all increase, in proportion to the increase of cardiac work. During upright exercise, venous return is relatively reduced, and LV end diastolic volume and pressure are similarly less than they would be during supine exercise (36).

Exercise echocardiography with a treadmill requires selection of an appropriate protocol tailored to the patient to exercise the patient for 7 to 10 minutes. Such a protocol obviously varies according to the patient’s age, gender, state of health, and physical fitness, so most laboratories traditionally use several protocols, including Bruce, modified Bruce, and Naughton. For diagnostic studies, we usually request that the patients withhold antianginal therapy at least on the day of testing. However, when testing is performed to assess the adequacy of therapy, medicines are continued up to the time of testing. Patients are advised to either fast or take only a light meal before undergoing stress. Electrodes are applied in the usual way for exercise testing, but electrodes in the V_2 and V_4/V_5 locations may be moved if they interfere with the echocardiographic windows. Before exercise, imaging is performed in the supine position, with digital capture of parasternal long and short and apical two- and four-chamber views into a quad-screen cine-loop display. After exercise is concluded for symptom-limited end points, post-stress images are obtained, preferably within 1 minute, and certainly within 2 minutes of exercise. The digital images are then remixed to display rest and stress images side by side to facilitate interpretation.

Bicycle exercise may be performed using an upright or supine ergometer. Stress protocols are tailored to the patient in the same way as treadmill protocols, but most frequently involve 2- to 3-minute increments of 20 to 25 W, following a startup workload of 0 to 25 W or more, depending on the patient's functional status. With respect to imaging, the same pre-stress and post-stress images are obtained, but in addition, a set of images is acquired in the upright (or semisupine if this is used) position before exercise and repeated during stress. If upright bicycle exercise is used, images may be obtained during exercise by leaning the patient forward to obtain the parasternal images and sometimes by elevation of the left arm to obtain apical images (37). These maneuvers facilitate the acquisition of all views during bicycle stress and ensure that the heart is imaged in the same orientation before, during, and at peak stress.

The merits and limitations of treadmill and bicycle stress are summarized in Table 50.2. In general, treadmill exercise is more widely accepted among patients and physicians in the United States. On the basis of peak and poststress imaging on the bicycle, it has been identified that a small reduction of sensitivity is possible if postexercise imaging is used. Lower workloads are attainable with bicycle than treadmill exercise, which needs to be traded off against the benefits of peak exercise imaging on the bicycle. It is currently not possible to identify an optimal approach for exercise echocardiography, and the decision between bicycle and treadmill exercise is dependent on local expertise and, to some extent, on the nature of the clinical question in each individual patient. The acquisition of multiple images at peak stress is attractive for making assessments of the functional severity of coronary stenoses, and peak exercise imaging is attractive for assessment of valvular lesions. Moreover, the performance of imaging during stress may facilitate definition of the ischemic threshold.

	Treadmill	Bicycle
Acceptance	Familiar to patient and physicians	Unfamiliarity
Adequacy of stress	Patients stress maximally	Premature termination due to leg fatigue Dependent on patient compliance
Imaging	Postexercise	Peak and postexercise

TABLE 50.2 ADVANTAGES AND DISADVANTAGES OF TREADMILL VERSUS BICYCLE STRESS FOR EXERCISE ECHOCARDIOGRAPHY

Sympathomimetic Stressors

Mechanism of Action

Although a number of sympathomimetic agents, including dobutamine, arbutamine, isoproterenol, dopamine, and even epinephrine, have been combined at echocardiography (38,39), dobutamine is the most widely used. The inotropic activity of these agents reflects a combination of alpha- and beta-stimulation (40,41). The effect of this stimulation is to enhance the inotropic state, heart rate, and blood pressure, all of which are determinants of myocardial oxygen consumption. Dobutamine was initially designed as an agent for use in the intensive care unit, and its chronotropic effect only emerges at high doses. The use of dobutamine for stress testing constitutes the "off-label" use of an approved drug.

Hemodynamic Response

The response to dobutamine is summarized in Figure 50.1. Generally, peak heart rates of 120 to 140 beats/min are attainable (42), this corresponding to at least 85% of age-predicted heart rate in most patients. The systolic blood pressure usually increases by 30 to 40 mm Hg, with peak pressures of 170 to 180 mm Hg, and peak rate-pressure products of approximately 20,000. However, considerable variability occurs between different patients with respect to both the extent and speed of these hemodynamic responses.

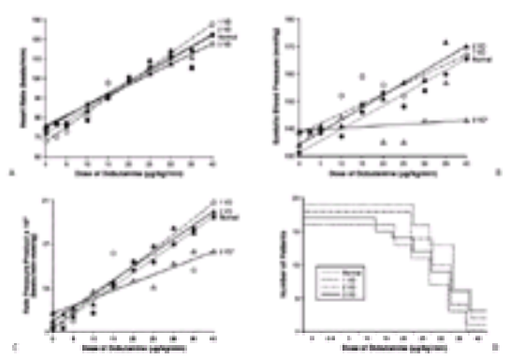


FIGURE 50.1 Hemodynamic responses to dobutamine, including heart rate **(A)**, systolic blood pressure **(B)**, and rate-pressure product **(C)**, according to the extent of coronary artery disease. **D:** The number of patients undergoing testing at each dose level of dobutamine, according to disease extent. 1 VD, one-vessel disease; 2 VD, two-vessel disease; 3 VD, three-vessel disease. (From Cohen JL, Greene TO, Ottenweller J, et al. Dobutamine digital echocardiography for detecting coronary artery disease. *Am J Cardiol* 1991;67:1311–1318, with permission.)

Side Effects

Many patients requiring dobutamine stress are elderly and have serious noncardiac diseases or even severe CAD and LV dysfunction. Despite the use of high doses of these agents, serious complications occur in approximately 3 in 1,000 (43).

Administration Protocol

The protocol for dobutamine administration is empiric. Initially, a peak dose of 20 µg per kg per minute was used with myocardial perfusion imaging (44) and later echocardiography (45). The currently employed high-dose protocols (to 40 µg per kg per minute) were initially described by Sawada and Cohen (42,46) and seem to be more sensitive than lower dose protocols (47), although low-dose protocols provide adequate stress if the duration of each stage is longer (e.g., 5 rather than 3 minutes) (48). Atropine has been combined with dobutamine at peak dose if the heart-rate target is not attained (49) and more recently has been administered earlier in an attempt to shorten test duration (50). When evidence of myocardial viability is being sought, it is important to recognize that augmentation of function may occur at lower doses of dobutamine, and some authors have suggested specific low-dose protocols (e.g., to 12.5 µg per kg per minute in 2.5-µg increments) for this purpose. However, the practice of our laboratory has been to use a single standard protocol (including high dose), which offers the versatility of identifying both viability and ischemia, while at the same time providing a study of acceptable length (Fig. 50.2). A rare exception is the situation in which peak dose is considered unsafe (e.g., history of hemodynamic instability); while caution should be exercised, the test appears safe for studying patients with severe LV dysfunction (51,52 and 53). Moreover, as discussed later in the chapter (see Extent and Severity of Disease), the biphasic response is the most reliable marker of recovery of LV function, and the detection of this usually requires a high-dose protocol. At present, none of the dobutamine protocols is clearly superior to the others, and the main consideration should be to ensure the adequacy of stress.

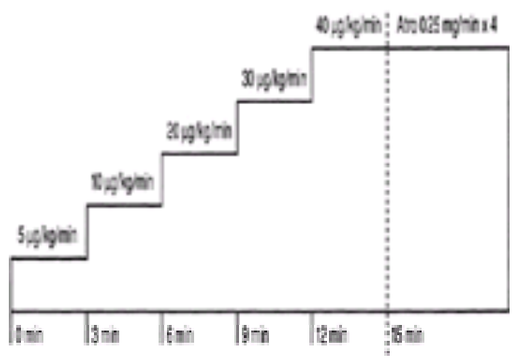


FIGURE 50.2 Dobutamine-atropine infusion protocol. Atro, atropine. (From Otto K. *Practice of clinical echocardiography*. Philadelphia: WB Saunders, 1996, with permission.)

The patient is usually requested to fast for a few hours before the test. It is desirable for antianginal medication (especially beta-blockers) to be withheld for diagnostic studies. The patient is attached to an ECG machine for the purpose of monitoring, although the accuracy of the ST-segment response for the identification of coronary disease is poor. Resting imaging is performed before stress, as with exercise echocardiography. Although we use the same dobutamine infusion protocol for all patients, our approach to imaging varies according to the clinical situation. When a dobutamine study is performed for the diagnosis of coronary disease, a single set of low-dose images (10 µg per kg per minute) is captured in digital format, and the remaining two quadrants of the quad-screen display are used to record prepeak (usually 30 µg per kg per minute) and peak (40 µg per kg per minute, or 40 µg per kg plus atropine). A complete set of images is recorded on videotape at each stage of the dobutamine protocol and in recovery. In patients with resting wall motion abnormalities, in which myocardial viability may be of interest, two sets of low-dose images (5 and 10 µg per kg per minute) are recorded in the second and third quadrants, followed by peak images. This facilitates the recognition of viable myocardium.

Vasodilator Stress

Mechanism of Action

The mechanism of effect of vasodilator agents in inducing ischemia is more complex than with other methodologies. In conjunction with myocardial perfusion imaging, vasodilator agents are used to achieve maximal coronary vasodilation in all vascular territories, and the diagnosis of ischemia is made if the regional hyperemia is compromised by a coronary stenosis. The identification of a stress echocardiogram result as positive is dependent on the induction of ischemia, for which the main mechanism with these agents is coronary steal (54), due to decreased proximal driving pressure caused by increased runoff to the normally vasodilated, patent vessel. This process may be either vertical (subepicardial from subendocardial) or horizontal (from stenosed territory to nonstenosed). Other potential contributors include collapse of the stenosis in the face of systemic hypotension, a minor increment of myocardial oxygen demand, or rarely coronary spasm. Generally, these phenomena occur in the setting of severe or extensive coronary disease. The dipyridamole test has also been used for the identification of myocardial viability, this process presumably reflecting a vasodilator effect in hibernating tissue, and perhaps increasing turgor in tissue with an intact hyperemic response.

Adenosine and dipyridamole differ in respect to the rate of onset and duration of their effects. Adenosine is a powerful endogenously occurring vasodilator, which acts directly on the vasculature, having a vasodilator efficacy equivalent to papaverine and dipyridamole (55,56). The action of dipyridamole is indirect, as this agent increases endogenous adenosine levels by reducing adenosine reuptake and metabolism (57). Thus, peak vasodilation occurs almost instantaneously with adenosine, but this process is delayed with dipyridamole. Similarly, the offset of the effect of adenosine is rapid (the half-life of this agent is less than 1 minute) while the half-life of the dipyridamole vasodilator effect is approximately 6 hours.

Hemodynamic Response

The hemodynamic effects of these stressors are minor. Blood pressure is little influenced by vasodilator stressors, although hypotension may occur. There may be a small increment of heart rate, which may occur in response to various side effects.

Side Effects

Serious side effects occur in approximately 1 in 1,000 patients. The most common side effects of dipyridamole and adenosine are headache and dyspnea, respectively (58,59). The speed of onset and potency of adenosine render its side effects less well tolerated, but these effects resolve rapidly with cessation of the drug. Both techniques are contraindicated in patients with untreated atrioventricular block and bronchospastic disorders, and abstinence from xanthene-containing foods and drugs is required before either stress.

Administration Protocol

The standard dipyridamole dose for myocardial perfusion imaging is 0.56 mg per kg administered over 4 minutes. For stress echocardiography, this dose induces ischemia only in patients with severe coronary disease. Thus, 0.56 mg per kg is administered first, but if ischemia is not induced, an additional 0.28 mg per kg is administered over 2 minutes. Atropine may be added if the response to dipyridamole is negative (60), and imaging is continued over 16 minutes. In some laboratories, dipyridamole is reversed with aminophylline. Although this is not usually necessary, aminophylline is useful for reversing the effect of dipyridamole in the presence of significant side effects. However, if aminophylline is needed for the treatment of severe ischemia, the supervising physician should be aware that the effect of dipyridamole may last longer than that of aminophylline, leading patients to become ischemic after they have left the stress laboratory.

The standard dose of adenosine for myocardial perfusion imaging is 0.14 mg per kg per minute intravenously over 4 minutes. This is also the most widely used dose for stress echocardiography, although both higher and lower doses have been studied. Although analogous to the dose of dipyridamole, higher dose protocols are constrained by dose-limiting side effects.

Combined Stressors

The simplest combined stressors are the combinations of dobutamine or dipyridamole with atropine, which have become part of the standard protocols using these agents. The combination of dipyridamole with dobutamine has been suggested as a means of producing a gradation of stress, with each stage of the test offering an increment of sensitivity for the detection of CAD (61). This protocol involves the initial administration of the two-phase dipyridamole stress described previously, followed by a standard dobutamine stress if the first test result is negative. Although this approach has increased the sensitivity of either of the pharmacologic techniques without a significant increment of side effects, it has the disadvantage of excessive length with commensurate high cost. Probably because of these practical considerations, this combined stress modality has not gained wide acceptance.

Pacing Stress

Of the nonpharmacologic approaches to nonexercise stress, pacing is the most widely used, although technical limitations and patient tolerance have limited the application of this modality. The mechanism of effect of this stress is to increase cardiac workload, although most of the increment is due to increased heart rate. To optimize the degree of stress, pacing may be combined with a pharmacologic stressor such as dobutamine; certainly this may be of use for the assessment of viable myocardium. Atropine is often administered to overcome atrioventricular block. The most widely used approach is transesophageal atrial pacing (62,63,64,65 and 66), although invasive pacing has also been studied (67). Despite the problem of lesser patient tolerance than the pharmacologic stressors (68,69), the attractions of this technique are that it is rapid, reliably produces tachycardia, and may be suddenly terminated, which renders this a relatively safe technique. Moreover, the rapid resolution of tachycardia in the presence of ischemia allows the evaluation of diastolic function, which is difficult at rapid heart rates (70).

A variety of pacing protocols have been studied. We use this technique in situations in which pharmacologic stressors are contraindicated, especially in patients on dialysis, in whom hypertension may be a limitation to standard dobutamine stress. Loss of capture is best avoided by using a short protocol; whereas previously we used an incremental protocol tailored to the patient (37), we now capture baseline images just above resting heart rate (to ensure ECG triggering works during pacing), increase to 85% predicted heart rate, and then 100% of predicted heart rate, each for 3 minutes. The most common side effect is esophageal discomfort if a large

current is required for atrial capture.

Other Techniques

Other stressors (e.g., isoproterenol) have been used in small numbers of patients and appear to be effective. A significant literature has developed regarding the use of ergonovine stress echocardiography for the diagnosis of coronary spasm. This agent is usually used in the angiography laboratory (where spasm is visualized directly), but it appears safe to apply noninvasively in patients without significant stenoses (71,72 and 73), as well as in some patient groups without preceding angiography (74,75). The standard protocol involves repeated bolus doses of ergonovine maleate at 5-minute intervals up to a total cumulative dosage of 0.35 mg, unless echocardiographic evidence of abnormal LV wall motion is detected.

Selection of the Optimal Stress Agent

Pharmacologic stressors enhance the feasibility of imaging, but they have a number of important disadvantages (Table 50.3). Generally, comparable levels of sensitivity are obtainable, although the performance of submaximal stress due to side effects is an important limitation. If a patient can exercise, we believe that he or she should undergo exercise echocardiography, unless the test has been performed for other reasons than the detection of myocardial ischemia (e.g., in specialized situations in which viability or coronary spasm are being evaluated). The development of new technologies such as tissue Doppler imaging, automated border detection, and contrast echocardiography have made pharmacologic stressors more attractive than exercise, but whether the incremental data offered by the addition of these features justifies the disadvantages of using a pharmacologic stressor in all patients remains to be established.

Evaluates exercise capacity
Correlates symptoms with physical workload
ST-segment evaluation
Cardiac workload is greater with exercise
Prognostic information
Probably greater sensitivity for ischemia

TABLE 50.3 BENEFITS OF EXERCISE OVER PHARMACOLOGIC STRESS

The type of pharmacologic stress may also be the source of debate. The frequency of side effects with dipyridamole and dobutamine stress is comparable, but the contraindications of each test are different. Thus, patients with asthma or untreated conduction system disease might be better tested using dobutamine echocardiography, whereas dipyridamole stress would be preferable in those with serious arrhythmias or severe hypertension. Most patients do not fall into these categories, so that either stressor might be used. In this situation, the choice might be based on physician preference, cost (dobutamine costs considerably less than dipyridamole in the United States, but the situation is reversed in Europe), and the clinical question to be addressed. If this relates to the diagnosis of coronary disease, the sensitivity of dobutamine echocardiography is somewhat greater than that of dipyridamole echocardiography, especially in patients with single-vessel disease. On the other hand, if the main interest is in prognostic evaluation, the agents are both attractive, and certainly a wealth of information is available regarding dipyridamole echocardiography as a prognostic test (see Prognostic Considerations in Coronary Artery Disease).

Imaging Techniques

Stress echocardiography is almost universally performed using transthoracic echocardiography, although transesophageal imaging is sometimes used in the setting of poor image quality. The procedure brings together facilities for stress testing, echocardiography, and at least two and sometimes three personnel including physician, sonographer, and nurse. To use all of these resources efficiently, there is a need to limit the duration of activities that precede and follow the stress, during which time all resources are required. Consequently, it is not possible to perform an exhaustive echocardiographic examination in the context of stress echocardiography. Nonetheless, a screening M-mode and color Doppler examination should be performed at the beginning of every study. If more complex (e.g., valvular) problems are identified, these issues should be analyzed by echocardiography at another time. Using this approach, it should be possible to perform a treadmill echocardiogram in approximately 35 minutes, a bicycle stress echocardiogram in 45 minutes, and a dobutamine stress echocardiogram in approximately 1 hour.

Analysis of digital loops is beneficial for the interpretation of all forms of stress echo. Side-by-side comparison of cine loops in a split-screen display permits easy comparison of regional wall motion at rest and stress, and frame-by-frame review facilitates definition of the endocardium as well as evaluation of the temporal sequence of contraction. The disadvantage of this approach, however, is the finite number of views that can be compared using the quad-screen display and the presentation of single cardiac cycles. Consequently, review of the videotape is an important part of stress echocardiographic interpretation (76).

The most common sources of poor image quality are obesity and the presence of superimposed lung in one of the transthoracic windows. Transesophageal stress echocardiography offers excellent endocardial visualization (77,78) and has been useful in situations in which definition of the endocardium is considered particularly important, e.g., in the identification of viable myocardium. Pharmacologic and pacing stresses have been combined with the transesophageal approach, but because of its invasiveness, and issues of patient acceptance, this technique has a limited role in routine practice. Moreover, harmonic imaging has dramatically improved the visualization of myocardial segments and the accuracy of stress echocardiography (79,80). In the current context, transthoracic images are interpretable in greater than 95% of patients, and the indications for transesophageal stress echo are fewer than previously.

Interpretation of Stress Echocardiography

Qualitative Approaches

A qualitative approach is currently used for the interpretation of stress echocardiography. Using a segmental model of the left ventricle, each segment is compared before, during, and after stress. It is important in this evaluation that myocardial thickening is examined wherever possible, in preference to myocardial motion, which may occur due to translational movement, or tethering. Table 50.1 illustrates the criteria used to identify ischemia, myocardial viability, and myocardial scar. In general, ischemia is identified by the development of a new or worsening wall motion abnormality. Subtle indices of ischemia include delayed contraction; a temporal evaluation of myocardial contraction can be appreciated by stepping through individual freeze-frame images in the digital cine loop. Stress-induced LV enlargement is often a marker of multivessel coronary disease, and changes of ventricular shape as well as size are useful diagnostic clues to ischemia. As summarized by Table 50.1, myocardial viability is characterized by improvement of a dyssynergic zone in response to *low-dose* dobutamine. It is especially important that myocardial thickening is sought in patients with extensive infarction, as tethering can induce wall motion in nonviable segments. The most specific indicator of myocardial viability in the setting of hibernation is deterioration of this zone showing initial augmentation in response to increasing dobutamine dose, the “biphasic” response (81). In contrast, stunned myocardium augments functioning in response to low-dose dobutamine, but does not subsequently deteriorate. The presence of augmentation at *peak doses* of dobutamine is a nonspecific response, which is poorly predictive of myocardial viability.

The subjectivity of current approaches to the interpretation of stress echocardiography is the greatest shortcoming of this technique. This has two major manifestations: first, the need for training, and, second, the problems posed for reproducibility of the test. The importance of training in stress echocardiography was studied by a comparison of experts in stress echocardiography and skilled echocardiographers without stress echocardiography experience (82). The experts demonstrated a significantly greater accuracy than the other echocardiographers, but after a training period, during which the trainees were instructed using 100 studies, this difference in accuracy became insignificant (Fig. 50.3). This training period may not need to be as long as 6 months, and we and others (83) have documented enhancement in reviewer accuracy over a 3-day course, during which fewer than 70 studies were reviewed. However, once this level of skill is attained, we believe that a regular workload is required to prevent it from attenuating. Finally, even among expert readers, while the concordance of interpretations within the same center is high (84), concordance between different centers may be less than or equal to 80% (85). Uniform interpretive criteria have reduced but still not avoided this problem of discordance (86). As this is particularly a problem in studies of poor technical quality, and in patients with milder forms of coronary disease, it is not surprising that technical advances including harmonic imaging and digital display have further improved observer agreement (87), although this remains imperfect.

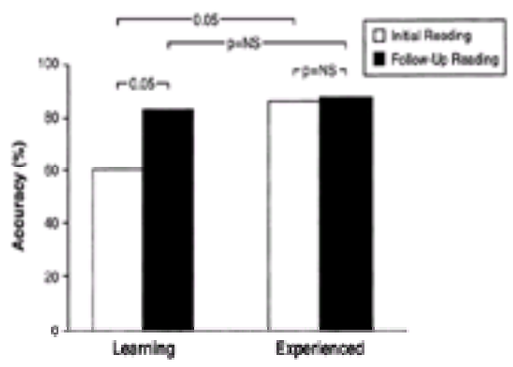


FIGURE 50.3 The learning curve of stress echocardiography. Over 6 months and 100 supervised echos, the trainees increased their accuracy from approximately 60% to 80%. NS, not significant.

To control issues related to subjectivity and concordance between observers, we review stress echocardiograms systematically. Quad-screen displays are first examined to assess their quality and the presence of technical limitations (e.g., gating problems); in technically limited studies, more reliance will need to be based on analysis of the videotape. Resting images are then examined in each view, using the American Society of Echocardiography 16-segment model to score regional wall motion (Fig. 50.4). Global function may be assessed subjectively by calculation of a wall motion scoring index or by measurement of the ejection fraction. The rest and stress images are then compared. The first step is to check for the presence of LV enlargement and shape changes, which are global indicators of ischemia, and in the case of the former, of multivessel disease. Each segment is then scored and compared with the equivalent segment at rest to identify the site, extent, and severity of abnormal function. If a bicycle or dobutamine stress study is used, the ischemic threshold is an important clue to the severity of ischemia. The report should therefore describe the site, extent, and severity of scar and ischemia, the global LV function before and after stress, and the presence of other abnormalities.

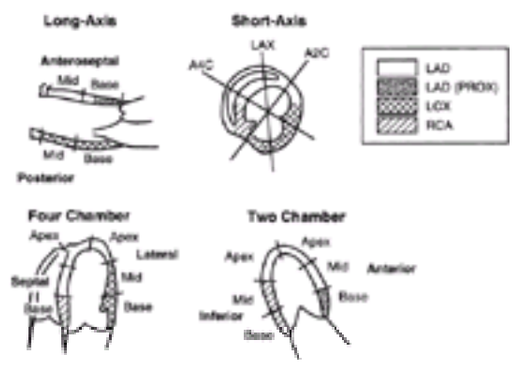


FIGURE 50.4 Systematic evaluation of the left ventricle using the 16-segment model of the American Society of Echocardiography. Each segment must be scored individually at rest and during, after, or both during and after stress. LAD, left anterior descending coronary artery; LAX, long axis; LCX, left circumflex coronary artery; PROX, proximal; RCA, right coronary artery.

Video 50.7 Apical two-chamber view of a dobutamine stress echo of a patient with peri-infarct ischemia in the distal anterior and distal inferior walls. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 50.8 Stress echo of a patient with left anterior descending coronary artery ischemia, parasternal long-axis and short-axis views. Note the deterioration of the anteroseptal wall (*upper right panel*) and the anteroseptum and anterior walls (*lower right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 50.9 Stress echo (apical views) of a patient with left anterior descending coronary artery ischemia. Note the worsening of the distal septum and entire anterior wall. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Quantitative Approaches

Given the limitations of the qualitative approach, a quantitative approach would seem desirable. Global systolic indices (e.g., ejection fraction or volumes) have limited value, as they are usually abnormal only in the setting of severe ischemia. Wall motion scoring is semiquantitative, but is similar to the standard qualitative approach. Quantitative techniques may be used for the measurement of radial or longitudinal function (Table 50.4).

	Radial	Longitudinal
Displacement	Centerline Acoustic quantification	M-mode
Thickening	Anatomic M-mode	Backscatter
Velocity (including velocity gradient)	Tissue Doppler	Tissue Doppler, strain
Timing	Tissue Doppler	Tissue Doppler

TABLE 50.4 QUANTITATIVE TECHNIQUES FOR THE EVALUATION OF STRESS ECHOCARDIOGRAPHY

Myocardial displacement may be measured in the short- or long-axis dimension. Although long-axis shortening is easily measured using M-mode echocardiography and the timing of long-axis contraction may be altered by ischemia (88), this is not specific for the location of ischemia. The centerline approach is well established as a means of measuring regional function (Fig. 50.5) and has been applied to the interpretation of stress echocardiograms (89). Using this technique, radial excursion is measured by tracing of the endocardial surface (thickening is sometimes possible to measure by tracing of endocardial and epicardial surfaces) at peak diastole and peak systole, and compared with a normal range. There are three major limitations with this technique. First, many stress echocardiograms are not of satisfactory quality to provide excellent border definition, although this has improved in the era of harmonic imaging. Second, the approach requires compensation for translational or rotational cardiac movement, and methodologies for compensating for these technical issues are not well defined. Third, the process of tracing the wall is time consuming and not applicable in a busy clinical laboratory.

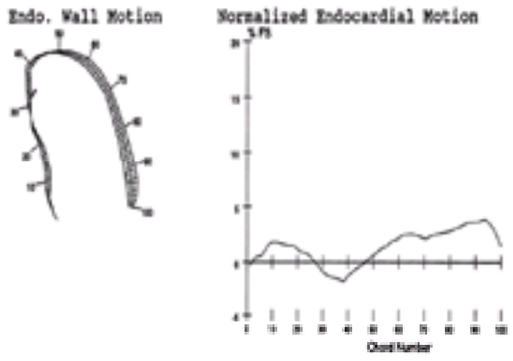
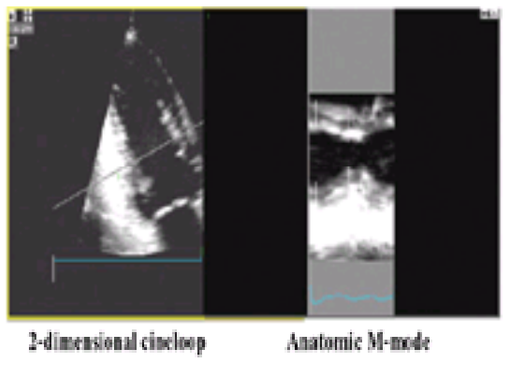


FIGURE 50.5 Quantitative stress echocardiography. A centerline is drawn between diastolic and systolic images and the excursion compared with a normal population. Endo., endocardial; FS, fractional shortening. (From Marwick T, ed. *Stress echocardiography*. New York: Kluwer, 1994, with permission.)

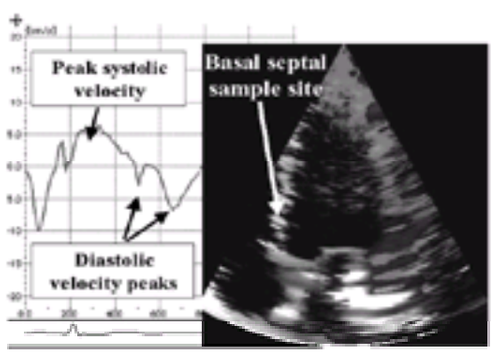
The latter limitation has been partly addressed by automated border recognition, although this remains dependent on good image quality. These methods involve using the difference between the backscatter of the myocardium and blood and pattern-recognition methods (including splines, snakes, and active appearance models) that are applicable to the two-dimensional images. Acoustic quantification techniques identify the blood-tissue interface based on the changes of backscatter within pixels as the wall moves across the pixel. It may be expressed by coloring successive frames to express the excursion in each frame over time throughout systole or diastole (90). The excursion within each segment may be compared with a normal range in histogram format. Unfortunately, this does not distinguish myocardial thickening from translational motion, and the technique is gain and angle dependent. The technique has been applied in the clinical setting, with favorable levels of accuracy reported in both exercise and dobutamine studies (90,91).

Myocardial thickening should be a more sensitive marker of ischemia than abnormal wall motion, and radial thickening may be measured using the same centerline approach. However, the measurement of thickening necessitates tracing of both epicardial and endocardial contours, and in many patients, the epicardium remains difficult to discriminate. M-mode echocardiography has traditionally been applied to the measurement of thickening but is constrained by the need to image structures in the orthogonal plane. An alternative approach (anatomic M-mode) is to reconstruct the M-mode image from high frame rate two-dimensional data (eFig. 50.5.1). However, although changes in thickening correspond to the pathology of the underlying segment, the degree of variation precludes the definition of a “cutoff” for identification of disease (92). This most likely relates to difficulties posed by discrimination of the epicardium. Finally, another approach to this could be the analysis of myocardial backscatter, which reflects myocardial fiber cross-over due to thickening, although it is unaltered by inotropic state (93). Changes in cyclic variation of this parameter correlate with ischemia (94), but at present, the analysis remains dependent on image quality and is too time-consuming for application.



***e*FIGURE 50.5.1** Anatomic M-mode (*right*) of the anterior and inferior walls showing myocardial thickness in diastole and systole, derived from a high frame-rate two-dimensional image (*left*) in the apical two-chamber view. (From Chan J. *Int J Cardiol Imaging* 2001;16:247–255, with permission.)

The velocity of myocardial contraction is reduced by ischemia (95), and this may now be reliably measured using myocardial tissue Doppler. Myocardial velocity may be assessed using either color or pulsed wave techniques, although the time taken to move the pulsed wave sample volume to each myocardial segment is unacceptable for combination with stress echocardiography. Postprocessing of the color data may be performed to generate a velocity profile (eFig. 50.5.2), but adequate resolution of the peak velocity and timing necessitate high color frame rates. Tissue velocity during exercise and dobutamine echocardiography has been shown to correlate with expert assessment of wall motion (96,97) and SPECT (98). More recently, the derivation of normal velocity ranges has permitted the test to be applied to the diagnosis of CAD; this modality has comparable accuracy with expert assessment (99). A number of problems with this technique remain: It is still somewhat dependent on image quality, does not visualize the apex, has unacceptable sensitivity for single-vessel disease, is no better than standard analysis for assessment of multivessel disease, and distinction of ischemia from scar tissue remains problematic. Nonetheless, tissue Doppler parameters appear to be feasible methods for quantifying stress echo and will be improved by further developments, including examination of myocardial velocity gradient and strain.



***e*FIGURE 50.5.2** Myocardial velocity profile obtained from tissue Doppler. The systolic velocity can be recognized as the first sustained wave after isovolumic contraction; peak velocity and time to peak are readily measured.

DIAGNOSIS OF CORONARY ARTERY DISEASE

Influences on Accuracy of Stress Echocardiography

Angiographic Considerations

The accuracy of tests for the detection of CAD is usually expressed as the sensitivity and specificity of the technique for the detection of angiographically demonstrated coronary stenoses. However, while the angiogram has been considered the gold standard for historical reasons, this test has important limitations as the arbiter of the presence or absence of CAD (100).

Stenoses limit the hyperemic response of the coronary vasculature when they exceed approximately 50% of the luminal diameter (18). However, a number of variables influence the physiologic effect of coronary stenoses, which include the site of the stenosis in the vessel, the length of the stenosis, and the size of the vessel. Indeed, there is a poor correlation between the anatomic severity of coronary stenosis and its physiologic consequences, particularly for stenoses of between 50% and 75%. Moreover, the coronary angiogram is a lumenogram, while coronary disease itself induces enlargement of the arterial wall in addition to reduction of the lumen. Consequently, reference segments of the coronary angiogram can be either larger or smaller than the size of the vessel without pathologic involvement. The result of this is respective overestimation and underestimation of coronary lesion severity. Taking these considerations into account, the comparison of any diagnostic test against an anatomic measure of coronary disease such as stenosis severity intrinsically precludes tests from attaining a perfect accuracy, merely because the reference standard is itself not a good marker of the severity of the disease.

Nature of the Study Population

A number of other variables influence the accuracy of diagnostic testing. Populations with a high prevalence of multivessel coronary disease and previous myocardial infarction are more likely to develop ischemia in response to stress. Indeed, the presence of a resting wall motion abnormality usually indicates the presence of coronary disease, although these may be seen with cardiomyopathies or conduction disturbances (which may consequently lead to false-positive identification of coronary disease). The strong association of resting wall motion abnormalities with coronary disease implies that the diagnosis may be made from resting echocardiography, without the need for stress. Studies examining the sensitivity and specificity of stress echocardiography for the diagnosis of coronary disease should therefore either exclude patients with prior myocardial infarction or at least analyze these separately.

Although sensitivity and specificity are less dependent on the population under study than are the predictive values of negative and positive test results, these results nonetheless may be influenced by population selection. It is important that the accuracy of the studies is assessed in a population that parallels that seen in clinical practice; examining the performance of the test in the sickest of the sick and the most well of the well will inevitably inflate both the sensitivity and specificity. When the test is used to decide which patients should undergo coronary angiography, distortion of the results obtained for sensitivity and specificity may occur. As patients with positive test results predominate in those proceeding to the reference standard test, this tends to inflate the sensitivity (as most tests have true-positive results) and reduce the specificity (as the majority of patients undergoing negative angiography have positive test results). Similarly, when the test is used for clinical purposes, a disproportionate number of “difficult” patients may be involved, with coronary stenoses of borderline severity, in whom, as discussed previously, the angiogram is not a good arbiter of the functional significance of disease.

Adequacy of Stress

The use of stress testing is inherent to all functional tests for the diagnosis of coronary disease. Failure to stress the heart maximally will not engender either maximal coronary hyperemia (used for myocardial perfusion imaging) or ischemia (used for stress echocardiography and ECG analysis). Thus, failure to stress the patient maximally will be associated with reduced sensitivity, especially for milder coronary disease. Indeed, in our experience of exercise echocardiography, apart from the number and severity of coronary stenoses, the only predictor of false-negative results was failure to obtain 85% of age-predicted maximum heart rate (101). As discussed previously, patients who are unable to exercise, or likely to exercise submaximally, should undergo pharmacologic stress testing.

The use of pharmacologic stress testing may be particularly useful in patients with previous myocardial infarction and resting wall motion abnormalities. In these situations, the identification of ischemia may be facilitated by the availability of low-dose augmentation in viable tissue (102), which may not be appreciated during exercise testing. This topic is discussed further in a later section (see Identification of Myocardial Viability).

Echocardiographic Considerations

Image quality is probably more important during stress echocardiography than during alternative stress imaging techniques. Poor image quality reduces concordance between expert observers (85), and likely reduces the accuracy of the test, if not for the identification of coronary disease (101) then at least the ability to recognize multivessel disease. Not all segments of the myocardium are equally well visualized; the lateral wall is usually parallel with the ultrasound beam in the apical four-chamber view, and the endocardium may be poorly defined, with consequent effects on the sensitivity for left circumflex disease. Fortunately, this problem has been improved by the development of lateral gain correction techniques as well as harmonic imaging. The basal inferoposterior walls are particularly difficult to interpret due to tethering to the plane of the mitral valve and poor endocardial definition. Wall motion abnormalities involving the latter segments should be identified only if adjacent segments are abnormal (103).

VIDEO

Video 50.10 Left circumflex territory ischemia. Despite the use of harmonic imaging, the lateral wall in the apical four-chamber view **(A)** is not well resolved, although it appears to contract less after exercise. The parasternal images **(B)** confirm abnormal wall motion in the posterior wall in the long axis and short axis (3 to 5 o’clock) views. This study illustrates the importance of integrating data from multiple views. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.11 Left circumflex territory ischemia. Despite the use of harmonic imaging, the lateral wall in the apical four-chamber view **(A)** is not well resolved, although it appears to contract less after exercise. The parasternal images **(B)** confirm abnormal wall motion in the posterior wall in the long axis and short axis (3 to 5 o’clock) views. This study illustrates the importance of integrating data from multiple views. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

As discussed in a previous section, stress echocardiography is interpreted qualitatively and subjectively, and several interpretive factors may influence the accuracy of the data. First, a low threshold for identifying wall motion abnormalities (e.g., identification of minor stress-induced wall motion abnormalities as ischemic, or identification of failure to enhance function as being indicative of ischemia) is attended by a high sensitivity, but a correspondingly low specificity. Interpreter bias may also be an important source of inaccuracy. It is important that the echocardiographic data are interpreted independent of the clinical and stress testing data; failure to do so may compromise accuracy (particularly the specificity). The experience of the reader is obviously an important determinant of accuracy during stress echocardiography. Factors responsible for false-negative and false-positive results are summarized in Table 50.5.

False-negative results	False-positive results
Inadequate stress	Overinterpretation, interpreter bias
Antianginal therapy	Localized basal inferior wall abnormalities
Mild coronary artery disease	Abnormal septal motion (left bundle branch block, post-coronary artery bypass grafting)
Left circumflex disease	Cardiomyopathies
Poor image quality	Hypertensive responses to stress
Delayed images post-stress	

TABLE 50.5 CAUSES OF FALSE-NEGATIVE AND FALSE-POSITIVE STRESS ECHOCARDIOGRAM RESULTS

Exercise Echocardiography

The feasibility of exercise echocardiography in the more recent studies has been approximately 100%. In significant studies of exercise echocardiography (greater than 100 patients), the sensitivity and specificity range from 74% to 97% and 64% to 86%, respectively (eTable 50.5.1) (27,101,104,105,106,107,108 and 109). Some variability is apparent, for the reasons discussed previously. The effect of differing criteria of stenosis significance is well illustrated in the study by Robertson (9), which showed a sensitivity of 100% but a specificity of 75%, using a cutoff including more severe lesions (e.g., greater than 75% diameter) in the sensitivity group. This cutoff makes it highly likely that any patient with anatomically defined disease would have ischemia, whereas patients with less than 75% stenoses may indeed have ischemia, particularly if the stenosis is in the 50% to 75% range.

***e*TABLE 50.5.1** SENSITIVITY AND SPECIFICITY OF DIGITAL EXERCISE ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF CORONARY ARTERY DISEASE (CAD) IN STUDIES OF GREATER THAN 100 PATIENTS

Author	Stress	No.	Multivessel (% all CAD)	Myocardial infarction (% all CAD)	Sensitivity, overall	Sensitivity, single-vessel disease patients	Sensitivity, myocardial infarction excluded	Specificity	Exclusions
Ryan et al. (27)	U/Bike	309	126 (60%)	132 (63%)	91% (n = 211)	86% (n = 85)	95% (n = 126)	78% (n = 98)	None
Crouse et al. (104)	Tml	228	106 (61%)	—	97% (n = 175)	92% (n = 66)	—	64% (n = 53)	None
Hecht et al. (105)	S/Bike	180	82 (60%)	38 (28%)	93% (n = 137)	84% (n = 55)	100% (n = 82)	86% (n = 43)	None
Marwick et al. (101)	Tml	150	54 (47%)	55 (48%)	84% (n = 114)	77% (n = 60)	80% (n = 59)	86% (n = 36)	None
Beleslin et al. (106)	Tml	136	11 (9%)	41 (34%)	88% (n = 119)	88% (n = 108)	83% (n = 78)	82% (n = 17)	Cardiomyopathy, congestive heart failure
Roger et al. (107)	Tml	127	—	—	88% (n = 107)	—	—	72% (n = 20)	None
Armstrong et al. (108)	Tml	123	59 (58%)	50 (50%)	88% (n = 101)	81% (n = 42)	78% (n = 51)	86% (n = 22)	None
Quinones et al. (109)	Tml	112	45 (52%)	—	74% (n = 86)	58% (n = 41)	—	81% (n = 26)	None

S/Bike, supine bike; Tml, treadmill; U/Bike, upright bike.

Using a 50% stenosis diameter cutoff at quantitative angiography, Shiekh reported a sensitivity of 81% and a specificity of 92% (110), and patients with single-vessel coronary disease and inducible wall motion abnormalities had a stenosis diameter of 1.0 mm, compared with patients without inducible ischemia in spite of detectable stenoses, among whom the diameter was 1.7 mm. A similar study by Agati et al. (111) used quantitative wall motion analysis to define abnormal function and identified an absolute lumen diameter of 0.7 mm, corresponding to an 85% diameter stenosis, as best predictive of inducible wall motion abnormalities, although the sensitivity of exercise echocardiography in that study may have been compromised by the quantitative criteria used for defining a positive test result.

The type of exercise probably also has an important effect on the accuracy of exercise echocardiography. Posttreadmill exercise echocardiography may be compromised by resolution of ischemia during the delay between peak exercise and echocardiographic imaging. Generally, this occurs in patients with mild, usually single-vessel, coronary disease. However, imaging at peak stress during either supine or upright bicycle exercise is attended by a greater sensitivity than postexercise imaging (26), although this occurs at the cost of specificity, presumably because of motion-induced artifactual wall motion abnormalities. Finally, although peak exercise imaging has been shown to be more sensitive than postexercise imaging using the bicycle, these data may be influenced by the lower level of exercise attainable with this form of stress. A single study of 74 patients (112) who underwent treadmill testing and supine bicycle stress showed maximum heart rate to be higher during treadmill echo, but systolic blood pressure was higher during supine bicycle exercise, so that the double product was comparable. The wall motion score index at maximal exercise and extent of myocardial ischemia were greater during supine bicycle stress, which had a greater sensitivity (82% vs. 75%) but lower specificity (80% vs. 90%). Because of the greater familiarity of treadmill exercise, this remains the most widely used technique.

Pharmacologic Stress Echocardiography

Dobutamine Stress Echocardiography

Significant studies (greater than 100 patients) of dobutamine stress echocardiography show a range of sensitivity of between 61% and 95%, whereas that for specificity ranged from 51% to 95% (eTable 50.5.2) (3,46,61,106,113,114,115,116,117,118,119,120,121,122 and 123). Again, some variability in the reported accuracy of the test is apparent. The addition of atropine increases sensitivity (49), as does the use of transesophageal echocardiography (77), although the feasibility of the latter is limited, as discussed previously.

***e*TABLE 50.5.2** SENSITIVITY AND SPECIFICITY OF DOBUTAMINE STRESS ECHOCARDIOGRAPHY FOR THE DIAGNOSIS OF CORONARY ARTERY DISEASE (CAD) IN STUDIES OF GREATER THAN 100 PATIENTS

Author	No.	Dobutamine protocol	Significant stenosis diameter of coronary artery (%)	Multivessel (% all CAD)	Myocardial infarction (% all CAD)	Sensitivity overall	Sensitivity, single-vessel disease	Specificity
Elhendy et al. (113)	96 women	40 μg/kg/min + atro	>50	142 (61)	214 (70)	76% (n = 62)	64%	94% (n = 34)
	210 men					73% (n = 171)	56%	77% (n = 39)
Dionisopoulos et al. (114)	288	40 μg/kg/min + atro	>50	122 (58)	—	87% (n = 209)	80% (n = 70)	89% (n = 79)
Marwick et al. (115)	217	40 μg/kg/min	>50	74 (52)	0 (0)	72% (n = 142)	66% (n = 68)	83% (n = 75)
Ling et al. (116)	183	40 μg/kg/min + atro	>70	109 (74)	105 (71)	95% (n = 148)	—	51% (n = 35)
Ostojic et al. (61)	150	40 μg/kg/min	>50	16 (12)	38 (29)	75% (n = 131)	—	79% (n = 19)
Marcovitz et al. (117)	141	30 μg/kg/min	>50	47 (43)	—	96% (n = 109)	95% (n = 62)	66% (n = 32)
Beleslin et al. (106)	136	40 μg/kg/min	>50	11 (9)	41 (34)	82% (n = 119)	82% (n = 108)	77% (n = 27)
Takeuchi et al. (118)	120	30 μg/kg/min	>50	37 (50)	62 (84)	85% (n = 74)	73% (n = 37)	93% (n = 46)
Anthopoulos et al. (119)	120	40 μg/kg/min + atro	>50	48 (40)	38 (30)	87% (n = 89)	74% (n = 19)	84% (n = 31)
Pingitore et al. (120)	110	40 μg/kg/min + atro	>50	42 (46)	25 (27)	84% (n = 92)	—	89% (n = 18)
Sawada et al. (46)	103	30 μg/kg/min	>50	14 (40)	35 (43)	95% (n = 81)	89% (n = 38)	77% (n = 22)
San Roman et al. (121)	102	40 μg/kg/min + atro	>50	34 (54)	0 (0)	77% (n = 63)	68% (n = 29)	95% (n = 39)
Hennessy et al. (122)	219	40 μg/kg/min + atro	>50	113 (66)	55 (24)	82% (n = 170)	74% (n = 57)	65% (n = 49)
Nagel et al. (3)	208	40 μg/kg/min + atro	>50	70 (64)	0 (0)	74% (n = 107)	67% (n = 39)	70% (n = 101)
Beleslin et al. (123)	168	40 μg/kg/min	>50	0 (0)	40 (24)	61% (n = 153)	61% (n = 153)	88% (n = 25)

atro, atropine.

At quantitative coronary angiography (124,125 and 126), the optimal correlates of a positive dobutamine test result are a lumen diameter of 1.07 mm, percent diameter

stenosis of 52%, and percent area stenosis of 75%, and minimal lumen diameter has the best predictive value for a positive dobutamine stress test result (sensitivity 94%, specificity 75%, odds ratio 51) (124). Stenoses less than 1 mm in diameter can be identified with a sensitivity of 86% (125,126). However, although quantitative angiography deals with the problem of reproducibility of angiographic interpretation, it still has the limitation of being an anatomic measure of disease severity, which may not necessarily correlate with functional indices. One such parameter that takes into account collateral flow is myocardial fractional flow reserve, which is calculated as the ratio of mean hyperemic distal coronary to aortic pressure. The magnitude of wall motion abnormalities correlated more closely with functional than anatomic markers of lesion severity, and dobutamine echocardiography was found to be a more sensitive marker of ischemia in lesions involving larger (greater than 2.6 mm in diameter) vessels than smaller vessels (125).

Some of the earlier studies of dobutamine echocardiography (46,117) show a sensitivity above the usual level (*e*Table 50.5.2), suggesting a decrement in the accuracy of dobutamine stress since its inception, reflecting clinical application of the test. As the technique is applied for clinical decision making, referral bias to angiography may inflate sensitivity but produce more adverse findings for specificity (127). Moreover, dobutamine is not a very robust stress, and sensitivity is likely to be compromised if the cardiac workload is reduced by medical therapy or dose-limiting side effects. Comparison of the quoted ranges (*e*Table 50.5.1 and *e*Table 50.5.2) suggests that the sensitivity of dobutamine echocardiography is somewhat less than exercise echocardiography, but its specificity is slightly greater. In studies in which exercise and pharmacologic stress echocardiography were performed in the same patients, the accuracy of stress echocardiography has been comparable with either stressor (106,128,129,130,131 and 132). In situations in which stress is submaximal because of side effects with pharmacologic agents, exercise is superior. Clearly, the converse is true when patients are unable to exercise maximally and a pharmacologic agent is more desirable. Nonetheless, the hemodynamic effects of the agents are different, so that the markers of severe (including left main) disease including LV cavity dilation and marked ST-segment depression occur more often with exercise than with dobutamine echocardiography (133). Because exercise is a more potent stress on the heart, a greater extent of abnormal wall motion may be induced, and this may compensate for the more difficult imaging with exercise (130,132). As discussed previously, a number of features favor the use of exercise testing over pharmacologic techniques, provided that the patient can exercise maximally.

VIDEO

Video 50.12 Stress echo of a patient with right coronary artery ischemia. *Upper panels:* Apical four-chamber view showing worsening of basal septum (rest images to left, stress images to right). *Lower panels:* Apical two-chamber view demonstrating deterioration of the basal and mid inferior wall. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.13 Stress echo (parasternal long- and short-axis views) of a patient with right coronary artery ischemia. Note the normal response to stress in the anteroseptal and posterior walls. The inferior ischemia is difficult to see in this short axis because of the papillary muscle. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.14 Parasternal long-axis view of a dobutamine stress echo of a patient with three-vessel coronary artery disease. Note the deterioration of the anteroseptal and posterior walls in this view and the chamber dilatation. The images are arranged from upper left image = rest, to upper right and lower left = low-dose infusion, to lower right = peak infusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.15 Parasternal short-axis view of a dobutamine stress echo showing three-vessel coronary artery disease. Note the chamber enlargement and the deterioration of all walls. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.16 Apical four-chamber view of a dobutamine stress echo with rest images in the upper left and peak infusion (*lower right*) of a patient with three-vessel coronary artery disease. Note the deterioration of the mid- and distal septum and the basal and midlateral wall. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.17 Apical two-chamber view of a dobutamine stress echo of a patient with three-vessel coronary artery disease. Note the deterioration of the inferior wall (*left*) and the anterior wall (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Vasodilator Stress Echocardiography

The ranges for the sensitivity and specificity of dipyridamole and adenosine stress echocardiography for the detection of CAD are 61% to 81% and 90% to 94%, respectively (*e*Table 50.5.3) (60,61,106,119,120 and 121,123,134,135). The low-dose dipyridamole protocol (0.56 mg per kg) is associated with low sensitivity. For the high-dose and adenosine protocols, more variability is present than for any of the other stressors, reflecting variations in the populations studied. The inclusion in some studies of patients with prior myocardial infarction has inflated the sensitivity of adenosine echocardiography, but the sensitivity of patients without prior infarction is only approximately 60% (136,137). Likewise, populations with a high prevalence of extensive coronary disease are associated with a high sensitivity, but single-vessel disease is more difficult to detect using this technique (137).

***e*TABLE 50.5.3** ACCURACY OF VASODILATOR (DIPYRIDAMOLE AND ADENOSINE) STRESS ECHOCARDIOGRAPHY (GREATER THAN 50 PATIENTS)

Author	No.	Stress	Definition of CAD (%)	Multivessel (% all CAD)	Myocardial infarction (% all CAD)	Sensitivity	Specificity
Picano et al. (134)	445	Dipy 0.84 mg/kg[a]	>50	119 (46)	0 (0)	96% (n = 256)	96% (n = 189)
Severi et al. (135)	429	Dipy 0.84 mg/kg[a]	>75	114 (46)	0	75% (n = 246)	90% (n = 183)
Beleslin et al. (123)	168	Dipy 0.84 mg/kg[a]	>50	0 (0)	40 (24)	61% (n = 153)	88% (n = 15)
Ostojic et al. (61)	150	Dipy 0.84 mg/kg[a]	>50	16 (12)	38 (29)	71% (n = 131)	89% (n = 19)
Beleslin et al. (106)	136	Dipy 0.84 mg/kg[a]	>50	11 (9)	41 (34)	74% (n = 119)	94% (n = 17)
Picano et al. (60)	130	Dipy 0.84 mg/kg + atr	>50	—	—	87% (n = 94)	94% (n = 36)
Anthopoulos et al. (119)	120	Adenosine 0.14 μg/kg/min[a]	>50	48 (40)	38 (30)	66% (n = 89)	90% (n = 31)
Pingitore et al. (120)	110	Dipy 0.84 mg/kg + atr	>50	—	—	82% (n = 92)	94% (n = 18)
San Roman et al. (121)	102	Dipy 0.84 mg/kg[a]	>50	34 (54)	0 (0)	77% (n = 63)	97% (n = 39)

atr, atropine; CAD, coronary artery disease; Dipy, dipyridamole.

[a]Low-dose positivity permits conclusion of study before stated "peak" dose.

The type of pharmacologic agent to select in a patient who is unable to exercise maximally remains a source of debate. Studies comparing dobutamine and vasodilator agents in the same patients have shown that the sensitivity of dobutamine is somewhat higher than that of dipyridamole echocardiography, this difference being mainly attributable to patients with single-vessel disease (*e*Table 50.5.4) (61,106,119,121,138). In an environment in which most of the studies are being performed for diagnostic purposes, dobutamine is probably more attractive as some patients may have single-vessel disease. In situations in which the main interest is prognostic evaluation, the agents are both attractive, and certainly a wealth of information is available regarding dipyridamole echocardiography as a prognostic test (see Prognostic Considerations in Coronary Artery Disease). Other factors influencing this decision, such as side effects and cost, have been discussed earlier (see Selection of the Optimal Stress Agent).

***e*TABLE 50.5.4** STUDIES COMPARING SENSITIVITY AND SPECIFICITY OF DOBUTAMINE AND VASODILATOR STRESS ECHOCARDIOGRAPHY IN GREATER THAN 100 PATIENTS

Author	No.	No. (% CAD)	Multivessel (% all CAD)	Myocardial infarction (% all CAD)	Sensitivity, dobutamine (%)	Sensitivity, dipyridamole (%)	Sensitivity, single-vessel disease, dobutamine (%)	Sensitivity, single-vessel disease, dipyridamole (%)	Specificity, dobutamine (%)	Specificity, dipyridamole (%)
Ostojic et al. (61)	150	131 (87)	16 (12)	38 (29)	75	71	—	—	79	89
Beleslin et al. (106)	136	119 (88)	11 (9)	41 (34)	82	74	82	72	77	94
Anthopoulos[a] et al. (119)	120	89 (74)	48 (40)	38 (30)	87	66	—	—	84	90
San Roman et al. (121)	102	63 (62)	34 (54)	0 (0)	77	77	69	62	95	97
Fragasso et al. (138)	101	56 (56)	—	—	88	61	88	61	80	91

CAD, coronary artery disease.

[a]Adenosine used instead of dipyridamole.

Stress Echocardiography Using Other Stress Techniques

The most commonly used nonexercise stress is performed with atrial pacing. The accuracy of this technique for the detection of coronary disease has ranged from 83% to 93%, with a specificity of 76% to 100% (62,63,65,66,69,139,140,141 and 142). Although the application of this approach has been limited by concerns regarding patient acceptance and feasibility, more recent work suggests that this test has a feasibility of 96% (143), a high level of acceptance, and good correlation with the results of dobutamine stress.

Important Limitations in the Diagnostic Use of Stress Echocardiography

Extent and Severity of Disease

Stress echocardiography is effective for the detection of severe coronary stenoses, as these are usually associated with more extensive wall motion abnormalities (125). Extensive coronary disease is also marked by an early onset of ischemia, at a low heart rate and rate-pressure product, or at a low dose of pharmacologic stressor. However, the sensitivity of stress echocardiography for single-vessel CAD has been quite limited in several studies and is probably less than that of myocardial perfusion scintigraphy. This reflects the need for ischemia to involve a significant extent of myocardium for the stress echocardiogram to be positive, which may not be fulfilled if the involved vessel is small or distal or if the stenosis is only mildly flow limiting.

The presence of extensive areas of ischemia, the development of global ventricular dysfunction (reduction of ejection fraction or LV enlargement), or both indicate the presence of multivessel disease (144). However, while the predictive value of these findings is high, the predictive value of their absence is dependent on the resting LV function. In patients with a history of previous myocardial infarction, the sensitivity of stress echocardiography for recognition of multivessel disease (effectively, "ischemia at a distance") is approximately 80% to 85%. In contrast, the sensitivity for multivessel disease in patients without previous infarction is approximately 50% (145). These data contrast with a sensitivity greater than 70% in this situation using myocardial perfusion scintigraphy (146). However, when the extent of ischemia defined by dobutamine echocardiography and perfusion scintigraphy was compared with the angiographic extent of disease (a modified Gensini score), the extent was comparable, and both underestimated the disease extent (137).

VIDEO

Video 50.18 Recognition of multivessel coronary artery disease. Apical four- and two-chamber views before (*left*) and after exercise show inducible wall motion abnormalities in the septum, apex, and anterior walls (left anterior descending), lateral wall (circumflex), and inferior walls (right coronary) associated with left ventricular cavity enlargement. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The identification of ischemia within areas of resting wall motion abnormalities is difficult, because of the problems posed by identification of minor gradations of wall motion in the setting of abnormal function. Comparison of the regional findings of exercise echocardiography and SPECT have shown this to be an important cause of discordant diagnoses (109). The problem is probably less during dobutamine stress because ischemic segments with abnormal resting function often show a biphasic response (102).

VIDEO

Video 50.19 Diagnosis of ischemia within an area of resting wall motion abnormality. Apical four-and two-chamber views at rest (*left*) show akinesis in the basal septum, with inferior wall hypokinesis. Post exercise (*right*), there is worsening of wall motion in the inferior segment, indicating scar with residual ischemia. Assessment of gradations of hypokinesis may be difficult and cause discordances between observers as well as between echocardiography and other imaging modalities. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

These aspects represent a fundamental limitation of an ischemia-based technique. Their solution will require either a more sensitive tool for assessment of wall motion or combination with a perfusion marker such as contrast echocardiography.

Site of Disease

Although the extent of coronary disease has an important influence on the accuracy of functional testing in general, the location of coronary disease may have important implications for the sensitivity of stress echocardiography in particular. The allocation of segments to particular vascular territories is ambiguous, especially in the apex (usually assumed to be within the territory of the left anterior descending coronary artery) and the posterior wall (usually assumed to be supplied by the left circumflex). Using exercise echocardiography, Marwick (145) reported regional sensitivities of 77% for the anterior descending, 67% for the left circumflex, and 70% for the right coronary, and Hecht (147) reported respective sensitivities of 95%, 78%, and 81%. However, Armstrong (148) reported a 22% sensitivity for the recognition of left circumflex disease, and Pozzoli (149) reported a sensitivity of 45% at this site. The sensitivity for circumflex disease may be limited by difficulties in the evaluation of the lateral wall due to unfavorable imaging characteristics.

COMPARISON WITH OTHER TECHNIQUES

Comparison with Stress Electrocardiography

The presence of ST-segment depression in response to exercise remains the simplest and most widely used test for the documentation of myocardial ischemia. However, the proportion of patients in whom adequate exercise is achieved and the ST segment is interpretable is less than 50% in many tertiary referral centers. In patients with left bundle branch block, ECG changes with stress are nondiagnostic (150). In patients with LV hypertrophy or resting ST- and T-wave changes, additional ST-segment changes are not specific markers for coronary disease, although the sensitivity of ECG (and hence the predictive value of a negative test result) is debated (151,152).

In patients who are unable to exercise maximally, the use of exercise testing is attended by inadequate sensitivity (153). Even if pharmacologic stress testing is performed, the combination of these stresses with ECG alone has limitations with respect to sensitivity (154,155 and 156).

In those who can exercise and have an interpretable ECG, exercise echocardiography has benefits in both sensitivity and specificity (17,101,109,157). This greater sensitivity of exercise echocardiography over the exercise ECG is not surprising in view of the earlier occurrence of wall motion abnormalities than ST-segment changes during stress; these data are analogous to those reported for thallium imaging. However, as it would be financially and logistically impossible to replace diagnostic exercise testing with imaging, we have sought subgroups in whom the standard stress test is unreliable, despite an interpretable ECG. These groups might include women and patients with LV hypertrophy.

The accuracy of exercise ECG in women has been extensively debated. Depending on the population studied, either the sensitivity or the specificity may be compromised (158,159,160 and 161). Although some of the differences from stress testing in men may be caused by lower disease prevalence, these results are influenced by non-Bayesian factors, including the presence of milder coronary disease in women than men, the likelihood of submaximal stress, and intrinsic gender-based differences in the ST-segment response. A number of large studies have now shown that the accuracy of stress echocardiography is not compromised in women (114,135,162,163), and these results are superior to those of the exercise ECG, even after correction for referral bias. A cost analysis suggested that the use of exercise echo as an initial test caused more initial expense but was cheaper in the long run because of the avoidance of unnecessary angiograms in patients with false-positive ECG responses (162).

Comparison with Nuclear Imaging

Nuclear ventriculography and perfusion scintigraphy have an established record for the detection of coronary disease. Although nuclear ventriculography and echocardiography appear to hold superficial similarities with respect to analysis of LV function during stress, the two are actually quite dissimilar. Stress nuclear ventriculography is the older technique, which is used for analysis of global functional response to stress, calculated as ejection fraction change, and measured using a count-based approach (164). The development of ischemia does not necessarily provoke a change of ejection fraction, because of compensatory hyperfunction of the nonischemic walls. This protective mechanism is less likely to occur in patients with multivessel coronary disease, in which a number of segments may become ischemic, and indeed stress nuclear ventriculography is most sensitive under these circumstances (164). Conversely, the development of global functional changes with stress is not necessarily an indicator of ischemia and may occur in the setting of hypertensive or valvular heart disease. Thus, the global parameters measured using nuclear ventriculography have proved to be of disappointing accuracy.

Regional LV function may also be analyzed using nuclear ventriculography, but various technical limitations have become apparent. First, the technique is not truly tomographic, usually involving only one or two views, so that only a limited amount of the myocardium can be visualized. Second, using the gated approach, numerous cycles are summated, causing some blurring of the endocardial border with respiratory movement. This has the effect of combining the function of normal and ischemic segments and blunting the extent of wall motion abnormalities due to ischemia. Third, the silhouette produced by the nuclear ventriculogram limits the analysis of regional ischemia and precludes analysis of thickening.

Nuclear ventriculography and stress echocardiography have been compared in three studies, involving a total of only 100 patients (13,14 and 15). These data suggest that stress echocardiography is more sensitive for the detection of regional LV dysfunction than nuclear ventriculography, a result consistent with the better definition of regional wall motion at echocardiography. Of the stress imaging tests used to examine regional function, stress echocardiography is currently favored.

Despite competition from echocardiography, perfusion scintigraphy remains the most widely performed stress imaging test in the United States, and its use continues to increase.

Theoretical Considerations

The presence of CAD is inferred at myocardial perfusion scintigraphy by the detection of perfusion heterogeneity during maximal coronary hyperemia. The latter is induced either directly (e.g., dipyridamole or adenosine stress) or indirectly, whereby endogenous adenosine is released secondary to increases in cardiac workload. Although only severe coronary stenoses compromise myocardial perfusion at rest, narrowings greater than 50% limit flow in the presence of maximal coronary vasodilation (165). Keeping in mind the ischemic cascade (see Ischemic Cascade, earlier in this chapter), it might be expected that these variations in myocardial perfusion would be more sensitive indicators of coronary disease than regional ischemia. However, both tests are imperfect measures of regional perfusion and ischemia, respectively. Thus, the comparison between these modalities does not reflect the underlying pathophysiology alone, but is also influenced by the limitations of the imaging techniques. Thus, despite their physiologic differences, the results of myocardial perfusion imaging and stress echocardiography are remarkably similar.

Comparison of Stress Perfusion Imaging and Stress Echocardiography

Studies of the accuracy of SPECT myocardial perfusion scintigraphy have shown that this technique has a sensitivity greater than 90% for the detection of CAD (166). However, they also show that the specificity is approximately 70%, partly reflecting the phenomenon of posttest referral bias (127) as well as the problems of false-positive results related to image artifacts. In a metaanalysis, the superior sensitivity of SPECT was balanced by a greater specificity with echocardiography, so that the accuracy of the techniques was comparable (167). However, although the analytic technique permitted correction of a number of population-based factors that influence the accuracy of diagnostic testing, including the prevalence of prior infarction and multivessel coronary disease, comparisons between separate studies of myocardial perfusion imaging and stress echocardiography are difficult, not the least because of the different level of maturity of the investigations, which affects the posttest referral bias effect. An alternate design involves head-to-head comparison in the same patients, in the presence of an additional test (e.g., coronary angiography) to act as the arbiter of which result is correct, even though this design has the disadvantage of studying a selected population who are undergoing angiography (168).

A number of large studies have compared the results of stress echocardiography and perfusion scintigraphy in the same patients using various stressors (109,115,118,137,149,169,170 and 171) (*e*Table 50.5.5). Comparisons of vasodilator stress echocardiography and perfusion scintigraphy have confirmed the insensitivity of adenosine stress, particularly for single-vessel disease. When exercise and dobutamine stress are used, however, the sensitivities of the two techniques have also been shown to be comparable, with most studies showing a minor benefit for perfusion scintigraphy. The slightly lower sensitivity of stress echocardiography than perfusion scintigraphy may reflect superiority of perfusion imaging (which does not require the development of ischemia in a metabolic or functional sense) for the identification of patients with single-vessel disease. For similar reasons, patients on therapy with antianginal agents may be better studied using perfusion scintigraphy (as ischemia does not need to be induced for the test result to be positive) than stress echocardiography. As discussed in the section on limitations, perfusion scintigraphy appears to be significantly more sensitive for the recognition of multivessel disease as such (146) and may be superior in the detection of ischemia in the setting of resting wall motion abnormalities, in which circumstance the recognition of worsening wall motion may be difficult (109). These issues cannot be measured by consideration of sensitivity and specificity. Finally, scintigraphy can be expected to be superior in patients with poor echocardiographic windows (e.g., due to pulmonary disease).

***e*TABLE 50.5.5** SENSITIVITY AND SPECIFICITY OF STRESS ECHOCARDIOGRAPHY AND MYOCARDIAL PERFUSION IMAGING FOR DIAGNOSIS OF CORONARY ARTERY DISEASE (CAD) (STUDIES GREATER THAN 75 PATIENTS)

Author	No.	Significant stenosis (%)	Patients with CAD	Multivessel CAD	Stress methodology	Nuclear methodology	Sensitivity, echocardiography (%)	Sensitivity, nuclear (%)	Sensitivity, single-vessel disease, echocardiography (%)	Sensitivity, single-vessel disease, nuclear (%)	Specificity, echocardiography (%)	Specificity, nuclear (%)
Marwick et al. (115)	217	>50	142	74 (52%)	Db 40 µg/kg/min	SPECT-MIBI	72	76	66	74	83	67
Smart et al. (262)	183	>50	119	58 (49%)	Db 40 µg + atro	SPECT-MIBI	87	80	84	71	91	73
Takeuchi et al. (118)	120	>50	74	37 (50%)	Db 30 µg/kg/min	SPECT-Tl	85	89	—	—	93	85
Quinones et al. (109)	112	>50	86	45 (52%)	Treadmill	SPECT-Tl	74	76	58	61	88	81

San Roman et al. (170)	102	>50	49	—	Db 40 µg + atro	SPECT-MIBI	78	87	—	—	88	70
San Roman et al. (170)	102	>50	49	—	Dipy 0.84 mg/kg	SPECT-MIBI	81	87	—	—	94	70
Marwick et al. (137)	97	>50	59	28 (47%)	Ad 0.18 mg/kg/min	SPECT-MIBI	58	86	52	81	87	71
Huang et al. (171)	93	>50	67	—	Db 40 µg	SPECT-Tl	93	90	—	—	77	81
Pozzoli et al. (149)	75	>50	49	16 (33%)	Upright bike	SPECT-MIBI	71	84	60	82	96	88

atro, atropine; Db, dobutamine; Dipy, dipyridamole; SPECT-MIBI, single-photon emission computed tomography, methoxyl isobutyl isonitrile; SPECT-Tl, single-photon emission computed tomography, thallium.

On the other hand, there appears to be a particular benefit of echocardiography over perfusion scintigraphy with respect to specificity. This difference is most marked in patients with LV hypertrophy and left bundle branch block. Breast attenuation artifacts and other issues have led to lower reported levels of accuracy of perfusion imaging in women, and the results of a metaanalysis suggest this may be a group better studied with stress echocardiography (172). Finally, stress echocardiography is versatile, rapidly performed, and less expensive than perfusion imaging. In situations in which other cardiac problems are present as well as ischemia (e.g., valvular, pericardial diseases), the selection of stress echocardiography avoids duplicate testing.

Practical Considerations

The selection between SPECT and stress echocardiography is influenced by numerous factors, some of which are summarized in Table 50.6. Of these, the most important is local expertise. Thus, at a center with an excellent nuclear laboratory and an echocardiographer inexperienced in stress echocardiography, the selection of the latter test would likely engender unfavorable results. The converse is true of facilities without the requisite nuclear experience.

Consideration		Stress echocardiography	Myocardial perfusion imaging
Application	Versatility	++	-
	Cost	++	-
	Credentialing	-	++ (Nuclear Regulatory Commission)
Interpretation	Training/quality control	±	±
	Artifacts	+ (better with contrast?)	+ (better with sestamibi?)
	Quantitation	-	++
Clinical value	Sensitivity	80-85%	90%
	Specificity	85%	70%
	Prognostic value	+	++ (established role)
	Familiarity	±	++
	Ancillary data	++	-

TABLE 50.6 ADVANTAGES AND DISADVANTAGES OF STRESS ECHOCARDIOGRAPHY AND MYOCARDIAL PERFUSION SCINTIGRAPHY

Comparison with Magnetic Resonance Imaging

Modern MRI protocols promise to deliver information of gross cardiac anatomy, details of structure, function, and perfusion, all of which are of value in the diagnosis and evaluation of ischemic heart disease and are discussed in another chapter (see Chapter 54). There is no question that MRI can provide information of similar accuracy to echocardiography during stress, both for identification of ischemia (3) and assessment of viable myocardium (173). The problems with the widespread application of this technology relate to issues of feasibility, access, and cost. It seems most likely that in the future, technically difficult studies will be performed using MRI, and that this modality will be especially useful for evaluation of complex problems such as detection of viable myocardium in severe LV dysfunction.

USE OF STRESS ECHOCARDIOGRAPHY IN MANAGEMENT DECISIONS

Evaluation of Patients undergoing Myocardial Revascularization

Patients undergoing myocardial revascularization procedures should have some documentation of the presence and site of ischemia (174). Although stress echocardiography can accurately localize disease, the assumptions inherent in allocating territories of the heart to individual coronary vessels may compromise its ability to designate a “culprit” lesion. This is particularly problematic if multivessel disease is present, in which case the most ischemic territory is most commonly detected.

Following both surgical (175,176) and percutaneous revascularization (177), stress echocardiography appears to have similar accuracy to its use in patients with native disease. However, its use in asymptomatic patients may be limited by Bayesian considerations.

Identification of Myocardial Viability

Background

In a number of acute animal models of myocardial stunning, the use of sympathomimetic amines such as isoproterenol and dobutamine have been shown to reverse regional LV dysfunction in stunned myocardium (178). The same response appears to be applicable to chronic ischemic LV dysfunction, which is often considered to be truly hibernating tissue. In the presence of dysfunctional but viable myocardium, regional function is enhanced by the inotropic effect of low-dose dobutamine (usually 5 to 10 µg per kg per minute), which enhances calcium cycling before dobutamine-induced tachycardia increases oxygen consumption and leads to ischemia. Dipyridamole also exerts similar effects at low dose, the mechanism of which is ill defined; increasing myocardial turgor has been suggested to produce a mini-Starling effect, and augmentation of coronary flow has also been suggested. Viable myocardium supplied by a patent infarct-related vessel (generally corresponding to stunned myocardium) demonstrates a sustained improvement during the infusion. Viable tissue supplied by a stenosed infarct-related artery (which may involve stunned or hibernating tissue) is characterized by an initial improvement followed by deterioration of regional function as the chronotropic effect becomes more prominent and myocardial work increases (Table 50.1).

VIDEO

Video 50.20 Parasternal long-axis view of a dobutamine stress echo demonstrating viability and ischemia in the left anterior descending coronary artery territory. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.21 Parasternal short-axis view of a dobutamine stress echo demonstrating a biphasic response (viability and ischemia) in the left anterior descending coronary artery territory. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 50.22 Apical four-chamber view of a dobutamine stress echo of a patient with a biphasic response (viability and ischemia) in the left anterior descending coronary artery territory. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 50.23 Apical two-chamber view of a dobutamine stress echo demonstrating a biphasic response in the left anterior descending coronary artery territory (viability and ischemia). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Accuracy for Detection of Improvement after Revascularization

In regions predicted to be viable by low-dose dobutamine echocardiography early (less than 2 weeks) after "incomplete" infarction (non–Q-wave infarcts, and infarction treated with lytic therapy), improvement may be observed spontaneously (179,180). Several studies have addressed the accuracy of dobutamine echocardiography to predict regional functional recovery at follow-up (179,180,181,182,183,184 and 185), although most studies involve small patient numbers (eTable 50.6.1). Later after myocardial infarction, myocardial hibernation might be expected to constitute an important source of reversible dysfunction in preference to myocardial stunning. Comparisons with positron emission tomography (PET) have suggested that a dobutamine response is more likely in the presence of preserved myocardial perfusion (stunning) than in the situation of a perfusion metabolism mismatch (hibernation) (181). Dobutamine echocardiography has been effective for the prediction of myocardial viability in this group of patients (186,187 and 188), possibly because recurrent episodes of myocardial stunning are an important source of viable tissue late following infarction (189). The evidence base for the accuracy of dobutamine echocardiography for the prediction of regional functional recovery after revascularization is larger (eTable 50.6.1). In these studies, the sensitivity of dobutamine stress to identify an improvement of systolic function in response to revascularization ranged from 69% to 86%, with a range of specificity from 57% to 100%.

***e*TABLE 50.6.1** SENSITIVITY AND SPECIFICITY OF PHARMACOLOGIC STRESS ECHOCARDIOGRAPHY FOR IDENTIFICATION OF MYOCARDIAL VIABILITY (SEGMENTAL ANALYSIS UNLESS OTHERWISE STATED) IN STUDIES GREATER THAN 50 PATIENTS

Author (ref.)	Stress	Patients	Sensitivity	Specificity	Comments
Smart et al. (179)	Dobutamine 12 µg/kg/min	51	86% (n = 22)	90% (n = 29)	Early post-MI
Poli et al. (184)	Dobutamine 10 µg/kg/min	51	72% (n = 78)	68% (n = 176)	Early post-MI
	Dipyridamole 0.28 mg/kg	51	51% (n = 78)	82% (n = 176)	Early post-MI
Vanoverschelde et al. (201)	Dobutamine 30 µg/kg/min	73	76% (n = 167)	86% (n = 277)	
Furukawa et al. (263)	Dobutamine 10 µg/kg/min	53	69% (n = 32)	100% (n = 26)	Akinetic
		53	86% (n = 50)	57% (n = 46)	Hypokinetic
Monin et al. (264)		54	83%	82%	
Baer et al. (173)	Dobutamine 10 µg/kg/min	103	82% (n = 28)	83% (n = 24)	Patient analysis

MI, myocardial infarction.

Comparison of Stress Echocardiography with Other Techniques for Identification of Viable Myocardium

The ability of dobutamine echocardiography and other techniques to predict recovery of regional function (Fig. 50.6) has been compared in metaanalyses (190,191) and direct comparison in individual patients. Both analyses suggest that the accuracy of dobutamine echocardiography for identification of viable myocardium is equivalent to that of thallium-201 reinjection imaging (188,192,193,194,195,196,197,198,199,200,201 and 202). In comparison with thallium imaging, dobutamine echocardiography was similarly somewhat less sensitive but substantially more specific. Pierard demonstrated that the prediction of myocardial viability using low-dose dobutamine echocardiography correlated with PET in 79% of segments (181). Similar levels of correlation have been reported from other centers (203); in our experience, although dobutamine echocardiography is less sensitive than PET, it is more specific (204). Finally, as mentioned previously, the accuracy of dobutamine echo and MRI are similar, especially if good echo images are obtained (173).

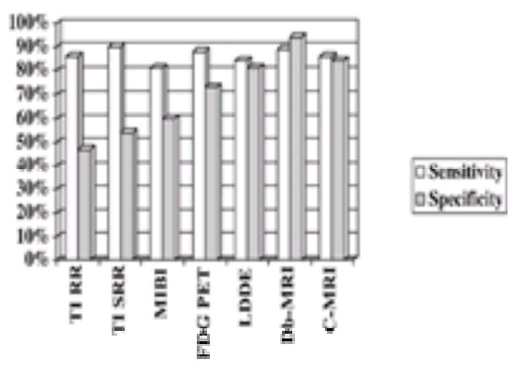


FIGURE 50.6 Prediction of viability (defined as recovery of regional function after revascularization) using thallium rest redistribution (Tl RR), thallium stress rest reinjection (Tl SRR), Tc-99m sestamibi (MIBI), positron emission tomography (FDG PET), low-dose dobutamine echocardiography (LDDE), dobutamine magnetic resonance imaging (Db-MRI), and contrast-enhanced MRI (C-MRI) for the detection of viable myocardium. (Modified from Bax JJ, Wijns W, Cornel JH, et al. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. *J Am Coll Cardiol* 1997;30:1451–1460; Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;343:1445–1453; and Baer FM, Theissen P, Schneider CA, et al. Dobutamine magnetic resonance imaging predicts contractile recovery of chronically dysfunctional myocardium after successful revascularization. *J Am Coll Cardiol* 1998;31:1040–1048.)

Prediction of Recovery of Functional Capacity

The evidence base regarding the accuracy of tests for prediction of myocardial viability is based on comparison with recovery of regional LV function. However, decision making regarding revascularization in patients with LV dysfunction is more influenced by the likelihood of improving ejection fraction, functional capacity, and quality of life.

Although ejection fraction is the most widely used index of global LV function and an important predictor of outcome, it is not a good marker for recovery of viable tissue, as it is load dependent and influenced by changes elsewhere in the heart. Hypercontractility in uninvolved regions of the myocardium may compensate for regional dysfunction; when these dysfunctional segments improve after revascularization, the compensating segments may resume normal function and the ejection fraction may remain unchanged. Nonetheless, improvement of ejection fraction can be expected if sufficient viable tissue is identified before revascularization; if greater than 25% of segments are viable (205) or if there is an improvement of ejection fraction with low-dose dobutamine (206), a significant (5%) improvement in ejection fraction can be predicted with an accuracy greater than 80%. Clearly, the response to revascularization is also dependent on a number of other variables, including the adequacy of revascularization target vessels, the overall status of the ventricle (very large ventricles are unlikely to recover dramatically), and the extent of scar tissue (thinned tissue is unlikely to recover). The extent of data regarding the ability to predict global functional recovery with dobutamine echocardiography is still limited. In patients with severe LV dysfunction, improvement in exercise capacity was predicted by the extent of viable myocardium, but PET appeared superior to dobutamine echocardiography (207). Extensive (greater than 25%) viability has also been associated with increased functional class after revascularization (208).

Prediction of Prognosis after Revascularization

Several observational studies have shown viable myocardium to be prognostically important. Medical treatment of patients with viable myocardium is associated with adverse outcome, whereas myocardial revascularization has been shown to improve survival in patients with viable tissue (209). Relatively recent data suggest that this effect is related to the extent of viable tissue (210).

PROGNOSTIC CONSIDERATIONS IN CORONARY ARTERY DISEASE

The previous sections have documented the large body of published data that support the diagnostic accuracy of stress echocardiography, in combination with various stressors. However, prognostic considerations are at least as important as diagnostic information in decision making. The prognostic implications of stress echocardiography are less extensively defined than other modalities because of its relative youth as a clinical tool. However, in more recent years the evidence base involving both exercise and nonexercise stress has increased, with significant contributions regarding patients with known stable chronic coronary disease, the evaluation of patients following myocardial infarction, and in risk stratification before major noncardiac surgery. Analysis of these data involve a comparison between the results of echocardiography and various end points, including “hard” events (death and myocardial infarction), hard and “soft” (progressive or unstable angina), and total events (all spontaneous cardiac events as well as myocardial revascularization).

Stable Chronic Coronary Artery Disease

In addition to information regarding the presence of ischemia and scar, exercise and pharmacologic stress testing offer adjunctive information that may be of prognostic significance. With exercise, these include exercise capacity, hemodynamic responses to exercise, and the ST-segment response. However, although ECG evidence of ischemia carries incremental prognostic value, most prognostic information derives from echocardiographic evidence of ischemia. Similarly, although prognostic analysis of stress testing data has shown reduced exercise capacity to be a strong predictor of adverse outcome, the presence of ischemia at stress echocardiography adds significant prognostic information. With dobutamine, the rate pressure product at the onset of ischemia is important, and the equivalent measure using dipyridamole stress testing (dipyridamole time) is also of prognostic value. However, as discussed previously, the ECG component of both dipyridamole and dobutamine stress testing is rather insensitive (154,155), and the development of hypotension during these tests is not meaningful prognostically.

Many patients who present for exercise testing are either unable to exercise or exercise submaximally, and these individuals have a high cardiac event rate (221). From the prognostic standpoint, the detection of ischemia during either dobutamine or dipyridamole stress is analogous to its development during exercise stress. Likewise, the detection of ischemia during dobutamine stress (relative risk 5.6) was a stronger predictor of outcome than most clinical variables and superior to the prognostic significance of significant coronary stenoses (215). Although ejection fraction is recognized as an important predictor of cardiac events, the change of ejection fraction in response to dobutamine does not appear to be predictive of outcome (222). Similar findings have been reported using dipyridamole echocardiography; in the largest reported study, death and hard events were predicted by the presence of a positive dipyridamole echo test result, together with ECG positivity and angina (135,220). In particular, the degree of stress required to induce ischemia (evidenced by the dipyridamole time) was most predictive of hard events, whereas total events were predicted by the wall motion score at peak stress, reflecting the extent of both ischemia and infarction. Moreover, a number of studies have reported that the stress data are not only independent of other variables, but also incremental to the information obtained clinically (135,211,212).

Stress echocardiography offers important prognostic material in patients with chronic stable coronary disease (*e*Table 50.6.2). The presence and time of onset of ischemia is clearly associated with increased events, and these data are adjunctive to exercise capacity and ST-segment changes. Unfortunately, only limited comparisons are available between stress echocardiography and perfusion scintigraphy in terms of their ability to predict events; these data suggest that the techniques are comparable (223).

***e*TABLE 50.6.2** PREDICTION OF EVENTS WITH STRESS ECHOCARDIOGRAPHY IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE (STUDIES GREATER THAN 200 PATIENTS)

Author (ref.)	Stress	No. of patients	Mean follow-up (mo)	Predictive value, positive test (%)	Predictive value, negative test (%)	Comments
Krivokapich et al. (211)	Tml	360	12	34	91	
Marwick et al. (212)	Tml	463	44	35	93	All events
				17	98	Hard events
McCully et al. (213)	Tml	1,325	36	—	97	Normal studies
Syed et al. (214)	Tml	949	12	17	98	Includes revascularization
Poldermans et al. (215)	Dob	430	17	26	87	
Kamaran et al. (216)	Dob	210	16	43	92	
Marcovitz et al. (217)	Dob	291	15	10–17	99	
Chuah et al. (218)	Dob	860	52	14	96	
Poldermans et al. (219)	Dob	1,659	36	8–20	96	Hard events
Picano et al. (220)	Dip (high dose)	539	36	26	94	
	Dip (low dose)	539	36	41	94	

Dob, dobutamine; Dip, dipyridamole; Tml, treadmill.

Postinfarct Risk Stratification

The factors predicting outcome following myocardial infarction include ejection fraction and the presence and extent of ischemic and viable myocardium. All of these may be identified using stress echocardiography, and a number of large studies have gathered prognostic data using stress echocardiography in postinfarction patients (224,225,226,227,228,229 and 230) (*e*Table 50.6.3). Most of these data have been obtained with pharmacologic stress, with only two small studies with exercise echocardiography (231,232). This may reflect reluctance to perform exercise stress in the early postinfarct period. In contrast to patients with chronic stable coronary disease, cardiac events more commonly occur than in patients without evidence of ischemia (reflecting the risk associated with LV dysfunction), but hard events occur in greater than 50% of those with positive stress echocardiographic results.

***e*TABLE 50.6.3** PREDICTION OF EVENTS IN PATIENTS AFTER MYOCARDIAL INFARCTION USING STRESS ECHOCARDIOGRAPHY (STUDIES GREATER THAN 200 PATIENTS)

Author	No.	Timing	Stress	Follow-up	Outcomes	Positive predictive value (%)	Negative predictive value (%)	Relative risk	*p* value
Bolognese et al. (224)	217		Dip	24 mo	Cardiac death	30	99	2.78	NS
					Cardiac death/reinfarction	80	98	3.47	NS
					Cardiac death/reinfarction/angina	33	90	3.24	.0001
Picano et al. (225)	925	10 d	Dip	14 mo	Cardiac death	6	98	3.05	<.002
Chiarella et al. (226)	251	70 h	Dip	13 d	Cardiac death	2	99	2.05	NS
					Cardiac death/reinfarction	8	98	4.11	<.04
					Cardiac death/reinfarction/angina	40	97	13.46	<.0001
Picano et al. (227)	1080	10 d	Dip	14 mo	Reinfarction	6	97	1.91	<.02
Carlos et al. (228)	214	2–7 d	Dob	>12 mo	Cardiac death/reinfarction/angina/ventricular tachycardia/congestive heart failure	72	81	3.85	<.0001
Sicari et al. (229)	778	12 d	Dob	9 mo	Cardiac death	2	99	2.01	NS
					Cardiac death/reinfarction	5	95	0.97	NS
					Cardiac death/reinfarction/angina	14	88	1.2	NS
Picano et al. (230)	314	12 d	Dob	9 mo	Cardiac death	5	98	2.24	NS
					Cardiac death/reinfarction	7	96	1.76	NS
					Cardiac death/reinfarction/angina	15	90	1.45	NS

Dob, dobutamine; Dip, dipyridamole; NS, not significant.

The timing of postinfarct risk stratification is a critical consideration as recurrent cardiac events may occur early after infarction. Because dipyridamole leads to a negligible increment of cardiac workload, this stress is attractive for early stress testing. In a report of a group of 250 patients who were studied with dipyridamole echocardiography 3 days following myocardial infarction (226), ischemia at dipyridamole stress testing was predictive of both total and hard events. In a multivariate model, the combination of both echocardiographic evidence of ischemia and angina was the strongest predictor of subsequent events, followed by ischemia alone, and anterior infarction.

As discussed in the previous section, hibernating myocardium may be identified by dobutamine echocardiography, with an accuracy of approximately 80% for the prediction of functional recovery (*e*Table 50.6.1). However, while the presence of this tissue is a positive feature if it is revascularized, it is associated with cardiac events if left unrevascularized; this finding appears to be the case whether this finding is identified by either PET (233,234 and 235) or dobutamine echocardiography (52).

In the evaluation of patients following myocardial infarction, the influence of resting wall motion abnormalities on the identification of ischemia is an important limitation of the interpretation of stress echocardiography. As discussed previously, this reflects the difficulty of judging minor deteriorations in the severity of wall motion abnormalities, which may denote the presence of myocardial ischemia. However, it should be emphasized that this problem concerns homozonal ischemia, and the presence of previous infarction does not compromise the ability to recognize ischemia in another zone. The ability of stress echocardiography to recognize heterozonal ischemia may explain the ability of stress echocardiography to predict events in postinfarction patients. In a small study from the Thoraxcenter (265), the presence of

ischemia at thallium scintigraphy was not predictive of total cardiac events over 2 years of follow-up, whereas ischemia at stress echocardiography was associated with a significantly worse prognosis than the absence of ischemia. Although this study involved few hard events, these findings imply that the interpretive challenge of resting wall motion abnormalities may not constitute a major limitation. Additional comparative data are needed between stress echocardiography and scintigraphy in this group.

Peripheral Vascular Disease

Anatomic evidence of CAD is present in over 80% of patients with aortic, lower limb, and cerebral vascular disease (236). However, the challenge of preoperative risk stratification is that although *anatomic* coronary disease is highly prevalent, serious perioperative cardiac complications are infrequent. For example, cardiac death and myocardial infarction occurs in 5% of unselected patients who have not undergone myocardial revascularization before undergoing vascular surgery (237). The identification of this small subgroup is a major challenge on Bayesian grounds, as the low pretest probability of an event influences the posttest probability, irrespective of the results of testing. This problem may at least in part be addressed by clinical evaluation (e.g., using Eagle's criteria for assigning the risk of a cardiac event). Patients with none of these factors (diabetes, age greater than 70 years, angina, myocardial infarction, or heart failure) have a negligible risk of cardiac complications, irrespective of the results of stress testing (238).

The inability of most of these patients to exercise maximally necessitates the use of pharmacologic stress testing. Just as perfusion scintigraphy has shown to be effective in predicting outcome in patients with vascular disease (239,240,241,242 and 243), a number of studies have shown dipyridamole and dobutamine echocardiography to be predictive of perioperative cardiac events (*e*Table 50.6.4) (244,245,246,247,248,249,250 and 251), and echocardiographic test results appear to be at least as predictive as those performed with nuclear imaging (252). The largest experience of the use of stress echocardiography for risk stratification of patients undergoing vascular surgery has been reported from the Thoraxcenter in Rotterdam. In the initial report of 136 patients, physicians looking after these vascular patients were blinded to the results of dobutamine echocardiography. During perioperative follow-up, five patients died, and ten suffered cardiac events; dobutamine echocardiography was positive in all patients with cardiac events and was the strongest predictor of events. In a multivariate model, only dobutamine echocardiography (odds ratio, 95; 95% confidence interval, 11 to 822) and age were predictive of cardiac complications.

***e*TABLE 50.6.4** USE OF STRESS ECHOCARDIOGRAPHY FOR PREDICTION OF EVENTS IN PATIENTS UNDERGOING VASCULAR SURGERY

	Stress	No. Events	Predictive value positive test (%)	Predictive value negative test (%)	Events
Tischler et al. (244)	Dip	109 8	78	99	MI, UAP, CHF
Sicari et al. (245)	Dip	121 9	25	98	Death, MI, UAP
Rossi et al. (264)	Dip	110 10		100	Death, MI, UAP
Pasquet et al. (247)	Dip	129 9	30	97	Death, MI, UAP
Poldermans et al. (248)	Dob + atropine	131 15	43	100	Death, MI, UAP, CHF
Poldermans et al. (249)	Dob + atropine	181 18	32	100	Death, MI, UAP, CHF
Poldermans et al. (250)	Dob + atropine	300 27	38	100	MI, AP, left ventricular failure
Ballal et al. (251)	Dob + atropine	233 8	ND	96	Death, MI, UAP

AP, angina pectoris; CHF, congestive heart failure; Dob, dobutamine; Dip, dipyridamole; MI, myocardial infarction; ND, not defined (all patients with positive test results revascularized); UAP; unstable angina pectoris.

In many studies of risk stratification, although a negative test result renders a cardiac complication unlikely, a positive result generally confers 20% to 30% risk of a cardiac complication. Risk stratification may be enhanced by considering the ischemic threshold (i.e., the cardiac workload necessary to induce myocardial ischemia). Using dobutamine stress (250), a low ischemic threshold rather than extensive ischemia was seen in patients suffering events, including death and infarction. The extent and time of onset of ischemia during dipyridamole echocardiography are also associated with cardiac events (245). The combination of clinical evaluation and the presence and threshold of ischemia may be integrated into a patient care algorithm as illustrated in Figure 50.7. First, the patient is stratified on clinical grounds. If the patient has clinical risk variables, he or she should undergo a dobutamine stress echocardiogram, and if this result is negative for ischemia, even if scar is present, the patient should proceed to surgery. If ischemia develops, a decision should be made as to its severity, based more on the ischemic threshold than the extent of ischemia. Patients with limited areas of ischemia, only appearing at peak dose, can probably safely proceed to surgery. Those with more extensive ischemia or that occurring at a low dose should either have an alteration of surgical planning or be considered for cardiac catheterization.

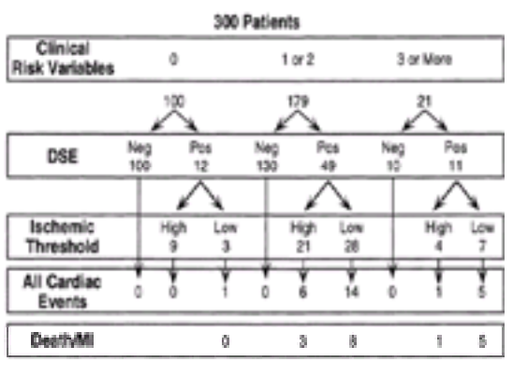


FIGURE 50.7 Integration of clinical data with ischemic threshold to dobutamine to predict events in patients undergoing vascular surgery. DSE, dobutamine stress echocardiography; MI, myocardial infarction; Neg, negative; Pos, positive. (From Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol* 1995;26:648–653, with permission.)

In summary, stress echocardiography offers useful prognostic data. More material needs to be obtained for the comparison between stress echocardiography and perfusion scintigraphy for prognostic purposes, both with respect to accuracy and cost effectiveness.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The use of stress echocardiography as a diagnostic tool is supported by a large evidence base. Although studies of the learning curve have been presented, there are limited data reflecting the accuracy of this technique outside of the hands of experts. However, the future of this technique is likely to be influenced by the balance between the training requirements of this methodology and technical developments. The growth of this methodology has been so dramatic that many studies are likely being performed by individuals with limited training in this discipline. The need for training and quality control in this, as in other diagnostic techniques, warrants attention. However, the development of new quantitative approaches may improve the reproducibility and robustness of this technique. Of the new technologies, myocardial Doppler and contrast echocardiography are most likely to offer lasting contributions.

Apart from the impetus of technological development, the driving forces behind the growth of stress echocardiography have been practical. In comparison with nuclear imaging, stress echocardiography is relatively inexpensive to perform; there are no disposables, equipment is cheaper, and less processing is required. A less costly test was attractive to the patient and insurer in the conventional fee-for-service model of care, but is even more so for the physician and hospital in the current era of managed care and capitation. Finally, although the new dual-isotope techniques are shorter to perform than the older thallium techniques, stress echocardiography is versatile and patient friendly. The results are available immediately after testing, and the equipment is relatively inexpensive and portable, enabling the service to be offered in the physician's office or at a satellite clinic.

As in other fields of medicine, the challenge of the future will be to balance the technological and financial forces supporting the growth of stress echocardiography with the need to maintain quality.

THE FUTURE

Quantitative Techniques for Interpretation of Stress Echocardiography

The development of harmonic imaging and contrast echocardiography has improved border detection to the extent that this is no longer the greatest limitation of the technique. Instead, the issue of training and expertise has become the most pressing problem, and a feasible quantitative approach to interpretation is needed. There is no doubt that, although Doppler myocardial imaging of longitudinal motion and integrated backscatter-based approaches are currently feasible, further developments will be needed before quantitation becomes a routine component of the interpretation of stress echocardiography.

Ancillary Techniques for Detecting Ischemia

The detection of myocardial ischemia is currently dependent on the detection of stress-induced wall motion abnormalities. As discussed in the limitations section, this may cause problems with the recognition of multivessel disease as such, the detection of single-vessel coronary disease, and the distinction of ischemia and scar. Techniques that detect more subtle evidence of ischemia, such as myocardial contrast echocardiography and analysis of cyclic backscatter variation, may supplement these findings and may indeed exceed the sensitivity of two-dimensional echocardiography alone for the detection of coronary disease.

Non–air-filled echocardiographic contrast agents traverse the lungs to reach high concentration in the left-sided heart chambers and thereby may enhance the reflectivity of the myocardium. Although these agents do not currently conform to the characteristics of diffusible tracers, analysis of the degree of myocardial opacification corresponds to the concentration of tracer and therefore gives a semiquantitative measure of regional myocardial perfusion. This field has developed a large evidence base, but for the purposes of this topic, it is important to recognize that myocardial contrast echocardiography has already been successfully applied during stress by several authors (253). Importantly, it has been shown to improve the sensitivity of the technique for recognizing all involved vascular territories in patients with multivessel disease. Although the application of the technique is currently constrained by technical complexity, it seems likely that the use of myocardial contrast will facilitate detection of coronary disease by examination of both wall motion and perfusion at stress echocardiography.

When myocardium becomes ischemic, its reflectivity changes. Using video densitometry, Picano et al. have shown that the backscatter profile of ischemic myocardium during angioplasty is altered before the development of wall motion abnormalities (254). Other authors have demonstrated that cyclic variation of backscatter is preserved in akinetic but viable myocardium (94,255). These findings remain to be applied to the routine clinical arena and at present are limited by considerations pertaining to image quality.

Use in Noncoronary Heart Diseases

The stress echocardiography literature mostly pertains to the detection of myocardial ischemia. However, the functional response to stress is important in the evaluation of myocardial and valvular heart diseases, and the importance of stress echocardiography for this purpose is likely to grow. Patients at risk for anthracycline toxicity may be detected using stress echocardiography (256,257). Similarly, loss of contractile reserve in response to stress also appears to be a marker of impending contractile dysfunction in patients with LV volume loading related to mitral regurgitation (Fig. 50.8) (258).

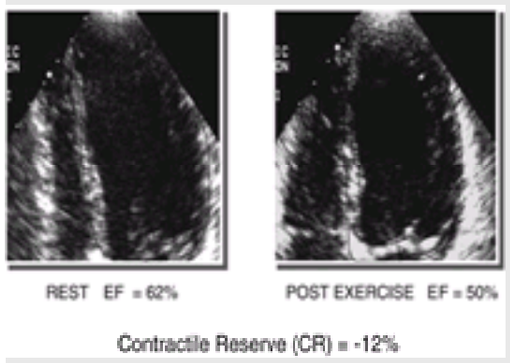


FIGURE 50.8 Determination of left ventricular contractile reserve in a patient with severe mitral regurgitation and preserved resting function (*left*). After exercise (*right*), the left ventricular cavity increases and ejection fraction (EF) falls. Despite normal left ventricular size and function at rest, this response implies that the ventricle is becoming compromised.

In patients with valvular stenosis, the response to stress may differentiate the interrelated influences of ventricular function and valvular disease on the production of gradients. The finding of a low gradient in a patient with aortic stenosis may reflect the influence of reduced ventricular function. Dobutamine echocardiography is able to distinguish a low-output state due to myocardial disease from tight aortic stenosis (Fig. 50.9) (259). Similarly, patients with latent LV outflow tract obstruction may demonstrate exercise-induced outflow tract obstruction in response to exercise or amyl nitrite (260).

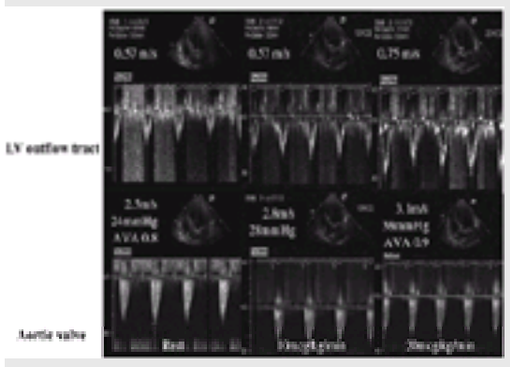


FIGURE 50.9 Application of dobutamine echocardiography to low output aortic stenosis. Resting Doppler measurements show a low gradient in the setting of left ventricular (LV) dysfunction. The increment of the valvular gradient (which exceeds that of the LV outflow tract velocity) signifies a primary valvular problem. AVA, aortic valve area.

Finally, measurement of tricuspid regurgitant velocity may be used to calculate pulmonary artery pressure after exercise. Exercise-induced pulmonary hypertension is a common pathway of cardiac decompensation following stress and may be a particularly useful measurement in patients with apparently moderate mitral stenosis at rest but marked decompensation with stress. The development of this response may correlate with a marked increment of diastolic gradient with exercise.

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DOPPLER ASSESSMENT

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Doppler echocardiography measures blood flow velocities. From flow velocities, pressure gradients can be calculated by the simplified Bernoulli equation in valvular and other stenoses. Doppler echocardiography has the highest sensitivity in the detection of valvular regurgitation of all diagnostic techniques, and regurgitant lesions can be graded at least semiquantitatively by several Doppler techniques. Using additional echocardiographic data, it is possible to obtain reliable estimates of cardiac output, systolic pulmonary artery pressure, and the magnitude of cardiac shunts. Doppler data can identify pathologic changes in diastolic left ventricular function, and the restrictive mitral flow pattern is associated with a reduced prognosis in various cardiac diseases. Doppler has an important role in diagnosing structural complications of myocardial infarction, aortic dissection, pulmonary embolism, cardiac tamponade, and other life-threatening cardiac diseases. Finally, tissue Doppler allows analysis of regional myocardial velocities and contraction and elongation (strain).

GLOSSARY

Aliasing: The maximal velocity unambiguously identifiable by pulsed (and color) Doppler is the aliasing velocity, which depends on the pulse repetition frequency, the frame rate, the sampling depth, and the carrier frequency (see Chapter 46 for more details).

Color Doppler flow mapping: A Doppler display that codes blood flow velocities by colors (red toward the transducer and blue away from the transducer) and superimposes this color map on the two-dimensional image. Thus, a cross-sectional display of blood flow velocities is created. Color Doppler is a way of simultaneously displaying Doppler data from multiple sites in an easily interpretable way. This modality serves for quick orientation about pathologic blood flow (turbulence, regurgitation, shunt flows) and for analysis of valvular regurgitation.

Continuous wave Doppler: A Doppler modality that measures velocities along one scan line. Any velocities are measured unequivocally, but along the scan line there is no spatial resolution. This modality serves to measure the high velocities encountered in valvular stenosis or regurgitation.

Flow profile: The plot of flow velocities measured by pulsed or continuous wave Doppler over time (e.g., diastole for the mitral valve). Essentially synonymous with spectral Doppler display.

Gradient: Pressure drop (or difference) across a restrictive orifice (e.g., a valve).

Jet: A flow stream created by discharge from a narrow orifice (e.g., valvular regurgitation occurs as a jet).

Orifice: See Restrictive orifice.

Pressure half-time: The time that it takes for a pressure gradient to decay to half of its peak value. The pressure half-time is used to evaluate mitral stenosis and aortic regurgitation.

Pulsed wave Doppler: A Doppler modality that measures blood flow velocity in a specific region, the *sample volume*. Thus, unlike continuous wave Doppler, pulsed wave Doppler allows the choice of the site of measurement. The tradeoff is that the maximal unequivocally identifiable velocity is limited (see Aliasing).

Restrictive orifice: Narrowing in the path of flow stream. Stenotic and regurgitant lesions are restrictions to forward and backward flow, respectively. Restrictive orifices have a geometric or anatomic orifice area, which is the smallest cross-sectional area between the solid boundaries of the lesion, and an effective area, which is the smallest cross section of the jet created by such a lesion.

Sample volume: The volume of blood or tissue from which an average velocity is measured by pulsed Doppler. Technically, the length of the sample volume depends on the pulse length (the number of ultrasound wavelengths in one pulse), and the axial position of the sample volume along the cursor depends on the range gate, which defines which time interval is allowed to elapse between transmit and receive. Spatial position and sample volume length can be chosen by the operator, and angle correction is also possible.

Spectral Doppler: Display of continuous or pulsed wave Doppler plotting blood flow velocity against time.

Strain: The deformation (lengthening or shortening) of myocardium during the cardiac cycle. It is dimensionless (e.g., a strain of 0.2 means a 20% elongation). Strain rate (strain divided by corresponding time, in 1/s units) is measurable by tissue Doppler between two chosen points in the myocardium by subtracting the tissue velocities at these points and dividing by the distance between the points. From strain rate, strain is obtained by temporal integration.

Stroke length, stroke distance: Synonymous with velocity-time integral.

Tissue Doppler: Pulsed or color Doppler modality measuring the velocity of solid cardiac structures (e.g., the movement of the myocardium with respect to the transducer over the heart cycle). Typically, these are low-velocity (rarely exceeding 20 cm per second), relatively high-amplitude signals, in contrast to transvalvular blood velocity measured by classic pulsed and color Doppler, which even in healthy subjects reaches 1 m per second and more and has relatively low amplitudes.

Turbulence: Characteristic of flow under certain conditions (especially at high velocities) in which fluid particle velocity and direction change rapidly and chaotically.

Velocity-time integral: The area enclosed by the envelope (the boundary) of the spectral pulsed or continuous wave Doppler display (unit, centimeters). This term is synonymous with stroke length.

HISTORICAL PERSPECTIVE

Christian Doppler, the Austrian physicist (1803 to 1853), first precisely analyzed the effect that motion of the observer relative to the source of a wave has on the perceived wave frequency, a phenomenon that has become known as the *Doppler effect* (1). With ultrasound waves, this effect has first been used in medicine to measure intravascular blood flow (2,3). Although the first instruments used a continuous emission of ultrasound, pulsed Doppler devices were introduced at the end of the 1960s (4,5). The breakthrough for Doppler ultrasound came with its success in quantifying pressure drops across valvular stenoses by means of the simplified Bernoulli equation (6,7) in the late 1970s. Since then, the Doppler technique has become progressively integrated into ultrasound equipment, and *duplex* instruments emerged, combining two-dimensional (2-D) imaging and Doppler blood velocimetry. With the use of multigated pulsed Doppler, a color-encoded display or *map* of velocities could be superimposed on M-mode and later 2-D echocardiographic images (8,9,10 and 11). Transesophageal Doppler recordings of aortic blood flow velocity were obtained as early as 1973 (12), and in the 1980s Doppler capabilities were added to transesophageal imaging probes. The first intravascular, catheter-mounted Doppler devices were introduced in the late 1960s (13,14 and 15). In 1971, the first Doppler-based velocimetry in the human coronaries was reported. Tissue Doppler was introduced in the early 1990s, both in color-coded and spectral form (16).

FROM DOPPLER SIGNALS TO HEMODYNAMICS: BASIC CONCEPTS

The Doppler Signal

The Doppler signal contains the following data: the Doppler frequency shift, the intensity of the signal, and the audio signal.

The Doppler frequency shift (between emitted and received ultrasound) quantifies the instantaneous velocity component of the moving reflectors (usually blood cells) toward or away from the transducer (in centimeters per second) at a site determined by the sample volume of the pulsed Doppler or along the scan line in continuous wave Doppler. The display of this instantaneous velocity over time is called the *spectral Doppler display* (Fig. 51.1). Usually, an electrocardiographic (ECG) signal is also displayed for the purpose of timing. The occurrence of flow faster than normal (in stenotic lesions), of flow in the opposite direction than normal (in regurgitant lesions), or of flow where usually no flow exists (in shunt lesions) can be detected. If velocities are integrated over time, the time velocity integral is obtained (in centimeters). With color Doppler, multiple measurements at different sites in the heart cavities are made simultaneously and represented qualitatively in colors (Fig. 51.1). Velocities toward the transducer are represented in shades of red and away from the transducer in shades of blue. Rapid variations in velocity, as in turbulent flow, are characterized by an admixture of green, which changes red hues to yellow and blue hues to cyan (17).

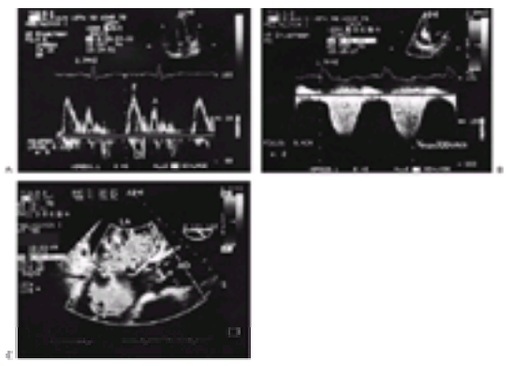


FIGURE 51.1 Pulsed, continuous, and color flow Doppler. **A:** Normal transmitral flow pattern. The sample volume is positioned at the tip of the mitral leaflets. Diastolic transmitral flow in sinus rhythm consists of an early, usually larger and higher E wave (E), and a late, usually smaller, A wave (A). Deceleration time (DT, *arrows*) of the E wave is the time between peak E-wave velocity and cessation of E wave. **B:** Continuous wave Doppler of tricuspid regurgitation in pulmonary hypertension. The maximal regurgitant velocity (v_{max}) of 330 cm per second implies a maximal systolic pressure gradient between the right ventricle and right atrium of 44 mm Hg, and, hence, a systolic pulmonary pressure of 44 mm Hg plus central venous pressure. **C:** Transesophageal color Doppler flow mapping of severe mitral regurgitation due to a posterior flail leaflet. The left atrium (LA) is on top. A proximal convergence zone (*black arrow*) is seen, as well as the eccentric, anteriorly directed turbulent jet in the left atrium (*white arrows*). AO, ascending aorta; LV, left ventricle.

The intensity (amplitude) of the signal is represented in shades of gray in the spectral display. It is related to the number of scatterers (red blood cells) found within the sample volume moving with the measured velocity. Characteristically, if a pulsed Doppler sample volume is positioned in a region where all scatterers move with approximately the same velocity, the result is a bright, narrow bandwidth display of this velocity over time. The width of the signal reflects the variation in velocity within the sample volume. The brightest line is the *modal* velocity, which is the velocity most frequently measured by the Doppler device in the sample volume (Fig. 51.1). This is important when calculating flow rates from cross-sectional areas and pulsed Doppler data. In contrast, continuous wave spectral displays are filled with white signals up to the maximal velocity, the envelope. The reason for this is that the continuous wave Doppler device measures velocities along a whole scan line, so that all

flow velocities that the scan line encounters are represented.

Experienced echocardiographers use the audible signal to optimize the angulation of the transducer. The magnitude of the Doppler shift for usual carrier frequencies lies within the audible range (under 20 kHz). Therefore, high pitch corresponds to high blood flow velocity, and purity of tone to a narrow range of flow velocities.

Use of Doppler Signals to Evaluate Obstruction to Flow

Valvular stenoses and other obstructions to blood flow (e.g., left ventricular outflow tract obstruction) can be quantified by Doppler. The mainstay of this evaluation is the calculation of maximal and mean pressure gradients across an obstruction from transstenotic blood flow velocities by the *simplified Bernoulli equation*:

$$\Delta p = 4v^2$$

(D*p*, pressure drop in millimeters of mercury; *v*, velocity in meters per second)

Another way to quantify stenoses is the calculation of effective stenotic orifice area, which is usually accomplished by the continuity equation (Fig. 51.2): $A_{EFF} = A_1 \times TVI_1/TVI_{MAX}$, where A_{EFF} is the effective stenotic orifice area, A_1 is the area of the flow cross section, usually calculated as p × $d^2/4$, where *d* is the left ventricular outflow tract diameter, TVI_1 is time velocity integral at another flow cross section (by pulsed wave Doppler), usually the left ventricular outflow tract, and $TVI_{MAX}$is the transstenotic time velocity integral (by continuous wave Doppler). Instead of time velocity integrals, the maximal transstenotic velocity and the maximal velocity in the outflow tract can be used.

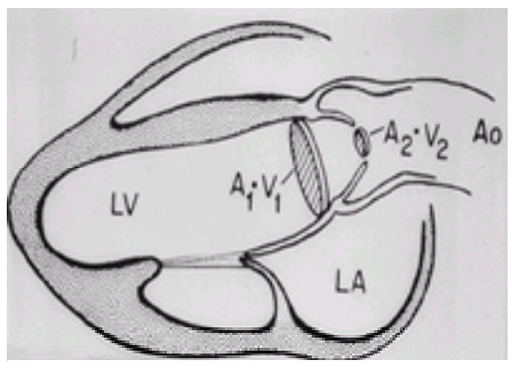


FIGURE 51.2 Schematic drawing of the continuity principle. By virtue of the conservation of mass between the left ventricular outflow tract and the aortic valve, the flow rate in the outflow tract ($A_1 \times v_1$, where A_1 is outflow tract area and v_1 is average blood flow velocity in the outflow tract) and the flow rate across the aortic valve ($A_2 \times v_2$, where A_2 is aortic valve area and v_2 is average velocity across the aortic valve) are equal. Hence, $A_2 = A_1 \times v_1/v_2$. For this calculation, the outflow tract is taken to be circular and calculated from outflow tract diameter *D* as A_1= p × $D^2/4$. AO, ascending aorta; LA, left atrium; LV, left ventricle. (From Weyman AE. *Principles and practice of echocardiography*, 2nd ed. Philadelphia: Lea & Febiger, 1994, with permission.)

Quantification of Regurgitant Lesions

Regurgitation is easily identified by spectral or color Doppler, but difficult to quantify. The *area of the regurgitant jet* by color Doppler is the easiest way to grade severity but does not reliably differentiate moderate and severe regurgitation. Useful other approaches are measurement of the proximal jet diameter immediately at the origin of the jet and the proximal flow convergence zone concept.

Quantification of Cardiac Output

Stroke volume across any flow cross section and thus across any valve can in theory be calculated by multiplying the time velocity integral across that valve by valve orifice area. Unfortunately, neither is easily and reliably measured. Usually, stroke volume (and, hence, by multiplication with heart rate, cardiac output) is measured by multiplying the time velocity integral of the pulsed Doppler signal of systolic transaortic flow by the aortic orifice area (calculated by p × $d^2/4$, where *d* is aortic annulus diameter).

Basic Hydrodynamic Principles

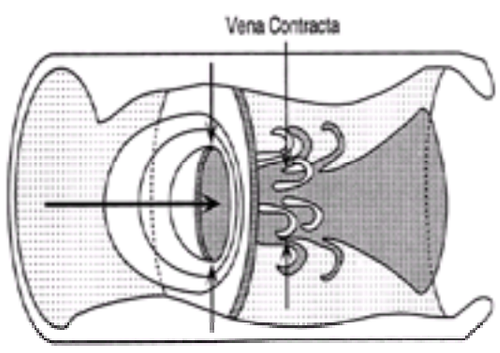
To derive information on hemodynamics from Doppler signals, some hydrodynamic principles governing flow must be understood (18,19).

Continuity Principle

The continuity principle is an application of the fundamental law of the conservation of mass in a closed system (Fig. 51.2). In steady flow of an incompressible fluid through a tube, the volume flow rate (milliliters per second) is equal at any cross section of the tube. Since flow rate is equal to the product of (mean) velocity *v* and cross-sectional area *A*, it follows that

$$v_1 \times A_1 = v_2 \times A_2$$

at any cross sections 1 and 2 of the flow stream. Thus, effective orifice area A_{EFF} of a narrowed flow cross section (e.g., a stenosis) can be calculated from the maximal flow velocity across the orifice v_{MAX}, cross-sectional area A_1, and mean flow velocity v_1 of any other cross section by $A_{EFF} = A_1 \times v_1/v_{MAX}$. The *effective* orifice area of flow is always smaller than the geometric orifice area and occurs slightly downstream from the restrictive orifice (eFig. 51.2.1). The ratio between effective and geometric area is called the *coefficient of contraction* and is always smaller than 1. Hence, effective orifice area by the continuity equation is smaller by a variable factor than orifice area by planimetry or by Gorlin's equation. Note also that the continuity principle is valid at each point in time, and thus effective area can be calculated both from the time-velocity integrals or the maximal velocities at two cross sections. Both are equal if the cross sections are constant over time.



***e*FIGURE 51.2.1** Schematic drawing of flow through a restrictive orifice. Upstream (*left*) from the restrictive orifice, a flow convergence zone develops, consisting of concentric isovelocity shells of approximately hemispheric shape. Downstream (*right*) a jet develops, which entrains stagnant fluid along its way. Immediately after

discharge from the orifice, the cross section diminishes to a minimal value (the vena contracta) and then reexpands further downstream.

Stenotic, Regurgitant, and Shunt Lesions

Stenotic, regurgitant, and shunt lesions involve a restriction to flow. Because of the continuity principle, any narrowing of the cross-sectional area of flow implies an increase in flow velocity. The *convective* flow acceleration necessary for this increase in flow velocity is the main cause of the pressure drop across cardiac restrictive lesions, whereas factors such as viscosity, pulsatile acceleration of stagnant blood, and others only play a minor role. In contrast, normal cardiac valves pose little restriction to flow, such that the energy consumed to propel blood across native valves is largely due to pulsatile acceleration of blood. The general relationship between pressure difference and velocity difference between two points along a stream line is expressed in Bernoulli equation, which is derivable from the more general Euler and Navier-Stokes equations of flow. It can be viewed as an application of the principle of energy conservation:

$$p_1 - p_2 = \frac{1}{2}\rho(v_2^2 - v_1^2) + \rho\int_1^2 \frac{dv(s,t)}{dt}\, ds + R(v)$$

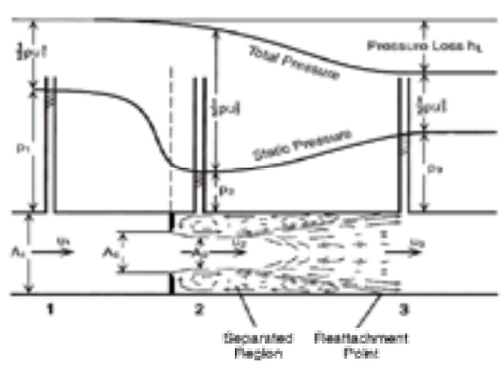
where p_1, v_1 and p_2, v_2 are pressure and velocity at points 1 and 2 on a stream line, respectively, $v(s,t)$ is blood velocity as a function of distance s along the stream line between points 1 and 2 and of time t, r is blood density (1.05 g per cm^3), and $R(v)$ is viscous friction loss between points 1 and 2 as a function of velocity. The first term on the right side describes convective acceleration, the second term flow describes acceleration over time (e.g., acceleration of stagnant blood at valve opening and closure), and the third term describes viscous loss. For clinical purposes in valvular stenoses, the proximal velocity v_1 and the second and third terms on the right are neglected, and Bernoulli equation is simplified to $Dp = 4v_{MAX}^2$, where Dp is the pressure drop in millimeters of mercury and v_{MAX} is the maximal velocity in meters per second. Under the following conditions, however, the simplified version does not apply:

1. High proximal velocities, as in subaortic obstruction or significant regurgitation coexisting with valvular obstruction. Here, the proximal velocity v_{PROX} has to be taken into account: $Dp = 4(v_{MAX}^2 - v_{PROX}^2)$.
2. Tunnel-like lesions, where the length of the obstruction is not negligible in relation to its width. For example, *in vitro* data indicate that at tunnel cross sections of 0.5 cm^2 or lower and lengths of 2 cm or higher the true pressure drop is higher than predicted from the simplified Bernoulli equation, because viscous friction loss becomes relevant (20). Here, Poiseuille's law, where pressure drop is directly and linearly proportional to flow rate, and inversely proportional to the fourth power of tube radius, becomes more appropriate to describe the relation between pressure drop and flow. Poiseuille's law can be expressed as:

$$\Delta p = Q \times 8 \times \eta \times L/(\pi \times r^4) = v \times 8 \times \eta \times L/r^2$$

$$\text{or } R = 8 \times \eta \times L/(\pi \times r^4)$$

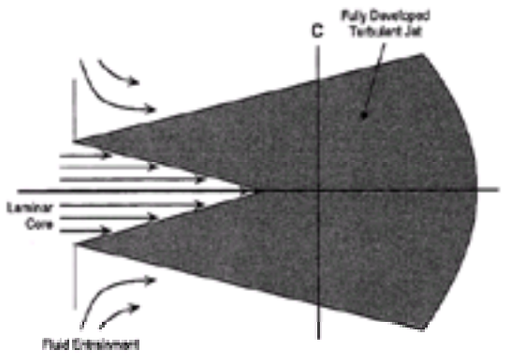
3. or $R = 8 \times h \times L/(p \times r^4)$
4. where Dp is pressure drop, Q is volume flow, R is vascular resistance, v is mean velocity, h is viscosity, L is tube length, and r is tube radius. However, such ratios of cross section and length are almost never encountered in echocardiography; nevertheless, they do exist in coronary stenoses.
5. In normal native valves. In this case, proximal velocity is not negligible in relation to maximal transvalvular velocity, and time-dependent flow acceleration is not negligible compared with convective acceleration.
6. If pressure recovery occurs. The kinetic energy present at the effective orifice area of restrictive cardiac lesions is partly dissipated in turbulent eddies and, ultimately, heat. This energy is lost irretrievably. However, restriction geometries that allow the jet to expand gradually until reaching the boundaries of the receiving chamber minimize eddy formation and allow some of the kinetic energy to be reconverted into static pressure energy downstream (eFig. 51.2.2). The most prominent example of this is seen in bileaflet prostheses in the aortic position (see Prosthetic Heart Valves, later in this chapter). The amount of pressure recovery depends on the morphology of the obstruction and the receiving chamber, being large in gradually tapering and flaring obstructions and low in abrupt narrowings.



***e*FIGURE 51.2.2** Schematic drawing of pressure recovery. Flow through a restrictive orifice of diameter A_0 is shown. Attached to the tube are pressure manometers showing the static pressure at different measurement sites (p_1, p_2, and p_3). Also shown is total pressure (the sum of static pressure and kinetic pressure $1/2ru^2$ at each site, with u flow velocity). At cross section A_1, flow velocity u_1 and kinetic pressure are low, and static pressure is high. Immediately distal to the restrictive orifice, at the vena contracta (A_2), flow velocity u_2 and kinetic pressure are maximal, and static pressure is minimal. Their sum is almost unchanged compared with A_1. Flow stream line separation from the solid boundaries occurs, and energy is irretrievably lost by dissipation in eddies. Some of the kinetic pressure present at the vena contracta A_2, however, is recovered and transformed back into static pressure where the stream lines reattach to the solid boundaries. Thus, p_3 is higher than p_2. The irretrievably lost energy is depicted as pressure loss h_L. Flow velocity u_3 is lower than u_2 and (by the continuity principle) equals u_1. The amount of pressure recovery is determined by the geometry and smoothness of the transition between restrictive orifice and downstream flow boundaries. (From Sugawara M, Kajiya F, Kitabatake A, et al., eds. *Blood flow in the heart and large vessels.* Tokyo: Springer, 1989, with permission.)

Laminar and Turbulent Flow

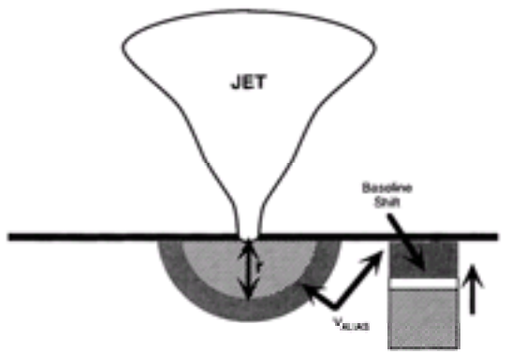
Steady flow of a viscous fluid in a tube occurs in concentric layers of increasing velocity without mixing between the layers, giving rise to a parabolic flow profile, in which the maximal velocity occurs at the central axis and is approximately twice the mean velocity. Poiseuille's law applies (see Stenotic, Regurgitant, and Shunt Lesions). In contrast, under certain circumstances turbulent flow behavior appears, which is characterized by random fluctuations of velocity and pressure at any location. These circumstances may be viewed as the relation of inertial to viscous forces in a flow field and are described by the dimensionless Reynolds number ($2r \times v \times r/h$), where r is radius of the flow cross section, v is mean velocity, r is density, and h is viscosity. Flow becomes turbulent if this number exceeds a cutoff of approximately 2,300; however, *in vivo*, the transition between laminar and turbulent flow may happen at somewhat lower or higher Reynolds numbers. Fluid velocity layers break down, and mixing occurs in eddies. The velocity profile is flattened and no longer parabolic. Poiseuille's law that pressure drop is linearly proportional to flow rate no longer applies; turbulent pressure drop is proportional to flow rate squared. Hence, flow resistance increases if flow becomes turbulent (19). Note that the continuity principle and Bernoulli equation are valid independently of the occurrence of turbulence. Turbulent jets at their orifice contain a small, tapering laminar flow core, which extends for approximately six orifice diameters or less (21) into the receiving chamber, after which the jet is fully turbulent (*e*Fig. 51.2.3). The jet maintains the maximal velocity in the laminar core; after becoming fully turbulent, flow velocity decays inversely proportional to the distance from the orifice. While flow through normal heart valves is laminar, stenotic and regurgitant cardiac lesions create turbulent jets.



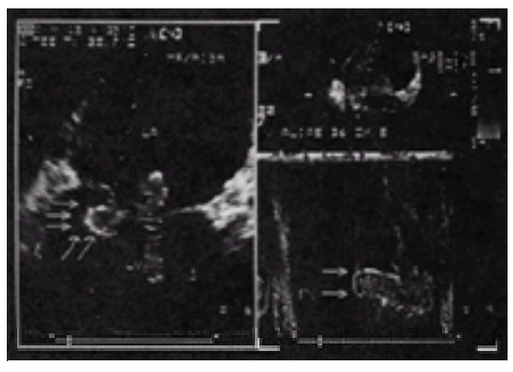
***e*FIGURE 51.2.3** Schematic drawing of the cross section of a turbulent jet. Jet velocity is highest across the orifice. Immediately downstream from the orifice, flow is still laminar, and the high velocity is preserved. This *laminar core* is progressively eroded downstream by turbulence occurring where high-velocity fluid and stagnant fluid mix. After a length of approximately five orifice diameters, the jet is fully turbulent. Mean velocities are now highest along the centerline and decrease laterally. By entrainment of stagnant fluid, the jet's volume and cross section increases, while flow velocities decrease. Jet momentum (jet fluid mass × velocity) is equal at each cross section C. (Adapted from Yoganathan AP, Cape EG, Sung HW, et al. Review of hydrodynamic principles for the cardiologist: applications to the study of blood flow and jets by imaging techniques. *J Am Coll Cardiol* 1988;12:1344–1353, with permission.)

Proximal Convergence Zone or Proximal Isovelocity Surface Area Concept

The proximal convergence zone or proximal isovelocity surface area concept is a continuity-based approach to measure flow rate through a regurgitant orifice by analysis of the flow velocity field proximal to the orifice (22,23 and 24) (eFig. 51.2.1, Fig 51.2.4, and Fig 51.2.5). For this purpose, it is assumed that the issuing chamber is large compared with the orifice, and that concentric hemispheric surfaces of fluid particles of the same velocity centered at the orifice are formed at each moment in time. The smaller the radius of the hemisphere, the higher the flow velocity toward the orifice. Because of the continuity principle, flow rate through the orifice is equal to flow rate across each hemisphere and is given as the product of hemisphere surface area and corresponding flow velocity. If the radius of such a hemisphere r and the corresponding velocity v are known, the instantaneous flow rate Q can be calculated as $Q = 2p\times r^2 \times v$. The assumption of a hemisphere is a simplification of the shape of the isovelocity surfaces, because solid boundaries, simultaneous intracardiac flows, flattening of the isovelocity surface close to the orifice, and other factors influence its shape.



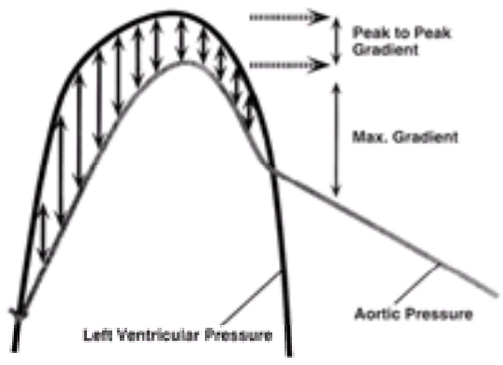
***e*FIGURE 51.2.4** Schematic drawing of the proximal flow convergence concept. Flow through a restrictive orifice is shown as imaged by color Doppler. Proximal to the orifice (lower third of drawing), concentric isovelocity shells of hemispheric shape develop. Two representative shells are shown: the outer, blue one depicts low velocity toward the orifice. At the distance r to the orifice, the aliasing velocity v_{ALIAS} occurs; the inner shell is red, depicting higher velocities. Flow rate is calculated by multiplying the surface of the shell with radius r by v_{ALIAS}. To increase r (and decrease the measurement error of r), the aliasing velocity can be lowered by moving the baseline of the color bar *in the direction of the jet* (i.e., upward in this example).



***e*FIGURE 51.2.5** Example of proximal convergence zone analysis by color Doppler with baseline shift. Mitral regurgitation viewed by transesophageal color Doppler. The circular proximal convergence zone (*arrows*) is seen on the ventricular side of the mitral valve. To increase the aliasing radius, the color bar baseline was shifted upward. The radius can also be measured from color M-mode (*lower right*). In this case, maximal instantaneous regurgitant flow rate was $2p \times (1.1\ cm)^2 \times 36$ cm per second = 274 cm^3 per second, corresponding to severe mitral regurgitation.

Evaluation of Restrictive Orifices: Pressure Gradients and Orifice Areas

A stenosis is a restriction to flow and thus is characterized by a pressure drop, a reduction in the geometrical cross section of flow, and an increase in local flow velocity, regardless of whether this occurs on a valvular or other level. The instantaneous pressure drop across the stenosis is calculated from the instantaneous flow velocity by the simplified Bernoulli equation (eFig. 51.2.6). Maximal and mean pressure drops, or gradients,* can be calculated and are in principle identical to hemodynamic maximal instantaneous and mean gradients (but not to "peak-to-peak" gradients). Maximal gradients are particularly prone to measurement error; thus, in general, mean gradients are preferable to characterize an obstruction. The mean gradient is the mean of $4v_1^2$, $4v_2^2$,..., where v_1, v_2,... are the maximal instantaneous velocities; thus, it is not identical to $4v_{MEAN}^2$ (this is correctly implemented in the analysis packages of available echo machines). However, the pressure drop depends not only on the stenotic orifice area, but also on a number of other factors, most prominently stroke volume. Thus, orifice area is considered to be a more characteristic and stable parameter of a stenotic lesion. It has long been assumed to be flow independent in aortic and mitral stenosis. Although there is evidence that this is not the case in a subset of stenotic lesions (25,26), current usage treats these lesions as fixed. Orifice area can be measured directly by planimetry from 2-D images in mitral and, transesophageally, in aortic stenosis. Alternatively, the continuity principle can be used, and stroke volume from another valve is divided by the time-velocity integral of the stenotic valve to yield the effective orifice area (if both valves are competent). It must be kept in mind, however, that the orifice area calculated by continuity is smaller than the planimetric or (hemodynamic) Gorlin orifice area. Native mitral stenosis can also be estimated using the pressure half-time concept. This concept, derived from hemodynamics, uses the time in which the pressure drop falls to one-half of its initial value as an estimate of the severity of obstruction, which is less flow dependent than the pressure drop itself. Additionally, resistance of a stenosis can also be calculated by dividing the mean pressure gradient (from the simplified Bernoulli equation) by the stroke volume. However, *in vitro* and *in vivo* experiments have clearly shown that resistance is also flow rate dependent, and there is no clear advantage over the more familiar parameters of obstruction pressure drop and orifice area (25,26).



***e*FIGURE 51.2.6** Schematic drawing of pressure gradients in aortic stenosis. Mean gradient is the average of the red arrows. Note that *peak-to-peak* gradient (difference between maximal left ventricular and maximal aortic pressure) never actually exists, because peak aortic pressure occurs after peak ventricular pressure. Peak-to-peak gradient is neither identical with maximal nor mean pressure gradient.

Evaluation of Regurgitation

Regurgitation is flow through a valve occurring in the wrong direction. Regurgitant flow velocities in the receiving chamber (e.g., the left atrium in mitral regurgitation) can be recorded by any Doppler modality. To search for and identify regurgitation, color Doppler is most convenient. In more than “trace” regurgitant lesions, regurgitant jets by color Doppler usually do not have a single color, but instead have a core region with a mosaic appearance containing all colors in a rapidly changing pattern, surrounded by larger regions of pure red or blue (Fig. 51.1). Most color Doppler algorithms also add a green hue to the basic colors red and blue to denote rapid velocity changes. The two main reasons for the mosaic appearance are that (a) jet core velocities in mitral and aortic regurgitation, and often in tricuspid regurgitation, are much higher than the aliasing velocity of the color map and thus, multiple aliasing occurs; and (b) regurgitant jets almost always are truly turbulent, so that flow velocities in all directions occur in random fashion. It should be kept in mind that the color Doppler mosaic appearance is not necessarily identical with the presence of a turbulent jet in the strict hydrodynamic sense; on the other hand, in severe regurgitation, when there is nearly pressure equalization between the issuing and receiving chambers, the driving pressure difference between the chambers may become so small that the classic color Doppler appearance of a turbulent regurgitant jet is absent. This observation has been made in severe prosthetic dehiscence (27). If the presence of regurgitation by color Doppler is unclear, pulsed Doppler confirmation of regurgitant flow velocities should be sought.

The easiest but most treacherous way to grade regurgitation severity is by eyeballing or measuring the maximal color jet area of the regurgitant jet in the frame and the cross section where it appears largest. Although a rough estimate of severity, it is stronger related to the square of regurgitant flow velocity than to flow rate and therefore is highly load dependent. Specifically, color jet area is proportional to momentum flux (the transfer of momentum over time) in the regurgitant jet (28). Momentum in physics is a parameter defined as the product of mass (in grams) times velocity (in centimeters per second). Importantly, the momentum of each cross section of a free jet ideally is the same (with little mass at high velocity at the orifice, and more entrained fluid mass at lower velocity downstream; *e*Fig. 51.2.3). Because color jet area is proportional to jet momentum flux, it is quadratically related to regurgitant flow velocity, whereas regurgitant volume or regurgitant fraction is linearly related to regurgitant velocity. In other words, a volume of blood regurgitating at a high velocity due to a high pressure difference has a larger color jet area than the same amount of blood regurgitating at a lower velocity due to a lower pressure difference. Another important problem is that jets often are eccentric and may spread out on an adjacent wall (in the left atrium) or hug the anterior mitral leaflet (in aortic regurgitation), thus making size assessment difficult. Eccentric jets in general are substantially underestimated when taken at face value (29). Finally, instrument settings, carrier frequency, and other factors influence the area of a regurgitant jet. Nevertheless, assessment of color jet size is the easiest and fastest way to roughly estimate regurgitation severity. Several other methods are available to assess the severity of regurgitant lesions:

1. The proximal jet diameter or cross-sectional area, measured as the smallest diameter or area immediately downstream of the jet’s anatomic orifice, ideally represents the diameter of the effective orifice area. Since this area is not necessarily circular, it can also be planimetered, or two orthogonal diameters can be measured to calculate an ellipse area. Cutoff values with good discriminating power have been reported, especially for mitral regurgitation. The limiting factors are image quality, influence of gain, and measurement error.
2. The stroke volume of different valves can be compared, if only one of them is insufficient. In mitral regurgitation, regurgitant volume is calculated by subtracting aortic stroke volume from total stroke volume, which is obtained either as mitral stroke volume or as the difference of diastolic and systolic left ventricular volumes. Aortic regurgitant volume can be calculated analogously. Although validated in dedicated hands, its accuracy depends obviously on the reliability of all the stroke volume calculations and is therefore subject to several potential errors (e.g., accuracy of orifice area, skewed velocity profiles, and others).
3. The proximal convergence zone method has been outlined (see Proximal Convergence Zone or Proximal Isovelocity Surface Area Concept, earlier in this chapter). This approach, which has been clinically validated for the atrioventricular valves, yields quantitative values for maximal regurgitant flow rates. Two derived parameters can be calculated from the maximal regurgitant flow rate Q_{max}:
   a. Effective regurgitant orifice area (ROA), for which maximal regurgitant flow velocity (v_{max}) must be additionally measured (by continuous wave Doppler): ROA = Q_{max}/v_{max}. Effective regurgitant orifice area is a useful parameter clearly less load dependent than maximal regurgitant flow rate, but apparently less fixed than effective orifice area of stenotic valvular lesions (30,31).
   b. Regurgitant volume (RV), which is the product of the regurgitant time velocity integral from continuous wave Doppler (TVI) and effective regurgitant orifice area: RV = TVI × ROA.
   c. Application of the proximal convergence zone method requires good image quality and works best for moderate or severe regurgitation, since then the proximal convergence zone is clearly and reproducibly visible. To maximize the radius of the convergence zone and improve definition of the convergence zone, the zero line of the color bar should be shifted in the direction of the regurgitant jet; thus, the aliasing velocity is lowered and the convergence zone radius is maximized (see *e*Fig. 51.2.5). Although applicable to any flow through a restrictive orifice, the method has been clinically validated for regurgitation of the atrioventricular valves and for mitral stenosis (32). Its application to aortic regurgitation is theoretically and clinically not well validated.

Evaluation of Flow Rates

Flow rate is calculated by multiplying the cross section of a flow stream with its average velocity. In pulsatile flow, the product of the cross-sectional area of flow and the time-velocity integral of the modal velocity measured by pulsed Doppler at the site of the cross section is used to calculate stroke volume. Cardiac output is calculated by multiplying the stroke volume with the heart rate. Usually, this principle is applied to the left ventricular outflow tract at the aortic annulus level. The diameter of the aortic annulus or left ventricular outflow tract immediately below the aortic valve is measured in a parasternal long-axis view, and a circular cross section of the outflow tract is assumed, which is calculated as p× r^2, with r one-half of the diameter. An apical long-axis view is used to acquire the pulsed Doppler recording, with the sample volume positioned at the annulus or, in the presence of aortic stenosis, in the outflow tract directly below the aortic valve. Cardiac output can also be measured analogously at the level of the mitral annulus or the pulmonary valve annulus. For mitral stroke volume, several methods have been proposed. The simplest uses diameter of the annulus in the four-chamber view, assumes a circular orifice, and multiplies the area with the time-velocity integral from pulsed Doppler at the annulus level. Alternatively, an elliptical annulus shape may be assumed with two diameters measured in the four-chamber and in the two-chamber views, with area p × D_1 × D_2/4. Since the mitral orifice area is neither circular nor constant over time, a more accurate, but more cumbersome, method measures maximal orifice area in a short-axis view, multiplies it with the ratio of mean to maximal mitral leaflet separation from a mitral M-mode to obtain a *mean orifice area*, and multiplies this value with the pulsed wave Doppler time-velocity integral at the leaflet tips (33). For pulmonary stroke volume, the maximal pulmonary annulus diameter is multiplied with the time-velocity integral at the pulmonary valve leaflet tips. From such calculations, regurgitant volumes or shunt ratios (Q_P/Q_S) are derived (as the ratio of pulmonary stroke volume and left ventricular outflow tract stroke volume, if no pulmonary or aortic regurgitation is present) (34). However, accuracy of stroke volume measurements depends on how accurately the cross section is measured and how well the modal velocity by pulsed Doppler reflects the average flow velocity at this site. Automated integration of color Doppler velocities is commercially available. The algorithm calculates flow rate by spatial and temporal integration of flow velocities across a flow cross section. This cross section is defined by a diameter and assumed to be circular. The diameter is represented by an electronic bar that can be positioned freely in the image sector. This is the equivalent of using multiple minute sample volumes instead of just one, as conventionally done, for example, in the left ventricular outflow tract. Within the limits of spatial and temporal color Doppler resolution, flow profiles are taken into account by this method (35).

CLINICAL DOPPLER EXAMINATION

General Considerations

Modern echo machines have imaging transducers with incorporated Doppler capabilities and show the Doppler cursor or sample volume in the current 2-D image. Additionally, guidance is provided by the audio output. However, in difficult continuous wave Doppler examinations (e.g., in aortic stenosis), a dedicated, stand-alone

transducer without imaging frequently is superior to the combined 2-D and Doppler transducer for technical reasons and because of the smaller transducer face size (e.g., for use with the suprasternal window). Furthermore, although carrier frequency for imaging ideally should be as high as possible to optimize spatial resolution, for pulsed Doppler there is a trade-off between spatial resolution and the maximal unambiguously identifiable flow velocity at a given range. Therefore, transducers often operate at a lower carrier frequency in Doppler mode than in imaging mode.

The following practical points should be observed:

1. The interrogating beam should be aligned with the direction of flow. This is difficult even using 2-D–guided Doppler, because the third dimension is missing. It is better to change the transducer position to enable optimal alignment than to use the angle correction option. Although angle correction is possible in available Doppler devices, it is likely to introduce more error than it corrects, unless the true direction of flow is evident, as in a vessel imaged in a long axis. Fortuitously, in truly turbulent flow, which is present in severe valvular stenosis and in left-sided regurgitation, high flow velocities occur in all spatial directions; therefore, optimal alignment is less critical in these instances. A few heart cycles should be recorded, especially in the presence of atrial fibrillation.
2. The visual and the audio output should be used to optimize the signal (see Instrument Settings, later in this chapter).
3. Timing of the Doppler signal should be compared with the corresponding ECG. For example, the mitral regurgitation signal, which may be mistaken for an aortic stenosis signal, begins earlier (immediately after mitral valve closure) than the aortic ejection signal. If the origin of the continuous Doppler signal is unclear, the timing of a 2-D–guided pulsed Doppler signal in relation to the ECG should be obtained for orientation.
4. The pitfalls include that clear flow velocity recordings by Doppler cannot be created *ex nihilo* (but they can represent a flow that was not intended to be recorded). An exception is mirror artifacts, which are created by high amplitude signals (or too high gain) and which duplicate an existing signal with inverse sign or reverberations of color Doppler signals, which also duplicate real existing flow at a manifold of the real depth (Fig. 51.3). An important example of the latter is *phantom flow* in transesophageal color Doppler images of the descending aorta, resulting in a *double-barrel* descending aorta. Conversely, there is never proof that the recorded velocities are truly the highest ones that exist, because there is always the possibility of false placement or malalignment of the echo beam. Thus, to minimize the first type of error, ECG timing, 2-D orientation, and characteristics of the flow profile should always be checked. Practically, the most important error is misreading mitral regurgitation for aortic stenosis. The second type of error is minimized by carefully using all echo windows, patience, and clinical judgment. If doubts remain, it is preferable to state that the echo examination is suboptimal than to report possibly false values without this caveat.

FIGURE 51.3 Phantom flow in the descending aorta. On top, the true descending aorta is seen by transesophageal echo with color Doppler imaging. At the twofold distance, a second lumen with phantom flow is seen (*arrows*). This “double-barrel” appearance of the descending aorta is frequently found and represents a mirror artifact, which can be misdiagnosed as dissection.

5. Normal values for forward flow velocities are, of course, dependent on cardiac output and heart rate, and in some instances also on other factors. For instance, the ratio of early to late velocity of transmitral flow decreases with age, as does the ratio of diastolic to systolic peak velocity of pulmonary venous flow. Minimal or trace regurgitation by color and pulsed Doppler is frequently seen in all valves without clinical evidence of heart disease. The incidence increases with age.

Anatomic Windows

All 2-D windows are used for Doppler recordings. However, the best transducer position for Doppler interrogation almost always is not the best position for imaging. Doppler recordings often are sufficient even if 2-D image quality is impaired, because the signal-to-noise ratio in Doppler recordings is higher than for 2-D echo. Right parasternal windows (for aortic stenosis, with the patient in the right lateral decubitus position) and suprasternal windows (mostly for aortic stenosis or aortic coarctation) are often helpful, as are epigastric windows.

Instrument Settings

Gain, scale (which in pulsed and color Doppler is equivalent to pulse repetition frequency), baseline, and filter settings should be individualized to obtain a well-defined signal. As little gain as possible while preserving the integrity of the velocity signal should be used to avoid artifacts, and, with pulsed Doppler, to achieve a narrow width of the envelope. In pulsed Doppler, the length of the sample volume can be varied. Better signal-to-noise ratio by a larger sample volume has to be weighed against the loss in spatial resolution. The wall filter, a high-pass filter, is intended to eliminate noise, but excessive wall filters, by excluding low flow velocities, obscure the onset and end point of flow. This is of importance when measuring isovolumic relaxation time. With color Doppler, gain should be increased until *random color pixels* appear, and then slightly decreased. The appearance of turbulent jets by color Doppler flow maps depends somewhat on the proprietary algorithms of the individual echo machines.

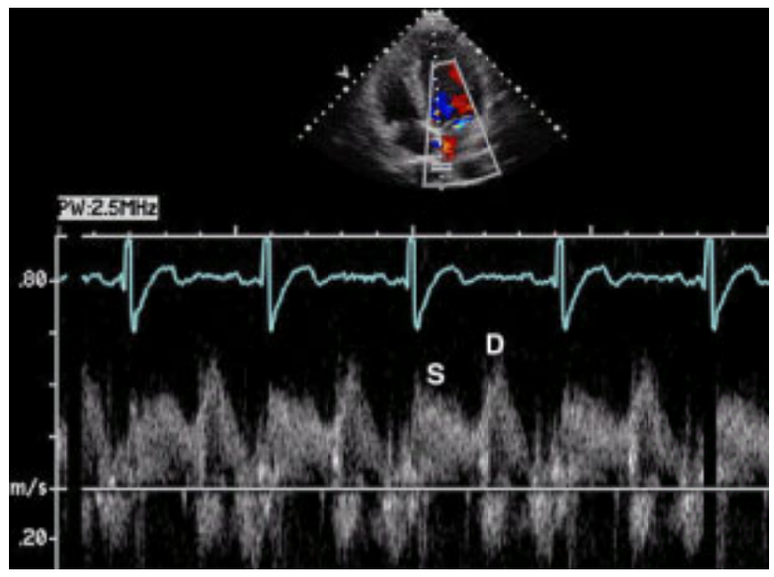
The Routine Examination

The Doppler examination is an integral part of the routine echocardiographic examination. However, specific pathologies (as in aortic stenosis or congenital heart disease) frequently require use of additional echo windows and additional examination time.

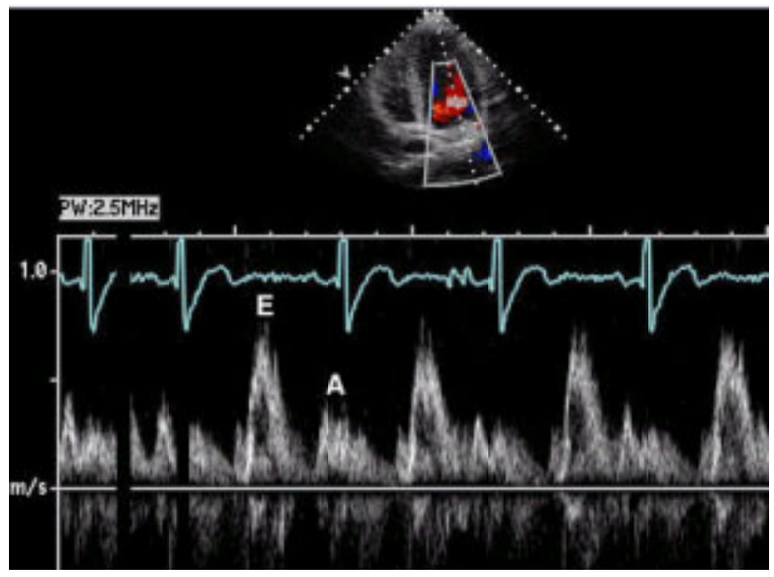
In the parasternal views, because the left heart flows are approximately orthogonal to the echo beam, velocity measurements are not practical. However, color Doppler reveals the occurrence and direction of mitral and aortic regurgitation. The width of these jets is well assessed in parasternal long-axis views, and the minimal cross section in appropriate basal short-axis views. Subaortic obstruction and ventricular septal defects can also be detected by color Doppler. Short-axis views at the aortic root level allow both pulsed or continuous wave Doppler and color Doppler assessment of the right ventricular inflow and outflow tract, including tricuspid and pulmonary forward and, if present, regurgitant flow. Congenital anomalies such as atrial septal defects, membranous ventricular septal defects, or a patent ductus arteriosus may also be detected.

In the routine examination, mitral and aortic valves and the left ventricular outflow tract should be examined by color Doppler in parasternal long-axis views. Also, color Doppler recordings of the tricuspid and pulmonary valves should be obtained in basal short-axis views.

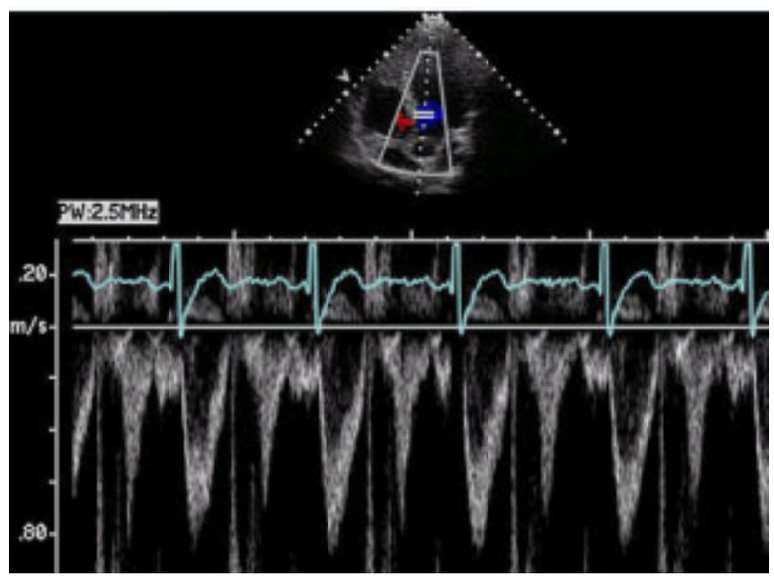
The apical views are ideally suited to record left ventricular inflow and outflow velocities. Transmitral flow is well assessed in four-chamber and two-chamber views. Flow velocities in the left ventricular outflow tract, at the aortic valve level, and in the first centimeters of the ascending aorta are recorded in the apical long-axis view. The four-chamber view also allows measurement of tricuspid flow. Furthermore, atrial and ventricular septal defects (especially of the muscular type) may be detected by color Doppler in the apical four-chamber view. Pulmonary venous flow may be interrogated in a slightly cranially angulated four-chamber view in the right upper pulmonary vein. In the routine examination, a transmitral flow profile should be obtained by pulsed Doppler at the leaflet tips (where transmitral velocities are highest); if cardiac output calculations are to be made, a recording at the mitral annulus level should also be obtained. Mitral regurgitation is sought by color Doppler in all apical views. A transaortic flow profile and an outflow tract profile are recorded by pulsed Doppler. An additional continuous wave Doppler recording of outflow tract and aortic valve is valuable to exclude an obstruction that may have been overlooked by 2-D imaging. Color Doppler of the outflow tract should also be recorded to exclude aortic regurgitation. The tricuspid valve is examined by color Doppler for the presence of regurgitation; if present, the maximal regurgitant velocity is recorded by continuous wave Doppler. By the simplified Bernoulli equation, the maximal systolic pressure difference between right ventricle and right atrium can be calculated from the maximal tricuspid regurgitant velocity. This is an estimate of maximal right ventricular, and, thus, pulmonary, pressure. The pressure difference either can be reported as such, or 10 mm Hg can be added as an estimate of right atrial pressure, or right atrial pressure can be assessed clinically by the collapse level of the neck veins. Further, a color Doppler map of flows in the proximity of the interatrial septum should be obtained to rule out atrial septal defect.



Pulmonary vein pulsed wave Doppler flow. Note the S (systolic) wave and the D (diastolic) wave.

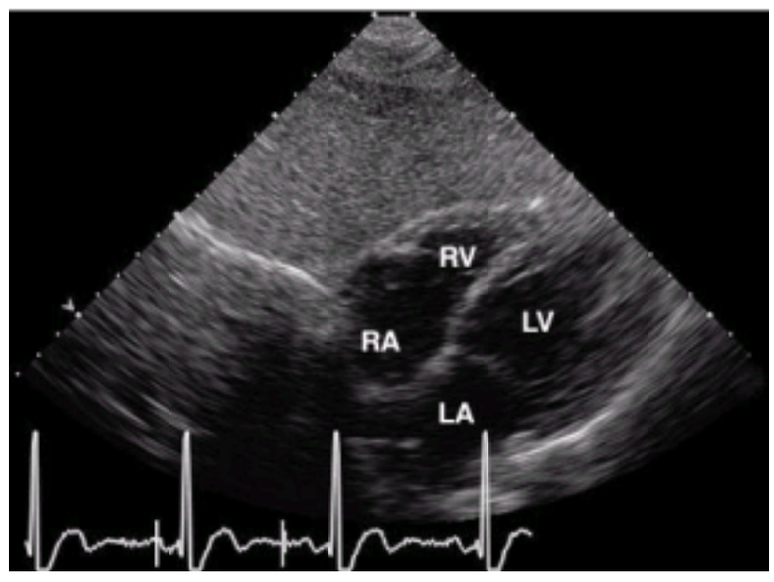


Pulsed wave Doppler signal from the mitral valve inflow. Note the E (early) and A (atrial) waves.



Normal pulsed wave Doppler signal from the left ventricular outflow tract. Note the maximal velocity is only 80 cm/second.

The subcostal views are rarely optimal windows for Doppler examination except for atrial septal defects, in which the echo beam orientation is more appropriate than in the apical four-chamber view. Routinely, the interatrial septum should be examined by color Doppler to rule out atrial septal defect. The subcostal views, however, provide a valuable alternative if more cranial windows are insufficient (e.g., in aortic stenosis). Aortic coarctation and aortic stenosis should be evaluated from the suprasternal position, which in adults often is difficult to use except with a dedicated continuous wave probe.

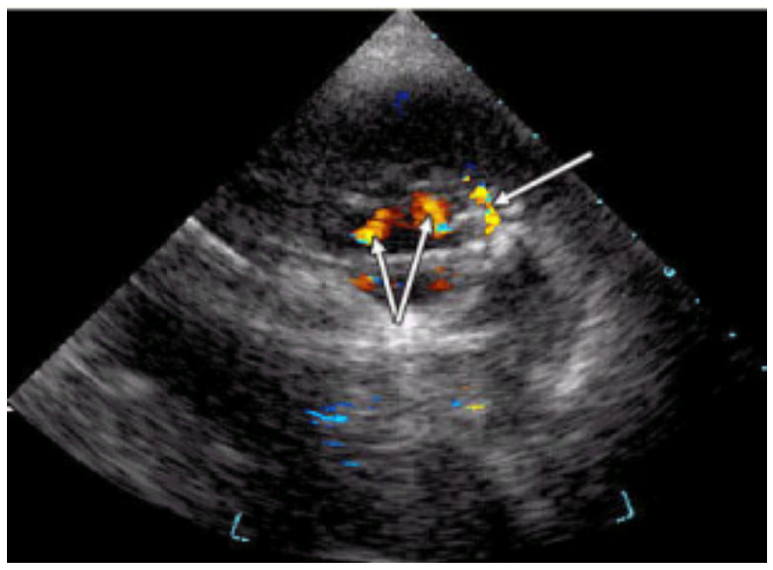


Long-axis view from the subcostal window of a transesophageal echo showing the left and right ventricles (LV and RV) and the left and right atria (LA and RA).

Transesophageal Doppler

Transesophageal echo offers a full set of echo windows for the 2-D and Doppler examination that are almost never obstructed (36). Evidently, transmitral flow can be studied under ideal conditions and even eccentric regurgitant jets are well depicted by color Doppler. Aortic regurgitation is well seen by color Doppler from transesophageal windows, especially long-axis views (at 130 to 160 degrees) of the left ventricular outflow tract. It is difficult, however, to obtain a good alignment of transvalvular aortic flow with the echo beam; this is best done from a transgastric position by rotating from the left ventricular short axis to a long-axis view or using maximal anteflexion of the instrument in the stomach. Tricuspid flow is also sometimes difficult to align with the echo beam. Continuous wave Doppler of the tricuspid valve may be contaminated with a mitral regurgitation signal, since the echo beam always first traverses the left atrium before reaching the tricuspid valve. The pulmonary valve is mostly not well visualized transesophageally. Transesophageal echo offers a unique access to measuring emptying and filling velocities in the left atrial appendage, which are related to thromboembolic risk. Furthermore, pulmonary venous flow is easily interrogated either in the left upper or right upper pulmonary

vein. Being the diagnostic procedure of choice in the setting of aortic dissection, entry and reentry jets and flow in the true and false lumen can be examined by transesophageal echocardiography. Given the excellent visibility of the interatrial septum, a color Doppler examination for an atrial septal defect should be performed. The sensitivity of transesophageal color Doppler for a patent foramen ovale, however, is inferior to that of contrast echo. If cardiac embolism is suspected, especially in atrial fibrillation, a pulsed Doppler recording of left atrial appendage flows should be obtained. Flow velocities in the ascending and descending aorta can be visualized by color Doppler, while absolute velocity values are unreliable because of the large angle between flow direction and echo beam.



Transgastric short-axis view during intraoperative transesophageal echo of a paravalvular leak of a CarboMedics mitral valve replacement. Note the two normal physiologic prosthetic jets of mitral regurgitation (within the sewing ring) as designated by the double arrow and the one abnormal, laterally originating jet outside the sewing ring (to the right of the screen) designated by the single arrow. There was significant mitral annular calcification (MAC), making it difficult to achieve close contact between the annulus and the sewing ring.

Video 51.1 Transgastric view (transesophageal echo) of the mitral valve in a patient with severe aortic insufficiency. Note the fluttering of the anterior mitral leaflet (*left*) due to the jet of aortic insufficiency hitting it (color flow seen on the left). (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 51.2 Long-axis 120-degree transesophageal view of a rheumatic aortic valve with central aortic insufficiency due to furled, restricted leaflets. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 51.3 Transesophageal echo with color Doppler showing tricuspid regurgitation after a myocardial biopsy of the right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Contrast-Enhanced Doppler

Injection of echo contrast agents enhances the amplitude and signal-to-noise ratio of the Doppler flow signal. Thus, echo contrast may be injected to improve the quality of recordings in difficult cases. Intravenous injection of a left-sided heart contrast agent can be helpful, especially in the evaluation of aortic stenosis (37) and of pulmonary venous flow by transthoracic Doppler.

Left-sided heart contrast agents also improve coronary vessel visibility by transesophageal color Doppler; in a study, satisfactory pulsed wave Doppler acquisition from the left anterior descending artery improved from 23% to 66% after injection of a galactose-based agent (38). Left-sided heart contrast agents, because of their small bubble size, have flow characteristics of red blood cells and therefore have potential as myocardial perfusion tracers. Several techniques are currently under evaluation to detect and semiquantitate these agents in the myocardium. Some of them are *power* Doppler techniques. Doppler power (the square of the amplitude of the Doppler signal) is primarily related to the number of scatterers, not to their velocity or direction. Contrast bubbles create power Doppler signals both by their motion and, most importantly, by ultrasound-induced destruction of contrast bubbles, which leads to the creation of a strong Doppler shift. It has been convincingly shown that power Doppler is better suited for measuring the amount of myocardial contrast than gray scale imaging (39).

Normal Transvalvular and Pulmonary Venous Flow Velocity Signals

The normal transmitral flow velocity signal consists of an early (E) wave, which is produced by the rapid decrease in left ventricular pressure caused by relaxation below the level of left atrial pressure (Fig. 51.4). E-wave upslope reflects the rapid growth of the early diastolic atrioventricular pressure gradient. When this pressure gradient ceases to exist, deceleration ensues, which reflects largely the passive compliance of the left ventricle and the left atrium, with a steep deceleration if compliance is low and a slow deceleration if compliance is high. The E wave in sinus rhythm is followed by the late diastolic atrial (A) wave, which is the result of atrial contraction and occurs after the ECG P wave. It reflects atrial contraction force and elastic properties of the left ventricle and atrium at end diastole.

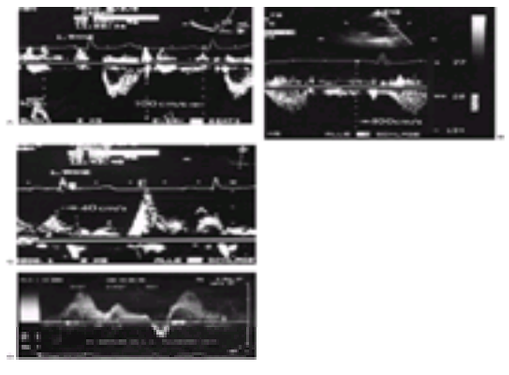


FIGURE 51.4 Normal flow velocity profiles by pulsed Doppler. (See Figure 51.1 for normal transmitral profile.) **A:** Normal transaortic flow pattern. The sample volume is positioned at the aortic valve annulus in an apical long-axis view. **B:** Normal transpulmonary flow. The sample volume is positioned in the pulmonary valve in a basal parasternal short-axis view. **C:** Normal transtricuspid flow pattern. The sample volume is positioned at the tricuspid leaflet tips in an apical four-chamber view. A, late atrial wave; E, early inflow wave. **D:** Normal pulmonary venous inflow pattern from the left upper pulmonary vein by transesophageal Doppler. Systolic (SYST) and

diastolic (DIAST) inflow into the left atrium is seen, as well as a short reverse (REV) wave representing atrial contraction.

Aortic flow velocities have an approximately triangular shape, with a slightly more rapid upslope than downslope (Fig. 51.4). The slopes reflect left ventricular contraction and relaxation and aortic resistance. Aortic flow ends before mitral flow begins, and the time between aortic valve closure and mitral flow onset is the isovolumic relaxation time (normally, approximately 60 ms). Conversely, mitral valve closure occurs before the onset of aortic flow (isovolumic contraction time).

Tricuspid forward velocities form an early diastolic wave and a late wave after atrial contraction, analogous to the transmitral flow pattern (Fig. 51.4). Transtricuspid flow velocities are the lowest of all valves, because the tricuspid valve has the largest orifice area. Pulmonary forward flow is represented by an approximately triangular-shaped systolic velocity signal with a symmetric upslope and deceleration. A steep upslope or a mid-systolic notch are typical of pulmonary hypertension.

Pulmonary venous flow velocities in sinus rhythm have a systolic and a diastolic portion directed toward the left atrium and a short low-velocity retrograde wave after atrial contraction (Fig. 51.4). Systolic and diastolic inflow velocities in young individuals are approximately equal. Diastolic inflow velocities decrease with age and in general behave as the transmitral E wave, because in diastole the atrium acts largely as a passive conduit. Note that peak diastolic pulmonary venous velocity follows peak transmitral E-wave velocity by approximately 50 ms (40), again because early diastolic left ventricular relaxation initiates transmitral left ventricular inflow, which in turn gives rise to pulmonary venous diastolic inflow.

Normal values for the flow velocities obtained during routine examination are given in Table 51.1.

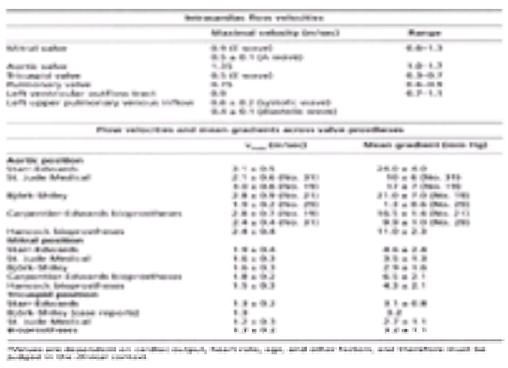


TABLE 51.1 NORMAL VALUES FOR FLOW VELOCITIES IN ADULTS COMPILED FROM SEVERAL REFERENCES (17,18,66,116,117)[a]

ACQUIRED VALVULAR HEART DISEASE

Mitral Valve

Mitral stenosis is best assessed in one of the apical views. Continuous wave Doppler recordings of transmitral flow should be obtained; in atrial fibrillation, at least a short and long diastolic period should be recorded to document the range of occurring gradients. The mean gradient and the pressure half-time should be calculated (Fig. 51.5). The latter is calculated from the downslope of the E wave or the single diastolic wave in atrial fibrillation. It is the time of decay from maximal velocity of flow (immediately after mitral valve opening) to $1/\sqrt{2}$ of the maximal velocity (the $1/\sqrt{2}$ factor is due to the quadratic relation between pressure drop and velocity in Bernoulli equation). The pressure half-time (PHT, in milliseconds) is relatively robust against changes in cardiac output and heart rate; a useful empiric relationship exists with mitral valve area (MVA, in centimeters squared), given by MVA = 220/PHT (41). However, pressure half-time also depends on left atrial and left ventricular compliance and the maximal pressure gradient.

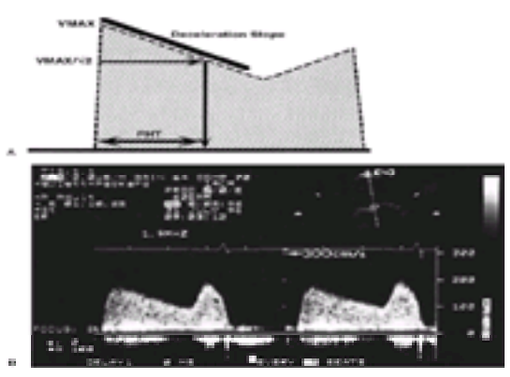


FIGURE 51.5 A: Schematic drawing of measurement of time-velocity integral and pressure half-time (PHT) in mitral stenosis. VMAX, maximal early diastolic velocity. The area surrounded by the dotted line is the time-velocity integral. See text for details. **B:** Transmitral flow by apical continuous wave Doppler in mitral stenosis with preserved sinus rhythm. Peak gradient is 15 mm Hg, mean gradient is 9 mm Hg, and pressure half-time is 228 ms, corresponding to an orifice area of 1 cm^2.

It can be shown analytically (36,37) that in mitral stenosis the following relationship between pressure half-time, MVA, maximal diastolic pressure drop (p_0), and net compliance of left ventricle and left atrium (C_{NET}) holds: PHT = 11.6 × C_{NET} × Öp_0/MVA. Thus, pressure half-time has an inverse relationship with mitral valve area but is also influenced by the other parameters. Furthermore, it is influenced by concomitant aortic regurgitation, which shortens pressure half-time, the presence of an atrial septal defect, or the presence and type of a prosthetic mitral valve (42,43 and 44). Thus, in these instances it is unreliable and should be used mainly for serial measurements, but not to calculate mitral valve area. Consequently, if mitral valve area by planimetry and by pressure half-time are discrepant, possible reasons are the presence of aortic regurgitation, an atrial septal defect, left ventricular diastolic dysfunction with elevated pressures, or, of course, an error in one of the two measurements. Other ways to calculate (effective) mitral valve area from Doppler data are to obtain cardiac output and to divide it by the time velocity integral of the mitral valve, or to use the diameters of the forward jet by color Doppler in the four-chamber view (D_{4CV}) and the two-chamber view (D_{2CV}) to approximate mitral valve area by p × D_{4CV} × D_{2CV}/4 (the ellipse formula). Alternatively, the proximal convergence zone principle may be used to calculate peak flow rate through a stenotic mitral valve and then to divide peak flow rate by peak velocity to yield effective regurgitant orifice (30). Peak flow rate is calculated as

$$Q_{MAX} = 2\pi r^2{}_{ALIAS}{}^2 \times v_{ALIAS}{}^2 \times \alpha/180°$$

where Q_{MAX} is peak flow rate, r_{ALIAS} is radius (distance from orifice) at which velocity aliases, v_{ALIAS} is aliasing velocity, a is the inflow angle subtended by the mitral leaflets (the factor a/180° corrects for the funnel-shaped inflow geometry in mitral stenosis).

Severity of mitral stenosis is graded as from invasively obtained pressure gradients or Gorlin areas. It has been reported that some amount of stretch of the orifice with increasing stroke volume may occur in patients with mild or moderate, not heavily calcified, mitral stenosis (45).

Mitral regurgitation should be evaluated by color Doppler using all available windows, especially the apical views. If doubtful by color Doppler, it should be confirmed by pulsed Doppler, with the sample positioned on the atrial side of the mitral valve. Mitral regurgitant jets often are eccentric, hugging the atrial walls (Fig. 51.1). Mitral valve prolapse creates jets directed toward the back side of the prolapsing leaflet, while flail mitral leaflets direct the jet to the opposite side (Fig. 51.1). Mitral

regurgitation caused by left ventricular dilatation usually results in central jets (46). Planimetry or eyeballing of maximal color Doppler jet size yields a rough estimate of severity. Division by left atrial area in the same view to *normalize* jet size has been proposed and is particularly convenient for eyeballing [with cutoff values of 20% and 40% of left atrial size (47)], but lacks theoretical justification. By transesophageal echo, where the atrium is not visualized fully in single views, the cutoff values for planimetry are 3 and 6 cm^2 (48). Eccentric, wall-hugging jets are underestimated by an average of 40% by the jet area method (27). Whereas very small and very large jets are usually well identified, the intermediate severities are impossible to reliably grade by color jet area. Two color Doppler–based approaches have been well validated and are clinically practical, if image quality is good (in particular, using transesophageal echocardiography):

Video 51.4 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis **(A)** showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. **B:** intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 51.5 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis **(A)** showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. **B:** intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

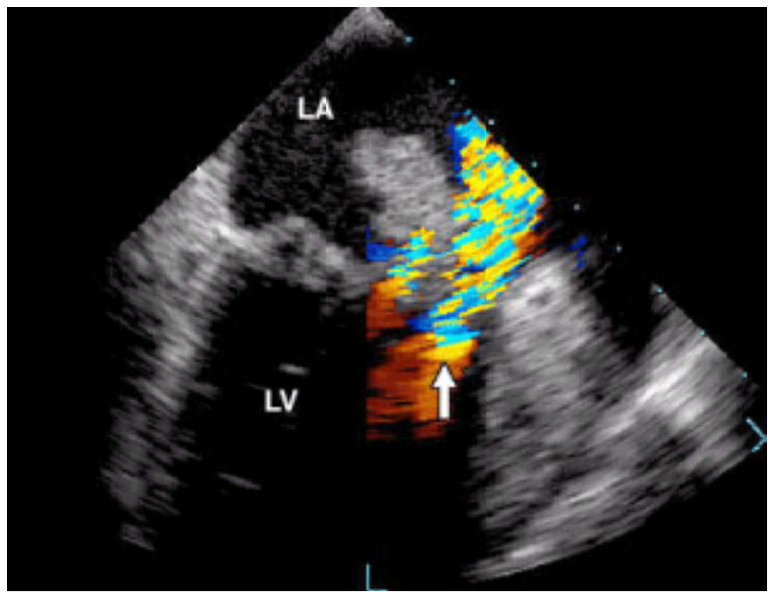
Video 51.6 Apical long-axis view of a patient with severe left ventricular dysfunction and annular dilatation causing 4+, centrally directed mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 51.7 Parasternal long-axis view of a rheumatic mitral valve with color Doppler. Mitral regurgitation is the primary problem seen by color Doppler, with only mild mitral stenosis due to the thickened and doming leaflets. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 51.8 Intraoperative transesophageal echo with color Doppler of a mitral valve with severe prolapse of the posterior mitral leaflet with 4+, anteriorly directed mitral regurgitation. A very prominent proximal convergence zone is seen in the left ventricle. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

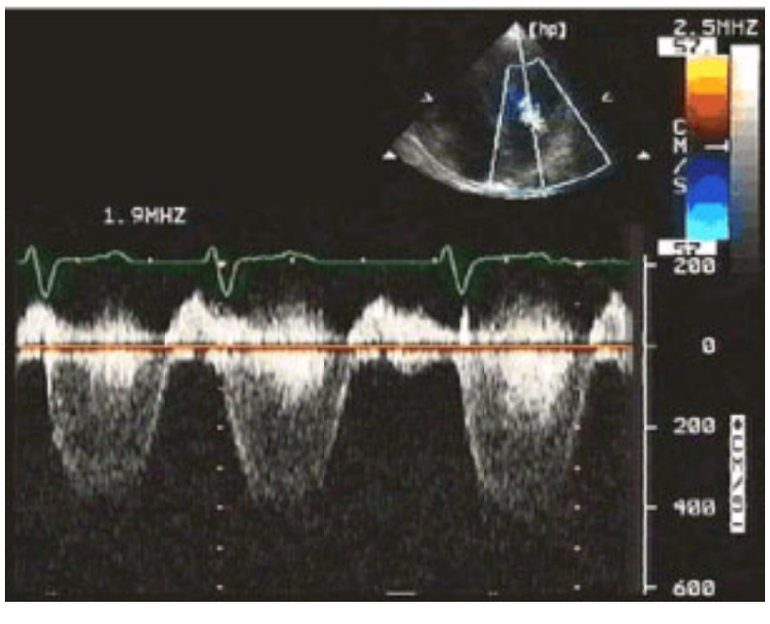
Video 51.9 Color Doppler of 0-degree intraoperative transesophageal echo with prolapse and flail of the posterior mitral leaflet causing very eccentric, anteriorly directed mitral regurgitation. This valve was successfully repaired. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 51.10 Postpump echo (with color Doppler) after repair of the flail posterior mitral leaflet. There is a Cosgrove-Edwards annuloplasty ring in place. There is no residual mitral regurgitation and there is no systolic anterior motion of the mitral leaflets, which can sometimes complicate mitral valve repair. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Color Doppler showing a perforation of the base of the anterior mitral leaflet from *Streptococcus* endocarditis. The patient's underlying pathology was myxomatous mitral valve disease with mitral valve prolapse. The proximal flow convergence of the mitral regurgitation jet is demonstrated by the arrow at

the orifice of the large perforation.



Apical continuous wave spectral Doppler recording of mitral regurgitation (systolic parabolic downward velocities). Note beat-to-beat variation due to atrial fibrillation.

1. Measurement of the proximal jet diameter. The smallest diameter of the jet should be measured, which is within millimeters of its origin (Fig. 51.6). The plane should be sought where the minimal diameter is largest. Jet diameter greater than 7 mm indicates severe regurgitation (49,50).

FIGURE 51.6 Measurement of proximal diameter of a severe mitral regurgitant jet (*horizontal arrows*). The proximal diameter is marked by the oblique arrows. Apical four-chamber view. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

2. The proximal convergence zone method. Although cutoff values have not been extensively validated, maximal regurgitant flow rates greater than 150 mL per second and effective regurgitant orifice areas greater than 0.3 cm^2 indicate grade III or IV mitral regurgitation (21,51). Because of enhanced image quality, this approach works particularly well with transesophageal echocardiography (eFig. 51.2.5).

A number of additional signs are helpful in grading mitral regurgitation. Severe mitral regurgitation creates a continuous wave signal that has a *shoulder* in late systole instead of the symmetric, parabolic appearance of less severe mitral regurgitation. This is due to rapidly increasing end systolic pressure in the left atrium in this circumstance. Pulmonary venous flow recordings show a reduction in the systolic portion of pulmonary venous inflow into the left atrium. In severe mitral regurgitation, the systolic portion of pulmonary venous flow may even be reversed and merge with the end diastolic retrograde flow wave, showing blood being pushed back into the pulmonary vein by the inflow of blood from the left ventricle into the atrium (Fig. 51.7). In eccentric jets, it may be useful to sample both upper pulmonary veins to detect flow reversal (52). Although this sign is quite sensitive, it is not very specific, because impaired systolic pulmonary venous inflow also occurs in atrial fibrillation or impaired systolic function.

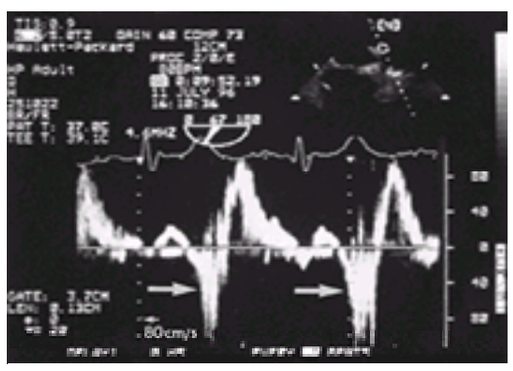


FIGURE 51.7 Pulmonary venous flow in the presence of severe mitral regurgitation. Registration by transesophageal pulsed Doppler from the left upper pulmonary vein. There is only a small positive systolic wave, followed by reversed systolic flow (*arrows*). Diastolic atrial inflow velocities are increased.

Aortic Valve

For the assessment of a stenotic aortic valve, three parameters should be obtained in the best possible quality: the transvalvular continuous wave Doppler, the subaortic pulsed Doppler, and the left ventricular outflow tract diameter (Fig. 51.8). Continuous wave Doppler signals should be recorded at least from two, preferably from three or more, windows (apical, subcostal, suprasternal, right parasternal), to ensure that the maximal velocities have been detected. Mean and maximal pressure gradients are calculated from the continuous wave tracing. In atrial fibrillation, several beats should be analyzed. A slowed early systolic rise in flow velocities across the aortic valve, resulting in an approximately symmetric upslope and downslope, indicates severe stenosis, analogous to the clinical finding of pulsus tardus in this condition (Fig. 51.9). Effective orifice area has traditionally been assumed to be independent of cardiac output and heart rate and thus to be particularly valuable in impaired left ventricular function, when a low-pressure gradient can reflect mild obstruction, low stroke volume, or both. Subaortic pulsed wave tracings and the left ventricular outflow tract diameter (D) are necessary to calculate the effective orifice area (A_{EFF}) by the continuity equation. It is valid to use the maximal velocities from continuous wave Doppler (v_{MAX}) and subaortic pulsed wave Doppler (v_{LVOT}) instead of the time velocity integrals: $A_{EFF} = 1/4p \times D^2 \times v_{LVOT}/v_{MAX}$. However, it has been reported that in some patients with aortic stenosis, orifice area is flow dependent and stretches with increasing cardiac output between 10% and 20% (23,24).

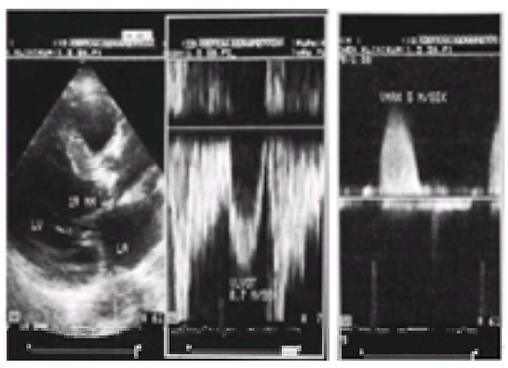


FIGURE 51.8 Aortic valve area calculation by the continuity principle (*top left*). Measurement of left ventricular outflow tract diameter in a parasternal long-axis view (19 mm, corresponding to an area of 2.8 cm^2). **Middle:** Pulsed wave Doppler recording in the left ventricular outflow tract. **Right:** Continuous wave Doppler recording of transstenotic flow velocities. By the continuity equation, an aortic valve area of 0.4 cm^2 was calculated.

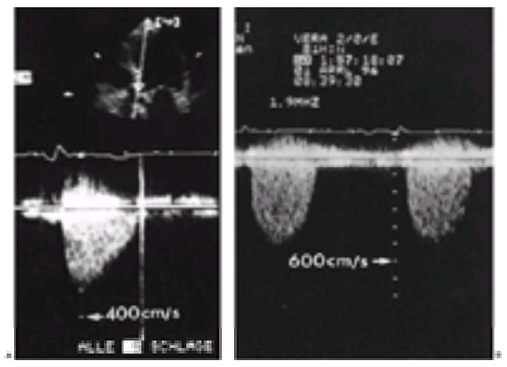
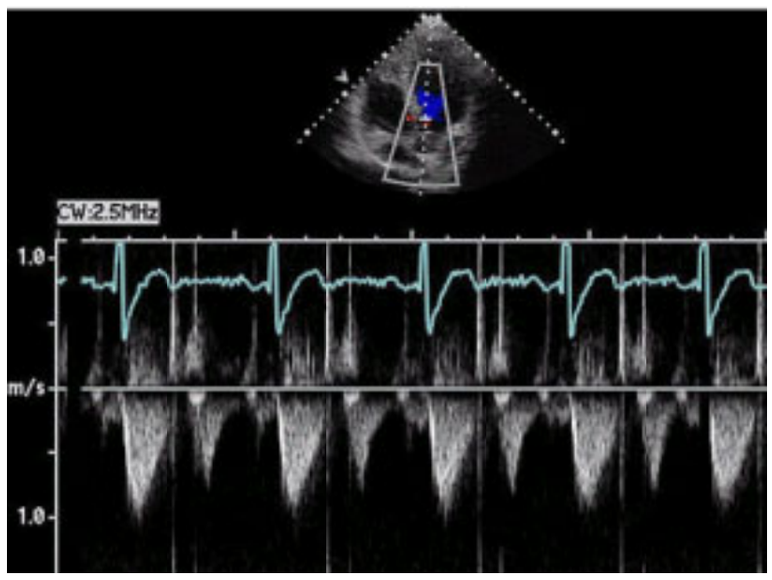
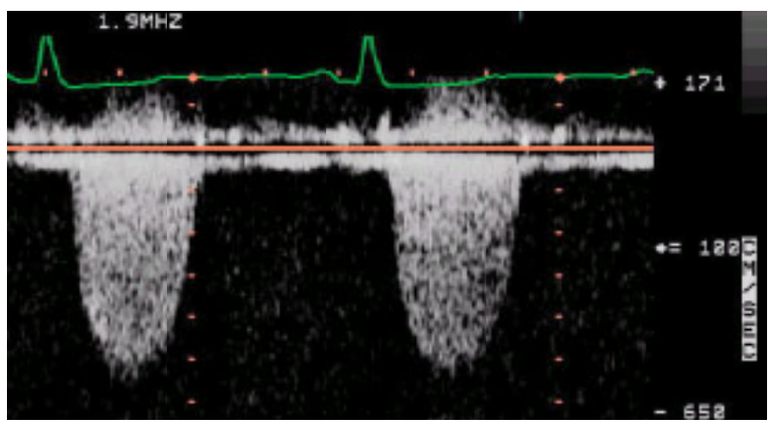


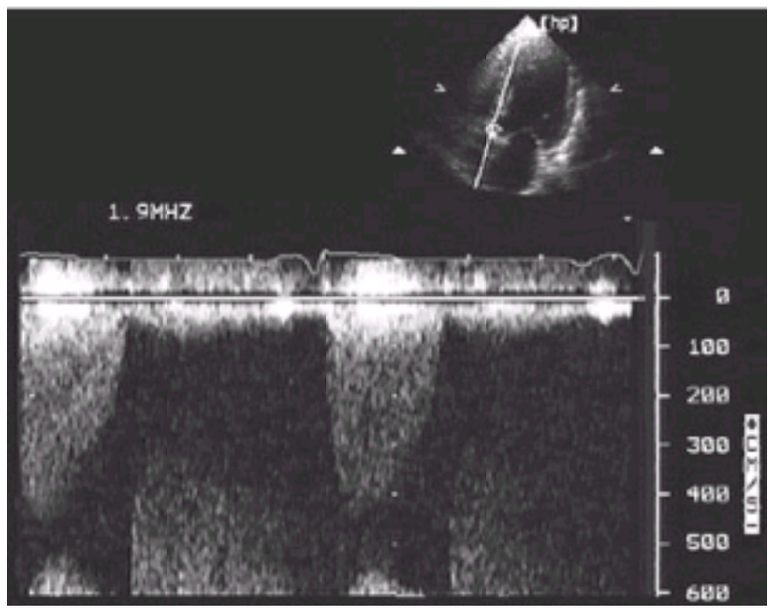
FIGURE 51.9 A: Moderate aortic stenosis with a triangular shape and steep upslope, and **(B)** severe aortic stenosis, with a parabolic shape and a slow upslope.



Normal continuous wave Doppler through the aortic valve by transthoracic echo. Note that the maximal velocity is approximately 1 m per second (capillary wedge pressure gradient = 4 mm Hg).



Continuous wave Doppler through a stenotic aortic valve. The maximal velocity is 5.5 m per second, consistent with a peak pressure gradient of 121 mm Hg.



Apical continuous-wave Doppler spectrum of aortic valve disease. Note high forward velocities in systole (V_{max} 4.5 m per second) and early peak of aortic stenosis. At the bottom, wrapped-around diastolic flow velocities from aortic regurgitation are seen.

If Doppler-derived parameters of aortic stenosis are in conflict with other clinical data, the following sources of error should be checked:

a. Doppler gradient too high: misreading the mitral regurgitation signal for aortic stenosis (check timing of velocities); neglect of high proximal velocities, as in aortic regurgitation or high cardiac output; pressure recovery; atrial fibrillation with high beat-to-beat variation in gradient.
b. Pressure recovery may have a clinically meaningful effect in native aortic stenosis if the ascending aorta has a diameter under 3 cm, leading to overestimation of peak and mean gradients by Doppler as compared with invasive hemodynamics. Formulae for estimating the amount of pressure recovery have been published (53,54).
c. Doppler gradient too low: missing the maximal signal (use all available windows).
d. The evaluation of patients with low cardiac output (e.g., due to impaired left ventricular function) and valvular stenosis, especially aortic stenosis, with a low transvalvular gradient is difficult. In these patients, relatively low gradients may be caused by low stroke volume, mild stenosis, or both. Augmentation of cardiac output by 10 to 20 µg per kg per minute of intravenous dobutamine may unmask a *stretch reserve* of the stenotic orifice area in some patients with mitral or aortic stenosis. If the stenosis gives in to dobutamine stress, it can be assumed to be less severe than apparent at baseline (55).

Aortic regurgitation is the most difficult valvular lesion to evaluate. The best parameter to assess severity is the size of the regurgitant jet by color Doppler in the left ventricular outflow tract (Fig. 51.10). Both the height in parasternal long-axis views or the area in short-axis views are used and normalized to the diameter or area of the left ventricular outflow tract, respectively. Twenty percent and 60% of the left ventricular outflow tract area (25% and 65% of the left ventricular outflow tract diameter) are the cutoff values for mild, moderate, and severe regurgitation (56). Another useful parameter is the pressure half-time of the continuous wave Doppler of regurgitant flow (57) (eFig. 51.10.1). This is sometimes difficult to record and may necessitate an orientation of the transducer different from the optimal orientation for recording forward transaortic flow velocity. The shorter the pressure half-time and the more rapidly pressure equalizes between the ascending aorta and the left ventricle, the more severe the aortic regurgitation. Values less than 300 ms indicate severe aortic regurgitation.

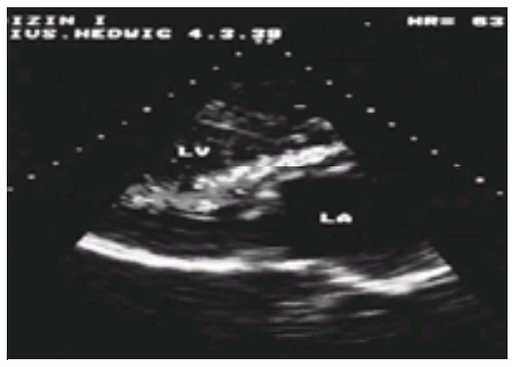
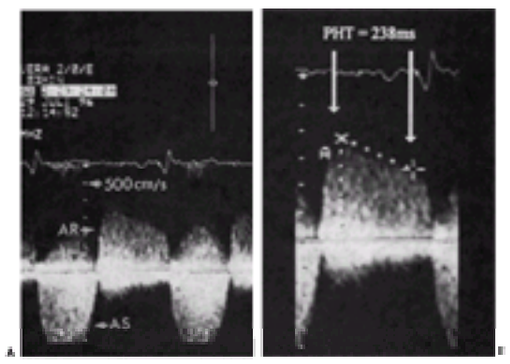
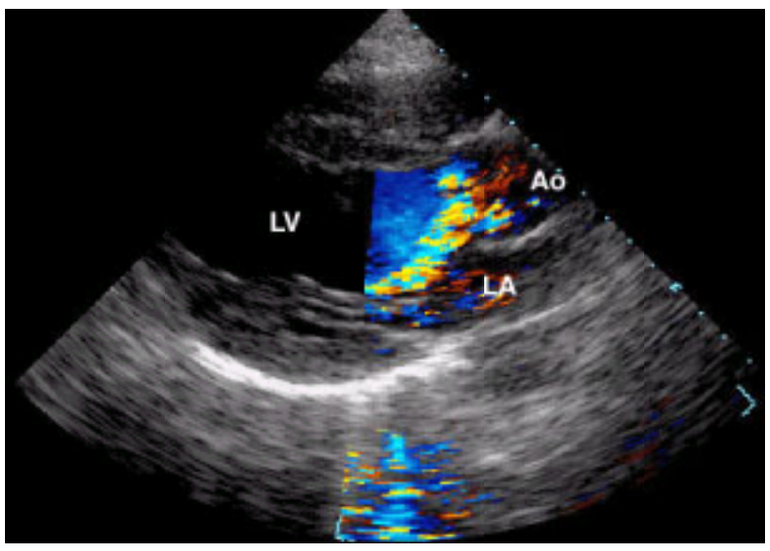


FIGURE 51.10 Aortic regurgitation. Color Doppler flow mapping in a parasternal long-axis view. The regurgitant jet is depicted in the left ventricular outflow tract and left ventricle, hugging the anterior mitral leaflet. LA, left atrium; LV, left ventricle.



***e*FIGURE 51.10.1 A:** Continuous wave Doppler of combined severe aortic stenosis (AS) and regurgitation (AR). **B:** Calculation of the pressure half-time (PHT) of the aortic regurgitation signal. Pressure half-time shortens with increasing severity of aortic regurgitation. The value of 238 ms indicates severe regurgitation.



Parasternal long-axis view (transthoracic echo) with color Doppler demonstrating the posteriorly directed aortic insufficiency caused by prolapse of the anterior leaflet of a bicuspid aortic valve. Note that the jet hits the anterior mitral leaflet.

VIDEO

Video 51.11 Parasternal long-axis view (transthoracic echo) of a bicuspid aortic valve with prolapse of the anterior leaflet causing posteriorly directed aortic insufficiency. The aortic insufficiency hits the anterior mitral leaflet, causing deformation of this leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 51.12 Intraoperative transesophageal echo (120-degree view) with color Doppler demonstrating aortic insufficiency due to aortic dilatation (sinuses measure 5.0 cm) causing failure of leaflet coaptation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 51.13 A magnified 103-degree transesophageal long axis view **(A)** of a ruptured sinus of Valsalva aneurysm of the right sinus of Valsalva. Note the remnant thinned, aneurysmal wall of the sinus bowing into the right ventricle (towards the bottom of the screen). Color Doppler interrogation of the aortic valve with sinus of Valsalva in a transesophageal long-axis view **(B)**. Note there is moderate anteriorly directed aortic insufficiency at the top of the screen, and the aortic to right ventricular shunt through the ruptured sinus of Valsalva aneurysm is seen at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 51.14 A magnified 103-degree transesophageal long axis view **(A)** of a ruptured sinus of Valsalva aneurysm of the right sinus of Valsalva. Note the remnant thinned, aneurysmal wall of the sinus bowing into the right ventricle (towards the bottom of the screen). Color Doppler interrogation of the aortic valve with sinus of Valsalva in a transesophageal long-axis view **(B)**. Note there is moderate anteriorly directed aortic insufficiency at the top of the screen, and the aortic to right ventricular shunt through the ruptured sinus of Valsalva aneurysm is seen at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

However, pressure half-time does not exclusively reflect severity of regurgitation (the size of the leak, or effective regurgitant orifice), but also depends on left ventricular diastolic compliance and on systemic arterial resistance. For example, if afterload is pharmacologically lowered, pressure half-time can be expected to decrease (due to more forward run-off of blood in diastole), erroneously indicating an increase in regurgitation, when the opposite may be the case (58,59).

Additionally, the presence of a holodiastolic flow signal on pulsed Doppler recordings from the ascending, descending, or (from the subcostal window) abdominal aorta (or a large systemic artery) can be taken as a sign of at least moderate aortic regurgitation (Fig. 51.11).

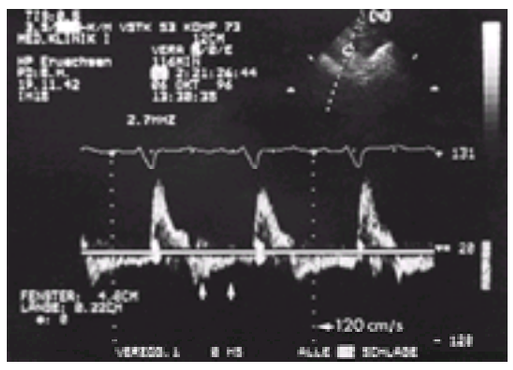


FIGURE 51.11 Holodiastolic flow reversal (*arrows*) in the descending aorta in severe aortic regurgitation. Pulsed Doppler recording from the suprasternal notch.

Tricuspid Valve

The tricuspid valve is examined in the apical four-chamber view, in a basal parasternal short-axis view, or in the (parasternal) right ventricular inflow view. The mean pressure gradient is calculated from continuous wave or pulsed wave Doppler recordings in analogy to transmitral gradients. The pressure half-time may be used for serial measurements, but its use to calculate orifice areas has not been validated in the tricuspid valve. Tricuspid regurgitation is best detected by color Doppler in the apical (or subcostal) four-chamber view (Fig. 51.12). By continuous wave Doppler, it produces a systolic regurgitant velocity spectrum of parabolic shape, similar to mitral regurgitation. As in mitral regurgitation, in severe tricuspid insufficiency there is a rapid late systolic decay of regurgitant velocities because of high end systolic right atrial pressure. The maximal regurgitant velocity is important to diagnose the presence of pulmonary hypertension.

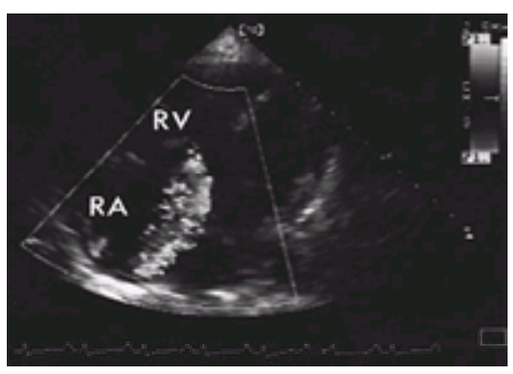
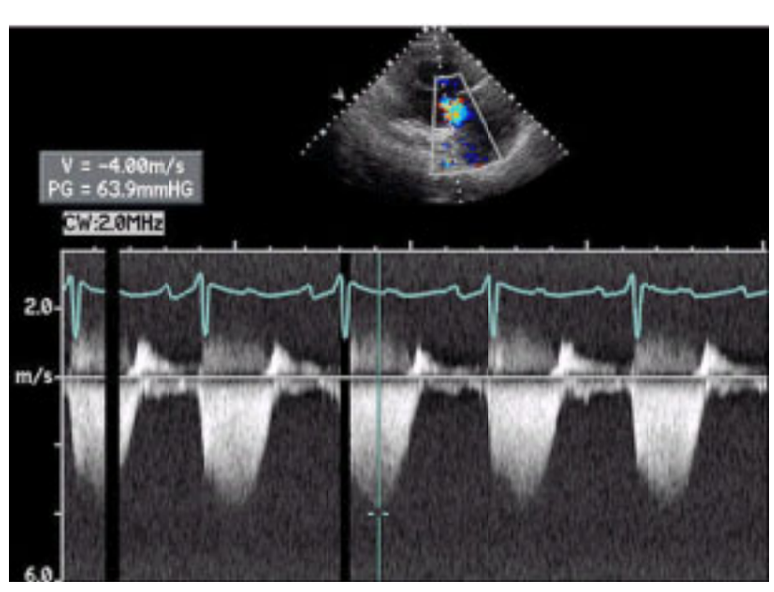


FIGURE 51.12 Moderate tricuspid regurgitation by color Doppler (apical four-chamber view). RA, right atrium; RV, right ventricle.



Continuous wave Doppler trace through the tricuspid valve of a patient with pulmonary hypertension. The maximal jet velocity of 4 m per second corresponds to a pressure gradient of 64 mm Hg or a PA pressure of approximately 80 mm Hg.

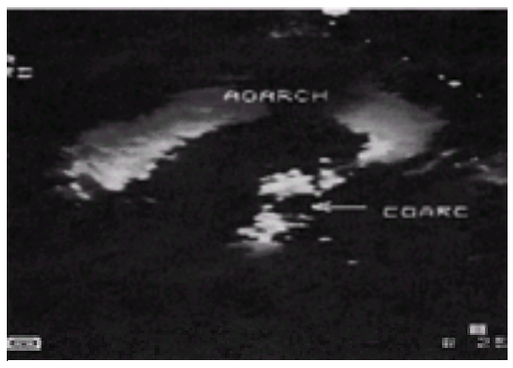
Pulmonary Valve

The pulmonary valve is best examined in the parasternal basal short-axis view or alternatively in a subcostal short-axis view. Minimal pulmonary regurgitation is

frequent in individuals without clinical evidence of cardiac disease. The color Doppler representation of an eccentric pulmonary regurgitant jet may be misread as a membranous ventricular septal defect signal. Pulmonary stenosis is evaluated reliably by the mean transvalvular gradient from continuous wave Doppler.

Aortic Pathology

From the suprasternal window, flow velocity in the ascending and descending aorta can be sampled. Aortic coarctation can be visualized by turbulence, and the gradient measured directly (eFig. 51.12.1). However, although the simplified Bernoulli equation in general is well applicable, it may underestimate the true pressure drop in long, tunnel-like obstructions, or overestimate the pressure drop in the presence of high proximal velocities or downstream pressure recovery. In aortic dissection, transesophageal evaluation is the procedure of choice. Color Doppler flow in the true lumen is usually brighter than in the false lumen, where it may be absent if stasis and thrombosis have ensued. Thus, color flow mapping should be used to confirm the existence of a true and a false lumen. Entry and reentry tears of the intima may also be detected (Fig. 51.13).



***e*FIGURE 51.12.1** Aortic coarctation. Color Doppler flow mapping from the suprasternal notch. On the left side, the ascending aorta is seen in red; on the right side, the descending aorta is in blue. At the stenotic segment (COARC), turbulent flow is present. AOARCH, aortic arch.

FIGURE 51.13 Aortic dissection (DeBakey type I/Stanford type A). Transesophageal image of the dilated ascending aorta (5 cm). An intimal flap is seen separating a false lumen (FL) from the true lumen (TL). A small entry jet is seen by color Doppler (ENTRY). LA, left atrium.

Video 51.15 Color Doppler interrogation of the coarctation demonstrating the high-velocity, turbulent flow across the focal narrowing in the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

PROSTHETIC HEART VALVES

Obstruction

Pulsed and continuous wave measurement of forward flow velocities across valvular prostheses is usually well obtainable even if 2-D image quality is impaired by prosthetic artifacts. Opening and closing clicks are seen on the spectral Doppler display as narrow, bright vertical lines (Fig. 51.14). Mean gradients should be calculated in the same way as described for native stenotic valves (60). Contrary to these, however, there is some degree of obstruction inherent in all prosthetic valves. The limits of normalcy are difficult to define mainly for two reasons: the influence of prosthesis design, and the match or mismatch of the implanted valve and the implantation site. The different prosthesis types and sizes involve different degrees of obstruction (e.g., the caged-ball Starr-Edwards prosthesis is much more obstructive than the St. Jude Medical valve). Normal values for transprosthetic flow velocities or gradients have been published, but because of the additional dependency on cardiac output and heart rate, these values offer only an orientation (61). Furthermore, especially the bileaflet valves by their design create high local gradients and pressure recovery downstream (62,63 and 64).

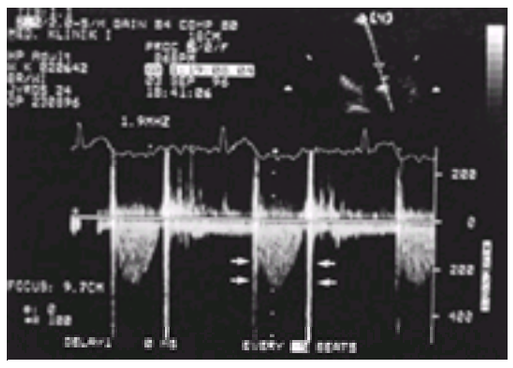
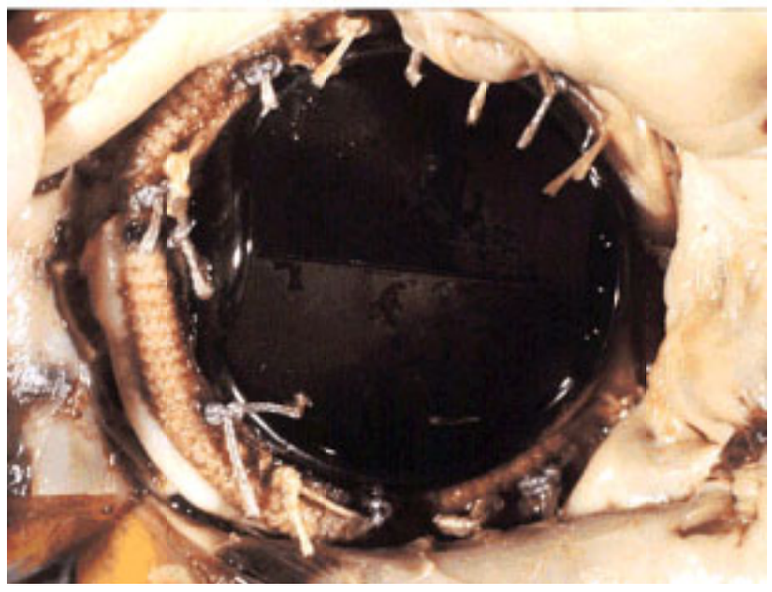
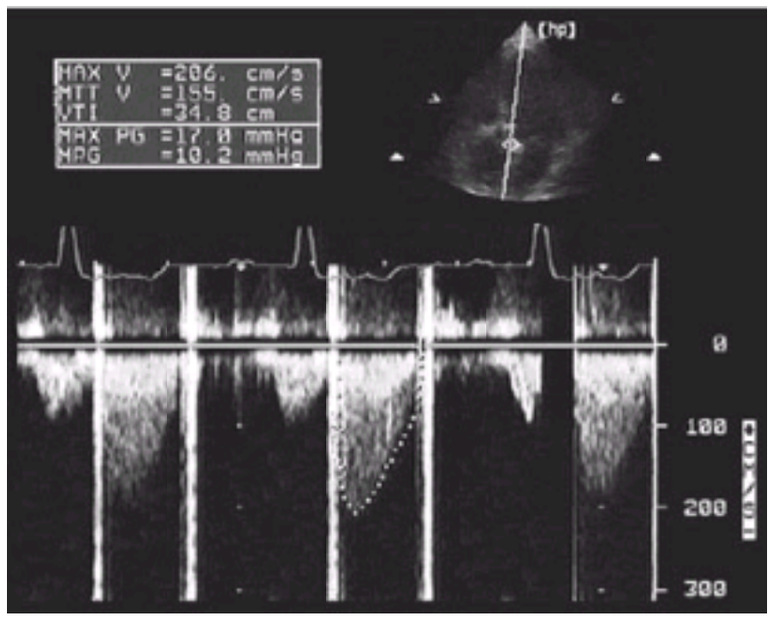


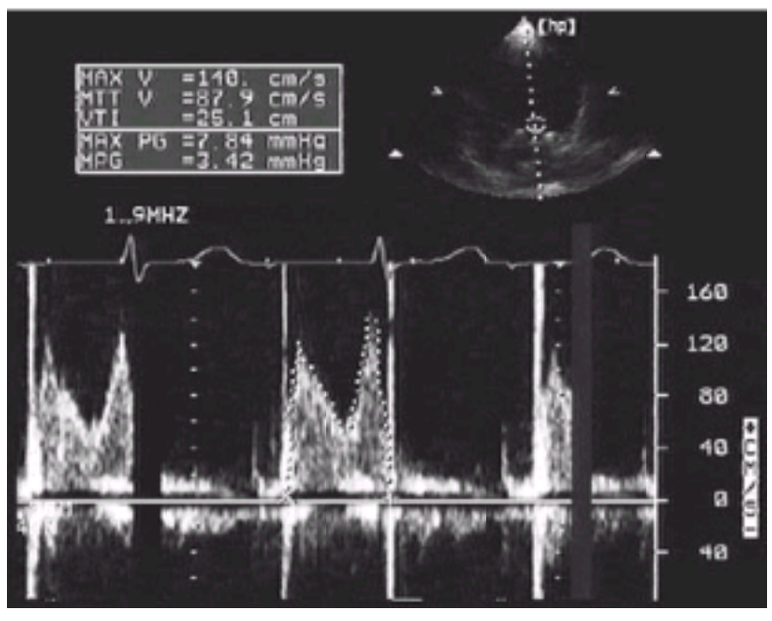
FIGURE 51.14 Aortic prosthetic forward flow in a normal mechanical bileaflet prosthesis (JYROS), with clicks (*arrows*).



Normal St. Jude valve in the mitral position.



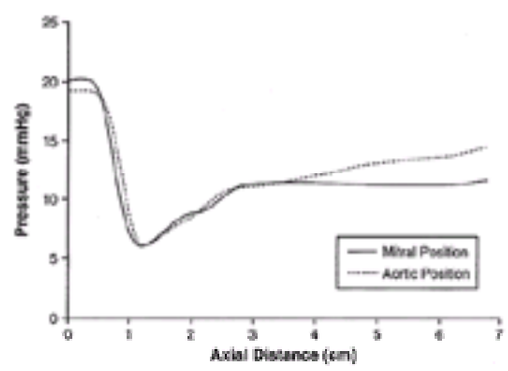
Continuous wave Doppler spectrum of mechanical prosthesis in the aortic position. Note opening and closing clicks and calculation of mean and maximal pressure gradients.



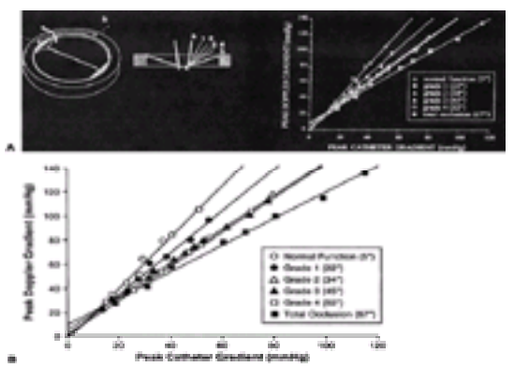
Apical pulsed wave spectral Doppler recording of a St. Jude medical bileaflet prosthesis in the mitral position. Note opening and closing clicks and calculation of mean gradient.

Video 51.16 Beall mitral valve prosthesis with normal antegrade flow seen with color Doppler by transesophageal echo. Note the typical antegrade flow around the disc with marked shadowing beyond the disc. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In these valves, the maximal velocity and pressure drop across the central orifice is higher than across the side orifices. Approximately one-third of the central pressure drop is recovered regardless of the position of the valve; additionally, a variable amount of further pressure recovery occurs depending on the geometry of the solid boundaries downstream, leading to the recovery of up to 58% of the maximal pressure drop across the central orifice. The maximal velocities by continuous wave Doppler therefore can lead to a calculated pressure drop higher than the net pressure drop between the left ventricle and the ascending aorta a few centimeters downstream from the prostheses (eFig. 51.14.1). Pressure recovery is particularly troublesome in the aortic position, especially if the aorta is small in diameter. Furthermore, it has been shown *in vitro* that in partial obstruction of the prosthesis, pressure recovery diminishes, because energy is lost in turbulent eddies and is not available any more for recovery downstream (65) (eFig. 51.14.2). Therefore, for bileaflet prostheses in the aortic position, a considerable gray zone between clearly normal and clearly pathologic transvalvular gradients exists, which necessitates imaging information on leaflet mobility (from 2-D echo or fluoroscopy) to exclude prosthetic dysfunction.



***e*FIGURE 51.14.1** *In vitro* pressure recordings obtained by catheter pullback through the central orifices of St. Jude Medical bileaflet valve prostheses in an experimental setup mimicking the mitral (*solid line*) and aortic (*dotted line*) position. There is pressure recovery in the proximal vicinity of the central orifice (6 mm Hg between cm 1 and 3); thereafter, there is additional pressure recovery in the *aortic*, but not *mitral*, setup (3 mm Hg between cm 4 and 7). (From Vandervoort PM, Greenberg NL, Powell KA, et al. Pressure recovery in bileaflet heart valve prostheses. Localized high velocities and gradients in central and side orifices with implications for Doppler-catheter gradient relation in aortic and mitral position. *Circulation* 1995;92:3474–3472, with permission.)



***e*FIGURE 51.14.2** *In vitro* effect of partial obstruction in bileaflet (CarboMedics) prosthetic valves. **A:** Left, experimental setup where the left leaflet opens freely and the right leaflet is kept in positions between open (position a) through positions 1 to 4 to complete occlusion (b) by an adjustable stop pin. The plot on the right shows corresponding peak pressure gradient measurements by Doppler and catheter. Catheters were positioned to measure "net" pressure gradients after pressure recovery had occurred, while Doppler measured peak local gradient before pressure recovery. **B:** The plot shows that (a) during normal function, Doppler peak gradients are twice as high as catheter peak gradients in this experimental setting, and (b) with increasing "malfunction" (partial occlusion), Doppler and catheter gradients approximate each other, because pressure recovery diminishes due to altered orifice geometry. (From Baumgartner H, Schima H, Kühn P. Effect of prosthetic valve malfunction on the Doppler-catheter gradient relation for bileaflet aortic valve prostheses. *Circulation* 1993;87:1320–1327, with permission.)

Mismatch obstruction results from the implantation of a prosthesis that is too small for the site and patient. This is mainly a problem in aortic valve replacement. For example, the effective orifice areas of ring size number 21 and smaller prostheses would be considered mild to moderate aortic stenosis in a native valve (see following discussion). This type of obstruction must be differentiated from new prosthetic obstruction due to thrombosis or pannus by comparison with earlier studies, by transesophageal echocardiography, or by fluoroscopy.

Note that pressure recovery and mismatch mainly create problems in the interpretation of velocities across *aortic prostheses*.

Other parameters of prosthetic obstruction have been proposed. The simplest one is *velocity index*, which is based on the continuity concept and is defined as the ratio of maximal outflow and maximal transprosthetic velocity. It is theoretically independent of cardiac output and obviates the need to measure left ventricular outflow tract diameter. Values less than 0.25 are considered pathologic. Continuity areas can also be calculated. Because these are effective areas, they are considerably smaller than areas predicted by sewing ring size. In 46 patients with a variety of small (less than 21 mm) aortic prostheses (mechanical or bioprostheses), effective areas ranged from 0.84 to 1.54 cm^2, mean gradients from 7 to 31 mm Hg, and the velocity index from 0.28 to 0.66 (66). In a survey of 335 stable postoperative patients with mechanical aortic valve replacement and without clinical evidence of prosthetic dysfunction including fluoroscopy, 11 were found with a maximal velocity over 3.5 m per second (67). The average mean gradient of these 11 patients was 48 ± 12 mm Hg. The majority were St. Jude Medical valves, and all valves were of ring size 19 to 23. Seven of these patients were studied invasively, yielding significantly lower gradients and no evidence of dysfunction. The problem of pressure recovery in bileaflet prostheses is not circumvented by calculating the continuity area. If maximal velocity is elevated due to an only locally existing pressure gradient, this results in a particularly small area calculated by the continuity equation that inadequately reflects the *net obstruction* between left ventricle and ascending aorta. For example, for intact St. Jude Medical number 21 aortic prostheses, effective orifice areas of 1.25 ± 0.21 cm^2 have been calculated in clinical studies (68), when the inner sewing ring (1.7 cm) diameter would predict a geometric orifice area of 2.3 cm^2. The advantage of calculating prosthetic resistance over the use of gradients and orifice areas has not convincingly been shown.

In severely stenotic tricuspid prostheses, systolic antegrade blood flow with accentuation in inspiration has been described (69).

For the reasons cited, it is important to document the baseline velocities or gradients of valvular prostheses postoperatively for later comparison. In bioprostheses, because of the well-described degenerative changes, an increase in obstruction with time may be expected.

Regurgitation

All mechanical prostheses, except for the caged-ball Starr-Edwards valve, exhibit some amount of in-built transvalvular leakage, which is intended to prevent the formation of microthrombi at the hinge points and to preclude sticking of the occluder in the closed position. Depending on the prosthesis type, typical spatial orientation patterns of the regurgitant jets are present (70) (Fig. 51.15). Bioprostheses, too, almost invariably present some transvalvular regurgitation. Wear-and-tear lesions in bioprostheses may lead to unpredictable, sudden increases in the severity of regurgitation. In addition to transvalvular regurgitation, paravalvular leakage is frequent in prosthetic valves (Fig. 51.16). Some of these leaks close spontaneously postoperatively; others may arise during follow-up as a result of suture failure or endocarditic tissue destruction. Transesophageal echocardiography is usually better suited than transthoracic imaging to characterize and classify prosthetic regurgitation (71).

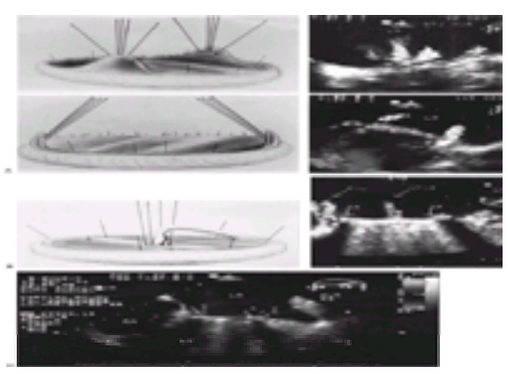


FIGURE 51.15 Normal regurgitant flow patterns of mechanical valves. **A–C:** St. Jude Medical bileaflet prosthesis. Normal regurgitation mainly occurs at the hinge points of the leaflets. Depending on the view of the valve, typical diverging and converging jet patterns occur. **A:** Schematic drawing. **B,C:** Flow imaging by transesophageal color Doppler. **D,E:** Medtronic-Hall tilting-disc prosthesis. Normal regurgitation mainly occurs across the central orifice. **D:** Schematic drawing. **E:** In the closed position, a normal central transvalvular regurgitation (NTVR) and a medial small paravalvular leak (PVL) are seen. SR, sewing ring. **F:** Björk-Shiley tilting-disc prosthesis in the mitral position with small peripheral normal regurgitant jets occurring between occluder and valve ring. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Flachskampf FA, Guerrero JL, O'Shea JP, et al. Patterns of normal transvalvular regurgitation in mechanical valve prostheses. *J Am Coll Cardiol* 1991;18:1493–1498, with permission.)

FIGURE 51.16 Paravalvular leakage by color Doppler. Paravalvular leakage of aortic St. Jude Medical prosthesis (AOV) in a short-axis (*left*) and long-axis (*right*) transesophageal view. The leakage cross section and the paravalvular path of the leakage are well seen. AOA, ascending aorta; LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract. (From Flachskampf FA, Hoffmann R, Verlande M, et al. Initial experience with a multiplane transesophageal echo-transducer: assessment of diagnostic potential. *Eur Heart J* 1992;13:1201–1206, with permission.)

VIDEO

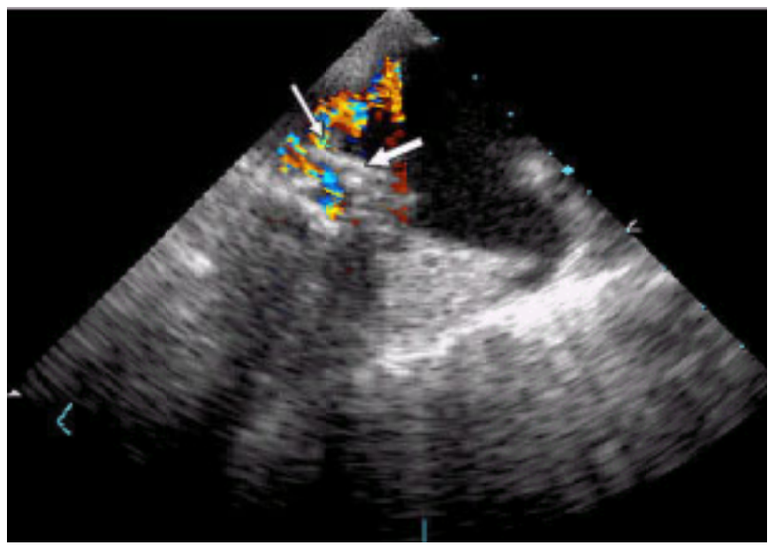
Video 51.17 Physiologic regurgitation of a St. Jude's mechanical valve in the mitral position. Transesophageal echocardiography demonstrates two converging regurgitant jets in the left atrium (LA). AO, aorta; LV, left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 51.18 Structural valve degeneration of a Carpentier-Edwards bioprosthesis in the mitral position demonstrated in a transesophageal echocardiogram (TEE). Color Doppler demonstrates intravalvular regurgitation. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 51.19 This is a long-axis 134-degree transesophageal view of a patient with prosthetic valve endocarditis of the aortic valve. Note the very large mobile mass or vegetation on the prosthesis accompanied by prosthetic stenosis and moderate insufficiency. The peak and mean pressure gradients across this valve were 90/27 mm Hg, and there was also a paravalvular abscess. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

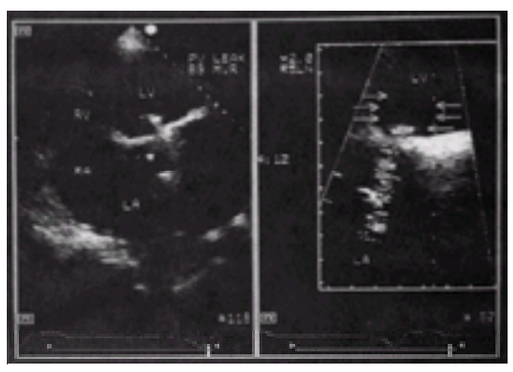


Intraoperative transesophageal echo in a patient with a Carpentier-Edwards prosthesis in the mitral position with infectious endocarditis. There is a paravalvular jet of mitral regurgitation (*thin arrow*), and the mitral prosthesis (*thick arrow*) is rocking. (The left atrium is towards the upper right of the screen, and the left ventricle is to the lower left.)

VIDEO

Video 51.20 Endocarditis involving a Carpentier-Edwards bioprosthesis in the aortic position demonstrated by transesophageal echocardiography. The arrows indicate a large vegetation and a paravalvular abscess, respectively. LA, left atrium; RA, right atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In the presence of mitral valve replacement, in particular if a mechanical prosthesis is present, the left atrium is obscured by artifacts and shadowing; therefore, special attention has to be paid to a parasternal or subcostal view, and transesophageal echocardiography should be considered. The assessment of severity follows the principles outlined for native mitral regurgitation. The occurrence of a clearly visible proximal convergence zone on the ventricular side of a mitral prosthesis indicates substantial regurgitation even if the atrium itself is not visualized; severe regurgitation by angiography corresponded to a maximal acceleration zone averaging 1 cm (2,72) (eFig. 51.16.1).



***e*FIGURE 51.16.1** Proximal convergence zone in a paravalvular leak of a Björk-Shiley mitral prosthesis. The regurgitant jet in the left atrium (*right*) is obscured by prosthetic artifacts. However, the proximal convergence zone (*arrows*) is clearly visible on the ventricular side. Modified apical four-chamber view. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Although aortic regurgitation is more easily identifiable, aortic prostheses are less well examined even by transesophageal echo than mitral prostheses. The principles outlined for the assessment of native aortic regurgitation apply.

CONGENITAL HEART DISEASE

Stenotic and Regurgitant Lesions

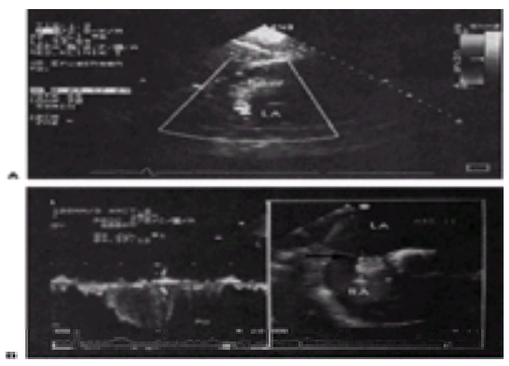
Congenital valvular lesions are evaluated in the same way as acquired valvular disease. It should be noted, however, that in serial or tunnel-like obstructions, the simplified Bernoulli equation may not apply. In general, however, the recorded flow velocities give a good idea of how significant an obstruction is and are clinically accepted by pediatric cardiologists to grade stenotic lesions.

VIDEO

Video 51.21 Color Doppler in the apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect by color flow and the overriding aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Shunt Flow

Atrial and ventricular septal defects mostly can be directly detected by color Doppler displaying the pathologic flow (*e*Fig. 51.16.2). Atrial septal defects are best examined from the subcostal window. Sinus venosus defects, however, may be overlooked and in doubtful cases may necessitate transesophageal echocardiography. Pulsed Doppler recordings of left-to-right shunt usually show a biphasic, mid-systolic to mid-diastolic, and late diastolic flow from the left to the right atrium, with a short reversal of direction (right to left) in early systole. Highest left-to-right velocities occur in late systole and rarely exceed 1 m per second. Atrial left-to-right shunt decreases in inspiration and increases in expiration.



***e*FIGURE 51.16.2** Atrial septal defect, secundum type. **A:** Subcostal color Doppler. **B:** Transesophageal color and pulsed Doppler recording of atrial septal defect (*arrow*). Note left-to-right flow velocities (downward in the transesophageal image orientation) in late systole and early diastole, followed by a smaller late diastolic wave. LA, left atrium; RA, right atrium.

VIDEO

Video 51.22 Subcostal view of a primum atrial septal defect with color Doppler showing the left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

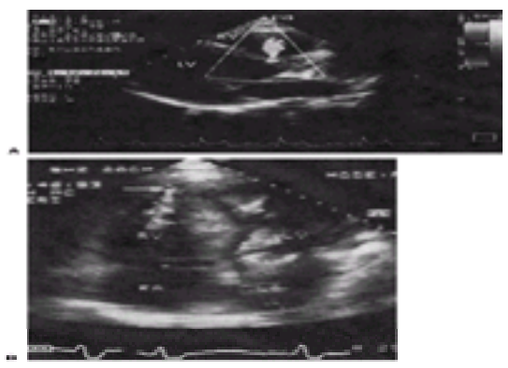
VIDEO

Video 51.23 Transesophageal echo with color Doppler flow demonstrating a secundum atrial septal defect with left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

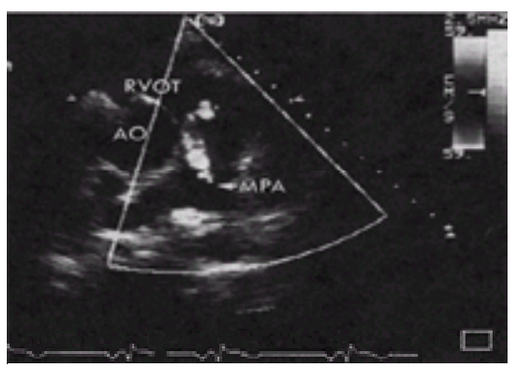
VIDEO

Video 51.24 Parasternal short-axis view (magnified) of an ostium primum atrial septal defect. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

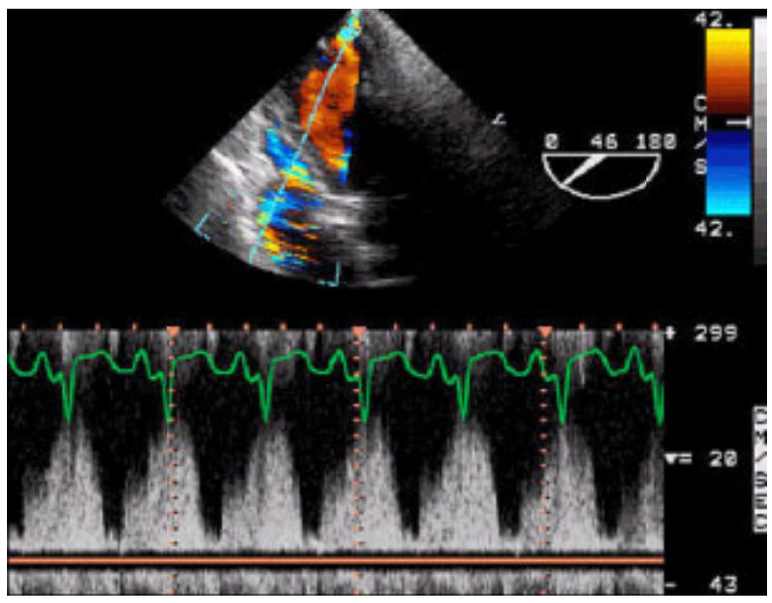
Ventricular septal defects are best detected by color Doppler; membranous defects usually are identified in parasternal views, and muscular defects either in parasternal views or in the apical or subcostal four-chamber view (*e*Fig. 51.16.3). Continuous wave Doppler tracings showing high systolic flow velocity toward the right ventricle allow one to calculate the maximal systolic pressure difference between left and right ventricle. This value should roughly match the difference between systemic arterial pressure and right ventricular systolic pressure calculated from tricuspid regurgitation. A patent ductus arteriosus is best visualized in suprasternal, parasternal, or subcostal views displaying a long axis of the pulmonary artery (*e*Fig. 51.16.4). Continuous wave Doppler reveals the shunt pattern, which in left-to-right shunt is systolic-diastolic with a late systolic peak. By color Doppler, a diastolic flow convergence region in the proximal descending aorta may be seen. In right-to-left shunts, maximal velocities are recorded at the aortic end of the duct, and retrograde flow in the descending aorta may be seen.



***e*FIGURE 51.16.3** Ventricular septal defect. **A:** Parasternal long-axis view with color Doppler depiction of a small congenital ventricular septal defect immediately below the aortic valve. Note the proximal convergence zone on the left ventricular side. **B:** Ventricular septal defect complicating anterior myocardial infarction. Color Doppler in the apical four-chamber view shows site of septal rupture in the apex (*arrow*) with a turbulent jet in the right ventricle. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.



***e*FIGURE 51.16.4** Color Doppler image of patent ductus arteriosus. Modified basal parasternal short-axis view. A jet coursing from the dilated main pulmonary artery (MPA) toward the pulmonary valve is seen. AO, ascending aorta; RVOT, right ventricular outflow tract.



Doppler recording of flow through an ischemic ventricular septal defect before surgical repair.

Video 51.25 Color Doppler view of a post infarct ventricular septal defect in the inferior septum. Note the color flow thru the large defect. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

To calculate the left-to-right shunt ratio, the ratio of cardiac output (by multiplying the time velocity integral by the orifice area of the valve) at the aortic and the pulmonary valve level is validated (32). The estimation of maximal systolic pulmonary pressure from maximal tricuspid regurgitant velocity is described in the section Right-Sided Heart Function and Pulmonary Hypertension, later in this chapter.

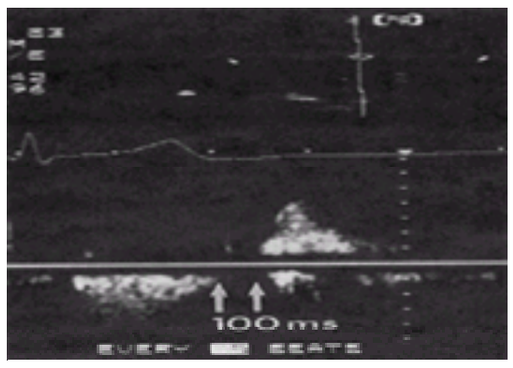
EVALUATION OF CARDIAC FUNCTION

Systolic Left Ventricular Function

The most straightforward Doppler parameter of systolic left ventricular function is cardiac output. In the presence of mitral regurgitation, the rate of increase of regurgitant velocities can be used to calculate the rise of the pressure gradient between the left ventricle and the left atrium throughout systole. This allows one to obtain an estimate of the rise of pressure in the left ventricle (dP/dT). However, since the pressure in the left atrium is not known, these values are an approximation. In practice, the time interval between the points where regurgitant velocity reaches 1 and 3 m per second is measured and the corresponding pressure drops (4 and 36 mm Hg) are used to calculate early systolic pressure rise as 32 mm Hg/D*t* (73). Note, however, that this is not necessarily *peak* dP/dT. Similarly, left ventricular pressure decline in late systole may be estimated, with the same caveat.

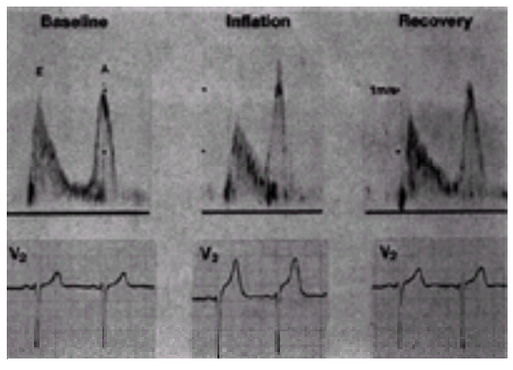
Diastolic Left Ventricular Function

Diastolic left ventricular function is in itself heterogeneous, comprising active (relaxation) and passive (chamber stiffness) characteristics of the left ventricle. It is characterized in classic hemodynamics by the diastolic time course of pressure and volume. Several parameters obtainable by Doppler have been proposed to evaluate left ventricular diastolic function (74,75). The most time honored is isovolumic relaxation time (the time from aortic valve closure to mitral valve opening; *e*Fig. 51.16.5), which depends on the velocity of myocardial relaxation (classically characterized by the time constant t), the end systolic pressure level of the aorta, and the early diastolic pressure level of the left atrium. Positioning the continuous wave Doppler beam in an apical long-axis view between left ventricular inflow and outflow, the end of outflow and the onset of inflow can be read from the spectral display.

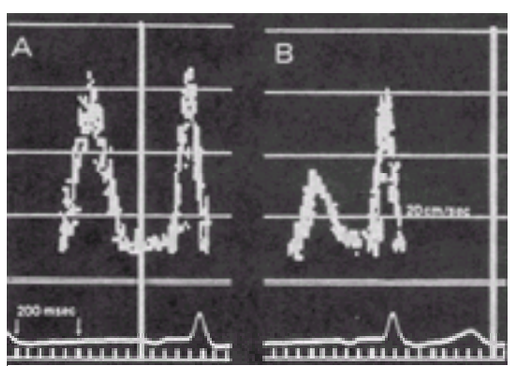


***e*FIGURE 51.16.5** Isovolumic relaxation time by continuous wave Doppler. The cursor is positioned between the left ventricular outflow and inflow tract. Isovolumic relaxation time is the time from cessation of outflow to beginning of inflow (between the arrows; 100 ms).

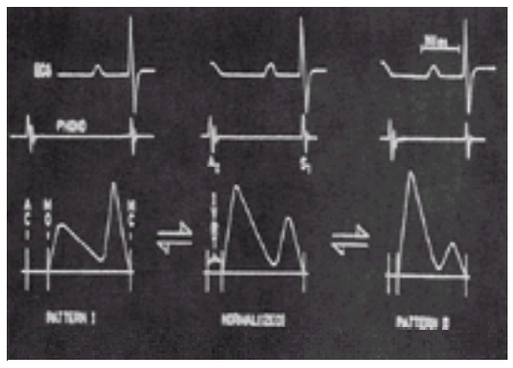
Intensive interest has focused on the characteristics of the mitral flow profile. Left ventricular filling in sinus rhythm occurs in two phases: an early E wave, which is caused by the pressure difference between the left atrium and the left ventricle, and a late A wave, which is caused by atrial contraction. In young healthy persons, maximal E velocity is slightly higher than A wave velocity. The following factors decrease the E wave: age, heart rate (in heart rates over 100 beats/min, there is generally E and A wave fusion), slowed left ventricular relaxation, and decreased left atrial pressure. Moreover, the site of measurement is important (E/A ratio is lower at the mitral annulus than at the leaflet tips). Increased left atrial pressure, conversely, increases maximal E wave velocity. Maximal A wave velocity depends on left atrial contraction and late diastolic left ventricular compliance. Because the E/A ratio is multifactorial, caution is necessary to interpret it, since *filling is not function*. It has been postulated that in early disease states with slowed relaxation, but normal left atrial pressures, the E/A ratio decreases (76). This, for example, has been demonstrated during acute ischemia during percutaneous transluminal coronary angioplasty balloon inflation (77) (*e*Fig. 51.16.6). However, this pattern can also be produced by preload reduction with normal relaxation (78) (*e*Fig. 51.16.7). If atrial pressure rises in the course of disease, the E/A ratio may again become normal: This has been termed *pseudonormalization*. In late disease states with high atrial pressures, the E/A ratio increases markedly, and isovolumic relaxation time is short, creating the so-called restrictive pattern (*e*Fig. 51.16.8 and *e*Fig. 51.16.9). These patterns of tran smitral filling can be found in different diseases, from coronary artery disease to dilated cardiomyopathy to amyloidosis. However, because of the preload dependency of the E/A ratio, interpretation of low or normal E/A ratios requires additional information. Such information can be gained from the study of pulmonary venous flow. Although the pattern of systolic and diastolic pulmonary venous inflow is not uniformly related to left atrial pressure (79,80), the size and duration of the reverse wave increases with left atrial pressure (81,82) (*e*Fig. 51.16.10). If the reverse pulmonary venous wave exceeds the transmitral A wave in duration, increased left atrial and left ventricular end diastolic pressures over 15 mm Hg are likely (67).



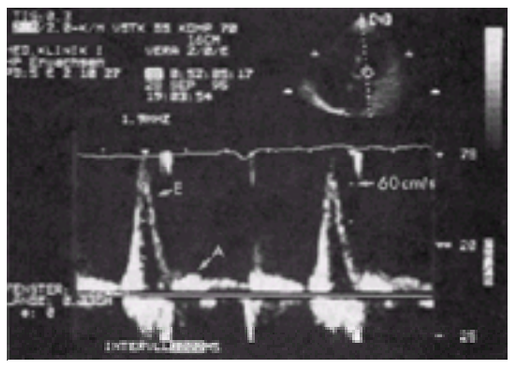
***e*FIGURE 51.16.6** Impaired relaxation pattern of transmitral flow during percutaneous transluminal coronary angiography of the left anterior descending artery (pulsed Doppler). At baseline and after recovery, there is a slightly decreased E/A ratio. During balloon inflation, there is a massive decrease of the E wave and some increase of the A wave, reflecting impaired relaxation by acute ischemia, also documented by ST elevation and high T waves in the electrocardiogram. (From Labovitz AJ, Lewen MK, Morton K, et al. Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischemia produced by angioplasty. *J Am Coll Cardiol* 1987;10:748–755, with permission.)



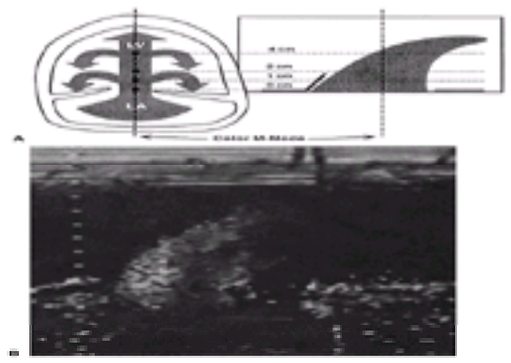
***e*FIGURE 51.16.7** Transmitral flow profile changes induced by changes in preload. Example from a patient before **(A)** and after **(B)** preload reduction by nitroglycerine. Pattern **B** is indistinguishable from “impaired relaxation” (see *e*Fig. 51.16.6). (From Choong CY, Herrmann HC, Weyman AE, et al. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. *J Am Coll Cardiol* 1987;10:800–808, with permission.)



***e*FIGURE 51.16.8** Schematic drawing of transmitral flow patterns and their relationship. Pattern I reflects “impaired relaxation” and is characterized by a prolonged isovolumic relaxation time (IVRT), a low E, and a high A wave. Pattern II reflects “restrictive physiology” and is characterized by a short IVRT, a high (and short) E wave, and a small A wave. Both patterns can be produced by cardiac diseases, and pattern I may change to pattern II, which is thought to represent advanced stages of disease, by going through a phase of pseudonormalization indistinguishable from the truly normal transmitral flow pattern. AC, aortic closure; MC, mitral closure; MO, mitral opening. (From Appleton CP, Jensen JL, Hatle LK, et al. Doppler evaluation of left and right ventricular diastolic function: a technical guide for obtaining optimal flow velocity recordings. *J Am Soc Echocardiogr* 1997;10:271–291, with permission.)



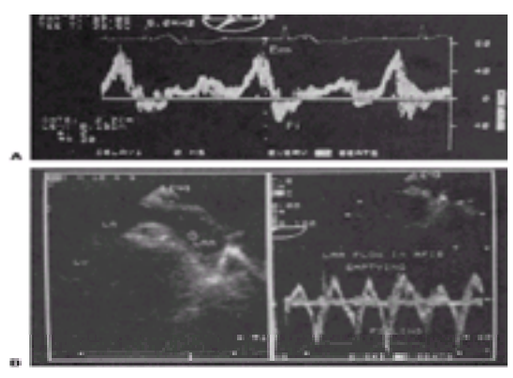
***e*FIGURE 51.16.9** Restrictive transmitral flow pattern. The pattern of high, short E waves and diminished A waves (E/A >2) with a short E-wave deceleration and short isovolumic relaxation time has been termed *restrictive*. It reflects high early diastolic filling pressure and low left ventricular compliance. This pattern has been observed in end-stage coronary heart disease, dilated cardiomyopathy, cardiac amyloidosis, and others.



***e*FIGURE 51.16.10** Flow propagation in the left ventricle. **A:** Schematic drawing. In diastole, blood from the left atrium propagates as a wavefront into the left ventricle. At the mitral valve level, this velocity corresponds to the E-wave velocity. Further into the left ventricle, propagation velocity continuously diminishes because of interaction with the stagnant ventricular blood pool. The velocity of flow propagation at each level can be measured from the slope of a transmitral color M-mode. **B:** Example of a transmitral color M-mode from the apical window showing diastolic flow propagation velocity into the left ventricle. Note curved outline of the color signal due to continuous decrease of propagation velocity toward the left ventricular apex. LA, left atrium; LV, left ventricle.

Presence of the restrictive mitral inflow pattern (E/A greater than 1.5), in particular presence of a short E wave deceleration time (less than 150 ms), has been convincingly shown to imply high pulmonary capillary pressure, impaired functional class, and bad prognosis in postinfarction patients (83,84), in dilated cardiomyopathy (85,86), in cardiac amyloidosis (87), and others (88). It can be shown theoretically that the slope of deceleration directly reflects the net compliance of the left atrium and left ventricle lumped together (36,37). Hence, a stiff diastolic ventricle leads to rapid E wave deceleration.

Another approach to the evaluation of diastolic function is to study the velocity of flow propagation into the left ventricle during diastole. This is the velocity with which the filling wave travels within the left ventricle from mitral annulus to apex (*e*Fig. 51.16.11). This velocity is less preload dependent than the E wave and can be measured as the slope of an apical color M-mode through the mitral valve during diastole. It has been shown in animal studies and in patients that flow propagation velocity strongly depends on left ventricular relaxation (89,90 and 91). However, reproducibility of this parameter is low.



***e*FIGURE 51.16.11** Left atrial appendage flow by transesophageal pulsed Doppler. **A:** Sinus rhythm. Note an emptying (Em, upward) wave before the R wave and a filling (Fi, downward) wave immediately thereafter. **B:** Atrial fibrillation. A fast succession of short emptying and filling waves is seen with maximal velocities greater than 50 cm per second, indicating preserved mechanical activity of the appendage.

Provided there is mitral regurgitation, an estimate of the rate of left ventricular pressure fall in late systole can be obtained. However, because mitral regurgitation velocities reflect the time course of ventriculoatrial pressure *difference*, these calculations only approximate the rate of left ventricular pressure fall.

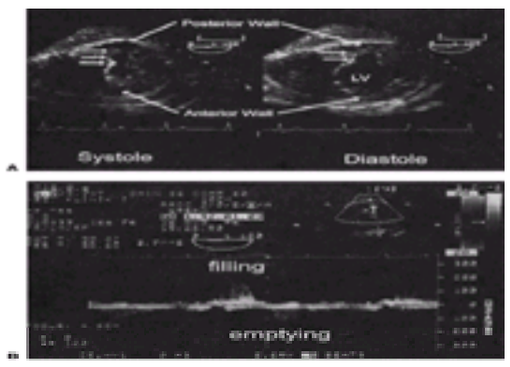
Right-Sided Heart Function and Pulmonary Hypertension

Right-sided heart output can be calculated at the pulmonary valve level by multiplying the pulmonary time velocity integral by the orifice area of the pulmonary valve ($pd^2/4$, where d is the diameter of the pulmonary annulus). The presence of pulmonary hypertension is easiest to assess from tricuspid regurgitation, which is present in almost all patients with pulmonary hypertension and particularly common in acute pulmonary hypertension due to pulmonary embolism. Peak tricuspid regurgitant velocity by continuous wave Doppler is converted to the maximal pressure drop during systole between the right ventricle and the right atrium by the simplified Bernoulli equation. Either this pressure drop can be taken as an estimate of pulmonary systolic pressure or an estimate of right atrial v wave pressure can be added by observing the collapse level of the jugular veins. Some echocardiographers simply add 10 mm Hg to the maximal ventriculoatrial pressure drop. Another useful index is pulmonary systolic flow acceleration time (the time from the onset of transvalvular flow to peak velocity). Acceleration time decreases with increasing pulmonary pressures from normal values of 130 ± 15 ms. The ratio of right ventricular preejection time (interval from Q wave to onset of pulmonary flow) to acceleration time has been shown to correlate well with mean pulmonary pressure, with values above 1.2 indicating pulmonary hypertension (92).

Left Atrial Appendage Flow

In sinus rhythm, the left atrial appendage shows four brief flow waves: a small emptying wave in early diastole and a larger one during atrial contraction after the P wave of the ECG. Both emptying waves are followed by a filling wave of similar velocity (*e*Fig. 51.16.12). Peak emptying and filling velocities occur immediately before and after the QRS complex and average 64 and 46 cm per second, respectively, in healthy individuals (93). These velocities can be recorded by transesophageal pulsed Doppler, with the sample volume well in the appendage cavity. In nonvalvular atrial fibrillation, although the transmitral A wave is absent and therefore there is no net effect of atrial contraction detectable at the mitral valvular level, emptying and filling velocities of the appendage still are well detectable in most patients. This is because the appendage encloses a small blood volume, on which the decreased wall motion during fibrillation still imparts enough acceleration to create inward and outward flow. In patients with large atria, especially in long-standing mitral stenosis, and apparently in rare cases of *left atrial appendage standstill* in sinus rhythm (94), these velocities are absent: The appendage is a static pouch, and these conditions are associated with frequent thrombus formation and thromboembolic events. Appendage flow velocities have been used with success retrospectively to stratify the thromboembolic risk of patients with nonvalvular atrial fibrillation, with peak

velocities less than 25 cm per second indicating a higher risk and therefore a strong argument for anticoagulation (95).



***e*FIGURE 51.16.12** Left ventricular pseudoaneurysm (*arrows*) after inferior infarction. **A:** Transgastric short-axis view in systole and diastole. **B:** Flow into (filling, upward, in systole) and out of the pseudoaneurysm (emptying, downward, in diastole) is detectable by pulsed Doppler. LV, left ventricle.

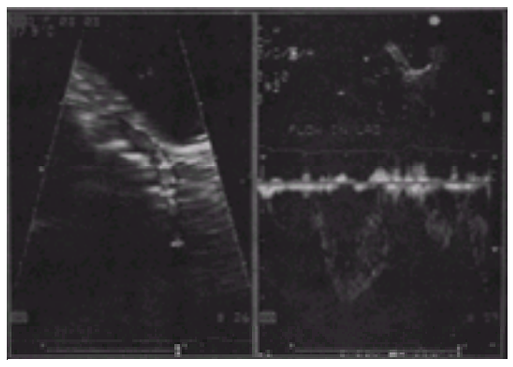
DOPPLER EVALUATION OF CORONARY ARTERY DISEASE

Impairment of left ventricular relaxation precedes systolic wall motion abnormalities in acute myocardial ischemia. Acute transmitral E/A ratio decrease has been documented during percutaneous transluminal coronary angioplasty balloon inflation (63). Similarly, during dobutamine stress echo, a decrease in peak E wave velocity and in E wave acceleration ratio was shown to be an excellent predictor of coronary artery disease superior to the detection of wall motion abnormalities (96). However, this has not been seen in exercise stress echo, presumably because after treadmill exercise the change to a supine position for the echo examination led to an increase in preload, blunting the response of filling parameters (97).

If depressed systolic left ventricular function is present after myocardial infarction, a decreased cardiac output can be measured. Doppler signs of impaired diastolic function are discussed in the section on Diastolic Left Ventricular Function, earlier in this chapter. The presence of a restrictive pattern (E/A greater than 1.5, E wave deceleration time less than 150 ms; eFig. 51.16.8 and eFig. 51.16.9) after myocardial infarction is associated with a poor life expectancy, even if controlled for systolic variables such as ejection fraction (74). Two large randomized placebo-controlled pharmacologic intervention trials in postinfarction patients with reduced systolic function have attempted to analyze diastolic function by echo. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, a decrease in E/A ratio under enalapril was ascribed to a reduction in atrial pressure due to a favorable influence of enalapril on ventricular remodeling and hypertrophy (98). In the Doppler Flow and Echocardiography in Functional Cardiac Insufficiency: Assessment of Nisoldipine Therapy (DEFIANT) trial, a small increment in E wave velocity and a small reduction in isovolumic relaxation time were seen under the calcium antagonist nisoldipine, and this was ascribed to improvement in left ventricular relaxation (99). It is ironic that these trials interpret opposite echo findings as indicative of a favorable pharmacologic influence on diastolic function.

Doppler has an important role in the identification of some structural complications of myocardial infarction, especially in septal rupture leading to a ventricular septal defect located mostly in the apical half of the septum and in acute mitral regurgitation after papillary muscle rupture. In left ventricular pseudoaneurysm, Doppler recordings at the rupture site reveal biphasic flow, with flow into the pseudoaneurysm during both systole and after atrial contraction, and flow from the pseudoaneurysm into the ventricle during early to mid-diastole (100) (eFig. 51.16.12).

Transesophageal echocardiography can visualize flow in the proximal coronary arteries directly by color Doppler. The proximal left anterior descending artery often can be interrogated by pulsed Doppler, showing the typical coronary flow signal with diastolic predominance (eFig. 51.16.13). In one study, in patients without coronary stenosis, mean diastolic velocity increased on average by a factor of 3 after intravenous administration of the vasodilator dipyridamole, whereas it increased by only 1.5 in patients with left anterior descending stenosis (101). Significantly increased peak diastolic flow velocity after successful angioplasty of the proximal left anterior descending artery has been reported in another small series (102). However, small diameter and tortuosity of the coronary vessels unfortunately only allow limited visualization and often marginal image quality, and thus this approach at present has little value for the evaluation of coronary artery disease.



***e*FIGURE 51.16.13** Coronary flow recording by transesophageal color and pulsed Doppler in the proximal left anterior descending coronary. Predominantly diastolic flow velocities are recorded. LA, left atrium.

DOPPLER EVALUATION OF THE CARDIOMYOPATHIES, CARDIAC TAMPONADE, AND THE TRANSPLANTED HEART

Dilated Cardiomyopathy

Apart from measuring a reduced cardiac output, Doppler examination is useful to estimate systolic pulmonary pressure by the peak tricuspid regurgitation velocity (see Right-Sided Heart Function and Pulmonary Hypertension, earlier in this chapter), to assess mitral regurgitation, and to evaluate the transmitral filling pattern. A restrictive pattern (E/A greater than 1.5, E wave deceleration time less than 150 ms) indicates high filling pressures and a reduced left ventricular compliance and is associated with a poor prognosis (103,104). Because mitral annular motion is reduced, systolic pulmonary venous inflow is also reduced in comparison with diastolic inflow.

Hypertrophic Cardiomyopathy

The main task of the Doppler examination is to detect and assess left ventricular outflow obstruction. For this purpose, a continuous wave Doppler recording with the echo beam passing through the left ventricular outflow tract in the apical long-axis view should be obtained. Hypertrophic obstructive cardiomyopathy characteristically produces a sabre-shaped, late-peaking systolic velocity profile different from the (mostly also present) mitral regurgitation in the continuous wave Doppler examination, which begins earlier and exhibits an earlier steep velocity increase (Fig. 51.17). Because continuous wave Doppler has no range resolution, the diagnosis should be confirmed by moving the sample volume of the pulsed Doppler systematically along the interventricular septum from the midventricle to the aortic valve to map the velocities toward the aortic valve. If intraventricular obstruction is present, this is seen in the pulsed Doppler recording, as the systolic velocities at the location of the obstruction abruptly exceed the range limit of the pulsed Doppler. Color Doppler typically shows turbulence in the left ventricular outflow tract.

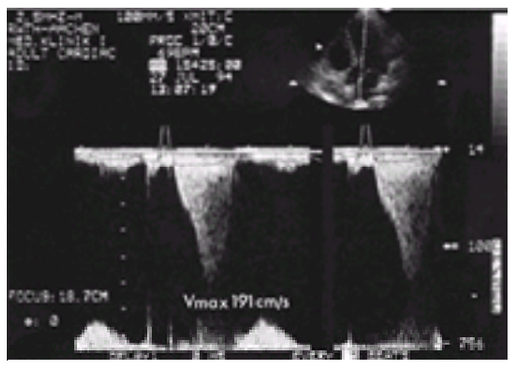


FIGURE 51.17 Left ventricular outflow tract obstruction in hypertrophic obstructive cardiomyopathy recorded by continuous wave Doppler from the apical window. A typical profile with a late systolic peak is recorded, which is well distinguished from the frequently concomitant mitral regurgitation.

A lowered E/A ratio of the transmitral filling pattern may be present because of impaired left ventricular relaxation, but because of concomitant mitral regurgitation and a possible increase in left atrial pressure, a normal E/A pattern does not exclude diastolic left ventricular dysfunction.

Constrictive and Restrictive Cardiomyopathy

The transmitral flow profile in constrictive and restrictive cardiomyopathies is frequently characterized by tall and short E waves and small A waves (the restrictive pattern) and a short isovolumic relaxation time. In constrictive pericarditis, but not in restrictive cardiomyopathy, accentuated influence of respiration on cardiac flow velocities is present during inspiration (a 10% inspiratory decrease in peak transmitral E wave velocity is seen in healthy subjects), transmitral flow velocities decrease, transtricuspid flow velocities increase, and left ventricular relaxation time also increases (Fig. 1.18). Recording is best done at a slow sweep speed to obtain several respiration cycles on one sweep. However, because inspiration image quality often is impaired, reliable documentation of this pattern frequently is difficult. The pulmonary venous flow in constrictive pericarditis decreases in inspiration, and this effect is more marked for diastolic than for systolic pulmonary venous inflow.

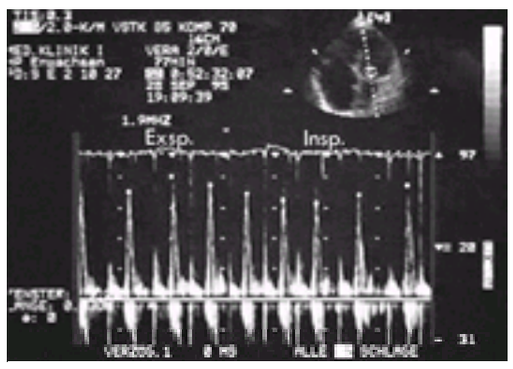
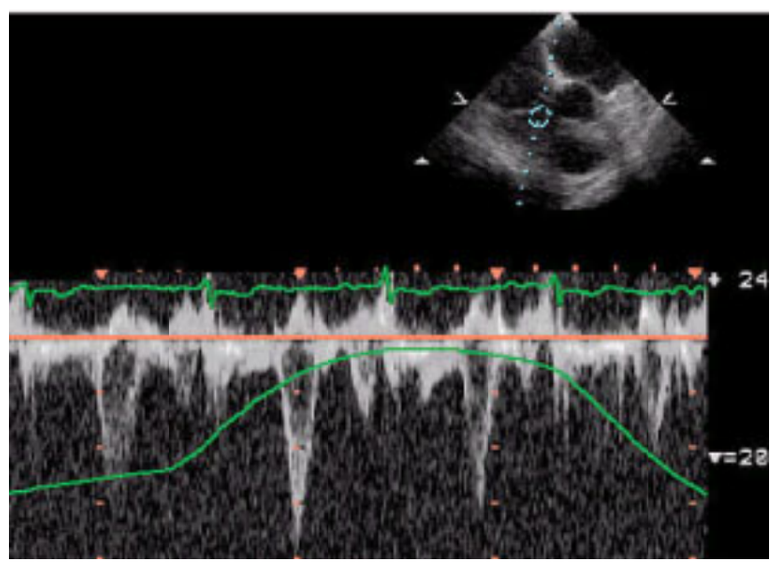
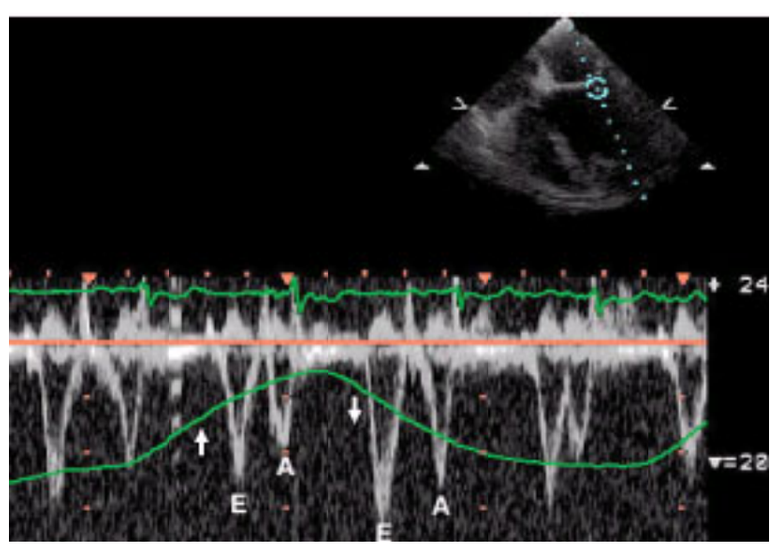


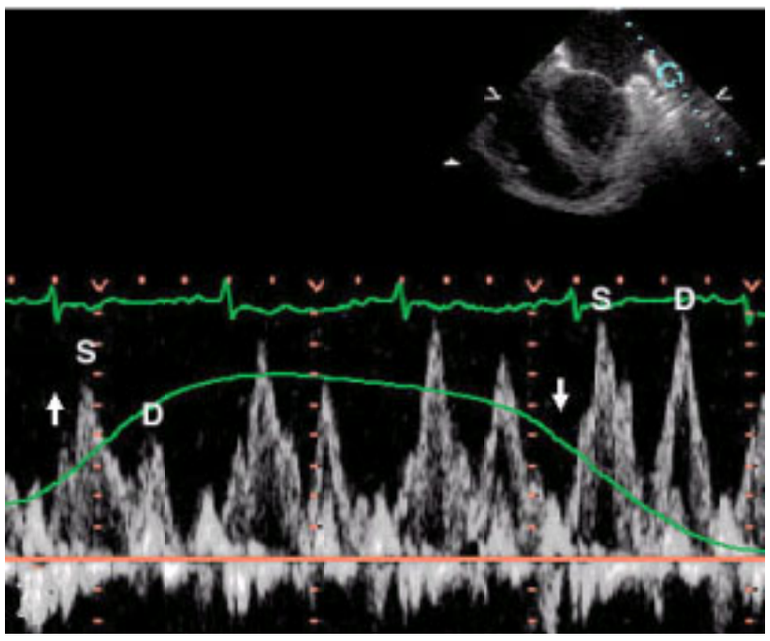
FIGURE 51.18 Transmitral flow profiles in constrictive pericarditis. A “restrictive” transmitral flow pattern with high and short E waves is seen. Peak E-wave velocities show pathologic respiratory variation (greater than 10%) with a decrease during inspiration (Insp.). Exsp., expiration.



Pulsed wave Doppler through the tricuspid valve of a patient with constrictive pericarditis. Note the decrease of the E wave with inspiration due to interventricular dependence.



Pulsed wave Doppler of the mitral valve inflows of a patient with constrictive pericarditis. Note the decrease of the E wave during inspiration (*upward arrow*) due to interventricular dependence, and the increase in the E wave during expiration (*downward arrow*) for the same reason.



Pulsed wave Doppler of the pulmonary veins of a patient with constrictive pericarditis. Note the inspiratory decrease of the S and P waves and the expiratory increase due to interventricular dependence. (Inspiration is denoted by the upward arrow and expiration by the downward arrow).

Restrictive cardiomyopathy exhibits no marked respiratory variation in mitral flow velocities and is characterized by particularly short mitral and tricuspid pressure half-times. Often, systolic mitral and tricuspid regurgitation are present following the E wave (105). There is usually at least moderate pulmonary hypertension, and ventricular walls are frequently thickened (e.g., in cardiac amyloidosis), which represents the most frequent and classical form of restrictive cardiomyopathy.

Cardiac Tamponade

The Doppler characteristics of cardiac tamponade resemble those of constrictive pericarditis. There is a marked (30% to 40%) inspiratory decrease of transmitral, transaortic, and diastolic pulmonary venous inflow velocities (corresponding to the clinical finding of pulsus paradoxus), and an even more pronounced (greater than 80%) increase in transtricuspid (and transpulmonic) flow velocities. Left ventricular isovolumic relaxation time increases in inspiration.

Doppler Examination of the Transplanted Heart

Patients with a transplanted heart almost always present mild or moderate mitral and tricuspid regurgitation. If the residual native atria still are electrically and mechanically active, two distinct and dissociated A waves can be recorded on pulsed Doppler transmitral or tricuspid flow profiles, one representing contraction activity from the residual recipient atria and one from the donor atria (106).

The noninvasive detection of graft rejection by Doppler has gathered much interest. Because alterations in systolic function ensue only late in the course of rejection, several diastolic parameters have been analyzed for this purpose, in particular, a decrease in isovolumic relaxation time and a decrease in E wave deceleration time or pressure half-time (a misleading term, since in nonstenotic valves the simplified Bernoulli equation does not apply). Both lead to a restrictive inflow pattern (107,108), which has been associated with acute rejection, and both are reversible after treatment. In a small subset of patients, a chronic restrictive physiology develops. Because all of these parameters are multifactorial and especially preload dependent, there is no definitive set of values reliably identifying acute rejection, but serial follow-up in a given patient seems to allow the noninvasive detection of at least moderate acute rejection by observing changes in isovolumic relaxation time and in E wave deceleration with sensitivity and specificity in the 80% to 90% range.

CONTROVERSIES AND PERSONAL PERSPECTIVES

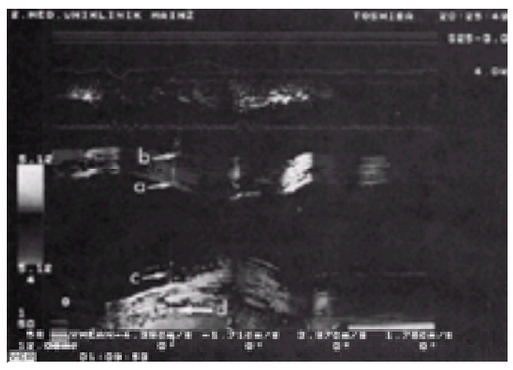
Although a tremendous success story, some problems in the echo-Doppler assessment of valvular stenosis and regurgitation remain. One fundamental limitation in the present quantitative Doppler approaches to regurgitation is the characterization of spatially complex three-dimensional flow velocity fields in the heart by severely limited data. For instance, a single pulsed Doppler sample volume is used in transvalvular flow rate calculations, or a 2-D color Doppler map in the proximal convergence method. These problems may ultimately be overcome by real-time, three-dimensional, multigated, pulsed Doppler. In the assessment of stenotic lesions, future three-dimensional echo capabilities could help solve the pressure recovery dilemma and reconcile the discrepancies between effective and geometric orifice areas by combining spatial morphologic and functional data. However, it is mostly the effect on myocardial function rather than the valvular lesion per se that clinically matters most, in particular in chronic regurgitant lesions. Thus, the quest for the single magic number representing the severity of a valvular lesion is misleading. A set of parameters measuring both valvular and myocardial function will be needed to fully characterize such lesions.

Much interest has focused on Doppler parameters of diastolic left ventricular function. A set of Doppler parameters (isovolumic relaxation time, E/A ratio, E deceleration, A wave duration, pulmonary venous reverse flow, and so forth) used cautiously together with other echo data generally allows prediction of elevated diastolic left ventricular pressures. However, because systolic and diastolic myocardial function are interrelated and both pervasively load dependent, the search for the one parameter exclusively reflecting *diastolic function* (itself an ill-defined term) is inadequate, and data should always be viewed in clinical and hemodynamic perspective.

FUTURE DIRECTIONS AND EMERGING TECHNICAL INNOVATIONS

Tissue Doppler and Strain Rate Imaging

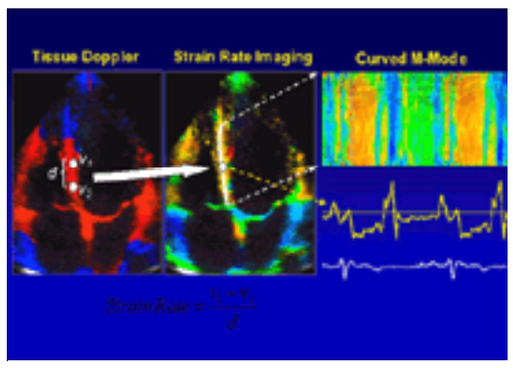
In conventional Doppler, filter settings are such that the low-amplitude, high-velocity signals from blood are recorded and the high-amplitude, low-velocity signals from solid cardiac structures such as the walls are suppressed (the low-velocity filter is appropriately named the *wall filter*). If this setting is reversed, the velocity of solid structures, especially the myocardium, can be recorded by pulsed or color Doppler (109,110) (*e*Fig. 51.18.1). They compare well with velocity measurements derived from sonomicrometry, M-mode, or 2-D echo registrations of moving solid structures. However, as in all Doppler measurements, only the velocity component in the direction of the echo beam is measured accurately.



***e*FIGURE 51.18.1** Example of tissue Doppler. Parasternal color M-mode at the left ventricular level. Note low velocities (±5 cm per second) on color bar on the left, coding the velocity of solid structures. Systolic contraction of the posterior wall is coded in yellow-red and of the septum in blue. After aortic valve closure (see second heart sound on phonocardiogram tracing), the posterior wall is coded in blue due to thinning of the wall. The transmural myocardial velocity gradient is represented by different color hues (the subendocardial posterior layer shows a bright yellow and the subendocardial layer a red hue in systole) and by intramyocardial pulsed Doppler measurements. These show local myocardial velocities of –4.4 cm per second (a, right ventricular half of septum), –1.7 cm per second (b, left ventricular half of septum), 4.0 cm per second (c, subendocardial layer of posterior wall), and 1.8 cm per second (d, subepicardial layer of posterior wall), respectively. (Courtesy of Uwe Nixdorff, MD, Erlangen, Germany.)

Interest has focused so far on regional analysis of myocardial wall motion (111). From the parasternal window, radial (inward and outward) motion of posterior and anterior segments is measured, and from the apical window longitudinal motion of left ventricular wall segments can be analyzed. There is a systolic contraction wave, leading to positive velocities toward the transducer, and two diastolic elongation waves, leading to negative velocities away from the transducer.

A derived measure is strain rate, which extracts the local deformation rate in the direction of the ultrasound beam (percentage elongation or contraction divided by time). Strain rate, and its temporal integral, strain, can be calculated by subtracting the simultaneous velocities at two myocardial points along a scan line and dividing the results by the distance between the two points (eFig. 51.18.2). These techniques can be used in several ways to analyze *regional* left ventricular systolic and diastolic function:



***e*FIGURE 51.18.2** Strain rate imaging. **Left:** Systolic color tissue Doppler image of a normal apical four-chamber view. Segments of the heart moving toward the transducer (upward) are depicted in red, apical segments moving away from the transducer (downward) are shown in blue. From the tissue Doppler velocity data, strain rate is calculated by subtracting two tissue velocities along a scanline (in this example, v_1 and v_2 from the midseptum) and dividing by their distance *d* (see formula). The strain rates are displayed again in color format in the mid-figure. Yellow-red depicts local tissue contraction, and blue local tissue elongation. Strain rate data from an arbitrary line in the tissue can be plotted over time as curved M-mode (*upper right*), showing periodic contraction and lengthening at the locations covered by the line. From each single point of the strain rate image, strain rate over time can be extracted (*lower right*). (From Voigt JU, Arnold MF, Karlsson M, et al. Assessment of regional longitudinal myocardial strain rate derived from Doppler myocardial imaging indexes in normal and infarcted myocardium. *J Am Soc Echocardiogr* 2000;13:588–598, with permission.)

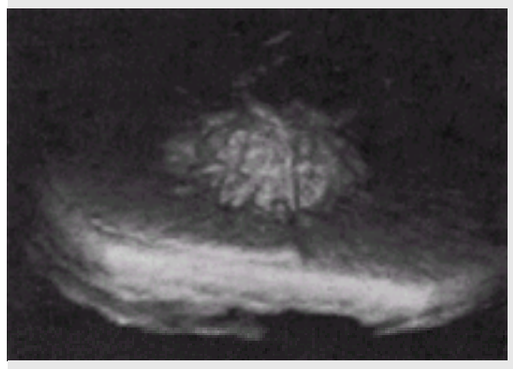
1. From an apical window, longitudinal contraction and elongation velocities can be measured in the left ventricular walls. Regional wall motion abnormalities (e.g., in ischemic, stunned, hibernating, or scarred myocardium) exhibit lower than normal velocities (112). Stress-inducible wall motion abnormalities lead to lower than normal contraction and lengthening myocardial velocities. Furthermore, in ischemia, there may be shortening extending from late systole into early diastole (*postsystolic thickening*). Unfortunately, discrimination of normal and abnormal velocities is not easy, because longitudinal contraction velocities decrease from base to apex, are age and heart rate dependent, vary by segment, and are subject to tethering by the physical continuity between segments and walls. Theoretically, measurement of strain or strain rate is more attractive (113), because it largely eliminates tethering and translational effects, truly reflecting local myocardial deformation (although only in the direction of the echo beam).
2. The subendocardial layer of the myocardium contracts more and more rapidly than the subepicardial layer. This transmural velocity gradient, which by definition is the same as radial strain rate, is a measure of contractile myocardial function. It is diminished in dilated cardiomyopathy and abolished in scar tissue, but not in viable myocardium. It can be analyzed by tissue Doppler, although so far only in parasternal views.
3. Evaluation of diastolic function benefits from tissue Doppler parameters. In the presence of normal relaxation, there is an early diastolic outward and lengthening motion of the myocardial walls slightly preceding the transmitral E wave, and a second outward and lengthening motion following the transmitral A wave. While in healthy hearts transmitral early filling follows early diastolic tissue elongation (active ventricular suction), in ischemic or scar tissue, this sequence is reversed, because filling is largely passive. Pseudonormalized transmitral flow patterns can be unmasked using this technique (114).
4. Tissue Doppler can locate preexcitation bundles by mapping the course of ventricular contraction. A further refinement comes from strain rate imaging. This is an imaging modality based on tissue Doppler, which instead of displaying local tissue velocities shows local tissue deformation or strain rates.

Strain rate (equivalent to myocardial velocity gradient) is calculated as the difference in velocities over a given distance, typically 1 cm or less; its unit is Hz (s^{-1}). Integrating strain rate over time yields strain, a dimensionless number indicating the fractional elongation or contraction (e.g., a strain of +0.3 means that the tissue has elongated by 30% compared with baseline). Strain rate imaging and strain calculations have the advantage of being unaffected by movements of the heart as a whole with respect to the transducer or by tethering from adjacent regions, because these cancel out when looking at the small distances over which these parameters are obtained. Therefore, strain rate is a truly regional parameter. Note, however, that so far strain or strain rate can only be directly measured in the direction of the ultrasound beam, while it is known (and can be visualized by magnetic resonance imaging) that myocardial tissue deformation in reality occurs in all three dimensions of space.

The potential of measuring these regional myocardial contraction and relaxation parameters for the characterization of regional myocardial contractility, ischemia, and viability is under investigation.

THE FUTURE

Several developments in particular will permit better calculation of flow rates. *Unwrapping* of high velocities will enable full mapping of the velocity field of regurgitant jets. Thus, jet momentum could be calculated, and because momentum is conserved in the cross sections of a jet, flow rate at the regurgitant orifice can be derived. Moreover, the length of the jet's laminar core has a fairly constant relationship with the diameter of the regurgitant orifice; measurement of the length of the laminar core would therefore allow estimation of regurgitant orifice size and, hence, severity of regurgitation (21). Automated integration of color Doppler velocities in two or three dimensions and three-dimensional Doppler of the proximal convergence zone are two other developments (eFig. 51.18.3), and use of Doppler power (amplitude squared) for flow calculations is a third (115).



***e*FIGURE 51.18.3** Three-dimensional reconstruction of color flow signals from the proximal convergence zone of a jet (*in vitro*). Color pixels are reconstructed as gray voxels. The approximately hemispheric shape of the proximal convergence zone is recognizable.

*In cardiology, *pressure gradient* is an unerasable misnomer for *pressure drop*. Both expressions are used synonymously in this text.

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TRANSESOPHAGEAL ECHOCARDIOGRAPHY

BRIAN P. GRIFFIN

"Indicates text or graphics that appear only in the electronic versions of this text."

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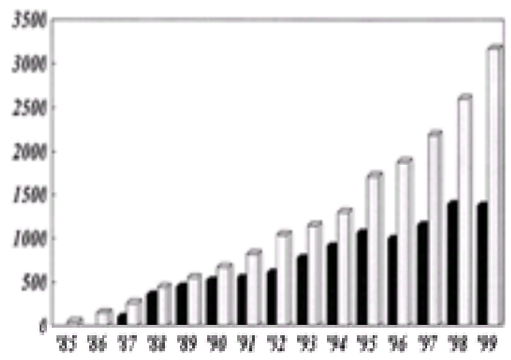
OVERVIEW

Transesophageal echocardiography (TEE) is an important tool in the evaluation of cardiac structure and function and for assessing the thoracic aorta. With TEE, images are acquired from an esophageal or gastric imaging window rather than from the chest wall (*e*Table 52.0.1). This is advantageous as the heart and aorta lie very close to the esophagus throughout much of its course. Esophageal imaging is therefore possible with a higher frequency transducer than is usually possible with transthoracic imaging. This and the absence of air-filled lung tissue in the imaging window allow improved image resolution. TEE images the heart from behind, which allows excellent resolution of posterior structures such as the atria, interatrial septum, and aorta as compared with transthoracic imaging. The posterior imaging approach is also advantageous in circumventing acoustic shadowing from strong reflectors of ultrasound such as prosthetic valves.

***e*TABLE 52.0.1** COMPARISON OF TRANSTHORACIC AND TRANSESOPHAGEAL ECHOCARDIOGRAPHY

	Transthoracic echocardiography	Transesophageal echocardiography
Imaging location	Chest wall, subcostal	Esophagus, stomach
Transducer frequency	2.0–5.0 MHz	3.5–7.0 MHz
Examination preparation	None	Sedation, anesthesia
Advantages	Widely applicable, noninvasive, multiple imaging windows, complete Doppler evaluation	High-resolution images, circumvents prosthetic shadowing, posterior structures (aorta, atria) well imaged
Disadvantages	Often suboptimal images, far-field structures (aorta, atria) and prostheses poorly imaged	Semiinvasive, imaging windows highly variable
Indications	Usually first-line cardiac ultrasound modality	When transthoracic echocardiography fails to adequately answer clinical question

TEE is invasive, as the transducer must be inserted into the esophagus and stomach. This usually requires local anesthesia and intravenous sedation. It is more consumptive of physician time, more expensive, and has less patient acceptance than transthoracic imaging. Transthoracic echocardiography (TTE) can provide adequate clinical information in many instances and is therefore usually acquired first. TEE is performed if additional information is required or if transthoracic image quality is suboptimal. In most adult echocardiography laboratories, less than 10% of all studies are performed by the transesophageal approach (*e*Fig. 52.0.1) (1,2). Major current indications for TEE are shown in *e*Table 52.0.2.



***e*FIGURE 52.0.1** Bar graph of transesophageal echocardiograms performed at The Cleveland Clinic Foundation from 1985 to 1999. Intraoperative studies are shown as stippled bars, and other transesophageal echocardiography examinations are shown as black bars.

***e*TABLE 52.0.2** INDICATIONS FOR TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Nondiagnostic transthoracic echocardiography images	Chronic obstructive pulmonary disease, obesity, dressings prevent adequate transthoracic echocardiography images

Atrial pathology and function	Atrial thrombus, spontaneous contrast, tumor
Interatrial septum	ASD, PFO, atrial septal aneurysm
Disease of thoracic aorta	Dissection, intramural hematoma, aortic trauma, atheroma
Endocarditis	Small vegetations, abscess, fistulae, prosthetic endocarditis
Native-valve disease	Flail valves, severity of mitral regurgitation, aortic valve morphology
Prosthetic valves	Prosthetic regurgitation, thrombosis, suspected dysfunction
Source of embolus	Atrial thrombus, PFO, atrial septal aneurysm, vegetation, valve strand, aortic atheroma, tumor
Coronary disease	Coronary anomalies and fistulae, stenoses, flow reserve, stress imaging
Critical care unit	Unexplained hypotension, complications of myocardial infarction, pulmonary emboli, post surgical tamponade
Congenital heart disease	Atrial situs, straddling atrioventricular valves, follow-up of Senning, Mustard, and Fontan procedures, pulmonary venous anomalies
Interventional procedures	Percutaneous mitral valvuloplasty, ASD, or ventricular septal defect closure, septostomy
Miscellaneous indications	Pulmonary vein pathology, assess hemodynamics, masses

ASD, atrial septal defect; PFO, patent foramen ovale.

HISTORICAL PERSPECTIVE

The close anatomical relationship of the esophagus to the heart has been used for many years to optimize cardiac physiological signals. Experimental esophageal ultrasound probes developed in the 1970s established the potential usefulness of the esophageal imaging window (3,4 and 5). The modern era of TEE began in 1980, when Hanrath and colleagues attached a phased-array ultrasound transducer to the tip of a flexible gastroscope (*e*Table 52.0.3) (6,7). Standard planes in which cardiac structures could be imaged from the esophagus and stomach were developed. Widespread use of TEE in the ambulatory setting occurred with the development of smaller transducers capable of imaging at a higher frequency and with full Doppler capabilities (pulsed, continuous-wave, and color-flow mapping) (8,9). Recent developments include smaller transducers for pediatric use and multiplane transducers capable of imaging in more than one plane (10,11).

***e*TABLE 52.0.3** KEY DATES IN THE DEVELOPMENT OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY

1906	Esophageal electrocardiography	Cremer (246)
1970	Esophageal Doppler examination of aorta	Side and Gosling (3)
1975	Esophageal M-mode	Frazin et al. (4)
1977	Esophageal two-dimensional echo probe (mechanical array)	Hisanaga et al. (5)
1980	Two-dimensional echo transducer mounted on modified gastroscope	Hanrath et al. and Souquet et al. (6,7)
1982	Pulsed Doppler transesophageal echocardiography	Schluter et al. (8)
1986	Color-flow imaging transesophageal echocardiography	de Bruijn et al. (9)
1989	Biplane transesophageal echocardiography	Omoto et al. (10)
1992	Multiplane transesophageal echocardiography	Flachskampf et al. (11)

ANATOMIC CONSIDERATIONS

The esophagus is approximately 25 cm in length and extends from the pharynx to the stomach (Fig. 52.1). The esophagus is narrowest at the junction with the pharynx. This is the most difficult area to cross when passing a transesophageal transducer. The esophagus descends vertically and slightly to the left, passing behind the trachea, left mainstem bronchus, left atrium, and left ventricle before passing through the diaphragm. The ascending aorta and arch lie anterior to the esophagus (*e*Fig. 52.1.1). The air-filled trachea and left mainstem bronchus interpose between the esophagus and portion of the ascending aorta and ascending arch and cause a “blind spot” in imaging the aorta from the transesophageal window. The esophagus twines around the descending aorta. It lies medial to the aorta in the midthorax, whereas the aorta lies behind it at the level of diaphragm. Therefore, the esophageal transducer must be rotated while imaging the descending aorta to keep it in view.

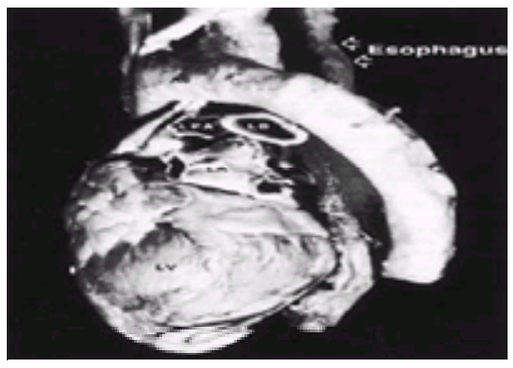
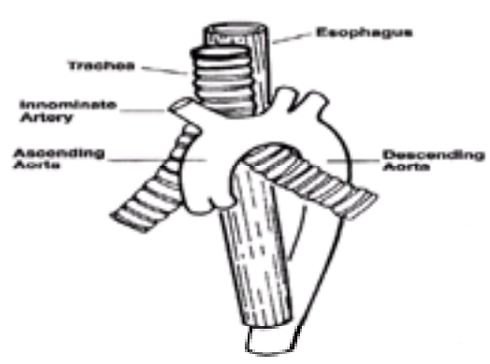


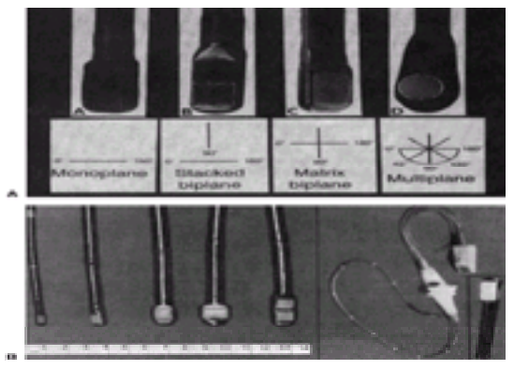
FIGURE 52.1 Anatomic specimen showing relationship of esophagus to heart and aorta. Ao, aorta; LA, left atrium; LB, left main bronchus; LPA, left pulmonary artery; LV, left ventricle. (From Weyman AE. *Principles and practice of echocardiography*, 2nd ed. Philadelphia: Lea & Febiger, 1994, with permission.)



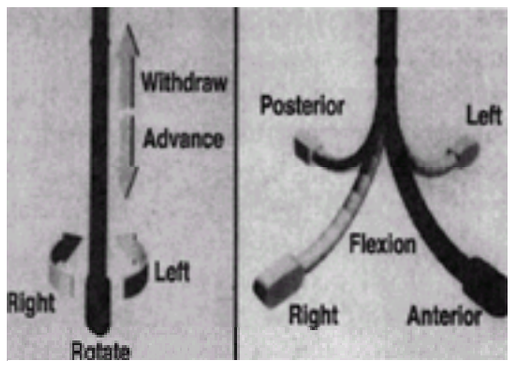
***e*FIGURE 52.1.1** Intertwining of aorta and esophagus from diaphragm to the arch. (From Weyman AE. *Principles and practice of echocardiography*, 2nd ed. Philadelphia: Lea & Febiger, 1994, with permission.)

TECHNOLOGY: TRANSDUCERS AND PROBES

TEE requires the use of a special esophageal probe that interfaces with a conventional cardiac ultrasound system. The esophageal probes currently in use consist of an ultrasound transducer(s) mounted at the end of a flexible gastroscope from which the fiberoptic cables and suction capability have been removed (*e*Fig. 52.1.2). The transducers typically used are phased-array and multielement and operate at multiple frequencies from 3.5 to 7.0 MHz. These probes are capable of performing all Doppler modalities, and M-mode, and two-dimensional imaging. The length of the gastroscope is typically 100 cm. The transducer represents the fixed portion of the probe. Adult transducers vary in length from 27 to 45 mm, are 14 to 17 mm wide, and are approximately 11 mm thick. The gastroscope cable is approximately 10 mm wide in adult probes. TEE probes 7 mm in diameter are now available and allow imaging even in infants as small as 3 kg (12). Esophageal probes have the standard gastroscope controls that allow remote movement of the transducer at the tip anteriorly, posteriorly, and to both sides. Specific positioning of the probe requires (a) advancing or withdrawing the probe within the esophagus, (b) rotation of the esophageal probe, and (c) manipulation of the tip of the probe using the controls described above (*e*Fig. 52.1.3).



***e*FIGURE 52.1.2 A:** Evolution of transesophageal ultrasound transducer technology. A, Monoplane device is a single-plane transducer typically perpendicular to the shaft. B, In stacked biplane device, the distal transverse plane is complemented by a separate proximal longitudinal plane parallel to the long axis of the scope. C, In a matrix biplane device, transverse and longitudinal planes array are interdigitated into a single footprint. D, Multiplane device uses a single array that can be rotated though 180 degrees so that a continuum of orientations relative to the shaft of the scope may be produced. **B:** Photograph of array of commercially available transducers.



***e*FIGURE 52.1.3** Flexion, extension, and lateral rotation of transducer. The tip of the scope may be advanced, withdrawn, rotated to the left or right, and flexed in four directions (anterior, posterior, left, and right).

Initially, esophageal probes consisted of a single transducer (*e*Fig. 52.1.2) mounted perpendicular to the long axis of the gastroscope. With this monoplane probe, cross-sectional or horizontal images of the heart are obtained, although additional imaging planes are possible by manipulation of the transducer tip. Biplane probes consist of two transducers mounted orthogonally on the probe (13). Multiplane probes are now standard with the major ultrasound systems (14,15). With this probe, the transducer is rotated either mechanically or electronically around a central axis through 180 degrees (Fig. 52.2). The horizontal transducer position is, by convention, at 0 degrees, whereas the longitudinal position is at 90 degrees. Planes not easily available with either the monoplane or biplane probe are available at intermediate degrees of rotation. The precise degree of rotation of the transducer is displayed graphically on the image.

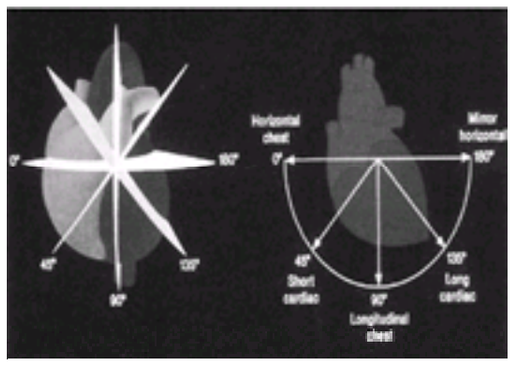


FIGURE 52.2 Scan planes of biplane and multiplane transducers. With the monoplane probe, the transducer is usually fixed and can image only in the transverse plane at zero degrees. Biplane probes have an additional transducer mounted to image in the longitudinal orientation at 90 degrees. In multiplane imaging, the transducer may rotate so that many additional imaging planes in between the transverse and longitudinal and mirror image of the transverse planes may be obtained. (From Khandheria BK. Transesophageal echocardiography in the evaluation of prosthetic valves. *Cardiol Clin* 1993;11:427–436, with permission.)

TECHNIQUE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY

TEE is performed in a manner similar to upper gastrointestinal endoscopy and requires experience in the safe intubation of the esophagus and stomach. Only operators who have adequate training in esophageal intubation and in echocardiography should perform this procedure.

Patient Selection

Patients should fast for at least 4 hours before the procedure (*e*Table 52.0.4). A detailed history should be obtained first, paying attention to a history of dysphagia, esophageal problems, and drug allergies. As the esophageal probe is passed blindly in TEE, any disorder of the esophagus that might interfere with the passage of the probe or that may lead to injury by the probe is considered a contraindication (Table 52.1). All oral prostheses and dentures are removed, and intravenous access is acquired. Blood pressure and electrocardiographic monitoring and oximetry are undertaken throughout the study. Resuscitation equipment, suction, and oxygen should be readily available. Although TEE may be performed without either pharyngeal anesthesia or sedation, both of these increase patient comfort and facilitate a thorough examination (16).

***e*TABLE 52.0.4** TRANSESOPHAGEAL ECHOCARDIOGRAPHY PROCEDURE
1. Appropriate indication
2. Informed consent
3. No specific contraindication or allergy to drug used in the procedure
4. Fasting >4 h
5. Monitoring of electrocardiogram, blood pressure, and oximetry
6. Pharyngeal anesthesia with topical lidocaine
7. Intravenous sedation with meperidine and midazolam
8. Left lateral decubitus position

1. Significant dysphagia of unknown origin
2. Significant esophageal pathology
Esophageal diverticulum (Zenker's)
Invasive esophageal tumor
Esophageal stricture—undilated
Esophageal tear, fistula, or rupture
Severe esophagitis or ulceration
Esophageal varices especially if recent bleed
3. Instability of the cervical vertebrae
4. Fasting <4 h
5. Uncooperative patient

TABLE 52.1 CONTRAINDICATIONS TO TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Anesthesia and Sedation

Pharyngeal anesthesia helps reduce retching and gagging on probe insertion. The pharynx is sprayed with lidocaine or benzocaine. The patient may also gargle viscous lidocaine 2% for additional anesthetic effect. The effects of anesthesia are apparent within a few minutes and persist for 30 to 45 minutes after the procedure. Patients should not eat or drink during this period because of the risk of aspiration. At The Cleveland Clinic, we use both a narcotic and a benzodiazepine agent for sedation. Meperidine at a dose of 12.5 to 50.0 mg is given intravenously for its anxiolytic action. We usually start by giving 12.5 or 25.0 mg, increasing the dose as necessary while monitoring the effects on heart rate, blood pressure, and oximetry. For additional sedation and amnestic action, we give midazolam in an initial dose of 0.5 to 1.0 mg. Incremental doses are given every 3 minutes until the required effect has occurred or the vital signs suggest that further medication is contraindicated. Midazolam is a short-acting drug that has a half-life of 1 to 4 hours and that is active within 5 minutes. It can cause respiratory depression. Specific antagonists are now available: Reversed for midazolam and Naloxone for meperidine. These should be available for use in the event of significant respiratory depression or other adverse event. Additional sedative medication may be required throughout the procedure to maintain patient comfort. Ambulatory patients should be accompanied so that they do not have to drive home under the influence of sedative and narcotic drugs.

Need for Antibiotic Prophylaxis

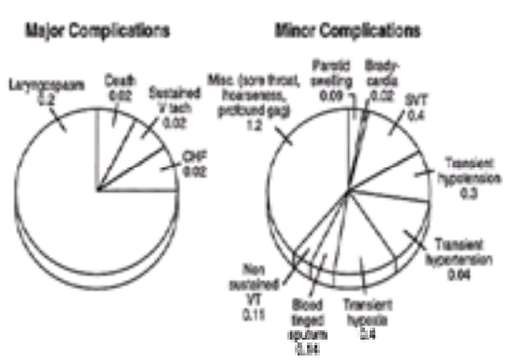
Upper gastrointestinal endoscopy is associated with bacteremia in 4% to 8% of reported series and in 45% of patients after esophageal dilatation (17). Many patients undergoing TEE have valvular or other lesions that pose a risk for endocarditis. Individual case reports have suggested that TEE was a causative factor in the development of endocarditis (18). Several studies involving a total of 522 patients have failed to detect significant bacteremia of oral flora associated with the TEE procedure or of clinical infection at follow-up (19,20 and 21). Therefore, the risk of endocarditis with TEE in experienced hands seems low. Routine prophylaxis for the procedure is not indicated. We do not routinely give antibiotic prophylaxis for patients with valve prostheses. Antibiotic coverage may be considered if the intubation is unexpectedly difficult or traumatic.

Probe Insertion

The probe is usually inserted by having the patient assume a lateral decubitus position while maintaining flexion of the neck. The probe is guided into the upper esophagus, and then the patient is asked to swallow. As the patient swallows, the probe is gently but firmly advanced into the distal esophagus. A bite block is inserted between the teeth to protect the probe, except in edentulous patients. Probe insertion in the ventilated patient is performed with the patient in the supine position. Probe passage is facilitated by removing nonessential tubes in the oropharynx, flexion of the neck, and manual advancement of the tongue and anterior pharyngeal wall in an anterior direction. The probe should never be forcibly advanced because this risks causing an esophageal tear. If the probe does not pass smoothly, assistance from an endoscopist should be sought. At the end of the procedure, the patient should be monitored until vital signs have returned to basal or at least normal values and the sedation has begun to wear off. The probe is washed and then sterilized by immersion in an antimicrobial solution (Cidex, Surgikos Inc.) for 20 minutes. The probe is rinsed and allowed to air dry.

SAFETY AND COMPLICATIONS OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Although TEE is invasive and is often performed on critically ill patients, successful intubation is possible in more than 98% of appropriately selected patients, and complications are uncommon (eFig. 52.2.1) (1,2). Inability to pass the probe is most often due to operator inexperience, patient noncompliance, and, rarely, pathologic lesions in the esophagus. Once successful probe passage has occurred, early cessation of the procedure occurs in less than 1% of cases. This is most often due to patient intolerance of the probe rather than the onset of a complication (1). The complication rate of TEE varies with the setting in which it is performed and the experience of the operator. TEE in the emergency room is reported to have a higher complication rate, likely due to the acuity of illness in this setting (22).



***e*FIGURE 52.2.1** Complications of transesophageal echocardiography depicted as percentages of the total number of transesophageal echocardiography procedures (q = 7,134) performed at the Mayo Clinic from 1988 to 1993. CHF, congestive heart failure; misc, miscellaneous; SVT, supraventricular tachycardia; VT or V tach, ventricular tachycardia. (From Khandheria BK, Seward JB, Tajik AJ. Transesophageal echocardiography. *Mayo Clin Proc* 1994;69:856–863, with permission.)

Major Complications

Major complications such as death, esophageal perforation, serious arrhythmia, congestive heart failure, and laryngospasm are uncommon and occur in less than 0.3% of patients (1). One death was reported out of 3,827 consecutive patients examined in one series. This was due to arrhythmia after the procedure in a patient with autopsy-proven myocarditis (2). Another death was reported in a series of 10,419 patients. This was due to esophageal perforation in a patient with unsuspected neoplasm that had invaded the esophagus (1). A third death after TEE has been reported in a patient with acute aortic dissection in whom aortic rupture occurred during a bout of severe retching and nausea after probe insertion (23). Serious esophageal injury may occur, and both esophageal perforation and tear have been reported (24). Absence of significant damage to the mucosal lining of the esophagus after prolonged TEE examination has been demonstrated in animals (25). Laryngospasm and severe bronchospasm occasionally occur because of aspiration of anesthetic agents or lubricants used for probe insertion and rarely from inadvertent passage of the probe into the airway (26).

Minor Complications

Minor complications such as transient hypoxia, hypotension, hypertension, angina, bronchospasm, atrioventricular block, supraventricular tachycardia, and nonsustained ventricular arrhythmia occur in less than 3% of cases (2). Transient vocal cord paralysis has been noted in patients undergoing neurosurgical procedures who were studied in the upright position (27). Compression of anomalous vascular structures by the esophageal probe has also been reported (28). Sore throat and mild dysphagia is common after the procedure and rarely is prolonged for more than 24 hours. Toxic and allergic reactions to the drugs used in patient preparation

occur but are uncommon. The most common reaction encountered is methemoglobinemia in susceptible subjects receiving topical anesthesia (29).

Technical Problems

A number of technical factors may affect the quality of the TEE examination. These include air in the esophagus and stomach and poor contact between the probe and the esophagus. Distorted anatomy from prior surgery, a tortuous aorta, or a large hiatal hernia may also interfere with imaging. Problems with the probe during the procedure such as mechanical or electronic failure occur but are uncommon (1,30).

IMAGING PLANES

The esophageal window imposes a number of challenges in imaging the heart and related structures in a standard format. The esophagus is not usually precisely aligned with the true long and short axis of the heart (Fig. 52.3). Furthermore, the relationship between the esophagus and cardiac structures is variable. Standard imaging planes have been described for TEE. However, the maneuvers required to acquire them are not always predictable but are facilitated by multiplane technology. Interpretation of esophageal images is often challenging initially despite their high quality. The orientation of the images is different to TTE, as the images are acquired from behind rather than from the front of the heart. The multiple imaging planes available and the ability to resolve structures rarely visible with other imaging modalities add to the initial difficulty. TEE requires a familiarity with the three-dimensional anatomy of the heart and aorta as imaged from the esophagus. This can best be obtained by performance of multiple procedures while supervised by an experienced operator. The transesophageal examination is usually goal-oriented. Specific questions unanswered by the prior transthoracic study are first addressed, followed by a comprehensive evaluation of other structures. It is important to follow a standard examination format encompassing all major cardiac structures and the aorta so that a complete examination is always performed.

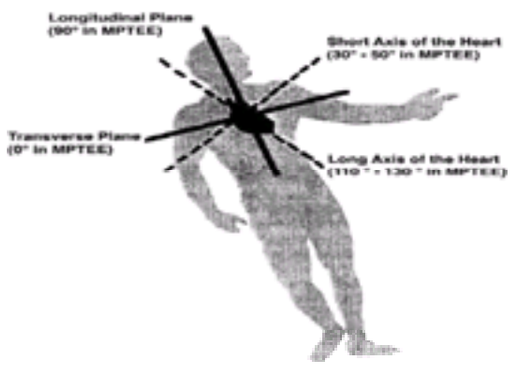


FIGURE 52.3 Relationship of horizontal and vertical vectors of the heart to those of the body and esophagus. The transverse (0-degree) and longitudinal (90-degree) esophageal imaging planes do not parallel the true short and long axis of the heart, which are imaged at 30 to 50 degrees and 110 to 130 degrees, respectively. The true short and long axis varies with individual habitus. MPTEE, multiplane transesophageal echocardiography. (From Schneider AT, Hsu TL, Schwartz S, Pandian NG. Single, biplane, multiplane, and three-dimensional transesophageal echocardiography. Echocardiographic-anatomic correlations. *Cardiol Clin* 1993;11:361–387, with permission.)

Base of the Heart

At approximately 30 cm from the incisors, the probe lies behind the left atrium and the base of the heart. In the transverse plane at this level, the aortic valve is seen in cross-section, with portions of the left and right atrium and interatrial septum (Fig. 52.4). Withdrawing the probe slightly from this view allows imaging of the left atrial appendage, the superior vena cava, the right ventricular outflow tract, ostia of the coronary vessels and the main pulmonary artery to its bifurcation, and a portion of the right pulmonary artery. The proximal portion of the ascending aorta is imaged in this view but it and the distal portions of the left pulmonary artery are difficult to image because of the interposition of air-filled large airways. The longitudinal imaging plane at this level provides important images of the great vessels, interatrial septum, left atrial appendage, and pulmonary veins. When the transducer is rotated to the left, a two-chamber view of the left atrium and left ventricle is seen. The left atrial appendage and the left pulmonary veins are often most easily imaged in this view. The mitral valve is also well seen in this view, and mitral regurgitation may be sought here. With clockwise rotation of the probe around its long axis, the right ventricular outflow tract, pulmonary valve, and main pulmonary artery may be imaged. With additional clockwise rotation, the aortic valve and ascending aorta are seen. This view is important in the evaluation of the ascending aorta particularly with regard to dissection and in assessing aortic regurgitation. Finally, with further clockwise rotation, the right atrium, interatrial septum, and superior vena cava may be imaged. This plane is important in the detection of a communication at the atrial level and in assessing pathology of the superior vena cava. Multiplane imaging is especially useful at this level in allowing the true long and short axis of the aortic valve and ascending aorta to be obtained. Typically, the true short axis is seen at approximately 30 to 60 degrees and the true long axis at 120 to 150 degrees (eFig. 52.4.1).

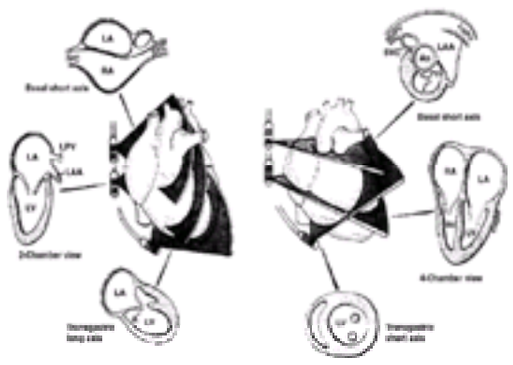
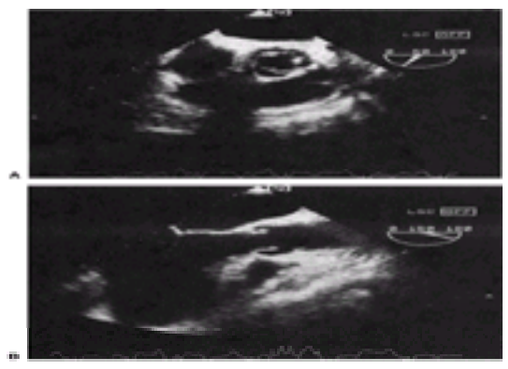


FIGURE 52.4 Transverse **(A)** and longitudinal **(B)** imaging planes at base of the heart, midesophagus, and transgastric windows. A, anterior leaflet of the mitral valve; Ao, aorta; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LPV, left pulmonary vein; LUPV, left upper pulmonary vein; LV, left ventricle; PV, pulmonary valve; RA, right atrium; RUPV, right upper pulmonary vein; RV, right ventricle; SVC, superior vena cava. (From Fisher EA, Stahl JA, Budd JH, Goldman ME. Transesophageal echocardiography: procedures and clinical application. *J Am Coll Cardiol* 1991;18:1333–1348, with permission.)



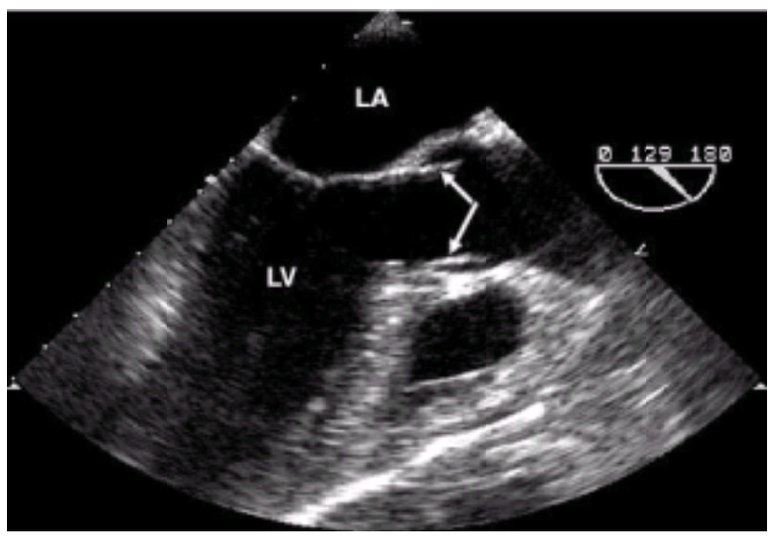
***e*FIGURE 52.4.1** Multiplane images of a normal aortic valve. The true short axis was seen at 60 degrees **(A)** and the true long axis **(B)** at 150 degrees in this patient.

Video 52.1 A 60-degree transesophageal short-axis view **(A)** of the aortic valve demonstrating a quadricuspid (as opposed to the typical trileaflet) valve. Note the presence of four leaflets and four commissures. The second video shows a 60-degree transesophageal short-axis view of quadricuspid aortic valve with color Doppler demonstrating moderate central aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

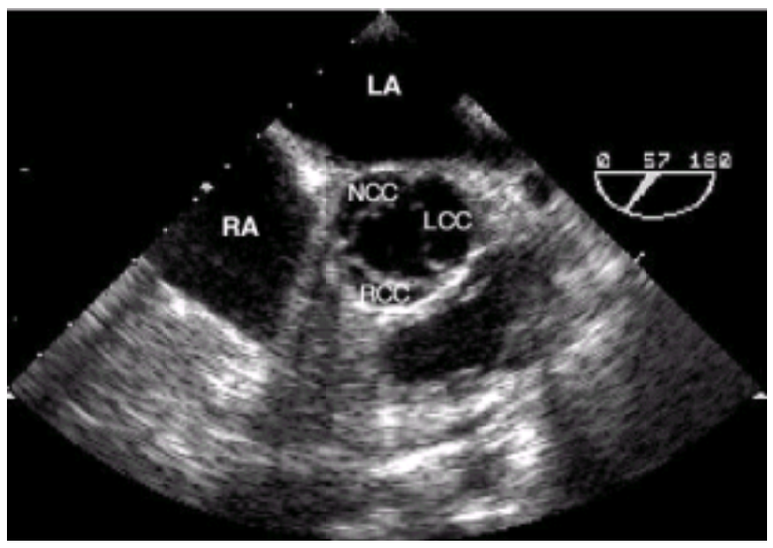
Video 52.2 A 60-degree transesophageal short-axis view **(A)** of the aortic valve demonstrating a quadricuspid (as opposed to the typical trileaflet) valve. Note the presence of four leaflets and four commissures. The second video shows a 60-degree transesophageal short-axis view of quadricuspid aortic valve with color Doppler demonstrating moderate central aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.3 A normal 120-degree transesophageal echo demonstrating a normal aortic valve in long-axis view and a normal mitral valve. The posterior mitral leaflet is towards the left of the screen, and the anterior mitral leaflet is in the center of the screen. The anterior/anteroseptal wall of the left ventricle is in the center of the screen, and the posterior wall is to the left. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

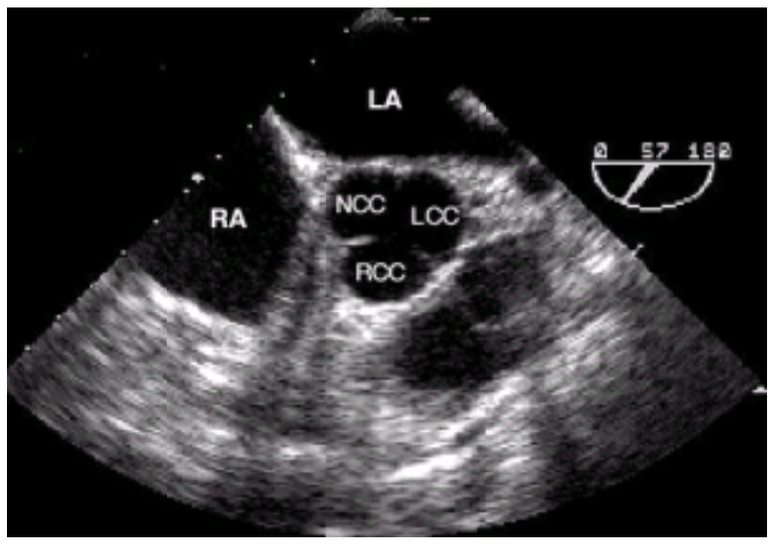
Video 52.4 A short-axis 60-degree transesophageal echo view of a normal, tri-leaflet aortic valve. The noncoronary cusp of the aortic valve is located toward the upper left of the screen, the left coronary cusp is towards the upper right, and the right coronary cusp is towards the bottom. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Systolic frame of a 120-degree transesophageal echo view demonstrating the long axis of the aortic valve. The aortic valve (*double arrow*) is open while the mitral valve to the left of the screen is closed.



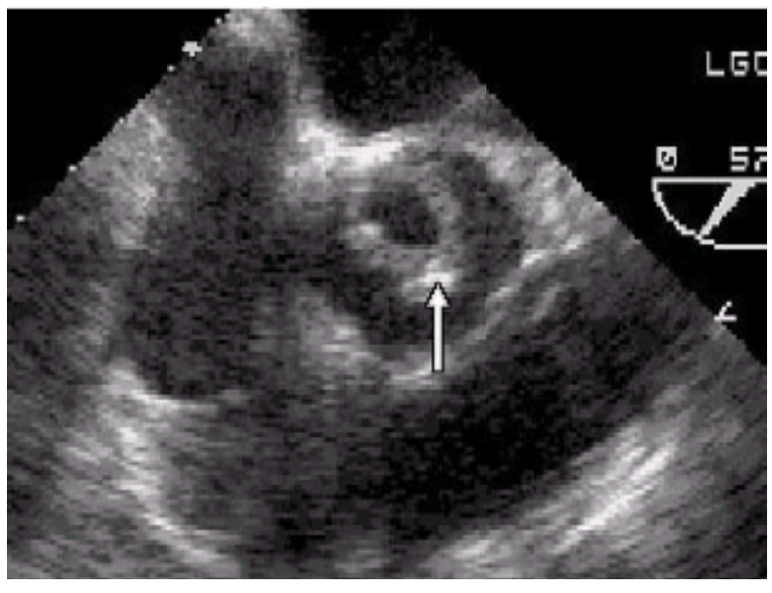
Short-axis transesophageal view demonstrating the aortic valve in systole. The noncoronary cusp is in the upper left of the screen and the left coronary cusp is in the upper right of the screen and the right coronary cusp at the bottom of the screen.



Short-axis transesophageal echo view of the aortic valve seen in diastole. Note the closed leaflets of the aortic valve.

Midesophageal Views

By advancing the probe into the midesophagus beyond the base of the heart, portions of both atria and ventricles, the interventricular septum, and the mitral and tricuspid valves are seen in the transverse imaging plane (Fig. 52.4). A four-chamber view is acquired at this level by flexing the probe posteriorly. This view is similar to the apical four-chamber view acquired transthoracically, except that the imaging plane does not cut through the true apex. This represents an inherent limitation of transesophageal imaging in the acquisition of ventricular volumes and in the detection of apical thrombus. This imaging plane is helpful in detecting regurgitation at the mitral and tricuspid valves and in global assessment of ventricular function. With slight counterclockwise rotation of the transducer, the left ventricular outflow tract and the proximal ascending aorta are seen. Longitudinal imaging at this level produces a two-chamber image of the heart already described. Multiplane images at this level are useful in distinguishing the individual leaflets of the mitral valve and the scallops of the posterior leaflet and in detecting eccentric jets of mitral regurgitation. Optimal differentiation between anterior and posterior mitral leaflet pathology is at approximately 140 degrees, whereas the full extent of the mitral closure line, from medial to lateral commissure, is at approximately 50 degrees.



Short axis transesophageal view of a unicuspid aortic valve with aortic stenosis. The arrow designates the single commissure present in this aortic valve. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)

VIDEO

Video 52.5 A normal 60-degree transesophageal echo view of a mitral valve demonstrating the medial commissure (*left*) and the lateral commissure (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.6 A 90-degree transesophageal echo view (with the probe rotated to the left) demonstrating a normal mitral valve and the left atrial appendage. The anterior mitral leaflet is towards the right of the screen, and the posterior leaflet is towards the left. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.7 Transesophageal echo view (90-degree with probe rotated to the right) demonstrating the right atrium with the inferior vena cava entering from the upper left and the superior vena cava from the right of the screen. The interatrial septum is at the top of the screen with the left atrium located superiorly. This view is useful to look for patent foramen ovules, atrial septal defects, and masses entering the right atrium from the inferior vena cava or attached to the septum. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.8 This 45-degree transesophageal echo view demonstrates the pulmonary artery bifurcation in the center of the screen and the aorta in cross section to the left. This can be useful to see a large saddle pulmonary embolus at the bifurcation. However, smaller, more distal emboli would be missed. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.9 A 90-degree transesophageal echo view of the left ventricle demonstrating the anterior wall on the right and the inferior wall on the left. The anterior mitral leaflet is to the right, and the posterior leaflet is to the left. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Transgastric Views

To obtain the transgastric series of views, the probe is advanced into the stomach. Generally, the tip of the probe must be flexed to bring the transducer in contact with the mucosa of the gastric fundus. In the transverse plane, a short-axis view of the left and right ventricle is acquired (Fig. 52.4). With increased anteflexion of the probe, the base of the heart and the mitral and tricuspid valves are imaged, whereas lesser degrees of anteflexion bring the image more toward the apex. This view allows an assessment of regional and global left ventricular function. The mitral valve apparatus and leaflets are also well seen in this view. This view is most often used when ventricular function is being monitored. A longitudinal view at this level allows the mitral valve and the left ventricle to be imaged in long axis. The anterior and inferior walls are well seen, as are the papillary muscles and chordae. The true apex of the heart is most likely to be displayed in this view. Rotation of the probe in the long axis frequently allows the left ventricular outflow tract to be aligned with the Doppler cursor so that a Doppler evaluation of the aortic valve and left ventricular outflow tract may be performed. Further rotation allows examination of the right ventricle and outflow tract. Multiplane imaging at this level facilitates the evaluation of the left ventricular outflow tract and examination of the tricuspid valve and its component leaflets. Another series of images is frequently possible by passing the probe further into the stomach and anteflexing (the deep transgastric view). In this view, the transducer is close to the apex, and the images obtained simulate those acquired in a transthoracic five-chamber or subcostal view. This view often optimizes Doppler interrogation of the aortic valve and outflow tract.

VIDEO

Video 52.10 Transgastric short-axis view of a mitral valve after the Batista left ventricular remodeling procedure. Note the Alfieri stitch placed in the mitral leaflet tips creating the characteristic figure-of-eight appearance of the mitral valve. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.11 A transgastric transesophageal echo view at 90 degrees demonstrating the left ventricle in long axis. The anterior wall is toward the bottom of the screen and the inferior wall is at the top with the left ventricular apex towards the left and the mitral valve towards the right. Note the inferior basal hypokinesis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

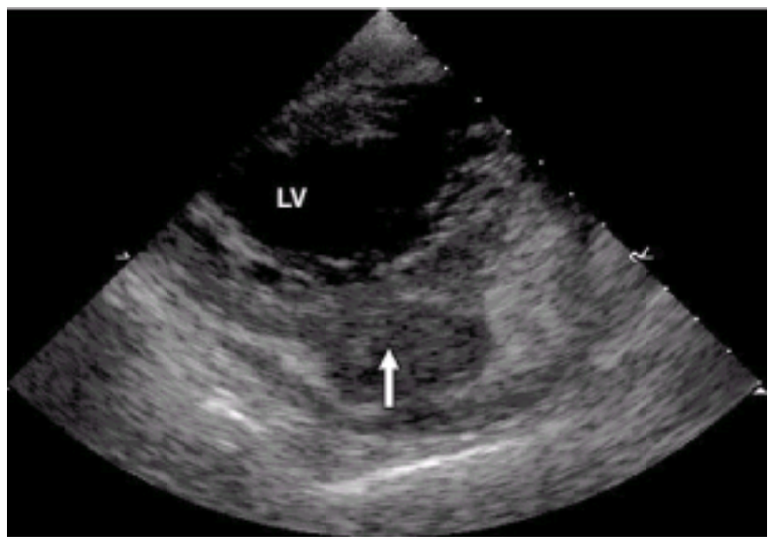
Video 52.12 A transgastric transesophageal echo short-axis view of the left ventricle. The inferior and posterior walls are at the top of the screen, the septum towards the left, the anterior wall at the bottom of the screen, and the lateral wall towards the right. Note the posterolateral hypokinesis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

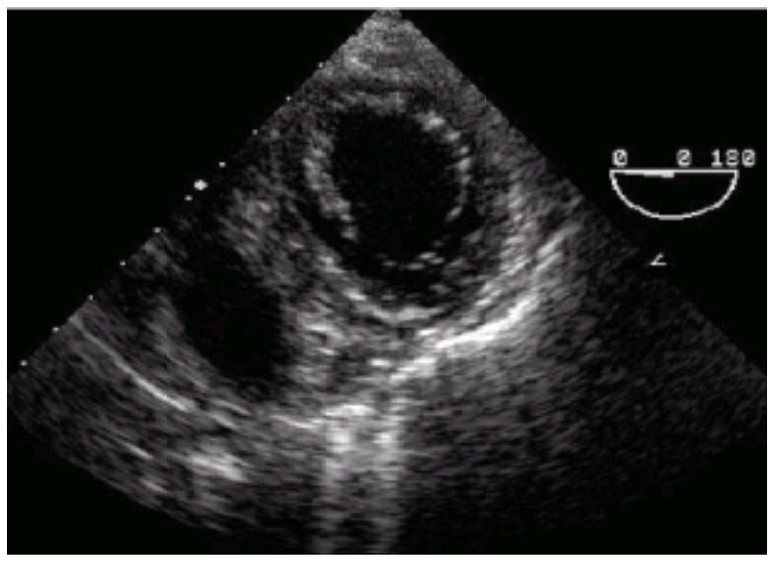
Video 52.13 A transgastric transesophageal echo view of the mitral valve in short axis. The posterior mitral leaflet is to the right of the screen with the anterior mitral leaflet to the left. The posteromedial commissure is at the top, and the anterolateral commissure is at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

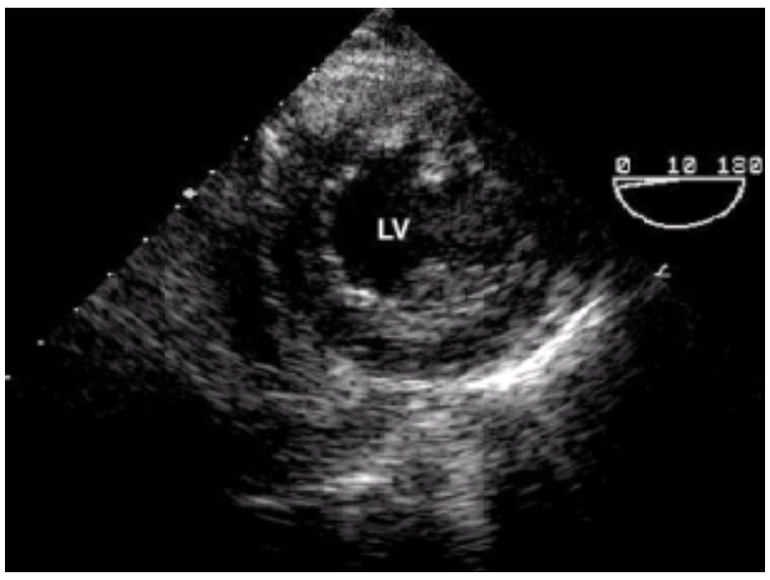
Video 52.14 Deep 90-degree transgastric view of the aortic valve obtained by starting with the transgastric long-axis view of the left ventricle and advancing the probe and retroflexing. This view is useful to measure aortic valve gradients. This patient has a heavily calcified aortic valve seen at the center of the screen. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



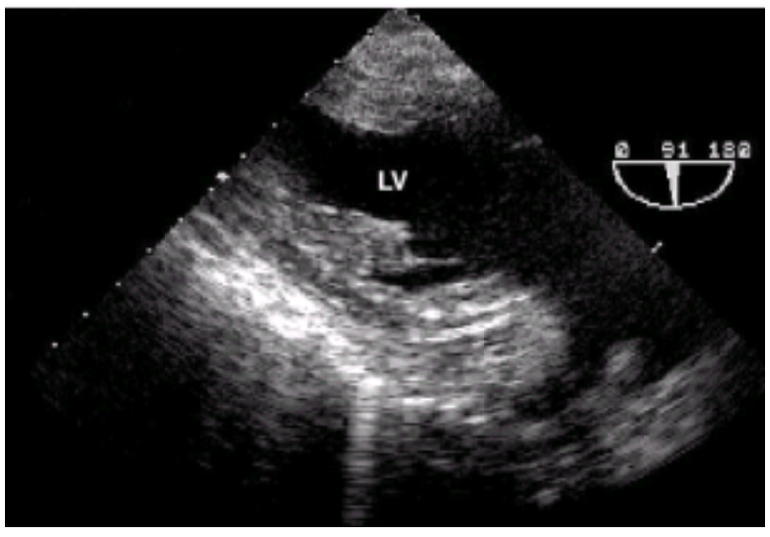
Transgastric long-axis view of a metastatic sarcoma within the anterior wall of the left ventricle at the bottom of the screen (designated by the arrow).



Transgastric transesophageal echo demonstrating the mitral valve in short axis. The anterior mitral leaflet is to the left of the screen and the posterior leaflet is to the right. The medial commissure is at the top while the lateral commissure is at the bottom of the screen.



Transgastric short-axis transesophageal view of the left ventricle. The inferior/posterior walls are at the top of the screen, the lateral wall to the right, the anterior wall at the bottom, and the septum to the left.



Transgastric transesophageal view of the left ventricle in long axis. The inferior wall is at the top of the screen, apex to the left, mitral valve to the right, and the anterior wall at the bottom of the screen.

Aorta

The aorta may be examined from the ascending aorta to below the diaphragm (Fig. 52.5). The examination of the ascending aorta has already been described. The distal portion of the ascending aorta cannot be examined using the transverse plane because of the interposition of the trachea. The longitudinal and multiplane imaging planes may allow an additional area of imaging, but not all of the ascending aorta can be identified. The descending aorta is evaluated by rotating the probe to the left and posteriorly at midesophageal level. The aorta is seen in cross-section using the transverse transducer at this level and in long axis using the longitudinal transducer. More distal portions of the aorta are examined by advancing the probe, whereas the proximal portions of the descending aorta are imaged by withdrawing the probe and rotating anteriorly and to the left to keep the aorta in view. As the probe is withdrawn to approximately 20 to 25 cm, the transverse arch and distal portions of the ascending aorta are seen. The transverse plane cuts the arch in long axis at this level, and the longitudinal plane provides a short-axis view. The proximal portions of the left subclavian and other head and neck vessels may be imaged with a longitudinal or multiplane transducer. Examination of the aortic arch is usually performed last, as the probe often elicits a gag reflex at this level, even in well-prepared patients.

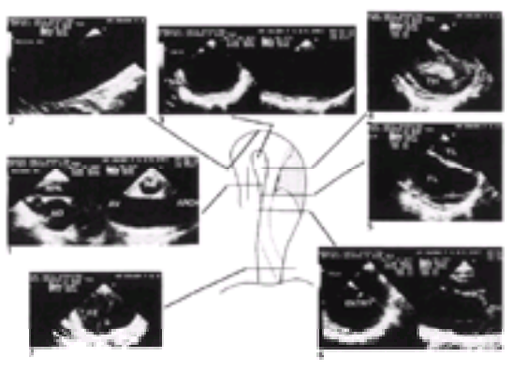
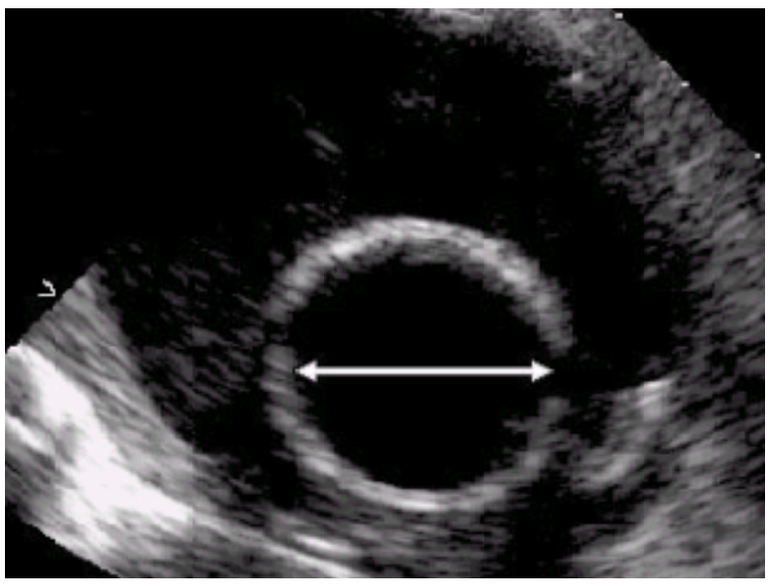


FIGURE 52.5 Imaging planes of aorta. Biplane imaging planes of the aorta illustrated in a patient with dissection flap confined to the distal aorta. **Panel 1:** Transverse (*left*) and longitudinal plane (*right*) images of the ascending aorta. **Panel 2:** Transverse plane image of the aortic arch. **Panel 3:** Transverse (*left*) and longitudinal (*right*) plane images of the proximal descending aorta at the junction with the arch. **Panels 4–7:** Transverse (**panels 4–7**) and longitudinal (**panel 6**, *right*) plane images of the aortic dissection flap and its variable orientation in various portions of the descending aorta. AO, aorta; AV, aortic valve; Entry, communication between true and false lumen; FL, false lumen; PA, pulmonary artery; RPA, right pulmonary artery; TH, thrombus; TL, true lumen. (From Matsuzaki M, Toma Y, Kusukawa R. Clinical applications of transesophageal echocardiography. *Circulation* 1990;82:709–722, with permission.)

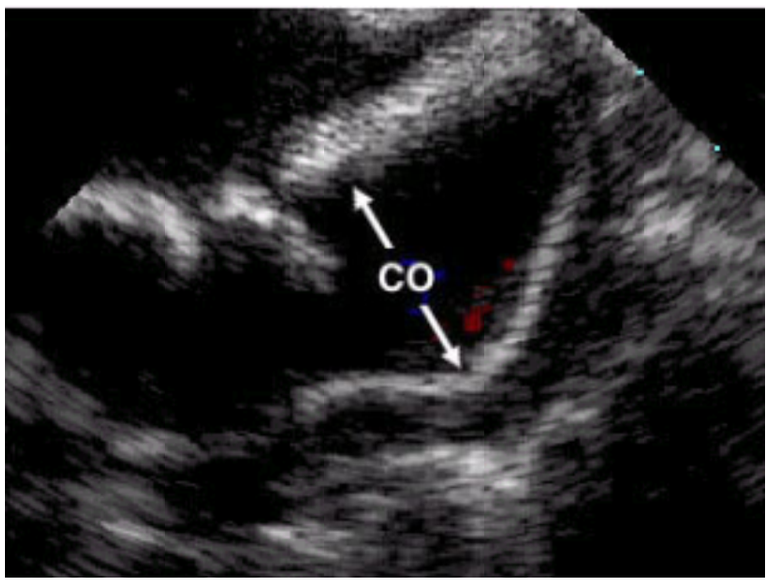
Aortic thrombus in a patient with lupus anticoagulant. A probe is placed behind the thrombus within the lumen of the aorta (*yellow arrow*).

VIDEO

Video 52.15 Aortic dissection (left anterior oblique). Type A dissection of the aorta is manifested on the cine image loop by a mobile intimal flap extending from the mid-ascending aorta to the descending thoracic aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



This short-axis view of the descending aorta is seen by intraoperative transesophageal echo showing the distal end of the aortic graft following the first stage of an elephant trunk procedure. Note the circular appearance of the graft within the aneurysmal descending aorta. The arrow demonstrates the diameter of the descending aortic graft.



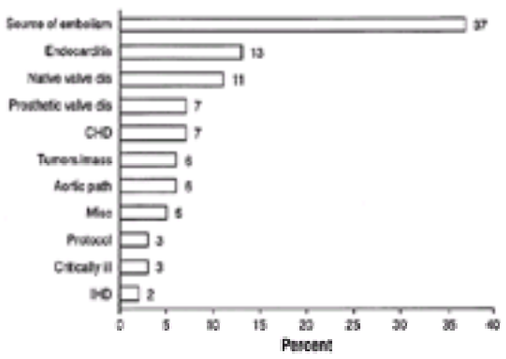
Intraoperative echo demonstrating the distal end of the aortic graft after the first stage of an elephant trunk procedure seen in long axis. Note the tubular free end of the graft within the aneurysmal descending aorta. CO designates the diameter of the conduit.

INDICATIONS FOR TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Left and Right Atria

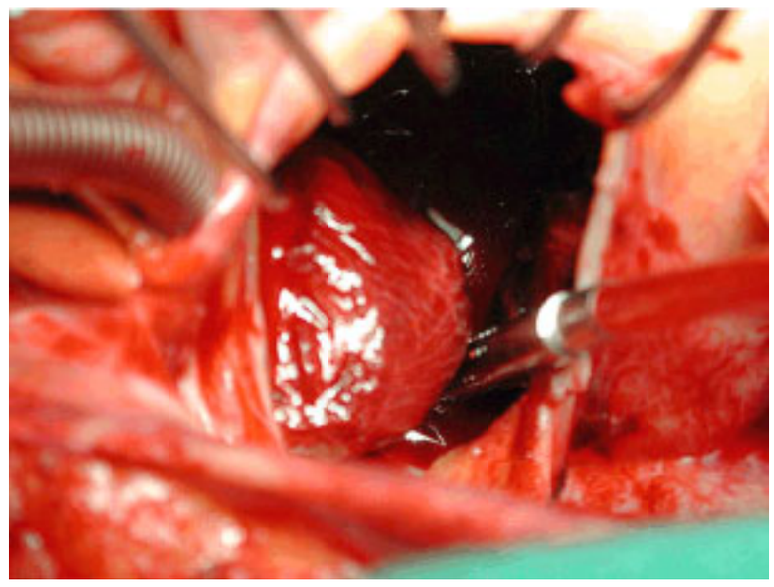
Atrial Thrombus

TEE is now the technique of choice in the evaluation of atrial thrombus (eFig. 52.5.1 and Fig. 52.6) and is superior to TTE in detecting atrial appendage thrombus (31,32). Left atrial thrombus is associated with mitral stenosis, atrial dilatation, atrial fibrillation, left ventricular dysfunction, or a combination of these factors (33) and is an independent risk factor for thromboembolism (34). The sensitivity and specificity of TEE in the detection of thrombus in both the body and appendage (32) of the left atrium are excellent and have exceeded 90% in a number of large series with surgical validation (35), as compared with less than 50% for TTE. TEE has shown that patients with atrial flutter are also at risk for development of atrial thrombus and are thus at risk of embolization especially with cardioversion (36). Patients with atrial fibrillation and mitral valve disease frequently undergo ligation of the atrial appendage. TEE has shown that flow may persist into the atrial appendage despite surgical ligation in more than one of three patients and who therefore remain at risk of thrombus formation and embolization from the atrial appendage. (37). TEE is also superior to TTE in the detection of right atrial thrombus (38).

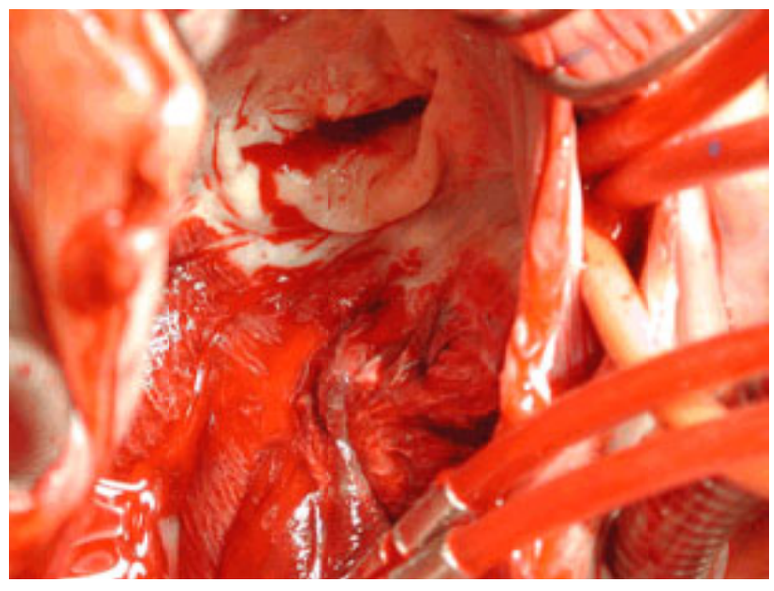


***e*FIGURE 52.5.1** Bar diagram of indications for 7,134 transesophageal echocardiography examinations performed at the Mayo Clinic from 1988 to 1993. CHD, congenital heart disease; IHD, ischemic heart disease; Misc, miscellaneous cardiac conditions; Path, pathologic conditions. (From Khandheria BK, Seward JB, Tajik AJ. Transesophageal echocardiography. *Mayo Clinic Proc* 1994;69:856–863, with permission.)

FIGURE 52.6 Left atrial appendage thrombus (*arrow*). LA, left atrium.



Intraoperative field looking into the left atrium of a patient with severe mitral stenosis who developed extensive clot within the left atrium. Notice the large mass in the center of the field, to the left of the opening within the left atrium. This is the largest portion of the left atrial thrombosis.

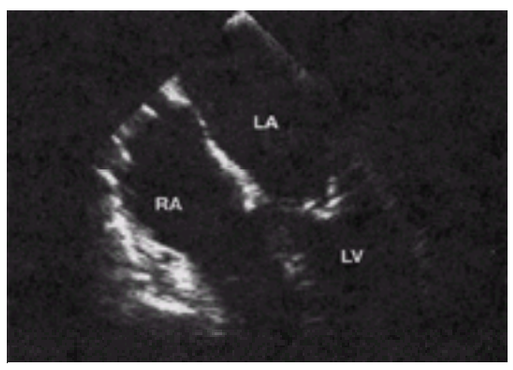


Intraoperative field looking into the left atrium after the large left atrial thrombus was resected demonstrating the rheumatic mitral valve at the top of the screen. Note the scarred, thickened, restricted mitral leaflets. This patient had severe mitral stenosis with a mean pressure gradient of 20 mm Hg across the valve and a mitral valve area of 0.7 cm^2.

Surgical specimen of the large left atrial mass explanted at the time of surgery. Note its somewhat pale, glistening surface, suggesting that the thrombus is not fresh and possibly endothelialized.

Spontaneous Contrast

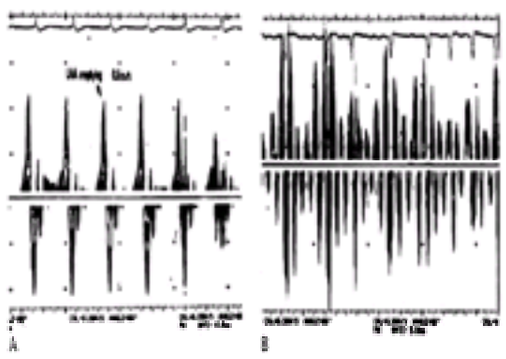
TEE often identifies swirling echoes of spontaneous contrast in the left atrium or appendage, especially in those with atrial fibrillation or atrial thrombus (eFig. 52.6.1) (39). This is reported in as many as 20% of all patients undergoing TEE but is rarely seen in TTE (39,40). The level of intensity of the contrast varies within the atrium and appendage and is most dense in areas of lowest flow such as the atrial appendage. The precise mechanism of its generation is uncertain but is thought to relate to rouleaux formation of red blood cells in areas of low flow (40,41). This theory is supported by the reduced incidence of this phenomenon after successful dilatation of stenotic mitral valves (42). Anticoagulation has not been shown to affect the prevalence or intensity of spontaneous contrast (40,41). Spontaneous contrast in the left atrium is an independent risk factor for systemic embolization in both mitral stenosis and nonvalvular atrial fibrillation (41,43). Spontaneous contrast occurs in 2% of patients with sinus rhythm and is an independent risk factor for stroke (44).



***e*FIGURE 52.6.1** Swirling echoes of spontaneous contrast in left atrium (LA) in a patient with mitral stenosis. LV, left ventricle; RA, right atrium.

Atrial Mechanical Function

TEE provides a unique window to atrial mechanical function (45). Investigators have measured the velocity and pattern of left atrial and appendage blood flow (46). Characteristic patterns of flow have been described in sinus and atrial rhythms (eFig. 52.6.2) (45). Reduced or absent flow and a fibrillatory pattern are most often associated with spontaneous contrast and thrombus formation (45). Others have noted that reduced velocity of flow in the posterior portion of the atrial body is associated with thrombus formation and systemic embolization (47). A reduction in appendage flow velocity immediately after cardioversion has also been noted (48). Atrial appendage velocity has been used to predict likelihood of successful cardioversion, maintenance of normal rhythm, and risk of thromboembolism, with variable results (49,50). A left atrial appendage emptying velocity of less than 20 cm per second is associated with poorer atrial function, greater likelihood of thrombus and spontaneous contrast, and a greater likelihood of subsequent events (51). Reduced left atrial appendage velocity is determined by factors such as hypertension, atrial size, atrial fibrillation, ischemic heart disease, and age (51) but remains an independent risk factor for embolism even when these factors are accounted for.



***e*FIGURE 52.6.2** Patterns of flow in atrial appendage by transesophageal echocardiography pulsed Doppler. **A:** Normal sinus rhythm. **B:** Atrial fibrillation.

Transesophageal Echocardiography Screening before Mitral Valvuloplasty and Cardioversion

Atrial thrombus poses a risk for embolization during percutaneous mitral valvuloplasty and electrical cardioversion of atrial fibrillation (52). TEE has been used to screen for atrial thrombus before these procedures. TEE detected atrial thrombus in 26% of 19 patients being considered for balloon valvuloplasty of the mitral valve, only one of which was detected by TTE (53). Patients with atrial thrombus detected by TEE were excluded from the procedure. TEE has also been used to allow early cardioversion of patients with chronic atrial fibrillation without the standard 3 to 4 weeks of systemic anticoagulation. In one prospective study of TEE cardioversion, left atrial thrombus was found in 15% of 233 patients with atrial fibrillation of unknown or prolonged duration (39). Cardioversion was performed without a prolonged interval of anticoagulation in those without evidence of atrial thrombus and no embolic complications were recorded (39). A prospective randomized trial of prolonged anticoagulation versus TEE cardioversion (Assessment of Cardioversion Using Transesophageal Echocardiography study) (54) has been completed. The embolic event rate in both the TEE and conventional group were lower than expected and similar. Although inadequately powered to show a difference between the two strategies, this study convincingly demonstrates a low embolic event rate associated with TEE-guided cardioversion. TEE cardioversion was associated with a shorter duration of anticoagulation but not with a greater likelihood of remaining in sinus rhythm (55). TEE cardioversion appears to be particularly cost-effective in patients with increased risk of hemorrhage with anticoagulation (56). Thromboembolic complications have been reported in patients who were cardioverted despite TEE results that were negative for atrial thrombus but who were inadequately anticoagulated (57). Temporary deterioration of atrial function after return of normal sinus rhythm with subsequent thrombus formation and embolization is postulated to account for these embolic events rather than embolization of thrombus undetected by TEE (46,48,58). The deterioration in atrial function occurs even with chemical cardioversion (59) and does not occur after delivery of a shock to the atrium in patients with normal sinus rhythm (60). The deterioration in atrial function is less after atrial flutter conversion as compared with atrial fibrillation (61). Anticoagulation for a number of weeks is indicated after cardioversion even when TEE does not show atrial thrombus to minimize the risk of embolism after the procedure.

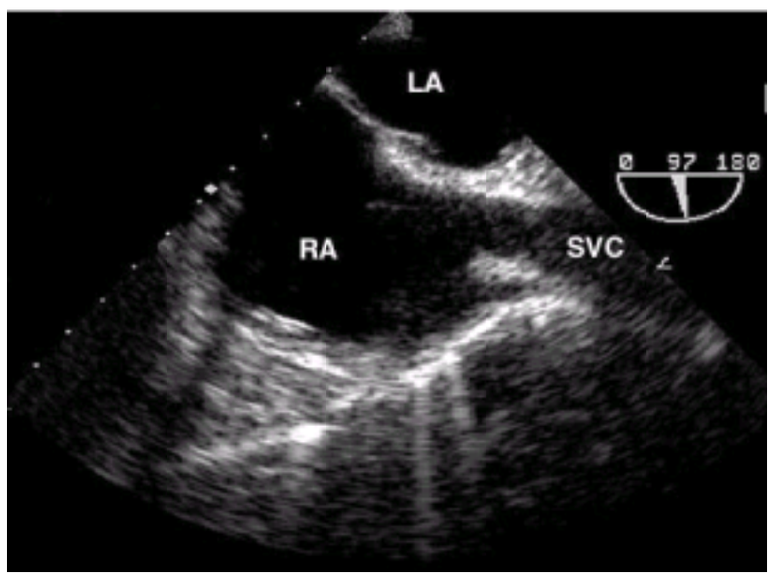
Interatrial Septum

Atrial Septal Defect

TEE is the technique of choice in the diagnosis of abnormalities of the interatrial septum. The atrial septum is visualized in the long-axis view of the base of the heart. TEE is especially useful in the detection of small atrial septal defects (less than 5 mm) (62) and of sinus venosus defects. In one study, TEE detected all sinus venosus defects, whereas only 25% were detected by TTE (63). Anomalous drainage of pulmonary veins, which often accompanies sinus venosus–type defects, is also reliably detected by TEE (63). TEE measurements of anatomic size and shunt flow compare well with those measured at the time of surgery (64).

VIDEO

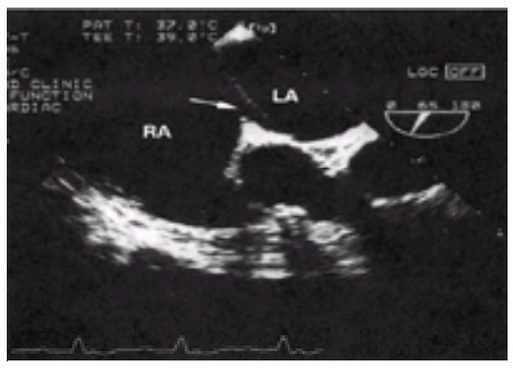
Video 52.16 Transesophageal echo with color Doppler flow demonstrating a secundum atrial septal defect with left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Transesophageal echo demonstrating the right atrium with the inferior vena cava entering from the upper left and the superior vena cava from the right of the screen. The interatrial septum and left atrium are located superiorly. This view is useful to evaluate patent foramen ovales, atrial septal defects, or masses entering the right atrium from the inferior vena cava or attached to the interatrial septum.

Patent Foramen Ovale

Patent foramen ovale occurs in 25% to 30% of the normal population and is more commonly found in those with unexplained stroke (eFig. 52.6.3) (65,66). The latter finding and the TEE demonstration of passage of a paradoxical embolus through a patent foramen ovale support its causative role in cerebral embolism (Fig. 52.7) (67). TEE is highly sensitive and specific in the detection of patent foramen ovale and is superior to TTE (68). In one study, TEE detected all of the defects subsequently found at autopsy (69). In another study, patent foramen ovale was detected by TEE in 22% of patients and only in 8% by TTE (70). Contrast venous injection is useful in the detection of right-to-left shunting, whereas color-flow imaging is the method of choice in detecting left-to-right shunting (71). Both color-flow and contrast techniques are performed in practice. Characteristics of patent foramen ovale by TEE that predict an increased likelihood of embolic event include larger size and increased shunt flow across the defect (72).



***e*FIGURE 52.6.3** Patent foramen ovale by multiplane transesophageal echocardiography (*arrow*). LA, left atrium; RA, right atrium.

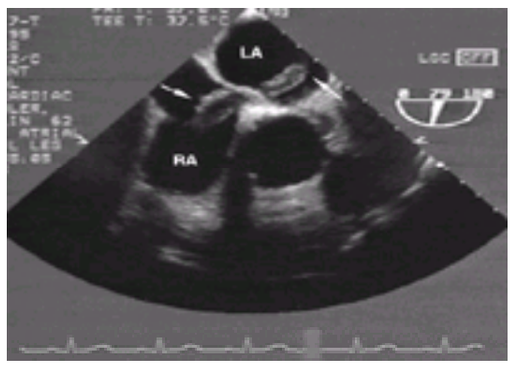


FIGURE 52.7 Embolus in transit across a patent foramen ovale (*arrows*). LA, left atrium; RA, right atrium.

Atrial Septal Aneurysm

Atrial septal aneurysm (ASA) is also a risk factor for cerebral embolism and is detected more frequently by TEE than by conventional echocardiography (73). ASA occurs in 2.2% of the population and is associated with a single patent foramen ovale or rarely with multiple fenestrations (74,75). It is three times more common in those with a history of cerebral ischemia (74). The embolic risk of this condition is due to the associated shunt or rarely to thrombus formation within the aneurysm, which occurs in 1% of patients with ASA (76). An ASA is recognized by the finding of a redundant highly mobile outpouching of the atrial septum that is at least 10 mm wide and 15 mm long. (Fig. 52.8). In a multicenter study, TEE detected 195 patients with this entity, whereas only half of these were detected by TTE (76). Half of the patients had evidence of an atrial shunt, whereas embolic events had occurred in 44%.

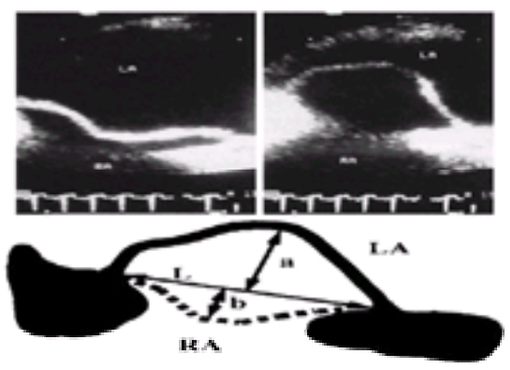
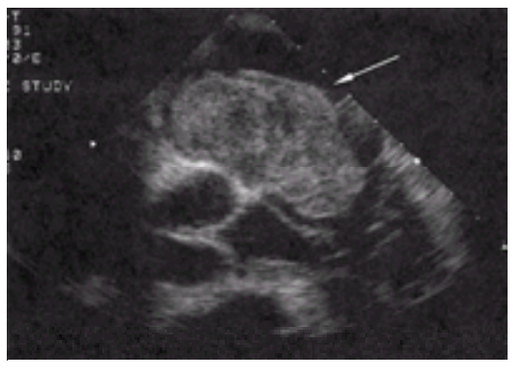


FIGURE 52.8 Mobile atrial septal aneurysm by transesophageal echocardiography. Bottom panel illustrates measurements. a and b, maximal extent of oscillation into left and right atrium, respectively; L, length; LA, left atrium; RA, right atrium. (From Mugge A, Daniel WG, Angermann C, et al. Atrial septal aneurysm in adult patients. A multicenter study using transthoracic and transesophageal echocardiography. *Circulation* 1995;91:2785–2792, with permission.)

Other Atrial Abnormalities

The membrane of cor triatriatum is particularly well-delineated by TEE. Atrial tumors such as myxomas are usually well-characterized by TTE. TEE is useful when there is diagnostic uncertainty and is superior in detecting the site of attachment to the wall and the composition of the tumor (eFig. 52.8.1) (77). It is also useful in elucidating the nature of other masses suspected by TTE and in distinguishing them from normal variants.

Video 52.17 Transesophageal view demonstrating the right atrium with the inferior vena cava off to the left of the screens, the superior vena cava to the right, and the left atrium at the top, with the interatrial septum in the middle. This view shows a hemangioma in the interatrial septum found incidentally at the time of preoperative transesophageal echo for mitral valve replacement for severe mitral regurgitation. Intraoperatively, the mass was highly vascular as expected and was resected. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 52.8.1** Large left atrial myxoma (*arrow*) prolapsing through mitral valve.

Endocarditis

Diagnosis

Echocardiography is now an integral part of the evaluation of suspected endocarditis (78). TEE is more sensitive in diagnosing endocarditis, as it provides better resolution of vegetations than TTE. In one study, TTE detected 63% of vegetations, whereas TEE detected all of them (Fig. 52.9) (79). In that study, TTE had equivalent diagnostic accuracy to TEE in detection of vegetations greater than 11 mm but only detected 25% of vegetations less than 5 mm in size and 69% of vegetations of a size between 6 and 10 mm. In other studies in which the ability of TEE and TTE to detect vegetations has been compared, the sensitivity of TTE has varied from 25% to 60%, whereas that of TEE has varied from 87% to 100% (79,80 and 81). Both TEE and TTE have a reported specificity in the diagnosis of vegetations of more than 90% (81,82). The superiority of TEE in the detection of prosthetic endocarditis is even greater than for native-valve disease (*e*Fig. 52.9.1). The sensitivity of TEE and TTE in detecting prosthetic endocarditis is more than 80% and less than 45%, respectively (83,84). Vegetations on the tricuspid valve are detected with equal frequency by TEE and TTE (85). However, endocarditis of the pulmonary valve is more often recognized by TEE than by TTE (86), as is endocarditis at unusual sites such as on pacemaker wires (87).

Video 52.18 Endocarditis involving a Carpentier-Edwards bioprosthesis in the aortic position demonstrated by transesophageal echocardiography. The arrows indicate a large vegetation and a paravalvular abscess, respectively. LA, left atrium; RA, right atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.19 Echocardiogram of patient with endocarditis on a prosthetic mitral valve. A St. Jude mechanical mitral valve is seen. Attenuation of the echocardiographic signal by the prosthetic valve creates shadowing that prevents an endocarditis lesion from being visualized. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

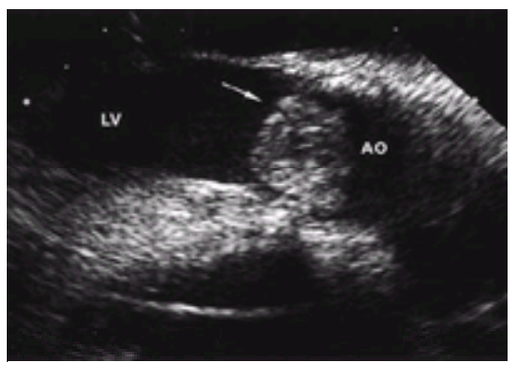
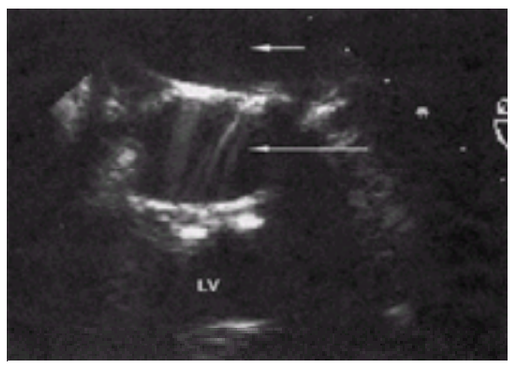


FIGURE 52.9 Long-axis view of fungal vegetation of aortic valve (*arrow*). AO, aorta; LV, left ventricle.



***e*FIGURE 52.9.1** Vegetation (*short arrow*) on atrial side of mechanical mitral prosthesis (*long arrow*) detected by transesophageal echocardiography. LV, left ventricle.

Complications

TEE is more reliable than TTE in detecting perforation of a valve leaflet in endocarditis (88). TEE can detect pyogenic complications of endocarditis such as abscess and fistula formation (Fig. 52.10 and *e*Fig. 52.10.1) more readily than TTE (89,90). These complications are associated with increased mortality, usually require operative intervention for successful treatment, and occur in approximately one-third of endocarditis cases. They occur most often with staphylococcal infections of the aortic valve and in prosthetic endocarditis (89,91,92). The sensitivity of TEE in the detection of abscess or infected pseudoaneurysm has been reported at 87% to 100%, whereas that of TTE has varied from 28% to 43% (89,92) (Fig. 52.10). TEE is more reliable (100% sensitive) than TTE (32% sensitive) in the detection of endocarditis in patients with *Staphylococcus aureus* sepsis. Endocarditis may exist in 25% of such patients and when present carries a fivefold increase in mortality as compared with sepsis without endocarditis (93). TEE has also been shown to be both useful and cost-effective in following patients with catheter-associated sepsis to determine the duration of antibiotic treatment (94).

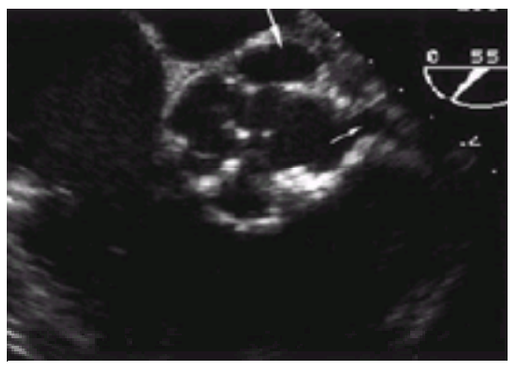
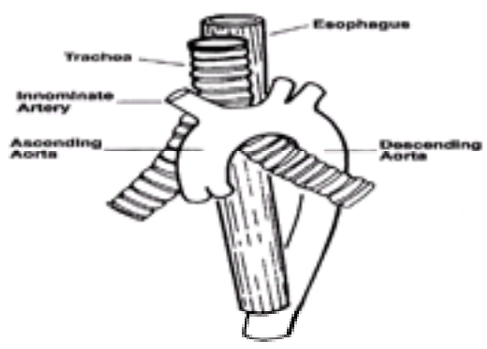
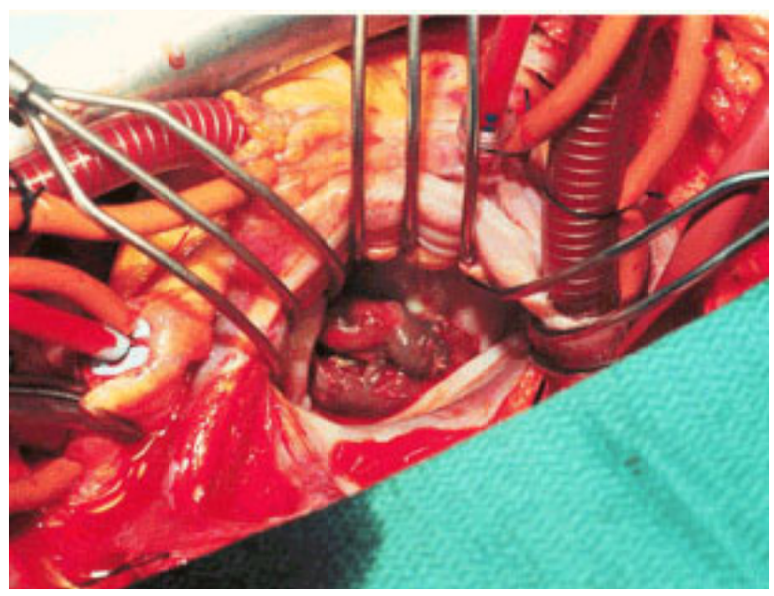


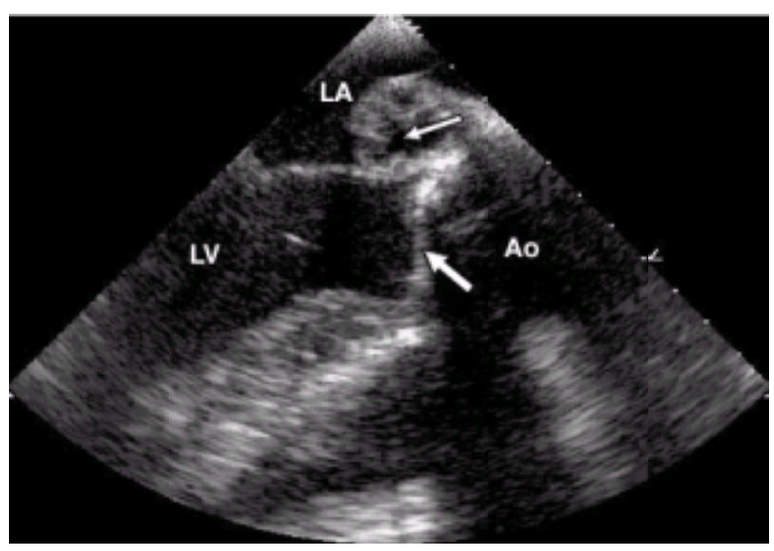
FIGURE 52.10 Short-axis view of abscess (*wide arrow*) of native aortic valve detected by multiplane transesophageal echocardiography. Left main coronary is shown by the narrow arrow.



***e*FIGURE 52.10.1** Fistula (*arrow*) from aorta (AO) to left atrium (LA) by transesophageal echocardiography color-flow imaging. LV, left ventricle.



Surgical field of a patient with infectious endocarditis and a large vegetation with perforation of the anterior mitral leaflet. The entire surgical view is filled with the large vegetation.



A 120-degree transesophageal echo of an aortic valve abscess seen in the inner annular fibrosa. The thin arrow designates the abscess cavity, while the thicker arrow demonstrates the aortic valve.

Video 52.20 Periaortic abscess without communication with the aortic lumen. A periaortic abscess is shown below the aortic valve on this chest wall echocardiogram. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Predictive Value and Usefulness of Transesophageal Echocardiography in Endocarditis

Failure of TEE to detect vegetations in suspected endocarditis has a high negative predictive value. In one study, no evidence of endocarditis was noted on TEE in 65 of 105 patients with suspected endocarditis (95). Of these 65, definite endocarditis developed in only five (7%) on subsequent follow-up. However, TEE may fail to detect endocarditis early in the course of the illness or after embolization of a vegetation. Serial studies are indicated if the clinical suspicion is high despite an initially negative TEE. Many findings on native and prosthetic valves may simulate vegetations. These include degenerative changes such as Lambl's excrescences on the aortic valve or suture material in the case of prostheses. Comparison with prior studies is very useful in these instances. Because of the high sensitivity, specificity, and negative predictive value of TEE in the detection of endocarditis, it has been advocated as the technique of choice in the evaluation of this condition. In one study, the addition of TEE to clinical criteria increased the case detection rate from 50% using clinical criteria to 100% with TEE (96). In a study addressing the incremental usefulness of transthoracic and TEE over clinical criteria in the diagnosis of endocarditis (97), TEE was incrementally useful in patients with intermediate or high probability of disease based on clinical criteria and TTE and in those with suspected prosthetic endocarditis. TEE and TTE were equivalent in excluding endocarditis in patients with a low likelihood of endocarditis on clinical grounds. Another study has indicated that in native-valve endocarditis, an adequate TTE without evidence of

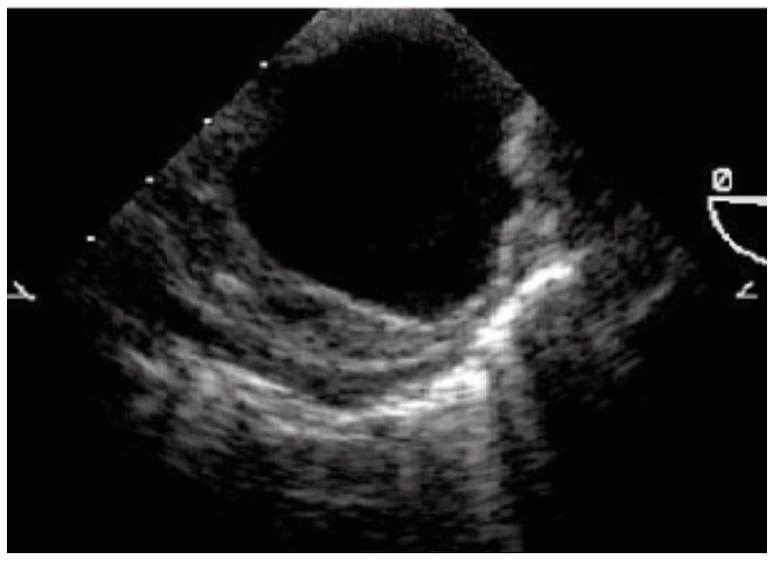
endocarditis was highly accurate in excluding this diagnosis (98). TEE has been shown to improve the diagnosis of native-valve endocarditis based on the Duke criteria and TTE in 11% of the study patients, most of whom had an intermediate likelihood of disease (99).

Guidelines for Use of Transesophageal Echocardiography in Endocarditis

TEE is indicated in all cases of suspected endocarditis involving prosthetic valves or cardiac devices such as pacemakers or defibrillators. TEE is also indicated in staphylococcal sepsis or in endocarditis in which pyogenic complications are common or suspected based on the clinical course. TEE should be considered if TTE imaging is inadequate or where the likelihood of endocarditis is of at least intermediate probability despite a negative TTE. TEE, because of its risk and invasiveness, should not be the primary method of excluding endocarditis when this is unlikely clinically. However, in certain situations in which a missed diagnosis might be catastrophic, such as in a patient with immune compromise, TEE should be considered, given its excellent negative predictive value. TEE may also be of value even in patients in whom a vegetation is evident on TTE in defining the presence of other complications and in helping decide the need for surgery. In one study in which patients with vegetations were subjected to serial TEE (100), failure of a vegetation to decrease in size on appropriate antibiotic therapy was associated with a significantly more complicated course.

Disease of the Aorta

TEE has become the technique of choice in many institutions in the diagnosis of acute dissection because of its high sensitivity, portability, and speed with which the diagnosis may be made (101). It is also used in diagnosis of aortic trauma and aortic atheroma. TEE is less often used as the primary diagnostic technique in evaluating other aortic pathologies, such as saccular aneurysm, which are effectively imaged by competing technologies such as computed tomography scanning and magnetic resonance imaging (MRI).



Transesophageal echo view of the descending aorta in short axis demonstrating significant atheromatous plaque.

VIDEO

Video 52.21 Long-axis view of the descending aorta from an intraoperative transesophageal echo after an elephant trunk procedure. Note the cylindrical structure within the dilated descending aorta; this represents the free end (distal) of the vascular graft with color flow within it. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.22 Short-axis view of the descending aorta from an intraoperative transesophageal echo after an elephant trunk procedure. Note the circular structure with in the larger, more dilated aorta. This represents the distal end of the vascular graft in short axis hanging free within the descending aortic aneurysm. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.23 Intraoperative transesophageal echo (120-degree view) with color Doppler demonstrating aortic insufficiency due to aortic dilatation (sinuses measure 5.0 cm) causing failure of leaflet coaptation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.24 Intraoperative short-axis 60-degree transesophageal echo of an aortic valve in a patient with a dilated ascending aorta (sinuses measure 5.0 cm) causing failure of the aortic leaflets to coapt centrally. This central gap caused severe aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.25 Intraoperative 120-degree transesophageal echo showing a long-axis view of the aorta in a patient with a dilated aorta causing failure of aortic leaflet coaptation resulting in severe aortic insufficiency. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Aortic Dissection

TEE has been used as the sole diagnostic tool in the evaluation of suspected dissection, with excellent results (102). In one study of 45 patients who underwent TEE for evaluation of suspected dissection, only one required a further study for additional information (103). None of the 24 patients without evidence of dissection on their initial examination required additional investigation of their aorta over 2 years of follow-up. Other imaging modalities used in the assessment of aortic dissection include MRI, angiography, and computed tomography scanning (104). *e*Table 52.1.1 provides a summary of the relative strengths and weaknesses of these imaging tests in the diagnosis of dissection and its complications.

***e*TABLE 52.1.1** SUMMARY OF RELATIVE MERITS OF VARIOUS IMAGING METHODS IN AORTIC DISSECTION

	Aortography + coronary arteriography	Computed tomography	Magnetic resonance imaging	Transesophageal echocardiography
Sensitivity	++	++/+++	+++	+++
Specificity	+++	+++	+++	++/+++
Site of tear	++	+	+++	++
Aortic regurgitation	+++	–	++	+++
Pericardial effusion	–	+++	+++	+++
Side branch involved	+++	+	++	+
Coronary involvement	+++	–	+	++
Acquisition speed	+	++	+	+++
Portability	–	–	–	+++
Invasiveness	+++	–	–	+
Contrast dye use	Yes	Yes	No	No
Cost	+++	+	++	+

+++, high; ++, moderate; +, fair; –, not capable.
Adapted and modified from Cigarrao JE, Isselbacher EM, DeSanctis RW, Eagle KA. Diagnostic imaging in the evaluation of suspected aortic dissection. Old standards and new directions. *N Engl J Med* 1993;328:35–43.

Ascending aortic dissection extending into the left main. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 52.26 Aortic dissection (left anterior oblique). Type B dissection of the aorta extending distally from the isthmus, just after the left subclavian artery, to the abdominal aorta. A communication between the true and false lumen is seen in the proximal portion of the descending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Diagnosis of Dissection

TEE has been reported to be more than 95% sensitive in the detection of aortic dissection in multiple studies (Fig. 52.11) (105,106 and 107). The detection rate reported is somewhat less for dissection involving the ascending aorta mainly because of the blind spot in the distal ascending aorta and proximal arch already described (105,108). The detection rate is also lower in patients who have had prior surgery of the aorta (109), when the dissection flap is very localized, or when the false lumen is thrombosed (110,111). The reported specificity of TEE in the detection of aortic dissection has varied from 68% to 100% (105,106 and 107,112). Studies that have shown perfect specificity have generally included only patients in whom the diagnosis was already established, whereas those with low specificity have used monoplane probes or less stringent criteria for diagnosis (106). False positives are most common in the ascending aorta and are often due to reverberation simulating a dissection flap (106,113). These may be minimized by the use of a biplane or multiplane probe (114). M-mode echocardiography is useful in timing and localizing reverberation (115). The presence of a flow disturbance on color-flow mapping at the site of the supposed dissection flap increases the likelihood of a true diagnosis. Recourse to other confirmatory techniques such as MRI or angiography should be made if the diagnosis is indeterminate by TEE (104). Operator experience is an important determinant of overall specificity.

Video 52.27 Intraoperative transesophageal echo with color Doppler of an ascending aortic dissection. Note the mobile flap with the color flow separation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.28 Transesophageal echo in a patient with severe left ventricular dysfunction and a descending aortic aneurysm with severe spontaneous echo contrast within the aorta (seen in short axis). Note the significant layering of thrombus along the wall of the aneurysm (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.29 Short-axis transesophageal echo view of a type I aortic dissection. Note the flap originating within the noncoronary cusp (leaflet upper left screen) and extending towards the ostium of the left main trunk. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.30 Intraoperative 120-degree transesophageal echo of an ascending aortic dissection. Note the large, complex flap in the ascending aorta seen originating near the origin of the right coronary artery. There is a small amount of aortic insufficiency. Flow is seen in the true lumen (*left*) whereas no flow is seen in the false

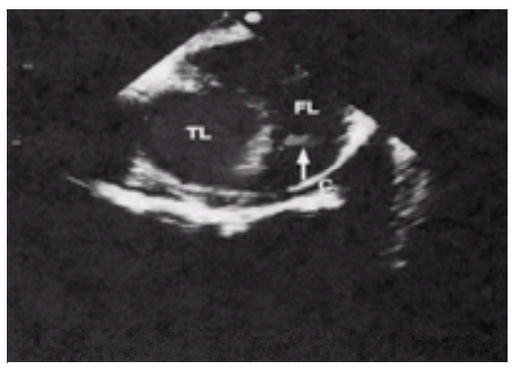
lumen (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.31 Iatrogenic aortic dissection after balloon angioplasty of the ostial right coronary artery with a cutting balloon in a 77-year-old female patient. The patient needed emergent surgical repair for a type I aortic dissection. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

FIGURE 52.11 Aortic dissection with flap in ascending aorta. **A:** Long axis. **B:** Short axis.

Assessment of Prognostic Features and Complications of Dissection

TEE provides important information concerning prognosis, complications, and surgical intervention in aortic dissection. Aortic dissection is most conveniently classified based on the presence (type A) or absence (type B) of a dissection flap in the ascending aorta. This classification is important prognostically. Type A aneurysms are considered for urgent surgery, whereas type B aneurysms are initially treated medically. The accuracy of classification of dissection by TEE has varied from 89% to 100% (102,112). Detection of the primary tear between the true and false lumen is important, as surgical plication of this communication may reduce and even obliterate flow in the false lumen and thus reduce the risk of late rupture. The primary entry site is most often in the ascending aorta and is detected in 73% to 89% of type A dissections (102,107). Other sites of communication between true and false lumen are frequently detected by TEE (eFig. 52.11.1).



***e*FIGURE 52.11.1** Communication (C) between true (TL) and false (FL) lumen in dissection involving the descending thoracic aorta.

Thrombus in the false lumen, a favorable prognostic feature, is also accurately detected by TEE. Important complications of dissection such as pericardial effusion, cardiac tamponade, the mechanism and severity of aortic regurgitation, and involvement of the coronary ostia are also accurately diagnosed by TEE. In one study, TEE correctly identified six of seven dissections involving the coronary ostia that were confirmed surgically (112). TEE can also detect other causes of chest pain when dissection is excluded. These include other aortic abnormalities and myocardial ischemia or infarction (116).

Limitations of Transesophageal Echocardiography in Dissection

Side branches, the head and neck vessels, and involvement of the abdominal aorta and branches and the distal coronaries are often not visualized by TEE. These are rarely crucial to surgical intervention for acute type A dissection. Supplemental imaging of the abdominal and head and neck vessels is possible with subcostal and suprasternal TTE. In chronic dissection, angiography and other imaging studies such as MRI may be performed to define the coronary anatomy and involvement of other branch vessels if surgery is planned.

Intramural Hematoma

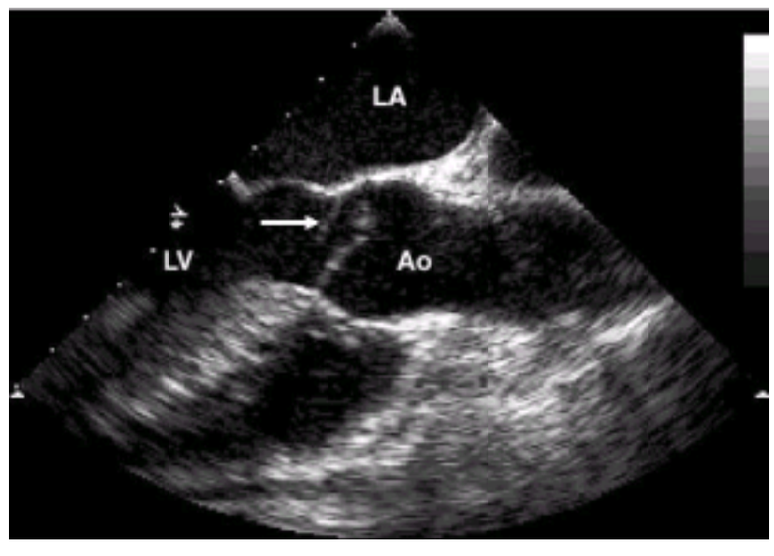
Intramural hematoma is a hemorrhage into and confined to the medial layer of the aortic wall. This is distinct from a true dissection, in which there is communication between the media and aortic lumen through an intimal tear. Intramural hematoma has a similar prognosis to aortic dissection and may develop into a dissection over time. It may involve any portion of the aorta (117). TEE is superior to angiography in its detection (118). It is recognized by TEE as a crescentic thickening of the aortic wall that extends for a variable length (119), with displaced intimal calcium. Intramural hematoma is most often seen in elderly patients and may be difficult to differentiate from atherosclerotic changes or thrombosis of a localized dissection.

Penetrating Atherosclerotic Ulcer of the Aorta

Penetrating ulcer is associated with hypertension and atheroma and may present with chest or back pain. It frequently coexists with intramural hematoma and a limited dissection. It is recognized by TEE as a localized outpouching of the aortic wall, which may be calcified (120). Pseudoaneurysm formation may also occur. TEE was recently shown to detect 88% of penetrating ulcers that were confirmed at surgery or by another imaging modality (121).

Aortic Trauma

TEE has become an important tool in the rapid evaluation of aortic injury after major trauma. Aortic trauma most often involves the aortic isthmus just distal to the ligamentum arteriosum. Subadventitial disruption requires immediate surgical intervention and is recognized echocardiographically as a dense, thick, mobile flap that represents the disrupted intima and media. Asymmetric aortic enlargement is seen in this area due to the formation of a pseudoaneurysm. TEE can be performed rapidly and safely in trauma patients and is accurate in the detection of significant aortic disruption (122). Sensitivity and specificity of more than 90% have been reported in a number of studies of TEE in aortic trauma patients (122,123).

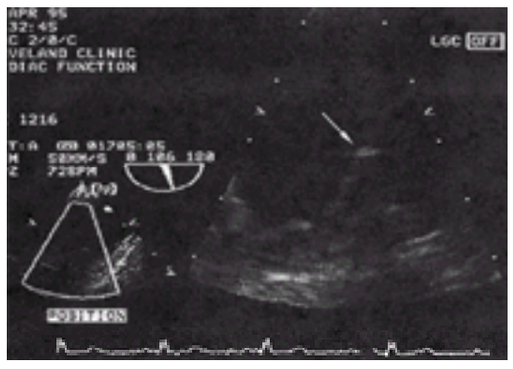


Traumatic left coronary cusp flail (*arrow*) of the aortic valve due to blunt trauma. There was resulting 4+ anteriorly directed aortic insufficiency.

Video 52.32 A 120-degree intraoperative transesophageal echo of a patient with aortic insufficiency due to blunt trauma causing a flail left coronary cusp. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Aortic Atherosclerosis

Aortic atheroma is seen as echodense thickening of the intimal surface with superimposed thrombus or calcification in many instances. Involvement of the aorta varies from discrete plaques to diffuse thickening. TEE detection and classification of aortic atheromatous plaque shows good agreement with the pathologic findings (124). Aortic atheroma is most commonly seen in the descending thoracic aorta, less often in the aortic arch, and least often in the ascending aorta (125). Aortic atheroma on TEE is a sensitive marker of significant coronary disease (126) and of extensive peripheral vascular and carotid disease (127). Plaque in the aortic arch of more than 4 mm in thickness by TEE was an independent risk factor for ischemic stroke in one study (128). This risk appears to be lowered to a greater degree by oral anticoagulation rather than by antiplatelet drugs (129,130). Other studies have indicated that aortic atheroma on TEE increases the risk of perioperative stroke in patients undergoing bypass surgery and of atherogenic embolism after other procedures (131,132). The morphology of the plaque has independent predictive value. The likelihood of an embolic event is greatest with complex mobile plaque and least with sessile plaque (eFig. 52.11.2). In one study, complex atherosclerotic plaque was seen in 7% of 556 consecutive patients being evaluated by TEE. Systemic thromboembolism subsequently occurred in 73% of these patients but only in 12% of those with sessile plaque (133). Protruding atheroma was an independent risk factor for stroke in another study (134). Complex atheroma has been shown to be associated with a high prevalence of high-intensity transient signals in cerebral arteries, which further supports its role in cerebral embolism (135). The presence of spontaneous contrast in the aorta is an independent embolic risk factor (136) as well as a risk factor for cardiac mortality (137). Recently, mobile thrombus has been detected by TEE in younger patients with systemic embolism in the absence of diffuse aortic atheroma. Underlying atherosclerosis at the insertion site of the thrombus has been demonstrated histologically in patients who have undergone surgical removal of the thrombus (138).



***e*FIGURE 52.11.2** Mobile aortic atheroma (*arrow*).

Other Aortic Conditions

TEE can characterize thoracic aneurysms involving the sinuses of Valsalva and the ascending and descending aorta. It is useful in improving the resolution of sinus of Valsalva aneurysm and in detecting communication with individual cardiac chambers.

Video 52.33 A magnified 103-degree transesophageal long axis view **(A)** of a ruptured sinus of Valsalva aneurysm of the right sinus of Valsalva. Note the remnant thinned, aneurysmal wall of the sinus bowing into the right ventricle (towards the bottom of the screen). Color Doppler interrogation of the aortic valve with sinus of Valsalva in a transesophageal long-axis view **(B)**. Note there is moderate anteriorly directed aortic insufficiency at the top of the screen, and the aortic to right ventricular shunt through the ruptured sinus of Valsalva aneurysm is seen at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.34 A magnified 103-degree transesophageal long axis view **(A)** of a ruptured sinus of Valsalva aneurysm of the right sinus of Valsalva. Note the remnant thinned, aneurysmal wall of the sinus bowing into the right ventricle (towards the bottom of the screen). Color Doppler interrogation of the aortic valve with sinus of Valsalva in a transesophageal long-axis view **(B)**. Note there is moderate anteriorly directed aortic insufficiency at the top of the screen, and the aortic to right ventricular shunt through the ruptured sinus of Valsalva aneurysm is seen at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Native-Valve Disease

Transthoracic imaging can usually provide a complete anatomic and hemodynamic profile of abnormal valves. TEE is used in addition when improved resolution of valve structure is needed or when the hemodynamic severity of a regurgitant lesion is in question. Assessment of valve lesions to determine their suitability for repair or

reconstruction is an increasing indication for TEE during cardiac surgery.

Video 52.35 Transesophageal echo in a patient with a subvalvular membrane in the left ventricular outflow tract. Note the normal mobility of the aortic valve. This patient had a significant pressure gradient across the left ventricular outflow tract/AV. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.36 Four-chamber transesophageal view of a patient with a cystic-appearing mass on the tricuspid valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.37 Transesophageal four-chamber view focusing on the tricuspid valve showing myxomatous tricuspid valve disease with severe prolapse causing severe tricuspid regurgitation (pre-operative). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.38 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

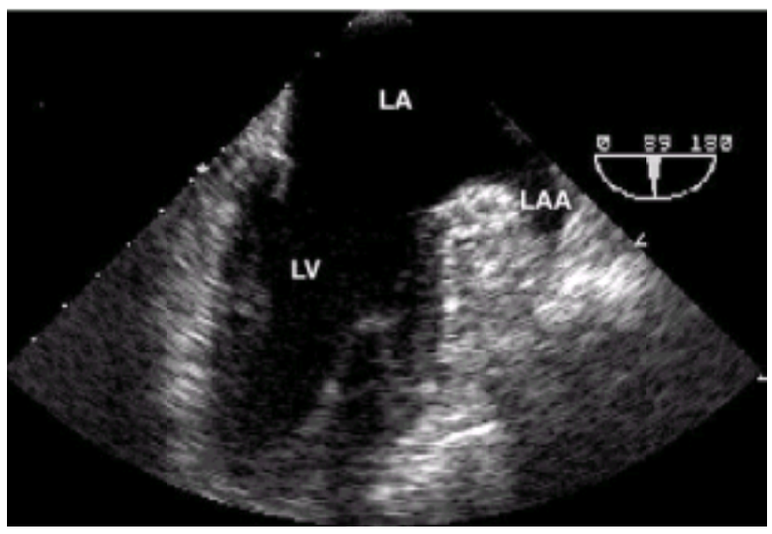
Video 52.39 Transgastric view (transesophageal echo) of the mitral valve in a patient with severe aortic insufficiency. Note the fluttering of the anterior mitral leaflet (*left*) due to the jet of aortic insufficiency hitting it (color flow seen on the left). (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.40 Long-axis 120-degree transesophageal view of a rheumatic aortic valve with central aortic insufficiency due to furled, restricted leaflets. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.41 Transesophageal echo with color Doppler showing tricuspid regurgitation after a myocardial biopsy of the right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.42 Apical long-axis view of a patient with severe left ventricular dysfunction and annular dilatation causing 4+, centrally directed mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.43 Transesophageal echo demonstrating a flail tricuspid valve after right heart biopsy in a transplant patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



A 90-degree transesophageal echo demonstrating the left ventricle and mitral valve in diastole. The anterior wall is to the right of the screen while the inferior wall is to the left and the mitral valve in the center and the left atrium at the top of the screen. The left atrial appendage (LAA) is at the far right of the image.

Mitral Valve

TEE is highly sensitive and specific in the detection of flail mitral valve leaflets and chordae and is superior to TTE in differentiating flail leaflets from vegetations (139,140). TEE is also superior in defining the mechanism of regurgitation, the site of regurgitation, the likelihood of repair, and a subset of patients at greatest risk for the development of complications such as systolic motion of the mitral valve after repair for myxomatous disease (141,142 and 143). It is more sensitive than either TTE or angiography in the detection of mitral regurgitation (Fig. 52.12). In one study, mitral regurgitation was present on TEE in 25% of patients in whom it could not be detected by TTE, and in 14% of these patients the regurgitation was at least of moderate severity (144). The superior ability of TEE to detect mitral regurgitation is most marked in critically ill ventilated patients with acute ischemia or infarction (145). TEE is superior to transthoracic echo in the detection of papillary muscle rupture in this population (146). Multiplane TEE is superior to TTE in the detection of eccentric regurgitant jets (114). The size of the regurgitant jet on color-flow mapping often appears larger by TEE than by TTE (147). This discrepancy is attributable to the proximity of the jet to the transducer and the higher carrier frequency of the Doppler used by TEE. When the area of high-velocity turbulent, or “mosaic,” flow alone is used in the assessment of regurgitant severity, a good correlation with angiographic grading is noted (148).

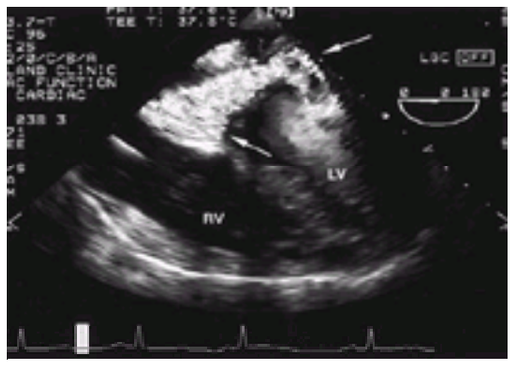
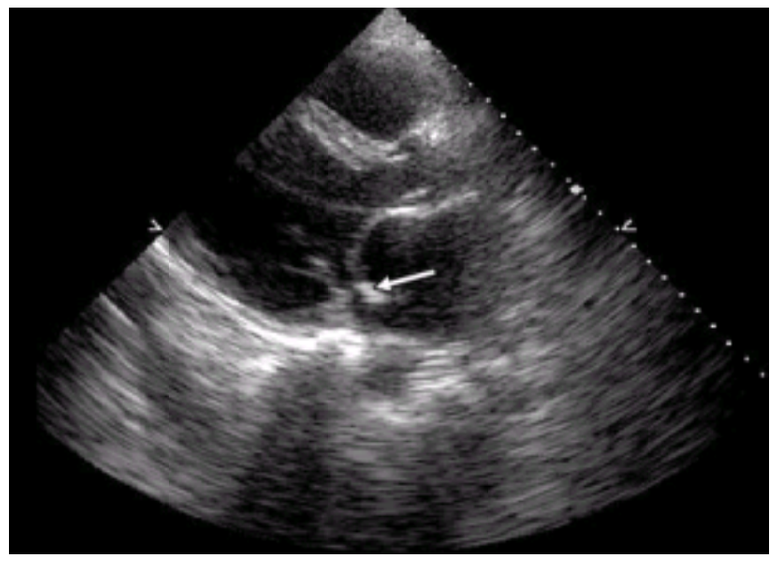
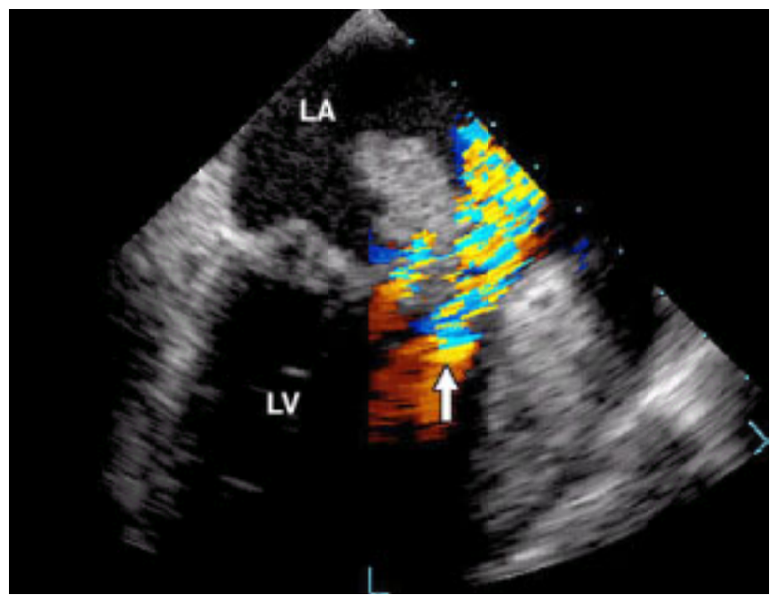


FIGURE 52.12 Severe anteriorly directed mitral regurgitation due to a flail posterior leaflet (*arrows*) imaged in the transverse four-chamber view. LV, left ventricle; RV, right ventricle.

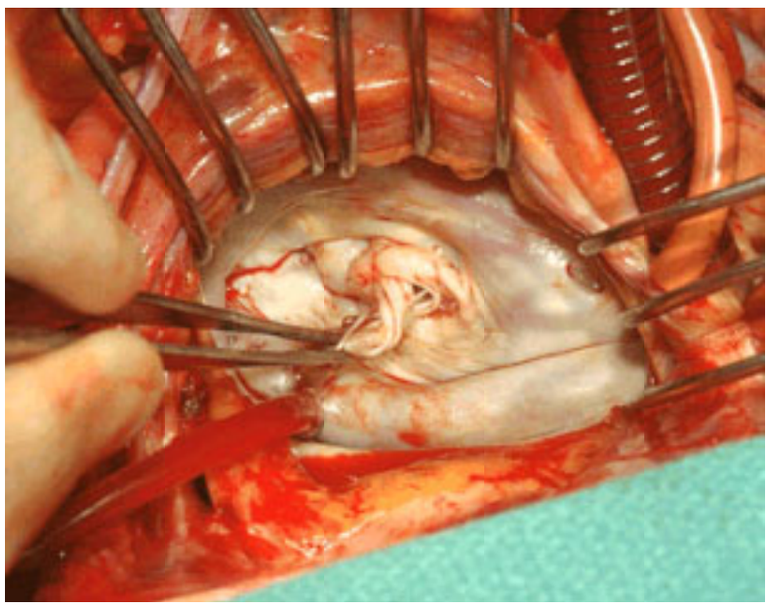
Video 52.44 Intraoperative 0-degree transesophageal echo showing a flail posterior mitral leaflet from a patient with myxomatous valve disease. Note the movement of the torn chordae attached to the tip of the leaflet (see color Doppler assessment). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Parasternal long-axis view of a papillary muscle rupture after myocardial infarction. Note the piece of papillary muscle attached to the tip of the anterior mitral leaflet as it flails into the left atrium (demonstrated by the arrow).



Color Doppler showing a perforation of the base of the anterior mitral leaflet from *Streptococcus* endocarditis. The patient’s underlying pathology was myxomatous mitral valve disease with mitral valve prolapse. The proximal flow convergence of the mitral regurgitation jet is demonstrated by the arrow at the orifice of the large perforation.



Intraoperative field demonstrating a mitral valve with a torn papillary muscle prolapsing across the mitral valve into the left atrium. The surgeon has the papillary muscle in forceps demonstrating the chordae attached to the posteromedial commissure, predominantly attached to the anterior mitral leaflet. (The patient's head is to the left of the screen and feet to the right.)

Surgical pathology specimen demonstrating a torn papillary muscle seen to the lower right of the screen, attached via chordae to a portion of the anterior mitral leaflet. Note the torn "ragged edges" at the bottom of the papillary muscle head.

VIDEO

Video 52.45 Color Doppler of 0-degree intraoperative transesophageal echo with prolapse and flail of the posterior mitral leaflet causing very eccentric, anteriorly directed mitral regurgitation. This valve was successfully repaired. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.46 Postpump echo (with color Doppler) after repair of the flail posterior mitral leaflet. There is a Cosgrove-Edwards annuloplasty ring in place. There is no residual mitral regurgitation and there is no systolic anterior motion of the mitral leaflets, which can sometimes complicate mitral valve repair. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.47 Intraoperative transesophageal echo showing bileaflet prolapse of the mitral valve. The color Doppler showed centrally directed mitral regurgitation. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

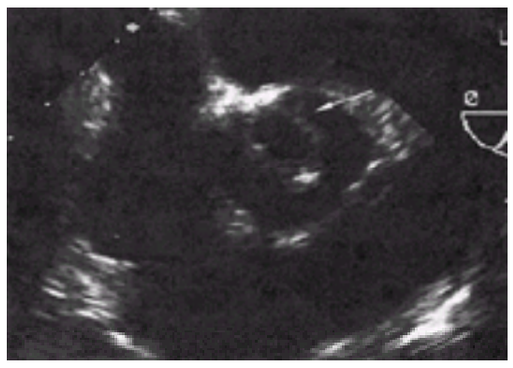
Video 52.48 Intraoperative 120-degree transesophageal echo of a flail posterior mitral leaflet prior to repair (two-dimensional). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Parameters other than regurgitant jet size are available with TEE in assessing severity of mitral regurgitation. These include the size of the regurgitant jet at its origin and the size of the area of flow acceleration just proximal to the regurgitant orifice (proximal flow convergence area). Both of these relate well to the size of the regurgitant orifice area and are less dependent on loading conditions than regurgitant jet area or length (149,150). Analysis of pulmonary vein flow is a useful parameter in confirming the severity of mitral regurgitation. High-quality Doppler recordings of both left and right pulmonary veins are readily obtained by TEE (151,152). Systolic flow reversal in a pulmonary vein is an accurate marker of severe mitral regurgitation. Blunting of the systolic flow is suggestive of significant mitral regurgitation in the setting of normal ventricular function and normal sinus rhythm but is unreliable otherwise (153). Quantification of mitral regurgitation is usually possible by TEE with methods based on both pulsed Doppler and the proximal flow convergence area with TEE (154,155). Planimetry of the mitral orifice in cross-section in mitral stenosis is more difficult with TEE than with TTE but is sometimes possible with multiplane imaging.

Aortic and Other Valves

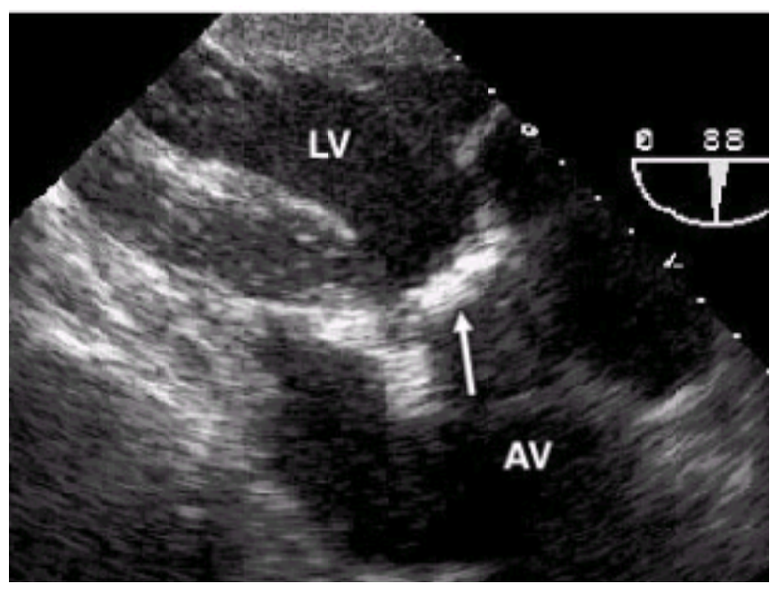
Multiplane TEE has facilitated imaging of the aortic valve and allows the true long and short axis to be acquired. High-resolution images obtained by this technique are useful in diagnosing a bicuspid valve or other structural abnormality when TTE is uncertain (eFig. 52.12.1). In a recent study with operative corroboration, multiplane

TEE was significantly better than TTE at detection of bicuspid aortic valves, with a sensitivity of 87% and specificity of 97% in their detection (156). Subaortic stenosis, especially subaortic membrane, is often better imaged by TEE than by TTE (eFig. 52.12.2) (157). Interrogation of the aortic valve with continuous-wave Doppler in the standard TEE imaging planes is more difficult than with transthoracic imaging. Planimetry of the aortic valve orifice is also feasible in many instances with multiplane transducers, and excellent agreement has been reported between the valve area planimetered by TEE and that measured at cardiac catheterization or by TTE (158). TEE provides excellent images of the tricuspid and pulmonary valve. However, the anterior situation of these structures in the chest allows adequate imaging in most circumstances by TTE, with little incremental benefit from TEE.

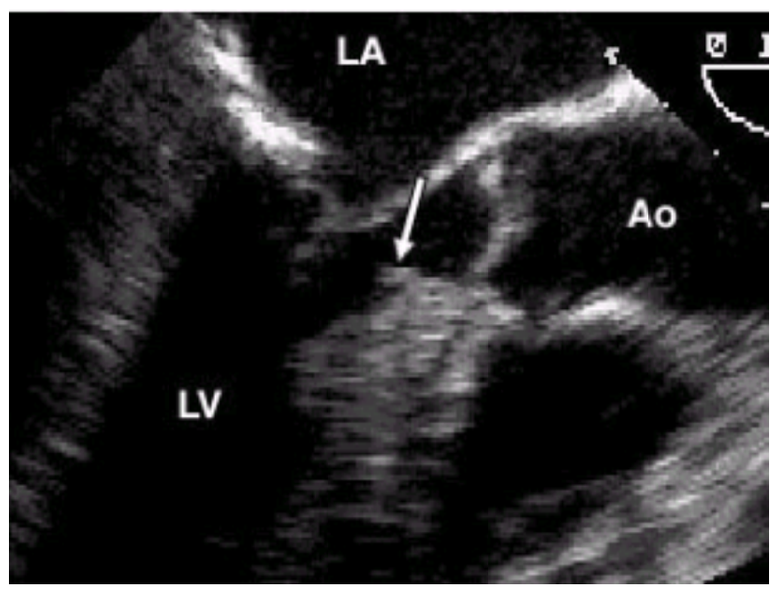


***e*FIGURE 52.12.1** Multiplane short-axis image of unicuspid aortic valve in systole (*arrow*).

***e*FIGURE 52.12.2** Narrowing of left ventricular outflow tract due to subaortic membrane (*arrow*). AO, aorta; LV, left ventricle.



Deep transgastric transesophageal echo view of the aortic valve in a patient with aortic stenosis. Note the heavily calcified aortic valve in the center of the screen (*arrow*), the posterior wall is at the top of the screen and the anterior/anteroseptal wall is towards the bottom. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)



Transesophageal echo at 120 degrees of the aortic valve with a subaortic membrane in the left ventricular outflow tract (designated by the arrow).

Prosthetic Valves

TEE allows improved resolution of prosthetic leaflets and regurgitation both at mechanical and bioprostheses as compared with TTE (83,159). In one study of 148 prosthetic valves (113 bioprostheses and 35 mechanical prostheses) in which abnormality was confirmed pathologically, TEE and TTE were 86% and 57% sensitive, respectively, in the detection of abnormalities (83). TEE was superior to TTE in the detection of abnormalities at mechanical prostheses (83% vs.22%), bioprostheses (87% vs. 65%), aortic prostheses (77% vs. 50%), and mitral prostheses (97% vs. 65%) (83). TEE may detect thrombus in patients with mechanical mitral valves that is clinically unsuspected but that is a risk factor for thromboembolic events (160).

Video 52.49 Transesophageal 138-degree view showing the Carpentier-Edwards mitral valve replacement with thickened leaflets with multiple mobile echo densities consistent with vegetations and a clot in a patient with prosthetic valve endocarditis. The mean transesophageal gradient was 20 mm Hg on surface echo. Note the

large left atrial thrombus to the right of the screen with significant spontaneous echo contrast in the left atrial cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.50 Beall mitral valve prosthesis with normal antegrade flow seen with color Doppler by transesophageal echo. Note the typical antegrade flow around the disc with marked shadowing beyond the disc. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.51 Normal motion of the discs of a St. Jude's valve in the mitral position shown by transesophageal echocardiography. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.52 Transesophageal echo of a patient with a Carpentier-Edwards mitral valve regurgitation. The pliable leaflets are suspended on the metallic struts. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

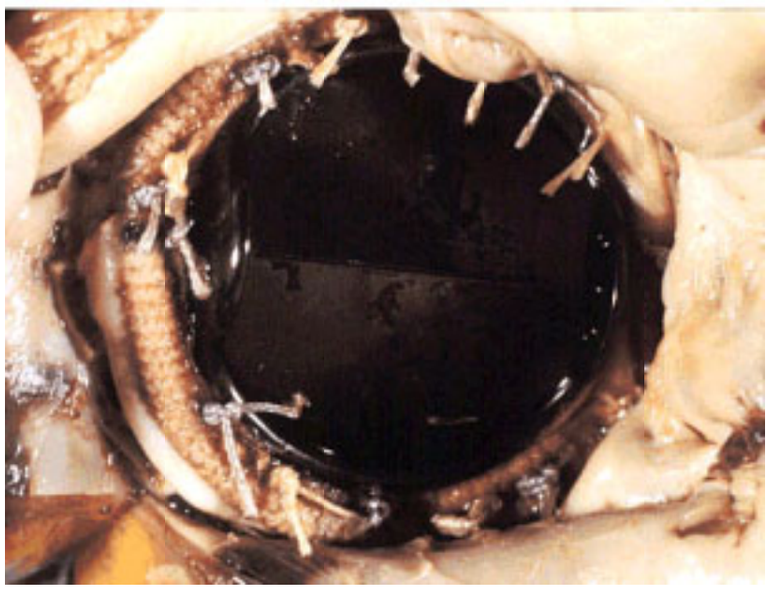
Video 52.53 Transesophageal view of a Starr-Edwards prosthesis in the mitral position. (The left atrium is toward the upper right side of the screen and the left ventricle is toward the lower left.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.54 Normal-functioning Starr-Edwards prosthetic valve in the mitral position. Note the full motion of the valve pop-it within the cage. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

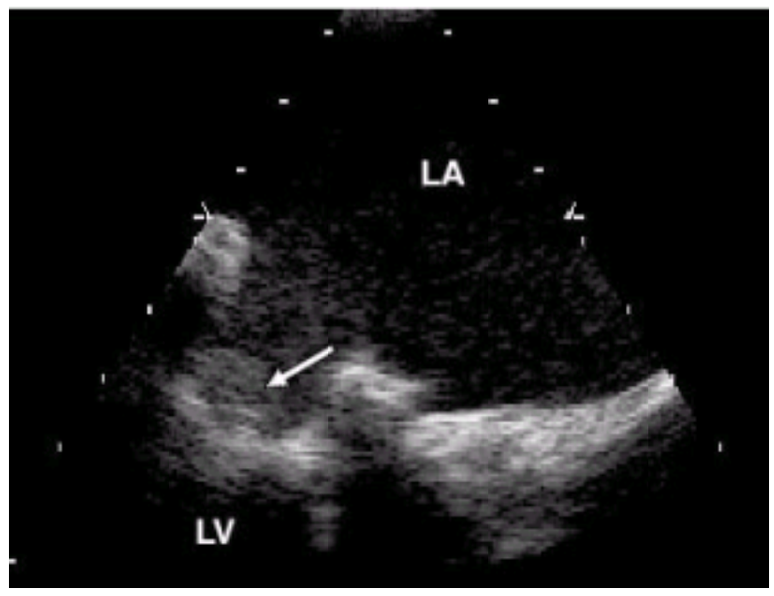
Video 52.55 Transesophageal echo demonstrating a normally functioning St. Jude mitral valve prosthesis. Note the tilting of the two metallic leaflets. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.56 Normal Björk-Shiley prosthetic valve in the aortic position. On fluoroscopy, the single valve disc moves normally with complete opening and closing. Björk-Shiley valves open 60 degrees or 70 degrees, depending on the model **(A,B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

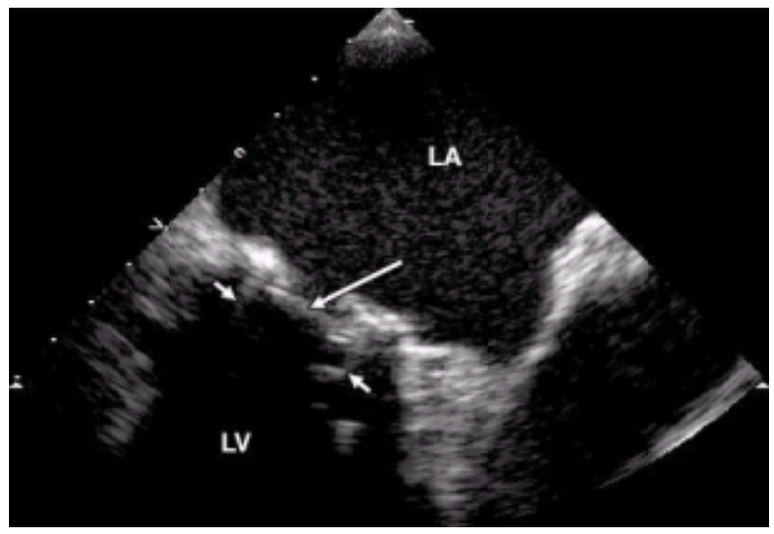
Video 52.57 Normal Björk-Shiley prosthetic valve in the aortic position. On fluoroscopy, the single valve disc moves normally with complete opening and closing. Björk-Shiley valves open 60 degrees or 70 degrees, depending on the model **(A,B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



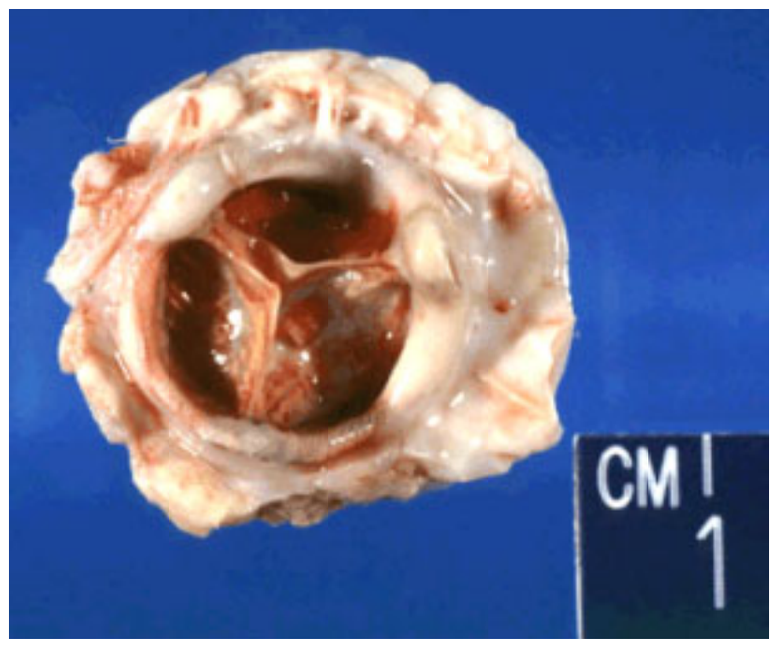
Normal St. Jude valve in the mitral position.



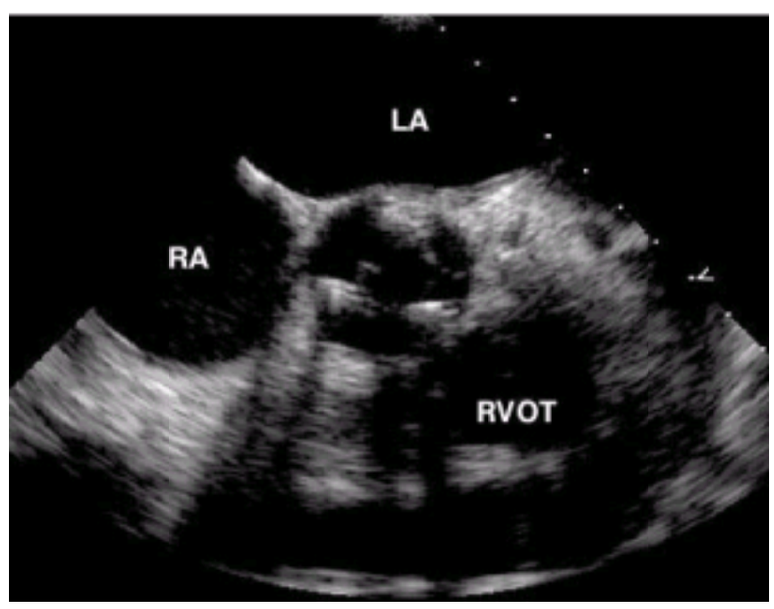
Magnified transesophageal view of a Starr-Edwards prosthesis (ball-and-cage valve) in the mitral position. This image was taken in systole with the ball (shown by the arrow) in the ventricular side of the cage.



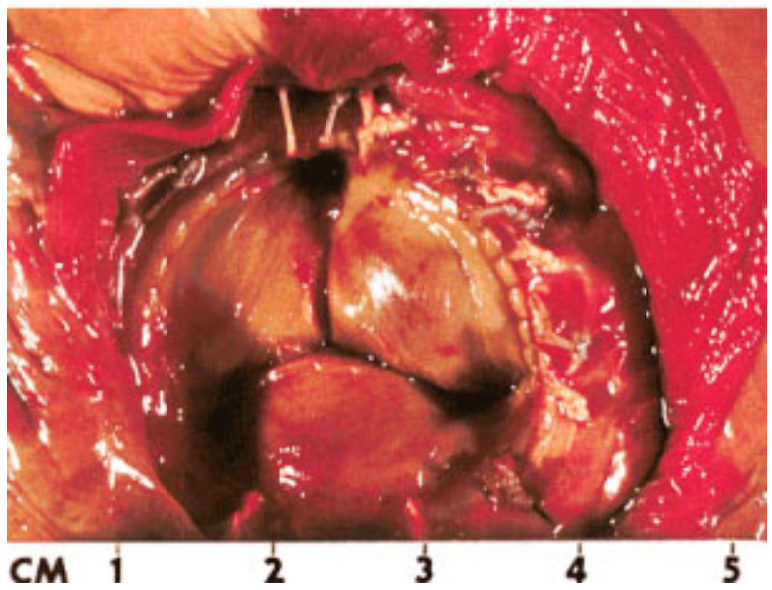
Beall mitral valve prosthesis showing the single disc within the cage in a 90-degree transesophageal view. The single arrow demonstrates the single disc of the prosthesis, and the two small arrows show the cage in which the disc is held.



Porcine prosthetic valve with severe fibrosis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



A short axis –60 degree transesophageal echo of a Carpentier-Edwards (CE) aortic valve. One can see the three mobile leaflets suspended from the struts.



Porcine prosthetic mitral valve. In this example, the valve is normal and the suture line is intact.

Prosthetic Regurgitation

A small amount of regurgitation occurs normally at mechanical prostheses by design. This is readily detected by TEE and less often by TTE. The pattern of regurgitation is specific to individual prosthetic types and is usually easily differentiated from abnormal regurgitation by the relative low velocity, short duration, and small size of the normal jets (161). Abnormal regurgitation at mitral prostheses is more reliably detected by TEE than TTE, but TEE's superiority in this regard is less for aortic prostheses (159,162). TEE is also more accurate than TTE in defining the origin of the prosthetic regurgitation (162,163). Prosthetic regurgitation, especially when paravalvular, is associated with intravascular hemolysis (Fig. 52.13). Regurgitant jets that produce a high shear stress on red blood cells and consequent hemolysis may be characterized using TEE (164). Structural abnormalities leading to regurgitation such as flail bioprosthetic leaflets are more also more reliably detected by TEE than by TTE (84).

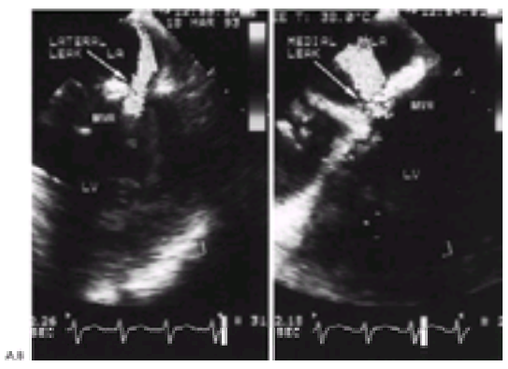


FIGURE 52.13 Two periprosthetic regurgitant leaks [lateral, **(A)**; medial, **(B)**] at a mitral mechanical prosthesis (MVR) demonstrated by multiplane transesophageal echocardiography. LA, left atrium; LV, left ventricle.

VIDEO

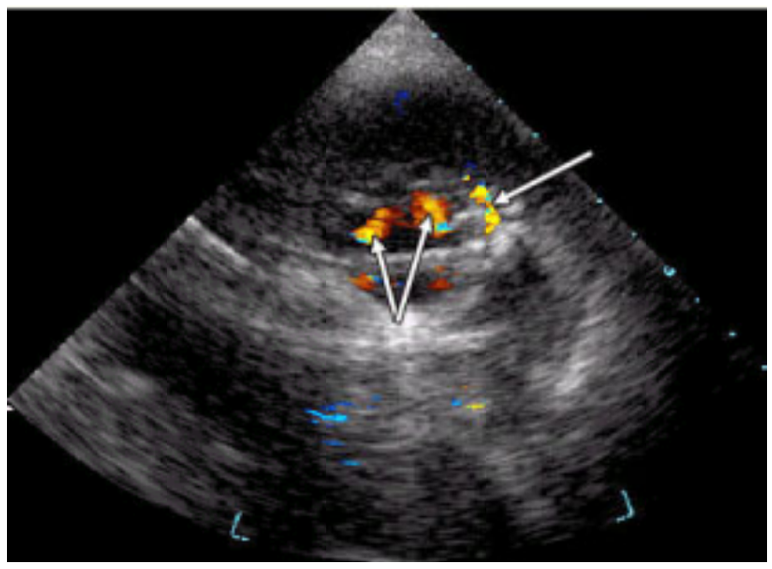
Video 52.58 Physiologic regurgitation of a St. Jude's mechanical valve in the mitral position. Transesophageal echocardiography demonstrates two converging regurgitant jets in the left atrium (LA). AO, aorta; LV, left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.59 Paravalvular regurgitation demonstrated by color Doppler in a patient with severe hemolysis. LA, left atrium; LV, left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

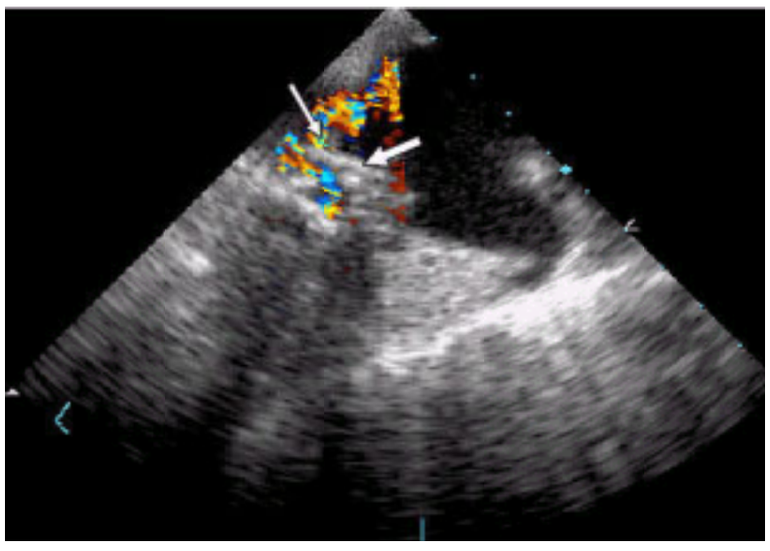
VIDEO

Video 52.60 Intraoperative transesophageal echo (transgastric short-axis view) of a CarboMedics mitral valve replacement with both physiologic prosthetic mitral regurgitation (two jets from within the sewing ring) and an abnormal, lateral paravalvular jet (outside the sewing ring to the right of the screen). Note that the paravalvular jet is arising between the sewing ring and an area of mitral annular calcification, making it difficult for the prosthesis to be in close contact with the annulus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Transgastric short-axis view during intraoperative transesophageal echo of a paravalvular leak of a CarboMedics mitral valve replacement. Note the two normal physiologic prosthetic jets of mitral regurgitation (within the sewing ring) as designated by the double arrow and the one abnormal, laterally originating jet outside the sewing ring (to the right of the screen) designated by the single arrow. There was significant mitral annular calcification (MAC),

aking it difficult to achieve close contact between the annulus and the sewing ring.



Intraoperative transesophageal echo in a patient with a Carpentier-Edwards prosthesis in the mitral position with infectious endocarditis. There is a paravalvular jet of mitral regurgitation (*thin arrow*), and the mitral prosthesis (*thick arrow*) is rocking. (The left atrium is towards the upper right of the screen, and the left ventricle is to the lower left.)

Prosthetic Stenosis

TEE is an important diagnostic tool in the assessment of prosthetic stenosis, especially at mechanical valves. Although TTE is used to characterize the valve gradients, TEE provides incremental information on structural abnormalities of the valve leaflets or sewing ring once stenosis is suspected. TEE is especially useful in the detection of thrombus on the prosthetic leaflets (165). Thrombus may not be apparent on TTE and may occur despite normal prosthetic gradients. In one study, TEE detected thrombus on a mechanical valve in 13% of 114 patients in whom it was unsuspected by TTE (165). In another study, TEE detected all eight prosthetic thrombi (100%), whereas TTE detected only one (13%) of them (83). TEE is useful in prediction of the response of thrombus to thrombolytic treatment, which is more likely to be successful with nonobstructive thrombus rather than when the thrombus is completely occluding the prosthesis (166). It is also useful in detecting resolution of thrombus after thrombolytic infusion and the need for further thrombolytic infusion (167). TEE also helps in identifying thrombus from pannus at mechanical valve prostheses (168,169). The high resolution of TEE may detect features on prosthetic valves of uncertain significance, which are not seen with other imaging modalities. Microbubbles are frequently seen emanating from mechanical prostheses, especially at mitral tilting-disc prostheses. These are thought to be due to cavitation of erythrocytes and are often a normal finding (170). Filamentous strands have also been detected on mechanical and even biologic prostheses (171,172). The precise nature and significance of these strands are uncertain.

VIDEO

Video 52.61 Frozen St. Jude prosthetic valve leaflet **(A)**. Image was obtained 5 days postoperative with suspected prosthetic valve dysfunction by echocardiography. Fluoroscopy reveals only one of the two leaflets moving normally (*arrow*). St. Jude prosthetic valve after reoperation *(B)*. Both leaflets now show normal excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.62 Frozen St. Jude prosthetic valve leaflet **(A)**. Image was obtained 5 days postoperative with suspected prosthetic valve dysfunction by echocardiography. Fluoroscopy reveals only one of the two leaflets moving normally (*arrow*). St. Jude prosthetic valve after reoperation *(B)*. Both leaflets now show normal excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.63 Björk-Shiley Convexo-Concave prosthetic valve in the aortic position in a left anterior oblique view. Abnormal function is demonstrated by less than a 60-degree opening excursion and incomplete closure. The differential diagnosis includes tissue in growth versus thrombosis of valve leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.64 Intraoperative 90-degree transesophageal echo of a patient with a St. Jude mitral valve prosthesis with a stuck metallic leaflet due to a small clot. (The immobile leaflet is to the right of the screen; the left leaflet moves normally.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.65 Structural valve degeneration of a Carpentier-Edwards bioprosthesis in the mitral position demonstrated in a transesophageal echocardiogram (TEE). The arrow demonstrates a flail prosthetic leaflet. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

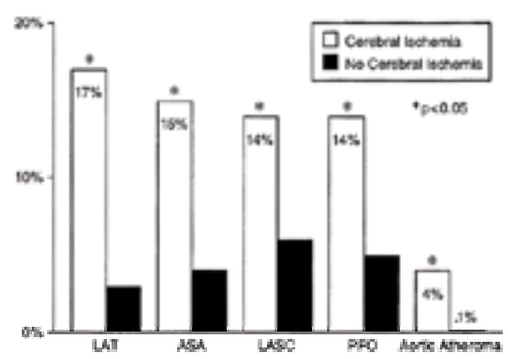
Video 52.66 Structural valve degeneration of a Carpentier-Edwards bioprosthesis in the mitral position demonstrated in a transesophageal echocardiogram (TEE). Color Doppler demonstrates intravalvular regurgitation. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Transesophageal Echocardiography to Detect Source of Embolism

The leading indication currently for TEE in most medical centers is in the evaluation of source of embolism. The prevalence of potential source of embolism in those undergoing TEE for evaluation of prior embolic event compared with those without a history of embolism is shown in *e*Fig. 52.13.1.

Video 52.67 Thrombosis of bioprosthetic valves in the mitral and tricuspid position (*arrows*) in a patient with antiphospholipid syndrome in the early postoperative period demonstrated by transesophageal echocardiography. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 52.68 Pacemaker vegetation. In this transesophageal echocardiogram, a huge mass is seen attached to the pacemaker wire as it passes through the right atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 52.13.1** Bar diagram comparing prevalence of potential source of embolism in those with and those without a history of cerebral ischemia. ASA, atrial septal aneurysm; LASC, left atrial spontaneous contrast; LAT, left atrial thrombus; PFO, patent foramen ovale.

Incremental Value of Transesophageal Echocardiography over Transthoracic Echocardiography

The yield of TTE in the evaluation of cardiac source of embolism is greatest in those with known cardiac disease (173). One study found that a cardiac source of embolism was as likely to be detected by TTE in a matched control population without a history of embolism as in those with an embolic history (174). A number of studies have indicated that TEE is more likely than TTE to detect a potential cardiac source of embolism in patients with cerebral ischemia (68,175,176). Additional potential causes of embolism detected more often by TEE than TTE include left atrial thrombus, left atrial spontaneous contrast, patent foramen ovale, ASA, valvular strands, vegetations, and aortic atheroma. TEE is more likely than TTE to detect a source of embolism in patients without a prior cardiac history. In one study of 79 patients with cerebral ischemia in the absence of cerebrovascular disease, a cardiac source of embolism was detected in 15% by TTE and in 57% by TEE (68). In patients without a cardiac history, a potential source of embolism was detected by TEE in 39% and in 19% by TTE. In another study of 50 patients without cerebrovascular disease with recent stroke or transient ischemic attack, TEE detected a potential source of embolism in 52% of all patients and in 33% of those without a cardiac history whereas TTE failed to detect a cardiac source of embolism in any patient (176). The finding of a source of embolism on TEE may have prognostic value in predicting recurrent events. In a prospective study of 145 patients with cerebral ischemia, TEE detected a source of embolism in 45% of those with unexplained stroke or transient ischemic attack. Recurrent cerebral ischemia was more common in patients with a TEE-detected source of embolism over a follow-up period of 18 months (177). Stratification of risk after stroke by TEE was highly predictive of subsequent events and death in a study of a group of patients without major clinical cardiac risk factors such as severe left ventricle dysfunction and atrial fibrillation (178). However, in contrast, a multicenter study of the use of TEE to assess embolic risk in patients with atrial fibrillation found that on univariate analysis, atrial size and thrombus were predictors of subsequent embolic events but that in multivariate analysis none of the TEE predictors were included. Independent risk factors of subsequent events were age, prior stroke, and hypertension (179).

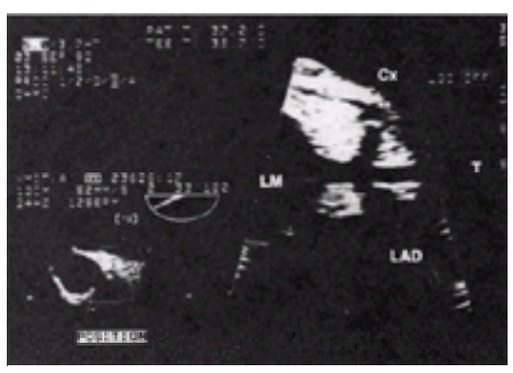
Indications for Transesophageal Echocardiography to Detect Source of Embolism

TEE is widely used in the assessment of cardiac source of embolism but its true usefulness in this setting is often in doubt. Many patients with unexplained embolic events are anticoagulated initially regardless of the echocardiographic findings. TEE, therefore, may be unnecessary in such patients. However, the usefulness of TEE as an initial diagnostic tool in patients with new-onset stroke has recently been supported by a cost-effectiveness study. A strategy in which TEE was used initially rather than TTE was more cost-effective in defining strategies that could reduce the risk of recurrent stroke (180). A number of small studies of the management implications of TEE in source of embolism have been reported. In one prospective study of 30 patients, TEE was thought to have changed management in only three of them (181). In another retrospective study of 39 patients with cerebral ischemia, TEE changed management in four (10%) and confirmed decisions about anticoagulation in 19 patients (49%). In 41% of patients, TEE had no effect on management decisions because of the overriding effect of other clinical information (182). Preliminary data from the VOTE study (Value of Transesophageal Echocardiography), which is investigating the usefulness of TEE in the management of cerebral ischemia, suggest that TEE alters the clinical management in 27% of patients and drug treatment in 16% (183). Prospective larger studies of the role of TEE in management of patients with suspected cardiac source of embolism are awaited (183).

TEE is unnecessary in the assessment of all patients with a potential cardiac source of embolism. Situations in which information from TEE is mostly likely to be of value include (a) younger stroke patients (younger than 60 years) without a history of cerebrovascular disease or obvious embolic source, (b) recurrent embolic events, (c) anticoagulation with a higher than normal risk due to comorbidities, (d) presence of prosthetic valve, and (e) suspected endocarditis.

Coronary Disease

TEE, although not a primary imaging modality for coronary disease, is capable of imaging the ostia and variable portions of the coronary tree. It can identify coronary anomalies and may detect and quantify coronary stenoses. The coronary vessels are most readily imaged in the basal short-axis view (*e*Fig. 52.13.2).



***e*FIGURE 52.13.2** Coronary vessels imaged by multiplane transesophageal echocardiography. Cx, circumflex; LAD, left anterior descending; LM, left main coronary; T, trification branch.

Imaging of Normal and Diseased Vessels

The left main coronary artery and proximal portions of the left anterior descending and circumflex artery are imaged in the majority of patients (184,185). The proximal right coronary artery is more difficult to image (184). Mid and distal portions of vessels are adequately imaged only in a minority, even with multiplane transducers (184). Coronary stenoses may be detected as areas of narrowing or of flow disturbance with Doppler (186). In one study, the left main coronary could be imaged in 90% of 67 patients. TEE identified 10 of 11 significant stenotic lesions, for a sensitivity of 91% and specificity of 100% (187). Other studies suggest that TEE can detect stenotic areas with reasonable accuracy in those portions of vessels that are adequately imaged (184,185). TEE is useful in confirming left coronary ostial stenosis when this is suspected at catheterization (188). It is also accurate in the detection and classification of anomalous coronary origin and fistula formation and of aneurysm formation (189,190).

VIDEO

Video 52.69 Transesophageal echo at 60-degree view just above the aortic valve showing the take off of the left main trunk at approximately 2 o'clock. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 52.70 Transesophageal echo view of a patient following a large left anterior descending coronary artery territory infarction with an apical aneurysm. Note the spontaneous echo contrast seen within the left ventricular cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Stress Imaging

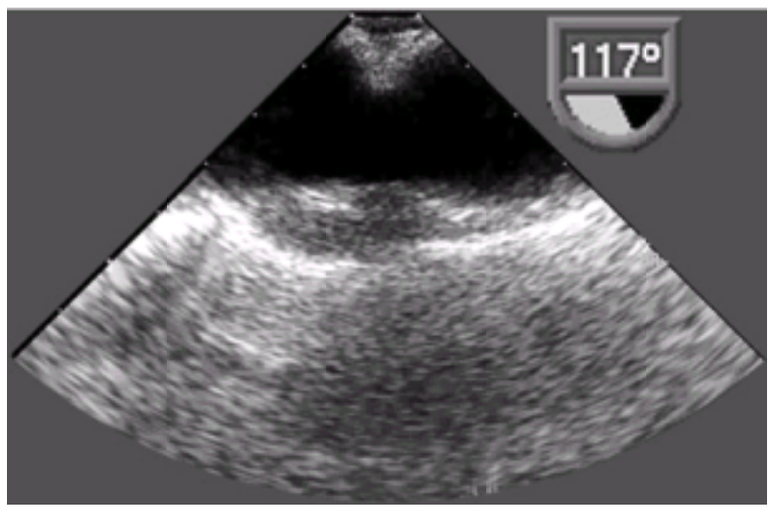
The transesophageal imaging window has been used to perform stress echocardiography. Excellent short- and long-axis images are obtained from the transgastric window, and all three major coronary territories are represented in this view (191). Excellent endocardial resolution is usually obtained, which facilitates detection of ischemic wall motion abnormalities. One limitation with TEE imaging is the evaluation of ischemia at the cardiac apex, which may be difficult to visualize even with multiple imaging planes. Esophageal pacing, intravenous vasodilators such as adenosine and dipyridamole (192), and inotropic agents such as dobutamine have been used to produce ischemia (193,194 and 195). A sensitivity and specificity of more than 80% in the detection of coronary disease have been reported for all of these stress TEE methods (193,194,196). The increased invasiveness of stress echocardiography from the transesophageal approach has limited its widespread application. Clinical use of TEE stress echocardiography has been confined to those in whom adequate images are not available from TTE, especially morbidly obese patients who cannot be evaluated by other methods (197).

Assessment of Coronary Flow Reserve

It is possible to measure flow velocity in individual large coronary vessels by pulsed Doppler (198). This is most often feasible in the left anterior descending artery and is facilitated by intravenous contrast agents, which cross the pulmonary circulation into the left heart (199,200). Coronary flow reserve has been estimated from the increase in flow produced by a coronary vasodilator such as adenosine or dipyridamole (198). Flow reserve in other disease states such as hypertrophic cardiomyopathy, aortic regurgitation, and syndrome X has also been assessed by TEE (201,202).

Transesophageal Echocardiography in Pediatric Cardiology and in Adult Congenital Heart Disease

Excellent TTE images are usually available in children. Nevertheless, TEE may provide additional diagnostic information in specific instances. Difficulty in passing the TEE probe in the pediatric population may occur with congenital esophageal anomalies such as atresia or with vascular rings. A number of studies have indicated that TEE is safe in neonates and young children, although general anesthesia is usually required (203,204). TEE has represented a significant advance in the evaluation of adults with congenital heart disease with complex anatomy (205,206 and 207). TEE is more reliable than TTE in the determination of atrial situs (203), in defining abnormalities in the systemic and pulmonary venous connections (208), and in defining the morphology of the chordal apparatus of atrioventricular valves (209). TEE long-axis imaging planes of right and left ventricular outflow tract often provide better definition than TTE of the site and nature of obstruction in the subvalvar area and in the pulmonary artery or aorta (204,207,210). It is also superior to TTE in detecting abnormalities of flow or leaks across the atrial baffle after Mustard or Senning procedures (211) and in identifying complications of the Fontan procedure (212,213). Complications associated with ventriculopulmonary conduits such as stenosis, regurgitation, or endocarditis are often best detected by TEE, especially in adults (204).



A still frame of a transesophageal echo demonstrating a coarctation of the aorta. Note the local narrowing of the aorta located at the junction of the distal arch and descending aorta. There was a 100–mm Hg pressure gradient across the coarctation as determined by continuous wave Doppler.

Unicuspid aortic valve (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

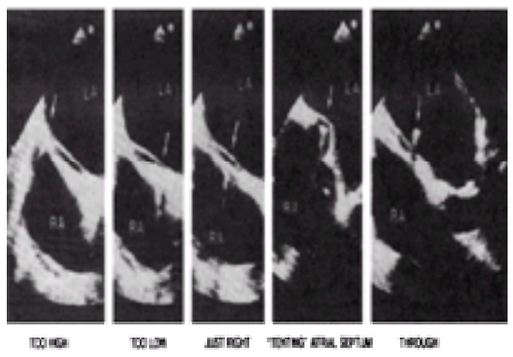
Transesophageal Echocardiography in Critically Ill Patients

TEE frequently provides vital information in the critically ill patient (191). Such patients often have inadequate TTE windows because of mechanical ventilation or dressings and may be too ill to undergo alternative imaging procedures such as computed tomography scanning or MRI. In one study, TTE was inadequate for diagnosis in 64% of intensive care unit (ICU) patients, whereas TEE was suboptimal in only 3% (214). The major indications for TEE in the critically ill patient include diagnosis of unexplained hypotension, suspected endocarditis, native and prosthetic valvular dysfunction, complications of myocardial infarction, source of embolus, pulmonary embolization, suspected dissection, and suspected tamponade (215,216). TEE may add information to TTE in between 25% to 59% of critically ill patients and alter the treatment plan in up to 25% of patients (215,217,218). In ICU patients with hypotension, TEE diagnosis of the cause of hypotension is prognostically powerful. Patients with reduced cardiac output because of valvular or pericardial disease have the best prognosis, whereas those with noncardiac disease or ventricular failure have a poorer outcome (214). TEE may also be of value in hemodynamic assessment in the ICU setting. Chamber volume can be estimated on a beat-to-beat basis using automated border detection algorithms based on changes in chamber area (219). Quantification of ejection fraction (220) and other volumetric indices using automated edge detection techniques has shown reasonable correlation with reference techniques.

Specific critical care situations in which TEE is superior to TTE include the detection of thrombus behind the right atrium that is compromising filling after open-heart surgery (221), the exclusion of significant cardiac abnormalities in potential cardiac donors (222), and the detection of the cause of a new systolic murmur in acute myocardial infarction. TEE is also highly sensitive in the detection of cardiac abnormalities in patients with blunt chest trauma (223). TEE has been used during cardiopulmonary arrest to determine the cause of the event and to evaluate the mechanism and adequacy of closed-chest compression in providing a forward cardiac output (224,225).The accuracy of TEE in diagnosis of the cause of the event is reported at 87%, and it may alter management in up to one in three cases in which it is used (226). It is also often diagnostic in patients with suspected acute pulmonary embolism (227,228). Thrombus in transit in the right heart and proximal pulmonary vessels is accurately detected, but distal pulmonary thromboembolism is not. TEE is reported to be 97% sensitive and 88% specific in the detection of central thromboembolism (227). However, artifact simulating thrombus in the pulmonary arteries is common, and the diagnosis of pulmonary thromboembolism should be entertained only in the appropriate clinical setting and after scanning in multiple planes. TEE may also detect thrombus *in situ* in the central pulmonary arteries of patients with significant chronic obstructive pulmonary disease in the absence of both pulmonary hypertension and pulmonary embolism, which are presumed to be a consequence of atherosclerotic disease in the pulmonary arteries of these patients (229).

Transesophageal Echocardiography in Interventional Cardiology

TEE has been used as a monitoring and diagnostic tool during many types of interventional procedure, although it is not absolutely required for any of these. Its major advantage is that it allows continuous imaging of structures of interest without interfering with the procedure. Although it is performed in awake patients in the supine position who are lightly sedated, it is well-tolerated, and few complications have been reported. The major indication for TEE in interventional cardiology is balloon valvuloplasty of the mitral valve (230). TEE is of value in optimizing the site of septal puncture and balloon placement within the mitral valve (eFig. 52.13.3). It can also determine the immediate effect of sequential balloon inflation on mitral valve structure, gradient, area and mitral regurgitation. Periprocedural complications may be rapidly detected. These include thrombus formation on catheters or at the site of endothelial injury, valve disruption, and pericardial effusion and tamponade (231). TEE is more sensitive than either oximetry or TTE in detecting a residual arterial septal defect after the septal puncture (64). TEE is also useful in percutaneous catheter closure of septal defects and patent ductus arteriosus (232,233). The exact position of the closure device can be ascertained and positional adjustments made to minimize residual shunt flow. Other interventional techniques in which TEE has been used include endomyocardial biopsy, electrophysiologic ablation procedures, and septostomy and other procedures in the pediatric group (234,235 and 236). TEE can assess the results of balloon dilatation of coarctation and intimal dissection, which commonly occurs with this procedure (237). It may be used instead of fluoroscopy in positioning catheters or pacemakers when radiation exposure is best avoided, such as in pregnancy (238).



***e*FIGURE 52.13.3** Transesophageal echocardiography–guided needle puncture of the interatrial septum. The arrows point to the transseptal needle in each panel. The corresponding description of the needle placement appears below each panel. LA, left atrium; RA, right atrium. (From Goldstein SA, Campbell AN. Mitral stenosis:

evaluation and guidance of valvuloplasty by transesophageal echocardiography. *Cardiol Clin* 1993;11:409–425, with permission.)

CONTROVERSIES AND PERSONAL PERSPECTIVES

A major controversy with regard to TEE is when should it be used as a primary diagnostic modality. TEE provides incremental information to that obtained by clinical examination and TTE in many selected instances of endocarditis, source of embolism, prosthetic dysfunction, disease of the aorta, native-valve disease, and atrial fibrillation. As outlined already, in specific situations such as suspected prosthetic endocarditis, the value of a TEE is such that it should be considered part of the normal workup. In other situations, such as in patients with stroke and atrial fibrillation, although TEE may detect a potential embolic source, it is unlikely to alter management, as the patient will most likely require chronic anticoagulation anyway. The usefulness and need for TEE in such situations are highly controversial. For instance, in the setting of embolic stroke, cost-effectiveness models have supported the use of TEE as a primary diagnostic modality (180). However, clinical variables have proven more predictive of outcome than TEE information in other studies of stroke in atrial fibrillation (179). TEE is an extremely accurate diagnostic tool. However, because of its invasiveness and cost, both economically and in physician time, it should be reserved for those situations in which information from it will likely alter patient management substantially. This will vary with the competency of the operator both in TTE and TEE in an individual institution and with variation in management algorithms in different institutions. Currently, TEE represents less than 10% of all studies performed in echocardiography laboratories. Although the indications for TEE have grown, improvement in TTE technology such as in contrast agents and harmonic imaging have reduced the need for TEE in many other situations such as the difficult-to-image patient. The proportion of echocardiograms being performed as TEE has not changed substantially over the last number of years, and this trend seems likely to continue.

THE FUTURE

Three-Dimensional Reconstruction

Multiple high-quality tomograms of the heart and aorta may be sequentially acquired with multiplane transesophageal transducers. Technological advances have led to the more rapid acquisition and reconstruction of images (239). These may be reconstructed by computer to derive a three-dimensional dataset. Three-dimensional reconstruction is of most value in the assessment of complex structures such as the mitral valve and in congenital heart disease (240) and in accurate estimation of chamber volume. Three-dimensional TEE may be especially useful in percutaneous interventional procedures such as closure of complex congenital shunts (241) and in assessing the mitral orifice in balloon valvuloplasty (242). The complex anatomy of the regurgitant orifice in myxomatous mitral valve disease may be reliably demonstrated and measured with three-dimensional TEE (239,243). Real-time acquisition of three-dimensional images is currently under investigation. This has the potential to greatly facilitate volumetric evaluation of the patient and to accelerate image acquisition. Once the three-dimensional dataset has been obtained, multiple tomograms through the heart may be generated later. Three-dimensional color Doppler is currently under investigation and appears to have potential in improving the detection and quantification of eccentric regurgitant jets (244). Although three-dimensional TEE is of great potential use, its diagnostic usefulness in a clinical setting is not sufficiently well-established for it to be used in routine clinical practice.

Miniaturization

The progress of TEE has been marked by increased miniaturization of the transducer and probe. Pediatric probes capable of imaging even neonates are currently available. Recently, transducers capable of passage through the nasopharynx have become available. Because of size constraints these have limited capabilities and are under investigation as an adjunct to monitoring left ventricle function in the ICU setting (245). Smaller transducers have the advantage of easier passage and have the potential to increase the patient acceptability of transesophageal imaging and reduce the need for conscious sedation in its use.

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NUCLEAR IMAGING TECHNIQUES

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"Indicates text or graphics that appear only in the electronic versions of this text."

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GLOSSARY

Attenuation: The reduction in the intensity of radiation that occurs when it passes through matter.

Background subtraction: Subtraction of nontarget counts from the target area; for example, left ventricular counts – background counts = background subtracted left ventricular counts.

Becquerel (Bq): The SI unit of radioactivity, equal to 1 disintegration per second. 1 mCi = 37 mBq.

Biologic half-life: The time interval over which the body eliminates one-half of a given amount of substance through biologic processes.

Compton scattering: The loss in photon energy that results from scattering by collision with electrons.

Effective half-life: The combined half-life of physical decay and biologic elimination.

mCi: The unit of activity that gives 3.7×10^{10} disintegrations per second.

Physical half-life: The time interval over which radioactivity decreases to exactly one-half.

Rad: Radiation absorbed dose.

Radioactive disintegration or decay: A process whereby an unstable nucleus becomes more stable by emitting charged particles.

Radionuclide generator: A system for producing short-lived isotopes by eluting a daughter radionuclide with short half-life from a parent radionuclide with a long half-life.

Rem: Roentgen equivalent, man. Dose in rem equals dose in rad for x-rays and for gamma rays.

Shielding: Any heavy materials used to block radiation.

Spatial resolution: Ability of a gamma camera to distinguish activities very close to each other; for example, separating lines.

Temporal resolution: Ability of a system to separate activities sequentially; for example, framing rate in first-pass study.

HISTORICAL BACKGROUND

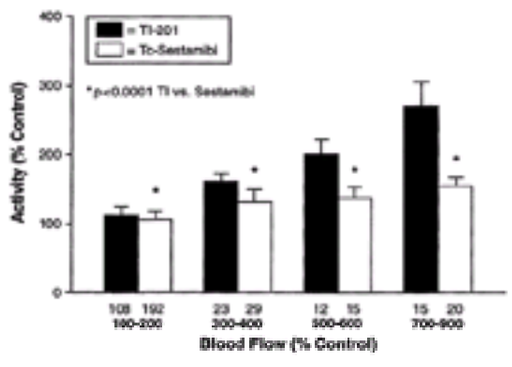
In the 1920s, nuclear techniques were applied for the first time to measure circulation time by injecting a radiotracer in one arm and monitoring the tracer's activity in the contralateral arm. Between 1950 and 1970, cardiac nuclear imaging techniques were used to detect pericardial effusion and pulmonary embolism. In the early 1970s, potassium-43 was used to study myocardial perfusion, radionuclide angiography (RNA) was used to study left ventricular function, and technetium-99m (Tc-99m) pyrophosphate was used to detect acute myocardial necrosis. In the mid-1970s, thallium-201 (Tl-201) was introduced for use in the study of myocardial perfusion. The U.S. Food and Drug Administration (FDA) approved two tracers (Tc-99m sestamibi and Tc-99m teboroxime) and a vasodilator stressor (dipyridamole) in 1991. Adenosine and Tc-99m tetrofosmin were approved in 1995, and indium-111 (In-111) antimyosin antibody was approved in 1996. In the late 1980s, a gradual shift from planar to single-photon emission computed tomographic (SPECT) imaging occurred. At the present time, gated SPECT perfusion imaging, attenuation/scatter

compensation, and SPECT fluorine-18-fluorodeoxyglucose (F-18-FDG) imaging are increasingly used. The first decade of contemporary nuclear cardiology can be characterized by its focus on diagnosis; the second decade, by its focus on risk assessment; and the third decade, by its focus on outcomes and cost-effectiveness. In 1993, the American Society of Nuclear Cardiology was created, and in September of 1996, the Certification Board of Nuclear Cardiology gave the first certification examination in nuclear cardiology.

TRACER KINETICS

Important differences exist between the kinetics of the current FDA approved perfusion tracers, Tl-201 and the three Tc-99m–labeled tracers [Tc-99m sestamibi (Du Pont Merck), Tc-99m teboroxime (Bracco Diagnostics), and Tc-99m tetrofosmin (Nycomed Amersham)] (1,2,3,4,5,6,7,8,9,10,11,12,13,14 and 15). Teboroxime is rarely used clinically at the present time. Tl-201 is a cationic element with low lipophilicity. Sestamibi is an isonitrile compound (2-methoxy-2-methyl propyl-isonitrile) and is marketed as Cardiolite. Tetrofosmin is a phosphine compound (1,2-Bis Bis 2-ethoxyethyl phosphine ethene) and is marketed as Myoview. Teboroxime is a Bato compound (boronic acid Tc dioxime) and is marketed as Cardiotec. Finally, Tc-99m-*N*-Noet (Cis bio), a cationic but neutral nitrido compound [Bis (*N*-ethoxy, *N*-ethyldithiocarbamato) nitrido], is undergoing clinical trials in Europe and the United States. The effective dose equivalent (rem/dose) is 1.05 for Tl-201, 1.06 for sestamibi, and 0.85 for tetrofosmin.

The kinetics of these tracers has been studied in cultured myocardial cells, in isolated perfused hearts, using *in vivo* animal models, and in humans (1,2,3,4,5,6,7,8,9,10,11,12,13,14 and 15). After intravenous injection, the blood activity decreases within minutes to a few percentage points of the initial concentration. In animal models of occlusion, reperfusion, stunning, and short-term hibernation, the uptake of Tl-201, sestamibi, and tetrofosmin reflects flow. The myocardial tracer concentration slightly overestimates flow in regions with low flow and underestimates it in regions with high flow. The trapping mechanism, which normally maintains the tracer inside the cell, disappears if necrosis occurs. Tl-201 is mostly localized in the cytoplasm, sestamibi and tetrofosmin in the mitochondria, and teboroxime on the cell membrane. The myocardial concentration of any tracer is a function of flow, extraction, and clearance. The extraction fraction of the available tracers is highest for teboroxime, followed by Tl-201, sestamibi, and tetrofosmin, in that order (9,10,13,14). There is a “roll off” in extraction as the flow rate exceeds 2.0 to 2.5 times the baseline level. The “roll off” is less severe for tracers with a higher extraction and more severe for those with a lower extraction (eFig. 53.0.1) (1,3,4,10). The myocardial clearance (washout) of teboroxime is faster than that of Tl-201. The clearance of sestamibi and tetrofosmin is negligible. Therefore, the myocardial retention—which is the net difference between extraction and clearance—for sestamibi and tetrofosmin is greater than that for Tl-201 and teboroxime. When the flow is very low, a slight increase in extraction fraction is noted with all tracers, as long as there is no myocardial necrosis. In the presence of myocardial necrosis, extraction diminishes, suggesting that these tracers are markers not only of flow, but also of viable myocardium.



***e*FIGURE 53.0.1** Bar graph showing mean myocardial thallium-201 (Tl-201, Tl) and technetium-99m sestamibi (Tc-Sestamibi) activities when these tracers were administered intravenously after intracoronary infusion of adenosine into the left anterior descending coronary artery of a patient (protocol 1). Activities are expressed as a percentage of control values and grouped by flow range. The numbers directly below each bar indicate the number of segments represented by each bar. Sestamibi activity was significantly less than that of Tl-201 in all flow ranges, and the difference between the tracers became progressively larger as flow increased. (From Glover DK, Ruiz M, Edwards NC, et al. Comparison between thallium-201 and Tc-99m sestamibi uptake during adenosine-induced vasodilation as a function of coronary stenosis severity. *Circulation* 1995;91:813–820, with permission.)

The myocardial uptake mechanism of Tl-201 is partly dependent on the sodium-potassium adenosinetriphosphatase system and is partly passive, dependent on concentration gradient, whereas the uptake of sestamibi and tetrofosmin essentially is passive, dependent on electric gradient. Tl-201 has an energy level in the range of 69 to 83 KeV and a smaller amount of gamma rays with energy levels of 165, 167, and 135 KeV. It has a half-life of 73 hours. Tc-99m has an energy level of 140 KeV and a half-life of 6 hours (eTable 53.0.1). Sestamibi and tetrofosmin are eliminated through the hepatobiliary and urinary systems. The hepatic clearance is faster with tetrofosmin than sestamibi, and lung activity is minimal with both in healthy subjects. A fatty meal after tracer injection does not affect the hepatobiliary clearance mechanism, although it may help to produce contraction of the gall bladder. The high energy level of Tc-99m, which labels sestamibi and tetrofosmin, produces less attenuation and scatter, improves spatial resolution, and allows simultaneous acquisition of perfusion and function by first-pass RNA or gated SPECT.

***e*TABLE 53.0.1** COMPARISON OF USE OF THALLIUM-201, SESTAMIBI, TEBOROXIME, AND TETROFOSMIN FOR CARDIOLOGIC IMAGING

Variable	Thallium-201	Sestamibi	Teboroxime	Tetrofosmin
Dose (mCi)	3.0	10–30	20–25	10–30
Energy (KeV)	80	140	140	140
Cyclotron product	Yes	No	No	No
Half-life	73 h	6 h	6 h	6 h
Extraction at normal flow	85%	65%	>90%	60%
Extraction at high flow	Lower	Lower	No change	Lower
Myocardial uptake	Adenosine triphosphatase	Unknown	Unknown	Unknown
Myocardial clearance	Fast, variable	Very slow	Very fast	Very slow
Hepatobiliary excretion	No	Yes	Yes	Yes
Perfusion-function studies[a]	No	Yes	Yes[b]	Yes
Gated perfusion	Possible	Yes	No	Yes
Stress redistribution	Yes	No	Possible	No
Stress rest	No	Yes	Yes	Yes
Time between injections (h)	NA	³2	³2	³2
Time to imaging (min)	<10	15–60[c]	<2	15–60[c]
Feasibility with pharmacologic stressor	Yes	Yes	Yes	Yes
Assessment of viability	Yes	Yes	Uncertain	Yes
Imaging protocol (d)	1	1 or 2	1	1 or 2

NA, not applicable.
[a]By first-pass RNA.
[b]Difficult because of high lung background.
[c]May be imaged up to several hours after the injection.

The myocardial washout (clearance) of Tl-201 depends on the gradient between its intracellular and intravascular concentrations (12). The clearance during stress imaging is more rapid in normal myocardium than in myocardium subtended by a diseased artery. The differential washout explains the disappearance of initial perfusion defects after 4 hours (redistribution). The washout is greater with exercise than with pharmacologic stress and is greater with maximal than with submaximal exercise (7). Minimal redistribution with sestamibi and tetrofosmin mandates the use of two separate injections to determine the nature of a perfusion abnormality (reversible or fixed).

IMAGING TECHNIQUES AND PROTOCOLS

The cardiac nuclear imaging techniques that have been applied to clinical imaging are summarized in eTable 53.0.2. At present, the most commonly used nuclear cardiac imaging procedure is myocardial perfusion imaging with the gated SPECT technique.

***e*TABLE 53.0.2** CARDIAC NUCLEAR IMAGING MODALITIES
Myocardial perfusion imaging

Thallium-201 chloride
Tc-99m sestamibi (Cardiolite)
Tc-99m tetrofosmin (Myoview)
PET (nitrogen-13 NH_3, oxygen-15 H_2O, rubidium-82)
Tc-99m teboroxime (Cardiotec)
Radionuclide angiography
First-pass
Blood pool (multiple-uptake gated acquisition)
Infarct-avid imaging (“hot spot”)
Tc-99m pyrophosphate
Indium-111 antimyosin antibody
Tc-99m glucarate
Ambulatory ventricular function (nuclear probes)
VEST
Cardioscint
Metabolic imaging
Fatty acids (iodine-123 IPPA, iodine-123 BMIPP)
Fluorine-18 (PET or SPECT)
Carbon-11 acetate (PET)
Sympathetic nerves
Iodine-123 MIBG (SPECT)
Carbon-11 hydroxyephedrine (PET)
Atherosclerosis imaging
Thrombus imaging

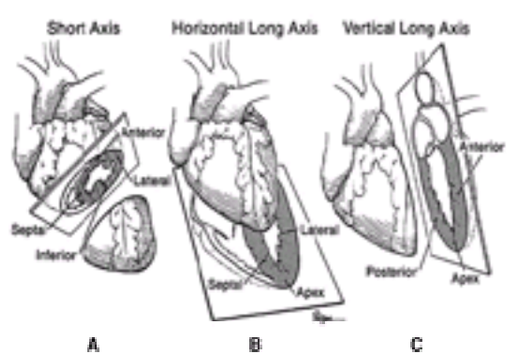
BMIPP, beta-methyl-*p*-iodophenylpentadecanoic acid; IPPA, iodophenylpentadecanoic acid; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; SPECT, single-photon emission computed tomography; Tc-99m, technetium-99m; VEST, left ventricular function detector.

Principles and Instrumentation for Radiation Detection

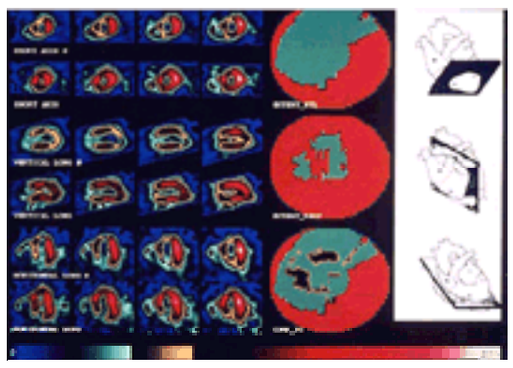
The basic principle of nuclear cardiac imaging is the detection of photons (gamma rays or x-rays) that are emitted from decay of radioactive tracers, by gamma cameras. These instruments use a large sodium iodide crystal at which the photons collide, producing scintillations. Several manufacturers now produce highly computerized digital gamma cameras with one, two, or three detector heads. Positron emission tomography (PET) cameras are designed to detect positrons (positively charged electrons) (see Chapter 55).

Acquisition Techniques and Views

Standard nuclear cardiology imaging uses either planar or tomographic (SPECT) techniques (16). During planar acquisition, images can be obtained in three or four different views. With SPECT imaging, sequential images can be acquired (32 or 64) at predetermined angular intervals. These individual images are then combined and reconstructed, followed by reorientation in three standard plans (eFig. 53.0.2), which allows a three-dimensional evaluation of the tracer activity in the heart. Most of the existing tomographic systems allow electrocardiographic (ECG) gating, dividing the cardiac cycle into 8 or 16 segments that, when viewed in cine mode, enable the interpreting physician to analyze the wall motion and systolic thickening in every segment of the left ventricle. Much of the currently available software allows quantification of the extent, severity, and reversibility of perfusion defects (eFig. 53.0.3). In addition, when gating is used, the left ventricular ejection fraction (LVEF) and left ventricular volumes can be calculated with well-validated software (17,18,19,20,21 and 22). The values of LVEF calculated by gated SPECT correlate well with those measured by cine magnetic resonance imaging, blood pool or first-pass RNA, contrast angiography, and echocardiography.



***e*FIGURE 53.0.2** Standard single-photon emission computed tomographic (SPECT) planes. Artist’s depiction of the three conventional planes during SPECT: short axis **(A)**, horizontal long axis **(B)**, and vertical long axis **(C)**. These three planes allow good visualization of all myocardial walls. (From Iskandrian AS, Verani MS. *Nuclear cardiac imaging: principles and applications*. Philadelphia: FA Davis, 1996, with permission).



***e*FIGURE 53.0.3** Single-photon emission computed tomographic images from a patient with high-grade left anterior descending artery stenosis in its proximal portion. A reversible defect during stress is depicted in the upper rows of each pair involving the anterior wall, septum, and apex. The polar maps on the right display the tracer activity during stress (*top*) and redistribution (*middle*). The lower polar maps localize the defect to the left anterior descending vascular territory.

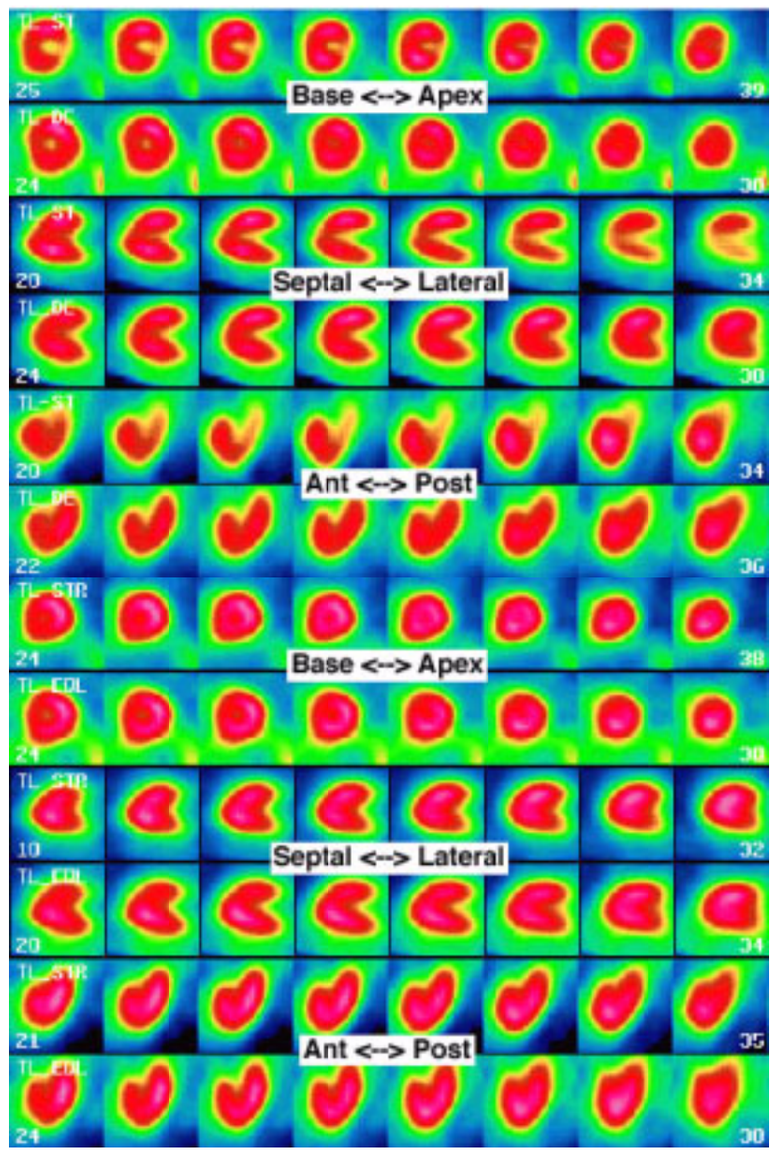
Radionuclide Angiography

RNA (16,23,24,25 and 26) can be performed using either a first-pass or a blood pool [also called *multiple-uptake gated acquisition* (MUGA)] technique (23). The first-pass technique is based on the fast acquisition of individual images as a bolus of a tracer (usually Tc-99m) traverses the central circulation. Ideally, it is done using a special camera with a high count rate (multicrystal camera). The gated blood pool technique is based on labeling of the red blood cells with Tc-99m. Images are obtained in three or four different positions and displayed in cine mode, where regional wall motion can be evaluated. Both techniques allow calculation of the left and right ventricular ejection fraction (EF), as well as left ventricular volumes. The EF measurements by RNA are computer-determined and, hence, extremely reproducible and accurate.

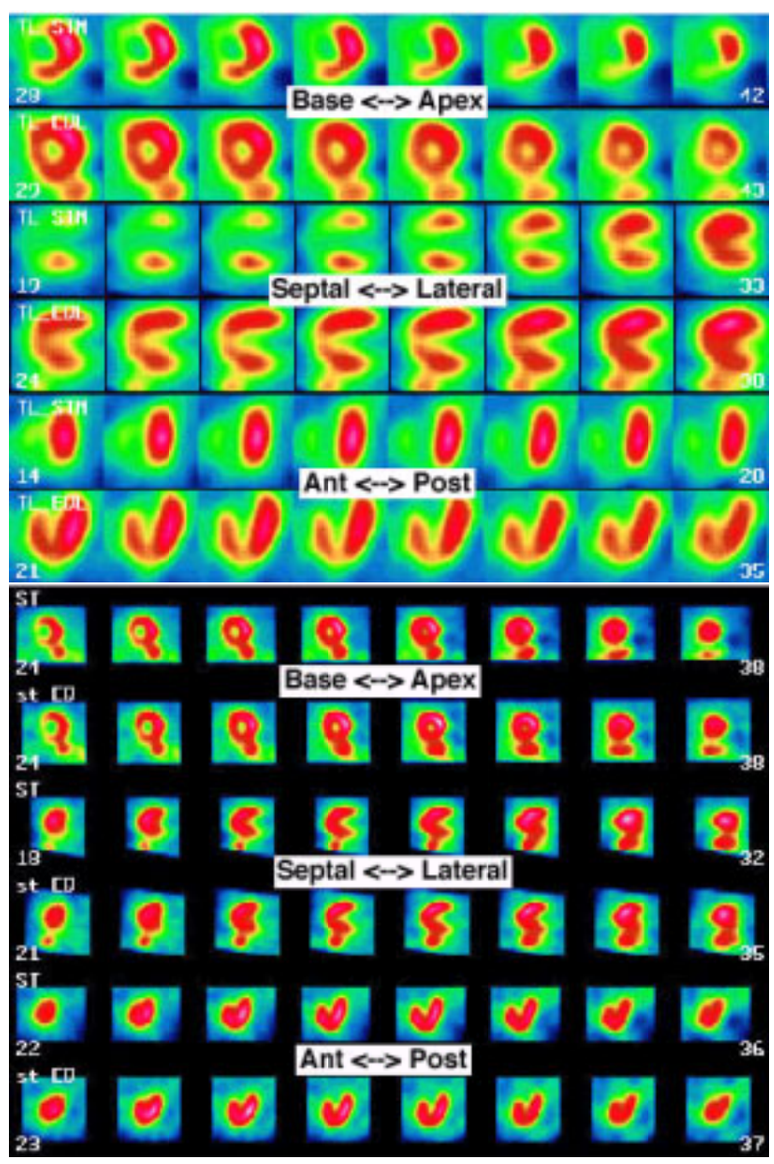
Imaging Protocols

Nuclear cardiac images can be acquired either at rest or during stress (exercise or pharmacologic). When the perfusion tracer is injected at peak stress, a separate rest

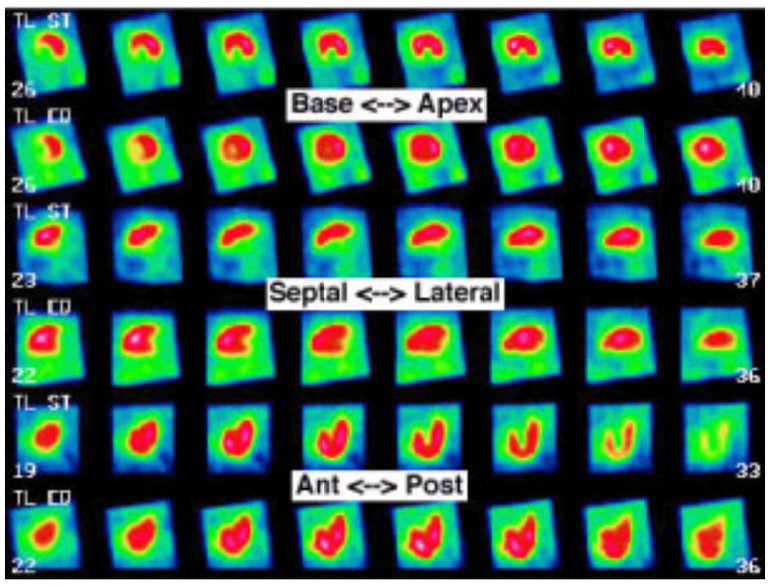
injection is often required if a Tc-99m labeled tracer (such as tetrofosmin or sestamibi) is used. Tl-201 images are obtained shortly after stress and repeated 4 hours later. Defects that are present during stress and improve 4 hours later (measured with Tl-201) or at rest (measured with Tc-99m tracers) denote myocardial ischemia, whereas lack of improvement denotes either scar or resting hypoperfusion. Reinjection of a small dose of Tl-201 (1 mCi) after the 4-hour redistribution images are taken as aids in distinguishing between ischemia and scar: Ischemic but viable areas improve after reinjection, whereas myocardial scar does not (27,28). A hybrid protocol (the dual isotope technique) uses a rest injection of Tl-201, followed by imaging, which is then followed by an injection within 1 hour of injection of a Tc-99m tracer during stress (29). In patients who are unable to exercise, pharmacologic stress with dipyridamole, adenosine, or dobutamine has been used successfully. With proper administration and monitoring, all three of these drugs are quite safe, although side effects are very common during the test (30,31).



Thallium-201 single-photon emission computed tomography stress and delayed images (A). Transverse, sagittal, and coronal plane images demonstrating lateral wall ischemia in a patient with severe proximal left circumflex artery stenosis. Thallium-201 single-photon emission computed tomography stress and equilibrium images (B). Transverse, sagittal, and coronal plane images obtained from a patient after successful intervention for severe proximal left circumflex artery stenosis (normal study).



Thallium-201 single-photon emission computed tomography stress and equilibrium images. A: Transverse, sagittal, and coronal plane images demonstrating anterior, septal, apical, and distal inferior ischemia in a patient with a severe proximal left anterior descending (LAD) artery stenosis in whom the LAD wraps around the left ventricular apex. B: Transverse, sagittal, and coronal plane images from the same patient as A after intervention for severe proximal LAD artery stenosis (normal study).



Thallium-201 single-photon emission computed tomography stress and equilibrium images. Transverse, sagittal, and coronal plane images demonstrating inferior and posterior wall ischemia in a patient with a severe proximal stenosis in a dominant right coronary artery

DETECTION AND EVALUATION OF CORONARY ARTERY DISEASE

In the past decade, myocardial perfusion imaging with SPECT has evolved into the preeminent noninvasive technique for assessment of coronary artery disease (CAD). Although RNA during stress remains a useful technique in selected patients, it is most often used in the risk-stratification of patients who have experienced myocardial infarction (MI) or heart failure.

Myocardial Perfusion Imaging

The basic principle underlying the detection of CAD by perfusion imaging is a differential blood flow distribution through the left ventricular myocardium, with a normal flow (and normal tracer uptake) in the myocardium perfused by normal coronary arteries and *relatively* diminished flow (and diminished tracer uptake) in regions perfused by stenotic vessels. A perfusion abnormality may be present at rest in patients with previous MI or fibrosis, or in patients with high-grade (>85% of the luminal diameter) coronary stenoses. However, most functionally significant coronary stenoses, including severe ones, are associated with normal resting myocardial blood flow and, hence, normal resting perfusion images. Consequently, to demonstrate these stenoses, it is necessary to perform imaging of these patients during stress.

During maximal exercise or pharmacologic stress, blood flow increases through the normal coronary arteries but increases less or even fails to increase (occasionally, it decreases) in vessels with significant (>50% of the luminal diameter) stenoses. This diminished coronary flow reserve in stenotic vessels is not an all-or-none phenomenon; rather, the flow reserve decreases gradually as the severity of the coronary stenosis progresses. The most severe stenoses (>85%) typically have no flow reserve left.

It is important to emphasize that the greater the flow differential between the normal arteries and the stenotic arteries, the greater the difference in tracer uptake and potentially the greater the likelihood that the stenosis will be detected. However, the relationship between myocardial blood flow and tracer uptake is only linear up to a flow of approximately 2.0- to 2.5-fold above the baseline values. Beyond these limits, the tracer uptake lags behind the flow (the so-called “roll-off” effect). This “roll-off” effect depends on two major factors: (a) the stress modality and (b) the flow tracer.

During exercise, the normal coronary flow increases approximately 2.5- to 3.0-fold over the baseline values. Although this is substantially less than the maximal normal coronary flow reserve in human beings, the relationship between flow and Tl-201 uptake remains approximately linear (12). During pharmacologic vasodilation induced by adenosine or dipyridamole, the coronary flow increases maximally or near-maximally (four- to sixfold above the baseline). However, when the flow is so high, tracer uptake diminishes considerably, so that the slope of the tracer uptake versus flow relationship becomes flattened. Tracers with high myocardial extraction, such as Tc-99m teboroxime and Tl-201, maintain a steeper slope, whereas tracers with lower myocardial extraction, such as Tc-99m sestamibi, Tc-99m tetrofosmin, and Tc-99m furofosmin, have a flatter slope. This nonlinear relation between flow and tracer uptake at high flow raises some theoretical concerns, especially about images acquired during pharmacologic stress. However, because the tracers with lower extraction fraction also have a longer residence time in the myocardium, it appears that the ability of pharmacologic stress to detect CAD is not compromised (24,32).

Exercise Myocardial Perfusion Imaging

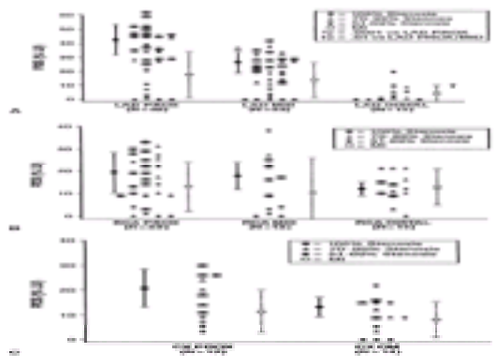
The most common indications for exercise perfusion imaging are listed in Table 53.1. Most studies are done to establish the diagnosis of CAD. The maximal diagnostic yield of SPECT imaging, according to Bayes’ theorem, is in patients with an intermediate likelihood (20% to 60%) of having CAD on the basis of their history. In patients with a very low pretest disease likelihood, a positive test is often false positive, whereas in patients with a very high pretest probability of CAD (e.g., middle-aged or older men with classical angina, in whom the pretest probability is ³80%), a negative test is often false negative. On the basis of these considerations, some authorities have suggested that perfusion imaging should not be applied to patients with a very low or a very high pretest likelihood of CAD. This line of reasoning, however, fails to consider the prognostic value of perfusion scintigraphy; that is, patients who have a low pretest disease likelihood but a large perfusion defect, especially with a multivessel distribution, may still be at increased risk, whereas patients who have a high pretest likelihood but a negative scan have a very low risk for future cardiac events, and, arguably, their condition could be managed medically without need for cardiac catheterization (33,34).

Diagnosis of coronary artery disease
Stable angina or chest pain of uncertain origin
Unstable angina, after initial stabilization
Positive exercise electrocardiogram without symptoms
Screening of high-risk, asymptomatic patients
Patients who are referred for exercise electrocardiographic testing but have an abnormal resting echocardiogram that hampers evaluation of ischemia
Prior nondiagnostic exercise electrocardiogram test
Assessment of functional importance of known coronary stenoses
Bordering stenoses (40% to 70%) by coronary angiography
Assessment of culprit lesion before coronary angioplasty
Stenoses of small branches or of distal location
Assessment of therapeutic benefits
After percutaneous coronary intervention
After coronary artery bypass surgery
After medical therapy
Risk-stratification
Stable angina
Unstable angina
Post-myocardial infarction
Preoperative risk
Demonstration of myocardial ischemia in patients with angiographically normal coronary arteries.

Modified from Iskandrian AS, Verani MS. Nuclear cardiac imaging: principles and applications. Philadelphia: FA Davis, 1996, with permission.

TABLE 53.1 INDICATIONS FOR EXERCISE PERFUSION SCINTIGRAPHY

Recent reports have confirmed the diagnostic utility of perfusion imaging in patients with normal and with abnormal resting ECG results (35). The information provided by myocardial perfusion scintigraphy during stress transcends the mere categorization of the test results as normal or abnormal. On the basis of the location of the perfusion abnormality, one can infer which arteries are involved. It has been shown that stenoses involving the left anterior descending artery generally lead to a larger perfusion defect than stenoses in the right coronary or circumflex arteries (36,37) (eFig. 53.0.4). Patients with multivessel CAD have larger perfusion defects than patients with single-vessel disease (38). In addition to the extent of hypoperfusion, the reversibility of the defects needs to be assessed during the redistribution (in the case of Tl-201) or the rest images (in the case of the Tc-99m tracers). It is important to assess also the severity of tracer uptake reduction in the stress and rest or redistribution images. Transient cavity dilation during exercise or pharmacologic stress and increased Tl-201 lung uptake during stress are powerful predictors of poor prognosis (25,33).



***e*FIGURE 53.0.4** Mean left ventricular perfusion defect size (PDS) in patients with (*solid line*) and without (*broken line*) myocardial infarction (MI) for the left anterior descending coronary artery (LAD) **(A)**, the right coronary artery (RCA) **(B)**, and the left circumflex coronary artery (CX) **(C)**, with proximal (PROX), middle (MID), or distal stenosis. Although LAD PROX stenosis generally led to a larger perfusion defect size than did LAD MID stenosis, significant individual vessel heterogeneity was seen. For the RCA, the mean perfusion defect size was similar whether stenoses were PROX, MID, or distal in location, although the range was wide. Similar heterogeneity was seen for the proximal and obtuse marginal (OM) CX stenosis. LV, left ventricle. (From Mahmarian JJ, Pratt CM, Boyce TM, et al. The variable extent of jeopardized myocardium in patients with single vessel disease: quantification by thallium-201 single photon emission computed tomography. *J Am Coll Cardiol* 1991;17:355–362, with permission.)

The use of exercise perfusion scintigraphy to screen asymptomatic patients is controversial. It certainly cannot be recommended across the board, but it may be very useful in selected populations who are at increased risk for CAD despite being asymptomatic (Fig. 53.1). For example, the test is useful in patients with a conglomerate of risk factors and in adolescents or young adults who have familial hypercholesterolemia (39). Middle-aged siblings of patients who have had an MI also are at increased risk for cardiac events and are good candidates for a stress perfusion study (40).

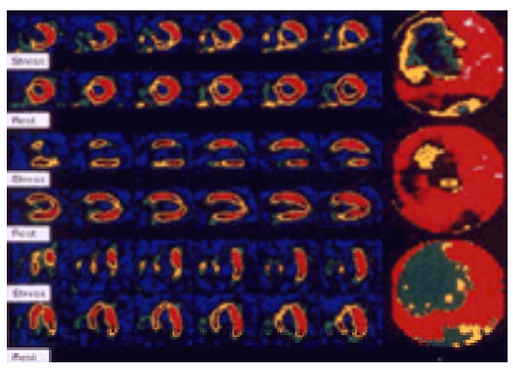
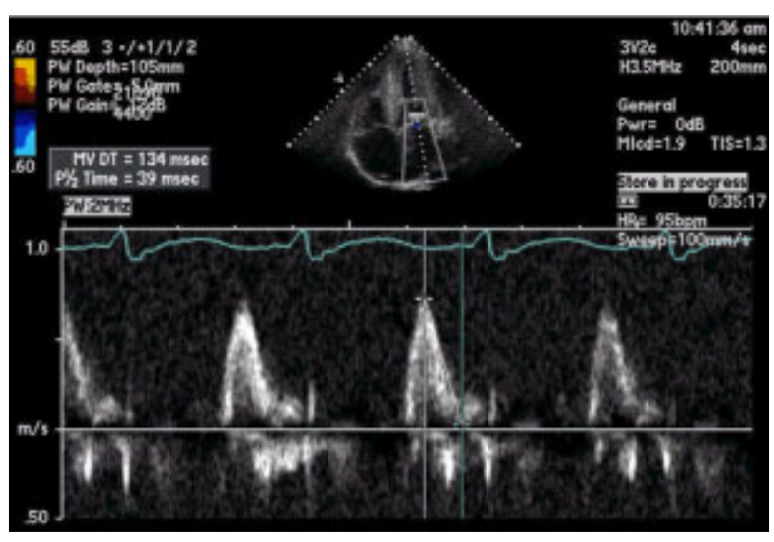
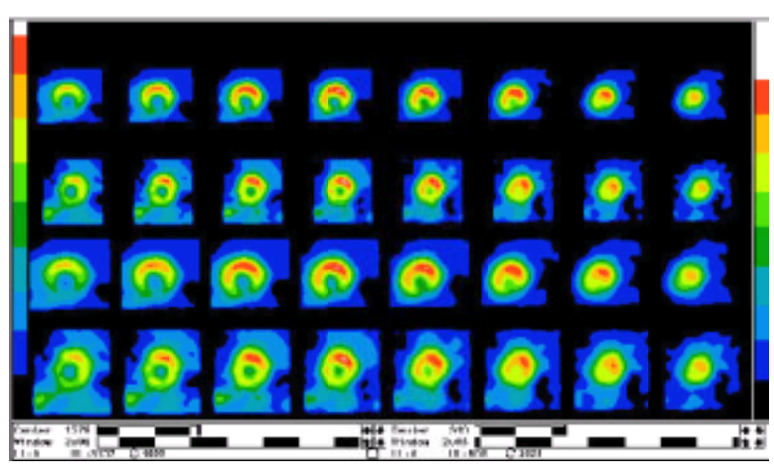


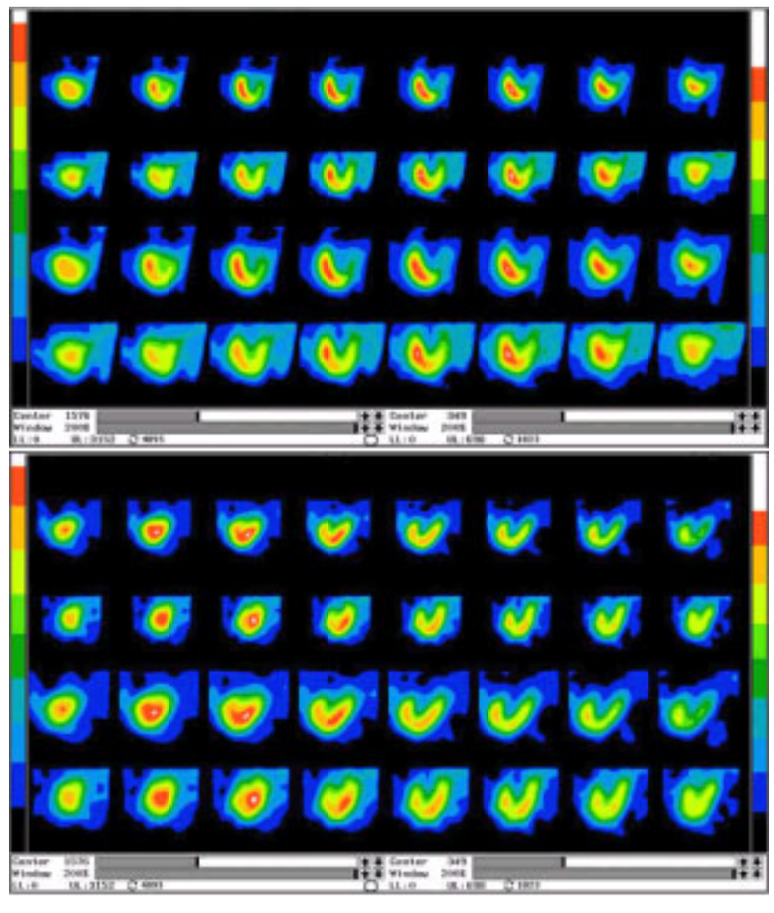
FIGURE 53.1 Technetium-99m single-photon emission computed tomographic images during exercise and at rest in a 52-year-old diabetic male who was asymptomatic. The images during stress depict large defects involving the anterior wall, septum, apex, and inferior and posterolateral walls, with substantial improvement at rest. Subsequent coronary angiography showed severe proximal left anterior descending (90%) and left circumflex (75%) stenoses.

An extensive review of published studies that used exercise Tl-201 qualitative planar scintigraphy, which included 52 publications and 5,160 patients (41), shows an overall sensitivity and specificity of 83% and 88%, respectively. Several studies assessed the value of quantitative Tl-201 planar scintigraphy during exercise for the diagnosis of CAD (24). The mean sensitivity and specificity are 90% and 80%, respectively. With exercise Tl-201 SPECT, the average sensitivity and specificity are 89% and 76%, respectively, by qualitative analysis (24).



Pulsed wave Doppler of the mitral valve inflow in a patient with amyloidosis demonstrating a short deceleration time (134 ms) consistent with restrictive physiology.





Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the inferolateral, inferior, and proximal to mid inferoseptal walls. The left anterior oblique cranially angulated view (*video*) shows severe stenosis of the distal right coronary artery before the posterior descending and posterolateral arteries in the same patient.

Video 53.1 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating ischemia of the inferolateral, inferior, and proximal to mid inferoseptal walls. The left anterior oblique cranially angulated view (*video*) shows severe stenosis of the distal right coronary artery before the posterior descending and posterolateral arteries in the same patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

A comparison between qualitative and quantitative analyses of Tl-201 SPECT images has not shown a major difference in sensitivity or specificity between these two techniques (38,42,43,44 and 45). However, detection of the individual coronary arteries involved may be moderately improved by quantitative analysis. This is particularly true for detection of circumflex artery stenoses and coronary stenoses of moderate severity (between 50% and 75% of the luminal diameter) (45).

Use of Technetium-99m Perfusion Tracers in the Diagnosis of Coronary Angiography Disease

The newer Tc-99m flow tracers represent a substantial improvement in nuclear cardiac imaging. The more favorable physical characteristics of Tc-99m, such as an optimal emission energy for imaging with gamma cameras, and less physical scatter and shorter half-life (which allows administration of a much higher tracer dose) than Tl-201, are definite advantages of these agents. Interestingly, the few studies that have directly compared Tl-201 with Tc-99m sestamibi, teboroxime, or tetrofosmin have not shown an overall superiority for detection of CAD with any of these newer agents. The overall sensitivity of Tc-99m sestamibi using planar imaging is 87%, with a specificity of 62% and a normalcy rate of 92%. When SPECT imaging is used, the overall sensitivity and specificity are 90% and 74%, respectively (24). As mentioned, Tc-99m sestamibi imaging during stress has also been used in combination with Tl-201 resting imaging (dual isotope imaging). With this strategy, a sensitivity of 91% and specificity of 75% have been found by Berman and coworkers (29).

Because the Tc-99m–labeled agents undergo less attenuation than agents labeled with Tl-201, they may be particularly useful for patients who are prone to attenuation artifacts, such as women with large breasts or breast implants and obese individuals (46). Tc-99m teboroxime has been used with planar imaging and with SPECT imaging. Despite its high myocardial extraction rate and its good correlation with determination of myocardial flow using microspheres, it has a very short residence time in the myocardium, rendering SPECT imaging a challenging proposition. The initial favorable reports (which indicated an average sensitivity of 87% and specificity of 62% with either planar or SPECT imaging) (47,48) notwithstanding, this tracer is not currently used for clinical imaging. New research has focused on the idea of measuring absolute myocardial blood flow using dynamic imaging with teboroxime (49).

Tetrofosmin is another attractive Tc-99m–labeled perfusion agent. A high concordance rate has been found between this agent and Tl-201, both with planar and SPECT imaging (50,51). As is the case for sestamibi, the sensitivity and specificity of tetrofosmin imaging appear to be comparable, but not superior, to those of Tl-201 imaging. In the largest reported series, from a phase III multicenter trial, that used planar imaging and included 252 patients from ten centers in the United States and Europe, tetrofosmin and Tl-201 had similar sensitivity and specificity for CAD detection. Other studies have confirmed the diagnostic accuracy of tetrofosmin (52,53,54 and 55) and confirmed that it is comparable to sestamibi (56).

Furofosmin is another Tc-99m–labeled compound that has been tested in the United States but has not received FDA approval. In a large multicenter trial comparing Tc-99m furofosmin SPECT with Tl-201 SPECT during exercise, an overall agreement in the results of 86% was found (57).

The principal advantage of the Tc-99m tracers is that they can be administered in higher doses, and, hence, high-quality images are feasible even for large or obese individuals and women with large breasts. Another very attractive feature is the ability to gate the SPECT images, which allows an evaluation of the global and regional ventricular function by observation of the motion of the perfused ventricular walls. These agents also enable assessment of left and right ventricular function during the injection of the Tc-99m tracers by first-pass RNA.

Pharmacologic Perfusion Imaging

Approximately 20% to 30% of patients with suspected or documented CAD are unable to perform an exercise stress test and, thus, are good candidates for pharmacologic stress imaging. Other clinical conditions for which pharmacologic stress imaging is appropriate are listed in Table 53.2. Adenosine produces maximal or near-maximal coronary vasodilation through its agonistic effect on the adenosine A2 receptors located in the coronary arterial wall. Dipyridamole has an indirect vasodilator effect, through the inhibition of the cellular reuptake and metabolism of adenosine (24,30), leading to an increase in the interstitial and perimembrane levels of adenosine. The principal difference between these two agents, which have similar hemodynamic effects (24), is the much shorter half-life of adenosine. Both produce frequent side effects, but the reported experience in large numbers of patients has indicated that both are quite safe when properly used (58,59 and 60). Investigators in Japan have used intravenous adenosine triphosphate as yet another option for pharmacologic stressor (61,62).

Patient unable to exercise
Preoperative risk-stratification
Early postinfarct risk-stratification
Left bundle branch block
Presence of fixed-rate ventricular pacemaker

Modified from Verani MS. Pharmacologic stress myocardial perfusion imaging. *Curr Probl Cardiol* 1993;18(8):481–525.

TABLE 53.2 INDICATIONS FOR PHARMACOLOGIC PERFUSION IMAGING

Studies comparing dipyridamole or adenosine Tl-201 scintigraphy with exercise Tl-201 scintigraphy have indicated excellent agreement between these stressors. The overall reported sensitivity with dipyridamole Tl-201 planar imaging is 82%, with a specificity of 75%. These values are slightly higher with SPECT imaging (89% and 78%, respectively). The average sensitivity of adenosine Tl-201 SPECT is 88%, with a specificity of 85% (24,30). Clinical studies have shown similar values when adenosine or dipyridamole is combined with Tc-99m sestamibi or tetrofosmin (63,64 and 65). Both adenosine and dipyridamole can be combined with a submaximal exercise test. The main advantage of such a combination is the decrease in splancnic uptake, which improves the quality of the images, especially with Tc-99m agents (66,67).

Adenosine and dipyridamole are contraindicated in patients who have active asthma or severe chronic obstructive pulmonary disease with wheezing. In these patients, dobutamine is a proven adequate stressor, with reported sensitivity ranging from 80% to 97% and specificity ranging from 74% to 89%, in combination with SPECT (24). Although a curious antagonism has been described between dobutamine and sestamibi in animal experiments (68), the reported sensitivity of this combination of agents in clinical patients is high thus far (69,70).

Causes of False-Negative Results of Myocardial Perfusion Scintigraphy

Table 53.3 lists several of the possible causes of false-negative myocardial perfusion images. Among these, the most frequent are an inadequate exercise stress test and concomitant administration of antiischemic medications. It must be emphasized that the gold standard for determination of diagnostic accuracy of perfusion imaging has traditionally been coronary angiography. The potential weaknesses of this gold standard have long been emphasized (71). It is not unusual for lesions that are considered “significant” by angiography to have a normal flow reserve. It is thus not surprising that some of them are also associated with normal myocardial perfusion images.

Inadequate exercise stress
Administration of antiischemic medications
Non–flow-limiting coronary stenoses
Overlap circulation
Collateral circulation
Hypoperfusion in segments with attenuation
Incorrect interpretation of angiograms
Incorrect interpretation of scans
Poor-quality images
"Balanced" hypoperfusion
Delay in obtaining thallium-201 stress images

Modified from Iskandrian AS, Verani MS. *Nuclear cardiac imaging: principles and applications*. Philadelphia: FA Davis, 1996, with permission.

TABLE 53.3 CAUSES OF FALSE-NEGATIVE RESULTS OF SCANS

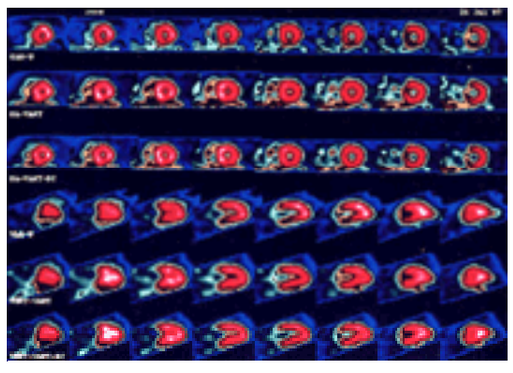
Causes of False-Positive Myocardial Perfusion Images

Table 53.4 lists some of the causes that may be associated with false-positive results of imaging. Among them, the most important is photon attenuation, which may have a different impact on different myocardial walls. For example, anterior wall attenuation is common in women with breast implants or large breasts, whereas diaphragmatic attenuation is frequent in obese, stocky patients (*e*Fig. 53.1.1). In individual patients, it may be extremely difficult to distinguish between attenuation artifacts and a true perfusion defect. The application of newly developed attenuation-correction techniques appears quite promising (72,73,74,75 and 76). Among the causes listed on Table 53.4, conduction defects are particular important, because they are potentially preventable. Patients who have a left bundle branch block often have perfusion defects involving the interventricular septum, which may be totally or partially reversible at rest, thus mimicking left anterior descending artery stenosis. These defects are much less frequently seen when dipyridamole or adenosine stress testing is used, and pharmacologic imaging with one of these agents is therefore preferable to exercise testing in patients with a left bundle branch block (22,24,30,77).

Regional photon attenuation
Poor technique
Conduction abnormalities*
Cardiomyopathies*
Coronary vasospasm*
Coronary anomalies*
Microvascular disease*
Recanalized coronary occlusion*
Posttest referral bias
Gold-standard pitfalls

*Causes "real" defects. The term false-positive is used in comparison with absence of stenoses as seen on coronary angiography.
Modified from Iskandrian AS, Verani MS. *Nuclear cardiac imaging: principles and applications*. Philadelphia: FA Davis, 1996.

TABLE 53.4 CAUSES OF FALSE-POSITIVE RESULTS OF SCANS



***e*FIGURE 53.1.1** Single-photon emission computed tomographic (SPECT) images of an asymptomatic, short, middle-aged man who weighed 245 lb. The images taken

during exercise show a postero-inferior defect (*first and fourth rows*) that disappears after photon attenuation correction (*second and fifth rows*) and after attenuation/scatter correction (*third and sixth rows*).

RISK ASSESSMENT

Risk Assessment in Patients with Stable Symptoms

The composition of atherosclerotic lesions varies considerably; some are rich in cholesterol (soft), and others are fibromuscular. The soft lesions are more likely to fissure or rupture. Plaques that are predominantly fibromuscular do progress, but rather slowly, and when they finally occlude the vessel, they may not precipitate acute MI, possibly because of the development of collaterals. There are trigger mechanisms that precipitate fissuring or rupture, such as unusual stress, hypertension, and a rise in catecholamine levels (78,79). Frequent episodes of sudden cardiac death shortly after the powerful earthquake in the Los Angeles area in 1994 were assumed to be the result of such a mechanism (80). It is estimated that only 10% of these plaques are predominantly lipid rich. Yet it is these plaques that most likely fissure and are followed by thrombosis and acute complications. The degree of underlying coronary stenosis in many patients with acute MI is only mild or moderate, and in patients with severe CAD, the artery responsible for the acute ischemic syndromes is not necessarily the artery with the most severe stenosis (24).

Cardiac events are defined either as “hard” (death or MI) or “soft” (e.g., increasing angina, the need for coronary revascularization, or the need for hospitalization). The predictors of hard and soft events may be different—in fact, the predictors of death may also differ from those of MI. For example, ischemic manifestation may predict an ischemic event such as acute MI or unstable angina, and left ventricular function or the overall extent of perfusion defect may predict death (81). Clinical, angiographic, and exercise variables have been identified that separate high- and low-risk groups for cardiac events. Califf and associates developed a risk-factor prediction chart that used age, gender, lipid profile, smoking history, systolic blood pressure, presence of diabetes or left ventricular hypertrophy, and fibrinogen level to separate patients into those with <1% risk of events and those with a 25% probability of having events during the 5 years after assessment (82).

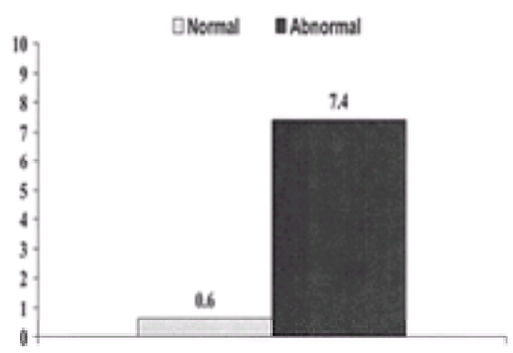
Early planar imaging and subsequent SPECT (using Tl-201– and Tc-99m–based tracers) in thousands of patients in multiple trials has yielded a strong message regarding the prognostic value of such tests. The message is consistent whether the imaging is done with exercise or with pharmacologic stress testing. Simply stated, perfusion imaging can separate patients at low risk from those at high risk. The relevance of such a conclusion on patient management is equally strong, because the condition of patients at low risk may be managed conservatively, without the need of coronary angiography or coronary interventions, whereas at least subgroups of high-risk patients may benefit from coronary revascularization (34,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109, 110,111,112,113, 114,115,116,117,118 and 119).

The major prognostic variables are listed in Table 53.5. The available data strongly suggest the following ten points:

Large zone of ischemia
Large zone of fixed defects
Perfusion abnormality in more than one vascular territory
Increased lung uptake
Left ventricular dilation (transient or fixed)
Left ventricular ejection fraction (by gated single-photon emission computed tomography)

TABLE 53.5 STRESS PERFUSION PREDICTORS OF RISK IN MEDICALLY TREATED PATIENTS WITH STABLE ANGINA

1. Normal stress images have a very high negative predictive value; hard event rate (death or nonfatal MI) is less than 1% per year (87,88,96,101,104,105).
2. Accordingly, the rate of coronary angiography is often very low in patients who have normal results of imaging (86,89,95,96,99,105).
3. The event rate is significantly higher (mean, 12-fold) in patients with abnormal results of imaging, based on review of data from more than 12,000 patients (*e*Fig. 53.1.2) (96,105).

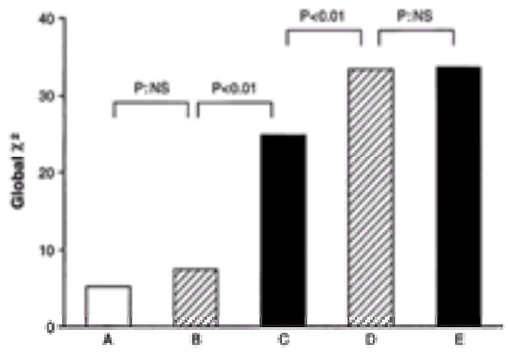


***e*FIGURE 53.1.2** Annual rate of death or myocardial infarction in patients who have normal and abnormal single-photon emission computed tomography sestamibi images. (Reproduced from Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol* 1998;32:57–62, with permission.)

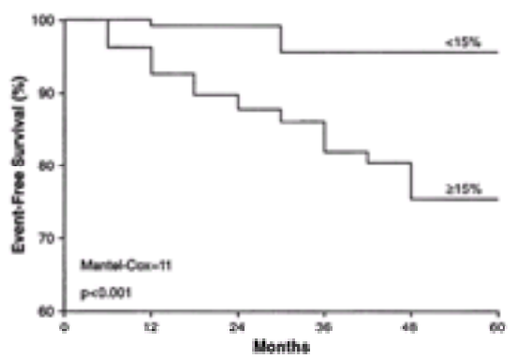
4. The event rate among patients who have abnormal results of imaging increases as a function of the severity of the perfusion abnormality. Patients with severe abnormality are at higher risk than patients with mild abnormality (85,96,105,109). The results are true in men and in women (90,102,115).
5. The results of exercise and pharmacologic stress testing using Tl-201, sestamibi, or tetrofosmin are comparable (96,105). The risk may be slightly higher among patients with normal results of dobutamine sestamibi imaging, possibly because ischemia is underestimated or because of a higher risk among the patient population in whom the use of dobutamine was studied (68).
6. Stress perfusion imaging provides statistically significant incremental information to support that provided by clinical evaluation, treadmill exercise testing, and coronary angiography (34,85,96).
7. The use of gated SPECT perfusion imaging enhances the prognostic power of imaging by incorporating left ventricular functional data, such as LVEF and left ventricular volumes, with perfusion data.
8. Diagnostic strategies based on the use of stress perfusion imaging as the initial test followed by selective referral of high-risk patients to coronary angiography are more cost-effective than routine use of coronary angiography on all patients. This advantage is accompanied by at least similar outcome (113,114 and 115).
9. The perfusion pattern may predict the type of subsequent events. Large fixed defects often predict cardiac death, and large reversible defects predict MI and total hard events (death plus MI) and, as expected, the need for coronary revascularization (34,104,105).
10. The “warranty” period associated with normal or mildly abnormal results of imaging depends on pretest likelihood of CAD; in high-risk patients and patients with established CAD, the test needs to be repeated at 18 to 24 months after revascularization, or earlier if symptoms change. In low-risk and intermediate-risk groups, the test needs to be repeated at 5 and at 3 years, respectively (85,96,105).

Pollock et al. (93) evaluated the hierarchical order of tests in terms of their prognostic importance. These tests were clinical evaluation, treadmill exercise stress testing, planar thallium imaging, and coronary angiography. When the perfusion data were considered, coronary angiography did not contribute additional prognostic value. We reached a similar conclusion using SPECT imaging (*e*Fig. 53.1.3). Importantly, when the catheterization data were not included and the model was based on clinical, exercise, and SPECT variables alone, the predictive power was as strong as when the catheterization data were included (85). Of all the variables analyzed, the size of the perfusion abnormality was the single most important discriminator between high- and low-risk groups. Patients with a large abnormality had a tenfold

higher event rate (death or MI) than did patients with small defects (eFig. 53.1.4). Similar results were observed in women (90). Despite a concern that the sensitivity of stress testing may be lower in women than men, SPECT imaging provides similar, if not better, risk assessment strategies for women (90,102). The receiver operating characteristic analysis by Hachamovitch and colleagues (102) showed superior discrimination in women than men in identifying high-risk patients by the results of stress SPECT imaging (area under the curve of 0.84 in women vs. 0.71 in men). Amanullah and coworkers (107) reported 0.9%, 4.1% and 7.5% event rates in women with mild, moderate, or severe perfusion abnormalities, respectively. Other groups have published similar results (109).



***e*FIGURE 53.1.3** Independent and incremental prognostic power of clinical, exercise, catheterization, and single-photon emission computed tomographic (SPECT) thallium variables. Data shown represent the c^2 statistic for clinical data (A); clinical and exercise data (B); clinical, exercise, and catheterization data (C); clinical, exercise, and SPECT thallium data (D); and clinical, exercise, catheterization, and SPECT data (E). The SPECT data provided incremental prognostic information. NS, not significant. [From Iskandrian AS, Chae SC, Heo J, et al. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. *J Am Coll Cardiol* 1993;22:665–670, with permission.]



***e*FIGURE 53.1.4** Actuarial event-free survival curves in patients with perfusion defect ³15% or <15% of the left ventricular myocardium. The prognosis is worse in patients with large perfusion defects. [From Iskandrian AS, Chae SC, Heo J, et al. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. *J Am Coll Cardiol* 1993;22:665–670, with permission.]

The group of patients with intermediate Duke scores—which often is the larger group—is problematic. Gibbons and associates (101), using data from four institutions, reported that the 5-year event-free survival rate among almost 5,000 patients was 99% among patients who had an intermediate Duke score and normal SPECT images. Shaw and coauthors (114) reported similar results: an annual mortality rate of 2.5% among patients with intermediate Duke scores in whom multivessel abnormality was seen on imaging versus 0.5% among patients whose scans were normal.

Diabetic patients pose a special problem because ischemia may be silent and autonomic neuropathy and peripheral vascular disease may affect exercise performance. Kang and colleagues (106) found a higher annual mortality rate among diabetic patients than among nondiabetic patients (4.3% vs. 2.3%). The annual mortality rate among diabetic patients was 1% to 2% in those with normal scans, 3% to 4% among patients with mildly abnormal scans, and >7% among patients with severely abnormal scans.

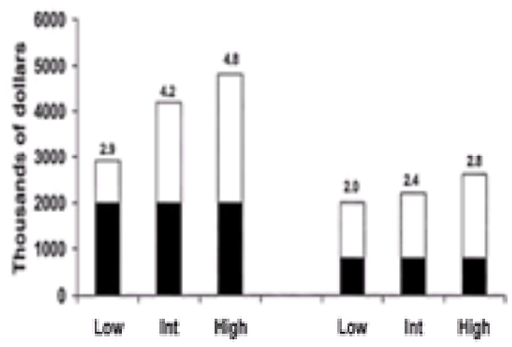
Vanzetto et al. (117,119) found that imaging results and the inability to exercise were the two most important predictors of outcome among diabetic patients. Patients with large defects had a 22% annual event rate, compared with 3% among those with normal results of imaging. In addition, the odds ratio for cardiac events was 6.8 among patients who had exercise limitations compared with patients who could exercise. Our experience supports these observations. The role of imaging in diabetes is being actively studied in two large studies (the Detection of Ischemia in Asymptomatic Diabetics trial and the Bypass Angioplasty Revascularization Investigation 2 Diabetes study).

Patients who have good exercise tolerance are often considered to be at low risk for cardiac events. Chatziioannou and colleagues (100) reported that even among this group of patients, SPECT imaging was able to discriminate between high-risk and low-risk patients (relative risk, 8.0). It should be noted, however, that 16 of the 21 events included in this study were soft events in the form of coronary revascularization.

The ability to perform gated SPECT perfusion imaging is a clear advantage in further improving the prognostic value of SPECT imaging. Sharir et al. (112) showed the importance of EF, end systolic volume, and the presence of ischemia. Patients with large areas of ischemia, low EF, and large end systolic volume are at the highest risk, whereas patients without ischemia who have normal EF and normal end systolic volume are at the lowest risk.

O'Keefe and associates (110) found a low event rate (2%) after 3 years among medically treated patients with mild perfusion abnormality, and only a few of these patients (9%) crossed over to coronary angiography. Other studies also show no advantage to the use of coronary revascularization rather than medical therapy in patients who have normal or mildly abnormal results of imaging (120,121). On the other hand, coronary revascularization proved superior to medical therapy among patients who had intermediate or large abnormalities (104). These results should be accepted with caution; they are not based on randomized studies, and the medical therapy was not optimized. Marie and colleagues (108) showed that beta-blocker therapy lowered the expected high event rate in patients with initially large defects who received medical treatment. Other studies also show that aggressive antiischemic therapy and statin therapy may decrease defect size and affect outcome. These observations are now being tested in randomized studies (the Intravascular Ultrasound Study of Predictor of Restenosis trial and the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial).

A large observational study involving 11,372 patients who had stable symptoms showed that the initial and follow-up costs were 30% and 41% higher for patients in whom coronary angiography was initially performed than for patients who underwent stress SPECT imaging and were selectively referred to undergo coronary angiography (113). The higher cost was not associated with a corresponding reduction in the mortality rate (3.3% vs. 2.8%) or MI (3.0% vs. 2.8%). The diagnostic costs were $1,320, $1,275, and $1,229 higher, respectively, for low-, intermediate-, and high-risk patients undergoing initial cardiac catheterization than for patients undergoing stress SPECT imaging as the initial test for detection of CAD (eFig. 53.1.5). Such a cost minimization approach has also been reported to be successful for women.



***e*FIGURE 53.1.5** Overall diagnostic and follow-up costs of care for direct catheterization and initial stress perfusion imaging. Diagnostic and follow-up costs were 30% and 41% higher for patients undergoing direct cardiac catheterization. Diagnostic costs are represented by solid bars; follow-up costs are represented by open bars. Low, intermediate, and high refer to pretest likelihood of coronary artery disease. Int, intermediate. [Reproduced from Shaw LJ, Hachamovitch R, Berman DS, et al. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Study Group. *J Am Coll Cardiol* 1999;33:661–669, with permission.]

From the extensive reported experience, it can be concluded that stress perfusion imaging may serve as a gatekeeper in a system in which referral to cardiac catheterization is based on the presence and severity of ischemia. Such a strategy could reduce health care costs, because coronary angiography could be avoided in patients who are shown to be at low risk by the results of imaging studies, regardless of clinical presentation and treadmill exercise test results. This recommendation is justified because of the low event rate among patients who have normal results of tests or small defects; it is unlikely that coronary interventions could lower the already low risk.

Recent data indicate that patients who have microvascular disease or endothelial dysfunction may not have as benign an outcome as was once thought, even in the absence of epicardial coronary disease (121,122 and 123). This became apparent when the follow-up period for such patients was extended to 7 to 10 years, rather than the usual 1 to 4 years used in most of the studies cited previously. Some of these patients are known to have reversible perfusion defects, which may suggest that at least some false-positive scans are not really false and may, in fact, identify endothelial dysfunction and possibly high patient risk for future events.

Risk Assessment: Noncardiac Surgery

Two issues are important with regard to patients who will undergo noncardiac surgery: (a) which patients need stress testing and (b) which patients need coronary angiography and coronary revascularization. Mangano and Goldman (124) used a scoring system to define the risk based on several clinical descriptors. Based on the total points, the patients are divided among four classes. The probability of perioperative complications increased from class I (low score) to class IV (high score) and was higher among patients undergoing major vascular surgery or urgent surgery than among patients undergoing minor surgery or elective surgery. Lee and coworkers (125) suggested a simple scoring system to predict outcome. They assigned 1 point to each of the following factors: high-risk surgery, history of CAD, history of heart failure, history of cerebrovascular disease, insulin-dependent diabetes, and creatinine level >7.0 mg per dL. The major complication rates were 0.4%, 0.9%, 7.0%, and 11.0% for 0, 1, 2, and >3 points, respectively.

The American College of Cardiology (ACC)/American Heart Association (AHA) Task Force report on guidelines for perioperative cardiovascular evaluation for noncardiac surgery reaffirmed the importance of clinical evaluation in risk assessment (81). Major predictors of increased perioperative risk include recent acute MI, unstable angina pectoris, decompensated congestive heart failure, significant arrhythmias, high degree of atrioventricular block and severe valvular disease. Intermediate predictors include mild angina pectoris, prior MI, compensated or prior congestive heart failure, and diabetes mellitus. Minor predictors include advanced age, abnormal resting ECG, normal rhythm on ECG, low functional capacity, history of stroke, and uncontrolled systemic hypertension.

High-risk surgical procedures include a major emergency operation, such as aortic and other major vascular surgery, and peripheral vascular surgery, especially in elderly patients. Intermediate-risk procedures include carotid endarterectomy, head and neck surgery, and intraperitoneal, intrathoracic, orthopedic, and prostate surgery. Low-risk procedures include endoscopic procedures, superficial procedures, cataract removal, and breast surgery.

Patients who are at low risk, especially if they are undergoing a low-risk surgical procedure, may not need preoperative stress testing. Surgery should be avoided, whenever possible, in patients who have experienced recent MI or unstable angina pectoris, until the clinical condition has been stabilized; if surgery must be performed, then coronary angiography is recommended. In many other patients, stress testing is indicated. The greatest amount of experience by far is in the use of pharmacologic perfusion imaging with dipyridamole or adenosine (126,127,128,129,130,131,132,133,134,135 and 136). Mangano and Goldman (124) summarized the results of large studies published in the literature (*e*Table 53.5.1). The results show that among patients in whom no evidence of ischemia is found, the event rate is extremely low (2%); on the other hand, among patients who have reversible defects, the event rate is 18% (relative risk, 9.0). These general conclusions are concordant with those of multiple other studies that involved smaller number of patients. Most of these studies did not include quantitative analysis to assess the size of jeopardized ischemic myocardium, although Brown and Rowen (134) demonstrated that the risk of perioperative events increased in proportion to the degree of abnormality (assessed as the number of abnormal segments on dipyridamole planar Tl-201 imaging).

***e*TABLE 53.5.1** PREDICTIVE VALUE OF DIPYRIDAMOLE-THALLIUM SCINTIGRAPHY IN PREOPERATIVE RISK-STRATIFICATION[a]

		Thallium redistribution		Major cardiac event		Predictive value (%)		
Category and study	**No. of patients**	**Yes**	**No**	**Yes**	**No**	**Positive**	**Negative**	**Relative risk**
Eagle et al. (128)	200	82	118	25	5	30	96	9.9
Brown and Rowen (134)	231	77	154	15	4	19	97	9.1
Hendel et al. (126)	327	167	160	24	5	14	97	5.2
Lette et al. (130)	415	182	233	37	2	20	99	29.5
Bry et al. (135)	237	110	127	11	3	10	98	4.6
Total for group	1,410	618	792	112	19	18	98	9.0
Mangano et al. (131)	60	22	38	6	7	27	82	1.5
Baron et al. (136)	457	160	297	31	55	19	82	1.0

[a]The definition of *cardiac complication* varied among studies but included preoperative myocardial infarction and death due to cardiac causes. The relative risks shown are the risk of a major cardiac event among patients with a positive test result divided by the risk among those with a negative test result.
Reproduced from Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med* 1995;333:1750–1756, with permission.

The ACC/AHA guidelines recommend coronary angiography should be performed in patients for whom the results of noninvasive testing indicate a high risk of cardiac events (presence of a large area of ischemia, perfusion defects in multiple vascular territories, left ventricular dilatation, or increased lung Tl-201uptake) or who have angina pectoris that is unresponsive to medical therapy (class I indication) (81). Among other patients, either coronary angiography is not indicated or there is a divergence of opinion about whether such testing is indicated. Patients in whom left ventricular dysfunction is demonstrated by clinical evaluation or by the results of measurement of EF and patients who have extensive fixed perfusion defects are at risk of developing congestive heart failure or serious ventricular arrhythmias during the perioperative period. The risk of ischemic events in these patients is low, but the long-term outcome is poor because of the underlying left ventricular dysfunction. Thus, extensive fixed perfusion defects do not have the same implication as reversible defects in the short run, but they do have an impact on long-term prognosis (24,81).

A randomized study showed that bisoprolol (a selective $beta_1$-blocker) reduced the perioperative (137) death/MI rate from 34% in the control group to 3.4% in the treatment group for high-risk patients with ischemia who are undergoing high-risk vascular surgery.

In summary, coronary revascularization should be performed before noncardiac surgery only in a small subset of high-risk patients, whereas preoperative testing should be limited to circumstances in which the results will affect patient treatment and outcome. It should be noted that patients with vascular disease have a substantial risk of MI and cardiac death over the next 5 to 10 years. Accordingly, these patients should be carefully evaluated by noninvasive testing to determine the extent of ischemia and left ventricular function, and some of these patients may benefit from coronary revascularization procedures after the major noncardiac surgery.

PATIENT EVALUATION AFTER PTCA AND CABG

Nuclear techniques are very useful in the selection of patients for whom coronary revascularization is appropriate, in the evaluation of the results of revascularization interventions, and to ascertain the presence of recurrent myocardial ischemia early or late after revascularization. Ideally, coronary revascularization should be reserved for patients in whom myocardial ischemia has been documented, especially those patients who have large ischemic areas involving multiple vascular territories and patients who have transient cavity dilation or increased lung uptake of Tl-201 during stress testing; these are the characteristics that identify patients who are at high risk for future events if they do not undergo revascularization. Conversely, patients who have normal myocardial perfusion during stress testing or who have only small perfusion defects involving one vascular territory (especially if the defect is fixed) are not in a high-risk category; in general, the condition of these patients should be managed medically. However, patients who present with heart failure or angina in whom the perfusion scans show only fixed defects should undergo reinjection of Tl-201 (or a separate rest redistribution protocol), because some of these defects may further improve after reinjection, which is characteristic of myocardial ischemia and viable myocardium (138). Fixed defects accompanied by mild to moderate reduction in tracer activity are consistent with viable myocardium and often improve after revascularization (139).

Substantial resolution of myocardial ischemia with amelioration of perfusion defects is the rule after successful percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) surgery (140,141,142,143,144,145,146,147 and 148). However, residual perfusion defects are common after coronary revascularization. The possible mechanisms of these defects are summarized in Table 53.6. The indications for perfusion imaging after PTCA or CABG are summarized in Table 53.7.

After PCI
Residual stenosis of dilated artery
Restenosis
Side-branch occlusion
After CABG
Graft disease (occlusion or stenosis)
After either PCI or CABG
Remote or periprocedure infarct
Incomplete revascularization
Disease progression

TABLE 53.6 MECHANISMS OF PERFUSION DEFECTS AFTER REVASCULARIZATION

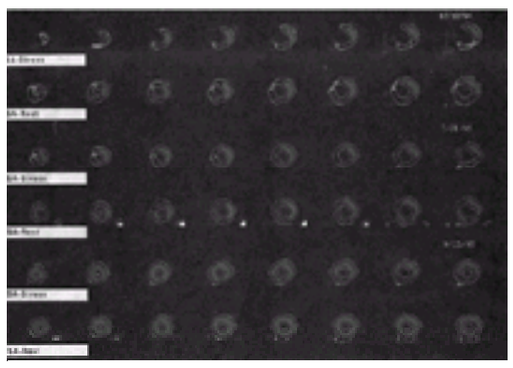
PCI
Early (<2 wk)
Uncertain or suboptimal results
Symptoms
Late (>2 wk)
Recurrence of symptoms
Silent ischemia before PCI
Multivessel disease with incomplete revascularization
High risk of coronary lesions
CABG
Recurrence of symptoms
Incomplete revascularization
Poor distal run-off
Silent ischemia before CABG surgery
Patient asymptomatic 3 to 5 yr after revascularization

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

TABLE 53.7 INDICATIONS FOR POSTREVASCULARIZATION PERFUSION IMAGING

Myocardial Perfusion Imaging after Percutaneous Transluminal Coronary Angioplasty

The ideal time to perform stress perfusion imaging after PTCA is controversial. Some authors have suggested that defects that occur very early after successful PTCA may later resolve (145). Others, however, have suggested that perfusion defects that appear early after PTCA are in fact highly predictive of late restenosis (143,146). It may be appropriate to delay myocardial perfusion imaging for 2 to 4 weeks after angioplasty. Alternatively, only patients with recurrent symptoms could be targeted for repeat myocardial perfusion imaging, although Hecht and colleagues (147) showed a similar rate of restenosis (61% vs. 59%) in asymptomatic and symptomatic patients, respectively, after PTCA (*e*Fig. 53.1.6). In both groups of patients, exercise perfusion imaging was highly accurate for detection of restenosis.



***e*FIGURE 53.1.6** Short-axis (SA) single-photon emission computed tomographic images from a patient with severe left anterior descending and circumflex artery stenoses before coronary angioplasty of both vessels (*top two rows*), 7 months after angioplasty and 2 months after coronary stenting of the left anterior descending artery. Perfusion defects involved the anterior wall, apex, and postero-inferior wall in the first study and clearly improved after angioplasty (*middle two rows*), although residual defects were still evident. After stenting of the left anterior descending artery, the images were normal (*bottom two rows*).

Myocardial Perfusion Imaging after Coronary Artery Bypass Graft Surgery

Contrary to PTCA, in which restenosis usually occurs within the first 3 to 6 months after the intervention, patients with CABG have a high early patency rate (90% at 1 year), with an attrition rate of 2% per year from years 1 to 7 and then 5% per year for years 7 to 12. At the end of 10 years, only approximately 40% of saphenous vein grafts are open and have a normal appearance. In contrast, internal mammary grafts have a patency rate of 85% to 95% after 7 to 10 years. Improved myocardial perfusion with normalization of ischemic perfusion defects is the rule after CABG (148), although residual defects after CABG resulting from the mechanisms listed in Table 53.6 are not infrequent. Myocardial perfusion imaging is also an effective way to assess graft patency after CABG. A new perfusion defect early (within the first 1 or 2 years) after CABG suggests a graft problem or incomplete revascularization, whereas defects appearing late (>5 years after CABG) suggest either graft disease or CAD progression (148). Tl-201 SPECT is very useful in the prognostic evaluation of patients who are examined late after CABG (149,150,151 and 152). The indications for perfusion imaging after CABG are listed in Table 53.7.

ACUTE CORONARY SYNDROMES

The main indications for nuclear imaging in acute coronary syndromes are listed in Table 53.8. Although Tc-99m pyrophosphate was introduced in the 1970s to detect acute myocardial necrosis, it is now rarely used, because positive results within the first 24 hours are unusual. In-111–labeled antimyosin antibody imaging is also likely to have limited clinical use for the same reason (images obtained earlier reflect blood pool activity). This tracer, however, has other useful clinical applications, such as the detection of myocarditis (which may occasionally need to be differentiated from acute infarction) and detection of anthracycline-induced cardiotoxicity. A new radiotracer (Tc-99m glucarate) is available that may permit early imaging; positive scans can be demonstrated within 1 to 2 hours of acute infarction, even in patients who did not receive thrombolytic therapy (153). This tracer is expected to undergo clinical trials in the near future. Infarct avid imaging and RNA are also helpful in detecting right ventricular infarction. Although RNA can be used to detect a left-to-right shunt (resulting from a ruptured ventricular septum) or mitral regurgitation (resulting from ruptured papillary muscle), these complications, as well as thrombus in the left ventricular cavity caused by large infarcts, are best detected by two-dimensional echocardiography. The issue of viability is discussed later in this chapter.

Detection of acute MI
Measurement of the size of MI
Assessment of myocardial salvage in response to thrombolytic therapy or primary angioplasty
Measurement of left ventricular ejection fraction
Identification of the culprit artery in patients with unstable angina pectoris
Triage of patients who present with chest pain in the emergency department
Risk assessment in patients with unstable angina pectoris
Risk assessment after acute MI
Detection of complications of acute MI
Viability assessment

MI, myocardial infarction.

TABLE 53.8 USES OF NUCLEAR IMAGING IN ACUTE CORONARY SYNDROMES

Because of the associated long myocardial retention and slow washout, Tc-99m–labeled tracers have been used to measure the size of MI and myocardial salvage. Injection of the tracer before thrombolytic therapy or primary angioplasty is initiated defines the area of myocardium at risk, even when the images are obtained several hours later. These images can be compared to a second set of images obtained several days later. The defect size reduction reflects the degree of myocardial salvage, and the final defect size reflects the area of residual necrosis. Further reduction in the size of a perfusion defect has been reported in approximately 70% of patients after 6 months, even without coronary intervention (154). Several studies have shown substantial variability in both the area at risk and the degree of salvage in patients with acute infarction. In general, both the area at risk and the absolute amount of salvaged myocardium are larger in patients with anterior than inferior or posterior MI (although, in relative terms, the percentage of salvage may be similar). The size of the defect seen on predischarge scan correlates well with indices of left ventricular function such as EF and end systolic volume and is also an important predictor of survival (155,156).

An emerging use of cardiac imaging in many institutions is in the triage of patients with chest pains who are seen in the emergency department (157,158,159,160,161,162,163 and 164). It is estimated that 36 million patients per year visit emergency departments in the United States for evaluation of chest pains. Although only 10% to 15% of these patients have acute MI, approximately 40% to 50% are admitted to the coronary care units to rule out acute infarction. Ironically, despite this high admission rate, approximately 5% of patients discharged from the emergency department will have acute MI, and of those, 15% to 25% will die. This misdiagnosis now accounts for the largest segment of malpractice lawsuits aimed against emergency departments. At the same time, the estimated cost for admitting patients for the purpose of ruling out acute MI is in the range of $13 billion per year. In any health system, unnecessary admissions amount to financial liability and, at the same time, reduce the availability of vital coronary care unit beds. Goldman et al. (165) developed a model based on resting ECG, systolic blood pressure, rales, and symptoms of unstable angina that helped to stratify patients into very low-risk, low-risk, moderate-risk, and high-risk groups (0.8%, 3.6%, 8.1%, and 21.5% event rate, respectively) for major events (i.e., serious arrhythmias, cardiogenic shock or recurrent ischemia requiring revascularization).

In many institutions, chest pain units have been established within the emergency department to screen for patients who need admission and monitoring and to identify those who may be discharged or need early stress testing. The precise algorithm varies from center to center, but generally patients with nondiagnostic ECG ST/T changes undergo clinical evaluation and serial cardiac enzymes measurements (including creatine kinase/MB and troponin I or T). When the results of these tests are negative, the patients undergo rest or exercise perfusion imaging (or both), depending on the probability of CAD. Injection of a tracer during chest pain or shortly after has shown perfusion defects in many patients with acute MI or unstable angina pectoris and nondiagnostic ECG changes. Varetto and colleagues (162) observed perfusion defects in 27 of 30 patients who subsequently were demonstrated to have acute coronary syndromes, but in 0 of 34 patients who subsequently showed no evidence of CAD. Hilton et al. (160) reported events in only 1 of 70 patients who had normal scans but in 71% of 32 patients with abnormal scans. The group of investigators (164) at the Medical College of Virginia have reported their extensive experience with emergency department imaging. Their pioneering work suggests that acute perfusion imaging may be an important addition to current screening modalities in the acute setting.

Risk Assessment

The risk among patients with acute MI for future cardiac events depends on the size of the infarction, clinical findings (e.g., third heart sound gallop, age, gender, presence of diabetes mellitus, rales, hypotension, serious ventricular arrhythmias, recurrent ischemia, infarction extension), LVEF and the results of coronary angiography (extent of CAD), exercise results, and imaging variables. Several studies made in the 1980s concluded that stress perfusion imaging (exercise or pharmacologic) (166,167) and the LVEF determined by RNA (168) performed in patients who had uncomplicated acute MI could stratify patients into low- and high-risk groups. These studies were carried out in the prethrombolytic era. For example, Gibson et al. (166) reported that 50% of patients who had multiple perfusion defects in more than one vascular territory or abnormal lung Tl-201 uptake on predischarge exercise testing subsequently experienced cardiac events. On the other hand, the event rate was only 6% in patients who had either a normal scan or fixed defects in the territory of the infarction. Other studies have also shown that stress perfusion imaging is clearly superior to ST segment changes in detecting multivessel disease in such patients. One of the most important markers of prognosis, judging by the results of the Multicenter Postinfarction Research group (168), has been the radionuclide-measured resting LVEF. In this study, patients with an EF >40% had a low event rate, whereas patients with an EF <40% had a significantly higher event rate, especially those with an EF <30%. In more recent studies involving patients who received thrombolytic therapy, the LVEF was still a strong predictor of outcome, but fewer patients had left ventricular dysfunction (Fig. 53.2) (169,170 and 171).

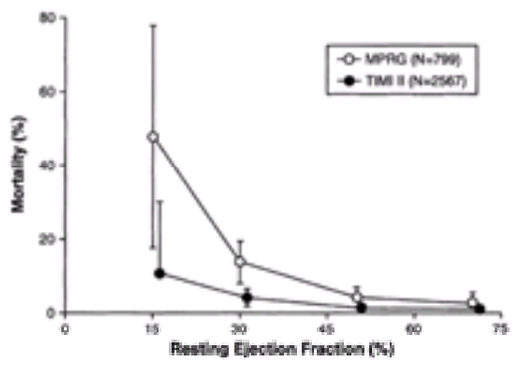
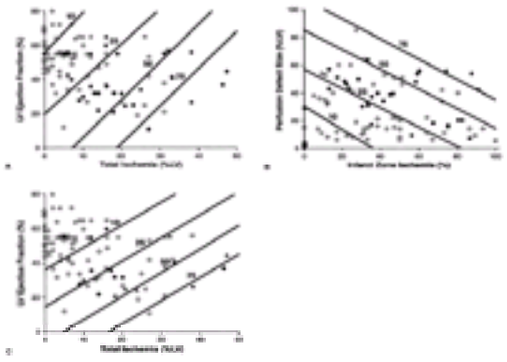


FIGURE 53.2 The relationship between resting left ventricular ejection fraction and survival in patients who have experienced acute myocardial infarction. The results from patients who received thrombolytic therapy [Thrombolysis in Myocardial Infarction phase II study (TIMI II)] are contrasted with those from the Multicenter Postinfarction Research Group (MPRG). [From Zaret BL, Wackers FJ, Terrin ML, et al. Value of radionuclide rest and exercise left ventricular ejection fraction in assessing survival of patients after thrombolytic therapy for acute myocardial infarction: results of Thrombolysis in Myocardial Infarction (TIMI) phase II study. *J Am Coll Cardiol* 1995;26:73–79, with permission.]

In the thrombolytic era, early studies have suggested that SPECT perfusion imaging is less accurate in risk assessment (172,173). However, more recent studies using exercise testing combined with quantitative Tl-201 imaging have shown that the size of the perfusion defect as well as the extent of ischemia and the LVEF are independent predictors of cardiac events. The perfusion data had incremental value to the LVEF (174). In nonselected patients who had acute infarcts, one-half of

whom had thrombolytic therapy, Mahmarian et al. (175,176) showed that traditional variables of perfusion imaging, such as the size of the perfusion abnormality and the extent of reversibility during adenosine SPECT Tl-201 imaging, were still important predictors of prognosis. Another important observation from the latter study is that the LVEF provided incremental value to the size of the perfusion defect (*e*Fig. 53.2.1). This observation is pertinent because the Tc-99m–labeled tracers allow simultaneous assessment of both the perfusion defect and the LVEF. Several studies have shown that pharmacologic vasodilatation with adenosine or dipyridamole is safe as early as 48 hours after an acute MI. A recent comparison between dipyridamole and submaximal exercise testing, both associated with SPECT imaging, showed the pharmacologic approach to be at least as good as exercise imaging, if not better (177). Another recent report has suggested that aggressive antiischemic therapy involving either revascularization or medical therapy substantially reduces perfusion defect size and may improve outcomes in these patients (178). Early testing may expedite the decision-making process and decrease hospitalization time. The relative value of vasodilator perfusion imaging compared with early exercise perfusion testing, however, remains unclear. There are no data on the safety of high-dose dobutamine perfusion imaging in risk assessment. The importance of perfusion imaging in risk assessment is emphasized in the new ACC/AHA guidelines on management of the condition of patients who have acute MI (179). The VANQWISH trial, which involved patients with non–Q-wave MI, used Tl-201 imaging as a risk-stratifying modality to identify patients randomly assigned to a conservative strategy who might have a high risk for cardiac events. These patients could cross-over to revascularization. The results of the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital trial suggested that a noninvasive strategy, in which assessment was performed by perfusion imaging, led to better outcomes than an invasive strategy (180). Recently published guidelines for management of non–Q-wave MI and unstable angina suggest that a noninvasive risk assessment strategy is appropriate for stable patients (181).



***e*FIGURE 53.2.1** Cox regression models displaying 1-year risk for a cardiac event according to left ventricular (LV) ejection fraction and total left ventricular ischemia **(A)** or infarct ischemia **(B)**. **C:** Regression model for predicting infarct-free survival. Diagonal lines indicate representative isobars of percentage risk. Patient risk for any cardiac event **(A,B)**, or specifically for death or nonfatal reinfarction **(C)**, increases as total LV ischemia increases and ejection fraction decreases. **A,B:** ●, events; ○, no events. **C:** ▲, death; ●, nonfatal myocardial infarction; ○, neither. (From Iskandrian AS, Verani MS. *Nuclear cardiac imaging: principles and applications*. Philadelphia: FA Davis, 1996; and Mahmarian JJ, Mahmarian AC, Marks GF, et al. Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. *J Am Coll Cardiol* 1995;25:1333–1340, with permission.)

Unstable Angina Pectoris

The indications for nuclear testing include differentiation between cardiac and noncardiac chest pains in patients with equivocal presentations, and risk assessment. Injection of Tc-99m–labeled tracers while the patient is at rest during or shortly after chest pain can be very helpful in determining the cardiac etiology of pain and, more specifically, the culprit vessel (Fig. 53.3). According to Bilodeau et al. (157), this method had a sensitivity of 62% and a specificity of 88% (ST segment shifts had a sensitivity of 38% only).

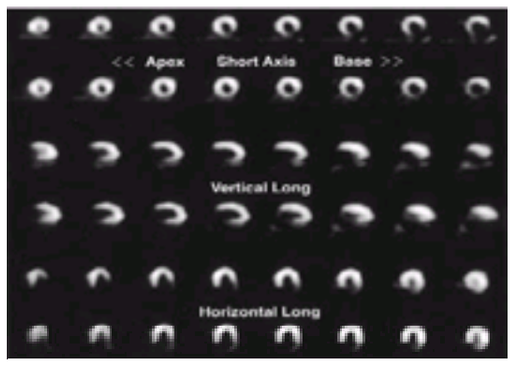


FIGURE 53.3 Resting single-photon emission computed tomographic technetium-99m sestamibi images obtained during spontaneous chest pain in a patient with unstable angina pectoris. The images show a large perfusion defect in the inferolateral regions (*first, third, and fifth rows*). The second set of images, obtained 24 hours later during an angina-free period, show partial redistribution (*second, fourth, and sixth rows*). Each set shows short-axis, vertical long-axis, and horizontal long-axis slices.

The guidelines on unstable angina pectoris suggest that in the following patients coronary angiography may be indicated: patients with previous MI or revascularization, those who fail to stabilize on medical therapy, those with high-risk clinical findings seen on noninvasive testing, and those with significant heart failure or left ventricular dysfunction (182). For patients who can be stabilized with medical therapy, a more conservative approach, using noninvasive testing, is generally preferable (181,182,183,184,185 and 186). Routine use of coronary angiography for all patients is not only expensive but also exposes many patients to unnecessary risk and interventions. Noninvasive risk-stratification can identify the patients most likely to benefit from additional invasive procedures.

Several studies have shown that myocardial perfusion imaging appears to be superior to ST segment response. For example, Brown et al. (183) found that the cardiac event rate was 26% in patients with reversible defects and 3% in those with no reversible defects; Stratmann et al. (184) found that the cardiac event rate was 25% in patients with reversible defects and 2% in those with normal scans; Madsen et al. (186) found a cardiac event rate of 21% in patients with reversible defects and 3% in patients with no reversible defects. Therefore, stress perfusion imaging may be used to risk-stratify patients with unstable angina who had no occurrence of ischemia for 48 to 72 hours while receiving medical therapy. Patients who are classified as high risk on the basis of scan results need coronary angiography, and patients classified as low risk can be treated medically.

RADIONUCLIDE ANGIOGRAPHY

The RNA techniques for assessing left ventricular and right ventricular functions include gated equilibrium (or MUGA) and first-pass methods. With gated RNA, Tc-99m pertechnetate is used to label the red blood cells, whereas with first-pass RNA, Tc-99m bound to pertechnetate, human serum albumin, DTPA (diethylenetriamine penta-acetic acid), or sulfur colloid can be used. Both the first-pass and MUGA techniques can be performed while the patient is at rest and during stress (exercise or pharmacologic). First-pass studies are usually obtained either in the anterior or right anterior oblique projection. Gated RNA images are obtained usually in three views, and with the dual head 90-degree detector systems, biplane studies may be carried out, providing four projections during two acquisitions. Both techniques allow measurement of LVEF (global and regional), volumes, wall motion, diastolic indices, and right ventricular EF and wall motion (*e*Fig. 53.3.1 and *e*Fig. 53.3.2). The EF is derived on the basis of count changes rather than geometric assumptions; this makes RNA probably the most reliable and reproducible method for EF measurement. A method of SPECT-gated RNA was used for the first time in 1980. The availability of multihead detector systems and high-performance dedicated computers that shorten the acquisition and processing time has renewed interest in the use of tomographic techniques (187,188). The advantages of tomographic MUGA are the abilities to avoid superimposition of different structures and to improve quantitative measurements. The images are displayed either as cineloops of multiple slices at end diastole and end systole or as a three-dimensional presentation showing the entire left ventricular silhouette and other cardiac structures. The left ventricular diastolic function can also be assessed using RNA. Some of the most common indices used include the peak filling rate, the time to peak filling rate, and percentage of left ventricle filling during early diastole compared to that during late diastole (due to atrial contraction). Abnormalities in diastolic indices have been found in patients with CAD (even in the absence of systolic dysfunction), in older patients, and in patients with hypertension, hypertrophic cardiomyopathy, and a number of other

cardiac disorders. As is true of systolic dysfunction, the diastolic dysfunction can be regional rather than global (23,24,25 and 26).

Video 53.2 Multiple gated acquisition scan illustrating a normal study in the anterior **(A)** and left anterior oblique **(B)** projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.3 Multiple gated acquisition scan illustrating a normal study in the anterior **(A)** and left anterior oblique **(B)** projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.4 Multiple gated acquisition scan of a patient showing a dilated right ventricle with an area of right ventricular apical dyskinesis suspicious for previous right ventricular infarction. Left ventricular function is severely reduced and there is mild septal hypokinesis; severe hypokinesis of the anterolateral and anterior segments; inferoposterior, posterolateral, and inferoapical akinesis; and apical dysfunction in the anterior **(A)** and lateral **(B)** projections. Calculated ejection fraction was 20%. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.5 Multiple gated acquisition scan of a patient showing a dilated right ventricle with an area of right ventricular apical dyskinesis suspicious for previous right ventricular infarction. Left ventricular function is severely reduced and there is mild septal hypokinesis; severe hypokinesis of the anterolateral and anterior segments; inferoposterior, posterolateral, and inferoapical akinesis; and apical dysfunction in the anterior **(A)** and lateral **(B)** projections. Calculated ejection fraction was 20%. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.6 Standard left anterior oblique view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating global hypokinesis and a reduced left ventricular ejection fraction of 25% in a patient with nonischemic dilated cardiomyopathy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.7 Standard anterior view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating global hypokinesis and a reduced left ventricular ejection fraction of 25% in a patient with nonischemic dilated cardiomyopathy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.8 Standard lateral view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating global hypokinesis and a reduced left ventricular ejection fraction of 25% in a patient with nonischemic dilated cardiomyopathy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

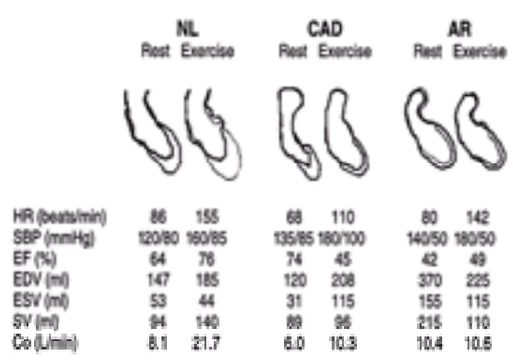
Video 53.9 Standard left anterior oblique view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating apical dyskinesis and a reduced left ventricular ejection fraction of 40% secondary to ischemic heart disease. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.10 Standard anterior view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating apical dyskinesis and a reduced left ventricular ejection fraction of 40% secondary to ischemic heart disease. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

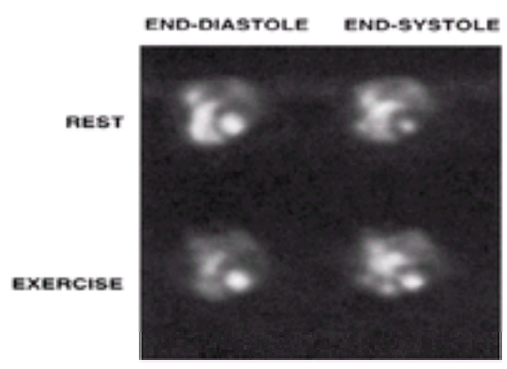
Video 53.11 Standard lateral view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating apical dyskinesis and a reduced left ventricular ejection fraction of 40% secondary to ischemic heart disease. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.12 Multiple gated acquisition scan of a patient with aortic insufficiency, ascending aortic aneurysm, and congestive heart failure. The ascending aorta is dilated, and there is moderate to severe left ventricular dilatation (ejection fraction approximately 30%). There is a prominent septal separation suggesting left ventricular hypertrophy. Analysis of regional wall motion reveals mild septal and posterolateral hypokinesis, moderate anterolateral and anterior hypokinesis, and inferoapical and apical dyskinesis in the anterior **(A)** and left anterior oblique **(B)** projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.13 Multiple gated acquisition scan of a patient with aortic insufficiency, ascending aortic aneurysm, and congestive heart failure. The ascending aorta is dilated, and there is moderate to severe left ventricular dilatation (ejection fraction approximately 30%). There is a prominent septal separation suggesting left ventricular hypertrophy. Analysis of regional wall motion reveals mild septal and posterolateral hypokinesis, moderate anterolateral and anterior hypokinesis, and inferoapical and apical dyskinesis in the anterior **(A)** and left anterior oblique **(B)** projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 53.3.1** First-pass radionuclide angiograms in a healthy subject (NL) show increases in ejection fraction (EF), end diastolic volume (EDV), stroke volume (SV), cardiac output (Co), and heart rate (HR) and a decrease in end systolic volume (ESV). There are no regional wall motion abnormalities at rest or during exercise. Responses from a patient with coronary artery disease (CAD) with exercise-induced wall motion abnormality show a decrease in EF and an increase in ESV between rest and exercise. The response from a patient with chronic aortic regurgitation (AR) shows a decrease in EDV. SBP, systolic blood pressure. (From Iskandrian AS, Verani MS. *Nuclear cardiac imaging: principles and applications*. Philadelphia: FA Davis, 1996, with permission.)



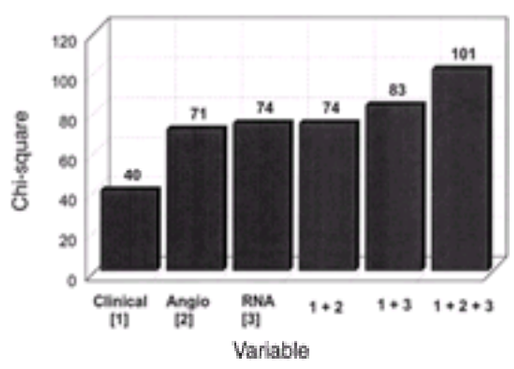
***e*FIGURE 53.3.2** Rest- and exercise-gated equilibrium radionuclide angiography in a patient with coronary artery disease. Resting left ventricular function is normal, but with exercise, wall motion abnormality and a decrease in ejection fraction are seen.

One of the chief advantages of exercise RNA has been in risk assessment. The Duke investigators have described the prognostic implication of exercise EF in patients with chronic CAD and have shown that exercise RNA variables provide independent and incremental prognostic value in addition to those obtained by clinical evaluation, exercise testing and cardiac catheterization (*e*Table 53.8.1) (189,190,191 and 192). In fact, measurement of the EF during exercise yielded most of the information provided by cardiac catheterization. Patients with an exercise EF >50% had a very low event rate; those with an exercise EF <35% had a high event rate; and those with an EF between 35% and 50% had an intermediate event rate. Shaw et al. (193) demonstrated that the prognostic power of a model based on clinical variables and RNA was slightly better than that of a model based on clinical variables and cardiac catheterization (c^2 = 83 vs. 74) (*e*Fig. 53.3.3). Other groups have shown similar results (194,195,196,197 and 198). The RNA predictors of risk are listed in *e*Table 53.8.2. Supino et al. (199) showed that the benefit of CABG was greatest in patients who had the greatest amount of ischemia before surgery, reflected in the change in EF from rest to exercise. Borer and colleagues (200) reported that the change in EF from rest to exercise, adjusted for end systolic wall stress, predicted long-term outcome in patients who had aortic regurgitation with no or minimal symptoms.

***e*TABLE 53.8.1** RELATIVE PROGNOSTIC IMPORTANCE OF RADIONUCLIDE ANGIOGRAPHY AND CLINICAL AND CATHETERIZATION VARIABLES IN PATIENTS WITH CORONARY ARTERY DISEASE

		Total model c^2	
Variable type	**Number of variables (df)**	**CV death**	**Total CV events**
Clinical	6	71	48
Catheterization	6	102	64
RNA	3	104	66
Clinical plus RNA	9	120	78
Clinical plus catheterization	12	124	82
Clinical plus catheterization plus RNA	15	138	93

CV, cardiovascular; df, degrees of freedom; RNA, radionuclide angiography.
Reproduced from Lee KL, Pryor DB, Pieper KS, et al. Prognostic value of radionuclide angiography in medically treated patients with coronary artery disease: a comparison with clinical and catheterization variables. *Circulation* 1990;82:1705–1717, with permission.



***e*FIGURE 53.3.3** The prognostic value of exercise multiple-uptake gated acquisition (MUGA) in medically treated patients with suspected or known coronary artery disease. Angio, coronary angiography; RNA, gated-equilibrium radionuclide angiography (MUGA). (Reproduced from Shaw LJ, Heinle SK, Borges-Neto S, et al. Prognosis by measurements of left ventricular function during exercise. *J Nucl Med* 1998;39:140–146, with permission.)

***e*TABLE 53.8.2** RADIONUCLIDE ANGIOGRAPHIC PREDICTORS OF RISK IN MEDICALLY TREATED PATIENTS WITH STABLE ANGINA

Resting LVEF
Exercise LVEF
Change in LVEF from rest to exercise
Wall motion abnormality at rest or during exercise
LV EDV (resting and exercise)
LV ESV (resting and exercise)
Contractility index (systolic blood pressure/ESV ratio) (resting and exercise)

EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; LV, left ventricular.
From Iskandrian AS, Verani MS. *Nuclear cardiac imaging: principles and applications*. Philadelphia: FA Davis, 1996, with permission.

First-pass RNA can be obtained with a multiwire gamma camera (Proportional Technologies, Inc., Houston, TX), which uses a proportional counter detector with a high count rate and improved image resolution (201). This system uses low-energy radionuclides such as tantalum-178, with energy of 55 to 65 KeV and a half-life of approximately 9 minutes. There is also a nonimaging nuclear probe (known as *VEST*), that allows beat-to-beat measurement of LVEF and relative volume over the course of relatively extended periods of observation in ambulatory patients, very much as a Holter monitor does (202).

MYOCARDIAL VIABILITY

It has long been recognized that some patients who have ischemic heart disease and depressed left ventricular function may exhibit improved function after CABG or PTCA enhances the coronary flow. The preoperative identification of myocardial viability is particularly important in patients with congestive heart failure and depressed LVEF, because these patients may improve remarkably after surgery if they have chronic myocardial hypoperfusion of otherwise structurally viable myocardium (hibernating myocardium). Conversely, revascularization carries a higher risk and would be expected to result in minimal, if any, benefits for patients who have extensive myocardial scarring.

Physiologic Basis

Although the myocardial uptake of all available myocardial perfusion tracers is directly proportional to myocardial blood flow (within physiologic limits), both extraction and retention depend on active metabolic processes. Tl-201 extraction, for example, depends in part on the sodium-potassium adenosinetriphosphatase pump, whereas retention depends on an intact cell membrane. Tc-99m sestamibi and Tc-99m tetrofosmin are extracted predominantly on the basis of a negative cellular transmembrane potential and a negative mitochondrial transmembrane potential. Maintenance of these transmembrane potentials requires active metabolic processes. Disruption of the cell membrane or of the mitochondrial function affects tracer extraction, retention, or both.

Clinical Use of Nuclear Imaging in the Assessment of Myocardial Viability

Several different tracers and protocols can be used for the assessment of myocardial viability (eTable 53.8.3). The presence of redistribution on Tl-201 images taken 4 hours after stress is indicative of myocardial ischemia and hence viability. However, regions with absent or incomplete redistribution may still be viable and may improve after revascularization (139,140). Early attempts to overcome this problem used 12- to 36-hour delayed imaging after the stress Tl-201 injection (203). Although filling in of defects in this late redistribution image identifies additional areas of viable myocardium, a considerable number of viable regions are still missed. Moreover, because of the typically poor count statistics associated with the 24-hour delayed Tl-201 images, interpretation of these studies may be difficult.

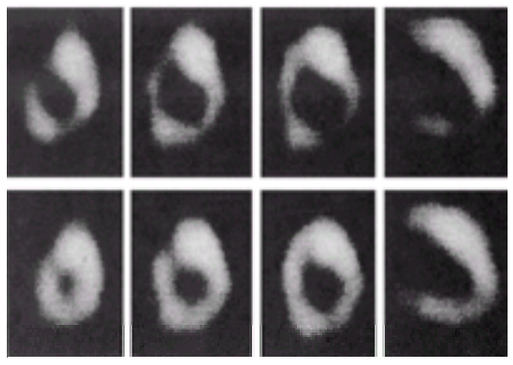
***e*TABLE 53.8.3** NUCLEAR METHODS OF ASSESSING MYOCARDIAL VIABILITY

Tl-201 stress-redistribution
Tl-201 reinjection
Tl-201 rest redistribution
Technetium-99m sestamibi stress-rest
Nitrate-augmented perfusion imaging
Fatty acids (I-123 IPPA, I-123 BMIPP)
Positron emission tomography: flow/fluorodeoxyglucose; rubidium-82 washout
Low-dose dobutamine SPECT

I-123 BMIPP, iodine-123-beta-methyl-*p*-iodophenylpentadecanoic acid; I-123 IPPA, iodine-123 iodophenylpentadecanoic acid; SPECT, single-photon emission computed tomography; Tl, thallium.

Tl-201 reinjection after the redistribution images may circumvent some of the deficiencies of the latter. As initially described by Dilsizian et al. (27), approximately 50% of defects that may appear fixed at 4 hours improve after reinjection, and most of these regions also show improved function after revascularization.

Although the identification of stress-induced ischemia is a superior indication of viable myocardium (204), incompletely resolved ischemia may also present as a persistent defect (scar) (139,140,203)—hence the current use of resting 4-hour redistribution Tl-201 imaging. It is recognized that asynergic myocardial regions perfused by coronaries with high-grade stenosis may display resting hypoperfusion (hibernating myocardium) during resting Tl-201 imaging (27,28,205,206). These defects may fill in over the course of the next several hours, thereby demonstrating viable myocardium (eFig. 53.3.4). It has also been shown that the higher the regional uptake of Tl-201, the more likely it is that the region is viable. Conversely, regions with very low uptake during rest redistribution or stress reinjection are likely to contain predominant scarring. An arbitrary 50% or 60% Tl-201 uptake, relative to that in normal regions, is a clinically useful threshold to differentiate between viable and nonviable myocardium (28,206,207 and 208). However, the identification of viable regions by rest redistribution Tl-201 imaging is still less than ideal, and positive and negative predictive accuracies range from 45% to 79% and 62% to 80%, respectively (205,209,210).



***e*FIGURE 53.3.4** Rest-redistribution single-photon emission computed tomographic thallium imaging showing severe reversible perfusion defects in multiple segments. The ejection fraction in this patient showed marked improvement after coronary artery bypass grafting. (From Iskandrian AS. Thallium reinjection imaging: the search for an optimal protocol. *J Nucl Med* 1993;34:743–746, with permission.)

Clinical Use of Technetium-99m Sestamibi in the Assessment of Myocardial Viability

Because Tc-99m sestamibi undergoes only minimal redistribution at 4 hours after the injection, sestamibi has been considered by some to be less useful for detecting viable myocardium than Tl-201 (211,212). More recently, Udelson and associates (207) and Kauffman and coauthors (213) compared sestamibi uptake, after a resting injection, with Tl-201 uptake in the rest redistribution images. Under those conditions, these authors found very similar sestamibi and Tl-201 activities. A sestamibi

activity >60% of maximal uptake had a positive predictive value of 80% and a negative predictive value of 96% for improvement in regional dyssynergy after revascularization. Dilsizian and colleagues (28) have also compared sestamibi uptake at 1 hour and 4 hours after a resting injection and observed that 40% of the segments had improved uptake over the course of time. These authors also compared sestamibi and Tl-201 uptakes by quantitative analysis, which markedly improved the concordance between these two tracers for viability detection. Recent investigations comparing the levels of Tc-99m sestamibi in perfusion defects with the extent of historically viable myocardium have indicated a high degree of correlation between the uptake of this tracer and the amount of viable myocardium (214,215).

Nitrate-Augmented Perfusion Imaging

Nitroglycerin administration may improve myocardial perfusion either by increasing coronary collateral flow or by dilating the stenosis slightly. Thus, it is not surprising that administration of nitroglycerin may improve perfusion defects. Galli et al. (216) reported that administration of nitroglycerin before sestamibi injection while the patient was at rest improved detection of myocardial viability. It has also been shown that nitrate administration before Tl-201 reinjection improved detection of viable myocardium (217). Therefore, nitroglycerin administration before either sestamibi or Tl-201 injection may further improve detection of myocardial viability (217,218).

Clinical Use of Fatty Acids for Detection of Myocardial Viability

Recent reports have suggested that iodine-123 iodophenylpentadecanoic acid (I-123 IPPA) may be a good marker for use in detection of myocardial viability (219,220). Iskandrian et al. (220) have reported a 91% agreement between IPPA and rest redistribution Tl-201 SPECT (Fig. 53.4). A recent multicenter trial (221) evaluated the utility of I-123 IPPA for predicting substantial increases in LVEF (=10%) after CABG in patients with a depressed preoperative LVEF (<40%). On multivariate analysis, the number of segments that were viable by IPPA was the most important predictor of recovery of function after revascularization.

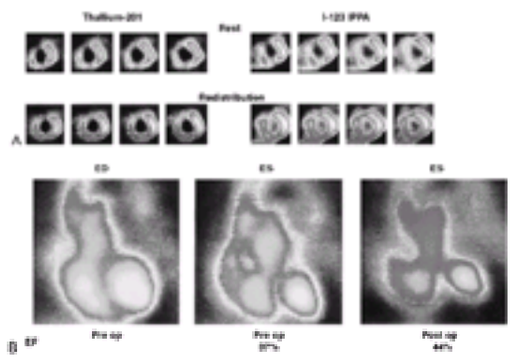
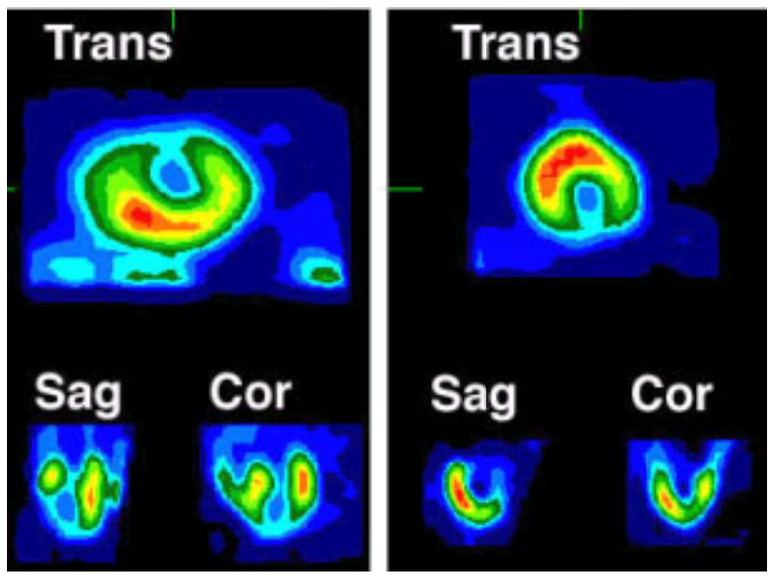


FIGURE 53.4 A: Rest-redistribution thallium-201 tomographic images and 5- and 30-minute iodine-123 iodophenylpentadecanoic acid (I-123 IPPA) tomographic images from a patient with severe three-vessel disease and left ventricular dysfunction. The thallium-201 and I-123 IPPA images reveal reversible defects. The reversibility is better seen with I-123 IPPA. **B:** This patient had improvement in left ventricular function after coronary artery bypass grafting. ED, end diastole; EF, ejection fraction; ES, end systole. (From Iskandrian AS, Powers J, Cave V, et al. Assessment of myocardial viability by dynamic tomographic iodine 123 iodophenylpentadecanoic acid imaging: comparison with rest-redistribution thallium-201 imaging. *J Nucl Cardiol* 1995;2:101–109, with permission.)

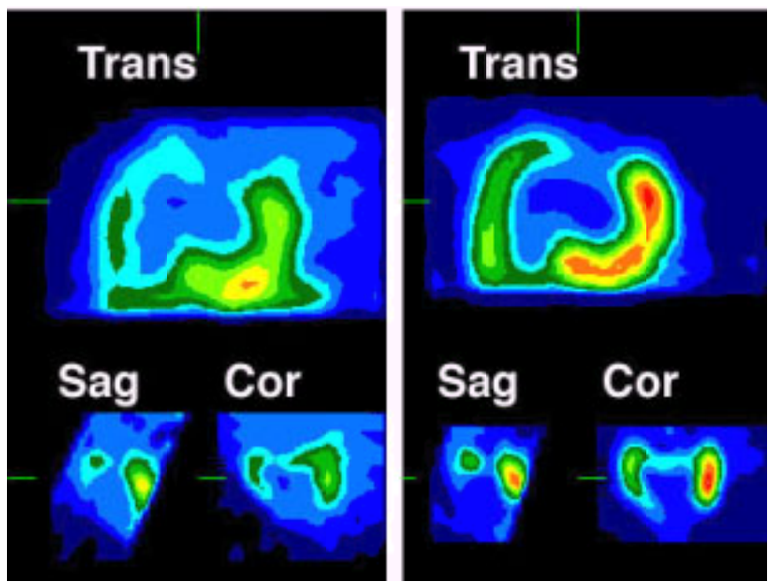
Another fatty acid that has been used, especially in Japan, for evaluation of myocardial viability is I-123-beta-methyl-*p*-iodophenylpentadecanoic acid (I-123-BMIPP). This agent has a structure that is remarkably similar to IPPA, with the addition of a methyl radical. However, it possesses a longer residence time intracellularly and therefore allows more convenient imaging. Although I-123-BMIPP has not yet been well studied as a viability marker, it has been suggested that areas with discordant BMIPP/Tl-201 uptake (greater decrease in BMIPP than Tl-201) are likely to show increased F-18-FDG uptake, a marker of myocardial viability (222).

Clinical Use of Positron Emission Tomography for Assessment of Myocardial Viability

At the present time, PET is probably the best technique for the assessment of myocardial viability. The best predictor of viable myocardium is a mismatch between flow (measured by oxygen-15 H_2O, nitrogen-15 NH3, or rubidium-82) and glucose metabolism (assessed by F-18-FDG) (208,223). Recently, F-18-FDG has been successfully imaged using standard SPECT cameras mounted with a special high-energy (511-KeV) collimator (224). Although the feasibility of this technique has been demonstrated, the quality of the F-18-FDG SPECT images is not as good as that of images obtained with PET. Moreover, the radiopharmaceutical cost remains a serious impediment to widespread clinical use of F-18-FDG.

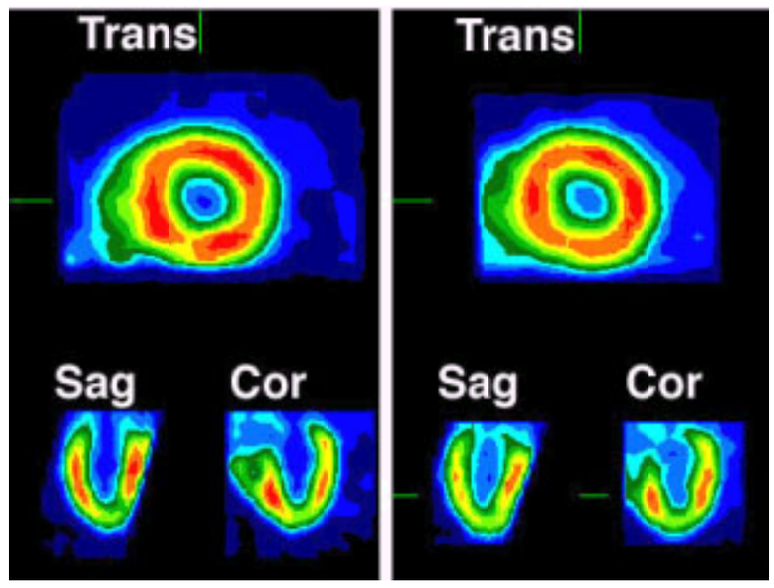


Matched resting rubidium (*left set*) and radiolabeled fluoro-deoxyglucose positron emission tomographic (*right set*) images. Transverse, sagittal, and coronal positron emission tomographic images demonstrating myocardial hibernation in the left anterior descending artery territory.



Matched resting rubidium (*left*) and radiolabeled fluoro-deoxyglucose (*right*) positron emission tomographic images. Transverse, sagittal, and coronal positron emission tomographic images demonstrating extensive scar in the left anterior descending and right coronary artery territories with evidence of

myocardial hibernation in the left circumflex artery territory and right artery territory (including the right ventricle).



No fixed or transient changes in between stress (*left*) and resting (*right*) rubidium-82 positron emission tomographic images on transverse, sagittal, and coronal slices, demonstrating a dilated left ventricular cavity and a lack of myocardial scar or ischemia in a patient with nonischemic dilated cardiomyopathy.

Video 53.14 A 55-year-old female patient with atypical angina. JR4 catheter engagement resulted in a large spiral dissection **(A)**. The dissection was successfully treated with coronary stenting **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 53.15 A 55-year-old female patient with atypical angina. JR4 catheter engagement resulted in a large spiral dissection **(A)**. The dissection was successfully treated with coronary stenting **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Other investigators have used PET imaging with carbon-11 acetate as an indicator of myocardial oxidative metabolism, which potentially could be a good marker of viability (225). The clearance of rubidium-82 has also been proposed as a marker of viability, but there is limited experience with this approach (226). A new protocol has been proposed to assess myocardial viability with low-dose dobutamine sestamibi SPECT (227,228). At this time, only preliminary data have been reported with this technique (229).

RECENT DEVELOPMENTS IN NUCLEAR CARDIOLOGY

A number of guidelines on training, competency, certification, and accreditation of radionuclide users and laboratories are now available. A variety of educational programs are also sponsored by the American Society of Nuclear Cardiology, including an annual scientific meeting. The new developments are summarized in Table 53.9. Newer generations of solid-state gamma cameras, nonimaging detectors, and micro-PET and micro-SPECT will enhance clinical and research applications of nuclear cardiology, including the ability to study myocardial metabolism and gene expression in small animals. Improvements in software to correct for attenuation, scatter, and depth resolution have been made, and such methods may be used at the present time (Table 53.9).

Hardware and software
New tracers
New stress agents
Molecular and vascular imaging
New applications

Adapted from Iskandrian AE, Verani MS, eds. Bar Harbor Invitation Meeting 2000. *J Nucl Cardiol* 2001;8(2):224–316, with permission.

TABLE 53.9 RECENT DEVELOPMENTS IN NUCLEAR CARDIOLOGY

Clinical studies on a number of compounds, such as Tc-99m Noet (for myocardial perfusion), Tc-99m glucarate (for acute MI), Tc-99m annexin V (for apoptosis and transplant rejection), Tc-99m nitro imidazole (for myocardial hypoxia), I-123 meta-iodobenzylguanidine (for sympathetic innervation), and a number of selective A_2 receptor agonists (used as vasodilators), are ongoing (119,230,231,232,233,234 and 235).

There is a heightened interest in molecular imaging, angiogenesis, and vascular imaging and gene expression. Significant strides continue to be made in this field in automation and quantification, including the possibility of absolute measurements such as the myocardial blood flow, which is now only possible by use of PET.

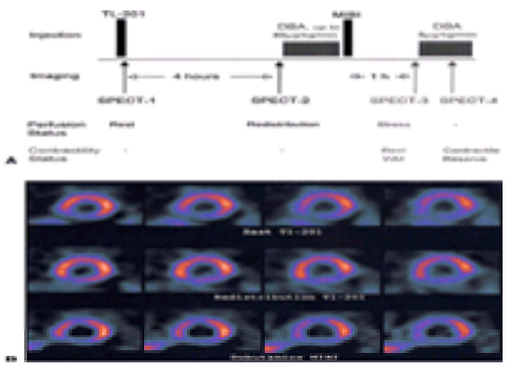
New applications are currently emerging, such as the use of acute imaging in emergency departments and in cases of sudden death and heart failure. Finally, there is a heightened interest in the detection of early atherosclerosis and characterization of unstable atherosclerotic plaques. These and other anticipated developments are likely to contribute to the continued growth of the field in the new millennium (234).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Three perfusion tracers are currently approved for routine clinical use: Tl-201, Tc-99m sestamibi, and Tc-99m tetrofosmin. All three tracers are useful in the assessment of diagnosis, risk-stratification, and myocardial viability.

The Tc-99m–labeled tracers provide significantly better image quality than Tl-201 and allow attenuation/scatter correction and first-pass RNA studies. The results with attenuation/scatter correction with Tl-201 are not yet convincing. The importance of EF measurement suggests that gated SPECT should be used in all patients. Today, >70% of perfusion studies are performed using Tc-99m–labeled tracers, and >90% are performed using gating; this is a remarkable change in a relatively short period of time.

For viability assessment, rest redistribution Tl-201 imaging provides a measure of hibernation (rest hypoperfusion) that, arguably, is not obtainable by Tc-99m–labeled tracers. The role played by ischemia in recovery of function, however, suggests that a stress rather than a resting study is needed for these patients. A hybrid protocol using rest redistribution Tl-201 and stress Tc-99m–labeled tracers may provide a complete assessment (eFig. 53.4.1) (235).



***e*FIGURE 53.4.1 A:** The methodology of a novel imaging protocol to assess myocardial viability using gated single-photon emission computed tomography (SPECT) that allows characterization of dysfunctional myocardium as stunned, hibernating, remodeled or infarcted. **B:** Selected SPECT slices showing rest-redistribution thallium and dobutamine (DBA) sestamibi (MIBI). The baseline and low-dose dobutamine functional images are not shown. Resting and stress-induced reversible defects are present. Tl-201, thallium-201; WM, wall motion. (From Narula J, Dawson MS, Singh BK, et al. Noninvasive characterization of stunned, hibernating, remodeled and nonviable myocardium in ischemic cardiomyopathy. *J Am Coll Cardiol* 2000;36;1913–1919, with permission.)

The strongest asset of nuclear imaging is the ability to provide quantitative measurements (e.g., EF, area of myocardium at risk, and infarct size). This is best achieved by tomographic imaging enhanced by gated perfusion imaging and by performing attenuation/scatter depth resolution compensation. Emerging techniques are likely to expand the applications beyond perfusion and function to include metabolic, receptor, and atherosclerosis imaging, and ultimately the ability to identify unstable plaques and gene expression.

Some argue that nuclear testing is prohibitively expensive, which it is in comparison to exercise ECG. However, cost is a market-driven value, and cost-effectiveness is a better index than cost.

Regarding the choice of stress modality, exercise continues to be preferred because of the known prognostic variables associated with stress ECG and exercise tolerance. From the standpoint of diagnostic accuracy, however, pharmacologic stress imaging appears to be at least equivalent to exercise imaging. Moreover, the image variables that indicate increased risk by exercise stress (e.g., large defects, multivessel defects, transient ischemia dilation, and LVEF and left ventricular size) are also powerful risk predictors when observed with pharmacologic imaging.

THE FUTURE

We believe the future will bring about important changes in the way that nuclear cardiology is practiced. First, newer tracers will be available that will allow imaging to be target-specific for studying myocardial perfusion, myocardial hypoxemia, myocardial necrosis, myocarditis, myocardial metabolism, sympathetic innervation, ventricular function, and coronary atherosclerosis. Targeting gene expression with specific nuclear markers will allow imaging of genetically engineered animal models and, later, of human beings. It may become possible to image vulnerable plaques in diverse arteries. Second, SPECT imaging will be used routinely with attenuation/scatter and depth resolution compensation, as well as with gating, three-dimensional imaging, and absolute quantification. These advances will increase the precision of the technique and improve quantification. Third, there will be increased applications of nuclear imaging in other groups of patients, such as patients with life-threatening ventricular arrhythmias, patients with congestive heart failure, asymptomatic patients who are at high risk, and in the evaluation of effects of therapeutic interventions such as gene therapy, lipid-lowering therapy, antianginal medications, and hormone-replacement therapy. Fourth, the quality of the nuclear images will improve through standardization of procedures, quality assurance measures, and certification and credentialing programs. Last, managed-care organizations will recognize that nuclear procedures are cost-effective for selecting patients who will benefit most from coronary angiography and percutaneous procedures and patients in whom routine coronary angiography is not justified.

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MAGNETIC RESONANCE IMAGING

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Cardiovascular (CV) magnetic resonance imaging (MRI) is uniquely well suited for the morphologic and physiologic evaluation of a wide range of acquired and congenital disease processes affecting the heart, pericardium, and great arteries and veins of the thorax. Its technological diversity permits MRI to provide four-dimensional (three spatial dimensions over the dimension of time) imaging of the CV system based on definition of high-detail anatomy, histologic characterization, intracardiac or intravascular blood flow, cardiac chamber contraction and filling, regional myocardial mechanics, and tissue perfusion. Already, CV MRI has established itself as a valuable noninvasive diagnostic imaging tool within the clinical arena, with its application largely limited by actual or perceived expense, lack of availability of dedicated CV MRI services compared with other imaging services (e.g., echocardiography), unportability of equipment to ill patients, difficulty in monitoring patients on life support or during induced stress, and contraindication to imaging certain implanted devices (e.g., pacemaker). Nevertheless, CV MRI has evolving roles being established in the following groups of CV diseases: (a) thoracic aortic disease (e.g., aortic dissection); (b) ischemic heart disease [e.g., determination of viability and post–myocardial infarction (MI) complications]; (c) myocardial disease [e.g., right ventricular cardiomyopathy (CM)]; (d) pericardial disease (e.g., constrictive pericarditis); (e) thrombi and masses (e.g., cardiac tumor); (f) adult congenital heart disease (CHD) (e.g., great vessel abnormality); (g) valvular heart disease (e.g., aortic regurgitation); and (h) pulmonary artery disease (e.g., pulmonary hypertension). The future of CV MRI will depend on (a) establishment of an important role in the evaluation of ischemic heart disease or related conditions (e.g., possibly by providing comprehensive profiles of the pertinent parameters); (b) unique definitions of aspects of CV diseases (e.g., myocardial characterization, load-independent measure of myocardial function, noninvasive arterial wall imaging), leading to high morbidity and mortality in this country; (c) cooperative efforts between services dealing with diagnostic imaging of CV diseases; or (d) all of these.

GLOSSARY

Cine: A dynamic gradient-echo imaging technique involving the rapid acquisition of multiple sequential images (10 to 20 images per cycle) at an anatomic level over the cardiac cycle, resulting in an image loop.

Delayed-enhancement technique: An MRI sequence (Turbo FLASH with inversion recovery) used to evaluate myocardial necrosis and viability without pharmacologic stress. Approximately 15 to 30 minutes after the injection of gadolinium-diethylenetriaminepentaacetic acid, hyperenhancement is visible in areas of myocardial necrosis because of concentration or retention of agent, whereas signal nulling occurs in viable regions because of lack of contrast agent.

Echo-planar imaging: A form of near real-time MRI, allowing the acquisition of images in approximately 50 ms using a single pulse repetition and rapid switching of a strong phase-encoding gradient in the presence of a weaker readout gradient to produce a series of echoes. As a result, this technique has the ability to acquire a complete image set of the heart within a breath-hold period.

Echo time (TE): The time between the initial radiofrequency perturbation and the return of the echo signal in an MRI pulse sequence.

Even-echo rephasing: The flow phenomenon in which the net spin phase associated with constant velocity flow is theoretically zero on even-numbered images from a multiple spin-echo sequence with balanced and symmetric gradient structures. It represents enhancement of spin-phase coherence and reduction of signal cancelling effects of proton spins in regions of nonturbulent, slow blood flow with even-numbered refocusing pulses with fixed –180 to +180 intervals and results in an absolute increase in signal intensity in regions of constant velocity on magnitude data images.

Gadolinium chelates: The only contrast agents approved for use in clinical MRI; they are paramagnetic.

Gating: The process of temporal referencing of image-data acquisition to the points of the cardiac and respiratory cycles to overcome blurring related to physiologic motion. In CV MRI, gating based on the electrocardiogram is almost universally used and is accomplished with an MRI-compatible sensing device to synchronize the phase-encoding steps in the image-data acquisition with a specific segment of the cardiac cycle.

Gradient-echo imaging: A common form of MRI using a low flip angle of 20 to 60 degrees for the initial radiofrequency pulse, which is followed by reversal of the polarity of the gradient to recall the gradient-echo signal; the low flip angle of the slice-selective radiofrequency pulse allows a sufficient number of spins to relax by T1 decay back to equilibrium in a short period of time, so that a rapid succession of such pulses with shortened repetition time (TR) can be applied while maintaining signal intensity for faster imaging. It results in the "bright blood" appearance.

k-space (Fourier space): The platform onto which MRI data are acquired, positioned, and then transformed into the desired image; data are acquired at discrete intervals to fill k-space as signal amplitude is stored as a function of the spatial frequencies along the readout and phase-encoding directions.

Longitudinal relaxation time (T1): A measure of the exponential rate of growth of the magnetization vector along the direction of the external magnetic field after perturbation of the nuclei by the radiofrequency pulse, thereby enhancing the signal.

Magnetic resonance angiography (MRA): An MRI technique for angiographic imaging that relies either on signals generated by the flow of fully magnetized protons into an imaging region or on phase shifts that are observed with moving protons during the application of magnetic field gradients.

Magnetic resonance imaging (MRI): The imaging modality using high-power static magnetic fields, low-power changing magnetic fields, and radiofrequency pulses to generate tomographic images from the inverse Fourier transform of the sampled k-space.

Nuclear magnetic resonance: A phenomenon in which atomic nuclei with odd numbers of protons or neutrons have magnetic moment (i.e., spin about an axis) aligned along the direction of a main magnetic field, causing them to precess when tipped from alignment with the main field.

Paramagnetic contrast agents: By virtue of possessing unpaired electrons with unopposed spins, these agents generate strong, fluctuating magnetic fields at nearby nuclei, thus stimulating relaxation; they predominantly shorten T1, and less so T2.

Phase-change effect: The signal-canceling effect of relative phase differences imparted to proton spins moving at different velocities through a magnetic gradient field. The range of velocities and the associated spin-phase shifts across a vessel lumen increase with rising mean flow velocity, as well as with voxel size.

Phase contrast: An MRI approach using subtraction to qualitatively or quantitatively register motion spatially; it exploits the fact that spin phase of moving protons (usually those in flowing blood) is sensitive to magnetic gradients and varies according to proton position in the gradient fields. While stationary protons accumulate phase during the first lobe of a bipolar gradient with known amplitude, they lose the phase change during the second lobe, which is symmetric but opposite in polarity to the first; moving blood protons gain phase during both lobes, resulting in a net phase accumulation. It is the basis for the qualitative phase-display and the quantitative phase-tracking and velocity mapping techniques.

Phase display: A qualitative phase-contrast technique for registration of motion-dependent phase changes corresponding spatially to the standard magnitude data image.

Phase tracking: The technique applying velocity mapping for the identification of movement of myocardial elements.

Prospective gating: Gating with the initiation or repetition of the MRI sequence being triggered by the physiologic marker (e.g., R wave).

Repetition time (TR): The duration between repeated applications of the initial radiofrequency perturbation pulse in an MRI sequence.

Retrospective gating: Gating in which the MRI sequencing is machine dependent, but the data are later referenced to an independently monitored physiologic signal; with this strategy, image-data sampling occurs at arbitrary points in the cardiac cycle, which then must be interpolated relative to a fixed reference time point in the physiologic recording.

Segmented k-space approach: Method for more rapid filling of k-space in which phase-encoding steps are covered in groups (segments).

Signal-loss cloud: The diffuse areas of intermediate flow-signal loss in regions of slow flow; this results from saturation effects as slowly moving proton spins remain in the imaging volume over a longer period of time and, hence, experience a greater number of excitation pulses.

Signal-void jet: The discrete areas of pronounced flow-signal loss on gradient-echo imaging resulting from complex flow, especially turbulent.

Spatial modulation of magnetization: The technique whereby tissue is tagged, before otherwise normal dynamic MRI, by a pair of nonselective radiofrequency pulses separated in time by the application of appropriate magnetic field gradient pulses to label myocardial proton spins for the purpose of assessing motion. It can be used to produce a parallel stripe pattern, which, when used in combination with a set of stripes directed perpendicularly to the first set, can result in a grid pattern in the myocardium.

Spin-echo imaging: The most common form of MRI in which images are produced after an initial slice-selective 90-degree radiofrequency pulse, followed by one or more 180-degree pulses for refocusing of the spin-echo signal. It results in the “dark blood” appearance.

Spin tagging: The most common approach to assessing myocardial mechanics by MRI. It involves the use of sequences applied once at the start of each cardiac cycle to directly label myocardial units during systole or diastole. In the simplest version, direct radiofrequency saturation is used to produce dark bands of myocardium that can be followed through time and space during dynamic MRI; another commonly used version is spatial modulation of magnetization.

T1 weighting: Imaging in which the intensity of image voxels depends greatly on the T1 relaxation time of tissues. For spin-echo imaging, this is accomplished with a short TR and TE.

T2 weighting: Imaging in which the intensity of image voxels depends greatly on the T2 relaxation time of tissues. For spin-echo imaging, this is accomplished with a long TR and TE.

Time of flight: An approach to MRI of flow that relies on signals generated by the flow of fully magnetized protons into an imaging region.

Transverse relaxation time (T2): A measure of the rate at which nuclear magnetic resonance–sensitive nuclei lose coherence with each other in the transverse plane following their perturbation by the radiofrequency pulse, thereby degrading the signal.

Ultrafast: An MRI technique using gradient-echo pulse sequences (i.e., Turbo FLASH) with extremely short TR and TE to acquire a cardiac image within 100 to 300 m per second. Thus, a snapshot of a portion of a single cardiac cycle can be obtained for the assessment of patterns of blood flow and tissue perfusion.

Velocity mapping: A quantitative phase-contrast technique to encode flow velocity either perpendicular or parallel to the imaging orientation; knowledge of the gradient structure allows for the spin-phase shifts detected with velocity mapping to be converted to absolute velocity values.

View sharing: A method used with segmented k-space cine acquisition in which a portion of the image data from one cardiac phase, represented by a segment, is combined with a portion of the data from an adjacent cardiac phase to form an image intermediate to the two phases. This effectively doubles the temporal resolution.

HISTORICAL PERSPECTIVE

Nuclear magnetic resonance is a phenomenon exhibited by certain atomic nuclei. Independently introduced by Block (1) and Purcell (2) in 1946, this technology was subsequently employed as a spectroscopic tool to analyze molecular structures (3). In 1973, Lauterbur (4) first described a method for producing images using related techniques and, as early as 1977, human whole-body images were already being produced by MRI (5), although diagnostically valuable images of the central CV system had to await solutions to motion-related degradation. By the early 1980s (6,7), high-quality static anatomic imaging of the central CV structures was being accomplished by electrocardiogram (ECG)-gated MRI, but the orientation of imaging was limited to the axes of the MRI scanner. However, capabilities for oblique imaging soon followed, permitting acquisition of images oriented along the axes of the CV structures (8). The mid- to late 1980s saw the development and clinical implementation of dynamic MRI techniques allowing physiologic assessment of cardiac function and blood flow (9,10); this was promoted by the use of the more rapid acquisition techniques (11). Since then, CV MRI has profited from technical advancements allowing the following capabilities: ultrafast/near real-time imaging (12,13), tissue tagging and tracking (14,15), and three-dimensional (3-D) acquisition and display (16); the result has been improvement in the assessment of myocardial physiology and complex and fine-detail anatomy of the CV system. Despite this rapid development of technology and associated clinical research, the routine implementation of CV MRI has been delayed for a variety of reasons (17). However, increasing awareness of the capabilities, as well as the limitations, of this imaging modality has created new momentum to promote the practical application of CV MRI.

In adults, the diagnostic information provided about CV disease by transthoracic echocardiography (echo) is often incomplete because of the larger body and the paucity of adequate imaging windows. Although this provides the incentive for using MRI, computed tomography (CT), and transesophageal echo, MRI has the advantage of providing imaging in any desired plane chosen by the operator. All the structures in the thorax are equally accessible to MRI without the CT limitations of x-ray exposure and need for contrast administration and the echo limitations of restrictive windows of access. Additional advantages of MRI include high spatial resolution and excellent soft tissue definition. The advantages of MRI may be offset, however, by the following factors: (a) high cost, (b) longer imaging time, (c) immobility of the scanner, and (d) the restricting physical environment of MRI.

PRINCIPLES AND TECHNIQUES

Detailed descriptions of the basic principles of MRI are available elsewhere (18) but are reviewed in this chapter. Although closely related to and, at times, intertwined with the technological development of MRI, spectroscopy is beyond the scope of this chapter.

Magnetic Resonance Imaging Principles

Atomic nuclei with odd numbers of protons or neutrons have a magnetic moment (i.e., spin about an axis), which can be aligned along the direction of a magnetic field. This characteristic is vital for nuclear magnetic resonance phenomena, because it causes nuclei to precess when tipped from alignment with the main magnetic field. Among nuclei sensitive to nuclear magnetic resonance (e.g., ^{31}P, ^{23}NA, ^{13}C), the proton (i.e., ^{1}H) has been most widely applied in MRI because of its natural abundance; therefore, this discussion refers to hydrogen-based MRI.

The MRI signal originates primarily from the hydrogen of water and less so from the small hydrogen content of lipids. However, the actual appearance of the image is affected by a variety of physical parameters. Some of these parameters are characteristic of the tissue sampled, and others relate to the MRI sequences.

An essential difference between MRI and other modalities is the control that the user has over how data are used. The agent of this control is k-space (Fourier space), the platform onto which data are acquired, positioned, and then transformed into the desired image (19). Raw image data are obtained during sampling through k-space, which depicts the spatial frequency domain. High spatial frequencies encode fine details, whereas overall contrast is encoded in the lower frequencies. Data are acquired at discrete intervals to fill k-space, as signal amplitude is stored as a function of the spatial frequencies along the readout and phase-encoding directions. An image is simply the inverse Fourier transform of the sampled k-space (20).

MRI uses high-power static magnetic fields, low-power changing magnetic fields, and radiofrequency (RF) pulses to generate tomographic images. Application of weak RF-modulated pulses of a specific frequency partially aligns the magnetic moments of protons within the tissue sample against the magnetic field and induces their resonance; the effect of this RF field is maximal when the nuclei have been deflected by 90 degrees. When the RF pulse ceases, the protons return to equilibrium. During this process, they emit the RF energy of the same frequency, which is then Fourier transformed by a computer into a spatially accurate image whereby differences in signal intensity result in differences in gray levels. The signal intensity is not only dependent on hydrogen density, but also on their longitudinal relaxation time (T1), reflecting the rate of realignment with the external magnetic field (enhancing the signal), and on their transverse relaxation time (T2), indicating the rate at which nuclei lose coherence with each other (degrading the signal). In normal myocardium, T2 is much shorter (i.e., 60 ms at 1.5 Tesla) than T1 (i.e., 500 ms). The characteristic T1 and T2 relaxation times are exploited to distinguish between normal tissues and to characterize disease processes. In general, MRI contrast improves with increasing hydrogen density, shortening of T1, and lengthening of T2.

Externally, MRI scanners have changed little over the past two decades, although the internal architectures have evolved. Basically, an MRI scanner consists of five major parts: magnet, transmitter, antenna, receiver, and computer. Most modern clinical MRI scanners have magnets, consisting of liquid helium–cooled, superconducting solenoids, operating at a field strength of 0.1 to 3.0 Tesla and with a bore size of approximately 1 m; MRI is best performed with a magnet with higher field strength and homogeneity to improve the signal-to-noise ratio. The transmitter is used for transmitting RF pulses to an antenna or coil, which in turn transmits RF power to the patient, and also receives the returning signal. The coil usually surrounds the patient or may be placed directly on their surface, depending on whether information is required from the whole body or from a selected organ of interest. Although surface coils provide higher sensitivity and, therefore, excellent spatial localization of signal, they have the disadvantage of an inhomogeneous RF field, which produces an inhomogeneous signal intensity distribution on images. The receiver amplifies the signal picked up by the coil, and the signal is processed by a computer, which is also needed to operate the entire MRI system.

Magnetic Resonance Imaging Techniques

Current MRI exists in two basic forms: spin-echo (S-E) imaging and gradient-echo (G-E) imaging. With an S-E sequence, images are produced after an initial slice-selective 90-degree RF pulse followed by one or more 180-degree pulses to refocus the S-E signal. The G-E technique uses a lower flip angle of 20 to 60 degrees for the initial RF pulse, which is followed by reversal of the polarity of the gradient to recall the G-E signal; the low flip angle of the slice-selective RF allows a sufficient number of spins to relax by T1 decay, back to equilibrium in a short period of time, so that a rapid succession of such pulses can be applied while maintaining signal intensity, for faster imaging.

In addition to flip angle, these sequences are described in terms of repetition time (TR), referring to the duration between repeated applications of the initial RF perturbation pulse, and echo time (TE), which refers to the time between the initial RF perturbation and the return of the echo signal. For multilevel S-E or G-E imaging and for dynamic G-E imaging, the TR is dependent on the gating strategy used, as described in this section. TE values for S-E imaging typically range from 15 to 60 ms depending on the tissue contrast sought, whereas the TE range for G-E imaging is only 4 to 15 ms.

Because the echo signal from the resonating protons recorded during MRI data collection is a vector defined uniquely by magnitude (i.e., intensity) and phase (i.e., direction) components, different types of reconstructions can be performed. The magnitude data are used to produce an anatomy-based image, whereas the phase component can be used to generate a motion-based image that reflects the movement of proton spins during the time interval between the RF excitation pulse and the center of the signal-sampling window (i.e., TE).

CV images are usually acquired as two-dimensional (2-D) tomographic slices of 1 cm thickness or less, although volume or true 3-D MRI is becoming more practical as the speed of imaging increases. Regardless of the form of MRI, temporal referencing of image-data acquisition to the points of the cardiac cycle (gating) is crucial to CV MRI; not only does it overcome blurring related to cardiac motion, it provides a basis for dynamic imaging.

For static S-E or G-E imaging, a multilevel acquisition may be used for production of a series of images of adjacent parallel anatomic levels; because of the time needed for data sampling at a level, each image in the series represents a slightly earlier point (e.g., 50 ms) in the cardiac cycle than the next image in the series (21). Thus, the first image usually represents the onset of systole and the last image, late diastole. Using standard phase-encoding schemes, a static multilevel series requires 5 to 7 minutes of imaging time, depending on desired image quality and heart rate. This type of acquisition can be significantly reduced with new approaches to phase encoding, including a segmented k-space approach, in which phase-encoding steps are covered in groups (segments), or partial k-space sampling (12,19). In addition, turbo S-E sequences have been employed to allow rapid static imaging within a breath-hold period (22). One of these sequences is considered a “snapshot” because it acquires each image slice in a single heartbeat (23).

Dynamic G-E imaging, also referred to as *cine*, involves the rapid acquisition of multiple sequential images (10 to 20 images per cycle) at an anatomic level over the cardiac cycle, resulting in an image loop with good temporal resolution. The repetition time used depends on the gating strategy used, but usually ranges from 20 to 50 ms (24). An image loop set can be produced within a breath-hold period with the segment k-space approaches (24) with a good temporal resolution (e.g., 25 ms).

On even-numbered images from a multiple S-E sequence with balanced and symmetric gradient structures, the net spin phase associated with constant velocity flow is theoretically zero. It represents enhancement of spin-phase coherence and reduction of signal-canceling effects of proton spins in regions of nonturbulent, slow blood flow with even-numbered refocusing pulses with fixed 180- to 180-degree intervals throughout. Such even-echo rephasing results in an absolute increase in signal intensity in regions of constant velocity on magnitude-data images, so that the intensity of the signal from blood moving at constant velocity resembles that of stationary blood (25). Application of gradients for flow compensation also produce the even-echo rephasing effect for constant velocity flow in G-E MRI (26). Because the rephasing occurs for a unique timing and amplitude relationship between gradient pulses applied along a given direction, a slight time shift can be introduced into the bipolar gradient to make the pulse sequence velocity sensitized, so that the associated signal becomes valuable for quantitative velocity measurements (27).

The spin phase of blood protons is sensitive to magnetic gradients, and it varies according to the position of the proton in the gradient fields. Phase-contrast sequences involve the application of a bipolar gradient of known amplitude (10,27). Stationary protons accumulate phase during the first lobe of the gradient, and then lose phase during the second lobe that is symmetric but opposite in polarity to the first. Although moving blood protons also accumulate phase during the first lobe, they will be in a different position during the second lobe, which results in a net phase accumulation. It is possible to use this velocity mapping technique to encode flow velocity either perpendicular or parallel to the imaging orientation. Knowledge of the gradient structure allows for the spin-phase shifts detected with velocity mapping to be converted

to absolute velocity values (centimeters per second) (28). Ultimately, the velocity value can be represented by a level on a gray scale on a voxel-by-voxel basis, building a map corresponding spatially to the magnitude-data image.

Furthermore, dynamic S-E or G-E techniques have been developed for assessment of cardiac wall mechanics. Of the two, spin tagging (14) and phase tracking (15), spin tagging has, to date, received the greatest attention. The spin-tagging sequences are applied once at the start of each cardiac cycle to label myocardial units during systole or diastole. In its simplest form, direct RF saturation is used to produce dark bands of myocardium that can be followed hrough time and space during dynamic MRI; a distinctive tagging pattern that has resulted involves radially oriented bands, extending outward from the center of the cavity of the left ventricle (LV) on transaxial or short-axis images (14). Another commonly used form of spin tagging has been spatial modulation of magnetization (SPAMM) (29). By SPAMM, the myocardial tissue is tagged before otherwise normal dynamic MRI by a pair of nonselective RF pulses separated in time by the application of appropriate magnetic field gradient pulses to label proton spins within the myocardium. It has popularized the parallel stripe pattern (5 to 10 mm separation), which, when used in combination with a set of stripes directed perpendicularly to the first set, can result in a grid pattern for orthogonal or oblique imaging. Phase tracking applies the aforementioned velocity mapping technique to the identification of movement of myocardial elements (15).

Ultrafast G-E pulse sequences, with extremely short TR and TE, have also been employed. The most commonly used of these sequences (i.e., Turbo FLASH) acquires a cardiac image within 100 to 300 ms; thus, a snapshot of a portion of a single cardiac cycle can be obtained (30). This technique, from here on referred to as *ultrafast*, allows the assessment of patterns of blood flow and tissue perfusion (31).

Another form of near real-time MRI, referred to as *echo-planar imaging* (EPI), allows the acquisition of images in approximately 50 m per second by rapidly switching magnetic field gradients (13). As a result, this technique has the ability to acquire a complete image set of the heart within a breath-hold period. Although this technique has great potential for evaluating cardiac function on a beat-to-beat basis, currently it is limited by relatively less spatial resolution, problems with flow quantitation, difficulties in performing oblique imaging, potentially adverse biologic effects (e.g., muscle stimulation), and the need for additional expensive hardware and software (32). EPI is currently available at only a few centers and is discussed in detail in this chapter.

Physiologic Demands

Motion degrades image quality in MRI. As a result of cardiac and respiratory activity, MRI of the CV system is particularly susceptible to motion artifacts. Therefore, it is critical to freeze frame the beating of the heart and moving thoracic vasculature to avoid blurring.

Gating to the cardiac cycle is recognized as being an essential component of all commonly used CV MRI techniques (21). Of the physiologic markers investigated for gating, the ECG markers for points in the cardiac cycle have been the most useful (33). While the ECG recordings may become degraded by magnetohydrodynamic effects and MRI-induced currents, these problems can be overcome by careful positioning of the leads and by electronic filtering of the signal. ECG gating is accomplished with an MRI-compatible sensing device to synchronize the phase-encoding steps in the image-data acquisition with a specific segment of the cardiac cycle.

Such gating is usually performed prospectively, with initiation or repetition of the MRI sequence being triggered by the physiologic marker (e.g., R-wave); the TR is then defined by the RR interval (33). With a standard multilevel series, image data from the first anatomic level is obtained before the second, which is before the third, and so forth, for a fixed amount of time that must not exceed the RR interval (21). This delay represents the time required for RF excitation pulsing and echo-signal acquisition at a particular level before the same process is executed at the next level.

An alternative used primarily for dynamic imaging of the complete cardiac cycle is retrospective gating, in which the MRI sequencing is machine dependent, but the data are later referenced to an independently monitored physiologic signal (26). With this gating strategy, image-data sampling occurs at arbitrary points in the cardiac cycle, which then must be interpolated relative to a fixed reference time point in the ECG recording. The maximum number of frames in an image loop corresponds to the number of sequence-TR intervals that can be inserted into the cardiac cycle. With this form of cine, the rapid repetition rates allow for one or several anatomic levels to be imaged at multiple nearly identical segments of the cardiac cycle during a single series. Because multiple levels of the CV system may need to be evaluated, simultaneous acquisition of image loops from more than one anatomic level is desirable because it reduces total imaging time; this is possible, but only with a decrease in temporal resolution. The interpolated data are reconstructed into a user-selected number of images, which then form an image loop in a manner resembling gated blood pool ventriculography.

Prospective gating can also be used to perform dynamic multiphasic imaging (21,26), with repetitive scanning at the same level or few levels, so that the inherent delay in the sequence leads to uniformly delayed images covering end diastole through systole into at least early diastolic filling. The prospective strategy for gating in cine has the advantage of being simpler than the retrospective strategy and obviating the need for postprocessing, thus allowing immediate use of the image loops. This has been the approach to segmented k-space G-E acquisitions allowing fast, respiratory, artifact-free cine to be performed at one level during a single breath-hold (24). However, in general, breath-hold cine has inferior temporal resolution because of acquisition of image data over the duration of the segments. In addition, it is somewhat limited by incomplete representation of the entire cardiac cycle; this is because of a variable dead time between the end of the triggered image-data acquisition and the appearance of the next R-wave trigger. A postprocessing technique developed to overcome some of these limitations is view sharing (34). With this technique a portion of the image data from one cardiac phase, represented by a segment, is combined with a portion of the data from an adjacent cardiac phase to form an image intermediate to the two phases. This effectively doubles the temporal resolution, creating a smoother image loop, although it does not provide for additional images deeper into end diastole.

Like cardiac motion, motion related to the excursion of the thorax during normal respiration degrades MRI (35). Respiratory motion produces a form of coherent noise distributed across the image as a periodic artifact; however, it tends to be less degrading than cardiac motion. Nevertheless, some MRI systems incorporate respiratory-sensing devices that coordinate the changes in chest position with the ECG gating to minimize image artifacts (36). Respiratory gating has theoretical advantages as far as minimizing such motion artifacts, but the associated significant increase in imaging time limits its application. Consequently, alternative means of compensation for respiratory motion have been used, and they vary considerably in their sophistication. The simplest method is encouragement of voluntary slow and shallow breathing by the patient, followed by the use of a restraining belt around the thorax to restrict chest expansion. At the other end of the spectrum are methods using phase-encoding reordering to destroy the periodicity of the respiratory motion (37). This need has been largely remedied by the introduction of fast imaging techniques permitting imaging during breath-holding (12).

Image Orientation

The orientations traditionally used for CV MRI are the transaxial, sagittal, and coronal planes; they are orthogonal to the thorax but oblique to the heart and great vessels. Complete sets of these images are most useful in gaining a global perspective of the relationships of the cardiac chambers, great vessels, and adjacent structures. They also serve as important localizing images for oblique imaging along the natural axes of the CV structures, such as with the long axis of the thoracic aorta. With further axial rotation, double-oblique imaging also can be performed to acquire images of the heart equivalent to the 2-D echo short-axis and long-axis orientations (e.g., two-chamber, four-chamber, LV outflow) (8,38).

Morphologic images depicting the lumina of large central or smaller peripheral vessels may be obtained using a variety of techniques, termed *magnetic resonance angiography* (MRA) (16). MRA methods rely either on signals generated by the flow of fully magnetized protons into an imaging region [time-of-flight (TOF) MRA], or on phase shifts that are observed with moving protons during the application of magnetic field gradients (phase-contrast MRA) (39). MRA is increasingly being employed to evaluate the great vessels, especially the thoracic aorta (40). Traditionally, sequential 2-D TOF approaches have been employed. More recently, MRI contrast agents have been used in combination with rapid 3-D TOF sequences to acquire a volume of data (41). Data sets from either type of acquisition may be reconstructed into multiple projection or reconstructed tomographic images (40).

Safety Issues

A major safety consideration in MRI was initially the production of ventricular fibrillation through induction of a current into the patient by rapidly changing magnetic fields. Based on experimental studies, however, the threshold rate of change of the magnetic field to produce ventricular fibrillation is far in excess of those experienced in clinical MRI scanners, indicating a large safety margin for patients (42).

From the standpoint of implants in patients, some are absolute contraindications for MRI. MRI should not be used in patients with vascular clips used for cerebral aneurysm surgery because of the potential risk of dislodgement from the vessel (43). At the present time, implanted cardiac pacemakers, cardiac defibrillators, and neurologic stimulators represent contraindications, and patients with these electronic implants should not undergo MRI because of the risks from malfunctioning of the device or current induction (43).

On the other hand, most of the recent manufactured coronary arterial stents and all prosthetic heart valves, including the prosthetic valves containing large amounts of alloy (e.g., Starr-Edwards pre-6000 series, Edwards Lifesciences Corporation, Irvine, CA), are now considered to be compatible with MRI (44,45). Aside from local

imaging artifacts, hemostatic clips, metallic sternal suture wires, or retained surgical epicardial pacing wires are not known to lead to complications from MRI (43).

Critically ill patients are less than optimal candidates for MRI, either because they are dependent on life support or continuous monitoring systems that cannot be brought near the scanner, or their clinical condition is too fragile for the limited monitoring that is compatible with the MRI environment. Nevertheless, such patients can be safely evaluated if physiologic monitoring is supplemented by close observation by trained personnel.

Finally, claustrophobia may impede MRI in up to 5% of patients. This problem can be controlled by premedicating the patient with sedative agents.

GENERAL INTERPRETATION GUIDELINES

The appearance of an MRI is dependent on the interactions between the components of the imaging sequence and the physical system being imaged.

Appearances of Flow

An understanding of flow phenomena and their variable appearances with different types of sequences is essential in the interpretation of MRI. Blood flow phenomena assume great importance in the CV system because of the dynamic and complex nature of the relatively large volumes of moving blood (46). Basic descriptions of blood flow are typically based on laminar flow velocity profiles (25,47). Blood flow in the heart and thoracic vasculature, however, is complex as a result of both pulsatility and movement through curving and branching structures. This results in deterioration of laminar flow, development of turbulence, and generation of flow-related artifacts, all of which must be considered.

For the most part, the hemodynamics in the cavities of the cardiac chambers and lumina of the thoracic vasculature are such that little to no signal is received from the intracardiac or intravascular blood pools on magnitude-data images from static S-E MRI; this results in the characteristic dark blood appearance (48). The two major factors accounting for loss of blood signal on these images are TOF effects and phase-change effects, which primarily influence flow perpendicular and parallel to the imaging plane, respectively (25). TOF dictates that flowing protons that traverse the full thickness of the imaging level in the interval between the initial excitation pulse and the refocusing pulse on the S-E sequence (i.e., TE/2) will generate no signal (46,47). The phase-change effect refers to the relative phase differences imparted to proton spins moving at different velocities through a magnetic gradient field (25). The range of velocities and the associated spin-phase shifts across a vessel lumen increase with rising mean flow velocity, as well as with voxel size.

Consequently, S-E sequences generally produce excellent differentiation between intracardiac or intravascular blood pools and the surrounding myocardial or vascular walls (49). However, under circumstances of blood flowing below a critical velocity, whether physiologic or pathophysiologic, increased intracardiac or intravascular signal may be noted on S-E MRI. There is normal physiologic variation in the S-E blood signal with the phase of the cardiac cycle represented, and relatively slow diastolic blood flow may generate signal (49). When blood flow is exceptionally sluggish or stagnant because of CV disease, abnormal flow signal caused by the reduction of TOF and phase-change effects is frequently observed even on systolic S-E images.

To overcome diagnostic limitations from such unwanted intracardiac or intravascular signal on S-E MRI, several approaches can be used. The simplest is to increase the TE, thereby allowing slowly flowing blood more time to move out of the imaging plane and cause TOF effects; unfortunately, this approach also introduces more time for movement of the CV structures, which is manifested as a motion artifact (50). Another approach is to apply additional RF excitation at levels above or below the levels of interest to saturate in-flowing blood (51); with this approach, the quality of the image of the CV structures tends not to be degraded.

A characteristic of slower flowing blood on images from multiple S-E sequences is even-echo rephasing (52). This phenomenon is manifested as an increase in intracardiac or intravascular signal intensity, both in absolute values and relative to other tissues, from an odd-echo image to the subsequent even-echo image. Because this signal variation is true only of proton spins moving at constant velocity, slow flow can often be differentiated from fixed material (e.g., thrombus), which also causes abnormal signal but without even-echo rephasing (53). Variability of the signal intensity of the fixed material may, however, result from differences in composition of its tissue (54).

Constant velocity slow blood flow can also be differentiated qualitatively from intracardiac or intravascular fixed material, using reconstructions of the phase data from S-E sequences (53,55). Averaged proton spin phase can be interpreted on a voxel-by-voxel basis from odd-echo data and used to produce a phase-display image that corresponds spatially to the standard magnitude-data image. For protons in stationary structures (e.g., vertebral body), the phase change is zero and is, by convention, assigned an intensity in the middle of the gray scale. On the other hand, spin-phase changes for protons in moving tissues (e.g., flowing blood) are expressed as positive or negative degree values ranging from +180 degrees to –180 degrees; increasing positive or negative phase values are represented by increasing intensity of whiteness or blackness, depending on the assignment of the positive and negative values. A variation of the phase-display technique has been used to produce images in which the motion-dependent phase changes appear as a series of stripes displaced in the direction of the motion (56).

Because of its fixed nature, a large intracardiac or intravascular mass (e.g., thrombus) is usually represented with the same gray intensity on standard phase display as a stationary structure (53,55). On the other hand, slowly flowing blood, because of its moving protons, has an appearance that is different; it is represented by shades of white or black. Unfortunately, any structure that is moving during the application of the gradients, such as the heart or a highly mobile intracardiac mass, may produce an observable phase change that may lead to improper identification. In addition, technical factors (e.g., inhomogeneity in the static magnetic field) may alter local phase progression, which may be misinterpreted as phase change caused by motion (57).

In G-E MRI, including cine, normally flowing blood has a high signal intensity that exceeds that of the surrounding myocardial or vessel walls. The bright blood appearance is related to (a) short TR minimizing TOF effects, (b) short TE reducing phase dispersion, (c) single non–slice-selective RF excitation pulses allowing constant influx of fully magnetized protons into the imaging volume, and (d) frequently used flow-compensation schemes, capturing otherwise lost signal from spin dephasing (9,11,26).

Normal and abnormal patterns of intracardiac or intravascular blood flow are still reflected by variations in signal intensity on cine. Normally, the blood pools show almost uniformly increased signal intensity during most of the cardiac cycle, although increases in intraarterial flow rates in systole are represented by increased intensity (9). Local signal loss caused by dephasing effects of nonuniform flow may, however, be observed during the cardiac cycle (58).

Basic phantom work using cine has aided the understanding of the phenomena noted on clinical images. It is now recognized that signal intensity increases on such images with increasing flow velocity up to a point (i.e., 60 cm per second), because partially saturated protons are washed out of the imaging plane and completely replaced by fully magnetized protons at a rapid rate. Beyond this point, signal loss occurs primarily because of spin-dephasing effects that increase with increasing TE (59). Phase cancellation, exaggerated by turbulent flow, is a common cause of signal void on cine in the setting of pathology. A combination of these effects appears to account for the characteristic focal, pronounced “signal-void jet” that is found with conditions causing complex flow, especially turbulent. Although there is a relationship between the prominence of a signal-void jet and the extent of flow disturbance, there are pitfalls in clinical use of parameters based on jet size. Along with physiologic factors (e.g., transorifice gradient), the following factors have been shown to influence signal-void jet extent (61,62): (a) window level or width; (b) TE (increased size with increased TE up to approximately 12 m per second); (c) imaging orientation; (d) flip angle; (e) gradient field strength; and (f) degree of motion compensation. A more diffuse intermediate “signal-loss cloud” in regions of slow flow appears to result from saturation effects, as these slowly moving proton spins remain in the imaging volume over a longer period of time and, hence, experience a greater number of RF excitation pulses (63).

Anatomic Evaluation with Magnetic Resonance Imaging

Magnitude data from S-E or G-E sequences are used to produce the static images most often used for anatomic evaluation of CV diseases, as described in this section. The distinct appearance of blood flow allows the differentiation of solid tissues (e.g., myocardium), which are in the range of intermediate signal intensity, from moving intracardiac and intravascular blood. Thus, for definition of the anatomic abnormalities associated with various CV diseases, standard ECG-gated, multilevel, single-echo S-E or G-E series are appropriate (9,64).

MRA data sets from S-E or G-E imaging may be postprocessed into multiple projection or reconstructed tomographic images for anatomic evaluation of vasculature (16,40,41). However, significant pitfalls with such image acquisition and postprocessing must be recognized, making the experience of the interpreter critical to interpretation (65). For example, MRA tends to overestimate the degree of stenosis for lesions that exceed 70% of diameter partly because of signal loss caused by complex flow (60).

Because S-E imaging is sensitive to longitudinal and transverse relaxation parameters, as well as to hydrogen density, image contrast can be weighted either to T1 or T2 differences by varying the parameters of TR and TE. By using short TR and TE, a T1-weighted image yields more signal for tissues with shorter T1 (e.g., fat). A T2-weighted image, which uses a long TR and TE, provides a greater signal intensity for tissues with longer T2 (e.g., edema). Although this is the basis for the

traditional approach to tissue characterization, it has limited application to CV MRI because of dependency of TR on the cardiac cycle.

MRI contrast media may have been used to improve the differentiation between normal and hyperperfused or hypoperfused tissues. Two classes of such contrast agents have been used for CV imaging. The paramagnetic contrast agents, which predominantly shorten T1, and less so T2, are usually used in a dose range to cause a higher signal intensity on T1-weighted S-E and G-E MRI; currently, the paramagnetic gadolinium (Gd) chelates are the only contrast agents approved for use in clinical MRI (66). The second group includes the susceptibility agents that cause local variations in the magnetic susceptibility of tissue and thereby induce a decrease in signal intensity in relation to their distribution; this effect is observed on T2-weighted S-E or G-E images (66).

In addition to qualitatively delineating anatomic abnormalities, multiphasic S-E or cine MRI may be used for assessing ventricular mass (67,68). Because multilevel MRI is essentially a 3-D technique, the accuracy of myocardial mass determinations from anatomically accurate images is not dependent on geometric models and assumptions that can alter the accuracy of planar imaging techniques (e.g., ventriculography), especially in the presence of myocardial damage (69). MRI also has a distinct advantage in the quantitation of the dimensions of the right ventricle (RV), which is particularly limited with geometric models because of its complex shape (70). For ventricular mass determination from multiphasic MRI, the endocardial and epicardial surfaces of the ventricle are outlined at end diastole or end systole from each dynamic tomogram, and the volume of the myocardium at each anatomic level is calculated based on both the number of voxels in the region outlined and the known volume of each voxel; the myocardial volumes calculated for each anatomic level representing the ventricular wall are then summed to provide the total ventricular wall volume by Simpson's method and then converted to mass. Myocardial mass measurements by MRI correlate well with those obtained with echo and ventriculography (70,71 and 72).

Physiologic Evaluation with Magnetic Resonance Imaging

Evaluation of the physiologic aspects of CV disease by MRI has been an ongoing pursuit. This effort has resulted in the development and implementation of many interesting techniques; some use magnitude data for the production of anatomically accurate images representing the different segments of the cardiac cycle, whereas others use phase data to demonstrate physical changes reflecting motion or flow (63,69).

Contraction or Filling Evaluation

S-E MRI is not typically used to assess ventricular function. However, from end diastolic and end systolic S-E images acquired by a preset trigger-delay technique and obtained at a single long-axis level, volumes have been calculated using the area-length method and have correlated well with those from LV ventriculography (73). Nevertheless, the deficiencies of this oblique 2-D approach for volume determination have been described (74); the need for geometric assumptions has been cited as a major drawback of the 2-D MRI approach to evaluate ventricular volumes. Logically, a tomographic imaging technique should acquire a set of contiguous slices, encompassing the ventricles for determination of the total ventricular cavity volume using Simpson's method (75). Therefore, measurements of ventricular volumes for both LV and RV obtained by the multilevel MRI approach are generally more accurate than unilevel measurements (71,72,74,75).

For deriving information about cardiac chamber contraction or filling, the S-E MRI techniques are generally limited by their poor temporal resolutions and long acquisition times (21). Thus, cine is generally preferred for the MRI evaluation of ventricular function (9,63,69). Standard and segmented k-space versions of cine provide accurate and highly reproducible measurements of LV volumes (68,71,76). LV end diastolic and end systolic volumes and ejection fraction (EF) values from cine have correlated well with EF values from 2-D echo and LV ventriculography (77,78).

Ventricular volume measurements (i.e., myocardial and cavity volume, should be equally accurate with either orthogonal or oblique imaging when the multilevel approach encompasses the entire heart (69). In fact, ventricular volumes determined from images in the transaxial orientation and those in the short-axis orientation have been found to be nearly identical (76).

A complete cine examination of the two ventricles provides the basis for 3-D determination of stroke volume (75). In normal volunteers, measurements of stroke volume for the RV and LV, derived from a multilevel cine series using Simpson's method, have been nearly identical (70). Therefore, in the absence of more than one volume-overloading condition affecting the ventricles (i.e., valvular insufficiency or shunt), several quantitative measures of CV pathophysiology can be determined using cine (69). Along with EF, these stroke volume measurements can provide the basis for determination of regurgitant or shunt volume or fraction.

Although ventricular wall thickening may be determined with S-E imaging (79), regional wall motion and thickening are more reliably determined by cine. Cine measures of regional wall thickening correlate well with 2-D echo and LV ventriculography (80). However, cine may be more accurate for defining regional myocardial dysfunction than ventriculography, because the latter depends on the evaluation of wall motion only. Although heterogeneity of systolic wall thickening has been observed on cine in healthy people, absence of systolic wall thickening on MRI has been shown to be a specific marker of regional dysfunction (80). Limitations in the measurement of cardiac chamber wall and cavity dimensions from orthogonal MRI have been emphasized; oblique imaging related to the cardiac axes should improve the precision of linear dimension measurements (i.e., wall thickness and cavity diameter) (38).

A fundamental problem with ventricular volumes and EF as indices of yocardial performance is that they are both dependent on hemodynamic loading conditions (81). Of the approaches to load-independent evaluation of myocardial performance, MRI estimates of ventricular wall stress have received the greatest attention (71,82). The calculation of ventricular wall stress is simplest for meridional stress (the force applied along the length of the ventricle to achieve shortening of that length); an analogous calculation can be used for circumferential stress, the force applied in the circumferential direction in the short-axis plane to achieve circumferential shortening. Cine has been applied for reproducible quantification of LV wall stress at end systole and end diastole, using graphic recordings of the carotid pulse for timing of the cardiac cycle and systemic arterial or ventricular pressure recording (71,82,83). However, when applied to many conditions affecting the LV, the MRI wall stress construct has the following important limitations: (a) it assumes homogeneity of LV function and symmetric geometry, neither of which applies to LV inhomogeneously configured or damaged; (b) it represents a global estimate of average midwall stress, rather than regional pathophysiology; and (c) it overlooks the complexity of the material properties of the myocardium, which is composed of individual fibers with their distribution of orientation varying from region to region and across the wall so that myocardium is anisotropic in its mechanical properties (81).

At the same time, for assessment of regional LV function by MRI, conventional wall-thickening analysis has the following limitations: (a) thickening is not uniform across the wall, with a maximum found in the subendocardium; (b) fiber angle differs across the wall, so that the principal direction of shortening may also vary transmurally; and (c) cardiac motion is complex relative to any single imaging plane, with in-plane deformation, rotational and nonrotational translation, through-plane deformation, and complex translation causing the location of a given segment to change over the cardiac cycle (81). Therefore, both transmural heterogeneity within a wall segment and relocation of the myocardium present in the image plane from end diastole to end systole are important confounding factors in analyzing regional dysfunction by MRI.

Currently, the most precise method for monitoring myocardial motion by MRI is the technique of spin tagging, from which the pattern, amplitude, and rate of displacement of the tags during the cardiac cycle can be used to identify abnormalities in contraction or filling (14,29,81,84). It allows precise tracking of normal and abnormal in-plane rotation and myocardial twist within the wall of a ventricle. Therefore, measurements of wall motion and wall thickening and motion can be corrected for myocardial displacement in 2-D or 3-D space; the problem of through-plane movement can be addressed by 3-D tagging or by tagging in the orthogonal planes (85). In addition, the technique has been used to quantify myocardial deformation as a measure of regional strain (14,86); this provides a method to assess ventricular nonuniformity, and differences in subendocardial and epicardial wall motion, both in normal and abnormal myocardium (84,87).

In the normal LV, 1-D analysis of tag stripe separations has been used to demonstrate that circumferential shortening has a transmural gradient in which subendocardial shortening exceeds subepicardial shortening (84); in addition, the absolute area of 2-D triangular subendocardial elements markedly decreases during systole, probably reflecting phasic alterations in myocardial blood volume that may be a marker of tissue perfusion (81). Whereas there is also a long-axis gradient in circumferential shortening, with shortening greater at the apex than base, there is no transmural gradient for longitudinal shortening; shortening is uniform along the length of the septum and lateral walls. On the other hand, for physiologic LV hypertrophy, reduced circumferential and longitudinal shortening with no change in transmural gradient of circumferential shortening or reduction in EF has been observed. This suggests that analysis of segment shortening is more sensitive to altered myocardial function than are global chamber indices of LV pump function. The coexistence of reduced intramural segment shortening with normal chamber pump function probably relates to the increased ratio of wall thickness to chamber diameter; thus, less shortening per unit from more myocardium results in normal EF (81).

Excellent reproducibility of end diastolic and end systolic wall thickness and percent wall thickening measurements derived with spin tagging have been demonstrated (88). LV wall thickening by spin tagging, especially by the volume method, correlates well with sonomicrometer measurements (87). Epicardial and endocardial cross-fiber strains have been found to be closely related to total wall thickening (89).

One limitation of spin tagging is that it labels only a limited number of points in the myocardial wall. To overcome this limitation, myocardial function can also be examined using phase tracking to directly measure the velocity at each myocardial voxel in the wall (15). Phase-tracking measurements of myocardial displacement have been validated in an animal model using implanted tantalum markers (90). Phasic longitudinal velocity measured in short-axis images in humans has revealed

significant differences in LV myocardial velocity between healthy subjects and patients (91).

A major hindrance to the clinical application of quantitative spin tagging and phase tracking has been the often lengthy data analysis. To overcome this limitation, automated approaches to postprocessing are being developed (92).

Flow Evaluation

Early attempts at flow measurement using S-E MRI were based on the TOF phenomenon (25). In TOF flow quantitation, proton spins are labeled by a 90-degree RF excitation pulse at one level and monitored after a 180-degree refocusing pulse is applied downstream at another level. Consequently, a signal at the downstream level originates only from the labeled spins within the unit of blood that has moved the distance between the excitation and refocusing levels. With knowledge of the time between labeling and readout, the velocity of flow can be determined. This concept of flow quantitation is also used in the dynamic bolus tracking technique, whereby the ECG triggers an initial 90-degree RF excitation pulse for presaturation of a slab of blood flowing perpendicular to the eventual imaging plane (93). Image-data acquisition with an otherwise conventional cine sequence is then performed at an anatomic level oriented with the long axis of the vessel. Tracking of the distance of displacement within vessels during known time intervals permits flow-velocity calculation.

Because the proton spin phase of the MRI signal is directly related to motion, a more practical approach to blood flow analysis is achieved using phase-contrast techniques, especially the aforementioned velocity mapping (10,27,28). In the application of velocity mapping, velocity-encoding limits are set to correspond to 30% to 50% greater than the expected peak velocity in the vessel investigated. For normal arterial blood flow in the aorta and pulmonary arteries, velocity-encoding limits are set at 150 to 200 cm per second. In slow-flow states (e.g., congestive heart failure), these limits may be set lower. Alternatively, to examine areas of stenosis (e.g., coarctation), higher velocity-encoding limits corresponding to 400 or 500 cm per second may be needed; these higher velocity mapping sequences are typically more difficult to perform accurately because of the need for very short TE to overcome rapid phase dispersion in the setting of complex flow (94,95). Velocity mapping may also be used to measure flow in venous structures (e.g., superior vena cava) (96,97); the velocity-encoding limits used for this purpose are typically lower than for arterial studies (e.g., 50 to 75 cm per second).

Velocity mapping is most often used for the assessment of bulk flow. Volume-flow data can be obtained by determining the cross-sectional area of the vessel of interest and multiplying it by the mean instantaneous velocity recorded by velocity mapping within that region (10,27,28). A region of interest applied to encompass the vessel on a magnitude-data image allows determination of the intravascular area (cm^2); this same region of interest over the corresponding velocity mapping image allows direct assessment of the mean flow velocity. This calculation, when performed at each phase represented in the cardiac cycle, may be converted to a flow-volume curve for the vessel of interest (98). An ascending aorta volume-flow curve, for example, can be integrated over the cardiac cycle to calculate stroke of the LV, which can then be used to derive cardiac output (99).

Detailed information on blood velocity profiles in the great arteries can be obtained with velocity mapping (100). On velocity mapping, normal blood flow curves from the ascending aorta typically show systolic increase and then decrease in velocity, followed by reversal of flow in early diastole (98,99). Volume-flow curves of the thoracic aorta, when plotted for the ascending and descending portions, reveal smaller volumes for the descending aorta than those for the ascending aorta because of flow runoff to the head and arms. Measurements of normal volume flow in the ascending aorta and main pulmonary artery obtained with velocity mapping have demonstrated close agreement and have been validated against ventricular volume changes determined by cine (98,99). In addition, when comparisons have been made between velocity mapping determinations of both total systemic venous return per cardiac cycle measured from the venae cavae and stroke volume of the LV measured from the ascending aorta, the correlations have been strong (99).

A stenotic lesion may be assessed by measuring the flow velocity in the jet of blood passing through that stenosis; with a given flow, increasingly stenosis leads to a higher flow velocity at the orifice. The relation between the velocity of the flow jet and the difference in pressure across the stenosis can be approximated, assuming negligible proximal velocity, by the modified Bernoulli's equation (94,95,98,99). This approach can be used to determine the peak instantaneous gradient across the stenosis. However, signal loss on cine found in the presence of stenosis-related turbulence generally indicates insufficient signal for accurate velocity measurement by velocity mapping (60). Fortunately, when short TE velocity mapping sequences have been used, the quantification of jet velocity has correlated well with invasive and noninvasive hemodynamics (101). For this purpose, peak velocity measurements may be obtained by examining those phases corresponding to peak systole. As opposed to determining mean velocities over the entire luminal area, individual pixels or groups of pixels can be evaluated to reveal the peak systolic velocity across the stenotic orifice (99).

Perfusion Evaluation

The development of ultrafast allows the monitoring of the first-pass kinetics of distribution of MRI contrast agents to assess regional tissue perfusion (30). Because currently available Gd chelates equilibrate rapidly in the extracellular space, the demarcation between normally and abnormally perfused myocardium requires rapid imaging to monitor the first passage of the intravenously administered agent. Because of its inherently reduced cardiac motion and enhanced coronary flow, diastole is usually used as the imaging period for these sequences; acquisition of sequential images of diastole during the first pass of a Gd chelate bolus permits the assessment of patterns of myocardial perfusion (31). The feasibility of ultrafast, as well as EPI, for evaluation of myocardial perfusion has been shown in animals (102,103) and in patients (104,105).

Methods for quantifying regional myocardial perfusion by using data acquired during first passage of MRI contrast agent have been proposed (106). In animal models with various grades of coronary stenosis, and after augmentation of flow with a vasodilator, myocardial blood flow has been quantified by analysis of signal intensity versus time curves; the inverse mean transit time of the Gd chelate displayed a linear correlation with absolute blood flow in the myocardium, as measured by microspheres (102). Thus, by treating Gd chelates mainly as extracted tracers, it is possible to measure myocardial perfusion from the pattern of myocardial enhancement. While the model assumes a linear relationship between tracer concentration and signal enhancement, this is only true for these extracellular agents at low concentrations (0.05 or 0.10 mmol per kg), as normally applied in clinical practice (106).

SPECIFIC CLINICAL APPLICATIONS

For the purpose of this discussion, application of MRI to CV diseases presenting in the adult are addressed.

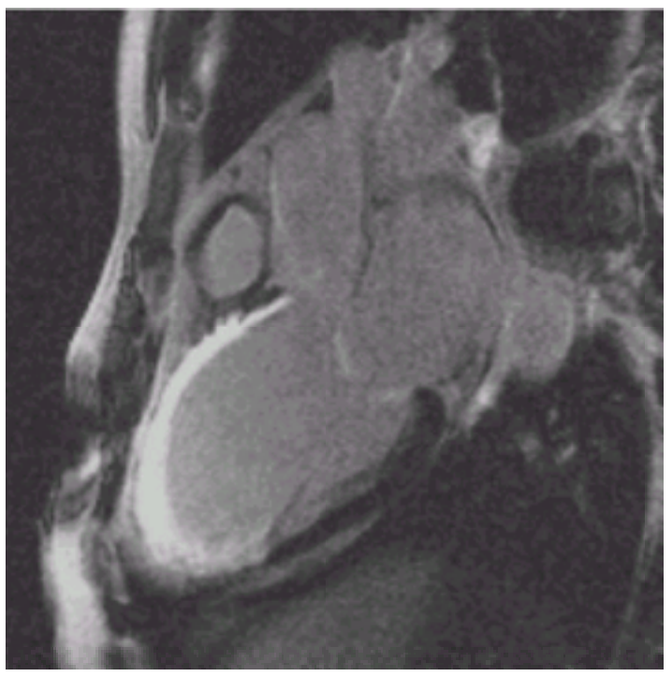
Ischemic Heart Disease

Assessment of Global Ventricular Function

Multiphasic MRI techniques have been used to estimate impaired EF as a result of ischemic heart disease. End diastolic and end systolic images of the LV have been obtained to evaluate EF and the resulting values derived, using the area-length method to correlate with those obtained by single-plane and biplane LV ventriculography (e.g., R = 0.79 and R = 0.95 for parallel and perpendicular to the interventricular septum, respectively) (73,74). Nevertheless, in the presence of LV asymmetry caused by MI with remodeling, formulas for calculating LV volumes by geometric models have serious limitations (107).

VIDEO

Video 54.1 Impaired systolic function and necrosis delineation in a chronic myocardial infarction region (long-axis). The SPAMM (spatial modulation of magnetization) video demonstrates contraction of the left ventricular inferior wall but akinesia of the anterior, apex, and infero-apical segments. The delayed-enhancement image demonstrates transmural hyperenhancement of the segments with impaired systolic function. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Impaired systolic function and necrosis delineation in a chronic myocardial infarction region (long-axis). The SPAMM (spatial modulation of magnetization) video demonstrates contraction of the left ventricular inferior wall but akinesia of the anterior, apex, and infero-apical segments. The delayed-enhancement image demonstrates transmural hyperenhancement of the segments with impaired systolic function.

After MI, LVEF values (determined from transaxial MRI, obtained using a multiphasic multilevel S-E technique) have been shown to correlate well with those from radionuclide or contrast LV ventriculography (108). However, the correlation varied with the damaged region, described by primary coronary artery distribution (e.g., R = 0.87 for right coronary artery and R = 0.48 for left anterior descending distributions). A semiquantitative measure of global post-MI LV function, based on segmental wall motion scoring from transaxial multiphasic multilevel images, also correlated regionally with ventriculographic EF values (e.g., R = 0.96 for left anterior descending and R = 0.62 for right coronary artery distributions) (38). Such regional variations have been attributed to the limitations of orthogonal imaging, including poor visualization of the undersurface of the LV adjacent to the diaphragm. This limitation is overcome when short-axis imaging is used.

Multilevel-multiphasic MRI for EF determination in patients with ischemic heart disease can be performed more efficiently and with better temporal resolution using cine (68,71,76). In patients imaged within 7 days of acute MI using cine, LVEF by MRI has been shown to correlate better with EF by contrast ventriculography (e.g., R = 0.94) than with EF by radionuclide ventriculography (e.g., R = 0.82) (109).

Despite its advantages, MRI continues to have difficulties in gaining acceptance in the assessment of ventricular volumes and function in patients with ischemic heart disease because of a lack of general availability of dedicated CV MRI services with full capabilities for performing the functional aspects of cardiac imaging, and the wider availability and general familiarity with echo (107). Although the precision and the reproducibility of echo measurements are less than those achieved with MRI, echo information generally can be relied on for clinical management.

Assessment of Regional Ventricular Function

Abnormal wall motion, and more specifically abnormal systolic thickening, in the LV indicates diminished regional myocardial function (110). Regional myocardial wall thickening abnormalities are frequently observed on MRI in association with ischemic heart disease, starting as early as 5 minutes after coronary artery occlusion (111).

Compared with other criteria, such as increased myocardial intensity and adjacent intracavitary blood signal, regional wall motion abnormality appears to be the most predictive and specific MRI finding associated with either a recent or remote MI (112). By analyzing the outline of the endocardial and epicardial borders on images acquired at various segments of the cardiac cycle using the different multiphasic MRI techniques, regions of hypokinesia, akinesia, or dyskinesia, accompanied by increasing degrees of impaired wall thickening, can be defined clinically (69,80,108). For the detection of a recent MI, using a multiphasic multilevel S-E MRI technique, sensitivity, specificity, and accuracy are improved when wall motion abnormalities are used along with myocardial intensity increase (e.g., 93%, 80%, and 87%, respectively) rather than intensity increase alone (e.g., 80%, 80%, and 80%, respectively) (113).

Regions of decreased LV systolic wall thickening caused by ischemic heart disease can be identified and quantitated using the various multiphasic S-E MRI techniques. Employing transaxial imaging and a multiphasic multilevel S-E MRI technique, absolute and percent wall thickening has been assessed in various cardiac diseases, including ischemic heart disease; MRI consistently demonstrated decreased systolic wall thickening measurements in regions damaged by MI when compared with normal myocardial regions in the same patients, and with the LV wall in normal individuals (38,79). When concurrent multilevel multiphasic S-E MRI and 2-D echo examinations of patients with a single MI were evaluated using a segment-by-segment point scoring of residual wall thickening, most of the LV segments, representing the left anterior descending distribution, showed significant agreement (38). In experimentally evaluating regional LV contractility in comparison with histochemical evidence of MI, determinations of mean maximal percent systolic thickening have been found to be significantly decreased in induced MI regions; with high sensitivity and moderate specificity, the same MRI approach identified reduced systolic wall thickening in segments recognized as akinetic or dyskinetic by LV ventriculography in patients with a history of MI (114).

More so than multiphasic S-E techniques, cine is suited to the evaluation of regional ventricular function in patients with ischemic heart disease (69,80,109,110). Assessments of LV wall motion by cine in patients with coronary artery disease (CAD) have correlated well with results of echo or LV ventriculography (80); impaired systolic wall thickening has proved to be a very specific marker of regional myocardial dysfunction (Fig. 54.1). Compared with contrast ventriculography, the concordance in regional wall motion has been similar for both cine (e.g., 69%) and radionuclide ventriculography (e.g., 65%) (109). Although a multilevel cine series gives the advantage of full representation of the ventricles, when patients with suspected CAD have been studied using only biplane cine and biplane LV ventriculography, 96% agreement in the right anterior oblique view and 92% agreement in the left anterior oblique view have been demonstrated (115).

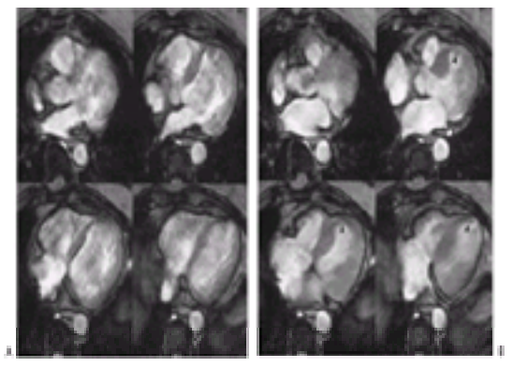
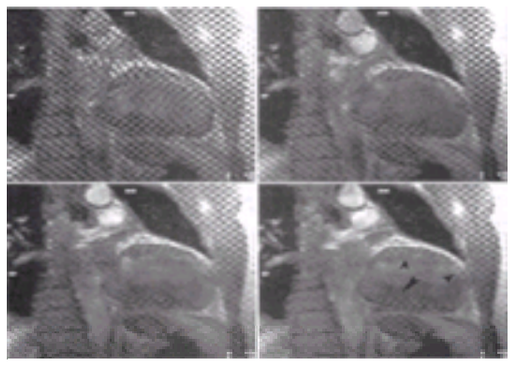


FIGURE 54.1 Regional myocardial dysfunction from coronary artery disease (cine; transaxial). From end diastole **(A)** to end systole **(B)**, four adjacent levels of the left ventricle reveal decreased anteroseptal and anteroapical wall thickening (*arrowheads*) from disease of the left anterior descending coronary artery.

Absence of systolic wall thickening in the presence of passive inward wall motion, which is potentially mistaken for hypokinetic viable myocardium on ventriculography, is detectable in MI regions on MRI because of direct LV wall visualization. Wall thickening of greater than 2 mm has been measured in all regions of the normal LV on cine; less thickening has been demonstrated at sites of prior MI (80,116,117 and 118). Cine has proved to be more accurate than echo in the measurement of LV systolic wall thickening (119).

More recently, myocardial tagging has been used to provide unique functional information about regions of MI and compensatory changes of noninfarcted portions of the LV (eFig. 54.1.1) (120). In patients with one-vessel disease leading to an acute MI, reduced intramyocardial circumferential shortening has been noted throughout the LV, including remote noninfarcted regions (121). Using SPAMM, LV dilatation and eccentric hypertrophy from remodeling have been shown to be associated with

persistent differences in segmental function and wall stress between adjacent and remote noninfarcted myocardium (121).



***e*FIGURE 54.1.1** Impaired systolic function in myocardial infarction region and compensatory changes in noninfarcted regions (spatial modulation of magnetization, two-chamber long axis). Decreased grid deformation in the infarcted anterior wall (*small arrowheads*) contrasts with the noninfarcted, hypertrophic inferior wall where deformation is preserved (*large arrowhead*).

Although the determination of wall motion, thickening, and mechanics by these forms of multiphasic MRI may eventually play an important role in the accurate detection and functional characterization of myocardial ischemia in patients with suspected or known CAD (122), their routine clinical use has been limited because of the aforementioned reasons.

Complications and Natural History of Myocardial Infarction

Tissue characterization by MRI has shown an inverse relationship between relaxation times and flow during experimental coronary artery occlusion (123). Acute MI is characterized by prolonged T1 and T2 (111,112 and 113,124). The alteration in relaxation times, and the associated signal increase, in acutely infarcted myocardium seems to primarily represent edema resulting from acute, irreversible ischemia (125). In addition, following an acute MI, maximum T1 values are observed at 2 weeks after the event, suggesting that cellular infiltration also contributes significantly to the appearance (126). However, other factors (e.g., hemorrhage, loss of myocyte membrane integrity, increased triglyceride content, free radicals, changes in magnetic susceptibility) also presumably contribute to the prolonged relaxation times (127).

Although an *in vivo* determination of these relaxation times is calculated from signal intensities detected on MRI, intensity does not depend only on T1 and T2 but, rather, is related to other physiologic characteristics (e.g., movement). Therefore, image-derived quantitation of the relaxation times for clinical purposes is influenced by hemodynamics and by cardiac and respiratory motions; hence, the obtained values for relaxation times differ from *ex vivo* measurements and are less reliable (111,112 and 113).

Nevertheless, increase in relative myocardial intensity is routinely seen as early as 30 minutes, but almost certainly 3 to 6 hours, after coronary occlusion when MI has occurred (113,124). The intensity reaches a maximum after 3 days, but then tends to decline after 20 days (113,128). Because T2 is prolonged, helping to enhance intensity in the region of an acute MI, the contrast between the MI region and normal regions is optimized on T2-weighted images (113,124).

Regional increase in S-E myocardial intensity, indicating acute MI (Fig. 54.2), has corresponded with the ECG location of the MI (113), enzymatic indicators (129), the presence of hypokinetic segments on ventriculography (113,129), and nuclear perfusion defects at rest (130). Although this characteristic pattern of myocardial S-E intensity is often noted in clinical cases during the first 2 weeks after MI, there are pitfalls in the clinical application of alterations in signal intensity (112). Increased myocardial intensity on T2-weighted images may be difficult to distinguish from slowly moving intraventricular blood (131), and it has been noted that T2 prolongation might not be a specific marker for acute MI and can also be observed in abnormally perfused myocardial segments of patients with unstable angina (132). In addition, increased intensity may often be seen in normal individuals, thereby reducing its value as a marker of MI. Thus, although the increased intensity of MI regions on S-E MRI can be considered a sensitive finding, it is of low specificity (112).

FIGURE 54.2 Regional increase in myocardial intensity from acute myocardial infarction (T2-weighted spin-echo; transaxial). Increased myocardial signal intensity in interventricular septum and anterior wall (*asterisk*) is caused by edema from an acute myocardial infarction.

Findings consistent with hemorrhagic MI have also been detected *ex vivo* on S-E imaging (133). Regions of decreased signal intensity, histologically proven to be hemorrhage, have been noted adjacent to or within the central zone of increased intensity that represents acute MI; good correlation has been found between the volume of hemorrhage measured at postmortem examination and the volume of such decreased signal intensity. The decreased myocardial intensity results from T2 enhancement produced by deoxyhemoglobin (134).

The use of Gd chelates enhances the ability to visualize a region of MI on T1-weighted S-E images (66,135,136), and it may also result in a higher specificity in detecting MI (137). Gd chelates at lower doses mainly shorten T1 of the myocardium and, because of the different washout rates, increase the contrast between MI and normal regions on T1-weighted images. *Ex vivo* MRI of perfused hearts using Gd chelates has shown increased contrast between normal and reperfused ischemic myocardium, when compared with both nonreperfused ischemic hearts after Gd chelate administration and reperfused ischemic hearts not given Gd chelate (138). However, this distinction has been less evident on S-E MRI performed *in vivo*.

The appearance of an acute MI after the injection of contrast media is regulated by whether images are acquired during the initial or early passage of the contrast media through the heart or during the equilibrium phase (66). The appearance also depends on the age of the MI, the dose of the medium, and the sequences applied (107). During the first pass, there is delayed entrance of the contrast medium into the ischemic region. Consequently, the region supplied by an occluded artery shows lower signal intensity than normal myocardium during the first few minutes after injection of a Gd chelate (107) (eFig. 54.2.1). On the other hand, there is greater enhancement of intensity of the MI region using T1-weighted images acquired during the equilibrium phase of distribution, because of a delayed washout of the medium in the occluded area or the enlarged extracellular space of the MI region (135,136); the differentiation persists 30 minutes after injection (137).

***e*FIGURE 54.2.1** Impaired perfusion of myocardium (short axis). There is a rapid first-pass enhancement of right ventricle cavity, left ventricle cavity, and then left ventricle viable myocardium by a bolus of gadolinium-diethylenetriaminepentaacetic acid. A region of no enhancement is visible in the anteroseptal wall, representing impaired myocardial perfusion at rest caused by an occlusion of the left anterior descending artery.

Although in patients, significantly greater myocardial intensity enhancement results from Gd chelate (i.e., 66% to 70% increase) in regions of MI when compared with normal regions (i.e., 20% to 35% increase) on T1-weighted images (136,137), it is not true on T2-weighted images (139). Because contrast between acute MI and normal regions is increased (e.g., 6% and 39% before and after Gd chelate, respectively), improved clinical discrimination has been possible, allowing for a more accurate diagnosis of MI (135,137,138). A new delayed-enhancement MRI technique (Turbo FLASH with inversion recovery) has been applied to study both acute and chronic MI after the administration of Gd chelate and has shown an excellent correlation with TTC staining histology in animal models (139). The sequence is employed 15 to 30 minutes after the injection of a double dose (0.2 mmol per kg) of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA), and the area of necrosis is delineated as an area of hyperenhancement and viable myocardium as an area of nulled signal (Fig. 54.3 and *e*Fig. 54.3.1).

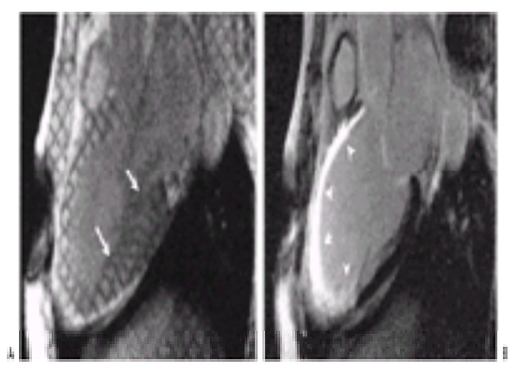
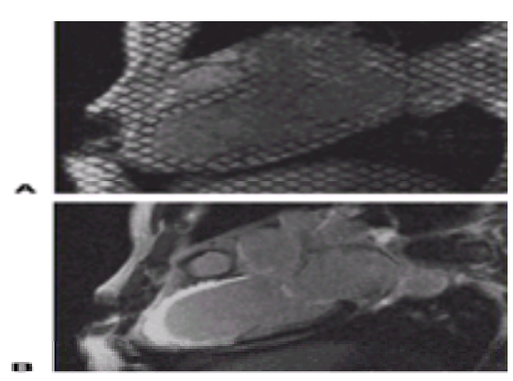


FIGURE 54.3 Delayed-enhancement magnetic resonance image of chronic myocardial infarction [spatial modulation of magnetization (SPAMM); Turbo FLASH with inversion recovery; long axis]. At end systole a SPAMM image **(A)** demonstrates contraction (*arrows*) (deformation of grid pattern with change from square to diamond shape) of the left ventricle inferior wall. Delayed-enhancement image **(B)** demonstrates transmural hyperenhancement of the anterior wall, apex, and apical inferior wall (*arrowheads*) caused by myocardial necrosis, corresponding to the area of absent contraction on the SPAMM image.



***e*FIGURE 54.3.1** Impaired systolic function and necrosis delineation in chronic myocardial infarction region (long axis). The spatial modulation of magnetization image **(A)** demonstrates contraction of the left ventricle inferior wall but akinesia of the anterior, apex, and inferoapical segments. The delayed-enhancement image **(B)** demonstrates transmural hyperenhancement of the segments with impaired systolic function.

Although a number of experimental and clinical studies have shown that MRI contrast agents improve the demarcation between acute or subacute MI and normal myocardium, it has been accomplished for a chronic MI (140). In addition, despite encouraging initial results, it has been shown that signal intensities measured 25 minutes after Gd chelate administration differentiate reperfused from nonreperfused MI when the delayed-enhancement technique is employed (140). In patients status-post thrombolytic therapy for acute MI, measured intensity ratios 6 to 8 minutes after injection of Gd chelate have been shown to be significantly different from those of MI regions subtended by occluded coronary arteries, indicating that assessment of the early dynamics of contrast enhancement using Gd chelates may identify successful reperfusion (138). It has also been shown that the morphologic appearance of contrast enhancement by Gd chelates may identify the presence or absence of reperfusion; reperfusion leads to no enhancement, whereas lack of reperfusion may be visualized as a hyperenhancement (140,141).

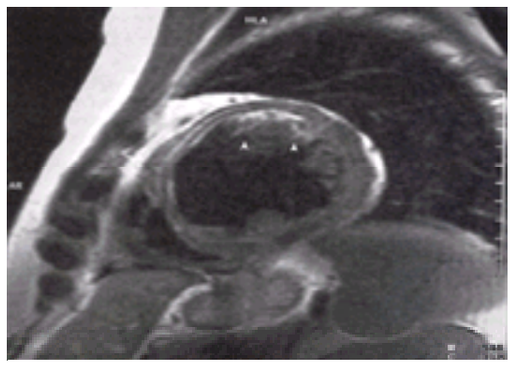
Chronic MI produces regions characterized by shortened T2 and decreased intensity on routine S-E and G-E imaging consistent with the replacement of myocardium with fibrous tissue (142). On ultrafast for first-pass assessment, 50% enhancement of chronic MI regions, compared with 134% in normal regions, has been observed after Gd chelate administration; the MI site on MRI corresponded with the location of wall motion abnormality on echo (143).

In addition to increased relaxation times, other morphologic MRI features of MI are valuable diagnostic parameters. Areas of thinning of the LV wall caused by remote MI are sharply demarcated from myocardium that is of normal thickness (130,142,144). Regional abnormalities are delineated better on systolic images than on diastolic images, because there is an accentuated disparity in the wall thickness. Compared with increased myocardial intensity and abnormal cavitary signal, relative regional wall thinning has been found to be the most predictive and specific marker for the presence of an acute MI during clinical evaluation by MRI (112).

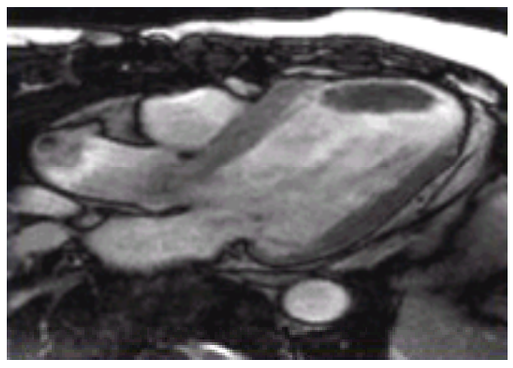
Damage to the LV wall segments is often indicated by intracavitary stagnant blood and thrombotic material (*e*Fig. 54.3.2). These intracavitary areas appear as abnormal signal on S-E and cine MRI (49,77,145). With S-E MRI, the differentiation between these two causes of such signal may be made, as described earlier, from multiple S-E magnitude-data images or the corresponding phase-display images. The presence of even-echo rephasing or significant motion-dependent phase changes indicates slow blood flow; the absence of these changes accompanies thrombus (146). On cine, their differentiation is achieved by finding fluctuating areas of intermediate signal loss (i.e., indicating slow blood flow) or fixed lower intensity areas (i.e., indicating thrombus) on the image loop (63) (*e*Fig. 54.3.3).

Video 54.2 Post–myocardial infarction true aneurysm (long-axis). Dyskinesia and thinning of the left ventricular apex due to an occlusion of left anterior descending artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 54.3 Post–myocardial infarction pseudoaneurysm (short-axis). Rupture of the inferolateral wall of the left ventricle due to circumflex artery occlusion. The pseudoaneurysm cavity is contained by pericardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 54.3.2** Intracavitary stagnant blood adjacent to the region of left ventricle wall damage (T1-weighted spin-echo; short axis). Bright intracavitary signal from stagnant flow (*arrowheads*) is noted along the thinned anterior myocardial infarction region of the left ventricle wall.



***e*FIGURE 54.3.3** Post–myocardial infarction apical thrombus (long axis). Akinesia of thin apical wall with adjacent thrombus.

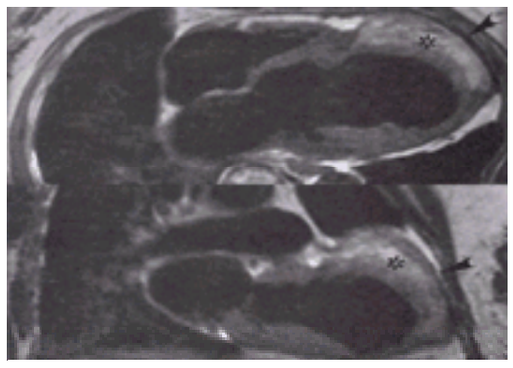
Because of its therapeutic and prognostic importance, MI sizing by MRI has been pursued. *Ex vivo* and *in vivo* measurements of relative MI size (i.e., percent LV), based on changes in myocardial signal parameters such as intensity on T2-weighted images after experimental coronary artery occlusion, have correlated closely with postmortem estimates (147). However, S-E imaging without the administration of contrast has tended to overestimate MI size and to demonstrate abnormal intensity extending well beyond the margins of the MI found on pathologic evaluation, suggesting that T2-weighted S-E MRI depicts not only MI damage but also some reversibly injured myocardium (148). In addition, MRI-determined MI size has correlated well with microsphere-determined reduction of blood flow of 25% or more (122). But with the new delayed-enhancement technique, an excellent correlation has been shown between MRI images and histology, either in acute or chronic MI (139).

Clinical MI size determinations, based on intensity at a mean of 9 days after the acute onset of symptoms, have been shown to correlate well with the region of severe hypokinesia visualized by ventriculography (113). Good agreement has been found between MI sizing based on T1 MRI maps and assessment by infarct-avid scintigraphy and ventriculography 5 to 7 days after MI (149). In addition, mean MI volume, based on signal changes, correlated well with segmentally quantitated dysfunction by ventriculography. In the setting of a recent MI, studied 5 to 20 days after the acute event, T2-weighted S-E MRI allows for the direct assessment of MI location and size (150).

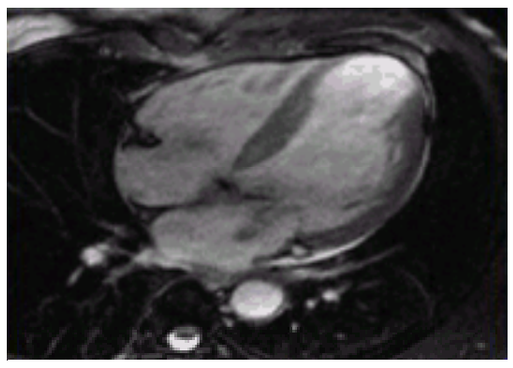
A good correlation between MI size measured with contrast-enhanced MRI and enzymatically determined MI size, 3 to 7 days after the acute event, has been demonstrated (151). Also, Gd chelates produce markedly increased myocardial intensity that correlates well with extent of acute or chronic MI on the delayed-enhancement MRI (139,140).

Another approach to evaluate MI may well be a correlation with the extent of regional wall thinning. Clinically, MI size has been measured based on regional LV wall thinning and dysfunction noted on multiphasic multilevel S-E MRI, and the resulting values correlated inversely with EF determinations by ventriculography (e.g., R = 0.88) (108). Nevertheless, significant reduction in MI size, based on myocardial signal on S-E MRI with (152) or without (153) contrast enhancement, has been shown in patients who did, compared with those who did not, receive intravenous streptokinase within hours of the onset of chest pain related to an acute MI.

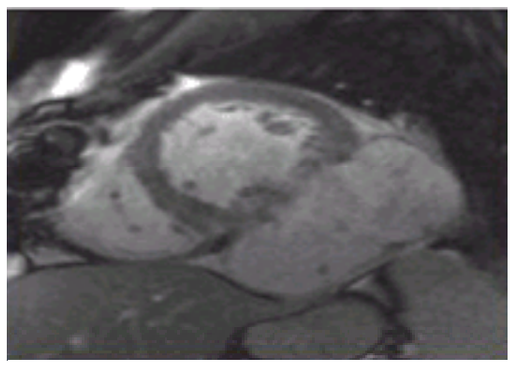
MRI is also capable of detecting long-term sequelae of MI. Complications of acute MI including ventricular aneurysm (*e*Fig. 54.3.4), ventricular septal perforation (154), mitral regurgitation, and LV thrombus also can be readily demonstrated by MRI (107,122). Post-MI LV aneurysms are identified as outwardly protruding myocardial wall segments associated with marked transmural thinning and occasionally mural thrombus (142,144). A true aneurysm (i.e., relatively wide neck,) can usually be differentiated from a pseudoaneurysm (i.e., relatively narrow neck), based on the relative size of the communication between the aneurysmal cavity and the main LV cavity (155,156) (*e*Fig. 54.3.5 and *e*Fig. 54.3.6).



***e*FIGURE 54.3.4** Post–myocardial infarction left ventricle aneurysm (T1-weighted spin-echo; horizontal and vertical long axis). Aneurysmal bulging of the anteroapical region (*arrowheads*) of the left ventricle wall contains a layered thrombus of variable age (*asterisks*).



***e*FIGURE 54.3.5** Post–myocardial infarction true aneurysm (long axis). Dyskinesia and thinning of the left ventricle apex caused by an occlusion of left anterior descending artery.



***e*FIGURE 54.3.6** Post–myocardial infarction pseudoaneurysm (short axis). Rupture of the inferolateral wall of the left ventricle caused by circumflex artery occlusion. The pseudoaneurysm cavity is contained by pericardium.

Although therapy is focused on minimizing the deleterious remodeling process in the LV after MI, imaging modalities have not been routinely used to guide or to assess the effect of this therapy (107). MRI used to show remodeling of the LV after acute MI (157), and attenuation of the remodeling process in response to drug therapy has been documented experimentally (158). In patients, cine has provided accurate quantification of myocardial mass of the abnormally shaped LV caused by a transmural MI (159).

In spite of the recognition that MRI can be used to evaluate many aspects of MI, there has been limited clinical use of it for these purposes (107). Perhaps the reason for this is that LV shape changes and complications after acute MI are well shown by echo, although MRI is able to produce a 3-D view of the LV and define with extreme accuracy the extension and size of MI.

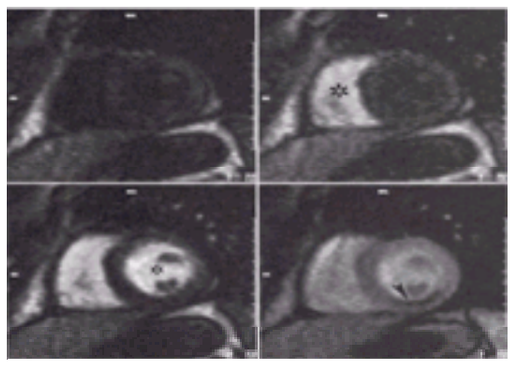
Assessment of Ischemia

Myocardial ischemia, like MI, is associated with increased myocardial signal as a result of prolonged relaxation times (160), and correlations have been observed between increases in T1 and T2 and the increase in tissue water content (161). However, in the clinical setting, the detection of myocardial intensity changes from induced reversible ischemia, moreover ischemia at rest, has not been reliable without the administration of Gd chelate. In contrast to irreversibly injured myocardium, reversibly ischemic myocardium does not necessarily alter myocardial relaxation times or intensity in the early phase. In unstable angina, S-E MRI has occasionally shown significantly increased T2 in reversibly ischemic myocardium. It also failed to distinguish reversibly from irreversibly ischemic regions, as determined by nuclear perfusion imaging (132). The detection of acute ischemia with unenhanced MRI does not occur until several hours after coronary occlusion.

The detection of myocardial ischemia by any imaging modality frequently requires some form of stress to induce disparity in blood flow between normal and potentially ischemic regions. In more recent years, pharmacologic stress has been applied in MRI for detection of functional abnormalities in patients with CAD, because physical exercise during MRI is difficult because of space restriction and it results in motion artifact. The agents used for this purpose increase flow by causing either direct coronary vasodilatation or secondary vasodilatation caused by augmented myocardial oxygen requirements, or both; regional myocardial dysfunction is then caused by either an absolute decrease in regional perfusion (i.e., coronary steal phenomenon) or inadequate increase in flow relative to augmented oxygen requirements (i.e., increased myocardial work) (107).

Using ultrafast, the assessment of myocardial blood flow in normal, reversibly ischemic and irreversibly ischemic myocardium, at rest and during dipyridamole-induced hyperemia, has been validated experimentally (102). With dipyridamole as the vasodilator, a direct relation has been found between myocardial blood flow and signal intensity after administration of Gd chelates (162). These experimental studies have stimulated the application of ultrafast in patients with CAD.

Applying ultrafast to patients with or without the use of pharmacologic stress, myocardial regions perfused by a severely stenosed coronary artery can be detected by an abnormal pattern of change in myocardial intensity. Several differences in intensity versus time curves between the normally perfused segments and the segments supplied by stenotic arteries have been observed after the bolus administration of Gd chelates (163). Some investigators have qualitatively observed an abnormal delay in signal increase of the hypoperfused myocardium; these areas have been shown to correlate well with abnormal areas shown on nuclear perfusion imaging (*e*Fig. 54.3.7) (106). Others have shown that regions with reduced perfusion can be quantitatively characterized on ultrafast, as areas of reduced peak intensity and diminished upslope of the intensity versus time curve compared with normal myocardium (163).



***e*FIGURE 54.3.7** Abnormal delay in signal increase of hypoperfused myocardium (ultrafast; short axis). First-pass enhancement of the right ventricle cavity (*large asterisk, top right*), followed by the left ventricle cavity (*small asterisk, bottom left*), and then the left ventricle myocardium by a bolus of gadolinium chelate is demonstrated on the sequential diastolic images. A region of delayed enhancement in the inferior wall (*arrowhead*) represents impaired myocardial perfusion at rest, caused by a high-grade stenosis of the distal right coronary artery.

Ultrafast for the resting assessment of patients with CAD before and after revascularization has demonstrated improvement in peak intensity and rate of signal increase in myocardium perfused by the treated vessel (163). However, ultrafast has more often been used during the peak effects of dipyridamole (Fig. 54.4) (164). When patients with CAD have been studied using Gd chelate-enhanced ultrafast and dipyridamole stress, sensitivity, specificity, and accuracy of 65%, 76%, and 74%,

respectively, have been noted (104).

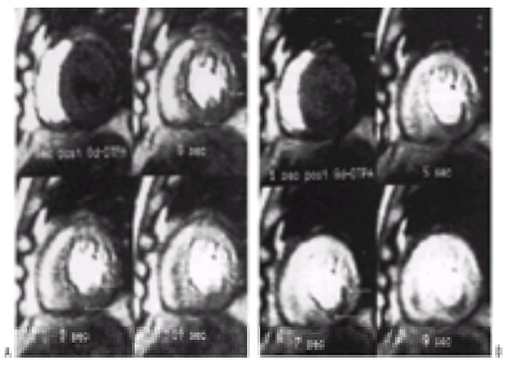


FIGURE 54.4 Dipyridamole-induced hypoperfusion in myocardial ischemia (ultrafast, short axis). On sequential diastolic images at rest **(A)**, only a moderate lack of signal enhancement is detected in the posterior wall of the left ventricle (*arrows*); this is caused by asymptomatic retrograde-filled occlusion of the right coronary artery. Following administration of dipyridamole **(B)**, resulting in angina, decreased signal intensity around the subendocardial layers (*arrows*) of the posterior wall is clearly differentiated from the higher signal intensity of the normal myocardium. Gd-DTPA, gadolinium-diethylenetriaminepentaacetic acid. (From Wilke N, Jerosch-Herold M, Stillman AE, et al. Concepts of myocardial perfusion imaging in magnetic resonance imaging. *Magn Reson Q* 1994;10:249, with permission.)

The limitation of all studies using ultrafast imaging is that the LV can be only partially sampled (usually 3 to 5 anatomic levels) while maintaining adequate temporal resolution (image at each level at 2- to 3-second intervals), whereas higher speed methods would allow multislice tomography to generate a 3-D perspective. Experimentally, EPI has been used to monitor the first pass of Gd chelates in hearts of normal animals and those with coronary occlusion (103) but has not yet been applied clinically. The results in animals and in humans suggest that perfusion imaging by MRI could become an important tool in the diagnosis of ischemic heart disease. A conclusion about the importance of perfusion MRI in relation to nuclear perfusion studies must await further publications (107).

An alternative to the assessment of perfusion abnormalities for the assessment of myocardial ischemia is the detection of reversible LV contractile dysfunction by multiphasic MRI. Multiphasic MRI may show regional LV dysfunction associated with induced reversible ischemia. In patients with known CAD and induced defects on nuclear perfusion examinations, corresponding regional LV functional abnormalities have been noted on MRI after administration of dipyridamole; these wall motion abnormalities occurred at the site of more extensive thallium defects and were associated with chest pain and more severe CAD (164). The 84% sensitivity and 89% specificity of dipyridamole-stress cine resembles that of stress nuclear perfusion imaging for detecting hemodynamically significant stenoses at coronary arteriography (165).

Compared with dipyridamole, dobutamine appears to be a more appropriate agent for eliciting wall motion abnormalities; dobutamine infusion is well tolerated during MRI (166). Cine has been used to visualize wall motion or wall-thickening abnormalities in the potentially ischemic myocardium provoked by dobutamine (Fig. 54.5) (117,166). In patients with CAD studied by both dobutamine-stress cine and nuclear perfusion imaging, comparison of perfusion defects and wall motion abnormalities showed 90% agreement (117,167). Studies of patients referred for coronary arteriography have shown that dobutamine-stress cine can identify wall motion abnormalities by such quantitative analysis with sensitivity, specificity, and accuracy of 91%, 80%, and 90%, respectively; the sensitivity for detection of one-vessel disease was 88%, two-vessel disease 91%, and three-vessel disease 100% (168). Dobutamine-stress MRI has been compared with dobutamine-stress echo and showed similar accuracy, but when echo images were suboptimal, the MRI accuracy was significantly higher than echo (169). Furthermore, dobutamine-stress MRI has been used in patients with poor acoustic window and not well suited for second harmonic stress echo, generating an accuracy of 83% when compared with coronary angiography (170).

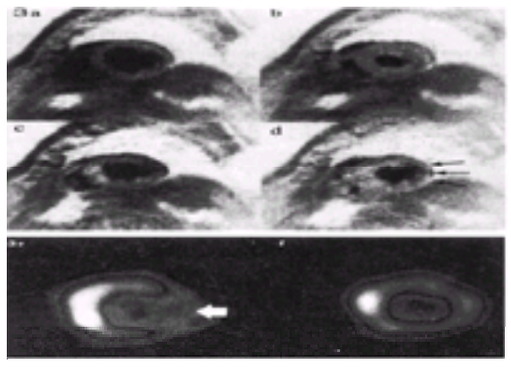


FIGURE 54.5 Dobutamine-induced contractile dysfunction in myocardial ischemia (cine and thallium single photon emission computed tomography, short axis). On end diastolic, **(left, 3a, 3c)** and end systolic **(right, 3b, 3d)** cine images (displayed in negative format) at rest **(above)**, baseline contraction is normal in all regions of the left ventricle. During dobutamine administration **(below, 3c, 3d)**, decreased systolic motion and wall thickening are noted in the lateral free wall of the left ventricle (*arrows*); these are caused by left circumflex coronary artery disease. Corresponding thallium single photon emission computed tomography images during stress **(3e)** and after redistribution **(3f)** demonstrate a reversible lateral free-wall perfusion defect (*large arrow*) corresponding to the wall motion abnormality on cine. (From Pennell DJ, Underwood SR, Manzara CC, et al. Magnetic resonance imaging during dobutamine stress in coronary artery disease. *Am J Cardiol* 1992;70:34, with permission.)

Myocardial tagging may improve the accuracy of MRI with dobutamine stress to detect regional dysfunction, including that limited to the subendocardium. However, to date, this application has been largely investigational in animal models.

Stress MRI is becoming an important tool for diagnosis of myocardial ischemia due to its capability of excellent spatial resolution and been able to define the endocardial border with high accuracy (166,167,168,169 and 170).

Assessment of Myocardial Viability

The distinction between viable and nonviable myocardium after MI is an important determinant of therapeutic options. The effectiveness of MRI in assessing the complete area at risk following acute coronary occlusion may depend on the use of MRI contrast agents to delineate the volume of jeopardized myocardium. Work in animal models has shown that the region of increased myocardial intensity correlates with the bed of myocardium at risk in reperfused myocardium, when Gd chelate is injected after 5 minutes of reperfusion (171). Also, with late injection (e.g., 15 to 30 minutes), an excellent correlation is noted if the delayed-enhancement technique is employed (139,140).

Ultrafast, during administration of Gd chelates, has been shown to provide clear differentiation between an occlusive (i.e., nonenhancing) and a reperfused (i.e., enhancing) MI (172) and between reversible and irreversible injuries in reperfused myocardium in experimental models (173). Although reperfused reversibly injured myocardium shows no significant difference in intensity compared with normal myocardium, irreversibly injured reperfused myocardium shows a substantial increase in intensity during equilibrium, probably as a result of greater distribution space for the contrast media in the jeopardized region because of expansion of the extracellular space (173). An occlusive MI shows a significantly greater enhancement of the peripheral zone than of the central zone, whereas reperfused MI shows homogeneous enhancement of the injured zone (173). EPI has also been used to compare the first pass of a Gd chelate in occluded and reperfused MI (174).

These studies performed in various animal models have been promising in characterizing different types of myocardial injuries, and studies in patients with an occlusive MI or a reperfused MI have shown that contrast-enhanced MRI with a delayed-enhancement technique is effective in differentiating between these two types of myocardial injury (175). When clinical results of delayed enhancement have been compared with positron emission tomography and dobutamine-stress echo, concordant results have been observed, and a correlation has been observed between the amount of enhancement transmurally and the percentage of nonviable segments determined by both techniques (176).

The capability of basic forms of MRI such as cine to provide functional information about myocardium in combination with assessment of diastolic wall thickness and systolic wall thickening makes it suitable for identification of myocardial viability (177). Regional end diastolic wall thickness of less than 6 mm and end systolic wall thickening of less than 1 mm on cine have been identified as features of nonviable myocardium, as defined by nuclear perfusion or metabolism imaging (178,179). A comparison of cine with low-dose dobutamine stress with positron emission tomography in patients with chronic MI showed that use of these parameters was accurate in assessing myocardial viability; wall thickening was found to be a better predictor (e.g., 96% positive predictive value) of residual metabolic activity than was end diastolic wall thickness (Fig. 54.6) (179). Cine and transesophageal echo with dobutamine stress have been assessed for their relative ability to detect induced contraction reserve; when results of each were compared against segmental assessments of viability by positron emission tomography, the sensitivities were 81% and 77% and the specificities were 100% and 94%, respectively (180).

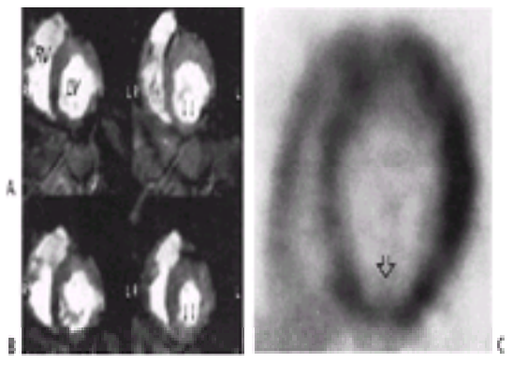


FIGURE 54.6 Post–myocardial infarction myocardial viability (cine and fluorine-18-fluorodeoxyglucose positron emission tomography; short axis). Despite an inferior myocardial infarction (*closed arrows*), viability in the injured region is represented on end diastolic **(left)** and end systolic **(right)** cine images by dobutamine-induced systolic wall thickening **(B)** of the akinetic-appearing inferior wall at rest **(A)**. The positron emission tomographic image **(C)** demonstrates preserved metabolism in the same region (*open arrow*). [From Baer FM, Voth E, Schneider CA, et al. Comparison of low-dose dobutamine-gradient-echo magnetic resonance imaging and positron emission tomography with (18F) fluorodeoxyglucose in patients with chronic coronary artery disease: a functional and morphological approach to the detection of residual myocardial viability. *Circulation* 1995;91:1006, with permission.]

Direct Assessment of Coronary Arteries

Noninvasive visualization of the coronary arteries is one of the ultimate challenges for MRI (122). Imaging of the coronary arteries by MRI has received a great deal of attention since the beginning of clinical CV MRI (181). Visualization of the coronary arteries with standard MRI approaches has been erratic and limited to the proximal segments of the vessels (181,182); only occasionally have readily recognizable vascular abnormalities been identified. Nevertheless, in the cardiac cycle between rapid filling in early diastole and atrial systole, there is a period of relative diastasis with high coronary flow; this has become a target for the many more recently introduced approaches to MRI of the coronary arteries employing static versus dynamic, structural versus flow-based, 2-D versus 3-D, and other variations (183).

Although angiographic forms of MRI are routinely used clinically for evaluation of the carotid and intracerebral vasculature, the great vessels of the chest and abdomen, and the arteries and veins of the extremities (40), angiography of the coronary arteries by MRI remains investigational. This is because of the greater technical difficulties related to the relatively small size of these arteries, their complex 3-D anatomy, normal cyclic variations in coronary flow, competing signal from neighboring blood pools, and their constantly changing position within the chest caused by cardiac and respiratory motion (107,122). To overcome these obstacles, several approaches have been proposed and have already achieved some success (183). To date, the greatest experience has been with 2-D G-E MRI with fat saturation to eliminate signal from adjacent adipose tissue and segmented k-space acquisition, allowing imaging at one level during a breath-hold to avoid excessive blurring from respiratory motion (184).

With the 2-D G-E approach, good visualization of all major vessels in healthy subjects has been reported (185), and good correlation between measurements made by MRA and coronary arteriography has been established (186). In patients with CAD, occluded coronary arteries have appeared on such MRA images as absent flow signal distal to the occlusion, while high-grade stenoses showed signal loss in the area of stenosis with visualization of the vessel distally (Fig. 54.7). Initial clinical work with the approach resulted in optimism about identifying hemodynamically significant stenoses (i.e., ³50% narrowing) of major coronary arteries. Using selective coronary arteriography as the gold standard, MRI-based angiography had 90% sensitivity and 92% specificity for identifying a diseased epicardial coronary artery on blinded analysis, although correspondence between lesion location within an individual coronary artery was not assessed; the corresponding positive and negative predictive values were 85% and 95%, respectively (187). The sensitivity and specificity of the technique were, respectively, 100% and 100% for the left main coronary artery, 87% and 92% for the left anterior descending artery, 71% and 90% for the left circumflex coronary artery, and 100% and 78% for the right coronary artery (187). Subsequent work, using the same approach (188) or a 3-D approach with respiratory compensation (189), however, showed much poorer results, which were attributable to patient selection biasing, independent evaluation, technique differences, and experience of the interpreter. More recently, contrast-enhanced 3-D approaches with breath holding have shown great promise (183).

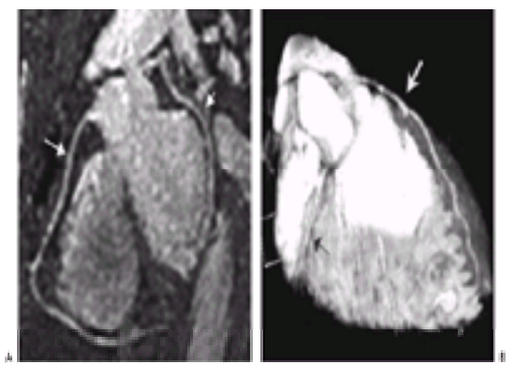


FIGURE 54.7 Magnetic resonance angiography of normal coronary artery (breath-hold, three-dimensional, segmented echo-planar imaging magnetic resonance angiography; maximal intensity projection). A maximal intensity projection image **(A)** demonstrates widely patent normal right coronary artery (*long arrow*) and left circumflex artery (*short arrow*). A volume-rendered reconstruction **(B)** of the same data set delineates the normal left anterior descending coronary artery (*white arrow*) and right coronary artery (*black arrow*). (Courtesy of Debiao Li, Ph.D., Northwestern University, Chicago, IL.)

The present spatial resolution and loss of signal caused by turbulence preclude accurate prediction of coronary artery stenosis severity by MRA. It has been shown that it is not possible to identify stenotic vessels based on quantification of signal intensity; no significant difference in signal was found between vessel segments of a normal coronary artery and vessel segments proximal to a significant stenosis (190). Nevertheless, MRA can be used to noninvasively identify patency of infarcted artery (191).

High-resolution MRI of the human coronary atheroma has developed significantly in the last years. The feasibility of imaging the coronary artery and determining the plaque content has been demonstrated (192). Although the plaque lipid material and the fibrous cap were identified in this preliminary work, further studies are needed to prove the applicability in a large population of this new and interesting technique to determine the morphology of the coronary plaques. In addition, its role relative to advancements in CT (subsecond multidetector scanning), which has also shown promise for plaque characterization, is unclear.

In addition to the morphologic approaches, an MRI method for evaluating flow in coronary vessels has been described (183,193). Results have indicated the feasibility of MRI for measuring flow in the native or simulated coronary arteries (194). Segmented velocity mapping has since been used to measure flow in the coronary arteries in healthy subjects; adenosine was used to increase coronary flow by several-fold, and an increase in velocity was shown (195). Others showed the feasibility of assessing increased coronary flow velocity using breath-hold velocity mapping or TOF EPI, during hand-grip exercise or after dipyridamole (196). Finally, coronary flow reserve in the left anterior descending coronary artery has been measured in an animal model (197) and in patients with CAD undergoing cardiac catheterization with

validation by intracoronary Doppler velocity and flow measurements (198). Thus, MRI may become a noninvasive technique to demonstrate reduced coronary flow reserve caused by hemodynamically significant coronary arterial stenoses.

Encouraging initial results with MRI evaluation of coronary artery bypass graft (CABG) patency has been noted. S-E MRI has been used to assess patency of CABGs; an accuracy of 84% to 95% for detection of graft patency and 72% to 85% for graft occlusion was demonstrated (199,200). After studies with the S-E technique, cine was used to assess CABG patency, with the expectation that the associated signal enhancement of flowing blood would improve evaluation. Cine achieved adequate sensitivities (88% to 93%), specificities (86% to 100%), and overall predictive accuracies (89% to 91%) for patency (201,202). Subsequently, velocity mapping was applied to the measurement of flow in internal mammary artery grafts (203) or aortocoronary vein grafts (204); the normal flow patterns for coronary artery grafts is biphasic with peaks in both diastole and systole. The potential of MRA to evaluate CABG patency has been recognized (Fig. 54.8).

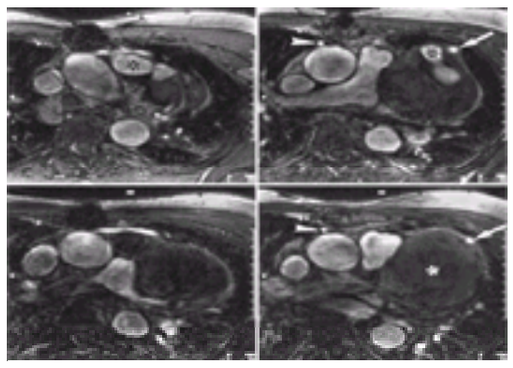


FIGURE 54.8 Coronary artery bypass graft patency and occlusion (contrast-enhanced, three-dimensional magnetic resonance angiography; oblique-transaxial). While patency of an internal mammary artery graft to the left coronary system (*arrows*) and a saphenous vein graft to the right coronary system (*arrowheads*) is confirmed, mid-graft occlusion of an aneurysmal, thrombus-filled saphenous vein graft to the left coronary system (*asterisks*) is detected.

MRA provides a new approach to the evaluation of the patency of coronary vessels. While preliminary work with small numbers of patients has been described, large population studies are needed to see how this new technique will ultimately perform. High-resolution coronary MRI is a new and exciting technique that might be able to discriminate the plaque content, but further studies in this area are also needed, including correlation with histologic specimens.

Valvular Heart Disease

Until the advent of the multiphasic techniques, MRI could provide little valuable information about valvular heart disease (64); for the most part, only indirect signs were offered by S-E MRI. Because of signal enhancement of the intracardiac and intravascular blood pools, morphologic changes of the leaflets may be demonstrated better on cine (63).

MRI generally produces less information about valvular disease than is offered by Doppler echo. However, MRI has the following advantages: Its 3-D nature makes it operator independent; it may be less susceptible to missing or underestimating eccentrically directed flow through a diseased valve; and it is free from geometric assumptions if cardiac chamber volumes are to be calculated (205). Echo has the advantage of providing true real-time imaging, whereas dynamic MRI techniques provide image loops composed of multiple averaged cardiac cycles. Nevertheless, in the setting of stenosis, thickening and calcification, decreased excursion or doming, and fusion of leaflets have been observed on MRI; predisposition to regurgitation, vegetation, prolapse, and flail can be detected on MRI (205).

Abnormalities of the adjacent chambers are easily detected with MRI. In the presence of stenosis (205), focal dilatation of the distal recipient chamber, concentric hypertrophy of a proximal ventricle, and generalized dilatation of a proximal atrium have been described; with regurgitation present (205,206), generalized dilatation of the proximal and distal chambers and eccentric hypertrophy of an associated ventricle have been noted.

The flow disturbances associated with valvular heart disease are also detectable by MRI. S-E MRI identifies abnormally increased signal caused by stagnant flow within a chamber proximal or distal to a diseased valve, especially an atrioventricular valve; on cine, the same flow disturbance creates an ill-defined cloud of low signal (49,63). On the other hand, in the setting of turbulence, a discrete jet of signal void extending from the diseased valve into the otherwise signal-enhanced recipient chamber characterizes poststenotic or regurgitant flow on cine (62,205,206). Such signal-void jets must be differentiated from physiologic signal loss from normal antegrade flow and from normal inflow, respectively (205,206 and 207). Jets from these valvular problems are easily detected and are distinguishable based on their direction of propagation and time of appearance (63).

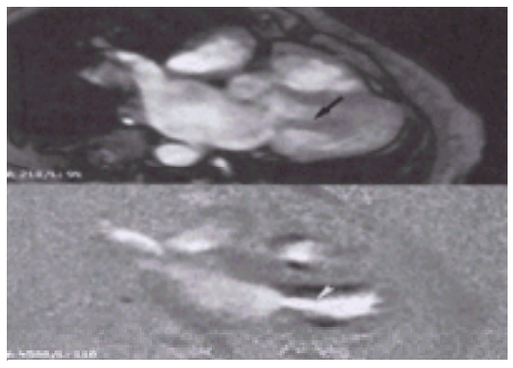
The semiquantitative or quantitative dynamic MRI assessment of the severity of flow disturbance caused by valve disease has been approached by several methods (205,206 and 207). The methods are based on the following measurements: (a) valve leaflet separation (208); (b) proximal convergent flow signal-void dimensions (209); (c) distal flow signal-void jet dimensions [e.g., length, area, or volume (absolute or relative to receiving chamber)] (207,210,211,212 and 213); (d) ventricular volumetrics (205,214); (e) transvalvular flow velocity (215); and (f) net volume flow (62,216).

Mitral Valve

Mitral Stenosis

The following anatomic abnormalities of mitral stenosis (MS) have been described by MRI: thickened leaflets with reduced diastolic opening, enlarged left atrium, abnormal left atrial signal, and abnormal diastolic transmitral signal (208,217).

A signal-void jet begins at the site of the mitral valve level and extends into the cavity of the LV during diastole on cine (205,206 and 207). More so than for the evaluation of regurgitation, evaluation of MS by cine is limited by the need for differentiation between the physiologic signal loss resulting from normal antegrade transvalvular flow and the abnormal flow through the stenotic mitral valve (eFig. 54.8.1). However, some studies indicate that significant MS can be easily detected and semiquantitatively evaluated using cine (208,217).



***e*FIGURE 54.8.1** Mitral stenosis (cine and velocity mapping; horizontal long axis). On cine (*above*), decreased diastolic opening of the mitral valve leaflets creates a jet of signal void (*arrow*) extending into the left ventricle cavity. A corresponding stream of high-velocity flow (*arrowhead*) is noted on velocity mapping (*below*).

Dynamic MRI has demonstrated its ability to quantitatively evaluate physiologic abnormalities associated with MS. The following have been assessed: valve leaflet separation (R = 0.81 vs. area by Doppler by pressure half-time method) (208), relative distal signal-void jet area (R = 0.77 vs. peak trans-valve gradient by

catheterization) (207), and peak trans-valve gradient (R = 0.89 vs. gradient by Doppler) (218).

Mitral Regurgitation

The anatomic abnormalities of mitral regurgitation on MRI resemble those of MS; however, dilatation of the LV is present (205,206 and 207).

Mitral regurgitation is readily identified on cine because of the signal-void jet of turbulent flow extending from the mitral valve level into the left atrial cavity during systole (Fig. 54.9). Based on the detection of a jet, mitral regurgitation is identified with a high degree of accuracy (94% to 100% sensitivity and 95% to 100% specificity vs. color Doppler) (210,219,220).

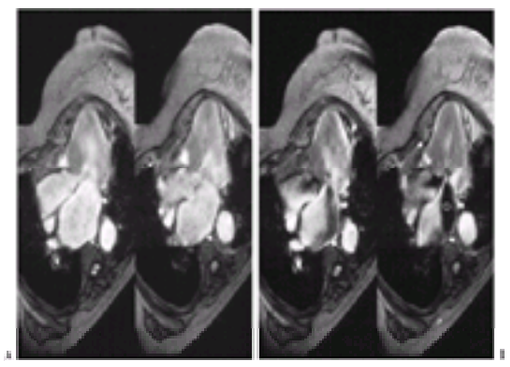


FIGURE 54.9 Mitral regurgitation (cine; left ventricle outflow tract). From end diastole **(A)** to mid-systole **(B)**, mitral regurgitation becomes identified by a signal-void jet of turbulent flow (*open circle*) extending from the mitral valve level into the left atrial cavity.

Quantitative physiologic assessment by dynamic MRI has included the following: distal signal-void jet grade [70% concordance vs. grade by color Doppler (221) and R = 0.77 vs. ventriculography (220)]; distal signal-void jet size [length, R = 0.74 vs. color Doppler (220); absolute area, R = 0.71 vs. color Doppler (220); relative area, R = 0.74 to 0.87 vs. color Doppler (219,220); volume, R = 0.84 vs. regurgitant volume by cine volumetric analysis (210,213)]; volumetric regurgitant fraction [R = 0.84 vs. ventriculography (221)]; volume-flow regurgitant fraction [R = 0.87 to 0.96 vs. grading by color Doppler (222,223)]; and combined volumetric and volume-flow regurgitant fraction [R = 0.96 vs. ventriculography (223)].

Aortic Valve

Aortic Stenosis

Anatomic abnormalities of aortic stenosis (AS) evaluated by MRI have included concentric LV hypertrophy, dilatation of the ascending aorta, reduced aortic valve area [R = 0.75 by S-E vs. catheterization or Doppler (224)], and mean difference by velocity mapping of 0.2 cm^2 versus catheterization by Gorlin formula and of 0.1 cm^2 versus Doppler by continuity equation (225). A double-oblique cine image taken through the aortic valve plane best demonstrates the cusps and their coaptation and serves to differentiate acquired AS from congenital AS with a bicuspid aortic valve. Because of its proven accuracy for quantifying LV mass (67,68), MRI may also be used to monitor the effects of AS on the LV before and after surgical repair or balloon valvuloplasty.

Video 54.4 Aortic stenosis and insufficiency (long-axis). A systolic signal-void jet of aortic stenosis is visible extending from the aortic valve into the ascending aorta. In addition, a diastolic signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricular cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

On cine, a signal-void jet of AS extends from the level of the aortic valve outward until its hemodynamic effects are dissipated within the blood pool of the ascending aorta (Fig. 54.10 and eFig. 54.10.1). AS jets are usually observed on cine throughout most of systole; however, some physiologic signal-void jets normally appear transiently just beyond the aortic valve after the initial opening of its leaflets. Nevertheless, significant AS can be detected using cine, and when there is a pressure gradient across the aortic valve, the severity of pressure drop and the length of the area of signal loss on cine show significant correlation (205,206 and 207). Mild, moderate, and severe AS can be differentiated based on jet size, but at pressure gradients above approximately 60 mm Hg, no further size increase is noted (207).

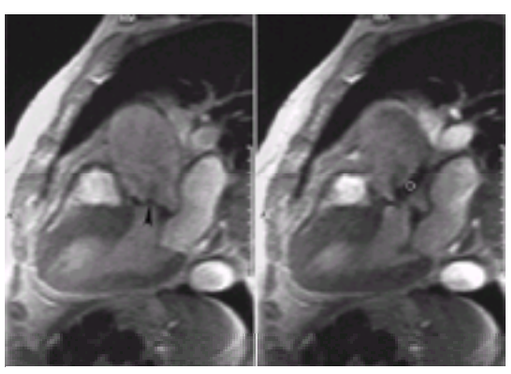
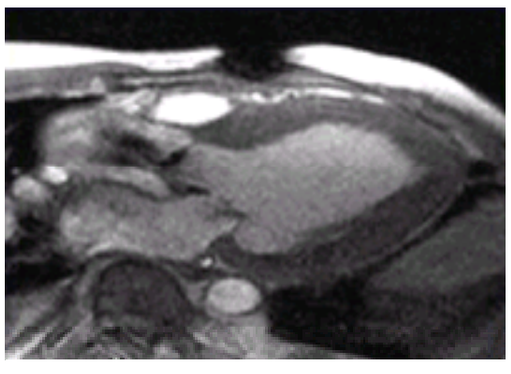


FIGURE 54.10 Aortic stenosis (cine; left ventricle outflow tract). From end diastole **(left)** to mid-systole **(right)**, a signal-void jet of turbulent flow (*open circle*), representing aortic stenosis, develops beyond the thickened aortic valve leaflets (*arrowhead*). HRA, high right atrium.



***e*FIGURE 54.10.1** Aortic stenosis and insufficiency (long axis). A systolic signal-void jet of aortic stenosis is visible extending from the aortic valve into the ascending aorta. In addition, a diastolic signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricle cavity.

Dynamic MRI has proved its ability to quantitatively evaluate physiologic abnormalities associated with AS. The following have been assessed: absolute distal signal-void jet length [R = 0.86 vs. peak trans-valve gradient by catheterization (207)] and peak trans-valve gradient [R = 0.96 vs. gradient by Doppler (225) and R = 0.67 to 0.97 vs. catheterization (225,226)].

Aortic Regurgitation

On MRI, the anatomic abnormalities of aortic regurgitation (AR) resemble those of AS, but instead of concentric hypertrophy, there is dilatation of the LV (205,206 and 207).

The signal-void jet of AR on cine has been fully described and evaluated for its potential to stage the severity of disease (Fig. 54.11 and *e*Fig. 54.10.1 and *e*Fig. 54.11.1) >(205,206 and 207). Qualitative assessment by cine has also involved proximal flow convergence detection (227) (87% sensitivity and 100% specificity vs. aortography) (209) and distal signal-void jet detection (89% to 92% sensitivity and 93% to 98% specificity vs. Doppler) (210). Velocity mapping has also received a great deal of attention for physiologic evaluation of AR, largely by assessing total reverse flow (62,205,206 and 207).

Video 54.5 Aortic insufficiency associated with annuloaortic ectasia of aortic root (oblique-coronal). An “onion-bulb” dilatation of the proximal ascending aorta and the sinuses of Valsalva is observed. A signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricular cavity during diastole. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

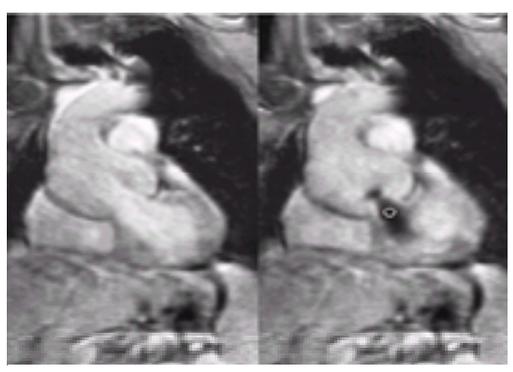
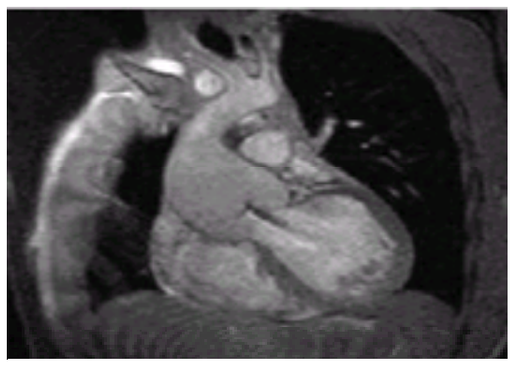


FIGURE 54.11 Aortic regurgitation (cine; oblique-coronal). A signal-void jet of aortic regurgitation (*open circle*) is seen extending from the dilated aortic root into the left ventricle cavity during diastole.



***e*FIGURE 54.11.1** Aortic insufficiency associated with annuloaortic ectasia of aortic root (oblique-coronal). An “onion-bulb” dilatation of the proximal ascending aorta and the sinuses of Valsalva is observed. A signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricle cavity during diastole.

For quantitative physiologic assessment, dynamic MRI has been used for proximal convergent flow signal-void area (significantly greater than for all grades by echo) (209); distal signal-void jet grade (93% concordance vs. grade by aortography) (228); distal signal-void jet size [area significantly greater than for moderate to severe vs. normal to mild 2-D echo grades (229)]; volume R = 0.84 versus regurgitant volume by cine volumetrics (210,212), significantly greater than for moderate versus mild and for severe versus moderate 2-D echo grades (210); volumetric regurgitant fraction (significantly greater than for moderate to severe versus normal to mild 2-D echo grades) (212); volume-flow regurgitant fraction [R = 0.97 to 98 vs. cine volumetrics (216,229); R = 0.80 vs. grading by aortography (230)] (Fig. 54.12).

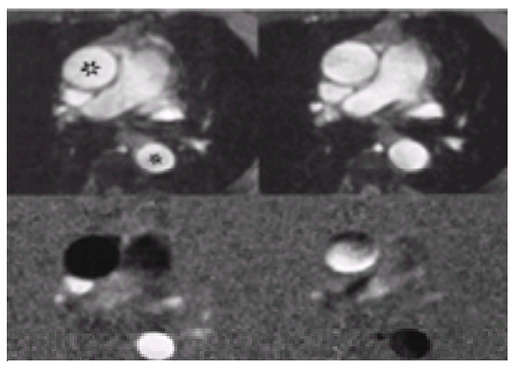


FIGURE 54.12 Aortic regurgitation (velocity mapping; oblique-transaxial). Corresponding to the magnitude data cine images (*above*) are the mid-systolic image (*left*) and mid-diastolic image (*right*) from velocity mapping (*below*). In systole, rapid antegrade-cranial flow in the ascending aorta (*large asterisk*) and antegrade-caudal systolic flow in the descending aorta (*small asterisk*) are represented by intense black and white shades, respectively. Because of significant aortic regurgitation, retrograde flow patterns are demonstrated in the thoracic aorta in diastole.

Tricuspid and Pulmonic Valves

Little work has specifically dealt with the issues of acquired right-sided valvular heart disease, although the value of MRI in assessing congenital tricuspid, including Ebstein’s anomaly or pulmonic valve disease, has been described (231). The principles correspond to the aforementioned for assessment of acquired left-sided valvular heart disease by MRI.

Volume-flow regurgitant fraction of pulmonic regurgitation has been validated (R = 0.93 vs. cine volumetrics) (232).

Prosthetic Valves

Normally Functioning Prosthesis

Studies *in vitro* and *in vivo* have shown that patients with artificial heart valves can be safely examined in high-field magnets (43,45). On MRI, little image distortion outside the immediate area of the prosthetic valve and no patient discomfort have been observed in related studies (233).

Abnormally Functioning Prosthesis

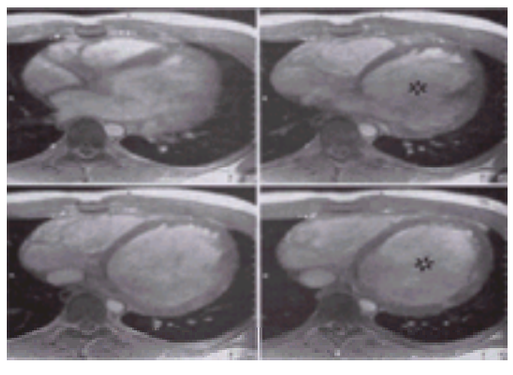
When the diagnostic value of cine for detecting regurgitation in prosthetic valves has been compared with that of transesophageal color Doppler echo, excellent (e.g., 96%) agreement between the methods in distinguishing physiologic from pathologic regurgitation was observed (234). In addition, quantitative physiologic evaluation of the severity of regurgitation has been promising [75% concordance of grade vs. grade by Doppler (234); R = 0.85 distal signal-void jet length, and R = 0.91 distal signal-void jet vs. Doppler (234)].

Myocardial Disease

Nonischemic myocardial disease (CM) is represented by the group of diseases in which the dominant feature is pathology of the myocardium unrelated to ischemic, hypertensive, congenital, valvular, or pericardial diseases. Of the variety of schemes that have been proposed for classifying the CMs, the following categorization is helpful: (a) dilated CM causing ventricular dilatation, contractile dysfunction; (b) hypertrophic CM associated with inappropriate hypertrophy of the LV, often with asymmetric septal involvement and usually with preserved contractile function, despite frequent regional impairment; (c) restrictive CM characterized by impaired diastolic filling; and (d) RV CM causing dilatation and regionally or globally impaired contractility of the RV related to dysplasia, with partial to total replacement of the myocardium by variable amounts of adipose and fibrosis tissue.

Dilated Cardiomyopathy

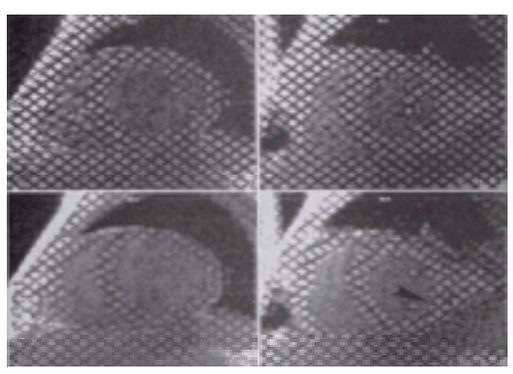
MRI can readily define the abnormally enlarged cavity size and globally depressed function (eFig. 54.12.1) of the LV and RV in cases of dilated CM (70,235). In contrast to healthy subjects, patients with dilated CM fail to demonstrate a gradient of progressively increasing systolic wall thickening from base to apex and have significantly decreased EF on cine (83,236), although improvement in LVEF from afterload reduction by angiotensin-converting enzyme inhibitor therapy has been demonstrated (237). The effects of such therapy on diastolic dysfunction have also been assessed using cine in patients suffering from dilated CM with and without MR; analysis of LV time-volume curves revealed improvements in both peak filling rate to end diastolic volume ratios and EF in the group without, but not in the group with, mitral regurgitation (238).



***e*FIGURE 54.12.1** Dilated cardiomyopathy (cine; transaxial). Marked enlargement of the left ventricle cavity (*asterisks*) is shown.

End systolic LV wall stress determined from cine has been determined to be abnormally elevated in patients with dilated CM, and inversely proportional to regional EF (239). In patients with dilated CM, significant increase in peak systolic wall stress, compared with normal values, has also been demonstrated (83). However, decreased end systolic wall stress following afterload reduction by angiotensin-converting enzyme inhibitor therapy has been shown using cine (237).

Myocardial tagging has been used in the assessment of the mechanical effects of surgical ventricular remodeling (eFig. 54.12.2) for treatment of LV failure; reshaping of the LV wall and improvement in contraction with surgery has been demonstrated.



***e*FIGURE 54.12.2** Ventricular remodeling surgery for dilated cardiomyopathy (spatial modulation of magnetization; short axis). From preremodeling (*left*) to the postremodeling (*right*), improvement in grid deformation from end diastole (*above*) to end systole (*below*) is noted in all left ventricle wall regions, except at the myectomy site (*arrowhead*); this indicates improved myocardial systolic function from the procedure.

Hypertrophic Cardiomyopathy

Various patterns of LV hypertrophy in hypertrophic CM (Fig. 54.13) have been defined using MRI (240). Unfortunately, S-E signal characteristics of the myocardium in hypertrophic CM have not been shown to differ from those found in healthy subjects or in patients with physiologic LV hypertrophy (241). Pathophysiologic characteristics associated with hypertrophic CM have also been demonstrated with MRI; in the setting of this condition, cine has been used to evaluate asymmetric LV systolic wall thickening, subaortic poststenotic flow related to systolic anterior motion of the anterior mitral leaflet, and related mitral regurgitation (Fig. 54.14 and eFig. 54.14.1) (242,243).

Video 54.6 Subaortic poststenotic flow in hypertrophic cardiomyopathy (long-axis). Asymmetric hypertrophy is noted, resulting in dynamic narrowing of the left ventricular outflow tract with a signal-void jet in the subaortic region. In addition, a signal-void jet in the left atrium is also seen, representing mitral regurgitation due to systolic anterior motion of the anterior leaflet of the mitral valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

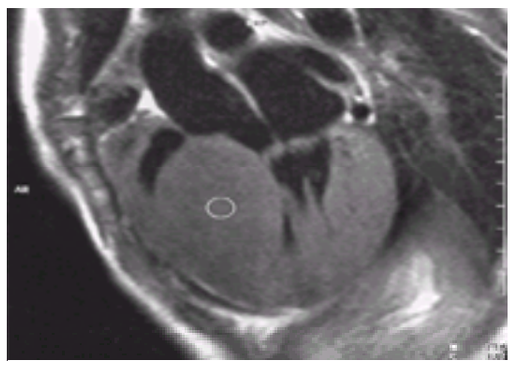


FIGURE 54.13 Left ventricular hypertrophy in hypertrophic cardiomyopathy (T1-weighted spin-echo; left ventricle outflow tract). Severe hypertrophy of the left ventricle wall, especially in the interventricular septum (*open circle*), is demonstrated.

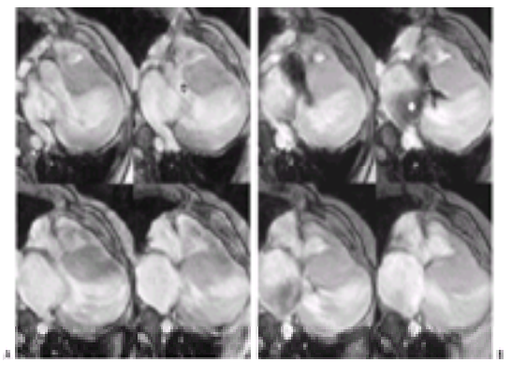
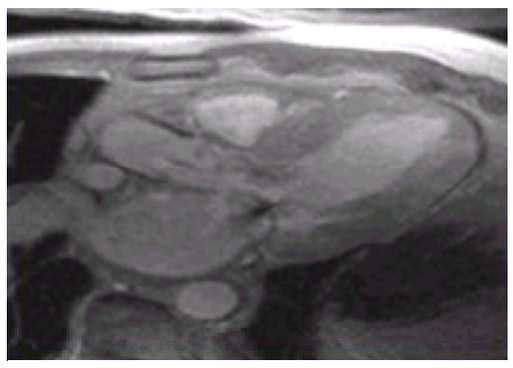


FIGURE 54.14 Subaortic poststenotic flow in hypertrophic cardiomyopathy (cine; horizontal long axis). On adjacent end diastolic images **(A)**, asymmetric left ventricle hypertrophy is noted; it results in fixed narrowing of the left ventricle outflow tract (*asterisk*). Because of systolic anterior motion of the anterior mitral leaflet in mid-systole **(B)**, abnormal subaortic signal void (*open circle*), representing stenosis, and left atrial signal void (*closed circle*), representing mitral regurgitation, develop.



***e*FIGURE 54.14.1** Subaortic poststenotic flow in hypertrophic cardiomyopathy (long axis). Asymmetric hypertrophy is noted, resulting in dynamic narrowing of the left ventricle outflow tract with a signal-void jet in the subaortic region. In addition, a signal-void jet in the left atrium is also seen, representing mitral regurgitation caused by systolic anterior motion of the anterior leaflet of the mitral valve.

Pronounced heterogeneous reductions in circumferential, longitudinal, and 3-D shortening, with the septal impairment exceeding the free-wall impairment, have been described in hypertrophic CM using MRI (Fig. 54.15) (244,245). Accentuated heterogeneity in strain rate, increasing in diastole, has also been demonstrated in hypertrophic CM (246). The degree of contractile dysfunction has been correlated with both its abnormal geometry (e.g., flattened to negative septal curvature) (247) and the severity of internal histopathology (i.e., myocardial fibrosis and myofiber disarray) (248). Using cine to evaluate RV time-volume curves in hypertrophic CM, abnormally depressed peak-filling rates and filling fractions have been demonstrated; these changes suggested diastolic dysfunction from associated restrictive physiology (249). Contrast-enhanced ultrafast has been used to study cases of hypertrophic CM; decreased diastolic first-pass enhancement of the septal myocardium correlated with increased amounts of characteristic histopathology (e.g., intramyocardial small vessel narrowing) (250).

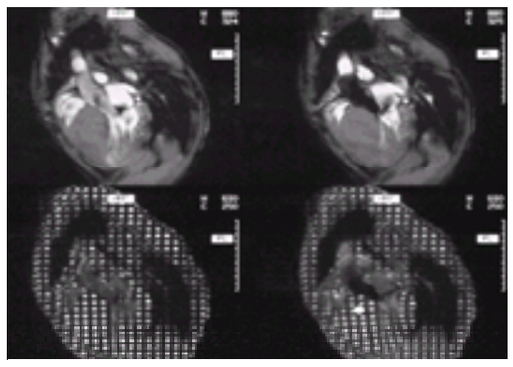


FIGURE 54.15 Regional variation in myocardial function in hypertrophic cardiomyopathy (cine and spatial modulation of magnetization; left ventricle outflow tract). With morphologic and hemodynamic abnormalities demonstrated on end diastolic cine (*above, left*) and end systolic cine (*above, right*) images, corresponding myocardial spin-tagging images (*below*) provide information about regional left ventricle function. Minimal deformation of the grid in the interventricular septum (*closed circle*), compared with the free wall, indicates its markedly impaired systolic mechanics.

Restrictive Cardiomyopathy

In cases of diastolic dysfunction caused by restrictive CM, rather than constrictive pericarditis, MRI is valuable in demonstrating the absence of abnormal pericardial thickening in the presence of indirect findings of impaired ventricular filling (e.g., dilatation of the inferior vena cava and right atrium) (251). MRI of cardiac amyloidosis (Fig. 54.16), a classic cause of restrictive physiology, has revealed increased thickness of the LV wall without cavity dilatation (252). Similar anatomic findings, in combination with slightly increased myocardial signal intensity, have been observed in some deposition diseases (e.g., Fabry's disease) resulting in diastolic dysfunction (253). However, for the most part, the myocardium of restrictive CM has normal MRI properties (e.g., T2) (254). There are notable exceptions in the setting of hemochromatosis: Prominent susceptibility-related loss of signal within the myocardium caused by iron deposition, especially on G-E images, has been demonstrated (255). Sarcoid heart disease, another potential cause of restrictive CM, is manifested on MRI in its acute inflammatory phase as discrete areas of high intensity that are associated with increased wall thickness within the LV septal and free wall myocardium (256) and chronically as focal areas of pronounced wall

thinning, possibly with aneurysm formation, in the same LV wall regions (eFig. 54.16.1).

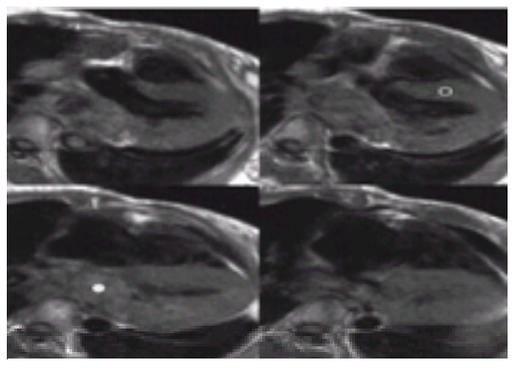
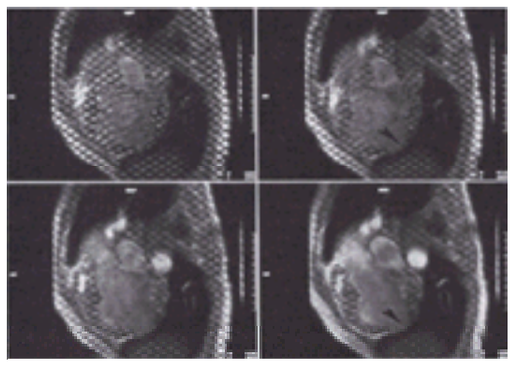


FIGURE 54.16 Cardiac amyloidosis (T1-weighted spin-echo; horizontal long axis). Generalized increase in left ventricle wall thickness (*open circle*), caused by protein deposition, is noted. Restrictive physiology is suggested by the presence of abnormal flow signal in the dilated left atrial cavity (*closed circle*).



***e*FIGURE 54.16.1** Chronic sarcoid heart disease (spatial modulation of magnetization; left ventricle outflow tract). A focal area of pronounced wall thinning, impaired systolic function, and early aneurysm formation (*arrowheads*) is demonstrated in the distal left ventricle free wall region on the sequential spin-tagging images.

An abnormally delayed pattern of ventricular filling caused by diastolic dysfunction associated with restrictive CM can be evaluated qualitatively or quantitatively using cine (257). In the initial stages of restrictive CM, sluggish early ventricular filling is noted with or without mild impairment of systolic function; late restrictive CM, on the other hand, is characterized by rapid early, but abruptly terminated late filling of the ventricles (as in constrictive pericarditis) and with significantly impaired systolic emptying of the ventricles (unlike constrictive pericarditis). Velocity mapping of ventricular myocardium has been used to demonstrate reduction in mean peak early diastolic velocity related to LV stiffening with aging (258).

By measuring the rate of flow across the tricuspid and mitral annuli in diastole, velocity mapping has been proposed as a method for assessing diastolic dysfunction, as found in restrictive CM (259). Using velocity mapping, abnormal flow patterns in the superior vena cava have been demonstrated in restrictive CM; a progressively decreasing ratio of peak flow in systole relative to that in diastole is found with worsening restrictive physiology, but such ratios do not differentiate restrictive CM from constrictive pericarditis (260).

Right Ventricular Cardiomyopathy

Along with dilatation of the cavity of the RV, thinning of its wall in regions of fibrosis (Fig. 54.17) and increased signal intensity in regions of replacement of its myocardium with fat (eFig. 54.17.1) have been well demonstrated in advanced cases of RV CM (arrhythmogenic RV dysplasia) using MRI (261,262). Greater reduction in RVEF and more pronounced structural and histologic changes in the RV, including evidence of fatty replacement of the myocardium, have been more often demonstrated in the setting of RV CM than with inducible ventricular tachycardia (263). Regional wall motion abnormalities, compatible with milder focal dysplasia, have been observed using cine in patients with the diagnosis of idiopathic RV outflow tract tachycardia (eFig. 54.17.2) (264).

Video 54.7 Arrhythmogenic right ventricular dysplasia (transaxial). Thinning the right ventricular wall with dyskinesia of the right ventricular free wall during systole is due to fibrous replacement of the myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

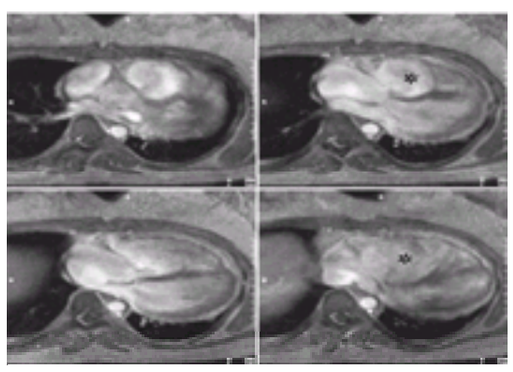
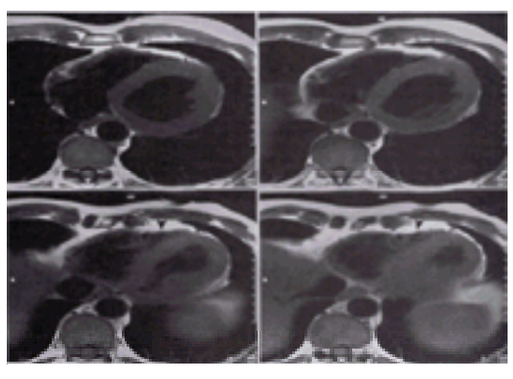
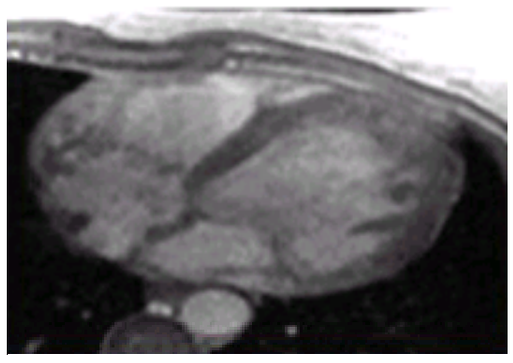


FIGURE 54.17 Arrhythmogenic right ventricle dysplasia (cine; transaxial). Marked dilatation of the cavity of the right ventricle (*asterisks*) and thinning of its wall in regions of fibrosis is shown on adjacent images.



***e*FIGURE 54.17.1** Right ventricle dysplasia with fatty replacement of the myocardium (T1-weighted spin-echo; transaxial). Increased signal intensity in the anterior right ventricle wall (*arrowheads*) near the interventricular septum indicates replacement of its myocardium with fat.



***e*FIGURE 54.17.2** Arrhythmogenic right ventricle dysplasia (transaxial). Thinning of the right ventricle wall, with dyskinesia of the right ventricle free wall during systole, is caused by fibrous replacement of the myocardium.

Pericardial Disease

To an acute injury, the pericardial sac responds with one of the following reactions: (a) congestion; (b) increased exudation of fluid into the sac; (c) exudation of both fibrin and acute inflammatory cells into the sac; or (d) a combination of these reactions (the composition of the pericardial fluid that results depends on the cause of pericardial insult). Pericarditis, an inflammation of the pericardial surfaces, has many infectious and noninfectious causes.

Effusion and Tamponade

The normal pericardium and the contained physiologic fluid appear on MRI as only a thin (usually 2 mm or less) curvilinear line situated between the epicardial and pericardial fat. MRI has an advantage over CT in differentiating a small pericardial effusion from pericardial thickening because different acquisition schemes may be employed in MRI to appreciate and characterize fluid (265).

Simple pericardial effusions are visualized on S-E MRI as low-intensity regions between the cardiac surface with its epicardial fat and the outwardly displaced pericardial fat (265,266). Because of cardiac motion, the signal intensity from simple pericardial effusions is less than that from simple pleural effusions (265,266 and 267). Although characterized by low signal intensity on T1-weighted images, its signal intensity may increase on T2-weighted images; this is particularly true of the most dependent portions of the pericardial effusion. Whereas simple pericardial effusions produce high signal intensity on G-E MRI and when imaged with cine, they demonstrate mobility and changing distribution during the cardiac cycle (267) (Fig. 54.18).

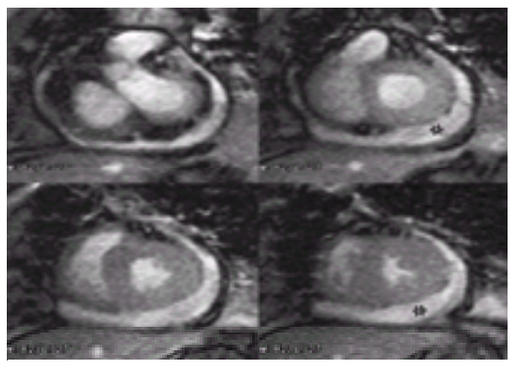
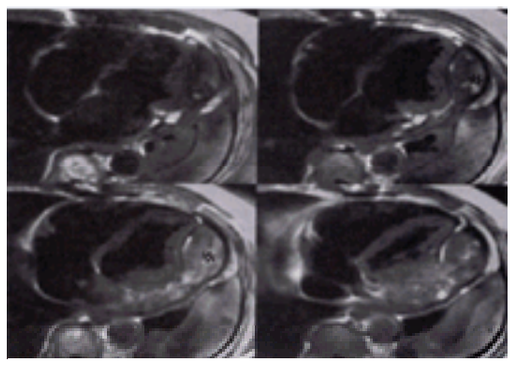


FIGURE 54.18 Simple pericardial effusion (cine, short axis). The bright appearance of the fluid (*asterisks*) separating the epicardial surfaces of the cardiac chambers from the dark-appearing pericardium indicates its simple nature.

Assessment of the distribution and general size of a simple pericardial effusion using MRI has shown good overall correlation with that by 2-D echo (266). However, when fluid volume has been quantitated by both techniques, the pericardial effusion has tended to measure larger by MRI (268). In fact, MRI has been shown to detect small pericardial effusions not visualized by echo, and to be better for detecting fluid located superiorly in the aortic pericardial reflection or superior pericardial recess, medially at the border of the right atrium, and posteriorly at the LV apex (266,268).

Because of T1 shortening from their high protein or cell content, complex pericardial effusions typically exhibit greater signal intensity than simple pericardial effusions on T1-weighted S-E MRI (266,267). Thus, on S-E MRI, regions of moderately increased signal within complex effusions probably represent exudate made relatively immobile by fibrinous material that has adhered to the pericardium. With exudative pericardial effusions, both the pericardium and pericardial adhesions may have greater signal intensities than a normal pericardium (266,269).

Hemopericardium and pericardial hematoma can generally be distinguished from other types of effusions because of the high, at times extremely intense, signal of the paramagnetic blood products on S-E MRI (266). However, these hemorrhagic pericardial effusions often contain areas of both medium and high signal intensity, reflecting the variable age of the bloody material (*e*Fig. 54.18.1) (266,269). Although hemorrhagic effusions have been shown to have significantly greater effusion-to-myocardial signal intensity ratios than nonhemorrhagic effusions on T1-weighted S-E MRI, differences in hematocrit are not reliably appreciated (270).



***e*FIGURE 54.18.1** Hemopericardium (T1-weighted spin-echo; horizontal long axis). A lobular intrapericardial mass lesion (*asterisk*) compressing the left ventricle free wall represents a pericardial hematoma; its variable internal signal intensity results from blood breakdown products.

MRI appears to be superior to echo in defining the nature and extent of processes causing clinical signs of cardiac chamber compromise from hemopericardium (265,269); compression of the cardiac chambers by hematoma indicates pericardial tamponade (267).

Pericarditis and Constriction

The low intensity of the pericardium on S-E MRI is explained partly by the presence of a phase discontinuity artifact. The shearing action between the visceral and parietal pericardium presumably results in a large local velocity variation, causing a reduction in signal intensity in the voxels spanning the pericardium (271). Absence of the low-intensity pericardial line on S-E MRI implies that the normal transpericardial shearing motion is also absent in that region (269). This change is caused by primary or secondary abnormalities of the pericardium (e.g., inflammatory disease).

Because MRI provides excellent direct visualization of the pericardium, it can readily define the presence and extent of pericardial thickening. Measuring pericardial thickness is of great value in the diagnosis of constrictive pericarditis; however, the presence of pericardial thickening does not indicate constriction. Pericardial thickening has been noted on MRI in several other clinical settings (e.g., after cardiac surgery) (266). Both pericardial thickening and effusion have been demonstrated in the setting of uremic or infectious pericarditis; because of inflammatory changes associated with both of these conditions, the pericardial signal is generally increased on S-E MRI, and adhesions between the irregularly thickened visceral and parietal pericardium may be detected (Fig. 54.19). Nevertheless, MRI can be used effectively in the differentiation between constrictive pericarditis and restrictive CM (266,269,272), both of which may result in similar clinical presentations; although restrictive CM could demonstrate pericardial effusion, it would not generally reveal significant pericardial thickening.

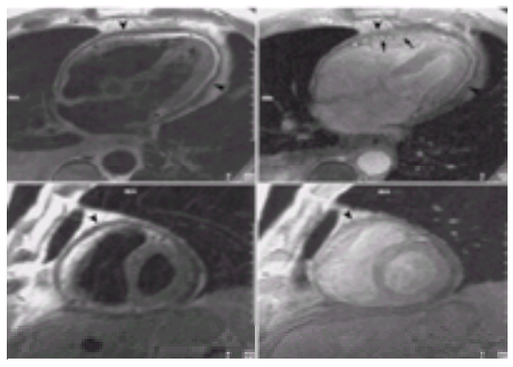


FIGURE 54.19 Pericarditis (subacute tuberculosis) (T1-weighted, spin-echo, and cine; horizontal long axis and short axis). Well shown on both the dark-blood **(left)** and bright-blood **(right)** images is the abnormally thickened pericardium (*arrowheads*) encasing the cardiac chambers, especially the ventricles, which appear compressed. The high concentration of small epicardial vessels along the right ventricular wall (*arrows*) is consistent with its inflammatory stage.

Although in constrictive pericarditis, increased thickness of the pericardium is evident on MRI (251,266,269,272), the associated conical or tubular narrowing of the generally nonhypertrophied ventricles, resulting from compression and confinement by the thick pericardium, is more specific for the diagnosis (Fig. 54.20). Secondary changes, such as atrial enlargement, systemic vein dilatation, hepatomegaly, ascites, and occasionally pleural effusion, may also be noted on MRI. When found in association with the appropriate clinical syndrome, these abnormal anatomic findings are strongly supportive of the diagnosis of constrictive pericarditis, with 93% accuracy documented (251). Unfortunately, MRI has not been able to differentiate reliably between fibrous tissue and calcification and, consequently, is of limited value compared with CT in the evaluation of calcification of the pericardium in the setting of calcific pericarditis (265).

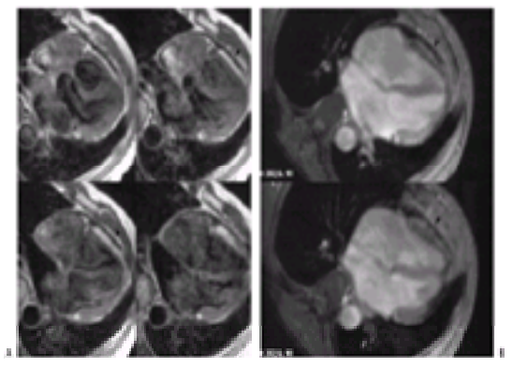


FIGURE 54.20 Constrictive pericarditis (T1-weighted, spin-echo, and cine; horizontal long axis). Constrictive pericarditis is manifested at adjacent levels on spin-echo **(A)** and cine **(B)** images by a thickened fibrotic and calcified pericardium (*arrowheads*), conical compression of the ventricles, biatrial dilatation, and abnormal intracardiac flow signal caused by diastolic dysfunction.

Cases of constrictive pericarditis may be evaluated functionally with MRI. Absolute and relative systolic wall thickening of the LV, measured with multiphasic S-E MRI, have not been found to be significantly different from that in normal volunteers (79). Cine is more useful than S-E techniques in functionally evaluating cases of diastolic dysfunction and in defining qualitatively or quantitatively the specific pathophysiologic abnormalities associated with constrictive pericarditis (63,267). Because of the higher temporal resolution provided with this technique, the abrupt limitation of late diastolic filling of the ventricles because of the abnormally thickened and confining pericardium in constrictive pericarditis is distinguishable from the delayed diastolic filling patterns of the ventricles caused by restrictive CM in the absence of significant pericardial thickening.

Using velocity mapping, abnormal flow patterns in the superior vena cava have been demonstrated in cases of constrictive pericarditis (260); improvement in diastolic return with pericardial stripping can be documented. In both healthy subjects and patients with right-sided disease, systemic venous flow measured without respiratory gating closely resembles its flow at end expiration (96).

Aortic Disease

Complete and timely imaging of the thoracic aorta is essential in that some disease entities are potentially life threatening and require prompt surgical intervention. The best surgical approach will be based on a complete depiction and understanding of the anatomy, which necessarily includes the thoracic aortic configuration and caliber, aortic wall characteristics, arch vessel origins, and descriptions of the aortic valve and the paraaortic structures.

MRI is now assuming an increasing and distinct role in furthering the evaluation and diagnosis of diseases of the thoracic aorta (273). In fact, the majority of CV MRI studies are currently performed for the evaluation of thoracic aortic disease (17). The ability of MRI to noninvasively depict abnormalities in anatomy or physiology in the thoracic aorta in multiple oblique planes or 3-D makes it ideally suited for initial diagnosis, monitoring during medical therapy, and postoperative assessment (273,274 and 275). Other parameters that are important to address in the evaluation of patients with thoracic aortic disease (e.g., origin of the coronary arteries) can also be evaluated effectively with MRI.

In addition, MRI provides a highly specific and sensitive method for detecting postoperative complications from thoracic aortic surgery (57,276,277). These complications include periprosthetic valve leak, graft infection, extension or development of dissection, rupture, or aneurysmal expansion.

Aneurysm

Accurate identification of the size, location, and extent of a thoracic aortic aneurysm is essential for management, preoperative planning, and follow-up; large aneurysms of the thoracic aorta should be surgically corrected because of the increased risk of spontaneous rupture when the diameter exceeds 5 cm. Thoracic aortic

aneurysms are categorized as being either true aneurysms, meaning that all three mural layers of the aortic wall are involved, or as pseudoaneurysms, in which there has been a break in the intima, and possibly media, leaving only the remaining wall to contain the intraaortic blood pool. These forms of aneurysm are characteristically represented by fusiform (i.e., circumferential enlargement of the involved segment) or saccular (i.e., asymmetric or focal outpouching of the involved segment) dilatations, respectively. The saccular configuration connotes a less stable condition than the other configuration. These characteristics of a thoracic aortic aneurysm can be easily delineated with MRI for planning of therapy or for clinical monitoring (273,276). In addition, because of the abilities of MRI to depict the configuration and associated mural changes, it is critical in differentiating the various etiologies of thoracic aortic aneurysms (278).

On MRI, atherosclerotic aneurysms may be found in any portion of the thoracic aorta and are characterized by fusiform enlargement, usually over long segments (Fig. 54.21). The aortic wall is thickened and irregular, secondary to atherosclerotic plaque (279). Mural calcification is common and is manifested by areas of focal signal absence on both S-E and cine, although it is better seen on CT. Intraluminal thrombus also is common and may be difficult to distinguish from atherosclerotic plaque, although thrombus usually has a smooth internal border as opposed to atherosclerosis, which typically is irregular (273,276). In atherosclerotic aneurysms involving the ascending portion, the sinotubular junction and aortic valve function usually are preserved—important characteristics appreciated on MRI.

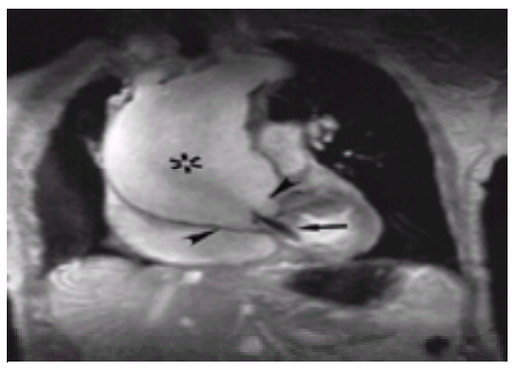


FIGURE 54.21 Atherosclerotic aneurysm (cine; oblique-coronal). Despite marked dilatation of the ascending aorta (*asterisk*), there is preservation of the sinotubular junction (*arrowheads*). Aortic regurgitation is also seen (*arrow*).

Aortic aneurysms that may occur secondary to aortic valvular disease are also characterized by relative preservation of the aortic root and sinotubular junction on MRI (273,276). In cases of AS, the aneurysmal dilation usually is limited to the midascending aorta where the poststenotic flow effects are most prominent (226). In AR, aneurysmal dilation of the thoracic aorta typically involves the ascending aorta but extends into the transverse arch because of the “water hammer” effect and, in long-standing cases, also may involve the descending thoracic aorta; often there is slight effacement of the sinotubular junction and dilatation of the aortic root in primary AR because of their relationship (228).

Equally important in the case of aneurysms involving the ascending aorta is the appreciation of annuloaortic ectasia that leads to characteristic “onion bulb” dilatation of the proximal ascending aorta and sinuses of Valsalva from pronounced effacement of the sinotubular junction (eFig. 54.11.1 and Fig. 54.22) (273,276). Indicating cystic medial necrosis, detection of annuloaortic ectasia on MRI connotes a worsened prognosis; Marfan syndrome and other connective tissue disorders characteristically result in weakening of the aortic wall, as a result of cystic medial necrosis. Typically, the associated dilation of the aortic root leads to suboptimal coaptation of the aortic valve cusps as the aortic annulus dilates and ultimately to significant AR. More serious and potentially ominous complications include ascending aortic dissection, rupture, or both (280).

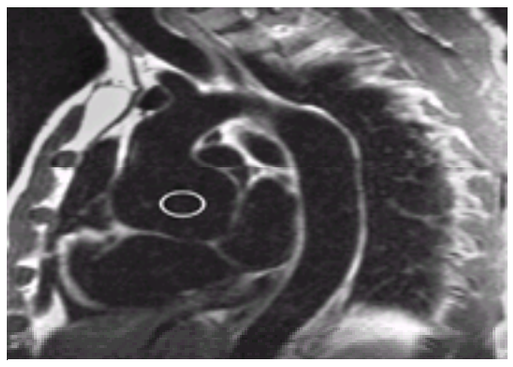
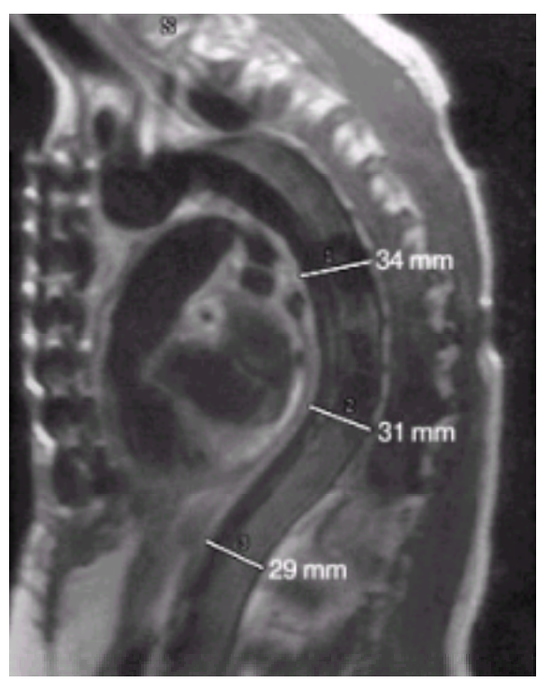


FIGURE 54.22 Annuloaortic ectasia of the aortic root (T1-weighted, spin-echo; left anterior oblique). An “onion-bulb” dilatation of the proximal ascending aorta and sinuses of Valsalva (*open circle*), associated with pronounced effacement of the sinotubular junction, is noted.



Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

Another configuration of thoracic aortic aneurysms that is important to identify on MRI is saccular dilatation from a mycotic or pseudoaneurysm. Mycotic aneurysms result from weakening of the aortic wall by infection (278), although pseudoaneurysms typically are caused by trauma (e.g., automobile accidents) and occur most commonly at the level of the ligamentum arteriosum or after surgery at anastomotic or cannulation sites (Fig. 54.23) (281).

FIGURE 54.23 Aortic pseudoaneurysm (magnetic resonance angiography surface reconstruction). A saccular outpouching (*asterisk*) from the undersurface of the aortic arch communicates with the aortic lumen through a narrow neck (*arrow*), indicating disruption of the layers of the aortic wall.

Dissection

Dissections are classified according to either the Stanford or DeBakey systems. The important distinction to be made clinically is whether the dissection flap involves the ascending aorta with or without transverse arch involvement (Stanford A; DeBakey I and II) (eFig. 54.23.1) or both the distal arch beyond the left subclavian artery origin and the descending aorta (Stanford B; DeBakey III) (eFig. 54.23.2). This distinction is important because the involvement of the ascending aortic is associated with a higher mortality and generally requires urgent surgical repair.

VIDEO

Video 54.8 Aortic dissection (left anterior oblique). Type A dissection of the aorta is manifested on the cine image loop by a mobile intimal flap extending from the mid-ascending aorta to the descending thoracic aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 54.9 Aortic dissection (left anterior oblique). Type B dissection of the aorta extending distally from the isthmus, just after the left subclavian artery, to the abdominal aorta. A communication between the true and false lumen is seen in the proximal portion of the descending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

***e*FIGURE 54.23.1** Aortic dissection (left anterior oblique). Type A dissection of the aorta is manifested on the cine image loop by a mobile intimal flap extending from the mid-ascending aorta to the descending thoracic aorta.

***e*FIGURE 54.23.2** Aortic dissection (left anterior oblique). Type B dissection of the aorta extending distally from the isthmus, just after the left subclavian artery, to the abdominal aorta. A communication between the true and false lumen is seen in the proximal portion of the descending aorta.

MRI is a highly sensitive and specific technique for the detection of aortic dissection that has proven to be superior to conventional angiography, CT, and transthoracic echo (282). It also has been compared with transesophageal echo; both techniques have demonstrated a similar high sensitivity (e.g., 98% to 100%), but MRI has a significantly higher specificity (e.g., 98% to 100%) than transesophageal echo (e.g., 68% to 77%) in high-risk populations (282). The advantages of MRI include an ability to evaluate not just the intravascular space and walls of the aorta, but also the extravascular space, which may yield further information, particularly in regard to more serious complications of aortic dissection (273). Nonetheless, most agree that transesophageal echo—because of its portability, speed, and ability to image in real time—is the preferred method of evaluation in the subset of unstable patients, such as those in the emergency room and intensive care settings.

The goals of MRI in aortic dissections, both acute and chronic, are to identify the intimal flap, its extent, orientation, and involvement with aortic arch branch vessels and coronary arteries, the location of entry and reentry tears of the intima, and to assess for areas of flow and thrombus within the false channel (273). In addition, potential complications such as pleural effusion, pericardial tamponade, and AR must be assessed.

Whether by S-E or cine imaging, aortic dissection is characterized by the inwardly displaced intraluminal intimal flap, surrounded by rapid flow within the true channel and usually slower flow, with or without thrombus formation in the false channel (Fig. 54.24) (273,282,283). Both primary and secondary tears of the intimal flap may be difficult to identify on the static images unless they are relatively large. Dynamic flow-based images (i.e., cine, SPAMM, or velocity mapping) are useful adjuncts to identify these sites of flow between the true and false channels and to observe the frequently dynamic motion of the intimal flap (eFig. 54.24.1) (273,284).

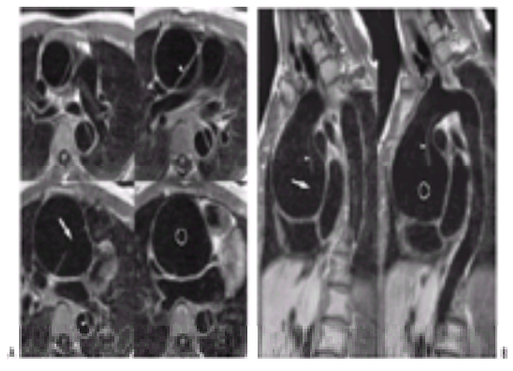
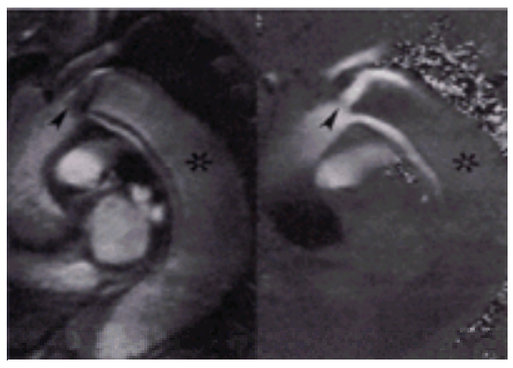


FIGURE 54.24 Aortic dissection (T1-weighted spin-echo; transaxial and left anterior oblique). Type A dissection of the aorta is manifested on representative transaxial **(A)** and oblique **(B)** images by the inwardly displaced intimal flap (*arrowheads*), extending from the dilated aortic root (*open circle*) to the descending thoracic aorta, and a large proximal intimal tear (*arrows*).



***e*FIGURE 54.24.1** Dynamic flow-based imaging of aortic dissection (cine and velocity mapping; left anterior oblique). The blood-flow patterns of this type B dissection of the aorta are manifested on systolic cine (*left*) and velocity mapping (*right*) images by rapid nonrestrictive flow through the large primary intimal tear (*arrowheads*) beyond the left subclavian artery and slower blood flow in the false channel (*asterisks*).

The patterns of flow within each channel can be further qualitatively or quantitatively assessed with these MRI techniques for the purposes of planning surgical repairs or interventional procedures (e.g., fenestration) in which the adequacy of blood supply to vital organs is often an issue (284). Velocity mapping, in particular, may identify retrograde patterns of flow within the false channel that may potentiate retrograde extension of a simple type B dissection into the arch and ascending aorta.

A common hurdle is the distinction between a thrombosed false channel within a chronic dissection from an intraluminal thrombus adherent to the wall of an aneurysm. These are not always possible to differentiate, as a chronic intraluminal thrombus may neoepithelialize, giving the appearance of an intimal flap overlying the chronic thrombus (273,284). Signs that have been reported to be more consistent with a diagnosis of thrombosed false channel associated with dissection are a compressed or eccentric patent channel and extensive thrombus with associated wall thickening over a length greater than 7 cm; these signs are easily appreciated on MRI (284).

The entity of noncommunicating dissecting intramural hematoma is being detected with increasing frequency with the development of tomographic imaging, including MRI. Technically, this may be described as dissection of the aortic wall without intimal rupture or tear; the etiology is unknown, but presumably is related to a weakening of the media. Clinically, the presentation is almost always similar to that of aortic dissection; the diagnosis of an intramural hematoma is entertained, once communicating aortic dissection has been excluded. On MRI designed to exclude communicating aortic dissection, an intramural hematoma is identified as a smooth crescentic to circumferential area of thickened aortic wall without evidence of blood flow in the false channel (e.g., velocity-dependent phase changes on velocity mapping or displacement of saturation bands on SPAMM) (284,285 and 286). Depending on the age of the hematoma, the area of thickening may be isointense or hyperintense relative to skeletal muscle on S-E MRI; the signal intensity is relatively isointense in the acute phase, and then becomes greatest in the subacute stages (Fig. 54.25) (286). If intramural bleeding stops, the intramural hematoma resolves with decreasing thickness and returns to S-E isointensity in the more chronic stages.

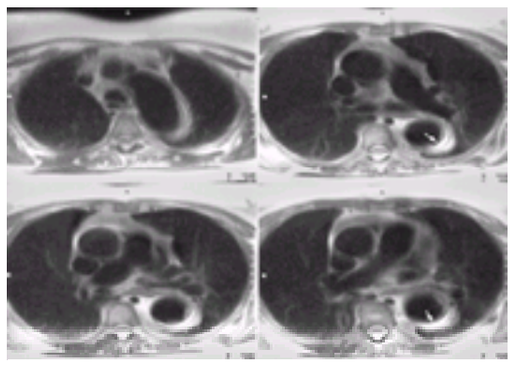


FIGURE 54.25 Intramural hematoma of the thoracic aorta (T1-weighted spin-echo; transaxial). A smooth crescentic collection within the wall of the descending thoracic aorta (*arrows*) indicates an intramural hematoma; its extremely bright signal intensity indicates its subacute nature.

At present, there is only limited knowledge regarding the natural course of an intramural hematoma. However, complete resolution or evolution to dissection have been demonstrated on MRI (285,286). Involvement of the ascending aorta by intramural hematoma has been shown to predispose the development of communicating aortic dissection in most cases; rebleeding before development of communicating dissection has been detected based on S-E intensity changes (285,286).

Atherosclerosis

The first attempt at MRI of atherosclerotic plaque involved the use of postmortem specimens of excised peripheral artery (287); good correlation between the morphology of the plaques on MRI and on histology was demonstrated. Atherosclerotic lesions were seen as vessel wall thickening with overall intermediate signal intensity, except in areas of calcium and lipids, where there were focally decreased and increased signal, respectively (287). Since these early studies, images obtained with more advanced MRI protocols in experimental models have proved to be useful in identifying various wall components in atheromatous artery samples on the basis of chemical composition, molecular motion, diffusion, physical state, or water content (288). These differences may be particularly important in determining the contributing factors related to plaque rupture, which depend strongly on the presence of soft lipid and collagenous fibers (289). Some studies using image processing have also shown that it may be possible to identify and quantify the types of materials present in atherosclerotic plaque (290,291).

High-resolution MRI has shown excellent contrast between fatty plaque components (i.e., foam cells, loose necrosis, and cholesterol) and solid components; signal loss in images was seen at locations where calcium existed (288,289). Experimental work has shown the potential of MRI to demonstrate (a) the variable nature of the collagen cap with underlying lipid-rich regions in more vulnerable plaques; (b) anatomic response of the atherosclerotic plaque to *in vitro* angioplasty; (c) the relationship between the nature of the lipids inside atheromatous plaques and the severity of vessel obstruction; and (d) “aging” changes of thrombi.

In the clinical setting, MRI currently has the capability of routinely providing valuable information regarding the patency of the arterial lumen, as well as the status of the arterial wall in patients with atherosclerotic vascular disease (40). Atherosclerotic lesions in humans consist of eccentric or concentric mural thickening with luminal narrowing and discrete plaques protruding into the vessel lumen. Although early studies using standard S-E techniques yielded promising results, limitations in

detecting calcified plaques by MRI were revealed (292).

Good accuracy of MRA for depicting peripheral stenoses and occlusions has been demonstrated clinically (60,293). However, because minor luminal irregularities, ulcers, or aneurysms may all lead to significant local turbulence and resultant intraluminal signal loss in the absence of an angiographically significant narrowing, an imperfect concordance between MRI and conventional forms of angiography may result. Nevertheless, measurements of the degree of stenosis on projectional MRA images have been shown to correlate reasonably well with conventional angiographic techniques (294). However, there are limitations that potentially interfere with clinical characterization of adjacent atherosclerotic plaques.

A penetrating atherosclerotic ulcer is an MRI-detectable entity, occupying an as yet uncertain place in the spectrum of aortic atherosclerotic disease (279). It usually appears as a shallow, wide-necked ulceration of an atheroma that extends through the intima to disrupt the underlying media; the mid- and distal descending aorta are the most common sites.

Pulmonary Artery Disease

Few options have been available for diagnosing disease of the pulmonary artery. The gold standard for diagnosis has been pulmonary artery catheterization with or without angiography. MRI has many unique capabilities that make it preferable to other noninvasive imaging methods and to angiography for the evaluation of some abnormalities of the pulmonary artery system. Aside from depicting intrinsic pulmonary artery disease, MRI is an ideal imaging method for evaluating the secondary effects of adjacent extravascular disease.

Pulmonary Emboli

Because all therapies for pulmonary emboli (PE) pose significant risks, an accurate diagnosis of such disease is mandatory before the initiation of treatment. For the diagnosis of PE, there has been no single noninvasive and accurate imaging procedure. Imaging by ventilation-perfusion scintigraphy is safe, but accurate interpretation in the presence of lung disease or cardiac conditions is reduced. Consequently, many individuals with suspected PE ultimately come to angiography because of diagnostic evaluations.

Because of the signal void of normally flowing blood, thrombus within a pulmonary artery can usually be readily discerned on systolic S-E images; the intensity of thrombus is variable, depending on its age. Because cases of pulmonary artery hypertension (PAH) are often present with symptoms requiring evaluation for suspected PE, and because abnormal systolic intravascular signal may also be caused by slow blood flow in PAH, the need for differentiation of thrombus from slow blood flow in MRI is common. This can be accomplished by noting that, unlike slow blood flow, a thrombus from PE demonstrates no even-echo rephasing on multiple S-E images, and no change in distribution on multiphasic images (295,296). Although it can be used to demonstrate a thrombus in a larger pulmonary artery, it is unlikely that S-E MRI can at the current time be considered reliable for the evaluation of PE beyond the level of a segmental pulmonary artery (296). Phase-display imaging may also be useful in detecting the phase changes related to slowly flowing blood and the absence of such phase changes related to a fixed thrombus.

Cine and SPAMM are adjuncts to S-E imaging, which potentially increase the diagnostic yield and capabilities for characterization of PE (296,297 and 298). In general, an intravascular thrombus from PE is manifested by a fixed area of signal void or preservation of saturation band patterns, respectively, which can be differentiated from the appearance of the surrounding flowing blood (Fig. 54.26). A complicating factor in thrombus detection would be slow blood flow caused by pulmonary artery obstruction by the thrombus or from superimposed PAH because of slow blood flow (296,297). PE diagnosed by cine has been shown to correspond to the locations of angiographic abnormalities and mismatched ventilation-perfusion defects on scintigraphy and has been able to assess the age of the embolic mass (299).

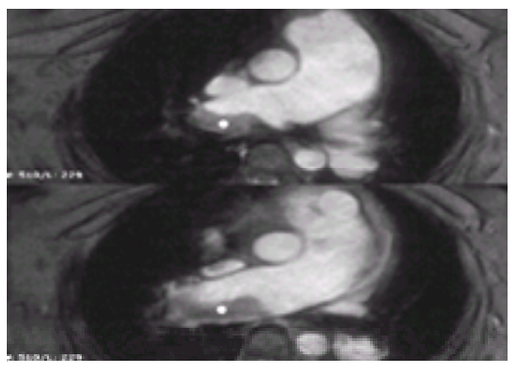


FIGURE 54.26 Intravascular thrombus from pulmonary emboli (cine; transaxial). Adjacent levels both demonstrate a fixed lobular area of relative signal void (*closed circles*), surrounded by flow enhancement, in the right central pulmonary artery; it represents pulmonary emboli.

Although some potential to identify the age of the thrombotic material within a pulmonary artery by MRI has been realized, it is more practically used for monitoring resolution of clotting during anticoagulation therapy. MRA techniques have created pleasing images of the branching pulmonary artery system, and the capability of reliably demonstrating PE is now being done (300).

Pulmonary Hypertension

The ability of S-E MRI to distinguish normally flowing from slowly flowing blood and slowly flowing blood from fixed intravascular lesions (e.g., thrombus caused by PE) indicates its value as an alternative to catheterization in assessing PAH. The increased risk of catheterization plus angiography for the diagnosis or exclusion of PE in cases of PAH has also emphasized the potential of MRI for this purpose.

Initially, the primary use of S-E MRI in evaluation of PAH was the description of secondary changes (301). Anatomic findings include RV hypertrophy in proportion to the pulmonary artery pressures; reversal of septal curvature when pulmonary artery pressures approximate systemic pressures; and pulmonary artery dilatation (Fig. 54.27).

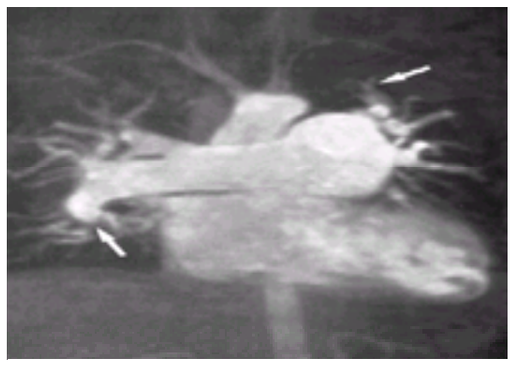
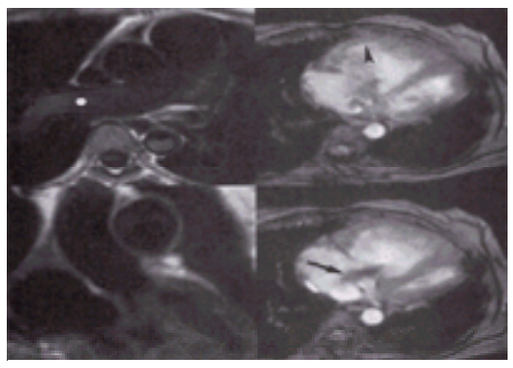


FIGURE 54.27 Pulmonary artery (PA) dilatation of pulmonary artery hypertension (contrast-enhanced three-dimensional magnetic resonance angiography; coronal). Marked dilatation of the main PA and each central PA is noted. Beyond the hilar regions, rapid tapering of PA branch caliber (*arrows*) is indicative of pulmonary artery hypertension.

In PAH, substantial elevation in pulmonary vascular resistance and dilatation of the pulmonary artery system result in diminished velocity of blood flow; the intensity of such abnormal intravascular signal has a direct linear relationship with the amount of pulmonary vascular resistance, showing the ability of S-E MRI to provide information about the severity of PAH (302). Combined use of multiple S-E and multiphasic techniques permits further description of the characteristic pulmonary artery

signal patterns typically found in the setting of PAH (eFig. 54.27.1) (295). Because of the presence of even-echo rephasing, as well as its fluctuating distribution during the cardiac cycle, abnormal intravascular signal from slow blood flow can be distinguished from that of intraluminal thrombus or tumor (295,303). Phase-display and cine images can also be used to properly identify abnormal intravascular signal from slowly flowing blood in PAH, through demonstration of velocity-dependent phase changes and saturation-related diffuse intermediate signal loss, respectively (296,297).



***e*FIGURE 54.27.1** Secondary effects of pulmonary artery hypertension (T1-weighted spin-echo and cine; transaxial and coronal). Because of pulmonary artery hypertension, pulmonary artery dilatation with slow flow signal (*closed circle*) is seen. Right ventricular dilatation, associated with flattening of the interventricular septum, is noted; hypertrophy of the right ventricle wall (*arrowhead*) is also demonstrated. Last, tricuspid regurgitation (*arrow*) is evident.

Pulmonary artery distensibility has been studied with S-E MRI in healthy subjects and in patients with PAH; distensibility was found to be significantly reduced in cases with PAH (304). When velocity mapping of the pulmonary artery flow was performed, all cases of PAH had totally irregular antegrade flow in systole with large velocity variations across the vessel lumen. PAH was also associated with abnormally slow net forward flow, but with earlier velocity peaking than in healthy subjects; abnormally large retrograde flow was noted in systole and diastole in PAH.

The multipotentiality of MRI is clearly evident in the assessment of patients undergoing evaluation for possible lung transplantation or for monitoring following this surgery. Improved RV function and enhanced pulmonary artery flow n transplanted lungs have been shown (305,306).

Thrombi and Masses

MRI has proved to be extremely valuable in assessing mass lesions located in the cardiac chambers or myocardium or adjacent to the heart in the pericardium, mediastinum, or lung (307). S-E MRI images provide excellent anatomic detail, sufficient for assessment of the extent of such lesions, indicating their site of origin, as well as the secondary effects on adjacent structures. Cine may provide additional information concerning their movement relative to the cardiac chambers; this insight may provide a better appreciation of sites of attachment and influence on myocardial and valve function (267). This anatomic and functional information has an important role in planning therapy for thrombi and cardiac masses (308).

MRI has been shown to outperform echo in demonstrating the presence, location (i.e., paracardiac vs. intramural vs. intracavitary), and extent of mass lesions (308,309). In a significant proportion of cases referred from echo to MRI for evaluation of a suspected cardiac mass lesion, the presence of a lesion is excluded by MRI (309). Thus, MRI can be used effectively in combination with echo to increase the certainty of diagnosis and plan therapy (267).

In addition to providing important morphologic data, MRI has the potential to assess the tissue composition of mass lesions. As is true elsewhere in the body, the use of both T1- and T2-weighted S-E images allows for some general degree of tissue characterization (308,311). Because lipomatous tissues have a uniquely short T1 and their signal intensity resembles that of subcutaneous fat on S-E imaging, cardiac lipomas have a relatively high signal intensity on T1-weighted images and a moderate signal intensity on T2-weighed images (267,310). Cystic cardiac lesions typically have long T1 and T2 relaxation times, resulting in a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted images (266,307,310). Most soft-tissue cardiac tumors have T1 and T2 relaxation times that are much shorter than those of cystic fluid, yet T1 and T2 are long enough to produce a relatively low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (267,307).

Like tumors elsewhere in the body, cardiac tumors have increased water content, resulting in prolongation of T1 and T2 relaxation times (267). The effects of edema in the surrounding tissue may make the distinction between the tumor and the surrounding tissues difficult. In addition, the presence of hemorrhage or necrosis within a tumor may alter its appearance. To complicate matters further, dense fibrous tissue and areas of calcification, possibly resulting from therapy, produce a low signal intensity on T1- or T2-weighted images because of a relative paucity of mobile protons.

Gd-DTPA accumulates in tumors more than in myocardium, improving detection and anatomic delineation of cardiac tumors (267,311). Enhancement helps to distinguish neoplasms from nonvascular masses, because the tumor must have a capillary blood supply to accumulate the extracellular contrast agent. However, similar to other organ systems, cardiac neoplasms show variable degrees of enhancement, and the kinetics are not specific for benignancy or malignancy. Thus, the early hope that MRI would permit the differentiation of benign from malignant masses has not been fulfilled.

Intracardiac Thrombi

The accuracy of MRI in the diagnosis of an LV thrombus is comparable with angiography, CT, and echo (145,146,267). Interpretation of S-E MRI is complicated by the presence of intraventricular flow signal, resulting from stagnant blood within areas of LV dysfunction. The demonstration of even-echo rephasing or phase shifts in regions of slowly flowing blood is helpful in excluding the diagnosis of a thrombus (267). Similarly, cine can exploit flow-related enhancement to distinguish slow flow from a thrombus (146) (eFig. 54.3.3).

Nevertheless, the signal intensities of intracardiac thrombi on S-E MRI have been variable and not reliably distinguishable from those of nonthrombotic masses (307,309).

Primary Cardiac Tumors

The exclusion or verification of the presence of an intracardiac mass suggested by a prior echo has been a frequent indication for MRI (267); this complementary role of MRI in the evaluation of intracardiac masses is now well established in clinical practice. Frequently, MRI excludes the presence of an intracardiac mass initially suggested by echo. In some cases, MRI identifies an anatomic variant (e.g., distortion of cardiac anatomy by a pectus deformity) as the source of the false-positive echo result (309).

Video 54.10 Transesophageal view demonstrating the right atrium with the inferior vena cava off to the left of the screens, the superior vena cava to the right, and the left atrium at the top, with the interatrial septum in the middle. This view shows a hemangioma in the interatrial septum found incidentally at the time of preoperative transesophageal echo for mitral valve replacement for severe mitral regurgitation. Intraoperatively, the mass was highly vascular as expected and was resected. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

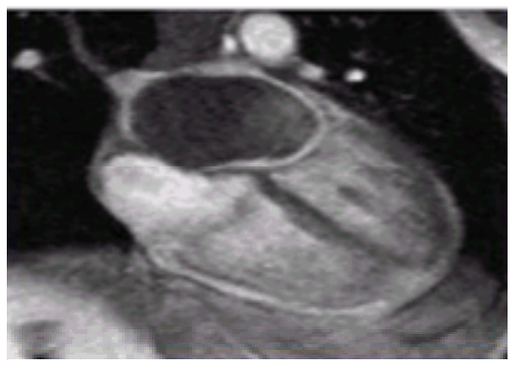
Video 54.11 Four-chamber transesophageal view of a patient with a cystic-appearing mass on the tricuspid valve. *This video must be viewed with QuickTime. If you do*

not have QuickTime you may download it here.

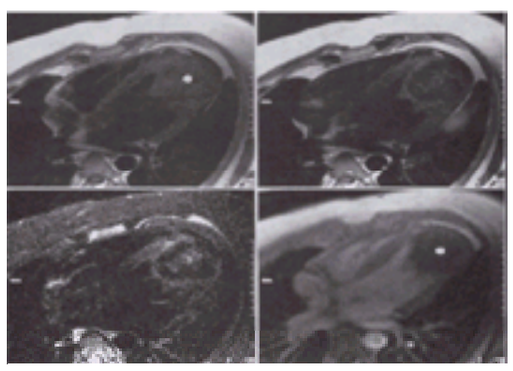
The ability of MRI to identify a variety of benign or malignant tumors primarily involving the cardiac chambers is well known (307,308,312). Studies comparing MRI with echo have indicated that MRI more clearly demonstrates the relationship of masses to normal intracardiac structures and extension into adjacent vasculature or the mediastinum (312,313). When MRI confirms the presence of a mass, definition of anatomy is the most useful parameter for establishing a specific diagnosis (267,307,312). For example, the location of the mass within the left atrium is the main criterion for differentiation between myxoma (i.e., almost always arises from the interatrial septum) and thrombus (i.e., usually occurs near the posterolateral wall or atrial appendage).

MRI tissue characteristics of intracardiac masses add some specificity to their diagnoses (267). Myxomas typically appear brighter than myocardium on T2-weighted S-E MRI because of their increased T2 relaxation times (307) (eFig. 54.27.2). Variability in the appearance of myxomas may reflect their variable composition of water-rich myxomatous tissue (long T2; high signal intensity) versus fibrous tissue and calcification (short T2, low proton density; low intensity). Similarly, fibromas show decreased signal intensity relative to myocardium (eFig. 54.27.3). Lipomatous hypertrophy or lipomas of the interatrial septum have the distinctive short T1 and high signal intensity of adipose tissue (Fig. 54.28). Various other benign intracardiac masses have been described.

Video 54.12 Atrial myxoma (long-axis). A myxoma attached to the interatrial septum is seen. During diastole, the myxoma moves through the mitral orifice into the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 54.27.2** Atrial myxoma (long axis). A myxoma attached to the interatrial septum is seen. During diastole, the myxoma moves through the mitral orifice into the left ventricle.



***e*FIGURE 54.27.3** Myocardial fibroma (T1-, T2-, and T1/T2-weighted spin-echo and ultrafast; horizontal long axis). A large intramyocardial mass of the left ventricle apex (*closed circles*) is characterized by low signal intensity, caused by fibrous tissue, on all four types of images. Lack of evidence of edema or hypervascularity indicates its benign nature.

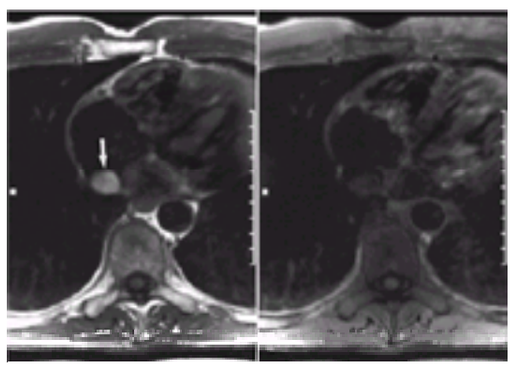


FIGURE 54.28 Atrial lipoma (T2-weighted spin-echo; transaxial). Because of its fatty composition, the signal intensity of the relatively bright, rounded intracardiac lipomatous mass (*arrow*) within the right atrium **(left)** is suppressed with application of fat-saturation techniques **(right)**.

The pattern of invasion by intracardiac malignancies is also well defined using MRI, which permits more accurate diagnosis and description than angiography, CT, or echo (267). MRI findings in cases of intracardiac malignancies have correlated extremely well with findings from surgical exploration or postmortem examination (313).

Various primary intracardiac malignancies have been detected by MRI (267,307). Angiosarcomas are typically found in the region of the right atrioventricular groove and are associated with significant pericardial disease, including complex effusion (Fig. 54.29).

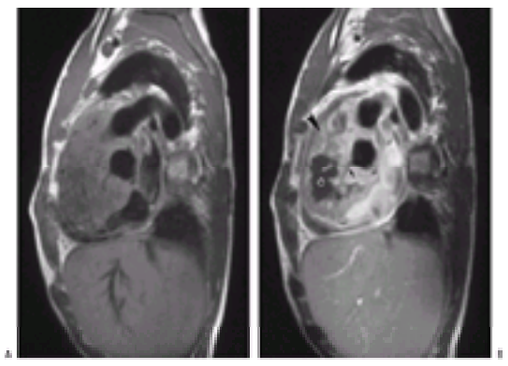


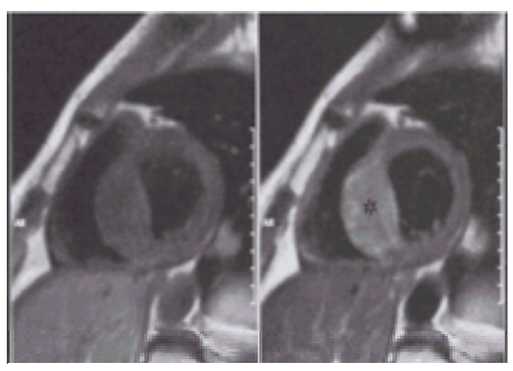
FIGURE 54.29 Angiosarcoma (T1-weighted spin-echo; short axis). Although the mass created by this primary cardiac tumor is easily seen in the right atrioventricular groove before administration of gadolinium chelate **(A)**, the use of contrast enhancement demonstrates peripheral hyperperfusion (*arrowhead*) and its central zone of necrosis (*open circle*) **(B)**; encasement of the right coronary artery (*arrow*) is better seen after injection of the magnetic resonance imaging contrast agent.

Anatomic relationships between primary paracardial tumors and the heart are well demonstrated on MRI (267). Signal intensity differences between tumor (long T1 and long T2), myocardium (long T1 and short T2), and pericardial and epicardial fat (short T1 and intermediate T2) provide excellent image contrast. Furthermore, MRI is useful in differentiating a variety of benign intrapericardial lesions from extrapericardial masses (314). Paracardiac masses external to the pericardial sac are often benign and their characteristics are easily appreciated on MRI (267).

Secondary Tumors

Secondary intracardiac malignancies may involve the cardiac chambers via intravascular or transmural extension. Few have been described by MRI (267).

Secondary paracardiac malignancies, including tumors directly extending or metastasizing to the pericardium or pericardial space, are well seen on MRI (315). Unfortunately, their MRI tissue characteristics are nonspecific (long T1 and long T2) (eFig. 54.29.1). Masses abutting the pericardium with penetration can be easily differentiated from those in which there is direct extension of the tumor to involve the pericardium or myocardium. Compression of the cardiac chambers, interposition of the masses between the spine and the left atrium, and extension of the invasive tumors through the wall of a cardiac chamber are readily demonstrated by S-E MRI. Cine can aid in assessing the extension of such tumors into the pericardium or cardiac chambers because of the appreciation of the relative motion of these structures. Various secondary paracardiac tumors have been evaluated using MRI (315,316).



***e*FIGURE 54.29.1** Myocardial metastasis (T1- and T2-weighted spin-echo; short axis). Seen as an isointense myocardial mass of the interventricular septum with T1-weighting (**left**), the metastatic lesion from a peripheral muscle sarcoma is represented as an area of increased signal intensity with T2-weighting (*asterisk*, **right**); this appearance is related to edema and hypervascularity from the tumor.

Congenital Heart Disease

Despite the plethora of reports demonstrating MRI to be an accurate modality for diagnosing many forms of CHD (231,317), its role in this area remains largely supportive to echo. In particular, in adults with CHD, the diagnostic information provided by transthoracic echo is often incomplete because of the larger body, associated chest deformities, and paucity of adequate imaging windows (318,319). This provides the incentive for using MRI and transesophageal echo, but MRI has the advantage over transesophageal echo of imaging in any desired plane chosen by the operator to include the structures of interests and related anatomy, thereby becoming useful for clarification of complex structural relations in space.

The unique role of MRI in the assessment of adult CHD is primarily in (a) noninvasive shunt quantitation; (b) pursuit of hard to find lesions; (c) evaluation of complex anomalies; (d) assessment of congenital great vessel disease; and (e) postoperative assessment.

VIDEO

Video 54.13 Coarctation of aorta (oblique). A signal-void jet is visible in the proximal descending aorta due to a short-segment narrowing representing a coarctation. Left ventricular hypertrophy is also present. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Noninvasive Shunt Quantitation

Direct quantitation of the amount of shunting as an indicator of the anatomic size of a defect is a useful parameter for planning corrective surgery. For this purpose, ventricular volumes can be accurately determined directly from a series of cine image loops encompassing the full extent of the RV and LV (69). For an atrial septal defect with left-to-right shunting, shunt quantitation can be accomplished with cine in the absence of associated valvular insufficiency or additional shunts by evaluating the difference between the larger RV and smaller LV stroke volumes. Shunt volume for a ventricular septal defect could theoretically be derived by subtraction of the smaller RV stroke volume from the larger LV stroke volume. However, it has been found that RV stroke volume may also be increased in such left-to-right shunts, depending on the location of the ventricular septal defect (154). Therefore, the ventricular volume method may not be as accurate in the setting of a ventricular septal defect.

Some of the previously mentioned limitations of ventricular volume analysis for shunt quantitation may be overcome using volume-flow analysis of great artery flow with velocity mapping. With this approach, quantitation of shunt size can be accomplished by measurement of net blood flow volumes within the main pulmonary artery and ascending aorta over a cardiac cycle. Shunts produce discrepant pulmonary and systemic arterial flows, with the former exceeding the latter in left-to-right shunts, and the converse in right-to-left shunts (Fig. 54.30) (320). This difference can be expressed either in absolute terms (e.g., shunt volume) or in relative terms (e.g., Qp/Qs). Values for shunting derived by volume-flow analysis have correlated well with the results from cardiac catheterization or nuclear first-pass ventriculography (320).

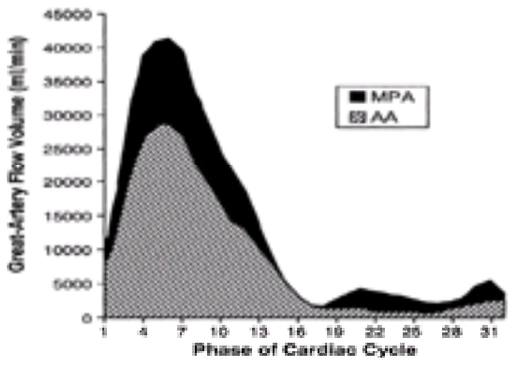


FIGURE 54.30 Flow-volume analysis of atrial septal defect with left-to-right shunting. Volume-flow analysis using velocity mapping permits direct measurement of great artery volume flows over the cardiac cycle after integration of the areas under the curves resulting from plotting of mean instantaneous volume flows passing through a cross section of each artery. The relative difference in volume flow between the main pulmonary artery (MPA), representing systemic stroke volume plus shunt volume, and the ascending aorta (AA), representing only stroke volume, may be used to derive a quantitative measure of left-to-right shunting, such as Qp/Qs. (From White RD. Magnetic resonance imaging of congenital heart disease. In: Pohost GM, ed. *Cardiovascular applications of magnetic resonance*. New York: Futura ublishing, 1993:59, with permission.)

Pursuit of Hard-to-Find Lesions

Echo provides a rapid, repeatable method for assessing the anatomy and functional significance of a simple congenital defect. Therefore, it remains the mainstay of noninvasive assessment of congenital heart disease. Nevertheless, some lesions remain elusive to echo in an adult. Examples of simple lesions often hard to find in the adult on echo, even when a transesophageal approach is used, are sinus venous atrial septal defect and partial anomalous pulmonary venous return (Fig. 54.31) (318,319).

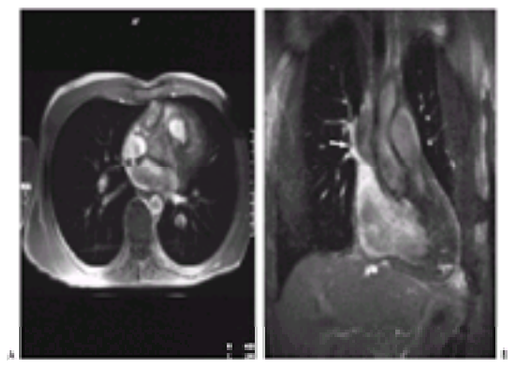


FIGURE 54.31 A hard-to-find sinus venosus atrial septal defect (cine; transaxial and oblique-coronal). High in the sinus venosus portion of the interatrial septum, immediately below the confluence of the superior vena cava with the right atrium, an atrial septal defect (*asterisk*) is noted **(A)**. The frequently associated anomalous return of the right upper pulmonary vein (*arrow*), in this case to the lower superior vena cava, is also demonstrated **(B)**.

Evaluation of Complex Anomalies

To capitalize on the anatomy that MRI demonstrates, application of the segmental approach has proven to be useful to characterize complex CHD in the adult (317,318 and 319,321). Although the morphology of the appendages may be helpful, the received veins generally offer the best clues as to the nature of the atria visualized on MRI; the normal state (atrial situs solitus) is easily distinguishable from the inverted condition (atrial situs inversus), and both conditions can be easily differentiated from classic isomerism (situs ambiguus with either bilateral right-sidedness or left-sidedness). The ventricular positions define the bulboventricular loop; in the dextro (D)-loop, the normal state, the morphologic RV is situated to the right of the morphologic LV, and the reverse occurs with a levo (L)-loop. The morphologic RV, generally the more trabeculated, is characterized by the infundibulum separating the semilunar and atrioventricular valves, whereas the LV, generally the smoother walled, has its atrioventricular valve in fibrous continuity with the associated semilunar valve. Definition of the relationship of the great arteries is also part of the segmental approach, and it is clearly demonstrated with MRI; normally, the ascending aorta is located posteriorly and to the right of the main pulmonary artery, but the relationship is more difficult to define in the setting of atresia of either great artery. This relationship is disrupted with transposition variants, whereby the ascending aorta may become positioned anterior-rightward (D-transposition), anterior-leftward (L-transposition), or alongside the main pulmonary artery. With generally high sensitivity at high specificity levels, MRI may be used to detect abnormalities of visceroatrial situs, venoatrial connection, atrioventricular connection, bulboventricular loop, ventriculoarterial connection, and great artery relationship (Fig. 54.32) (319,321).

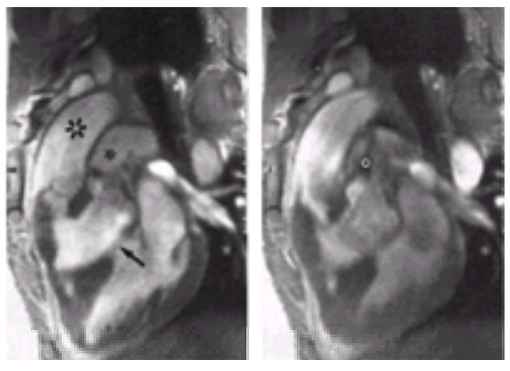


FIGURE 54.32 Complex congenital heart disease with abnormal ventriculoarterial connection and great artery relationship (cine; oblique-sagittal). In communication with an anatomic left ventricle through a muscular ventricular septal defect (*arrow*) is a small hypertrophic anatomic right ventricle, giving rise to both the aorta (*large asterisk*) and the main pulmonary artery (*small asterisk*) in a transposed arrangement. Valvular pulmonic stenosis is manifested by a signal-void jet (*open circle*).

Assessment of Congenital Great Vessel Disease

Imaging of the great arteries and veins by conventional echo can be problematic in adults, because imaging windows are limited by the surrounding lungs (318,319). Because MRI does not require an imaging window, the great vessels and their connections are visualized with the same clarity as cardiac structures.

Congenital Abnormalities of the Aorta

Coarctation

Defining the anatomy of coarctation is important, and for this reason MRI is of particular value (318). With MRI, the whole of the thoracic and abdominal aorta can be visualized with precise anatomic detail. Thus, MRI is a sensitive tool in the investigation of coarctation; the type of coarctation and the severity of stenosis can be seen easily on these images (Fig. 54.33 and *e*Fig. 54.33.1) (317,322). Other details, including the length of the stenotic segment, the presence of arch or isthmic hypoplasia,

the relationship of the coarctation to the aortic arch branches, and the presence of a ductus, are also accurately demonstrated.

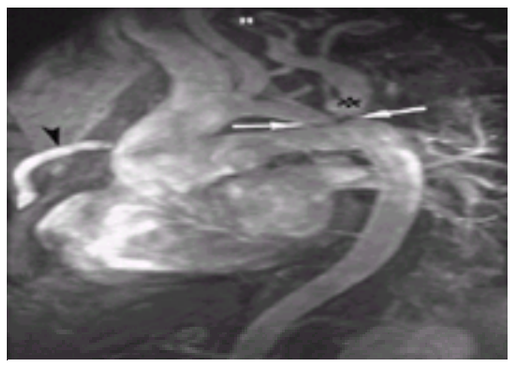
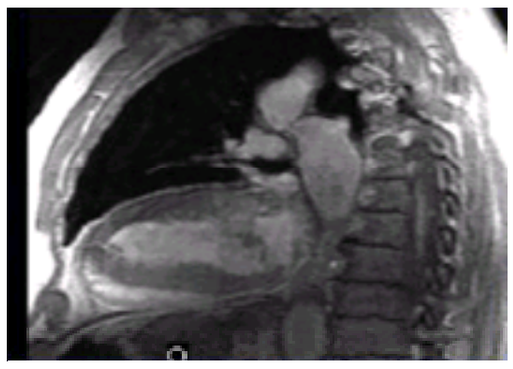


FIGURE 54.33 Complete interruption of the aorta (contrast-enhanced, three-dimensional magnetic resonance angiography; maximal intensity projection). Immediately beyond the stenotic origin of the dilated left subclavian artery (*asterisk*), there is complete interruption of the juxtaductal region of the aortic isthmus (*arrows*). A large internal mammary artery (*arrowhead*) serves as a systemic collateral vessel.



***e*FIGURE 54.33.1** Coarctation of aorta (oblique). A signal-void jet is visible in the proximal descending aorta caused by a short segment narrowing representing a coarctation. Left ventricular hypertrophy is also present.

Although the anatomy and degree of luminal stenosis are clearly visible on S-E images, a pressure gradient cannot be determined. However, the use of cine can both detect basic hemodynamic alterations resulting from stenosis and the resulting pressure gradient and provide further valuable insight into the collateralization from the nature of the turbulent downstream jet (231,318,323). Specifically, a low-signal jet can be visualized passing through and distal to the area of a significant stenosis, although this signal loss must be differentiated from normal signal decrease caused by antegrade flow (323). However, in the setting of complete or high-grade narrowing, flow may be primarily through collaterals and a transcoarctation jet may not be present. Velocity mapping allows quantitative assessment of the coarctation severity based on measurement of transstenosis velocity (99,324). In addition to the site and severity of aortic narrowing, other abnormalities associated with coarctation (e.g., collateral vessels and poststenotic dilatation) may be seen with MRI.

MRI is particularly valuable when applied on a serial basis during regular follow-up of patients who have undergone coarctation repair; it can provide high-resolution images of the repair site and determine the extent of recoarctation (317,318). In patients who have undergone balloon dilatation of either a native coarctation or recoarctation, MRI provides an ideal serial investigation to watch for the development of aneurysm formation at the dilatation site.

Aortic Arch Branching Abnormalities

The value of MRI in the detection of congenital anomalies of the aorta has been well established (322,325). The morphology of the arch, its branching pattern, and its effect on adjacent structures can be recorded with a high degree of detail.

All types of vascular rings and the various anomalous branching patterns of the aortic arch (e.g., double aortic arch) are reliably seen on MRI (324,325). In older patients, or in those who have undergone surgery, MRI shows arch anomalies with greater clarity than transthoracic echo (322). Three-dimensional displays are often valuable for visually relating or connecting in a single image the often tortuous and obliquely oriented arterial components of a vascular ring (326).

Congenital Pulmonary Artery Abnormalities

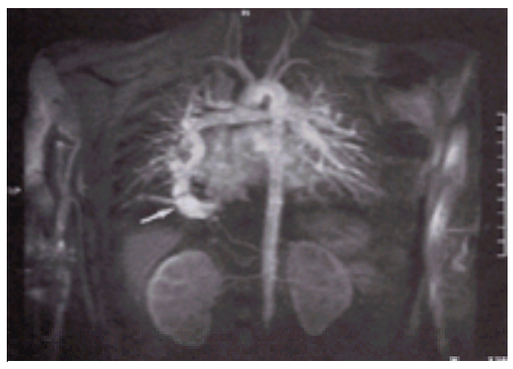
Because MRI is not limited by the acoustic penetration of ultrasound or by the vascular access required for angiography, visualization of central pulmonary vessels (whether a true pulmonary artery or one arising from systemic-to-pulmonary collaterals) can be readily imaged with a high degree of spatial resolution (318,327). The origin, size, and morphology of these vessels can be determined with relative ease using MRI. Stenoses of the main pulmonary artery and central arteries are detected better using cine than S-E imaging; pulmonary artery stenoses result in flow disturbances manifested by jets of signal void on cine (328).

Although MRI accurately delineates the anatomy of the central pulmonary artery system and can identify the aortic origin of major collateral vessels, it often fails to demonstrate the intrapulmonary segments of the arteries and collaterals, thus making the diagnosis of peripheral pulmonic stenoses difficult (319). Although evaluation of the pulmonary artery system within the lungs may be problematic for MRI, evaluation of the main pulmonary artery and central arteries appears to be as accurate as angiography and more accurate than transthoracic echo.

Congenital Abnormalities of the Pulmonary and Systemic Veins

Although the proximal portions of the pulmonary veins near their insertions into the left atrium are usually easily demonstrated with S-E MRI, G-E imaging has the advantage of displaying flow-related signal enhancement within the veins, thereby readily identifying them within the lungs (329). Consequently, cine or MRA is preferable to S-E MRI for the identification of anomalous pulmonary venous drainage, and it may aid in the diagnosis of congenital abnormalities of the systemic veins (330).

MRI has been shown to be effective for demonstration of all types of anomalous pulmonary venous connections, comparable with or more accurate than echo and angiography (321,329,330). In addition to showing anomalous connections (*e*Fig. 54.33.2), venous stenosis or stenosis at an anastomotic site is accurately demonstrated. Reduced sensitivity for detecting the return connections of the pulmonary veins by S-E imaging, compared with G-E MRI or MRA, is probably related to the aforementioned inherent limitations in this technique.



***e*FIGURE 54.33.2** Anomalous pulmonary venous connection (contrast-enhanced, three-dimensional magnetic resonance angiography; maximal intensity projection). The right pulmonary venous system is shown to collect into a common pulmonary vein (*arrow*) draining inferiorly into the junction of the inferior vena cava with the right atrium.

Postoperative Assessment

As more patients with CHD undergo corrective surgery and survive longer, postoperative clinical evaluation becomes increasingly important. MRI is an important adjunct to echo and an alternative to angiography for morphologic examination of CHD after surgery (318,319). The combination of capabilities described earlier for the evaluation of anatomic aspects makes MRI uniquely suited for this pursuit. In contrast to echo, MRI is not severely restricted by postoperative scarring.

The course and patency of extracardiac shunts (e.g., Blalock-Taussig shunt) may be well visualized using S-E or G-E MRI (331), with G-E images more sensitive to identification of blood flow through vascular structures and differentiation between vessels and airway. MRI is somewhat less important for the evaluation of intracardiac postsurgical changes because its morphology is demonstrated as well or better with echo. However, in those instances in which an echo does not provide sufficient intracardiac detail, such as in older patients, MRI remains an important alternative diagnostic modality (330,332).

Important postoperative anatomic features of various surgical procedures for CHD (e.g., Fontan procedure for tricuspid atresia) have been successfully detected and delineated using S-E MRI (331,332). Cine has also been used successfully for postoperative evaluation of CHD patients (330); it has the advantage over S-E MRI of improved differentiation between blood vessels and air-filled structures. Finally, using cine, postoperative complications (e.g., peripatch leak after defect repair) have also been detected based on the presence of signal-void jets. However, the artifacts from metallic surgical materials are more prominent on G-E imaging than on S-E imaging because of greater sensitivity of the former to local magnetic field inhomogeneities, and this may increasingly hinder adequate visualization of structures using cine.

With an increasing number of interventional therapeutic devices, such as umbrellas, coils, and stents, as well as surgical materials being placed for therapy in patients with CHD, there may be increasing limitations of the postoperative diagnostic capabilities of MRI because of increasing problems related to artifacts (319).

FUTURE DIRECTIONS

There is a need for better understanding of the disease processes affecting the heart and vasculature, particularly for (a) their early prevention; (b) improved accuracy for diagnosis and therapeutic planning; and (c) cost-effective, minimal risk, and reproducible monitoring. An improved understanding of three basic and extremely important aspects of CV disease appears to be feasible in the near future because of unique attributes of MRI; these aspects include (a) myocardial characterization; (b) load-independent measures of myocardial function; and (c) noninvasive arterial wall imaging. Anticipated insights from application of MRI to these three aspects should greatly enhance our understanding of the various forms of CV disease, from the standpoint of natural course, manifestations (histologic, anatomic, and physiologic), modes of prevention, and yields from various therapies.

The most common disease process affecting the myocardium is ischemic injury, representing a spectrum with induced reversible ischemia at one end and frank MI at the other. The characterization of intermediate stages of ischemic injury (e.g., “stunning,” resting ischemia, or “hibernation”) has remained a topic of great interest because of the importance in therapeutic planning, and because of the inability of other imaging modalities to completely or reliably meet this challenge. MRI permits direct high-resolution, 3-D visualization of the myocardium and can potentially characterize the myocardium based on assessments of tissue composition, geometry, perfusion, contraction, and relaxation and filling. An important advance in cardiac MRI is the delineation of necrotic myocardium with the delayed-enhancement technique, being the only cardiac imaging modality that is able to directly visualize the amount of necrosis transmurally.

Unfortunately, the commonly used measures of myocardial function are flawed. Consequently, more meaningful measures of myocardial contraction and relaxation and filling, independent of interpatient and intrapatient variability in loading, are needed for a better understanding of the outcome and the effects of different therapies, overall and per patient.

In many patients dying suddenly of CAD, there are no previous signs, such as angina caused by flow-limiting coronary narrowing. Thus, there is a compelling need to appreciate, directly (in the coronary artery itself) or indirectly (in another more easily imaged but representative artery), the presence of unstable nonstenotic atherosclerosis potentially affecting the coronary arteries.

It is reasonable to assume that further development of MRI as a noninvasive diagnostic imaging modality for comprehensive evaluation of CV diseases, especially ischemic heart disease, will be a future pursuit. Packaging of the various capabilities of CV MRI into comprehensive studies establishing unique imaging profiles, such as an atherosclerosis profile, a myocardial ischemia profile, or a post-MI reperfusion profile, seems feasible. For example, a post-MI reperfusion profile might be based on the assessment of myocardial signal indicating postreperfusion edema or hemorrhage; the assessment of myocardial mechanics, with or without low-level pharmacologic stress, to differentiate between residual endocardial and epicardial contraction; or the assessment of flow within an MI-related artery or of distal myocardial perfusion within its distribution to determine adequacy of an acute intervention. Such profiles could appropriately direct patients toward or away from invasive, costly procedures.

CONTROVERSIES AND PERSONAL PERSPECTIVES

In several large institutions, such as ours, MRI has been actively applied to the routine clinical evaluation of a variety of CV diseases over a number of years. In some clinical settings, MRI has gained great acceptance and is now regarded as the diagnostic imaging procedure of choice, whereas in other settings, the yield has been disappointing and MRI is regarded as, at most, an infrequently used adjunct to other modalities, such as echo. Based on our experience, which includes over 1,700 clinical CV MRI examinations per year, a practical weighting of the relative value of MRI, compared with state-of-the-art echo and ECG-referenced multidetector CT, is presented in Table 54.1; in this weighting, relative study cost, portability, and clinical stability of the patient are considered.

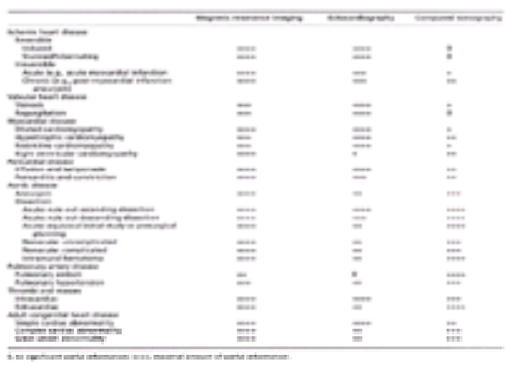


TABLE 54.1 PRACTICAL VALUE OF CARDIOVASCULAR MAGNETIC RESONANCE IMAGING RELATIVE TO OTHER AVAILABLE NONINVASIVE DIAGNOSTIC IMAGING MODALITIES BY DISEASE GROUP

Probably more than any other modality currently available, MRI has the potential to contribute to the improved understanding of CV diseases based on diagnostic imaging; this potential is now rapidly gaining increased attention by the medical community and manufacturers of medical imaging equipment. For this potential to be realized, however, several types of obstacles must be overcome.

Not the least of these obstacles is the current medical environment with its increasing emphasis on cost containment and capitated reimbursement; in this environment, expensive technology, in particular MRI, has already been targeted. Included in this environment are (a) pressures on ordering physicians to avoid use of CV MRI, even when it is thought to be the best first-line diagnostic imaging study and possibly the only one needed, because the charge per examination is relatively greater

(e.g., approximately $200 more than transesophageal echo and $600 more than CT at our institution); (b) increasing demands on physicians involved in CV MRI to pursue clinical productivity in more basic diagnostic imaging areas, where reimbursement may be better established; (c) greater and greater limitations on research time and institutional support for needed clinical investigation in CV MRI; and (d) decreasing availability of MRI equipment for CV imaging because of reduced numbers of scanners or increasing limitations on scheduled scan time for greater patient throughput.

Another obstacle has been largely created by the MRI community itself. It is the problem related to lack of a history of meaningful large clinical studies dealing with outcome and efficacy. Since the advent of clinical MRI, research has rewarded the development of cutting-edge technology in which only alterations in acquisition and postprocessing schemes along with the speculation, but no proof, of improved clinical care have been sufficient to gain recognition in the form of grant funding, support from manufacturers, and relatively unchallenged acceptance of written reports for publication in peer-reviewed journals. In an area with such seemingly endless technologic potential as MRI, this tendency has created a rewarding path of least resistance in clinical investigation with a heavy emphasis on uniqueness and individualism. An unfortunate outcome that now hinders the future of CV MRI has been the passive discouragement of large multicenter patient studies addressing the clinical value of information about CV diseases provided by the more widely available, nonproprietary, and validated MRI techniques; the common argument against past efforts to develop such outcomes and efficacy studies is the anticipation of technologic obsolescence by the time of their completion. Consequently, there is currently little ammunition to fight off cost-containment efforts directed against CV MRI.

Finally, another obstacle that must be overcome is the issue of “ownership,” whether it be that dealing with control of patients or of equipment. MRI is an expensive technology, with scanner costs alone exceeding those of echo and CT by approximately tenfold and twofold, respectively. Siting costs in MRI, which in some circumstances match equipment costs, greatly add to the relatively greater expense of MRI compared with other imaging modalities, especially echo with its negligible siting needs. Although the manufacturers of medical imaging equipment are now demonstrating the ability to reduce the costs of purchasing and installing MRI systems, there appears to be a limit to which the costs can be reduced before the research and development of MRI is no longer regarded as being economically viable. In addition, as long as MRI continues to evolve, the regular allocation of significant funds for hardware and software upgrades, along with the significant routine maintenance costs, will have to be factored annually into institutional budgets. Therefore, a state-of-the-art MRI will probably need to be viewed increasingly, from an economic standpoint, as a technology that is most appropriate for larger medical facilities.

In the case of CV MRI, its potential will be best realized at major CV centers, if it is regarded as an institutional effort, and the leadership responsibility is shared among the following groups: (a) radiology, (b) adult and pediatric cardiology, and (c) cardiothoracic and vascular surgery. To this common effort, radiology departments can contribute expertise in the application of general imaging and MRI principles and in the interpretation and use of the resulting data; experience with quality assurance of an MRI facility; oversight of the performance of routine CV imaging and non-CV issues that arise; and direction in the implementation of new acquisition and postprocessing schemes originating from the general imaging and MRI communities. Adult and pediatric cardiology departments can contribute to the identification of new medical applications of MRI to the evaluation of acquired and congenital CV diseases; leadership in overseeing the monitoring and the manipulations (e.g., stress testing) of patients during physiologic CV MRI examinations; expertise in the interpretation and use of physiologic data from MRI and its correlation with other findings, such as from echo; and experience in conducting meaningful large clinical research studies of CV diseases using MRI. Finally, cardiothoracic and vascular surgery, the clinical groups probably profiting the most to date from CV MRI, can contribute to the identification of new applications of MRI to the presurgical and postsurgical evaluation of CV diseases; expertise in the interpretation and use of morphologic data from MRI; and leadership in exploring the possibility of less invasive surgical therapies, incorporating indirect anatomic visualization by MRI rather than direct surgical visualization. This type of cooperative effort should allow MRI to develop further as a valuable clinical tool for the evaluation of CV diseases.

THE FUTURE

With diseases of the CV system cumulatively representing the number one killer in the United States, there is a need for better understanding of the fundamental histologic, anatomic, and physiologic manifestations of disease processes affecting the heart and vasculature. Technical advances, applicable to the assessment of the CV system, may facilitate MRI’s gaining a more significant role in evaluating these areas. Because MRI permits direct high-resolution, 3-D visualization of the myocardium, it can potentially characterize the myocardium based on assessments of tissue composition, geometry, perfusion, contraction, and relaxation and filling.

It is difficult to determine which, if any, of the expensive technologic advancements currently under investigation in MRI might have a future role in CV imaging. Current research and development with high-field spectroscopic MRI (333), interventional MRI (334), metabolic MRI contrast agents (335), and high-resolution vessel-wall characterization (289) may eventually find clinical applications to future work in CV MRI.

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POSITRON EMISSION TOMOGRAPHY

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OVERVIEW

Positron emission tomography (PET) represents the most advanced scintigraphic imaging technique developed for *in vivo* quantification of cardiac physiology and biochemistry. The state-of-the-art PET instrumentation allows delineation of regional tracer activity with high spatial (4 to 8 mm) and temporal resolution (few seconds per image). A large number of radiopharmaceuticals have been developed to study myocardial perfusion, energy metabolism, and autonomic innervation of the heart. Initial research applications included assessment of fatty acid and glucose metabolism, followed by the quantification of regional myocardial perfusion in patients with coronary artery disease (CAD). More recently, newer tracers such as radiolabeled beta-receptor antagonists allow the presynaptic and postsynaptic evaluation of sympathetic cardiac innervation. Metabolic imaging with fluorine-18-fluorodeoxyglucose (F-18-FDG) has emerged as an important clinical application for assessment of tissue viability in patients with impaired left ventricular function with well-validated diagnostic and prognostic information. F-18-FDG has also been used in combination with single-photon emission computed tomography (SPECT) imaging to exploit the physiologic information, without the need for expensive imaging technology such as PET. PET, in combination with perfusion tracers, provides accurate diagnosis and localization of CAD. The development of less costly PET imaging devices and new radiopharmaceuticals for specific tissue characterization is needed to ensure that PET remains a competitive research and clinical tool in cardiology.

GLOSSARY

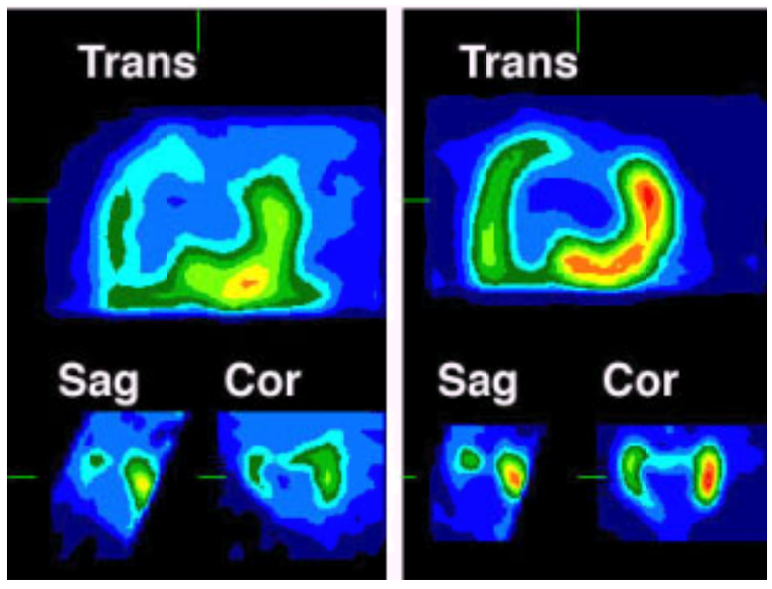
Polar map: Planar representation of tracer accumulation in the left ventricular myocardium, determined by volumetric sampling of the scintigraphic data.

Tracer: Very small amount of substance, labeled with a radioactive isotope, and the decay can be detected externally.

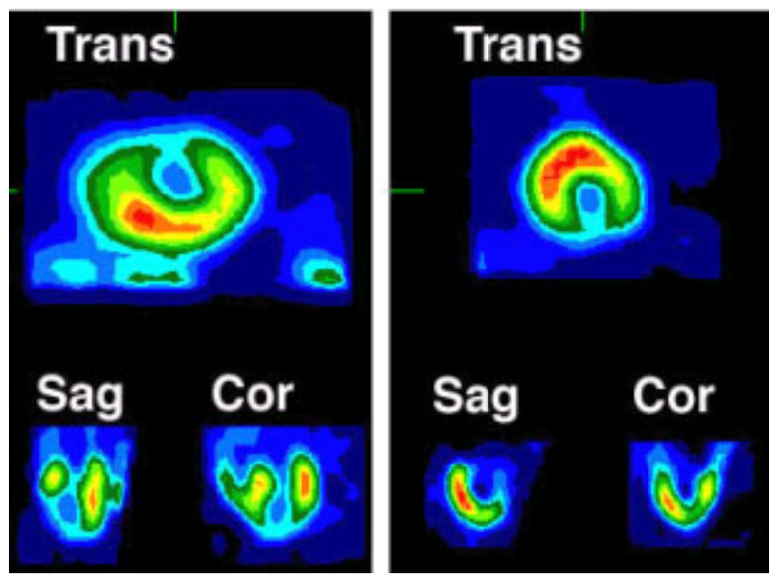
Transmission scan: Measurement of photon attenuation using external sources. Data are used for correction of emission data.

HISTORICAL PERSPECTIVE

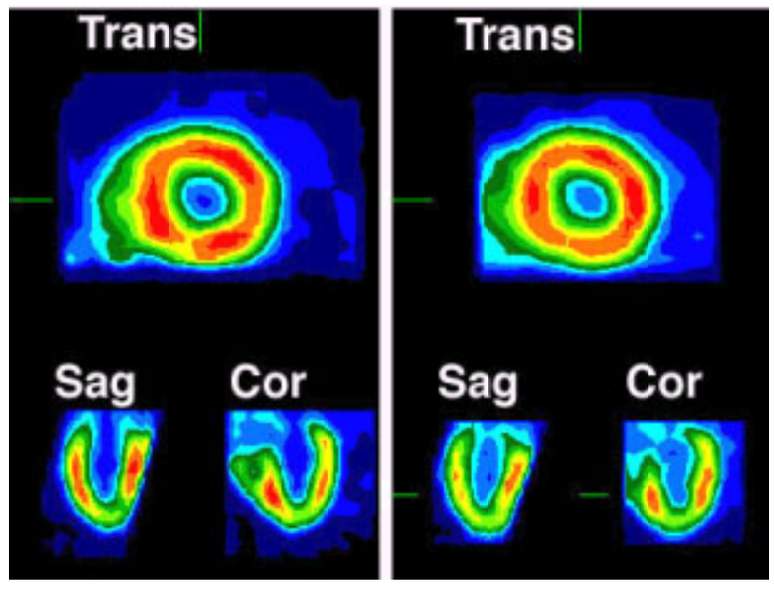
PET was developed as a noninvasive method for quantitative imaging of tissue tracer distribution *in vivo* (autoradiography). Three important technical requirements contribute to this method: the labeling of a biologic substance with short-lived positron emitters, the detection of the annihilation radiation, and the reconstruction of the two-dimensional tracer distribution in transversal slices through the body. Radiopharmacy, instrumentation, and data processing have evolved since the discovery of artificial radioactivity by I. Curie and F. Joliot in 1934. Radioactive isotopes such as carbon-11 (C-11), nitrogen-13 (N-13), or F-18 became available in the late 1930s and early 1940s after the development of the cyclotron by E. O. Lawrence and were used in biologic (1) and the first human studies (2). The advantage of using coincidence measurements for collimation became apparent and was implemented for the first time in a positron probe by Brownell (3) and in a positron scanner for brain studies by Aronow (4). Short-lived radionuclides proved useful for metabolic studies and the first cyclotron that was dedicated to medical application was installed at the Hammersmith Hospital in 1955. With the tomographic imaging of single photon emitters, Kuhl introduced transverse section scanning using a backprojection algorithm (1963) (5). These advances in reconstruction also promoted the development of tomographs for positron imaging in the early 1970s, when the research group of Hoffmann, Phelps, and Ter Pogossian at Washington University built the first positron emission tomograph for brain imaging (6).



Matched resting rubidium (*left*) and radiolabeled fluoro-deoxyglucose (*right*) positron emission tomographic images. Transverse, sagittal, and coronal positron emission tomographic images demonstrating extensive scar in the left anterior descending and right coronary artery territories with evidence of myocardial hibernation in the left circumflex artery territory and right artery territory (including the right ventricle).



Matched resting rubidium (*left set*) and radiolabeled fluoro-deoxyglucose positron emission tomographic (*right set*) images. Transverse, sagittal, and coronal positron emission tomographic images demonstrating myocardial hibernation in the left anterior descending artery territory.



No fixed or transient changes in between stress (*left*) and resting (*right*) rubidium-82 positron emission tomographic images on transverse, sagittal, and coronal slices, demonstrating a dilated left ventricular cavity and a lack of myocardial scar or ischemia in a patient with nonischemic dilated cardiomyopathy.

PET was introduced in the 1970s as a new imaging modality in cardiology by investigators at Washington University in St. Louis (7). Initial studies used metabolic tracers such as F-18-FDG and C-11 palmitate for the noninvasive characterization of myocardial substrate metabolism. These investigations took advantage of the availability of biologically active tracers labeled with short-lived isotopes such as C-11 and F-18 and demonstrated the ability of PET to describe the interaction of various substrates for cardiac energy metabolism. With the introduction of flow markers such as N-13 ammonia and oxygen-15 (O-15) water, the application of PET shifted toward the evaluation of myocardial perfusion primarily in patients with CAD. Since then, the technical advances of PET have allowed sophisticated biochemical and physiologic investigations of the heart, using a large number of radiopharmaceuticals to examine not only flow and metabolism, but also the autonomic innervation of the heart. The method provides quantitative measurements of spatial as well as temporal distribution of radioactivity within the blood and myocardium. Although other imaging modalities provide similar information, PET should be considered the most validated and accurate tool to measure myocardial perfusion and to allow quantitative tissue characterization assessing various aspects of cardiac function.

This chapter reviews the current role of PET in the functional evaluation of CAD and other cardiovascular disorders. Established clinical applications, as well as experimental concepts, are discussed. Finally, the results obtained with PET are compared with those derived from SPECT and other imaging modalities to define the clinical role of PET in cardiology.

IMAGING PRINCIPLES

Imaging of regional tracer concentration is accomplished by the unique properties of positron decay and annihilation. Positron-emitting radionuclides have a nuclear imbalance characterized by an excess of protons. To restore stability to the nuclear structure, a proton is converted to a neutron, and a positron is emitted. This energetic positron traverses a few millimeters through the tissue until it becomes thermalized by electrostatic interaction between the electrons and the atomic nuclei of the media and combines with a free electron to form a two-particle atom-like entity called a *positronium*. The positronium quickly decays by annihilation, which converts the positron and electron mass into energy and generates a pair of gamma rays. Conservation of energy and momentum of the positronium before annihilation require the photons to travel in nearly opposite directions (180 degrees apart) with an energy of 511 keV each (Fig. 55.1). The opposed photons from positron decay can be detected by using pairs of colinearly aligned detectors. Gamma rays interact with these aligned detectors within a predefined time window and are registered as radioactive events (coincidence counting). The detector pairs of a PET system are installed in a ring-like pattern, which allows measurement of radioactivity along lines through the organ of interest at a series of angles and radial distances. This angular information is used to reconstruct tomographic images of regional radioactivity distribution. State-of-the-art PETs consist of multiple, closely packed rings of detectors that enable simultaneous imaging of several image planes.

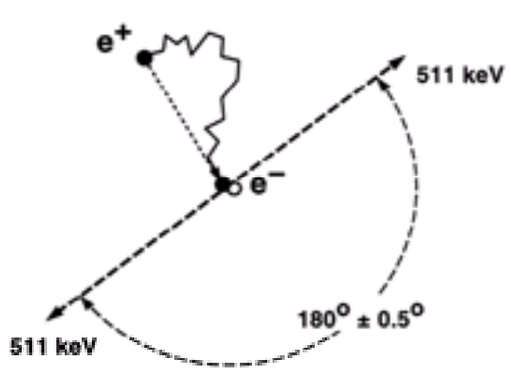


FIGURE 55.1 Positron emission and decay. The energetic positron (e^+) travels several millimeters in the tissue before it combines with an electron (e^-). The positron and electron annihilate, resulting in two opposing gamma rays with 511 keV each. See text for details.

Because the left ventricular wall is approximately 10 mm thick, high spatial resolution is necessary for the quantitative analysis of tissue tracer concentration (Fig. 55.2). The spatial resolution of PET approaches 5 to 7 mm in all axes and is expected to improve to approximately 2 to 3 mm in the future. Myocardial movement and change in wall thickness during the cardiac cycle affect the image resolution. PET data quality can be improved by ECG gated acquisitions (8).

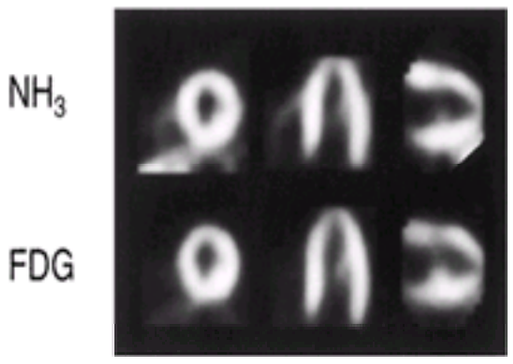


FIGURE 55.2 Positron emission tomographic images of normal volunteer with nitrogen-13 ammonia (NH_3) and fluorine-18-fluorodeoxyglucose (FDG).

Correction of photon attenuation is a prerequisite for tracer distribution measurements in the heart to avoid artifacts caused by tissue surrounding the heart. External sources are used to perform a transmission scan, which allows estimates of regional attenuation factors. Ring or rotating pin sources made of positron emitters are used for this purpose (9,10).

The PET detector system has to perform linearly over a wide range of count rates and allow for short scan time intervals to monitor the rapid uptake and release of tracers. Most of the current commercial tomographs use block detectors made of scintillation crystals (bismuth germanate) and photomultipliers (11). New detector materials such as lutetium oxyorthosilicate and lutetium aluminum perovskite may improve imaging performance at a reasonable cost. Lutetium oxyorthosilicate has a shorter scintillation light-decay time, higher light output, and approximately the same attenuation length compared with bismuth germanate (12).

Collimators have been designed for imaging 511-keV gamma rays from positron emitters with SPECT systems. Although spatial resolution (15 to 20 mm) and detection efficiency (eight times less) are lower in these systems compared with PET, good imaging quality can be achieved for cardiac studies. The concept of dual-head SPECT cameras without collimators in coincidence mode was introduced. By exploiting the electronic collimation inherent in coincidence detection, sensitivity is increased. Using conventional nuclear medicine instrumentation could facilitate the widespread use of imaging positron emitters (13,14).

PRINCIPLES OF RADIONUCLIDE PRODUCTION AND RADIOCHEMISTRY

C-11, N-13, O-15, and F-18 are the most common positron-emitting radionuclides, all of which have a short physical half-life ranging from 122 seconds for O-15 to 110 minutes for F-18 (Table 55.1).

Radionuclide	Physical half-life	Radiopharmaceutical	Application
Rubidium-82	76 sec	Rubidium	Flow
Oxygen-15	120 sec	Water	Flow
Nitrogen-13	10 min	Ammonia	Flow
Carbon-11	20 min	Palmitate	Fatty acid metabolism
		Acetate	Oxygen consumption
		Hydroxyephedrine	Catecholamine uptake
		CGP-12177	Beta-receptor density
Fluorine-18	110 min	Deoxyglucose	Glucose metabolism
		Misonidazole	Hypoxia
		FTHA	Fatty acid metabolism

FTHA, 14(R,S)-[18F]-fluoro-6-thiaheptadecanoic acid.

TABLE 55.1 TRACERS COMMONLY AVAILABLE FOR CARDIAC POSITRON EMISSION TOMOGRAPHIC APPLICATIONS

These radionuclides do not occur naturally; they must be produced using a nuclear reaction. The predominant and most efficient production method is to modify the nuclear structure of specific stable radionuclides by accelerated particle bombardment with either protons or deuterons. A cyclotron is a particle accelerator used most often for radioisotope production in PET imaging (15,16).

Few positron-emitting radionuclides are generator produced. A generator consists of a parent–daughter radionuclide pair in an apparatus that permits a separation and extraction of the daughter compound from the parent. The daughter radionuclide is replenished continuously by decay of the parent. The most common generator system in cardiology is strontium-82/rubidium-82 (17). The preparation of radiopharmaceuticals for PET requires a dedicated radiopharmaceutical facility. Because of the short half-lives of the isotopes, novel adaptations of sometimes complex synthetic procedures are needed to prepare useful amounts of molecules. Because there are positron-emitting radionuclides of oxygen, carbon, and nitrogen, it is theoretically possible to label any organic compound of interest, whether it is a natural substance or a synthetic drug. Fluorine, although not often found in naturally occurring molecules, can be readily substituted for a hydrogen or hydroxyl group and is a favorite of radiochemists designing new pharmaceuticals. With these four radionuclides a large number of positron-emitting tracers can be synthesized and used in clinical studies.

TRACER KINETIC MODELING

Current PET instrumentation allows for the acquisition of scintigraphic data, with high temporal resolution necessary for the description of tracer kinetics in myocardial and vascular structures. In contrast to other organs, the large blood chambers of the right and left ventricle allow simultaneous measurements of radioactivity in blood and tissue. Several studies have validated the accuracy of this approach for the noninvasive determination of the arterial input function without the need for arterial blood sampling (18).

Combining temporal sequencing of activity changes in blood and myocardium, tracer tissue uptake rates as well as clearance of activity from tissue can be quantitated (19). Depending on the radiopharmaceutical used, tracer kinetic models can be used to derive estimates of myocardial blood flow, metabolic rate, and tissue tracer retention. The most commonly used kinetic models are two- or three-compartment models. Although physiologic processes are more complicated than can be described by such simple models, limitations in counting statistics and duration of data acquisition require a simplification of the physiologic process with such models. Please refer to references 19 and 20, both excellent reviews that discuss details of tracer kinetic modeling.

ASSESSMENT OF MYOCARDIAL BLOOD FLOW

Flow Tracer

Blood flow tracers can be classified based on their physiologic behavior. O-15 water, for example, represents a freely diffusable tracer that washes in and out of myocardial tissue as a function of blood flow. The first-pass extraction of O-15 water in the heart is not diffusion limited, nor is O-15 water tissue extraction affected by any metabolic pathways (21,22 and 23) (Fig. 55.3).

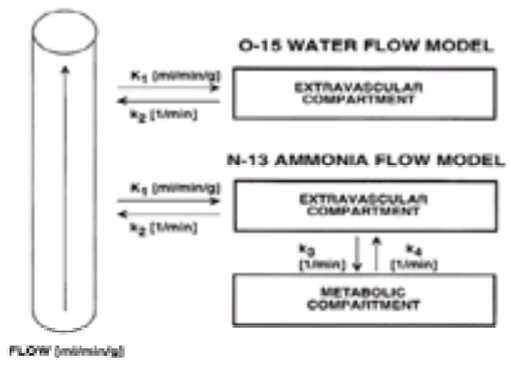


FIGURE 55.3 Schematic diagram illustrating the compartment models for oxygen-15 water (*top*) and nitrogen-13 ammonia (*bottom*).

The second group of flow markers are radiotracers, which are retained in myocardial tissue proportional to myocardial blood flow. For these radiopharmaceuticals, the initial tracer extraction (first-pass extraction) and their tissue retention are important factors defining their suitability as blood flow tracers. N-13 ammonia is highly extracted by myocardial tissue in the form of N-13 ammonia (24,25 and 26). Within the tissue, the tracer can either back diffuse into the vascular space or be trapped in the form of N-13 glutamine.

Ionic tracers such as rubidium-82, rubidium-81, or potassium-38 display similar tracer kinetics to thallium-201 (27). Initial extraction of these compounds ranges between 50% and 70%. For both N-13 ammonia retention and ionic tracer extraction, a nonlinear relationship exists between blood flow and tissue tracer extraction (27,28).

Clinical Application

Qualitative Assessment of Regional Myocardial Blood Flow

Initial applications of PET for the detection of CAD consisted of the visual assessment of regional myocardial tracer distribution under rest and stress conditions (29,30,31,32 and 33). In most studies, pharmacologic stress testing has been used to assess coronary reserve (29). The advantage of this approach is the standardized stress procedure, which can be performed in the PET gantry without moving the patient between rest and stress imaging (34).

The most commonly used tracers are rubidium-82 and N-13 ammonia (24,32). With rubidium-82, the rest/stress protocol can be completed in approximately 1 hour, whereas N-13 ammonia blood flow studies require approximately 2 hours. Extensive clinical data exist with both radiopharmaceuticals to document the high diagnostic accuracy with sensitivity and specificity values ranging from 85% to 95%. Demer et al. demonstrated that there is little difference between the use of either tracer for the detection of CAD (33). Most studies used visual data analysis similar to the methods used routinely for thallium-201 or technetium-99m sestamibi SPECT imaging (25,30,35,36). Automated techniques for semiquantitative data analysis, similar to those used for SPECT imaging, have also been developed for PET flow studies (37,38) (Fig. 55.4).

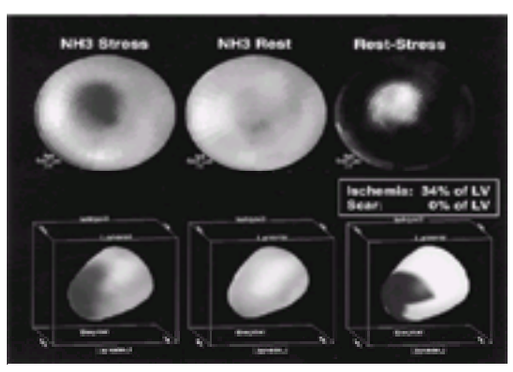
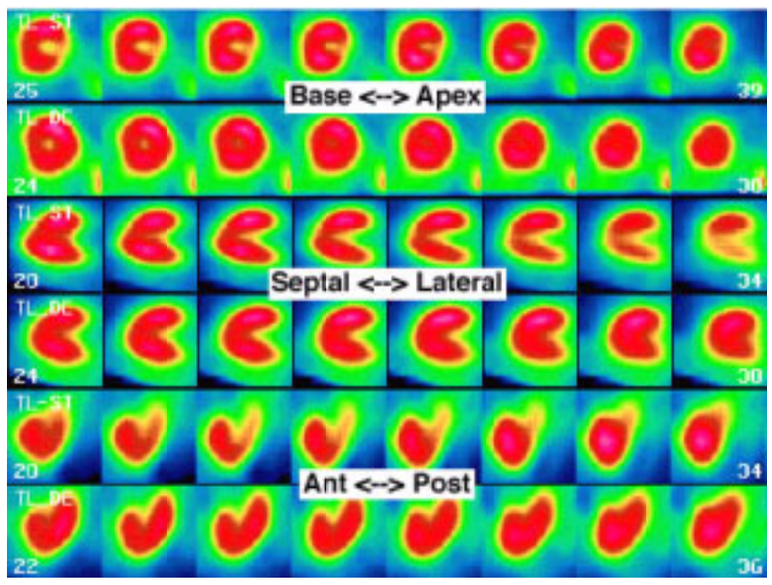
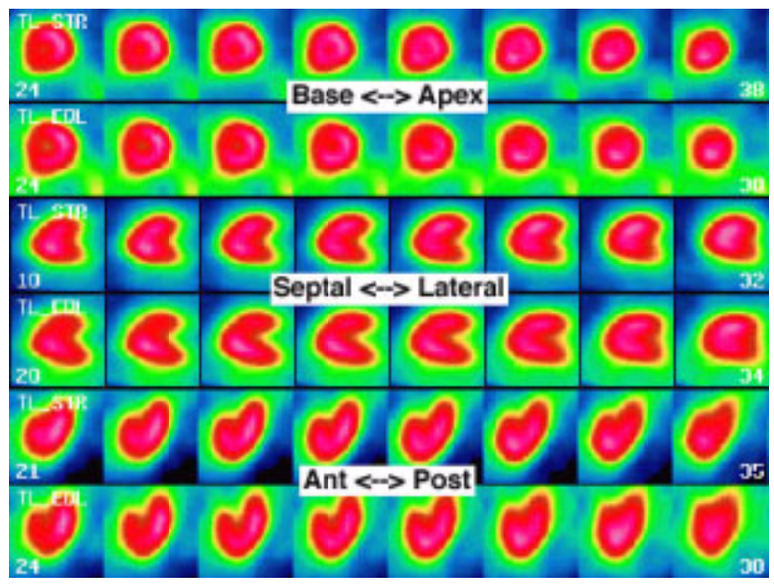


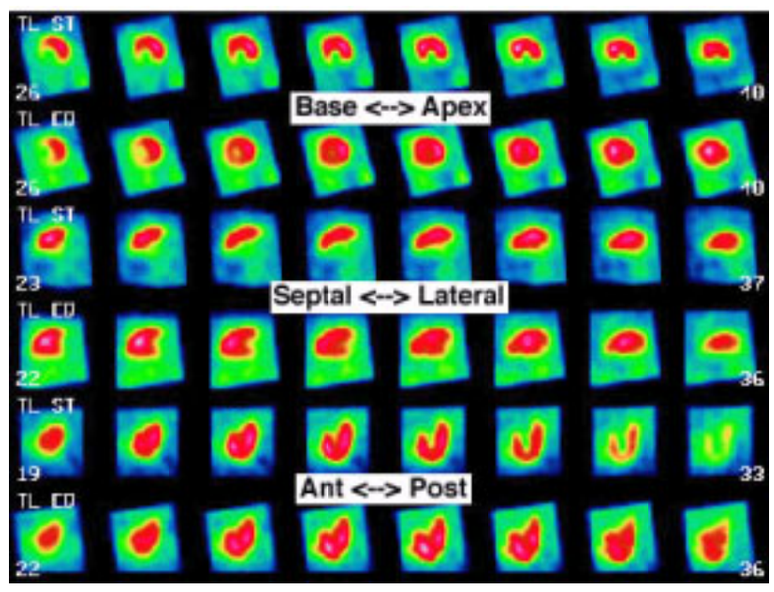
FIGURE 55.4 Polar maps (*top*) and three-dimensional visualization (*bottom*) of nitrogen-13 ammonia (NH_3) uptake in a patient with a stress-induced defect. Results provide semiquantitative assessment of ischemic and scar tissue. LV, left ventricle.

Although PET investigations are more expensive than conventional SPECT imaging or stress echocardiography, data by Patterson et al. (39) indicate that the use of PET in the diagnostic workup of patients with suspected CAD may be cost-effective, especially when patients with low and intermediate pretest likelihood for CAD are evaluated.





Thallium-201 single-photon emission computed tomography stress and delayed images (A). Transverse, sagittal, and coronal plane images demonstrating lateral wall ischemia in a patient with severe proximal left circumflex artery stenosis. Thallium-201 single-photon emission computed tomography stress and equilibrium images (B). Transverse, sagittal, and coronal plane images obtained from a patient after successful intervention for severe proximal left circumflex artery stenosis (normal study).



Thallium-201 single-photon emission computed tomography stress and equilibrium images. Transverse, sagittal, and coronal plane images demonstrating inferior and posterior wall ischemia in a patient with a severe proximal stenosis in a dominant right coronary artery.

Video 55.1 Stress echo of a patient with left anterior descending coronary artery ischemia, parasternal long-axis and short-axis views. Note the deterioration of the anteroseptal wall (*upper right panel*) and the anteroseptum and anterior walls (*lower right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 55.2 Stress echo (apical views) of a patient with left anterior descending coronary artery ischemia. Note the worsening of the distal septum and entire anterior wall. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Demer et al. demonstrated that the severity of perfusion abnormalities determined by PET imaging correlated with the angiographically predicted coronary reserve measurements for a given vascular territory (33). More recently, Gould et al. reported a significant gradient in regional perfusion from base to apex in patients with mild but diffuse arteriographic disease, suggesting greater downstream flow abnormalities in the absence of regional limiting stenoses (40).

In addition to the diagnosis of CAD, the follow-up of patients with CAD by noninvasive means is of clinical interest (41). Longitudinal studies evaluating the effect of therapeutic or lifestyle interventions provide objective outcome criteria and are especially important in patients considered at high risk for progression of disease severity. Gould et al. have used PET and angiography to follow 20 patients undergoing cholesterol-lowering diets over 5 years. The semiquantitative PET parameters describing severity and extent of stress-induced perfusion abnormalities indicated much more profound changes following therapy as compared with angiographic criteria (Fig. 55.5). The relative magnitude of changes in size and severity of PET perfusion abnormalities was comparable with or greater than the magnitude of changes in percent diameter stenosis, absolute stenosis lumen area, or stenosis flow reserve documented by quantitative coronary arteriography (42).

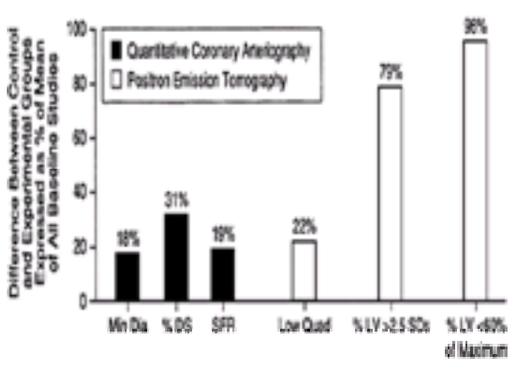


FIGURE 55.5 Comparison of changes by positron emission tomography and quantitative coronary arteriography. The positron emission tomography measures were myocardial quadrant with the lowest average activity (Low Quad), percentage of left ventricle (LV) outside 2.5 standard deviations of normals, and percentage of LV activity less than 60% of maximal activity. Measurements by quantitative coronary arteriography were minimum absolute lumen diameter (Min Dia), percent diameter stenosis (% DS), and stenosis flow reserve (SFR) derived from the integrated effects of absolute lumen diameter, % DS, and cumulative length effects based on fluid dynamic equations. The absolute difference in changes between the control and experimental groups was expressed as a percentage of the mean of each measurement at baseline for all patients. (From Gould KL, Ornish D, Scherwitz L, et al. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *JAMA* 1995;274:894–901, with permission.)

Quantitative Assessment of Myocardial Blood Flow

The potential of PET for the quantitative assessment of myocardial blood flow represents a major advantage over SPECT imaging. Such measurements provide flow estimates in milliliters per minute per 100 g of tissue, which can be used to assess myocardial microcirculation under resting and stress conditions as well as before and after pharmacologic interventions. For such flow measurements, dynamic data acquisition is necessary to describe arterial input function as well as tissue response.

Oxygen-15 Water

O-15 water can be administered either as bolus injection or O-15–labeled CO_2 inhalation (22,23,43,44). Radiolabeled CO_2 is rapidly converted to water in lung tissue and transported to the heart as O-15 water. Both approaches use the uptake as well as washout of radioactivity from the myocardium, assuming a constant partition coefficient (0.80 to 0.90) of water between vascular and tissue space (Fig. 55.3). The water method also assumes homogeneous tissue within the region of interest used for quantitation of myocardial blood flow. To delineate myocardial tissue boundaries, the blood pool contribution has to be removed from O-15 water studies. For this purpose, a separate inhalation of O-15–labeled CO is commonly used (23). More recently, spectral analysis of dynamic O-15 water has been shown to allow for delineation of myocardial structures. The tracer kinetic model approach for O-15 water flow measurement includes a term correcting for the geometric distortion caused by limited image resolution provided by PET (partial volume effect, activity cross-contamination) (21,23,45). The use of O-15 water (as a blood flow marker) has been validated in various animal models and has demonstrated close agreement with microsphere flow measurements (45,46 and 47). Correction of flow values with the perfused tissue fraction leads to a determination of an index describing the relative amount of perfused tissue within a myocardial segment (48). In addition, methods have been developed to quantify not only flow, but also oxygen metabolism using O-15 water (49).

Nitrogen-13 Ammonia

Several approaches have been introduced to describe the myocardial kinetics of N-13 ammonia using a compartmental model that relates the N-13 activity in the vascular, free intracellular, and metabolic space (50,51 and 52) (Fig. 55.3). Assuming the first transit extraction (EF) of N-13 ammonia is approximately 100%, the model estimate (K_1) serves as a quantitative index of perfusion (F) ($F = K_1 \times EF$) (24). These methods have been validated in the animal laboratory comparing N-13 ammonia perfusion measurements with microsphere measurements as a gold standard, or with O-15 reference PET measurements (46,52,53).

Other Tracers (Rubidium-82, Copper-62 PTSM, Potassium-38)

Rubidium-82 has been proposed for quantitative flow measurements (54,55). Data in the animal model and preliminary clinical results demonstrate the feasibility of using this radiopharmaceutical for quantitative flow measurements. Copper-62 PTSM [pyruvaldehyde bis(N4-methyl)thiosemicarbazone] has also been used for the assessment of myocardial blood flow (56). Quantitative flow estimates are limited because of the rapid sequestration of activity in red blood cells, which alters the arterial input function and the availability of tracer to tissue.

Clinical Application

The quantitation of regional coronary flow reserve has been advocated by Gould et al. for the functional assessment of the severity of coronary artery stenosis in patients with CAD (57). The parameter flow reserve describes not only the functional significance of a given coronary lesion but also vascular reactivity and collateral blood flow in the poststenotic vascular territories. Such functional measurements complement the anatomic description of CAD and link the morphologic alterations of epicardial arteries with perfusion patterns assessed at the level of microcirculation. Limitations of angiographic characterization of CAD are widely appreciated because of the complex three-dimensional nature of atherosclerotic plaques as well as considerable interobserver variability in angiographic data interpretation (41,57,58 and 59).

PET approaches have been extensively validated in animals and in healthy volunteers. There is good reproducibility of blood flow measurements under resting as well as stress conditions in volunteers and patients with CAD, as shown by the consistent measurements of coronary reserve values (60,61). Coronary flow reserve over 2.5 times resting flow must be considered *normal* based on the standard deviation of measurements in individuals at low likelihood of CAD (62,63).

A relationship between coronary reserve measurements and age in subjects without CAD has been demonstrated (64,65). However, there are other factors, such as left ventricular hypertrophy, hypertension, and syndrome X, which may affect coronary reserve measurements in the absence of vascular abnormalities defined by angiography (66). Animal and clinical data have indicated that arterial hypertension leads to reduced coronary flow reserve. It also has been shown, using PET, that therapy of patients with arterial hypertension may improve regional coronary reserve measurements (67).

Relationship Between Positron Emission Tomography Flow Measurements and Angiographic Assessment of Coronary Artery Disease

In patients with CAD, coronary flow reserve measurements are reduced (62,68,69,70 and 71). A correlation between the severity of coronary artery disease and severity of flow reserve impairment has been documented (62,70,71 and 72) (Fig. 55.6).

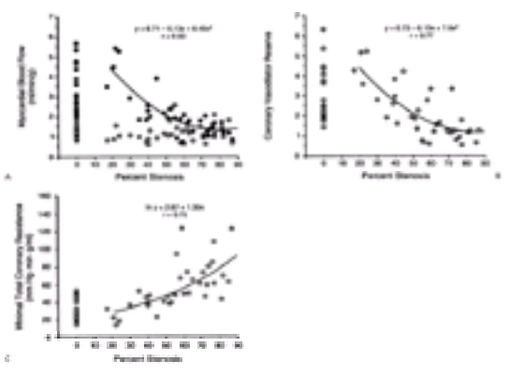


FIGURE 55.6 Myocardial blood flow **(A)**, coronary flow reserve **(B)**, and coronary resistance **(C)** in relation to stenosis expressed as percent of vessel diameter. (From Uren NG, Melin JA, De-Bruyne B, et al. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med* 1994;330:1782–1788, with permission.)

Detection of Preclinical Coronary Artery Disease by Flow Measurements

Comparing the incidence of abnormal coronary flow reserve with the severity of stenosis, as defined by quantitative angiography, reveals a high sensitivity of coronary flow reserve measurements for the detection of severe coronary artery stenosis (greater than 95%). The high incidence (approximately 30%) of abnormal coronary flow reserve in territories with only mild CAD is surprising as defined by angiography (63). These data have been confirmed by several laboratories, indicating that coronary flow reserve with pharmacologic stress agents may provide more sensitive means to detect early CAD than angiographic criteria alone (62,73). This hypothesis has been addressed by several investigators (74,75,76 and 77), who have demonstrated that coronary flow reserve was abnormal in asymptomatic male patients without clinical evidence of myocardial ischemia, but at high risk for the development of CAD based on risk factor profile. A significant relationship between the impairment of coronary flow reserve and plasma cholesterol, low-density lipoprotein, high-density lipoprotein, and oxidized low-density lipoprotein has been reported. Coronary flow reserve has been shown to be reduced in young men with familial hyperlipidemia, especially with combined abnormalities in cholesterol and triglyceride serum levels (phenotype IIB) (78). Furthermore, reduction of flow reserve has been observed in asymptomatic patients with insulin-dependent and non–insulin-dependent diabetes mellitus (74). The pathophysiologic mechanism of the reduced coronary flow reserve in territories with no or only mild angiographic evidence of stenoses is not yet known but may represent a complex interplay of vascular alterations, as well as endothelial dysfunction (79). The hemodynamic response to dipyridamole or adenosine can be modified by alpha- or beta-receptor blockade enhancing the range of coronary flow measurements (80,81). First results using cold pressor stress testing in combination with PET confirm the results obtained in the catheterization laboratory using intracoronary acetylcholine infusion (82,83). In addition, mental stress has

been used to investigate coronary vascular reactivity in normal and CAD patients, which demonstrated reduced flow response in this patient group (84).

PET measurements have been used to assess the acute and chronic effect of smoking on dipyridamole-induced flow changes. Smoking during the PET study decreased the dipyridamole-induced hyperemia and coronary reserve (77). The effects of smoking on coronary vascular reactivity can be reversed by intravenous L-arginine (82) or administration of the antioxidant vitamin C (77).

Cardiovascular conditioning is thought to favorably alter the natural history of CAD. Czernin et al. (85) investigated patients undergoing a short-term exercise and diet program. The beneficial effect of this program on heart rate, blood pressure, and cholesterol was associated with a significant increase in flow reserve. Pharmacologic therapy with lipid-lowering drugs (simvastatin, fluvastatin) is associated with improvement of coronary flow reserve (86,87 and 88). Guethlin et al. reported a delayed response when flow measurements at 2 months were compared with those obtained at 6 months after initiation of lipid-lowering therapy. These data suggest that other factors than only lipid serum levels may be responsible for the beneficial effects of statins on vascular reactivity.

Quantitative regional flow measurements may be useful in preclinical CAD, identifying abnormal vascular reactivity as an early marker of the atherosclerotic process with diagnostic and prognostic value (76,89). In advanced disease PET provides a means to monitor pharmacologic interventions as well as to assess the effect of regional revascularization by percutaneous coronary intervention and surgery (90,91,92,93,94,95,96,97 and 98).

Other Cardiovascular Diseases

Quantitative flow measurements with PET have been used in patients with cardiac transplantation to study coronary physiology in this patient population. Several studies have indicated that coronary reserve is maintained in the cardiac transplant patient (69,99). Wolpers et al. (100) also demonstrated a relationship between angiographic evidence of vasculopathy and PET flow reserve. In contrast to angiography, flow reserve values were homogeneously reduced, suggesting a diffuse obstruction of the microvascular bed in patients with posttransplant vasculopathy. Quantitative PET flow measurements were also performed in patients with cardiomyopathy (101). Patients with hypertrophic cardiomyopathy display a reduced coronary reserve, which not only affects the hypertrophied interventricular septum but also the free lateral wall (68). These findings indicate that the pathophysiologic process involving the myocardium of patients with hypertrophic cardiomyopathy may not be limited to the hypertrophied interventricular septum (68). In patients with dilated cardiomyopathy, there appears to be a reduction in coronary flow reserve, which may provide prognostic information (102,103). Studies by Merlet et al. (104) indicate that PET blood flow measurements are in close agreement with invasive assessment of flow velocity by Doppler methods in this patient population. Furthermore, data by Parodi et al. (105) show that the flow response to pacing and dipyridamole is altered in patients with dilated cardiomyopathy, suggesting endothelial dysfunction. This hypothesis is supported by data reporting decreased flow response to cold pressor testing in this patient population (106).

ASSESSMENT OF SUBSTRATE METABOLISM

Several PET radiopharmaceuticals have been developed to investigate the myocardial energy metabolism that depends on the oxidation of various substrates (Table 55.1). Under fasting conditions, the majority of cardiac adenosine triphosphate production relies on the oxidation of free fatty acids (107,108). Free fatty acids are avidly extracted by the myocardium where long-chain acyl-coenzyme A (CoA) is rapidly formed. Activated fatty acids are used in the synthesis of triglycerides or phospholipids. The majority of acyl-CoA, however, is transported via the carnitine shuttle into the mitochondria where beta-oxidation takes place (Fig. 55.7). The end product of beta-oxidation is acetyl-CoA, which enters the tricarboxylic acid cycle, the final pathway of oxidative metabolism of all substrates. In the presence of high free fatty acid and low insulin plasma levels, only a small amount of glucose is extracted by the myocardium. However, in the postprandial state, glucose transport into the cell is enhanced and the glycolytic rate is increased. But even after carbohydrate loading, only approximately 30% to 50% of overall cardiac substrate metabolism depends on oxidative metabolism of glucose (109). During physical exercise, plasma lactate levels increase and contribute to myocardial energy metabolism (110).

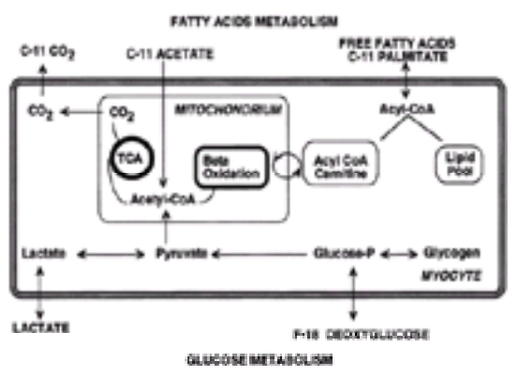


FIGURE 55.7 Conceptual model illustrating metabolic fate of various substrates in the myocardium. Acyl-CoA, acyl-coenzyme A; TCA, tricarboxylic acid cycle.

Aside from the physiologic increase of glycolysis in the postprandial state, glycolysis plays an important role during and after myocardial ischemia. Experimental studies have shown that myocardial glucose transport and metabolism are upregulated during myocardial ischemia with production and release of lactate (111,112). However, after ischemic episodes, glycolysis remains enhanced, with evidence of oxidative and nonoxidative use of exogenous glucose. There is preliminary evidence that enhanced myocardial oxidative glucose metabolism persists after an ischemic episode, most likely because of an upregulation of glucose transport (113,114 and 115). Biopsy studies in patients with severe CAD and chronic dysfunction of left ventricular segments have shown increased glycogen storage, as evidence of chronic alterations of glucose metabolism in hibernating myocardium (116). Such a metabolic pattern may reflect cell dedifferentiation in repetitively ischemic myocardium with predominant glycolytic metabolism (117) as a protective mechanism to avoid cell death in the form of apoptosis or acute necrosis (118).

Fatty Acid Metabolism

The first radiopharmaceutical used in combination with PET for the assessment of regional cardiac metabolism was C-11 palmitate. Experimental studies changing cardiac workload or cardiac substrate availability demonstrated changes in C-11 palmitate kinetics (119). To avoid the complexity of substrate interaction defining the relative contribution of long-chain fatty acids and carbohydrates to overall oxidative metabolism, C-11 acetate has been proposed as an alternative probe to describe oxidative metabolism. C-11 acetate is converted to C-11 acetyl-CoA in the mitochondria and enters the TCA cycle. C-11 activity equilibrates within TCA cycle intermediates and C-11 activity clears from the myocardium in the form of C-11–CO_2 (Fig. 55.7). Several studies have indicated that C-11 acetate kinetics, as assessed by dynamic PET imaging, correlate closely with myocardial oxygen consumption. Kinetics of C-11 acetate are only sparsely affected by substrate interactions and thus allow quantification of myocardial oxygen consumption, yielding parameters of oxidative metabolism as well as blood flow (120,121,122,123 and 124).

Glucose Metabolism

F-18-FDG traces transmembranous transport, as well as phosphorylation of exogenous glucose (125,126). F-18-FDG-6-phosphate does not enter any further metabolic pathways but accumulates in myocardium proportional to glucose transport and phosphorylation (127,128). Experimental studies in isolated rabbit septum as well as canine models demonstrated a close relationship of FDG uptake and exogenous glucose metabolism measured by Fick's principle (128). However, FDG molecules display different affinities for glucose transport and phosphorylation than the glucose molecule. To correct this discrepancy, a correction term is necessary for the quantification of exogenous glucose use of the myocardium by FDG. This correction term (lumped constant) is assumed to be constant under physiologic and most pathophysiologic conditions. More recent data, however, indicate that under rapidly changing conditions the lumped constant may actually change as a function of altered affinities for glucose transport, as well as for the hexokinase reaction (129). Exogenous glucose use can be quantified using a simple fitting procedure of FDG myocardial kinetics and parametric display of regional metabolic data (130). The comparison of C-11 acetate uptake and clearance with regional FDG kinetics in normal volunteers demonstrated an inhomogeneity of regional glucose use in the heart (131). Regional FDG uptake is increased in the lateral wall of the left ventricle and slightly decreased in the area of intraventricular septum (132). FDG measurements have been performed to evaluate cardiac glucose metabolism in patients with insulin-dependent and non–insulin-dependent diabetes mellitus. In patients with insulin-dependent diabetes, there was no significant difference in overall glucose use as compared with a control population, if insulin was substituted by an euglycemic-insulin clamp (133,134 and 135). The quantitative nature of the PET measurements allows for *in vivo* studies under varying conditions to study the relationship of insulin and glucose metabolism in heart and skeletal muscle (136).

Clinical Application of Metabolic Imaging

Ischemic Heart Disease

Specific changes in regional substrate use can occur during acute myocardial ischemia and in patients with chronic ischemic heart disease as demonstrated by PET imaging (137,138,139 and 140). Myocardial ischemia results in impaired oxidative metabolism of fatty acids and increased myocardial glucose use (112). Comparing regional myocardial FDG uptake and myocardial blood flow, as assessed by microspheres during acute myocardial ischemia, showed a dissociation of myocardial blood flow and glucose use (112). In severe ischemia, however, both blood flow and glucose use are reduced, whereas there is evidence for increased FDG uptake during moderate ischemia. Marshall et al. were the first to investigate the relationship of increased FDG uptake in patients with acute myocardial infarction and clinical signs of ongoing ischemia, as well as electrocardiographic changes (141). This study indicated that in a considerable number of patients with acute myocardial infarction, residual metabolic activity could be demonstrated in the infarct territory, which was associated with a higher incidence of postinfarct angina and electrocardiographic signs of recurrent ischemia.

Metabolic Evaluation of Dysfunctioning Myocardium

Animal and clinical studies using FDG as metabolic tracer have shown that reversible left ventricular dysfunction (stunned, hibernating myocardium) is associated with maintained or even increased tissue FDG uptake (137,140,142). Experimental data support the notion that reversible chronic left ventricular dysfunction in patients with advanced CAD does not represent ongoing ischemia but downregulation of function (118,143). There are two experimental conditions that may serve as a model for the clinical presentation of reversible dysfunction in ischemic heart disease. First, transient ischemia with restoration of blood flow leads to slow functional recovery on the basis of *stunning* (144). Second, chronic reduction of blood flow in the animal model is associated with metabolic adaptive changes that minimize the imbalance of oxygen supply and demand, limiting the development of irreversible cell injury (hibernation) (145,146). There is increasing evidence that similar mechanisms are involved in the pathophysiology of reversible chronic dysfunction in patients with advanced CAD (147,148). Rahimtoola (147) first described this condition as *hibernating myocardium*. His definition included chronic reduction of blood flow as a culprit for the observed dysfunction, implying chronic ischemia. However, subsequent studies with PET have shown that blood flow either can be normal or only slightly decreased in dysfunctioning viable myocardium. Vanoverschelde et al. demonstrated near normal perfusion in collateral-dependent viable, but dysfunctioning, myocardium distal to an occluded coronary artery. Sophisticated measurements of blood flow corrected for tissue loss (perfused tissue fraction) also indicate that dysfunctioning myocardium may not be limited by oxygen supply under resting conditions (48,149). Based on these results, there is ongoing discussion as to whether reversible left ventricular dysfunction in severe ischemic heart disease reflects repetitive stunning or hibernation (143). The clinical situation in most patients is characterized by a heterogeneous ischemic injury, consisting of necrosis or scar in the subendocardium surrounded by viable but compromised tissue. The dynamic nature of ischemic heart disease renders these segments ischemic during daily life activities, which may lead to repetitive stunning. On the other hand, severe flow restriction may result in chronic hypoperfusion fulfilling the original criteria of hibernation. One can speculate that both conditions coexist in patients with advanced CAD and impairment of left ventricular function (150). From a clinical point of view, the pathophysiologic discussion is less important because many studies have shown that revascularization results in functional improvement of both stunned and hibernating myocardium (150). Therefore, differentiation between reversible and irreversible dysfunction in patients with severe impairment of left ventricular function has become a major clinical question for the decision-making process concerning revascularization. Qualitative evaluation of PET flow studies demonstrated decreased N-13 ammonia and increased FDG uptake (mismatch) in viable myocardium, which has been considered the scintigraphic hallmark of hibernation (140) (Fig. 55.8). Although such a pattern suggests reduced blood flow, the intensity of tracer uptake depends not only on flow, but also on left ventricular wall thickness (partial volume effect). Therefore, reduction of N-13 ammonia uptake may reflect wall thinning or an admixture of viable and scarred myocardium (151). Flow measurements with O-15 water are less sensitive to partial volume effects, but may overestimate transmural flow (152). In contrast, the FDG signal indicates a relatively higher FDG extraction compared with N-13 ammonia. Using information on both blood flow and glucose metabolism, sensitive specific identification of viable myocardium can be performed. This was first shown by Tillisch et al. (140), who compared relative FDG uptake in patients with advanced CAD and impaired regional and global function before and after revascularization. This study demonstrated that maintained FDG uptake in dysfunctioning segments with reduced flow is associated with functional recovery after revascularization, whereas segments with concordantly decreased flow and metabolism did not recover after restoration of blood flow. Subsequently, a large number of similar studies confirmed the predictive value of FDG imaging. Table 55.2summarizes clinical PET results, which were collected from several laboratories documenting the high predictive value of PET metabolic imaging for tissue recovery after revascularization. In all studies, recovery of regional function after revascularization served as the gold standard for tissue viability. It has been shown that functional recovery of hibernating myocardium may require several months (150,153).

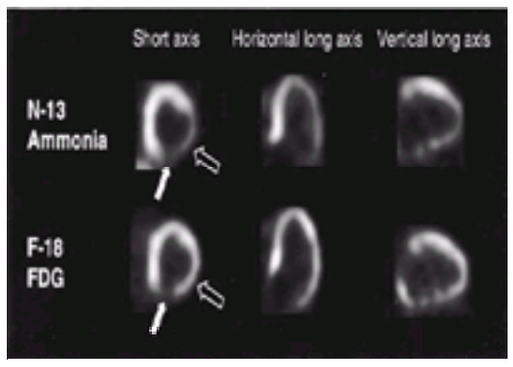


FIGURE 55.8 Positron emission tomographic images using nitrogen-13 ammonia and fluorine-18-fluorodeoxyglucose (F-18-FDG) of a patient with a perfusion to metabolism mismatch pattern (hibernating myocardium, *open arrows*) and scar (*filled arrows*).

Reference	Patients	Dysfunctional segments	Predictive accuracy (%)	Positive predictive accuracy (%)	Negative predictive accuracy (%)
Tillisch (140)	17	67	88	85	92
Tamaki (212)	22	46	78	78	78
Tamaki (213)	11	56	82	80	100
Marwick (211)	16	85	74	82	79
Ludyanski (210)	14	54	91	95	80
Carrel (209)	21	23	83	84	75
Gropler (208)	16	53	81	79	83
vom Dahl (151)	37	45	85	88	84
Total	154	428	82	82	83

TABLE 55.2 PREDICTIVE VALUE OF VIABILITY ASSESSMENT

Comparison with Other Imaging Modalities

Numerous investigations exist comparing regional FDG uptake with electrocardiographic criteria, standard thallium-201 and Tc-99m flow agents, imaging stress echocardiography, and MRI imaging (154,155). Early observations of discrepant results between FDG distribution and thallium-201 redistribution patterns emphasized the limitations of thallium-201 redistribution imaging for assessment of tissue viability, which are partly overcome by reinjection techniques (156). Tc-99m sestamibi also provides clinically useful information on tissue viability. In combination with nitrate application, the predictive value of Tc-99m sestamibi imaging can be enhanced. Comparing scintigraphic data with those obtained after positive inotropic interventions, it appears that tracer retention provides more sensitive markers of viable myocardium, whereas assessment of contactile reserve is associated with higher specificity for reversible myocardial dysfunction (156,157).

Prognostic Significance of Metabolic Imaging

Aside from the predictive value of FDG for tissue recovery, the prognostic information provided by FDG uptake in segments with reduced perfusion as assessed by N-13 ammonia PET has been emphasized by several groups (Table 55.3). Retrospective data analysis revealed a high incidence of cardiovascular complications in patients with decreased blood flow, but maintained FDG uptake in patients who did not undergo revascularization (158,159 and 160). In contrast, the incidence of cardiovascular complications was similar in groups with scintigraphic evidence of scar or normal myocardium, regardless of whether they were revascularized. These data indicate that the mismatch pattern identifies a subgroup of patients at increased risk for cardiovascular complications. The prognostic information appears independent of the traditional markers such as left ventricular ejection fraction or New York Heart Association classification, which were not different among the

investigated subgroups. Survival was significantly higher in revascularized patients with mismatch, as demonstrated by DiCarli et al. (161,162).

		References	Number	Left ventricular ejection fraction (%)	Complication
Hibernating	Drug therapy	Tamaki (160)	21	–	12 (59%)
		Eitzman (158)	18	33	9 (50%)
		Maddahi (159)	17	24	7 (41%)
Scarred	Drug therapy	Tamaki (160)	17	–	1 (6%)
		Eitzman (158)	24	32	3 (13%)
		Maddahi (159)	33	24	3 (9%)
Hibernating	Percutaneous transluminal coronary angio-	Eitzman (158)	26	36	3 (12%)
	plasty or coronary artery bypass grafting	Maddahi (159)	26	25	3 (12%)
Scarred	Percutaneous transluminal coronary angio-	Eitzman (158)	14	31	1 (7%)
	plasty or coronary artery bypass grafting	Maddahi (159)	17	25	1 (6%)

TABLE 55.3 PROGNOSIS OF POSITRON EMISSION TOMOGRAPHY

The degree of functional recovery of patients after revascularization can be predicted based on the scintigraphic pattern, as well as extent of mismatch (151,162). DiCarli et al. reported an 80% likelihood of functional improvement in the presence of mismatch exceeding 18% of the left ventricle. Pagano et al. indicated that the extent of viability correlates not only with functional recovery, but also survival (163). Furthermore, delay of revascularization in these patients is associated with increased mortality, confirming the prognostic significance of the identification of viable, but jeopardized, myocardium (164). Patients with severe left ventricular dysfunction are at higher risk for complications associated with revascularization. Dreyfus et al. (165) reported that assessment of tissue viability in such patients before surgery improves the selection process for revascularization with low perioperative mortality. Haas et al. (166) confirmed this prognostic role of PET by comparing short- and midterm survival after surgical revascularization in two groups of patients with three-vessel disease and impaired left ventricular function. Attempts to exploit the clinical significance of the FDG signal by less costly means included the use of high-energy collimators for SPECT systems and coincidence circuitry in gamma cameras. Initial results indicate the feasibility of such approaches with comparable diagnostic and prognostic performance (157,167).

Carbon-11 Acetate in the Assessment of Tissue Viability

Regional FDG uptake is modulated by plasma substrate levels and hormonal milieu. Many patients with CAD have diabetes mellitus or prediabetic conditions affecting glucose tolerance. Therefore, the image quality following oral glucose loading and intravenous injection of FDG is limited in some patients undergoing tissue viability studies (133). As an alternative, C-11 acetate has been proposed for the assessment of residual oxidative metabolism in patients with severe CAD. Studies by Gropler et al. demonstrated that C-11 acetate may also be useful in the assessment of tissue viability in patients with chronic stable CAD (168,169). More recently, Gerber et al. applied C-11 acetate kinetics to investigate the relationship between flow and oxygen consumption in patients with unstable angina. Reversible dysfunctioning myocardium displayed normal flow and oxygen consumption, suggesting the presence of stunning in these patients (170). C-11 acetate serves as an alternative to FDG imaging. However, the assessment of C-11 acetate kinetics requires dynamic data acquisition and sophisticated image processing, limiting widespread clinical use (168,169).

Metabolic Imaging in Patients with Other Cardiovascular Diseases

Dilated Cardiomyopathy

C-11 palmitate has been used to study fatty acid metabolism in patients with dilated cardiomyopathy. Observations by Geltman revealed a heterogeneous fatty acid metabolism in patients with dilated cardiomyopathy in the presence of relatively homogeneous perfusion, as measured with thallium-201 scintigraphy (171). Kelly et al. (172) addressed the role of C-11 palmitate in probing mitochondrial enzyme defects resulting in an impairment of beta-oxidation. These investigators were able to demonstrate that oxidation of C-11 acetate was dissociated from that of C-11 palmitate in patients affected with this enzyme disorder. As discussed previously, C-11 acetate allows the noninvasive assessment of myocardial oxygen consumption (173). This tracer approach can be used to probe myocardial oxygen consumption in healthy as well as diseased cardiac muscle. In addition, this technique can be used to assess right ventricular oxygen consumption, as demonstrated by Hicks et al., who described a close relationship between right ventricular acetate kinetics in patients and pulmonary artery pressure (174). Wolpers et al. first introduced the concept of noninvasively assessing myocardial efficiency by PET as defined by external work of the left ventricle divided by oxygen consumption (175). Such a parameter allows the assessment of the link between mechanical performance and metabolic demand under various pathophysiologic conditions as well as after therapeutic interventions (122,176).

Beanlands et al. applied this method in patients with cardiomyopathy before and after therapy with dobutamine and nitroprusside (177). Myocardial efficiency increased after both pharmacologic interventions. In both instances, the improvement in cardiac efficiency was most related to changes in left ventricular afterload. More recently, Beanlands et al. demonstrated the beneficial effect of beta-blockade (metoprolol) on metabolic left ventricular performance in heart failure patients using C-11 acetate (122).

ASSESSMENT OF AUTONOMIC INNERVATION

Tracer approaches are uniquely suited to the assessment of specific tissue function. Although tracers have been developed for the parasympathetic nervous system, the sparse cholinergic innervation of the left ventricle limits the presynaptic evaluation of this system *in vivo*. Therefore, most imaging approaches focus on the scintigraphic delineation of the presynaptic and postsynaptic sympathetic nervous systems because the left and right ventricles are densely innervated by sympathetic fibers. Figure 55.9 displays the nerve terminal, which is an important functional unit of the sympathetic nervous system.

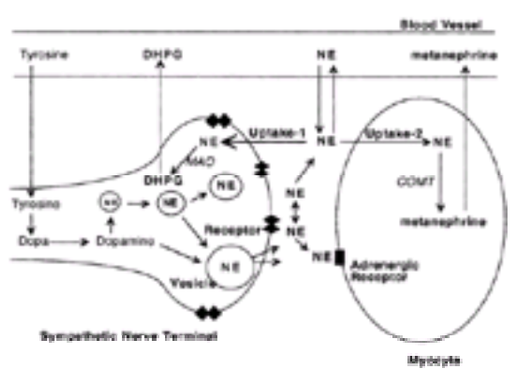


FIGURE 55.9 Conceptual model of sympathetic nerve terminal. COMT, catechol-*O*-methyl transferase; DHPG, 3,4-dihydroxyphenylglycol; MAO, monoamine oxidase; NE, norepinephrine.

Postganglionic sympathetic fibers travel along vascular structures on the surface of the heart. On entering the myocardial wall, the fibers branch into multiple sympathetic varicosities. These nerve terminals include vesicles, which represent the storage pool for neurotransmitters, enzymes, and other proteins (178). Norepinephrine, the predominant cardiac neurotransmitter, is synthesized from the amino acid tyrosine by several enzymatic steps (Fig. 55.9) and is released on nerve stimulation by exocytosis. Several receptor systems have been postulated to exist on the membrane of the presynaptic nerve terminal, modulating norepinephrine release. As much as 80% of the norepinephrine that is released from the nerve terminal is taken up via a mechanism known as *uptake 1*. Reuptake is an important mechanism to regulate the norepinephrine concentration in the extraneuronal space. A fraction of the released norepinephrine diffuses back into the vascular space where it can be measured as norepinephrine spillover in the coronary sinus venous blood (179). Only a small amount of norepinephrine in the synaptic cleft activates receptors on the surface of the myocytes or enters cardiac cells directly (uptake 2 mechanism). Norepinephrine undergoes rapid metabolism in neuronal and extraneuronal tissue. Metabolism of the neurotransmitter in the neuronal tissue is mediated by the enzyme monoamine oxidase, while extraneuronal norepinephrine is

metabolized by the catechol-*O*-methyltransferase enzyme system.

Imaging of Presynaptic Nerve Terminals

The use of radiolabeled norepinephrine or analogs appears to be most promising for the visualization of the sympathetic nerve terminals. C-11 hydroxyephedrine (HED) has been synthesized at the University of Michigan (Fig. 55.10) (180). This norepinephrine analog is taken up by the nerve terminal but is not metabolized by the intraneuronal enzyme systems. The myocardial retention of this tracer reflects the activity of uptake 1 mechanism and, to a lesser degree, the storage of norepinephrine in nerve terminals (181). In contrast, the more recently introduced compound C-11 epinephrine is not only taken up by the nerve terminal, but also stored in the vesicles of nerve terminals (182). A further analog of epinephrine is phenylephrine, which enters the nerve terminal via uptake 1, but is primarily metabolized by the monoamine oxidase enzyme system (183). Phenylephrine, therefore, allows the evaluation of the enzymatic integrity of the nerve terminal. Other radiopharmaceuticals for the characterization of the presynaptic nerve terminal include F-18 dopamine and F-18 norepinephrine, as well as MBBG (metabromobenzylguanidine) (184,185 and 186).

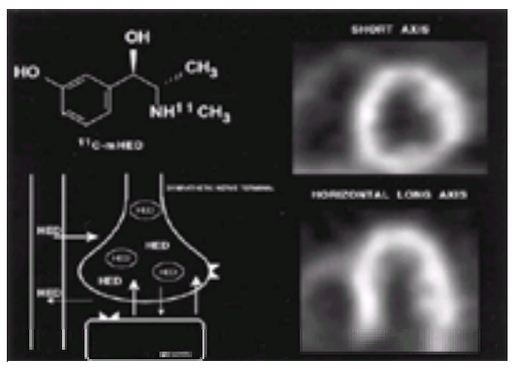


FIGURE 55.10 Illustration of molecular structure of carbon-11 hydroxyephedrine (HED), a model of the uptake mechanism, and positron emission tomographic images of the tracer in a healthy volunteer, showing homogeneous distribution of the tracer.

Clinical Application

Initial clinical applications of C-11 HED show excellent image quality with high contrast between myocardial tracer activity and blood pool, as well as lung tissue surrounding the heart (Fig. 55.10). The specificity of the tracer approach for neuronal tissue has been well documented by studies in cardiac transplant patients, which showed a marked reduction of tracer uptake, suggesting only little nonspecific binding of this tracer (181), which allows for quantitative image analysis (187). Studies in transplant patients at various time points following surgery indicate partial reinnervation of transplanted myocardium by retention of C-11 HED in the anterior septal segments of the left ventricle in transplant recipients several years after operation (188). These data suggested for the first time that regional reinnervation occurs in the human transplant. First results comparing this scintigraphic pattern with heart rate variability suggest that the partial reinnervation of the left ventricle is associated with electrophysiologic evidence of functional reinnervation (189,190 and 191). Allman et al. used C-11 HED in the assessment of patients with acute myocardial infarction undergoing thrombolytic therapy (192). Experimental data indicated that the extent of neuronal damage following transient ischemia is larger than the area of tissue necrosis. Wolpers et al. demonstrated a decreased retention fraction of C-11 HED in reperfused canine myocardium, suggesting a high sensitivity of neurons to ischemic injury. Similar data have been observed in the clinical setting (193). The area of neuronal dysfunction, as evidenced by C-11 HED defects, was significantly larger than the area of perfusion abnormalities in patients with acute myocardial infarction and correlated closely with the area of risk as assessed by Tc-99m sestamibi imaging in the same patients, confirming the experimental data (194). C-11 HED PET studies were also performed in patients with diabetic neuropathy. These studies revealed a correlation between the results of autonomic nervous system testing and the abnormalities of HED distribution. The finding that regional cardiac denervation represents a heterogeneous process in patients with diabetic neuropathy was surprising. C-11 hydroxyephedrine defects were most severe in the apical segments of the left ventricle and least severe in the proximal segments of the left ventricle (195,196 and 197). Comparison of neuronal dysfunction and blood flow measurements by PET revealed impaired vasodilator response in diabetic patients (198).

Preliminary studies suggest the possible role of HED imaging in patients with congestive heart failure. Several investigators demonstrated decreased HED uptake in patients with severely impaired left ventricular function, suggesting neuronal damage in this patient population (199,200). Again this process appears to be heterogeneous with pronounced abnormalities in the apical segments of the left ventricle.

Postsynaptic Receptor Sites

The development of radiotracers and the initial clinical validation of tracer methods for the visualization of the adrenergic receptor system have been initiated by Syrota et al. The specific visualization of cardiac beta-receptors became possible by the successful radiosynthesis of a more hydrophilic beta-receptor antagonist (CGP-12177). This nonselective C-11–labeled beta-receptor antagonist provided excellent image quality of the postsynaptic binding sites in the heart (201). A tracer kinetic model approach has yielded estimates of receptor densities in agreement with *in vitro* beta-receptor density assessments (202). Clinical validation of this approach confirmed the *in vitro* demonstrated reduction of beta-receptor density in patients with congestive heart failure. This approach has also been adapted by Camici et al. and used in patients with hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and syndrome X (203,204,205 and 206). These PET studies demonstrated a reduction in beta-receptor density as well as presynaptic function in patients with hypertrophic cardiomyopathy. The reduced beta-receptor density was not limited to the intraventricular septum, but included the entire left ventricular myocardium, suggesting a global change in beta-receptor density. These initial studies using beta-receptor antagonists for visualization of the adrenergic receptor system indicate the potential of PET imaging in monitoring pathophysiologic alterations in beta-receptor density and in probing the effect of various pharmacologic interventions on the sympathetic neurotransmission (207).

SUMMARY OF CURRENT STATUS

The improved imaging technology of PET, including attenuation correction and high spatial resolution, allows for the highly accurate detection of CAD. Coronary reserve measurements may be useful in the early detection of vascular abnormalities and follow-up of therapeutic interventions designed to halt or reverse CAD. Finally, such measurements can serve as end points in the evaluation of new drugs altering endothelial function.

Assessment of tissue viability has become an important application for PET in cardiology. Metabolic imaging documented the high incidence of reversible dysfunction in patients with severe CAD. These PET findings resulted in increasing diagnostic efforts to identify viable myocardium by various methods. At the current time, PET must be considered the reference method for identification of tissue viability with established diagnostic and prognostic value. In patients with high-risk interventions and in transplant candidates, PET best supports the selection process for revascularization. Finally, new tracer approaches designed to map cardiac innervation may not only prove useful in clinical research assessing neurophysiology of various cardiovascular disorders, but also provide important prognostic information in patients with congestive heart failure.

CONTROVERSIES AND PERSONAL PERSPECTIVES

PET imaging of the heart provides important clinical information and promising new avenues for clinical research. The quantitative nature, as well as the in-depth validation, of this technology, makes it an attractive research tool. For example, PET represents the most validated noninvasive method to quantitate regional myocardial perfusion. Although there are defined clinical indications for the use of regional quantification of myocardial perfusion, there are many scientific questions regarding coronary physiology and cardiac microcirculation, which can be addressed noninvasively by PET. However, this technology is not widely available and requires a well-developed academic infrastructure to exploit its research potential. It is expected that physiologic parameters beyond flow will gain importance in the future. It is, however, difficult to predict whether the resolution of scintigraphic methods will ever permit the study of the vascular wall of the coronary arteries. Specific tracers, which provide high contrast for a given physiologic process (e.g., thrombocytes activation inflammation), may enable imaging of vulnerable coronary plaques. In addition, tracer approaches may be useful in the monitoring of gene expression (208). Emphasis on further development of molecular imaging by PET clearly depends on basic cardiovascular research, providing new insights into the cell signaling and receptor systems. Tracer approaches are uniquely suited to study physiologic and biochemical consequences of altered cell interaction, providing *functional genomics*. This potential to characterize the phenotype may not only apply to human studies but may also be especially attractive for research in transgenic animals.

Metabolic imaging with PET provided the first insights into the adaptive processes in response to repetitive cellular stress (e.g., ischemia). Based on clinical

observations in hibernating myocardium, new experimental models are being developed to study the consequences of ischemia on myocardial substrate metabolism using molecular biology approaches. Similar interaction between imaging of human pathology and experimental work can be envisioned for other systems modifying cardiac performance—for instance, autonomic innervation of the failing heart.

There seems to be a gap between the technical potential of modern imaging modalities and the integration of functional information in the clinical decision-making process. Despite advances in functional imaging, physiologic and biochemical signals are often too complex to be readily accepted and exploited in daily patient care.

THE FUTURE

The future clinical role of PET depends primarily on the development of simplified PET methods, centralized distribution of radiopharmaceuticals, and the clinical acceptance and integration of complex physiologic information. It is expected that PET and SPECT technology will overlap in the future, and the uniqueness and usefulness of clinical information provided by each of these modalities will define their place in clinical cardiology.

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56

COMPUTED TOMOGRAPHY OF THE HEART

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J. JEFFREY CARR

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Cardiac computed tomography (CT), like echocardiography, provides image slices or tomograms of the anatomic features of the heart. These two modes of tomographic imaging complement each other. On the one hand, the natural echocardiographic contrast difference between fluid and solid tissues allows noninvasive visualization of intracavitary and endovascular lumina and even the visualization of detail in valve leaflets and occasionally the lumen of the left coronary artery. This distinction of blood and tissue would require injection of contrast with CT. On the other hand, the higher spatial resolution of CT allows visualization of coronary arteries both with and without contrast enhancement. The accentuated absorption of x-rays by elements of high atomic number such as calcium and iodine allows excellent visualization of small amounts of coronary calcium as well as the contrast-enhanced lumina of medium-sized coronary arteries. Figure 56.1 illustrates the major differences between these two types of imaging.

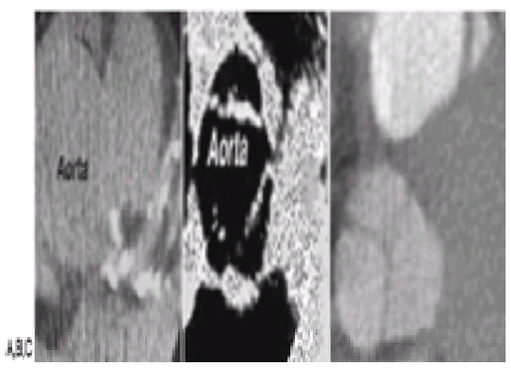


FIGURE 56.1 A: A computed tomographic (CT) scan at the level of the aortic valve. **B:** An echocardiogram at approximately the same anatomic location. **C:** A contrast-enhanced CT image of the aortic valve. The figure illustrates important differences between noncontrast CT, contrast CT, and echocardiography. The presence and severity of coronary calcium are easily seen in the left coronary artery in the computed tomogram on the left, whereas it is invisible in the echocardiogram. The distinction between valve leaflets and aortic wall from aortic blood pool can only be seen on the ultrasound image and the contrast-enhanced CT image. The periarterial fat is shown as a dark area around the left coronary artery on the CT image on the left, whereas this is not seen at all on the echo.

There are significant tradeoffs when comparing CT with ultrasound imaging. CT capable of accurately imaging the heart is relatively unavailable, often more expensive, and involves the use of ionizing radiation and often iodinated contrast injection. Without the latter, CT, like all radiographic imaging, cannot distinguish intracavitary and intraluminal blood from the muscular walls of vessels and cardiac chambers. Echocardiography is capable of this distinction even without injections.

There are large initial expenses involved in the purchase and installation of CT scanners. These costs, particularly regarding electron beam CT scanning, have induced some medical centers to invest in unusual public marketing campaigns of their technologies. Indeed, the frequent marketing of this technology to the American public, since the early 1990s, is a striking example of how the need to balance large initial and ongoing maintenance costs with needed revenues can influence the application of a diagnostic test.

The authors of this chapter are ardent proponents of cardiac CT and coronary calcium scanning. We believe that this exciting technology should and will find a useful place in the diagnostic armamentarium of physicians. We also believe that the development of this application should be evidence based and linked to the guidelines published by the professional societies.

This chapter presents all aspects of rapid CT scanning of the heart but emphasizes its most common use, which is, for better or worse, coronary calcium screening.

GLOSSARY

Calcium score: A mathematical calculation related to the amount of calcium determined by multiplying the area of calcified plaque by a weighting factor based on the CT number or Hounsfield unit of the calcified plaque. Weighted volume of calcium.

Spatial resolution: Quality of image as a function to resolve minute anatomic features.

Temporal resolution: Quality of image as a function of speed of acquisition.

Tomogram: Image slice of the body.

TECHNICAL ASPECTS

Scanning the Heart: A Technical Challenge

CT of the heart presents significant technical obstacles and dilemmas. The heart is far from quiet, and its continuous rhythmic displacement as well as even small degrees of respiratory motion cause great difficulty for imaging with standard CT techniques. Conventional scanners, whose exposure time exceeds one-half of a second, cannot possibly “freeze” this motion. More rapid scanning of the heart has been limited by the speed with which a single tomogram can be acquired. To better understand some of the advances that have allowed crisp images of cardiac anatomy and pathology, we have written this section.

Types of Computed Tomography Systems or Scanners

Two kinds of scanners are used to image the heart. Electron beam scanners use an x-ray source, which consists of a 210-degree arc ring of tungsten, and are activated by bombardment from a magnetically focused beam of electrons fired from an electron gun behind the scanner ring. For most scanning applications, it takes one-tenth of a second to complete a rotation of the electron beam using electron beam computed tomography (EBT) scanners. Subsecond, non–electron beam [multidetector computed tomography (MDCT)] scanners use a rapidly rotating x-ray tube and several rows of detectors, also rotating. The tube and detectors are fitted with slip rings that allow them to continuously move through multiple 360-degree rotations. Present versions complete a 360-degree rotation in approximately one-half of a second. These scanners’ exposure times can be decreased to as little as 0.25 seconds by using only a portion of the 360-degree rotation. Further reduction is also possible but at the expense of increased radiation or less rapid acquisition of progression from one tomographic image to the next. For coronary calcium noncontrast scanning, the EBT scanner can acquire only one tomogram at a time; the MDCT scanner can acquire up to four tomograms at a time. Both the speed and the maximum number of tomograms are likely to increase for both types of scanners.

MDCT is also known as *multislice* and is an evolution from single-slice helical or spiral CT systems. The MDCT systems use a rotating x-ray tube and detectors with variable rotation times of less than 1 second. These scanners operate in two modes, helical and sequential, and it is somewhat misleading to call them *helical scanners*. Helical or spiral CT scanning refers not to a different type of scanner but rather to a different method for acquiring and reconstructing images. When used normally, in sequential scanning mode, modern scanner tables move the patient through the scanner ring by a set increment of length (from 1 to 15 mm). Between table increments, the x-ray exposure occurs, during which the x-ray tube and detector array rotate slightly greater than a full 360 degrees. These exposures usually have a thickness (collimation) equal to the table increment. With a modern generation MDCT system, rather than a single 10-mm row of detectors, there is a detector array. The detector array allows the same 10-mm slice (x-ray beam collimation) to be divided into four channels or slices. So instead of one 10-mm slice, four 2.5-mm slices are obtained. Likewise, an eight-channel MDCT system could produce eight 1.25-mm slices. Thinner slices improve spatial resolution along the z-axis (head to foot).

Helical or spiral mode is possible secondary to the development of the slip-ring interconnect. This allows the x-ray tube and detectors to rotate continuously during image acquisition because no wires directly connect the rotating and stationary components of the system (i.e., no need to unwind the wires). With the gantry continuously rotating, the table moves the patient through the imaging plane at a predetermined speed. The relative speed of the gantry rotation table motion is the scan pitch. Figure 56.2 shows how both kinds of scanning work. The smooth rapid table motion or pitch in helical scanning allows complete coverage of the cardiac anatomy in 15 to 25 seconds. A disadvantage of this method in cardiac scanning, however, is an increase in radiation dose.

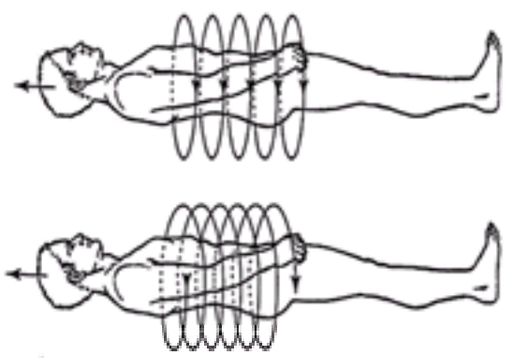


FIGURE 56.2 The top figure shows sequential scanning. The bottom figure shows helical scanning.

How Do Scanners Create Images?

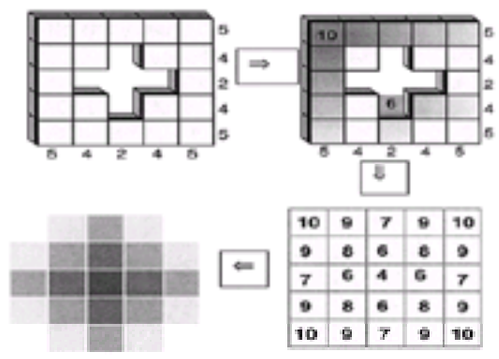
All CT systems create images using the same basic principles. An x-ray source is used to create a filtered and collimated beam of x-ray photons, which irradiate the patient from a known point. On the other side of the patient, a detector array measures the x-ray photons, which exit the patient. The source and possibly the detector array rotate around the patient, providing different views or projections. These views fill a mathematical matrix referred to as *radon space*. This information is then transformed through a filtered backprojection algorithm to create an x-ray attenuation map of the area or slice evaluated, which is generally recognized as the CT image.

Gating and Reconstruction

Gating refers to timing exposures to a point in the cardiac cycle when the heart is most still. EBT scanners have usually used 80% of the electrocardiographic RR interval for scanner triggering, although there are some more recent reports showing that earlier diastolic triggering might provide better images with less motion artifact (1,2 and 3). MDCT scanners usually trigger at 50% of the RR interval (4). *Reconstruction* refers to the computer calculations, which convert the digitally transformed data from the scanner’s x-ray detectors into images of the heart and surrounding structures.

Image reconstruction was the breakthrough that won Dr. Hounsfield the Nobel Prize in 1972 and that makes any kind of CT scanning possible.

Reconstruction can be understood with a simple diagram (*e*Fig. 56.2.1). Assume that the x-ray source has two possible positions, on top of and to the left of the object scanned. Assume that the heart, in this simplified scanner ring, consists of blocks, as shown in the figure. As the x-rays pass through the blocks, they are absorbed and the total absorption is registered on the detectors, as shown on the right and the bottom. We can do our own reconstruction now by adding the numbers at the ends of the rows and columns and putting the results in the blocks where the rows and columns intersect.



***e*FIGURE 56.2.1** Cross (*upper left*) is exposed to two perpendicular sources of x-rays. One source is directed down, the other to the right. The image is created by computation (addition) of x-ray absorptions from both projections (*lower left*).

The array of digital numbers, when translated into tiny blocks of light with brightness proportional to their values, is the reconstructed image. Of course, this is an oversimplification of a more complex process, but we at least can see why the tomograms are called *computed*. Each individual tomogram can be thought of as a virtual slice of tissue consisting of blocks (voxels) containing numbers, each of which is proportional to the absorption of x-rays at that point and with a thickness and width determined by the reconstruction. Figure 56.3 shows a diagram of a tomogram.

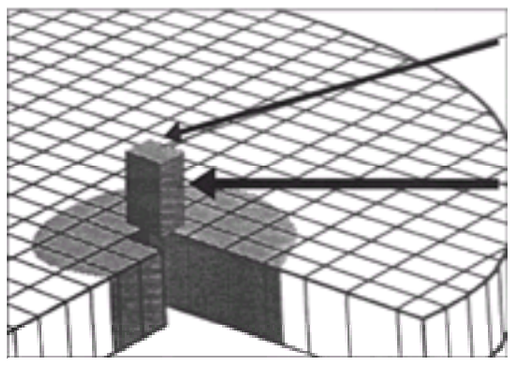


FIGURE 56.3 Each tomogram consists of voxels of given thickness (*thick arrow*) and width (*thin arrow*). One number between –1,000 and 2,000 represents each voxel.

Specific Problems with Specific Scanners

If time per scan were everything, the EBT scanners would be ahead of the pack. For at least a few years, the MDCT scanners will not be able to drive exposure times down to one-tenth of a second or better without sacrificing other important advantages they enjoy. Furthermore, it is unlikely that Imatron, the only company in the EBT business, will remain inactive. They are likely to further decrease their exposure times and otherwise improve the quality of their images.

There are few carefully executed, head-to-head comparisons between the two scanner types. EBT scanners are still better for most cardiac applications. However, present EBT scanners have some distinct disadvantages, including excessive image noise, especially in obese patients. The limitation to only one or two detector rows is another concern. This limits the speed with which the entire heart can be imaged. Increased expense and difficult maintenance as well as relatively poor image quality for scanning other parts of the body are significant problems.

Motion Artifact versus Misregistration

Despite their high speed, modern CT scanners still suffer from motion blurring due to the rapid motion of the base of the heart in diastole. Motion artifact, when it is in the plane of an image slice (*x*,*y*-plane), causes degradation of images and measurements made from them. When motion is in the long axis of the body (*z*-axis), it causes misregistration of image data between image levels. This problem is especially acute when imaging small structures, such as coronary arteries, particularly the right coronary artery.

Perhaps more problematic is the inevitable misregistration of the tomograms caused by even small degrees of chest motion or errors in electrocardiographic gating. This misregistration causes gaps or overlaps between image levels. This effect results in large rescan variability for many measurements (5,6 and 7). Current generation scanners, by virtue of their slower temporal resolution of 250 to 500 ms, are prone to greater motion artifact. This motion artifact results in blurring, which leads to quantitative errors in analyzing images.

Noisy Images

When an x-ray beam encounters thick layers of tissue, absorption and scattering of x-ray photons within the tissue increase and thus fewer direct photons reach the detectors to record the image. Scattered x-ray photons result in noise. The signal-to-noise ratio is used as a measure of image quality. If the CT detector arrays record a high number of direct x-ray photons relative to scattered photons and other sources of noise within the CT system, then a clear and high-resolution image of acceptable signal-to-noise ratio will be obtained.

Current generation EBT scanners are unable to increase the number of x-ray photons without increasing image time. Thus, high levels of noise in the resulting images are observed, particularly for obese individuals. For this reason, EBT scanners cannot be used for subjects who weigh more than 300 lb. MDCT scanners usually have an upper limit of weight of at least 400 lb and have the added advantage of a variable tube current for obese subjects. The ability to increase tube current with patient size allows for image noise to be independent of patient size.

CLINICAL APPLICATIONS

Coronary Calcium: Pathophysiology

Atherosclerotic calcification is an organized process similar to bone formation in cartilage plates (8). It occurs when the other aspects of atherosclerosis are present. Gla-containing proteins that are involved in the transport of calcium out of vessel walls are also involved in atherosclerotic calcification. Calcified plaque also contains mRNA for bone morphogenetic protein, a potent factor for osteoblastic differentiation as well as cells that are capable of osteoblastic transformation (9). These cells may be the precursors of vascular calcifying cells. Calcification is thus an active process and not simply passive calcium phosphate precipitation. Although calcification is found more frequently in advanced lesions, it may also occur in the lesions that are seen as early as the second decade of life. The relation of arterial calcification to the probability of plaque rupture is unknown. Though the extent of calcification is directly related to the volume of plaque, this relationship is far from perfect, and it is not known if the amount of calcium tracks the amount of plaque over time. Teleological speculations and some empirical evidence (10) lead us to believe that calcification may represent an attempt to protect threatened myocardium by strengthening weakened atherosclerotic plaque that is prone to rupture.

Coronary Calcium: Historical Perspective

Other Modalities: Chest Radiography and Fluoroscopy

Units for acquiring plain chest radiographs are universally available. Lenck (11) reported a chest radiograph showing left coronary calcification in 1927. In 1950,

Hobbe and Wright (12) reported a chest radiographic prevalence of 3% among hospitalized patients. In 1978, Souza and Bream proposed the examination of the *CAC triangle* (coronary artery calcification triangle) in every adult chest radiograph (13). In 1983, Kelley and Newell (14) reported that by using a higher energy, the sensitivity of the chest radiograph could be greatly increased for detecting coronary calcium.

Individual physician-scientists who were searching for more accurate diagnoses drove research in this field. Despite encouraging initial results, we know of no further research or clinical interest in using the plain chest radiograph for detecting coronary calcium, although there remains continued interest in evaluating arterial calcification of the aorta and other vascular beds with conventional radiography as indicated by studies evaluating aortic calcium and arterial calcium with mammography.

The fluoroscopic image intensifier has been standard equipment in hospitals for decades. With the advent of cardiac catheterization laboratories, image intensifier sales blossomed. These units were somewhat expensive, but the demand for better diagnosis spurred increased use for angiographic studies in patients with chest pain.

The first reports on the use of noninvasive fluoroscopy for detecting coronary calcium appeared in the 1960s (15,16). There was a surge of interest, which culminated in the late 1980s with a metaanalysis (17) and the development of two modifications, which increased sensitivity and accuracy (18,19). The metaanalysis concluded that although the sensitivity of fluoroscopy appeared to be low, its specificity was high and its accuracy compared well with most forms of stress testing. The most striking and encouraging finding was that of Margolis et al. (20), who followed a group of symptomatic adults who had undergone cardiac fluoroscopy and angiography and found that fluoroscopic calcium predicted a fourfold increase in future mortality and that calcium was an independent predictor of mortality even after controlling for extent of angiographic disease. Due to a dearth of economic pressure, and despite promising research results, neither medical centers nor professional societies gave serious consideration to the clinical application of cardiac fluoroscopy in the diagnosis of coronary heart disease.

Computed Tomography

CT scanners have been used since the 1970s. Scanners, like image intensifiers, are expensive. They serve for imaging multiple organs, both with and without contrast injections. Reinmuller and Lipton (21) in 1987 reported CT for coronary calcium to be more sensitive but less specific than fluoroscopy for predicting angiographic stenoses. Masuda et al. (22) and Timmins and Pinsk (23) also found CT to have increased sensitivity for stenoses, and Moore et al. (24) found that coronary calcium identified on CT scans predicted a worse outcome in symptomatic patients. The increased contrast resolution of CT is the reason for its expected increase in sensitivity. Localization of calcifications is also more accurate and easier with tomography than with projection imaging such as fluoroscopy.

Electron Beam Computed Tomography

Figure 56.4 shows an EBT scan, positive for coronary calcium. EBT scanners were introduced into the American market in the 1980s and represented a remarkable breakthrough in CT technology. The ability of EBT scanners to obtain rapid scan acquisition, as fast as 50 ms, makes them well suited for imaging the heart. To date, design tradeoffs to acquire these extremely high temporal resolution images have resulted in EBT not being widely accepted by the medical community for general CT imaging of the brain, liver, and other body parts.

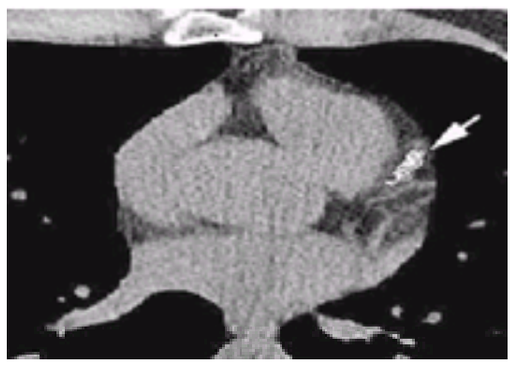


FIGURE 56.4 Tomogram from a study showing calcification in the left coronary artery (*arrow*).

Reports on their potential for imaging coronary calcifications began early with the papers of Tannenbaum and Kondos (25) and Agatston et al. (26). Tannenbaum and Kondos (25) were the first investigators to report the association of EBT coronary calcium with angiographic stenoses. Several other investigators (27,28 and 29) reported accuracies for predicting angiographic stenoses that are comparable with those of exercise testing. We know of one metaanalysis that shows encouraging results in this regard (30). Despite the fact that proponents of EBT frequently claim that it is far more accurate and useful for calcium assessment than either conventional CT or fluoroscopy, there have been few head-on comparisons. We believe that the accuracy of EBT exceeds that of other imaging modalities, but, in the case of multirow subsecond scanning, this difference in accuracy is modest or nonexistent (31,32).

After considering three possible clinical indications for calcium assessment using EBT, the American Heart Association concluded that there was a clear indication only in symptomatic adults with atypical chest pain (33). This was similar to the conclusions of the metaanalysis, published almost a decade earlier regarding cardiac fluoroscopy (17).

Some investigators have also done studies to determine the value of coronary calcium detected with this technique for predicting future coronary events in asymptomatic adults (34,35). These studies in asymptomatic subjects have received enormous attention and have produced widely divergent results and conclusions.

Measures of Coronary Calcium

All measures of coronary calcium depend on an inherent definition of a calcified lesion. Such definitions depend on two factors: a minimum brightness value (Hounsfield number) assigned to a pixel in the anatomic distribution of the coronary tree and a minimum number of adjacent or contiguous pixels that have that brightness value. The National Institutes of Health standard set by the Multi-ethnic Study of Atherosclerosis (MESA)/Coronary Artery Risk Development in Young Adults (CARDIA) CT committee is a brightness value of at least 130 Hounsfield units and four contiguous pixels using a 35-cm field of view.

The most popular measure of coronary calcium is the calcium score (26). This is a radiographic density-weighted volume of plaques whose pixel numbers exceed 130. A simpler and perhaps more reproducible measure is the calcium area or volume (26,36). The calcium volume is the total volume of all voxels with a Hounsfield number of at least 130. Callister et al. have developed an interpolated volume scoring method, which smooths adjacent voxel numbers between image slices (36). They have found their method to be more reproducible, although this remains to be confirmed. Few reports have conclusively shown that any of the other measures are superior in accuracy and reproducibility when compared with the calcium score.

Prevalence

The prevalence of coronary calcium in asymptomatic as well as symptomatic persons is well known. Table 56.1 (26,37,38 and 39) shows the prevalence in young asymptomatic men and women of various ages. The prevalence in women lags behind that of men until well into the postmenopause period. The table shows the prevalence of coronary calcium in persons generally symptomatic and undergoing coronary angiography. These data thus indicate that the prevalence in symptomatic persons is generally higher than that in asymptomatic persons, and prevalence is age dependent. The prevalence in men is evidently higher than the prevalence in women. The lower prevalence of coronary calcium in those with myocardial infarction and negative coronary angiogram results is not shown in the table.

	Symptomatic (%)	Asymptomatic (%)	
Decade (yr)	Men and women	Men	Women
30–40	26	21	11
40–50	43	44	28
50–60	81	70	50
60–70	83	84	73
70–80	—	94	89
>80	—	100	100

TABLE 56.1 PREVALENCE OF CORONARY CALCIUM IN SYMPTOMATIC AND ASYMPTOMATIC ADULTS

Reproducibility and Progression

Serial coronary calcium studies have been proposed to follow the progression of atherosclerosis. Such studies would be useful if the following conditions were met: (a) The progression of coronary calcium tracked the progression of unstable coronary plaque; as noted previously, the extent to which this is true is still a matter of debate; and (b) the measurement error, defined as the rescan percent variability, was much lower than the percent physiologic change over time.

Although coronary calcium is known to progress (40,41), the extent to which this progression tracks the progression of atherosclerotic plaque is unknown. Unfortunately, many who investigate temporal changes in calcium score over time have not considered that our understanding of the significance of atherosclerotic calcification is poor. A well-publicized retrospective nonrandomized review of subjects undergoing multiple scans showed decreased progression of calcification in a subgroup on effective lipid-lowering therapy (41).

Furthermore, the ability to track progression of calcium depends on the rescan variability compared with the expected rate of progression. If the former is much smaller than the latter, then progression within a year or two will be easy to detect in a single individual. If this is not true, it may take several years to be sure that progression is real and not due to measurement error.

The results of studies on reproducibility are listed in Table 56.2. Variability is seen to be at least 30% in most studies. Percent variability decreases rapidly for higher amounts of calcium. The reason for this is obvious because small calcium amounts can increase by 100% for spurious reasons.

Author	Year	No.	Variability (difference/mean; %)
Kajinami et al. (5)	1993	25	34
Bielak et al. (7)	1994	177	51
Shields et al. (42)	1995	50	38
Devries et al. (43)	1995	42	49
Wang et al. (3 mm slice) (6)	1996	72	29
Wang et al. (6 mm slice) (6)	1996	77	14

TABLE 56.2 RESCAN VARIABILITY IN FIVE STUDIES

Examination of age-dependent scores in cross-sectional data can most easily assess expected changes or progression over time. The approximate yearly increase in calcium score in such studies is between 20% and 35%. There are a few prospective studies showing similarly rapid progression of coronary calcium over time (40,41,44,45). Statistical arguments suggest that even with this rapid rate of progression, at least 4 years would have to pass before perceived changes in calcification could be judged to be significant in a single individual. This limitation on the clinical use of CT calcium assessments is similar to that seen for other types of vascular imaging such as coronary angiography (46). This drawback has far less effect on the utility of coronary calcium assessments for research studies when used in samples of at least 100 persons (47).

Coronary Calcium and Coronary Angiography

Available evidence suggests that a negative CT scan result for calcium does not completely exclude the presence of atherosclerotic plaque, but does imply a low likelihood of significant luminal obstruction. Most patients with angiographically normal coronary vessels have negative scan results and a low risk of coronary heart disease within 4 years after their scans. A positive scan result does indicate the presence of atherosclerotic plaque. Table 56.3 and references 7, 28, 29, and 47,48,49,50 and 51 give the sensitivities and specificities of CT coronary calcium for predicting angiographic stenoses. Shemesh et al. (48) have found that infarct-related arteries are less likely to be heavily calcified than those not related to myocardial infarctions. These results remain to be confirmed.

Author	No. of patients	Mean age (yr)	Sensitivity	Specificity
Breen et al. (28)	100	47	100	47
Fallavolita et al. (29)	106	44	85	45
Bielak et al. (7)	256	45	90	62
Devries et al. (49)	140	58	97	41
Rumberger et al. (50)	139	52	99	62
Budoff et al. (51)	710	58	95	44

TABLE 56.3 RELATIONSHIP WITH CORONARY ANGIOGRAPHY

All of these studies show that although sensitivity of coronary calcium for predicting coronary stenoses is high, specificity is low. This gives coronary calcium a high predictive value for ruling out but a low predictive value for identifying stenoses. It is on this basis that the American Heart Association writing group approved the use of coronary calcium for assessing patients with atypical chest pain (33). More recently, however, the combined American College of Cardiology/American Heart Association consensus panel took a more conservative stance on the same issue (52).

Screening and Predicting Events

This is an area that has generated much controversy and debate. The monograph by Morrison (53) contains an excellent definition of the purpose of screening for chronic diseases. “Screening for disease control can be defined as the examination of asymptomatic people in order to classify them as likely or not likely to have the disease that is the object of screening. . . . The goal of screening is to reduce morbidity and mortality from disease among the people screened by early treatment of

the cases discovered."

There are two aspects of this definition that are unfortunately ignored during much of the debate regarding calcium screening. The first is that experiments to evaluate clinical screening should use asymptomatic research subjects. The second is implied in the phrase "reduce morbidity and mortality." If this goal cannot be achieved, then screening will not achieve its purpose and cannot be deemed effective. For example, cholesterol screening is effective only because lipoproteins are clinically effective targets for preventive therapy; mammographic screening for breast cancer and occult blood screening for colon cancer have been proven to be effective in certain groups, not solely because they predict clinical disease and mortality, but also because screening leads to a course of action proven to save lives.

Before we can endorse massive coronary calcium screening of the entire population, or even a subpopulation, of adults, we need to have a screening test that leads to effective preventive therapy when applied to asymptomatic persons. Thus, the test must predict clinical disease in asymptomatic persons in a way that allows therapeutically effective decisions to be made based on the results.

It is sometimes argued that coronary calcium measurements can be helpful in certain subsets of persons, based on risk factor status and specifically on lipoprotein levels. For example, some would aggressively treat a 45-year-old man with reductase inhibitors, angiotensin-converting enzyme inhibitors, and aspirin if his low-density lipoproteins were in the range between 100 and 160 and he had a coronary calcium score of 400 (well above the ninetieth percentile for age and gender). They would argue: "I know he has coronary disease. Therefore, he should be in a secondary prevention category, and I should treat him as if he had suffered a myocardial infarction." Logical though it seems, this argument has an important flaw. The flaw lies in the expanded definition of coronary heart disease from *clinical* to *preclinical* disease. A calcium score of 400 is simply not the same as a prior myocardial infarction. Those with prior infarctions have been proven to benefit from aggressive low-density lipoprotein lowering. Those with calcium scores of 400 may also receive such benefit, as the recent Air Force Coronary Artery Prevention Study (AFCAPS) has shown (54). However, even if a score of 400 in this person predicted a grave prognosis, we could not be sure that any benefit would be garnered from intervention.

One might argue, of course, that treatment could be justified based on high risk alone. If those with scores over 200 are more than ten times more likely to develop clinical disease, then one probably should not wait for a clinical trial of calcium screening to make a decision to treat. We would agree that if, indeed, there were conclusive proof of a large increased probability (at least eight times) of a morbid coronary event based on a coronary calcium score, treatment would be justified even in the absence of a corroborative clinical trial.

How well does coronary calcium predict coronary events? O'Malley et al. (55) have reviewed most of the literature on using CT calcium to predict future events in asymptomatic adults. Their results are summarized in Table 56.4. We see from the table that the relative risk of calcification varies from 1 to 22 with a weighted mean of 4. There seems to be general agreement that calcium predicts events. There is little agreement as to how well it can do this. Thus, the predictive value of coronary calcium for new cardiac events still remains to be determined. The National Heart, Lung and Blood Institute has sponsored a study called MESA that will examine this issue as one of its major hypotheses. MESA will use a cohort of 6,500 American adults who will undergo CT scanning and will be followed for coronary events for 7 years.

Author	Relative risk	95% Confidence interval
Detrano et al. (34)	2.3	1.2, 4.4
Agatston et al. (56)	16.9	1.0, 286.3
Arad et al. (35)	22.1	2.7, 179.0
Sullivan et al. (57)	1.0	0.3, 20.5
Raggi et al. (58)	7.2	2.5, 20.5
Overall	4.2	1.6, 11.3

TABLE 56.4 RELATIVE RISKS OF CORONARY CALCIUM ACCORDING TO PUBLISHED PROGNOSTIC STUDIES

Position of the Professional Societies

In 1996, the American Heart Association, at the persistent suggestion of the proponents of scanning, assembled a writing group on the application of EBT coronary calcium scanning. This group concluded that EBT had not yet been proven to be useful for screening asymptomatic subjects and that more research was needed (33).

Interestingly, this enormously expensive technology is the only one that has found a limited degree of acceptance and popularity in the medical community. Of the more than 40 EBT scanners in the United States, most are used almost exclusively for coronary artery calcium screening. This technology—not fluoroscopy, not conventional CT—has been the subject of not one, but three reviews by national consensus panels (33,52,59,60 and 61).

The application of calcium assessments has been confined largely to screening asymptomatic populations for whom there are only scanty supportive data. This use began long before the publication of any prognostic data and before most of the cross-sectional studies were reported. An estimated 60,000 Americans have been so screened.

Fortunately, the American Heart Association and the American College of Cardiology have taken responsible positions on this issue. In Table 56.5 we suggest the potential indications for which coronary calcium scanning should and should not be considered as indicated, based on the consensus documents published by the professional societies.

	Screening asymptomatic adults	Selected patients with intermediate risk (e.g., low-density lipoprotein [100–160], etc.)	Diagnosis in those with chest pain	Prognostication in those with known coronary disease
Definitely indicated	-	-	-	-
Probably indicated	-	+	-	-
Possibly indicated	-	-	Atypical chest pain only	-

+, indicated; -, not indicated.

TABLE 56.5 INDICATIONS FOR CORONARY CALCIUM SCANNING

In this paradigm, a clinical examination including history, blood pressure measurement, and lipoproteins should always be used to determine the indication for a coronary calcium examination. General screening of asymptomatic adults should be discouraged, and coronary calcium studies should be restricted to those at intermediate risk who might benefit from aggressive risk factor modification and possibly to those with atypical chest pain.

Computed Tomographic Coronary Angiography

Medical and surgical management of coronary heart disease is in large part predicated on alterations in the lumen of the coronary arteries as demonstrated at coronary angiography. Although it is becoming clear that stenosis is only one domain of a complex process, as detailed in other chapters, the presence and distribution of arterial diameter reduction remain important determinants of patient management.

Cardiac CT, like cardiac magnetic resonance imaging (MRI), can produce a four-dimensional image of the beating heart. Although cardiac MRI provides superior tissue contrast, velocity mapping, myocardial tagging, and kidney-friendly intravascular contrast agents, cardiac CT has several characteristics that, with continued technological advances, may make it a major and perhaps front-line technique for cardiac and coronary imaging. Several advancements in CT technology are driving the renewed interest in contrast-enhanced cardiac CT. These include continued evolution of EBT techniques using equipment with improved gating, detector arrays, and table motion. For helical CT systems, the development of 0.5-second gantry rotation time, the addition of cardiac gating, the development of four- and eight-slice detector arrays with sub–1-mm slice thickness and sophisticated multiphasic volumetric reconstruction algorithms are driving a renewed interest in contrast-enhanced cardiac CT. This section reviews current and developing techniques and application of contrast-enhanced CT in the heart.

VIDEO

Video 56.1 Contrast-enhanced computed tomographic (CT) angiography with angioscopy. This video demonstrates a volume rendering of the heart and coronary arteries in the left frame, axial images in the upper right hand frame, and the lumen-view, or angioscopy, in the lower right frame. As the movie plays, the indicator on the volume images cross references the location of the lumen view within the left anterior descending coronary artery as it approaches and then passes through the stent located in the left anterior descending coronary artery. Techniques like this are under development. Efforts to reduce the amount of human and computer postprocessing required and increasing the spectrum of patients that can be imaged reliably and with high quality are under way. Further validation of these techniques is needed before introduction into clinical practice, but there is significant promise for these methods. Contrast-enhanced CT coronary angiography study performed on a Siemens Volume Zoom four-slice multidetector CT system operating in helical mode with cardiac gating. (Images courtesy of Christoph R. Becker, University of Munich—Klinikum Grosshadern.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Without the addition of an intravascular contrast agent, differentiation of the vessel wall from the vessel lumen is not possible in most instances with CT. This is due to the similar x-ray attenuation of blood and soft tissue. Cardiac CT is a four-dimensional multiplanar imaging technique. This multiplanar capability can provide quantitative information on vessel lumen, relatively irrespective of stenosis orientation, with a single acquisition (Fig. 56.5). In the next section we consider current technical aspects of contrast-enhanced CT imaging of the heart, review the published scientific literature, and conclude with areas of active research.

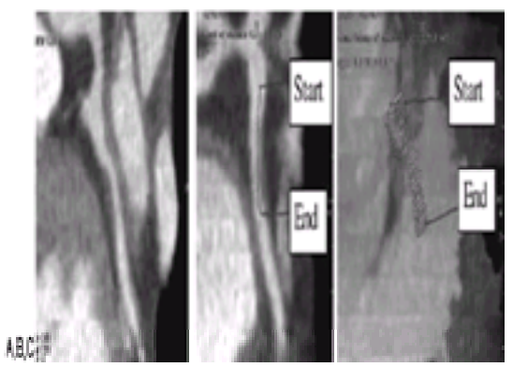


FIGURE 56.5 A–C: Contrast-enhanced computed tomographic coronary angiography. Left circumflex: curved reformatted image through the center of the lumen of the proximal left circumflex (segment 11) from a contrast-enhanced multidetector computed tomography study, helical acquisition with retrospective cardiac gating (General Electric Medical Systems LightSpeed Plus). Three-dimensional computer processing of the computed tomographic image data allows identification of the start and end points of various coronary segments with a potential stenosis **(B)** and determination of the central path of the vessel contrast column. From the central path, the orthogonal vessel cross-sectional area can automatically be determined and quantitative indices of stenosis measured from a wireframe representation **(C)**. Although there remain numerous challenges to validating techniques such as this for clinical application, they have the potential to provide quantitative information concerning coronary artery luminal dimensions noninvasively.

Technique

The goal of CT angiography is to image the coronary arteries during arterial enhancement after the intravenous injection of contrast material. In most instances, the test can be performed on an outpatient basis in 45 minutes of patient time. Procedure-related complications are rare and are related to the power injection of contrast media (venous extravasation), anaphylactoid reactions to contrast, and nephrotoxicity.

The generic examination consists of one or more planar scout images, unenhanced cardiac-gated CT, a timing scan, and a contrast-enhanced CT angiogram.

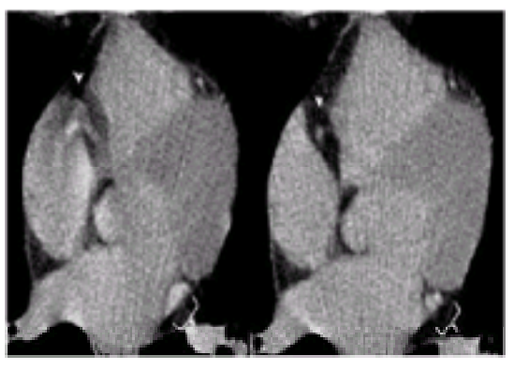
Scout images are planar tomograms, “landmarked” to the patient by a laser alignment system. The CT operator uses the scout images to prescribe subsequent scan volumes.

The unenhanced cardiac-gated CT is used to identify the location of coronary calcium, stents, catheters, foreign bodies, or other findings that partially obscure the contrast agent.

The timing scan is used to determine the transit time of contrast from the injection site to the ascending aorta. This sequence typically consists of a single slice repeated at some time interval (every 2 to 10 seconds) using a low-dose technique in the ascending aorta to determine the transit time of contrast. The transit time is then used as the delay time from the start of the contrast injection to imaging start for the CT coronary angiogram. The patient-specific delay time ensures that images are obtained in conjunction with the arrival of the intravenous contrast at the coronary circulation.

Contrast-enhanced EBT of the coronary arteries typically uses a sequential scan mode with prospective ECG triggering. Overlapping 3-mm slices are obtained by incrementing the table only 2 mm for each table position. Debate remains as to the optimal trigger point within the RR interval.

As discussed previously, MDCT systems can operate in either the sequential or helical mode. In the sequential mode, a four-or eight-slice scanner can acquire four or eight simultaneous data channels of image information. Thus, an eight-channel system can acquire, within the same cardiac cycle, 10 mm or 20 mm in coverage per heartbeat. In the helical or spiral mode of operation, a four or eight MDCT system can acquire four or eight simultaneous data channels while there is continuous motion of the CT table. The relative motion of the rotating x-ray tube to the table speed is called the *scan pitch* and is particularly important for cardiac gating in the helical mode. By combining information from each of the detector rows, the effective temporal resolution of the images can currently be set at between 100 and 200 ms, and the various cardiac phases can be reconstructed (*e*Fig. 56.5.1). An advantage of the helical acquisition mode is that there is a continuous model of the heart from base to apex, as opposed to the sequential cine mode in which there are discrete slabs of four or eight slices that have been obtained in a “step and shoot” fashion.



***e*FIGURE 56.5.1** The figure to the left demonstrates a standard half-scan reconstruction with a temporal resolution of 400 ms, with image data acquired on a four-channel multidetector computed tomography system, 1.25-mm slice collimation, 0.6 gantry speed, and a heart rate of 77 beats/min (General Electric LightSpeed Plus). The image to the right demonstrates the same helical scan data but processed with a two-sector reconstruction algorithm, resulting in an effective temporal resolution of 180 ms. Note how the proximal right coronary artery (*arrowhead*) and the left circumflex and great coronary vein (*bracket*) are resolved and motion-free on the multisector reconstructed image.

Computed Tomographic Angiography: Clinical Studies

Dr. Stephan Achenbach and colleagues have performed pioneering research in CT angiography with both EBT and MDCT. They have reviewed the ability of contrast-enhanced EBT to evaluate coronary artery bypass grafts (62), detect high-grade restenosis after percutaneous transluminal angioplasty (63), and determine patency of an infarct-related coronary vessel (64). They have also compared EBT coronary angiography with catheter-based coronary angiography in a study of 125 patients (65,66). The study was a direct comparison of the proximal and middle segments of the major coronary arteries, using the American Heart Association reporting system with both EBT and conventional coronary angiography. In this study, 25% of coronary vessels could not be evaluated (124 of 500 vessels), mostly because of respiratory artifacts and coronary calcifications. The number of patients with none of the four major coronary arteries of sufficient quality to evaluate was 15%. After excluding the 124 vessels, which could not be evaluated, EBT angiography correctly categorized 69 of 75 (92%) coronary vessels as having high-grade stenoses or occlusions, and 282 of 301 (94%) vessels were normal or had stenoses of less than 75% reduction in vessel diameter as compared with the standard of conventional catheter-based angiography (Fig. 56.6).

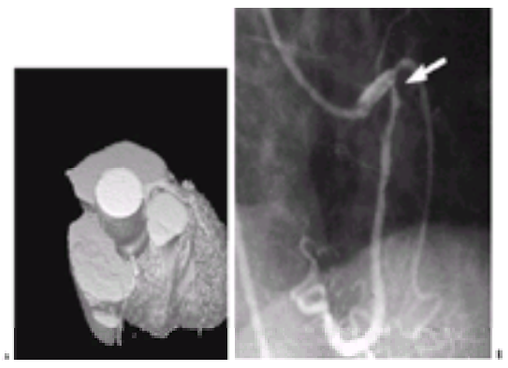
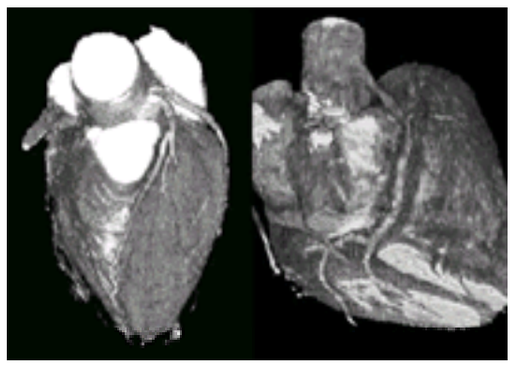


FIGURE 56.6 High-grade stenosis of proximal right coronary artery. Shaded surface display of a high-grade stenosis of the right coronary artery is demonstrated with contrast-enhanced cardiac computed tomography **(A)** (Imatron C150) and compared with stenosis (*arrow*) in the conventional coronary angiogram **(B)**. [Courtesy of S. Achenbach, Department of Internal Medicine II (Cardiology), University of Erlangen-Nuremberg.]

The authors noted that the majority of missed stenoses (false-negative results) were located in the right and left circumflex coronary arteries, in the segments coursing perpendicular to the transverse imaging plane where the 3-mm slice thickness and volume averaging may be important factors. They concluded that when image quality is sufficient, EBT contrast-enhanced coronary angiography “may be useful to detect or rule out high-grade coronary-artery stenoses and occlusions.”

Budoff and colleagues performed an additional study comparing EBT to conventional coronary angiography in 52 patients (67). They had similar high agreement between the two techniques for identifying coronary stenosis and reported good agreement between observers with the technique (kappa, 0.86). They also noted technical difficulties in the right and left circumflex coronary arteries related to “cardiac and respiratory motion and poor electrocardiographic gating.”

More recently, Achenbach and colleagues have evaluated MDCT in a study of 25 patients who at coronary angiography were excluded from having a hemodynamically significant stenosis (*e*Fig. 56.6.1) (65). They found no significant difference in measured coronary artery diameters at 100 points and a high correlation between MDCT-measured diameters and those at quantitative coronary angiography (R = 0.86). This initial study of contrast-enhanced cardiac-gated MDCT is encouraging in several respects. Greater lengths of the major coronary arteries were demonstrated with the four-channel MDCT than with previous validation studies using EBT and MRI, and there was a high correlation with quantitative coronary angiography. However, there remain unresolved problems of right coronary artery motion artifacts, limitations in image quality secondary to changes in heart rate during the scan acquisition, and radiation dose concerns.



***e*FIGURE 56.6.1** Normal computed tomographic coronary angiography (Siemens Volume Zoom). **Left:** The left anterior descending coronary artery from origin to cardiac apex is demonstrated. The proximal extent of the left circumflex coronary, which originates directly from the ascending aorta, is also seen. **Right:** The same three-dimensional data are viewed such that the origin and course of the right coronary artery is demonstrated in the atrioventricular groove. [Images were displayed using a volume rendering technique and are courtesy of S. Achenbach, Department of Internal Medicine II (Cardiology), University of Erlangen-Nuremberg.]

The continued rapid technological advancement of MDCT and EBT suggests that there will be further improvements in CT coronary angiography. Early efforts have demonstrated the feasibility of CT coronary angioscopy. In the near term, the development and introduction of MDCT systems with more than eight channels is likely. A 16-channel MDCT system could use the additional detector rows to improve temporal resolution, reduce breath-hold time, and reduce contrast dose. We will observe continued rapid advancement in CT for coronary angiography and a series of comparative studies evaluating these new CT techniques with existing measures of coronary heart disease.

Computed Tomographic Evaluation of Coronary Revascularization

Aortocoronary bypass grafts can be well demonstrated by modern CT techniques (Fig. 56.7). Through appropriate positioning of the imaging volume over the graft origin in the ascending aorta, the entire length of the graft can be imaged. When technically adequate studies are obtained, extremely high sensitivity and specificity for graft occlusions and hemodynamically significant stenosis can be achieved (Fig. 56.8) (62). Problems remain regarding poor breath holding and improper positioning of the imaging volume, which results in the proximal aspect of the aortocoronary graft not being imaged. Visualization of internal mammary grafts is often problematic. For all grafts, the presence of metallic surgical clips results in streak artifacts. These metallic artifacts typically prevent evaluation for stenosis at their location.

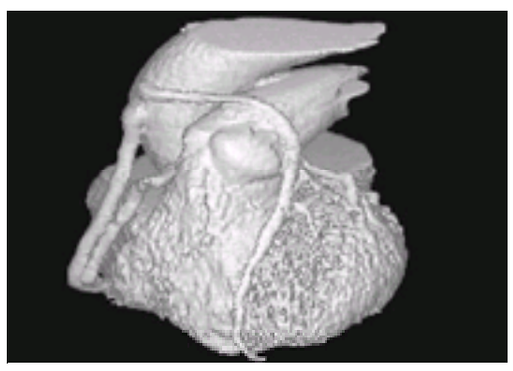


FIGURE 56.7 Patent aortocoronary vein grafts, patent (EBT Imatron C150). Two patent grafts are demonstrated in this three-dimensional shaded surface display. The more superior venous graft from the ventral aspect of the ascending aorta crosses the main pulmonary artery before anastomosis with the left anterior descending artery. The second vein graft courses alongside of the proximal right coronary before the anastomosis. [Courtesy of S. Achenbach, Department of Internal Medicine II (Cardiology), University of Erlangen-Nuremberg.]

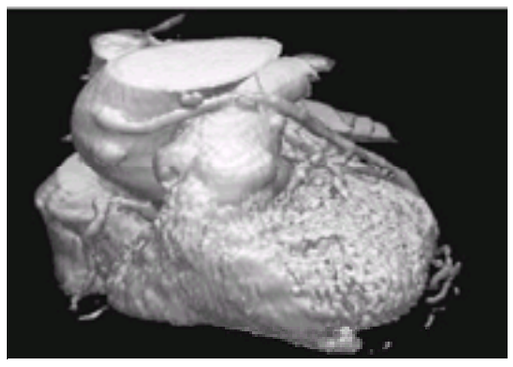


FIGURE 56.8 Aortocoronary vein graft occlusion (EBT Imatron C150). A patent aortocoronary graft to the left circumflex coronary is demonstrated. Note the proximal occlusion of the vein graft to the right coronary, which is identified as only a slight outpouching at the graft origin from the ascending aorta. [Courtesy of S. Achenbach, Department of Internal Medicine II (Cardiology), University of Erlangen-Nuremberg.]

Coronary stents have become one of the mainstays of interventional cardiology. Cardiac-gated CT can accurately describe stent location. Flow through stents can be evaluated and occlusion assessed. However, the metal intrinsic to current generation stents prevents CT from imaging the stent interior (Fig. 56.9).

FIGURE 56.9 Coronary stent (General Electric LightSpeed). A metallic coronary stent is demonstrated in the left anterior descending coronary artery. Although contrast enhancement can be seen proximal and distal to the stent, the higher attenuation of the metallic stent prevents direct visualization of the stent interior in most cases with existing computed tomographic reconstruction techniques. (Courtesy of Drs. Geoffrey Rubin and Curtis Coulam, Stanford University.)

Cardiac Valves and Chambers

Transthoracic echocardiography remains the major modality for imaging cardiac valves. However, in cases in which emphysema, obesity, or body habitus make transthoracic echo difficult, either transesophageal echo, MRI, or rapid CT can be used. Valve and mitral chordal thickening and valve stenosis can be identified using rapid CT. Vegetations and ring abscesses can also be detected. EBT has been used to image paravalvular pathology (68).

Rapid CT in patients with valvular abnormalities can reliably detect left atrial thrombus. Tomada et al. (69) studied 23 patients with valvular heart disease by conventional CT and found that it accurately detected left atrial thrombus. All patients with thrombus detected by CT had thrombus at surgery and 13 patients with no thrombus by CT were found to have no thrombus at surgery. Helgason et al. (70) compared EBT with transthoracic echocardiography in 40 patients presenting with stroke. EBT detected evidence of left atrial or left ventricular thrombus in 12 patients, whereas echo detected thrombus in only two patients.

Assessing Ventricular Function and Cardiomyopathies

Here too, however, rapid CT plays a supportive role to echocardiography. Employing the cine mode protocol provided on rapid CT scanners, the entire left and right ventricles can be imaged throughout the cardiac cycle. Sufficient contrast enhancement is usually achieved with 30 to 40 mL of contrast medium injected in a peripheral arm vein. These images accurately define the endocardial boundaries and allow precise measurements of ventricular volumes, ejection fraction, and left ventricular mass (71,72). In single-valve regurgitation, rapid CT can measure regurgitant fraction. The ability of contrast-enhanced rapid CT to quantify regional ventricular wall motion is important in the assessment of coronary artery disease. Ventricular function can also be evaluated during dobutamine infusion in a manner similar to that in echocardiography (73).

One interesting application of rapid CT is in the evaluation of patients with known cardiomyopathy, in whom the knowledge as to etiology might assist in management. Both EBT and MDCT have shown capability of distinguishing ischemic from nonischemic cardiomyopathy by the detection of coronary calcium (74,75).

Pericardial Disease

The fat found on the surface of the heart and the surrounding air-filled lung provides natural contrast that permits easy identification of a normal pericardium. Thickening of the pericardium can easily be identified, and this technology surpasses any other in identifying chronic pericarditis, particularly when it is calcific (Fig. 56.10). CT is therefore ideal for differentiating constrictive pericarditis from restrictive cardiomyopathy. The presence of normal pericardial thickness (i.e., 2 to 3 mm) excludes the diagnosis of constriction (76).

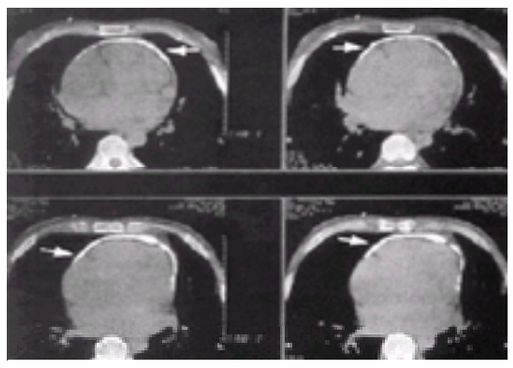


FIGURE 56.10 Thick, calcified pericardium is clearly demonstrated (*arrows*).

The tomographic format of CT makes it an excellent method to define primary and metastatic tumors of the pericardium. Extension into nearby mediastinal structures and to the lung can also be identified (77).

Congenital Heart Disease

Management of patients with congenital heart disease requires accurate information regarding structure and function of the cardiac chambers and great vessels. The traditional way of obtaining this has been with cardiac catheterization, and this remains the standard against which other imaging modalities are used in some institutions. Echocardiography is particularly useful and has replaced angiography to a great extent. There have been many reports of the use of CT as a modality to define abnormalities in structure and function of the heart. However, the role of CT in this application remains largely supportive to angiography and perhaps even more so to echocardiography.

In some adults with congenital heart disease, the diagnostic information provided by transthoracic echocardiography is limited because of chest deformities and difficulties finding adequate imaging windows. In these cases, ancillary methods such as transesophageal echocardiography, MRI, and CT can be of great help. The choice of these modalities depends largely on local experience and availability.

When imaging the hearts of infants and small children, it is essential to use a slice thickness that is small enough not to miss small structures such as the ductus arteriosus or anomalous coronary arteries. Most rapid scanners have the option of a 1.5-mm slice thickness or less. Another consideration in imaging tiny hearts is temporal resolution. There is little experience using MDCT scanners for imaging the hearts of infants. The experience with EBT scanners would suggest that the best temporal resolution achievable would be needed.

The most prominent role of CT in the assessment of congenital heart lesions involves structures that are relatively inaccessible to the ultrasonic probe, such as the pulmonary artery, the aorta's ascending and descending branch and arch, and the right ventricle.

These studies nearly always involve injection of contrast agent and, therefore, standard precautions should be taken. Scanning should begin within 10 to 20 seconds after injection of contrast. Usually a dose of 1 to 2 mL per kg is sufficient per injection. MDCT and EBT scanners should not require more than one injection to obtain high-quality images of cardiac chambers and vessels. Most scanners operate in a mode that allows visualization of the washin and washout of contrast from the cardiac chambers. When using EBT scanners, this is called the *flow mode*. Blood flow and shunt calculations can be done in a manner similar to that using indicator dilution methods in the cardiac catheterization laboratory. However, this is fraught with some difficulty due to beam hardening and other physical errors.

Specific problems for which rapid CT is indicated include determining the origin of the coronary arteries (78), visualization of the pulmonary arteries in cyanotic congenital heart disease (79), precise definition of aortic geometry in Marfan's disease (80), and partial or total anomalous pulmonary venous drainage (81). CT can also be used for visualization and assessment of patent ductus arteriosus (79,82) and aortic coarctation (83,84 and 85).

Aortic Disease

The thoracic aorta is an integral component of the cardiac CT examination and thoracic imaging in general. CT is the primary means of imaging the lung, thoracic trauma (blunt and penetrating), aneurysms, and aortic dissections (86). In the situation of an acute life-threatening event, CT can provide extensive information concerning the heart, aorta, and great vessels. In addition, during the same examination, the brain and spinal canal can be evaluated. The entire global CT examination (head, cervical spine, chest, abdomen, and pelvis) can be completed on modern MDCT systems in less than 15 minutes. These capabilities have made modern CT an indispensable tool in emergency departments and medical centers worldwide, and the development of the four-channel MDCT systems have further expanded these capabilities (87).

In the setting of blunt and penetrating trauma, CT of the chest can be extremely useful in diagnosis and as an aid to surgical management (86,88,89). Contrast CT can rapidly identify aortic tears, intramural hematoma, and dissection. In addition, the presence of mediastinal hematoma and other associated injuries can be assessed. These examinations are performed in critically ill patients who may require mechanical ventilation, invasive monitoring, intravenous infusion pumps, and cardiac pacing. The well-designed CT imaging suite is hospitable to life-support equipment, which can remain in the room and operational throughout the imaging procedure.

CT is playing an increasingly important role in the diagnosis and management of thoracic aortic pathology (90,91 and 92). Although MRI and transesophageal echocardiography can provide exquisite and unique information, the robust nature of CT often makes it the imaging modality of choice.

Contrast-enhanced CT can identify and classify aortic dissections and aortic aneurysms (Fig. 56.11 and Fig. 56.12) (93).

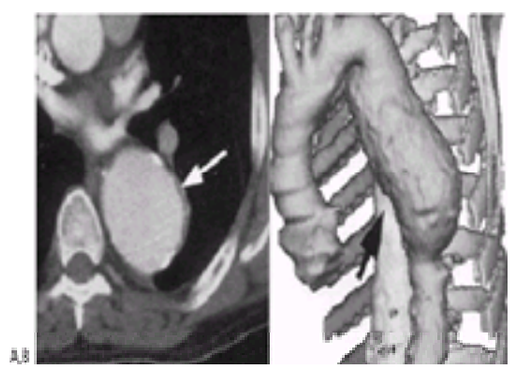


FIGURE 56.11 Descending thoracic aortic aneurysm. **A:** Image slice of atherosclerotic aneurysm (*arrow*). **B:** Three-dimensional reconstruction of thoracic aneurysm (Imatron C-150). Arrow points to large, cyndrical aortic aneurysm.

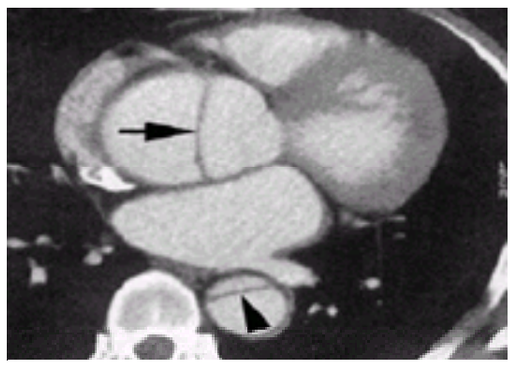


FIGURE 56.12 DeBakey type I or Stanford type A aortic dissection. Intimal flap is seen in both ascending and descending aorta (*arrows*) (Imatron C-150).

Advantages are the ability to image the entire aorta and beyond, demonstration of surrounding structures and organs, quantitative measures of aneurysm size and location, and a rapid examination time. Limitations are the negative effects of iodinated contrast on renal function, the rare adverse reactions to iodinated contrast, and the inability to directly measure blood flow. A current MDCT protocol for CT angiography provides high-resolution arterial phase images from the thoracic inlet to the femoral arteries. This coverage incorporates the entire aorta, as well as the organs of the chest, abdomen, and pelvis. Beyond classifying dissections as involving the ascending (Stanford type A) or descending (Stanford type B), CT can demonstrate associated findings critical to patient care such as mediastinal hematoma, pericardial effusions, pseudoaneurysm formation, and active extravasation of contrast from the aorta. Quantitative measurement of aneurysm size, location, and relation to branch vessels can be used for planning operative or intravascular repair and for monitoring postprocedure anatomy. The necessity for precise and quantitative measurements with CT has become more critical with the continued advancements in endovascular repair with stent grafts (94).

CONTROVERSIES AND PERSONAL PERSPECTIVES

To ensure efficacy and safety, national governments, including our own, have instituted regulatory agencies such as the Food and Drug Administration to ensure that research results and conclusions are accurate and appropriate. These measures are costly and something of a nuisance, but they protect the populace and the medical community from unscrupulous and evangelical crusades such as those of the laetrile enthusiasts of the 1960s. Much diagnostic testing has escaped from legal regulation (94). Doctors order and patients refer themselves for tests in order to discover hidden pathology and arrive at effective treatment. Much of this testing has questionable scientific validity.

During the 1990s, headlines appeared in the popular press regarding a new procedure for detecting heart disease and predicting heart attacks. At that time, there was no supportive scientific literature regarding the value of the new test, EBT, and for its stated purpose, to say nothing about its usefulness in improving outcomes.

Due to the initial popularity of the test, venture capital firms, small marketing operations, and university medical centers strapped for sources of income initiated and supported more coronary calcium screening projects. These grew into a kind of industry, organized by its strong bond to the, until relatively recently, unique manufacturer of CT equipment capable of performing this test. This industry promises to continue to mutate into other varieties of unproven radiographic self-diagnosis. Some coronary calcium screening centers already offer lung cancer screening and a few have expanded to “full body examinations,” which proclaim themselves capable of finding multiple pathologies.

Participants in this new calcium screening industry compiled calcium score databases and followed participants for coronary events. These research subjects rarely knew they were a part of a study and were usually not asked to sign consent forms verifying that they had agreed to participate in the evaluation of an investigational test. In 1999, the calcium screeners founded a new society, The Society of Atherosclerosis Imagers. They state that this new organization is dedicated to unbiased research regarding all aspects of arterial imaging. However, in its initial years, the major focus of the society has been to attempt to validate the conclusions that its members have already accepted, i.e., that EBCT and only EBCT can be used to guide therapy for coronary atherosclerosis.

Greed is not the major factor motivating the new society or the spread of coronary calcium screening adventures. The primary leadership of the calcium screening industry are well meaning enthusiasts who believe that they are executing rigorous scientific research. Indeed, the coronary calcium screeners have made important contributions toward the understanding of subclinical atherosclerosis. However, they often design their research not around hypotheses that require proof, but instead around preconceived conclusions that are then engineered backward into manipulated analyses of specially selected data.

It is hoped that this chapter can provide some balance to the almost exclusive opinion that has been heard, not only in the professional journals but on radio advertisements and commercial Web sites. In our opinion, CT of the heart will have an important role in medicine. In order to realize that role, researchers and clinicians must base medical decisions on evidence rather than on marketing.

SUMMARY

Rapid cardiac CT has remained outside of the realm of commonly used imaging technologies for the past two decades. This is partly due to justified reluctance of the medical community to accept new concepts and to limitations in available technology. It is probably largely due to the relative unavailability of scanners with the rapid exposure times required to image the beating heart.

Only now is rapid CT finding its place in the armamentarium of imaging technologies. Its application to screening for subclinical heart disease has received a limited endorsement from the American College of Cardiology and American Heart Association. The newer technology of MDCT is less expensive, more available, and probably equally accurate for cardiac imaging. We estimate that there are approximately 300 MDCT scanners made by four manufacturers and located in the United States that are capable of imaging the heart if fitted with the proper software and operated by knowledgeable personnel.

This has stimulated greater interest in CT imaging of the heart among cardiologists and radiologists. The failure of MRI coronary angiography to produce adequate endoluminal images and the promise of this achievement from rapid CT has sparked a flurry of trials of CT angiography of the coronary arteries.

Accepted applications of this technology at this time include evaluating for the presence of subclinical atherosclerosis in those at intermediate risk, evaluation of certain congenital heart lesions when other methods are not available or fail to produce adequate images, evaluation of aortic dissection or other aortic pathology when other methods are not available or fail to produce adequate images, and evaluation of the patency of aortocoronary bypass grafts and stents. The *a priori* use of CT coronary angiography, although promising, still awaits an accepted niche in cardiac diagnosis.

We hope that some of the readers of this chapter will take sufficient interest in this exciting field to pioneer further research and development of this evolving technology.

THE FUTURE

The recent history of CT coronary imaging has been unique in two ways.

First, until relatively recently, only one company produced equipment (EBCT) capable of obtaining accurate images of coronary calcium and of contrast-filled coronary lumina. Fortunately, several large medical imaging firms are now producing comparable equipment, which produces the same results at a reduced technical cost. This healthy industrial competition will lead not only to better images but also to more credible research.

Second, radiologists have largely rejected the accuracy of the older EBCT technology for scanning other organs or body parts due to high noise levels and other artifacts. Thus, once purchased, EBCT instruments must be used almost exclusively and extensively for coronary artery screening and CT angiography, or those responsible for the purchase must admit large fiscal mistakes. The advent of the newer MDCT scanning technology has obviated this problem in that these scanners can be shared between departments and have multiple approved uses.

These two features have stimulated the extreme positions taken by many in the coronary calcium screening industry that advocates therapeutic decisions based only on arbitrary thresholds of calcium score. This screening vogue is another American aberration soon to be cured by that even more American phenomenon, the free market.

MESA (47) will shed considerable light on the validity of coronary calcium screening. The results of MESA will determine whether a clinical trial similar to those that have proven the benefits of mammography is needed. If MESA shows powerful predictive values (relative risks greater than 8) for coronary events, then such a trial may not be necessary. However, if, on the other hand, the results of MESA are more modest, a decision as to whether or not such a trial is needed will have to be made.

ACKNOWLEDGMENT

The editorial assistance of Zephyr Detrano is deeply appreciated.

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57

INTRAOPERATIVE ECHOCARDIOGRAPHY

WILLIAM J. STEWART

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Intraoperative echocardiography (IOE), mostly using transesophageal methods, provides an important means of assessing cardiac structure and function during cardiac and noncardiac operations (1,2,2a). IOE helps refine surgical plans immediately before cardiac surgery by defining the surgical mission and determining the severity and mechanism of the cardiac dysfunction. This provides the surgeon with an up-to-the-minute definition of the patient's anatomy and physiology, to help define or refine the objectives for surgery and to optimally plan repair of the dysfunctional valves, congenital abnormalities, coronary problems, and other disease. After surgery, the postpump IOE provides a safety net for immediately checking the success of the procedure at a time when further surgery can be performed (a second pump run) during the same thoracotomy. The frequency of changes in operative management varies directly with the difficulty of the procedure involved and is substantial for valve repair of various types, especially high for aortic valve repair, aortic homograft implantation, and myectomy for hypertrophic cardiomyopathy. This chapter describes the history, purposes, methodology, and effectiveness of IOE, as well as its impact on numerous types of surgeries. It is likely that IOE will contribute to the future development of innovative and emerging surgical procedures.

GLOSSARY

Contrast echocardiography: Imaging during injections to increase visualization of selected structures.

Epicardial echocardiography: Performed with the transducer placed directly on the surface of the heart during surgery.

Loading conditions: Factors related to intravascular volume and the pressures on the input and output sides of the heart.

Postpump: Refers to the IOE done after discontinuation of cardiopulmonary bypass.

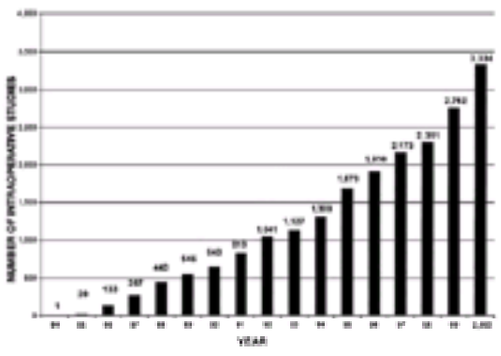
Prepump: Refers to the IOE done before institution of cardiopulmonary bypass.

Second pump run: A second run of cardiopulmonary bypass for additional surgery done to correct residual problems after the initial surgery was thought to be sufficient.

Valve repair: Surgery to correct valve dysfunction using the native valve tissue, without removing or replacing the valve.

HISTORICAL PERSPECTIVE

IOE has grown substantially over the last decade (*e*Fig. 57.0.1). Its first use was in 1972 by Johnson et al. (3) with the premise, now substantiated, that immediate evaluation of valve function would aid in mitral valve operations. In 1975, M-mode transesophageal echocardiography (TEE) was reported by Frazin et al. (4); from 1977 to 1981, two-dimensional TEE for black and white imaging was reported (5,6). However, imaging of the quality available then, without flow information, provided little practical benefit to the surgical process. The first modern use of intraoperative TEE was reported by Kremer et al. from San Francisco in 1982 (7,7a) during general surgery. Topol et al. (8) in 1984, using TEE with imaging alone without Doppler, looked at recovery of dysfunctional segments immediately after coronary bypass surgery. In the same year, Goldman et al. (9) showed the first practical use of IOE in valve surgery, with epicardial contrast echocardiography using transthoracic transducers. Soon thereafter, color flow mapping was applied to the evaluation of valve repair using epicardial techniques (10,11,12 and 13). TEE with color Doppler became available in 1987 (14,15) and has become the dominant mode used in the practice of IOE over the past 14 years (16). The advent of biplane (1989) (17) and multiplane (1992) (18) TEE probe technology further added to the clinical capabilities of IOE. Newer technologies including parallel processing, harmonic imaging, Doppler tissue imaging, three-dimensional imaging, and digital storage place intraoperative TEE in the forefront of the development of modern cardiac surgery.



***e*FIGURE 57.0.1** The Cleveland Clinic experience with 20,509 intraoperative echocardiography studies, performed from 1984 to 2000, showing the number of intraoperative studies done per year.

PREPUMP INTRAOPERATIVE ECHOCARDIOGRAPHY: GENERAL CONSIDERATIONS

Purposes

IOE before cardiopulmonary bypass (prepump) is useful in certain groups of patients undergoing cardiac surgery, for several important reasons. It provides an accurate way to determine the mechanism and severity of the problem requiring surgery (19). The prepump study is also helpful to obtain baseline information about an anesthetized patient that may be of better quality or reflect interval changes compared with preoperative studies.

Performed appropriately, echocardiography has the attribute of completeness, with its ability to diagnose the structure and function of all cardiac valves (19a) and chambers, even those that are not the primary problem mandating surgery. Dysfunction of other valves that is not treated effectively can lead to serious and potentially life-threatening complications and be mistaken for failure of the primary operation. This results from mistakes in the preoperative definition of the patient's problem or from changes that occur in the interval between workup and surgery. The prepump TEE often finds problems that were not detected on the preoperative evaluation, most commonly, a clot in the left atrial appendage or a patent foramen ovale.

A final purpose of the prepump IOE is to define methods of cannulation. This is particularly important when there is severe aortic atheroma, with its potential to embolize if disrupted by the operative process. It is also important in placement of intracardiac devices such as those used for port access surgery (19b). The prepump study has also been used to define optimal methods of cardioplegia administration (19c). For example, aortic regurgitation (AR) of even moderate severity may limit the effectiveness of antegrade cardioplegia administration via the aortic root (20). Placement of a coronary sinus catheter for retrograde cardioplegia can also be confirmed by TEE (21,22).

Transesophageal echo view of the descending aorta in short axis demonstrating significant atheromatous plaque.

Severe calcific atherosclerosis of aorta. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Methods

Two methods of intraoperative imaging have been employed, TEE and epicardial echocardiography. TEE has substantial advantages in most situations, including the ability to monitor cardiac function without an echocardiographic transducer entering the sterile field or interrupting the surgical process. Posterior structures such as the atria and pulmonary veins are seen better with transesophageal echocardiography.

However, there is a small risk of serious trauma with the TEE probe (23), including a slight increase in swallowing problems (23a). After use of intraoperative TEE, a 12% incidence of transient postoperative hoarseness has been reported (24), although this may result also in part from the endotracheal tube. One study of 7,200 intraoperative TEEs found severe odynophagia in 0.1%, dental injury in 0.03%, endotracheal tube malpositioning in 0.03%, upper gastrointestinal hemorrhage in 0.03%, and esophageal perforation in 0.01% (24a).

The TEE transducer is introduced after the patient is anesthetized, the trachea intubated, an orogastric tube inserted temporarily to remove stomach contents, and the hypopharynx filled with liberal amounts of water-soluble lubricant. If “blind” passage of the TEE scope with gentle anterior traction on the jaw is unsuccessful in passing the scope beyond the hypopharynx (20-cm depth), then a laryngoscope is employed to guide insertion of the transducer. Further details on TEE probe insertion in awake patients are provided in Chapter 52.

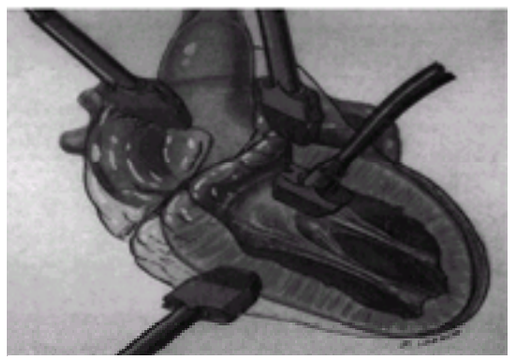
For epicardial echocardiography of the heart itself, a standard transthoracic phased array transducer (3.5 to 5.0 MHz) is used. Epicardial echocardiography has the advantage that certain anterior structures, including the left and right ventricular outflow tracts and ascending aorta, are in the near field (25,26). For epivascular imaging, a standard pediatric transthoracic phased array transducer (5 to 8 MHz) or a linear array transducer (6 to 10 MHz) is used. The probe is inserted inside two sterile sleeves with sterile lubricant between them and on the surface of the probe to eliminate air (13). The transducer is placed on the surface of the beating heart or the aorta (27,28).

During epicardial echocardiography, the surface of the heart should be moistened with saline, but the pericardium does not need to be filled with fluid. Although it is not needed for most purposes, a standoff device, such as a glove filled with saline, is a valuable way to see the near field within the first few millimeters of the face of the transducer. The echocardiographer, who is scrubbed for surgery, must verbally direct another individual who is in the nonsterile portion of the operating room to adjust the instrument controls on the echocardiographic machine in concert with the designs of the study.

Epicardial and epivascular echocardiography is now used mainly for epiaortic scanning for atheroma. It is also used for selected other cases when the available TEE capability falls short of the clinical needs, for example, for recording the left ventricular (LV) outflow tract gradients in hypertrophic cardiomyopathy (26), recording the right ventricular outflow tract gradients in congenital pulmonic stenosis, or other cases in which TEE data appear to be suboptimal or unobtainable.

Imaging Planes

The tomographic planes available for diagnosis using multiplane TEE have been described in multiple publications (29,30,30a,30b) and elsewhere in this book. We have described four epicardial transducer positions and imaging planes (*e*Fig. 57.0.2) making up a complete evaluation of cardiac anatomy and physiology (13,31,32). The parasternal and subcostal equivalent views are similar to the transthoracic windows of the same name. The aorta–pulmonary artery sulcus view is obtained by placing the transducer against the left side of the aorta, in the sulcus between it and the pulmonary artery, using the aorta as a standoff device so that the primary areas of the left heart are in the focal zone of a standard transducer. A fourth view, the aorta–superior vena cava view, is obtained by placing the transducer against the right side of the ascending aorta, pointing inferior toward the LV outflow tract and aortic valve. The latter is extremely useful for measuring LV outflow tract velocities using continuous wave Doppler-echocardiography.



***e*FIGURE 57.0.2** The four standard positions for epicardial transducer placement: the parasternal equivalent view, the aorta–pulmonary sulcus view, the subcostal equivalent view, and the aorta–superior vena cava view. (From Cosgrove DM, Stewart WJ. Mitral valvuloplasty. *Curr Probl Cardiol* 1989;14:359–415, with permission.)

Goal-Oriented Study

IOE is usually time-limited by the pressing needs to reduce anesthetic and personnel time. The design of the IOE study should provide an efficient balance between the objectives of focusing on the primary surgical mission versus obtaining a complete imaging and Doppler examination of the entire heart and great vessels. The first thing to examine should be the structures related to the objectives that mandated the IOE study (e.g., the anatomy and physiology of the valve on which surgery is planned) (32a). Doing this in the first few minutes may become particularly important if the patient thereafter becomes hemodynamically unstable, the electrocautery must begin, or the surgical team must prematurely initiate cardiopulmonary bypass. In most cases, there is sufficient time after the most important questions are answered to record a complete study, involving a long-axis and short-axis view of all four chambers, the great veins and arteries, and all four valves, using various imaging and Doppler modalities.

Idealizing Room and Loading Conditions

For diagnostic intraoperative studies, the imaging conditions, instrument controls, and transducer contact should be optimized, including dimming the operating room lights, avoiding electrocautery during key periods, and periodically relubricating the imaging portion of the esophagus with water-soluble lubricant.

Usually the amount of valvular dysfunction on the TEE matches that of the preoperative assessments (33). However, the loading conditions in the operating room can sometimes be quite aberrant. Often there is relatively less sympathetic tone and less intravascular volume during anesthesia, compared with ambulatory conditions. Therefore, the ejection fraction, amount of valvular regurgitation, or stenotic gradient found by IOE is often slightly different from what it was in the echocardiography laboratory or the catheterization laboratory (31,34), which is probably more reflective of the patient’s real life. Manipulation of loading conditions may change the amount of regurgitation (35). To optimize diagnostic information in some cases, it is useful to give hemodynamic challenges, such as increasing intravascular volume or transiently raising afterload with multiple 100-µg boluses of intravenous phenylephrine.

Record Keeping and Image Archival

A written record of the diagnoses made by TEE is an important part of the job of IOE. In addition, archiving images either by videotape or digital methods (35a) is important for comparison with previous and subsequent studies. Both of these issues are important when medical-legal issues regarding the operation are raised.

Indications for Intraoperative Echocardiography

The types of patients for whom intraoperative TEE is useful are detailed by the groups of disease states listed in this chapter. Thys et al. have published guidelines for perioperative echocardiography, delineating three categories: category I for those supported by strong evidence of clinical value for improving outcome; category II for

applications supported by weaker evidence; and category III for applications that are uncertain to have clinical benefit (35b). This chapter discusses most of these indications in detail.

Outcome Studies for Prepump Intraoperative Echocardiography

One study by Chaliki et al. compared the prebypass TEE findings with surgical observations in a large group of 918 cases; TEE information was found to be quite reliable, showing discrepancies with operative findings in only 2.5% of cases (35c).

Several studies have determined the frequency with which the prepump IOE contributes to a change in surgical management. In several studies of mixed multiple groups of valvular lesions, prebypass imaging diagnosed unsuspected findings that changed the planned operation in 10.8% to 19.0% of patients (36,36a). In another study of 246 patients with ischemic mitral regurgitation (MR), prepump TEE resulted in a change in the operative plan with respect to the mitral valve in 27 patients (11%), involving less MR than expected in 22 patients and more MR in five patients (34). In patients who come to the operating room in an emergent situation with unstable hemodynamics, the emergency intraoperative TEE has an even larger impact on clinical outcome, with new findings discovered in 80% of patients and an alteration of the planned surgical procedure in 23% (36b).

Ungerleider et al. (37) studied 328 patients before surgery for congenital heart disease and found that IOE played a role in surgical planning in 44% and discovered previously unappreciated details of anatomy in 18% of patients. Another author found a major problem on the prebypass echocardiogram that led to a change in plans in 6.7% (37a). In an early study of a mixed group of 426 consecutive patients with a mixture of valvular problems, our group found that 40 patients (9%) had a change in the operative mission based on the prepump IOE (unpublished data). In another study from our institution, Secknus et al. (38) evaluated 121 patients in whom prepump intraoperative TEE studies were performed to assess MR and the need for mitral repair; changes in operative plan occurred in 6.1%, mostly in cases in which less mitral disease was found than was expected on the basis of the preoperative workup.

Some findings, such as a thrombus in the left atrial appendage, should prompt operative removal. When this is found in a patient without mitral valve disease, removal may require bicaval rather than single-stage cannulation for the venous return to the heart-lung machine. However, it is not certain whether closure of the appendage should be recommended, as it remains at least partly open even after attempted closure in 36% of such cases (37b).

Click et al. from the Mayo Clinic reported a large series of 3,245 patients undergoing IOE, in whom new information was found before bypass in 15% of patients. This directly affected surgery in 14% of the patients. The most common new prepump finding was a patent foramen ovale, which was closed in the majority of patients (38a). The series by Click et al. is probably the most intensively reported large group of patients undergoing IOE. The important changes in plans included a decision to do something that had not been planned in 9.6% of the total, including a new decision to close a patent foramen ovale in 2.7%, to perform valvular surgery in 2.7%, and to remove a previously undiagnosed thrombus in 1.1% of the total. There were also decisions based on the prepump echocardiogram *not* to do something that had been planned in 3.9% of the total, which were mostly decisions not to do surgery on a valve for which the preoperative workup had indicated a need for surgery (3.6% of the total of 3,245 patients) (38a).

Another more recent study by Couture et al. found that prepump IOE led to a modification of planned surgical intervention in 30% of cases, with a frequency of 39% in complex surgical procedures, 19% in valvular surgery, and 10% in coronary artery bypass surgery (38b). Still another study of 5,016 cases by Mishra et al. found that prebypass imaging yielded unsuspected findings that either helped or modified the surgical plan in 12% of valve procedures and in 27% of coronary procedures (38c).

Of note, the decision not to do surgery that had been planned by the physicians who referred the patient for surgery is a change in plans that should not be taken lightly. Doing the right surgery is as important as doing it well. All patients who have cardiac surgery should have complete preoperative evaluation to decide on the surgical mission. As in all clinical medicine, decisions must be based on an integrated picture of the patient's age, overall health, ventricular function, and myriad other valvular and nonvalvular determinations. The prepump study should not be a substitute for a thorough workup before the patient enters the operating room. Because the physician performing the IOE often has not had extensive contact with the patient before surgery, integrating the IOE examination with the preoperative and general health considerations of the patient must often be done through the chart. When new considerations arise with the IOE, a telephone call to the primary clinician who referred the patient for surgery may help to integrate the intraoperative decisions. Only in dire circumstances should one rely solely on the prepump IOE to define the objectives of the operation.

POSTPUMP INTRAOPERATIVE ECHOCARDIOGRAPHY: GENERAL CONSIDERATIONS

Purposes

The primary purpose of echocardiography done after cardiopulmonary bypass (postpump) is to determine the success of the primary surgical mission. Like the prepump study, the postpump study should be goal oriented, examining the most important issues first (32a), with one modification. The postpump IOE should first evaluate the most vulnerable aspect of the surgery for immediate failure, which may be different from the primary indication for surgery. For example, in a patient with mitral stenosis with severe mitral calcification and functional tricuspid regurgitation (TR), the mitral replacement may be more important in the clinical improvement than tricuspid repair, but the most important problem to examine first on the postpump TEE study is the tricuspid repair, because the mitral prosthesis is less likely to have initial failure.

The postpump TEE is much more relevant if performed after establishing hemodynamic stability under conditions that match the ambulatory state, whereas misinformation can result from studies done during aberrant transient conditions early after coming off bypass. Imaging should be done before administration of protamine and removal of the arterial and venous cannulae, so that cardiopulmonary bypass can be reinstituted if problems are found. The exception to this is the patient with mild periprosthetic regurgitant jets found on postpump TEE, which have a tendency to improve after protamine is given (38e).

In some cases, the primary problem mandating surgery persists (e.g., residual valvular regurgitation after attempted repair of that valve). In occasional cases, new problems occur, such as new regurgitation of an additional valve not previously abnormal, or another complication. In general, we consider *no* valvular regurgitation to be the ideal result of surgery and mild (1+) regurgitation to be an acceptable outcome. Moderately severe or severe (3+ or 4+) are problematic and warrant a "second pump run" for further surgery during the same thoracotomy to correct the problem. In most cases of moderate (2+) regurgitation, further surgery is usually indicated, but the situation must be individualized, depending on the patient's age and overall condition. In such cases, we recommend careful, complete echocardiographic evaluation for a period of 5 to 10 minutes, without giving protamine or decannulating, during which time the hemodynamic conditions should be idealized and even provoked. Sometimes the regurgitation decreases in severity with recovery of ventricular function. In other cases, the regurgitation is obviously bad enough for further surgery. In many cases with moderate residual regurgitation, we find it useful to increase mean arterial pressure, observing the amount of regurgitation with this "afterload stress" echocardiogram. If the amount of MR or AR persists at a moderate (2+) level, or increases, the patient should probably undergo further surgery with a second pump run.

Numerous types of intraoperative provocation can be used to bring out postpump valvular dysfunction in cases in which the amount of residual problems is borderline or when loading conditions might otherwise lead to false reassurance. The most commonly used is the phenylephrine challenge, which is useful for borderline amounts of aortic and MR (39). Boluses of 100 µg of phenylephrine are given every 30 to 120 seconds to bring mean arterial pressure up to approximately 110 transiently. If moderate or more regurgitation results, consideration should be given to further surgery on that valve. Other types of provocation used in the operating room include isoproterenol for hypertrophic cardiomyopathy, intravascular volume challenge for any lesion, and partial pulmonary artery occlusion for TR. It is far better to know of a latent problem immediately in the operating room than to learn about it a day or a week after surgery.

Another purpose of postpump intraoperative imaging is to diagnose complications of surgery. These include iatrogenic problems generic to cardiac surgery, including outflow and inflow obstruction, aortic dissection at the site of aortic cannulation (38d), atrial septal defect, periprosthetic regurgitation, and intraoperative myocardial infarction. Definition of these cases by IOE allows a rational basis for pharmacologic management or for performing further surgery during the same thoracotomy.

The frequency of second pump runs overall is 5.4% of IOE studies in our series (19a), and it varies depending on the type of surgery performed and its complexity (Table 57.1). The procedures at highest risk of initial failure are myectomy for hypertrophic cardiomyopathy and aortic valve repair. Which surgery is most vulnerable to initial failure should be a factor in deciding which patients to invest resources for IOE and which problem to address first with the postpump study (16). Surprisingly, over the past 15 years, the frequency of second pump runs at our institution has essentially stayed the same, both overall and within each of the categories followed.

	Cases (no.)	Second pump runs (no.)	Second pump runs (%)
Total	9,826	531	5.4
Mitral repair	3,032	199	6.6
Aortic repair	516	74	14.1
Tricuspid repair	518	28	5.3
Congenital	681	39	5.7
Hypertrophic cardiomyopathy	232	42	17.9
Thoracic aneurysm	560	21	3.8

From Grimm RA, Stewart WJ. The role of intraoperative echocardiography in valve surgery. *Cardiol Clin* 1998;16:477–489, with permission.

TABLE 57.1 FREQUENCY OF SURGERIES STUDIED WITH INTRAOPERATIVE ECHOCARDIOGRAPHY AND SECOND PUMP RUNS PERFORMED (1984 TO 1996)

In the large study from the Mayo Clinic by Click et al., new information was found by IOE after bypass in 6% of the patients, resulting in a change in surgery or hemodynamic management in 4% of the total; it was highest in a selected group of patients with coronary artery bypass graft surgery (CABG), aortic surgery, and hypertrophic cardiomyopathy (38a). Michel-Cherqui et al. reported a frequency of 2.5% of 203 cases in which immediate surgical intervention was required on account of the postpump TEE findings (36a).

The converse of these data is that the postpump study finds a satisfactory result with resolution of the initial problem in the majority (94% to 97%) of patients; this also provides a substantial benefit to the patient. When abnormal hemodynamic changes occur outside the operating room in the early postoperative period, the management team can be confident that the changes are not due to failure of the primary surgical mission if the postpump study has shown that it was accomplished.

Another purpose of the postpump study is to reassess ventricular function. It is important to document changes resulting from elimination of the primary surgical problem and to determine a new baseline for later comparison. However, early after cessation of cardiopulmonary bypass, LV function may be transiently depressed by residual effects of hyperkalemic cardioplegia or air embolization to the coronary bed. Finally, IOE can define the location and severity of intracardiac air to assist in its removal.

Outcome Studies

In the case of residual lesions on the postpump study, there is the opportunity to correct the problem while the chest is still open during the same thoracotomy. Although one study showed a good correlation between residual regurgitation found by the postpump IOE and postoperative angiography results (40), the amount of regurgitation found with both studies is subject to variations in loading conditions (40a). Selective performance of second pump runs for further surgery may improve patient outcome. However, no controlled trials exist to determine the eventual outcome if persistent valvular dysfunction or other problems are not immediately addressed. Furthermore, determination of the exact threshold for second pump runs is difficult, also because of the lack of adequate case-control studies.

In our experience with patients having second pump runs for mitral repair, there was no excess in-hospital mortality or complication rates compared with matched controls who had no problems evident on postpump imaging (41). However, Duran et al. did find a higher mortality (16.6%) in those whose initial repair failed, requiring a second pump run, compared with the mortality in patients who had initially successful repair (1.4%) or mitral replacement (4.0%) on the initial pump run (42). This obviously depends on the threshold of going back on pump and whether there were predisposing factors about those patients that were associated with higher risk to begin with.

The policy of performing further surgery after procedures that are less than completely successful was reinforced by an early study by Sheikh et al. (36), in a group of 154 consecutive patients having valvular surgery. Because of the newness of IOE and uncertainty about its validity, the surgery was not revised, despite moderate to severe postpump valvular dysfunction. The patients with residual valve dysfunction on the postpump study had a greater risk of early postoperative complications (86% vs. 15%) and mortality (43% vs. 5%).

In one study of wall motion after coronary bypass, postpump ischemia diagnosed by TEE was a significant predictor of outcome. One-third of patients with postbypass ischemia by TEE had adverse outcomes versus none of those without TEE ischemia (43).

In several groups of patients, a borderline amount of valvular dysfunction after surgery was present on the postpump study that was at or below the threshold for second pump runs, usually mild or moderate (1+ or 2+) regurgitation. This group was compared with patients with an “echo perfect” result who had no residual valvular dysfunction by postpump TEE. In the case of mitral valve repair (44), homograft aortic valve replacement (45), and aortic valve repair (45d), there is greater risk of reoperation in early follow-up that is predicted by mild to moderate postpump valvular dysfunction by IOE. In one follow-up study of mitral repair, the group of patients who had intraoperative echocardiographic studies performed were less likely to require reoperation within 10 years of follow-up than patients who did not have IOE (45a).

MITRAL VALVE REPAIR

In mitral valve dysfunction, IOE is particularly useful for determination of the mechanism of the problem, prediction of the methods that will be required for surgical repair, diagnosis of complications of repair, and assessment of the postrepair results of the surgery.

The prepump IOE has been found to change the operative plans in 6% to 17% of cases (36a,38). With both imaging and color Doppler, the mitral valve is investigated systematically by TEE using a short-axis view from the transverse transgastric window, and multiple midesophageal long-axis views (2,45b,45c). Most of the long-axis views help define *which leaflet* is involved. For examining which *portion* of the leaflet is most involved (Fig. 57.1), the best views are the short-axis transgastric view and the midesophageal intercommissural long-axis view. The latter is obtained from the midesophageal window with the multiplane angle at approximately 60 degrees, with the plane parallel to the line between the mitral commissures.

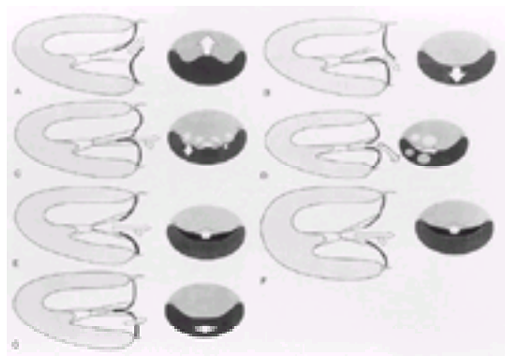


FIGURE 57.1 Mechanisms of mitral regurgitation, determined by echocardiographic assessment of leaflet motion and Doppler assessment of jet direction. Diagrams show long-axis views (left side of each pair) and short-axis views (right side of each pair). **A:** Posterior leaflet flail or prolapse with an anterior jet direction. **B:** Anterior leaflet flail or prolapse with a posterior jet direction. **C:** Bileaflet chordal elongation, flail, or prolapse with a central or posterior jet direction. **D:** Posteromedial papillary muscle infarction causing elongation or disruption of support to both leaflets at the commissure with a jet emanating from the medial commissure, directed posterolaterally. **E:** Leaflet restriction with a central or posterior jet direction. **F:** Ventricular-annular dilation displacing the papillary muscles outward with a central or posterior jet direction. **G:** Leaflet perforation with an eccentric location of the jet origin, originating from the leaflet body, away from the coaptation line. (From Stewart WJ, Currie PJ, Salcedo EE, et al. Evaluation of mitral leaflet motion by echocardiography and jet direction by Doppler color flow mapping to determine the mechanisms of mitral regurgitation. *J Am Coll Cardiol* 1992;20:1353–1361, with permission.)

Quantitating the severity of MR (a topic covered in Chapter 51) is accomplished using a weighted average of information from left atrial spatial mapping (31,46,47), proximal jet width (48), pulmonary vein pulsed Doppler (49), and proximal flow convergence information (50). It appears that TEE and epicardial echocardiography give relatively equivalent assessments in quantifying MR (51). Both are more sensitive than transthoracic echocardiography. As mentioned previously, hemodynamics in the operating room often include less intravascular volume and less afterload than the ambulatory state, which often decreases the amount of MR (51a).

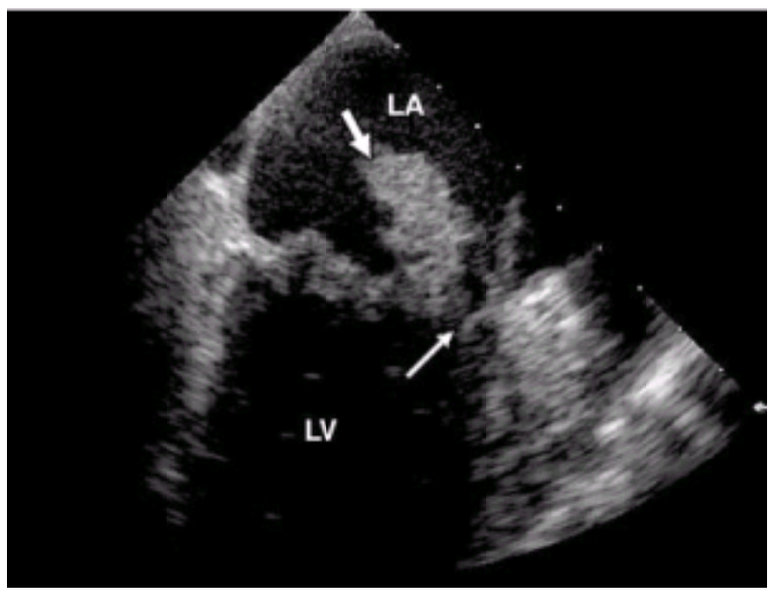
Determining the Mechanism of Mitral Regurgitation from Leaflet Motion and Jet Direction

For determination of the mechanism of MR, IOE uses two-dimensional evaluation of leaflet motion and color flow Doppler evaluation of jet direction (19). Leaflet motion is separated into MR associated with excessive, normal, and restricted leaflet motion, a system derived from the surgical system used by Carpentier et al. (52). These leaflet motion groups, associated with jet direction characteristics, characterize the various mechanisms of MR (Table 57.2).

Leaflet motion	Problem	Jet direction	Leaflet surgery	Annulus
Excessive				
	PL MVP	Anterior	Quad resection	Annuloplasty
	AL MVP	Posterior	Chordal transfer (chordal shortening, artificial chordae)	Annuloplasty
	Bileaflet MVP	Central*	Quad resection	Annuloplasty
	Papillary muscle rupture	Commissural	Papillary muscle reimplantation	Annuloplasty
	Commissural chordal rupture	Commissural	Suture commissure, chordal transfer	Annuloplasty
Normal				
	LVE, apical tethering	Central/posterior	None	Annuloplasty
	Perforation	Eccentric origin	Suture, patch	Annuloplasty
Restricted				
	Restricted leaflets	Central/posterior	CMC, debridement, division of fusion	Annuloplasty

AL, anterior leaflet; LVE, left ventricular enlargement; MVP, mitral valve prolapse; CMC, open mitral commissurotomy; PL, posterior leaflet.
*In bileaflet prolapse, jet direction reflects the most dominant problem; may be anteriorly directed with posterior greater than anterior prolapse, or posteriorly directed with anterior greater than posterior prolapse.

TABLE 57.2 INFLUENCE OF JET MECHANISM AND CHARACTERISTICS ON SURGICAL PLANNING



Intraoperative transesophageal echo of a myxomatous mitral valve with large vegetation (*thick arrow*) and a large perforation (*thin arrow*) at the base of the anterior mitral leaflet from endocarditis. One can easily see this hole on two-dimensional imaging, and the color flow can be seen on image.

Each mechanism demands specific surgical techniques for optimal correction, and the feasibility of repair varies by the mechanism of regurgitation as defined by the preoperative echocardiogram (Table 57.3) (53) and by the etiology (54). In valves that are extensively calcified, fibrotic, or destroyed by endocarditis, repair is impossible. No matter what the mechanism of MR, almost all patients undergo annuloplasty as a component of the repair, in addition to the other surgical maneuvers, detailed in the following sections.

	No.	Feasibility of repair (%)	Initial failure of repair (second pump runs)
Excessive	222	82.9	4.4
Posterior	109	89.0	1.8
Anterior	49	61.2	8.2
Posterior and anterior	64	82.8	0
Restricted	140	35.7	10.0
Normal	65	84.6	0
Total	427	67.7	4.5

From Sun JP, Yang XS, Wayer DL, et al. Mitral valvular leaflet excursion by echo is a marker for the feasibility of repair and risk of failed repair. Circulation 1999;[illegible]

TABLE 57.3 PREDICTION OF THE FEASIBILITY OF REPAIR BASED ON THE PREOPERATIVE ECHOCARDIOGRAM

For *excessive* leaflet motion, the jet is deflected *away* from the most abnormal leaflet. The easiest type to repair is a flail or prolapsing posterior leaflet (Fig. 57.2), which most commonly involves the middle scallop and can be repaired in 89% of cases (55). The excessive leaflet motion is readily detected by two-dimensional echocardiography and the jet is deflected anteriorly, as assessed by color Doppler in the operating room before cardiopulmonary bypass. This problem is corrected by quadrilateral resection of the unsupported leaflet followed by suture closure of the gap (54).

Video 57.1 Color Doppler of 0-degree intraoperative transesophageal echo with prolapse and flail of the posterior mitral leaflet causing very eccentric, anteriorly directed mitral regurgitation. This valve was successfully repaired. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 57.2 Intraoperative 120-degree transesophageal echo of a flail posterior mitral leaflet prior to repair (two-dimensional). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

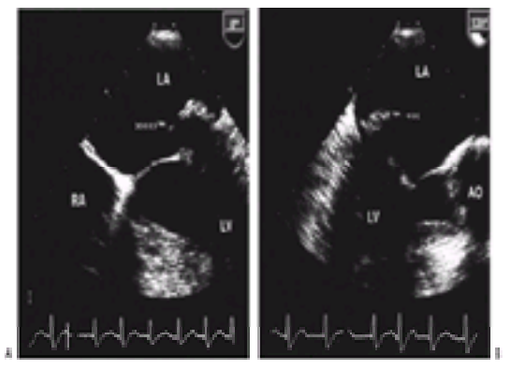


FIGURE 57.2 Posterior leaflet flail causing severe mitral regurgitation. **A:** Transverse midesophageal view (0 degrees) showing the flail posterior leaflet (*arrowheads*). **B:** Midesophageal long-axis (138 degrees) view showing the posterior leaflet flail (*arrowheads*). AO, aorta; LA, left atrium; LV, left ventricle; RA, right atrium.

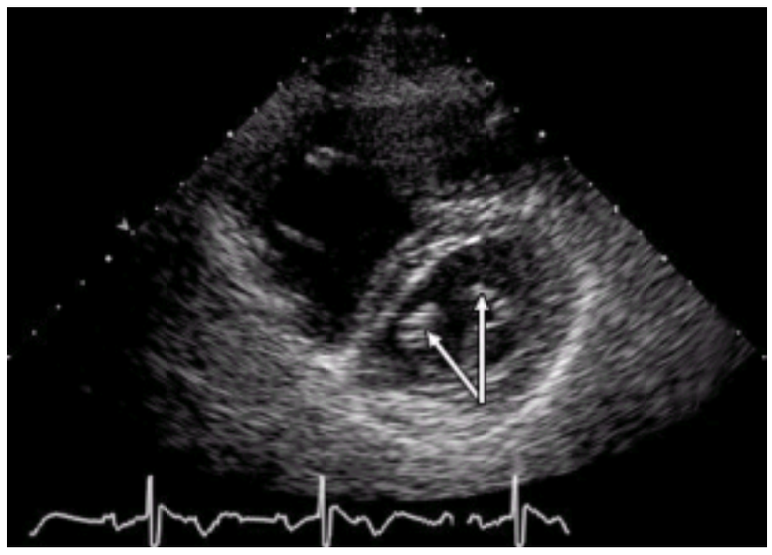
By comparison, other types of MR are more difficult to repair. For example, it is feasible in 61% of cases to repair MR due to prolapse or flail of the anterior leaflet (Table 57.3). This is diagnosed by its characteristic posterior jet direction (19). Repair requires a surgical maneuver to provide chordae to the unsupported anterior leaflet, which can be done with chordal transfer, or less commonly with chordal shortening (54) or replacement with artificial chordae (56). Repair of MR due to prolapse of both leaflets can usually be corrected by surgery only on the posterior leaflet, involving a quadrilateral resection, without anterior leaflet maneuvers (56a). However, when there is extensive destruction and flail of both leaflets, repair is feasible in only 41% of cases (55).

For MR due to *restricted* leaflet motion, the jet is directed *toward* the most abnormal leaflet. Most commonly the jet direction is posterior, with a fixed posterior leaflet, or central, from balanced bileaflet restriction. This occurs mostly from rheumatic mitral valve disease, and only 36% of cases can be repaired. In these patients, repair is more likely when there is a lower echocardiogram score, or “splitability index,” an echocardiographic measure defined by four assessments, each on a scale of 1 to 4, of leaflet mobility, leaflet thickness, calcification, and subvalvular involvement, for a total score of up to 16 (57,58). Repair is more feasible in younger patients, but carries a greater risk of progressive disease and reoperation (59,60), likely due to more active fibrosis or recurrent valvulitis.

Patients with significant mitral stenosis with a low splitability index (not associated with calcification or extensive fibrosis) are usually candidates for percutaneous balloon valvotomy. In more recent years, the ones who come to surgery are those who are not suitable for balloon valvotomy, because they have a splitability index that is high (greater than 9) or concomitant MR. Therefore, most of the surgical repairs currently involve more extensive débridement, decalcification, and commissurotomy, as well as annuloplasty (60). When the echocardiography score (splitability index) is high, however, there is less likelihood of successful repair and more likely early failure of the repair (60a).

Patients with *normal* leaflets have a *central* (or sometimes posterior) jet direction. This type of MR is usually due to LV enlargement and dysfunction, which cause “relative restriction of normal leaflets” due to outward displacement of the papillary muscles, and therefore apical displacement of the coaptation line (61). This “apical tethering” results most commonly from ischemic MR (62). It is a misunderstood entity and really does not result from annular dilation, but rather from change in the shape of the LV (sphericalization), which makes the leaflet-chordal-papillary muscle length relatively short compared with the increased distance outward to the LV walls. The mitral annulus in these patients also appears to have reduced cyclic variation in annular shape and area (62a). Paradoxically, repair is currently accomplished with an annuloplasty alone. This is feasible in 85% of patients (Table 57.3) but is associated with a significant rate of return of MR over months to years, mainly due to progression of LV dysfunction, often due to repeat infarction or volume overload.

Occasionally, patients with MR due to normal leaflets have a leaflet perforation or congenital cleft (62b). This can generally be sewn primarily or patched with a piece of pericardium, as long as there are no additional problems, such as disrupted leaflets or chordae from endocarditis. Of note, in patients with congenital cleft mitral valves, it is difficult to obtain a long-lasting repair, particularly in patients with Rastelli’s type A or a divided inferior mitral leaflet.



Parasternal short-axis view (transesophageal echo) of a cleft mitral valve. Notice the cleft in the center of the anterior mitral leaflet with its characteristic opening. (This patient also had a primum atrial septal defect, a commonly associated lesion). The double arrow demonstrates the two halves of the split anterior mitral leaflet.

VIDEO

Video 57.3 Parasternal short-axis view of a cleft mitral valve. Note the characteristic opening (split appearance) of the cleft anterior mitral leaflet. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Postpump Imaging and Second Pump Runs

After valve repair for MR, the vast majority of patients have a successful result, as defined previously and evidenced by the postpump IOE (Fig. 57.3). In the series from our institution, 6.6% of patients had problems discovered on the postpump TEE that warranted further surgery during the same thoracotomy (19a).

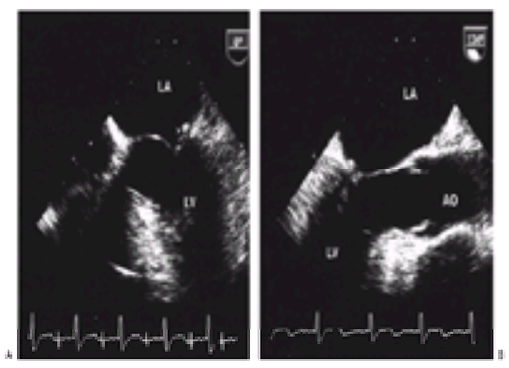
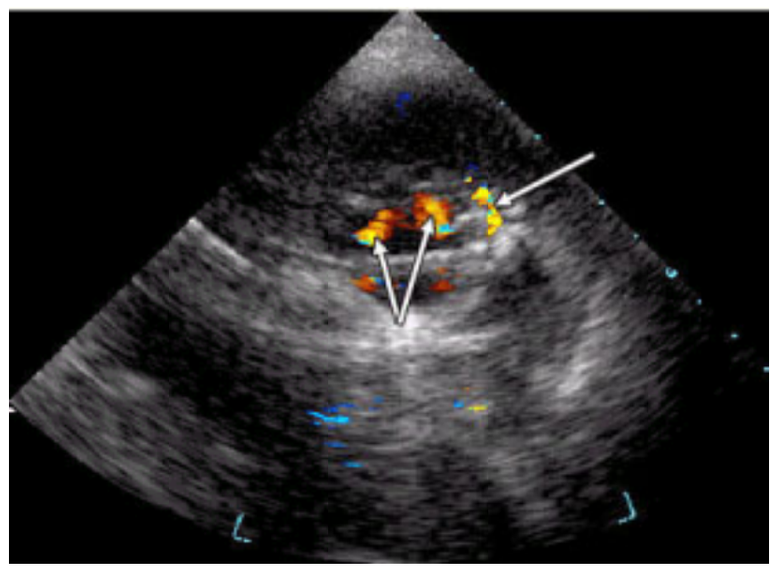


FIGURE 57.3 Postpump images after successful repair of mitral regurgitation from the same patient shown in Figure 57.2. **A:** Transverse (0 degrees) midesophageal four-chamber view showing no prolapse or flail. The annuloplasty is shown (*arrowhead*). **B:** Long-axis midesophageal view (134 degrees) showing no residual prolapse or flail. AO, aorta; LA, left atrium; LV, left ventricle.



Transgastric short-axis view during intraoperative transesophageal echo of a paravalvular leak of a CarboMedics mitral valve replacement. Note the two normal physiologic prosthetic jets of mitral regurgitation (within the sewing ring) as designated by the double arrow and the one abnormal, laterally originating jet outside the sewing ring (to the right of the screen) designated by the single arrow. There was significant mitral annular calcification (MAC), making it difficult to achieve close contact between the annulus and the sewing ring.

Video 57.4 Postpump echo (with color Doppler) after repair of the flail posterior mitral leaflet. There is a Cosgrove-Edwards annuloplasty ring in place. There is no residual mitral regurgitation and there is no systolic anterior motion of the mitral leaflets, which can sometimes complicate mitral valve repair. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 57.5 Two-dimensional intraoperative 120-degree view imaging of a mitral valve after repair. Notice the annuloplasty ring in place without any residual prolapse or flail and no systolic anterior motion of the mitral leaflet (a complication that can be seen after surgical repair). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Others have reported frequencies ranging from 2% to 8% (34,63,64,64a,65). Primarily, the second pump run has been done for persistent MR. After repair for MR, the incidence of mitral stenosis as the problem found by postpump imaging mandating a second pump run is small, 0.7% in one series (64a), occurring mostly in rheumatic MR patients and those repaired using commissural plication or other suture plication such as the edge-to-edge technique. In the majority of patients, the surgery done in the second pump run is repair, particularly if the TEE after the initial attempt is able to find a fixable mechanism that explains the residual dysfunction. In these cases, there is significant pressure on the echocardiographer to define precisely what is wrong to facilitate further repair. Use of the same leaflet motion and jet direction techniques described previously is again helpful. The most common etiologies of persistent regurgitation are residual prolapse, residual flail, or a perforation at the site of leaflet resection or sliding plasty.

In patients who undergo nonprosthetic surgery for pure mitral stenosis (i.e., open mitral commissurotomy), the frequency of immediate problems leading to further surgery during the same thoracotomy is approximately 9%, mostly entailing replacement in patients with more extensive valvular scarring and calcification (60a).

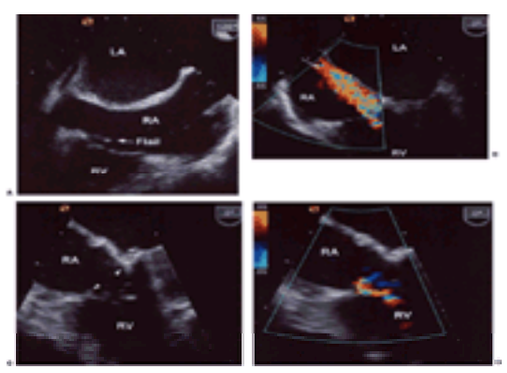
In 1% to 2% of cases after mitral valve repair, dynamic outflow tract obstruction occurs, with systolic anterior motion (SAM) of the mitral valve (31,64). SAM occurs most commonly in patients with redundant myxomatous mitral valves and LVs that are normal or small in size and normal or hyperdynamic in function. It is more common when the annuloplasty is performed with a stiff ring (66). Outflow tract obstruction is associated with anterior displacement of the mitral coaptation line, which results mainly from a large, redundant posterior leaflet (67). In many circumstances, SAM resolves in response to increasing intravascular volume and stopping catecholamine medications (68,69). If it persists, SAM can often be corrected using the sliding posterior leaflet advancement technique (70,71). This can be done as a preventive measure during the initial repair or during a second pump run in response to finding SAM on the postpump TEE. Rarely, mitral valve replacement or septal myectomy is required (31,72).

The mechanism of MR also affects the durability after repair for valvular regurgitation caused by degenerative disease. Durability is greatest after quadrangular resection and annuloplasty for posterior leaflet prolapse (45a).

TRICUSPID VALVE REPAIR

IOE is also useful in performing tricuspid valve repair. TR causing the need for tricuspid surgery arises most commonly due to left-sided congestive heart failure of any cause. Both intravascular volume overload and pulmonary hypertension can cause enlargement of the right ventricle, causing TR. In chronic conditions, the tricuspid annulus also dilates. Of patients having surgery for mitral or aortic valvular heart disease, tricuspid surgery is needed in approximately 25% (73). Over 93% of tricuspid surgery entails repair (74), in contrast to much lower percentages in other valves.

The tricuspid valve is assessed by TEE using a midesophageal four-chamber view at a 0-degree multiplane angle, a midesophageal 45-degree view at the level of the short axis of the aortic valve, a midesophageal 135-degree view at the level of the right atrium and tricuspid valve (eFig. 57.3.1), and a transgastric view at 90 degrees showing the long axis of the right ventricle and right atrium. Additional value is obtained from deep transgastric views of the hepatic vein and inferior vena cava to detect systolic flow reversal using pulsed Doppler as an indicator of severe TR.



***e*FIGURE 57.3.1** Transesophageal echocardiogram images before and after tricuspid repair for flail leaflet. **A:** Midesophageal two-dimensional image at 126 degrees showing a long-axis view of the right atrium (RA), including the flail tricuspid leaflet (*arrow*). **B:** Midesophageal transverse color flow image at 0 degrees showing moderately severe 3+ tricuspid regurgitation (*arrow*) in the RA before repair. **C:** Postrepair two-dimensional image at 0 degrees showing the tricuspid annuloplasty band (*arrowheads*) and no tricuspid prolapse or flail. **D:** Midesophageal transverse color flow image at 0 degrees showing mild 1+ tricuspid regurgitation (*arrow*) after repair. LA, left atrium; RV, right ventricle.

In doing the prepump IOE for tricuspid valve surgery, semiquantitative assessment of the amount of TR correlates with preoperative assessments (75,76). However, compared with other valves, the severity of TR is even more volatile and extremely dependent on loading conditions. Evaluating leaflet morphology such as prolapse or rheumatic leaflet restriction is important as the former may enhance and the latter may reduce the likelihood of successful repair. In addition, measurement of the maximum tricuspid annulus diameter may identify patients who need repair because the TR is less likely to resolve merely by fixing the left-sided valvular abnormalities (76).

VIDEO

Video 57.6 Postoperative four-chamber transesophageal echo after tricuspid valve repair with placement of an annuloplasty ring. Note that although there is still prolapse of tricuspid valve tissue, there is only minimal residual tricuspid regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Postpump Assessment after Tricuspid Repair

TEE of TR after repair (77,78 and 79) uses similar techniques as the prepump study. In some cases, TR is found to be new or increased compared with that on prepump studies; this requires a second pump run for repair (80). At our institution, second pump runs were required in 5.3% of tricuspid repairs, based on the results of the postpump IOE (19a).

Again, the patient should be stabilized off cardiopulmonary bypass and ambulatory conditions established before assessments. In borderline cases of moderate or more regurgitation, tricuspid competency should be retested during provocation, using additional intravascular volume and increased right ventricular afterload by transient partial occlusion of the pulmonary artery.

In a study of 401 patients undergoing tricuspid valve surgery, mostly with other concomitant cardiac surgery, the surgical plan was altered at the time of surgery to ensure a successful outcome in 32 (10%) of 335 patients based on IOE findings (80a). Despite a successful result of tricuspid repair on the postpump study, some patients still develop TR in follow-up (79). This may reflect new myocardial dysfunction or the severity of the underlying cardiac pathology causing right ventricular volume overload, rather than the effectiveness of the tricuspid repair (81).

Several groups reported performing DeVega annuloplasty with the ends of the sutures brought out to the external surface of the heart. If the TEE showed persistent TR after the patient came off cardiopulmonary bypass, these sutures were tightened by the surgeon to eliminate the TR (82,83). Externally adjustable rings have also been used for mitral and tricuspid valve annuloplasty, allowing adjustment of tension after the initial postpump TEE (84).

AORTIC VALVE REPAIR

Compared with the past, when only bioprosthetic and mechanical prosthetic valve replacement was available, surgery for aortic valve disease has newly expanded options including aortic valve repair, homograft implantation, stentless bioprostheses, and Ross procedure. There are advantages and disadvantages of each option, but none of these is an ideal substitute for a normal native valve. Which surgery is best to use in each individual patient depends on the nature, etiology, and severity of the aortic valve dysfunction, and the clinical characteristics, age, and personal preferences of the patient. The prepump IOE has been found to change the operative plans in 15% of cases undergoing aortic valve surgery (38).

Aortic valve repair is applicable only to a small, highly selected subset of patients undergoing aortic valve surgery (85,86 and 87), particularly those with pure AR who are free of appreciable fibrosis or valvular thickening. Like mitral repair, this surgery demands the most from the echocardiographer and the surgeon, because of the necessity to understand the mechanism of the dysfunction. The prepump IOE is extremely useful in this group (88,89) to determine the mechanism and severity of regurgitation and the size of the aortic annulus and ascending aorta.

Determination of the Severity and Mechanism of Aortic Regurgitation

The severity of AR is judged intraoperatively from a weighted average of information from LV outflow tract spatial mapping (90), the flow convergence on the superior side of the regurgitant orifice, and the downstream events of descending aortic diastolic flow reversal (91) (see also Chapter 22). The proximal jet width in long-axis views and the jet area in short-axis views provide important and reliable criteria for severity (91a). Similar to MR, it is useful to separate the leaflet motion in AR into groups with normal, excessive, and restricted leaflet motion. Most patients with aortic valve disease have restricted leaflet motion resulting from degenerative and rheumatic etiologies. However, the vast majority of patients with AR has restricted leaflet motion, because of the predominance of degenerative, rheumatic, and fibrocalcific etiologies of aortic valve disease. These processes cause retraction of the leaflet size, leaving a central leak; 70% of patients have a central jet origin and direction (94). This type of aortic valve disease is not generally amenable to durable repair.

VIDEO

Video 57.7 Intraoperative transesophageal echo (120-degree view) with color Doppler demonstrating aortic insufficiency due to aortic dilatation (sinuses measure 5.0 cm) causing failure of leaflet coaptation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The primary group of patients in whom repair is feasible have noncalcified, nonstenotic valves with pure regurgitation resulting from aortic valve prolapse. Prolapse occurs most commonly in the settings of a congenital bicuspid aortic valve (Fig. 57.4) or a trileaflet valve with prolapse of one coronary cusp, usually the right. Prolapse of a trileaflet valve may result from leaflet fenestration or a congenital membranous ventricular septal defect (VSD) (92,93). In any of these categories, the regurgitation results from excessive length of the edge of the prolapsing leaflet, causing it to have a lower diastolic position. In 70% of patients with excessive leaflet motion, the jet is deflected to the opposite side of the LV outflow tract by the prolapsing leaflet (94). AR resulting from prolapse is surgically corrected using triangular resection of a small portion of the prolapsing leaflet, to adjust the length of the leaflet edge, causing its diastolic position to be at the same level as the opposing ones, thus promoting coaptation. In addition, pledgeted sutures at the commissures, a “commissuroplasty,” bring the points of suspension of leaflets inward to improve coaptation (85,95).

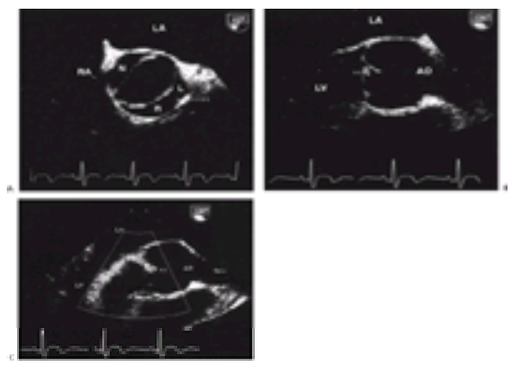


FIGURE 57.4 Aortic regurgitation amenable to valve repair. **A:** A short-axis, 62-degree, midesophageal view of the same patient, showing fusion of what would be the right (R) and left (L) cusps into a larger anterior cusp, compared with the posterior cusp, which would otherwise be the noncoronary (N) cusp. Arrowheads show the anterior raphe. **B:** Long-axis, 136-degree, midesophageal view of the aortic valve showing the aortic valve prolapse (*arrowheads*). **C:** Black and white copy of a color image in a long-axis view of the outflow tract, showing the posteriorly directed jet of aortic regurgitation emanating from the coaptation line (*arrowheads*) at the site of prolapse (*arrows*). AO, aorta; AR, aortic regurgitation; LA, left atrium; LV, left ventricle; RA, right atrium.

Repair can also be successful in certain patients with regurgitation from normal aortic leaflets. This type of AR has a central jet direction emanating from central failure of coaptation of a trileaflet valve. The regurgitation usually results from ascending aortic dilatation, because of outward displacement of the sinotubular ridge, causing “relative restriction of normal leaflets” similar to MR from LV dilatation, as detailed earlier in this chapter. AR from aortic dilatation is also repaired with a commissuroplasty. In certain cases, a structurally normal native aortic valve can be resuspended during surgery for conduit placement in patients with ascending aortic dilatation or aneurysm (96 and 97a).

In patients with restricted leaflets, for whom other options are available, repair is not the first choice of operation. When the clinical situation favors repair, such as in underdeveloped countries (98) for whom the cost of a prosthesis is unacceptable or anticoagulation is impossible, repair of this type of AR can be accomplished (99,100). Although the initial results are adequate, regurgitation redevelops quickly (101).

Another role for the prepump IOE in aortic valve disease is to look at the anatomy of the ascending aorta, especially the relative diameters in the long-axis view of the aortic annulus (at the hinge points of the aortic valve), and the sinotubular junction. Normally, these two measurements are approximately equal and roughly 19 to 23 mm. In bicuspid valves and other congenital aortic valve disease, the annular diameter is usually enlarged (approximately 26 to 32 mm). In patients who have central regurgitation with normal aortic leaflets, the diameter of the sinotubular junction is often larger than the annular diameter.

Postpump Intraoperative Echocardiography in Aortic Valve Repair

After aortic repair, the amount of regurgitation, the valve anatomy, and the mechanism of residual dysfunction are again checked (86,88,102). Because aortic valve repair is more difficult to accomplish than mitral repair, the frequency of initial failure of repair is higher, occurring in 14.4% of aortic valve repairs (19a).

In successful repair, the aortic valve is still morphologically abnormal. Valvular densities from the sutures at the triangular resection site and at the commissures are often visible in the short-axis view. After successful repair of a prolapsing valve, the amount of valvular prolapse is less, and the two leaflets coapt at the same level with a diastolic shape that reflects good apposition. Systolic doming in long axis also persists in patients with bicuspid valves, which still have two leaflets in short axis, because the conjoined leaflet is not split by the repair.

As in other cases mentioned previously, an acceptable result after repair is to have no regurgitation or mild regurgitation. Note that the incidence of persistent AR, making up the initial failure of repair, is higher than that after mitral repair, also reflecting the increased difficulty of aortic repair. When there is significant regurgitation, it is quite important to determine the mechanism of persistent leak, to facilitate repair on the second pump run. Because of the difficulty of aortic repair, the majority of second pump runs involves valve replacement (88,89).

In follow-up studies of 150 patients after aortic valve repair at our institution, the subgroup of 19 patients with a less than “echo perfect” result (more than 1+ regurgitation) on the postpump study, compared with those with no postpump AR, carried a greater risk of recurrent AR (61% vs. 17%, p <.05) in follow-up over 27 ± 16 months (103). Among another group of patients having repair for regurgitation of a bicuspid valve, 89.5% were free from reoperation at 24 months (95).

AORTIC HOMOGRAFTS, STENTLESS BIOPROSTHETIC VALVES, AND ROSS PROCEDURE

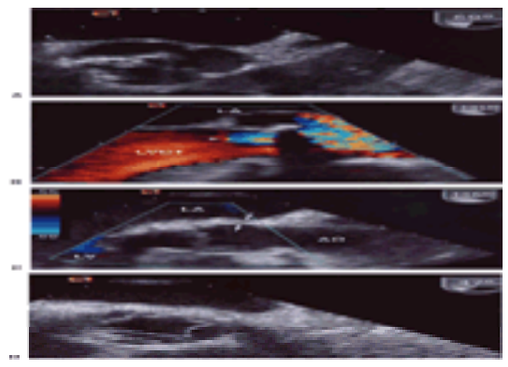
A case can be made for routine TEE (104) in the course of a standard aortic or mitral valve replacement, as it is unquestionably more sensitive for detection of prosthetic dysfunction than transthoracic echocardiography (105,106). However, because of limited resources and the low incidence of changes in operative management based on echocardiography, IOE is not performed routinely when a standard prosthesis is planned. IOE is useful in aortic valve replacements with a homograft (human valve) or pulmonary autograft (the patient’s own pulmonic valve) (107).

The homograft and autograft are particularly useful for younger patients and those with active endocarditis (108). The cryopreserved homograft is an excellent form of aortic valve replacement, which has a low transvalvular gradient and a remarkably good durability, with 10-year freedom from reoperation for graft-related causes of 92% (108a). Ross procedure entails replacing the aortic valve with a pulmonary autograft, and replacing the pulmonic valve with a pulmonary homograft (81). The autograft may have advantages in the young due to the ability of the living tissue to grow with the patient. It has been used successfully in patients with aortic valve endocarditis (108b). Both procedures are more technically difficult, because they entail working with malleable biologic tissue. There is no stiff sewing ring or Dacron annulus as there is in a conventional heterograft or mechanical prosthesis. Because the coronary arteries must be reimplanted, there is also some additional potential for ischemic difficulties.

With implantation of the new nonstented heterografts (108c,109), intraoperative echocardiography appears to be quite useful. It reveals contraindications to implantation of the nonstented valve and allows measurement of the aortic annulus and sinotubular junction diameters for correct prediction of prosthesis size (109a). Some small periprosthetic jets seen by postpump IOE appear to improve or resolve spontaneously and may not require intervention with a second pump run (109b).

Prepump Intraoperative Echocardiography in Homograft and Ross Procedures

In addition to determining the severity of valvular dysfunction, ventricular function, and the status of other valves, the prepump study is useful for determination of the diameters of the aortic and pulmonic valve annulae and the sinotubular junction. The supply of aortic homografts is limited, and most range from 19 to 22 mm in size. The measurement that corresponds to homograft size is the maximum obtainable aortic annulus diameter, measured at the level of the hinge points of the aortic valve, in a true long-axis view, usually the mid-esophageal view at approximately 130-degrees (*e*Fig. 57.4.1). Making this measurement with echocardiography before cardiopulmonary bypass can save approximately 20 minutes of ischemic time that is otherwise wasted if the homograft is not thawed until the valve is measured by the surgeon after the aortotomy (110,110a). In 51 patients undergoing prepump IOE studies before homograft implantation, the aortic annular size, obtained in a true long-axis view, differed from the annular size measured by the surgeon by an average of 0.6 mm, being less than 2 mm in all and less than 1 mm in 94% of patients (112). The diameter of the sinotubular junction is also measured by the prepump IOE, because normal valve relationships depend on normal proportions between valve size and the supravalvular ridge (111).



***e*FIGURE 57.4.1** Transesophageal echocardiogram of a patient with aortic stenosis undergoing aortic homograft valve replacement. **A:** Prepump midesophageal short-axis view of the aortic valve at 68 degrees showing the calcified aortic valve with thickened edges of all three leaflets. **B:** Magnified midesophageal long-axis view at 131 degrees of the aortic valve in systole showing the flow convergence (*arrowhead*) on the left ventricular outflow tract (LVOT) side and the turbulent flow pattern on the aortic side due to aortic stenosis. **C:** Midesophageal long-axis view at 146 degrees of the newly implanted homograft aortic valve. Note the thickness (*arrows*) of the sinuses of Valsalva, which includes both donor and recipient aortic tissue. **D:** After aortic valve replacement midesophageal short-axis view at 47 degrees showing normal opening of the newly implanted homograft. AO, aorta; LA, left atrium; LV, left ventricle.

Another consideration for the prepump study is to discern the likely etiology of valve dysfunction from the valve morphology. When the aortic valve dysfunction results from rheumatic heart disease, progressive valvulitis may develop in the autograft or homograft, causing early postoperative aortic valve dysfunction (113).

When Ross procedure is planned, the integrity of the pulmonic valve is checked on the prepump echocardiogram. Significant pulmonic valve dysfunction or distortion of morphology (e.g., a bicuspid valve) on the prepump study, a rare occurrence, should cancel plans for Ross procedure.

It is also important to compare the annular diameter of the pulmonic and aortic valves. In a series of 58 patients undergoing Ross procedure, the echocardiographic measurements of annular size had an impact on outcome, with less postpump and early postoperative regurgitation of the autograft when the difference between the aortic and the pulmonic annular diameters measured on the prepump imaging was less than 3 mm (45).

Postpump Echocardiography after Homograft Valve Replacement or Ross Procedure

IOE is also useful for checking the result after these two procedures (114). Because the level of surgical difficulty is higher than, for example, mitral valve repairs, the frequency of initial failure of surgery is also higher. Second pump runs were required in 10 (11.6%) of 86 homograft patients in our experience (112), although it was only 3% of patients in another report (115). Similarly, second pump runs have been needed after 7 (12.1%) of 58 Ross procedures.

VIDEO

Video 57.8 A 120-degree postpump intraoperative transesophageal echo after placement of an aortic valve replacement conduit. The St. Jude aortic valve replacement is toward the left of the screen, and the aortic graft can be seen in the center of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

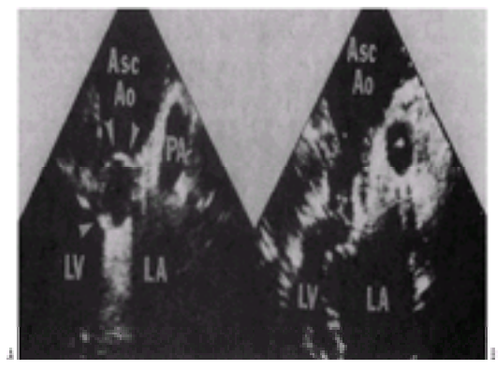
VIDEO

Video 57.9 Postpump intraoperative echo after placement of an aortic valve homograft. Notice that the leaflets look like a native valve. The only clue that it is a homograft is the thickening at the annulus and the proximal ascending aorta due to the double thickness of the graft cuff with the native aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The primary problems found on the postpump TEE are persistence of regurgitation of the new aortic valve, myocardial ischemia from the reimplanted coronaries, or (rarely) regurgitation of the pulmonic homograft (45). In one study, there was a 10% incidence of ischemia found by the postpump TEE after Ross procedure; this ischemia was more frequent in patients with bicuspid aortic valve and coronary anomalies and resolved completely in most patients with revision of the coronary implantation (115a).

Attention to the mechanism of persistent leak on the postpump study can facilitate its correction. Most homografts are now done as a miniroot procedure, which is easier and more reliable than a freehand subcoronary implantation. Even so, postpump TEE has found in some patients that the valve was not suspended appropriately. If the image shows that the valve prolapses and one side of the wall of the sinuses of Valsalva is more lax, this indicates the need to suspend the commissure higher on that side by removing tissue from the aortic wall above the sinotubular junction on that side.

Where the valve is implanted as an inclusion cylinder, bleeding and hematoma can develop in the potential space between the donor and recipient walls of the sinuses of Valsalva, causing distortion of the root or even outflow obstruction (*e*Fig. 57.4.2). In patients with a dilated ascending aorta having an inclusion cylinder implanted, it is normal to see some echo-free space that is not completely eliminated despite optimal surgery; this resolves in weeks to months. However, after implantation, there should be no high-velocity flow within the space as assessed by color flow mapping. Localizing the high-velocity flow by color flow mapping marks the point of dehiscence of the upper or lower suture line, which can be repaired with a second pump run.



***e*FIGURE 57.4.2** Epicardial images after implantation of an aortic homograft. **A:** A hematoma (*arrowheads*) between the inclusion cylinder and the native ascending aorta (Asc Ao) caused a 47 mm Hg gradient. **B:** After evacuation of the hematoma, the images show resolution of the obstruction. LA, left atrium; LV, left ventricle; PA, pulmonary artery. (From Currie PJ, Stewart WJ. Intraoperative echocardiography for surgical repair of the aortic valve and left ventricular outflow tract. *Echocardiography* 1990;7:273–288, with permission.)

Follow-up studies on patients undergoing Ross procedure showed a greater incidence of significant recurrent AR, in five (50%) of ten patients whose postpump IOE

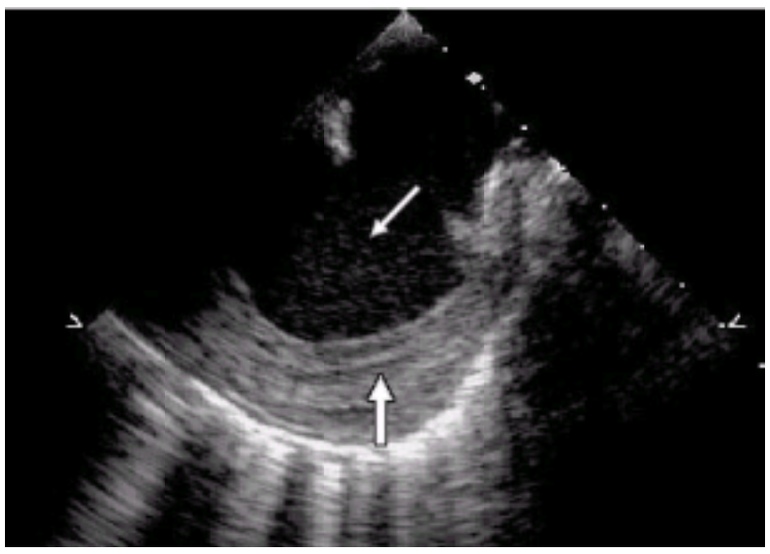
showed 1+ or more AR, compared with 1 (2%) of 43 patients whose postpump IOE showed an “echo perfect” surgical result (45). Although stenosis of the pulmonary homograft does not occur at the time of the immediate postpump image, it has developed in some patients at the time of midterm follow-up, with progressive right ventricular dysfunction. In homograft and Ross procedure patients, long-term studies will be required to compare the outcome with that of standard aortic valve replacement using mechanical and bioprosthetic valves.

AORTIC ANEURYSM SURGERY

With its rapidity and portability, TEE is extremely useful in the preoperative management of patients with aortic aneurysms and aortic dissection (116). By the time the patient comes to the operating room, in some cases a significant time interval has elapsed since the preoperative studies. Because the potential exists for interval progression or development of more complications, repeat evaluation in the operating room before surgery is often useful. TEE is also useful in transluminal endovascular stenting to repair thoracic aortic aneurysms, for navigating the graft placement and tailoring without intimal damage, and especially to assess perigraft leakage (116a) and graft kinking immediately after deployment (116b).

Prepump Intraoperative Echocardiography in Aortic Aneurysms

In patients with thoracic aorta aneurysms, IOE is helpful in defining the pathology to assist with operative planning. Prepump IOE results change the operative mission in 18% to 33% of cases (36a,117). The preoperative and prepump objectives for TEE diagnosis in this disease (118) include (a) diagnosing the presence and location of the aneurysm (the DeBakey or Stanford type), (b) identifying the presence and location of the dissection, (c) determining the morphology and functional status of the aortic valve, (d) identifying pericardial fluid or hemopericardium, (e) assessing ventricular function and myocardial infarction, (f) identifying entry and exit sites of the dissection through the intimal flap (119), and (g) detecting involvement of branch vessels in the dissection, particularly coronary arteries and great vessels. Of these, TEE is accurate for all but the last. After femoral cannulation and institution of cardiopulmonary bypass, TEE can verify retrograde flow in the true lumen (120).



Transesophageal view of the aortic arch demonstrating an arch aneurysm (*thin arrow*) with layering of thrombus inferiorly (*thick arrow*).

VIDEO

Video 57.10 Long-axis view of a descending aortic aneurysm. There is severe spontaneous echo contrast seen within the aorta with layering of thrombus at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 57.11 Intraoperative transesophageal echo with color Doppler of an ascending aortic dissection. Note the mobile flap with the color flow separation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

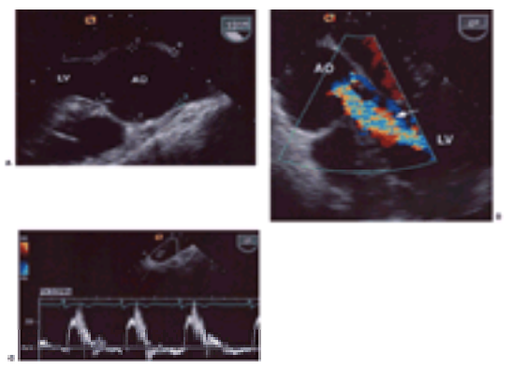
VIDEO

Video 57.12 Short-axis transesophageal echo view of a type I aortic dissection. Note the flap originating within the noncoronary cusp (leaflet upper left screen) and extending towards the ostium of the left main trunk. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 57.13 Intraoperative 120-degree transesophageal echo of an ascending aortic dissection. Note the large, complex flap in the ascending aorta seen originating near the origin of the right coronary artery. There is a small amount of aortic insufficiency. Flow is seen in the true lumen (*left*) whereas no flow is seen in the false lumen (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In certain patients, the aortic valve can be preserved during ascending aortic conduit placement, using either a supracoronary graft or the David procedure with resuspension of the native aortic valve within the ascending aortic conduit (96,97) (eFig. 57.4.3). Knowing the aortic valve anatomy and physiology can help plan for the optimal surgical options. For example, the amount of dissection of the valve annulus correlates with the amount of leaflet prolapse (97a). AR in ascending aneurysms can occur due to upward leaflet tethering by the dilated aortic root, leaflet prolapse due to disrupted leaflet attachments, or prolapse of the dissection flap through the valve orifice (120a).

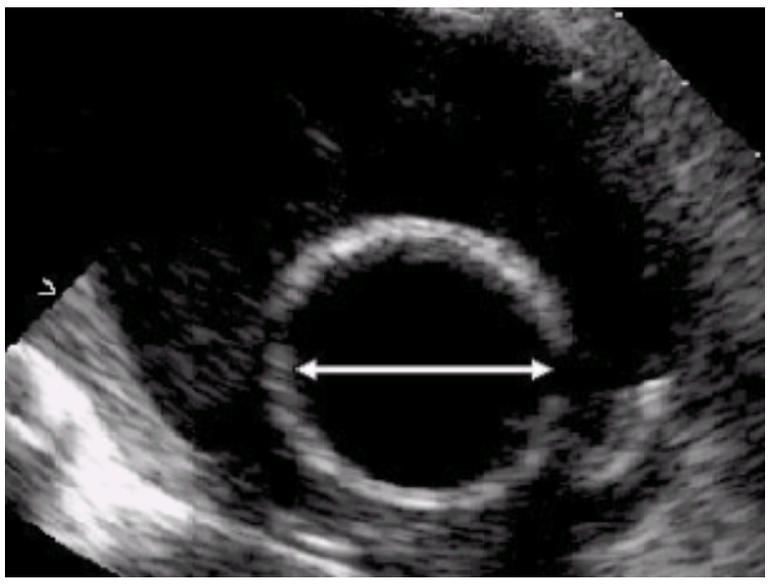


***e*FIGURE 57.4.3** Prepump transesophageal echocardiographic images showing functional aortic regurgitation of normal leaflets due to ascending aortic dilation, amenable to aortic valve resuspension. **A:** Midesophageal long-axis view of the aortic valve showing the methods of measuring the diameters of the (1) aortic annulus at 2.2 cm, (2) sinuses of Valsalva at 4.1 cm, and (3) sinotubular junction at 2.8 cm. **B:** Midesophageal transverse view showing severe aortic regurgitation (*arrow*) with a central jet. **C:** Pulsed Doppler recording of the proximal aortic arch, showing (*top*) the position of the sample volume, and (*bottom*) antegrade flow in systole (above the horizontal line) and retrograde flow (below the horizontal line) in diastole from the severe aortic regurgitation. AO, aorta; LV, left ventricle.

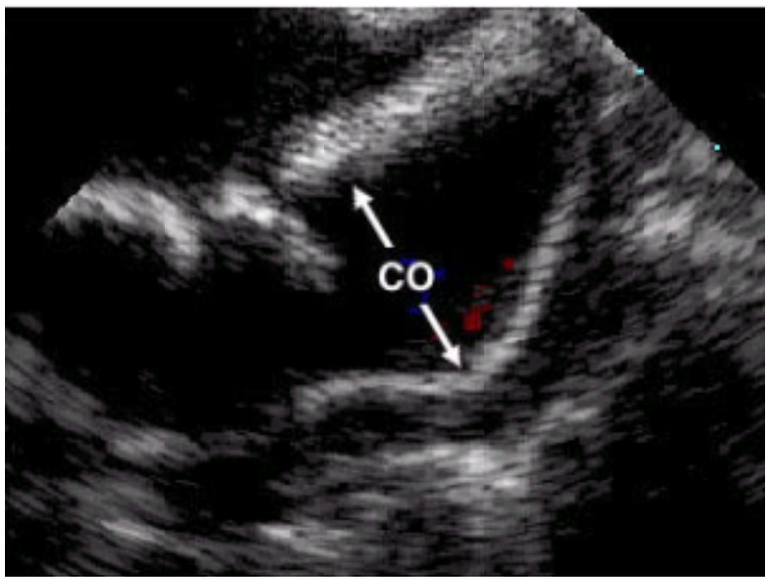
In addition, aortic aneurysms can be complicated, with involvement of branch vessels such as the coronaries, the great vessels, the spinal arteries, and the abdominal organs. When extensive resection is planned, such as for a thoracoabdominal aneurysm, TEE is particularly helpful. In some cases, the surgery is staged in two portions, doing the ascending aorta and arch first, and leaving the free end of the conduit hanging in the descending aorta like an “elephant trunk.” At a later date, a lateral thoracotomy is done to implant a descending aortic conduit that is hooked up to the previously implanted conduit (121,122).

Postpump Intraoperative Echocardiography

After aneurysm surgery, IOE is used to evaluate the anastomoses of the conduit, aortic valve, LV (for ischemia or infarction), and major aortic branches (to confirm that sufficient flow is present, particularly if they are fed by the false lumen) (10). When the aortic valve has been resuspended in the setting of aortic aneurysm surgery, the likelihood of persistent regurgitation increases, which may require a second pump run for valve replacement. Another important new finding is a new segmental wall motion abnormality, which might imply difficulty with coronary reimplantation. The frequency of second pump runs is 3.8% after aortic aneurysm surgery (19a).



This short-axis view of the descending aorta is seen by intraoperative transesophageal echo showing the distal end of the aortic graft following the first stage of an elephant trunk procedure. Note the circular appearance of the graft within the aneurysmal descending aorta. The arrow demonstrates the diameter of the descending aortic graft.



Intraoperative echo demonstrating the distal end of the aortic graft after the first stage of an elephant trunk procedure seen in long axis. Note the tubular free end of the graft within the aneurysmal descending aorta. CO designates the diameter of the conduit.

VIDEO

Video 57.14 Long-axis view of the descending aorta from an intraoperative transesophageal echo after an elephant trunk procedure. Note the cylindrical structure within the dilated descending aorta; this represents the free end (distal) of the vascular graft with color flow within it. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

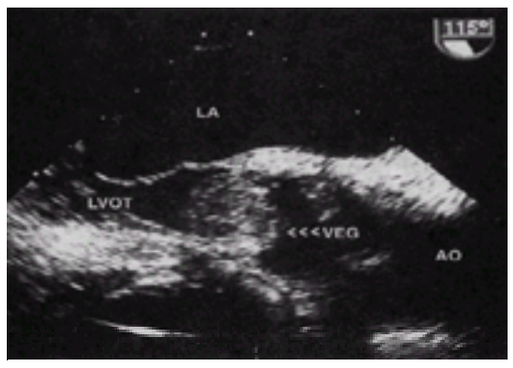
Video 57.15 Short-axis view of the descending aorta from an intraoperative transesophageal echo after an elephant trunk procedure. Note the circular structure with in the larger, more dilated aorta. This represents the distal end of the vascular graft in short axis hanging free within the descending aortic aneurysm. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The descending aorta and arch should be examined after surgery for flow in the false lumen and true lumen, as well as intramural hematomas. It appears that the presence of flow in the false lumen and the absence of thrombus are variables that carry an adverse prognosis, greater risk of extension of the dissection to additional parts of the aorta, and a reason for closer follow-up (116).

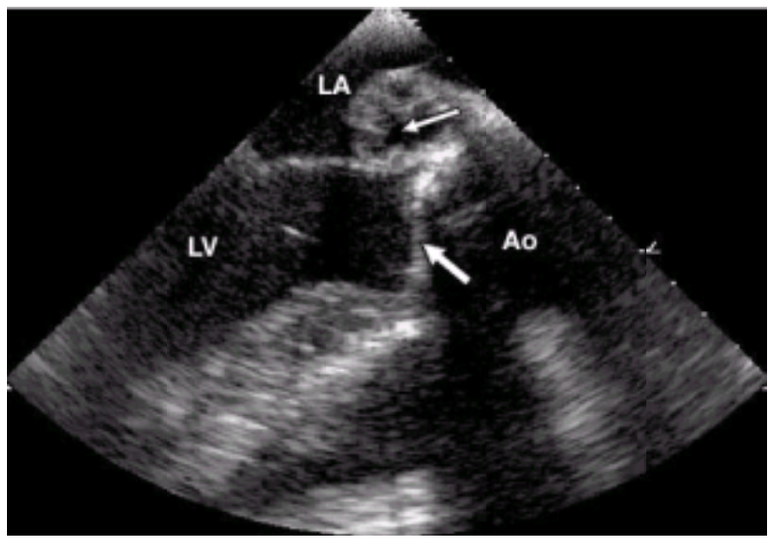
ABSCESSES OR FISTULAS OF THE HEART

IOE is extremely useful in patients who have endocarditis, both for preoperative definition of the surgical mission and for postoperative verification of successful results. The prepump TEE is particularly valuable to characterize the vegetations (*e*Fig. 57.4.4) and to look for additional sites of infection in patients in whom there has been an interval of time between the preoperative workup and surgery. The TEE plays an essential role in surgery for abscesses and fistulas of the heart (123), a dreaded

complication of endocarditis.



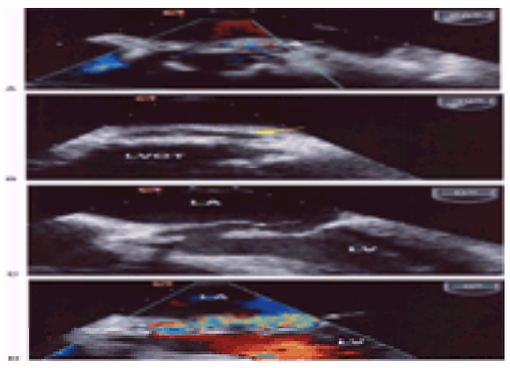
***e*FIGURE 57.4.4** Long-axis (115 degrees) midesophageal view of the left ventricular outflow tract (LVOT) in a patient with endocarditis showing a large vegetation (VEG) attached to the aortic valve. The intraoperative echocardiography was important to exclude interval spread of infection, especially additional sites of infection and involvement of the perivalvular tissue, because the preoperative echocardiographic workup had preceded surgery by 4 days. AO, aorta; LA, left atrium.



A 120-degree transesophageal echo of an aortic valve abscess seen in the inner annular fibrosa. The thin arrow designates the abscess cavity, while the thicker arrow demonstrates the aortic valve.

In endocarditis, infection may also spread from one valve to another valve, due to endocardial abrasion from a regurgitant jet hitting another area of the heart, causing the endocardial surface to be abraded and allowing tissue invasion. This occurs most commonly in patients with AR in which the jet hits the anterior mitral leaflet and causes an abscess, perforation, or a fistula into the left atrium (124).

Deep tissue and multivalvular infections occur predominantly in patients with prosthetic valves in place because of the foreign body phenomenon predisposing to infections. As the tissue becomes weakened, a fistula may develop where the high-pressure LV vents into another space. Around an aortic prosthesis, the shunt may go from the periaortic portion of the LV outflow tract to the right ventricle (VSD), to the right atrium (like a Gerbode VSD), to the left atrium (perforated anterior mitral leaflet), to the adjacent intervascular space (pseudoaneurysm), or to the aorta (periprosthetic leak) (eFig. 57.4.5). In fistulae around a mitral prosthesis, the shunt may go from the perimitral portion of the LV to the left atrium (periprosthetic leak), to the coronary sinus (left-to-right shunt), or to the pericardial space (pseudoaneurysm).



***e*FIGURE 57.4.5** Prepump transesophageal echocardiographic image in a patient with a periprosthetic abscess and mitral leaflet perforation. **A:** Midesophageal short-axis view of the aortic prosthesis showing high-velocity flow shown in color (*arrow*) within a pocket seen within the posterior aortic annulus. **B:** Magnified midesophageal view at the level of the short axis of the left ventricular outflow tract (LVOT) showing the echo-free space (*arrow*) in the posterior aortic annulus. **C:** Perforation of the base of the mitral leaflet (*arrow*) shown in a midesophageal transverse view of the left atrium (LA) and left ventricle (LV). **D:** Magnified midesophageal transverse view showing mitral regurgitation through the mitral anterior leaflet perforation (*arrow*).

IOE is important in the management of these patients to determine the location and extent of infection to completely extirpate the infection. Sometimes, this entails débriding significant infected tissue and even excising important structures of the heart such as the intervalvular fibrosa. In such cases, TEE is useful after reconstruction of those structures.

VIDEO

Video 57.16 Complicated prosthetic aortic valve endocarditis. Transesophageal echocardiography demonstrates fistulous tracts communicating the left ventricular outflow tract (LVOT) with left (LA) and right atria (RA). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 57.17 Periaortic abscess with communication with the aortic lumen. Color flow Doppler reveals turbulence present in the circular abscess mass below the aortic valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 57.18 Periaortic abscess without communication with the aortic lumen. A periaortic abscess is shown below the aortic valve on this chest wall echocardiogram. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The surgeon can sometimes use pericardium to reconstruct the defect. In addition, it is an advantage to avoid implantation of prosthetic material; therefore, valve repair (125) or homograft valves (126,127) are good options, although technically demanding. All of these surgeries are complex and unique, and TEE is useful before and after to guide the planning and check the results.

MASSES AND TUMORS OF THE HEART

The removal of a mass in the heart is also assisted substantially by the prepump and postpump use of TEE. Unexpected masses found during prepump IOE in a patient coming for surgery for something else are not uncommon. The most common is a thrombus in the left atrial appendage in a patient with atrial fibrillation or mitral valve disease. In suspected pulmonary emboli, epicardial echocardiography can be used to visualize the proximal right and left pulmonary arteries and pick out the exact location of thrombi (126a).

Some of the masses are tumors, of which most are benign and noncancerous. The most common tumor coming to surgery is a myxoma, which most frequently is attached to the interatrial septum; however, they can be seen in the right atrium, in both atria, or in the ventricles. The presence of a mobile mass on a valve in a patient who is not infected is commonly a fibroelastoma, most commonly seen on the aortic side of the aortic valve. However, many fibroelastomas occur on valves that are thickened by other degenerative or fibrotic processes and are seen by TEE but not identified as being a tumor until the histology of the resected valve tissue is done (127a).

VIDEO

Video 57.19 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis **(A)** showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. **B:** intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 57.20 Color Doppler of a myxomatous mitral valve with *Streptococcus* endocarditis **(A)** showing a large vegetation and perforation of the anterior mitral leaflet causing severe mitral regurgitation. Notice the large proximal convergence zone on the ventricular side of the base of the anterior mitral leaflet. **B:** intraoperative echo of a patient with infectious endocarditis with a large vegetation on the anterior mitral leaflet with a perforation at its base causing severe mitral regurgitation. The patient had myxomatous valve disease with mitral valve prolapse predisposing her to endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 57.21 Intraoperative transesophageal echo of a rocking prosthetic mitral valve due to infectious endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 57.22 Intraoperative transesophageal echo showing a Carpentier-Edwards mitral prosthesis in a patient with infectious endocarditis. The mitral prosthesis is rocking, and there is a paravalvular jet of mitral regurgitation to the left of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 57.23 Intraoperative transesophageal echo of a mitral valve with multiple, large, highly mobile vegetations from endocarditis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

For any patient coming to surgery with a mass of unknown histology type, a complete preoperative evaluation with TEE in the echocardiography laboratory and magnetic resonance imaging is mandatory. The malignancies are particularly challenging and unpredictable. Malignancies are most commonly seen in the right heart, pericardium, and infiltrating into the left atrium from the pulmonary veins. The prepump echocardiogram is useful for defining the location and extent of the tumor invasion and planning the extent of resection. The postpump echocardiogram is helpful in redefining the integrity of cardiac chambers and valvular function. In perivalvular masses, it is often possible to resect a tumor and reconstruct the valve, given the safety net of having valvular function checked reliably with TEE. In the series of 75 patients from the Mayo Clinic coming to surgery for mass removal, intraoperative TEE affected intraoperative management in 12 (16%), including return to bypass for valve repair in three patients (127b).

Tumor within the heart by extension from a venous structure is another important indication for IOE. The most common scenario is a renal cell carcinoma that has extended up the inferior vena cava, sometimes into the right atrium. In some patients, radical nephrectomy should be performed with the patient on cardiopulmonary bypass, to assist with safe removal of the mass in the right side of the heart. Tumor migration and air embolus can be detected by TEE and corrected immediately (127c,127d).

VIDEO

Video 57.24 Transesophageal echo of a large mobile mass seen in the right atrium, entering from the inferior vena cava. This patient had renal cell cancer that invaded the inferior vena cava. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

MYECTOMY FOR HYPERTROPHIC CARDIOMYOPATHY

For patients with surgical indications for myectomy, there is a particular need for IOE. This results from the variability of the location and extent of hypertrophy in patients with hypertrophic cardiomyopathy and the dynamic nature of the outflow tract obstruction. Echocardiography is an indispensable tool in planning and instituting effective surgical relief of the obstruction (128,129).

Prepump Echocardiography in Myectomy

Both transesophageal and epicardial echocardiography are useful in patients undergoing myectomy (Fig. 57.5). Either can define the location of hypertrophy and the location of the SAM. The location of the systolic contact of the mitral valve with the intraventricular septum and its distance from the aortic annular line in a long-axis view of the outflow tract are determined. This zone of SAM-septal contact is used as a guide to the best location for the myectomy. The surgeon must know the septal thickness in this region, to plan the extent of myectomy with the goal to resect all but approximately 1 cm of septal thickness at that location. It is also important to extend the myectomy beyond the zone of SAM-septal contact, especially in an apical direction. Measurement of the LV outflow tract velocity by continuous wave Doppler is also important during the prepump study, as a baseline for improvements that result from myectomy.

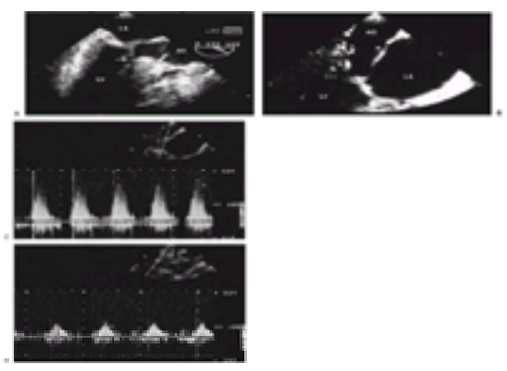


FIGURE 57.5 A patient with hypertrophic obstructive cardiomyopathy undergoing myectomy. **A:** A midesophageal image at a multiplane angle of 139 degrees showing the thick upper septum and the systolic anterior motion of the mitral valve touching the septum (*arrow*) causing dynamic outflow tract obstruction. **B:** An epicardial image taken from the aorta–superior vena cava transducer position, from which clean Doppler measurements of the outflow tract velocities can reliably be recorded. Arrowheads show the systolic anterior motion touching the septum. **C:** Prepump continuous wave Doppler recorded from an epicardial transducer, showing a 4.7 m per second maximum velocity (at the *X*, marked *A*), indicating a gradient of 88 mm Hg. **D:** Postpump continuous wave Doppler, showing a 1.7 per second maximum velocity (at the *X*, marked *A*), indicating an insignificant gradient of 12 mm Hg after myectomy. AO, aorta; LA, left atrium; LV, left ventricle.

With a TEE probe, the deep transgastric view can be used for measurement of the outflow tract velocity in some patients, but the transgastric measurements are not adequate in all patients. Occasionally, the midesophageal view can be used for this, but the continuous wave Doppler-echocardiographic signal of MR is often mixed with the LV outflow tract signal from this vantage point. To be certain that the correct jet is recorded, the TEE-derived continuous wave Doppler recordings should show a clean velocity envelope with a clear-cut, sigmoid-shaped, early systolic rising shape (26). Epicardial continuous wave Doppler-echocardiography is more reliable in obtaining the highest velocity to estimate the maximum instantaneous gradient (26). From the aorta–superior vena cava transducer position on the right side of the ascending aorta (Fig. 57.5B), outflow tract velocities can be reliably recorded. When resting gradients are normal, the degree of inducible obstruction is assessed using continuous wave recordings during infusions of isoproterenol, usually at around 10 µg per minute or when the contractility of the heart is visibly increased. Pacing does not suffice as a substitute inducement for latent obstruction.

MR resulting solely from dynamic outflow tract obstruction may occur later than the timing of mitral closure, due to the “eject-obstruct-leak” sequence (130). It is also important to assess the morphology of the mitral valve on the prepump study because of the frequent concomitant presence of myxomatous mitral valve disease (131). In patients without independent mitral valve disease, LV outflow tract gradients average 23, 44, 70, and 104 mm Hg, for trivial, mild, moderate, and severe MR, respectively (131a).

Postpump Intraoperative Echocardiography

After myectomy, patients are studied both at rest and during isoproterenol infusion at approximately 10 µg per minute to bring out latent obstruction. A successful result is present if the patient does not, either at rest or during provocation, have significant SAM that touches the intraventricular septum, significant MR, or an outflow tract gradient of more than 50 mm Hg. If these thresholds are exceeded after myectomy, the echocardiographic imaging is used to determine the location of residual SAM-septal contact, which is where further myectomy should be performed during a second pump run to relieve the obstruction (129). If moderate or more MR is found on the postpump TEE, a more aggressive search for a significant LV outflow tract gradient or intrinsic mitral valve disease should be considered and investigated.

The frequency of second pump runs in myectomy is 17.9%, the highest frequency of any type of cardiac surgery that our group has studied, which underscores the difficulty in the surgical approach to this lesion. The percentage of second pump runs in hypertrophic obstructive cardiomyopathy is high in part because of the policy of giving isoproterenol to all patients insisting on elimination of even latent outflow tract obstruction or significant MR (19a).

CONGENITAL HEART DISEASE

IOE is extremely useful in many types of congenital heart surgeries. Epicardial echocardiography has been traditionally used in a higher frequency of pediatric patients than adults, particularly in children smaller than appropriate for the available transesophageal probes (132,133). However, since the availability of the smaller pediatric TEE probes (133a,134), epicardial echocardiography has become much less common.

Ventilatory compromise is infrequent in small infants undergoing TEE examination and can be avoided by careful ventilatory monitoring (134a). TEE is useful in this population to guide accurate placement of central venous catheters in congenital heart surgery patients (134b). However, esophagoscopy after intraoperative TEE shows minor traumatic abnormalities, particularly in patients weighing less than 9 kg, although no long-term feeding or swallowing difficulties were noted (134c).

Epicardial echocardiography may also be required in defining certain problems not easily visualized with TEE, such as abnormalities of the LV outflow tract (25) and right ventricular outflow tract (135), which are in the far field of TEE. Doubly committed subarterial VSD is particularly difficult to diagnose by TEE (136). For either epicardial echocardiography or TEE, a segmental approach to cardiac anatomy should be used, analyzing cardiac situs, atrioventricular connections, ventricular arterial connections, and expected anatomic variants. Using both color flow imaging and contrast imaging is more sensitive to detect shunts than is either one alone (137).

Prepump Imaging in Congenital Heart Disease

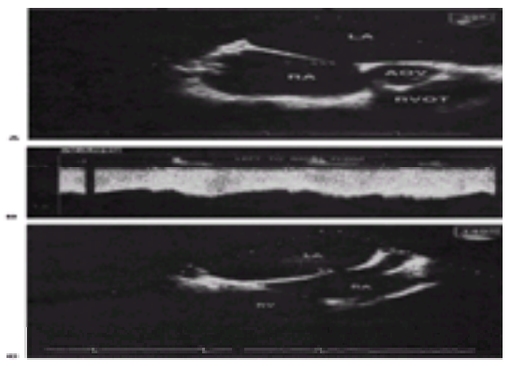
Because of the difficulties in doing outpatient TEE in young people, the operating room is the most common place where children with congenital heart disease are first examined with TEE. The additional window to the anatomy often provides improved image quality and imaging planes different from those of transthoracic imaging.

Most simple abnormalities, like atrial and VSDs, are well diagnosed by transthoracic echocardiography. In some cases, however, the prepump study finds additional information not discovered preoperatively, despite apparently good clinical and echocardiographic workup (eFig. 57.5.1). This is particularly true when there are multiple congenital abnormalities. For example, it is not uncommon for TEE to find an endocardial cushion or muscular VSD where only a membranous defect was expected.

VIDEO

Video 57.25 This is an intraoperative transgastric transesophageal view of an ischemic ventricular septal defect after an acute inferior myocardial infarction. Note the

location of the large defect in the inferior septum. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 57.5.1** This atrial septal defect was not discovered until intraoperative transesophageal echocardiography was done in a patient with congenital mitral valve disease. **A:** The two-dimensional image from a transesophageal echocardiographic multiplane angle of 39 degrees shows the defect (*arrowheads*). **B:** Continuous wave Doppler shows the continuous systolic and diastolic left-to-right flow across the defect. **C:** The image from an angle of 148 degrees also shows the defect (*arrowheads*), which was easily closed during surgery. AOV, aortic valve; LA, left atrium; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract.

In a study by O'Leary et al. (138), the prepump imaging findings had "significant impact" on intraoperative management in 16.3% of congenital heart surgeries and led to alteration of the planned procedure in 10.6%. Gussenhoven et al. (139) similarly found that IOE contributed to an alteration of the surgical approach in 13% of cases. In a study by Stumper et al. (140), prepump IOE found important new information in 25% of patients. IOE is better than preoperative transthoracic echocardiography in identifying VSDs (92). More recently, Durongpisitkul et al. found a significant impact of postpump IOE in 14% of congenital cases, of which approximately one-half were found primarily by the echocardiogram (37a). However, one author found no difference on TEE compared with preoperative studies (140a).

IOE has also been useful as a hemodynamic monitor during certain surgical procedures done for congenital heart disease, for example, to monitor right ventricular function and outflow tract gradients during pulmonary artery banding. During ligation of congenital arteriovenous fistulas, TEE can monitor the locations of venous drainage and look for myocardial ischemia (141). Balloon atrial septostomy can be performed using TEE guidance, providing better control and management of therapy (142).

Postpump Imaging in Congenital Heart Disease

After congenital heart surgery, the postpump IOE provides an important safety net on the results of surgery. The most common problems found after congenital surgery are new or persistent valvular regurgitation or new or persistent obstruction of the right ventricular or LV outflow tract. The frequency of second pump runs at our institution is 5.7% (19a). In the largest series of 1,000 patients undergoing a wide spectrum of congenital heart surgery, Ungerleider et al. (143) reported that 44 patients (4.4%) underwent intraoperative revision of their repair during a second pump run based on echocardiographic findings, of which 39 had successful elimination of the problem.

In a study by Gussenhoven et al. (139), the postpump imaging information led to immediate further surgery during the same thoracotomy in 3% and to inotropic drug therapy in 2% of patients. In a cohort at the Mayo Clinic, postbypass biplane TEE led to immediate revision of the initial repair in 8.7% of cases (138). Sheil and Baines found moderate or severe residual defects in 11.0% of cases, with 5.3% of the total group returning to bypass for further surgery, with which most, 4.0% of the total group, achieved complete or adequate amelioration (140a).

In surgery for tetralogy of Fallot, residual gradients across the right ventricular outflow tract are found in some patients, requiring a second pump run in up to 12% of patients (143a). Kaushal et al. considered significant gradients to be those with a gradient above 40 mm Hg, a right ventricular to LV pressure ratio above 0.85, or a fixed appearance by imaging, with no change in right ventricular outflow tract dimensions during the cardiac cycle. By comparison, dynamic obstruction in which dimensions increased appreciably in diastole appear to improve significantly without revision, irrespective of their severity (143a). However, the postpump TEE can miss residual pulmonary branch stenosis in patients with tetralogy (143b).

Patients who undergo modified Fontan's operations or subaortic resections had the greatest frequency of second pump runs, 40% and 33%, respectively, in one study (138). Stumper et al. (140) found an 18% incidence in patients with Fontan's procedures. Using IOE in Fontan's procedures, Fyfe et al. (144) found that TEE can nicely visualize atriopulmonary and cavopulmonary anastomoses and lead to second pump runs in 42% of cases.

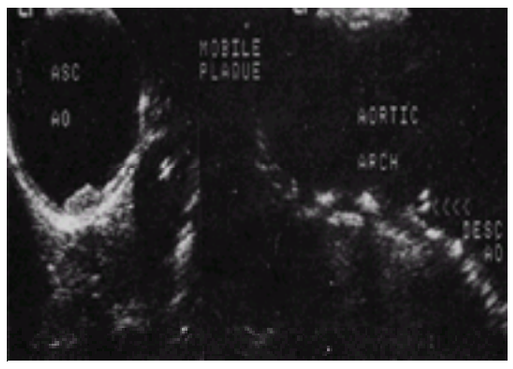
After closure of VSDs, IOE often finds residual shunts, particularly at the edges of the VSD patch, some of which do not require repair. Hsu et al. (146) found residual defects in 11 of 25 patients after VSD repair; one required a second pump run, and eight defects resolved spontaneously. Similarly Yang et al. found a residual VSD in one-third of 294 patients after VSD repair, of which two-thirds closed spontaneously by TEE before hospital discharge; nine patients (3% of the group) returned to bypass for further surgery, all with residual VSD color jet diameters greater than 3 mm (146a). However, Gussenhoven et al. (147) found postpump residual shunts in 10% of VSD repairs, 60% of which were reoperated on during the same thoracotomy, with the common findings of partial patch dehiscence. Two studies have suggested using intraoperative oximetry to determine pulmonary to systemic flow ratio, using a threshold of a pulmonary-to-systemic flow ratio of greater than 1.50 as a criterion for intervening with a second pump run (145,146a).

DEFINING THE LOCATION AND SEVERITY OF AORTIC ATHEROMA

Of the complications that can occur after cardiac surgery, one of the most devastating is the phenomenon of atheroemboli. This can cause extensive microcapillary occlusion, with end-organ damage in the brain, liver, kidneys, spleen, and skin and is a common cause of perioperative death (148). Diffuse atheroemboli produce the phenomenon of the "blue toe" syndrome (149). Despite that atherosclerotic lesions in the aorta are common in patients undergoing surgery for coronary or aortic atherosclerosis, observable events are surprisingly infrequent. Risk factors for clinical embolization include age, smoking, peripheral vascular disease, previous stroke, diabetes, and aortic knob calcification on chest radiographic films (151). Events are more common in patients who have larger atheromas of the thoracic aorta as defined by echocardiography (150)—as high as 15% in one series (151a).

Methods of Definition of Atheroma from Echocardiography

Echocardiography is one of the best ways of defining the location and presence of atheroma. The farther the atheroma protrudes into the lumen and the more mobile it is (*e*Fig. 57.5.2), the more likely that showers of atheroemboli will occur spontaneously (152) with a high risk of death (153).



***e*FIGURE 57.5.2** Epicardial intraoperative echocardiography of a patient with significant atheroma of the ascending aorta (AO) (*arrowheads*), viewed in the short (*left*)

and the long axis (*right*). This put the patient at higher risk of perioperative stroke. (From Stewart WJ. Intraoperative echocardiography. In: Skorton D, ed. *Cardiac imaging—principles and practice*. Philadelphia: WB Saunders, 1996:566–581, with permission.)

In one IOE study, patients with mobile atheroma had a 25% incidence of stroke versus 2% in those without a mobile atheroma (154). Emboli of atheromatous material also occur in response to surgical manipulation, such as aortic cross-clamping, aortotomy for valve surgery, aortic venting, placement of catheters for cardioplegia, and proximal vein graft anastomoses. In addition, flow from the arterial cannula for cardiopulmonary bypass may causes a “sand blasting” effect on the inside of the aorta, with the likelihood of dislodging atheroma and causing stroke (155).

IOE is used to learn the location and severity of aortic plaques to help to avoid such complications. By epiaortic echocardiography, the finding of nonisoechoic walls correlates with the risk of deformities at the cross-clamping site and the presence of atheroma as assessed by the histology of tissue punched from the ascending aortic wall at the location of proximal vein graft anastomosis (155a).

It is clear that intraoperative aortic palpation is not sensitive to atheroma at risk for embolization (156). In fact, both manual palpation and TEE are inaccurate methods for detection of atheroma in the ascending aorta (156a). TEE is insensitive in the ascending aorta, probably because of far-field attenuation and because of the 2- to 4-cm blind spot anterior to the trachea (157). The ascending aorta is imaged best by epivascular echocardiography, using a high-frequency sector transducer or a linear array transducer (158,159).

The routine for evaluating the ascending atheroma with epivascular echocardiography entails four parts. First, the sleeved high-frequency transducer is placed directly on the ascending aorta and moved up and down to obtain a set of short-axis and a set of long-axis views of the posterior wall of the ascending aorta. Then the short- and long-axis views are repeated using a standoff device to systematically view all portions of the anterior wall of the ascending aorta. Without using a standoff device, such as a glove partially filled with warm saline solution, the anterior wall is hidden in the near-field “bang” artifact.

Changes in Surgery Based on Echocardiographic Findings

Based on the echocardiographic information, several aspects of the process of cardiac surgery can be changed if it is expected that this will reduce the likelihood of dislodgment of atheroma. The arterial cannula can be placed in a different location in the ascending aorta to avoid areas of atheromatous plaque, particularly the soft friable ones. The arterial cannula can be placed elsewhere, such as the brachiocephalic, axillary, or femoral artery (160). The location or mode of giving cardioplegia or attachment of proximal portions of vein grafts can also be changed. Cardioplegia can be administered solely in a retrograde fashion through the coronary sinus, rather than making another wound in the ascending aorta. Another potential change is placing the aortic cross-clamp where it will do the least damage, particularly avoiding the dense calcified plaques. In cases in which the ascending aorta is severely diseased, internal balloon occlusion of the ascending aorta can permit exclusion of the systemic arterial flow from the operative field (161). In addition, cold ischemic circulatory arrest can be used during coronary grafting instead of cardiopulmonary bypass (156,162). The best option may be off-pump coronary bypass, using internal mammary arteries, doing coronary grafting on the beating heart without touching the aorta, which usually avoids atheroemboli (162a). Finally, in selected patients with severe atheroma at high risk for embolization if standard surgical techniques are used, replacement of the most diseased section of the aorta with a synthetic conduit is an option (163). One option that is not beneficial is endarterectomy, which was associated with a threefold increase in perioperative stroke (151a).

Wareing et al. (164) published an extensive series of patients who underwent cardiac operations with the guidance of epivascular echocardiography. This population had extensive aortic atherosclerosis at 10% or more risk of neurologic complications, according to historical controls. They obtained low complication rates using an echocardiography-guided approach. Despite the high risk of embolization and an extensive list of special modifications of surgical technique, no patient had a permanent neurologic deficit, compared with a 1% incidence in the patients at lower risk who did not have IOE.

MINIMALLY INVASIVE CARDIAC SURGERY

Surgical techniques have been developed in which certain cardiac surgical procedures can be performed through smaller incisions, avoiding a full midsternal thoracotomy (165,166) and avoiding some of the trauma of the traditional methods of cardiac surgery. These minimally invasive procedures have also been called less invasive operations, or sometimes “keyhole surgery.” In some circumstances, there appear to be advantages, including fewer complications, less pain, less bleeding, less recovery time, and less in-hospital expense. However, numerous disadvantages occur, including the inability to directly visualize the anterior epicardial surface of the heart and the inability to lift the cardiac apex for needle evacuation of air. Another disadvantage is the additional cost of special equipment that enables the surgery or cardiopulmonary bypass to be accomplished with special methods.

Several varieties of minimally invasive procedures have been developed, including hemisternotomy, port access operations, videoscopic surgery, and off-pump coronary bypass. In our experience with approximately 1,700 hemisternotomy cases, most of which were single mitral or aortic valve procedures, less than 1% of surgeries begun using minimally invasive procedures have developed problems requiring conversion to a midsternal thoracotomy, using a larger incision. The bleeding rates, morbidity, length of stay, and hospital costs have all been lower than with use of a standard midsternal incision, and the reoperation rates are unchanged.

Purposes of Intraoperative Echocardiography in Minimally Invasive Surgery

In minimally invasive procedures, IOE is useful for determining ventricular filling, ventricular function, and the presence of intracardiac air. In addition, IOE is useful in delineating the exact cardiac pathology that requires surgery and excluding additional problems that the surgeon is otherwise unable to determine due to lack of exposure (167).

Intraoperative echocardiography can detect new wall motion abnormalities to define intraoperative myocardial ischemia, which is associated with reduced postoperative prognosis (167a). TEE has also been used in hemisternotomy cases to determine the precise location for “T’ing” off the sternotomy, rather than approximating the sternotomy site by physical examination and chest radiography (167b).

In port access procedures, TEE is useful for correct positioning of various devices, including the endopulmonary vent catheter, the coronary sinus retrograde cardioplegia catheter, the venous cannula, and the aortic balloon catheter (endoclamp) used for internal occlusion of the aorta. The latter is used to exclude the systemic circulation receiving pressurized cardiopulmonary flow without the trauma of external aortic cross-clamping, but the balloon must be monitored by TEE constantly during the procedure, as it can migrate up or down, affecting the endoaortic occlusion or even damaging the aortic valve (166a,167c). TEE is also used to visualize the coronary sinus for placement of the retrograde cardioplegia catheter, obviating the need for fluoroscopy (166b).

Coronary bypass surgery can be done off pump, which has been called *minimally invasive direct coronary bypass* or MIDCAB, which appears to be useful in some situations (167a). The distal coronary graft anastomosis is done using heart-stabilizing instruments. Proximal anastomoses are avoided if possible by the preferential use of *in situ* mammary arteries, sometimes with side branches or an additional venous jump graft off the mammary. However, to perform the distal anastomosis requires temporary occlusion of the coronary artery, which causes focal wall motion abnormalities as defined by TEE in two-thirds, most of which are transient. However, in approximately 10% of patients, the wall motion abnormality persists to the time of chest closure, in which case they are likely to be permanent, with higher levels of cardiac enzyme release, more ST-T changes on the electrocardiogram, and more clinical problems than patients in whom the wall motion abnormality resolves before chest closure (167f). Intraoperative contrast echocardiography has been used in off-pump CABG to assess flow and verify the patency of the coronary artery (167g), similar to the Allen’s test. This can help to determine which graft to place first to cause the least ischemia.

Because they are done without aortic cross-clamping, both minimally invasive direct coronary bypass and port access techniques are excellent for management of patients with severe aortic atheroma, to avoid trauma to the ascending aorta and systemic embolization of debris. In a series of port access operations, the patient survival rate was 99%, the incidence of perioperative stroke was 1%, and the incidence of aortic dissection was 1% (19b), which are better statistics than historical controls in this population.

After the minimally invasive surgery is finished, IOE is useful to define the adequacy of volume filling and inotropic drug therapy and to assess the success of the primary surgical mission. Because the surgeon cannot see the LV, IOE is important for determining optimal fluid replacement.

TEE is also useful for defining the presence of intracardiac air, most commonly seen in the anteroapical LV and the anterior portions of the left atrium. Additional surgical measures or more time on cardiopulmonary bypass may be necessary for removal of the air. In our experience, new LV dysfunction on the immediate postpump TEE was noted in 20% of 112 patients having minimally invasive valvular surgery, being more common (30%) in patients with extensive air by IOE compared

with those without extensive air (10%) (168a). These LV wall motion abnormalities usually resolve.

From the literature about standard midsternal thoracotomy surgery, numerous factors are known about intracardiac air. First, it is seen more commonly after valvular than coronary surgery and generally needs no specific treatment if it is not excessive (168). Particularly after procedures in which the heart is actually opened, larger amounts of air pool in anterior structures (169), including the right upper pulmonary vein, LV apex, left atrium, right coronary sinus of Valsalva, left atrial appendage, left upper pulmonary vein, and pulmonary artery (170). When excessive amounts of intracardiac air are present in the ascending aorta, coronary embolization occurs readily (171). The right coronary ostium is anterior in the ascending aorta and therefore the more likely site for air, causing inferior infarctions, usually small in magnitude, in up to 5% of patients undergoing mitral repair using a standard midsternal incision in one report (172).

TREATMENT OF SEVERE LEFT VENTRICULAR DYSFUNCTION

Several devices are useful for treatment of patients who are critically ill or in cardiogenic shock, including the ventricular assist device, the extracorporeal membrane oxygenator, and the intraaortic balloon pump. For patients who require these devices, echocardiography has a role in implantation, positioning, safety, and determination of the hemodynamic effects on the patient.

In patients with hypotension, mechanical causes including pericardial tamponade (176), occult valvular disease (177), and hypovolemia can be diagnosed by echocardiography. In patients with heart failure, echocardiography can also be influential in diagnosing the etiology. In cardiogenic shock patients, TEE can guide therapy and help adjust pharmacologic treatment.

For patients who require an intraaortic balloon pump, TEE is useful for its insertion, to define the location of the distal tip in the upper descending aorta (173,174), and to determine its effects on LV function, aortic atheroma, and myocardial ischemia. During placement of the intraaortic balloon pump, the guidewire can easily be detected by TEE as it appears in the descending aorta. As the catheter itself is introduced, its prominent echocardiographic reflections can be tracked up the descending aorta. The tip of the catheter should be in the upper descending aorta below the distal aortic arch. If the catheter is placed too far superiorly, its tip may raise a flap of intima, which TEE can detect as a linear projection into the lumen (175).

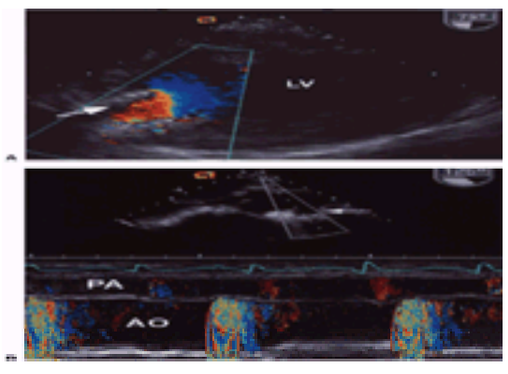
IOE has also been used in heart transplantation, particularly in patients with suspected atrial thrombi or TR (178). When the postimplantation TEE notes clinically significant right ventricular volume overload, it is important to assess the integrity of interatrial anastomosis for atrial shunting (179) and the valves for regurgitation, especially the tricuspid valve. In lung transplantation, TEE can monitor improvement in right ventricular function as the severe pulmonary hypertension resolves (180) and assess patients for subpulmonic obstruction secondary to long-standing right ventricular hypertrophy.

Extracorporeal membrane oxygenation is a temporary support system for patients who have cardiogenic shock with severe hypoxia. Blood is taken out of a large artery or vein using a large cannula, bubbled through a membrane to absorb oxygen and release carbon dioxide, and pumped back into a systemic vein. At the point of weaning the patient off of extracorporeal membrane oxygenation in the intensive care unit, TEE is used to monitor cardiac function while the output of the pump is reduced. If the patient's blood pressure falls, the echocardiographic images are used to determine how and why cardiac function is inadequate.

The temporary assist device is an external pump used in patients with severe left-sided heart failure to take over the mechanical function of the left side (LVAD) or the right side (right ventricular assist device) of the heart. A large cannula is placed into the left atrium to remove blood, oxygenate it, and pump it at systemic arterial pressure into an artery such as the ascending aorta or femoral artery (181). TEE can detect malfunction of the device (182,182a). It also may define resolution of transient cardiac abnormalities that may allow discontinuation of support (183), as well as complications such as intracardiac thrombi that can develop (184).

Echocardiography in the Implantable Left Ventricular Assist Device

In contrast to the temporary type, ventricular assist devices that are implantable have been increasingly used to provide a bridge to transplantation. In these, the entire pump and the conduits are inside the body, with the body of the pump usually placed in the anterior abdominal wall inferior to the ribs. Instead of the left atrium, the LV apex is the site where the outflow cannula is inserted (*e*Fig. 57.5.3). Use of the implantable LVAD has substantially improved the physical condition of many patients at the time they undergo heart transplantation (185).



***e*FIGURE 57.5.3** Postpump transesophageal echocardiographic color images after insertion of an implantable left ventricular assist device. **A:** Transgastric long-axis view of the left ventricle (LV) at 79 degrees showing flow out of the LV into the inflow cannula (*arrow*) of the left ventricular assist device. **B:** Midesophageal long-axis image of the ascending aorta (*top*) showing the position of the cursor through the outflow cannula and (*bottom*) the color M-mode illustrating the timing of flow from the pump into the ascending aorta (AO), which occurs less frequently than flow in the pulmonary artery (PA), which occurs lined up with systole on the electrocardiographic tracing above it.

IOE is a useful adjunct before insertion of an implantable LVAD. Importantly, several specific cardiac abnormalities should be ruled out, including right ventricular dysfunction, patent foramen ovale, LV apical thrombus, AR, and ascending aortic atheroma (182a,186,187). When discovered, a patent foramen ovale should be corrected in the process of LVAD implantation. If correction is not accomplished, a right-to-left shunt may result when left atrial pressure is reduced by the LVAD. The same applies to significant AR found by TEE. When AR is present, the LVAD creates a continuous loop of ineffective flow, so aortic valve surgery may be indicated during LVAD implantation.

After implantation, examination of the functional integrity of the LVAD is useful. Under normal conditions of LVAD demand function, the aortic valve often does not open because it is bypassed in the circuit. An item of interest is that during demand function, the flow into the LV apical cannula occurs in a dyssynchronous fashion with respect to ventricular contraction. However, the LV apical outflow cannula can become angulated, causing partial obstruction, which tends to increase the velocity of flow above 2 m per second. In addition, the bioprosthetic valves at the inlet and outlet of the cannula can malfunction by degenerative changes or infection. A sudden increase in the output of the pump weeks to months after implantation should signal a need to look for LVAD valve regurgitation.

CORONARY ARTERY BYPASS SURGERY

Purposes and Indications for Intraoperative Echocardiography

The purposes of the prepump study in patients undergoing CABG are to define global ventricular function, assess segmental LV function in each coronary artery territory, define the need for intravascular volume replacement, determine indications for inotropic drug therapy, plan arterial cannulation, and identify the presence and severity of valvular dysfunction. We do not use TEE during every coronary bypass operation, although some centers do (188). IOE is particularly useful in CABG patients who are at high risk of complications, particularly those with significant LV dysfunction, older age, concomitant vascular atherosclerosis, or unstable hemodynamics. Michel-Cherqui et al. reported that the prepump IOE changed the operative plans in 4.6% of coronary bypass cases (36a). In addition, patients with complications of myocardial infarction (189) such as ischemic VSD (190,191) or MR (192) benefit substantially from intraoperative TEE.

Savage et al. (200) studied a consecutive series of 83 high-risk patients undergoing coronary bypass who did not have other indications for IOE on the basis of valvular disease or other factors. This group represented a population with a high incidence of vascular disease, myocardial dysfunction, and unstable hemodynamics. In 33% of patients, the IOE altered the surgical decision process. This included changes in the arterial cannulation site or methods, decisions to do coronary bypass without

cardiopulmonary bypass or on circulatory arrest, unplanned valve procedures, unplanned additional coronary grafts, decisions to rush the patients onto bypass, and institution of an LVAD. The postpump study found problems that necessitated a return to bypass in 3% of the group studied. In this group of high-risk coronary bypass patients, IOE initiated major anesthetic or hemodynamic changes in 51% (200).

Transesophageal Echocardiographic Anatomy Corresponding to Coronary Artery Distributions

It is important to understand the regional anatomy of each coronary artery bed with respect to the tomographic imaging planes available with TEE. Figure 57.6 shows a diagram of three midesophageal long-axis views and one transgastric short-axis view of the LV, coded for the distribution of each coronary artery. These four views allow analysis of all 16 segments of the LV surface, composing the segmental model used by the American Society of Echocardiography. Obviously, the dominance of the right versus circumflex coronary artery supply determines which artery supplies the posterior segments of the heart. Other individual anatomic variations also affect, for example, whether the basilar posterior wall is perfused by the right or the circumflex coronary artery, whether the midseptum is perfused by the right or the left anterior descending artery, and whether the midlateral wall is perfused by the circumflex or the left anterior descending artery.

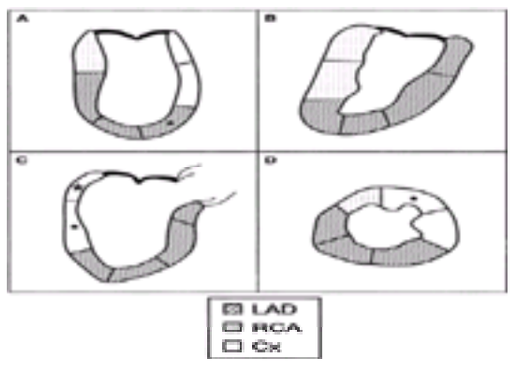


FIGURE 57.6 The four standard transesophageal echocardiographic monitoring views showing the distributions of the left anterior descending (*hatched*), right (*stippled*), and circumflex (*white*) artery territories. **A:** Basilar transverse (0 degrees) plane showing the septal (*left*) and lateral (*right*) walls from apex to base. **B:** Basilar 60-degree view showing the inferior (*left*) and anterior (*right*) walls. **C:** Basilar 120-degree plane showing the posterior (*left*) and anteroseptal (*right*) walls. **D:** Lower right transgastric short-axis view showing the midventricular segments of all six walls. The star and asterisks indicate segments that vary in their coronary artery supply depending on the dominance of the circulation.

Methodology of Analysis of Left Ventricular Segmental Function

Similar to stress echocardiography, side-by-side simultaneous moving images in a gated loop format are best for qualitative assessment of subtle differences in segmental wall motion. It is useful to store standard cine loops in a digital format from each of the four basic planes at baseline for later comparison. The methods of evaluating LV size, segmental function, and ischemia (see the section Decisions in Noncardiac Surgery Based on Intraoperative Echocardiography) for noncardiac surgery are equally applicable in coronary bypass patients.

IOE can also be useful in following improvement in LV systolic wall thickening after CABG. Wall thickening improves most in those segments with the abnormal preoperative function that had chronic ischemia or hibernation preoperatively (8,197). More immediate improvement is seen in severely abnormal, chronically underperfused segments than in mildly hypokinetic segments, presumably because of reversal of hibernation (198).

Before CABG, some have advocated evaluating segmental wall motion during an infusion in the operating room of 5 to 10 µg per kg per minute of dobutamine, to determine which walls would benefit the most from revascularization (193). Augmentation in response to low-dose dobutamine of a segment that has abnormal function at rest was predictive, in one published series, of sustained improvement of the segment after CABG (194).

Diagnosis of Ischemia after Coronary Bypass

TEE can be used to evaluate myocardial ischemia after bypass surgery on the basis of new wall motion abnormalities; however, the frequency of this occurrence is quite variable depending on the population and the methods. At one extreme, Leung et al. (195) diagnosed myocardial ischemia using the postpump TEE in 30% of patients undergoing coronary bypass. At the other, Deutsch et al. (104) found immediate vein graft occlusion that was not otherwise suspected in only 2 (4%) of 50 patients undergoing TEE after coronary bypass.

One study found that perioperative ischemic episodes were infrequently triggered by changes in hemodynamics. These episodes of wall motion abnormalities found by TEE could not be predicted by pulmonary artery or arterial pressure monitoring. The authors suggested that a primary decrease in myocardial oxygen supply may be an important mechanism for most perioperative ischemia as manifested by a regional abnormality on echocardiography (196). Whether this represents spasm, activity within unstable atherosclerotic plaques, or another mechanism is not clear. Another surprising result is that there is more deterioration of wall motion early after surgery in segments subtended by new internal mammary artery grafts than by new vein grafts (199).

Contrast Echocardiography in Coronary Bypass Surgery

Contrast echocardiography has been used for endocardial border opacification, Doppler signal enhancement, and myocardial perfusion evaluation. The first two are not usually necessary in surgery because access to the heart is usually so good. Perfusion imaging is still in its infancy, and most of the details of how to perform it and how to analyze the imaging data are still debated and not ready for clinical use. Contrast echocardiography prolongs the operation by 10 to 15 minutes and does not cause perioperative complications (201).

Contrast echocardiography has been proposed before coronary bypass surgery as a means to determine collaterals and assess the exact perfusion beds of each coronary artery. Contrast agents can be injected into the aortic root in an effort to define hypoperfused areas of the myocardium. Echocardiographic images of the LV in multiple planes are evaluated for contrast enhancement with time-intensity curve analysis (202,203 and 204). This can provide information about the magnitude and topographic distribution of runoff of coronary artery bypass grafts and enable identification of poorly perfused myocardial regions (205). Pulsing the ultrasound to destroy the bubbles, then evaluating the rate of replenishment, can objectively quantitate flow (206).

Identification of perfusion beds of diseased vessels that receive collateral perfusion flow has been studied using contrast IOE (207). Contrast echocardiography can help to determine the optimal sequence of coronary grafting. By grafting the most ischemic vessel first, perioperative ischemic damage might be lessened. Contrast agents can also be injected into the free proximal end of a venous graft after coronary anastomosis, while the heart is arrested. Intraoperative contrast opacification has been used to determine adequacy of myocardial perfusion and can predict regional myocardial function 1 week after surgery (207a). In theory, finding regions of poor flow could guide the need for additional grafts.

Contrast echocardiography can be used for evaluation of the intensity and distribution of cardioplegia delivery, which may relate to intraoperative myocardial protection and eventual ventricular function (208). This might be important in avoiding perioperative ischemia of the territories of the most severely diseased vessels. In some cases in which antegrade cardioplegia does not reach specific coronary beds, retrograde cardioplegia may provide effective local myocardial protection (209).

After bypass, contrast can identify improvements in myocardial flow and failure to reperfuse, which correlates with preoperative coronary stenoses (204). Contrast echocardiography has also been used experimentally to identify the patterns indicative of successful versus inadequate coronary perfusion from an internal mammary graft to the left anterior descending artery (210) and to determine the effects of transmyocardial laser revascularization of the ischemic myocardium.

DECISIONS IN NONCARDIAC SURGERY BASED ON INTRAOPERATIVE ECHOCARDIOGRAPHY

IOE is quite useful in patients undergoing noncardiac surgery. The purposes are to monitor development of myocardial ischemia, assess ventricular volume for fluid replacement, and define other cardiovascular abnormalities that affect hemodynamics and perioperative management. IOE is useful in a selected minority of

noncardiac operations, particularly when the risk of problems is higher because of the type of surgery planned or the patient's underlying cardiac condition (211).

IOE is particularly useful in vascular surgery involving cross-clamping of the upper abdominal aorta (212) in which a sudden increase in afterload occurs, causing an increase in myocardial oxygen demand (213). During insertion of a cemented femoral hip prosthesis, there is a substantial incidence of new segmental wall motion abnormalities (214). TEE has also been used to determine the intraoperative occurrence of intrapulmonary shunting, presumably due to fat embolization, to help develop new cementing techniques during hip replacement (214b). Similarly, IOE benefits cases such as liver transplantation, in which a sudden or severe shift in intravascular volume status occurs. In operations done in the sitting position, intraoperative TEE can help detect venous air embolism (214a).

Detection of Myocardial Ischemia

Intraoperative TEE helps to determine the presence and severity of myocardial ischemia to facilitate pharmacologic treatment (215). In many circumstances, detection of segmental abnormalities due to ischemia is enabled by judicious use of simultaneous, side-by-side, gated cine loop displays, showing matched imaging planes before or after the onset or cessation of an abnormality. As a baseline at the beginning of each case, it is useful to store the standard LV views in a quad-screen format, including the transgastric short-axis view and midesophageal long-axis views at multiplane angles of 0, 60, and 120 degrees (Fig. 57.6). These are recalled for direct comparisons with later images at a time when ischemia or hypovolemia is clinically suspected or must be ruled out.

TEE detection of intraoperative myocardial ischemia has good concordance with, but is more sensitive than, electrocardiographic monitoring (215,216). Side-by-side cine loop comparisons are much more definitive than serial observation for qualitative diagnosis of new wall motion abnormalities and mild changes in blood volume (217). These may be quite subtle and difficult to see if viewed sequentially from tape playback. The detection of wall motion abnormalities has an intraobserver variation in only 5% of segments, whereas the interobserver variation is only 9% of segments (218).

However, one should be aware of the impact of plane orientation on apparent wall motion. Off-axis cuts can produce patterns that look similar to segmental wall motion abnormalities. In addition, false-negative assessments for ischemia are obtained if an inadequate number of imaging planes are assessed or side-by-side comparisons are not made with great care (219). One biplane TEE study found that 20% of segmental wall motion abnormalities were found by the transverse plane alone, 35% by the longitudinal plane alone, and 45% were detected in both planes (220).

In one study of patients at high risk of ischemia undergoing vascular surgery, alterations in ventricular wall motion were noted in almost 50% of patients, in whom 71% of the alterations were completely reversed by immediate and specific fluid and pharmacologic interventions without any evidence of permanent myocardial infarction (221). When acute segmental wall motion abnormalities persist to the conclusion of surgery, myocardial infarction is likely to have occurred (216) and postoperative intensive monitoring is mandatory.

Determination of the Adequacy of Intravascular Volume

Intraoperative TEE provides a useful direct means of visualizing the adequacy of LV volume. At the extremes, this can rapidly be determined subjectively by the presence of a contracted or expanded LV (222,223). However, subtle shifts in ventricular volume are best assessed qualitatively by serial imaging from the same imaging plane (224).

In many respects, TEE images of LV volume provide more direct, better quality data about LV filling than does the capillary wedge pressure from the pulmonary artery catheter, which is relatively inaccurate for determining adequacy of preload (225). It is also important to remember that LV cavity size is also affected by afterload, increasing with phenylephrine even in the absence of a change in intravascular volume (226), so blood pressure must be monitored, along with either TEE or a pulmonary artery catheter.

Although it takes more effort to obtain quantitative assessment of forward flow, TEE can also determine cardiac output accurately, using combined diameter and spectral Doppler velocity measurements, with accuracy that is comparable with thermodilution measurements (227,228 and 229). Similarly, quantitation of ventricular systolic and diastolic volumes can be accurately done with a modicum of effort. Although care must be taken to avoid foreshortening the long-axis diameter, quantitation can be done from TEE images using hand tracing (230) or automatic boundary detection (231). The latter is an automated technique that requires experience in its operation, with the potential for inaccurate estimates, especially if the echocardiographer is not diligent to ensure that the primary images remain on axis and optimally recorded (232). With qualitative or quantitative techniques, careful attention to the quality of the primary ultrasound images is essential.

Echocardiography of Diastolic Function and Ventricular Filling

Numerous pulsed Doppler velocity patterns assessed by TEE can be useful adjuncts to direct visualization of the ventricles in determining the adequacy of ventricular filling during noncardiac surgery (233,234).

For example, elevated LV filling pressures are evidenced on the LV inflow recordings by a short mitral valve deceleration time, an elevated E-wave velocity, and an elevated E/A ratio (235). High filling pressures also cause systolic blunting of the pulmonary vein systolic velocity or a long duration or high velocity of the atrial reversal (236). These patterns are typical of the restrictive filling patterns and elevated preload (237). On the converse are the delayed relaxation patterns, which often indicate relatively low LV filling pressures. These are characterized by a low E-wave velocity, reduced E/A ratio, and long deceleration time on pulsed Doppler of the LV inflow (237), while the pulmonary vein flow velocity profile shows a normal or high systolic-to-diastolic ratio and a short, low-velocity atrial reversal wave (236). The entire constellation of intracardiac velocity patterns, integrated with images of right ventricular and LV size, are better than taking one measurement out of context (235).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Anesthesiology versus Cardiology Qualifications: Who Should Do What in the Operating Room?

Various considerations are relevant to the question of who should perform IOE. Experience and training are more important than the specialty of the person doing the echocardiogram (237a).

Because the anesthesiologist is present during the entire case, he or she may naturally be the best person to do IOE for cardiac surgery, provided the individual has training and expertise in echocardiography. Because of their management role in surgery, the anesthesia team is also more likely than a cardiologist to use the TEE information to optimally manage the patient in surgery, especially when monitoring is the primary function. However, the anesthesiologist who is responsible for hemodynamic management is often busy doing just that, so it is best to have a second person do the echocardiography. The most crucial times to image the heart are also the times of most clinical instability, when the anesthesiologist needs to concentrate on patient management. Whether the second person who is doing TEE is from one specialty or the other, it is useful to have another experienced echocardiographer for backup when the TEE is primarily managed by the person who is also giving anesthesia.

In other respects, the cardiologist is the best person to do IOE, provided the geographic considerations make him or her available at the appropriate times. The people who are most current and skilled at performing diagnostic TEE studies, often the cardiologist who does them in the echocardiography laboratory, are likely to also provide the most reliable determinations for valvular problems, complex congenital heart disease, and other diagnostic determinations that are needed in surgery (238). However, most cardiologists are not consistently available for IOE, nor are they comfortable with the process or politics of the operating room. Many of the hemodynamic perturbations regarding cardiopulmonary bypass and anesthesia are unfamiliar to the cardiologist unless he or she has developed substantial experience in surgery.

In some cases, it works well for the surgeon to take the trouble to learn echocardiography and perform the IOE studies. The easiest method for many surgeons is to use epicardial echocardiography (28,239). This usually requires the presence of a separate person outside the sterile field, sometimes a sonographer, who operates the machine controls. One disadvantage of this is that the surgeon is therefore also the diagnostician and may be biased against finding fault with the procedure(s) he or she has just performed, in contrast to a separate person who can usually be more objective.

No matter what the specialty is from which a physician launches into IOE, the process requires education and experience in echocardiographic diagnosis and knowledge of ultrasound technology, image acquisition, interpretation, and clinical applications in the operating room environment (241,242). There is clearly a long learning curve (242a) to become an expert in echocardiography (243). Each of the potential contributors to the IOE team has a challenging learning curve, and who the best person to do IOE is depends on the situation in each individual hospital.

Training and Credentialing for Intraoperative Echocardiography

Training for performance and interpretation of IOE has been the subject of some investigations and policy statements. The decisions required from intraoperative echocardiography make accuracy and reliability of diagnosis with this technique quite important. The educational goals for individuals desiring to develop competence in TEE in the operating room include a substantial amount of tutored learning and precepted performance of echocardiographic studies (241,241a). Participation in IOE without appropriate training appears to adversely affect the prevalence and detection of significant residual problems and the outcome of patients undergoing complex operations (243a). The Society of Cardiovascular Anesthesia and the American Society of Echocardiography have recognized the need for a policy that will likely lead to new recommendations for fellowship training programs in cardiovascular anesthesia. In addition, the accreditation of echocardiography laboratories and the availability of board certification in echocardiography may affect the requirements for performance of TEE and other advanced echocardiographic practice.

A major disparity between idealism and reality was pointed out in an interesting study of intraoperative TEE credentialing and performance (240). Based on a 1995 survey of practice patterns at 108 anesthesiology residency programs, of which 91% use intraoperative TEE, interpretations were rendered by anesthesiologists in 54% and by cardiologists in 46%. However, only 35% of anesthesiologists had formal echocardiography training in residency or fellowship, only 42% leave a formal interpretation on the chart, and only 43% bill specifically for performing TEE. Only 32% of programs reported that their institutions actually mandated formal credentials for performance of intraoperative TEE (240).

A decade ago, we instituted a training program in which a series of anesthesiology staff have each undertaken a 6-month fellowship for training in echocardiography, including a substantial time in the echocardiographic laboratory (242). Although this is not possible for most anesthesiologists who need to do IOE, an equivalent learning experience obtained on the job with available resources, such as a consulting cardiologist-echocardiographer, is necessary to achieve competence in this field (244).

It is important to maintain good records of IOE studies, including difficulties encountered with probe insertion (for medical-legal reasons) and a written chart report for *every* patient studied. An ongoing continuous quality improvement program should evaluate record keeping, accuracy, and quality of imaging, as judged by independent reviewers who should generate objective evidence of reviews performed (245,246).

Cost versus Efficacy

IOE involves finding the unexpected, monitoring for unanticipated problems, and imaging repeatedly to diagnose the change or lack of change expected from surgery. Despite the known frequencies of second pump runs in each type of surgery, it is not possible for the surgeon to predict the need for a revision based on his or her confidence in the repair. All of the patients who have had a second pump run were thought by the surgeon to have a good enough result to come off pump, but IOE revealed the need for operative revision.

When patients do return to the operating room later in their hospitalization for revision of a repair not fixed initially, the additional hospital costs are estimated to be much greater than for those whose repairs are revised during the initial thoracotomy ($94,000 vs. $21,000) (143). More important, many hidden costs arise in the patient whose initial surgery is unsuccessful, including additional hospitalizations for treatment of complications or reoperation.

Benson and Cahalan (247) performed a detailed cost-benefit analysis of IOE, being careful to keep estimates of direct and indirect costs liberal (high) and estimates of benefits conservative (low). They concluded that IOE results in a minimum savings of $600 per case for congenital heart surgery, $450 per case for valve repair surgery, and $150 per case for coronary bypass. Siwik et al. also looked at the cost-effectiveness of IOE in a series in which surgical therapy was altered by TEE findings in 3%, finding that the superior information reduced the need for additional postoperative studies in the intensive care setting (247a).

THE FUTURE

New technological and clinical developments are likely to be quickly applied to intraoperative diagnosis and treatment. Nowhere is successful clinical application of new techniques as likely to reap benefits in terms of quality, safety, and cost-effectiveness than in cardiac surgery. Innovations in cardiac surgery will undoubtedly continue to require the “safety net” of IOE. There is always a learning curve to a new practice and the potential for mistakes to occur. Therefore, IOE will probably be an important partner in future developments of new diagnostic and therapeutic techniques.

Three-Dimensional Echocardiography in the Operating Room

A technological innovation in cardiac ultrasound technology that is likely to achieve major steps in the near future is three-dimensional echocardiography (see Chapter 46). Three-dimensional echocardiography has already been studied preliminarily for its contribution to planning the surgical approach. With the capability to move the vantage point of viewing a three-dimensional data set to any angle or perspective, three-dimensional echocardiography has the potential to simulate surgical visualization of intracardiac anatomy and to dynamically represent intracardiac structure (248). This might be useful for planning surgery and evaluation of its probable results ahead of time by manipulating images to simulate various surgical options (e.g., determining the size and fit of implantable devices, valves, or other material). In addition to cardiac structure, the three-dimensional morphology of abnormal flow in the heart has also been studied (248c,248d).

Three-dimensional echocardiography may be particularly useful in certain types of surgeries. For valve surgery, it can provide new additional information not provided by two-dimensional echocardiography (248a). It is able to depict the shape, motion, and contour of the mitral annulus (62a,253). The size of prolapsing portions of the mitral valve correlate well between three-dimensional echocardiographic measurements and surgical findings (248b). For some types of congenital surgeries, it appears to add spatial comprehension (249,250). In congenital heart disease, three-dimensional echocardiography is particularly helpful in patients with VSDs (250a), especially doubly committed subarterial and restrictive VSDs and those associated with double inlet LV, as well as subaortic stenosis and supravalvar mitral membrane (251).

Three-dimensional echocardiography is also valuable in patients with cardiac tumors (252). It provides a better appreciation of the complex anatomy and aids in planning resection and deciding if curative surgery is feasible. The representations of cardiac anatomy are in some ways superior to standard intraoperative visualization in that they demonstrate the heart as a dynamic moving structure, as opposed to the empty, nonbeating heart the surgeon observes while the patient is on cardiopulmonary bypass (254).

Application to New Surgical Procedures

With the pace of developments in the field, it is likely that new cardiac surgery techniques will be developed. New practices have an inherent learning curve with the potential for mistakes to occur. Therefore, it is likely that IOE will be an important partner in future developments of new surgical techniques. For example, it is likely that IOE will contribute to the future development of procedures such as mitral homografts (255a), partial left ventriculectomy (255b), transmyocardial laser revascularization, complete correction of congenital heart disease, robotic and video-assisted thoracoscopic surgery (166a,167d), and autologous tissue valves (256), as well as numerous other emerging surgical innovations.

Intraoperative TEE is essential in video-assisted thoracoscopic surgery, which has already been successfully applied to surgical interruption of patent ductus arteriosus (167d) and mitral valve repair. In the latter, a computer-enhanced surgical telemanipulation system is used to robotically perform the surgery remotely from a surgical console; TEE found an inadequate repair in only one of ten patients, allowing further repair through an enlarged left thoracotomy (167e).

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58

MECHANISMS OF CARDIAC ARRHYTHMIAS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Progress in our understanding of the mechanisms of cardiac arrhythmias has been dictated by the development of tools to resolve the electrical activity of the heart at several levels. Current approaches extend from electrogram recordings in the *in situ* heart to the recording of electrical activity of single cardiac ion channels in isolated membrane patches.

Available data indicate that the majority of cardiac arrhythmias results from the function of the channels that are responsible for the normal action potential. However, disease states may change the level of expression of the normal channel and alter the ionic gradients that control ion movement through membrane channels. Changes in the intracellular and extracellular milieu may also alter channel gating. In a small, but important, group of patients—those with the long QT and Brugada syndromes—defects have been identified in the genes that code for specific ion channels or their regulatory subunits. Alteration of cardiac structure at a microscopic and macroscopic level that result from myocardial infarction, hypertrophy, or the aging process may also be crucial in the development of arrhythmias.

Reentry is the likely mechanism of most recurrent arrhythmias in chronic heart disease. Its treatment requires drugs that act on ion channels with minimal or no functional disturbance. Specificity and therapeutic index are low. Strategies to limit myocardial scarring following injury may prevent arrhythmias. Abnormal impulse formation, as evidenced by early and delayed after-depolarizations, are the second major cause of clinical arrhythmias. The clinical setting—family history, drug use, or electrolyte imbalance—and electrocardiographic (ECG) findings may suggest these mechanisms. It is important that arrhythmias resulting from abnormal impulse formation be identified so that treatment of greater specificity can be offered. Disturbances in the normal mechanisms of impulse generation in the sinus node are a rare cause of clinical arrhythmias.

HISTORICAL PERSPECTIVE

This chapter reviews normal impulse generation and propagation in the heart and the ways that disturbances of either mechanism result in cardiac arrhythmias. Emphasis is placed on observations made at the cellular and subcellular levels. Analysis of the mechanisms of arrhythmias at the higher levels of tissues and in the *in situ* heart are the focus of Chapter 60 and Chapter 62.

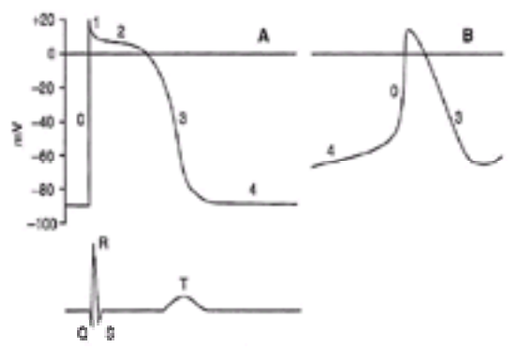
Progress in understanding the mechanisms of cardiac arrhythmias has been dictated by the new tools developed to study cardiac excitability and structure. The recording of unipolar and bipolar electrograms using sensitive string galvanometers replaced measurement of contractility as a means of following the regional spread of electrical activity. Lewis and colleagues used the accurate extracellular recordings to relate propagation velocity to underlying structure (1). Miniaturization of electrode spacing to a few millimeters has given way to the use of voltage-sensitive dyes that permit the tracking of the spread of excitation at the resolution of microns. These approaches provided clear descriptions of the spread of excitation in the basal state and during arrhythmias. The basis for normal and abnormal excitation had to await techniques that permitted *transmembrane* potential recordings. Ling-Genard capillary microelectrodes permitted transmembrane action potential recordings from groups of cells with little apparent damage to the cells. Those studies documented the relationship between the initial QRS complex and the T wave on the ECG to periods of rapid depolarization (phase 0) and repolarization (phase 3) of the action potential. Analysis of the ionic basis of the action potential proved more formidable. Membrane potential was varying with time (dV/dT greater than 0) as excitation propagated over the surface of the heart (dV/dX greater than 0). Marmont and Cole recognized that the analysis of excitation required that one of the independent variables (time *t*, or distance *x*) had to be controlled (zero) as the experimenter varied V (2,3). They developed the voltage clamp technique, which permitted measurement of the underlying current as a function of time as membrane voltage V was varied. This required that V should not vary with distance (i.e., dV/dX = 0, space clamping). The complexity of naturally occurring cardiac preparation severely limited space clamping. However, the preparation of single calcium-tolerant cardiac myocytes by Powel and Twist enabled a quantitative voltage clamp of several of the major currents that contribute to the action potential (4).

Neher and Sakmann introduced the patch clamp technique that permitted quantitative voltage clamp of even the smallest cardiac cells such as those of the sinoatrial (SA) and atrioventricular (AV) nodes (summarized in reference 5). The technique also permitted the resolution of current through single ion channels. All the major ion channels that contribute to the generation of the action potential have now been cloned and functionally expressed. Subgroups of arrhythmias occurring in the structurally normal heart have been shown to be monogenetic, arising from mutations of ion channel genes (6,7). The more common arrhythmias, such as ischemic-induced ventricular tachycardia and atrial fibrillation, are of multifactorial origin, with susceptibility genes playing an important role. Analysis of these and other arrhythmias starts with the premise that aberration of the normal mechanisms of impulse initiation and propagation are central to the genesis of arrhythmias. Therefore, normal impulse initiation and propagation are the starting point for the analysis of arrhythmia mechanisms.

Atrial fibrillation. Narrow complex QRS with irregular RR intervals. Ventricular rate is controlled.

BASIC ELECTROPHYSIOLOGY OF THE ACTION POTENTIAL

The form of the action potential recorded from a ventricular cell is illustrated in *e*Figure 58.0.1. Five phases—0, 1, 2, 3, and 4—are described. Phase 4 describes the membrane potential during diastole. Working myocardial cells maintain a steady diastolic level of approximately –85 mV. Conduction system myocytes in the SA and AV nodes, excitable cells of the mitral and tricuspid value, and the coronary sinus exhibit slow diastolic depolarization during phase 4. Excitation of resting cells results in a rapid transition from phase 4 to phase 0. This phase represents a period of rapid depolarization resulting in reversal of the transmembrane potential, and lasts less than 1 ms. Phase 1 is a period of rapid repolarization that returns the membrane to the level of the plateau. This phase shows the greatest variability between various regions of the heart and between various species. It is prominent in both Purkinje's and epicardial cells and is diminutive or absent in endocardial cells. Phase 2 is the plateau phase of the action potential and lasts up to several hundred milliseconds. It is the phase that most clearly distinguishes the cardiac action potential from the brief action potential of skeletal muscle and nerve. Phase 3 marks the period of terminal repolarization when the membrane potential is restored to its resting level.



***e*FIGURE 58.0.1** Idealized action potentials of nonpacemaker and pacemaker cells. **A:** The action potential of a nonpacemaker cell is shown. Five phases of the action potential, 0, 1, 2, 3, and even 4 can be identified. The membrane potential during phase 4 is stable at approximately –90 mV. The electrocardiogram in the lower section of **A** shows the relationship to the various phases of the action potential: The QRS complex corresponds to phase 0 and the T wave to phase 3. The QT interval approximates the action potential duration. **B:** The action potential from a pacemaker cell is shown. The membrane potential gradually declines during phase 4.

An uneven (nonequilibrium) distribution of ions across the cell membrane is an essential basis for the action potential and is summarized in *e*Table 58.0.1. Under physiologic conditions, the Na^+/K^+ pump moves three Na^+ ions out of the cell in exchange for two extracellular K^+ ions; one molecule of adenosine triphosphate (ATP) is consumed in the process. Because the stoichiometry of ion movement is not 1:1, the Na^+/K^+ pump generates outward current. The overdrive suppression of pacemaker activity following rapid stimulation results from the hyperpolarizing effect of the Na^+/K^+ pump current. Arrhythmias resulting from digitalis intoxication are secondary consequences of pump inhibition. The sodium/calcium (Na^+/Ca^{2+}) exchanger uses the Na^+ gradient established by the Na^+/K^+ pump to transport Ca^+ across the cell membrane. The Na^+/Ca^{2+} exchanger transports Ca^{2+} into the cell at plateau levels of membrane potential and Ca^{2+} out of the cell during diastole. Since the stoichiometry of the exchanger is approximately 3:1, it is also electrogenic. The Na^+/H^+ and HCO_3^-/Cl^- exchangers also contribute to the uneven distribution of ions across the cell membrane.

***e*TABLE 58.0.1** INTRACELLULAR AND EXTRACELLULAR ION CONCENTRATIONS IN CARDIAC MUSCLE

Ion	Extracellular concentration (mmol)	Intracellular concentration (mmol)	E_x (mV)
Na^+	145	20	+52
K^+	4	135	–92
Ca^{2+}	2	10^{-4}	+129
Cl^-	120	10	–64

Ca^{2+}, calcium ion; Cl^-, chloride ion; K^+, potassium ion; Na^+, sodium ion.

During the action potential, selectively permeable ion channels open or close, and the direction of ion movement (and the resulting current) is determined by the ratio of the intracellular and extracellular concentration of each ion and the membrane potential. Ion movement is passive. We now review the ion channels that are crucial to each phase of the action potential in more detail.

Phase 4 of the Action Potential

Nonpacemaker Cells

For cells with a stable resting (phase 4) membrane potential, the inward rectifier K^+ channel I_K has the highest conductance. The membrane potential E_m is only a few millivolts positive to the equilibrium potential for potassium, E_K. The small deviation between E_m and E_K reflects the limited permeability of the I_K channel to Na^+ and the finite conductance of other ion channels at the level of the resting potential. Elevation of the extracellular potassium reduces the membrane potential according to Nernst's relationship:

$$E_m = RT/F \ln[K_o]/[K]_I$$

where R is the universal gas constant, T the absolute temperature, F the Faradays constant, and $[K_o^+]$ and $[K_1^+]$ the extracellular and intracellular K^+ concentrations, respectively. The conductance of most ion channels is independent of the electrochemical driving force, $(E_m–E_x)$, acting on the permeant ion x. In the case of the inward rectifier, channel conductance is increased by elevations in extracellular K^+ concentration. Marked elevation in $[K_o^+]$ around cells is an early event during myocardial ischemia and may play a critical role in arrhythmias associated with acute myocardial ischemia.

Pacemaker Cells

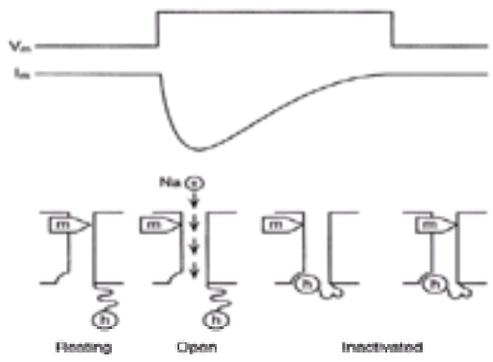
Cells in the SA and AV nodes and the His-Purkinje system undergo slow diastolic depolarization during phase 4. Three ionic currents contribute to this depolarization: (a) a background inward current carried by Na^+ ions; (b) the delayed rectifier current activated during the preceding depolarization; and (c) a hyperpolarization-activated current, I_f, carried by Na^+ and K^+ ions. Pacemaker activity in the SA and AV nodes is primarily dependent on a and b, whereas c plays a more important role in Purkinje's cells (8,9). The relative conductance of other ion channels compared with that of the inward rectifier K^+ channel is substantial in pacemaker cells. These cells are much less sensitive to elevation of $[K_o^+]$, and this may explain the persistence of SA and AV node function in states of marked hyperkalemia.

The rate of discharge of pacemaker cells may be slowed by increasing the maximum diastolic potential, decreasing the slope of phase 4, or decreasing the threshold potential; the opposite changes accelerate discharge rate. Sympathetic and parasympathetic stimulation changes pacemaker rates by two mechanisms: (a) They shift the primary site of the pacemaker within the SA node, and (b) they modify the kinetics of the currents that control pacemaker activity. Vagal stimulation produces a caudal shift in the site of the primary pacemaker; sympathetic stimulation produces a cephalad shift. Acetylcholine increases the maximum diastolic potential by activating the inward K^+ current I_{KACh}. Acetylcholine also shifts the voltage dependence of I_f activation to more negative potentials. As a result, a smaller component of I_f is activated during the pacemaker potential. Beta-adrenergic stimulation has the opposite effect on the activation of I_f.

Phase 0 of the Action Potential

Nonpacemaker Cells

In nonpacemaker cells, an inward voltage-dependent Na current is responsible for phase 0 of the action potential. It is the prototype of voltage-dependent ion channels. The properties of the Na^+ channel are described in detail to illustrate some of the general properties of voltage-dependent ion channels. Two distinct properties, gating and ion permeation, define the behavior of ion channels. *Gating* describes the opening and closing of the ion channel. Voltage-gated channels such as the Na^+ channel have an intrinsic charge and respond to membrane potential with a change in conformational state. During phase 4, Na^+ channels are closed. They open transiently (less than 1 ms) in response to membrane depolarization. The generally accepted gating model is based on the seminal work of Hodgkin and Huxley (10) in the 1950s and illustrated in eFigure 58.0.2. Ion movement through the Na^+ channel is under the control of two gates: the activation, or m, gates and the inactivation, or h, gate. At normal resting potentials, the activation gates are closed and the inactivation gate is open. The activation gates open during depolarization and Na^+ ions move into the cell down their electrochemical gradient. Closure of the inactivation gate follows with a brief delay, and ion permeation is terminated. Repolarization to high levels of membrane potential is required for recovery from inactivation.



***e*FIGURE 58.0.2** The Hodgkin-Huxley model of Na^+ channel gating. The upper trace (V_m) shows a voltage step, and the middle trace (I_m) shows the resulting membrane current. A physical model to account for the transient current is shown in the lower trace. The Na^+ channel is represented as a pore spanning the membrane. In the resting state, the activation (m) gate is in the closed position, and the inactivation (h) gate is in the open position. Following depolarization, the m gate assumes the open position. With both gates open, Na^+ ions move into the cell. The h gate then moves into the closed position, blocking ion movement. When the membrane is returned to the resting level, the m gate moves into the closed position, a process termed *deactivation*. After a variable interval, the h gate moves into the open position, a process termed *recovery from inactivation* (not shown). Na^+ indicates sodium ion.

Membrane depolarization decreases the fraction of Na^+ channel available for opening; at a membrane potential of approximately –75 mV, only 50% of Na^+ channels are available for opening. This voltage-dependent inactivation is important in the genesis of arrhythmias and in antiarrhythmic drug action. Most membrane depressants, such as hyperkalemia and acidosis associated with ischemia and myocardial stretch, cause membrane depolarization and Na channel inactivation. Class I antiarrhythmic drugs decrease the availability of Na^+ channels at all membrane potentials. Some drugs such as lidocaine also bind preferentially to inactivated Na^+ channels and are therefore more effective in blocking conduction in partially depolarized ischemic tissue.

Ion permeation is the second important property of ion channels. The selective permeability to specific ions forms the most common basis for the classification of ion channels. The Na^+ channel has a selectivity ratio for Na^+:K^+ of 12:1. The simplest ion channel would permit inward and outward ion movement with equal facility. This is not the case with many ion channels. A channel is said to rectify in the inward direction if a voltage displacement produces a larger current when ions are moving in the inward direction compared with the outward current produced by a voltage displacement of the same amplitude but opposite direction. Inward rectification is a common property of K^+ channels. Depolarization to positive potentials should markedly increase outward K^+ current as the membrane potential moves positive to the K^+ equilibrium potential. However, K^+ current decreases at depolarized potentials because of inward rectification. Inward rectification of some K^+ channels results from blockade by intracellular polyamines and magnesium (Mg^{2+}) (11).

Pacemaker Cells

At the depolarized level of the maximum diastolic potential of pacemaker cells (approximately –60 mV), the Na^+ channels are inactivated. Inward Ca^{2+} current is responsible for phase 0 of the action potential. Of the two types of Ca^{2+} channels in cardiac muscle, L and T, it is the former that makes the major contribution to phase 0. Like Na^+ channels, Ca^{2+} channels exist in resting, open, and inactivated states. However, the magnitude, kinetics, and ion permeation characteristics differ from the Na^+ channel: (a) Peak amplitude is less than 10% that of the Na^+ current; (b) activation and inactivation occur at more depolarized potentials and are somewhat slower; and (c) Ca^{2+} is the only physiologic charge carrier.

Phase 1 of the Action Potential

A transient, outward K^+ current is responsible for phase 1 of the action potential. Calcium-dependent and calcium-independent K^+ channels are responsible for this current component. The distribution of these channels is consistent with the magnitude of phase 1 of the action potential: The channel density is high in the epicardium and is low in the endocardium. A reduction in the magnitude of the transient outward current is consistently observed in left ventricular hypertrophy and congestive heart failure (12). The resulting prolongation of the action potential duration (APD) may account for the increased susceptibility to arrhythmias in these states.

Phases 2 and 3 of the Action Potential

Phase 2 of the action potential may last tens (atrium) to hundreds of milliseconds (His-Purkinje system and ventricle). A delicate balance of inward and outward currents results in little change in membrane potential. The principal inward currents are the L-type Ca^{2+} current and a small residual component of inward Na^+ current. The significance of the latter has been highlighted by studies of the molecular basis of the long QT syndrome. Several kindreds have been identified in whom the genetic defect has been pinpointed to the locus on chromosome 3 that encodes the cardiac Na^+ channel (13). Genetic defects that have been identified include single amino acid substitutions and a three–amino acid deletion (13,14). The consequence of the defect is a failure of or reversibility of inactivation resulting in an increase in the magnitude of the residual slow component of Na^+ current during phase 2. The increased inward current prolongs the duration of action potential and the QT interval on the surface ECG.

A delayed rectifier current, consisting of rapid and slow components I_{Kr} and I_{Ks}, is activated at depolarized potentials. I_{Kr} is activated rapidly, shows inward rectification, and is unchanged by beta-adrenergic stimulation. I_{Ks} is approximately ten times larger than I_{Kr}, does not rectify, and is increased by beta-adrenergic stimulation. Mutations in the genes encoding I_{Kr} and I_{Ks} or their regulatory subunits may result in a reduction of outward K current, APD and QT interval prolongation, and torsades de pointes. The Na^+/Ca^{2+} exchanger and the Na^+/K^+ pump provide minor current components during phase 2. The activation of I_{Kr} and I_{Ks} initiates phase 3 repolarization. As the resting potential is approached, I_{K1} makes an increasingly important contribution to the net membrane current and hence to terminal repolarization.

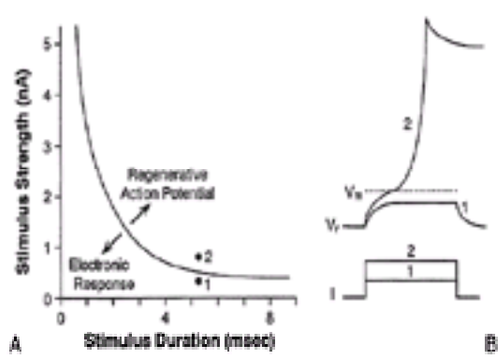
A 51-year-old female patient with torsades de pointes.

Other Ion Channels Contributing to Multiple Phases of the Action Potential

Certain ion channels make a contribution to the action potential only under special circumstances. K_{ATP} channels are present in high density in cardiac cells. Opening of the K_{ATP} channels depends on the adenosine diphosphate (ADP):ATP ratio. Micromolar concentrations of ATP close the channels. Reduction in the ATP concentration during ischemia causes a small fraction of these channels to open. Because of their density, substantial outward current is produced, markedly reducing the APD. As K^+ ions scape into a restricted extracellular space, $[K^+]_o$ rises substantially. Sulfonylureas open these channels and shorten the APD. Chloride-selective channels are present in cardiac cells. Under normal circumstances, they do not account for significant membrane current. However, the chloride current is markedly activated by sympathetic stimulation and may play a role in repolarization under these circumstances.

EXCITABILITY

Excitability is the ability of a cell or group of cells to respond to a stimulus with a regenerative action potential. The membrane potential must be displaced from its resting level, V_r, to a threshold potential, V_{TH}, at which the inward current (Na^+ or Ca^{2+}) becomes regenerative. Excitability depends on the passive and active properties of the cell membrane. The passive properties include the membrane resistance and capacitance and the intercellular resistance. A certain minimum charge has to be applied to the cell membrane to elicit a regenerative response. Excitability is inversely related to the charge required for excitation. The relationship between stimulus amplitude and duration is summarized in the familiar strength-duration curve shown in eFigure 58.0.3. As stimulus duration is increased, the threshold stimulus declines and approaches an asymptotic value at long times. The voltage-dependent properties of the inward current determine the threshold potential.



***e*FIGURE 58.0.3** Stimulus strength-duration relationship of a ventricular cell. **A:** The strength-duration curve represents the minimum stimulus strength (ordinate) required to elicit a regenerative action potential as a function of stimulus duration (abscissa). **B:** Effect that a subthreshold stimulus (point 1) and suprathreshold stimulus elicits (point 2) on the membrane potential. The subthreshold stimulus elicits a nonregenerative (electronic) membrane depolarization. The suprathreshold stimulus elicits a regenerative action potential.

Extracellular electrolytes such as K^+ and antiarrhythmic drugs have a complex effect on excitability. Domiguez and Fozzard (15) showed that small elevations of $[K^+]_o$ increase excitability by reducing the difference between the resting and threshold potentials ($V_r - V_{TH}$); large elevations of $[K^+]_o$ reduce excitability by inducing Na channel inactivation. Antiarrhythmic drugs influence excitability by changing both the passive membrane properties and the inward Na^+ current. Na channel blockers reduce excitability, shifting the curve upward and to the right. K channel blockers shift the curve in the opposite direction and increase excitability. These changes in excitability are reflected in the energy requirements for internal and external defibrillation.

Excitability is particularly important in the analysis of the ability of cardiac cells to undergo reexcitation during phase 3 of the action potential. In addition to the factors discussed previously, the time-dependent changes in current are also crucial.

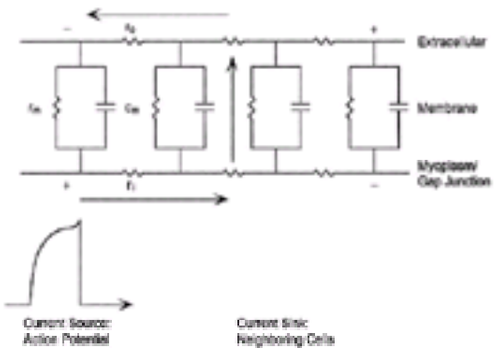
REFRACTORINESS

Refractoriness describes the ability of a cell to respond to repetitive stimulation. This property is important for the normal function of the heart and is a determinant of susceptibility to arrhythmias. Stimulation during phase 2 results in no response, and the cell is said to be absolutely refractory. Stimulation during the middle and late parts of phase 3 may result in a response. However, during most of phase 3, the stimulus intensity has to be increased. There is a brief period in phase 3, the supernormal period, when the required stimulus is actually less than that during phase 4. For reexcitation, repolarization has to occur to a sufficiently negative potential that Na^+ current required to support a response can be activated. As the recovery of the Na^+ channel from inactivation is not instantaneous, the available Na^+ current at each potential during phase 3 is less than that predicted by the steady-state inactivation curve. The time interval between phase 0 of the action potential and the time that a second propagated response can be initiated is the effective refractory period of the cell. The effective refractory period of the cell is one of the determinants of the minimum path length for reentry.

The recovery of normal excitability closely parallels the duration of the action potential. The refractory period may be prolonged by increasing the duration of the action potential or by slowing the rate of recovery of the Na^+ channel from inactivation. Class I antiarrhythmic drugs dissociate from the Na^+ channel slowly and as a result, they decrease the fraction of available Na^+ channels during phases 3 and 4. They also prolong refractoriness on the basis of the change in Na^+ channel kinetics.

CONDUCTION

For effective contraction, atria and ventricles have to be activated synchronously. The successful propagation of the cardiac impulse depends on the coupling of current sources and sinks. An action potential at a given site acts as a current source to excite neighboring cells (the current sinks). Large inward currents during phase 0 favor rapid propagation. Reduction of the magnitude of the inward current (e.g., by membrane depolarization and Na^+ channel blocking drugs) slows conduction. Propagation from a current source occurs by the spread of local circuit currents between neighboring cells. The pathway for current spread is illustrated in *e*Figure 58.0.4 and includes the coupling impedance between cells and the impedance of the sarcolemma, and the extracellular fluid local circuit current discharges the capacity of the membrane of neighboring cells, bringing their potential to threshold. Low intercellular impedance favors rapid conduction. Specialized intercellular connections termed *nexuses* or *gap junctions* are the preferential sites for intercellular current. The gap junctions are formed by a family of proteins, the connexins. They aggregate at the sites of intercellular contacts such as the intercalated disks. Units from each of two neighboring cells associate to form fluid-filled channels. These channels have a gating mechanism that is controlled by intracellular pH and $[Ca^{2+}]_i$. Connexin expression is low in the SA and AV nodes and may be reduced during myocardial ischemia.



***e*FIGURE 58.0.4** Equivalent circuit model of a cardiac fiber. The components of cardiac cells are modeled as equivalent electrical circuit elements. The unit membrane resistance is r_m. The intracellular resistance (r_i) consists of the series resistance of the myoplasm and gap junctions. The resistance of the extracellular space is r_o. c_m is the unit membrane capacitance. The action potential on the far left is the source of current for excitation of this patch of membrane. The current pathway is through r_i, r_m, c_m, and r_o, completing the circuit back to the source.

Until relatively recently, propagation in cardiac muscle was analyzed using a theory developed for current spread in homogeneous medium. Spach et al. (16,17) have emphasized that at both the microscopic and macroscopic levels, cardiac muscle is not a homogeneous excitable medium. The low-resistance gap junctions are not uniformly distributed over the cell surface membrane. Gap junction density is greatest in the direction of fiber orientation. Hence, intercellular impedance is less in the longitudinal than in the transverse direction. With increasing age, connective tissue septae are laid down between fiber bundles and further distort the cardiac architecture. These structural changes may play a crucial role in the genesis of arrhythmias and are discussed in more detail in the section Reentry, later in this chapter.

Changes in Ionic Currents during Pathologic States

Certain clinical states such as myocardial ischemia or reperfusion cardiac failure and myocardial hypertrophy are associated with an increased incidence of cardiac arrhythmias. As the currents that generate normal action potential play a central role in most arrhythmias, these clinical states must exert some effect on the membrane currents. There are relatively few ways that membrane ion currents can be modified. Pathologic states may modify channel function by changing the transmembrane gradients for the permeant ions; alter channel gating by changing intracellular Ca^{2+}, intracellular and extracellular pH, intracellular [ATP], and autonomic tone; and alter the level of expression of ion channels.

Myocardial ischemia is associated with an early rise in $[K^+]_o$, a fall in intracellular and extracellular pH and [ATP], and an increase in $[Ca^{2+}]_i$ and $[Na^+]_i$. Lysophospholipids also accumulate in the ischemic tissues. Elevation of $[K^+]_o$ has two major effects: membrane depolarization and an increase in the inward rectifier K^+ current. The fall in intracellular [ATP] and the associated rise in ADP activates the ATP-sensitive K^+ channel. In general, most ionic currents are reduced by a fall in intracellular and extracellular pH. The threshold for this effect is variable between ion channels. The lysophospholipids, such as lysophosphatidylcholine, block ion channels. They may also change channel gating (e.g., inactivation of the Na^+ current is slowed) (18). In experimental models of acute ischemia, reperfusion is associated with a high incidence of ventricular tachycardia and ventricular fibrillation. Indeed, the prevalence of arrhythmias during reperfusion may exceed that during the proceeding ischemic period. In the clinical setting, vasospastic angina and percutaneous transluminal coronary angioplasty are associated with reperfusion after a variable period of ischemia. Accelerated idioventricular rhythm is the most common arrhythmia in clinical reperfusion; ventricular fibrillation has a much lower prevalence than in the experimental setting. Reperfusion is associated with a restoration of $[K^+]_o$, pH toward normal, and generation of oxygen-derived free radicals. $[Ca^{2+}]_i$ may rise further and reduce the conductance of junctional channels.

An 81-year-old male patient with ventricular tachycardia.

Idioventricular rhythm. Note wide complex QRS with absence of P waves and slow ventricular rate.

Cardiac hypertrophy and failure are associated with a prolongation of the action potential. The most consistent finding is a reduction of the transient outward current. Available data suggest that the decrease in I_{to} is the result of decreased expression of the channel. The mediators of this suppression are not known. Cytokines may play a role.

ELECTROPHYSIOLOGIC MECHANISMS OF CARDIAC ARRHYTHMIAS

Cardiac arrhythmias may result in abnormalities of impulse initiation or conduction. Normal and abnormal automaticity and triggered activity are potential bases for abnormal impulse initiation. Arrhythmias that result from abnormal conduction are based on reentrant excitation. Abnormalities of impulse initiation and conduction may act in concert to induce arrhythmias. A spontaneous beat, by its timing in the cardiac cycle, may result in a functional disturbance in conduction and reentry. In the past, it was proposed that arrhythmias arising from abnormalities of impulse initiation and conduction could be distinguished on the basis of their response to premature stimulation; reentrant arrhythmias could be initiated and abruptly terminated by premature stimulation. It is now apparent that arrhythmias that result from triggered activity share some of these properties.

Abnormalities of Impulse Initiation

Enhanced Normal Automaticity

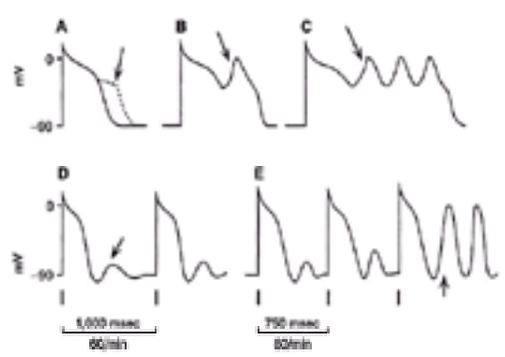
Enhancement of normal phase 4 depolarization in SA and AV node cells and Purkinje's cells is a relatively uncommon mechanism of cardiac arrhythmias. The conclusion that this mechanism is a basis for specific clinical arrhythmias is largely inferential. Inappropriate sinus tachycardia is thought to arise by this mechanism. Patients with this arrhythmia have inappropriately high resting heart rates, and a disproportionate increase in the heart rate in response to exercise and beta-adrenergic stimulation (19). Accelerated idioventricular rhythm also may result from enhanced normal automaticity in Purkinje's cells.

Abnormal Automaticity

Membrane depolarization may result in repetitive activity in most cardiac cell types. A current of injury between depolarized ischemic and relatively normal cells may lead to repetitive activity in the normal cells. The injury current provides the "background current" the decline of the delayed rectifier K^+ current activated during the preceding action potential provides the time-dependent change in current. At high resting membrane potentials (negative to –60 mV), Na^+ current would account for phase 0. The ease of arrhythmia induction is enhanced by adrenergic stimulation. This mechanism of arrhythmia can be readily demonstrated *in vitro*. The accelerated idioventricular rhythm and ventricular tachycardia that occur 24 to 72 hours following myocardial infarction may arise by this mechanism, but confirmation in an experimental model or in humans is lacking.

Triggered Activity

Triggered activity is a form of impulse initiation that arises from after-depolarizations of a preceding or triggering action potential. After-depolarizations are oscillations in membrane potential that may occur during phases 2 and 3 of the action potential (early after-depolarizations) or following complete repolarization (delayed after-depolarizations). These types of after-depolarizations are caused by distinct mechanisms and are illustrated in *e*Figure 58.0.5. *e*Table 58.0.2 contrasts the properties of these two types of after-depolarizations.



***e*FIGURE 58.0.5** Early and delayed after-depolarizations (*arrows*). After-depolarizations are oscillations in membrane potential that may occur during phases 2 and 3 of the action potential (early after-depolarizations B,C) or following complete repolarization (delayed after-depolarizations D,E). (From Wit AL, Rosen MR. Cellular electrophysiology of cardiac arrhythmias. Part 1. Arrhythmias caused by abnormal impulse generation. *Mod Concepts Cardiovasc Dis* 1981;50:1–6, with permission.)

***e*TABLE 58.0.2** COMPARISON OF THE MODULATION OF EARLY AND DELAYED AFTER-DEPOLARIZATIONS

	Early after-depolarizations	**Delayed after-depolarizations**
Slow heart rate	↑↑	↓↓
Low K^+	↑	↑
High Ca^{2+}	↑ or ↓	↑↑
Beta-adrenergic agonists	↑	↑↑
Caffeine	↑	—
Ischemic metabolites (e.g., lysophosphatidylcholine)	—	↑↑
Digitalis	—	↑↑

Ca^{2+}, calcium ion; K^+, potassium ion.

Early After-Depolarizations

Early after-depolarizations occur in the setting of action potential prolongation. An inward shift in net membrane current by an increase in Ca^{2+} current or the late Na^+ current produce the oscillations of early after-depolarization. Alternatively, blockade of the outward current may produce the net inward current shift. Early after-depolarizations are enhanced by slowing the heart rate and suppressed by increasing the heart rate. Both clinical and experimental data suggest that early after-depolarizations are the cellular basis of torsades de pointes observed in congenital and acquired forms of QT prolongation (20).

Genetic, molecular biologic, and biophysical techniques have been combined to determine the basis of congenital QT prolongation associated with normal hearing (Ramano-Ward syndrome). This effort has been led by Keating and colleagues (21,22). The four variants of the syndrome and the underlying defects are summarized in eTable 58.0.3. Three of the defects have been tentatively associated with mutations of K^+ channels. The molecular defect may be the result of a single amino acid mutation or premature chain termination of one of the monomers that form the tetrameric K^+ channel. The result is a dominant negative defect: a reduction of repolarization K^+ current. These mutants presumably result in reduced outward (repolarizing) current. Bennett et al. (23) have described the phenotype of the Na^+ channel mutant in detail. Reversibility of the inactivation process is markedly increased. As a result, a significant component of inward current persists at the plateau levels of membrane potential. The late component of Na^+ current is blocked by mexiletine and lidocaine (24,25). The definition of the molecular basis of this often fatal arrhythmia opens the possibility for more specific treatment.

***e*TABLE 58.0.3** LONG QT (LQT) SYNDROME: MOLECULAR GENETICS, PHYSIOLOGY, AND TREATMENT

Pattern	**Locus**	**Chromosome**	**Gene**	**Protein**	**Mechanism**	**Specific therapy**
Inherited autosomal dominant	LQT1	11	?	?	?	?
	LQT2	7	HERG	I_{kr}	Dominant negative loss of K^+ channel function leading to reduced myocellular repolarizing current	K^+
	LQT3	3	SCN5A	I_{na}	Altered sodium channel function leading to late depolarizing Na^{2+} current	K^+ channel openers Na^{2+} channel blockade
	LQT4	?	?	?	?	?
Inherited autosomal recessive	?	?	?	?	?	?
Acquired	?	?	?	?	Reduced I_{kr} secondary to drug, hypokalemia, genetic factors	K^+

?, unknown; K^+, potassium ion; Na^{2+}, sodium ion.

Most acquired forms of the prolonged QT syndrome are drug induced. A genetic predisposition may be important in some patients. Drugs and metabolic derangements that are significantly associated with QT prolongation and torsades de pointes are summarized in eTable 58.0.4. In most of the circumstances in which detailed electrophysiologic experiments have been performed, the defect is blockade of the rapid component of the delayed rectifier K^+ current.

***e*TABLE 58.0.4** PRECIPITANTS OF ACQUIRED QT PROLONGATION

Antiarrhythmic drugs
Quinidine
Procainamide

Disopyramide
Sotalol
Ibutilide
Central nervous system agents
Tricyclic antidepressants
Phenothiazines
Nonsedating antihistamines
Terfenadine
Antimicrobials
Pentamidine
Erythromycin
Trimethoprim-sulfamethoxazole
Chloroquine

From Martyn R, Somberg JC, Kerin NZ. Proarrhythmia of nonantiarrhythmic drugs. *Am Heart J* 1993;126:201–205, with permission.

Delayed After-Depolarizations

Delayed after-depolarizations arise from the repolarized membrane during phase 4. If their amplitude is sufficiently large, the threshold potential is attained and one or more triggered beats result. The reduction of the membrane potential during delayed after-depolarizations may also result in Na^+ channel inactivation and a slowing of conduction. Their amplitude is enhanced by rapid stimulation. This may be a basis for the observation that arrhythmias dependent on delayed after-depolarizations show overdrive acceleration. Delayed after-depolarizations occur in states of Ca^{2+} overload. Increases in internal [Na^+] (e.g., by Na^+/K^+ inhibition) can decrease Ca^{2+} extrusion by the Na^+/Ca^{2+} exchanger and produce Ca^{2+} overload. Delayed after-depolarizations may also occur in normal fibers (i.e., those of the mitral valve leaflet and the coronary sinus) during heightened sympathetic stimulation.

Two ionic mechanisms of delayed after-depolarizations have been proposed. In states of Ca^{2+} overload, the release of Ca^{2+} from the sarcoplasmic reticulum becomes oscillatory. The increase in cytoplasmic [Ca^{2+}] activates a nonspecific inward current carried by cations. The second potential mechanism of delayed after-depolarization is an inward current generated by the Na^+/Ca^{2+} exchanger. Both mechanisms may be operative *in vivo*. Digitalis toxic arrhythmias of certain catecholamine-sensitive and ischemia reperfusion arrhythmias are widely believed to be dependent on delayed after-depolarizations. The response of some of these arrhythmias to rapid stimulation and Na^+ and Ca^{2+} channel blocking drugs supports this proposed mechanism.

REENTRY

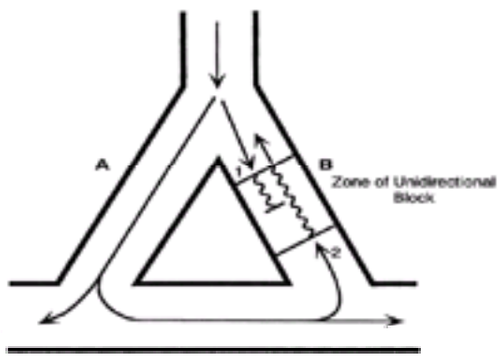
Definition

Following initiation of the cardiac impulse in the sinus node, the wave of depolarization activates the atria, AV node, bundle of His, bundle branches, and ventricles in a sequential manner before being extinguished through encountering recently excited refractory tissue or the anatomic and electrically inexcitable boundaries of the fibrous mitral and tricuspid valve annuli. Since the refractory periods of atrial and ventricular muscle are long (180 to 300 ms) and conduction velocity is rapid, reactivation of recently excited tissue during a single cardiac impulse is normally prevented. Sufficient time must elapse (electrical diastole) to allow recovery of tissue from refractoriness before the sinus node activation can reexcite the heart. However, if a group of muscle fibers fails to be initially activated during a wave of depolarization, they may recover from refractoriness sufficiently early to allow the same wave of depolarization to excite them in a retrograde direction. This phenomenon is known as *reentry*.

Mines (26) proposed three criteria for implicating reentry as the basis for an arrhythmia: (a) demonstration that a region of unidirectional block is necessary for tachycardia initiation; (b) observation that the wave of excitation travels in one direction around the pathway, returns to its site of initiation, and then continues to propagate around the same pathway; and (c) termination of tachycardia by cutting the circuit at a single point.

Requirements for Reentrant Excitation

A basic property of all forms of reentry is that the cardiac impulse is prevented from traveling along its normal course by encountering a region of transient or permanent unidirectional conduction block. The impulse must therefore deviate along an alternative pathway. If conduction time down the alternate pathway is sufficiently slow, an opportunity may arise for the impulse to reenter and excite the previously refractory tissue proximal to the region of unidirectional block, after it has recovered excitability. This schema is illustrated in the simplified circuit of classical reentry depicted in eFigure 58.0.6. The requirements for initiation and maintenance of reentrant excitation are well established and include (a) a region of transient or permanent unidirectional conduction block, (b) a pathway (substrate) over which the impulse may propagate, (c) sufficiently slow conduction within the reentrant circuit to allow recovery of excitability and reexcitation of tissue proximal to the site of unidirectional block, and (d) triggering factor(s) that invoke the necessary electrophysiologic milieu for initiation of reentry.



***e*FIGURE 58.0.6** Classical anatomic reentrant circuit illustrating the requirements for unidirectional block and slow conduction. A premature impulse encounters an area of depolarized myocardium in pathway B, where it blocks (1). The impulse then proceeds in the anterograde direction down pathway A before returning to conduct slowly through the previously depolarized region retrogradely (2). If retrograde conduction through this zone of unidirectional block is slow enough to permit recovery of excitability in proximal tissues, sustained reentry may occur. (From Hoffman BF, Rosen MR. Cellular mechanisms for cardiac arrhythmias. *Circ Res* 1981;49:1–15, with permission.)

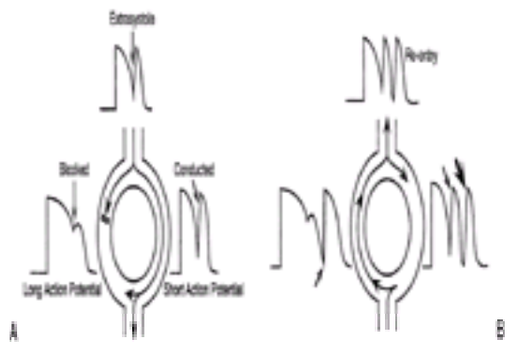
Unidirectional Block

Transient or permanent unidirectional block may arise from functional changes in the active membrane properties that determine excitability and refractoriness of cardiac tissue, nonuniformities of tissue architecture both physiologic and pathologic that influence cardiac conduction, or an interaction between both elements.

Functional Determinants of Unidirectional Block

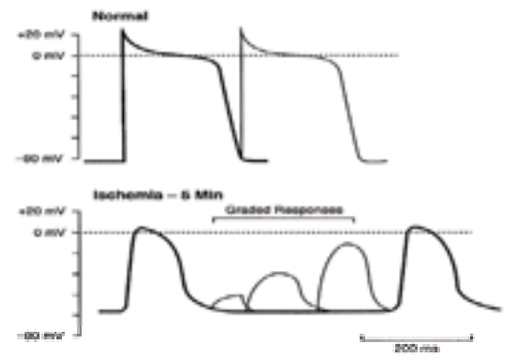
Heterogeneous Recovery of Excitability. The refractoriness of atrial, ventricular, and His-Purkinje cells is determined by the prevailing availability of Na^+ channels for excitation and the ability of the cell membrane to depolarize to threshold voltage required for Na^+ channel activation. Normally, the time course of recovery of excitability closely parallels that of action potential repolarization such that the cell is fully excitable as membrane potential returns to its resting level of approximately –80 mV. However, there is a degree of physiologic heterogeneity or dispersion of APD and hence refractoriness. This dispersion of refractoriness, defined as the difference between the longest and shortest refractory periods, is in the order of 30 to 40 ms in both atrial and ventricular tissue (27,28). Under normal circumstances, this degree of inhomogeneity is insufficient to result in unidirectional conduction block. If, however, a critically timed premature depolarization occurs, Allessie et al. have shown that unidirectional block and sustained reentry can be initiated in atrial muscle at sites on the border between regions with only small differences in refractory periods (less than 20 ms) (28). The mechanism by which a critically timed premature depolarization may produce unidirectional block and initiate reentry is illustrated in eFigure 58.0.7. Premature stimuli are frequently responsible for the initiation of clinical reentrant tachycardias such as supraventricular tachycardia and

monomorphic ventricular tachycardia complicating myocardial infarction and are used to induce these arrhythmias during diagnostic electrophysiologic studies.



***e*FIGURE 58.0.7** Initiation and maintenance of reentry in a ring model based on dispersion of action potential duration and refractoriness. Action potentials from different sites within the circuit are depicted. **A:** An extrasystole blocks after encountering tissue with long action potential durations and hence refractoriness. It is able to conduct through the alternate pathway where action potential duration and refractory periods are shorter. **B:** The impulse conducts retrogradely through the previously blocked pathway, which has now repolarized and recovered excitability. It is then able to reexcite tissue in the site of origin of the original extrasystole and potentially recirculate around the same pathway to cause reentry. (From Wit AL, Hanse MJ. *The ventricular arrhythmias of ischemia and infarction: the electrophysiological mechanisms*. Mount Kisco, NY: Futura, 1992, with permission.)

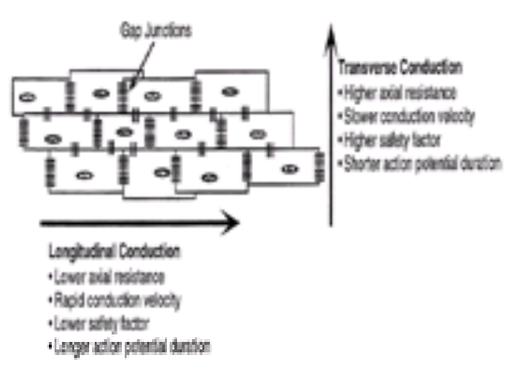
Regional inhomogeneity in refractoriness, and hence the propensity for unidirectional block, may be increased by pathologic processes including myocardial ischemia, reperfusion, and infarction. Another feature of the electrophysiology of ischemic tissue that may increase the likelihood of unidirectional block is prolongation of refractoriness well beyond the time of full repolarization, a phenomenon termed *postrepolarization refractoriness*. Impulses that encounter ischemic tissue within this period of prolonged repolarization only generate action potentials with low amplitude and slow upstroke velocities (graded responses) that conduct slowly or fail to propagate, thus creating localized regions of functional conduction block that may predispose to reentry (eFig. 58.0.8).



***e*FIGURE 58.0.8** Slow conduction of “graded responses” during ischemia due to postrepolarization refractoriness. Schematic representations of the ventricular action potential under normal conditions (*upper panel*) and after 5 minutes of ischemia (*lower panel*). In the normal cell, recovery of excitability coincides with complete repolarization. During ischemia, recovery of excitability is delayed until well after full repolarization (postrepolarization refractoriness). Impulses falling within this prolonged refractory period elicit time-dependent graded responses with decreased maximum upstroke velocity and conduction velocity. (From Whalley DW, Wendt DJ, Grant AO. Effects of acute ischemia and reperfusion and their role in the genesis of cardiac arrhythmias. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia: mechanisms, diagnosis and management*. Baltimore: Williams & Wilkins, 1995:109–130, with permission.)

Structural Determinants of Unidirectional Block: Myocardial Architecture

Although, at a macroscopic level, rapid conduction of an impulse through the cardiac syncytium appears to be a continuous process, at a microscopic level, conduction is inherently discontinuous due to nonuniformity in the distribution of gap junctions, and hence axial resistance (17). In ventricular and His-Purkinje cells, gap junctions are distributed in greatest density at the ends of cells to facilitate preferential conduction in the longitudinal direction, whereas gap junctional density and hence conduction velocity are typically three to five times slower when an impulse excites fibers in the transverse direction (17,29). In addition, the direction of activation also influences APD and refractoriness, with APD being longer during longitudinal propagation compared with transverse propagation (30). This dependence of conduction velocity and refractoriness on fiber orientation is termed *anisotropy*, and under certain circumstances the anisotropic properties of the myocardium can produce the necessary unidirectional block and slow conduction required for reentry (31). In a systematic study of anisotropic reentry in canine atrial muscle, Spach et al. (17) found that unidirectional block was more likely to occur in the longitudinal direction of fiber orientation, possibly due to the larger requirements for excitatory current (lower safety factor) resulting from a lower axial resistance and a greater membrane capacitance compared with the higher resistance and safety factor encountered with transverse propagation. A critically timed impulse may fail to conduct in the longitudinal direction but propagate slowly in the transverse direction, thereby allowing time for recovery from block and reentrant excitation. The electrophysiologic characteristics of anisotropic conduction are illustrated schematically in eFigure 58.0.9. A variety of disease processes, including chronic ischemia and hypertension, as well as the normal aging process, may increase the density of collagen in the extracellular matrix resulting in loss of side-to-side gap junctional coupling between myocytes (32,33). This process, termed *microfibrosis*, changes the electrical properties of involved myocardium from those of uniform to nonuniform anisotropy and is thought to result in a greater propensity to reentrant arrhythmias such as atrial fibrillation (32) and ventricular tachycardia following myocardial infarction (33,34).



***e*FIGURE 58.0.9** Characteristics of anisotropic conduction in the normal working myocardium. Uniform anisotropy: Myocytes are densely packed and electrically coupled via gap junction channels located within intercalated disks. The density of gap junctions is greater at end-to-end intercellular connections than at regions of side-to-side cell apposition. This results in lower axial resistance and more rapid conduction in the longitudinal direction than in the transverse orientation.

Slow Conduction

Unidirectional block is usually insufficient to initiate reentry without the coexistence of conduction slowing. Under physiologic conditions the prime determinant of the magnitude of I_{Na} is the availability of Na^+ channels. Any factor that decreases their availability potentially produces conduction slowing. Such factors include depolarization of the resting membrane potential, which occurs during acute ischemia and during hyperkalemia, a shift in the voltage dependence of Na^+ channel

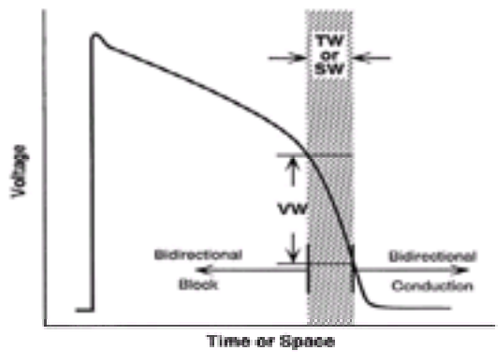
inactivation to more hyperpolarized potentials, and premature stimulation of tissue before full repolarization.

The zone of slow conduction within a reentrant circuit may also arise from tissues that normally display slow upstroke and Ca^{2+} channel–dependent action potentials such as the AV node and sinus node. An example is the role of slow conduction with the AV node in initiating and sustaining orthodromic reentrant tachycardia in patients with accessory AV bypass tracts.

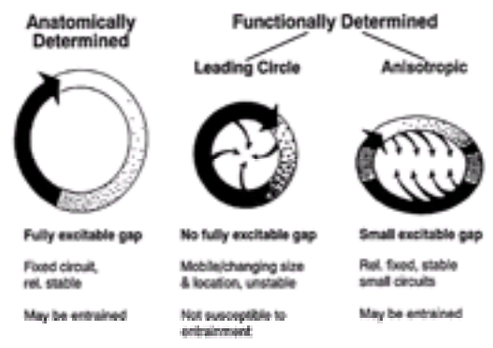
Conduction velocity is also influenced by passive membrane properties, the resistive elements that determine the ease and rate of axial propagation of local circuit current along the cell membrane and between electrically coupled cells. As described previously, the anisotropic properties of cardiac muscle arising from nonuniform spatial distribution and density of gap junctions may result in a significant increase in intercellular resistance and conduction slowing as impulses move transversely across muscle fiber bundles. This slow conduction occurs without any decrease in the maximum upstroke velocity of the propagating action potential. In addition to these microarchitectural determinants of conduction velocity, intercellular coupling resistance is regulated by dynamic changes in the conductance of the gap junctional channels. Elevation of intracellular Ca^{2+} and intracellular acidosis, for example, during acute ischemia, decreases gap junctional conductance and slows conduction velocity (35,36). If ischemia continues for a sufficient time, cell-to-cell uncoupling may occur, an event that has been demonstrated to temporally correlate with the onset of ventricular arrhythmias in the ischemic porcine heart model (37).

Characteristics of the Initiation, Maintenance, and Termination of Reentry

Experimental mapping studies (38,39) and theoretical computer modeling (40,41,42 and 43) have provided important insights into the factors that initiate, perpetuate, and terminate reentry. The ease by which reentry can be initiated may be described by the concept of the *vulnerable window*, defined as the time, voltage window, or both during the refractory period of the propagating action potential (repolarization) in which unidirectional block and reentry may be induced (43). The concept is illustrated in *e*Figure 58.0.10. Premature impulses applied earlier in the refractory period than the vulnerable window undergo complete bidirectional block, whereas those occurring after the vulnerable window propagate without block. The vulnerable window can be widened, and reentry facilitated by factors that (a) increase the spatial inhomogeneity of refractoriness, and (b) decrease cellular coupling via gap junctions. Maintenance of reentrant excitation depends on the critical relationship between the conduction velocity (CV) of the leading edge or “head” of the circulating wavefront, and the refractory period (RP) of tissue in the “tail” of the circuit (eFig. 58.0.11). This relationship is expressed as the wavelength of the propagating impulse, *l*, which is the product of the conduction velocity and refractory period: $l = CV \times RP$ (39). Reentry can only occur if the head of the circuit continuously encounters tissue that has recovered, at least partially, from its refractory period. If it collides with fully refractory tissue in the tail, the circuit would be extinguished. The wavelength of reentry must therefore be shorter than or equal to the path length of the circuit for sustained reentry to occur (i.e., l less than or equal to path length). Using this concept, stability of a reentrant circuit is promoted by any factor that (a) decreases l, such as shortening of refractoriness or decreasing conduction velocity; or (b) increases the length of the circuit. Conversely, the probability of termination of reentry is increased by factors that enhance conduction velocity, prolong refractoriness within the circuit, or both. The *excitable gap* is defined as the portion of a reentrant circuit that has recovered excitability and that can potentially be penetrated by an appropriately timed premature stimulus to modify or terminate reentry (44). The gap may be fully excitable if tissue has recovered fully from refractoriness, or partially excitable if tissue remains relatively refractory due to incomplete recovery of Na^{+} channels from time and voltage-dependent inactivation. The presence and size of the excitable gap reflect the margin of safety for propagation within the circuit and are important distinguishing features between the various types of reentry mechanisms to be discussed subsequently. Beat-to-beat oscillations in the cycle length of a reentrant arrhythmia are frequently seen in experimental models and clinically and may herald the termination of reentry (43,44 and 45). Theoretical modeling has concluded that these oscillations represent a dynamic interaction between the excitatory head of the wavefront and the refractory tail and that they facilitate termination by premature extrastimuli (43).



***e*FIGURE 58.0.10** The vulnerable window (VW) for unidirectional block and reentry: schematic representation of the VW within the refractory period of a propagating action potential. The VW may be considered as a voltage window, time window (TW), or spatial window (SW) during which unidirectional block may arise. Impulses arriving earlier or later in repolarization than the VW will either block or conduct bidirectionally, thereby precluding reentrant excitation. (From Rudy Y. Reentry: insights from theoretical simulations in a fixed pathway. *J Cardiovasc Electrophysiol* 1995;6:294–312, with permission.)



***e*FIGURE 58.0.11** Characteristics of the major types of reentrant excitation.

Types of Reentrant Excitations

Anatomic Reentry

The earliest experimental model of reentry described a simple ring of circus movement in which the wavefront propagated around an anatomically defined circuit with a central anatomic obstacle providing a zone of conduction block. In this classical form of reentry, the length and location of the pathway of reentry are relatively fixed. Anatomic reentry is characterized by the presence of an excitable gap that enables penetration of the circuit by premature stimuli occurring spontaneously or by programmed electrical stimulation and overdrive pacing. Introduction of single premature stimuli or pacing maneuvers during anatomic reentry may terminate, reset, or produce entrainment of the tachycardia, whereby with rapid overdrive pacing the circuit is penetrated and the tachycardia rate is accelerated to the pacing rate without termination (46). If the wavelength of reentry is significantly shorter than the path length of the circuit, there will be a significant fully excitable gap. If, however, the wavelength is only slightly shorter than path length, the excitatory head will encounter tissue in its relative refractory period, conduction velocity will be slowed, and there will only be a small gap of partially excitable tissue. Class III antiarrhythmic drugs, by prolonging APD, may terminate reentrant tachycardia by extinguishing the excitable gap, particularly in arrhythmias in which this gap is small (47). Features of anatomic reentry are illustrated in *e*Figure 58.0.11.

Clinical examples of arrhythmias believed to be based on anatomic reentry include orthodromic AV reentrant tachycardia (ORT) using an accessory pathway, AV junctional reentrant tachycardia, human type 1 atrial flutter, and some forms of ventricular tachycardia (48).

Functional Reentry

In functional reentry, the circuit is not constrained or determined by anatomic obstacles, but is defined by dynamic heterogeneities of electrophysiologic properties in

the involved tissue. There are two well-described forms of functional reentry, leading circle and anisotropic reentry (eFig. 58.0.11).

Leading Circle Reentry. Using isolated rabbit atrial myocardium, without any central anatomic obstacle, Allessie et al. (39) initiated sustained circus movement reentry with premature stimuli. In this leading circle model, the circulating impulse rotates around a central core of functionally refractory tissue. The tissue within this core is maintained in a state of refractoriness by constant centripetal bombardment from the circulating wavefront. The leading circle is the smallest possible pathway in which the propagating wavefront has enough excitatory efficacy to depolarize tissue ahead of it in its relative refractory period (39). The length of the reentry circuit equals the wavelength of the impulse ($CV \times RP$), and as a result, there is generally no fully excitable gap. Since the head of the advancing wavefront is constantly encountering its tail in a state of relative refractoriness, conduction velocity is slowed. Path length is therefore not anatomically determined but is governed by the electrophysiologic properties of the involved tissues. The circuit length is prolonged and tachycardia is slowed by an increase in refractoriness or a decrease in stimulating efficacy of the advancing wavefront. In contrast to anatomic reentry, circuits based on leading circle reentry are often unstable, and their size and location are continuously changing. The lack of a fully excitable gap renders this form of reentry less susceptible to reset, entrainment, and termination by premature stimuli and pacing maneuvers. The characteristics of leading circle reentry are summarized schematically in eFigure 58.0.11.

Based on high-density mapping studies in animal models and human myocardium, leading circle–type functional reentry is thought to be an underlying mechanism for atrial and ventricular fibrillation and at least some of the ventricular arrhythmias associated with acute ischemia (36,49).

Anisotropic Reentry. The functional characteristics underlying anisotropic reentry are directional differences in axial resistance arising from variation in the degree of cell-to-cell electrical coupling via gap junctions, rather than depression of action potential upstroke or resting membrane potential. Anisotropic reentry is typically initiated by a premature stimulus that blocks in the direction of propagation parallel to the long axis of the cells, then propagates slowly in the transverse direction of fiber orientation due to high axial resistance. There is a central line of functional block parallel to the long axis of fibers, and circuits are typically ellipsoid reflecting the directional differences in conduction velocity (eFig. 58.0.11). They are usually relatively stable circuits in size, shape, and location and have an excitable gap allowing entrainment and termination by overdrive pacing.

Studies based on the canine model have demonstrated that anisotropic reentry may be responsible for sustained ventricular tachycardia arising from the epicardial border zone region of healed myocardial infarcts (34,50). Although indirect evidence suggests nonuniform anisotropy as a mechanism of sustained monomorphic ventricular tachycardia in chronic human myocardial infarction, this has yet to be firmly established (34).

Spiral Wave Reentry. The classical schematic representations of functional reentry illustrated in eFigure 58.0.11 depict circular or ellipsoid circuits in two dimensions. Computer simulations and high-resolution optical mapping experiments using canine ventricular and atrial muscle have shown that functional reentrant circuits may actually propagate intramurally as drifting or migrating spiral waves (rotors) (42,51,52 and 53). This theory proposes that at points of critical curvature in the reentrant wavefront, an increased current load imposed by transverse conduction results in failure of propagation. The fundamental difference between this form of reentry and the leading circle mechanism is that the core of spiral waves is potentially excitable by virtue of having well-polarized maximum diastolic potentials, but is not excited, whereas the core of leading circle reentry is inexcitable. Indeed, these studies, together with reassessment of the earlier experiments of Allessie et al. (39), have cast doubts on the leading circle hypothesis of functional reentry and led some investigators to postulate that spiral waves are the primary mechanism of functional reentry (54).

Interaction of Enhanced Automaticity and Reentrant Mechanisms in Arrhythmogenesis: The Evolving Paradigm of Atrial Fibrillation

Although we have discussed abnormal automaticity and reentry as separate mechanisms of arrhythmogenesis, it is clear that both may interact to contribute to initiation and maintenance of a tachyarrhythmia. This is perhaps most clearly illustrated by the syndrome of focal atrial fibrillation in which rapidly discharging foci generally arising from the pulmonary veins (abnormal automaticity) trigger sustained multiple wavelet atrial fibrillation (functional reentry) (55). Furthermore, frequent or sustained episodes of tachyarrhythmia may modify the electrophysiologic properties of cardiac myocytes so as to facilitate the likelihood of further initiation of the tachyarrhythmia: the phenomenon of electrical remodeling (56). In both animal models of atrial fibrillation and studies in humans, atrial fibrillation is associated with shortening of atrial refractoriness, diminished rate adaptation of APD and refractoriness, increased dispersion of atrial refractoriness, and a decrease in conduction velocity within the atria (57), changes that are known to be profibrillatory by reducing the wavelength for reentry. The ionic basis for electrical remodeling and the intracellular signaling pathway(s) involved are under intense investigation and appear to involve downregulation of I_{CaL}, I_{to}, and I_{na} (56,58).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Over the past decade, the major thrust in cardiac electrophysiology research has been in the area of membrane biophysics. This has permitted the quantitative analysis of all the membrane currents that contribute to the action potential. Several molecular defects of membrane ion channels have been identified in patients with the congenital long QT syndrome, Brugada syndrome, and heart block. Identifying the polygenetic basis of common arrhythmias will pose a greater challenge. A small but significant amount of work has been done in the systematic reconstruction of the action potential, normal and abnormal impulse generation, and conduction. A major drawback in systematically reconstructing action potential is that model parameters for the membrane currents have been obtained from different preparations under varying experimental conditions. This compromises a thorough integration of the data available. Nevertheless, there is sufficient information to reconstruct the propagating action potential at the microscopic level. Greater effort should be applied to analyze and reconstruct arrhythmias at the macroscopic level. This is particularly true in the case of arrhythmias that occur in the healed myocardial infarct and in the fibrotic aging atrium. In the former, the normal electrophysiologic properties of the cells surviving in the scarred areas are a clear indication of the importance of abnormal structure. Here, the ion channels do not appear to be the problem. It is unlikely that ion channel-blocking drugs will favorably influence normal cells surviving in the scar and yet have little effect on normal cells in the remainder of the heart. There is a clear need to focus research on the prevention of scarring and fibrosis following insults such as myocardial ischemia and abnormal hypertrophy.

Atrial fibrillation is the most common sustained arrhythmia observed clinically. In the past, it had not enjoyed its rightful place as an important and fruitful area for basic and clinical investigation. More recent studies have demonstrated remodeling of the electrophysiologic properties of the atrium after brief periods of atrial fibrillation. The refractory period of the atrium is shortened by atrial fibrillation. This “electrical remodeling” favors perpetuation of atrial fibrillation. Therefore, more urgent efforts should be made to restore normal sinus rhythm. This has to be balanced against the likelihood that sinus rhythm will be maintained in the face of persistent factors that originally precipitated the arrhythmia.

The study of cardiac arrhythmias from the level of single ion channels to the integrated heart under autonomic control remains a fruitful and exciting area of research, with many implications to patient care. As newer techniques are applied to the study of the problem, significant advances can be anticipated over the next decade.

THE FUTURE

Major research efforts in cardiac arrhythmia mechanisms over the past decade have focused on the molecular basis of arrhythmias. The uncommon inherited arrhythmias that result from single gene defects have been analyzed. Significant advances should be made in determining the polygenetic mechanisms of common arrhythmias such as atrial fibrillation. The combination of molecular biology and membrane biophysics will permit a realistic reconstruction of the critical components of ion channels that control gating and ion permeation. This will permit the development of more selective and effective drugs. Drug therapy will also remain an important complement to physical methods of arrhythmia prevention and treatment such as ablation and implantable devices.

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ELECTROCARDIOGRAPHY

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QRS Complex
Q Wave
ST Segment
QT Interval
T Wave
U Wave
Electrical Alternans
Ventricular Hypertrophy
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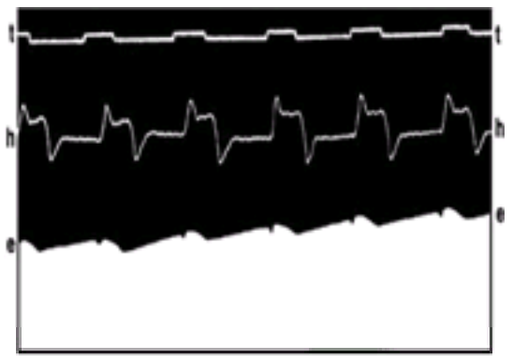
HISTORICAL PERSPECTIVE

The first demonstration of human cardiac activity was made during a congress of physiologists in London by Augustus Waller, who in May 1887 published the first single-lead electrocardiogram (ECG) (1). Waller recorded the electrical activity of the heart from a chest lead with a capillary electrometer (a glass tube filled with mercury) (2). When the electrometer was placed on the body's surface, the current was transmitted from the chest to the mercury column, which expanded or contracted. This movement could be observed only through a microscope and had to be projected onto photographic paper (eFig. 59.0.1).



***e*FIGURE 59.0.1** Reproduction of the first recording of an electrocardiogram by Waller. The electrical activity of the heart is recorded by movement on the surface of a mercury column (*e*). Chest wall movement is recorded by a mechanical lever (*h*). Time is indicated by *t*. [From Waller AD. A demonstration in man of electromotive changes accompanying the heart's beat. *J Physiol (Lond)* 1887;8:229–234, with permission.]

The pioneer of clinical electrocardiography, however, was Willem Einthoven. Einthoven had a background in physics and mathematics and had been present during Waller's demonstration (3). To refine Waller's concept, Einthoven worked in his laboratory in the Netherlands for several years, first with the electrometer and later with the string galvanometer (2). The galvanometer was an instrument developed in 1897 by Clément Ader for telegraphic transmissions. It reduced the distortion of the electrometer because it consisted of a thin wire extended between the poles of a magnet, but it still required the use of both a microscope and photographic paper. Einthoven presented his idea of applying the galvanometer to the recording of the cardiac electrical activity in 1903 (2). He also coined the term *elektrokardiogramm* in German (the dominant language at the time for scientific publications) and labeled the recorded waveforms P, Q, R, S, T, and U to differentiate them from the original—but incomplete—A, B, C, and D described by Waller. The selection of letters from the last part of the alphabet may have been related to a geometricians' convention at the time (which dictated that designations for curved lines should begin at the letter *P*) (2). Einthoven also described numerous abnormal findings and created the bipolar limb lead system known as *Einthoven's triangle* (2).

This progress was observed skeptically by Waller, who in 1911 expressed doubts on the clinical value of electrocardiography (4). The early electrocardiograph was extremely unwieldy and difficult to operate. It required a continuous-flow water jacket for cooling the electromagnet. The camera and the optical system were an integral part of the apparatus, and an arc lamp projected the shadow of the string onto photographic paper. The electrodes were large bowls of saline solution in which the subject immersed his or her hands or feet. The machine occupied two rooms, and five people were required to operate it (5).

Only after many years of these initial efforts did the ECG come to be regarded as a potentially useful tool in clinical practice (6). Several companies in Europe and in the United States initiated the commercial manufacture of electrocardiographs. The first table-model electrocardiograph assembled in London was leased to Sir Thomas Lewis in 1911. Lewis worked intensively in recording both normal and abnormal cardiac activity, and provided a strong impulse to clinical electrocardiography. His work was pivotal in shifting the available knowledge from the laboratory to the clinical field. Keith and Flack had reported on the existence of the sinus node in 1907, and Lewis ascribed the origin of the cardiac impulse to it. He also proved the origin of ectopic tachycardias, studied atrial fibrillation, and introduced the concept of aberrant conduction. Lewis published several books, including the first textbook of electrocardiography (3).

During World War I, Lewis had a prominent disciple named Franklin Wilson, the youngest of a group of American cardiologists selected to work in England with him. At the end of the war Wilson returned to the University of Michigan at Ann Arbor and obtained a string galvanometer. He worked with the galvanometer under the hospital stairwells, the only space appropriate for the large apparatus, which was smaller than the original model but still needed a wheeled trolley for transportation. Wilson's investigations with these limited resources resulted in the theory of the ventricular gradient and in detailed descriptions of the bundle branch blocks (7). Perhaps Wilson's best known contribution is his creation of a unipolar chest lead system connected to a central electrode (8).

By 1920, myocardial infarction had been recognized as an entity because of the cases reported by Herrick (9) and Pardee (10). Although Einthoven was awarded the Nobel Prize in 1924 for his contribution, the relevance of electrocardiographic information to clinical cardiology was not yet fully appreciated. Wilson himself published a paper on disorders of the heartbeat in 1936 with no mention of electrocardiography (11).

Subsequent improvements to the original galvanometer led to further reduction in its size and to the current electronic technology. The first portable model was introduced in 1926, and with it Lewis' vision of electrocardiography as a standard diagnostic tool became a reality (5).

At that time, two distinguished electrocardiographers and investigators, Langendorf and Pick, were attending medical school in Prague. Both physicians made their main scientific contributions later in the United States by perfecting the methodology of deductive reasoning for complex cardiac arrhythmias (12). In 1948—long before the introduction of clinical electrophysiologic studies—Langendorf brilliantly deciphered a pivotal mechanism of arrhythmias and coined the term *concealed conduction* to describe it. As Fisch has pointed out, an understanding of this concept is key to the analysis of most cardiac disturbances (12).

The "post-Wilson era" that began in the mid-1950s has witnessed less radical, but still important, developments in electrocardiography. By means of ingenious clinical-pathologic-electrocardiographic correlations, investigators from different parts of the world elucidated the ECG manifestations of the many cardiac conditions. Outstanding contributors include Lepeschkin, Surawicz, and Castellanos in the United States; Sodi-Pallares and Cabrera in Mexico City; Rosenbaum in Buenos Aires; Schamroth in Cape Town; and Durrer and Wellens in the Netherlands. The introduction of invasive clinical electrophysiologic studies only confirmed in most cases the deductions of these pioneers (13).

In more recent years, emphasis in electrocardiographic research has shifted to the study of dynamic patterns inherent in certain parameters (especially ventricular repolarization) with the aid of the ambulatory recording devices first introduced by Holter in 1961 and then by newer, potent digital storage and analysis techniques. The advent of effective myocardial reperfusion therapies has renewed interest in the electrocardiographic manifestations of the acute ischemic syndromes. Finally, attempts to improve the resolution of standard electrocardiography have relied on increasing the number of recording electrodes (body surface mapping) and on improving the signal-to-noise ratio of the higher frequency signals by averaging and filtering (signal-averaged electrocardiography). Initial results with these techniques are promising, but their roles in clinical practice are still unclear.

Despite the development of more sophisticated and expensive cardiac diagnostic tests, the standard 12-lead ECG remains an integral part of the clinical evaluation of all cardiac patients, particularly those with ischemic heart disease or rhythm disturbances.

ANATOMIC REFERENCES

The position of the heart within the body determines the "view" of the cardiac electrical activity recorded from any ECG electrode on the body surface. When the patient is in the supine position, the heart is a conical structure that lies relatively horizontally with the atria at its base and the ventricles at its apex (14). Because the heart is rotated over its long axis, the right atrium and ventricle are more anterior than the left chambers, and the right and left sides of the heart are not aligned with the homonymous sides of the body (15,16). Thus, the interventricular septum is almost parallel with the frontal—not the sagittal—plane, and the left ventricular free wall (usually considered a lateral structure) includes nearly 300 degrees of the left ventricular circumference and faces superiorly, posteriorly, and inferiorly (14).

ELECTROCARDIOGRAPHIC RECORDING

The 12 Electrocardiographic Leads

Cardiac electrical activity is recorded through 12 surface leads designated I, II, III, aVR, aVL, aVF, V_1, V_2, V_3, V_4, V_5, and V_6. The electrodes that record the first six points are located on the limbs, whereas leads V_1 to V_6 are recorded from the chest (Fig. 59.1).

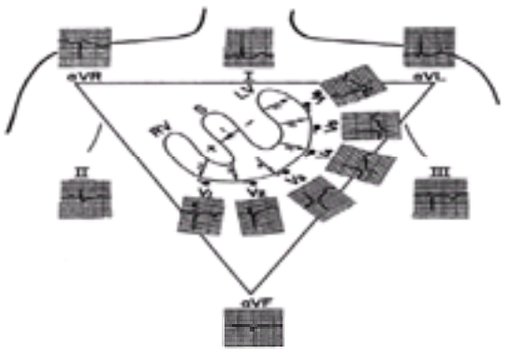


FIGURE 59.1 The standard 12 leads are shown with their recording sites. Both the frontal and the horizontal planes are depicted. Vectors 1 to 7 show the normal sequence of activation of the septum (S) and ventricles from the horizontal plane. LV, left ventricle; RV, right ventricle. (From Gazes PC, ed. *Clinical cardiology: a bedside approach.* Chicago: Year Book, 1983:39, with permission.)

Leads I, II, and III were first used when Einthoven placed recording electrodes on both arms and the left leg to form an equilateral triangle. An additional electrode on the right leg was used for grounding. Leads I to III are bipolar because they record potential differences between two electrodes. For lead I, the left arm electrode is the positive pole and the right arm electrode is the negative pole. Lead II, with its positive pole on the left leg and its negative pole on the right arm, provides a view of the electrical activity along the long axis of the heart. Lead III has its positive pole on the left leg and its negative pole on the left arm. Between leads I, II, and III are 60-degree angles. These wide viewing gaps are filled with the augmented unipolar (aV) leads aVR, aVL, and aVF, which record the electrical activity between the exploring limb electrode and a reference created by connecting the other two limb electrodes together through a 5,000-ohm resistor (Wilson's central terminal) (17). Lead aVF, for example, measures the potential difference between the left leg and the average of the potentials at the right and left arms. The addition of these three aV leads to the triaxial reference system in the frontal plane produces a hexaxial system, with the six leads separated by angles of only 30 degrees. The gap between leads I and II is filled by lead aVR, that between leads II and III by lead aVF, and that between leads III and I, by lead aVL. This provides a perspective of the frontal plane as illustrated in Figure 59.1. The limb leads are presented in the order I, II, III, aVR, aVL, and aVF, which spatially correspond to 0, 60, 120, –150, –30, and 90 degrees, respectively.

The last set of leads introduced into clinical practice were the six unipolar precordial leads (V_1 to V_6) (8). Augmentation is not necessary because the recording electrodes are close to the heart. Wilson's central terminal provides their negative poles, whereas the sites of the exploring electrodes are determined by bony landmarks on the anterior and left lateral aspects of the precordium (*e*Table 59.0.1, Fig. 59.2). The angles between the six transverse plane leads are slightly smaller than those between the six frontal plane leads. Lead V_1 is located where the extension of the heart short axis (i.e., a perpendicular to the interatrial and interventricular septa) intersects with the precordial body surface. Because V_1 provides a right anterior to left posterior view, it distinguishes better between left and right cardiac electrical activity than does a lead providing a right lateral to left lateral view (such as lead I).

***e*TABLE 59.0.1** PLACEMENT OF PRECORDIAL LEAD ELECTRODES

V_1	Fourth intercostal space, right sternal border
V_2	Fourth intercostal space, left sternal border
V_3	Equidistant between V_2 and V_4
V_4	Fifth intercostal space, at the midclavicular line
V_5	Anterior axillary line, at the level of lead V_4
V_6	Midaxillary line, at the level of lead V_4
V_7	Posterior axillary line in the fifth intercostal space
V_8	Midscapular line
V_9	Left paraspinal border
V_3R	Equidistant between V_1 and V_4R
V_4R	Right midclavicular line, fifth intercostal space
V_5R	Right anterior axillary line in the same horizontal plane as V_4R
V_6R	Right midaxillary line in the same horizontal plane as V_4R

Note: Lead V_2R is the same as V_1.

FIGURE 59.2 Location of the precordial lead electrodes. (From The electrocardiogram: fundamentals. In: Goldschlager N, Goldman MJ, eds. *Principles of clinical electrocardiography.* Stamford, CT: Appleton & Lange, 1989:1–10, with permission.)

Limitations of the Current 12-Lead System

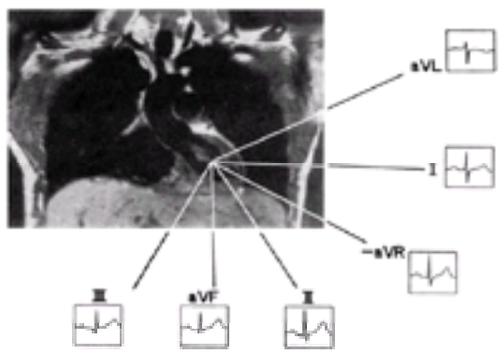
Poor Orthogonality and Redundancy

A set of three ECG leads is considered orthogonal if their lead vectors are at 90-degree angles with each other, which permits the accurate detection of the onset and offset of ECG waveforms in all spatial directions. Orthogonality is meager in the current 12-lead system because the limb leads record poorly the sagittal and anteroposterior components of cardiac activity, whereas precordial leads miss the vertical components (18).

The current 12-lead system provides for superfluous recording points. Estimates are that only eight components of the standard ECG capture independent information on cardiac electrical activity (19).

Inappropriate Lead Sequencing and Gap in the Frontal Plane

The display of the precordial leads represents an orderly progression in the horizontal plane. Leads V_1 to V_6 faithfully show the spatial sequence of electrical activation (from the basal right ventricle to the midposterior left ventricular wall). The limb leads, instead, depict a disordered spatial sequence. Leads I, II, III, aVR, aVL, and aVF correspond spatially to 0, 60, 120, –150, –30, and 90 degrees, respectively. Such an array has been consecrated by usage but is counterintuitive. If an analogous distribution were selected for the horizontal plane, the precordial leads would be reordered as V_2, V_4, V_6, $–V_3$, V_1, and V_5 (20). This would considerably compromise the ability of the interpreter to rapidly understand the electrical phenomena taking place in that plane. A more logical sequencing for the limb leads would be aVL, I, –aVR, II, aVF, and III (or –30, 0, 30, 60, 90, and 120 degrees); the inclusion of a negative aVR would allow recording or ECG phenomena at –30 (eFig. 59.2.1).



***e*FIGURE 59.2.1** The panoramic display of the 12-lead electrocardiogram in an ideal sequential spatial order. (From Anderson ST, Pahlm O, Selvester RH, et al. Panoramic display of the orderly sequenced 12-lead ECG. *J Electrocardiol* 1994;27:347–352, with permission.)

Special Leads

Some leads are not considered part of the standard ECG but are useful in specific circumstances. Posterior leads (V_7, V_8, and V_9) (eTable 59.0.1) increase the ECG sensitivity for injury in the posterior wall (21). Right precordial leads (V_3R, V_4R) (eTable 59.0.1) are particularly useful for the diagnosis of right ventricular infarcts and some congenital abnormalities (22). A routine use of the negative aVR (at 30 degrees) would add useful information to the standard ECG, and it would be less likely to be overlooked during routine ECG interpretation (23,24).

The P wave is not always seen distinctly in the 12-lead ECG, but it may be easily identified with the use of special leads. Distinct P waveforms can be seen by placing the right and left arm leads in various chest positions (if possible, parallel to the vector of atrial depolarization) while recording lead I (Lewis lead). Atrial activity can also be recorded semiinvasively from leads placed in the esophagus because the anterior wall of the esophagus lies against the left atrium. In patients with dual-chamber pacemakers, atrial electrograms can be recorded by telemetry from the pacing electrodes. In patients recovering from cardiac surgery, the placement of temporary epicardial pacing electrodes allows the direct recording of atrial activity.

Electrocardiograph Equipment

Electrocardiographs are calibrated to give a deflection of 10 mm per millivolt (this calibration is usually seen at the beginning or end of the ECG); thus, 1 mm equals 0.1 V. Electrocardiographic paper is graph paper divided in little squares of 1 mm each and larger squares of 5 mm each. The speed of the paper is standardized to 25 mm per second.

Commercial systems provide ECG programs with stereotyped methodologies of measurement. The only ECG limb leads that digital electrocardiographs record are leads I and II; the remaining limb leads are calculated in real time based on the Einthoven law (I + III = II) and using relationships derived from lead vectors for the aV leads. For the calculation of the electrical QRS axis, the entire QRS complex area is used. This is an advantage over the manual QRS-axis estimation, which is based mainly on R-wave measurements.

Modern electrocardiographs use digital technology. Analog data are converted into digital signals that are later processed (25). The use of compression techniques allows storage and subsequent retrieval of serial ECG recordings, as well as remote transmission of electrocardiographic data (e.g., to hand-held computers for “real time” interpretation by a cardiologist) (26). Output data after digital transmission or after retrieval of serial measurements can be compared with input data.

Minute measurement methods (e.g., those for individual waveforms) differ to some extent from one another across ECG programs. This occurs partly because at the time many automated ECG systems were adopted for clinical use, the technical features that are pivotal to produce and process the ECG signal had not been standardized. Some of these features include data compression, storage, and retrieval; filters; sampling rate; and requirements for signal fidelity (25). The existence of such limitations should be considered when ECG automated reports are evaluated and compared.

BASIC PRINCIPLES

Membrane Properties, Action Potential, and Cardiac Activation

Myocytes maintain a potential difference between the interior and the exterior of the cell of approximately –90 mV. This electrical transmembrane gradient depends on the chemical transmembrane gradient, which exists because the concentration of negative ions is higher inside the cell than outside. Such uneven distribution of ions is sustained by a sodium pump housed in the cell membrane (27). Electrical stimuli change the resting potential inside the cell from –90 mV to approximately +30 mV (*depolarization*), and the electrical activity recorded during this process is the *action potential*. Depolarization initiates the propagation of the impulse along both the interior and the exterior of the “polarized” membrane. Thus, the electrical front—which can be represented as a vector—flows from the positively charged (depolarized) to the negatively charged (resting) cells. The earliest ventricular activation occurs in the left side of the septum. The depolarization front then proceeds to the right side of the septum and to the anterior wall, following an inside-out course. Isolated myocytes from endocardium and epicardium have markedly different action potential shapes and durations. This is secondary to differences in the distribution of currents (and channel proteins) among different cardiac layers (28).

Electrical systole continues until the positively charged ions exit the cell, which causes *repolarization* (i.e., restitution of membrane polarity) (27). Atrial repolarization proceeds in the same direction as atrial depolarization, and thus the polarity of the repolarization waveform is opposite to that of depolarization. Ventricular repolarization, however, follows an inverted pattern. The process begins in the epicardium and ends in the endocardium, and therefore the polarity of the repolarization waveform is the same as that of depolarization.

This behavior is the basis for the concept of *ventricular gradient*. The ventricular gradient measures the magnitude of the integral between the QRS complex and the T wave (i.e., between depolarization and repolarization). If all ventricular action potentials had the same magnitude and duration, the ventricular gradient would be zero (29). In the mammalian heart, however, the duration of the repolarization forces is greater in some areas of the ventricles than in others. The resultant mean QRS vector and mean T vector form a narrow angle (27). Repolarization has not yet been mapped simultaneously in all layers of the human heart, but evidence suggests that the areas that depolarize last are the first in completing repolarization (30). The basis for this particular behavior is not known; theories regarding temperature or other gradients have been refuted.

Cardiac Impulse Formation and Conduction

The heart can be considered as a dipole with a positive and a negative charge. At any given time, cardiac cells are in various stages of activation (i.e., depolarization and repolarization). The formation (i.e., pacemaking) and timely conduction of an electrical impulse depends on strategically placed cardiac cells. These cells are arranged in nodes, bundles, and branching networks of fascicles (Purkinje cells). They lack contractile capability but are able to achieve spontaneous electrical impulse formation (act as pacemakers) and to alter the speed of electrical conduction. The intrinsic pacemaking rate is most rapid in the specialized cells in the sinus node

(located in the right atrium) and slowest in the specialized cells in the ventricles. After leaving the sinus node, the wavefront travels through the right and left atria in a centrifugal manner. On arrival at the atrioventricular (AV) node, the impulse is delayed, which allows for a sequential, rather than simultaneous, contraction of the ventricles after the atria. The intraventricular conduction network includes the common bundle of His and its right and left bundle branches, proceeding along the septal surfaces to their respective ventricles. The left bundle branch is a diffuse structure that fans broadly over the ventricular septum toward the two papillary muscles of the mitral valve (31). Two divisions of the left bundle branch can usually be distinguished; they are called anterior and posterior but are indeed superior and inferior, respectively. Because the right bundle branch remains compact until it reaches the distal interventricular septal surface (where it branches into the septum and toward the lateral right ventricular wall), many authors consider that the intraventricular conduction system is trifascicular (32,33 and 34). These intraventricular conduction pathways are composed of Purkinje cells with specialized capabilities for both pacemaking and rapid conduction of electrical impulses. Purkinje fibers in turn branch into networks that extend just beneath the surface of the ventricular endocardium. Because the Purkinje system provides a specialized path for rapid activation, the entire ventricular mass can be depolarized in a short time—similar to the depolarization time in the atria, structures of much smaller mass. The impulses then proceed slowly from endocardium to epicardium throughout the right and left ventricles (35). The normal activation sequence begins at the midseptum, continues at the epicardial right ventricular wall near the apex, then at the lateral and basal left ventricle, and ends at the basal septum (Fig. 59.3).

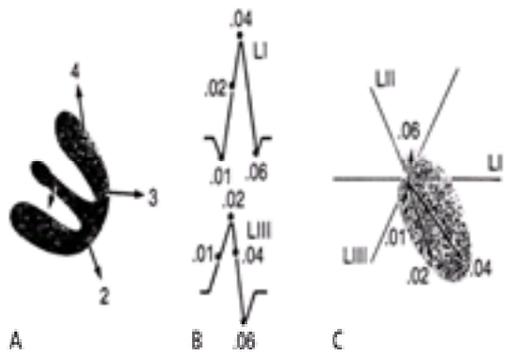


FIGURE 59.3 Correlation between the order of ventricular activation **(A)**, scalar electrocardiogram **(B)**, and vectorcardiogram **(C). A:** The sequence of ventricular activation is represented by four instantaneous frontal plane vectors. **B:** The four vectors plotted on leads I and III at the appropriate time during inscription of the QRS. **C:** Each of the four vectors is derived in the frontal plane. A line joining the ends of the vectors results in a frontal plane QRS loop. L, lead. (From Fisch C. Electrocardiography and vectorcardiography. In: Braunwald E, ed. *Heart disease: a textbook of cardiovascular medicine,* 4th ed. Philadelphia: WB Saunders, 1992:116–160, with permission.)

Electrical Bases for Electrocardiography and Vectorcardiography

Differences in cardiac potentials of a single cardiac cell or a small group of cells do not produce enough current to be detected on the body surface. Electrical representation on the ECG depends on the activation of most of the atrial and ventricular masses. The depolarization process produces a relatively high-frequency ECG waveform, which varies according to the action potential properties, the spread of excitation, and the heart geometry. The earliest QRS complex is recorded in right precordial leads. Although depolarization persists, the ECG recording returns to baseline. Myocardial repolarization is then represented by a waveform of lower frequency, the T wave (36). Once the cells are in their resting state, the ECG records a flat baseline.

Only 10% to 15% of the ventricular activation process can be seen on the 12-lead ECG; the remaining activation forces cancel each other. The normal right ventricle, for example, has no representation on the ECG because its forces are obscured by the dipoles generated in the massive left ventricle. The summation of all cardiac electrical forces can be represented with a single vector that originates at the center of the Einthoven triangle and whose arrowhead points to the positive pole. If all instantaneous single vectors were plotted consecutively, a vector loop would be formed in each of the three spatial planes (frontal, sagittal, and horizontal). Such recording constitutes a vectorcardiogram (Fig. 59.3). The vectorcardiogram integrates two surface leads out of three (named X, Y, and Z) in an orthogonal system and depicts a separate loop for each of the ECG components (P wave, QRS complex, T wave, and U wave). The advantage of the vectorcardiogram over the 12-lead ECG is that it provides information not only on magnitude and direction (i.e., positive or negative) of the signals but also on spatial orientation.

Specific situations in which the vectorcardiogram is superior to the ECG (which is a scalar representation of forces) include the diagnosis of left atrial enlargement and right ventricular hypertrophy, and myocardial infarction with left bundle branch block (LBBB) or left fascicular block (37). Since the vectorcardiogram gives no information on heart rhythm and is expensive to produce, its clinical use has gradually been abandoned. Because it positions the electrocardiographic waveforms in a three-dimensional framework, however, it is still useful as both a teaching and a research tool.

THE NORMAL ELECTROCARDIOGRAM

Overview of the Electrocardiographic Waveforms

Figure 59.4 depicts the waveforms of the normal ECG.

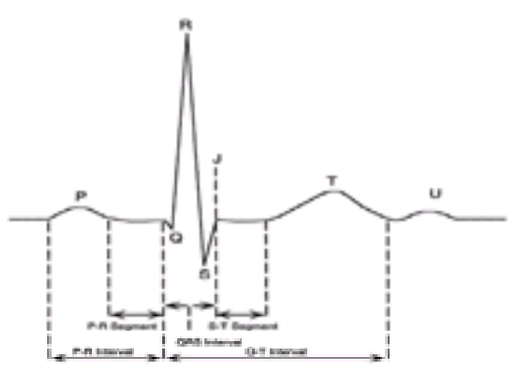


FIGURE 59.4 Waveforms and intervals of the electrocardiogram. (From Wagner GS, ed. *Marriott's practical electrocardiography,* 9th ed. Baltimore: Williams & Wilkins, 1994:13, with permission.)

The origin of the cardiac impulse in the sinus node is electrocardiographically mute; the initial electrical wave of each cardiac cycle is the P wave, which represents the spread of the activation through the atria. The QRS complex is the recording of the ventricular activation and it may appear as one (monophasic), two (diphasic), or three (triphasic) individual waveforms. Low-amplitude or narrow waves are denoted with lowercase letters (e.g., 'q' wave) and taller, wider waves with capital letters (e.g., Q wave).

The T wave represents ventricular recovery and is sometimes followed by a small upright deflection called the U wave. The ST segment is the interval between the end of ventricular activation and the beginning of ventricular recovery. The QT interval measures the time from the onset of ventricular activation to the end of ventricular recovery. This term is used whether the QRS complex begins with a Q or an R wave.

At low heart rates, the PR, ST, and TP segments are at the same horizontal level and form the isoelectric line. This line is considered as the baseline for measuring the amplitudes of the various waveforms. The TP segment disappears at higher heart rates when the T wave merges with the following P wave (38).

P Wave

The first part of the P wave represents the activation in the right atrium, and the middle and final sections of the P wave are recorded during left atrial activation. The normal P wave is rounded and upright in leads I and II and from V_2 to V_6. Its maximum amplitude is 0.25 mV in lead II (or 25% of the R wave) and its duration is 0.08 second. The P-wave axis is approximately 60 degrees. Because of the position of the right and left atria in the thorax, the activation front is directed first anteriorly and then posteriorly. Lead V_1 faces the right atrium; thus, the initial part of the P wave appears positive, whereas its terminal part appears negative.

Ta Segment

The Ta segment (or Ta wave) represents atrial repolarization. It may be seen in normal individuals but is more often obscured by the QRS complex and the early part of the ST segment. The orientation of the Ta wave is opposite that of the P wave. A normal but prominent Ta wave may mimic a pathologic Q wave by producing PR-segment depression.

PR Interval

The time from the onset of the P wave to the onset of the QRS complex constitutes the PR interval, whether the first wave in this complex is a Q or an R wave. The normal PR interval measures 0.12 to 0.22 second and it encompasses the time between the onset of atrial depolarization in the myocardium adjacent to the sinus node and the onset of ventricular depolarization in the myocardium adjacent to the fibers of the Purkinje network.

A major portion of it is inscribed during the slow conduction through the AV node, which is under the influence of the autonomic nervous system. Normally, the PR interval increases with age and shortens with increasing heart rates during exercise or stress. This effect depends on higher sympathetic and lower vagal tones. Incremental atrial pacing at rest, however, *prolongs* the PR interval. The time from the end of the P wave to the onset of the QRS complex is called the PR *segment.*

QRS Complex

The QRS complex represents ventricular activation. The contour of the QRS complex is peaked rather than rounded because it is composed of higher frequency signals than the P and T waves (Fig. 59.4). The normal ventricular activation can be summarized in four vectors (Fig. 59.3): (a) initial septal activation from left to right and anteriorly (inferiorly or superiorly), producing a positive deflection (R wave) at right recording sites; (b) an overlapping wave of excitation involving both ventricles, with the vector directed inferiorly and slightly to the left, which inscribes the midportion of the QRS complex; (c) unopposed activation of the apical and central portions of the left ventricle and of the right ventricle with a resultant vector oriented posteriorly, inferiorly, and to the left. Because the posteriorly positioned left ventricle is much thicker, its activation predominates over that of the anteriorly placed right ventricle, which results in a negative deflection (i.e., S wave) in aVR and in right precordial leads, and in an R wave in leads I, II, III, aVL, and left precordial leads. And (d) activation of the posterior basal portion of the left ventricle and septum with a vector directed superiorly and posteriorly, which completes the S wave in V_5 and V_6.

The QRS complex is measured from the beginning of the first-appearing Q or R wave to the end of the last-appearing R, S, or R' wave, and it tends to be slightly longer in men than in women. Computerized QRS measurements are usually reliable because they integrate information from the 12 ECG leads. The onset of the QRS complex is not recorded simultaneously in all ECG leads; this has implications for measurements of QRS duration. The earliest QRS onset is recorded in right precordial leads in both normal subjects and patients with heart disease (39).

The normal duration of the QRS complex is 0.07 to 0.10 second, and it increases with the subject's height (probably because it correlates with cardiac size) (40).

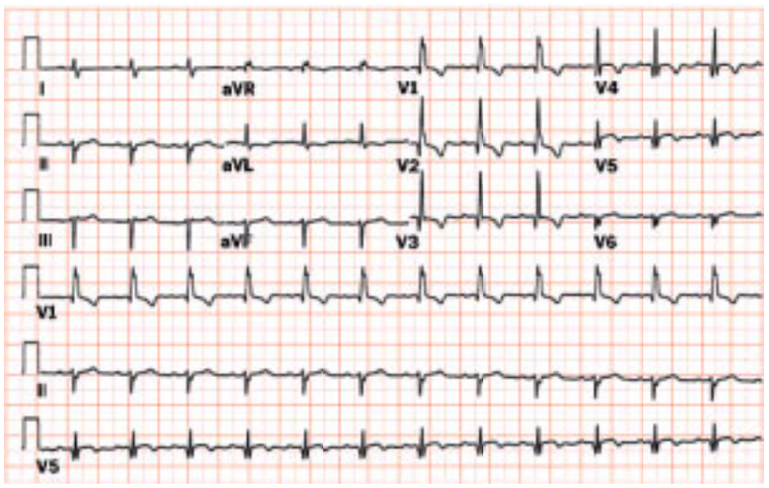
Q Wave

A Q wave is a negative deflection at the onset of the QRS complex. It indicates that the net direction of early ventricular depolarization forces is oriented away from the positive axis of the lead in question, at least by 90 degrees. Normal septal activation results in a rapid 'q' wave in leads I, II, III, aVL, V_5, and V_6 (*e*Table 59.0.2). The presence of Q waves in leads V_1, V_2, and V_3 or the absence of small 'q' waves in leads V_5 and V_6 should be considered abnormal (41).

***e*TABLE 59.0.2** NORMAL VALUES OF THE Q WAVE

Limb leads		**Precordial leads**	
Lead	**Upper limit (sec)**	**Lead**	**Upper limit (sec)**
I	<0.03	V_1	0
II	<0.03	V_2	0
III	—	V_3	0
aVR	—	V_4	<0.02
aVL	<0.03	V_5	<0.03
aVF	<0.03	V_6	<0.03

Modified from Wagner GS, Freye CJ, Palmen ST, et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. I: Specificity and observer agreement. *Circulation* 1982;65:345.



Anterior myocardial infarction. Note anterior Q waves in setting of underlying right bundle branch and left anterior fascicular block.

Positional factors may also result in the inscription of prominent but narrow Q waves. If the septal vector is horizontal, Q waves may appear in lead aVF; if the electrical axis is vertical, Q waves may be present in aVL. Precordial lead electrodes misplaced in a high position may determine a pseudoinfarction pattern from the inscription of Q waves.

In right precordial leads, QR and QS complexes may be normal; they were found in 25% of subjects in V_6R, in 9.7% in V_5R, and in 2.4% in V_4R (42,43).

R Wave

The first positive wave of the QRS complex is the R wave, regardless of whether or not it is preceded by a Q wave. The second vector results in an R wave in leads II and III, and the third vector produces an R wave in leads I, II, III, aVL, aVF, V_5, and V_6. The precordial leads provide a panoramic view of cardiac electrical activity progressing from the right ventricle to the thicker left ventricle, and consequently the R wave increases its amplitude and duration from V_1 to V_4 or V_5. Normal subjects present an rS pattern in leads V_3R and V_4R (42). Larger R waves in V_5 and V_6 may indicate left ventricular enlargement.

The amplitude of the R wave in leads V_5 and V_6 varies directly with left ventricular dimension during exercise and also with variations in the distance of the left ventricle

to the chest wall during positional changes (44). Reversal of the normal sequence with larger R waves in V_1 and V_2 can be produced by right ventricular enlargement.

When a second positive deflection occurs in any lead, it is called R'.

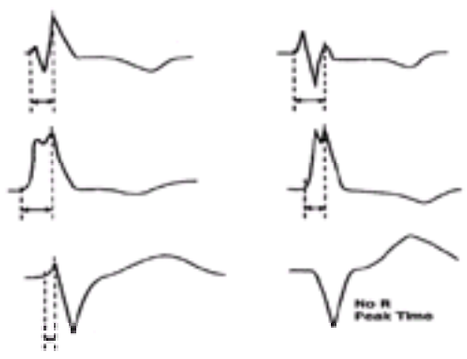
A 42-year-old female patient with right ventricular hypertrophy.

S Wave

A negative deflection after an R wave is an S wave. The third vector produces an S wave in leads aVr, V_1, V_2, V_3, and occasionally V_4. The S wave in the precordial leads is large in V_1, larger in V_2, and then progressively smaller from V_3 through V_6. As with the R wave, ventricular enlargement could alter this sequence. The last vector, directed superiorly and posteriorly, may result in a terminal S wave in leads I, V_5, and V_6. Leads V_4R and V_3R show an rS morphology in 80% of normal subjects (43).

Intrinsicoid Deflection

The time from the beginning of ventricular activation (onset of the QRS complex) to the point at which the impulse arrives under a particular electrode is called the *ventricular activation time*. The downward deflection that follows is the *intrinsicoid deflection.* By definition, the intrinsicoid deflection can only be measured in precordial leads, but some authors have applied this name to the turning point of the cardiac vector along the lead axis for the limb leads as well. For practical purposes, the "R peak time" is preferred as an estimate of the intrinsicoid deflection. It is measured from the onset of the QRS to the peak of the R wave or R' wave (eFig. 59.4.1). The R peak time is 0.04 second or less in V_1 and V_2, and 0.05 second or less in V_5 and V_6 (45).



***e*FIGURE 59.4.1** Measurement of the R peak time. (From Willems JL, Robles De Medina EO, Bernard R, et al. Criteria for intraventricular conduction disturbances and pre-excitation. *J Am Coll Cardiol* 1985;5:1261–1275, with permission.)

QRS Axis

The QRS axis can be manually determined in the frontal plane in three steps: (a) the lead with the equiphasic deflection (defined as positive and negative components of the QRS complex of similar amplitudes) is identified; (b) the lead that is perpendicular to the initial lead is identified; (c) if the predominant direction of the QRS complex in the lead identified in step (b) is positive, the axis is equal to the positive pole of that lead; if the direction is negative, the axis is equal to the negative pole of that lead. The normal electrical axis measures between –30 and +90 degrees (Fig. 59.5). QRS axes between 0 and –30 degrees are considered "left-axis deviation."

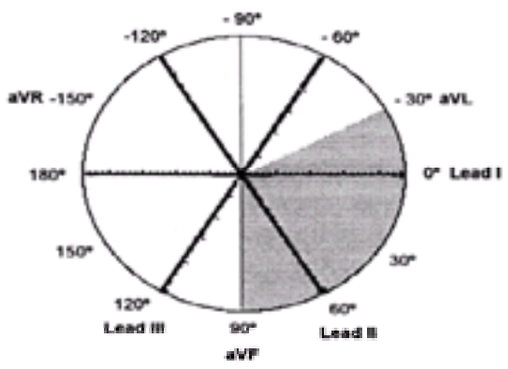
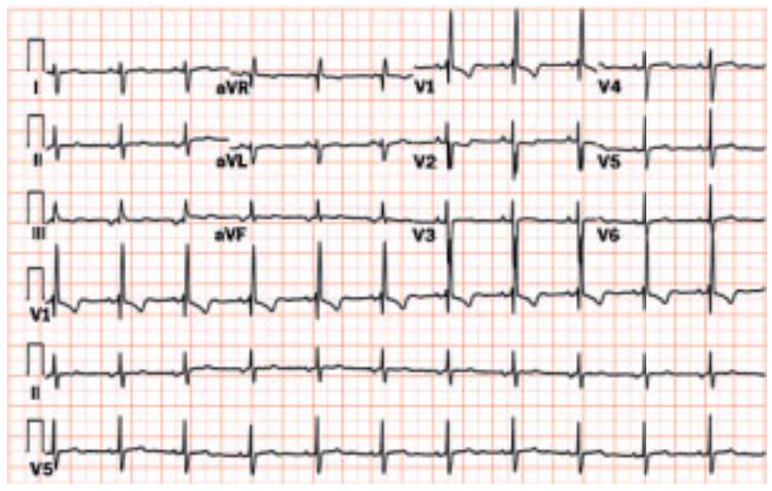


FIGURE 59.5 Frontal plane hexaxial reference system. The normal QRS axis in adults lies between –30 degree and +90 degrees (*area in gray*).

Deviations beyond –30 degrees are abnormal. The normal QRS complex is predominantly positive in both leads I (with its positive pole at 0 degrees) and II (with its positive pole at +60 degrees). If the QRS is positive in lead I but negative in II, the axis is deviated leftward between –30 and –120 degrees. If the QRS is negative in I but positive in II, however, the axis is deviated rightward between +90 and ±180 degrees. The axis is rarely opposite to normal (with a predominantly negative QRS orientation in both leads I and II).

Acute anterolateral myocardial infarction. Note ST segment elevation in the anterior precordial leads as well as leads I and aVL. New left anterior fascicular block suggests proximal left anterior descending infarct location.



Right ventricular hypertrophy. Note incomplete right bundle branch block pattern, right axis deviation, and ST-T–wave changes secondary to right ventricular hypertrophy.

The normal QRS axis is rightward in the neonate, moves to a vertical position during childhood, and then gradually moves to a more horizontal position during adulthood. In normal adults the electrical axis is almost parallel to lead II, but it is more vertical in thin individuals and more horizontal in heavy individuals.

Because the cardiac base is firmly attached to the intrathoracic structures, true (i.e., anatomical) rotation of the heart on its long axis is limited to superior or inferior shifts of the relatively mobile cardiac apex. Most QRS-axis deviations observed in the ECG in ventricular hypertrophies or fascicular blocks correspond, rather, to changes in the balance of epicardial versus endocardial activation forces, or to different routes taken by the activation forces.

ST Segment

The ST segment represents the time period in which the ventricular myocardium remains depolarized. The term *ST segment* is used regardless of whether the final wave of the QRS complex is an R or an S wave. At its junction with the QRS (i.e., J point), the ST segment forms a nearly 90-degree angle and then proceeds horizontally until it curves gently into the T wave.

The ST segment is normally isoelectric with the PR and TP segments. Slight upsloping (particularly in leads V_1 to V_3 and in V_4R to V_3R), downsloping, or horizontal depression of the ST segment may occur as normal variants. The length and appearance of the ST segment are influenced by factors that alter the duration of ventricular activation, such as exercise or bundle branch block.

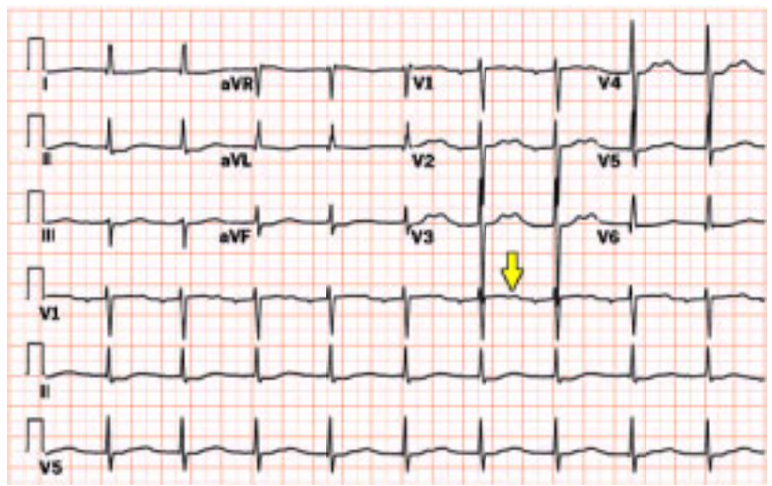
T Wave

The T wave represents exclusively uncancelled potential differences of ventricular repolarization; thus, it accounts for 8% or less of the total time-voltage product of the heart (46). The shape of the T wave is rounded but asymmetric, because the initial deflection is longer than the terminal deflection. The end of the T wave marks the completion of ventricular recovery, and it is not always easily identifiable. Slight “peaking” of the T wave is normal. The amplitude of the T wave does not normally exceed 0.5 mV in limb leads or 0.10 mV in precordial leads.

The direction of the T wave should be evaluated in relation to that of the QRS complex. The T wave is always positive in lead I, nearly always positive or isoelectric in lead II, and may have any polarity in leads III and aVF (27). In precordial leads the T wave is usually upright, except in 50% of women who present negative T waves in V_1.

U Wave

The U wave may be either absent or present as a small, rounded wave following the T wave. In a particular ECG lead, it shows the same direction as the T wave and it reaches approximately 10% of the amplitude of the latter. It is most prominent in leads V_2 through V_3. The origin of the U wave is uncertain. One theory attributes U-wave genesis to the repolarization of Purkinje fibers, and another to potentials generated during ventricular relaxation (47). Anatomic and electrophysiologic studies suggest that the U wave represents repolarization of the “M” cells, a population of subepicardial cells with unique activation properties, but this also has been questioned (48,49).



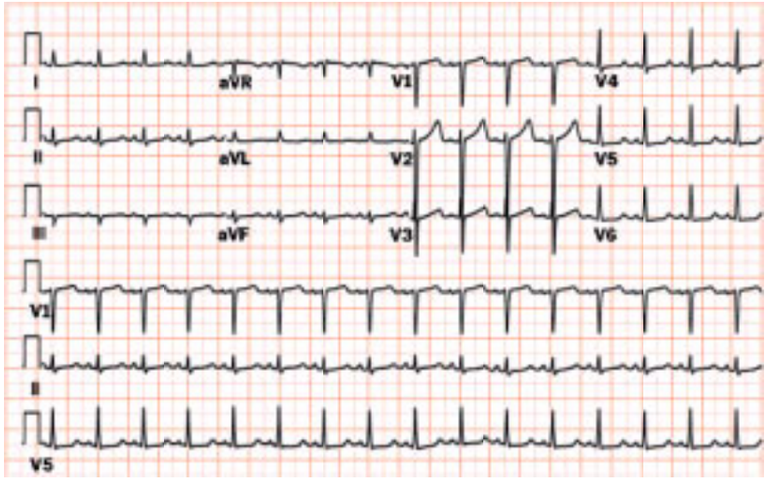
Hypokalemia. Prominent U waves are seen.

QT Interval

The QT interval measures the time from the beginning of the QRS complex until the end of the T wave. It estimates the duration of both ventricular depolarization and repolarization, but is mainly used as an estimate of ventricular recovery time. Repolarization measured as JT (i.e., the interval between the J point and the end of the T

wave) is significantly longer in women than in men (316 ± 31 ms vs. 262 ± 31 ms). Presumably, QT intervals are also shorter in men because of the modulating effect of testosterone on repolarization (50). Ethnic differences in the QT interval have not been demonstrated (51).

The value of the information provided by the QT interval is often limited by the difficulty in identifying the end of the T wave. The terminal portion of the T wave may be isoelectric, or a U wave may merge with the T wave. According to Lepeschkin, if the interval between two peaks in a notched T wave is 150 msec or more, the second peak is a U wave (47). The onset of the U wave should be considered the approximate end of the QT interval. At faster heart rates, the P wave may merge with the T wave and create a TP junction. The end of the QT interval in this instance is measured at the onset of the P wave. Considering these inherent limitations, the fact that methods for QT measurement vary among investigators and that efforts for standardization have not succeeded is not surprising (52,53 and 54). Recommended techniques include measuring the QT interval in leads with an initial Q wave, in leads in which the T wave is most distinct, in lead II or in aVL—in which the U wave is usually isoelectric—and in leads in which the QT is longest (usually V_2 or V_3) (52,55,56).



Hypocalcemia. Marked prolongation of the QT segment is appreciated in lead II.

A 30-year-old male patient with U waves secondary to hypokalemia.

Others advocate the use of a multichannel electrocardiograph with simultaneous recordings of limb and precordial leads, preferably at a paper speed of 50 mm per second (57,58). The QT interval should be measured in three or more consecutive beats (excluding those preceded by premature beats) and averaged to increase precision. Even when the QT interval can be measured with confidence, its reproducibility has been questioned. Intra- and interobserver variability is usually high (59,60). Automated QT analysis using computer programs to analyze digital ECG signals has not entirely resolved the problem (61,62).

The QT interval varies with rate, and normal QT values can be determined only by adjusting for the heart rate. Most automated ECG analyses include the corrected QT interval (QTc interval) in addition to the measured one. The inverse relationship between the RR and the QT intervals is not linear. With an increase in heart rate, a marked shortening of the QT interval occurs initially, followed by a more gradual shortening. Of several methods proposed for QT correction, the Bazett formula (QTc = QT/RR) is the most widely used (63). The normal value of QTc is up to 0.39 second in men and 0.44 second in women.

The Bazett formula has been criticized for several reasons. First, it was derived from observations made on only 34 subjects, some of them children, in a variety of physiologic states. Second, it does not properly adjust the QT at extreme rates. The QTc remains undercorrected (i.e., artificially shortened) during bradycardia, whereas it is paradoxically lengthened at faster rates (64). In a study of 1,300 normal subjects, Macfarlane and Lawrie found that the mean QTc was 0.434 second in persons with heart rates between 80 and 89 beats/min, and 0.446 second in those with rates between 90 and 99 beats/min (65). The upper limit of Bazett's QTc ranged from 0.463 second in young men to 0.506 second in older women, which thus suggests that 0.44 second is inadequately short as the upper limit of normality. Macfarlane and Lawrie proposed the equation QTc = QT + 1.75 (ventricular rate – 60) for QT correction.

Others have proposed alternative formulas to model the relationship between the RR and the QT intervals (64,66,67). Most of them function properly and produce nearly equivalent results for heart rates between 55 and 85 beats/min. The corresponding QTc values for this range are 350 to 420 ms, which in a study of over 14,000 subjects covered the distribution area of 50% of the paired QT/RR values. Outside this range, the discrepancies among investigators in the perceived usefulness of different correction formulas are marked (68,69). Conceivably, more than one formula is necessary to accurately describe the behavior of the QT interval over the entire range of heart rates (70).

Perhaps because no agreement has been reached regarding the ideal QT correction formula, the Bazett formula is still in use. The ultimate goal of the corrected QT is to serve as a prognostic indicator; thus, homogeneous databases including patients with a particular disease as well as information on age and sex are necessary to determine the boundaries of normality (71). Until a better correction method becomes available, both the corrected and the measured QT intervals should be reported.

An additional parameter, QT dispersion, has been proposed as a noninvasive marker of dispersion of refractoriness. It is calculated by subtracting the shortest from the longest QT interval, that is, $QT_{max} – QT_{min}$ (72). The QT dispersion may provide independent prognostic information regarding risk of ventricular tachyarrhythmias in patients with myocardial infarction, congenital and acquired long QT syndrome, hypertrophic cardiomyopathy, alcoholism, and congestive heart failure. Its poor reproducibility (73), however, which persists despite the use of magnifying techniques (74), and the fact that it may be only a surrogate for QT prolongation (75) suggest that the value of QT dispersion in scientific publications may have been exaggerated.

Normal Variants

ECGs as screening tests are requested daily by clinicians, surgeons, and cardiologists for a number of purposes. A normal ECG is a good predictor of normal left ventricular function, and it greatly reduces the need to request an echocardiogram to assess systolic function (76).

RSR'Pattern in Lead V_1

An RSR' (or rSr') pattern in lead V_1 with a QRS duration of less than 0.12 second is present in 2.4% of normal persons (77). The R' wave may correspond to relatively late activation of the crista supraventricularis (78).

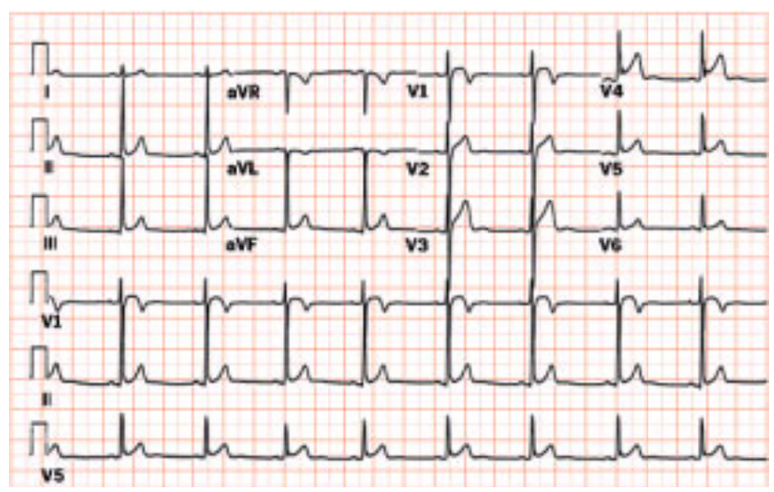
$S_1S_2S_3$ Pattern

The $S_1S_2S_3$ pattern has been observed in 20% of healthy subjects (77). The S waves in standard leads are inscribed when the terminal vector of the QRS complex originates in the outflow tract of the right ventricle or in the posterobasal septum and is directed rightward and superiorly. The typical $S_1S_2S_3$ pattern (with all S waves larger than their preceding R waves) is not as common as the case in which the amplitude of the S wave in lead I is smaller than that of the R wave.

Early Repolarization

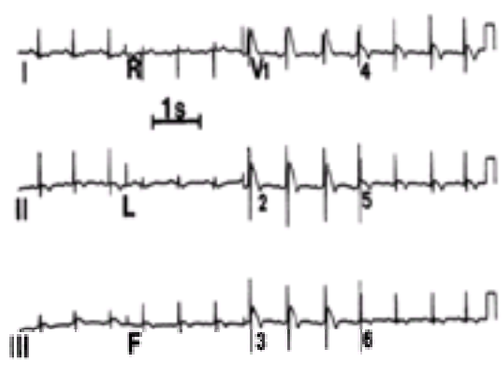
Some individuals show marked (i.e., more than 0.1 mV) ST-segment elevation, which may be present in all precordial leads (79) (Fig. 59.6). Normal young men (particularly African-Americans) may have ST elevation of up to 0.4 mV in leads V_1 through V_3, mimicking acute myocardial infarction or pericarditis (80). Possible causes are early ventricular repolarization or a mild intraventricular conduction delay in the right ventricle. A distinct notching on the downstroke of the R wave, an upward concavity of the ST segment, and symmetric, prominent T waves may also be present (80). Early repolarization appears to be an independent marker of enhanced aerobic condition (81).

FIGURE 59.6 Electrocardiogram of patient with early repolarization and sinus tachycardia (19-year-old African-American woman). ST elevation is present in both inferior and precordial leads.



Early repolarization. Note diffuse J-point elevation, early R-wave transition, with notched downstroke of R wave in lateral precordial leads. These changes are characteristic of early repolarization in this 28-year-old African-American male.

Differentiating early repolarization from an electrocardiographic pattern consisting of right bundle branch block (RBBB) and coved ST-segment elevation in right precordial leads may be difficult. This pattern (the Brugada syndrome) is associated with ventricular tachyarrhythmias and sudden death, and seems to be an autonomically transmitted condition (82,83 and 84) (*e*Fig. 59.6.1). An almost identical syndrome to the Brugada syndrome but with a pathologic substrate of right ventricular dysplasia has been reported (84,85). The possibility also exists that a common pathophysiologic ground might exist for Brugada syndrome and early repolarization (86).



***e*FIGURE 59.6.1** Electrocardiogram of patient with right bundle branch block and ST elevation in leads V_1 to V_4 (Brugada syndrome). (From Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20:1391–1396, with permission.)

Unusual T Waves

Negative T waves, particularly in precordial leads (from V_6R to V_2, and sometimes through V_6) may be seen in young, usually African-American, vagotonic persons (87,88). These T waves may show intermittent changes in polarity, and in some cases follow a slightly elevated ST segment (early repolarization syndrome). Transient inverted T waves have been documented in normal subjects after meals (89) or after drinking cold water (90). Bifid T waves (i.e., T waves with two peaks different from a U wave) are present in 20% of children; their incidence decreases with age (91). Usually found in precordial leads, bifid T waves are more prevalent in V_1 and V_2 in younger groups, and shift toward V_5 and V_6 in older subjects. A likely mechanism producing bifid T waves is a delayed right ventricular repolarization; an asynchronous repolarization of the anterior and posterior walls would inscribe two separate peaks in the T wave. The probability of an underlying heart disease increases with age.

APPROACH TO ELECTROCARDIOGRAPHIC DIAGNOSIS

Sensitivity, Specificity, and Predictive Accuracy

The ECG is a highly valuable diagnostic tool. ECG diagnoses are made by inference, however, and are therefore subject to error (92). To obtain maximum benefit from electrocardiographic information, one must apply the principles of sensitivity, specificity, and predictive accuracy. Sensitivity is the number of persons with a condition who have a target ECG sign. A sign with perfect sensitivity is positive in all patients with the condition; the absence of the sign rules out the disorder. Specificity is the number of persons without a condition who do not have the target ECG sign. A sign with perfect specificity is negative in all persons free of the condition; the presence of the sign makes a positive diagnosis.

At the time an ECG is requested, when one does not know whether a particular disorder is present, the concept of predictive value is most helpful. The positive predictive value is the proportion of patients with positive test results who have the condition. The negative predictive value is the proportion of patients with negative results who do not have the condition. Predictive accuracy is the degree to which a positive or negative ECG sign represents what it is actually intended to represent, or

its ability to discriminate between two competing states. Accuracy can be assessed by comparison with reference techniques or gold standards (93).

Predictive values are a good measure of overall clinical usefulness in particular settings because they incorporate information on both the test (i.e., the ECG) and the population being tested (94). As postulated in the Bayes theorem, the presence of a sign (or a positive test result) is less informative in a clinically healthy population. An ECG abnormality detected during screening procedures is associated with a two to four times lower incidence of new cardiovascular events than an abnormality discovered during a clinical evaluation (95). Disorder prevalences between 40% and 60% result in the maximum drop or rise from pretest to posttest probability (96). Sensitivity and specificity, on the other hand, do not depend on the prevalence of the condition in the population, but they do depend on the spectrum of patients under study. Autopsy has too often been used as a gold standard in electrocardiography. This may potentially bias the spectrum of patients toward those with more severe manifestations. The increasing availability of noninvasive tests that provide accurate anatomical information (i.e., two-dimensional echocardiography, magnetic resonance imaging) has allowed for new correlations in living patients.

Choice of a Cutoff Point

Most ECG information relies on continuous values, and a decision must be made as to what constitutes a positive sign. For values that follow a normal distribution, abnormal results are defined as two standard deviations from the mean of the reference population. Thus, 5% of normal subjects have abnormal test results. Selecting a cutoff point involves trading a high sensitivity for a low specificity, or vice versa. Setting a cutoff point of ST-segment elevation of 0.4 mV in two ECG limb leads in patients with chest pain would provide a high specificity for acute myocardial infarction; however, it would also have poor sensitivity, because many patients with acute infarction do not have this much ST-segment elevation. Setting the cutoff at 0.05 mV identifies virtually all patients with acute infarction, but many persons without infarction would also be included.

The clinician must weigh the relative importance of the sensitivity and specificity of the sign selected for each patient and set the cutoff point accordingly. If false-positive results must be avoided, the cutoff point should be set to ensure a high specificity. When false-negative results are undesirable, the cutoff point should be set to ensure a high sensitivity. The role of these trade-offs needs to be clearly understood to prevent inadequate expectations regarding the diagnostic capabilities of the ECG—a problem not unusual among internal medicine doctors (97).

Receiver operating characteristic curves provide a graphic way to examine the relation between a test's sensitivity or specificity (96). The values of the test or sign are plotted along a curve, and their true-positive and false-positive rates (i.e., sensitivity and 1 – specificity, respectively) can be determined at each cutoff point. The upper-left-hand corner of the curve denotes an ideal electrocardiographic sign, with a true-positive rate of 0.1 and a false-positive rate of 0. A worthless electrocardiographic sign would follow the diagonal from the lower left to the upper right corners; each incremental gain in sensitivity would be matched with an equal loss in specificity. Receiver operating characteristic curves permit the formal comparison of different diagnostic signs (or set of signs). The better the sign, the closer its curve to the upper left corner.

THE ABNORMAL ELECTROCARDIOGRAM

QRS-Axis Deviation

Although QRS axes between 0 degrees and –30 degrees are sometimes called "left-axis deviations," they are truly a normal variant. Severe left-axis deviations (QRS axes between –30 degrees and –90 degrees) are considered abnormal; yet they are found in 2% of healthy adults (77,98).

Although the term *left-axis deviation* is often used interchangeably with left anterior fascicular block (LAFB), isolated left superior displacement of the QRS axis may occur in the absence of LAFB (in inferior myocardial infarction and other disorders). In some patients, the extent of left-axis deviation varies over short periods of time. The significance of this finding is uncertain; it may result from conduction delays affecting selectively different groups of fibers in the fan-like anterior division of the left bundle branch (27).

P-Wave Abnormalities

Abnormalities of the P wave reflect disorders of atrial pressure or volume, or an anomalous origin of the cardiac impulse.

Mitral stenosis. Left atrial enlargement and right ventricular hypertrophy have developed secondary to mitral stenosis, causing fixed pulmonary hypertension.

Right Atrial Abnormality

Right atrial enlargement has classically been diagnosed in the presence of (a) tall, peaked P waves in leads II, III, and aVF (0.25 mV or more in lead II) ("P pulmonale"), (b) a P-wave axis of 75 degrees or more, and (c) a positive deflection of the P wave in V_1 or V_2 of 0.15 mV or more (99). The correlation of these ECG signs with anatomic findings is poor, however. The amplitude of the P wave may paradoxically decrease as right ventricular hypertrophy progresses. Also, P-wave signs have relatively low sensitivity to detect "pure" right atrial enlargement. In a population with low prevalence of coronary disease, no associated chronic obstructive pulmonary disease, and no left heart pathology, QRS changes in lead V_1 (R/S of 1 or more; presence of Q) in the absence of RBBB were as specific and much more sensitive than a P-wave height of 0.25 mV or more in lead II. In addition, ST depression of 0.05 mV or more in II or aVF [probably representing a prominent atrial repolarization (Ta) wave] was almost 100% specific (100).

Left Atrial Abnormality

Left atrial enlargement is characterized by (a) a notched P wave with a duration of 0.12 second or more ("P mitrale"), best observed in leads II and V_1, and (b) a wide terminal negative deflection in lead V_1 (0.1-mV amplitude per 0.4-second duration) (Fig. 59.7). The terminal force of the P wave correlates better with left atrial volume than with pressure, which may also explain the moderate correlation of the P terminal force with the left atrial weight (101). Interestingly, no characteristics of the P wave correlate with atrial size. The left atrial enlargement pattern indicates an intraatrial conduction disturbance, and thus the term *left atrial abnormality* is preferred (102).

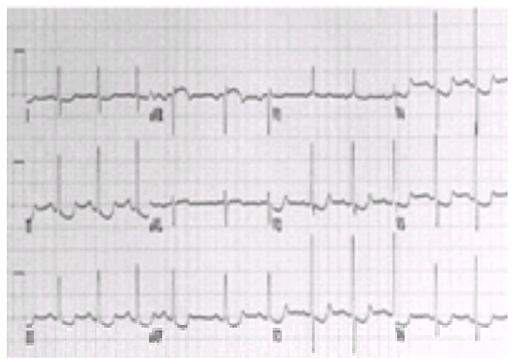


FIGURE 59.7 Left atrial abnormality. The P-wave duration is 0.125 second, and a prominent negative deflection is seen in V_1. Incomplete right bundle branch block and repolarization changes induced by digitalis are also present.

The term *pseudo–P pulmonale* denotes a prominent P wave in inferior leads that is caused by left atrial rather than right atrial abnormality. Detailed examination of the P wave reveals that its terminal portion is increased, whereas the initial portion is normal. Participation of the left atrium in the genesis of the pseudo–P pulmonale is confirmed by identifying a marked negative terminal component of the P wave in V_1.

Biatrial Enlargement

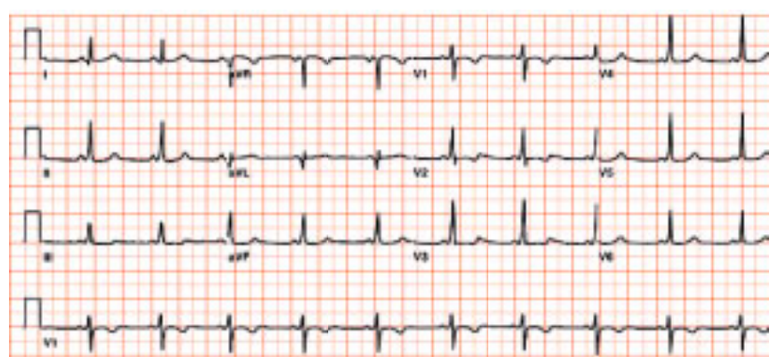
Biatrial enlargement is characterized by tall P waves in lead II, and notched and broad P waves in leads I and II with a terminal negative deflection in V_1.

Ta Wave

Ta waves may be prominent in atrial hypertrophy or infarction and during pericarditis. In the presence of atrial enlargement the Ta wave is prolonged and may displace the ST segment, which appears depressed.

PR Interval

A short PR interval in the presence of a normal P-wave axis suggests an abnormally rapid conduction pathway within the AV node or in its surroundings (i.e., a bundle of cardiac muscle connecting atria and ventricles, bypassing the AV node). Early activation of the ventricular myocardium (ventricular preexcitation) creates the potential for electrical impulse reentry into the atria, producing a tachyarrhythmia (Wolff-Parkinson-White, or WPW, syndrome). When a short PR interval is accompanied by an abnormal P-wave direction, the site of impulse origin has moved from the sinus node to a position closer to the AV node.



A 44-year-old female patient with Wolff-Parkinson-White syndrome.

A prolonged PR interval in the presence of a normal P-wave axis indicates a delay in impulse transmission at some point in the pathway between the atrial and ventricular myocardium. When a long PR interval is accompanied by an abnormal P-wave axis, the possibility that the P wave is associated with the preceding rather than the next QRS complex should be considered. This is a manifestation of retrograde activation from ventricles to atria, and the PR interval is usually longer than the preceding PR interval.

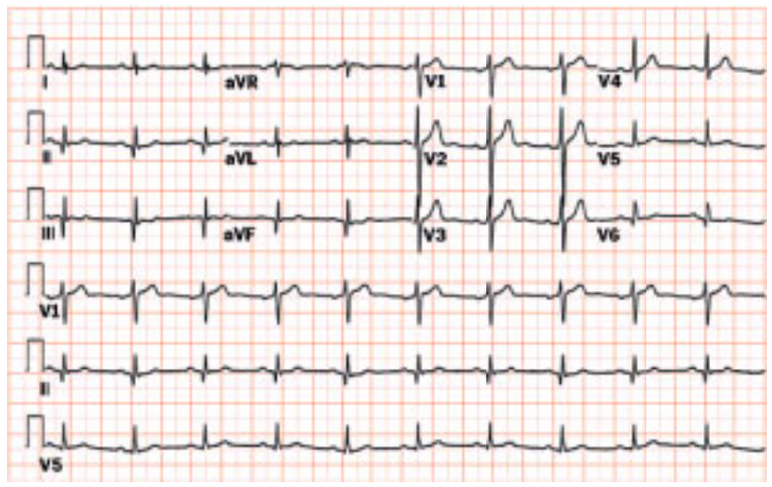
QRS Complex

Absence of R-wave progression from V_1 to V_5 may indicate left ventricular myocardial necrosis. The presence of notching and slurring of the QRS complex in the precordial leads is more sensitive than the presence of Q waves to detect anterior infarction, but is less specific (103). A rightward mediastinal shift in left pneumothorax may produce apparent loss of left precordial R waves (104). In dextrocardia, normal R-wave progression may be restored by recording leads V_1 to V_5R on the right side of the precordium.

Dextrocardia. Notable findings include a positive R wave in aVR and counterclockwise rotation in the precordial leads.

Q Wave

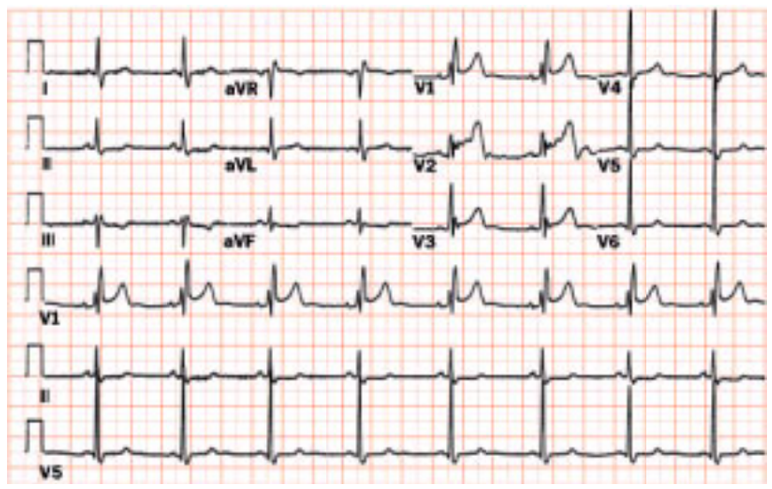
Conditions associated with abnormal Q waves include myocardial infarction or injury, ventricular hypertrophy or dilatation, and intraventricular conduction disturbances (LBBB, ventricular pacing, and WPW syndrome). Less frequent causes of Q waves include infiltrative myocardial disease, chronic obstructive pulmonary disease (in precordial leads), acute pulmonary embolism (in lead aVF), pneumothorax, and misplacement of precordial electrodes (105).



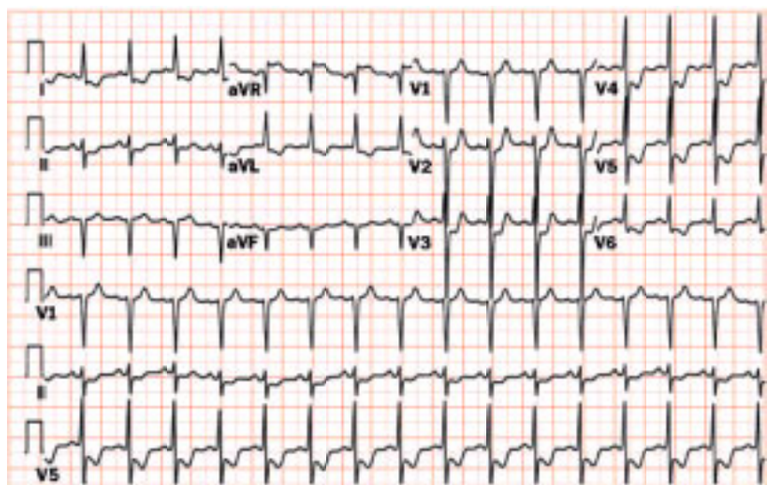
Inferior myocardial infarction. Prominent Q waves in the inferior leads are associated with T-wave inversions.

ST Segment

Alterations of the ST segment include elevation and depression. The most important cause of ST-segment elevation is transmural injury. Outside the acute setting, ST elevation can be found in combination with other signs of remote or recent infarction and is associated with ventricular asynergy, and can be seen in other pseudoinfarction patterns (106). Depression of the ST segment occurs when myocardial ischemia is present and when ventricular repolarization is altered.



Anterior myocardial infarction in setting of right bundle branch block. ST-segment elevation in the anterior precordial leads as well as primary T-wave changes support acute anteroseptal myocardial infarction.



Subendocardial ischemia. Anterolateral ST-segment depression is consistent with diffuse subendocardial ischemia versus non–Q-wave myocardial infarction.

QT Interval

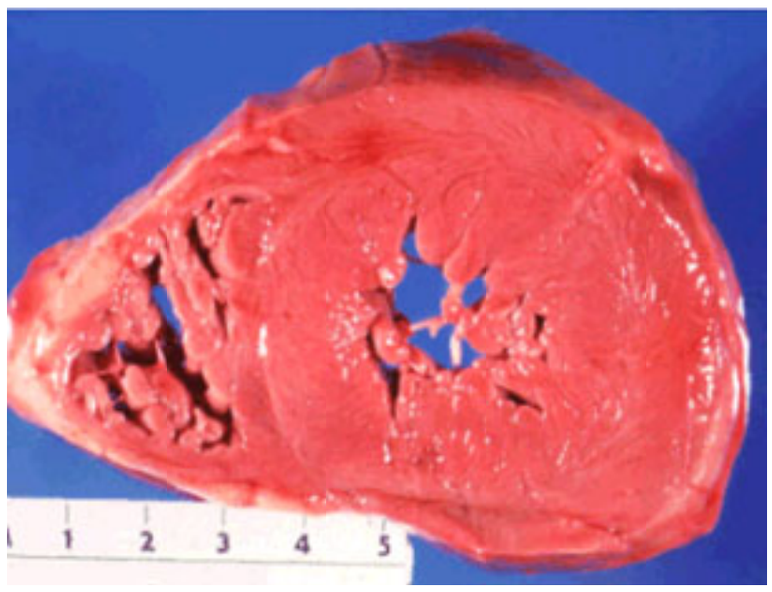
Causes of abnormal prolongation of the QT interval include myocardial ischemia, cardiomyopathies, hypokalemia, hypocalcemia, autonomic influences, drug effects, hypothermia, and congenital long QT syndrome. A prolonged QTc is a predictor of cardiovascular mortality even in the absence of overt heart disease (107).

Ischemia

Acute myocardial ischemia may induce an initial, transient QT shortening followed by extreme QT prolongation. Changes in the QT interval often accompany T-wave or U-wave inversion (108). The QT interval usually returns to its normal value within 72 hours of the acute coronary event, whereas inverted T waves may persist.

Hypertrophic Cardiomyopathy

The QTc is prolonged in patients with hypertrophic cardiomyopathy; a modest correlation is found between QTc and left ventricular wall thickness. QTc dispersion is also increased, which probably reflects the inhomogeneous ventricular refractoriness that predisposes to ventricular arrhythmias (109).



Massive left ventricular hypertrophy as well as concentric hypertrophic cardiomyopathy. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The

Cleveland Clinic Foundation.)

Hypothermia

Core temperatures of 35°C or less are associated with ECG manifestations that are probably induced by changes in ionic currents, an enhanced vagal tone, or both. Prolongation of the QT interval is usually related to the sinus bradycardia that accompanies hypothermia, but in some patients the QTc interval is also abnormal.

Autonomic Dysfunction

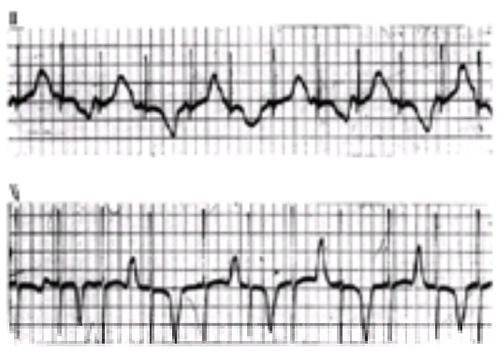
Patients with diabetes, alcoholism, and other disorders that cause autonomic dysfunction may show prolonged QT and QTc intervals (110).

Drugs

Antiarrhythmic drugs, the antibiotics erythromycin and ketoconazole, the antihistamine agents astemizole and terfenadine, the phenothiazines, and terodiline (a drug used for treatment of incontinence) have been associated with prolongation of the QT and QTc intervals, torsades de pointes, and sudden death (111). A continuously updated list of drugs associated with QT prolongation can be found on the Internet (112).

Congenital Long QT Syndrome

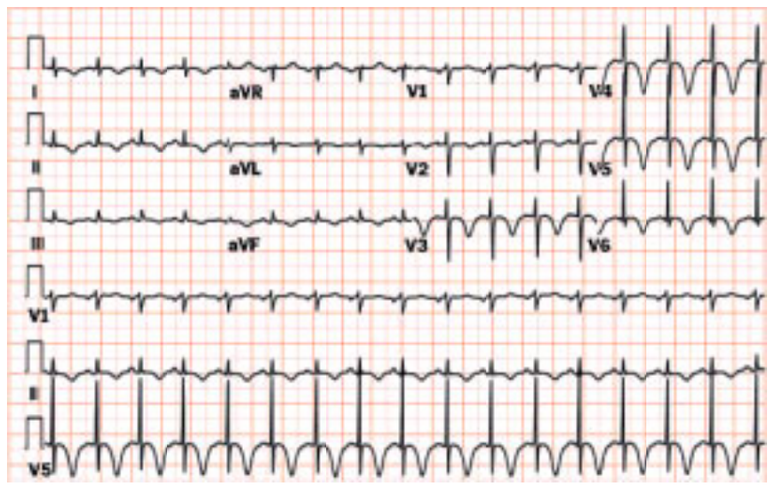
The congenital long QT syndrome is an autosomal dominant disorder in which the QTc interval measures longer than 0.46 second. Five percent to 10% of gene carriers for this disorder, however, have QTc durations within the normal range (113). Patients with this syndrome may also have marked sinus bradycardia and other repolarization abnormalities. The T wave is often notched or biphasic, or alternates its morphology or polarity (T-wave alternans; *e*Fig. 59.7.1) (114,115 and 116). Prominent U waves may also be present. The extreme prolongation of the QT interval can result in pseudo 2:1 AV block when every other P wave falls during or before the preceding T wave (114).



***e*FIGURE 59.7.1** Marked T-wave alternans in a patient with congenital QT prolongation. (From Sharma S, Nair KG, Gadekar HA. Romano-Ward prolonged QT syndrome with intermittent T wave alternans and AV block. *Am Heart J* 1981;101:500–501, with permission.)

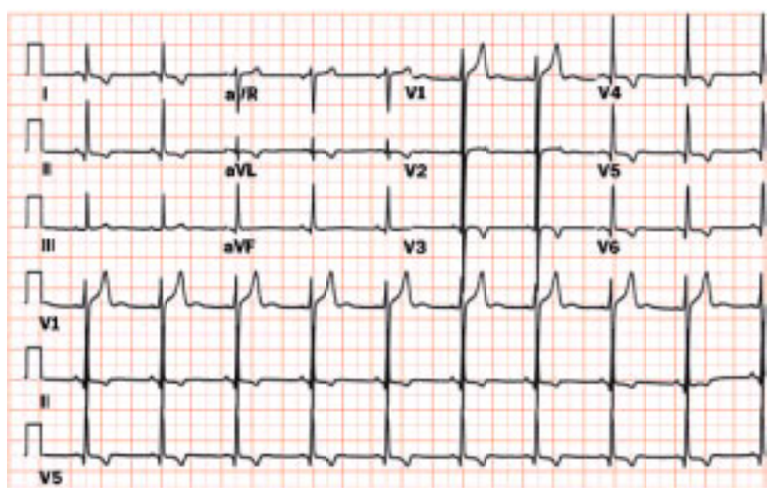
T Wave

Abnormalities of the T wave (usually consisting of inverted T waves) are seen in a number of conditions. Although the T wave is a sensitive detector of repolarization differences over the myocardium, the magnitude of T-wave changes is not proportional to the extent of myocardium with repolarization abnormalities (27,30). Negative T waves are considered “primary” when the preceding sequence of ventricular depolarization is normal, and “secondary” when it is altered. Primary T waves often accompany ST-segment changes and are observed during myocardial ischemia, myocarditis, pericarditis, and mitral valve prolapse, and are induced by some drugs (phenothiazines, class Ia antiarrhythmic agents, and amiodarone hydrochloride). Postprandial status, a recent paroxysmal tachycardia, and the injection of contrast into coronary arteries all may induce primary T-wave abnormalities (27,30). Research has shown that the negative T waves that develop in infarct-related ECG leads shortly after thrombolysis may be powerful markers for improved 30-day survival, which calls into question the name “T-wave abnormality” (117). However, such T waves must be dynamic (i.e., revert to positive with time, exercise, or dobutamine hydrochloride treatment) to predict myocardial viability and favorable outcome (118,119).



Neurogenic T waves. These deep, symmetric T-wave inversions developed after intracranial hemorrhage.

Secondary T waves are those associated with bundle branch block, ventricular pacing, ventricular hypertrophy, cardiomyopathies (120), and WPW syndrome. Less than 1% of ECGs recorded for any reason show giant, rather permanent negative T waves. The most frequent correlates are left ventricular hypertrophy and coronary artery disease (121).



Hypertrophic cardiomyopathy. Inverted precordial T waves associated with hypertrophic cardiomyopathy.

T-Wave Alternans

Electrical alternans of the T wave is a consequence of alternation of the duration or the shape of the action potential, or both. It has been documented in patients with the congenital long QT syndrome (*e*Fig. 59.7.1), in patients with hypocalcemia, and in patients treated with quinidine or amiodarone (122,123).

T-Wave "Memory"

The term *T-wave memory* describes the aspect of the T waves that seems to "remember" an abnormal activation pattern. The T-wave polarity follows the polarity of a preexistent ectopic QRS (124). Transient abnormal T waves are recorded in normally conducted beats after cessation of ventricular pacing or intermittent LBBB (124,125) (*e*Fig. 59.7.2). Also, in patients with WPW syndrome who undergo catheter ablation of the accessory pathway, the polarity of the T wave is that of the former delta wave. T waves appear negative in leads that showed a negative delta wave (126). Whether the memory T waves follow previous ectopic QRS complexes or delta waves, the magnitude and persistence of the T-wave changes increase proportionally with the duration of the abnormal ventricular activation.

***e*FIGURE 59.7.2** Memory T waves in a patient with complete atrioventricular block in whom a permanent pacemaker had been temporarily inhibited. The intrinsic rhythm shows a right bundle branch block pattern with deep, wide, negative T waves (positive in aVR) that follow the QRS morphology of the previously paced QRS complex.

U Wave

Positive, prominent U waves are usually induced by hypokalemia (127), but they may also be seen in patients taking digitalis or quinidine and in patients with the congenital long QT syndrome. Negative U waves are highly specific for the presence of heart disease (128). The three most common conditions associated with negative U waves are systemic hypertension, valve regurgitation, and ischemic heart disease.

Electrical Alternans

Electrical alternans is defined as alternation of the QRS complex or T-wave morphology, usually in a 2:1 ratio (*e*Fig. 59.7.1). The PR interval or the ST segment is affected more rarely. Causes of this phenomenon include myocardial ischemia, ventricular dysfunction, rapid tachycardias, significant pericardial effusion, and acute pulmonary embolism (129,130).

Pericardial tamponade. Low QRS voltage and electrical alternans are characteristic findings of tamponade.

The significance of electrical alternans varies with the underlying condition. The QRS alternans seen during pericardial effusion is a manifestation of mechanical alternans and suggests imminent tamponade. Alternans of the ST segment indicates transmural injury and probable coronary spasm. Overt repolarization alternans (affecting the ST segment, the QT interval, or the T wave) has been associated with ventricular arrhythmias and is relatively common in the congenital long QT syndrome (27).

VENTRICULAR HYPERTROPHY

Left Ventricular Hypertrophy

Left ventricular hypertrophy is a response to a pressure or volume overload. Because of the increase in myocardial mass, a longer time is required for the spread of the electrical activation from endocardium to epicardium. The intrinsicoid deflection, the R peak time, and the overall QRS duration are all prolonged (*e*Fig. 59.7.3). Because the thickness of the ventricular muscle correlates with the magnitude of the depolarization front, left ventricular hypertrophy exaggerates the normal ECG pattern of left ventricular predominance. An augmented mean QRS vector is oriented toward the left, posteriorly and superiorly, which thereby causes a positive deflection in leads I, II, aVL, V_5, and V_6. The precordial transitional zone is shifted to the left. An rS pattern is usually observed in V_1 and V_2, although sometimes the initial 'r' wave disappears.

***e*FIGURE 59.7.3** Left ventricular hypertrophy. Electrocardiograms recorded in two elderly women with left ventricular pressure overload due to aortic stenosis. Note the left ventricular conduction delay and intermittent ventricular premature beats in **A**, and left ventricular strain in **B**. (From Wagner GS, ed. *Marriott's practical*

electrocardiography, 9th ed. Baltimore: Williams & Wilkins, 1994:69, with permission.)

Several explanations have been proposed for the left-axis deviation observed in left ventricular hypertrophy (14). First, the prolonged epicardial activation separates in time the vectors generated in the last region of the left ventricle (i.e., superior and posterior) from the preceding vectors. This determines that the terminal vector (i.e., the last 0.06-second vector; Fig. 59.3) is more exclusively contributed from the superior and posterior regions. Second, in left ventricular hypertrophy the diameter of the mitral and aortic orifices remains normal. This causes the free wall to become more bowed superiorly and posteriorly, and the terminal vectors of the left ventricle move in that direction. Third, the increased magnitude of the terminal QRS vectors (oriented leftward and posteriorly) also causes left-axis deviation. Finally, intraventricular conduction defects could develop.

Left ventricular repolarization is also delayed in the presence of hypertrophy. The epicardial cells no longer repolarize early, which causes the spread of recovery to proceed from endocardium to epicardium. The reversal of the direction of the recovery process produces negativity of both the ST segment and the T wave in leads with leftward or posterior orientation. This is called *ventricular strain* (131). The development of strain correlates well with left ventricular mass as determined by echocardiography (132), although myocardial ischemia and intraventricular conduction delays may also contribute.

Left ventricular dilatation ("volume overload") secondary, for example, to aortic or mitral regurgitation enlarges the surface area of the left ventricle and displaces the myocardium closer to the precordium. This increases the amplitudes of leftward and posteriorly directed QRS waveforms (131). Volume overload may produce prominent but narrow Q waves in the leads facing the left side of the septum—that is, I, aVL, V_5, and V_6—and a reciprocal R wave in V_1 and V_2. The amplitude of the S wave is increased in leads V_2 and V_3 and that of the R wave is increased in leads V_5 and V_6. Thus, the suggestion has been made that the ECG cannot reliably distinguish between left ventricular dilatation and hypertrophy (133).

Electrocardiographic Diagnosis of Left Ventricular Hypertrophy

Classic electrocardiographic criteria for the detection of left ventricular hypertrophy are listed in eTable 59.0.3 (also see eFig. 59.7.3). These criteria are specific but not sensitive (134,135). The presence of obesity further decreases the sensitivity of the ECG for the detection of left ventricular hypertrophy (136). Of all criteria, high QRS voltage in precordial leads is the most sensitive, and the gender-specific Cornell voltage is the most closely correlated with left ventricular mass (137,138). The product of QRS duration and gender-specific Cornell voltage (the "Cornell product") seems to provide the best overall accuracy and is not significantly affected by the presence of bundle branch block (139). Left atrial abnormality is a strong independent predictor of increased left ventricular mass; each 0.1 mV per second of increase in left atrial abnormality predicts a 30-g increase in left ventricular mass (140).

***e*TABLE 59.0.3** CRITERIA FOR THE DIAGNOSIS OF LEFT VENTRICULAR HYPERTROPHY

Romhilt-Estes scoring system	
1. R or S in any limb lead ³0.20 mV	
or S in lead V_1 or V_2	
or R in lead V_5 or V_6 ³0.30 mV	3 points[a]
2. Left ventricular strain	
ST segment and T wave in opposite direction to QRS complex	
without digitalis	3 points
with digitalis	1 point
3. Left atrial enlargement	
Terminal negativity of the P wave in lead V_1 is ³0.10 mV in depth and ³0.04 second in duration	3 points
4. Left-axis deviation of ³–30 degrees	2 points
5. QRS duration ³0.09 second	1 point
6. Intrinsicoid deflection in lead V_5 or V_6 ³0.05 second	1 point
Total	13 points
Sokolow-Lyon criteria	
S wave in lead V_1 + R wave in lead V_5 or V_6 >3.50 mV	
Or	
R wave in lead V_5 or V_6 >2.60 mV	
Cornell voltage criteria	
Women, R wave in lead aVL + S wave in lead V_3 >2.00 mV	
Men, R wave in lead aVL + S wave in lead V_3 >2.80 mV	

[a]Left ventricular hypertrophy, 5 points; probable left ventricular hypertrophy, 4 points.
Modified from Romhilt DW, Bove KE, Norris RJ, et al. A critical appraisal of the electrocardiographic criteria for the diagnosis of left ventricular hypertrophy. *Circulation* 1969;40:185; Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 1949;37:161; and Casale PN, Devereux RB, Alonso DR, et al. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. *Circulation* 1987;75:565.

The ECG diagnosis of left ventricular hypertrophy is difficult regardless of physician training and testing conditions (40). Computers may not perform significantly better. In a comparison of several automated algorithms, left ventricular hypertrophy was correctly identified only 50% to 76% of the time (141). These difficulties may be explained by differences across populations in the prevalence of left ventricular hypertrophy (with better ECG correlations for white nonobese men) (142), distortion in the perceived prevalence of left ventricular hypertrophy by physicians (143), and variations in the spectrum of hypertrophy severity (144).

Left Ventricular Hypertrophy with Left Bundle Branch Block

Because most patients with LBBB also have anatomic left ventricular hypertrophy, determining the cause of increased QRS duration in a particular subject is difficult. The best correlation between QRS duration and ventricular mass is obtained at QRS widths of 135 ms or less (145). Criteria for left ventricular hypertrophy are more sensitive in the presence of left-sided intraventricular conduction disturbances, probably because patients with LAFB or LBBB tend to have more severe left ventricular hypertrophy than patients who do not.

Left atrial abnormality is a strong independent predictor of increased left ventricular mass in the presence of LBBB (140). A sum of the amplitudes of the S wave in V_2 and the R wave in V_6 of 4.5 mV or more has a sensitivity of 86% and a specificity of 100% for detection of left ventricular hypertrophy in patients with LBBB (146). Less useful criteria are S-wave amplitude in V_3 of 2.5 mV or higher (sensitivity, 56%; specificity, 90%) and R + S in any precordial lead of 4 mV or higher (sensitivity, 63%; specificity, 66%). A QRS duration of 0.16 second or higher is sensitive (75%) but not specific (34%); a QRS axis at –30 degrees or more, on the other hand, is highly specific (100%) although not sensitive (30%) (147).

Left Ventricular Hypertrophy with Left Anterior Fascicular Block

Left ventricular hypertrophy superimposed on LAFB increases the S wave in lead III and the R or S wave (or both) in precordial leads. An index that includes these changes [i.e., (R + S) maximal precordial ³3.0 mV + SIII] has 87% specificity and 96% sensitivity for left ventricular hypertrophy, with a positive predictive value of 89% and a negative predictive value of 95% (148).

Left Ventricular Hypertrophy with Right Bundle Branch Block

The presence of RBBB decreases the sensitivity of the ECG criteria for left ventricular hypertrophy, particularly for precordial signs. In nonobese patients with RBBB, a Sokolow index of 3.5 mV or above is 100% specific for left ventricular hypertrophy (149). Another useful sign when both disorders coexist is left atrial abnormality. The presence of a P-wave terminal force in lead V_1 increases the sensitivity for left ventricular hypertrophy to over 70%, with an approximate specificity of 80% (150). Each 0.1-mV increase in the P terminal force is associated with approximately 25 g of increase in left ventricular mass (151).

Right Ventricular Hypertrophy

Right Ventricular Hypertrophy and Right Bundle Branch Block

The right ventricle dilates either during compensation for a volume overload or after hypertrophy eventually fails to compensate for a pressure overload. This dilatation causes stretching of the right bundle branch, which courses from base to apex on the endocardial surface of the right side of the interventricular septum. When the impulse conduction within these right bundle and Purkinje fibers has slowed so much that electrical activation arrives at the right ventricle only after it has already been activated by impulses spreading from the left ventricle, RBBB has developed.

A 22-year-old Caucasian female patient with primary pulmonary hypertension.

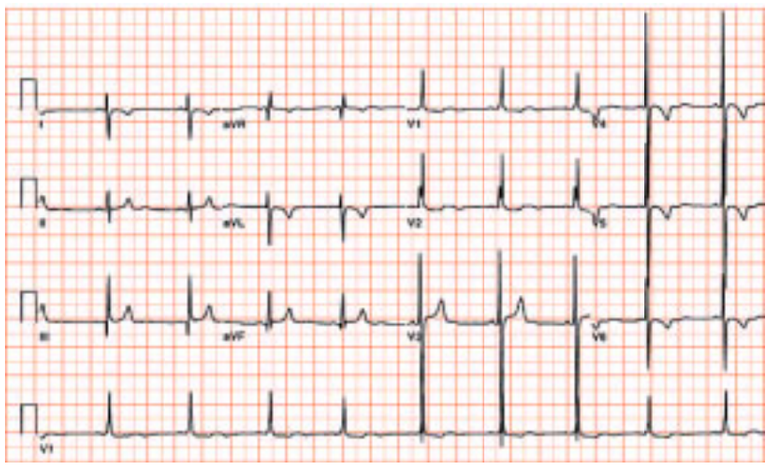
Electrocardiographic Diagnosis of Right Ventricular Hypertrophy

Right ventricular hypertrophy is normal in the neonate because during fetal development resistance is greater in the pulmonary than in the systemic circulation. Hypertrophy of the right ventricle persists during the first months of life. The QRS axis measures 100 degrees or more, and the QRS complex is predominantly positive in lead V_1 and predominantly negative in V_6. Such a highly specific pattern for neonatal right ventricular hypertrophy can rarely be found later in life. In adults, changes in response to right pressure overload are less typical because the right ventricular mass must be sufficiently large to overcome the left forces (152). Initially, the QRS complex in lead V_1 loses its negative predominance and a late positive R' wave may appear. With moderate hypertrophy the initial QRS forces move anteriorly (increased R wave in V_1), and the terminal QRS forces move rightward (increased S wave in lead I). Marked hypertrophy results in a predominantly positive QRS complex in V_1; the R wave is greater than 0.7 mV, the R/S ratio is greater than 1, and the S wave is less than 0.2 mV (153,154). Repolarization of the right ventricular myocardium is delayed, which produces negativity of both the ST segment and the T wave (ventricular strain).

The ECG criteria have poor sensitivity for detecting right ventricular hypertrophy. Right-axis deviation of 110 degrees or more identifies only 12% of cases, and the sensitivity of R-wave amplitude and R/S ratio in V_1 is lower than 10%. The specificity of all the criteria is moderate (155).

Biventricular Hypertrophy

Enlargement of both ventricles may lead to cancellation of opposite forces and result in a normal ECG. In some patients, tall R waves develop in all precordial leads with prominent, biphasic QRS complexes in midprecordial leads. Biventricular hypertrophy may also be considered when, coexisting with a pattern of left ventricular hypertrophy, the ECG shows (a) right-axis deviation to 90 degrees or more in the frontal plane, or (b) an R wave greater than the Q wave in aVR and an S wave greater than the R wave in V_5 (156).

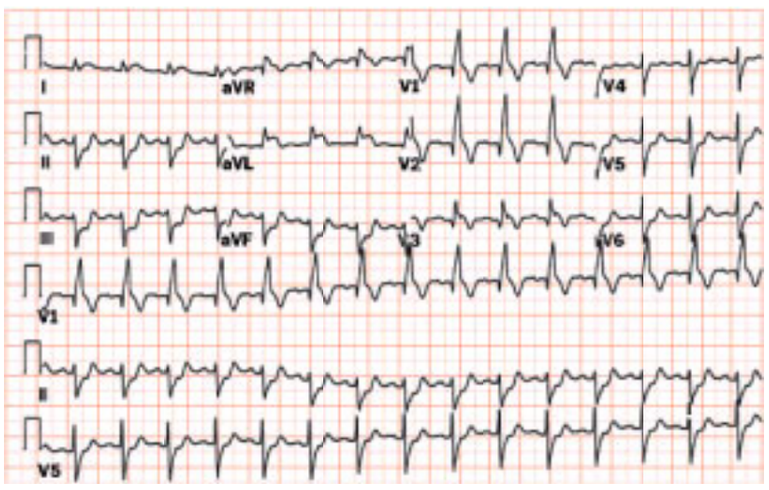


A 16-year-old male patient with biventricular hypertrophy secondary to ventricular septal defect and Eisenmenger's syndrome.

BUNDLE BRANCH AND FASCICULAR BLOCKS

An isolated conduction delay in the common bundle of His has a similar effect on activation of both ventricles; therefore, it does not alter the appearance of the QRS complex. The intraventricular conduction disturbances are termed *unifascicular blocks* when the ECG shows evidence of blockage of either the right bundle branch (RBBB), the left anterior fascicle (LAFB), or the left posterior fascicle (left posterior fascicular block, LPFB). The mildest manifestation of intraventricular conduction defects may be left-axis deviation. The normal conduction time (estimated when the QRS axis is at +90 degrees) increases linearly by a few milliseconds for each shift of the QRS axis toward the left (up to –90 degrees). At –30 degrees, the increase is 25 ms (157).

In *bifascicular blocks* the conduction is interrupted in two fascicles (i.e., LBBB, RBBB with LAFB, and RBBB with LPFB). The Purkinje system is not represented on the surface ECG, and conduction blocks at its level must be detected indirectly by their effects on myocardial activation and the QRS complex.



Acute anterolateral myocardial infarction complicated by conduction disturbance. ST-segment elevation in the anterior precordial leads as well as leads I and aVL is associated with right bundle branch block and left anterior hemiblock.

Conduction blocks vary in nature from anatomical lesions that interrupt impulse transmission in the specialized fibers to permanent or transient delays caused by nonuniformity of refractoriness, changes in membrane responsiveness, or decreased transmembrane action potential secondary to phase 4 of depolarization. These electrophysiologic conditions may result from ischemia, electrolyte imbalances, or cardioactive drugs. A stereotyped ECG pattern of bundle branch block develops regardless of the mechanism involved or the precise site of the conduction abnormality.

Electrocardiographic criteria for bundle branch and fascicular blocks are listed in *e*Table 59.0.4.

***e*TABLE 59.0.4** CRITERIA FOR THE DIAGNOSIS OF BUNDLE BRANCH AND FASCICULAR BLOCKS
Definition of ventricular conduction delays
A. Complete bundle branch blocks
Qualifying statements:
(S1) QRS duration ³0.120 sec (adults)
(S2) Supraventricular rhythm
(S3) Absence of WPW pattern
Criteria for a complete bundle branch block:
(a) S1 and S2 and S3
1. Complete RBBB
Qualifying statements:
(S1) R' or r' in V_1 or V_2
(S2) S duration >R duration in I and V_6
(S3) S duration >0.040 second in I and V_6
(S4) R peak time >0.050 second in V_1 or V_2
Criteria for RBBB:
(a) S1 and S2 or
(b) S1 and S3 or
(c) S4 and (S2 or S3)
2. Complete LBBB
Qualifying statements:
(S1) Broad and notched or slurred R in I and V_5 or V_6
(S2) Absence of Q wave in I and V_5 and V_6
(S3) R peak times ³0.060 sec in V_5 or V_6
Criteria for LBBB:
(a) S1 and S2 and S3
3. Nonspecific (unspecified) intraventricular block
All cases with QRS duration >0.12 sec that do not meet the criteria for LBBB or RBBB
B. Incomplete bundle branch blocks
1. Incomplete LBBB
Qualifying statements:
(S1) QRS duration ³0.100 sec and QRS duration <0.120 sec
(S2) Absence of Q waves in I and V_5 or V_6
(S3) R peak time >0.060 sec in V_5 or V_6
Criteria for incomplete LBBB:
(a) S1 and S2 and S3
2. Incomplete RBBB
Qualifying statements:
(S1) QRS duration <0.120 sec
(S2) r' or R' in V_1 or V_2
(S3) R' >R in V_1 or V_2
(S4) R peak time >0.050 sec in V_1 or V_2
Criteria for incomplete RBBB:
(a) S1 and S2 and S3 or
(b) S1 and S4
C. Fascicular blocks
1. LAFB
Qualifying statements:
(S1) QRS duration <0.120 sec
(S2) QRS axis £–45 degrees
(S3) QRS axis £–30 degrees and QRS axis >–45 degrees
(S4) rS pattern in II and III and aVF
(S5) qR pattern in aVL
(S6) R peak time ³0.045 sec in aVL
(S7) Slurred R downstroke in aVL
(S8) Slurred S in V_5 or V_6
Criteria for uncomplicated LAFB:
(a) S1 and S2 and S4 and S5 and S6 or
(b) S1 and S2 and S4 and S5 and S7 or
(c) S1 and S2 and S4 and S5 and S8
Qualifying statement:
(S4 is usually present with criteria a, b, and c above. If there is a QS in lead II, LAFB cannot be differentiated from interior myocardial infarction.
Criteria for possible uncomplicated LAFB:
(a) S1 and S3 and S4 and S5 and S6 or
(b) S1 and S3 and S4 and S5 and S7 or
(c) S1 and S3 and S4 and S5 and S8
2. LPFB
Qualifying statements:
(S1) QRS duration <0.120 sec
(S2) QRS axis >90 degrees and QRS axis <180 degrees
(S3) R in III > R in II (note that S3 is a consequence of S2)
(S4) qR pattern in III and aVF with Q duration £0.040 sec
(S5) absence of other causes of right-axis deviation
Criteria for LPFB:
(a) S1 and S2 and S3 and S4 and S5

LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block; WPW, Wolff-Parkinson-White syndrome.
From Willems JL, Robles Da Medina EO, Bernard R, et al. Criteria for intraventricular conduction disturbances and pre-excitation. *J Am Coll Cardiol* 1985;5:1261–1275, with permission.

Right Bundle Branch Block

The right ventricle contributes minimally to the normal QRS complex. Thus, RBBB produces little distortion during the time required for left ventricular activation; Figure 59.8 illustrates the slight changes of the early portion of the QRS complex contrasting with the marked distortion of its late portion. Late activation of the normal right ventricular myocardium via the spread of impulses from the left ventricle produces a late prominent R' wave in lead V_1 that follows the R wave produced by normal left-to-right activation of the septum. The presence of an RSR' configuration of the QRS complex is pivotal for the diagnosis of RBBB (*e*Table 59.0.4). However, this pattern may also be produced by a terminal conduction delay—vectorcardiographically dissimilar to either RBBB or LBBB—typical of posterior infarction (158). When the QRS duration is less than 0.12 second, the RSR' pattern may correspond to incomplete RBBB or a normal variant.

FIGURE 59.8 Right bundle branch block. The patient may also have right ventricular hypertrophy.

Fascicular Blocks

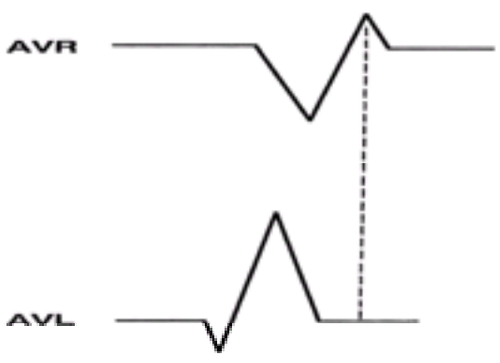
The anterior fascicle activates a portion of the left ventricle that is superior and to the left of that activated by the posterior fascicle. When both fascicles are intact, the impulse travels through them at the same time to depolarize the myocardium. The wavefronts from each fascicle then collide near the end of ventricular depolarization. An interruption or delay of impulse conduction in one fascicle results in asynchronous activation of the left ventricle.

LAFB is common and benign; LPFB is rare (159). Fascicular blocks are often associated with coronary artery disease. In autopsy studies, the most frequent finding underlying LAFB is anterior infarction with proximal left anterior descending (LAD) artery occlusion. Posterior infarction, however, is not usually associated with LPFB; autopsy examination in LPFB shows massive infarct of the septum (compromising both the anterior and posterior areas) and widespread damage to the left bundle branch (160).

Left Anterior Fascicular Block

In epidemiologic surveys, LAFB is the most common conduction abnormality, perhaps because the left anterior fascicle is located in the outflow tract and in apposition to the aortic ring; this makes it susceptible to increases in intraventricular pressure and disorders of the aortic valve (161). The initial ventricular activation in LAFB spreads inferiorly and rightward via the left posterior fascicle (13). Block in the anterior fascicle removes the competition from activation directed superiorly and leftward, and Q waves appear in leads with the positive electrode on the left arm (I and aVL) (Fig. 59.9). The impulse arrives at the inferior and apical myocardium retrogradely from the posterior fascicle with a minimal delay that prolongs the QRS by 0.02 second. The remainder of the left anterior ventricular wall is activated in a superior, leftward, and counterclockwise direction. These terminal forces are first represented in lead aVL and then in aVR. Thus, the peak of the terminal R in lead aVL precedes the peak of the terminal R wave in a simultaneous lead aVR (eFig. 59.9.1) (162). The R waves in leads I and aVL are prominent, and the large amplitude of the R wave in aVL may mimic left ventricular hypertrophy. Prominent S waves are seen in leads II, III, and aVF, causing a leftward shift of the QRS axis. This QRS-axis deviation is the major criterion for the diagnosis of LAFB (eTable 59.0.4). The original QRS-axis criterion proposed by Rosenbaum (and adopted by the World Health Organization/International Society and Federation for Cardiology Task Force) of –45 degrees has been considered highly specific but rather insensitive to detect LAFB (45); other authors use –30 degrees.

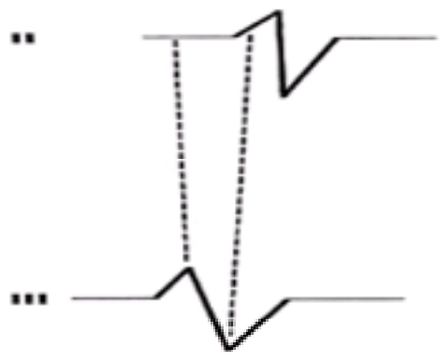
FIGURE 59.9 Left anterosuperior fascicular block. (From Wagner GS, ed. *Marriott's practical electrocardiography,* 9th ed. Baltimore: Williams & Wilkins, 1994:89, with permission.)



***e*FIGURE 59.9.1** Relation of the terminal QRS portion in leads aVR and aVL for the diagnosis of left anterior fascicular block. (From Warner RA. Recent advances in the diagnosis of myocardial infarction. *Cardiol Clin* 1987;5:381–392, with permission.)

The diagnosis of LAFB in the presence of inferior myocardial infarction is difficult because both entities produce left-axis deviation. In addition, inferior infarcts tend to produce a superior deviation of the initial depolarization forces, while LAFB directs them inferiorly, which thus counteracts the manifestations of inferior infarct. Warner and colleagues have proposed several criteria for the diagnosis of coexistent LAFB and inferior infarct, based on the correspondence of the QRS complex portions between simultaneous leads (162) (eTable 59.0.5, eFig. 59.9.2).

***e*TABLE 59.0.5** CRITERIA FOR THE DIAGNOSIS OF INFERIOR INFARCTION WITH LEFT ANTERIOR FASCICULAR BLOCK
Leads aVR and aVL both end in R waves, with the peak of the terminal R wave in lead aVR occurring later than the peak of the terminal R wave in lead aVL.
The points of maximum deflection of the QRS complex in lead III precede the points of maximum deflection of the corresponding portions of the QRS complex in lead II.
Q wave of any magnitude is seen in lead II.



***e*FIGURE 59.9.2** Relation of the initial QRS portion in leads II and III for the diagnosis of left anterior fascicular block in the presence of inferior infarct. (From Warner RA. Recent advances in the diagnosis of myocardial infarction. *Cardiol Clin* 1987;5:381–392, with permission.)

Left Posterior Fascicular Block

LPFB is usually associated with RBBB; its isolated form is rare. Rosenbaum and colleagues attributed the low incidence of LPFB to the fact that the posterior fascicle is short and thick and it is the first group of fibers to depart from the bundle of His. The posterior fascicle may also be protected by its dual blood supply from the anterior and posterior descending coronary arteries and because it lies in the less turbulent left ventricular inflow tract (13).

Aside from its association with coronary artery disease, LPFB has also been identified in cardiomyopathies, aortic valve disease, and calcification of the left ventricular skeleton (163). The initial activation of the left ventricular free wall when the left posterior fascicle is blocked occurs via the left anterior fascicle (13). The excitation front is directed superiorly and leftward. No forces travel inferiorly or rightward, and thus Q waves appear in leads with the positive electrode on the left leg (leads II, III, and aVF). Next, the activation wave spreads over the remainder of the left ventricular free wall in an inferior and rightward direction. This produces prominent R waves in leads II, III, and aVF and prominent S waves in leads I and aVL, which cause a rightward shift of the QRS axis to at least +90 degrees (164) (*e*Fig. 59.9.3). The QRS duration is slightly prolonged (by 0.02 second). The diagnosis of LPFB can only be made in the absence of right ventricular hypertrophy, because this condition itself can produce an LPFB pattern.

***e*FIGURE 59.9.3** Probable left posteroinferior fascicular block, suggested by extreme right axis deviation, in electrocardiogram of a 73-year-old woman. (From Wagner GS, ed. *Marriott's practical electrocardiography,* 9th ed. Baltimore: Williams & Wilkins, 1994:90, with permission.)

Midseptal Fascicle and Midseptal Fascicular Block

Application of the term *trifascicular* to the intraventricular conduction system alludes to the existence of two divisions (fascicles) of the left bundle branch in addition to the right bundle branch (33). The use of the term *trifascicular* by some authors to describe an additional subdivision of the bundle of His creates confusion (165). Histopathologic studies have identified discrete midseptal fibers in the anterior wall of the left ventricle (between the anterior and posterior fascicles), which stem separately from the bundle of His and may contribute to the propagation of the cardiac impulse (31,166,167). In this case, the intraventricular conduction system would comprise four fascicles, and the term *quadrifascicular* would apply (168).

Controversy exists regarding the existence of a distinct midseptal fascicle. Yet some investigators have reported clinical ECG observations compatible with midseptal fascicular block. A study of patients with no evidence of right ventricular hypertrophy described an ECG pattern mimicking posterior infarct with a narrow QRS complex shifted anteriorly in the horizontal plane but normally oriented in the frontal plane, with relatively tall R waves in lead V_1 and prominent R waves in leads V_2 through V_4. Angiography in these patients showed LAD artery (rather than right coronary) occlusion and akinesia of the left anterior ventricular wall, which suggests that the electrocardiographic pattern may have been caused by ischemic midseptal block.

The approximate incidence of anterior conduction delay with extreme QRS-axis deviation in the horizontal plane is 2% in normal subjects, but it may be much higher (e.g., approximately 25%) in patients with coronary artery disease or cardiomyopathy (167). Properly timed atrial extrastimuli in patients with normal QRS during sinus beats reproduce the QRS morphology of the conduction defect (169). Thus, anterior conduction delay has also been considered a borderline defect between a "true block" and a normal variant (which would result from a disproportion in the lengths of several fascicles of the left bundle branch, the left anterior fascicle being the longest and the anterior midfibers the shortest).

Other authors disagree with the notion that tall R waves in V_2 secondary to LAD occlusion represent midseptal block. The left midseptal fascicle receives its blood supply from midseptal perforator branches of the LAD (170). When an angioplasty balloon is inflated in the mid-LAD, the initial anterior vectors are reduced, with a *decrease* of the R wave in V_2 (171). The same result is obtained with properly timed extrastimuli (172). Thus, ischemically induced prominent R waves in V_2 may rather correspond to right septal conduction delay, reproducible with occlusion of the distal LAD (170).

Left Bundle Branch Block

LBBB produces marked distortion of the QRS complex (Fig. 59.10), and it may be caused by disease either in the main left bundle branch (predivisional) or in its fascicles (postdivisional). The presence of LBBB signs in a screening ECG correlates well with left ventricular systolic dysfunction (76).

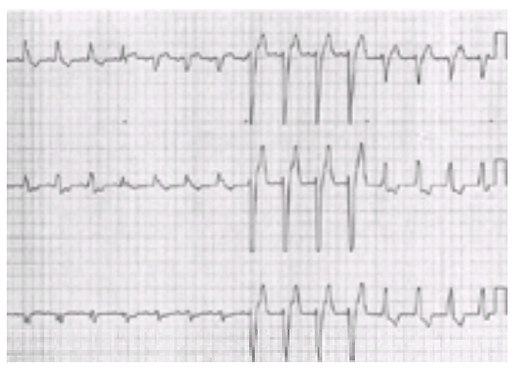


FIGURE 59.10 Uncomplicated left bundle branch block.

Left bundle branch block. Wide QRS complex, negative in lead V_1, is associated with secondary T-wave inversions.

The interventricular septum is normally activated from left to right. This produces an initial R wave in the right precordial leads and a Q wave in leads I and aVL as well as in the left precordial leads. During LBBB, the septum is activated from right to left. Initial Q waves are inscribed in the right precordial leads and the normal Q waves in V_5 and V_6 disappear. The ventricular activation front then proceeds from the left interventricular septum to the adjacent anterior superior and inferior walls, to the posterolateral free wall. This sequence of activation tends to produce monophasic QRS complexes: QS in lead V_1 and R in leads I, aVL, and V_6.

LBBB is characterized by secondary repolarization changes of opposing polarity to that of the main QRS deflection. For leads with a predominantly negative QRS complex, this results in an ECG pattern of ST-segment elevation with positive T waves, similar to the current of injury of acute coronary occlusion. Uncomplicated LBBB thus resembles anterior wall myocardial infarction (Fig. 59.10), and when left-axis deviation is also present, the repolarization pattern mimics that of inferior infarct.

The most important differential diagnosis of LBBB is the QRS pattern of the “corrected” transposition of the great vessels. In this condition, the initial QRS force shows the same direction as in LBBB because propagation of the impulse is inverted, but the QRS duration is normal.

Left Bundle Branch Block with Left-Axis Deviation

Several authors have reported a more severe organic heart disease and longer H-V intervals in patients with LBBB with left-axis deviation than in those with normal axis, which suggests a more diffuse pathologic compromise involving the left anterior fascicle (173,174). In most patients with intermittent LBBB and left-axis deviation, however, the QRS axis is normal during normally conducted beats (159,175). This suggests that left-axis deviation during LBBB results from a different septal activation pattern (i.e., site and extent of reengagement of the left-sided ventricular specialized conduction system after transseptal conduction) and not from a direct anatomical compromise of the left anterior fascicle.

Nonspecific Intraventricular Block

A QRS duration of 0.11 second or greater that does not satisfy the criteria for either RBBB or LBBB is considered a nonspecific intraventricular block (45).

Right Bundle Branch Block with Left Anterior Fascicular Block

LAFB not only appears as a unifascicular block much more commonly than LPFB, it also accompanies RBBB more often than does LPFB. The diagnosis is made by the late prominent R or R’ wave in V_1 typical of RBBB, and the initial R waves and prominent S waves in leads II, III, and aVF seen in LAFB. The QRS duration should be at least 0.12 second and the frontal plane axis should be between –45 degrees and –120 degrees (*e*Fig. 59.10.1).

***e*FIGURE 59.10.1** Right bundle branch block and left anterior fascicular block. The patient is a 66-year-old man with fibrosis of the conduction system. The markedly prolonged QRS duration (0.20 second) suggests underlying left ventricular hypertrophy. (From Wagner GS, ed. *Marriott’s practical electrocardiography,* 9th ed. Baltimore: Williams & Wilkins, 1994:94, with permission.)

Right Bundle Branch Block with Left Posterior Fascicular Block

The combination of RBBB with LPFB is less common than the combination of RBBB with LAFB. Even if ECG changes are typical, the diagnosis can be made only if no clinical evidence of right ventricular hypertrophy is present. The diagnosis of RBBB with LPFB should be considered when typical changes of RBBB are seen in V_1 and the initial R waves and prominent S waves of LPFB are present in I and aVL. The QRS duration should be at least 0.12 second and the frontal plane axis at 90 degrees or more (*e*Fig. 59.10.2).

***e*FIGURE 59.10.2** Combination of right bundle branch block and left posterior fascicular block. Electrocardiograms from a 71-year-old woman **(A)** and a 77-year-old man **(B)** with probable fibrosis of the conduction system. Note the prolonged PR interval in **B**, which suggests involvement of the left anterosuperior fascicle in addition. (From Wagner GS, ed. *Marriott’s practical electrocardiography,* 9th ed. Baltimore: Williams & Wilkins, 1994:95, with permission.)

Prognostic Significance of Bundle Branch Block

Isolated RBBB was found in 0.18% and LBBB in 0.1% of 110,000 subjects screened in Ireland. In the absence of clinically overt cardiac disease, bundle branch block was not associated with increased overall mortality. Isolated LBBB, however, carried a risk of development of cardiovascular disease and increased cardiac mortality (176). The most common abnormalities in patients with newly acquired LBBB are hypertension, cardiomegaly, and coronary artery disease. These entities have usually been diagnosed before the appearance of the conduction defect (174). In chronic coronary disease, the presence of LBBB is an independent predictor for mortality (177).

Trifascicular Blocks

Electrocardiographic documentation of trifascicular block during 1:1 AV conduction is rare and requires the presence of alternating RBBB and LBBB or fixed RBBB with alternating LAFB or LPFB (13). If both bundle branches are simultaneously affected by block, the ECG shows complete AV block. When the degree of block differs between the two bundle branches, ECG manifestations vary and include, for example, a shorter PR interval preceding either RBBB or LBBB, or a complete bundle branch block with prolonged PR interval (27). The combination of bifascicular block (RBBB + LAFB; RBBB + LPFB; or LBBB) with first-degree AV block on the surface ECG cannot be considered trifascicular block because the site of AV block can be either the AV node or the His-Purkinje system (178). His bundle electrocardiography may be necessary to evaluate conduction in the remaining fascicle in symptomatic patients with bifascicular block.

A 93-year-old male patient with trifascicular block.

ABERRANCY

Aberrant intraventricular conduction is the abnormal, asynchronous propagation of an impulse through the His-Purkinje system resulting in an altered QRS complex. This definition excludes conduction of supraventricular impulses via accessory pathways that bypass the AV node. Changes in the QRS complex may affect its duration, axis, or amplitude; successive aberrant beats may mimic ventricular tachycardia (179). The occurrence and extent of aberrancy are determined by (a) prematurity of the supraventricular impulse (i.e., excitation before completion of repolarization), (b) basic RR cycle and RR cycle preceding the premature beat, (c) velocity of AV nodal conduction, (d) refractoriness of the bundle branch, and (e) level of diastolic depolarization of the bundle branch system. The right bundle branch is more frequently involved in aberrant conduction than the left, probably because of its longer action potential duration at normal rates. Common manifestations of aberrancy include aberrant conduction of atrial premature beats, the Ashman phenomenon, acceleration-dependent (phase 3) aberrancy, deceleration-dependent (phase 4) aberrancy, concealed transseptal conduction (linking), and diffuse myocardial depression of conduction. “Pseudo–bundle branch block” was first demonstrated in patients by Castellanos and colleagues. It is induced by concealed premature impulses arising in the bundle branches (180).

Ashman’s phenomenon. Underlying rhythm is atrial fibrillation. QRS complex with right bundle branch block morphology after long-short coupling interval is diagnostic of Ashman’s phenomenon.

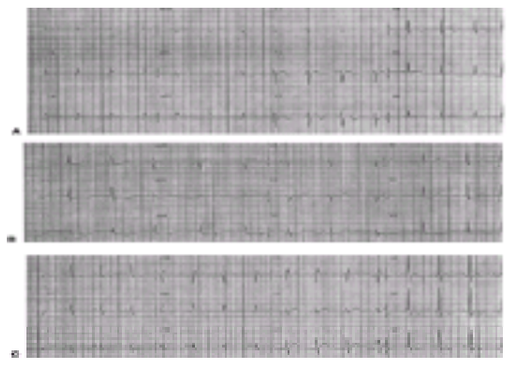
ISCHEMIC HEART DISEASE

Myocardial Ischemia and Injury: General Electrophysiologic Principles

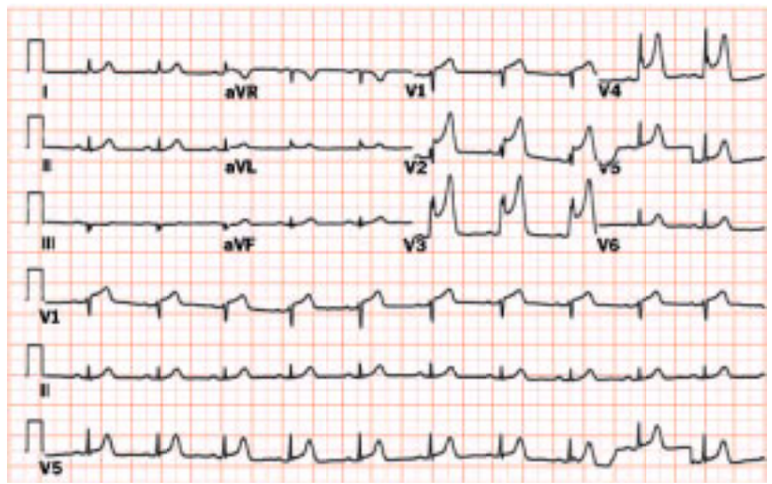
Myocardial ischemia results in two main electrophysiologic changes. First, myocytes partially depolarize and their membrane resting potential is reduced (i.e., becomes less negative). Second, the action potential duration and amplitude decrease. Local injury currents develop between ischemic and nonischemic cells that manifest in the ECG as ST-segment deviation toward the specifically involved area. During diastole, injury currents flow from ischemic to normal cells; during systole, injury currents flow in the opposite direction. Traditionally, ECG changes caused by an increase in myocardial metabolic demand or a decrease in coronary blood flow are called *ischemia* when changes affect only the T wave, and *injury* when changes affect the ST segment. Epicardial (or transmural) injury is characterized by ST-segment elevation and endocardial (“subendocardial”) injury by ST-segment depression.

Electrocardiographic Ischemia (T-Wave Changes)

The first ECG change during transmural ischemia is the development of peaked, tall T waves; this usually precedes ST-segment elevation (181). The ischemic zone is electrically more negative than its surrounding myocardial area during the recovery phase. Thus, while ST elevation is still present or after it has subsided, the T waves become inverted in relation to the QRS complexes (*e*Fig. 59.10.3). Normally the angle between the directions of the QRS complexes and the T waves is less than 45 degrees in the frontal plane and less than 60 degrees in the horizontal plane. When the angles are increased, the presence of myocardial ischemia should be considered. The T-wave inversion may regress within minutes or persist for several months (27). These primary T-wave changes are not specific or sensitive for the diagnosis of myocardial ischemia (181).



***e*FIGURE 59.10.3** Three resting electrocardiograms have various abnormalities in addition to T-wave inversion, which suggest ischemia in various areas of the left ventricle. **A:** Anteriorly in the distribution of the anterior descending artery. **B:** Inferiorly in the distribution of the posterior descending artery. **C:** Laterally and apically in the distribution of the diagonal branch of either the anterior descending or the circumflex artery. (From Wager GS, ed. *Marriott's practical electrocardiography,* 9th ed. Baltimore: Williams & Wilkins, 1994:131, with permission.)



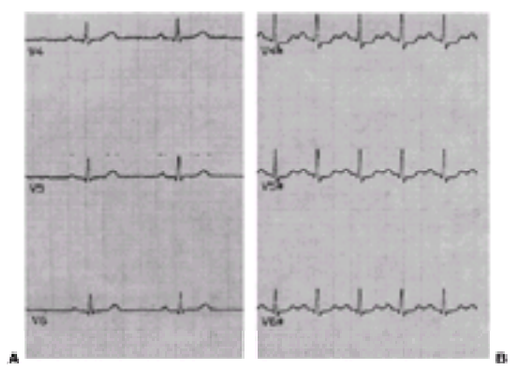
Acute anteroseptal myocardial infarction. Dramatic ST segment elevations in leads V_1 through V_5 with associated hyperacute T-wave changes are noted.

For some patients with chest pain presenting to the emergency room, negative T waves may be the first electrocardiographic finding observed—perhaps because ST elevation has already subsided. Biochemical changes may indicate acute or subacute (i.e., non–Q wave) myocardial infarction. These negative T waves and those observed after documented ST-elevation infarction have been labeled "postischemic" (27). Yet negative T waves that appear soon after ST-elevation infarction seem to be predictors of improved survival (117). Thus, other factors aside from ischemia (e.g., reperfusion) possibly may have a role in the genesis of such T waves (181,182).

Electrocardiographic Injury (ST-Segment Changes)

Subendocardial Injury (ST-Segment Depression)

Ischemia secondary to an increased metabolic demand affects initially the subendocardium, the area most vulnerable to ischemic damage. Changes involve mainly the ST-T waveforms (and much less the QRS complex), because myocytes are less susceptible to ischemia during electrical depolarization than during electrical recovery. Diastolic injury currents produce TQ segment elevation in the surface ECG that results in apparent ST-segment depression, whereas systolic currents produce "true" ST-segment depression. Initial changes include a depression of the J point of at least 0.10 mV and a horizontal or downward sloping of the ST segment toward the T wave (*e*Fig. 59.10.4). The T wave may or may not be altered in the same direction as the ST segment. T-wave inversion may be secondary to ST depression (i.e., the T wave is "dragged" by the ST segment), or it may change as a direct manifestation of delayed repolarization in the ischemic myocardium.



***e*FIGURE 59.10.4** The electrocardiographic recording of a 67-year-old woman has a normal resting appearance of leads V_4 to V_6 **(A)** but 0.1-mV ST-segment depression in lead V_4 during exercise **(B)**. (From Wagner GS, ed. *Marriott's practical electrocardiography,* 9th ed. Baltimore: Williams & Wilkins, 1994:129, with permission.)

The current of injury occurs at the time that the subendocardial cells complete their activation process, and therefore it affects the QRS complex. The QRS waveforms deviate in the same direction as the ST segment. This distortion affects the amplitude but not the duration of the QRS complex and alters its later part more than its initial part (183). The ST-segment depression of subendocardial injury resolves rapidly after removal of the cardiovascular stress. When the ST-segment depression persists in the absence of increased left ventricular workload, the diagnosis of subendocardial infarction should be considered.

Transmural or Epicardial Injury (ST-Segment Elevation)

Transmural injury is caused by interruption of the blood supply to the myocardium because of occlusion of one of the three coronary arteries or their branches. The first ECG change is tall, peaked T waves (181). Then the ST segment appears elevated in the ECG leads that face the ischemic area and may appear depressed in the opposite ECG leads.

One of the following criteria must be met for the diagnosis of transmural injury: (a) elevation of the origin of the ST segment at the J point of 0.10 mV or higher in two or more limb or precordial leads V_4 to V_6, or of 0.20 mV or higher in two or more precordial leads V_1 to V_3 (*e*Fig. 59.10.5, Fig. 59.11); or (b) depression of the origin of the ST segment at the J point of 0.10 mV or higher in two or more of leads V_1 to V_3, or ST-segment elevation greater than 0.10 mV in two or more of leads V_7 to V_9.

***e*FIGURE 59.10.5** Acute anterior myocardial infarction. Transmural injury is manifested by ST elevation of greater than 0.2 mV in leads V_1 to V_3.

FIGURE 59.11 A: Acute anterior myocardial infarction, with ST elevation in precordial leads (day 1). The presence of ST elevation in leads I and aVL, plus ST depression in leads III and aVF, suggests proximal left anterior descending artery occlusion. **B:** Subacute anterior myocardial infarction (day 2). ST elevation is regressing, and negative T waves and new Q waves are developing.

A highly specific marker of transmural injury is alternans of the ST segment. Electrical alternans consists of alternans of the degree of ST elevation and is secondary to variations in action potential duration or amplitude; alternating ST elevation and depression have not been reported (129).

Severe degrees of ischemia are associated with distortion of the later part of the QRS, which reverses after the acute phase (184). The ECG manifestations of transmural injury vary in duration. Those observed in patients during coronary angioplasty or in patients with coronary vasospasm disappear rapidly when the coronary occlusion is removed (171), whereas in patients with transmural injury secondary to coronary thrombosis they resolve gradually after spontaneous or therapeutic restoration of flow. When insufficient coronary blood flow persists after the myocardial metabolic reserves become depleted, the process of necrosis begins (185). In most patients, permanent new Q waves develop at some point after ST elevation or depression has occurred. In ECG leads in which rapid Q waves are normally present (eTable 59.0.2), they may become pathologically wide.

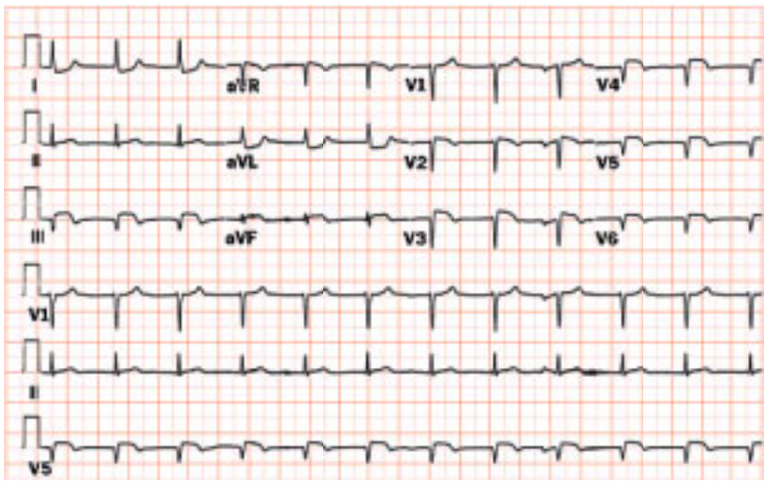
Acute Myocardial Infarction

The evolutionary changes during acute infarction include (a) ST elevation, often preceded by tall T waves, (b) abnormal Q waves, and (c) return of ST elevation to baseline with T-wave inversion. Tall or peaked T waves may be an early manifestation of transmural injury. The most typical change involves ST-segment elevation, which decreases significantly after the first 12 hours of chest pain (186) (Fig. 59.11). In some patients, multiple episodes of ST-segment elevation and resolution have been documented after thrombolytic therapy. A moderate ST elevation persists usually for several days; when observed beyond 2 weeks of the acute event, it suggests ventricular aneurysm. If coronary reperfusion is rapidly achieved, negative T waves usually develop and Q waves do not.

Lateral myocardial infarction. ST segment elevation in leads I and aVL associated with inferior reciprocal changes. Note preexisting anteroseptal myocardial infarction.

ECG DURING ACUTE MI

The diagnostic accuracy of the ECG depends on the extent and location of transmural injury or necrosis. In general, the 12-lead ECG is specific but only moderately sensitive for detection of acute myocardial injury (187,188). Systematically recording leads V_4R, V_8, and V_9 (i.e., a 15-lead ECG) increases the probability of detecting ST elevation from 47% to 59%, with no decrease in specificity (22). The infarction descriptors *anterior*, *inferior*, and *lateral* have classically been attributed to occlusions of the LAD, right coronary artery (RCA), and circumflex artery (LCX), respectively. Other terms such as *apical*, *septal*, *high lateral*, and *posterior* are also in use. The 12-lead ECG is only moderately accurate in determining the anatomic location of acute infarction, however, and the correspondence of some ECG terms with the pertinent site of infarction is rather poor (189). The ECG is most sensitive for detecting acute occlusion of the LAD and least sensitive for detecting involvement of the circumflex artery. Automated diagnoses of infarction (i.e., provided by the electrocardiographer) are specific but not sensitive; their most promising application is in the prehospital setting (190,191 and 192).



Right ventricular infarction. ST-segment elevation in leads V_4R and V_5R reveals right ventricular involvement complicating the inferior infarct.

Acute Anterior/Anteroseptal/Anterolateral Infarction (Left Anterior Descending Artery Occlusion)

During acute anterior injury, V_2 is the most sensitive lead for recording ST elevation (sensitivity, 99%) and for identifying the culprit lesion in the LAD. Other powerful predictors of proximal LAD occlusion include ST elevation in aVL and concomitant ST depression in inferior leads (193,194) (Fig. 59.11). ST elevation that extends to leads I and aVL often coexists with inferior ST depression. The magnitude of ST depression in inferior leads correlates better with that of ST elevation in leads I and aVL than with the ST elevation of precordial leads. The maximal ST elevation is best recorded in V_2 as well as V_3 (195) (eFig. 59.10.5; Fig. 59.11). Highly specific signs for occlusions at the level of the first septal perforator include ST elevation in aVR (196), disappearance of preexistent septal Q waves in lateral leads (197,198), and ST depression in V_5 (196).

Evolution of acute anterolateral myocardial infarction at 1 hour. Note "tombstoning" ST segments across the precordium as well as the lateral leads. Inferior reciprocal changes are seen.

Occasionally, ST elevation is also present in lead V_1. Lead V_1 captures electrical phenomena from the right paraseptal area, which is supplied by the septal branches of the LAD. In most patients the septum is additionally protected by a conal branch of the RCA (double circulation), and this explains why patients with anterior myocardial infarction usually have no ST elevation in V_1 (196). The presence of ST elevation in V_1 (eFig. 59.10.5) correlates strongly with ST elevation in V_3R and predicts the less common anatomical scenario in which a small conal branch of the RCA does not reach the interventricular septum (199).

Acute Inferior Infarction (Right Coronary or Circumflex Artery Occlusion)

The typical ECG pattern of inferior infarction consists of ST-segment elevation in leads II, III, and aVF (Fig. 59.12). In 80% to 90% of cases the culprit lesion is in the RCA (200); the remainder of the patients have LCX occlusion. Higher ST elevation in lead III than in lead II strongly suggests RCA occlusion (201,202). Because lead aVL faces the superior part of the left ventricle and directly opposes the inferior wall, ST-segment depression in aVL usually indicates RCA occlusion (sensitivity, 94%; specificity, 71%) (203). Precordial ST depression accompanying inferior injury is more likely to develop from LCX than from RCA occlusion (Fig. 59.13). Horizontal ST depression with initially negative then upright T waves in leads V_1 to V_3 or V_4 (Fig. 59.13) is associated with posterior wall motion abnormalities (204). Concomitant ST elevation in leads V_5 and V_6 also indicates posterolateral ischemia—triggered by either RCA or LCX occlusion (205). When this ST elevation is significant (more than 0.2 mV), it is likely a sign of infarction related to a "megaartery" (RCA or LCX), with a large ischemic burden (205).

FIGURE 59.12 Acute inferior myocardial infarction. Transmural inferior injury is accompanied by ST-segment depression in leads I, aVL, and V_1 to V_3.

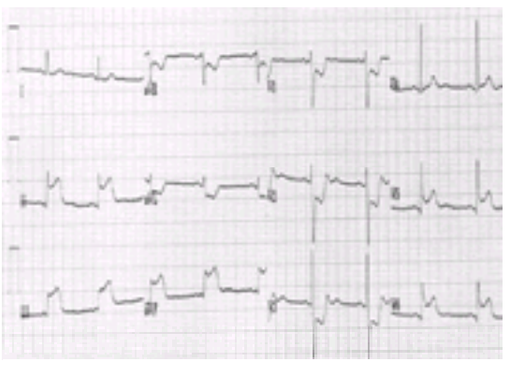
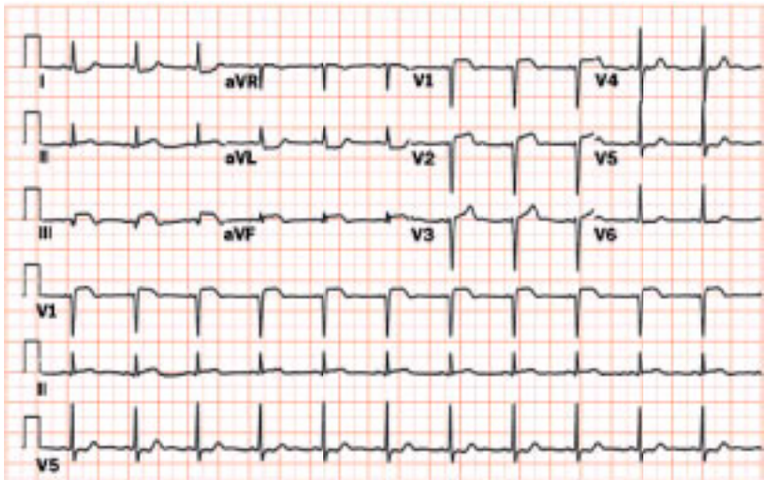


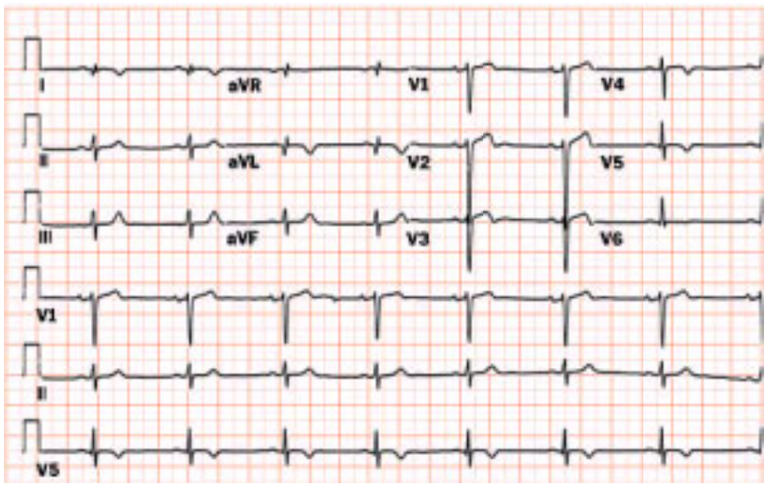
FIGURE 59.13 Acute inferior myocardial infarction produced by circumflex artery occlusion. ST elevation is present in leads V_5 and V_6 (suggesting "megaartery" occlusion), and ST depression with prominent U waves is seen in leads V_1 to V_3. The ST depression in aVL is unusual.



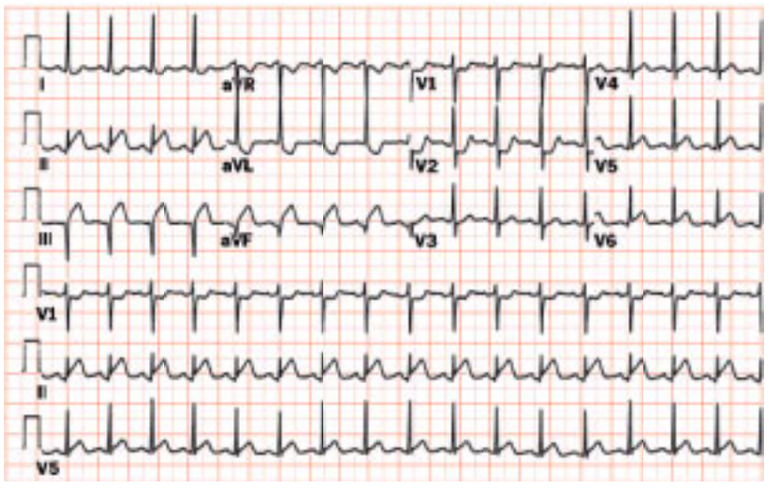
Acute inferior myocardial infarction with right ventricular involvement. Inferior ST-segment elevation associated with elevation in lead V_1. See right precordial leads.

Acute Lateral and Posterior Infarctions (Circumflex Artery Occlusion)

The vascular beds of the LCX show broad anatomic variability and supply a rather small ventricular area. This is why the standard 12-lead ECG displays ST-segment elevation in less than half of cases of LCX occlusion. When present, ST elevation is more often seen in leads II, III, and aVF, followed by leads V_5, V_6, and aVL (206). In some cases, a concomitant ST depression is seen in leads V_1 to V_3 (Fig. 59.13).



High lateral infarction, age unknown. Note prominent Q waves in leads I and aVL, associated with T-wave inversions.



Acute inferoposterior myocardial infarction. Note ST segment elevation in leads II, III and aVF with ST depression in leads V_1 and V_2.

One-third of patients with chest pain secondary to spontaneous LCX occlusion present with isolated ST depression. ST depression in V_1 and V_2 is a sensitive sign (203,206). Another one-third of patients present without any changes in the 12-lead ECG. In a study of 33 consecutively treated patients with LCX occlusion, however, ST elevation in V_7 through V_9 was always detected and was associated with posterior wall motion abnormalities (207). Leads V_7 to V_9 are more specific than precordial leads for detection of posterior infarction (84% vs. 57%), with similar sensitivity (approximately 80%) (208).

Acute Right Ventricular Infarction

Transmural injury of the right ventricle translates into ST-segment elevation of 0.1 mV or more in precordial leads. ST elevation in V_1 is highly specific for proximal RCA occlusion (202). In approximately 7% of patients, ST elevation extends to lead V_5, which suggests anterior infarction. This ST elevation decreases toward V_4, however, whereas in anterior injury from LAD occlusion, the ST segment is more elevated in V_2 and V_3 than in V_1 (209).

Right ventricular infarction is usually concurrent with infarcts of the inferior wall (eFig. 59.13.1). Half of patients with inferior injury have ST elevation in V_4R (sensitivity and predictive accuracy for right ventricular infarction are both 93%) (210). Isolated right ventricular infarction is rare and occurs mainly in patients with right ventricular hypertrophy (211).

***e*FIGURE 59.13.1** Inferior infarct with right ventricular compromise. Right-sided precordial leads V_2R to V_6R show ST elevation.

ST-Segment Depression in Patients with Acute Coronary Syndromes

Isolated ST-Segment Depression

In a study of 136 patients presenting with isolated ST-segment depression in the 12-lead ECG, evolution to infarction was observed in 54% of cases. One-year mortality was high for patients both with and without infarction (212). In general, ST depression is associated with older age, multivessel or left main coronary artery disease, multiple infarctions, or poor left ventricular function (213,214). A common cause of primary ST depression is the subocclusion of the left main coronary artery, and the ECG frequently shows a combination of ST depression in leads I, II, and V_4 to V_6 with ST elevation in aVR. A sum of ST changes of 18 mm is 90% sensitive for left main artery disease (215). A maximum ST depression in leads V_2 and V_3, on the other hand, indicates LCX occlusion (specificity, 96%; sensitivity, 70%). Recognizing this is important, because patients with isolated ST depression from LCX occlusion benefit from thrombolysis (216). Isolated ST depression in inferior leads may be caused by either inferior subendocardial ischemia or by a prominent atrial repolarization (Ta) wave during right atrial enlargement (100).

ST-Segment Depression Concomitant with ST Elevation

Many patients with acute chest pain present with “reciprocal” ST-segment depression, that is, ST depression concomitant with ST elevation in a different lead group. The mechanism underlying such ST depression is assumed to be mirroring, a phenomenon of electrical reflection of the transmural injury onto the opposite ventricular wall. The ST depression is captured by a lead placed at 180 degrees to the lead recording ST elevation, but the terms *reciprocal* and *mirror* are loosely applied to other recording points as well (217). For example, ST depression that is maximal in leads V_5 and V_6 may be related to acute ischemia of the right ventricle; it is the reciprocal of ST elevation in V_3R (181).

Another possible mechanism for ST depression is regional subendocardial ischemia or infarction. Although strictly speaking mirroring is also involved in the ST depression of subendocardial ischemia (because the ST elevation in the subendocardial layer is reflected onto the epicardial layer), most clinicians consider this ST depression “nonmirror” because it is a primary manifestation of artery occlusion, not secondary to ST elevation in a different territory (218). In patients with chest pain and predominant ST depression in any lead except aVR, ST depression of at least 0.4 mV is 97% specific (and 20% sensitive) for acute infarction (212). Several investigators have found that inferior ST depression during anterior injury is not accompanied by inferior ischemia (as assessed by perfusion imaging), which suggests that mirroring—rather than inferior subendocardial ischemia—is responsible for the ST depression (217,218). Over 85% of patients with ST depression in lead aVF have a culprit lesion in the proximal LAD. On the other hand, the significance of anterior ST depression accompanying inferior injury may depend on the leads involved. ST depression in leads V_1 through V_3 or I through aVL seems to correspond to mere mirroring, often from LCX occlusion. On the other hand, ST depression deeper in V_4 through V_6 than in V_1 through V_3 is associated with anterolateral or septal subendocardial injury from a severe lesion in the LAD or in the left main coronary artery (219) (Fig. 59.14).

FIGURE 59.14 Electrocardiogram recorded in a patient with ST elevation in inferior leads from acute right coronary thrombosis. The concomitant precordial ST depression, maximum in V_3 to V_6, probably corresponds to concurrent subendocardial injury. (From Wagner GS, ed. *Marriott’s practical electrocardiography,* 9th ed. Baltimore: Williams & Wilkins, 1994:140, with permission.)

Nonischemic ST Depression

The most important differential diagnosis in patients with ST depression and chest pain (with or without abnormal levels of creatine kinase) (220) is aortic dissection. As many as 50% of patients with dissection of the thoracic aorta may present with ECG abnormalities, mainly ST-segment depression (221), unless the origin of a coronary artery is involved in the dissection and signs of transmural injury develop.

Diagnosis of Acute Myocardial Infarction in the Presence of Confounding Factors

Right Bundle Branch Block

The diagnosis of evolving acute anterior infarction in patients with RBBB can be suspected when secondary T waves (opposite to the QRS complex) in leads V_1 to V_3 or V_4 are replaced by T waves of concordant polarity with the QRS (“pseudonormalization”). ST elevation is often easily detected (Fig. 59.15).

FIGURE 59.15 Acute anterior myocardial infarction with right bundle branch block (RBBB). Primary T waves have replaced the secondary T waves observed in RBBB.

Left Bundle Branch Block

In patients who present with acute chest pain and LBBB, ECG interpretation is difficult because the normal sequence of ventricular activation can be altered by both LBBB and acute myocardial injury. During either occlusion of a coronary artery by an angioplasty balloon or acute infarction, however, further ST-segment elevation does occur in LBBB (222,223 and 224). In a study that analyzed all published criteria for the diagnosis of acute infarction in the presence of LBBB, the ECGs of 131 patients who had LBBB and enzyme-confirmed acute infarction were compared with 131 ECGs of external controls who had chronic coronary artery disease and LBBB (*e*Table 59.0.6, Fig. 59.16). Criteria were validated in an independent sample of patients with acute coronary syndromes and LBBB. A scoring system suggested that a highly specific diagnosis of acute infarction could be made with a total score index of 3 points or higher (*e*Table 59.0.6). This score was associated with specificities of 90% or higher in both the derivation and the validation samples (225,226).

***e*TABLE 59.0.6** CRITERIA FOR THE DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION IN THE PRESENCE OF LEFT BUNDLE BRANCH BLOCK

Electrocardiographic criterion	**Score**
↑ ST ³1 mm concordant with QRS polarity	5
↓ ST ³1 mm in V_1, V_2, or V_3	3
↑ ST ³5 mm discordant with QRS polarity	2

↑, elevated; ↓, depressed.
From Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Engl J Med* 1996;334:481–487, with permission.

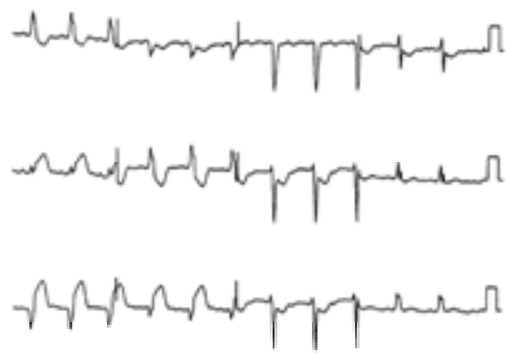


FIGURE 59.16 Electrocardiogram recorded in a patient with left bundle branch block and acute myocardial infarction. ST elevation greater than 0.3 mV is present in lead II (with concordant QRS polarity), ST elevation greater than 0.4 mV is present in leads III and aVF (with discordant QRS polarity), and ST depression is present in leads V_2 and V_3. (From Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Engl J Med* 1996;334:481–487, with permission.)

Ventricular Pacing

In patients with permanent pacemakers and chest pain, the presence of ST elevation of 0.5 mV or more in leads with a negative QRS complex has a specificity of 88% and a sensitivity of 53% for the diagnosis of acute infarction. Two other criteria with high specificity but low sensitivity are ST elevation of 0.1 mV in leads with concordant QRS polarity and ST depression of 0.1 mV or more in lead V_1, V_2, or V_3. No criteria involving the QRS complex or isolated T waves is highly specific (227).

Nondiagnostic Electrocardiograms

As many as 15% to 18% of acute myocardial infarctions do not produce changes in the initial ECG, and an additional 25% produce nonspecific changes (228). Recording serial ECGs increases the probability of detecting acute infarction (229). Maximizing the information provided by the *admission* ECG is ideal, however, because reperfusion therapies are more effective when administered early. A 15-lead ECG that includes leads V_4R, V_8, and V_9 should be obtained in all patients without ST elevation in the 12 standard leads; this increases the detection rate of ST elevation from 47% to 59% with no decrease in specificity (22). In patients with nondiagnostic ECGs at admission, the most frequent culprit artery is the circumflex (230). Once patients with acute infarction and normal admission ECGs have undergone angiographic evaluation and survived hospitalization, the frequency of involvement of the infarct-related artery is similar for the three major arteries. Patients who never develop ECG changes have lesions in branch vessels (231). In the absence of confounding factors, nondiagnostic ECGs in patients with suspected acute infarction are associated with a low incidence of in-hospital events and mortality (232).

Individuals who present to the emergency department with chest pain and signs of left ventricular hypertrophy in the ECG may pose a particular diagnostic challenge because secondary T waves and ST-segment changes act as confounders. Remarkably, a multicenter study concluded that patients with both acute chest pain and electrocardiographic signs of left ventricular hypertrophy are four times less likely to have acute myocardial infarction and one-third less likely to have ischemia than patients who do not show ECG signs of left ventricular hypertrophy (233).

ESTABLISHED MYOCARDIAL INFARCTION

Q-Wave Infarction

Although the ST segment is still elevated during ongoing transmural injury, abnormal Q waves begin to develop as a consequence of both the loss of electrical forces in the necrotic area and the predominant effect of the resultant force directed away from the area (Fig. 59.11). The deviation of the ST segments may confound the capability to measure the amplitudes of the QRS waveforms. Pathologic Q waves are recorded from all myocardial regions that depolarize early during the cardiac cycle. The posterobasal area depolarizes late, which thereby produces a positive QRS waveform in the precordial leads opposing this zone (i.e., V_1 and V_2).

In most patients, necrotic Q waves persist indefinitely after the acute event, but in 15% to 30% of cases they disappear or become nonsignificant. These regression changes are similar for patients with anterior and inferior infarcts (234,235). Small, rapid ‘r’ waves may also result from recovery of electrical activity in a necrotic area when QS complexes developed immediately after the acute episode. The presence of an initial ‘r’ wave of less than 20 ms in lead V_2, for example, is an excellent discriminator between presence and absence of anterior infarction (236).

Non–Q-Wave Infarction

After an episode of cardiac chest pain, even if accompanied by biologic markers of cardiac necrosis, some patients do not develop pathologic Q waves. Only small ‘q’ waves or ‘r’ waves of diminished amplitude appear. The labeling of these alternative ECG changes as Q-wave or non–Q-wave infarctions varies among authors (237).

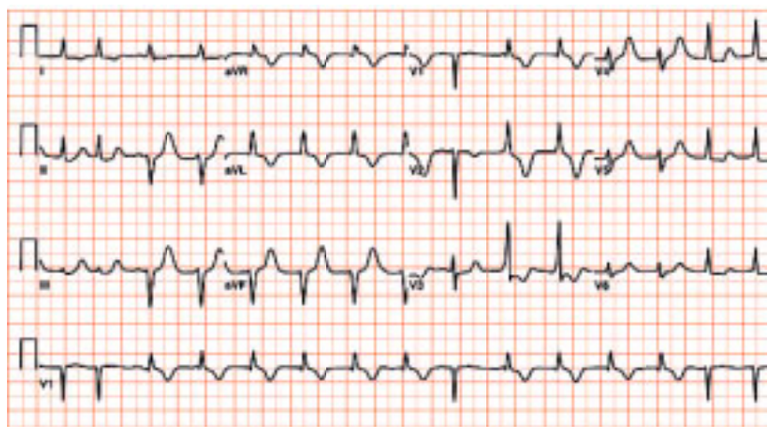
The most conspicuous changes of non–Q-wave infarction involve repolarization. Patients may present with ST elevation, depression, or both, or with isolated negative T waves (238). Early ECG changes cannot accurately predict evolution to non–Q-wave infarction. Also, approximately 9% of “non–Q-wave” infarctions result indeed from transmural injury of the left inferoposterior wall. These patients present with isolated ST depression in leads V_1 to V_4. A distinctive feature of anterior non–Q-wave infarction is a downsloping ST depression (as opposed to a horizontal ST depression in posterior infarcts) with precordial T-wave inversion (181).

The underlying angiographic finding in many patients with non–Q-wave infarction is a recanalized vessel (239). When a culprit vessel is identified, in 60% of cases it is the circumflex (240). The absence of Q waves does not seem to correlate anatomically with nontransmural necrosis (241). The prognosis of non–Q-wave infarction among patients treated with thrombolysis is better than that of Q-wave infarction, and it is markedly predicted by the repolarization changes in the admission ECG (242). Changes restricted to the T wave predict much lower morbidity and mortality than changes consisting of ST depression (243,244 and 245).

Unstable angina versus non–Q-wave myocardial infarction. ST-segment depression in leads V_2 through V_5 supports acute ischemic syndrome.

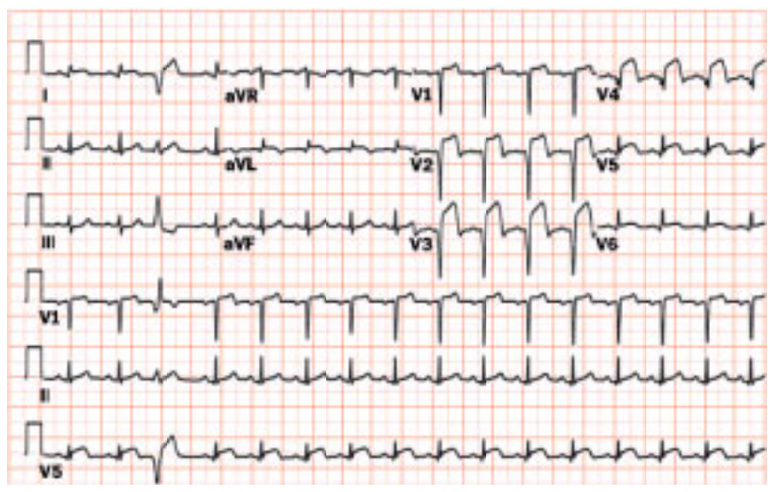
Electrocardiogram during and after Thrombolysis

Thrombolytic therapy accelerates the ECG evolutionary changes of acute infarction. Early T-wave inversion and a rapid resolution of ST-segment elevation have been associated with patency of the infarct-related artery (244,245). Additional elevation of the ST segment within the first hour of thrombolytic therapy occurs in 59% of patients, usually preceding a subsequent rapid decline of the ST elevation (246). Reperfusion obtained through primary coronary angioplasty is associated with additional ST elevation in only 12% of cases (246). Achieving a steady-state ST deviation within 100 minutes of thrombolysis is highly sensitive and specific for patency of the infarct-related artery (247). The second most common electrocardiographic change during effective reperfusion is the presence of accelerated idioventricular rhythm (246).

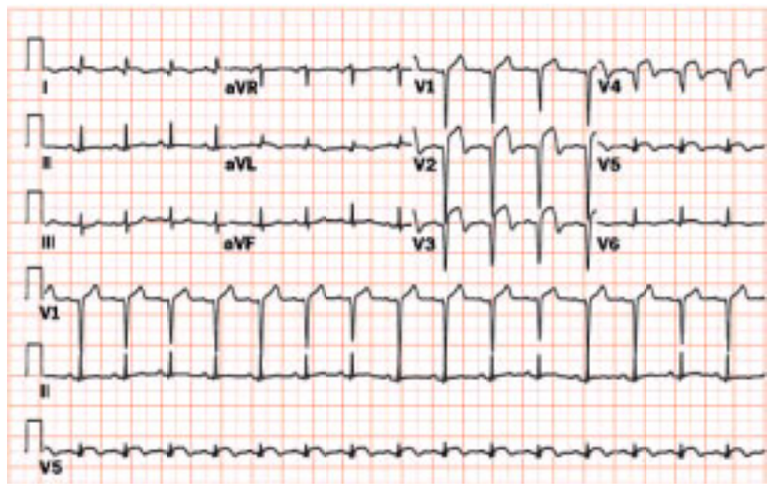


A 51-year-old patient with reperfusion accelerated idioventricular rhythm after thrombolytic therapy. Prior electrocardiogram documented ST elevation in leads II, III, and AVF, which resolved with thrombolytic therapy.

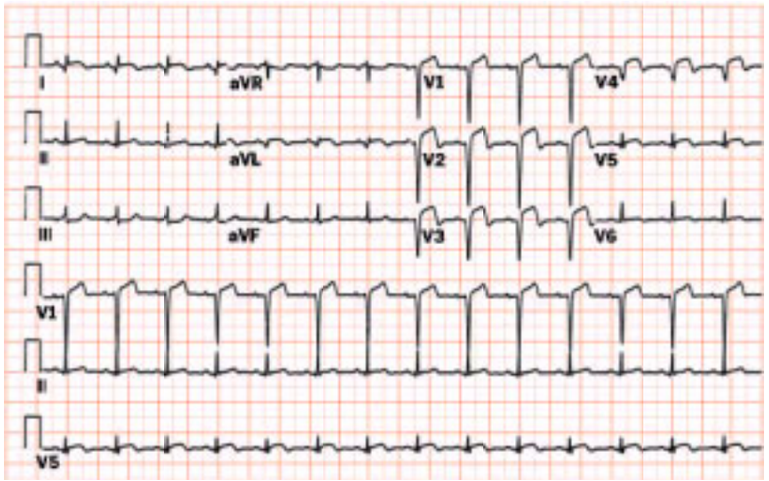
Subsequent evolution of infarction after thrombolysis is characterized by decrease in R-wave amplitude and by Q-wave development of smaller magnitude than that observed among patients not receiving thrombolysis (248); non–Q-wave infarctions are also common (242).



Evolution of acute anterolateral myocardial infarction at 3 hours. Tombstoning is less prominent with the onset of T-wave inversions in the anterior precordium. Reciprocal changes are resolving.



Evolution of acute anterolateral myocardial infarction at 24 hours. Prominent Q waves have developed across the anterior precordium and leads I and aVL. ST segment elevation persists, however.



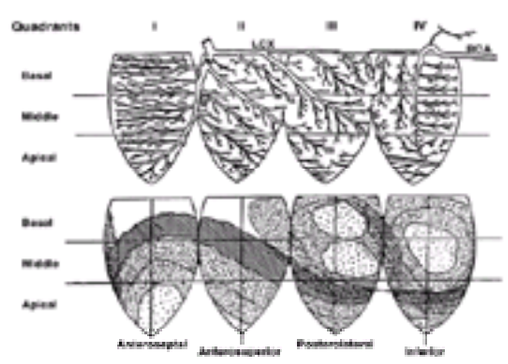
Evolution of acute anterolateral myocardial infarction at 72 hours. Q-wave pattern in the anterolateral leads is well established. Persistent ST-segment elevation suggests complication by aneurysm or pericarditis.

ECG IN ESTABLISHED MI

Autopsy, echocardiographic, and angiographic studies have shown that the 12-lead ECG has a limited capability to diagnose established myocardial infarction (249,250). The accuracy of the ECG depends on both the location and size of the infarct, and may be hampered by the presence of intraventricular conduction defects, LAFB, Q-wave regression, multiple infarctions (e.g., an anterior infarct may reduce tall R waves in V_1 and V_2 from a previous posterior infarct), and left ventricular hypertrophy.

Infarct Location

The presence of abnormal Q waves in two or more leads of a lead group permits the identification of the particular infarcted ventricular region (eFig. 59.16.1). Studies of wall motion dynamics have suggested that the classic electrocardiographic designation of certain infarct areas may not be accurate. For example, abnormal Q waves in leads I, aVL, V_5, and V_6 are often associated with apical, rather than lateral, wall motion abnormalities in ventriculograms (251). Anteroseptal infarct has classically been defined by the presence of Q waves in leads V_1 to V_3 (252). Echocardiographic and angiographic examination of patients with ST-segment elevation in these leads, however, has shown anteroapical infarcts and normal septa (253,254). Anatomically defined septal infarcts result instead in disappearance of septal Q waves in inferior leads and in leads I, V_5, and V_6. These changes are preceded by ST depression in the same leads during the acute phase, or, if the infarction was inferoseptal, by precordial ST depression. Initial R waves may be reduced in V_1 to V_3 (198,255).



***e*FIGURE 59.16.1** The 12 sectors of the left ventricular myocardium are defined by the four quadrants and the three levels. The distributions of the coronary arteries (*top*) are related to the distributions of infarctions that result from their occlusions (*bottom*). The four grades of shading from light to dark indicate infarct size as small, medium, large, and very large, respectively. LCX, left circumflex coronary artery; RCA, right coronary artery. (From Califf RM, Mark DB, Wagner GS. *Acute coronary care in the thrombolytic era*. Chicago: Year Book, 1988:20–21.)

Prominent right precordial R waves have been classically attributed to posterior infarct (Fig. 59.17), which may be a misnomer, because the term *posterior* applies better to the thoracic wall facing these areas of the left ventricle than to the left ventricle itself. Prominent R waves in V_1 (duration 0.04 second or more, R/S greater than 1) are nearly 100% specific and have a 91% positive predictive value for basal *lateral* asynergy of the left ventricle (sensitivity, 36%) (256). Specificity and positive predictive value drop slightly for prominent R waves in V_2, but the sensitivity increases to 61%. Asynergy of adjacent inferior and lateral segments is common in these patients. Abnormal R waves in V_1 in patients with chest pain are 96% specific for circumflex artery occlusion (206), and in autopsy studies 50% of lateral infarctions are associated with tall precordial R waves (257). The coronary artery more severely involved in posterior or inferoposterior infarcts is the circumflex, usually in association with significant disease of the RCA (258). In some patients, a taller R wave in V_1 and frankly prominent R waves in V_2 and V_3 may develop after LAD occlusion (259). Prominent R waves in this case do not correspond to posterior infarction but may rather represent a functional conduction disturbance (i.e., right conduction defect or midseptal block) (170,260).

FIGURE 59.17 Inferoposterior infarction.

The amplitude and duration of R waves may also be used for the diagnosis of established infarction (251). Because the electrical activation of the right ventricular free wall is insignificant in comparison with that of the left ventricular myocardium, infarction of the right ventricle rarely induces significant alteration of the QRS complex. Usually, only a slight voltage reduction occurs (261). When present, Q waves in both V_3R and V_4R are specific markers for right ventricular infarction (specificity, 100%; sensitivity, 78%) (42).

Diagnosis of Established Infarction in the Presence of Left Bundle Branch Block or Ventricular Pacing

The presence of Q waves in lead I is a highly specific sign for anterior infarction in patients with LBBB (262). A late notching of the S wave in V_3 to V_5 (Cabrera sign) was found to be both sensitive (91%) and specific, but this finding was not consistent in all studies (263,264). A 100% specificity for anterior infarction is reached by a

combination of two Q waves (in leads I, aVL, V_5, or V_6), with R wave regression in V_1 to V_4. For inferior infarcts, the presence of Q waves or R-wave notching in two inferior leads has poor sensitivity but high specificity (265).

In patients with heart pacing, the pacemaker can often be inhibited to disclose the underlying activation pattern, but sometimes this is not a viable resource. Examination of the QRS complex in precordial leads may show a qR morphology, which indicates anterior infarct. Initial 'q' waves in leads I, aVL, V_5, and V_6 are 100% specific for the diagnosis of anterior infarct (266). Although a QS pattern in inferior leads is normal during uncomplicated pacing, the presence of a qR or QR pattern has a 100% specificity for inferior infarcts (266).

Initial studies of pacing and infarction, however, may be biased toward patients with larger infarcts who required ventricular pacing (267). In patients without pacemakers who underwent apical pacing during electrophysiologic evaluations, only the sign of Cabrera was associated with previous infarction (268). This sign and QRS notching in inferior leads had a specificity of 92%.

Limitations to the electrocardiographic diagnosis of remote infarction during right ventricular pacing include variations in the position of precordial electrodes between recordings and slight displacement of the catheter away from its original implant site.

Infarct Size

Selvester and coworkers developed a method for estimating the total percentage of the left ventricle infarcted using a weighted scoring system (269) (eFig. 59.16.1). Computerized simulation of the sequence of electrical activation of the normal left ventricle formed the basis for a 32-point scoring system, with each point accounting for 3% of the ventricle.

The Selvester QRS scoring system includes 54 criteria from 10 of the 12 standard leads with weights ranging from 1 to 3 points per criterion. Criteria are defined in precordial leads V_1 and V_2 for both anterior and posterior infarct locations. This system for size estimation also contains criteria relating to the S wave. Satisfaction of only a single Selvester criterion may represent either a normal variant or an extremely small infarct.

ATRIAL INFARCTION

Atrial infarction is rarely recognized in the ECG. Atrial infarction is most unlikely in the absence of ventricular compromise, but it may occur in 1% to 17% of patients with acute myocardial infarction (270). The injury current affects atrial repolarization and results in elevation of the Ta wave with reciprocal changes in opposite leads. This produces displacement of the PR segment, better appreciated in patients with AV block (271).

PSEUDOINFARCTION PATTERNS

Conditions that suggest the ECG diagnosis of acute myocardial injury include severe hyperkalemia (Fig. 59.18), pericarditis, uncomplicated LBBB (Fig. 59.10), primary and secondary cardiac tumors (eFig. 59.18.1), acute pulmonary embolism, and ventricular aneurysm (272,273,274 and 275).

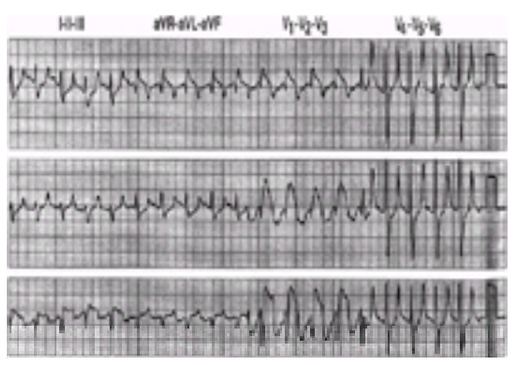
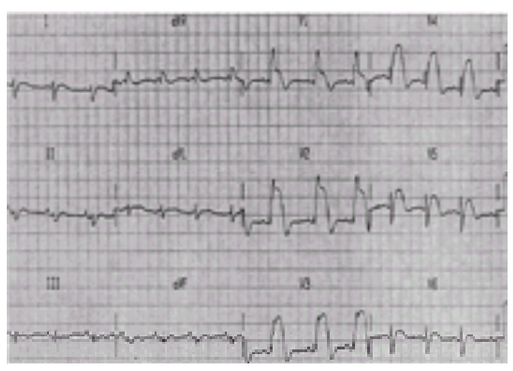


FIGURE 59.18 Pseudo–acute myocardial infarction mimicked by hyperkalemia. Peaked T waves are best seen in this case in leads V_4 to V_6. (From Kamimura M, Hancock W. Acute myocardial infarction in diabetic ketoacidosis. *Hosp Pract* 1992;27:28–30, with permission.)



***e*FIGURE 59.18.1** Pseudo–acute myocardial infarction mimicked by a cardiac tumor. (From Houghton JL, Sinden JR, Gross CM. Acute presentation of pseudo–myocardial infarction secondary to metastatic cancer. *Am J Med Sci* 1992;303:170–173, with permission.)

An 83-year-old female patient with hyperkalemia.

A 9-year-old male patient with hyperkalemia and QRS widening.

The presence of myocardial necrosis with pathologic Q waves or decrease in R-wave amplitude may be mimicked by left ventricular hypertrophy, fascicular blocks, ventricular preexcitation, infiltrative heart disease, lead misplacement, pulmonary emphysema, pleural effusion (276), and epicardial implantable defibrillator systems (277). LBBB and ventricular pacing may mimic the electrocardiographic appearance of either acute or remote myocardial infarction (278).

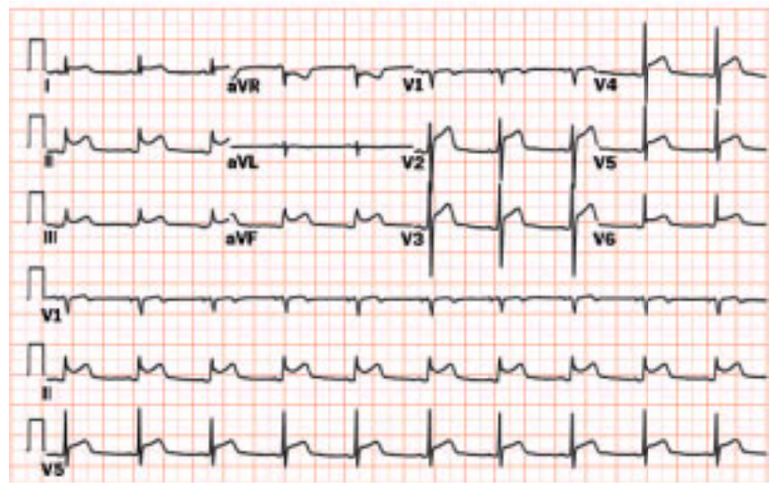
A 65--year-old male patient with a ventricular pacemaker.

MISCELLANEOUS CAUSES OF ELECTROCARDIOGRAPHIC ABNORMALITIES

Acute Pericarditis

Early ECG abnormalities during acute pericarditis include diffuse ST-segment elevation and upright T waves. Because the myocardial area injured by the inflammation is only partially depolarized, new ST vectors develop, directed away from the ventricular cavity and toward the apical epicardium. Thus ST-segment elevation may be seen in all leads except aVR, which shows ST depression. Lead V_1 may also record ST depression because it faces the right atrium. Although the P wave is usually not affected, PR (STa)-segment depression may develop (80).

Acute pericarditis persists for 3 or 4 weeks. When the ST segment normalizes, the T waves become inverted. In some patients, the T-wave inversion may be the only documented ECG change.



Acute pericarditis. Note diffuse, marked ST-segment elevation with PR-segment elevation in lead aVR.

The ECG changes of pericarditis may need to be differentiated from those of acute myocardial infarction, myocarditis, early repolarization syndrome, acute pulmonary embolism, pneumothorax, and pneumomediastinum. One must consider that pericarditis can complicate both acute myocardial infarction and myocarditis. The T-wave changes in postinfarction pericarditis may consist of persistently positive deflections after 48 to 72 hours or gradual, premature reversal of initially inverted T waves. The premature restoration of the concordance of the ST segment and T wave is a pivotal ECG manifestation (sensitivity, 100%; specificity, 77%). This evolution of the T wave after infarction is deceptive because it renders the ECG appearance more “normal” (245).

Electrolyte Abnormalities

Because the cardiac action potential results from transmembrane ionic movements, changes in electrolyte concentration may alter cardiac depolarization, repolarization, and conduction properties.

Hyperkalemia

Potassium is a depressant of cardiac activation. In general, the sinus node and the bundle of His tolerate hyperkalemia better than the ventricular myocardium (27). The correlation between serum potassium levels and ECG changes is poor. The earliest manifestation of hyperkalemia consists of symmetrical, peaked (“tented”) T waves, best seen in leads II, III, and V_2 to V_4 (Fig. 59.18). This typical change, however, is seen in only 22% of patients. As potassium levels increase, the P wave decreases its amplitude and increases its duration. The PR interval also prolongs, which reflects AV conduction delay. More severe hyperkalemia induces complete flattening of the P wave and widening of the QRS complex. A pattern resembling RBBB, LBBB, or nonspecific conduction defects may develop; the R-wave amplitude is reduced, the S wave becomes prominent, and ST-segment depression follows. The QRS complex in hyperkalemia usually differs from the bundle branch block or preexcitation patterns because the QRS is uniformly wide (27).

A 41-year-old with hyperkalemia.

Sinoatrial block (either Wenckebach or Mobitz II) is not uncommon. Sometimes the ST segment deviates from the baseline and mimics an acute infarction pattern. If hyperkalemia remains untreated, sinoventricular conduction, AV block, or ventricular fibrillation occurs.

Hypokalemia

Low plasma potassium levels are common in patients with acute myocardial infarction, after out-of-hospital cardiac arrest, and during treatment with diuretics. Hypokalemia prolongs repolarization. The initial ECG signs are T-wave flattening or inversion, ST-segment depression, and prominent U waves; the latter is the most characteristic change (27,127). As potassium levels decrease, the T wave fuses with the U wave, so that the ending of the QT interval is obscured (27).

More severe hypokalemia is manifested by a slight increase in the QRS complex and P-wave amplitudes and by prolongation of the PR interval. Ectopic atrial and ventricular beats are not unusual at potassium concentrations lower than 3.3 mEq per liter because automaticity is increased. Severe hypokalemia is associated with atrial tachycardia with block and with AV dissociation, and finally with ventricular arrhythmias (torsades de pointes). Patients taking digitalis are especially prone to arrhythmias in the presence of hypokalemia.

Hypokalemia is often found in hypertensive patients treated with diuretics. In these patients, a positive Sokolow-Lyon index could represent a false-positive finding, as the index correlates better with hypokalemia than with left ventricular mass (279).

Hypercalcemia

A high concentration of calcium increases the excitability threshold and has an inotropic effect. Hyperkalemia shortens both the ST segment and the QT interval and prolongs the PR interval and the QRS complex. Severe hypercalcemia may be associated with second- or third-degree AV block (27).

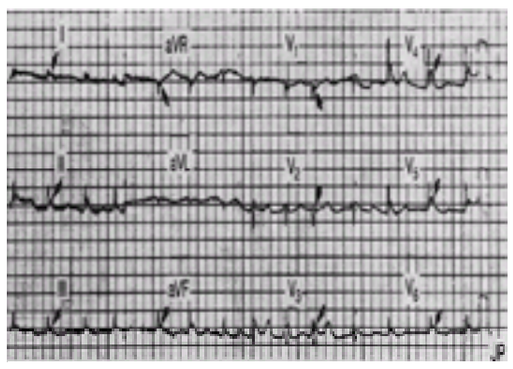
A 54-year-old male patient with hypercalcemia.

Hypocalcemia

Hypocalcemia prolongs the ST segment and the QT interval. The duration of the ST segment is inversely related to the calcium blood level. The T wave remains relatively normal (27).

Hypothermia

The electrocardiographic changes of hypothermia include bradycardia, flattening of P waves, and prolongation of the PR, QRS, and QT intervals. Irregularities of the isoelectric line may be seen as a consequence of muscular tremor or atrial fibrillation. A typical sign—observed in approximately 80% of patients with hypothermia—is the appearance of a J wave. The J (or Osborn) wave is a deflection that distorts the QRS-ST junction and is more commonly observed in leads II, III, aVF, V_5, and V_6 (eFig. 59.18.2). The J wave disappears with normothermia. Prolonged QT intervals may persist after the body temperature and the QRS complex have normalized (280).



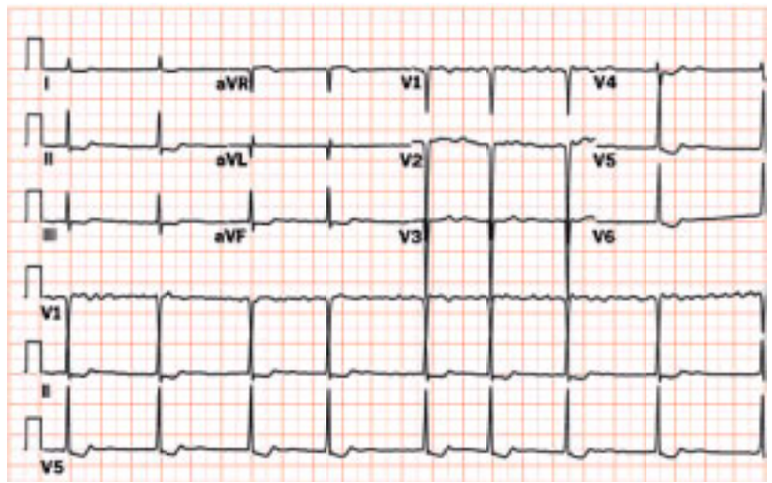
***e*FIGURE 59.18.2** Electrocardiogram obtained in a patient with hypothermia. The J waves are marked by arrows. (From Patel A, Getsos JP, Moussa G, et al. The Osborn wave of hypothermia in normothermic patients. *Clin Cardiol* 1994;17:273–276, with permission.)

Drug Effects

Therapeutic or toxic cardiac effects of various medications may be detected on the ECG.

Digitalis

Digitalis accelerates ventricular repolarization, particularly in the subendocardium. This manifests on the ECG first by a T-wave flattening and by prominent U waves with a shorter QT interval. The most typical change, however, consists of a coved ST depression (Fig. 59.7). The T wave appears biphasic, with its first portion negative and merging with the ST segment. These repolarization changes do not correlate well with therapeutic or toxic blood levels of the drug.



Digitalis effect. Note controlled ventricular rate with short, scooped ST segments in the lateral leads.

Digitalis intoxication is often manifested by arrhythmias similar to those seen in severe hypokalemia (i.e., atrial tachycardia with block and AV dissociation). However, no particular arrhythmia is pathognomonic of digitalis intoxication (281).

Characteristics of digitalis-induced atrial tachycardia include atrial rate between 140 and 250 per minute, inferior-to-superior direction of atrial activation, and 2:1 AV block. During 2:1 AV conduction, the PP interval including a QRS complex is usually shorter than the one not including a QRS complex. This resembles the ventriculophasic arrhythmia of complete AV block and is probably caused by comparable changes in the autonomic tone during the cardiac cycle (281). Nonparoxysmal junctional tachycardia at a rate between 70 and 130 beats/min (generally with AV dissociation) is frequent (271).

Quinidine and Class Ia Antiarrhythmic Drugs

Quinidine blocks the fast sodium channel in the cell membrane, and it prolongs both the action potential duration and the repolarization. The effects of quinidine include narrowing and then inversion of the T waves, prominent U waves, and prolonged QT interval (282). Quinidine effects are exaggerated by the presence of digitalis. Prolongation of the QRS complex by 25% to 50%, AV block, ventricular arrhythmias (torsades de pointes), and sick sinus syndrome are toxic effects of quinidine. The psychotropic agents phenothiazines, tricyclic antidepressants, and lithium produce ECG changes similar to those of quinidine.

Propafenone and Class Ic Antiarrhythmic Drugs

Propafenone hydrochloride, flecainide acetate, and encainide prolong the AH and HV intervals and the atrial and ventricular refractory periods. The QRS duration is increased. All class Ic drugs may induce ventricular arrhythmias (proarrhythmic effect). The JT interval is not prolonged.

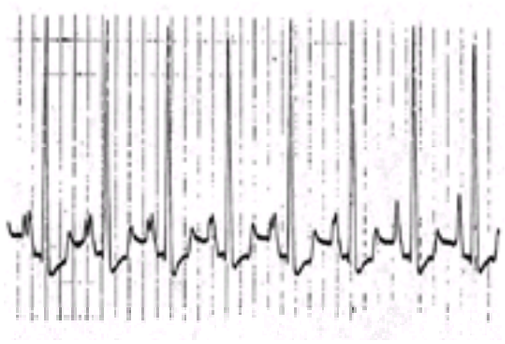
The Transplanted Heart

Incomplete or complete RBBB is the most prevalent abnormality in transplanted patients, but it is unrelated to pre- or intratransplantation hemodynamic factors or to ischemia (283,284). The PR and QT intervals are shorter and the precordial transitional zone is displaced to the left in the transplanted patients in comparison with the last recorded ECGs in the donors. The shift in the transitional zone and the conduction delay of the right bundle would indicate a clockwise rotation of the heart on its vertical axis. The increased prevalence of RBBB during follow-up, however, may be associated with mildly increased pulmonary pressures (285).

A 55-year-old African-American male patient status post cardiac transplant. Note the accessory atrial rhythm as evidenced by the extra P waves in the inferior leads.

Soon after transplantation, supraventricular arrhythmias are common and self-limited (284). The sudden appearance of first-degree AV block, however, should suggest acute cardiac rejection (286).

A curious finding soon after transplantation is that of remnant recipient atrial activity (*e*Fig. 59.18.3), which usually decreases with time (285). Modern surgical techniques, however, provide for a complete excision of the recipient atria, which will probably abolish their electrocardiographic manifestations in future transplant recipients.



***e*FIGURE 59.18.3** Electrocardiogram strip from a patient with heart transplantation showing a progressive change from an apparent P mitrale configuration to an apparent P pulmonale at the end of the strip. The illusion is produced by imposition of both the remnant (recipient) and the donor atrial activity. (From Malcolm I. P mitrale–P pulmonale variation [Letter]. *Am Heart J* 1996;132:1322, with permission.)

Pulmonary Abnormalities

Acute Cor Pulmonale

The ECG changes in acute cor pulmonale (*e*Table 59.0.7) reflect acute pulmonary hypertension with dilatation of the right chambers and perhaps myocardial ischemia. The classic “right heart strain” patterns, $S_IQ_{III}T_{III}$ and S_IQ_{III} (probably secondary to clockwise rotation), are not constant.

***e*TABLE 59.0.7** ELECTROCARDIOGRAPHIC MANIFESTATIONS OF ACUTE PULMONARY EMBOLISM

Incomplete or complete right bundle branch block, usually with ST-segment elevation and positive T wave in V_1
S waves >0.15 mV in leads I and aVL
Rightward shift of the QRS axis to >90 degrees or an indeterminate axis
Shift in the transition zone in the precordial leads to V_5 (clockwise rotation)
Q waves in lead III and less commonly in aVF, but not in lead II
Low-voltage QRS complex of <0.5 mV in the limb leads
T-wave inversion in leads III and aVF or leads V_1 to V_4
Atrial fibrillation or atrial ectopy

Several studies have found that the only ECG signs that are significantly more frequent among consecutively treated patients with confirmed acute pulmonary embolism than among those with suspected pulmonary embolism are sinus tachycardia and incomplete RBBB (287). A diagnosis of acute pulmonary embolism can be considered probable when three or more of these changes coexist in the admission ECG (288). Interestingly, the degree of right QRS-axis deviation, the presence of incomplete or complete RBBB, and the rate of sinus tachycardia correlate with the extent of embolization (289).

Pulmonary Emphysema

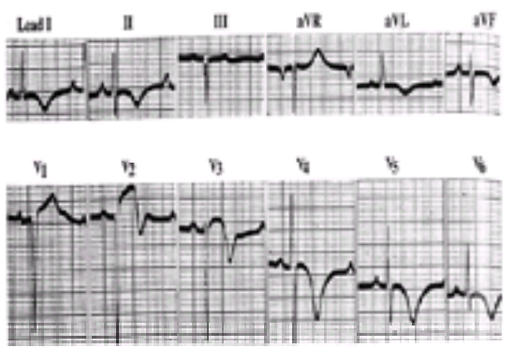
The overinflated lungs in pulmonary emphysema produce anatomic changes. The diaphragm is lowered and the cardiac electrical axis becomes more vertical and rotates clockwise. In the ECG, the most typical findings include prominent P waves [more than 0.25 mV; indeed, a P pulmonale predicts pulmonary emphysema or low diaphragm position better than it does right atrial enlargement (155)] and exaggerated atrial repolarization (Ta) waves producing more than 0.10 mV of ST-segment depression in inferior leads; a rightward shift of the QRS axis to 90 degrees or more in the frontal plane; decreased progression of the R-wave amplitudes in precordial leads; and low voltage of the QRS complexes, especially in the left precordial leads (290).

None of these criteria is highly specific for pulmonary emphysema. The degree of QRS-axis deviation is related to the degree of airway obstruction, but only 8% of patients present deviations to 90 degrees or more. Frontal-plane axes of 60 degrees or greater are more common but nonspecific (291). Other patients show indeterminate axes.

Autopsy studies indicate that right ventricular hypertrophy is present in 60% to 70% of cases of chronic cor pulmonale, but it can be detected only in one-fourth of living patients.

Neurogenic Manifestations on the Electrocardiogram

Patients with acute or chronic diseases of the nervous system may show repolarization changes in the ECG. Negative T and U waves, ST-segment changes, and QT prolongation may appear during subarachnoid hemorrhage (*e*Fig. 59.18.4), ischemic stroke, radical neck dissection, spinal cord trauma, and electroconvulsive therapy (90,292,293 and 294).



***e*FIGURE 59.18.4** Electrocardiogram recorded in a patient with subarachnoid hemorrhage showing T-wave changes mimicking myocardial ischemia. (From Chou TC, Susilavorn B. Electrocardiographic-pathological conference: electrocardiographic changes in intracranial hemorrhage. *J Electrocardiol* 1969;2:193–196, with permission.)

Certain localizing factors are constant throughout different patient groups. Subarachnoid hemorrhages associated with negative T waves and QT prolongation are usually left-sided (292), and tumors of the limbic system are associated with QT and QTc prolongation three times more often than tumors in other areas (295).

Misplacement of Electrocardiographic Leads

Misplacement of ECG leads is common. A study of 11,432 ECGs detected reversals involving the left arm and foot or adjacent precordial electrodes in 2% of the recordings (296). Estimates are that of the 300 million ECGs recorded annually in the world, approximately 6 million contain a lead reversal. The proportion may be higher when other combinations of lead reversals are considered.

Reversal of the Right and Left Arm Cables

When the electrodes attached to the arm cables are reversed, “lead I” shows negative P and T waves, and a predominantly negative QRS complex. “Lead II” is indeed lead III, and “lead aVR” is indeed lead aVL, and vice versa (297). Thus, the limb leads suggest the diagnosis of dextrocardia. The precordial leads, however, show the normal progression of R waves through V_6.

Limb lead reversal. Note upright QRS complex and P wave in lead aVR with inverted QRS in leads I and aVL.

Reversal of Each Arm Cable with Its Corresponding Leg Cable

When the arm cables are switched with the leg cables, “lead I” shows a flat line that records the potential difference between both legs. “Lead II” is an inverted (upside-down) lead III, because the positive electrode is now in the left arm. “Lead III” mirrors its image, because the polarity of its two components is inverted. “Lead aVR” is a replica of “lead aVL,” because both leads now record potentials derived from comparing each leg (aVF) with the same central terminal.

Misplacement of Precordial Lead Electrodes

In a prospective study in which precordial leads were deliberately misplaced, 2-cm changes in electrode position (too high or too low) resulted in significant ECG abnormalities (298). Variations included changes in R-wave amplitude, ST segments, Q waves, and the transition zone. The most important differential diagnosis when precordial lead electrodes are misplaced in a high position is anterior infarction, because QS complexes or low-voltage R waves may appear. The use of device-guided lead placement improves accuracy and reproducibility in interpretation of precordial waveforms (298).

HIGH-RESOLUTION ELECTROCARDIOGRAPHY

Standard recording techniques cannot detect low-amplitude bioelectric potentials from the body surface. Potentials generated by the His-Purkinje system and by depressed ventricular myocardium ("late potentials") are difficult to identify because their signals are smaller than the electrical noise produced by various sources (299). Two techniques have been developed to overcome this problem: (a) temporal averaging (usually referred to as "signal averaging"), which is applicable only to repetitive electrocardiographic signals; and (b) spatial averaging, which can record the His-Purkinje signal and late potentials on a beat-to-beat basis. Signal averaging (the most frequently used technique) can analyze potentials in either time domain, frequency domain, or a combination of both. Results of these analyses in patients with acute or remote myocardial infarction have shown an increased incidence of low-amplitude, high-frequency components within the QRS complex. These components are attributed to fragmentation of the depolarization front by fibrous tissue and to a decrease in electromotive force (300). The risk of ventricular arrhythmias in postinfarction patients and of cardiac death in patients with coronary artery disease or hypertrophic cardiomyopathy who have nonsustained ventricular tachycardia can be stratified on the basis of signal-averaging information (301). Although signal-averaged ECG is an interesting research tool, its clinical applications are currently limited.

BODY SURFACE MAPPING

Body surface mapping records cardiac electric events with numerous electrodes (from 16 to 200) and thus contributes additional information to that of the standard ECG. Cardiac field mapping provides details on the spatial and temporal sequence of cardiac excitation and recovery. Local intraventricular conduction disturbances, preexcitation, premature ventricular beats, and repolarization disorders can be precisely located (302). After a discriminant analysis of body torso maps derived from 120 leads in patients with various types of infarcts, the conclusion was that six torso sites accounted for a specificity of 96% and a sensitivity of 94%. Unfortunately, these sites did not coincide with any of the conventional 12-lead positions (303). Visual inspection of the ECG maps does not suffice for diagnostic purposes; sophisticated statistical and deterministic models are necessary. The difficulty in interpretation and the cumbersome recording and acquisition processes explain why the cost-effectiveness ratio for this technique is still unfavorable and confine it to the research arena.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Proficiency and Accuracy in Electrocardiographic Recording and Interpretation

Perhaps because the ECG is widely available and easy to obtain, its recording and interpretation are regarded as minor tasks (92). The responsibility of ECG recording has shifted from physicians to nurses, technicians, or medical students, and cardiologists are rarely present at the time of a patient's initial evaluation. This is conducive to suboptimal ECG data collection. First, lead misplacements and noise are common (304). Second, in most acute clinical settings, only 12 ECG leads with few QRS complexes per lead are obtained. Special ECG leads and prolonged rhythm strips (other than in lead II) are underused in daily practice (305). The need to change the patient from the supine position or to use equipment beyond the standard provided with current ECG machines may be a deterrent to the addition of posterior or esophageal leads. Thus, acute myocardial infarctions, arrhythmias, and intermittent bundle branch block may remain inadequately documented.

In addition to these shortcomings of the ECG recording, interpretation may also be limited. The ever-increasing competition between electrocardiography and other procedures for the attention of the young physician may conspire against acquisition of a high level of individual competence in ECG principles and diagnosis (92). Even experienced physicians usually examine only 11 leads of the 12 available; lead aVR (and the information it may provide) is ignored (24).

The self-perception of proficiency in ECG interpretation may be overly optimistic. In a study of 100 consecutively treated cases of fatal myocardial infarction, 47% were missed throughout hospital evaluation (306). Residents in family practice programs missed acute infarctions in 21% of ECG recordings, and their expertise did not improve with the year of residence (307). General practitioners performed better in identifying normal ECGs (82% specificity) than in recognizing acute infarction (33% to 61% sensitivity) (308). Emergency physicians participating in a multicenter study classified as normal 41% of abnormal ST segments. Misreading was related to suboptimal triage and unnecessary cardiac care unit admissions (309). A study using electrocardiographer judgment as the gold standard found a 67% accuracy for family physicians versus a 91% accuracy for cardiologists (310). Because cardiologists perform better than internists (311), the specific medical training of the interpreter may play a role in diagnostic accuracy. Although obvious ST-segment or Q-wave changes are absent in most cases of missed infarctions, approximately one-fourth of missed infarctions could be diagnosed with adequate competence in ECG reading (228,312). Fisch has suggested that the inevitable use of automated diagnoses "may be, in fact, an obstacle to the acquisition of ECG skills" (313).

Reproducibility

High variability within or between readers may put into question the validity of ECG analyses. Unfortunately, intra- and interobserver agreement rates are seldom tested or reported. Studies that systematically evaluated the reproducibility of ECG interpretations found approximately 80% intraobserver and 30% interobserver agreement rates (314,315 and 316). Discrepancies in ECG interpretation are related to the ECG waveform or interval under analysis, to variability in consecutive ECG recordings, and to the interpreter. For example, measurements of the ST segment are highly reproducible from beat to beat, but those of QT interval are not (59,226). The limb leads III, aVF, and aVL may be responsible for most intraobserver variation in the diagnosis of established infarction (314). For precordial recordings, variability is often a consequence of differences in lead placement (298). Day-to-day variability of the 12-lead ECG has been documented within normal persons and is associated with circadian influences and meal consumption (41). The role of expertise in the reproducibility of ECG interpretation is uncertain. At least among internal medicine residents, experience may be more important for intraobserver than for interobserver agreement; the latter rates may not improve after observers undergo training programs in electrocardiography (314). Comparative reproducibility between cardiologists and other physicians has been scrutinized only in limited settings and has been found to be acceptable (317).

Role of Computerized Electrocardiogram Interpretation

Computer-assisted ECG interpretation is now widely available. Ideally, automated measurements of ECG waveforms and intervals can significantly reduce physician time in ECG analysis while providing readings that are precise at the microvolt and millisecond level. In general, however, computer-derived intervals are longer than those determined visually. Reasons for the discrepancy include examination of multiple-lead versus single-lead measurements (in automated versus visual readings, respectively), and paper speed and amplification. Manual measurements performed with an amplification factor of 10 or 20 produce significantly wider intervals, similar to computer-derived results (45). Many computer programs apply longer-than-standard upper and lower normal limits for ECG intervals (e.g., minimum PR = 130 ms; maximum QRS complex = 0.126 ms) (318). Additional limitations of computerized readings include minute-to-minute variability, inability to determine the anteroposterior direction of electrical forces, and discrepant measurements among programs (319,320 and 321). Automated diagnoses (e.g., "left ventricular hypertrophy") may be less reliable and accurate than automated raw measurements, because the rapid expansion of ECG digital technology during the 1980s outpaced most efforts to evaluate the quality of the product (53). Many diagnostic programs in electrocardiographs are now 25 years old (313). An investigation of commonly used ECG software found a variety of systematic errors. The accuracy rate for clinically validated ECG diagnoses of myocardial infarction or left ventricular hypertrophy was 70% for computer analysis versus 76% for visual readings by cardiologists (315,321).

Further refinement in automated ECG interpretation is expected in the near future. At present, computer-analyzed ECGs require overreading by an experienced cardiologist.

THE FUTURE

The clinical use of the ECG has withstood the passage of time, and the contribution of ECG information to the care of cardiac patients remains unique. Despite the development of more sophisticated and expensive noninvasive diagnostic and prognostic techniques, the ECG is still the initial (and sometimes the only) test demonstrating cardiovascular abnormalities. Medical education must emphasize the value of the ECG, however. Systematic instruction and supervised practice in ECG diagnosis are fundamental to maintain proficiency in ECG interpretation.

Current emphasis in ECG research is on the study of dynamic patterns inherent in certain parameters (especially ventricular repolarization) with the aid of ambulatory recordings and newer, potent digital storage and analysis techniques. Correlation of findings from the ECG with those from emerging techniques such as electromechanical left ventricular mapping (which displays a color-coded map of the activation process) may help to further understanding of newly described ECG patterns (322).

Attempts to improve the resolution of standard electrocardiography have relied on an increase in the number of recording electrodes (body surface mapping) and on an improvement in the signal-to-noise ratio of the higher-frequency signals by averaging and filtering (signal-averaged ECG). Initial results with these techniques are promising, but their roles in clinical practice are still unclear.

The advent of effective myocardial reperfusion therapies has renewed the interest in the ECG manifestations of the acute ischemic syndromes. More recently, wireless technology is allowing the transmission of 12-lead ECG waveforms from remote locations to cardiologists' hand-held computers. Because intraobserver agreement among cardiologists is high when interpreting both paper ECGs and their liquid-crystal–displayed counterparts, remote interpretation may become widely adopted and contribute to decreased time to treatment for patients in need of reperfusion or those with complex arrhythmias (26).

Overall, the standard 12-lead ECG will continue to expand in clinical importance and will remain an integral part of the evaluation of all cardiac patients, particularly those with ischemic heart disease or rhythm disturbances.

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ELECTROCARDIOGRAPHIC DIAGNOSIS OF ARRHYTHMIAS

HEIN J. WELLENS

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OVERVIEW

By using information provided by intracardiac recordings and programmed cardiac stimulation, diagnosing correctly the site of origin and the mechanism of an arrhythmia on a 12-lead electrocardiogram (ECG) has markedly improved in recent years. This chapter reviews how to use a 12-lead ECG in patients with supraventricular tachycardia (SVT), ventricular tachycardia (VT), and preexcitation.

A systematic approach to ECGs is essential for optimal interpretation. Correctly diagnosing an arrhythmia is important not only to prognosis and the selection of appropriate antiarrhythmic drugs, but also because of the possibility of completely curing an arrhythmia by radiofrequency catheter ablation.

INTRODUCTION AND HISTORY

This chapter is intended to serve as an introduction to the chapters in this textbook that cover supraventricular and ventricular arrhythmias (see Chapter 64, Chapter 65, Chapter 66, and Chapter 67). The ECG is a valuable tool to diagnose these arrhythmias, and the major features that differentiate key supraventricular and ventricular arrhythmias are reviewed in this chapter. Although the chapters that follow provide an in-depth discussion of each arrhythmia, this chapter relies heavily on graphic examples to illustrate rapid and accurate diagnosis of these important rhythm disturbances.

The electrical impulse that is responsible for normal cardiac rhythm originates in the sinus node, spreads over the atrium, passes from atria to ventricles only by way of the atrioventricular (AV) node–His pathway, and spreads over the ventricles through the bundle branches and the Purkinje system. The ECG recording of this regularly occurring event characteristically shows a P-QRS-T complex with each of the components well defined as to its width, height, axis, and interrelation (Fig. 60.1).

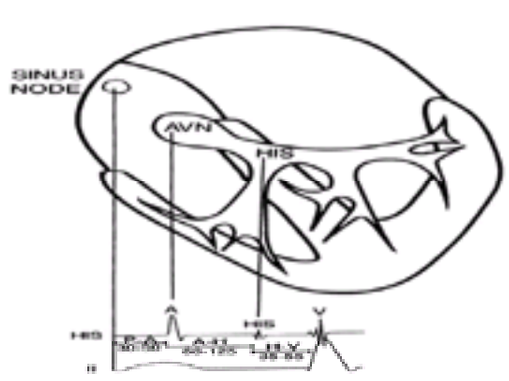
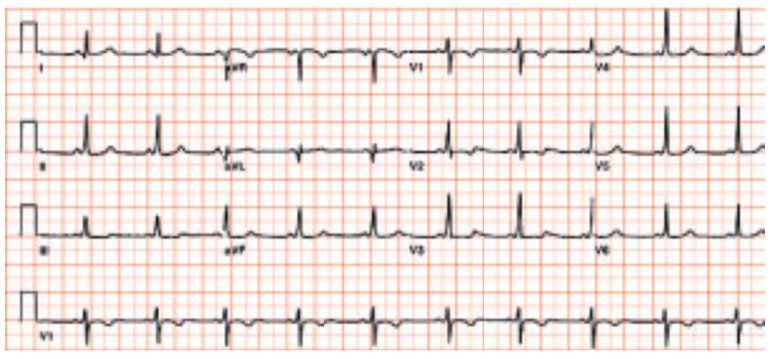


FIGURE 60.1 Time relations between the electrical activation of the different parts of the heart during sinus rhythm. A bundle of His electrogram and lead II are shown to illustrate the different time intervals. AVN, atrioventricular node.

Ventricular Preexcitation

In the normal heart, the AV node–His pathway is the only connection between the atria and the ventricles. However, some people are born with an extra connection between the atrium, AV node, and ventricle (1). Conduction over these pathways after a supraventricular beat results in earlier activation of the ventricle (*preexcitation*) than during conduction over the AV node–His pathway only. The most common type of preexcitation is caused by a direct connection between the atrium and ventricle. In this situation, described by Wolff et al. in 1930 (2), arrhythmias are often present.



A 44-year-old female patient with Wolff-Parkinson-White syndrome.

Electrocardiogram in Preexcitation

When two AV pathways [the AV node–His pathway and the AV accessory pathway (AP)] are present, the conduction properties of the two pathways and the location of the AV AP determine the configuration of the QRS complex during sinus rhythm. This is shown in Figure 60.2. The typical picture of a short PR interval, a delta wave (representing ventricular activation over the AP) and a broad QRS complex, is present when there is a major contribution to ventricular activation by AV conduction over the AP. When contribution to ventricular activation over the AP is small because of the AP location or rapid transmission of the sinus impulse over the AV node, the ECG shows minimal changes pointing to ventricular preexcitation. Figure 60.3 illustrates a 12-lead ECG during sinus rhythm in the two situations shown in Figure 60.2.

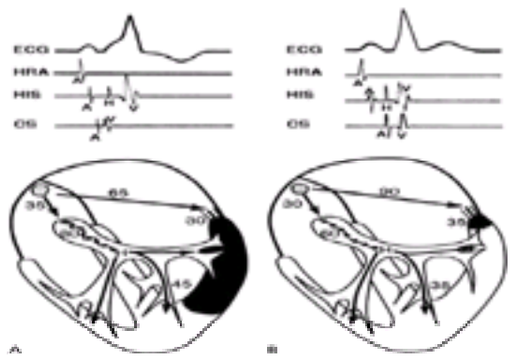
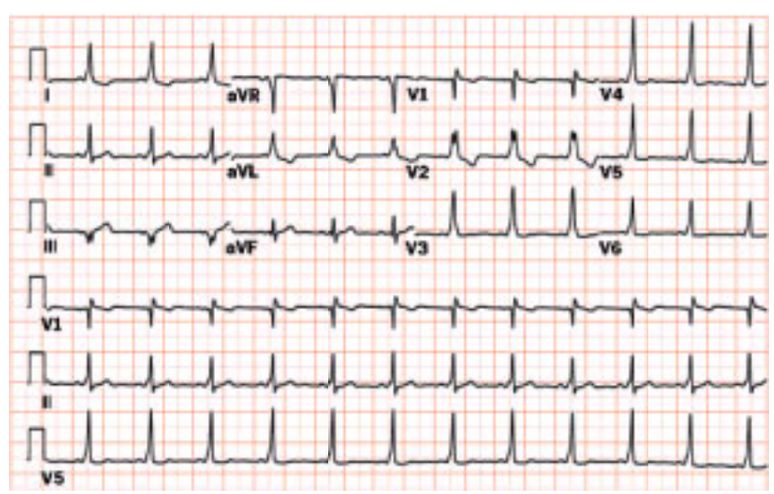


FIGURE 60.2 Factors determining the degree of ventricular preexcitation during sinus rhythm in a patient with Wolff-Parkinson-White (WPW) syndrome during sinus rhythm. The corresponding electrocardiographic (ECG) and intracavitary recordings from the high-right atrium (HRA), bundle of His region (HIS), and coronary sinus (CS) are shown in the upper part of the figure. In the heart in **A**, atrioventricular (AV) conduction time from the sinus node over the normal AV nodal–His pathway is 160 ms. The time required to travel from the sinus node to the atrial insertion of the AP is 65 ms, and the left-sided accessory pathway (AP) conduction time is 30 ms (total of 95 ms). Because of the shorter conduction time over the AP, an important part of the ventricle is preexcited, resulting in a short PR interval, a distinct delta wave, and a widened QRS complex. In the heart in **B**, there is longer conduction time from the sinus node to the atrial insertion of the AP, a longer conduction time over the AP itself, and a shorter conduction time over the AV node. Thus, the impulse arrives in the ventricles simultaneously through the AV node and the AP, producing a normal PR interval and a narrow QRS complex.

FIGURE 60.3 Electrocardiographic examples of the two diagrams shown in Figure 60.2. **A** and **B** in this figure correspond to **A** and **B**, respectively, in Figure 60.2. Note the prominent delta wave in **A**, indicating that a much larger area of the ventricle is preexcited than is shown in **B**.



Wolff-Parkinson-White syndrome. Note short PR interval with classic delta wave due to accessory pathway conduction.

As is discussed elsewhere (see Chapter 66), APs may not only be present as connections between atrium and ventricle, but also as fibers connecting the AV node with the ventricle (Mahaim fibers or nodoventricular fibers) (3) or the atrium with the bundle of His (atriofascicular fibers). It is also important to know that accessory connections may conduct anterogradely and retrogradely, only anterogradely, or only retrogradely. When conduction over the accessory connection is possible only in the retrograde direction, the term *concealed accessory conduction* is used.

Localizing accessory connections is important, because it is possible to interrupt conduction in these connections by the application of radiofrequency energy. As is pointed out elsewhere, exact localization requires catheter mapping of cardiac activation. However, the ECG can be very useful in identifying the atrial and the ventricular ends of an accessory AV connection.

Figure 60.4 provides a schematic representation of the four zones of AV AP locations along the AV ring; Figure 60.5 gives representative examples. Although this is an oversimplification, it helps in understanding how to use the delta-wave axis (during preexcited sinus rhythm or preexcited tachycardia) or the P-wave axis [during tachycardias with ventriculoatrial (VA) conduction over the AV AP] for localizing the ventricular end and the atrial end of the AV AP.

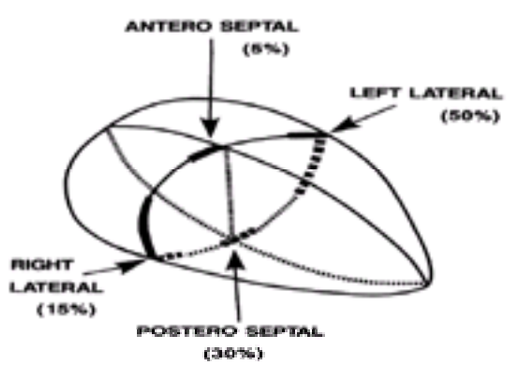


FIGURE 60.4 Frontal look at the heart, depicting the localization and incidence of the four most common types of accessory atrioventricular pathways. This drawing helps to explain how in the frontal plane the ventricular end (the delta wave) and the atrial end (the P wave during orthodromic circus-movement tachycardia) of the accessory pathway can be localized using the 12-lead electrocardiogram.

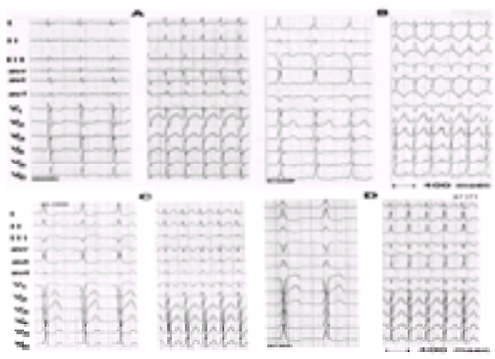
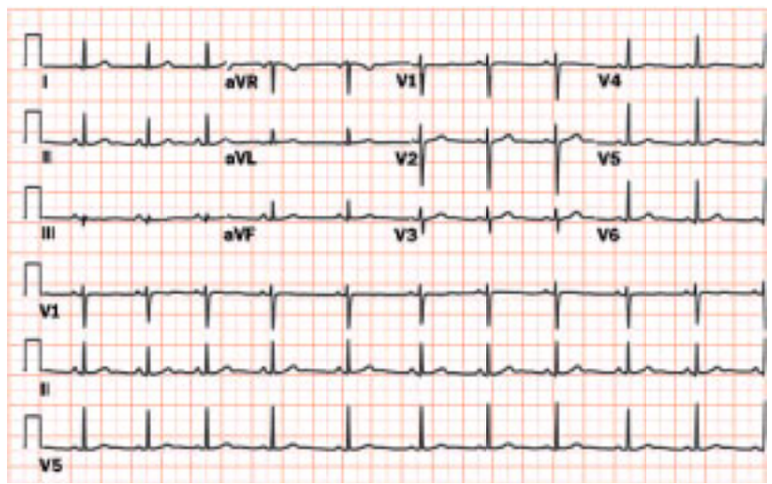


FIGURE 60.5 Twelve-lead electrocardiogram during sinus rhythm and orthodromic circus-movement tachycardia in a left free wall **(A)** and a posteroseptal accessory pathway (AP)**(B)**. Twelve-lead electrocardiogram is depicted during sinus rhythm and orthodromic circus-movement tachycardia in a right free wall**(C)** and anteroseptally located accessory pathway **(D)**.

Diagnosing an Arrhythmia

An arrhythmia is characterized on an ECG as a deviation from the normal sinus rhythm in rate [i.e., too fast (tachycardia) or too slow (bradycardia)], regularity (one or more heartbeats occurring earlier or later than expected), or a different pattern of activation of the cardiac muscle. These changes can be registered on the ECG, allowing clinicians not only to make the diagnosis of an arrhythmia but frequently to recognize its site of origin and mechanism. These aspects are important to prognosis and selection of therapy.

Normal sinus rhythm is regular or shows slight respiration-related rate changes, referred to as *sinus arrhythmias*. The rate of sinus rhythm is determined by several factors, such as activity of the autonomic nervous system (vagal vs. sympathetic stimulation), hormones, body temperature, and so forth. A sinus rate of greater than 100 beats/min is referred to as a *sinus tachycardia*; a sinus rate of less than 60 beats/min is known as a *sinus bradycardia*.



Sinus arrhythmia. Young female patient with sinus rhythm characterized by irregular RR intervals.

When impulse formation occurs outside the sinus node during a regular sinus rhythm, it is termed a *premature beat* if such impulse formation occurs earlier than the expected beat of the basic rhythm (Fig. 60.6); an *escape beat* refers to an impulse formation that occurs outside that of the basic rhythm and terminates an interval longer than the preceding basic rhythm (Fig. 60.7).

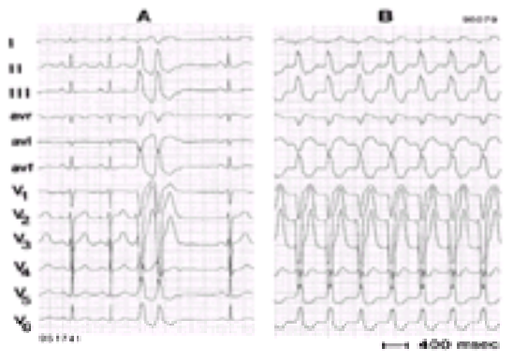


FIGURE 60.6 A: Two consecutive premature ventricular beats. The second one shows retrograde conduction to the atrium.**B:** A monomorphic ventricular tachycardia is present coming from the same area as the premature beats in **A** (the outflow tract of the right ventricle).

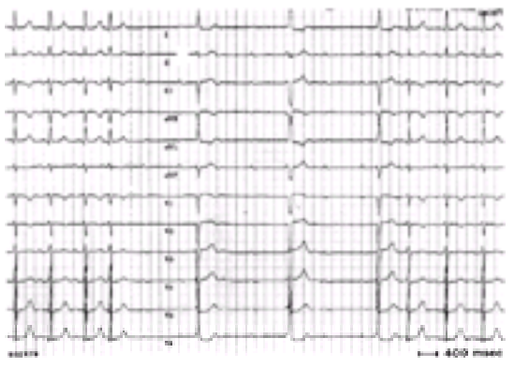


FIGURE 60.7 Escape beats terminating a pause that is longer than those of the QRS intervals of the preceding conducted sinus beats.

Premature or ectopic beats may arise anywhere in the heart. They may occur individually, two or three in a row [i.e., doublets (Fig. 60.6) or triplets], or continuously, resulting in a tachycardia.

When premature beats have a fixed time relation to the previous normal depolarization, they are referred to as *coupled* premature beats. If they have no fixed relation to normal beats but occur at fixed interectopic intervals, they may arise in a *parasystolic* focus (Fig. 60.8). Such a focus is completely or partially protected from other impulses. Partial protection may result in slight changes in interectopic intervals, known as *modulated parasystole* (4).

FIGURE 60.8 Atrial parasystole. Apart from sinus rhythm, there is ectopic impulse formation at the atrial level. Ectopic impulse formation is totally independent of the basic sinus rhythm. As shown, depending on the prematurity of the atrial ectopic beat, the QRS differs in configuration because of different degrees of aberrant conduction.

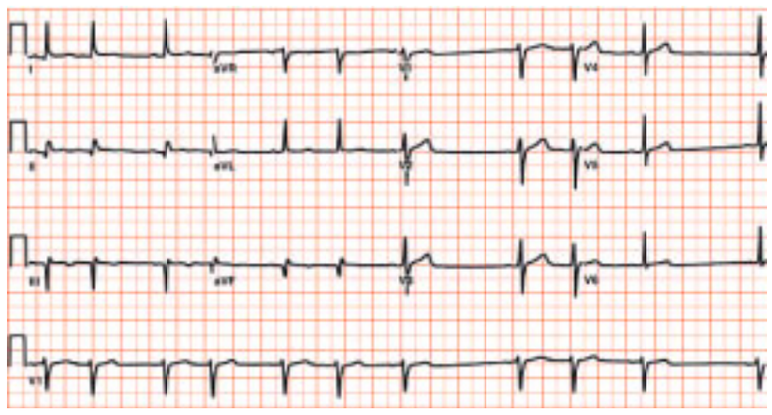
A tachycardia may show a regular or an irregular rhythm. The regularity or irregularity may be at the atrial level, at the ventricular level, or at both levels. When all complexes of a tachycardia show the same configuration, the tachycardia is termed a *monomorphic* tachycardia (Fig. 60.6). When the tachycardia complexes show marked differences in configuration, the tachycardia is referred to as a *polymorphic* tachycardia. If a tachycardia stops spontaneously within 30 seconds, it is defined as a *nonsustained* tachycardia; when the tachycardia persists for more than 30 seconds or does not stop spontaneously, it is termed a *sustained* tachycardia.

Site of Origin of an Arrhythmia

Arrhythmias may arise anywhere in the heart. For practical purposes, they are divided into those arising in the atrium, the AV nodal region, and the ventricle and those that use extra connections between the atrium and ventricle in their arrhythmic mechanism. Identification of the site of origin is based on (a) the relation between the P wave and QRS complex; (b) the width and configuration of the P wave, which indicate how the atria are activated during the arrhythmia; and (c) the width and configuration of the QRS complex, which indicate how the ventricles are activated during the arrhythmia.

Aberrant Conduction

Figure 60.8 illustrates the occurrence of *premature atrial beats* during sinus rhythm due to a parasystolic atrial focus. It should be noted that these beats occur earlier and have a P-wave configuration that differs from that of the P waves during sinus rhythm. Conduction of the premature atrial beat from atrium to ventricle depends on the prematurity of that beat. A very early atrial beat is not conducted to the ventricle because of refractoriness of the AV conduction system. When conducted to the ventricle, the QRS configuration of the premature atrial beat depends on the time of arrival in the ventricle and, therefore, on the degree of refractoriness of the bundle branches. The amount of change (aberrancy) of the QRS complex following the premature atrial beat is related to the prematurity of that beat and the refractory state of the bundle branches, which, in turn, is related to the length of the RR interval that precedes the premature atrial complex (Fig. 60.8).



A 56-year-old male patient with nonconducted premature atrial contractions.

Aberrant conduction is quite common during the sudden rate change at the onset of an SVT, because the supraventricular impulse arrives at the bundle branches at such an early time that one of the bundle branches is still refractory (Fig. 60.9). The mechanism of aberrant conduction is thus termed a *phase 3*– or *tachycardia-dependent aberrancy*. Another cause of persistent aberrant conduction during SVT is retrograde invasion into one of the bundle branches (5). An example is given in Figure 60.10.

FIGURE 60.9 Aberrant conduction follows the onset of a supraventricular tachycardia (phase 3 aberrancy). Note that the right bundle branch block aberrancy disappears after 15 tachycardia complexes.

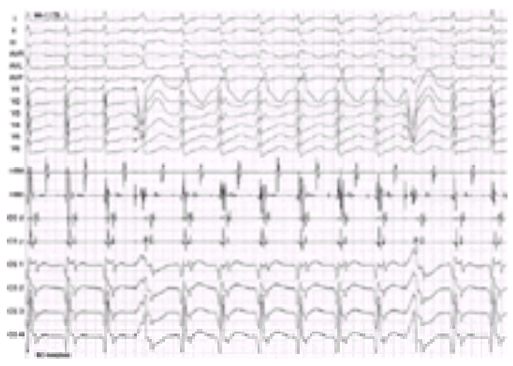


FIGURE 60.10 Supraventricular tachycardia with aberrant conduction due to retrograde invasion into the right bundle branch. Retrograde invasion was produced by an electrically induced right ventricular premature beat and persists until another induced right ventricular premature beat restores normal conduction over the right bundle branch. Apart from the 12-lead electrocardiogram, several intracardiac leads are shown. CS, coronary sinus; HBE, bundle of His electrogram; HRA, high-right atrium.

TACHYCARDIAS

Atrial Tachycardia

During atrial tachycardia, impulse formation is in the atrium, outside the sinus node. The P wave precedes the QRS complex. The polarity of the P wave indicates the site of origin in the atrium. Two types of atrial tachycardias must be distinguished. *Paroxysmal* atrial tachycardia is the most common and is characterized by a sudden onset and cessation of the arrhythmia (Fig. 60.11). A rare, but more serious, type of atrial tachycardia is a *permanent* or *incessant* atrial tachycardia, with the arrhythmia being present for more than 50% of the day (Fig. 60.12). In these patients, the rate of impulse formation in the atrium frequently increases during sympathetic stimulation (e.g., during exercise). Administration of antiarrhythmic drugs usually fails to prevent 1:1 AV conduction during exercise in these patients. The incessant nature of the arrhythmia and the difficulty in controlling the ventricular rate may lead to dilated (tachycardia-induced) cardiomyopathy (6). A fuller discussion of atrial tachycardia can be found in Chapter 65.

FIGURE 60.11 Paroxysmal atrial tachycardia. The tachycardia shown here starts after three sinus beats.

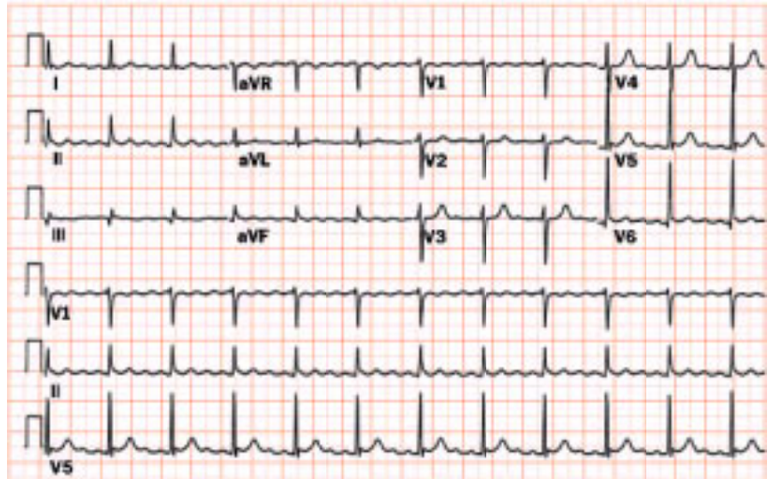
FIGURE 60.12 Incessant atrial tachycardia. Atrioventricular conduction of 2:1 is present in the left panel, changing into 1:1 atrioventricular conduction. The origin of the arrhythmia is low in the intraatrial septum.

A 57-year-old female patient with atrial tachycardia and 2:1 atrioventricular conduction.

Atrial Flutter

Atrial flutter is typically characterized by a regular atrial rhythm, a rate of 250 to 350 beats/min, and an atrial activity with a sawtooth pattern. Identifying atrial activity during atrial flutter can be facilitated by carotid sinus massage (CSM) (Fig. 60.13). Depending on the pattern of atrial activation during flutter, the shape and polarity of the flutter waves may differ. The ventricular rate during atrial flutter depends on the conduction characteristics of the AV conduction system and usually varies from a 2:1 AV relation to higher degrees of AV block. A fuller discussion of atrial flutter can be found in Chapter 65.

FIGURE 60.13 Atrial flutter. Shown here is an atrioventricular conduction of 2:1, changing in the middle to 4:1 atrioventricular conduction during carotid sinus massage.



Atrial flutter. Atrial rate of 300 beats/min with upright P waves inferiorly. This is consistent with atypical atrial flutter.

Atrial flutter. Inverted "saw-tooth" waves in the inferior leads suggest typical atrial flutter.

Atrial Fibrillation

During atrial fibrillation (AF) atrial activity is characteristically rapid, with a rate of 350 to 500 beats/min, and shows an irregular rhythm that varies continuously in shape (Fig. 60.14). Depending on the shape and duration of the fibrillatory waves, one can distinguish coarse from fine AF. The underlying mechanism cannot be identified by such ECG characteristics of AF. The ventricular rate during AF depends on the electrophysiologic properties of the AV conduction system. The refractory period of AV nodal and subnodal tissue and concealed conduction in the AV node determine the ventricular frequency during AF, which, in the absence of a refractory period prolonging drugs, is from 130 to 180 beats/min.

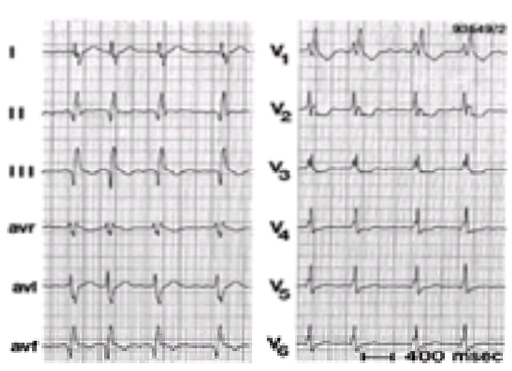


FIGURE 60.14 Atrial fibrillation. Characteristic of atrial fibrillation are the changes in atrial activation pattern and the irregularity of the RR intervals.

When two connections between the atrium and ventricle are present and are able to conduct the impulses from the atrium to the ventricle during preexcitation, the ventricular rate during AF relates to the duration of the refractory period of the two connections (7). When the AV AP has a short anterograde refractory period, a very high ventricular rate may occur during AF (Fig. 60.15). This high ventricular rate may deteriorate into ventricular fibrillation and may result in sudden cardiac death. The characteristic ECG feature of AF in the presence of ventricular preexcitation is a rapid, irregular ventricular rhythm with wide QRS complexes. The QRS configuration changes according to the contribution of the two AV pathways to ventricular activation. A fuller discussion of AF can be found in Chapter 64.

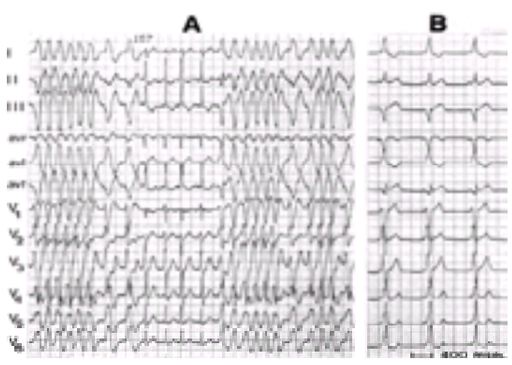
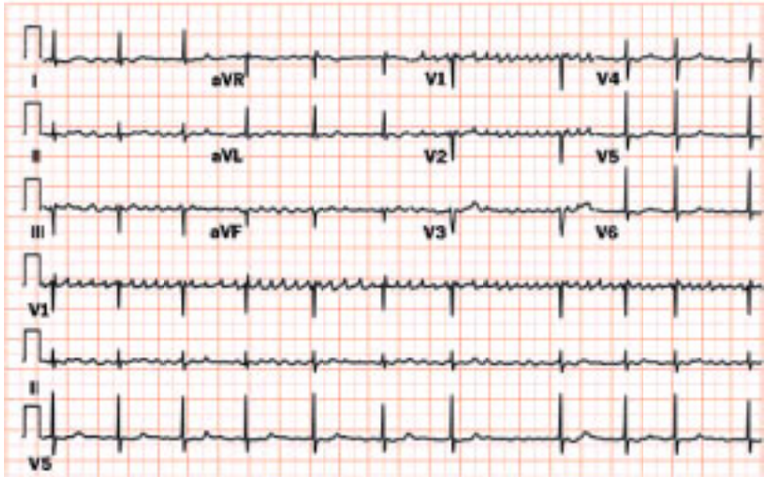


FIGURE 60.15 A: Atrial fibrillation in a patient with the Wolff-Parkinson-White syndrome. Note atrioventricular (AV) conduction over the accessory pathway (AP) on the left and right sides of the panel, with AV conduction over the AV node in the middle. As shown, the ventricular rate can become very high during AV conduction over the AP. **B:** Posteroseptal location of the AP is shown during sinus rhythm.



Atrial fibrillation. Narrow complex QRS with irregular RR intervals. Ventricular rate is controlled.

Tachycardias Located in the Atrioventricular Nodal Region

During these arrhythmias, there is usually 1:1 conduction from the AV nodal region to the atrium and to the ventricle (see Chapter 66), and because of the simultaneous activation of the atrium and the ventricle, the P waves are generally hidden within the QRS complex, or they may fall in the terminal part of the QRS complex, mimicking S waves in leads II, III, and aVF and a pseudo-incomplete right bundle branch block (RBBB) pattern in lead V_1 (Fig. 60.16); this is the *common* form of AV nodal tachycardia. The P wave rarely follows the QRS complex with an RP interval longer than the PR interval; this is an *uncommon form* of AV nodal tachycardia. In contrast to the common form of AV nodal tachycardia, the uncommon form is usually short lived and self-terminates within seconds to minutes.

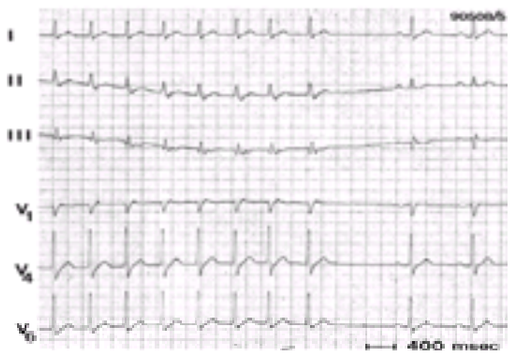


FIGURE 60.16 Common form of atrioventricular nodal tachycardia. Note the pseudo-S wave in leads II and III and the pseudo, incomplete right bundle branch block pattern in lead V_1caused by the P wave during tachycardia.

Atrioventricular nodal reentrant tachycardia. Note retrograde P wave buried within the ST segment.

Occasionally, 2:1 block develops between the AV node and the ventricle. The P wave typically is exactly in the middle between two QRS complexes. Because atrial activation starts low in the intraatrial septum, the P wave is narrow and negative in leads II, III, and aVF (Fig. 60.17). A fuller discussion of these tachycardias can be found in Chapter 66.

FIGURE 60.17 Atrioventricular (AV) nodal tachycardia with 2:1 block between the AV node and the ventricle and 1:1 conduction from the AV node to the atrium. As shown in the bundle of His recording (HIS), the 2:1 block is located in the distal part of the AV node. RA, right atrium; RV, right ventricle.

Tachycardias Using Extra Connections between Atrium and Ventricle: Circus-Movement Tachycardia

The presence of more than one connection between the atrium and ventricle creates a possible pathway for a reentry circuit resulting in a tachycardia. During tachycardia, AV conduction occurs over one AV connection, and VA conduction occurs over the other. Depending on the pathway used for AV conduction, the tachycardia may show (a) a narrow QRS complex or a typical RBBB or left bundle branch block (LBBB) configuration when AV conduction occurs over the AV node–His pathway or (b) a preexcited QRS complex when AV conduction occurs over the accessory connection (Fig. 60.18).

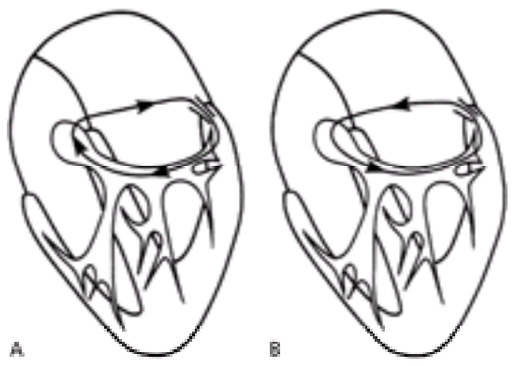


FIGURE 60.18 The two types of circus-movement tachycardias (CMT) in a patient with an accessory atrioventricular (AV) pathway. **A:** Orthodromic CMT with AV conduction over the AV node and ventricular conduction over the accessory pathway. **B:** CMT in the reverse direction—antidromic CMT.

In the first type of tachycardia, termed *orthodromic circus-movement tachycardia* (*CMT*), the AP is the retrograde limb in the tachycardia circuit. If the AP rapidly conducts the impulse, a short RP interval results. Less frequently, an AP has slower conduction properties and the RP interval is long (Fig. 60.19 and Fig. 60.20). In the second type of tachycardia, referred to as an *antidromic CMT*, AV conduction occurs over the accessory connection, resulting in a wide QRS complex that shows pronounced slurring of its initial portion; such a wide QRS complex with pronounced slurring is due to ventricular activation starting outside the intraventricular conduction system (Fig. 60.21). VA conduction during this tachycardia may occur either by way of the His–AV node axis or by way of a second accessory connection. A fuller discussion of CMTs can be found in Chapter 65.

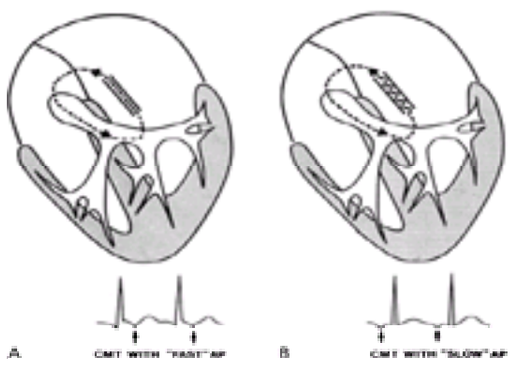


FIGURE 60.19 Two types of accessory pathways (AP) and their effect on the RP interval during circus-movement tachycardia (CMT). **A:** Rapidly conducting AP resulting in a short RP interval during orthodromic CMT. **B:** Slowly conducting AP leads to a long RP interval during tachycardia.

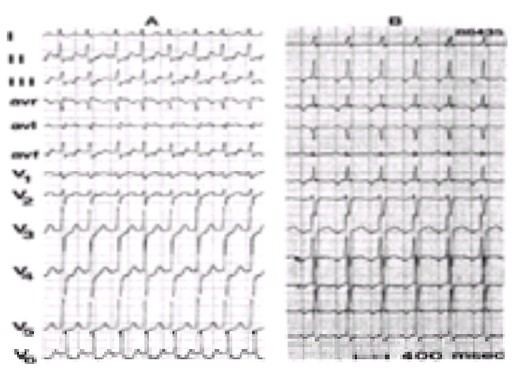


FIGURE 60.20 Examples of the two types of tachycardias for which the tachycardia circuit is shown in Figure 60.19. **A:** Ventriculoatrial conduction over the rapidly conducting accessory pathway. **B:** Conduction over a slowly conducting accessory pathway.

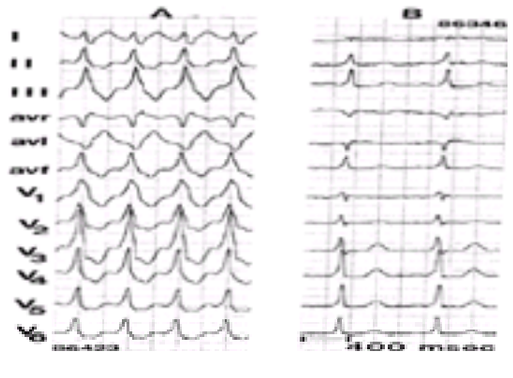


FIGURE 60.21 A: Antidromic circus-movement tachycardia with atrioventricular conduction over a left posterior accessory pathway. **B:** Same patient during sinus rhythm.

Additional Features That Are Helpful in Differentiating Supraventricular Tachycardias

Electrical Alternans

During a regular SVT, the QRS configuration and the T wave may alternate in height (Fig. 60.22). This phenomenon is more common in orthodromic CMT than in atrial or AV nodal tachycardia (8). It especially occurs during high rates of the tachycardia and can only be considered suggestive of orthodromic CMT when alternation occurs for longer than 5 seconds after the beginning of the tachycardia.

FIGURE 60.22 Electrical alternans of the QRS complex during a circus-movement tachycardia using a “concealed” atrioventricular accessory pathway. The tachycardia terminates when block occurs in the atrioventricular nodal part of the circuit.

Effect of Bundle Branch Block on the Tachycardia Rate

When one of the bundle branches is incorporated into the tachycardia circuit, block in that bundle branch during tachycardia usually slows the tachycardia rate (9). As shown in Figure 60.23 and Figure 60.24, this can only occur in *orthodromic* CMT.

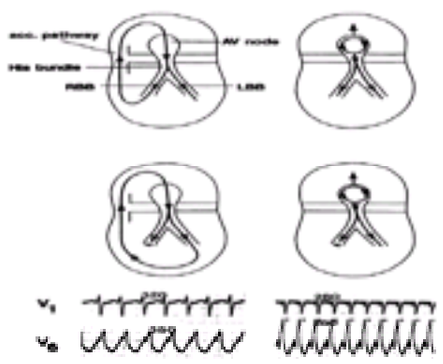


FIGURE 60.23 Effect of a bundle branch block during circus-movement tachycardia using an accessory (acc.) pathway that is on the same side of the heart as the bundle branch block. As shown, the circuit becomes longer when right bundle branch block (RBB) develops in a patient with a right-sided accessory pathway. Nothing happens to the tachycardia rate when bundle branch block develops during atrioventricular (AV) nodal reentrant tachycardia (measurements are in ms). LBB, left bundle branch block.

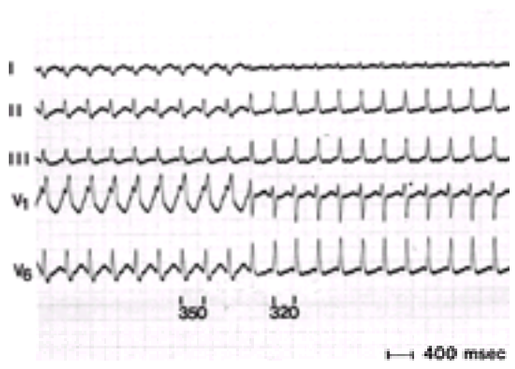


FIGURE 60.24 Example of rate change during right bundle branch block in a patient with an orthodromic circus-movement tachycardia using a right-sided accessory pathway. During right bundle branch block, the RR interval is 30 ms longer compared with the RR interval during nonaberrant conduction.

Value of Carotid Sinus Massage

CSM can be very helpful in differentiating regular from irregular tachycardias. This is illustrated in Table 60.1. Table 60.2 summarizes the ECG features of the most common types of regular SVTs.

Type of supraventricular tachycardia	Effect of carotid sinus massage
Sinus tachycardia	Gradual and temporary slowing of the heart
Atrial tachycardia	
Paroxysmal	Cessation of tachycardia or no effect
Incessant	Temporary slowing of ventricular rate (because of AV block) or no effect
Atrial flutter	Temporary slowing of ventricular rate (because of AV block) or no effect
AVNRT	Cessation of tachycardia or no effect
CMT	Cessation of tachycardia or no effect

AV, atrioventricular; AVNRT, AV nodal reentry tachycardia; CMT, circus-movement tachycardia (using an AV accessory pathway and the AV node).

TABLE 60.1 EFFECT OF CAROTID SINUS MASSAGE ON SUPRAVENTRICULAR TACHYCARDIA

ECG signs	AT	CMT	AVNRT
AV block (spontaneous or by CSM)	If present, may not only be useful for diagnosing AT but also for differentiating atrial flutter (atrial rate >250/min) from AT	Rules out CMT	Unusual, but 2:1 block is possible
Electrical alternans	Rare	Common (especially at high tachycardia rates)	Rare
P-wave location in relation to QRS complex	Present between R waves; PR length varies with atrial site of origin and AV nodal conduction time	Present between R waves: RP<PR in fast AP, RP>PR in slow AP	Hidden in QRS or distorting the distal portion of the QRS
P polarity	Varies with the location of atrial impulse formation	Varies according to location of atrial end AP	Always negative in leads II, III, and AVF
Aberrant conduction	Rare	Common	Rare

AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVF, atrioventricular fibrillation; AVNRT, atrioventricular nodal reentry tachycardia; CMT, circus-movement tachycardia incorporating AP; CSM, carotid sinus massage; ECG, electrocardiogram.

TABLE 60.2 SUMMARY OF ELECTROCARDIOGRAPHIC FEATURES OF THE MOST COMMON TYPES OF REGULAR SUPRAVENTRICULAR TACHYCARDIAS

Wide QRS Tachycardia

Correctly identifying the site of origin of a wide QRS tachycardia is not only important to proper treatment of the arrhythmia but also to the prognosis. VT usually has a more ominous prognosis than does SVT.

Table 60.3 and Figure 60.25 illustrate the possible causes of a wide QRS tachycardia. To correctly diagnose such a tachycardia, it is essential to use a 12-lead ECG. This should be used systematically, checking for independent atrial and ventricular activity (AV dissociation) and for characteristics of a QRS tachycardia such as its width, axis, and configuration.

A supraventricular tachycardia (SVT) with preexisting or functional bundle branch block; this includes sinus tachycardia, atrial tachycardia, atrial flutter, atrial fibrillation, and atrioventricular (AV) nodal reentry tachycardia
Orthodromic circus-movement tachycardia (CMT) using the AV node in the anterograde direction and an accessory pathway (AP) in the retrograde direction with preexisting or functional bundle branch block
An SVT with conduction over an AP
Antidromic CMT using an AP in the anterograde direction and the AV node or another AP in the retrograde direction
A reentry tachycardia using a nodoventricular fiber in the anterograde direction and the bundle branch–His pathway or another AP in the retrograde direction
A ventricular tachycardia

TABLE 60.3 POSSIBLE CAUSES OF A WIDE QRS TACHYCARDIA

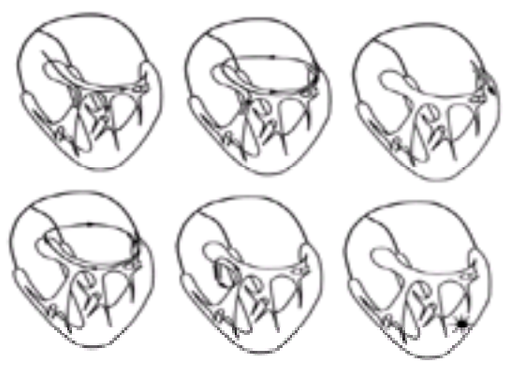


FIGURE 60.25 Six possible causes of a wide QRS tachycardia. See Table 60.3 for a full description.

Wide complex tachycardia. Atrioventricular dissociation confirms ventricular origin.

Atrioventricular Dissociation

Independent atrial and ventricular activity during a wide QRS tachycardia has been correctly considered a hallmark of VT. However, during VT some form of VA conduction may be present, especially when the VT rate is relatively slow (10). When AV dissociation is present during VT, the atrial rate is usually slower than the ventricular rate, except in atrial tachycardia, atrial flutter, or AF. During VT, part or all of the ventricle may occasionally be activated by a supraventricular impulse (e.g., a sinus beat), which is conducted through the AV conduction system and arrives in the ventricle when the ventricle is partly or completely excitable. This typically occurs when the VT rate is relatively slow. This phenomenon results in capture or fusion beats (Fig. 60.26).

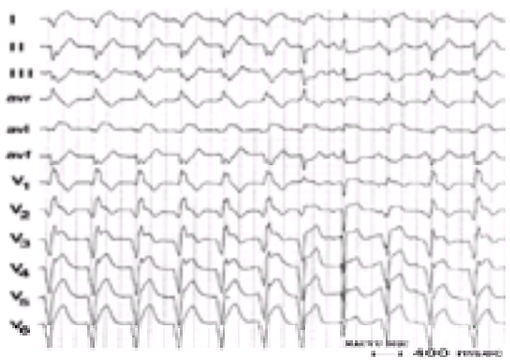


FIGURE 60.26 Ventricular tachycardia with a relatively slow rate, allowing the occurrence of capture and fusion beats. The tracing was recorded in a patient with a recent anterior wall myocardial infarction. Note the QR pattern in several leads during ventricular tachycardia.

Width of the QRS Complex

Absence or delay in RBB conduction during a supraventricular rhythm results in an RBBB configuration and a QRS complex with a width of 120 ms. When conduction

in the LBB is blocked, the width of the QRS complex may become as long as 140 ms. These facts are of value in distinguishing an SVT from a VT. The wider the QRS complex, the more likely that the tachycardia is ventricular in origin. This is typically the case when ectopic ventricular impulse formation occurs in the free wall of the right or left ventricle and when activation of the two ventricles occurs sequentially rather than simultaneously. This finding prompted Wellens et al. (10) to evaluate the role of the width of the QRS complex in distinguishing an SVT from a VT complex. For several reasons, however, an SVT has a QRS width of greater than 140 ms. They include (a) SVT in the presence of BBB with additional intramyocardial conduction delay, (b) SVT with AV conduction over an AV, and (c) marked QRS widening during SVT because of the use of antiarrhythmic drugs that prolong intraventricular conduction.

An 81-year-old male patient with ventricular tachycardia.

VT may have a QRS width of less than 140 ms. Such is the case for VTs that originate in or close to the specific conduction system of the left ventricle (Fig. 60.27).

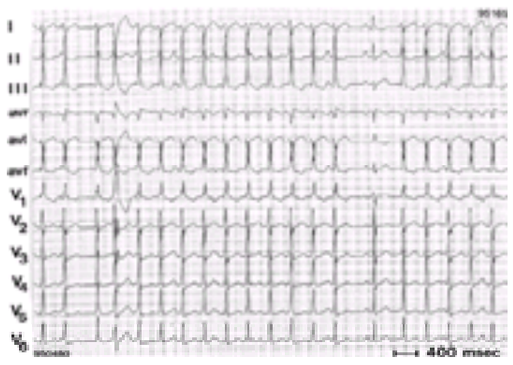


FIGURE 60.27 Idiopathic ventricular tachycardia arising in or close to the anterior fascicle of the left bundle branch. Note atrioventricular dissociation during ventricular tachycardia. Note also that the QRS width during ventricular tachycardia is only 120 ms.

QRS Axis in the Frontal Plane

When impulse formation originates in the ventricle, the frontal plane axis is frequently abnormal. This axis depends on the site of origin of the VT. In 1976, Wellens et al. (10) observed that a frontal plane axis to the left of –30 degrees during tachycardia was suggestive of a VT. This observation still holds true in VT with an RBBB configuration but remains questionable in VT with an LBBB shape (11).

The etiology of VT with an LBBB shape is usually either (a) an anterior or inferoposterior scar from a previous myocardial infarction (MI) in or close to the interventricular septum, (b) an idiopathic VT arising from the outflow tract of the right ventricle, or (c) a VT in arrhythmogenic right ventricular (RV) dysplasia. Whereas in the first and third etiologies the exit point of the VT and, therefore, of the QRS axis may vary, in idiopathic VT from the RV outflow tract the frontal plane axis is typically vertical or to the right. In general, in a patient with a wide LBBB-shaped tachycardia, marked left-axis deviation (i.e., to the left of –60 degrees) or marked right-axis deviation (i.e., to the right of +90 degrees) suggests a ventricular arrhythmia.

Configurational Characteristics of the QRS Complex

Right Bundle Branch Block–Shaped QRS Complex

In SVT with RBBB, leads V_1 and V_6 usually have a triphasic pattern (10,12). Lead V_1 has an rSR' pattern, with the initial r reflecting normal septal activation, the S wave reflecting left ventricular activation, and the R' wave reflecting delayed activation of the right ventricle. Lead V_6 shows a narrow q wave resulting from normal septal activation, an R wave representing left ventricular activation, and an S wave reflecting delayed RV activation. In lead V_6 the R:S ratio is typically greater than 1:1.

In VT with an RBBB shape, lead V_1 shows a monophasic or biphasic QRS complex (i.e., R, qr, rs). The presence of a deep S wave in lead V_6 with an R:S ratio of less than 1:1 supports a diagnosis of VT (10). This is typically the case when left-axis deviation is present. In the case of right-axis deviation, the R:S ratio in lead V_6 is usually greater than 1:1 (Fig. 60.28).

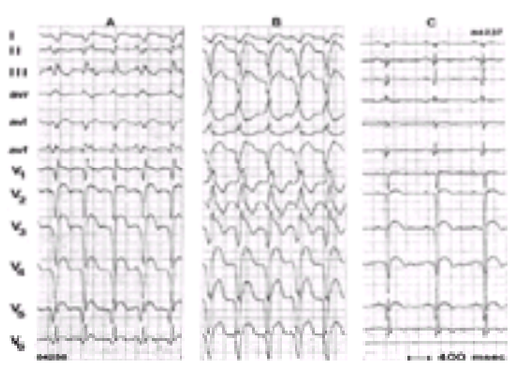


FIGURE 60.28 Two types of ventricular tachycardias in a patient with an old anteroseptal and apical myocardial infarction **(A)**. In **B** and **C**, a right bundle branch block pattern is present, with a QR and a monophasic R, respectively, in lead V_1. QRS negativity or positivity in lead V_6 is related to the frontal plane axis. A QS complex during left-axis deviation is shown in **B**, and a QR complex during right-axis deviation is shown in **C**. During ventricular tachycardia, atrioventricular dissociation is clearly present in **B** and in **C**.

Left Bundle Branch Block–Shaped QRS Complex

Leads V_1, V_2, and V_6 are the important ECG leads to use in distinguishing a VT from an SVT with LBBB (11). If an r wave is present in either lead V_1 or V_2, it is narrow (i.e., <0.04 second) in SVT with LBBB. Moreover, the downstroke of the S wave is fast, without slurring or notching, and the distance from the beginning of the QRS to the nadir of the S wave is 0.06 second or less. If in lead(s) V_1 or V_2, or both, the r wave is greater than 0.04 second and the downstroke of the S wave is slurred and

delayed, a diagnosis of VT is likely (Fig. 60.29). A Q wave in lead V_6 is diagnostic of VT (11).

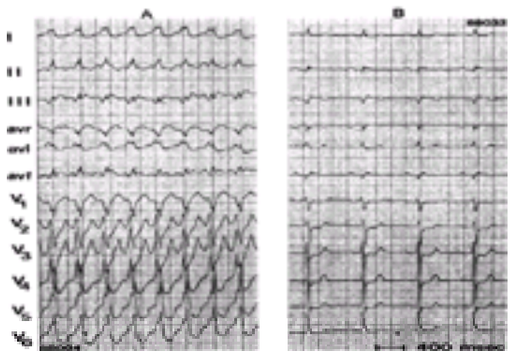


FIGURE 60.29 A: Ventricular tachycardia with a left bundle branch block shape. Note initial positivity of the QRS in lead V_1 (>0.04 second), slurring of the S wave in leads V_1 and V_2, and a distance from the beginning of the QRS to the nadir of the S wave of 120 ms in leads V_1 and V_2. **B:** An old inferior myocardial infarction.

Concordant Pattern in the Precordial Leads

Leads V_1 through V_6 may all show positive or negative QRS complexes, referred to as *positive* and*negative concordancy*. Negative concordancy is diagnostic of VT (Fig. 60.30). Positive concordancy occurs not only in VT originating in the posterobasal area of the left ventricle but may also be seen in tachycardias with AV conduction over an AP inserting into the posterobasal left ventricle (Fig. 60.21).

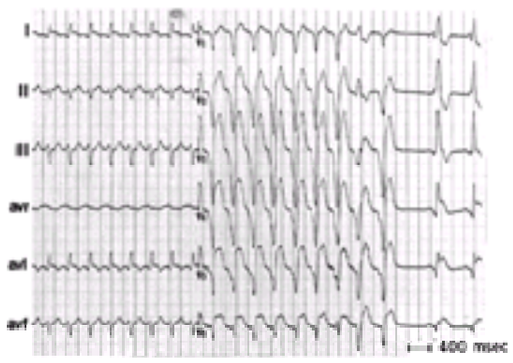


FIGURE 60.30 Ventricular tachycardia (VT) shows a negative concordant pattern in the precordial leads. This is diagnostic of VT. The QRS following termination of VT shows an old anteroapical myocardial infarction.

Presence of Q Waves during Tachycardia

As a rule, QR complexes during a wide QRS tachycardia are highly suggestive of VT (Fig. 60.26, Fig. 60.28, 60.29) unless identical QR complexes are present in the same leads during sinus rhythm (13). However, Qr complexes may occur, although rarely, during tachycardia and sinus rhythm in the same leads in the presence of a bundle branch reentrant tachycardia (14) (Fig. 60.31). As is shown in Table 60.4, in patients with VT following MI, approximately 40% have a QR complex in one or more of the ECG leads. QR complexes during VT typically occur in patients with a localized ventricular scar, as in those with a previous MI or localized infiltrative or inflammatory myocardial disease.

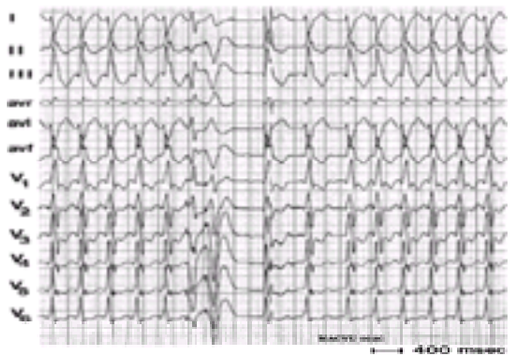


FIGURE 60.31 Ventricular tachycardia based on bundle branch reentry. After two electrically induced premature ventricular beats, the tachycardia terminates in the middle of the recording. However, it resumes after three conducted sinus beats. QRS is identical during sinus rhythm and tachycardia. During electrophysiologic study, the tachycardia was found to be based on bundle branch reentry, with the right bundle branch as the retrograde pathway. The tachycardia was cured by radiofrequency ablation of the right bundle branch.

	LBBB morphology (n = 58) (%)	RBBB morphology (n = 75) (%)
Presence of a QR in any lead except aVR during VT	25/58 (43)	28/75 (37)
Correlation between the site of QR pattern during VT and site of myocardial infarction during sinus rhythm (in ≥1 lead)	21/25 (84)	20/28 (71)

LBBB, left bundle branch block; RBBB, right bundle branch block; VT, ventricular tachycardia.

TABLE 60.4 INCIDENCE OF QR COMPLEXES IN PREVIOUS MYOCARDIAL INFARCTION AND THE CORRELATION BETWEEN QR PATTERN DURING VENTRICULAR TACHYCARDIA AND SITE OF MYOCARDIAL INFARCTION DURING SINUS RHYTHM

Interval from Onset of QRS to Nadir of the S Wave in Precordial Leads

As already indicated in Left Bundle Branch Block–Shaped QRS Complex, the interval from the onset of QRS to the nadir of the S wave in precordial leads is increased

in VT. Brugada et al. (15) have suggested that an RS interval of greater than 100 ms in one or more precordial leads is highly suggestive of VT. The clinician must be careful, however, because such a duration may occur in SVT with AV conduction over an AP, SVT during the administration of drugs that slow intraventricular conduction, and SVT with preexistent BBB, especially LBBB.

ECG INWIDE QRS TACHYCARDIAS

It is essential to follow a systematic approach when analyzing ECGs in patients with wide QRS tachycardias. Table 60.5 reviews the different signs that should be systematically checked for when analyzing a regular wide QRS tachycardia. Correctly diagnosing the tachycardia is imperative, because incorrectly diagnosing an SVT may lead to selecting inappropriate antiarrhythmic drugs and to deleterious results (16,17). Such an error is one of the most frequent mistakes made in treating arrhythmias; hence, familiarity with the criteria described herein should almost invariably prevent such a misdiagnosis.

Atrioventricular (AV) dissociation suggests ventricular tachycardia	(VT), but ventriculoatrial conduction may be present during VT.
A *QRS width* of ≥160 ms suggests VT, but one needs to rule out	(a) preexistent bundle branch block (BBB, especially left BBB (LBBB), (b) supraventricular tachycardia (SVT) with AV conduction over an accessory pathway (AP), and (c) use of drugs that slow intraventricular conduction delay (class IA, IC, amiodarone).
Keep in mind: VT arising close to or in the intraventricular con-	duction system may have a width of ≤140 ms.
Left-axis deviation (to the left of −30 degrees) suggests VT but is	not helpful in (a) LBBB-shaped QRS, (b) SVT with conduction over a right-sided or posteroseptal AP, and (c) SVT during use of class IC drugs.
Right-axis deviation (to the right of +90 degrees) suggests VT in	LBBB-shaped QRS.
QR complexes in leads other than aVR suggest VT unless the	same QRS configuration is present in the same leads during sinus rhythm (unless bundle branch reentry is present).
Concordant pattern in precordial leads suggests VT, but positive	concordancy may occur during SVT with AV conduction over a left posterior AP.
R-nadir ≥100 ms in one or more precordial leads suggests VT	but may be found in (a) SVT on drugs that slow intraventricular conduction, (b) SVT with AV conduction over an AP, and (c) preexistent BBB (especially LBBB).
In the presence of capture or fusion beats, rule out (a) fusion	with a contralateral premature ventricular beat and (b) fusion with a ventricular echo beat.

TABLE 60.5 VALUE AND LIMITATIONS OF SIGNS IN DIAGNOSING REGULAR WIDE QRS TACHYCARDIA

THE FUTURE

Requirements in catheter ablation techniques will make it possible to cure an increasing number of different types of arrhythmias in the future. Additional improvements in ECG interpretation will facilitate rapid identification of the most appropriate treatment in patients with arrhythmias.

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61

AMBULATORY AND SIGNAL-AVERAGED ELECTROCARDIOGRAPHY AND T-WAVE ALTERNANS

STEPHEN C. HAMMILL

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Ambulatory electrocardiography (ECG) records a patient's ECG during routine activities, when the effect of autonomic tone, exercise, emotion, and other stresses can be evaluated. The technique assesses cardiac rhythm, myocardial ischemia, QT interval duration, signal-averaged ECG, and heart-rate variability. Newer solid-state recording systems digitize the ECG signal and all QRS complexes recorded during the 24 hours are available for analysis. These systems are replacing previously used tape systems. Intermittent and memory-loop ambulatory recorders are helpful for documenting symptoms that occur too infrequently to be assessed by 24-hour ambulatory ECG. The implantable memory-loop recorder is useful in assessing patients with symptoms that occur infrequently and are technically difficult to record with an intermittent or memory-loop recorder.

Ambulatory ECG monitoring in persons without apparent heart disease has identified a wide range of arrhythmias, a finding that must be kept in mind when patients are evaluated. Monitoring results must be placed in context with the patient's clinical condition and associated symptoms. Ambulatory monitoring is helpful when assessing patients with cardiogenic syncope, although memory-loop recorders are proving to be of more benefit. Ventricular arrhythmias recorded by 24-hour monitoring after myocardial infarction identify patients at risk for further cardiac events and can be helpful in combination with other prognostic tests to identify high-risk patients in whom intervention may improve survival.

Evaluating therapy using ambulatory monitoring must be done with the knowledge that a significant spontaneous variation occurs in the frequency and complexity of ventricular arrhythmias. For an antiarrhythmic drug to demonstrate efficacy, the frequency of ventricular ectopy should be suppressed by 80% to 90% with all repetitive forms eliminated. Ambulatory ECG monitoring is an important test that is useful in the evaluation of patients with arrhythmia or ischemia, and in assessing factors associated with increased risk of sudden death.

Signal-averaged ECG averages multiple QRS complexes, minimizing the level of noise that contaminates the periodic ECG signal, thereby exposing signals at the microvolt level that are normally hidden within noise. These signals at the end of the QRS complex are termed *late potentials* and represent delayed conduction through diseased myocardium and a potential physical substrate for reentry ventricular tachycardia. Late potentials usually arise from the border zone surrounding the scar of a previous myocardial infarction, but they can also be present in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, myocarditis, and infiltrative heart disease. The use of time-domain analysis to identify late potentials and to predict risk for ventricular arrhythmias has been validated in numerous studies and is the method used in commercial equipment. Frequency-domain analysis is less widely used, and diagnostic end points have not been standardized. Signal-averaged ECG using time-domain methods is not reliable in patients with prolonged QRS duration because of ventricular conduction delay.

Criteria to define the presence of late potentials depend on the lead configuration, filter, and processing algorithm; they need to be defined individually for each commercial system. The peak incidence of late potentials occurs in the first week after myocardial infarction and slowly decreases during follow-up, with 50% of patients having late potentials before being dismissed from the hospital and 25% at 5 years after infarction. Fewer than 5% of patients who do not have late potentials after myocardial infarction develop late potentials during long-term follow-up in the absence of another myocardial infarction. Late potentials are an independent risk factor for the development of ventricular arrhythmias after myocardial infarction, with a positive predictive accuracy of 20% and a negative predictive accuracy of 95%. Patients at high risk for serious arrhythmic events after myocardial infarction are best identified by combination of the results of signal-averaged ECG with other clinical and laboratory risk factors. Similarly, signal-averaged ECG in patients with cardiogenic syncope and a history of myocardial infarction is predictive of inducible ventricular tachycardia at electrophysiologic testing. The frequency of late potentials is decreased after thrombolytic therapy for acute myocardial infarction. The efficacy of antiarrhythmic drugs cannot be assessed using signal-averaged ECG.

T-wave alternans (TWA) is an ECG pattern characterized by changing morphology of the T wave on an every-other-beat basis. TWA is rarely seen on the ECG, but, when seen, is associated with pathophysiologic conditions that may give rise to ventricular arrhythmias, including Prinzmetal's angina, electrolyte abnormalities, acute ischemia, and long QT syndrome. With the advent of advanced signal-processing methods, TWA can now be measured at the microvolt level, even though visual inspection of the ECG shows no abnormality. Animal studies have demonstrated that microvolt-level TWA is a predictor of susceptibility to ventricular arrhythmias. TWA is caused by local alteration in the duration of the action potential as documented during electrophysiologic mapping studies. The development of reentrant ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, is hypothesized to be caused by local action potential alternans, which leads to spatial dispersion of recovery and the fractionation of depolarizing wavefronts, allowing reentry. Recent literature has supported the use of microvolt-level TWA to identify patients at risk for life-threatening ventricular arrhythmias and sudden cardiac death.

GLOSSARY

Complex ventricular ectopy: Nonsustained ventricular tachycardia, more than 10 premature ventricular complexes per hour.

Continuous ambulatory ECG: ECG recording for 24 to 48 hours that stores every heartbeat.

Delayed ventricular potentials: Another term for late potentials.

FQRSD: Filtered QRS duration. The total duration of the QRS complex is measured after filtering to determine whether late potentials are prolonging the QRS complex.

Frequency-domain signal-averaged ECG: A method of assessing late potentials by mathematical methods to measure frequency content of the QRS waveform.

High-resolution ECG: Another term for signal-averaged ECG.

Intermittent ambulatory ECG: ECG recording in which ECG data is stored only when the device is activated. Data is stored after the device is activated.

k: The alternans ratio used to define whether TWA is present.

LASD: Low-amplitude signal duration. The terminal QRS below 40 µV is measured to assess whether low-level late potentials are present.

Late potentials: Low-level electrical signals at the end of the QRS complex that represent slow conduction through abnormal myocardium.

Modulating factor: Variable that interacts with triggers and substrate to initiate an arrhythmia. Modulating factors include electrolytes, ischemia, and autonomic tone.

Memory-loop ambulatory ECG: ECG recordings taken for several days to weeks with ECG data stored to permanent memory only when the device is activated. The ECG preceding and following device activation is stored.

RMSV: Root mean square voltage. The last 40 ms of the QRS complex is assessed to determine whether a late potential is present.

Signal-averaged ECG: The standard ECG is filtered, and multiple QRS complexes are averaged, allowing identification of late potentials.

Time-domain signal-averaged ECG: A method of assessing late potentials by measuring their duration and amplitude.

Trigger: Cardiac events that initiate a sustained arrhythmia. Triggers include premature atrial and ventricular extrasystoles and alteration in cycle length.

TWA: T-wave alternans.

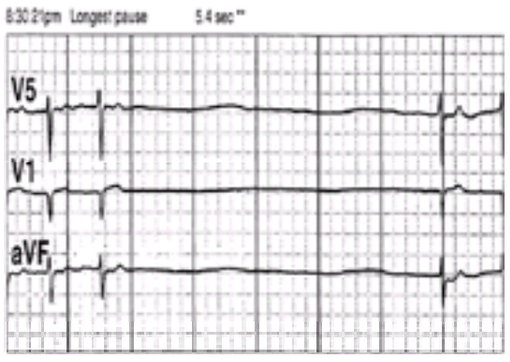
V*alt*: The alternans voltage used to define whether TWA is present.

AMBULATORY ELECTROCARDIOGRAPHY

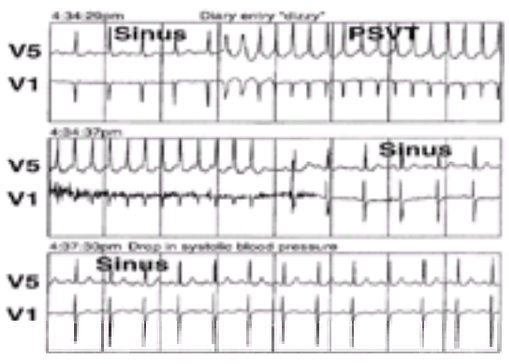
Historical Perspective

Ambulatory ECG was introduced by Holter and Gengerelli in 1949 (1); they used radiofrequency transmission with large, cumbersome equipment. Recording techniques improved, leading to the magnetic tape recording unit in 1961 (2). During the subsequent four decades, extensive clinical experience has developed, and ambulatory ECG monitoring has demonstrated that the test is useful for the diagnosis and management of cardiac arrhythmias and for assessing prognosis in populations of patients at high risk for life-threatening cardiac arrhythmias (3). The ambulatory ECG allows recording of a patient's ECG during routine activities, when the effect of 24-hour variation in autonomic tone, exercise, emotion, and other stresses on cardiac rhythm can be evaluated. Such effects may not be present during continuous monitoring in the hospital.

The ambulatory ECG was initially used to assess patients for the presence of tachycardia or bradycardia (*e*Fig. 61.0.1 and *e*Fig. 61.0.2). The technique evolved to be used for evaluation of myocardial ischemia by recording changes in the ST segment, of the QT interval duration as a prognostic factor for serious ventricular arrhythmia, of signal-averaged ECG to identify late potentials and substrate for serious ventricular arrhythmias, and of changes in the RR interval, reflecting heart-rate variability, a strong prognostic indicator for serious cardiac events.



***e*FIGURE 61.0.1** A 24-hour ambulatory electrocardiographic (ECG) recording in a patient with episodes of near syncope. The ECG demonstrates a 5.4-second sinus pause that occurred when the patient was resting and that was not associated with symptoms.



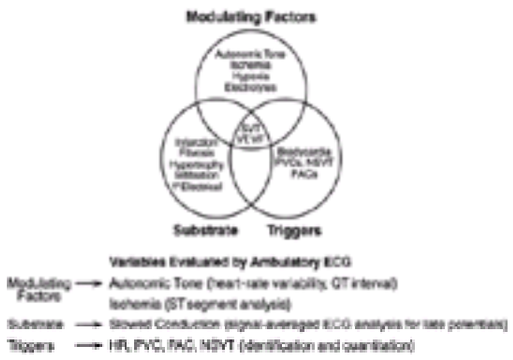
***e*FIGURE 61.0.2** A 24-hour ambulatory electrocardiographic (ECG) recording in a patient with episodes of "dizziness" and orthostatic hypotension. A 24-hour ambulatory ECG and a blood pressure recording were obtained. The ECG demonstrates an episode of paroxysmal supraventricular tachycardia (PSVT) associated with a complaint of feeling "dizzy." The patient was asymptomatic during decreases in systolic blood pressure at a time when the rhythm remained sinus.

The equipment used to record the ambulatory ECG has also evolved, with improved recording fidelity, reduction in size and weight, improved data acquisition using solid-state technology, and use of computer-enhanced analysis systems. In addition, patient-activated event recorders allow intermittent ECG recording at the time that infrequent symptoms occur. Recently, an implantable automatic and patient-activated ECG recording system was developed to document the cardiac rhythm during

symptomatic episodes that may occur as infrequently as every 12 months.

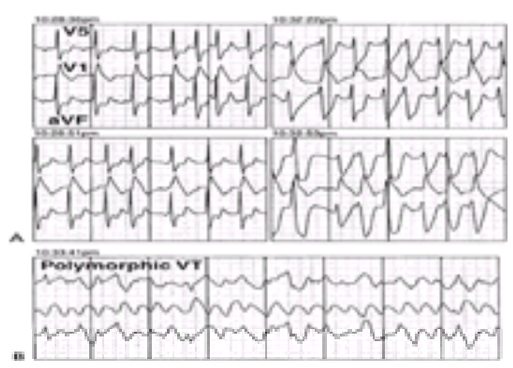
Pathophysiology of Cardiac Arrhythmias

The ambulatory ECG records the effect of changing autonomic tone and environmental factors on the development of cardiac arrhythmias. Sustained tachycardia is dependent on the interaction of triggers, substrate, and modulating factors (4) (eFig. 61.0.3). Triggers include premature atrial complexes and premature ventricular complexes (PVCs), nonsustained ventricular tachycardia (NSVT), and alterations in cardiac cycle length produced by ectopic beats and bradycardia. Arrhythmia triggers interact with a substrate: ischemic heart disease with either a fixed area of scar or transient abnormal conduction due to ischemia; hypertrophy in patients with advanced hypertrophic cardiomyopathy, hypertensive heart disease, or aortic stenosis; myocardial dilatation associated with cardiomyopathy; and inflammation and infiltration of the myocardium. Modulating factors interacting with substrate and triggers may be required before an arrhythmia occurs. Modulating factors include changes in sympathetic and parasympathetic tone, electrolytes, and ischemia (5).



***e*FIGURE 61.0.3** Pathophysiologic interactions resulting in arrhythmia. Venn diagram of the interaction of modulating factors, triggers, and substrate for the genesis of cardiac arrhythmias. The 24-hour ambulatory electrocardiogram (ECG) evaluates several of the interacting factors accounting for arrhythmias. HR, heart rate; PAC, premature atrial complex; PVC, premature ventricular complex; NSVT, nonsustained ventricular tachycardia; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

The ambulatory ECG is extremely helpful in identifying substrate, triggers, and modulating factors that interact to cause cardiac arrhythmias (eFig. 61.0.4). At first, the ambulatory ECG assessed triggers of cardiac arrhythmias, including PVCs, NSVT, and premature atrial complexes. The technique now also identifies late potentials by signal-averaged ECG, a marker of substrate capable of supporting a reentrant arrhythmia, and heart-rate variability, a modulating factor reflecting sympathetic tone.



***e*FIGURE 61.0.4** A 24-hour ambulatory electrocardiographic (ECG) recording in a patient with coronary artery disease and episodes of lightheadedness. **A:** At 10:28:36, the ECG records ST depression in leads aVF and V_5, with ST elevation in lead V_1. Over the next 4 minutes, the changes of acute injury progress. **B:** The rhythm degenerates into polymorphic ventricular tachycardia, from which the patient was resuscitated. This demonstrates the interaction of myocardial ischemia and subsequent ventricular arrhythmia. VT, ventricular tachycardia.

Individuals with symptomatic palpitations and symptoms suggestive of an arrhythmia often relate that their spells occur at different times of the day or are associated with different activities. The ambulatory ECG allows for assessment of bradycardia- or exercise-induced arrhythmias. Such rhythms include torsades de pointes with prolongation of the QT interval, atrial fibrillation that is dependent on enhanced vagal tone and heart-rate slowing, and cardiac arrhythmias that follow sympathetic tone increases during exercise.

Technical Aspects of Ambulatory Electrocardiographic Monitoring

Ambulatory ECG monitoring includes continuous and intermittent ECG recording. Continuous ambulatory ECG recording is performed for periods of 24 to 48 hours and allows assessment of cardiac rhythm on a continuous basis. Intermittent ambulatory ECG recordings can be obtained over longer periods of observation using a memory-loop recorder.

Continuous Ambulatory Electrocardiographic Monitoring

The two common recording systems are *tape-based* and *solid-state*. The tape-based system is a battery-powered device that records at an extremely slow tape speed, with two or three ECG amplifiers and an analog tape recorder. The typical analog amplifier records ECGs at frequencies similar to the standard 12-lead ECG (.05 to 100 Hz). Not all ambulatory ECG recording devices have this full-frequency response; a narrower response may limit fidelity, reducing the accuracy of recording dynamic changes in ST segments. The recording accuracy depends on the quality of the tape-drive motor and gearing. Irregularities in the tape drive can create artifacts that simulate tachycardia or bradycardia; this effect can be lessened or more easily identified with systems that record a simultaneous timing signal on an additional channel. Ambulatory ECG recorders have an event marker that allows patients to document the times at which they are feeling their typical symptoms, which can then be correlated with the ECG during playback. The recorders cannot be immersed in water.

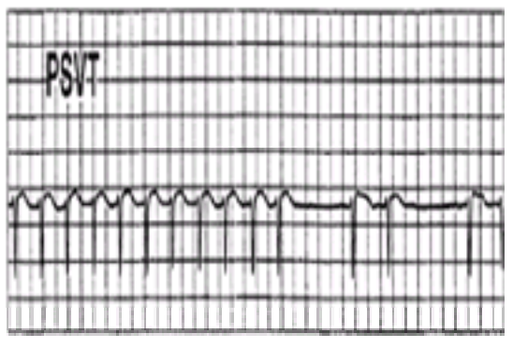
With the conventional tape-based system, recorded data is processed by a scanner, where it is digitized and analyzed with close interaction by an experienced operator. Abnormalities are then quantitated, and sample ECG rhythm strips or full-disclosure pages are recorded for subsequent review and documentation. In addition, the more sophisticated systems allow for assessment of RR interval and heart-rate variability, ST segment deviations, QT interval changes during 24 hours, and signal averaging to detect late potentials. The simplest scanner will not do data processing or tabulation, only full disclosure of the entire ECG recording. This system allows for identification of significant rhythm abnormalities but is inaccurate for quantitating abnormalities or performing any sophisticated processing. Using a system that does not incorporate computer-assisted analysis, the operator can miss as many as one-third of ventricular or supraventricular arrhythmias (6). Computer-assisted analysis systems significantly improve the sensitivity and specificity of ECG monitoring, increasing accuracy for quantitating ectopic complexes to approximately 95% (7,8). In the preferred system, experienced operators use computer-based analysis. Although this approach increases costs, it improves accuracy.

Solid-state recording systems digitize the incoming ECG signal from two or three channels and then store this data in the solid-state memory. The digital signal is assessed by intricate algorithms to determine whether the QRS complex is normal or represents an ectopic beat or part of a run of tachycardia. Older systems did not store every beat recorded during the 24 hours, but only samples of what were considered to be normal and abnormal complexes as determined by the algorithm. Such systems had problems with artifact being misinterpreted and stored as abnormal rhythm, or of ECG being stored if a patient felt symptoms at a time when the system interpreted the ECG as normal (9). Newer solid-state systems are capable of recording every heartbeat during a 24-hour period. This allows the ECG to be analyzed in a manner similar to analysis of the data from a tape-based system. Such systems combine the advantages of the tape-based system, in which all ECG complexes are recorded and analyzed, with the advantages of a smaller, quieter, and easier to maintain solid-state system. Solid-state devices are dependent on efficient and accurate coding algorithms. As the algorithms for cardiac arrhythmia, heart-rate variability, and tabulation of ectopic complexes improve (10,11), the ability to analyze and process incoming data in real time will simplify subsequent analysis after the recording is obtained. The increased cost of the recorder is a disadvantage of a

solid-state system.

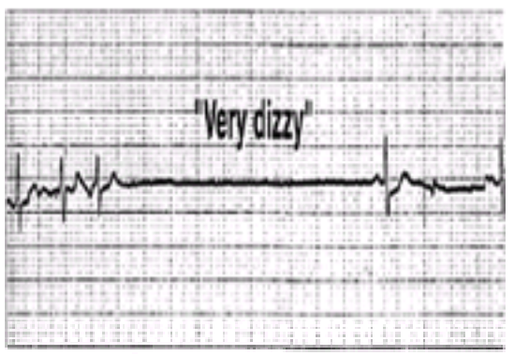
Intermittent and Memory-Loop Ambulatory Electrocardiographic Recording

Intermittent recorders are capable of storing only a limited number of short, patient-activated ECG recordings (12) (eFig. 61.0.5). These devices are lightweight, and some are as small as a thick credit card. Their advantage over continuous ambulatory systems is that the ECG is more likely to be obtained while the patient is experiencing clinical symptoms, thus allowing a direct correlation between the patient's symptoms and the ECG recorded at that instant (13,14,15,16 and 17). Current devices use solid-state technology that allows recording of 1 to 5 minutes of ECG for three to five occasions on which the patient is feeling symptoms. The ECG is stored in the solid-state memory of the device and transmitted by telephone to the base station at a time that is convenient for the patient.



***e*FIGURE 61.0.5** Intermittent memory-loop electrocardiographic (ECG) recording of a patient with palpitations. The rhythm strip documents an pisode of paroxysmal supraventricular tachycardia (PSVT) that terminates spontaneously, converting to sinus rhythm. The patient's symptoms occurred once every 2 to 3 weeks and were too infrequent to be recorded during 24-hour ambulatory ECG monitoring.

Development of this technology led to memory-loop circuitry, which is a hybrid between the ambulatory ECG monitor and the solid-state event recorder. With the memory-loop recorder, electrodes are applied to the patient and the device is worn on a continuous basis. When the patient activates the device, a permanent recording of stored ECG data is obtained that includes periods from 1 to 4 minutes before and 30 to 60 seconds after the recording button is pressed (*e*Fig. 61.0.6). The data can then be transmitted by telephone at the patient's convenience. This device has the disadvantage that it must be worn on a continuous basis, but the clear advantage that it obtains ECG data recorded before the patient presses the button and, thus, documents the rhythm at the onset of the patient's palpitations and the initiating event. Memory-loop devices are extremely helpful for documenting events that are associated with significant symptoms but occur on an infrequent basis. Ninety-five percent of symptomatic calls for suspected transient cardiac arrhythmias occur within 4 weeks of use of this device, and serious arrhythmia is documented in 52% of patients (18). Approximately 25% of patients who have recurrent syncope obtain diagnostically useful information using this device. Memory-loop recorders are limited by malfunction and by the inability of 20% of patients to properly use the device (19).



***e*FIGURE 61.0.6** Event recorder. Memory-loop electrocardiographic recording in a patient with symptoms of near syncope and palpitations. The recording documents an episode of atrial fibrillation, converting to sinus rhythm with an intervening pause. The patient had symptoms at the time of the pause that were similar to typical spells.

The most recent development in this technology is a small implantable memory-loop recorder that is placed subcutaneously in the left upper chest, allowing continuous ECG recording using a loop-based memory system capable of recording for up to 18 months (20). The device can be activated by the patient or set to automatically record an arrhythmia that is below or above a predetermined heart rate. Information is stored before the device is activated to record the onset of an arrhythmic or symptomatic event. The data is then downloaded into a computer for analysis and review. This system has the unique advantage of not being dependent on patient interaction, avoiding problems caused by patients who are unable to activate the device or place the recording leads. The device can be used for extended periods of time, as opposed to the standard memory-loop recorder, which is less practical after 3 to 4 weeks because of skin irritation from the patch electrodes. The implantable memory-loop recorder also allows the ECG to be recorded while the patient is exposed to water, when other systems cannot be used. A report of 85 patients who had syncope and negative ambulatory monitoring, tilt-table, and electrophysiologic testing showed that 58 patients (68%) had recurrent syncope at a mean of 10.5 months after implantation (21). The diagnosis of the syncopal mechanism included bradycardia in 18 patients and tachycardia in three patients; normal rhythm was recorded at the time of syncope in the remaining patients, suggesting a vasodepressor mechanism.

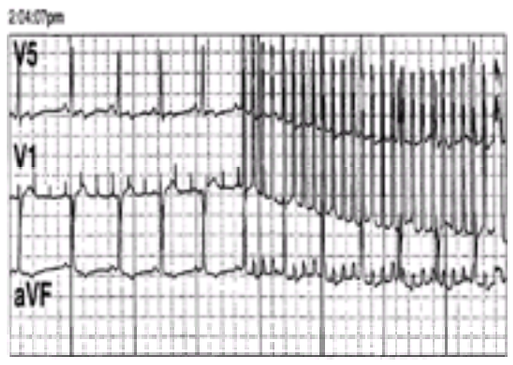
Selection of 24-hour continuous ambulatory versus intermittent ECG recording depends on the patient and the symptoms (22). Both recording systems are most useful when a patient has typical symptoms while the ECG is being recorded. The absence of any significant rhythm abnormality while symptoms are occurring is helpful in patient management, because it eliminates arrhythmia as a possible cause of the symptoms. An abnormal rhythm that occurs without symptoms may be a cause of the patient's clinical symptoms, or it may be only a spontaneous arrhythmia that could be recorded in a normal, asymptomatic individual. Monitoring does not help patient management in this situation.

Continuous 24-hour ambulatory ECG is helpful and provides the most useful, direct approach to documenting the ECG in patients with daily symptoms. Patients with infrequent symptoms are more likely to benefit from the intermittent or memory-loop recorder. An intermittent recorder is useful for a patient who has several minutes of arrhythmia that occur too infrequently to justify the continuous application of ECG electrodes required by the memory-loop recorder. The memory-loop recorder is most useful for patients who are expected to have symptoms within 4 weeks after they begin using the device and in whom symptoms are brief and not expected to last long enough to find, apply, and record with the intermittent recorder. The implantable memory-loop recorder is helpful for patients who have syncope or near syncope of unknown etiology despite standard evaluation, but who have spells too infrequently to justify a standard memory-loop recorder. A study of 43 patients with palpitations showed the event recorder to be superior to 24-hour ambulatory monitoring for diagnosing the mechanism of the palpitations. Event recorders detected clinically important arrhythmia in 19% of the patients, whereas ambulatory monitoring failed in all patients (23). Kus and coworkers (24) reported that continuous and intermittent recordings were complementary and that combined use increased the diagnostic yield for arrhythmia. Clinical judgment and experience are important in selecting the best diagnostic test for an individual patient; cost per management decision based on ambulatory ECG findings ranges from $550 for assessing drug therapy to $14,000 for assessing stroke (25).

Recording Artifact

Experienced operators are aware that artifact can simulate arrhythmia. Ambulatory ECG artifacts are important to recognize and can occur with tape slippage, excessive damping, inappropriate calibration, or saturation of the amplifier (26,27). The P-wave, QRS, and T-wave morphology may change in relation to body position and respiration (*e*Fig. 61.0.7). Electrical artifacts (*e*Fig. 61.0.8) can simulate pacemaker malfunction, and tape distortion or slippage may result in prolonged intervals that simulate sinus pauses or tachycardia. These problems occur less often with digital solid-state systems.

***e*FIGURE 61.0.7** Ambulatory electrocardiographic monitoring demonstrating a change in the QRS morphology in lead V_5 when the patient stands.



***e*FIGURE 61.0.8** Electrical artifact recorded during 24-hour ambulatory electrocardiographic monitoring demonstrating the value of recording different electrocardiography leads.

Ambulatory Electrocardiographic Findings in Normal, Asymptomatic Persons

Ambulatory ECG monitoring in persons without apparent heart disease has identified a wide range of arrhythmias (*e*Table 61.0.1). Brodsky and colleagues (28) reported heart rates for healthy male medical students that ranged from 37 to 180 beats/min during waking periods and 33 to 115 beats/min during sleep. Twenty-four percent of the subjects had heart rates below 40 beats/min during sleeping periods, and sinus pauses of more than 1.75 seconds were noted in 28% of subjects. When comparing healthy young males and females, females had a higher average heart rate while awake and asleep, less bradycardia below 40 beats/min, less junctional escape rhythm, and similar frequency of arrhythmia (29). Transient second degree atrioventricular (AV) block has been documented in 2% to 6% of trained athletes and young, otherwise healthy males and females (28,29 and 30). These arrhythmias often occur during sleep and are vagally mediated (31). Supraventricular and ventricular premature complexes are found in healthy control subjects, although the absolute number is low (28,32). The frequency of arrhythmias increases with age (33,34 and 35). In the Framingham Heart Study, Bikkina and associates (36,37), using 1-hour ambulatory monitoring in 2,727 men and 3,306 women with no history of heart disease or symptomatic arrhythmia, reported that complex ventricular arrhythmias increased with age. Approximately 5% of men younger than 60 years, 18% aged 60 to 69 years, and 35% older than 70 years had complex ventricular arrhythmias. In contrast, approximately 7% of women younger than 60 years, 12% aged 60 to 69 years, and 25% older than 70 years had asymptomatic complex ventricular ectopy. Manolio and associates (38) reported cardiac arrhythmias in 234 women and 158 men older than 65 years who had no evidence of coronary artery disease, hypertension, or diabetes. They identified ventricular arrhythmias in 11% of men and 20% of women, supraventricular arrhythmias in 54% of women and 63% of men, and bradycardia or conduction block in 0.9% of women and 55.1% of men. In athletes (39,40), 24-hour ambulatory ECG monitoring, in comparison to controls, identified a significantly lower average minimum heart rate (38 vs. 45 beats/min), more sinus pauses that were longer than 2 seconds (37% vs. 6%), more episodes of Mobitz I block (23% vs. 6%), and more junctional rhythm (20% vs. 0%), but no significant difference in the number of PVCs (33% vs. 43%). The finding of arrhythmia in asymptomatic healthy individuals must be kept in mind when patients are evaluated. The results of ambulatory ECG monitoring should be placed in context with the patient's clinical condition and associated symptoms.

Acute inferior myocardial infarction complicated by Wenckebach block. Note inferior ST-segment elevation and Q waves as well as progressive prolongation of the PR interval with grouped beating.

***e*TABLE 61.0.1** ARRHYTHMIA OCCURRENCE DURING AMBULATORY ELECTROCARDIOGRAM MONITORING IN HEALTHY PATIENTS

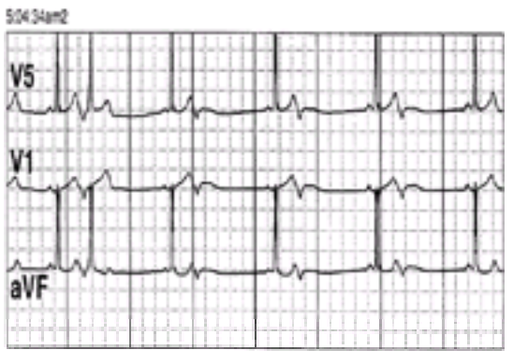
Study	Number of patients	Male/ female	Age (yr)	Monitoring duration	HR range	Minimum HR during sleep	PVCs	VT	PACs	SVT	Sinus pause >2.0 sec	Junctional rhythm	Mobitz I AV block
Clarke	86	41/45	16–45	48 h	Female: 65–95 Male: 60–85	—	>5/h –8%	2%	—	5%	0	10%	2%
Glasser	13	—	60–84	24 h	—	—	>15/h –15% Pairs: 23%	0	—	54%	0	8%	0
Hinkle	46	46/0	52–58	6 h	—	—	>10/1000 QRS –2%	0	>10/1,000 –6%	—	2%	—	2%
Manolio	392	158/234	>65	24 h	—	<40 beats/min –3%	>15/h or VT –15%	—	>15/h or SVT –58%	—	—	—	9%
Brodsky	50	50/0	23–27	24 h	37–180	43 ± 5	>50/24 h –2%	2%	>100/24 h –4%	—	4%	22%	6%
Sobotka	50	0/50	22–28	24 h	37–189	48 ± 6	>50/24 h –2%	2%	>100/24 h –2%	—	0	2%	4%

AV, atrioventricular; HR, heart rate; PACs, premature atrial complexes; PVCs, premature ventricular complexes; SVR, systemic vascular resistance; SVT, sustained ventricular tachycardia.

Ambulatory Recordings in Specific Clinical Syndromes

Cardiogenic Syncope

Patients who experience sudden loss of consciousness are best evaluated with techniques other than ambulatory monitoring because of the severity of their symptoms. Such patients are often admitted to the hospital for long-term ECG assessment and then considered for electrophysiologic testing, tilt-table testing, or exercise assessment to identify the cause of their spells. Patients with syncope who undergo ambulatory ECG monitoring experience lightheadedness, presyncope, or syncope during the recording 25% of the time (41,42 and 43). Approximately 2% to 15% are identified as having an associated cardiac arrhythmia when the symptoms occurred, and 35% have no associated ECG abnormality (32,42,44). Extending the recording to 3 days increases the number of patients who experience symptoms to 50%, and extending the recording to 5 to 21 days increases the number of patients who experience symptoms to 75% (43). Bass and coworkers (45) identified ECG abnormalities in 27% of 95 patients with syncope, using 72 hours of ambulatory ECG monitoring. Twenty-four hours of ambulatory monitoring often is not enough to identify potentially important arrhythmias in patients with syncope. Monitoring may need to be extended to 48 hours if recordings from the first 24 hours are normal (45) (*e*Fig. 61.0.9 and *e*Fig. 61.0.10).



***e*FIGURE 61.0.9** A 24-hour ambulatory electrocardiographic (ECG) recording in a patient with symptomatic bradycardia. The ECG demonstrates nonconducted atrial premature complexes occurring in bigeminy, resulting in bradycardia, which was asymptomatic at the time of this recording.

***e*FIGURE 61.0.10** A 24-hour ambulatory electrocardiographic (ECG) recording in a patient with near-syncope. The ECG demonstrates right bundle branch block with a premature ventricular complex followed by four nonconducted P waves. This high-grade atrioventricular block occurred during sleep and was not associated with symptoms.

The criteria for determining a significant arrhythmia in the absence of associated symptoms are difficult to establish. For example, many authors indicate that a sinus pause of 2.0 to 2.5 seconds is abnormal, but other authors have shown that sinus pauses of 3 seconds or longer may not cause symptoms and do not predict an adverse prognosis (46,47). Therefore, a sinus pause should be correlated with symptoms before intervention is considered.

Ambulatory ECG monitoring can be useful in identifying patients who would benefit from the use of electrophysiologic studies to assess unexplained syncope. Linzer and associates (48) evaluated a model of clinical characteristics for its usefulness in predicting outcome of electrophysiologic studies in 141 patients with unexplained syncope (49). They demonstrated that a combination of clinical, ECG, and ambulatory ECG findings can predict outcome of electrophysiologic testing. Patients who have cardiogenic syncope and associated heart disease, cardiac arrhythmia on ambulatory ECG monitoring, or abnormal 12-lead ECG results should be considered for electrophysiologic testing. Patients without these abnormalities are generally considered for tilt-table testing. Thirty percent of patients with negative electrophysiologic and tilt-table studies continue to have syncope and may benefit from use of a memory-loop recorder. The implantable memory-loop recorder should prove to be uniquely beneficial in this group of patients.

Atrial Fibrillation

In patients with paroxysmal atrial fibrillation, 24-hour ambulatory ECG monitoring can help identify the onset of the arrhythmia and potential approaches to treatment. Patients with vagal-dependent atrial fibrillation typically demonstrate a slowing of the sinus rhythm with the onset of atrial fibrillation (50). This arrhythmia occurs most commonly when patients are sedentary or sleeping and is aggravated by medications that slow sinus rhythm, such as beta-adrenergic blockers or digoxin. Atrial fibrillation may occur after an episode of supraventricular reentrant arrhythmia. Patients with a manifest or concealed accessory pathway or reentry within the AV node may initially develop their usual reentrant arrhythmia, which then disorganizes into atrial fibrillation. Atrial fibrillation can be successfully eliminated by preventing the reentrant arrhythmia.

The 24-hour ambulatory recording system is also helpful in assessing a patient's rate control during atrial fibrillation. Patients may demonstrate adequate rate control while they are sedentary but experience a rapid heart rate and symptoms when they are active. A treadmill exercise test can assess the heart-rate response to exercise, but 24-hour ambulatory monitoring is often more useful because it identifies heart-rate response during a patient's more usual activities, which include both physical and emotional stresses. Finally, 24-hour ambulatory monitoring may be helpful in identifying patients in whom a pulmonary vein focus is the cause of atrial fibrillation.

Atrial fibrillation. Narrow complex QRS with irregular RR intervals. Ventricular rate is controlled.

Ventricular Arrhythmias after Myocardial Infarction

The role of complex ventricular ectopy in predicting mortality after myocardial infarction has been confirmed in several multicenter trials (51,52). The definition of complex ventricular ectopy has included NSVT, multiple morphologies, and PVC frequency. PVC frequencies of more than 3 and of more than 10 per hour (51,52) have been found to be predictors of myocardial events and are independent of ejection fraction and heart rate (eTable 61.0.2). These studies were performed before the widespread use of thrombolysis, which has significantly decreased the mortality associated with acute myocardial infarction.

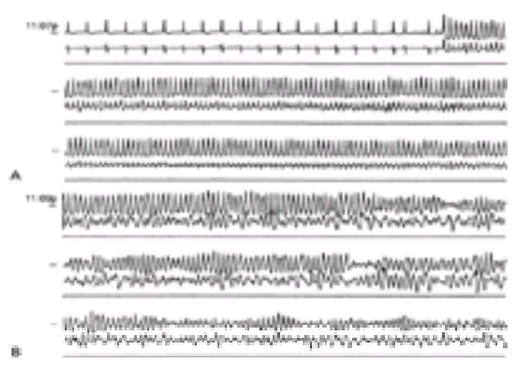
***e*TABLE 61.0.2** FREQUENCY OF PVCS AND RELATIONSHIP TO MORTALITY IN PATIENTS WITH MYOCARDIAL INFARCTION

Study	Patients (n)	Follow-up (mo)	PVCs/h <10	PVCs/h ³10	Total mortality based on PVCs <10/h (%)	Total mortality based on PVCs ³10/h (%)	SCD based on PVCs <10/h (%)	SCD based on PVCs ³10/h (%)	Sensitivity[a] (%)	Specificity[a] (%)	Positive predictive value[a] (%)
Ruberman	1739	24	1285	454	13	27	5	15	54	76	15
Mukharji (53)	533	18	455	78	9	29	4	13	34	87	13
Bigger (54)	819	22	657	162	10	19	6	12	33	81	12
Kostis (51)	1640	25	1429	211	9	20	4	9	25	88	9
Farrell	416	20	332	84	18	40	18[b]	54[b]	54	82	16

PVCs, premature ventricular complexes; SCD, sudden cardiac death.
[a]For sudden cardiac death only.
[b]Includes sudden death and sustained ventricular tachycardia.
Adapted from Shen WK, Hammill SC. Survivors of acute myocardial infarction: who is at risk for sudden death? *Mayo Clin Proc* 1991;66:950–962.

A 1996 study by Statters and associates (55) reported that PVCs continue to be an independent predictor of mortality after myocardial infarction in patients who undergo thrombolytic therapy. They assessed 680 patients who underwent 24-hour ambulatory ECG monitoring 6 to 10 days after myocardial infarction, 379 of whom received thrombolytic therapy. At a sensitivity level of 40%, the positive predictive accuracy of PVCs to predict cardiac mortality and arrhythmic events in patients receiving thrombolytic therapy was 19.4% and 25.8%, respectively, compared to 16% and 16%, respectively, for patients who did not receive thrombolytic therapy. The PVC frequency for dichotomizing patients into high- and low-risk groups was 25 PVCs per hour after thrombolytic therapy and 10 PVCs per hour without thrombolytic therapy. In the study, PVC frequency was more highly predictive of prognosis after myocardial infarction in patients who had undergone thrombolytic therapy than in those who had not, using this higher frequency of dichotomy. Maggioni and colleagues (56) identified similar findings in patients receiving thrombolytic therapy in the GISSI-2 trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico), which included 8,878 patients.

Studies of this nature emphasize the importance of PVC triggers associated with structural heart disease in the development of life-threatening ventricular arrhythmias after myocardial infarction (57). Risk factors that can be assessed by 24-hour ambulatory monitoring, including PVC frequency, abnormal autonomic tone assessed by reduced heart-rate variability, and ischemia monitoring of ST segment changes, further delineate the dynamic relationship between PVC trigger, substrate, and modulating factors that can converge to create a life-threatening arrhythmic event (eFig. 61.0.11). The optimum duration of recording to risk-stratify patients who have experienced infarction is not clear. Most studies use 24 hours of monitoring. However, some studies have reported that more than 1 hour of monitoring was unnecessary (58,59). NSVT with reduced ejection fraction has been used to identify postinfarction patients who are at potential risk for a cardiac event and would benefit from further evaluation by means of electrophysiologic testing (3).



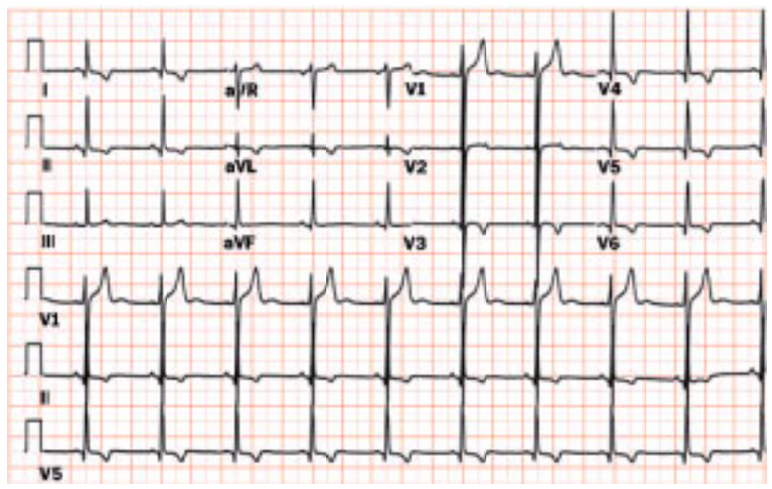
***e*FIGURE 61.0.11** A 24-hour ambulatory electrocardiographic recording in a patient with coronary artery disease. **A:** The patient has a premature atrial complex, a pause, and then a normal complex, followed by a premature ventricular complex, which initiates a run of sustained monomorphic ventricular tachycardia. **B:** The monomorphic ventricular tachycardia degenerates into polymorphic ventricular tachycardia.

The suppression of asymptomatic PVCs after myocardial infarction was postulated to decrease mortality; however, recent clinical trials have not borne this out (60,61,62 and 63). Although antiarrhythmic medication may reduce the frequency with which arrhythmias are triggered, it may also increase the susceptibility of the myocardium to more serious arrhythmia. This does not negate the usefulness of PVCs in identifying high-risk patient groups for selection for other treatments (55).

Dilated and Hypertrophic Cardiomyopathy

Ventricular arrhythmias recorded by 24-hour ambulatory ECG monitoring independently predict subsequent death in patients with dilated cardiomyopathy (64). DeMaria and coworkers (65) evaluated 88 patients who did not have PVCs, 63 who had PVC pairs, and 67 who had NSVT on ambulatory monitoring with associated dilated cardiomyopathy. Survival at 24 months was approximately 95% in patients without PVCs and 80% in patients with PVC pairs and NSVT (p <.05). The use of angiotensin-converting enzyme inhibitors has significantly increased survival in patients with moderately symptomatic congestive heart failure and reduced ventricular function. Nonetheless, approximately 25% to 50% of deaths in patients with congestive heart failure are related to cardiac arrhythmias, despite the use of angiotensin-converting enzyme inhibitors (66,67). As with patients who have ischemic heart disease, ambulatory monitoring in patients with dilated cardiomyopathy identifies patients at increased risk for sudden death.

In 1981, NSVT recorded during 24-hour ambulatory monitoring was reported to be associated with sudden death (68,69), with an 8% annual mortality rate in patients with hypertrophic cardiomyopathy. A subsequent study by Spirito and associates (70) reviewed 151 asymptomatic patients with hypertrophic cardiomyopathy in whom the finding of NSVT on ambulatory monitoring was associated with a relative risk of sudden death of 2.4, compared with patients without NSVT. Although the risk of sudden death was slightly higher in the presence of NSVT, these authors did not recommend that a finding of NSVT should lead to the initiation of antiarrhythmic therapy. Chang and coworkers (71) and Fananapazir and colleagues (72) reported the results of ambulatory ECG monitoring, electrophysiologic testing, and cardiac catheterization in 230 patients with hypertrophic cardiomyopathy, with 115 patients having NSVT on ambulatory monitoring. The only two independent predictors of subsequent death or arrhythmic events were sustained ventricular tachycardia on electrophysiologic study and a history of cardiac arrest or syncope. NSVT was associated with a worse prognosis only in patients with symptoms of impaired consciousness, and, thus, it was not recommended that asymptomatic patients with NSVT undergo further testing. The finding of NSVT on ambulatory monitoring should not automatically lead to antiarrhythmic therapy, but it should alert the physician that further evaluation of the patient is needed (73).



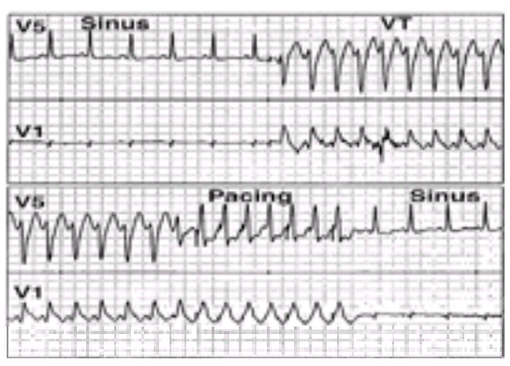
Hypertrophic cardiomyopathy. Inverted precordial T waves associated with hypertrophic cardiomyopathy.

Evaluating Therapy

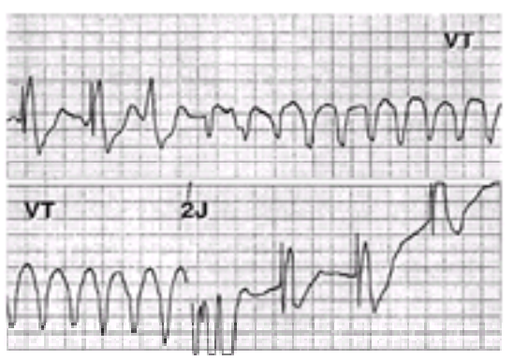
Twenty-four-hour ambulatory ECG monitoring is useful in assessing the response to antiarrhythmic therapy, the performance of a permanent pacemaker, and the causes of shocks from an implantable defibrillator.

Generally, 24-hour ambulatory monitoring is used in conjunction with electrophysiologic and treadmill exercise testing to assess the response of serious ventricular arrhythmias to antiarrhythmic drug therapy. Response to antiarrhythmic therapy can be judged using serial ambulatory monitoring in patients who have a high density of spontaneous ventricular arrhythmias and in whom a ventricular arrhythmia is not induced at electrophysiologic testing (74,75). This approach should be used with caution because of the spontaneous variation that occurs in the frequency of cardiac arrhythmias during 24-hour ambulatory monitoring. Multiple studies have emphasized the importance of long-duration recordings (76,77,78,79,80,81 and 82) to help diminish the effect of spontaneous variability. It is not uncommon for arrhythmias to diminish during sleep and increase with activity. Statistically significant reduction in PVC activity is observed only when a 90% reduction in PVCs occurs over the course of 24 hours. Spontaneous variability in complex ventricular arrhythmias, including runs of ventricular tachycardia, is significantly higher in patients with coronary artery disease (77,78). Ambulatory monitoring may be less effective in predicting clinical outcome with amiodarone (83). Ambulatory monitoring is useful in patients with atrial fibrillation, atrial flutter, and atrial tachycardia to determine whether adequate rate control is achieved with AV nodal–blocking drugs during activity and periods of emotional stress, while avoiding prolonged pauses during periods of inactivity or sleep.

Questions of pacemaker function are often assessed with 24-hour ambulatory monitoring. Failure to sense or pace that is not easily detected during a brief interrogation of the pacemaker may be apparent during 24-hour monitoring. Finally, older implantable cardioverter defibrillators lack the ability to record intracardiac electrograms to identify the mechanism of an arrhythmia that initiated antitachycardia therapy or defibrillation (eFig. 61.0.12 and eFig. 61.0.13). Such patients may present with frequent shocks but without symptoms that suggest cardiac arrhythmia. Shocks may be inappropriate, and sinus tachycardia or atrial fibrillation may be misinterpreted as ventricular tachycardia. In addition, lead problems can result in oversensing and inappropriate shocks from the device. Twenty-four-hour ambulatory monitoring and memory-loop event recording are useful to identify the rhythm that initiates device therapy. Newer implantable cardioverter defibrillators have monitoring as part of their solid-state circuitry that allows recording and displaying of the intracardiac electrogram to confirm that the device is functioning appropriately.



***e*FIGURE 61.0.12** A 24-hour ambulatory electrocardiographic recording in a patient with an implantable cardioverter defibrillator who is experiencing multiple episodes of palpitations and occasional shocks. The ambulatory recording documents sinus rhythm, then the onset of ventricular tachycardia (VT) that is appropriately detected and terminated with antitachycardia pacing.



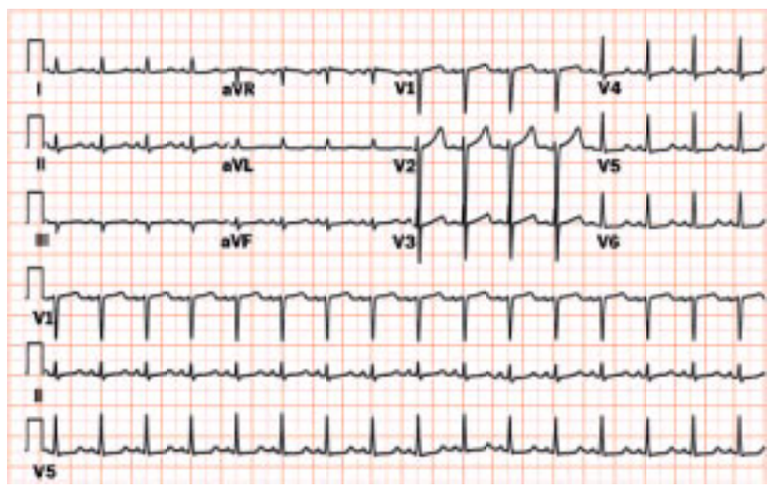
***e*FIGURE 61.0.13** Memory-loop electrocardiographic recording in a patient using an implantable cardioverter defibrillator for management of ventricular tachycardia (VT) who is now experiencing shocks without any additional symptoms. A recording during one of the shocks documents an episode of VT, appropriately converting to sinus rhythm after a 2-J shock.

Heart-Rate Variability, ST Segment Changes, and QT Interval

Ambulatory ECG monitoring has proved helpful for assessing autonomic tone, through measurement of RR intervals and assessment of heart-rate variability (seeChapter 77), and for ascertaining the frequency of silent and symptomatic myocardial ischemia through ST segment analysis (seeChapter 16). QT interval prolongation is a marker of repolarization changes associated with malignant ventricular arrhythmia, termed *torsades de pointes* (84).

A 51-year-old female patient with torsades de pointes.

Twenty-four-hour ambulatory monitoring identifies dynamic changes in the QT interval (85). Formulas used to correct the QT interval for heart rate introduce distortion that may cause abnormal values to appear at slow and rapid heart rates (86). Preliminary evaluation of healthy patients shows a longer corrected QT interval (QTc) during ambulatory monitoring (445 ± 12 ms) than is seen on the resting ECG, with women having a longer QTc than men. The QTc is longest immediately after awakening. Molnar and associates (87), assessing 21 healthy patients, reported that peak prolongation in QTc and maximum variability occurred shortly after patients woke up, reflecting increased autonomic instability during early waking hours that corresponds with the peak period for increased vulnerability to ventricular tachycardia and sudden death. A study by Algra and colleagues (88) evaluated the effects of variability in the duration of the QT interval on the occurrence of sudden death, comparing ambulatory recordings in 104 patients who died suddenly with 201 patients randomly drawn from a cohort of 6,693 consecutive patients undergoing 24-hour monitoring. Both prolonged mean QTc and shortened mean QTc over the course of 24 hours were associated with a more than twofold risk of sudden death, compared with intermediate mean QTc values.



Hypocalcemia. Marked prolongation of the QT segment is appreciated in lead II.

Personal Perspectives

Ambulatory ECG is useful for stratifying a patient's risk for malignant ventricular events after acute myocardial infarction. Use of ambulatory ECG to assess rhythm abnormalities as a cause of intermittent symptoms will decrease and be replaced by use of memory-loop recorders that are either worn externally or implanted. These devices are better than ambulatory monitoring for assessing infrequent but worrisome symptoms that suggest cardiac arrhythmia.

Conclusions

Ambulatory ECG monitoring is an established clinical test that demonstrates increasing usefulness for evaluating patients who have arrhythmia and ischemia and for assessing factors associated with increased risk of sudden death. Technological advances will continue to enhance ambulatory ECG, making reductions in the size of recorders, longer recording periods, and more rapid and accurate analysis possible. The technique increasingly will be used to assess predictors of sudden cardiac death, including prolongation of the QT interval and assessment of autonomic tone with heart-rate variability. These risk factors will be used in combination to better select patients at the highest risk who will benefit from the implantable cardioverter defibrillator. Enhancement of algorithms used to measure QT interval, heart-rate variability, and signal-averaged ECG will make ambulatory recording an integral part of risk-stratification after myocardial infarction. Memory-loop recorders will play an increasingly important role in assessment of patients who have intermittent symptoms that suggest cardiac arrhythmia. The implantable memory-loop recorder will be used commonly in patients who have infrequent episodes of near syncope and syncope.

SIGNAL-AVERAGED ELECTROCARDIOGRAPHY

Historical Perspective

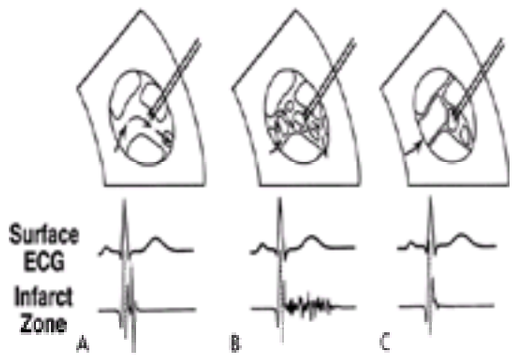
Signal averaging of the surface ECG is a noninvasive computerized method of analyzing standard ECGs that identifies patients who are at risk for ventricular tachycardia (89,90,91,92 and 93). This high-resolution ECG technique averages multiple QRS complexes, minimizing the level of noise that contaminates the periodic ECG signal, thereby exposing signals at the microvolt level that are normally hidden within noise (92). The technique identifies electrical signals at the end of the QRS complex, termed *late potentials*, that represent delayed conduction through diseased myocardium and thus a potential physical substrate for reentrant ventricular tachycardia. Late potentials have been correlated with clinical ventricular tachycardia, ventricular tachycardia inducibility at the time of electrophysiologic testing, and arrhythmic events after myocardial infarction (93).

Signal averaging was first used in ECG to noninvasively record a bundle of His electrogram (94,95). Han and associates (96) then demonstrated in 1969 that electrical activity may persist beyond the QRS complex after myocardial infarction in the canine heart. These potentials were referred to as *delayed ventricular potentials* and were later recorded by Durrer and coauthors in 1971 (97). The relationship of late potentials to the genesis of ventricular arrhythmias was subsequently demonstrated in the early 1970s (98,99,100,101 and 102). Simson (103) reported methods for recording and analyzing late potentials in patients. These technical advances introduced time-domain analysis of the signal-averaged ECG and subsequent correlation of late potentials with ventricular arrhythmias.

Pathophysiology of Late Potentials

In 1973, Boineau and Cox (102) demonstrated that electrograms recorded from ischemic regions of the canine myocardium were fractionated and delayed beyond the QRS complex and into the ST segment. Delayed activation is the substrate for reentrant ventricular tachycardia in patients with acute or remote myocardial infarction (98,99,101,104). Josephson and associates (105) described intracardiac recordings of low-level diastolic electrical activity during ventricular tachycardia, representing reentry within the border zone of the infarction. The low-level late potentials recorded directly from the heart can also be recorded from the body surface using a method of high amplification, band-pass filtering, and signal averaging (106).

Late potentials are usually found in border zones surrounding the scar of a previous myocardial infarction. Fibrosis forms an insulating boundary between muscle bundles and Purkinje tissue that slows and fragments the wave of electrical depolarization as it sweeps through the ventricular myocardium, constituting the substrate for reentry. Endocardial recordings of electrical depolarization from a border zone demonstrate conduction delay and fragmentation (eFig. 61.0.14). The border zone is both the source of late potentials and the substrate for reentrant ventricular tachycardia. Signal-averaged ECG has subsequently been demonstrated to record delayed electrical activation through the myocardium in several pathologic conditions in addition to myocardial ischemia. Abnormal conduction and delayed potentials are present in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, myocarditis, and infiltrative heart disease. The technique has been extended to the atrium, where measures of atrial conduction delay correlate with the development of atrial fibrillation.



***e*FIGURE 61.0.14** Late potentials occurring in the border zone of experimental myocardial infarction in the canine model. **A:** No conduction delay with a normal QRS complex recorded by both the surface electrocardiogram (ECG) and the electrode from the infarct zone. **B:** Conduction delay through myocardial cells that are surrounded by areas of infarction. The surface ECG continues to be normal, because the mass of myocardium affected by the conduction delay is too small to generate a complex that can be recorded by the surface ECG. In contrast, the electrode recording from the infarct zone demonstrates delayed conduction, or late potentials, as the impulse traverses through the abnormal myocardium. It is this area of delayed conduction that is recorded by the signal-averaged ECG, which amplifies the low-level signal and reduces the associated noise. **C:** Conduction block and inability of the electrical impulse to penetrate or conduct through the infarct zone. (Adapted from El-Sherif N, Scherlag BJ, Lazarr R, et al. Reentrant ventricular arrhythmias in the late myocardial infarction period. I: Conduction characteristics in the infarction zone. *Circulation* 1977;55:686.)

Technical Aspects of Signal-Averaged Electrocardiography

Commercially available equipment for performing signal averaging includes ECG leads, an amplifier, an analog-digital converter, and a personal computer with software that can be used to average the QRS waveforms and store data. Signal-averaged ECG originally required dedicated equipment but now may be included as part of a standard ECG machine. The patient interface and front-end electronics are of primary importance for data acquisition and analysis.

The patient's skin must be cleansed and mildly abraded before attachment of the electrode to help reduce noise generated by artifact from the electrode-skin interface. A significant clinical problem with recording low-level bioelectrical signals from the heart is extraneous noise; reduction of such noise is necessary, because the amplitude of delayed ventricular activity is usually smaller than the amplitude of electrical noise produced by the patient or environmental sources. The noise in ECG recording generally ranges from 8 to 10 mV and primarily has three origins: (a) skeletal muscle, principally from respiratory muscles; (b) 50 or 60 Hz from electrical equipment; and (c) electrical feedback from amplifiers and electrodes (92). The purpose of signal averaging is to improve the signal-to-noise ratio to allow the detection of low-amplitude bioelectrical signals (107).

Bipolar XYZ leads are most commonly used to obtain a signal-averaged ECG, with each lead amplified from 1 × 104 to 2.5 × 104 and converted in a digital format at a sampling frequency of 1,000 to 2,000 times per second. Effective signal averaging requires that the signal of interest remain constant and unchanging so that it can be separated from the more random signal generated by noise. Only identical QRS complexes are averaged, because complexes with noise or aberrant conduction mask low-level late potentials. Typically, systems analyze a set number of QRS cycles or until the noise has been reduced to a satisfactory level. The resulting waveform appears smooth and continuous, and the noise, because it is random, is reduced by the averaging technique. In general, noise is proportional to the square root of the number of averaged cycles and is reduced to less than 1 mV by proper signal averaging techniques.

Signal averaging is the first of several electronic signal processing steps used to detect late potentials (108). High-pass filtering is used to remove the ST segment and the T wave; both are slowly changing, low-frequency signals relative to the late potential and QRS complex, and they may obscure the small low-level late potentials. The high-pass filters most commonly used are 25, 40, and 80 Hz. The 40-Hz filter is used most frequently.

Time-Domain Methods

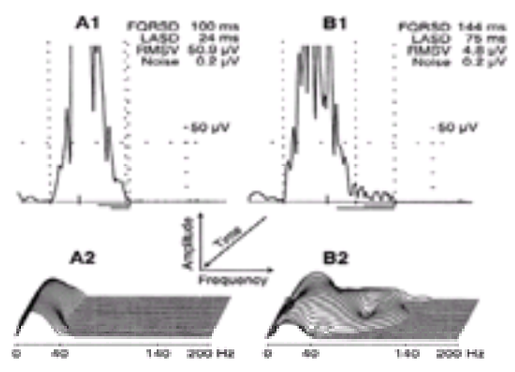
Commercially available signal-averaged ECG systems use time-domain analysis to detect late potentials either with uncorrected bipolar XYZ lead signals processed by a bidirectional Butterworth filter (109,110,111,112,113,114 and 115), with bipolar XYZ leads and a bispectral filter, or with Frank XYZ leads and a spectral filter (116,117). The bidirectional Butterworth and spectral filters both have merits and drawbacks, and neither method of filtering is superior (118). Used bidirectionally, the Butterworth filter is excellent for detecting the end of the QRS complex, but it is not suitable for obtaining accurate measurements of the root mean square amplitude or energy of the major waves of the QRS (118). The spectral filter can be designed so that is has a well-defined frequency response and can attenuate the ST segment, but it will prolong the duration of the QRS complex and P wave (119). Whichever signal-averaged ECG system is used, the criteria used to identify late potentials must be developed specifically for that recording system (109).

Frequency-Domain Methods

Time-domain analysis of the signal-averaged ECG has several limitations: It may be difficult to define the end of the QRS complex; high-pass filters may attenuate or abolish late potentials; and late potentials may be difficult to distinguish from random noise. Frequency-domain analysis of the signal-averaged ECG has the advantage that it does not require complex high-pass filtering. Fast Fourier transform analysis is an analytical method used for signal processing in the frequency domain that avoids some of the limitations of high-gain amplification and signal filtering that come with time-domain analysis (120).

The QRS complex is a periodic signal that may be represented by the mathematical summation of a series of sine waves of different frequencies and amplitudes (120). The lowest-frequency sinusoidal component of the QRS complex is called the *fundamental*, and it has a repetition rate equal to that of the periodic signal under evaluation. All higher sinusoidal components of the signal in question have frequencies that are multiples of this fundamental frequency. Fast Fourier transform analysis is a computer-based mathematical algorithm that allows determination of the amplitudes of the various harmonic components that comprise a complex periodic waveform, such as the QRS complex. For each time-domain signal, there is one and only one frequency-domain presentation (120). Frequency-domain analysis evaluates the terminal QRS complex and has the advantage that it does not require decisions about the optimal choice of high- and low-pass filters, and thus it reduces the risk that the late potential will inadvertently be removed from the analyzed signal (121). The likelihood of distorting the underlying signal by amplification and filtration is also reduced using fast Fourier transform analysis.

Other frequency analysis methods that can be used to evaluate the terminal portion of the QRS complex include time-window techniques, such as spectral temporal mapping (122,123) and spectral turbulence analysis (124), and autoregressive methods, such as maximal entropy (125) and adaptive frequency determination (126) (*e*Fig. 61.0.15). Frequency-domain analysis using a window function is not suitable if specific frequency peaks are required, but it is suitable if identification of frequency bands is optimal (91). If spectral peaks, in addition to timing information, are required for signal analysis, then the moving time-window and autoagressive methods must be used. These techniques have been reported (127,128) to overcome the need to use different criteria in patients with bundle branch block and conduction defects and are less dependent on noise levels occurring during signal-averaged ECG recording. Satisfactory end points of spectral analysis have not been standardized.



***e*FIGURE 61.0.15** Time-domain and spectral temporal mapping recordings from a patient without (A1 and A2) and a patient with (B1 and B2) ventricular tachycardia. In the patient without ventricular tachycardia, the time domain (A1) is normal, and the corresponding spectral temporal map (A2) is normal, with no frequency content

between 40 and 140 Hz. In the patient with ventricular tachycardia, clear late potentials are recorded by time-domain analysis (B1), and the corresponding spectral temporal map (B2) demonstrates high-frequency components between 40 and 140 Hz. FQRSD, QRS duration after filtering; LASD, low-amplitude signal duration; RMSV, root mean square voltage. (Adapted from Kulakowski P, Malik M, Poloniecki J, et al. Frequency versus time domain analysis of signal averaged electrocardiograms. II: Identification of patients with ventricular tachycardia after myocardial infarction. *J Am Coll Cardiol* 1992;20:135–143.)

Comparison of Time- and Frequency-Domain Methods

The value of time-domain analysis for the identification of late potentials and selection of patients at risk for ventricular arrhythmias has been confirmed in numerous studies. Similarly, several studies have shown that differences in the frequency content of the QRST segment help to identify patients with ventricular tachycardia (120,127,129). Cain and associates (120) reported that 15% of patients without and 8% of patients with sustained ventricular tachycardia showed an increase in the amplitude of the high-frequency components in the terminal QRS complex. In a subsequent study, the same authors (129) demonstrated that the terminal 40 ms of the QRS complex and the ST segment contained ten- to 100-fold greater amplitude of components in the 20- to 50-Hz range in patients with ventricular tachycardia compared to those without tachycardia. Similar findings were reported by Haberl and coauthors (127). However, there has been controversy as to the value and reproducibility of frequency-domain analysis (121,130,131,132 and 133). Worley and associates (121) reported that the results of frequency analysis depended on the length of the analyzed segment and that only magnitude area ratios in the intervals starting 60 ms after the onset of the QRS complex differentiated patients with and without ventricular tachycardia. Kelen and associates (134) reported that a 3-ms change in the length of the analyzed segment resulted in marked changes in area ratio and that frequency-domain analysis could not distinguish patients with ventricular tachycardia or late potentials from patients without ventricular tachycardia or late potentials.

Spectral temporal mapping has been reported to be a possible solution to some of the technical difficulties in attaining reproducibility with frequency-domain methods (135,136). Haberl and associates (123) reported that spectral temporal analysis of the terminal QRS complex, including the ST segment, correlated well with the diagnosis of late potentials using criteria based on time-domain analysis, and that this technique performed better than time-domain analysis in identifying patients with ventricular tachycardia. These findings were challenged by Odemuyiwa and coworkers (133), who reported that time-domain analysis was superior to spectral temporal mapping in predicting arrhythmic events in postinfarction patients. Malik and associates (131) compared the reproducibility of frequency-domain and time-domain analysis of signal-averaged ECGs in 40 subjects and found that reproducibility was significantly higher for the time-domain method than for spectral temporal mapping. Kulakowski and coauthors (132) compared the results of time-domain, frequency-domain, and spectral temporal mapping analysis of the signal-averaged ECG in 30 postinfarction patients with and 30 postinfarction patients without spontaneous sustained ventricular tachycardia. They concluded that, compared with time-domain analysis, frequency-domain analysis and spectral temporal mapping did not improve the identification of postinfarction patients with ventricular tachycardia. Similar results were reported by Mittleman and colleagues (137) in a study including 50 patients who had histories of coronary disease and ventricular tachycardia and 25 normal subjects. Time-domain analysis was superior to spectral temporal mapping, including in patients with bundle branch block. Spectral temporal mapping analysis has a significant problem with false-positive results and less favorable reproducibility.

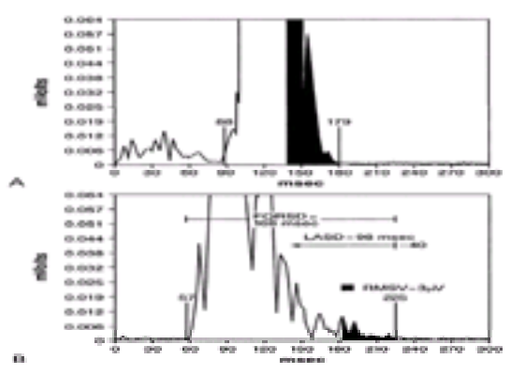
At this time, it must be concluded that spectral temporal mapping and frequency-domain analysis of the ECG are less useful than time-domain analysis for predicting arrhythmic events in postinfarction patients. It is still not clear if frequency-domain analysis of patients with bundle branch block may have a role in risk-stratification. The remainder of this chapter will deal with time-domain analysis of the signal-averaged ECG.

Recordings Using Ambulatory Electrocardiography

Signal-averaged ECG has been applied to 24-hour ambulatory ECG monitoring in an attempt to gain additional diagnostic information from the ambulatory ECG (138). Ambulatory signal-averaged ECG monitoring has several technical differences from signal-averaged ECG obtained at the patient's bedside. The signal-averaged ECG uses XYZ recording leads, and the ambulatory method uses V_1, V_5, and aVF. The diagnostic criteria for signal averaging has been developed with XYZ data and, therefore, may not be directly applicable to data obtained by different lead sets. Other significant differences include the recording bandwidth, the sampling rate, and the filter used (138). Ambulatory signal-averaged ECG requires more cardiac beats—more than 1,000—to be averaged to allow adequate noise reduction. Despite technical differences, clinical studies have described close correlation of signal-averaged ECG parameters in standard and ambulatory signal-averaged ECG (139). The 24-hour monitoring period has the potential advantage of evaluating individuals under various conditions, including physical and emotional stress that may not be present when the standard signal-averaged ECG is obtained. However, ambulatory signal-averaged ECG needs to be restricted to quiet activities that do not induce skeletal-muscle myopotential artifact or noise.

Late Potential Criteria

After the signals are averaged and filtered, three methods are used to identify the presence or absence of late potentials at the terminal QRS (eFig. 61.0.16). The first method is to assess the total QRS duration after filtering (FQRSD). Because late potentials are continuous with the end of the QRS, they increase the overall QRS duration. The second method is to calculate the root mean square voltage (RMSV) of the last 40 ms of the vector magnitude QRS complex. Late potentials are low-amplitude signals, and the measurement is much smaller when late potentials are present. The third method is to calculate how much of the terminal vector magnitude complex lies below the 40-µV level, the low-amplitude signal duration (LASD). Once the computer software program determines the baseline noise level, it moves backward in time to identify the offset of the QRS complex and then the point at which the QRS complex increases to the 40-µV level. That point in time is marked, and a calculation is made to determine how much of the terminal vector magnitude QRS complex in ms lies under the 40-µV level. Averaging to lower noise levels results in longer QRS duration and affects reproducibility (140).



***e*FIGURE 61.0.16 A:** Normal signal-averaged electrocardiogram (ECG) showing a QRS duration after filtering (FQRSD) of 91 ms, a root mean square voltage (RMSV) of 96 µV, and a low-amplitude signal duration (LASD) of 18 ms. **B:** A signal-averaged ECG obtained in a patient with a prior anterior myocardial infarction and ventricular tachycardia. The QRS demonstrates a prolonged FQRSD of 168 ms, a reduced RMSV of 3 µV, and a prolonged LASD of 98 ms. This signal-averaged ECG meets the criteria for the presence of late potentials, whereas **(A)** does not. See text for details.

Commercially available signal-averaging systems use different lead configurations, filters, and processing algorithms. Therefore, criteria to define the absence or presence of late potentials and establish a normal range (eTable 61.0.3) need to be developed for each system (109). The important, pioneering work of Simson (103) set out criteria developed with a bidirectional 25-Hz Butterworth filter and uncorrected bipolar XYZ leads. Since this initial work, further studies have indicated that the 40-Hz filter is preferable to the 25-Hz filter, because it provides improved sensitivity and reproducibility (112,113,114 and 115). Gomes and associates (141), using a 40-Hz bidirectional Butterworth filter with uncorrected bipolar XYZ leads, determined optimal criteria for identifying late potentials in 25 normal subjects: FQRSD >114 ms, LASD >38 ms, and RMSV <20 µV. Denes and colleagues (112), using a system with a 40-Hz Butterworth filter and uncorrected bipolar XYZ leads in 42 normal subjects, determined that late potentials were identified by FQRSD >120 ms, LASD >38 ms, and RMSV <20 µV.

***e*TABLE 61.0.3** NORMAL LIMITS FOR SIGNAL-AVERAGED ELECTROCARDIOGRAPHY PARAMETERS

	FQRSD (ms)	LASD (ms)	RMSV (µV)
Butterworth filter, bipolar XYZ leads, 40- to 250-Hz filtering			
Gomes (141)[a] (n = 25)	114	38	20
Danford (142)[a](n = 32)	119	47	NA
Raineri (143)[a](n = 63)	115	48	2

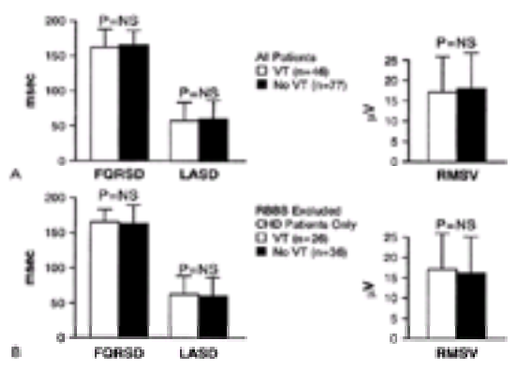
Fourier transform filter, frank XYZ leads			
Timmermans (116)[b]			
Men (n = 100)	122	41	20
Women (n = 85)	115	41	20

FQRSD, filtered QRS duration; LASD, low-amplitude signal duration (<40 µV); NA, not applicable; RMSV, root mean square voltage terminal 40 ms.
[a]Mean ± 2 standard deviations for FQRSD; low 5% confidence limits for RMSV.
[b]Ninetieth percentile for FQRSD, LASD; lower tenth percentile for RMSV.

A system using a 40-Hz high-pass filter, Frank XYZ leads, and fast Fourier transform filter was evaluated by Timmermans and coworkers (116) in a study of 185 patients without heart disease. The study included 85 women and 100 men and took into account information on gender and body-size differences in the definition of late potentials. They reported the following gender-specific normal values: in men, FQRSD <122 ms; in women, FQRSD <115 ms; and in both genders, LASD <41 ms and RMSV >20 µV. Other authors (142,143) have reported similar gender differences for FQRSD, with women having shorter FQRSD. Separate FQRSD criteria should be used for men and women. Signal-averaged ECG criteria are different in children and adolescents because of the shorter QRS duration (144).

Signal-averaged ECG criteria were reported in 182 patients with known coronary artery disease and previous myocardial infarction who underwent programmed ventricular stimulation (117). The signal-averaged ECG variables that best characterized control subjects and separated patients with and without inducible ventricular tachycardia were an FQRSD <120 ms, an LASD <38 ms, and an RMSV >20 µV. El-Sherif and coworkers (145) evaluated 1,158 patients in the Cardiac Arrhythmia Suppression Trial and reported that an FQRSD >120 ms was the most predictive criterion for arrhythmic events.

Evaluation of the signal-averaged ECG using time-domain variables has excluded patients with conduction defects. A conduction defect, including bundle branch block or intraventricular conduction delay, with late depolarization of a large muscle mass may mask diagnostic late potentials. This difficulty was reported by Buckingham and associates (146) when they used altered criteria (longer FQRSD and LASD and lower RMSV) to maintain sensitivity and specificity in patients with conduction defects. Although they attained good results with their model, other investigators have found the signal-averaged ECG to be of limited value in patients who show conduction defects (100,109). Ommen and coauthors (147) reported 123 patients with a standard QRS >118 ms who underwent signal-averaged ECG and subsequent electrophysiologic testing (*e*Fig. 61.0.17). No signal-averaged ECG variables differed significantly between patients with and patients without inducible ventricular tachycardia. The study concluded that signal-averaged ECG time-domain variables cannot be used to predict inducibility of ventricular tachycardia during electrophysiologic testing in patients who display conduction defects. Frequency-domain analysis may improve the predictive accuracy in patients who show bundle branch block (148), although the findings have been difficult to reproduce.

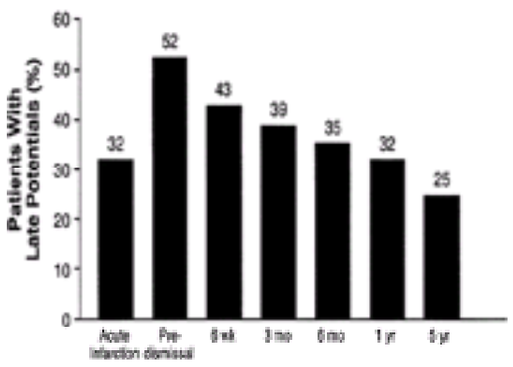


***e*FIGURE 61.0.17** Signal-averaged electrocardiography (ECG) in patients with conduction defects. **A:** One hundred twenty-three patients were evaluated, and 46 patients had ventricular tachycardia (VT) induced at electrophysiologic testing. Using multivariate analysis, no signal-averaged ECG criteria separated patients with ventricular tachycardia from patients without ventricular tachycardia. **B:** No signal-averaged ECG criteria separated the 26 patients with ventricular tachycardia from the 36 patients without ventricular tachycardia, despite the exclusion of right bundle branch block and the inclusion of only those patients who had known coronary heart disease. FQRSD, QRS duration after filtering; LASD, low-amplitude signal duration; NS, not significant; RMSV, root mean square voltage. (Adapted from Ommen SR, Hammill SC, Bailey KR. Failure of signal-averaged electrocardiography with use of time-domain variables to predict inducible ventricular tachycardia in patients with conduction defects. *Mayo Clin Proc* 1995;70:132–136.)

Signal-Averaged Electrocardiography in Specific Clinical Syndromes

Late Potentials after Myocardial Infarction

Late potentials increase during the initial days after myocardial infarction and slowly decrease over subsequent months (*e*Fig. 61.0.18) (148). McGuire and associates (149) studied the natural history of late potentials after myocardial infarction, obtaining serial signal-averaged ECGs early after admission and at the time of hospital dismissal. Early after the onset of myocardial infarction, approximately 30% of patients have late potentials that increase to 50% at the final predischarge study (150). A subsequent study by Kuchar and associates (151) followed 234 patients after myocardial infarction and reported that 18% of patients who had late potentials at hospital discharge no longer had an abnormal signal-averaged ECG at 6 weeks, 39% had lost late potentials by 12 months, and 52% of 5-year survivors demonstrated a resolution of late potentials. Importantly, fewer than 5% of patients without late potentials at the initial recording subsequently developed late potentials in the absence of another myocardial infarction.



***e*FIGURE 61.0.18** Natural history of late potentials after myocardial infarction. Fifty-two percent of patients have late potentials at the time of dismissal after myocardial infarction. This incidence slowly decreases during follow-up, with only 32% having late potentials at 1 year and 25% at 5 years. Fewer than 5% of patients who do not have late potentials before hospital dismissal will develop late potentials during follow-up in the absence of an intervening myocardial infarction.

Late potentials are an independent risk factor for developing ventricular arrhythmias after myocardial infarction (*e*Table 61.0.4) (149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166 and 167) and have been detected in 39% to 93% of patients who subsequently develop a ventricular arrhythmia or experience sudden cardiac death (101). Among patients with late potentials, between 8% and 48% develop sustained ventricular tachycardia or sudden death, and fewer than 5% of patients without late potentials will have arrhythmic complications. The negative predictive accuracy ranges from 88% to 99%, and the positive predictive accuracy ranges from 8% to 29% (101). The majority of studies show a positive predictive accuracy of approximately 20% for the ability of signal-averaged ECG to identify risk for malignant ventricular arrhythmias in patients recovering from myocardial infarction. It is this low-positive predictive accuracy that makes the test less useful as a single diagnostic study for identifying patients at risk of ventricular arrhythmia. Typically, the signal-averaged ECG results are combined with ejection fraction, ventricular arrhythmia on ambulatory monitoring, or heart-rate variability to improve predictive accuracy (*e*Table 61.0.5).

The use of thrombolytic therapy has had a significant effect on the presence and prognostic implications of late potentials identified by the signal-averaged ECG (168). The presence of an open artery after reperfusion therapy reduces the incidence of late potentials (168,169,170 and 171) (*e*Fig. 61.0.19). Late potentials are present in

25% to 65% of patients with a closed infarct-related artery, whereas an open infarct-related artery reduces the incidence of late potentials to 6% to 34%. Thrombolytic therapy is associated with an incidence of late potentials of 5% to 17%. The use of thrombolytic therapy has significantly reduced the incidence of death after myocardial infarction, and this reduced event rate has negatively affected the predictive value of the signal-averaged ECG.

***e*TABLE 61.0.4** VALUE OF THE SIGNAL-AVERAGED ELECTROCARDIOGRAM FOR PREDICTING SUDDEN DEATH OR VENTRICULAR TACHYCARDIA AFTER MYOCARDIAL INFARCTION

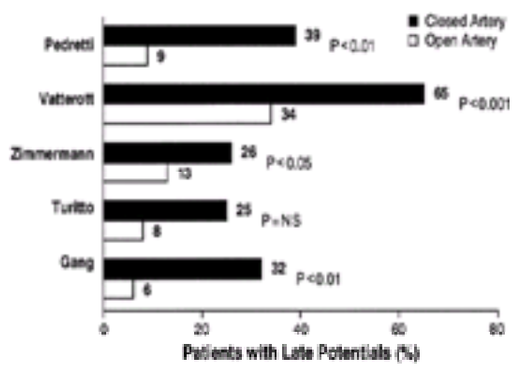
			Predictive value (%)	
Study	**Number of points**	**% Treated with thrombolysis**	**Positive**	**Negative**
Breithardt (164)	160	—	17	96
Kuchar (151)	157	—	17	99
Kuchar (159)	200	—	17	99
Denniss (158)	403	—	19	96
Gomes (93)	102	—	29	96
Cripps (155)	176	—	22	99
El-Sherif (163)	156	—	23	97
Verzoni (157)	220	—	8	99
Steinberg (156)	182	—	15	95
Zimmerman (166)	223	26	16	98
Farrell (161)	416	48	17	81
Pedretti (160)	174	39	18	98
Pedretti (162)	303	54	16	97
McClements (165)	301	68	11	98

Adapted from Cain ME, Anderson JL, Arnsdorf MF, Mason JW, Scheinman MM, Waldo AL. Signal-averaged electrocardiography. *J Am Coll Cardiol* 1996;27:238–249.

***e*TABLE 61.0.5** ADDITIVE VALUE OF PROGNOSTIC TESTS TO IDENTIFY PATIENTS AT RISK FOR SUDDEN DEATH OR VENTRICULAR TACHYCARDIA AFTER MYOCARDIAL INFARCTION

	% Adverse outcome	
	For normal test result	**For abnormal test result**
SAECG + EF[a]	0–1	31–38
SAECG + Holter	0–1	27–35
EF + Holter	7	29
SAECG + EF[a] + Holter	0	50
SAECG + EP	2	27
SAECG + HRV	7	33
SAECG + HRV + Holter	4	43

EF, ejection fraction; EP, electrophysiologic testing; HRV, heart-rate variability; SAECG, signal-averaged electrocardiogram.
[a]EF £40%.
Adapted from Cain ME, Anderson JL, Arnsdorf MF, et al. Signal-averaged electrocardiography. *J Am Coll Cardiol* 1996;27:238–249, using data from Kuchar DL, Thorburn CW, Sammel NL, et al. Late potentials detected after myocardial infarction: Natural history and prognostic significance. *Circulation* 1986;74:1280–1289; El-Sherif N, Ursell SN, Bekheti S, et al. Prognostic significance of the signal-averaged ECG depends on the time of recording in the postinfarction period. *Am Heart J* 1989;118:256–264; Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1991;18:687–697; Pedretti R, Etro MD, Laporta A, et al. Prediction of late arrhythmic events after acute myocardial infarction from combined use of noninvasive prognostic variables and inducibility of sustained monomorphic ventricular tachycardia. *Am J Cardiol* 1993;71:1131–1141; and Gomes JA, Winters SL, Stewart D, et al. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction: Based on signal-averaged electrocardiogram, radionuclide ejection fraction, and Holter monitoring. *J Am Coll Cardiol* 1987;10:349–357.



***e*FIGURE 61.0.19** The effect of reperfusion on the percentage of patients with late potentials recorded by signal-averaged electrocardiography. The presence of a closed infarct-related artery significantly increases the number of patients who show late potentials compared with patients whose infarct artery is opened by thrombolytic therapy or direct angioplasty. NS, not significant. (Adapted from Vatterott PJ, Hammill SC, Bailey KR, et al. Late potentials on signal-averaged electrocardiograms and patency of the infarct-related artery in survivors of acute myocardial infarction. *J Am Coll Cardiol* 1991;17:330–337; Pedretti R, Laporta A, Etro MD, et al. Influence of thrombolysis on signal-averaged electrocardiogram and late arrhythmic events after acute myocardial infarction. *Am J Cardiol* 1992;69:866–872; Zimmermann M, Adamee R, Ciaroni S. Reduction in the frequency of ventricular late potentials after acute myocardial infarction by early thrombolytic therapy. *Am J Cardiol* 1991;67:697–703; Gang ES, Lew AS, Hong M, et al. Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1989;321:712–716; and Turitto G, Risa AL, Zanchi E, et al. The signal-averaged electrocardiogram and ventricular arrhythmias after thrombolysis for acute myocardial infarction. *J Am Coll Cardiol* 1990;15:1270–1276.)

Malik and coworkers (171) reported 331 survivors of acute myocardial infarction, 130 of whom were receiving thrombolytic therapy, who were followed for 10 months. An arrhythmic event occurred in 8.5% of patients without and 6.2% of patients with thrombolytic therapy. The usefulness of late potentials to predict subsequent arrhythmic events was substantially worse in the patients who were receiving thrombolytic therapy than in those who were not receiving thrombolytic therapy, with a threefold lower positive predictive accuracy. McClements and Adgey (165) evaluated 301 survivors of myocardial infarction, of whom 68% received thrombolytic agents. The signal-averaged ECG and ejection fraction were independent predictors of subsequent events. Steinberg and associates (172) reported the results of signal-averaged ECG in 159 patients who were receiving thrombolytic therapy 6 to 24 hours after myocardial infarction and 151 patients who did not receive thrombolytic therapy. Thrombolytic therapy reduced the frequency of an abnormal FQRSD >120 ms from 19% to 12%. This change was confined to the subgroup of patients who showed ST elevation on their presenting ECG.

Similar results were reported by Hohnloser and colleagues (173) in 173 patients with acute myocardial infarction, of whom 51% were treated with thrombolytic therapy. An open infarct-related artery was documented in 136 patients. When multivariate analysis was performed, an occluded infarct-related artery and the presence of regional wall motion abnormalities were the strongest independent predictors for the development of late potentials, which occurred in 24% of patients. During a mean follow-up of 12 months, the mortality rate was 4.1%; seven patients died suddenly or experienced ventricular fibrillation, and two patients had sustained monomorphic ventricular tachycardia. Multivariate analysis revealed that only an occluded infarct-related artery was an independent predictor of arrhythmic complications, and that late potentials were less helpful in identifying patients at risk for sudden death. Signal-averaged ECG should be combined with other prognostic tests to improve its predictive accuracy in identifying patients at risk for an arrhythmic event after thrombolytic therapy.

Sustained Ventricular Tachycardia with Ischemic Heart Disease

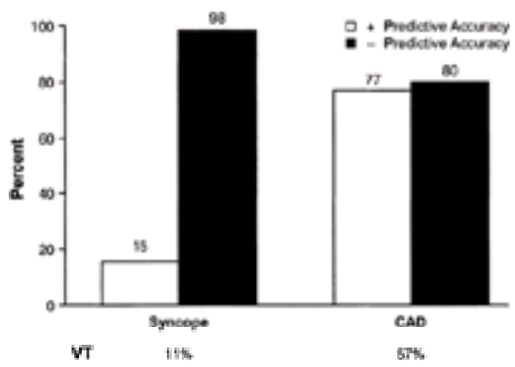
The majority of patients who have documented ventricular tachycardia and ischemic heart disease also have late potentials; the incidence ranges from 52% to 90% (91) (*e*Table 61.0.2). Late potentials are identified in 21% to 65% of patients who present with ventricular fibrillation (174,175). The test is less useful in these two populations, because they have already presented with cardiac arrhythmia. The signal-averaged ECG is most useful for predicting which patients are at risk for subsequent arrhythmia, rather than in patients who have already presented with clinical arrhythmia, because treatment is dependent on the arrhythmia and not on the

presence or absence of late potentials.

The value of detecting late potentials by signal-averaged ECG to predict ventricular tachycardia during electrophysiologic testing in patients with ischemic heart disease is well accepted (113,114 and 115). A study of 182 patients with coronary artery disease who were undergoing electrophysiologic testing for multiple reasons, including a history of syncope, NSVT, and sustained ventricular tachycardia, showed a sensitivity of 87%, a specificity of 65%, and a positive predictive value of 77% for identifying patients at risk for inducible ventricular tachycardia (117).

Predictive Power of Late Potentials Depends on the Prevalence of Coronary Artery Disease

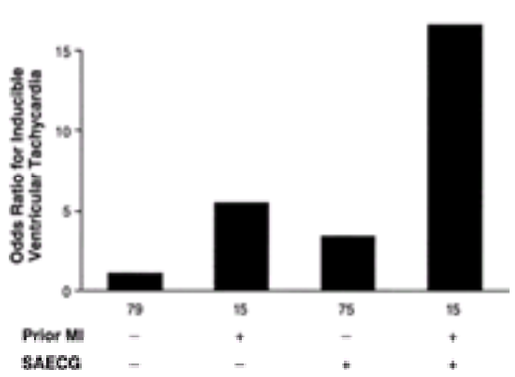
The negative predictive accuracy of signal-averaged ECG is noted to be 95% to 99% in patients with syncope and in patients after myocardial infarction. These patients have a low incidence of ventricular events and, therefore, a high-negative predictive accuracy would be expected. The signal-averaged ECG has a low-positive predictive accuracy of 15% to 20% for identifying patients at risk for subsequent malignant ventricular arrhythmia. In patients with known coronary artery disease and suspected ventricular tachycardia who subsequently undergo electrophysiologic testing, the negative predictive accuracy decreases to 80%, and the positive predictive accuracy improves to 77% (*e*Fig. 61.0.20) because of the increased disease prevalence. A lower-negative predictive accuracy is expected in testing these patients. When the suspicion for ventricular arrhythmia is high, the signal-averaged ECG should not be used to exclude further testing.



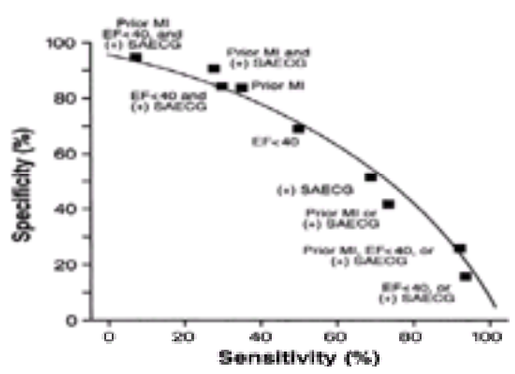
***e*FIGURE 61.0.20** The predictive accuracy of the signal-averaged electrocardiogram (SAECG) for identifying patients who will subsequently have ventricular tachycardia (VT) induced at electrophysiologic testing depends on the frequency of VT in the population studied. Patients with syncope have a low incidence of inducible VT (11%), a low-positive predictive accuracy (15%) and a high-negative predictive accuracy (98%). In contrast, patients with coronary artery disease (CAD) who are suspected of having VT have a higher inducibility (57%) and a higher-positive predictive accuracy (77%), but a lower-negative predictive accuracy (80%). Patients in whom there is a strong suspicion for VT should not be eliminated from electrophysiologic testing based solely on the results of the SAECG. (Adapted from Vatterott PJ, Bailey KR, Hammill SC. Improving the predictive ability of the signal-averaged electrocardiographic with a linear logistic model incorporating clinical variables. *Circulation* 1990;81:797–804; and Hammill SC, Tchou PJ, Kienzle MG, et al. Establishment of signal-averaged electrocardiographic criteria with Frank XYZ leads and spectral filter used alone and in combination with ejection fraction to predict inducible ventricular tachycardia in coronary artery disease. *Am J Cardiol* 1992;70:316–320.)

Syncope

Patients with syncope may undergo electrophysiologic testing to assess whether they have sustained ventricular tachycardia that is inducible and is a presumed cause of their clinical event. A negative signal-averaged ECG may preclude the need for electrophysiologic testing in such patients (176). Lacroix and associates (177) evaluated 100 patients who presented with syncope and underwent electrophysiologic testing. They reported that the signal-averaged ECG had a positive predictive value of 39% for predicting sustained monomorphic ventricular tachycardia. Kuchar and associates (178) reported on 150 consecutive patients who were evaluated for syncope by signal-averaged ECG and electrophysiologic testing, with late potentials identified in 29 patients, 16 of whom subsequently had inducible ventricular tachycardia. In their study, the signal-averaged ECG had a positive predictive value of 55% and a negative predictive value of 94%. Steinberg and associates (179) reported a multicenter study of 189 patients who were evaluated for unexplained syncope. Ventricular tachycardia was induced in 15% of the patients, and the signal-averaged ECG was the most sensitive test but had poor specificity. By multivariate analysis, the signal-averaged ECG and a history of a previous myocardial infarction were independently predictive of ventricular tachycardia, with the risk increasing 17-fold in patients with both abnormalities (*e*Fig. 61.0.21). In patients with no history of previous myocardial infarction, no additional testing was useful in identifying those at risk for inducible ventricular tachycardia. They concluded that the signal-averaged ECG was the most sensitive noninvasive test available for predicting sustained monomorphic ventricular tachycardia in patients with syncope, but that it yielded false-positive results in many patients, with a specificity of 55%. These authors stress the importance of combining different tests to improve predictive accuracies (*e*Fig. 61.0.22).



***e*FIGURE 61.0.21** The signal-averaged electrocardiogram (SAECG) is extremely helpful when it is combined with a history of myocardial infarction (MI) in predicting inducible ventricular tachycardia at electrophysiologic testing in patients with cardiogenic syncope. Patients with both a history of myocardial infarction and an abnormal SAECG have an odds ratio of 17 for inducible ventricular tachycardia. (Adapted from Steinberg JS, Prystowsky E, Freedman RA, et al. Use of the signal-averaged electrocardiogram for predicting inducible ventricular tachycardia in patients with unexplained syncope: relation to clinical variables in a multivariate analysis. *J Am Coll Cardiol* 1994;23:99–106.)



***e*FIGURE 61.0.22** Patients at risk of atrial fibrillation (AF) have a prolonged P-wave duration by signal averaging. The P-wave duration in patients without AF measured 116 ms, in contrast to the P-wave duration in patients with AF, which measured 162 ms. (Adapted from Guidera SA, Steinberg JS. The signal-averaged P-wave duration: a rapid and noninvasive marker of risk of atrial fibrillation. *J Am Coll Cardiol* 1993;21:1645–1651.)

Dilated, Hypertrophic, and Arrhythmogenic Right Ventricular Cardiomyopathy

Information in the literature is in conflict considering the usefulness of signal-averaged ECG in patients with dilated cardiomyopathy (180,181 and 182). Mancini and colleagues (183) reported on 114 patients with dilated cardiomyopathy and a mean ejection fraction of 22%. The 1-year survival rate was 50% in 54 patients with an abnormal signal-averaged ECG and 100% in 66 patients with a normal signal-averaged ECG. This report conflicts with the study by Turitto and coworkers (184), who reported on 80 patients who had NSVT, a mean ejection fraction of 20%, and dilated cardiomyopathy. Neither electrophysiologic testing nor signal-averaged ECG predicted arrhythmic events, total death rate, or survival rate.

Few studies have evaluated the usefulness of signal-averaged ECG in patients with hypertrophic cardiomyopathy (71,185). Cripps and associates (185) reported on 64 patients with hypertrophic cardiomyopathy, compared with 50 age- and gender-matched control subjects. An abnormal signal-averaged ECG was present in 20% of patients and only 4% of control subjects, with a significant correlation between the presence of NSVT on 48-hour ambulatory monitoring and an abnormal signal-averaged ECG. There was no association between an abnormal signal-averaged ECG and a family history of premature sudden death, syncope, maximum left ventricular wall thickness, or symptomatic status. This study included only a few patients who had experienced a significant cardiac event, and definite recommendations on the use of signal-averaged ECG in patients with hypertrophic cardiomyopathy cannot be made at this time.

Nava and associates (186) evaluated the signal-averaged ECG in 138 patients with arrhythmogenic right ventricular cardiomyopathy compared to 146 healthy control subjects. A high correlation was seen between patients who had the disease and the presence of ventricular tachycardia (94%; p <.02). Overall, the signal-averaged ECG was abnormal in 57% of patients and 4% of subjects.

Effect of Interventions on Late Potentials

Surgical procedures that remove the area of myocardium responsible for ventricular arrhythmia are associated with a reduction in the incidence of late potentials (187,188). The majority of patients have late potentials before surgery, and 56% continue to have late potentials after surgery. In patients who do not show late potentials after surgery, 90% will have no inducible ventricular tachycardia, whereas 85% to 100% of patients who do show late potentials will have sustained ventricular tachycardia that remains inducible after surgery.

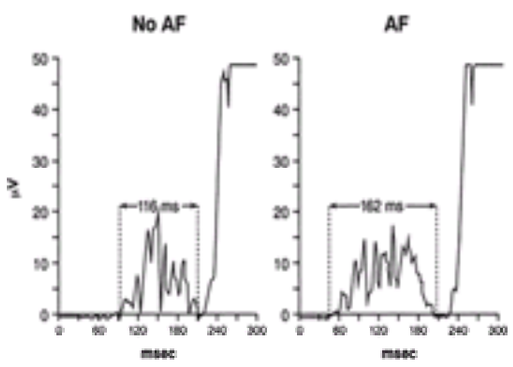
Angioplasty during acute myocardial infarction (189) reduces the incidence of late potentials. Reports are inconsistent as to whether signal-averaged ECG abnormalities are improved after the angioplasty procedure in patients with chronic coronary artery disease (190,191). In patients with coronary artery disease who are undergoing coronary artery bypass grafting, the signal-averaged ECG after surgery rarely detects abnormalities in patients without a history of myocardial infarction, but in patients with a history of myocardial infarction, abnormalities may resolve or improve after surgery (192). Twidale and coauthors (193) reported that radiofrequency ablation had no effect on late potentials in four patients in whom ablation of ventricular tachycardia was successful.

Cardiac Transplantation

The use of the signal-averaged ECG to identify patients who are experiencing cardiac transplant rejection has been reported in a few studies (194,195). Keren and associates (194) reported that temporal analysis of the signal-averaged ECG demonstrated a sensitivity of 65%, a positive predictive accuracy of 92%, and a negative predictive accuracy of 68% for identifying acute rejection. Lacroix and associates (195) reported that an 11% decrease in the RMSV using a 70-Hz high-pass filter provided a sensitivity of 88% and a specificity of 78% for the presence of rejection.

P-Wave Signal Averaging

Preliminary reports have evaluated the usefulness of signal averaging of the P wave in predicting patients at risk for atrial fibrillation (196,197,198,199 and 200) (eFig. 61.0.23). Both time- and frequency-domain analysis are helpful in assessing abnormal P waves (200). Increased P-wave duration and magnitude are associated with paroxysmal atrial fibrillation in patients after cardiac surgery (196) and in patients with hyperthyroidism (197). Steinberg and associates (196) reported on 133 patients who underwent P-wave signal averaging after cardiac surgery, of whom 33 developed atrial fibrillation at a mean of 2.6 days after surgery. A P-wave duration of more than 140 ms predicted atrial fibrillation with a positive predictive accuracy of 37% and a negative predictive accuracy of 87%. Standard technique and definition for identifying an abnormal P wave by signal-averaged ECG have not been established, although this does appear to be a promising method for identifying patients at risk for subsequent atrial fibrillation.



***e*FIGURE 61.0.23** Patients at risk of atrial fibrillation (AF) have a prolonged P-wave duration by signal averaging. The P-wave duration in patients without AF measured 116 ms, in contrast to the P-wave duration in patients with AF, which measured 162 ms. (Adapted from Guidera SA, Steinberg JS. The signal-averaged P-wave duration: a rapid and noninvasive marker of risk of atrial fibrillation. *J Am Coll Cardiol* 1993;21:1645–1651.)

Personal Perspectives

Signal-averaged ECG is proving to be less helpful as a single technique to risk-stratify patients. The low-positive predictive accuracy reduces the test's sefulness. The negative predictive accuracy is only high in a population of patients who are at low risk for an arrhythmic event. As the risk for an arrhythmic event increases (as determined by other factors, such as reduced ventricular function, presence of coronary artery disease, and complex ventricular arrhythmias), the negative predictive accuracy decreases. Therefore, a negative result of signal-averaged ECG should not preclude electrophysiologic testing in patients who are strongly suspected of having a ventricular arrhythmia. Signal-averaged ECG should be used in conjunction with other tests and clinical parameters to identify high-risk patients. Little further development will take place in time-domain analysis methods and diagnostic criteria. Frequency-domain analysis methods will continue to improve and, hopefully, will allow detection of delayed conduction in parts of the heart that are now obscured, either because they occur early in the QRS complex, as in anteroseptal infarction, or because they are masked by a ventricular conduction delay. Frequency-domain analysis is difficult to reproduce and to perform reliably outside of research institutions. Signal-averaged ECG has a minimal role in the evaluation of patients with dilated or hypertrophic cardiomyopathy and in assessing rejection in cardiac transplantation. P-wave signal averaging identifies patients at risk for atrial fibrillation, but it has little benefit for clinical management at this time.

Future Directions

The signal-averaged ECG identifies delayed conduction that represents the substrate for ventricular arrhythmia. Time-domain methods of analysis are used with criteria to define late potentials developed for each recording system. The test is not clearly useful in patients with conduction defects. Recommendations for use of the signal-averaged ECG have been published (*e*Table 61.0.6). The presence of late potentials after myocardial infarction identifies patients at risk for arrhythmic events, although the predictive accuracy is reduced after thrombolytic therapy. The signal-averaged ECG, combined with other prognostic tests and with patient history, identifies patients with syncope who are at risk for induced ventricular tachycardia on electrophysiologic testing. Signal-averaged ECG is less helpful in patients with dilated and hypertrophic cardiomyopathy and is not useful for predicting antiarrhythmic drug efficacy. New methods of analyzing the signal-averaged ECG may improve the test's predictive accuracy. The test is most useful for identifying patients at risk for ventricular tachycardia when combined with other prognostic tests. Research and development efforts will continue to focus on using frequency-domain analysis to identify delayed conduction that may not be observed using time-domain analysis, such as late potentials occurring early in the QRS complex in patients who have an acute anteroseptal myocardial infarction or late potentials masked by ventricular conduction defects.

***e*TABLE 61.0.6** RECOMMENDATIONS FOR USE OF SIGNAL-AVERAGED ELECTROCARDIOGRAM

Established value
Stratification of risk of development of sustained ventricular arrhythmias in patients recovering from myocardial infarction who are in sinus rhythm without electrocardiographic evidence of bundle branch block or intraventricular conduction delay (QRS complex >120 ms)
Identification of patients with ischemic heart disease and unexplained syncope who are likely to have inducible sustained ventricular tachycardia
Valuable in clinical care, further supportive evidence desirable
Stratification of risk of development of sustained ventricular arrhythmias in patients with nonischemic cardiomyopathy
Assessment of success of operation for sustained ventricular tachycardia
Promising but currently unproved
Detection of acute rejection of heart transplants
Assessment of efficacy or proarrhythmic effects of antiarrhythmic drug therapy in patients with ventricular arrhythmias
Assessment of success of pharmacologic, mechanical, or surgical interventions to restore coronary artery blood flow
Not indicated
Patients with ischemic heart disease and documented sustained ventricular arrhythmias
Stratification of risk of development of sustained ventricular arrhythmias in asymptomatic patients without detectable heart disease

From Cain ME, Anderson JL, Arnsdorf MF, et al. Signal-averaged electrocardiography. *J Am Coll Cardiol* 1996;27:238–249, with permission.

Spectral temporal mapping, spectral turbulence analysis, and autoregressive methods, including maximal entropy and adaptive frequency determination, may prove to be more useful than time-domain analysis in identifying delayed conduction. Models that incorporate clinical factors and results of noninvasive testing, including signal-averaged ECG, will increasingly be used to identify patients at highest risk for sudden death. Signal averaging of the P wave will gain importance as it becomes commercially available and is more commonly used to identify patients at risk for atrial fibrillation.

T-WAVE ALTERNANS

Historical Perspective

Electrical alternans must be distinguished from mechanical alternans, which occurs in the setting of pericardial effusion when the entire heart moves in an alternating pattern, resulting in a change in QRS amplitude. This is often diagnosed as electrical alternans when the heart rotates on its cardiac electrical axis on an every-other-beat basis. In contrast, true electrical alternans represents alternation in the intrinsic cardiac electrical activity. Described as early as 1909 (201,202), electrical alternans has been associated with Prinzmetal's angina (203), acute ischemia (204), electrolyte abnormalities (205), and the long QT syndrome (206). These conditions are associated with increased risk for ventricular arrhythmias, and TWA can be visible on the surface ECG, particularly in patients with long QT syndrome while they are experiencing emotional or exercise stress (eFig. 61.0.24). In general, TWA that is visible on the surface ECG is rare and is generally considered an ECG curiosity not specifically associated with arrhythmic risk.

***e*FIGURE 61.0.24** Electrocardiogram from a 44-year-old woman with acquired long QT syndrome. The electrocardiogram demonstrates T-wave alternans before the onset of torsades de pointes.

Pericardial tamponade. Low QRS voltage and electrical alternans are characteristic findings of tamponade.

Pathophysiology of T-Wave Alternans

Electrical alternans is believed to be a marker of increased susceptibility to reentry arrhythmias (207), owing to the dispersion of refractoriness and to some areas of the myocardium having the ability to conduct only on an every-other-beat basis. This alternation in conduction is reflected as electrical alternans on the ECG. TWA is caused by an alternation in the duration of the action potential that occurs in diseased tissue with a well-described cellular and ionic basis (208,209). Experimental studies (209,210) suggest that TWA is caused by localized alternation in action-potential duration that then leads to the development of reentrant arrhythmias.

Technical Aspects of Measuring T-Wave Alternans

Because TWA involves microvolt-level changes in T-wave morphology, it is not detected by visual inspection of the surface ECG. The spectral method (211) was developed for the detection of microvolt-level TWA and allows sampling of a series of T-wave amplitudes, with subsequent assessment of the power spectrum of these beats using fast Fourier transform analysis techniques. A composite power spectrum is developed by averaging separate spectra for different points in the T wave. Two numerical indices of alternans are determined: V*alt*, the alternans voltage, which corresponds to the square root of the amplitude of the alternans peak above the background noise levels, representing the magnitude of the alternating variation in T-wave morphology compared to the mean T wave; and *k*, defined as the alternans ratio, which is the amplitude of the alternans peak above the background noise level measured in units of the standard deviation of the noise. Using these two indices, levels have been developed to define normal and abnormal.

Clinical Evaluation of T-Wave Alternans

Rosenbaum and associates (212) assessed 83 patients who underwent invasive electrophysiologic study for a variety of clinical indications. At 20 months of follow-up, 81% of the patients with a positive TWA experienced a ventricular event (defined as sudden death, cardiac arrest, sustained ventricular tachycardia, or ventricular fibrillation), whereas only 6% of patients with a negative TWA experienced such an event. Testing for TWA was equivalent to invasive electrophysiologic testing as a predictor of ventricular tachyarrhythmic events in this study. Hohnloser and colleagues (213) evaluated ten measures of arrhythmic risks in 95 patients who received an implantable cardioverter defibrillator for clinical indications. The implantable defibrillator served as the monitor for documenting ventricular tachyarrhythmic events. Among the various measures of predicting ventricular events, only TWA and left ventricular ejection fraction were statistically significant univariate predictors of

implantable cardioverter defibrillator discharge. Adachi and associates (214) assessed the ability of TWA to predict the occurrence of spontaneous ventricular tachycardia or fibrillation in 58 patients with nonischemic dilated cardiomyopathy. TWA was highly correlated with the occurrence of spontaneous ventricular tachycardia or fibrillation (p <.001) in this population, in whom invasive electrophysiologic testing is generally not regarded as a useful predictor of spontaneous ventricular arrhythmias. Ikeda and colleagues (215) reported on 102 patients who were assessed with TWA, signal-averaged ECG, and left ventricular ejection fraction after myocardial infarction. TWA was a significant predictor of a tachyarrhythmic event (p <.006), with the highest relative hazard (16.8) compared to signal-averaged ECG (5.7) and left ventricular ejection fraction (4.7). At the end of 12 months of follow-up, 28% of the patients with TWA had experienced a clinical event. Klingenheben and associates (216) assessed 107 patients with New York Heart Association class II and III congestive heart failure but no history of ventricular arrhythmia. TWA was a highly significant predictor of ventricular arrhythmic events (p <.0036); none of the other predictors were statistically significant, including left ventricular ejection fraction, the presence or absence of NSVT, baroreceptor sensitivity, measures of heart-rate variability, and signal-averaged ECG. In this study, no ventricular arrhythmic events occurred in patients who had a negative TWA.

Personal Perspectives

TWA testing joins an increasing list of techniques used to identify patients at high risk for ventricular arrhythmia and sudden cardiac death who potentially may benefit from use of the implantable cardioverter defibrillator. At this time, no definitive clinical data have demonstrated benefits of treatment that is based on TWA status, but the technique does appear to have promise as an aid in risk-stratifying these patients. Prospective clinical trials are required to determine the exact role of TWA in guiding patient management.

Conclusions

Microvolt-level TWA testing is a promising technique that appears to be an effective, noninvasive predictor of risk for ventricular arrhythmias and sudden death in the studies published to date. This test appears to be comparable to invasive electrophysiologic testing but needs to be assessed in controlled clinical trials to determine whether management based on TWA findings improves the survival of patients at risk for life-threatening ventricular arrhythmias.

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62

ELECTROPHYSIOLOGIC TESTING

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

An electrophysiologic study (EPS) provides a safe and effective method for evaluation, risk stratification, and treatment of known and suspected arrhythmias. This chapter emphasizes EPS indications, techniques, and normal findings.

An EPS permits assessment of individual portions of the cardiac electrical system. These assessments include evaluation of spontaneous function, responses to stresses, and vulnerability to induced tachyarrhythmias. Indications and guidelines for EPS have been established for a broad range of situations and clinical problems (1) (*e*Table 62.0.1).

***e*TABLE 62.0.1** MAJOR INDICATIONS FOR ELECTROPHYSIOLOGIC TESTING

ACC/AHA/NASPE 1995	Class I	Class II	Class III
Sinus node function	Symptomatic patients: sinus node dysfunction is suspected but unproved.	Patients with documented sinus node dysfunction in whom evaluation of AV or ventriculoatrial conduction may aid choice of pacer	Symptomatic patients with documented association between rhythm and symptoms, therapy would not change with EPS
		Sinus brady: intrinsic vs. autonomic or drug effects	Asymptomatic sinus brady only with sleep, including sleep apnea
		Symptomatic patients with sinus brady, to rule out other causes	
Acquired AV block	Symptomatic patients with HV block suspected but unproved.	Patients with second- or third-degree AV block where site of block or response to measures (e.g., drugs) could affect therapy	Symptomatic patients with symptoms and AV block correlated with ECG
	Paced patients with AV block who are still symptomatic.	Suspected concealed junctional depolarizations causing pseudo-AV block	Asymptomatic patients with transient AV block associated with sinus slowing (e.g., nocturnal type I second-degree AV block)
Chronic intraventricular conduction defects	Symptomatic patients, cause unknown.	Asymptomatic patients with bundle branch block in whom pharmacologic therapy that could cause block is contemplated	Asymptomatic patients with intraventricular conduction defects
			Symptomatic patients in whom symptoms correlate with or are excluded by ECG
Narrow QRS complex tachycardia	To choose treatment for patients with poorly tolerated tachy that does not respond adequately to drugs.	Patients with frequent episodes to be treated with drugs, but there is concern about proarrhythmia, or drug effects on sinoatrial node or AV conduction	Patients well controlled by vagal maneuvers or drugs and not candidates for nonpharmacologic treatment
	Patients who prefer ablation.		
Wide QRS complex tachycardias	Correct diagnosis is needed for treatment, but is unclear on ECG.	None	Diagnosis of supraventricular tachycardia or VT certain from ECG
			However, EPS data may be useful in guiding subsequent treatment
Prolonged QT intervals	None.	To identify proarrhythmic effects of a drug in a patient with cardiac arrest on the drug	Manifest long QT, with or without arrhythmias
		Patients with syncope and with or without long QT or TU waves, to unmask abnormal QT, for example, with a catecholamine	Acquired long QT syndrome with identifiable cause
Wolff-Parkinson-White syndrome	Patients being evaluated for catheter ablation.	Asymptomatic patients with family history of sudden death; or who engage in high-risk activities (insurance?)	Asymptomatic patients not covered above
	Patients with deltas who have had arrest or SUO.	Patients with deltas undergoing other cardiac surgery	
	Symptomatic patients in whom EPS data could affect treatment.	Asymptomatic patients not covered above	
Ventricular premature contractions, couplets, and VT-NS	None.	Patients with other risk factors (e.g., low ejection fraction, abnormal sinoatrial ECG, VT-NS on Holter, if EPS will be used to guide treatment if sustained VT is induced	Patients with syncope of known cause whose treatment will not be altered by EPS findings

		Highly symptomatic patients considered for catheter ablation	
SUO	Patients with suspected structural heart disease and SUO.	Patients with recurrent SUO, without structural heart disease, and with a negative tilt test result	Patients with syncope of known cause whose treatment will not be altered by EPS findings
Cardiac arrest survivors	Survivors without new Q-wave MI. Arrest >48 h after acute MI.	Arrest caused by bradyarrhythmia Arrest possibly due to congenital long QT syndrome	Arrest in first 48 h after acute MI Arrest from clear cause (e.g., acute ischemia, aortic stenosis, or long QT syndrome)
Unexplained palpitations	Rapid pulse felt by medical personnel, without ECG. Palpitations followed by syncope.	"Significant" palpitations where EPS may help in diagnosis, risk assessment, or treatment	Palpitations documented to be due to noncardiac cause (e.g., hyperthyroidism)
Guiding drug therapy	Patients with sustained VT or arrest, especially if prior MI. Patients with AV nodal reentry tachycardia, AV reentrant tachycardia, or atrial fibrillation with an accessory pathway in whom drug therapy is planned.	Sinoatrial node reentry tachycardia, A-tachy, atrial fibrillation, or atrial flutter, without deltas Patients with arrhythmias not inducible at baseline EPS	Isolated atrial premature contractions or ventricular premature contractions Ventricular fibrillation with a clearly identified reversible cause
Related to implantable devices	Before and during implant, and before discharge to confirm performance. After implant to determine if a factor has altered the performance of the device. Test interactions if two devices are to be used.	In patients with documented indications for pacing, to optimize pacing mode and sites	Patients who are not device therapy candidates

ACC/AHA/NASPE, American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology; AV, atrioventricular; brady, bradycardia; ECG, electrocardiography; EPS, electrophysiologic study; MI, myocardial infarction; NS, nonsustained; SUO, syncope of undetermined origin; tachy, tachycardia; VT, ventricular tachycardia.
From Zipes DP, DiMarco JP, Gillette PC, et al., with Fisher JD for ablation section. Guidelines for clinical intracardiac electrophysiological and catheter ablation procedures. A report of the ACC/AHA Task Force on Practice Guidelines (Committee on Clinical Intracardiac Electrophysiological and Catheter Ablation Procedures), developed in collaboration with NASPE. *J Am Coll Cardiol* 1995;26:555–573; *Circulation* 1995;92:675–691; *J Cardiovasc Electrophysiol* 1995;6:652–679.

GLOSSARY

AH interval: The interval from the first rapid deflection of the atrial electrogram on the bundle of His lead to the first inscription of the bundle of His depolarization.

Cycle length: Interval in milliseconds. During EPS, cycle lengths or intervals often change from beat to beat, so that these measures are more relevant than an overall rate that is expressed in beats per minute (beats/min). The use of rates in beats/min is retained mostly to facilitate communications with physicians who are more comfortable with this terminology.

Effective refractory and conduction periods: Measurements of impulse propagation at various levels in the heart (see text for detailed definitions).

Functional refractory and conduction periods: Measurements of impulse propagation at various levels in the heart (see text for detailed definitions).

HV interval: The interval from the first inscription of the bundle of His potential to the first evidence of ventricular depolarization on the surface electrocardiogram or the bundle of His lead.

PA interval: The interval from the first evidence of sinus node depolarization whether on the intracardiac or surface electrocardiogram, to the atrial deflection as recorded in the bundle of His lead.

S_1, S_2, S, . . ., N: S_1 refers to the baseline or drive stimuli in a series, with each of the series of S_1s being of equal intervals. S_2 is the first extrastimulus, with the S_1–S_2 interval almost always shorter than the S_1–S_1. S_3, S_4, S, . . ., N are the second, third, Nth extrastimulus. See text for details.

HISTORICAL PERSPECTIVE

The leap from the experimental animal laboratory to the clinical arena and clinical cardiac electrophysiology was made possible by the development of cardiac catheterization and transvenous pacing techniques. Intracardiac recordings from the right atrium, bundle of His region, and right ventricle allowed direct rather than inferential analysis of normal and abnormal rhythms (2,3). Electrophysiologic testing was quickly established as the definitive method for diagnosis and subsequently for treatment of cardiac rhythm disorders.

INTRODUCTION

A complete EPS consists of a series of tests that are designed to evaluate the heart from top to bottom (i.e., from the sinus node to the ventricle, with steps in between). Depending on the purpose of the EPS for a given patient, all or only some of these regions may be tested, in an à la carte fashion.

The testing techniques used to evaluate each region are remarkably similar. Pacing at increasing rates and programmed electrical stimulation form the core of testing at each level, supplemented by various pharmacologic probes and physical maneuvers.

This chapter emphasizes the indications for EPS; matters related to patient preparation, vascular access, stimulation, and recording techniques; and an outline of EPS related to the major parts of the heart's electrical system. Other chapters in this text cover the details of specific arrhythmias.

Indications for Electrophysiologic Study

The earliest practical application of EPS was assessment of the conduction system. This was followed in rapid succession by EPS for characterization of various tachycardias; as a guide for antiarrhythmic drug efficacy; identification of the cause of syncope of undetermined origin; arrhythmia mapping before and during open heart surgery; and as an integral part of the procedure for catheter ablation of tachycardias. Guidelines on the indications for EPS have been published from time to time by the American College of Cardiology together with the American Heart Association, and by the North American Society for Pacing and Electrophysiology (1) (eTable 62.0.1). An update of these guidelines is due in the near future.

Patient Preparation

Education and Consent

Patients are often quite anxious about the prospect of an invasive study. Most diagnostic EPSs involve only venous access and are, therefore, safer than coronary angiography. The latter is a procedure that many patients are familiar with and tend to take for granted. Electrophysiologists often have patients referred to them who have been told by the referring physician that EPS is a minor, low-risk procedure. These patients may be alarmed to learn that no procedure is risk free, and that EPS may require several hours. Therefore, it is important for realistic patient education to begin with the referring physician. The electrophysiologist should put the various risks in context. Patients can understand analogies, such as the risks versus the benefits of walking across a busy street. Patients should also have a realistic idea of the benefit they may derive from undergoing EPS, including the possibility that the study result may be negative or equivocal.

Preprocedure Preparations

Traditionally, diagnostic EPS was performed in the postabsorptive, nonsedated state. There are of course some problems with this idea. There is great variation among patients in the anxiety experienced during invasive procedures. As EPSs became longer and more complex, it became clear that sedation would be required for many

of these subjects.

Twelve-Lead Electrocardiography

It is helpful to have a 12-lead electrocardiography (ECG) available, particularly when tachyarrhythmias are expected during the procedure, or in patients for whom ischemia is an issue. It is desirable for the 12 leads to be recorded simultaneously, or in just a few seconds, in case the arrhythmia is fast, slow, or transient.

Defibrillator Pads

Using preapplied adhesive defibrillator pads avoids the need to disrupt the sterile field in the event that electrical defibrillation or cardioversion is needed during the procedure.

Arterial Line

Arterial lines are used routinely in a *minority* of EPS laboratories, except in unstable patients or for certain ablation procedures. Automated cuff blood pressure devices are usually adequate.

Sedation

Many patients benefit from minimal sedation. Longer procedures and ablations are now routinely performed using intravenous conscious sedation. Guidelines are published by the North American Society for Pacing and Electrophysiology (4).

Urinary Problems

Urinary retention may occur in both genders during lengthy EPSs, particularly if combined with sedation and a tachycardia-related diuresis. When this situation is anticipated, it is useful to insert a Foley catheter before the procedure. Lubrication and topical anesthesia of the urethra using a commercially available lidocaine jelly injector system makes catheterization both acceptable and well tolerated by the patient.

Oxygen and Carbon Dioxide Monitoring

Monitoring of O_2 saturation has become virtually routine in many laboratories and is of particular value in sedated patients. If patients are receiving supplemental oxygen, the O_2 saturation may be misleadingly high. Expired CO_2 monitors are useful in preventing hypercapnia in such situations and are recommended in the guidelines for conscious sedation.

Universality of Stimulation Techniques

There is a relatively small menu of stimulation techniques useful in the study of both bradycardias and tachycardias.

Stimulus Amplitude and Pulse Duration (Pulse Width)

Most EPS laboratories use outputs at two to four times diastolic threshold. Twice threshold is more common. In general, refractory periods (see Conduction and Refractory Periods, later in this chapter) are somewhat longer when determined using twice threshold, and this may reduce the incidence of induction of nonclinical tachyarrhythmias. At four times threshold, one is at the beginning of the more vertical portion of a strength-interval curve, which may have several advantages (5,6).

A pulse duration of 1 or 2 ms is most commonly used. This dates from the early days of clinical EPS when implanted pacemakers had similar pulse durations, as do current temporary pacemakers. This pulse duration is now out of synchrony with those used in implantable devices, but it has been retained for the sake of consistency in EPS protocols done over long periods of time.

Most commercial EPS stimulators emit constant current pulses. Initially, this too was in keeping with the norm for implantable pacemakers. The latter are now nearly universally constant voltage devices. Testing of patients with and without clinical tachycardias with both constant voltage and constant current stimulation, all at four times diastolic threshold, produced no significant difference in any of the results.

Incremental versus Decremental

Both terms are in regular use and have opposite meaning depending on whether one is considering *rate* in beats/min or *cycle length* in milliseconds. In the paragraphs that follow, the most conventional usage is employed.

Straight Pacing

The pacing rate or cycle length is maintained throughout the duration of the stimulation. There are several common applications for straight pacing.

1. *Rate incremental pacing.* After pacing at a given rate for a predetermined number of stimuli or seconds, the rate is then increased (with or without intervening pauses) in a series of steps until predetermined end points are reached. Rate incremental pacing terminology is derived from stimulators controlled by an analog dial. Digitally controlled devices often increase the rate by choosing a sequence of cycle length *decrements*, but the term *incremental pacing* may still be used.
2. S_1–S_1 *drive stimuli*. The heart is paced, or driven, at a specified rate and duration (typically eight beats) after which a premature extrastimulus is delivered (see Extrastimulus Technique). The eight drive beats are each termed S_1 *stimuli*. These S_1s may be followed by first, second, third, and *N*th premature extrastimuli and are designated S_2, S_3, S_4, and S_N. When extrastimuli follow a series of sinus beats, the latter may also be designated as S_1s. S_1–S_1 drive stimuli are sometimes called *trains*, but this can be confused with ultrarapid train stimulation (see Ultrarapid Train Stimulation, later in this chapter), which are also referred to as *trains*.
3. *Burst pacing for tachycardia induction.* Stimuli are delivered at a constant rate for a relatively short duration, but at successively faster rates with each burst until a predetermined maximum rate or minimum interval (i.e., cycle length) has been reached.
4. *Bursts for termination of tachycardia*. Bursts for termination of tachycardia is similar to the technique used for induction. The initial pacing rate is faster than that of the tachycardia.
5. *Underdrive pacing for tachycardia termination.* Underdrive pacing is pacing at a rate slower than the tachycardia at a constant rate. Therefore, stimuli fall at differing points in the tachycardia cycle.

Ramps

Ramp pacing implies a smooth change in the interval between successive stimuli. Ramps, too, can be incremental or decremental as defined by either rate or cycle length. Several applications for ramps are presented here.

1. As a test for conduction, long ramps with small cycle length decrements between successive stimuli provide results comparable with stepwise rate incremental pacing (7).
2. For tachycardia induction, the ramp is decreased in duration, but the steepness of the slope is increased (i.e., interstimulus intervals are decreased more rapidly). Successive ramps go to higher and higher rates (shorter intervals) up to a predetermined limit.
3. Tachycardia termination is somewhat similar to tachycardia induction. It is commonly used in antitachycardia pacing algorithms in implantable cardioverter defibrillators (ICDs). Programmed rate incremental ramps are also known as *autodecremental pacing*.

Extrastimulus Technique

One or more extrastimuli (designated S_2, S_3, and S_N) are introduced at specific coupling intervals based on previous drive S_1s, or spontaneous beats. Thereafter, the S_1–S_2 interval is altered, usually in 10- to 20-ms steps, until an end point is reached, such as tissue refractoriness or termination or induction of a tachycardia. It is

usual to begin late in diastole and successively decrement the S_1–S_2 interval. When the physician is satisfied with the results of S_1–S_2 testing, a second extrastimulus (S_3) may then be introduced with the S_2–S_3 interval altered in a fashion similar to that used for S_1–S_2.

Two methods are in common clinical use for decrementing the S_1–S_2 and S_3–S_4 intervals (8,9). In the *tandem method*, the S_1–S_2 is decremented until S_2 does not capture, and then the S_1–S_2 interval is increased by 40 to 50 ms and held there. S_3 is then introduced, and the S_2–S_3 interval decremented until S_3 fails to capture. At that point, the S_1–S_2 interval is decremented, and S_3 retested to see if it captures. From that point on, the S_1–S_2 and S_2–S_3 are decremented in tandem until refractory, so that they and the S_3–S_4 interval are altered in a fashion similar to that used for S_2–S_3. In the *simple sequential method*, the S_1–S_2 interval is decremented until it no longer captures, and then incremented until it does (usually 10 ms). The S_1–S_2 interval is then held constant, while the S_2–S_3 interval is decremented in a similar fashion to that used for S_1, and then the same for S_3–S_4. The tandem method can be looked on as more conservative, because it favors relatively longer intervals and gives a larger number of stimulation runs before moving on to the next extrastimulus. Prospective studies comparing the two methods have shown no differences between the two methods in any of outcomes assessed (8). The choice of the simple sequential or tandem method therefore remains a matter of investigator's choice.

Ultrarapid Train Stimulation

Stimuli are delivered at short intervals (10 to 50 ms) for a duration sufficient to result in a desired number of captures (10,11). The technique has long been used experimentally (with sequentially increasing stimulus amplitudes) for induction of ventricular fibrillation. It is now used clinically for that purpose with ICDs. Shorter trains have also proved useful in termination of tachycardias (10) and in induction of monomorphic tachycardias (11). Of all the techniques described, ultrarapid trains are the least universally employed, except for ventricular fibrillation induction with ICDs.

Stimulation Protocols

Adequacy is more important than universality. Bodies such as the North American Society for Pacing and Electrophysiology have published guidelines on the minimum standards for an acceptable protocol (12). In addition to suggesting reasonable ranges of stimulation sites, drive cycle lengths, numbers of extrastimuli, and amplitudes and pulse durations of the extrastimuli, the guidelines also suggest outcome criteria. For example, the protocol used should be able to induce sustained monomorphic ventricular tachycardia in at least 90% of patients with coronary artery disease who present with such a rhythm.

Signal Filtering and Interelectrode Distance

The surface ECG is usually filtered at 0.1 to 100.0 Hz. The bulk of the energy is in the 0.1- to 20.0-Hz range. Because of interference from alternating current (AC), muscle twitches, and similar relatively high-frequency interference, it is sometimes necessary to record the surface ECG over a lower frequency range or to use notch filters. Timing of events with respect to QRS onset is often important during EPS, but it is cumbersome to display all 12 leads of the regular surface ECG. Orthogonal lead systems (X,Y,Z) are logical but not commonly used. It is more typical to use mutually perpendicular leads (I, AV_F, and V_1), often supplemented by lead II, which gives an indication as to the presence of abnormal left-axis deviation. Many electrophysiologists have their own personal favorite lead selections.

Intracardiac leads can be placed strategically at various positions within the heart. Therefore, it is desirable to record *local* events in the region of the lead, rather than far field events. This is accomplished by filtering intracardiac electrograms, typically at 30–40 to 500 Hz. Note that this eliminates the spectrum with the greatest energy that reaches the surface ECG. The higher frequency waves carry much less energy and may be difficult to detect more than a centimeter away from the recording lead. Bipolar electrograms are generally used, and smaller interelectrode distances record increasingly local events.

Timing of Local Events

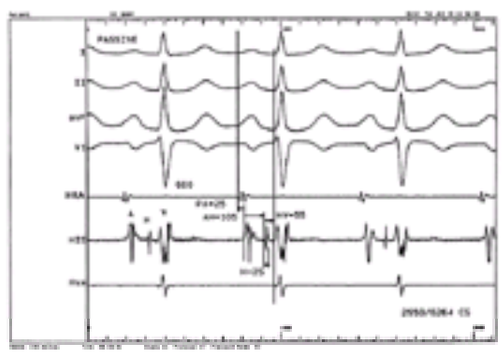
With an "unfiltered" bipolar lead, an approaching wavefront creates a positive deflection that quickly reverses itself as the lead passes directly under the electrode. This rapid reversal constitutes the "intrinsic deflection" of the electrogram and represents the timing of the most local event (i.e., at the site of the bipole) (13). Electrograms are filtered at 30–40 to 500 Hz and have a much more jagged appearance. When recorded simultaneously with an unfiltered electrogram, the midpoint of the intrinsic deflection of the unfiltered electrogram occurs at the same time as a similar deflection on the filtered electrogram, or at the peak positive or negative deflection of the filtered electrogram. The slew rate or dV/dT of the filtered electrogram is so rapid in normal heart tissue that the difference between the peak and the nadir of the deflection is 5 ms or less. Identification of the local event is therefore easy with either filtered or unfiltered electrograms in normal tissue. However, diseased myocardium may conduct very slowly with fractionated electrograms that make local events harder to identify. The electrophysiologist must then decide whether to use onset rather than local criteria for timing of events. Even in normal tissue, onset deflections are usually less crisp than the local deflection. Tradition plays a large role in the choices of deflections used for timing of events (see Baseline Intervals, later in this chapter). At times, there may be a deflection that is of particular interest, such as a His or bundle branch deflection that is small relative to the size of surrounding electrograms. This is particularly true when the gain must be markedly increased to produce a measurable deflection. In such instances, a "limiter" or "clipper" option on the amplifier and recorder system can eliminate the highly amplified surrounding signals to allow concentration on the deflection of interest. However, limiters also eliminate the ability to determine the timing of the intrinsic deflection (local timing) of the signals being limited.

Catheterization Techniques

The percutaneous technique is used almost exclusively. The bundle of His electrogram (HBE) is most commonly recorded using a lead inserted via a femoral vein and advanced through the right atrium across the tricuspid into the right ventricular inflow area. Some other areas are more easily reached through the superior vena cava. Insertion sites can also include the antecubital, jugular, and subclavian veins.

Choices of Surface and Intracardiac Signals

A classic display would include three or four surface ECGs; a recording from the high right atrium (HRA); the HBE, which includes the low medial right atrium, the bundle of His deflection, and the right ventricular inflow deflection; and a recording from the right ventricular apex. Depending on the type of study and the information sought, stimulation and recording from other sites may be appropriate (eFig. 62.0.1).



***e*FIGURE 62.0.1** Normal intracardiac electrograms. This is a "passive HBE" (i.e., a bundle of His electrogram and accompanying recordings during sinus rhythm with no ongoing manipulations, stimuli, or intentional stresses). Semiorthogonal leads 1, AV_F, and V_1 are used together with lead 2, which is helpful in determining axis. The measurement of intervals is demonstrated. HRA, high right atrium; RVA, right ventricular apex.

ELECTROPHYSIOLOGIC STUDY

Baseline Intervals

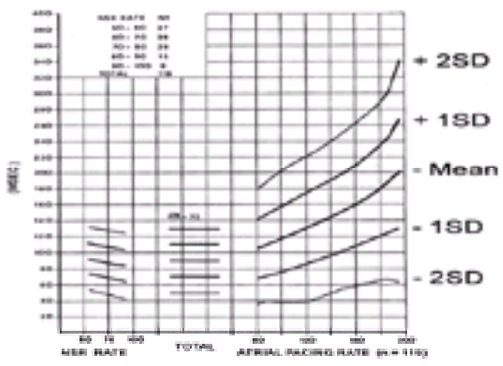
Using intracardiac electrograms, the PR interval of the surface ECG can be further subdivided (eFig. 62.0.1). During sinus rhythm, the earliest atrial activity is identified using the HRA electrogram from the sinus node region at the junction of the superior vena cava and the right atrium. The P wave is then timed from the earliest

evidence of such atrial activity, whether first seen in the HRA lead or in the surface ECG. Next, conduction through the right atrium to the region of the atrioventricular (AV) node and bundle of His is then measured as the PA interval. This is defined as the interval from the P wave as just defined, to the *first rapid* depolarization of the atrium recorded on the HBE lead. AV node conduction is measured by the interval from the *first rapid* deflection of the A wave in the HBE lead to the*first evidence* of bundle of His depolarization on the HBE lead; this is designated the AH interval. Conduction through the bundle of His and bundle branches is then measured as the timing from the *first evidence* of the bundle of His deflection to the *first evidence* of ventricular deflection on the HBE lead *or* on the surface ECG, whichever comes first. Normal values for these intervals based on a compilation of sources (14,15,16,17,18,19,20,21 and 22) are found in eTable 62.0.2. Note that the traditional use of *first rapid* deflections can be quite subjective compared with *first evidence* or the local or *intrinsic deflection*.

***e*TABLE 62.0.2** NORMAL CONDUCTION INTERVALS (±2 SD)

	PA intraatrial	AH atrioventricular node	His HV, His to V	P-LA interatrial
Passive/baseline	10–45	55–130	<2530–55	40–130
Atrial paced	10–75	[a]	<2530–55	65–150

[a]Progressive prolongation; see eFig. 62.0.5.
Based on a compilation of sources (13,14,15,16,17,18,19,20 and 21).



***e*FIGURE 62.0.5** The AH interval during normal sinus rhythm (NSR) and during high right atrial pacing. Mean and standard deviations (SD) are shown for subjects without evidence of atrioventricular nodal disease. [From Fisher JD. *Primer of cardiac electrophysiology*. Armonk, NY: Futura (*in press*); modified from Fisher JD. Role of electrophysiologic testing in the diagnosis and treatment of patients with known and suspected bradycardias and tachycardias. *Prog Cardiovasc Dis* 1981;24:25, with permission.]

A minority of authors use the HQ interval rather than the HV interval. The HQ interval is the interval from the onset of the bundle of His potential to the onset of the QRS and the surface ECG. Logically, one might also use information from the right ventricular apical lead or other intracardiac leads (14,23), but these are not part of the conventional measurements. The bundle of His potential itself should be crisp and distinct and less than 25 ms in duration. *Interatrial* conduction is measured from the HRA to the left atrium. Normal values appear in eTable 62.0.2.

Influences on the Timing of Cardiac Intervals

Sympathetic and parasympathetic tone can influence the heart rate and timing of cardiac intervals (24,25 and 26). Changes in neurohumoral tone can result from anxiety, sedation, exercise, sleep, ischemia, metabolic state, pharmacologic agents, and maneuvers such as carotid sinus massage (CSM). Some of these are discussed further in relevant sections of the EPS.

Carotid Sinus Massage

In most patients, cardioinhibitory effects on the sinus node are most apparent with right CSM, whereas the AV node is more likely to be affected by left CSM, but this distinction is by no means universal (15,27,28,29,30,31 and 32). Sinus node inhibition results in sinus bradycardia or sinus arrest. Inhibition of the AV node can result in prolongation of the AH interval or in block at the AH level. If CSM results in sinus arrest, concurrent *atrial* pacing will determine whether there is block at the AV node level as well.

CSM may be particularly revealing in patients who have the Wenckebach phenomenon at the time of their EPS. In one of those “paradoxical responses” of medical lore, Wenckebach at the HV level sometimes seems to improve with CSM. This is because the sinus node may be slowed, giving the bundle of His and bundle branches (which are much less affected by vagal tone) time to recover and resume conduction. In a patient with the Wenckebach phenomenon, therefore, CSM that produces worsening of the block is “good” because such a block is usually at the AV node level. This is more benign than block at the HV level, which leaves the patient with an idioventricular escape rhythm. Improvement of block with CSM may therefore be bad.

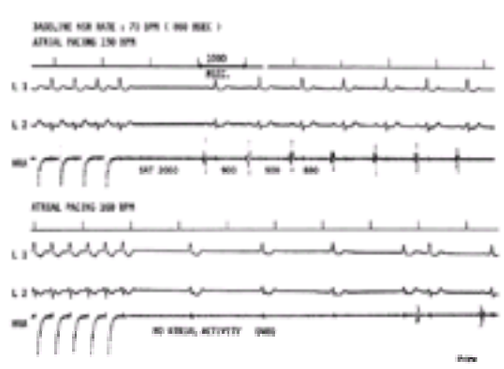
Carotid Sinus Massage Normal Values

Sinus pauses of 3 seconds or more in response to CSM are considered abnormal. In a control group of 98 patients without a history of AV block, bradycardia, or syncope (32), the mean sinus interval with firm right or left CSM was 1,252 ms, and +2 SD was 2,364 ms. Only 1% of patients had pauses of 3 seconds or more, and 2% had second- or third-degree AV block.

Sinoatrial Node Function Tests

Sinus Node Recovery Times

The sinus node is the archetype of an automatic focus. Automatic rhythms are characterized by spontaneous depolarization, overdrive suppression, and postoverdrive warm-up or return to baseline cycle length (15,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51, 52,53,54,55,56,57,58 and 59). Pacing at rates in excess of the spontaneous rate of an automatic focus results in temporary inhibition of spontaneous depolarization, with gradual return to the original cycle length over several beats following cessation of pacing (eFig. 62.0.2).



***e*FIGURE 62.0.2** Prolonged sinus node recovery times. This patient had a baseline sinus rate of 70 beats/min (860 ms). After pacing the high right atrium (HRA) at 130 beats/min, the sinus recovery time (SRT) was 2,060 ms, which is markedly prolonged. In the bottom panel, after pacing at rate 160, there is no SRT for 6,480 ms, although there is a junctional escape rhythm at approximately 40 beats/min. NSR, normal sinus rhythm.

Importance of Multiple Pacing Rates

Clinically, the sinus node recovery time (SNRT) is used to test sinus node automaticity. Pacing at rates near the baseline cycle length causes no overdrive suppression so that the interval between the last paced beat and the next sinus beat is comparable with the baseline cycle length. If the SNRT after pacing at 500 ms is shorter than after 600 ms, or there is marked variation (greater than 250 ms) in the SNRTs if multiple tests are performed after pacing at 500 ms, this may imply that some impulses have not penetrated the sinus node (i.e., that some degree of sinoatrial block exists). At pacing cycle lengths shorter than 500 ms, there is usually little further prolongation of the SNRT; on the contrary, changes in neurohumoral tone may result in shorter SNRTs. In patients with sinus node disease, faster pacing rates may result in marked prolongation of the SNRT.

Pacing durations beyond 15 seconds usually have little effect on the SNRT in *healthy* subjects. Patients with sinus node disease may have marked suppression after longer pacing durations. It is best to perform multiple SNRTs at multiple paced cycle lengths, and to use pacing durations of 1 to 2 minutes in some of these trials.

Sinus Node Recovery Time

Normally, the SNRT is less than 1,500 ms, with a scatter on multiple tests of less than 250 ms. SNRTs tend to be shorter with shorter sinus cycle lengths, and therefore a variety of “corrections” have been introduced. Values derived from such tests are then called the SNRTC or CSNRT.

$$\text{CSNRT} = \text{SNRT} - \text{sinus cycle length}$$

This is the most common correction. Normal values have been reported from 350 to 550 ms, with 500 ms being most commonly used.

$$\text{CSNRT} = \text{X\% of sinus cycle length}$$

P>Normal values range up to 160%.

$$\text{CSNRT} = 1.3\ (\text{mean sinus cycle length in ms}) + 101\ \text{ms}$$

Beware of the use of corrections at slow sinus rates because results can be absurd. For example, a patient with symptomatic bradycardia at 1,400-ms cycle length and an SNRT of 1,800 ms = CSNRT 400 ms with the first method. In this case, the abnormal uncorrected SNRT of 1,800 is more accurate; in fact, one does not need an SNRT to make the clinical diagnosis.

Recovery Beats (Total Recovery Time)

After the SNRT, the pattern of subsequent beats returning to the basic sinus cycle length should also be analyzed. A variety of such patterns exist. One helpful measure is the total recovery time (i.e., how long it takes to return to the basic sinus cycle length) (14,15,56,60).

Secondary Pauses

Secondary pauses are identified when there is an initial shortening of the cycle length after the SNRT, followed by an unexpected lengthening of the cycle length (44). In some instances, this is a sign of sinus node disease. In others, it can be a normal reflex following hypotension induced by pacing at rapid rates, or in response to pressure overshoot in the first recovery beat because of the prolonged filling time.

Overview of Sinus Node Recovery Time

The previous discussion should make it clear that a phrase such as “the SNRT was normal” is too simplistic. The number provided for “the” SNRT is most often the maximum or longest SNRT of several runs. Others may report the average SNRT. Sometimes, only a single SNRT is done as part of a superficial study. A full interpretation requires all the information from several runs at different paced rates, together with data from subsequent beats. The sensitivity of a *single* SNRT is approximately 35% in patients with sinus node disease. This rises to greater than 85% when multiple SNRTs at different rates are recorded, along with scatter and total recovery time, with a specificity of greater than 90%.

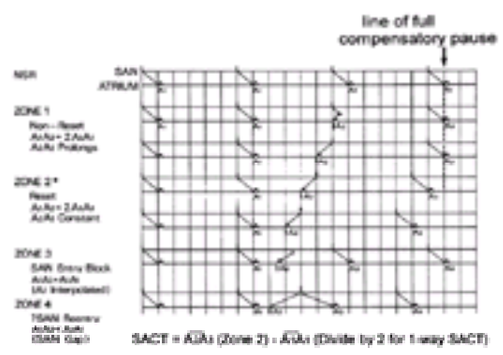
Sinoatrial Conduction Time

Direct Recordings

The sinus node atrial depolarization can be recorded directly in some patients, using high-gain unfiltered electrograms (54,55,61,62,63,64,65 and 66). Signal-averaging techniques have also been used to measure the sinoatrial conduction time (SACT) noninvasively (67).

Strauss Technique

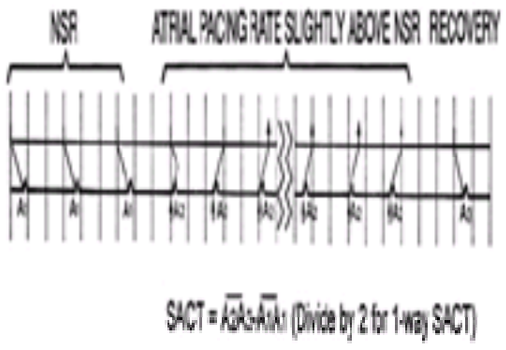
The Strauss technique (15,39,41,49,51,52,53,54 and 55,59,65,68,69,70,71 and 72) uses the extrastimulus technique to assess SACT (eFig. 62.0.3). Baseline sinus beats are designated A_1. The premature beats (A_2) are delivered after every eighth A_1, and the timing of the recovery beat (A_3) is measured. Very long A_1–A_2 intervals generally do not affect the timing of the A_3 (i.e., A_1–A_3 = 2 A_1–A_1, a complete compensatory pause, designated *zone 1*). Shorter A_1–A_2 intervals result in penetration of the sinus node with resetting so that the resulting pause is less than compensatory. This is termed *zone 2*, and the SACT is calculated as the mean of several zone 2 A_2–A_3 intervals minus the corresponding mean of A_1–A_1 intervals (SACT = A_2–A_3 – A_1–A_1). This value is often divided by 2 to estimate the one-way SACT, although it is understood that conduction times into and out of the sinoatrial node may be different. The upper limit of normal (one-way) is approximately 145 ms. Reducing the A_1–A_2 interval further finally results in peculiar responses indicating sinus node entry block (zone 3) or reentry (zone 4). This technique had been anticipated in analyses of ECGs (73) and earlier clinical electrophysiologic studies (74).



***e*FIGURE 62.0.3** Sinoatrial conduction time (SACT): Strauss method. See text. The sinoatrial node (SAN) depolarizes unseen and results ultimately in atrial depolarization, designated here as A_1. Premature atrial beats (A_2) are introduced with increasing prematurity, and the timing of the return cycle (A_3) is analyzed. The dashed line near the right of the figure indicates the line of complete compensatory pause. The SACT is calculated from zone 2 responses. NSR, normal sinus rhythm. [From Fisher JD. *Primer of cardiac electrophysiology*. Armonk, NY: Futura (*in press*); modified from Fisher JD. Role of electrophysiologic testing in the diagnosis and treatment of patients with known and suspected bradycardias and tachycardias. *Prog Cardiovasc Dis* 1981;24:25, with permission.]

Narula Method

The Narula method (75) for measuring the SACT is simpler. This assumes that pacing the atrium at rates of 10 beats/min or less above the sinus rate will not result in significant overdrive suppression of the sinus node, but that the pacing beats will gradually penetrate and reset the sinus node (*e*Fig. 62.0.4). The calculation of the SACT is the same as for the Strauss method.



***e*FIGURE 62.0.4** Sinoatrial conduction time (SACT) by Narula method. As in the previous illustration, the sinoatrial node depolarizes unseen and ultimately results in atrial depolarization (A_1). Instead of premature beats, atrial pacing at a rate slightly above that of the sinus rate is used as A_2. It is assumed that such atrial pacing will depolarize the sinus node without significant overdrive suppression. The SACT is then calculated using the same formula as the Strauss method. NSR, normal sinus rhythm. [From Fisher JD. *Primer of cardiac electrophysiology*. Armonk, NY: Futura (*in press*); modified from Fisher JD. Role of electrophysiologic testing in the diagnosis and treatment of patients with known and suspected bradycardias and tachycardias. *Prog Cardiovasc Dis* 1981;24:25, with permission.]

Kirkorian-Touboul Method

Kirkorian, Touboul, and their colleagues (76) developed a method designed to determine the SACT independently of baseline sinus cycle length, which can normally be somewhat variable. It is less widely used than the other methods.

Comments on Sinoatrial Conduction Time Methods

The Strauss method is useful as part of an overall EPS when information is also sought on conduction system refractoriness or possible dual or accessory pathways during sinus rhythm. The Narula method is the quickest and easiest to perform, but gives only the SACT. The Kirkorian-Touboul method may have several advantages, but has not yet reached the level of use of the other methods.

The SACT appears to be *directly* related to sinus cycle length (55,65), and the sinoatrial node refractory period is *directly* related to drive cycle length (76).

Autonomic Effects and Manipulations (Intrinsic Heart Rate)

The sinus node is the archetype of the automatic rhythm, but it is subject to a wide variety of neurohumoral influences. To eliminate these, chemical denervation of the sinus node on a temporary basis can be achieved by injection of 0.2 mg per kg of propranolol (or 0.22 mg per kg of atenolol) in divided doses followed by 0.04 mg per kg of atropine (38,49,52,54,77,78). The normal intrinsic heart rate is age related, according to the formula: intrinsic heart rate = 118.1 – (0.57 × age); normal values are ±14% for age less than 45, and ±18% for age greater than 45.

Testing of SNRTs and SACT may yield improved results after autonomic blockade (36,49,51,52,54).

Atrioventricular Conduction and Refractoriness

Impulses traveling from the atrium to the ventricle must traverse the atrium, AV node, bundle of His, and bundle branches (His-Purkinje system). The AV node and the His-Purkinje system are considered separately. The discussion of the sinus node touched briefly on the concepts of conduction and refractoriness. These concepts require further attention for understanding of impulse propagation from atrium to ventricle.

Conduction and Refractory Periods

Capture of the heart by a pacer stimulus and propagation of the wavefront to other points can be assessed using tests of conduction and of refractoriness (7,79,80,81,82,83,84,85,86,87,88 and 89). Conduction is assessed by observing the propagation of wavefronts during pacing at progressively incremental rates (decremental cycle lengths). Refractoriness is tested by pacing at designated cycle lengths followed by introduction of increasingly premature extrastimuli. Results from the two methods are closely correlated, but not interchangeable. For example, with incremental pacing, block usually occurs at the AV node level, whereas the extrastimulus method may result in block at any of several different levels or noncapture at the site of stimulation.

Conduction

Rate incremental pacing is delivered to a selected site in the heart, and propagation to a selected distal point is assessed. During tests of conduction, it is usual for capture to be maintained at the site of stimulation and block to occur at a distal point (7,81). As an example, stimulation of the HRA may be used for assessment of AV conduction. The stimulated wavefront traverses the right atrium, passes through the AV node, the bundle of His, and the bundle branches. As the pacing rate increases, there is normally a slight increase in the intraatrial conduction time, a progressive increase in the AV node conduction time (the AH interval), and little change in the HV interval, with block usually at the AV node level.

The following examples continue with the model of HRA pacing in the assessment of AV conduction.

Stepwise Rate Incremental (Cycle Length Decremental) Pacing (Straight Pacing)

Pacing is delivered to the HRA at a constant rate. The ability of tissue to conduct is affected by the baseline rate or cycle length of the preceding beats. Therefore, the initial stimuli at any given rate may produce different effects from those observed several seconds later. This is called the *period of accommodation* (90) and may last up to 45 seconds, although 10 seconds is usually sufficient. For clinical testing, 15 seconds at any given rate is the minimum time at which intervals should be analyzed; 45 to 60 seconds is preferable, and mandatory if intervals have not stabilized by 15 seconds.

The stepwise, straight pacing method can be used simultaneously for the assessment of SNRTs as described earlier.

During straight atrial pacing at a constant rate, look for block at the HV level at a point at which the AH interval is not prolonging at that paced rate (i.e., before the development of AV nodal Wenckebach). This is an abnormal finding, except in some children and adults with very short AH intervals or others able to conduct through the AV node at higher rates than usual.

There are disadvantages to the straight pacing method. The prolonged pacing required at each rate is time consuming. Rapid pacing may provoke sensations or hypotension in patients who produce neurohumoral responses that can alter results.

Rate Incremental Ramp Pacing

Ramps for assessment of conduction are often an attractive alternative to the stepwise method (7,87,88 and 89). The pacing rate is slowly increased at 2 to 4 beats/min per second until block occurs. This method avoids prolonged rapid pacing and is particularly suitable when multiple assessments of conduction are planned (e.g., after therapeutic interventions) and in the assessment of retrograde conduction. Because each successive paced interval differs from its predecessor by only a few milliseconds, the interval at which block occurs can be determined more precisely using the ramp method.

Comparative studies of the ramp and stepwise incremental pacing methods in assessment of anterograde and retrograde conduction have shown them to be comparable (7,87,89).

Conduction Periods

At pacing rates below those causing conduction block, there is a 1:1 relationship between stimulus and response at a distant site. Conduction time may be prolonged, so that the stimulus to response time is prolonged. For symmetry with the terminology used for refractory period testing, the comparable terminology has sometimes been used (81).

Refractory Periods

Refractory periods are determined by assessing the effects of extrastimuli (S_2, S_3, S_N) delivered decrementally after a series of spontaneous or paced beats (S_1). Many variables are considered in the assessment of refractory periods. These include the stimulus amplitude and the drive rate or cycle length. Longer cycle lengths are generally associated with longer refractory periods, but refractory periods of different parts of the conducting system do not respond comparably with changes in drive cycle lengths (15,79,91).

1. The *relative refractory period* is the drive to extrastimulus interval (S_1–S_2) that produces slowing in conduction (an increase in stimulus to distal response time). Conduction is slowed when a wavefront encounters tissue that is not completely repolarized.
2. In the *absolute refractory period* the tissue cannot be depolarized, even by an extrastimulus of great amplitude.
3. The *effective refractory period* (ERP) is the longest S_1–S_2 at a *designated stimulus amplitude* (usually two to four times diastolic threshold) that fails to capture.
4. The *functional refractory period* (FRP) is the shortest interval at which a specified (usually distal) site can be depolarized by any S_1–S_2 interval.

It is helpful to think of the ERP as a stimulus-to-stimulus measurement, and the FRP as a response-to-response measurement (91).

The anterograde ERP and FRP of the AV conduction system are defined in the following ways:

1. Atrial ERP is the longest S_1–S_2 interval that fails to achieve atrial capture.
2. Atrial FRP is the shortest A_1–A_2 interval recorded at a designated site (often the bundle of His region) before failure of S_1–S_2 to capture the atrium.
3. AV node ERP is the longest A_1–A_2 not propagating to the bundle of His. Although often based on HRA stimulation, the A_1–A_2 *should* be measured at the His region to avoid the confounding effects of changes in atrial conduction times.
4. AV node FRP is the shortest H_1–H_2 in response to any A_1–A_2. Patterns of AV nodal conduction and refractoriness are often complex (91), based on Wit et al. (82).
5. His-Purkinje System ERP is the longest H_1–H_2 not propagating to the ventricles.
6. His-Purkinje System FRP is the shortest V_1–V_2 interval before reaching the ERP of the His-Purkinje system.
7. Bundle branch ERP and FRP are as for the His-Purkinje system, but based on production of right or left bundle branch block or fascicular block.

It is important to note that atrial conduction may materially affect determination of refractory periods. Note that *refractory periods should not be timed from the site of stimulation, but from the point in the conduction cascade that is being assessed*. For example, if the HRA is stimulated in a patient with a left lateral Kent bundle, an early extrastimulus may encounter the relative refractory period of the atrium, so that intraatrial conduction time is prolonged. Thus, the timing of the S_1–S_2 stimuli in the HRA would be shorter than the timing of the propagated impulse when it arrives at the region of the Kent bundle as the local A_1–A_2 interval.

Limitations of Tests of Conduction and Refractoriness

It is *unusual* to be able to collect a complete set of numbers (81,82,83,84 and 85). With conduction testing, block most commonly occurs at the AV node level. With refractory period testing, the ERP of the atrium is often longer than the ERP of the AV node so that one encounters atrial refractoriness before AV nodal refractoriness, obviating the possibility of assessing the latter (81,82,83,84 and 85).

An atrial stimulus cannot be used to test the His-Purkinje system if the impulse is blocked at the AV node level. This is a limitation that applies to the majority of patients undergoing either conduction or refractory period testing. One implication is that patients whose His-Purkinje system conduction periods or refractory periods *can* be tested are unusual, and therefore the data may be suspect. This should be kept in mind when reading literature or protocols that involve reporting of refractory periods at various levels of the conduction system.

It is possible to assess anterograde conduction and refractoriness distal to the AV node by direct pacing of the bundle of His (92,93). This is not part of the routine EPS evaluation, however, and is reserved for instances when the information is particularly desired.

Atrium

Passive Recordings

During normal sinus rhythm, earliest atrial depolarization occurs in the region of the sinus node at the junction of the superior vena cava and the high lateral right atrium (18,21,94,95,96,97,98,99,100,101,102,103,104,105,106,107 and 108). Normal *intraatrial* conduction (PA interval) and *interatrial* conduction intervals appear in eTable 62.0.2.

Histologically distinct pathways comparable with bundle branches do not occur in the atrium. The “internodal pathways” are physiologic manifestations related to fiber orientation and thickness (94,95,96 and 97). Intraatrial conduction may be slow, but block rarely occurs (100,103,104 and 105).

Rate Incremental Atrial Pacing (Stepwise or Ramp)

The PA interval may prolong gradually, as does the interatrial conduction time (eTable 62.0.2). It is usually possible to maintain 1:1 capture with incremental pacing techniques to 250 to 300 beats/min. At such pacing rates, precipitation of atrial fibrillation is not rare and is not necessarily an abnormal response. Pacing threshold normally tends to increase at faster rates (21).

Extrastimulus Testing

This technique is used for assessment of atrial refractory periods and for induction of arrhythmias. As with incremental pacing, there is prolongation of intraatrial and interatrial conduction, which is more pronounced in patients with a history of atrial arrhythmias (19,101,102). Development of a fractionated atrial electrogram is more often seen in patients who have a history of atrial fibrillation (101,102,107,108). Intraatrial blocks in response to extrastimuli are unusual (103).

Occasionally, double or triple extrastimuli induce atrial fibrillation in patients with no history of atrial rhythm disorders. Such episodes usually terminate spontaneously and are not clinically relevant in the absence of a history of known or suspected atrial arrhythmias.

Autonomic and Pharmacologic Effects

Vagal tone and medications such as adenosine and edrophonium may slow the sinus rate, but they tend to shorten the refractory period of the atrium. This makes the atrium more vulnerable to induction of atrial fibrillation. Patients with vagal-dependent atrial fibrillation typically have episodes during sleep and the condition may be

worsened by the vagotonic effects of digitalis therapy.

Atrioventricular Junction

The *AV junction* is not synonymous with the *AV node*. The junction is defined as that portion of the conduction system from the proximal portion of the AV node to the distal portion of the bundle of His before its bifurcation.

Junctional Recovery Times

Some individuals have what appears to be a stable junctional rhythm in the absence of a conducted atrial rhythm (109). If these patients are asymptomatic, the question of the need for pacing arises, and the junctional recovery time (JRT) (analogous to the SNRT) helps in the assessment. Following atrial or ventricular pacing, a corrected JRT (CJRT = JRT – basic cycle length) of 200 ms or less, either in the baseline state or after 2.0 to 2.5 mg of atropine, is typical in asymptomatic patients with junctional pacemakers located *either* in the AV node or the bundle of His. Patients with longer CJRTs, if symptomatic, may require pacing.

Atrioventricular Node

Normal ranges for the AH interval, which reflects AV nodal conduction times, are shown in eTable 62.0.2. AV nodal anatomy and physiology are too complex to review here in detail (110). From a clinical electrophysiologist's viewpoint, the node has several pathways entering from the atrium, whose characteristics have been estimated by subtraction (i.e., by assessing function after catheter ablation of alternative pathways) (111,112). A *slow posterior pathway* arises near the coronary sinus ostium and proceeds anteriorly near the tricuspid annulus to the compact node. Use of this pathway is associated with slow conduction velocity (long AH and PR intervals) but ability to conduct at rapid rates in beats/min (shorter ERP and conduction limit). The *fast anterior pathway* is near to the His recording site and has properties that are the opposite of the slow pathway. There is also a presumed transseptal or left-sided input, and many variations on all of these. Within the node itself there is a network of many potential pathways that normally merge to cause synchronous input at the nodal bundle of His junction (113). It is clear that there is a wide spectrum of normal AV nodal physiology (114,115 and 116).

Rate Incremental Atrial Pacing

The AH interval normally prolongs smoothly with incremental pacing until just before block when there may be a marked increase (15) (eFig. 62.0.5) that can be graphed as a smooth curve. AV block at the AV node level occurs normally over a broad range of pacing rates, from approximately 100 to 200 beats/min (15). This range encompasses two standard deviations, but there is a continuum of possible normality that may extend somewhat below 100 beats/min or above 200 beats/min. Age is also a factor, with younger individuals often having shorter AH intervals at a given pacing rate, and Wenckebach at higher rates.

Atrioventricular Node: Extrastimulus Testing and Refractoriness

Extrastimulus testing may produce evidence of longer refractory periods at shorter pacing cycle lengths (eTable 62.0.3). However, this may hold true only for adults (80) and at relatively low pacing rates. Patterns of AH and AV curves in response to increasingly premature extrastimuli can be complex (82).

eTABLE 62.0.3 NORMAL REFRACTORY PERIODS AT VARIOUS CYCLE LENGTHS[a]

	Adults								Children (7 mo to 15 yr)							
	Effective refractory period				Functional refractory period				Effective refractory period				Functional refractory period			
	No.	Mean	SD	+2 SD	No.	Mean	SD	+2 SD	No.	Mean	SD	+2 SD	No.	Mean	SD	
CL: longest assuring atrial capture[b]																
Atrium[c]	26	236[d]	49	334	26	274[d]	47	368	40	187[d]	53	293	35	217[d]	45	
AV node	46	289[d]	44	377	45	406[d]	46	498	40	241[d]	56	353	38	345[d]	71	
RBB	5	412[d]	72	(556)	—	—	—	—	11	323[d]	39	401	—	—	—	
LBB	2	473	67	(607)	—	—	—	—	9	361	52	(465)	—	—	—	
CL: 850–600																
Atrium	28	232	80	392	28	275	49	373	10	206	80	366	6	247	53	
AV node	28	290	50	390	26	401	48	497	8	303	81	(465)	8	427	74	
RBB	4	443	42	(525)	—	—	—	—	1	390	—	—	—	—	—	
LBB	4	434	59	(552)	—	—	—	—	6	404	31	(466)	—	—	—	
CL: 599–460																
Atrium	30	232[d]	54	340	30	271[d]	49	369	37	199[d]	43	285	34	234[d]	43	
AV node	30	328[d]	56	440	29	406[d]	57	520	37	260[d]	55	370	37	354[d]	66	
RBB	6	367	28	423[d]	—	—	—	—	10	365	35	435	—	—	—	
LBB	1	365	—	—	—	—	—	—	6	370	61	(492)	—	—	—	
CL: 459–280																
Atrium	23	199[d]	28	255	23	252[d]	34	320	57	165[d]	37	239	54	200[d]	35	
AV node	16	280[d]	52	384	13	345[d]	27	399	55	219[d]	45	309	49	299[d]	46	
RBB	4	328	16	(360)	—	—	—	—	22	298	28	354	—	—	—	
LBB	0	—	—	—	—	—	—	—	12	330	34	398	—	—	—	

AV, atrioventricular; CL, cycle length (ms); LBB, left bundle branch; RBB, right bundle branch.
[a]Numbers in parentheses emphasize small sample.
[b]Longest CL assuring atrial capture: 698 ± 107 for adults, 535 ± 89 for children.
[c]Atrium, recording in bundle of His area after high right atrial stimulation.
[d]p <.05 between adult and pediatric values.
From Denes P, Wu D, Dhingra R, et al. The effects of cycle length on cardiac refractory periods in man. *Circulation* 1974;49:32; Dubrow IW, Fisher EA, Amat-Y-Leon F, et al. Comparison of cardiac refractory periods in children and adults. *Circulation* 1975;51:485, with permission.

The alternative *Rosenbleuth hypothesis* is that there is a one-step delay in a refractory barrier (117,118 and 119), and that AV nodal refractoriness actually shortens with shorter drive cycle lengths if calculations are made based not on overall conduction delay but at a single layer in the AV node.

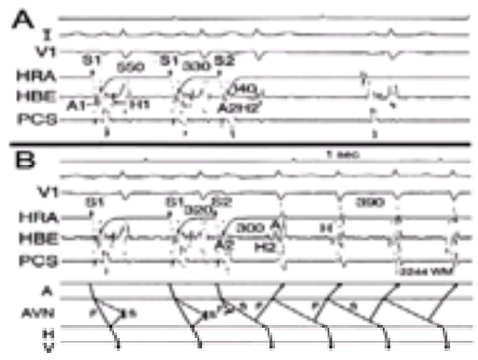
The site of atrial pacing may also affect AV nodal conduction, with shorter AH intervals associated with pacing from the coronary sinus (119,120,121,122 and 123). The AH interval is similar with high and low right atrial pacing (123,124).

Echo Beats

The AV node is not a single pipeline from the atrium to the bundle of His, but rather a network of many potential pathways, with mostly similar conduction and refractory characteristics. Even in healthy individuals, a premature beat or extrastimulus may encounter refractoriness in one pathway. Conduction in one pathway may allow recovery of the previously refractory pathway, so that it is then able to conduct in a retrograde direction. This then emerges into the atrium as an AV nodal echo beat.

Dual Atrioventricular Node Physiology

Rate incremental pacing, or the extrastimulus technique, generally results in a smooth prolongation of the AH curve. If shortening of the paced cycle length by 10 ms (14) or shortening of the S_1–S_2 extrastimulus interval by 10 ms (14,126) results in an increase of 50 ms or more in the AH interval, this is diagnostic of dual AV node pathway physiology (125) (eFig. 62.0.6). Dual pathway physiology is the hallmark of AV node reentry tachycardia, but can also be encountered in some patients with no history of such an arrhythmia. Sometimes, there will be evidence of multiple AH jumps, triple or quadruple pathway physiology.



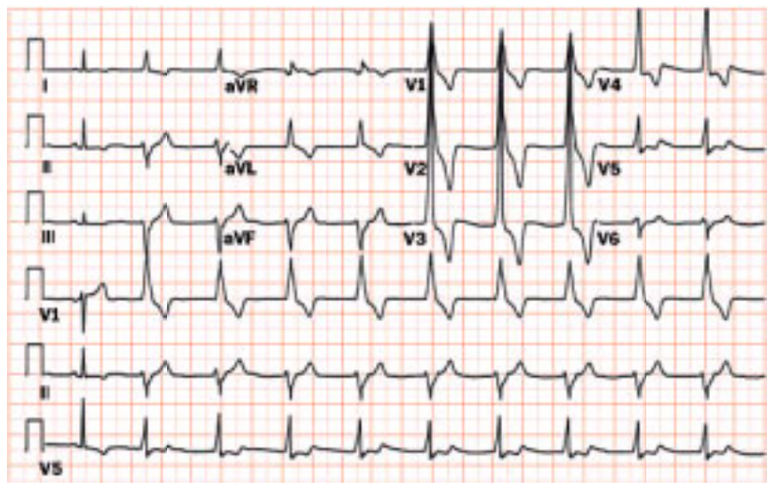
***e*FIGURE 62.0.6** Dual atrioventricular node physiology and induction of atrioventricular nodal (AVN) reentrant tachycardia. **A:** Surface leads 1 and V_1 are displayed together with tracings from the high right atrium (HRA), bundle of His electrogram (HBE), and proximal coronary sinus (PCS). During HRA pacing at a cycle length of 550 ms, an extrastimulus (S_2) is introduced at 330 ms. This produces an A_2–H_2 interval of 140 ms. **B:** When the S_1–S_2 interval is reduced from 330 to 320 ms, the A_2–H_2 "jumps" to 300 ms, indicating the effective refractory period of the fast pathway, and engagement of the slow pathway, initiating AVNRT. This is also shown on the ladder diagram at the bottom, where *F* is fast pathway and *S* is slow pathway.

Atrioventricular Node Responses to Exercise versus Pacing

The PR and AH intervals change little in response to exercise and may in fact decrease somewhat due to a decrease in parasympathetic tone and increase in circulating catecholamines. With incremental atrial pacing in a recumbent patient, autonomic tone is changed only indirectly in response to factors such as anxiety or hypotension. The AH interval, therefore, prolongs markedly with atrial pacing (eFig. 62.0.5), and this is normal.

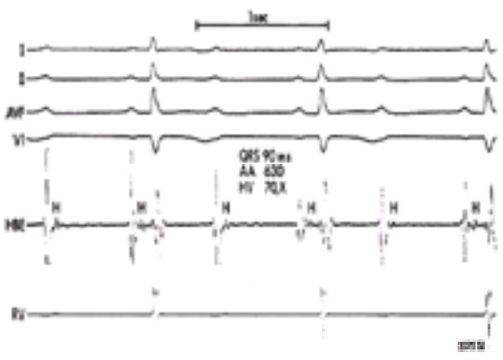
His-Purkinje System (Infranodal Conduction, HV Interval)

Measurement of the HV interval has been discussed in Baseline Intervals and elsewhere in this chapter. Complete heart block at the HV level leaves the patient with an idioventricular rhythm. This may be slow enough to cause syncope or worse. Block at the infranodal HV level is an important diagnosis to make in a patient with unexplained syncope or heart block at a previously undetermined level (3).

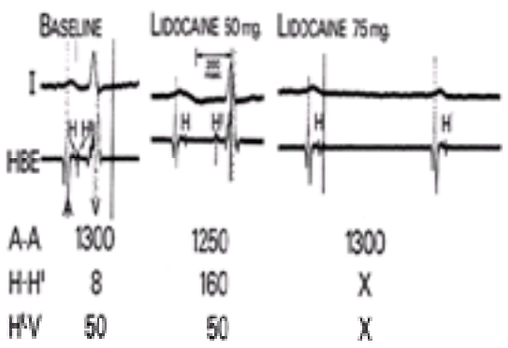


Idioventricular rhythm. Note wide complex QRS with absence of P waves and slow ventricular rate.

Beware the conventional rule of thumb that AV block in the presence of a narrow QRS implies disease at the AV node level, and block in patients with a wide QRS complex or bundle branch block implies that the block is at the His-Purkinje level. The rule of thumb is approximately 85% accurate. It may not matter if one does not pace a patient with a wide QRS who has block at the AV node level (127), but it may be quite important if one does not pace a patient with block at the HV level because the QRS complex is narrow (128). The latter situation can occur with intra-Hisian block or with balanced first-degree bundle branch block (127,128 and 129) (eFig. 62.0.7 and eFig. 62.0.8).



***e*FIGURE 62.0.7** HV block in a patient with a narrow QRS interval. There is 2:1 HV block, with conducted HV intervals prolonged at 70 ms. The prolonged HV interval together with a narrow QRS may indicate balanced bilateral 1-degree HV block (see eFig. 62.0.8). HBE, bundle of His electrogram; RV, right ventricle.



***e*FIGURE 62.0.8** Intra-Hisian block confirmed with lidocaine. Elderly woman with recurrent syncope and a normal 12-lead electrocardiogram. Brief periods of complete heart block were documented, but without accompanying symptoms. The baseline bundle of His electrogram (HBE) revealed a multiphasic or ragged bundle of His potential. After administration of 50 mg of lidocaine (*middle panel*), there was little change in the heart rate, but the multiphasic bundle of His potential split into two deflections labeled *H* and H^1. After an additional 25 mg of lidocaine, there was complete atrioventricular block following the proximal component of the bundle of His potential. (From Fisher JD. Role of electrophysiologic testing in the diagnosis and treatment of patients with known and suspected bradycardias and tachycardias. *Prog Cardiovasc Dis* 1981;24:25, with permission.)

Incremental Atrial Pacing and Conduction Analysis

The HV interval normally remains constant at all paced rates (eTable 62.0.2). HV block that occurs unexpectedly during straight pacing at a rate not producing AV node Wenckebach is usually abnormal (130) and may be grounds for implantation of a permanent pacemaker (131). HV block and bundle branch block can be observed or induced by myriad mechanisms (14,126), summarized in the previous and following sections. The physician must differentiate abnormal from physiologic responses.

Programmed Extrastimuli and Refractory Periods

The HV interval usually remains constant with increasingly premature extrastimuli, because the refractory period of the AV node is usually longer than that of the His-Purkinje system. However, with closely coupled extrastimuli that are conducted through the AV node, refractoriness may be encountered in the bundle of His or the right or left bundle branch. In such cases, determination of the ERP and FRP of these structures is possible. At times, extrastimulus testing produces block that disappears with further prematurity of the extrastimuli. This “gap phenomenon” is discussed in a later section (see Gap Phenomenon).

Pharmacologic Agents

Lidocaine (132,133), procainamide (133,134 and 135), and ajmaline (136,137) have all been used as pharmacologic stresses to the His-Purkinje system. Typical doses of lidocaine (75-mg bolus given twice at 30- to 45-second intervals) produce little alteration of the HV interval. Block within or below the His is an abnormal finding (eFig. 62.0.8). Procainamide (133,134 and 135) 10 mg per kg over 15 to 20 minutes can normally prolong the HV interval by up to 30%. Prolongation beyond that point and block in response to pacing are abnormal responses. HV block in response to lidocaine or procainamide is unusual in patients without suspected conduction disease, or even in patients with bifascicular block who do not have a history of AV block or unexplained syncope (132,133,134 and 135).

Clinical Significance of the HV Interval

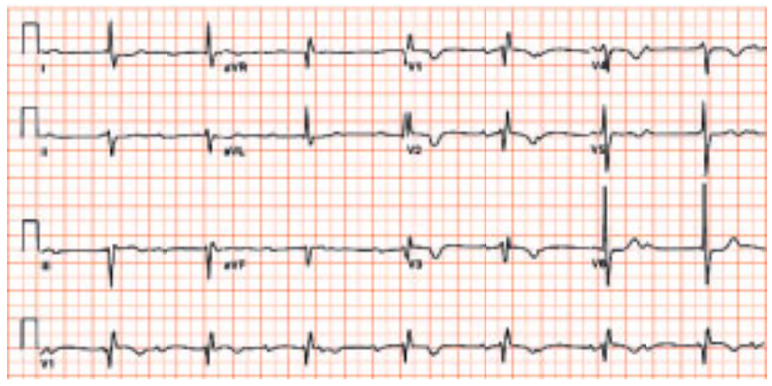
After two decades, this has remained a matter of lively dispute (138,139,140,141,142,143 and 144). Asymptomatic patients with prolonged HV intervals may enjoy a favorable prognosis, although pacing is usually recommended for HV intervals longer than 100 ms (131). In patients with unexplained syncope and no abnormal findings other than an HV interval between 60 and 100 ms, there is a broad range of opinion regarding whether syncope should be attributed to probably intermittent HV block. Analysis is complicated by the fact that many patients with syncope may have had several other plausible causes for syncope. In addition, the HV interval may normally be longer in patients with left branch bundle block (145), due to the longer course of the right branch bundle before ventricular insertion. Bundle of His pacing may be able to differentiate proximal from peripheral left branch bundle block (146,147), which may have different prognostic implications.

Catheter Bumping

The right bundle is particularly vulnerable to block due to mild trauma from the bundle of His recording catheter. This can produce a right branch bundle block pattern or (in patients with left branch bundle block) marked prolongation of the HV interval or even complete block at the HV level. Such blocks are almost always transient.

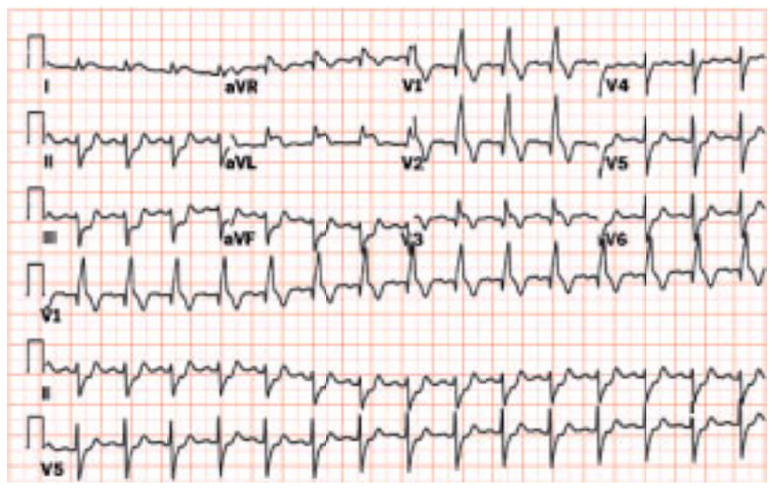
Conduction System in Acute Myocardial Infarction

High-degree AV block, new bundle branch block, and a prolonged HV interval are all associated with an unfavorable prognosis (148,149,150,151,152 and 153). Many such patients succumb to tachyarrhythmias or pump failure rather than AV block, so that the role of permanent pacing remains uncertain, unless the patient has had transient or sustained complete heart block associated with bifascicular or trifascicular disease (131,150). EPS performed during the course of hospitalization for acute myocardial infarction often reveals disease that is more widespread or even in a different location than suggested by the ECG (153,154). Serial changes in the HV interval during the course of hospitalization for an acute infarction suggest that the outcome is more favorable for when initially prolonged HV intervals subsequently normalize (151). These studies, together with prospective trials such as the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT), underscore the value of EPS for risk stratification in high-risk postinfarction patients.



An 83-year-old patient with complete heart block, junctional escape rhythm, left anterior hemiblock, and complete right bundle branch block.

Trifascicular block. Note right bundle branch block, left anterior hemiblock, and associated first-degree atrioventricular block.



Acute anterolateral myocardial infarction complicated by conduction disturbance. ST-segment elevation in the anterior precordial leads as well as leads I

and aVL is associated with right bundle branch block and left anterior hemiblock.

Retrograde Conduction (Ventriculoatrial Conduction)

Absence of ventriculoatrial (VA) conduction at any paced rate is both common and normal (155,156,157,158,159 and 160). When present, normal VA conduction uses the normal AV conduction system, with the first atrial depolarization usually in the septal region in proximity to the AV node. In some instances, the slow posterior pathway is preferentially engaged so that first atrial depolarization is somewhat posterior to the AV node.

With rate incremental ventricular pacing or with ventricular extrastimulus testing, the VA interval prolongs smoothly in a manner analogous to that for AV conduction. Dual physiology can be diagnosed in the VA direction in some patients.

To rule out an (nondecremental) accessory pathway, the extrastimulus technique is usually more effective than rate incremental ventricular pacing at demonstrating normal prolongation of the VA interval. If uncertainty continues to exist, adenosine can be extremely helpful. This drug is much more likely to block AV nodal conduction than an accessory pathway.

Retrograde conduction of ventricular extrastimuli can be affected by the baseline sequence of cardiac activation (e.g., sinus rhythm vs. AV pacing with a short AV interval, vs. ventricular pacing) (157).

Multilevel Disease

Many patients with heart disease have prolongation at multiple levels in the conduction system (100,103,104 and 105,161,162 and 163). It is not rare to see prolongations of the PA, AH, and HV intervals. Conversely, some patients with sick sinus syndrome have impaired AV conduction. Before permanent atrial pacing is used for such patients, the physician should be satisfied that there is no significant conduction system disease.

Ventricles

Ventricular stimulation is used to assess retrograde (VA) conduction and refractory periods, to assess retrograde activation patterns including sequences that may indicate an accessory pathway, and in the assessment of vulnerability to inducible ventricular arrhythmias. Details of ventricular stimulation for specific arrhythmias are provided in other chapters. What follows is a more general discussion of ventricular stimulation protocols, supplementing the information presented earlier in this chapter.

Rate Incremental Ventricular Pacing

Straight/stepwise incremental pacing or ramp pacing increasing at 2 to 4 beats/min per second are used in the assessment of retrograde conduction (7). It is unusual to provoke arrhythmias with these tests, even in patients with known ventricular arrhythmia (7,9,164).

Burst Pacing

Again, rate-incremental stimuli are delivered during sinus or other baseline rhythm (9,164,165). The protocol is more aggressive than that used for assessment of retrograde conduction. A typical example would include stimuli resulting in 10 to 15 captures beginning at 150 beats/min (400 ms) with repeated bursts in incremental steps of 25 beats/min until a specified upper rate (commonly 300 beats/min per 200 ms) is achieved, or 1:1 capture is lost

(Steep) Ramp Pacing

In contrast to ramps used for assessment of conduction, this is a steep ramp somewhat analogous to the burst technique just described (9,164,165). Stimuli resulting in 10 to 20 captures are delivered initially at a rate range beginning at 150 beats/min and ramping up quickly to 200 beats/min (400 to 300 ms); repeat ramps are delivered to incremental maximum rates in steps, again with a typical upper limit of 300 beats/min or 200 ms, or failure to maintain 1:1 capture. Because myocardial refractoriness is set by the prior interstimulus interval, it is usually possible to capture at faster rates with the ramp technique than with bursts.

Extrastimulus Technique or Programmed Electrical Stimulation

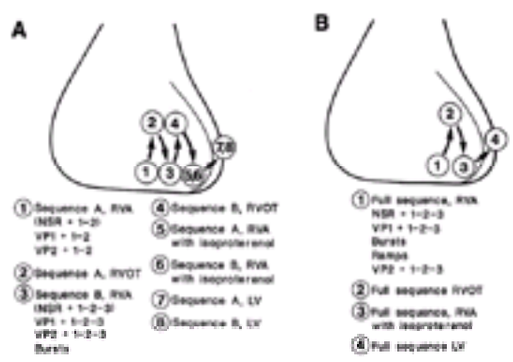
Refractory Periods

The extrastimulus technique or programmed electrical stimulation is used for establishment of refractory periods as described earlier. In the ventricle, the ERP is the longest S_1–S_2 interval that fails to capture. The FRP is dependent on investigator definitions of the site at which the resulting wavefront is measured. The FRP is the shortest coupling interval between depolarizations arriving at the designated site in response to any S_1–S_2 interval.

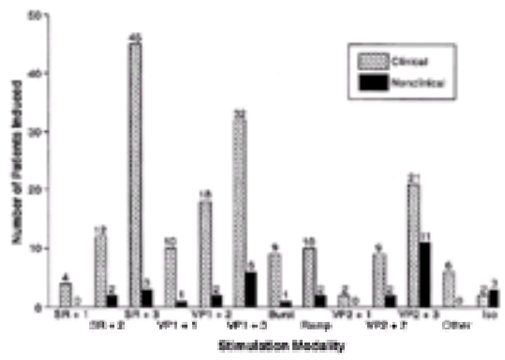
In the study of ventricular arrhythmias (and this applies to atrial stimulation protocols as well), double and triple extrastimuli are often delivered. The refractory periods in response to double and triple extrastimuli must be described in somewhat altered terminology (166). For example, the ERP is usually described as the longest S_1–S_2 interval that *fails* to capture. If extrastimuli are given in 10-ms decrements, the shortest S_1–S_2 interval that does capture is thus only 10 ms longer than the classical ERP. If one is to measure refractory periods of the second and third extrastimulus (S_3 and S_4), then S_1 must continue to capture. Therefore, the terminology is slightly adjusted, with the ERPs being the shortest S_1–S_2, S_2–S_3, and S_3–S_4 intervals that do capture.

Standard Protocols

There is no universally accepted standard protocol, but rather an agreement that an acceptable protocol should meet minimum standards, such as those established by the North American Society of Pacing and Electrophysiology (12) (*e*Fig. 62.0.9 and *e*Fig. 62.0.10). Major variations are the tandem versus simple sequential method (8,9) of delivering sequential extrastimuli and the sequence for delivery of single, double, and triple extrastimuli (*e*Fig. 62.0.9) (8,164,166). Comparative studies of these methods have shown the results to be comparable (8,9).



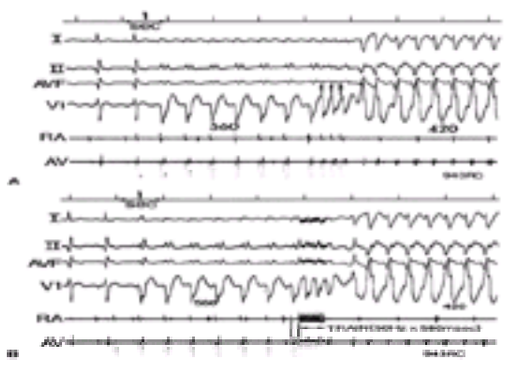
***e*FIGURE 62.0.9** Stimulation sequences. **A:** A complex sequence intended to minimize induction of nonclinical arrhythmias by completing double extrastimuli during sinus rhythm and two ventricular paced rates [normal sinus rhythm (NSR) + 1–2, VP1 and VP2 + 1–2] at the right ventricular apex (RVA) and outflow tract (RVOT) before moving to triple extrastimuli. Some variations complete single extrastimuli at the RVA and RVOT before moving to doubles; very conservative and very time-consuming. **B:** A simpler, but still effective, sequence. LV, left ventricular. (From Fisher JD, Kim SG, Ferrick KJ, et al. Programmed electrical stimulation of the ventricle: an efficient, sensitive, and specific protocol. *PACE* 1992;15:435, with permission.)



***e*FIGURE 62.0.10** Frequency of induced clinical and nonclinical arrhythmia with each stimulating modality (protocol step) in a consecutive series of patients with inducible ventricular tachycardia. All patients received all steps. The sequence actually used is displayed on the abscissa. The ordinate indicates the percent of uses of each modality that resulted in a clinical (*hatched*) or nonclinical (*solid*) arrhythmia. Each of the bar graphs is capped by a number indicating more precisely the percent of arrhythmias induced. SR, sinus rhythm; VP1, the slower paced drive rate; VP2, the faster rate. Numbers 1, 2, and 3 indicate the number of extrastimuli. Note that SR + 3 was more efficacious than either VP1 + 2 or VP2 + 2, and that VP1 + 3 was superior to VP2 + 2. In addition to the *p* values indicated, VP2 + 3 was more likely to induce nonclinical arrhythmias than NSR + 3 or VP1 + 3 (*p* <.05). (From Artoul SG, Fisher JD, Kim SG, et al. Stimulation hierarchy: optimal sequence for double and triple extrastimuli during electrophysiological studies. *PACE* 1992;15:790, with permission.)

Ultrarapid Train Stimulation

Ultrarapid train stimulation of a duration to produce single, double, and triple captures can be used as an efficient alternative to the extrastimulus technique (11) (eFig. 62.0.11).



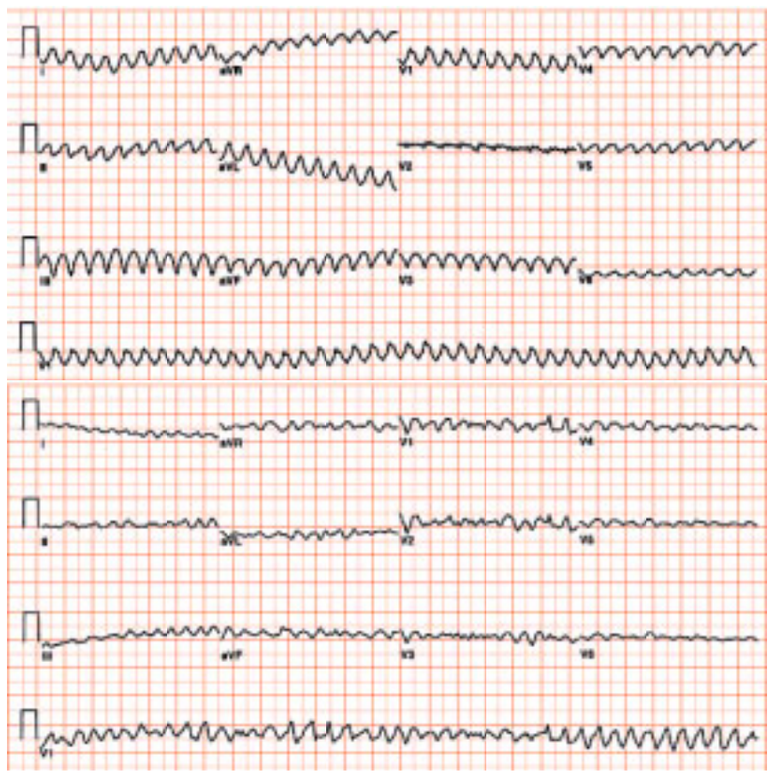
***e*FIGURE 62.0.11** Conventional programmed electrical stimulation and ultrarapid train stimulation. **A:** Surface leads I, II, AVF, and V1 are displayed together with intracardiac recordings from the right atrium (RA) and the atrioventricular junction (AV). Following two sinus beats, eight drive stimuli are delivered at a cycle length of 560 ms, resulting in seven captures. These are followed by triple programmed extrastimuli, which result in induction of ventricular tachycardia with a right bundle branch block morphology and a cycle length of 420 ms. **B:** In the same patient, after ventricular drive pacing at 560 ms, 50 Hz (20 ms) trains produce three captures and ventricular tachycardia of the same morphology and rate produced by conventional programmed electrical stimulation. (From Fisher JD, Platt SB, Cua MC, et al. Ultrarapid train stimulation: an efficient alternative to conventional programmed electrical stimulation for induction of ventricular arrhythmias. *J Intervent Cardiac Electrophysiol* 1997;1:15–21, with permission.)

Other Enhancements

In some patients isoproterenol, prolonged pacing to provoke ischemia, or postural changes may be helpful in producing a desired arrhythmia (see Chapter 58, Chapter 65, Chapter 66, and Chapter 72) (164,166). A variation on the more usual programmed electrical stimulation methods is the sudden change in cycle length protocol, which may enhance dispersion of refractoriness and thereby promote arrhythmia induction (164,167).

Sensitivity and Specificity

Acceptable stimulation protocols should be able to induce sustained monomorphic ventricular tachycardia in 90% of patients with coronary artery disease who present with this arrhythmia (12). Induction of other ventricular arrhythmias (ventricular fibrillation or polymorphic ventricular tachycardia) in patients with a history of such arrhythmias may be as low as 60% (14,164). Induction of sustained monomorphic ventricular tachycardia in patients without a known or suspected history of such arrhythmias is rare (164). Induction of polymorphic ventricular tachycardia or ventricular fibrillation in patients without a history of these arrhythmias may occur in up to 15% of subjects (164).



Ventricular flutter (A). Same patient with degeneration into ventricular fibrillation (B).

An 81-year-old male patient with ventricular tachycardia.

Electrophysiologic Features of Miscellaneous Diseases and Conditions

Mitral Valve Prolapse

Mitral valve prolapse is associated with a variety of sinus node, atrial, and ventricular arrhythmias, the last being sometimes attributable to stressing of the papillary muscles (167,168 and 169). There is a tendency toward cardiac hyperreflexia including neurocardiogenic syncope.

Aortic Valve Disease

AV block may occur, typically at the AV node level in aortic regurgitation and at the His-Purkinje level with aortic stenosis (169,170 and 171).

Congestive Cardiomyopathy

Prolongation of the HV interval is common (172,173 and 174). Conduction disease does not correlate with the degree of ventricular enlargement or end diastolic pressure. Atrial arrhythmias and fatal ventricular arrhythmias are not rare. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is a multicenter randomized clinical trial designed to determine whether antiarrhythmic treatment (ICD or amiodarone) is better than placebo.

Hypertrophic Cardiomyopathy

Prolongation of the HV interval is common, and block at that level is not rare. Atrial arrhythmias and fatal ventricular arrhythmias are not rare (175,176,177 and 178).

Infiltrative Cardiomyopathy

In sarcoidosis, amyloidosis, hemochromatosis, and microfibrillar cardiomyopathy, atrial and ventricular tachycardias, sinus node disease, and AV block occur all too commonly (179,180 and 181). Recently described microfibrillar cardiomyopathy (181) is associated with atrial or ventricular arrhythmias, but preservation of ventricular function occurs and it has a prognosis that appears to be more benign than the other conditions.

Collagen Vascular Diseases

Arrhythmias and block may occur and are an adverse prognostic sign (182,183 and 184). Congenital complete heart block is common in offspring of mothers with connective tissue diseases.

Infectious Processes

Viral myocarditis may be associated with ventricular arrhythmias, either acutely or as a result of the subsequent development of dilated cardiomyopathy (185,186 and 187). Varicella myocarditis is associated with malignant ventricular arrhythmias and has a poor prognosis. Bacterial infections may result in heart block. In South America, Chagas' disease is a common cause of heart block and tachycardias (188).

Thyroid Disease

Thyrotoxicosis has been associated with sudden death, ventricular arrhythmias, heart block, and myocardial infarction (189,190). Hyperthyroidism has been reported to cause AV block, but facilitation of AV conduction and sinus tachycardias are more common. Hypothyroidism may cause AV block at the AV node and His-Purkinje levels, and there is prolongation of myocardial action potentials.

Other Phenomena

Phase 3 Block

Phase 3 block (tachycardia-dependent block) (79,80,191,192,193 and 194) occurs when an impulse arrives at tissues that are still refractory (*e*Table 62.0.3) due to incomplete repolarization. Manifestations include bundle branch block and fascicular block as well as complete AV block.

Phase 4 Block

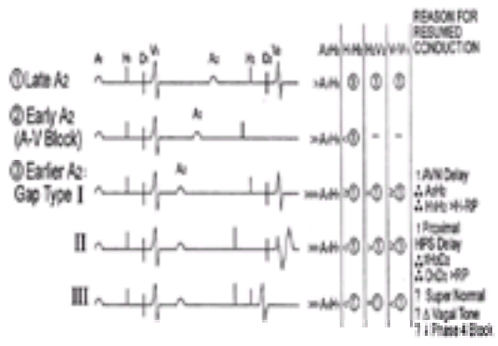
Phase 4 block (bradycardia-dependent block) (79,80,191,192,193,194,195 and 196) occurs when conduction of an impulse is blocked in tissues that are well beyond their normal refractory periods.

Distal Gate and Bundle Branch Reentry

The longest refractory periods in the His-Purkinje system are found most distally, at or near the Purkinje-myocardial junction (197,198). This creates a distal gate that inhibits retroconduction of early ventricular extrasystoles. Thus, when early extrastimuli are delivered to the right ventricular apex, the nearby distal gates of the right bundle branch may still be refractory, preventing retroconduction. However, the impulse may propagate to the left ventricle, and by that time retroconduction up the left bundle branch may be possible (199). In as many as 50% of healthy individuals, the impulse propagated up the left bundle branch may then proceed in an anterograde direction through the right bundle branch to create a bundle branch reentry repetitive response (198). Such bundle branch reentries rarely last more than one or two beats in healthy individuals, but are an occasional cause of sustained tachycardia, particularly in dilated hearts (199,200).

Gap Phenomenon

Using the extrastimulus (A_2) technique in the atrium, AV block or bundle branch block may occur at a certain S_1–S_2 interval, and yet with further prematurity conduction resumes (103,201,202,203,204,205,206,207,208,209,210 and 211) (*e*Fig. 62.0.12). This gap in conduction occurs for many reasons, the most common of which are summarized in *e*Figure 62.0.12.



***e*FIGURE 62.0.12** The gap phenomenon. In line 1, a late atrial extrastimulus (A_2) conducts with prolongation of the A_2–H_2 compared with the A_1–H_1. In line 2, an earlier A_2 fails to conduct because the H_1–H_2 interval is within the effective refractory period of the bundle of His. In line 3, an earlier A_2 results in resumption of conduction due to prolongation of the A_2–H_2 interval such that the H_1–H_2 now exceeds the refractory period of the bundle of His. This is type I gap. The next line shows type II gap in which conduction resumes after delayed conduction through the His-Purkinje system (HPS). In type III gap, conduction is resumed for any of several speculative reasons. A-V, atrioventricular; AVN, atrioventricular node. (Modified from Fisher JD. Role of electrophysiologic testing in the diagnosis and treatment of patients with known and suspected bradycardias and tachycardias. *Prog Cardiovasc Dis* 1981;24:25, with permission.)

Type I gap is most common. An atrial extrastimulus conducted with modest delay through the AV node finds the bundle of His still refractory, causing block. With increasing prematurity of the atrial extrastimulus A_2, the A_2–H_2 interval prolongs further so that the H_1–H_2 interval now exceeds the refractory period of the bundle of His, and conduction resumes. The same principle applies to all levels of the atrium, the AV conduction system, and the ventricle, so that there are virtually endless possibilities for gaps in both the anterograde and retrograde directions.

The gap phenomenon is not an abnormality, but reflects the interplay between conduction velocity and refractory periods in different parts of the heart. Demonstration of the gap phenomenon can be enhanced by creating changes in neurohumoral tone or heart rate.

Supernormality

A stimulus that is precisely timed to occur immediately following repolarization may produce capture at a stimulus amplitude that fails to capture if delivered slightly earlier or later (212,213). This supernormal excitability can be seen clinically (e.g., when a failing pacemaker captures just at the end of the T wave, but not elsewhere in the cardiac cycle). Supernormality has been demonstrated in the His-Purkinje system, Bachmann's bundle in the dog, and in working myocardium of the atrium and ventricle, but not in the AV node. In a somewhat comparable fashion, supernormal *conduction* exists when a precisely timed beat results in restoration or improvement of conduction in a previously depressed or blocked area.

COMPLETE, SCREENING, AND TARGETED ELECTROPHYSIOLOGIC STUDIES

Philosophical, practical, and ethical considerations materially affect not only the decision to perform an EPS, but the thoroughness of the study itself.

Complete Diagnostic Electrophysiologic Study

The complexity and number of possible maneuvers that can be performed during an EPS make it virtually impossible to do a truly complete study. For example, one pharmacologic stress could interfere with other portions of the EPS, so that a second session would be needed to complete a thorough evaluation. In addition to the many tests and maneuvers outlined in this chapter, there are many other variations that can be applied for specific indications related to patients with known or suspected bradycardias or tachycardias (see Chapter 63, Chapter 64, Chapter 65, Chapter 66, Chapter 67, Chapter 68, Chapter 70, Chapter 71, Chapter 72, and Chapter 73). A more complete evaluation is needed when an EPS is performed for evaluation of a patient with syncope of undetermined origin, compared with an EPS performed to assess the efficacy of a drug given to prevent induction of an arrhythmia that has previously been characterized.

Ethical considerations arise on many levels: Is there a true indication for the EPS? How thorough an examination must be done before billing for a "complete diagnostic EPS"?

CONCLUSION

EPSs are appropriate and necessary for a broad range of indications (3). EPS has become indispensable not only for diagnosis and risk stratification, but for selection and assessment of therapies such as pacemakers and drugs and for interventional procedures such as radiofrequency catheter ablation. EPS is associated with low levels of risk compared with diagnostic interventional cardiac angiographic procedures.

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BRADYCARDIAS: SINUS NODAL DYSFUNCTION AND ATRIOVENTRICULAR CONDUCTION DISTURBANCES

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"Indicates text or graphics that appear only in the electronic versions of this text."

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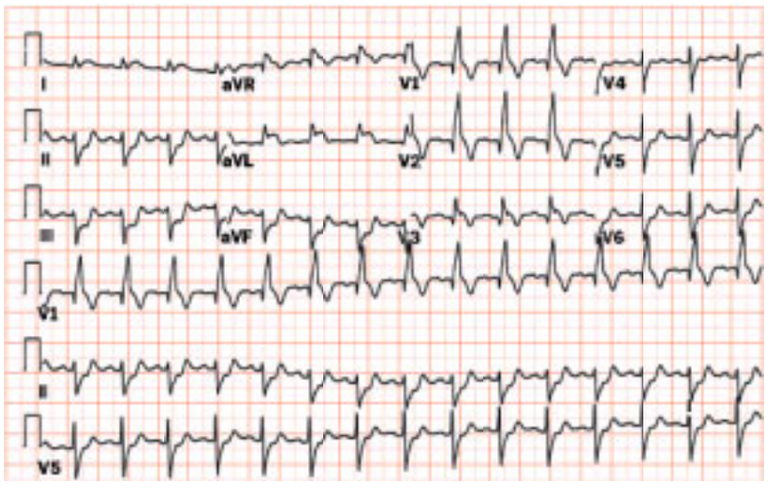
OVERVIEW

Sinus nodal dysfunction and atrioventricular (AV) block account for the majority of significant bradyarrhythmias. In addition to structural abnormalities, drug effects and autonomic influences can cause sinus nodal dysfunction. Acquired AV block is most commonly caused by idiopathic fibrosis, acute myocardial infarction, or drug effects. Patients with asymptomatic sinus bradycardia or sinus pauses have a good prognosis and do not require treatment. On the other hand, those with tachycardia-bradycardia syndrome have a much worse prognosis, because of their risk of thromboembolic complications. Therefore, the aim of therapy is prevention of atrial fibrillation. Atrial pacing and anticoagulation can greatly reduce the incidence of stroke in this high-risk group. Once appropriate pacing has been established for AV block, the prognosis is primarily dependent on the extent of the associated heart disease. The availability of dual-chamber and rate-responsive pacing has greatly improved the lifestyle and prognosis of symptomatic patients. In many instances, the challenge for physicians is documenting sinus nodal dysfunction or AV block in association with symptoms.

GLOSSARY

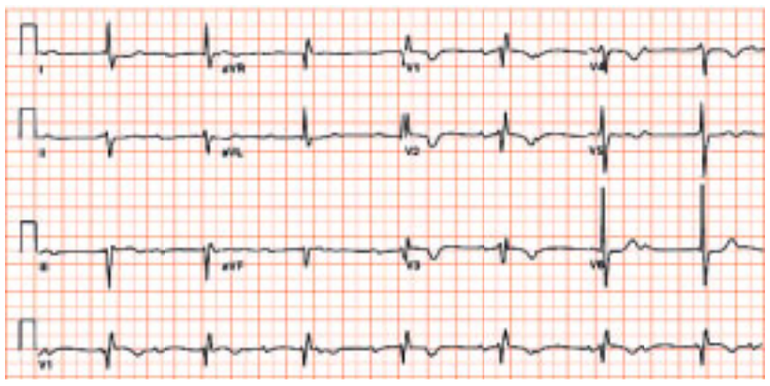
Acquired complete heart block: Third-degree AV block present as a result of some insult to the specialized conduction system, but not present at birth. Usually it is associated with block below the AV node.

Bifascicular block: Conduction delay in two fascicles; right bundle branch block with left anterior fascicular block, right bundle branch block with left posterior fascicular block, or left bundle branch block.



Acute anterolateral myocardial infarction complicated by conduction disturbance. ST-segment elevation in the anterior precordial leads as well as leads I and aV_L is associated with right bundle branch block and left anterior hemiblock.

Congenital complete heart block: Third-degree AV block present from birth and seen as completely dissociated P waves and QRS complexes, each firing at their own pacemaker rate. The level of block is usually within the AV node.



An 83-year-old patient with complete heart block, junctional escape rhythm, left anterior hemiblock, and complete right bundle branch block.

Inappropriate sinus bradycardia: A sinus rate less than 60 beats/min, which is persistent and does not increase appropriately with exercise.

Sick sinus syndrome: See *tachycardia-bradycardia syndrome*.

Sinoatrial conduction time: An indirect measurement obtained during an electrophysiology study. Premature atrial extrastimuli are introduced at the high right atrium at progressively shorter intervals during sinus rhythm until atrial refractoriness is found. Calculations can then be made to estimate the conduction time.

Sinoatrial exit block: A period of asystole resulting from the generated sinus impulse not leaving the sinus nodal region, caused by delay in conduction or block.

Sinus arrest: Used interchangeably with the term *sinus pause*. A result of transient failure of impulse formation at the sinoatrial node during which time no P wave is seen.

Sinus nodal dysfunction: Any abnormality in sinus nodal function, including inappropriate sinus bradycardia, sinoatrial exit block, sinoatrial arrest, or alternating sinus bradycardia and atrial tachyarrhythmias. The term does not indicate a specific etiology or the presence of symptoms.

Sinus nodal recovery time: An indirect measurement obtained invasively by overdrive pacing of the sinus node. The interval between the last paced P wave and the first spontaneous atrial deflection is the sinus nodal recovery time.

Tachycardia-bradycardia syndrome: Frequently referred to as *sick sinus syndrome*. This common manifestation of sinus nodal dysfunction refers to intermittent sinus or junctional bradycardia alternating with atrial tachycardia (usually paroxysmal atrial fibrillation). Symptoms may result from either the bradycardia or the tachycardic phase.

Trifascicular block: Slowed conduction in all three fascicles; PR prolongation in addition to a bifascicular block.

Trifascicular block. Note right bundle branch block, left anterior hemiblock, and associated first-degree atrioventricular block.

Wenckebach periodicity: Type I second-degree AV block, demonstrating the following features: (a) progressive lengthening of the PR interval, (b) lengthening of the RR intervals at progressively decreasing increments, (c) a pause including the nonconducted P wave that is less than the sum of any two consecutively conducted beats, and (d) shortening of the PR interval postblock, compared with the PR interval just preceding the blocked cycle.

Acute inferior myocardial infarction complicated by Wenckebach block. Note inferior ST-segment elevation and Q waves as well as progressive prolongation of the PR interval with grouped beating.

INTRODUCTION

Bradycardia is most commonly secondary to sinus nodal dysfunction. Bradyarrhythmias secondary to AV block at the level of the AV node or distal to the bundle of His also account for a large number of patients who have bradyarrhythmias. In this chapter, we review basic and anatomic concepts, clinical profiles, and therapeutic strategies relevant to the recognition and treatment of patients with bradyarrhythmias.

SINUS NODAL DYSFUNCTION

Historical Perspective

Rhythm disturbances resulting from sinus nodal dysfunction include sinus bradycardia and pauses, as well as atrial tachyarrhythmias alternating with bradyarrhythmias. As early as 1909, episodes of atrial standstill of 4 to 8 seconds in duration were documented by Laslett in a patient with syncope, using combined jugular venous pulse and radial artery tracings (1). This report was followed by Mackenzie's recordings of digitalis-induced atrial standstill (2). These early reports identified the association of atrial standstill with syncope and the possible adverse effects of drugs on the patient with sinus nodal dysfunction. However, the concept of sinus nodal dysfunction as a clinical syndrome did not appear until Short described alternating bradycardia and tachycardia in patients with syncope (3). Some clarification of this association between bradycardia and tachycardia was provided by Katz and Pick in 1956 in their description of overdrive suppression of the sinus node, resulting sinus standstill, and the danger of asystole when subsidiary pacemakers fail (4). In 1967, Lown coined the phrase *sick sinus syndrome* for describing chaotic atrial activity combined with bradycardia postcardioversion (5). This term was further popularized by Ferrer, who defined the spectrum of arrhythmias involved (6,7). The clinical entity of sick sinus syndrome became widely accepted as a frequent and important management problem. Although *sick sinus syndrome* is still used, the terms *sinus nodal dysfunction*, *sinoatrial disease*, and *sinoatrial dysfunction* are more commonly used to describe this syndrome.

Oral medications have not been found useful in treating the symptoms associated with bradyarrhythmias secondary to sinus nodal dysfunction (3,8). Before the availability of permanent pacemakers, replacement of paroxysmal atrial flutter with chronic atrial fibrillation provided the best hope for resolution of symptoms (3). The current management for many patients with sinus nodal dysfunction includes a pacemaker for treatment of their bradycardias, along with antiarrhythmic drug therapy for control of their tachycardias.

Anatomic Considerations

The origin of the normal heartbeat arises from the sinus node, which is located laterally in the epicardial groove of the sulcus terminalis, near the junction of the superior vena cava and right atrium. An early anatomic description by Katz and Pick defined the sinus node as having a head (diameter of 5 mm) and a body and tail

(diameter of 2 mm). Starting epicardially at the junction of the superior vena cava and atrium, it courses downward and to the left, to end subendocardially (4). The sinus node is composed of “nests” of principal pacemaker cells, which spontaneously depolarize and are situated within a fibrous tissue matrix. However, what at first appeared to be a simple concept is now known to be vastly more complex. Instead of a discrete point of impulse initiation, the sinus node is in reality a region, which is functionally larger and less well-defined than initially realized (9). The blood supply to the region is variable, making it more vulnerable to damage during operative procedures (10). The blood supply predominantly comes from the sinus nodal artery, which is a branch of the right coronary artery in 65% of patients. Based on findings in the rabbit sinus node, the zone containing the principal pacemaker cells may be small and contains only a few thousand cells (11). These cells have been referred to as *P cells* because of their relatively pale appearance on electron micrography. In addition to this principal nest of cells, other nests contain cells with slower intrinsic depolarization rates and serve as backup pacemakers in response to changing physiologic and pathologic conditions. The principal pacemaker site shifts within the sinus nodal region, resulting in subtle changes in P-wave morphology (9,12,13).

Normal conduction velocities within the sinus node are slow, on the order of 2 to 5 cm per second, increasing the likelihood of intranodal conduction block (14). Fibrosis no longer appears to be the predominate cause of problems in sinoatrial conduction. Furthermore, the innervation of the sinus node is complex. Both parasympathetic and sympathetic mediators influence the rate of spontaneous depolarization in pacemaker cells and may cause a shift in the principal pacemaker site within the sinus nodal region (14,15). Acetylcholine, from parasympathetic nerve endings, reduces the rate of cell depolarization and prolongs cell refractoriness (16). Therefore, increased parasympathetic activity can produce sinus bradycardia, sinus arrest, and sinoatrial exit block. On the other hand, sympathetic mediators, such as norepinephrine and epinephrine, can increase the sinus rate and reverse sinus arrest and sinoatrial exit block (17). The anatomy and physiology of the sinus node are currently active areas of research.

Electrocardiographic Features of Sinus Nodal Dysfunction

Inappropriate Sinus Bradycardia

Sinus bradycardia (sinus rate less than 60 beats/min) (Fig. 63.1) is considered inappropriate when it is persistent and does not increase appropriately with exercise. This arrhythmia should be distinguished from asymptomatic resting sinus bradycardia in young athletes and in normal adults during sleep (18,19). Chronotropic incompetence is not present in these individuals, as it is in patients with sinus nodal dysfunction.

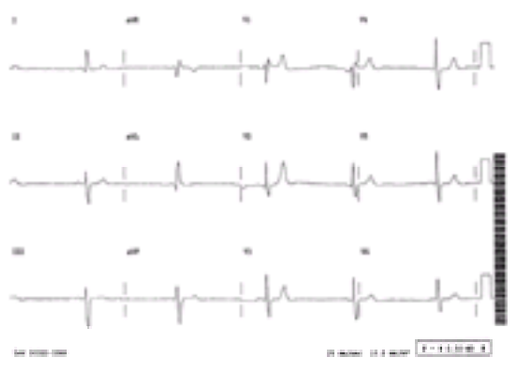


FIGURE 63.1 This electrocardiogram shows sinus bradycardia at a rate of 30 beats/min. Right bundle branch block and left anterior fascicular block are also present. aVF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead; aVR, augmented voltage unipolar right arm lead.

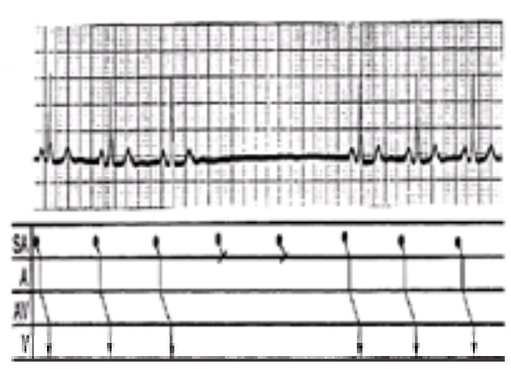
Sinus Arrest

The terms *sinus arrest* (Fig. 63.2) and *sinus pause* are used interchangeably and are a result of the sinus node’s principal pacemaker cells failing to fire. The pause is not an exact multiple of the preceding PP interval. Pauses greater than 3 seconds are rare in normal individuals and may or may not be associated with symptoms, but are usually caused by sinus nodal dysfunction (20,21). In contrast, asymptomatic pauses greater than 2 seconds (but less than 3 seconds) are seen in 11% of normal patients during 24-hour Holter monitoring and are especially common in trained athletes (22).

FIGURE 63.2 These rhythm strips of leads V_1 and V_5 were recorded simultaneously and depict sinus pauses of 3.0 and 2.8 seconds posttermination of atrial tachycardia.

Sinoatrial Exit Block

Like sinus arrest, sinoatrial exit block is characterized by a period of asystole without the expected P wave seen. In patients with sinus nodal dysfunction, an escape beat does not appear, but instead the sinus block is terminated by a sinus beat. In theory, sinoatrial exit block can be distinguished from sinus arrest because the exit block pause is an exact multiple of the baseline PP interval (eFig. 63.2.1). In actuality, the distinction is often not possible because of sinus arrhythmia, causing normal beat-to-beat variations in the sinus rate. Sinoatrial exit block results when a normally generated sinus impulse does not leave the sinus nodal region because of delay in conduction or block. The most common site of block is probably within the sinus node itself, caused by the slow conduction in this region.

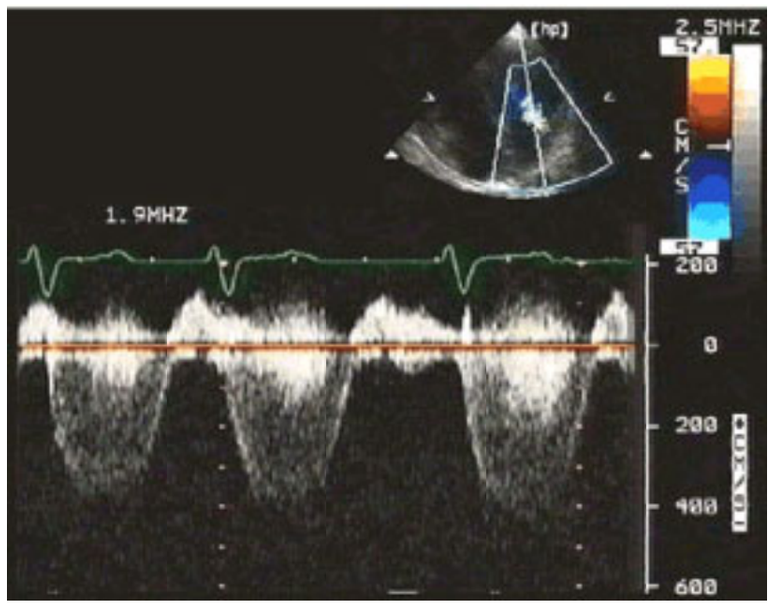


***e*FIGURE 63.2.1** This rhythm strip is an example of sinoatrial exit block. Note that the exit block pause is an exact multiple of the baseline PP interval. The bottom half of the figure is a ladder diagram illustrating conduction from the sinoatrial (SA) region through the atrium (A), atrioventricular (AV) node to the ventricle (V) in the case of the sinus beats. However, the impulse does not exit the SA region during the pause, and no P waves are seen on the surface electrogram.

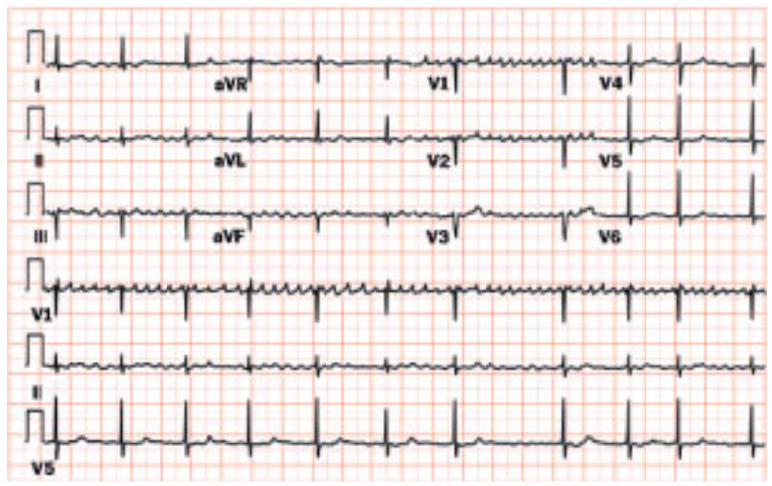
Exit block is classified into three types, analogous to that of AV block. First-degree sinoatrial block is caused by abnormal prolongation of the sinoatrial conduction time. The impulse reaches the atrium, but is delayed. This conduction abnormality cannot be identified from surface electrography, but needs to be verified either by direct recording or indirect measurement of sinoatrial conduction time during an electrophysiologic study. Second-degree sinoatrial exit block is marked by intermittent failure of the sinus impulse to exit the node. This is viewed as Wenckebach periodicity of the P wave on surface electrography. Progressive shortening of the PP interval preceding the dropped P wave is seen. In higher grade, second-degree sinoatrial exit block, abrupt absence of one or more P waves results from failure of the atrial impulse to exit the sinus node. As noted previously, the atrial pause should be an exact multiple of the immediately preceding PP interval. However, normal variations in the sinus rate caused by sinus arrhythmia may obscure this measurement. Third-degree or complete sinoatrial exit block is seen as a pause in the sinus rhythm and cannot be distinguished from prolonged sinus arrest. However, determining the difference is not necessary from a clinical standpoint, as both entities will likely be symptomatic.

Chronic Atrial Fibrillation

The presence of chronic atrial fibrillation in a patient with a slow ventricular response not secondary to drug therapy is a sign of sinus nodal dysfunction. In some cases, cardioversion results in a long sinus pause before the appearance of sinus rhythm, or junctional escape rhythm. Although a combination of sinus nodal and AV conduction disease may be present in many instances, examples of rapid ventricular responses during atrial tachyarrhythmias can frequently be found.



Apical continuous wave spectral Doppler recording of mitral regurgitation (systolic parabolic downward velocities). Note beat-to-beat variation due to atrial fibrillation.



Atrial fibrillation. Narrow complex QRS with irregular RR intervals. Ventricular rate is controlled.

Tachycardia-Bradycardia Syndrome

Tachycardia-bradycardia syndrome refers to the presence of intermittent sinus or junctional bradycardia alternating with atrial tachycardia (usually paroxysmal atrial fibrillation) in the same patient (Fig. 63.3). This condition, frequently referred to as *sick sinus syndrome*, is a common manifestation of sinus nodal dysfunction. The highest incidence of syncope associated with sinus nodal dysfunction probably occurs in this group (3). Syncope typically occurs secondary to a long sinus pause after the spontaneous termination of atrial fibrillation.

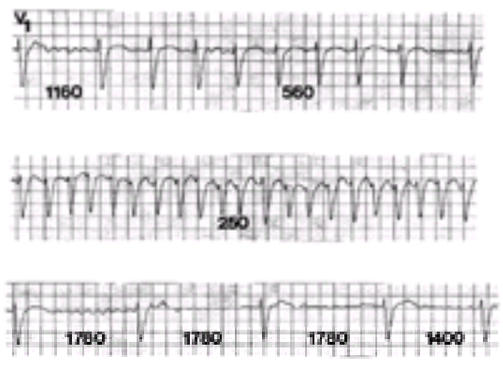


FIGURE 63.3 These three rhythm strips were obtained from the same patient at different times and illustrate the marked variability of heart rates in patients with tachycardia-bradycardia syndrome. The labeled cycle lengths are in milliseconds.

Pathophysiology

Intrinsic Sinus Nodal Dysfunction

Idiopathic degenerative disease is probably the most common cause of intrinsic sinus nodal dysfunction (Table 63.1). Pathologic studies have shown an increase in fibrous tissue in the area of the sinus node with age. Why some individuals develop sinus nodal dysfunction whereas others do not, is not easily explained by fibrous tissue replacement only (23,24). Coronary artery disease may be responsible for one-third of cases of sinus nodal dysfunction. This estimation is based on a study by Shaw et al. (25), in which angiography was used to demonstrate the extent of coronary artery disease in the sinus nodal artery in patients with sinus nodal dysfunction. Transient slowing of the sinus rate, or sinus arrest, can complicate an acute myocardial infarction. This is usually seen with an acute inferior wall myocardial infarction, is caused by neural influences, and rarely persists (26). Cardiomyopathy, long-standing hypertension, infiltrative disorders, collagen vascular diseases, inflammatory processes, and surgical trauma can also result in sinus nodal dysfunction. Orthotopic cardiac transplantation is associated with a high incidence of sinus nodal dysfunction in the donor heart. In an Austrian study with a series of 90 transplant patients, 45% were found to have sinus nodal dysfunction postoperatively, and 21%

required permanent pacing. However, sudden death caused by donor sinus nodal dysfunction appears to be a rare occurrence in post–cardiac transplantation (27). The musculoskeletal disorders of myotonic dystrophy or Friedreich's ataxia are rare causes of sinus nodal dysfunction. A familial form of sinus nodal dysfunction accounts for a small number of cases (28).

Intrinsic causes
Idiopathic degenerative disease
Coronary artery disease
Cardiomyopathy
Hypertension
Infiltrative disorders (amyloidosis, hemochromatosis, tumors)
Collagen vascular disease (scleroderma, lupus erythematosus)
Inflammatory processes (myocarditis, pericarditis)
Surgical trauma (orthotopic cardiac transplantation)
Musculoskeletal disorders (myotonic dystrophy, Friedreich's ataxia)
Congenital heart disease (postoperative or in absence of surgical correction)
Extrinsic causes
Drug effects
Beta blocking agents
Calcium channel blocking agents
Digoxin
Sympatholytic antihypertensives (clonidine, methyldopa, and reserpine)
Antiarrhythmic drugs
Type IA (quinidine, procainamide, disopyramide)
Type IC (flecainide, propafenone)
Type III (sotalol, amiodarone)
Others (lithium, cimetidine, amitriptyline, phenytoin)
Autonomic influences
Excessive vagal tone
Carotid sinus syndrome
Vasovagal syncope
Well-trained athletes
Electrolyte abnormalities
Hyperkalemia
Hypercalcemia
Endocrine disorders: hypothyroidism
Increased intracranial pressure
Hypothermia
Sepsis

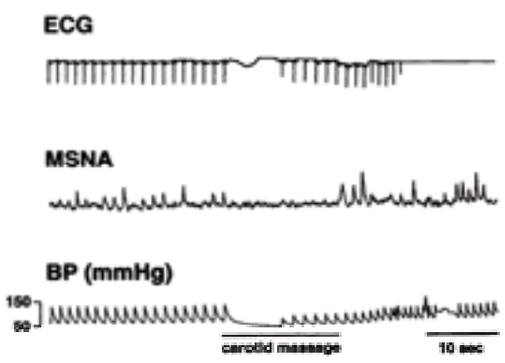
TABLE 63.1 CAUSES OF SINUS NODAL DYSFUNCTION

In the pediatric population, most cases of sinus nodal dysfunction can be attributed to surgical trauma (see Chapter 70 for a further discussion of this subject). Most commonly associated with this complication is Mustard's procedure for transposition of the great arteries (29) and repair of atrial septal defects, especially of the sinus venosus type (30). Sinus nodal dysfunction can occur in children with congenital heart disease, such as secundum atrial defects, even though no surgery has been performed (31). In some children with sinus nodal dysfunction, no structural heart disease is known (32).

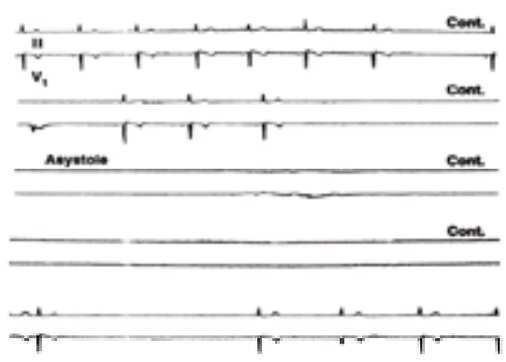
Extrinsic Sinus Nodal Dysfunction

In the absence of structural abnormalities, the predominant causes of sinus nodal dysfunction are drug effects and autonomic influences (Table 63.1). Drugs known to depress sinus nodal function include beta-blockers, calcium channel blockers, digoxin (33), and sympatholytic antihypertensives (e.g., clonidine, methyldopa, and reserpine) (34). Types IA, IC, and III antiarrhythmic drugs can depress sinus nodal function (33) and, occasionally, may produce proarrhythmias in patients with sick sinus syndrome. Paroxysmal primary atrial tachycardias and pause-dependent ventricular tachycardia have been described (35,36). Other drugs reported to affect sinus nodal function include lithium, cimetidine, amitriptyline, and phenytoin (33).

Sinus nodal dysfunction may sometimes result from excessive vagal tone in individuals without intrinsic sinus nodal disease. The transient bradyarrhythmias produced can include marked sinus bradycardia, sinus pauses, or sinoatrial exit block (37,38). Autonomically induced asystole has been reported to occur rarely and may result in sudden death (39). Hypervagatonia can be seen in carotid sinus syndrome (eFig. 63.3.1) and vasovagal syncope (eFig. 63.3.2). Well-trained athletes with increased vagal tone may require some deconditioning to help prevent symptomatic bradyarrhythmias (40). Less common extrinsic causes of sinus nodal dysfunction include hyperkalemia, hypothyroidism, increased intracranial pressure, hypothermia, hypercarbia, and sepsis.



***e*FIGURE 63.3.1** Sinus pause during carotid sinus massage. Note the decrease in muscle sympathetic neural activity (MSNA) during duration of carotid sinus massage and loss of blood pressure (BP) during sinus pause. ECG, electrocardiogram. (Unpublished data from J. Luck and U. Leuenberger.)



***e*FIGURE 63.3.2** Example of prolonged asystole during vasovagal syncope. (Unpublished data from J. Luck.)

Clinical Profile

Incidence

Few data are available regarding the incidence of sinus nodal dysfunction in the general population. However, a Belgian study involving cardiac patients estimated the incidence in patients over 50 years of age to be 3 in 5,000 (41). Sinus nodal dysfunction affects men and women equally (42).

Symptoms

The symptoms reported by patients with sinus nodal dysfunction are varied, and many times nonspecific. Syncope and presyncope are the most frequent symptoms associated with significant bradycardia. Fatigue, angina, and shortness of breath can also be seen. Elderly patients may have the more subtle symptoms of gastrointestinal distress or change in mental status. Patients with tachycardia-bradycardia syndrome may only experience palpitations associated with the tachycardia or embolic events. Syncope in an individual with paroxysmal atrial fibrillation is classically associated with the long sinus pause at the spontaneous termination of the tachycardia. The intermittent nature of these symptoms makes documentation of the associated rhythm disturbance difficult at times. In other cases, marked sinus bradycardia and sinus pauses may be asymptomatic (6,42,43).

Diagnostic Techniques

Both noninvasive and invasive means of diagnosing sinus nodal dysfunction are available. Generally, the noninvasive methods of electrocardiographic (ECG)

monitoring, exercise testing, and autonomic testing are used first. However, if symptoms are infrequent, invasive electrophysiologic testing may be pursued.

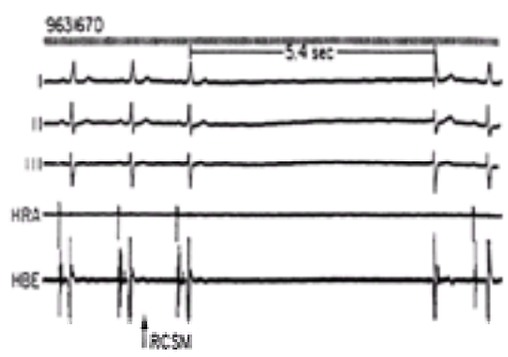
Noninvasive Testing

A 12-lead ECG needs to be obtained in the patient with syncope or near syncopal episodes. However, the diagnosis of sinus nodal dysfunction as the etiology of these symptoms is rarely made from the simple ECG. If symptoms are frequent, 24- or 48-hour ambulatory Holter monitoring can be useful. Documentation of symptoms in a diary by the patient while wearing the Holter monitor is essential for correlation of symptoms with the heart rhythm at the time. In some cases, the Holter monitor can exclude sinus nodal dysfunction as the cause of symptoms, if normal sinus rhythm is documented. In contrast, sinus pauses recorded may not be associated with symptoms. Several Holter monitor studies (21,44) have demonstrated the futility of treating asymptomatic pauses, even if 3 seconds or longer. Most pauses, ranging from 2 to 15 seconds, were asymptomatic, and pacing did not benefit those without associated symptoms. The length of the pause correlated poorly with symptoms and prognosis.

A relatively newer diagnostic tool is the event recorder, or loop recorder, which is useful in patients whose symptoms occur infrequently. This device is used to record the heart rhythm only during symptoms. Later, the recorded ECG is sent transtelephonically by the patient to a central monitoring station.

Exercise testing is of limited value in diagnosing sinus nodal dysfunction. However, in some cases, it is useful in differentiating those patients with hronotropic incompetence from patients with resting bradycardia who demonstrate a normal heart rate increase with exercise. Certain patients with sinus nodal dysfunction and chronotropic incompetence exhibit abnormal heart rate responses to exercise. The increase in heart rate at each stage of exercise may be less than normal, with a plateau seen below the maximum predicted heart rate (adjusted for age). Other patients with sinus nodal dysfunction may achieve an appropriate peak heart rate during exercise but may have a slow heart rate acceleration in the initial stage or rapid deceleration of heart rate in the recovery stage. These abnormal chronotropic responses can help to identify the cause of exercise intolerance in some patients with sinus nodal dysfunction and can help to determine their pacemaker prescription (45,46).

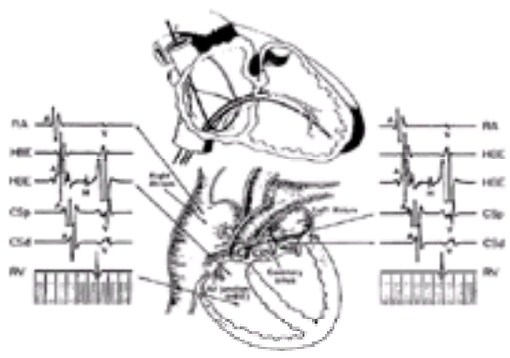
Autonomic testing of the sinus node includes various pharmacologic interventions and maneuvers to test reflex responses. An abnormal response to carotid sinus massage (pause greater than 3 seconds) may indicate sinus nodal dysfunction (*e*Fig. 63.3.3), but this response may also occur in asymptomatic elderly individuals (47). Heart rate response to Valsalva's maneuver (normally decreased) or upright tilt (normally increased) can also be used to verify that the autonomic nervous system is itself intact. The most commonly used pharmacologic intervention is used to determine the intrinsic heart rate. Complete autonomic blockade is accomplished by administering atropine, 0.04 mg per kg, and propranolol, 0.20 mg per kg. The resulting intrinsic heart rate represents the sinus nodal rate without autonomic influences. The normal intrinsic heart rate is age dependent and can be calculated using the following equation: intrinsic heart rate = 118.1 – (0.57 × age) beats/min (48). A low intrinsic heart rate is consistent with abnormal intrinsic sinus nodal function. A normal intrinsic heart rate in a patient with known sinus nodal dysfunction suggests abnormal autonomic regulation.



***e*FIGURE 63.3.3** Abnormal sinus node slowing with carotid sinus massage. During sinus rhythm, right carotid sinus massage (RCSM, *arrow*) was applied, and the patient had a prolonged asystolic pause (5.4 seconds) closed by a junctional escape before resumption of sinus rhythm. This exaggeration of the normal response of the sinus node to carotid sinus massage represents a hypersensitive carotid sinus reflex but may not always be responsible for symptoms. HBE, bundle of His recording; HRA, high right atrial recording. (From Miles MM, Klein LS. Sinus nodal dysfunction and atrioventricular conduction disturbances. In: Naccarelli GV, ed. *Cardiac arrhythmias: a practical approach*. Mount Kisco, NY: Futura, 1991:250, with permission.)

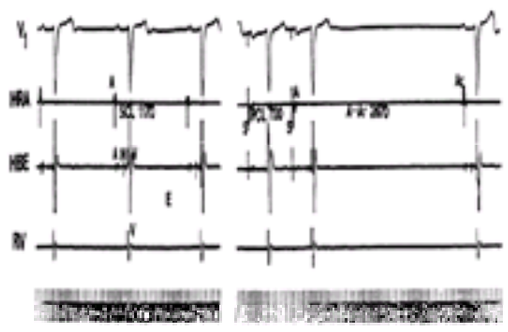
Invasive Testing

Sinus nodal function can also be evaluated invasively with an electrophysiologic study (*e*Fig. 63.3.4). This is usually reserved for symptomatic patients in whom sinus nodal dysfunction is suspected but cannot be documented in association with symptoms by noninvasive means. The pacing tests most commonly used are sinus nodal recovery time and sinoatrial conduction time. However, even when performed appropriately, the ability of these tests to provide a definitive diagnosis is limited. Since the early 1970s, overdrive suppression of the sinus node has been viewed as a marker of sinus nodal dysfunction (49). A delay in the return of spontaneous pacemaker activity is a normal finding immediately after rapid atrial pacing. In those with sinus nodal dysfunction, however, the sinus node generally takes longer to recover. The mechanism of overdrive suppression of the sinus node is unclear. Depression of sinus nodal automaticity is only partially involved. Other factors include the proximity of the pacing site to the sinus node, the local concentrations of acetylcholine and norepinephrine, and the conduction time in and out of the sinus node (up to 250 ms).



***e*FIGURE 63.3.4** Sites of catheter placement and example of intracardiac recordings obtained during electrophysiologic studies. Multipolar catheters can be placed for purposes of simultaneous electrogram recording and pacing in the high right atrium, bundle of His area, right ventricular apex, and coronary sinus. A, atrial activation; AV, atrioventricular; CSd, distal coronary sinus; CSp, proximal coronary sinus; H, bundle of His potential; HBE, bundle of His electrogram; RA, right atrium; RV, right ventricle; V, ventricular activation.

The pacing protocol used to measure the sinus nodal recovery time generally involves pacing at the high right atrium for 30 seconds at several different cycle lengths in the range of 300 to 700 ms (*e*Fig. 63.3.5). The sinus nodal recovery time is the interval between the last paced P wave and the first spontaneous atrial deflection. A better measurement, however, is the corrected sinus nodal recovery time, which is obtained by subtracting the sinus cycle length before pacing from the sinus nodal recovery time. Thus, a patient with an abnormally long sinus nodal recovery time (greater than 1,400 ms) could have a normal corrected sinus nodal recovery time (less than 550 ms) (50).



***e*FIGURE 63.3.5** Intracardiac electrograms demonstrate a prolonged sinus node recovery time. Surface electrogram lead V_1, in addition to a high right atrial recording (HRA), bundle of His electrogram (HBE), and right ventricular electrogram (RV), is demonstrated. In the left panel are the patient's recordings during spontaneous sinus rhythm (notice A_1-A_1 is 1,070 ms or a rate of 57 per minute). In the right panel are recordings during atrial pacing at a cycle length of 400 ms (rate of 150 per minute). On termination of atrial pacing, note the long period of asystole measured from the last paced atrial electrogram to the first recovery atrial electrogram (Ar). By subtracting the resting heart rate (1,170 ms) from the total recovery time (2,670 ms), a prolonged corrected sinus node recovery time of 1,500 ms can be calculated. A, atrial activation; H, bundle of His potential; PCL, pacing cycle length; SCL, spontaneous cycle length; V, ventricular activation. (From Weeks LC, ed. *Advanced cardiovascular nursing*. New York: Blackwell Science, 1986:518, with permission.)

The conventionally obtained sinus nodal recovery time measurement is an indirect one and is therefore associated with several limitations. The corrected sinus nodal recovery time reflects both sinoatrial conduction time and sinus automaticity. Only a direct sinus node electrogram can accurately identify which abnormality is present in sinus nodal dysfunction. Also, indirect sinus nodal recovery time measurements can be confounded by sinus nodal entrance block during rapid atrial pacing, with resultant shortening of the sinus nodal recovery time, and by sinus nodal exit block postpacing, thereby prolonging the apparent sinus nodal recovery time. An abnormal sinus nodal recovery time is not found in all patients with sinus nodal dysfunction. This is due partly to sinus nodal dysfunction not being a homogenous entity from a pathologic standpoint. Despite these limitations, the indirect corrected sinus nodal recovery time is frequently used in the evaluation of sinus nodal function.

Although direct sinus node electrograms are possible to accomplish, they are difficult to obtain, and the technique is rarely used in the electrophysiology laboratory. Comparison of measurements by direct and indirect methods has shown direct sinus nodal recovery time values to be generally shorter. Additionally, direct recordings reveal nonconducted sinus node electrograms during postpacing atrial pauses that go undetected during conventional indirect sinus nodal recovery time measurements.

Additional tools can be used to improve the sensitivity and specificity of the traditional sinus nodal recovery time measurement. Complete autonomic blockade with determination of the intrinsic heart rate during atrial pacing can help identify the mechanism of the sinus nodal dysfunction (abnormal autonomic regulation vs. intrinsic sinus nodal function). The pacing cycle length with the longest sinus nodal recovery time has been found to be less than or equal to 600 ms in normal individuals. However, in patients with sinus nodal dysfunction, the maximum sinus nodal recovery time often occurs at slower pacing cycle lengths (greater than 600 ms), even though a normal sinus nodal recovery time was found. An abnormal perinodal refractory period may explain this observation (51). In some patients with sinus nodal dysfunction, the sinus nodal recovery time is normal, but the following PP intervals are longer. These secondary pauses are uncommonly found in normal subjects. After autonomic blockade, patients with abnormal intrinsic heart rates continue to have secondary pauses, whereas those patients with normal intrinsic heart rates no longer have secondary pauses (52). When the previously mentioned measures are employed, and corrected sinus nodal recovery time is used along with the sinoatrial conduction time in a symptomatic patient, the sensitivity and specificity for sinus nodal dysfunction approach 70% and 90%, respectively (53).

The other commonly used invasive pacing test, the sinoatrial conduction time, is traditionally measured indirectly from the high right atrium (54). The most popular method of pacing involves introducing premature atrial extrastimuli (A_2) at progressively shorter intervals during sinus rhythm (A_1). The A_2 is first introduced in late diastole and brought in until atrial refractoriness is found, thus scanning diastole. The A_2 reverses sinoatrial activation for that cycle. The return cycle (A_2-A_3) is then assumed to be equal to the previous sinus cycle (A_1-A_1), plus the time required for A_2 to enter the node and the time needed for the next sinus beat to exit the node and result in A_3. Estimation of the sinoatrial conduction time by this method is obtained by calculation of the following: (A_2-A_3 interval) – (A_1-A_1 interval). Next, an average of multiple A_2 responses is determined for the sinoatrial conduction time. Several assumptions are used to obtain the calculation; the sinus nodal automaticity is assumed not to be affected by the premature beat, conduction in and out of the sinus node is assumed equal, and the premature atrial beat is assumed not to cause a shift in the principal pacemaker site. An additional limitation of the sinoatrial conduction time test is the need for a regular cycle length in sinus rhythm. Sinus arrhythmia may make calculation of the sinoatrial conduction time by this method impossible. In an effort to circumvent the sinus arrhythmia problem, brief atrial pacing at a rate just above the sinus rate is used. The sinoatrial conduction time becomes the difference between the postpacing interval and sinus cycle length (55).

Estimation of the sinoatrial conduction time by direct sinus node electrograms is less practical than the indirect method and rarely used. As the indirect estimation, the direct measurement is subject to inaccuracy in the presence of sinus arrhythmia. The sinus node electrogram has been used to validate the indirect pacing methods that are used to assess sinus nodal dysfunction. Indirect sinoatrial conduction time measurements are generally shorter but tend to correlate well with direct values obtained using sinus node electrograms (56,57).

Estimation of the sinus node effective refractory period has been proposed as another method of identifying patients with sinus nodal dysfunction. The sinus node effective refractory period is represented by the interpolation zone, or the zone where an atrial extrastimulus fails to enter the node and is interpolated between two sinus impulses. One clinical study found a significant difference between sinus node effective refractory period values in normal individuals and those with sinus nodal dysfunction (58).

Most patients with sinus nodal dysfunction do not require invasive electrophysiologic testing. Invasive sinus nodal evaluation should be reserved for symptomatic patients with suspected sinus nodal dysfunction, but attempts to document dysfunction in association with symptoms by noninvasive means have been unsuccessful. Patients with asymptomatic sinus bradycardia or sinus pauses should not undergo invasive testing. Patients with previously documented sinus nodal dysfunction in association with symptoms do not require further testing, unless the assessment of AV anterograde and retrograde nodal conduction would aid in the pacemaker prescription.

Natural History

The natural history of sinus nodal dysfunction depends largely on the type of dysfunction and the presence of concomitant cardiovascular disease. The worst prognosis is associated with the tachycardia-bradycardia syndrome, whereas sinus bradycardia is much more benign. Those with sinus pauses have a prognosis intermediate to the other two types of sinus nodal dysfunction. These differing outlooks are most likely related to their relative risk for thromboembolic complications, probably the most important cause of death in this group. Because stroke is associated with atrial fibrillation, patients with sinus nodal dysfunction complicated by chronic or intermittent atrial fibrillation have an increased risk of embolization.

In a literature review by Sutton and Kenny (59), the incidence of new onset atrial fibrillation in patients with sinus nodal dysfunction was 5.2% per year. New atrial tachyarrhythmias occurred with less frequency in patients who were atrially paced (3.9%), compared with a greatly increased incidence of similar arrhythmias in those only ventricularly paced (22.3%). A more recent review (60) reported a weighted mean atrial fibrillation per year incidence of 6.8% for VVI pacing, compared with 2.6% (a 62.0% risk reduction) for dual-chamber pacing.

As noted previously, thromboembolic complications are a major cause of morbidity and mortality in patients with sinus nodal dysfunction. Sutton and Kenny's review found a 15.2% incidence of thromboembolism among unpaced patients with sinus nodal dysfunction. Those patients only ventricularly paced did not fare much better (13%). In contrast, atrially paced patients enjoyed a greatly decreased thromboembolic event incidence (1.6%) (59). In the future, increased use of atrial pacing and anticoagulation therapy should significantly reduce the incidence of stroke in high-risk patients with tachycardia-bradycardia syndrome. Several ongoing prospective trials are testing the hypothesis that physiologic pacing reduces the risk of cardiovascular death and stroke.

Of clinical interest is the incidence of concomitant AV nodal disease in patients with sinus nodal dysfunction. In the previously mentioned review (59), 17% of the patients had some degree of AV conduction system disease at the time of diagnosis of sinus nodal dysfunction. New AV conduction abnormalities developed at a rate of approximately 2.7% per year. These data indicate a low frequency and slow progression rate of AV conduction system disease in patients with sinus nodal dysfunction.

Principles of Management

Because of the broad range of symptoms associated with a variety of arrhythmia presentations in patients with sinus nodal dysfunction, treatment modalities must be individualized. For the patient with asymptomatic bradycardia or pauses and no atrial fibrillation, no treatment is necessary. In the case of symptomatic patients with sinus nodal dysfunction and atrial fibrillation, therapy depends on whether the symptoms are related to the tachycardia or bradycardia episodes. Depending on the etiology of the symptoms, drug therapy may be needed to control rapid ventricular response, pacing may be advised to prevent bradycardia, or both treatment modalities may be required. Ideally, if a patient with symptomatic bradycardia is on a drug known to depress sinus nodal function, the drug should be stopped. However, many times this is not possible, as the drug is needed for control of symptomatic tachycardia, ischemia, or hypertension. In these cases, permanent pacing may be required to allow continued use of the needed drug.

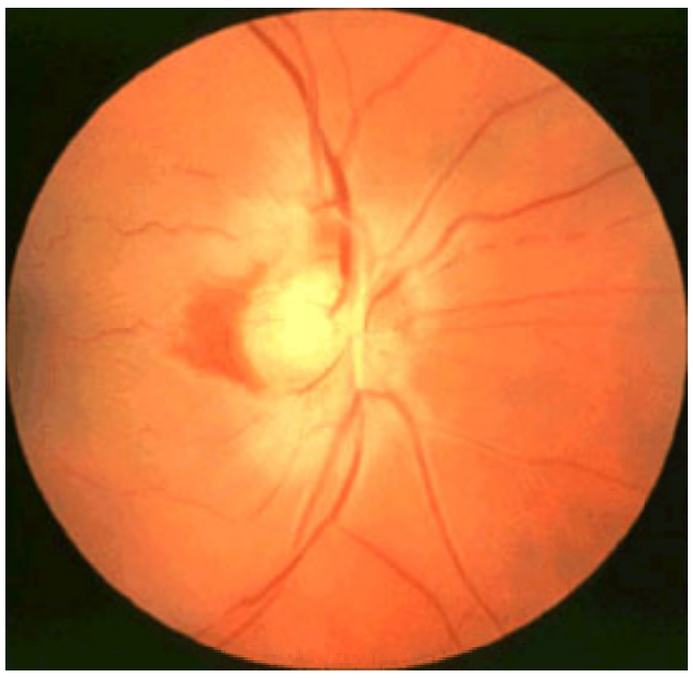
Sinus nodal dysfunction is currently the most common reported diagnosis for pacemaker implantation. However, once the decision to pace is made, choosing the optimal pacemaker prescription is essential to decrease stroke risk and improve quality of life. As discussed previously, a significant number of patients with sinus nodal dysfunction have concomitant atrial fibrillation or develop new atrial tachyarrhythmias after being diagnosed with sinus nodal dysfunction. Atrial pacing has been shown to greatly decrease the incidence of atrial fibrillation and thromboembolism in this population, whereas those who are only ventricularly paced have not seen a similar benefit (59). For those patients with sinus nodal dysfunction who have normal AV conduction, a single-chamber atrial pacemaker is a reasonable consideration. Of course, single-chamber ventricular pacing is still appropriate for individuals with sinus nodal dysfunction and chronic atrial fibrillation. The use of rate-adaptive pacing is important for improving exercise tolerance in single-chamber and dual-chamber pacing devices. Additionally, the development of the mode-switching feature in some dual-chamber devices allows for automatic mode change between DDDR and DDIR (or VVIR) in a patient with intermittent atrial tachyarrhythmias. The DDIR mode permits continued AV synchrony. However, because there is no atrial tracking, unwanted rapid ventricular pacing will not occur during atrial tachycardia. Guidelines for implantation of pacemakers in patients with sinus nodal dysfunction have been established by a task force from the American College of Cardiology and American Heart Association (*e*Table 63.1.1) (61).

***e*TABLE 63.1.1** INDICATIONS FOR PERMANENT PACING IN SINUS NODAL DYSFUNCTION

Class I	Sinus nodal dysfunction documented in association with symptomatic bradycardia and caused by factors that are irreversible or caused by essential drug therapy
Class II	No clear association between sinus nodal dysfunction (with heart rate <40 beats/min) and symptoms can be documented
Class III	Sinus nodal dysfunction with marked sinus bradycardia or pauses, but no associated symptoms

[a]Class I indications are conditions for which it is generally agreed that pacing is needed. Class II indications are conditions associated with varying opinions as to the necessity of pacing. Class III indications are conditions in which pacing is thought not to be indicated.

As discussed previously, because of the high risk of thromboembolic events in patients with chronic or intermittent atrial fibrillation, anticoagulation with warfarin should be instituted in these patients. Warfarin has been clearly shown to be superior to placebo in the prevention of stroke in patients with atrial fibrillation (62). However, the role of aspirin therapy in this population is controversial (63). Patients with contraindications to warfarin or those with lone atrial fibrillation—defined as atrial fibrillation in the absence of underlying heart disease—may be considered candidates for aspirin therapy alone. For the other patients with atrial fibrillation, warfarin therapy to achieve an international normalized ratio between two and three is optimal to decrease stroke risk. A metaanalysis of the five major controlled trials of anticoagulation in atrial fibrillation has shown that patients at the highest risk for strokes are those with hypertension, recent congestive heart failure, or previous thromboembolism (64). The reader is referred to Chapter 64 for a more in-depth discussion of these anticoagulation issues.



Central retinal artery occlusion. There are indistinct margins to the optic disc and pallor of the central retinal artery territory.

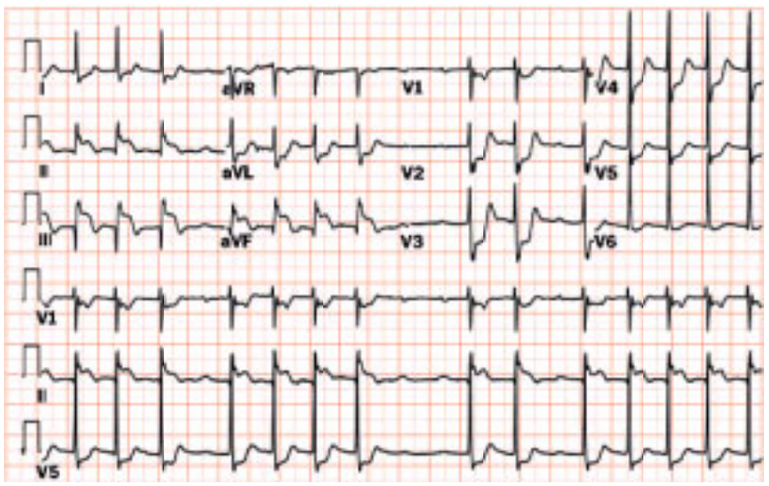
Embolus. Dislodged thrombus that embolized to the toes and caused gangrene (*arrows*).

ATRIOVENTRICULAR NODAL DYSFUNCTION

Historical Perspective

Adams (1827) (65) and Stokes (1846) (66) first described syncope associated with a slow heart rate. In 1906, by analyzing the jugular venous pulse waves, Wenckebach (67) and Hay (68) were able to distinguish two types of second-degree AV block. Once the ECG became available, Mobitz (69) classified them as types I and II. With the development of intracardiac electrocardiology and bundle of His recordings in the late 1960s (70), knowledge of AV conduction was expanded. The ability to localize the site of the block to the AV node, bundle of His, or bundle branch fascicular system was facilitated. After the development of chronic transvenous ventricular pacing in the mid-1960s, the natural history of the patient with symptomatic heart block greatly changed, and mortality significantly decreased. Further

advancements in pacing over the years—namely, dual-chamber and rate-responsive pacing—have improved the quality of life of these patients.



Acute inferior myocardial infarction with Mobitz II atrioventricular block. Note ST-segment elevation in the inferior leads as well as intermittently dropped QRS complexes.

Anatomic Considerations

The AV node lies beneath the right atrial endocardium at the apex of the triangle of Koch, which is formed by the tendon of Todaro and the septal leaflet of the tricuspid valve. This positions the AV node directly above the insertion of the septal leaflet of the tricuspid valve and anterior to the ostium of the coronary sinus. Two different approaches have been commonly used in describing the anatomy of the AV node. One considers the AV node as part of the AV junctional area (71). The area is divided into three regions: the transitional zone, compact portion, and penetrating part of the AV bundle. The transitional cells, or nodal approaches, connect the atrial myocardium to the compact portion of the AV node. At its distal end, the compact portion of the AV node enters the central fibrous body, becoming the penetrating portion, or bundle of His. The other approach more closely correlates nodal anatomy with the physiologic activity of its different cell types (72). Three functional regions of the AV node have been identified based on the differing conduction properties of the cells. The three regions are called atrionodal (AN), nodal (N), and nodal-His (NH) (73). These three regions correspond to the transitional zone and the compact portion and penetrating AV bundle, although there is much overlap of the cell groups. Also, a number of intermediate cell types are found within each group (74). The slowest conduction time (0.03 m per second) occurs in the N region. Whereas the AN and NH regions display spontaneous diastolic depolarizing activity, the N region has no automaticity (75).

The blood supply to the AV node is via the AV nodal artery, a branch of the right coronary artery in 90% of hearts, with the remaining 10% arising from the circumflex artery (76).

As the sinus node, the AV node is richly innervated by sympathetic and parasympathetic fibers (77). Although sympathetic neural input to the sinus node and the AV node overlap substantially, different branches of the vagal and sympathetic nerves act predominantly on certain regions. As a result, if innervation to the sinus node is damaged, neural input to the AV node remains intact (78). The sinus node and AV node are both influenced by the right and left vagus nerves and stellate ganglia. However, stimulation of the nerves on the right has less effect on AV nodal conduction than on sinus nodal rate. Conversely, left-sided autonomic stimulation exerts stronger influence on AV nodal conduction than on sinus rate. Evidence suggests acetylcholine release is predominantly around the N region of the AV node (79).

His-Purkinje System

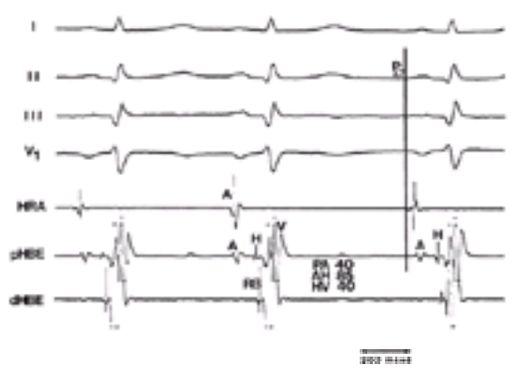
The cells of the proximal bundle of His resemble those of the compact AV node, whereas the distal cells are similar to the cells in the proximal bundle branches. The bundle of His is contained within the connective tissue of the central fibrous body and membranous septum. It courses in the base of the membranous septum or along the left side of the crest of the interventricular septum in most cases. However, right-sided bundles of His do occur, which influence the configuration of the proximal bundle branches. The anatomy of the left bundle branch (LBB) is subject to much variability. The fibers generally travel as a broad band onto the left septum below the noncoronary aortic cusp. In a minority of cases, the origin of the LBB is narrow, even though it arises from a left-sided bundle of His. In the case of a right-sided bundle of His, the LBB originates from the right as a narrow stem. The right bundle branch (RBB) extends unbranched from the bundle of His, traveling down the right side of the interventricular septum to the apex of the right ventricle, and the base of the anterior papillary muscle. Discrete bifascicular subdivisions with anterosuperior and posteroinferior branches of the LBB are not the norm. Where subdivisions are present, they have multiple interconnections. In other cases, a network is seen without clear divisions (80). Despite this anatomic variability, the concept of the left anterior and posterior fascicular blocks remains clinically useful (81). The bundle branches end in Purkinje's fibers, forming a network over the surface of the endocardium of the ventricles. Their interweaving configuration allows the cardiac impulse to reach the entire right and left ventricular endocardium almost simultaneously. Purkinje's fibers have a rapid conduction time of 2.4 m per second.

The bundle of His has a dual blood supply from branches of the anterior and posterior descending coronary arteries. Dual blood supply from the left and right coronary arteries is the usual case for the bundle branches (81).

Electrocardiographic and Electrophysiologic Findings

Normal Atrioventricular Conduction

On the surface ECG, the PR interval is normally between 120 and 200 ms in duration. This interval reflects the conduction time from the high right atrium to the point of ventricular activation. To measure the different components of the conduction system that the PR interval includes, intracardiac tracings from the high right atrium and bundle of His region are needed (*e*Fig. 63.3.6). The PA interval—measured from the high right atrial electrogram to the low right atrial deflection in the bundle of His electrogram—gives an indirect approximation of the right atrial conduction time. The AH interval, measured from the low atrial to the bundle of His deflection, reflects conduction time through the AV node. The HV interval, measured from the bundle of His deflection to the earliest ventricular depolarization on the surface electrogram, represents the conduction time from the proximal bundle of His to the ventricular myocardium (82) (Table 63.2). The AH interval can vary greatly in an individual because of changes in sympathetic and parasympathetic tone. In contrast, the HV interval should remain constant, because this interval is not significantly affected by changes in autonomic tone.



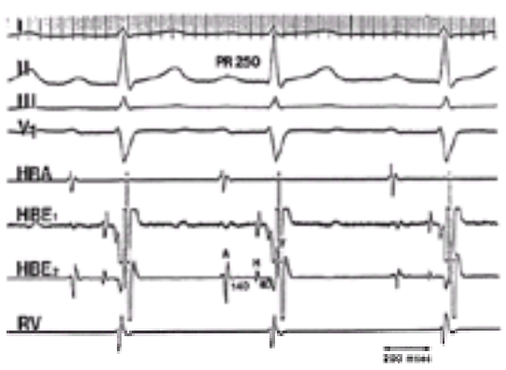
***e*FIGURE 63.3.6** Surface and intracardiac electrograms recorded during sinus rhythm. Surface electrogram leads I, II, III, and V_1 are recorded simultaneously with a high right atrial (HRA) electrogram and proximal (pHBE) and distal bundle of His electrograms (dHBE). Notice that the atrial activation sequence starts in the high right atrium and goes down to the atrial electrogram (A wave) in the bundle of His lead. This lower atrial activity is being recorded from the atrium near the atrioventricular node. See text for details of measuring the PA, AH, and HV intervals. RB, right bundle branch block. (From Weeks LC, ed. *Advanced cardiovascular nursing*. New York: Blackwell Science, 1986:517, with permission.)

Type	Interval (ms)
PA	20–50
AH	50–140
HV	35–55
H	10–25

TABLE 63.2 NORMAL CONDUCTION INTERVALS IN ADULTS

First-Degree Atrioventricular Block

First-degree AV block on the surface ECG is seen as a PR interval >0.20 seconds in adults or >0.18 seconds in children. Each P wave is followed by a QRS complex with a constant, prolonged interval. Although the conduction delay can be anywhere along the system, the PR prolongation is usually caused by delay within the AV node (87% when the QRS complex is narrow). On the bundle of His electrogram, this would be seen as an AH interval >130 ms with a normal HV interval (*e*Fig. 63.3.7). In cases in which first-degree AV block is seen in the presence of a bundle branch block, a bundle of His electrogram is necessary to localize the site of block (83,84 and 85) (*e*Fig. 63.3.8). Infranodal conduction delay is present in 45% of these cases. A combination of delay within the AV node and in the His-Purkinje system must also be considered (86). In certain cases of congenital structural heart disease, such as Ebstein's anomaly of the tricuspid valve or endocardial cushion defects, intraatrial conduction delay can cause first-degree AV block. In addition, intra-Hisian conduction delay can cause first-degree AV block. On the bundle of His electrogram, a split His potential can be seen, resulting in a prolonged His potential, HV, and PR intervals (86). Dual AV nodal physiology can produce transient, abrupt, or alternating first-degree block caused by block in the fast AV nodal pathway (which is normally used), with conduction down the slow pathway instead. The change in the PR interval seen on the surface electrogram corresponds with a jump in the AH interval viewed on the bundle of His electrogram (87).



***e*FIGURE 63.3.7** Bundle of His electrocardiogram in a patient with first-degree atrioventricular (AV) block (PR 250 m per second). Note in the proximal bundle of His lead (HBE_2) that the AH interval is prolonged (140 m per second) and the HV interval is normal (40 m per second). Therefore, the conduction delay causing the first-degree AV block is in the AV node. HRA, high right atrial recording; RV, right ventricular recording. (From Weeks LC, ed. *Advanced cardiovascular nursing*. New York: Blackwell Science, 1986:523, with permission.)

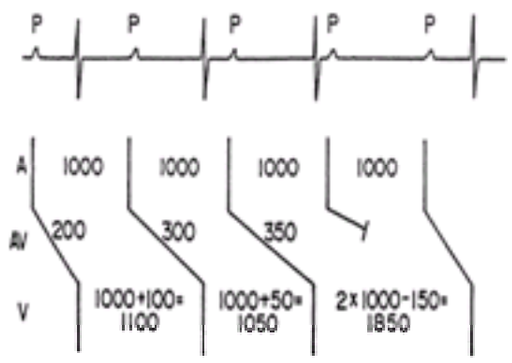
***e*FIGURE 63.3.8** Bundle of His electrogram in a patient with first-degree atrioventricular block (PR 250 ms) secondary to a prolonged HV interval of 165 ms. Because the AH interval is normal (80 ms), the conduction delay causing the block is occurring distal to the bundle of His in the His-Purkinje system. Note the bundle branch block pattern on the surface electrogram. HBE, bundle of His recording; HRA, high right atrial recording. (From Weeks LC, ed. *Advanced cardiovascular nursing*. New York: Blackwell Science, 1986:523, with permission.)

A 47-year-old male patient with Ebstein's anomaly.

Second-Degree Atrioventricular Block

Type I

Type I second-degree AV block, or Wenckebach block, features on the surface electrogram progressive prolongation of the PR interval before failure of an atrial impulse to be conducted to the ventricles. The PR interval immediately postblock returns to its baseline interval, and the sequence begins again. Features of typical Wenckebach periodicity include the following (*e*Fig. 63.3.9):



***e*FIGURE 63.3.9** Schematic of typical Wenckebach periodicity. The top panel shows a schematic electrocardiogram of a 4:3 Wenckebach cycle with prolonging PR intervals until the fourth P wave fails to conduct to the ventricle. On the bottom is a diagram illustrating the atrial (A), atrioventricular (AV) junctional, and ventricular (V) levels. Note that there is increasing conduction delay with each PR interval, but the amount of increase in conduction delay with each subsequent PR interval decreases. Therefore, the longest RR interval at the right of the figure is less than twice as long as the shortest RR interval immediately preceding it (see text for discussion). (From Miles MM, Klein LS. Sinus nodal dysfunction and atrioventricular conduction disturbances. In: Naccarelli GV, ed. *Cardiac arrhythmias: a practical approach*. Mount Kisco, NY: Futura, 1991:261, with permission.)

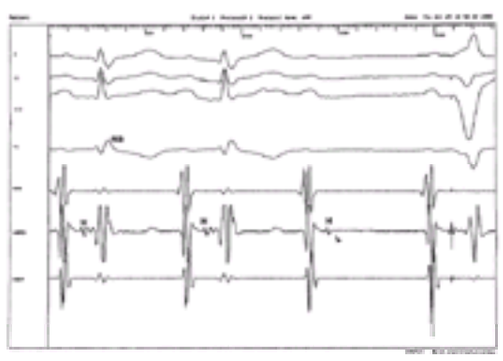
- Progressive lengthening of the PR interval throughout the Wenckebach cycle
- Lengthening of the RR interval occurring at progressively decreasing increments, resulting in progressive shortening of the RR intervals
- A pause including the nonconducted P wave that is less than the sum of any two consecutively conducted beats
- Shortening of the PR interval postblock, compared with the PR interval just preceding the blocked cycle

Less than 50% of type I AV block cases follow this typical pattern (88). Atypical patterns are more likely found with longer Wenckebach periods, >6:5. Differentiating atypical from typical patterns, however, is of little clinical significance.

Wenckebach block is almost always within the AV node when a narrow QRS complex is present (88). Intra-Hisian block is the rare exception (89). When type I block is seen with a bundle branch block, the block is still more likely to be in the AV node, but it could also be localized below the bundle of His. A bundle of His electrogram would be needed to accurately identify the level of block. Wenckebach block in the AV node is characterized by progressive prolongation of the AH interval, until an atrial deflection is not followed by a bundle of His or ventricular deflection. In type I block secondary to block below the bundle of His, progressive prolongation of the HV interval is followed by an H deflection without an associated ventricular depolarization.

Type II

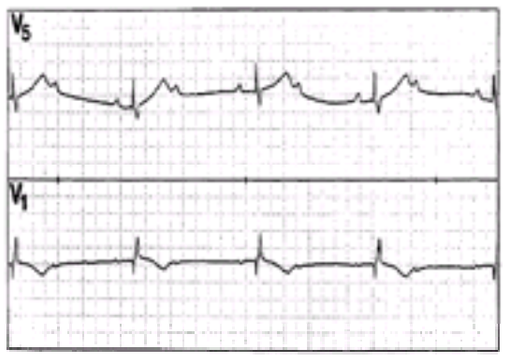
Type II, or Mobitz II, second-degree AV block is characterized on the surface electrogram by a constant PR interval, followed by sudden failure of a P wave to be conducted to the ventricles. The PP intervals remain constant, and the pause including the blocked P wave equals two PP intervals. Therefore, Mobitz II block should not be confused with a nonconducted premature atrial complex. Mobitz II block is usually associated with bundle branch block or bifascicular block. In a majority of these cases, the site of block is within or below the bundle of His (*e*Fig. 63.3.10) (84,86). When presumed Mobitz II block is seen in conjunction with a narrow QRS complex, Mobitz I with only minimal PR variation should be suspected. Only rarely is Mobitz II found with a narrow QRS complex and is caused by intra-Hisian block (90). The bundle of His electrogram is useful in verifying the site of the Mobitz II block. The blocked cycle features atrial and bundle of His deflections without a ventricular depolarization. The conducted beats usually show evidence of infranodal conduction system disease, with a prolonged HV interval, or even a split bundle of His potential (86).



***e*FIGURE 63.3.10** The surface leads I, II, III, and V_1 show first-degree atrioventricular block and right bundle branch block (RB). The third P wave is not followed by a QRS complex. The intracardiac tracings [HRA, high right atrial recording; proximal (HBEP) and distal bundle of His electrograms (HBED)] reveal the diagnosis of block within the bundle of His. The His deflection (H) is fractionated. The third beat shows only the first half of the His, and no ventricular electrogram follows.

2:1 Atrioventricular Block

Fixed 2:1 AV block poses a diagnostic dilemma because it is usually impossible to classify as type I or II block by a surface electrogram alone (*e*Fig. 63.3.11). A narrow QRS complex and recently seen Wenckebach block is highly suggestive of block at the AV nodal level. A 2:1 block associated with a wide QRS complex is likely infranodal, but it could still be at the level of the AV node. A definitive diagnosis can only be made with an intracardiac recording at the bundle of His region.



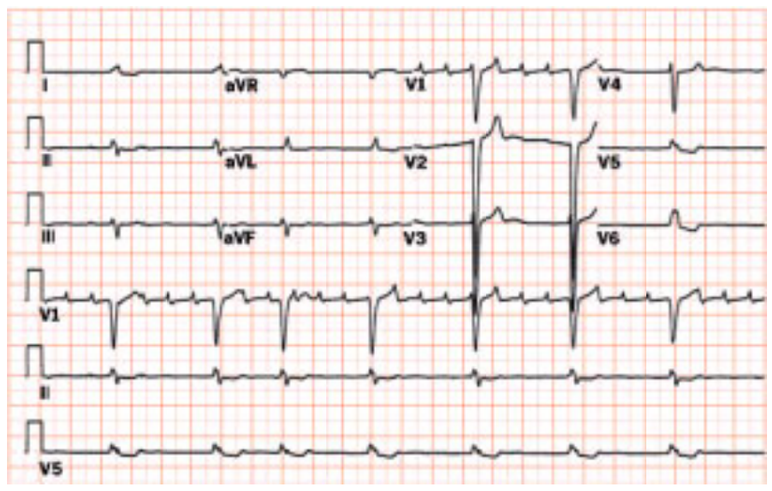
***e*FIGURE 63.3.11** Simultaneous surface tracings of leads V_1 and V_5 showing fixed 2:1 atrioventricular block and narrow QRS complexes. A definite diagnosis of either type I or II atrioventricular block cannot be made using this tracing alone.

Nonconduction of two or more consecutive P waves when AV synchrony is otherwise maintained is sometimes termed *high-degree AV block*. The level of block can be at the AV node or the His-Purkinje system. When high-degree AV block is caused by block in the AV node, QRS complexes of the conducted beats are usually narrow. Wenckebach periodicity is also seen, and atropine administration produces 1:1 conduction. Features pointing toward block in the His-Purkinje system are conducted beats with bundle branch block and no improvement in block with atropine. Bundle of His recordings are sometimes needed to confirm the site of block.

Third-Degree Atrioventricular Block

Third-degree, or complete, AV block is seen on the surface electrogram as completely dissociated P waves and QRS complexes, each firing at their own pacemaker rate. The atrial impulse is never conducted to the ventricles, but different levels of block are possible. The level of block determines the QRS morphology along with the site and rate of the escape rhythm. Congenital complete heart block is characterized by a narrow QRS complex with an escape rate between 40 and 60 beats/min, which tends to increase with exercise or atropine. This is consistent with block within the AV node. Acquired complete heart block is usually associated with block in the His-Purkinje system, resulting in a wide QRS complex with an escape rate between 20 and 40 beats/min. The intracardiac electrogram shows bundle of His deflections consistently following the atrial electrograms, but the ventricular depolarization is completely dissociated from these. Block below the bundle of His is thus demonstrated. In contrast, complete heart block at the AV nodal level is seen on the intracardiac tracings as bundle of His potentials consistently preceding each ventricular depolarization. The atrial electrograms are dissociated from the HV complexes (*e*Fig. 63.3.12). The sinus rate is faster than the ventricular rate in patients with complete heart block. Data collected from patients with congenital complete heart block have showed the atrial rate to usually be age appropriate (92). It is important to note that complete antegrade AV block does not always predict retrograde (VA) conduction. Retrograde conduction may be intact in an individual with complete antegrade AV block (Fig. 63.1).

***e*FIGURE 63.3.12** Congenital complete heart block located within the atrioventricular (AV) node. Sinus arrhythmia with a cycle length of approximately 860 ms is completely dissociated from a regular junctional escape rhythm with a cycle length of 1,360 ms. There is no relationship between atrial and ventricular depolarizations. There is no bundle of His deflection after any atrial depolarization. A bundle of His electrogram with a normal HV interval precedes each junctional escape complex in the bundle of His lead. Therefore, the site of AV block is within the AV node. Note the normal (narrow) morphology of the junctional escape QRS complexes. HBE, bundle of His electrogram; HRA, high right atrial recording. (From Miles MM, Klein LS. Sinus nodal dysfunction and atrioventricular conduction disturbances. In: Naccarelli GV, ed. *Cardiac arrhythmias: a practical approach*. Mount Kisco, NY: Futura, 1991:269, with permission.)



High-grade atrioventricular block. Note marked discrepancy between atrial and ventricular heart rates.

Atrioventricular Dissociation

AV dissociation is a secondary phenomenon that results from a primary conduction disorder. It is characterized by the atria and ventricles depolarizing independent of each other. By definition, there is no retrograde conduction from the ventricles to the atria. AV dissociation may occur because of slowing or a failure of impulse formation or conduction from the sinus node. In this situation, the atrial rate may become slower than a subsidiary escape focus from the AV junction or ventricle. Thus, a competing AV junctional or idioventricular rhythm may develop. AV dissociation may occur if there is an increase in the automaticity of a subsidiary pacemaker, such as accelerated junctional rhythm or ventricular tachycardia.

AV dissociation may be complete or incomplete (91). In complete AV dissociation, both the atrial and ventricular rates remain constant, and, therefore, the PR interval varies, with none of the atrial complexes conducted to the ventricles. In incomplete AV dissociation (interference dissociation), ventricular capture beats occur because some of the atrial impulses arrive at the AV junction when the AV junction is no longer refractory. This phenomenon is common in advanced AV block with periodic capture beats.

Pathophysiology

The term *AV block* denotes a delay or nonconduction of an atrial impulse to the ventricles when the AV junction is not physiologically refractory. Table 63.3 lists the majority of causes of AV block that have been identified. In each case, the abnormality may vary from a delay in conduction to intermittent or complete conduction failure.

TABLE 63.3 CAUSES OF ATRIOVENTRICULAR BLOCK

Drug effects are a common cause of acquired AV block in adults. Digoxin and beta-blocking agents act indirectly on the AV node through their effect on the autonomic nervous system. Calcium channel blockers and other antiarrhythmic drugs, such as amiodarone, act directly to slow conduction in the AV node. Type I and III antiarrhythmic drugs can also affect conduction in the His-Purkinje system, resulting in infranodal block. Drugs that have a significant effect on blocking the sodium channels, such as flecainide, have the most effect on slowing conduction in the His-Purkinje system. When AV block occurs secondary to antiarrhythmic therapy, it is usually in cardiac patients with preexisting conduction abnormalities. Patients with normal conduction system function rarely develop complete heart block as a result of

using antiarrhythmic agents.

Acute myocardial infarction is associated with varying degrees of AV block and is the most common cause of acquired complete AV block. Second- and third-degree AV blocks occur in up to 30% of patients presenting with acute myocardial infarction (93,94).

Abnormalities in AV nodal conduction are seen in 20% of patients hospitalized for acute inferior myocardial infarction (95), with the onset of block falling in a bimodal distribution (96,97). Eleven percent of those presenting in the first hour of symptoms are found to have second- or third-degree AV block (96). In contrast, the incidence of heart block is low in the second hour of symptoms. The majority of conduction abnormalities occur between 2 and 72 hours (95,98). Because of the short duration of the early conduction abnormalities and their favorable response to atropine, an increase in vagal tone associated with acute inferior myocardial infarction is the probably etiology of this early phenomenon (99). Type I AV block occurring later in the course of an acute inferior myocardial infarction is less responsive to atropine and probably is associated with reversible ischemia of the AV node or the release of adenosine during acute infarction (100). In this setting, type I AV block rarely progresses to more advanced block and commonly resolves within 2 to 3 days of onset.

Type II AV block occurs in only 1% of patients with acute myocardial infarction, but it has a worse prognosis than type I block. It is associated with bundle branch infarction during an acute anterior myocardial infarction and frequently progresses to complete heart block.

Complete heart block can occur with either anterior or inferior acute myocardial infarction. The site of the block in inferior myocardial infarction is usually at the level of the AV node, resulting in a junctional escape rhythm with a rate of 50 to 60 beats/min and narrow QRS complex. The abnormality tends to be reversed with vagolytic drugs or exercise and usually resolves in several days. Complete heart block in the setting of acute anterior myocardial infarction is usually associated with infarction of the bundle branches (101,102). The escape rhythm is approximately 40 beats/min, with a wide QRS complex originating from the bundle branch and Purkinje's system. It is less likely to be reversible. In general, patients who develop either transient or irreversible AV block are older and have a larger area of damage associated with their acute myocardial infarction. Other markers seen in this group include high levels of cardiac enzymes, bundle branch block, right ventricular infarction, or left ventricular failure (93,103,104,105 and 106).

In addition to acute myocardial infarctions, chronic ischemic heart disease can result in persistent AV block (107). Transient AV block can occur not only during angina pectoris (108), but during episodes of Prinzmetal's variant angina (109).

The most common cause of acquired conduction system disease is progressive idiopathic fibrosis. Lev's disease (110) is a result of proximal bundle branch fibrosis. It is postulated as a hastening of the aging process by hypertension and arteriosclerosis of the blood vessels supplying the conduction system. Lenègre's disease (111) is a degenerative process occurring in a younger population and involving the more distal portions of the bundle branches.

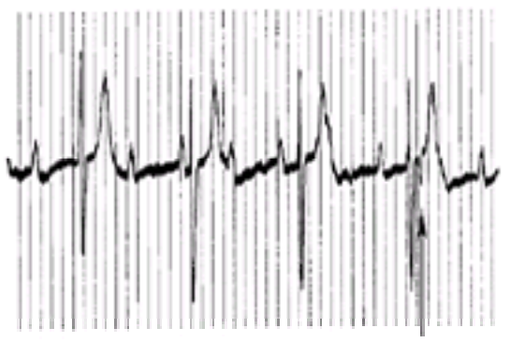
Calcification of the aortic or mitral valve annulus can extend to the nearby conduction system and produce AV block (112,113). The incidence is more frequent with aortic than mitral stenosis. AV block can also result from a stenotic bicuspid aortic valve (114,115). Other causes of AV block include infiltrative cardiomyopathies such as amyloidosis (116), sarcoidosis (116,117), and hemochromatosis (118,119), as well as the collagen vascular diseases of scleroderma (120), rheumatoid arthritis (121), Reiter's syndrome (122), systemic lupus erythematosus (123), ankylosing spondylitis (124), and polymyositis (125).

Complete heart block occurs in 3% of cases of infective endocarditis, with the aortic valve being involved more frequently than the mitral valve (126,127). A variety of viral, bacterial, and parasitic etiologies of myocarditis result in varying degrees of AV block and include Lyme disease, rheumatic fever, Chagas's disease (128), tuberculosis, measles, and mumps. Transient AV block is the most frequently seen cardiac abnormality associated with Lyme disease. First-degree block is almost always observed in these cases, representing up to 8% of those infected. Complete heart block can develop in 50% of those with first-degree block, especially if the PR interval exceeds 0.30 seconds (129,130). Acute rheumatic fever almost invariably results in PR prolongation when carditis is present (131,132). Second-degree block occurs only occasionally, and progression to complete heart block is rare (133).

Cardiac surgery can be complicated by varying degrees of AV block caused by trauma and ischemic damage to the conduction system. Block is most frequently associated with aortic valve replacement (134). In the absence of myocardial infarction or a long ischemic time, block is rarely seen post–coronary artery bypass grafting. Repair of congenital heart defects in the region of the conduction system—such as endocardial cushion malformations, ventricular septal defects, and tricuspid valve abnormalities—can lead to transient or persistent AV block (see Chapter 70). The block is usually temporary and thought to be secondary to postoperative local inflammation. However, block can appear years later, usually in those who had transient block just after the operation (135).

Intracardiac catheter manipulation can inadvertently produce complete heart block, which is usually temporary. This can occur during a right-sided heart catheterization in a patient with preexisting left bundle branch block, or even during left ventricular angiography in a patient with previous right bundle branch block (136,137 and 138). Radiofrequency catheter ablation techniques are used to modify the AV nodal junction or to produce complete heart block in patients with supraventricular tachyarrhythmias that cannot be controlled by medical therapy alone (139). AV block can also complicate radiofrequency catheter ablation used to treat AV nodal reentrant tachycardia or AV reentrant tachycardia. The incidence of complete heart block complicating this procedure is low when performed by experienced operators and when the bundle of His region is avoided (140,141).

Other causes of acquired AV block include hyperkalemia (142), hypermagnesemia, Addison's disease (143), tumors that infiltrate the heart (144), and neuromyopathic disorders (145,146 and 147). Additionally, transient AV block can be seen with carotid sinus syndrome (eFig. 63.3.13) (148) and vasovagal syncope (149).



***e*FIGURE 63.3.13** Electrogram of acquired complete atrioventricular block. The P-wave cycle length is 840 ms and is independent of the regular wide QRS escape mechanism at 1,800 ms (less than 40 per minute). There is no relationship between the P waves and the QRS complexes at any time during the recording until the next to the last P wave (*arrow*), where there is early retrograde atrial activation representing ventriculoatrial conduction despite complete anterograde atrioventricular block. Therefore, in some patients, retrograde conduction may be intact, even though anterograde conduction is not, or vice versa. (From Miles MM, Klein LS. Sinus nodal dysfunction and atrioventricular conduction disturbances. In: Naccarelli GV, ed. *Cardiac arrhythmias: a practical approach*. Mount Kisco, NY: Futura, 1991:269, with permission.)

Congenital complete AV block is thought to result from abnormal embryonic development of the AV node (150) and is thought to occur in 1 of every 25,000 live births (151). As the defect usually occurs proximal to the bundle of His, the QRS complex is narrow. This abnormality is found in otherwise structurally normal hearts in 50% of cases, whereas the rest have concurrent congenital heart disease (see Chapter 70) (152). Corrected transposition of the great vessels (153), ventricular septal defects, ostium primum atrial septal defects, and Ebstein's anomaly of the tricuspid valve (154) are all associated with AV nodal defects. Congenital complete heart block is also associated with collagen vascular disease in the mother, especially lupus erythematosus (155).

Clinical Profile

Incidence

PR prolongation, or first-degree AV block, is rarely found in young healthy adults, but the incidence increases with age and in those with heart disease. An epidemiologic study involving a large population of asymptomatic male pilots revealed PR intervals more than 0.2 seconds in only 0.52% (156). Two percent of adults over 20 years of age in Tecumseh, MI, were found to have a PR greater than or equal to 0.22 seconds (157). Both studies noted the PR interval to vary over time in young, healthy adults. Frequently in this population, the PR shortens with an increase in heart rate, suggesting vagal influence (156,157). Other epidemiologic surveys

have shown a 5% incidence of first-degree AV block in men over 60 years of age and as high as 10% in older patients with cardiac disease (158,159).

In the large study of a population of healthy pilots, type II second-degree block was found to be extremely rare. In contrast, type I (Wenckebach) block can be seen in young athletes at rest and has been documented by ambulatory Holter monitoring in healthy teenagers during rest or sleep (160). Wenckebach periodicity in these settings disappears with exercise and should be considered a normal variant. On the other hand, in a population of patients with heart disease, the incidence of second-degree AV block (types I and II) was 2.7% (161).

Congenital complete heart block is estimated to occur in 1 of 15,000 to 25,000 live births, with a 60% female predominance (162,163). Acquired complete heart block is rarely seen in young individuals without heart disease (156). The highest incidence occurs in the seventh decade, and there is a 60% male predominance (164,165).

Symptoms

Individuals with first-degree AV block are asymptomatic. Symptoms of dizziness or syncope usually occur with acquired high-grade or complete AV block. With time, the majority of these patients experience a Stokes-Adams attack (166). Other symptoms can occur as a result of low cardiac output, including fatigue, congestive heart failure (166), dyspnea on exertion, angina, or even mental status changes.

Most children and adolescents with congenital complete heart block are asymptomatic, but some go on to develop symptoms later as adults. Those with concomitant structural heart disease, a wide QRS complex, long QT, or complete heart block discovered at an early age have an increased risk of developing symptoms, and some may die suddenly (167,168 and 169).

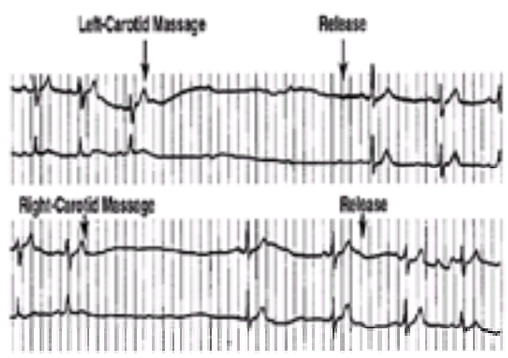
Diagnostic Techniques

Because the prognosis and the treatment differ in AV block depending on whether block is within the AV node or infranodal, determining the site of block is important. In many cases, this can be done noninvasively. As described previously, the QRS duration, PR intervals, and ventricular rate on the surface electrogram can provide important clues in localizing the level of block. Several noninvasive interventions may also prove helpful, such as vagal maneuvers, exercise, or administration of atropine. These methods take advantage of the differences in autonomic innervation of the AV node and His-Purkinje system. Whereas the AV node is richly innervated and highly responsive to both sympathetic and vagal stimuli, the His-Purkinje system is influenced minimally by the autonomic nervous system. Carotid sinus massage increases vagal tone and worsens AV nodal block. Exercise or atropine improves AV nodal conduction because of sympathetic stimulation. In contrast, carotid sinus massage improves infranodal block, whereas exercise and atropine worsen infranodal block because of the change in the rate of the impulses being conducted through the AV node.

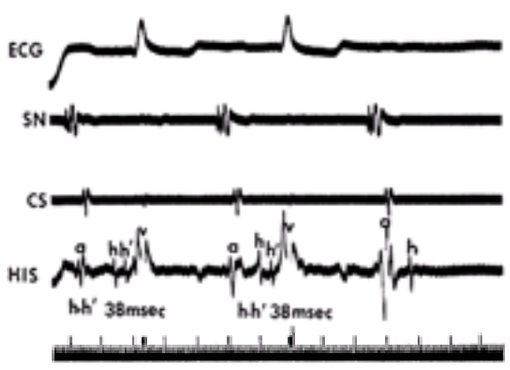
Exercise testing is a useful tool to help confirm the level of block already suspected in second- or third-degree block caused by a narrow or wide QRS complex. Patients with presumed type I block or congenital complete heart block and a normal QRS complex usually enjoy an increased ventricular rate with exercise. On the other hand, patients with acquired complete heart block and a wide QRS complex usually show minimal or no increase in ventricular rate.

An electrophysiologic study is indicated in a patient with suspected high-grade AV block as the cause of syncope or presyncope, when documentation cannot be obtained noninvasively. In patients with coronary artery disease, it may be unclear whether symptoms are secondary to AV block or ventricular tachycardia; therefore, an electrophysiologic study can be useful in establishing the diagnosis. Some patients with known second- or third-degree block may benefit from an invasive study to localize the site of AV block to help determine therapy or assess prognosis. Once symptoms and AV block are correlated by ECG, further documentation by invasive studies is not required, unless additional information, as discussed previously, is needed. Others who should not undergo electrophysiologic studies are asymptomatic patients with transient Wenckebach block associated with increased vagal tone.

The electrophysiology study allows analysis of the bundle of His electrogram, as well as atrial and ventricular pacing to look for conduction abnormalities and inducible ventricular tachycardia. The AH and HV intervals are measured from the bundle of His electrogram. A markedly prolonged HV interval greater than or equal to 100 ms is associated with a high incidence of progression to complete heart block (170). A His potential greater than or equal to 30 ms in duration or frankly split into two deflections is indicative of intra-Hisian conduction delay (eFig. 63.3.14). When the bundle of His electrogram is observed during atrial pacing, the AH interval normally gradually lengthens until Wenckebach block is seen. The HV interval normally remains consistent, despite different pacing rates. Abnormal AV nodal conduction produces Wenckebach block at slower atrial-paced rates than what is normally seen (i.e., greater than 500 ms). To determine whether AV nodal disease is truly present or just under the influence of excessive vagal tone, atropine or isoproterenol is given to see if conduction improves. As discussed in the section Third-Degree Atrioventricular Block, infranodal block is present when the atrial deflection is followed by the bundle of His electrogram, but no ventricular depolarization is seen. Block below the bundle of His is abnormal, unless associated with short paced cycle lengths (350 m per second or less) (eFig. 63.3.15) (171).



***e*FIGURE 63.3.14** The top tracing demonstrates advanced atrioventricular block during left carotid massage. Two consecutive P waves are seen without following QRS complexes. The bottom tracing shows a sinus pause during right carotid massage. (Unpublished data from J. Luck.)



***e*FIGURE 63.3.15** A prolonged His potential of 38 m per second is seen, along with a split His (h-h') on the intracardiac electrogram. CS, carotid sinus; ECG, electrocardiogram; SN, sinus node. (Unpublished data from R. DeJoseph.)

Natural History of Atrioventricular Blocks

The prognosis of any AV block is primarily dependent on the extent of the associated heart disease. First-degree AV block is usually benign and carries no increased mortality risk when seen as an isolated finding (157). However, first-degree AV block can be found in conjunction with bifascicular block or infranodal disease, therefore increasing the risk of progression to complete heart block.

Type I second-degree, or Wenckebach, AV block is generally benign, usually being transiently observed in the setting of acute inferior myocardial infarction or

associated with increased vagal tone in healthy, athletic individuals. However, as with first-degree AV block, when type I AV block occurs in association with bifascicular or trifascicular block the risk of progression to complete heart block is significantly increased because of probable infranodal disease. Type II second-degree AV block, usually seen with bundle branch block, and associated with acute anterior myocardial infarction, carries a high risk of progression to advanced or complete AV block. The prognosis of 2:1 AV block depends on whether the site of block is within or below the AV node.

Before the availability of pacemakers, the prognosis for patients with symptomatic complete heart block was dismal, regardless of the extent of underlying heart disease. The 1-year survival rate after the first Adams-Stokes attack was less than 50% (172). Presently, once appropriate pacing therapy has been established, the prognosis depends on the underlying disease process (173). Patients who develop complete heart block as a result of an anterior myocardial infarction have a poor prognosis because of extensive cardiac damage. In contrast, those who develop complete heart block from idiopathic bundle branch fibrosis and who have no additional cardiac disease have a prognosis similar to those of similar age without heart block.

Congenital complete heart block generally carries a more favorable diagnosis than the acquired form when not associated with underlying heart disease. However, data have shown a significant risk of syncope, sudden death, and acquired mitral insufficiency in this group (174).

Principles of Management

Pacing is now the mainstay of treatment for symptomatic heart block. Medical therapy is only effective as a short-term emergency measure, until pacing can be accomplished. Before the availability of permanent pacing, drugs were used, but only because they were the only known therapies; no effective long-term medical therapy existed.

Complicated acute inferior myocardial infarction. Note inferior ST-segment elevation as well as atrioventricular dissociation secondary to complete heart block.

Before instituting permanent pacing, the possibility of a reversible cause of the heart block should be investigated (Table 63.3). Any offending drugs, such as digoxin, calcium channel blockers, or membrane-active antiarrhythmic drugs, should be withdrawn, if possible, to see if the block improves. Electrolyte abnormalities should also be looked for and then corrected. The possibility of infectious processes should be considered and then treated.

The key point in the decision to provide permanent pacing in AV block is the presence of symptoms. Intermittent block may make correlating bradycardia with symptoms difficult. However, once this is done, pacing should be instituted. Patients with complete heart block and syncope have clearly been shown to have improved survival with permanent pacing (175). Most patients with acquired complete heart block are symptomatic and require pacing. Patients with congenital complete heart block are more likely to be asymptomatic, but prophylactic pacemaker implantation is an appropriate consideration (174). Block in the AV node is less likely to be associated with slow ventricular rates, progression to complete heart block, and symptoms than is infranodal block.

The decision to pace is not always clear when dealing with the asymptomatic patient. However, investigation data and the American College of Cardiology/American Heart Association task force report (61) are helpful in providing some general guidelines (eTable 63.3.1). Permanent pacing is recommended in asymptomatic awake patients with documented pauses of greater than 3.0 seconds or a ventricular escape rhythm of less than 40 beats/min. When type II second-degree heart block is found in an asymptomatic individual, an electrophysiologic study is warranted to determine if the block is infranodal. If this is the case, prophylactic pacing may be considered because of the high risk of progression to complete heart block (176). Permanent pacing is recommended in asymptomatic children with congenital heart block when found in association with a wide complex escape rhythm, complex congenital heart disease, ventricular dysfunction, or a long QT interval. Additionally, exercise intolerance, abrupt pauses in the intrinsic rate, and average ventricular rate inappropriate for the child's age are criteria for pacing in this population (eTable 63.3.2) (177,178 and 179). It is now recognized that dual-chamber pacing can be beneficial in some patients with marked first-degree AV block (>3.0 seconds) to reduce symptoms similar to pacemaker syndrome (180). Additionally, patients with left ventricular dysfunction and a long PR interval may see hemodynamic improvement once paced with a shorter AV delay. In both scenarios, improvement in symptoms, hemodynamics, or both should be documented with temporary AV pacing before the implantation of a permanent device (181).

***e*TABLE 63.3.1** INDICATIONS FOR PERMANENT PACING IN ACQUIRED ATRIOVENTRICULAR (AV) BLOCK[a]

Class I
Symptomatic complete heart block (including associated congestive heart failure, angina, or confusional states)
Asystole ³3 seconds or escape rhythm <40 beats/min in asymptomatic, awake patients with complete heart block
Symptomatic second-degree AV block (regardless of site of block)
Symptomatic bradycardia resulting from required cardiac drugs
After catheter ablation of the AV junction
Class IIa
Asymptomatic complete heart block with ventricular rate >40 beats/min
Asymptomatic type II second-degree AV block
Asymptomatic type I second-degree AV block at intra-His or infra-His levels
Symptomatic first-degree AV block (similar to pacemaker syndrome)
Class IIb
Marked first-degree AV block (>0.3 seconds) shown to cause hemodynamic compromise in patients with left ventricular dysfunction
Class III
First-degree AV block
Asymptomatic type I second-degree AV block at the level of the AV node

[a]Class I indications are conditions for which it is generally agreed that pacing is needed. Class II indications are conditions associated with varying opinions as to the necessity of pacing. The efficacy of pacing is less well established for class IIb than for class IIa. Class III indications are conditions in which pacing is thought not to be indicated.

***e*TABLE 63.3.2** INDICATIONS FOR PERMANENT PACING IN CHILDREN[a]

Class I
Symptomatic second- or third-degree AV block
Symptomatic sinus nodal dysfunction
Advanced second- or third-degree AV block persisting 7 days post–cardiac surgery
Congenital AV block with wide QRS or ventricular dysfunction
Congenital AV block in an infant with a ventricular rate <50 beats/min (or <70 beats/min with congenital heart disease)
Sustained, pause-dependent ventricular tachycardia, with or without prolonged QT, when efficacy of pacing is documented
Class IIa
Tachycardia-bradycardia syndrome with antiarrhythmic drug therapy needed
Long QT syndrome with 2:1 AV block or third-degree AV block
Average heart rate <50 beats/min or abrupt ventricular pauses two or three times the basic cycle length in a child (over 1 year old) with congenital third-degree AV block
Resting heart rate <35 beats/min or ventricular pauses >3 seconds in an asymptomatic child with complex congenital heart disease and sinus bradycardia
Class IIb
Transient third-degree AV block post–cardiac surgery that reverts to bifascicular block

Asymptomatic child of any age with congenital third-degree AV block and an appropriate heart rate, normal ventricular function and narrow QRS complex
Adolescent with congenital heart disease and asymptomatic sinus bradycardia with a resting heart rate <35 beats/min or ventricular pauses >3 seconds
Class III
Asymptomatic postoperative bifascicular or trifascicular block
Transient postoperative AV block that reverts to normal conduction within 7 days
Asymptomatic sinus bradycardia in an adolescent with a heart rate >40 beats/min and the longest RR interval <3 seconds
Asymptomatic type I second-degree AV block

AV, atrioventricular.
[a]Class I indications are conditions for which it is generally agreed that pacing is needed. Class II indications are conditions associated with varying opinions as to the necessity of pacing. The efficacy of pacing is less well established for class IIb than for class IIa. Class III indications are conditions in which pacing is thought not to be indicated.

Temporary pacing is sometimes required in patients with acute myocardial infarction (anterior more often than inferior wall). Patients with asymptomatic first-degree or type I second-degree block do not require pacing. However, patients with type II second-degree or complete heart block should be temporarily paced, even if asymptomatic.

If type II second-degree block or complete AV block persists once out of the periinfarct period, permanent pacing is indicated. Even if the type II or third-degree block was transient but associated with bundle branch block, studies suggest permanent pacing of the postmyocardial infarction patient improves long-term survival (182). In the setting of myocardial infarction, the criteria for permanent pacing depends less on the presence of symptoms (*e*Table 63.3.3).

***e*TABLE 63.3.3** INDICATIONS FOR PERMANENT PACING POST–MYOCARDIAL INFARCTION[a]

Class I
Persistent high-grade or complete AV block with bilateral bundle branch block (infranodal)
Transient high-grade AV block associated with bundle branch block
Persistent, symptomatic second- or third-degree AV block
Class IIa
None
Class IIb
Persistent high-grade block at the AV nodal level
Class III
Transient AV block without intraventricular conduction defect
Transient AV block with isolated left anterior (or posterior) fascicular block
New left anterior (or posterior) fascicular block without AV block
First-degree AV block with new bundle branch block

AV, atrioventricular.
[a]Class I indications are conditions for which it is generally agreed that pacing is needed. Class II indications are conditions associated with varying opinions as to the necessity of pacing. The efficacy of pacing is less well established for class IIb than for class IIa. Class III indications are conditions in which pacing is thought not to be indicated.

The need for permanent pacing because of advanced or complete AV block post–myocardial infarction appears to be significantly reduced by reperfusion therapy. The anticipated result of early reperfusion would be greater myocardial salvage, making damage to the conduction system less likely. Although few data are available to confirm this hypothesis, an analysis of a large series of patients with acute myocardial infarction treated with thrombolytic therapy, who also underwent continuous 12-lead ECG monitoring for 36 to 72 hours, shows the occurrence of persistent bundle branch block to be reduced in this group (5.3%, compared with 8% to 18% reported in the prethrombolytic era) (183). In this study population, patients with persistent bundle branch block had lower ejection fractions, and most had left anterior descending artery infarcts. The higher mortality associated with bundle branch block is caused by the associated increased risk of complete heart block and sudden death in this group. Despite thrombolytic therapy, the occurrence of persistent bundle branch block still identifies a subset of patients with higher mortality than those with either transient or no bundle branch block.

BUNDLE BRANCH BLOCKS

Although the trifascicular concept is not consistent with pathologic findings, it remains clinically useful and provides an accepted framework for the discussion of intraventricular conduction abnormalities. It should be noted that even though we refer to intraventricular conduction disorders as *block*, they are more accurately described as slowed conduction in one or more portions of the fascicles, or partial blocks. ECG criteria have been established for recognition of right and left bundle branch blocks and hemiblocks (*e*Table 63.3.4). Bifascicular block is defined as conduction delay in two of the fascicles: right bundle branch block with left anterior fascicular block, right bundle branch block with left posterior fascicular block, or left bundle branch block. Trifascicular block is recognized with slowed conduction in three fascicles, namely PR prolongation in addition to bifascicular block. In some cases, progressive slowing of multiple areas of conduction can result in complete heart block. Acquired intraventricular conduction delay is most commonly a product of idiopathic degenerative conduction disease. The incidence is 0.6% in the total population and increases with age (up to 2% in those more than 60 years of age). There is a high association with structural heart disease, especially coronary artery disease (184).

A 93-year-old male patient with trifascicular block.

***e*TABLE 63.3.4** ELECTROCARDIOGRAPHIC CRITERIA OF BUNDLE BRANCH BLOCKS AND HEMIBLOCKS

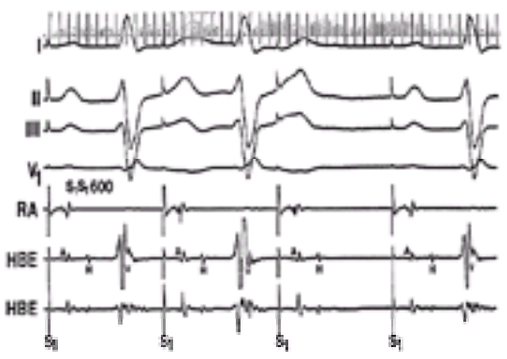
Electrocardiographic criteria for right bundle branch block
QRS duration ³120 ms
Lead V, with rsR[1] or rSR[1] morphology
Leads I, aVL, and V_6 with qRS, where terminal S deflection is wide
Electrocardiographic criteria for left bundle branch block
QRS duration ³120 ms
Leads V_6, I, and aVL showing broad monophasic R wave
Lead V_1 with rS or QS morphology
ST and T wave directed opposite to the predominate deflection of the QRS complex
Electrocardiographic criteria for left anterior fascicular block
Left axis deviation (³ –45 degrees)
rS pattern in leads II, III, and aVF
QR pattern in aVL with a delayed intrinsicoid deflection
Peak of the terminal R wave in aVL preceding the peak of the terminal R wave in aVR
Peak of the initial R wave in lead III preceding the peak of the initial R wave in lead II
Electrocardiographic criteria for left posterior fascicular block
Right axis deviation (³120 degrees)
S_1 Q_3 pattern, with rS in lead I and qR complexes in leads II, III, and aVF
Delayed intrinsicoid deflection in lead aVF

aVF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead; aVR, augmented voltage unipolar right arm lead.

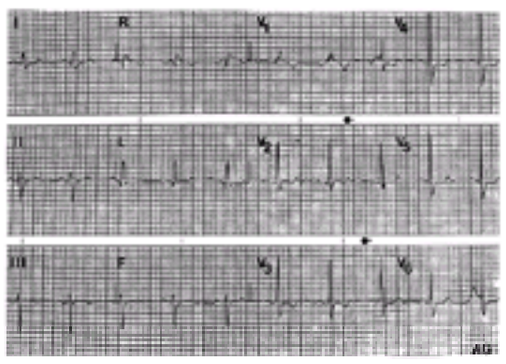
Right bundle branch block is more common than left bundle branch block (185). It rarely progresses to AV block or produces symptoms. There is not an increased association with coronary artery disease (186). Left bundle branch block is less common than right bundle branch block, but it is commonly associated with heart disease (187) and an increased mortality that rises significantly when the abnormality is newly acquired (188). Left anterior fascicular block is more frequently found than right bundle branch block. Left posterior fascicular block is seen less frequently than left bundle branch block (187) and is almost always associated with right bundle branch block.

Left bundle branch block. Wide QRS complex, negative in lead V_1, is associated with secondary T-wave inversions.

Right bundle branch block in association with left anterior fascicular block is the most common type of bifascicular block (*e*Fig. 63.3.16 and *e*Fig. 63.3.17); however, only 6% of these cases go on to complete heart block. Right bundle branch block with left posterior fascicular block is rare, but progression to complete heart block is higher, presumably because of more widespread conduction disease. Patients with left bundle branch block and left axis deviation have a 6% incidence of progressing to complete heart block. Those patients with left bundle branch block alone have a much lower rate of progression (189).



***e*FIGURE 63.3.16** Bundle of His electrograms (HBE) during high right atrial (RA) pacing (S_1-S_1 600 m per second, 100 beats/min) in a patient with right bundle branch block and left anterior hemiblock documenting block distal to the bundle of His. Note that after the third atrial depolarization there is a His deflection but no ventricular depolarization. Therefore, block of the impulse occurred distal to the bundle of His. (From Weeks LC, ed. *Advanced cardiovascular nursing*. New York: Blackwell Science, 1986:525, with permission.)



***e*FIGURE 63.3.17** Twelve-lead electrocardiogram demonstrating right bundle branch block and left anterior fascicular block.

The prognosis of patients with bifascicular block depends on the extent of underlying heart disease. There is no group in which a high incidence of progression to AV block can be predicted by surface ECG alone. However, the bundle of His electrogram is useful to identify a group at higher risk of developing complete AV block. If the HV interval is found to be markedly prolonged (90 to 100 ms), or if block below the bundle of His is seen during atrial pacing, prophylactic pacing is indicated because of a high progression of complete heart block (*e*Table 63.3.5) (170,190).

***e*TABLE 63.3.5** INDICATION OF PERMANENT PACING IN BIFASCICULAR AND TRIFASCICULAR BLOCK[a]

Class I
Bifascicular block with intermittent complete heart block
Bifascicular or trifascicular block with type II second-degree AV block
Class IIa
Bifascicular or trifascicular block in syncope patient in which complete heart block is the presumed (but not proven) etiology
HV interval >100 ms
Pacing-induced block below the bundle of His that is not physiologic
Class IIb
None
Class III
Asymptomatic fascicular block with first-degree AV block

AV, atrioventricular.

[a]Class I indications are conditions for which it is generally agreed that pacing is needed. Class II indications are conditions associated with varying opinions as to the necessity of pacing. The efficacy of pacing is less well established for class IIb than for class IIa. Class III indications are conditions in which pacing is thought not to be indicated.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The proper choice of the most appropriate, cost-effective pacemaker is often straightforward. A patient with chronic atrial fibrillation who needs a pacemaker should be prescribed a VVI or VVIR device. A patient with complete AV block and normal sinus node function should receive a dual-chamber device. In patients with chronotropic incompetence, a rate-responsive device should be prescribed. Because of technologic breakthroughs, industry continues to tempt physicians to use the smallest,

newest, most sophisticated, dual-chamber, rate-responsive pacemakers in almost all patients, even though this approach may not be cost effective. *e*Table 63.3.6 lists current recommendations for optimal pacing modes recommended by the British Pacing and Electrophysiology Group (191).

***e*TABLE 63.3.6** RECOMMENDATIONS OF THE BRITISH PACING AND ELECTROPHYSIOLOGY GROUP

Diagnosis	Optimal mode	Alternative mode	Inappropriate mode
Sinus nodal disease	AAIR	AAI	VVI VDD
Atrioventricular block	DDD	VDD	AAI DDI
Sinus nodal disease and atrioventricular block	DDDR DDIR	DDD DDI	AAI VVI
Chronic atrial fibrillation and atrioventricular block	VVIR	VVI	AAI DDD VDD
Hypersensitive carotid sinus syndrome	DDI	DDD VVI	AAI VDD
Malignant vasovagal syndrome	DDI	DDD	AAI VVI VDD

Many investigators propose that dual-chamber devices should be implanted in all patients who need pacemakers, unless the patient has chronic atrial fibrillation. This approach preserves AV synchrony under all scenarios except for paroxysms of atrial tachyarrhythmias. Retrospective studies have suggested that atrial-based pacing leads to fewer cases of chronic atrial fibrillation and thromboembolism and a possible reduction in mortality when compared with single-chamber ventricular pacing systems (60). In addition, dual-chamber systems minimize the occurrence of pacer syndrome, which can occur in 8% to 10% of patients with VVI pacemakers (192).

Antagonists of the previously mentioned position argue that these data are based on retrospective, uncontrolled trials. A metaanalysis of a large number of trials suggested that the data are not convincing for the superiority of dual-chamber pacing (60).

Several prospective trials are testing the hypothesis of the long-term superiority of dual-chamber or atrial-based pacing compared with single-chamber ventricular-based pacing. The Canadian Trial of Physiologic Pacing completed a 3-year follow-up of patients with sinus nodal dysfunction. Although the rate of atrial fibrillation was significantly lower in the physiologically paced group, more perioperative complications were noted caused by implantation of an atrial lead. The rate of cardiovascular death and stroke was similar in the two groups, as well as overall mortality and hospitalizations for heart failure (192). In a smaller Danish trial (193), a significant reduction in mortality was found with atrial pacing after 5.5 years, but not after only 3.3 years of follow-up. Therefore, the Canadian Trial of Physiologic Pacing investigators have elected to follow their cohort for an additional 3 years to see if a delayed benefit of physiologic over ventricular pacing occurs (194).

The results of the Pacemaker Selection in the Elderly Trial showed that patients with sinus nodal dysfunction—but not AV block—experienced improved quality of life and cardiovascular functional status with dual-chamber pacing as opposed to ventricular pacing (195). The Mode Selection Trial should help further define the benefits of dual-chamber versus single-chamber ventricular pacing in patients with sinus nodal dysfunction (196). The United Kingdom Pacing and Cardiovascular Events Trial is designed to answer the same question in elderly patients with high-degree AV block (197). Both studies have completed enrollment of 2,000 patients each and are now in their follow-up phases. The results of these trials, along with the extended follow-up Canadian Trial of Physiologic Pacing data, will likely provide the information needed for definitive evidence-based recommendations on pacemaker mode prescriptions (195).

THE FUTURE

Decreased pacemaker size along with software enhancements and increased battery longevity will help make the implantation and follow-up of pacemakers safer and more cost effective. Outcome studies will ultimately help us develop the most cost-effective and efficient strategies for prescribing and following pacemaker patients.

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ATRIAL FIBRILLATION

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"Indicates text or graphics that appear only in the electronic versions of this text."

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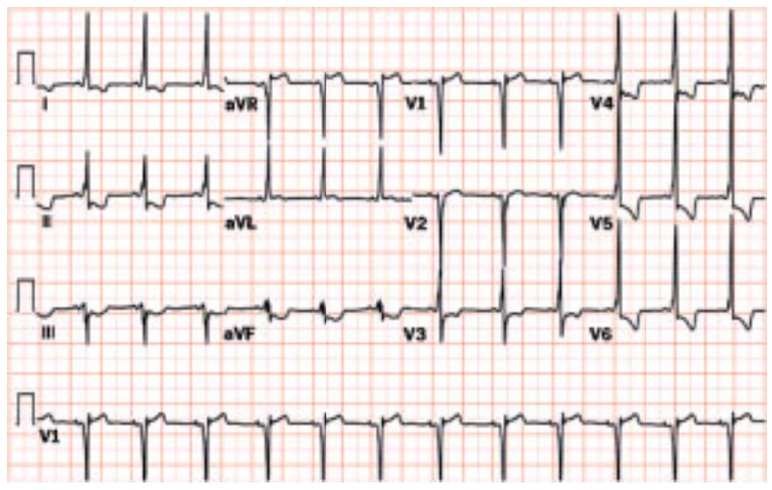
OVERVIEW

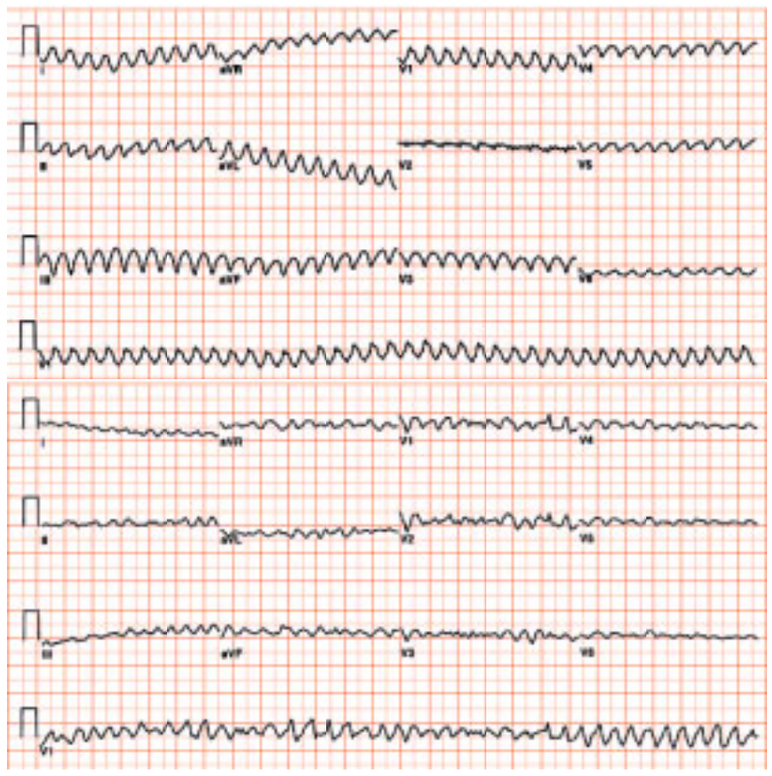
Atrial fibrillation is the most common sustained arrhythmia affecting humans. Pathology studies have found loss of atrial myocardium with fibrosis and fatty infiltration, but many similar changes can occur as a result of aging alone. Maintenance of atrial fibrillation likely depends on reentry, with multiple wavelets occurring simultaneously. The initiation of atrial fibrillation in many patients may be caused by a rapidly firing focus, often in the pulmonary vein(s). Although the atrial rate is rapid, typically greater than 300 beats/min, the ventricular response depends on atrioventricular (AV) node conduction properties and the level of autonomic tone. AV node conduction is facilitated by sympathetic tone and inhibited by parasympathetic tone. A variety of medical conditions are associated with atrial fibrillation, most frequently hypertension, coronary artery disease, and valvular heart disease. Many patients have idiopathic, or lone, atrial fibrillation. There are three major tenets of therapy: (a) restoration and maintenance of sinus rhythm, (b) ventricular rate control, and (c) prevention of thromboembolism. One or more of these may be indicated in a particular patient. Several antiarrhythmic agents are effective for restoring and maintaining sinus rhythm, and selection of a particular drug depends on many factors, including the presence and type of underlying heart disease, concomitant illnesses, and renal or hepatic dysfunction. Beta-adrenergic blockers and calcium channel blockers are more effective than digoxin in controlling ventricular response, although digoxin is the first-line treatment for patients who have congestive heart failure. In patients who have Wolff-Parkinson-White syndrome (WPW), intravenous procainamide or ibutilide is the preferred therapy for blocking conduction over the accessory pathway during atrial fibrillation, and digoxin, adenosine, beta-adrenergic blockers, and calcium channel blockers are contraindicated. In patients at high risk for thromboembolism, anticoagulation therapy using warfarin is recommended, aiming for an international normalized ratio (INR) of 2.0 to 3.0. Anticoagulation is also recommended for patients who are undergoing pharmacologic or electrical cardioversion, if atrial fibrillation has been present for at least 48 hours. Nonpharmacologic approaches to therapy include atrial pacing, radiofrequency catheter ablation, surgery, and implantable atrial defibrillators.

Historical Perspective

Atrial fibrillation is the most common sustained arrhythmia affecting humans. Interest in it has waxed and waned for decades, and recently it has taken a back seat to research into arrhythmias such as AV reentry (WPW), AV node reentry, sustained ventricular tachycardia, and ventricular fibrillation. However, there has been a resurgence in interest in the mechanisms and treatment of patients with atrial fibrillation, especially in the potential for curing this arrhythmia using intracardiac catheter ablation techniques. The following is a brief summary of luminaries who have made important observations concerning atrial fibrillation.



Wolff-Parkinson-White syndrome. Eleven-year-old patient with manifest preexcitation consistent with Wolff-Parkinson-White.



Atrioventricular nodal reentrant tachycardia. Note retrograde P wave buried within the ST segment.

Ventricular flutter (A). Same patient with degeneration into ventricular fibrillation (B).

Evaluation of the peripheral pulse has fascinated physicians for centuries. In approximately 1187, Moses Maimonides (1) wrote aphorisms pertaining to the pulse. He described an irregular pulse that was regularly irregular and one that becomes completely irregular. He was at least partially correct when he mentioned, with regard to the origin of the regularity, “all types of pulses which are irregular in more than one beat are a direct result of an abnormal constitution of the heart which is also irregular or due to an affliction arising in the stomach or in one’s strength” (p. 62). Before the electrocardiographic confirmation of atrial fibrillation, many observant physicians commented on grossly irregular pulses that, in at least some cases, were likely atrial fibrillation. William Stokes (2), in his classic 1853 text on heart disease, stated, “It has happened often to me to find the action of the heart, which, for many months together, had been in the highest degree irregular, suddenly restored to a condition in which the rhythm and sounds were perfectly natural.” In 1904, Wenckebach (3) published a monograph on cardiac arrhythmias. He described cases of excessive irregularity, or “delirium cordis.” One such example is accompanied by a pulse tracing that demonstrates a very irregular rhythm, likely atrial fibrillation.

Cushny (4), Mackenzie (5), Rothberger and Winterberg (6), and especially Lewis (7) made significant early observations concerning atrial fibrillation. The magnum opus of Sir Thomas Lewis is a must-read for any student of atrial fibrillation. The pioneering work of Einthoven (8) enabled clinical investigators to record the electrocardiographic representation of the clinical observations of atrial fibrillation.

EPIDEMIOLOGY

Atrial fibrillation has a profound effect on morbidity and mortality among hundreds of thousands of patients and on health care costs in the United States (9). One report analyzed 3,806,000 patient hospital discharges in 1990 from 678 hospitals to determine the frequency with which arrhythmia was the principal diagnosis (10). Approximately 1.5% of all hospital discharges listed arrhythmia as a principal diagnosis, and atrial fibrillation accounted for nearly 35% of the arrhythmias noted. The epidemiology of atrial fibrillation has changed substantially since the early part of the twentieth century, primarily because of the dramatic decrease in rheumatic fever and the longer life span of the population (Table 64.1) (11,12,13,14,15 and 16). The patient populations evaluated in Table 64.1 differ substantially. For example, two studies included patients admitted through the emergency department (13,14), and one evaluated only outpatients (15). Regardless, it is obvious that rheumatic heart disease plays a relatively minor role in the current etiology of atrial fibrillation in the Western world, whereas hypertension and, to a lesser extent, coronary artery disease currently are major etiologic factors in atrial fibrillation. The incidence of lone atrial fibrillation is quite variable and is influenced by the intensity of the diagnostic workup, the definition of *lone atrial fibrillation* used, and the patient population studied. Kannel and associates (12) reported a 31% incidence of lone atrial fibrillation, but some of their patients had obvious heart disease identified by an enlarged heart on chest radiography. Thus, these data are problematic. In contrast, Prystowsky and colleagues (15) studied only patients who had no known etiologic factors for atrial fibrillation and normal ventricular function identified by echocardiography. However, in their study, only outpatients were evaluated. It is clear that the prevalence and types of etiologic factors for atrial fibrillation depend on the setting in which atrial fibrillation is evaluated, including the country of origin.

Author	Year	Country	Number of patients	Rheumatic heart disease (%)	Hypertensive heart disease (%)	Coronary heart disease (%)	Hyperthyroidism (%)	No heart disease (%)
Lewis (7)	1910	England	73	64	–	–	–	–
Parkinson and Campbell (11)	1930	England	200	22	24	–	14	9
Kannel et al. (12)[a]	1982	United States	98	18	48	10	–	31
Davidson et al. (13)[b]	1989	Israel	704	23	–	35	4	5
Lok and Lau (14)	1995	Hong Kong	291	11	29	25	6	29
Prystowsky et al. (15)[c]	1996	United States	285	4	56	19	11	35

[a]Some patients with no heart disease had cardiac stigmata.
[b]Atherosclerotic cardiovascular disease included hypertension.
[c]Consecutive series of outpatients only.

TABLE 64.1 ETIOLOGY OF ATRIAL FIBRILLATION

Changes in etiology of atrial fibrillation may affect the course of atrial fibrillation, especially the evolution of paroxysmal atrial fibrillation into established atrial

fibrillation. In a study involving 1,212 patients from Denmark, three time periods, 1940 through 1948, 1949 through 1957, and 1958 through 1967, were evaluated (16). Atherosclerotic heart disease was present in 23%, 37%, and 38% of patients, respectively; hypertensive heart disease was present in 8%, 7%, and 10% of patients, respectively; and rheumatic heart disease occurred in 27%, 17%, and 15% of patients, respectively. During follow-up, the transition rate from paroxysmal to established or permanent atrial fibrillation varied according to the etiology of the disease and was 27% among patients with atherosclerotic heart disease, 40% among patients with hypertensive heart disease, and 66% among patients with rheumatic heart disease. Few data are given on the use of antiarrhythmic drugs to prevent transition to established atrial fibrillation. However, given the dates of the study, only quinidine would have been used with any frequency. These data suggest that the transition from paroxysmal to established atrial fibrillation is not inevitable, especially among patients without rheumatic heart disease. It is quite possible that antiarrhythmic therapy may further decrease the number of patients with established atrial fibrillation. This issue is discussed in more detail in the section Therapy of Atrial Fibrillation.

Effect of Age and Gender

The prevalence of atrial fibrillation increases with age and is 0.5% for patients aged 50 to 59 years and 8.8% for those aged 80 to 89 years (17). Men are affected slightly more often than women. In the Framingham data, excluding individuals with rheumatic heart disease, the 2-year incidence of development of atrial fibrillation was 0.04% and 0.00% for men and women, respectively, aged 30 to 39 years, and 4.6% and 3.6%, respectively, for men and women aged 80 to 89 years (18). Thus, the number of patients who have atrial fibrillation will rise pari passu with the aging of the population. In the first two decades of life, atrial fibrillation is relatively rare (9). When it is found in patients in this age group, it is usually associated with heart disease or the presence of an accessory pathway.

PATHOLOGY

Changes Associated with Aging

The incidence of atrial fibrillation increases with age, and the condition is especially prevalent among individuals aged 60 years or more. Thus, it is important, in attempts to identify the pathologic changes associated with atrial fibrillation, to consider changes that are associated with the aging process in and of itself. Macroscopic and microscopic alterations in atrial tissue begin in the first year of life (19). By the fourth and fifth decades, small fat spots appear in the right atrium in the region of the AV node and septum. There is accentuation of the thickening of the plaques in later decades. In the left atrium, the endocardial thickening is diffuse. With aging, increased thickening occurs, especially at the mitral valve annulus. Calcification and fatty infiltration may be present in the annulus. Histologic examination reveals an endothelial lining, beneath which is a fibroelastic core. With aging, there is focal or diffuse proliferation of smooth muscle cells, elastic fibers, or both and, in some cases, collagen fibers. This process has been termed *endocardial hypertrophy* (19). In the fourth decade, hypertrophic and sclerotic changes occur in previously uninvolved portions of the right atrium, and in the fifth decade, atrophy of smooth muscle layers can be seen. Increased sclerotic changes occur in the sixth decade (*e*Fig. 64.0.1). By the fourth decade, the entire left atrium appears to be affected by hypertrophy and sclerosis, and collagen replacement is frequent. The changes associated with aging result in eventual loss of myocardial fibers and an increase in fatty metamorphosis and connective tissue in the sinus node, the AV node, and the atrial approaches to these structures (19).

***e*FIGURE 64.0.1** Pathology of the atrium associated with aging. E, thickened endocardium; F, fatty infiltration; Fi, fibrosis of the myocardium. (From Bharati S, Lev M. Histology of the normal and diseased atrium. In: Falk RH, Podrid PJ, eds. *Atrial fibrillation: mechanisms and management*. New York: Raven Press, 1992, with permission.)

Pathology of the Atrium in Atrial Fibrillation

One study analyzed pathologic changes in the atria in 145 patients with atrial fibrillation (20). Etiologies were diverse and included conditions such as rheumatic fever, hypertension, hyperthyroidism, and coronary artery disease. The hearts of 35 control subjects were compared with those of patients who had atrial fibrillation. No distinctions that would account for the atrial fibrillation were seen in the atria of the control subjects and those of patients with atrial fibrillation. Indeed, the author speculated that no specific histologic syndrome is associated with atrial fibrillation (20).

In another study, lesions of the sinus node were evaluated in the hearts of 65 patients (21). The anatomy of the sinus node was compared with clinical data in a blinded manner. The sinus node was obviously damaged in 15 patients, and an established arrhythmia, usually atrial fibrillation, was seen in 14 patients. The sinus node was not identified with certainty in one patient who had established atrial fibrillation. The sinus node was normal in 49 patients, and atrial fibrillation had been present in 5 patients. These data are interesting and important clinically, because it is well established that atrial fibrillation and sinus node dysfunction often occur in the same patient (this has been termed *tachycardia-bradycardia syndrome*). The common association in this study between sinus nodal damage and a clinical history of atrial fibrillation supports the idea that sick sinus syndrome is a panatrial disorder in many patients.

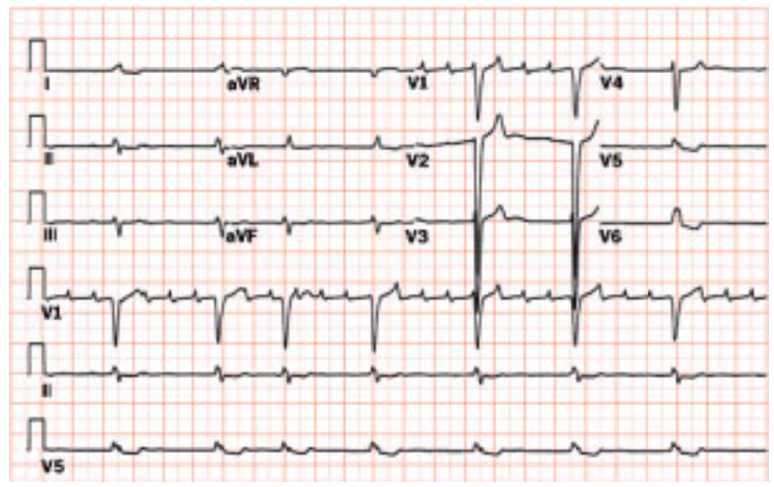
One of the most important pathologic studies of the atria of patients with atrial fibrillation was done by Davies and Pomerance (22). These authors analyzed the hearts of 100 patients with atrial fibrillation and subgrouped them into patients who had atrial fibrillation for less than 2 weeks before death and those who had atrial fibrillation for more than 1 month before death. Among patients who had long-term atrial fibrillation, cor pulmonale, rheumatic heart disease, and ischemic heart disease were the most frequently associated clinical conditions. In nearly 75% of cases of chronic atrial fibrillation, sinus node muscle loss, internodal tract muscle loss, and atrial dilatation of some degree were present. Notably, left atrial appendage thrombosis was identified in 46 patients with long-term atrial fibrillation, and cerebral infarction was identified in 19. However, only 3 of 19 patients with short-term fibrillation had left atrial thrombus, and only 1 patient with cerebral infarction. These authors offered an important hypothesis concerning the origin of pathologic changes in the atria. They stated that “while it is conventional to regard the fibrotic changes in the node and atria as the cause of atrial fibrillation, it is also possible that they result from the arrhythmia and consequent disordered function of the chamber” (22). This prescient observation supports the current belief that atrial fibrillation begets atrial fibrillation, therefore making it possible to retard or even prevent the development of permanent atrial fibrillation in some patients by maintaining sinus rhythm, which may beget sinus rhythm (see the section Therapy of Atrial Fibrillation.).

In recent studies involving patients with lone atrial fibrillation, atrial biopsies have shown histologic changes consistent with myocarditis (23), and high serum levels of antibodies against myosine heavy chains have been found (24). The pathophysiologic significance of these findings is unclear.

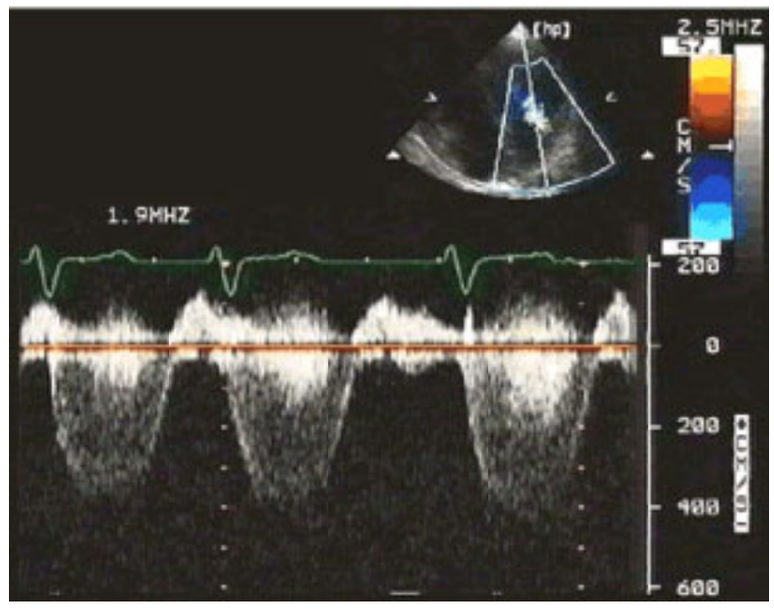
PATHOPHYSIOLOGY

Electrophysiologic Mechanism of Atrial Fibrillation

A wealth of data suggests that reentry is the primary mechanism of atrial fibrillation. An alternative theory, the ectopic focus theory, was championed by Scherf and coworkers (25,26). Using topical application of aconitine to the atria, several observations were made that appeared to indicate that there was a focal mechanism for atrial fibrillation. Aconitine could be applied to the appendix of the right or left atrium and yield arrhythmias that were similar in appearance. Clamping off the area of application from the rest of the atrium allowed the arrhythmia to continue in the area that was clamped off, but not in the rest of the atria. Similarly, cooling of the area on which aconitine had been applied terminated fibrillation. The experiments with aconitine suggested that atrial fibrillation depended on a single focus. However, atrial fibrillation induced by topical application of acetylcholine did not terminate when the area in which drug had been applied was cooled (26). The authors postulated that the AV node was able to maintain atrial fibrillation in this situation. These observations led to the supposition that an additional mechanism of atrial fibrillation existed, one with multiple (tachysystolic) foci.



High-grade atrioventricular block. Note marked discrepancy between atrial and ventricular heart rates.



Apical continuous wave spectral Doppler recording of mitral regurgitation (systolic parabolic downward velocities). Note beat-to-beat variation due to atrial fibrillation.

The ectopic focus theory for atrial fibrillation was essentially smothered by the overwhelming weight of observations indicating that reentry is the mechanism of atrial fibrillation. However, recent observations made during intracardiac radiofrequency catheter ablation of atrial fibrillation have rekindled interest in the ectopic focus theory (27,28 and 29). These authors (27,28) were able to terminate atrial fibrillation with discrete applications of energy, primarily in the area of the pulmonary veins in the left atrium, although right atrial sites have also been identified (29). In such cases, it is likely that atrial fibrillation results from rapid, focal atrial tachycardia, a form of tachycardia-induced tachycardia (see the section Tachycardia-Induced Tachycardia). Thus, elimination of the primary inciting arrhythmia prevents the secondary arrhythmia. The pulmonary veins are most frequently the origin of these rapid atrial foci, and studies have confirmed that cardiac muscle extends onto the pulmonary veins in humans (30) and have found automaticity in an experimental model (31).

In a classic paper, Mines (32) demonstrated reentry in the myocardium. He used various experimental preparations and showed reciprocating rhythm in an AV preparation. In one experiment, using a tortoise heart, stimulation of one portion of the heart was followed by an orderly sequence of activation using the atrium and ventricle repeatedly without any further stimulation. He suggested that this mechanism was the cause of atrial fibrillation. Working independently, Garrey (33) performed innovative experiments that implicated reentry as the mechanism of fibrillation. He further proposed that persistence of fibrillation is directly proportional to the size of the tissue mass involved. Indeed, atrial fibrillation is relatively rare in children with normal-sized hearts (9).

A key development in our understanding of the mechanism of atrial fibrillation was the multiple wavelet hypothesis proposed by Moe and coauthors (34,35). They noted, “the grossly irregular wave front becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered as independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery” (34). Thus, the larger the number of wavelets that present, the more likely it is that the arrhythmia will sustain. The number of wavelets depends on the atrial mass, the refractory period, and the conduction velocity of various areas of the atria. In essence, a large atrial mass with short refractory periods and conduction delay would yield increased wavelets and would present the most favorable situation for atrial fibrillation to be sustained. In the work of Moe and many other investigators, atrial fibrillation could only be sustained during constant vagal stimulation. This is consistent with Moe’s hypothesis, because vagal stimulation shortens refractoriness in many atrial cells, a condition that should allow more wavelets to be present. A computer model of atrial fibrillation supported the multiple wavelet hypothesis (35).

Experimental validation of the multiple wavelet hypothesis was demonstrated by Allessie and colleagues (36). They analyzed the excitation of canine atria during induced atrial fibrillation with two egg-shaped multiple electrodes inserted into the cavities of the atria. Each electrode contained 480 recording electrodes, with an interelectrode distance of 3 mm. This enabled the first highly detailed activation sequencing of atrial fibrillation. As noted by other investigators, enhanced vagal tone was necessary for maintenance of atrial fibrillation, and infusions of acetylcholine were used for this purpose. Figure 64.1 demonstrates an arbitrary moment during atrial fibrillation and reveals seven wavelets (36). These reentrant wavelets were not stable, and over the course of time, various pathways of reentry could be demonstrated. When only three wavelets existed, there was a high chance that all would cease to exist, but when six wavelets were present, spontaneous termination of atrial fibrillation did not occur.

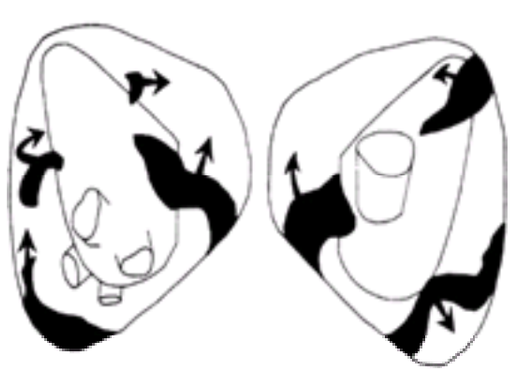
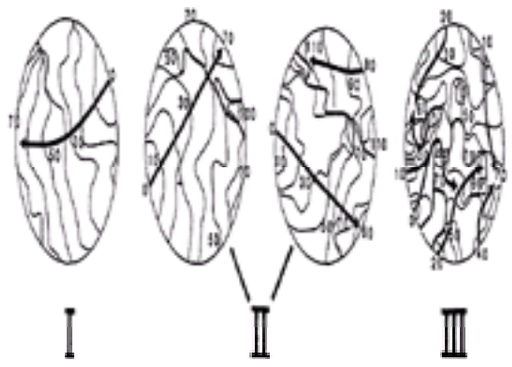


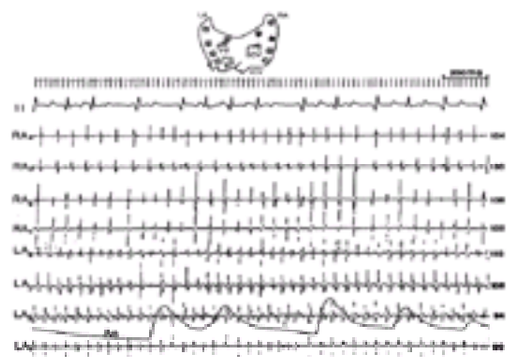
FIGURE 64.1 Canine atria with multiple propagating wavelets during sustained atrial fibrillation. Seven wavelets are present—three in the right atrium and four in the left atrium. The black contours mark the atrium that has been excited during the last 10 ms. (From Allessie MA, Lammers WJEP, Bonke FIM, et al. Experimental evaluation of Moe’s multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, eds. *Cardiac arrhythmias.* New York: Grune & Stratton, 1985:265–276, with permission.)

Multiple simultaneous electrode mapping of human atrial fibrillation has been accomplished during surgery (37,38). In one study, wavefronts of activation appear to turn around functional arcs of conduction block and natural anatomic obstacles (37). In another study, high-density electrode mapping was obtained in the free wall of the right atrium during surgery in patients with WPW, using 244 unipolar electrodes (38). Activation patterns during atrial fibrillation were quite variable between patients and ranged from single broad wavefronts to extremely complex multiple wavefronts. The authors define three types of activation, although they stressed that the activation maps were part of a continuous spectrum of increasing complexity (eFig. 64.1.1) (38). Right and left atria were mapped simultaneously in eight patients, five of whom showed the same type of activation during atrial fibrillation, but three different activation patterns were noted. The simultaneous appearance of various

activation patterns during atrial fibrillation is likely more common than was demonstrated by this study, which examined relatively short-duration atrial fibrillation. In fact, multiple-site simultaneous electrogram recordings during sustained atrial fibrillation in canine atria often demonstrate various local atrial rates and electrogram morphologies (eFig. 64.1.2) (39). Indeed, dissimilar atrial rhythms are commonly observed by electrophysiologic study during atrial fibrillation in humans (eFig. 64.1.3).



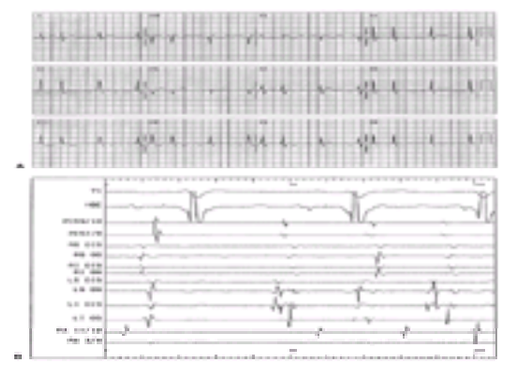
***e*FIGURE 64.1.1** Classification of activation maps during atrial fibrillation. Type I is a single uniformly propagating wave; type II involves single nonuniformly conducting waves or the presence of two wavelets; type III is characterized by the presence of three or more wavelets with arcs of conduction block and areas of slow conduction. Numbers denote activation sequence. (From Konings KTS, Kirchhof CJ, Smeets JRLM, et al. High-density mapping of electrically induced atrial fibrillation in humans. *Circulation* 1994;89:1665–1680, with permission.)



***e*FIGURE 64.1.2** Local atrial rates in left and right atria during sustained atrial fibrillation in the canine heart. Ao, aortic pressure; ICV, inferior caval vein; LA, left atrium; PV, pulmonary vein; RA, right atrium; SCV, superior caval vein. (From Morillo CA, Klein GJ, Jones DL, et al. Chronic rapid atrial pacing: structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation* 1995;91:1588–1595, with permission.)

***e*FIGURE 64.1.3** Dissimilar atrial activation in different parts of the atria. Differences are most marked between the electrographic pattern in the high right atrium (HRA) and those in the coronary sinus (CS). A, atrial depolarization; CS_1 through CS_4, unipolar electrograms from the coronary sinus; HBE, bundle of His electrogram. (From Prystowsky EN, Klein GJ. *Cardiac arrhythmias: an integrated approach for the clinician*. New York: McGraw-Hill, 1994, with permission.)

Traditionally, it has been thought that reentry requires a significant mass of tissue. The seminal work of Spach and associates (40,41) on conduction led to the understanding that anisotropic reentry is possible. Typically, propagation in the myocardium is faster in the longitudinal direction than in the perpendicular direction, and this anisotropic propagation can be uniform or nonuniform. Nonuniform conduction is associated with decreased side-to-side electrical coupling between small groups of cells, which typically occurs with aging (40). During investigation of human atrial pectinate muscle bundles obtained at surgery, reentry was demonstrated in 1 to 2 mm areas (eFig. 64.1.4). Even if the maintenance of reentry in atrial fibrillation requires the presence of multiple wavelets throughout the atria, this important observation may explain the initiation of atrial fibrillation in some circumstances, for example, in patients with tachycardia-induced tachycardia who have AV reentry, in which disorganization of the right atrium typically precedes that of the left atrium (Fig. 64.2) (42). An alternative mechanism for tachycardia-induced atrial fibrillation may be induction of a rapidly firing atrial focus, for example, in the superior right pulmonary vein, with initial activation observed at the right atrial recording site.



***e*FIGURE 64.1.4** Microreentry in older, nonuniform anisotropic bundle. The upper left drawing demonstrates locations of recording sites. Transverse propagation (TP) reveals markedly polyphasic extracellular waveforms consistent with loss of side-to-side electrical coupling. Longitudinal propagation (LP) demonstrates uniphasic electrogram waveforms. The pacing cycle length is 350 ms, and premature stimuli are introduced. A premature interval of 233 ms does not produce reentry. A premature interval of 228 ms initiates reentry, schematically demonstrated in the lower right portion of the figure. Note that decremental transverse propagation occurred (sites 1 and 2), but block appears to occur after recording site 4 in the longitudinal direction. (From Spach MS, Dolber PC, Heidlage JF. Influence of the passive anisotropic properties on directional differences in propagation following modification of the sodium conductance in human atrial muscle: a model of reentry based on anisotropic discontinuous propagation. *Circ Res* 1988;62:811–832, with permission.)

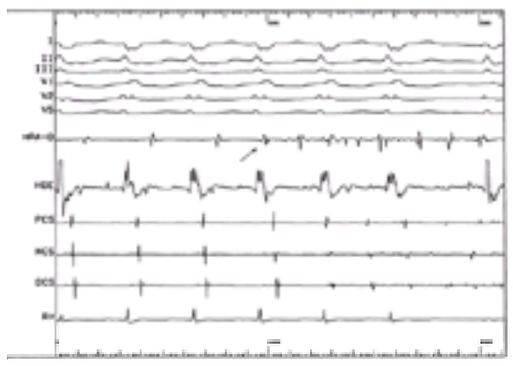


FIGURE 64.2 Patient with atrioventricular reentry using a left-sided accessory pathway in which atrioventricular reentry degenerates to atrial fibrillation. The arrow notes the earliest disorganization in the high right atrial electrogram, positioned near the junction of the right atrium and the superior vena cava. DCS, distal coronary sinus; HBE, bundle of His electrogram; HRA-D, high right atrium–distal; MCS, midcoronary sinus; PCS, proximal coronary sinus; RV, right ventricle.

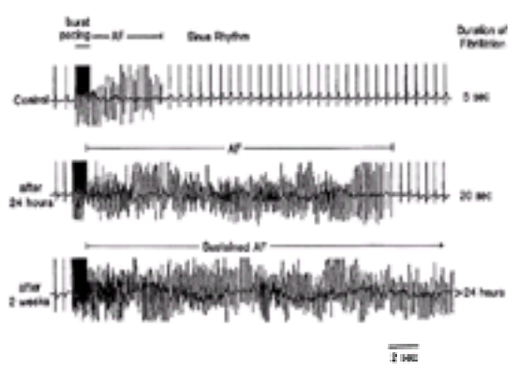
The mechanism of initiation of atrial fibrillation is not certain in most cases and likely is multifactorial. Even the example given in this chapter of tachycardia-induced tachycardia is merely descriptive, and the actual mechanism for induction of atrial fibrillation might be related to the tachycardia cycle length, to intrinsic atrial vulnerability, to contraction-excitation feedback, or to a combination of these factors (42). If reentry is assumed to be the mechanism of atrial fibrillation, initiation would require an area of conduction block and a wavelength of activation that is short enough to allow the reentrant circuit in the myocardium. The normal aging process results in anatomic changes likely to yield inhomogeneity in conduction that may create the milieu necessary for the development of reentry (19,40). These changes are likely magnified by the presence of certain disease processes, for example, those of coronary artery disease. Using high-density mapping of the left atrium of a rabbit, inhomogeneity in conduction was found to be significantly increased by the presence of single close-coupled atrial premature complexes and further increased by the presence of multiple premature complexes (43). Of particular note was the marked inhomogeneity in conduction that occurred with rapid atrial pacing. The clinical counterpoint of this phenomenon is the presence on electrophysiologic study in humans of relatively frequent accidental initiation of atrial fibrillation during rapid atrial pacing, and the necessity that a relatively rapid rate of tachycardia be present for either AV or AV node reentry to initiate atrial fibrillation (42).

In a successful reentrant circuit, the wavefront of excitation must encounter excitable cells or the tachycardia will terminate. The wavelength of the electrical impulse is defined as the conduction velocity multiplied by the refractory period of the tissue involved in the circuit, which defines the anatomic size of the circuit. In a macroreentrant circuit such as WPW reentry, the anatomic circuit is clearly longer than the wavelength of the tachycardia. However, most forms of intramyocardial reentry require a substantial decrease in conduction velocity to enable sustained reentry. The wavelength formula makes it clear that a decrease in conduction velocity or a shortened refractory period results in a decrease in the wavelength or a lessening of the amount of tissue needed to sustain reentry. This situation favors initiation and maintenance of reentry, especially atrial fibrillation. Alternatively, an increase in conduction velocity or prolongation of refractoriness will prolong the wavelength of excitation, and in this situation, a larger anatomic circuit will be necessary to sustain reentry. If a larger circuit is not possible, initiation or maintenance of tachycardia cannot occur. Anisotropic reentry can occur over a very small area. In a canine atrial model, the type of atrial arrhythmia initiated correlated with the wavelength of the premature beats. Atrial flutter was initiated at a wavelength less than 9.7 cm, and atrial fibrillation occurred at wavelengths less than 7.8 cm (44). Administration of acetylcholine substantially shortened the wavelength, primarily because of a decrease in the refractory period (38). This is consistent with the well-reported facilitation of initiation and maintenance of atrial fibrillation by heightened vagal tone.

Tachycardia-Induced Atrial Cardiomyopathy

It has been recognized for several decades that a persistently fast ventricular rate secondary to supraventricular tachycardia can lead to ventricular cardiomyopathy, which is reversible if recognized in time. In fact, this is not an uncommon phenomenon in patients who present with atrial fibrillation and dilated cardiomyopathy. But might such a situation lead to tachycardia-induced atrial cardiomyopathy? It is not only possible, but probable, although this has not been investigated in detail until recently (45). Notably, this concept was put forth in an earlier study on the pathology of atrial fibrillation, in which the authors suggested that the fibrotic changes in the sinus node and atria may be the result of atrial fibrillation rather than its cause (22). More recently, the effect of persistent atrial fibrillation on changes in atrial size was investigated in 15 patients who showed no evidence of significant structural or functional cardiac abnormalities other than atrial fibrillation (46). Normal left atrial size was among the inclusion criteria. During an average follow-up period of 20.6 months, mean left atrial volume increased from 45.2 to 64.1 cm^3. Similarly, right atrial volume significantly increased, from 49.2 to 66.2 cm^3. These changes in atrial size are consistent with the observation that atrial fibrillation begets atrial fibrillation. In another study, atrial size was evaluated at 6 months' follow-up after cardioversion in patients in whom sinus rhythm persisted and in patients in whom atrial fibrillation recurred (47). Importantly, in the 28 patients in whom sinus rhythm was maintained, left atrial volume decreased from 72.6 ± 15.1 to 58.5 ± 13.8 cm^3 and right atrial volume decreased from 68.7 ± 14.6 to 58.6 ± 11.6 cm^3 (p <.05). In contrast, atrial size did not change in patients in whom atrial fibrillation recurred. Thus, a window of opportunity appears to be present for reversal of the atrial dilatation that is often noted in association with atrial fibrillation.

Persistence of atrial fibrillation also produces changes in the electrophysiology of the atrium (39,48). In dogs subjected to sustained rapid atrial pacing, electrophysiologic, anatomic, and pathologic changes were noted to occur over the course of time (39). Biatrial enlargement, disruption of the sarcoplasmic reticulum, increases in mitochondrial size, decreases in atrial refractoriness, and the ability to induce atrial fibrillation were observed. In an elegant study by Wijffels and associates (48), electrophysiologic changes in the atria of chronically instrumented goats were observed. They observed that the initial episode of atrial fibrillation usually terminated within seconds. However, when atrial fibrillation was maintained for longer periods of time, the duration of the induced episodes of atrial fibrillation also increased (*e*Fig. 64.2.1). The atrial effective refractory period and the median fibrillation interval shortened during the first 24 hours of atrial fibrillation (48). These electrophysiologic changes are consistent with a milieu that would promote sustained atrial fibrillation. The electrophysiologic changes were noted to be reversible within 1 week in a small number of goats tested in whom atrial fibrillation had been present for 2 to 4 weeks. Recent data from humans suggest that episodes of atrial fibrillation shorter than 10 minutes can cause a transient decrease in the atrial effective refractory period (49). Changes in action potential shortening may be related to decreased inward current through L-type calcium channels (50).



***e*FIGURE 64.2.1** Duration of atrial fibrillation (AF) is prolonged after AF has been maintained for progressively longer periods of time. The top panel represents the first episode of induced AF, which spontaneously terminates within seconds. The middle panel records AF of 20 seconds' duration after 24 hours of repeated induction of AF. The bottom panel demonstrates a sustained episode of AF that occurred after 2 weeks of electrically maintained AF. (From Wijffels MC, Kirchhof CJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation* 1995;92:1954–1968, with permission.)

Evidence for a tachycardia-induced atrial cardiomyopathy is supported further by echocardiographic observations before and after cardioversion (51,52). Using transesophageal echocardiography, left atrial appendage blood flow velocity and contractile function were assessed in patients with atrial fibrillation (52). The mean duration of atrial fibrillation was 49 months, and an inverse correlation was seen between the duration of the arrhythmia and left atrial appendage peak outflow velocities. Patients who spontaneously cardioverted to sinus rhythm had significantly greater left atrial appendage outflow velocities. The course of recovery of atrial systolic function after cardioversion was evaluated using transthoracic Doppler echocardiography (51). Within the first week after cardioversion, atrial mechanical function was greater in patients with atrial fibrillation of 2 weeks or less compared with those patients who had atrial fibrillation greater than 6 weeks in duration. Over the course of time, atrial mechanical function improved in all groups of patients. Thus, atrial mechanical function appeared to recover compared that measured before cardioversion, and the time to recovery was a function of the previous duration of atrial fibrillation. However, because atrial mechanical function before atrial fibrillation

was unknown, the degree to which atrial mechanical function approached normal for individual patients remains unclear.

In summary, persistence of atrial fibrillation results in a cascade of electrical and anatomic changes in the atria that promote the persistence of atrial fibrillation. The result is perpetuation of atrial fibrillation and a decrease in atrial mechanical function secondary to tachycardia-induced atrial cardiomyopathy. If sinus rhythm is restored within a reasonable period of time, electrophysiologic changes appear to normalize, atrial size decreases, and restoration of atrial mechanical function occurs. These observations lend support to the idea that the negative downhill spiral in which atrial fibrillation begets atrial fibrillation can be arrested with sinus rhythm that perpetuates sinus rhythm. Two major questions remain unanswered: What duration of atrial fibrillation results in substantial irreversible changes, and can maintenance of sinus rhythm prevent the transition of intermittent atrial fibrillation to permanent atrial fibrillation? These are the subjects of future investigations.

Atrioventricular Conduction

In the absence of an accessory pathway, AV conduction occurs over the AV node during atrial fibrillation. The resultant ventricular rate depends on the intrinsic conduction and refractoriness of the AV node, the rate and organization of atrial inputs to the AV node, and the state of autonomic tone. The compact AV node is located anteriorly in the triangle of Koch (53). The compact AV node is surrounded by transitional cells with various microelectrode action potential characteristics. Maximal conduction slowing occurs predominantly in the zone of N cells in the AV node (53). There are two distinct atrial inputs to the AV node, anteriorly via the interatrial septum and posteriorly via the crista terminalis. Experiments in a rabbit AV nodal preparation demonstrated that propagation of impulses during atrial fibrillation through the AV node to the bundle of His was critically dependent on the relative timing of activation of septal inputs to the AV node at the crista terminalis and interatrial septum (54). Other investigators showed that the ventricular response also depended on atrial input frequency (55,56). Concealed conduction likely plays the predominant role in determining ventricular response during atrial fibrillation (55,57). Concealed conduction into the AV node occurs with atrial impulses that enter the AV node but do not conduct to the ventricle, leaving a wake of refractoriness that is encountered by subsequent impulses. The constant bombardment of atrial impulses into the AV node undoubtedly creates substantial and varying degrees of concealed conduction.

Alterations of autonomic tone can have profound effects on AV nodal conduction (58,59 and 60). Enhanced parasympathetic and sympathetic tone have negative and positive dromotropic effects, respectively, on AV nodal conduction. This can be seen in Figure 64.3, in which recordings of atrial fibrillation during the awake state and during sleep are shown. Note the substantial slowing of ventricular response, even with pauses, during sleep, a state in which there is heightened parasympathetic and decreased sympathetic tone.

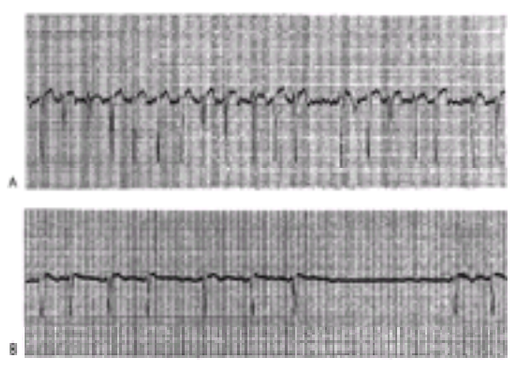
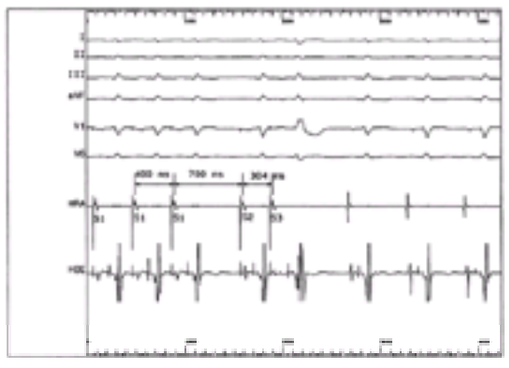


FIGURE 64.3 Effect of autonomic tone on atrioventricular node conduction during atrial fibrillation. **A:** Relatively rapid ventricular response during the awake state. **B:** Slow ventricular response recorded during sleep.

Aberrant conduction commonly occurs during atrial fibrillation. It is important to distinguish aberrant conduction from ventricular ectopy, especially when repetitive wide QRS complexes occur. The refractoriness of the His-Purkinje tissue decreases as the heart rate increases (61). Thus, slower heart rates favor aberrancy. The gross irregularity of ventricular response during atrial fibrillation yields an abundance of RR cycle lengths, which statistically increases the chance for a long-short cycle length combination that will produce aberrant conduction. This phenomenon was described well by Gouaux and Ashman ("Ashman phenomenon") (62) and Lewis (63) and confirmed experimentally by Moe and coworkers (64). Figure 64.4 demonstrates an example of right bundle branch (RBB) block aberrancy during atrial flutter/fibrillation initiated during electrophysiologic study. RBB aberrancy results from the sudden lengthening of the preceding cycle length (long-short sequence), which prolongs RBB refractoriness. RBB block aberrancy is more common than left bundle branch block aberrancy, probably because the RBB has a longer refractory period at slower heart rates (65). To complicate matters further, it has been demonstrated that cycle lengths preceding the pause may also affect the chance for aberrancy after the pause (eFig. 64.4.1) (66).

FIGURE 64.4 Right bundle branch block aberrancy caused by sudden lengthening of the preceding cycle length. See text for details. HBE, bundle of His electrogram; HRA, high right atrium. (From Prystowsky EN, Klein GJ. *Cardiac arrhythmias: an integrated approach for the clinician*. New York: McGraw-Hill, 1994, with permission.)



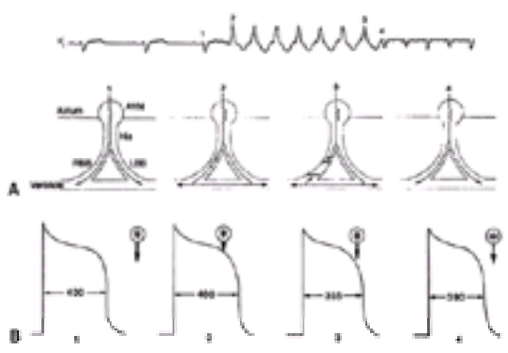
***e*FIGURE 64.4.1** Initiation of right bundle branch block aberrancy at electrophysiologic study. During a pacing cycle 400 ms in length with premature atrial stimulation, no right bundle branch block aberrancy was noted. However, when eight consecutive atrial complexes at 400 ms (150 per minute) were introduced preceding a pause of 700 ms, a premature atrial interval of 304 ms resulted in right bundle branch block aberrancy. HBE, bundle of His electrogram; HRA, high right atrium.

It is important to differentiate between aberrant ventricular conduction and ventricular tachycardia when repetitive wide QRS complexes occur during atrial fibrillation. This can usually be accomplished by careful analysis of the rhythm strip and application of certain guidelines (Table 64.2) (61,67,68). eFigure 64.4.2 is an example of repetitive bundle branch block aberrant complexes induced during electrophysiologic study with sudden onset of rapid atrial pacing. The first three

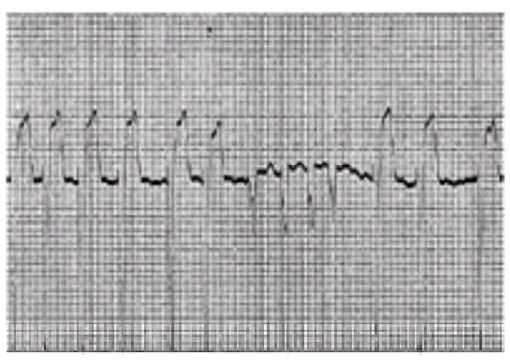
complexes are sinus rhythm, and pacing started with complex number 2. Note that the long-short sequence produces RBB block, which persists for seven complexes, followed by normalization of the QRS complex. The first RBB block complex (number 2) occurs because the premature atrial interval encounters the RBB refractory period. Two mechanisms have been postulated for the persistence of RBB block aberrancy. The first is schematically represented in part A of the figure. In this situation, retrograde concealed conduction from the left bundle branch into the distal RBB occurs, and when retrograde conduction fails, the RBB can recover, resulting in normalization of the subsequent QRS complex. This is the likely mechanism when bundle branch block aberrancy persists for long periods of time, and it has been confirmed experimentally (64). An alternative mechanism is schematically shown in part B of the figure. In this case, continued bundle branch block aberrancy is caused by persistence of the prolonged action potential duration, which progressively shortens after several complexes, allowing normalization of conduction. This mechanism is most likely the cause of short runs of bundle branch block aberrancy (69). An example of ventricular tachycardia is shown in *e*Figure 64.4.3. Note that the ventricular rate during atrial fibrillation is relatively slow, and there is no reason to expect a sudden acceleration in heart rate unless some profound increase in sympathetic tone occurs, which was not present in this instance. Further, the first wide QRS complex is not short coupled.

Long-short cycle length sequence
Typical right bundle branch block
Relatively rapid ventricular rate
Lack of compensatory pause
Absence of bundle branch block with shorter cycle length without preceding pause
Normalization of QRS complexes with minimal change in cycle length

TABLE 64.2 FACTORS FAVORING ABERRANT VENTRICULAR CONDUCTION



***e*FIGURE 64.4.2** Potential mechanisms for repetitive bundle branch block aberrancy. See text for details. AVN, atrioventricular node; His, bundle of His; LBB, left bundle branch; RBB, right bundle branch. (From Prystowsky EN, Klein GJ. *Cardiac arrhythmias: an integrated approach for the clinician*. New York: McGraw-Hill, 1994, with permission.)



***e*FIGURE 64.4.3** Nonsustained ventricular tachycardia in a patient with underlying atrial fibrillation. See text for details.

The presence of a grossly irregular, very rapid ventricular response during atrial fibrillation is diagnostic of conduction over an accessory pathway, with rare exceptions (Fig. 64.5). At very fast heart rates, a tendency toward regularization of the RR intervals is present, but careful measurement always discloses definite irregularities. It would be rare for such rapid responses to result from conduction over the AV node, and the only other alternative is ventricular tachycardia. It is axiomatic that rapid, irregular ventricular tachycardia is unstable and quickly degenerates into ventricular fibrillation. Thus, when a rapid, irregular wide QRS complex tachycardia is noted in a patient who has a reasonably stable hemodynamic state, preexcitation is the most likely diagnosis. The ability to conduct rapidly over an accessory pathway is determined primarily by the intrinsic conduction and refractory properties of the accessory pathway. However, as with AV node conduction, factors such as spatial and temporal characteristics of atrial wavefronts during atrial fibrillation, autonomic tone, and concealed conduction influence activation over the accessory pathway (70,71 and 72).

FIGURE 64.5 Twelve-lead electrocardiogram in a patient with ventricular preexcitation during atrial fibrillation who had a rapid preexcited ventricular response.

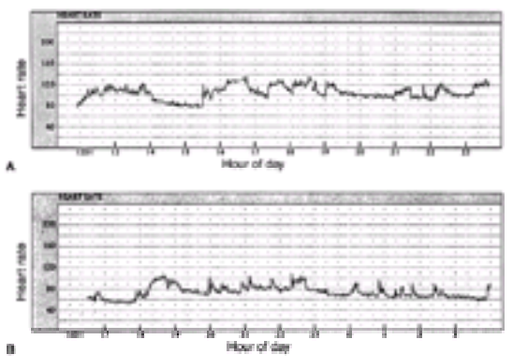
Tachycardia-Induced Ventricular Cardiomyopathy

Patients with idiopathic dilated cardiomyopathy commonly have atrial fibrillation. The usual assumption is that atrial fibrillation is caused by the cardiomyopathy. Importantly, the reverse is often documented—that is, a persistently rapid ventricular response during atrial fibrillation results in a tachycardia-induced ventricular cardiomyopathy (73,74,75,76,77,78 and 79). This phenomenon has been well recognized in patients with long-standing incessant or nearly incessant supraventricular tachycardia other than atrial fibrillation. In fact, the first patient who underwent successful surgical ablation of an accessory pathway at Duke University had congestive

heart failure and dilated myopathy that disappeared over the course of time after surgery, with restoration of sinus rhythm (80). Recognition of the possible presence of tachycardia-induced ventricular cardiomyopathy is critical, because control of ventricular response over the course of time may lead to partial or complete reversal of the myopathic process. In general, unless the cardiomyopathy is known to have preceded the onset of atrial fibrillation, it should always be assumed that the fibrillation is potentially reversible, and every effort should be made to control the ventricular response as part of the therapeutic plan.

Amelioration of tachycardia-induced cardiomyopathy can occur with multiple mechanisms of rate control, including persistence of atrial fibrillation with rate control using drugs or ablation of the AV junction, or after cardioversion to sinus rhythm. In one study of ten patients, sinus rhythm was restored in five, and better rate control was achieved in the other five patients (75). Importantly, patients had minimal awareness of palpitations, even though the mean heart rate during atrial fibrillation was 145 beats/min. After appropriate rate control or restoration of sinus rhythm, the median left ventricular ejection fraction increased from 25% to 52%. In another study evaluating improvement in left ventricular function after ablation of the AV junction with insertion of a permanent pacemaker, changes in left ventricular ejection fraction were evaluated a mean of 14 months after ablation (77). In the 12 patients who had a left ventricular ejection fraction less than or equal to 50% before ablation, the ejection fraction increased significantly, from 43% ± 8% to 54% ± 7%. However, no change was seen in left ventricular ejection fraction in patients in whom the ejection fraction was greater than 50% before ablation. The time course of hemodynamic changes after cardioversion of atrial fibrillation to sinus rhythm was evaluated in another study (78). In the eight patients studied, the resting ventricular response during atrial fibrillation before cardioversion was 123 ± 28 beats/min, and this decreased to 81 ± 16 beats/min after cardioversion. The ejection fraction before cardioversion was 36% ± 13%, and improvement was minimal at 1 week, but a significant increase, to 53% ± 8%, occurred after 1 month; minimal change was seen thereafter. Although this study suggests that maximal hemodynamic improvement occurs within 1 month, other observations suggest that it may take several months for full improvement in ejection fraction and decrease in left ventricular size to occur. Interpatient variability obviously exists, and some of this may relate to the duration of atrial fibrillation or concomitant disease processes.

Rate control has a salutary effect on improvement of left ventricular function in at least some patients who have dilated cardiomyopathy and atrial fibrillation. It matters little what mechanism is used to control rate: cardioversion to sinus rhythm, drugs that control the ventricular response, or ablation of the AV junction with pacemaker insertion. Many patients who undergo such treatment have minimal symptoms and are first diagnosed with cardiomyopathy with atrial fibrillation. It is especially important in this circumstance to assume reversibility of all or part of the myopathic process and to make every effort to control the ventricular response by whatever mechanism is most appropriate for that patient. *e*Figure 64.5.1 is from an 82-year-old man who presented with atrial fibrillation that was detected during a routine physical examination. His ejection fraction was 25%, and global hypokinesis was identified by echocardiography. Note the persistently elevated ventricular response that is present before therapy, with heart rates greater than 100 to 120 beats/min present in many hours. Slow-release verapamil was prescribed, and repeat Holter monitoring was performed, which demonstrated excellent rate control during the 24-hour observation period. Ejection fraction 6 months later was 45%, and the patient remains free of symptoms.



***e*FIGURE 64.5.1** Heart-rate trends in a patient with atrial fibrillation before therapy **(A)** and while receiving verapamil slow release, 240 mg daily **(B)**. Note the marked reduction in overall heart rate during verapamil therapy.

CLINICAL PROFILE

Associated Disease States

Atrial fibrillation has been reported to occur in patients with a wide variety of diseases, many of which are listed in Table 64.3. Why a particular disease results in atrial fibrillation is often unclear. In some cases—for example, hypertension—both occur with increased frequency in the elderly, and it is possible that a cause-and-effect relationship does not always exist. However, echocardiographic studies of left atrial function in patients who have hypertension have demonstrated that patients with paroxysmal atrial fibrillation had left atrial enlargement and depression of atrial contractile function associated with an increased ventricular inflow during early diastole (81). It is unclear whether these changes cause or are the result of paroxysmal atrial fibrillation. In contrast, in patients with mitral valve disease with progressive enlargement of the atria, a pathophysiologic link between the disease state and the onset of atrial fibrillation is easier to understand.

Hypertension
Coronary heart disease
Cardiomyopathy
Dilated
Hypertrophic
Mitral valve disease
Stenosis
Regurgitation
Thyrotoxicosis
Sick sinus syndrome
Congenital heart disease
Atrial septal defect
Ebstein's anomaly
Cardiac surgery
Pericarditis
Tumors
Alcohol
Lung disease
Neurogenic
Tachycardia-induced tachycardia
Lone (idiopathic)

TABLE 64.3 FACTORS ASSOCIATED WITH ATRIAL FIBRILLATION

Thyrotoxicosis

Thyroid hormone affects the circulatory system and myocardium (82). There is a decrease in total systemic vascular resistance, an increase in total blood volume, and a decrease in circulation time. This leads to an increase in preload and a reduction in afterload. There is also an increase in sinus rate and a reduction in the electrical threshold for excitation of the atrium. There appears to be an interaction between excess thyroid hormone and catecholamine action, including potentiation of catecholamine effect and an increased number of cardiac beta-adrenergic receptors (82). Atrial fibrillation is not uncommonly associated with thyrotoxicosis, is more frequent among men than among women, and increases with age. It occurs in more than 25% of patients aged 60 years or older, but it is rare in patients younger than 40 years. Although exclusion of occult thyrotoxicosis as a cause for atrial fibrillation is recommended, situations in which it is the cause are very uncommon. Notably, in one study, a low serum thyrotropin concentration in patients aged 60 years or older who show no evidence of hyperthyroidism was associated with a threefold higher risk of development of atrial fibrillation during a 10-year follow-up period (83). An increased risk of arterial thromboembolism is seen in association with thyrotoxicosis, mandating use of warfarin in patients with atrial fibrillation until a euthyroid state and sinus rhythm are achieved. The dose of warfarin necessary to maintain an INR of 2.0 to 3.0 may be smaller initially because of increased plasma clearance of vitamin K–dependent clotting factors, and a higher dose may be necessary as the thyroid hormone concentration decreases (82).

Congenital Heart Disease

Atrial fibrillation is relatively common in two forms of congenital heart disease in particular: atrial septal defect and Ebstein's anomaly. In patients with atrial septal defect, the incidence of atrial fibrillation is greater as patients age and has been reported to be more than 50% in a study involving patients aged 60 years or older (84). In general, the incidence of atrial fibrillation begins to increase in the fourth decade of life.

Ebstein's anomaly is commonly associated with atrial fibrillation, often at an early age (85). Atrial fibrillation may be caused by the underlying atrial dysfunction or, more commonly, may be a consequence of concomitant WPW. In patients who have WPW and AV reentry, atrial fibrillation is relatively common and most often secondary to degeneration of AV reentry into atrial fibrillation (42). Among patients who underwent surgical ablation of the accessory pathway and were followed up for 6.2 years, atrial fibrillation was documented in 42% of the patients before surgery, and this was reduced to 9% postoperatively (86). Thus, in patients with Ebstein's anomaly, the most significant etiologic factor for atrial fibrillation appears to be concomitant WPW.

Cardiac Surgery

Atrial fibrillation is the most frequent atrial arrhythmia noted after cardiac surgery. New atrial fibrillation develops in 25% to 50% of adult patients who undergo cardiac surgery (87). It is usually benign and self-limiting, but it may be associated with hemodynamic compromise, prolonged hospitalization, and embolic stroke (88). Patients most likely to develop atrial fibrillation are those with a history of atrial fibrillation before surgery who are in sinus rhythm initially after the operation (89).

Patients undergoing coronary artery bypass graft surgery are the group most likely to have a first episode of atrial fibrillation postoperatively. Development of atrial fibrillation is multifactorial, and several risk factors have been identified. Postoperative discontinuation of beta-adrenergic blockers that were taken regularly before surgery increases the risk of atrial fibrillation during the postoperative period; this complication can be expected in approximately 40% of patients in such a situation (90). Increased postoperative sympathetic activity demonstrated by elevated norepinephrine levels is associated with an increased risk of atrial fibrillation (91). Age is a major risk factor, and atrial fibrillation occurs in approximately 4% and 30% of patients aged less than 40 and 70 or more years, respectively, who are undergoing coronary artery bypass graft surgery (87). Other risk factors include chronic obstructive pulmonary disease, chronic renal disease, decreased postoperative serum magnesium level, history of paroxysmal atrial fibrillation, premature atrial complexes in the preoperative period, the presence of severe right coronary artery stenosis, and a history of congestive heart failure (91,92,93 and 94). The type of cardioplegia does not appear to correlate with the development of atrial fibrillation after cardiac operation (87,95). Notably, minimally invasive cardiac valve surgery may not reduce the incidence of postoperative atrial fibrillation (96).

Neurogenic

It has been known for decades that sustained atrial fibrillation is facilitated by increased parasympathetic tone. The atrial refractory period is decreased by acetylcholine, which shortens the wavelength, making it easier for atrial fibrillation to be sustained (44). Earlier investigators were aware of the profound influence of heightened vagal tone on atrial fibrillation (97,98,99,100,101 and 102). It was noted that rapid atrial stimulation in the presence of acetylcholine alone induced atrial fibrillation, and atrial fibrillation would continue in the absence of stimulation until the acetylcholine infusion was discontinued (100). Importantly, a nonuniform distribution of vagal effects on the refractoriness of the atrium has been found (102). In one study, right atrial refractoriness was determined at various sites before and during vagal stimulation (102). In the control state, atrial refractoriness differed by no more than 40 ms between sites. However, during vagal stimulation there was marked shortening of atrial refractoriness at some sites and minimal change at others. Because dispersion of refractoriness often promotes the development of reentry, this may be one mechanism by which heightened vagal tone facilitates the initiation of atrial fibrillation.

In some patients, atrial fibrillation occurs during enhancement of vagal tone. The patient's clinical history usually provides clues for this mechanism. For example, onset of atrial fibrillation during swallowing of a cold substance (e.g., ice cream or an ice cube) indicates that a vagal reflex may initiate atrial fibrillation. A specific syndrome of vagal atrial fibrillation has also been described (103), with occurrence at time of heightened vagal tone such as at night, during rest, or after consumption of food or alcohol. Reportedly, patients with vagal atrial fibrillation have an increased number of attacks during therapy involving beta-blockers and digitalis (103). Although many patients relate a tendency towards increased episodes of atrial fibrillation during periods of presumed increased vagal tone, in our experience, it is rare for patients to have atrial fibrillation only during enhanced parasympathetic tone.

An adrenergic form of atrial fibrillation has also been described (103), with onset exclusively during the daytime hours and often preceded by emotional stress or exercise. In contrast to vagal atrial fibrillation, beta-adrenergic blockers are the treatment of choice.

Tachycardia-Induced Tachycardia

Tachycardia-induced tachycardia is a phenomenon in which one tachycardia degenerates into another tachycardia (42). A relatively common example is rapid ventricular tachycardia that degenerates into ventricular fibrillation. Several different tachycardias can degenerate into atrial fibrillation (42). Atrial flutter and atrial tachycardia are likely the most common causes of tachycardia-induced tachycardia that results in atrial fibrillation, but arrhythmias as diverse as ventricular tachycardia, AV node reentry, and AV reentry may also initiate atrial fibrillation (Fig. 64.2) (42,104,105 and 106). In WPW, transition of AV reentry into atrial fibrillation can produce dire consequences, with a rapid preexcited ventricular response that degenerates into ventricular fibrillation leading to sudden death (Fig. 64.6) (61,107,108,109,110 and 111).

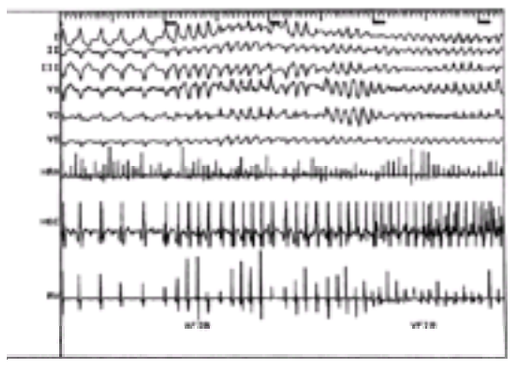


FIGURE 64.6 Atrial fibrillation in a patient with Wolff-Parkinson-White syndrome with degeneration from atrial fibrillation to ventricular fibrillation. AFIB, atrial fibrillation; HBE, bundle of His electrogram; HRA, high right atrium; RV, right ventricle; VFIB, ventricular fibrillation. (From Prystowsky EN, Knilans TK, Evans JJ. Diagnostic evaluation and treatment strategies for patients at risk for serious cardiac arrhythmias. II. Ventricular tachyarrhythmias and Wolff-Parkinson-White syndrome. *Mod Concepts Cardiovasc Dis* 1991;60:55, with permission.)

Several factors may affect the conversion of a variety of sustained tachycardias into atrial fibrillation. These include tachycardia cycle length, intrinsic atrial vulnerability, the electrophysiologic characteristics of accessory pathways, and contraction-excitation feedback (42). Shorter atrial pacing cycle lengths appear to increase atrial vulnerability (112). In one study (113), the cycle length of AV reentry in patients with WPW who had a history of atrial fibrillation was 304 ± 40 ms, compared with 321 ± 54 ms in patients without a history of atrial fibrillation. Further, using electrophysiologic studies, AV reentry cycle length was found to be significantly shorter (289 ± 26 ms vs. 316 ± 51 ms; $p < .005$) in cases in which AV reentry degenerated into atrial fibrillation (113). It has also been postulated that the accessory pathway network itself may play a role in the initiation or maintenance of atrial fibrillation in some patients with WPW. Whatever the exact mechanism(s) of atrial fibrillation in patients with WPW, it is well reported that successful ablation of the accessory pathway prevents episodes of atrial fibrillation in more than 90% of these individuals (113,114).

Intrinsic atrial vulnerability may also play a role in the initiation of atrial fibrillation in tachycardia-induced tachycardia. Observations made using electrophysiologic study of patients with WPW have commonly demonstrated that atrial degeneration is observed first in the high right atrial region (Fig. 64.2). Of course, catheters are not located throughout all portions of the atria during study, and the initiation may occur in another area, for example, in a pulmonary vein. The high right atrium may be particularly susceptible to atrial fibrillation. Human atrial pectinate muscle bundles from the atrial appendage obtained during surgery may be involved in macroreentry caused by anisotropy (41). It is possible that this portion of the atria may be responsible for the initiation of atrial fibrillation in many situations, even if the area is not critical to maintenance of the tachycardia.

One other potential mechanism for degeneration into atrial fibrillation is contraction-excitation of feedback (115). During the era of surgical ablation of accessory pathways, it was typical to observe, during open-chest surgery in humans, a sudden dilatation of the atria shortly after the onset of AV reentry. The effects of sudden stretching of atrial tissue can produce electrophysiologic alterations in atrial refractoriness (116,117 and 118). In one study (116), increases in right atrial pressure were associated with prolongation of the right atrial effective refractory period, but a shortened right atrial refractory period was noted by other investigators (118). Regardless, under appropriate experimental conditions in humans, dilatation and increased pressure in the atria can cause changes in refractoriness, which could, in a

susceptible individual, facilitate initiation of atrial fibrillation.

Identification of the role of tachycardia-induced tachycardia as a mechanism for atrial fibrillation has important therapeutic implications. It presents an opportunity for the clinician to prevent further episodes of atrial fibrillation, not by treating atrial fibrillation itself, but by directing therapy at the initiating arrhythmia. The paradigm for this is ablation of an accessory pathway in a patient with AV reentry. Likewise, in patients who have atrial flutter predominantly with occasional episodes of atrial fibrillation, electrocardiographic confirmation that atrial fibrillation is caused by atrial flutter may allow cure using ablation of the atrial flutter reentrant circuit.

Lone (Idiopathic) Atrial Fibrillation

Certain patients have no clear etiologic factors that explain the presence of atrial fibrillation; in such patients, the condition is called *idiopathic* or *lone atrial fibrillation*. Our definition for lone atrial fibrillation is the absence of any potential etiologic factor and the lack of evidence of ventricular dysfunction on echocardiography (15). We do not use an age cutoff point to designate lone atrial fibrillation. The prevalence of lone atrial fibrillation depends on the population of patients studied, as demonstrated in Table 64.1.

Awareness of lone atrial fibrillation has existed for decades (7,11,119,120,121,122 and 123). Clearly, because normal atria do not spontaneously fibrillate, some anatomic or electrophysiologic milieu must allow emergence of atrial fibrillation in these patients. In some cases, autonomic perturbations may be the etiology and likely are transient in nature. In other patients, left atrial size is increased, even though ventricular function is normal, and these patients may have some unidentified anatomic pathophysiologic basis for atrial fibrillation (15).

Investigators have attempted to identify electrophysiologic differences between patients who have lone atrial fibrillation and control subjects (124,125). Patients with atrial fibrillation have shorter atrial refractory periods, a larger dispersion of refractoriness, and a higher incidence of sinus nodal dysfunction (124,125). Because atrial fibrillation can shorten atrial refractoriness (48,49), it is impossible to know whether alterations in refractoriness preceded or were caused by atrial fibrillation. Further, in a recent investigation of canine subjects, several weeks of atrial fibrillation was shown to prolong sinus nodal recovery time (126), raising the possibility that in some patients with tachycardia-bradycardia syndrome, sinus node dysfunction may result from atrial fibrillation.

Familial atrial fibrillation is extremely uncommon in our experience. However, a genetic locus for familial atrial fibrillation has been described recently, and lone atrial fibrillation was present in almost all patients with this genetic marker (127). Of particular note was the relatively early age of onset of atrial fibrillation, with a mean age of less than 20 years. The gene responsible for atrial fibrillation was located on chromosome 10q in the region of 10q22 to 10q24; the genes for the beta-adrenergic receptor and alpha-adrenergic receptor are located on 10q23 to 10q26. Further work in the genetics of atrial fibrillation may shed light on the pathogenesis of idiopathic atrial fibrillation.

We agree with most investigators regarding the excellent long-term prognosis for patients with lone atrial fibrillation (11,120,121,128,129). In the Framingham study, a significant stroke rate was seen, but the mean age was greater than 65 years in those subjects (130).

Definition of Atrial Fibrillation

Traditionally, atrial fibrillation has been termed *paroxysmal* or *chronic atrial fibrillation*. However, no standardization regarding these terms has ever been achieved, and quite disparate time frames have been proposed for each category. A new classification has been proposed by the American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines for the Management of patients with Atrial Fibrillation (131). Paroxysmal atrial fibrillation is self-terminating; persistent atrial fibrillation requires treatment for termination; in permanent atrial fibrillation, sinus rhythm cannot be restored, or the decision to avoid cardioversion has been made.

Symptoms of Atrial Fibrillation

Atrial fibrillation is associated with a diverse group of symptoms, palpitation being the most common (15,121,132). In one study that compared symptoms in patients with and without heart disease, palpitations occurred in 59% of patients with heart disease and in 77% of those with no heart disease (p <.002) (15). Other frequent symptoms were presyncope, fatigue, and dyspnea, and less common symptoms were chest pain and syncope. In a small group of patients, atrial fibrillation caused no symptoms. Care should be taken in ascribing a specific symptom to the actual occurrence of atrial fibrillation, because it is well documented that patients may have similar symptoms in the presence of sinus rhythm (132,133). Patients who experience dizziness, presyncope, or syncope may have associated carotid sinus hypersensitivity or neurally mediated syncope (134,135).

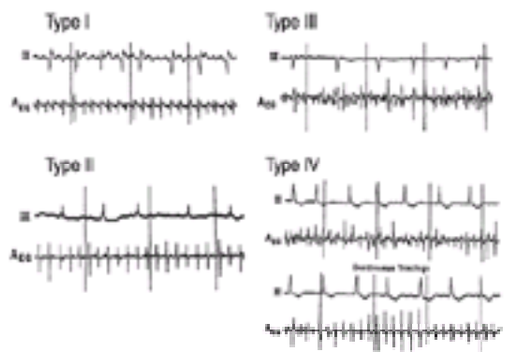
Why atrial fibrillation occurs at a particular point in time is unclear. In some patients, the onset may be related to a relative increase in parasympathetic tone, as demonstrated by an increased prevalence at night (136). Because patients with atrial fibrillation can have asymptomatic recurrences (137), it is possible that atrial fibrillation occurs even more frequently at night. In certain individuals, the reason for onset of atrial fibrillation is more obvious, for example, an alcoholic binge. For the majority of patients, no specific time of day, level of activity, or obvious inciting factor underlies each occurrence of atrial fibrillation, and initiation is likely multifactorial.

Electrocardiography of Atrial Fibrillation

During atrial fibrillation, electrocardiography demonstrates a lack of clearly defined P waves, with an undulating baseline that may alternate between recognizable atrial activity and a nearly flat line (Fig. 64.3). The ventricular response is irregular, and the rate depends on multiple factors, including intrinsic AV nodal conduction properties, level of parasympathetic and sympathetic tone, and the presence of negative dromotropic drugs such as beta-adrenergic blockers, calcium channel blockers, and digitalis. The underlying atrial rate is typically greater than 300 beats/min, but may vary considerably at different sites in the atria. The electrocardiographic appearance at any moment in time depends on the predominant underlying atrial activation, which is often protean (*e*Fig. 64.6.1).

***e*FIGURE 64.6.1** Twelve-lead electrocardiogram recorded at the same time as intracardiac atrial electrogram. **A:** The 12-lead electrocardiogram reveals atrial fibrillation with coarse atrial activity that resembles P waves in certain leads. **B:** The patient had a permanent pacemaker that was interrogated, and the intracardiac right atrial appendage electrogram showed an organized atrial rhythm of approximately 240 ms.

The variable electrocardiographic pattern that is seen during atrial fibrillation is not surprising, considering the multiple potential types of atrial activation that may be present at the same time at different locations throughout the atria. The presence of coarse versus fine atrial fibrillation has been recognized for many years (138). In one study, in an attempt to codify atrial fibrillation, right atrial epicardial electrograms were studied after cardiac surgery (139). Four distinct types of atrial fibrillation were identified (*e*Fig. 64.6.2). Type I atrial fibrillation showed atrial electrograms with discrete complexes of variable morphology separated by an isoelectric baseline. The mean atrial rate ranged from 291 to 405 beats/min. Type II atrial fibrillation demonstrated discrete atrial electrograms in the absence of an isoelectric baseline. The mean atrial rate was 383 beats/min. Type III atrial fibrillation was characterized by the absence of discrete atrial complexes or isoelectric intervals. Type IV atrial fibrillation involved alternation of type III with either type I or type II electrograms. Recent observations analyzing unipolar atrial electrograms during high-density mapping of the right atrium at surgery have clarified the etiology of the various types of atrial electrogram morphologies (140). The fragmented potentials recorded in type III atrial fibrillation likely represent areas of slow conduction or pivot points during atrial fibrillation.



***e*FIGURE 64.6.2** Types of atrial fibrillations recorded using bipolar right atrial electrograms (A_{EG}) in humans after cardiac surgery. See text for further description. (From Wells JL, Karp RB, Kouchoukos NT, et al. Characterization of atrial fibrillation in man: studies following open heart surgery. *Pacing Clin Electrophysiol* 1978;1:426–438, with permission.)

Echocardiography

An echocardiogram is an important test to obtain in patients with atrial fibrillation. It allows evaluation of atrial size, right and left ventricular function, and the presence of valvular lesions. Echocardiography, especially transesophageal echocardiography, has been valuable in investigating atrial function in patients with atrial fibrillation (45,51,52). Transesophageal echocardiography, but not transthoracic echocardiography, can provide valuable information on the presence of atrial thrombi, typically in the left atrial appendage (Fig. 64.7) (141,142,143 and 144). Atrial thrombi have been detected in as many as 15% of patients before cardioversion. Importantly, new thrombi can occur after successful cardioversion and may cause embolic events (142). Thus, at least two mechanisms are possible for thromboembolism after cardioversion: dislodgment of a preexisting thrombus and formation of a new hrombus after cardioversion.

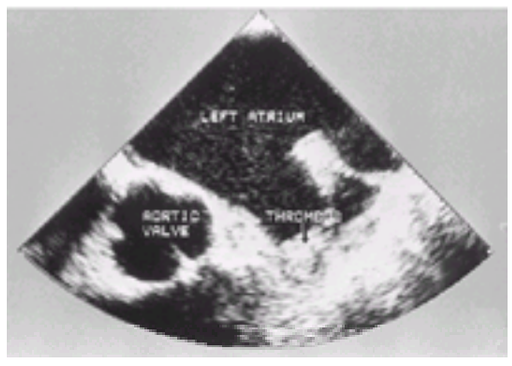
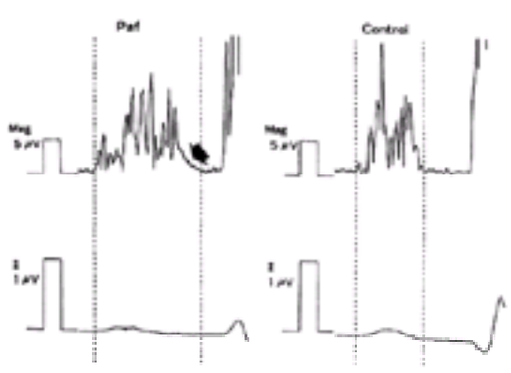


FIGURE 64.7 Transesophageal echocardiogram demonstrating left atrial appendage thrombus (*arrow*). (Courtesy of Drs. J. Bates and J. Steinmetz, the Care Group, St. Vincent Hospital, Indianapolis, IN.)

Signal-Averaged P-Wave Electrocardiography

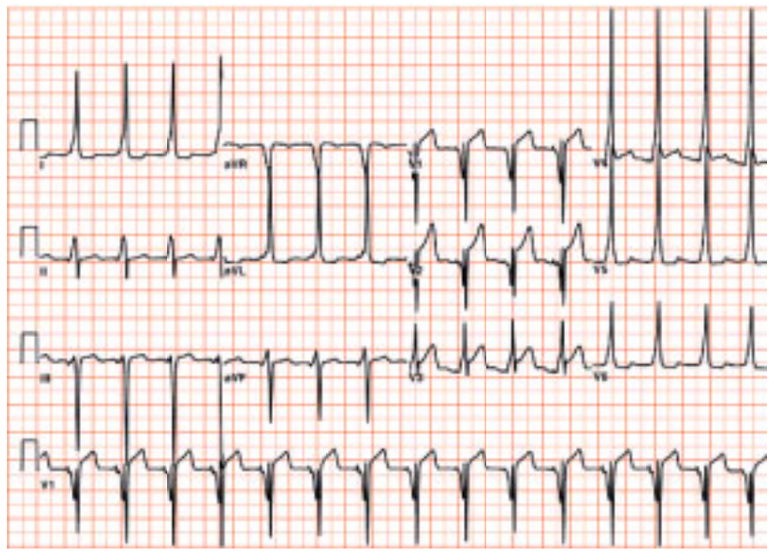
The signal-averaged electrocardiogram has been used for years to detect areas of slow conduction in the QRS complex during depolarization. More recently, P wave–triggered signal-averaged electrocardiograms have been performed to evaluate atrial abnormalities in patients who have atrial fibrillation (145). The authors of this study demonstrated the presence of atrial late potentials in patients with atrial fibrillation (*e*Fig. 64.7.1). Using various methods to analyze the root mean square voltage of the terminal portion of the filtered P wave and the duration of the filtered P wave, they developed criteria that yielded a sensitivity of 91% and a specificity of 76% for defining the atrial late potential. The use of signal-averaged P-wave electrocardiography has been evaluated for prediction of atrial fibrillation after cardiac surgery (146). Atrial fibrillation occurred in 25% of patients at a mean of 6.2 days after surgery. The signal-averaged P-wave duration was significantly longer among patients who developed atrial fibrillation (152 ± 18 ms vs. 139 ± 17 ms; p <.001). However, use of a filtered P-wave duration greater than 140 ms yielded a sensitivity of 77%, a specificity of 55%, a positive predictive accuracy of 37%, and a negative predictive accuracy of 87%. As is true for the use of signal-averaged electrocardiography of the QRS complex, negative predictive accuracy is far better than positive predictive accuracy. More data are needed to define the role of signal-averaged P-wave electrocardiography in clinical practice.



***e*FIGURE 64.7.1** Signal-averaged electrocardiogram of P waves in a patient with paroxysmal atrial fibrillation (Paf) versus those in a control patient. Arrowhead points to low-amplitude signal in the terminal portion of the filtered P wave, referred to as an *atrial late potential*. Mag, magnitude. (From Fukunami M, Yamada T, Ohmori M, et al. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by P wave–triggered signal-averaged electrocardiogram. *Circulation* 1991;83:162–169, with permission.)

Wolff-Parkinson-White Syndrome

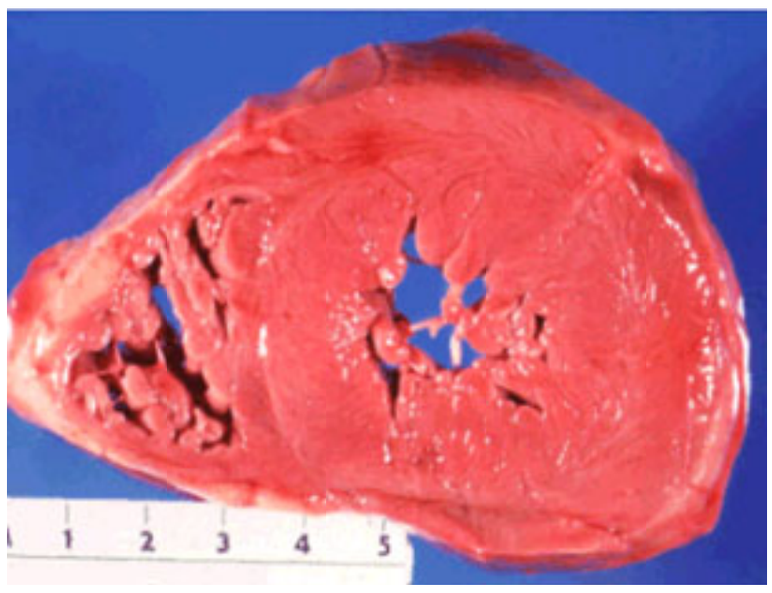
Atrial fibrillation in patients who have preexcitation can result in ventricular fibrillation and sudden cardiac death. This sequence of events occurs most commonly when a rapid preexcited ventricular response is present (Fig. 64.5), and degeneration to ventricular fibrillation may follow (Fig. 64.6). In our opinion, patients with ventricular preexcitation who have symptoms suggestive of tachycardia or documented arrhythmias should undergo electrophysiologic evaluation and, if indicated, endocardial catheter ablation of the accessory pathway (see Chapter 73). A more difficult situation exists for asymptomatic patients who have ventricular preexcitation during sinus rhythm (147). Some of these patients may be at risk for sudden cardiac death, although this is rarely the initial presentation of WPW. Because patients resuscitated from ventricular fibrillation invariably have a preexcited RR interval seen on electrophysiologic study during induced atrial fibrillation that is, at its shortest, less than 250 ms, the possibility for screening asymptomatic patients to detect those at risk for ventricular fibrillation exists (147). In general, we do not favor mass screening of asymptomatic patients who have ventricular preexcitation (147). Instead, we tend to screen patients who have a familial history of sudden death or tachycardia, patients who are considering competitive athletics, or individuals who are in certain occupations (e.g., airline pilots). See Chapter 66 for a more detailed discussion of this problem.



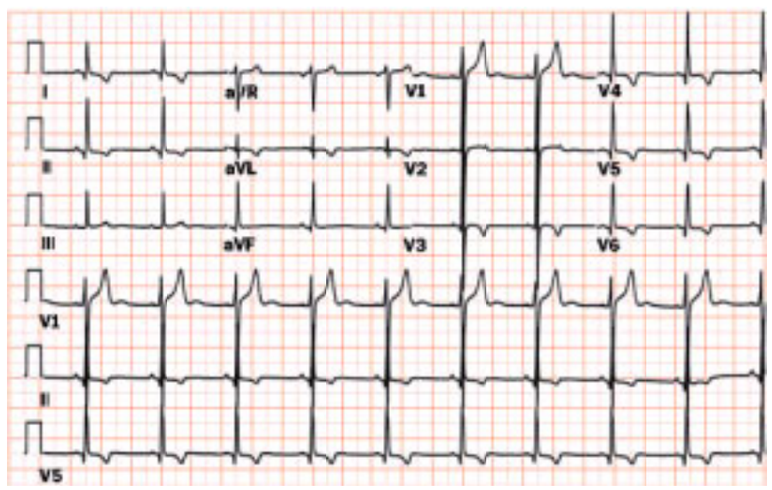
A 16-year-old male patient with Wolff-Parkinson-White syndrome.

Hypertrophic Cardiomyopathy

Approximately 15% of patients with hypertrophic cardiomyopathy develop atrial fibrillation (148). In these individuals, atrial fibrillation can result in profound hemodynamic deterioration, leading to chest pain, presyncope, syncope, and even sudden cardiac death (148,149 and 150). In one retrospective study, the acute onset of atrial fibrillation resulted in deterioration by at least one New York Heart Association functional class in the majority of patients (148). Importantly, the mean values for maximal left ventricular wall thickness may be lower among patients with atrial fibrillation compared with those of patients with sinus rhythm (151). Thus, prediction of which patients are most likely to develop atrial fibrillation using analysis of ventricular wall thickness may not be possible. The weight of clinical data strongly suggests that efforts should be directed at maintaining sinus rhythm in these individuals, to avoid functional deterioration and the possibility of sudden cardiac death.



Massive left ventricular hypertrophy as well as concentric hypertrophic cardiomyopathy. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Hypertrophic cardiomyopathy. Inverted precordial T waves associated with hypertrophic cardiomyopathy.

THERAPY OF ATRIAL FIBRILLATION: GENERAL PRINCIPLES

There are three potential therapeutic goals of treatment for patients with atrial fibrillation (Fig. 64.8) (152). These include restoration and maintenance of sinus rhythm, rate control during atrial fibrillation, and prevention of thromboembolism. The decision to try to maintain sinus rhythm rather than use ventricular rate control should be individual to each patient, based on analysis of the risk-benefit ratio for that individual. No large prospective, randomized clinical trials have demonstrated that either approach has a survival advantage. Advantages of sinus rhythm include amelioration of symptoms, possible retardation or prevention of the transition from intermittent to permanent atrial fibrillation, and a theoretical, though not proven, benefit in reduction of the risk for thromboembolic stroke. The primary risk is proarrhythmia, which can cause sudden death (153). The option of allowing atrial fibrillation to persist but controlling the ventricular response has the advantage of not exposing patients to the potential proarrhythmic effects of antiarrhythmic drugs. Two major disadvantages are continuation of symptoms in many patients, although symptoms may be lessened, and the absolute need for continued anticoagulation in patients at risk for thromboembolism. The longer a patient remains in atrial fibrillation, the greater are the chances that progressive electrophysiologic and anatomic atrial changes will occur, which over the course of time make it more difficult to maintain or even to restore sinus rhythm. Thus, the clinician should decide within a short period of time which approach is best for the patient.

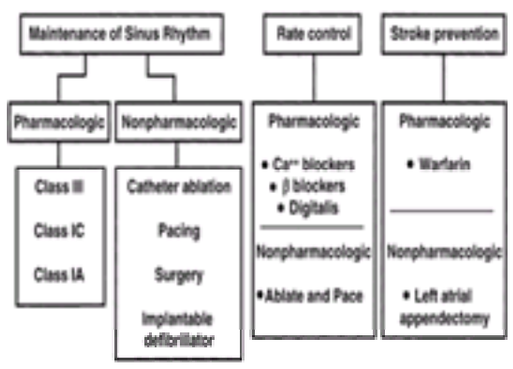


FIGURE 64.8 Therapeutic options in the treatment of patients with atrial fibrillation. See text for details. (From Prystowsky EN. Management of atrial fibrillation:

therapeutic options and clinical decisions. *Am J Cardiol* 2000;85:3D–11D, with permission.)

PHARMACOLOGIC THERAPY

Use of Intravenous Agents to Restore Sinus Rhythm

Use of intravenous verapamil, digitalis, esmolol, or propranolol is not useful to terminate atrial fibrillation (9,154,155 and 156). An exception might be the use of beta-adrenergic blockers in patients after cardiac surgery. In general, drugs that alter atrial electrophysiologic properties are useful to terminate atrial fibrillation (Table 64.4) (9).

Drug	Dosage
To decrease ventricular response[a]	
Verapamil	5–10 mg i.v. over the course of 2 min; additional 5–10 mg i.v. every 4–6 h for rate control
Diltiazem	0.25 mg/kg i.v. over the course of 2 min; if response is inadequate, a second dose of 0.35 mg/kg over the course of 2 min may be given 15 min later; bolus may be followed with constant infusion of ≤10 mg/h for rate control.
Propranolol	1 mg/min i.v. to total dose of 0.15 mg/kg or 12 mg total; additional 1 mg doses as needed for control of heart rate
Esmolol	Initial load of 500 μg/kg/min i.v. for 1 min followed by 50 μg/kg/min for 4 min; if response inadequate, then repeat in 5 min with 500 μg/kg/min for 1 min and 100 μg/kg/min for 4 min; continue to titrate every 5 min until desired heart rate is reached; 50–200 μg/kg/min is usual maintenance dose
Digoxin	0.5–1.0 mg i.v., followed by 0.25 mg every 2–4 h, with total 24 h dose <1.5 mg
For pharmacologic conversion to sinus rhythm	
Procainamide	50 mg/min i.v. to total dose of 10–14 mg/kg
Ibutilide	1 mg i.v. over the course of 10 min; may repeat if atrial fibrillation is present after 20 min

[a]Avoid use of this agent in patients with ventricular preexcitation.

TABLE 64.4 ACUTE DRUG THERAPY (INTRAVENOUS) FOR ATRIAL FIBRILLATION

Procainamide

In one study, 9 of 21 patients converted to sinus rhythm while receiving procainamide at a mean dose of 13.3 ± 3.6 mg per kg (157). Notably, the left atrial diameter seen on echocardiography was less than 4.0 cm in all patients who converted to sinus rhythm, whereas it was greater than 4.0 cm in all but one of the patients who did not convert. Further, the range of duration of atrial fibrillation among patients who converted was 2 hours to 1 day. In another investigation, patients who converted to sinus rhythm had a shorter mean duration of atrial fibrillation than did patients who did not convert (6 ± 7 days vs. 79 ± 88 days; p <.01) (158). Among patients with atrial fibrillation of less than 24 hours' duration, 92% were converted to sinus rhythm when intravenous flecainide was administered, compared with 65% who converted when intravenous procainamide was administered (159). Procainamide also appears to be useful in converting atrial fibrillation after cardiac surgery (160).

Ibutilide

Ibutilide prolongs refractoriness by enhancing an inward sodium current during the plateau, although it also may block outward potassium current (161). It may increase the QT interval, and torsades de pointes can occur with its use. It is effective for converting atrial fibrillation to sinus rhythm (162,163 and 164). The typical recommended dose is 1.0 mg administered over 10 minutes, which can be repeated if atrial fibrillation does not terminate during or within 10 minutes after the end of the initial infusion (163). The dosage can be adjusted downward for patients who weigh less than 60 kg. The conversion rate for atrial fibrillation in one study was 31%, and the success rate was higher among patients with shorter duration of atrial fibrillation (10 ± 13 days vs. 18 ± 15 days) (163). Further, conversion to sinus rhythm occurred in 67% of patients who had a left atrium of normal size compared with only 27% of patients who had an enlarged left atrium. Torsades de pointes may be associated with ibutilide infusion, but in almost all instances, it occurs either during infusion or within a few hours after termination of the final ibutilide infusion. Thus, administration of ibutilide, as well as procainamide, should be performed under circumstances in which resuscitative measures can be readily performed.

Amiodarone

Unlike oral amiodarone, minimal prolongation of the effective refractory period of the right atrium and right ventricle occurs shortly after administration of intravenous amiodarone (5 mg/kg) (165). In some studies, the effectiveness of intravenous amiodarone was similar to that of placebo in restoring sinus rhythm (166,167), whereas other studies suggest that amiodarone has a more beneficial effect (168). Oral quinidine is as effective or more effective in converting atrial fibrillation to sinus rhythm (169,170), but we rarely use it for this purpose because of the significant associated side effects. Intravenous amiodarone has the added effect of significantly slowing ventricular response. This can prove very useful when other agents, such as beta-adrenergic blockers and slow calcium channel blockers, are relatively contraindicated.

Flecainide, Propafenone, Sotalol, and Dofetilide

Intravenous flecainide, propafenone, and sotalol are not available for use in the United States. Intravenous flecainide is very effective in converting atrial fibrillation to sinus rhythm (159,167,171,172 and 173). Intravenous propafenone is useful in converting recent-onset atrial fibrillation to sinus rhythm, but it is ineffective in patients in whom atrial fibrillation has lasted many months (174,175). Intravenous sotalol is minimally effective in converting atrial fibrillation to sinus rhythm (176). Intravenous dofetilide, which prolongs refractoriness, appears to be useful in terminating atrial fibrillation (177,178 and 179).

Use of Oral Antiarrhythmic Agents for Restoration and Maintenance of Sinus Rhythm

A variety of antiarrhythmic drugs with disparate electrophysiologic actions can terminate or prevent atrial fibrillation. These include disopyramide, quinidine, procainamide, propafenone, flecainide, sotalol, dofetilide, amiodarone, and morizicine (180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203 and 204). A single oral loading dose of 300 to 600 mg of propafenone or 200 to 300 mg of flecainide is successful in restoring sinus rhythm in more than 50% of selected patients with recent-onset atrial fibrillation (181,182). Few comparative studies exist that assess the efficacy of various agents in maintaining sinus rhythm during long-term follow-up. Overall, approximately 50% of patients maintain sinus rhythm for at least 6 months during antiarrhythmic therapy. Flecainide and propafenone appear to have equal efficacy (187). Quinidine is more useful than sotalol for conversion of atrial fibrillation to sinus rhythm (192), but the two drugs are equally effective in maintaining sinus rhythm (191). In one study, propafenone prevented atrial fibrillation more often than sotalol (193), but there was no difference between them in another investigation (190). Amiodarone is considered by some to be the most effective agent for drug-refractory recurrent atrial fibrillation, although few prospective comparative data are available (205). In small groups of patients, amiodarone prevented atrial fibrillation more often than quinidine or disopyramide (198,199). Amiodarone maintains sinus rhythm in nearly two-thirds of patients for up to 1 year follow-up (194,195,196 and 197). Typically, amiodarone has been associated with frequent side effects, some life-threatening (e.g., pulmonary toxicity). However, lower doses likely will decrease the risk of nuisance and serious side effects. In one study, in which amiodarone was administered at 600 mg daily for 4 weeks, approximately 16% of patients converted to sinus rhythm (197). During long-term therapy, the mean dose was 204 mg, and sinus rhythm was maintained in 53% of patients after 3 years with minimal serious side effects (197). The efficacy of antiarrhythmic drug therapy in maintaining sinus rhythm can be enhanced using a serial drug approach (206,207). Several large prospective trials have demonstrated the efficacy of dofetilide in maintaining sinus rhythm (202,203 and 204). Although procainamide is useful in preventing atrial fibrillation, in our opinion, its substantial side-effect profile precludes long-term use.

The efficacy of antiarrhythmic drug therapy should not be judged solely on the basis of whether atrial fibrillation recurs during follow-up (152). Preventing all episodes of atrial fibrillation over the course of years of treatment is exceedingly difficult. Therapeutic success should be based on the reduction in frequency and duration of symptomatic episodes of atrial fibrillation. For example, in a patient who has several episodes of atrial fibrillation weekly before treatment, recurrence of one or two short-lived episodes per year during drug therapy is an outstanding success. Recurrence of atrial fibrillation should not be equated with arrhythmias such as sustained ventricular tachycardia or ventricular fibrillation. An analogy can be made with treatment for angina or congestive heart failure. In both conditions, the need for occasional nitroglycerin use or an increase in diuretics, respectively, in patients who otherwise are well compensated is readily accepted.

Proarrhythmia

Proarrhythmia is the most serious side effect of antiarrhythmic drug therapy (9,153). Proarrhythmic events can be caused by tachyarrhythmias or bradyarrhythmias.

Proarrhythmia caused by tachyarrhythmia is the most dangerous and life threatening, and torsades de pointes is the most frequently observed proarrhythmic event in this category (Fig. 64.9) (153). Torsades de pointes can occur during use of any drug that prolongs QT interval; amiodarone appears to have the lowest incidence among such agents. It has been postulated that early after-depolarizations initiate torsades de pointes (153). Conditions that favor early after-depolarizations are ventricular hypertrophy, slow heart rate, hypokalemia, and the presence of potassium channel blocking drugs (153), which commonly occur in patients with atrial fibrillation. Torsades de pointes is uncommon during atrial fibrillation in patients who have a relatively rapid ventricular response. It is more likely to emerge after restoration of sinus rhythm, with a resultant slower heart rate (153), which has been referred to as the "paradoxical risk of sinus rhythm for sudden cardiac death" (144). Other types of malignant ventricular arrhythmias can occur. Use of flecainide should be avoided in patients who have experienced myocardial infarction (208), and an enhanced mortality was reported among patients with atrial fibrillation and heart failure who were treated with drugs such as quinidine and procainamide (209). However, amiodarone and dofetilide do not appear to increase mortality in patients with congestive heart failure (202,210,211).

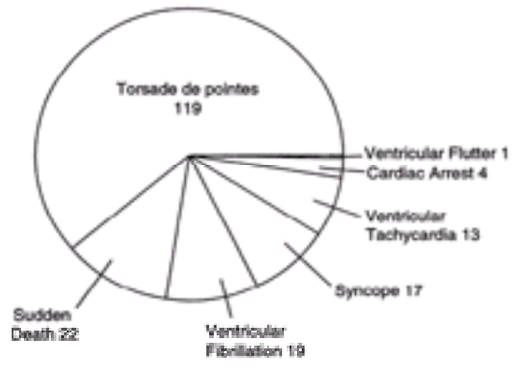


FIGURE 64.9 Types of proarrhythmic events (n = 195) occurring during drug therapy for supraventricular tachycardia. [Modified from Prystowsky EN. Proarrhythmia during drug treatment of supraventricular tachycardia: paradoxical risk of sinus rhythm for sudden death. *Am J Cardiol* 1996;78(8A):35–41.]

Bradyarrhythmias, including sinus nodal dysfunction and AV conduction disturbances, may also complicate antiarrhythmic drug therapy. One type of proarrhythmia, 1:1 AV conduction with conversion of atrial fibrillation to atrial flutter or tachycardia, is clearly preventable. This more frequently occurs with drugs such as propafenone and flecainide, which can markedly slow atrial tachycardia rates (9). It is important to prescribe concomitant AV nodal blocking agents to avoid this complication, especially for patients who are receiving propafenone or flecainide (152). Administration of concomitant AV nodal blocking agents is not necessary when sotalol or amiodarone is used, because both agents substantially decrease conduction through the AV node.

Antiarrhythmic Drug Selection

Reversible causes of atrial fibrillation (e.g., excess alcohol intake) should be considered and treated if possible. Correction of electrolyte abnormalities and cardiovascular problems such as heart failure need to be addressed before an antiarrhythmic agent is administered. Prophylactic drug therapy typically is not necessary for patients who have experienced a single detected episode of atrial fibrillation, or for patients who have infrequent, transient, and well-tolerated paroxysmal atrial fibrillation.

Every effort should be made to minimize the chance for proarrhythmia and other drug side effects. Antiarrhythmic drug therapy should be initiated in the hospital for patients who have heart disease, especially for patients with a history of congestive heart failure (9,152). Outpatient initiation of therapy appears to be reasonable for individuals who have normal QT intervals and no or minimal heart disease (9,131,152). Because no antiarrhythmic drug has been shown conclusively to be superior to other agents, selection of initial drug therapy is based more on avoidance of serious side effects than on predicted efficacy. Figure 64.10 shows our current scheme for choosing initial and subsequent antiarrhythmic agents to prevent atrial fibrillation. For patients who have lone atrial fibrillation, we prefer to use drugs that have minimal organ toxicity; initial choices are flecainide, propafenone, and sotalol. For patients who have congestive heart failure, amiodarone and dofetilide are our treatments of choice (202,210,211). Sotalol is our initial selection for patients who have coronary artery disease, because we prefer to use beta-adrenergic blockers for such individuals. Sotalol has both beta-adrenergic blocker and class III antiarrhythmic activity, and safety data are available for its use in such patients (212). Amiodarone and dofetilide also have safety data in patients after myocardial infarction (213,214 and 215). Patients with hypertension and left ventricular hypertrophy may be at increased risk for torsades de pointes, because hypertrophied ventricles appear more prone to develop early after-depolarizations (153). Thus, we prefer to start with flecainide or propafenone. If a patient has substantial left ventricular hypertrophy, use of flecainide and propafenone carries concerns about an increased proarrhythmic risk, and we prefer to use amiodarone.

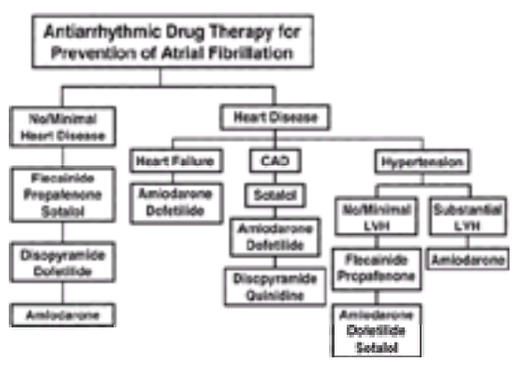


FIGURE 64.10 General scheme for selecting antiarrhythmic drug therapy for the prevention of atrial fibrillation. See text for details. CAD, coronary artery disease; LVH, left ventricular hypertrophy.

Use of Drug Therapy to Control Ventricular Rate

In the absence of ventricular preexcitation, drugs that decrease conduction in the AV node are useful in controlling ventricular rate in patients who have atrial fibrillation (Table 64.4). It is very important to control ventricular rate, not only to decrease symptoms, but to prevent tachycardia-mediated cardiomyopathy (see the section Tachycardia-Induced Ventricular Cardiomyopathy). Drugs that depress conduction and prolong refractoriness in the AV node include digoxin, beta-adrenergic antagonists, and calcium channel blockers (9,155,156,216,217,218,219,220,221,222 and 223). Notably, the electrophysiologic effects of digoxin on the AV node are indirect and depend on an intact autonomic nervous system (224). Thus, whereas digoxin may slow ventricular response at rest, it is relatively ineffective in controlling the ventricular rate during exercise (220). Beta-adrenergic blockers and calcium channel blockers are preferred over digoxin for rate control in patients who have not experienced heart failure (9). Beta-adrenergic blockers are also recommended in situations in which sympathetic tone is increased, such as thyrotoxicosis (9). In patients who have congestive heart failure, digitalis is the first-line treatment (9). As noted previously, both sotalol and amiodarone may be used as monotherapy because they depress conduction through the AV node. In some patients, control of ventricular response can be facilitated with the use of combination drug therapy, for example, digoxin and a calcium channel blocker or a beta-adrenergic blocker. In this situation, rate control may be achieved without undue side effects. Preliminary data on the use of clonidine suggest that such agents may have a role in controlling ventricular response in patients who have atrial fibrillation (225).

In patients who have WPW, control of the rapid preexcited ventricular response requires the use of agents that depress conduction over the accessory pathway. In the acute setting, intravenous procainamide or ibutilide are the treatments of choice, unless the patient is unstable and requires urgent electrical cardioversion. The use of drugs such as digoxin, calcium channel blockers, beta-adrenergic blockers, and adenosine are contraindicated in this situation. They do not block conduction over the accessory pathway and may accelerate the ventricular response, resulting in a potentially very unstable clinical situation.

Treatment of Atrial Fibrillation after Cardiac Surgery

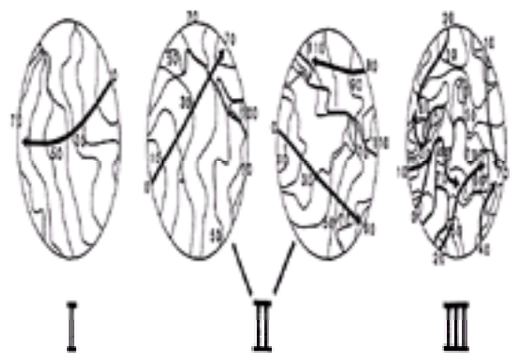
Beta-adrenergic blockers are the best treatment currently available for prevention of atrial fibrillation after cardiac surgery (90,226,227,228 and 229). In a randomized, controlled study, sotalol demonstrated superiority to placebo in prevention of atrial fibrillation (230). Administration of intravenous amiodarone, 1 g per day for 2 days

starting immediately after cardiac surgery, reduced the incidence of postoperative atrial fibrillation compared with placebo (231). Administration of oral amiodarone, starting at least 1 week before surgery, may also decrease postoperative atrial fibrillation (232).

The optimum approach to treating atrial fibrillation in the postoperative period is unclear. In most patients who experienced no preoperative atrial fibrillation, atrial fibrillation is a transient arrhythmia and typically is not a long-term problem (233). If simple measures such as administration of beta-adrenergic blockers do not prevent atrial fibrillation, additional therapy can be pursued to restore and maintain sinus rhythm or merely to control the ventricular response. In the latter situation, anticoagulation therapy should be started as soon as it is considered safe. The patient should be reevaluated 4 to 6 weeks after surgery.

PREVENTION OF THROMBOEMBOLISM

Prevention of stroke is key to the management of the condition of patients with atrial fibrillation (Fig. 64.8). A hypercoagulable state appears to exist in patients with atrial fibrillation (234,235). A high stroke risk has been well described for years in patients with atrial fibrillation and mitral stenosis or prosthetic mitral valves. Recently, several prospective multicenter, randomized clinical trials have conclusively demonstrated that warfarin is highly effective in reducing the incidence of ischemic stroke among patients with atrial fibrillation (*e*Fig. 64.10.1) (9). Overall, a combined risk reduction of 68% is seen.



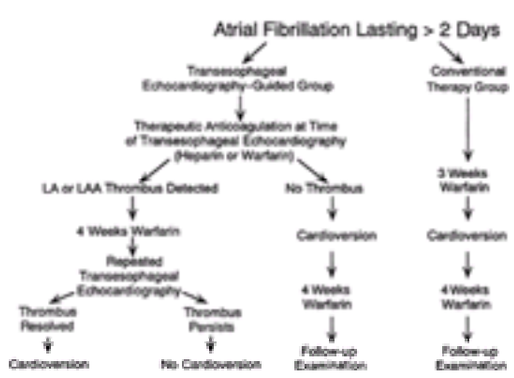
***e*FIGURE 64.10.1** Plot of risk-reduction strategy for five randomized clinical trials that compared atrial fibrillation patients receiving warfarin for prevention of ischemic stroke with control patients. Horizontal lines represent 95% confidence intervals for each trial. AFASAK, Atrial Fibrillation, Aspirin, and Anticoagulant Therapy study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation study; SPAF, Stroke Prevention in Atrial Fibrillation study; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation study. (From Prystowsky EN, Benson DW, Fuster V, et al. Management of patients with atrial fibrillation: a statement for healthcare professionals from the subcommittee on electrocardiography and electrophysiology, American Heart Association. *Circulation* 1996;93:1262–1277, with permission.)

Embolus. Dislodged thrombus that embolized to the toes and caused gangrene (*arrows*).

Independent predictors of thromboembolic risk have been identified (9,131). High-risk patients have a 5% to 7% or greater yearly risk of thromboembolism. High-risk variables from prospective trials include a history of hypertension, prior stroke or transient ischemic attack, diabetes, recent heart failure, and age greater than 65 years (9). Notably, paroxysmal atrial fibrillation has not been found to be an independent predictor of thromboembolic risk. Other studies have considered coronary artery disease to place a patient at high risk for stroke (131). At present, high-risk patients who can receive anticoagulation therapy should be treated with warfarin, with the INR adjusted to between 2.0 and 3.0. Patients greater than 75 years old should be observed carefully, because bleeding complications increase in elderly patients. Patients with atrial fibrillation who have low risk for stroke may be treated with 325 mg of aspirin daily (9). Patients with lone atrial fibrillation who are less than 60 years old do not require specific therapy for prevention of thromboembolism. Some physicians prescribe aspirin to this group of patients, but few data are available to support this approach. Recent guidelines offer more detailed information (131).

Anticoagulation for Cardioversion

Electrical and pharmacologic cardioversion can result in thromboembolism (9). Prior anticoagulation appears to decrease the risk of emboli (9,45,236,237,238 and 239). In patients who have atrial fibrillation of unknown duration or duration greater than 48 hours, current recommendations are to administer warfarin for 3 weeks before and 4 weeks after cardioversion, maintaining an INR of 2.0 to 3.0 (9). In high-risk patients, warfarin therapy should be continued on a long-term basis after cardioversion. In an alternative approach, transesophageal echocardiography is used (9,131,141,144) (eFig. 64.10.2). The use of transesophageal echocardiography appears to offer an advantage to patients who are already hospitalized or in whom restoration of sinus rhythm is more urgent. However, the widespread use of this method for outpatient cardioversion cannot be supported at this time (45).



***e*FIGURE 64.10.2** Protocol for the ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) study. Patients with atrial fibrillation were randomly assigned to be treated by the conventional approach or to have treatment guided by transesophageal echocardiography. LA, left atrial; LAA, left atrial appendage. (From Klein AL, Grimm RA, Black IW, et al. Cardioversion guided by transesophageal echocardiography: the ACUTE pilot study. A randomized, controlled trial. *Ann Intern Med* 1997;126:200–209, with permission.)

NONPHARMACOLOGIC THERAPY

Pharmacologic treatment has been used for decades for cardioversion and prevention of recurrent atrial fibrillation. Use of antiarrhythmic drugs is associated with substantial side effects and mortality in some groups of patients. Accordingly, it is not surprising that nonpharmacologic techniques for managing atrial fibrillation have been developed, including external and internal electrical cardioversion, atrial pacing methods to prevent atrial fibrillation, surgery, radiofrequency catheter ablation procedures, and use of implantable atrial defibrillators.

Electrical Cardioversion

Transthoracic Electrical Cardioversion

The technique of transthoracic direct current (DC) electrical cardioversion of atrial fibrillation was developed by Lown and associates (240). Lown (241) reported that "sinus rhythm was reinstated in 94% of the 456 episodes of atrial fibrillation." Although any patient who has atrial fibrillation may be a candidate for transthoracic DC cardioversion, certain characteristics predict immediate success and long-term maintenance of sinus rhythm. The best candidates are patients without mitral valve disease or a very large left atrium and patients who have atrial fibrillation of relatively short duration. Early echocardiographic studies suggested that there was minimal possibility of achieving or maintaining sinus rhythm when the anterior-posterior diameter of the left atrium was greater than 4.5 cm (242). In contrast, a recent randomized study showed that the size of the left atrium was not related to the success of cardioversion or to recurrence of atrial fibrillation (243). At present, no universally accepted threshold value for left atrial size or severity of mitral stenosis that would preclude attempts at cardioversion exists. It is our policy to attempt cardioversion at least once in most patients with atrial fibrillation in whom we think sinus rhythm would be preferable. Exceptions might be individuals known to have had atrial fibrillation for many years.

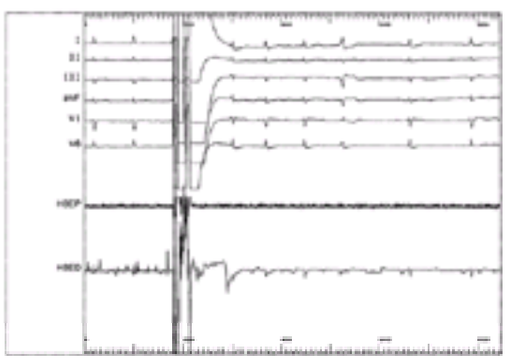
In patients undergoing transthoracic DC cardioversion, antiarrhythmic drugs are frequently used to maintain sinus rhythm (207). Drug therapy should be considered before use of cardioversion in patients with long-standing atrial fibrillation (e.g., more than 3 months), to lessen the chance of relapse into atrial fibrillation in the first few days after cardioversion. Digitalis therapy is not a contraindication to elective cardioversion, although it is customary to withhold digoxin on the day of cardioversion, a custom that is based on few scientific data. On the other hand, attempts to cardiovert arrhythmias associated with digitalis toxicity are hazardous and should be avoided (244). Concomitant antiarrhythmic drug therapy may increase energy requirements for successful cardioversion. In a nonrandomized series of 57 patients, flecainide was associated with a higher energy requirement than class Ia or III drugs, although overall success was similar in all groups (245).

Success of transthoracic DC cardioversion to restore sinus rhythm depends on several technical factors (246). The optimal electrode size is 12 to 13 cm in diameter. Initial electrode placement is right anterior–left posterior or left anterior–left posterior. If cardioversion with these electrode orientations is unsuccessful, a right anterior–apical electrode position can be tried. The clinician must be flexible and willing to try several electrode orientations. Application of firm pressure to the anterior electrode during full expiration may facilitate delivery of current to the heart. For most patients, we use an energy delivery of 360 J synchronized to the QRS complex for the first shock (246,247). Appropriate anesthesia is mandatory before shock delivery. If reversion to sinus rhythm is not achieved after multiple shocks have been given using various electrode positions, adjunctive measures can be used, such as higher energy levels (248), pretreatment with ibutilide (249), and internal cardioversion (250). More experience with transthoracic cardioversion using biphasic shocks will likely improve success of treatment at lower energies (251).

Intracardiac Defibrillation

Intracardiac defibrillation is used to decrease the amount of extracardiac tissue involved in the current path, which maximizes the potential gradient within the atrial tissue and increases the success rate of atrial defibrillation. In 1974, Mirowski and colleagues (252) demonstrated the efficacy of low-energy defibrillation of atrial fibrillation using an intracavitary lead system in a canine model of atrial fibrillation. In recent years, there has been substantial interest in development of a catheter-based lead system for internal atrial defibrillation. High- and low-energy systems have been studied.

The high-energy method defibrillates the atrium between a back patch electrode and a standard quadripolar electrode catheter positioned in the posterior right atrium. Shocks of 200 to 300 J successfully defibrillated 9 of 10 patients with atrial fibrillation that was resistant to external DC cardioversion in one study (*e*Fig. 64.10.3) (253). A comparison of external and internal cardioversion demonstrated superiority of internal defibrillation (250). Low-energy internal atrial defibrillation has been performed in animals and humans (254,255). Defibrillation between the coronary sinus and the right atrium offered the lowest defibrillation threshold of the available transcatheter techniques, with use of an energy level of 1.1 to 8.9 J. Low-energy transcatheter atrial defibrillation is safe and is associated with low complication and high success rates (256). However, even though low energy levels are used, the shocks are often painful and intolerable to the patient (257). This has impeded the clinical usefulness of "stand alone" implantable atrial defibrillators.



***e*FIGURE 64.10.3** Example of internal cardioversion through a catheter in the right atrium connected to a defibrillator pad on the back. Note that no deflection from the bundle of His occurs on the distal electrode (HBED), because the catheter has been positioned in the posterior portion of the atrium. A 200-J shock restored sinus rhythm, as can be noted on the right-hand portion of this figure. HBEP, proximal electrode pair from the His electrogram.

Atrial Pacing

Patients with sick sinus syndrome commonly develop supraventricular tachycardias, predominantly atrial fibrillation (tachycardia-bradycardia syndrome). Much debate has occurred about whether use of atrial-based or of ventricular-based pacing is preferred for patients with sick sinus syndrome. Retrospective data indicate that the incidence of atrial fibrillation is reduced among patients who receive atrial-based pacing (258). A randomized, prospective study compared AAI to VVI pacing (259,260). The results show a trend toward an increased incidence of atrial fibrillation and stroke in patients receiving VVI pacing. Thromboembolic events occurred in 17.4% of the VVI group and in only 5.5% of the AAI group (p = .0083). No difference in mortality or development of congestive heart failure was seen. In summary, the data support use of atrial-based pacing for patients with sick sinus syndrome. For patients who have no indication for pacing, data from multiple studies on various pacing techniques to prevent atrial fibrillation have yielded mixed results, and no clear consensus has yet emerged (261,262 and 263). See Chapter 74 for more details on this subject.

A 72-year-old patient with atrial pacing with transition to ventricular pacing.

Intraatrial conduction block results in a very delayed activation of the left atrium and may be associated with an increased incidence of atrial tachyarrhythmias. In a preliminary study involving 28 patients, permanent atrial resynchronization resulting from simultaneous right atrial and coronary sinus pacing corrected the intraatrial dyssynchrony expressed by reduction of P-wave duration (261). In 21 patients, this biatrial synchronous pacing prevented arrhythmia recurrences during a follow-up period of 34 ± 15 months (261). Use of dual-site atrial pacing in the high right atrium and coronary sinus os was evaluated in a prospective study involving patients with paroxysmal atrial fibrillation who had bradyarrhythmias warranting permanent pacemaker implantation (264). Dual-site atrial pacing with use of an optimal drug regimen resulted in a marked decline in atrial fibrillation recurrences. Multisite atrial pacing is feasible and safe and appears to be effective. Further research may demonstrate that this pacing modality should be considered as a primary mode of treatment for prevention of atrial fibrillation.

Catheter Ablation

Atrioventricular Block

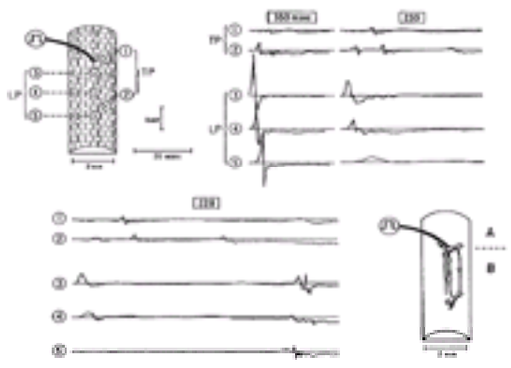
For some patients who have permanent atrial fibrillation, drug therapy used to control ventricular response is either ineffective or not tolerated. An alternative approach is endocardial catheter ablation of the AV junction that results in complete heart block (265,266). Such patients require a permanent rate-responsive pacemaker. This technique can also be used for treatment of patients who have transient or persistent atrial fibrillation, in lieu of drugs that suppress AV node conduction. Improvement in exercise tolerance and quality of life has been demonstrated with this procedure (267). Radiofrequency catheter ablation is currently the method of choice for accomplishing these goals (see Chapter 73 for further details).

Atrioventricular Node Modification

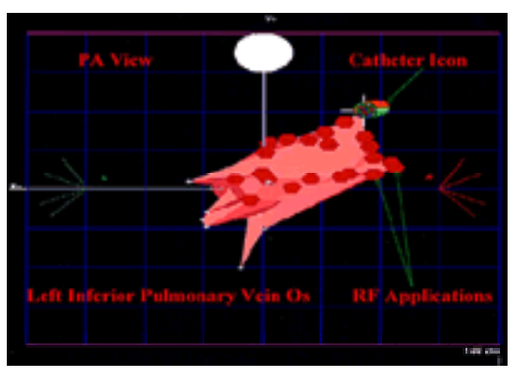
Complete AV junction ablation requires pacemaker implantation. Another technique to slow the ventricular rate during atrial fibrillation without creating irreversible heart block has been developed: modification of AV node conduction to prevent rapid ventricular rates. Several studies have demonstrated the feasibility of modifying AV node function without creating AV block (268,269). AV node modification is effective in approximately 70% of patients. Inadvertent AV block may occur in 16% to 21% of patients, and one episode of sudden death has been reported (269). We prefer complete AV block to AV node modification. In complete block, regularization of the ventricular rate occurs, which reduces or eliminates palpitations while improving cardiac output.

Primary Prevention

Advances in ablation therapy have led to its routine use in nearly all arrhythmias, with the exception of atrial and ventricular fibrillation. The maze procedure has been the primary surgical treatment of atrial fibrillation (37). Endocardial compartmentalization of the atria by linear lesions and creation of a maze-like result have been tried, using radiofrequency catheter ablation energy (270). Right atrial approaches have not been very successful (271). Left atrial approaches, especially focal ablation typically in the pulmonary veins, are promising and much more successful in curing atrial fibrillation (27,28 and 29,272) (*e*Fig. 64.10.4 and *e*Fig. 64.10.5). Improvements in catheter design and energy sources (273,274), as well as in our understanding of the electrophysiology of atrial fibrillation in humans, will undoubtedly elevate catheter ablation to a primary treatment for atrial fibrillation.



***e*FIGURE 64.10.4 A:** Twelve-lead electrocardiogram from a patient with atrial fibrillation originating from a focus in the left inferior pulmonary vein (LI). **B:** Intracardiac recordings made during the onset of atrial fibrillation. The earliest atrial depolarizations originate in the LI. DIS, distal; HBE, bundle of His electrogram; LS, left superior pulmonary vein; OS, ostium; PCS, proximal coronary sinus; RA, right atrium; RI, right inferior pulmonary vein; RS, right superior pulmonary vein.



***e*FIGURE 64.10.5** Successful ablation of the ostium of the left inferior pulmonary vein. Using an electroanatomic mapping system, a series of ablations (*red hexagons*) were placed around the ostium of the vein, curing this patient of atrial fibrillation. Os, ostium; PA, postero-anterior; RF, radiofrequency.

Surgery

The maze surgical procedure for treatment of atrial fibrillation was developed by Cox and associates (37). Multiple atrial incisions are made to direct sinus impulses through a path, or a “maze,” to reach the AV node. The idea is to prevent formation of a critical mass of contiguous atrial tissue that would sustain atrial fibrillation. Further, at least some atrial contractility is maintained. The results of the maze operation have been promising. Alternative operations are the left atrial isolation technique, the “corridor” operation, and simple encircling of the pulmonary veins (275,276 and 277). However, surgery for atrial fibrillation as a primary indication has not gained much momentum and is infrequently used for this problem. We have found it useful for patients with atrial fibrillation who are undergoing other cardiac surgery. Because the left atrial appendage is the usual site of thrombus, we recommend removal of this structure in patients undergoing other cardiac surgery, especially if the patient has a history of atrial fibrillation.

Implantable Atrial Defibrillators

As noted earlier, atrial defibrillation can be accomplished with low-energy shocks (256,257). Clinical trials of implantable atrial defibrillators in humans demonstrated safety and efficacy, but patient intolerance was a major problem. Advances in technology are required to enable defibrillation to occur at energies below the pain threshold to make this a more attractive form of treatment.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Sinus Rhythm versus Rate Control

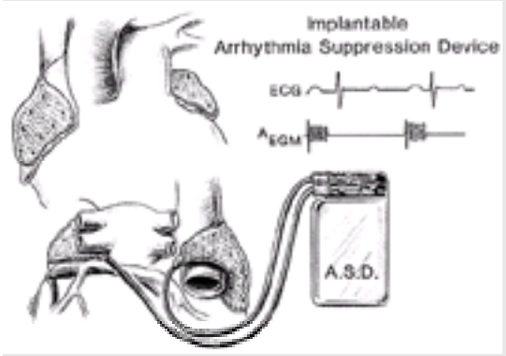
A controversy currently exists regarding the relative merits of administering antiarrhythmic drugs to maintain sinus rhythm versus allowing atrial fibrillation to persist and using drugs to control ventricular rate. No large, randomized, prospective trials have demonstrated the superiority of either approach. Clearly, some patients do well with rate control only. For other patients, sinus rhythm must be achieved to ameliorate symptoms. Sinus rhythm perpetuates sinus rhythm, which is the antithesis of atrial fibrillation begetting atrial fibrillation. Thus, if sinus rhythm can be maintained most of the time, it may be possible to prevent the anatomic and electrophysiologic abnormalities that result from atrial fibrillation. In our experience, if aggressive attempts are made to preserve sinus rhythm shortly after atrial fibrillation occurs, it is possible to prevent or markedly reduce atrial fibrillation recurrences in more than 60% of patients. With regard to the safety of antiarrhythmic drugs, we do not live in a risk-free environment, and it is impossible to guarantee a complete absence of proarrhythmic risk. However, with appropriate selection of antiarrhythmic agents, initiation of drug therapy in-hospital for patients at substantial risk for proarrhythmia, and careful follow-up, morbidity and mortality from proarrhythmia is 1% or less in our experience. For many patients, the risk is worth the gain.

Inpatient versus Outpatient Initiation of Therapy

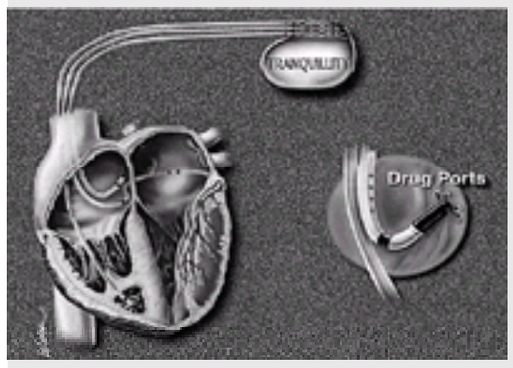
Initiation of antiarrhythmic drugs to restore or maintain sinus rhythm can be performed on an inpatient or an outpatient basis. The risk of proarrhythmia is low, even among patients who have significant heart disease, and starting treatment in the hospital likely will not be cost-effective. Regardless, we feel that patients who have significant heart disease should be monitored during initiation of antiarrhythmic drug treatment, to identify any potential serious problems, especially proarrhythmia. However, patients who have paroxysmal atrial fibrillation with no or minimal heart disease may start antiarrhythmic drugs as outpatients. Before therapy is begun, normal electrolyte status should be confirmed. When an agent that prolongs the QT interval, such as sotalol, is prescribed, we begin with the lowest dose and obtain an electrocardiogram after 2 to 3 days before increasing the dose. This process is repeated until the desired dose is obtained. Event recorders might be used for this purpose. We have not had any significant problems with proarrhythmia using this approach. It is very important to advise patients about over-the-counter and prescription drugs that may interact with the antiarrhythmic agent. For example, antihistamines that may increase the QT interval should not be given to patients taking drugs that prolong the QT interval. We generally ask patients to call us before starting any new drug. When flecainide or propafenone is prescribed, beta-blockers or calcium channel blockers should be given initially to prevent atrial flutter with a 1:1 ventricular response.

THE FUTURE

New and innovative approaches for the treatment of patients with atrial fibrillation are likely to emerge (278). Technological advances in catheter design and energy sources should facilitate a catheter-based approach to curing atrial fibrillation. This may be intracardiac or extracardiac (e.g., use of a thoracoscope). Antiarrhythmic drug development likely will target specific ionic channels in the atrium that do not involve the ventricles, improving efficacy and decreasing ventricular proarrhythmia. Novel cardiac pacing techniques may provide a nonpharmacologic alternative to prevention of atrial fibrillation. An implantable arrhythmia suppression device may be developed that will use subthreshold atrial stimulation to prevent emergence of atrial fibrillation (eFig. 64.10.6) (279). An alternative new device, Tranquillity, will contain an implantable cardioverter-defibrillator/pacemaker/drug-delivery system (eFig. 64.10.7) (280). This unit will have the capability of atrial and ventricular defibrillation and dual chamber pacing, and it can deliver one or more drugs through the atrial lead. It should manage any potential arrhythmic problem.



***e*FIGURE 64.10.6** Schematic diagram of an implantable arrhythmia suppression device (ASD) used for the prevention of atrial fibrillation. ECG, electrocardiogram; EGM, electrogram. [From Prystowsky EN. Future expectations of implantable cardioverter defibrillator therapy. *Pacing Clin Electrophysiol* 1995;18(Pt II):609–615, with permission.]



***e*FIGURE 64.10.7** “Tranquillity,” the future implantable cardioverter device. [From Prystowsky EN. Screening and therapy for patients with nonsustained ventricular tachycardia. *Am J Cardiol* 2000;86(Suppl):34K–39K, with permission.]

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ATRIOVENTRICULAR NODAL–INDEPENDENT SUPRAVENTRICULAR TACHYCARDIAS

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OVERVIEW

The clinical presentation of patients with atrioventricular (AV) nodal–independent arrhythmias is quite variable and may include nonspecific symptoms. The 12-lead electrocardiogram (ECG), 24-hour ambulatory ECG (Holter) monitor, and ECG event recorder usually establish the diagnosis. In addition, electrophysiologic studies have now become an important diagnostic tool, particularly with the emergence of effective nonpharmacologic therapies. In patients with frequent or incessant atrial arrhythmias, sustained rapid ventricular rates can lead to a tachycardia-mediated cardiomyopathy (CM) and congestive heart failure (CHF). Therefore, considerable caution should be exercised before attributing cardiac decompensation to worsening intrinsic myocardial disease in the presence of such an arrhythmia.

The management of atrial arrhythmias has improved due to a better understanding of the causative mechanisms. Most AV nodal–independent arrhythmias are due to reentry: atrial flutter, sinus-node reentry, and intraatrial reentrant tachycardia. However, AV nodal–independent arrhythmias may also occur due to automaticity or triggered activity. Regardless, acute treatment consists of obtaining prompt control of the ventricular rate and, if possible, restoring sinus rhythm.

A thorough characterization of the underlying cardiac substrate is usually indicated before embarking on long-term therapy. Catheter-ablation techniques provide the best hope of obtaining a permanent cure in most patients with these arrhythmias. Large clinical experiences now support the use of catheter ablation as primary therapy in symptomatic patients with atrial flutter, atrial tachycardia, and sinus-node reentry tachycardia. Alternative treatments consist of antiarrhythmic drugs to suppress recurrent symptomatic episodes, recognizing that occasional recurrences are common and do not represent drug failure.

INTRODUCTION

This chapter examines the AV nodal–independent tachycardias, with the exception of atrial fibrillation. This chapter deals principally with atrial flutter, the most common of these arrhythmias. The other arrhythmias discussed include atrial tachycardia, inappropriate sinus tachycardia, sinus node reentrant tachycardia, and multifocal atrial tachycardia (MAT).

Atrial tachyarrhythmias are associated with a wide spectrum of potential presentations, including palpitation, syncope, near-syncope, dyspnea, fatigue, malaise, and new or worsening CHF. Many, if not most, of these symptoms are primarily related to the associated rapid ventricular rate and the physiologic adaptation to that rapid rate. This is most fully discussed in the section on atrial flutter (see Atrial Flutter: Epidemiology and Clinical Significance), which serves as a reference for the other atrial tachyarrhythmias. Similarly, many, if not most, of the principles of treatment of atrial flutter apply to the other atrial tachyarrhythmias, particularly those due to a reentrant mechanism.

In the management of patients with an atrial tachyarrhythmia, identification of the mechanism of the atrial arrhythmia remains one of the cornerstones of successful therapy. Such an understanding now provides the opportunity for a definitive cure in many instances. However, providing successful therapy also mandates a careful evaluation of the patient, especially of the overall cardiac milieu. In many instances, non–AV nodal–dependent arrhythmias are associated with a cardiac substrate abnormality of consequence, such as ventricular hypertrophy, valvular heart disease, coronary artery disease, or left ventricular (LV) dysfunction. An assumption of this chapter is that the cardiac milieu must be adequately addressed as a necessary part of the treatment of atrial tachyarrhythmias.

Finally, regardless of the atrial tachyarrhythmia, if it is incessant or frequent and the ventricular response rate is rapid, a tachycardia-induced CM may result. Recognition of this possibility is particularly important, as primary therapy of this CM should be directed at the atrial tachyarrhythmia. An incessant, atrial tachyarrhythmia–induced dilated CM may be entirely reversible with correction of the tachyarrhythmia or control of the ventricular rate. In patients with preexisting heart

disease, frequent or incessant atrial tachyarrhythmias may cause additional cardiac decompensation that may go unrecognized or may be incorrectly attributed to worsening of the underlying structural heart disease. This, too, should be improved or reversed with correction of the tachyarrhythmia or control of the ventricular rate.

ATRIAL FLUTTER

Historical Perspective

After atrial fibrillation, atrial flutter is the most common atrial tachyarrhythmia. Although it was first described eight decades ago (1), until recently, knowledge regarding the mechanism was primitive. Lewis (2) originally thought atrial flutter was due to a single focus firing rapidly. He and colleagues later ascribed it to reentry around the great veins (3). Over the ensuing years, a controversy developed regarding which of these mechanisms, either a single focus firing rapidly or some form of reentry, was responsible (4). Techniques for the diagnosis and management of atrial flutter changed little for decades. Diagnosis rested almost entirely on the 12-lead ECG. Treatment options included the use of a digitalis compound to slow and control the ventricular rate, and/or the use of either quinidine or procainamide in an attempt to convert the rhythm to sinus or to prevent recurrence of atrial flutter once sinus rhythm was established.

A 59-year-old female patient with atrial flutter with 4:1 atrioventricular conduction.

The past 25 years have produced major changes. A series of studies advanced our understanding of the mechanism(s) of atrial flutter (4). Old techniques to diagnose atrial flutter have been refined, and new diagnostic and therapeutic techniques have been developed (5,6 and 7).

Beginning with the advent of direct current (DC) cardioversion in the 1960s (8,9), major advances in the therapy of atrial flutter have been made. Beta-blockers and calcium channel blockers now are available for use in lieu of digitalis therapy to control the ventricular rate (10,11,12 and 13). New antiarrhythmic agents are available to suppress atrial flutter or to convert it to sinus rhythm (14,15,16,17 and 18). Atrial pacing techniques to interrupt or suppress atrial flutter have evolved (5). Catheter-ablation techniques either to cure atrial flutter (19,20 and 21) or to control the ventricular rate (22) have been developed. Related surgical therapies (23,24) have been used.

Potential Mechanisms

Many studies, most of which have been performed in experimental models but many also in humans, indicate that atrial flutter is due to reentry in the right atrium. Lewis et al. (3) concluded that atrial flutter was the result of circus movement in the atria, principally around the great veins.

Many years later, Rosenblueth and Garcia-Ramos (25) created a crush lesion between the vena cavae in the canine heart, demonstrating that atrial flutter resulted from intraatrial reentry around the vena cavae using the lesion. More recently it has been shown that in the presence of a similar lesion extending toward the right atrial appendage to make a Y lesion, atrial flutter may be explained by circus movement around the tricuspid valve annulus (26,27). The latter explanation may have a clinical counterpart in atrial flutter seen in patients after repair of complex congenital heart disease that includes large incisions in the right atrium (28,29). Several subsequent canine right atrial free wall lesion models (30,31) have also shown that a stable reentrant wavefront can travel around such a lesion if it is long enough, thereby producing stable atrial flutter.

Relatively early after the recognition of atrial flutter as a clinical entity, a single focus firing rapidly has been believed to be a possible mechanism of atrial flutter (2). Experimental evidence supporting this belief came subsequently from the studies of Scherf and colleagues (32,33), later confirmed by Kimura et al. (34), in which atrial flutter was shown to occur in the canine atria after applying aconitine to a single site. Whether there is a clinical counterpart to this model remains uncertain. Recent findings suggest that a single focus firing rapidly, particularly in the pulmonary veins, may be responsible for some forms of atrial flutter (35,36).

Models that have not required applying substances or creating primary atrial lesions are more likely to be experimental counterparts of spontaneous atrial flutter in patients. The acetylcholine model studies of Allessie et al. (37,38) in the canine heart have shown that atrial flutter due to intraatrial reentry can occur superiorly or inferiorly in either atrium as well as in the absence of an anatomic obstacle. In this model, the atrial rates were extremely fast (more than 600 beats/min), unstable, and may be models for atrial fibrillation in which a reentrant circuit of very short cycle length drives the atria and causes fibrillatory conduction. Other models of atrial flutter in the canine heart that do not demonstrate reentry around an anatomic obstacle include a spontaneous example of atrial flutter in a single dog (39) and one of right atrial enlargement secondary to creation of tricuspid regurgitation and pulmonary artery banding (40,41).

The sterile pericarditis model of atrial flutter described by our laboratory (42) and studied by us (43,44,45,46,47 and 48) and others (49,50 and 51) was believed to be due to functional reentry in the right atrial free wall. However, simultaneous multisite mapping studies have recently demonstrated a critical septal component to the reentrant circuit (52). In this model, either a single reentry loop very similar to that in patients or a figure-of-eight reentry loop where two reentrant circuits use a common pathway in the right atrial free wall may be present. Interestingly enough, figure-of-eight reentry atrial flutter has recently been described in a patient after repair of a congenital lesion (53). Also, atrial flutter due to reentry around a line of block in the right atrial free wall has also been described in a patient (54). Mapping of a canine model of atrial reentry in mitral regurgitation showed that several reentrant circuits, including one resulting from reentry confined to the right atrium, had no anatomic obstacle (55).

Mapping of atrial flutter in humans began in the 1950s with the studies of Prinzmetal et al. (56). Photographic techniques with the heart exposed were used during thoracic surgery. Later, Wellens et al. (57) used sequential-site atrial epicardial mapping to study atrial flutter during human cardiac surgery. On the basis of these studies, both groups suggested that atrial flutter was due to a single focus firing rapidly. Pacing studies by Rosen et al. (58) of the human coronary sinus showed that a single focus firing rapidly could generate the classic clinical ECG of atrial flutter. Nevertheless, this mechanism has not been supported by numerous other mapping studies in humans that primarily have used electrode catheter techniques during electrophysiologic studies. As summarized by Rytand (59), initial and limited catheter mapping studies in the 1950s and 1960s suggested that atrial flutter was an intraatrial reentrant rhythm. The mapping studies of Puech and colleagues (60,61) demonstrated that the entire duration of the atrial flutter cycle length may be explained by circus movement activation of the right atrium alone, with the impulse traveling up the septum and down the right atrial free wall.

Demonstration of transient entrainment and interruption of atrial flutter in humans (62,63 and 64) provided additional strong evidence that atrial flutter was an intraatrial reentrant rhythm with an excitable gap (Fig. 65.1). Subsequent mapping studies, usually in concert with atrial pacing, have confirmed that the atrial flutter reentrant circuit is virtually always confined to the right atrium. Thus, the studies of Cosio et al. (65,66 and 67), Olshansky et al. (68,69), nd Klein et al. (23) indicated that the reentrant circuit in typical atrial flutter in humans involved counterclockwise reentrant excitation in the right atrium in which the impulse traveled in a caudocranial direction in the interatrial septum and in a craniocaudal direction in the right atrial free wall. Atypical, or rare (uncommon), atrial flutter was shown to use the same reentrant circuit but in the opposite direction (70).

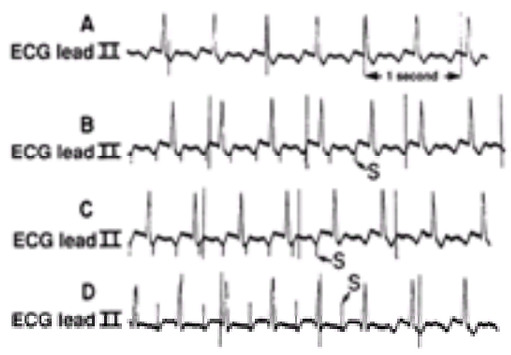


FIGURE 65.1 Electrocardiogram (ECG) lead II recorded during atrial flutter of an atrial cycle length of 264 ms **(A)** and at the end of 30 seconds of rapid atrial pacing from a high right atrial site at a cycle length of 254 ms **(B)**, at a cycle length of 242 ms **(C)**, and at a cycle length of 232 ms **(D)**. The atrial flutter was transiently entrained at each pacing rate. Note that when comparing the morphology of the atrial complexes during atrial pacing at each cycle length, especially that of the atrial complexes during atrial pacing in **D** with that in **A** and **B**, progressive fusion has occurred. Timelines are at 1-second intervals. S, stimulus artifact. (From Waldo AL, MacLean WAH, Karp RB, et al. Entrainment and interruption of atrial flutter with atrial pacing: studies in man following open-heart surgery. *Circulation* 1977;56:737–745, with permission.)

The studies of Cosio et al. (65,66 and 67) and Olshansky et al. (68,69) have also provided evidence that an area of slow conduction is present in the postero-inferior aspect of the right atrium. The central area of block around which the reentrant wavefront circulates likely includes an anatomic component and a functional component in the interatrial septum (65,66,70).

Catheter mapping techniques, including entrainment mapping, have localized the area of slow conduction in the reentrant circuit principally to an isthmus bounded by the coronary sinus ostium, the tricuspid annulus, inferior vena cava, and eustachian ridge (21,71,72 and 73). However, others have suggested that this atrial flutter isthmus is not an area of slow conduction during atrial flutter (74).

Exquisite anatomic and angiographic studies have examined the underlying milieu of the atrial flutter circuit. Marked anatomic variations in the subeustachian isthmus are present in normal hearts. The arrangement of the subendothelial fibers in the isthmus recesses was unique among autopsy specimens (75,76). Furthermore, an angiographic study demonstrated that the inferior subeustachian isthmus is wider in patients with atrial flutter when compared with a control population (77). These studies demonstrate a strong anatomic contribution to the requisite atrial flutter reentrant circuit.

Mapping techniques have demonstrated the critical role of the region of the crista terminalis as one boundary for the reentrant circuit and the role of the tricuspid ring as another boundary of the reentrant circuit (71,72 and 73). Differences in the electrophysiologic properties of the crista terminalis have been identified in patients with atrial flutter (78,79). Specifically, transverse conduction block across the crista terminalis occurs at longer cycle lengths in patients with atrial flutter. This difference may in part explain the absence of atrial flutter in all individuals. But it remains clear that block, probably functional, in a region between the vena cavae is critical to establish stable atrial flutter. Nevertheless, a recent study (80) dismissed the role of the crista terminalis as a critical boundary for atrial flutter. A functional line of block was described in the postero-medial right atrium in the sinus venosa region. This was observed in 28 consecutive patients with atrial flutter. Additional mapping studies are needed to resolve this controversy.

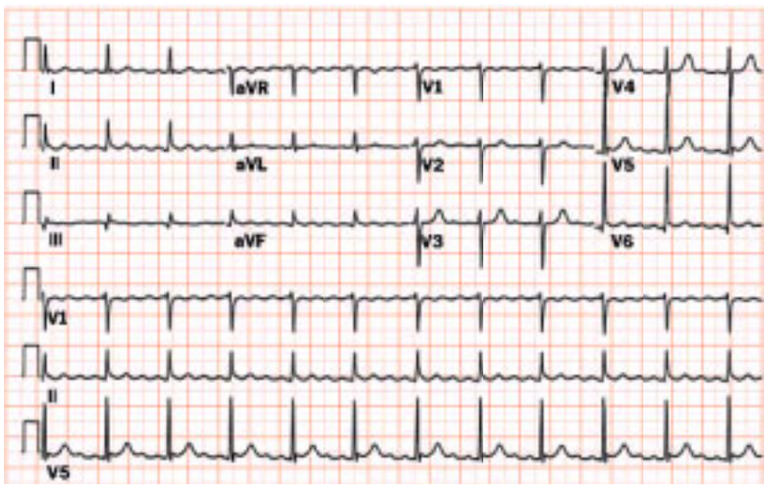
Other locations can support an atrial flutter reentrant circuit and have been identified in humans. These atrial flutter circuits may or may not use the subeustachian isthmus. Locations include (a) the right atrial free wall, (b) the pulmonary veins in the left atrium, (c) nonpulmonary vein sites in the left atrium, (d) lower-loop reentry breaking through the crista terminalis and using the subeustachian isthmus, and (e) double-wave reentry using the usual right atrial flutter reentrant circuit. Better mapping data from studies in humans may well improve our understanding of the various reentrant circuits observed in humans and animals (81,82).

Furthermore, most instances of atrial flutter are preceded by a period of atrial fibrillation, usually brief, during which time the functional components of the atrial flutter reentrant circuit form (83). Anchoring of the multiple reentrant circuits seen in atrial fibrillation to components of the atrial flutter circuit likely explains the transition from atrial fibrillation to flutter. Conversely, breakdown of one or more functional components of the previously stable flutter circuit via crista terminalis breakthrough as seen in lower-loop reentry or via another boundary in the circuit likely explains the transition from atrial flutter to fibrillation.

Classification

With the availability of new mechanistic information, many terms have been used to describe atrial flutter, and considerable confusion has grown regarding terminology. Classification of atrial flutter has always included an atrial rate range, generally 240 to 340 beats/min (84), and a remarkably regular rate with the most constant beat-to-beat cycle length of any tachycardia (85).

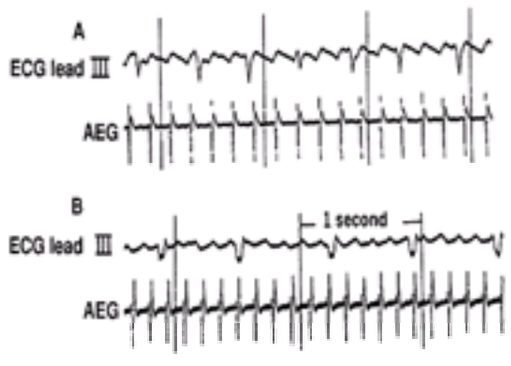
Atrial flutter was first classified by Jolly and Ritchie (1) in 1911. Little change occurred in the classification until the description of the subclasses so-called typical and atypical atrial flutter (86). Typical atrial flutter had the negative, sawtooth flutter waves in ECG leads II, III, and aVF. Atypical atrial flutter was described as having positive atrial complexes in ECG leads II, III, and aVF, although the atrial rate was sometimes slower than that of typical atrial flutter. These two subclasses were subsequently also called *common* and *rare* (uncommon) *atrial flutter*, respectively. We now know that atypical (rare or uncommon) atrial flutter uses the same reentrant circuit as typical (common) atrial flutter, but that the reentrant wavefront travels in the opposite direction. Based on the atrial activation sequence as seen in the left anterior oblique view, the terms *clockwise* and *counterclockwise* atrial flutter were also used. Thus, several names have evolved when describing subclasses of atrial flutter: typical, or counterclockwise, or common atrial flutter and atypical, or clockwise, or rare, or uncommon atrial flutter.



Atrial flutter. Atrial rate of 300 beats/min with upright P waves inferiorly. This is consistent with atypical atrial flutter.

Atrial flutter. Inverted "saw-tooth" waves in the inferior leads suggest typical atrial flutter.

Following the studies of Wells et al. (85), two overall types of atrial flutter were characterized: type I and type II (eFig. 65.1.1). They are distinguished by the fact that type I atrial flutter can always be interrupted by rapid atrial pacing, whereas type II atrial flutter cannot (5,85). Typical (common, counterclockwise) and atypical (rare, uncommon, clockwise) atrial flutter can always be interrupted by rapid atrial pacing techniques and are all categorized as type I atrial flutter. Differentiation of type I from type II atrial flutter has also been made in terms of the range of atrial rates and the ability or inability to interrupt atrial flutter with rapid atrial pacing (26). In the absence of drug therapy, type I atrial flutter is characterized by atrial rates ranging from 240 to 340 beats/min, and type II atrial flutter by atrial rates ranging from 340 to 433 beats/min. Overlap likely exists between the upper range of rates of type I and the lower range of rates of type II atrial flutter.



***e*FIGURE 65.1.1** These tracings demonstrate simultaneous recording of electrocardiogram (ECG) lead III and a bipolar atrial electrogram (AEG) during **(A)** type I atrial flutter with an atrial rate of 296 beats/min and during **(B)** type II atrial flutter with an atrial rate of 420 beats/min. In each example, note the constant beat-to-beat cycle length, polarity, morphology, and amplitude of the recorded atrial electrogram signal. (From Wells JL Jr, MacLean WAH, James TN, Waldo AL. Characterization of atrial flutter: studies in man after open-heart surgery using fixed atrial electrogram. *Circulation* 1979;60:665–673, with permission.)

Little is actually known about the natural history and treatment of type II atrial flutter. It may be due to reentry of very short cycle length or a single focus firing rapidly, either of which can produce fibrillatory conduction (the rest of the atrial tissue cannot follow 1:1) and thereby atrial fibrillation. The reentry may be around the pulmonary vein(s), or the single focus may be from a pulmonary vein (35,36). We continue to learn more about type II atrial flutter.

In view of the new information about atrial flutter as well as the explosion of terms to describe it, the European Society of Cardiology/North American Society of Pacing and Electrophysiology Working Group has offered a new classification based on mechanism (Table 65.1). Any reentrant circuit which requires use of the atrial flutter (subeustachian) isthmus is called *typical atrial flutter*. Usually in typical atrial flutter, the reentrant circuit travels up the septum and down the right atrial free wall (Fig. 65.2A). Atrial flutter that uses the same circuit but in the opposite direction is called *reverse typical atrial flutter*. Lower-loop reentry atrial flutter (Fig. 65.2B) and double-wave reentry atrial flutter (Fig. 65.2C) also use the subeustachian isthmus and thus are classified as types of typical atrial flutter (87,88).

Typical forms of atrial flutter (atrial flutter isthmus dependent)
Typical atrial flutter
Reverse typical atrial flutter
Lower-loop atrial flutter
Double-loop atrial flutter
Atypical forms of atrial flutter (nonatrial flutter isthmus dependent)
Left atrial flutter
Lesion reentry
Atypical atrial flutter

TABLE 65.1 ATRIAL FLUTTER CLASSIFICATION

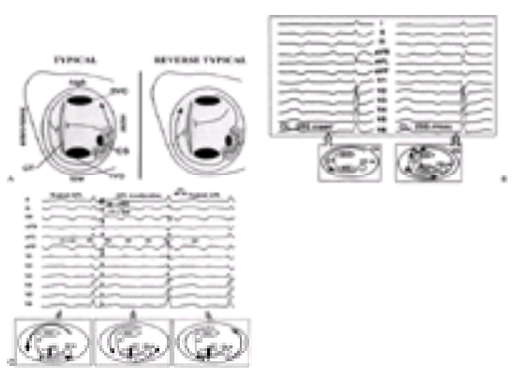


FIGURE 65.2 A: Schematic representation of typical and reverse typical atrial flutter circuits. The left anterior oblique view of the right atrium shows the endocardium through the tricuspid ring in a wide-angle perspective. The endocardium is shaded. The orifices of the superior and inferior caval veins (SVC and IVC) and coronary sinus (CS) are shown in black. The terminal crest (CT) is shown as a bundle of parallel lines linking the lateral aspects of the caval veins. The shaded area around the coronary sinus suggests the probable location of a slow conduction zone. Curved arrows indicate directions of activation. (Adapted from Cosio FG, Lopez-Gil M, Arribas F, Gonzalez HD. Mechanisms of induction of typical and reversed atrial flutter. *J Cardiovasc Electrophysiol* 1998;9:281–291.) **B:** Sustained spontaneous atrial flutter with two cycle lengths was observed in the same patient. Tracings on left show typical atrial flutter with a cycle length (CL) of 285 ms. Tracings on right show lower-loop reentry with a cycle length of 255 ms. Note the similar flutter wave morphologies despite different cycle lengths and different activation sequences, although there is a subtle difference in the terminal portion of the flutter waves in the inferior leads. Drawings depict the circuit anatomy. The hollow star delineates the breakthrough site, and the double line is the site of collision. His, His bundle. (Adapted from Cheng J, Cabeen WR, Scheinman MM. Right atrial flutter due to lower loop reentry, mechanism and anatomic substrates. *Circulation* 1999;99:1700–1705.) **C:** Critically timed atrial extrastimulus (AES) induced atrial flutter (AFL) acceleration. Surface 12-lead electrocardiogram showed P-wave morphology during AES-induced acceleration identical to that of flutter wave during spontaneous AFL. The accelerated flutter cycle length showed beat-to-beat variation (numbers are cycle length in milliseconds). The three diagrams schematically depict the positions of the

activation wavefronts at induction, during, and at termination of double-wave reentry. Two wavefronts transiently are circulating in the typical AFL circuit and at the same time. Decremental conduction results in a cycle length greater than half the cycle length of the typical AFL circuit. (Adapted from Cheng J, Scheinmann MM. Acceleration of typical atrial flutter due to double-wave reentry induced by programmed electrical stimulation. *Circulation* 1998;97:1589–1596.)

At least 90% of atrial flutters fall into the typical category. Atrial flutter in which the reentrant circuit is confined to the left atrium is called *left atrial flutter*. Reentry around an incisional line of block in the rate range of atrial flutter is called *lesion atrial reentry*. All other forms of reentrant atrial tachycardia in the rate range of atrial flutter that are not described by the above are called *atypical atrial flutter*.

Epidemiology and Clinical Significance

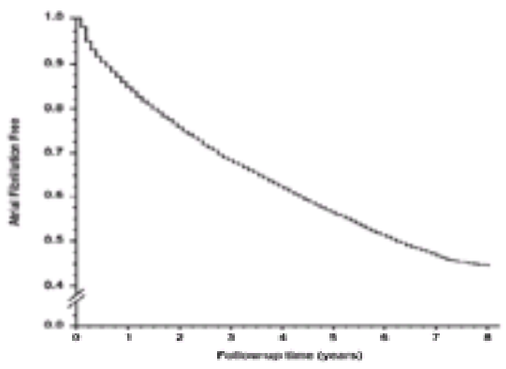
Atrial flutter can be a persistent rhythm, but more typically it is paroxysmal, often lasting for seconds to hours. A stable, chronic rhythm is unusual in atrial flutter because it usually reverts either to sinus rhythm or to atrial fibrillation, spontaneously or as a result of therapy. However, atrial flutter has been reported to be present for up to 20 years or more (89).

The incidence of atrial flutter is uncertain. Based on a review of hospital ECGs (89), atrial flutter has been reported to occur in one in every 81 patients, in every 133 patients, in every 217 patients, and in every 238 patients. A recent review (90) estimated an overall incidence of atrial flutter at 88 per 100,000 person-years in the general population. Atrial flutter was more common in men, in patients with chronic obstructive pulmonary disease, and in patients with heart failure.

Atrial flutter is usually spontaneously induced by premature atrial beats or a transitional rhythm that appears to be atrial fibrillation (91). It can occur in patients with ostensibly normal atria but more commonly in patients with abnormal atria. It is associated with enlargement of the atria, especially the right atrium, from valvular disease or any cause (29). Patients with atrial flutter not uncommonly demonstrate sinus bradycardia or other manifestations of sinus node dysfunction.

Atrial flutter frequently develops in patients in the first week after open-heart surgery, with an overall incidence of 10% to 20% (5). It may also occur after surgical repair of certain congenital cardiac lesions especially in which the Mustard, Senning, or Fontan procedure is used (28,29,92). After congenital heart surgery, the typical atrial flutter isthmus is usually requisite for the atrial arrhythmia, although in a minority of cases the suture line is critical, and the atrial arrhythmia does not involve the typical flutter isthmus (93).

Atrial flutter frequently occurs in association with atrial fibrillation (94,95). In fact, the two rhythms can occur in the same patient, going back and forth between one another. Analysis of a Medicare cohort of patients (96) demonstrated that after an initial hospitalization with atrial flutter, more than 50% of patients were rehospitalized with atrial fibrillation (*e*Fig. 65.2.1). The presence of lung disease, heart failure, hypertension, or coronary disease did not predict which patients would represent with atrial fibrillation.



***e*FIGURE 65.2.1** The incidence of rehospitalization for atrial fibrillation after an index hospitalization for atrial flutter. Atrial fibrillation is common after an episode of atrial flutter. (From Biblo LA, Yuan Z, Quan KJ, et al. Risk of stroke in patients with atrial flutter. *Am J Cardiol* 2001;87:346–349, with permission.)

Atrial flutter is often perceived as a nuisance arrhythmia. However, an episode of atrial flutter can have devastating consequences. The clinical significance lies largely in its association with systemic embolization and stroke, with atrial fibrillation, and with a rapid ventricular response rate. The rapid ventricular rate is primarily responsible for the associated symptoms, including ischemia, hypotension, or heart failure. In the presence of the Wolff-Parkinson-White syndrome or a very short PR interval in the absence of a delta wave, 1:1 AV conduction may occur with even more dire consequences. Furthermore, if the duration of the rapid ventricular rate is prolonged, ventricular dilatation and CHF may result. In fact, atrial flutter can solely cause or exacerbate an existing dilated CM.

Physical Examination and Associated Hemodynamic Effects

Atrial flutter frequently results in a regular ventricular response with either 2:1 or 4:1 AV conduction. However, atrial flutter also can be associated with an irregular ventricular response rate. As a result, the physical examination may mimic that of atrial fibrillation, with an irregular ventricular rate auscultated at the precordium associated with an irregular peripheral pulse rate with dropped beats (i.e., the apical ventricular rate is higher than the peripheral ventricular rate). If neck veins are clinically apparent, examination of the neck may reveal regular jugular venous pulsations at a rapid rate (i.e., the atrial rate). The jugular venous pulsations will be more rapid than the peripheral or apical pulsations, reflecting the degree of AV nodal blockade (e.g., 2:1, 4:1).

Hemodynamic effects depend on the underlying disease, the ventricular rate, the duration of the rhythm, the presence of concurrent medications, and whether the patient is at rest or at exertion (97). At rapid ventricular rates, a decline in cardiac output is usually seen. The abrupt onset of an increased rate typically affects blood pressure with an initial decline and subsequent rise. The blood pressure response, in fact, depends largely on peripheral adaptation (98). The initial decline in blood pressure may be associated with presyncope or even syncope in some cases. There may also be a significant decrease in coronary blood flow and a rate-related increase in myocardial oxygen consumption despite maintenance of baseline cardiac output. The decrease in coronary artery flow is inversely proportional to the ventricular rate and decreases progressively to a maximum of 60% of baseline. During atrial flutter, if the ventricular rate is rapid, this reduction in coronary blood flow is induced by changes in both systolic and diastolic function. First, the diastolic interval is significantly shortened, thereby reducing the time for coronary flow. Second, the mean aortic pressure declines, thereby reducing the coronary artery perfusion pressure. Third, with the associated ischemia or diastolic dysfunction, LV end diastolic pressure rises as the rapid ventricular rate continues. This combination of factors explains the association of symptomatic ischemia with supraventricular tachycardias, including atrial flutter (97).

Diagnosis

Electrocardiogram

Atrial flutter usually can be diagnosed from the ECG. Whenever atrial flutter is suspected, the diagnosis should be clearly established before initiating therapy unless the patient is clinically very unstable. Atrial flutter waves in the ECG, particularly sawtooth atrial complexes in leads II, III, and aVF, remain the standard for diagnosis of atrial flutter (Fig. 65.3). Flutter waves appear as atrial complexes of constant morphology, polarity, and cycle length, with a rate ranging from 240 to 340 beats/min (85).

FIGURE 65.3 A 12-lead electrocardiogram of typical atrial flutter is shown. The atrial rate is 290 beats/min, and the ventricular rate is 145 beats/min; 2:1 atrioventricular conduction is present. Notice that the atrial activity is best seen in leads II, III, and aVF, but is barely perceptible in lead I.

Typical and reverse typical atrial flutter can occur in the same patient at different times. Usually the reverse typical atrial flutter has a slower rate than the typical atrial flutter (eFig. 65.3.1). Atrial fibrillation with prominent (more than 0.2 mV) fibrillatory waves is often confused with atrial flutter (99). Care must be taken to ensure absolute regularity of atrial complexes before making a diagnosis of atrial flutter.

***e*FIGURE 65.3.1** These 12-lead electrocardiogram tracings were obtained from the same patient at different presentations to the same emergency department. Both tracings document typical forms of atrial flutter. **A:** Typical atrial flutter. **B:** Reverse typical atrial flutter. Note the slower atrial rate observed in the reverse typical atrial flutter.

The atrial rate may be slower if the rhythm is present after therapy with antiarrhythmic drugs (i.e., class IA drugs, especially class IC drugs, moricizine, and amiodarone). If the ventricular response is half that of the atrial flutter rate, identifying the flutter waves on the ECG leads may be difficult due to temporal superimposition on other ECG deflections such as the QRS complex or the T wave.

As described in this section, the ventricular rate in atrial flutter is frequently 2:1 or 4:1 and is therefore regular. However, it may be irregular when there is variable AV conduction. Rarely, AV conduction may even be 1:1. The latter may be seen when an accessory AV connection is operative and may also be present in patients who have a very short PR interval during sinus rhythm. AV conduction may be enhanced during exertion, during therapy with catecholamines, or during administration of sympathomimetics for other underlying clinical problems. The ventricular response may paradoxically increase with slowing of the atrial flutter rate secondary to antiarrhythmic therapy (Fig. 65.4).

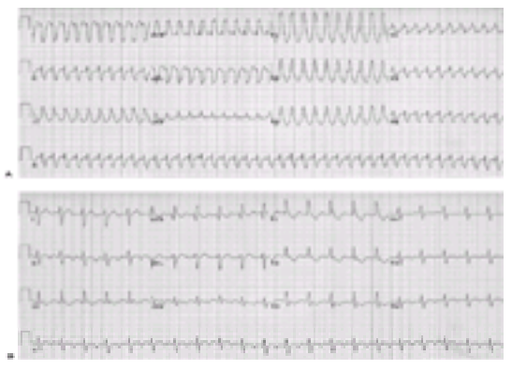


FIGURE 65.4 This patient presented 1 week after initiation of flecainide therapy for atrial flutter. **A** depicts 1:1 atrioventricular (AV) conduction. This was made possible by the slowing of the atrial rate (the pretherapy atrial rate was 300 beats/min with 2:1 AV conduction), now permitting 1:1 AV conduction, which “paradoxically” increased the ventricular rate. **B** was obtained 5 minutes later after therapy with esmolol, which decreased the ventricular response due to 2:1 AV conduction.

The QRS complex during atrial flutter is often identical to that during sinus rhythm. However, atrial flutter beats may be aberrantly conducted due to functional bundle branch block, most frequently a right bundle branch. However, even with normal ventricular conduction, the QRS complex may be distorted by temporal superimposition of flutter waves in the QRS complex. Thus, the QRS complex may acquire a new or larger R, S, or Q wave. A terminal addition to the QRS complex by the flutter wave may result in a false-positive signal-averaged ECG, as pseudo–late potentials may appear (*e*Fig. 65.4.1) (100).

***e*FIGURE 65.4.1** This patient’s signal-averaged electrocardiogram was positive due to the flutter waves abutting the terminal portion of the QRS complex generating a “pseudo–late potential.”

If a diagnosis of atrial flutter is not clear from the ECG, other atrial tachycardias should be considered. In patients with a narrow QRS complex with 2:1 AV conduction,

atrial flutter must be differentiated from (a) sinus tachycardia, (b) AV nodal reentrant tachycardia, (c) AV reentrant tachycardia, (d) an atrial tachycardia with 1:1 AV conduction, (e) an accelerated AV junctional tachycardia, and (f) sinus node reentrant tachycardia. An atrial rate of 300 beats/min with an ensuing ventricular response of 150 beats/min is suggestive of atrial flutter. In patients with a wide QRS complex tachycardia and underlying bundle branch block, atrial flutter must not only be differentiated from all the above rhythms, but also from ventricular tachycardia.

Other Complementary Diagnostic Approaches

If the diagnosis of atrial flutter is not clear from a 12-lead ECG and circumstances permit, vagal maneuvers (e.g., carotid sinus massage, Valsalva) may be used to transiently block AV conduction while continuously recording the ECG (preferably at least leads II and V_1). This should permit the atrial flutter complexes to be readily identified on the ECG tracing. If the diagnosis remains uncertain despite a vagal maneuver and if the clinical status permits, any of the following diagnostic approaches may be used:

1. Record directly from the atria by (a) placement of an esophageal electrode, (b) transvenous atrial placement of a catheter electrode, or (c) use of a temporary atrial epicardial wire electrode placed during open-heart surgery (mode of choice in patients after open-heart surgery).
2. A pharmacologic agent may be administered, such as adenosine, esmolol, or diltiazem, to transiently block AV conduction, thereby revealing the atrial complexes.

The advantage to the electrode/electrogram strategy is that it permits a definitive diagnosis and also provides an opportunity to treat the atrial flutter with rapid atrial pacing. The advantage to the pharmacologic approach is that it does not require an invasive procedure, and esmolol, verapamil, or diltiazem can be administered intravenously to slow the ventricular rate, giving the clinician additional time to determine the next course of therapy. However, when the patient has a wide QRS complex tachycardia, because the rhythm may represent a ventricular tachycardia and not a supraventricular tachycardia with aberrant ventricular conduction, most interventions using drugs to slow the ventricular rate are fraught with hazard.

Clinical Electrophysiologic Studies

For patients with paroxysms of tachycardia in whom atrial flutter is suspected but has yet to be documented, one of several types of ECG monitoring is recommended. For most patients, particularly those with infrequent episodes of tachycardia, use of an event recorder is preferred to a 24-hour Holter monitor.

At present, electrophysiologic studies have become more important with the advent of catheter-based procedures to cure atrial flutter. Although no standards of programmed stimulation for the initiation of atrial flutter have evolved, the most reliable method is to pace the atria very rapidly to initiate atrial fibrillation and then await the evolution to atrial flutter (92). Initiation of atrial flutter by introducing premature atrial beats after a drive train is a much less reliable technique for inducing atrial flutter. Atrial pacing techniques may not reliably induce atrial flutter even in patients with a known history of atrial flutter.

Electrode catheter mapping studies (101) of atrial flutter are generally performed to help identify the location and type of the reentrant circuit. The mapping study must identify a vulnerable isthmus in the reentrant circuit that can be ablated to ensure success. In most patients with atrial flutter, such a location is thought to be the atrial flutter isthmus between the tricuspid valve orifice and the orifice of the inferior vena cava (19,20 and 21,71,72 and 73). owever, as discussed previously, atrial flutter can operate independent of this isthmus (102,103). Techniques including entrainment mapping, electroanatomic mapping, and virtual electrode mapping play an important role in identifying the vulnerable isthmus.

Acute Treatment

Antiarrhythmic Drugs

When the diagnosis of atrial flutter is established, three acute nonablative options are available to restore sinus rhythm: (a) administer an antiarrhythmic drug, (b) initiate DC cardioversion, or (c) initiate rapid atrial pacing to interrupt atrial flutter. Treatment largely depends on the clinical status of the patient. In the past, the preferred option to interrupt atrial flutter was either DC cardioversion or rapid atrial pacing. However, the recent introduction of ibutilide provides another viable option, as use of that antiarrhythmic drug is associated with a 60% likelihood of converting recent onset atrial flutter to sinus rhythm (18). Antiarrhythmic drugs also may be used before initiating DC cardioversion or rapid atrial pacing for the following purposes:

1. To slow the ventricular response rate using a beta-blocker, a calcium channel blocker, digoxin, or some combination of these drugs
2. To enhance the efficacy of rapid atrial pacing in restoring sinus rhythm by using quinidine, procainamide, disopyramide, or ibutilide (104,105 and 106)
3. To enhance the likelihood that sinus rhythm will be maintained after effective DC cardioversion by using a class IA, class IC, or class III antiarrhythmic agent

For many years, standard initial treatment was administration of a digitalis preparation, usually intravenously, until atrial flutter either converted to atrial fibrillation with a controlled ventricular response rate or to sinus rhythm. This mode of treatment is now not the treatment of choice (5). Whenever rapid control of the ventricular response rate to atrial flutter is desired, intravenous administration of a calcium channel blocker (e.g., verapamil or diltiazem) or of a beta-blocker (usually esmolol, although propranolol or metoprolol can also be used) is usually effective.

Previously, administration of an antiarrhythmic drug to convert atrial flutter to sinus rhythm was not recommended because the antiarrhythmic drugs that were available, such as quinidine or procainamide, frequently only slowed the atrial flutter rate without interrupting the arrhythmia. Ibutilide now provides a reasonable expectation of successful conversion of atrial flutter to sinus rhythm (18). Ibutilide dramatically prolongs ventricular repolarization and consequently the QT interval. Therefore, a low incidence of torsades de pointes is associated with its use (107). However, should these episodes occur, they are usually self-limiting, and because of the short half-life of this drug, the period of risk appears brief (i.e., less than 1 hour). Nevertheless, one should be prepared to administer magnesium and even perform DC cardioversion to treat a prolonged episode of torsades de pointes should it occur when using ibutilide. Flecainide and propafenone, when used intravenously (108,109) or when used orally but in a single high dose (300 mg flecainide or 600 mg propafenone) (110,111), reportedly have been effective in cardioverting this rhythm and atrial fibrillation to sinus rhythm. Again, when using class IC agents, care must be taken to avoid 1:1 AV conduction of a significantly slowed atrial flutter rate.

Direct Current Cardioversion/Rapid Atrial Pacing

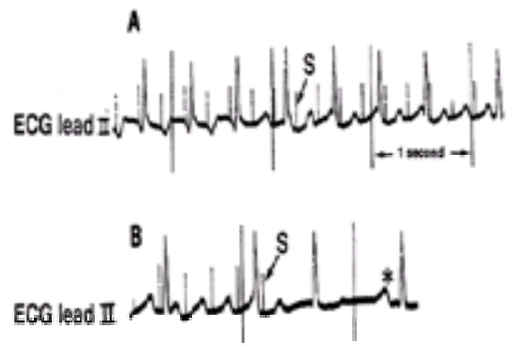
Selecting DC cardioversion, atrial pacing, or antiarrhythmic drugs for acute treatment of atrial flutter depends on the clinical presentation of the patient and on both the clinical availability and ease of applying these techniques. DC cardioversion requires administration of an anesthetic agent. Therefore, this approach may be undesirable in patients who have recently eaten or in patients who have severe lung disease. These patients usually are best treated with antiarrhythmic drugs, rapid atrial pacing, or agents to slow the ventricular response rate. For patients with atrial flutter after open-heart surgery, the use of temporary atrial epicardial electrodes to perform rapid atrial pacing is clearly the treatment of choice (112,113).

Rapid Atrial Pacing to Interrupt Atrial Flutter

When initiating atrial pacing, pacing should be started at a slow rate to demonstrate that ventricular capture is not inadvertently produced. Several effective atrial pacing techniques are available. Pacing should be performed from the high right atrium. A change in the polarity of the atrial complexes (flutter waves in ECG lead II evolve from negative to positive) is the hallmark of interruption of typical atrial flutter (112).

Ramp atrial pacing is the preferred technique. Bipolar atrial pacing is initiated at a rate 10 to 20 beats/min faster than the spontaneous atrial flutter rate while continuously recording ECG lead II. After demonstrating atrial capture, the atrial pacing rate is gradually increased until the atrial complexes in ECG lead II become positive. Atrial pacing may be then either abruptly terminated, or the pacing rate may be rapidly slowed to a desirable atrial pacing rate. The latter permits control of the atrial rhythm in patients with underlying sick sinus syndrome.

Another satisfactory pacing method is the constant rate technique. The most successful rate for interrupting atrial flutter is approximately 120% to 130% of the spontaneous atrial rate (112). When using this technique, atrial pacing is generally initiated at a rate within this range of the spontaneous atrial flutter rate and continued for 15 to 30 seconds, or until the atrial complexes in ECG lead II become positive (eFig. 65.4.2). Pacing is then either abruptly terminated or rapidly slowed to a desirable atrial pacing rate. If pacing at the initially selected rate does not interrupt the atrial flutter, the atrial pacing rate should be increased in increments of 5 to 10 beats/min until atrial flutter is successfully interrupted.



***e*FIGURE 65.4.2 A:** Electrocardiogram (ECG) lead II recorded during high right atrial pacing at a cycle length of 224 ms. Note that with the seventh atrial beat in this tracing, after 22 seconds of atrial pacing at a constant rate, the atrial complexes suddenly became positive. **B:** Electrocardiogram lead II recorded at the termination of atrial pacing in the same patient. With abrupt termination of pacing, sinus rhythm occurs (*asterisk*). Timelines are at 1-second intervals. S, stimulus artifact. (From Waldo AL, Maclean WAH, Karp RB, et al. Entrainment and interruption of atrial flutter with atrial pacing: studies in man following open-heart surgery. *Circulation* 1997;56:737–745, with permission.)

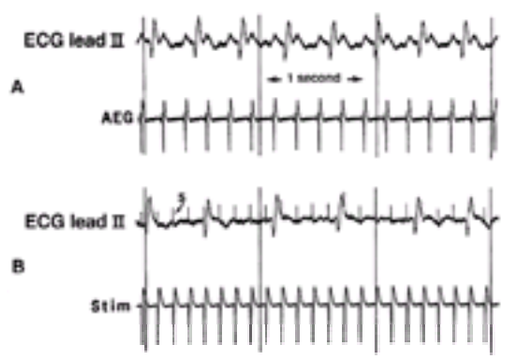
Regardless of the pacing technique used, if the atria are paced at rates faster than the spontaneous rate and the atrial flutter is still not interrupted despite achieving atrial capture, rapid atrial pacing may, in fact, still prove to be successful. This scenario indicates that the selected pacing rates have only transiently entrained the atrial flutter (5,112). Therefore, under the circumstances, successful interruption of atrial flutter will require pacing at a more rapid rate. Atrial pacing rates of more than 400 beats/min occasionally may be required to interrupt atrial flutter, although it should be emphasized that pacing at such a rapid rate usually induces atrial fibrillation. In addition, a critical duration of pacing (average, 11 seconds) at the critical pacing rate is required especially when using the constant rate pacing technique (5,112). Whether using epicardial or endocardial pacing techniques, the stimulus strength required for atrial capture at the rapid rates necessary to interrupt atrial flutter is usually high (113), and either a loss of atrial capture or a failure to capture the atria may occur unless sufficient stimulus strength is applied. It is recommended that pacing be initiated with a stimulus strength of at least 10 mA. However, it is not unusual for up to 20 mA to be required, and on occasion, even stronger stimulus strength may be necessary (5,112,113).

Esophageal Pacing to Interrupt Atrial Flutter

When esophageal pacing is used to interrupt atrial flutter, the suggestions earlier in this section apply with two important exceptions. First, to capture the atria, the stimulus width must be at least 9 to 10 ms, and the stimulus strength needed may be as much as 30 mA (114). Using a pacemaker without these characteristics decreases the chances of successful atrial capture from an esophageal location. Second, because pacing via the esophagus may be somewhat painful (i.e., it usually causes a stinging sensation), pacing should be as brief as possible. Therefore, a pacing rate likely to interrupt atrial flutter should be selected at the outset to minimize the number of pacing attempts required to interrupt atrial flutter.

Precipitation of Atrial Fibrillation (Inadvertent and Deliberate)

Despite appropriate care taken in performing any of these pacing techniques, rapid atrial pacing will provoke atrial fibrillation in some patients. Such atrial fibrillation is usually transient, lasting seconds to minutes, before spontaneously converting to sinus rhythm. When atrial fibrillation persists, it is almost always associated with a slower ventricular response rate than that during atrial flutter. Furthermore, the ventricular rate during atrial fibrillation is usually readily controlled with standard agents. Thus, precipitating atrial fibrillation may be a satisfactory, short-term clinical outcome. In fact, for those patients in whom atrial flutter recurs despite successful interruption by rapid atrial pacing, continuous rapid atrial pacing to precipitate and maintain atrial fibrillation may be indicated (5,112). The latter technique may be especially appropriate in patients who develop transient atrial flutter after open-heart surgery (eFig. 65.4.3) (115).



***e*FIGURE 65.4.3 A:** Electrocardiogram (ECG) lead II recorded simultaneously with a bipolar atrial electrogram (AEG) during typical atrial flutter at a rate of 320 beats/min with 2:1 atrioventricular conduction, producing a ventricular rate of 160 beats/min. After open-heart surgery, the atrial flutter was interrupted successfully on several occasions by rapid atrial pacing but recurred each time. Therefore, as shown in **B**, continuous rapid atrial pacing at 450 beats/min was initiated, which precipitated and sustained atrial fibrillation. This was associated with a slowing of the ventricular rate to approximately 120 beats/min. Continuous rapid atrial pacing to sustain atrial fibrillation to control the ventricular rate was required for 26 hours while antiarrhythmic drugs (digoxin and quinidine) were administered. When rapid atrial pacing was finally terminated, atrial fibrillation spontaneously converted to sinus rhythm. Timelines are 1-second intervals. S, stimulus artifact. (From Waldo AL, MacLean WAH, Karp RB, et al. Continuous rapid atrial pacing to control recurrent or sustained supraventricular tachycardias following open-heart surgery. *Circulation* 176;54:245–250, with permission.)

Direct Current Cardioversion to Convert Atrial Flutter to Sinus Rhythm

DC cardioversion of atrial flutter to sinus rhythm has a very high likelihood of success. It may also require as little as 25 J. However, as 100 J is virtually always successful and virtually never harmful, it should be considered for the initial shock. A high degree of success will thereby avoid the need for delivering a second shock and extending the duration of anesthesia. Low-energy shocks (i.e., less than 3 J and often less than 2 J) delivered between special electrode catheters placed in the coronary sinus and right atrium also have been shown to be highly effective. This latter technique may be applied by using a permanently implanted atrial cardioverter/defibrillator device (116) or during electrophysiology studies to avoid repeated external shocks. It should be noted that when either standard external cardioversion techniques or newer internal cardioversion techniques are used, atrial fibrillation might result. The shock may be delivered during a vulnerable atrial period, as synchronization to the QRS complex is requisite.

Long-Term Treatment

Improvements in the efficacy of catheter-ablation techniques and the long-recognized difficulty in achieving adequate chronic suppression of atrial flutter with drugs have significantly altered the approach to long-term treatment of atrial flutter. In short, if in any patient atrial flutter is an important problem, characterization of the mechanism of atrial flutter followed by catheter ablation (cure) is now recommended.

Antiarrhythmic Drugs

For many years, standard therapy used the class IA antiarrhythmic agents (i.e., quinidine, procainamide, or disopyramide) to prevent recurrence. However, the type IC antiarrhythmic drugs, flecainide and propafenone, appear to be equally, if not more, effective than class IA drugs (15,16). Class IC agents are generally better tolerated and likely have less organ toxicity than class IA agents. Primarily because of serious adverse effects demonstrated in the Cardiac Arrhythmia Suppression Trial I (117), class IC agents should not be used in patients with underlying ischemic heart disease. This notion has generally been extrapolated to include underlying structural

heart disease. However, class IC agents should be considered early on for long-term suppression in patients without structural heart disease.

Moricizine, a class I drug with A, B, and C properties, also may be effective in treating atrial flutter (118). The long-term data from the Cardiac Arrhythmia Suppression Trial II (119) suggested that moricizine and placebo were no different in terms of mortality. Thus, moricizine may be a good choice for patients with atrial flutter and coronary artery disease late (more than 6 months) after myocardial infarction. More data are required to establish efficacy in this clinical setting.

Class III antiarrhythmic agents may also be quite effective (16,17). When using sotalol, care must be taken to avoid QT interval prolongation beyond 500 ms (120) and precipitation of torsades de pointes. Amiodarone appears to be quite effective (17), but several toxicities make widespread use of this drug to treat atrial flutter problematic (121). In fact, several large placebo-controlled studies using low-dose amiodarone (200 mg per day) (although not in patients with atrial flutter) have demonstrated dropout rates as high as 45.0% (122) and 42.5% (123). Thus, using amiodarone as the first-choice drug should be limited to patients with depressed LV function (i.e., an ejection fraction of less than 25%). The safety and efficacy of several other new type III antiarrhythmic agents are currently being evaluated. Dofetilide has recently been marketed for treatment of patients with atrial flutter and fibrillation. Recurrence rates of atrial arrhythmias were similar to sotalol. Like sotalol, caution with regard to QT prolongation and the hazard of torsades de pointes is warranted.

The overall perspective remains that atrial flutter is quite difficult to suppress with drug therapy. In fact, based on available long-term data, drug therapy offers a limited ability to maintain sinus rhythm without occasional to frequent recurrences, even when multiple agents are used (124). Thus, when evaluating drug therapy, an important measure of efficacy should be the frequency of recurrent atrial flutter rather than a single recurrent episode. For instance, recurrence only at long intervals (e.g., once or twice per year) should be classified as successful therapy.

Anticoagulants

The risk of stroke associated with atrial flutter is of concern. An early study (125) found neither evidence of atrial clot formation nor stroke associated with atrial flutter in a relatively small cohort of patients after open-heart surgery. No large prospective studies have been performed to confirm this finding in other patient populations. However, several recent studies (126,127 and 128) indicate that an increased risk of stroke is present in patients with atrial flutter.

Analysis of a Medicare cohort of 17,000 patients with atrial flutter (96) demonstrated a significant increase in the risk of stroke relative to a control population. This risk was concentrated entirely in those patients with atrial flutter who later experienced atrial fibrillation (Fig. 65.5). Unfortunately, no combination of clinical factors in this study could predict which patients with atrial flutter would develop atrial fibrillation. At present there is no consensus statement on the use of anticoagulation in patients with atrial flutter, whether it be acute, ablated, recurrent, or chronic. However, given the above studies, administering warfarin therapy to achieve an international normalized ratio of 2 to 3 is strongly recommended. Anticoagulation for the acute cardioversion of atrial flutter should require the same standards as used for the acute cardioversion of atrial fibrillation.

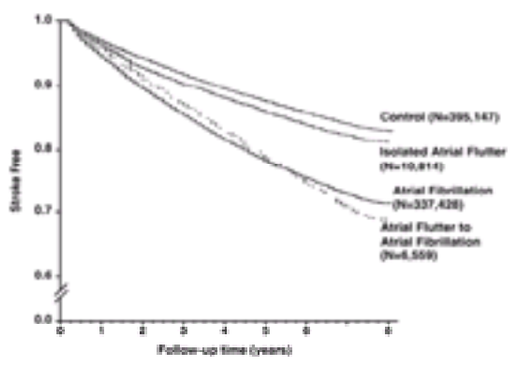


FIGURE 65.5 Medicare patients with an index hospitalization for atrial flutter were followed and compared with atrial fibrillation and control cohorts. The risk of stroke was concentrated almost entirely in the atrial flutter patients, who were rehospitalized at a later time with atrial fibrillation. (From Biblo LA, Yuan Z, Quan KJ, et al. Risk of stroke in patients with atrial flutter. *Am J Cardiol* 2001;87:346–349, with permission.)

Catheter Ablation

Catheter ablation primarily uses radiofrequency energy delivered to selected portions of the heart by an electrode catheter. Initially, success in atrial flutter ablation was reportedly at 60% to 70%, with subsequent recurrence rates of approximately 50% (19,20). However, recent advances in both mapping and ablation techniques have improved efficacy rates to approximately 95%, with little subsequent risk of recurrence (129,130 and 131).

Catheter ablation first involves mapping the atria during atrial flutter to identify a critical isthmus of slow conduction in the atrial flutter reentrant circuit. When this area is identified, usually the atrial flutter isthmus, ablative energy is delivered to create a line of bidirectional block. This isthmus has irregular topography and therefore in some cases may be difficult to ablate successfully. In fact, it was believed that this was the principal cause of most ablation failures. However, combined pacing and mapping techniques have improved, allowing for the reliable determination of complete bidirectional conduction block in this region (132,133,134 and 135).

It must be emphasized that electrode catheter mapping and pacing are necessary not only to demonstrate the completeness of block in the atrial flutter isthmus, but also to confirm the critical participation of the atrial flutter isthmus. Although most types of atrial flutter are isthmus-dependent, atrial flutter can also be due to reentry in the right atrial free wall or in the left atrium. Finally, successful ablation of the atrial flutter reentrant circuit usually does not prevent the occurrence of atrial fibrillation (136,137).

Recently, a catheter ablation experience was reported in patients with left atrial flutter (138). Complete atrial mapping was used to identify a vulnerable isthmus for ablation. Variability was present in circuit locations; however, a left atrial “silent area” characterized most patients with this entity. The area of presumed atrial fibrosis appeared to create a lateral border, stabilizing rotation around the mitral valve.

Ablation has proven effective in lesion reentry atrial tachycardia, as well. In these patients, the lesion is often due to an atriotomy scar after a remote cardiac surgical procedure. Radiofrequency energy is used to extend the scar to a fixed anatomic border (often the tricuspid valve). Thus, rotation of the reentrant circuit around the scar is no longer possible, and the patient is cured of this tachycardia.

For patients in whom the atrial flutter is resistant to catheter ablation, reassessment of the mechanism of the atrial flutter must ensue. Entrainment techniques should be repeated to ensure the proper circuits and mechanisms have been delineated. Resistant atrial flutter (139) is often due to abnormalities in the atrial flutter isthmus region. Anatomic formations such as an unusually large isthmus or a deep, corrugated subeustachian pouch may be present. High-gain, low-noise signals are required to adequately record conduction gaps. Failure rates have declined greatly as a result of these careful and systematic approaches to atrial flutter ablation.

Summary

Atrial flutter is primarily due to reentrant excitation in the right atrium using the subeustachian isthmus. The 12-lead ECG remains the cornerstone for clinical diagnosis. Acute treatment requires control of the ventricular rate and, if possible, restoration of sinus rhythm. Antiarrhythmic drugs to suppress recurrent episodes of atrial flutter may prove useful but are now clearly second-tier therapy in symptomatic patients with atrial flutter. At present, catheter ablation provides a definitive cure, although atrial fibrillation may occur after a successful ablative procedure.

ATRIAL TACHYCARDIA

Background and Classification

The term *atrial tachycardia* encompasses several types of tachycardias that originate in the atria. In the past, classification schemes were largely descriptive and included terms such as *paroxysmal* or *incessant atrial tachycardia* and *atrial tachycardia with block*. Now the term *atrial tachycardia* refers to relatively regular arrhythmias that originate in the atria, do not require participation of the AV node for maintenance, and are neither atrial flutter nor atrial fibrillation. The

subclassifications of atrial tachycardia are based on the mechanisms involved and include reentrant atrial tachycardia, ectopic automatic tachycardia, and triggered atrial tachycardia.

A 57-year-old female patient with atrial tachycardia and 2:1 atrioventricular conduction.

Mechanisms of Atrial Tachycardia

It is generally accepted that there are three different mechanisms responsible for atrial tachycardia: (a) intraatrial reentry, (b) ectopic automaticity, and (c) triggered activity due to delayed afterdepolarizations (DADs). Surprisingly, the details of the reentrant circuit in atrial tachycardia have not been well studied. Consequently, the characteristics of the reentrant circuit are not well delineated.

Atrial tachycardia due to an ectopic automatic focus also has not been well studied. The tachycardias described to date appear to be generated by a focus or foci that cluster around the crista terminalis in the right atrium and around the base of the pulmonary veins in the left atrium (140,141). These tachycardias can be neither initiated nor terminated by atrial pacing.

Triggered activity as a mechanism of atrial tachycardia is thought to be due to DADs largely from digitalis toxicity, but catecholamines can also precipitate atrial tachycardia induced by this mechanism (142). DADs caused by catecholamines have been recorded in the canine heart by microelectrodes placed in atrial fibers of the mitral valve (143), in atrial fibers lining the coronary sinus (144), and in atrial fibers in the inferior right atrium (145). They have also been recorded in human hearts with CM (146).

A recent publication (147) has classified atrial tachycardias as focal or macroreentrant. Focal tachycardia was defined on the basis of (a) centrifugal activation pattern, (b) dissociation of nearly the entire right and left atria from the tachycardia with programmed atrial extra-stimuli, (c) and the absence of entrainment criteria. Macroreentry was defined if initiated or terminated with programmed stimulation and one of the following: (a) continuous electrical activity throughout the cardiac cycle with low-amplitude fractionated signals or (b) any of the entrainment criteria.

The focal versus macroreentrant classification is of benefit in the electrophysiology laboratory but cannot be directly extrapolated to “macroreentrant equals intraatrial reentry” and “focal equals triggered or automatic.” Features consistent with automatic atrial tachycardia were failure to initiate or terminate with programmed stimulation, transient suppression with adenosine, and insensitivity to verapamil. Features consistent with triggered activity were repetitive monomorphic atrial tachycardia, initiation and termination with programmed stimulation, and sensitivity to adenosine and verapamil. Most, but not all, macroreentrant atrial tachycardias were insensitive to adenosine. Those macroreentrant tachycardias that terminated with adenosine were believed to use decremental tissue (outside the AV node).

A new mechanism has also recently been reported: lidocaine-sensitive atrial tachycardia (148). This report describes eight patients with a unique atrial arrhythmia that was suppressed by lidocaine. The arrhythmia could not be initiated or terminated with pacing, making reentry less likely. The arrhythmia occurred at slow heart rates and did not respond to verapamil, making DADs less likely. Overdrive suppression was absent, making automaticity unlikely. The authors speculate that early DAD-like activity in the atria may be responsible for this entity.

Epidemiology and Clinical Significance

The incidence of atrial tachycardia appears to increase with age, reportedly occurring in up to 13% of elderly patients (149,150 and 151). An increased incidence has been reported in patients with myocardial infarction (152,153), nonischemic heart disease (154,155), obstructive lung disease (156), serum electrolyte disorders, and drug toxicity, especially from digitalis (157,158). However, atrial tachycardia may occur in healthy individuals (159,160), and nonsustained episodes have been noted in 2% of healthy young adults (161,162). Most episodes of atrial tachycardia are paroxysmal (usually due to reentry or triggered activity), but some may be incessant (usually due to enhanced automaticity) (163). In patients with incessant tachycardia, a tachycardia-induced CM may result.

Intraatrial Reentry

Patients with reentrant atrial tachycardia often have associated structural heart disease (164,165). In addition, many of these patients have other arrhythmias, specifically atrial fibrillation, atrial flutter, or both. Common symptoms include palpitation, dyspnea, and fatigue. Although patients with this tachyarrhythmia are usually symptomatic, hemodynamic compromise is unusual. Syncope and near-syncope may occur if the underlying heart disease is severe or if the ventricular rate is rapid; however, 2:1 AV conduction very frequently is present so that the ventricular response rate is well controlled (90 to 120 beats/min).

Automatic Atrial Tachycardia

Patients with atrial tachycardia secondary to an automatic mechanism are generally younger, with a mean age of 30 years (165). In fact, automatic atrial tachycardias have been well described in children (166). Automatic atrial tachycardias demonstrate a warm-up phenomenon, do not respond to vagal maneuvers, and often display an incessant nature. When incessant, they are frequently associated with a dilated CM and CHF (165,166).

Triggered Atrial Tachycardia

Atrial tachycardia due to a triggered mechanism appears to be the least common of these tachyarrhythmias. In one series, the mean age of patients was 60 years, and in no instance was the triggered atrial arrhythmia incessant (165). This feature may help clinically distinguish this mechanism from an automatic mechanism, in which the atrial tachyarrhythmia frequently is incessant.

Physical Examination and Associated Hemodynamic Effects

In patients with atrial tachycardia, the findings on physical examination are similar to those of atrial flutter. The atrial rate of the tachycardia will usually determine the ventricular rate. Thus, at relatively slower atrial rates (140 to 150 beats/min) the ventricular response is most often 1:1. With faster atrial rates, variable AV conduction often results, although 1:1 AV conduction at up to rates of 180 beats/min or more may occur. However, with faster atrial rates, 2:1 AV conduction is usually present. The nature of AV conduction may be affected by drugs such as digoxin, calcium channel blockers, or beta-blockers. Adverse hemodynamic effects are more common in patients with 1:1 AV conduction and associated atrial rates of 180 beats/min or more.

Diagnosis

The initial diagnosis of atrial tachycardia is made by the atrial rate (usually 140 to 240 beats/min), on analysis of the 12-lead ECG. However, the range of both the atrial and the ventricular rates may overlap with that of AV nodal–dependent tachycardias and sinus tachycardia. Atrial tachycardia may be confused with atrial flutter if AV conduction is 2:1.

A standard way to determine the presence or absence of an AV nodal–independent atrial tachycardia is to demonstrate that with AV conduction block, the rhythm continues (Fig. 65.6). However, as seen from the following discussion, the confounding effects of many diagnostic interventions can make such differentiation quite

difficult.

FIGURE 65.6 A: A 12-lead electrocardiogram was recorded in a 37-year-old man 29 years after repair of tetralogy of Fallot. The patient noted recurrent palpitation associated with lightheadedness. This 12-lead electrocardiogram documented a tachycardia in which the QRS complex morphology was quite similar to that recorded during sinus rhythm. No P waves could be readily identified. **B:** A Valsalva maneuver induced transient, high-degree atrioventricular block. The underlying atrial tachycardia (cycle length of 360 ms) was then easily demonstrated.

Intraatrial Reentry

In patients with reentrant atrial tachycardia, the rhythm generally can be induced by programmed electrical stimulation. During the arrhythmia, the criteria for either manifest or concealed entrainment usually can be demonstrated, and the interval between the initiating beat and the first beat of the atrial tachycardia is usually inversely related (165). These observations strongly suggest a reentrant mechanism.

As noted in this chapter, terminating a supraventricular tachycardia by a drug that causes transient conduction block (second-degree or third-degree) at the AV node generally would be expected to suggest a diagnosis of an underlying AV nodal–dependent reentrant tachycardia. However, in one reported study (165), adenosine terminated 24 of 27 ostensibly reentrant tachycardias, although in another study (167), in none of the five patients with intraatrial reentrant tachycardia did administration of adenosine affect the tachycardia. The different responses to adenosine observed in these two studies emphasize the need to characterize these rhythms more thoroughly. In any event, termination of an atrial tachyarrhythmia after intravenous administration of adenosine cannot be used per se to characterize the rhythm as AV nodal–dependent. The same seems to be true for beta-blockers, as their use terminated an ostensibly reentrant atrial tachycardia in 13 of 20 patients in one study (165), although they had no effect in three patients reported in another study (167).

Automatic Atrial Tachycardia

Automatic atrial tachycardia may be induced during treadmill testing or after administration of isoproterenol (165,167). Predictably, programmed atrial stimulation will neither initiate nor terminate atrial tachycardia due to this mechanism (145). Propranolol has been shown to suppress putative automatic atrial tachycardias, but neither verapamil nor adenosine has been shown to do so. However, adenosine may transiently slow the atrial rate (165,167).

Triggered Atrial Tachycardia

Triggered atrial tachycardia can be initiated by rapid atrial pacing and has been shown to be cycle length–dependent (165). The onset of the arrhythmia induced by pacing is not pause-dependent. Because these rhythms can be caused by catecholamines, it should not be surprising that isoproterenol and treadmill testing may initiate this form of atrial tachycardia in some patients. Monophasic action potential recording may suggest DADs, and entrainment criteria should not be present. Verapamil and adenosine have been shown to terminate this form of atrial tachycardia.

Summary

The small number of published studies indicates the complexity of identifying the correct underlying mechanism of an atrial tachycardia. Invasive electrophysiologic studies have become an important tool in characterizing the mechanism of this arrhythmia. Induction by programmed stimulation with fulfillment of any of the criteria for entrainment lends support to a reentrant mechanism. The inability to induce or entrain the arrhythmia suggests, but does not prove, either an automatic or triggered mechanism. Thus, when programmed stimulation cannot induce the arrhythmia, successful termination with adenosine suggests a triggered etiology, whereas slowing of the arrhythmia by adenosine suggests an automatic mechanism. Additional insights can be garnered by mapping studies.

Treatment

Reentrant Atrial Tachycardia: Catheter Ablation

For reentrant atrial tachycardia, catheter ablation is now the primary therapy for symptomatic patients. However, radiofrequency ablation appears to be more challenging in these patients than in patients with atrial flutter because the location of the reentrant circuit is not as anatomically consistent as that in most patients with atrial flutter (141). Regardless, if a vulnerable isthmus in a reentrant circuit is found, ablation should prove effective. Reports on catheter ablation for reentrant atrial tachycardia have suggested a success rate of more than 75% (168,169).

Reentrant Atrial Tachycardia: Antiarrhythmic Drugs

Antiarrhythmic drug therapy for reentrant atrial tachycardia is similar to that for atrial flutter and atrial fibrillation. The important message is that overall efficacy as measured by simple recurrence is poor because this rhythm tends to recur in at least half of patients treated. The measure of drug efficacy should be the frequency of recurrence. Occasional arrhythmic recurrences may be quite acceptable in these patients because recurrences are rarely life-threatening and are usually well tolerated. Thus, should the arrhythmia recur and if it does not revert spontaneously, cardioversion to sinus rhythm should be considered. The patient should then be followed on the same antiarrhythmic regimen. When recurrences are too frequent or intolerable, the pharmacologic regimen should be changed. Finally, reentrant atrial tachycardia can be acutely treated with rapid atrial pacing techniques virtually identical to those used to treat atrial flutter.

Nonreentrant Atrial Tachycardia

Patients with nonreentrant atrial tachycardia who have minimal symptoms should be treated with either a beta-blocker or a calcium channel blocker. Automatic atrial tachycardia appears more responsive to beta-blockers, whereas triggered arrhythmias appear to respond best to calcium channel blockers. Extrapolation from acute studies suggests that such therapy is logical (Fig. 65.7). For patients in whom the tachycardia is due to digitalis toxicity, the dose of digitalis should either be stopped or reduced. In patients with clinically important symptomatic or incessant nonreentrant atrial tachycardia, catheter ablation is preferred. A combination of pace mapping, entrainment analyses, and identification of the earliest atrial activation site at electrophysiologic study are complementary methods to ensure an excellent ablative result. Long-term results are excellent (170).

FIGURE 65.7 A 27-year-old woman complained of episodic palpitation. The 12-lead electrocardiogram (ECG) documented salvos of an atrial tachycardia. An echocardiogram was normal. At electrophysiologic study, an arrhythmia was not induced by programmed stimulation. Initial therapy with a beta-blocker proved ineffective, but subsequent therapy with diltiazem resulted in complete suppression of the arrhythmia.

Summary

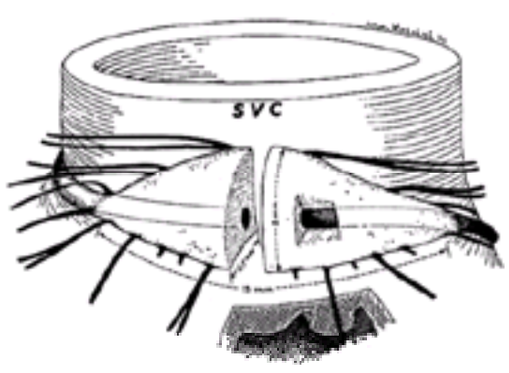
Atrial tachycardia encompasses a wide spectrum of clinical presentations and mechanisms. Current classification schemes focus on mechanism. Therapy should be aggressive for those patients with significant symptoms, and whenever possible radiofrequency ablation is preferable. Despite the mechanistic heterogeneity of atrial tachycardia, radiofrequency catheter ablation is usually successful. Drug therapy remains an acceptable alternative for minimally symptomatic patients with an atrial tachyarrhythmia.

INAPPROPRIATE SINUS TACHYCARDIA

Background

Sinus rhythm is generated by spontaneous phase 4 depolarization of pacemaker cells located in the sinus node. The sinus node lies just beneath the subepicardial surface and is located at the junction of the superior vena cava and the right atrium. As summarized by MacLean et al. (171), the sinus node artery is perhaps the best guide to locating the sinus node. The sinus node artery arises from the proximal 2 to 3 cm of the right coronary artery in 55% of human hearts and from the proximal few millimeters of the left circumflex artery in 45%. Other origins are quite rare. Regardless of origin, the sinus node artery courses along the anterior aspect of the ipsilateral atrial wall to the base of the superior vena cava, which it then encircles.

The exact position of the sinus node varies with the manner of encirclement of the superior vena cava by the sinus node artery. The sinus node is more anterior when the artery courses clockwise when viewed from above. The position of the sinus node can be determined grossly as the point where the artery can no longer be easily dissected from the epicardium. At that point, the sinus node completely surrounds the artery and is located just beneath the epicardium and just below the sulcus terminalis. The anterior margin of the node sits very close (1 to 10 mm) to the crest formed by the junction of the anterior margin of the right atrial appendage and the superior vena cava. The posterior margin is at the junction of the trabeculated right atrium and the sinus intercavarum. The sinus node is shaped like “Napoleon’s hat” and measures approximately 15 mm in length, 5 mm in height, and 1.5 mm in thickness (*e*Fig. 65.7.1). It has neither a head nor a tail, despite common references to these terms. The inferior margins of the sinus node abut on the antrum atrii dextri, which is the endocardial recess between the crista terminalis and the lateral wall of the right atrium.



***e*FIGURE 65.7.1** This drawing illustrates the location and shape of a normal human sinus node and demonstrates the anatomic relationship between the sinus node and the sinus nodal artery. SVC, superior vena cava. (From MacLean WAH, Waldo AL, James TN. Formation and conduction of the cardiac electrical impulse. In: Yu PN, Goodwin JF, eds. *Progress in cardiology*. Philadelphia: Lea & Febiger, 1974:37–74, with permission.)

The sinus node possesses the fastest rate of normal automaticity in the heart. This rate is determined by the rate of rise of phase 4 depolarization, the level of the threshold potential, and the level of the maximum diastolic potential of the pacemaker cell. The sinus rate in humans is normally 60 to 100 beats/min. Alterations in sinus rate primarily depend on the influence of autonomic innervation and secondarily on variations in local environment (e.g., pH, potassium, oxygen partial pressure, calcium, and cardioactive drugs).

Sinus tachycardia is usually the result of an appropriate reflex-controlled response. In adults, *sinus tachycardia* is defined as a rhythm originating from the sinus node at a rate of more than 100 beats/min. The normal maximum heart rate achieved by adults during strenuous exercise is rarely more than 180 beats/min, and it can be calculated using the formula of 220 minus the patient’s age (years). Sometimes during sinus tachycardia, the P-wave morphology in the ECG may change subtly compared with that during sinus rhythm. Such changes associated with rate are thought to represent a shift in the location of the dominant pacemaker cells in the sinus node area, with a consequent change in the initial excitation of the atrium. Treatment of appropriate sinus tachycardia rarely is directed at the sinus node pacemaker, but rather at the underlying trigger. Thus, management first focuses on identifying and then treating the underlying precipitant. A long list of potential causes of appropriate sinus tachycardia includes infection, hypotension, anemia, dehydration, hyperthyroidism, and pheochromocytoma.

In recent years, a syndrome originally called *nonparoxysmal sinus tachycardia* (172), but now called *inappropriate sinus tachycardia*, has been described (173). This entity is characterized by an incessant and symptomatic sinus tachycardia due to inappropriately enhanced automaticity of sinus node pacemaker cells.

Potential Mechanisms

There is only limited information available about the potential mechanisms of inappropriate sinus tachycardia because only a small number of patients have been studied and reported. One study (172) in which inappropriate sinus tachycardia was defined as an atrial rate of more than 100 beats/min on all waking ECGs for 3 months with no demonstrable underlying cause described seven patients with this syndrome. Each patient underwent invasive electrophysiologic testing to exclude a reentrant arrhythmia. Based on resting heart rate responses to propranolol, excessive sympathetic tone was noted in two patients, and deficient resting vagal tone was noted in the other five patients. Three of the seven patients demonstrated an abnormal intrinsic heart rate. The P-wave morphology on the 12-lead ECG was normal.

Another study (173) described six patients with this syndrome. Inappropriate sinus tachycardia was defined as the following:

1. An atrial rate of 100 beats/min or more at rest or with minimal activity
2. A normal P-wave axis and morphology on 12-lead ECG during tachycardia
3. Absence of an underlying cause

The cardiovagal response in these patients as judged by the cold pressor test was blunted compared with that in normal patients. Hypersensitivity to isoproterenol was

noted in all patients. A high intrinsic heart rate (mean of 129 beats/min) was noted in all patients after administration of intravenous propranolol and atropine. Based on the results of complete autonomic blockade, Morillo et al. (173) concluded that the major abnormality in this syndrome appears to be a primary sinus node abnormality exacerbated by autonomic dysfunction.

In still another study of 16 patients (174), the resting sinus rate was not significantly different from the resting heart rate after catheter ablation of the sinus node (85.5 ± 7.8 beats/min versus 79.0 ± 4.9 beats/min). However, the mean baseline measurement of intrinsic heart rate (118.6 ± 8.6 beats/min) was significantly higher than the mean predicted intrinsic heart rate (97.7 ± 1.7 beats/min; p <.01). However, the intrinsic heart rate was within normal range in five of the 11 patients who had a baseline measurement. Patients who underwent exercise treadmill tests had an inappropriate chronotropic response to a light workload (mean heart rate of 141.2 ± 5.1 beats/min after only 1.5 minutes of stage 1 of the Bruce protocol).

In summary, the mechanism of this entity is not well understood, and there is a clear need for improved understanding. It appears that inappropriate sinus tachycardia may be due to enhanced automaticity of sinus node pacemaker cells, a dysautonomia, or both. The dysautonomia appears to include beta-adrenergic hypersensitivity and depression of the efficient cardiovagal reflex, often superimposed on an abnormally high intrinsic heart rate.

Epidemiology and Clinical Significance

Patients with inappropriate sinus tachycardia usually are relatively young and have an abnormally high resting heart rate. This rate increases disproportionately with activity. Patients frequently are disabled by persistent palpitations, extreme dyspnea, chronic fatigue, and near syncope. It is noteworthy that patients frequently have been called neurotic. To date, many of the patients described with this syndrome have been health care employees. Patients reported to date (173,174) have been overwhelmingly female. The heart rate varies with activity but appears to be set 30 to 40 beats/min higher than normal. Surreptitious drug use and Munchausen syndrome must be excluded. During sinus tachycardia, stroke volume is maintained due to a complex interplay of neurohumoral reflexes and changes in peripheral resistance. Thus, in contrast to other atrial tachyarrhythmias, adverse hemodynamic findings are infrequently observed during sinus tachycardia despite rapid rates. Nevertheless, with sustained rapid ventricular rates, a dilated CM may evolve. Although no instances of an inappropriate sinus tachycardia–induced CM have been reported, we have treated one patient with inappropriate sinus tachycardia and an idiopathic CM. In this patient, LV ejection fraction improved from 44% to 67% after radiofrequency modification of the sinus node with associated normalization of the heart rate. The patient also improved clinically from New York Heart Association class III heart failure to class I heart failure.

Diagnosis

To diagnose inappropriate sinus tachycardia, the following criteria should be satisfied:

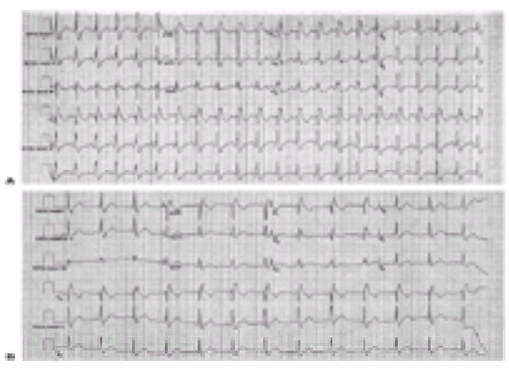
1. The resting heart rate should be 100 beats/min or more or should increase to 100 beats/min or more with minimal exertion (e.g., when rising from the sitting position or when walking slowly).
2. The P-wave morphology and axis in the 12-lead ECG during the tachycardia should be quite similar or, better still, identical to that during sinus rhythm.
3. Secondary causes of sinus tachycardia (e.g., fever, anemia) should be excluded.
4. Symptoms of palpitation, presyncope, or both should be documented to be related to resting or easily provoked sinus tachycardia to differentiate inappropriate sinus tachycardia from severely deconditioned individuals who may otherwise fulfill the above criteria.

Additional testing should prove helpful. Thus, electrophysiologic testing should demonstrate that the tachyarrhythmia could not be initiated or terminated by atrial pacing techniques. In addition, atrial mapping should show that the tachycardia originates from the sinus node region. Producing autonomic blockade to identify the so-called intrinsic sinus rate may not prove helpful to diagnosis because approximately half of patients with this syndrome may have a normal intrinsic sinus rate, which supports the notion that this syndrome may have more than one etiology.

Sinus tachycardia with blocked premature atrial contraction. Premature atrial beat fails to conduct, producing a pause.

Treatment

Finding effective drug therapy for patients with this syndrome is often quite difficult. However, beta-blockers appear to be the most effective for ameliorating symptoms by normalizing heart rate. Effectiveness of therapy is best judged by serial 24-hour ambulatory ECGs (Holter monitor). Sinus node ablation or modification using radiofrequency energy and electrode catheter techniques recently has proven to be effective (174,175). Ablation of the sinus node appears to be more effective when guided by activation mapping (176) to identify the appropriate endocardial ablation sites. Successful sinus node ablation is often associated with a superior shift in the P-wave axis (*e*Fig. 65.7.2). Long-term results vary considerably from institution to institution, with success in up to 66% of patients.



***e*FIGURE 65.7.2 A:** A 40-year-old former health care worker presented with fatigue and dyspnea. The 12-lead electrocardiogram (ECG) documented sinus tachycardia with a right bundle branch block pattern. A 24-hour ambulatory ECG monitor recording showed a mean sinus rate of 120 beats/min. Cardiac catheterization showed normal coronary artery anatomy but a globally dilated left ventricle with an estimated left ventricular ejection fraction of 0.25. **B:** After sinus node modification using catheter-based radiofrequency energy, a 12-lead ECG documented a change in P-wave morphology and rate. A 24-hour ambulatory ECG monitor recording obtained after the ablation documented a mean heart rate of 85 beats/min. This was associated with resolution of all symptoms. Two months later, the left ventricular ejection fraction returned to normal.

Summary

Inappropriate sinus tachycardia is a newly described entity that appears to be rare. The entity remains largely descriptive but may be due to a dysautonomia or a

primary sinus node abnormality. Before initiating definitive therapy, the physician must carefully search for an underlying precipitant.

SINUS NODE REENTRANT TACHYCARDIA

Background

Sinus node reentrant tachycardia is believed to be due to reentry within the tissue in or near the sinus node. This tachycardia is characterized by an atrial rate of 105 to 150 beats/min and a P-wave morphology in the ECG similar to that of sinus rhythm (Fig. 65.8). Marked variation in cycle length during tachycardia is very common.

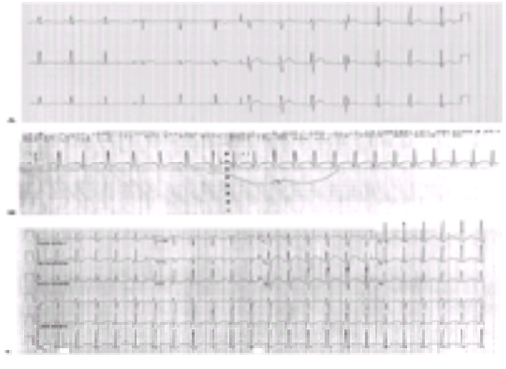


FIGURE 65.8 A: A 64-year-old man complained of episodic palpitation. A baseline 12-lead electrocardiogram (ECG) documented normal sinus rhythm. **B:** A telemetry strip documented the abrupt onset of tachycardia, which proved to be due to sinus node reentry. **C:** A 12-lead ECG obtained during palpitation showed that the P-wave morphology was quite similar to that on the baseline ECG.

Mechanism

As is evident from its name, this rhythm is due to reentry involving the sinus node and perinodal tissue. It usually can be reproduced during electrophysiologic study using standard programmed pacing techniques in the atria. Vagal maneuvers and administration of adenosine or verapamil terminate the arrhythmia (177). A noticeable association with coronary artery disease—specifically with inferior myocardial infarction—has led to speculation that ischemia or infarction in the sinus node area may provide the milieu for reentry.

Epidemiology and Clinical Significance

The majority of patients with sinus node reentrant tachycardia have structural heart disease. Sinus node reentry tachycardia can be associated with any of the classic symptoms associated with any tachycardia, including palpitation, dyspnea, near-syncope, or syncope (see Atrial Flutter: Epidemiology and Clinical Significance) (178,179). Although associated tachycardias have been believed to occur infrequently, one recent study noted one or two additional tachyarrhythmias (atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, bundle branch reentrant tachycardia, atrial tachycardia) in nine of 11 patients (179). In patients with prolonged, sustained sinus node reentrant tachycardia, dilated CM may result.

Diagnosis

The rhythm is characterized by rapid rates (usual range of 120 to 150 beats/min) in which the P-wave morphology in the 12-lead ECG is virtually identical to that during sinus rhythm. Its spontaneous onset and offset are abrupt. The tachycardia behaves classically to interventions known to perturb or interrupt ordered reentrant rhythms. Thus, the tachycardia can be initiated or terminated with atrial pacing techniques; it can also be terminated with adenosine or with maneuvers that increase vagal tone. Mapping during electrophysiologic study demonstrates an atrial activation sequence similar to that of sinus rhythm.

Treatment

Intravenous adenosine and verapamil as well as vagal maneuvers have been used over the short term to terminate sustained episodes of sinus node reentry tachycardia. In several small series of studies, radiofrequency ablation of the sinus node region has been shown to prevent recurrence of sinus node reentrant tachycardia (180). Long-term drug therapy has not been systematically studied. However, digitalis, a calcium channel blocker, or a beta-blocker alone or in combination may prove effective.

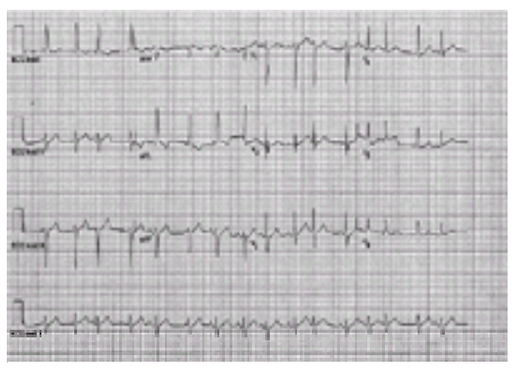
Summary

Sinus node reentrant tachycardia is an infrequent tachyarrhythmia. Definitive therapy with catheter ablation should prove successful.

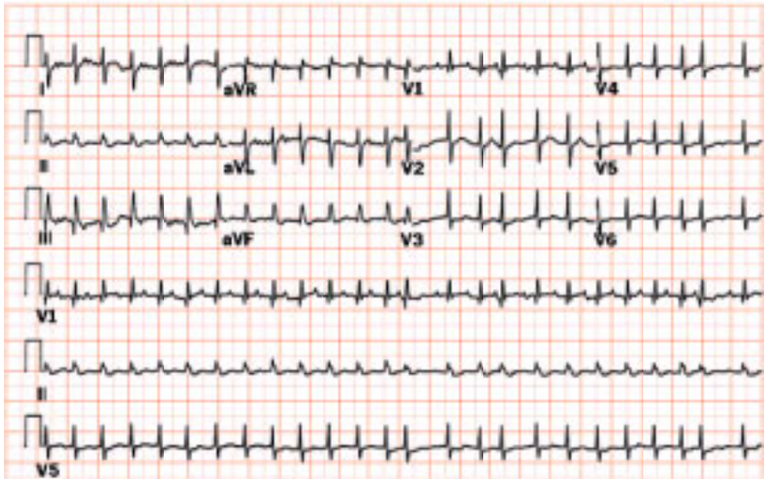
MULTIFOCAL ATRIAL TACHYCARDIA

Background

MAT remains largely a descriptive entity with a need for better characterization (181). MAT is usually diagnosed by ECG criteria that include an atrial rate of more than 100 beats/min with P waves of at least three distinct morphologies. Diagnosing MAT can be difficult. The chaotic nature of its P-wave morphology with varying AV intervals frequently may cause it to be confused with atrial fibrillation (*e*Fig. 65.8.1).



***e*FIGURE 65.8.1** This 12-lead electrocardiogram (ECG), obtained from a 70-year-old man with severe obstructive lung disease, demonstrated multifocal atrial tachycardia. There were more than three different P-wave morphologies. The tachycardia in this example occurs at a relatively slow rate; however, it is shown here because the multiple P-wave morphologies can be well seen.



Multifocal atrial tachycardia. Narrow-complex tachycardia associated with three or more different P-wave morphologies.

Potential Mechanism(s)

The mechanism(s) underlying MAT remain unknown. Several reports have noted that MAT cannot be induced or initiated by programmed stimulation. Thus, reentry seems an unlikely mechanism. Anecdotal reports of successful treatment of MAT with calcium channel blockers or beta-blockers are consistent with both automatic and triggered mechanisms.

Epidemiology and Clinical Significance

MAT is often observed in patients with acute pulmonary disorders and associated hypoxia. Patients with MAT usually are acutely ill and often are receiving beta-agonists or theophylline preparations. As such, both beta-agonists and theophylline have been causally implicated. There are no data to support these observations as more than associations. Regardless, it seems reasonable to discontinue these agents in affected patients. Anecdotal reports have also noted an association of MAT with pulmonary embolism, coronary artery disease, CHF, and electrolyte disturbances.

Treatment

The therapeutic issues revolve around the extent to which the rapid ventricular response rate during MAT affects the clinical condition of the patient. If ventricular response can be controlled, which is usually difficult, MAT per se probably will not affect the patient's clinical course.

The basis for therapy should primarily be correction of the underlying pulmonary problem. DC cardioversion has not proved successful in patients with MAT. Only limited experience has been reported with use of standard antiarrhythmic drugs. Beta-blockers have been used successfully in selected patients. Precipitation of bronchospasm may be a potentially fatal complication when beta-blockers are used in acutely ill patients. Thus, short-acting $beta_1$-specific agents such as esmolol seem most appropriate for initial use. Calcium channel blockers have been used with limited success.

Beta-Blockers

Arsura et al. (182) compared both beta-blockers and calcium channel blockers in a blinded crossover study of patients with MAT. During this 22-month study, 16 of 79 consecutive patients with MAT were randomly assigned to placebo, verapamil, or metoprolol. Of the nonrandomized patients, unstable blood pressure and audible wheezing accounted for most of the exclusions. Patients were given either placebo or verapamil, 5 mg intravenously over 5 minutes, or metoprolol, 5 mg intravenously over 5 minutes. A statistically significant difference in the net decrease in heart rate was observed only when patients treated with metoprolol were compared with patients treated with placebo. Metoprolol-treated patients showed a decrease in heart rate of approximately 25%. Six of the study patients died during hospitalization. Unfortunately, this mortality does not differ from that reported in other studies. Although the data set is obviously small, Arsura et al. (182) cautiously concluded that in selected patients beta-blockers may play a role in the treatment of patients with MAT. It remains questionable whether antiarrhythmic drugs can affect outcome in this dramatically ill group of patients.

Calcium Channel Blockers

Salerno et al. (183) investigated the use of calcium channel blockers in treating patients with MAT. There has been concern regarding use of intravenous calcium channel blockers because of the potential of vasodilation-induced hypotension. Intravenous verapamil was administered at doses of up to 1 mg per minute to 16 consecutive patients with MAT. The mean heart rate decreased from 129 to 101 beats/min. Sinus rhythm was restored in eight patients. Patients who received pretreatment with calcium (1 g of calcium gluconate intravenously over 1 to 2 minutes) showed a systolic blood pressure drop of 11%. However, systolic blood pressure dropped by 27% in those patients who were not pretreated with calcium gluconate. No differences in antiarrhythmic efficacy were observed between the two groups. Salerno et al. (183) concluded that pretreatment with intravenous calcium gluconate was reasonable in patients receiving verapamil for MAT.

Nonpharmacologic Methods

A recent report (184) has advocated AV junction ablation and permanent pacing for those patients with refractory MAT. In this series, both improvement in quality of life and LV function was noted. Of note, right ventricular function did not improve. This study was not powered to examine mortality. Thus, this therapy should be reserved only for extremely symptomatic patients.

Summary

In summary, when precipitating causes of MAT have been corrected, specific drug therapy may be reasonable to help slow the ventricular rate. Although it appears logical that slowing of the ventricular rate would be desirable, there are no data supporting a meaningful change in outcome in these patients by such treatment. MAT remains a paraphenomenon. As such, therapy should not focus on the arrhythmia. The underlying cardiopulmonary substrate must be engaged therapeutically, with little emphasis placed on the arrhythmia.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Clinical Presentation

A chronic or frequent atrial tachyarrhythmia can lead to ventricular dilatation and CHF. The full spectrum of symptoms associated with cardiac dysfunction is possible from pulmonary edema to a nonspecific cough. We believe that this syndrome, tachycardia-induced CM, is grossly unrecognized. Many nonischemic CMs may be entirely due to such an incessant arrhythmia. Equally important, frequent episodes of atrial tachyarrhythmias may exacerbate underlying cardiac disease, resulting in an exacerbation of symptoms and a worsening quality of life. We believe that many physicians attribute such a decompensation to the progression of underlying coronary disease, valve disease, and so forth. The possibility that the frequent arrhythmia is the culprit must be recognized and appropriately treated to ensure the best outcome for each patient. Not only must cardiologists recognize this possibility, but front-line physicians (e.g., internists and family practitioners) must screen for this diagnostic possibility as well.

Therapy

The traditional initial treatment for most AV nodal–independent atrial arrhythmias has been antiarrhythmic drugs. An increasing volume of data has confirmed an excessive mortality risk in those patients with structural heart disease who have been treated with class IA or class III antiarrhythmic drugs. Thus, catheter ablation should assume a greater role as primary therapy for many atrial arrhythmias in these patients.

THE FUTURE

A more thorough understanding of the mechanisms of atrial arrhythmias has brought this field to the forefront of cardiology. More advances in understanding the underlying mechanism(s) of atrial arrhythmias will enable us to better target medications for specific rhythm disturbances. Advances in mapping techniques in the electrophysiology laboratory will further ensure more successful treatment of patients with atrial arrhythmias. Sophisticated mapping systems using a single intracavitary probe or thoracic multielectrode vests will facilitate identification of target sites for successful ablation. A “Star Wars”-like atmosphere has occurred in the electrophysiology laboratory. More advanced systems will decrease the time needed for testing, the radiation exposure to patients and practitioners, and the complication rates to patients undergoing these procedures.

To date, with most atrial arrhythmias, the mechanistic approach has used whole organ physiology. However, a mechanistic approach emphasizing molecular genetics will evolve, and therapies analogous to those under way in patients with long QT syndrome will become commonplace.

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ATRIOVENTRICULAR NODAL–DEPENDENT TACHYCARDIAS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Atrioventricular (AV) nodal–dependent tachycardias comprise a specific subgroup of rapid, regular supraventricular arrhythmias that critically depend on conduction through the AV node for their perpetuation. The most common are AV reentrant tachycardias that use an accessory pathway (AP) as the retrograde limb of the circuit and AV nodal reentrant tachycardia in which both anterograde and retrograde components of the reentrant substrate are within or near the compact portion of the AV node and neighboring bundle of His. The anatomic location around the mitral or tricuspid annulus of APs can be precisely identified at the time of electrophysiologic testing but can also be predicted with high accuracy based on the morphology of retrograde P waves during tachycardia or characteristic delta waves in those patients in whom these arrhythmias occur as a component of Wolff-Parkinson-White (WPW) syndrome. AV nodal–dependent tachycardias are typically initiated by premature atrial or ventricular extrastimuli and have reasonably specific characteristics that allow their differentiation. Although both are short RP tachycardias, AV reentrant tachycardia must have a ventriculoatrial (VA) or RP interval of at least 70 ms, whereas most AV nodal reentrant tachycardias have intervals of less than 60 ms, with retrograde P waves presenting as a pseudo-R wave in surface electrocardiogram (ECG) lead V_1 during tachycardia. In some patients with APs, a reversed-direction tachycardia with anterograde conduction through the AP may occur, producing a maximally preexcited QRS complex on the surface ECG. Some patients with WPW syndrome are at potential risk for atrial fibrillation degenerating into ventricular fibrillation. APs with unusual conduction characteristics contribute to the occurrence of preexcitation variants, including the permanent form of junctional reciprocating tachycardia and atriofascicular reentry. Because of their dependence on AV nodal conduction for their maintenance, AV nodal–dependent arrhythmias may be acutely terminated by vagal maneuvers or administration of adenosine or verapamil. Wide-complex tachycardias in these patients must be carefully approached without using drugs that accelerate AP conduction, which can lead to ventricular fibrillation. Both pharmacologic and nonpharmacologic therapies may be applied in the long term for managing patients with these arrhythmias. Drug therapy may be directed at the AV node, the AP, or the initiating atrial or ventricular extrastimuli. Ablative therapy has also emerged as the mainstay of nonpharmacologic treatment of these arrhythmias.

GLOSSARY

Anterior fibrous trigone: The region of convergent, dense, fibrous tissue of the posterior aortic and anterior mitral valve annuli.

Antidromic reciprocating tachycardia: A reversed-direction AV nodal–dependent tachycardia in which anterograde conduction occurs through the AP, whereas return retrograde atrial activation proceeds through the normal VA conduction system.

Atriofasciculoventricular Mahaim fiber: An atypical AP with AV node–like properties typically located in the anterior or anterolateral region of the tricuspid annulus. This pathway serves as a bridge between atrial and right bundle branch tissue.

Atriofasciculoventricular or "Mahaim" reentrant tachycardia: A preexcitation variant tachycardia that uses an atriofascicular fiber as its anterograde limb.

AV nodal reentrant tachycardia: An AV nodal–dependent tachycardia in which both anterograde and retrograde components of the reentrant substrate are located within or near the compact portion of the AV node.

AV nodal–dependent tachycardia: A tachycardia that critically depends on conduction through the AV node for its perpetuation.

AV reentrant tachycardia: An AV nodal–dependent tachycardia with the AV conduction system as the anterograde and the AP as the retrograde limb of the tachycardia circuit.

Concealed AP: AP with retrograde-only conduction existing without evidence of anterograde ventricular activation through that pathway.

Discontinuous conduction: Characteristic of dual AV nodal physiology in which a more than 50-ms abrupt prolongation of AV nodal conduction time occurs with a

10-ms decrease in the coupling time of an atrial premature complex (APC), producing anterograde conduction through the AV node.

Dual AV nodal physiology: Electrophysiologic manifestation of two AV nodal pathways with different anatomic and/or physiologic properties that serve as a substrate for AV nodal reentrant tachycardia.

Koch's triangle: A triangular space in the medial portion of the right atrium formed by the septal component of the tricuspid valve annulus, the coronary sinus orifice, and the tendon of Todaro. The AV node lies in the apex of this triangle.

Long RP tachycardia: Tachycardia with a retrograde P wave describing atrial activation occurring close to the succeeding QRS complex. These tachycardias have an RP interval that is more than 50% of the RR interval seen during tachycardia.

Permanent junctional reciprocating tachycardia (PJRT): Preexcitation variant in which retrograde atrial activation occurs through an AP with node-like or decremental electrical conduction properties. These long RP tachycardias may be incessant and show negative P waves in leads II, III, and aVF.

Preexcitation: Early ventricular activation before that proceeding through the normal AV conduction system, as seen in patients with APs.

Short RP tachycardia: Tachycardia with a retrograde P wave describing atrial activation that occurs close to the preceding QRS complex. These tachycardias have an RP interval that is less than 50% of the RR interval seen during tachycardia.

VA interval: The VA interval beginning with the local ventricular activation and ending with earliest retrograde atrial activation. The surface ECG correlate is the RP interval from onset of the surface QRS to the retrograde P wave.

INTRODUCTION

AV nodal–dependent tachycardias comprise a specific subgroup of rapid, regular supraventricular arrhythmias that critically depend on conduction through the AV node for their perpetuation. These arrhythmias typically use the normal AV conduction system as the anterograde limb of the reentrant circuit and therefore present with a narrow QRS complex on the surface ECG, as shown in Figure 66.1. Unlike atrial flutter or atrial tachycardias, which may continue despite the presence of high-grade AV block, AV nodal–dependent tachycardias are typically eliminated by vagal, drug, or nonpharmacologic interruption of AV nodal conduction. As such, with infrequent exceptions (e.g., AV nodal reentrant tachycardia with 2:1 A:V or V:A conduction), AV nodal–dependent tachycardias show a classic 1:1 AV relationship, unlike their AV nodal–independent counterparts that may have a 2:1 or more AV relationship, with or without these interventions (Fig. 66.1).

FIGURE 66.1 Electrocardiogram tracings from atrioventricular (AV) nodal–dependent and AV nodal–independent tachycardias. **A:** Narrow QRS complex tachycardia with a 1:1 AV relationship in a patient with an AV nodal reentrant tachycardia. **B:** Classic atrial flutter persisting despite variable AV block.

The most common of the AV nodal–dependent arrhythmias are AV reentrant tachycardias, in which an AP is used as the retrograde limb of the tachycardia circuit (Fig. 66.2), and AV nodal reentrant tachycardias (Fig. 66.2) in which both anterograde and retrograde components of the reentrant substrate are within or near the compact portion of the AV node and neighboring bundle of His. Some AV nodal–dependent arrhythmias, such as antidromic reciprocating tachycardias, less frequently use the AV conduction system as the retrograde component and an AP as the anterograde limb of the tachycardia circuit. Therefore, the QRS complex on the surface ECG during tachycardia is maximally preexcited.

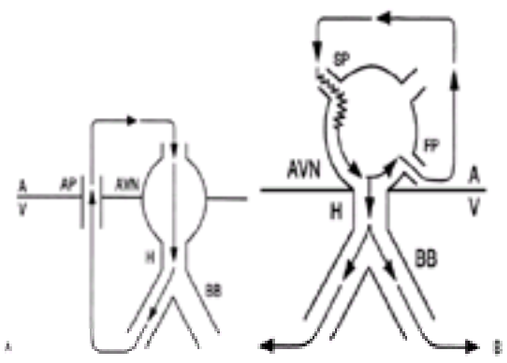
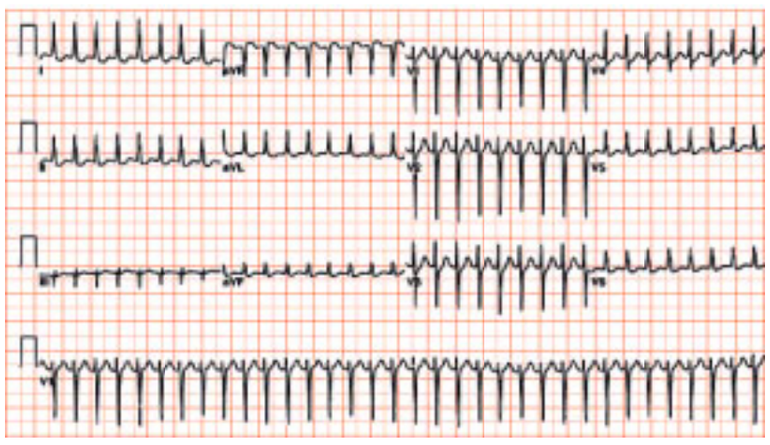
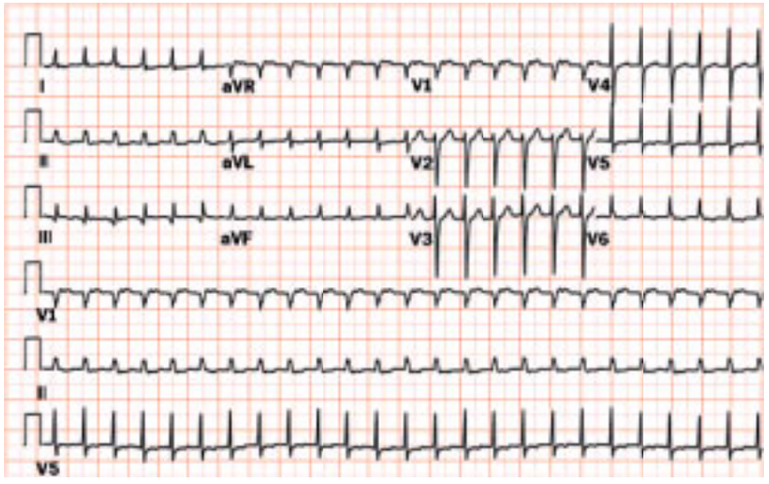


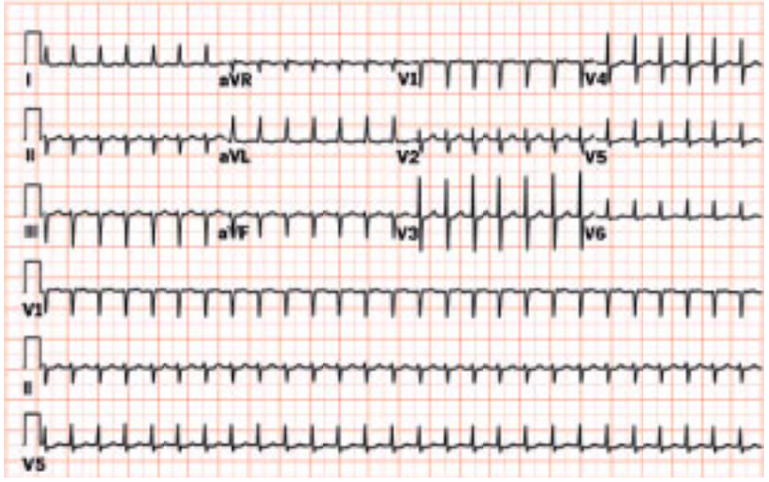
FIGURE 66.2 Mechanism of atrioventricular (AV) reentrant and AV nodal reentrant tachycardias. In both arrhythmias, the AV node serves as a mandatory component of the reentrant circuit. **A:** AV reentrant tachycardia in which the AP serves as the retrograde limb of the reentrant circuit. **B:** AV nodal reentrant tachycardia circuit with anterograde conduction through SP with return retrograde conduction through FP. AP, accessory pathway; AVN, atrioventricular node; BB, bundle branch; FP, fast pathway; H, bundle of His; SP, slow pathway.



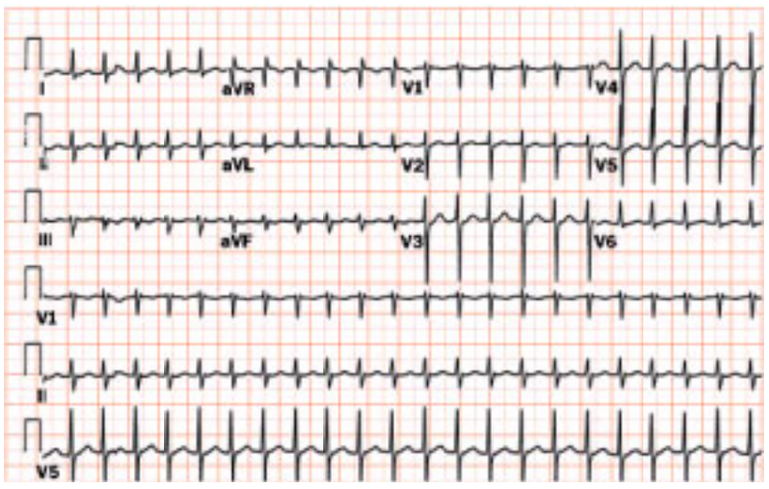
A 58-year-old female patient with supraventricular tachycardia. Arrhythmogenic right ventricular dysplasia diagnosed with electrophysiologic stimulation.



Supraventricular tachycardia. Note narrow QRS complex with short RP interval.



Supraventricular tachycardia. P wave is not visible in this example, suggesting atrioventricular nodal reentry tachycardia.



Atrioventricular nodal reentrant tachycardia. Note retrograde P wave buried within the ST segment.

HISTORICAL PERSPECTIVE

AV nodal–dependent tachycardias have been a focus of extensive clinical interest during the past 100 years and have prompted numerous studies to clarify the underlying electrophysiology. In studying AV conduction, Kent (1) examined a variety of different mammalian hearts and found a “complex system of branching and anastomosing fibers” penetrating the fibrous annular tissue between the atria and ventricles, which we now refer to as the *normal AV conduction system*. Mines provided the first description of reentry in the AV node in 1913, and his explanation of the possible physiologic mechanism of this arrhythmia is essentially what we now refer to as *dual AV nodal physiology* (2). In addition, Kent (3) identified anomalous muscular bundles connecting the auricles and ventricles, which were particularly prevalent at the anterolateral region of the tricuspid ring. Building on Kent’s observations, Mines (4) suggested that such a pathway may serve as a component of a possible reentrant circuit.

By the end of the first decade of the twentieth century, a variety of case reports documented the occurrence of relatively benign, rapid regular tachycardias accompanied by palpitations (5,6,7 and 8). In 1913, Cohn and Frazier (6) reported two patients in whom supraventricular tachycardia (SVT) was documented by ECG recordings for the first time in the United States. The second of these patients had a short PR interval and preexcited QRS complex after vagal termination of the narrow complex tachycardia. Several years thereafter, Wood et al. (7) reported a patient with a short PR interval and prolonged QRS complex who died during an attack of paroxysmal tachycardia. Serial histologic sections of a portion of this patient’s AV groove showed three muscular connections at the right lateral border of the heart between the right auricle and ventricle, as described by Kent (3). Wolferth et al. (5) hypothesized that such accessory connections capable of AV conduction may be responsible for both ventricular preexcitation during sinus rhythm and the paroxysms of tachycardia in these patients. The mechanism depicted in figure 4 of that reference (5) has since been firmly established as underlying these electrophysiologic phenomena.

In 1930, the combination of paroxysmal tachycardias of this type along with a bundle branch block QRS morphology and a short PR interval was codified as WPW syndrome (8). The existence of apparent dual AV nodal physiology as an additional avenue of AV conduction was suggested by others (9,10 and 11), and, in 1962, Kistin postulated the existence of multiple AV nodal pathways in humans (12). Other investigators subsequently also described the possibility of triple or multiple AV nodal pathways (13,14,15,16,17 and 18).

The understanding of the rhythm disorders created by these connections took a giant leap forward with the advent of catheter-based electrophysiologic studies (19,20,21,22,23 and 24). By positioning multiple recording electrodes within the heart and through the use of electrical stimulation techniques, the roles of the AV node and AP in SVTs have been elucidated. Furthermore, this information has also expanded our understanding of macroreentrant arrhythmias in general. In this regard, the AV nodal–dependent SVTs, with their discrete anatomic components, can be viewed as the “schoolmaster” of reentrant arrhythmias. Since then, volumes have been written about the preexcitation syndromes, their accompanying SVTs, and AV nodal reentrant tachycardias (25,26,27 and 28).

These tachycardias also provided the substrate for the first foray into nonpharmacologic therapy for arrhythmias. In the late 1960s, several institutions (29,30) attempted to interrupt APs as a definitive cure for SVT. The first successful division of such a pathway by Sealy et al. (30,31) in 1968 permanently cured a North Carolina fisherman of his recurrent palpitations, firmly established the reentrant nature of AP–dependent arrhythmias, and ushered in the era of nonpharmacologic management of cardiac arrhythmias. Since then, several thousand APs have been surgically interrupted (32,33,34,35,36 and 37).

Building on lessons learned from such surgical interruption of APs, drug therapy for these arrhythmias has been largely supplanted by development of closed-chest, catheter-based ablation of these reentrant circuits. In the early 1980s, ablation of the AV conduction system using direct current energy was applied to patients with AV nodal–dependent tachycardias in whom drug therapy had failed (38,39). Obviously, this approach cured the AV nodal–dependent arrhythmia at the expense of permanent pacemaker dependency. Nevertheless, success with this technique provided incentive for developing the tools to ablate APs directly. Radiofrequency (RF) ablation, originally applied in 1987 (40), has been further refined by a number of investigators (41,42,43,44,45 and 46) and applied to tens of thousands of patients with AV reentrant and other AV nodal–dependent tachycardias. Because of the high success rates and low accompanying risk, this approach has nearly replaced drug therapy as the mainstay of treatment for AV nodal–dependent arrhythmias. Each of these historic milestones marks important progress in both our understanding of these arrhythmias and the development of effective clinical management strategies.

ANATOMIC CONSIDERATIONS

Atrioventricular Conduction System

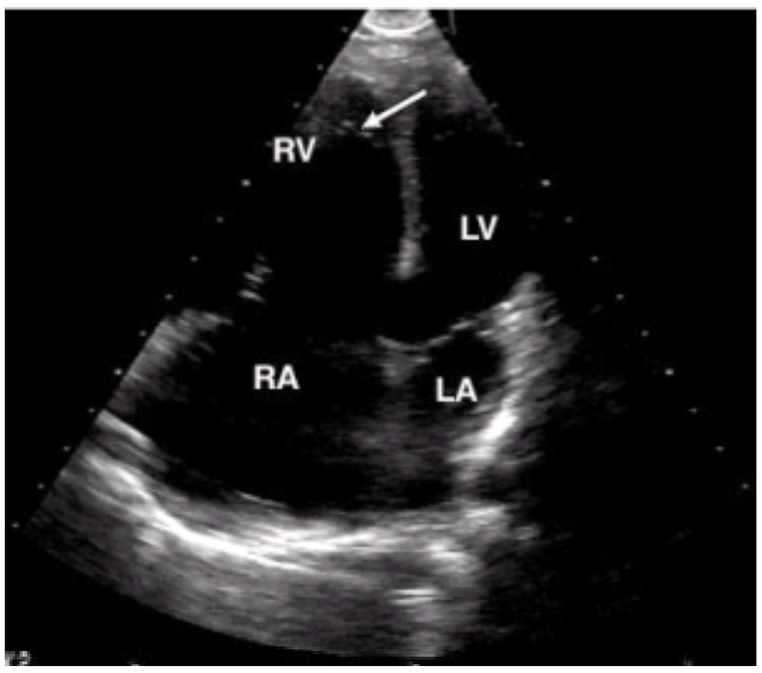
The occurrence of an AV nodal–dependent reentrant tachycardia, like other classic reentrant arrhythmias, requires two anatomically distinct components or pathways to create the tachycardia circuit (4). By definition, the first is the AV nodal conduction system. The AV node is a dense, compact subendocardial structure located in the low, medial portion of the right atrium at the apex of Koch's triangle (47,48,49 and 50), which, in turn, is formed by the septal component of the tricuspid valve annulus, the coronary sinus orifice, and the tendon of Todaro. The bundle of His arises from the distal extent of the AV node and penetrates the superiormost membranous interventricular septum to divide into right and left bundle branches with septal components. Conduction in most AV nodal–dependent tachycardias travels anterogradely through this AV conduction system to produce the classic narrow QRS complex seen on the ECG.

Microscopically, the N cells of the compact AV node are connected to atrial tissue by relatively distinct regions of transitional cell inputs located in the posterior aspect of the AV node along the tricuspid annulus near the coronary sinus orifice, in the anterior and superior aspect of the node near the origin of the bundle of His, and from the left side of the intraatrial septum entering the compact node on its medial aspect. Conduction in the AV node is driven by inward calcium currents and highly modulated by both sympathetic and parasympathetic nerve input, which accelerate or slow conduction, respectively.

Unlike AV nodal tissue, propagation in the His-Purkinje system critically depends on large-amplitude inward sodium currents and is less effectively modulated by autonomic nerve inputs.

Accessory Pathways

APs involved as the retrograde limb of the AV reentrant tachycardia circuit are formed by minute, electrically conducting muscle bundles that transverse the AV groove. These pathways establish a nonnodal avenue for AV or VA electrical propagation across the mitral and tricuspid annuli, which otherwise electrically isolate the atria from the ventricles. These fibers may cross the AV groove directly, proceed on an angle, or in some cases arborize with one or more branch points before insertion into either ventricular or atrial muscle (51,52,53 and 54). Whether atrial or ventricular muscle tissue comprises the AP remains unclear. The observation that APs follow Ebstein's malformation of the tricuspid valve to the anatomic left heart in patients with transposition of the great arteries suggests that the tissue is more likely to be of a ventricular origin.



Ebstein's anomaly of the tricuspid valve. Note marked apical displacement of the tricuspid leaflets, especially the septal leaflet. The arrow designates the septal leaflet of the tricuspid valve.

With the exception of the region near the anterior fibrous trigone between the aortic and mitral valves, which is usually void of APs, these AV connections are distributed anywhere along the mitral or tricuspid annuli. As noted in Figure 66.3, surgical and catheter ablation studies have demonstrated that, on average, 55% of these AV connections serve as a bridge between the left atrium and ventricle in a free wall location. Furthermore, 25% are in the posteroseptal region, 15% are in a right free wall location, and 5% are in the anteroseptal region (33,35,36 and 37,41,43,44 and 45,55). In addition, 7% to 15% of patients may have more than one AP (24,41,43,44 and 45,56,57,58 and 59). More recently, a unique AP involving a connection between the right atrial appendage and right ventricle has been described (60,61,62 and 63). This type of AP may be difficult to ablate with standard techniques endocardially, and successful catheter ablation with a percutaneous epicardial instrumentation approach has been described (61).

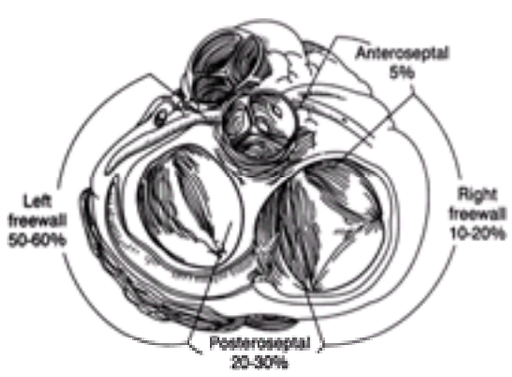


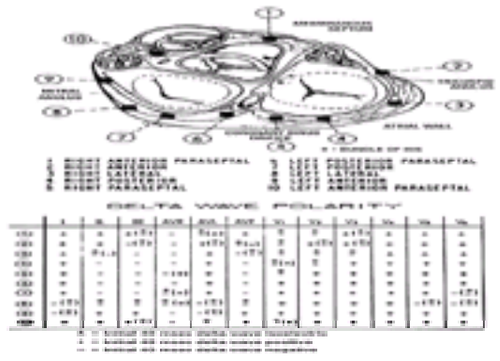
FIGURE 66.3 Distribution of accessory pathways (APs) around the mitral and tricuspid annuli. The left free wall position is the most common AP location.

Of all pathways described in reported studies of typically symptomatic patients, 2% to 3% conduct in an anterograde direction only, whereas 20% to 31% conduct in the retrograde/ventricular-to-atrial direction only (41,43,44 and 45,64). These connections are referred to as *concealed APs*. The mechanism of such concealment is further related to atrial and ventricular anatomy or the characteristic electrical properties of conduction through the pathway. Several investigators (65,66) have demonstrated that under certain circumstances, the electrical activity propagating from a small volume of tissue, or "source," into a narrow isthmus of tissue such as AP may be inadequate to bring a larger volume of tissue such as the ventricles, or "sink," to threshold. A potential explanation of this phenomenon is related to the curvature of the wavefront emerging from an AP. Cabo et al. (67) demonstrated a critical relationship between the dimension of the isthmus and the likelihood of bringing a larger "sink" region of tissue to threshold. With small isthmus dimensions, curvature of the wavefront substantially increases, and conduction velocities decrease. These conditions, in turn, may lead to anterograde conduction block out of the isthmus. Propagation into the electrically narrowest of pathways conceivably may increase curvature of the wavefront, leading to anterograde block and therefore concealment. In contrast, wider and effective sources of ventricular activation may produce overt preexcitation.

An alternative mechanism for concealment of a pathway is related to the preferential spread of electrical activation from the normal AV conduction system across the ventricle, and retrogradely into the AP, thus preventing anterograde impulse conduction through the pathway to the ventricle (26,68,69 and 70). The effects of tissue architecture, fiber orientation, and cell-to-cell coupling in the region of the AV grooves undoubtedly further produce directional differences in electrical conduction.

The specific anatomic location of an AP may be inferred from a variety of clinical and electrophysiologic indicators. The most readily available of these is the delta-wave morphology inscribed on the surface ECG. Rosenbaum and colleagues (71) first identified variations in anatomic location based on the precordial QRS morphology and

divided WPW syndrome into type A, with a large R wave in surface lead V_1, and type B, with S or QS morphology in this same lead. Giraud et al. (72) subsequently speculated that the type A pattern was due to posterobasilar preexcitation of the left ventricle, whereas type B was due to right ventricular preexcitation. A variety of different algorithms have since been developed to predict more specifically the anatomic location of single pathways with anterograde conduction based on the surface ECG (73,74,75,76,77 and 78). The earliest of these, developed by Gallagher et al. (64), is shown in *e*Figure 66.3.1.



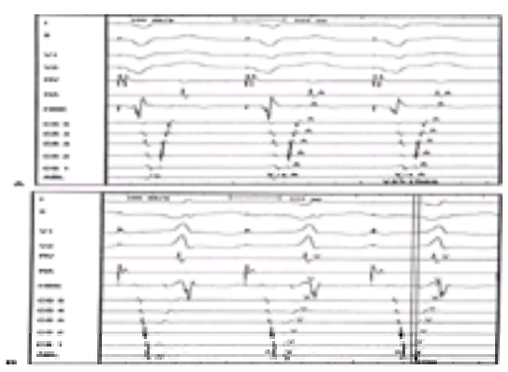
***e*FIGURE 66.3.1** Electrocardiogram algorithm for predicting the location of an accessory pathway based on surface electrocardiogram delta-wave morphology. (From Gallagher JJ, Pritchett EL, Sealy WC, et al. The preexcitation syndromes. *Prog Cardiovasc Dis* 1978;20:285–327, with permission.)

Similarly, pathway location can be discerned from the morphology of the retrograde P wave, when evident. Garcia et al. (79) have shown that a positive P-wave morphology in lead V_1 during SVT is suggestive of a left free wall pathway, whereas a negative deflection is more consistent with a right-sided pathway. Tai et al. (80) have developed a stepwise algorithm for predicting AP location with an accuracy of 88% based on retrograde P-wave morphology in leads I, II, III, aVF, and V_1.

The specific anatomic pathway location is more precisely identified by the earliest site of retrograde atrial activation during tachycardia or ventricular pacing on electrophysiologic testing. As shown in *e*Figure 66.3.2, the location of a free wall AP capable of retrograde conduction is suggested by the presence and site of eccentric atrial activation during tachycardia (22,64). Under normal circumstances, retrograde atrial activation produced by ventricular pacing proceeds through the normal VA conduction system and initially activates concentrically the low, medial aspect of the right atrial septum. All other atrial activation occurs after atrial depolarization at that midline site. In patients with free wall APs, earliest retrograde atrial activation during tachycardia or ventricular pacing emerges from the atrial insertion of the AP. This activation is said to be *eccentric*, or anatomically removed from the midseptal region of the atria. Because this type of atrial activation can be seen with a free wall atrial tachycardia, other markers of pathway presence and participation in the tachycardia must also be established at electrophysiologic testing.

***e*FIGURE 66.3.2** Recording of atrioventricular reentrant tachycardia in a patient with a left free wall accessory pathway. Shown are surface leads I, II, and V_1, as well as intracardiac leads from the right ventricular apex (RVA), high right atrium (HRA), bundle of His region (HBE), and the proximal (P) and distal (D) coronary sinus (CS). An eccentric sequence of retrograde atrial activation with earliest local depolarization along the left free wall is present. Here, the ventriculoatrial interval from the onset of the surface QRS to the local atrial activation is the shortest, as is the local ventriculoatrial conduction time.

More specifically, the pathway site is indicated by the shortest VA conduction time as measured both from the onset of the surface QRS to the earliest atrial depolarization and the point of minimum local conduction time between ventricular and atrial deflections as recorded from a mapping catheter positioned at that site (*e*Fig. 66.3.3). This information is supplemented by the site of earliest ventricular activation and the shortest local AV conduction time during normal sinus rhythm, atrial pacing, or atrial fibrillation, indicating the site of the anterogradely preexciting pathway (*e*Fig. 66.3.3).



***e*FIGURE 66.3.3** Localization of a left free wall pathway during ventricular and atrial pacing. Shown are surface leads I, II, V_1, V_2, and intracardiac electrograms from the right ventricle (RV), right atrium (RA), bundle of His region (HBE) from five pairs of coronary sinus (CS) electrograms, and at the sites of successful pathway ablation (ABL). **A:** Ventricular pacing at cycle length of 500 ms. Again, an eccentric sequence of retrograde atrial activation is seen with a local ventriculoatrial conduction time of 15 ms at the pathway site. **B:** Atrial pacing at a comparable cycle length with moderate preexcitation. The earliest local ventricular activation is seen along the distal CS and precedes the onset of the surface QRS by 20 ms.

PHYSIOLOGIC MECHANISMS OF ATRIOVENTRICULAR NODAL–DEPENDENT TACHYCARDIAS

Tachycardia Initiation

AV nodal–dependent tachycardias require not only the appropriate anatomic substrate for reentry, but also an initiating event. In most cases, initiation is related to the occurrence of atrial or ventricular extrasystolic activity that conducts into and blocks in one of the anatomically distinct components of the reentrant circuit (19,68). An APC, for example, may enter and block within an AP capable of bidirectional conduction (Fig. 66.4). If ventricular activation occurs through the normal AV conduction system, followed by return retrograde atrial activation over the AP back toward the interatrial septum and the AV node, the reentrant circuit is completed. As such, both ventricular and atrial tissue are critical components of the reentrant tachycardia circuit in this arrhythmia. Completing this circuit may be facilitated by delay within the AV node in response to the APC, allowing additional time for the AP to recover before the return impulse arrives at the ventricular end of the pathway (81). Isoproterenol or other adrenergic enhancement may be required to initiate tachycardia in those cases in which AV node conduction under baseline conditions

precludes the onset of arrhythmia.

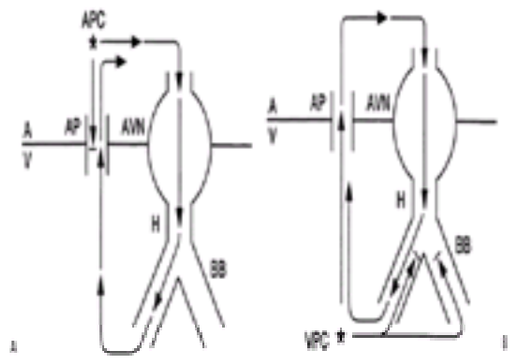


FIGURE 66.4 Initiation of atrioventricular (AV) reentrant tachycardia with an atrial premature complex (APC) or ventricular premature complex (VPC). **A:** APC that conducts into and blocks within the accessory pathway (AP). Additional conduction through the normal AV conduction system followed by return retrograde atrial activation through the AP leads to reentrant arrhythmia. **B**: Similar initiation with a VPC that first blocks retrogradely in both sides of the His-Purkinje system. Subsequent retrograde atrial activation through the AP with return conduction through the normal AV conduction system completes the reentrant circuit. AVN, atrioventricular node.

AV reentrant tachycardia can also be initiated by a ventricular premature complex (VPC) or pacing. Here, the initiating VPC typically blocks retrogradely in both sides of the His-Purkinje system, conducts to the atrium through the AP, and completes the circuit by reactivating the ventricles through the normal anterograde AV conduction system, as shown in Figure 66.4 (82,83).

Tachycardia Maintenance

Although ventricular activation occurs rapidly through the His-Purkinje system, the distance of the AP from the bundle of His region dictates that the time from onset of the surface QRS to the local atrial activation at the site of the pathway, referred to as the *VA interval*, must be at least 65 to 70 ms (64,84). For this reason, the ECG correlate of this VA interval, the “RP” interval, from the onset of the QRS complex to the P wave is usually more than 80 ms in duration. This specific VA activation time predicts that the inscription of the retrograde P wave will occur early in the ST segment or on the upslope of the T wave of the surface ECG, closer to the preceding than the succeeding QRS complex, as shown in Figure 66.5. If the RP interval is less than 50% of the RR interval from one QRS complex to the next, the tachycardia is considered to be a short RP tachycardia (Fig. 66.6).

FIGURE 66.5 Narrow complex supraventricular tachycardia due to an atrioventricular reentrant mechanism. Note the retrograde P waves inscribed in the inferior and precordial ST segments and the short RP tachycardia appearance.

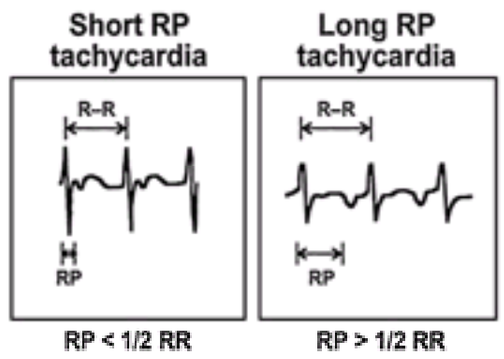
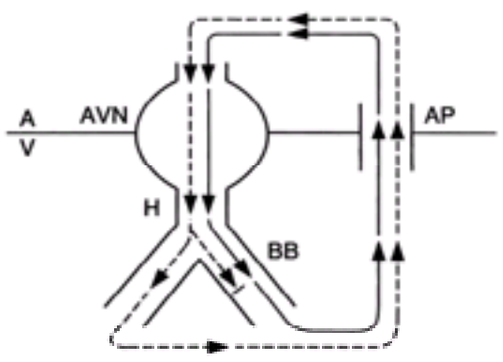
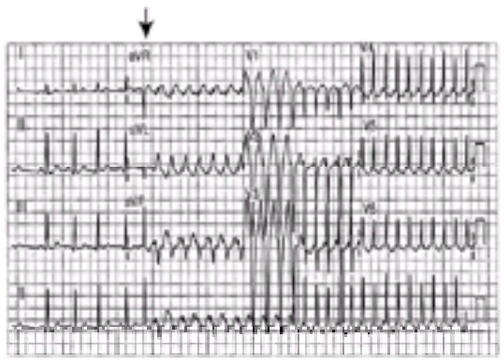


FIGURE 66.6 Classification of short and long RP tachycardias. The left panel shows a retrograde P wave in tachycardia that occurs closer to the preceding than succeeding QRS. Supraventricular arrhythmias with such an RP interval of less than 50% of the RR interval are designated “short” RP tachycardias. The right panel shows a retrograde P wave closer to the following QRS due to prolonged retrograde conduction time. An RP interval longer than 50% of the RR cycle length qualifies as a “long” RP tachycardia.

These VA or RP intervals during tachycardia typically use an AP and are relatively constant. An important exception to this is the more than 35-ms prolongation of the VA interval seen with the emergence of bundle branch block ipsilateral to the AP during the AV reentrant arrhythmia, as shown in *e*Figure 66.6.1 (85,86), because ventricular activation in the presence of bundle branch block must proceed through the contralateral bundle branch, with subsequent slower transseptal conduction and return propagation to the ventricular origin of the AP through ventricular muscle. For example, patients with left free wall pathways who develop left bundle branch block show classic prolongation of the VA interval during tachycardia. The alternative is true in patients with right free wall pathways who develop right bundle branch block. Unless this activation slowing is offset by reciprocal acceleration of conduction through the normal AV conduction system, the tachycardia in such patients is slowed. Conversely, acceleration of the tachycardia with abrupt resolution of bundle branch block, as seen on the surface ECG in *e*Figure 66.6.2, is virtually pathognomonic for an AP-related tachycardia. In contrast, patients with posteroseptal pathways show VA interval changes of 10 to 30 ms only with the emergence of left bundle branch block, whereas patients with anteroseptal pathways may develop a comparably limited VA interval change during onset of right bundle branch block (85).

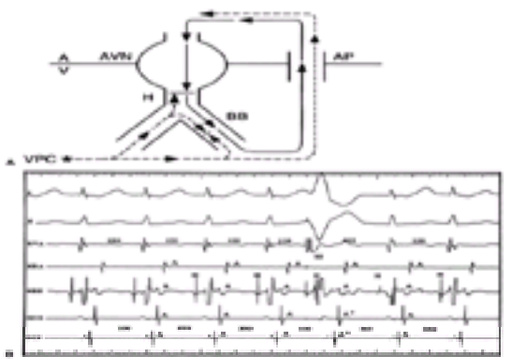


***e*FIGURE 66.6.1** Change in the ventriculoatrial (VA) interval with development of bundle branch (BB) aberration during tachycardia. During normal conduction (*solid line*), the interval from the onset of the surface QRS to the earliest retrograde atrial activation (VA interval) is at least 70 ms because of the component conduction properties. With BB block ipsilateral to the pathway, the additional conduction time due to transseptal and intramyocardial propagation (*dashed line*) to the accessory pathway (AP) prolongs the retrograde VA conduction time. AVN, atrioventricular node; H, bundle of His.



***e*FIGURE 66.6.2** Electrocardiogram showing transition from left bundle branch block to normal QRS supraventricular tachycardia. Atrioventricular reentrant tachycardia with left bundle branch block morphology begins with an atrial premature complex (*arrow*). Midway through the V_1 to V_3 precordial leads, the left bundle branch block resolves, resulting in a decrease in tachycardia cycle length from 300 to 250 ms (200 to 240 beats/min). This is indicative of tachycardia using an ipsilateral or left free wall accessory pathway.

An additional indication of an AP that is participating in a narrow QRS complex tachycardia that can be elucidated on electrophysiologic testing is based on the response to VPCs introduced during the tachycardia. An AP is present if a VPC introduced late in the tachycardia diastolic interval advances or preexcites retrograde atrial activation without changing the atrial activation sequence (87,88). As shown in *e*Figure 66.6.3, such advancement occurs through an AP, because the VPC cannot retrogradely penetrate the AV node or bundle of His, as the immediately preceding anterograde impulse during tachycardia placed these tissues into a state of refractoriness. Furthermore, termination of tachycardia by a premature impulse at a time when the bundle of His is refractory that does not produce retrograde atrial activation must occur within ventricular or His-Purkinje tissue, thus establishing such tissue as critical components of the reentrant circuit. This is even stronger evidence that narrow complex tachycardias critically depend on an AP as their retrograde limb (26,27 and 28).



***e*FIGURE 66.6.3** Retrograde atrial preexcitation with a ventricular premature complex (VPC) introduced during atrioventricular (AV) reentrant tachycardia. Panel **A** diagrammatically shows a VPC introduced from the right ventricular apex (RVA), which collides retrogradely (*dashed line*) in the His-Purkinje system with an anterograde impulse (*solid line*) from the previous tachycardia cycle. Retrograde atrial activation thereafter proceeds exclusively through the accessory pathway (AP), advancing the tachycardia circuit. **B:** Intracardiac tracings demonstrating an AV reentrant tachycardia with a cycle length of 350 ms. With the introduction of a critically timed VPC (S_2) at a coupling interval of 235 ms, retrograde atrial activation (*asterisk*) is advanced by 20 ms without altering the atrial activation sequence. Note that the VPC occurs at a time when the bundle of His (H) is refractory. Shown are surface leads I and II as well as intracardiac leads with a similar configuration, as shown in *e*Figure 66.3.2 and *e*Figure 66.3.3. AVN, atrioventricular node; BB, bundle branch.

Physiology of Preexcitation

When the AV reentrant tachycardia occurs in a patient with early or “preexcited” anterograde ventricular activation through the AP during normal sinus rhythm, a delta wave and a short PR interval are evident on the surface ECG (Fig. 66.7), and the criteria for WPW syndrome are met (8). The degree of accompanying preexcitation observed on a surface 12-lead ECG, however, depends on relative local ventricular activation proceeding through the normal AV conduction system versus that through the AP. This in turn depends on the relative time required for a propagating impulse from the sinus node to reach and traverse the AV node and His-Purkinje system or the AP (*e*Fig. 66.7.1). The additional activation time required to reach an AP well removed from the sinus node along the far left lateral region of the mitral annulus decreases the likelihood of expressing ventricular preexcitation during normal sinus rhythm with this pathway location. In the setting of increased sympathoadrenergic tone as that which accompanies exercise, ventricular activation through the normal AV conduction system is enhanced and can precede that which occurs through the AP (*e*Fig. 66.7.1). During such circumstances, no or minimal ventricular preexcitation may be evident. At the other extreme, ventricular activation through the pathway, yielding moderate or marked preexcitation, may be more evident with pathways closer to the sinus node or in those conditions in which conduction through the AV node is slowed by intrinsic nodal factors, withdrawal of sympathetic tone, or heightened vagal tone (*e*Fig. 66.7.1). In some cases, the rapid intravenous (i.v.) administration of 6 to 12 mg of adenosine as a diagnostic maneuver exposes an anterograde AP by blocking or slowing AV node conduction (89,90). As such, the presence and degree of ventricular preexcitation in patients with WPW syndrome depend dynamically on a variety of different factors, chief of which is the autonomic modulation of the AV node.

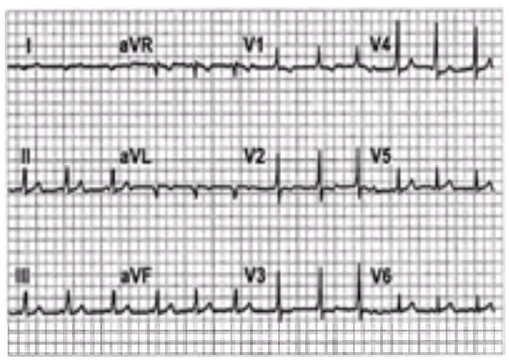
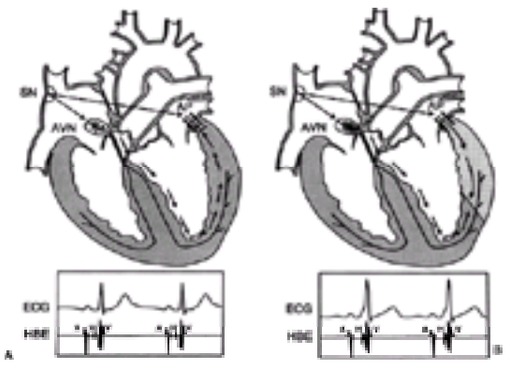
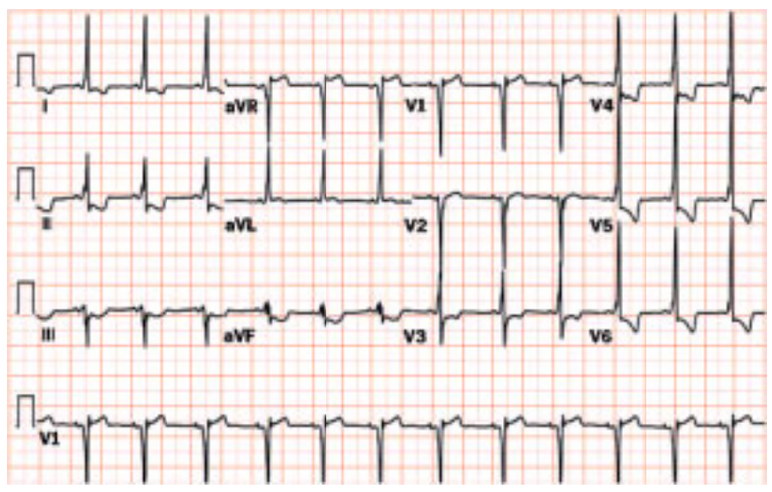


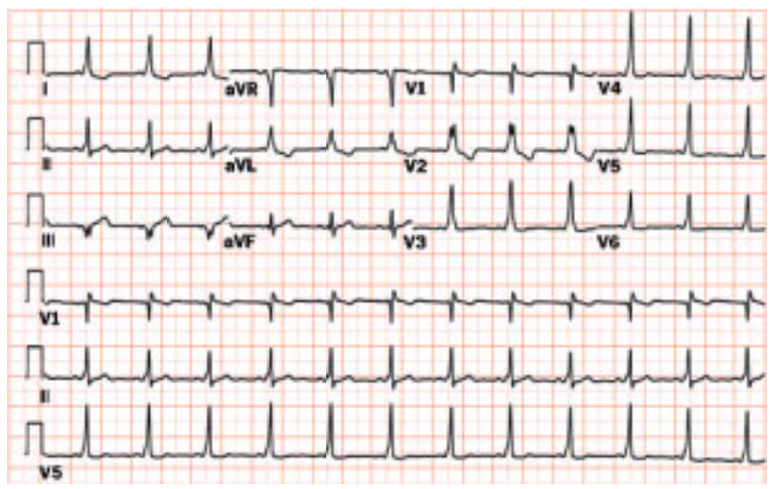
FIGURE 66.7 Electrocardiogram with ventricular preexcitation across a left free wall accessory pathway. Note the widened QRS complex with a slurred upstroke and a shortened PR interval consistent with a diagnosis of Wolff-Parkinson-White syndrome.



***e*FIGURE 66.7.1** Variable preexcitation dependent on relative conduction through the atrioventricular (AV) node and accessory pathway (AP). **A:** Minimal preexcitation in the setting of enhanced AV nodal conduction and an accessory pathway distant from the sinus node (SN). Prolonged conduction time to this site provides a relative advantage to ventricular activation through the AV node. Note the normal AV interval of 40 ms on the diagrammatic electrogram **(inset)**. **B:** Moderate to marked preexcitation related to relatively greater ventricular activation through the accessory pathway. Here, conduction time through the AV node is prolonged, yielding a relative advantage for conduction through the accessory connection. The His deflection occurs after the onset of ventricular activation through the pathway. A, atrial electrogram; AVN, atrioventricular node; ECG, electrocardiogram; H, bundle of HIs; HBE, bundle of His electrogram; V, ventricular electrogram.

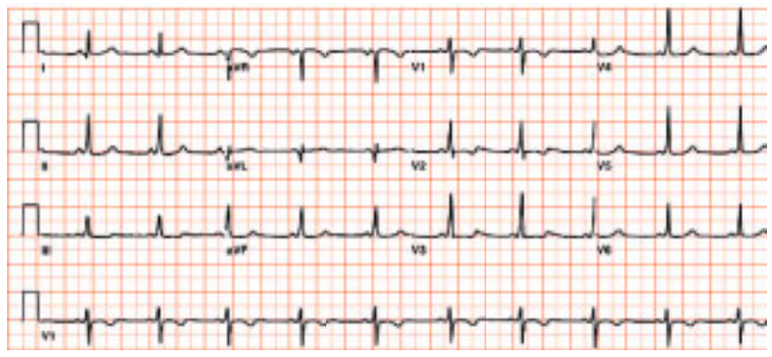


Wolff-Parkinson-White syndrome. Eleven-year-old patient with manifest preexcitation consistent with Wolff-Parkinson-White.

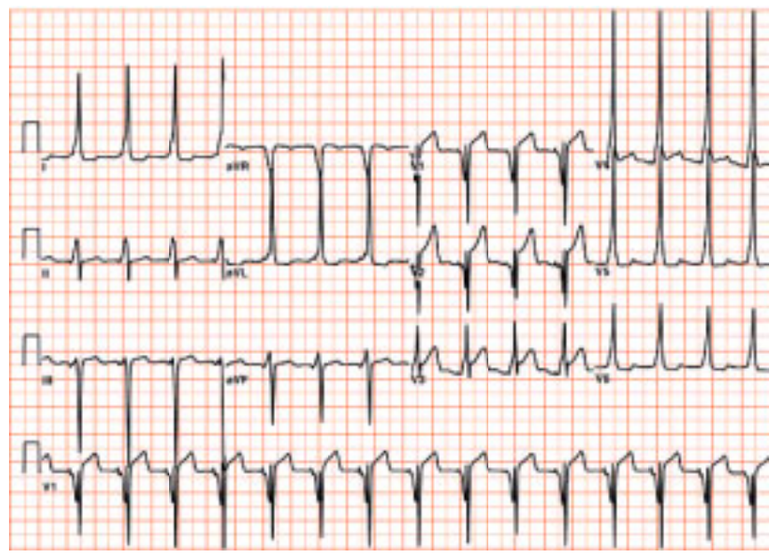


Wolff-Parkinson-White syndrome. Note short PR interval with classic delta wave due to accessory pathway conduction.

Intermittent delta wave. Intermittent conduction via accessory pathway is noted (*arrow*).



A 44-year-old female patient with Wolff-Parkinson-White syndrome.



A 16-year-old male patient with Wolff-Parkinson-White syndrome.

The degree of preexcitation can also be enhanced with atrial pacing, as performed on electrophysiologic testing (28). With pacing directly over the AP, inherent intraatrial conduction delay from the sinus node to the atrial origin of the AP is eliminated. In addition, increments in rapid atrial pacing rates increase preexcitation by progressively slowing or decrementing conduction within the normal AV conduction system. The QRS complex thereby becomes more preexcited unless block in the AP occurs and the QRS complex narrows as conduction proceeds exclusively through the normal AV conduction system.

Preexcited Atrioventricular Nodal–Dependent Tachycardias

Although most AV nodal–dependent tachycardias use the AV conduction system as the anterograde limb of the tachycardia circuit, the reentrant circuit is reversed in the presence of antidromic reciprocating tachycardia, as seen in Figure 66.8. With this arrhythmia, the AV node is the requisite retrograde limb of the circuit, and ventricular activation proceeds through the AP, producing maximum QRS preexcitation (Fig. 6.9). This tachycardia can be induced on electrophysiologic testing in 6% to 8% of patients with an AP (55,91,92 and 93), although only 2% to 3% of patients clinically develop this arrhythmia (55,91,93).

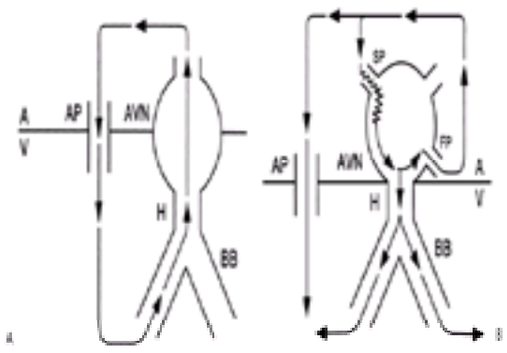


FIGURE 66.8 Mechanisms of preexcited atrioventricular (AV) nodal–dependent tachycardias. **A:** Antidromic reciprocating tachycardia with anterograde conduction through the accessory pathway (AP) and retrograde atrial activation through the normal ventriculoatrial conduction system. **B:** AV nodal reentry with a classic mechanism involving anterograde conduction through the slow pathway (SP) and retrograde or return atrial activation through the fast pathway (FP). Preexcitation occurs because of additional bystander conduction through the neighboring AP. AVN, atrioventricular node; BB, bundle branch; H, bundle of His.

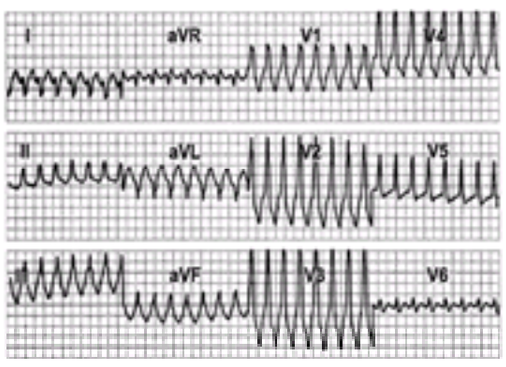


FIGURE 66.9 Antidromic reciprocating tachycardia with marked preexcitation. This electrocardiogram pattern occurs because of exclusive ventricular activation through the accessory pathway. Retrograde activation occurs through the normal ventriculoatrial conduction system.

AV nodal reentry with bystander conduction through a coexistent AP is a second preexcited AV nodal–dependent tachycardia. In this arrhythmia, perpetuation of the tachycardia depends on classic AV node reentry using anterograde and retrograde limbs found within or near the compact portion of the AV node. The wide or preexcited QRS morphology seen on ECG is due to concomitant ventricular activation through an AP. Ablation of the AP, although eliminating preexcitation, would not necessarily eliminate the tachycardia. Although AV nodal reentrant tachycardia may be seen in 10% to 20% of patients with an AP (94,95,96 and 97), concurrent anterograde conduction through an AP is seen in less than 2% of patients (96). When evaluating patients with these types of AV nodal–dependent tachycardias, alternative mechanisms of preexcited tachycardias such as any atrial tachycardia or flutter with ventricular activation through an AP should be considered. Well-defined criteria for differentiating these types of tachycardias from antidromic reciprocating tachycardia have been established (93,98).

Pathophysiology of Atrial Fibrillation

Regardless of whether a patient has antidromic tachycardia, the greatest concern in patients with WPW syndrome is the possibility of onset of atrial fibrillation with a rapid ventricular response rate and further degeneration into ventricular fibrillation. This requires both the onset of atrial fibrillation and the propensity for rapid conduction through the pathway. Although atrial fibrillation may develop as an isolated or primary process in WPW patients, the disorganization of AV reentrant tachycardia is a more likely mechanism for its occurrence in patients with an AP (99,100 and 101). In one-third of patients, atrial fibrillation arises in the region of the AP during AV reentrant tachycardia (99). This raises the possibility of disorganizing reentrant wavelets within the pathway apparatus itself. Atrial fibrillation, however, emerges more frequently at a distance from the pathway (99,100 and 101). Even in these patients, the presence of the rapid, pathway-dependent tachycardia produces electrophysiologic changes in the atria that facilitate the onset of atrial fibrillation. Rate-dependent decreases in atrial refractoriness along with additional increases in the inhomogeneity of electrophysiologic properties accompanying the increasing left and right atrial pressures observed during tachycardia have been reported. In this regard, rapid tachycardia that uses an AP appears to contribute to the onset of atrial fibrillation but is not always sufficient for atrial fibrillation to emerge. The role of the AP or tachycardia in this process is also inferred from the substantial reduction in clinical atrial fibrillation after curative surgical or catheter-ablative procedures (102,103,104 and 105). Evidence that AV reentrant tachycardia is not mandatory for onset of atrial fibrillation, however, is the occurrence of atrial fibrillation in patients who do not have AV reentrant tachycardia and in whom pathways are capable of only anterograde conduction (103).

CLINICAL PRESENTATION

General Considerations

Screening 12-lead ECG studies reveal that 1.0 to 1.5 in 1,000 patients demonstrate preexcitation. Population-based studies (106) have suggested that 50% to 60% of these patients show symptoms ranging from palpitations to syncope. In others, tachycardia may be accompanied by dyspnea, decreased exercise tolerance, chest pain or tightness, anxiety, dizziness, presyncope, or syncope. The latter is more likely in AV nodal reentrant tachycardia in which atrial and ventricular contractions accompanying respective electrical activation occur nearly simultaneously. Atrial contraction at the time of mitral valve closure may limit cardiac output and be accompanied by increases in right and left atrial pressure. These increases in turn may precipitate a posttachycardia diuresis due to release of atrial paracrine factors such as atrial natriuretic peptides. Of those patients with symptomatic arrhythmias, 85% have underlying AV reentrant tachycardias that use the AP as a retrograde limb (28,55,64). Only 2% to 3% of patients show clinical antidromic reciprocating tachycardia (93,107,108), whereas 30% to 40% of patients develop atrial fibrillation (55,64,109,110,111 and 112).

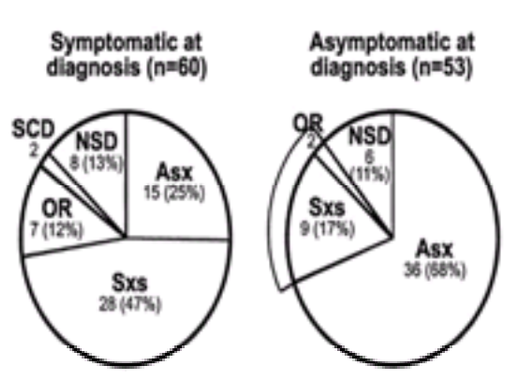
Unlike most ventricular tachycardias, which occur in patients with pump dysfunction, most AV nodal–dependent tachycardias occur in the absence of any other organic heart disease. Any underlying process that does occur, such as mitral valve prolapse or hypertrophic cardiomyopathy, is therefore a chance occurrence. The one exception is coexistent Ebstein's malformation of the tricuspid valve and an AP (55,64,95). Of those patients with APs reported in larger studies (113,114), 7% to 10% have this coexistent structural abnormality. This finding is of clinical importance because these patients typically have a higher prevalence of multiple APs and the success rate of RF ablation in patients with tricuspid valve abnormalities is lower.

Natural History of Atrioventricular Reentrant Tachycardias

Predicting the likelihood and frequency of recurrent arrhythmias would be useful in deciding which patients should be treated for supraventricular arrhythmias. Unfortunately, the natural history of patients with AV nodal–dependent arrhythmias remains unestablished. Available data are limited and contradictory. Several small studies have suggested that recurrent tachycardia after a first event is common and is related to several factors. After monitoring 40 patients for an average of 24 years, Lundberg (115) established younger patient age at the time of diagnosis and the presence of preexcitation as predictors of recurrent tachycardia. For example, 65% of infants with manifest preexcitation had recurrent tachycardia. This was more common than the 46% incidence in youngsters aged 1 to 10 years, the 53% incidence in children older than 10 years, or the 50% incidence of tachycardia in those patients in their third decade of life. In contrast, of those patients studied who had no ventricular preexcitation, 46% of infants, 6% of children aged 1 to 10 years, 9% of children older than 10 years, and 25% of patients in their third decade of life had recurrent tachycardia. In another longitudinal study, Chen et al. (116) followed 113 older patients over a 9-year period and found that the original tachyarrhythmias disappeared over time in 10% of patients, whereas 15% developed other arrhythmias, and 38.5% of patients developed atrial fibrillation. This latter occurrence was significantly more likely in those with manifest anterograde pathway conduction. In still another study of recurrent tachycardia (117), 17 of 31 patients showed a decrease in frequency of tachycardia, five had more frequent episodes, and nine patients reported no clear change over the course of 21 years of follow-up. Fifteen of these patients also continued to show ECG preexcitation during normal sinus rhythm.

In contrast, in a review of patients with symptomatic SVTs, Clair et al. (118) found that older patients were more likely to suffer recurrent episodes of tachycardia. Of 57 patients younger than 38 years, 30% suffered a recurrent episode of premature SVTs in the first 30 days of follow-up. In contrast, nearly 70% of the 56 older patients suffered a recurrent episode of arrhythmia over the same period. These findings are similar to those described by other investigators (119).

Population-based studies, however, suggest a substantially lower rate of recurrent arrhythmia. In an analysis (106) of 113 patients with WPW syndrome in Olmsted County, Minnesota, 60 (53%) were symptomatic at the time of first diagnosis. Over the course of 11.8 years of long-term follow-up, 28 (47%) remained symptomatic, 15 (25%) became asymptomatic, and seven (12%) required surgery (eFig. 66.9.1). The difference between this study and others reflects differences between general populations of patients and those selected by increasing symptoms requiring referral for medical evaluation.



***e*FIGURE 66.9.1** Long-term follow-up in a population-based evaluation of Wolff-Parkinson-White syndrome. The left panel shows the outcome in 60 patients with symptoms at the time of diagnosis of Wolff-Parkinson-White during long-term follow-up. The right panel shows follow-up over 1,338 patient-years in 53 patients who were asymptomatic at the time of initial diagnosis of Wolff-Parkinson-White. Asx, asymptomatic; NSD, noncardiac sudden death; OR, surgery; SCD, sudden cardiac death; Sxs, symptomatic. (From Munger TM, Packer DL, Hammill SC, et al. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953–1989. *Circulation* 1993;87:866–873, with permission.)

In contrast, other patients with APs remain asymptomatic throughout life (120,121). In examining the persistence of preexcitation in 63 asymptomatic patients with ECG delta waves, Leitch et al. (120) demonstrated a 95% probability of remaining arrhythmia-free and a 50% loss of preexcitation over 232 patient-years of follow-up (average, 3.6 years). Similarly, in a population-based study involving 1,338 patient-years of follow-up, Munger et al. (106) demonstrated that only 11 of 53 (21%) patients who were asymptomatic at the time of initial diagnosis developed symptoms over time (eFig. 66.9.1), whereas 36 (68%) remained symptom-free. Consistent with the findings of Leitch et al. (120), Munger et al. (106) also demonstrated that an asymptomatic patient older than 40 years was highly unlikely to develop progressive symptoms thereafter.

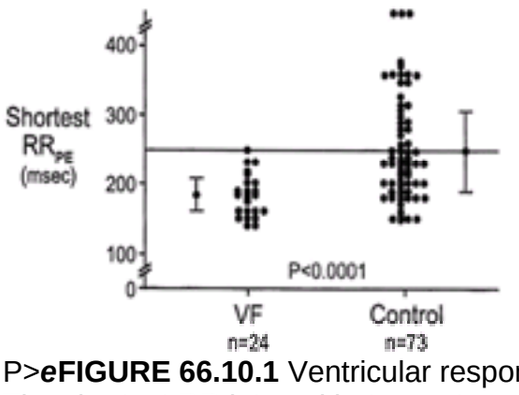
Therefore, taken together, these data suggest several characteristics of patients likely to have recurrent tachycardias. First, the bimodal distribution of symptomatic arrhythmia predicts an initial decrease in symptoms during childhood followed by an increase in tachycardia in young adulthood. Second, the presence of anterograde conduction through an AP increases the likelihood of recurrence. Third, although 25% of patients become asymptomatic over time, more than one-half of patients with an episode of AV reentrant tachycardia will experience a recurrence. Fourth, arrhythmia occurrence is unlikely to occur in asymptomatic patients with no preexcitation, particularly those older than 40 years. Obviously, more extensive longitudinal studies are required to establish the accuracy of any of these or other predictors.

Risk Stratification in Patients with Wolff-Parkinson-White Syndrome

Atrial fibrillation occurs in 30% to 40% of patients with WPW syndrome. Of greatest concern is the propensity of rapid conduction through the AP with accompanying risk for atrial fibrillation degenerating into ventricular fibrillation (Fig. 66.10). The degree of risk is related in part to the symptom status of the patient at the time of initial evaluation. In symptomatic patients from tertiary referral centers, the prevalence of patients with a history of aborted sudden cardiac death (SCD) is 2% to 11% (64,106,122). In contrast, population-based studies (106) demonstrate a lower incidence of SCD—0.0015 events per patient year, or approximately 0.15% per year—occurring exclusively in previously symptomatic individuals. Several other studies (106,120) have also shown that patients who are asymptomatic at the time of diagnosis are unlikely to suffer a subsequent cardiac arrest. This is related to relatively benign AP conduction capabilities in these patients (63,120,123).

FIGURE 66.10 Atrial fibrillation with a rapid ventricular response rate during Wolff-Parkinson-White syndrome. Initial atrioventricular reentrant tachycardia degenerates into atrial fibrillation (*arrow*). The shortest RR interval in this case was 240 to 250 ms, which indicates an increased risk for sudden cardiac death.

A variety of testing methods have been proposed for stratifying the risk for atrial fibrillation degenerating into ventricular fibrillation, including ambulatory recordings, exercise testing, and the response to drugs. The most direct method of assessment is the actual induction of atrial fibrillation and determination of the propensity for rapid conduction as judged by the interval between consecutively preexcited QRS or "RR" complexes. Klein et al. (124) showed that those patients who survived a prior episode of ventricular fibrillation had the shortest preexcited RR intervals (i.e., less than 250 ms in duration) (eFig. 66.10.1). Although this has been regarded as a highly sensitive marker for risk, it is of lower specificity. As such, the positive predictive value of this finding is only 20% over short-term follow-up. On the other hand, the shortest preexcited RR interval of more than 250 ms has a negative predictive value of more than 95%. Other indicators of risk include an average RR interval during atrial fibrillation of 360 ms or less (125). A posteroseptal AP with accompanying rapid AV conduction capability and prior atrial fibrillation also suggests a higher risk (122,125).



P>***eFIGURE 66.10.1*** Ventricular response intervals in patients with ventricular fibrillation (VF) and without a history of VF and aborted sudden cardiac death (control). The shortest RR interval between two consecutive complexes was 250 ms or less in patients with a history of VF. Intervals of more than 250 ms occurred exclusively in those patients with no history of VF. (From Klein GJ, Bashore TM, Sellers TD, et al. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *N Engl J Med* 1979;301:1080–1085, with permission.)

Other findings on noninvasive testing, if present, indicate a lower risk for SCD. The demonstration of intermittent preexcitation on a 12-lead ECG or ambulatory monitor strip as shown in Figure 66.11 indicates the presence of precarious conduction through an AP (126). It must be noted, however, that the term *intermittent preexcitation* specifically denotes the *abrupt* loss of preexcitation from one beat to the next on a rhythm strip or ECG; it cannot be extended to include the loss of preexcitation on an ECG from one office visit to the next. Depending on the effect of autonomic tone on AV nodal conduction, ventricular activation may proceed exclusively through the normal AV conduction system, thus masking the anterograde conduction capability of the pathway on an ECG. The next ECG, if obtained at the time of heightened parasympathetic tone, alternatively may show increased preexcitation due to preferential ventricular activation through the pathway. This variability is of no predictive value and is of particular concern in patients with left free wall pathways in which the distance of the pathway from the sinus node decreases the chance of manifest preexcitation.

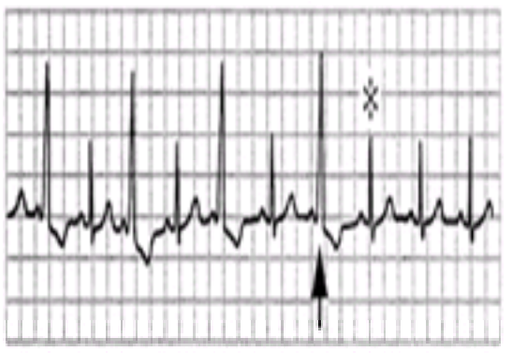


FIGURE 66.11 Rhythm strip showing intermittent preexcitation in a patient with Wolff-Parkinson-White syndrome. Both preexcited (*arrow*) and nonpreexcited (*asterisk*) QRS complexes are seen. Note the loss of QRS preexcitation from one beat to the next.

Exercise testing has also been proposed as a means of identifying patients with long AP refractoriness (127,128). Although several groups have shown that the *abrupt* loss of preexcitation during exercise (Fig. 66.12) is indicative of a low propensity for rapid conduction through an AP, this is an infrequent finding. Preexcitation more frequently disappears gradually during exercise because of enhanced conduction through the normal AV conduction system. Because of the low likelihood of an abrupt loss of preexcitation on exercise testing, persistent preexcitation during exercise testing is reasonably sensitive for identifying patients at risk for an untoward event. Unfortunately, the specificity for excluding those who are not at risk is less than 30%, which is substantially less than that of the shortest RR interval between two preexcited QRS complexes of 250 ms or less. Furthermore, the predictive accuracy of exercise testing is even lower than possible with the induction of atrial fibrillation (128).

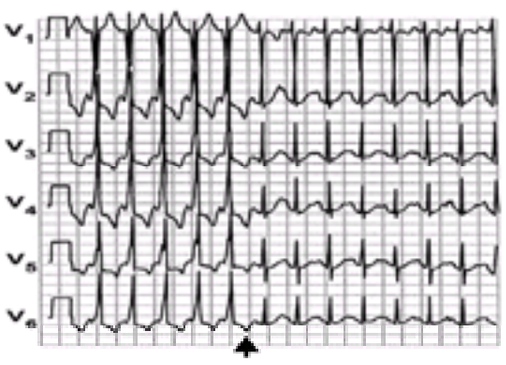


FIGURE 66.12 Electrocardiogram rhythm strip of leads V_1 to V_6 recorded during exercise in a patient with a left free wall accessory pathway. With an increasing workload, an abrupt loss of preexcitation (*arrow*) was seen. This indicates a low-risk pathway. Gradual loss of preexcitation accompanying exercise-induced enhancement of atrioventricular nodal conduction is of no prognostic significance.

Others have reported the use of drug testing measures to stratify risk. This is based on the presumption that the loss of AP conduction with administration of an agent such as procainamide or ajmaline (129,130) indicates a low-risk pathway. Again, however, findings using such testing maneuvers appear to be falsely reassuring (28,128,130,131). In a previous report (130), the response to 10 to 12 mg per kg of procainamide in 56 patients with WPW syndrome failed to support infusion of this medication for establishing risk. Risk stratification is discussed in greater detail in other studies (28).

The most direct means of stratifying risk in symptomatic patients is initiation of atrial fibrillation. This can be performed in a relatively noninvasive way with atrial pacing using an esophageal lead (90,132,133). In those patients in whom risk stratification is important, this allows direct determination of risk at the level of ventricular response rate during atrial fibrillation. This is preferable to using surrogate indicators of risk available on ambulatory recordings or exercise testing or to the response to drugs that only indirectly predict pathway effective refractoriness or ventricular rates in atrial fibrillation.

Furthermore, the overall risk of an untoward event in an asymptomatic patient is clearly not zero but appears to be sufficiently low that additional evaluation of asymptomatic individuals showing ventricular preexcitation on 12-lead ECG is unnecessary (134). The risks associated with drug or ablative therapy in these patients may be equal to or greater than the risks associated with an underlying AP. Potential exceptions to this include patients with a family history of SCD, competitive athletes, and patients with high-risk occupations whose performance may be unacceptably impaired by the unlikely occurrence of tachycardia or atrial fibrillation, with or without rapid ventricular response rates. In contrast, symptomatic patients, particularly those with a history of atrial fibrillation, are at higher risk for more rapid conduction through an AP during atrial fibrillation and warrant further evaluation (109,112,125).

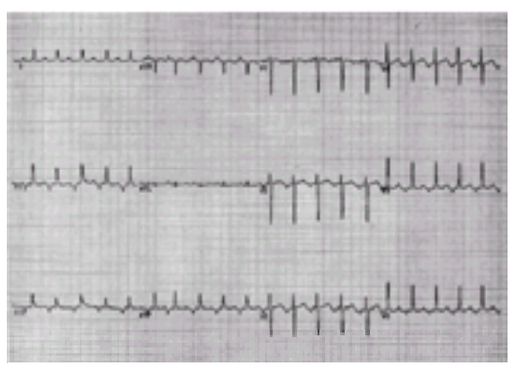
PREEXCITATION VARIANTS

Unlike the more classic presentations seen in most patients with WPW syndrome, other individuals have arrhythmias related to atypical APs with distinctive anatomic and physiologic characteristics. The most common of these are PJRT and preexcited tachycardia related to atriofascicular fibers. The hallmark of these preexcitation variants is the presence of unusual APs that show node-like or decremental electrical conduction properties. Here, progressively slower conduction across the pathway occurs with faster stimulation rates.

PERMANENT JUNCTIONAL RECIPROCATING TACHYCARDIA

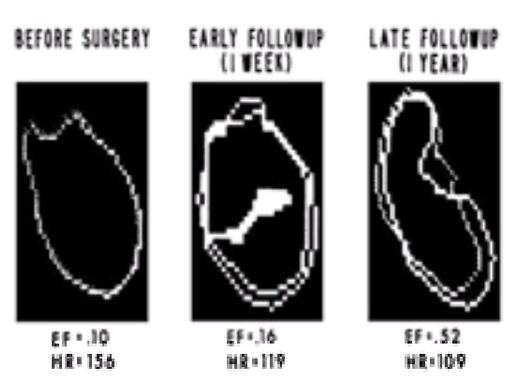
Most patients with PJRT have posteroseptal APs within 1 cm of the coronary sinus orifice (25,135,136), although free wall pathway locations have been described (136,137). Like more typical APs, these connections also participate as the retrograde limb of an AV nodal–dependent tachycardia. In addition to characteristic decremental conduction properties, these pathways also have a long circuitous route from ventricle to atrium, contributing to prolongation of retrograde conduction times (138,139). These pathways also appear to conduct in the retrograde direction only, although several instances of emergent anterograde conduction and more classic ventricular preexcitation have been reported after ablation of the normal AV conduction system (140). This suggests that preablation anterograde conduction into the pathway is blocked in part by retrogradely concealing penetration of impulses into the pathway from the ventricular end of the normal AV conduction system during sinus rhythm. Unlike typical reentrant tachycardias, this arrhythmia may occur spontaneously with alterations of the sinus rate without preceding APCs or VPCs. In such cases, return conduction through the AP and subsequent reactivation of the anterograde AV nodal limb of the circuit perpetuate the tachycardia (25,135).

Slow reverse VA conduction results in inscription of the retrograde P wave in late diastole or closer to the succeeding QRS than the preceding QRS, as shown in eFigure 66.12.1 (25,135). The finding of an RP interval of more than 50% of the RR tachycardia interval invokes the descriptor, long RP tachycardia. Because the low atrial septum is most frequently the first site of atrial activation, P waves during PJRT are typically negative in leads II, III, and aVF, indicating a low-to-high retrograde atrial activation sequence.



***e*FIGURE 66.12.1** Twelve-lead electrocardiogram showing tachycardia in a patient with permanent junctional reciprocating tachycardia. Inspection of leads II, III, and aVF demonstrate the presence of a long RP tachycardia with negative P waves indicative of a low- to high-atrial activation sequence.

Many patients with this process develop rapid, nearly incessant, tachycardias, hence the designation PJRT. Because of the incessant nature of the tachycardia, the development of a tachycardia-induced cardiomyopathy (eFig. 66.12.2) that resolves after elimination of the pathway is not uncommon (141). Other patients with this type of pathway show only frequent paroxysmal junctional reciprocating tachycardia.



***e*FIGURE 66.12.2** Serial radionuclide studies demonstrating resolution of a tachycardia-induced cardiomyopathy in a patient with permanent junctional reciprocating tachycardia. The ejection fraction (EF) was initially 10% but showed progressive improvement to 52% 1 year after interruption of the accessory pathway. HR, heart rate. (From Packer DL, Bardy GH, Worley SJ, et al. Tachycardia-induced cardiomyopathy: a reversible form of left ventricular dysfunction. *Am J Cardiol* 1986;570:563–570, with permission.)

Atriofascicular (Mahaim) Reentrant Tachycardias

Another type of tachycardia, referred to as *atriofascicular*, or *Mahaim, reentrant tachycardia*, is due to a similar decrementally conducting AP located in the right anterior or anterolateral aspect of the tricuspid annulus. When first described (142,143), these pathways were believed to originate in the upper portion of the AV node, with distal insertion in the ventricle or right bundle branch system. lectrophysiologic studies (144,145) have demonstrated more recently that the vast majority of patients with left bundle branch block left-axis deviation Mahaim tachycardias have pathways located several centimeters away from the AV node, as suggested in Figure 66.13. Local His-like potentials are usually seen when recording immediately over this pathway site. As with the normal AV node, conduction in these pathways is strongly altered by adenosine or verapamil. This pathway, which also shows progressively longer conduction times at faster pacing rates, inserts into the right bundle branch system (146), giving a left bundle branch block left-axis deviation QRS morphology on the surface ECG during tachycardia (eFig. 66.13.1). In addition, small,

sharp R waves are typically seen in lead V_1, and the transition from negative to positive QRS morphology seen in the precordial leads typically occurs after V_4 (108). Like antidromic reciprocating tachycardias, the VA conduction system serves as the retrograde limb of this circuit. Because of its left bundle branch block appearance, this arrhythmia must be differentiated from other tachycardias with a left bundle branch block morphology, such as any atrial or AV nodal–dependent tachycardia with bundle branch aberrancy, antidromic tachycardias using a right free wall AP, right ventricular tachycardia as seen in patients with arrhythmogenic right ventricular dysplasia, and bundle branch reentrant ventricular tachycardias.

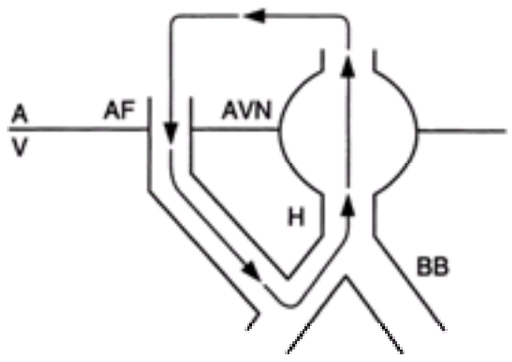
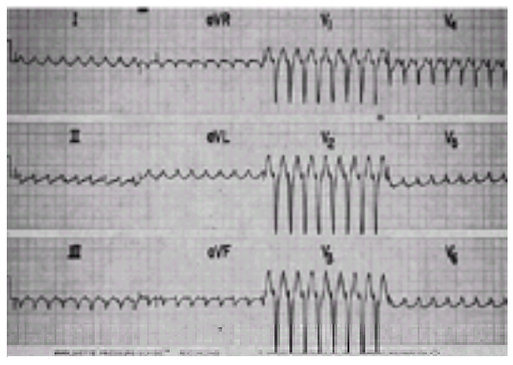


FIGURE 66.13 Mechanism of atriofascicular (AF) (Mahaim) reentrant tachycardias. Anterograde preexcitation typically occurs through a right anterolateral, decrementally conducting accessory pathway (AP) or AF pathway that inserts into the region of the right bundle branch (BB). Retrograde atrial activation occurs through the normal bundle of His (H) and atrioventricular (AV) node (AVN).



***e*FIGURE 66.13.1** Wide complex tachycardia through an atriofascicular fiber. Because of the distal insertion of the extra connection in the region of the right bundle branch block, the tachycardia shows a left bundle branch block left-axis–deviation morphology with small, sharp R waves in lead V_1. Note also the characteristic late transition of QRS complexes in the precordial leads.

Fasciculoventricular Mahaim Fibers

A final variant of the preexcitation syndromes is created by a fasciculoventricular Mahaim fiber (64). Here, a conducting strand of tissue bypasses the distal component of the His-Purkinje system, resulting in earlier ventricular activation than expected through the normal His-Purkinje network. This is manifested at the time of electrophysiologic testing by a shortened HV interval recorded on the bundle of His electrogram. Unlike with atriofascicular fibers, bundle of His pacing fails to eliminate this preexcitation because pacing at these sites is upstream from the site of the bypassing fiber.

ATRIOVENTRICULAR NODAL OR JUNCTIONAL REENTRANT TACHYCARDIAS

Anatomic Considerations

The most common mechanism of AV nodal–dependent tachycardia is AV nodal or junctional reentry, as shown in Figure 66.14. Approximately 60% (147,148 and 149) of all narrow QRS complex SVTs seen in the clinical setting are due to reentry within at least two parallel components in or near the AV nodal portion of the normal AV conduction system. The precise anatomic construction of these pathways remains a subject of controversy, with debate centering on the existence of common pathways both at the entry and exit points of the AV conduction system. It had been accepted that two pathways with differing conduction properties were confined to the compact portion of the AV node, as shown in Figure 66.14. Recently other investigators have argued that at least a portion of the circuit lies outside the compact region of the AV node, as shown in Figure 66.2B (42,49,150,151).

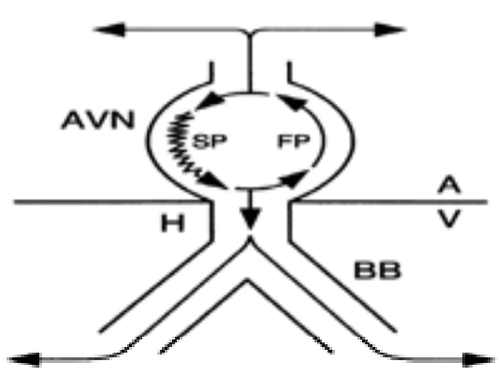


FIGURE 66.14 Microanatomy of atrioventricular (AV) nodal reentrant tachycardia. Here, dual physiologically or anatomically dissociated AV nodal pathways are confined to the compact portion of the AV node (AVN). Note the upper and lower final common pathways at the proximal and distal ends of the compact node. This is in contrast to the AV nodal reentrant circuit involving extranodal atrial tissue seen in Figure 66.2B, where the retrograde atrial activation proceeds through the fast pathway (FP), which exits near the distal portion of the compact AV node. A variable portion of the atrium is subsequently traversed by a reentrant impulse that then reenters the AV conduction system through a posterior slow pathway (SP). H, bundle of His.

In addition, early studies suggested that these functionally, if not anatomically, separate pathways joined at the upper and lower regions of the compact AV node to exit into the surrounding atrial or His-Purkinje tissue, respectively, through single, final, common pathways. This concept is supported by the uncommon occurrence of atrial dissociation from the remaining portion of the AV nodal reentrant circuit during tachycardia (147,152,153). Additional evidence for a final, lower, common pathway is found in the occurrence of dissociation of the ventricles from the tachycardia circuit, as well as the inability to retrogradely preexcite the atria when introducing a VPC at a time when the His-Purkinje system is refractory.

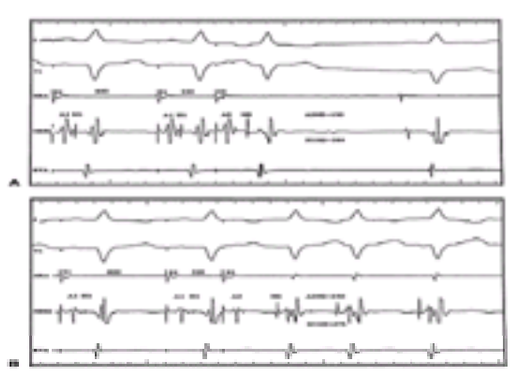
In contrast, other investigators (42) have argued that at least a component of the reentrant circuit lies outside the compact region of the AV node, passing through atrial tissue, as depicted in Figure 66.2B. The presence of a different retrograde atrial activation sequence with conduction through a fast pathway (FP) versus a slow pathway (SP) further argues against a final common upper pathway, as do recent pacing studies (154). Both surgical- and catheter-based studies have demonstrated that retrograde activation through the FP typically exits the compact portion of the AV node both anteriorly and superiorly to the distal portion of the AV node near the origin of the bundle of His. In contrast, earliest retrograde activation through the SP occurs 2 to 3 cm further posteriorly along the tricuspid annulus near the coronary

sinus orifice (42,49,150,151). Investigators have described an unusual occurrence of atypical AV nodal reentrant tachycardia with eccentric retrograde left-sided activation that may be confused with AV reentrant tachycardia using a concealed left AP. Interestingly, these tachycardias were cured with catheter ablation at the posteroseptal region of the right atrium (155). Catheter ablation of the AV nodal SP for typical AV nodal reentrant tachycardia from the left atrial septum via a transseptal approach when conventional right-sided techniques failed has also been described (156,157). Both left and right posterior extensions of the human compact AV node have been described from human autopsy studies and have been speculated to be involved in SP conduction (158).

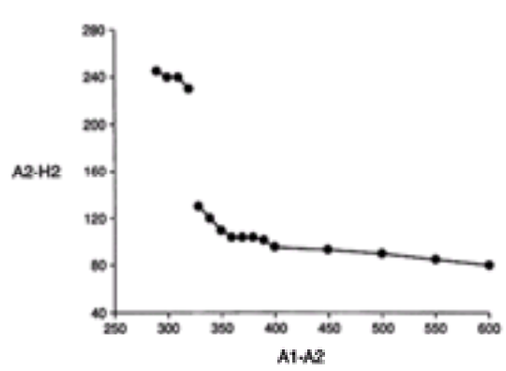
The response to extrastimulus testing has also been proposed as an indication of separate pathways connected by atrial tissue. The advancement of bundle of His activation with an APC introduced in the posterior part of the intraatrial septum near the coronary sinus orifice at a time when the anterior portion of the septum near the FP has already been activated suggests an atrial component of the circuit external to the AV node (42).

Physiologic Mechanisms

Regardless of the anatomy of the circuit, pacing studies clearly demonstrate physiologically discontinuous, or longitudinally separate, conduction through the two or more components of the involved AV conduction system (10,11,16,150,159,160). During sinus rhythm, during slow atrial pacing, or with the introduction of late coupled APCs, AV conduction typically occurs through the faster of the dual functionally or anatomically distinct AV nodal pathways. Here, conduction times are short, and the PR interval inscribed on the surface ECG may be less than 140 ms. With faster pacing or with the introduction of progressively earlier APCs, a critical point of refractoriness or effective recovery time within the FP is reached. With subsequent decrements in the timing of the APC, AV conduction switches to the “slower” component of the dual AV conduction system, typically with a more than 50-ms prolongation of the AH interval conduction time through the AV node, as shown in *e*Figure 66.14.1. This jump from the FP to the SP over a 10-ms decrease in the APC coupling time produces a discontinuity in the plot of the trans-AV nodal conduction time or the AH interval given as a function of the timing of the premature impulse or A_1 to A_2 interval (*e*Fig. 66.14.2); hence, the descriptor, *discontinuous conduction*. Some patients may have several discontinuities, suggesting multiple SPs. Furthermore, the presence of such conduction may not, in and of itself, be “abnormal,” because up to 70% of patients undergoing electrophysiologic testing who do not have clinical AV nodal reentrant tachycardia reportedly have such anterograde or retrograde conduction discontinuities (161,162 and 163).

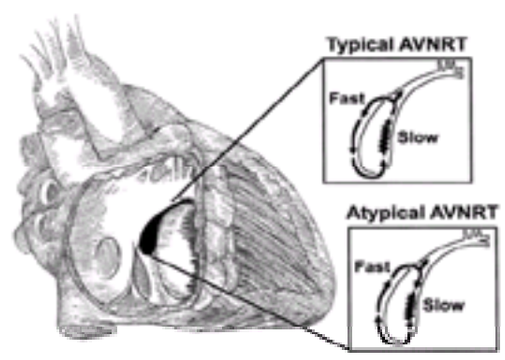


***e*FIGURE 66.14.1** Intracardiac tracings showing dual atrioventricular (AV) nodal physiology and initiation of AV nodal reentrant tachycardia. Lead configurations are similar to those seen in *e*Figure 66.3.2 and Figure 66.3.3. An atrial premature complex introduced with an A_1 to A_2 interval of 330 ms conducts through the fast pathway **(A)**. **B:** With a 10-ms decrement to 320 ms, block is followed by conduction through the slow pathway and a 100-ms prolongation of the A_2 to H_2 interval. Thereafter, AV nodal reentrant tachycardia with a ventriculoatrial interval of 40 ms is observed. HBE, bundle of His region; HRA, high-right atrium; RVA, right ventricular apex.



***e*FIGURE 66.14.2** Discontinuous atrioventricular (AV) nodal conduction curves resulting from dual AV nodal physiology. The abrupt prolongation in the A_2 to H_2 interval with a decrease in the A_1 to A_2 interval from 320 to 310 ms, which indicates a jump from the AV nodal fast pathway to slow pathway is readily apparent. Some patients may have multiple discontinuities, which indicates more than one slow pathway.

In 85% to 95% of patients, a slow/fast–type AV nodal–dependent tachycardia is seen in which the SP with the longest conduction time of the two AV nodal tracts comprises the anterograde limb of the reentrant circuit. This pathway is typically encountered in or near the posterior aspect of the compact portion of the AV node. Return or retrograde impulse propagation, as shown in *e*Figure 66.14.3, proceeds through the FP with a shorter conduction time located in the anterior and medial aspect of the compact portion of the AV node near the origin of the bundle of His. The inscription of a rapid electrogram deflection immediately after local atrial activation during sinus rhythm along the posterior aspect of the tricuspid annulus near the coronary sinus orifice has been shown to emanate from the SP. Similarly, a high-frequency deflection can also be observed before atrial activation during retrograde conduction through the SP (41). The exact origin of these potentials is unclear, however, as they may also result from the specific atrial architecture underlying the posteroseptal region (164,165 and 166).



***e*FIGURE 66.14.3** Mechanisms of typical slow/fast and atypical fast/slow atrioventricular nodal reentrant tachycardia (AVNRT). **Top inset** shows anterograde conduction occurring through the slow pathway with return retrograde atrial activation through the fast pathway. The completion of the return portion of the circuit occurs simultaneously with or shortly after concomitant conduction through the His-Purkinje system to activate the ventricle. **Bottom inset** shows atypical fast/slow AVNRT in which the direction of the reentrant circuit is reversed. Because of the prolonged atrial activation times through the slow pathway, a long RP tachycardia is present.

In 3% to 20% of patients, the tachycardia circuit direction is reversed and a fast/slow or atypical type of AV nodal reentrant tachycardia is observed, as shown in *e*Figure 66.14.3 (16,167,168,169,170 and 171). In this case, anterograde conduction proceeds down the faster of the two pathways, with return activation through the SP. Given the potential of multiple SPs and therefore multiple discontinuities, the circuit involved in this atypical arrhythmia may not be the same as that involved in the

slow/fast type of AV nodal reentrant tachycardia seen in the same patient. Furthermore, up to 9% of individuals also display a slow/slow type of AV nodal reentrant tachycardia in which both anterograde and retrograde conduction occurs through such multiple SPs (14,151,160,169,170,172).

Initiation of Tachycardia

AV nodal reentrant tachycardia is most frequently initiated when a critically timed APC blocks in the FP with longer refractoriness and conducts through the SP. If the impulse then returns retrogradely to the atria through the FP, which has since recovered from the anterogradely conducting and blocking APC, the reentrant circuit is completed. This is facilitated by the substantive delay within the SP, giving the FP sufficient time to recover from the original block created by the APC (10,81,159,173,174).

AV nodal reentrant tachycardia is initiated less frequently by a VPC that conducts to the atria through the retrograde FP but reenters with return conduction through the SP (175). This mechanism of initiation is also more common in atypical or fast/slow AV nodal reentrant tachycardia. In such cases, retrograde activation after the VPC proceeds through the slower AV nodal pathway, with return ventricular activation through the faster of the dual AV nodal physiologic or anatomic pathways.

Presentation on Electrocardiogram

Because return atrial activation and P-wave generation during typical AV nodal reentrant tachycardia is rapid, the earliest atrial deflection on the bundle of His electrogram during tachycardia is usually less than 60 ms (84). Although such a short VA interval excludes the possibility of a reentrant tachycardia using an AP, longer VA intervals do not eliminate the possibility of AV nodal reentrant tachycardias that use an SP as the retrograde limb of the reentrant circuit. As such, a short VA interval for diagnosing all AV nodal reentrant tachycardias is not completely sensitive, although its positive predictive value is very high.

Therefore, a retrograde P wave is inscribed within or at the end of the QRS complex or ECG. This dictates that this arrhythmia is a short RP tachycardia (46,84,149,176,177). If the P wave occurs at the end of the QRS complex on the surface 12-lead ECG, a pseudo–R-wave deflection in V_1 not present during normal sinus rhythm may be seen, as shown in Figure 66.15 (80,176,177). This is a highly sensitive and specific indicator of AV nodal reentry as the mechanism for a narrow QRS complex tachycardia (80,149,177).

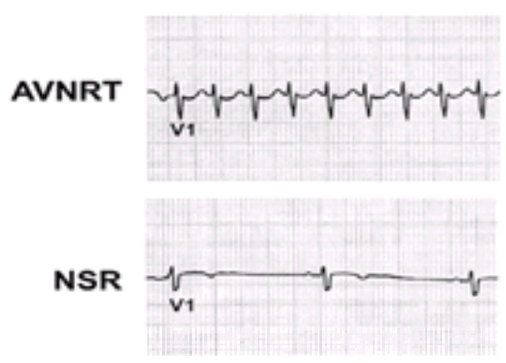


FIGURE 66.15 V_1 rhythm strips showing pseudo rSR' QRS configuration in a patient with atrioventricular nodal reentrant tachycardia (AVNRT). In the **upper panel**, the short ventriculoatrial conduction time during tachycardias results in inscription of the retrograde P wave at the end of the QRS complex, giving the “rSR prime” configuration. In the **lower panel**, normal sinus rhythm in the same lead shows resolution of that component. This is highly indicative of atrioventricular nodal reentry as the mechanism of the arrhythmia.

In contrast, atypical AV nodal reentrant tachycardia with retrograde conduction through the SP, such as PJRT, inscribes its retrograde P wave later in the RR diastolic interval, more closely coupled to the following QRS complex (42,148,168,170). Thus, criteria for a long RP tachycardia are met. By virtue of the posteroseptal site of retrograde atrial activation, retrograde P waves typically observed during this arrhythmia are negative in leads II, III, and aVF, again indicating a low-to-high atrial activation sequence.

This arrhythmia and PJRT must be distinguished from other long RP tachycardias (80,178). Sinus tachycardia, sinus node reentry, and a variety of atrial tachycardias in the absence of marked PR interval prolongation also show a close association between the P wave and the subsequent QRS complex. Given their AV nodal–independent mechanisms, these atrial tachycardias persist when higher-grade AV block occurs spontaneously or after vagal or drug interventions. Furthermore, many of these tachycardias show a high-to-low atrial activation sequence, unlike that seen with PJRT or atypical AV nodal reentry.

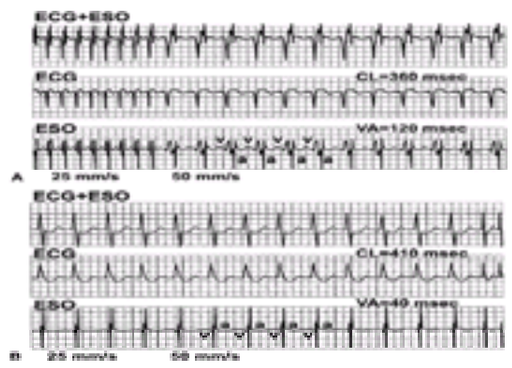
DIFFERENTIATING ATRIOVENTRICULAR NODE REENTRANT FROM ATRIOVENTRICULAR REENTRANT TACHYCARDIAS

Distinguishing AV reentrant from AV nodal or junctional reentrant narrow-complex tachycardias is important in planning therapeutic strategies for these tachycardias. An understanding of these aforementioned mechanisms provides the needed clues for such differentiation. It was once believed that both the tachycardia rate and the presence of QRS alternans were useful in establishing a diagnosis of AV reentrant tachycardia (149). Although AV reentrant tachycardias may be faster in some patients, the overlap in heart rates with these two mechanisms makes this factor unhelpful in establishing a diagnosis of AV reentrant tachycardia. Furthermore, the presence of QRS alternans, as shown in Figure 66.16, has since been shown to be a function of heart rate and not of the specific underlying mechanism (46).

FIGURE 66.16 QRS alternans during reciprocating tachycardia. Note the alternating amplitude of the R wave in leads V_1 and V_4. This is a rate-related process and is not predictive of the underlying mechanism.

The positions of the P wave and the RP intervals in tachycardia are more useful in distinguishing these two reentrant mechanisms (46,80,176,177). P waves inscribed within the ST or T segments observed in AV reentry (46,68,149,176,179,180) contrast with the even shorter RP intervals and accompanying P waves producing the r' in lead V_1, which is highly predictive of an AV nodal reentrant mechanism (80,176,177). Obviously, in some cases the P waves are not obvious on the surface ECG, and recordings using an esophageal lead are required to determine the RP or VA interval.

*e*Figure 66.16.1 shows representative tracings from patients with AV reentrant and AV nodal reentrant tachycardias. The patient in the left panel had a VA interval of 120 ms, consistent with retrograde conduction through an AP. In contrast, the right panel shows a VA conduction time of 40 ms, which is too short for occurrence through an AP. This was recorded from a patient with AV nodal reentrant tachycardia.



***e*FIGURE 66.16.1** Esophageal lead tracings in patients with atrioventricular (AV) reentrant and AV nodal reentrant tachycardias. Shown here are the surface electrocardiogram (ECG), esophageal (ESO), and combination ECG and ESO recordings at a paper speed of 50 mm per second. The retrograde ventriculoatrial conduction time is 120 ms in the patient with AV reentrant tachycardia seen in **(A)**. Panel **B** shows a retrograde ventriculoatrial conduction time of 40 ms in a patient with AV nodal reentrant tachycardia.

Finally, it should be noted that 10% to 20% of patients with WPW syndrome also have AV nodal reentrant tachycardia with a narrow QRS morphology (94,96,97,162,181,182). Therefore, the presence of a narrow QRS SVT in a patient with WPW syndrome does not necessarily indicate AV reentrant tachycardia. In these patients, clarification of the precise mechanisms of arrhythmias requires more detailed electrophysiologic evaluation.

PRINCIPLES OF MANAGEMENT

Short-Term Therapy for Narrow Complex Tachycardias

The dependence of both AV reentrant and AV nodal reentrant tachycardias on AV nodal conduction has important implications for the short-term management of patients with these arrhythmias. As reviewed in Figure 66.17, the simplest approach to tachycardia termination takes advantage of vagal modulation of AV nodal conduction. In many patients, a Valsalva maneuver, carotid sinus massage, or application of ice water to the face will terminate the tachycardia by increasing vagal tone. If these approaches prove unsuccessful, the use of drugs with significant negative dromotropic effects on the AV node may also readily terminate either type of SVT. Adenosine, administered in a rapid bolus at an initial dosage of 6 mg i.v. (Fig. 66.18), will terminate 62% of tachycardias, whereas 91% of these tachycardias respond to 12 mg of adenosine from a peripheral i.v. site (183). Alternatively, 5 to 10 mg of i.v. verapamil will terminate up to 90% of tachycardias (184,185 and 186). The high success rate of these i.v. drugs has supplanted the use of edrophonium (a short-acting cholinesterase inhibitor), phenylephrine, or beta-blockers, which had been used at one time for this purpose. Although i.v. esmolol, a short-acting beta-blocker, may also be effective, accompanying hypotension has been reported (187). The use of these drugs or of vagal maneuvers is also useful to the diagnosis because the development of higher-grade AV nodal block during tachycardia, as shown in Figure 66.1 and Figure 66.19, virtually excludes the presence of an AV nodal–dependent tachycardia. It should be noted that under rare circumstances AV nodal reentrant tachycardia may show 2:1 AV block due to physiologic impairment of infra-His conduction; however, this is unlikely to occur with vagal or drug interventions.

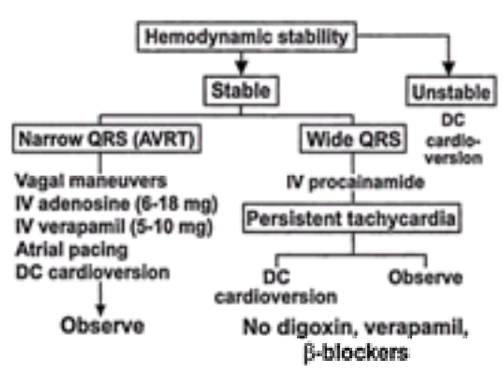


FIGURE 66.17 Algorithm for the acute management of patients with atrioventricular nodal–dependent tachycardias. AVRT, atrioventricular reentrant tachycardia; DC, direct current.

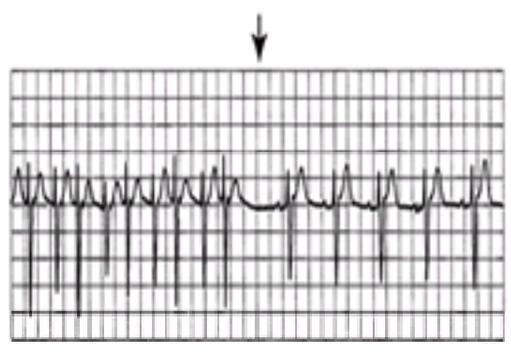


FIGURE 66.18 Termination of supraventricular tachycardia with adenosine. Twelve mg of adenosine given intravenously results in abrupt termination of narrow complex tachycardia in a patient with atrioventricular nodal reentry. Note the alternating tachycardia cycle lengths before termination.

FIGURE 66.19 Effect of carotid sinus massage on atrioventricular conduction in a patient with an ectopic atrial tachycardia. On the left side of the figure, a narrow QRS complex tachycardia was observed with a 1:1 atrioventricular relationship, as seen in leads V_1 to V_3. With carotid sinus massage, high-grade atrioventricular nodal block, which readily discloses the continuing atrial tachycardia, appears as 1:1 conduction and resumes after resolution of the carotid sinus massage effect.

Intravenous flecainide, propafenone, sotalol, or amiodarone may also prove effective in restoring sinus rhythm, although these drugs may take longer to produce

clinically relevant effects. Although i.v. ibutilide is effective in terminating the acute onset of atrial fibrillation and its class III properties may effectively block AP conduction, the safety and efficacy of this agent for treating narrow, complex AV nodal–dependent tachycardia have not been established. The same is true for dofetilide and azimilide, which have been studied almost exclusively in atrial fibrillation and atrial flutter, the latter of which is not available in i.v. forms in the United States.

Nonpharmacologic therapies for patients with narrow, complex SVTs are also available to restore normal sinus rhythm. Atrial pacing using an esophageal lead positioned behind the atria proves routinely effective in terminating AV nodal–dependent tachycardia (38,188,189 and 190). With this approach, current strengths of 10 to 20 mA with pulse widths between 10 and 20 ms may be required. Although this approach is effective, it also produces some esophageal discomfort and can initiate atrial fibrillation. Administration of a low-energy direct current shock to stop tachycardia is an alternative, but it is rarely required, given the efficacy of pharmacologic and other nonpharmacologic measures.

Short-Term Management of Wide-Complex Tachycardias

The presence of a wide QRS complex tachycardia warrants careful consideration of several additional issues. Although the prolongation of the QRS complex may simply represent aberrancy accompanying an AV nodal–dependent tachycardia, the diagnosis of ventricular tachycardia should be carefully considered. The presence of underlying coronary artery disease or prior myocardial infarction has an accuracy of more than 90% in predicting a ventricular mechanism for wide-complex arrhythmias (191). These issues are reviewed in greater detail in Chapter 60. An additional mechanism of wide QRS tachycardia in patients with AV nodal–dependent arrhythmias is that of an antidromic reciprocating tachycardia that uses an AP as its anterograde limb, atrial fibrillation, or other atrial tachycardias with ventricular preexcitation through the accompanying pathway. Each of these arrhythmias should be manifest by their characteristic slurred upstroke delta waves seen in the first 40 ms of the wide QRS complex. During atrial fibrillation with a rapid ventricular response rate, however, the characteristic preexcited QRS pattern may be difficult to discern. Preexcitation may be most evident in the QRS complexes after the longest RR intervals during irregular tachycardias. Ventricular activation during atrial fibrillation in patients with multiple APs may proceed by several alternating avenues, thus mimicking torsades de pointes on a single rhythm strip. As with evaluation of any wide-complex arrhythmias, a surface 12-lead ECG is indispensable in correctly identifying the underlying mechanism.

The short-term treatment of wide-complex tachycardia first and foremost depends on the patient's underlying hemodynamic status. In the presence of hemodynamic compromise, direct current cardioversion after appropriate anesthesia is warranted. It is not uncommon for direct current cardioversion to require at least 200 J to restore normal sinus rhythm in patients with WPW syndrome and atrial fibrillation. In the presence of stable hemodynamics, several different i.v. antiarrhythmic agents are available. Intravenous procainamide has been most widely used for this purpose. This agent not only alters propagation through the APs, but it may also directly restore normal sinus rhythm. Use of beta-blockers (187,192,193,194 and 195) and lidocaine (192,196,197) is not effective for either purpose. Intravenous propafenone, flecainide, and sotalol are effective in both slowing the ventricular response rate during atrial fibrillation and restoring normal sinus rhythm in patients with APs. These drugs, however, are not commercially available in the United States. Intravenous amiodarone is also effective, although the time to conversion with this agent may be longer, and the overall conversion rate may be low. Intravenous ibutilide may also restore normal sinus rhythm, although its safety and efficacy in this setting have not been documented.

Several i.v. agents can also accelerate AV conduction through an AP, causing atrial fibrillation to degenerate into ventricular fibrillation. Digoxin, although slowing atrial fibrillation in some patients, clearly accelerates the ventricular response rate in others (198). This deterioration has also been described after use of i.v. verapamil (199,200,201,202 and 203). A similar reduction in the shortest RR interval during atrial fibrillation has also been observed after i.v., but not oral, diltiazem (13). This acceleration may be due to direct pathway effects, enhancement of peripheral sympathetic activity related to the precipitation of hypotension, or the reduction in retrograde concealment into the AP by generation of higher-grade AV nodal block. In the presence of atrial fibrillation in a patient with an anterogradely conducting AP, ventricular activation proceeds through the pathway or the normal AV conduction system. The latter avenue of propagation may be accompanied by impulse propagation across the ventricle in a reverse direction into the pathway. This retrograde penetration or concealment blocks ventricular activation proceeding anterogradely through the pathway because of impulse collision. This produces a net effect of slowing ventricular activation. Higher-grade AV nodal block can reduce this beneficial effect by withdrawing retrograde concealment. Ventricular fibrillation after adenosine administration in a patient with WPW syndrome and atrial fibrillation has also been reported (204). Because of this and the potential hemodynamic deterioration of ventricular tachycardia, these drugs should not be routinely used in patients with wide-complex tachycardias. This does not mean that their use is prohibited in patients with narrow QRS complex tachycardias, although the possibility of degeneration of such arrhythmias into atrial fibrillation dictates that facilities dealing with such unlikely transitions should be available.

Long-Term Therapy for Atrioventricular Nodal–Dependent Tachycardias

Drug Therapy

In selecting appropriate therapy for patients with supraventricular arrhythmias, several general principles should be carefully considered. The inherent risk for untoward events accompanying the target arrhythmia, as well as its impact on the patient's quality of life, must be carefully weighed against the anticipated treatment's efficacy and accompanying risks. Furthermore, the effectiveness and risks, including side effects, of a given strategy must be carefully compared with those of other treatment options. In the case of increased risk for SCD in symptomatic patients with WPW syndrome, aggressive evaluation and treatment are warranted. Here, the risks of intervention are likely to be small compared with the risks associated with the underlying arrhythmia. These patients are best treated with definitive ablative procedures. This is in part because of the relatively limited efficacy of antiarrhythmic therapy on AP conduction in those patients with the most rapid underlying conduction capabilities (205). This is a particularly true of class Ia antiarrhythmic agents.

In contrast, in the absence of a propensity for rapid anterograde conduction through an AP during atrial fibrillation or of marked neurologic symptoms, such as presyncope or syncope, the majority of AV nodal–dependent tachycardias are relatively benign. As such, therapy is warranted if prevention of symptomatic arrhythmia improves quality of life and can be accomplished without undue risk to the patient. The benefit of achieving such arrhythmic suppression must be weighed against possible side effects, the proarrhythmic risk from drug therapy, or complications from ablation. In those cases of single or infrequent tachycardia episodes with relatively mild symptoms, expectant observation without treatment or with sole use of vagal maneuvers to terminate tachycardia, where effective, may suffice. In such cases, ablative therapy is unnecessary. Patients with frequently recurring palpitations clearly related to an AV nodal–dependent tachycardia, those with problematic, associated cardiac or central nervous system symptoms, those in whom drugs are either ineffective or accompanied by side effects, or individuals facing lifetime medical therapy are best treated with catheter ablation. The exception to this approach is those patients in whom the risks associated with catheter ablation may be greater than the risk of the underlying arrhythmia. For example, patients with an AP located close to the normal AV conduction system in which the risk for high-grade or complete heart block is high may be better treated with medical therapy. Obviously, if such therapy proves ineffective or if the patient is at risk for SCD the potential complications of catheter ablation may be unavoidable to provide symptomatic relief and protection for the patient.

Other patients will benefit from the more readily available drug therapies. In the absence of anterograde preexcitation or atrial fibrillation, patients with AV reentrant tachycardia may be effectively managed using calcium channel blockers, such as verapamil or diltiazem (13,206,207 and 208), or any one of a number of beta-blockers (187,193) that target the AV node, as shown in Figure 66.20. The latter may be useful in those patients with exercise-related tachycardia. These agents are also effective in modifying conduction within the SP in AV nodal reentrant tachycardia and within the AP involved in PJRT or atriofascicular reentrant tachycardia. Efficacy rates of 40% to 50% in eliminating or significantly reducing the frequency of AV nodal–dependent tachyarrhythmias have been reported. Furthermore, the risk for proarrhythmia using these agents is very low and most of these drugs can be administered in single daily doses.

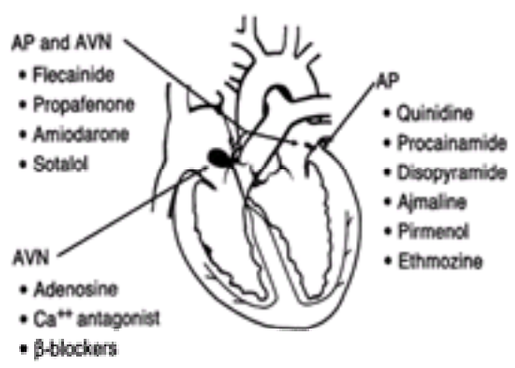


FIGURE 66.20 Antiarrhythmic drug effects in patients with Wolff-Parkinson-White syndrome. Shown here are drugs with exclusive accessory pathway (AP) effects, with exclusive atrioventricular nodal (AVN) actions, and with both AP- and AVN-modifying properties. Pharmacologic modulation of the fast pathway in AVN reentrant tachycardia is similar to that of an AP. The slow pathway behaves in a manner similar to that of AVN tissue.

In contrast, class Ia agents such as quinidine (209,210), procainamide (209,210 and 211), or disopyramide (212,213) produce beneficial effects on the AP but not on the normal AV conduction system. Other class I agents such as propafenone (214,215,216 and 217), flecainide (218,219,220,221 and 222), and moricizine and class III drugs such as sotalol (223,224,225 and 226) and amiodarone (71,227,228,229,230 and 231) have demonstrable effects on both the AV conduction system and the AP (Fig. 66.20). Because the FP used as the retrograde limb of AV nodal reentrant tachycardia has many properties similar to those of APs, class I agents also produce beneficial effects on both the frequency and severity of this arrhythmia (208,232,233,234,235 and 236). Class Ic and class III drugs may also sufficiently modify the anterograde SP to reduce the occurrence of arrhythmias. These agents produce additional beneficial effects in patients with either type of AV nodal–dependent arrhythmia by reducing tachycardia-induced atrial or ventricular ectopy. Regardless of the specific underlying mechanism, the efficacy of these agents in treating AV nodal–dependent arrhythmia is 60% to 80% over short-term follow-up.

The choice of a specific membrane-active antiarrhythmic agent for use in patients with AV reentrant tachycardia depends on several factors. These include (a) the presence or absence of structural heart disease or other organ system problems; (b) the presence of preexcitation; and (c) the side effect profile of a given agent, including organ toxicity, negative inotropic effects, and propensity for proarrhythmias. In the absence of underlying heart disease, any one of the class Ic, III, or Ia drugs may be effective in managing AV reentrant tachycardias. Of these, flecainide, propafenone, disopyramide, and sotalol are less likely to produce organ toxicity or nuisance side effects. In this setting, the risk of a proarrhythmic event is low and ranges from 0.5% to 2.0%. In the presence of underlying heart disease, those agents such as disopyramide and flecainide, and to a lesser extent, propafenone and sotalol, that may have significant negative inotropic effects, should be used with caution, if at all. Although these agents are not absolutely contraindicated in patients with EFs of 30% to 45%, the presence of congestive heart failure should dictate an alternative choice of therapy. In the presence of congestive heart failure or prior myocardial infarction, amiodarone is least likely to produce a proarrhythmic effect. The risk for proarrhythmia with other class I and class III drugs may be as high as 5% to 8%, particularly with the class Ia agents producing significant QT interval prolongation in the presence of underlying heart disease. Specific drug therapy for these tachycardias and dosing strategies are reviewed in greater detail in other studies (26,27 and 28).

Nonpharmacologic Therapy: Radiofrequency Ablation

Although drug therapy was the mainstay of treatment for AV nodal–dependent tachycardias for many years, the advent and improvement of surgical techniques in the 1970s ushered in an era of nonpharmacologic therapy. Those patients with an AP who were at risk for SCD, those in whom antiarrhythmic therapy had failed because of inefficacy or side effects, or those patients who faced lifelong medical therapy were increasingly managed with surgical ablation. During the past 6 years, even this approach has been replaced by RF ablation. As described in greater detail in Chapter 73, success rates of 90% to 98% are routinely possible (41,43,44). A 5% to 8% recurrence rate of AP conduction nevertheless may occur (41,43,44). This ablative approach is accomplished at low risk, and the benefits to patients are achievable at lower cost and substantially less hospitalization and recovery times than are possible with surgical ablation. Hence, RF ablation is a reasonable first-line modality in patients with recurrent arrhythmias. Again, potential exceptions to this approach are encountered in patients who are at higher risk for complete heart block due to pathways in close proximity to the AV conduction system or to other factors that increase the risks of invasive procedures.

In patients with AV nodal reentrant tachycardias, similar success rates are now possible with ablation of the SP or atrial approaches to that pathway, which lies posteriorly along the tricuspid annulus. The risk for heart block in these patients is 0.5% to 3.0%, depending to some extent on the experience of the perator and on the apparent SP location. This approach has virtually supplanted the alternative ablation of the FP, which has been accompanied by heart block rates of 5% to 25% (42,46,237,238).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Risk Stratification in Patients with Asymptomatic Preexcitation

Although much of the physiology of the AV nodal–dependent arrhythmias has already been elucidated and management and treatment methods established, several areas of controversy remain. It is the opinion of the author (D.L.P.) that risk stratification in patients with asymptomatic preexcitation is not necessary, unless extenuating circumstances exist. Some clinicians, however, continue to be strong proponents of risk stratification in all patients. As discussed above, the likelihood of rapid conduction through an AP in the absence of symptoms is low; moreover, the risk of SCD has been shown in population-based studies to be very low. Still, the risk for an untoward event is not zero. On rare occasions, patients present with ventricular fibrillation as their first manifestation of WPW syndrome. As such, clinicians cannot give patients a blanket guarantee of freedom from untoward events over the long term. It is important that this uncertainty be discussed with patients to provide them with the necessary understanding needed to make informed decisions about proceeding with additional evaluation and treatment and any accompanying risks, if they are asymptomatic. If risk stratification is to be undertaken, it should be by direct initiation of atrial fibrillation and assessment of the ventricular response rate. Noninvasive methods are insufficiently predictive to be of any significant use. If rapid conduction through an AP is identified, the patient should have sufficient information to either accept the risks associated with such rapid conduction or the risks associated with ablation of the offending AP. When presented with the juxtaposition of the risks associated with no intervention versus those of catheter ablation, some patients may well opt for conservative follow-up. Others may wish to face the risks of ablation immediately rather than confront continued pathway-related risks, no matter how low, over time.

Anatomy of Atrioventricular Nodal Reentrant Tachycardias

Another area of controversy is outlined previously in this chapter. Some clinicians argue that the circuit resides within the compact portion of the AV node. Others argue that at least a component of the reentrant circuit lies outside the compact region of the AV node. In the latter case, the SP is viewed as arising from atrial tissue, with insertion into the compact AV node. Given the various considerations on both sides of this argument, it seems most likely that an appreciable component of the reentrant circuit resides outside the AV node within atrial tissue. In fact the FP and SP may even be variable manifestations of anisotropic tissue architecture in the interatrial septum. It is therefore likely that the anterograde limb of the circuit is actually composed of both the atrial tissue inputs into the posterior region of the AV node and a component of AV nodal tissue itself. As such, successful SP ablation may simply mean that the atrial inputs into the AV node have been sufficiently modified to make onset of tachycardias unlikely.

Radiofrequency Ablation as First-Line Therapy for Atrioventricular Nodal–Dependent Tachycardia

Finally, in some quarters, the propriety of RF ablation as first-line treatment for AV nodal–dependent arrhythmias remains controversial. Some clinicians believe that patients with AV reentrant tachycardia in the absence of manifest preexcitation and those with AV nodal reentrant tachycardias should be managed with antiarrhythmic drugs that target the AV node. Ablative therapy is reasonable first-line therapy if (a) a patient faces lifelong medical therapy, (b) there is an arrhythmia refractory to previous medical treatment, (c) the patient is at risk for an untoward event, or (d) the patient resides in an area where medical therapy for tachycardia is less readily available. Again, the risks of this therapy must be weighed against the alternative of using membrane-active antiarrhythmic drugs. Although most of these agents are reasonably tolerated when appropriately administered, constitutional side effects and the risk of potentially lethal proarrhythmia remain a reality. In the hands of experienced interventionalists, the risks associated with ablation remain very low; moreover, ablation has the added advantage of curing the arrhythmia. RF catheter ablation of SVT has been shown to be cost-effective and improve quality of life for patients with WPW who survive cardiac arrest or who experience SVT or AF (239) and for highly symptomatic patients with AV nodal reentrant tachycardia or AV reentrant tachycardia using a concealed AP (240). Here again, patients should be informed of their options so they may participate in choosing an approach that best meets their needs.

CONCLUSIONS

Over the past 15 to 20 years, substantial progress has been made in the treatment of AV nodal–dependent tachycardias. This has been facilitated by the development of catheter-based electrophysiology study techniques that elucidate the underlying arrhythmic mechanisms, the development of better drugs for acute and chronic management, and the refinement of nonpharmacologic therapy such as RF catheter ablation for curing these arrhythmias. This progress has not only elucidated these arrhythmias, but has also provided the foundation for extrapolating these refinements to the more complicated AV nodal–independent atrial and ventricular tachycardias. An appreciation of these issues should improve the efficacy of therapies and reduce their risk in patients with AV nodal–dependent tachycardias.

THE FUTURE

Substantial progress has already been made in the area of AV nodal–dependent tachycardias. Excellent therapies are already available and have been applied successfully in thousands of patients. In the future, however, we will undoubtedly better define the cost-effectiveness of the various treatment modalities through outcome-based studies. A better understanding of the natural history of AV nodal–dependent arrhythmias will be forthcoming. Technology will be developed to facilitate noninvasive substrate localization and establishment of mechanisms. Nonfluoroscopic multisite mapping for creating three-dimensional maps of specific arrhythmias and improved energy sources and delivery techniques will also be forthcoming. With the anticipated progress during the next 5 to 10 years, it would not be surprising if arrhythmogenic substrate could be eliminated through energy delivery from the body surface.

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VENTRICULAR TACHYCARDIA

PATRICK J. TCHOU

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OVERVIEW

Ventricular tachyarrhythmias are a major cause of sudden cardiac death, which makes up approximately 50% of all cardiac-related deaths. Most ventricular tachycardias are due to a reentrant mechanism but focal automatic as well as triggered automaticity play a role in certain types of ventricular tachycardias. The most common cause of ventricular tachycardia in the Western world is ischemic coronary artery disease. Both ischemia and the scarred tissue of old myocardial infarction can contribute to the initiation and sustainment of ventricular tachycardia in the setting of coronary artery disease. After a myocardial infarction, several clinical factors appear to indicate a high risk of spontaneous occurrence of ventricular tachycardia or sudden death in a patient. Depressed left ventricular function, presence of nonsustained ventricular tachycardia, occurrence of syncope, presence of late potentials on the signal-averaged electrocardiogram (ECG), decreased heart rate variability, presence of microvolt T-wave alternans, and inducible sustained ventricular tachycardia during an electrophysiologic study are all predictors of this risk. Antiarrhythmic drug therapy is used infrequently as a primary therapy for sustained ventricular tachycardia in the setting of structural heart disease. When used, amiodarone and sotalol are the most common medications. The implantable cardioverter-defibrillator (ICD), especially with the improved technology that allows transvenous implantation of the electrode and pectoral implantation of a small generator, is the most reliable approach to reduce arrhythmic deaths. Catheter ablation is a modality that is useful for special circumstances.

Wide complex tachycardia. Atrioventricular dissociation confirms ventricular origin.

Reentry using the His-Purkinje system is seen more often as the cause of sustained ventricular tachycardia in patients with nonischemic cardiomyopathy than in postmyocardial infarction patients. Recognition of this type of ventricular tachycardia is important because of the comparable ease of ablating this reentrant circuit when compared with ablation of myocardial scar–related ventricular tachycardia.

Both monomorphic and polymorphic types of tachycardias can occur in patients with otherwise structurally normal hearts. For the monomorphic varieties, radiofrequency catheter ablation in well-trained hands has a high success rate in eliminating the tachycardia. Long QT syndrome is a major cause of the polymorphic varieties. These tend to have a more malignant presentation, with syncope and sudden death. New genetic discoveries of the molecular defects associated with long QT syndrome can dramatically change our approach to treatment of this entity. The acquired form of polymorphic ventricular tachycardia associated with long QT is related to drug therapies and electrolyte imbalances that delay repolarization of the action potential and prolong the QT interval on the ECG. Treatment of these malignant arrhythmias is accomplished by removal of the offending drug, correction of electrolyte imbalance, and temporary pacing as needed.

A variety of inflammatory and infiltrative diseases can cause ventricular tachycardia. The most prominent are arrhythmogenic right ventricular dysplasia, sarcoidosis, acute myocarditis, muscular dystrophies, and Chagas' disease.

GLOSSARY

Delayed afterdepolarization (DAD): The normal action potential in the myocardium returns to the resting membrane potential after repolarization brought on by phase 3. Under abnormal conditions, which can be produced by digitalis toxicity and sympathetic stimulation, an oscillation of the transmembrane potential can occur after full repolarization, which can depolarize the membrane back up to threshold and cause repetitive generation of action potentials. These late depolarizations that occur after full repolarization of the transmembrane potential are called *delayed afterdepolarizations*.

Dispersion of refractoriness: The refractory period is the time after initiation of an action potential at a particular myocardial site during which another action potential cannot be elicited. *Dispersion of refractoriness* refers to the termination of refractory periods at different myocardial sites at varying times such that some areas of the myocardium may still be refractory, whereas others are ready for activation.

Early afterdepolarization: Early afterdepolarizations occur with membrane depolarization starting from the early portion of phase 3 of the action potential. Phase 3 is the repolarization phase driven mostly by potassium current. These early depolarizations take off from the early portion of phase 3. The onset of the afterdepolarizations can bring repetitive firing of action potentials. Drugs and electrolyte changes that prolong the action potential duration have a tendency to activate these afterdepolarizations. They are called "early" afterdepolarizations to distinguish them from the "delayed" type, which are activated after full membrane

repolarization.

Monomorphic ventricular tachycardia: Ventricular tachycardia in which the QRS morphology of each beat remains constant in any particular ECG lead. To make that assessment, it is best to compare QRS complexes that are 2 to 3 seconds apart rather than adjacent ones. Occasionally, the changes in QRS morphology may be quite subtle on a beat-to-beat basis. Over several beats, however, these subtle changes become quite obvious.

Polymorphic ventricular tachycardia: Ventricular tachycardia in which the QRS morphology of each sequential beat changes such that over multiple beats, the QRS morphology distinctly changes in at least one ECG lead. Furthermore, the QRS morphology of a polymorphic ventricular tachycardia continues to change over time. The demarcation between polymorphic ventricular tachycardia and ventricular fibrillation is unclear. In general, however, one can visually appreciate distinct initiation and termination of QRS complexes on the surface ECG in polymorphic ventricular tachycardia despite their changing morphologies, whereas that distinction cannot be appreciated during ventricular fibrillation.

QT prolongation: The QT interval changes in relationship to the heart rate, being longer at slower rates and faster at higher rates. Thus, an absolute value cannot be used to define a prolonged QT interval. The corrected QT interval is normalized to the heart rate and can be derived by the Bizet's formula, QTc (ms) = QT (ms)/[RR (sec)]$^{1/2}$, where RR is the cycle length of the heart rate measured in seconds. The upper limits of normal for the QTc is 440 ms.

Reentry: Propagation of a single action potential wavefront, or multiple simultaneous wavefronts, along a path or paths that allows reactivation of individual sites repetitively.

Sustained and nonsustained ventricular tachycardia: The demarcation of what constitutes sustained versus nonsustained ventricular tachycardia is somewhat arbitrary. In most literature describing induction of ventricular tachycardia during programmed ventricular stimulation, a sustained tachycardia is defined as one that lasts at least 30 seconds or one that caused significant hemodynamic compromise such that it needed termination by pacing or direct current cardioversion before 30 seconds. Tachycardias that terminate spontaneously in less than 30 seconds are considered nonsustained.

INTRODUCTION

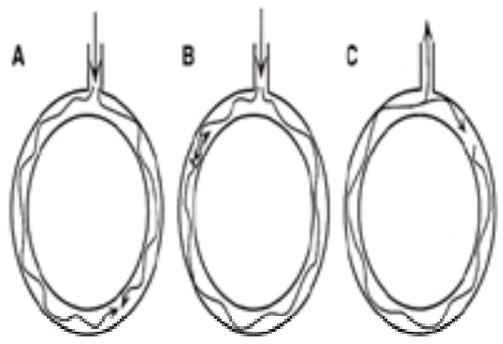
The recognition of the underlying causes of ventricular tachycardia and the available options for treatment have dramatically changed since the early 1970s. Before that time, treatment of ventricular tachycardia was restricted to the use of a small number of antiarrhythmic medications that are now generally recognized as having limited efficacy in the treatment of most common forms of ventricular tachycardia. Although there was an appreciation of the association of ventricular tachycardia with various forms of cardiac disease, there was unclear understanding of the functional mechanisms and the microanatomic substrate responsible for these tachycardias. The last three decades have indeed seen a substantial growth in this understanding. With this understanding, there has also been a growth in the tools available to treat ventricular tachycardia and to prevent sudden cardiac death. Newer medications such as amiodarone and sotalol may have a higher efficacy rate than those available before them. The development of the ICD has dramatically altered the risk-versus-benefit analysis of using antiarrhythmic medications for the prevention of sudden cardiac death. Surgical resection and cryoablation of ventricular tachycardia sources, although not used frequently now, remains a viable option for treating ventricular tachycardia in special circumstances. Lastly, catheter ablation techniques together with enhanced mapping technologies have offered curative therapies that eliminate the substrate for tachycardia and could be all the therapy needed in some circumstances. Indeed, curative ablation therapies now offer perhaps the best option for treatment of monomorphic ventricular tachycardia in structurally normal hearts afflicting younger, otherwise healthy patients.

SIGNIFICANCE OF VENTRICULAR TACHYCARDIA

It is estimated that approximately half of the deaths due to cardiac diseases are sudden (1,2). Ambulatory ECG recordings of sudden deaths have indicated that these are mostly due to ventricular tachyarrhythmias (3,4). Thus, ventricular tachyarrhythmias are the immediate cause of a large number of deaths, estimated at approximately 300,000 annually in the United States. Death occurs through its interference with the cardiac pumping function.

MECHANISM OF VENTRICULAR TACHYCARDIA

Most clinical ventricular tachycardias are related to reentry over a fixed reentrant circuit, usually involving diseased tissue generating slow conduction of impulses, which allows sustained reentry to occur. Several electrophysiologic conditions are required for initiation and sustainment of reentry. The first requirement for sustainment of a reentrant ventricular tachycardia is the existence of a circuit made up of electrically active tissue that can complete a reentrant path. During normal rhythm, cardiac impulses usually enter these reentrant circuits at one or more points and propagate through the tissues of the reentrant pathway. However, an impulse entering this circuit at a point will propagate in both directions and will extinguish itself when the two limbs of propagation collide with each other some place within the circuit (*e*Fig. 67.0.1A). An initiating mechanism must exist to begin a circulatory movement of electrical activation within the reentrant circuit. Therefore, a second requirement is the initiating "trigger." This is generally supplied as a premature beat. However, it could occur during spontaneous regular rhythm. Such a trigger beat must penetrate the reentrant circuit. Its propagation down one limb of the circuit must be blocked at some point of the circuit. The propagation down the other limb of the reentrant circuit must achieve adequate conduction delay so that arrival of this impulse at the site where the opposing impulse blocked is late enough to allow tissue recovery and continued propagation (*e*Fig. 67.0.1B). This sequence of events initiates the first reentrant beat. However, a sustained reentrant propagation of an impulse around the reentrant circuit can occur only when a third requirement is achieved: Every link of the reentrant circuit is capable of repeated activation at the cycle length of the tachycardia (*e*Fig. 67.0.1C). These three requirements apply in general to all reentry and can form the framework of analyzing reentrant tachycardias whether they are supraventricular or ventricular in origin. Some forms of reentrant tachyarrhythmias may not require a fixed reentrant circuit—that is, their reentrant pathways may be continuously changing. Ventricular fibrillation, as well as some forms of polymorphic ventricular arrhythmias, may fall into this category. The exact pathways over which electrical propagation occur may change from moment to moment. New pathways may develop while existing pathways extinguish. However, the rhythm will sustain itself as long as at least one electrical wavefront continues to propagate.



***e*FIGURE 67.0.1** The three electrophysiologic requirements for initiating and sustaining a reentrant tachycardia. **A** indicates the presence of a reentrant circuit. With every nontachycardia beat, the wavefront depolarizing the heart can enter the reentrant circuit and propagate via both limbs of the reentrant circuit. Reentry does not occur, however, as a result of collision and annihilation of the impulses propagating down both pathways. **B** illustrates the initiation of the first reentrant beat. The impulse entering the circuit again enters into both limbs. It must block in one direction (superior direction in this illustration) and propagate in the opposite direction. The time for the conducting impulse to arrive at the site of block must be long enough to allow sufficient recovery at the blocked site so that the propagating impulse can conduct through this site of block and complete the first reentrant beat. Once the first reentrant beat occurs, the tachycardia can continue as long as every site within the reentrant circuit can maintain conduction at the cycle length of the tachycardia, as illustrated in **C**.

Several electrical mechanisms causing tachyarrhythmias are believed to be focal in nature. Enhanced automaticity may be the cause of the so-called accelerated idioventricular response. Enhanced automaticity is generally ascribed to phase 4 depolarization of the action potential. It is more often seen in the His-Purkinje tissues of the ventricle but can also occur in the myocardium under abnormal metabolic conditions.

DADs are spontaneous depolarizations that develop after complete repolarization of an action potential. These depolarizations can achieve a high enough transmembrane voltage that repeated action potentials are triggered (5). DADs occur as a result of calcium loading of the cell. Experimentally, these can be elicited in isolated tissue or myocyte preparations by digitalis and sympathetic stimulation. Calcium channel blockers can suppress these arrhythmias (6).

Early afterdepolarizations occur during the recovery phase of the action potential. During the repolarization process, a renewed depolarization can occur when the repolarizing current is weak or when a strong enough depolarizing current persists. Drugs that interfere with the repolarization process such as the type I antiarrhythmic medications that block the potassium channels can cause this type of afterdepolarization (7). Quinidine is a typical type Ia antiarrhythmic drug that can produce these early afterdepolarizations that are enhanced by bradycardia and are suppressed with increased extracellular potassium and magnesium concentrations (8). Thus, electrolyte imbalances such as hypokalemia and hypomagnesemia may contribute to this mechanism in the clinical setting. This mechanism is probably involved in the initiation of some forms of tachyarrhythmias such as torsades de pointes during antiarrhythmic drug therapy (9).

ANATOMIC SUBSTRATE OF VENTRICULAR TACHYCARDIA RELATED TO ISCHEMIC MYOCARDIAL DISEASE

Because ischemic heart disease is still the most common cardiac disease in North America, ischemic myocardial scars remain the most common substrate for sustained monomorphic ventricular tachycardia. When arterial blood supply is interrupted to a portion of the ventricular myocardium, causing myocardial infarction, not all the muscle fibers die within that region. Especially within the subendocardial and subepicardial layers, surviving muscle fibers can be electrically active and may even generate normal-appearing action potentials. However, because of the interweaving of scar tissue within these muscle fibers, propagation of electrical impulses through this tissue may take a circuitous route. Cell-to-cell propagation may also be slowed due to a variety of factors associated with the scarring process and persistence of ischemia. Refractory periods within regions of surviving muscle in the scar may also be prolonged in comparison with the surrounding normal muscle. Recordings of electrical propagation in these scarred areas tend to show fractionated, low-amplitude, and prolonged signals. These properties form the basis of unidirectional block and slow conduction necessary for initiation and sustainment of a reentrant wavefront (10,11 and 12).

Risk Factors for Ventricular Tachyarrhythmia and Sudden Death in Ischemic Heart Disease

Patients who have experienced a myocardial infarction have the potential for reentrant ventricular tachycardia. Several clinical factors are useful for assessing the risk of experiencing sustained ventricular tachycardia. The probability that sustained ventricular tachycardia or sudden death would occur in a person after a myocardial infarction appears to be directly related to the size of the infarct and the consequent reduction in systolic ventricular function. Several reports have described a direct relationship between ventricular dysfunction and increased mortality rates in post–myocardial infarction patients (13,14). Sudden deaths make up a significant proportion of this mortality and are largely due to ventricular tachycardia and ventricular fibrillation. The extent of myocardial damage, as reflected by the patient's left ventricular ejection fraction and functional class, is probably the most important predictor of sudden arrhythmic deaths.

The occurrence of syncope, the presence of late potentials on a signal-averaged ECG, decreased heart rate variability, the presence of T-wave alternans, the occurrence of high-grade ventricular ectopy and nonsustained ventricular tachycardia, and the inducibility of sustained ventricular tachycardia during programmed ventricular stimulation are also predictors of mortality and occurrence of clinical sustained ventricular tachycardia (15,16,17,18 and 19).

A signal-averaged ECG is a high-gain ECG that attempts to detect low-voltage electrical propagation through scarred areas of the myocardium extending beyond the QRS. Although having low amplitudes, these signals tend to have high-frequency content. Because such conduction is slowed through a scarred region of the myocardium, late activation of cells in this region can occur after the completion of the QRS complex on the surface ECG. The presence of such "late potentials" indicates the existence of substrate for a potential reentrant circuit. These late potentials are generally too low in amplitude to be appreciated on a standard 12-lead ECG. The use of signal-averaging techniques to reduce electronic noise permits high-amplification recording and detection of these potentials. Such techniques were first applied to human ECG recordings in the early 1980s (20,21). Subsequent studies have demonstrated a correlation between the presence of these late potentials on a signal-averaged ECG and the inducibility of sustained monomorphic ventricular tachycardia as well as the clinical occurrence of sustained ventricular tachyarrhythmia (15,22,23 and 24). In these studies, the absence of late potentials on the signal-averaged ECG after myocardial infarction was associated with a low incidence of sudden death or clinical occurrence of sustained ventricular tachycardia, in the range of 4% over a 2-year period. On the other hand, the presence of late potentials was associated with a 16% to 28% incidence of sudden death or sustained ventricular tachycardia. In two of these studies (15,23), patients with a combination of left ventricular ejection fraction of less than 40% and the presence of late potentials on the signal-averaged ECG had around a 35% incidence of sudden death or sustained ventricular tachycardia during a mean follow-up of 12 to 14 months.

The variability of heart rate during sinus rhythm on a beat-to-beat basis reflects the presence of vagal tone, which may have a protective effect against the triggering of ventricular arrhythmias. Such variability can be quantified using short-term (minutes) or long-term (24 hours) ECG recordings. The absence of normal heart rate variability has been found to be a predictor of mortality in patients after myocardial infarction (25). In patients with congestive heart failure, heart rate variability appears to be an independent predictor of mortality, especially in those patients with moderately reduced functional status (26,27). In fact, even in patients without overt cardiac disease, lower heart rate variability appears to be associated with a higher probability of developing coronary heart disease and mortality (28).

Another noninvasive test currently being investigated that may demonstrate clinical usefulness is the detection of T-wave alternans, especially during a stress test. Alternating T-wave amplitudes of small magnitudes occurring on an every-other-beat basis may be a marker for potential malignant ventricular arrhythmia in the presence of ischemia (29). These microvolt alternations in T-wave amplitude reflect alternation in repolarization gradients within the myocardium. Such gradients are linked to the vulnerability of the heart to initiation of ventricular tachycardia and ventricular fibrillation in response to a triggering premature beat (30,31). Several smaller studies have demonstrated increased mortality associated with increased T-wave alternans (32,33). Large-scale clinical evaluation of this test will be needed to demonstrate its clinical usefulness in predicting sudden arrhythmic deaths.

Programmed electrical stimulation of the heart during an electrophysiologic study has also been used to assess the risk of a patient experiencing sustained ventricular arrhythmias. Several studies have shown an increased risk of sudden death or sustained ventricular tachycardia if such arrhythmias can be induced with programmed stimulation in patients after myocardial infarction (34,35 and 36). In these studies, the predicted risk of a sustained ventricular arrhythmic event was low (2% to 7%) in those who had no inducible sustained ventricular tachycardia, whereas that risk was quite high, approximately 30%, in those who had induced sustained ventricular tachyarrhythmia.

The occurrence of syncope in patients who have previously suffered myocardial infarctions should be a warning sign that they may be experiencing rapid ventricular tachycardia. Syncope in patients with significant heart disease, particularly if accompanied by congestive heart failure, appears to be a strong predictor of sudden death (37,38). In patients with both ischemic as well as nonischemic dilated cardiomyopathy, the occurrence of syncope appears to portend an increased risk of arrhythmic death (39,40). An electrophysiology study can be helpful in identifying an arrhythmic cause of syncope in such patients. Inducible sustained ventricular tachyarrhythmias in patients with syncope correlates with a high incidence of ICD therapy for sustained ventricular tachycardia (41). If electrophysiology study is unsuccessful in identifying a cause of syncope, ECG patient-actuated event recorders can be used and are generally more helpful than Holter monitors. In addition, implantable loop recorders, a thin, thumb-size device capable of automatic recording of cardiac rhythm during tachycardia or bradycardia, as well as patient-actuated recordings, can be very helpful in revealing a cardiovascular or a neurologic cause of syncope (42).

The largest risk factor for arrhythmic death appears to be the prior occurrence of sustained ventricular tachyarrhythmia, especially one that causes hemodynamic collapse requiring resuscitation.

Ischemia as a Cause of Ventricular Tachycardia

During ischemia, myocardial cells may undergo changes in their action potentials that could promote ventricular tachycardia. Depending on the degree of ischemia, refractoriness can be prolonged, action potentials can shorten, myocytes can become electrically uncoupled, or the cell can become electrically inert (43). Metabolic changes such as increased extracellular potassium concentration and acidosis can further affect cellular electrical activation. Toxic lipid metabolites can accumulate in the ischemic area to provoke ventricular arrhythmias (44). The ventricular tachycardia seen during the acute ischemic event generally tends to be polymorphic ventricular tachycardia or ventricular fibrillation rather than a sustained monomorphic ventricular tachycardia. Marked ischemia can cause prolongation of the QT interval, usually associated with inversion of the T wave. QT interval prolongation, for example, can be seen during an acute myocardial infarction. However, myocardial ischemia may not prolong the QT interval. In fact, the presence of polymorphic ventricular tachycardia, sustained or nonsustained, in the absence of QT prolongation should be a clue that ischemia is likely to be an underlying cause (Fig. 67.1). Although nonischemic causes of polymorphic ventricular tachycardia can occur as described below, they are rare in comparison. Thus, high-grade coronary disease should be the first consideration in an adult patient with any coronary risk factor who manifests polymorphic ventricular tachycardia without QT prolongation.

FIGURE 67.1 Polymorphic ventricular tachycardia related to cardiac ischemia. This figure illustrates the initiation of sustained polymorphic ventricular tachycardia resulting from ischemia without evidence of ST elevation. This polymorphic ventricular tachycardia should be distinguished from torsades de pointes (see Fig. 67.9). Note that the QT intervals were not prolonged, and initiation of polymorphic ventricular tachycardia was not preceded by a long RR interval.

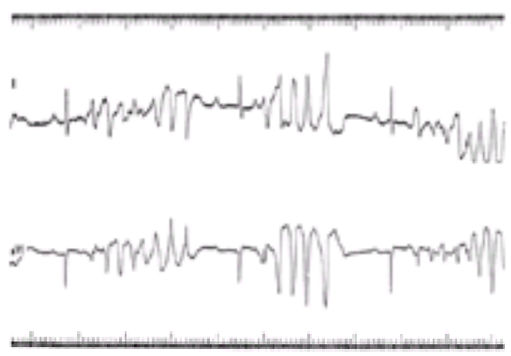


FIGURE 67.9 Typical characteristics of torsades de pointes. The initiation of the first ventricular ectopic beat of the tachycardia tends to occur after a pause. The QRS of this first beat initiates on the T wave, making it difficult to appreciate where the T wave ends. There is a beat-to-beat change in the QRS axis in a sinusoidal pattern. The rate of the tachycardia tends to be slower than the polymorphic ventricular tachycardia seen during cardiac ischemia, as shown in Figure 67.1 and Figure 67.3.

FIGURE 67.3 Polymorphic ventricular tachycardia related to coronary spasm. **A**, **B**, and **C** show Holter electrocardiographic tracings from a 38-year-old patient in the hospital after a cardiac arrest at home where ventricular fibrillation was documented. He had complained of chest pain just before the cardiac arrest. **A:** Baseline rhythm. **B:** Beginning of ST elevation. One minute later, the ST segments are markedly elevated **(C)**, accompanied by short nonsustained runs of polymorphic ventricular tachycardia. Cardiac catheterization in this patient showed minimal coronary disease, and the ischemic events were attributed to coronary spasm. Note that the QT intervals in Figure 67.2 and this figure are not prolonged. Although QT interval may prolong during acute ischemia, especially with T-wave inversion, it is not a common accompanying finding in ischemia-induced polymorphic ventricular tachycardia.

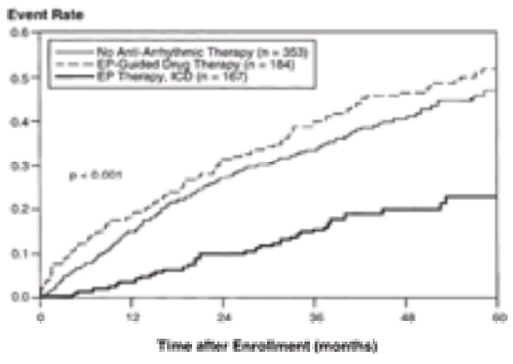


FIGURE 67.2 Survival of patients in the Multicenter Unsustained Tachycardia Trial: comparison of antiarrhythmic drug therapy, no therapy, and implantable cardioverter-defibrillator (ICD) therapy. The study enrolled post–myocardial infarction patients who had left ventricular ejection fraction of 40% or less and inducible sustained ventricular tachycardia during electrophysiology study. Patients who were treated with antiarrhythmic drugs had no better outcome than those who were not treated at all. Those treated with an ICD had significantly improved survival. EP, electrophysiologic. (From Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;341:1882, with permission.)

Animal models have shown that acute ischemia is associated with prolongation of activation time in the ischemic region, resulting in the dispersion of activation from site to site, which may be directly related to the onset of ventricular tachycardia (45). Multiple studies have shown that the presence of an open artery, even in an infarcted area of myocardium, appears to have a protective effect against ventricular arrhythmias. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries I Trial demonstrated that restoring brisk coronary artery blood flow (thrombolysis in myocardial infarction grade 3) early, within 90 minutes, reduces 30-day mortality by 50% (46). Similarly, reocclusion of an initially opened artery was associated with a tenfold higher 30-day mortality (47). One can argue that early reperfusion improves survival due to reduction of infarct size and improvement of residual ventricular function. However, other studies have demonstrated a survival benefit of late patency of the artery supplying an infarct site even when there is no appreciable impact on residual ventricular function (48,49). Thus, continued patency of an infarct-related artery may have beneficial effects such as improved electrical stability of the area (50), especially in the border zone of the infarct where ischemic but viable tissue may generate unstable ventricular tachyarrhythmias.

Assessment of Risk after a Myocardial Infarction

The assessment of risk for ventricular tachycardia and sudden death in a patient after myocardial infarction is a multifactorial process. At the minimum this should include an assessment of left ventricular function and the presence of nonsustained runs of ventricular tachycardia on ECG monitoring. An assessment of any persistent ischemia either surrounding the infarct zone or in another portion of the myocardium unrelated to the infarct artery should be made. The use of a signal-averaged ECG may provide additional information to enhance or reduce the apparent risk of a particular patient. The other noninvasive tests such as heart rate

variability and T-wave alternans, as discussed above, may prove to be good risk assessments. Those patients who appear to be at high risk as determined by the above noninvasive testing should undergo electrophysiologic testing. The inducibility of sustained ventricular tachycardia during an electrophysiologic study confirms the high risk, whereas the inability to induce sustained tachycardia suggests a lower risk.

Prevention and Treatment of Ventricular Tachycardia after Myocardial Infarction

As a general approach to the prevention of sustained ventricular tachyarrhythmia, patients who have an ischemic cardiomyopathy should have optimal therapy to relieve congestive heart failure and ischemia. The proper use of diuretics, potassium and perhaps magnesium supplements, angiotensin-converting enzyme inhibitors, beta-blockers, and digoxin as needed should form the basis of heart failure therapy. Significant ischemia should be relieved, where possible, by revascularization and minimized with drug therapies, especially beta-blockers. Beta-blockers and angiotensin-converting enzyme inhibitors in some studies have been shown to improve overall as well as arrhythmic mortality in this population (51,52 and 53).

With the possible exception of amiodarone, the use of antiarrhythmic medications has not improved or has worsened survival. Several clinical trials with amiodarone have demonstrated no detrimental effects and may, in selected subgroups, improve survival.

Large-scale and smaller clinical trials have demonstrated the potential harmful effects of type I antiarrhythmic medications given to suppress ventricular premature beats in post–myocardial infarction patients. The Cardiac Arrhythmia Suppression Trial (54) represents the most prominent of these trials. Other trials have demonstrated the lack of beneficial effects of type Ia and Ib medications (55,56). Teo et al. provided an excellent summary of these trials, reviewing the outcomes of 138 trials involving 98,000 patients (57). None of these trials showed a beneficial effect of type I antiarrhythmic drugs in post–myocardial infarction patients. The only post–myocardial infarction survival trial reported so far with a “pure” type III antiarrhythmic, D-sotalol, showed a higher mortality in the drug treatment limb than in the placebo arm (58). The results of another study, Azimilide Post-Infarct Survival Evaluation Trial, using azimilide, are pending (59).

Although earlier studies (60) have suggested that amiodarone may be beneficial in lowering arrhythmic mortality, a more recent report, the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (61), did not show a significant advantage in using this medication as prophylactic therapy to prevent arrhythmic deaths in a large group of patients with congestive heart failure, including patients with ischemic heart disease. Two trials of empiric amiodarone in post–myocardial infarction patients (Canadian Myocardial Infarction Amiodarone Trial and European Myocardial Infarct Amiodarone Trial) were recently completed. The European Myocardial Infarct Amiodarone Trial enrolled more than 1,400 post–myocardial infarction patients with a left ventricular ejection fraction of 40% or less. They were randomized to treatment with amiodarone or placebo. Despite a reduction of mortality classified as arrhythmic, overall mortality and cardiac mortality did not differ significantly (62). Further subgroup analyses have suggested that those patients in the European Myocardial Infarct Amiodarone Trial who had greater reduction of left ventricular ejection fraction (30% or less), faster resting heart rates, or less heart rate variability or who were treated with beta-blockers may have an improved overall mortality when treated with amiodarone (63,64). The Canadian Myocardial Infarction Amiodarone Trial enrolled 1,202 post–myocardial infarction patients who had more than ten premature ventricular complexes per hour. They were also randomized to treatment with amiodarone or placebo. The trial, however, was designed to assess the primary end point of resuscitated ventricular fibrillation or arrhythmic death and was not powered to assess all-cause mortality differences. The trial demonstrated that patients treated with amiodarone had a significant reduction in risk of experiencing the primary end point of resuscitated ventricular fibrillation or arrhythmic death (65). However, the difference in all-cause mortality between the amiodarone-treated patients and those who received placebo did not reach statistical significance. Of particular interest, a combination of beta-blockers with amiodarone may have a synergistic survival benefit, as suggested in a combined analysis of the European Myocardial Infarct Amiodarone Trial and Canadian Myocardial Infarction Amiodarone Trial (66).

In contrast to the antiarrhythmic drug studies, two studies have now reported improved survival in high-risk post–myocardial infarction patients treated with an ICD. The Multicenter Automatic Defibrillator Implantation Trial demonstrated that patients with nonsustained ventricular tachycardia after a myocardial infarction who have left ventricular ejection fractions of 35% or less and who have inducible sustained ventricular tachycardia at electrophysiologic study are best treated with an ICD rather than with antiarrhythmic medications. The antiarrhythmic medication used in this trial consisted primarily of amiodarone (74%), with a small number of patients taking sotalol (7%). Patients treated with the implanted device had approximately one-half the mortality of the drug-treated group (67). The Multicenter Unsustained Tachycardia Trial (MUSTT) enrolled 704 post–myocardial infarction patients with left ventricular ejection fractions of 40% or less who had nonsustained ventricular tachycardia on monitoring and inducible sustained ventricular tachycardia during electrophysiologic testing. In contrast to the Multicenter Automatic Defibrillator Implantation Trial, MUSTT contained a no-therapy arm. Antiarrhythmic treatment consisted of medications guided by the results of programmed ventricular stimulation or the ICD. Forty-six percent of the patients receiving therapy were given an ICD. The group of patients receiving the ICD had the best arrhythmic and all-cause mortality. Patients receiving antiarrhythmic drug therapy did no better than those who received no antiarrhythmic therapy (Fig. 67.2) (68). These two studies taken together have demonstrated that the particular group of patients characterized by prior myocardial infarction, reduced left ventricular ejection fraction, clinical nonsustained ventricular tachycardia, and inducible sustained ventricular tachycardia are at high risk for arrhythmic mortality and that treatment with an ICD results in lower arrhythmic and overall mortality.

Patients who have already experienced a clinical episode of sustained ventricular tachycardia or ventricular fibrillation are at the highest risk of recurrence (69). Unless one can clearly demonstrate that such an occurrence was associated with a reversible cause, a reliable therapeutic approach should be used to minimize the risk of sudden death. The therapy of choice is now clearly the ICD. Publication of several studies have demonstrated that ICD therapy yields better survival outcomes in these patients when compared with antiarrhythmic drug therapy with sotalol or amiodarone.

The Antiarrhythmic Versus Implantable Defibrillator Trial, published in 1997, enrolled 1,016 patients who were resuscitated from cardiac arrest and had clinical sustained ventricular tachycardia with syncope or with a left ventricular ejection fraction of 40% or less. These patients were randomized to treatment with ICD or with antiarrhythmic drugs, predominantly amiodarone. The survival outcome was clearly better in the ICD arm of the study (70). The Canadian Implantable Defibrillator Study is a smaller study that enrolled 659 patients who had prior cardiac arrest, sustained symptomatic ventricular tachycardia, or syncope with documentation of ventricular tachycardia on monitoring or during electrophysiology study. These patients were randomized to treatment with amiodarone or with an ICD. The study showed a trend toward improved arrhythmic and overall survival in the ICD-treated patients, but this trend did not reach statistical significance (71). A subanalysis demonstrated that those patients with the lowest left ventricular ejection fraction, older age, and the worst New York Heart Association class benefitted the most from ICD therapy (72). A metaanalysis of three different trials (Antiarrhythmic Versus Implantable Defibrillator Trial, Canadian Implantable Defibrillator Study, and Cardiac Arrhythmia Study Hamburg) comparing the ICD with drug therapy in the prevention of arrhythmic deaths in patients who had already experienced a prior major ventricular arrhythmic event revealed that the risk of overall mortality was 28% lower in the ICD group. This lower mortality was largely due to a 50% decrease in the risk of arrhythmic mortality (73).

The assessment of an antiarrhythmic medication for its ability to suppress clinical recurrence of ventricular tachycardia is problematic. The utility of the electrophysiology study to test drug suppression of ventricular tachycardia as a means of predicting clinical efficacy has been questioned by the results of the Electrophysiologic Study Versus Electrocardiographic Monitoring Trial (74). With the publication of MUSTT, programmed ventricular stimulation as a means of predicting antiarrhythmic drug efficacy for preventing sustained ventricular tachycardia has been seriously challenged. Given the poor outcomes of post–myocardial infarction patients in that study who were treated with antiarrhythmic drugs guided by programmed stimulation, one can no longer recommend this approach (68).

Although use of antiarrhythmic medications as the sole method of preventing recurrence of sustained ventricular tachyarrhythmia is declining, its use as adjunctive therapy with an ICD is still quite common. Approximately 50% of patients with ICDs are on antiarrhythmic medications (75,76). Antiarrhythmic medications are used for preventing atrial fibrillation as well as decreasing the frequency of ventricular tachycardia causing reception of shocks by the patient.

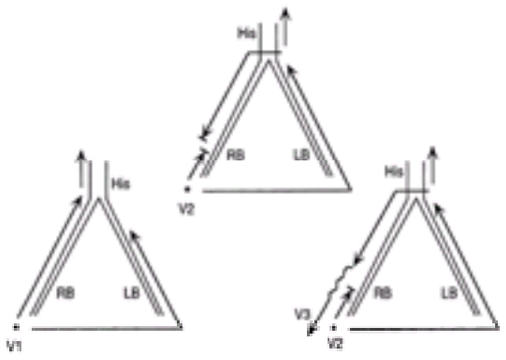
An alternative to drug therapy of ventricular tachycardia associated with ischemic heart disease is catheter ablation. Current approaches mainly use radiofrequency energy. Success in eliminating a particular reentrant ventricular tachycardia is in the 50% to 70% range by most reports (77,78). At present, this technique is still mostly used as an adjunctive therapy for patients who have an ICD already but are having frequent or slow ventricular tachycardias that complicate device therapy.

Ischemic Ventricular Tachycardia Unrelated to Atherosclerotic Coronary Artery Disease

Although not related to atherosclerotic obstruction of the coronary arteries, several other causes of sudden death, presumably from ischemic polymorphic ventricular tachycardia and ventricular fibrillation, should be considered, especially in competitive athletes (79). Anomalous takeoff of the left coronary artery from the right coronary cusp or the right coronary artery from the left coronary cusp are potential, although rare, etiologies. Anatomically, this anomalous takeoff can result in compression of the artery, resulting in ischemia. Hypertrophic cardiomyopathy and other causes of myocardial hypertrophy such as aortic stenosis may also trigger ventricular fibrillation by an ischemic mechanism. Embolic occlusion of coronary arteries can also occur from blood clots or vegetations generated by endocarditis. Lastly, coronary spasm can induce ischemic polymorphic ventricular tachycardia and cardiac arrest (Fig. 67.3). In all these entities, the therapeutic approach is to prevent or alleviate the conditions leading to ischemia. Although medications may be helpful in cases such as coronary spasm, an ICD should be considered as back-up protection should medications fail to completely prevent ischemia.

VT RELATED TO HIS-PURKINJE DISEASE

The His bundle and the bundle branches together with the Purkinje network and the myocardium form a potential reentrant pathway that could become the substrate for ventricular tachycardia. The ability of the normal His-Purkinje to generate reentrant beats during right ventricular premature stimulation was first described in the 1970s (80,81). It had been recognized that a stimulated right ventricular premature beat (V2) was frequently followed by another ventricular beat (V3) that had a QRS morphology similar to that of V2. Akhtar and colleagues (80,81) demonstrated that the reentrant circuit of the V3 phenomenon involved the bundle branches as shown in eFigure 67.3.1. These reports were the first demonstration that the normal human His-Purkinje/myocardial system was capable of acting as a reentrant circuit. However, the electrophysiologic characteristics of the normal His-Purkinje system, fast conduction and long refractory periods, prevent sustainment of this reentrant process. When these normal electrophysiologic characteristics are altered by disease processes, however, this reentrant circuit can become the substrate for sustained tachycardia.



***e*FIGURE 67.3.1** Schematic mechanism of bundle branch reentrant beats elicited by right ventricular premature stimulation. Programmed ventricular stimulation is usually done by delivering a string of constant cycle length pulses (six or eight) followed by one or more premature pulses. The ventricular depolarization associated with the constant cycle length stimulation pulses are called *V1s*, whereas the ventricular depolarization associated with a premature pulse is labeled *V2*. In this figure, the left panel demonstrates electrical activation of the bundle branches during the V1 complexes. Because the stimulation is done in the right ventricle, the wavefront propagates up the left bundle later than it propagates up the right bundle due to the additional transseptal conduction time. The middle panel shows the conduction pattern of the premature beat (V2) that blocks retrogradely in the right bundle. When V2 occurs with sufficient prematurity, its conduction up the right bundle is blocked due to normal refractory properties of the right bundle. Transseptal propagation of V2 can then invade the left bundle branch system and propagate retrogradely to activate the bundle of His. Because of the longer propagation path of V2 from the site of stimulation to the bundle of His, the interval between V2 to His bundle activation (V2–H2) is longer than that seen in the left-sided panel (V1–H1). In the middle panel, the wavefront activating the bundle of His can also antegradely activate the right bundle and propagate down to the site of retrograde block. With sufficient V2–H2 conduction delay, this antegrade right bundle wavefront can penetrate through the area of retrograde V2 block and conduct to the myocardium, generating a reentrant ventricular complex, V3. LB, left bundle branch; RB, right bundle branch.

Several reports have defined the specific criteria useful in identifying the bundle branch reentrant mechanism in a ventricular tachycardia (82,83,84 and 85). In these reports, all patients had underlying His-Purkinje system disease as demonstrated by prolonged HV conduction time during sinus rhythm and the presence of intraventricular conduction defects on their surface 12-lead ECGs. Many had enlarged hearts due to various underlying cardiac diseases. However, there are reported cases in which isolated conduction system disease without other significant structural heart diseases can be the sole underlying cause of sustained bundle branch reentrant ventricular tachycardia (86). Myotonic dystrophy with its associated conduction system disease has been associated with bundle branch reentrant ventricular tachycardia (87). In the largest reported series (88), approximately half of the patients had nonischemic dilated cardiomyopathy; the other half had ischemic cardiac disease. However, when one looks at the frequency of bundle branch reentry as a mechanism of sustained tachycardia in these disease categories, the differences are quite striking. Bundle branch reentry can be the mechanism of tachycardia in 30% to 50% of patients with nonischemic dilated cardiomyopathy who have inducible sustained monomorphic ventricular tachycardia during programmed stimulation, although the incidence of inducing this tachycardia is no more than 5% to 6% in patients who have ischemic cardiac disease.

The tachycardia rate of bundle branch reentry tends to be fast, frequently above 200 beats/min. The most common clinical and laboratory-induced tachycardias have a left bundle branch block pattern (Fig. 67.4). Only isolated cases of right bundle branch block QRS morphologies have been reported. His-Purkinje system reentry generating a right bundle branch block QRS morphology on the surface ECG can also be due to fascicular reentry.

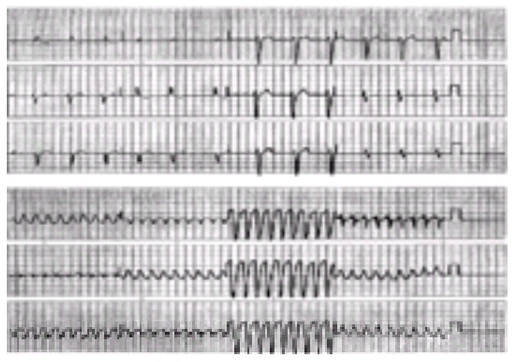
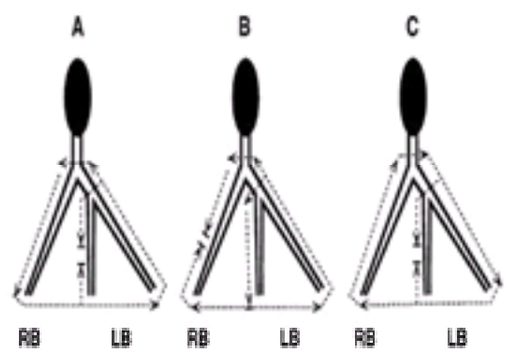


FIGURE 67.4 Electrocardiographic characteristics of a typical bundle branch reentrant ventricular tachycardia. This 12-lead electrocardiogram shows the typical characteristics of the common form of bundle branch reentrant ventricular tachycardia (*lower panel*). The anterior chest leads have a left bundle branch block QRS morphology with rapid downstroke of the S wave. The tachycardia is rapid. The QRS in sinus rhythm (*upper panel*) shows an intraventricular conduction defect of the left bundle branch type.

His-Purkinje system reentrant circuits can be classified into three different types, as shown in eFigure 67.4.1 (89). Type A involves retrograde conduction via the left bundle branch and antegrade conduction via the right bundle branch. The QRS morphology of type A reentry has a typical left bundle branch block pattern. Type B is a fascicular reentry in which retrograde conduction occurs via a left-sided fascicle and antegrade conduction is via the other fascicle. Because the ventricles are activated via the left bundle system, the QRS has a right bundle branch block morphology. Because this reentrant circuit is entirely contained within the left bundle branch, the right bundle is not necessary for reentry and may be activated strictly as a bystander. This form of tachycardia is quite infrequently seen but should be suspected when a typical right bundle branch block QRS morphology is seen during a sustained tachycardia in a patient with His-Purkinje system disease. Type C is the reversed circuit of type A and involves retrograde propagation via the right bundle branch and antegrade ventricular activation via the left bundle branch. This tachycardia would also have a right bundle branch block QRS on the surface ECG but can be differentiated from type B during electrophysiologic study. Because of the electrophysiologic properties of retrograde conduction via the right and left bundle branches (70), this form of tachycardia is quite rare, probably because initiation of this reentrant circuit is difficult with ventricular premature beats. Coexistence of two types of His-Purkinje system reentrant tachycardias, bundle branch reentry and fascicular reentry, has been reported in the same patient (90).



***e*FIGURE 67.4.1** The three types of His-Purkinje system reentrant circuits. Type A is the most commonly seen type of bundle branch reentrant ventricular tachycardia, both clinically as well as in the electrophysiology laboratory. Retrograde conduction occurs via the left bundle branch (LB) and antegrade conduction occurs via the right bundle branch (RB). This yields a ventricular tachycardia in which the QRS has a left bundle branch block pattern as seen in Figure 67.4. Type B is a fascicular reentrant ventricular tachycardia, in which the retrograde limb of the reentrant circuit is one of the fascicles, whereas the antegrade limb is the opposing fascicle. Because the ventricle is activated via the left bundle branch, the QRS has a right bundle branch block morphology. The QRS axis will depend on which fascicle serves as the antegrade route of ventricular activation. The right bundle is activated in a bystander fashion and is not necessary for sustaining the tachycardia. Type C is a reentry using the bundle branches in the opposite direction as shown for type A. Because ventricular activation occurs via the left bundle, the QRS morphology will also be right bundle branch block as in type B. Electrophysiologic distinction between the two types is important, because right bundle ablation will be curative for type C but will have no effect on type B tachycardia. (From Mehdirad AA, Keim S, Rist K, et al. Asymmetry of retrograde conduction and reentry within the His-Purkinje system: a comparative analysis of left and right ventricular stimulation. *J Am Coll Cardiol* 1994;24:177, with permission.)

Although one can suspect the presence of bundle branch reentry as a mechanism of tachycardia based on clinical presentation and ECG characteristics, its diagnosis can be made only during a careful electrophysiologic study. Several studies have detailed the diagnostic criteria that have been summarized in a review of the topic (91).

The therapy of choice for this tachycardia is radiofrequency catheter ablation, usually of the right bundle branch (92,93). Left bundle ablation should be pursued only when there is a clear indication that antegrade conduction down the left bundle is not reliable. These patients frequently have an already depressed left ventricular function that can be further compromised with the development of complete left bundle branch block.

Long-term survival in these patients depends ultimately on the underlying cardiac disease and identification and appropriate treatment of other ventricular tachycardia. A report (94) of survival among 16 patients undergoing radiofrequency ablation of the right bundle and followed for a mean duration of 22 ± 10 months showed one sudden death and one death due to congestive heart failure. Three of those patients had ICDs, two of which were implanted before the ablation. Two patients underwent heart transplant during their follow-up.

MONOMORPHIC VENTRICULAR TACHYCARDIA IN AN OTHERWISE NORMALLY FUNCTIONING HEART

Primary electrophysiologic abnormalities of the heart can be associated with ventricular tachycardia with no hint of heart disease or dysfunction on the echocardiogram or the ECG during sinus rhythm. These ventricular tachycardias are sometimes referred to as “normal heart” ventricular tachycardias. It is important to recognize the source of these tachyarrhythmias, as some of them respond to calcium channel blockers and, thus, may mistakenly be called supraventricular tachycardia. Two distinct types of normal heart monomorphic ventricular tachycardias are described. One type originates from the outflow tract regions near the pulmonic and the aortic valves. On the 12-lead ECG, this tachycardia has a characteristic appearance of left bundle branch block and inferior axis (Fig. 67.5), a QRS morphology typically seen with outflow area pacing.

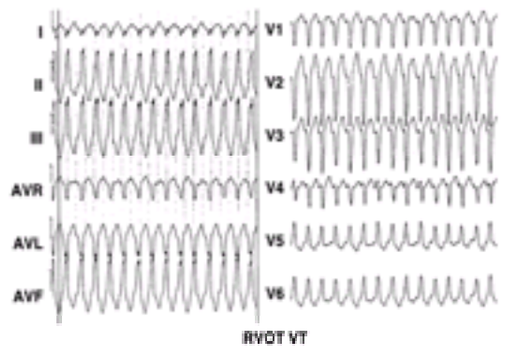


FIGURE 67.5 Twelve-lead electrocardiogram of a ventricular outflow tachycardia (RVOT). The ventricular outflow tract tachycardia typically seen in structurally normal hearts has a characteristic QRS morphology that is similar to that seen with pacing at the pulmonic and aortic valve regions. The QRS has a left bundle branch block morphology with an inferior right axis. This QRS morphology is diagnostic for ventricular tachycardia (VT), as it is highly unusual for aberrant conduction to manifest this type of QRS.

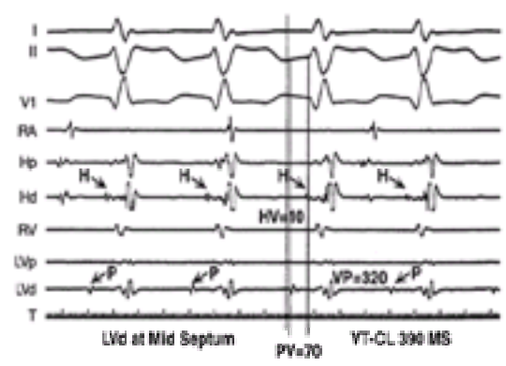
Several electrophysiologic characteristics of this tachycardia suggest that it originates from an automatic focus, perhaps related to delayed afterdepolarizations (94,95 and 96). The occurrence of the afterdepolarizations is enhanced by calcium loading and adrenergic stimulation (97,98 and 99). Clinically, these tachycardias can be exercise-induced or occur at other times of adrenergic stimulation. At times, these may manifest as frequent and virtually incessant ventricular premature beats to the extent that the patient may be in ventricular bigeminy constantly. A variation of the sustained tachycardia originating from the ventricular outflow region is the syndrome of repetitive monomorphic ventricular tachycardia. This syndrome is characterized by repetitive bursts of nonsustained ventricular tachycardia. These have also been shown to respond to calcium channel blockers, beta-blockers, as well as adenosine (100). Although the original descriptions suggested that the right ventricular outflow and the pulmonic valve area are the source of these ventricular tachycardias and premature ventricular complexes, more recent reports have found that the origin may also be located on the left side of the heart near the aortic valve (101,102). This type of ventricular tachycardia may respond to calcium channel blockers, beta-blockers, or a combination of both. However, they may also respond to a variety of antiarrhythmic agents, including type Ia and Ic agents. They may also be sensitive to adenosine, suggesting that cyclic adenosine monophosphate may function as an intracellular mediator (103,104).

Because of its focal nature, catheter ablation has an excellent chance of obtaining a cure when the tachycardia can be reproduced within the electrophysiologic study (105,106). Alternatively, drug therapy with verapamil, diltiazem (107), beta-blockers, or another antiarrhythmic agent may prevent clinical recurrence of this tachycardia. This ventricular tachycardia does not appear to associated with a progressive myopathy or other diseases of the heart except where it is incessant and could cause a tachycardia-mediated myopathy. The outflow-tract tachycardias should be distinguished from other right ventricular tachycardias that could be due to bundle branch reentry or to right ventricular dysplasia (see below).

A second type of normal heart ventricular tachycardia originates near the apex of the left ventricle. On the 12-lead ECG, this tachycardia has a typical right bundle branch block QRS morphology with a superior axis (Fig. 67.6). The earliest reports of this ventricular tachycardia described the typical response to verapamil treatment by slowing and terminating (108,109). However, other antiarrhythmic medications may also suppress it. The tachycardia originates from within the left-sided His-Purkinje system and has been described as a fascicular tachycardia in normal hearts (110). Success in ablating this tachycardia in competent hands is near 100%, and long-term survival after ablation is excellent (111).

FIGURE 67.6 Ventricular tachycardia originating from the left ventricular apex in a structurally normal heart. The left ventricular origin of this ventricular tachycardia generates a typical right bundle branch block QRS morphology on the 12-lead electrocardiogram. Early ventricular activation occurs in the apical inferior septal region of the ventricle, giving the QRS a superior axis.

This tachycardia is most likely reentrant in nature, using decrementally conducting tissue that inserts into the Purkinje network and is sensitive to calcium channel blockade (112,113). This tachycardia does not appear to be a part of a progressive cardiac disease, although when incessant, it can cause a tachycardia-mediated cardiomyopathy. Radiofrequency applications during ablation can be targeted to early ventricular activation sites or to the Purkinje source of the tachycardia. Fractionated potentials and slower-frequency components in the mid-diastolic time during tachycardia have been recorded, perhaps representing activation within the slow conduction zone (*e*Fig. 67.6.1).



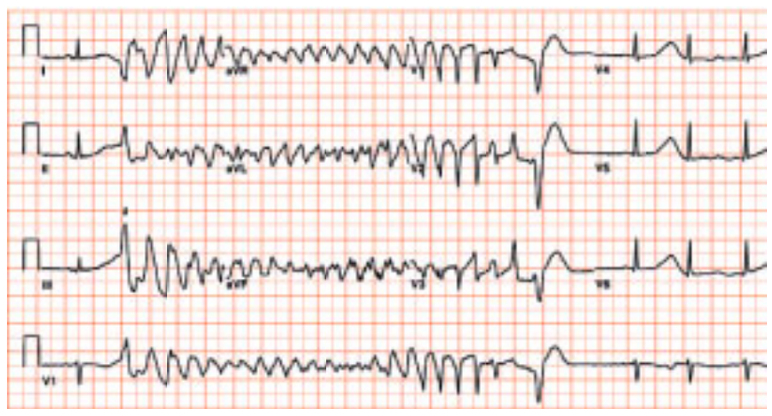
***e*FIGURE 67.6.1** Electrophysiologic recordings of mid-diastolic potential in a normal heart with left ventricular tachycardia. This tracing is from an electrophysiologic study and shows the mid-diastolic potential recorded from the left ventricular septum during ventricular tachycardia. There is a bundle of His electrogram in front of each V electrogram, but the HV interval is only 10 ms, much shorter than during normal antegrade activation. The bundle of His is passively activated retrogradely just before ventricular activation, indicating the fascicular origin of this tachycardia. The site of mid-diastolic potential (P), which is recorded 70 ms before ventricular activation, is also the site of successful radiofrequency ablation of this tachycardia, demonstrating that this potential is associated with the structure responsible for the mechanism of tachycardia.

Lastly, occasional monomorphic ventricular tachycardias are seen in normal hearts that do not necessarily fit into the two categories listed above. Some may originate in the left ventricle but do not have the typical QRS morphologies described above. Others are located at the mitral or tricuspid annulus. These tachycardias usually respond to type Ic agents such as flecainide, calcium channel blockers, or beta-blockers. They can also be treated with catheter ablation.

An 81-year-old male patient with ventricular tachycardia.

POLYMORPHIC VENTRICULAR TACHYCARDIA AND FIBRILLATION IN THE NORMAL HEART

Polymorphic ventricular tachycardia and ventricular fibrillation can also occur in the setting of a structurally normal heart. Whereas the monomorphic varieties typically do not present with syncope and cardiac arrest, the polymorphic varieties are more malignant and are associated with a high incidence of syncope and sudden death. These can be categorized into two general classes, those associated with prolonged QT intervals and abnormal-appearing T waves and those apparently unassociated with QT abnormality.



A 51-year-old female patient with torsades de pointes.

Jervell and Lange-Nielsen (114) reported in 1957 a family with congenitally deaf children, prolongation of the QT interval, and sudden death. Subsequent reports have demonstrated an autosomal recessive inheritance of this syndrome. Romano et al. (115) and Ward (116) subsequently reported familial clustering of sudden death and long QT without deafness. This more common form of long QT syndrome is inherited in an autosomal recessive pattern. In addition to these two reported inherited syndromes, there are occasional cases of new mutation causing this syndrome in a person who has no family history of such a genetic abnormality.

Recent advances in the genetics of long QT syndrome have revealed that they are associated with abnormalities of transmembrane ion channels causing the repolarization abnormality. Mutations associated with at least six genes coding for ion channel functions have been identified that cause clinical long QT syndrome. Within each gene or genetic locus, there can be multiple specific mutations that interfere the function of the ion channels. Each one of these mutations is usually seen

in a particular family. The clinical long QT syndromes associated with these mutated genes or chromosomal loci have been named sequentially in order of their discovery, long QT syndrome 1 to long QT syndrome 6 (Table 67.1).

	Gene (alternate names)	Chromosome	Affected cardiac channel/current
LQT1	*KvLQT1 (KCNQ1)*	11	Potassium/I_{Ks}
LQT2	*HERG (KCNH2)*	7	Potassium/I_{Kr}
LQT3	*SCN5A*	3	Sodium/I_{Na}+
LQT4	Not identified	4	Unknown
LQT5	*minK (KCNE1, IsK)*	21	Potassium/I_{Ks}
LQT6	*MiRP1 (KCNE2)*	21	Potassium/I_{Kr}

LQT, long QT syndrome.

TABLE 67.1 GENETIC ABNORMALITIES ASSOCIATED WITH LONG QT SYNDROME

Long QT syndrome 1 and long QT syndrome 2, the first two to be identified, are associated with mutations on chromosome 11 and 7, respectively (117,118,119 and 120), and demonstrate abnormalities of potassium channels responsible for the repolarization current in myocardial cells. The gene associated with long QT syndrome 1, called KvLQT1 or KCNQ1, codes for an ion channel involved in the delayed rectifier potassium current, I_{Ks}. Long QT syndrome 2 is associated with abnormalities of the *HERG* gene (human ether-a-go-go–related gene), which codes for a protein involved in another delayed rectifier current, I_{Kr}.

Long QT syndrome 3 is due to a mutation of the sodium channel gene. The mutation was initially mapped to a locus on chromosome 3 (121) and later identified as a mutation on the gene *SCN5A* (122). The mutation, although not affecting activation of the channel, prevents proper inactivation of the sodium channel after phase 0 of the action potential. The persistence of some inward sodium current during the plateau phase of the action potential causes prolongation of the action potential. Interestingly, mutations of the same gene causing improper activation of the sodium channel have been identified as the cause of Brugada syndrome (see below).

Long QT syndrome 4 appears to be a rare syndrome associated with a mutation mapped to chromosome 4 (123), but the exact gene has not yet been identified. The gene for long QT syndrome 5, known as *minK*, codes for a potassium channel protein, which, when combined with the *KVLQT1* gene product, forms the slowly activating delayed rectifier current I_{Ks}. The mutated gene causes prolongation of action potential by delaying repolarization. Long QT syndrome 6 has been correlated with an abnormality in the *MiRP1* gene, also located on chromosome 21 (124). This gene codes for a potassium channel protein that coassembles with the *HERG* gene product to form the delayed rectifier current I_{Kr}.

Correlation of the genetic abnormality with ECG T-wave pattern has revealed characteristic patterns that seem to be associated with different forms of the long QT syndrome (Table 67.1). Moss et al. (125) have described three different ECG QT patterns associated with long QT syndrome 1, long QT syndrome 2, and long QT syndrome 3 (Fig. 67.7). These different types of long QT syndromes also appear to have different responses to heart rate acceleration. In long QT syndrome 3, increase in heart rate appears to markedly shorten the QT interval; such is not the case in long QT syndrome 2 (92). The different forms of long QT syndrome also respond differently to pharmacologic interventions aimed at shortening the QT interval. In long QT syndrome 2, in which the defect is in a delayed rectifier potassium channel, potassium loading appears to shorten the QT interval (126). On the other hand, in long QT syndrome 3, in which the defect is in the persistent opening of an abnormal sodium channel, mexiletine, a sodium channel blocker, appears to shorten the QT interval (92).

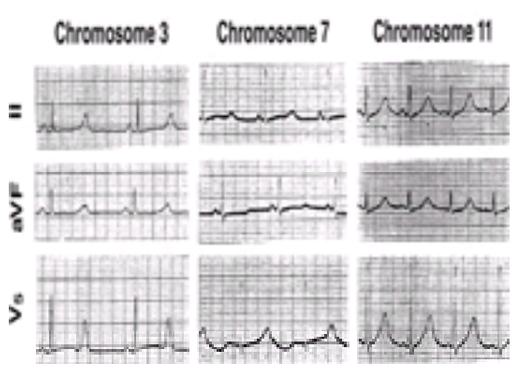


FIGURE 67.7 The QT abnormalities associated with long QT syndrome 1, long QT syndrome 2, and long QT syndrome 3. This figure shows some of the characteristic ST- and T-wave abnormalities associated with some of the long QT syndromes. The electrocardiogram in long QT syndrome 1, associated with an abnormality on chromosome 11, shows broad-based T waves with robust amplitudes. The T wave in long QT syndrome 2, associated with a genetic abnormality on chromosome 7, is also broad-based but tends to have lower amplitudes. Long QT syndrome 3, which comes from an abnormality on chromosome 3, shows a late-initiating and late-peaking T wave with a rather narrow base. (From Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation* 1995;92:2929, with permission.)

The greatest clinical concern with patients who have long QT syndrome is sudden death and syncope. Those patients who have already experienced such an event appear to be at the highest risk. Patients with long QT interval and first-degree family members who have experienced sudden death are also at significantly increased risk (127). Treatment of high-risk patients with the long QT syndrome may soon be undergoing a marked change as the molecular abnormalities associated with specific channel proteins are identified. Traditionally, the treatments have used beta-blockers (98), pacemakers (128), cervicothoracic sympathectomies (129), careful avoidance of drugs that could prolong the QT interval (Table 67.2), and ICDs. Sympathetic tone, especially when associated with sudden arousal, may be a potent stimulant for the development of polymorphic ventricular tachycardia in these patients. Beta-blockers serve to block this effect of sympathetic tone. Pacemakers can prevent bradycardia, which may be another trigger for polymorphic tachycardia. Left-sided sympathectomy may function in a similar manner as beta-blocker therapy but limits its effect to neurally mediated sympathetic stimulation of the heart. However, this approach is no longer used commonly. ICDs, of course, are intended as rescue devices rather than prevention of the arrhythmia. With the pacing function available in current devices, ICDs could potentially perform a dual role of prevention as well as rescue. These traditional approaches, however, may be quickly changing. Recent advances in the understanding of the different manners in which long QT syndrome 3 and long QT syndrome 2 respond to heart rate acceleration, sodium channel blockers, potassium loading, and potassium channel openers, for example, may dramatically alter our approach to therapy and may provide a more rational approach to selection of the traditional therapies in conjunction with possible new pharmacologic approaches.

Antiarrhythmic medications
Type Ia: quinidine, procainamide, disopyramide
Type Ic: encainide (due to metabolites)
Type III: sotalol, amiodarone, ibutilide, dofetilide, *N*-acetyl procainamide
Type IV: bepridil
Antibiotics
Erythromycin, trimethoprim-sulfamethoxazole, ketoconazole, pentamidine
Antihistamines
Terfenadine, astemizole
Psychoactive compounds
Phenothiazines, haloperidol, tricyclic and tetracyclic antidepressants
Chloral hydrate
Miscellaneous
Diuretics (hypokalemia and hypomagnesemia related)
Probucol, cisapride
Corticosteroids
Organophosphate poisoning

Updated list on the World Wide Web: http://georgetownmert.org/
qtdrugs_forsales.asp.

TABLE 67.2 DRUGS ASSOCIATED WITH QT PROLONGATION AND TORSADES DE POINTES

The occurrence of polymorphic ventricular tachycardia and fibrillation in the absence of prolonged QT interval, cardiac ischemia, or marked metabolic abnormalities has been called *idiopathic ventricular fibrillation*. Three syndromes have been described and many isolated cases reported. Brugada and Brugada (130) reported a group of patients with recurrent polymorphic ventricular tachycardia leading to cardiac arrest who had characteristic ECG abnormalities during sinus rhythm. The precordial recordings in the standard 12-lead ECG showed ST elevation mimicking a right bundle branch block (Fig. 67.8). A genetic abnormality of the sodium channel has been identified with this syndrome (131).

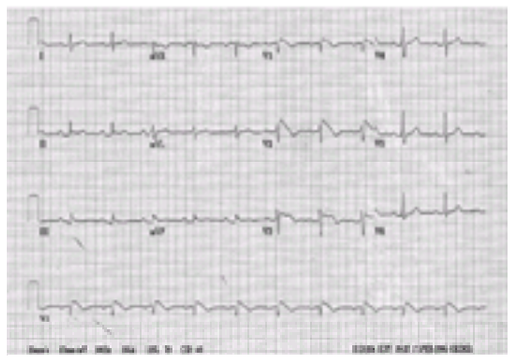


FIGURE 67.8 A 12-lead electrocardiogram from a patient with the Brugada syndrome. Note the ST elevation in the anterior chest leads, especially V1, which mimics the appearance of right bundle branch block. The ST segment slopes gently downward into the inverted T wave, giving the so-called saddleback appearance.

Interestingly, the same gene, *SCN5A*, is implicated in both long QT syndrome 3 and the Brugada syndrome. In contrast to the “gain-of-function” mechanism in long QT syndrome 3, whereby the sodium channel persists in conducting the sodium current by not inactivating adequately, the sodium channel in Brugada syndrome does not generate an adequate sodium current through several different mechanisms: slower recovery from inactivation by a prior depolarization, faster inactivation during depolarization, and a more “sluggish” response to membrane voltage changes (132). In the anterior right ventricular region of the epicardium, this reduced sodium current during phase 0 of the action potential together with the enhanced repolarization current of phase 1 (ITO) seen in the epicardium aborts the usual plateau (phase 2) of the action potential in this region. The voltage gradient between this region and the adjacent myocardium causes the “ST elevation” seen on the ECG. This voltage/repolarization gradient can generate premature ventricular beats and allow wavefront reentry, leading to ventricular fibrillation (133). Although different genetic abnormalities of the *SCN5A* gene have been identified in both the long QT syndrome 3 and Brugada syndrome, a single genetic abnormality may generate both ECG findings, prolonged QT interval and ST elevation, under differing physiologic conditions (134).

The ECG findings of Brugada syndrome may not be persistent and administration of a sodium channel–blocking agent such as flecainide or ajmaline may be necessary as a challenge to reveal this abnormality (135). In symptomatic patients with ventricular fibrillation or syncope, treatment with an ICD is indicated. Asymptomatic patients with the ECG abnormality, either persistent or induced with drug challenge, who have a family history of sudden death at a young age should be treated as well. However, there is a low prevalence (0.05% to 0.10%) of this abnormal ECG finding in the general population without any symptoms or associated family history. Whether any treatment of these individuals is needed remains controversial (136).

Leenhardt et al. (137), reported on a group of young patients who had documented clinical polymorphic ventricular tachycardia and ventricular fibrillation. These arrhythmias appear to be triggered by sympathetic tone and can be reproduced with exercise testing. They frequently present with syncope and seizure-like events. Symptoms are generally triggered by physical or emotional stress. These children have no underlying heart disease and have normal resting ECGs and echocardiograms. The tachyarrhythmia responds well to beta-blocker therapy and a long-acting beta-blocker such as nadolol is the therapy of choice.

Leenhardt and co-authors (138) also reported a syndrome they termed “short-coupled variant of torsades de pointes.” The QT interval is not prolonged. The polymorphic ventricular tachycardia is typically triggered by early ventricular premature beats with short coupling intervals of approximately 250 ms. These patients also have no structural heart disease, but they have a high incidence of sudden death. Beta-blockers do not seem to suppress these arrhythmias. Verapamil may have a beneficial effect. However, an ICD appears to be the most reliable means of preventing sudden death.

DRUG-INDUCED MONOMORPHIC AND POLYMORPHIC VENTRICULAR TACHYCARDIA

Ventricular tachycardia can be seen in certain toxic or idiosyncratic reactions generated by drugs or electrolyte imbalances. Polymorphic ventricular tachycardia associated with drugs that prolong the QT interval is an example. The term “torsades de pointes” was coined by Dessertenne (139) to describe polymorphic ventricular tachycardia where the QRS axis appears to be twisting around a baseline. Torsades has been associated with a variety of antiarrhythmic drug therapies, electrolyte disturbances, and bradycardia due to heart block and hypothyroidism (140,141,142 and 143). A long cycle length, the pause, typically precedes the initiation of this arrhythmia (144) and appears to be a hallmark of drug-induced torsades de pointes (Fig. 67.9). This malignant arrhythmia frequently progresses to sustained ventricular fibrillation and cardiac arrest. Many of the drugs that produce marked QT prolongation in susceptible individuals appear to affect the *HERG*/I_{Kr} potassium repolarization current (145). Thus, a genetic predisposition is most likely present. When QT intervals prolong to 600 ms or when the QTc prolongs more than 500 ms, there is a significant incidence of torsades. Interestingly, amiodarone, although capable of prolonging the QT interval, appears to have a low incidence of causing torsades de pointes (146,147). Table 67.2 lists some of the medications and other conditions that have been shown to produce QT prolongation and torsades de pointes. The list of drugs that could cause QT prolongation and torsades de pointes, especially in patients with the prolonged QT syndrome, is frequently updated and can be obtained from the Georgetown Center for Education and Research on Therapeutics by accessing their Web page on the International Registry for Drug-Induced Arrhythmias (http://georgetowncert.org/qtdrugs_torsades.asp). Besides medications, hypokalemia, hypomagnesemia, hypocalcemia, bradycardia associated with hypothyroidism, and heart block are also potential causes of torsades de pointes. Clinically, torsades de pointes appears to have a predilection for the female gender (148). The cause of this predilection is unclear but may be related to a protective effect of testosterone.

Two potential mechanisms contribute to torsades de pointes. Prolongation of the action potential duration by suppressing the repolarizing transmembrane potassium current is associated with the development of early afterdepolarizations. Myocytes in the middle layers of the ventricular myocardium (M cells) have the longest action potential durations at baseline and may be the source of these afterdepolarizations when the heart is exposed to an agent that prolongs repolarization (149). These early afterdepolarizations are bradycardia-dependent in a similar manner as torsades de pointes. The persistence of the polymorphic ventricular tachycardia and its degeneration into ventricular fibrillation may result from reentry facilitated by the dispersion of repolarization seen in the myocardium when the QT interval is prolonged (150). Interestingly, although amiodarone can prolong QT intervals as readily as other antiarrhythmics, it seems to generate less dispersion of repolarization, perhaps explaining its low associated incidence of torsades de pointes (114).

Treatment of acquired torsades de pointes involves a two-pronged approach—acute therapy to prevent a cardiac arrest and removal of the offending factors generating the prolonged QT interval. Electrolyte levels, specifically those of potassium, magnesium, and calcium, should be checked and corrected to a normal range. Offending drugs should be stopped. Bradycardia due to sinus slowing or atrioventricular block should be corrected quickly with temporary pacing or isoproterenol infusion. Bringing the heart rate up to 100 beats/min is generally adequate to suppress the onset of polymorphic ventricular tachycardia. Intravenous magnesium has been found useful in acutely suppressing torsades de pointes, as it has been demonstrated to suppress early afterdepolarizations in experimental preparations (151). Two grams can be given over 10 to 15 minutes intravenously and repeated if needed. Raising the serum potassium level into the high normal range may also be helpful, as extracellular potassium is known to inhibit the potassium channel–blocking activity of antiarrhythmic drugs (152). These measures should be maintained until the etiologic factors can be removed. In the case of drugs, this may take several days or even longer if amiodarone is the offending agent.

Digitalis toxicity can also induce a ventricular tachycardia, although it is typically a monomorphic ventricular tachycardia. The mechanism by which digitalis causes ventricular tachycardia is through the generation of delayed afterdepolarizations. In experimental preparations, digitalis is one of the agents known to enhance DADs (153). The combination of digitalis toxicity and enhanced sympathetic tone may be a particularly potent stimulus for DADs. Rarely, digitalis toxicity can manifest as a bidirectional ventricular tachycardia. More commonly, it is monomorphic. Clinically, these often manifest as automatic fascicular tachycardias that respond to verapamil but not to adenosine. Because fascicular tachycardia can sometimes have a somewhat narrow QRS and because this tachycardia can respond to verapamil, it is

sometimes misdiagnosed as supraventricular tachycardia (Fig. 67.10). Although the tachycardia will acutely respond to calcium channel blockers such as verapamil, the definitive therapy is to remove digoxin from the tissue through the infusion of digoxin antibody fragments.

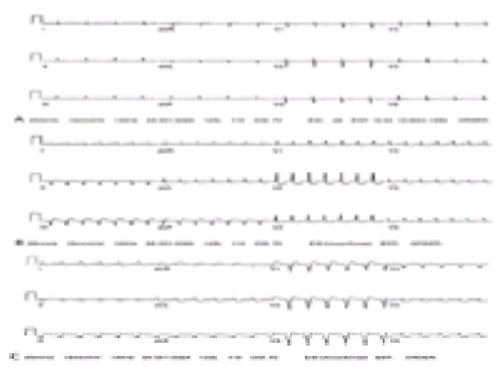


FIGURE 67.10 Ventricular tachycardia induced by digoxin toxicity. This figure illustrates ventricular tachycardia resulting from digoxin toxicity. This patient was in an intensive care unit as a result of acute exacerbation of chronic obstructive lung disease. Digoxin was being administered orally and intravenously because of episodes of atrial fibrillation. **A:** Sinus rhythm. **B,C:** Two different ventricular tachycardias that were initially mistaken for supraventricular tachycardias because of the relatively narrow QRS in **B** and the termination of these tachycardias with intravenous infusions of verapamil. The response of a tachycardia to verapamil cannot be used to indicate the involvement of the atrioventricular node in the tachycardia, as several forms of ventricular tachycardia can respond to this drug. At the time of occurrence of these ventricular tachycardias, the patient's digoxin level was higher than 5 ng per mL.

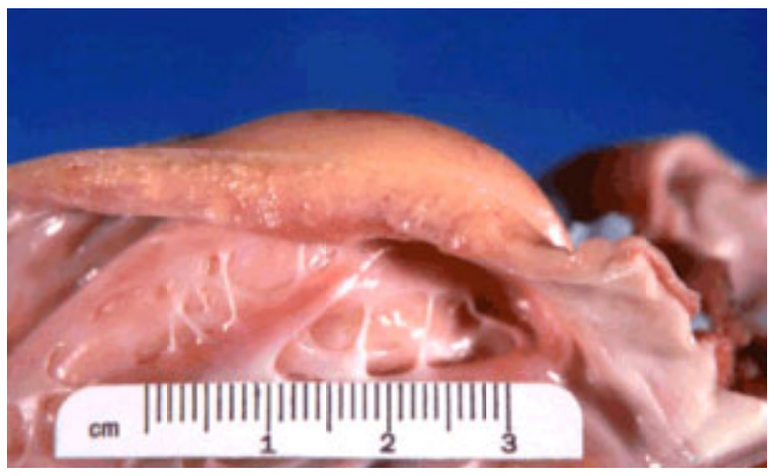
In the case of drug-facilitated ventricular tachycardia, the underlying substrate such as a reentrant circuit within the scarred portion of the myocardium already exists and may even be able to sustain a reentrant tachycardia. However, the electrophysiologic characteristics of the circuit may make the tachycardia difficult to initiate and sustain. In the presence of a drug that modifies these electrophysiologic characteristics, the tachycardia may become more easily initiated and sometimes can even become incessant. The most frequent cause of drug-facilitated ventricular tachycardia is antiarrhythmic medications that slow conduction of the action potential—that is, class I drugs with sodium channel–blocking activity. When such a drug causes frequent or incessant tachycardia, the best therapy is to discontinue the drug. However, clinical management of the patient may be difficult while the drug is being eliminated. Another cause of ventricular tachycardia in susceptible patients comes from the injection, ingestion, or inhalation of sympathomimetics or bronchodilators such as ephedrine (154) or terbutaline (155). Most likely, these patients have a sympathetic-mediated ventricular tachycardia as described above associated with structurally normal hearts. Under more intense sympathetic stimulation while receiving these drugs, the ventricular tachycardia may become sustained for the first time.

MISCELLANEOUS CAUSES OF VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION

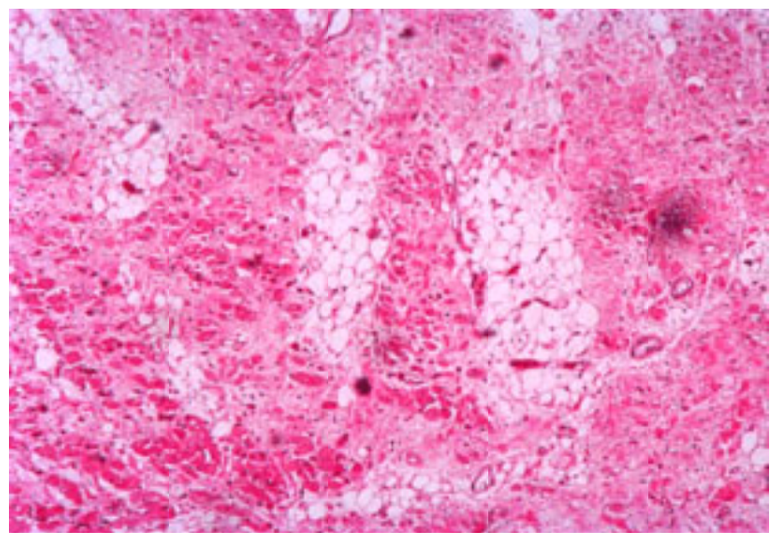
Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic right ventricular dysplasia, an entity first described in the 1970s and better characterized in the early 1980s (156), is a cardiomyopathy that begins in the right ventricle. It is characterized by right ventricle dilation, decreased contractile function, fatty infiltration and scarring of the myocardium, and ventricular tachycardia. The disease process is progressive and eventually affects the left ventricle as well (157,158). Ventricular tachycardia is frequently the first clinical presentation. The tachycardia is most likely reentrant in nature and arises from the right ventricle. Epicardial mappings have shown late potentials in the right ventricular free wall, and signal-averaged ECGs are generally positive for late potentials (159), both indicating that slow activation of parts of the myocardium occur as a result of the fatty infiltration and scarring of the myocardium. This slow conduction forms the substrate for reentry.

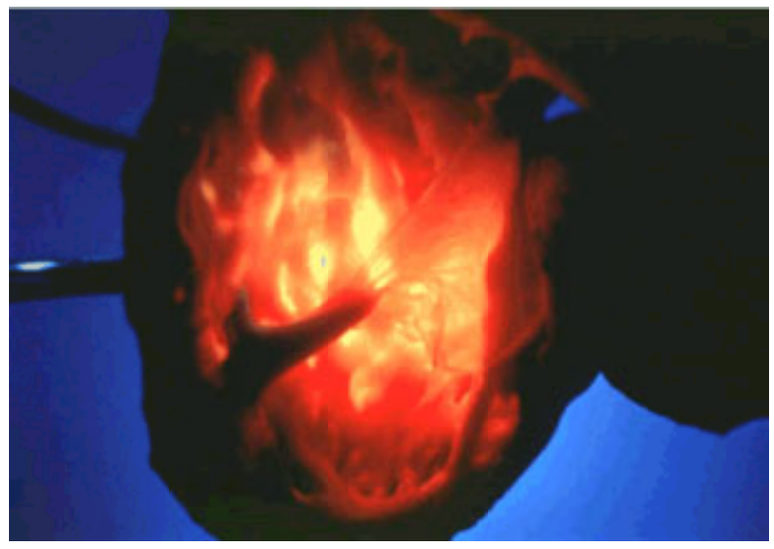
Muscular hypertrophy of the arterial wall in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



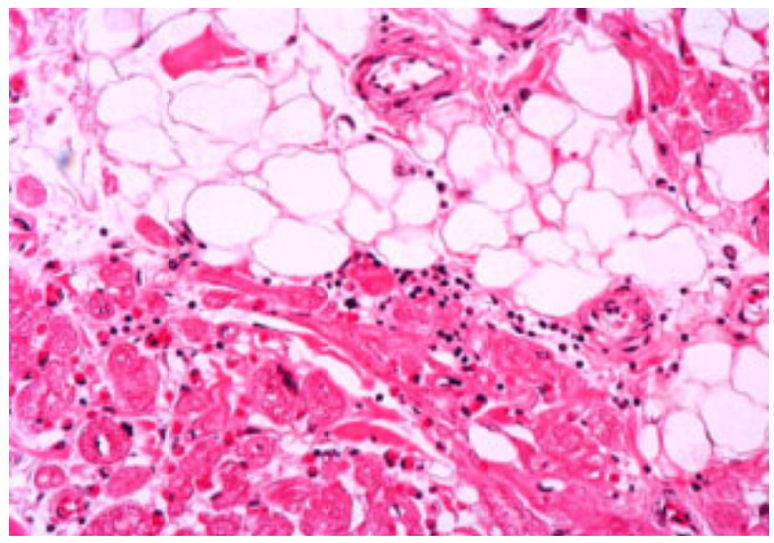
Right ventricle completely replaced by fat in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Arrhythmogenic right ventricular dysplasia with transmural fatty infiltration. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Arrhythmogenic right ventricular dysplasia. Illumination reveals thinned right ventricular wall. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)

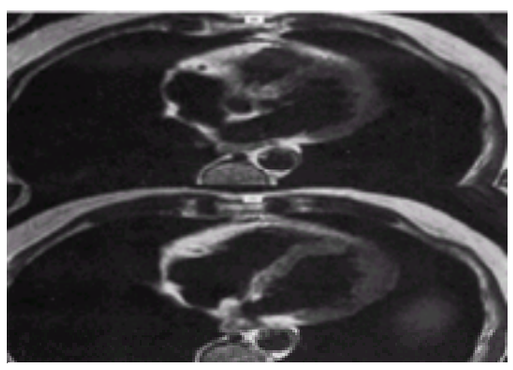


Focal chronic inflammation in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)

VIDEO

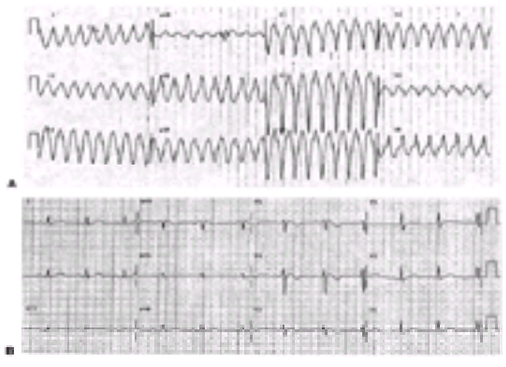
Video 67.1 Arrhythmogenic right ventricular dysplasia (transaxial). Thinning of the right ventricular wall with dyskinesia of the right ventricular free wall during systole is due to fibrous replacement of the myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The pathology of the myocardium can be appreciated by magnetic resonance imaging (eFig. 67.10.1), computed tomography, and direct biopsy. The enlargement of the right ventricle with hypocontractile areas can also be observed on magnetic resonance imaging, by right ventricular angiography, and sometimes on the echocardiogram. The right ventricular angiogram demonstrates a characteristic scalloped appearance of the endocardial outline. The ventricular tachycardia usually has a left bundle branch block pattern due to its origin in the right ventricle. However, it does not usually have the typical appearance of a left bundle branch block QRS, as seen in bundle branch reentrant ventricular tachycardia (eFig. 67.10.2A). The 12-lead ECG during sinus rhythm typically has inverted T waves in the anterior precordial leads (eFig. 67.10.2B), and occasionally one can appreciate a notching of the terminal portion of the QRS, suggesting an incomplete right bundle branch block. This notching has been termed an *epsilon wave*. The generalized infiltration process within the myocardium can create multiple different reentrant circuits. Although there are many sporadic cases, there are also familial clusters of right ventricular dysplasia as well as concurrent presence of the disease in twins, suggesting a genetic abnormality as the etiology (160). Several specific genetic loci have been associated with familial right ventricular dysplasia (161,162 and 163). Thus, there may be multiple genetic abnormalities contributing to this entity. In one family, the genetic abnormality was identified as the mutated plakoglobin gene responsible for generating a protein important in cell-to-cell adhesion, suggesting that disruption of cell junction may play a role in the etiology of this syndrome (164).



***e*FIGURE 67.10.1** Two transverse sections from a gated magnetic resonance image of the thorax in a patient with right ventricular dysplasia. The upper panel shows the right atrium to the left, the right ventricle at the top, and the left ventricle below and to the right. There is increased intensity of the image at the right atrioventricular

groove surrounding the right coronary artery consistent with the fat pad normally seen surrounding the blood vessels of the groove. This increased intensity extends into the right ventricular free wall, indicating infiltration of the free wall with fatty tissue. Near the apex of the right ventricle, there is thinning of the free wall. The lower panel shows a section just below the level of the upper panel, demonstrating that there is extensive fatty infiltration of the entire right ventricular free wall. Note the normal appearance of the left ventricular free wall on these two images. (Images courtesy of Dr. Richard White, The Cleveland Clinic Foundation.)



***e*FIGURE 67.10.2** Electrocardiographic characteristics of arrhythmogenic right ventricular dysplasia. **A:** Twelve-lead electrocardiogram of a ventricular tachycardia having a left bundle branch block QRS morphology and a left axis deviation. This indicates that the tachycardia is originating from the apex of the right ventricle. This patient had extensive dysplasia of the right ventricle with fatty infiltration. **B:** The 12-lead electrocardiogram in the same patient during sinus rhythm. Note the inverted T waves across the anterior chest leads and the slurring of the terminal portions of the QRS in the same leads, suggestive of an incomplete right bundle branch block. This slurring has been called an *epsilon wave*.

Contrary to early descriptions of the disease in middle-aged patients, there is a considerable risk of arrhythmic death in patients who are found to have this disease at a younger age, especially in childhood (165). The risks of ventricular tachycardia and sudden death appear to correlate with the extent of right ventricular involvement (166). Sympathetic stress such as exercise may trigger ventricular tachycardia. Patients who have experienced sustained ventricular tachycardia, syncope, or cardiac arrest are at the highest risk and need to be treated. Large-scale clinical trials comparing various therapies are not available. Among the antiarrhythmic medications, sotalol appears to be most effective, perhaps because of its beta-blockade properties in combination with type III antiarrhythmic effects (167). The usual type I antiarrhythmics appear to have very little success. Amiodarone at higher doses can also work well but may not be well tolerated chronically. Catheter ablation can be used to ablate a particularly frequent or incessant tachycardia. However, because of the multifocal nature of the disease, other tachycardias are frequently present or become manifest later. Thus, catheter ablation can be a palliative therapy but is unlikely to be a curative treatment. ICDs may be the only reliable therapy for the prevention of sudden death in these patients. Despite concerns regarding the safety of implanting an ICD lead into the right ventricle in these patients, experience with ICDs in patients with hemodynamically compromising ventricular tachycardia or cardiac arrest has been positive (168,169).

Sarcoidosis

Cardiac sarcoidosis can cause a variety of cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and complete heart block (170). Occasionally, sudden death may be the presenting symptom. Sarcoidosis in general and its cardiac involvement seem to affect women more than men.

Cardiac involvement with sarcoidosis can be confirmed with nuclear imaging such as thallium-201, gallium-67, or technetium-99m pyrophosphate scans. Magnetic resonance imaging has also been reported to be useful (171). Patients presenting with ventricular tachycardia, syncope, or aborted sudden death are at particularly high risk. Early in the disease process, corticosteroids and other immunosuppressive therapy may be helpful in resolving ventricular arrhythmias (126,172). However, in most patients presenting with sustained ventricular arrhythmias, steroid therapy appears to have no suppressing effects on the arrhythmia (173). Sustained ventricular tachycardia is usually inducible with programmed ventricular stimulation. Drug suppression of inducibility, as in other etiologies of ventricular tachycardia, does not necessarily translate to clinical prevention of recurrence. The main approach to antiarrhythmic drug therapy is the use of amiodarone and sotalol. However, some have advocated the ICD as the best approach in combination with drug therapy as needed in this high-risk group of patients (129,174).

Acute Myocarditis

Acute myocarditis has been associated with both polymorphic as well as monomorphic ventricular tachycardia. Conduction disturbances, ST-segment changes, and T-wave abnormalities can all be seen in acute myocarditis. Some authors have reported favorable responses to steroid therapy (175). Others have reported mixed results, in which ventricular arrhythmias persist even after resolution of acute myocarditis after steroid therapy (176). A combination of antiarrhythmic drug therapy with an attempt at suppressing the inflammation with steroid therapy appears to be needed in these patients.

Muscular Dystrophies

Ventricular arrhythmia and conduction system disturbances have been associated with some of the muscular dystrophies. In particular, Duchenne's muscular dystrophy and myotonic dystrophy have a high incidence of ventricular arrhythmia and occasional sudden death (177,178). In both these entities, signal-averaged ECGs have shown late potentials consistent with delayed cardiac activation, probably originating from myocardium affected by the disease process (179,180). Whereas patients with Duchenne's dystrophy tend not to survive beyond the teenage years, patients with myotonic dystrophies generally survive well into adulthood. In myotonic dystrophy, conduction system disease is a prominent component of its myocardial involvement. This can lead to the development of bundle branch block as well as complete heart block. Besides ventricular tachycardia originating from the affected myocardium, bundle branch reentry and fascicular reentry resulting from the conduction system disease have been reported in these patients (181).

Chagas' Disease

Chagas' disease, a chronic infection with the parasite *Trypanosoma cruzi*, causes a cardiomyopathy secondary to chronic multifocal myocarditis (182). Patients chronically infected with this agent can develop congestive heart failure, conduction system disease, and ventricular tachycardia. The signal-averaged ECG is frequently positive for late potentials in patients with ventricular tachycardia (183). There is a high incidence of sudden death among these patients, probably due to ventricular tachycardia, although complete heart block may contribute to some of these sudden deaths (184,185). Patients with more advanced congestive heart failure are at the highest risk for sudden death. Treatment includes drug eradication of the parasite, therapy for the congestive heart failure, antiarrhythmic drug therapy, pacemakers, and ICDs (186). Catheter ablation of ventricular tachycardia can be successful (187), although recurrence of tachycardia from other foci is frequent.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Although the last 30 years have seen the development of a deeper understanding of the mechanisms of ventricular tachycardia and of several technologies for the treatment of ventricular tachycardia, the application of such technologies is frequently the subject of debate among physicians. With the publication of the Multicenter Unsustained Tachycardia Trial, extending the results of the Multicenter Automatic Defibrillator Implantation Trial, it is now generally accepted that high-risk patients with inducible sustained ventricular tachycardia form a group who are best treated with the ICD as opposed to currently available antiarrhythmic medications.

The use of the electrophysiology study, however, is a costly and invasive means of assessing increased risk for arrhythmic deaths in post–myocardial infarction patients. Whether less invasive means such as T-wave alternans, heart rate variability, and signal-averaged ECG may substitute as well are questions that remain to be answered. Furthermore, debate remains as to whether patients with decreased ventricular function, due to coronary disease or other processes, are all at a high enough risk for arrhythmic deaths to benefit from antiarrhythmic drug or ICD therapy. Several ongoing clinical trials may answer this question in the near future.

How to approach treatment to prevent sudden arrhythmic deaths among patients with nonischemic dilated cardiomyopathy is still undergoing debate. Besides ejection fraction, functional class, prior resuscitation from cardiac arrest, and perhaps the clinical occurrence of syncope, there are no other clinical factors that have a strong predictive value for arrhythmic deaths. Although the presence of nonsustained ventricular tachycardia appears to be associated with increased mortality (188,189), it is unclear whether this increase is due to sudden arrhythmic deaths (190) or if the predictive value of such a finding will be useful (191). Clinical studies have not demonstrated significant benefit of amiodarone in this population as a whole in preventing sudden death. Similarly, no studies exist on the use of ICD implantation. Yet,

given the known increased risk of sudden death among these patients with poor ventricular function, should one consider ICD therapy because of its demonstrated ability to lower sudden death rates in other patients? Some would argue that such an approach is not justifiable until the extent to which life can be usefully prolonged by this approach has been demonstrated by clinical study. Clinical trials specifically aimed at this patient population may yield an answer to this question.

THE FUTURE

Despite a number of unanswered and perhaps unanswerable questions, the direction in which therapy of ventricular tachycardia has moved in the past three decades indicates that it will have an exciting future. The development of preventive medicine aimed at eliminating the underlying disease processes that generate the substrate for ventricular tachycardia is already well under way for coronary artery disease. Similar preventive treatments may develop for the nonischemic cardiomyopathies. Treatment of congestive heart failure with better drugs, transplants, and mechanical hearts may considerably lessen if not eliminate the problem of arrhythmic sudden deaths in these patients. For those who are still at risk, the development of a very small ICD that is relatively inexpensive to insert will minimize the risk of sudden arrhythmic death at an acceptable cost. New mapping technologies that are now being explored combined with new ablation approaches perhaps using different energy sources will make catheter ablation of ventricular tachycardia a reliable and highly successful tool in selected patients. Lastly, the blossoming understanding of the molecular and genetic basis of certain syndromes such as long QT syndrome will allow the application of genetic cures or drug therapies targeted specifically at the molecular defects that promote ventricular arrhythmias and cause sudden deaths in these patients. Those advances would provide not only treatments but also an understanding of those physiologic properties that promote a stable rhythm as opposed to those that facilitate the development of lethal tachyarrhythmias.

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68

SUDDEN CARDIAC DEATH

SANJAY S. DESHPANDE
MASOOD AKHTAR

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Sudden cardiac death is a manifestation of a variety of cardiovascular diseases, most commonly coronary artery disease. The usual mechanism of death is a ventricular tachyarrhythmia. Identification of high-risk subgroups by risk stratification techniques is critical to focus therapies. Aside from beta-blockers and amiodarone in some subgroups, antiarrhythmic drug therapy has no proven benefit in sudden death prevention. In contrast, the implantable cardioverter defibrillator (ICD) provides unparalleled protection from sudden cardiac death, and its role in therapeutics continues to be defined. In reality, a multifaceted approach incorporating community awareness and education in cardiopulmonary resuscitation, primary and secondary prevention of coronary disease, and accurate and timely risk prediction is essential to exact an optimal outcome.

HISTORICAL PERSPECTIVE

Cardiovascular diseases are the leading cause of death in industrialized nations (1,2), and approximately one-half of these deaths occur suddenly, accounting annually for more than 300,000 sudden death fatalities in the United States alone (3,4 and 5). The usual mechanism of death is a ventricular tachyarrhythmia in the presence of structural heart disease (6,7,8 and 9). This chapter reviews the prevalence, mechanisms, evaluation, and management of patients with sudden cardiac death.

The accurate and meaningful classification of death as an adverse outcome is of vital importance in evaluating epidemiologic trends and the outcome of clinical trials. The working definition of sudden cardiac death has been evolving and has come under much scrutiny and criticism. The earlier definition of *sudden cardiac death* established in the 1960s (10) was primarily time based and implied unexpected cardiovascular death occurring within 24 hours of the onset of the fatal event; more recent definitions use 1 hour. The mechanism of death, whether arrhythmic or nonarrhythmic, cannot be always inferred from the time course alone, however. Most sudden cardiac deaths are unwitnessed and unmonitored, and autopsies are rarely done, so categorization of death is somewhat arbitrary (11).

CAUSES OF SUDDEN CARDIAC DEATH

Epidemiology

The estimated more than 300,000 cases per year in the United States are linked primarily to underlying coronary artery disease. A declining trend in death rates from coronary artery disease over the past three decades (12,13 and 14) is related to both the declining incidence and fatality of myocardial infarction (MI) and the improved survival of these patients (15), who would have had fatal ventricular arrhythmias. This trend reflects the combined success of several interventions: primary prevention measures that have affected the incidence of MI, improved public awareness and emergency services, advances in acute medical care for MI, and secondary prevention strategies, which have improved long-term survival. Nonetheless, sudden cardiac death remains an enormous public health problem that exacts a significant toll on the economy, medical resources, and society. It spares no age, race, or gender, and its preponderance in older men is a reflection of the prevalence of coronary artery disease in the population. Based on several large-scale population-based studies, it is known that the incidence of sudden cardiac death increases with age, although it is proportionately greater in younger persons (16). Sudden cardiac death is the initial and only manifestation in 20% of coronary deaths. Women have a lower incidence of sudden cardiac death, although it may represent the first manifestation of underlying coronary artery disease (17). Cigarette smoking and left ventricular (LV) hypertrophy, on a background of coronary artery disease, have been identified as predictive of arrhythmic death (18,19). Limited information is available regarding the incidence of sudden cardiac death in minority groups. A higher incidence among African-Americans compared with white Americans has been observed in some (20,21 and 22), but not all (23), studies. A disturbingly high incidence has been observed among Hispanic persons (23). This disparity in part may be accounted for by inequitable levels of health care access and delivery for minorities compared with whites (24).

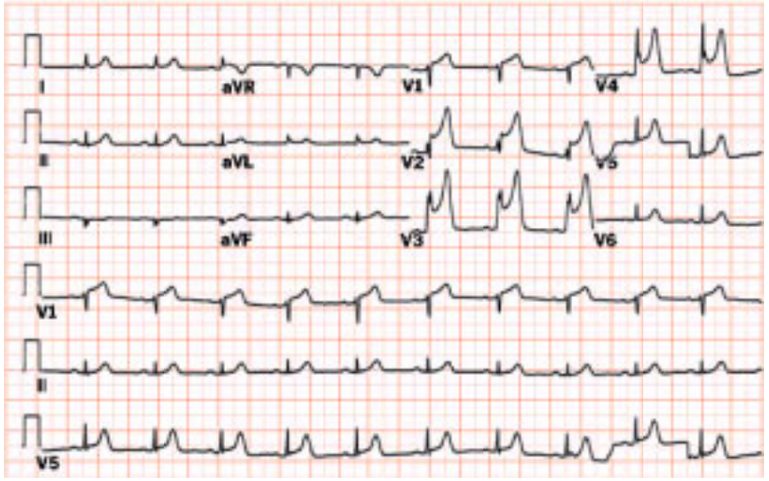
Cardiac Pathology Associated with Sudden Cardiac Death

A variety of structural abnormalities have been identified in sudden cardiac death victims (eTable 68.0.1), and atherosclerotic coronary artery disease remains unquestionably the predominant substrate in autopsy studies. Rarely, despite a thorough evaluation, neither gross examination nor histologic studies are revealing, and cellular abnormalities or transient functional disturbances are presumed to be responsible.

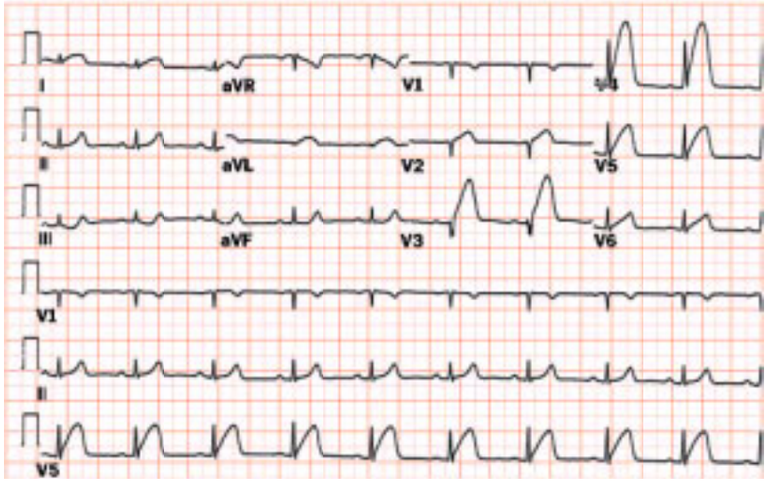
***e*TABLE 68.0.1** CAUSES OF CARDIAC ARREST
Coronary artery disease
Idiopathic dilated cardiomyopathy
Hypertrophic cardiomyopathy and left ventricular hypertrophy
Long QT syndrome (congenital or acquired)
Arrhythmogenic right ventricular dysplasia
Coronary artery anomalies or other congenital heart diseases
Myocarditis
Idiopathic ventricular fibrillation
Other causes (Wolff-Parkinson-White syndrome, conduction system disease)

Acute occlusion of a coronary artery may occur as a result of disruption of an existing plaque or consequent thrombosis or spasm, which may cause a lethal ventricular tachyarrhythmia or, rarely, acute ventricular dysfunction, cardiogenic shock, or ventricular rupture. This event usually occurs in an existing plaque of mild to moderate dimensions. Most patients are asymptomatic or have nonspecific and vague complaints of chest pain in the weeks before the event but had no known atherosclerotic coronary artery disease (25). An acute MI is noted only in approximately 20% to 40% (26,27 and 28), even when active coronary lesions are evident; histologic changes of myocardial necrosis take hours to develop. In contrast, an old MI is commonly observed and frequently active coronary lesions coexist (29,30). Spontaneous fibrinolysis of an acute thrombotic occlusion may leave no apparent trace, although it led to ventricular fibrillation (VF). In the patient with a prior MI, new

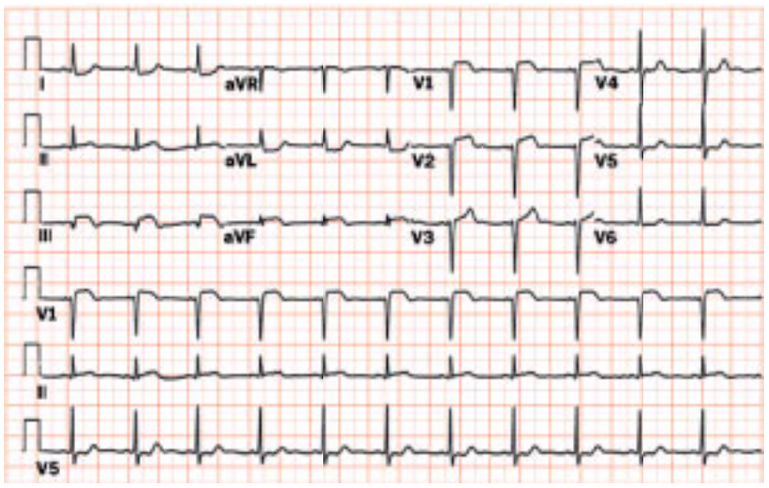
ischemia is the predominant cause of a lethal ventricular tachyarrhythmia. In addition, in approximately 20% of these persons, no evidence of active lesions or any MI is detected, although inactive plaques are observed (31). Vasospasm is a strong possibility as an alternative mechanism in these deaths.



Acute anteroseptal myocardial infarction. Dramatic ST segment elevations in leads V_1 through V_5 with associated hyperacute T-wave changes are noted.



Acute anterolateral myocardial infarction. Note classic "tombstoning" of ST-T waves in the anterolateral precordial leads.



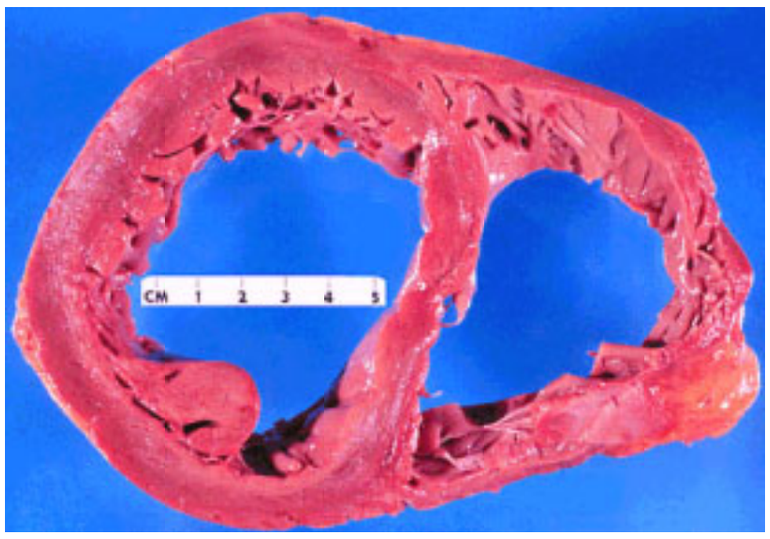
Acute inferior myocardial infarction with right ventricular involvement. Inferior ST-segment elevation associated with elevation in lead V_1. See right precordial leads.

Cardiac rupture after acute transmural anteroseptal myocardial infarction. The yellow arrow indicates the site of rupture.

Recent myocardial infarction with free wall rupture of the anterior wall of the left ventricle. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The

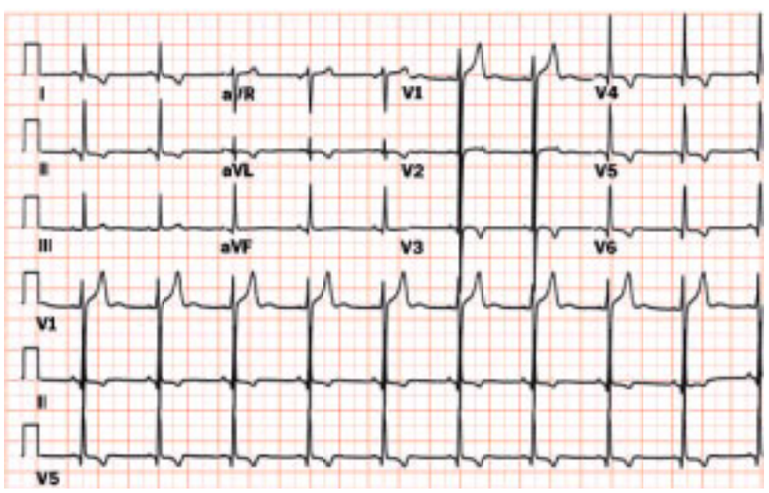
Cleveland Clinic Foundation.)

Nonischemic dilated cardiomyopathies have gained increasing importance in the spectrum of cardiac diseases underlying sudden cardiac death, especially in the face of a declining incidence of coronary artery disease. It is characterized by dilatation of the ventricles, subendocardial scarring, and patchy fibrosis, with impairment of systolic function. By definition, no cause has been identified, although viral infections, autoimmune mechanisms, or genetic abnormalities have been implicated (32,33). Histologically, the idiopathic variety of this disease is characterized by nonspecific findings of interstitial and perivascular fibrosis within the myocardium (33).



Dilated congestive cardiomyopathy. Both the left and right ventricles are significantly enlarged. In this example, the left ventricular wall thickness falls within normal limits.

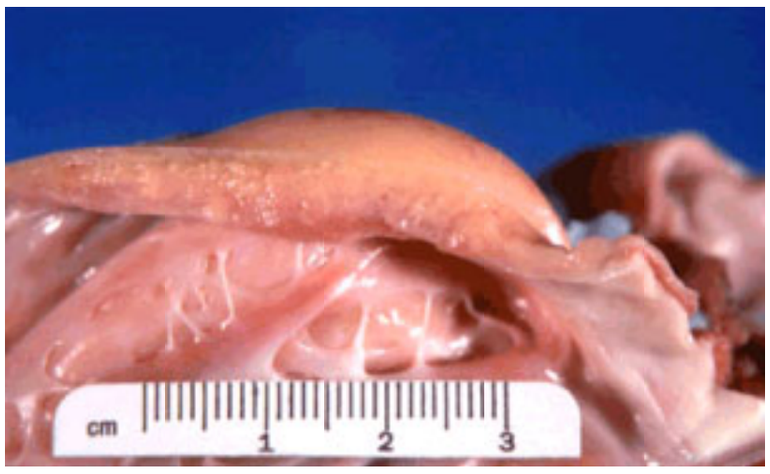
The characteristic feature of hypertrophic cardiomyopathy is a variable pattern of hypertrophy in the disease, and the involvement may be primarily within the septum, posterior LV wall or the apex, or it may be restricted to the mid-LV cavity (34). Histologically, there is gross disorganization of the muscle bundles, fiber orientation, and cellular myofibrillar structure (35). Intercellular communications are disturbed as a result of abnormalities in the gap junction and accumulation of connective tissue. These complex structural and functional abnormalities constitute the altered electrophysiologic milieu in this disease.



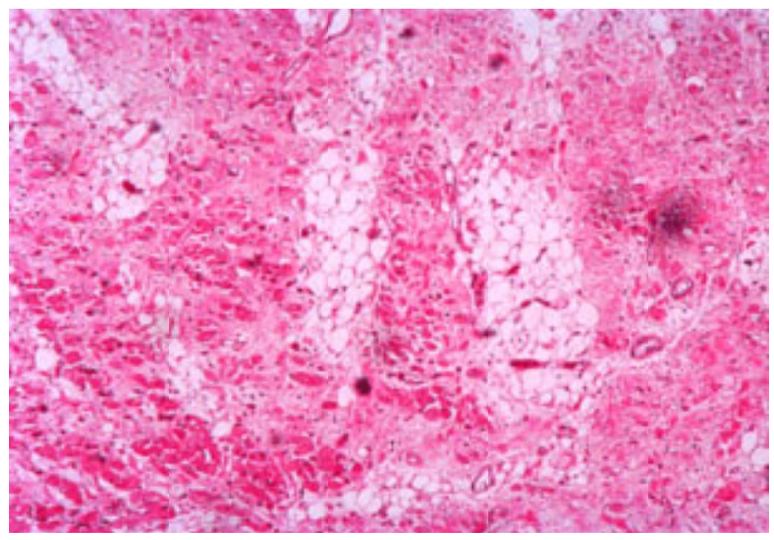
Hypertrophic cardiomyopathy. Inverted precordial T waves associated with hypertrophic cardiomyopathy.

Arrhythmogenic right ventricular dysplasia may be difficult to diagnose even at autopsy in the mildest form of the disease, although it is obvious in the advanced form, where marked ventricular dilatation and replacement of myocardium with fibrous tissue are apparent. Histologic findings are characteristic, with fatty infiltration, thinning of the ventricular wall, and replacement with fibrous tissue (36,37). The intervening myocardial fibers form the arrhythmogenic substrate for ventricular reentry. LV involvement has been associated with a poor prognosis (38).

Muscular hypertrophy of the arterial wall in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Right ventricle completely replaced by fat in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



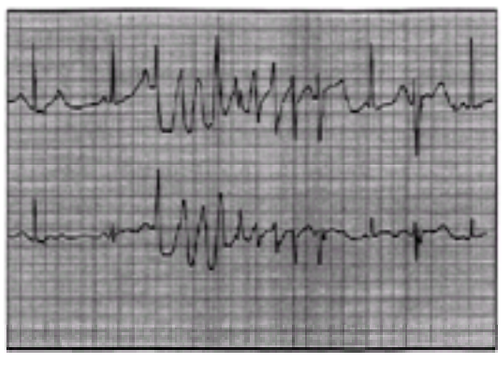
Arrhythmogenic right ventricular dysplasia with transmural fatty infiltration. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)

Arrhythmogenic right ventricular dysplasia. Illumination reveals thinned right ventricular wall. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)

VIDEO

Video 68.1 Arrhythmogenic right ventricular dysplasia (transaxial). Thinning of the right ventricular wall with dyskinesia of the right ventricular free wall during systole is due to fibrous replacement of the myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

It is postulated that the genetic abnormality in the congenital long QT syndrome influences myocardial ionic channels (39,40), increasing cellular susceptibility to autonomic influences. The inciting mechanism for polymorphic ventricular tachycardia (VT) and VF has not been well established, although bradycardia and prolonged repolarization act as the substrate, and sympathetic stimulation acts as the trigger, in some form of interaction (eFig. 68.0.1). Congenital coronary artery malformations have been occasionally implicated in young victims of sudden death (41,42,43 and 44). The most common of these is the anomalous origin of the left coronary artery from the right sinus of Valsalva (44). Primary disease of the myocardium, such as myocarditis, sarcoidosis, and amyloidosis, and congenital or infiltrative disorders of the specialized conduction system may rarely be causative. There is a rare association of sudden death in patients with myxomatous mitral valve disease (45). The Wolff-Parkinson-White (WPW) syndrome also has been associated with sudden death (46,47), but despite its notoriety, the occurrence of sudden death is distinctly rare, especially in asymptomatic persons (48,49). LV hypertrophy in systemic hypertension is being increasingly recognized as an ominous harbinger of cardiac mortality, based on epidemiologic data (50). There is an increased incidence of ventricular arrhythmias with LV hypertrophy (51,52), and the association of asymptomatic ventricular ectopy and LV hypertrophy confers an increased risk of sudden death (53,54 and 55).



***e*FIGURE 68.0.1** A self-terminating episode of torsades de pointes in a young female patient with recurrent presyncope and the congenital form of the long QT syndrome.

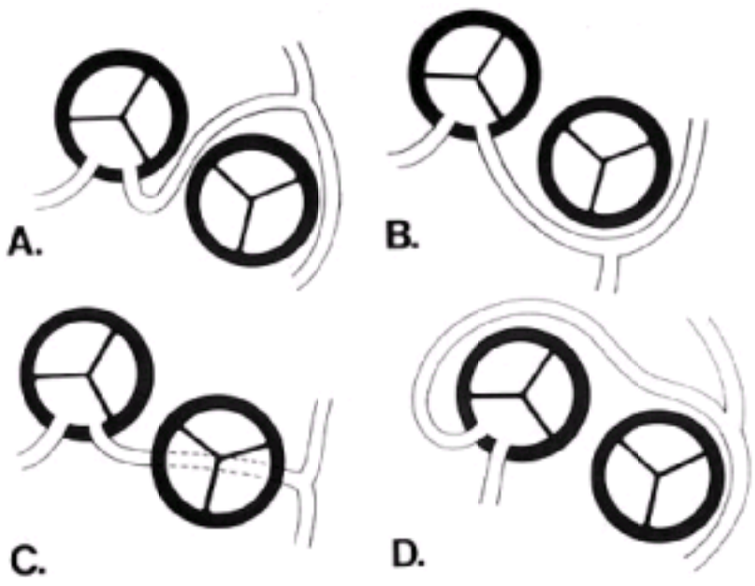


Diagram depicting the variations of the left coronary artery originating from the right sinus of Valsalva. Panel A depicts the left coronary artery arising from the right sinus of Valsalva and coursing between the pulmonary artery and the aorta. Panel B depicts origin of the left coronary artery from the right sinus of Valsalva coursing anterior to pulmonary artery. Panel C depicts the origin of the left coronary artery from the right sinus of Valsalva and coursing intramyocardially in the crista supraventricularis. Panel D depicts the origin of the left coronary artery from the right sinus of Valsalva coursing posterior to the aorta.

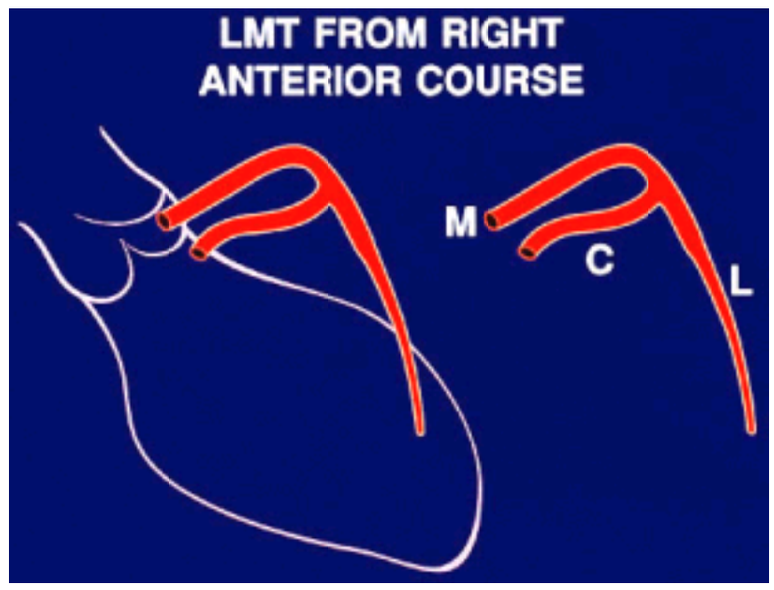
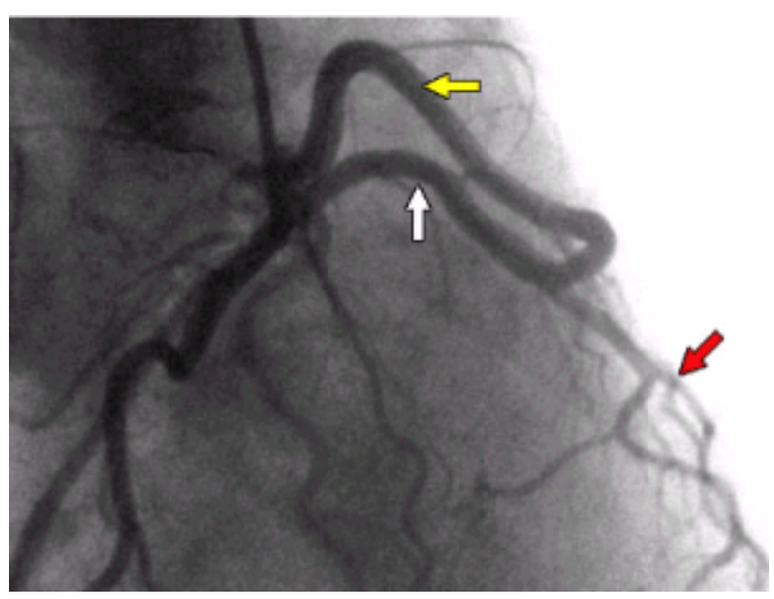


Diagram of the left coronary artery originating from the right sinus of Valsalva with an initial course anterior to the pulmonary artery. Left panel depicts a right anterior oblique projection of the geometry of the left coronary artery as it originates from the right sinus of Valsalva and coursing anterior to the pulmonary artery. The right panel depicts the geometry of the left main trunk (M) with the left circumflex (C) and the left anterior descending artery (L) as seen from the right anterior oblique projection.



Left coronary artery originating from the right sinus of Valsalva with an anterior course. This right anterior oblique projection demonstrates the diagnostic appearance and geometry of the left coronary artery originating from the right sinus of Valsalva and coursing anterior to the pulmonary artery (*yellow arrow*) and bifurcating into the left circumflex (*white arrow*) and the left anterior descending artery (*red arrow*).

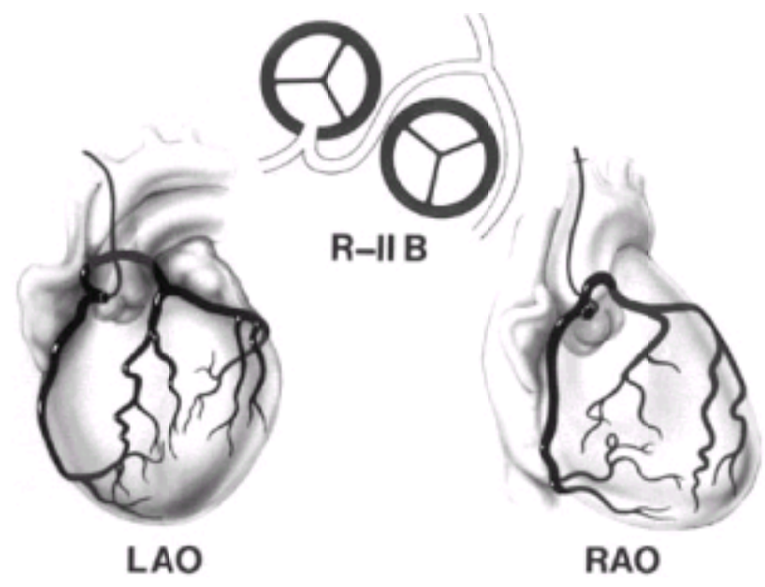


Diagram of a single coronary artery originating from the right sinus of Valsalva with the left coronary trunk coursing between the pulmonary artery and aorta. Left panel depicts a left anterior oblique projection of the single coronary artery originating from the right sinus of Valsalva with a left coronary artery trunk coursing between the pulmonary artery and aorta. The right panel depicts the right anterior oblique projection of the same.

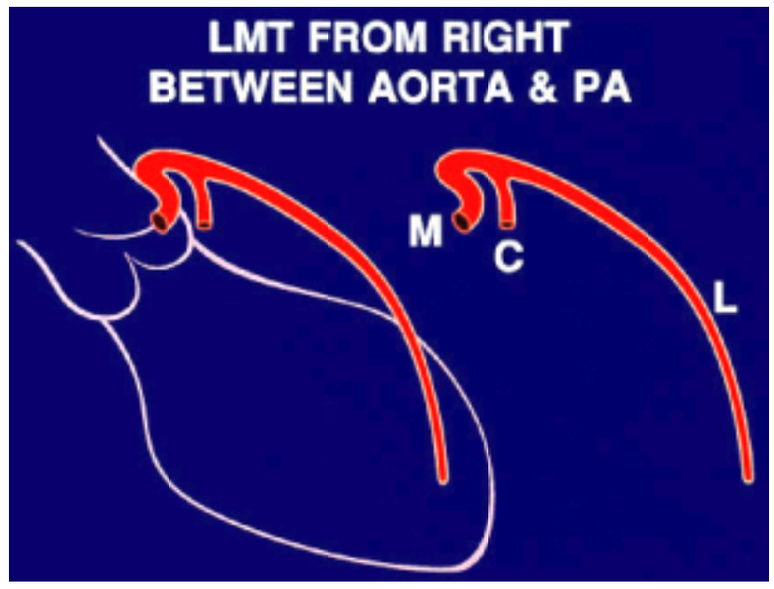
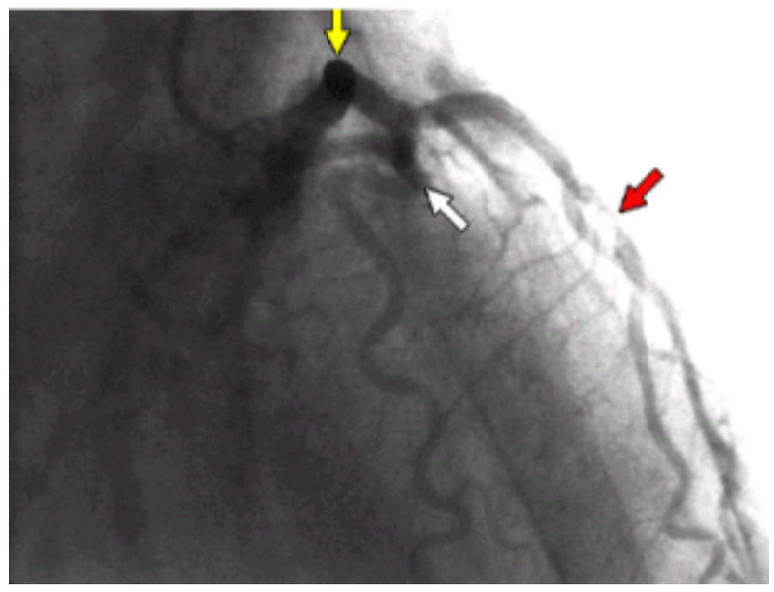


Diagram depicting left coronary artery originating from the right sinus of Valsalva and coursing between the aorta and pulmonary artery. Left panel depicts a right anterior oblique projection of the geometry of the left coronary artery originating from the right sinus of Valsalva coursing between the aorta and pulmonary artery. Right panel depicts the diagnostic appearance and geometry of the left main trunk (M) and the left circumflex (C) and the left anterior

descending artery (L) as seen from the right anterior oblique projection.



Left coronary artery originating from the right sinus of Valsalva and coursing between the pulmonary artery and aorta. This right anterior oblique projection demonstrates the diagnostic appearance of the left main trunk (*yellow arrow*) originating from the right sinus of Valsalva and coursing between the pulmonary artery and aorta to give rise to the left circumflex artery (*white arrow*) and the left anterior descending artery (*red arrow*).

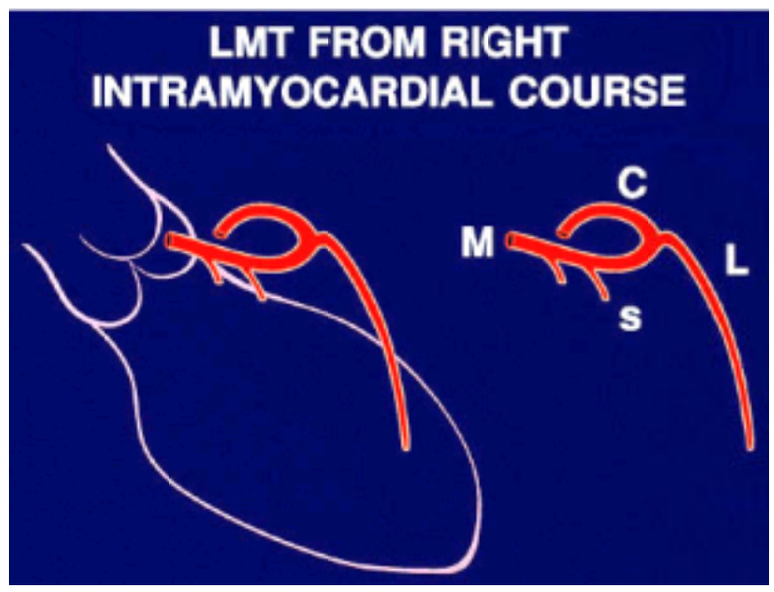
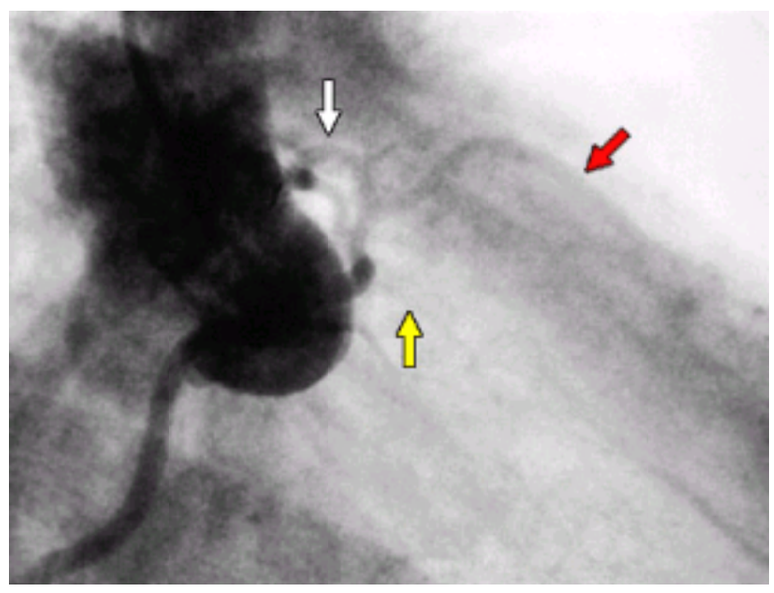
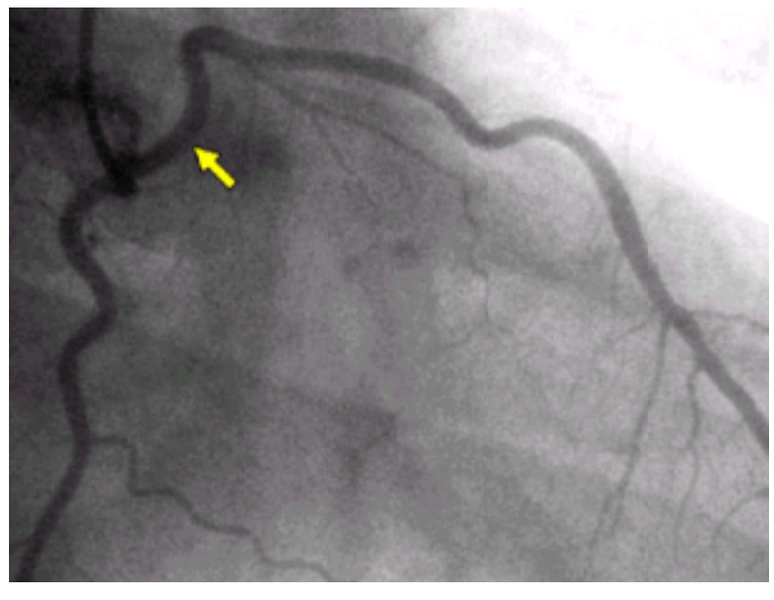


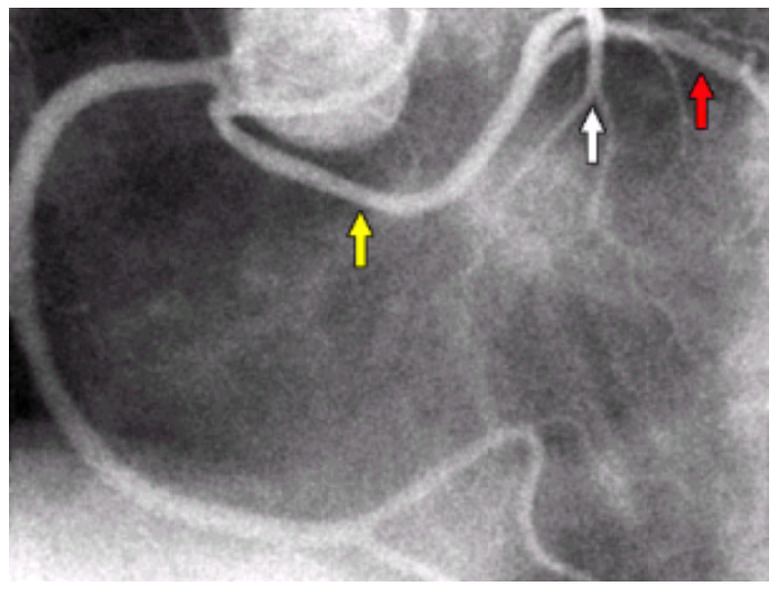
Diagram depicting left coronary artery originating from the right sinus of Valsalva and coursing intramyocardially to give rise to left anterior descending artery and the left circumflex artery. Left panel depicts a right anterior oblique projection of the left coronary trunk originating from the right sinus of Valsalva and coursing intramyocardially before giving rise to the left circumflex and the left anterior descending artery. Right panel depicts the diagnostic appearance and geometry of the left main trunk (M) coursing intramyocardially and giving rise to septal perforating branches (S) before giving rise to the left circumflex (C) and the left anterior descending artery (L).



Left coronary artery originating from the right sinus of Valsalva and coursing intramyocardially to give rise to the left circumflex and the left anterior descending artery. Flush injection of the right coronary sinus depicts a left coronary artery originating from the right sinus of Valsalva and coursing intramyocardially and giving rise to septal perforating branches (*yellow arrow*) and ultimately giving rise to the left circumflex (*white arrow*) and the left anterior descending arteries (*red arrow*).



Right anterior oblique projection demonstrating left anterior descending artery arising from dual outlet trunk with ostium in the right coronary sinus. The geometry of the proximal left anterior descending artery (*yellow arrow*) in this right anterior oblique projection is diagnostic for a course between the aorta and the pulmonary artery.



Left anterior oblique cranial projection of a right coronary sinus flush injection demonstrating the left coronary trunk (*yellow arrow*) originating from the right sinus of Valsalva and coursing posterior to the aorta and pulmonary artery to give rise to the left circumflex (*white arrow*) and the left anterior descending artery (*red arrow*).

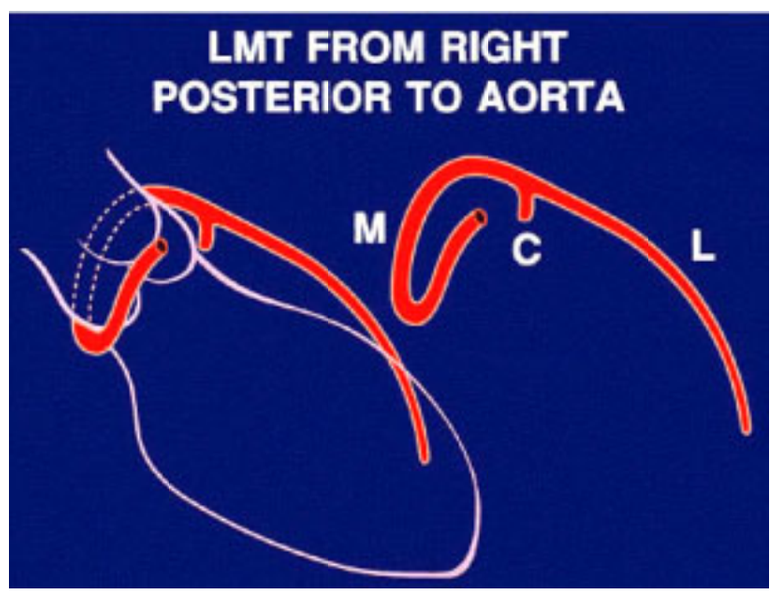
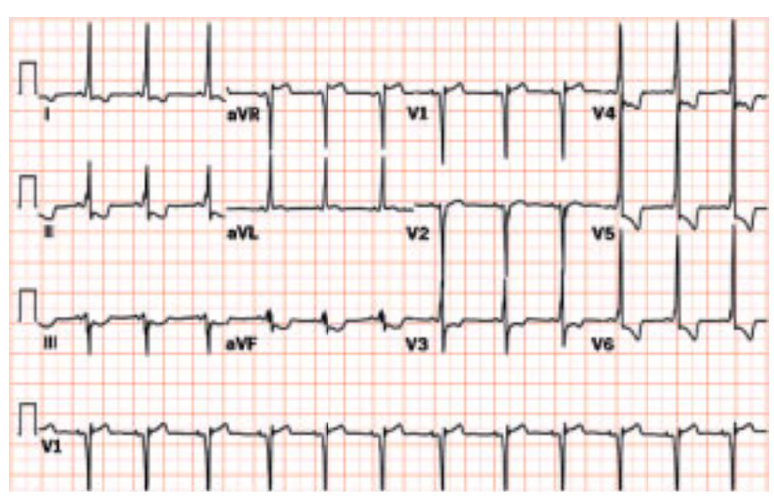


Diagram of the left coronary artery originating from the right sinus of Valsalva and coursing posterior to the aorta and the pulmonary artery to give rise to the left circumflex and the left anterior descending artery. Left panel depicts a right anterior oblique projection of the left coronary artery originating from the right sinus of Valsalva and coursing posterior to the aorta and the pulmonary artery to give rise to the left circumflex and the left anterior descending artery. Right panel depicts the diagnostic appearance and geometry of the left coronary trunk (M) originating from the right sinus of Valsalva and coursing posterior to the aorta and pulmonary artery to give rise to the left circumflex (C) and the left anterior descending arteries (L).



Wolff-Parkinson-White syndrome. Eleven-year-old patient with manifest preexcitation consistent with Wolff-Parkinson-White.

Sudden Cardiac Death in Advanced Ventricular Dysfunction

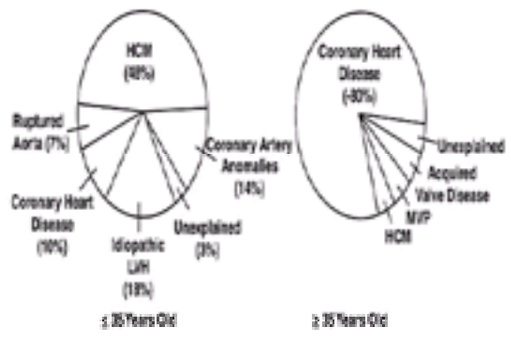
Approximately 4.8 million persons are affected by heart failure in the United States, and this population is growing (56,57). The survival of these patients is limited not only by progressive pump dysfunction but also by the risk of sudden cardiac death (58,59,60,61,62 and 63). Although VF is the usual mechanism of sudden cardiac death in the out-of-hospital setting, bradyarrhythmias and electromechanical dissociation are much more common in this population (6,64,65) (*e*Table 68.0.2). Monomorphic VT is relatively uncommon in these patients, but when induced, bundle branch reentry is identifiable as the mechanism in up to 36% of those with nonischemic cardiomyopathy (66). Intramyocardial fibrosis, small vessel disease, and ventricular hypertrophy (67,68) constitute the major substrate abnormalities and are accompanied by cellular derangements such as abnormal resting membrane potentials, increased temporal dispersion of repolarization, and abnormal intracellular handling. Fluctuations in potassium or magnesium concentrations induced by diuretic or angiotensin inhibitor use, myocardial stretch from ventricular dilatation, and a high sympathetic tone and parasympathetic withdrawal are invariable accompaniments of advanced heart failure and have been implicated in arrhythmogenesis.

***e*TABLE 68.0.2** CARDIAC ELECTRICAL ACTIVITY AT THE TIME OF CARDIAC ARREST

Sudden death	**Patients (n)**	**Bradyarrhythmia/electromechanical dissociation (%)**	**Ventricular tachycardia/ventricular fibrillation (%)**
Ambulatory (268)	157	16.5	83.5
Advanced heart failure (64,65,267)	53	58.0	42.0
Heart transplantation waiting list (64,267)	24	68.0	32.0

Athletes

The occurrence of sudden death in an athlete is an unexpected and catastrophic event, because it epitomizes the paradox of physical fitness (69). Most of these athletes are virtually asymptomatic before the event and usually collapse during intense physical activity. Epidemiologic data with regard to age, gender, and race are sparse. A heterogeneous spectrum of occult cardiovascular disease is found to be responsible (41,42,43,44,45,46,47,48,49,50,51,52,53,54 and 55,70,71 and 72) (*e*Fig. 68.0.2), although the most common underlying entity is hypertrophic cardiomyopathy. Other causes include congenital coronary anomalies (41,42,43 and 44), arrhythmogenic right ventricular dysplasia, myocarditis, idiopathic dilated cardiomyopathy, valvular and aortic root disease, and sarcoidosis. Coronary artery disease may be putative, especially in the older athlete (73,74). In a few cases, despite careful pathologic evaluation, no evidence of structural cardiovascular disease is found. In such cases, the abnormality may have been missed, substance abuse and high-risk behavior may be contributory, or a dynamic event such as the long QT syndrome or coronary spasm may be speculated as the mechanism of death. The use of drugs such as heroin, tricyclics, alcohol, and particularly cocaine poses a risk for sudden death irrespective of the dose, mode of administration, or frequency of use; heart disease is not a prerequisite (75).



***e*FIGURE 68.0.2** The causes of sudden death in competitive athletes differ in the younger (younger than 35 years) and older athlete (older than 35 years). HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; MVP, mitral valve prolapse. (From Maron BJ, Roberts WC, McAllister HA, et al. Sudden death in young athletes. *Circulation* 1980;62:218–229, with permission.)

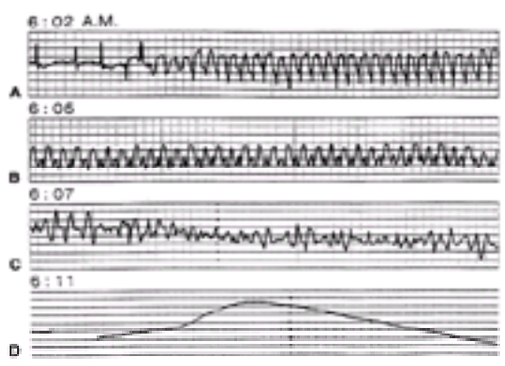
Pediatric Population

In contrast to adults, in whom coronary artery disease is the predominant etiology for sudden cardiac death, a wide variety of disorders are responsible in the pediatric population. Epidemiologic data for this population are scant, yet pooled data (76) report rates ranging from 1.3 to 8.5 per 100,000 patient-years, which translates into several thousand sudden cardiac deaths annually. Sudden death in an apparently healthy child is rare, and here hypertrophic cardiomyopathy, coronary artery anomalies, myocarditis, conduction system abnormalities, and valvular and aortic root disorders may be responsible. Most deaths mechanistically are due to ventricular tachyarrhythmia or atrioventricular (AV) block. Supraventricular tachycardias almost never cause sudden death in the pediatric population. Children who have undergone surgery for congenital heart disease remain at risk for late sudden cardiac death as well, and the risk depends on the nature of the underlying abnormality. Commotio cordis, or nonpenetrating blunt trauma to the anterior chest wall from a baseball or hockey puck, during amateur sporting activities, may lead to a fatal arrhythmia (VF or bradycardia) in a person with a healthy heart (69,77,78). Rarely, sudden death may be a result of extreme bulimia or anorexia nervosa (79) in adolescents or teenagers. Sudden infant death syndrome remains an unexplained entity, although QT abnormalities are suspected to be the basis.

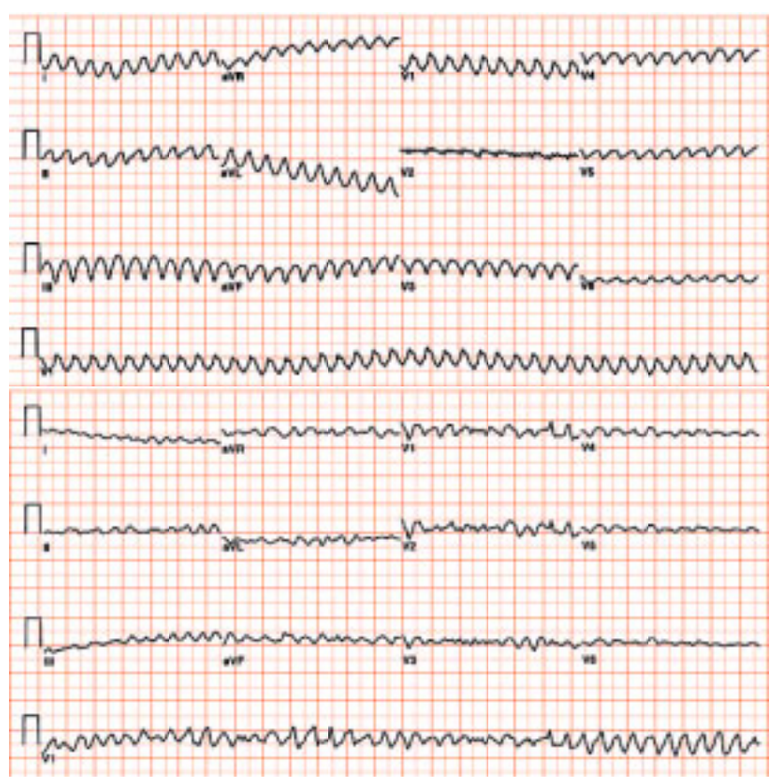
MECHANISMS OF SUDDEN CARDIAC DEATH

Arrhythmic Sudden Death

Whenever electrocardiographic monitoring is available at the onset of sudden cardiac death, it appears that VT or VF is the most common initial rhythm. Ambulatory electrocardiographic recordings obtained from a large series of patients who were wearing a Holter monitor at the time of cardiac arrest (eFig. 68.0.3) show that ventricular tachyarrhythmias, including monomorphic VT that transformed to VF, were the primary event in 83% of patients and bradyarrhythmias in 17% (6), regardless of the underlying heart disease. Similar findings were reported by others (80). These data should, however, be interpreted with caution because the patient population they represent had a high proportion of antiarrhythmic drug use. Rarely, supraventricular arrhythmias are the primary event that degenerate into VF (81).

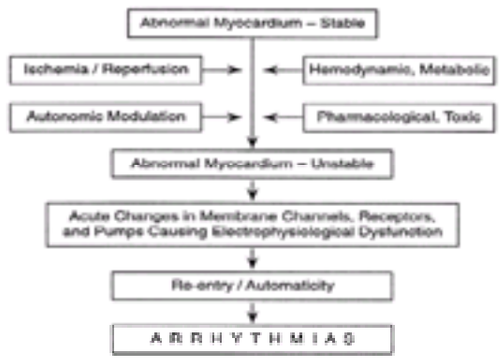


***e*FIGURE 68.0.3** Typical sequence of events culminating in sudden cardiac death are depicted in a Holter recording obtained from a patient. This figure also illustrates the transformation of rhythm from ventricular tachycardia to ventricular fibrillation and finally asystole with time. (From Akhtar M, Garan H, Lehmann H, et al. Sudden cardiac death: management of high risk patients. *Ann Intern Med* 1991;114:499, with permission.)



Ventricular flutter (A). Same patient with degeneration into ventricular fibrillation (B).

In a simplistic sense, the genesis of an arrhythmia requires the interaction between a structurally abnormal substrate and its modulation by a transient perturbation (eFig. 68.0.4). Nearly all forms of structural heart disease are associated with a roughly equal risk of sudden cardiac death, and statistically coronary artery disease and the cardiomyopathies are the most prevalent in the general population. Each may be viewed as a stable substrate with identifiable electrophysiologic abnormalities, which may be transiently altered by dynamic modulating influences, generating a lethal arrhythmia. A discussion follows of these evanescent and variable triggers, and eTable 68.0.3 outlines them.



***e*FIGURE 68.0.4** The influence of functional modulation of an underlying anatomic substrate ultimately leading to the development of ventricular arrhythmias. An electrophysiologically stable substrate is transformed by one or more factors, leading to cellular electrophysiologic dysfunction. This may result in ventricular tachyarrhythmias. (From Myerburg RJ, Kessler KM, Castellanos A. Pathophysiology of sudden cardiac death. *Pacing Clin Electrophysiol* 1991;14:935–943, with permission.)

***e*TABLE 68.0.3** POTENTIAL TRIGGERS OF SUDDEN CARDIAC DEATH
Transient ischemia or reperfusion
Sympathovagal imbalance
Metabolic derangements
Proarrhythmia (antiarrhythmic and other drug use)
Hemodynamic alterations
Electrical triggers (bradycardia, premature ventricular complex)

Transient Ischemia and Reperfusion

Both transient ischemia and reperfusion have significant electrophysiologic effects in cardiac tissue. The primary effects of ischemia are alteration in the regional conduction velocities and creating or enhancing dispersion of conduction patterns and refractoriness, thereby facilitating reentry. In the presence of prior infarction, acute ischemia is even more arrhythmogenic (82). The phenomenon of reperfusion has distinct and possibly additive electrophysiologic consequences and should not be viewed merely as undoing of ischemia. Reperfusion primarily causes calcium overloading and automatic activity (83), and its effects are proportional to the duration of the conditioning ischemic event (i.e., the most serious reperfusion arrhythmias occur with a short prior ischemic episode) (84).

Circadian variations in the occurrence of sudden cardiac death with a higher event rate in the early morning hours appear to parallel those of other cardiovascular events, such as transient myocardial ischemia, thrombotic stroke, and MI (85,86). This occurrence appears to be the culmination of a number of physiologic processes that also have diurnal variations, including morning peaks in heart rate, blood pressure, catecholamine and cortisol levels (85,87), and coronary vascular tone (88). Diurnal variations in the platelet clotting system and intrinsic fibrinolytic system also coincide in the morning hours, increasing the thrombotic risk (89,90).

Role of the Autonomic System

Compelling evidence now exists linking the autonomic nervous system and sudden cardiac death (91,92 and 93), and this is addressed more thoroughly in Chapter 77. Animal data show that in the setting of acute MI, enhanced sympathetic activity promotes malignant ventricular tachyarrhythmias, and beta-blockade or increased vagal tone provides a protective antifibrillatory effect (94,95). This phenomenon is evident even when acute ischemia is superimposed on chronic infarction. Interruption of sympathetic and parasympathetic nerve fibers in the region of transmural MI and consequent denervation hypersensitivity create vulnerability for VF (96). The consequent regional sympathovagal imbalance and hypersensitivity may thus promote VF through complex interactions in coronary artery disease. The results of the beta-blocker trials after MI showed significant reductions in subsequent sudden death and total mortality and reinfarction rates (97,98 and 99), presumably by modifying the autonomic influences. Torsades de pointes has been linked to after-depolarizations, and in the congenital variety the trigger appears to be adrenergic stimulation.

Metabolic and Proarrhythmic Factors

Metabolic disturbances are inevitable in the context of cardiovascular disease. Hypoxemia and acid–base abnormalities, especially in the setting of advanced ventricular dysfunction, can provoke lethal arrhythmias (58,100). Hypokalemia caused by diuretic use prolongs repolarization and has been linked to torsades de pointes. Diuretics have been associated with an increased risk of sudden and total cardiovascular mortality (101). Antiarrhythmic drug therapy can facilitate reentry by stabilizing preexisting circuits or by creating new areas of functional conduction block. The distribution of antiarrhythmic drugs and their actions also are significantly modulated by coronary blood flow, local pH, resting membrane potential, and disease states that alter distribution or metabolism of these drugs. Torsades de pointes as a proarrhythmic response was first observed with the use of quinidine (102). It has since been seen with other class I agents, class III agents, and noncardiovascular drugs, such as pentamidine, erythromycin, terfenadine (Seldane), and psychotropics. In contrast, flecainide and encainide contribute an additive risk to acute ischemia rather than a direct effect, occurring on a background of a prior MI, as was evident in the Cardiac Arrhythmic Suppression Trial (103). The salutary effects of oral inotropic agents, such as amrinone in heart failure, were offset by the adverse effects on mortality, presumably by a proarrhythmic mechanism.

Hemodynamic Factors

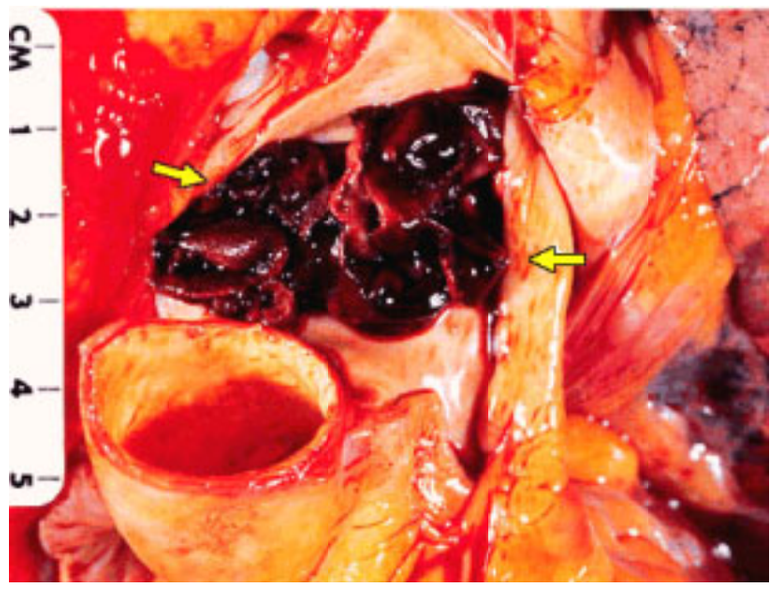
Experimental data support alteration of refractoriness with increasing ventricular volume (104,105), and in the setting of an old MI, these changes may be regionally disparate (106), facilitating ventricular arrhythmias. Clinical data support a higher sudden cardiac death risk in advancing ventricular dysfunction and an association between worsening arrhythmias and hemodynamic decompensation (107). It is likely that other triggers also may be facilitatory.

Role of Electrical Triggers

Electrical triggers are specific electrophysiologic mechanisms that can trigger ventricular tachyarrhythmias. Despite the prevalent view that premature ventricular beats trigger monomorphic VT, in reality this seldom occurs (108). It has been proposed that repetitive concealed reentry within a preexisting circuit (in association with myocardial fibrosis) continually occurs during each beat of the native rhythm; however, this process usually is aborted by depolarization of the boundaries of the reentrant circuit. The late potentials on a signal-averaged electrocardiogram (SAECG) (109) and development of incessant VT after antiarrhythmic drug therapy (110) are clinical correlates of abortive concealed reentry. Alteration of the conduction characteristics both within or around the reentrant circuit may be facilitated by autonomic, hemodynamic, or pharmacologic influences, which can lead to manifest reentry producing either a single premature ventricular complex or a repetitive response (VT). The acquired form of torsades de pointes is usually triggered not by a premature ventricular complex but by the ensuing pause. The arrhythmia also may occur in the clinical setting of sinus bradycardia or AV block, in susceptible individuals. Bradycardia is an uncommon initial event in sudden cardiac death and is more likely a result in advanced heart failure. When it occurs, even in a monitored situation, salvage by cardiac pacing is usually not feasible.

Nonarrhythmic and Noncardiac Causes of Sudden Death

Classification of death as sudden and cardiac generally implies that it was arrhythmic. Nonarrhythmic and noncardiac causes of death can simulate the clinical circumstances of instantaneous cardiac death, even when witnessed (11). Rupture of an abdominal or thoracic aortic aneurysm, intracerebral hemorrhage, massive pulmonary embolism, and prosthetic valve dysfunction also can mimic sudden cardiac death. Although clinical information may be helpful in identifying these as the mechanism of death, a carefully performed autopsy is the most credible method.

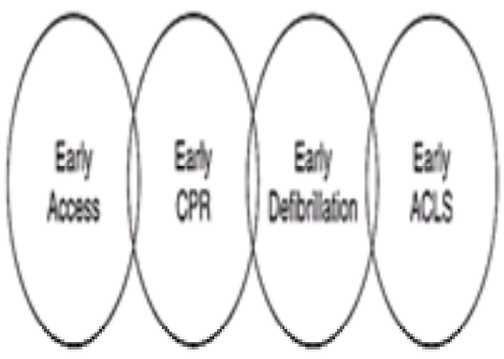


Saddle embolism of the pulmonary artery. The pulmonary artery has been opened via an anterior incision. Multiple fragments of thrombi protrude from the open pulmonary artery and are wedged into both the left and right pulmonary artery branches (*yellow arrows*).

MANAGEMENT OF OUT-OF-HOSPITAL SUDDEN CARDIAC DEATH

A substantial proportion of sudden cardiac arrests occur outside the hospital (3); however, only 1% to 20% of these patients survive to hospital discharge (111,112,113 and 114). The initial rhythm depends on the time elapsed from the onset of cardiovascular collapse to the first electrocardiographic recording (*e*Fig. 68.0.3). VF is present in 95% of cases and asystole in 5% if the elapsed time is less than 4 minutes (115). This proportion changes to 71% VF and 21% asystole when the time from collapse is 12 to 15 minutes, supporting the theory that asystole and electromechanical dissociation are usually secondary to prolonged VF and its metabolic consequences. When the elapsed time is unknown, VF is the initial rhythm in 40%, asystole in 40%, electromechanical dissociation in 20%, and VT in 1% (116). Cardiac arrest may begin as a VT that rapidly degenerates into VF, although this is less common than is generally perceived. Long-term survival is related directly to the initial recorded rhythm and is poor with asystole or electromechanical dissociation (1% and 6%, respectively), and approximately 25% with VF. Those patients who are found in VT at the time of initial contact have the best short-term outcome (117).

A person's chance of surviving cardiac arrest is influenced strongly by the time elapsed from collapse to cardiopulmonary resuscitation. The American Heart Association emphasizes the concept of the "chain of survival" in the approach toward sudden cardiac death (*e*Fig. 68.0.5). The links in this chain are defined as early access (recognition of symptoms and signs of cardiac arrest and mobilization of emergency services), early cardiopulmonary resuscitation, prompt defibrillation, and early advanced care. The success of this approach is critically dependent on the sequential activation and operation of each link. A delay in calling for help is frequently cited as a significant factor affecting outcome, despite public awareness and media campaigns. The local unavailability of a tiered emergency response system, overloaded phone lines and operators, and difficulties in reaching victims promptly because of traffic patterns also contribute to the weakness in the chain. Persons receiving bystander cardiopulmonary resuscitation are more likely to survive than those who do not (118) (*e*Table 68.0.4). However, despite this glaring fact, cardiopulmonary resuscitation is infrequently attempted by bystanders, including family members, who are the usual witnesses. This reluctance stems from a multitude of factors, such as the fear of doing more harm than good, concerns regarding transmission of the human immunodeficiency virus or other pathogens, and inadequate knowledge of cardiopulmonary resuscitation techniques.



***e*FIGURE 68.0.5** The schematic chain of survival to optimize the chance of successful resuscitation. ACLS, advanced cardiac life support; CPR, cardiopulmonary resuscitation. (From Cummins R, Ornato JP, Thies WH, et al. Improving survival from sudden cardiac arrest: the "chain of survival concept." *Circulation* 1991;83:1831–1847, with permission.)

***e*TABLE 68.0.4** NEUROLOGIC OUTCOMES OF CARDIAC ARREST

	With bystander cardiopulmonary resuscitation (n = 36)	**No bystander cardiopulmonary resuscitation (n = 82)**	***p* Value**
Purposeful activity at admission	18/36 (50%)	5/82 (6.1%)	<.001
Conscious by 24 hours	22/36 (61%)	7/82 (9%)	<.001
Confused at discharge	1/27 (4%)	18/38 (47%)	<.001
Vegetative state at discharge	0	3/38 (8%)	<.001

From Cobb LA, Hallstrom AP. Community-based cardiopulmonary resuscitation: what have we learned? *Ann N Y Acad Sci* 1982;382:330–342, with permission.

Prompt defibrillation substantially improves the likelihood of survival after out-of-hospital cardiac arrest (8,119). The newer automatic external defibrillator, which prompts commands during its use, is considerably easier to use by a less skilled person than a manual defibrillator. These automatic external defibrillators, when used in communities where prehospital defibrillation is lacking, have provided good results (113,116). Survival to hospital discharge has been up to 50% when automatic external defibrillators have been deployed by police and paramedics (120) and up to 26% when used in airline cardiac arrest programs (121). Intravenous amiodarone has been advocated in the initial resuscitative attempts for refractory VT or VF (122).

During the past two decades, prehospital care has evolved to shorten the time from collapse to defibrillation, and elaborate systems of emergency prehospital care have been established to provide improved resuscitative efforts. The best results from bystander-initiated cardiopulmonary resuscitation and rapid deployment of an experienced emergency response system are evident in Seattle, Washington, where field resuscitation rates of 43% have been noted; however, these rates are a dismal 0% to 8% for African-Americans in Chicago (123). Socioeconomic constraints may hinder widespread implementation of this "best case scenario" of rescue systems throughout the nation.

WORKUP AND MANAGEMENT OF THE CARDIAC ARREST SURVIVOR

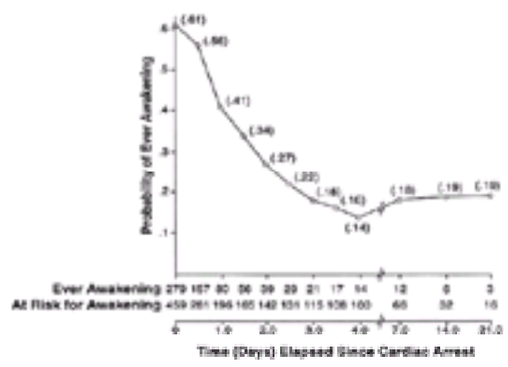
Even though each survivor represents a unique set of circumstances, the approach to the victim of sudden cardiac arrest is generally the same. It encompasses initial stabilization, determination and characterization of the underlying substrate, and assessment for future arrhythmic risk. The latter is also discussed in the context of the individual who is at risk but has not yet had a cardiac arrest.

Initial Phase

The initial phase aims at stabilization of the patient, a preliminary assessment of the cause, and developing a sense of the overall prognosis. The patient is best managed for a duration of approximately 48 to 72 hours in an intensive care unit setting. The initial rhythm documented in the field, whether bystander cardiopulmonary resuscitation was instituted promptly, the time to restoration of a perfusing rhythm ("down time"), the age of the patient, and the location of the event, whether at home or in a public place, provide important prognostic information (8,118,124). The patient should be assessed for any complications related to the resuscitative effort, particularly hemodynamic failure, oral and upper airway damage during intubation, pneumothorax, aspiration pneumonia, and chest wall trauma. The adequacy of

oxygenation and assessment of metabolic abnormalities requires appropriate laboratory analysis. Myocardial dysfunction is common following cardiopulmonary resuscitation and may transiently require some form of circulatory support. Ventilator support is often required in the initial period and may require heavy sedation or muscular paralysis to facilitate care. Interpretation of hypokalemia post–cardiac arrest is sometimes difficult because it may not reflect the prearrest state. Continuous electrocardiographic monitoring is essential because arrhythmias frequently are encountered after resuscitation and may be the mechanism of the cardiac arrest or may be unrelated and due to factors associated with resuscitation, and their management should be individualized based on some general principles. Any reversible factors such as hypokalemia, acidosis, and ischemia should be promptly identified and corrected. Antiarrhythmic therapy (such as lidocaine, procainamide, or pacing) should be appropriately selected for hemodynamically compromising arrhythmias, and these drugs should be discontinued before electrophysiologic evaluation so that they do not confound the decision regarding long-term therapy.

The patient's neurologic status on admission likely reflects the duration of the circulatory arrest (125,126). Generally, only a few patients are conscious at admission (118), and these persons have no significant residual neurologic deficit. Initial assessment of the comatose patient may be difficult, especially if sedation and muscular paralysis have been used. Often seizure activity may develop and require therapy as well. The persistence of coma beyond 72 hours after resuscitation indicates an unfavorable prognosis with a high in-hospital mortality and high likelihood of significant long-term neurologic impairment (126) (*e*Fig. 68.0.6).



***e*FIGURE 68.0.6** Likelihood of neurologic recovery after out-of-hospital cardiac arrest counts in the two rows above the *x*-axis depict actual numbers of patients ever awakening and of patients who were alive but not yet awake at each specified time. Most patients who awakened did so by day 3. (From Longstreet WT Jr, Inui TS, Cobb LA, et al. Neurologic recovery after out-of-hospital cardiac arrest. *Ann Intern Med* 1983;98:588, with permission.)

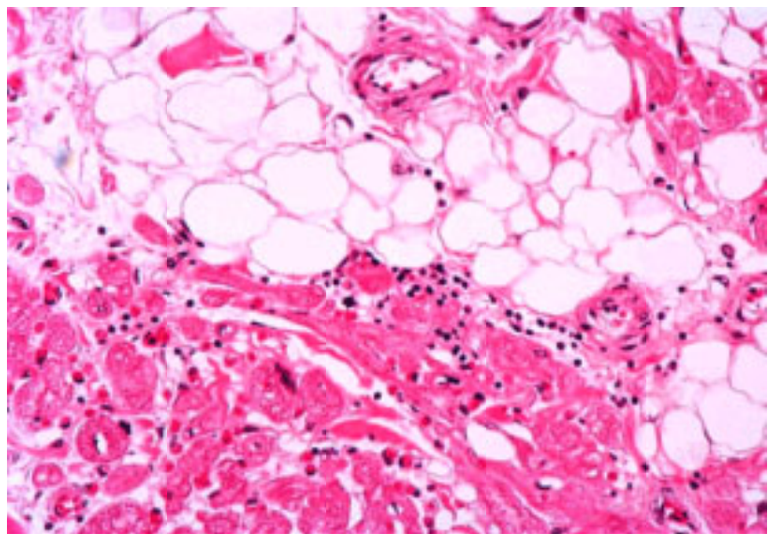
The long-term survival of patients resuscitated from cardiac arrest depends on several factors. An assessment of in-hospital mortality and outcome can be based on prearrest variables, resuscitation variables, and factors identified on admission to the hospital (*e*Table 68.0.5). The decision to withdraw life-sustaining measures is a complex one involving ethical issues and may be made with the consideration of the previously mentioned assessment and a close discussion with family members and peers (127,128).

***e*TABLE 68.0.5** DETERMINANTS OF ADVERSE LONG-TERM SURVIVAL IN CARDIAC ARREST
Prearrest
Older age
Lower socioeconomic status
Significant comorbid disease states
Homebound lifestyle
Resuscitation
Out-of-hospital cardiac arrest
Lack of bystander cardiopulmonary resuscitation
Delay in defibrillation
Asystole or electromechanical dissociation as initial documented rhythm
Absence of spontaneous circulation for >25 min
Hospitalization
Significant comorbid disease states
Neurologic status (coma >72 h)
Structural heart disease
Left ventricular dysfunction
Nonsuppressibility of induced ventricular tachycardia by drug

Definition of the Underlying Substrate

The next logical step is to define the underlying substrate. A detailed account from all witnesses regarding the circumstances of the event, antecedent symptoms, and whether physical exertion was involved provides important information. Anginal chest pain before the event may suggest underlying coronary disease. A family history of sudden cardiac death may point toward hypertrophic cardiomyopathy, long QT syndrome, the Brugada syndrome, right ventricular dysplasia, or coronary artery disease. The social history of the individual patient may indicate high-risk behavior and implicate substance abuse as a possibility. Preexisting known coronary artery disease or other cardiac disease and noncardiac disease (sarcoidosis, vasculitides) may narrow the focus in the search for a cause. Comorbidity is a predictor of adverse survival following out-of-hospital cardiac arrest, although this is an underrecognized issue (129). A comprehensive drug history and screening (prescription and over-the-counter medications) is imperative because these may have been proarrhythmic. The physical examination may provide evidence of cardiac disease (valvular disease, cardiac enlargement, and dysfunction) and associated noncardiac disease that may have been causative or may affect management and prognosis. Markers of myocardial necrosis should be assessed serially to determine the presence of an acute MI. A toxicologic screen may be appropriate when substance abuse or drug overdose is suspected.

The initial electrocardiogram can provide useful information regarding the underlying substrate. Evidence of a prior MI is more common than an acute MI. Other specific abnormalities may indicate the presence of LV hypertrophy, hypertrophic cardiomyopathy, QT prolongation, arrhythmogenic ventricular dysplasia, an accessory pathway, the Brugada syndrome, or AV block. Further definition of the cardiac substrate requires additional evaluation. Cardiac anatomic and functional assessment may be performed by two-dimensional echocardiography, which provides an estimate of cardiac chamber dimension and relationships, valvular structure and function, and ventricular wall thickness and function. Ventricular function, including the presence of wall motion abnormalities, alternatively may be assessed by gated nuclear imaging. Global ventricular dysfunction observed early following resuscitation may resolve after a few days. The diagnosis of arrhythmogenic right ventricular dysplasia may be missed by echocardiography, and magnetic resonance imaging is a valuable tool in suspected cases (130). An endomyocardial biopsy may assist in the diagnosis of myocarditis or infiltrative myopathies, such as sarcoidosis when they are clinically uspected.



Focal chronic inflammation in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac

Pathologists at The Cleveland Clinic Foundation.)

Endomyocardial biopsy demonstrating multiple granulomas in a case of sarcoidosis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Cardiac catheterization and angiography should be performed in virtually all survivors to establish the presence and severity of atherosclerotic coronary artery disease. It also may be useful to define coronary anomalies and other forms of congenital heart disease. These results may need to be interpreted in conjunction with perfusion imaging to assess the physiologic significance of the documented coronary artery disease. Angiographic evidence of complex coronary lesions, such as an ulcerated plaque or thrombus, may point to the mechanism of the arrest. More commonly, multivessel disease on a background of a prior MI with compromised pump function is observed. A segmental wall motion abnormality or ventricular aneurysm may be seen with coronary artery disease, idiopathic cardiomyopathy, or ventricular dysplasia. Coronary artery spasm as an etiology may be identified by provocative testing, although it may not be excluded by a negative test result (131). Abnormal histologic findings also have been noted in right and LV endomyocardial biopsies (103); however, this is subject to sampling errors and the vagaries of interpretation.

In a few cardiac arrest survivors, no evidence of structural heart disease or electrical and metabolic abnormality is demonstrable despite extensive evaluation (9,132,133). The diagnosis of primary electrical disease or idiopathic ventricular tachyarrhythmia in these patients is therefore made by a process of exclusion. Typically younger, these patients, despite having experienced a documented clinical ventricular tachyarrhythmia with no demonstrable heart disease or inducible ventricular tachyarrhythmia, remain at high risk for recurrent cardiac arrest (133). A practical approach to the cardiac arrest survivor is outlined in *e*Table 68.0.6.

***e*TABLE 68.0.6** PRACTICAL APPROACH TO THE CARDIAC ARREST SURVIVOR
Cardiac arrest survivor
▼
Initial stabilization
▼
Identify reversible causes
▼
Define cardiac anatomy (catheter, two-dimensional echo, magnetic resonance imaging, and so forth)
▼
Define arrhythmia (electrophysiology study, exercise, Holter)
▼
Select therapy based on previous items

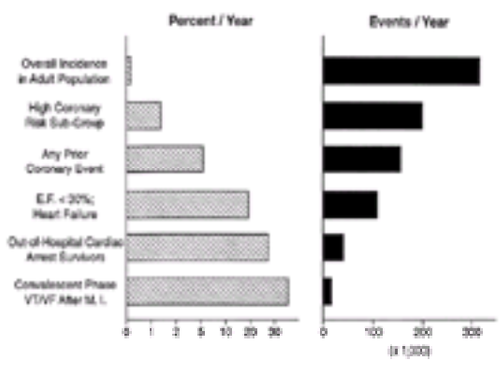
From DiMarco JP. Work-up and management of sudden cardiac death survivors. *Cardiol Clin* 1993;11:11–19, with permission.

Arrhythmic Evaluation and Risk Prediction

The primary role of arrhythmic evaluation in the cardiac arrest survivor has been to define and characterize the arrhythmic mechanism and form the basis for management strategies by risk stratification (134). Earlier data showed that patients resuscitated from cardiac arrest not associated with a new Q-wave infarction remain at high risk for recurrent cardiac arrest and sudden cardiac death during long-term follow-up (114,135,136 and 137). Two decades ago, this risk was reported as high as 30% at 1 year and 45% at the end of 2-year follow-up (114,138). More recent natural history studies are unavailable, although this risk remains significant (139). Based on two more recent studies, the significance of VT or VT in the first 72 hours following an index MI is more ominous than previously assumed. In a retrospective analysis of the Global Utilization of Streptokinase and t-PA for Occluded Arteries database, the occurrence of VT or VF during the index hospitalization conferred an adverse 1-year mortality (140). In another single-center retrospective analysis, the manifestation of nonsustained VT 13 hours after MI indicated a higher 1-year total mortality (141).

The major focus in the management of the cardiac arrest survivor was previously directed toward secondary prevention measures. However, significant attrition occurs during the primary event, and there has been a progressive change in management strategies over the past two decades, with increasing emphasis toward primary prevention measures. The rationale of this multifaceted approach is well justified because it is more cost effective and more successful in that a significant proportion of events occurs in persons known to be at high risk.

Sudden cardiac death also may be the first expression of occult heart disease. A significant proportion of these deaths may be predictable because they occur in patients who may be categorized as high risk. Naturally, screening of an unselected general population is impractical; hence, efforts at risk stratification should be directed toward those with structural heart disease. Focusing these efforts on patients within high-risk population subgroups results in increasing specificity within these subgroups so that interventions may be targeted in a cost-effective manner, without exposing a larger population to the risks of needless intervention. However, the absolute numbers of patients who experience sudden cardiac death progressively diminish as the clinical subgroups identified by currently available techniques become more specific (*e*Fig. 68.0.7). The role of arrhythmia evaluation in risk stratification for sudden cardiac death in several clinical circumstances is also addressed here.



***e*FIGURE 68.0.7** Inverse relationship between the incidence and total number of sudden cardiac deaths per year in population subgroups. Although the overall incidence in the adult population is 0.1% to 0.2% per year, this segment accounts for more than 300,000 sudden deaths per year. The addition of risk factors results in a progressively higher incidence but a progressively smaller percentage of total events. E.F., ejection fraction; M.I., myocardial infarction; VT/VF, ventricular tachycardia/ventricular fibrillation. (From Kleiger RE. The relationship between clinical features of acute myocardial infarction and ventricular runs 2 to 1 year after infarction. *Circulation* 1981;63:64–70, with permission.)

A person who has a history of coronary artery disease, even if it is asymptomatic, faces an increased risk of sudden cardiac death. A history of cardiac arrest in the absence of an acute MI is the most significant risk factor for recurrence. A history of syncope is of ominous significance in patients with idiopathic dilated cardiomyopathy (142). Sudden cardiac death in WPW is rare and almost always occurs in a previously symptomatic person. Clinical presentation at a young age and a family history of sudden cardiac death are of prognostic importance in hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, or the long QT syndrome. Cigarette smoking may predispose to sudden death in those with coronary artery disease; however, no other modifiable risk factors help discriminate

between the risk of sudden versus nonsudden coronary death.

Noninvasive and invasive diagnostic data obtained during the cardiovascular evaluation have significant usefulness in risk stratification. This aspect has been studied most extensively and validated in the patient with coronary artery disease.

1. LV dysfunction is a potent predictor of risk of short- and long-term cardiac death in the post-MI population (143,144,145,146,147 and 148) and is anatomically indicative of infarct size and regardless of the location of the MI (149). LV dysfunction is also a predictor of sudden cardiac death, and the presence of frequent or complex ventricular ectopy detected by Holter monitoring provides additive risk (143,144,147,150). LV function may be assessed by a variety of techniques, such as gated radionuclide studies, echocardiography, or contrast angiography, and should be performed routinely in the evaluation of the cardiac arrest survivor.
2. Ambulatory electrocardiography: The presence of complex ventricular ectopy in cardiac arrest survivors and after MI is an independent risk factor for sudden cardiac death; hence, it was presumed that Holter monitoring may be useful both for risk stratification and assessment of response to drug therapy (143,144 and 145,151). There are some serious limitations of Holter monitoring that need to be taken into account, such as day-to-day and long-term variability in spontaneous ectopy (152,153) and that few cardiac arrest survivors have significant ambient ectopy (151). Third, although the complexity and frequency of ventricular ectopy dramatically increase with advancing ventricular dysfunction (154), this is predictive of total cardiac mortality but does not reliably discriminate between sudden and nonsudden death in this population (153,154).

   Asymptomatic nonsustained VT in the setting of a prior MI and LV dysfunction is associated with a 2-year mortality in the range of 30% (150). Holter monitoring is useful in the post-MI state for identification of the high-risk person. The value of Holter monitoring in other substrates, such as idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, or LV hypertrophy, is not well established (155,156,157 and 158). Ischemia detected by Holter monitoring may be a marker for biologically unstable coronary artery disease, which has been predictive of an adverse short-term outcome (159). It may also be useful in monitoring patients with suspected long QT syndrome, in whom dynamic fluctuations of the QT interval may be evanescent.
3. SAECG is used as a predictor of risk because of its ability to detect late potentials. This association is more specific in coronary artery disease. The presence of late potentials is predictive of increased arrhythmic events, including sudden cardiac death in the post-MI population (148,160,161), and in those with VT or VF is predictive of inducible VT (162). The combination of late potentials with LV dysfunction has been associated with a 34% incidence of arrhythmic events (163), and the addition of frequent ventricular ectopy to these findings raises the positive predictive value to just over 50% (160,161,162 and 163). In contrast to its poor positive predictive value, SAECG combined with other markers has an excellent negative predictive value of over 90%.
4. Heart rate variability, baroreflex sensitivity, QT variability index, and T wave alternans are indices of cardiac autonomic activity that have been validated clinically in identifying persons at high risk of arrhythmic death following an MI (93,164,165,166 and 167). Their positive predictive value is somewhat improved when combined with other noninvasive variables such as ventricular function, Holter monitoring, and the SAECG (161,164,168).
5. The electrophysiologic study is an essential component of the evaluation for cardiac arrest. The study is usually performed after the underlying cardiovascular substrate has been defined, and the end point of the study is the induction or noninducibility of a sustained ventricular tachyarrhythmia. Inducibility of a sustained ventricular tachyarrhythmia is a prerequisite for using the electrophysiologically guided approach in cardiac arrest survivors. Sustained ventricular tachyarrhythmias can be initiated during the electrophysiologic study in up to 85% of cardiac arrest survivors (169,170,171,172,173,174,175 and 176). Patients with significant coronary artery disease are more likely to have an arrhythmia induced than those with idiopathic cardiomyopathy or a structurally normal heart. Sustained monomorphic VT is the most commonly identified arrhythmia in up to 51% of cardiac arrest survivors and is more likely in the subset of patients in whom this arrhythmia was identified as the initiating mechanism for cardiac arrest. The initiation of VF during the electrophysiologic study with triple extrastimuli may be a nonspecific finding (177), but the transformation to inducible monomorphic VT with the use of procainamide in the setting of a prior MI has been suggested as a specific response (178).

   The electrophysiologic study has been used for serial antiarrhythmic drug testing in cardiac arrest survivors who are inducible at a baseline study. Successful suppression of the ventricular tachyarrhythmia as inferred by noninducibility of a previously inducible arrhythmia following drug therapy has been predictive of a more favorable outcome than persistent inducibility (172,173,174 and 175) and suppression can be found in 26% to 80% of cardiac arrest survivors (169,173,174). Those most likely to be rendered noninducible are the minority who have preserved ventricular function (173,179). However, noninducibility overall has not translated into improved survival, and reported recurrent sudden death rates range from 12% to 31% at 2 years (173,176,180,181 and 182). The electrophysiologic study can also identify patients suitable for map-guided surgical ablation of monomorphic VT. Postoperative noninducibility allows prediction of arrhythmia-free outcome (103,183,184). There are no long-term supportive data for catheter ablation in this situation.

   In approximately 20% to 30% of cardiac arrest survivors, a ventricular tachyarrhythmia cannot be induced during the electrophysiologic study. This proportion is higher if the underlying substrate is idiopathic cardiomyopathy or in the absence of structural heart disease. These patients do not have a benign outcome as previously believed, particularly in the setting of LV dysfunction (171,179,185,186). Serial drug testing cannot be used as a strategy in these patients. Rarely, a supraventricular arrhythmia is identified as the initiating mechanism for cardiac arrest, especially in the WPW syndrome and hypertrophic cardiomyopathy (81,186).

   The routine use of electrophysiologically guided risk stratification in the post-MI survivor has a low positive predictive value but a high negative predictive value (187,188) and currently is not recommended. Instead, the focus has shifted to refining risk in myocardial infarct survivors, with asymptomatic nonsustained VT associated with LV dysfunction (150,189,190 and 191). Overall, however, clinical variables such as functional class, nonsustained VT, and ejection fraction used with the electrophysiologic study may provide a better risk profile than inducibility alone. The predictive value of the electrophysiologic study under similar circumstances is less clear in noncoronary heart disease such as idiopathic dilated cardiomyopathy or hypertrophic cardiomyopathy (157,182,192,193,194 and 195). In the WPW syndrome, although sudden death is rare, the risk may be assessed by the conduction characteristics of the accessory pathway. There is currently no consensus regarding the use of electrophysiologic risk stratification in the asymptomatic patient with hypertrophic cardiomyopathy, the long QT syndrome, LV hypertrophy, or arrhythmogenic right ventricular dysplasia.

The relative merits of noninvasive and invasive tests in the prediction of sudden cardiac death are outlined in *e*Table 68.0.7.

***e*TABLE 68.0.7** EVALUATION OF THE RISK OF CARDIAC ARREST

Test	Utility	Relative importance
12-Lead electrocardiogram	Old or recent myocardial infarction, QT prolongation, intraventricular conduction delay, preexcitation	+++
Left ventricular ejection fraction estimation	Strong correlate of cardiovascular mortality	+++
Echocardiogram	Identify structural disease (prior myocardial infarction, left ventricular hypertrophy, myopathy)	+++
Coronary angiography	Define need for revascularization, anomalies in circulation	+++
Electrophysiology study	Define inducibility of VT or ventricular fibrillation to guide therapy	+++
Sinoatrial electrocardiogram	Prediction of recurrence, inducibility of VT	+
Holter monitor	Premature ventricular complex density, detection of nonsustained VT	+
Heart rate variability, baroreflex sensitivity	Indices of autonomic tone for risk prediction	++
Exercise testing	Identify provocable ischemia, VT, functional class	++

VT, ventricular tachycardia.

MANAGEMENT STRATEGIES FOR CARDIAC ARREST

Primary Prevention of Sudden Cardiac Death

The goal of primary prevention is to reduce sudden death and favorably affect total mortality; however, the Achilles heel of this approach is the identification of the population at risk. Although coronary artery disease is found in the majority of cardiac arrest survivors, it is impractical to institute mass screening to identify those at risk a priori. Three groups of patients that are known to be at high risk, therefore, are the focus of discussion.

Post–Myocardial Infarction

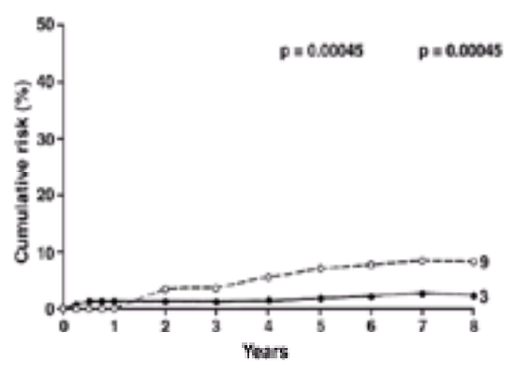
The risk of arrhythmic and nonarrhythmic cardiac death in MI survivors is highest in those with lower ejection fractions, and those with complex ventricular ectopy. Adjunctive therapy with aspirin, angiotensin-converting enzyme inhibitors, and hydroxymethylglutaryl coenzyme reductase inhibitors has also been shown to improve survival (196,197). Data from several well-designed, placebo-controlled, double-blind studies suggest that beta-adrenergic receptor blocking drugs reduce overall mortality as well as the incidence of sudden cardiac death following acute MI (97,98 and 99,198,199). The beneficial effect of beta-blockers as a class is limited to those with lipophilic properties and those without intrinsic sympathetic activity (200). It is believed that the antiarrhythmic and antiischemic properties of these drugs contribute to the observed effect, which is most evident in the highest risk population with ventricular dysfunction and complex ectopy. Suppression of ectopy is not a prerequisite for reduction in sudden death. The beta-blockers nullify the effect of the circadian rhythm in the incidence of sudden death (201) and defibrillator discharges for ventricular tachyarrhythmia. Despite this evidence, there is a low use of beta-blockers in clinical practice because of unfounded fears of side effects, and even in clinical

trials, conventional therapy with other agents noted previously is inconsistently and inadequately applied.

Although the concept of arrhythmia suppression using antiarrhythmic drugs for prevention of sudden death is appealing, the results of earlier trials have discouraged this naïve approach. Cardiac Arrhythmic Suppression Trials I and II tested the hypothesis that suppression of ventricular ectopy post-MI would translate into reduction of sudden death in this population (202,203). However, a higher incidence of sudden death in the drug-treated group led to premature termination of the study and dispelled the simplistic myth regarding the mechanism of sudden death, but it provided some important lessons. The study underscored the futility of using these drugs in an evolving substrate characterized by myocardial remodeling, neurohormonal influences, and progression of coronary artery disease, and it highlighted the serious risks of antiarrhythmic drug therapy.

Since that time, there has been a renewed interest in the class III agents, particularly amiodarone and sotalol. The BASEL Antiarrhythmic Study of Infarct Survival demonstrated reduced total mortality benefit for amiodarone in survivors of MI infarction with frequent ventricular ectopy (204). Curiously, the improved survival with low-dose amiodarone was limited to patients with LV ejection fractions over 40%, and the effect lasted for several years despite termination of therapy at 1 year (205,206). In the European Myocardial Infarction Amiodarone Trial and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, amiodarone was beneficial in reduction of arrhythmic death, but did not alter total mortality (207,208 and 209). The Polish Trial (210) showed similar results in post-MI patients who were not candidates for beta-blocker therapy. Overall, amiodarone has shown consistent safety in the post-MI population, and the effect of amiodarone was separate and complementary to that of beta-blockers. In the Survival with Oral D-Sotalol trial, the prophylactic use of sotalol in a post-MI population resulted in excess mortality, believed to be as a result of proarrhythmia (211). Both dofetilide and azimalide have similarly shown no improvement in total mortality in the post-MI patients (212,213).

Intuitively, preventing or reducing ischemia would favorably affect the incidence of sudden death in those with coronary disease. Data from large trials, such as the Coronary Artery Surgery Study and the European Coronary Artery Study Group, comparing coronary artery bypass surgery and medical therapy in patients with chronic stable angina, show surgical therapy to be associated with a significantly lower incidence of sudden and total cardiac mortality (214,215). The incidence of sudden death was 5.2% in patients assigned to medical therapy, compared with 1.8% in those who underwent surgery during a 4.6-year follow-up in the Coronary Artery Surgery Study report. The difference in favor of surgical therapy was even greater when congestive heart failure was present (216). In the European study, the risk of sudden death at 8 years was 3% in the surgical group versus 9% in the medical group (*e*Fig. 68.0.8). Myocardial revascularization is also beneficial in reducing sudden death risk in patients who have provocable ischemia during stress testing (217) and those who have silent ischemia on Holter monitoring. Accumulating evidence also supports a favorable effect of intervention at the time of acute MI on the subsequent development of ventricular tachyarrhythmias. Both short- and long-term results of thrombolytic therapy and percutaneous transluminal coronary angioplasty translate into a lower incidence of late potentials and inducibility during programmed stimulation (218,219). It is likely that these interventions extend benefit not only by preserving jeopardized myocardium but also by limiting infarct size, influencing ventricular remodeling, and stabilizing the electrophysiologic matrix.



***e*FIGURE 68.0.8** Prospective evaluation of cumulative risk of sudden cardiac death in patients assigned to medical (*open circles*) versus surgical therapy (*closed circles*) in coronary artery disease. [From Varnauskas E, and the European Surgical Study Group. Survival, myocardial infarction, and employment status in a prospective randomized study of coronary bypass surgery. *Circulation* 1985;72(Suppl V):V-90, with permission.]

The Beta-Blocker Strategy Plus Implantable Cardioverter Defibrillator (BEST-ICD) Trial is under way to determine whether in a subgroup of patients with recent MI already receiving beta-blockers, a therapeutic strategy guided by electrophysiologic testing and ICD implant in those inducible for VT, can improve survival when compared with conventional therapy (220).

Cardiomyopathy

Patients with dilated cardiomyopathy, whether ischemic or nonischemic, constitute the largest identifiable at-risk population, with a formidable mortality linked to their functional class. Both sudden and nonsudden death is high, although the more functional patient is more likely to die suddenly (221,222). In a metaanalysis of 11 studies, in which patients were classified according to their functional class, those in classes I and II had a yearly mortality of 12% to 15%, but the sudden death risk was 50% to 60%. In contrast, patients who were classes II and IV had a yearly mortality of 60%, but the sudden death rate was 20% to 30% (223) (*e*Table 68.0.8). The majority of patients with cardiomyopathy has ventricular arrhythmias, usually asymptomatic. Advances in the medical management of heart failure have led to significant amelioration of symptoms, improved functional class, and prolonged survival. This leap from palliation to prolongation of life has been effected primarily by beta-blockers, angiotensin enzyme inhibitors, and nitrates in combination with hydralazine. Carvedilol, losartan, and bisoprolol have all shown survival benefit in heart failure (62,224,225,226 and 227). A clear reduction of sudden versus nonsudden death in these trials was identified only in the Vasodilator Heart Failure Trial (V-HeFT) II trial, in which enalapril was compared with hydralazine, supporting a nonarrhythmic mechanism for the other drugs. Nonetheless, a considerable risk of sudden death remains in 28% to 68% of these patients (62,227), and cardiac transplantation remains the most viable option for long-term survival. However, almost twice as many are accepted into transplant lists each month than those undergoing transplantation (228).

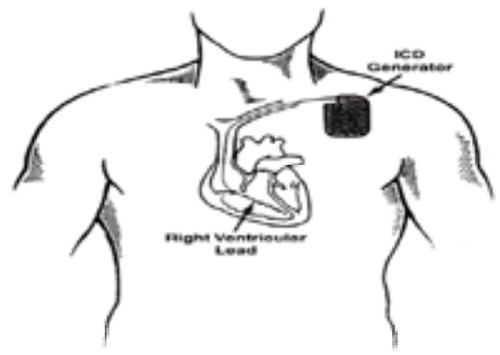
***e*TABLE 68.0.8** SUDDEN DEATH DEPENDENT ON THE SEVERITY OF CONGESTIVE HEART FAILURE

New York Heart Association functional class	Mortality per year (%)	Sudden death (%)
II	5–15	50–80
III	20–50	30–50
IV	30–70	5–30

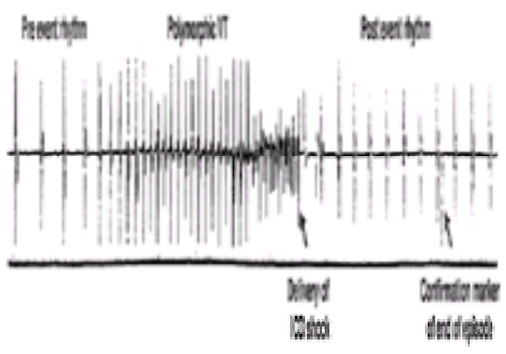
From Uretsky BF, Sheahan RG. Primary prevention of sudden cardiac death in heart failure: will the solution be shocking? *Am Coll Cardiol* 1997;30:1589–1597, with permission.

There are no data that class I antiarrhythmics prolong survival in patients with congestive heart failure, but ample evidence supports the low efficacy and high proarrhythmic rates (229,230). Amiodarone used in those with advanced ventricular dysfunction and asymptomatic ventricular arrhythmias improved survival in nonischemic dilated cardiomyopathy in the Grupo de Estudio de la Sobrevida en al Insuficiencia Cardiaca en Argentina trial (231), in which only 40% of patients had a prior MI. In contrast, in the Veterans Administration Trial, CHF-STAT, in which 70% of patients had ischemic cardiomyopathy, amiodarone did not show mortality benefit (232). Overall, although an apparently safe drug with a demonstrated statistical reduction in mortality from metaanalysis of trials, the results of an ongoing randomized trial SCD-HeFT will confirm the position of amiodarone in heart failure (233).

Because most sudden deaths are believed to result from ventricular tachyarrhythmias, prompt termination of the arrhythmia by a defibrillator conceivably would save lives. This concept was extended to the development of an implantable unit by Mirowski and Mower and has been refined further by many to its current state. In a simple sense, the unit consists of a series of components: rate-sensing electrodes that convey beat-to-beat information to logic circuitry contained in a can, which also houses a battery capable of developing a charge when a tachyarrhythmia is detected. This charge is delivered through high-voltage electrodes to the heart, invariably terminating the arrhythmia (*e*Fig. 68.0.9 and *e*Fig. 68.0.10). Currently available ICDs are sophisticated multiprogrammable units that use sensitive and more specific detection algorithms and deliver tiered therapy, depending on need: antitachycardia or dual-chamber bradycardia pacing, low- or high-energy atrial or ventricular cardioversion, and defibrillation. Implantation is performed with comparative ease and minimal risk today, using the transvenous route. Combined with impressive long-term sudden death survival results, these factors have led to an unprecedented acceptance of this form of therapy in sudden death.

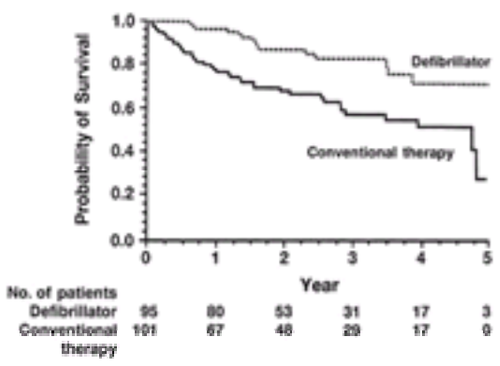


***e*FIGURE 68.0.9** Schematic representation of the currently used implantable cardioverter defibrillator (ICD). (From Deshpande S, Vora A, Axtell K, Akhtan M. Sudden cardiac death. In: Brown DL, ed. *Cardiac intensive care*. Philadelphia: WB Saunders, 1996, with permission.)

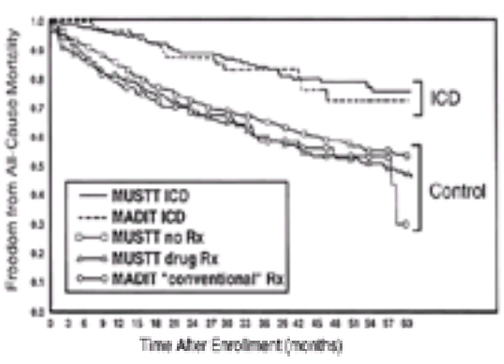


***e*FIGURE 68.0.10** Spontaneous episode of polymorphic ventricular tachycardia (VT) terminated by delivery of a shock from an implantable cardioverter defibrillator (ICD). The tracing was retrieved from the electrogram storage of the device.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) was the first randomized trial to demonstrate that the ICD could improve survival in a high-risk group of patients. It targeted post-MI patients with asymptomatic nonsustained VT and ischemic cardiomyopathy, a population associated with a mortality of 30% within 2 years (150,190). ICD implantation in patients who had inducible monomorphic VT not suppressed by procainamide at electrophysiologic testing resulted in a superior total survival compared with administration of conventional therapy (234). The 5-year total mortality was 16% in the ICD group, and 39% in the conventional arm (*e*Fig. 68.0.11). Although almost one-half of the patients in the conventional arm were on amiodarone, the study was not powered to draw any conclusions comparing amiodarone and the ICD. Cost analysis of this study estimated that this approach would cost $27,000 per life-year saved (235). The Multicenter Unsustained Tachycardia Trial (MUSTT) enrolled a similar population of 2,202 patients and randomized 704 inducible patients to no therapy or electrophysiologically guided antiarrhythmic drug therapy with class IA, propafenone, sotalol, or amiodarone, or the ICD as a last resort (191). A 27% reduction in the primary end point of arrhythmic death or cardiac arrest in the electrophysiologically guided group was entirely due to the use of the ICD during a mean follow-up of 39 months. The overall 5-year mortality for those who received an ICD was 24% compared with 55% in those who did not. Despite the differences in study design, MADIT and MUSTT both demonstrated the superior survival advantage with the ICD (*e*Fig. 68.0.12).



***e*FIGURE 68.0.11** The probability of survival in the defibrillator and conventional therapy groups in Multicenter Automatic Defibrillator Implantation Trial. The defibrillator group had a significantly increased survival over conventional therapy. (From Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933–1940, with permission.)



***e*FIGURE 68.0.12** Kaplan-Meier survival curves for all-cause mortality in Multicenter Unsustained Tachycardia Trial and Multicenter Automatic Defibrillator Implantation Trial. ICD, implantable cardioverter defibrillator. [From Prystowsky EN, Nisam S. Prophylactic implantable cardioverter defibrillator trials: MUSTT, MADIT, and beyond (editorial). 2000, with permission.]

The prophylactic role of the ICD in patients with LVEF less than 35% and positive SAECG who were undergoing coronary artery bypass grafting was examined in the Coronary Artery Bypass Grafting Study (236). This population of patients also has a high incidence of sudden death, as reported in data from the CASS registry. Patients were randomized to the ICD or non-ICD limb, but no reduction in total mortality was noted with the use of the ICD despite an approximately 50% device shock rate at 1 year. The SAECG may not have been the ideal marker to use in this study since it is well known that it identifies patients at risk for VT but not for VF. It is likely that the selection of patients based on the SAECG and the beneficial effect of concomitant myocardial revascularization may have accounted for the discordant results compared with MADIT and MUSTT.

The ICD has been proposed as an empirical “bridge to transplantation” in patients with advanced ventricular dysfunction (237,238). Unfortunately, despite the reduction of sudden cardiac death, the ultimate survival benefit in this population is questionable due to attrition from other causes such as heart failure, bradycardia, electromechanical dissociation, and noncardiac causes. In this setting, because the hypothetical benefit of the ICD in unselected patients with advanced heart failure is low, the ICD is probably most appropriate in those with a realistic chance of transplantation. This issue is being prospectively examined in the Cardiomyopathy Trial

with total mortality and sudden deaths as end points. The SCD-HeFT (Sudden Cardiac Death Heart Failure Trial) is a placebo-controlled trial of amiodarone versus the ICD in patients with cardiomyopathy and no prior history of sustained ventricular arrhythmias (233). MADIT II is an extension of the first trial but does not require demonstration of complex ventricular ectopy or need inducibility of VT (239). In both the latter trials, total mortality will be the primary end point, and "conventional" therapy will be used. More recent studies showing benefit of biventricular pacing have yet to show any mortality benefit, but trials are ongoing.

Structural Heart Disease

Certain rare cardiac diseases are associated with high rates of sudden death and pose a dilemma for management. Sudden death is well recognized frequently in young asymptomatic patients with hypertrophic cardiomyopathy, and its prevention continues to remain a major challenge. The role of amiodarone is unclear at this time because of the conflicting data in regard to reduction of sudden death risk, primarily to the lack of concurrent controls (240,241). Studies involving the ICD with small numbers of patients have had mixed results (242,243 and 244), and essentially, there is currently no consensus or standard prophylactic indication designated for the ICD in this disease. The clinical presentation with syncope was most likely to result in ICD implant in one multicenter study (245). Beta-blockers also serve as the cornerstone of therapy in symptomatic patients and some asymptomatic family members of patients with the long QT syndrome for the prevention of sudden cardiac death. The prophylactic use of the ICD in selected high-risk patient with long QT syndrome, arrhythmogenic right ventricular dysplasia, the Brugada syndrome, a family history of sudden death, and hypertrophic or dilated cardiomyopathy is widely practiced based on retrospective nonrandomized studies or case reports and personal experience. It is anticipated that genetic and clinical risk factors will emerge in these diseases and will aid in identifying those at risk for ventricular arrhythmias so cost effective use of therapy may be implemented (246).

Secondary Prevention Strategies for Sudden Cardiac Death

In contrast to the larger high-risk population of patients who have never experienced a cardiac arrest, the absolute numbers of patients who survive a cardiac arrest and are at high risk for recurrence are small; yet their relative risk in regard to recurrence is exceedingly high (eFig. 68.0.7). Candidates for secondary prevention strategies, therefore, are a small subset in the overall population of cardiac arrest victims, in whom aggressive intervention is warranted to optimize survival. It is equally important to realize that the risk of sudden death is predicated by the presenting clinical arrhythmia and LV function. The patients with well-tolerated VT or syncopal VT do not carry the same risk as a sudden death survivor, although they are frequently lumped together in studies regarding management strategies for sudden death. There is, however, a clearly established time dependence of risk after a cardiac event (such as cardiac arrest, MI, or onset of congestive heart failure). The risk of sudden cardiac death is highest within the first 6 to 18 months after the index cardiovascular event; following this initial attrition, this risk reduces to the preexisting level for that subgroup (151,247). This time dependence of risk should be taken into consideration when management strategies are considered.

Antiarrhythmic Drug Therapy

Empiric antiarrhythmic drug therapy with class I drugs is now considered ineffective and unsafe in the management of sustained VT or VF, but amiodarone may be used in selected cases. Drug therapy for VT or VF has also been guided either by serial electrophysiologic testing or using Holter monitoring. Several pitfalls in the utility of either strategy may limit their use. The Electrophysiologic Testing Versus Holter Monitoring trial was the most recent large-scale randomized trial of antiarrhythmic drug therapy addressing the efficacy of an electrophysiologically guided versus Holter-guided approach in the treatment of ventricular tachyarrhythmias (181). Although the study concluded that both methods were equivalent, what was evident was that class I drugs were inferior to sotalol, and neither method was effective in predicting arrhythmia-free survival because all drugs had a high failure rate. Despite this, sotalol had an arrhythmia recurrence rate of over 50%, a 20% risk of arrhythmic death at 4 years for all drugs, and a 15% sudden death risk for sotalol in apparent drug "responders" at 2-year follow-up (248). In clinical practice, this may permit the selection of sotalol for hemodynamically stable VT associated with preserved LV ejection fraction. On the background of the Electrophysiologic Testing Versus Holter Monitoring trial, the efficacy of D,L-sotalol was compared directly with the ICD in a population of patients with VT and VF (249). In this case control study, ICD therapy was more effective than electrophysiologically guided therapy with D,L-sotalol in sudden death prevention and total mortality. No sudden deaths occurred in the ICD group and total mortality at 3-year follow-up was 15%. In contrast, the sudden death rate, despite demonstrable suppressibility with D,L-sotalol, was 15%, and total mortality was 25%.

Amiodarone is a potent antiarrhythmic agent with complex electrophysiologic effects. Its ability to suppress inducible VT and VF is relatively low, yet initiation of VT during therapy does not necessarily preclude a favorable clinical response (250,251). In general, however, failure of suppression, easier mode of induction, or hemodynamic instability during the induced tachycardia foretell the recurrence of arrhythmia or cardiac arrest (250,251 and 252). This disparity in the electrophysiologic and clinical outcome has been the basis for the empirical use of amiodarone in sudden death survivors. Empirical therapy with amiodarone for VT and VF was associated with a sudden death risk of approximately 21% during a 5-year follow-up in two large series (253,254). There are no placebo-controlled trials of amiodarone in VT or VF. In the Cardiac Arrest in Seattle Conventional versus Amiodarone Drug Evaluation trial, 228 cardiac arrest survivors were randomized between empirical amiodarone or electrophysiologically guided or Holter-guided antiarrhythmic drug therapy (255). An ICD was assigned to equal numbers of patients in both limbs. This is the only randomized trial of amiodarone versus other antiarrhythmic drugs. The amiodarone group fared better than the group treated with conventional antiarrhythmics in terms of cardiac mortality, syncope, and recurrent cardiac arrest, yet only approximately 40% of the amiodarone group was free of cardiac death or sustained arrhythmia at a 6-year follow-up. Amiodarone was associated with significant toxicity in this trial. Empiric beta-blocker therapy has limited value as monotherapy for secondary prevention, even in conditions such as long QT syndrome, idiopathic VT, exercise-induced VT, or VF. It should, therefore, be used as adjunctive therapy with other specific antiarrhythmic therapy.

Role of Myocardial Revascularization

Myocardial revascularization is a rational therapeutic component of secondary prevention strategies when myocardial ischemia is suspected or documented as an acute initiating event. Both preoperative and postoperative inducibility and the type of ventricular tachyarrhythmia induced during the electrophysiologic testing are important in decision making. Revascularization may be the only therapy required in a cardiac arrest survivor with critical coronary stenosis and significant myocardium in jeopardy, with normal ventricular function, and inducible VF preoperatively, but who is noninducible postoperatively (256,257 and 258). Revascularization alone is insufficient in patients with either preoperative clinical or inducible monomorphic VT. These patients also require arrhythmia surgery, ICD implantation, antiarrhythmic drug therapy, or combinations of these. At present, extrapolating these long-term data regarding the role of myocardial revascularization to catheter-based coronary interventions such as angioplasty or intracoronary stents to protect from cardiac arrest is difficult (258). This is particularly important because restenosis or acute closure, which occasionally complicates these interventions, may have catastrophic consequences.

Role of Arrhythmia Surgery and Catheter Ablation

The ideal candidate for arrhythmia surgery is one with a single clinical monomorphic VT that is inducible and mappable, a post-MI anterior aneurysm, no significant disease in the other coronaries, and normal contractility of the other segments of the LV. Map-directed surgical cryoablation or subendocardial resection has a high success rate of cure (90% to 100%), with a perioperative mortality of approximately 10% in experienced centers (184). However, this therapy is not feasible in most survivors of cardiac arrest because monomorphic VT is uncommon as an initial rhythm, other selection criteria are usually not met, and there is a growing reluctance to use this in the era of the transvenous ICD. Catheter ablation may be curative in a few cardiac arrest survivors when the putative mechanism is VT due to bundle branch reentry or right ventricular dysplasia or is documented to be a primary supraventricular tachycardia (accessory pathway or AV nodal reentry).

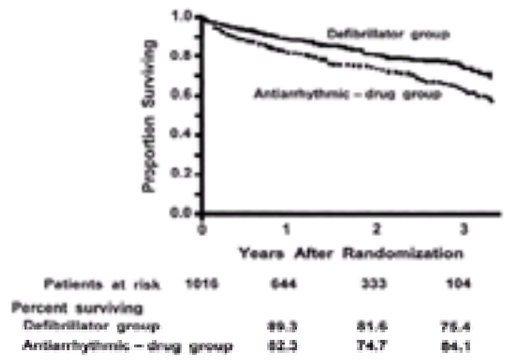
Role of the Implantable Cardioverter Defibrillator

The ICD was conceived, developed, and used as a secondary prevention strategy for those at high risk of sudden death due to failure of "conventional antiarrhythmic therapy." The effectiveness of the ICD in this regard, using historical controls, was demonstrated in several large populations over the long-term (259,260), albeit without randomization. Sudden death rates with the ICD are approximately 4% to 5% at 5-year follow-up, and the operative mortality with present systems is roughly 1%. In response to nagging doubts as to whether the sudden death reduction by the ICD translates into total mortality reduction, four prospective randomized trials were completed.

In the Dutch study, 60 cardiac arrest survivors were randomized to either early ICD as first-choice therapy or a conventional electrophysiologically guided strategy. The primary objective was to compare the effectiveness and cost of each approach. Early ICD implantation was superior for overall survival (4 deaths vs. 11 in the conventional arm) and more efficient and cost effective than the conventional electrophysiologically guided approach (261,262). The Cardiac Arrest Study Hamburg randomized cardiac arrest survivors to receive propafenone, metoprolol, amiodarone, or the ICD without concomitant drug therapy, with total mortality as a primary end point (263). The propafenone limb of the study was discontinued after an interim analysis because of excess total mortality, sudden death, and cardiac arrest recurrence compared with the ICD group. The investigators have reported a 2-year 39% reduction in total mortality in the ICD arm compared with the drug arm (amiodarone and metoprolol), and curiously, no difference in mortality between amiodarone and metoprolol (264).

The Antiarrhythmics versus Implantable Defibrillators trial (AVID) was the first large-scale randomized study comparing the ICD with antiarrhythmic drugs in patients with documented VT or VF (265). The mean follow-up for the 1,016 randomized patients was approximately 19 months. Total mortality in the ICD group was 10.7%, 18.4%, and 24.6% at 1, 2, and 3 years, which compared with the antiarrhythmic group at 17.7%, 25.3%, and 35.9%, respectively, represents a 39%, 27%, and 31% annual mortality reduction by the ICD over the 3 years (eFig. 68.0.13). The majority of the ICD benefit occurred in the first 9 months and in those patients with an

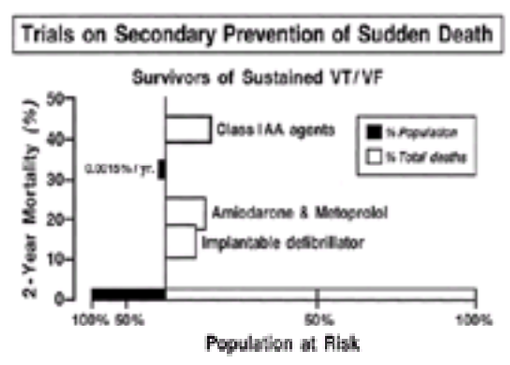
ejection fraction less than 35%.



***e*FIGURE 68.0.13** Total mortality in the Antiarrhythmics versus Implantable Defibrillators trial. [From The Antiarrhythmic versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576–1583, with permission.]

The Canadian Implantable Defibrillator Study (CIDS) (266) randomized 659 patients with hemodynamically unstable VT or cardiac arrest survivors to an ICD or empiric amiodarone. There were 98 and 83 deaths in the amiodarone and ICD groups, respectively. Those patients who were most likely to benefit from the ICD were identifiable by the clinical variables of age greater than 70, LV ejection fraction less than 35%, and New York Heart Association class III or IV. These findings suggest that those with moderate to severe LV dysfunction benefit the most, and as in AVID, this subgroup appears to bestow the mortality benefit to the entire ICD-treated group.

Overall, the results of the Dutch study, AVID, Cardiac Arrest Study Hamburg, and CIDS have established the ICD as front-line therapy in the realm of secondary prevention (eFig. 68.0.14). The magnitude of all-cause mortality benefit from ICD therapy varied depending on the competitive therapy evaluated (i.e., ICD benefit is greater than comparing it with class I drugs). Trials of ICD therapy versus amiodarone consistently demonstrate an approximate 28% relative mortality reduction with the ICD. In all these trials, ICD therapy was affected by the evolution of technology, and it is likely that ICD risk was higher with the thoracotomy systems. Patients with VF were enrolled in all four trials; patients with unstable VT were enrolled in two trials and accounted for 41% (CIDS) and 55% (AVID) of all enrollments; CIDS also enrolled patients with unmonitored syncope and otherwise documented VT, accounting for 14% of the study. Patients with cardiac arrest contribute to less than 1% of all deaths among patients at risk. The inconsistencies in the use of beta-blockers, sotalol, and amiodarone in the non-ICD limbs in these trials has confounded the interpretation of the data to some degree.

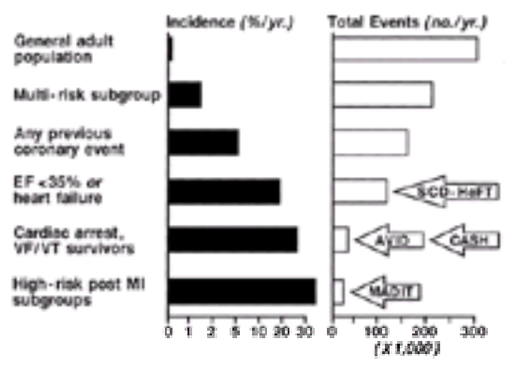


***e*FIGURE 68.0.14** Relationship of subgroup 2-year mortality risk (*vertical axis*) to subgroup size as proportion of total population (*left horizontal*) and proportion of all-cause mortality among population subgroups based on therapy assignment in the four randomized controlled trials on secondary prevention of sudden death. VT/VF, ventricular tachycardia/ventricular fibrillation. (From Cappato R, Kuck KH. Secondary prevention of sudden death. *J Intervent Cardiac Electrophysiol* 2000;4:39–44, with permission.)

CONTROVERSIES AND PERSONAL PERSPECTIVES

Bystander cardiopulmonary resuscitation is rarely performed, resulting in significant loss of life. These practices are based largely on unfounded fears of side effects and complications of intervention, when in reality the risk is far lower than perceived. Public awareness and education in cardiopulmonary resuscitation are also woefully inadequate and need to become part of the basic educational curriculum. Despite the precedence of sound clinical data, there appears to be an underuse of validated prevention strategies in sudden cardiac death. Based on surveys of physician practices, only a fraction of patients with established coronary artery disease or hypercholesterolemia actually receive aggressive cholesterol-lowering therapy. Even fewer receive beta-blockers post-MI or angiotensin-converting enzyme inhibitors, especially if they have ventricular dysfunction, although they stand to gain the most. Similarly, a significant proportion of eligible patients do not receive prompt thrombolytic therapy or revascularization to limit infarct size.

The ICD, initially used as secondary prevention therapy, has gained increasing attention in prophylactic therapy in the patient at high risk of sudden cardiac death as an alternative to the inevitable vagaries, relative inefficacy, and risks of antiarrhythmic drug therapy. There are now trial data to support the ICD in those who have survived a cardiac arrest or syncopal VT and in the high-risk patient with ischemic cardiomyopathy and asymptomatic nonsustained VT. The young cardiac arrest survivor with preserved LV function and the older survivor with advanced ventricular dysfunction are both at high risk, but one must have different expectations of the degree of ICD benefit each would receive because arrhythmic death constitutes only a fraction of total cardiac death, and this component varies with the population selected. The ICD as a bridge to cardiac transplantation is a theoretically sound concept that appears to be most appropriate for patients with a realistic chance of transplantation, because of the competing causes of mortality in this population, and ongoing studies such as SCD-HeFT will likely clarify the dilemma in the large population with advanced ventricular dysfunction (eFig. 68.0.15).



***e*FIGURE 68.0.15** Influence of emerging implantable cardioverter-defibrillator trials in at-risk population subgroups. SCD-HeFT is likely to affect larger subsets than MADIT, AVID, and CASH. EF, ejection fraction; MI, myocardial infarction; VF/VT, ventricular tachycardia/ventricular fibrillation. (From Myerburg M, Mitrani R, Interian A, et al. The interpretation and clinical application of data from trials on sudden death. *J Intervent Cardiac Electrophysiol* 2000;4:95–102, with permission.)

The issues, therefore, that need clarification are defining the high-risk population that stands to benefit the most and quantifying the degree, quality, and cost of life prolongation by the ICD as a clinical benefit. The issue of whether ICDs prolong life is a foregone conclusion.

THE FUTURE

Continued advances in several fronts will shape the future of sudden cardiac death. The application of primary prevention measures, such as cholesterol reduction and coronary substrate-oriented strategies (thrombolytics and revascularization), intuitively hold promise for the long-term reduction of risk of sudden cardiac death. Defining the person at risk by genetic markers (as in those with ventricular hypertrophy, hypertrophic cardiomyopathy, and long QT syndrome) and improved indices of autonomic dysfunction will facilitate primary prevention. Community awareness and education in cardiopulmonary resuscitation, especially with the availability of automatic external defibrillators, can greatly affect survival. Meanwhile, the role of the ICD needs to be defined and validated for primary prevention in the high-risk subgroups, such as those with advanced ventricular dysfunction.

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69

CARDIOPULMONARY RESUSCITATION

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Closed-chest cardiopulmonary resuscitation (CPR), first described in 1960, circulates blood throughout the body by two different mechanisms: direct cardiac compression (the cardiac pump) and changes in intrathoracic pressure (the thoracic pump).

The most common victim of sudden, unexpected cardiac arrest is a male who is between 50 and 75 years of age and who has underlying coronary artery disease. The most common initial rhythm is pulseless ventricular tachycardia or ventricular fibrillation.

The most effective approach to resuscitation is to establish a strong chain of survival with early access, early CPR, early defibrillation, and early advanced cardiac life support. Public access to defibrillation is a promising new strategy for strengthening the early defibrillation link in the chain.

A variety of monitoring techniques can, and should, be used during clinical resuscitation.

There is little evidence that high-dose epinephrine is any better than standard 1-mg doses of epinephrine. Vasopressin is now considered to be an acceptable alternative for the first dose only in treating pulseless ventricular tachycardia or ventricular fibrillation in the adult. Sodium bicarbonate is of very limited value in most cardiac arrest cases, unless hyperkalemia is present or the patient has taken an overdose of a tricyclic antidepressant or barbiturates. Intravenous amiodarone is now the preferred antiarrhythmic agent for treating pulseless ventricular tachycardia or ventricular fibrillation. Several promising new CPR techniques are currently undergoing clinical testing.

GLOSSARY

Automated external defibrillator (AED): A defibrillator that automatically determines the cardiac rhythm and advises rescuers of the need to defibrillate using voice prompts. Fully automated devices charge and deliver the defibrillation energy with no input from the user. Semiautomated devices prompt the user to defibrillate when ventricular fibrillation is detected by the device.

Chain of survival: A coordinated system for treating victims of cardiac arrest that provides early access to emergency medical services, early cardiopulmonary resuscitation (CPR), early defibrillation, and early advanced cardiac life support (ACLS).

High-dose epinephrine: Doses of epinephrine of greater than 1.0 mg in adults (typically 3 to 15 mg).

Public access defibrillation: The use of AEDs by laypersons.

Pulseless electrical activity (PEA): During cardiac arrest, an organized cardiac rhythm that does not generate a pulse. Previously known as electromechanical dissociation (EMD).

HISTORICAL PERSPECTIVE

Numerous and often barbaric methods to restore life to the newly deceased have been attempted for centuries (1). It was not until the last 50 years that the era of modern-day CPR was born. The field of resuscitation that exists as we enter the twenty-first century is an integrated science combining chest compression, ventilation, defibrillation, and pharmacotherapeutics with widespread use in both the prehospital and in-hospital arenas. Although it is difficult for us today to imagine these elements independently, that is precisely how they began.

Artificial Ventilation

Nearly 200 years of effort and experimentation to determine an effective method of artificial respiration culminated in the work performed by Archer Gordon in 1949. Gordon attempted to compare various methods of artificial respiration. For 1 year, with no salary and no funding, Gordon slept in Cook County Hospital in Chicago, where he was on call 24 hours a day. He would insert a tube into the trachea of fresh corpses and perform multiple posturing techniques such as lifting the arms and pressing on the back or chest, lifting the hips, or rocking the deceased patient. He would then observe the effects of these procedures via a respirometer connected to the tracheal tube. These results were first published in *Journal of the American Medical Association* in 1950 (2).

In 1951, Gordon performed similar studies on medical students anesthetized with curare. Later that year he published a wealth of data (3) supporting the notion that these techniques were able to provide some degree of manual respiration. There were two limitations to Gordon's relentless efforts. The first was that he alluded only

to the idea of mouth-to-mouth ventilation and did not evaluate this technique; the second was that all of his data were collected in intubated patients in whom the airway was fully protected.

Simultaneous with these efforts, James Elam discovered that by merely using expired air, one could oxygenate humans adequately. His discovery was born out of a need to ventilate patients suffering form acute paralysis during the polio epidemic in 1946. From his repeated experience in performing mouth-to-nose breathing over a several-year period, he was convinced of its value. To scientifically document his beliefs, in 1954 Elam studied intubated, anesthetized, nonbreathing postoperative patients. He merely blew into their tracheal tubes with his own exhaled air and documented that by doing this he could maintain normal arterial oxygen saturation.

It was not until 1956 that fate brought Elam and his data together with Peter Safar. Lively discussion enticed Safar to begin experiments with mouth-to-mouth artificial respiration. By 1957, Safar had proven that the mouth-to-mouth technique was clearly superior to the manual ventilation techniques that were currently used and that it could be performed quite easily by laypersons (4). He was also able to document that by tilting a person's head backward, the airway would usually remain open, thus enhancing previous data that used patients with protected airways.

By 1958, the works of Gordon, Elam, and Safar persuaded the American Medical Association and the U.S. military to adopt the mouth-to-mouth technique as the official means to provide artificial respiration.

Electrical Therapy

Electrotherapy was used as common practice for a variety of ailments ranging from paresis to death throughout much of the eighteenth and nineteenth centuries. Unfortunately, there was little known about electrical forces or the ailments they purportedly treated, and there was no benefit to survival from their use. Quite comically, it took several decades to link electricity to the appropriate treatment for many instances of sudden death. Until the development of the electrocardiograph, ventricular fibrillation was a diagnosis that could be made only by observing the heart. It was first described in 1850 by Karl Ludwig in the dog laboratory (5). Ludwig noted that he could induce ventricular fibrillation by applying galvanic currents directly to a dog's heart. Although this was likely the first link between electricity and sudden death, the connection was ignored for decades. In 1889, John McWilliam refuted the notion that sudden cardiac death was caused by ventricular standstill by describing a fibrillating heart in the dog laboratory. He documented, as others had before him, that electricity could induce this event in the canine model (6). Unfortunately, he never attempted to use electricity to terminate the events. Although he postulated that a similar scenario may occur in humans, he did not pursue this. It was not until a decade later that two French physiologists, Frederic Battelli and Jean Louis Prevost, reported that, although a weak current passed through the heart could cause fibrillation, a stronger current was capable of terminating it (7). This singularly important discovery remained dormant for the next several decades.

In the late 1920s the Electric Company and Edison Power Company reconsidered the idea of coupling electricity with defibrillation. They commissioned William Kouwenhoven, Donald Hooker, and Orthello Langworthy at Johns Hopkins University to research electrical effects on the heart. This group quickly documented that weak shocks could induce ventricular fibrillation and stronger shocks could eradicate it. They were the first to discover that defibrillation could be successfully performed without opening the chest (8). The group also coined the term "countershock," which was used synonymously with *defibrillation*. An initial shock placed the heart into ventricular fibrillation and a subsequent countershock could terminate it. None of these researchers pursued the possibility of using this countershock in humans to terminate ventricular fibrillation.

Two decades passed until Claude Beck successfully defibrillated a patient. Based on the work of Kouwenhoven, Hooker, and Langworthy, Beck constructed an alternating current internal defibrillator. Although he was successful in resuscitating a pediatric patient who developed ventricular fibrillation during cardiac surgery, it took another 8 years for him to successfully use his device on another patient.

In 1955, Paul Zoll developed an external alternating current defibrillator. On a case-by-case basis, he documented that external defibrillation could be performed safely and effectively (9).

Defibrillators using alternating current were quite heavy and cumbersome. It was very difficult to transport this equipment to needy patients in an emergency situation. In 1960, Bernard Lown developed a direct current defibrillator that was battery operated and readily transportable. This piece of equipment was the first in a long line of modern direct current defibrillators.

Closed-Chest Compressions

The first documented case of closed-chest compression for the treatment of cardiac arrest in the United States was in 1904 (10). Without the aid of defibrillation or pacing to restart the heart, the concept was not particularly useful and never gained extensive popularity. It was not until the late 1950s that the technique of closed-chest massage was stumbled on once again. Kouwenhoven and Guy Knickerbocker were studying fibrillation in their animal laboratory at Johns Hopkins University. While performing experiments to determine how long a canine's heart could be left fibrillating and still be successfully cardioverted, Knickerbocker noted that when he placed the defibrillator paddles snugly against the closed chest of the dog there was a slight increase in arterial pressure. The investigators noted that by applying the paddles in a repetitive motion they could prolong the time that the heart could stay in fibrillation and be defibrillated successfully. James Jude joined the group, and the team began performing multiple studies using the hands to compress the chest. Through a series of trial and error experiments, it was determined that downward pressure of 1.5 to 2.0 in. on the lower sternum at a rate of 60 to 80 per minute was the optimal way to perform this maneuver. The investigators published data derived from patients suffering from in-hospital cardiac arrest in 1960. Fourteen of 20 patients survived to discharge from the hospital (11). It was finally understood that closed-chest compressions could "buy time" for the patient with a fibrillating heart until the external defibrillator arrived.

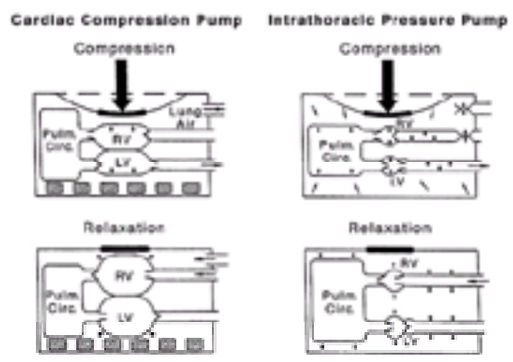
Modern-Day Cardiopulmonary Resuscitation

It was not until Safar, Kouwenhoven, and Knickerbocker presented their scientific data at the Maryland Medical Society meeting September 16, 1960, that artificial ventilation was combined with artificial circulation to create CPR. The trio lectured around the world to promote the concept of CPR. Gordon produced a training film in 1962 that coined the mnemonic ABC (*a*irway, *b*reathing, *c*irculation). The popularity of this technique that could be performed by anyone anywhere spread quickly.

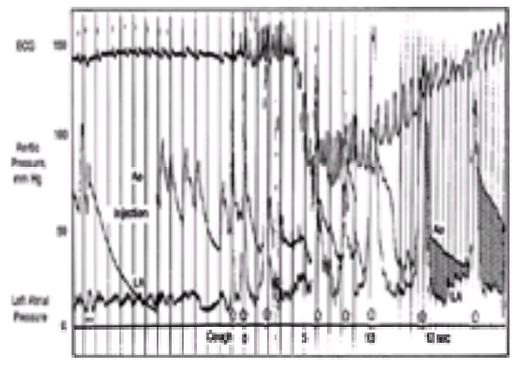
The American Heart Association officially endorsed CPR in 1963 and developed a CPR committee. In 1966 the National Research Council of the National Academy of Sciences brought together representatives from more than 30 organizations, such as the American Red Cross, and established official recommendations regarding standardized training and performance of CPR (12). Since then, the American Heart Association has hosted special conferences in 1973, 1979, 1985, 1992, and 2000 to establish consensus recommendations for resuscitation. Each of these conferences was followed by publication of educational documents that have been used worldwide to teach the science of resuscitation (13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37 and 38).

MECHANISM OF BLOOD FLOW DURING CARDIOPULMONARY RESUSCITATION

For 15 years after the discovery of closed-chest compression, it was generally believed that blood flow during CPR is caused by direct compression of the heart between the sternum and the spine ("cardiac pump" theory) (eFig. 69.0.1). In the 1970s, the cardiac pump theory was challenged by investigators who observed that increased intrathoracic pressure alone (without precordial compression) can generate blood flow. Criley et al. (39) reported that increases in intrathoracic pressure by repeated coughing could maintain adequate systemic blood pressure and flow to maintain consciousness without precordial compression in a patient who developed ventricular fibrillation during cardiac catheterization (eFig. 69.0.2). This observation was confirmed by Niemann et al. (40), lending further support to the notion that pressurization of the thoracic cavity could generate blood flow and pressure by forcing blood out of both the heart and thoracic vessels. A sudden increase in the intrathoracic pressure causes air trapping in the alveoli and small bronchioles during chest compression, creating a pressure gradient between the intrathoracic and extrathoracic cavities (41). According to this "thoracic pump" theory, the heart functions as a passive conduit (eFig. 69.0.1) (42). Pressurization of the thorax collapses veins at the thoracic inlet, preventing venous backflow (43). Forward flow occurs because the more muscular arteries remain open, particularly if epinephrine is administered exogenously.



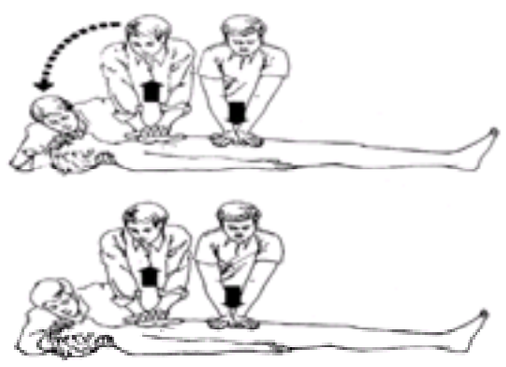
***e*FIGURE 69.0.1** Mechanisms of blood flow during cardiopulmonary resuscitation. LV, left ventricular; Pulm. Circ., pulmonary circulation; RV, right ventricular. (From Halperin HR. Mechanisms of forward flow during external chest compression. In: Paradis NA, Halperin HR, Nowak RM, eds. *Cardiac arrest: the science and practice of resuscitation medicine*. Baltimore: Williams & Wilkins, 1996:253, with permission.)



***e*FIGURE 69.0.2** Cough cardiopulmonary resuscitation. Ao, aortic pressure; ECG, electrocardiogram; LA, left atrial pressure. (From Criley JM, Blaufuss AH, Kissel GL. Self-induced form of cardiopulmonary resuscitation. *JAMA* 1976;236:1246–1250, with permission.)

The relative contribution of the cardiac and thoracic pump mechanism has been debated (42,44,45 and 46). Transesophageal echocardiography (TEE) studies during CPR demonstrate that both mechanisms are operative in humans (45,47,48,49 and 50). Sternal compression virtually always squeezes blood out of the right ventricle (cardiac pump), whereas the amount of left ventricular compression is highly variable among patients (48). Physiologic studies in experimental models (51) and humans (52) suggest a strong role for the thoracic pump. In addition, active decompression of the chest by application of negative pressure or suction to the sternum can further enhance cardiac output by improving venous inflow (*e*Fig. 69.0.3) (53,54,55,56,57 and 58). Finally, interposing an abdominal compression between each chest compression has also been tried in an attempt to mimic the physiologic effects of intraaortic balloon counterpulsation (*e*Fig 69.0.4) (59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81 and 82).

***e*FIGURE 69.0.3** Active compression-decompression cardiopulmonary resuscitation. (From Cohen TJ, Tucker KJ, Lurie KG, et al. Active compression-decompression. A new method of cardiopulmonary resuscitation. *JAMA* 1992;267:2916–2923, with permission.)



***e*FIGURE 69.0.4** Interposed abdominal compression cardiopulmonary resuscitation. (From Babbs CF, Tacker WA Jr. Cardiopulmonary resuscitation with interposed abdominal compression. *Circulation* 1986;74:IV37–IV41, with permission.)

CLINICAL PROFILE OF SUDDEN, UNEXPECTED CARDIAC ARREST

Most episodes of sudden, unexpected cardiac arrest in adults occur in the home or workplace (83,84,85 and 86). The most common victim is a male who is between 50 and 75 years of age (83,85). The majority of these individuals has significant underlying structural heart disease such as coronary artery atherosclerosis, hypertension, left ventricular hypertrophy, and/or congestive heart failure (84,87,88,89 and 90).

Most cardiac arrests occur without an obvious immediate precipitant, although many families of cardiac arrest victims will report that the patient experienced a variety of nonspecific symptoms such as chest pain, dyspnea, fatigue, or malaise in the days preceding the event (84,87). On rare occasions, a dramatic emotional event can trigger cardiac arrest (91,92,93,94 and 95).

There is a definite circadian pattern to the onset of sudden, unexpected cardiac arrest. The incidence of cardiac arrest is lowest during sleep and begins to rise rapidly soon after awakening (96,97 and 98). Heart rate variability studies show that, at such times, vagal activity is relatively low and sympathetic activity is high, especially in patients with reduced left ventricular function (99).

In more than 80% of patients who develop out-of-hospital, primary cardiac arrest during ambulatory electrocardiographic monitoring, the initiating event is a ventricular

tachyarrhythmia (ventricular tachycardia) degenerating rapidly to ventricular fibrillation in 62%, torsades de pointes in 13%, and "primary" ventricular fibrillation in 8% (100). Less than 70% of patients are in ventricular tachycardia or ventricular fibrillation by the time rescue personnel arrive on the scene [typically 5 to 10 minutes after the onset of collapse in most efficient emergency medical services (EMS) systems] (101). Most of the remaining patients (31%) are in a pulseless, bradycardic rhythm or asystole.

The outcome of field resuscitation is strongly influenced by the patient's initial cardiac rhythm. In one series of 352 consecutive out-of-hospital cardiac arrest patients, 67% of the patients with ventricular tachycardia and 23% of those who were initially in ventricular fibrillation survived to hospital discharge (102). None of the patients who presented with an initial bradyarrhythmia survived to hospital discharge. Similar observations have been made by others (103). One plausible hypothesis is that pulseless bradycardia or asystole may be a marker for a prolonged downtime interval or a more severe underlying disease process (104). Because ventricular tachyarrhythmias represent the most common, potentially treatable mechanism of sudden cardiac arrest in adults, the best in-hospital and out-of-hospital resuscitation programs have been designed to deliver rapid defibrillation to as many patients as possible.

PRINCIPLES OF MANAGEMENT

"Chain of Survival" Approach to Treatment

Survival from pulseless ventricular tachycardia or ventricular fibrillation is inversely related to the time interval between its onset and termination. Each minute that a patient remains in ventricular fibrillation, the odds of survival decrease by 7% to 10% (105). Survival is highest when CPR is started within the first 4 minutes of arrest and ACLS, including defibrillation and drug therapy, is started within the first 8 minutes (106). The American Heart Association's Emergency Cardiovascular Care Committee and its Advanced Cardiovascular Life Support Subcommittee began to widely publicize the "chain of survival" concept in 1991. This symbolic phrase represents a sequence of events that should occur in most cardiac arrest cases to maximize the odds of successful resuscitation (105). The steps include early recognition of the problem and activation of the EMS system by a bystander, early CPR, rapid provision of defibrillation for patients who need it, and ACLS (e.g., intubation, administration of medications). Schematically, this sequence can be depicted by a "chain of survival" (Fig. 69.1).

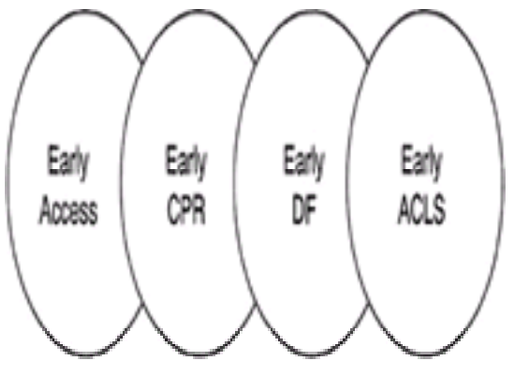


FIGURE 69.1 Chain of survival to optimize outcome from resuscitation. ACLS, advanced cardiac life support; CPR, cardiopulmonary resuscitation; DF, defibrillation.

Early Access

The victim is rarely in a position to activate the EMS system before his or her collapse because most out-of-hospital cardiac arrests occur suddenly and without immediate premonitory symptoms. The same problem exists for in-hospital cardiac arrests that occur in unmonitored patients. Bystanders who witness the event can significantly improve the victim's chance to survive by alerting the emergency response system to the presence of the problem. All too often, an untrained bystander only further delays treatment of the out-of-hospital cardiac arrest victim by attempting to inform relatives, call the neighbors, or contact the patient's personal physician instead of calling the local community emergency telephone number (in most places it is 9-1-1) (107,108).

Before EMS rescuers can aid the victim, the bystander must recognize that there is a problem, locate a telephone, make a correct call, and give accurate and precise information to the dispatcher. Once the alarm has been sounded, rescuers must travel to the scene, physically arrive at the patient's side, and perform an initial, cursory assessment.

Public education can improve bystander behavior significantly when a cardiac emergency occurs in the community. Citizens can be trained to summon help quickly and to initiate lifesaving CPR. For example, bystanders in Seattle initiated CPR in only 5% of cardiac arrests in 1970 to 1971, but by 1976, 34% of cardiac arrest victims were receiving bystander CPR as a result of a widespread, pioneering, public education campaign (105). Since then, the American Heart Association and the American Red Cross have trained millions of citizens to recognize cardiac emergencies, call for help, and perform CPR.

Availability of the simple three-digit 9-1-1 emergency number in the United States can reduce confusion and decrease delay in activating the EMS system. In Minneapolis, the percentage of emergency callers who could activate the EMS system in less than 1 minute rose from 63% before institution to 82% after institution of a 9-1-1 number (109). Only two states currently have 9-1-1 available everywhere within their borders. One community in North Carolina lists 85 different emergency numbers in the local telephone book (110,111). The American Heart Association has recommended that all communities implement an enhanced 9-1-1 system that displays the caller's location automatically on the dispatcher's terminal when the call is received (105). Having a similar, easy-to-remember number would also be useful for in-hospital emergencies.

Early Cardiopulmonary Resuscitation

The next link in the chain is early initiation of CPR, preferably by bystanders. One way to ensure initiation of early CPR is to educate and train a "critical mass" of the general population. The effectiveness of such training has varied widely. In Seattle, approximately 50% of the population has been trained to perform CPR (87), whereas in Minneapolis only 23% of adults surveyed have received such training (112). In smaller cities and in less affluent areas, the number of trained citizens is often much lower. What percentage of adults need to be trained in CPR to provide reasonable protection in the community is difficult to determine with certainty. As a rule of thumb, the American Heart Association recommends that at least 20% of the adult population should be trained in basic CPR to reduce mortality from out-of-hospital cardiac arrest (113). It is also important to train a critical mass of in-hospital personnel to ensure that proper CPR can be performed on all cardiac arrest victims in all areas of the hospital while awaiting arrival of "code team" personnel.

There are a number of problems associated with training the public to perform CPR. For example, it can be argued that we have trained the wrong rescuers. The typical cardiac arrest victim is male, is 60 to 65 years old, and usually arrests at home, often in the presence of a spouse of similar age (85). Most citizens who have taken CPR training are younger than 30 years of age; typically, less than 10% live with family members known to have heart disease (114). Most citizens who have received CPR training never actually witness or participate in managing a cardiac arrest; conversely, bystanders who witness a cardiac arrest usually do not know how to perform CPR (87,115). For example, only 10% of CPR-trained citizens in Minneapolis have witnessed an arrest, whereas only 30% of citizens present at the site of a cardiac arrest were trained in CPR (112). The majority of laypersons who attempt to perform CPR out-of-hospital are actually employed or volunteer their services as health professionals (116). The best solution to the problem seems to be targeting CPR training to "high-risk" individuals, such as middle-aged persons, senior center residents and staff, and family members (particularly the spouse) of patients who are survivors of myocardial infarction or cardiac arrest or who have other risk factors for cardiac arrest (114,117).

Skill retention is also a problem because CPR is a psychomotor technique that deteriorates rapidly over time unless practiced or used. In Belgium, 46% of bystanders who performed CPR forgot to perform mouth-to-mouth breathing; chest compressions were not done 17% of the time (118,119). It is important for laypersons or health care professionals who perform CPR infrequently to receive at least annual reinforcement. However, only about 20% of trainees return for annual training in the United States (87,112). Fear of communicable disease, particularly infection with the human immunodeficiency virus, that is disproportionate to the known minimal risk of disease transmission may decrease the likelihood that trained rescuers will actually perform mouth-to-mouth ventilation on strangers (120).

Although the value of bystander CPR was once debatable, virtually all studies have shown that initiation of bystander CPR within 4 minutes of the patient's collapse results in up to a 12-fold improvement in the odds for survival (105). The mechanism by which early CPR improves outcome is unclear but may be due to CPR's ability to keep coarse ventricular fibrillation from degenerating to asystole for a few extra minutes until rescuers arrive. Recent evidence from Seattle suggests that a brief

period (90 seconds) of CPR actually improves the odds of successful defibrillation if more than several minutes elapse before defibrillation can be provided (121).

Early Defibrillation

The rationale for the use of early defibrillation stems from four observations: (a) Ventricular tachyarrhythmias are the most common cause of sudden out-of-hospital cardiac arrest in adults; (b) defibrillation is the most effective treatment for pulseless ventricular tachyarrhythmias; (c) the effectiveness of defibrillation diminishes rapidly over time; and (d) unless treated promptly, ventricular fibrillation becomes less coarse and eventually converts to the less treatable rhythm of fine ventricular fibrillation or asystole.

The best outcomes from sudden arrhythmic cardiac arrest in adults have been reported from cardiac rehabilitation programs, where defibrillation can be performed within the first minute or two. In such “ideal” settings, 85% to 90% of patients are resuscitated and can be returned to their prearrest neurologic status (122,123 and 124). Survival from out-of-hospital cardiac arrest treated by EMS personnel has been considerably lower, averaging 15% to 20% or less, with a maximum survival of 30%, depending on the EMS system configuration (105).

The best survival is attained in EMS systems that can provide early defibrillation to a large percentage of patients. In most cases, this is most cost-effectively accomplished by a “tiered response” system, in which large numbers of rapid “first-response” firefighters or emergency medical technicians (EMTs) are trained and equipped to provide first aid, CPR, and early defibrillation using an AED.

Unfortunately, not all communities in the United States have yet implemented a comprehensive tiered EMS system. Some systems, particularly in suburban or rural areas, have only EMTs who are neither trained nor equipped to defibrillate. For such areas, adding rapid defibrillation capability offers a cost-effective alternative that can significantly improve survival from out-of-hospital ventricular fibrillation or pulseless ventricular tachycardia (125,126). In 1991, the American Heart Association issued a position statement advocating the widespread implementation of rapid defibrillation programs throughout the nation. The American Heart Association endorses the position that

“All emergency personnel should be trained and permitted to operate an appropriately maintained defibrillator if their professional activities require that they respond to persons experiencing cardiac arrest. This includes all first responding emergency personnel, both hospital and nonhospital (e.g., emergency medical technicians (EMTs), non-EMT first responders, firefighters, volunteer emergency personnel, physicians, nurses, and paramedics).

To further facilitate early defibrillation, it is essential that a defibrillator be immediately available to emergency personnel responding to a cardiac arrest. Therefore, all emergency ambulances and other emergency vehicles that respond to or transport cardiac patients should be equipped with a defibrillator” (127).

There has been continued progress in improving the chain of survival in every community. The American Heart Association is implementing “Operation Heartbeat” on a national level, which helps communities to identify and correct weaknesses in their chain of survival locally.

More novel strategies have also been tried to increase the availability of rapid defibrillation in the hospital and in the community at large. Kaye et al. pioneered the use of AEDs by non–intensive care nurses in an in-hospital setting (128,129). There has also been an increasing effort to place AEDs in high-risk public locations for use by trained laypersons.

Early Advanced Cardiac Life Support

Physicians provide prehospital ACLS by staffing specially equipped ambulances in many countries (e.g., Western Europe, Scandinavia, Canada). In the United States, “intermediate”-level EMTs or paramedics provide most prehospital ACLS intervention (e.g., defibrillation or synchronized cardioversion, endotracheal (ET) intubation, intravenous fluid therapy, drug administration). Intermediate EMTs (often called *cardiac technicians*) typically receive several hundred hours of training; paramedics usually receive 1,000 or more hours. Adding field ACLS capability appears to favorably impact survival from out-of-hospital cardiac arrest.

Some EMS systems have upgraded all transporting ambulances to ACLS status to eliminate the possibility that dispatchers might send a basic life support unit on a call that needs a higher level of care. An “all-ACLS” system eliminates the potential “failure point” in the 9-1-1 center because there is no triage of calls to an ACLS or basic cardiac life support response. Existing basic cardiac life support ambulances or first-responding vehicles can be upgraded to automated defibrillation capability with minimal expense. Automated defibrillators cost approximately $5,000 to $8,000 and require only 2 to 4 hours of additional training for first responders or EMTs. This is a nominal expense compared with the cost of a typical ambulance ($50,000 to $100,000) or fire truck ($250,000 to $500,000). In Richmond, Virginia, upgrading from a half basic cardiac life support/half ACLS system to an all-ACLS system added less than 1% to the cost of ambulance service (only $2.88 per patient transported) (130).

Algorithm Approach to Resuscitation

The American Heart Association’s ACLS algorithms provide a “framework for dealing with the life-threatening cardiopulmonary emergencies in a logical sequence” (17,18). There are algorithms for initiating CPR (Fig. 69.2), treating patients with ventricular fibrillation or pulseless ventricular tachycardia (Fig. 69.3), bradycardia (Fig. 69.4), asystole (Fig. 69.5), or PEA (Fig. 69.6), which was formerly known as EMD. However, the algorithms are “not appropriate for every unique clinical circumstance, and the team leader must adapt them and the general ACLS principles when necessary.” Resuscitation team leaders are encouraged to function as “thinking cooks” when applying these cookbook procedures.

FIGURE 69.2 Comprehensive emergency cardiovascular care algorithm for cardiac arrest. ACS, acute coronary syndrome; BLS, basic life support; CPR, cardiopulmonary resuscitation; OD, overdose; VF/VT, ventricular fibrillation/ventricular tachycardia. (From *American Heart Association Guidelines*. 2000:I-144, with permission.)

FIGURE 69.3 Ventricular fibrillation/pulseless ventricular tachycardia algorithm. CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia. (From *American Heart Association Guidelines*. 2000:I-147, with permission.)

FIGURE 69.4 Symptomatic bradycardia algorithm. AV, atrioventricular; BP, blood pressure; ECG, electrocardiogram. (From *American Heart Association Guidelines*. 2000:I-156, with permission.)

FIGURE 69.5 Asystole algorithm. CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia. (From *American Heart Association Guidelines*. 2000:I-153, with permission.)

FIGURE 69.6 Pulseless electrical activity algorithm. ACS, acute coronary syndrome; CPR, cardiopulmonary resuscitation; EMD, electromechanical dissociation; OD, overdose; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia. (From *American Heart Association Guidelines*. 2000:I-151, with permission.)

Ventricular Fibrillation or Pulseless Ventricular Tachycardia

Electrical countershock is the treatment of choice for ventricular fibrillation and pulseless ventricular tachycardia. If three initial countershocks at increasing monophasic energies (200, 200 to 300, and 360 J), intubation, epinephrine, and a fourth countershock (360 J) fail to terminate the arrhythmia (refractory ventricular fibrillation or ventricular tachycardia) or if, as in many cases, the arrhythmia rapidly recurs (recurrent ventricular fibrillation or ventricular tachycardia), antiarrhythmic drug therapy is indicated (17). There is increasing evidence that biphasic defibrillation waveforms using lower energy (typically 125 to 175 J) defibrillate successfully and are at least as effective as higher-energy, escalating monophasic waveforms (131,132,133,134,135,136 and 137). The American Heart Association now considers biphasic waveforms to be an acceptable alternative to the traditional escalating monophasic waveforms (17,138).

Pulseless Electrical Activity

PEA is present when there is organized electrical activity on the electrocardiogram but no effective circulation. There are potentially many underlying causes, but the most common denominator may involve myocardial ischemia and dysfunction due to intramyocardial increases in carbon dioxide (139). Prognosis is generally poor unless a discrete and treatable etiology for PEA can be discerned and corrected. Because of the poor prognosis when a correctable etiology cannot be defined, efforts should be directed toward detecting causes such as hypovolemia, tension pneumothorax, and pericardial tamponade (17). Normal saline or Ringer's lactate solution should be infused rapidly if there is evidence of hypovolemia. Suspected pneumothorax or pericardial tamponade should be confirmed by needle aspiration of the chest or pericardium, respectively. If confirmed, more definitive surgical management (chest tube or thoracotomy) is usually required.

Scrutiny of the neck veins may be helpful in attempting to define an etiology for PEA. Most patients with cardiac arrest have high right-sided filling pressures and distended neck veins. When neck veins are not visible in this setting and PEA is present, hypovolemia should be suspected. In the "trauma" cardiac arrest victim (e.g., a patient with a gunshot wound of the chest), however, prominent neck veins should lead to the suspicion of pericardial tamponade or tension pneumothorax (140).

General measures such as (a) support of ventilation, (b) properly performed closed-chest compression, and (c) frequent doses of epinephrine to maintain arterial perfusion pressure and coronary and cerebral perfusion are recommended for treatment of PEA (17). Bradycardia may be treated with atropine. Although catecholamines are frequently given, there are no data to suggest a specific benefit (other than improvement in coronary and cerebral blood flow during closed-chest compression). Calcium chloride has not been shown to affect clinical survival in controlled trials (141,142). In addition, the pathologically high serum calcium levels caused by its administration (143,144) may exacerbate reperfusion injury (145).

If penetrating cardiac trauma is present, open-chest massage can be life saving (146). In other settings, open-chest massage is rarely of value, partly because it is usually initiated late after the onset of the arrest (147). Prehospital trauma victims who are pulseless and have asystole or agonal electrical cardiac activity (heart rate of less than 40 beats/min) have such a poor prognosis that some authors believe that they should be pronounced dead at the scene of injury (148).

Bradyasystole

Bradyasystole is one of the most common and least understood problems that can occur during resuscitation. For purposes of definition, *bradyasystole* efers to a cardiac rhythm that has a ventricular rate of below 60 beats/min in adults and/or periods of absent heart rhythm (asystole). Bradyasystolic states are clinical situations during which bradyasystole is the dominant heart rhythm.

Survival is poor (generally 1% to 3% or less), regardless of therapy for patients who present with bradyasystole. It is always important to exclude disconnection of a

lead or monitor electrode before concluding that a “flatline” is the patient’s rhythm. Because some patients with a flatline may have ventricular fibrillation (a rhythm more amenable to treatment) masquerading as asystole (149), the monitor lead configuration should be quickly switched to a second lead to confirm the diagnosis before treatment (17). Other general measures recommended for the treatment of bradyasystole include support of ventilation; properly performed closed-chest compression; and frequent doses of epinephrine to maintain arterial perfusion pressure and coronary and cerebral perfusion (17).

Treatment with atropine sulfate may improve outcome in patients with bradyasystolic cardiac arrest that is due to excessive vagal stimulation, but atropine is less effective when asystole or pulseless idioventricular rhythms are the result of prolonged ischemia or mechanical injury in the myocardium (150).

For patients with bradyasystolic cardiac arrest, a 1-mg dose of atropine is administered intravenously and is repeated every 3 to 5 minutes if asystole persists. Three mg (0.04 mg per kg) given intravenously is a fully vagolytic dose in most patients (151). The administration of a total vagolytic dose of atropine should be reserved for patients with bradyasystolic cardiac arrest. ET atropine produces a rapid onset of action similar to that observed with intravenous injection. The recommended adult dose of atropine for ET administration is 1.0 to 2.0 mg diluted in 10 mL of sterile water or normal saline.

Pacing (transvenous, transthoracic, or transcutaneous) rarely influences survival in the unwitnessed cardiac arrest patient who is initially found with asystole or bradycardia without a pulse (152,153 and 154). However, pacing is extremely useful for bradycardic patients with a pulse and in selected patients in whom a pacemaker can be placed immediately after the development of the conduction disturbance (153,154). In such cases, a precordial thump can also stimulate ventricular complexes and a pulse (“fist pacing”) (155).

Endogenous adenosine released during myocardial hypoxia and ischemia relaxes vascular smooth muscle, decreases atrial and ventricular contractility, depresses pacemaker automaticity, and impairs atrioventricular conduction (156). The cellular electrophysiologic effects of adenosine can be competitively antagonized by methylxanthines but not by atropine. A specific adenosine antagonist (BW-A1433U) has been shown to reverse and prevent postdefibrillation bradyasystole and hemodynamic depression in a domestic pig model (157).

Aminophylline, a competitive nonspecific adenosine antagonist, has been shown to restore cardiac electrical activity within 30 seconds in 12 of 15 in-hospital, bradyasystolic cardiac arrest patients who were refractory to atropine and epinephrine (158). Other anecdotal case reports seem to indicate that adenosine blockade may restore normal sinus rhythm in some bradyasystole patients who do not respond to conventional therapy (159). In a relatively small, randomized, prospective clinical trial on adults with asystole refractory to epinephrine and atropine, there was a trend toward improved return of spontaneous circulation (ROSC) in patients who received aminophylline versus placebo, but the results did not reach statistical significance (160). Forty-five patients were assigned to the placebo group, and 37 received aminophylline. Nine of 45 controls (20%; 95% confidence interval, 10% to 35%) achieved ROSC compared with 10 of 37 (27%; 95% confidence interval, 14% to 44%) in the aminophylline group. Although further clinical research will be necessary to determine the potential value of adenosine blockade for bradyasystolic cardiac arrest, it is clear that these agents should not be used when ventricular fibrillation is present because they may make it more difficult to terminate this arrhythmia (161).

Physiologic Monitoring during Resuscitation

Real-time hemodynamic data can provide the team leader with a sound physiologic basis for altering the approach to clinical resuscitation when the standard algorithms either fail or do not apply.

Arterial Pressure Measurement during Cardiopulmonary Resuscitation

Maintenance of both the systolic and diastolic arterial pressure is vital during CPR. Because flow to most vital organs (except the heart) occurs during systole, a minimal systolic arterial pressure of 50 to 60 mm Hg is usually required to resist arteriolar collapse (162). Diastolic pressure is also important because it is a critical determinant of the coronary perfusion pressure (CPP) (CPP = aortic diastolic – right atrial pressure) during CPR. CPP is one of the best hemodynamic predictors of ROSC in both animal models (46,163,164,165,166,167,168,169,170,171,172 and 173) and humans (174). A minimal threshold gradient for CPP of approximately 15 mm Hg (usually corresponding to an aortic diastolic pressure of 30 to 40 mm Hg) provides a level of myocardial blood flow that is necessary to meet the metabolic needs of the arrested myocardium (175) and to achieve ROSC (174).

A cuff manometer can be used to estimate the systolic arterial pressure during CPR by palpating the brachial artery or listening over it for flow with a peripheral Doppler device (176). More accurate, invasive measurements of systolic and diastolic pressure can be obtained by inserting an arterial line into the radial, brachial, or femoral artery (52,177,178,179,180,181,182,183 and 184). *e*Table 69.0.1 summarizes recent published invasive arterial pressure measurements during resuscitation in adult humans. Conventional CPR generates systolic, diastolic, and CPPs that are inadequate to sustain blood flow and function in vital organs (e.g., the brain). These measurements explain why cardiac arrest patients are rarely conscious during CPR.

***e*TABLE 69.0.1** ARTERIAL PRESSURE MEASUREMENTS DURING CARDIOPULMONARY RESUSCITATION IN HUMANS

Author	*N*	Systolic	Diastolic	Coronary perfusion pressure
Chandra et al. (180)	8	60 ± 4	23 ± 2	11 ± 2
Gonzalez et al. (183)	10	47 ± 5	18 ± 2	NR
McDonald (178)	15	104 ± 51	NR	NR
Omato et al. (179)	12	48 ± 6	17 ± 2	NR
Paradis et al. (184)	76	NR	NR	2 ± 9 (no ROSC)
	24	NR	NR	13 ± 9 (with ROSC)
Sanders et al. (181)	6	27 ± 18	11 ± 10	0 ± 8
Swenson et al. (182)	9	61 ± 29	13 ± 10	9 ± 11
Taylor et al. (177)	8	60 ± 14	NR	NR

NR, not reported; ROSC, return of spontaneous circulation.
From Ornato JP. Hemodynamic monitoring during CPR. *Ann Emerg Med* 1993;22:289–295.

Pulmonary Artery Catheter Recordings

Generation of a satisfactory arterial pressure is a prerequisite for adequate flow to vital organs; however, the presence of a reasonable arterial pressure does not ensure that there will be sufficient flow to meet metabolic needs. Pulmonary artery catheters are inserted infrequently during resuscitation because they are time-consuming to set up and technically difficult to position. The low flows generated by CPR do not favor ready passage of the balloon-flotation catheter through the right heart. In addition, it is difficult to determine the catheter tip’s position from pressure recordings because the pressures in the intracardiac chambers and great vessels are similar to each other during closed-chest CPR (51,185,186,187,188 and 189). Fluoroscopy is of little value during CPR, even if it is available, because it is not easy to continue chest compression impeded by the machine’s C-arm. TEE offers the greatest promise as a means to visualize and help position intracardiac catheters successfully during CPR.

Despite these technical limitations, there have been several published reports of intracardiac pressure and flow measurements in humans who were already being monitored invasively in an intensive care unit at the time of their cardiac arrest (190,191,192 and 193). Conventional closed-chest CPR in adult humans produces a hemodynamic state resembling profound cardiogenic shock, with a low systemic arterial pressure, markedly reduced cardiac output, and high intravascular filling pressures.

Pulmonary edema is noted commonly after CPR, either clinically if the resuscitation is successful or on autopsy if it is not. Dohi (192) found that 20 of 71 short-term survivors of CPR showed clinical signs of pulmonary edema; nine of these patients had overt signs of pulmonary edema (e.g., massive discharge of pink-foaming secretions through the ET tube). Nagel et al. (194) reported that 46% of 2,228 victims of out-of-hospital cardiac arrest had pulmonary edema on autopsy. Although there are multiple causes for pulmonary edema after CPR (e.g., aspiration, iatrogenous fluid overload, neurogenic stimuli, physical damage to the pulmonary capillary membrane, alteration of lymphatic drainage), the finding that pulmonary capillary pressure is high during CPR and returns to the patient’s baseline quickly after successful resuscitation suggests that hydraulic forces during the low blood flow state may be the most common mechanism responsible for the development of pulmonary edema during resuscitation (190). Hemodynamic monitoring post-CPR may be useful for managing selected patients who survive resuscitation, but the risks, potential benefits, and cost implications must be weighed on a case-by-case basis (193).

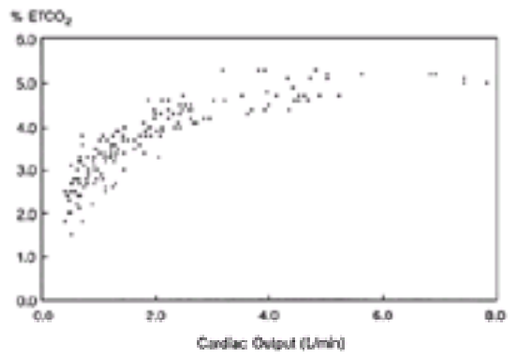
End-Tidal Carbon Dioxide Monitoring and Use of the Esophageal Detector Device during Resuscitation

The percentage of carbon dioxide contained in the last few milliliters of gas exhaled from the lungs with each breath is known as the end-tidal carbon dioxide

concentration (P_{ETCO_2}) (195,196). It can be measured by passing an infrared beam through exhaled gases and measuring the decrease in voltage output from a photoelectric cell calibrated to the wavelength at which carbon dioxide absorbs light. It can also be estimated by attaching an inexpensive, disposable, plastic, colorimetric device in-line between the ET tube and the ventilation device. Color indicators on the device change hue as the exhaled gases pass through the monitor's pH-sensitive membranes. The membrane's color can be compared with the adjacent color chart on the device, thus indicating the percentage P_{ETCO_2}.

Two important terms need to be defined with respect to end-tidal carbon dioxide monitoring. *Capnography* refers to any technology that displays and/or prints the actual capnographic waveform. If an unmistakable capnographic waveform is detected when a capnographic probe is attached to a patient who is being ventilated, then the airway device is unequivocally ventilating the lungs. *Capnometry* refers to the measurement or estimation of the P_{ETCO_2}. It can be displayed in analog or digital format, or it can be approximated using a colorimetric detection device. Capnometry often provides useful information as to the anatomic location of an airway device (e.g., ET tube); however, it does not provide the degree of definitive certainty as does the presence of a capnographic waveform.

During normal respiration and circulation, the P_{ETCO_2} averages 4% to 5%. Two units of measure are popularly used in reporting the P_{ETCO_2}: % and mm Hg (1% is approximately 7 mm Hg). There is a logarithmic relationship between the P_{ETCO_2} and the cardiac output (eFig. 69.6.1) (197). At normal or elevated levels of cardiac output, ventilation is the rate-limiting factor responsible for eliminating the large amount of carbon dioxide traversing the pulmonary circuit (e.g., hyperventilation lowers, and hypoventilation raises, the P_{ETCO_2}). In this range, if blood flow and arterial pressure are kept reasonably constant, the P_{ETCO_2} closely approximates arterial carbon dioxide tension (P_{aCO_2}) and can be used as a "real-time" guide to the adequacy of ventilation (the P_{ETCO_2} actually lags behind real-time events by a few seconds, the amount of time it takes for exhaled gas to be drawn into the machine and analyzed) (198).



***e*FIGURE 69.6.1** Relationship between cardiac output and the end-tidal carbon dioxide concentration ($ETCO_2$). (From Ornato JP, Garnett AR, Glauser FL. Relationship between cardiac output and the end-tidal carbon dioxide tension. *Ann Emerg Med* 1990;19:1104–1106, with permission.)

The P_{ETCO_2} can also be used to confirm ET tube airway placement, particularly in the non–cardiac arrest patient who has a pulse and an adequate blood pressure (where the sensitivity and specificity of the P_{ETCO_2} for detecting correct ET tube placement approach 100% and 90%, respectively) (183,199,200,201,202 and 203). The ET tube cuff should be inflated when the P_{ETCO_2} monitoring device is attached to be sure the gas being sampled is from the structure (i.e., trachea or esophagus) in which the tube resides. Ventilation through an ET tube that has been properly inserted in the trachea yields a P_{ETCO_2} of 4% to 5% in a patient with a normal cardiac output and no significant ventilation-perfusion gradient; ventilation through an ET tube that has been inadvertently inserted into the esophagus results in a P_{ETCO_2} of less than 0.5%. The only important exception occurs when the ET tube is inserted into the esophagus of a patient who has recently ingested a carbonated beverage (e.g., beer, soda). In such a case, the initial P_{ETCO_2} will appear to be normal or high on the first few ventilations but will typically decrease rapidly to less than 0.5% by the sixth or seventh ventilation (204).

At low levels of cardiac output (below approximately 50% of normal in animal models), ventilation has much less effect on the P_{ETCO_2}. Instead, the pulmonary blood flow (and the subsequent ventilation/perfusion mismatch) is the rate-limiting factor determining the P_{ETCO_2}. If ventilation is kept relatively constant in this range, an increase or a decrease in the cardiac output will usually be reflected by a rise or fall in the P_{ETCO_2}, respectively.

During CPR, the cardiac output falls typically to between one-fourth and one-third of normal (191,205,206 and 207). The P_{ETCO_2} also decreases to between one-fourth and one-third of normal as the reduced cardiac output and pulmonary blood flow present less blood and carbon dioxide to the lungs for exchange with oxygen in the pulmonary capillary (208,209,210,211,212,213,214 and 215). As carbon dioxide builds up in venous blood, hyperventilation cleanses the reduced quantity of venous blood traversing the lungs of carbon dioxide. The result is a low arterial (P_{aCO_2}) and a high central venous carbon dioxide concentration (a venoarterial carbon dioxide and pH gradient) (216). Within seconds after ROSC, the improved cardiac output returns large quantities of carbon dioxide–rich venous blood to the lungs, and the P_{ETCO_2} suddenly climbs to normal or above normal levels (208,216). The dramatic change from a low to a high P_{ETCO_2} due to venous carbon dioxide washout is often the first clinical indicator that ROSC has occurred (208). The P_{ETCO_2} typically returns to normal (4% to 5%) within 2 to 5 minutes after ROSC if the patient maintains a good cardiac output.

Knowledge of the physiologic relationship between P_{ETCO_2} and the cardiac output can guide clinicians during low blood flow states such as CPR. There are several important clinical corollaries and pitfalls. For example, inadequate chest compression is usually accompanied by a very low (i.e., less than 1%) P_{ETCO_2}, which increases linearly with increasing sternal compression depth and force (179,197). Administration of sodium bicarbonate intravenously causes a transient rise in P_{ETCO_2} (197). Epinephrine causes a dose-dependent decrease in P_{ETCO_2} (183,217,218 and 219). Disorders that cause significant ventilation-perfusion mismatch (e.g., pulmonary embolization), or decrease in production of carbon dioxide (e.g., hypothermia) are accompanied by a low P_{ETCO_2} (220). Disorders that increase the production of carbon dioxide (e.g., fever) increase the P_{ETCO_2} (197).

The P_{ETCO_2} can also be used to help confirm whether an ET tube has been positioned in the trachea or the esophagus in the cardiac arrest patient. If the P_{ETCO_2} during CPR is very low (below 0.5%) on at least the seventh breath after intubation, it is highly likely that esophageal insertion has occurred (204). Conversely, a moderately low (above 0.5% but below 2.0%) P_{ETCO_2} does not necessarily indicate esophageal placement of the ET tube because there are many other causes for this finding during CPR. Thus, a low P_{ETCO_2} during resuscitation should alert the rescuers that something is wrong with ventilation, perfusion, and/or carbon dioxide production and should prompt a search for correctable causes (221).

The American Heart Association recommends secondary confirmation of ET tube location immediately after intubation in all patients using either an end-tidal carbon dioxide detector device and/or an esophageal detector device (33). The latter devices create a suction force at the tracheal end of the ET tube, either from pulling back a plunger on a large syringe or compressing a flexible bulb. If the ET tube is in the esophagus, the suction will pull the esophageal mucosa against the distal end of the detector and prevent movement of the device plunger or reexpansion of the suction bulb (eTable 69.0.2).

***e*TABLE 69.0.2** COMMON CAUSES OF A LOW (<2%) END-TIDAL CARBON DIOXIDE CONCENTRATION DURING CARDIOPULMONARY RESUSCITATION

Inadequate ventilation
Unrecognized esophageal intubation
Airway obstruction
Inadequate blood flow
Inadequate chest compression
Tension pneumothorax
Pericardial tamponade
Ventilation-perfusion mismatch
Pulmonary embolism
Decreased metabolic production of carbon dioxide
Hypothermia

The initial P_{ETCO_2} has prognostic value in animal models and humans (203,214,215,222,223,224,225,226,227 and 228). Patients or animal models that attain ROSC

tend to have a higher initial P_{ETCO_2} before the use of agents that can significantly affect its value such as high-dose adrenergic agents than those who never attain ROSC (approximately 2% vs. 1% P_{ETCO_2}, respectively) (183,209,218,219,229,230,231 and 232). In pre-hospital cardiac arrest patients, there is suggestive evidence that the P_{ETCO_2} is lower in patients who have a prolonged "downtime interval" before initiation of resuscitation (203). Further clinical research is needed to determine whether it is appropriate to consider the P_{ETCO_2} as a factor in the decision to continue resuscitative efforts.

Echocardiographic Monitoring during Resuscitation

Echocardiography is one of the most promising technologies that has recently been applied as a research tool during resuscitation (45,47,48,49 and 50,233,234,235,236,237,238,239,240,241,242,243 and 244). Conventional transthoracic echocardiography is of limited value because it is difficult to image the heart from a chest wall that is in motion during closed-chest compression. In contrast, TEE can provide high-resolution, real-time images of all four cardiac chambers and the great vessels by positioning a single or biplane Doppler ultrasound probe in the esophagus. Clinical experience indicates that TEE provides a stable platform for imaging during CPR. So far, TEE has been used to better define the mechanisms of blood flow during chest compression. It has also been helpful during resuscitation to (a) determine the presence of pericardial effusion, intracardiac tumor, chamber enlargement or hypertrophy, severe volume depletion, pneumothorax, or thoracic aortic dissection; (b) better define the cause of PEA; (c) evaluate global and regional wall motion after ROSC; and (d) provide a visual guide for positioning intracardiac catheters and pacemaker wires.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Need for Mouth-to-Mouth Ventilation during the First Few Minutes of Cardiopulmonary Resuscitation

In the United States, debate continues about the need to provide artificial ventilation during the first few minutes of CPR because of fear of contracting infectious diseases. Surveys of CPR instructors and other health care providers indicate great reluctance on the part of many rescuers to perform mouth-to-mouth ventilation on strangers (120,245,246,247,248,249,250,251 and 252).

It is not clear that it is necessary to provide mouth-to-mouth ventilation for the first several minutes of resuscitation as long as chest compression is performed and the airway is patent. Chandra et al. (253) assessed the time course of change in arterial blood gases during resuscitation in a canine experimental model during ventricular fibrillation. The dogs had no ET tube in place during CPR and received only chest compression (no ventilation). Prearrest arterial pH, carbon dioxide partial pressure (P_{CO_2}), and oxygen saturation were 7.39 ± 0.02, 27.0 ± 1.5 mm Hg, and 97% ± 11.5%, respectively. After 4 minutes of chest compression alone, the corresponding values were 7.39 ± 0.03, 24.3 ± 3.1 mm Hg, and 93.9% ± 3.0%. Mean minute ventilation during the fourth minute of CPR, measured with a face mask pneumotachometer, was 5.2 ± 1.1 L per minute. These findings suggest that, in the dog model of witnessed arrest, chest compression alone during CPR can maintain adequate gas exchange to sustain the oxygen saturation above 90% for at least 4 minutes. These findings appear to be confirmed by the observation that survival from cardiac arrest is almost as good in humans when bystanders perform only chest compressions as occurs when bystanders perform both chest compressions and mouth-to-mouth ventilation (119). Some investigators believe that mouth-to-mouth ventilation may not be essential during the first few minutes of CPR because chest compression alone with a patent airway generates a reasonable minute ventilation and the quantity of oxygen needed is reduced significantly during low blood flow states (249). Some investigators have even questioned whether mouth-to-mouth ventilation with exhaled gas containing as much as 4% carbon dioxide and less oxygen than air might even have adverse effects during CPR (248).

The American Heart Association recommends that rescuers perform mouth-to-mouth ventilation along with chest compressions because clinical data indicate that this combination results in the highest rate of neurologically intact survival (38,119). If rescuers are unwilling to perform mouth-to-mouth ventilation, bystanders should activate the EMS system immediately and initiate chest compressions (38).

In a recent prospective clinical trial in Seattle, telephone EMS dispatchers gave bystanders at the scene of apparent cardiac arrest instructions to perform chest compressions alone or chest compression plus mouth-to-mouth ventilation (254). Data were analyzed for 241 patients randomly assigned to receive chest compression alone and 279 assigned to chest compression plus mouth-to-mouth ventilation. Complete instructions were delivered in 62% of episodes for the group receiving chest compression plus mouth-to-mouth ventilation and 81% of episodes for the group receiving chest compression alone (p = .005). Instructions for compression required 1.4 minutes less to complete than instructions for compression plus mouth-to-mouth ventilation. Survival to hospital discharge was better among patients assigned to chest compression alone than among those assigned to chest compression plus mouth-to-mouth ventilation (14.6% vs. 10.4%), but the difference was not statistically significant (p = .18). The authors concluded that the outcome after CPR with chest compression alone is similar to that after chest compression with mouth-to-mouth ventilation, and chest compression alone may be the preferred approach for bystanders inexperienced in CPR.

Spontaneous agonal respirations often contribute to respiratory exchange of gases. In one case series, agonal respirations occurred in 40% of 445 out-of-hospital cardiac arrests (255). Agonal respirations were present in 46% of arrests caused by a cardiac etiology compared with 32% in other etiologies (p <.01). Fifty-five percent of witnessed arrest patients had agonal activity compared with 16% of unwitnessed arrest patients (p <.001). Agonal respirations occurred in 56% of arrests due to ventricular fibrillation compared with 34% of cases with a non–ventricular fibrillation rhythm (p <.001). Twenty-seven percent of patients with agonal respirations were discharged alive compared with 9% without them (p <.001). These findings suggest that there is a high incidence of agonal respiratory activity associated with out-of-hospital cardiac arrest, and the presence of agonal respirations appears to be associated with increased survival.

It is important to point out that assisted ventilation, particularly when performed with supplemental oxygen through a properly inserted ET tube, is clearly beneficial during CPR if resuscitation efforts continue beyond the first few minutes (246). Until the airway is protected by a properly inserted and secured ET tube, each mouth-to-mouth or bag-valve-mask ventilation must be delivered with a slow inspiratory flow rate to allow adequate time for lung inflation and to prevent gastric insufflation (38). This is necessary because the lungs become very stiff during resuscitation due to decreased compliance (256). Forceful efforts to inflate the lungs rapidly will only result in elevation of the pharyngeal pressure effect, which will be transmitted down the esophagus to the esophageal-gastric sphincter, causing it to open and allow passage of air into the stomach (257).

Is There a Need for "High-Dose" Epinephrine during Resuscitation?

Epinephrine, an endogenous catecholamine with both alpha-and beta-adrenergic activity, is the vasopressor of choice for use during resuscitation. Epinephrine's potent $alpha_1$- and $alpha_2$-adrenergic effects improve cerebral blood flow by preventing arterial collapse and by increasing peripheral vasoconstriction (163,166,167,168,169 and 170,258,259). Epinephrine also enhances CPP, which is the major determinant of the ROSC after cardiac arrest (164,167,260). An aortic diastolic blood pressure of 30 to 40 mm Hg markedly improves survival during resuscitation in animal models (64,164,167,171,173,217,260,261,262,263 and 264). Restoration of myocardial blood flow facilitates the resynthesis of high-energy phosphates within myocardial mitochondria and enhances cellular viability and contractile force. However, the increased myocardial blood flow is at least partially antagonized by the increased myocardial oxygen consumption caused by epinephrine's beta-adrenergic actions (265,266).

The optimal dose of epinephrine to augment aortic diastolic blood pressure in humans during closed-chest compression is unknown. The American Heart Association currently recommends a 1.0-mg dose based on studies in dogs weighing approximately 20 kg (17). In a 70-kg male, the current recommendations provide only 7.5 to 15 µg per kg of epinephrine every 5 minutes.

Some studies have concluded that dosages of more than 15 µg per kg may be required during closed-chest CPR in animal models. Kosnik et al. showed that a dose of epinephrine of 15 µg per kg (the upper range of the recommended human dose) did not maintain an aortic diastolic blood pressure above 40 mm Hg during closed-chest compression in dogs (267). Larger doses (45, 75, and 150 µg per kg) effectively raised aortic diastolic blood pressure. High-dose (10 µg per kg) constant infusions of epinephrine have been shown to significantly increase aortic diastolic blood pressure and coronary blood flow during closed-chest compression in dogs (268). Epinephrine (0.02, 0.2, and 2.0 mg per kg) also produced significant dose-dependent improvement in regional myocardial and cerebral blood flow during closed-chest compression in animal models (269,270,271,272,273,274,275 and 276). Preliminary data in humans suggested a similar dose dependence with respect to aortic blood pressure (277).

From these studies it appeared that higher doses of epinephrine might be required in adult humans to improve hemodynamics and to achieve successful resuscitation. Anecdotal case series and retrospective studies published in the late 1980s and early 1990s (277,278,279,280 and 281) set the stage for prospective randomized clinical trials. Unfortunately, none of these trials has shown any convincing evidence that higher doses of epinephrine than those which are used customarily (1 mg) are associated with any better survival to hospital discharge in adults or children (232,282,283,284,285,286,287,288,289 and 290).

Could higher doses of epinephrine be of value to some subgroups of patients and harmful to others? One of the high-dose epinephrine trials showed a threefold increase in hospital discharge rates in patients presenting with EMD and asystole when treated with 5.0 mg versus 1.0 mg of epinephrine as the initial dose, but this difference did not reach statistical significance (285). Another study showed that patients older than 65 years and those in ventricular fibrillation did better with standard doses of epinephrine (284). However, additional clinical trials have failed to show benefit from the use of high versus standard doses of epinephrine in adults

(288,290,291) or in children (282,289).

Most of the patients who survive cardiac arrest respond to early defibrillation and never receive epinephrine. What percent of those who do not respond are salvageable is unclear. However, because patients who are defibrillated did not qualify for these clinical trials, the survival rates of patients studied were low regardless of the dosage of epinephrine. Of some comfort is the fact that these trials did not demonstrate significant harm from higher doses of epinephrine. These studies emphasize the importance of the “standard” early interventions: airway management, chest compression, and rapid defibrillation. They suggest that epinephrine (whether at low or high dosages) as well as other late interventions represent a last desperate effort to resuscitate individuals who have a very poor chance for survival.

Based on available clinical data, the American Heart Association continues to recommend an intravenous epinephrine dosage of 1 mg (10 mL of a 1:10,000 solution) every 3 to 5 minutes during resuscitation in adults (30). If the dose is given by peripheral injection, it should be followed by a 20-mL flush of intravenous fluid to ensure drug delivery into the central compartment. Higher doses of epinephrine are not recommended for routine use but can be considered if 1-mg doses fail.

The recommended pediatric epinephrine dosage for bradycardia, asystolic, or pulseless arrest is 0.01 mg per kg (0.1 mL per kg of a 1:10,000 solution) by the intravenous or intraosseous route or 0.1 mg per kg (0.1 mL per kg of a 1:1,000 solution) by the ET route (17). Repeated doses are recommended every 3 to 5 minutes for ongoing arrest. The same dose of epinephrine is recommended for second and subsequent doses for unresponsive asystolic and pulseless arrest, but higher doses of epinephrine (0.1 to 0.2 mg per kg; 0.1 to 0.2 mL per kg of a 1:1,000 solution) by any intravascular route may be considered. If high-dose epinephrine is used, extra care should be taken to avoid dosing errors because two different dilutions of epinephrine are needed. The recommended pediatric ET dosage of epinephrine is 0.1 mg per kg (0.1 mL per kg of a 1:1,000 solution).

Intracardiac administration should be used only during open cardiac compression or when other routes of administration are unavailable. Intracardiac injections increase the risk of coronary artery laceration, cardiac tamponade, and pneumothorax and cause interruption of external chest compression and ventilation.

During cardiac arrest, epinephrine also may be administered by continuous intravenous infusion. The dose should be comparable to the standard intravenous dose of epinephrine (1 mg every 3 to 5 minutes). This is accomplished by adding 1 mg of epinephrine hydrochloride to 250 mL of normal saline or dextrose 5% in water (D5W) to run at 1 µg per minute and increased to 3 to 4 µg per minute (30). A continuous infusion of epinephrine should be administered by central venous access to reduce the risk of extravasation and to ensure good bioavailability.

Autooxidation of catecholamines and related sympathomimetic compounds is pH-dependent. Contact of epinephrine with other drugs that have an alkaline pH (e.g., sodium bicarbonate) can cause autooxidation, but the reaction rate is too slow to be clinically important when epinephrine is given by bolus injection or when it is infused rapidly. Epinephrine should not be added to infusion bags or bottles that contain alkaline solutions.

H4>Use of Vasopressin during Resuscitation

Vasopressin produces significantly higher CPP and myocardial blood flow than epinephrine during closed-chest CPR in a pig model of ventricular fibrillation (292) and in humans during CPR (293). Both vasopressin and adrenocorticotropin concentrations are higher during CPR in patients in whom resuscitation is successful compared with those in whom it fails (294). Because of these observations, there has been considerable interest in the use of vasopressin for supporting CPP during CPR in humans.

In a small, blinded, randomized clinical study, 40 patients with out-of-hospital ventricular fibrillation resistant to electrical defibrillation were treated with either epinephrine (1 mg intravenously; n = 20) or vasopressin (40 U intravenously; n = 20) during resuscitation (295). Seven (35%) patients in the epinephrine group and 14 (70%) in the vasopressin group survived to hospital admission (p = .06). At 24 hours, four (20%) epinephrine-treated patients and 12 (60%) vasopressin-treated patients were alive (p = .02). Three (15%) patients in the epinephrine group and eight (40%) in the vasopressin group survived to hospital discharge (p = .16). Neurologic outcomes were similar in both groups.

The *American Heart Association Guidelines* considers vasopressin to be an effective vasopressor and recommends it as an alternative to epinephrine for the treatment of adult shock refractory ventricular fibrillation cardiac arrest (30). Although vasopressin may also be effective in patients with asystole or PEA, data were insufficient to recommend the use of vasopressin for these conditions in the latest *Guidelines* recommendations. The recommended dosage is 40 units intravenously in place of the first dose of epinephrine in the pulseless ventricular tachycardia/ventricular fibrillation algorithm. Although its pharmacokinetics are not fully understood yet, it is generally believed that this single dose should last approximately 10 to 20 minutes, after which epinephrine should be resumed if ROSC has not occurred.

It is not clear whether vasopressin should be used at all in children or infants. Unfortunately, vasopressin was less effective than epinephrine in a piglet model of prolonged asphyxial cardiac arrest (296). At this time, the American Heart Association does not recommend the use of vasopressin in infants or children because data are inadequate to evaluate its efficacy and safety (21).

Use of Buffers during Resuscitation

The marked fall in cardiac output during closed-chest compression critically reduces tissue oxygen delivery. Cells shift to anaerobic metabolism, gradual building up lactic acid as a waste product (297,298,299 and 300). During anaerobic metabolism, the carbon dioxide concentration increases rapidly inside cells. Anoxic arrest of the heart causes a progressive increase in the concentration of P_{CO_2} inside heart muscle cells that may reach very high levels (90 to 475 mm Hg) (301). Above an intramyocardial P_{CO_2} of approximately 475 mm Hg, PEA is present, and the heart cannot be resuscitated (301). Intracellular carbon dioxide eventually diffuses into capillary blood and returns to the heart and lungs in venous blood.

Central (mixed) venous blood during closed-chest compression is acidotic (pH f approximately 7.15) and hypercarbic (Pa_{CO_2} of approximately 74 mm Hg) (216). With hyperventilation, carbon dioxide is removed as blood flows through the lungs. Accordingly, arterial blood is less acidotic. Arterial blood pH during well-performed closed-chest compression is usually normal, slightly acidotic, or mildly alkalotic (152,154,155 and 156,216,300,302,303). Arterial blood can be slightly alkalotic while the venous blood is acidotic because pulmonary blood flow is only a fourth to a third of normal amount during closed-chest compression (this phenomenon has been termed the *venous paradox*) (216). It is, in fact, not a paradox but part of normal physiology that occurs when anaerobic metabolism is required (e.g., during strenuous exercise), at which time the intramyocardial pH is much closer to the venous than the arterial pH.

Severe arterial acidosis during closed-chest compression is usually due to inadequate ventilation (304). The best solution is usually to improve the technique of closed-chest compression and to increase ventilation, if possible. If severe acidosis is present despite hyperventilation, correct intubation, and properly performed external chest compression, an alternate method for providing assisted circulation (e.g., open-chest compressions or venoarterial bypass) may need to be considered.

In the past, administration of sodium bicarbonate was recommended during closed-chest compression because of the belief that bicarbonate would buffer the H+ ion produced during anaerobic metabolism. However, sodium bicarbonate itself contains a high concentration of carbon dioxide (260 to 280 mm Hg) (305). In plasma, the carbon dioxide is released and diffuses into cells more rapidly than HCO_3^-, causing a paradoxical rise in intracellular P_{CO_2} and a fall in intracellular pH. The increases in intracellular P_{CO_2} in heart muscle cells decrease cardiac contractility, cardiac output, and blood pressure (306,307). Paradoxical acidosis of cerebrospinal fluid also can occur after the use of sodium bicarbonate (308) and may be responsible for prolonged confusion after a successful resuscitation as the venous acidosis increases. Sodium bicarbonate causes other potentially harmful effects, including hyperosmolality, alkalemia, and sodium overload.

At present, there are no convincing data proving treatment with sodium bicarbonate is of benefit during closed-chest compression and it does not improve survival in experimental animals (166,309,310 and 311). Sodium bicarbonate should not be given during a routine cardiac arrest because it provides minimal, if any, benefit and adds significant risk. If used at all, bicarbonate should not be used until proven interventions such as defibrillation, cardiac compression, support of ventilation including intubation, and pharmacologic therapies such as epinephrine and antiarrhythmic agents have been used (17). If used, the initial dose of sodium bicarbonate is 1 mEq per kg. No more than half of the original dose should be given every 10 minutes thereafter.

Measurement of arterial pH during closed-chest compression is rarely helpful because of the markedly reduced cardiac output and the venous paradox in pH. P_{ETCO_2} will increase in keeping with the delivered load of carbon dioxide and will no longer reflect pulmonary perfusion (312). Ready-to-use, prefilled injection syringes containing 8.4% sodium bicarbonate (50 mEq per 50 mL) are recommended for use during CPR. The administration of sodium bicarbonate may help to buffer hydrogen ions washed out after reestablishment of spontaneous circulation. In this situation, the use of bicarbonate should be guided by arterial blood gas measurement. However, bicarbonate in this situation may still depress cardiac function (313,314). In certain circumstances, such as patients with preexisting metabolic acidosis, hyperkalemia, or tricyclic or phenobarbital overdose, bicarbonate is beneficial. Sodium bicarbonate can be administered by continuous infusion when the therapeutic goal is gradual correction of acidosis or alkalinization of blood (i.e., tricyclic antidepressant overdose) or urine (e.g., barbiturate overdose). A 5% sodium bicarbonate solution (297.5 mEq per 500 mL) can be used to administer a sodium bicarbonate infusion. The infusion rate should be guided by arterial blood gas

monitoring. Avoid attempting to completely correct the base deficit to minimize the risk of alkalosis.

Alternate buffer agents have not yet been shown to improve survival during cardiac resuscitation. Tromethamine (THAM) (TRIS buffer) is a potent amine buffer that actively binds H^+ ions. It combines with carbonic acid, increasing the amount of bicarbonate anion available. THAM penetrates into cells and may neutralize acidic ions in the intracellular fluid. In dogs, THAM corrects the metabolic acidosis that occurs during cardiac arrest (315). Anecdotal reports suggest that THAM may be of value during prolonged cardiac resuscitations in humans (316), but more research is needed. Dichloroacetate reduces the serum lactate concentration by stimulating pyruvate dehydrogenase, the enzyme that catalyzes the rate-limiting step in the oxidation of lactate to pyruvate (317). It is a safe and effective adjunct for the treatment of patients with lactic acidosis but does not affect intramyocardial pH during closed-chest compression in experimental animals (303).

In a recent Scandinavian study, 502 adults with asystole or ventricular fibrillation with failure of the first defibrillation attempt were entered into a prospective, randomized, double-blind, controlled trial comparing the use of a combination buffer agent (Tribonat, containing 250 mL of a sodium bicarbonate-THAM-acetate-phosphate mixture with a buffering capacity of 500 mmol per L) and 250 mL of 0.9% saline placebo (318). Eighty-seven patients (36%) receiving buffer were admitted to the hospital, and 24 (10%) were discharged from the hospital alive versus 92 (36%) and 35 (14%) receiving saline (no significant difference between groups). Thus, this landmark clinical trial lends further evidence to the belief that buffer therapy does not improve patient outcome from routine cardiac arrest.

Use of Antiarrhythmic Drugs for Refractory Ventricular Fibrillation

Frequently used agents for treatment of refractory ventricular fibrillation or pulseless ventricular tachycardia include lidocaine, bretylium tosylate, procainamide, beta blockers, magnesium sulfate, and intravenous amiodarone. With the exception of intravenous amiodarone, there are no randomized controlled clinical trial data confirming whether any of the other agents are any better than just repeated electrical countershocks.

The American Heart Association considers lidocaine to be acceptable therapy for pulseless ventricular tachycardia/ventricular fibrillation that persists after defibrillation and administration of a vasopressor agent (epinephrine or vasopressin). The primary basis for this recommendation is historical precedent and no evidence of significant harm (31). An initial dose of 1.0 to 1.5 mg per kg is suggested. For refractory ventricular fibrillation and pulseless ventricular tachycardia, an additional bolus of 0.5 to 0.75 mg per kg can be given over 3 to 5 minutes if necessary. The total dose should not exceed 3 mg per kg (or more than 200 to 300 mg during a 1-hour period). Administration of antiarrhythmic agents after ROSC is controversial, but it is common to initiate a lidocaine intravenous infusion at a rate of 1 to 4 mg per minute. Recurrence of ventricular tachyarrhythmias during a constant infusion should be treated with a small bolus dose (0.5 mg per kg) and an increase in the infusion rate in incremental doses (maximal infusion rate of 4 mg per minute). The dosage should be reduced and/or blood levels monitored if the patient remains on lidocaine for 24 hours or more because the half-life of the drug increases after 24 to 48 hours of continuous therapy.

Bretylium is a class 3 antiarrhythmic that increases myocardial electrical stability by elevating the ventricular fibrillation threshold and by reducing the disparity in action potential duration and refractory periods between ischemic and nonischemic myocardium. Nowak et al. (319) reported a higher rate of successful resuscitation when bretylium was used (35%) than after placebo (6%) alone in prehospital cardiac arrest victims but their retrospective analysis left substantial questions concerning the comparability of the groups. Other studies also support the efficacy of bretylium for prehospital ventricular fibrillation (320,321). However, no difference in clinical outcome has been observed in prospective randomized studies comparing bretylium and lidocaine for the treatment of prehospital ventricular fibrillation using intravenous doses of bretylium (0.5 to 1.0 g) and lidocaine (100 to 200 mg) (322) or bretylium (10 to 30 mg per kg) and lidocaine (2 to 3 mg per kg) (320). Neither study found a significant difference in the incidence of conversion from ventricular fibrillation and tachycardia to a more organized rhythm or survival. Bretylium is presently unavailable due to a shortage of substrate to manufacture the agent. It has been removed from the American Heart Association treatment algorithms and guidelines because of its high incidence of side effects, the availability of other equally effective alternatives, and limited availability (31).

Procainamide, a class 1A antiarrhythmic agent, is a presynaptic ganglionic blocker; it vasodilates and induces modest negative inotropic effects, especially in patients with left ventricular dysfunction. Procainamide-induced hypotension is most pronounced after rapid intravenous injection or when high plasma concentrations of procainamide are present.

During resuscitation, procainamide is usually given by infusion at 20 mg per minute until the tachyarrhythmia is suppressed, hypotension and/or QRS prolongation by 50% from its original duration has occurred, or 17 mg per kg has been given (31). Bolus administration can result in significant hypotension and toxicity. In urgent situations, up to 50 mg per minute can be given up to a total of 17 mg per kg. The maintenance infusion dosage of procainamide is 1 to 4 mg per minute. Blood levels should be monitored in renal failure patients or in those receiving more than a 3-mg-per-minute intravenous infusion for more than 24 hours.

Occasionally, ventricular fibrillation or ventricular tachycardia without a pulse will remain refractory to, or will recur incessantly, despite repeated electrical countershocks and conventional pharmacologic treatment. In such cases, additional treatment options should be considered. The use of intravenous beta-blockers, traditionally with intravenous propranolol (1 mg every 5 minutes intravenously up to a total dose of 0.1 mg per kg) or esmolol, is worthy of consideration.

Underlying metabolic derangements should also be sought and corrected. Arterial hypoxemia should be reversed or minimized by ET intubation and ventilation with 100% oxygen. Acidosis is best prevented (or treated) during closed-chest compression by optimizing CPR techniques to improve blood flow and hyperventilation. Electrolyte abnormalities are common during resuscitation, either as primary disturbances that may have triggered the arrest or as secondary phenomena due to intracellular shifts and therapeutic interventions; such electrolyte abnormalities should be corrected if present.

Resuscitation from refractory ventricular fibrillation is less likely to be successful if hypokalemia and/or hypomagnesemia are present. Hypokalemia is common in cardiac patients and occurs in 23% to 40% of individuals treated with thiazide diuretics (323). When loop and thiazide diuretics are used in combination, the incidence approaches 100% (323,324). Hypokalemia can trigger ventricular fibrillation in experimental animal models and in patients with heart disease (especially acute myocardial infarction) (324,325). Hypokalemia is also common (up to 50%) in survivors of out-of-hospital ventricular fibrillation (326,327). Hypokalemia after resuscitation may be due to a shift in the distribution of potassium between the extracellular and intracellular space induced by metabolic events during resuscitation. Many patients (55% in one study) have predisposing risk factors for the development of hypokalemia before cardiac arrest (327).

Hypokalemia in the patient with cardiac arrest and refractory ventricular fibrillation must be treated aggressively. Guidelines for potassium replacement that are acceptable in the less emergent clinical circumstance may be inadequate to correct hypokalemia in a timely fashion during cardiac arrest (328). One regimen that has been suggested includes administration of 10 mEq of potassium chloride diluted in 50 mL D5W over 20 minutes. This dose can be repeated as necessary while rechecking serum levels.

Hypomagnesemia should be corrected if present because it can precipitate ventricular fibrillation in experimental models in association with hypokalemia and can hinder the replenishment of intracellular potassium (329,330). Magnesium sulfate is no longer recommended for routine management of pulseless ventricular tachycardia or ventricular fibrillation unless hypomagnesemia is suspected or present or the patient has torsades de pointes because two clinical in-hospital trials have not shown benefit (31,331,332).

For acute administration during ventricular tachycardia or fibrillation with known or suspected hypomagnesemia or for torsades de pointes, 1 or 2 g of magnesium sulfate (2 to 4 mL of a 50% solution) is diluted in 50 to 100 mL of D5W and administered over 5 to 60 minutes. Caution should be used when magnesium is administered to safeguard against clinically significant hypotension or asystole. A 24-hour magnesium infusion (8 g of magnesium sulfate in 500 mL D5W at eight drops per minute) should be considered in patients with documented magnesium deficiency. Magnesium toxicity is rare, but side effects from rapid administration include flushing, sweating, mild bradycardia, and hypotension. Hypermagnesemia can produce depressed reflexes, flaccid paralysis, circulatory collapse, respiratory paralysis, or diarrhea.

Other treatment strategies can also be used in managing incessantly refractory or recurrent ventricular fibrillation or pulseless ventricular tachycardia. The possibility that there has been a proarrhythmic drug effect that may be exacerbating the arrhythmia must be considered. Proarrhythmic drug effects, hypokalemia, and/or hypomagnesemia can induce ventricular arrhythmias such as torsades de pointes. Torsades de pointes should be treated by stopping medications known to prolong the QT interval and correcting any electrolyte abnormalities. Other interventions can be tried, including administration of magnesium sulfate or the use of pacing or other forms of overdrive suppression (including the cautious use of isoproterenol if there are no contraindications) (333).

There has been considerable interest in the use of intravenous amiodarone to treat patients with recurrent arrhythmias (334,335,336,337,338,339,340,341,342,343 and 344). Despite prolonged resuscitative efforts before the administration of intravenous amiodarone, 11 of 12 patients with refractory ventricular tachyarrhythmias responded, and eight left the hospital alive (334). In one recent double-blind clinical trial, 302 patients with refractory hemodynamically destabilizing ventricular tachycardia or ventricular fibrillation were randomly assigned to therapy with intravenous bretylium (4.7 g) or intravenous amiodarone administered in a high dose (1.8 g) or a low dose (0.2 g). The arrhythmia event rate during the first 48 hours of therapy showed comparable efficacy between bretylium and high-dose (1,000 mg per 24 hours) amiodarone, and both bretylium and high-dose amiodarone were better than low-dose (125 mg per 24 hours) amiodarone. Overall mortality in the 48-hour double-blind period was 13.6% and was not significantly different among the three treatment groups. Significantly more patients treated with bretylium had hypotension compared with the two amiodarone groups. It was concluded that bretylium and amiodarone have comparable efficacy for the treatment of highly malignant ventricular

arrhythmias. Bretylium use, however, may be limited by a high incidence of hypotension.

In a recent randomized controlled clinical prehospital trial conducted on 504 cardiac arrest patients with recurrent and/or refractory ventricular tachyarrhythmias, the administration of a single 300-mg bolus of intravenous amiodarone at the time of the first intravenous epinephrine administration resulted in 26% greater survival to hospital admission compared with standard ACLS therapy (345,346). There was no significant difference between the amiodarone and placebo groups in the duration of the resuscitation attempt (42 ± 16.4 and 43 ± 16.3 minutes, respectively), the number of shocks delivered (4 ± 3 and 6 ± 5), or the proportion of patients who required additional antiarrhythmic drugs after the administration of the study drug (66% and 73%). More patients in the amiodarone group than in the placebo group had hypotension (59% vs. 48%, $p = .04$) or bradycardia (41% vs. 25%, $p = .004$) after receiving the study drug. These side effects usually respond readily to therapy (volume infusion and vasopressors; atropine and/or electrical pacing). Recipients of amiodarone were more likely to survive to hospital admission (44% vs. 34% of the placebo group; $p = .03$). The adjusted odds ratio for survival to admission to the hospital in the amiodarone group as compared with the placebo group was 1.6 (95% confidence interval of 1.1 to 2.4; $p = .02$). The trial did not have sufficient statistical power to detect differences in survival to hospital discharge, which differed only slightly between the two groups.

The manufacturer adds polysorbate 80 to the intravenous amiodarone preparation to keep the latter in solution (amiodarone is relatively insoluble in water). Because diluent is a “soapy” compound, it can create bubbles if the vial is shaken before the amiodarone is drawn up into the syringe. It is recommended that the vial not be shaken. The bubbling phenomenon can usually be kept to a minimum by drawing up the drug with a large needle (18 gauge or larger). If bubbles do appear in the syringe, it should be held vertically as it is being injected into the intravenous tubing, and the bubbles should not be injected into the patient.

The American Heart Association currently recommends the use of amiodarone after defibrillation and a vasopressor (either epinephrine or vasopressin) in cardiac arrest with persistent or recurrent pulseless ventricular tachycardia or ventricular fibrillation (31). In this setting, it is usually administered as a 300-mg rapid infusion diluted to 20 to 30 mL with saline or D5W. Supplementary doses of 150 mg by rapid infusion can be given for recurrent or refractory pulseless ventricular tachycardia or ventricular fibrillation up to a maximum dosage of 2,000 mg for 24 hours (31,346). For patients not in cardiac arrest, intravenous amiodarone is usually diluted and administered as 150 mg over 10 minutes followed by a 1-mg-per-minute infusion for 6 hours, and then 0.6 mg per minute.

U.S. Food and Drug Administration Issues of Informed Consent

Most clinical trials that involve research on emergency patients who cannot give prospective informed consent (including all resuscitation research) have been halted in the United States by a regulatory moratorium. The issues and problems surrounding the ban were of concern to federal regulators and many researchers for several years. In May 1993, the U.S. Food and Drug Administration (FDA) prematurely terminated a clinical resuscitation trial involving a comparison of the Ambu CardioPump (Ambu Inc., Denmark) and standard CPR because the FDA believed that the device involved “significant risk” to the subjects and that there were no means for the subjects to give informed consent to participate in the trial (347,348).

Widespread public attention became focused on the issue in May 1994 when a congressional subcommittee questioned whether existing laws and regulations governing the FDA and the U.S. Department of Health and Human Services (DHHS)/National Institutes of Health permit inclusion of unconscious human subjects who cannot give informed consent in clinical trials dealing with emergency medical conditions. The subcommittee charged these two federal agencies with the task of working together with other interested parties to develop consistent guidelines that local institutional review boards (IRBs) can follow to permit such research.

Until the congressional hearing, investigators in the United States customarily conducted such research by receiving a waiver of informed consent from their IRB or by using the method known as “deferred consent” (349). In retrospect, IRBs have creatively interpreted and adapted prevailing rules to permit such research.

FDA regulations require informed consent in all clinical trials over which they have jurisdiction. The FDA regulations permit an “emergency exception” to this requirement for immediate, one-time use of an investigational device or drug for compassionate use to a single individual when (a) a patient is confronted by a life-threatening situation necessitating the investigational use of the drug or device; (b) informed consent cannot be obtained from the patient because of an inability to communicate with, or to obtain legally effective consent from, the patient; (c) time is insufficient to obtain consent from the patient’s legal representative; and (d) no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient’s life.

The DHHS also has jurisdiction over the conduct of research in humans by means of its Office for Protection from Research Risks. This agency oversees research in humans by a different set of rules and regulations than that of the FDA. DHHS regulations do not contain an emergency exception. However, they provide a mechanism for waiver or alteration of informed consent when (a) the research involves no more than “minimal risk” to the subjects; (b) the waiver or alteration will not adversely affect the rights and welfare of the subjects; and (c) the research could not practicably be carried out without the waiver or alteration. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

“Minimal risk” is defined in the DHHS regulations by the following test: “[T]he probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” No resuscitation technique (standard or experimental) would pass this test of “minimal risk.”

Thus, neither the FDA nor the DHHS rules and regulations provide a legal means for IRBs to approve emergency medical research in humans where it is impossible to obtain informed consent. On October 25, 1994, the Coalition Conference of Acute Resuscitation and Critical Care Researchers was held in Washington, D.C., to discuss informed consent in emergency research. Representatives from more than 20 organizations worked diligently to explore the issues and produced consensus recommendations for resolving some of the difficult issues that surround emergency medical research.

These recommendations and many other ideas were presented and discussed at the FDA/National Institutes of Health Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances, held in Bethesda, Maryland, January 9–10, 1995. Although this was not a consensus conference, the discussion appeared to indicate that legislative change is needed to give the FDA and the DHHS a common set of tools that will make it legal for them to oversee the conduct of legitimate, ethical, scientifically sound emergency care research. The next step is to translate the consensus statement drafted at the October meeting and ideas emanating from the Bethesda conference into legislative language and to introduce a congressional bill that will correct the deficiencies in the existing rules and regulations.

In the meantime, the only clinical resuscitation trials that are permitted in the United States are in-hospital studies in which potential cardiac arrest victims are approached and give their informed consent to participate in the trial if, by chance, they should experience a cardiac arrest during their hospitalization. Such a process has been used successfully before (80,350) but may require the screening of hundreds of potential individuals for every subject enrolled in the trial. Such a procedure is expensive and time-consuming. More important, it may result in a biased sample of patients.

Clearly, these have sobering implications for resuscitation research in the United States and throughout the world. The issue is not whether such research is morally, ethically, scientifically necessary and justifiable. These are, of course, absolute prerequisites. The real question is whether each country’s laws, rules, and regulations explicitly permit emergency medical research when subjects cannot give informed consent. The FDA and the DHHS have recently released new rules that are intended to allow at least limited resumption of resuscitation research in humans.

Unfortunately, initial experience with these new rules has been problematic. In the first 4 years of the new FDA/DHHS rules, no prospective resuscitation drug or device trials have been completed or initiated successfully in the United States. In fact, several trials have been abandoned because of the expense and difficulty of complying with the new regulations (351,352 and 353). The American College of Cardiology has recently convened a Bethesda Conference on Emergency Cardiac Care that, in part, discussed problems with the waiver of informed consent procedures and proposed potential solutions (354).

New Experimental Cardiopulmonary Resuscitation Techniques

Investigators have begun to exploit the physiologic opportunities afforded by understanding the mechanisms of blood flow during CPR in an attempt to overcome the hemodynamic shortcomings of conventional chest compression. Standard chest compression of the sternum to a depth of 1.5 to 2.0 in. at a rate of 80 per minute as recommended by the American Heart Association produces only about one-fourth to one-third of the normal cardiac output and less than half of the normal arterial perfusion pressure (14,221). This is usually inadequate to generate the 25 to 35 mm Hg aortic diastolic pressure needed to restart the arrested heart (184,262).

Applying higher compression force to displace the sternum farther than the 1.5 to 2.0 in. recommended by the American Heart Association can improve arterial systolic pressure and cardiac output significantly (179). However, there is a practical limit to the amount of extra force that can be applied safely without causing physical injury to the chest and underlying structures. Computer modeling indicates that substantially greater force is required to generate adequate coronary and cerebral pressure and flow than that which can be provided safely by conventional sternal compression (355).

Circumferential Compression Cardiopulmonary Resuscitation

Circumferential application of force to the chest using a pneumatic vest can generate enough intrathoracic pressure to provide virtually normal systemic arterial pressure and flow in animals and humans during cardiac arrest (356,357,358 and 359). The device looks like a large blood pressure cuff that is wrapped around the patient's thorax. It contains a bladder that can be inflated and deflated in cycles by a pneumatic pump. Compression duration, inflation pressure, and rate are all controlled by the device. Typical inflation pressure is 250 mm Hg, and the chest compression rate is 60 per minute. A small positive pressure is maintained between the chest and the vest to provide a tight fit between the two, but the device totally deflates during ventilation to provide for chest expansion. The total force applied to the chest with "vest CPR" is much greater than that which can be applied safely with conventional CPR. Despite this, "vest CPR" is much less traumatic than standard CPR because it distributes force over a much larger surface area (the entire chest).

When the pneumatic vest was applied to 29 patients who repeatedly did not respond to conventional CPR, defibrillation, and drug therapy for 42 ± 16 minutes, vest CPR increased the peak aortic pressure from 78 ± 26 mm Hg to 138 ± 28 mm Hg (p <.001) and the CPP from 15 ± 8 mm Hg to 23 ± 11 mm Hg (p <.003) (358). Despite prolonged unsuccessful manual CPR, spontaneous circulation returned with vest CPR in 4 of the 29 patients. An additional 34 patients were randomly assigned to undergo vest CPR (17 patients) or continued manual CPR (17 patients) after initial manual CPR (mean duration, 11 ± 4 minutes) was unsuccessful. Spontaneous circulation returned in eight of the 17 patients who underwent vest CPR as compared with only three of the 17 patients who received continued manual CPR (p = .14) (358). More patients in the vest CPR group than in the manual CPR group were alive 6 hours after attempted resuscitation (six of 17 vs. one of 17) and 24 hours after attempted resuscitation (three of 17 vs. one of 17), but none survived to leave the hospital.

Despite the fact that preliminary experience with the pneumatic vest has been encouraging, clinical trials using the device early in resuscitation have been halted due to the difficulties with the FDA/DHHS process of obtaining a waiver of informed consent (352). Alternative mechanical methods for providing circumferential chest compression using less energy than that required by a pneumatic device are being explored. Although the device is not presently FDA-approved or marketed in the United States, the American Heart Association considers vest CPR to be an acceptable alternative to standard CPR in-hospital or during ambulance transport (32).

Active Compression-Decompression Cardiopulmonary Resuscitation

Active compression-decompression CPR (ACD-CPR) is similar to conventional CPR, but it also provides negative intrathoracic pressure during the relaxation phase using a device that resembles a toilet plunger (eFig 69.0.3). ACD-CPR is performed with a suction-cup device called the *Ambu CardioPump*.

The ACD-CPR device consists of three parts: (a) a neoprene suction cup, (b) a plastic circular handle with an undercut handgrip, and (c) a force gauge. The gauge can be calibrated to a fixed depth, which usually is similar to standard CPR (1.5 to 2.0 in.). To ensure proper function by the operator, the decompression force is also measured up to –30 pounds by the gauge. The device is positioned at the midsternum in alignment with the nipples.

Initial studies on ACD-CPR in both experimental animal models and human subjects late after cardiac arrest have demonstrated improved cardiopulmonary hemodynamics when compared with standard manual CPR (54,55,58,360,361 and 362). In one clinical study, conventional CPR was compared with ACD-CPR in 21 patients undergoing routine induction of ventricular fibrillation as part of a transvenous lead cardioverter/defibrillator implantation procedure (360). Mean CPP was increased throughout the entire CPR cycle with ACD-CPR (compression of 21.5 ± 9.0 mm Hg; decompression of 21.9 ± 8.7 mm Hg) compared with conventional CPR (compression of 17.9 ± 8.2 mm Hg; decompression of 18.5 ± 6.9 mm Hg; p <.02 and p <.02, respectively). Unfortunately, despite promising initial clinical results (347), several recent randomized clinical trials have not shown any superiority of ACD-CPR over conventional CPR (363,364,365 and 366). However, one trial conducted in Paris has reported benefit in short-term survival with this technique (367).

The American Heart Association considers ACD-CPR to be an acceptable alternative to standard CPR when rescue personnel adequately trained in use of the device are available (32); however, the device is not FDA approved for sale in the United States.

Interposed Abdominal Compression

Interposed abdominal compression CPR (IAC-CPR) (eFig 69.0.4), also known as *abdominal counterpulsation CPR*, attempts to mimic intraaortic balloon counterpulsation. Two rescuers are needed to perform this technique: One rescuer compresses the sternum, and the other rescuer interposes abdominal compressions between each chest compression. Several investigators have demonstrated improvements in coronary perfusion, carotid and cerebral blood flows, and augmented venous return using IAC-CPR compared with standard CPR (59,61,71).

An early prehospital clinical trial in the mid-1980s failed to demonstrate any improvement in survival when IAC-CPR was compared with conventional CPR (368). Recently, IAC-CPR has been shown to improve survival in 143 consecutive patients experiencing in-hospital cardiac arrest with an initial arrest rhythm of asystole or EMD (78). Patients were randomized to receive either IAC-CPR or conventional CPR. The rate of ROSC was significantly higher in the group receiving IAC-CPR compared with the group receiving conventional CPR (49% vs. 28%, p = .01). At 24 hours, there were significantly more patients alive in the IAC-CPR group than in the conventional CPR group (33% vs. 13%, p = .009). No complications were demonstrated in a small subset of patients who died and underwent autopsy.

Similar findings were noted in another randomized clinical trial involving 135 resuscitation attempts in 103 patients (80). The rate of ROSC was significantly greater in the group receiving IAC-CPR compared with the group receiving conventional CPR (51% vs. 27%, p = .007). At hospital discharge, a significantly greater proportion of patients were alive in the IAC-CPR group than in the conventional CPR group (25% vs. 7%, p = .02). Eight (17%) of 48 patients who received IAC-CPR survived to hospital discharge neurologically intact compared with only three (6%) of 55 patients from the conventional CPR group (not significant). Thus, IAC-CPR appears to be a promising technique that may improve survival in selected cardiac arrest patients. The American Heart Association recommends the use of IAC-CPR for in-hospital resuscitation as an alternative to standard CPR whenever sufficient personnel trained in the technique are available (32).

Other Cardiopulmonary Resuscitation Techniques

A number of other interesting CPR techniques have been evaluated recently. Some of these techniques have been unequivocally shown to be of little or no clinical value. For example, the use of abdominal binding with a pneumatic antishock garment (also known as *military antishock trousers*, or *MAST*) during resuscitation does not improve survival even though it increases mean arterial pressure (369). The problem is that it raises central venous pressure by the same amount as the increase in arterial pressure, thus failing to increase the CPP. Similarly, simultaneous compression-ventilation CPR has been shown to decrease survival from cardiac arrest compared with conventional CPR, perhaps by causing collapse of arteries exiting the thorax and/or by creating significant barotrauma (370,371).

On the other hand, "cough" CPR has been shown to be of value in experimental animals and in clinical use (40,372,373,374 and 375). At the onset of lethal arrhythmias such as asystole, profound bradycardia, ventricular tachycardia, or fibrillation, coughing may assist in maintaining consciousness and an adequate systolic blood pressure. In some cases, it may also play a role in terminating the arrhythmia. The simplicity and effectiveness of this technique warrant its consideration for greater clinical use by health care providers. Similarly, "high-impulse CPR" using a rapid downstroke velocity may, in some circumstances, improve blood flow by transferring greater energy into the thorax and, perhaps, by enhancing the "cardiac pump" mechanism (44,45).

An impedance threshold valve has been developed to enhance the return of blood to the thorax during the chest decompression phase (376). This new device enhances negative intrathoracic pressure during chest wall recoil or the decompression phase, leading to improved vital organ perfusion during both standard CPR and ACD-CPR (376,377,378,379,380 and 381). With ACD-CPR, addition of the impedance threshold valve results in sustained diastolic pressures of more than 55 mm Hg in patients in cardiac arrest. The new valve shows promise for patients in asystole or shock refractory ventricular fibrillation, when enhanced return of blood flow to the chest is needed to "prime the pump." The American Heart Association considers this device to be acceptable as an adjunct to be used with ACD-CPR (32).

Public Access Defibrillation

Another innovative idea is termed "public access defibrillation," so named because the intent is to have non–health care citizens perform early defibrillation. So far, early attempts to train family members of high-risk patients or community workers in the use of AEDs have met with variable success. For example, Eisenberg et al. trained family members of 59 patients who had survived out-of-hospital cardiac arrest in King County, Washington (382). Only six of the 10 cardiac arrests that occurred in these patients were defibrillated successfully, and only one patient survived for a few months and sustained new neurologic impairment.

In contrast, Swenson et al. reported three successful resuscitations out of five cardiac arrests in 48 patients whose families had been trained to use an AED (383). More encouraging results have been obtained when community first responders have been trained to use automated defibrillators. For example, 160 security officers were trained to use these devices at Vancouver's World Expo 1986. Five cardiac arrests occurred among the 22.1 million visitors. Security personnel applied the AED correctly in all cases. In two cases, the initial rhythm was ventricular fibrillation. and defibrillation was successful. Both patients had a pulse and were regaining consciousness by the time EMS personnel arrived on the scene (384). Other experimental approaches to rapid defibrillation in the workplace include use on

commercial aircraft, airports, British rail stations, oil platforms in the North Sea, electricity plants, casinos, passenger cruise ships, and merchant marine vessels (385,386,387,388,389,390 and 391).

In Las Vegas casinos, security officers were trained and equipped to use AEDs on suspected cardiac arrest victims (388). AEDs were placed in the casinos at strategic locations to permit rapid defibrillation in 3 minutes or less from collapse. Out of 105 patients whose initial cardiac rhythm was ventricular fibrillation, 56 (53%) survived to hospital discharge. Among the 90 patients whose collapse was witnessed (86%), the clinically relevant time intervals were a mean (± standard deviation) of 3.5 ± 2.9 minutes from collapse to attachment of the defibrillator, 4.4 ± 2.9 minutes from collapse to the delivery of the first defibrillation shock, and 9.8 ± 4.3 minutes from collapse to the arrival of the paramedics. The survival rate was 74% for patients who received their first defibrillation no later than 3 minutes after a witnessed collapse and 49% for those who received their first defibrillation after more than 3 minutes.

AEDs are also becoming common on commercial aircraft (389,390,391 and 392). American Airlines was the first U.S. carrier to deploy this technology. In a recent report on the carrier's experience, American Airlines reported that AEDs were attached to 200 patients (191 on the aircraft and nine in the terminal), including 99 with documented loss of consciousness. Electrocardiographic data were available for 185 patients. A shock was advised in all 14 patients who had electrocardiographically documented ventricular fibrillation, and no shock was advised in the remaining patients (sensitivity and specificity of the defibrillator in identifying ventricular fibrillation of 100%). The first shock successfully defibrillated the heart in 13 patients (defibrillation was withheld in one case at the family's request). The rate of survival to discharge from the hospital after shock with the AED was 40%. A total of 36 patients either died or were resuscitated after cardiac arrest. No complications arose from use of the AED as a monitor in conscious passengers.

The National Heart, Lung, and Blood Institute and the American Heart Association are encouraging research into the safety, efficacy, and potential cost-benefit of this interesting concept (393,394,395,396 and 397). A multicenter, prospective, randomized, controlled clinical trial is currently under way to further assess the safety, efficacy, and cost-benefit of more widespread use of AEDs by trained laypersons in a public setting (397).

THE FUTURE

Better understanding of the mechanisms responsible for blood flow during closed-chest compression is leading to new CPR devices and techniques. It is highly probable that one or more of these innovations will result in significant improvement in the likelihood of successful resuscitation. If this occurs, the greatest challenge will be to better define from a medical and ethical perspective who should, or should not, receive such intervention. In addition, there will likely be much broader implementation of public access defibrillation.

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ARRHYTHMIAS IN CONGENITAL HEART DISEASE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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Chapter References

OVERVIEW

Atrial tachyarrhythmias, especially atrial fibrillation (AF), are associated with certain unoperated congenital heart defects as patients get older and the atria become progressively more volume overloaded, especially in cases of atrial septal defect (ASD), Ebstein's anomaly of the tricuspid valve, and patent ductus arteriosus (PDA). Other unoperated congenital heart defects may be associated with increased risk for high-grade ventricular ectopy or sudden death as hemodynamics worsen, such as elevated pulmonary artery pressure in patients with ventricular septal defect (VSD) and increased wall stress in patients with aortic valve stenosis. There is an increased incidence of atrioventricular (AV) reciprocating tachycardia related to coexisting accessory AV connections in patients with Ebstein's anomaly of the tricuspid valve, L-transposition of the great arteries (L-TGA), and tricuspid atresia (TA). In contrast, congenital or progressive AV block may occur in patients with L-TGA or the heterotaxes due to coexisting abnormalities of the penetrating AV bundle. There is an increased incidence of sudden cardiac death (SCD) in patients with severe Ebstein's anomaly of the tricuspid valve, severe aortic valve stenosis, Eisenmenger physiology, and certain congenital coronary artery anomalies.

After congenital heart surgery involving the atria, especially the Mustard or Senning operations for D-TGA and the modified Fontan operation for single-ventricle variants, there is a progressive incidence of sinoatrial node dysfunction (SAND) (the "tachy-brady syndrome") over time, which may be difficult to control despite antiarrhythmic drugs, bradycardia pacing, antitachycardia pacing, and radiofrequency ablation. After surgery on the ventricles, especially for tetralogy of Fallot, there is a progressive risk over time for ventricular tachycardia (VT) or SCD, which seems to be related to older age at repair and to residual hemodynamic abnormalities.

GLOSSARY

Atrial effective refractory period: A clinical measurement of atrial muscle refractoriness, defined as the longest atrial paced interval not resulting in an atrial propagated response by the second pacing stimulus.

Bulboventricular foramen: The continued patent channel between the primitive ventricle and the *bulbus cordis* after fusion of the cushions of the *bulbus cordis* and after development of the primitive ventricular septum. This channel is the VSD in patients having a double-inlet left ventricle.

Concealed entrainment: Pacing from an anatomic point in the critical tachycardia circuit that does not fulfill the four primary criteria for entrainment but that is associated with a postpacing interval identical with the tachycardia cycle length. During concealed entrainment the tachycardia speeds up to the pacing rate but with no change in the tachycardia morphology or activation sequence.

Corrected sinus node recovery time: The time between the last atrial paced event and the first sinus recovery beat after a 30-second period of atrial pacing at a rate faster than the intrinsic sinus rate, corrected for the intrinsic sinus rate, either by subtracting the intrinsic sinus cycle length from the recovery interval or by dividing them. This is thought to represent one measurement of sinus node automaticity.

Drive train cycle length: A stable pacing rate, usually of eight beats' duration, used as part of standard pacing protocols for evaluating conduction properties or induction of reentry tachycardias.

Entrainment with termination: Pacing during a reentry tachycardia at a rate faster than the tachycardia rate for a sufficient duration that the paced wavefronts collide with the previous wavefront in both orthodromic and antidromic directions, resulting in termination of tachycardia when pacing is stopped.

Fontan operation: Any of a variety of operations designed to direct systemic venous return to the pulmonary arteries without the interposition of a ventricle. This is performed in patients with single-ventricle physiology.

Mustard operation: Operation designed for patients with D-TGA in which there is redirection of systemic and pulmonary venous returns to the mitral and tricuspid valves, respectively. Prosthetic material or pericardium is used.

Orthodromic reciprocating tachycardia: Any paroxysmal reentry supraventricular tachycardia that uses as a necessary component of the circuit the normal AV conduction system and whereby the circuit progresses down the normal conduction system in the antegrade direction.

Primary interventricular foramen: An embryologic term representing the connection between the primitive ventricle and the *bulbus cordis* in the developing

embryologic heart tube.

Senning operation: Similar to the Mustard operation in principle, but it consists almost exclusively of native atrial wall.

Sinoatrial conduction time: A measurement of conduction from the sinus node into the atrium, either by placing single premature atrial beats at progressively closer coupling intervals to sinus beats or after an eight-beat drive train. The two methods used are the Strauss method and the Narula method, respectively.

Triple extrastimuli: The placement of three premature beats into an intrinsic or paced rhythm for purposes of inducing a reentry tachycardia.

Ventricular paired pacing: The pacing technique designed to effectively slow the hemodynamic response rate to a pathologically accelerated ventricular rate, whereby an externally paced event is closely coupled to the previous intrinsic or paced event, resulting in ventricular electrical activation but no hemodynamic response.

Zones of slow conduction: Critical parts of reentry tachycardia circuits that may be identified by concealed entrainment and appear to be especially vulnerable to radiofrequency ablation for treatment of reentry tachycardia.

INTRODUCTION

Cardiac rhythm abnormalities related to congenital heart defects may occur in response to hemodynamic influences on chamber dimensions, muscle mass, and the specialized conduction system; may occur in response to metabolic effects on myocardial tissue; or may be due to coexisting congenital abnormalities of the specialized conduction system. This chapter reviews the clinical arrhythmias associated with unoperated congenital heart defects, arrhythmias of clinical importance that occur immediately after congenital heart surgery, and arrhythmias that occur long term after surgery for congenital heart defects. Management issues are emphasized in the sections regarding postoperative arrhythmias, with emphasis on newer treatment modalities.

ARRHYTHMIAS ASSOCIATED WITH UNOPERATED CONGENITAL HEART DEFECTS

Rhythm abnormalities in children with congenital heart defects before surgical intervention may occur directly related to the malformation complex or may occur secondary to progressive alterations caused by the defect(s). eTable 70.0.1 summarizes the incidences of arrhythmias in the more common unoperated congenital heart defects.

***e*TABLE 70.0.1** INCIDENCE OF PREOPERATIVE ARRHYTHMIAS IN PATIENTS WITH RELATED CONGENITAL HEART DEFECTS

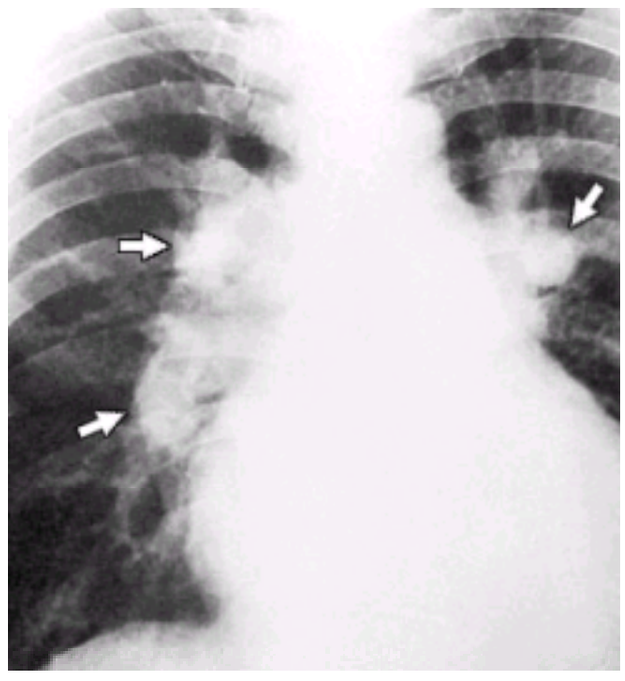
Congenital heart defect	Atrial fibrillation/flutter	Paroxysmal supraventricular tachycardia	Ventricular tachycardia	Sudden death	Sinus bradycardial junctional rhythm	Atrioventricular block
Secondary and sinus venosus atrial septal defect	$^{+}$ to $^{+++}$ [a]				$^{+}$ to $^{++}$	0 to $^{+}$
Ebstein's anomaly	$^{+}$ to $^{++}$ [a]	$^{++}$		[b]		
Ventricular septal defect			$^{+}$	$^{+}$		
Patent ductus arteriosus	0 to $^{++++}$ [a]					
Tetralogy of Fallot			0 to $^{+++}$ [a]			
Aortic valve stenosis				[b]		
L-Transposition of the great arteries		$^{++}$		[b]		
Eisenmenger physiology			$^{++}$	$^{++}$	[b]	
Polysplenia		$^{++}$			$^{+}$ to $^{++++}$ [a]	$^{++}$
Asplenia		$^{+}$		[b]		$^{+}$

$^{+}$, up to 10% incidence; $^{++}$, 10% to 40% incidence; $^{+++}$, 40% to 60% incidence; $^{++++}$, 60% to 90% incidence.
[a]Incidence increases with age.
[b]Incidence increases with lesion severity or associated defects.

Atrial Septal Defect

In both ostium secundum and sinus venosus ASDs, chronic left-to-right shunting results in dilatation of the right atrium and right ventricle. Compared with children having other types of congenital heart defects, those having ASDs had longer PR (154 vs. 135 ms) and PA (52 vs. 29 ms) intervals, but AH and HV intervals were not significantly different (1). It has been believed that the dilated right atrium in those with ASDs resulted in slowed intraatrial conduction. Typically, the electrocardiogram (ECG) in patients with an ASD also shows right ventricular hypertrophy, manifest as an RSR' in V_1 and an RS in I and V_6.

Video 70.1 Transesophageal echo with color Doppler flow demonstrating a secundum atrial septal defect with left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Chest x-ray in atrial septal defect. There is plethora of the pulmonary vasculature with prominent main pulmonary arteries (*white arrows*).

Clark and Kugler evaluated 15 children (16 months to 18 years old) preoperatively with 24-hour ambulatory ECG monitoring and intracardiac electrophysiologic testing (2). Ten had prolonged corrected sinus node recovery times, five had evidence of AV nodal dysfunction (prolonged AH interval or abnormally slow AV nodal Wenckebach periodicity), but only two had ectopic atrial rhythms during ambulatory monitoring. Those having evidence of SAND tended to be older and to have a greater pulmonary-to-systemic flow ratio. In a separate report, Clark et al. demonstrated SAND in 18% of patients having sinus venosus but only 4% of those having secundum ASDs (2). From among 109 patients having sinus venosus defects, Kyger et al. reported the clinical courses of 109 patients (1 to 72 years old; median age, 14 years) with sinus venosus ASDs (3). Fourteen percent had preoperative arrhythmias, including four who were 10 years and younger (three with low atrial rhythms

and one with junctional rhythm).

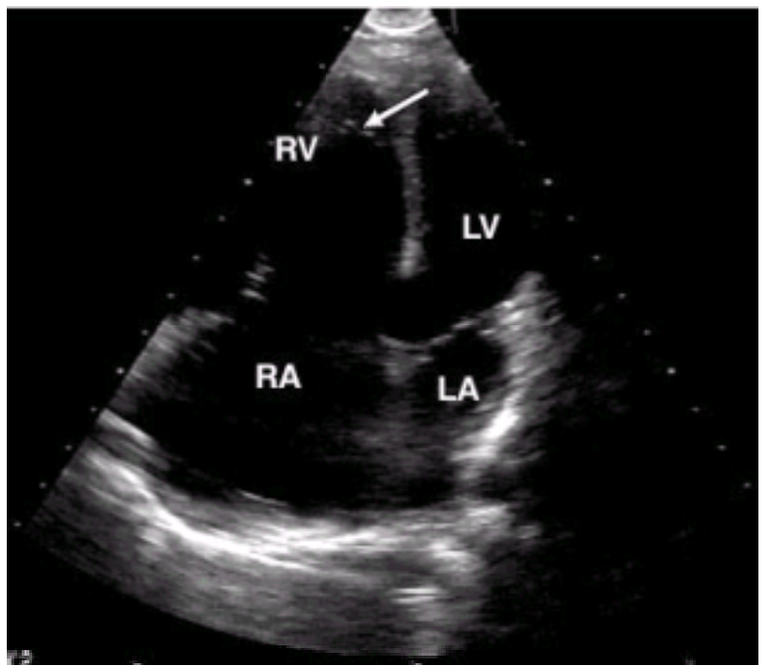
A great deal more data are available in adults having ASDs. Older patients having unrepaired defects have increased likelihood of having atrial flutter or AF. Combining data from 454 patients from four reports, this incidence ranged from 4% to 24% of patients younger than 40 years old up to 51% to 63% of those 50 to 79 years old (4,5,6 and 7). This risk has also been demonstrated to increase with increasing pulmonary-to-systemic flow ratio (4), pulmonary resistance (8), or pulmonary artery pressure (9). Benedini et al. reported preoperative sinus node function in 26 adults (17 to 56 years old) having secundum ASDs (10). Both ambulatory ECG monitoring and intracardiac electrophysiologic measurements were used to identify SAND, but all 17 patients who were described as having SAND had only prolonged sinoatrial conduction times or sinus node recovery times. The Holter evaluations were normal. The authors concluded that SAND was “concealed” and could manifest itself postoperatively. In a large report of 384 patients (16 to 72 years old) by Hamilton et al., 8% had AF or flutter on routine ECG, 1% had third-degree AV block, 8% had minor conduction abnormalities, and 82% were in sinus rhythm (8). Although 44% complained of palpitations, only 20% had documented arrhythmias, with only eight patients having AF or flutter.

In summary, preoperatively, ASDs are infrequently associated with SAND, with the possible exception of sinus venosus defects, perhaps related to the anatomic proximity of the defect to the sinus node. Atrial tachyarrhythmias are more common in older persons and in those having the greatest degree of hemodynamic derangement. Although measurements of sinus node and atrial muscle automaticity or conduction may be abnormal in children, clinically important arrhythmias are uncommon.

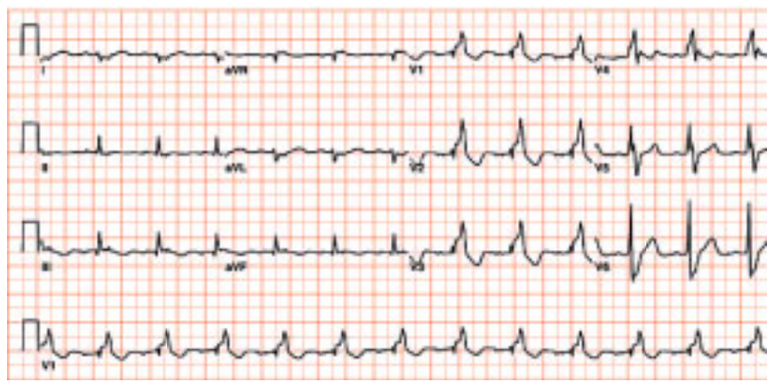
Ebstein’s Anomaly of the Tricuspid Valve

Ebstein’s anomaly of the tricuspid valve occurs when there is an abnormality in separation of the right atrium from the right ventricle with downward displacement of the tricuspid valve leaflets into the right ventricle. This results in the presence of an “atrialized” portion of the right ventricle, often resulting in significant tricuspid regurgitation. In moderate or severe cases, it is associated with chronic cyanosis, severe volume overload of both atria, and sometimes right ventricular outflow tract obstruction. Dysplasia of part of the right ventricle and accessory AV connections are intrinsic malformations which are variably present. This combination of physiologic and anatomic abnormalities results in a patient group with a high incidence of arrhythmias. Even from early childhood, the ECG from moderately or severely affected patients shows marked right atrial enlargement and right ventricular conduction delay (*e*Fig. 70.0.1).

Epstein’s anomaly. Right anterior oblique projection of a right ventriculogram demonstrating Epstein’s anomaly.

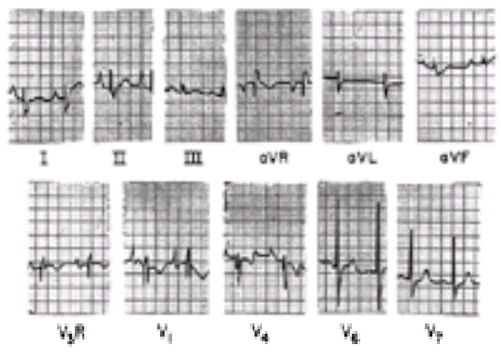


Ebstein’s anomaly of the tricuspid valve. Note marked apical displacement of the tricuspid leaflets, especially the septal leaflet. The arrow designates the septal leaflet of the tricuspid valve.



A 47-year-old male patient with Ebstein’s anomaly.

A 19-year-old male patient with Ebstein's anomaly.



***e*FIGURE 70.0.1** Typical electrocardiogram from a teenager with moderately severe Ebstein's anomaly, showing right atrial enlargement, first-degree atrioventricular block, and right ventricular conduction delay. (From Hypoplastic right heart. In: Krovetz LJ, Gessner IH, Schiebler GL, eds. *Handbook of pediatric cardiology*, 2nd ed. Baltimore: University Park Press, 1979:297–308, with permission.)

In a large collaborative study reported by Watson (11), data from 505 patients were reviewed. Four hundred thirty-eight were younger than 25 years old. In the total group, 28% had reported paroxysmal arrhythmias, and 10% had Wolff-Parkinson-White (WPW) syndrome. Of 363 who underwent cardiac catheterization, 90 (25%) had arrhythmias during the procedure, including 46 (13%) with paroxysmal supraventricular tachycardia (PSVT), 11 (3%) with AF/flutter, 10 (3%) with VT, 23 (6%) with more than one tachyarrhythmia, and 1% each with complete AV block or severe bradycardia. During catheterization, 13 patients died (3.6%), and six additional patients survived after cardiopulmonary resuscitation (1.7%), all related to arrhythmias. Neither the presence of WPW syndrome nor a history of paroxysmal arrhythmias was predictive of arrhythmias or death at cardiac catheterization or for subsequent SCD. Gentles' retrospective analysis of 48 patients also failed to demonstrate a relationship between the coexistence of either WPW syndrome (21% of patients) or PSVT and early death (12). However, from among older patients, of 32% who had died, a history of AF was more common than in survivors (p = .03). From among 17 patients who had presented in infancy, seven (41%) died by 5 months, none due to arrhythmia.

In natural history studies, the incidence of arrhythmia increased with age at presentation (13,14 and 15). In Celermajer's report of 220 cases of Ebstein's (13), actuarial survival was only 59% at 10 years, but among 58 deaths, only eight were sudden. Although arrhythmias were the major contributor to morbidity, they rarely were fatal. Oh et al. reviewed 52 consecutive patients with Ebstein's anomaly at the Mayo Clinic (15), 12% of whom had WPW syndrome. Although a variety of arrhythmias were observed in 79% of patients, they were older than the group not having symptomatic or proven arrhythmias (21 vs. 9 years, p £.01).

Supraventricular tachycardias associated with accessory pathways can now be treated using catheter ablation techniques. Due to the abnormal anatomy and complex electrophysiology in Ebstein's patients, this technique is more challenging than in patients having normal hearts. In a multiinstitution report involving 65 Ebstein's patients, there were 82 nondecremental accessory pathways, nearly all right free wall or septal, and 17 other supraventricular tachycardias (one atrial ectopic tachycardia, seven AV node reentry tachycardias, five Mahaim fiber–related tachycardias, and four intraatrial reentry tachycardias) (16). Catheter ablation success rates ranged from 75% for those not involving accessory pathways to 89% for septal accessory pathways. The overall recurrence rate was 30%. Smaller patient size and lesser degrees of tricuspid regurgitation predicted better acute and long-term success rates.

Pulmonary Valve Stenosis

Valvar pulmonic stenosis causes right ventricular hypertrophy relative to the severity of outflow tract obstruction. Surgical or balloon valvuloplasty may relieve obstruction but result in pulmonary valve regurgitation with subsequent right ventricular volume overload. In their Report from the Second Joint Study on the Natural History of Congenital Heart Defects (NHS-2), Wolfe et al. reviewed arrhythmias from 182 patients with pulmonic stenosis (17). The only significant arrhythmia in this group was premature supraventricular beats (PSVBs), occurring at a rate exceeding 0.5 per hour (upper limits of normal) in 22% of patients. The remainder of this report involves patients who had undergone surgical valvotomy, which is discussed in the section Arrhythmias after Repair of Other Congenital Heart Defects.

Severe right ventricular hypertrophy resulting from pulmonary hypertension. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 70.2 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 70.3 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 70.4 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The

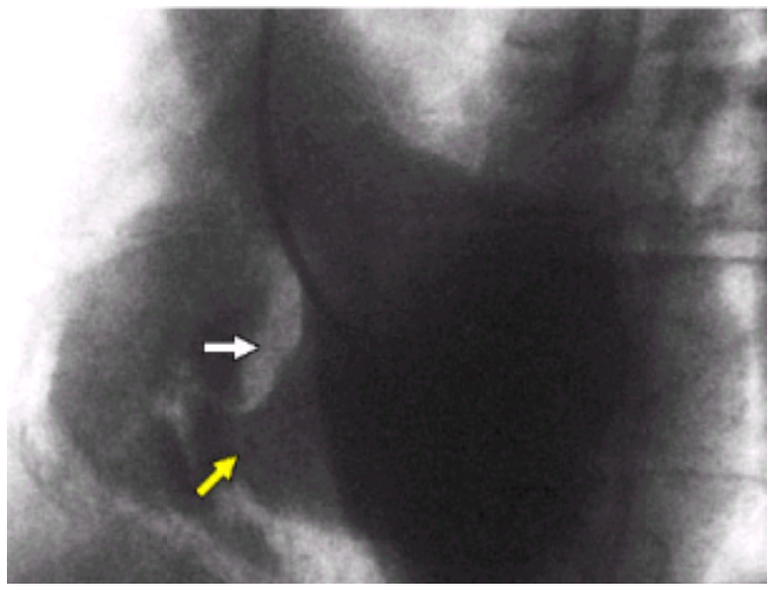
heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 70.5 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Ventricular Septal Defect

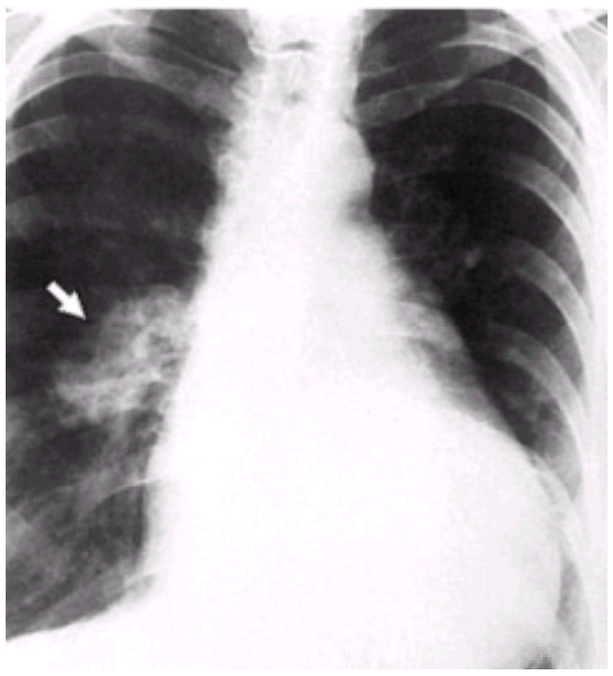
Patients having an unoperated VSD generally have ECG abnormalities or arrhythmias related to the severity of hemodynamic disturbance. Most moderate or large defects are associated with ECG findings of right and left ventricular hypertrophy and left atrial enlargement, as well as a variety of arrhythmias in both children and adults. In the NHS-2, Wolfe et al. reviewed 24-hour ECG data from 439 patients having a VSD (17). Of the younger group (younger than 40 years), 58 (15.3%) had more PSVBs and 22 (10.6%) had more premature ventricular beats (PVBs) than the control population. Ventricular couplets (17.3%) and multiform PVBs (26.3%) were more prevalent than expected among patients younger than 50 years old, and 5.7% of all patients had at least one episode of ventricular tachycardia (p <.0001 vs. controls). In this group of patients who had not had surgery, the best independent predictors for having serious arrhythmias were the mean pulmonary artery pressure at the time of entry into the first Natural History Study (NHS-1) and age at the NHS-2.



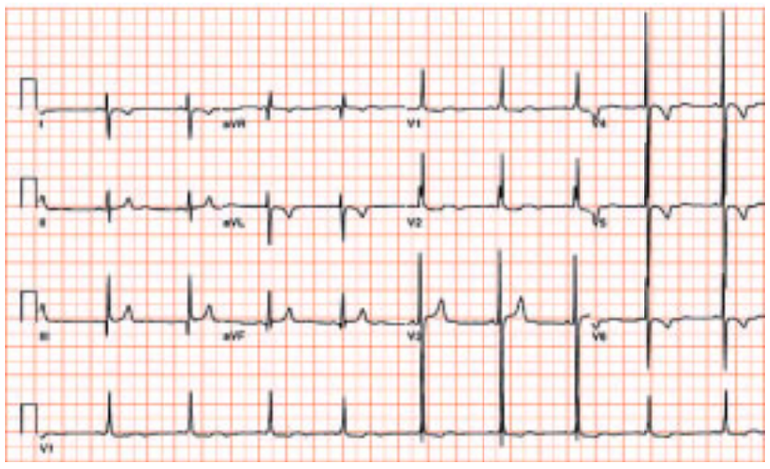
Muscular ventricular septal defect. This left anterior oblique left ventriculogram demonstrates the presence of a muscular ventricular septal defect (*yellow arrow*) with opacification of the right ventricular cavity and pulmonary outflow tract. The ventricular septum (*white arrow*) is seen to divide the right and left ventricular chambers.

VIDEO

Video 70.6 A 72-year-old asymptomatic female patient with a small ventricular septal defect. Left anterior oblique ventriculogram shows contrast filling the right ventricle during left ventricular injection. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Chest x-ray in patient with a congenital ventricular septal defect. There is fullness in the hilum secondary to an enlarged pulmonary artery (*white arrow*).



A 16-year-old male patient with biventricular hypertrophy secondary to ventricular septal defect and Eisenmenger's syndrome.

In a separate study, among 109 Norwegian adults 16 to 65 years old (52 were younger than 25 years old) having VSD, 37 complained of palpitations and atypical chest pain, although AF was documented in only one patient with a large defect (18). In a more recent report of 188 young adults (mean age, 29.2 years), all of whom had a *small* VSD (19), age-related symptomatic tachycardias were documented in 8.5%, mostly AF.

Atrioventricular Septal Defect

In all forms of AV septal defect (AVSD), the AV node maintains its position between the insertion of the inlet ventricular septum and the atrial septum (20). This results in postero-inferior displacement of the AV node and left bundle branch (21), a longer than normal penetrating bundle (20), and relative hypoplasia of the anterior portion of the left bundle branch (21). This gives the familiar left-axis deviation of the QRS complex with the superior counterclockwise vector loop in the frontal plane. Chamber enlargement as reflected by the ECG depends on the associated hemodynamics. For example, in the presence of "complete AVSD," the ECG typically shows biventricular hypertrophy and biatrial enlargement. In patients with an ostium primum ASD or with a complete AVSD but a small VSD, the ECG will show left-axis deviation and right atrial and ventricular enlargement. In older children or adults with unoperated AVSDs, Eisenmenger physiology will have supervened, resulting in marked right ventricular hypertrophy.

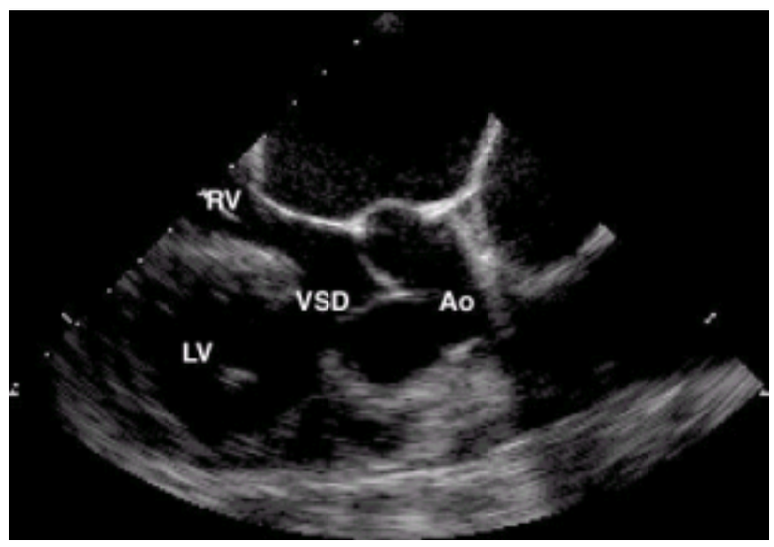
Electrophysiologic data from 18 children (median age, 3 years) with preoperative AVSDs showed only first-degree AV block in five (prolonged PA interval in one, prolonged AH intervals in two, and normal intervals in two), prolonged PA intervals with normal PR intervals in four, and sinus node dysfunction in one (22). Accessory AV connections and PSVT may also exist in association with this congenital defect. In our experience, they tend to be posteroseptal in location.

Patent Ductus Arteriosus

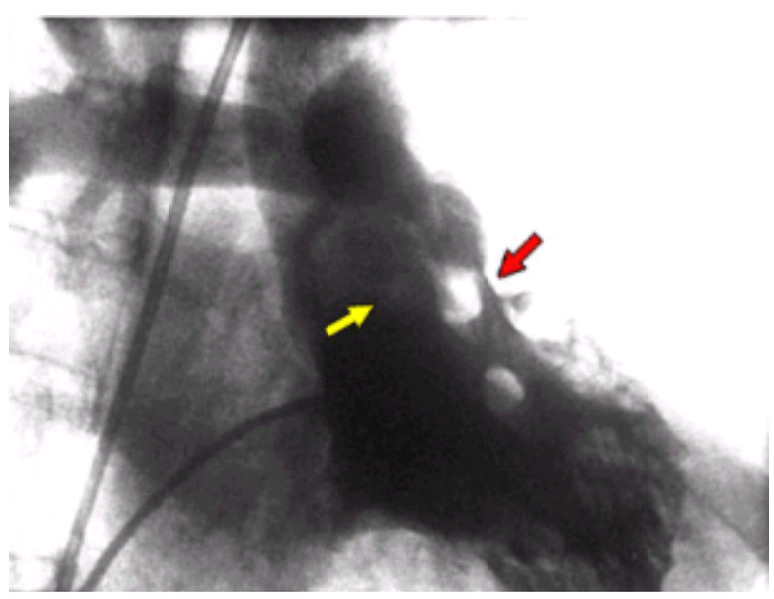
Like VSD, PDA results in volume loading of the left atrium and the left ventricle as long as the shunt remains left-to-right. Arrhythmias are most unusual in the infant, child, or teenager with an isolated PDA. Marquis et al. (23) reported the 37 patients who survived beyond 50 years from among 804 with PDAs who were seen in Edinburgh from 1940 to 1979. AF accompanied congestive heart failure by the fifth or sixth decades of life inexorably among those not undergoing surgical repair and persisted even in the majority undergoing ligation. Other arrhythmias were uncommon. These findings were corroborated by McManus' report of 46 adults with a PDA (24). When ECGs were available, 18 of 21 patients had persistent or intermittent AF.

Tetralogy of Fallot

Tetralogy of Fallot is characterized by hypoplasia and anterior malalignment of the infundibular septum, infundibular and often valvar pulmonic stenosis, overriding aorta, and perimembranous-to-outlet VSD. The hemodynamic findings in patients preoperatively with tetralogy of Fallot include right ventricular hypertension with associated hypertrophy, normal pulmonary arteriolar resistance, and variable degrees of systemic arterial desaturation with secondary polycythemia. The preoperative ECG shows right ventricular hypertrophy and right-axis deviation. There is an age-related increase in ventricular arrhythmia in these patients. Among 60 unrepaired patients (3 months to 63 years old), Deanfield et al. noted that 20% of those older than 8 years had significant ventricular ectopy (Lown grade II or higher), and 58% of those 16 years and older were affected, including four (21%) with 3- to 12-beat runs (25). Similarly, supraventricular arrhythmias were only found in children older than 8 years; three children had episodes of PSVT. These findings were corroborated by Sullivan et al. who noted that, among 50 preoperative patients, those younger than 7 years old never had ectopy worse than Lown grade I preoperatively compared with 44% of 18 patients 30 to 43 years old (26).



Parasternal long-axis view of Tetralogy of Fallot. Note the aortic valve overriding the ventricular septum and the ventricular septal defect.



Tetralogy of Fallot. This right anterior oblique right ventriculogram demonstrates some of the findings of tetralogy of Fallot with subpulmonic or infundibular stenosis (*red arrow*) and overriding aorta (*yellow arrow*) and prominent trabeculation of the right ventricle consistent with right ventricular hypertrophy.

Video 70.7 Parasternal short-axis view of tetralogy of Fallot. Note the ventricular septal defect just beneath the right coronary cusp of the aortic valve. The infundibular pulmonic stenosis can be seen superiorly while the pulmonary valve with its vegetation can be seen to the upper right of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 70.8 Parasternal long-axis view of tetralogy of Fallot. Note the ventricular septal defect and the aorta and aortic valve overriding the interventricular septum. *This*

video must be viewed with QuickTime. If you do not have QuickTime you may download it here.

VIDEO

Video 70.9 Color Doppler in the apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect by color flow and the overriding aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

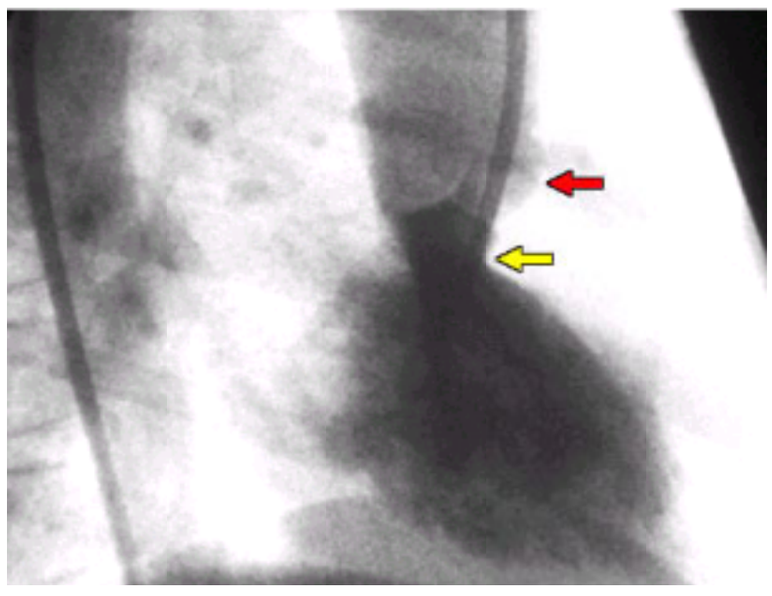
Video 70.10 Apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect, the overriding aorta, and the right ventricular hypertrophy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

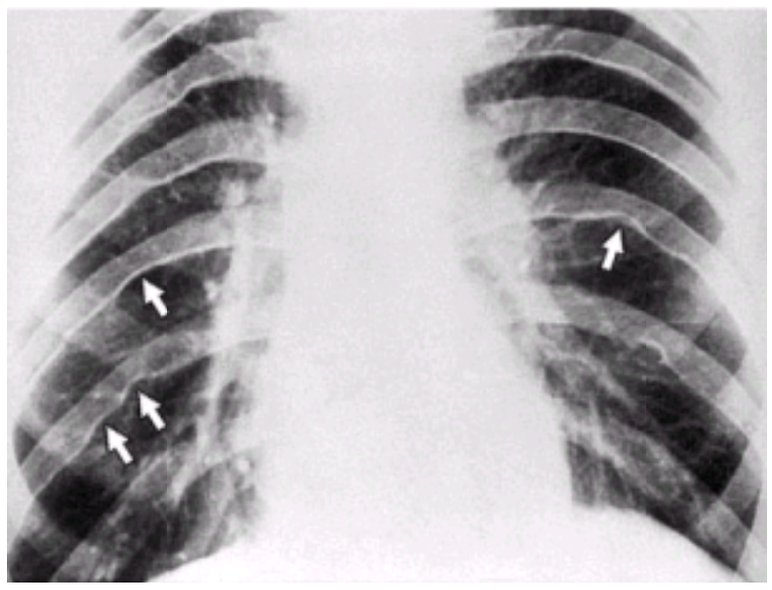
Audio 70.11 Tetralogy of Fallot. Auscultation performed in a 25-year-old male with newly diagnosed tetralogy of Fallot. Note the mid-systolic ejection murmur probably related to right ventricular outflow tract obstruction. Left lower sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Defects Causing Left Ventricular Outflow Tract Obstruction

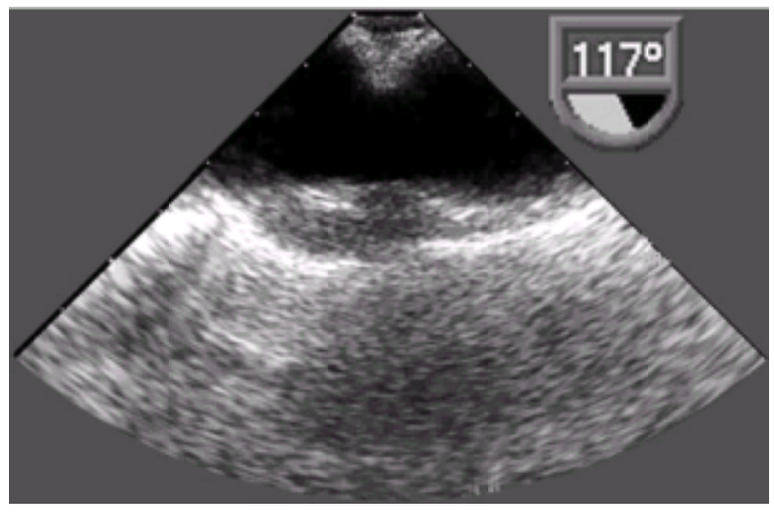
Congenital heart defects causing left ventricular outflow tract obstruction include subvalvar, valvar, and supravalvar aortic stenosis (AS) and coarctation of the aorta. Increased left ventricular wall stress with secondary hypertrophy occurs related to severity of obstruction. Bush et al. performed electrophysiologic evaluations on right atrial tissue obtained from 58 children and adults having valvar AS at the time of aortic valve surgery (27). Only 18% of those younger than age 20 years but 67% of those older than age 40 years had postoperative supraventricular arrhythmias—almost entirely AF/flutter in the older group. Diffuse phase 4 depolarizations and local conduction abnormalities were present in right atrial tissue from the older patients. These findings were absent from both the younger patients and from age-matched older patients not having AS, suggesting that there is a progressive influence on the electrophysiologic milieu of the right atrium by the long-standing hemodynamic effects of AS.



Subaortic stenosis. This right anterior oblique left ventriculogram demonstrates the presence of a stenosis in the left ventricular outflow tract (*yellow arrow*) just below the level of the aortic valve (*red arrow*).



Chest x-ray in coarctation of the aorta. There is prominent rib notching (*white arrows*).



A still frame of a transesophageal echo demonstrating a coarctation of the aorta. Note the local narrowing of the aorta located at the junction of the distal arch and descending aorta. There was a 100–mm Hg pressure gradient across the coarctation as determined by continuous wave Doppler.

Video 70.12 Color Doppler interrogation of the coarctation demonstrating the high-velocity, turbulent flow across the focal narrowing in the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

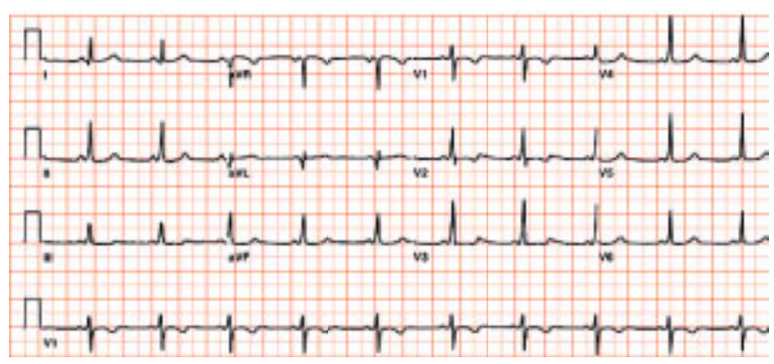
AS in children is only occasionally associated with arrhythmias. Bisset et al. identified no conduction defects or arrhythmias in 15 children about to undergo aortic valve replacement (28). In a study by Bricker et al., of 2,761 children and young adults who had undergone exercise testing at Baylor University, only six patients had developed exercise-related bundle branch block, but two had subvalvar AS and one valvar AS (29). These three represented a relatively significant percentage (0.5%) of the total number having AS.

In distinction from children, Klein demonstrated high-grade ventricular ectopy by ambulatory ECG monitoring in 34% of adult patients having AS and no coronary artery disease compared with only 6% of controls (30). von Olshausen et al. (31) and Santinga et al. (32) confirmed these findings and further showed that the degree of ectopy correlated with a lower left ventricular ejection fraction and higher wall stress and not with the magnitude of peak systolic ejection gradient across the aortic valve. Possible mechanisms for sudden death in this lesion are paroxysmal ischemic changes, AV dissociation, electrical standstill, VT, and nonsustained ventricular flutter.

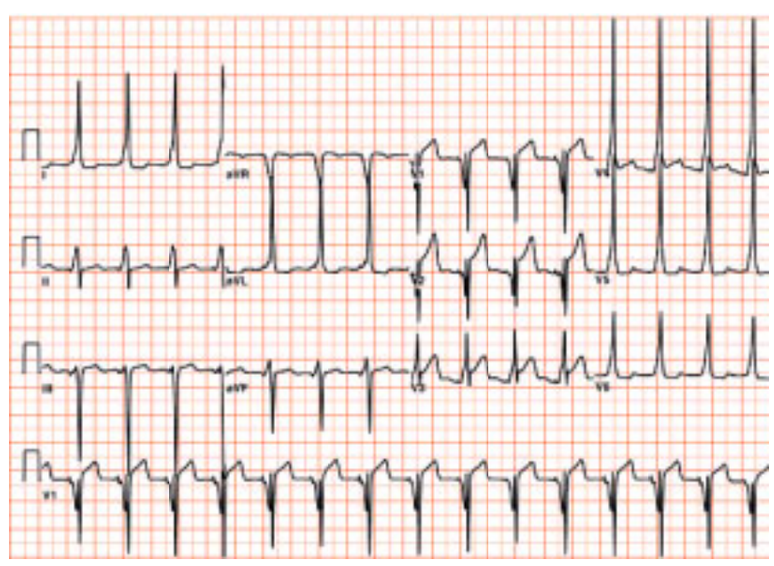
Wolfe et al. reviewed 24-hour ECG monitored data from 134 patients with AS as part of the ongoing NHS-2 investigation (17). PSVBs occurred with greater than normal frequency in this patient group than in controls. However, the prevalence of PVBs was not greater than expected.

Conduction abnormalities may complicate native aortic valve infective endocarditis. In a report by DiNubile et al., 9% of 211 patients with infective endocarditis developed conduction abnormalities (33). This was more likely in those having aortic valve disease than in those having other valve involvement, especially if the infection had spread beyond the valve anulus. Progressive AV or bundle branch block was an independent predictor of death, suggesting that valve replacement is indicated in the presence of unstable AV conduction, especially when the aortic valve is involved. Similarly, echocardiographic demonstration of a perivalvular abscess involving the right and/or noncoronary cusps mandates particularly close monitoring of AV conduction.

In patients having unrepaired coarctation of the aorta, there usually is discrete narrowing of the aorta just distal to the takeoff of the left subclavian artery. This results in hypertension of the proximal aorta and left ventricle, manifest as left ventricular hypertrophy on the ECG. Coarctation is rarely associated with congenital AV block (34) and with WPW syndrome (35). Two cases of sudden death have been reported, one in a 31-year-old after several years of Stokes-Adams attacks and progressive AV block (36) and the other in a 20-year-old with recurrent episodes of AF 9 years after surgical repair of coarctation of the aorta (37). Although subarachnoid hemorrhage and ruptured aorta are the most frequently considered causes of sudden death in those with coarctation of the aorta, both of these patients had marked histologic abnormalities of the AV conduction system at postmortem examination.



A 44-year-old female patient with Wolff-Parkinson-White syndrome.



A 16-year-old male patient with Wolff-Parkinson-White syndrome.

Supravalvar AS may exist as an isolated defect or in association with Williams syndrome, in which case pulmonary and coronary artery hypoplasia may also exist. Sudden death from myocardial infarction may occur in severely affected patients (38).

D-Transposition of the Great Arteries

Babies born with D-TGA have ventriculoarterial discordance with an anterior aorta arising from the right ventricular outflow tract and a pulmonary artery arising posteriorly from the left ventricle. As long as the right ventricle remains the systemic ventricle (as it must preoperatively or after an atrial redirection operation), the ECG maintains a pattern of right ventricular hypertrophy in these patients. Because the normal newborn's right ventricle has been at systemic pressure antenatally anyway,

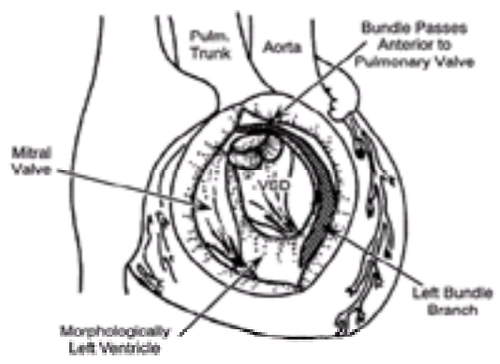
the newborn with D-TGA usually has a normal ECG (for age). The high incidence of rhythm disturbances after atrial redirection procedures for simple D-TGA prompted two large investigations on preoperative patients with this malformation.

Southall et al. reviewed the heart rhythms from 120 consecutive patients with D-TGA, admitted over a 6-year period (39). Eighty percent had undergone balloon atrial septostomy, 2.5% atrial septectomy, and 17.5% neither. One of the 120 had first-degree AV block, and a second acquired first-degree AV block during cardiac catheterization. Both had complete AV block postoperatively. Preoperative 24-hour ambulatory ECG monitoring from 19 patients demonstrated periods of second-degree and complete sinoatrial block in 10 (one with additional premature atrial beats and six with periods of junctional rhythm), premature atrial beats alone at less than 12 per hour in two others; and periods of junctional rhythm in one additional patient. The lowest rates observed were at least 50 per minutes in all but two children. When compared with results of 134 healthy newborns and 92 healthy juveniles, the authors concluded that the ECG patterns in these 19 children were normal.

Martin et al. reported their preoperative findings from 92 survivors of the Mustard operation from among 115 patients over a 10-year period (40). Eighty-three percent of children were in normal sinus rhythm; 12.2% had Lown grade I ventricular ectopy; and there was one child each with frequent premature atrial beats, AF, and Lown grade V ventricular ectopy. These authors also concluded that the preoperative rhythm in children with D-TGA was not different from that of normal children.

L-Transposition of the Great Arteries

In patients with L-TGA (also known as *congenitally corrected transposition* or *ventricular inversion*), there is AV and ventriculoarterial discordance; hence, desaturated systemic venous return enters the pulmonary arteries, and fully saturated pulmonary venous return is directed to the aorta as it should. The aorta arises from a left-sided right ventricular outflow tract, leftward and anterior to the pulmonary artery. In this condition, the ventricles are said to be levo-looped (L-looped), as contrasted to the normal ventricular dextro-looping (D-looping). Associated congenital heart defects include VSD and/or pulmonic stenosis in the majority and tricuspid valve (the left AV valve that functions as the systemic AV valve) insufficiency in up to one-third of patients (41). The specialized AV conduction system is structurally different as well, usually giving a QS or qR pattern in V_1 and an rS or RS pattern in V_6 on standard ECG (*e*Fig. 70.0.2).



***e*FIGURE 70.0.2** The specialized conduction system in a heart having L-transposition of the great arteries, illustrating its relationship to the pulmonary valve and, when present, a ventricular septal defect (VSD).

As described by Anderson et al. from a small series of explanted hearts having L-TGA (42), the connecting AV node is located anteriorly in the right atrium at the mitral-pulmonary junction with an anteriorly positioned bundle of His that encircles the anterolateral region of the pulmonary valve. The bundle of His bifurcates on the anterior ventricular septum and always borders the anterior/superior quadrant of a VSD, when present. A hypoplastic posterior AV node is also usually present just anterior to the coronary sinus, but rarely does it connect with the ventricular mass. In specimens from older patients, the elongated encircling bundles were infiltrated with fibrous tissue or completely disrupted. Five patients had ECG evidence of complete AV block. Congenital AV block due to a lack of continuity between the atria and specialized conduction system in patients with L-TGA has also been reported (42).

Further clinical correlation with these pathologic findings is provided by a large series by Huhta et al., who reviewed the data on 107 patients with L-TGA ranging in age from 2 to 76 years at follow-up (41). Twenty-two percent of patients had complete AV block: 4% congenitally, and 19 others developmentally from ages 4 months to 52 years (mean, 18.1 years). Data analysis showed an approximately 2% per year risk of developing AV block after diagnosis. The risk was higher in those *not* having a VSD, and the risk was not increased after VSD closure if intraoperative AV block did not occur. The only death in their series was a 28-year-old patient who died suddenly during exercise 4 years after onset of AV block. The authors concluded that prophylactic pacemaker placement was not necessary in children as long as their heart rates were greater than 50 beats/min.

Tachyarrhythmias also occur more frequently than in the general population, although the actual incidence is unreported. PSVT, usually AV reentry tachycardia using an accessory AV connection associated with the tricuspid valve (generally left free wall or septal if patient has situs solitus), is most common among these (*e*Fig. 70.0.3) (43,44); multiple left-sided pathways may be present. Symptomatic VT has also been reported in unoperated older patients having L-TGA (45,46).

***e*FIGURE 70.0.3** Electrocardiogram using mirror-image lead placement from a 12-year-old patient having *situs inversus totalis*, “corrected” transposition of the great arteries in *situs inversus*, and two manifest accessory pathways related to the pulmonary venous right-sided tricuspid valve—one posterior and one posteroseptal. (From Kanter RJ, Garson A. Arrhythmia in congenital heart disease. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia.* Baltimore: Williams & Wilkins, 1995:1131–1160, with permission.)

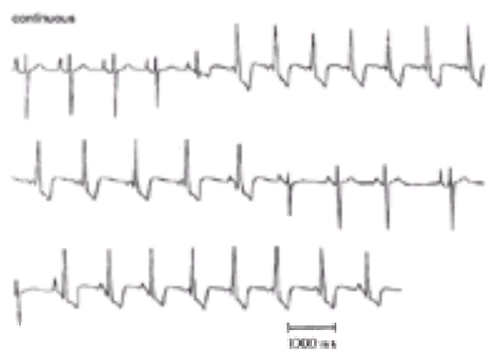
Arrhythmias secondary to hemodynamic abnormalities include atrial tachycardias, which seem to be ubiquitous in these patients starting in the fifth decade (46), especially in the presence of tricuspid (left-sided AV valve) regurgitation. Tricuspid valve replacement carries risk for AV block. In the report by Prieto et al. of 40 patients with L-TGA (47), the 20-year survival rates in unoperated patients were 60% for those having and 100% for those not having significant tricuspid regurgitation (systemic AV valve); not all deaths were arrhythmic, however.

Cardiac Defects Associated with Heterotaxy Syndromes

Heterotaxy syndromes refer to patterns of malformation thought to occur after failure of lateralization of thoracic and abdominal viscera into either situs solitus or situs inversus. They frequently involve the cardiovascular system, often with severe congenital malformations (*e*Fig. 70.0.4). Although they are usually categorized as either right (RAI) or left atrial isomerism (LAI), there is great variability within each group. The cardiac conduction system is usually structurally abnormal, and congenital or acquired AV block is the most important clinical conduction defect.

***e*FIGURE 70.0.4** Characteristic visceral abnormalities, including congenital heart defects in patients having right atrial isomerism or "asplenia" **(A)** and left atrial isomerism or "polysplenia" **(B)**. **A:** Characteristic features of asplenia: (1) bilateral eparterial bronchi, (2) bilateral trilobed lungs, (3) bilateral morphologic right atria, (4) pulmonary venous anomalies, (5) cardiac malformations, (6) systemic venous anomalies, and (7) symmetric liver and right- or left-sided stomach. **B:** Characteristic features of polysplenia: (1) bilateral hyparterial bronchi, (2) bilateral lobed lungs, (3) bilateral morphologic left atria, (4) pulmonary venous anomalies, (5) cardiac malformations, (6) systemic venous anomalies, (7) symmetric liver and right- or left-sided stomach, and (8) multiple spleens. (From Van Mierop LHS, Gessner IH, Schiebler GL. Asplenia and polysplenia syndromes. *Birth Defects* 1972;8:36–43, with permission.)

Histopathologic studies have demonstrated bilateral sinus node–like structures in patients with RAI, each at the superior vena caval–right atrial junction when bilateral cavae are present (48,49). This is consistent with the observed inferior P-wave axis or axes in almost every ECG from the combined 109 patients with RAI reported by Wren et al. (50) and by Momma et al. (51). In the latter series, the sinus rate remained stable over time in all but two patients. We have observed two P-wave axes at different times in two patients each with RAI (*e*Fig. 70.0.5).



***e*FIGURE 70.0.5** Continuous rhythm strip from a 16-year-old boy having right atrial isomerism. A change in atrial pacemaker is followed by a change in PR interval, followed in turn by a change in QRS polarity and morphology. The patient had duplication of the atrioventricular node and penetrating bundle of His. (From Kanter RJ, Garson A. Arrhythmia in congenital heart disease. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia*. Baltimore: Williams & Wilkins, 1995:1131–1160, with permission.)

In the report by Wren et al., 67 patients had LAI, and the P-wave axis was 0 degrees to –90 degrees in 8%, –90 degrees to –180 degrees in 41%, 0 degrees to 90 degrees in 37%, and 90 degrees to 180 degrees in 14% of the ECGs reviewed (50). Among 14 patients who had 24-hour ECG monitoring, only four had a stable "sinus" P-wave axis and almost one-third demonstrated subsequent P-wave shifts of 90 degrees or more. Momma et al. also reported a dominance of superior P-wave axes in children (mean age, 7.4 years) with LAI, with 70% being –30 degrees to –90 degrees (51). There was also a tendency toward atrial rate slowing over time. By age 15 years, two-thirds had slow atrial or junctional rhythms. Dickinson et al. showed that patients with LAI had sinus node–like tissue, often hypoplastic, in the lateral atrial wall of seven of nine patients, and it was entirely absent in two (49).

Complete AV block, congenital or acquired, occurs in up to 15% of patients with LAI (50). Case reports of congenital AV block also exist in instances of RAI (48), although the incidence appears to be lower in patients with RAI than in those with LAI. In the report by Dickenson et al., a detailed analysis of the histopathology of the AV conduction system of 13 patients with LAI and RAI may explain this clinical observation (49). All four patients with RAI had anterior and posterior AV nodes and penetrating bundles. In only one was there discontinuity between the anterior AV node and corresponding bundle. However, of nine with LAI, two had discontinuity between anterior and posterior AV nodes and their bundles. All three patients with LAI, ventricular D-looping, and two ventricles had a normal (single posterior) AV node and continuous bundle of His, meaning that among those six patients with LAI and single ventricle and/or ventricular L-looping, two had complete AV block. A connecting sling of conduction tissue between the anterior and posterior penetrating bundles was identified in all patients in whom both penetrating bundles existed. Its clinical relevance is unknown. One patient with LAI had an accessory AV connection and WPW syndrome on ECG.

Clinically important tachycardias are less frequent than AV block. When WPW syndrome is present, AV reentry tachycardia may occur. A macroreentry supraventricular tachycardia involving two AV nodes and successful catheter ablation of the AV node having poorer anterograde conduction has also been reported (52). Atrial flutter (50) may be related to atrial stretch from volume loading due to AV valve regurgitation, left atrial enlargement from left-to-right shunting in the presence of a VSD, or to chronic changes caused by chronic tissue hypoxemia and polycythemia.

The clinical relevance of all arrhythmias in this group of patients is heightened by the associated hemodynamic abnormalities imposed by the structural defects. Tachycardia suppression and support of unduly slow rate with artificial pacing are of great importance.

Tricuspid Atresia

TA is a congenital abnormality of alignment in which there is absence of AV connection to the morphologically right ventricle (53). The ventricular septum maintains its early developmental position; therefore, the AV node is located in the normal location or posterolateral to the blind-ending dimple in the floor of the right atrium. It is related normally to the tendon of Todaro and coronary sinus (20).

The surface ECG in these patients demonstrates right atrial enlargement in almost all, left-axis deviation in approximately three-fourths (54), a short PR interval in approximately 12% (55), and the WPW syndrome in between 0.29% (56) and 0.51% (55). When Zellers et al. systematically evaluated 183 patients with TA, they found that only one of nine fulfilling ECG criteria for WPW syndrome had an accessory pathway (55). The other eight had normal or enhanced AV nodal conduction, prompting the term "pseudopreexcitation." Surprisingly, of those nine patients, five had had clinical PSVT.

As in all patients requiring aortopulmonary shunts to augment pulmonary blood flow, atrial tachyarrhythmias become problematic if atrial volume overloading is long-standing.

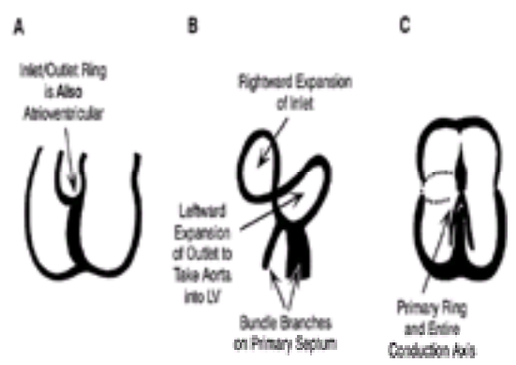
Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome includes a spectrum of abnormalities ranging from mitral and aortic atresia with no demonstrable left ventricular chamber to a very small left ventricle with mitral and/or aortic valve hypoplasia. It is the most common form of functional single ventricle but before recent improvements in surgical technique and perioperative management, interest in arrhythmias in these patients was academic. The specialized conduction system in hypoplastic left heart syndrome is normal, but there may be a higher than expected incidence of atrial ectopic tachycardia, especially in cases of familial hypoplastic left heart syndrome (57).

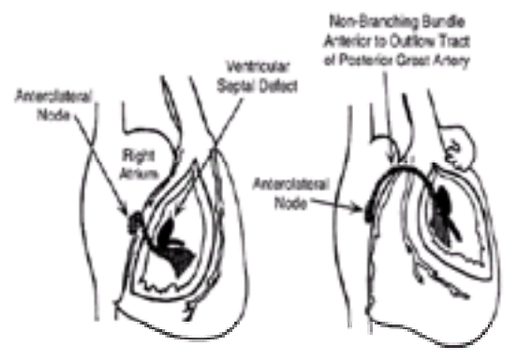
Single Ventricle

Other congenital heart defects in which there is only one functional ventricle include defects that usually have abnormalities of the specialized conduction system. Knowledge of the embryology of the specialized conduction system in the normal heart may help explain the abnormalities encountered in these malformed hearts

(eFig. 70.0.6). It is also useful to consider these entities according to whether there is left ventricular dominance or right ventricular dominance and according to whether there is ventricular D-looping or L-looping. When the main ventricle is L-looped, there may be two AV nodes, one posteriorly located and the other along the anterolateral margin of the right AV orifice. All of these considerations influence the course of the conduction system and potential for natural or surgical AV block (eFig. 70.0.7).



***e*FIGURE 70.0.6** Development of the specialized atrioventricular conduction system. Initially, it forms a ring around the primary interventricular foramen **(A)**. As the heart tube loops rightward and the atria gain their eventual relationship with both the primitive ventricle and the *bulbus cordis*, the dorsal portion of the ring of conduction tissue occupies the inner margin of the heart tube **(B)** as well as the right margin of the atrioventricular junction **(C)**. LV, left ventricle. (From Anderson RH, Ho SY. The morphologic substrates for pediatric arrhythmias. *Cardiol Young* 1991;1:159–176, with permission.)



***e*FIGURE 70.0.7** The relationship between the specialized atrioventricular conduction system to the ventricular septal defect in double-inlet left ventricle in hearts that have ventricular D-looping **(left)** and ventricular L-looping **(right)**. Because the vestigial right ventricle usually gives rise to the aorta, the ventricular septal defect must be unrestrictive for the patient to maintain systemic blood flow. Knowledge of the conduction system location will permit surgical enlargement, when necessary.

Double-inlet left ventricle may occur with either D- or L-looping of the ventricular mass and results from persistent connection of the right atrium to the left ventricle. Neither atrium connects with a vestigial right ventricular outlet chamber, and the ventricular septum does not extend to the crux but contacts the AV ring anteriorly. Embryologically, the primary ring of conduction tissue forms to the right of the interatrial septum, causing the AV node to form anterior and lateral to the atrial septum to connect to the trabecular septum (20). There is a difference in location of the penetrating bundle with respect to the persistent bulboventricular foramen (functional VSD) in L- versus D-looped hearts (20). Additionally, as in hearts with two ventricles and L-TGA, hearts with double-inlet left ventricle and ventricular L-looping (a) may have two AV nodes (in which case the posterior rarely makes contact with the ventricular septum) and (b) are prone to fibrous degeneration of the bundle of His and complete AV block. When complete atresia of the right AV orifice occurs, there is a single anterolateral or posterolateral AV node, similar to that found in classic TA (58).

When there is a dominant right ventricle, the ventricular septum contacts the crux of the heart and the AV node is normally located. In patients with double-inlet right ventricle, or straddling of the right AV valve plus ventricular L-looping, there may be an additional “sling” of conduction tissue between two AV nodes (58). In the presence of ventricular D-looping and a dominant right ventricle, the AV node is normally positioned with respect to atrial landmarks, and the penetrating bundle directly enters the ventricular septum (59).

Eisenmenger’s Syndrome

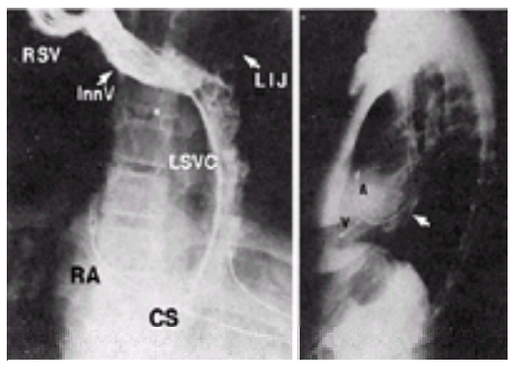
Eisenmenger’s syndrome is defined as the presence of irreversible elevation of pulmonary vascular resistance in certain congenital heart defects in which there initially was increased pulmonary artery blood flow or increased pulmonary artery pressure. With the elevation in pulmonary arteriolar resistance, patients shunt right to left, resulting in myocardial hypoxia, polycythemia, increased blood viscosity, and interstitial fibrosis. Sudden unexpected death has been reported to occur in 12% (60) and 18% (61) of patients, and the prior existence of supraventricular tachyarrhythmias has been identified as an independent predictor of mortality in affected adults (62).

In Wolfe’s natural history series of VSD patients (17), 20 had Eisenmenger’s syndrome. During 24-hour ECG monitoring, 80% had a frequency of PVBs exceeding that of a normal population, 72.2% had ventricular couplets, 88.9% had multiform PVBs, and 20% had greater than one ventricular tachycardia episode. These prevalences far exceeded those from all other patient groups with VSDs, AS, or pulmonic stenosis. However, the relationship of these findings to risk of sudden unexpected death is unproved, and hemodynamic etiologies may be more important. There is speculation that a sudden additional rise in pulmonary vascular resistance could be the cause of sudden death in some of these patients.

Persistent Left Superior Vena Cava

Persistent left superior vena cava occurs as an isolated finding in approximately 0.5% of the general population and has no hemodynamic significance. This structure courses across the posterolateral wall of the left atrium where the oblique ligament of Marshall would have existed, before it enters the right atrium by way of the great cardiac vein and coronary sinus. When it accompanies a sinus venosus–type ASD, a low atrial rhythm (so-called coronary sinus rhythm) having a superior P-wave axis may be expected (63). If there is a persistent left and no right superior vena cava, impaired sinus node function may occur. This combination plus AV node dysfunction was thought to cause fatal bradycardia in a report of two children (64).

If transvenous pacemaker implantation is required, there are special considerations. In the presence of a coexisting right superior vena cava, that approach is preferable. If the left subclavian vein must be used, the size of the innominate vein must be assessed, as it is often small. In such cases and when there is no right cava, the ventricular lead must be passed through the coronary sinus and looped in the right atrium so that it may enter the right ventricle. Prior knowledge of the existence of a left superior vena cava should permit successful placement of an active fixation system using biplane imaging (eFig. 70.0.8). Reported complications have included atrial perforation and thrombosis of the coronary sinus (65,66).



***e*FIGURE 70.0.8 Left:** Anteroposterior projection of a right innominate venogram in a 13-year-old patient having absent right superior vena cava and mirror-image venous return to a left superior vena cava (LSVC), which enters the right atrium (RA) via the coronary sinus (CS). His rhythm was low atrial and junctional. **Right:** Lateral chest radiograph from an adult with similar anatomy, illustrating the posterior and inferior location (*arrowhead*) of both atrial and ventricular pacing leads as they enter the right atrium. The ventricular lead must then loop almost 180 degrees before entering the tricuspid valve and right ventricle. A, atrium; InnV, innominate vein; LIJ, left internal jugular vein; RSV, right subclavian vein; V, ventricle. (From Van Nooten G, Verbeet T, Deuvaert FE. Atrial perforation by a screw-in electrode via a left superior vena cava. *Am Heart J* 1990;119:1439–1440, with permission.)

Congenital Abnormalities of the Coronary Arteries

Congenital abnormalities of the origin and courses of the coronary arteries are rare but disproportionately important defects because they may be associated with sudden myocardial ischemia, ventricular fibrillation, and death. When the left coronary artery arises from the pulmonary artery, symptoms almost always occur, usually in early infancy, but if collateral coronary blood supply from the right coronary artery is adequate, symptoms may occur as late as adolescence (67).

In another group of defects, the left main coronary artery may arise from the right sinus of Valsalva (68,69,70 and 71), or less frequently, the right may arise from the left sinus (72,73). In either instance, the aberrantly arising coronary artery tends to have a partial intramural course, may have a narrowed origin, and may be prone to compression between the ascending aorta and pulmonary artery during exercise. Sudden death may result, and ventricular tachycardia has been observed in nonfatal cases. In four autopsy series reporting sudden death in children and young adults, one of these defects existed in 5% to 35% of cases (74,75,76 and 77). In another autopsy series by Barth and Roberts, 61% of 38 patients having the left main coronary artery arising from the right sinus had died by 20 years of age (71), and when the clinical histories from autopsy specimens having this defect were reviewed, death was sudden and unexpected in the great majority. The risk of sudden death in the case of anomalous right coronary artery is less well established, but probably is not as great (78).

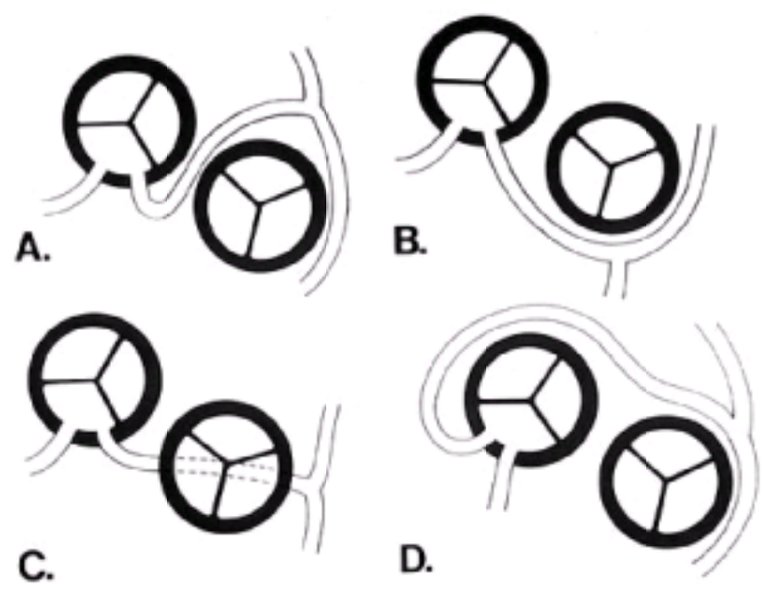


Diagram depicting the variations of the left coronary artery originating from the right sinus of Valsalva. Panel A depicts the left coronary artery arising from the right sinus of Valsalva and coursing between the pulmonary artery and the aorta. Panel B depicts origin of the left coronary artery from the right sinus of Valsalva coursing anterior to pulmonary artery. Panel C depicts the origin of the left coronary artery from the right sinus of Valsalva and coursing intramyocardially in the crista supraventricularis. Panel D depicts the origin of the left coronary artery from the right sinus of Valsalva coursing posterior to the aorta.

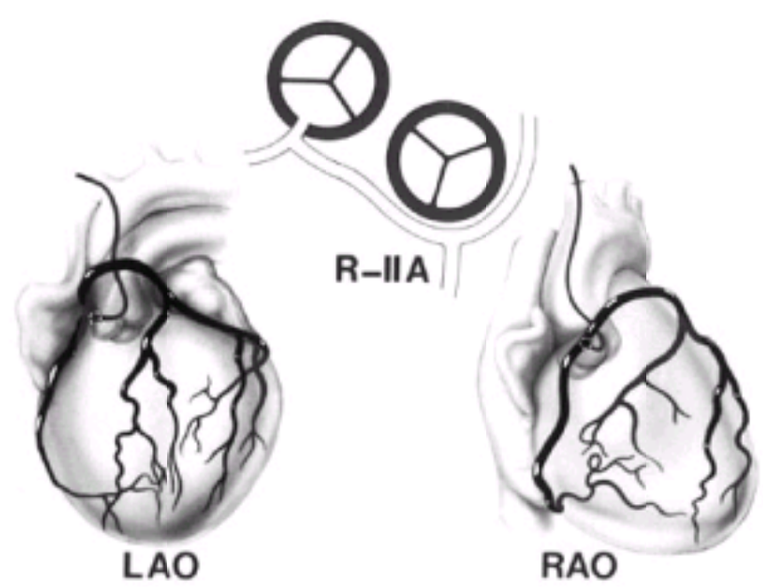


Diagram of a single coronary artery originating from the right sinus of Valsalva with an initial course of the left coronary trunk anterior to the pulmonary artery. The left panel depicts a left anterior oblique projection of a single coronary artery originating from the right sinus of Valsalva with the left coronary trunk coursing anterior to the pulmonary artery. The right panel depicts the right anterior oblique projection of the same.

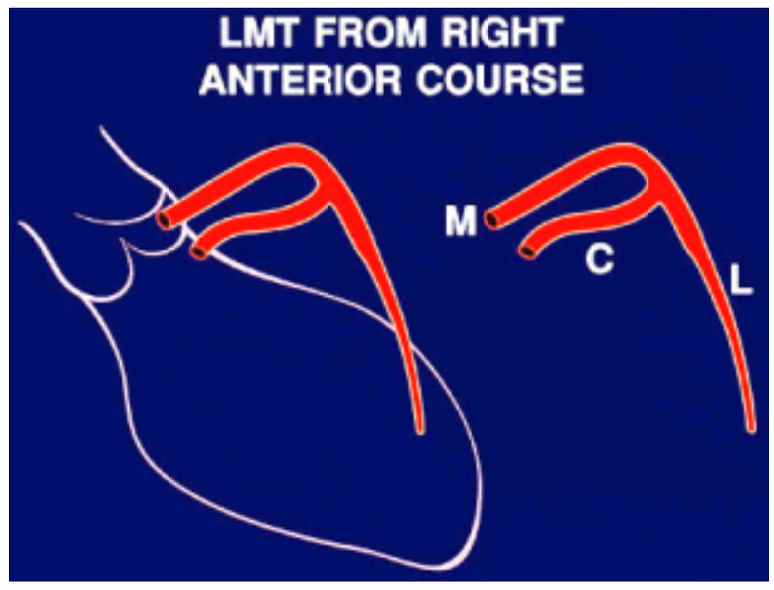
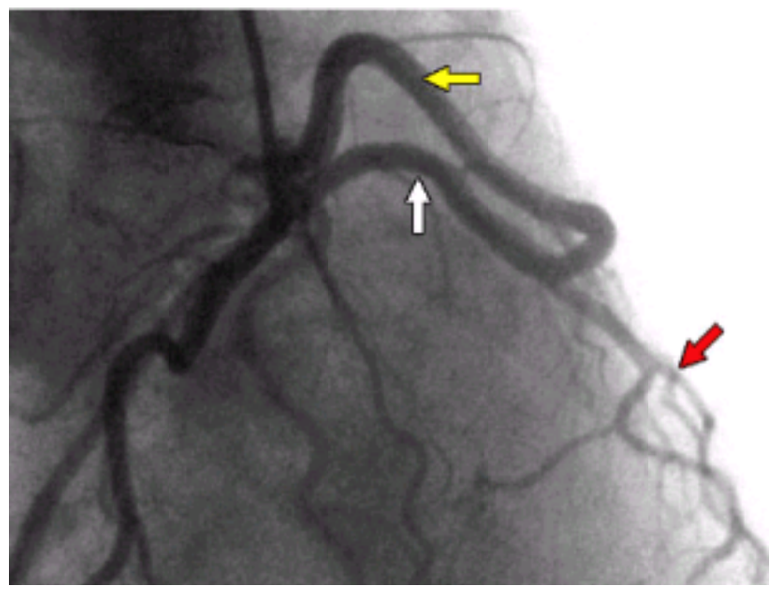


Diagram of the left coronary artery originating from the right sinus of Valsalva with an initial course anterior to the pulmonary artery. Left panel depicts a right anterior oblique projection of the geometry of the left coronary artery as it originates from the right sinus of Valsalva and coursing anterior to the pulmonary artery. The right panel depicts the geometry of the left main trunk (M) with the left circumflex (C) and the left anterior descending artery (L) as seen from the right anterior oblique projection.



Left coronary artery originating from the right sinus of Valsalva with an anterior course. This right anterior oblique projection demonstrates the diagnostic appearance and geometry of the left coronary artery originating from the right sinus of Valsalva and coursing anterior to the pulmonary artery (*yellow arrow*) and bifurcating into the left circumflex (*white arrow*) and the left anterior descending artery (*red arrow*).

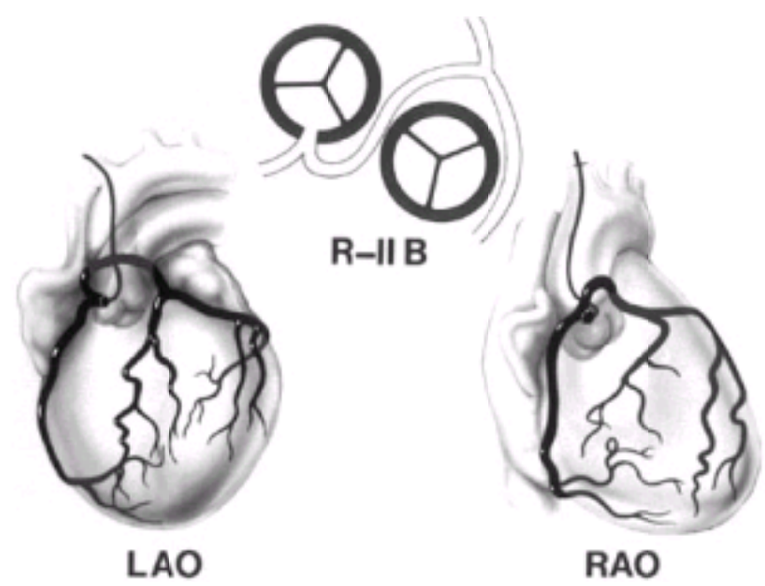


Diagram of a single coronary artery originating from the right sinus of Valsalva with the left coronary trunk coursing between the pulmonary artery and aorta. Left panel depicts a left anterior oblique projection of the single coronary artery originating from the right sinus of Valsalva with a left coronary artery trunk coursing between the pulmonary artery and aorta. The right panel depicts the right anterior oblique projection of the same.

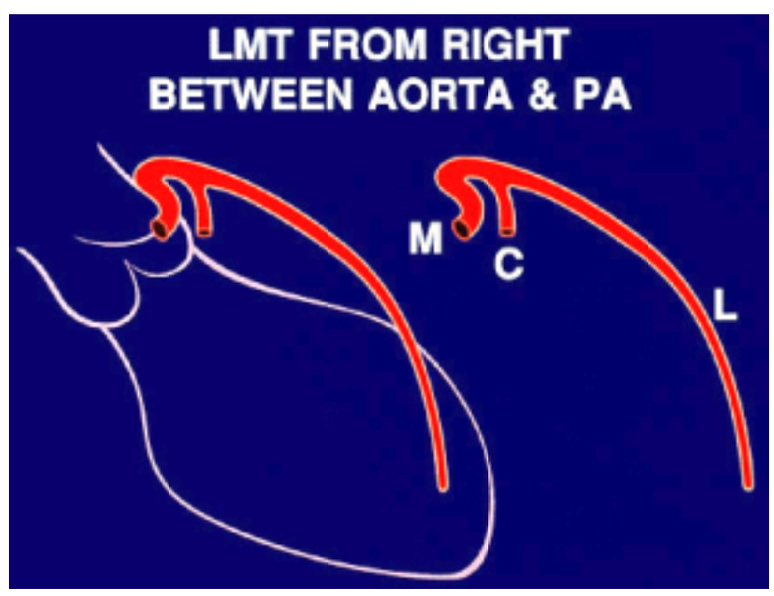
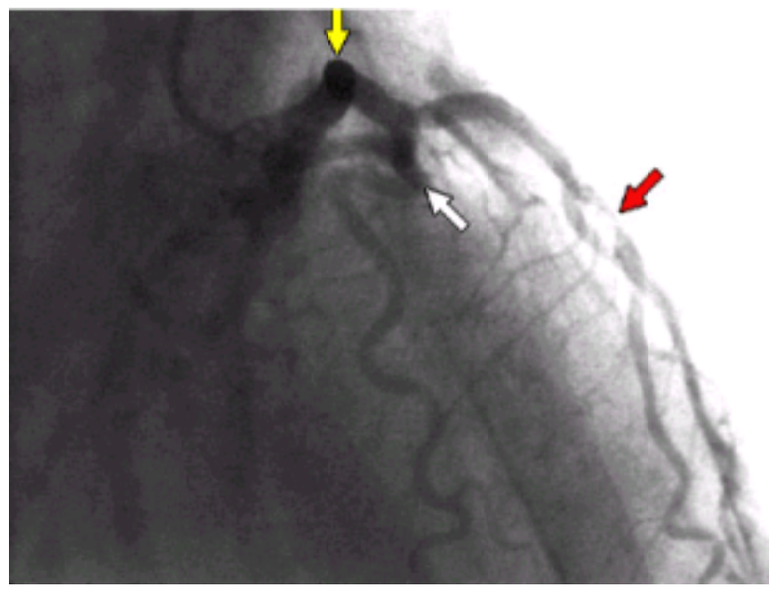


Diagram depicting left coronary artery originating from the right sinus of Valsalva and coursing between the aorta and pulmonary artery. Left panel depicts a right anterior oblique projection of the geometry of the left coronary artery originating from the right sinus of Valsalva coursing between the aorta and pulmonary artery. Right panel depicts the diagnostic appearance and geometry of the left main trunk (M) and the left circumflex (C) and the left anterior descending artery (L) as seen from the right anterior oblique projection.



Left coronary artery originating from the right sinus of Valsalva and coursing between the pulmonary artery and aorta. This right anterior oblique projection demonstrates the diagnostic appearance of the left main trunk (*yellow arrow*) originating from the right sinus of Valsalva and coursing between the pulmonary artery and aorta to give rise to the left circumflex artery (*white arrow*) and the left anterior descending artery (*red arrow*).

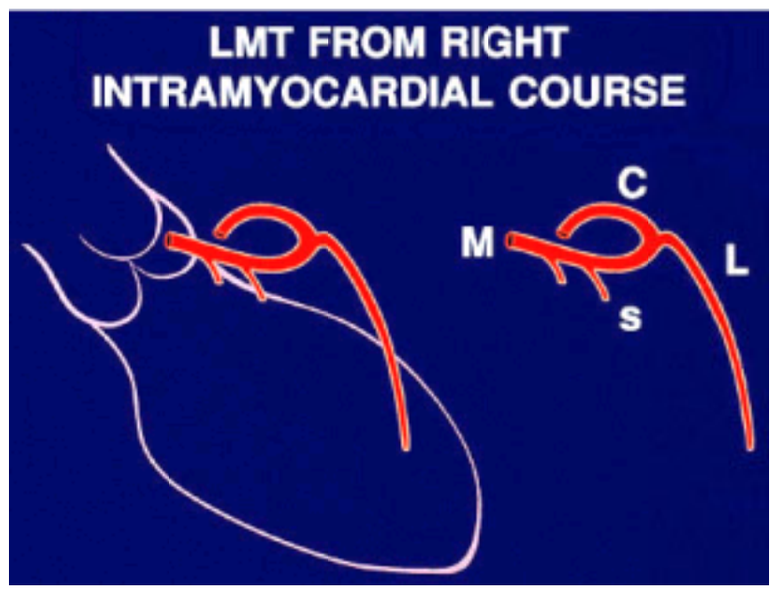
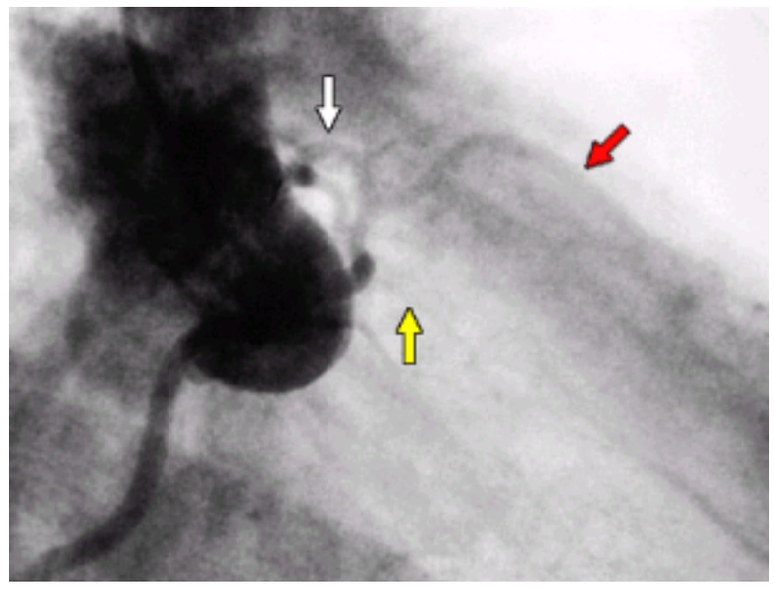


Diagram depicting left coronary artery originating from the right sinus of Valsalva and coursing intramyocardially to give rise to left anterior descending artery and the left circumflex artery. Left panel depicts a right anterior oblique projection of the left coronary trunk originating from the right sinus of Valsalva and coursing intramyocardially before giving rise to the left circumflex and the left anterior descending artery. Right panel depicts the diagnostic appearance and geometry of the left main trunk (M) coursing intramyocardially and giving rise to septal perforating branches (S) before giving rise to the left circumflex (C) and the left anterior descending artery (L).



Left coronary artery originating from the right sinus of Valsalva and coursing intramyocardially to give rise to the left circumflex and the left anterior descending artery. Flush injection of the right coronary sinus depicts a left coronary artery originating from the right sinus of Valsalva and coursing intramyocardially and giving rise to septal perforating branches (*yellow arrow*) and ultimately giving rise to the left circumflex (*white arrow*) and the left anterior descending arteries (*red arrow*).

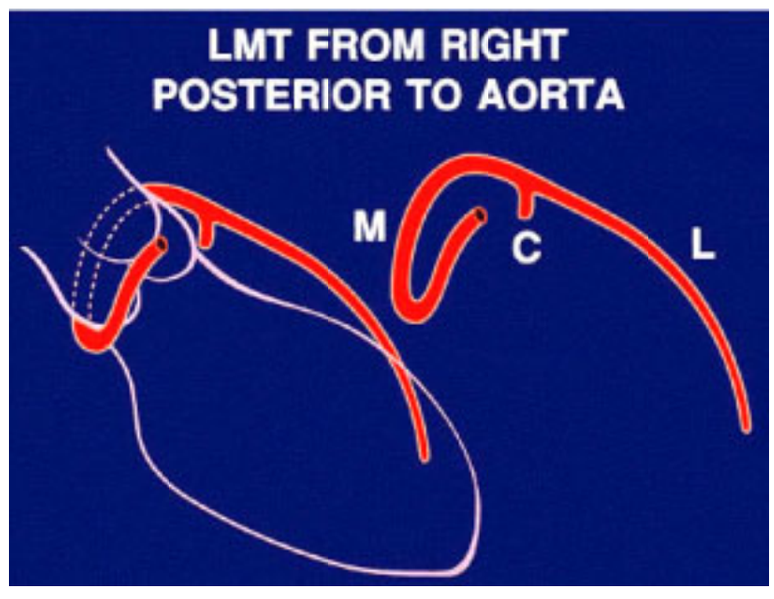
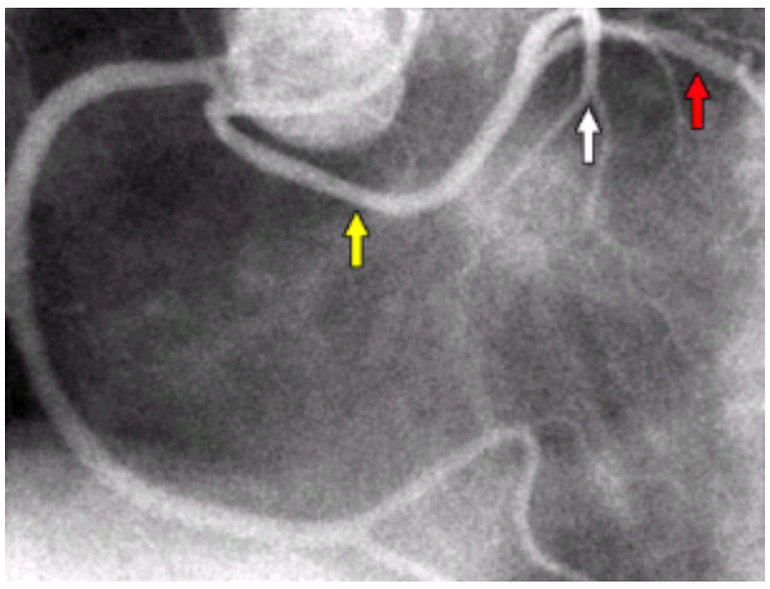
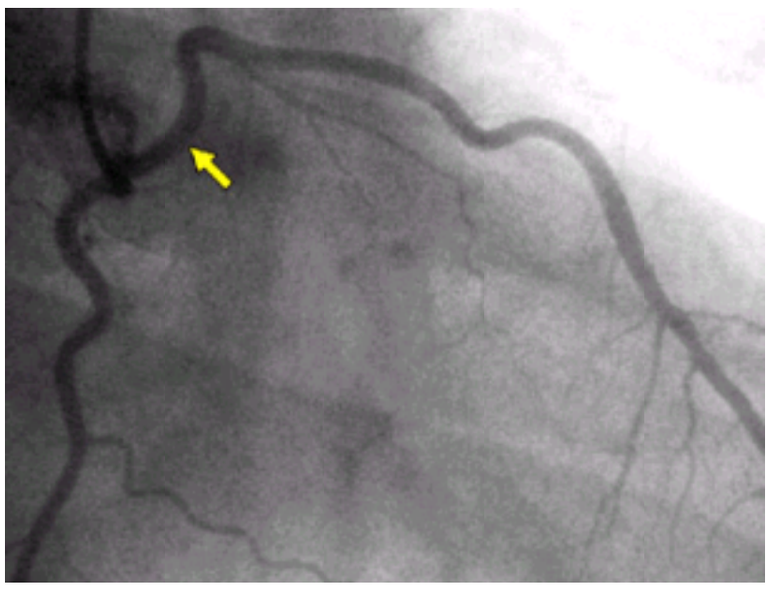


Diagram of the left coronary artery originating from the right sinus of Valsalva and coursing posterior to the aorta and the pulmonary artery to give rise to the left circumflex and the left anterior descending artery. Left panel depicts a right anterior oblique projection of the left coronary artery originating from the right sinus of Valsalva and coursing posterior to the aorta and the pulmonary artery to give rise to the left circumflex and the left anterior descending artery. Right panel depicts the diagnostic appearance and geometry of the left coronary trunk (M) originating from the right sinus of Valsalva and coursing posterior to the aorta and pulmonary artery to give rise to the left circumflex (C) and the left anterior descending arteries (L).



Left anterior oblique cranial projection of a right coronary sinus flush injection demonstrating the left coronary trunk (*yellow arrow*) originating from the right sinus of Valsalva and coursing posterior to the aorta and pulmonary artery to give rise to the left circumflex (*white arrow*) and the left anterior descending artery (*red arrow*).



Right anterior oblique projection demonstrating left anterior descending artery arising from dual outlet trunk with ostium in the right coronary sinus. The geometry of the proximal left anterior descending artery (*yellow arrow*) in this right anterior oblique projection is diagnostic for a course between the aorta and the pulmonary artery.

Video 70.13 Left anterior descending coronary artery originating from separate origin near the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 70.14 Anomalous origin of the right coronary artery from the left coronary sinus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 70.15 Anomalous origin of the left main trunk from the right coronary sinus with a course anterior to the pulmonary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Myocardial overbridging of the left anterior descending coronary artery in association with hypoplasia or absence of the posterior descending coronary artery and septal fibrosis has been found in otherwise healthy teenagers or young adults dying during strenuous exercise (78). Isolated myocardial overbridges may be a normal variant, however, and have been identified in 0.5% to 2.7% of otherwise normal coronary angiograms (79).

Video 70.16 Severe myocardial bridging of the mid–left anterior oblique in a 30-year-old male patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Ventricular Aneurysms and Diverticula and Left Ventricular False Tendons

Congenital ventricular diverticula may be muscular and arise from the apex in association with midline abnormalities in other parts of the body or may be fibrous and arise from the apex or left ventricular base (80). Although these patients most commonly present with congestive heart failure, valvular insufficiency, or embolic events, nonsustained and sustained ventricular tachycardia and sudden death have been reported (80,81). These rare lesions may present at any age, and reports of successful abolition of ventricular tachycardia after surgical repair exist (80). Even rarer are right ventricular diverticula.

Left ventricular false tendons are chordal strands that connect the ventricular septum to other left ventricular structures. They are present in more than 50% of healthy persons (82), so their association with ventricular ectopy is difficult to interpret. Suwa et al. reported surgical correction of paroxysmal sustained ventricular tachycardia in a 31-year-old man by resecting one such false tendon (83). The mechanism for tachycardia was not proved, but the false tendon did contain Purkinje fibers,

prompting speculation that postural and other volume changes might have caused traction on this structure with resultant ectopic beats.

Primary Cardiac Tumors in Children

Primary cardiac tumors in infants and children are rare, accounting for 0.002% to 0.080% (84,85 and 86) of cases in autopsy series. Tumor types most frequently observed to be associated with cardiac rhythm disturbances are rhabdomyomas, fibromas, histiocytoid tumors, and—even more rarely—hemangiomas, teratomas, and primary malignant cardiac tumors.

Rhabdomyomas are associated with tuberous sclerosis; tend to be multiple; and involve the ventricular septum, ventricular free wall, papillary muscles, and atrial wall (87). Rhabdomyomas usually present younger than 2 years of age and therefore are considered true congenital lesions. Although their hemodynamic effects are emphasized in most reports, ventricular tachycardia is frequent (84,87), and complete AV block (87) and WPW syndrome with PSVT (87,88) have also been reported. In a report by Case et al., the management difficulties of such arrhythmias are highlighted by an infant who died despite tumor cryoablation, pacemaker implantation, and aggressive antiarrhythmic drug therapy (88). This infant had monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, and antidromic reciprocating tachycardia.

Another benign cardiac tumor of early infancy is the fibroma. It tends to be single; occurs most commonly in the left ventricular free wall or septum; and has been associated with PSVT, VT, and sudden death (87).

Incessant and frequently fatal VT may occur in patients who at autopsy or surgery are found to have single or multiple small, flat, pale, tan-colored lesions variously described as localized histiocytoid cardiomyopathy, Purkinje cell tumors, or myocardial hamartomas. They present from birth to 30 months of age (mean, 10 months) (89,90) and seem to have a female predilection. In Garson's series of 21 infants, the clinical presentation was cardiac arrest in 11 and congestive heart failure in six, and three had coexisting WPW syndrome (90). Electrophysiologic studies localized the VT focus to the left ventricle in 17 and the right ventricle in four patients. Because antiarrhythmic drugs failed to eliminate incessant VT, all patients underwent surgery. Myocardial hamartoma was the diagnosis in 15 patients, all of whom underwent successful resection or cryoablation.

Myxosarcoma, hemangiosarcoma, and malignant teratomas are very rare malignant childhood cardiac tumors that have been associated with right ventricular conduction delay, right bundle branch block, left bundle branch block, short PR interval, and complete AV block (87).

ARRHYTHMIAS IMMEDIATELY AFTER CONGENITAL HEART SURGERY

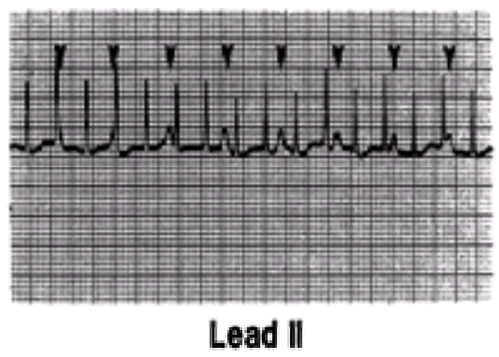
In the immediate postoperative period, children with congenital heart defects may develop tachyarrhythmias due to impaired ventricular contractility, subendocardial ischemia, effects of residual defects, injury to the specialized conduction system, metabolic imbalances, or central nervous system injury. Rarely, postoperative endocarditis will present with new-onset ventricular or atrial ectopy.

Junctional Tachycardia

Junctional tachycardia (JT), also called *junctional ectopic* or *His bundle tachycardia*, generally occurs within 24 hours of congenital heart operations and has been reported to occur in up to 8% of open-heart operations (91). It most commonly occurs after tetralogy of Fallot repair, Mustard operation for D-TGA, VSD closure, AVSD repair, repair of total anomalous pulmonary venous return, and the Fontan operation (91,92 and 93).

When there are suture lines near the bundle of His, the pathogenesis of JT is thought to be related to local edema. Procedures remote from this structure may also cause JT, probably from stretch on the bundle, as may occur with postoperative pulmonary artery hypertension. JT has a significant mortality rate, caused by the adverse effects of both rate-related reduction in ventricular filling and AV asynchrony.

Clinically, postoperative JT is a regular tachycardia with a rate usually greater than 200 per minute and a QRS morphology identical to that seen during sinus rhythm. There is usually ventriculoatrial dissociation, with a ventricular rate faster than atrial and with occasional sinus capture beats (*e*Fig. 70.0.9). This can be best demonstrated by epicardial wire electrograms. Occasionally there is ventriculoatrial conduction, with negative P-waves in the inferior leads. In those instances, JT may be confused with supraventricular tachycardia. JT appears to be due to an automatic mechanism and cannot be terminated by pacing maneuvers or by direct current cardioversion. These maneuvers may result in overdrive suppression, which may last a few seconds before a gradual "warm-up" to the previous rate (94).



***e*FIGURE 70.0.9** Junctional tachycardia after congenital heart surgery. Atrioventricular dissociation is evident. Sinus P waves are indicated by arrowheads. (Full standard; 25 mm per second.)

JT resolves as the patient's hemodynamic status improves, generally within 2 to 10 days (93). Because the agents used to improve inotropic function tend to increase the rate of JT, attempts should be made to limit exogenous catecholamine therapy. The goals of therapy are to reduce the ventricular rate so that the atria may be paced at a slightly faster rate (93). Successful reduction in rate has been reported in small series of patients using a variety of antiarrhythmic agents, including digoxin (91), flecainide (93), propafenone (94), moricizine (95), and amiodarone (96) or by creating moderate hypothermia (32°C to 34°C) by surface cooling. Hypotension may result from intravenous propafenone (97) or amiodarone (96), and hypothermia requires paralysis to avoid shivering and acidosis (98). Walsh et al. used a systematic approach in evaluating treatment options in 71 consecutive children having postoperative JT (99). They proceeded in the following order: reduction in exogenous catecholamines, correction of fever, atrial pacing, digoxin, phenytoin or propranolol or verapamil, procainamide or hypothermia, and finally, procainamide plus hypothermia. Only correction of fever and combined procainamide plus hypothermia appeared to be efficacious. Amiodarone was not used in this study.

Patients refractory to all measures may be considered for transcatheter (100,101,102 and 103) or surgical bundle of His ablation and dual chamber pacemaker implantation.

Other Arrhythmias in the Immediate Postoperative Period

Virtually any arrhythmia may occur immediately postoperatively, depending on hemodynamic or metabolic alterations. In general, onset of new tachyarrhythmias in the early postoperative period warrants investigation of the etiology. Correction of the hemodynamic, mechanical, or metabolic problem should be attempted first. The decision to use pharmacologic therapy must weigh the risks of coexisting hemodynamic deterioration caused by the arrhythmia or potential for worse arrhythmias against adverse side effects from the drugs themselves.

An unusual but recognized cause for sudden hypotension and bradycardia in the immediate postoperative period has been reported in four infants within 18 hours of completion of intracardiac surgery (104). Their responses to intravenous atropine boluses and infusions suggested to the authors that a hypervagotonic response to myocardial stretch (Bezold-Jarisch reflex) was the etiology. If other causes of sudden hypotension and bradycardia have been ruled out (e.g., airway obstruction, pericardial tamponade), this etiology should be considered and treated with atropine.

EVALUATION AND MANAGEMENT OF PATIENTS WITH CHRONIC ARRHYTHMIAS AFTER SURGERY FOR CONGENITAL HEART

DISEASE

eTable 70.0.2 summarizes the incidences of arrhythmias after the more commonly performed congenital heart operations.

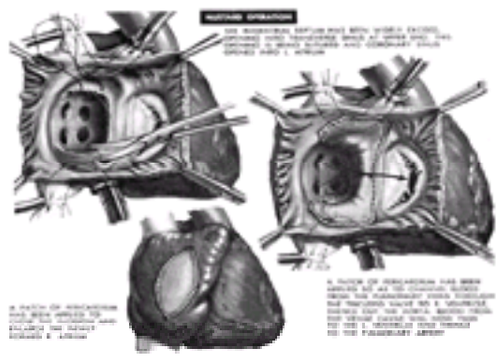
***e*TABLE 70.0.2** INCIDENCE OF ARRHYTHMIAS AND RELATED PROBLEMS IN PATIENTS FOLLOWING SELECTED OPERATIONS FOR CONGENITAL HEART DEFECTS

Operation	Atrial fibrillation/flutter	Ventricular tachycardia	Sudden death	Sinus/junctional bradycardia	Atrioventricular block	Pacemaker requirement
Mustard/Senning operation	++ to +++	+++[a]	++ to ++++[a]	+++ to ++++[b]	+ to ++	+++
Fontan operation	+++++	+++[a]	++[a]	++++	++[a]	+++
Tetralogy of Fallot repair	+ to ++	+ to ++++[a]	++[a]		++	+ to ++
Atrial septal defect closure	+ to +++++[c]			+ to ++	+	+ to ++
Ventricular septal defect closure		+ to +++++[a]	+ to ++[a]			0 to +++[a]
Pulmonic stenosis repair		0 to +++[b]	+			
Aortic stenosis repair		+++ to ++++[a]	++ to +++[a]			

+, 0% to 1% incidence; ++, 1% to 5% incidence; +++, 5% to 10% incidence; ++++, 10% to 20% incidence; +++++, 20% to 60% incidence.
[a]Increased with worse hemodynamic status or associated defects.
[b]Related to increased time since surgery.
[c]Increased with older age at time of surgery.

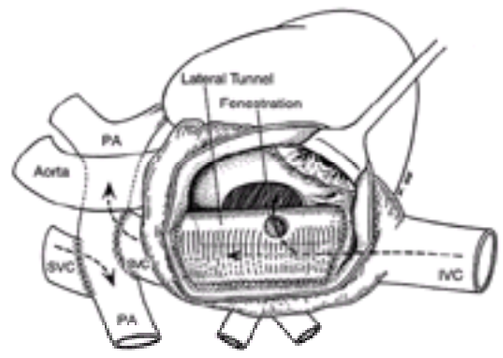
Chronic Arrhythmias after Operations on the Atria

The greatest experience with arrhythmias after atrial surgery is with the Mustard and Senning operations for D-TGA. Creation of an intraatrial baffle with prosthetic material or pericardium (Mustard operation) (eFig. 70.0.10) or with atrial wall itself (Senning) results in damage to the sinus node, perinodal structures, and their blood supplies (105) and to atrial pacemaking tissue throughout the atrium. Symptomatic bradycardia presents as exercise intolerance, fatigue, early morning headaches, or rarely presyncope and syncope. Intraatrial reentry tachycardia (or flutter) also occurs and in certain circumstances may rarely predispose to sudden death.



***e*FIGURE 70.0.10** Netter figures illustrating the Mustard operation. The salient features of the procedure include an atrial septectomy and placement of an intraatrial baffle. Suture lines involve the region of the head of the sinus node, the anterior remnant of the atrial septum, and the isthmus between the tricuspid valve and the inferior vena cava. (From Netter FH. Transposition of the great vessels. In: Yonkman FF, ed. *The Ciba collection of medical illustrations: heart*, vol 5. Rochester: CIBA, 1978:155–156, with permission.)

All variations of the Fontan operation are designed to direct systemic venous return to the pulmonary arteries in patients with a single ventricle (eFig. 70.0.11). These operations usually result in all or part of the right atrium having a chronically elevated mean pressure. Hence, hemodynamic factors in addition to surgical scars likely account for the atrial tachycardias observed in these patients.

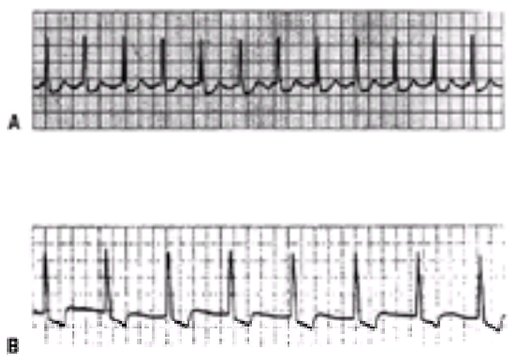


***e*FIGURE 70.0.11** At present, the most frequently performed type of modified Fontan operation, also called *total cavopulmonary anastomosis* or *lateral tunnel*, in which inferior vena cava return is directed to the superior vena cava by a partial intraatrial tube. It is hoped that this arrangement will result in a lower incidence of atrial arrhythmias. IVC, inferior vena cava; PA, pulmonary artery; SVC, superior vena cava.

After repair of ostium secundum or sinus venosus atrial septal defects or partial or total anomalous pulmonary venous return, sick sinus syndrome may also occur.

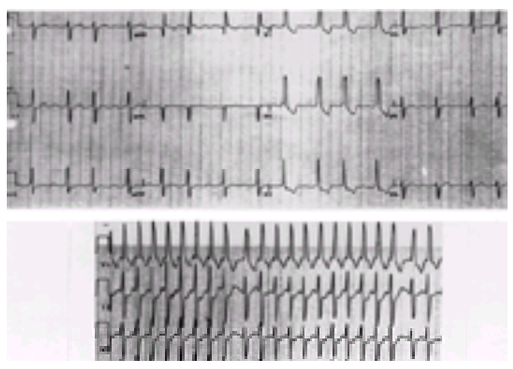
Incidence and "Natural History"

After the Mustard operation, there is a progressive decrease in the percentage of patients having sinus rhythm. When evaluated by routine ECG or 24-hour Holter 5 to 10 years postoperatively, between 20% and 40% are in sinus rhythm (106,107,108 and 109), between 7% and 35% are in junctional rhythm (106,108,109), up to 40% are in slow ectopic atrial rhythm (109), and 10% have atrial flutter (eFig. 70.0.12) (106,108,110,111). In their series of 249 patients, Gewillig et al. reported a 2.4% per year loss of sinus rhythm, and the presence of junctional rhythm carried a 2.1-fold increased risk of developing atrial flutter (p <.05) (108). In a multiinstitution report of 182 patients, the prevalence of atrial tachyarrhythmias was relatively constant, at 2.1% to 7.1% over 4.5 to 8.3 years of mean follow-up (111). In these reports, pacemakers were implanted in 5% to 11% of patients (112,113), usually for unacceptably low heart rates, for syncope, or as adjunctive therapy to antiarrhythmic drugs other than digoxin. Recently, even longer-term follow-up (23 years' median follow-up) after the Mustard operation in 86 patients has shown a 48% incidence of supraventricular tachycardia (mostly atrial flutter), and 22% had pacemakers (114). Risk factors for supraventricular tachycardia included pulmonary hypertension, right ventricular dysfunction, and junctional rhythm. This high incidence of SAND appears to be significantly greater in Mustard than in Senning patients late after repair (115).

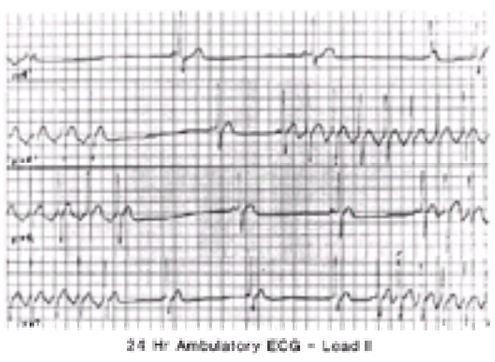


***e*FIGURE 70.0.12** Atrial flutter with 2:1 atrioventricular conduction **(A)** in a 25-year-old patient after Mustard operation. After cardioversion, rhythm is junctional **(B)**.

Sudden death occurs late after these operations in between 3% and 15% of patients (106,108,114,116), and this risk appears to be higher in the presence of poorer right ventricular function (117) and in patients having a history of atrial flutter (108). The latter point was also emphasized in a large collaborative study of 380 children with atrial flutter (110). The most frequent diagnosis was "postoperative Mustard operation," and the 6-year mortality rate in this subgroup was 21%. The risk of sudden death among those whose atrial flutter could not be eliminated was fourfold that of those who had had no recurrences. The mechanism of sudden death was thought to be 1:1 AV conduction during atrial flutter either directly causing ventricular fibrillation or followed by marked overdrive suppression of all subsidiary pacemakers with resultant asystole (*e*Fig. 70.0.13 and *e*Fig. 70.0.14). It is probable that another cause of sudden death in this group of patients is ventricular tachycardia, especially in those patients who have depressed right ventricular function or in those who have had additional ventricular surgery for VSDs or left ventricular outflow tract obstruction.



***e*FIGURE 70.0.13** Chronic atrial flutter in a 30-year-old man after Mustard operation. At rest, there is 2 to 3:1 atrioventricular conduction **(top)**, but with exercise there is 1:1 atrioventricular conduction **(bottom)**. (From Kanter RJ, Garson A. Arrhythmia in congenital heart disease. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia*. Baltimore: Williams & Wilkins, 1995:1131–1160, with permission.)



***e*FIGURE 70.0.14** The "tachy-brady syndrome" after the Mustard operation, in which atrial flutter, spontaneous terminations, and severe bradycardias are illustrated. ECG, electrocardiogram. (From Kanter RJ, Garson A. Arrhythmia in congenital heart disease. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia*. Baltimore: Williams & Wilkins, 1995:1131–1160, with permission.)

Arrhythmias after Fontan operation are of increasing interest because of improved long-term survival in this patient group. Driscoll et al. found 20% of 352 Fontan patients required antiarrhythmic drugs and/or pacemaker implantation at 5 to 15 years' follow-up (118). They attributed right atrial stretch, impaired ventricular function, and AV valve insufficiency as potential causes for the tachy-brady syndrome, although postoperative AV block occurred in several instances, and VT occurred in 6% of patients. Gewillig et al. found an 18% incidence of arrhythmias at 8-year follow-up, based on 78 long-term modified Fontan survivors (119). Multivariate analysis disclosed older age, increased right atrial size, and elevated pulmonary artery pressures as risk factors for arrhythmia development (p <.001). The most sobering report comes from the National Heart Hospital in London, England, where the actuarial arrhythmia-free survival for hospital survivors was only 60% at 10 years (120). Again, these patients tended to have higher mean right atrial pressures and lower ejection fractions.

Among Fontan patients, the specific surgical technique probably plays a role in the short- and medium-term incidences of supraventricular tachycardias. Animal studies have suggested that the total cavopulmonary connection (TCPC) is less arrhythmogenic acutely than the atriopulmonary connection, especially if the anterior suture line does not involve the crista terminalis (121). Clinical reports have shown a lower incidence of immediate and medium-term (2 to 8 years) postoperative atrial tachycardias in TCPC patients (122,123,124 and 125), and the 5-year arrhythmia-free survival rate is as high as 78% (122). The logic of reducing the portion of the right atrium included in the higher pressure systemic venous part of the circuit has been furthered by use of a complete extracardiac conduit. Amodeo et al. (126) reported late tachyarrhythmias in only four of 54 such patients, with a 5-year arrhythmia-free survival rate of 92%. Orthodromic reciprocating tachycardia has occasionally been observed in patients having undergone a Bjork-type Fontan operation (direct right atrial appendage to right ventricular outflow tract anastomosis) for TA. Presumably, they acquire conduction across the suture line (127).

Infants having hypoplastic left heart syndrome generally undergo the final stage (Fontan) at ages younger than has been conventional for other forms of single ventricle, often at younger than 2 years. Limited long-term follow-up has not shown more atrial tachyarrhythmias than have been observed in the other patient groups (128).

The incidence of pacemaker requirement after the Fontan operation ranges from 5% to 15% (118,129,130). The indications include tachy-brady syndrome, congenital AV block, or postoperative AV block and may be affected by surgical technique. There is evidence that the staged approach involving the "hemi-Fontan" procedure before the TCPC may increase risk of developing SAND (131). Finally, the reported incidence of late arrhythmic death overall is 2% to 3% (118,129,132).

Reports of small numbers of patients after total anomalous pulmonary venous connection (133) or ostium primum ASD (134) repairs have shown a high incidence of conduction abnormalities, including sinus, ectopic atrial, or junctional bradycardia or atrial flutter or fibrillation. Complete AV block may occur after ostium primum repair. Murphy et al. reported the natural history of 123 patients who had undergone repair of ostium secundum or sinus venosus ASDs at the Mayo Clinic (135). Late follow-up (27 to 32 years) revealed that the incidence of atrial flutter or fibrillation increased directly with age at repair: 4% if operated on at 11 years old or younger, 17% if at 12 to 24 years, 41% if at 25 to 41 years, and 59% if at older than 41 years. The incidence of pacemaker requirement was low for all groups (4% of total, including two with AV block). A more recent report has also shown that late postoperative atrial flutter or fibrillation was associated with older age at surgery (older than 40 years), the presence of preoperative atrial flutter or fibrillation, or the occurrence of immediate postoperative atrial arrhythmias (136).

It is pertinent to this discussion to note that most babies born today with simple D-TGA undergo the arterial switch operation instead of the Mustard or Senning procedure. Mid-term follow-up (24 to 29 months) after the arterial switch operation at two centers failed to demonstrate significant rhythm disturbances by 24-hour ECG monitoring from 250 infants (137,138). Electrophysiologic testing of 158 patients undergoing the arterial switch operation at Children's Hospital, Boston, revealed normal corrected sinus node recovery times and AH intervals in 97% of patients but a high incidence of simple atrial ectopy (139). At 2.1 years' mean follow-up, the incidence of supraventricular tachycardia was 5% and of VT, less than 1%.

Noninvasive Evaluation

Ambulatory rhythm recording is the cornerstone of patient surveillance after atrial surgery. Unless there are symptoms of sinus node dysfunction, 24-hour ambulatory ECGs are sufficient every 2 to 5 years. In patients having chronic fatigue and in those having syncope or dizziness at rest or with exercise, a 24-hour ECG and exercise test should be performed. Hesslein et al. performed treadmill tests on 25 children after Mustard operation at an average age of 10.2 years (140). Using a modified Bruce protocol, the maximum attained heart rates were more than two standard deviations below predicted in 70.4% of patients (p <.001). In 59.3%, heart rates remained abnormally low 5 minutes after exercise (p <.001). This relatively sudden drop in heart rate immediately after exercise may correlate with the frequently observed fatigue and dizziness that many patients experience immediately after exercise. Forty-seven percent of the patients tested had abnormally low exercise capacity. For patients having less frequent paroxysmal episodes of dizziness or palpitations, newer ambulatory ECG monitoring systems are invaluable. Syncopal episodes may merit a combined approach of invasive electrophysiologic testing and ambulatory event recording.

Electrophysiologic Testing

Electrophysiologic measures of sinoatrial node function have been reported to be abnormal in 33% to 50% of Mustard patients (141,142) and in 50% of Fontan patients (143). Atrial muscle electrophysiologic properties are abnormal in 41% to 90% (141,142 and 143), and atrial reentry tachycardia is inducible in 27% of Fontan patients (143) and in approximately one-half of Mustard patients (109). The clinical usefulness of these findings in the absence of symptoms is unproved. Therefore, we recommend *diagnostic* electrophysiologic studies after atrial surgery only in patients who have developed syncope or in those having palpitations suggestive of a sustained tachyarrhythmia and in whom noninvasive studies are inconclusive. Diagnostic cardiac catheterization and electrophysiologic study may also be helpful before pacemaker implantation to evaluate AV nodal function and to demonstrate anatomic patency of venous and atrial structures pertinent to permanent lead implantation. The usefulness of electrophysiologic studies for catheter ablation is discussed below.

Management

The recommendations of the American Heart Association/American College of Cardiology Joint Committee on Pacing as they relate to patients who have undergone atrial surgery (144) are to insert a pacemaker in any patient with (a) "symptomatic" bradycardia, defined as dizziness, lightheadedness, and near or frank syncope; marked exercise intolerance; or congestive heart failure (class I indication); (b) tachy-brady syndrome and a tachyarrhythmia requiring treatment with an antiarrhythmic drug other than digitalis that could suppress the sinus node (i.e., beta-blocking drugs, verapamil, quinidine, procainamide, disopyramide, flecainide, propafenone, sotalol, and amiodarone) (class IIa indication); or (c) complex congenital heart disease and asymptomatic sinus bradycardia with a resting rate of less than 35 beats/min or pauses exceeding 3 seconds (class IIa indication for children; class IIb indication for adolescents).

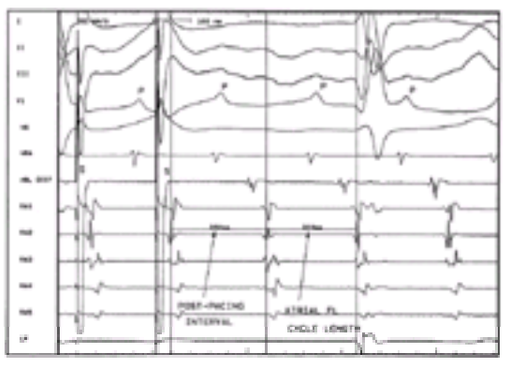
If symptoms are convincing but cannot be reproduced by ambulatory monitoring, tachyarrhythmias are not inducible, and there is moderate bradycardia while awake (less than 60 per minute in an infant younger than 2 years, less than 50 per minute in children aged 2 to 10 years, or less than 40 per minute in patients older than 10 years), then we recommend pacemaker implantation.

The second indication is reasonable in view of most clinicians' observations that progressive bradycardia and AV conduction abnormalities may occur in patients treated with many of these drugs. Implanting a pacemaker in such a patient may also protect against the severe bradycardia that may result after an episode of atrial flutter.

Atrial pacing after Mustard, Senning, or Fontan operations is now a standard part of the care of some of these patients (*e*Fig. 70.0.15) (145,146 and 147). In some instances, novel approaches to lead placement may be required. Advances in interventional catheterization have benefited some patients when superior vena caval baffle obstruction is present. Catheter-delivered stents not only relieve untoward hemodynamic abnormalities, but also may permit placement of intravenous pacing systems. If inadequate AV conduction is also present, dual chamber pacing is necessary. AV synchrony is especially important in Fontan patients, and ventricular pacing alone—even with rate adaptiveness—may not be acceptable (148). Dual-chamber epicardial lead systems or transvenous atrial and epicardial ventricular lead systems are required in these instances.

***e*FIGURE 70.0.15** Chest radiograph **(top)** from an 18-year-old woman after Mustard operation who has atrial reentry tachycardia requiring sotalol. Single-chamber pacing was performed with an active fixation atrial lead in the anatomic left (systemic venous) atrium. During electrophysiologic study, 1:1 atrioventricular conduction continued up to 150 beats/min. Twelve-lead electrocardiogram **(bottom)** from same patient showing atrial pacing, 1:1 atrioventricular conduction, and severe right ventricular hypertrophy.

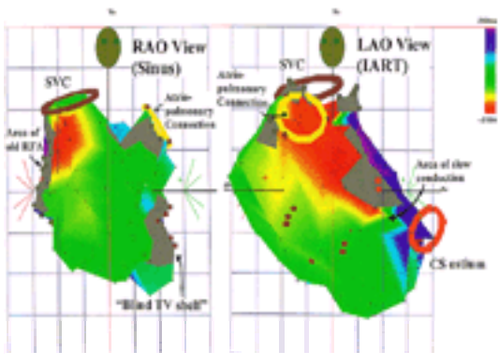
Tachyarrhythmias after the Senning or Mustard operations usually must be aggressively treated because sudden death in these patients is most likely linked to *tachy*arrhythmias. Patients who present with atrial flutter should undergo transvenous or transesophageal overdrive pacing termination or direct current cardioversion. Chronic therapy may not be necessary after an initial episode unless associated symptoms are severe or the patient has poor ventricular function. Treatment options include class III antiarrhythmic drug therapy, antitachycardia pacing (plus AV node–blocking drugs), and radiofrequency catheter ablation. Implantation of an antitachycardia pacemaker may obviate the need for second-line drugs, but efficacy of this modality must be demonstrated by electrophysiologic testing in the drug-free state. Radiofrequency ablation of atrial reentry tachycardia can now be performed with success rates at medium-term follow-up of 70% to 80% (149,150). This is now our preferred approach in patients with recurrent intraatrial reentry tachycardia (*e*Fig. 70.0.16).



***e*FIGURE 70.0.16** Electrophysiologic study from a 10-year-old patient with atrial flutter (FL) after Mustard operation. Illustrated is concealed entrainment with the postpacing interval approximating the tachycardia cycle length from the medial isthmus on the systemic venous side near the orifice of the inferior vena cava. Application of radiofrequency energy at the site interrupted the atrial flutter circuit. ABL DIST, proximal bipole atrial recording from mapping catheter within medial

isthmus; HRA, high right atrial channel; LV, left ventricular channel; P, surface P waves during atrial flutter; RA1–5, atrial recordings from a multipole electrode catheter positioned along the inferior limb of the systemic venous baffle, with RA5 being most superior and RA1 being at the mid-isthmus.

After the modified Fontan operation, medical suppression of tachyarrhythmias may be difficult. The requirements for AV synchrony and adequate diastolic filling time make arrhythmia control especially crucial (151). For these challenging patients, combinations of antiarrhythmic drugs, often including amiodarone, is sometimes necessary. Antitachycardia pacing is sometimes possible (147) but may result in acceleration of one atrial tachycardia to another. Radiofrequency catheter ablation of intraatrial reentry tachycardia substrates is being performed in these patients with increasing success rates. Standard techniques to identify areas critical to common atrial flutter circuits in the normal heart are being successfully applied, including recognition of presystolic and split potentials and entrainment with concealed conduction and a short postpacing interval. Successful ablation of more than 70% of these circuits is now being achieved (152,153 and 154). Even better results can be expected with the recent advent of electroanatomic mapping techniques (*e*Fig. 70.0.17) (155) and chilled-tip ablation catheters.



***e*FIGURE 70.0.17** Electroanatomic maps from a 27-year-old man who had undergone Fontan operation (atriopulmonary connection) for tricuspid atresia and who had undergone a prior attempt at radiofrequency ablation (RFA) (old radiofrequency ablation) for intraatrial reentry tachycardia (IART) with recurrence. On the left is a right anterior oblique (RAO) projection of the right atrium in sinus rhythm. On the right is a left anterior oblique (LAO) projection of the right atrium during IART. Successful RFA was performed in the “area of slow conduction.” CS, coronary sinus; SVC, superior vena cava.

Among Fontan patients having undergone an atriopulmonary connection and who have intraatrial reentry tachycardia and suboptimal hemodynamics, a surgical approach has recently been reported (156). This involves conversion to a TCPC-type Fontan with concomitant intraoperative mapping and cryoablation of intraatrial reentry tachycardia circuits. These patients experienced improvement in hemodynamic status as well as arrhythmia control. The inferomedial right atrium, superior rim of the old ASD patch, and the lateral right atrium were the regions generally requiring cryoablation lesions. At 25 months’ median follow-up, only two of 12 patients still required antiarrhythmic drugs (157).

Chronic Arrhythmias after Operation on the Ventricles

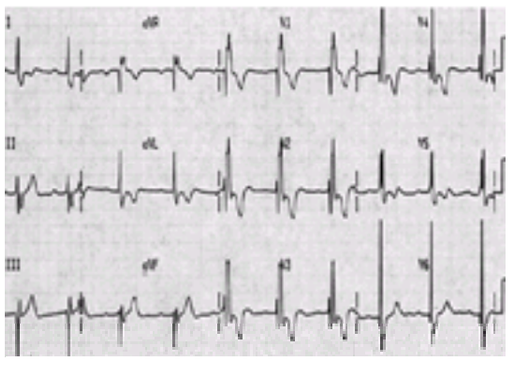
Most studies of chronic arrhythmias occurring after operation on the ventricles have been done in patients with tetralogy of Fallot (158,159,160,161,162 and 163). In general, the less serious the defect, the less serious the outcome. For example, late sudden death occurs in approximately 4% of patients who have had VSD repair (22,164), 0% to 5% of those who have had tetralogy of Fallot repair (158,163), 18% of those who have had double-outlet right ventricle repair (165), and 18% of those who have had surgery for truncus arteriosus with single pulmonary artery (166).

The surgical repair of tetralogy of Fallot always involves patch closure of the VSD and resection of some infundibular muscle, usually through a right infundibulotomy. Pulmonary regurgitation will always result if the right ventricular outflow tract enlargement must extend across the pulmonary valve annulus.

Conduction Disturbance

Incidence

After repair of tetralogy of Fallot, approximately 80% of patients have complete right bundle branch block; an additional 11% have the combination of right bundle branch block with left-axis deviation; and 3% have the combination of right bundle branch block, left-axis deviation, and first-degree AV block (*e*Fig. 70.0.18) (158). Early studies in these patients suggested that the combination of right bundle branch block with left-axis deviation (167) or with additional first-degree AV block (168) was a predictor of late sudden death. More recent experience has found that late sudden death is not often due to conduction disturbances.



***e*FIGURE 70.0.18** Twelve-lead electrocardiogram from a 15-year-old patient after repair of tetralogy of Fallot, illustrating first-degree atrioventricular block, left-axis deviation, and right bundle branch block.

Clinical Significance

Among patients having syncope after ventricular repair of congenital heart defects, electrophysiologic findings of prolonged HV interval or abnormally slow rate of AV Wenckebach block may help guide clinical decision making (see below). However, the very common finding of right bundle branch block after right ventriculotomy appears to carry a benign early- and mid-term prognosis. It only obscures the ECG with regard to interpretation of ventricular dilatation or hypertrophy. Perhaps more important, in those patients with “true” (proximal?) right bundle branch block, the development of left bundle branch block that occasionally accompanies atherosclerotic heart disease later in life will place these patients at risk for complete AV block.

Evaluation

On follow-up ECG, the patterns of right bundle branch block, right bundle branch block/left-axis deviation, and right bundle branch block/left-axis deviation/first-degree AV block are usually associated with normal HV intervals in instances when intracardiac studies were performed (169). The recommendation has therefore been made that terms such as *bifascicular* and *trifascicular block* not be applied to these patients.

Even if intracardiac conduction intervals support the diagnosis of “true” bifascicular or trifascicular block, we become concerned only if there is type II second-degree AV block, complete AV block, marked HV interval prolongation (more than 100 ms) (even in the absence of symptoms), or syncope with any HV interval prolongation (and no inducible tachyarrhythmias). In the presence of transient postoperative second-degree AV block or complete AV block (lasting less than 7 days

postoperatively), 24-hour ECG monitoring should be performed before discharge and then regularly. All patients after ventricular surgery involving the ventricular septum should have 24-hour ECG monitoring every 2 to 5 years. In the patient who has had an operation on the ventricles and a negative noninvasive evaluation but has syncope or presyncope, electrophysiology study is indicated. The cause of syncope could be AV block, ventricular arrhythmias, or atrial flutter with rapid AV conduction.

Limited data are available from intracardiac assessment of the conduction system in these patients. Friedli and Bolens found AV conduction abnormalities in 10 of 52 patients after repair of tetralogy of Fallot (169). Three patients developed block below the bundle of His with atrial pacing rates of less than 120 per minute, and two of them developed complete AV block within 5 years. Based on these limited data, we would consider electrophysiologic testing in a patient with AV Wenckebach rates of less than 120 per minute during exercise testing to assess the level of block. Otherwise, routine electrophysiologic testing in an asymptomatic patient is not indicated.

Management

A pacemaker should be implanted in any child with second-or third-degree AV block lasting more than 7 days postoperatively after heart surgery. Otherwise, the late onset of paroxysmal changes in level of consciousness merit some combination of 24-hour Holter monitoring, ambulatory event monitor placement, and invasive electrophysiologic testing. If for any reason electrophysiologic testing is performed and there is a prolonged HV interval or AV block below the His at atrial paced rates of less than 120 per minute, these patients should be followed closely even if asymptomatic. The value of exercise testing to determine the maximum conducted sinus rate in these patients is unproved.

Occasional patients undergo pacemaker insertion in the postoperative period but regain AV conduction shortly thereafter. Data are not available to predict their risk of recurring AV block. The issue usually comes to bear once their pulse generator reaches depletion parameters and elective replacement is required. In such instances, we would use stringent criteria from 24-hour ECG monitoring and electrophysiologic testing (normal AV Wenckebach rate and normal HV interval) before considering discontinuation of pacing.

Ventricular Tachyarrhythmias

Incidence

During long-term follow-up of repair of tetralogy of Fallot (5 to 10 years), ventricular arrhythmias were evident in approximately 5% to 10% of patients on routine ECG (158,170,171), 20% to 40% on treadmill testing (158,170,171), and 40% to 60% by 24-hour ECG monitoring (158,163,170,171). The severity of ventricular ectopy appears be related to older age at repair (163,172,173), elevation of right ventricular systolic pressure (158,163,170,173), and duration since surgery (163,170,173). Depressed right ventricular ejection fraction (173), elevation of right ventricular end diastolic pressure (170), duration of cardiopulmonary bypass during repair, and presence of a Potts anastomosis (172) have also correlated with incidence of ventricular arrhythmia in single reports. In contrast to these reports, Walsh et al. reported on 184 late-surviving patients, all of whom had had tetralogy of Fallot repair before 18 months of age (161). At a mean of 60 months' follow-up, there were no late deaths caused by arrhythmias, and only one of 41 patients had greater than Lown grade I ventricular ectopy by Holter monitoring. It appears that the earlier age of repair may protect the heart from deleterious changes accrued from long-standing right ventricular hypertension, left ventricular volume overloading, and systemic desaturation.

The overall incidence of late SCD after repair of tetralogy of Fallot ranges from 1.5% to 5% (158,163,168,172). Most recent reports suggest ventricular arrhythmias to be the etiology (158,163,168,170,172).

Experimental Basis for Ventricular Arrhythmias

The histopathologic findings in the right ventricles in patients who have died after repair of tetralogy of Fallot include obvious scars in the infundibular region and generalized increase of fibrous tissues throughout the right ventricle compared with age-matched controls (20). In the investigation of Anderson and Ho, this was most prominent in the hearts of children repaired after age 5 years (20).

Insight into the pathogenesis of ventricular arrhythmias after right ventricular surgery is provided by a canine model, in which puppies underwent right ventriculotomy, pulmonary artery banding, or both (174). At a follow-up period representing adolescence, ambulatory ECG monitoring and ventricular programmed stimulation revealed a higher incidence of nonsustained ventricular ectopy in the group having right ventricular hypertension from pulmonary artery banding compared with both control animals and those having undergone only ventriculotomy. The group having undergone both ventriculotomy and banding had, in addition, a higher incidence of inducible sustained ventricular tachycardia.

The effect of postoperative right ventricular volume overloading caused by pulmonary valve insufficiency has also been investigated in dogs (175). When compared with control animals undergoing only right ventriculotomy, dogs having pulmonary valve insufficiency, with and without right ventricular outflow tract obstruction, had more PVBs by postoperative Holter monitoring. The relationship of spontaneous single PVBs to development of sustained arrhythmias in this group was not reported.

In summary, the preoperative milieu of chronic right ventricular hypertension and systemic desaturation likely predisposes patients to postoperative ventricular arrhythmias, making earlier age of repair standard practice at the present time. *Post*operative right ventricular hypertension and probably volume overloading place patients at additional risk.

Evaluation

The main goal of routine evaluation of patients after ventricular surgery is to identify individuals who are at risk for symptoms or death from ventricular arrhythmias. Unfortunately, there is no gold standard for determining such risk. he 12-lead ECG, chest radiograph, 24-hour rhythm monitoring, treadmill exercise test, and echocardiogram all have roles in the outpatient surveillance of these patients. In those with poor hemodynamics, follow-up is stricter than in those with excellent hemodynamics (eFig. 70.0.19). Equivocal or minor symptoms may be evaluated with event recorders, but paroxysmal palpitations or syncope merit invasive electrophysiologic study.

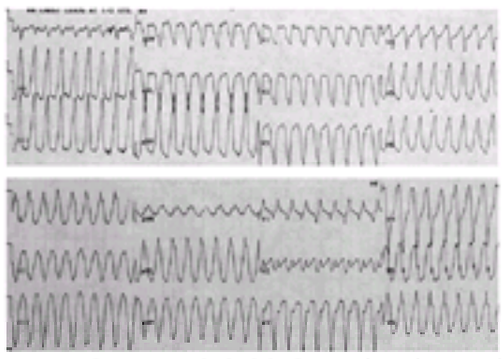
***e*FIGURE 70.0.19** Continuous Holter recording from a 13-year-old patient after repair of tetralogy of Fallot with residual right ventricular hypertension due to multiple peripheral pulmonary artery stenoses. Patient was receiving quinidine at the time. Illustrated is ventricular bigeminy, nonsustained monomorphic ventricular tachycardia, and nonsustained torsades de pointes ventricular tachycardia. During electrophysiology study, polymorphic ventricular tachycardia was inducible with double ventricular extrastimuli. Patient's Holter normalized and the tachycardia was rendered noninducible with mexiletine. (From Kanter RJ, Garson A. Arrhythmia in congenital heart disease. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia*. Baltimore: Williams & Wilkins, 1995:1131–1160, with permission.)

Recent reports have shown that excessive duration of the QRS complex may prove to be a valuable screen for patients at risk of having dangerous ventricular arrhythmias (ventricular tachycardia and sudden death). The QRS duration appears to be sensitive (176) and perhaps specific (177) for such risk, with a cutoff value of 180 ms or more providing the greatest accuracy. The coexistence of increased JT interval dispersion may enhance the predictive value, suggesting that both repolarization and depolarization abnormalities are important. One study also found a correlation between an increased cardiothoracic ratio by chest radiograph and QRS prolongation (176).

Although there may be some correlation between the occurrence of complex ventricular arrhythmias (couplets, multiform PVBs, or ventricular tachycardia) on 24-hour rhythm monitoring and inducibility of ventricular tachycardia by electrophysiologic testing (163), the relationship of such ectopy to clinical events is controversial. Garson et al.'s report of 488 patients showed that 33% of 21 patients having high-grade ventricular ectopy by Holter monitoring later died, compared with none of the 421 having no ventricular ectopy (178). These findings were recently corroborated, particularly in patients having poor ventricular function or residual structural defects (179). However, the value of Holter monitoring has been called into question by Cullen et al.'s report of 47 patients prospectively followed for 12 years after an original postoperative Holter (180). Those originally having high-grade ventricular ectopy (including seven with nonsustained ventricular tachycardia) were no more likely to later have clinical VT or to die suddenly than those not originally having ventricular ectopy, irrespective of hemodynamic status. To summarize, we view the presence of high-grade ventricular arrhythmias by ambulatory monitoring to merit further investigation and/or treatment when associated with poor ventricular function, pressure or volume loading of the right ventricle, significant cardiomegaly, or a QRS duration of 180 ms or more.

The value of other noninvasive tests to help manage patients who have undergone ventricular surgery for congenital heart disease is in evolution. Exercise testing (170), cardiopulmonary testing with inspired gas analysis, signal-averaged ECG (181), spectral analysis of heart rate variability, and magnetic resonance imaging will all likely play roles in the care of this diverse patient group.

Symptoms requiring invasive electrophysiologic testing after ventricular surgery include sustained palpitations and syncope (eFig. 70.0.20). The demonstration of symptomatic sustained monomorphic ventricular tachycardia by noninvasive means is an indication for electrophysiologic testing as a guide for antiarrhythmic drug selection (162) or for radiofrequency catheter ablation. In the absence of symptoms, we would also consider ventricular programmed stimulation if a patient has echocardiographic or catheterization-proven impairment of hemodynamics (see above), as well as either Lown grade III ectopy or greater by 24-hour ECG or high-grade ventricular ectopy during exercise testing.



P>***e*FIGURE 70.0.20** Sustained ventricular tachycardia having two morphologies during electrophysiologic study from a 25-year-old man having recurrent syncopal episodes after tetralogy of Fallot repair. Photoargon- and cryoablation during surgery successfully interrupted the tachycardia circuit(s) emanating from around the right ventricular outflow tract patch. (From Kanter RJ, Garson A. Arrhythmia in congenital heart disease. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia.* Baltimore: Williams & Wilkins, 1995:1131–1160, with permission.)

Electrophysiologic studies have not been standardized in this patient group with respect to indications and pacing protocols. Using a high-specificity protocol (two extrastimuli) from a single institution, Garson et al. showed that sustained or nonsustained VT was more commonly inducible in patients having elevated right ventricular systolic pressure, reduced right ventricular ejection fraction, high-grade ventricular ectopy by Holter monitoring, or a history of syncope compared with control tetralogy patients (170). Similar results were reported by Chandar et al. in a multicenter study (163). Interestingly, in this report, of five late deaths, none had had inducible ventricular tachycardia, but all had at least one risk factor as defined above. More recently, Alexander and coworkers applied sophisticated statistical methods to a group of 130 patients who had undergone programmed ventricular stimulation; 33% had tetralogy of Fallot, 25% D-TGA, and 12% left ventricular outflow tract obstructive lesions (182). A positive study was associated with a six-fold increased risk of decreased survival and was 87% sensitive in predicting mortality. However, of 21 patients having had documented clinical VT, only 14 had a positive study. Further, the positive predictive value of SCD was only 20%. This group of patients had a 3% annual mortality and event risk, much higher than any previous reports. The subjective decision to perform ventricular programmed stimulation identified a group with a high prevalence of poor outcome.

It is becoming evident that a search for supraventricular tachycardias is also indicated in symptomatic patients after ventricular surgery (182,183), especially atrial flutter and AV node reentry tachycardia. Among 53 tetralogy patients at 23 years' median age, Roos-Hesselink et al. demonstrated atrial flutter or fibrillation in 23% and other supraventricular tachycardias in 11% (183).

Management

When considering treatment for ventricular arrhythmias after ventricular surgery, two questions usually need to be answered: whom to treat and by what means should efficacy be established?

In two small series, serial electrophysiology studies identified antiarrhythmic drugs (mostly phenytoin and propranolol) that effectively suppressed ventricular tachycardia reinducibility (162,184). In follow-up, no patient had clinical ventricular tachycardia, but the positive predictive value is less well established. We have found that quinidine and procainamide are not very useful drugs for sustained ventricular tachycardia in these patients, and class IC agents may be especially proarrhythmic (185). Anecdotal experience has shown the value of amiodarone or sotalol in some patients.

Because of potential drug side effects, nonpharmacologic therapy has become more attractive in recent years. After complete tachycardia circuit mapping in the electrophysiology laboratory, surgical resection, cryoablation (186), and argon photoablation have all met with variable success. Radiofrequency catheter ablation has been used to successfully interrupt macroreentry VT circuits in several patients (187,188), even when there are multiple VT circuits and when VT is poorly hemodynamically tolerated (188). Finally, implantable cardioverter-defibrillators provide antitachycardia pacing as well as the safety net of cardioversion or defibrillation, if necessary (189).

Less clear are the indications for treating asymptomatic patients with high-grade ventricular ectopy by 24-hour ECG monitoring or exercise testing. If their hemodynamics are acceptable, we would only follow these patients closely. In those with poor hemodynamics, we would consider ventricular programmed stimulation to help identify patients with inducible sustained tachycardia and to help guide medical therapy. Until there are randomized clinical trials involving treatment and nontreatment of such patients with induced ventricular tachycardia, we recommend treatment with antiarrhythmic drugs. Drugs with low proarrhythmic risk (beta-blocker, phenytoin, mexiletine, and perhaps sotalol) are emphasized in these patients.

Arrhythmias after Repair of Other Congenital Heart Defects

Ebstein's Anomaly of the Tricuspid Valve

In the oldest series of Ebstein's patients undergoing surgical repair, the procedure included accessory pathway interruption in those six with WPW syndrome (15). At 40 months' mean follow-up, one patient still had WPW syndrome, 22% of 18 having PSVT had persistent symptoms, and 30% of those having had AF/flutter had recurrences. Newer surgical techniques for improving tricuspid valve and right heart function, as introduced by Carpentier, have been shown to nearly eliminate atrial tachycardias at 58 months' median follow-up (190).

Although surgical ablation of accessory pathways is rarely currently required, it is at least of historical interest that in the Duke University experience of 422 patients having WPW syndrome and undergoing surgical ablation, those 38 also having Ebstein's had similar postoperative 10-year survival (92.4%), freedom from significant arrhythmias (82%), incidence of AF (9%), and incidence of becoming disabled (9.4%) to the control group having only WPW syndrome (191). Transcatheter ablation of accessory pathways is nevertheless more attractive than surgical and may make subsequent congenital surgery less risky in this disease.

Pulmonary Valve Stenosis

The NHS-2 by Wolfe et al. followed 182 patients with pulmonary valve stenosis, and 92.8% had undergone surgical valvotomy (17). Patients in all age groups had supraventricular premature beats at a rate exceeding the upper limits of normal for age. For all ages, 11.2% of the 169 surgically managed patients (p <.001 vs. control) had PVBs at a rate exceeding upper limits of normal, and six (8.3%) had ventricular tachycardia. At least one serious arrhythmia was present in 28% of the surgically treated group. Age on admission was the only independent predictor of occurrence of a serious arrhythmia. The authors concluded that prevalence of arrhythmias was higher for these patients than for the control population but that serious arrhythmias were less commonly observed than in patients with either aortic

valve stenosis or VSD. Furthermore, the occurrence of sudden unexpected death (0.05%) was significantly lower than in patients with either of the other defects (p <.0001).

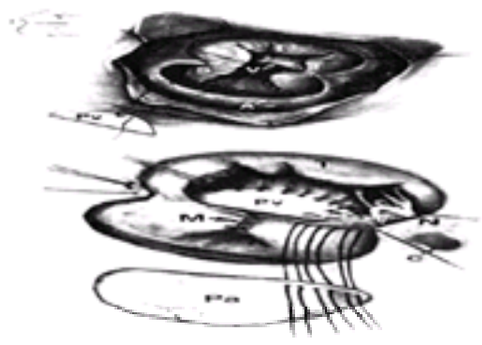
There is new evidence that balloon valvotomy may be associated with less ventricular ectopy than observed after surgical valvotomy at medium-term follow-up (192), probably due to the fact that there is less pulmonary insufficiency after balloon valvotomy. It has not yet been proved whether reduction in pulmonary insufficiency by homograft valve insertion will reduce ventricular ectopy (193).

Ventricular Septal Defect

The most extensive data from patients after surgical closure of VSD comes from the NHS-2 (15). Serious arrhythmias (as defined in the section Pulmonary Valve Stenosis and excluding patients with Eisenmenger physiology) were present in 36.8% of patients. Of those having undergone surgery, the risk of having serious arrhythmias was increased in those functioning at worse than New York Heart Association class I or in those having cardiomegaly. At the time of final status, the occurrence of sudden unexpected death was 4.2%.

Atrioventricular Septal Defect

Repair of this defect requires suture lines near the specialized conduction system. In a small series of 14 patients, postoperative electrophysiologic studies demonstrated first-degree AV block in nine (AH prolongation in two, HV prolongation in one, and both in three), sinus node dysfunction in three, “AV nodal dysfunction” in four, and right bundle branch block in 13 (22). Postoperative complete AV block is now uncommon after repair of this lesion, related to modification in surgical technique (eFig. 70.0.21).



***e*FIGURE 70.0.21** Modern repair of complete atrioventricular septal defect. An atrial septal defect patch (Pa) is sutured along the mitral side of the inferior bridging leaflet of the common atrioventricular valve to avoid damage to the posteriorly deviated atrioventricular node (N). The ventricular septal defect patch (Pv) is sutured slightly off the margin of the crest of the ventricular septum (V) to avoid damage to the penetrating bundle. A, rim of atrial septum; C, coronary sinus ostium; M, sutured cleft in newly formed mitral valve; S, superior bridging leaflet of common atrioventricular valve; T, tricuspid. (From Ungerleider RM. Congenital heart disease. In: Sabiston DC, ed. *Atlas of cardiothoracic surgery.* Philadelphia: WB Saunders, 1995:255–372. with permission.)

Postoperative evaluation by Holter monitoring has demonstrated a 33% incidence of ventricular and a 10% incidence of atrial arrhythmias in 106 patients (194). Ectopy was more likely in larger (and therefore older) patients if they had a higher postoperative right ventricular end diastolic dimension, if they had a larger VSD, or if there was postoperative right bundle branch block. There were no reported episodes of sudden death.

Left Ventricular Outflow Tract Obstructive Lesions

In a series of 117 young patients with AS (younger than 40 years old), in which 61 underwent surgical valvulotomy and 30 underwent valve replacement (17), the prevalences of both PSVBs and PVBs were higher than a control population. Serious arrhythmias occurred in 44.8% of patients and were significantly more likely in surgically managed patients (p = .0056), although ventricular tachycardia occurred in 10.1% of the valvotomy and 13.9% of the valve replacement groups. Both were significantly greater than the general population (p <.0001). An elevated left ventricular end diastolic pressure, the coexistence of aortic insufficiency, and male gender were associated with increased risk of having a serious arrhythmia. Of greatest concern, at last follow-up, the occurrence of sudden unexpected death was 5.4%, significantly higher than in the group with pulmonic stenosis. Silka et al. demonstrated incremental risk of sudden death after 20 years *despite repair* of AS or coarctation of the aorta (195).

CONTROVERSIES AND PERSONAL PERSPECTIVES

The majority of clinically important arrhythmias associated with congenital heart disease are either bradycardias caused by surgical injury to the specialized conduction system or reentrant tachycardias related to artificial or natural conduction obstacles often in combination with residual hemodynamic perturbations.

Most patients having postoperative sinus or AV node dysfunction may be adequately paced using current technology. However, when epicardial pacing is required in a heavily scarred heart, such as after the Fontan procedure or when there are residual intracardiac shunts, active fixation leads having a high impedance and a low chronic pacing threshold are still not available. The only current steroid-eluting epicardial lead must be sutured to the epicardium, which may be covered by fibrotic scar from prior surgeries. Thus, a permanent plunge electrode having all of the desired electrical properties would be ideal. Implantation of epicardial systems may someday be performed thoracoscopically, eliminating the need for repeat thoracotomies. This will be important even for atrial leads following the newer types of Fontan surgery because transvenous lead placement may be obviated by the exclusion of natural atrial tissue from the systemic venous circulation. With regard to replacing old systems, removal of transvenous leads because of lead failure or fracture or because of infection will soon be facilitated by new laser extractor technology.

Physiologic sensors for patients with chronotropic incompetence and who require epicardial pacing systems are not yet available. Motion sensors are adequate for most of these patients, but for those with sinus node dysfunction and poor ventricular function, a system responding more to the autonomic nervous system would be desirable.

Atrial reentrant tachycardias after Mustard or Senning surgery will be only of historical interest within about four decades, as the indications to perform those procedures will continue to be very limited compared with those in the past because the success of the arterial switch operation for simple transposition of the great arteries. But until then, improved catheter ablation techniques hold promise for the majority of these patients. Newer channel-specific, potassium channel–blocking drugs may be of value for the remainder. After the Fontan operation, catheter ablative therapies of atrial reentry tachycardias will improve with multiplane mapping systems and electrical activation–directed targets instead of fluoroscopy guidance. However, the best option will be surgical innovations designed to eliminate the atria altogether from the high-pressure systemic venous circuit, reducing the incidence of these tachyarrhythmias. When this is not possible, collaboration between the surgeon and electrophysiologist to create “prophylactic incisions” that prevent reentrant circuits at the time of the Fontan operation is an exciting concept on the horizon.

Therapies for ventricular tachyarrhythmias after ventricular surgery are sufficiently advanced to prevent SCD and maintain a reasonably good quality of life in the vast majority of affected individuals. Improved outcomes from radiofrequency ablation of macroreentrant circuits related to suture lines will be seen when higher energies can be used with chilled-tip catheters. Among patients having hemodynamically stable monomorphic VT, radiofrequency ablation should become first-line therapy. Patients having faster VT or who have survived episodes of near SCD will continue to benefit from the rapid advances in implantable cardioverter-defibrillator technology. However, far more difficult than the therapeutic options remains the task of ascertaining which patients are at risk for VT or SCD. Controlled studies are hampered by (a) the inability to ethically create control groups; (b) the relatively low incidence of these diseases compared with that of other cardiovascular diseases in Western society and, hence, the dependence on multiinstitution trials; and (c) the nonuniformity of surgical techniques between institutions and between surgical eras within each institution. The specific questions to be answered appear to center around the value of noninvasive testing—that is, ventricular ectopy by ambulatory monitoring, ectopy produced by exercise testing, right ventricular systolic function and diastolic volume, left ventricular function, the presence of late potentials, and the QRS duration—and of ventricular programmed stimulation in predicting which patients are at risk for SCD or sustained VT. It is likely that the risk factors are quite different and that ventricular function is relatively more important in predicting those at risk for SCD, whereas macroreentrant VT is more determined by a combination of surgical technique and ventricular dilatation. A prospective approach uniformly using serial invasive and noninvasive techniques in all patients with any of the currently accepted risk factors—that is, age at repair, elevated right ventricular systolic pressure, severe pulmonary valve insufficiency, left ventricular dysfunction, QRS

duration of more than 0.14 seconds, increase in ectopy during exercise, or high-grade ectopy during ambulatory monitoring—would be most likely to bring order to the field. This would require institutional commitment, as its completion would take decades and, therefore, generations of investigators.

THE FUTURE

Ongoing natural history studies will continue to help determine the optimal timing of congenital heart surgery in an effort to minimize long-term postoperative arrhythmias. Modifications in surgical techniques are also being designed to help reduce the risk for postoperative arrhythmias. This is especially important in the Fontan operation. New therapeutic techniques include (a) development of steroid-eluting active fixation leads, so vital after many congenital heart operations; (b) new antiarrhythmic drugs, especially channel-specific potassium channel blockers; and (c) advances in intracardiac mapping of reentry tachycardias to help guide radiofrequency ablation of intramuscular reentrant circuits. Finally, it is likely that multiinstitution collaborative efforts similar to the study of coronary artery disease will be performed in patients after tetralogy of Fallot repair so that we may determine who truly is at risk for ventricular tachyarrhythmias and SCD, thus making possible a standard approach to screening these patients.

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71

SYNCOPE

DAVID G. BENDITT

“ Indicates text or graphics that appear only in the electronic versions of this text.”

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OVERVIEW

Syncope—a syndrome of relatively limited duration with subsequent spontaneous recovery and characterized by the sudden loss of consciousness and postural tone—is a common medical problem and an important cause of emergency department visits and hospital admissions (1,2,3,4,5,6,7,8,9 and 10). It has been estimated that approximately one-third of individuals experience a syncopal episode during their lifetime (10). Susceptibility to syncope increases in association with advancing age and increasing infirmity (10,11). Thus, in the Framingham experience (10), the prevalence of “isolated” syncope (i.e., syncope in the absence of apparent neurologic or cardiovascular disease) increased from 8 in 1,000 person-examinations in the 35- to 44-year-old age group to approximately 40 in 1,000 person-examinations in the >75-year-old age group. However, in a presumably more infirm population (i.e., elderly individuals confined to long-term care institutions), Lipsitz et al. (11) reported an annual incidence of syncope as high as 6%.

Apart from first syncopal events, approximately 35% of syncope patients experience recurrences within 3 years of follow-up (10,11,12 and 13). A history of recurrent syncope at the time of initial presentation—especially if the recurrences have been spread over a relatively long period—is a strong predictor of future recurrences (12,13). In one report, more than five lifetime syncope recurrences were associated with a 50% chance of recurrence in the following year (12).

PATHOPHYSIOLOGY

The minimum oxygen requirements needed to maintain consciousness have been estimated to be in the range of 3.5 mL per 100 g tissue per minute (14,15). In healthy young or middle-aged individuals, cerebral blood flows are typically 50 to 60 mL per 100 g tissue per minute; consequently, minimum oxygen delivery requirements are easily met. However, in older or ill patients with reduced oxygen carrying capacity or diminished cardiac output, the safety factor for oxygen delivery may be more precarious. It has been estimated that a drop in cerebral oxygen delivery of ³20% is sufficient to cause loss of consciousness.

Cerebral perfusion is critically dependent on systemic arterial pressure. Thus, factors that diminish systemic arterial pressure (e.g., decreased cardiac output or peripheral vascular resistance) may impair cerebral perfusion. In syncope patients, decreased venous filling is often a major factor in triggering a reduced cardiac output. Excessive pooling of blood in dependent parts of the body or diminished blood volume predisposes the patient to syncope. Impaired cardiac output may also be the result of tachyarrhythmias or bradyarrhythmias, especially in the setting of left ventricular dysfunction, valvular heart disease, volume depletion, or abnormal vascular reactivity. In terms of vascular resistance, inadequate vasoconstriction or inappropriate vasodilatation may contribute to syncope by undermining cerebral perfusion pressure. In fact, inappropriate vasodilatation is the main cause of fainting in reflex syncopal syndromes. Vasodilatation resulting in diminished cerebral perfusion also can contribute to lightheadedness and syncope in association with thermal stress (e.g., hot environments, excessive exercise). Impaired capacity to increase vascular resistance adequately during upright posture is critical in orthostatic hypotension, syncope associated with use of vasoactive drugs, and patients with autonomic neuropathies (14,15,16,17 and 18). Cerebral hypoperfusion may also result from an abnormally high cerebral vascular resistance (e.g., due to low carbon dioxide tension in hyperventilation syndromes).

CLASSIFICATION OF THE CAUSES OF SYNCOPE

The classification of the causes of syncope is found in Table 71.1.

TABLE 71.1 SYNCOPE: DIAGNOSTIC CLASSIFICATION

Neurally Mediated Reflex Syncopal Syndromes

The neurally mediated syncopal syndromes (Table 71.2) comprise a variety of pathophysiologically related conditions. For the most part, clinical distinctions are based on the source of the “trigger” for the episodes (e.g., pain, carotid sinus stimulation, cough, micturition). In this regard, the presumed triggering neural signals may arise

within the central nervous system (CNS) itself (e.g., syncope associated with fear or anxiety), or from any of a number of peripheral “receptors” that respond to stimuli of various types (e.g., mechanical, chemical, painful). The nature of these receptors is perhaps best understood in carotid sinus syncope and postmicturition syncope. In carotid sinus syndrome, the afferent aspect of the reflex loop typically is believed to arise from stimulation of autonomic receptors in the cervical region. However, it now seems likely that, to trigger the syndrome, carotid sinus stimulation may need to interact with the failure of parallel CNS inputs from the ipsilateral neck muscles (19). In typical vasovagal syncope (Fig. 71.1), the location and nature of the trigger sites are usually less certain. Cardiac mechanoreceptors, along with other central mechanoreceptors and chemoreceptors, appear to contribute to the afferent neural traffic (20,21,22,23,24,25 and 26).

Emotional syncope (common or vasovagal faint, malignant vasovagal faint)
Carotid sinus syncope
Gastrointestinal stimulation
Swallow syncope, defecation syncope
Micturition syncope
Cough syncope
Sneeze syncope
Glossopharyngeal neuralgia
Airway stimulation
Raised intrathoracic pressure
Brass or wind instrument playing, weightlifting

TABLE 71.2 NEURALLY MEDIATED SYNCOPAL SYNDROMES

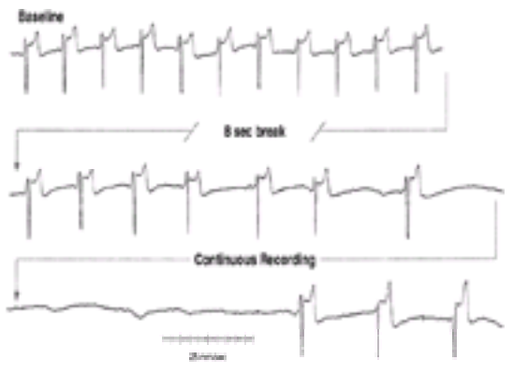


FIGURE 71.1 Recording from an in-hospital electrocardiogram monitor illustrating bradycardia associated with a spontaneous vasovagal faint accompanying an abrupt hemorrhage after an invasive cardiac procedure.

The afferent neural signals in neurally mediated syncopal syndromes initiate (via the medullary cardiovascular control areas) an efferent response comprised of bradycardia, which may be marked or “relative,” and vasodilation. In terms of causing symptomatic hypotension, the relative importance of bradycardia and vasodilatation differs among patients—perhaps even within patients at various times. Thus, certain syncopal events may be characterized as primarily “cardioinhibitory” (due to bradycardia), whereas other events are principally “vasodepressor” (due to vasodilation). The majority of cases are, in fact, due to a combination of bradycardia and vasodilation (“mixed” response).

Orthostatic Syncope

Orthostatic syncope is often termed *postural hypotension* or *orthostatic hypotension* (Table 71.3). Volume depletion (often iatrogenic) (22,23,27,28,29,30,31,32,33 and 34) or neurologic disturbances of vascular control due to concomitant disease are the most frequent causes of orthostatic syncope. In certain cases, however, patients may manifest a form of primary autonomic failure with inadequate reflex adaptations to upright posture.

Primary autonomic failure
Pure autonomic failure
Autonomic failure with multiple system atrophy
Parkinson’s disease with autonomic failure
Secondary autonomic failure
Diabetes mellitus
Volume/fluid depletion
Autoimmune acute and subacute dysautonomias (e.g., Guillain-Barré syndrome, myasthenia gravis)
Autonomic neuropathy associated with malignancies
Metabolic diseases (e.g., porphyria, Fabry’s disease)
Central nervous system infections (e.g., syphilis, Chagas disease)
Hypothalamic and midbrain lesions/tumors (e.g., craniopharyngioma)
Spinal cord lesions/tumors
Drug/toxin-induced autonomic failure
Alcohol
Diuretics
Sedatives/tranquilizers: phenothiazines, barbiturates
Vasodilators (e.g., peripheral and central sympatholytic agents)
Angiotensin-converting enzyme inhibitors
Tricyclic antidepressants

Modified from Bannister R, ed. Autonomic failure. A textbook of clinical disorders of the autonomic nervous system. Oxford: Oxford University Press, 1988.

TABLE 71.3 SYNCOPE OF ORTHOSTATIC ORIGIN: A CLASSIFICATION OF CAUSES

Several forms of primary neurologic disturbance may cause orthostatic syncope. The most important disturbances are pure autonomic failure, multisystem atrophy, or Parkinson’s disease with autonomic failure. However, secondary causes of autonomic failure due to other disease processes (e.g., diabetic neuropathy, infectious neuropathies) or drugs (e.g., diuretics, vasodilators) and alcohol are far more common.

Volume depletion is also a common cause of orthostatic syncope. Often, volume depletion is a consequence of drug treatment (e.g., diuretics), but it may also occur as a result of inadequate volume intake in hot or dry environments, excessive fluid loss with diarrhea or vomiting, or as a result of hemorrhage (Table 71.3). In regard to the latter, the occurrence of syncope in association with acute blood loss—even small amounts, as in venipuncture—is a relatively frequent event; in this case, blood loss and other associated neurally mediated reflexes contribute to symptoms (22,23,27,28,29,30,31,32,33 and 34).

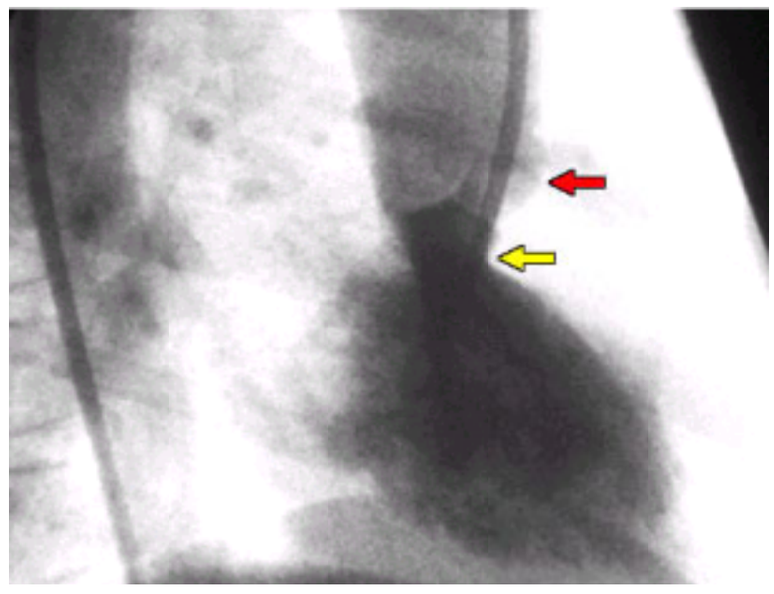
Cardiac Arrhythmias as Primary Causes of Syncope

Among syncope patients with underlying congenital or acquired structural heart disease, a primary cardiac arrhythmia is probably the most common cause of symptoms. Primary cardiac arrhythmias encompass those rhythm disturbances associated with intrinsic cardiac disease, accessory conduction pathways, or other structural abnormalities (e.g. congenital anomalies, postoperative disturbances), as well as disturbances due to proarrhythmic effects of cardioactive drugs (e.g., cardiac glycosides, positive inotropic agents, antiarrhythmic drugs).

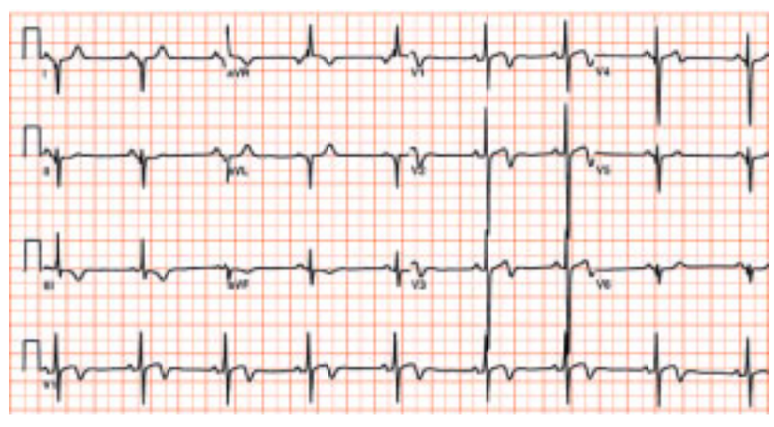
The basis for syncope is readily apparent in patients with long periods of severe bradycardia or cardiac asystole in the setting of sinus node dysfunction or atrioventricular (AV) conduction disease. The same is true in individuals with extremely rapid tachyarrhythmias. However, in many cases, hypotension is multifactorial; it is dependent on the interaction between heart rate, ventricular function, central volume status, and peripheral vascular reactivity. In this regard, assessment of response to upright posture (i.e., tilt-table testing during induced or spontaneous arrhythmia) may be crucial in understanding the hemodynamic impact of arrhythmias (35).

Structural Cardiovascular or Cardiopulmonary Disease

Cardiac arrhythmias are the most frequent causes of syncope in patients with structural cardiac disease. However, other hemodynamic disturbances may also be responsible for symptomatic hypotension. Acute myocardial ischemia or infarction is probably the most important of these disturbances (36,37). In this setting, the basis of the faint is multifactorial; it is, in part, dependent on neural reflex effects leading to inadequate peripheral vascular compensatory response. Similarly, syncope associated with aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM) is due not only to mechanical obstruction, but also to neurally mediated inappropriate vascular responsiveness (38,39 and 40). Prosthetic valve disorders also require consideration as causes of syncope in patients who have previously undergone such surgery.



Subaortic stenosis. This right anterior oblique left ventriculogram demonstrates the presence of a stenosis in the left ventricular outflow tract (*yellow arrow*) just below the level of the aortic valve (*red arrow*).



A 28-year-old Caucasian male patient with hypertrophic obstructive cardiomyopathy.

Video 71.1 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy **(A)**. Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy **(B)** for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 71.2 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy **(A)**. Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy **(B)** for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Noncardiac cardiovascular structural disturbances may also be associated with syncope. For instance, in subclavian steal syndrome, dizziness and syncope may develop during upper extremity exercise in association with ipsilateral stenosis of the subclavian artery near its origin. Syncope also is associated with pulmonary hypertension and acute pulmonary embolism. In these latter conditions, the basis for the faint encompasses reduced blood flow, diminished oxygenation, and neural reflex vascular disturbances.

Cerebrovascular Syncope

Transient global diminution of cerebral nutrient flow is, for the most part, a necessary requirement for development of syncope. However, it is exceedingly rare for this diminution to occur solely as a result of cerebrovascular disease (i.e., in the absence of a cardiac arrhythmia, orthostatic stress, or other precipitating factor). One example in which cerebrovascular disease could cause transient loss of consciousness without global disturbance of nutrient supply is in intracerebral vascular “steal.” In this case, diversion of blood flow away from regions of the brain controlling wakefulness is presumed to be the basis for syncope. Currently, establishing such a diagnosis in the clinic is, essentially, impossible.

Miscellaneous Nonsyncopal Conditions Associated with Impaired Consciousness

In most circumstances, metabolic disturbances of sufficient severity to cause loss of consciousness are not typically transient and self-correcting. Consequently, the clinical picture is not that of true syncope. However, impaired consciousness associated with metabolic and endocrine disturbances does occur. The presumed pathophysiology of this condition is a disturbance of cerebral nutrient availability (e.g., marked hypoglycemia), a major perturbation of acid/base or electrolyte environment, or both. Hyperventilation of presumably psychogenic origin, with consequent marked reduction of the partial pressure of carbon dioxide and reduced cerebral blood flow due to vasospasm, is probably the only relatively common problem in this class.

In regard to more well-established primary neurologic diseases (e.g., aneurysms, tumors, seizure disorders), episodes of loss of consciousness are, once again, usually not true syncope. Nevertheless, making a clinical diagnostic distinction can prove challenging. Astatic or akinetic seizures are particularly difficult to distinguish from syncope (41). Drop attacks may also be included in this category. The basis of drop attacks remains unclear, but because loss of consciousness is not an issue,

these attacks are excluded from the category of true syncope.

The pathophysiology of psychiatric disturbances (e.g., somatization disorders) known to mimic syncope (see the section Psychiatric Disorders) is poorly understood. For the most part, these disturbances do not result in true syncopal events. However, patients manifesting such disturbances may have a greater tendency to be subject to the emotional faint or other forms of neurally mediated syncope (see the section Neurally Mediated Reflex Syncopal Syndromes). Additionally, these patients may be prescribed certain medications that increase syncope risk (e.g., phenothiazines, tricyclics).

GENERAL CLINICAL CONSIDERATIONS IN THE EVALUATION OF SYNCOPE

In the clinical evaluation of the syncope patient, the principal goal is to establish an accurate diagnosis; only after a definitive diagnosis is made can an appropriate treatment strategy be embarked on. Given the numerous causes of syncope and the unpredictable nature of syncopal events, achieving this goal is difficult, and special testing is often essential (Fig. 71.2). This is especially true when symptoms are recurrent. However, even solitary syncopal events may warrant such steps when risks to the patient or public may be excessive (e.g., syncope associated with substantial physical injury or motor vehicle accident, syncope in individuals with high-risk occupations such as pilots, commercial truck drivers, or competitive athletes).

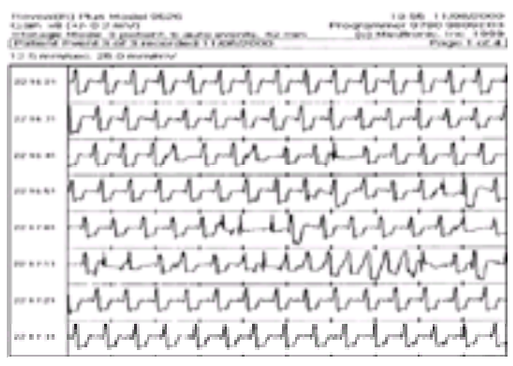


FIGURE 71.2 Recording from an implantable loop recorder. Patient complained of lightheadedness but had no symptoms of rapid heart action. The recording illustrates a wide-QRS nonsustained tachycardia suggestive of nonsustained ventricular tachycardia.

The circumstances surrounding syncopal episodes are highly variable. However, upright posture (standing or, occasionally, sitting) is usually implicated. Thereafter, the clinical picture is dictated by the underlying problem. Thus, in patients with syncope due to supraventricular tachycardia (SVT) or ventricular tachycardia (VT), palpitations may be reported. Frequently, however, rapid beating of the heart is not perceived and, consequently, is not part of the medical history (Fig. 71.2). In patients with vasovagal syncope, hypotension often is associated with a preceding sense of apprehension and nausea and is characterized by pallor and diaphoresis. On the other hand, in many individuals, warning symptoms are entirely absent. This seems to be the case in older patients, and a lack of symptoms of hypotension is common with carotid sinus syndrome. Consequently, while there is no doubt that the medical history of a syncopal event is crucial for differentiating syncope from other conditions—especially seizures—and providing clues to possible causes, it is often inconclusive (42).

SPECIFIC CONDITIONS

Neurally Mediated Syncopal Syndromes

Syncope of neurally mediated reflex origin encompasses vasovagal syncope, carotid sinus syndrome, and other, much less frequent forms of neurally mediated syncope (e.g., cough, deglutition, and micturition syncope) (Table 71.2). The electrophysiologic and hemodynamic picture associated with a neurally mediated syncopal event may be quite variable (43). Most patients present a mixed vasodepressor and cardioinhibitory response (43,44,45,46,47 and 48).

Vasovagal syncope may be triggered by any of a variety of situational factors. Some of these factors are unpleasant sights (e.g., sight of blood), pain, and extreme emotion. Common venues for fainting are churches, hospitals, queues, and restaurants. In many, but not all, cases, this type of faint is easy to diagnose because a clear history of preceding dizziness, together with other typical phenomena, is obtained (49). The patient may report feelings of lack of air, a change in breathing pattern, sweating, loss of hearing, and nausea before partial or total loss of consciousness. Pallor is a common physical finding in association with these faints, and witnesses to the event should be queried directly in regard to their recollection of this finding. During the recovery phase, there is rapid return of orientation. However, fatigue, weakness, nausea, and headache may last from minutes to hours. Often, in older individuals, warning symptoms may be brief or nonexistent, thereby complicating establishment of the diagnosis. In such cases, syncope may occur without apparent warning. Such an outcome often results in falls and physical injury—presentations difficult to distinguish by history alone from syncope complicating conduction disturbances of the heart. This variant of the vasovagal faint has been termed *malignant vasovagal syndrome* (50).

In instances in which vasovagal syncope is suspected by clinical history but in which uncertainty remains, tilt-table testing diagnostic techniques have been of value (23,45,46,47,48,49,50,51,52,53 and 54). Tilt-table testing has a specificity of approximately 90%, a reproducibility in the short term of 80% to 90%, and a reproducibility in the longer term (i.e., more than 1 year) of approximately 60% (54). Tilt-table testing is the only investigation that provides the opportunity to precipitate a typical attack under the eyes of the investigator and allows the victim to confirm the associated symptoms. A recent American College of Cardiology expert consensus document addresses the role of tilt-table testing and appropriate laboratory protocols (54).

Carotid sinus syndrome is probably the second most common form of the neurally mediated syncopal syndromes (55,56,57 and 58). In this setting, syncope often presents without warning (i.e., absence of premonitory symptoms). Although rare, a history suggesting that head movements trigger dizziness or syncope supports this diagnosis. As a rule, the condition almost exclusively afflicts older people, especially men.

In clinical practice, carotid sinus syndrome is often overlooked. The reasons for this include failure to perform carotid sinus massage routinely in syncope patients or failure to record blood pressure and heart rate responses when carotid massage is undertaken. As in other forms of neurally mediated reflex syncope, vasodepressor and cardioinhibitory features participate in most cases of carotid sinus syncope. In the absence of adequate arterial pressure measurements, a clinically important vasodepressor response may be missed.

Carotid massage resulting in dizziness or syncope due to hypotension with or without bradycardia is the key diagnostic finding in patients suspected of having carotid sinus syndrome. Testing is best conducted with the patient upright on a tilt table, using continuous digital plethysmography or intraarterial pressure measurements to record beat-to-beat arterial pressure changes. Firm carotid sinus massage for 5 to 10 seconds is recommended. A cardioinhibitory response is presumed to predominate when carotid sinus massage is associated with symptom reproduction in conjunction with asystole or a paroxysmal AV block of 8 to 10 seconds or longer (23,44,55,56). However, the vasodepressor component must be assessed separately during the maneuver by beat-to-beat arterial pressure monitoring while preventing bradycardia with a temporary dual-chamber pacing system. The magnitude of the vasodepressor part of the reflex can also be estimated by examining the rate of blood pressure recovery after resumption of the native heart rate. A systolic blood pressure drop ³50 mm Hg is generally accepted as diagnostic of a clinically important vasodepressor response. In most cases, both the cardioinhibitory and vasodepressor features are present (i.e., mixed response). In the absence of symptom reproduction, the demonstration of a pause of 5 seconds or longer, a systolic blood pressure fall ³50 mm Hg, or both is probably relevant and can be considered to support a “presumptive diagnosis” (54,57,58).

Among the other forms of neurally mediated reflex syncope, postmicturition syncope, swallow syncope, and cough syncope are probably the next most frequent. The remaining conditions (Table 71.2) are only rarely encountered.

Orthostatic Syncope

Presyncopal or syncopal symptoms associated with abrupt assumption of upright posture are common occurrences (Table 71.3). Elderly persons, less physically fit individuals, or patients who are, for whatever reason, dehydrated or volume depleted are at greatest risk for orthostatic syncope. Iatrogenic factors such as excessive diuresis or overly aggressive use of certain antihypertensive agents are important contributors. Environmental factors (e.g., excessive heat), complications associated with certain medical conditions (e.g., hemorrhage), or diseases (e.g., diabetes insipidus, adrenal insufficiency) may also play a role in specific cases. Patients

previously diagnosed with idiopathic orthostatic hypotension may be considered to be manifesting autonomic dysfunctions; these dysfunctions may be primary neurologic disturbances (e.g., pure autonomic failure) or secondary to other diseases or drug effects.

In general medical practice, specific primary autonomic nervous system dysfunctions leading to disturbances of vascular control are considered to be relatively infrequent causes of syncope. Nevertheless, as the broad spectrum of these disturbances and their potentially subtle manifestations become more widely appreciated by physicians, these diagnoses will be made more often (41,59,60,61 and 62). More commonly, neuropathies associated with chronic diseases (e.g., diabetes) or toxic agents (e.g., alcohol) are the source of the problem.

Clinically, syncope associated with orthostatic disturbances of blood pressure control tends to be most frequent early in the day. Susceptibility is accentuated if the patient has recently had an enforced period of bedrest, is exposed to hot environments, has recently completed a period of vigorous exercise, or is being treated with any of a variety of cardioactive drugs that deplete central circulatory volume (e.g., diuretics, sympatholytics). Furthermore, unlike vasovagal faints, these syncopal episodes typically are not associated with bradycardia, sweating, or marked pallor.

In a review of 155 patients referred for assessment of suspected orthostatic hypotension, Low et al. (63) found that among the most severely affected symptomatic patients (n = 90; mean age, 64 years), pure autonomic failure accounted for 33%, multisystem atrophy accounted for 26%, and autonomic/diabetic neuropathy accounted for 31%. The most frequently reported symptoms in these individuals were lightheadedness (88%), weakness or tiredness (72%), cognitive difficulties (47%), blurred vision (47%), tremulousness (38%), and vertigo (37%). The prominence of fatigue and weakness has raised the as-yet-unsettled issue regarding the possible relationship between these conditions and so-called “chronic fatigue syndrome” (64). Patients with postural orthostatic tachycardia syndrome, on the other hand, tended to be symptomatic during upright posture but did not typically manifest sufficient hypotension to result in syncope or marked hypotension.

The clinical evaluation of orthostatic hypotension is facilitated by the availability of tilt-table testing facilities. However, tilt-table test results, as in the case of vasovagal syncope, are affected by various factors such as the volume status of the patient, temperature, and chronobiologic issues. Consequently, the diagnosis of the various forms of autonomic failure using tilt-table testing and other autonomic testing procedures (63,65,66) require a level of experience that is available in relatively few centers. A relatively abrupt drop in systolic pressure of ³50 mm Hg is probably diagnostic, but it is better supported by the concomitant development of symptoms.

Cardiac Arrhythmias as Primary Causes of Syncope

Arrhythmias due to intrinsic conduction system disturbances—usually acquired but occasionally congenital—are important causes of syncope. However, it is often difficult to substantiate the relationship between syncope and a suspected arrhythmia in free-living individuals (e.g., by ambulatory electrocardiographic monitoring) due to the unpredictable occurrence of symptomatic events. Thus, implantable long-term loop recorders are becoming more widely applied. In some cases, invasive electrophysiologic testing may be indicated.

Sinus node dysfunction—commonly termed *sick sinus syndrome*—encompasses an array of sinus node and atrial arrhythmias that result in persistent or intermittent periods of inappropriate slow or fast beating of the heart (67,68,69,70,71 and 72). The electrocardiographic manifestations of sinus node dysfunction include sinus bradycardia, sinus pauses, sinoatrial exit block, inexcitable atrium, and chronotropic incompetence, as well as various atrial tachyarrhythmias—principally, atrial fibrillation or atrial flutter (Fig. 71.3). For the most part, sinus node dysfunction is closely associated with underlying fibrosis or chamber enlargement. However, extrinsic factors (e.g., autonomic nervous system influences, cardioactive drugs) are also frequent contributors. Of these factors, drug-induced disturbances are, clinically, the most important (69,70 and 71).

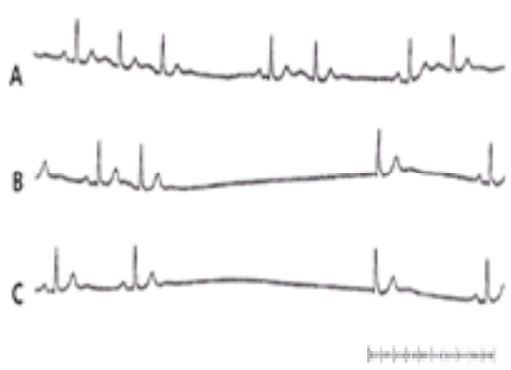


FIGURE 71.3 Symptomatic sinus pauses of varying duration recorded during ambulatory electrocardiogram monitoring in a 70-year-old woman with recurrent dizziness.

In the sinus node dysfunction patient with syncope, the cause may be a transient severe bradyarrhythmia, tachyarrhythmia, or both. Most often, it is believed that the arrhythmias associated with syncope in sinus node dysfunction patients are those that produce relatively long periods (i.e., 10 to 15 seconds or longer) of severe bradycardia (i.e., sinus pauses and sinoatrial block) with consequent inadequate cerebral blood flow. For example, Rubenstein et al. (67) found that among 56 patients with severe bradyarrhythmias or bradycardia-tachycardia syndrome, 25 (45%) presented with syncope, and an additional 15 (27%) reported various presyncopal symptoms. In the majority of these cases (80%), bradyarrhythmias were considered to be the principally responsible rhythm disturbance. Similarly, among 22 patients with sinus node dysfunction and syncope, Sutton and Perrins (72) reported resolution of symptoms with prevention of bradycardia by cardiac pacing in 16 (73%) cases. Of the patients with residual symptoms, treatment failure due to pacing system dysfunction occurred in one case, whereas symptomatic tachyarrhythmias were ultimately uncovered in several others.

Sinus node dysfunction patients, in large part due to their age and tendency to harbor coexisting diseases (especially cardiovascular disorders), are also susceptible to loss-of-consciousness spells that may not be due to primary arrhythmias. Orthostatic syncope, thromboembolism, myocardial ischemia, and new onset seizure disturbances are important considerations. In the past (i.e., before more widespread use of anticoagulation), it is notable that thromboembolism was the principal factor accounting for the excess morbidity and mortality in sinus node dysfunction patients (69,73,74 and 75).

Atrioventricular Conduction Disturbances

Acquired disturbances of AV conduction are most often associated with syncopal symptoms. Progressive idiopathic fibrosis of the cardiac conduction system is the most common cause of acquired conduction system disease with AV block (76,77). Acute myocardial infarction is also associated with the various forms of AV block and is another common cause of acquired complete AV block. Chronic ischemic and valvular heart disease, complications associated with cardiac surgical procedures, and administration of various antiarrhythmic drugs are other potential contributors.

Drug effects also deserve special consideration because they are a particularly common and potentially reversible cause of AV conduction disturbances (69,78,79). Cardiac glycosides, beta-blockers, and calcium-channel blockers are, perhaps, the most widely recognized drugs in this regard. Antiarrhythmic drugs may act directly, as well as through effects on the autonomic nervous system, to alter conduction in the AV node. At usual doses, however, antiarrhythmic drugs are rarely associated with *de novo* development of complete AV block. Patients with preexisting infranodal conduction system disease are at highest risk. Once again, however, syncope in this setting cannot be assumed to be bradycardic in origin because drug-induced tachycardias (i.e., the proarrhythmic effects of antiarrhythmic drugs) are also a consideration in this situation. Torsades de pointes is the most important example of this type of tachycardia.

As a solitary finding, first degree AV block is almost never the cause of syncope. When syncope does occur in this setting, there is usually no direct causal relationship. However, the presence of first degree AV block, especially in the absence of structural heart disease, may suggest hypervagotonia and thereby raise suspicion of neurally mediated syncope. Rarely, symptoms—typically presyncope, with true syncope occurring only in exceptional cases—may occur if the PR interval is sufficiently prolonged such that, during exercise, successive P waves are so far in front of the QRS complex as to be superimposed on preceding T waves (i.e., pseudopacemaker syndrome) (80,81).

Type I second degree AV block generally is considered to be a relatively innocent conduction disturbance when the QRS complex is narrow and there is no evidence of associated infranodal conduction system involvement. In this setting, bradycardia is rarely of sufficient severity to account for syncope. On the other hand, when Type I second degree block occurs in the setting of evident infranodal conduction system disease (e.g., wide QRS), the delay is often within the intraventricular specialized conduction system, and the risk of progression to higher grades of AV block is great. Additionally, when Type I second degree block occurs in elderly patients (>70

years), the prognosis may be more worrisome, and pacing should be considered. Type II second degree AV block generally is agreed to carry a worrisome prognosis and to cause a predilection for syncopal attacks, as well as the development of higher grades of AV block (Fig. 71.4). Type II block is most often seen in conjunction with bundle branch block and is indicative of severe disease of the infranodal specialized conduction system.

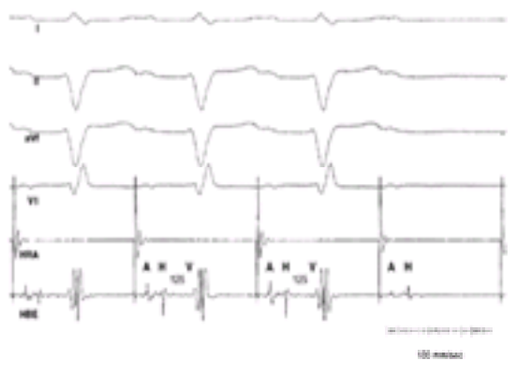
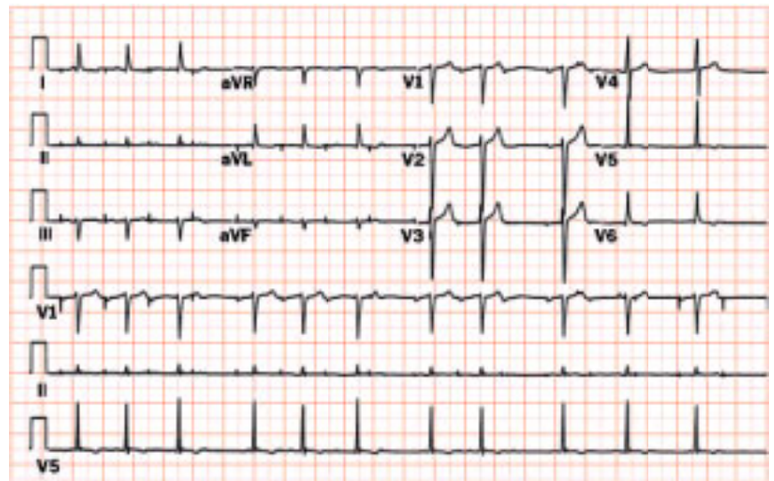
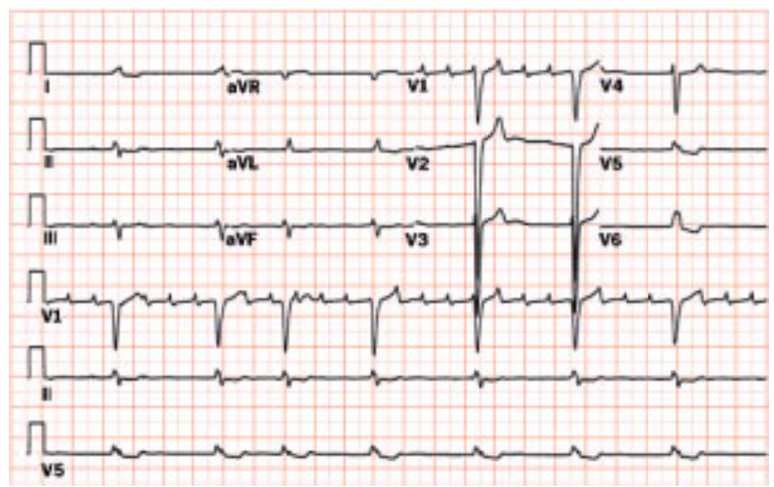


FIGURE 71.4 Electrocardiogram and intracardiac recordings illustrating a prolonged HV interval and infra-His block (Mobitz II) in a patient undergoing electrophysiologic evaluation for recurrent syncope of unknown cause. HBE, bundle of His electrogram; HRA, high rate atrium.



Mobitz I second-degree atrioventricular block. Note electronic atrial pacemaker with progressive PR segment prolongation before dropped QRS complex.

Third degree AV block may be high-grade (i.e., in which multiple P waves are blocked) or complete. In either case, the cardiac rhythm depends on subsidiary pacemakers located within the proximal portions of the specialized conduction system (e.g., bundle of His) that may result in relatively narrow QRS complexes, or within more distal aspects of the His-Purkinje system, resulting in wide QRS complexes. Syncope is a common feature in these cases [reported in 38% to 61% (82,83)], because the back-up pacemakers are usually relatively slow and often unreliable.



High-grade atrioventricular block. Note marked discrepancy between atrial and ventricular heart rates.

In general, the risk for syncope or dizziness is greatest at onset of AV block, before “warm-up” of a subsidiary rhythm (Fig. 71.4). Thereafter, the ventricular rhythm often stabilizes and may average 35 to 40 beats/min in acquired third degree AV block. In fixed complete AV block, syncope may occur as a result of the unreliability of subsidiary pacemakers or of the inability of the heart-rate–limited circulation to provide sufficient cerebral blood flow during periods of exercise or stress. In both cases, the close association with severe underlying heart disease also raises concern regarding tachyarrhythmia-induced syncope, including increased proarrhythmia risk in patients treated with antiarrhythmic drugs.

Traditionally, congenital complete AV block has been accorded a more benign prognosis than that accorded to acquired AV block (84,85). The site of block in patients with congenital AV block is typically at the level of the AV node. Generally, the QRS complexes are narrow, and the block usually is associated with a reasonable subsidiary rhythm, which tends to increase in rate with exercise. Recently, however, concern has been raised regarding the supposedly benign natural history of congenital AV block (86), and further evaluation of this issue is needed. In the meantime, syncope and dizziness, along with exertional intolerance, are accepted indications for pacing in these patients.

Bifascicular conduction system disease is a relatively common electrocardiographic finding. However, in most cases, progression to more severe forms of AV block is slow. Susceptibility to higher-grade block (i.e., blocks that may be long enough to cause syncope) increases the longer the HV interval is, particularly for HV ³100 ms (87,88 and 89). However, once again, it should be borne in mind that syncope in patients with evident conduction system disease may not be solely the result of bradyarrhythmias. VT is a concern in these cases because of the usual presence of significant underlying heart disease.

Supraventricular and Ventricular Tachyarrhythmias

Supraventricular tachyarrhythmias have been reported to be the causes of syncope in approximately 15% of patients referred for electrophysiologic evaluation (6). When syncope does occur, it is typically at the onset of an arrhythmic episode and before adequate peripheral vascular compensation can occur. A number of factors determine whether syncope or dizziness occurs in patients with SVT, including the tachycardia rate, the volume status and posture of the patient at onset of the arrhythmia, the presence of associated valvular, left ventricular, or pulmonary vascular disease, the mechanism of the arrhythmia, and the integrity of reflex peripheral vascular compensation. Additionally, it has come to be recognized that neural reflex responsiveness may be less efficient in individuals susceptible to syncope with SVT (90).

Electrophysiologic testing in SVT patients offers the possibility of obtaining direct evidence of the role played by the arrhythmia in the patient’s symptoms. However, to document symptomatic hypotension, it may be necessary to induce the arrhythmia with the patient in the head-up posture on a tilt table.

Sustained VT has been reported to be the cause of syncope in up to 20% of syncope patients referred for electrophysiologic testing (6). This diagnosis is of particular concern in the setting of underlying structural heart disease or long-QT syndrome (congenital or acquired). In regard to VT susceptibility, a detailed medical history should be supplemented with assessment of the status of underlying cardiac disease. In this regard, an echocardiographic study is adequate in most cases, but other imaging modalities—including angiography—may be required as well. Although the utility of a signal-averaged electrocardiogram (ECG) is controversial, it may be an appropriate consideration in individuals with ischemic heart disease in whom VT is a concern. If the signal-averaged ECG is normal, the likelihood that VT is the cause

of syncope is low (91,92).

Nonsustained ventricular tachycardia (NSVT) remains a difficult dilemma for physicians evaluating syncope patients. NSVT is a common finding during ambulatory electrocardiographic monitoring in patients with structural heart disease. Consequently, finding NSVT in a syncope patient usually is not helpful in the absence of concomitant symptoms (Fig. 71.2). Similarly, induced NSVT during electrophysiologic testing, especially if polymorphic, is not a reliable diagnostic finding. However, if reproducible periods of hypotensive NSVT are easily inducible, and there is no other apparent explanation for syncope, it is probably prudent to proceed with pharmacologic or device prophylaxis. The Multicenter Unsustained Tachycardia Trial data, although not directly focused on a syncope population, seem to provide additional support for this argument (93).

Particularly perplexing is the appropriate approach to be taken in the setting of syncope in patients with severe underlying left ventricular dysfunction (e.g., dilated cardiomyopathy) but without evident NSVT or inducible sustained VT. In such cases, evidence suggests that there is high risk for symptom recurrence and sudden death (94,95 and 96). As a result, prophylactic placement of an implantable cardioverter-defibrillator is often recommended. Whether this approach is justifiable awaits prospective evaluation.

Structural Cardiovascular or Cardiopulmonary Disease

Apart from cardiac arrhythmias, the most common cause of syncope attributable to left ventricular disease is acute myocardial ischemia or infarction. Other relatively common acute medical conditions associated with syncope include pulmonary embolism and pericardial tamponade. The basis of syncope in all of these conditions is multifactorial, including the hemodynamic impact of the specific lesion and neurally mediated reflex effects.

Syncope may also occur in conditions in which there is fixed or dynamic obstruction to left ventricular outflow (e.g., aortic stenosis, HOCM). In such cases, symptoms often are provoked by physical exertion but may also develop if an otherwise benign arrhythmia should occur (e.g., atrial fibrillation). In part, the basis for the faint may be inadequate blood flow due to the mechanical obstruction. However, especially in the case of valvular aortic stenosis, ventricular mechanoreceptor-mediated bradycardia and vasodilatation are thought to be important contributors (38).

Subclavian steal syndrome is an uncommon cause of syncope. In this setting, narrowing of the subclavian artery at its origin results in syncope or dizziness in conjunction with ipsilateral upper extremity exercise as blood is shunted from the brain to the exercising limb via the vertebral artery system. Other, even less common, conditions in this category include left ventricular inflow obstruction in patients with mitral stenosis or atrial myxoma. Similarly, right ventricular outflow obstruction and right-to-left shunting secondary to pulmonic stenosis or pulmonary hypertension may be associated with syncope.

Cerebrovascular Causes of Syncope

Cerebrovascular disease, including severe carotid artery disease, rarely causes syncope. Occasionally, however, transient disturbances of cerebrovascular blood flow may initiate a true syncopal spell. For example, arterial entrapment with intermittent obstruction of posterior circulation vessels can occur in conjunction with cervical spine disease. In such cases, any concomitant problems with the anterior circulatory supply may result in syncope.

Migraine may be associated with syncope. In such cases, extracranial vascular spasm may trigger neural reflex syncope, although cerebrovascular spasm might also occur. In any case, historical features of migraine and migraine susceptibility usually are sufficient to distinguish the diagnosis. Finally, symptoms secondary to cerebrovascular disease may be referred for evaluation as a syncopal episode. In particular, transient ischemic attacks due to vertebrobasilar disease may mimic syncope (41,59). In such cases, there are usually concomitant findings (e.g., vertiginous complaints, ocular disturbances, or speech problems) not typically encountered in the syncope patient.

Miscellaneous Causes of Impaired Consciousness: Syncope Mimics

Metabolic and Endocrine Disturbances

Metabolic and endocrine disturbances are more often responsible for confusional states or behavioral disturbances, rather than true syncope. However, it may be difficult to make a clear-cut distinction between such symptoms and syncope by medical history alone. One potentially useful distinguishing feature is that, unlike true syncope, conditions such as diabetic coma and severe hypoxia or hypercapnia do not resolve without active therapeutic intervention. In the case of syncope due to psychogenic hyperventilation, tilt-table testing may prove helpful for reproducing the event and permitting its documentation by blood gas analysis of arterial samples obtained from a previously placed indwelling catheter.

Psychiatric Disorders

Syncope may be mimicked by anxiety attacks, hysteria, or other psychiatric disturbances. Anxiety attacks are frequently associated with hyperventilation and hypocapnia. Hysteria, however, tends to be characterized by its “drama” because it can occur in the presence of onlookers and is not associated with marked alterations of heart rate, systemic pressure, or skin color.

Central Nervous System Causes

In Kapoor’s extensive review of more than 400 patients presenting with syncope, only a few were found to have abnormal neurologic studies (9). Typically, any diagnostic confusion is due to the fact that these conditions may result in a clinical picture, at least from a lay viewpoint, that may be mistaken for syncope. However, the differences are usually clearly distinguishable by careful history taking and neurologic physical examination.

Seizures may be mistaken for syncope, and vice versa (7,9,41,59,97). In some patients, temporal lobe seizures may so closely mimic or induce neurally mediated reflex bradycardia and hypotension, that differentiation from true syncope is difficult. Astatic or akinetic seizures are characterized by the patient slumping to the ground—or, if the patient is supine, by a period of muscular hypotonia—combined with unresponsiveness (41,59). However, these conditions are uncommon. More often, a careful history permits differentiation of seizures from true syncope.

Seizures tend to be positionally independent, whereas true syncope is most commonly associated with upright posture. Furthermore, seizures often are preceded by an aura and, occasionally, sensory hallucinations, whereas true syncope is not. Seizures are often associated with convulsive activity and loss of bowel or urinary continence, whereas any abnormal motor activity in true syncope is less severe, and incontinence is unusual (97). Finally, seizures are typically followed by a confusional state, whereas true syncope is typically followed by prompt restoration of mental state, although fatigue may persist.

Cataplexy, an uncommon condition characterized by abrupt onset of generalized muscle weakness, can be confused with syncope. As in the case of vasovagal syncope, symptoms may be triggered by emotional reactions or surprise. A narcoleptic sleep may follow. Cataplexy generally can be distinguished from syncope because the patient can be aroused. Electroencephalographic findings compatible with rapid eye movement sleep differentiate the narcoleptic state from a postictal event.

Drop attacks refer to a poorly defined condition in which abrupt loss of postural tone occurs but consciousness is generally preserved. The etiology of these attacks is unknown. In certain cases, drop attacks appear to be associated with atherosclerotic cerebrovascular disease, especially within the vertebrobasilar system, and are presumed to be the result of transient nutrient insufficiency to corticospinal tracts, which results in sudden atonia in the lower extremities (41). The dramatic clinical presentation of a fall often leads to syncope being the initial diagnosis.

MANAGEMENT: DIAGNOSIS AND TREATMENT

Strategy for Diagnostic Evaluation of the Syncope Patient

The goal of diagnostic testing in syncope patients is to obtain a sufficiently strong correlation between syncopal symptoms and detected abnormalities to permit confident statement of the cause of the faint, an accurate assessment of prognosis, and initiation of an appropriate treatment plan.

A detailed medical history—with particular attention to bystander observations—and a thorough physical examination may lead the physician to suspect the basis for syncope. However, unless these findings are classic, it is usually necessary to undertake selected diagnostic studies to establish the etiology with a greater degree of

certainty. In all cases, testing should be carefully targeted. The ordering of routine hematologic and biochemical screens is not productive. Similarly, routine application of specialized neurologic tudies (e.g., computed tomography, magnetic resonance imaging) has a low yield (9). A practicable strategy for the syncope evaluation is depicted in Fig. 71.5. As a rule, the first step—apart from excluding a history of seizure disorder—is differentiation of individuals with normal cardiovascular status from those with evident cardiac or cardiovascular disease. Usually, physical examination and echocardiographic assessment is sufficient for this purpose, although exercise testing should also be undertaken if syncope occurred with exertion or if ischemic heart disease is suspected.

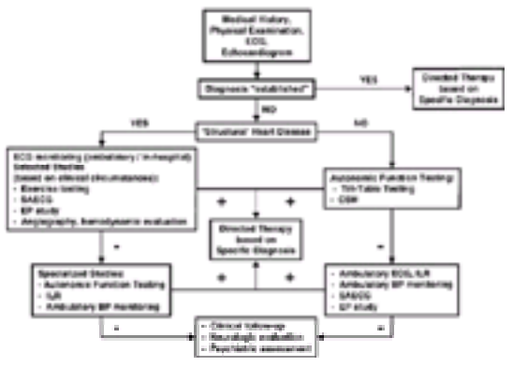


FIGURE 71.5 A proposed strategy for syncope evaluation. BP, blood pressure; CSM, carotid sinus massage; ECG, electrocardiogram; EP, electrophysiologic; ILR, implantable loop recorder; SAECG, signal-averaged electrocardiogram.

In the absence of structural heart disease, tilt-table testing is usually the next diagnostic step. On the other hand, in patients with abnormal cardiac findings, functional studies of the structural disturbance (e.g., hemodynamic, angiographic) and evaluation of susceptibility to tachyarrhythmias and bradyarrhythmias by conventional electrophysiologic testing is appropriate. In patients with demonstrable vascular disease, appropriate studies to assess the hemodynamic significance of observed arrhythmias (e.g., ultrasound) are needed. Thereafter, tilt-table testing should follow if the diagnosis remains in doubt. In only a few instances should special neurologic studies be elected as an initial step.

Specific Diagnostic Testing

Electrocardiographic Recordings

Electrocardiographic documentation during a spontaneous syncopal event is usually a high priority, because cardiac arrhythmias are so frequently the cause of syncope. In this regard, the 12-lead ECG is usually too brief to identify or exclude an arrhythmic cause. However, on occasion, findings such as ventricular preexcitation (e.g., Wolff-Parkinson-White syndrome) or QT interval prolongation suggest a potential mechanism. Other relatively common findings such as sinus bradycardia, ventricular ectopic beats, bundle branch block, or even NSVT often are not particularly helpful. Similarly, exercise testing is usually of limited utility in the evaluation of syncope, unless the events are clearly exertionally related by history. Only in rare instances does exercise testing uncover certain helpful findings [e.g., rate-dependent AV block, exertionally related tachyarrhythmias, severe degrees of chronotropic incompetence, excessively rapid heart rate deceleration after exercise, or the exercise-associated variant of neurally mediated syncope (98,99 and 100)]. For the most part, obtaining ECG documentation during spontaneous symptoms—if feasible at all—necessitates an extended period of cardiac monitoring using Holter monitors or event recorders. The latter systems can be used in a continuous-loop mode for patients whose symptoms preclude responding appropriately when the episode begins. Recently, the introduction of implantable loop recorders (Reveal, Medtronic, Inc., Minneapolis, MN) has added a powerful new diagnostic tool. The ability of these devices to be programmed for automatic storage of rhythm strips in which heart rates fall outside a predetermined range is particularly advantageous (101).

As a rule, if ambulatory ECG monitoring is successful in providing a symptom-arrhythmia correlation, the need for additional diagnostic testing may be diminished but not necessarily eliminated. For example, documentation of symptomatic bradycardia does not exclude the possibility of a neurally mediated etiology in which a concomitant vasodepressor element could complicate treatment.

Echocardiography and Vascular Ultrasound

Echocardiography rarely provides a definitive basis for syncope. Nevertheless, the echocardiogram has become essential for assessment of underlying structural heart disease. Furthermore, echocardiographic findings may be suggestive of a basis for syncope if evidence is obtained for HOCM, atrial myxoma, severe valvular aortic stenosis, or anomalous origin of one or more coronary arteries. Ultrasound techniques also are appropriately used to assess vascular disturbances detected on physical examination when these disturbances are deemed potential contributors to syncope. Thus, assessment of the carotid and subclavian systems may be an appropriate step in selected individuals.

Invasive Electrophysiologic Testing

In general, invasive electrophysiologic testing is useful for defining potential arrhythmic causes of syncope in individuals with underlying structural heart disease, including conduction system disturbances and the various forms of preexcitation syndromes. This is especially true when tachyarrhythmias are at fault. On the other hand, such testing is less successful among patients without apparent structural substrate for arrhythmia (5,6,102,103 and 104). For example, in one report (6), electrophysiologic testing was deemed to provide a diagnosis in 56% of all patients. However, the testing was clearly more successful in patients with evident structural cardiac disease (71%) than in patients without such disease (36%).

As with any test, care must be taken in interpreting findings of invasive electrophysiologic studies. This seems to be particularly a concern when evaluating potential bradyarrhythmic causes of syncope. In this regard, Fujimura et al. (105) undertook such studies in patients in whom bradyarrhythmias were known to be the cause of syncope; there were 21 syncopal patients with known symptomatic AV block or sinus pauses. Electrophysiologic testing only correctly identified three of eight patients with documented sinus pauses (sensitivity 37.5%) and 2 of 13 patients with documented AV block (sensitivity 15.4%). On the other hand, other abnormalities not known to have occurred spontaneously were often induced during electrophysiologic study. Tilt-table testing was not carried out in these patients; had it been undertaken, the additional findings may have been helpful in placing the apparently “false positive” electrophysiologic findings in perspective.

Head-Up Tilt-Table Testing

The importance of identifying susceptibility to vasovagal reactions in syncope patients is readily evident, given the frequency with which vasovagal syncope appears to be responsible for patient symptoms. To date, the head-up tilt-table test is the only diagnostic tool subjected to sufficient clinical scrutiny to assess its effectiveness in this setting.

Several reports have provided strong evidence that the symptomatic hypotension-bradycardia associated with a positive head-up tilt-table test is comparable to the spontaneous neurally mediated vasovagal syncope (106,107,108,109,110 and 111). Furthermore, tilt-table testing, especially when undertaken in the absence of provocative pharmacologic agents, appears to discriminate between symptomatic patients and asymptomatic control subjects with a level of precision considered acceptable for other clinically useful medical testing procedures (51,52,53 and 54).

de Mey and Enterling (112) reported only 8 instances of hypotension-bradycardia among 40 apparently normal subjects (20%). In a follow-up report, these investigators noted abnormal responses in 7 of 35 individuals (20%). Similarly, Fitzpatrick et al. (51,113) indicated that 60-degree upright tilt for 45 minutes was accompanied by development of syncope in only 7% of 27 subjects without a history of syncope (mean time to syncope, 35 ± 5 minutes). Finally, in regard to the potential impact of pharmacologic agents on the specificity of tilt-table testing, Natale et al. (114) examined the outcome of tilt-table testing at various angles and with various doses of isoproterenol provocation in 150 volunteers with no history of syncope or presyncope. These investigators found tilt-table testing at 60, 70, and 80 degrees to exhibit specificities of 92%, 92%, and 80%, respectively, when low doses of isoproterenol were used. In summary, most studies suggest that tilt-table testing at angles of 60 to 70 degrees and in the absence of pharmacologic provocation exhibits a specificity of approximately 90%. In the presence of pharmacologic provocation, test specificity may be reduced, although the magnitude of this reduction is unclear.

The response to upright tilt-table testing in patients with suspected neurally mediated syncope differs from the response observed in syncope patients in whom other diagnostic studies have provided a firm basis for symptoms. For example, Fitzpatrick et al. (113) found that 60-degree upright tilt reproduced symptoms in 53 of 71

patients (75%) with unexplained syncope; 40 patients exhibited both hypotension and bradycardia, whereas 13 subjects manifested primarily a vasodepressor response. As a result of this and many other studies, head-up tilt-table testing has become a key component of the diagnostic strategy in patients suspected of having neurally mediated syncope.

Combined Electrophysiologic and Tilt-Table Studies in Syncope

The addition of tilt-table testing to electrophysiologic testing has substantially enhanced diagnostic capabilities in syncope patients. For example, Sra et al. (102) reported results of electrophysiologic testing in conjunction with head-up tilt-table testing in 86 consecutive patients referred for evaluation of unexplained syncope. Electrophysiologic testing was abnormal in 29 patients (34%), with the majority of these (21 patients) having inducible sustained monomorphic VT. The remainder comprised inducible SVTs (five patients), sinus node dysfunction (one patient), and conduction system disease (two patients). Among the remaining patients, head-up tilt-table testing proved positive in 34 cases (40%), whereas 23 patients (26%) remained undiagnosed. During follow-up, syncope recurrence occurred in approximately 13% of patients. Importantly, however, syncope recurrence in patients in whom treatment was directed by electrophysiologic testing or tilt-table testing seemed to be highly associated with discontinuation of recommended therapies.

A further evaluation of the combined use of electrophysiologic testing and head-up tilt-table testing in the assessment of syncope is provided in the report by Fitzpatrick et al. (51). Among 322 syncope patients evaluated between 1984 and 1988, conventional electrophysiologic testing provided a basis for syncope in 229 of 322 cases (71%), with 93 patients having a normal electrophysiologic study. In terms of abnormal electrophysiologic findings, AV conduction disease was diagnosed in 34% of patients, sinus node dysfunction in 21%, carotid sinus syndrome in 10%, and inducible sustained tachyarrhythmias in 6%. As noted above, in the 93 patients with normal conventional electrophysiologic studies, tilt-table testing was undertaken in 71 cases; the testing reproduced syncope consistent with a vasovagal mechanism in 53 of these cases (75%).

Carotid Sinus Massage

The technique for undertaking carotid sinus massage and the interpretation of the test has been previously discussed. In general, the test has proved very safe; however, care should be exercised in using this test in patients with carotid bruits or prior strokes.

Neurologic Studies

Conventional neurologic laboratory studies (e.g., electroencephalogram, computed tomography of the head, and magnetic resonance imaging) have had a relatively low yield in the syncope patient. Consequently, these studies should be restricted to situations in which other clinical observations suggest organic nervous system disease (see the section Central Nervous System Causes). On the other hand, given the importance of orthostatic causes of syncope, tilt-table testing and other tests of autonomic function play an increasingly important role.

Treatment

Neurally Mediated Syncopal Syndromes

In the case of neurally mediated syncopal syndromes, treatment strategies remain in evolution. Specific treatment should, when possible, be directed at relieving apparent trigger factors. Thus, alleviating or suppressing the cause of cough in cough syncope or treating esophageal abnormalities in swallow syncope are desirable approaches. However, in conditions such as carotid sinus syncope and vasovagal syncope, comparable approaches usually are not available. Therefore, in carotid sinus syncope, cardiac pacing has become a primary treatment modality—recognizing that, in many instances, additional consideration must be given to the concomitant vasodepressor element of the syndrome.

In the case of vasovagal syncope, the mainstay in treatment is education and reassurance. This approach proves most effective when there is a prodrome of sufficient duration to permit the patient to take suitable evasive action. Patients whose symptoms demand more than mere reassurance are those whose attacks have minimal or no prodrome (especially if they have had resulting injury), those who cannot be taught to abort attacks, and those whose attacks are complicated by seizure-like activity or incontinence. Of particular concern are patients with high-risk occupations or avocations in which syncope might lead to injury to themselves or others (e.g., pilots, commercial drivers, window washers, swimmers).

In patients in whom a more aggressive treatment strategy is needed, volume expanders (e.g., increased dietary salt and electrolyte intake with salt tablets or fluids such as sports drinks) or moderate exercise training appear to be among the safest initial approaches. Additionally, in highly motivated patients with recurrent vasovagal symptoms, the prescription of progressively prolonged periods of exposure to still upright posture (i.e., tilt training) may be beneficial (115,116). Beyond these measures, a variety of pharmacologic approaches have been proposed, but few randomized clinical studies are available to confirm their utility. In this regard, beta-adrenergic blocking drugs, disopyramide, and vasoconstrictor agents [e.g., midodrine (117,118)] are the principal agents. Other drugs that appear to be useful in selected cases are serotonin-reuptake inhibitors (119,120).

Cardiac pacing has proved highly successful in carotid sinus syndrome when bradycardia has been documented (121). Currently, dual-chamber pacing is widely acknowledged to be the treatment of choice in all but the mildest forms of carotid sinus syndrome. Single-chamber atrial pacing is contraindicated due to the propensity for these patients to exhibit paroxysmal high-grade AV block during the episodes. Clinical experience with pacing in vasovagal syncope and other forms of neurally mediated syncope has been more limited than in carotid sinus syncope (122,123,124,125 and 126). However, the effectiveness of pacing in selected highly symptomatic patients with recurrent vasovagal faints has been supported by findings of two important multicenter randomized controlled trials (124,125).

In the two multicenter randomized trials examining the effectiveness of pacing in vasovagal fainters, the focus was treatment of individuals who appeared to demonstrate predominantly cardioinhibitory faints. In the case of the North American Trial (124), there was an actuarial first-year rate of recurrent syncope of 18% for pacemaker patients and 60% for controls. The results of the pacing arm of the European Vasovagal Syncope International Study (VASIS) (125) were similar but with a longer follow-up in less severely affected—thus, perhaps more typical—patients. Thus, in vasovagal syncope, pacing may play a useful role when reserved for severe cases in which cardioinhibition appears to be responsible for symptoms. In this setting, only a dual-chamber system is capable of slowing the fall of cardiac output in the face of diminishing venous return.

Orthostatic Syncope

In orthostatic syncope, the mainstay of treatment is avoidance or removal (to the extent possible) of drugs that aggravate volume status (e.g., diuretics) and vasoconstriction (e.g., vasodilators). The desire is to favor expansion of central circulating volume. To this end, certain pharmacologic approaches are well accepted; specifically, administration of increased salt in the diet or use of salt-retaining steroids (e.g., principally fludrocortisone) is usually the first step (117,118,119 and 120). Additional benefit has been reported with the use of erythropoietin, but it is not widely used for this indication. A second element in the treatment strategy of orthostatic syncope is reduction of the tendency for central volume to be displaced to the lower extremities with upright posture. To this end, physical training (e.g., tilt training, aerobic exercise) and directly and indirectly acting vasoconstrictors have been used. In regard to drugs, clonidine has been reported to be helpful, but there appears to be little ongoing enthusiasm for its use. Of greatest current interest is midodrine—an agent that has prominent venoconstrictive properties (117,118). Physical maneuvers such as the use of counter-pressure clothing (e.g., fitted stockings, abdominal compression devices) can be helpful. Unfortunately, fitted clothing is often uncomfortable, especially in hot climates, and exposes the patient to even worse symptoms when removed. In some cases, support stockings contain latex, thereby opening the door to latex allergy.

Apart from drug-induced orthostatic hypotension, in recent years, there has been increased recognition of patients with symptomatic autonomic disturbances. Treatment of these patients remains unsatisfactory. Indeed, apart from placement of greater emphasis on physical maneuvers [e.g., tilt training, counter-pressure clothing, leg-crossing, sleeping with the head of the bed elevated (115,116,127,128 and 129)], the treatment of orthostatic syncope is, in many respects, similar to that of neurally mediated syncopal syndromes.

Primary Cardiac Arrhythmias

The appropriate treatment of patients in whom tachyarrhythmias or bradyarrhythmias are the cause of syncope is relatively well understood. Patients in whom the correlation between syncope and bradycardia is well defined do well with cardiac pacemaker therapy (130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148 and 149). However, other factors are often important in the treatment decision process. For instance, in the case of individuals with sinus node dysfunction, optimal selection of treatment necessitates consideration of not only the culprit arrhythmic disturbance, but also the effects of drugs on sinus node and AV conduction properties and on ventricular function and proarrhythmic tendency. Additionally, current indications for and available modes of cardiac pacing and the role of anticoagulation must be incorporated into the overall treatment strategy. Finally, bundle of His

ablation with placement of a permanent cardiac pacemaker remains an important tool in treatment of selected sinus node dysfunction patients who are symptomatic due to rapid ventricular rates during atrial fibrillation (131).

Pacing techniques that endeavor to maintain a normal AV relationship are generally preferred in sinus node dysfunction and AV block patients. These pacing modes are more effective than ventricular pacing for diminishing bradycardia-related symptoms; at the same time, these modes tend to diminish the likelihood of later development of atrial fibrillation and its consequent risk of thromboembolism (132,133,134 and 135). In regard to the latter, stroke risk reduction by anticoagulation is an important element in the treatment of individuals with paroxysmal or persistent atrial fibrillation. In this regard, there is solid evidence supporting the use of warfarin therapy (for review, see reference 136).

In patients with syncope resulting from paroxysmal SVTs, drug and transcatheter ablation treatment options can be highly effective, although the former is often preferable, if available.

Many paroxysmal supraventricular tachyarrhythmias can be adequately controlled by conventional antiarrhythmic drug treatment. Beta-adrenergic blockers or calcium-channel blockers may be effective alone or, if necessary, in combination with class I antiarrhythmics—particularly class IC drugs such as flecainide and propafenone. Sotalol may also be used effectively, although there is greater concern regarding QT interval prolongation and its potential proarrhythmic consequences. However, long-term drug treatment is not readily maintained in many patients due to side-effects, issues of compliance, and, occasionally, expense. Transcatheter ablation has become a reasonable and highly effective treatment option (137,138). In the case of paroxysmal reentrant SVT associated with syncope, transcatheter ablation is probably the treatment of choice. For the most part, implantable devices for treatment of SVTs recently have been out of favor. However, the role of devices in difficult-to-control conditions may be making a resurgence with the availability of atrial implantable defibrillators and improved antitachycardia pacing systems (e.g., AT500, Medtronic, Inc., Minneapolis, MN).

Currently, surgical and transcatheter techniques for ablation of atrial fibrillation remain in early development. However, in patients with recurrent syncope associated with onset of atrial fibrillation, the application of these techniques may be warranted. Surgical methods for direct treatment of atrial fibrillation currently are confined to a selected small number of patients who are undergoing heart surgery for other reasons (139,140). However, transcatheter techniques for altering atrial electrophysiologic milieu and reducing susceptibility to atrial fibrillation are developing quickly, and the potential for such procedures to be of benefit to patients with recurrent syncope is an exciting possibility (141,142 and 143). Transcatheter ablation for control of atrial flutter is highly effective, but in the setting of recurrent syncope, ablation is best reserved for patients in whom atrial flutter is the primary atrial tachycardia causing syncope, or for situations in which atrial flutter seems to trigger deterioration to symptomatic atrial fibrillation.

In the case of syncope due to VT, underlying heart disease—especially left ventricular dysfunction—of varying severity is usually present. The latter also increases the proarrhythmic risk associated with antiarrhythmic drug therapy, especially with class I agents. Consequently, pharmacologic therapeutic strategies often involve early consideration of class III agents, principally sotalol or amiodarone, but also dofetilide to an increasing extent. However, given the difficulty of assuring effective prophylaxis in this apparently high-risk patient population (94,95 and 96,104), in many cases, the use of implantable cardioverter-defibrillators (ICDs) has become an important element of the overall treatment plan. In this context, Middlekauff et al. (95) noted that among patients with severe left ventricular dysfunction, the presence of a history of syncope was accompanied by a worrisome 1-year mortality (65% vs. 25% in comparable patients without syncope) and a greater tendency to sudden death (45% of deaths vs. 12% in comparable patients).

Currently, ablation techniques are appropriate first choices in patients with right ventricular outflow tract tachycardia and bundle branch reentry tachycardia. The future may bring more extensive use of such techniques into the treatment of a broader range of VT patients (144,145 and 146).

Structural Cardiovascular or Cardiopulmonary Disease

In cases of structural cardiovascular or cardiopulmonary disease, syncope is often only one of several possible types of symptoms being experienced by the patient with underlying structural disease. In such cases, treatment is best directed at amelioration of the specific structural lesion or its consequences. Thus, in syncope associated with myocardial ischemia, pharmacologic therapy or revascularization is clearly the appropriate strategy. If successful, syncope susceptibility—whether the result of tachyarrhythmias, bradyarrhythmias, or neural reflex effects—is reduced. Similarly, when syncope is closely associated with surgically addressable lesions (e.g., valvular aortic stenosis, pericardial disease, atrial myxoma, congenital cardiac anomaly), a direct, corrective approach is often feasible. On the other hand, when syncope is caused by certain difficult-to-treat conditions (e.g., primary pulmonary hypertension or restrictive cardiomyopathy), it is often impossible to ameliorate the underlying problem adequately. Even modifying outflow gradients in HOCM is not readily achieved surgically. In HOCM, the effectiveness of standard pharmacologic therapies remain uncertain (147,148); consequently, despite ongoing controversy, recent success with cardiac pacing techniques offers considerable promise to symptomatic individuals (149).

Cerebrovascular Causes

Treatment of cerebrovascular causes of syncope are critically dependent on an accurate diagnosis. Imaging studies and neurologic or neurosurgical consultation assistance should be sought. For the most part, cerebrovascular disease rarely accounts for syncope; consequently, its evaluation is generally a low priority in the absence of new neurologic signs or other nervous system symptoms. On the other hand, the possibility of such a cause should not be completely ignored. For example, arterial entrapment in conjunction with cervical spine disease is correctable but so rare that it is almost never considered.

Miscellaneous Disturbances

Syncope-like states occurring in the setting of conditions such as diabetic coma or severe hypoxia or hypercapnia obviously require addressing the underlying problem. True syncope is rarely, if ever, solely caused by these conditions. Syncope due to psychogenic hyperventilation is the most important to consider and, over the long haul, challenging to treat. Psychiatric assistance is essential in such cases. Pharmacotherapy, counseling, and biofeedback may be needed in combination.

Recognition of temporal lobe seizures, akinetic seizures, and drop attacks requires considerable clinical acumen, appropriate laboratory testing, and expert neurologic consultation. The first two conditions are controllable with antiepileptic medications, whereas drop attacks have proven difficult to control. Migraine is far more common, and, while an infrequent cause of syncope, pharmacologic treatment is highly effective.

Syncope accompanying anxiety attacks and hysteria can prove to be a chronically recurring problem. A psychiatric diagnosis for symptoms has to be considered carefully before the “label” is applied. Subtle disturbances of autonomic control may be overlooked in this setting.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Despite the strides that have been taken in the assessment of the syncope patient, many aspects of this multifaceted problem remain to be settled. This is particularly true in the management of patients with neurally mediated syncope. For example, although tilt-table testing is generally accepted as the “gold standard” in terms of confirming susceptibility to vasovagal syncope, its role in the assessment of treatment effectiveness continues to be controversial. In my view, the effectiveness of pharmacologic management of syncope patients cannot be reliably predicted by tilt-table testing. However, other treatment techniques such as tilt training may be able to take advantage of the laboratory’s ability to assess tolerance to upright posture. Why there should be a difference between the usefulness of tilt-table testing in assessing physical maneuvers as opposed to that of pharmacologic interventions is certainly not obvious, and I cannot claim any scientific basis for this opinion; time will tell whether it is valid.

In regard to treatment of neurally mediated syncopal syndromes, progress has been made since publication of the last edition of this book. Specifically, tilt training has become an important addition to the armamentarium and should be used in preference to drug treatments in most vasovagal fainters. Furthermore, there are now two multicenter randomized trials supporting the value of cardiac pacing in patients with frequently recurrent vasovagal syncope. On the other hand, the evaluation of pharmacologic therapies remains generally disappointing. There are as yet no large randomized drug treatment trials to report.

Still uncertain is the point at which patients with syncope should be referred for specialty evaluation. It continues to be my view that this referral is warranted if any of the following are present: (a) episodes are recurrent (i.e., >2 within a 1-year period); (b) there is evidence of underlying structural heart or cardiovascular disease; (c) physical injury has occurred; (d) the patient is at risk of economic loss (e.g., job loss); (e) the public is at risk due to his or her occupation (e.g., pilot, bus driver); or (f) the patient or his or her family indicates alarm regarding possible recurrences. The establishment of practice guidelines addressing these and related issues is essential in assuring that all syncope patients receive optimal care.

Recently, trends in medical care reimbursement in the United States and other countries have not been favorable to the introduction and study of new technologies. In the case of the syncope evaluation, large insurers (e.g., Medicare, Blue Cross–Blue Shield) continue to attempt to save money in the short-term by denying payment or

compensating at miniscule levels for techniques such as tilt-table testing, despite substantial literature documenting its value. The ability to clarify diagnoses and address new therapies is a long-term economic saving that these insurers have tended to ignore. Hopefully, concerted efforts by physician-investigators, practitioners, and professional organizations ultimately will overcome this shortsightedness.

Finally, a recent “crisis” in the United States has surrounded the disappearance of isoproterenol from the marketplace. This drug has multiple uses in the electrophysiologic laboratory, but it has been particularly important in tilt-table testing. It appears that the principal supplier has had manufacturing problems, and the relatively limited income derived from the drug does not seem to merit the supplier’s making the necessary investment to clear this up. Despite the fact that this may be a sound, if somewhat ruthless, business decision, physicians—and especially electrophysiologists—should make every effort to encourage the development of means by which “niche” agents can be made available to the marketplace. In the meantime, perhaps we can avoid the use of other products from suppliers who place their economic advantage ahead of patient needs.

SUMMARY

Prevention of recurrent syncope is critically dependent on establishing the basis for symptoms in each patient. The principal diagnostic step is differentiation of individuals with normal cardiovascular status from those with evident structural disease. In the former, assuming that the medical history or physical examination has not identified another system problem, tilt-table testing should be undertaken. In the latter group of patients, a functional assessment of the suspected structural disturbance and evaluation of susceptibility to tachyarrhythmias and bradyarrhythmias by conventional electrophysiologic testing are appropriate at an early stage. Tilt-table testing should follow if the diagnosis remains in doubt. In only a few instances should special neurologic studies be selected as an initial step. In all cases, the ultimate objective is to obtain a sufficiently strong correlation between the syncopal symptoms and detected abnormalities to permit an accurate assessment of prognosis and initiation of an appropriate treatment plan.

In cases in which structural cardiac or vascular disturbances or primary cardiac arrhythmias are determined to have caused syncope, therapy is relatively well defined. On the other hand, whereas considerable progress is being made, the treatment of neurally mediated reflex syncope, orthostatic syncope, and various neurologic and psychiatric conditions that can mimic syncope is less well established.

THE FUTURE

In recent years, considerable progress has been made in understanding the causes of syncope and the relative frequency with which each class of causes occurs. However, important diagnostic dilemmas remain. Most important, we continue to be limited in our ability to undertake long-term diagnostic monitoring in syncope patients. In this regard, the development of easy-to-use implantable electrocardiographic loop recorders (e.g., Reveal Plus, Medtronic, Inc., Minneapolis, MN) has been important. However, documenting electrocardiography is only part of the problem. Next-generation devices must focus on some assessment of systemic pressure recording. Furthermore, by using wireless communication from implantable devices, it should be possible to effect more rapid recognition of symptomatic rhythm and blood pressure problems, thereby permitting more efficient resolution of potentially hazardous conditions.

Syncope is a multifaceted disorder involving many organ systems. The most important and least understood of these systems is the CNS. In particular, the role of the CNS in neurally mediated syncope, syncope associated with orthostatic hypotension, and the dysautonomias remains a mystery. Future studies need to be directed at better understanding the multiple neurotransmitters and neural pathways associated with these disorders. Studies should address the molecular and genetic factors leading to the apparent increased susceptibility certain individuals exhibit with respect to these forms of syncope. Development of an understanding of these topics will have important implications in terms of the treatment of individuals and, in the most severe cases, the appropriate direction for advice regarding prognosis and family counseling.

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ANTIARRHYTHMIC DRUGS

DAN M. RODEN

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

It is increasingly recognized that drugs used for treating cardiac arrhythmias may not be completely effective and carry substantial risks for adverse effects. These adverse effects can be grouped into three broad categories.

1. *Noncardiovascular adverse effects*. Examples are (a) diarrhea with quinidine, (b) pulmonary toxicity with amiodarone, or (c) tinnitus with lidocaine. Some of these effects are related to high plasma concentrations, and others are not. The expected incidence of these noncardiovascular side effects frequently determines the choice of specific drugs in specific patients.
2. *Proarrhythmia*. Specific syndromes of proarrhythmia can be recognized and associated with specific mechanisms of drug action. These syndromes include (a) torsades de pointes, (b) atrial flutter with 1:1 atrioventricular (AV) conduction, (c) exacerbation of sustained ventricular tachycardia (VT), and (d) an increased incidence of sudden cardiac death (SCD) during long-term antiarrhythmic therapy.
3. *Other cardiovascular adverse effects*. These include (a) bradyarrhythmias and (b) exacerbation of congestive heart failure (CHF).

Despite these shortcomings, antiarrhythmic drugs retain a place in the treatment of cardiac arrhythmias. A solid understanding of the mechanisms that underlie these adverse effects and of the drugs' pharmacokinetics can help minimize the likelihood of adverse effects during long-term treatment.

HISTORICAL PERSPECTIVE

The use of drugs to treat cardiac arrhythmias dates to the mid-eighteenth century, with the initial description of digitalis therapy for "rebellious palpitations," presumably atrial fibrillation (AF) (1). In the early twentieth century, Wenckebach (2) described a Dutch sailor who found he could revert episodes of paroxysmal AF by taking an antimalarial agent derived from the bark of the *Cinchona* plant. Quinidine was found to be the most potent of a series of compounds isolated from this plant, and it became part of the antiarrhythmic armamentarium in the 1920s. Local anesthetic drugs and their derivatives, notably procainamide and lidocaine, began to be used as antiarrhythmics in the 1950s.

From these empiric beginnings, many of the subsequent developments in antiarrhythmic drug therapy have focused on developing better-tolerated compounds that mimic one or more of the important electrophysiologic actions of quinidine, procainamide, or lidocaine. Such focus resulted in the marketing of a number of new compounds in the late 1970s and 1980s.

1. Flecainide and encainide emerged from a search for more potent sodium channel–blocking analogs of procainamide.
2. Disopyramide emerged from a search for drugs that would mimic the effects of quinidine.
3. Mexiletine and tocainide were developed as lidocaine analogs.

Cardiac Arrhythmia Suppression Trial

Although antiarrhythmic drugs have diverse electrophysiologic and other pharmacologic properties, they all block cardiac sodium channels. In 1989, the Cardiac Arrhythmia Suppression Trial (CAST) investigators (3) reported that therapy with encainide and flecainide unexpectedly increased mortality in patients who were recovering from myocardial infarction (MI). This finding, along with an evaluation of a third sodium channel blocker, moricizine, by the CAST investigators (4) and other large but less well-controlled trials (5,6) that reported nevertheless suggestive data, raised serious concerns about the safety of sodium channel–blocking drugs.

Action Potential Prolongation

As a consequence of CAST, drug development moved rapidly away from sodium channel blockade and toward action potential (AP) prolongation as an antiarrhythmic intervention. In animal models (7,8,9 and 10), drugs that prolong cardiac APs have been shown to prevent ischemic ventricular fibrillation (VF), lower defibrillation energy requirements, and improve cardiac contractility. These are all desirable antiarrhythmic drug effects and are in direct contrast to the effects of sodium channel blockers (9,11). As described in more detail in this chapter, virtually all available drugs that prolong cardiac AP do so by blocking one specific cardiac ion current, termed I_{Kr}. An apparent class action of I_{Kr} blockers is the occasional development of marked QT prolongation and polymorphic VT called *torsades de pointes*. In 1995, the gene that encodes the protein responsible for I_{Kr} was identified, and mutations in the gene were found to be one cause of the congenital long QT syndrome (LQTS),

also associated with a high incidence of torsades de pointes (12,13). These molecular data suggest that if AP prolongation is to be successful as an antiarrhythmic mode of drug action, I_{Kr} blockade may not be the safest means of achieving this goal.

Calcium Channel Blockers

In the mid-1970s, calcium current was identified as playing a crucial role in mediating conduction under normal circumstances in some tissues, such as the sinus node and AV node (see Chapter 58, Chapter 65, and Chapter 66). Thus, drugs such as verapamil or diltiazem that block cardiac calcium channels at clinically useful dosages exert antiarrhythmic effects that slow ventricular response in AF or flutter and terminate or prevent reentrant arrhythmias that include the AV node as part of their circuit. Other calcium channel blockers such as nifedipine and other dihydropyridines target vascular tissue and do not exert antiarrhythmic properties. In fact, the sympathetic activation that may occur with dihydropyridine-mediated vasodilation can precipitate arrhythmias. In some animal models (14), calcium channel blockade can prevent ischemic VF. However, large clinical trials (15) have generally failed to demonstrate substantial effects of calcium channel blockade on mortality after MI. In fact, calcium channel blockers may increase mortality when used in patients with advanced ventricular dysfunction (16).

Beta-Blockers

The one drug effect that has repeatedly been shown to reduce mortality in patients who are recovering from MI is beta-blockade. In the early 1980s, three large trials (17,18 and 19) that used metoprolol, timolol, and propranolol demonstrated reduction in mortality with beta-blockade, and data from these and other studies (20) suggest that such blockade is mediated at least in part by a reduction in ischemic VF. Whether drugs with intrinsic sympathomimetic activity exert this mortality-sparing effect is the subject of some controversy. In addition, it cannot be assumed that drugs that produce beta-blockade and other important pharmacologic actions necessarily exert the same mortality-sparing effect. The mechanism by which beta-blockers reduce mortality after MI remains unclear. Studies using animal models (20) have found that beta-blockers usually exert only modest effects on the electrophysiology of the normal ventricle but that they produce a potent suppressant effect on ischemic VF. It is also possible that beta-blockers reduce mortality by some mechanism not directly related to an electrophysiologic effect; prevention of plaque rupture due to reduced intracoronary shear is one possibility.

Amiodarone

Amiodarone is a thyroid hormone analog that was developed in the 1960s to interfere with the actions of thyroid hormone on the heart, thereby decreasing angina (21). Indeed, amiodarone exerts coronary vasodilatory properties. Subsequently, amiodarone was found to prolong cardiac AP (22) and to be an effective antiarrhythmic in a number of clinical settings (23). The mechanisms by which amiodarone exerts its arrhythmia-suppressing effects are not known, and the drug has many pharmacologic properties including antiadrenergic effects that may explain its antiarrhythmic actions. The effects of amiodarone have also been evaluated in patients who are recovering from MI. Two large trials, the European Myocardial Infarction Amiodarone Trial (EMIAT) and the Canadian Myocardial Infarction Amiodarone Trial (CAMIAT), have studied amiodarone versus placebo in patients with recent MI (24,25). These trials had some differences in study design. CAMIAT randomized patients with recent MI and premature ventricular complexes [regardless of ejection fraction (EF)], whereas EMIAT randomized those with recent MI and an EF of less than 40% (regardless of premature ventricular complexes). CAMIAT was powered to detect a 50% reduction in arrhythmic mortality, whereas in EMIAT the primary end point was a 35% decrease in total mortality. In neither trial was the primary end point reached, although survival was no worse with amiodarone. Also, a high incidence of dropout occurred in both studies (e.g., 42% dropout rate on amiodarone vs. 29% dropout rate on placebo in CAMIAT). The main reason for study dropout was hypothyroidism (10%) and pulmonary infiltrates (3%). Thus, amiodarone is safer than sodium channel blockers in post-MI patients who require antiarrhythmic therapy for other reasons. It does not appear to be as effective as beta-blockers in reducing mortality, although head-to-head comparisons have not been performed, and some patients with reduced ventricular function tolerate amiodarone but not beta-blockers. Retrospective analyses of these trials have also indicated that combined therapy with amiodarone and beta-blockers, if tolerated, may be superior to either drug alone (26).

Changing Indications

A historical perspective on antiarrhythmic drugs includes not only the chronology in which drugs were developed and became available to practicing physicians but also a consideration of evolving concepts on which patients are or are not appropriate candidates for antiarrhythmic drugs. A major shift in philosophies has occurred since the late 1980s because of the increasing awareness of the risks of long-term antiarrhythmic therapy (i.e., notably an increase in mortality as exemplified in CAST and the increasingly appreciated risk for torsades de pointes with some QT-prolonging drugs) as well as the availability of new therapies, such as ablation or implanted devices, for long-term management of some arrhythmia syndromes. Although in the mid-1980s it was common practice to use drugs to suppress minimally symptomatic, or even asymptomatic, nonsustained arrhythmias detected incidentally (e.g., by Holter monitoring), this is no longer the case due to the increasing appreciation of the risks of such therapy. CAST found that suppressing asymptomatic ventricular ectopic activity did not reduce long-term mortality. However, CAST findings do not alter the fact that patients with nonsustained VT and depressed left ventricular (LV) performance are at high risk for SCD. Prospective identification of even asymptomatic patients at very high risk may allow effective therapies to be implemented. Indeed, the Multicenter Autonomic Defibrillator Implantation Trial (MADIT) (27), which studied a small group of high-risk individuals (n = 196), suggested that patients benefited from an implantable cardioverter-defibrillator (ICD). In Antiarrhythmics versus Implanted Devices (AVID), patients who were resuscitated from SCD did better with ICD therapy than with antiarrhythmics (28). In the Multicenter Unsustained Tachycardia Trial (MUSTT), asymptomatic “high-risk” (low EF, ventricular premature contractions, coronary disease) patients with sustained ventricular arrhythmias induced by programmed stimulation had improved survival with antiarrhythmic therapy (as opposed to no specific therapy for arrhythmias), but benefit was confined to patients who received ICDs, and in fact patients with inducible arrhythmias who received antiarrhythmic drugs fared slightly worse than individuals receiving no specific antiarrhythmic therapy (29).

For many patients with paroxysms of regular tachycardia (i.e., atrial tachycardia, AV nodal reentrant tachycardia, AV reentrant tachycardia, or VT), ablative therapy or antitachycardia pacing approaches are gaining wider acceptance for long-term management. Thus, the major indications for long-term antiarrhythmic drug therapy are AF, prevention of recurrent VF or rapid VT (often in conjunction with an ICD), and management of other arrhythmic syndromes that for some specific reason (e.g., ablation failure, general infirmity) make nonpharmacologic therapy less attractive. These considerations do not apply to therapy that is designed to terminate an ongoing tachycardia acutely, in which case drug therapy and direct current cardioversion continue to play a primary role.

Treatment of cardiac arrhythmias has moved from the completely empiric basis of the mid-eighteenth century to an increasing appreciation of the diverse mechanisms that may underlie cardiac arrhythmias and of the molecular mechanisms of action of older as well as newly available compounds. It seems entirely likely that as this knowledge continues to expand, new compounds devoid of serious toxicity that target specific arrhythmic mechanisms may well develop, supplanting the highly nonspecific and poorly tolerated drugs currently available.

PATHOPHYSIOLOGY

The three major mechanisms that underlie cardiac arrhythmias—enhanced automaticity, triggered activity, and reentry—are discussed in detail elsewhere (see Chapter 58). In most cases, choosing an antiarrhythmic drug for terminating ongoing arrhythmias or for suppressing recurrent episodes is based not on an understanding of specific mechanism(s) but on clinical experience. This experience includes not only determining what drug is likely to be effective against a particular arrhythmia but also estimating the risk for serious cardiac side effects from a particular drug in a particular patient, as well as estimating the risk for noncardiac side effects. This approach has proved effective because the drugs that are available are quite nonspecific (i.e., they produce a multiplicity of cardiac and noncardiac effects) and detailed characterization of the mechanisms underlying individual arrhythmic syndromes has not been considered part of routine clinical care until recently. The underlying mechanisms of individual arrhythmic syndromes have increasingly been characterized. As such information becomes available, it may be possible to choose antiarrhythmic therapy on the underlying basis of the mechanisms of individual arrhythmias and on the likelihood that an individual drug will disrupt a weak link in those mechanisms, restoring normal rhythm. This approach, popularized as the Sicilian Gambit in the early 1990s (30), seems self-evident. However, for many arrhythmias, there is insufficient information detailing the mechanisms, or in other cases appropriate drugs are not yet available to target weak links in individual arrhythmias. Conversely, an understanding of the putative mechanism underlying an individual arrhythmia in a particular patient may help the clinician avoid using drugs that are likely to prove ineffective or to exacerbate an individual arrhythmia. eTable 72.0.1 lists the mechanisms of the specific arrhythmias and provides clinical examples of arrhythmias caused by those mechanisms as well as drug effects that may be antiarrhythmic (or are contraindicated) in those mechanisms.

***e*TABLE 72.0.1** ANTIARRHYTHMIC DRUG THERAPIES, TARGETED TO AN UNDERSTANDING OF UNDERLYING MECHANISMS[a,b]

		Drug actions that may be antiarrhythmic					
		Na^+ channel block					
Arrhythmia mechanism	**Clinical examples**	**Lidocaine + congeners[c]**	**Others[d]**	**Beta-blockade**	**Ca^{2+} channel block**	**↑ APD[e]**	**Other**
Enhanced normal automaticity	Sinus tachycardia			✔			
	Some “idiopathic” VTs		✔				
Abnormal automaticity	Ectopic atrial tachycardia						

	Suppress arrhythmia		✔		✔	✔	
	Control rate			✔	✔		
	Accelerated idioventricular rhythm	✔	✔				
EAD-related triggered activity	Torsades de pointes					✘	
	Shorten APD	✔					Pacing; isoproterenol
	Block triggering			✔	[✔]		Magnesium
DAD-related triggered activity	Digitalis toxicity						Antidigoxin antibodies
	Exercise-induced VT originating in RVOT or (L) posterior fascicle			✔	✔		Adenosine
Reentry using defined circuit(s)	AV nodal reentry/AV reentry[f]		✔	✔	✔	✔	Adenosine [digitalis] [increased vagal tone (phenylephrine, edrophonium)]
	Atrial flutter						
	Slow ventricular rate			✔	✔		Digitalis: ✔
	Terminate tachycardia		✔			✔	
	Prevent recurrence		✔			✔	
	VT with LV scarring (e.g., post-MI)						
	Acute termination	✔	✔/✘[g]		✘	✔	
	Prevent recurrence	✔	✔/✘[g]	✔		✔	
Reentry without defined circuit	Atrial fibrillation						Digitalis: ✔
	Slow ventricular rate			✔	✔		
	Terminate tachycardia		✔?			✔	
	Prevent recurrence		✔			✔	
	Atrial fibrillation with ventricular preexcitation				✘		Digitalis: ✘
	Slow ventricular rate		✔			✔	
	Terminate arrhythmia		✔			✔	
	VF						
	Acute termination	✔	✔			✔	
	Prevent recurrences	✔	✔	✔		✔	

✔, indicated; ✘, contraindicated; [], approaches that are not widely used clinically or that are theoretical but as yet unproven; APD, action potential duration; AV, atrioventricular; DAD, delayed afterdepolarization; EAD, early afterdepolarization; LV, left ventricular; MI, myocardial infarction; RVOT, right ventricular outflow tract; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]For further discussion of the choice of drugs in individual arrhythmias, see specific chapters.

[b]For some arrhythmias, nonpharmacologic approaches may be the acute or long-term treatment of choice; see text and specific chapters for a fuller discussion. In addition, the mechanisms underlying isolated ectopic beats, in the atrium or ventricle, have not been established and may be multifactorial; these generally require no therapy.

[c]Lidocaine congeners: mexiletine, tocainide.

[d]Includes disopyramide, flecainide, moricizine, procainamide, propafenone, and quinidine.

[e]Includes drugs such as amiodarone, bretylium, disopyramide, procainamide, quinidine, and sotalol that produce other important effects, as well as ibutilide.

[f]Acute termination is generally accomplished with adenosine or verapamil; prevention of recurrences with verapamil (in the absence of preexcitation) or flecainide.

[g]Contraindications specifically include flecainide and moricizine (see text).

Basic electrophysiologists have identified multiple ion currents in individual cardiac cells. This information allows not only identification of specific currents that are blocked by the drugs described in this chapter but also of factors such as rate and hypokalemia that can modulate this block. As described in this chapter, these data have direct implications for the clinical use of antiarrhythmic drugs. More recently, a combination of cellular electrophysiologic and molecular biologic techniques has enabled the cloning of individual genes whose protein products are responsible for individual ion currents. Studies (31,32) have identified specific regions on these proteins, and occasionally even specific amino acids, at which drug binding occurs. This information may ultimately prove useful in designing new antiarrhythmic molecules. It should be pointed out that virtually no data are available attesting to the long-term safety of any drug whose primary mode of action is to block an ion channel. Thus, another implication of such advanced molecular information is that entirely new targets may be identified at which new drugs may act to modify cardiac electrophysiology in clinically effective and safe manners.

CLINICAL PROFILES

Schemes that classify antiarrhythmic drugs by their major ionic mechanisms of action are commonly used. Their usefulness lies in the fact that they may allow clinicians to predict the therapeutic outcome of one drug based on the outcome of another. However, as mentioned previously, a major limitation of many currently available drugs is the likelihood of noncardiac side effects, which do not track with classification schemes. Moreover, members of the same drug class or subclass may exert subtle, or sometimes not so subtle, differences in pharmacologic actions, leading to different outcomes.

Sodium Channel Blockade

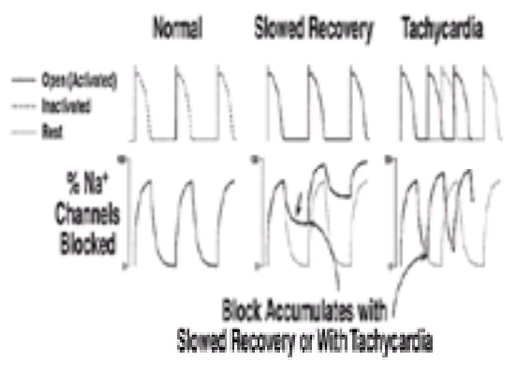
Although many antiarrhythmic drugs block cardiac sodium channels (eTable 72.0.2), their clinical electrophysiologic effects vary. A major factor that underlies this variability is the rate at which a drug dissociates from the sodium channel (33). During each AP, drug associates with the channel, and with each diastolic period, drug dissociates. If this dissociation rate is rapid [e.g., a time constant (t) <1 second], no channels are blocked with the next AP (eFig. 72.0.1). Thus, substantial sodium channel blockade only occurs with a rapidly dissociating drug such as lidocaine at fast rates (*shorter diastole*) or under conditions in which dissociation is slowed (e.g., ischemia). On the other hand, with flecainide, dissociation is so slow that substantial sodium channel blockade occurs even at slow rates. If sodium channel blockade accumulates (with lidocaine, at fast rates; with flecainide, at any rate), the most important electrophysiologic effect in cardiac tissue is to slow conduction; this is manifested by widening of the QRS interval. Thus, drug-induced sodium channel blockade is greater at fast rates, and hence QRS prolongation is exaggerated at more rapid rates. With rapidly dissociating drugs, such as lidocaine, no widening of the QRS interval manifests at usual rates. With other drugs, such as flecainide or quinidine, QRS prolongation is the rule at therapeutic dosages. Sodium channel blockade can also alter pacing and defibrillation energy requirements; the latter has become less of a problem with the implementation of biphasic waveforms in ICDs. Conduction slowing is actually a *pro*arrhythmic effect in reentrant arrhythmias (see Chapter 58). The mechanisms by which sodium channel blockade suppresses arrhythmias are not completely understood but may include a bidirectional block in reentrant circuits (by effects on impulse propagation or on refractoriness) or suppression of abnormal automaticity.

***e*TABLE 72.0.2** MAJOR PHARMACOLOGIC EFFECTS OF ANTIARRHYTHMIC DRUGS

	Na^+ channel block[a]				Autonomic effects		
	t <1 sec	**t >1 sec**	**↑ APD**	**Ca^{2+} channel block**	**Beta-blockade**	**Other**	**Comments/other actions**
Adenosine							✔: adenosine receptor blockade
Amiodarone	✔		✔	✔		✔[b]	✔: potent inhibitor of depolarization-induced automaticity
Beta-blockers					✔		
Bretylium			✔[c]			✔: initial sympathetic stimulation, followed by inhibition of norepinephrine reuptake	
Calcium channel blockers				✔			
Digitalis glycosides						✔: vagolytic	✔: inhibitor of Na^+-K^+ pump
Disopyramide		✔	✔			✔: anticholinergic	
Dofetilide			✔				
Flecainide		✔	[✔]	[✔]			
Ibutilide			✔				
Lidocaine	✔						
Magnesium				✔?			
Mexiletine	✔						
Moricizine		✔					

Procainamide	✔		✔			✔: ganglionic blockade (especially i.v.)	
Major metabolite: NAPA			✔				
Propafenone		✔			✔		Extent of beta-blockade genetically determined
Quinidine		✔	✔	[✔]		✔: alpha-blocker	
Sotalol			✔		✔		
Tocainide	✔						

APD, action potential duration; NAPA, *N*-acetylprocainamide; [ ], minor effects that may not be clinically important.
[a]The clinical effects of sodium channel blockers depend in part on the time constant for recovery from block (t), as described in the text (*e*Fig. 72.0.1).
[b]The antiadrenergic effect produced by amiodarone resembles that of beta-blockers, but it is "noncompetitive"—that is, it cannot be overcome by increasing doses of an agonist such as isoproterenol.
[c]QT interval prolongation is not prominent with bretylium; the major effect appears to be reduction in dispersion of repolarization times.



***e*FIGURE 72.0.1** Rate dependence sodium channel blockade. The left panel shows a series of action potentials (APs), along with the extent of sodium channel blockade (*bottom panel*). The sodium channel shuttles among three states during the AP: open, inactivated, and rest, as indicated in the top APs. Most sodium channel blockers that are used clinically bind to open or inactivated channels, or both. Therefore, sodium channel blockade increases during the AP and decreases during each diastolic (rest) interval. A rapidly dissociating drug, such as lidocaine, is shown here. If the dissociation rate of the drug from the channel is decreased (*middle*), the extent of drug blockade can increase even in the absence of a change in rate. This is the case with lidocaine during ischemia or with flecainide. The right panel shows that even with a rapidly dissociating drug such as lidocaine, sodium channel blockade can develop if the rate is accelerated. In the middle and right panels, the dotted lines indicate the data presented in the left panel. (From Roden DM, Echt, DS, Murray KT, Lee JT. Clinical pharmacology of antiarrhythmic agents. In: Josephson ME, ed. *Sudden cardiac death*. Malden, MA: Blackwell Science, 1993:163–210, with permission.)

Proarrhythmic Effects of Sodium Channel Blockers

Therapy using sodium channel blockers such as flecainide has been associated with suppression of nonsustained ventricular arrhythmias and of paroxysmal AF. However, conduction slowing in patients with known atrial flutter and in some patients with atrial flutter or AF with no history of atrial flutter may sometimes lead to a marked slowing, but not termination, of the atrial flutter rate. With sufficient slowing, 1:1 AV conduction may ensue. To complicate the clinical picture further, because drugs such as flecainide block sodium channels more extensively at rapid than at slow rates, the ventricular complexes broaden and occasionally may even become aberrant. Thus, the clinical picture of this form of arrhythmia exacerbation is a patient with AF in whom wide, complex regular tachycardia then develops; it is not a surprise, therefore, that this arrhythmia is frequently misdiagnosed as VT (34,35). Management of this arrhythmia consists of acknowledging the possibility of its occurrence, withdrawing the potentially offending antiarrhythmic agent, and using AV nodal blocking drugs. Adenosine may be useful in establishing the diagnosis.

Conduction slowing in the ventricle usually only results in QRS prolongation. However, when a reentrant circuit due to ventricular scarring is present (e.g., in the post-MI patient), conduction slowing by sodium channel blockers can increase the frequency of VT while often slowing its rate. Such drug-facilitated VTs may be very resistant to cardioversion and may prove fatal (36). Some animal and a limited number of human studies (37,38) have suggested that sodium boluses may be effective in this setting.

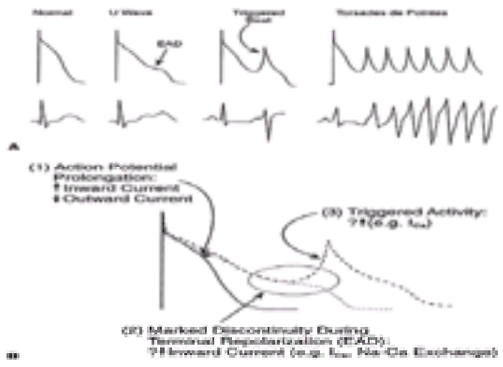
Another proarrhythmic effect of sodium channel blockers is the increase in mortality observed in CAST. The mechanism(s) responsible for this finding remain(s) unclear. However, evidence from animal studies and the CAST database (39,40 and 41) strongly suggests that in the presence of sodium channel blockade, recurrent myocardial ischemia may enhance the likelihood of fatal ventricular arrhythmias such as VF. For example, pretreatment with the sodium channel blocker aprindine in dogs before coronary occlusion was found to increase the incidence of VF following occlusion (42). In CAST, the relative risk of encainide or flecainide therapy in patients with transmural MI was 1.7 compared with those given placebo. However, among those patients with non–Q-wave MIs, a group thought to be at much higher risk for subsequent ischemic events, the relative risk was much higher, 8.7 (39).

Action Potential Prolongation

The hallmark of AP prolongation, a so-called class III effect, is QT prolongation. Drugs that produce this effect share a number of desirable features, including decreased defibrillation energy requirement, efficacy in models of ischemic VF, and increased contractility. Their major antiarrhythmic action is probably attributable to the prolongation of refractoriness that accompanies increased AP; this, in turn, is thought to suppress reentrant arrhythmias by decreasing the likelihood of unidirectional block (see Chapter 58).

Mechanisms of QT Prolongation Drug-Induced Torsades de Pointes

Although most drugs that prolong cardiac AP have the potential to cause torsades de pointes, amiodarone is an exception (43). Important clinical features of this syndrome include hypokalemia and a typical series of cycle-length changes (i.e., short-long-short), leading to an apparent bradycardia—or pause—dependence. Studies have shown that exposure of AP from the canine conducting system that is exposed to analogous clinical conditions (i.e., the presence of QT-prolonging antiarrhythmic, low extracellular potassium is slow drive rate) results in discontinuities in terminal repolarization, known as early *after-depolarizations* (*EADs*). Occasionally, *de novo* upstrokes can develop from EADs, and it is thought that these triggered beats are the likely initiators of torsades de pointes (*e*Fig. 72.0.2). The mechanisms that underlie the maintenance of the arrhythmia, and its frequent spontaneous termination, are speculative, but either repetitive triggered activity or reentry across the ventricular wall, perhaps dependent on heterogeneity of AP durations across the wall, have been suggested (44). Current thinking suggests that multiple cellular electrophysiologic changes are required to initiate EADs and triggered upstrokes (*e*Fig. 72.0.2). The first is a change in the balance between inward (*depolarizing*) currents, such as the sodium or calcium current, and outward (*repolarizing*) currents, generally potassium or chloride currents. Most antiarrhythmic drugs that prolong the QT interval do so by blocking outward currents and, in particular, by blocking one component of outward current known as I_{Kr} (45). Enhancement of inward current has been suggested for at least one available drug, ibutilide (46), but this remains controversial (47,48). However, enhanced inward current or decreased outward current cannot explain EADs and triggered activity. Rather, it seems likely that with sufficiently delayed repolarization, a normally functioning calcium current or the sodium-calcium exchanger provides a secondary source of inward current, accounting for the EAD and the upstroke (49,50,51 and 52). Torsades de pointes can occur not only with exposure to QT-prolonging antiarrhythmic drugs but also with the congenital LQTS. Identification of mutations in the genes that encode I_{Kr} or other K^+ channels [I_{Ks}] (to decrease outward current) or the cardiac sodium channel (to increase inward current) provides an explanation for the striking similarities between the congenital and the drug-induced syndromes (12,53).

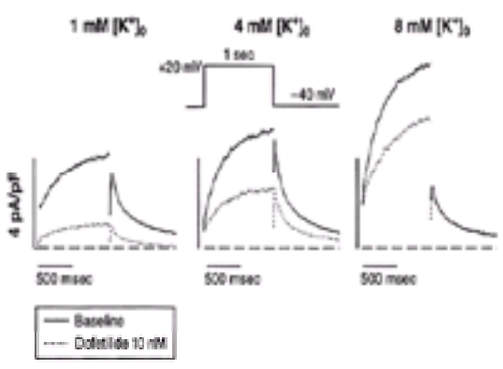


***e*FIGURE 72.0.2** Electrophysiologic mechanisms underlying torsades de pointes. Shown in **A** is one relationship between action potential (AP; *top*) and electrocardiographic complexes (*bottom*). It is thought that triggered beats arising from early after-depolarizations (EADs) produce single-triggered beats and torsades de pointes. The mechanism whereby triggered activity results in torsades de pointes remains speculative. Shown in **B** are electrophysiologic abnormalities resulting in EADs and triggered activity. At least three abnormalities are present. I_{Ca}, calcium current. (From Roden DM. Early afterdepolarizations and torsades de pointes: implications for the control of cardiac arrhythmias by controlling repolarization. *Eur Heart J* 1993;14:56–61, with permission; and Roden DM, Lazzara R, Rosen MR, et al., for the SADS Foundation Task Force on LQTS. Multiple mechanisms in the long QT syndrome: current knowledge, gaps, and future directions. *Circulation* 1996;94:1996–2012, with permission.)

A 51-year-old female patient with torsades de pointes.

Therapies for QT Prolongation Drug-Induced Torsades de Pointes

An understanding of these mechanisms can lead directly to an appreciation of therapies that are effective in torsades de pointes. The clinician should recognize torsades de pointes not simply by the presence of polymorphic VT; a markedly prolonged QT interval, often with prominent U waves, and the bradycardia-dependent onset of the tachycardia should also be present. The presence of polymorphic VT in the absence of QT changes before or after the arrhythmia suggests that other mechanisms, often acute myocardial ischemia, may be operative. Therapies such as isoproterenol infusion that are useful in torsades de pointes can be devastating in other forms of polymorphic tachycardia. Withdrawal of any QT-prolonging drugs and correction of serum potassium are the next steps in management. *In vitro* studies (54,55) have suggested that elevating extracellular potassium has two important effects in torsades de pointes: (a) It increases the magnitude of activating I_{Kr} (and thereby shortens the QT interval), and (b) it appears to reduce the potency of I_{Kr} blockers (*e*Fig. 72.0.3), another antiarrhythmic effect in this setting.



***e*FIGURE 72.0.3** Tracings of the outward (rectifier) potassium current (I_{Kr}) are shown at baseline (*solid lines*) and after exposure to the specific I_{Kr} blocker, dofetilide (*dotted lines*). The zero current level is indicated by the dashed line in each panel. The currents were elicited by 1-second depolarization to +20 mV, followed by repolarization to –40 mV, as indicated in the middle panel. In the absence of the drug, outward current during the step to +20 mV was greatest when extracellular potassium was elevated (*right panel*). In contrast, the extent to which the drug blocked the current was greatest with low extracellular potassium (*left panel*). These data help explain the clinical findings that action potentials and the QT interval are prolonged in hypokalemia and that hypokalemia appears to markedly potentiate the QT-prolonging effects of drugs such as dofetilide and quinidine. pA/pF, current per unit cell surface area.

Strong, albeit anecdotal, evidence (56) indicates that magnesium therapy can prevent recurrences of torsades de pointes. The likely mechanism is a block of the secondary inward current (e.g., the L-type calcium current) because magnesium therapy does not generally shorten the QT interval. The mainstay of therapy for recurrent torsades de pointes is to increase the heart rate, either with isoproterenol infusion or with external or transvenous pacing. In patients with congenital LQTS, long-term therapy with beta-blockers or other antiadrenergic interventions can be quite effective, presumably by reducing L-type calcium current. The description of specific mutations in ion channel genes in congenital LQTS has led to identification of specific subsets of patients with the condition. For example, among patients with lesions that interfere with normal sodium channel inactivation, torsades de pointes commonly occurs at rest or during sleep, the QT interval shortens normally (or even supernormally) with exercise, and the QT interval can be shortened by sodium channel blocking drugs such as mexiletine or flecainide (57,58). Whether such therapy reduces the incidence of SCD remains to be determined.

Continue or Discontinue QT-Prolonging Therapy in Drug-Induced Torsades de Pointes?

A vexing question in the management of patients with drug-induced torsades de pointes is whether they should ever be exposed again to QT-prolonging drugs. Often, a triggering factor such as bradycardia or hypokalemia is present at the time of the arrhythmia, which has been corrected. Most clinicians, however, are somewhat reluctant to continue QT-prolonging therapy in such individuals because a risk factor(s) of which we are not yet aware or which is not readily correctable may still be present and confer an increased risk for subsequent torsades de pointes. Unfortunately, there are no solid data addressing this point. Other risk factors for torsades de pointes may include AF [in which cases torsades de pointes frequently occurs after conversion to normal rhythm (59)], left ventricular hypertrophy, and female gender (60). For most drugs that may induce torsades de pointes, higher doses or higher plasma concentrations elevate the risk; quinidine is an exception. Subclinical mutations in genes such as those that encode K^+ channels or the sodium channel have been identified in some patients with drug-induced torsades de pointes, although the extent to which the development of torsades de pointes is genetically determined is not yet established (61,62).

PRINCIPLES OF DRUG USE

The fundamental principles of using antiarrhythmic drugs are no different from those applied when using any other drug.

1. Define a benefit for therapy.
2. Define an end point for therapy.

3. Minimize the risks (and ensure that these do not outweigh the expected benefits).
4. Define the need for therapy.
5. Consider alternative therapies.

Because the risks of antiarrhythmic therapy, particularly with long-term treatment, are relatively high and the benefits of treatment in many cases are at least partially illusory, it is important to adhere closely to these principles (63).

In acutely terminating ongoing sustained arrhythmias, there is little doubt that intravenous (i.v.) antiarrhythmic drugs can be highly effective.

1. Adenosine or verapamil is highly effective for AV-nodal reentrant tachycardia.
2. Lidocaine, procainamide, amiodarone, or sotalol (in Europe) is effective for sustained VT.
3. Ibutilide is effective for AF or flutter.
4. Procainamide, bretylium, lidocaine, or amiodarone is effective for recurrent VT or VF.

In each setting, risks are well recognized, but because the patient is being continuously monitored, these risks can be identified early and prevented or treated. With long-term antiarrhythmic therapy, it has been much more difficult to establish a clear benefit for treatment; risks, including proarrhythmia, other cardiovascular side effects such as CHF or bradyarrhythmias, and noncardiovascular toxicities, become a much greater concern.

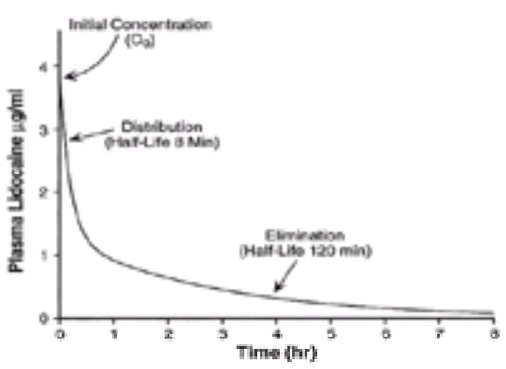
A specific arrhythmia diagnosis should be established before therapy is initiated. For example, verapamil may be an effective drug for treating VT that arises in the right ventricular outflow tract in patients with a structurally normal heart, whereas it is dangerous to use in reentrant VT in patients with remote MI (64).

For long-term therapy of paroxysmal arrhythmias, it is important to recognize the phenomenon of ascertainment bias. Patients with symptomatic arrhythmias, such as paroxysmal AF or frequent ICD discharges due to sustained VT, frequently display spontaneous unexplained variability in arrhythmia events. Such symptomatic patients are most likely to present to a physician during a period of high arrhythmia event frequency. Thus, institution of even ineffective therapy can appear to lower the frequency of arrhythmic events. In the case of AF, it is useful to establish some sense of the frequency of the arrhythmic episodes before initiating therapy. This approach is not usually possible for patients with very frequent ICD discharges that cannot be controlled in other ways (e.g., device reprogramming). However, even here, the physician should remain vigilant to the possibility that apparently effective antiarrhythmic therapy may, in fact, play very little role in reducing the frequency of arrhythmic episodes, and if drug side effects develop, discontinuation of the antiarrhythmic can still be considered.

Pharmacokinetic Principles

Because there is a small margin between dosages of antiarrhythmic drugs that may suppress arrhythmias and dosages that can produce serious or even life-threatening toxicities, an understanding of the principles that determine drug disposition is useful in guiding therapy. The processes that determine drug disposition, absorption, distribution, metabolism, and elimination are generally first order; that is, the rate of each process is determined by the amount of drug present. A characteristic of any first-order process is that it occurs exponentially as a function of time and is therefore conveniently described using half-lives. In one half-life, 50% of a given process is complete; in two half-lives, 75%; in three half-lives, 87.5%; in four half-lives, 93.75%; and so forth. Thus, any first-order process is near complete in four to five half-lives.

When drugs are administered intravenously, the time course of drug disappearance from plasma is often biexponential (eFig. 72.0.4). The usual explanation is that distribution occurs rapidly (accounting for a first exponential term), whereas elimination occurs more slowly (accounting for the slower exponential terms). For example, when a bolus of lidocaine is administered intravenously, plasma concentrations drop precipitously, with a half-life of 8 minutes. This reflects distribution of lidocaine into peripheral site(s). As one drug is distributed, elimination, a second slower process that occurs with a half-life of 2 hours, becomes more important (eFig. 72.0.4).



***e*FIGURE 72.0.4** Plasma concentration-time profile following a rapid bolus of lidocaine. Plasma concentrations decline biexponentially. The first phase of very rapid decreases in plasma lidocaine corresponds to distribution, with a half-life of 8 minutes. The terminal phase corresponds to elimination by metabolism, with a half-life of 2 hours. The plasma concentration directly after the bolus (C_0) can be used to estimate the central volume of distribution (dose $\neq C_0$).

Absorption and Metabolism

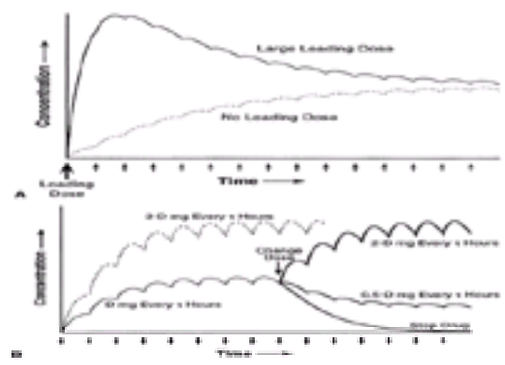
Distribution processes are generally most apparent with intravenously administered drugs. When a drug is given orally, absorption usually occurs sufficiently slowly so as to mask any rapid distribution. The amount of drug that actually reaches the systemic circulation, expressed as a percentage of total administered dose, is referred to as *bioavailability*. Bioavailability is commonly less than 100% following administration of a drug for two major reasons. First, the physicochemical characteristics of some drugs may not permit the gastrointestinal (GI) tract to absorb 100% of the drug. Amiodarone is only 30% to 50% bioavailable (65), probably for this reason. Second, some drugs are completely absorbed but undergo extensive metabolism, usually in the liver (or gut wall), before reaching the systemic circulation (66). The extent of this first-pass metabolism can be quite large and accounts for the fact that for some drugs much greater dosages must be given orally rather than intravenously to achieve therapeutic effects. Verapamil and propranolol are excellent examples; several hundred milligrams must be given orally to achieve the same plasma concentrations as less than 10 mg i.v.

Protein Binding

Another factor that can determine drug effect is protein binding. Many drugs are bound to plasma proteins, usually albumin. Another common ligand for many antiarrhythmic drugs is $alpha_1$-acid glycoprotein, an acute-phase reactant whose plasma concentrations are elevated with stresses such as acute MI or trauma. When $alpha_1$-acid glycoprotein is elevated, the amount of unbound drug that is available to exert pharmacologic effects is reduced. Thus, for example, some patients require (and tolerate) higher than usual lidocaine or quinidine concentrations to suppress arrhythmias shortly after MI (67).

Elimination Half-Life

Loading doses can be used to achieve a desired therapeutic drug effect rapidly. The magnitude of a loading dose can be estimated from the central volume of distribution (eFig. 72.0.4). However, the eventual steady-state plasma concentration that is achieved is determined by the elimination rate: Steady state is approached in four to five elimination half-lives, and this time is not abbreviated by the use of loading regimens (eFig. 72.0.5). Therefore, loading regimens are appropriate when a rapid drug effect is desired (e.g., to terminate an arrhythmia acutely) or when the elimination half-life of the drug is so long that no therapeutic effect would occur in a reasonable time with the institution of maintenance dosages only (e.g., amiodarone). In the absence of these two situations, the use of loading dosages carries some increased risk for side effects (and little added benefit) and therefore is not recommended.



***e*FIGURE 72.0.5** Effect of loading doses and of dose changes during chronic oral therapy. **A:** Hypothetical plasma concentrations are plotted as a function of time during long-term oral therapy. The arrows on the abscissa indicate the times at which a dose is administered, and the heavy arrow at the intercept indicates a loading dose. The administration of a loading dose does not abbreviate the time required to achieve steady-state concentrations, and it does not alter the steady state achieved. **B:** Concentration-time profiles in the absence of a loading dose. The tracings (*left*) show the time course of drug accumulation to steady state. The steady state achieved is twice as great when the dosage is doubled (*dashed line*), but the time course of accumulation to steady state remains the same. Following a change in dosing regimen (or discontinuation of the drug), the time required to achieve the new steady state is similarly four to five elimination half-lives. (From Roden DM, Echt DS, Murray KT, Lee JT. Clinical pharmacology of antiarrhythmia agents. In: Josephson ME, ed. *Sudden cardiac death*. Malden, MA: Blackwell Science, 1993:163–210, with permission.)

Clearance

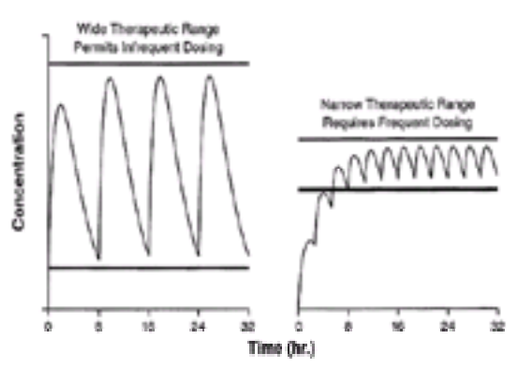
Although the time to steady state is determined by the elimination half-life, the actual steady state achieved is determined by the dose administered (eFig. 72.0.5) and by clearance, most readily defined as dose divided by mean plasma concentration. Clearance and elimination half-life are not synonymous, because elimination half-life is determined not only by clearance but also by volume of distribution. For example, in the case of lidocaine, volume of distribution and clearance are reduced in CHF, leaving elimination half-life unchanged (68). Therefore, loading regimens must be reduced in CHF (*volume of distribution effect*), and maintenance infusions should be reduced to avoid toxicity (*clearance effect*). However, the time required to achieve steady state, four to five elimination half-lives (8 to 10 hours), remains the same in CHF.

Drug Elimination in the Face of Organ Dysfunction

It is self-evident that if there is dysfunction (due to disease or by administration of other drugs) of a route of drug elimination, such as hepatic metabolism or renal excretion, the drug may accumulate in plasma and tissues, and toxicity may ensue. The greatest risk for such adverse events occurs when a drug has only a single major route of elimination. Specific hepatic enzymes are responsible for the biotransformation of antiarrhythmic (and other) drugs. It is increasingly well recognized that these enzymes are not expressed in a uniform fashion in all individuals and that such variability in expression can account for some of the clinically observed variability in response to therapy. The examples of propafenone and procainamide are discussed in this chapter. This variability in enzyme activity can be genetically determined or can be the result of coadministration of enzyme inhibitors. A particularly dangerous situation can arise when a drug is metabolized by a single pathway. In this case, administration of an inhibitor can result in marked increases in parent drug concentrations, with attendant toxicity. Torsades de pointes following administration of terfenadine, astemizole, or cisapride is determined by just this mechanism (69). Each drug is an I_{Kr} blocker that is eliminated by a specific enzyme, CYP 3A4. Therapy with CYP 3A4 inhibitors, such as erythromycin or ketoconazole, is now well recognized as the cause of most cases of torsades de pointes with these agents; indeed, these agents were withdrawn from the market because of the continuing occurrence of these interactions. Many drug interactions that elevate digoxin plasma concentrations and cause digoxin toxicity are also attributable to the problem of a single route of drug elimination. Digoxin is eliminated not by metabolism but by renal and biliary excretion mediated by a specific drug transport molecule, P-glycoprotein. The inhibition of P-glycoprotein–mediated digoxin transport by drugs such as amiodarone, quinidine, cyclosporine, verapamil, and erythromycin likely underlies their clinical effects to cause digoxin toxicity (70).

Monitoring Plasma Drug Concentrations

For some drugs, monitoring plasma drug concentrations and maintaining these in a “therapeutic range” are useful adjuncts to minimizing the risk for adverse effects and maximizing potential benefits of therapy; lidocaine, digoxin, and procainamide are examples. Unfortunately, many adverse reactions to antiarrhythmic therapy are not clearly related to high plasma drug concentrations but rather occur at usual drug concentrations in patients with advanced underlying heart disease or other predisposing factors (e.g., hypokalemia). In addition, the elimination of some drugs is highly variable, with an additional variable contribution to clinical effects by active metabolites (e.g., propafenone); plasma concentration measurements are virtually impossible to interpret under these conditions. Monitoring plasma drug concentrations can be especially useful when adjusting dosages in the face of fluctuating renal or hepatic function and to establish whether a patient is compliant with therapy. It is a common misconception that long-term drug therapy should be administered once every half-life. In fact, the minimum time between doses is determined by the rate of drug elimination and by the margin between maximally tolerated and minimally effective plasma concentrations (eFig. 72.0.6). If this margin is small and the drug is eliminated rapidly, frequent dosing is required. If, on the other hand, the margin is large, infrequent dosing may suffice even for a rapidly eliminated drug.



***e*FIGURE 72.0.6** The width of the therapeutic range of plasma concentrations, not the elimination half-life, determines frequency of dosing. Two therapeutic ranges, one wide (*left panel*) and one narrow (*right panel*), are shown. Plasma concentrations during administration of the same drug are illustrated. With a wide therapeutic range, dosing every 8 hours allows plasma concentrations to remain within the therapeutic range. In contrast, dosing every 2.7 hours is required to maintain plasma concentrations within the narrow therapeutic range (*right panel*). (From Roden DM, Echt DS, Murray KT, Lee JT. Clinical pharmacology of antiarrhythmia agents. In: Josephson ME, ed. *Sudden cardiac death*. Malden, MA: Blackwell Science, 1993:163–210, with permission.)

INDIVIDUAL ANTIARRHYTHMIC DRUGS

The relevant clinical pharmacokinetics and pharmacologic actions of individual antiarrhythmic drugs are presented in eTable 72.0.2 and eTable 72.0.3. A brief summary of issues that are important in the clinical use of individual antiarrhythmics is given in this section. The drugs are presented in alphabetical order.

***e*TABLE 72.0.3** DISPOSITION CHARACTERISTICS OF ANTIARRHYTHMIC DRUGS

	Elimination half-life			Elimination route			Dosage adjustments	Drug interactions			
Drug	**Seconds-minutes**	**Hour**	**>12 h**	**Hepatic**	**Renal**	**Other**	**Heart failure**	**Decreased antiarrhythmic dose**	**Increased antiarrhythmic dose**	**Impairing the disposition of other drugs**	**Therapeutic plasma concentrations[a]**
Adenosine	<10 sec					✔		Dipyridamole	Methylxanthines		

Amiodarone		wk–mo	✔					Digoxin, flecainide, procainamide, warfarin	0.5–2 µg/mL
Beta-blockers									
Esmolol	5–10 min				✔			Lidocaine	
Propranolol		4–6	✔					Lidocaine	
Bretylium		7–15		✔					
Digoxin		36 h		✔			Amiodarone, cyclosporine, quinidine, verapamil		0.5–2 ng/mL
Diltiazem		4	✔						
Disopyramide		4–10	✔	✔	✘				2–5 µg/mL
Dofetilide		8–10		✔			Verapamil (?), cimetidine (?)		
Flecainide		10–18 h	✔	✔	✘		Amiodarone		<1 µg/mL
Ibutilide		6[a]	✔[b]						
Lidocaine	120 min		✔		↓Load ↓ Maintenance rate		Beta-blockers, cimetidine		1.5–5 µg/mL
Magnesium				✔					
Mexiletine		11–15 h	✔				Phenytoin		0.5–2 µg/mL
Moricizine		2–3 (?)	✔						
Procainamide		3–4	✔	✔	↓Dose (i.v.)		Amiodarone		4–10 µg/mL
N-acetylprocainamide		6–8		✔					10–20 µg/mL
Propafenone		2–32	✔		✘		Fluoxetine, quinidine, tricyclics		<1 µg/mL
Quinidine		4–10	✔				Amiodarone	Phenytoin	Propafenone	2–5 µg/mL
Sotalol		8		✔	✘				<3 µg/mL
Tocainide		15 h		✔					3–11 µg/mL
Verapamil		6–12	✔		✘				

✘, avoid or use with caution; ✔, yes.

[a]As discussed in the text, monitoring plasma drug concentrations and maintaining them in a therapeutic range may be a useful adjunct to managing therapy with some drugs. Where no therapeutic range is presented, plasma concentration monitoring is of no value.

[b]The arrhythmia-terminating actions of ibutilide depend on transient achievement of high concentrations; the dissipation of pharmacologic effects may result from rapid distribution rather than drug elimination.

Adenosine

Adenosine is used for the acute termination of supraventricular tachycardias that use the AV node as part of their circuit (e.g., AV nodal reentry, AV reentry; see Chapter 65 and Chapter 66) (71). Adenosine can also be used to deliberately create transient AV block to diagnose arrhythmias such as VT. Unlike virtually any other drug, adenosine must be administered in as rapid a fashion as possible, because the drug undergoes very rapid elimination from the circulation, primarily by cellular uptake. Uptake is inhibited by dipyridamole, which, therefore, potentiates effects of the adenosine. Adenosine receptors are blocked by methylxanthines, such as caffeine and theophylline, which can therefore inhibit adenosine action. Most patients who receive adenosine complain of an uncomfortable feeling of chest tightness, the mechanism for which is not entirely explained. The absence of such symptoms with an adenosine bolus suggests that under these circumstances the drug may have been given too slowly or that a receptor blocker is present.

Intravenous Amiodarone

Amiodarone given i.v. can be effective in patients with recurrent episodes of life-threatening ventricular tachyarrhythmia (sustained VT or VF) (72,73). Because placebo-controlled trials are virtually impossible to conduct in this setting, clinical efficacy was demonstrated in trials showing that higher doses were more effective than lower doses and that the drug was somewhat more effective than bretylium. In these trials, the mortality remained high (approximately 20% at 48 hours), presumably reflecting the severity of illness in patients being tested. Because i.v. amiodarone is administered for short periods of time, the toxicity that can characterize long-term oral therapy (see the section Oral Amiodarone) is not a problem. Rather, hypotension, exacerbation of CHF, bradyarrhythmias, and phlebitis (if the drug is not given by central line) can occur. The mechanism whereby i.v. but not oral amiodarone exerts a prompt antiarrhythmic effect is not well understood but may involve a prominent sympatholytic action. A large placebo-controlled trial in patients with out-of-hospital cardiac arrest and refractory ventricular tachyarrhythmias showed improved survival to the hospital but no change in hospital discharge rates with i.v. amiodarone (74). Nevertheless, i.v. amiodarone is now considered first-line therapy in this setting (75). In Europe, i.v. amiodarone has been used to control ventricular response in AF; it is not very effective to convert AF to sinus rhythm.

Oral Amiodarone

One of the most important pharmacologic features of amiodarone is its very long elimination half-life (76). This necessitates the use of oral loading regimens to abbreviate the time from initiation of therapy to achievement of an antiarrhythmic effect. Another result of the slow elimination is that the minimum dose required to maintain an antiarrhythmic effect during long-term therapy is poorly defined. An advantage of very slow elimination is that missing a dose does not generally result in arrhythmia recurrence.

Efficacy of (Oral) Amiodarone

Amiodarone's efficacy has been evaluated in a number of clinical settings. In the Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) trial (77), empiric therapy with oral amiodarone was found to be superior to treatment with conventional drugs (quinidine, procainamide), selected by response to programmed stimulation, in patients resuscitated from cardiac arrest. However, rates of recurrence with amiodarone in CASCADE were relatively high (e.g., 18% in 2 years). In addition, side effects necessitating discontinuation of drug therapy were common, with 10% of patients being taken off one drug by 2 years for pulmonary symptoms and a total side effect rate of 25% at 2 years.

In patients who are recovering from MI (as assessed in CAMIAT and EMIAT), amiodarone produces a slight, statistically insignificant survival benefit when the end point is total (and not arrhythmic) mortality and an intention-to-treat analysis is used (78). In patients with CHF and arrhythmias, clinical trials have provided conflicting results. In one study [Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT)] (79), there was no survival benefit for amiodarone versus placebo, whereas in another study [Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA)] (80), amiodarone-treated patients had significantly lower mortality. In both studies, amiodarone-treated patients tended to have improvement in EF compared with placebo-treated patients. The difference may reflect a greater proportion of patients with nonischemic cardiomyopathy in GESICA. These findings suggest that in patients with sustained symptomatic arrhythmias in the setting of advanced CHF, amiodarone is a reasonable treatment option.

In the Canadian Trial of Atrial Fibrillation (CTAF), there were significantly fewer recurrences of symptomatic AF with oral amiodarone (approximately 35% over 16 months) compared to sotalol or propafenone (approximately 70%) (81). Amiodarone therapy before bypass surgery reduced the incidence of postoperative AF (82).

Long-Term Use of Amiodarone: Side Effects

Side effects can be a major problem during long-term therapy with amiodarone, with dropout rates in large trials approaching 40% in 2 years (25,77,81). The most serious side effect during long-term amiodarone therapy is pulmonary fibrosis. The incidence appears higher with longer duration of therapy, higher dosages (especially more than 400 mg per day during chronic therapy), and the presence of pulmonary disease (83). With total daily dosages of 200 mg per day or less, pulmonary fibrosis is unusual. Routine surveillance chest x-rays or pulmonary function studies have been advocated to detect incipient pulmonary toxicity, but their utility remains to be determined; some patients present with fulminant respiratory failure. Monitoring plasma concentrations of amiodarone during chronic therapy has not been useful in

either limiting toxicity or increasing efficacy.

Amiodarone can cause a number of relatively common adverse effects that may not be life threatening but of which the patient should be aware. Photosensitivity is frequent, and patients should be warned to use sunscreens. Corneal microdeposits are routinely detectable after 3 months of therapy but are rarely symptomatic; the major symptom is visual halos. Hypo- and hyperthyroidism, proximal muscle weakness, and hepatic dysfunction (usually asymptomatic but rarely proceeding to cirrhosis) can occur. Unlike other drugs that prolong the QT interval, torsades de pointes is rare with amiodarone therapy. The mechanism is unknown but may relate to the drug's sympatholytic or direct calcium channel–blocking actions. Drug interactions are also frequent with amiodarone: Warfarin and digoxin requirements should be monitored closely because they may require downward adjustments in dosages.

Bretylium

Bretylium is useful in the management of recurrent VF or sustained VT (84). The drug has prominent effects on the sympathetic nervous system, with initial norepinephrine release (which may not be clinically obvious), followed by inhibition of norepinephrine reuptake in presynaptic neurons. As a result, hypotension is a characteristic feature of bretylium therapy. This does not usually indicate myocardial depression but is generally due to peripheral vasodilation. Evidence indicates that these sympatholytic effects are not required to produce the drug's antiarrhythmic effects, which presumably reflect a direct drug effect on myocardial cells (85). Because of its hypotensive effects, bretylium should be avoided in patients in whom vasodilation would be particularly hazardous (e.g., those with hypertrophic cardiomyopathy, aortic stenosis).

Digoxin and Other Digitalis Glycosides

Digoxin and other digitalis glycosides are used to control ventricular response in AF or flutter. Rate control can generally be achieved while the patient is at rest but is frequently lost during even modest exertion. The symptoms of digoxin toxicity include confusion, visual scotomas, and arrhythmias. The latter include atrial arrhythmias (often with AV block), bigeminy, bidirectional VT, and bradyarrhythmias due to suppression of sinus node function and AV block. With suicidal digoxin overdose, poisoning with sodium-potassium adenosine triphosphatase can result in extraordinary degrees of hyperkalemia. A number of regimens have been proposed to treat arrhythmias related to digitalis intoxication. When arrhythmias that are sufficiently serious to warrant specific therapy are present, the treatment of choice is antidigoxin antibodies. Lesser degrees of arrhythmias (e.g., asymptomatic slow ventricular rates in patients with AF) can be treated with discontinuation of the drug and monitoring.

Disopyramide

Disopyramide exerts quinidine-like electrophysiologic effects (sodium channel block, AP prolongation). However, it lacks quinidine's alpha-blocking actions and instead produces prominent anticholinergic effects (86). These account for many of disopyramide's adverse effects, including constipation, urinary retention (more common among men with prostatism), glaucoma, and dry mouth. In addition, disopyramide depresses myocardial contractility, and exacerbation of symptoms of CHF is common, especially among those with underlying LV dysfunction.

Dofetilide

Dofetilide is a high-potency blocker of I_{Kr} and does not exert significant other pharmacologic effects. Double-blind placebo-controlled trials have shown that it is effective in preventing recurrences of AF after cardioversion, but no significant effect was demonstrated in patients with paroxysmal AF or with VT. In two large placebo-controlled trials in patients with advanced heart failure or recent MI, dofetilide did not alter mortality, and a trend to decreased hospitalization for recurrent heart failure was found, possibly due to decreased AF (87). Torsades de pointes is the major toxicity of dofetilide. In all clinical trials, dofetilide was initiated in monitored in-patients because of the concern for this proarrhythmia. The incidence was 0.8% to 3.3% and was highest in patients with heart failure. In the United States, dofetilide is currently only available to practitioners who have taken a short course in the drug's use, and the labeling mandates in-patient initiation. Because of the drug's specificity of action, other side effects are unusual (88).

Flecainide

Flecainide defined the "class Ic" drug: It is a potent suppressor of chronic ventricular ectopic activity, it routinely prolongs PR and QRS intervals by approximately 25% during chronic oral therapy, and it produces remarkably few "nuisance" side effects during chronic treatment (unlike drugs such as quinidine or procainamide) (89). In patients with advanced LV dysfunction, especially among those with regional wall motion abnormalities and recurrent sustained VT, flecainide commonly exacerbates the underlying arrhythmia. It increased mortality in CAST. Atrial flutter with 1:1 AV conduction can occur, and flecainide can exacerbate CHF. On the other hand, among patients with no structural heart disease and supraventricular arrhythmias (including AF, atrial flutter, and reentrant supraventricular tachycardias), mortality during flecainide therapy is virtually unheard of (90). From a practical point of view, it is only in the latter group of patients that flecainide is currently used.

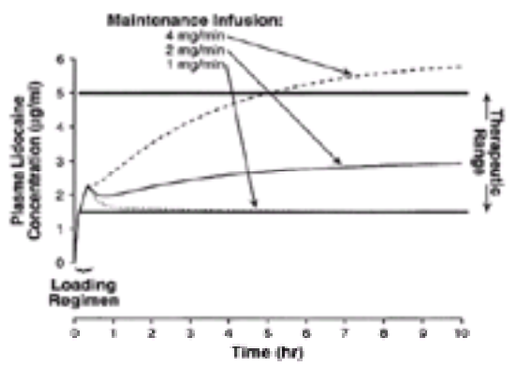
Ibutilide

Ibutilide is used for acute termination of AF or flutter. It is somewhat more effective in terminating atrial flutter (~60% of cases) versus AF (~30%). In AF, it is more effective if the arrhythmia has not been long-standing (e.g., months) and if the left atrium is not dilated. Ibutilide pretreatment can enhance the efficacy of direct current cardioversion in AF (91). Ibutilide acts by prolonging AP, and torsades de pointes occurs in 3% to 8% of patients. Other side effects are unusual (92).

Lidocaine

Lidocaine is useful for the acute suppression of recurrent VF or sustained VT, although amiodarone is increasingly viewed as the drug of first choice in these settings (75). Its efficacy, especially in sustained VT that is unrelated to ongoing myocardial ischemia, is not well established. In a head-to-head comparison, it was less effective than i.v. sotalol for sustained monomorphic VT (93).

Understanding the pharmacokinetics of lidocaine is helpful in minimizing toxicity and maximizing efficacy with the drug. After a bolus of lidocaine, plasma concentrations of the drug (which correlate with its antiarrhythmic activity) drop precipitously, not as a result of elimination but as a result of distribution. Therefore, an appropriate loading regimen of lidocaine administers approximately 3 to 4 mg per kg (200 to 300 mg total in an adult), either as a series of divided boluses or a rapid infusion over 20 to 30 minutes. Reduction in the size of this loading regimen is required in patients with advanced CHF (68). After loading, plasma concentrations approach true steady state in four to five elimination half-lives: Lidocaine elimination half-life is approximately 2 hours in normal individuals and in subjects with CHF and longer in those with liver disease. Thus, steady-state concentrations of lidocaine are achieved only many hours (³8 to 10 hours) after the initiation of therapy (eFig. 72.0.7). If the maintenance dosage is too low, the steady state may be subtherapeutic, with a late recurrence of arrhythmia. If, on the other hand, the rate of the maintenance infusion is too high, plasma concentrations rise slowly into the toxic range hours after initiation of apparently successful therapy. Under these circumstances, lidocaine toxicity is frequently characterized by relatively nonspecific symptoms such as dysarthria or disorientation (common among patients in intensive care units). Plasma lidocaine concentrations should be measured when steady state is approached, when arrhythmia recurs, or with suspected toxicity. Doses should be adjusted to maintain concentrations in the therapeutic range of 1.5 to 5.0 µg per mL.



***e*FIGURE 72.0.7** Plasma lidocaine concentrations during maintenance infusions. After administration of a loading regimen, plasma concentration-time profiles during approach to steady state over four to five elimination half-lives (8 to 10 hours) are shown. If the maintenance infusion is excessive, high plasma concentrations can develop many hours after institution of effective therapy (*dashed line*). On the other hand, if the maintenance infusion chosen is insufficient, plasma concentrations of lidocaine may drop to subtherapeutic levels many hours after institution of what was anticipated to be effective therapy. (From Roden DM. Treatment of cardiovascular disorders: arrhythmias. In: Melamine KL, Morrelli HF, Hoffman BB, Nierenberg DW, eds. *Clinical pharmacology: basic principles in therapeutics*. New York:

McGraw-Hill, 1992:151–185, with permission.)

Magnesium

Magnesium has assumed an increasingly prominent role in the therapy of recurrent or ongoing sustained ventricular tachyarrhythmias despite lack of data documenting that it is effective. Poorly controlled trials (56,94) suggest that it may have a role in suppressing torsades de pointes and atrial arrhythmias characteristic of digoxin toxicity. When it is used to treat long QT-related arrhythmias, the arrhythmia may resolve without marked shortening of the QT interval. No evidence has been found that magnesium is useful in treating other arrhythmias.

Mexiletine and Tocainide

P>Mexiletine (95) and tocainide (96) are structural analogs of lidocaine that were developed to permit long-term oral therapy. They are occasionally useful in the treatment of ventricular arrhythmias, especially in combination with sotalol or quinidine. Tocainide has a relatively high incidence of agranulocytosis, and for this reason, it is not widely used.

Moricizine

Moricizine was evaluated in CAST (4), and although it did not appear to increase mortality to the same extent as did flecainide, the mortality was definitely increased early during treatment. Thus, moricizine is rarely used in treating ventricular arrhythmias. Anecdotal evidence suggests some efficacy in supraventricular arrhythmias, including AF.

Procainamide

Procainamide produces electrophysiologic effects that are similar to those of quinidine and disopyramide. It lacks quinidine's alpha-blocking actions, but when it is administered intravenously, it exerts ganglionic blocking effects that may result in hypotension. When procainamide is used for long-term oral therapy, most patients develop antinuclear antibodies and a minority develop symptoms such as arthralgia or rash indicating the lupus syndrome; this reaction is commoner among patients who are genetically slow acetylators (~50% of patients) (97). Newer formulations allow administration of procainamide two to four times a day. Nevertheless, because of the problem of lupus as well as frequent GI intolerance, the drug is not widely used as primary therapy for atrial or ventricular arrhythmias. Torsades de pointes can occur during procainamide therapy and is most often due to accumulation of the AP-prolonging (non–sodium channel–blocking) metabolite *N*-acetylprocainamide (NAPA). Procainamide is eliminated by hepatic metabolism to NAPA and by direct renal excretion, whereas NAPA is eliminated by renal excretion alone. Thus, the most frequent setting in which NAPA accumulation occurs is renal failure.

Monitoring plasma procainamide and NAPA concentrations during long-term therapy can be useful to prevent toxicity. At concentrations of 8 to 10 µg per mL or greater, procainamide frequently produces GI upset, whereas NAPA concentrations associated with torsades de pointes are frequently 30 µg per mL or greater. It is common practice to add procainamide and NAPA concentrations together to develop a single plasma drug concentration for monitoring purposes. However, because the drugs exert different electrophysiologic effects, produce different toxicities, and use different elimination mechanisms, this approach is inappropriate. Rather, concentrations of the compounds should be considered individually with regard to their potential toxicity. Bone marrow aplasia may occur in 0.2% of patients and does not appear to be related to high plasma concentrations.

Propafenone

Propafenone (98) has sodium channel–blocking properties that are similar to those of flecainide and quinidine *in vitro*. Propafenone can exacerbate VT and produces electrocardiographic changes similar to those of flecainide; therefore, although it was not evaluated in CAST, most clinicians avoid its use in ventricular arrhythmias because its effects so closely resemble those of flecainide.

The major route of propafenone elimination is catalyzed by CYP 2D6, a hepatic enzyme that oxidizes the drug to an active metabolite, 5-hydroxy-propafenone (98). Propafenone exerts beta-blocking activity *in vitro*, whereas its metabolite does not. In patients who are genetically deficient in this elimination pathway (~7% of the white and black populations), propafenone elimination is impaired, and high plasma concentrations of the drug can be measured. It is in these patients that symptoms referable to beta-blockade can occur (99). CHF and bradycardia can also occur during propafenone therapy and are notably more common in poor metabolizers. In addition, some drugs, notably quinidine, tricyclic antidepressants, and selective serotonin reuptake inhibitors such as fluoxetine, can inhibit propafenone biotransformation, elevate its plasma concentrations, and thus increase the risk for adverse effects.

At present, propafenone is most frequently used in the suppression of AF or flutter. In this setting, propafenone, like flecainide and quinidine, can cause atrial flutter with 1:1 conduction and wide complexes, which can be misdiagnosed as VT.

Quinidine

Quinidine has been used for antiarrhythmic therapy since the 1920s. Side effects, including proarrhythmia, are a major concern with quinidine therapy. Very high concentrations generated by aggressive quinidine dosing regimens that were formerly used to convert AF can result in sustained VT similar to that seen with flecainide intoxication. Even low concentrations of quinidine can produce torsades de pointes (100). Although the mechanisms by which "subtherapeutic" plasma concentrations of quinidine produce torsades de pointes are not completely understood, it is now known that the drug blocks I_{Kr} at very low concentrations (55). Because blockade (or mutations in the channel responsible for I_{Kr}) is known to produce torsades de pointes, it seems likely that this can explain why marked QT prolongation and torsades de pointes may develop in some patients at even very low plasma quinidine concentrations. Some analyses (101,102) have suggested that mortality may be increased with long-term use of quinidine in patients with atrial arrhythmias, perhaps due to torsades de pointes, which has been reported in 2% to 10% of patients treated with quinidine for AF. Other side effects, notably diarrhea, are very common. With high plasma quinidine concentrations, a syndrome known as *cinchonism*, which includes tinnitus and headache, can occur. Immunologic reactions have also been reported with quinidine and include thrombocytopenia and, occasionally, the lupus syndrome. Most side effects from quinidine therapy, with the exception of cinchonism, are unrelated to high drug concentrations or any known metabolites.

Drug interactions can also occur during quinidine therapy. Quinidine is an inhibitor of CYP 2D6, responsible for the metabolism of propafenone (and of other drugs, such as beta-blockers, that use the same enzyme for their elimination). In addition, digoxin and digitoxin concentrations predictably double during quinidine therapy, with a corresponding rise in symptoms of digitalis toxicity. This likely reflects inhibition of P-glycoprotein–mediated digoxin excretion (70).

At the beginning of the 1990s, quinidine was the most widely prescribed antiarrhythmic in North America. Because side effects are so common and the awareness of torsades de pointes is increasing, quinidine has assumed an increasingly minor role in antiarrhythmic therapy. Currently, it is probably best reserved for patients with depressed LV performance and recurrent symptomatic arrhythmias (e.g., AF or frequent ICD shocks for VT) in whom other therapies such as amiodarone are deemed undesirable.

Sotalol

Sotalol is a nonselective beta-blocker with prominent AP-prolonging characteristics (103). It is useful in the treatment of ventricular and supraventricular arrhythmias. Side effects are confined to those related to beta-blockade and to torsades de pointes. The incidence of the latter is unknown, although comparative trials suggest it as approximately equivalent to (or perhaps somewhat less than) that seen with quinidine. Because the incidence of torsades de pointes during sotalol therapy appears to be dose related (in contrast to quinidine), most clinicians would avoid using high dosages (e.g., >160 mg twice a day). Unlike other beta-blockers, sotalol has not been shown to reduce the incidence of mortality among patients who are recovering from MI. However, the major trial (104) in which it was studied used a dose of 320 mg once a day. Thus, it is conceivable that the lack of a significant effect on mortality reflects a tradeoff between a mortality-sparing effect due to beta-blockade and a torsades de pointes–inducing effect. In support of this idea, the use of sotalol in patients with ICDs has been shown to reduce the incidence of device discharges or death (105).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Antiarrhythmic drug use is declining because effective nonpharmacologic therapies are becoming more widely available and because of an increasing recognition of

the limited efficacy and the potential for serious side effects during antiarrhythmic therapy, particularly during long-term treatments. Much of the long-term antiarrhythmic therapy has now devolved to amiodarone, a drug that the author believes is neither as effective nor as safe as its most ardent proponents believe. Nevertheless, among therapies that are available for long-term antiarrhythmic treatment, amiodarone has been demonstrated to be more effective and probably no more dangerous than drugs such as quinidine or procainamide, which heretofore have been considered conventional. Similarly, a number of studies suggest that sotalol is better tolerated and as effective as (if not more effective than) conventional drugs. Thus, it is now appropriate to relabel amiodarone and sotalol as conventional therapies and to reserve other drugs, such as quinidine or procainamide, for those unusual situations in which conventional drugs are contraindicated or ineffective and alternative therapies are not available.

All available antiarrhythmic drugs were developed at a time when the mechanisms that underlie the target arrhythmias and the antiarrhythmic drug effects were incompletely defined at best; indeed, this is still the case. Catheter ablation is a superb example of a therapy that has evolved to become an effective modality from an understanding of the underlying disease mechanisms. During the past decade, our understanding of the molecular and cellular events that underlie arrhythmogenesis has grown tremendously. Thus, we are in the paradoxical position of understanding better the mechanisms underlying the proarrhythmic effects of antiarrhythmic drugs than those that underlie the antiarrhythmic effects of these same agents. It seems clear that the molecular entities targeted by many of the antiarrhythmic drugs, notably the sodium channel and the rapidly activating component of the cardiac-delayed rectifier, I_{Kr}, may not be the best targets for suppressing atrial or ventricular arrhythmias. The author remains hopeful that better understanding of the mechanisms of arrhythmias may well allow identification of molecular and cellular targets for new antiarrhythmic entities that may prove to be highly effective and safe in treating common arrhythmia scenarios such as AF or patients at risk for VT or VF.

THE FUTURE

Use of antiarrhythmic drugs will continue to decline because of their recognized limited efficacy and serious side effects, especially during long-term therapy. Continuing research resulting in an improved understanding of the mechanisms of arrhythmias will allow identification of molecular and cellular targets for new antiarrhythmic entities. Such new entities may well provide highly effective and safe treatment of common arrhythmias.

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CATHETER ABLATION THERAPY FOR ARRHYTHMIAS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The rationale behind ablative therapy is that, for any arrhythmia, there exists a critical anatomic substrate that allows propagation of that arrhythmia. If that substrate is irreversibly damaged or destroyed, then the arrhythmia should no longer occur spontaneously or with provocation.

A number of methods of catheter ablation have been attempted experimentally and clinically, but radiofrequency catheter ablation has emerged as the safest and most effective modality.

Radiofrequency energy heats myocardium by the passage of the radiofrequency electrical current through the tissue, resulting in resistive tissue heating.

Deeper tissue heating results in larger lesions. Larger electrodes, higher temperatures, and very high-power deliveries coupled with irrigated or cooled tip catheters increase lesion size.

Radiofrequency ablative lesions are thermally mediated. Temperatures exceeding 50°C result in breakdown of the sarcolemmal membrane and cell death.

The mechanisms of paroxysmal supraventricular tachycardia are varied and include atrioventricular (AV) reciprocating tachycardia, AV nodal reentrant tachycardia, atrial fibrillation, atrial flutter, and atrial tachycardia of focal automatic or reentrant mechanisms.

Catheter ablation of accessory pathways responsible for the Wolff-Parkinson-White syndrome and AV reciprocating tachycardias may be accomplished at either the atrial or ventricular insertion sites of the pathway with a high (greater than 95% at experienced centers) success rate.

Catheter modification of the AV node is highly successful in eliminating AV nodal reentrant tachycardia. In most cases, ablation in the low septal region results in elimination or marked modification of the slow AV nodal pathway and prevents tachycardia recurrence.

Atrial flutter is a macroreentrant rhythm that travels around the tricuspid valve annulus and through the isthmus between the valve and the inferior vena caval inlet. A linear ablative lesion placed across this isthmus results in successful ablation of the atrial flutter. However, concomitant atrial fibrillation is not altered by this ablation and will likely recur unless additional therapy is prescribed.

Atrial fibrillation may have a reentrant mechanism or, particularly in patients with frequent paroxysmal atrial fibrillation and normal atrial size, may originate from rapid firing from a pulmonary vein focus.

Ablation of focal origins of atrial fibrillation initiation is moderately successful in eliminating this arrhythmia in highly selected patients.

Common atrial fibrillation has a reentrant mechanism. Cure with ablation usually requires successful creation of long transmural continuous linear lesions in left and right atria. This has been difficult to achieve with catheter-based technologies.

Ventricular tachycardia may be idiopathic or caused by the presence of underlying structural heart disease.

Idiopathic ventricular tachycardia from the right ventricle is usually focal in origin, with a likely mechanism of abnormal automaticity or triggered activity. It may be ablated with a high likelihood of success.

Ventricular tachycardia in the setting of structural heart disease is usually caused by a reentrant mechanism in regions of patchy fibrosis. Ablation may be accomplished at sites within the zone of slowed electrical conduction that is identified with techniques such as activation and entrainment mapping.

GLOSSARY

Accessory pathway: An anomalous bridge of electrically conducting tissue between the atrium and ventricle, which is responsible for Wolff-Parkinson-White syndrome and AV reciprocating tachycardias, also known as a *bundle of Kent* or *bypass tract*.

Activation mapping: Multipoint electrogram acquisition during ongoing tachycardia demonstrates sites where the local electrical activity precedes the onset of the surface QRS complex. These sites represent exit points from the slow conduction zone for reentrant tachycardias or sites of arrhythmia origin for automatic or triggered tachycardias.

AV nodal modification: (a) Ablation of the slow AV nodal pathway to treat AV nodal reentrant tachycardia; (b) nonspecific ablation of the AV node to impair anterograde conduction and decrease the ventricular response rate to atrial fibrillation.

Coagulum: When boiling occurs at the electrode tip, coagulated protein from tissue and blood adhere to the tip of the electrode.

Convective cooling: The process by which thermal energy is removed by circulating blood flow through the heart.

Dispersive electrode: An electrode with a large surface area that is placed in contact with the patient's skin (usually with electrically conductive gel) to complete the electrical circuit during ablation with radiofrequency electrical current.

Electrical impedance: The resistance and capacitance of the radiofrequency electrical circuit, including the electronic components, conducting wires, point of conduction between the ablation electrode and the heart, tissue between the heart and the skin, and junction between the skin and the dispersive electrode.

Entrainment mapping: Pacing slightly faster than ongoing reentrant ventricular tachycardia from various sites in the ventricle. When one is in or near the slow conduction zone, the morphology of the resulting complex matches the tachycardia morphology exactly, and the time from the stimulus to the QRS complex is prolonged (concealed entrainment).

Impedance rise: If boiling and coagulum adherence occur, the available surface area for radiofrequency current conduction decreases, resulting in a sudden increase in system impedance.

Pace mapping: During sinus rhythm, pacing is performed from a variety of ventricular sites. For ventricular tachycardias of focal origin, the electrocardiograms during pacing should be almost identical to those during tachycardia if the pacing site is in close proximity to the arrhythmia origin.

Radiofrequency energy: High-frequency alternating electrical current; when passed through a resistive medium, it creates heat.

Slow and fast AV nodal pathways: The AV node has multiple atrial inputs that have varying properties, including conduction time. In typical AV nodal reentrant tachycardia, electrical activation travels anterograde down a slowly conducting AV nodal pathway and retrograde up a fast conducting pathway.

Tricuspid-inferior vena cava isthmus: The narrow anatomic region between the tricuspid annulus and the inferior vena caval orifice in the right atrium through which atrial flutter reentrant circuits conduct. This is the usual site targeted for atrial flutter ablation.

Ventricular preexcitation: Pattern seen on surface electrocardiograms characterized by delta waves (slurred QRS upstrokes) and resulting from the presence of an accessory pathway that conducts in an anterograde fashion. Wolff-Parkinson-White syndrome is the most common form of preexcitation syndrome.

Ventricular tachycardia slow conduction zone: Region in the border zone of scar in the ventricle bounded by areas of anatomic or physiologic conduction block, which has a slow conduction velocity. Conduction through this region accounts for the diastolic period of electrical silence on the surface electrocardiogram during ongoing reentrant ventricular tachycardia.

Volume heating: Heating from radiofrequency energy or other energy source that is direct and not a result of heat conduction from a contiguous region of heated tissue.

INTRODUCTION

Ablative therapy for the management of arrhythmias is based on the observation that most arrhythmias arise from a focal origin or are critically dependent on conduction through a defined anatomic structure. If those critical regions are irreversibly damaged or destroyed, then the arrhythmia should no longer occur spontaneously or with provocation. Traditionally, ablation was performed with open surgical techniques. It was discovered, however, that focal endocardial injury could also be achieved by a controlled delivery of destructive energy through a catheter. In the past decade, catheter designs have evolved to improve site access dramatically, and our knowledge and understanding of the anatomy of the heart and the sources of arrhythmia origin have significantly expanded. In response to this progress, the indications for catheter ablation have continued to broaden, and it is now the therapy of choice for a number of arrhythmias.

HISTORY OF CATHETER ABLATION

The concept of ablative therapy for the treatment of arrhythmias was well established in the surgical literature throughout the 1970s. Since the original description of the surgical division of an accessory pathway by Sealy et al. in 1969 (1), there have been several reports of surgical treatment of the Wolff-Parkinson-White syndrome (2,3) and ventricular tachycardia (4,5). In these series, the concept of curative ablative therapy was proved. However, the obvious limitation to this approach was that an open thoracotomy and, in most cases, cardiopulmonary bypass were required. Although researchers were pursuing a variety of approaches to decrease surgical morbidity and mortality, it was not thought possible to eliminate these arrhythmic substrates without direct visualization.

In 1979, a complication of transthoracic cardioversion was reported. Catheters had been placed for recording in the bundle of His position, and multiple direct current (DC) shocks were administered transthoracically to terminate an episode of ventricular tachycardia. At the conclusion of the cardioversion, complete heart block was observed. It was hypothesized that shunting of defibrillator current through the His bundle catheter caused irreversible damage to the AV conduction system (6). After this report, Scheinman et al. (7) and Gallagher et al. (8) published the first series of catheter ablation of the AV junction in patients with atrial fibrillation and a rapid ventricular response rate that could not be controlled with drugs. In these cases, high-voltage DC electrical energy was intentionally delivered between the tip of an electrode catheter placed contiguous to the bundle of His and a dispersive patch electrode placed on the skin. The field of catheter ablation was born. Subsequently, investigators reported successful catheter ablation of accessory pathways (9,10 and 11) and ventricular tachycardia (12,13) with this approach. Unfortunately, a relatively high complication rate was also reported, including pericardial tamponade, cardiogenic shock, and death (14).

The technique of high-energy DC shock catheter ablation was effective, but it was extremely difficult to control. The high voltage delivered to the tissue and surrounding blood routinely resulted in formation of an expanding gas bubble with subsequent dielectric breakdown and electrical arcing. The barotrauma created by the rapid gas expansion was uncontrolled and could lead to cardiac perforation. Additionally, the high voltage field was associated with transient or sometimes permanent depression of myocardial contractility. An alternative energy source for controlled ablation of myocardium was needed. A variety of different energy sources had to be employed to heat or ablate targeted tissues in the fields of neurosurgery and oncology. In 1985, Huang et al. described their use of radiofrequency electrical energy for controlled catheter ablation of the AV junction in dogs. Radiofrequency catheter ablation resulted in controllable, well-circumscribed endocardial lesions (15). It was discovered that lesion formation could be nicely controlled by either titrating power (16) or temperature measured at the catheter tip (17). Efficacy of radiofrequency catheter ablation in the clinical setting was unacceptably low, however. The next major advance in the field came with two improvements in the catheter design. First, it was recognized that a larger ablation electrode might increase lesion size (18). With an increase in the electrode tip size from 2 to 4 mm, an appreciable increase in procedure efficacy was realized (19). Second, catheter design pioneers such as Will Webster constructed catheters that had a distal segment that could be deflected by manipulation of the control handle. This greatly improved site access and catheter stability.

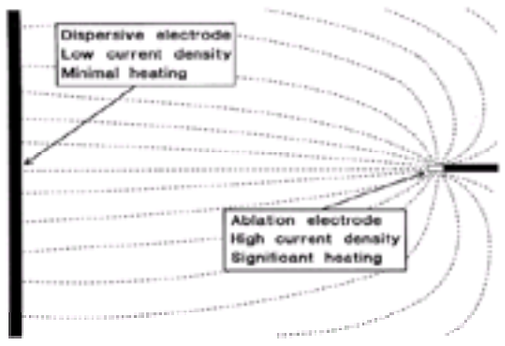
The modern era of radiofrequency catheter ablation was entered with the first report of successful catheter ablation of an accessory pathway with high-frequency alternating (radiofrequency) electrical current by Borggrefe et al. (20). Based on the important work of Jackman, Kuck, Haissaguerre, Morady, and others, the correlations between electrographic patterns, anatomic locations of accessory pathways, and access to those sites with ablation catheters were elucidated (21,22 and 23). Success rates exceeding 90% were reported by investigators in the treatment of paroxysmal supraventricular tachycardia (24,25 and 26). In the present day, experienced operators achieve greater than 95% success rates in the ablation of these patients. The indications for radiofrequency catheter ablation continue to expand, and it has become a dominant therapeutic modality for many varieties of symptomatic tachycardia.

BIOPHYSICS OF RADIOFREQUENCY CATHETER ABLATION

Radiofrequency electrical energy is employed to create thermal lesions in the heart. The frequencies generally employed are 300 to 1,000 kHz. It is important to note that, although this energy is similar to that employed for broadcast radio, the radiofrequency energy is electrically conducted, not radiated, during catheter ablation. The radiofrequency current is similar to low-frequency alternating current or DC with regard to its ability to heat tissue and create a lesion, but it oscillates so rapidly that cardiac and skeletal muscles are not stimulated, thereby avoiding induction of arrhythmias and decreasing the pain perceived by the patient. As the electrical current passes through the myocardium, the energy dissipates as heat. Direct resistive myocardial heating (volume heating) is proportional to the radiofrequency power density (or the square of the current density) that decreases in proportion to the fourth power of the distance from the electrode. Therefore, most of the volume heating occurs within the first 2 mm of depth from the electrode (17). Heating to deeper tissue layers occurs by heat conduction from the region of volume heating.

The radiofrequency current is generally delivered in a unipolar fashion between the tip of the ablation electrode and a dispersive electrode applied to the patient's

skin. Because the surface area of the ablation electrode is much smaller than that of the dispersive electrode, the current density is higher at the ablation site, and heating occurs preferentially at that site (eFig. 73.0.1). If, however, ablation is performed with a high-amplitude current and skin contact by the dispersive electrode is poor, it is possible to cause skin burns. The geometry of the radiofrequency current field is defined by the geometry of the ablation electrode and is relatively uniform in the region of volume heating. Thus, the position of the dispersive electrode has little effect on the geometry of the resulting lesion. Sometimes it is advantageous to increase the surface area of the dispersive electrode. The system impedance comprises the impedance of the generator, transmission lines, catheter, electrode-tissue interface, dispersive electrode-skin interface, and the interposed tissues. The energy dissipated at the tip of the ablation electrode (which is converted from electrical to thermal energy) is proportional to the square of the current density, the local impedance, and the time. If an ablation is power-limited, heat production at the catheter tip will therefore vary with the proportion of the local electrode-tissue interface impedance to the overall system impedance. If the impedance at the skin-dispersive electrode interface is high, then a smaller amount of energy is available for tissue heating at the electrode tip. Nath et al. (27) demonstrated that the tissue temperatures achieved during catheter ablation were similar, whether the dispersive electrode was placed on the patient's back between the scapulae or placed on the thigh. In patients who had a baseline system impedance of greater than 100 W, using two dispersive electrodes resulted in more effective heating than using a single electrode.



***e*FIGURE 73.0.1** Schematic representation of a catheter ablation electrode and a skin dispersive electrode during radiofrequency energy delivery. The dashed lines represent the electrical field. Note that because the available electrode surface area of the ablation electrode is much smaller than that of the dispersive skin electrode, the current density and its associated tissue heating of the former are much greater. In addition, the electrical field around the ablation electrode is relatively uniform, irrespective of the location of the dispersive electrode.

It has been demonstrated *in vitro* that, at steady state, the tissue temperature decreases radially in proportion to the distance from the ablation electrode and that, at steady state, the lesion size is proportional to the temperature measured at the interface between the tissue and the electrode (28). In addition, lesion size has also been shown to be proportional to the radiofrequency power amplitude (28,29). By using higher powers and achieving higher tissue temperatures, lesion size may be increased. However, once the peak tissue temperature exceeds the threshold of 100°C, boiling at the electrode-tissue interface may ensue (29). When boiling occurs, denatured serum proteins and charred tissue adhere to the electrode, forming an electrically insulating *coagulum* (30), which is accompanied by a sudden increase in electrical impedance preventing further current flow into the tissue and further heating. The consequences of this adverse event could include char embolism or excess disruption of the endocardium with subsequent thrombus formation and associated risk of thromboembolism. Conventional electrode catheters with temperature monitoring only report the temperature from the center of the electrode mass with one design or from the apex of the tip of the catheter with another design, and it is likely that the measured temperature underestimates the peak tissue temperature. Therefore, it is best if target temperatures not exceeding 70° to 80°C are selected in the clinical setting. Because the rate of temperature rise at deeper sites within the myocardium is slow (31), a continuous energy delivery of at least 60 seconds is often warranted to maximize depth of lesion formation. Tissue temperatures continue to rise somewhat after termination of radiofrequency energy delivery (32). This thermal latency effect can account for the observation that patients undergoing AV modification procedures who demonstrate transient heart block during radiofrequency energy delivery may progress to persisting complete heart block even if radiofrequency energy delivery is terminated immediately.

The dominant factor opposing effective heating of myocardium is the convective cooling from the circulating blood pool. If the catheter position is not stable, or if it is positioned in a region of high blood flow, the magnitude of convective cooling is increased (33). Efficiency of energy delivery to the tissue may vary from approximately 70% to 10% *in vivo.* The effects of convective cooling have been exploited to increase the size of catheter ablative lesions. To eliminate the risk of overheating at the electrode-tissue contact point but increase the magnitude of power delivery and the depth of volume heating, investigators have employed porous-tipped electrodes for open irrigation of the electrode tip (34) or closed irrigation systems for electrode tip cooling (Fig. 73.1) (35). Nakagawa et al. achieved temperatures of 95° ± 9°C at depths of 3.5 mm and lesion dimensions of 10 ± 1 mm depth by 14 ± 2 mm diameter with ablation through an irrigated-tip electrode in a superfused canine thigh muscle preparation. However, superheating within the tissue with a resulting sudden explosive release of the expanding steam to the surface (the so-called pop lesion) was observed in 7.5% of the ablations (34). Thus, increasing power delivery and convective cooling may create large lesions, but lesion production is somewhat difficult to control.

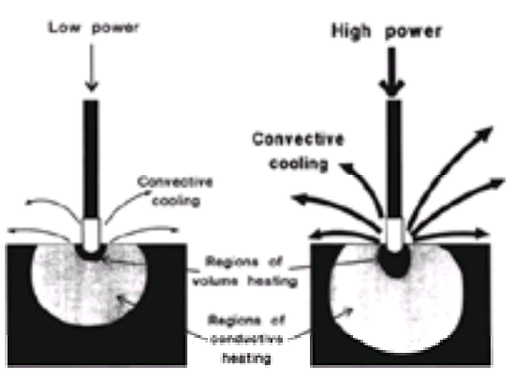


FIGURE 73.1 Schematic representation of two conditions during radiofrequency catheter ablation. The left panel depicts conventional conditions with a moderate degree of convective cooling. A low magnitude of radiofrequency power is applied to achieve heating at the electrode-tissue interface. This results in a small depth of volume heating and a moderate depth of conductive heating that create the final pathologic lesion. The right panel depicts radiofrequency ablation in the setting of increased convective cooling, either by active tip cooling with perfused or circulating saline or by unstable catheter-tissue contact. A high magnitude of radiofrequency power is applied, but the electrode-tissue interface does not exceed 100°C because of convective dissipation of heat at the tissue surface. The higher-applied power results in a greater depth of volume heating and a larger overall lesion size.

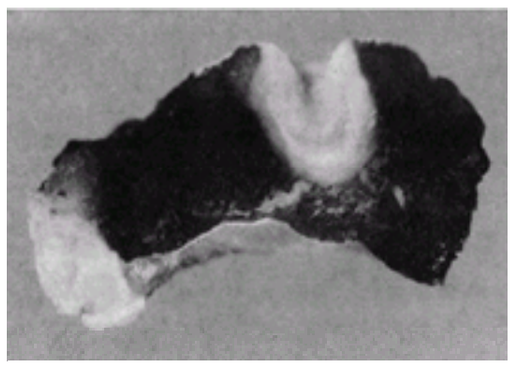
Because the success of radiofrequency catheter ablation in the clinical setting is sometimes limited by the relatively small size of the lesion, attempts have been made to increase the size of those lesions reliably and safely. One approach to this end is to increase the size and surface area of the electrode. The radiofrequency power needs to be increased comparably in order to achieve a similar current density and temperature at the electrode-tissue interface, and the result is a greater depth of volume heating and a larger lesion (18). The introduction of the larger 4-mm ablation electrode was an important factor in the improved success rates of present-day catheter ablation (35). Investigators are continuing to pursue novel electrode geometries for special applications of radiofrequency catheter ablation (36).

MECHANISMS OF MYOCARDIAL INJURY CAUSED BY RADIOFREQUENCY CATHETER ABLATION

It is likely that the major mechanism of tissue injury from radiofrequency catheter ablation is thermal. Heating of the myocardium occurs reproducibly during radiofrequency energy delivery, and the association of clinical effect and temperature measured at the electrode-catheter interface has been established. Experimentally, lesions created from a radiofrequency or microwave source have a reliable isotherm of irreversible tissue injury of 52° to 55°C (37). In the clinical setting, successful ablations were associated with a mean temperature measured at the electrode-tissue interface of 62° ± 15°C (38). During ablation of the AV junction, the reversible physiologic effect of an accelerated junctional rhythm was observed at temperatures of 51° ± 4°C, whereas temperatures of 58° ± 6°C were required to achieve heart block (39). Clinical effects of radiofrequency ablation have been observed with electrode tip temperatures of less than 40°C (40), indicating that the electrical effects of radiofrequency current may alter tissue properties as well.

Tissue Effects of Radiofrequency Catheter Ablation

Changes in myocardial tissue are apparent immediately on completion of the radiofrequency lesion. Pallor of the central zone of the lesion is attributable to myoglobin denaturation with an associated color change. Some volume loss in the central region of lesion formation is apparent as evidenced by a slight deformation at the point of catheter contact. Fibrin usually adheres to the endocardial surface and, if a temperature of 100°C has been exceeded, adherent char and thrombus are often apparent. On sectioning, the central portion of the lesion shows desiccation, with a surrounding region of hemorrhagic tissue, then normal appearing tissue (eFig. 73.1.1) (41,42). The histology of an acute lesion shows typical coagulation necrosis with basophilic stippling consistent with intracellular calcium overload. Immediately surrounding the central lesion is a region of hemorrhage and acute monocellular and neutrophilic inflammation. The progressive changes seen in the evolution of a radiofrequency lesion are typical of healing after any acute injury. Within 2 months of the ablation, the lesions show fibrosis, granulation tissue, chronic inflammatory infiltrates, and significant volume contraction (41). The lesion border is well demarcated from the surrounding viable myocardium without evidence of patchy fibrosis. This likely accounts for the absence of proarrhythmia side effects of radiofrequency catheter ablation. Because of the high-velocity blood flow within the epicardial coronary arteries, these vessels are continuously cooled and are spared from injury despite nearby delivery of radiofrequency energy (43). However, high radiofrequency power delivery in small hearts, such as in pediatric patients, may potentially cause coronary arterial injury, so caution is warranted (44).



***e*FIGURE 73.1.1** Example of a typical radiofrequency lesion created in an experimental preparation and stained with the histochemical dye nitro blue tetrazolium. The electrode-tissue contact point shows volume loss and dimpling. The viable myocardium (*dark stain*) is sharply demarcated from the nonviable lesion (*light stain*). The lesion width is narrower at the endocardial surface than at a 2-mm depth because of surface convective cooling from endocardial blood flow.

The border zone around the acute pathologic lesion is a region that can demonstrate initial stunning and then early or late recovery of function, or show late progression of physiologic block resulting in a “delayed cure” in some cases (45). Significant diminution in microvascular blood flow is observed in this region. Electron microscopic examination of the border zone has demonstrated marked ultrastructural abnormalities in tissue that appears to be viable by routine histologic examination. The microvessels appear severely damaged with loss of the basement membrane, disruption of the endothelial cell plasma membrane, and erythrocyte stasis (46). The myocytes show significant ultrastructural injury of the plasma membrane, mitochondria, sarcomeres, sarcoplasmic reticulum, and gap junctions. The most thermally sensitive structures appear to be the plasma membrane and gap junctions, which show morphologic changes as far as 6 mm from the edge of the pathologic lesion (47). It has, therefore, been documented that the effects of radiofrequency lesion formation extend well beyond the acute pathologic lesion and are characterized by marked ultrastructural abnormalities of the microvascular and myocytes acutely, and a typical inflammatory response later. Therefore, the recovery of electrophysiologic function after successful catheter ablation in the clinical setting may be caused by healing of the damaged, but surviving, myocardium. The progression of the electrophysiologic effects after completion of the ablation procedure may be caused by further inflammatory injury and necrosis in the border zone region.

Cellular Effects of Radiofrequency Ablation

Hyperthermic injury to the cell is both time and temperature dependent. This injury to the myocyte may be caused by changes in the membrane, protein inactivation, cytoskeletal disruption, nuclear degeneration, or a number of other potential mechanisms.

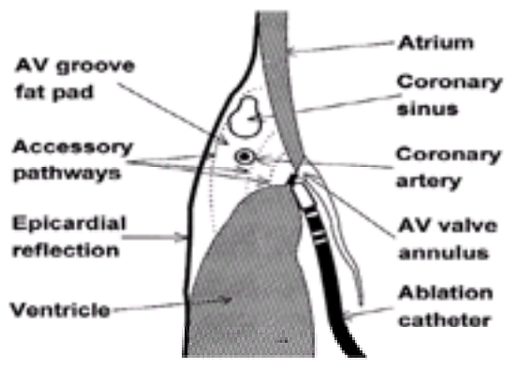
Experimentally, brief exposure to heat results in prominent changes in the electrophysiology of the myocyte. In one study, guinea pig papillary muscles were exposed to temperatures between 37° and 55°C, and transmembrane potentials were measured. In the low hyperthermic range (37° to 45°C), a minor change was seen in the resting membrane potential and action potential amplitude, and the action potential duration shortened significantly. In the intermediate hyperthermic range (45° to 50°C), progressive depolarization of the resting membrane potential, loss of action potential amplitude, abnormal automaticity, and reversible loss of excitability were seen. In the high temperature ranges (greater than 50°C), marked depolarization of the resting membrane potential, permanent loss of excitability, and contracture of the preparation were observed (48). Another study examined the effects of hyperthermia on conduction velocity of a preparation of epicardial shavings from canine left ventricular free walls. Conduction velocity was greater than at baseline between 38.5° and 45.4°C, but above 45.4°C, a progressive decrease in conduction velocity was seen, followed by temporary (49.5° to 51.5°C) then permanent (51.7° to 54.4°C) conduction block (49). It is hypothesized that these electrophysiologic changes may be caused by nonspecific ion transit through thermally induced transmembrane pores. In particular, intracellular calcium levels increase at temperatures above 45°C and result in cellular contracture as temperatures approach 50°C. Blockade of the intracellular calcium buffering system by the sarcoplasmic reticulum results in increased thermosensitivity, suggesting that acute calcium overload may be the mechanism of myocyte death with catheter ablation (50).

In addition to the thermal effects of radiofrequency catheter ablation, some of the cellular injury may be caused by a direct electrical effect. Electroporation is a technique of forming temporary pores in the phospholipid membrane with high-intensity electrical fields. Radiofrequency field stimulation has been used for the introduction of genetic material into a variety of host cells (51). Jones et al. have demonstrated that tested high-intensity DC fields created sarcolemmal microlesions in cultured chick myocytes (52). Although the amplitude of the electrical fields at which physiologic effects have been reported are higher than those associated with radiofrequency catheter ablation, it is hypothesized that a synergistic effect of electrical field stimulation and membrane heating may occur, resulting in membrane pore formation, cellular depolarization, calcium overload, and cell death.

ABLATION OF SPECIFIC SUPRAVENTRICULAR ARRHYTHMIAS

Accessory Pathway–Mediated Arrhythmias

A giant step forward was achieved with the first successful catheter ablations of accessory pathways (20). Before the catheter ablation era, patients with Wolff-Parkinson-White syndrome and concealed accessory pathways frequently required open surgical ablation of their extranodal pathways. The ability to map precisely the location of accessory pathways and deliver a precise ablative lesion with radiofrequency energy not only proved to be a valuable therapeutic modality, but also greatly enhanced the understanding of the physiologic and anatomic correlates of this relatively common abnormality. Important preliminary work by Jackman et al. identified electrogram patterns that correlated precisely with accessory pathway insertions in the atria and ventricles (21). The ultimate validation of the origin of these potentials arrived when small, discrete radiofrequency lesions placed at those locations resulted in elimination of both anterograde and retrograde accessory pathway conduction (*e*Fig. 73.1.2) (24,25 and 26,53). It has been proposed that the pathways frequently follow a slanting course with separation of atrial and ventricular insertion points by 4 ± 30 mm, and that they may be composed of multiple closely spaced fibers (21). The majority of accessory pathways has a discrete and narrow ventricular and atrial insertion. The presence of occasional branching accessory pathway insertions may be assumed in cases in which accessory pathway conduction is modified but not blocked by one lesion, and then is blocked by a second application of energy at a second discrete site. The high success rate of radiofrequency catheter ablation delivered from the endocardial approach implies that most pathways are situated closely to the endocardial surface. However, a small proportion of left free wall accessory pathways (1% to 4%) can only be ablated successfully from the epicardial approach via the coronary sinus and probably represent true epicardial pathways (54).



***e*FIGURE 73.1.2** Schematic representation of a cross section of the left atrioventricular (AV) groove with the position of a typical ablation catheter relative to the anatomic structures in this region. The possible courses of three accessory pathways are diagrammed. One accessory pathway follows a subepicardial course and can only be successfully ablated via the coronary sinus. Another pathway passes close to the coronary artery. The convective cooling of intracoronary blood flow protects the vascular endothelium from thermal injury by endocardial ablation with conventional ablation catheters.

The successful catheter ablation of accessory pathways is directly related to the skill and experience of the operator (55). Careful mapping of the accessory pathway atrial and ventricular insertion points before any radiofrequency energy delivery greatly enhances the efficiency of the ablation procedure and minimizes the risk of distortion of local electrograms by poorly placed ablative lesions. In patients with manifest ventricular preexcitation (Wolff-Parkinson-White syndrome), mapping is best performed in the anterograde direction during sinus or atrial-paced rhythm. The local ventricular activation recorded from the mapping and ablation catheter should precede the onset of the delta wave on the surface electrocardiogram by at least 10 ms (optimally an interval of at least 20 ms should be pursued), and the electrographic pattern should be stable, indicating stable catheter-tissue contact (Fig. 73.2). An excellent ablation site shows the presence of a high-frequency accessory pathway potential immediately preceding the local ventricular activation and a relatively short atrial-to-ventricular electrographic interval (56,57). This latter finding, however, should not be used to guide ablation catheter positioning, because parallel activation of atrium and ventricle distal to the insertion point of the accessory pathway may result in short AV times, but late ventricular electrogram timing relative to the delta wave onset.

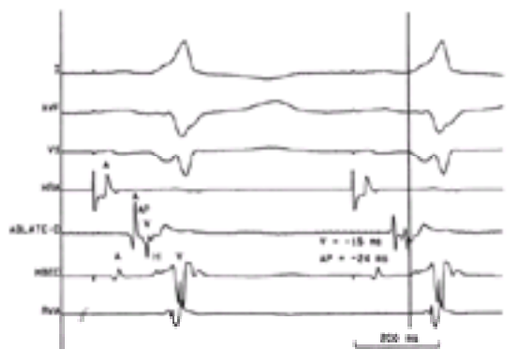


FIGURE 73.2 Surface electrocardiogram tracings I, aVF, and V_1, and intracardiac recordings from the high right atrium (HRA), distal ablation catheter bipole (ABLATE-D), the distal bundle of His bipole (HBED), and the right ventricular apex (RVA) in a patient with the Wolff-Parkinson-White syndrome. The vertical line indicates the onset of the delta wave on the surface electrocardiogram. The recording from the ablation electrode shows a discrete atrial (A) and ventricular (V) potential with an interposed high-frequency negative deflection that arises from the accessory pathway (AP). The local AP activation precedes the delta wave onset by 24 ms, and the local ventricular activation precedes the delta wave by 15 ms. H, bundle of His.

In cases in which the accessory pathway is concealed (absent anterograde but intact retrograde conduction), mapping of retrograde activation during ventricular pacing or ongoing orthodromic AV reciprocating tachycardia must be pursued. Some patients do not tolerate the prolonged periods of sustained tachycardia necessary for complete mapping, and the former approach must be employed. Discrimination between retrograde AV nodal conduction and conduction up the accessory pathway may be enhanced by pacing near the pathway's ventricular insertion site. The atrial insertion of the accessory pathway is determined by identifying the site with the shortest interval between the reference ventricular electrogram and the local atrial activation from the mapping and ablation electrode. One must be cautious not to confuse late components of the local ventricular electrogram as early atrial signals. As with anterograde mapping, the presence of a local high-frequency accessory pathway potential is an excellent marker for successful ablation sites.

Using electrogram criteria as described previously, Jackman et al. reported an initial accessory pathway catheter ablation success rate of 99% using a median of three radiofrequency energy deliveries (24). In a comparison of the electrograms from 49 successful versus 462 failed ablation sites, an interval of the local ventricular electrogram to delta wave onset of greater than 10 ms had a sensitivity of 98% for successful ablation, but only a positive predictive value of 11% (57). The low specificity of this finding may have been caused, in part, by inadequate tissue heating by the ablation catheter despite optimal site selection. The presence of ongoing atrial fibrillation can complicate and prolong mapping of accessory pathways because of the absence of consistent atrial electrograms and inability to measure the AV times. However, if the same criteria of local ventricular electrogram to delta wave interval and presence of accessory pathway potentials are employed, a high (95%) success rate can still be achieved (58). The characteristic of the local unipolar electrogram is also useful in identifying successful ablation sites. If the recording electrode is placed directly on the accessory pathway insertion site, all conduction into the ventricle (during anterograde mapping) or atrium (during retrograde mapping) follows a vector away from the electrode. Thus, a QS unipolar electrogram pattern should be more favorable than an electrogram pattern with any initial positive deflection. The positive predictive values of this feature reviewing 186 separate ablation sites in 56 patients were 86% and 92% for ventricular and atrial mapping, respectively. The negative predictive value overall was 92% (59).

Catheter placement for ablation of accessory pathways on the left free wall may be accomplished by two approaches. The catheter may be passed across a small puncture hole in the fossa ovalis (transseptal) (60) or may be prolapsed across the aortic valve and manipulated in the left ventricle back to the mitral annulus (retrograde) (24,25). Direct comparisons of the two techniques have yielded similar success rates (61), although in children and patients older than 65 years, complication and failure rates may be higher with retrograde versus transseptal catheter placement (62). Catheter ablation of right free wall pathways is technically challenging and has a lower success rate than ablation of left free wall pathways (55). It is difficult to stabilize the catheter position on the tricuspid annulus. Because the catheter is relatively fixed with regard to translational movement as it enters the right atrium, the catheter naturally tracks toward the septum and away from the free wall, and the normal movement of the heart in the mediastinum throughout the cardiac cycle causes the catheter tip to slide on the endocardial surface. Multiple accessory pathways are more frequently found in association with right free wall pathways than other locations (up to 10% of cases). A subset of patients with Ebstein's anomaly has a high prevalence of Wolff-Parkinson-White syndrome, often with multiple accessory pathways. Catheter ablation in this group of patients is made more difficult by the fact that the tricuspid valve (the normal anatomic landmark for catheter placement) is displaced downward from the true anatomic annulus where the accessory pathways are located. Septal accessory pathways may be divided into anteroseptal, midseptal, and posteroseptal locations. Anteroseptal and midseptal pathways are located in close contiguity to the normal AV conduction system. Therefore, catheter ablation in these regions may be associated with a higher than normal risk of complete heart block. However, with careful mapping and limited application of radiofrequency energy, successful ablation may be accomplished safely (63,64 and 65). The posteroseptal space is a complex anatomic region characterized by a broad region where the AV valve annuli are offset and diverge, resulting in a region of fatty and connective tissue that is not immediately accessible from endocardial ablation electrode positions and frequently requires ablation from within the coronary sinus (24,54,66).

The anatomic courses of slowly and decrementally conducting accessory pathways that activate the ventricle with a left bundle branch block configuration (previously referred to as *Mahaim's pathways*) have been demonstrated to commonly originate from the right atrial free wall. Discrete pathway potentials may be mapped from the tricuspid annulus, along the right ventricular endocardial surface to arborized insertions into the right bundle branch. Application of radiofrequency energy along this course successfully ablates the pathways and prevents further AV reciprocating tachycardia (64,67,68).

A number of large clinical series of radiofrequency catheter ablations of accessory pathways have been published with excellent overall results (Table 73.1). Presently, experienced electrophysiology laboratories routinely achieve acute procedure success rates in the ablation of accessory pathways of greater than 95%, with recurrence rates of less than 5%. The procedure duration and fluoroscopic exposure have shortened dramatically with increasing knowledge and experience in this field. Accordingly, the indications for catheter ablation of accessory pathways have broadened to include all patients with symptomatic arrhythmias who are refractory to

suppressive drug therapy or who prefer a drug-free lifestyle (69). Although there is little rationale for performing catheter ablation on patients with asymptomatic ventricular preexcitation, this may be pursued on occasion in patients with high-risk or special occupations (such as commercial airline pilots) in whom a single arrhythmic occurrence could have serious consequences.

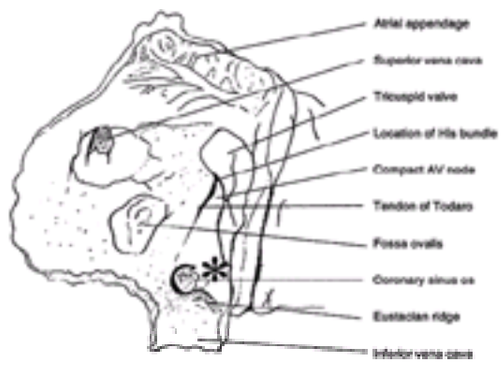
Authors	Year	No. of patients	Location of pathways	Acute success (%)	Complication rate (%)	Recurrence rate (%)
Jackman et al. (24)	1991	146	All	99	3	9
Calkins et al. (25)	1991	56	All	93	2	2
Schluter et al. (53)	1991	92	All	86	3	3
Calkins et al. (55)	1999	500	All	93	7*	8
Kay et al. (26)	1993	262	All	95	1	–
Swartz et al. (60)	1993	114	LFW	95	2	9
Lesh et al. (62)	1993	106	LFW	96	8	3
Deshpande et al. (61)	1994	100	LFW	100	6	7
Schluter and Kuck (65)	1992	12	Anteroseptal	100	0	0
Haissaguerre et al. (64)	1994	8	Anteroseptal	100	0	0
Xie et al. (63)	1994	48	Posteroseptal	92	4	–
Dhala et al. (66)	1994	50	Posteroseptal	100	6	12

LFW, left free wall.
*Total major complication rate for all patients, including atrioventricular nodal modification, accessory pathway ablation, and atrioventricular nodal ablation.

TABLE 73.1 CLINICAL RESULTS OF RADIOFREQUENCY CATHETER ABLATION OF PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME OR ATRIOVENTRICULAR RECIPROCATING TACHYCARDIA CAUSED BY CONCEALED ACCESSORY PATHWAYS

Atrioventricular Nodal Reentry

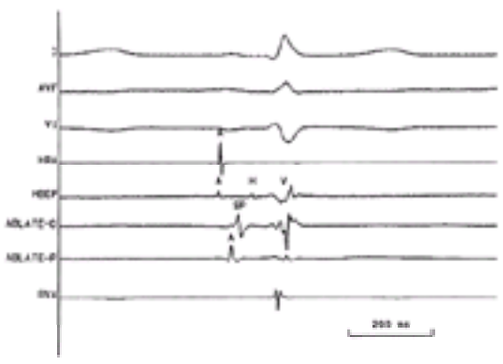
The AV node is located anatomically within the triangle of Koch, which is bounded by the tricuspid annulus, the tendon of Todaro, and the coronary sinus os. The compact AV node is located at the apex of the triangle and makes its transition with nodal-His cells to the common bundle of His. Spreading throughout the remainder of Koch's triangle are atrial transitional cells (atrial-nodal cells) and atrial myocytes. The mechanism of AV nodal reentrant tachycardia is reentrant, using a slowly conducting and a fast conducting pathway in the AV node. The typical form of this arrhythmia has anterograde slow and retrograde fast conduction, whereas the atypical form has the opposite conduction sequence or employs two separate slow pathways for the two limbs of the reentrant circuit. Before the era of catheter ablation, it was commonly hypothesized that the entire reentry circuit was within the compact AV node. However, that notion was challenged by the observation that surgical dissection of the perinodal region successfully eliminated the tachycardia (70). Anatomic study of the AV nodal region has demonstrated the presence of multiple anatomic insertions of atrial myocardium into the transitional cells of the AV nodal region (71). It is currently proposed that these pathways participate as separate pathways in AV nodal reentrant tachycardia. Typically, the atrial insertion of the slowly conducting pathway is located at the inferior-posterior extent of the triangle of Koch, near the coronary sinus os (72). The fast conducting pathway (which is thought to account for "normal" anterograde AV nodal conduction in most cases) is located in the anterior-superior region of the triangle, close to the compact node (eFig. 73.2.1). It is likely that part of the atrium participates in the reentrant circuit, but this point is unproved and somewhat controversial.



***e*FIGURE 73.2.1** Drawing of the right atrium from a right anterior oblique projection with the anterolateral atrial wall cut away. The triangle of Koch is bounded by the tricuspid annulus anteriorly, the tendon of Todaro posteriorly, and the coronary sinus inferiorly. The bundle of His is located at the apex of the triangle. The typical site for mapping and ablation of the slow atrioventricular (AV) nodal pathway is indicated by the asterisk.

Attempts have been made to map the slow pathway region and develop electrophysiologic criteria to identify the optimal site for selective slow pathway ablation. A pattern of double atrial potentials and late atrial activity is often observed along the tricuspid annulus at the base of the triangle of Koch from sites at which the slow pathway may be successfully ablated. It has been suggested that the late atrial potentials may represent slow pathway activation (73). Careful studies comparing the local electrophysiology and histopathology of canine and porcine hearts indicate that late atrial potentials may be attributed to asynchronous activation of the coronary sinus septum and the atrial tissue between the os and tricuspid valve, or to simultaneous activation of superficial transitional AV nodal tissue and a contiguous layer of atrial tissue along the tricuspid annulus (74). Microelectrode impalements in the region of slow potentials have demonstrated action potentials with AV node characteristics (75). This electrographic pattern may represent conduction through the slowly conducting AV nodal pathway but more likely originates from the distal extent of the compact AV node.

Initially, the fast pathway was targeted for ablation, but lower success rates and high rates of symptomatic heart block have led most operators away from this approach and toward slow pathway ablation (76). The technique for slow pathway ablation involves positioning the catheter in the inferior-posterior position of the triangle of Koch at a site where a typical pattern of slow pathway potentials is observed (eFig. 73.2.2). Subsequent catheter movement can be anatomically (77) or map guided (73). Similar success rates and complication rates between the two approaches have been observed (78). During radiofrequency energy delivery at successful sites, one may observe an accelerated junctional rhythm and 1:1 junctional to atrial conduction. The earliest site of retrograde atrial activation in this setting is superior to the tendon of Todaro, suggesting that the automaticity arises distal to the ablation site with conduction through the compact AV node and retrograde up the fast pathway (79).



***e*FIGURE 73.2.2** Surface electrocardiogram tracings I, aVF, and V_1, and intracardiac recordings from the high right atrium (HRA), the proximal bundle of His bipole (HBEP), distal and proximal ablation catheter bipoles (ABLATE-D, ABLATE-P), and the right ventricular apex (RVA) in a patient with typical atrioventricular nodal reentrant tachycardia. The atrial (A), bundle of His (H), and ventricular (V) deflections are labeled. On the distal bipolar tracing from the ablation electrode, a discrete high-frequency potential is observed 25 ms after the contiguous atrial potential measured on the proximal bipole. This electrogram pattern is a marker for local slow pathway (SP) activation.

The clinical success rates for catheter ablation of AV nodal reentrant tachycardia that have been generally reported are high (greater than 95%), and the complication rates low (less than 2%). The results of more recent clinical series are shown in Table 73.2. The major complication that has been reported in conjunction with this procedure is symptomatic heart block, with a prevalence of 0% to 4%. The lower prevalence of heart block in later clinical series compared with earlier may be attributable to an increased use of the posterior (slow pathway) approach, an increased understanding of the electrophysiology and anatomy of the AV nodal region, and improved skills of the individual operators (80). Aside from careful stepwise manipulation and positioning of the catheter, the most useful approach to prevent anterograde heart block is to terminate power delivery if there is evidence of loss of retrograde 1:1 conduction from a junctional tachycardia to the atrium via the fast pathway, because this implies that there is evolving injury to the compact AV node (80). Faster rates of junctional tachycardia have been observed in patients with anterograde heart block versus those without it (cycle length 363 ± 44 ms vs. 558 ± 116 ms, respectively) (81), because accelerated junctional rhythm implies proximity to the compact AV node (82). Some patients show evidence of impaired anterograde conduction before the ablation procedure. Although this may suggest the presence of fast pathway pathology, slow pathway ablation may still be pursued with a low risk of complete heart block (83). The reported recurrence rates of AV nodal reentrant tachycardia after initial successful AV nodal modification procedures are 2% to 15%. The majority of recurrences are reported within the first 2 months of the procedure. Some authors have found an association between persisting dual AV nodal physiology (presence of single AV nodal echo beats or evidence of a shift in anterograde conduction from a fast to a slow pathway) and late clinical recurrence of tachycardia (84), but this is in contrast to the experience of other operators who have not observed that association (85,86). The common practice among most operators is to terminate the ablation procedure once tachycardia can no longer be initiated at baseline or during infusion of isoproterenol and to accept the presence of persisting but impaired slow pathway function.

Author	Year	No. of patients	Primary approach[a]	Acute success (%)	Heart block (%)	Other complications (%)	Recurrence rate (%)
Jackman et al. (73)	1992	80	SP	99	1[c]	1.3	3
Jazayeri et al. (77)	1992	46	FP/SP	98	4[c]	3	4[c]
Kay et al. (85)	1992	34	SP	100	3[c]	6	3
Langberg et al. (78)	1993	127	FP	87	7	3	15
Wu et al. (80)	1993	100	FP/SP	97	3[c]	—	1
Lindsay et al. (87)	1993	39	SP	100	2[c]	3	2
Saksler et al. (84)	1994	140	SP	99	4	—	7
Mandel et al. (88)	1994	55	SP	100	0	0	13
Kanhanong et al. (89)	1995	62	FP	96	0	0	6
Calkins et al. (90)	1999	371	SP	97	1	3[e]	5

[a] Fast pathway; SP, slow pathway.
[b] Crossovers from slow to fast pathway ablation approach reported in 0% to 10% of slow pathway ablations.
[c] Heart block occurred during slow pathway ablation (either as primary approach or after crossover).
[d] Heart block occurred during fast pathway ablation (either as primary approach or after crossover).
[e] Tachycardia induced at electrophysiologic study.
[f] Total major complication rate for all patients, including atrioventricular nodal modification, accessory pathway ablation, and atrioventricular nodal ablation.

TABLE 73.2 CLINICAL RESULTS OF RADIOFREQUENCY CATHETER ABLATION OF PATIENTS WITH ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA

Atrial Flutter

It has been observed that the dominant activation wavefront during atrial flutter is cranial to caudal along the lateral atrial wall, and caudal to cranial up the septum. Cosio et al. originally determined that the mechanism of this rhythm was macroreentry using the tricuspid annulus as an anatomic barrier. It was hypothesized that the difference between “typical” type I atrial flutter and “atypical” type I atrial flutter was that the former had reentrant activation sequence in a counterclockwise direction around the tricuspid valve in the frontal plane (viewed from apex to base), whereas the latter had a clockwise activation pattern (Fig. 73.3). Cosio et al. also observed that the necessary prerequisite for this arrhythmia was a region of physiologic conduction block between the posterior and lateral atrial walls (90). Without this region of block, the reentrant wavefront would conduct rapidly from the septum around the posterior wall of the atrium and render the lateral wall of the atrium refractory, thus preventing propagation of the subsequent reentrant wavefront. Subsequent mapping studies in humans using intracardiac ultrasound and careful entrainment mapping techniques have demonstrated physiologic conduction block in the posteromedial (sinus venosa) region of the right atrium during atrial flutter (91).

FIGURE 73.3 Surface electrocardiogram tracings I, aVF, and V_1, and intracardiac recordings from ten bipolar recording pairs (RA1 to RA10) positioned around the tricuspid annulus. RA1 is located on the low interatrial septum, RA3 is on the high septum, RA7 is on the high lateral wall, and RA10 is on the low atrial wall. The distal bipole of the ablation catheter (ABLATE-D) is positioned at the tricuspid-inferior vena cava isthmus. The arrows demonstrate the pattern of activation during ongoing atrial flutter. This is an example of typical “counterclockwise” atrial flutter in that the pattern of activation (viewing the heart from apex to base) rotates in that direction.

Understanding the path of reentry of atrial flutter led researchers to identify critical sites of conduction that would be amenable to catheter ablation in order to cure this arrhythmia (92,93). Cosio et al. pioneered the present-day approach of anatomically guided catheter ablation of atrial flutter. They reasoned that the reentrant circuit should always uses the subeustachian isthmus between the inferior vena cava orifice and the tricuspid annulus as a requisite limb of the reentrant circuit. They then demonstrated that a line of radiofrequency ablative lesions traversing this isthmus was successful in terminating atrial flutter (94).

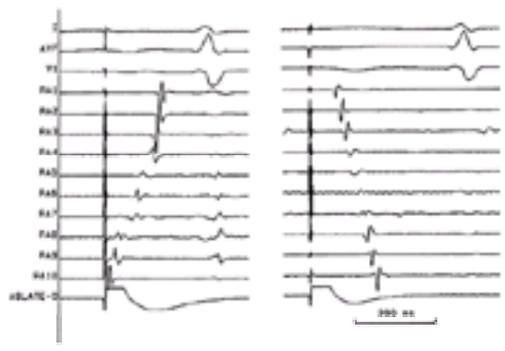
The anatomically guided techniques that are currently used in radiofrequency ablation of typical atrial flutter typically employ an ablation catheter with a large tip electrode placed via the inferior vena cava across the tricuspid valve. The catheter is positioned across the subeustachian isthmus on the tricuspid valve, radiofrequency power is turned on, and the electrode is pulled back in a line until the catheter crosses the eustachian valve. Continued conduction across the subeustachian isthmus can be discerned by identification of a site where double potential (indicating electrical activation on either side of a line of conduction block) merges to a single breakthrough potential (95). Useful end points indicating conduction block include a reversal of activation sequence through the isthmus or change in bipolar electrographic polarity beyond the line of ablation (96,97). If conduction across the isthmus persists, further radiofrequency applications may be made to those sites. Wide variability of the anatomy of the subeustachian isthmus among patients has been observed, including width of the isthmus and its position and angle relative to the inferior vena cava (98). Thus, patients with significant right atrial hypertrophy or enlargement have thicker, wider, or more angled geometries in the isthmus region, have arrhythmia recurrence (99), and require a greater number of ablative applications to achieve procedure success (98).

The results of clinical series are presented in Table 73.3. The acute success rate of this procedure now exceeds 90% when performed by experienced operators, and the late atrial flutter recurrence rate is 10% to 20%. Confirmation of bidirectional block of electrical conduction through the isthmus between the tricuspid valve and inferior vena cava has been demonstrated to be an important criterion for the procedure’s success. Despite successful termination and prevention of reinduction of atrial flutter by ablative lesions, some patients still have residual conduction through the isthmus that can result in clinical arrhythmia recurrence (eFig. 73.3.1) (99,100). Success rates may also be improved with the use of irrigated-tip ablation catheters (101). Despite successful ablation of atrial flutter, the patient will likely have clinical recurrence of atrial fibrillation or type II atrial flutter if these arrhythmias were observed clinically before the ablation procedure (98,102,103 and 104). After initiation of antiarrhythmic drugs, particularly type 1C agents, some patients with atrial fibrillation or a combination of atrial fibrillation and atrial flutter convert to pure type I atrial flutter. In these cases, a combination of drug and atrial flutter ablation therapy may be effective in preventing arrhythmia recurrence (105).

Author	Year	No. of patients	Acute success (%)	Isthmus block confirmed	Complication rate (%)	Recurrence rate (%)	
						Atrial flutter	Atrial fibrillation
Feld et al. (93)	1992	12	83	No	0	17	0
Cosio et al. (94)	1993	5	78	No	0	0	5
Poty et al. (95)	1995	12	100	Yes	–	8	–
Philippon et al. (103)	1995	19	90	No	–	9	26
Fischer et al. (106)	1995	80	90	No	0	17	5
Cauchemez et al. (108)	1996	20	100	Yes	–	15	5
Haydak et al. (104)	1998	110	98	Yes[a]	–	5	25
Chen et al. (96)	1999	20	100	Yes	0	5	–
Heidbuchel et al. (98)	2000	100	99	Yes	1	0	30

[a]Isthmus block confirmed in a subgroup of 10 patients.

TABLE 73.3 CLINICAL RESULTS OF RADIOFREQUENCY CATHETER ABLATION OF PATIENTS WITH ATRIAL FLUTTER

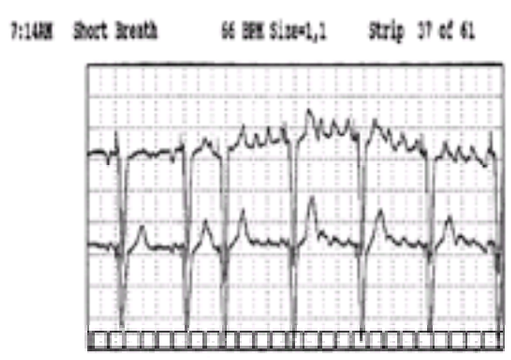


***e*FIGURE 73.3.1** Surface electrocardiogram tracings I, aVF, and V_1, and intracardiac recordings from ten bipolar recording pairs (RA1 to RA10) positioned around the tricuspid annulus as described in Figure 73.3. The roving ablation and pacing catheter (ABLATE-D) is used for pacing after completion of a linear ablation in the isthmus between the tricuspid valve annulus and the inferior vena cava. The left panel demonstrates pacing from a site that is lateral to the line of block. The atrial activation sequence is in a clockwise direction, up the lateral wall and down the interatrial septum. The right panel shows pacing on the low interatrial septum, with the opposite (counterclockwise) atrial activation sequence. These sequences indicate complete bidirectional conduction block at the line of ablation.

Atrial Fibrillation: Palliative Therapy

Atrial fibrillation is the most common sustained arrhythmia in the world, with a reported prevalence of 1.9% for patients under 65 years of age, and 5% to 6% for the population of patients over age 65 (107). The morbidity and mortality of this arrhythmia may be attributed primarily to three factors: the propensity of the fibrillating atria for thrombus formation with the sequelae of systemic thromboembolism including stroke; the loss of atrial systolic function as a contributor to ventricular filling; and the irregular and rapid ventricular rate response leading to symptoms of palpitations and reduction of diastolic filling time. Therefore, the two main strategies for management of patients with atrial fibrillation are maintenance of sinus rhythm with suppressive antiarrhythmic agents or rate control and anticoagulation. If the latter strategy is pursued, warfarin anticoagulation can significantly reduce (but not eliminate) the risk of thromboembolism. Symptomatic palpitations may be reduced with appropriate use of digitalis, beta-sympathetic blockers, or calcium channel blockers. Unfortunately, these drugs are often poorly tolerated, and because the AV nodal blocking action of digitalis is mediated through central vagotonic effects, the ventricular response rate to atrial fibrillation increases dramatically in settings of spontaneous vagolysis (such as exercise). Frequently, adequate doses of AV nodal blocking agents result in symptomatic bradycardia, requiring pacemaker implantation. Therefore, nonpharmacologic means of rate control are sometimes required.

The palliative ablative procedures that are available for the treatment of atrial fibrillation are AV junctional ablation and AV nodal modification. The goal of AV junctional ablation is to interrupt completely the AV conduction with an ablative lesion placed in the vicinity of the compact AV node. In most cases, the patient has a slow but tolerable junctional escape rhythm after AV junctional ablation, which arises from the low compact AV node or high bundle of His region, immediately distal to the site of ablation. This escape rhythm is usually adequate to prevent hemodynamic embarrassment, but not adequate to maintain a normal heart rate at rest or with activity. Therefore, permanent pacemaker implantation is always required. Selection of a single-chamber rate-responsive ventricular pacemaker is appropriate for patients who are in chronic atrial fibrillation. Patients with paroxysmal atrial fibrillation benefit most from implantation of a dual-chamber rate-responsive pacemaker with mode-switching capabilities. These devices maintain AV synchrony when the patient is in sinus rhythm, thus avoiding symptoms of pacemaker syndrome. After atrial fibrillation onset, the device automatically recognizes the atrial tachycardia and effectively converts from a dual-chamber to a single-chamber pacing mode, which prevents the pacemaker from tracking the atrium and pacing the ventricle at a high rate (*e*Fig. 73.3.2).



***e*FIGURE 73.3.2** A monitor strip is shown from a patient with paroxysmal atrial fibrillation and flutter, complete heart block after catheter ablation of the atrioventricular junction, and implantation of a mode-switching dual-chamber pacemaker. The initial rhythm is normal sinus with appropriate atrial sensing and ventricular pacing by the pacemaker (DDD mode). There is onset of atrial flutter, but after 1 second of tachycardia, mode-switching criteria are met, and the pacemaker switches to single-chamber pacing (VVI), maintaining a regular rhythm at 60 beats/min.

The goal of AV nodal *modification* procedures is to damage but not destroy all AV nodal conduction. In the ideal case, the patient has adequate basal rates, but the rapid heart-rate acceleration exercise is prevented. It is important to note that the atria continue to fibrillate after AV junctional ablation or modification despite excellent heart-rate control and resolution of the patient's symptoms. Therefore, the patient is still at risk for thromboembolic events, and ongoing treatment with warfarin is recommended.

One successful technique of AV junctional ablation employs a temporary backup pacing catheter that is placed in the right ventricular apex, and an ablation catheter that is positioned across the high septal portion of the tricuspid annulus, where the maximal His deflection is observed. The catheter is then withdrawn 5 to 10 mm to the atrial side of the annulus such that the atrial and ventricular electrogram amplitudes are equal, and the bundle of His deflection is low amplitude. In a small minority of cases, it is not possible to achieve AV block with ablation from the right septal approach because of anatomic variation or technical reasons. In these cases, the proximal bundle of His may be approached by advancing the ablation catheter retrograde across the aortic valve and positioning it on the high septum at a site with a large His deflection (108). A marker of successful site selection and ablation is the occurrence of an accelerated junctional rhythm at electrode-tissue interface temperatures above 51°C. Complete AV block is reliably observed at temperatures greater than 58°C (109). If an accelerated junctional rhythm is not observed despite adequate heating, then the catheter should be repositioned and ablation attempted again. When the goal of catheter ablation is modification, not complete ablation of AV conduction, the operator positions the catheter inferior and posterior to the site of maximal bundle of His deflection. Initial ablation attempts should employ low powers or temperatures, which should gradually be increased until the desired effect is achieved. The end point of this procedure is reached when a significant

diminution of ventricular rate response to ongoing atrial fibrillation is observed.

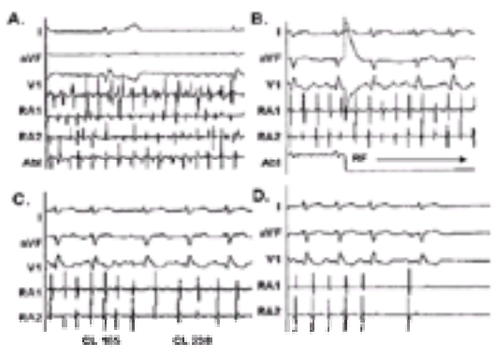
The technical success rate of AV junctional ablation is excellent, ranging from 95% to 100%, when performed by experienced operators (26,108,109 and 110). In appropriately selected patients, marked improvement in symptoms can be anticipated, with decreases in palpitations and effort dyspnea, asthenia, and exertional intolerance. Improvements in exercise time and ventricular function have been measured 3 months postablation (111). In one study of patients with atrial fibrillation and reduced left ventricular function, 90% of patients had improvement in their left ventricular ejection fractions and a decrease in left ventricular and atrial dimensions (112).

The acute success rate of AV nodal modification procedures is approximately 70% (113,114). Because the injury to the AV node is nonspecific, there is a high prevalence of complete heart block with this procedure. Clinical outcome has been favorable in patients with an initial successful response over short-term follow-up, although one late sudden death in a patient with dilated cardiomyopathy has been reported. Even with successful heart-rate control, patients treated with AV nodal modification continue to have an irregular ventricular response to their atrial fibrillation and may have persistent symptomatic palpitations. For this reason, AV junctional ablation and pacemaker implantation is the procedure of choice in most cases.

Atrial Fibrillation: Curative Therapy

The understanding of the pathophysiology of atrial fibrillation has advanced considerably in recent years. The long-standing hypothesis of atrial fibrillation has been that multiple wavelets of reentrant atrial activity conduct throughout both atria, and that reactivation of new wavelets of reentry perpetuate this arrhythmia. Factors that promote the formation and increase the number of wavelets have been associated with clinical atrial fibrillation propagation (115,116). An alternative hypothesis of reentrant atrial fibrillation propagation is that a dominant rotor of atrial reentrant activation drives the arrhythmia and the remaining atrium is passively activated (117). The regions of dominant periodic electrical activity measured in experimental atrial fibrillation have a characteristic frequency of 7 to 10 Hz, corresponding to atrial rates of 400 to 600 beats/min. In 1997, Jais et al. made the groundbreaking observation that some patients had atrial fibrillation on the basis of rapid firing of arrhythmogenic foci (118). These foci were found to arise predominantly from the pulmonary veins, and some patients had two or more focal sources of arrhythmia origin (119,120). Patients with atrial fibrillation of focal origin tend to be younger, have multiple brief paroxysms of arrhythmia, and most commonly have normal hearts. However, a continuum probably exists between these patients and those with persistent atrial fibrillation, structural heart disease, and a reentrant mechanism of atrial fibrillation. It is likely that patients with minimal to moderate heart disease and recurrent episodes of atrial fibrillation that are prolonged or persistent have focal initiation of their arrhythmia with reentrant propagation.

Atrial fibrillation that is dependent on reentrant propagation requires a minimal geographic region for the maintenance of the driving wavelets or rotor. If lines of anatomic conduction block are placed such that this critical circuit size cannot be achieved, then the fibrillation cannot propagate. This was the theoretical basis of the surgical maze procedure (121). It was hypothesized that similar long linear atrial lesions could be achieved by catheter ablation. Experimental studies have demonstrated that multiple linear lesions in the right and left atria can prolong atrial fibrillation cycle length and, ultimately, terminate this ongoing arrhythmia (eFig. 73.3.3) (122). The first cases of linear atrial fibrillation ablation in patients were reported by Swartz et al., who employed a technique of dragging a typical 4-mm tip ablation electrode on multiple lines along the atrial wall during ongoing radiofrequency energy delivery. Chronic atrial fibrillation could be successfully terminated in the majority of cases, but over one-half of the patients had arrhythmia recurrence and required at least a second ablation session. In addition, significant complications including stroke were observed (123). Haissaguerre et al. employed a multiple-ring electrode catheter that, when positioned tangentially to the atrial walls, allowed sequential multiple electrode radiofrequency energy delivery and achieved long linear lesions. In his series of 45 patients with drug-refractory paroxysmal atrial fibrillation, a staged procedure was performed with linear ablation, focal atrial tachycardia ablation, or both in the right, left, or both atria. Success, defined as less than one symptomatic episode of 6 hours' duration in 3 months with or without additional suppressive antiarrhythmic drug therapy, was achieved in 21 patients (47%) (124).



***e*FIGURE 73.3.3** Surface leads I, II, and aVF and intracardiac tracings from two right atrial (RA) sites and an ablation catheter (Abl) during linear atrial ablation for persistent atrial fibrillation. **A:** The rhythm at baseline before any linear ablations. The atrial fibrillation is disorganized and rapid. **B:** The onset of radiofrequency energy delivery (RF) after completion of a partial set of linear atrial ablations. The atrial fibrillation has been organized to a type II atrial flutter by the previous lesions. **C:** A transition from fast to slower atrial reentrant tachycardia during ongoing radiofrequency energy delivery. This suggests that the remaining reentrant circuit size was suddenly increased as conduction through a residual gap in the linear lesions was blocked and the reentrant circuit increased in length. **D:** With ongoing radiofrequency energy delivery, the slower tachycardia is ultimately terminated.

Linear atrial ablation can be accomplished by a point-to-point technique, a "drag" approach, or with multiple electrode side-contact catheters. At this time, the lines that are targeted are anatomically determined. Most investigators agree that some approach to isolate the pulmonary veins and a tricuspid-caval isthmus lesion is important for procedure success. Other lesion locations that are of potential value include a lesion that connects the encircling pulmonary vein lesions to the mitral annulus, a lesion extending anteriorly from the pulmonary vein lesions to Bachmann's bundle, a vertical intercaval lesion in the right atrium, and a vertical right or left septal lesion. Although a pattern of transition from disorganized to organized atrial fibrillation has been described as a favorable observation in the modification of atrial fibrillation wavelet conduction, most present-day linear ablation procedures are anatomically guided, not map guided. Because the relationship of the linear lesions to anatomic structures and the contact between the catheter and tissue are important factors in procedure success, advanced imaging modalities such as intracardiac echocardiography have been useful tools in this procedure (125).

Reported series of linear atrial ablation have employed a variety of techniques and tools to achieve continuous and transmural linear lesions (Table 73.4). Comparison among trials is difficult for a variety of reasons. The patients studied likely include a mix of both focal and reentrant mechanisms. The ablation targets vary among right atrial, left atrial, and biatrial procedures. The definitions of procedure success may or may not include concomitant suppressive antiarrhythmic drug therapy. Finally, the follow-up durations of all the studies are relatively short. Some common themes in linear ablation are emerging. Many investigators have concluded that ablation in the right atrium alone has a low success rate, and in most cases left atrial or biatrial ablation is required. A consequence of creation of incomplete lesions is arrhythmia exacerbation (proarrhythmia) caused by the production of scar-related left atrial "flutter" (126). The complexity and long duration of these procedures may increase their complication rate relative to standard catheter ablation procedures. The field of linear atrial ablation is still evolving, but available data suggest that transcatheter approaches achieve a far lower success rate than that observed with open surgical procedures such as the maze operation. This outcome is most likely caused by residual gaps in linear ablation lines from the catheter-based approaches that allow for the continued propagation of reentrant atrial fibrillation wavelets (127). As the technology of catheter-based linear ablation improves, success rates may ultimately approach those of the open surgical procedure. Alternatively, minimally invasive surgical maze procedures may supplant the catheter approaches if high success rates can be achieved with minimal surgical morbidity.

Author	Year	No. of patients	Structural heart disease (%)	Paroxysmal atrial fibrillation (%)	Right atrial/left atrial ablation	Percent cured (no antiarrhythmic drugs)	Percent improved (with antiarrhythmic drugs)	Complication rate (%)	Follow-up duration (mo)
Haissaguerre et al. (124)	1998	45	29	100	45/0	18	47	–	11 ± 4
Gaita et al. (125)	1998	16	0	50	16/0	25	56	0	–
Walcott et al. (126)	1998	15	53	0	15/0	20	60	26	18 ± 10
Garg et al. (127)	1999	12	33	67	12/0	0	67	0	21.3 ± 11.2
Pappone et al. (128)	1999	21	7	100	21/0	66	71	4	16.5 ± 3.0
Ernst et al. (129)	1999	45	0	62	44/10	4	–	11	–
Natale et al. (130)	2000	18	11	100	18/0	28	50	11	22 ± 11
Haines et al. (131)	2000	23	61	74	23/0	22	48	26	8 ± 12

TABLE 73.4 CLINICAL RESULTS OF LINEAR ATRIAL ABLATION OF PATIENTS WITH ATRIAL FIBRILLATION

Identification of a focal mechanism of atrial fibrillation initiation led to advances in curative therapy for atrial fibrillation in selected patients. It was initially described by Jais et al. that foci of rapid electrical firing could trigger atrial fibrillation (118). Follow-up studies from the same group in a larger series (119), as well as studies from Chen et al. (120), confirmed that focal atrial fibrillation is a significant clinical entity and is very treatable by limited catheter ablation techniques. The majority of triggering foci for atrial fibrillation arises from the sleeve of muscular tissue that extends from the left atrial body into the pulmonary veins. The average extension of these muscle fibers into the vein is greater for the superior pulmonary veins (30 to 40 mm) than the inferior pulmonary veins (15 to 20 mm) (120). Although mapping studies indicate that they are truly focal in nature (135), the precise mechanism of these beats (microreentrant, automatic, or triggered) has not been clearly defined. In many cases, the focal activity is increased by adrenergic stimulation or rapid pacing and blocked by beta-adrenergic blocking drugs and calcium channel blockers (120), suggesting triggered activity as the most likely arrhythmia mechanism. The reason for the clustering of triggering foci in the pulmonary veins is unknown at this time. Other less prevalent sites of origin of triggering foci include the ligament of Marshall (a remnant of the left superior vena cava on the posterior left atrium) (136), the crista terminalis in the right atrium, and the superior vena cava (137).

The techniques of focal atrial fibrillation ablation are still in evolution. However, most investigators perform extensive pulmonary vein mapping via a single- or double-transseptal catheterization technique to attempt to identify the site(s) of arrhythmia origin. Advanced technologies such as multielectrode basket catheters, noncontact mapping, electroanatomic mapping, and intracardiac echocardiographic imaging have all been useful adjuncts toward successful ablation of the arrhythmogenic substrate. Some investigators have proposed using an anatomically derived procedure, with ablation of the bases of all pulmonary veins, foregoing the requirement for mapping (138). Because approximately 90% of the sites of arrhythmia origin seem to arise from the pulmonary veins, the anatomically guided ablation approach may ultimately be the most effective and time efficient. Unfortunately, the limitations of current ablation catheter technology coupled with the significant anatomic variability of pulmonary veins have curtailed the success of this approach.

VIDEO

Video 73.1 An isopotential activation map recorded from a 64-pole multielectrode basket mapping catheter placed in the left superior pulmonary vein in a patient with atrial fibrillation of focal origin. Two sequential atrial activation sequences are shown. The first beat shows activation of a sinus beat from the left atrium to the base of the pulmonary vein (*bottom*) and into the body of the vein (*top*). The second beat shows activation of a premature atrial beat initiating atrial fibrillation. The origin of activation is within the vein at site H3 with conduction around the vein body to the opposite wall. Of note: techniques may evolve, but it is likely that the overall outcome statistics will not change significantly. The main frontiers remaining in catheter ablation are curative therapy from atrial fibrillation and reentrant ventricular tachycardia. A wide variety of ablation tools are being developed for atrial fibrillation. But more importantly, selective linear atrial ablation will help us understand the pathophysiology of this complex arrhythmia, and direct us to the optimal ablation targets to achieve arrhythmia cure. Reentrant ventricular tachycardia is often hemodynamically unstable precluding prolonged periods of mapping. New mapping tools will allow for rapid ablation site section. Because ablation targets are frequently mid-myocardial or subepicardial, larger and deeper lesions that can be created with conventional radiofrequency energy ablation will be required for procedure success. Future innovative catheter designs and new ablation energy sources may solve this present limitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The early clinical series of pulmonary vein ablation are listed in Table 73.5. Acute success rates of this procedure are high (greater than 95%), but overall success rates are much lower (60% to 86%). There are several possible explanations for the high recurrence rate of atrial fibrillation observed after this procedure. First, the sensitivity of provocative maneuvers for initiating focal trigger activity is limited in some patients. Thus, despite successful ablation of all apparent triggering foci at the time of the procedure, some quiescent foci may emerge later. The more focal sites of origin identified, the lower the procedural success rates (140). Second, the triggering foci can be variable in their activity and can “turn off” coincident with catheter manipulation. Thus, the appearance of successful ablation can be achieved acutely with late recurrence due to reactivation of the focus. Finally, if a pulmonary vein isolation technique is employed, the line of ablation required to isolate the vein may range from 1 to 4 cm in length. Any recovery of conduction along the line of ablation results in conduction of the rapid atrial impulses from the targeted vein. Complications in focal atrial fibrillation ablation include all those related to all catheter ablation procedures. In addition, the unique complication of pulmonary vein stenosis may occur if ablation powers and temperatures are not limited (120,141). Also, the risk of systemic thromboembolism is probably higher than that observed with other left-sided ablation procedures because of the increased instrumentation and longer procedure duration, but the exact prevalence of this complication is not known.

Author	Year	No. of patients	No. of foci ablated per patient	Structural heart disease (%)	Percent cured (no antiarrhythmic drugs)	Percent multiple procedures	Complication rate (%)	Follow-up duration (mo)
Haissaguerre et al. (119)	1998	45	1.5	31	62	56	0	8 ± 6
Chen et al. (120)	1999	79	1.5	42	86	9	9[a]	6 ± 2
Lauer et al. (139)	1999	7[b]	1.0	0	86	0	0	—
Haissaguerre et al. (140)	2000	98	2.2	19	71	58	6	8 ± 5
Natale et al. (138)	2000	15	3.1	40	60	0	27	9 ± 2
University of Virginia series[c]	2001	40	1.0	12	72	10	7	9 ± 5

[a]Forty-two percent of patients had angiographic pulmonary stenosis, of whom 7% were symptomatic.
[b]Three of seven patients had persistent atrial fibrillation.
[c]Consecutive patients undergoing intracardiac echocardiographically guided focal atrial fibrillation ablation at the University of Virginia Health Sciences Center.

TABLE 73.5 CLINICAL RESULTS OF FOCAL ATRIAL ABLATION OF PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION

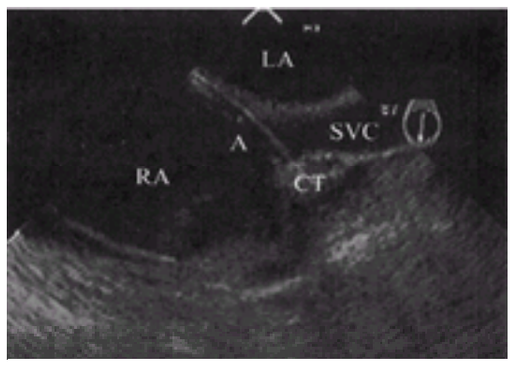
The ultimate success of atrial fibrillation ablation will rest with the development of the ablation tools and further understanding of the pathophysiology of this arrhythmia in different patient subsets. Ultimately, the proof of its value will depend on its ability to eliminate symptoms, restore normal left atrial mechanical activity, and prevent late thromboembolic complications.

Other Atrial Arrhythmias

Tachycardias that arise from the sinus node region include sinoatrial reentrant tachycardia and “inappropriate” sinus tachycardia. The former is characterized by its paroxysmal nature, the ability to initiate and terminate the rhythm with programmed atrial stimulation, and a P-wave morphology and intraatrial activation sequence that are indistinguishable from normal sinus rhythm. This is an uncommon arrhythmia and therefore the experience with ablative therapy is somewhat limited. It typically has its origin in the high atrial region at the junction between the atrium and superior vena cava in the classical sinus node anatomic region. The optimal site of ablation may be identified by searching for the earliest site of atrial activation relative to the P-wave onset. Ablation in this region results in termination of the tachycardia and frequently results in a slight shift of sinus node activation to a lower site along the crista terminalis (142,143). Although most patients have normal sinus node function postablation, sinus node dysfunction requiring pacemaker implantation is a potential risk. The reported clinical series are limited, but include one description of 11 patients who were identified out of a cohort of 343 consecutive patients referred for electrophysiologic evaluation of supraventricular tachycardia. Nine of the 11 patients had additional tachycardia mechanisms identified. Radiofrequency catheter ablation was successful in all ten patients in whom it was attempted, and no complications were noted (143).

Inappropriate sinus tachycardia is similar in P-wave morphology and atrial activation sequence to sinoatrial reentry and normal sinus rhythm, but does not follow a paroxysmal pattern and sometimes occurs incessantly. Patients with this arrhythmia have an exaggerated heart-rate response to minor physiologic stresses and often have heart rates greater than 100 beats/min at rest. It is important to confirm that patients presenting with apparent inappropriate sinus tachycardia do not have the postural orthostatic tachycardia syndrome (144). These patients have a marked compensatory sinus tachycardia because of failure of peripheral autonomic vascular response to orthostatic stress. “Successful” sinus node ablation in these patients may result in crippling hypotension. For patients with true inappropriate sinus tachycardia, catheter ablation has been successfully performed by targeting a relatively broad region of the superior crista terminalis for radiofrequency energy delivery (*e*Fig. 73.3.4). Lee et al. used intracardiac echocardiography to assist catheter positioning and were able to achieve complete sinus node ablation in four of four

patients, and successful arrhythmia modification (defined as a 25% reduction in sinus rate) in 12 of 12 patients (145). However, permanent atrial pacing was required in two patients, arrhythmias recurred in short-term follow-up in two patients, and two patients had significant procedural complications (transient superior vena cava syndrome and phrenic nerve injury). Thus, catheter ablation for inappropriate sinus tachycardia may be useful in the management of these challenging patients, but it should not be considered as first-line therapy.



***e*FIGURE 73.3.4** Transesophageal echocardiogram of a patient undergoing modification of the sinoatrial node. The image is oriented as follows: superior to the right; inferior to the left; posterior on the top; and anterior on the bottom. A longitudinal sector through the left atrium (LA), right atrium (RA), and superior vena cava (SVC) is seen. The ablation catheter (A) is positioned in contact with the superior aspect of the crista terminalis (CT). Earliest atrial activations during episodes of inappropriate sinus tachycardia were mapped to this site.

Atrial tachycardia is a rhythm that may originate from either the left or right atrium and may be caused by reentry or triggered or abnormal automaticity. In the right atrium, it commonly arises from the crista terminalis, although its origin may also be low atrial septum or right atrial appendage. In the left atrium, the arrhythmia origin is most often from the origins of the pulmonary veins. Surface electrocardiography can be useful to determine the arrhythmia site of origin. A positive or biphasic P wave in surface lead aVL suggests a right atrial origin, whereas a positive P wave in V_1 and a negative P wave in aVL imply a left atrial arrhythmia origin (146).

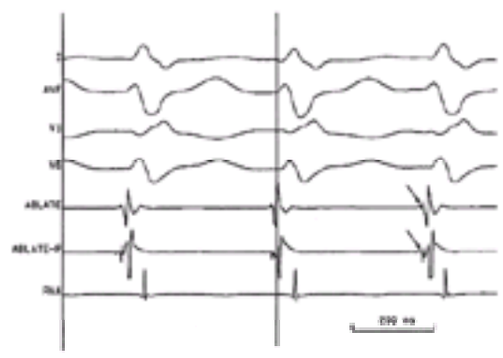
Because the right pulmonary veins are located posterior and rightward from the right atrial septum, the surface P-wave morphology can sometimes be inaccurate in predicting the arrhythmia site of origin. Mapping of atrial tachycardia is best achieved with activation mapping to identify local atrial activity before onset of the surface P wave, pace mapping to identify a site where the paced P wave is identical to the spontaneous tachycardia P wave, and paced activation sequence mapping where the relative activation timing from multiple atrial recording sites is identical between pacing and spontaneous tachycardia. Using this approach, Tracy et al. successfully ablated eight of ten patients, one of whom had multiple foci. Two patients had clinical recurrence, and one was successfully reablated (147).

ABLATION OF SPECIFIC VENTRICULAR ARRHYTHMIAS

Idiopathic Ventricular Tachycardia

Patients with structurally normal hearts may have ventricular tachycardia with a variety of underlying arrhythmia mechanisms. Idiopathic ventricular tachycardia most commonly arises from the right ventricle in the outflow tract below the pulmonic valve. These arrhythmias tend to fall into two main categories. Repetitive monomorphic ventricular tachycardia is characterized by multiple repeating bursts of nonsustained ventricular tachycardia and high-density premature ventricular beats. These arrhythmias may be increased in the setting of catecholamine stress, but frequently are suppressed in the setting of catecholamine-induced increases in sinus rate. It is hypothesized that the mechanism for repetitive monomorphic ventricular tachycardia is abnormal automaticity (148). Catecholamine-sensitive ventricular tachycardia may be nonsustained or sustained. Because these arrhythmias are catecholamine sensitive, they are frequently exercise induced. They should terminate in response to intravenous adenosine or verapamil bolus infusions. It is hypothesized that the mechanism for these arrhythmias is triggered automaticity. The typical features of these arrhythmias on 12-lead electrocardiograms include a left bundle branch block morphology, an inferior frontal plane axis, and a relatively isoelectric complex in surface lead (149,150). Idiopathic ventricular tachycardia of left ventricular origin is typically a reentrant tachycardia that uses Purkinje's network as part of its reentrant circuit. The site of slowed conduction in the reentry circuit has not been well characterized, but it is typically sensitive to verapamil and not to adenosine (151,152). This feature allows for differentiation of this arrhythmia from the rare left ventricular form of adenosine-sensitive left ventricular tachycardia that has a presumed triggered automatic mechanism (45). As anticipated, idiopathic left ventricular tachycardias have a right bundle branch block morphology on the surface 12-lead electrocardiography.

The mapping techniques used to ablate idiopathic ventricular tachycardias of focal origin include activation mapping, pace mapping, electroanatomic mapping, and body surface electrocardiographic mapping. Episodes of sustained or nonsustained ventricular tachycardia should be initiated with rapid ventricular pacing, isoproterenol infusion, or both. During ongoing tachycardia, the local ventricular activation should precede the onset of the surface QRS complex by 20 to 80 ms. Pacing from that site should result in a 12-lead electrocardiogram or body surface electrocardiogram that is identical in all leads to that recorded during tachycardia (149,153,154,155,156,157,158 and 159). Since these tachycardias are focal in origin, unipolar mapping at optimal ablation sites yields rapid negative deflections that precede the QRS onset, indicating that all local activations are emanating from, and conducting away from, those locations (160). Because these arrhythmias are autonomically sensitive and sometimes cannot be initiated in the artificial setting of the electrophysiology laboratory, precise mapping of the site of origin is not possible. Some patients, however, have unifocal premature ventricular contractions that are identical in morphology to those of ventricular tachycardia and presumably share the same origin and mechanism. In these cases, it is appropriate to map the unifocal premature beats as a guide to catheter ablation. A marker for successful site selection for catheter ablation is immediate acceleration then termination of the ventricular tachycardia coincident with the delivery of radiofrequency current. The site of origin of idiopathic verapamil-sensitive left ventricular tachycardia may be best identified by activation mapping during ongoing tachycardia. Discrete high-frequency Purkinje's potentials precede the site of earliest ventricular activation during tachycardia by 15 to 42 ms. These potentials are identified in the mid- or distal inferior septum or free wall and also precede local ventricular activation during sinus rhythm (155). In the same anatomic region, late diastolic potentials may be identified preceding Purkinje's potential activation by a mean of 35 ms. During entrainment, the interval between the late diastolic potentials and Purkinje's potentials shows decremental conduction properties (161). Catheter ablation at the site of fusion of the Purkinje's potential into the early ventricular potential yields a high success rate of arrhythmia termination and cure (eFig. 73.3.5) (155).



***e*FIGURE 73.3.5** Surface electrocardiographic leads I, aVF, and V_1 and intracardiac electrograms from the distal (ABLATE) and proximal (ABLATE-P) poles of the mapping and ablation catheter, and the right ventricular apex (RVA). The rhythm is idiopathic left ventricular tachycardia. The vertical line corresponds to the onset of the surface QRS complex and is preceded by local ventricular activity recorded by the ablation electrode. The arrows represent Purkinje's potentials, which precede local ventricular activation at this site. Catheter ablation at this location terminated this ventricular tachycardia.

The reported clinical success rate of catheter ablation of idiopathic ventricular tachycardia is 76% to 100% and generally greater than 90% for those arrhythmias arising from the right ventricular outflow tract (Table 73.6). The reported complications with this procedure have been infrequent. Two cases of pericardial effusion (one requiring pericardiocentesis) were observed in a series of 44 patients undergoing radiofrequency ablation of ventricular tachycardia in the right and left ventricles (161). One case of catheter-induced mitral regurgitation has been reported as a consequence of catheter manipulation in the left ventricle (155).

Author	Year	No. of patients	Ventricular tachycardia location	Acute success (%)	Complication rate (%)	Recurrence rate (%)
Klein et al. (153)	1992	16	RVOT	100	0	6
Calkins et al. (154)	1993	18	RVOT (90)*	72	0	8
			RV (5)*			
			LV (5)*			
Wilber et al. (148)	1993	7	RVOT	100	0	8
Nakagawa et al. (155)	1993	8	LV	100	13	13
Wen et al. (156)	1997	7	LV	100	–	8
Peters et al. (158)	1999	19	RVOT (90)	89	5	12
			LV (5)			
Tsuchiya et al. (159)	1999	16	LV	100	–	8

LV, left ventricle; RV, right ventricle (excluding outflow tract); RVOT, right ventricular outflow tract.
*Two tachycardias identified in each of two patients.

TABLE 73.6 CLINICAL RESULTS OF RADIOFREQUENCY CATHETER ABLATION OF PATIENTS WITH IDIOPATHIC VENTRICULAR TACHYCARDIA

Reentrant Ventricular Tachycardia with Structural Heart Disease

Patients with structural heart disease have varying degrees of fibrosis interspersed among bundles of surviving myocardial bundles. The most common arrhythmogenic substrate among patients with reentrant ventricular tachycardia is chronic ischemic heart disease. The central portion of a complete transmural scar from prior infarction is commonly electrically inactive, but some broad wavefronts of slowed conduction can occur across this region in a thin surviving endocardial layer (162). The border zone of the scar is extremely heterogeneous, making it an ideal substrate for reentry. A typical reentrant circuit uses these small myocardial bundles at the scar border zone as regions of slowed conduction (163). Conduction through these regions accounts for the isoelectric period between QRS complexes on surface electrocardiography, particularly with slower tachycardias. The return circuit is complex and uses the surrounding myocardium on one or both sides of the central conduction zone, thereby creating a circular or a figure-eight conduction pattern (164,165). In patients with posterior scars, the central conduction zone is often the isthmus between the scar and the mitral valve annulus (166). The slow conduction zone is characterized by a zigzag activation sequence through regions of patchy fibrosis. Most of the conduction delay is seen at the site of conduction from one fiber to another perpendicular to the fiber orientation (167).

The precise courses of the reentrant wavefronts in the ventricular tachycardias of patients with nonischemic myopathies are not well understood. Diffuse regions of fibrosis mingling with normal or hypertrophied myocytes are typically observed and create a substrate for reentrant rhythms (168). However, the diffuse nature of the structural abnormalities allows for dynamic changes in the reentrant circuits beat to beat and makes these patients more prone to polymorphic ventricular tachycardias. An interesting variant of ventricular tachycardia found predominantly in patients with dilated cardiomyopathy is bundle branch reentrant tachycardia. This is a macroreentrant tachycardia that uses one limb of the bundle branches in an anterograde fashion and another limb in a retrograde fashion (167). It is important to recognize this arrhythmia mechanism because bundle branch reentrant tachycardia is easily treated by ablation of the right or left bundle branch (170,171). Unfortunately, many of these patients have concomitant ventricular tachycardias of myocardial origin that require treatment despite elimination of the bundle branch reentry.

The critical zone for propagation of ventricular tachycardia is located in the septum or left ventricular free wall in most patients with reentrant ventricular tachycardia and structural heart disease. The one notable exception is ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia. A clinical presentation of a patient with normal left ventricular size and function and a tachycardia with a left bundle branch block morphology might suggest the diagnosis of idiopathic ventricular tachycardia. Careful evaluation of these patients with high-quality echocardiography of the right ventricle or contrast cine right ventriculography is necessary to identify those rare cases of right ventricular dysplasia (172). Mapping and entrainment studies of ventricular tachycardia in these patients have demonstrated that the common locations of the reentrant circuit sites were around the tricuspid annulus and in the right ventricular outflow tract (173). Of interest, a cohort of patients undergoing repeated attempted ablation of ventricular tachycardia arising from the right ventricular outflow tract underwent magnetic resonance imaging scanning. Despite normal right ventricular size and function and the presumptive diagnosis of idiopathic focal ventricular tachycardia, 65% of these selected patients had evidence of fatty deposition, wall thinning, or dyskinesis (174).

Mapping and ablation of reentrant ventricular tachycardia is challenging, associated with a lower overall success rate than those of other tachycardias, and currently limited to a highly selected subset of patients. Identification of the optimal ablation site is time-consuming and is usually performed while the patient is in ongoing tachycardia. Therefore, only patients with slower, monomorphic, hemodynamically tolerated tachycardias are good ablation candidates. A nonfluoroscopic mapping system relies on point-to-point mapping, but has the unique feature of precise spatial localization of the catheter tip within a low-level magnetic field. This allows the operator to map without using fluoroscopy and builds an anatomic as well as an electrical map of the ventricle (175). Multielectrode basket catheters with up to 64 recording electrodes or multielectrode balloon catheters that create a high-resolution endocardial map by employing a mathematical technique called the *inverse solution* may allow for rapid localization of the tachycardia site of origin with acquisition of complete mapping data from only two or three beats of tachycardia, thereby allowing mapping in some patients with tachycardias that are poorly tolerated hemodynamically (176,177). The ultimate clinical utility of these and other advanced mapping tools remains to be demonstrated.

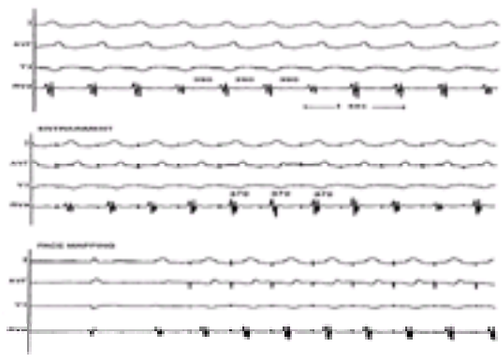
VIDEO

Video 73.2 An isopotential activation map during sustained monomorphic ventricular tachycardia is shown. Electrograms are recorded from a 64-pole multielectrode basket mapping catheter placed in the left ventricle and replayed in a global three-dimensional looping format at slow speed. Electrograms from seven bipoles from one recording spline are shown in the left window. The bottom window shows surface electrogram lead II. The right window shows that basket electrode in a right anterior oblique orientation. The base of the catheter emanates from the aortic valve. The earliest ventricular activation, representing the exit site from the slow conduction zone of the tachycardia, is observed on the high basal interventricular septum. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The critical slow or central conduction zones of reentrant ventricular tachycardias are often found in the midmyocardial or subepicardial planes (178). Conventional radiofrequency catheter ablation produces a relatively small and shallow lesion that may not be adequate to disrupt deeper arrhythmogenic substrates. New technologies, including the chilled tip (35) and the perfused tip (34) radiofrequency catheters and microwave (37), laser (179), or ultrasound (180) catheter ablation, may ultimately achieve reliable transmural ventricular lesions and improve ablation success rates.

The techniques routinely employed for mapping reentrant ventricular tachycardias include activation mapping and entrainment mapping. Activation mapping entails identification of sites with local electrograms that precede the onset of the surface QRS complex during ongoing tachycardia. These sites, which manifest presystolic activation, represent the exit sites of the reentrant rhythm from the central or slow conduction zone. Pace mapping from these locations often results in surface 12-lead electrocardiograms that closely match the ventricular tachycardia morphology. The anatomic substrate of this arrhythmia is complex, however, and a number of potential exit sites probably exist. Radiofrequency ablation at exit sites may change the tachycardia morphology, but unfortunately, it is rarely completely eliminated.

Entrainment mapping appears to be the best method for identification of the optimal site for ventricular tachycardia ablation. Pacing is performed at a rate that is slightly faster than the ongoing tachycardia from a mapping catheter positioned on or near the reentry circuit. In this case, each paced beat advances the tachycardia slightly by entering the excitable gap between the depolarizing wavefront of reentry and the tail of refractoriness of the previous beat, and the tachycardia becomes *entrained.* If pacing is performed directly on a critical part of the circuit that is isolated from conduction to the remainder of the heart with the exception of the tachycardia exit site, then the surface QRS complex during entrainment exactly matches that of the tachycardia. These sites of *concealed entrainment* correspond to the zone of slowed conduction and are optimal sites for attempted catheter ablation (eFig. 73.3.6). Stevenson et al. reported that sites of successful ventricular tachycardia termination by radiofrequency energy were more likely to fulfill criteria for concealed entrainment than unsuccessful sites. Optimal sites also had intervals measured from the last paced beat to the next tachycardia, which were nearly identical to the tachycardia cycle lengths when measured at the pacing site. This finding indicates that the pacing site is likely to be within the reentry circuit, rather than in a “blind alley.” Success of catheter ablation was also highest when radiofrequency ablation was performed near the middle of the slow conduction zone (defined by a stimulus to QRS interval during entrainment pacing of greater than 60 ms and less than 70% of the ventricular tachycardia cycle length) or when isolated diastolic potentials, continuous electrical activity, or both were recorded from the ablation catheter (181). Other criteria for successful ablation site selection include an exact QRS match between entrained and spontaneous ventricular tachycardia, and an activation time between the local electrogram to the onset of the surface QRS almost identical to the stimulus to QRS interval during spontaneous ventricular tachycardia (182,183).



***e*FIGURE 73.3.6** Surface electrocardiographic leads I, aVF, and V_1 and intracardiac electrograms from the right ventricular apex (RVA) in a patient with sustained ventricular tachycardia and a history of prior myocardial infarction. Ongoing tachycardia with a cycle length of 390 ms (*top panel*). Entrainment pacing at a cycle length of 370 ms during ongoing tachycardia (*middle panel*). Note that the QRS morphology during pacing is identical to that of ventricular tachycardia (concealed entrainment), and that there is a delay between the pacing artifact and the QRS onset, indicating that the pacing site is within the zone of slow conduction in the reentrant circuit. Pace mapping during sinus rhythm from the same site (*bottom panel*). The similar QRS morphology to that of ventricular tachycardia suggests that this site is near the exit point of the slow conduction zone, thereby resulting in a similar spread of ventricular activation during pace mapping as seen during tachycardia.

The clinical series of radiofrequency catheter ablation of reentrant ventricular tachycardia are small and comprise a highly selected subset of patients. Because patients must be able to tolerate their tachycardia hemodynamically to allow for mapping, patients with rapid, life-threatening tachycardias are not included in these series. The mean cycle lengths of the tachycardias in the reported clinical series of ablations were greater than 350 ms (less than 171 beats/min), and the patients undergoing ablative therapy made up only 10% to 20% of the overall ventricular tachycardia population. The results of the largest clinical series are summarized in Table 73.7. The reported success rates on the suppression of “clinical” tachycardias with radiofrequency catheter ablation range from 64% to 81%. Patients frequently have “nonclinical” tachycardias, defined as sustained monomorphic ventricular tachycardias with morphologies that have never been observed to occur spontaneously in the clinical setting but that can be induced by programmed ventricular stimulation. In these cases, adjunctive therapy with an implantable defibrillator is usually warranted. An expanding indication for ventricular tachycardia ablation is for patients in whom an implantable defibrillator has been previously implanted, but who are now suffering frequent or incessant runs of slower ventricular tachycardia, resulting in multiple device discharges. Radiofrequency catheter ablation can successfully palliate a significant number of these patients (187,190).

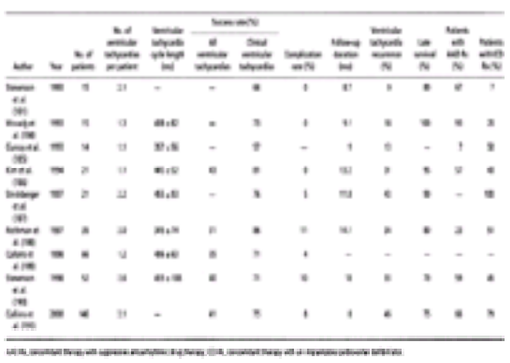


TABLE 73.7 CLINICAL RESULTS OF RADIOFREQUENCY CATHETER ABLATION OF PATIENTS WITH VENTRICULAR TACHYCARDIA IN PATIENTS WITH STRUCTURAL HEART DISEASE

An uncommon but important subset of patients with ventricular tachycardia are those with bundle branch reentrant tachycardia. This is a macroreentrant rhythm most commonly found in patients with dilated cardiomyopathy and conduction system disease. The reentrant wavefront uses one bundle branch in an anterograde fashion and one bundle branch for retrograde conduction. It is a rapid, potentially life-threatening rhythm found in as many as 5% of patients with ventricular tachycardia (192) and is readily treatable with catheter ablation. Bundle branch reentrant tachycardia may be identified by the presence of a bundle of His deflection that precedes each ventricular depolarization and shows identical beat-to-beat variability as the subsequent ventricular beats. In typical cases in which the right bundle branch is one limb of the circuit, the ablation catheter is positioned across the tricuspid valve beyond the common bundle of His, and the right bundle branch is selectively ablated. Using this approach, bundle branch reentrant tachycardia was successfully ablated in 42 of 42 patients in one clinical series (193). However, the presence of other concomitant ventricular tachycardias and underlying myopathic disease portends a poor prognosis even with successful ablation. In the previously mentioned studies, 23 of 42 patients died during the 16-month follow-up, and 13 of these died suddenly.

COMPLICATIONS OF CATHETER ABLATION

The field of radiofrequency catheter ablation has been met with tremendous enthusiasm by physicians and patients alike and had tremendous growth in its first decade in both numbers of procedures performed and in indications for the procedure (194). A natural consequence of this phenomenon is that the number of interventional electrophysiologists has also dramatically increased. The time and intensity of training required to become proficient in this field are considerable. It is necessary that the ablating physician have a detailed understanding of electrophysiologic mechanisms of arrhythmias, an excellent three-dimensional conceptualization of the anatomy of the cardiac chambers in which the ablation catheters are manipulated, and exceptional technical skill in catheter manipulation. For these reasons, success rates and complication rates of catheter ablation are first and foremost related to the skill and experience of the primary operator (195,196).

The overall reported complication rate from radiofrequency catheter ablation (excluding risks associated with outmoded techniques or tools) is low, ranging from 1.8% to 4.0% (197). The risk of major, irreversible complications is approximately 0.5% to 1.0% and includes events such as complete heart block, myocardial infarction, valvular injury, irreversible stroke, and death. The Multicentre European Radiofrequency Survey documented complications from a total of 4,398 catheter ablation procedures from 68 European institutions between 1987 and 1992. In patients undergoing catheter ablation for treatment of supraventricular tachycardia, the potential complications and their rates were complete heart block (fast pathway ablations excluded), 0.66%; significant vascular injury, 0.63%; pericardial tamponade, 0.60%; clinically significant pericardial effusion, 0.53%; pulmonary embolism, 0.13%; systemic embolism, 0.44%; irreversible stroke, 0.06%; and death, 0.06%. The complications among the 320 patients undergoing catheter ablation for ventricular tachycardia showed similar rates (198). Because this study was characterized by data from a large number of centers near the beginning of their experience with this procedure, the complication rates may be lower now than those initially reported. The data, however, depended on voluntary reporting, and 21% of the institutions solicited for participation did not report data, so there was a possibility of underreporting of events.

Another large study reported data from 1,400 patients who underwent radiofrequency catheter ablation at a single institution. In this large experience, the total prevalence of complications was 3.1%. There were no deaths. The complications reported included systemic embolism, 0.21%; stroke, 0.14%; valve trauma, 0.07%; tamponade, 0.21%; vascular injury, 0.62%; and complete heart block, 0.05%. The risk of complications was significantly higher in patients undergoing radiofrequency catheter ablation than in those undergoing routine diagnostic electrophysiologic study (3.1% vs. 1.1%). Predictors of complicated procedures by multiple logistical analysis included older age and the presence of comorbid systemic disease (199). The overall low risk of complications in this study may be attributable, in part, to the fact that it was performed in a high-volume center with experienced operators.

The final risk assumed by the patient and laboratory staff during catheter ablation procedures is the radiation exposure. Unlike diagnostic procedures in which the total fluoroscopy time is usually under 10 minutes, exposures of greater than 30 minutes occur frequently with ablation procedures. Manipulation of catheters within the cardiac chambers to difficult ablation sites often requires extensive fluoroscopic guidance, and maximum fluoroscopic exposure to the patient and operator can exceed 2 hours. Calkins et al. examined the degree of fluoroscopic exposure during radiofrequency catheter ablation in 31 unselected patients and found that median radiation doses to the thyroid, the ninth vertebral body, and to the iliac crest were 0.46, 7.26, and 2.43 rem, respectively. This translated into a lifetime risk of radiation-induced fatal malignancy of 0.1% for every hour of fluoroscopic exposure, and a risk of genetic defects of 20 per 1 million births (200). New fluoroscopy units that use pulsed energy delivery and improved ablation tools that decrease the time of ablation site access have significantly decreased radiation exposure in recent years, but it still

remains a point of significant concern.

CONTROVERSIES AND PERSONAL PERSPECTIVES

In the last 15 years, radiofrequency catheter ablation has become a dominant modality in the treatment of a number of symptomatic arrhythmias. The popularity of catheter ablation is due in large part to the extremely low complication rate observed by practitioners. The major factor that has limited the number and severity of complications is that the volume of injury produced by radiofrequency catheter ablation is small. Thus, small lesions are associated with minimal endocardial disruption, a low prevalence of significant thrombus formation, a low rate of transmural injury with left ventricular lesions (which eliminates the risk of free wall rupture and significant ablation-induced ventricular dysfunction), and rare prevalence of coronary arterial injury, even though most accessory pathway ablations are performed in close proximity to the epicardial coronary arteries. However, with small lesions come higher skill requirements for target selection. In addition, some targets are inaccessible because of their location deep within the myocardium away from the endocardial plane. For these reasons, investigators have been working to increase dramatically the size of ablative lesions by using novel catheter designs and new energy sources. As the depth and volume of myocardial injury increase with catheter ablation, it is likely that the complications will increase as well. The lingering effects of this injury in young people may not be realized for decades when they present with premature coronary artery disease. Intramural superheating and sudden “popping” result in crater-like lesions with a small but real risk of free wall perforation.

The popularity of catheter ablation therapy may be attributed to the observation that it has been curative in the majority of cases, and the procedure-related morbidity and mortality have been extremely low. Thus, the indications for catheter ablation have continued to broaden. In fact, the majority of patients presenting for catheter ablation of paroxysmal supraventricular tachycardia at the University of Virginia has never failed drug therapy but simply desires a drug-free lifestyle. Although it is often an appropriate decision to subject an otherwise healthy patient to the risk of an invasive procedure if one can eliminate the requirement of lifelong drug therapy, not all patients with arrhythmias amenable to catheter ablation should undergo this therapy. It is still appropriate to pursue vagal maneuvers and medical therapy with AV nodal blocking drugs before performing interventional therapy. Although a supraventricular tachycardia may cause significant symptoms, it is not a life-threatening arrhythmia.

Most arrhythmia experts will agree that symptomatic patients with the Wolff-Parkinson-White syndrome should undergo diagnostic electrophysiologic testing to determine if they have an increased risk of fatal arrhythmias. Because the main morbidity of catheter ablation is caused by the placement of multiple diagnostic catheters in the heart, it is common practice to proceed with ablation of the accessory pathway even if it is determined to be low risk. The approach toward asymptomatic patients with evidence of ventricular preexcitation on the electrocardiogram is somewhat variable. The natural history of these patients suggests that no evaluation or therapy is needed until and unless they develop symptoms. However, a potential for dangerous arrhythmias may exist in pediatric patients who have yet to present with clinical arrhythmias. Thus, there is some rationale for studying and ablating pediatric Wolff-Parkinson-White patients.

The field of curative atrial fibrillation ablation is advancing rapidly. The outcomes of catheter ablation for atrial fibrillation with a focal mechanism are good enough that many practitioners are offering this as a clinically indicated procedure. Presently, there is significant variability among laboratories as to the techniques employed and the patient selection criteria. Thus, determining the best approach to employ has been difficult. It is clear that this procedure is becoming more anatomically guided. It is hoped that with development of the tools for this procedure, procedure times will decrease and success rates will increase. Presently, patients with frequent bursts of self-terminating atrial fibrillation and atrial tachycardia and normal hearts should be strongly considered for ablative therapy. Patients with structural heart disease and longer, less frequent atrial fibrillation episodes should probably only be considered for curative catheter ablation as a final alternative to AV junctional ablation and pacemaker implantation. Linear ablation is presently investigational only and should not be considered as an alternative to drug therapy. Highly motivated patients who have failed multiple drug trials are appropriate candidates for this procedure, but it must be acknowledged that the risks of the procedure may ultimately outweigh its benefits.

Catheter ablation for the treatment of ventricular tachycardia in patients with structural heart disease has not emerged as a dominant modality. In fact, most practitioners employ catheter ablation as a palliative therapy only, because almost all patients with ventricular tachycardia and ischemic cardiomyopathy have multiple tachycardia morphologies. Therefore, although one can often modify or eliminate the clinical tachycardia, a number of different (usually faster) tachycardias with morphologies not previously seen can be induced with programmed ventricular stimulation. Each investigator and practitioner may choose to define clinically significant tachycardia and procedure success differently. Therefore, it is not clear when, if ever, it is appropriate to leave a patient without any antiarrhythmic therapy after a successful catheter ablation when one or more nonclinical tachycardias could still be induced. In these cases, patients at the University of Virginia almost uniformly receive an implantable cardioverter defibrillator if one is not already in place. Similarly, catheter ablation is rarely offered as first-line therapy for patients with reentrant ventricular tachycardia and structural heart disease.

Advanced mapping systems and more extensive ablation techniques may improve ablation results over time for a variety of arrhythmias. Clearly, many of the mapping systems can recreate the anatomic relationships and create improved electroanatomic correlations. Some systems provide global mapping information on individual beats, whereas others require point-to-point data acquisition from multiple points. One feature is common among all mapping systems: Procedure cost is increased. In addition, some systems require placement of additional large-diameter mapping catheters into the chamber being mapped, increasing the potential for catheter-related complications. The risk-benefit relationship for advanced mapping systems and the impact of the added procedural cost have not been fully explored, but their use is probably of benefit in select cases.

The number of catheter ablation procedures increased exponentially in the years for which survey data are available. This has been associated with a dramatic growth in the number of practitioners who perform catheter ablation procedures. Curative catheter ablation is cost-effective, and expansion of case numbers has not been held in check by financial disincentives, because reimbursement by third-party payers has not been restricted. The proliferation of catheter ablation procedures may be associated with some undesirable phenomena, including inappropriate self-referral for invasive catheter ablation procedures and performance of catheter ablation procedures by inadequately trained and inexperienced operators. The number of catheter ablation procedures required for adequate training and maintenance of skills has not been determined, but it is proposed that trainees have experience with at least 75 cases as primary operators, and practitioners maintain a volume of at least 50 cases per year in order to be certified to perform catheter ablation procedures. These numerical guidelines will undoubtedly trigger outraged cries of “restraint of trade,” but ultimately the patients and the field of interventional electrophysiology will benefit. The most important criteria for selecting a physician and laboratory to whom a patient should be referred are the chronologic and numerical experience of the primary operator and laboratory staff in catheter ablation procedures. Operators with limited experience may achieve excellent outcomes through careful patient selection, but may be inadequately prepared to diagnose and treat unusual arrhythmia variants.

Catheter ablation of supraventricular and ventricular arrhythmias has advanced rapidly and is now a widely accepted modality of therapy for symptomatic arrhythmias, along with drugs and devices. The tools for ablation are continuing to improve, thereby increasing procedure efficacy and decreasing the risk of complications. This has resulted and will continue to result in expanding indications for ablative therapy. Although the opportunity to cure a patient suffering from an arrhythmia is extremely attractive, one must be vigilant to present all aspects of the risks and benefits to the patient. It is inappropriate to treat an electrocardiographic abnormality in an asymptomatic patient with a potentially morbid intervention. Similarly, if easy, well-tolerated medical therapy is effective in suppressing an arrhythmia, one should not be compelled to send the patient for catheter ablation. More intensive catheter ablative therapies such as curative atrial fibrillation ablation have lower success rates, higher complication rates, and unclear long-term benefits. Patients need to be well informed of these issues before undergoing these interventions. Ultimately, if the patient understands and is willing to accept the small but real risks associated with the procedure in order to achieve improved arrhythmia control or arrhythmia cure, then catheter ablation should be pursued.

THE FUTURE

Curative catheter ablation of common forms of supraventricular tachycardia has exceeded most expectations with regard to both safety and efficacy. Although catheter designs and ablation techniques may evolve, it is likely that the overall outcome statistics will not change significantly. The main frontiers remaining in catheter ablation are curative therapy for atrial fibrillation and reentrant ventricular tachycardia. A wide variety of ablation tools are being developed for atrial fibrillation ablation. More important, selective linear atrial ablation will help us understand the pathophysiology of this complex arrhythmia and direct us to the optimal ablation targets to achieve arrhythmia cure. Reentrant ventricular tachycardia is often hemodynamically unstable, precluding prolonged periods of mapping. New mapping tools will allow for rapid ablation site selection. Because ablation targets are frequently midmyocardial or subepicardial, larger and deeper lesions than can be created with conventional radiofrequency energy ablation will be required for procedure success. Future innovative catheter designs and new ablation energy sources may solve this present limitation.

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PACEMAKERS

DAVID L. HAYES

"Indicates text or graphics that appear only in the electronic versions of this text."

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Venous Thrombosis
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Lead Insulation Defect
Exit Block
Lead Dislodgment
Loose Set-Screw Connection
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Extracardiac Stimulation
Erosion
Pacemaker System Infection
Retained Lead Fragments
Lead Extraction
Pacemaker Allergy
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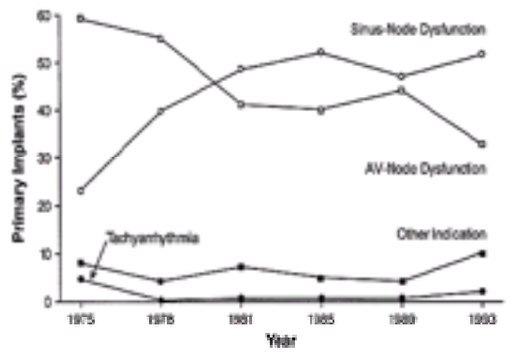
OVERVIEW

When pacemaker implantation is being considered, the clinician should be able to document that implantation is justified and the pacemaker will benefit the patient clinically. This is valuable for long-term care of the patient and subsequent pacing needs as well as for purposes of reimbursement.

The selection of the pacing mode should be based on the immediate needs of the patient and the potential long-term benefit of specific pacing modes. When determining the most appropriate pacing mode for a patient, the clinician should consider the patient's activity level, need for atrioventricular (AV) synchrony, need for chronotropic support, and associated medical conditions. When choosing a pacemaker, remember that rate-adaptive pacing technology allows, for most patients, restoration of a near normal chronotropic response.

Potential interference from outside electrical sources is always of concern to both the patient with a pacemaker and referring physicians. The most common sources of electromagnetic interference for permanent pacemakers are found in a hospital environment (e.g., electrocautery, cardioversion, and magnetic resonance imaging).

The utilization and sophistication of permanent pacemakers have increased steadily since the first pacemaker implantation in 1958 (eFig. 74.0.1) (1,2). Initially, pacemakers were indicated only for the prevention of Stokes-Adams attacks, but the indications have broadened as the technology has advanced. According to the estimates of four manufacturers, there were 152,909 primary pacemaker implantations (571 per million population) in 1997 and 37,946 pacemaker pulse generator replacements (3). Despite the continued sophistication and, at times, complexities of permanent pacemakers, they have become such a mainstay of therapy that it is imperative for clinical cardiologists to have a working knowledge of these devices.



***e*FIGURE 74.0.1** Trends in pacemaker indications in the United States, 1975 to 1993. AV, atrioventricular. (From Bernstein AD, Parsonnet V. Survey of cardiac pacing and defibrillation in the United States in 1993. *Am J Cardiol* 1996;78:187–196, with permission of Excerpta Medica.)

GLOSSARY

AAI/AAIR: Single-chamber atrial pacing modes, with *R* noting the capability of rate adaptation.

Blanking period: Temporary disabling of pacemaker-sensing amplifiers following the delivery of an output pulse. This prevents inappropriate sensing of residual energy from the pacemaker output pulse and, in dual-chamber pacemakers, prevents sensing of pacemaker output pulses or intrinsic events in the chamber other than that in which the event occurs.

DDD/DDDR: Dual-chamber pacing modes, with *R* noting the capability of rate adaptation.

Electromagnetic interference: Any strong source of electromagnetic interference potentially could interfere with the pacemaker and alter its function.

Functional pacing abnormalities (e.g., functional undersensing or functional failure to capture): Failure to sense or capture that is appropriate because of imposed pacemaker refractory periods or myocardial refractoriness due to a previous intrinsic atrial or ventricular event.

Mode switch: Capability of a dual-chamber pacemaker to switch automatically from an atrial-tracking (P synchronous) mode to a non–atrial-tracking mode in the presence of an atrial rhythm that the pacemaker determines to be pathologic. When the atrial rhythm meets the criteria for a physiologic rhythm, the mode switches back to an atrial-tracking mode.

Postventricular atrial refractory period: The period during which the atrial-sensing circuit is refractory following a sensed ventricular event. The purpose of this is to avoid sensing retrograde atrial activity that could initiate an endless-loop tachycardia.

Total atrial refractory period: The period during which the atrial channel of a dual-chamber or VDD pacemaker ignores intrinsic atrial activity or other activity sensed on the atrial-sensing circuit.

Ventricular safety pacing: Delivery of a ventricular output pulse, following atrial pacing, if a signal is sensed by the ventricular channel during the early portion of the AV interval (AVI). This is used to ensure that ventricular depolarization occurs if the sensed event was something other than an intrinsic ventricular depolarization.

VVI/VVIR: Single-chamber ventricular pacing modes, with *R* noting the capability of rate adaptation.

HISTORICAL PERSPECTIVE

Since the first totally implantable pacing system was used by Senning in 1958 (4), the evolution of pacemaker technology has been rapid. Senning's epicardial pacing system was followed by the first transvenous system by Furman and Schwedel (5), also in 1958. Sophistication of sensing circuitry led to the introduction of single-chamber demand pacing systems in 1963 (6). Although atrial-synchronous systems and dual-chamber systems were described in the 1950s (7,8), these devices were not used clinically for many years. The 1970s were significant for the introduction of lithium batteries and programmability (9). Milestones of the 1980s included greater acceptance of dual-chamber pacing systems and the introduction of rate-adaptive pacing systems. The 1990s witnessed continued sophistication of sensor technology as well as increasing automaticity of many programmable features. Also, newer applications for pacing, including pacing for hypertrophic and dilated cardiomyopathy and for the prevention of atrial fibrillation, began in the 1990s and continues.

PACEMAKER NOMENCLATURE

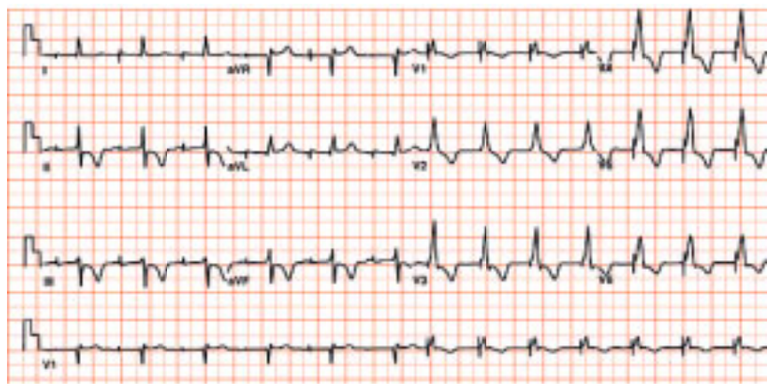
A three-letter code describing the basic function of the various pacing systems was first proposed in 1974 by a combined task force from the American College of Cardiology and the American Heart Association (ACC/AHA) (10). Since then, the responsibility for periodically updating the code has been assumed by the North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group. The code is designated by the NBG code for pacing nomenclature (11) (Table 74.1). The code has five positions, but the fifth position is rarely used. It is a generic code and does not describe specific or unique functional characteristics of each device.

Position[a]	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Programmability, rate modulation	Antitachyarrhythmia function(s)
	O = None A = Atrium V = Ventricle D = Dual (A + V) S = Single (A or V)	O = None A = Atrium V = Ventricle D = Dual (A + V) S = Single (A or V)	O = None T = Triggered I = Inhibited D = Dual (T + I)	O = None P = Simple programmable M = Multiprogrammable C = Communicating R = Rate modulation	O = None P = Pacing (antitachyarrhythmia) S = Shock D = Dual (P + S)
Manufacturer's designation only					

[a]Positions I through III are used exclusively for antibradyarrhythmia function.
From Bernstein AD, Camm AJ, Fletcher RD, et al. The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive-rate pacing and antitachyarrhythmia devices. Pacing Clin Electrophysiol 1987;10:794–799, with permission of Futura.

TABLE 74.1 NBG CODE

The first position reflects the chamber or chambers in which stimulation occurs: A, atrium; V, ventricle; and D, dual chamber; or both A and V.



A 72-year-old patient with atrial pacing with transition to ventricular pacing.

The second position refers to the chamber or chambers in which sensing occurs. The letters are the same as those for the first position. (Manufacturers also use *S* in both the first and second positions to indicate that the device is capable of pacing only a single cardiac chamber.)

A 67-year-old male patient with atrial fibrillation and intermittent demand ventricular pacing.

The third position refers to the mode of sensing, or how the pacemaker responds to a sensed event. An *I* indicates that a sensed event inhibits the output pulse and causes the pacemaker to recycle for one or more timing cycles. *T* means that an output pulse is triggered in response to a sensed event. *D* means that both T and I responses may occur. This designation is restricted to dual-chamber systems. An event sensed in the atrium inhibits the atrial output but triggers a ventricular output. Unlike a single-chamber–triggered mode (VVT or AAT), in which an output pulse is triggered immediately on sensing, there is a delay between the sensed atrial event and the triggered ventricular output to mimic the normal PR interval. If a native ventricular signal or R wave is sensed, it inhibits the ventricular output and possibly even the atrial output, depending on where sensing occurs.

The fourth position of the code reflects both programmability and rate modulation. An *R* in the fourth position indicates that the pacemaker incorporates a sensor to control the rate independently of intrinsic cardiac activity. From a practical standpoint, R is the only indicator commonly used in the fourth position. Other indicators are described in Table 74.1.

The fifth position is restricted to antitachycardia functions and is rarely used.

INDICATIONS FOR CARDIAC PACING

According to the criteria established by a joint committee of the ACC/AHA, the indications for pacing are divided into three categories: generally indicated, may be indicated, and not indicated (12,13). The clinician prescribing permanent pacing systems should be aware of the published indications and the controversies regarding the indications. Although some indications for permanent pacing are relatively certain or unambiguous, others require considerable expertise and judgment.

The clinical need for pacing and appropriate objective data, such as electrocardiographic tracings, must be documented clearly in the patient's medical record to ensure reimbursement by Medicare or third-party payers.

Indications are considered here for the categories of acquired AV block, congenital AV block, chronic bifascicular and trifascicular block, sinus node dysfunction, and neurocardiogenic syndromes. Potential hemodynamic indications for permanent pacing are discussed separately.

Acquired Atrioventricular Block

Traditionally, AV block is classified into first-, second-, and third-degree (or complete) heart block. Alternatively, it can be defined anatomically as supra-, intra-, or infra-Hisian. If the QRS is wide, there is a greater probability that the conduction disturbance is infra-Hisian. Most commonly, acquired AV block is idiopathic and related to aging, but it has many potential causes (Table 74.2). The indications for permanent pacing in acquired AV block are listed in Table 74.3.

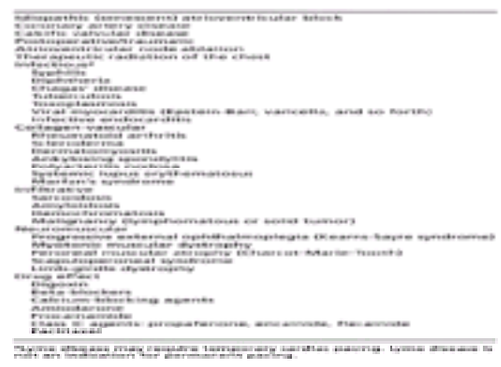
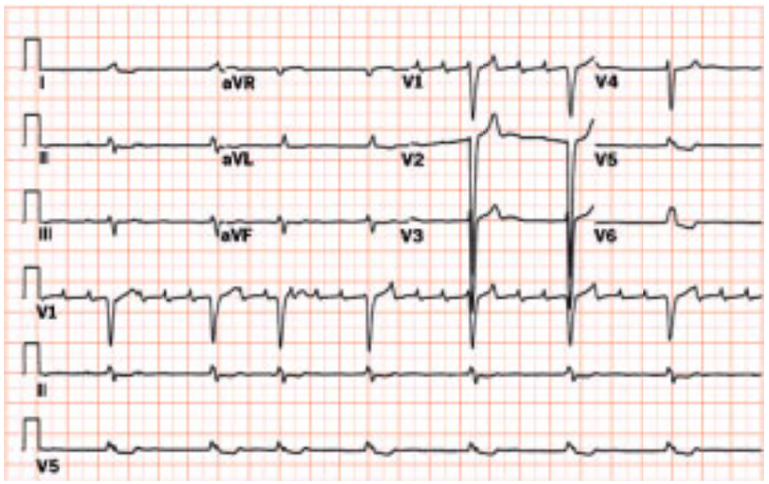


TABLE 74.2 ACQUIRED ATRIOVENTRICULAR BLOCK: DIFFERENTIAL DIAGNOSIS

Degree	Pacemaker necessary	Pacemaker probably necessary	Pacemaker not necessary
Third	Symptomatic congenital CHB		
	Acquired symptomatic CHB		
	Atrial fibrillation with CHB		
	Acquired asymptomatic CHB		
Second	Symptomatic type I	Asymptomatic type II	Asymptomatic type I at supra-His
	Symptomatic type II	Asymptomatic type I at intra-His or infra-His levels*	(atrioventricular nodal) level
First			Asymptomatic or symptomatic*

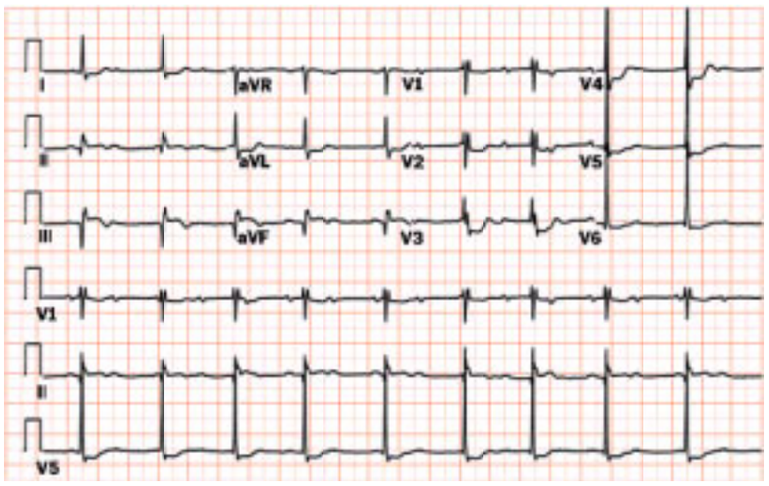
CHB, complete heart block.
*Data from Campbell RW. Chronic Wenckebach type I second degree atrioventricular block. Has its importance been underestimated? [Editorial]. Br Heart J 1980;53:585-588.

TABLE 74.3 INDICATIONS IN ATRIOVENTRICULAR BLOCK

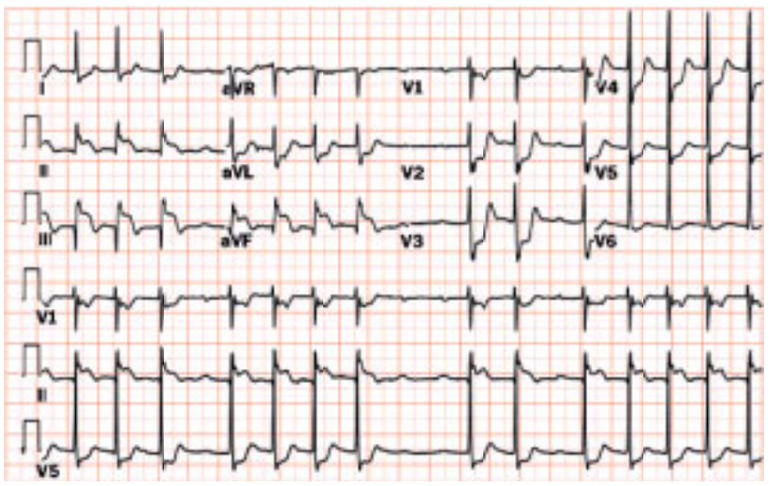


High-grade atrioventricular block. Note marked discrepancy between atrial and ventricular heart rates.

Indications for permanent pacing for AV block that occurs with myocardial infarction are more controversial. Generally, a pacemaker is considered to be indicated if complete AV block, Mobitz II block, or bilateral or alternating bundle branch block persists longer than 72 hours after the acute event. Some clinicians would consider new and persistent bifascicular block an indication for pacing, and others would consider pacing for a new left anterior or left posterior hemiblock alone.



Complicated acute inferior myocardial infarction. Note inferior ST-segment elevation as well as atrioventricular dissociation secondary to complete heart block.



Acute inferior myocardial infarction with Mobitz II atrioventricular block. Note ST-segment elevation in the inferior leads as well as intermittently dropped QRS complexes.

An 83-year-old patient with complete heart block, junctional escape rhythm, left anterior hemiblock, and complete right bundle branch block.

Congenital Complete Heart Block

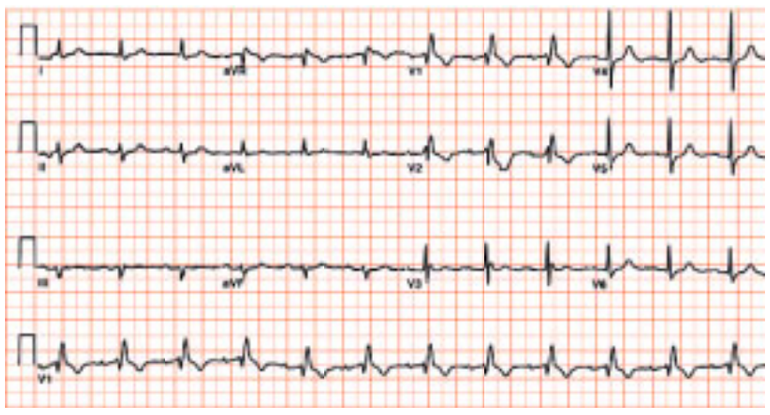
Although some controversy remains about when patients with congenital complete heart block should have pacing, the tendency now is to provide pacing to these patients earlier.

In pediatric patients, pacemaker implantation is recommended for the following indications: congestive heart failure, average heart rate less than 50 beats/min in an awake infant, history of syncope or presyncope, significant ventricular ectopy, or exercise intolerance (14). Prophylactic pacemaker implantation is generally considered appropriate in adults, even if asymptomatic, because of a high incidence of unpredictable syncope with significant mortality from initial attacks, a gradual decrease in heart rate, and a high incidence of acquired mitral insufficiency (15). This author recommends permanent pacing in all adults with congenital complete heart block.

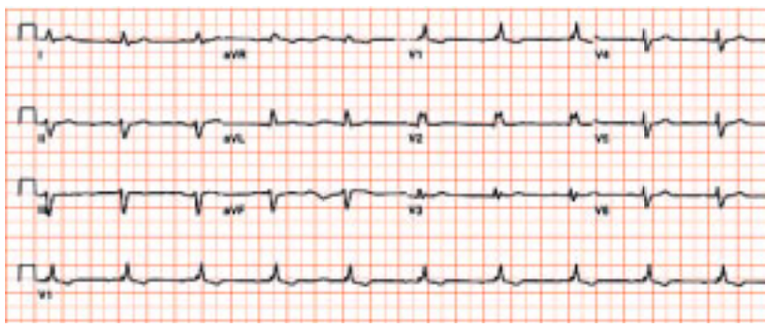
Chronic Bifascicular or Trifascicular Block

If the bifascicular or trifascicular block is associated with symptoms or transient complete heart block, pacing is clearly indicated. If the bifascicular or trifascicular block is associated with high-grade AV block without symptoms, pacing is also indicated. An important class II ACC/AHA indication is the probable necessity for pacing in a patient with bifascicular or trifascicular block and syncope that cannot be attributed to any other cause. If fascicular block is noted in an asymptomatic patient, pacing is not indicated (16).

Trifascicular block. Note right bundle branch block, left anterior hemiblock, and associated first-degree atrioventricular block.



A 93-year-old male patient with trifascicular block.



A 75-year-old male patient with trifascicular block.

Sinus Node Dysfunction

Tachycardia-bradycardia syndrome, sick sinus syndrome, symptomatic sinus bradycardia, sinus arrest and sinus pauses, and chronotropic incompetence are all variants of sinus node dysfunction and the terms are often used synonymously. The definition of bradycardia varies, but it generally is accepted to be rates less than 40 beats/min during waking hours. There is disagreement about the absolute cycle length at which treatment should be required. Although every patient needs to be considered individually, most clinicians would agree that sinus pauses of 3 seconds during waking hours should be considered abnormal and may warrant pacing. Pauses that occur during sleep are more difficult to categorize. Because of vagal influences, many healthy persons may have pauses significantly longer than 3 seconds during sleep and, in the absence of symptoms or rhythm disturbances during waking hours, should not require treatment. Permanent pacing should be considered for any patient who has symptomatic bradyarrhythmias when the cause of the bradyarrhythmia is not reversible (Table 74.4).

Pacemaker necessary	Pacemaker probably necessary	Pacemaker not necessary
Symptomatic bradycardia Symptomatic sinus bradycardia due to long-term drug therapy of a type and dose for which there is no accepted alternative	Symptomatic patients with sinus node dysfunction with documented rates of <40 bpm/min without a clear-cut association between significant symptoms and the bradycardia	Asymptomatic sinus node dysfunction

TABLE 74.4 INDICATIONS FOR PERMANENT PACING IN SINUS NODE DYSFUNCTION

Permanent pacing for patients with sinus node dysfunction after myocardial infarction is reserved for those who have symptoms. If drug therapy results in symptomatic bradycardia, criteria for permanent pacing should follow the guidelines given for sinus node dysfunction in Table 74.4.

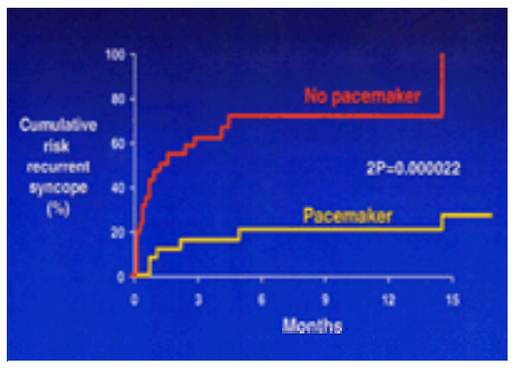
Neurocardiogenic Syncope

Permanent pacing may be indicated for some of the several types of neurally mediated syncope. Understanding the physiology involved is crucial to understanding the clinical manifestations (17,18 and 19). The carotid sinus reflex is the physiologic response to pressure exerted on the carotid sinus. Stimulation activates the baroreceptors within the wall of the carotid sinus. Vagal efferents then result in cardiac slowing. Although this reflex is physiologic, some persons have an exaggerated or even pathologic response. The reflex has two components: a cardioinhibitory response and a vasodepressor response. A cardioinhibitory response results from increased parasympathetic tone and may be manifested by any or all of the following conditions: sinus bradycardia, PR prolongation, and advanced AV block. The vasodepressor response is due to decreased sympathetic activity and secondary hypotension. Although a pure cardioinhibitory or pure vasodepressor response may occur, a mixed response is most common.

Tilt testing can provide the physiologic environment to reproduce malignant vasovagal syncope (20). With head-up tilt, susceptible patients have decreased venous return and a subsequent decrease in left ventricular filling, which may result in efferent vagal discharge. Stimulation of baroreceptors and adrenergic discharge may also result in efferent vagal discharge. Vasodilatation and hypotension as well as cardiac slowing may result from efferent vagal discharge. It is important to document whether the predominant cause of symptoms is cardioinhibitory or vasodepressor in origin, because therapy differs. Tilt-table testing is often helpful in determining the predominant cause.

This abnormality is difficult to categorize by the ACC/AHA classification because of the controversy about treatment. Historically, some studies have strongly supported initial treatment with beta-blockers (6) and others have advocated permanent pacing (21). In the more recent randomized North American Vasovagal Pacemaker Study (22), 46 patients with recurrent syncope and positive findings on the tilt test were randomly assigned to either dual-chamber pacemaker with a special feature known as *rate drop* or no pacemaker therapy. (The rate drop algorithm allows the pacemaker to pace at a faster rate if bradycardia suddenly occurs.) Although Vasovagal

Pacemaker Study 1 was stopped prematurely because of the benefit observed with pacemaker therapy, it showed that only 17% of patients with pacing had recurrent syncope compared with 59% of those without pacing (i.e., an 85% risk reduction) (eFig. 74.0.2). Another study randomly assigned 60 patients with carotid sinus hypersensitivity to pacing or no pacing (23). At a mean follow-up of 36 months, syncope recurred in 9% of the pacing group compared with 57% of the group without pacing. Although pacing may not be required in the majority of patients with neurally mediated syncope, a specific subset of patients with drug-resistant syncope and a predominant bradycardic component definitely benefit from permanent dual-chamber pacing (24,25).



***e*FIGURE 74.0.2** In the North American Vasovagal Pacemaker Study-I, there was an 85% risk reduction of syncope in the group of patients who received a pacemaker. [From Connolly SJ, Sheldon R, Roberts RS, et al. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol* 1999;33:16–20, with permission of the American College of Cardiology.]

Additional trials, Vasovagal Pacemaker Study 2, Vasovagal Syncope International Study (26), and SAFE PACE2 (Syncope and Falls in the Elderly Pacing and Carotid Sinus Evaluation), are under way to assess pacing therapy in both neurocardiogenic syncope and carotid sinus hypersensitivity.

NONBRADYARRHYTHMIC INDICATIONS FOR PACING

Hypertrophic Obstructive Cardiomyopathy

Dual-chamber pacing has been proposed as a therapeutic modality for patients with severe, symptomatic hypertrophic obstructive cardiomyopathy (27,28,29 and 30). Several investigators have reported a significant decrease in the left ventricular outflow tract gradient and symptomatic improvement in patients with hypertrophic obstructive cardiomyopathy after implantation of a dual-chamber pacemaker (Fig. 74.1).

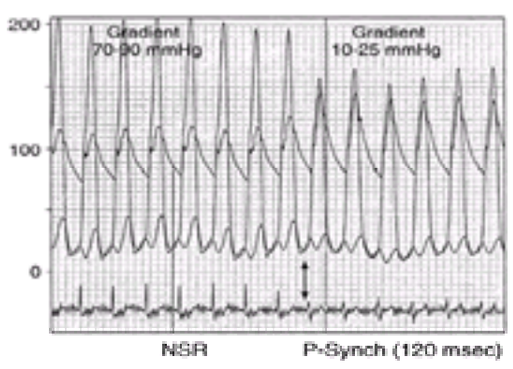
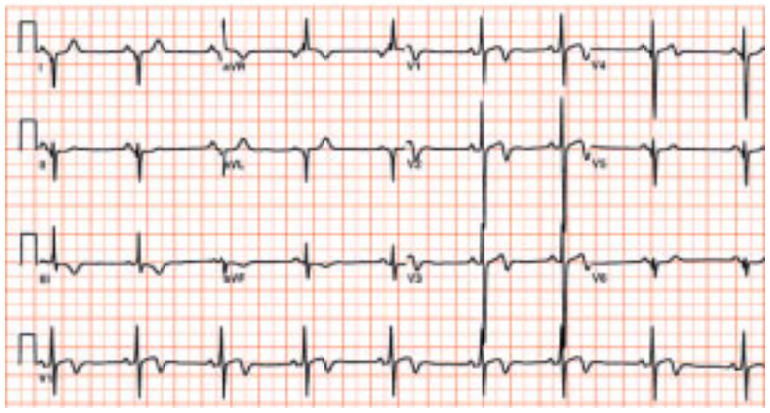


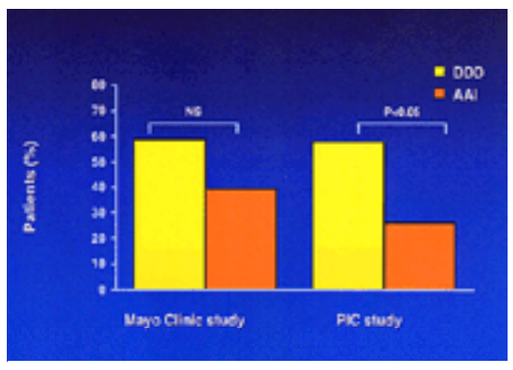
FIGURE 74.1 Hemodynamic tracing demonstrating left ventricular outflow gradient reduction during a temporary pacing study. During normal sinus rhythm (NSR), the patient exhibits marked left ventricular outflow obstruction, with a gradient of 70 to 90 mm Hg. With initiation of P-synchronous pacing at an AV interval of 120 ms, the gradient is decreased to 10 to 25 mm Hg. (From Symanski JD, Nishimura RA. The use of pacemakers in the treatment of cardiomyopathies. *Curr Probl Cardiol* 1996;21:385–443, with permission of Mosby.)



A 28-year-old Caucasian male patient with hypertrophic obstructive cardiomyopathy.

It has been recognized that AV timing is critical if optimal hemodynamic improvement is to be achieved (31). Although some patients with hypertrophic obstructive cardiomyopathy have optimal improvement with a very short AVI, others may have hemodynamic deterioration if the AVI is too short. Also, it has been recognized that depolarization of the ventricle must occur via the pacemaker. Some have advocated AV nodal ablation to ensure paced ventricular depolarization if rapid intrinsic AV nodal conduction prevents total ventricular depolarization via the pacing stimulus (32).

In the Pacing in Cardiomyopathy study, a multicenter, randomized, cross-over study, dual-chamber pacing resulted in a 50% decrease of the left ventricular outflow tract gradient, a 21% increase in exercise duration, and improvement in New York Heart Association (NYHA) functional class compared with baseline status (33). When clinical variables, including chest pain, dyspnea, and subjective health status, were compared between DDD and backup AAI pacing, the difference was not significant, again suggesting an important placebo effect (eFig. 74.1.1).



***e*FIGURE 74.1.1** Two trials have demonstrated significant placebo effect from pacemaker placement in patients with hypertrophic cardiomyopathy. The yellow bars depict symptom improvement when paced in the DDD pacing mode, and the orange bars depict symptom improvement when paced in a backup AAI mode (i.e., no

effective pacing). Despite the lack of pacing in the AAI pacing mode, a significant subset of the study population in both studies reported symptomatic improvement. NS, not significant. (From Sorajja P, Elliott PM, McKenna WJ. Pacing in hypertrophic cardiomyopathy. *Cardiol Clin* 2000;18:67–79, with permission of WB Saunders.)

In another randomized, double-blinded, cross-over study, the Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy trial, no significant differences were evident with randomization between pacing and no pacing, either subjectively or objectively, when exercise capacity, quality-of-life score, treadmill exercise time, and peak oxygen consumption were compared (34). The investigators concluded that pacing should not be regarded as a primary treatment for hypertrophic obstructive cardiomyopathy, and subjective benefit without objective evidence of improvement should be interpreted cautiously.

Currently, pacing for the treatment of medically refractory hypertrophic obstructive cardiomyopathy is a class IIb indication by the ACC/AHA guidelines (2).

Dilated Cardiomyopathy

Dual-chamber pacing has been reported to be effective in the treatment of selected patients with dilated cardiomyopathy of idiopathic or ischemic cause (35).

Treatment of idiopathic dilated cardiomyopathy with short AVI DDD pacing was first reported by Hochleitner et al. (36). They treated 16 patients with idiopathic dilated cardiomyopathy refractory to pharmacologic therapy who were in NYHA functional class III or IV. These authors reported marked improvement in NYHA functional class and a decrease in mortality over that expected at 1 year.

Hochleitner et al. (37) subsequently published long-term follow-up results of their original patient cohort. Excluding four patients who received transplants, median survival in this critically ill population was 22 months. Improvements in hemodynamic function continued throughout the follow-up period for the five patients with disease of known cause; except for one death due to cancer, all deaths were caused by embolic events and not from continued deterioration in ventricular function. No patient needed rehospitalization because of worsening heart failure after pacemaker implantation.

The mechanism by which standard dual-chamber permanent pacing may produce improvement probably is due to optimization of AV synchrony (38). However, standard dual-chamber pacing resulted in improvement in only a limited number of patients (39,40 and 41). Subsequently, it was hypothesized that, in addition to the need for optimization of AV synchrony, the correction of intraventricular conduction disturbances might result in clinical improvement. Ventricular dyssynchrony is common among the heart failure population and has been associated with paradoxical septal wall motion, decreased left ventricular pressure, prolonged duration of mitral regurgitation, and decreased diastolic filling times in patients with left bundle branch block.

Biventricular or left ventricular pacing may counter the decreased septal contribution to stroke volume caused by late left ventricular activation occurring as the septum has begun repolarizing and help to increase the ejection fraction (Fig. 74.2).

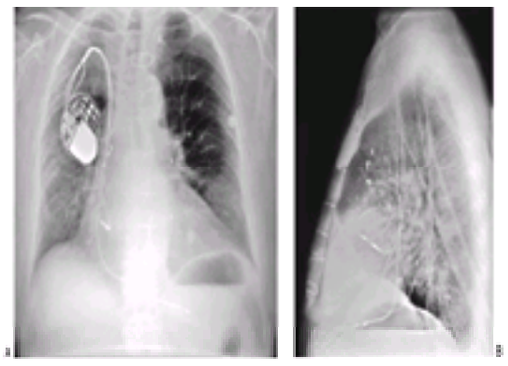


FIGURE 74.2 Postero-anterior **(A)** and lateral **(B)** chest radiographs demonstrating a ventricular lead that courses posteriorly in the coronary sinus and into a cardiac vein, probably a tributary of the posterior cardiac vein. From the postero-anterior view alone, this determination cannot be made. (From Hayes DL, Zipes DP. Cardiac pacemakers and cardioverter-defibrillators. In: Braunwald E, Zipes DP, Libby P, eds. *Heart disease: a textbook of cardiovascular medicine*, 6th ed. Philadelphia: WB Saunders, 2001:775–814, with permission.)

To date, the data have been promising (42), but randomized prospective trials are needed to prove the efficacy and safety of cardiac resynchronization. An early nonrandomized trial, InSync, demonstrated improvement in 6-minute walking, quality of life, and NYHA functional class. Randomized trials that have demonstrated similar outcomes include Pacing Therapy in Congestive Heart Failure (43) and MUSTIC (Multisite Stimulation in Cardiomyopathies) (44).

Pacing for the Prevention of Atrial Fibrillation

There is considerable interest in the potential prevention of recurrent atrial tachyarrhythmias by dual-site or alternate-site atrial pacing (45,46 and 47). The proposed mechanism of this technique is to decrease the refractoriness of dispersion of the atrium by simultaneously depolarizing both left and right atria. Early applications of dual-site atrial pacing have had some success, and this has significant promise.

The optimal method of pacing for prevention of atrial fibrillation has not been established, but it should be determined by the numerous trials that are being conducted. Techniques include dual-site or alternate-site pacing, with the alternate site usually being an atrial septal position.

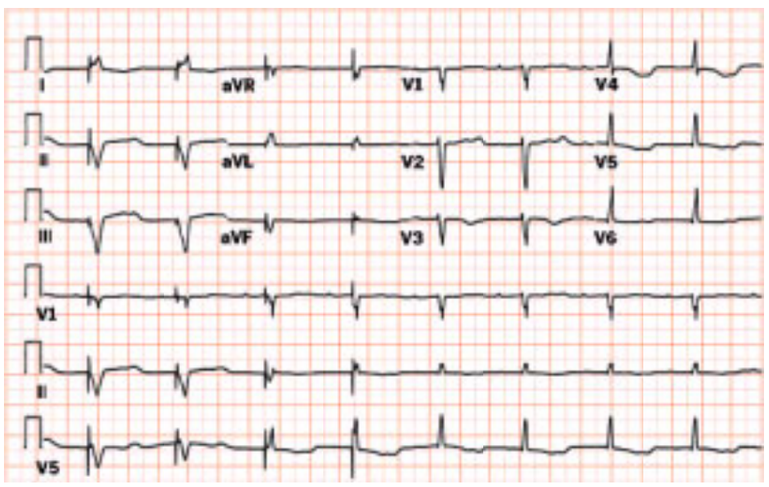
SELECTION OF THE APPROPRIATE PACING MODE

In selecting the optimal pacing mode, the patient's overall physical condition, associated medical problems, exercise capacity, and chronotropic response to exercise must be considered in conjunction with the underlying rhythm disturbance (48). Table 74.5 describes clinical applications of various pacing modes in three classifications: conduction disorders for which a given pacing mode is indicated, those for which a given pacing mode is controversial, and those for which a given pacing mode is contraindicated.

TABLE 74.5 INDICATIONS FOR VARIOUS PACING MODES

It is difficult to comprehend completely the advantages and disadvantages of each of the pacing modes unless the timing cycle of each mode is also understood.

Single-chamber–triggered pacing (AAT and VVT) releases an output pulse every time a native event is sensed. This feature increases the current drain on the battery, which accelerates its rate of depletion, and deforms the native signal, thus compromising interpretation of the electrocardiogram. However, it can serve as an excellent marker for the site of sensing within an intrinsic complex and can prevent inappropriate inhibition from oversensing when the patient does not have a stable native escape rhythm. Also, it can be used for noninvasive electrophysiologic studies, with the already implanted pacemaker tracking chest wall stimuli created by a programmable stimulator.



Demand ventricular pacemaker. As sinus rhythm accelerates, ventricular pacing is inhibited.

A 50-year-old female patient with atrial pacing during an acute inferior myocardial infarction.

Ventricular-inhibited (VVI) pacing incorporates sensing on the ventricular channel, and pacemaker output is inhibited by a sensed ventricular event (Fig. 74.3). VVI pacemakers are refractory for a period after a paced or sensed ventricular event, the *ventricular refractory period*. Any ventricular event occurring within this period is not sensed and does not reset the ventricular timer.

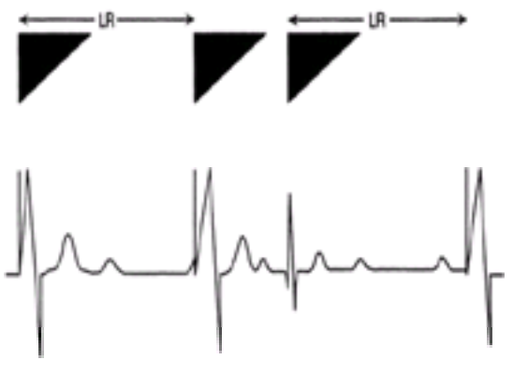


FIGURE 74.3 The VVI timing cycle consists of a defined lower rate (LR) limit and a ventricular refractory period (*black triangle*). When the LR limit timer is complete, a pacing artifact is delivered in the absence of a sensed intrinsic ventricular event. If an intrinsic QRS occurs, the LR limit timer is started from that point. A ventricular refractory period begins with any sensed or paced ventricular activity. (From Hayes DL, Levine PA. Pacemaker timing cycles. In: Ellenbogen KA, ed. *Cardiac pacing*. Boston: Blackwell Scientific, 1992:263–308, with permission.)

Worldwide, VVI pacing is the most commonly used pacing mode. Although VVI pacing protects the patient from lethal bradycardias, it has significant limitations in that it does not restore or maintain AV synchrony or provide rate responsiveness in patients with chronotropic incompetence. Also, some patients with VVI pacing experience symptomatic hemodynamic deterioration with ventricular pacing (49,50). Adverse hemodynamics associated with a normally functioning pacing system that result in overt symptoms or limit the patient's ability to achieve optimal functional status are referred to as *pacemaker syndrome* (Fig. 74.4). Pacemaker syndrome was recognized initially with ventricular (VVI) pacing, but it may occur with any pacing mode if there is AV dissociation. The incidence of pacemaker syndrome is difficult to determine and depends on how the syndrome is defined. If the definition is restricted to patients with clinical limitations during any pacing mode that results in AV dissociation, the incidence, as estimated in an older review by Ausubel and Furman (49), is probably in the range of 7% to 10% of patients with VVI pacing. In a study by Heldman et al. (50), patients with DDD pacemakers who were randomly assigned to DDD or VVI pacing mode for 1 week and subsequently to the alternate mode completed questionnaires comparing 16 symptoms experienced during each pacing mode. Some degree of pacemaker syndrome was thought to be present in 83% of those studied. The most common symptoms reported were shortness of breath, dizziness, fatigue, pulsations in the neck or abdomen, cough, and apprehension. It can be concluded from this study that if patients with VVI pacing have some basis for comparison, they may be more aware of symptoms with VVI pacing.

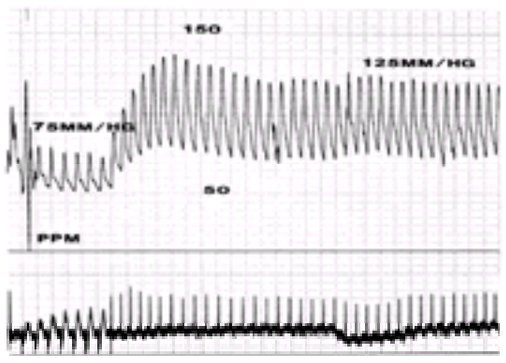


FIGURE 74.4 Hemodynamic tracing of a patient with pacemaker syndrome. In the initial portion of the tracing, there is ventricular pacing, with a systolic arterial pressure of approximately 75 mm Hg. The patient's intrinsic sinus rhythm inhibits ventricular pacing, and the arterial systolic pressure increases to approximately 125 mm Hg. PPM, pulses per minute. (From Hayes DL, Holmes DR Jr. Hemodynamics of cardiac pacing. In: Furman S, Hayes DL, Holmes DR Jr. *A practice of cardiac pacing*, 3rd ed. Mount Kisco, NY: Futura, 1993:195–218, with permission.)

Atrial-inhibited (AAI) pacing incorporates the same timing cycles, with the obvious difference that pacing and sensing occur from the atrium, and pacemaker output is

inhibited by a sensed atrial event (Fig. 74.5). An atrial-paced or sensed event initiates a refractory period during which nothing is sensed by the pacemaker. Confusion can arise when multiple ventricular events occur while there is atrial pacing. For example, in addition to the intrinsic QRS that occurs in response to the paced atrial beat, if a premature ventricular beat follows, it does not inhibit an atrial pacing artifact from being delivered. When the atrial timing cycle ends, the atrial pacing artifact is delivered regardless of ventricular events, because an AAI pacemaker should not sense anything in the ventricle. The single exception to this rule is far-field sensing; that is, the ventricular signal is large enough to be sensed inappropriately by the atrial lead. In this situation, the atrial timing cycle is reset. Sometimes, this anomaly can be corrected by making the atrial channel less sensitive or by lengthening the refractory period.

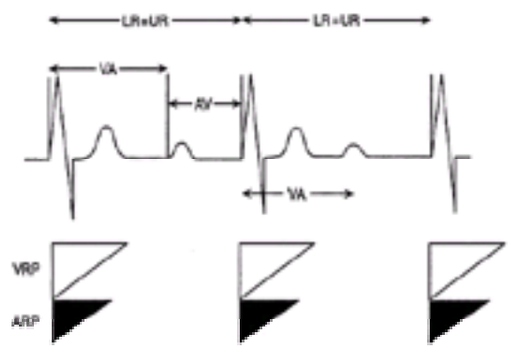
FIGURE 74.5 The AAI timing cycle consists of a defined lower rate (LR) limit and an atrial refractory period. When the LR limit timer is complete, a pacing artifact is delivered in the atrium in the absence of a sensed atrial event. If an intrinsic P wave occurs, the LR limit timer is started from that point. An atrial refractory period begins with any sensed or paced atrial activity. (From Hayes DL, Levine PA. Pacemaker timing cycles. In: Ellenbogen KA, ed. *Cardiac pacing*. Boston: Blackwell Scientific, 1992:263–308, with permission.)

AAI pacing is appropriate for patients with sinus node dysfunction. The obvious disadvantage of atrial pacing is lack of ventricular support should AV block occur. If the patient with sinus node dysfunction is evaluated carefully for the presence of AV nodal disease at the time of pacemaker implantation, the occurrence of clinically significant AV nodal disease is low, 2% per year (51). The evaluation before the use of an AAI system should include incremental atrial pacing at the time of pacemaker implant. Although criteria vary among institutions and implanting physicians, adult patients should be capable of one-to-one AV nodal conduction to rates of 120 to 140 beats/min.

AV sequential, ventricular-inhibited pacing (DVI) is rarely used as the preimplantation pacing mode of choice. By definition, DVI provides pacing in both the atrium and the ventricle (D), but provides sensing only in the ventricle (V). The pacemaker is inhibited and reset by sensed ventricular activity, but it ignores all intrinsic atrial complexes.

At one time, DVI pacemakers were implanted in a large number of patients, often with a satisfactory outcome. However, DVI pacing is limited by the absence of atrial sensing, which prevents atrial tracking. In addition, lack of atrial sensing may lead to competitive atrial pacing and initiation of atrial rhythm disturbances. For these reasons, DVI pacing is rarely selected as the mode of choice at the time of implantation, but it is still a programmable option in many dual-chamber pacemakers.

AV sequential, non–P-synchronous pacing with dual-chamber sensing (DDI) incorporates atrial sensing as well as ventricular sensing, which prevents competitive atrial pacing that can occur with DVI pacing (*e*Fig. 74.5.1). The DDI mode of response is inhibition only (i.e., no tracking of P waves can occur). Therefore, the programmed rate, which by definition is the lower rate since only a single rate exists, is the fastest paced rate that can occur.



***e*FIGURE 74.5.1** The timing cycle in DDI consists of a lower rate (LR) limit, an atrioventricular (AV) interval, a ventricular refractory period (VRP), and an atrial refractory period (ARP). The VRP is initiated by any sensed or paced ventricular activity, and the ARP is initiated by any sensed or paced atrial activity. DDI can be thought of as DDD pacing without the capability of P-wave tracking or DVI without the potential for atrial competition by virtue of atrial sensing. The LR limit cannot be violated even if the sinus rate is occurring at a faster rate. For example, the LR limit is 1,000 ms, or 60 pulses per minute, and the AV interval is 200 ms. If a P wave occurs 500 ms after a paced ventricular complex, the AV interval is initiated, but at the end of this interval, 700 ms from the previous paced ventricular activity, a ventricular pacing artifact cannot be delivered because it would violate the LR limit. UR, upper rate; VA, ventriculoatrial. (From Hayes DL, Levine PA. Pacemaker timing cycles. In: Ellenbogen KA, ed. *Cardiac pacing*. Boston: Blackwell Scientific, 1992:263–308, with permission.)

DDI is rarely the preimplantation mode of choice, but it remains a programmable option in most dual-chamber pacemakers (52).

Atrial synchronous (P-tracking) pacemakers (VDD) pace only in the ventricle, sense in both the atrium and ventricle, and respond both by inhibition of ventricular output by intrinsic ventricular activity and by ventricular tracking of P waves. The VDD mode also has become increasingly available as a single-lead pacing system. In this system, a single lead is capable of pacing in the ventricle in response to sensing atrial activity by way of a remote electrode situated on the intraatrial portion of the ventricular pacing lead (53).

A sensed atrial event initiates the AVI. If an intrinsic ventricular event occurs before the termination of the AVI, ventricular output is inhibited and the lower rate timing cycle is reset (Fig. 74.6). If a paced ventricular beat occurs at the end of the AVI, this beat resets the lower rate. If no atrial event occurs, the pacemaker escapes with a paced ventricular event at the lower rate limit (i.e., the pacemaker displays VVI activity in the absence of a sensed atrial event).

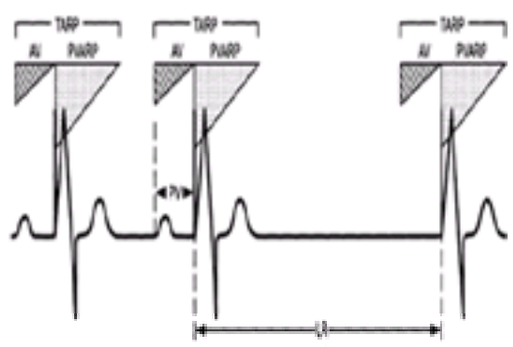


FIGURE 74.6 The timing cycle of VDD consists of a lower rate (LR) limit, an atrioventricular (AV) interval, a ventricular refractory period, a postventricular atrial refractory period (PVARP), and an upper rate limit. A sensed P wave initiates the AV interval (during this interval, the atrial-sensing channel is refractory). At the end of the AV interval, a ventricular pacing artifact is delivered if no intrinsic ventricular activity has been sensed (i.e., P-wave tracking). Ventricular activity, paced or sensed,

initiates the PVARP and the ventriculoatrial interval (the LR limit interval minus the AV interval). If no P-wave activity occurs, the pacemaker escapes with a ventricular pacing artifact at the LR limit. PV, postventricular; TARP, total atrial refractory period. (From Hayes DL, Zipes DP. Cardiac pacemakers and cardioverter-defibrillators. In: Braunwald E, Zipes DP, Libby P, eds. *Heart disease: a textbook of cardiovascular medicine*, 6th ed. Philadelphia: WB Saunders, 2001:775–814, with permission.)

VDD pacing may be appropriate for patients who have normal sinus node function and conduction disease of the AV node.

Dual-chamber pacing and sensing with inhibition and tracking (DDD) are reasonably easy to comprehend. The basic timing circuit associated with lower rate pacing is divided into two sections: the ventriculoatrial (VA) interval and the AVI. The AVI may be defined by AV sequential pacing, initiated (a) by pacing, with subsequent intrinsic ventricular conduction, or (b) by a native P wave, with subsequent ventricular pacing (Fig. 74.7). The total atrial refractory period, which consists of the AVI and the postventricular atrial refractory period (PVARP), defines the maximal tracking rate of the pacemaker.

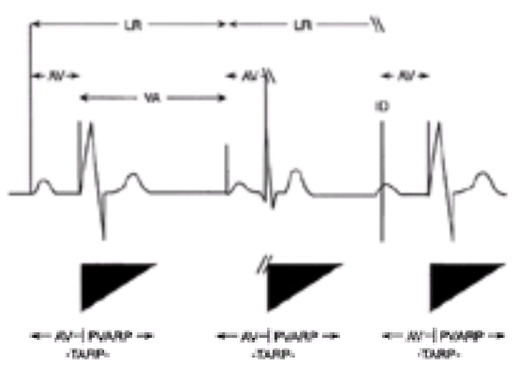


FIGURE 74.7 The timing cycle in DDD consists of a lower rate (LR) limit, an atrioventricular (AV) interval, a postventricular atrial refractory period (PVARP), and an upper rate limit. The AV interval and PVARP together constitute the total atrial refractory period (TARP). There are four variations of the DDD timing cycle. If intrinsic atrial and ventricular activity occurs before the LR limit times out, both channels are inhibited and no pacing occurs. If no intrinsic atrial or ventricular activity occurs, there is AV sequential pacing (first sequence). If no atrial activity is sensed before the ventriculoatrial (VA) interval is completed, an atrial pacing artifact is delivered, which initiates the AV interval. If intrinsic ventricular activity occurs before the termination of the AV interval, the ventricular output from the pacemaker is inhibited [i.e., atrial pacing (second sequence)]. If a P wave is sensed before the VA interval is completed, output from the atrial channel is inhibited. The AV interval is initiated, and if no ventricular activity is sensed before the AV interval terminates, a ventricular pacing artifact is delivered [i.e., P-synchronous pacing (third sequence)]. ID, intrinsic deflection. (From Hayes DL, Levine PA. Pacemaker timing cycles. In: Ellenbogen KA, ed. *Cardiac pacing*. Boston: Blackwell Scientific, 1992:263–308, with permission.)

In summary, four different rhythms can occur as a result of normal DDD function: (a) normal sinus rhythm, (b) atrial pacing, (c) AV sequential pacing, and (d) P-synchronous pacing. The DDD pacing mode is most appropriate for patients with normal sinus node function and AV block. Some consider DDD pacing the mode of choice in neurocardiogenic syndromes with symptomatic cardioinhibition.

DDD pacing has limitations in patients with sinus node dysfunction. P-synchronous pacing is not possible in the presence of chronic atrial fibrillation or in patients with a paralyzed or nonexcitable atrium. Also, DDD pacing is not able to restore rate response in a patient with chronotropic incompetence (a patient in whom atrial rate is unable to increase appropriately with exercise). In a patient with chronotropic incompetence, DDD pacing is suboptimal because rate responsiveness is not restored.

INDICATIONS FOR RATE-ADAPTIVE PACEMAKERS

Single-chamber rate-adaptive pacing modes (AAIR, VVIR) have timing cycles that are not significantly different from those of their non–rate-adaptive counterparts. The difference lies in the potential variability of the paced rate (Fig. 74.8). Depending on the sensor incorporated and the level of exertion of the patient, the basic interval is shorter than the programmed lower rate limit. Shortening requires that an upper rate limit be programmed to define the absolute shortest cycle length allowable.

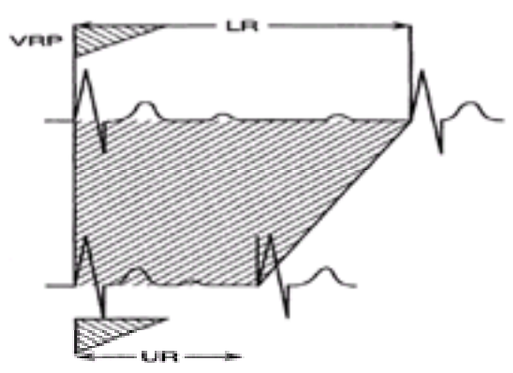


FIGURE 74.8 The VVIR timing cycle consists of a lower rate (LR) limit, an upper rate (UR) limit, and a ventricular refractory period (VRP) (*triangle*). As indicated by sensor activity, the VV cycle length shortens accordingly. (The striped area represents the range of sensor-driven VV cycle lengths.) In most VVIR pacemakers, the VRP remains fixed despite the changing VV cycle length. In selected VVIR pacemakers, the VRP shortens as the cycle length shortens. (From Hayes DL, Levine PA. Pacemaker timing cycles. In: Ellenbogen KA, ed. *Cardiac pacing*. Boston: Blackwell Scientific, 1992:263–308, with permission.)

VVIR pacing, like VVI, is contraindicated if ventricular pacing results in retrograde (VA) conduction, a decrease in blood pressure, or both. VVIR pacing should not be used as an excuse to forego attempts at placing an atrial lead in a patient who is undergoing pacemaker implantation, has normal sinus node function, and would benefit from rate-adaptive pacing. If the sinus node is intact, P-synchronous pacing should still be considered the optimal rate-adaptive parameter and be used when possible.

AAIR pacing can be considered in patients with sinus node dysfunction and normal AV node function, because this mode restores rate responsiveness and maintains AV synchrony. If AAIR pacing is contemplated, normal AV node conduction must first be determined as discussed previously for AAI pacing.

AV sequential, non–P-synchronous, rate-adaptive pacing with dual-chamber sensing (DDIR) is the same as DDI pacing except that paced rates can exceed the programmed lower rate limit through sensor-driven activity. An upper rate limit must be programmed to define the shortest cycle length allowable.

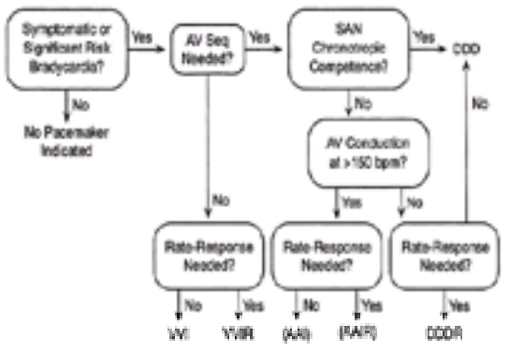
At one time, DDIR pacing was popular for patients requiring permanent pacing who had associated paroxysmal supraventricular tachyarrhythmias. Now, DDDR pacing with mode switching is considered the optimal pacing mode for such patients.

Dual-chamber rate-adaptive (DDDR) pacemakers are capable of all the variations described for DDD pacemakers. In addition to using P-synchronous pacing as a method for increasing heart rate, the sensor incorporated in the pacemaker may also drive heart rate. The resulting rhythm may be sinus-driven (alternatively called *atrial-driven* or *P-synchronous*) or sensor-driven.

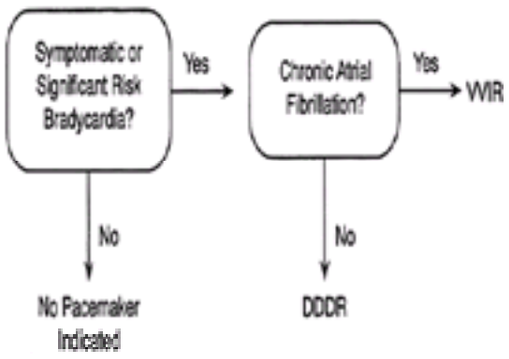
The patient ideal for DDDR pacing has combined sinus node and AV node dysfunction, allowing restoration of rate responsiveness and AV synchrony.

Algorithms for determining the appropriate pacing mode for patients with sinus node disease and AV node disease are given in eFigure 74.8.1 and eFigure 74.8.2. eFigure 74.8.1, a more complex algorithm, considers most of the available pacing modes. The algorithm in eFigure 74.8.2 is simpler and assumes that a pacemaker

capable of rate adaptation will be used.



***e*FIGURE 74.8.1** Algorithm for pacemaker mode selection allowing choice of VVI, VVIR, AAI, AAIR, DDD, and DDDR. AV, atrioventricular; SAN, sinoatrial node. (Courtesy of M. D. McGoon, MD.)



***e*FIGURE 74.8.2** Simple algorithm for pacemaker mode selection using only VVIR and DDDR. (Courtesy of M. D. McGoon, MD.)

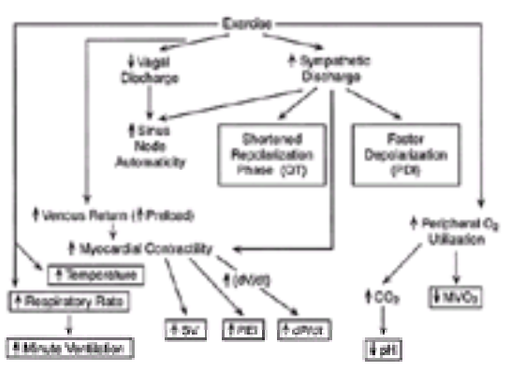
CHOOSING THE PACEMAKER SYSTEM HARDWARE

After the appropriate pacing mode has been selected, the actual pacemaker must be selected. The advising physician or the one performing the implantation should select a pacemaker that provides the specific features needed for the patient. It is imperative that the physician responsible for following the patient be completely familiar with the pacemaker implanted.

Lead selection should also be individualized. This requires a thorough knowledge of the available leads as well as the performance records of specific models (54,55).

Selecting the Appropriate Sensor for Rate-Adaptive Pacing

To classify sensors on the basis of their response to physiologic variables, Rossi (56) divided them into five orders (*e*Table 74.5.1). A variety of sensors appropriate for rate-adaptive pacing have been developed and are shown in *e*Figure 74.8.3 as end points of some physiologic response.



***e*FIGURE 74.8.3** Physiologic responses that have been investigated or used clinically for rate adaptation of permanent pacemakers. The boxed terms represent the end points used for rate adaptation. MVO_2, mixed venous oxygen; PEI, pre-ejection interval; SV, stroke volume.

*e*TABLE 74.5.1 CLASSIFICATION OF SENSORS BY RESPONSE TO PHYSIOLOGIC VARIABLES

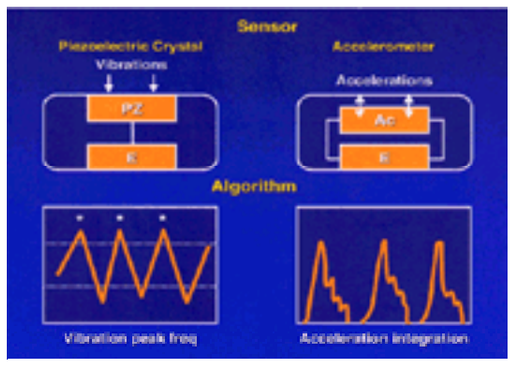
Order	Physiologic variable
First: Sensor that directly measures O_2 consumption or energy expenditure	Oxygen uptake
Second: Sensor with a linear relationship to sensors of the first order	Cardiac output, minute ventilation,[a] atrioventricular O_2 difference
Third: Sensor with a linear relationship to sensors of the second order	Heart rate,[a] stroke volume,[b] mixed O_2 saturation,[b] respiratory rate, tidal volume
Fourth: Sensor that relies on changes in sympathetic activity and circulating catecholamines	QT interval,[a] right ventricular dP/dT,[b] preejection interval,[b] ventricular depolarization gradient[b]
Fifth: Sensor that responds to physiologic feedback mechanisms in terms of metabolic activity or receptor reflexes	Central venous pH, central venous temperature,[a] right atrial pressure,[b] mixed venous lactate and bicarbonate levels

[a]Available clinically in the United States or Europe.
[b]Under investigation.
Data from Rossi P. Rate-responsive pacing: biosensor reliability and physiological sensitivity. *Pacing Clin Electrophysiol* 1987;10:454–466, with permission.

Activity Sensors

Currently, activity-controlled pacing with vibration detection (piezoelectric crystal or accelerometer) is the most widely used form of rate adaptation, because it is simple, easy to apply clinically, and rapid in onset of rate response (57,58).

The main difference between the piezoelectric crystal sensor and the accelerometer is that the crystal senses vibration from up and down motion and the accelerometer also senses anterior and posterior motion (*e*Fig. 74.8.4). Some investigators (57,58) have shown that with accelerometer-based pacemakers, heart-rate response tends to be more physiologic and less responsive to local pressure and tapping than with piezoelectric crystal-based pacemakers.



***e*FIGURE 74.8.4** Comparison of piezoelectric crystal and accelerometer. (Data from Wilkoff BL. Cardiac chronotropic responsiveness. In: Ellenbogen KA, Kay GN, Wilkoff BL, eds. *Clinical cardiac pacing*. Philadelphia: WB Saunders, 1995:432–446, with permission.)

Subsequent variations of activity sensors have included a gravitational sensor able to discriminate changes in vertical gravitational acceleration (59) and to measure electrical signals from a moving magnetic ball (60).

Minute-Ventilation Sensors

Minute volume (respiratory rate multiplied by tidal volume) has an excellent correlation with metabolic demand. In a rate-adaptive pacing system, minute volume is measured by emitting a small charge of known current from the pacemaker and measuring the resulting voltage at the lead tip (61) (Fig. 74.9). When both current and voltage are known, transthoracic impedance can be measured between the ring electrode and the pacemaker can. Because transthoracic impedance varies with respiration and its amplitude varies with tidal volume, the impedance measurement can be used to determine respiratory rate and tidal volume. A pacing algorithm uses the minute-volume measurements to alter pacing rate (62). Long-term reliability of the minute-volume sensor has been excellent (63), and this sensor is increasingly being used.

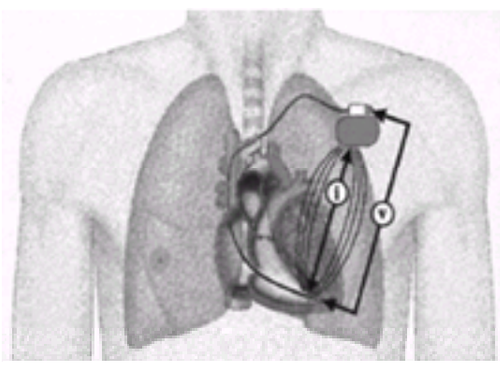


FIGURE 74.9 The mV sensor signal for rate change is derived by measuring the changes in transthoracic impedance. Ohm's law, R = V/I. (Courtesy of Guidant Inc., St. Paul, MN.)

Stimulus-T or QT-Sensing Pacemaker

The interval from the onset of a paced QRS complex to the end of the T wave has been used for rate adaptation for many years (64,65). This *stimulus-T interval* is affected by autonomic activity and heart rate. This relationship allows measurement of the stimulus-T interval to be used for rate adaptation. The QT-sensing rate-adaptive pacing system has been successful clinically. Response characteristics of this sensor make it a reasonable partner for activity sensors in dual-sensor systems.

Many other sensors have been incorporated, with varied success, in rate-adaptive pacing sensors. Other variables that have been used for rate-adaptive pacing include temperature, preejection interval, dP/dT, paced depolarization integral, and mixed venous oxygen saturation. These are discussed in the accompanying CD-ROM and in the online version of this text.

Temperature Sensors

Because central venous temperature increases with exercise, it is reasonable to consider this variable as the basis for a physiologic sensor. The increase in temperature can be measured with a thermistor contained within the right ventricular portion of the pacing lead (66). At the onset of exercise, core body temperature decreases as cooler peripheral blood is returned to the central circulation. Temperature-sensing rate-adaptive pacemakers have been available for many years but have never gained widespread acceptance, in part because a special pacing lead is required and rate response is less adequate at low workloads owing to the relatively slow response of central venous temperature (64).

Other Sensors

The *preejection interval* is the systolic time interval from the onset of electrical ventricular depolarization to the onset of ventricular ejection. In terms of ventricular pacing, the preejection interval is the interval between a right ventricular pacing stimulus and the onset of contraction determined by an impedance catheter (67,68). The preejection interval shortens as exercise workload increases, and this can be used as a signal to increase the pacing rate. An increase in heart rate does not appreciably affect the preejection interval (i.e., no significant positive feedback occurs). Stroke volume, also measured by an impedance catheter in the right ventricle, can be used for rate-adaptive pacing by incorporation of a pacing algorithm that alters the pacing rate to keep the right ventricular stroke volume relatively constant and within physiologic values (68).

Change in right ventricular pressure, dP/dT, has been used for rate-adaptive pacing. It is measured by incorporating a pressure transducer in the right ventricular portion of the pacing lead (69,70). In clinical investigations and in follow-up, the sensor has performed well.

Mixed venous oxygen saturation, measured with hemoreflectance oximetry, varies with physical activity and changes rapidly with the onset of exercise. For a rate-adaptive pacing system, the oximeter is incorporated in the right ventricular portion of the pacing lead. The greatest challenge has been to find a stable sensor. The results of the initial studies in animals and humans are encouraging (71).

Paced depolarization integral is a less well-known physiologic sensor (72,73). The concept of paced depolarization integral refers to the vector integral of the paced QRS, or ventricular depolarization gradient. Lau (74) explained the clinical response of this gradient as follows: During fixed-rate ventricular pacing, exercise and the effect of circulating catecholamines decrease the ventricular depolarization gradient. An increase in pacing rate increases the gradient.

Dual-Sensor Combinations

The overall performance of market-approved, single-sensor, rate-adaptive systems has been excellent. However, the perfect sensor would mimic the response of the normal sinus node at all levels of activity and during emotional stress.

Clinical problems with available rate-adaptive pacing systems have been minimal. Both activity-sensing and minute-ventilation devices may respond to nonphysiologic stimuli. For example, with activity-sensing systems, rate acceleration may occur when the pacemaker is tapped or the patient rolls over on the pacemaker. A

paradoxical rate response has also been shown (e.g., sensor-driven rate response is often faster during descent of stairs than during ascent). Although response to nonphysiologic stimuli represents less than perfect specificity of the sensor response, both activity sensing and minute ventilation have served patients very well.

The perfect sensor also would be resistant to nonphysiologic stimuli. A multisensor rate-adaptive pacing system could improve specificity by having one sensor verify or cross-check the other (75). For example, if one sensor indicated a rate increase and the other did not, a rate increase would not occur. Both sensors would have to indicate a rate increase before it would be allowed. Sensor combinations that are in use include QT interval/activity and activity/minute ventilation.

EFFECT OF PACING MODE ON MORBIDITY AND MORTALITY

An early study by Rosenqvist and colleagues stimulated much of the current interest in the effect of pacing mode on survival (76,77 and 78). Although their study is not without criticism, the 4-year analysis of the data remains impressive. At 4 years of follow-up, atrial fibrillation had occurred in 47% of the VVI group versus 7% of the AAI group (p = .0005), congestive heart failure in 37% of the VVI group versus 15% of the AAI group (p = .005), and mortality of 23% in the VVI group versus 8% of the AAI group (p = .025).

The Swedish study of Rosenqvist et al. (78) prompted many other investigators to perform retrospective reviews to assess the effect of pacing mode on mortality (*e*Table 74.5.2). Despite the retrospective nature of all the studies [except for that of Rosenqvist et al. (78)] and all the inherent weaknesses of retrospective analyses, the similar outcome of all the studies listed in *e*Table 74.5.2 (79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96 and 97) cannot be dismissed easily. This subject has been reviewed extensively and critiqued by Barold and Santini (98).

*e*TABLE 74.5.2 STUDIES ASSESSING ATRIAL FIBRILLATION AND MORTALITY WITH MODE OF PERMANENT PACING

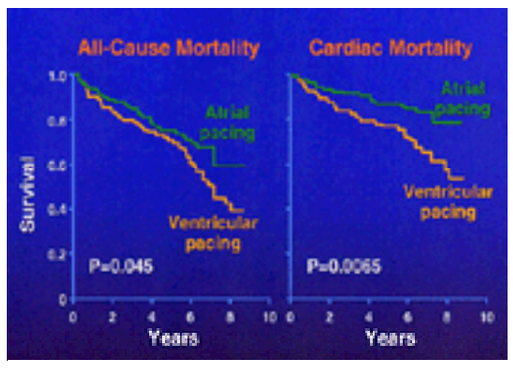
Author (reference)	Patients (no.)	Months of follow-up	trial fibrillation (%)	Deaths (%)	Difference in survival, *p* £.05[a]	Only patients with sinus node dysfunction analyzed[b]
Alpert et al. (79)						
DDD or DVI	49	1–18 yr	NA	16	NA	Yes
VVI	79	1–18 yr	NA	27		
Bianconi et al. (80)						
AAI/DDD	153	44	18	14	No	Yes
VVI	150	59	39	31	0.08	
Feuer et al. (81)						
DDD or DDI	110	40	8	7	NR[c]	NR
VVI	110	48	18	15		
Grimm et al. (82)						
DDD	41	32	2	NA	NA	No
VVI	203	69	32	NA		
Hayes et al. (83)						
DDD or DVI	172	1–13 yr	NR	29	Yes	No
VVI	389	1–13 yr	NR	43		
Hesselson et al. (84)						
DVI/DDD	58/308	2–14 yr	5/8	33/20	Yes	No
VVI	193	2–14 yr	26	47		
Kosakai et al. (85)						
AAI/AV sequential	87/57	NR	16/23	NA	NA	No
VVI	51	NR	57	NA		
Langenfeld et al. (86)						
DDD	43	63	2	NA	NA	No
CCI	203	63	31	NA		
Markewitz et al. (87)						
AAI/DDI	67/69	51/13	14/3	NA	NA	Yes
VVI	87	32	27	NA		
Nürnberg et al. (88)						
AAI/DDD	15/22	41	13/18	27/23	Yes	No
VVI	93	41	38	47		
Rosenqvist et al. (78)						
AAI	89	44	7	8	Yes	Yes
VVI	79	47	47	23		
Santini et al. (89)						
AAI/DDD	135/79	60	4/12	13/16	Yes	Yes
VVI	125	60	44	30		
Santamauro et al. (90)						
DDD	186	51	NR	17	Yes	No
VVI	204	51	NR	28		
Sasaki et al. (91)						
AAI/DDD	17/24	39	0	13	Yes	Yes
VVI	34	62	36	24		
Sethi et al. (92)						
AAI	40	47	3	10	No	Yes
VVI	47	50	21	15		
Stangl et al. (93)						
AAI	110	40	6	17	Yes	Yes
VVI	112	33	19	27		
Sutton and Kenny (94)						
AAI	410	33	4	NA	NA	Yes
VVI	651	39	22	NA		
van Erckelens et al. (95)						
DDD	44	99	2	NA	Yes	No
VVI	163	99	14	NA		
Witte et al. (96)						
AAI/DDD	1,092/152	NR	NA	11	Yes	Yes
VVI	3,440	NR	NA	23		
Zanini et al. (97)						
AAI	53	45	4	9	Yes	Yes
VVI	57	40	18	18		

NA, not available; NR, not reported.
[a]Study included patients with other rhythm disturbances, but data in this table reflect the sinus node dysfunction subset only.
[b]Difference in survival statistically significant when AAI or dual-chamber pacing mode is compared with VVI mode.
[c]No *p* value reported, but results suggest a significant difference in survival.
Adapted from Hesselson AB, Parsonnet V, Bernstein AD, et al. Deleterious effects of long-term single-chamber ventricular pacing in patients with sick sinus syndrome: the hidden benefits of dual-chamber pacing. *J Am Coll Cardiol* 1992;19:1542–1549.

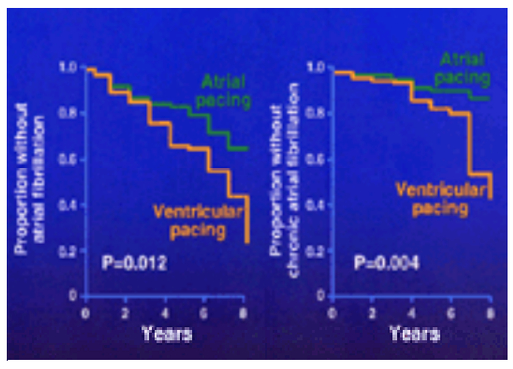
Lamas et al. (99) reported survival in a large population (n = 20,948) of patients with sinus node dysfunction. The population was a random sample of the complete U.S. cohort of Medicare patients who had pacing for sinus node dysfunction from 1988 through 1990. DDD/DDDR pacing mode was an independent correlate of survival.

In a 1992 review and critique of the retrospective literature on the effect of pacing mode on the development of atrial fibrillation and survival, Lamas et al. (100) recommended a prospective randomized controlled trial, because the retrospective data did not allow definitive recommendations to be made regarding atrial pacing to prevent atrial fibrillation in patients with sick sinus syndrome.

Andersen et al. (101) published the first prospective data on pacing mode and survival. Of the 225 patients (mean age, 76 years) with sinus node dysfunction randomly assigned to AAI or VVI pacing, the VVI group had a higher incidence of atrial fibrillation (23% of the VVI group vs. 14% of the AAI group, $p = .12$) and thromboembolism ($p = .0083$) than the AAI group. Although no difference in mortality could be detected at the initial analysis at 3.3 years, a subsequent analysis at 5.5 years showed improved survival and less heart failure in the AAI group (102). In addition, there was a persistent reduction in the incidences of atrial fibrillation and thromboembolic events (eFig. 74.9.1 and eFig. 74.9.2).



***e*FIGURE 74.9.1** All-cause (*left*) and cardiac mortality (*right*) in a Danish pacing trial contrasting atrial and ventricular pacing. (From Andersen HR, Nielsen JC, Thomsen PEB, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997;350:1210–1216, with permission.)

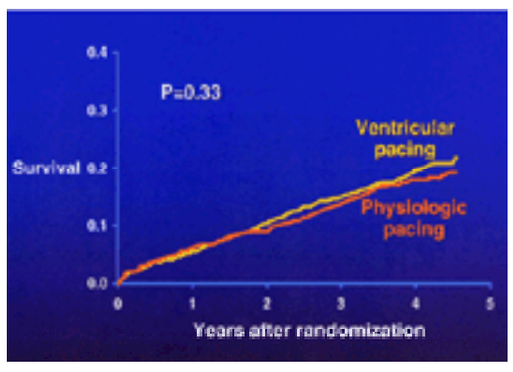


***e*FIGURE 74.9.2** AAI versus VVI pacing modes. **Left:** Patients with any episodes of atrial fibrillation in atrial versus ventricular pacing modes. **Right:** Incidence of chronic atrial fibrillation with atrial versus ventricular pacing modes. (From Andersen HR, Nielsen JC, Thomsen PEB, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997;350:1210–1216, with permission.)

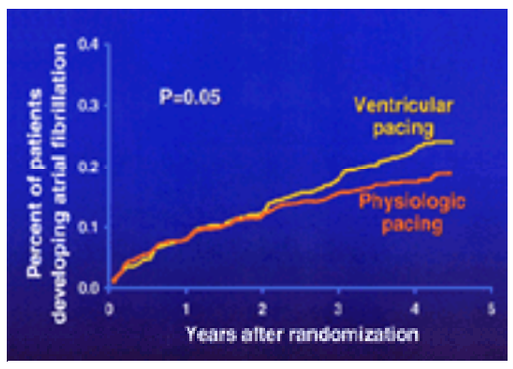
The Pacemaker Selection in the Elderly trial, a prospective, randomized, multicenter trial, entered a total of 400 patients and assessed quality of life as a primary end point in patients with pacemakers programmed to DDDR and VVIR pacing modes (103). Secondary end points included all causes of mortality; hospitalization for congestive heart failure, cerebrovascular accidents, or both; and atrial fibrillation. No significant difference was noted between DDDR and VVIR pacing for quality of life or any of the secondary end points. There was a trend toward superiority of DDDR pacing in the sinus node dysfunction group, but it was not statistically significant.

The Pacemaker Selection in the Elderly study was the template for the Mode Selection Trial. In this study, 2,000 patients with sinus node dysfunction will be randomly assigned to either VVI or DDD pacing. Primary end points will be all causes of mortality as well as cerebrovascular accidents.

The Canadian Trial of Physiologic Pacing (CTOPP) compared VVIR with DDDR or AAIR and had primary end points of overall mortality and cerebrovascular accidents (eFig. 74.9.3) and secondary end points of atrial fibrillation (eFig. 74.9.4), hospitalizations for congestive heart failure, and death due to a cardiac cause (104). CTOPP demonstrated that physiologic pacing (DDD/AAI) was associated with a decreased rate in the development of chronic atrial fibrillation, from 3.78% to 2.87% per year at the 3-year analysis. However, no difference in quality of life or mortality was demonstrated.



***e*FIGURE 74.9.3** From the Canadian Trial of Physiologic Pacing, the cumulative risk of stroke or death from a cardiovascular cause. (From Connolly SJ, Kerr CR, Gent M, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. *N Engl J Med* 2000;342:1385–1391, with permission of the Massachusetts Medical Society.)



***e*FIGURE 74.9.4** From the Canadian Trial of Physiologic Pacing, the incidence of atrial fibrillation was greater with VVI than physiologic pacing modes. (From Connolly SJ, Kerr CR, Gent M, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. *N Engl J Med* 2000;342:1385–1391, with permission of the Massachusetts Medical Society.)

A prospective randomized British trial (UK PACE) is comparing DDD with VVI pacing modes in 2,000 patients 70 years and older requiring permanent pacing for second- or third-degree AV block.

PACEMAKER IMPLANTATION

Guidelines for appropriate training for pacemaker implantation and follow-up have been established by the North American Society of Pacing and Electrophysiology as well as the American College of Cardiology (105,106). These guidelines are summarized in *e*Table 74.5.3.

*e*TABLE 74.5.3 RECOMMENDED TRAINING REQUIREMENTS FOR PACEMAKER IMPLANTATION

Core knowledge base for pacemaker follow-up
Participate in at least 100 pacemaker follow-up visits
Participate in at least 50 initial transvenous pacemaker implantations as the primary operator (recommended that at least one-half of these be dual-chamber)
Participate in at least 20 revisions of pacing systems
Exposure to lead extraction techniques (suggested)
Thorough knowledge of recognition and treatment of pacemaker and surgical complications and emergencies

Data from Hayes DL, Naccarelli GV, Furman S, et al. Report of the NASPE Policy Conference training requirements for permanent pacemaker selection, implantation, and follow-up. North American Society of Pacing and Electrophysiology. *Pacing Clin Electrophysiol* 1994;17:6–12; and Josephson ME, Maloney JD, Barold SS, et al. Guidelines for training in adult cardiovascular medicine. Core Cardiology Training Symposium (COCATS). Task Force 6: training in specialized electrophysiology, cardiac pacing and arrhythmia management. *J Am Coll Cardiol* 1995;25:23–26.

Actual implantation techniques are described in many textbooks, and interested readers should consult these sources (107). However, because a physician not participating in implantation may be involved in follow-up care of the patient, it is important for the physician to recognize and understand measurements made at the time of implantation and how they affect long-term management and the potential complications of implantation (see Pacemaker Complications, later in this chapter).

Also, a newer consideration in implantation technique is the effect of lead placement on hemodynamics. The ventricular pacing lead traditionally has been positioned in the right ventricular apex. However, more recent investigations have suggested that cardiac output may be improved by placing the ventricular lead in other portions of the right ventricle (108,109 and 110). More work is necessary to determine optimal lead site(s).

For the purpose of optimizing hemodynamics, reports of trichambered pacing (biventricular and right atrial) and four-chambered pacing are encouraging (111,112). Additional investigations are also necessary to determine the optimal number of chambers to be paced and optimal site(s) of lead placement.

Implantation Measurements

The position of the pacing leads must be tested acutely to establish that myocardial stimulation and sensing of intrinsic cardiac electrical activity are adequate and reliable. Stimulation threshold may be defined as the smallest amount of electrical activity that produces consistent myocardial capture outside the refractory period. The threshold may be affected by several factors, including the duration of the stimulus (pulse width), type of electrode and its age, site of stimulation, electrolyte status, and state of the myocardium.

The threshold, acute or chronic, is described in terms of voltage or current (milliampere) requirements for capture. Acceptable values for ventricular stimulation thresholds should be 1.0 V or less at a pulse width of 0.5 ms. The acceptable values for atrial pacing thresholds should certainly be less than 1.5 V at a pulse width of 0.5 ms, and with the atrial leads available currently, the threshold usually should be less than 1.0 V. Acute impedance measurements can range from 300 to 1,500 W, depending on the type of lead used.

The thresholds increase shortly after implantation and then usually decrease, reaching a stable value at approximately 6 weeks after implantation (113). The early increase in threshold is thought to be due to an inflammatory reaction at the electrode–myocardial interface. This reaction is minimized with leads capable of steroid elution (114,115).

Although the threshold for stimulation is described in terms of voltage and current, it is equally important that the pulse duration (the amount of time a given amount of energy is delivered) is also known. The shortest duration of an electrical impulse that produces consistent capture (at a constant pulse amplitude) represents the threshold of stimulation as a function of pulse duration. The strength-duration curve can be generated by comparing stimulation thresholds at various pulse widths (Fig. 74.10). This measurement is particularly important because the proper adjustment of pulse duration and output voltage allows long-term pacing with maximal conservation of energy.

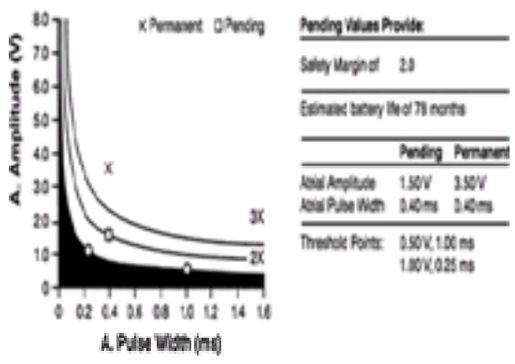


FIGURE 74.10 Atrial strength-duration threshold curve generated by the pacemaker programmer. The voltage amplitude is represented on the *y*-axis and the pulse width in milliseconds on the *x*-axis. The shaded area of the graph represents amplitude/pulse width combinations that would not allow successful capture or depolarization. The upper two curves represent output combinations that would result in two times and three times safety margin (i.e., areas above the capture threshold), which is represented by the lowermost of the three curves. The X is the pacemaker-derived suggested point of permanent programming, in this example, 3.5 V and 0.4-ms pulse width.

The lead impedance, or resistance to current flow, is determined by Ohm's law: $R = E/I$, in which E is voltage, I is current in milliamperes, and R is resistance in ohms. By simultaneously measuring voltage and the resultant current, the resistance can easily be calculated by transposing the equation. Average impedance tends to decrease slightly after initial implantation of the lead and then stabilizes. In the absence of lead complications or myocardial abnormalities, the long-term values for impedance tend to remain constant and do not differ significantly from the original value. Measurement of lead impedance is equally important at the time of pacemaker replacement in determining the integrity of the pacing lead.

Postimplantation Management

The length of time the patient is kept in the hospital after pacemaker implantation varies considerably among institutions. Many physicians who perform implantation allow patients who are not pacemaker dependent to ambulate the evening of the procedure, with dismissal the following morning. The patient's condition is usually monitored to assess normalcy of pacing in the immediate postimplantation period. Before dismissal, thresholds are documented and the pacemaker is programmed to its final settings. If a rate-adaptive pacemaker has been implanted, informal exercise is performed the morning after implantation and the rate-responsive parameters are adjusted to the needs of the patient. Pacemaker-dependent patients may be kept in the hospital one night. When the patient's pacemaker reaches battery depletion indicators, replacement is performed as an outpatient procedure.

Many physicians now perform initial pacemaker implantation as an outpatient procedure. Some perform outpatient implantation only in non–pacemaker-dependent patients, whereas others do not consider dependency status. Possibly, ambulatory pacemaker implantation with outpatient follow-up the next day may become the more usual approach (116).

PACEMAKER PROGRAMMING

All currently available pacemakers have some degree of programmability. In most markets, the simplest single-chamber pacemaker available is capable of rate, pulse width, voltage amplitude, sensitivity, refractory period, and polarity programmability. An attempt is being made to automatize many programmable features to allow optimal programming at all times. Programmable options that are available in many current pacemakers are listed in Table 74.6.

TABLE 74.6 POTENTIAL PROGRAMMABLE OPTIONS

Programming of Energy (Pulse Width and Voltage Amplitude)

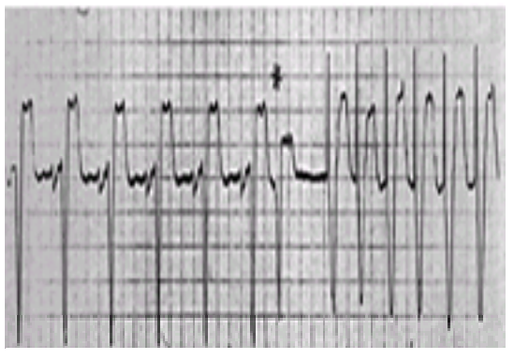
Output programming is probably the most important aspect of programming that should be accomplished routinely. The output must be high enough to allow an adequate pacing margin of safety but should also be programmed with the intent of maximizing pacemaker longevity.

One manufacturer has pacemakers capable of calculating and graphically displaying a strength-duration curve as well as suggesting optimal output parameters (Fig. 74.10).

Automatic programming of output functions has been investigated actively for more than a decade, but only recently have manufacturers developed this as a reliable option.

Refractory Periods

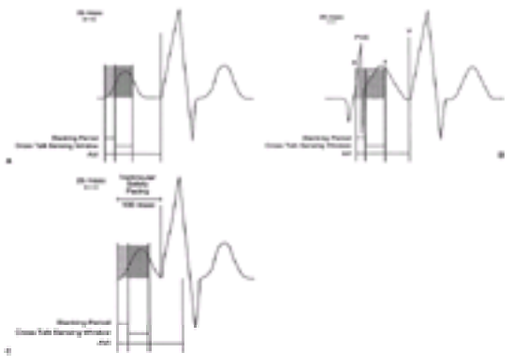
Every pacemaker capable of sensing must include a refractory period in its basic timing cycle. Refractory periods prevent the sensing of early inappropriate signals, such as the evoked potential and repolarization (T wave). The *PVARP* is the period after a sensed or paced ventricular event during which the atrial sensing circuit is refractory. Any atrial event occurring during the PVARP is not sensed by the atrial-sensing circuit. If a P wave occurs after the PVARP and is sensed, no atrial pacing artifact is delivered at the end of the VA interval. Because the maximal tracking rate of the pacemaker is determined by the total atrial refractory period, the PVARP is a significant determinant of the upper rate limit. The PVARP is especially important for the prevention of endless-loop or pacemaker-mediated tachycardia. In the presence of intact VA conduction, any event that uncouples AV synchrony may allow retrograde atrial activation. (The most common stimulus for VA conduction is a premature ventricular contraction.) If the atrium is refractory at the time of VA conduction, the atrium will be depolarized and the atrial depolarization will initiate the AVI. Paced ventricular depolarization may once again result in VA conduction, establishing a reentrant or endless-loop tachycardia (eFig. 74.10.1) (117). This often symptomatic tachyarrhythmia can be prevented by extending the PVARP so that the retrograde P wave is not sensed and, thus, does not initiate the AVI. In an effort to avoid a long PVARP, which in turn would limit the upper rate limit, most dual-chamber pacemakers have the option of PVARP extension. With this feature, the pacemaker extends the PVARP, usually for one cycle, if the pacemaker recognizes an event as a premature ventricular contraction. Most pacemakers define a premature ventricular contraction as occurring when there are two consecutively sensed ventricular events without an intervening atrial event. Most dual-chamber pacemakers also have algorithms capable of interrupting an established pacemaker-mediated tachycardia. The pacemaker usually recognizes a pacemaker-mediated tachycardia as a paced ventricular rate at the programmed maximum tracking rate. The algorithms usually require that a predefined number of VV cycles at the maximum tracking rate occur to meet the definition of pacemaker-mediated tachycardia.



***e*FIGURE 74.10.1** Electrocardiographic example of a pacemaker-mediated tachycardia in a patient programmed to the VDD pacing mode. A premature ventricular contraction (*asterisk*) results in retrograde atrial activation. The retrograde P wave must occur in the postventricular atrial refractory period and does not result in ventricular pacing. In the absence of another intrinsic atrial event, a paced ventricular event occurs at the lower rate limit. The resulting retrograde P wave is sensed, with ventricular pacing occurring at a cycle length of approximately 500 ms, which corresponds to the programmed upper rate limit of 120 beats/min. (From Hayes DL, Osborn MJ. Pacing. A. Antibradycardia devices. In: Giuliani ER, Gersh BJ, McGoon MD, et al., eds. *Mayo Clinic practice of cardiology*, 3rd ed. St. Louis: Mosby, 1996:909–976, with permission of Mayo Foundation.)

Atrioventricular Interval

To properly program the AVI, the components of a normal AVI have to be understood (eFig. 74.10.2A).



***e*FIGURE 74.10.2 A:** The atrioventricular interval (AVI) should be considered a single interval with two subportions. The entire AVI corresponds to the programmed value (i.e., the interval after a paced or sensed atrial beat allowed before a ventricular pacing artifact is delivered). The initial portion of the AVI is the blanking period.

This interval is followed by the cross talk–sensing window. **B:** The initial portion of the AVI in most dual-chamber pacemakers is designated as the *blanking period*. During this portion of the AVI, sensing is suspended. The primary purpose of this interval is to prevent ventricular sensing of the leading edge of the atrial pacing artifact. Any event that occurs during the blanking period, even if it is an intrinsic ventricular event, as shown in this figure, is not sensed. In this example, the premature ventricular beat (PVC) that is not sensed is followed by a ventricular pacing artifact delivered at the programmed AVI and occurring in the terminal portion of the T wave. **C:** If the ventricular sensing circuit senses activity during the cross talk–sensing window, a ventricular pacing artifact is delivered early, usually 100 to 110 ms after the atrial event. This has been referred to as *ventricular safety pacing*, *110-ms phenomenon*, and *nonphysiologic AV delay*. (From Hayes DL, Levine PA. Pacemaker timing cycles. In: Ellenbogen KA, ed. *Cardiac pacing*. Boston: Blackwell Scientific, 1992:263–308, with permission.)

Ventricular Safety Pacing

Cross talk is the sensing of the pacemaker output in the unintended chamber (i.e., sensing the atrial pacing output on the ventricular sensing circuit). (Other noise sensed on the ventricular lead could also result in the appearance of cross talk.) The major concern is the sensing of an atrial stimulus in the ventricular sensing circuit. To prevent ventricular inhibition by cross talk, a blanking period begins in the ventricular channel simultaneously with the atrial stimulus. During this period, the sensing circuits are insensitive. This interval most commonly is in the range of 12 to 50 ms, depending on the pacemaker, and is programmable in many pacemakers. If the blanking period is too long, a spontaneous R wave, occurring soon after the atrial stimulus, is not sensed and a competitive ventricular stimulus is emitted (eFig. 74.10.2B). If the blanking period is too short, the possibility exists that cross talk and ventricular inhibition may result. Cross talk occurs more frequently as the voltage output of the atrial stimulus increases or, less commonly, as pulse duration increases. The potential for cross talk should be evaluated carefully and the blanking period appropriately lengthened if necessary.

In an effort to create the safest situation possible while retaining a relatively short blanking period, this period is followed in most dual-chamber pacemakers by another portion of the AVI, during which activity sensed in the ventricular channel results in forced early ventricular pacing (eFig. 74.10.2C). This occurrence has been referred to as *ventricular safety pacing* or the *nonphysiologic AV delay*. Both terms are descriptive, because the paced interval is often shorter than the programmed AVI and is present to ensure ventricular pacing when cross talk or other noise is sensed in the early portion of the AVI. Because the safety stimulus occurs at a fixed delay after the beginning of the safety pacing interval, the total AVI is likely to be abbreviated. Because several early pacemakers had a ventricular safety pacing interval of 110 ms, the designation *110-ms phenomenon* has also been used.

Differential Atrioventricular Interval

An option of a differential AVI is an attempt to provide a PR interval (i.e., the hemodynamic interval) of equal duration whether the atrial contraction is paced or sensed. The AVI following a sensed atrial event is shorter than that following a paced atrial event. In some pacemakers, the differential is programmable, and in others, a preset differential is used when this feature is programmed *on*.

Rate-Variable or Rate-Adaptive Atrioventricular Interval

Some DDDR pacemakers have the capability of shortening the AVI during AV sequential sensor-driven pacing. Rate-adaptive or rate-variable AVI is intended to optimize the cardiac output by mimicking the normal physiologic decrease in the PR interval that occurs in the normal heart as the atrial rate increases (118,119). There is ongoing investigative work to automatize the AVI (120).

Mode Switching

Mode switching refers to the ability of the pacemaker to change automatically from one mode to another in response to an inappropriately rapid atrial rhythm (121,122). Mode switching is particularly useful for patients with paroxysmal supraventricular rhythm disturbances. In the DDD or DDDR pacing modes, if a supraventricular rhythm disturbance occurs and the pathologic atrial rhythm is sensed by the pacemaker, rapid ventricular pacing may occur. Any pacing mode that eliminates tracking of the pathologic rhythm (i.e., DDI, DDIR, DVI, DVIR) also eliminates the ability to track normal sinus rhythm, which is usually the predominant rhythm. Mode switching avoids this limitation.

Current mode switching combinations include DDDR to VVIR, DDDR to DDIR, DDD to VVI, DDD to VVIR, and VDDR to VDD.

PROGRAMMING GOALS OF RATE ADAPTATION

The most important aspect of programming rate-adaptive pacemakers is optimization of the patient's chronotropic response. It is negligent to implant a rate-modulating pacemaker and program the sensor to on without assessing rate response. To date, all pacemakers capable of rate modulation are packaged with the sensor off. To effect rate modulation, the sensor must actively be programmed on. Although the manufacturer usually states nominal values for rate-response parameters, the nominal values are not appropriate for all patients. Some form of exercise is necessary. It is not necessary to use formal exercise testing routinely.

For patients who are limited to activities of daily living, we perform informal exercise testing (e.g., walking at a casual and brisk pace in the hospital corridor or in the outpatient facility). Alternatively, rate adaptation can be assessed with diagnostic tools incorporated within the pacemaker. There are many variations, including histograms of rate response and ambulatory monitoring capabilities.

If formal exercise testing is performed, the chronotropic exercise assessment protocol (123), as developed at The Cleveland Clinic, or a low-intensity exercise protocol may be preferable to a standard Bruce protocol. The chronotropic exercise assessment protocol allows for a gradual increase in speed and grade and thus mimics more levels of exercise that are apt to occur during activities of daily living. In determining appropriate heart-rate response, the patient's age and usual activities must be considered (124).

If the pacemaker is capable of automatically programming rate response parameters, the patient still must be evaluated to determine whether the automatically programmed parameters result in the appropriate rate response for the patient.

PACEMAKER COMPLICATIONS

Complications can occur directly from the implantation technique or from failure of a component of the pacing system (125). Many complications are related directly to the experience of the physician performing the implantation.

Implant-Related Complications

Most patients undergoing pacemaker implantation have some discomfort at the site of the incision in the early postoperative period, and mild analgesics may be required. Mild ecchymoses around the incision are common.

Access to the subclavian vein, commonly used for implantation of an endocardial pacemaker lead, is usually accomplished by subclavian vein puncture with a modified Seldinger technique. Because of the relationship of the subclavian vein with the apex of the lung, traumatic pneumothorax and hemopneumothorax are always possible when a subclavian puncture technique is used. Hemothorax can be caused by laceration of the subclavian artery and hemopneumothorax by laceration of the lung and subclavian artery.

The anatomy of the area must be considered before subclavian puncture is undertaken. In a patient with unusual anatomic relationships, specifically, concern that the subclavian vein may be displaced, peripheral injection of contrast media and fluoroscopic guidance of the subclavian puncture help minimize complications (126).

Other potential complications of subclavian puncture include inadvertent arterial puncture, air embolism, arteriovenous fistula, thoracic duct injury, subcutaneous emphysema, and brachial plexus injury. These risks are minimized by careful technique and contrast-guided puncture.

Hematoma Formation

Because local ecchymoses are common after pacemaker implantation, a small or large ecchymosis that is not expanding is treated with observation only. Discrete hematoma formation at the site must be managed on the basis of its secondary consequences. Aspiration or evacuation of the hematoma should be considered only if there is continued bleeding or potential compromise of the suture line or skin integrity or if pain from the hematoma cannot be managed with analgesics.

To avoid hematoma formation, patients should have a normal prothrombin time before pacemaker implantation, and heparin administration should have been discontinued long enough to allow a normal partial thromboplastin time. Ideally, the patient should not recently have taken aspirin or other platelet-inhibitory drugs. For patients who have been receiving platelet-inhibitory drugs, hemostasis during implantation is often quite difficult. Careful attention to hemostasis before closure of the incision should prevent complications in most patients taking platelet-inhibitory drugs.

For patients who require therapeutic anticoagulation, a 48-hour delay after implantation is ideal before resuming full heparinization. If heparinization is started in less than 48 hours, bleeding may be minimized by avoiding a bolus dose and beginning with a maintenance dose only. Warfarin (Coumadin) usually can be administered safely 24 hours after implantation, but 48 hours is preferable if it does not compromise the patient's condition. Warfarin treatment should be started at the patient's maintenance dose and not at the higher doses that would be used to initiate therapy. The absolute timing for reinstitution of anticoagulant therapy varies from patient to patient. Anticoagulation at greater than therapeutic levels can result in late hematoma formation.

Arterial Lead Puncture and Cannulation

Introduction of the lead(s) into the subclavian artery, the aorta, and the left ventricle usually is readily recognized because of the pulsatile flow of saturated blood. If this is recognized promptly and the needle removed, it is unlikely that a problem will occur. Hemothorax may occur if the artery is lacerated, but this is an extremely rare complication. However, entry into the artery may not be recognized because of desaturation of the arterial blood, making it appear venous, or because of loss of pulsatile arterial flow due to hypotension or diminution of the arterial pulse pressure. Once the lead is within the great arteries, its passage into the left ventricle is as easy as passage into the right ventricle via the venous system.

Usually, entry into the artery can be recognized fluoroscopically as passage into the left ventricle, as viewed in the anteroposterior projection, and is significantly medial to the entry into the right ventricle. If a lateral view is used, a right ventricular lead will be anterior (i.e., posterior to the sternum), and a left ventricular lead will be in the posterior aspect of the heart.

In right ventricular pacing, the electrocardiogram shows a left bundle branch block pattern, and during left ventricular pacing, it shows a right bundle branch block pattern.

A pacing lead may also be placed in the left ventricle by passing it across an unsuspected atrial or ventricular septal defect. In patients with a ventricular septal defect, endocardial pacing should be avoided because small emboli potentially could cross the ventricular septal defect, causing symptoms in the arterial circulation.

Although left ventricular pacing may be permanently secure, it has been associated with thrombus formation, embolization, and, consequently, stroke. Reports of long-term uncomplicated left ventricular endocardial pacing exist, but the risk of embolization continues. The left ventricular lead should be removed if left ventricular placement is recognized early after implantation. If it is recognized after long-term uncomplicated pacing and anticoagulation can be performed, it may be best to leave the endocardial lead in place.

Lead Perforation

Ventricular perforation may be asymptomatic. The only sign may be a rising stimulation threshold. In other patients, the signs may include (a) right bundle branch block pattern from a lead placed in the left ventricle (depending on lead position, it is also possible to see this pattern when the lead is within the right ventricular cavity); (b) contraction of intercostal muscle or the diaphragm; (c) friction rub after implantation; and (d) pericarditis, pericardial effusion, or cardiac tamponade.

Ventricular perforation may be suggested by radiographic, electrocardiographic, and echocardiographic findings. After the perforation has been identified, lead withdrawal and repositioning usually are uncomplicated and rarely result in pericardial bleeding or tamponade.

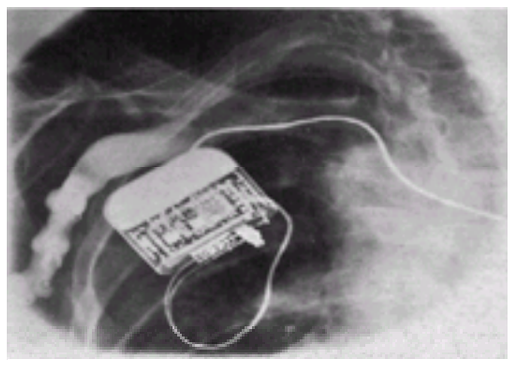
If the patient has mild symptoms or signs compatible with lead perforation (e.g., pericardial pain, friction rub) but a persistent perforation cannot be identified, it is reasonable to observe the patient. If the symptoms or signs resolve over 24 to 48 hours, it probably will not be necessary to reposition the lead. If an echocardiogram shows a small pericardial effusion but no definite perforation, serial echocardiograms should be performed to confirm that the effusion is not hemodynamically significant or enlarging.

Lead Damage

Leads may be damaged acutely by sharp instruments or by the stylets. Such damage is infrequently recognized, and the true frequency with which it occurs is unknown.

Venous Thrombosis

Partial or silent inconsequential thrombosis following transvenous lead placement is not uncommon and usually is clinically insignificant. Such partial or silent thrombosis may limit venous access at the time of pacing system revision (*e*Fig. 74.10.3) (127).



***e*FIGURE 74.10.3** Peripheral dye injection reveals contrast media in a dilated axillary/subclavian vein that subsequently is occluded at or near the lead entry site. (From Hayes DL, Holmes DR Jr, Furman S. Permanent pacemaker implantation. In: Furman S, Hayes DL, Holmes DR Jr, eds. *A practice of cardiac pacing,* 3rd ed. Mount Kisco, NY: Futura, 1993:261–307, with permission.)

If thrombosis involves the superior vena cava, axillary vein, or area around the pacemaker lead in the right atrium or right ventricle, several problems can develop, including occlusion of the superior vena cava and superior vena cava syndrome; thrombosis of the superior vena cava, right atrium, or right ventricle, with hemodynamic compromise or pulmonary embolism; or symptomatic thrombosis of the subclavian vein, with an edematous, painful upper extremity.

Lead Fracture

Lead fractures most often occur adjacent to the pacemaker or near the site of venous access (i.e., at a stress point). Although uncommon, direct trauma may damage the pacing lead. If a bipolar lead fractures and the pacemaker is polarity programmable, it may be possible to restore pacing by reprogramming to the unipolar

configuration. This is a short-term solution and should not be a substitute for replacing the lead.

Lead Insulation Defect

Insulation defects and conductor fractures may be caused by crush injury, specifically at the costoclavicular space, when the lead is placed via the subclavian puncture technique. In bipolar coaxial leads, the insulation defect often occurs internally (i.e., the layer of insulation between coils) as opposed to an external, outer surface insulation defect.

Thresholds, lead impedance, and electrograms are helpful in distinguishing insulation defect from conductor fracture. This information may be obtained with measurements made during implantation or with the telemetric capabilities of many pacemakers (*e*Table 74.6.1).

*e*TABLE 74.6.1 INTRAOPERATIVE EVALUATION OF PACING SYSTEM

Defect	Voltage threshold	Current threshold	Lead impedance
Wire fracture	High	High, normal, or low	High
Insulation break	Low	High	Low
Lead dislodgment	High	High	Normal
Exit block	High	High	Normal

Exit Block

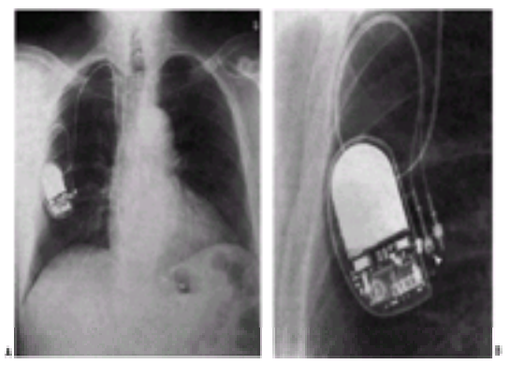
The most commonly accepted clinical definition of exit block is high pacing thresholds, often progressive, that cannot be explained on the basis of radiographic dislodgment or perforation. (If normal thresholds are achieved and maintained after the lead has been repositioned, then the term *exit block* does not apply.) Exit block is uncommon and appears to represent an abnormality at the interface of myocardial tissue and the electrode. Steroid-eluting leads are often effective in preventing exit block.

Lead Dislodgment

Active and passive fixation mechanisms common to current pacing leads have significantly decreased the incidence of lead dislodgment. Dislodgment has been classified by some as *macrodislodgment* and *microdislodgment*. Macrodislodgment is evident radiographically, and microdislodgment is not. Adequate lead position is assessed by postero-anterior and lateral chest radiographs. It must be remembered that on chest radiographs, lead placement may appear excellent in patients with microdislodgment.

Loose Set-Screw Connection

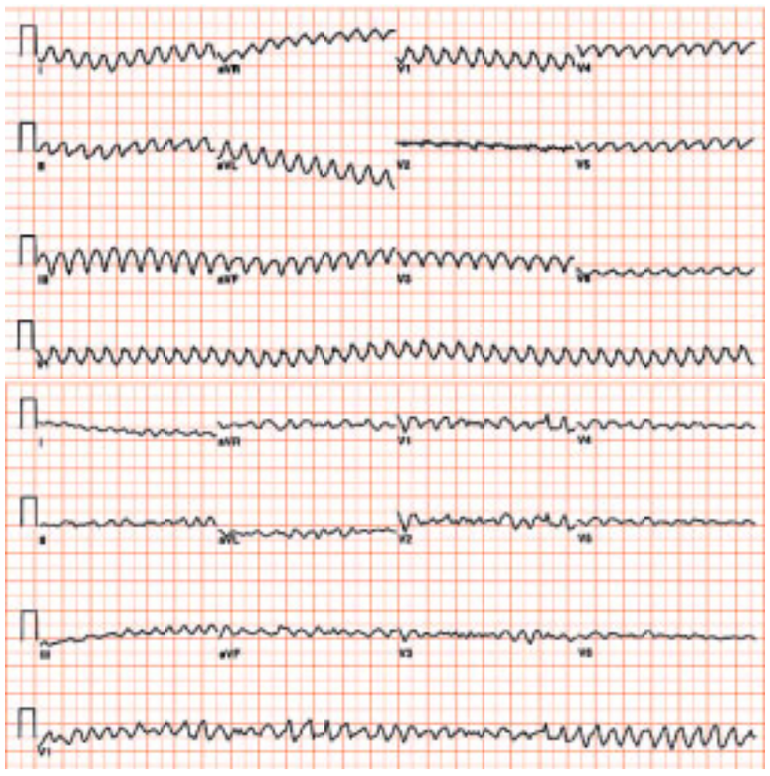
Intermittent or complete failure of output can occur because of a loose connection at the pacing lead–connector block interface (*e*Fig. 74.10.4). This usually occurs because the lead was secured inadequately at the time of implantation. When a connection is loose, manipulating the pacemaker may reproduce the problem. The poor connection may be evident radiographically.



***e*FIGURE 74.10.4 A:** Postero-anterior chest radiograph of a patient with a VVI pacemaker and a bifurcated bipolar ventricular lead. The patient presented with recurrent near syncope and intermittent failure to output. **B:** Close-up of the pacemaker reveals that the lower connector pin is not securely in the connector block (*arrowhead*). (From Hayes DL. Pacemaker complications. In: Furman S, Hayes DL, Holmes DR Jr, eds. *A practice of cardiac pacing*, 3rd ed. Mount Kisco, NY: Futura, 1993:537–569, with permission.)

Pacemaker-Related Arrhythmias

Supraventricular and ventricular arrhythmias are often encountered during pacemaker implantation and are usually inconsequential.



Ventricular flutter (A). Same patient with degeneration into ventricular fibrillation (B).

*Tip extrasystol*es may be seen in the early postimplantation period. These are ventricular complexes with morphology similar to that of the paced beats, because they originate at the same site as the paced beats but are not preceded by a pacemaker stimulus (Fig. 74.11). Tip extrasystoles occur most often during the first 24 to 48 hours after implantation and usually resolve spontaneously. Rarely is it necessary to suppress tip extrasystoles pharmacologically.

FIGURE 74.11 Electrocardiographic tracing from a patient with a newly implanted dual-chamber pacemaker. The paced beats are followed by ventricular complexes of similar morphology. The patient had not displayed ventricular ectopy before implantation, and the tip extrasystoles had resolved the morning after implantation.

Runaway pacemaker describes a sudden increase in pacing rate caused by circuit malfunction. This phenomenon is rare with current pacemakers. In more recent years, the rare reports of runaway pacemaker have usually described it as a complication of pacemaker exposure to therapeutic radiation, with subsequent circuit damage (128).

Pacing either cardiac chamber could induce rhythm disturbances if pacing occurred during a vulnerable portion of the cardiac cycle. This could happen with asynchronous pacing (VOO, AOO, DOO) if a pacing stimulus occurred during the vulnerable portion following intrinsic depolarization. From a practical standpoint, induction of atrial or ventricular arrhythmias during asynchronous pacing is uncommon. Historically, the induction of atrial rhythm disturbances was seen with DVI pacing, which allowed atrial pacing but not atrial sensing, and ventricular rhythm disturbances were described with VAT pacing, which allowed ventricular pacing but not ventricular sensing.

Endless-loop tachycardia is another well-recognized pacemaker-related rhythm disturbance (see previous discussion). In the presence of intact VA conduction, any event that uncouples AV synchrony may allow retrograde atrial activation. (The most common stimulus for VA conduction is a premature ventricular contraction.) If the atrium is refractory at the time of VA conduction, the atrium will be depolarized and the atrial depolarization will initiate the AVI. Paced ventricular depolarization may once again result in VA conduction, establishing a reentrant or endless-loop tachycardia (117).

Extracardiac Stimulation

Extracardiac stimulation usually involves the diaphragm or pectoral muscle. Diaphragmatic stimulation may be due to direct stimulation of the diaphragm (usually stimulation of the left hemidiaphragm) or stimulation of the phrenic nerve (usually stimulation of the right hemidiaphragm). At the time of implantation, if any extracardiac stimulation is noted when pacing at 10 V, the pacing lead should be repositioned. Because this usually is tested with the patient supine, it does not eliminate the possibility of diaphragmatic stimulation when the patient is upright. Diaphragmatic stimulation occurring during the early postimplantation period may be due to either microdislodgment or macrodislodgment of the pacing lead. (Although perforation of the myocardium by the pacing lead may result in diaphragmatic pacing, perforation is uncommon.) Stimulation may be minimized or alleviated by decreasing the voltage output or pulse width, or both. (An adequate pacing margin of safety must be maintained after decreasing the output parameters.) Local muscle stimulation occurs more often with unipolar than with bipolar pacemakers and usually is noted in the early postimplantation period.

Pectoral muscle stimulation may also be due to an insulation defect of the pacing lead, current leakage from the connector or sealing plugs, or erosion of the pacemaker's protective coating. If the problem is due to an insulation defect on either a unipolar pacemaker or the pacemaker lead, the stimulation may be minimized by decreasing the voltage output or pulse width or both, but it may be necessary to replace the defective portion of the system. If pectoral muscle stimulation occurs in a polarity-programmable pacemaker that is programmed unipolar, reprogramming to the bipolar configuration may alleviate the problem.

Erosion

Erosion is an uncommon complication that usually occurs because of an indolent infection. With the small size of current pacemakers, it is unlikely that erosion is due to insufficient pocket size, but this is possible.

If the patient seeks medical attention before the pacemaker has eroded through the skin, it may be possible to revise the pocket and reimplant the pacemaker (129). Impending erosion (i.e., skin thinned to the point of transparency) should be managed as an emergency. When any portion of the pacemaker has eroded through the skin, the only choice is surgical revision of the pacemaker site. If associated with infection, the entire system (both the pacemaker and the lead) probably will need to be removed and a completely new pacing system implanted at a clean site. In rare situations, it may be possible to revise the pacer site, enlarge the pocket, and fashion a satisfactory skin flap. Revision can be undertaken only in the absence of infection. Because infection may be present even if there is no purulent material, the pocket should be cultured and proven negative before pocket revision. Adherence of the pacemaker to the skin strongly suggests the presence of an infection, and salvage of the site may not be possible.

Pacemaker System Infection

The incidence of infection after pacemaker implantation should be less than 2% and, in most series, has been less than 1%. Careful attention to surgical details and sterile procedures are paramount in avoiding infection of the pacemaker site. Prophylactic antibiotic therapy before implantation and in the immediate postoperative period is controversial (130). Most studies have not shown any significant difference in the rate of infection between patients who have had prophylactic antibiotic treatment and those who have not. Irrigation of the pacemaker pocket with an antibiotic solution at the time of implantation probably is more important in preventing infection.

VIDEO

Video 74.1 Pacemaker vegetation. In this transesophageal echocardiogram, a huge mass is seen attached to the pacemaker wire as it passes through the right atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pacemaker infection must be recognized and treated properly. It may appear as local inflammation and abscess formation in the area of the pacemaker pocket, as erosion of part of the pacing system through the skin with secondary infection, or as fever associated with positive findings on blood culture, with or without a focus of infection elsewhere. The most common clinical presentation is infection around the generator; septicemia is an uncommon mode of presentation. Early infections usually are caused by *Staphylococcus aureus*, are aggressive, and are often associated with fever and systemic symptoms. Late infections commonly are caused by *Staphylococcus epidermidis* and usually are more indolent, without fever or systemic manifestation. Treatment for both organisms requires removal of the entire infected pacing system, pacemaker and leads. Many other organisms have been reported in pacemaker system infections.

There is controversy about how to proceed after the infected system has been removed (131). In the absence of septicemia, a one-stage surgical approach involves implantation of a new pacing system at a distant clean site after explantation of the infected pacing system. In the presence of septicemia, or as a preferred approach (regardless of sepsis), others favor removal of the infected system, an interim period of temporary pacing (if required), and antibiotic management in the interim, with implantation of a new system at a later date.

Retained Lead Fragments

Multiple leads usually can safely be left in place as long as none of them has been part of an infected system (132). If the pacing system is infected, it is essential that

all the hardware be removed.

Lead Extraction

A detailed description of extraction techniques is beyond the scope of this textbook, but these techniques include various approaches: simple traction, locking stylet/telescoping sheaths with countertraction, laser-assisted extraction, electrodessication-assisted extraction, and open surgical techniques (133,134).

Pacemaker Allergy

Pacemaker allergy is a rare but reported complication (135). Usually, the allergy is to the pacemaker can, but the patient may be allergic to any exposed portion of the pacing system. The most common materials used in a pacing system that may be responsible for an allergy include titanium, epoxy, silicone rubber, and polyurethane. Proof of such an allergy requires sophisticated allergy testing, and correction of the problem may require changing to another type of system. Some of the cases of allergy, in fact, are low-grade *S. epidermidis* infections, which should be treated as infections rather than as allergies. No diagnosis of allergy should be made until infection has been ruled out thoroughly.

TROUBLESHOOTING ELECTROCARDIOGRAPHIC ABNORMALITIES

Electrocardiographic abnormalities in a patient with pacing can be grouped broadly into failure to capture, failure to output, undersensing, oversensing, and inappropriate rate change (136,137).

Failure to capture indicates that a pacing artifact is present without subsequent cardiac depolarization (Fig. 74.12). The differential diagnosis for failure to capture includes the following items:

FIGURE 74.12 Electrocardiographic tracing from a patient with a DDD pacemaker. The second ventricular pacing artifact fails to result in ventricular depolarization, failure to capture, and is followed by an intrinsic ventricular escape beat after a PR interval of approximately 300 ms. AP, atrial-paced event; AS, atrial-sensed event; VP, ventricular-paced event; VS, ventricular-sensed event.

- High thresholds with an inadequately programmed output
- Partial conductor coil fracture
- Insulation defect
- Lead dislodgment or perforation
- Impending total battery depletion
- Functional noncapture
- Poor or incompatible connection at connector block
- Circuit failure
- Air in pocket (unipolar pacemaker)
- Increased thresholds due to drugs or metabolic abnormality

Failure to output is sometimes used synonymously with *failure to capture*, but this is not appropriate. Failure to output is often due to oversensing and inhibition of output, but it also can be due to true failure to output from the pacemaker or circuit interruption such that the electrical signal cannot reach the heart (Fig. 74.13). The differential diagnosis for failure to output includes the following items:

FIGURE 74.13 Electrocardiographic tracing from a patient with a DDD pacemaker with a lower rate of 55 beats/min. The tracing begins with atrioventricular (AV) sequential pacing for two cycles. The next atrial pacing artifact results in atrial capture but is not followed by a ventricular pacing artifact at the programmed AV interval. (The programmed AV interval can be determined from the two initial paced cycles.) Following the intrinsic ventricular beat is a pause of 1,520 ms, which is greater than the programmed lower rate of 55 beats/min, or 1,090 ms. The first event that is recognized by the pacemaker is a P wave, which is designated as an atrial beat that occurs within a refractory period (AR). Whatever extrinsic, noncardiac event that has been oversensed has initiated a refractory period(s), because there is no evidence of any intrinsic cardiac event that has initiated the refractory period. AP, atrial-paced event; VP, ventricular-paced event; VS, ventricular-sensed event.

- Circuit failure
- Complete or intermittent conductor coil fracture
- Intermittently or permanently loose set screw
- Internal insulation failure (bipolar lead)
- Oversensing any noncardiac activity
- Total battery depletion
- Lack of anodal connector contact (examples include unipolar lead in bipolar generator, bipolar lead in a pacemaker programmed unipolar, air in the pocket of a unipolar device, unipolar pacemaker not in the pocket)
- Cross talk

The differential diagnoses of failure to capture and failure to output overlap. For example, electrocardiographic manifestations of a conductor coil fracture may include failure to capture due to significant leakage of current at the incomplete fracture site, leaving inadequate current to result in stimulation. Nonetheless, the pacemaker stimuli may appear. Alternatively, escaping current may be sensed by the pacemaker and inhibit pacemaker output. If the conductor coil is completely fractured, rendering the circuit incomplete, no pacemaker output will be detected on the electrocardiogram. Also, secondary sensing abnormalities may be noted.

Insulation defects may also present with oversensing and failure to output or with failure to capture, although the most common presentation of insulation failure is sensing abnormalities.

As the pacemaker battery reaches the end stages of depletion, either failure to capture due to dropping voltage output or failure to output due to total battery depletion may be seen. This degree of battery depletion could and should be avoided with appropriate pacemaker follow-up.

Apparent failure to capture will be noted if a pacemaker stimulus occurs during the refractory period of a spontaneous beat. This is referred to as *functional noncapture*.

Sensing abnormalities can be divided into true abnormalities, including undersensing (failure to recognize normal intrinsic cardiac activity; Fig. 74.14), oversensing (see Fig. 74.13), unexpected sensing of intrinsic or extrinsic electrical signals, and functional sensing abnormalities. The differential diagnosis for undersensing includes the following items:

FIGURE 74.14 Electrocardiographic tracing from a patient with a DDD pacemaker programmed to a lower rate of 85 beats/min. There is atrial failure to sense throughout the tracing. The arrow indicates an atrial-paced event (AP) that occurs immediately after an intrinsic atrial event and does not represent failure to capture but functional noncapture. When atrioventricular sequential pacing does occur, the atrioventricular interval is approximately 100 ms. This represents ventricular safety pacing that occurs because the intrinsic ventricular beat is occurring in the cross talk–sensing window. VS, ventricular-sensed event.

- Morphology of intrinsic event different from that measured at implantation
- Lead dislodgment or poor lead positioning
- Lead insulation failure
- Circuit failure
- Magnet application
- Malfunction of reed switch
- Electromagnetic interference
- Battery depletion

Most commonly, true undersensing is due to lead dislodgment or inadequate initial lead placement. Sensing abnormalities commonly are due to insulation defects and uncommonly to intermittent conductor fracture.

Occasionally, a normally functioning pacing system fails to detect atrial or ventricular extrasystoles. The intrinsic events measured at the time of implantation generate an electrogram at the electrode tip. If an extrasystole is occurring elsewhere in the heart, the sensing vector would be different from that of the normal intrinsic beat and the resulting voltage generated may not be great enough to be sensed by the pacemaker. This cannot be anticipated unless extrasystoles of the same morphology occur during implantation and can be measured. It is reasonable to attempt reprogramming the sensitivity to allow sensing of extrasystoles, but if this is unsuccessful, it is rarely, if ever, necessary to reposition the lead for this abnormality.

Functional undersensing is present when an intrinsic cardiac event is not sensed because it falls within a programmed refractory period (136). For example, if an intrinsic atrial event occurs within the PVARP, the event will not and should not be sensed. However, if the timing cycle is not understood thoroughly, it may appear as though there is true undersensing.

Fusion and *pseudofusion* beats occur as a result of superimposition of an ineffective pacemaker stimulus on a spontaneously occurring P wave or QRS complex (Fig. 75.15). Fusion is present when the morphology of the cardiac event is a hybrid of the intrinsic morphology and the paced morphology. Pseudofusion is present when the pacemaker artifact occurs late enough that the intrinsic morphology is not deformed. It usually is the consequence of pacemaker discharge during the refractory period of atrial or ventricular activity before sufficient intracardiac voltage is generated to activate the sensing circuit. This would be expected to occur when the pacing rate and the intrinsic rate are similar. Pseudofusion beats also may be the result of the delayed arrival of ventricular activity in a VVI system because of intraventricular conduction abnormalities at the site of the sensing electrodes.

FIGURE 74.15 Electrocardiographic tracing from a patient with a VVI pacemaker. The first two complexes represent fully paced ventricular depolarizations. The third and fourth events result in different paced morphology and represent fusion beats. This is followed by failure to capture and a single ventricular escape. VP, ventricular-paced event.

Every pacing mode has a defined lower rate limit, and dual-chamber pacemakers, as well as rate-adaptive pacemakers, also require a defined upper rate limit. One must be familiar with the timing cycle of a particular pacing mode as well as any idiosyncrasies of the specific pacemaker to determine whether the paced rate is appropriate. There are multiple causes of a paced rate that appear to be different from the programmed rate. The differential diagnosis includes the following items:

- Circuit failure
- Battery failure
- Magnet application
- Hysteresis (Fig. 74.16)
- Cross talk
- Undocumented reprogramming of the pacemaker
- Oversensing
- Runaway
- Malfunction of the electrocardiographic recording equipment, alteration in paper speed

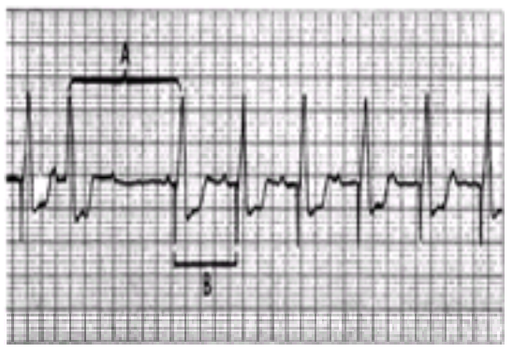


FIGURE 74.16 Electrocardiographic tracing from a patient with a VVI pacemaker programmed to a lower rate of 60 beats/min and hysteresis rate of 40 beats/min. The longer cycle **(A)** follows an intrinsic ventricular beat. The shorter cycle **(B)** represents the programmed lower rate of 60 beats/min (1,000 ms). (From Hayes DL. Pacemaker electrocardiography. In: Furman S, Hayes DL, Holmes DR Jr, eds. *A practice of cardiac pacing*, 3rd ed. Mount Kisco, NY: Futura, 1993:309–359, with permission.)

Drugs may affect sensing and pacing thresholds and result in electrocardiographic abnormalities (136). Although many drugs have been reported to affect pacing thresholds, the class IC agents are the only drugs that commonly cause a problem. Encainide, flecainide, propafenone, and moricizine have the potential to increase pacing thresholds. If these drugs are administered to a patient with a pacemaker, treatment should be monitored for an increase in pacing threshold. Class IC agents also have been reported to cause sensing abnormalities.

Electrolyte and metabolic abnormalities may also affect pacing and sensing thresholds. Hyperkalemia is the electrolyte abnormality that most commonly causes clinically significant problems, but severe acidosis or alkalosis, hypercarbia, severe hyperglycemia, hypoxemia, and myxedema should also be considered (136).

PACEMAKER DIAGNOSTICS

Various diagnostic functions are available in many current generation pacemakers and can be extremely helpful during pacemaker troubleshooting. Diagnostic capabilities vary widely from pacemaker to pacemaker (e.g., real-time telemetry of programmed parameters and battery status, lead impedance, electrograms, annotated electrocardiograms, histograms, or long-term recordings of rate variations, or a combination of these). A full discussion of this topic is beyond the scope of this textbook, but outstanding summaries of pacemaker diagnostics are available (138).

ELECTROMAGNETIC INTERFERENCE

Electromagnetic interference can be defined as any signal, biologic or nonbiologic, occurring within a frequency spectrum that may be detected by the sensing circuitry of the pacemaker. Electromagnetic interference can result in rate alteration, sensing abnormalities, magnet mode response, or reprogramming.

Biologic signals that may be responsible for oversensing include T waves, myopotential interference, afterpotential delay, and P waves. Isoelectric extrasystoles may give the appearance of oversensing (136,137).

Although there are many potential nonbiologic sources of electromagnetic interference, few sources of electromagnetic interference are truly a threat to patients with a pacemaker. Hospital sources of potentially significant electromagnetic interference are listed in Table 74.7. The effects of electrocautery and guidelines for cardioversion and defibrillation in the patient with a pacemaker are given in Table 74.8. There are additional potential nonbiologic sources of electromagnetic interference and oversensing that are listed in *e*Table 74.8.1 (139).

Electrocautery/cardiovascular/defibrillation
Magnetic resonance imaging
Lithotripsy
Radiofrequency ablation
Electroshock therapy
Diathermy

TABLE 74.7 SOURCES OF ELECTROMAGNETIC INTERFERENCE IN THE HOSPITAL ENVIRONMENT

Reprogramming
Permanent damage to the pulse generator
Pacemaker inhibition
Reversion to a fall-back mode, noise reversion mode, or electrical reset
Myocardial thermal damage
Cardioversion/defibrillation of the pacemaker patient
Ideally place paddles in the anterior-posterior position
Try to keep paddles at least 4 in. from the pulse generator
Have the appropriate pacemaker programmer available
Interrogate the pacemaker following the procedure

TABLE 74.8 EFFECTS OF ELECTROCAUTERY

*e*TABLE 74.8.1 POTENTIAL SOURCES OF ELECTROMAGNETIC INTERFERENCE

Source	Pacer damage	Total inhibition	One-beat inhibition	Asynchronous/noise	Rate increase
Acupuncture	N	Y	Y	Y	N
Airport detector	N	N	Y	N	N
Antitheft device	?	?	Y	Y	?
Arc welder	N	Y	Y	Y	N
Cardioversion	Y	N	N	Y	Y
Cautery/coagulation	Y	Y	Y	Y	Y[ab]
CB radio	N	N	Y	N	N
Cellular telephone	N	Y	Y	Y	Y
Computed tomographic scanner	N	N	N	N	N
Defibrillation	Y	N	N	Y	Y
Diathermy	Y	Y	Y	Y	Y
Drill, electric	N	N	Y[c]	N	N

Electric blanket	N	N	Y[c]	N	N
Electric shaver	N	N	Y[c]	N	N
Electric switch	N	N	Y[c]	N	N
Electroconvulsive therapy/electroshock therapy	N	Y	Y	Y	Y[c]
Electrolysis	N	N	Y	Y	N
Electrotome	N	N	Y[c]	N	N
Ham radio	N	N	Y	N	N
Heating pad	N	N	N	Y	N
Lithotripsy	Y[b]	Y[c]	Y[c]	Y[c]	Y[d]
Magnetic resonance imaging	?	N	Y	Y	Y
Metal detector	N	N	Y[c]	N	N
Microwave	N	N	N	N	N
Positron emission tomographic scanner	?	N	N	N	N
Power line	N	N	N	Y	N
Radar	N	N	Y[c]	N	N
Radiation, diagnosis	N	N	N	N	Y
Radiation, treatment	Y	N	N	N	Y
Radiofrequency ablation	Y	Y	N	N	Y
Television remote	N	N	N	N	N
Transcutaneous electrical nerve stimulator	N	Y	N	Y	Y
Ultrasound, diagnosis	N	N	N	N	N

[a]Impedance-based pulse generators.
[b]Piezoelectric crystal-based pulse generators.
[c]Remote potential for interference.
[d]DDD mode only.
Modified from Telectronics: electromagnetic interference and the pacemaker patient. *Technical Notes* May 1991;110.

Electromagnetic interference during the last portion of the refractory period of a pacemaker, the *noise-sampling period*, can disable the demand function of the pacemaker and cause reversion to a fixed-rate mode for one cycle, creating the impression of undersensing.

Currently, there is considerable interest in cellular telephones (140) and antitheft devices (141) as potential sources of electromagnetic interference. The information available suggests that analog cellular telephones are safe for patients with pacemakers. Digital cellular telephones have a greater potential for electromagnetic interference, and pacemaker-dependent patients who use a telephone with digital technology should exercise caution. If the patient avoids having the telephone over the pacemaker, either from random motion of the telephone or from carrying the activated telephone in a breast pocket over the pacemaker, it is unlikely that any adverse clinical event will occur; however, research is being conducted on this question.

Antitheft devices also potentially can interfere with pacemakers (142,143 and 144). Patients with a pacemaker or an implantable cardioverter defibrillator (ICD) should be aware of electronic equipment for surveillance of articles and should avoid leaning on or lingering near such devices. If the patient passes through the equipment at a normal pace, adverse effects are unlikely. Any patient who feels unusual in any way when near electronic surveillance equipment should move away.

Hospital sources of potentially significant electromagnetic interference are electrocautery, cardioversion, defibrillation, magnetic resonance imaging, lithotripsy, radiofrequency ablation, electroshock therapy, and diathermy. The most important aspect of pacemaker or ICD care after exposure to any of these sources of electromagnetic interference is to reassess the device to be certain that the programmed parameters have not been changed.

Frequently, the question is asked about how to manage a patient with a pacemaker or ICD during a surgical procedure, given the potential effects of electrocautery and guidelines for cardioversion and defibrillation. Routine interrogation of the device and deactivation of ICD therapy should be performed before the operation. After the operation, the device should be reinterrogated and ICD therapy reinitiated. (During the time ICD therapy is off, the patient must be monitored.) For pacemaker-dependent patients, it is reasonable to program the pacemaker to an asynchronous pacing mode, VOO or DOO, or to achieve the same effect by placing a magnet over the pacemaker throughout the procedure. The potential effects of electrocautery are myocardial thermal damage, reprogramming, permanent damage to the pulse generator, pacemaker inhibition, and reversion to a fall-back mode, noise reversion mode, or electrical reset.

LIMITATIONS FOLLOWING PACEMAKER IMPLANTATION

In the early postimplantation period, it is reasonable to limit motion of the ipsilateral shoulder and arm. However, complete immobilization may result in a frozen shoulder and should be discouraged. Complete range of motion can be resumed in 2 to 4 weeks.

Although most patients with a pacemaker should be able to resume driving, reasonable advice is to wait 1 or 2 weeks after pacemaker implantation, for medicolegal reasons.

Few, if any, activities are totally contraindicated after implantation. Currently, magnetic resonance imaging is usually denied to patients with a pacemaker.

Any activity with the potential for creating a significant electromagnetic field near patients with a pacemaker should be approached with caution. The classic warnings given to these patients include avoidance of arc welding and working directly over combustion engines. Although pacemakers progressively have become more resistant to electromagnetic interference, caution is still warranted. If the livelihood or hobby of a pacemaker-dependent patient involves strong electromagnetic fields, pacemaker function should be monitored during exposure to the electromagnetic interference. The initial exposure should be controlled, with an assistant present to prevent sustained exposure should the electromagnetic interference result in sustained inhibition of the pacemaker. During exposure to electromagnetic interference, pacemaker function may be monitored with an ambulatory electrocardiogram or by monitoring capabilities incorporated within the pacemaker.

Younger patients with a pacemaker should be cautioned about contact sports. Although not absolutely contraindicated, the patient needs to understand that the system, especially the pacing lead(s), can be damaged by direct trauma.

FOLLOW-UP OF PATIENTS WITH PACEMAKERS

After the pacemaker has been implanted, the physician who performed the procedure or the institution where it was performed should assume responsibility for or arrange follow-up. Follow-up may be performed at the institution or at several commercial pacemaker follow-up centers.

There are several follow-up requirements (16,145). Although many centers have specific follow-up routines, the exact timing and location of follow-up, as well as programming routines, need to be established by the individual center to best meet its needs and institutional capabilities. The following requirements are included:

- Initial programming and optimization of rate response for all rate-adaptive pacemakers should be done.
- In-clinic follow-up should be done at 2 to 4 months to reassess energy output needs: Increase output if safety margin is inadequate, and decrease output to increase pacemaker longevity when appropriate. At the same follow-up visit, rate-adaptive parameters should be reassessed. Special attention also should be given to the incision and pacemaker pocket.
- Routine follow-up should assess battery status. In the United States, most patients have transtelephonic follow-up. The approved Medicare schedule for transtelephonic monitoring is more frequent than that followed by some centers. Regular transtelephonic follow-up should occur every 3 months until the first sign of battery depletion indicators (i.e., change in magnet rate or widening of pulse width), at which time the patient begins calling monthly until elective replacement indicators are reached; this has been shown to be an effective and safe follow-up schedule. Routine transtelephonic transmissions should include electrocardiographic monitoring with and without a magnet. Ideally, these records should be stored and available for retrieval for subsequent comparison should questions arise about change in pacemaker function.
- All patients should be reevaluated in the clinic setting at least once annually. Depending on the individual center's transtelephonic schedule, the center may prefer to have the patient assessed in the clinic more frequently.

Ideally, the pacemaker center will have all of the patient data in a computer database. This allows the nurse or technician who receives a transtelephonic call or the health care specialist evaluating the patient in the clinic to retrieve data about the last follow-up, the most recent measured pacing parameters, appropriate magnet

response of the pacemaker, age of the pacemaker and lead, programmed settings, and so forth.

TEMPORARY PACING

Familiarity with temporary cardiac pacing is essential for those involved in permanent cardiac pacing and the treatment of patients in coronary care units and postoperative units. Knowledge of the indications, techniques, and routes of implantation, postinsertion management, and risk-benefit ratio for each patient is required for safe, reliable pacing.

Temporary pacing may be used for diagnostic or therapeutic purposes (146). Most commonly, it is used for short-term management of symptomatic bradycardias, either as a bridge to permanent pacing or for self-limited bradycardias (e.g., bradyarrhythmias associated with Lyme disease).

The indications for temporary pacing include both bradycardia and tachycardia (Table 74.9). There are two general categories: (a) patients with symptomatic bradycardia, and (b) patients with asymptomatic bradycardia or conduction defects. The decision to proceed with temporary pacing depends on assessment of the risk of development of symptomatic bradycardia. With the advent of reliable and readily available external temporary pacing, it is less common to place a temporary transvenous pacemaker in patients with asymptomatic conduction disturbances.

Third-degree atrioventricular block
Symptomatic congenital complete heart block
Symptomatic acquired complete heart block
Postoperative symptomatic complete heart block
Symptomatic second-degree atrioventricular block
Acute myocardial infarction with:
Symptomatic bradycardia
Complete heart block
New bundle branch block with transient complete heart block*
Alternating bundle branch block*
Sinus node dysfunction
Symptomatic bradyarrhythmias
Tachycardia, prevention or treatment
Bradycardia-dependent arrhythmias
Long QT syndrome with ventricular arrhythmias

*If asymptomatic, could consider observation and readily available external pacing. Transvenous temporary pacing only if external pacing is required.

TABLE 74.9 INDICATIONS FOR TEMPORARY PACING

Temporary Pacemaker Placement

Temporary pacing usually is performed by a transvenous approach. The clinical setting determines the urgency with which pacing is required and, to a certain extent, the venous access chosen. The basic equipment required for temporary transvenous pacing includes a surgical pack with instruments to obtain venous access, a pacing catheter, an external pulse generator, and, under usual circumstances, a procedure room for placement.

Various temporary pacing catheters are available. Although dual-chamber temporary pacing can readily be accomplished, single-chamber ventricular pacing is the most common approach.

Management of Temporary Pacemakers

Patients with transvenous temporary pacemakers must have continuous electrocardiographic monitoring to ensure continued reliable pacing and to detect any other significant arrhythmias.

Pacing and sensing thresholds should be checked daily. Changing thresholds may be the first manifestation of lead dislodgment. Chest radiographs and electrocardiograms should be obtained periodically, and physical examination should be performed daily to identify any complications or change in pacing function.

If the patient's intrinsic rate is dominant, the pacemaker rate is increased to approximately 10 beats above the intrinsic rate so that the paced activity can be evaluated. The stimulation current then is decreased slowly until capture is lost. The point at which capture is lost is recorded in the medical record. Next, the output is increased to at least three times the threshold value, usually at least 3 to 5 mA.

Meticulous nursing care is essential for patients with temporary transvenous pacemakers. Rhythms should be recorded regularly, and connections between the pacing lead and the external generator should be checked daily to ensure that they are secure.

The entry site should be assessed regularly, with the area covered with a self-adhesive semipermeable transparent dressing. Careful attention to site care significantly reduces the potential for infection. The pacing catheter should be immobilized as much as possible at the skin entry site.

Esophageal Pacing

The esophagus can be used as a route for obtaining cardiac electrograms as well as for cardiac pacing (147). A conventional coronary sinus lead can be placed through the nares, or a small French quadripolar catheter or a pill electrode catheter can be used. The catheter is advanced and positioned to record the largest and most distinct atrial electrogram. Fluoroscopy is not required. Recording the electrogram is helpful in the diagnosis of the mechanism of arrhythmias (e.g., atrial flutter when flutter waves are not seen on the standard electrocardiogram).

In addition, the timing of the relationship of atrial and ventricular potentials can be helpful in analyzing the underlying electrophysiologic substrate. The same catheter can also be used for stimulation for attempts at inducing or terminating supraventricular tachycardia to assess antiarrhythmic therapy. Complications with transesophageal pacing are uncommon, but they may produce some discomfort for patients.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Controversies regarding the effect of pacing mode on morbidity and mortality continue. It was hoped that the publication of the CTOPP trial would bring some closure to the controversy, but it did not (104). With CTOPP failing to show a difference in mortality but a decreased incidence of atrial fibrillation with physiologic pacing, we now need to wait for longer follow-up of this population and for other trials that are under way.

Biventricular or left ventricular pacing for subjective and objective improvement in patients with congestive heart failure remains controversial but is becoming less so. With the publication of several randomized trials that have demonstrated clinical improvement, the controversy is no longer about whether pacing may be of benefit in a subset of this patient population but about the selection of patients and the optimal pacing site(s).

ICD therapy is discussed in Chapter 75. However, ICDs with extensive dual-chamber pacing capabilities are gaining widespread acceptance, and increasingly the clinical disciplines of cardiac pacing and cardiac defibrillation overlap.

Continued automaticity of permanent pacemakers undoubtedly will lead to better optimization of implanted devices and provide patients greater benefit from devices that previously may not have been tailored optimally to their needs.

Overall, permanent pacing was one of the remarkable success stories of the twentieth century. Having entered the twenty-first century, there are no signs that continued improvements in pacing therapy are slowing.

THE FUTURE

With the next decade, permanent pacemakers will continue to become more sophisticated, with automatic functions being the most prominent refinement. Also, dual-sensor rate-adaptive pacemakers will increasingly be accepted.

Prospective information is still limited about the effect of pacing mode on survival, but this information will become available within the next 2 to 3 years. The results of these prospective studies likely will support the results of retrospective studies, which consistently have shown lower morbidity and mortality with atrial-based pacing systems.

Biventricular and left ventricular pacing will gain increasing acceptance for the treatment of congestive heart failure, but it is too early to speculate whether either one may be used for patients with asymptomatic left ventricular dysfunction and an intraventricular conduction delay. If coronary lead placement becomes increasingly easier and reliable with the development of better leads and placement techniques, it could replace standard right ventricular apical pacing if a hemodynamic advantage can be shown. Pacing for the prevention of atrial fibrillation will also gain acceptance. A combination of alternate atrial pacing sites, either septal or left atrial pacing via the coronary sinus, with pacing algorithms that respond to premature atrial contraction will be the most likely successful application.

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IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

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OVERVIEW

Randomized controlled trials have demonstrated the superiority of the implantable cardioverter-defibrillator (ICD) over antiarrhythmic drug treatment in patients with serious ventricular arrhythmias. At the same time, technological advances have made ICDs small, easy to implant, and very versatile. The surgical mortality rate has dropped to less than 1%. Antitachycardia pacing allows for the painless termination of many episodes of sustained monomorphic ventricular tachycardia (VT), whereas defibrillation shocks are needed for more rapid or polymorphic VT or for ventricular fibrillation (VF). However, complications including lead failure, infection, spurious shocks for supraventricular tachyarrhythmias, and psychological morbidity still occur. In the next few years, ongoing randomized studies will clarify the role of ICDs in the management of larger populations at risk for sudden cardiac death. These trials will assess not only the impact of ICDs on overall survival, but also their effects on quality of life and their cost-effectiveness. If these studies show positive results, ICDs will become the preeminent clinical tool for the prevention of sudden cardiac death. Future technological developments will continue to improve the performance of ICDs, expand their therapeutic capabilities for treatment of heart failure and supraventricular arrhythmias, and reduce complications associated with their use.

GLOSSARY

Biphasic waveform: Shock waveform that consists of two phases of opposite polarity.

Dedicated bipolar: Defibrillator lead in which sensing of the depolarization signal and pacing are delivered between a distal-tip electrode and a closely positioned ring electrode, neither of which participates in the defibrillation pathway.

Defibrillation threshold: Minimal shock strength that terminates induced VF during implant or follow-up testing.

Detection enhancements: Optional programmable criteria (e.g., sudden onset or rate stability) used to increase the specificity of detection algorithms for VT.

Integrated bipolar: Defibrillator lead in which sensing of the depolarization signal and pacing are delivered between a distal-tip electrode and a more proximal defibrillation coil that is part of the defibrillation pathway.

Upper limit of vulnerability: Shock strength at and above which VF is not induced, even when the shock is delivered during the ventricular vulnerable period.

HISTORICAL PERSPECTIVE

The ICD was conceived and developed by Mirowski and colleagues during the 1970s (1,2). It was inspired by the success of prompt external defibrillation in terminating VF complicating acute myocardial infarction in the coronary care unit and by the high recurrence rate in patients resuscitated from out-of-hospital cardiac arrest. Initially, the concept of an ICD met strong resistance in the academic community (3). After prolonged preclinical investigation, the first human implant was performed in 1980 (4). Early ICDs were primitive by current standards. The generators were bulky, nonprogrammable, and lacked shock synchronization capability. A thoracotomy was required to position at least one defibrillation patch epicardially.

The next generation of devices allowed programming of the rate and duration for arrhythmia detection, as well as of the initial shock energy. Several different manufacturers joined the first in researching, developing, and marketing ICD systems, accelerating the technological progress. In the early 1990s, the advent of transvenous-subcutaneous defibrillation leads obviated the need for thoracotomy (5). The adoption of biphasic shock waveforms improved defibrillation efficiency, and the addition of extensive telemetric and diagnostic capabilities refined patient follow-up.

Current ICDs deliver not only high-energy defibrillation shocks, but also low-energy shocks, antitachycardia pacing for VT, and pacing for bradyarrhythmias. They are £40 mL in size and are implanted transvenously with techniques similar to those used for implantation of standard pacemakers. As with other therapeutic modalities, technological advances preceded progress in the elucidation of the role of the ICD in different patient populations. More recently, randomized controlled trials have clarified the indications for ICD therapy.

CURRENT STATUS OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR TECHNOLOGY

ICD systems consist of two main components: the pulse generator, which harbors the electronic circuitry, power sources, and memory; and the lead electrode system that interfaces with the heart (6). Among the important components of ICD generators, the microprocessor orchestrates the interplay between the various subsections of the system. The read-only memory contains instructions that determine the general functional characteristics of the device, and individualized programming and diagnostic information are stored in random access memory. Lithium/silver vanadium oxide batteries provide the power source. The predicted longevity of current generators varies between 5 and 9 years, depending on the model and the frequency of activation. The pacing and high-output sections convert the 3 to 10 V provided by the batteries into device discharges that range from less than 1 V (for pacing) to 750 V (for defibrillation). The circuitry for delivering pacing pulses is similar to that found in standard bradycardia pacemakers, and high-voltage pulses are provided by capacitors. Batteries and capacitors consume two-thirds of the volume of current devices. The sense amplifier section adapts continually to the intracardiac ventricular depolarization signal, which may vary dramatically in amplitude (i.e., from sinus rhythm to VF) while avoiding significant signal drop and oversensing of T waves or extracardiac interference. This adaptation is achieved by adjusting either the gain or the sensing threshold. The communications section allows the ICD to exchange information with the dedicated programmer.

Transvenous defibrillation leads have complex multielectrode designs because of the need for combined pacing, sensing, and shocking capabilities (7). Fixation to the endocardium is achieved with tines (passive fixation) or screws (active fixation). Detection of low-amplitude signals in VT requires bipolar sensing, which is accomplished between a dedicated pacing/sensing electrode pair (dedicated bipolar) or between a single pacing/sensing electrode and a shocking coil electrode in close proximity (integrated bipolar). Integrated bipolar systems are convenient, because they permit two defibrillating coils in the same lead, and they may be more efficient, because they minimize the distance between the defibrillating coil and the endocardium. However, they also may be more susceptible than dedicated bipolar systems to oversensing of endogenous or exogenous interference (8).

ELECTROPHYSIOLOGIC MECHANISMS

Ventricular Fibrillation

During the last quarter of the nineteenth century and the first half of the twentieth century, work by MacWilliam, Prevost, Batelli, King, Wiggers, Kouwenhoven, and Beck established the effects of the application of electrical currents to the heart and the possibility of terminating VF by a timely electrical countershock (9). Active research on the mechanisms of VF and defibrillation during the last two decades has provided a rational basis for the development of ICD technology.

VF has been extensively studied in models of ischemia and reperfusion and after induction by a large premature stimulus during the vulnerable period of the cardiac cycle. Depending on the model, both reentrant and nonreentrant mechanisms can be responsible for the initiation of VF, but its maintenance depends mainly on reentrant mechanisms. Cinematographic (10) and computerized mapping studies demonstrate four stages of VF. In the early undulatory stage, the transition from sinus rhythm to VF is often briefly preceded by organized epicardial activation that represents functional reentry around a single circuit (11,12). A second premature stimulus given to the same site at a critical coupling interval (the protective zone) may terminate this functional reentry (12). The second stage, convulsive incoordination, lasts for 15 to 40 seconds and is characterized by more frequent, asynchronous waves of activation that have complicated patterns (13). Complete reentrant wavefronts are uncommon and, when present, have a small and unstable core, a short life span, and a short cycle length. Most of the time, multiple disorganized wandering wavelets that follow constantly changing pathways are present. The third stage, tremulous incoordination, lasts for 2 to 3 minutes. The final stage is atonic fibrillation. Timely ICD shocks are delivered during the first two stages.

Ventricular Defibrillation

Defibrillation is best described as a dose-response phenomenon that can be depicted with a sigmoidal curve of energy versus probability of success (14). Construction of a probability-of-success curve in patients is impractical, because it requires at least 20 to 30 fibrillation-defibrillation trials. Determination of the defibrillation threshold (i.e., the lowest energy that successfully terminates VF) is clinically more applicable (15). The defibrillation threshold determined by clinical protocols generally identifies energies with 50% to 75% probability of success (Fig. 75.1).

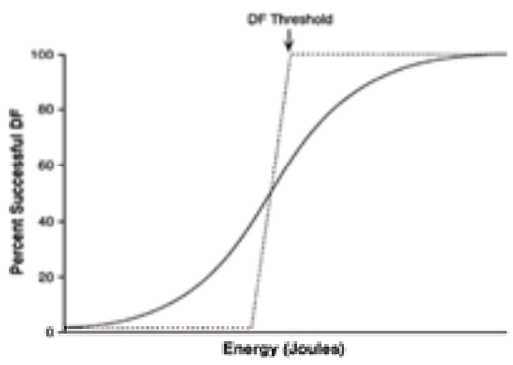


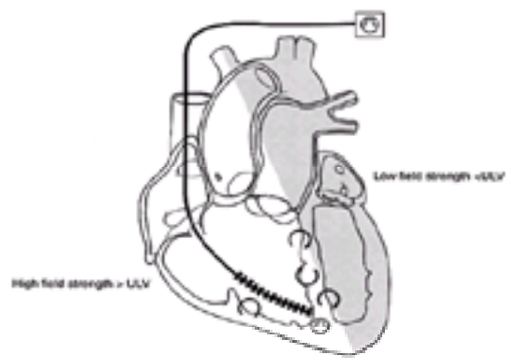
FIGURE 75.1 Comparison of defibrillation (DF) probability-of-success curve and DF threshold concepts. A probability-of-success curve implies a dose-response relationship in which increasing energies are associated with a higher percentage of success, whereas a DF threshold implies a clear-cut distinction between effective and ineffective energies. (Reproduced from Davy JM, Fain ES, Dorian P, et al. The relationship between successful defibrillation and delivered energy in open-chest dogs: reappraisal of the “defibrillation threshold” concept. *Am Heart J* 1987;113:77–84, with permission from Mosby–Year Book.)

A defibrillation shock generates uneven potential gradients and current densities through the myocardium. The potential gradient is a measure of how quickly the electrical field changes over space, typically expressed in volts per centimeter. High-gradient areas are produced close to the electrodes, and low-gradient areas exist at distant sites (16). These extracellular potential gradients result in changes in the transmembrane potential of myocytes that are ultimately responsible for the process of defibrillation. The exact nature of the relationship between the distribution of extracellular potential gradients and the transmembrane potential is a topic of active research (17). Shock-induced prolongation and homogenization of refractoriness seem to be important determinants of the defibrillation process (18). Recent optical mapping studies showed that electrical shocks can induce areas of negative polarization (i.e., hyperpolarization) known as *virtual electrodes*, whose effects on membrane potential might last beyond the end of the shock. Negative polarization can “deexcite” cardiac cells, creating regions of excitable tissue through which wavefronts can propagate. These wavefronts can result in new reentrant circuits, inducing fibrillation or causing defibrillation to fail. In addition, deexcitation can lead to rapid propagation through newly excitable regions, resulting in the elimination of excitable gaps soon after the shock and causing defibrillation to succeed (19).

Mapping the electrical activity immediately before and after successful and failed shocks in animal models has provided valuable information about the mechanism of defibrillation. Successful defibrillation shocks halt all existing fibrillatory wavefronts without creating new wavefronts that reinduce fibrillation (20,21). Unsuccessful shocks may also halt fibrillatory wavefronts, but at the same time they induce new wavefronts (generally originating in a low-gradient area) that reinitiate the fibrillation (22). Preshock intervals at the sites activated early after these failed shocks are not distributed randomly, which suggests the presence of a vulnerable period in VT activations (23).

These observations tend to rule out the critical mass hypothesis as the mechanism of ventricular defibrillation. According to this hypothesis, successful defibrillation depends on the depolarization of a critical mass of myocardium: a shock could fail to halt the fibrillatory wavefronts in a region of myocardium smaller than the “critical mass” and still defibrillate the heart (24). The upper limit of vulnerability hypothesis better accounts for experimental findings (25). The upper limit of vulnerability is a shock strength at and above which VF is not induced, even when the shock falls in the vulnerable period of the cardiac cycle (26). This shock strength correlates well with the defibrillation threshold in animals (26) and patients (27).

The critical potential gradient that leads to the induction of VF during the vulnerable period of regular rhythm is very similar to the potential present in low-gradient areas that are responsible for reinitiation of fibrillation after a failed shock. Therefore, to defibrillate consistently, a shock must be strong enough to create fields above the upper limit of vulnerability throughout the myocardium. For example, with a transvenous electrode in the right ventricular apex, a shock may generate a low-gradient field in distant areas, such as the base of the ventricles, while the field is above the upper limit of vulnerability in the remainder of the ventricles (eFig. 75.1.1). In this latter area, all fibrillation wavefronts are eliminated and none can be reinitiated, resulting in cessation of fibrillation activation. In the low-gradient area, the results depend on the timing of the shock with regard to the local activation. A weak shock may terminate fibrillation only if it falls in the protective zone (28). This may explain the probabilistic nature of defibrillation. The critical potential at the low-gradient areas cannot be achieved by simply delivering shocks of very high strength, because such shocks produce functional and cellular damage in the high-gradient areas close to the electrodes (29).



***e*FIGURE 75.1.1** Mechanism of ventricular defibrillation. This figure shows a pectorally implanted implantable cardioverter-defibrillator in which shocks are delivered between a single coil positioned into the right ventricular apex and the case of the generator. A defibrillation shock resulted in a high-gradient field [higher than the upper limit of vulnerability (ULV)] in the right ventricle. The field strength of the left ventricle was low (lower than the ULV). In the area in which field strength was high, the shock terminated all reentrant wavefronts without initiating new ones. However, in the area in which field strength was low, the effect of the shock followed a probability function and was determined by whether the reentrant wavefronts were n the protective zone.

The type of defibrillation waveform and the surface area, impedance, and geometry of the defibrillation electrodes are crucial determinants of the energy requirements for defibrillation; clinical variables are less important (30). The ICDs currently in use deliver biphasic shocks (i.e., the pulse has two phases of opposite polarity). This waveform markedly decreases the energy requirements for defibrillation in comparison with the earlier monophasic waveform (31). However, identification of the optimal waveform remains elusive. Variables that influence the efficiency of the biphasic waveform are the duration and relative amplitude of each phase (32), and capacitance (32,33). With current ICD systems, a high defibrillation threshold (i.e., 23 J) is more likely to occur in patients with idiopathic dilated cardiomyopathy (as opposed to coronary artery disease) and in patients taking amiodarone or other antiarrhythmic drugs with sodium channel blockade activity (34).

CLINICAL TRIALS OF THE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

Recent trials have examined the role of the ICD in secondary prevention of sudden cardiac death (i.e., in patients who have already had a clinical episode of life-threatening ventricular arrhythmia) and primary prevention of sudden cardiac death (i.e., in patients at high risk for this outcome who have not yet experienced a serious arrhythmic event) (Table 75.1 and Fig. 75.2).

Study	Control intervention	Population	Findings
Antiarrhythmics versus Implantable Defibrillator Trial (AVID)	Amiodarone or sotalol	Cardiac arrest survivor or syncopal ventricular tachycardia or symptomatic sustained ventricular tachycardia with left ventricular ejection fraction ≤0.40	Significant improvement in overall survival with ICDs.
Canadian Implantable Defibrillator Study (CIDS)	Amiodarone	Cardiac arrest survivor or syncopal ventricular tachycardia or symptomatic sustained ventricular tachycardia with left ventricular ejection fraction ≤0.35 or syncope and inducible ventricular tachycardia	Nonsignificant improvement in overall survival with ICDs.
Cardiac Arrest Study—Hamburg (CASH)	Propafenone, metoprolol, or amiodarone	Cardiac arrest survivor	Nonsignificant improvement in overall survival with ICDs.
Multicenter Automatic Implantable Defibrillator Trial (MADIT)	Conventional therapy	Prior myocardial infarction and left ventricular ejection fraction ≤0.35 and nonsustained ventricular tachycardia and inducible ventricular tachycardia and not suppressible with intravenous procainamide	Significant improvement in overall survival with ICDs.
Coronary Artery Bypass Graft–Implantable Cardioverter-Defibrillator Study (CABG Patch)	None	Coronary bypass surgery and left ventricular ejection fraction ≤0.35 and positive signal-averaged electrocardiogram	No difference in overall survival
Multicenter Unsustained Tachycardia Trial (MUSTT)	None	Previous myocardial infarction and left ventricular ejection fraction ≤0.40 and asymptomatic, unsustained ventricular tachycardia and inducible ventricular tachycardia	Significant improvement in overall survival in patients randomly assigned to electrophysiologically guided therapy. All the benefit in this arm occurred in patients who received ICDs.
Amiodarone versus Implantable Cardioverter-Defibrillator Randomized Trial (AMIO/VHT)	Amiodarone	Nonischemic cardiomyopathy and left ventricular ejection fraction ≤0.35 and nonsymptomatic nonsustained ventricular tachycardia	No difference in overall survival

TABLE 75.1 COMPLETED RANDOMIZED TRIALS OF THE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR (ICD)

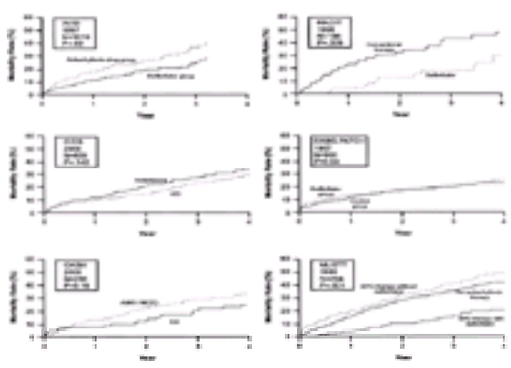


FIGURE 75.2 Plots of actuarial total mortality rate end points for published multicenter controlled trials involving use of implantable cardioverter-defibrillators. The mortality rates and follow-up periods have been normalized for each study so that the control and intervention mortality rates can be compared. The legends show year of publication, total number of patients enrolled, and two-tailed *p* value for each study. AMIO, amiodarone; AVID, Antiarrhythmics versus Implantable Defibrillators Trial; CABG Patch, Coronary Artery Bypass Graft–Implantable Cardioverter-Defibrillator Study; CASH, Cardiac Arrest Study—Hamburg; CIDS, Canadian Implantable Defibrillator Study; EPG, electrophysiologic; MADIT, Multicenter Automatic Defibrillator Implantation Trial; METO, metoprolol; MUSTT, Multicenter Unsustained Tachycardia Trial.

Secondary Prevention of Sudden Death

Despite the unquestionable efficacy of the ICD in terminating VF and preventing sudden death, competing causes of death in ICD recipients (e.g., heart failure) may limit the overall survival benefit (35). Early nonrandomized studies suggested the superiority of the ICD over antiarrhythmic drugs in patients who had life-threatening ventricular arrhythmias (36), but the presence of selection bias, the use of controversial end points, and a lack of adequate controls limited the applicability of their implications. After controlled studies demonstrated an increase in the mortality rate with class I or pure class III antiarrhythmic drugs, only amiodarone (37) and sotalol (38) remained viable alternative therapies for ventricular arrhythmias. Well-powered randomized controlled trials were needed to assess the impact of the ICD on survival of patients with life-threatening ventricular arrhythmias.

The Antiarrhythmics versus Implantable Defibrillators Trial (AVID) (39) studied 1,016 patients with VF, sustained VT with syncope, or sustained VT with serious symptoms and left ventricular ejection fraction £0.40 that was not believed to be secondary to correctable or reversible causes. Patients were randomly assigned to receive an ICD or antiarrhythmic drugs (empiric amiodarone or guided sotalol). The study essentially compared the ICD to amiodarone, because only 2.6% of patients randomized to the antiarrhythmic drug limb were discharged on sotalol. ICD patients had better survival throughout the course of the study (unadjusted survival at 1 year, 89% among patients with ICD vs. 82% among patients treated with amiodarone, and at 3 years, 75% vs. 61%; $p < .02$). The corresponding reductions in mortality rates in the ICD group were 39% and 31% at 1 and 3 years, respectively. The ICD significantly decreased the incidence of cardiac arrhythmic death but had no effect on nonarrhythmic deaths (40). No significant differences were seen in the benefit conferred by ICD therapy among prespecified subgroups categorized according to age, degree of left ventricular dysfunction, presence of coronary artery disease, or presenting rhythm. More patients in the ICD group were treated with beta-blockers, but adjusting for this imbalance did not change the estimate of the mortality rate reduction attributable to the ICD. Several design features of this study, including the enrollment of a wide spectrum of patients with little evidence of selection biases [as supported by a concomitant comprehensive registry (41)], the almost exclusive use of transvenous defibrillators, and the comparison of ICD use against the best available antiarrhythmic drug therapy, make extrapolation of its findings to clinical practice valid.

The Cardiac Arrest Study—Hamburg (CASH) (42) randomly assigned cardiac arrest survivors to ICD implantation or treatment with propafenone, metoprolol, or

amiodarone. The propafenone limb was prematurely concluded when interim analyses suggested that the mortality rate in that limb was higher than in the ICD limb. The trial continued its comparison of ICDs, metoprolol, and amiodarone in 288 patients. Nearly one-half of the ICDs were implanted by thoracotomy. Over the course of a mean follow-up period of 57 ± 34 months, the crude mortality rates were 36.4% (95% confidence interval, 26.9% to 46.6%) in the group who received ICDs and 44.4% (95% confidence interval, 37.2% to 51.8%) in the groups receiving amiodarone or metoprolol. Overall survival was higher, though not significantly so, in patients assigned to ICD than in those assigned to drug therapy (one-sided p = .081; hazard ratio, 0.76). In ICD patients, the percentages of reduction in all-cause mortality were 42% at 1 year, 28% at 3 years, and 9% at 7 years of follow-up. No statistically significant differences were seen in global or sudden death rates between patients receiving amiodarone and patients receiving metoprolol.

The Canadian Implantable Defibrillator Study (CIDS) (43) included 659 patients who had been resuscitated after cardiac arrest or who had syncopal VT, presyncopal VT with a heart rate <150 beats/min or accompanied by left ventricular ejection fraction <0.36, or unmonitored syncope with subsequent spontaneous or inducible VT. Patients were randomly assigned to receive ICD implantation or treatment with empiric amiodarone. The 3-year mortality rate was 25% in the group who received ICD and 30% in the group being treated with amiodarone. A nonsignificant reduction in the risk of death was observed with the ICD, from 10.2% per year to 8.3% per year (relative risk reduction, 19.7%; 95% confidence interval, –7.7% to 40%; p = .142). A nonsignificant reduction in the risk of arrhythmic death was observed, from 4.5% per year to 3.0% per year (relative risk reduction, 32.8%; 95% confidence interval, –7.2% to 57.8%; p = .094).

A pooled analysis of AVID, CIDS, and CASH (44) showed that the estimates of ICD benefit from the three studies were consistent. A 28% reduction in the relative risk of death was seen with use of ICDs that was owed almost entirely to a 50% reduction in arrhythmic death. Survival was extended by a mean of 4.4 months by use of ICDs during a follow-up period of 6 years. Subgroup analysis showed that patients with left ventricular ejection fraction £0.35 derived significantly more benefit from ICD therapy than patients with better-preserved left ventricular function.

Primary Prevention of Sudden Death

Sudden cardiac death represents a major public health challenge that requires continuing development of new, multifaceted approaches for primary prevention. Use of the ICD is a potentially useful intervention, but the expense and invasiveness involved make accurate identification of candidates imperative. Efficient interventions require methods of identifying higher-risk clusters within the lower-risk subgroups (45). Target populations considered for prophylactic ICD implantation include patients with various combinations of left ventricular dysfunction, congestive heart failure, complex ventricular ectopy, late potentials on signal-averaged electrocardiography, depressed heart-rate variability, exercise-induced microvoltage T-wave alternans, and inducibility of VT at electrophysiologic study.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) (46) examined the efficacy of the ICD versus conventional therapy for prolonging survival in 196 patients with prior myocardial infarction, left ventricular ejection fraction £0.35, spontaneous nonsustained VT, and inducible VT not suppressed by intravenous procainamide at electrophysiologic study. Amiodarone was the most frequently used therapy in the group of patients receiving conventional therapy. ICD patients had better survival throughout the course of the study (actuarial survival at 1 year, 97% among patients who had ICDs vs. 77% among patients receiving conventional therapy; at 3 years: 83% vs. 56%; p <.009). This translated into a 54% reduction in death from all causes. More patients in the ICD group were treated with beta-blockers (26% vs. 8% 1 month after enrollment; 27% vs. 5% at last contact). Separate analyses revealed no evidence that antiarrhythmic medications, including amiodarone and beta-blockers, other cardiac medications being given 1 month after enrollment, or any of 11 preselected baseline variables had a meaningful influence on the magnitude of the ICD effect.

The Multicenter Unsustained Tachycardia Trial (47) was a randomized, controlled trial that tested the hypothesis that electrophysiologically guided antiarrhythmic therapy would reduce the risk of sudden death among patients with coronary artery disease, a left ventricular ejection fraction £0.40, and asymptomatic, unsustained VT. A total of 704 such patients in whom sustained ventricular tachyarrhythmias were induced by programmed stimulation were randomly assigned to receive either antiarrhythmic therapy, including drugs or use of ICDs (as indicated by the results of electrophysiologic testing), or no antiarrhythmic therapy. The 5-year incidence of the primary end point of cardiac arrest or death from arrhythmia was 25% among patients who received electrophysiologically guided therapy and 32% among those assigned to receive no antiarrhythmic therapy (relative risk, 0.73; 95% confidence interval, 0.53–0.99; relative risk reduction, 27%). The 5-year estimates of overall mortality rates were 42% and 48%, respectively (relative risk, 0.80; 95% confidence interval, 0.64–1.01). All the observed benefit occurred in patients who were given ICDs before discharge after failure to identify an effective drug during serial electropharmacologic testing. The risk of cardiac arrest or death from arrhythmia among the patients who received treatment with ICDs was significantly lower than that among the patients discharged without ICDs (relative risk, 0.24; 95% confidence interval, 0.13–0.45; p <.001). Neither the rate of cardiac arrest or death from arrhythmia nor the overall mortality rate was lower among patients who were assigned to electrophysiologically guided therapy and treated with antiarrhythmic drugs than among the patients who were assigned to no antiarrhythmic therapy.

The Coronary Artery Bypass Graft–Implantable Cardioverter-Defibrillator Study (CABG Patch) (48) randomly assigned 900 patients with left ventricular ejection fraction £0.35 and late-potentials on signal-averaged electrocardiography who were scheduled for coronary bypass surgery to treatment with ICD (implanted at the time of bypass surgery) or to no antiarrhythmic treatment. The study was halted prematurely after an average follow-up of 32 months when interim analysis showed no difference between the treatment groups (hazard ratio, 1.07; 95% confidence interval, 0.81–1.42).

The Amiodarone versus Implantable Cardioverter-Defibrillator Randomized Trial (49) randomly assigned 103 patients with nonischemic dilated cardiomyopathy and nonsustained VT to receive treatment with an ICD or with amiodarone. During a mean 21-month follow-up, no significant difference was seen in mortality rate between the groups, and the trial was stopped early because it met the futility criteria.

The divergent results of CABG Patch, MADIT, and the Multicenter Unsustained Tachycardia Trial highlight the importance of selecting populations at high risk for sudden death as targets for ICD therapy. In CABG Patch, most of the deaths were perioperative and not potentially preventable by an effective antiarrhythmic strategy. Only 29% of the deaths in the control group were classified as arrhythmic. Therefore, the 45% decrease in arrhythmic death that was seen in patients who were treated with use of ICDs did not translate into a significant reduction in the overall mortality rate (50). Other ongoing, large-scale, multicenter trials are evaluating the role of prophylactic ICDs in various high-risk populations, including patients with coronary artery disease and left ventricular dysfunction (51), patients with recent myocardial infarction and high-risk markers (52,53), patients with heart failure (54,55), and patients with nonischemic dilated cardiomyopathy (56) (*e*Table 75.1.1). It has been estimated that, depending on the definitions of the targeted populations, up to 1,000,000 patients could become candidates for ICD therapy in the United States in the next few years. At current costs, this would represent between $20 billion and $25 billion in hardware alone. Given the fiscal impact of such a radical change in indications, solid scientific backing for the move is needed.

***e*TABLE 75.1.1** ONGOING RANDOMIZED TRIALS OF THE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

Study	Control intervention	Population	Status
Second Multicenter Automatic Implantable Defibrillator Trial (MADIT II)	Conventional therapy	Prior myocardial infarction *and* left ventricular ejection fraction £0.30	Ongoing; plans to recruit 700 patients
Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)	Placebo or amiodarone	Congestive heart failure class II or III *and* left ventricular ejection fraction <0.35	Ongoing; plans to recruit 2,500 patients
Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial	Conventional therapy *or* biventricular pacing	Congestive heart failure class III or IV *and* left ventricular ejection fraction <0.35 *and* QRS duration ³120 ms	Ongoing; plans to recruit 2,200 patients
Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)	None	Recent myocardial infarction *and* left ventricular ejection fraction <0.35 *and* mean 24-hour heart rate >80 beats/min *or* depressed heart-rate variability	Ongoing; plans to recruit 525 patients
Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE)	Heart failure medications plus beta-blocker	Nonischemic cardiomyopathy *and* left ventricular ejection fraction <0.35 *and* symptomatic heart failure *and* nonsustained ventricular tachycardia *or* >10 ventricular premature depolarizations per hour	Ongoing; plans to recruit 408 patients

INDICATIONS AND CONTRAINDICATIONS FOR USE OF THE IMPLANTED CARDIOVERTER-DEFIBRILLATOR

Indications for ICDs are evolving as technology improves and results from clinical trials are incorporated into clinical practice (Table 75.2) (57). ICDs should be considered first-line therapy for patients who have survived episodes of cardiac arrest or hemodynamically significant sustained VT that is not caused by reversible causes and for patients who have coronary artery disease, left ventricular dysfunction, and nonsustained VT and in whom sustained ventricular tachyarrhythmias can be induced during electrophysiologic testing.

Secondary prevention
Patients with at least one clinical episode of ventricular fibrillation or hemodynamically significant ventricular tachycardia without reversible, correctable cause
Patients with unexplained syncope and inducible sustained ventricular tachycardia on electrophysiologic study
Patients with structural heart disease and sustained monomorphic ventricular tachycardia, regardless of hemodynamic tolerance[b]
Patients with idiopathic dilated cardiomyopathy and unexplained syncope despite electrophysiologic testing[b]
Primary prevention
Patients with coronary artery disease, at least moderate left ventricular dysfunction, spontaneous nonsustained ventricular tachycardia, and inducible sustained ventricular tachycardia
Patients with familial or inherited conditions who have a high risk for life-threatening ventricular tachyarrhythmias such as long QT syndrome or hypertrophic cardiomyopathy[b]

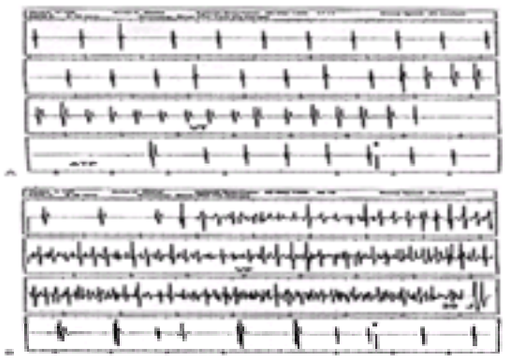
[a]Several other indications are being evaluated in ongoing randomized studies.
[b]Experts may differ regarding the appropriateness of implantable cardioverter-defibrillator therapy in these patients.

TABLE 75.2 CURRENT INDICATIONS FOR IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR IMPLANTATION[a]

Although most ICD recipients involved in clinical trials had coronary artery disease or idiopathic dilated cardiomyopathy, growing evidence from nonrandomized trials suggests that patients with other forms of cardiomyopathy and primary electrical disorders may benefit from use of ICDs. In a retrospective multicenter study of 128 patients with hypertrophic cardiomyopathy who were judged to be at high risk for sudden death, the rate of appropriate ICD discharge was 7% per year. The study suggested that VT or VF is the principal mechanism of sudden death in patients with hypertrophic cardiomyopathy, and that the ICD has an important role in its prevention (58). Some experts recommend ICD implantation (in conjunction with treatment with beta-blockers) as a fail-safe back-up therapy in high-risk patients who have congenital long-QT syndrome, especially those who have experienced an aborted cardiac arrest (59). Use of the ICD is also indicated in patients with idiopathic VF, including those with Brugada syndrome (60). Children who have life-threatening ventricular arrhythmia can also be successfully treated with ICDs (61).

Patients with syncope of undetermined origin and inducible sustained VT have a high incidence of appropriate defibrillator discharge (62,63) and also appear to benefit from ICD implantation. Patients with unexplained syncope, nonischemic dilated cardiomyopathy, and negative results of electrophysiologic examination have also been considered as candidates for ICD implantation because of the difficulties in risk-stratification. In a small series of 14 such patients, the incidence of appropriate shocks was high (50%) and similar to the rate observed in patients with idiopathic cardiomyopathy who were resuscitated from cardiac arrest (64). Other series have reported a lower (but not negligible) incidence of appropriate ICD intervention (65). Another retrospective analysis reported improved survival in patients who had nonischemic cardiomyopathy and unexplained syncope and were treated with ICDs (66). On the basis of this observational evidence, ICD implantation appears reasonable in this group of patients after other causes of syncope have been ruled out.

The role of the ICD in patients who have structural heart disease and present with nonsyncopal sustained monomorphic VT is unclear. Such patients had a low risk of sudden death in nonrandomized observational studies of antiarrhythmic drug therapy (67). On the other hand, a relatively high incidence of shocks for rapid, potentially life-threatening ventricular arrhythmias has been reported in a selected population of patients with stable VT who were treated with ICDs (68) (*e*Fig. 75.2.1). Furthermore, among 3,559 patients enrolled in the AVID registry who had documented sustained ventricular tachyarrhythmias, the hemodynamic impact of the index arrhythmia did not influence overall survival (69). Until more information is gathered, we believe that use of the ICD should be strongly considered in all patients who have structural heart disease and sustained VT. Catheter ablation of the tachycardia circuit(s) is another potentially curative option in these patients (70), but we believe it should, for now, be reserved as adjunctive therapy in patients who have ICDs and frequently recurring VT (71).



***e*FIGURE 75.2.1** Unexpected ventricular fibrillation (VF) in a patient with recurrent sustained monomorphic ventricular tachycardia (VT). The patient was being treated with amiodarone, 300 mg/day. The implantable cardioverter-defibrillator was programmed to treat tachyarrhythmias in two “zones.” Two electrograms (EGMs; 32 seconds each) were retrieved from device memory. **A:** Monomorphic VT initiated by a late-coupled ventricular pacing device on 6 March 1996, which is terminated by the first burst on antitachycardia pacing (ATP). Such episodes occurred on at least a monthly basis. **B:** An episode of VF initiated by an earlier-coupled ventricular pacing device (2 May 1996). The device detected it correctly and terminated it with a 20-J shock. There was no clear trigger for this episode. Arrows mark the redetection of sinus rhythm by the implantable cardioverter-defibrillator.

ICDs should not be implanted in patients whose ventricular tachyarrhythmias have been triggered by acute ischemia or infarction, correctable toxic or metabolic factors, or atrial fibrillation in the Wolff-Parkinson-White syndrome. The assessment of the reversibility of ventricular tachyarrhythmias in patients who have myocardial ischemia or severe coronary disease but not acute infarction is difficult and often inaccurate. Coronary artery disease was present in 81.5% of 270 patients in the AVID Registry who were thought to have VT or VF due to transient or correctable causes. Revascularization was performed in approximately one-half of the patients, and most of them were discharged without specific antiarrhythmic treatment. Actuarial 3-year survival was only 71% (lower than the 73% observed in patients in the same registry who had VT thought to be from uncorrectable causes) (41). The decision to perform surgical or percutaneous revascularization in patients with life-threatening ventricular arrhythmias should be based on grounds similar to those used in other clinical settings (e.g., presence of large areas of viable, ischemic myocardium). Observational studies suggest that the prognosis is good with revascularization alone in patients who have VF and normal left ventricular function, but arrhythmias frequently recur in patients who have left ventricular dysfunction or who present with VT. The value of using programmed ventricular stimulation after the revascularization procedure has been debated (72,73).

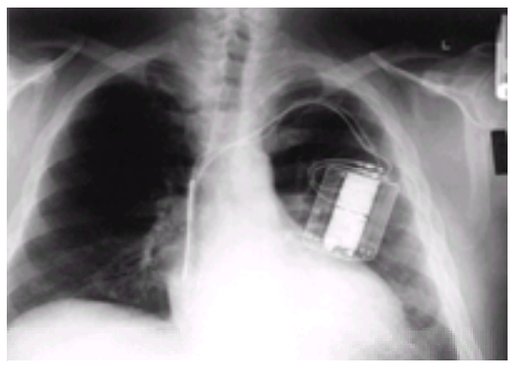
Patients with very frequent VT or VF that is not responsive to drugs, ablation, or antitachycardia pacing should not receive ICDs, because such arrhythmias would trigger frequent shock therapy. The low morbidity of current ICD implant techniques has made surgical or medical contraindications less relevant than in the past. However, patients who have terminal illness or a life expectancy of less than 6 to 12 months are not good candidates for ICD implantation. Patients awaiting cardiac transplantation have a high incidence of sudden death, but the use of the ICD as a “bridge” to transplantation remains controversial (74).

CLINICAL MANAGEMENT OF PATIENTS WITH IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Implantation

Implantation of transvenous ICDs by clinical electrophysiologists is safe and efficient (75). Similarly high rates of success and acceptable complication rates are achieved when the implant is performed in the electrophysiology laboratory as when it is performed in the operating room (76). In most institutions, cost considerations favor the use of the electrophysiology laboratory. Shortened procedure times and reduced tissue dissection have essentially eliminated the need for general anesthesia. Implantation can be safely performed under local anesthesia, supplemented with intravenous sedation, administered by nonanesthesiologists (77,78).

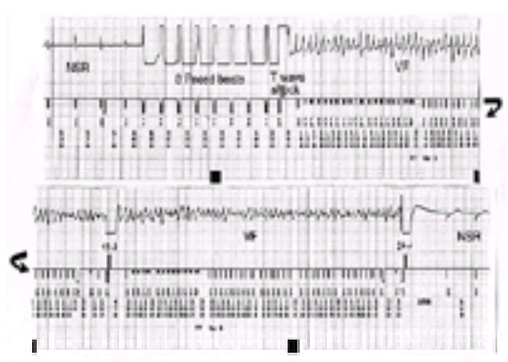
ICDs are implanted via the subclavian, axillary, or cephalic veins. A right ventricular lead is used for sensing and pacing. Shocks are delivered between a coil in this lead and the case of the generator. Leads incorporating a second coil at the level of the superior vena cava are often preferred, because the resulting bidirectional shocking vector improves the efficiency of defibrillation (79). Defibrillators capable of dual-chamber pacing require an additional pacing lead in the right atrium (*e*Fig. 75.2.2). Some ICDs can also deliver electrical therapy for atrial tachyarrhythmias, including cardioversion shocks for atrial fibrillation (80). This can be achieved with conventional systems that include a coil electrode in the superior vena cava (81). However, the lowest atrial fibrillation cardioversion thresholds are achieved when a coil electrode is added in the coronary sinus (82). Newer units that provide resynchronization therapy for heart failure (i.e., biventricular pacing) require insertion of an additional lead into a coronary vein to achieve left ventricular capture (83) (Fig. 75.3).



***e*FIGURE 75.2.2** Posteroanterior chest radiograph after implantation of a dual-chamber implantable cardioverter-defibrillator. An active-fixation bipolar pacing lead was positioned in the right atrial appendage. A dual-coil active-fixation defibrillation lead was positioned in the right ventricular apex.

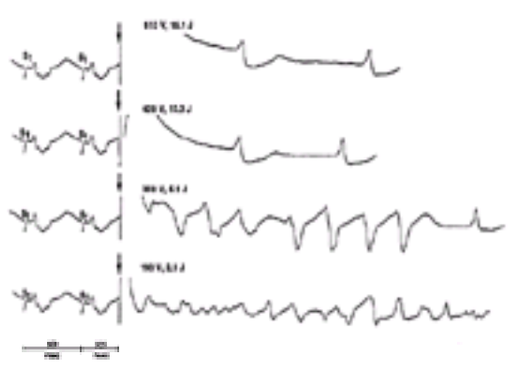
FIGURE 75.3 Posteroanterior chest radiograph after implantation of a triple-chamber implantable cardioverter-defibrillator capable of biventricular pacing. In addition to the atrial and defibrillation leads, a unipolar pacing lead was advanced via the coronary sinus into the middle segment of the anterior interventricular coronary vein.

The generator is implanted in a subcutaneous pocket in the pectoral area, although a submuscular plane is of value in patients who have a thin layer of subcutaneous tissue (84). The left side is preferred because of the smoother venous route to the heart and the more favorable shocking vector (85). Intraoperative testing is performed to establish appropriate pacing thresholds and adequate sensing during sinus rhythm and VF (86). The system's defibrillation capabilities are also tested, and the shocking lead configuration is optimized. In many institutions, this is accomplished by determining the ventricular defibrillation threshold (i.e., the minimal energy that terminates induced VF) (15), which is usually between 5 and 15 J. This ensures an adequate safety margin for defibrillation in most cases, because the maximum output of currently available ICDs ranges between 26 and 38 J (*e*Fig. 75.3.1). A safety margin can also be established by step-down protocols that do not require a failed shock.



***e*FIGURE 75.3.1** Assessment of the defibrillation threshold during implantable cardioverter-defibrillator implantation. Intracardiac electrograms and markers during an induction of ventricular fibrillation (VF) show initial normal sinus rhythm (NSR). VF is induced by a low-energy shock delivered during the vulnerable period (T-wave shock) after eight paced beats. VF is promptly detected. The first shock (15 J) does not terminate the arrhythmia. The device promptly recharges and restores NSR with a 24-J shock.

Defibrillation threshold testing requires the repetitive induction of VF. Although it is generally well tolerated, this procedure can result in myocardial depression in some patients (87). Alternatively, the upper limit of vulnerability is determined. Shocks of progressively smaller energy are delivered around the apex of the T wave during a paced or spontaneous rhythm until VF is induced (*e*Fig. 75.3.2). The last energy level that does not induce fibrillation is the upper limit of vulnerability. Accurate determination of the upper limit of vulnerability requires delivery of three shocks at the peak of the T wave and 20 and 40 ms before the peak (88). The upper limit of vulnerability predicts the energy level associated with a high rate of successful ventricular defibrillation and appears to be a convenient and reproducible method of determining defibrillation energy requirements without the need to induce multiple episodes of VF.



***e*FIGURE 75.3.2** Determination of the upper limit of vulnerability during implantable cardioverter-defibrillator implantation. Recordings on electrocardiographic lead II during baseline (S_1) pacing at 500 ms and S_1–S_2 interval of 325 ms. Shocks of 510 V (15.1 J) and 420 V (10.3 J) did not induce ventricular tachycardia or fibrillation. A 300-V (5.1-J) shock induced nonsustained ventricular tachycardia, which spontaneously converted to sinus rhythm. A 190-V (2.1-J) shock induced ventricular fibrillation. (Reproduced from Chen P-S, Feld GK, Kriett JM, et al. Relation between upper limit of vulnerability and defibrillation threshold in humans. *Circulation* 1993;88:186–192, with permission from the American Heart Association.)

The operative mortality rate after implantation of ICDs is less than 1% (89). Most patients can be discharged to their homes on the same day or the next day after surgery. Complications are similar to those accompanying pacemaker implantation and include pneumothorax, hemothorax, cardiac perforation, pericardial tamponade,

pocket hematoma (90), lead dislodgment, skin erosion, venous thrombosis, and frozen shoulder (91). Infection occurs in up to 2% of patients (92). Complete system removal and intravenous antibiotic therapy are generally needed to cure infection (93). Percutaneous extraction of chronic defibrillator leads is technically challenging, but it can be performed at low risk by trained operators equipped with specially designed tools (94). A large-bore (16 French) excimer laser sheath is particularly useful (95).

A thoracotomy approach using epicardial defibrillation patches is reserved for the rare patient who cannot be successfully defibrillated with a transvenous system and for patients with mechanical tricuspid valve prostheses. Implantation of an ICD via thoracotomy during concomitant cardiac surgery is rarely indicated, because it is associated with increased morbidity and death (96). Implantation of a transvenous system soon after recovery from the initial surgery is recommended instead.

Programming

The therapeutic target of ICD therapy should be the complete prevention of sudden death and syncope due to ventricular tachyarrhythmias using only sporadic delivery of high-energy shocks. Antitachycardia pacing is useful mostly for monomorphic VTs with rates lower than 200 beats/min (97). For these tachycardias, pacing and low-energy cardioversion both have a success rate of approximately 80% and have a similar risk of tachycardia acceleration (98). Antitachycardia pacing has the advantages of much better patient tolerance, lower energy consumption, and lack of atrial proarrhythmia (Fig. 75.4 and *e*Fig. 75.4.1).

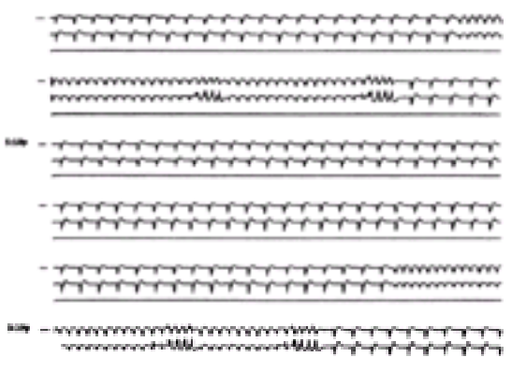


FIGURE 75.4 Antitachycardia pacing. Holter monitor shows that during a 2-minute period, two episodes of monomorphic ventricular tachycardia were converted by the scanning antitachycardia pacing algorithm (both in the second attempt). The patient remained asymptomatic. (Reproduced from Pinski SL, Simmons TW, Maloney JD. Troubleshooting antitachycardia pacing in patients with defibrillators. In: Estes NAM, Wang P, Manolis A, eds. *Implantable cardioverter-defibrillators: a comprehensive textbook*. New York: Marcel Dekker, 1994:445–477, with permission.)

***e*FIGURE 75.4.1** Stored atrial and ventricular electrograms (EGMs) and markers of an episode of ventricular tachycardia (VT) terminated by antitachycardia pacing (ATP) in a patient with a dual-chamber implantable cardioverter-defibrillator. Normal sinus rhythm (NSR) is interrupted by VT at a cycle length of approximately 320 ms with two-to-one ventriculoatrial conduction. A six-beat “ramp” of ATP restores NSR.

VF can be successfully treated only with a defibrillation shock. Charging to approximately 30 J (700 V) takes 5 to 13 seconds, depending on the model and battery status of the ICD (99). A first shock energy ³30 J, however, is not universally necessary. Programming of the initial energy at 5 J above the upper limit of vulnerability (100) or at twice the defibrillation threshold when it is <15 J (101) still results in almost 100% successful conversion of spontaneous arrhythmia episodes during follow-up. The shorter charge time decreases the risk of arrhythmia-induced syncope. If the first shock fails, the device will recharge and deliver up to five additional high-output shocks. Spontaneous episodes of de novo VF are not common, even in patients with a history of this arrhythmia (102). Most episodes begin as fast monomorphic VT, which the ICD detects and cardioverts before it has an opportunity to spontaneously degenerate into fibrillation.

ICDs recognize ventricular tachyarrhythmias based on programmable rate and duration criteria. Assuming correct sensing of the cardiac depolarization signal, this ensures 100% sensitivity for tachycardias above the programmed cutoff rate, but the specificity may be poor (103). Underdetection of tachycardias is uncommon when adequate sensing has been demonstrated during implantation. With some integrated bipolar leads, underdetection of VF has occurred after a failed shock. Increasing the distance between the distal tip and coil has largely averted this problem (104).

Failure to discriminate between supraventricular and ventricular tachyarrhythmias results in clinically inappropriate ICD interventions. Many of these spurious interventions can be avoided by adequate device programming. The cutoff rate for tachycardia detection should ideally be programmed to be higher than the patient’s maximal exercise-induced sinus rate. However, in many patients (more frequently in those on antiarrhythmic drugs), the sinus and VT rates overlap. Detection enhancements can be programmed that will improve the accuracy of arrhythmia diagnosis. The sudden onset criterion helps to discriminate between sinus tachycardia and VT, and the rate stability criterion is useful in rejecting atrial fibrillation with a rapid ventricular response (105). Morphology criteria assess the differences (e.g., width) in the intracardiac QRS electrogram between beats of supraventricular and ventricular origin. The incorporation of these enhancements into the detection algorithms represents a trade-off between sensitivity and specificity; a perfectly specific algorithm may fail to detect some episodes of hemodynamically significant VT (106,107). However, empiric enabling of conservative discrimination criteria is safe and effective in reducing the occurrence of inappropriate shocks (108). In some devices, a programmable sustained high rate criterion overrides the other enhancement criteria and allows therapy delivery for persistent tachycardia episodes that did not fulfill enhancement criteria. Dual-chamber ICDs can achieve better discrimination between ventricular and supraventricular arrhythmias by incorporating information that originates in the atrium into the detection algorithms (109) (Fig. 75.5 and *e*Fig. 75.5.1). However, the diagnostic performance of these devices is algorithm dependent, and in some cases, it may not surpass that of single-chamber devices with optimal programming (110).

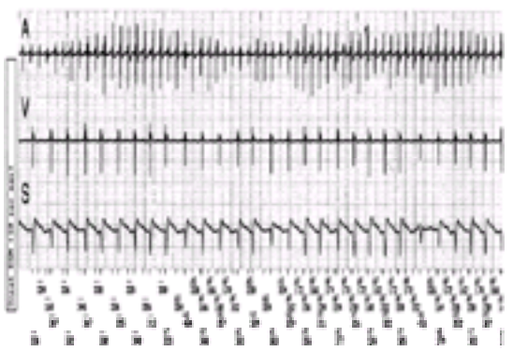
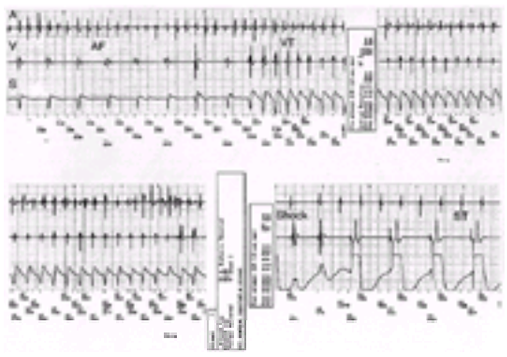


FIGURE 75.5 Accurate rejection of atrial fibrillation with rapid ventricular response by a dual-chamber implantable cardioverter-defibrillator. Stored atrial (A), ventricular (V), and shocking lead (S) electrograms (EGMs) show a very rapid atrial rate (approximately 350 beats per minute) and an irregular ventricular rate of approximately 165 beats per minute. Despite the fact that the ventricular rate was within the programmed ventricular tachycardia detection window, the device interpreted the fast

atrial rate and the slower and irregular ventricular rate as representing atrial fibrillation and appropriately withheld intervention.



***e*FIGURE 75.5.1** Appropriate detection of “dual” tachycardias by a dual-chamber implantable cardioverter-defibrillator. Atrial (A), ventricular (V), and shocking leads (S) stored electrograms (EGMs) show initial atrial fibrillation (AF) with paced ventricular rhythm followed by the sudden onset of fast ventricular tachycardia (VT). The VT is detected and a 31-J shock terminates both arrhythmias. A sinus (or atrial) tachycardia (ST) that is faster than the upper tracking rate ensues. The device initiates atrial-synchronous ventricular pacing with a two-to-one response.

The VVI(R) antibradycardia pacing in single-chamber ICDs is useful in patients who have intermittent or shock-induced bradyarrhythmias, but it has a more limited role in patients who need permanent pacing. It has been estimated that up to 55% of patients could benefit from use of a dual-chamber ICD (111). Widely accepted indications for dual-chamber pacing may be present in as many as 30% of patients who require ICD implantation (111,112). The frequent need to add drugs that have negative chronotropic effects (e.g., amiodarone or sotalol) in patients in whom ICDs have been implanted for control of VT may justify use of a dual-chamber ICD system in some patients who do not have documented bradycardia (113). Industry surveys estimate that in 1999, 50% of the ICDs implanted in the United States and 30% of those implanted in Europe had dual-chamber pacing capabilities (113).

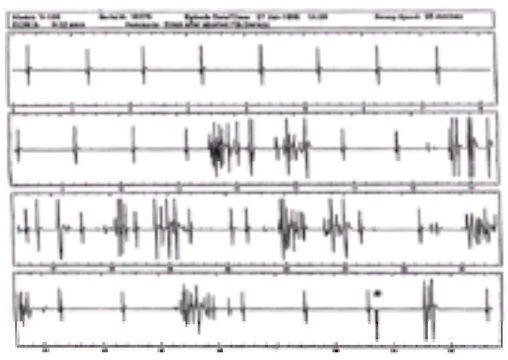
ICDs capable of dual-chamber, rate-responsive pacing have nearly eliminated the need for separate pacemakers while increasing the clinical importance of recognizing ICD pacing malfunction, especially in pacemaker-dependent patients (114). ICDs can display the same causes of pacing malfunctions seen in permanent pacemakers, including oversensing of interference, lead dislodgment or failure, exit block, premature battery depletion, random component failure, and software error. It is recommended that higher pacing outputs be programmed for approximately 1 minute to prevent failure to capture immediately after a defibrillation shock. Because of their higher sensitivity, ICDs are more likely than pacemakers to oversense extracardiac (e.g., myopotentials or electromagnetic fields) or intracardiac (e.g., T waves) interference. The lack of magnet-triggered or programmable asynchronous pacing modes makes the management of pacing-dependent ICD patients difficult during procedures that involve sources of electromagnetic interference.

ICD interventions can have proarrhythmic effects, which are rarely fatal but increase the morbidity associated with device therapy (115). ICD-induced proarrhythmia often results from inadequate programming. Prevention of proarrhythmia triggered by appropriate device interventions (e.g., tachycardia acceleration) is based on tailoring of antitachycardia therapies to the individual patient. When acceleration of VT occurs, prompt delivery of a high-output shock will generally prevent syncope (116) (*e*Fig. 75.5.2). Prevention of proarrhythmia resulting from the delivery of inappropriate therapies depends on the optimization of sensing parameters and detection algorithms, the suppression of the triggering rhythms, or both.

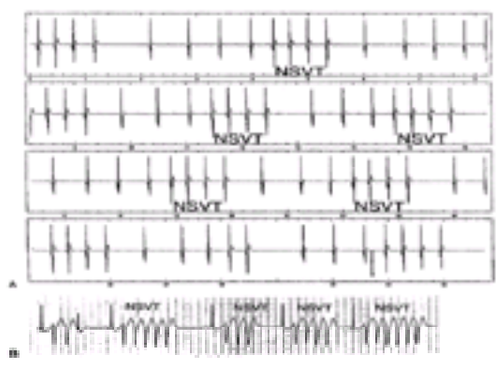
***e*FIGURE 75.5.2** Acceleration of ventricular tachycardia (VT) by antitachycardia pacing (ATP). Stored ventricular electrogram and marker show initial VT with a cycle length of approximately 310 ms. A seven-beat “ramp” of ATP accelerates the VT to a cycle length of approximately 250 ms. The faster tachycardia is detected in the ventricular fibrillation “zone” and promptly terminated with a 19.9-J shock. The patient felt lightheaded but had no syncope. NSR, normal sinus rhythm.

Follow-Up and Long-Term Complications

Follow-up of ICD patients is best carried out in a focused device clinic (117). Routine follow-up should include taking a careful history with regard to interim symptoms of tachyarrhythmias and ICD discharges; device interrogation (including real-time telemetry of battery status and retrieval of diagnostic data from the memory) (*e*Fig. 75.5.3 and *e*Fig. 75.5.4); and determination of pacing and sensing thresholds. Radiologic examination can demonstrate lead displacement or migration but is less useful for the identification of lead fractures (118). Routine predischarge noninvasive arrhythmia induction in the electrophysiology laboratory is no longer recommended (119). It should be selectively performed when satisfactory testing is not achieved during implantation or when treatment with antiarrhythmic drugs that can decrease defibrillation efficacy is added during follow-up (120). The relative merits of empiric programming of detection and therapeutic algorithms (121) for VT versus fine-tuning based on the results of noninvasive arrhythmia induction are not clear (122).



***e*FIGURE 75.5.3** Stored electrograms (EGMs) from a patient with lead fracture. The breakdown produced “make-and-break” signals that were recognized as a ventricular tachyarrhythmia. Because the signals were present intermittently, the device could not “reconfirm” the arrhythmia, and the shock was not delivered. The lead was replaced. Early identification of the problem prevented premature battery depletion.



***e*FIGURE 75.5.4** Value of stored electrograms (EGMs) in patients with aborted shocks. Stored EGM **(A)** of a patient who has multiple aborted shocks caused by frequent nonsustained runs of ventricular tachycardia (NSVT). The diagnosis was confirmed with electrocardiographic monitoring **(B)**, and the arrhythmia was suppressed pharmacologically.

Approximately 40% of patients receive appropriate discharges during the first year of follow-up after implantation of an ICD. The rate of new first shock drops by 10% each year after the first (123,124). Appropriate device activation occurs sooner and more often in patients with spontaneous (123) or inducible sustained monomorphic VT (124). There is a morning peak in device activation for rapid ventricular tachyarrhythmias, which is observable in patients with and without ischemic heart disease (125). Some studies have found a similar prognosis in patients whose devices did or did not fire (124), whereas other studies have demonstrated worse outcome in patients who present with ventricular arrhythmias that trigger shocks, especially in patients in whom more than one shock is necessary for termination of arrhythmia (126). The occurrence of clusters of VT that require multiple shocks is also associated with a poor outcome (127,128).

Complete withdrawal of antiarrhythmic drugs is a desirable (but not always attainable) goal in patients with ICDs (129). Indications for concomitant antiarrhythmic drug therapy include suppression of frequently recurring ventricular arrhythmias that trigger device intervention, suppression of supraventricular arrhythmias, and slowing of VT to avoid syncope and facilitate pace termination. In a double-blind, placebo-controlled study of 302 patients, sotalol was significantly effective in reducing the incidence of death from any cause or the delivery of a first shock for any reason (including appropriate and inappropriate shocks) (130). In a smaller study of 70 patients with ICDs, metoprolol was significantly more effective than sotalol in preventing recurrences of ventricular tachyarrhythmias (131). Amiodarone is also used often to decrease the incidence of shocks, although definitive controlled data regarding its efficacy for this indication are lacking. Treatment with amiodarone seems to decrease the incidence of shocks compared with treatment with class I drugs (124,132). Potentially significant interactions between antiarrhythmic drugs and ICD systems include dose-dependent increases in defibrillation [lidocaine (133), procainamide, flecainide, and amiodarone (134)] or pacing (flecainide) energy requirements; slowing of VT rate below the programmed cutoff (135); and increases in latency or conduction time leading to double counting, reduced efficacy of antitachycardia pacing, and proarrhythmic effects.

Long-term complications are not uncommon during ICD therapy. Transvenous defibrillator leads have a relatively high structural failure rate (e.g., conductor fracture or insulation cracking) causing spurious shocks (delivered or aborted), undersensing, or loss of pacing capture and requiring operative lead replacement (91,136). The incidence of lead failure may be higher when subclavian puncture is used for venous access (137). Rarer hardware problems include inadvertent device inactivation by electromagnetic fields, premature battery depletion, random component failure, and twiddler's syndrome.

Even with dual-chamber discrimination algorithms, some supraventricular tachyarrhythmias are detected as ventricular, resulting in spurious shocks (138). The incidence of spurious shocks is higher (>20% of patients) with single-chamber ICDs, especially when they are left at nominal programming settings (89). In patients with spurious shocks, reprogramming of detection criteria to increase specificity should be attempted first. It is often necessary to add pharmacologic therapy to reduce the sinus rate, prevent recurrences of paroxysmal atrial tachyarrhythmias, or slow AV conduction. Catheter ablation may also be considered.

Quality of Life

Most patients adapt well to living with the ICD, in a process described as "securing life through technology acceptance" (139). Studies examining quality of life measured before and after ICD implantation have showed unchanged or improved quality-of-life scores after implantation (140,141). Common concerns in ICD patients include fear of shocks, fear of device malfunction, fear of public shocks and embarrassment, and altered body image (142). Younger patients worry about the need for repeat surgeries, the cosmetic appearance of the device and the scar, and risks during pregnancy (143). However, ICD implantation is compatible with subsequent normal pregnancy and delivery (144).

Experiencing an ICD shock can be frightening. Most patients perceive ICD shocks as quite uncomfortable, comparing them with a jolt from an electric socket or a kick in the chest. Fewer than 15% of patients lose consciousness during the lag between arrhythmia onset and device discharge (145). Patients who receive multiple shocks have higher levels of anxiety, anger, and depression (146,147). A few patients develop adjustment disorders specific to the ICD, such as anticipatory anxiety with secondary panic reaction and phobia, imaginary shocks, and defibrillator dependence, abuse or withdrawal (148). Patient support groups provide a valuable opportunity for dissemination of relevant information, alleviation of anxiety, and promotion of a positive attitude toward device therapy (149). Psychotherapeutic counseling, behavioral therapies (150), and psychotropic medication may be required. Some antidepressant and antipsychotic drugs have proarrhythmic effects similar to those of antiarrhythmic drugs and should be used with caution in patients with ICDs.

Safety issues arise frequently during the follow-up of patients with ICDs. Most of these patients are able to exercise safely when appropriate clinical guidelines are provided (151). The ability to drive is an important determinant of quality of life; however, although prohibition from driving is a major inconvenience, safety must be the most important consideration. Arrhythmia-induced impairment of consciousness during driving could harm the patient or others.

The risks associated with noncommercial driving by ICD patients appears to be low. Using an equation incorporating the time the patient spends driving, the type of vehicle driven, the risk of sudden death or incapacity, and the probability that sudden death or incapacity that occurs while the patient is driving will result in death or injury to others, it can be estimated that the annual risk of harm to others is 1 in 45,000 for noncommercial drivers with ICDs. The annual risk for commercial drivers is unacceptably high, at 1 in 2,100 (152). A survey of U.S. physicians reported 30 motor vehicle accidents (nine of which were fatal) involving ICD patients over a 12-year follow-up period (153). Eight patients, one passenger in a car driven by a patient with an ICD, and no bystanders were killed. Based on these data, the fatality and injury rates for patients with ICDs were estimated to be significantly lower than in the general population.

Most U.S. states do not have specific laws governing driving by ICD patients. A joint statement by the American Heart Association and the North American Society of Pacing and Electrophysiology (154) advised that patients who had ICDs implanted for sustained ventricular tachyarrhythmias refrain from private driving for 6 months after implantation and for 6 months after each subsequent shock. [In survivors of VT or VF, the risk of arrhythmia recurrence is higher soon after an index event and decreases to <0.7% per month after the seventh month (155).] Noncommercial driving should not be restricted in patients who receive ICDs for prophylactic indications. Commercial driving should be prohibited entirely in ICD patients. Slightly different recommendations have been issued by the Working Groups on Cardiac Pacing and Arrhythmias of the European Society of Cardiology (156). These restrictions could represent a hardship, especially for patients with sporadic nonsyncopal arrhythmias that trigger single shocks that do not warrant pharmacologic suppression, who may display low compliance (157). Many ICD patients resume driving early, against physician recommendations, but they tend to drive only when absolutely necessary, avoiding rush hour, highways, and night driving (158).

Because many patients who receive ICDs are of advanced age and have severe heart disease, they often retire before ICD implantation. For those who are still working, the type of work and the effect of the index event on physical or mental performance influences whether they return to work (159). Approximately 60% of patients do return to work, a figure similar to that seen after coronary bypass surgery (160). Ability to work may be transiently or permanently hindered by the need to restrict motion of the ipsilateral arm for several weeks after implantation, by private driving limitations, by the risk of syncope during operation of machinery, by the risks associated with electromagnetic radiation in the workplace (e.g., arc welders), and by prohibition of commercial driving.

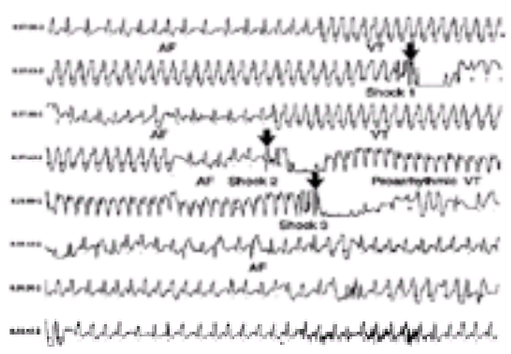
Patients frequently ask about the risks of electromagnetic radiation sources they may encounter during daily life (161). Microwave ovens represent no hazard. When traveling, patients should notify airport security personnel that they have an ICD. It is not dangerous to walk through the security gate as instructed, although it may detect the metal device. A quick pass of the hand-held weapon detector is innocuous, but prolonged exposure to its magnetic field should be avoided. Cellular telephones are unlikely to interact deleteriously with ICDs. However, it has been recommended that patients not carry or place cellular telephones within 15 cm (6 in.) of an ICD, to minimize risks. Walking through electronic antitheft devices at a normal pace has no consequences, but prolonged exposure can result in pacing inhibition, spurious shocks, or both (162).

Management of Emergencies

Guidelines for the management of medical emergencies in ICD patients have been published (163,164). Patients with ICDs should carry identification cards with information about the manufacturer, model, and lead system of the ICD and a 24-hour emergency contact telephone number. An overpenetrated radiograph including the generator permits identification of the model by a radiopaque identifier. During emergencies, placement of a magnet on top of the device when the specific programmer is not readily available can temporarily disable recognition and treatment of tachyarrhythmias. The magnetic field closes a reed switch in the generator circuit, triggering a response that differs among models. In general, tachyarrhythmia recognition and treatment is disabled as long as the magnet remains close to the generator. Pacing is not affected.

The presence of an ICD should not deter standard resuscitation techniques. If VF is documented, it should be assumed that the device is inoperative, and external defibrillation should be administered promptly. Transvenous ICD systems do not affect the energy requirements for external defibrillation. Anyone administering cardiopulmonary resuscitation might feel a mild electric shock on the patient's body surface from an ICD discharge. Although these shocks do not pose a risk to people (165) or to monitoring equipment, it is advisable, when possible, to deactivate the ICD during cardiopulmonary resuscitation. Supraventricular tachycardias with adequate perfusion are common during resuscitation maneuvers and can trigger ICD discharges that may reinduce VT or VF (115).

Multiple defibrillator discharges within a short period require prompt attention (eFig. 75.5.5). Multiple shocks can be a manifestation of ICD system failure; can result in significant battery drainage, leading to premature depletion; and may produce psychological morbidity. Accurate diagnosis is needed for correct management (eTable 75.2.1). Initial evaluation of patients with multiple ICD shocks should be performed in a setting in which electrocardiographic monitoring and advanced cardiac resuscitation are possible. The device should be interrogated as soon as possible. Detailed event logging and storage of interval-by-interval cycle length data and intracardiac electrograms of detected tachyarrhythmias facilitate the diagnosis. Electrical storm (i.e., frequently recurring VT or VF) occurs in 10% of patients (166). Patients with electrical storm should be admitted to an intensive care unit. Sympathetic blockade and intravenous amiodarone are often effective in treating this condition (167). If spurious firing is documented, the ICD should be deactivated and the patient placed under continuous electrocardiographic monitoring. Consultation with the cardiac electrophysiologist is required for definitive treatment (reprogramming or hardware revision). The ICD should be reactivated only after the condition that triggered the spurious shocks is controlled.



***e*FIGURE 75.5.5** Multiple appropriate and inappropriate shocks. Monitor lead shows atrial fibrillation (AF), followed by ventricular tachycardia (VT). A first shock terminates VT, but VT reinitiates before the device algorithms can declare the "end" of the arrhythmia episode. This second run of VT self-terminates, but a second shock is nevertheless delivered during AF because of idiosyncrasy in the arrhythmia confirmation algorithm. This "committed" shock is proarrhythmic, triggering a faster VT, which is finally terminated by a third shock. AF persists afterwards.

***e*TABLE 75.2.1** MANAGEMENT OF PATIENTS WITH MULTIPLE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR SHOCKS

Cause for implantable cardioverter-defibrillator shocks	Acute management	Definitive management
Appropriate discharges for sustained ventricular tachyarrhythmias		
Frequently recurring VT or VF (electric storm)	Treatment of reversible triggering causes	Optimization of oral AADs
	Sedation	Antitachycardia pacing
	Sympathetic blockade	Surgical or catheter ablation of VT
	i.v. AADs (especially, i.v. amiodarone)	
	Consider temporary device inactivation	
Multiple shocks required for termination of VT or VF	External cardioversion/defibrillation	Optimization of oral AADs
Acute ischemia	Treatment of reversible triggering cause	Device reprogramming
Programming of inappropriately low shock output	Avoid class I AADs	Surgical revision of the system
Antiarrhythmic drug effect		
Shocking lead dislodgment or failure		
Inappropriate (spurious) discharges		
"Committed" shocks for nonsustained ventricular arrhythmias	i.v. AADs	Device reprogramming
	Consider temporary device inactivation	Optimization of oral AADs
Supraventricular tachyarrhythmias	Temporary device inactivation	Device reprogramming
	AV nodal–blocking drugs	Optimization of oral AADs
	Pharmacologic or electrical cardioversion	Catheter ablation of arrhythmia circuit
		Catheter ablation of AV junction
Oversensing during sinus (or paced) rhythm	Temporary device inactivation	Device reprogramming
Oversensing of intracardiac (e.g., T waves) or extracardiac (e.g., myopotentials) signals		Surgical revision of the system
Sensing of external electromagnetic interference		

AADs, antiarrhythmic drugs; AV, atrioventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

Many diagnostic and therapeutic procedures involve sources of electromagnetic radiation that could affect ICD function (161). Possible effects include cessation or intermittent delivery of antibradycardia pacing, inadvertent delivery of antitachycardia therapy, resetting of programmed parameters, and damage to the pulse generator, the tissues interfacing with the electrodes, or both. Most diagnostic and therapeutic maneuvers, including electrosurgery, shock wave lithotripsy (168), electroconvulsive therapy (169), and most imaging methods, can be safely performed under continuous electrocardiographic monitoring in ICD patients. Trained personnel should be readily available to deactivate the device before the procedure and to reactivate it and confirm that it is operating appropriately afterward. Magnetic resonance imaging is contraindicated in ICD patients because of the very strong electromagnetic fields involved.

COST-EFFECTIVENESS OF THE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

ICD hardware is expensive. In the United States, the cost to the hospital of a modern ICD system ranges between $20,000 and $25,000. In comparison, a rate-responsive dual-chamber pacemaker system costs approximately $7,000, and the retail cost of a 1-year supply of 400 mg of amiodarone daily is $2,200. So far, competition among ICD manufacturers has not resulted in the substantial decreases in hardware price that could be expected in an economically efficient market.

Appraisal of the cost-effectiveness of ICD therapy is difficult, because continuous technological advances and changes in practice patterns make analyses obsolete rapidly (170). The cost-effectiveness of the ICD has been estimated in mathematical models and from empirical data prospectively collected during randomized studies. Both approaches have limitations. The conclusions of cost-effectiveness models differ greatly according to the many assumptions that are introduced. In a detailed analysis, Owens and colleagues (171) estimated that to become economically "attractive" (i.e., cost less than $50,000 per quality-adjusted life year gained), the ICD would have to reduce total mortality by at least 30% relative to amiodarone (a magnitude of benefit observed in some, but not all, randomized studies). When a reduction in the total mortality rate of 40% was assumed, the cost of one quality-adjusted life year afforded by treatment with the ICD was $37,300. Sensitivity analysis showed that reductions in perioperative death and implantation costs and prolongation of battery longevity (already realized in current practice) would significantly improve the cost-effectiveness of the ICD.

Measurement of costs (or charges) has been an integral part of randomized studies comparing the ICD and pharmacologic therapy of ventricular tachyarrhythmias. These analyses depend critically on the relevance of the control maneuver and the treatment effect observed in the study. Furthermore, changes in ICD technology

and practice patterns tend to make results less relevant by the time they become available.

An early, small study by Wever and associates (172) involving survivors of cardiac arrest with prior myocardial infarction compared early ICD implantation to the (then more conventional) strategy of serial electropharmacologic testing, followed by direct arrhythmia surgery or ICD implantation in case of drug failure. The study was terminated prematurely after the enrollment of 60 patients because of a survival advantage in the ICD group. After a follow-up period of 24 months, 13% of patients in the early implantation ICD group died versus 35% in the conventional strategy group ($p = .07$). The costs per patient per day alive were $63 and $94 for ICD and electrophysiology-guided strategies, respectively. This amounted to a net cost-effectiveness of $11,315 per life-year saved by early ICD implantation. The ICD group also underwent fewer invasive procedures and spent fewer days in the hospital. Although in this small study, early ICD implantation was dominant (i.e., more effective and cheaper), the results are difficult to extrapolate because the control group did not reflect current optimal management.

In MADIT, the cost per life-year gained with ICD treatment was $27,000 (173). Sensitivity analyses highlighted the impact of technological advances and hardware price in the cost-effectiveness of ICD therapy. Exclusive use of transvenous systems (in MADIT, approximately one-half of the patients received thoracotomy defibrillators) would decrease the cost per life-year gained to $22,800; a 25% decrease in device cost would reduce the cost per life-year gained to $13,100. This very favorable cost-effectiveness ratio was partially driven by the impressive survival benefit (54%) conferred by the ICD, which appears to be at the upper end of plausible results. Furthermore, the costs of screening for eligible patients were not factored.

The economic analysis in CIDS included the first 430 patients enrolled in the study (174). Costs were provided in 1999 Canadian dollars (C$1 ~ U.S.$0.65). Over 6.3 years, mean cost per patient in the ICD group was C$87,715 versus C$38,600 in the amiodarone group (difference, C$49,115; 95% confidence interval, C$25,502 to C$69,508). Life expectancy for the ICD group was 4.58 years versus 4.35 years for amiodarone (difference, 0.23; 95% confidence interval, –0.09 to 0.55), for incremental cost-effectiveness of ICD therapy of C$213,543 per life-year gained. ICD benefit was greater in patients with low left ventricular ejection fraction (<35%), and cost-effectiveness in this group was more attractive (C$108,484). Alternative extrapolations of survival benefit and costs to 12 years indicated cost-effectiveness in the range of C$100,000 to C$150,000 per life-year gained. The results of the economic analysis in AVID are eagerly awaited.

Streamlining of clinical practices will result in improved cost-efficiency. For example, ICD implantation after a major arrhythmic event without extensive electrophysiologic evaluation may decrease costs without compromising outcome (175). Modeling in AVID suggested that for every 1-day differential reduction in the initial length of the hospital stay, the cost-effectiveness ratio of the ICD would improve by $6,300 (174). Likewise, a reduction in hospitalizations for multiple appropriate or inappropriate shocks [a prominent source of health care expenditures in ICD patients (176)] that is achievable with improved device diagnostic and therapeutic algorithms should also make the ICD more cost-effective.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Knowledge about basic electrophysiologic mechanisms is accumulating rapidly. However, despite advances in the understanding of the structure and function of cardiac ion channels (177), the electrophysiologic heterogeneity of myocardial cells (178), and the fundamental mechanisms of reentry (179), clinical applications remain scarce (180,181). The development of widely effective and safe gene (182), pharmacologic, or ablative therapies for ventricular arrhythmias is not likely in the foreseeable future. In the long run, the best strategy for preventing sudden cardiac death will be the prevention of coronary artery disease and its sequelae. We believe that, in the meantime, ICDs will become a key clinical tool in the fight against sudden death.

During the next decade, progress in ICD therapy will occur on both the clinical and technological fronts. Primary prevention trials will identify additional populations who will benefit from ICD implantation. Current validated indications restrict prophylactic use to patients with previous myocardial infarction and are based on inducibility of VT at invasive electrophysiologic study. Identification of ICD candidates with other substrates and with noninvasive methods could greatly expand the application of this therapy. If that is the case, the cost-effectiveness of ICDs will be very carefully scrutinized. In view of the potential allocation of scarce resources to diverse therapies and populations, society will have to decide the extent to which ICDs should be used.

Two avenues have been proposed to improve cost-effectiveness: more refined risk-stratification (183) (cost-effectiveness should be most favorable in patients at high risk for sudden death but at low risk of dying from competing causes) and reduced costs. It is quite apparent that not all patients with ventricular tachyarrhythmias have the same prognosis (69). The pooled AVID/CIDS/CASH analysis showed significantly higher benefit in patients with severe left ventricular dysfunction (44). The CIDS investigators devised a clinical prediction rule to identify patients likely to benefit from ICD therapy that included two or three of the following: age ³70 years, left ventricular ejection fraction £0.35, and New York Heart Association class III or IV (184). However, post hoc prediction rules should not be accepted without prospective validation. When the same rule was applied to the AVID population, it lacked discriminatory power (185). It is likely that the relationship between severity of heart disease and benefit from ICD has an inverted U shape. Patients with severe (but not end-stage) heart disease should benefit the most, but patients with severe heart failure and those with almost normal heart function will benefit less. However, specific thresholds for identifying patients who will not benefit are unlikely. Furthermore, patients who have life-threatening ventricular arrhythmias but mild structural heart disease have a low risk of dying from competing causes, and a survival benefit should be apparent with longer follow-up.

It has been speculated that manufacturers could make prophylactic ICD therapy more cost-attractive by making stripped-down devices available (i.e., single-chamber shock-only units capable of delivering only a limited number of shocks and with shorter longevity) at a significant discount. However, we foresee strong resistance from clinicians in the United States to implanting suboptimal hardware that could require premature replacement in at least some patients. The approach may be more viable in countries with centralized financing of health care.

Paradoxically, the ICD may help to develop safe and effective pharmacologic therapies by providing a safety net in randomized clinical trials of new antiarrhythmic drugs (186). Advances in storage, retrieval, and accurate interpretation of ICD electrograms may allow the use of an ICD end point as a clinical surrogate for sudden death. However, the extent to which the results of data on antiarrhythmic drug efficacy and safety acquired in the context of an ICD endpoint trial might be extrapolated to patients not using the device is controversial.

The debate over whether surgical or medical practitioners should be providers of ICD therapy has been largely settled, and, at least in the United States, cardiac electrophysiologists now perform most implants (187). However, because of the broadly accepted indications and the ease of implantation, the debate has now shifted within the cardiology community as cardiologists without specific electrophysiology training have begun to indicate ICD treatment, implant the devices, and follow up after implantation in some institutions (188). The body of knowledge and the experience for such practices have been promulgated by professional organizations, and the implementation of ICD therapy by unqualified practitioners should be viewed with great concern. For example, training guidelines for ICD implantation from the American College of Cardiology require that a clinician perform 20 procedures as the primary operator, and they also consider the maintenance of established competence critical (189). For pacemaker implantation, inexperience (e.g., performance of fewer than 12 implants per year) is the main determinant of surgical complications (190), and a similar association can be expected for ICDs. The availability of systems with very different capabilities, from the simple single-chamber unit to the complex combined atrioventricular defibrillators or triple-chamber units that provide resynchronization therapy, makes understanding the value and limitations of these devices in relation to the individual patient's needs crucial.

The increasing versatility of the devices has made programming and troubleshooting complicated and time-consuming. The untrained physician who is a "casual" follower of ICDs may rely excessively on the expertise of manufacturer representatives to determine appropriate device function. This practice is questionable on both medical and ethical grounds and cannot guarantee optimal results (191). As stated by professional organizations, cardiac electrophysiologists should prescribe the type of ICD, be involved in the implant, and provide follow-up care of ICD patients (57).

THE FUTURE

ICD technology will continue to evolve. The next generation of devices will be smaller, owing to improvements in battery and capacitor technology and optimization of shock waveforms and electrodes. Emphasis will be placed on decreasing the complexity of programming, device interrogation, and patient monitoring during routine patient follow-up. The addition of sensors to assess the hemodynamic impact of tachyarrhythmias will further refine therapy delivery and eradicate spurious device interventions. Continuous monitoring for myocardial ischemia (192), subtle hemodynamic decompensation (193), and electrical instability (194) will be feasible. The device could warn the patient, automatically transmit data to a Web-based server accessible by authorized health care staff, and then initiate corrective action. The capability to intervene before an arrhythmia occurs is particularly desirable (195). Future research should produce reliable methods of predicting impending VT or VF. VF may be a form of deterministic chaos whose development is compatible with the quasiperiodic route seen in fluid dynamics (196). Potential preventive interventions include multisite pacing (197,198), pacing algorithms aimed at the suppression of long-short cardiac cycle sequences (199), subthreshold stimulation of arrhythmogenic tissues exploiting the phenomenon of cardiac inhibition (200), and the timely infusion of antiarrhythmic or antiadrenergic agents via a venous port. Specific pacing algorithms also have the potential to prevent atrial fibrillation. During the next decade, we will witness the culmination of the evolution of the ICD from a "shock-box" to a smart, multimodal monitoring, communications, and therapeutic unit.

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TRANSTHORACIC ELECTRICAL DEFIBRILLATION AND CARDIOVERSION

GORDON A. EWY

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Few therapies are more dramatic or more decisive to patient outcome than electrical defibrillation of ventricular fibrillation (VF). Untreated VF is invariably fatal within minutes. The sooner that electrical defibrillation shocks are delivered, the greater the likelihood of survival. Transthoracic electrical defibrillation is accomplished by passing an adequate current density of appropriate waveform through the fibrillating myocardium. Evidence is increasing that biphasic waveforms are more effective and safer than the monophasic damped sine waveform (MDS) that has been in use over the past four decades.

To assure success, the operator needs to know how to operate the external defibrillator, the proper electrode position, and, unless the defibrillator is automated, the appropriate shock strength. The operator also needs to know the factors that determine transthoracic resistance or impedance to defibrillator shock so as to assure adequate current delivery and the factors to consider and the actions to take if the patient fails to defibrillate.

The optimal approach to electrical cardioversion of reentrant-type supraventricular arrhythmias requires proper placement. Disposable electrode pads are commonly used and work most of the time, but in larger adults, metal electrodes, gels with excellent conductance characteristics, and other techniques that assure the lowest transthoracic impedance may be necessary.

GLOSSARY

Amps: A measurement of electrical current.

Cardiac arrest, primary: Cardiac arrest in a patient without severe heart failure or cardiogenic shock.

Cardiac arrest, secondary: Cardiac arrest in a patient with severe heart failure or cardiogenic shock.

Cardioversion: The termination of tachycardia or fibrillation by an electrical shock.

Current: The flow of electricity.

Defibrillation: The termination of ventricular fibrillation, irrespective of the resulting rhythm.

Energy: The exertion of power; the capacity to do work.

Impedance: The opposition to changing electrical flow or current.

Joule (J): One joule is equal to 1 watt-second.

Resistance: The opposition to steady electrical flow or current.

Threshold, defibrillation: The minimal energy level at which defibrillating shocks produce defibrillation.

Volt: Unit of electrical pressure or electromotive force.

Voltage: Electromotive force, electrical pressure, or potential expressed in volts.

Watt: A unit of electrical power. One watt is the power available when the current is 1 A and the electromotive force is 1 V.

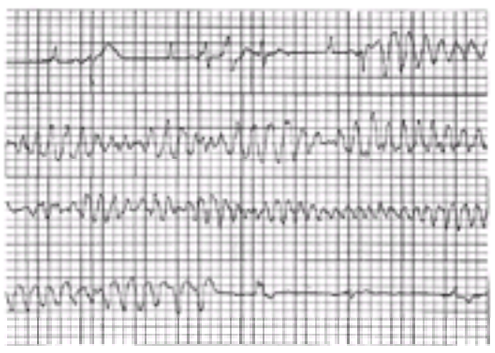
Waveform, defibrillation: The shape of the current, voltage, or power wave from a defibrillator discharge.

INTRODUCTION

The dictionary defines *defibrillation* as the arrest of fibrillation of the cardiac muscle (atrial or ventricular) with the restoration of normal rhythm (1) and *cardioversion* as the restoration of the heart's rhythm to normal by electrical countershock (1). Thus defined, these terms have significant overlap. Practically, however, the medical community uses the term *defibrillation* to mean the termination of VF, irrespective of the resulting rhythm, and *cardioversion* to mean the termination of a tachycardia or fibrillation by drugs, pacing, or electrical shock. Defibrillation and termination of reentrant tachycardias can be accomplished by electrical, mechanical, or pharmacologic means. This chapter addresses transthoracic electrical defibrillation and cardioversion. Implantable cardioverter-defibrillators are the subject of Chapter 75.

Defibrillation

Within minutes, untreated VF is invariably fatal. Accordingly, few therapies are more dramatic or more decisive to patient outcome than electrical defibrillation. In rare instances, spontaneous reversion of VF occurs, but many of these are in fact instances of polymorphic ventricular tachycardia (*e*Fig. 76.0.1) that is incorrectly assumed to be VF.



***e*FIGURE 76.0.1** Electrocardiographic monitor lead showing torsades de pointes in a 78-year-old man who had recurrent syncope. Note the spontaneous conversion to a perfusing rhythm.

The shock of electrical defibrillation is designed to depolarize a critical mass of the ventricles. Provided the factors that initiated the VF are no longer present, this shock depolarizes the ventricles and allows the development of a potentially perfusing rhythm. The exact mechanism of defibrillation by the shock is unknown but is thought to prolong the action potential duration of a significant number of myocytes, blocking the reentrant circuit. However, if the shock is delayed, there are longer periods of nondepolarization of the action potentials, and defibrillation success decreases (2). With further delays, prolonged underperfusion of the contracting myocytes results in depletion of their energy stores. Delayed defibrillation in effect allows the ventricles to "autoinfarct." In this situation, even if VF is terminated, the resulting rhythm is most likely to be idioventricular or asystole.

This chapter reviews transthoracic electrical defibrillation and cardioversion and updates previous authored and coauthored chapters and reviews (3,4,5 and 6).

Cardiac Arrest

The most common cause of cardiac arrest is VF. This is fortunate, because this arrhythmia responds to therapy more often than does asystole or pulseless electrical activity, the other major causes of cardiac arrest.

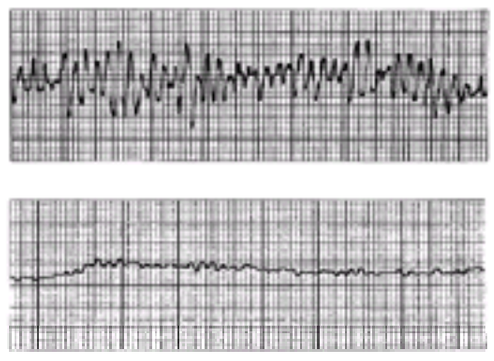
Cardiac arrest from VF has been divided into primary and secondary causes. Patients with primary electrical disturbances have a better prognosis than do those with VF secondary to periods of prolonged myocardial hypoperfusion from severe hypotension or shock.

It is well recognized that the more important determinant of survival from unexpected or primary cardiac arrest is the interval between the onset of VF and defibrillation (7). If defibrillation is delayed, the speed with which basic life support is initiated becomes the second most important determinant.

VENTRICULAR FIBRILLATION

Etiology

VF (*e*Fig. 76.0.2) results from the chaotic electrical excitation of the ventricles (2,3,6,8). It is best explained by reentrant depolarization of the myocardium, initially in waves that then take more circuitous routes and degenerate into smaller reentry circuits (3,8,9). The hemodynamic consequence is the loss of coordinated contractions of the myocytes, resulting in the loss of the rhythmic contractile function of the ventricles, which is so essential to life.



***e*FIGURE 76.0.2** Electrocardiographic recordings of subjects in ventricular fibrillation. **Top:** Coarse ventricular fibrillation. **Bottom:** Fine ventricular fibrillation.

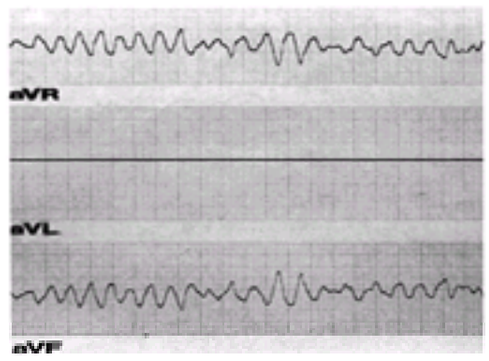
The larger and more diseased the heart, the easier it is to fibrillate. Small hearts are difficult to fibrillate. It is difficult to kill a rodent by VF, as once the 60-Hz fibrillating current is removed, the heart often returns to sinus rhythm. If a fibrillating heart of a larger animal is cut in two, both halves continue to fibrillate, but when cut again and again fibrillation stops when the remaining ventricular muscle size is too small to sustain the reentrant circuits of VF (4). It is difficult to fibrillate a puppy's heart but easy to fibrillate an adult dog heart. These facts have immense clinical importance, as cardiac arrest in neonates and children is most commonly due to asystole from respiratory arrest or prolonged periods of inadequate myocardial perfusion and not due to VF. In contrast, the diseased, dilated, or hypertrophied adult heart is prone to VF.

VF is most frequently the result of deterioration of ventricular tachycardia or is from myocardial ischemia or infarction. The most common cause of ventricular

tachycardia is scarring from an old myocardial infarction. It is of extreme interest, however, that in patients who have an open coronary artery to the infarcted area after myocardial infarction, the incidence of sudden cardiac death is less, suggesting that the incidence of VF is less (10). Thus, the scarring or remodeling process, or both, after myocardial infarction must predispose to reentrant ventricular arrhythmias. Another important cause of VF is heart failure, because more than one-third of patients with severe heart failure die of sudden death. VF has many other causes, including right ventricular dysplasia, hypertrophic cardiomyopathy, and atrial fibrillation in patients with preexcitation syndromes, to list just a few.

Ventricular Fibrillation Masquerading as Asystole

The electrocardiographic reflection of VF is characteristically a chaotic irregular pattern that frequently passes through but spends no time at the isoelectric point (*e*Fig. 76.0.2). Although VF is easy to recognize, in some subjects and in some leads, it can appear as a very fine VF or even as a straight line (9) (*e*Fig. 76.0.3).



***e*FIGURE 76.0.3** Simultaneously recorded electrocardiographic leads aVR, aVL, and aVF from a subject in ventricular fibrillation. This type of recording illustrates that ventricular fibrillation can appear as asystole if only one lead is monitored.

Soon after we described VF masquerading as asystole (9), McDonald (11) published a case report of this phenomenon in humans. A few years later, Ornato and associates (12) studied the effectiveness of countershocks for asystole. They found that during the course of resuscitation, countershock appeared to be effective in treating asystole, “suggesting that the rhythm diagnosed as asystole may actually be VF in many cases” (12). VF disguised as asystole has been identified by echocardiography (13). Nevertheless, most instances of fine fibrillation and asystole are the result of prolonged untreated VF. Over time, the fibrillation waves get smaller and smaller and finally become a straight line.

Ventricular Fibrillation Depletes Myocardial Energy Stores

VF is not an innocuous rhythm, even when the circulation is supported by artificial means. The rapid asynchronous contraction of the muscles increases myocardial oxygen consumption to the level that it depletes adenosine triphosphate and other energy stores (14).

The longest duration of VF that the author has observed was approximately 2 weeks! The patient was in the intensive care unit with an implanted left ventricular assist device when VF developed. Several attempts at defibrillation were not successful, and the patient was left in VF. He was sitting in a chair reading the paper, but the electrocardiographic monitor showed VF. Each day the amplitude of the VF became less coarse; a week or so later, the fibrillatory waves became fine. As the patient became more hypotensive, his electrocardiogram became a straight line. A donor heart was not available for cardiac transplantation, and he died. VF results in a greater myocardial oxygen demand than can be supplied by the coronary perfusion pressure afforded by a left ventricular assist device or by external chest compression during attempted cardiopulmonary resuscitation (CPR).

In addition to the fall in myocardial adenosine triphosphate, VF results in a marked increase in the coronary sinus concentrations of adenosine, lactate, epinephrine, and norepinephrine (15). Adenosine levels increased more than 12-fold, whereas lactate levels increased by twofold (15). Increases were also seen in epinephrine and norepinephrine concentrations (15). Increased adenosine concentrations have been associated with an increased defibrillation threshold (see the section Defibrillation Threshold).

EXTERNAL ELECTRICAL DEFIBRILLATION

Historical Perspective

The era of clinical defibrillation was initiated a half-century ago, when Beck applied alternating current (AC) directly to the fibrillating human heart. The young man was successfully defibrillated and resuscitated (3). Because, at that time, an open chest was required, defibrillation was rarely used outside the surgical suite until the mid-1950s, when closed-chest ventricular defibrillation was reported. Even this method had limited clinical application, as survival was rare because defibrillation was rarely prompt. Kouwenhoven’s experimental studies found that if the shock was delivered within 30 seconds of VF, 98% of his animals survived; if the shock was delayed just 2 minutes, only 27% lived (3). This short window of opportunity was the major barrier to the successful application of electrical defibrillation. In 1960, this time window was extended by the discovery of the closed-chest compression technique for CPR (3). When this time limit became longer, there was increased enthusiasm for defibrillators and for the development of portable defibrillators. The ensuing decades witnessed a number of improvements in defibrillators, and their clinical use became commonplace. Authority for their use was extended first to the coronary care unit nurse-specialist, then to the paramedic, to the emergency medical technician, and, during the last decade with the development of the automated external defibrillator (AED), to nontraditional providers and even to the lay public.

The history of defibrillating waveforms is one of progression from AC, to the spike-like waveform of a pure capacitor discharge, to damped sinusoidal waveforms, to trapezoidal waveforms, to the biphasic waveforms.

Indications and Contraindications to Defibrillation

With rare exceptions, the presence of VF is an indication for defibrillation. Defibrillation is contraindicated when the patient’s desire not to be resuscitated is clearly documented in his or her medical record or other legal document (16,17), when continued resuscitation efforts are determined to be futile (18), or in the extremely rare situation in which there is significant danger to the rescuers due to the patient’s location or environment.

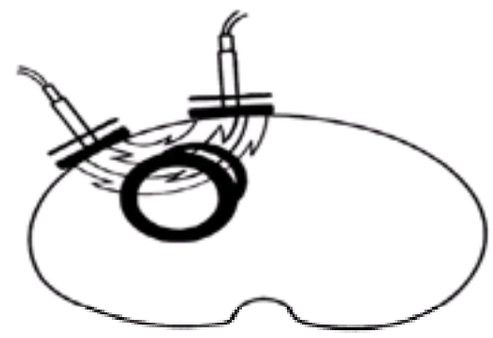
The operation of an AED is relatively easy. The electrodes are placed, and the patient is not touched until the AED analyzes the rhythm and either automatically delivers the shock or advises the operator to press a button, which causes the unit to deliver a shock. The major disadvantage of some AEDs is that, because they measure thoracic impedance, they delay defibrillation until gasping and all motion stop. The analysis takes time, and for each minute delay, resuscitation success is decreased by 10%. Although the early reports indicated that the overall time from power-on to first shock was 1.1 minutes, a post–market surveillance study found that the overall time from AED power-on to first shock was 39 ± 26 seconds and the time from pad placement to first shock was 21 ± 10 seconds (19). The arrival time in the latter report was greater than 8 minutes—a time when most spontaneous respirations would have ceased (19).

Following application of a defibrillation shock, the patient in cardiac arrest should be reassessed, clinically and electrocardiographically. If after three shocks there is still no pulse, chest compression should be initiated. If the patient remains in VF, repeated shocks or antiarrhythmic medications, or both, may be necessary. When repeated shocks fail to defibrillate, a reevaluation of the techniques used is necessary.

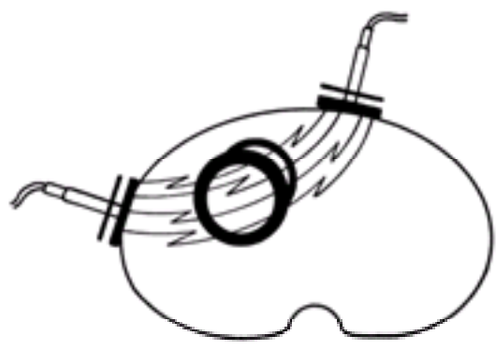
Electrode Position

Electrical defibrillation is accomplished by passing an adequate current density of appropriate waveform through the fibrillating myocardium. Because it takes a critical mass of muscle to sustain fibrillation, it is not necessary to “defibrillate” every myofibril. However, it appears that most of the myocardial mass must be defibrillated. This requires, among other things, appropriate electrode size and placement. The electrodes cannot be placed just anywhere on the chest. If they are too close together, the current tends to shunt between the electrodes and does not depolarize enough of the left ventricular mass (*e*Fig. 76.0.4). For most emergency defibrillation, the recommended electrode position is the so-called anterior-apical position. One paddle electrode is placed anteriorly under the right clavicle just to the right of the

sternum and the other above the bottom of the ribcage, in the left mid-axillary line (eFig. 76.0.5).



***e*FIGURE 76.0.4** Illustration of current flow with defibrillation paddle electrodes that are too close together.

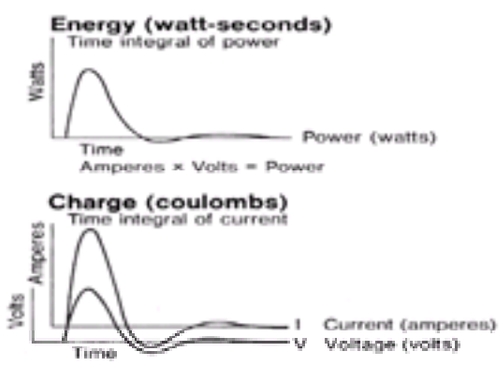


***e*FIGURE 76.0.5** Illustration of current flow with defibrillator paddle electrodes in a more optimal position.

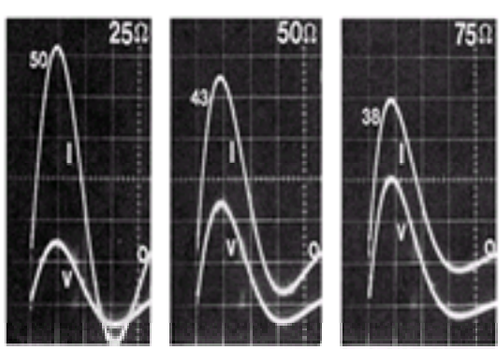
Others and we have found that the same principles of electrode size and placement held true for transcatheter or catheter electrode to subcutaneous electrode defibrillation. To be effective the current path had to be through the major ventricular muscle mass (20,21).

Defibrillation Energy, Current, and Voltage

When one selects the strength of the shock for defibrillation, one chooses an energy level in watt-seconds or joules. However, it is the current delivered to the myocardium that defibrillates. When the defibrillator capacitor discharges, the output can be measured in current, voltage, and energy. To help physicians understand current and voltage, an analogy can be made with the cardiovascular system. When the heart ejects blood, the result can be measured in terms of blood flow and blood pressure. The current is analogous to the flow and the voltage to the pressure. When the defibrillator capacitor is charged, this charge is measured only in volts, as there is no current flow. On discharge, if the instantaneous voltage is multiplied by the instantaneous current, the result is expressed in watts. The watt is a unit of power. If this multiplication is done at each point along the discharged current and voltage wave, a power wave can be constructed (eFig. 76.0.6). When the area under the power wave is integrated with time in seconds, one derives energy measured in watt-seconds or joules. One watt-second is equal to 1 J. Energy is the unit of strength that is indicated on almost all defibrillators. As shown in eFigure 76.0.7, when the simultaneous current and voltage waves from a defibrillator with the same stored energy are delivered into 25, 50, and 75 W of resistance or impedance the delivered peak current decreases with increasing resistance or impedance (2,3). Because it is the current that defibrillates, impedance is important. With constant energy selected, defibrillation effectiveness is related to the resistance between the defibrillator and the patient's heart. At a near threshold shock strength, the lower the resistance or impedance the higher the defibrillation success (22).



***e*FIGURE 76.0.6** Illustration of the power and of the current and voltage waves of a defibrillator discharge delivering damped half-sinusoidal waveforms.



***e*FIGURE 76.0.7** Simultaneous current (I) and voltage (v) waves from a defibrillator with the same stored energy delivered into 25, 50, and 75 W of impedance. Delivered peak current decreases with increasing impedance.

When using defibrillators that deliver monophasic shocks (damped sinusoidal or truncated exponential), impedance becomes critical to success (22,23). The design of the new defibrillators that deliver biphasic waveforms is such to minimize the importance of transthoracic impedance to defibrillator discharge. Some models (Zoll) maintain the same waveform over a wide range of transthoracic impedance. As discussed in the following section, others have some variations in waveform with higher impedances.

Factors Determining Transthoracic Impedance

Several factors influence transthoracic impedance to defibrillation or cardioversion discharge. One factor is the diameter of the electrode. As one increases the diameter of the electrodes, the impedance decreases. Therefore, with lower impedance, defibrillation effectiveness should improve, and in our canine cardiac arrest model this proved to be true. Standard 8-cm-diameter paddles applied within the first minutes of VF successfully defibrillated 71%. A larger paddle with a 12.8-cm diameter successfully defibrillated 88% (23). Kerber (24) showed lower impedance with larger (13-cm) paddles in human defibrillation and, when coupled with firm pressure to the chest, better current delivery. If very large electrodes are used, the impedance is even lower, but defibrillation effectiveness falls, as much of the current is wasted because it is not going through the heart. This demonstrates that it is not current but the current density through the heart that is the major factor in defibrillation (22,23,24,25,26,27,28 and 29). In studies of very small to very large animals, Geddes and associates (28) found that the optimal electrode size is approximately the same as the size of the animal's heart. Optimal paddle size in human defibrillation remains uncertain, but the author predicts that the optimal size might be close to 12-cm-diameter electrodes for human adults. Many electrodes in clinical use today are not this large.

A second factor that is known to affect transthoracic impedance, and thus defibrillation success, is the interface used between the skin of the chest wall and the electrode (29). Impedance is relatively high if the electrodes are applied directly to the skin without some form of conductive medium (29). The impedance is lower if appropriate electrode-skin interfaces are used (29).

We found a wide discrepancy in the impedance of commercially available creams, pastes, and gels used on metal electrodes. Of the 26 products tested, we found 4 to have the lowest impedance to defibrillator discharge (29,30). Of these, Redux Paste (Hewlett-Packard, Waltham, MA) is the only one that is still commercially available. One should avoid gels that have not been shown to have a low resistance. For example, the gels used for echocardiography are very poor conductors of electricity, and when used on metal electrodes for defibrillation or cardioversion, they result in a very high impedance (29,30 and 31). Hummel and associates (32) confirmed our findings and showed that repeated defibrillator shocks via high-impedance gels might produce sparking.

Alternatives to gels include saline-soaked gauze pads and commercially available disposable electrode pads. We compared the transthoracic impedance of metal electrodes using Redux Paste as the interface with saline-soaked gauze pads and with disposable electrodes and found that the impedance was lowest with the metal electrodes with Redux Paste (29). Kerber and his associates (33) also measured impedance to defibrillation discharge using R2 Corporation (Eagan, MN) electrode pads. They studied 80 patients who received 267 shocks. All but two patients achieved defibrillation or cardioversion at least once. The measured transthoracic impedance of the disposable pads was 75 ± 21 W, similar to previous results by these investigators with standard hand-held electrode paddles (67 ± 36 W) (33). More recently, Bissing and Kerber (34) reported transthoracic impedance in 11 nonhirsute individuals using self-adhesive defibrillation pads to be 103 ± 6 (standard error) W. They reported a transthoracic impedance of 162 + 11 W in hirsute subjects that decreased to 105 + 3 W after shaving the hirsute chest (34). In our study of impedance to the cardioversion shock in humans, we delivered an initial shock of 100 J via a research defibrillator-cardioverter. With hand-held paddles with metal electrodes placed in the anterior (8 cm)-posterior (12.8 cm) position and using Redux Gel as an interface, we found a mean impedance of 50 ± 12 W in those who successfully cardioverted and 59 ± 10 W in those not cardioverted with an initial 100-J shock (35). These resistance or impedance values from Redux Paste and metal electrodes are lower than those of the previous reports in which the disposable self-adhesive defibrillation electrode pads were used.

Although the self-adhesive, disposable electrode pads are effective for routine defibrillation and cardioversion and provide an advantage in certain circumstances such as in the electrophysiologic laboratory and in transportation of the high-risk patient with cardiac disease, because of the somewhat higher impedance with defibrillation shock (33,34) many of the presently available disposable electrodes are, in the author's opinion, not optimal for cardioversion or defibrillation in patients who are very large or have a barrel or hirsute chest.

Adequate pressure must be applied to the paddles to ensure a low-impedance electrode thoracic interface. Recommendations are for application of at least 25 lb of pressure (24). Another disadvantage of disposable self-adhesive electrodes is the lack of firm pressure during defibrillation or cardioversion. This can be overcome by folding a towel, placing it over the anterior electrode, and having a bystander apply firm pressure. The bystander does not feel the shock if he or she is not touching anything else.

Another determinant of transthoracic impedance to direct current (DC) shock is the phase of respiration. Our laboratory has demonstrated higher impedance and decreased defibrillation effectiveness when shocks are delivered at full inspiration (from bag-valve–induced ventilation) rather than in expiration (35). Likewise, defibrillation is rarely possible if there is a left-sided pneumothorax, one of the rare indications for open-chest defibrillation.

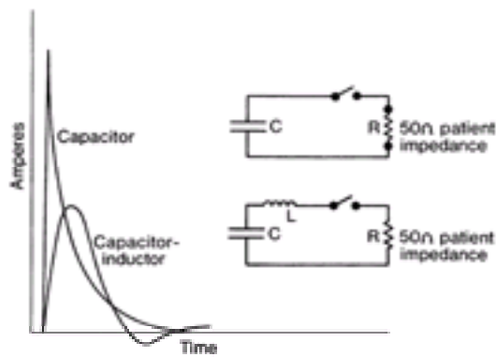
Other factors that have been shown to affect transthoracic impedance to defibrillation shocks include the number, strength, and time interval of previous shocks (24,36). The impedance drops slightly with repeated shocks. This may help to explain why in some patients it may take several maximal defibrillator shocks to defibrillate.

Kerber and associates (37) have shown that for at least 1 month after open-heart surgery, the transthoracic impedance remains lower. The impedance is higher with greater distance between the electrodes or if one of the electrodes is placed on a female breast (38). *e*Table 76.0.1 lists the determinants of transthoracic resistance (or trans-chest impedance) to defibrillator shocks.

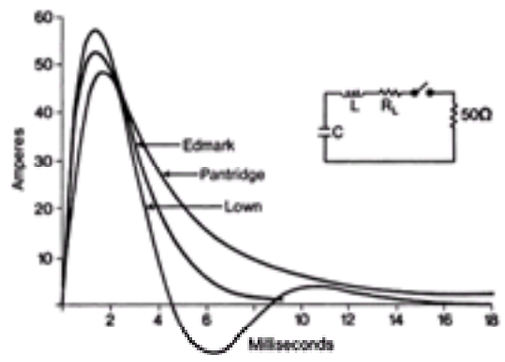
***e*TABLE 76.0.1** FACTORS INFLUENCING TRANSTHORACIC IMPEDANCE TO DEFIBRILLATOR OR CARDIOVERTER SHOCK
Electrode size
Electrode-skin interface
Electrode placement
Pressure on the electrode
Phase of respiration
Shock strength
Number of previous shocks
Time interval between shocks
Previous cardiac surgery

Defibrillation Waveform

The first waveform that was used for ventricular defibrillation was the 60-Hz AC, the same as is used as standard household current. Because of myocardial damage caused by AC current and the problem of the induction of VF from prolonged AC current, units were developed that used a pure capacitance discharge. The pure or undamped capacitor discharge with a short time constant is described mathematically by a curve called an undamped *exponential* (*e*Fig. 76.0.8), and therefore the waveform was given this name (21). These pure DC defibrillators also caused significant cardiac damage. This led to the addition of an inductance coil (*e*Fig. 76.0.8), which rounded the initial, sharp, high-voltage peak that is thought to be responsible for the dysfunction. It is this "damped exponential" waveform that has been in clinical use for transthoracic defibrillation for nearly four decades (21). Depending on the capacitance, inductance, and resistance of a particular model of defibrillator and the impedance of the subject, the waveform is either "critically damped" (Edmark or Pantridge waveform), so that it does not oscillate below the baseline, or "underdamped" (Gurvich or Lown waveform), so that with low impedance it oscillates and has a negative component (*e*Fig. 76.0.7 and *e*Fig. 76.0.9).

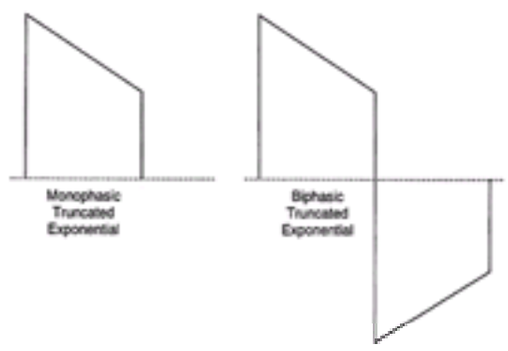


***e*FIGURE 76.0.8** Illustration of an undamped and a damped sinusoidal (capacitor-inductor) waveform from direct current capacitor (C) discharge. L, inductance coil; R, resistance.



***e*FIGURE 76.0.9** Sinusoidal waveforms illustrating a critically damped capacitor (C) discharge (Edmark and Pantridge) and an underdamped C discharge (Gurvich or Lown) waveform. L, inductance coil; R_L, resistance of inductance coil.

With the advent of internal defibrillators, new waveforms were required because the large induction coils that are used for transthoracic defibrillation initially could not be made small enough for implanted devices. To avoid the high-voltage, sharp peaks associated with the underdamped capacitor discharge, the internal defibrillators used underdamped discharges with long time constants that were then truncated so that they were near square wave (low-tilt or trapezoidal) (21) (*e*Fig. 76.0.10).



***e*FIGURE 76.0.10** Monophasic and biphasic square or trapezoidal (truncated exponential) waveforms from defibrillator discharge.

The development of transvenous lead systems prompted the search for more effective defibrillator waveforms. Another stimulus for the development of new waveforms was a new theory of defibrillation (21,39). These hypotheses led to the trial of newer waveforms. Jones (21) confirmed in tissue culture Schuder's findings in animals, that the biphasic waveforms were more effective than monophasic waveforms. This finding was then confirmed in humans. Consequently, modern implantable defibrillators deliver biphasic waveforms (see Chapter 75).

In 1995, it was shown that truncated biphasic pulses of low energy (115 J) were as effective as 200-J damped sine-wave shocks for standard transthoracic defibrillation (40). The mechanisms of electrical defibrillation by the newer defibrillator waveform have been reviewed by Blanchard and Ideker (41).

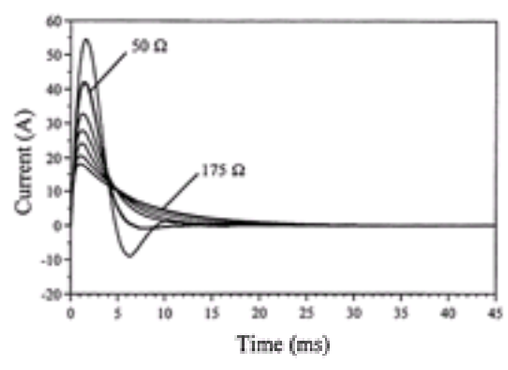
The finding that biphasic waveforms were more effective than monophasic waveforms prompted a reevaluation of the effectiveness of the different sinusoidal waveforms that are used for transthoracic defibrillation. A study of the defibrillation effectiveness of the critically damped capacitor discharge (Edmark) versus the underdamped capacitor discharge (Lown) waveforms revealed that the underdamped sinusoidal waveform (Lown) that more closely resembled the biphasic waveform was more effective. As noted above, with a defibrillator that delivers an underdamped capacitor discharge, the lower the resistance, the more the delivered current becomes more biphasic; the higher the resistance, the more the delivered current becomes more monophasic (*e*Fig. 76.0.7).

The newer biphasic waveforms are probably more effective than monophasic damped sine waves for transthoracic defibrillation. In 2000, Schneider and associates (42) reported a comparison of a monophasic (200–360 J) and a biphasic (150 J) AED for out-of-hospital cardiac arrest. Their study included 115 patients who presented with VF as their initial monitored rhythm (42). The time from the emergency call to first shock was 8.9 ± 3.0 minutes. Defibrillation with three or fewer shocks occurred in 69% of patients who received monophasic shocks and 98% of patients receiving biphasic shocks. Return of spontaneous circulation occurred in 54% of patients who received monophasic shocks and 76% of those receiving biphasic shocks. The study was not powered to show differences in patient survival, and indeed survival to hospital discharge was not different (31% vs. 28%). However, neurologic outcome appeared better in patients who received the biphasic shock, as 21% of those receiving monophasic shocks were in a coma on hospital discharge compared with none of the patients who received biphasic shocks (42).

Mittal and associates compared 200-J damped sine-wave monophasic shocks and 120-J rectilinear biphasic shocks of the Zoll defibrillator in 184 patients in whom VF was induced in the electrophysiology laboratory (43). First shock success was 93% with the monophasic and 99% with the biphasic shock (43). The major difference in defibrillation success was in patients who had high transthoracic impedance. Those with transthoracic impedance of greater than 90 W had a defibrillation success rate of less than 65% with the monophasic shock and near 100% with the biphasic shock (43).

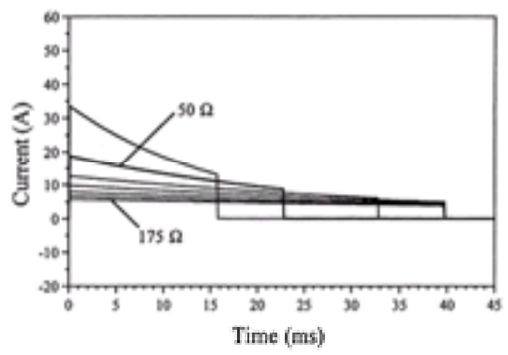
Tang and associates (44) reported better defibrillation effectiveness and less postresuscitation myocardial dysfunction with up to three 150-J shocks with biphasic waveform compared to the conventional sequence of 200-, 300-, or 360-J monophasic waveform shocks. Niemann and associates (45), using a similar protocol, concluded that monophasic and biphasic waveforms were equally effective in terminating prolonged VF with the first shock and that there was no apparent clinical disadvantage of subsequent low-energy biphasic shocks compared with progressive-energy monophasic shocks.

*e*Figure 76.0.11 represents "current plots" of traditional MDSs, and *e*Figure 76.0.12 represents current plots of monophasic, truncated exponential waveforms as a function of load impedance from 25 to 175 W in 25-W increments (46). *e*Figure 76.0.11 illustrates that the shape of the monophasic current waveform changes passively as a function of the impedance (46). With defibrillators that deliver the MDS, the peak delivered current decreases dramatically with increasing impedances. In contrast, with defibrillators that deliver the monophasic truncated exponential waveform, increasing load impedance not only decreases the peak delivered current of the delivered current wave but also prolongs the waveform length (46). Animal studies show that the effectiveness of a monophasic truncated exponential waveform decreases for waveform durations greater than 20 ms (47,48 and 49). Because lower peak current and longer-length monophasic waveforms are not as effective, impedances to defibrillator discharge using defibrillators that deliver MDSs or monophasic waveforms are not as effective at high transthoracic impedances. Increasing impedance distorts sinusoidal monophasic (*e*Fig. 76.0.11) and square-wave monophasic (*e*Fig. 76.0.12) waveforms.



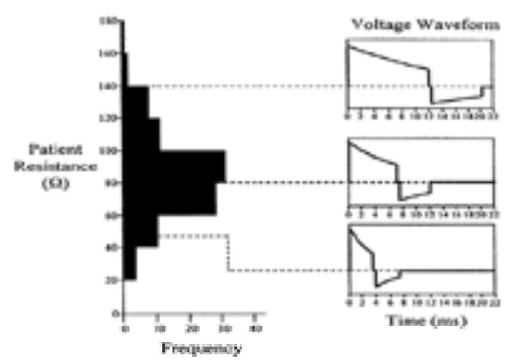
***e*FIGURE 76.0.11** Representative current plots of traditional monophasic damped sine waveforms as a function of load impedance from 25 to 175 W in 25-W increments. (From Gliner BE, Jorgenson DB, Poole JE, et al. Treatment of out-of-hospital cardiac arrest with a low-energy impedance-compensating biphasic

waveform automatic external defibrillator. *Biomed Instrum Tech* 1998;32:631–644, with permission.)



***e*FIGURE 76.0.12** Representative current plots of traditional monophasic truncated exponential waveforms as a function of load impedance from 25 to 175 W in 25-W increments. (From Gliner BE, Jorgenson DB, Poole JE, et al. Treatment of out-of-hospital cardiac arrest with a low-energy impedance-compensating biphasic waveform automatic external defibrillator. *Biomed Instrum Tech* 1998;32:631–644, with permission.)

Will the transthoracic load impedance to defibrillator discharge distort the biphasic waveform as it does the monophasic waveforms? In some commercially available units, the answer is yes. However, they have been engineered so that the changes are not as dramatic. Some of the clinically available biphasic waveform defibrillators are single capacitor. As such, the voltage and width of the second or phase 2 part of a biphasic waveform are dependent on phase 1 pulse characteristics (*e*Fig. 76.0.13). The Heartstream AED is designed with low-energy impedance-compensating biphasic-voltage waveforms that vary the duration of phase 1 and phase 2 so that the total duration is 5.66 ms at an impedance of 25 W and 20 ms at an impedance of 125 W or greater (*e*Fig. 76.0.13). To keep the biphasic waveform more optimal, the tilt of the two phases is decreased at lower impedance, because animal studies have shown higher energy requirements when total tilt is greater than 80%. The use of two separate output capacitors avoids these limitations. Studies of Yamanouchi and associates (50) using two separate output capacitors to produce tailored biphasic waveforms have shown higher defibrillation efficacy. The Zoll biphasic defibrillator has a constant waveform over a wide range of load impedances.



***e*FIGURE 76.0.13 Left:** Distribution of shock resistances (impedances) for 100 patients presenting in ventricular fibrillation. **Right:** Voltage waveforms of the Fore Runner AED, SMART Biphasic defibrillator at 140, 80, and 45 W. (From Gliner BE, Jorgenson DB, Poole JE, et al. Treatment of out-of-hospital cardiac arrest with a low-energy impedance-compensating biphasic waveform automatic external defibrillator. *Biomed Instrum Tech* 1998;32:631–644, with permission.)

It is not known whether one of these newer biphasic defibrillators is more effective than the other. The impedance-compensating biphasic waveform would be significantly longer than the Zoll biphasic waveform at high impedance and in theory might be less effective. Encouraging, however, is a post–market surveillance study of AEDs incorporating 150-J impedance-compensating biphasic truncated exponential waveforms (ForeRunner AED, SMART Biphasic, Heartstream, Inc., Seattle, WA) that failed to show decreased effectiveness at transthoracic impedance over 100 W versus that of patients with an impedance of less than 100 W (19).

New experimental evidence has shown that the triphasic or small shock before the biphasic shock is the most effective waveform for ventricular defibrillation (51,52).

Current Density

The importance of electrode size to transthoracic resistance or impedance is discussed in the section Factors Determining Transthoracic Impedance. If shock strength and resistance are held constant, the major determinant of current density is the electrode size. If the shock strength is high and the electrode size is too small, the current density is high and myocardial damage is more likely (53). If the electrode size is too large, the current density will be too diffuse and the amount of current delivered to the heart may not be adequate for defibrillation (22,28).

Defibrillation Threshold

Irrespective of the theories of defibrillation, there is a defibrillation threshold. Shock strength below this threshold does not defibrillate and must be above the defibrillation threshold to defibrillate. Several factors affect the defibrillation threshold. For example, the defibrillation threshold increases with durations of VF of more than 30 to 60 seconds (54). Metabolic mechanisms have been proposed for this increase. One mechanism may be the intracellular accumulation of potassium (21). Neither hypoxia, metabolic acidosis, nor alkalosis appears to affect the defibrillation threshold adversely (54,55). Catecholamine levels are markedly elevated during VF, but catecholamines are known to decrease the defibrillation threshold (15,56).

Lerman and Engelstein (15) postulated that adenosine mediated this phenomenon. In their experimental study these investigators showed that the increase in defibrillation threshold was blocked before treatment with the adenosine A_1 receptor antagonist 8-cyclopentyl theophylline. They further postulated that these effects are mediated through an antiadrenergic mechanism, because the effect of adenosine on the defibrillation threshold was blocked by denervation (propranolol, 0.2 mg per kg, plus bilateral vagotomy) (15).

Some antiarrhythmic drugs, including lidocaine, encainide, and flecainide and perhaps high doses of the class I antiarrhythmics, increase the defibrillation threshold. If the patient has an implanted cardioverter-defibrillator, these drugs must be added to the medical regimen with caution.

Defibrillation Shock Strength and Cardiac Damage

Shock strength must be adequate for defibrillation (3,28). Shocks delivered below the defibrillation threshold are of insufficient strength to defibrillate. Shock strength in excess of this threshold causes myocardial damage or may reinitiate fibrillation, or both (53,57).

Geddes et al. (28) showed that over a wide range of body size, the smaller the animal, the less energy was needed for defibrillation. Larger animals require higher shock strength to defibrillate. Less energy is needed to defibrillate small children than is needed to defibrillate large adults.

In the 1970s, shock strengths of 6 J per kg body weight were recommended. At about this time, Ewy and others demonstrated myocardial damage at very high shock strengths (53,57). Adgey and associates found that many patients could be defibrillated with energies as low as 100 to 200 J (58,59).

In 1982, Weaver and associates (60) demonstrated in an out-of-hospital study that a 175-J MDS shock defibrillated as well as a 320-J shock but without the negative side effects of an increased postshock incidence of atrioventricular block. Defibrillation rates were not different, and the proportion of patients who were successfully

resuscitated and discharged from the hospital was also similar (60). In 1996, Bardy et al. (61) showed in an in-hospital electrophysiology study that a 200-J MDS shock defibrillated as well as a 360-J MDS shock but with less electrocardiographic evidence of myocardial injury from the shock.

In 1983, Kerber and colleagues (62) reported a prospective in-hospital study of 183 patients who required defibrillation. They found no difference in first shock or accumulative success rates in patients who received initial monophasic countershocks of either 200 J or 300 to 400 J (62).

As reviewed above, biphasic waveform defibrillation shocks at lower energies appear to be more effective than monophasic shocks. Evidence also shows that the biphasic defibrillation shocks produce less myocardial damage and postshock myocardial dysfunction (61). Reddy and associates (43) found that biphasic transthoracic defibrillation causes less electrocardiographic ST-segment elevation after a defibrillation shock than does monophasic transthoracic defibrillation shock. Studies in animals have demonstrated that defibrillation waveform and energy dose affect postresuscitation myocardial function (63,64 and 65).

Transthoracic impedance declines with repeated shocks (36,63). Such a decline in transthoracic impedance results in greater current delivery to the myocardium using the same energy of shock and should enhance the possibility of achieving successful defibrillation. However, the decrease in trans-chest impedance with rapidly delivered shocks is small, and therefore, the present recommendation that the second monophasic shock strength be 300 J is reasonable. If VF continues after the second attempt of 200 or 300 J, higher energy level (360-J) monophasic should be used for the third and subsequent shocks. As noted above, if repeated 360-J shocks do not defibrillate, sequential monophasic shocks, using two defibrillators, or biphasic defibrillator shocks should be considered. The energy level for defibrillation with biphasic waveform shocks is less and ranges from 120 to 180 J.

VF may recur after successful defibrillation. In such circumstances, it is reasonable to use energy levels similar to those that were previously effective. Particularly in the cases in which VF reoccurs frequently, shock strength should be kept as low as possible to minimize myocardial damage. Myocardial injury associated with defibrillation corresponds not only with total joules used (energy) but also with the time interval between the defibrillation shocks (53). Ideally, defibrillation shocks should be of sufficient strength to stop fibrillation but not so strong that they decrease cardiac function, cause myocardial necrosis, or reinitiate fibrillation.

Sequential Shocks from Two Defibrillators

Sequential shocks from two defibrillators have been shown to be more effective than repeated shocks from a single defibrillator. VF that is refractory to transthoracic shocks can occur in up to 0.1% of electrophysiologic studies (64). Hoch and associates (64) reported that 5 of 2,990 consecutive patients experienced refractory VF during routine electrophysiologic studies. Multiple shocks were delivered by means of a single defibrillator. Double sequential shocks were delivered externally 0.5 to 4.5 seconds apart by means of two defibrillators with separate pairs of electrodes. The five patients in whom repeated standard defibrillation shocks were unsuccessful were all successfully defibrillated using the two sequential shocks (64).

Another approach is to use a defibrillator that delivers a biphasic waveform shock, because these units have been shown to be more effective than defibrillators that deliver the monophasic sine waveform.

TIMING OF DEFIBRILLATION

Importance of Early Defibrillation

The time between an arrest due to VF and the application of defibrillation shocks is a major determinant of survival from cardiac arrest (65,66,67,68,69 and 70). This fact is now well appreciated. Each minute that defibrillation is delayed after the first minute, survival decreases an average of 10%. This fact was a major determinant in the paradigm to develop the internal cardiac defibrillator and the development of the AED that can be used with minimal training.

Automated External Defibrillators

The development of automatic and semiautomatic external defibrillators has allowed some communities to staff many first-responding units with the ability to defibrillate early (71,72 and 73). AEDs have algorithms that are specific and sensitive for the identification of VF (46,71,73). Once placed and activated, the automatic device advises a shock if VF is present. In others, the advice to shock is withheld until absence of respiration is documented, usually by the lack of impedance change between the electrodes. Several studies have shown improvement in survival rates for out-of-hospital cardiac arrest with the use of AEDs (73,74,75,76,77,78,79 and 80). Interest in the wider use of the devices continues, particularly where there is a large public gathering (79,80,81,82,83 and 84) and in airplanes (80).

Valenzuela and associates (79) reported the best out-of-hospital survival rates to date by supplying AEDs and training security guards in casinos. Overall, 56 of 105 (53%) patients whose initial rhythm was VF survived to hospital discharge. The mean time from collapse to first shock was 4.4 ± 2.9 minutes. The mean time of arrival of the paramedics was 9.8 ± 4.3 minutes. Survival was 74% in the patients who received their first shock within 3 minutes. Survival was 49% in patients who received their first shock after 3 minutes. The authors concluded that intervals of no more than 3 minutes from collapse to defibrillation are necessary to achieve the highest survival rates (79).

In summary, rapid electrical countershock of patients in VF by emergency medical technicians who are trained to defibrillate has been shown to save lives in urban (77,85), suburban (86), and rural (87) settings and by nontraditional providers, such as security guards in gambling casinos (79). The following questions should now be asked: In what specific setting will the AEDs be cost effective? Should they become more readily available to the general public, much like fire extinguishers, or should they be placed in areas where there is a high likelihood of cardiac arrest? The recommendations of the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiac Care International Consensus (88) are (a) that public access defibrillation programs should be in locations where the frequency of cardiac arrest events is such that there is a reasonable probability of one AED use in 5 years, or one sudden cardiac arrest per 1,000 patient-years; and (b) that the emergency medical system's call-to-shock time interval of less than 5 minutes cannot be reliably achieved (88). However, emotional considerations may lead to the placement of AEDs in schools and in many other locations. Identifying these venues will be one of the challenges of the next few years.

Defibrillating Shocks after Prolonged Arrest

In view of the evidence supporting the effectiveness of early defibrillation in improving cardiac arrest survival, the International Guidelines Committee for Emergency Cardiac Care recommends that patients with cardiac arrest who are in VF undergo three attempts at external defibrillation as the initial step to resuscitation (88). These recommendations for immediate defibrillation are not without some controversy. Yakaitis et al. (89) confirmed that when defibrillation was performed within minutes of the onset of cardiac arrest, no CPR or drug therapy was needed. However, we found that if cardiac arrest continued for more than 5 minutes before defibrillation was attempted, administration of epinephrine and a number of external chest compressions before defibrillation shocks helped restore a perfusing rhythm (89). Neimann et al. (90), using an animal model of VF cardiac arrest, found that after 7.5 minutes of untreated VF, animals that were initially given epinephrine and manual closed-chest CPR before defibrillation attempts had a higher resuscitation rate (9 of 14) than those treated with initial countershock (3 of 14). These findings suggested that, after prolonged VF, a brief period of enhanced myocardial perfusion before countershock may improve successful resuscitation.

The relevance of these early animal studies was confirmed in humans by the study by Cobb and associates (91). They noted a decrease in the out-of-hospital survival of cardiac arrest in the Seattle paramedic system once they had changed from standard defibrillators to AEDs. They noted that, before this change, the paramedics had been instructed to perform a short period of chest compression and assisted ventilation before they attempted defibrillation. They instituted a new protocol in which 90 seconds of CPR was performed before defibrillation (91). They compared the outcome of 639 patients before the change and 478 patients after the change. Overall survival improved from 24% to 30%. Survival in the group in whom paramedic arrival was longer than 4 minutes improved from 17% to 27%. Favorable neurologic function at hospital discharge improved from 71% to 79% (91).

OTHER METHODS OF DEFIBRILLATION

Precordial Thump

The precordial thump is the easiest, although least effective, form of defibrillation. First reported in the early 1960s as being capable of defibrillating VF as well as converting ventricular tachycardia, it became apparent that precordial thumps could also convert ventricular tachycardia to VF (92). Because of that concern, the American Heart Association Guidelines Committee recommended in 1986 that a precordial thump be used only in patients with "monitored VF or in witnessed cardiac arrest if a defibrillator is unavailable" (93). Precordial thumps defibrillate only 2% of patients with very recent onset of VF (94). Nevertheless, in individuals with witnessed hemodynamic collapse, precordial thump appears justified because of its rapidity and ease of delivery. However, a defibrillator should be available before application of precordial thump in patients with ventricular tachycardia who have a pulse, because the mechanical stimulus can induce VF (93).

Open-Chest Defibrillation

The most common use of open-chest defibrillation is during cardiac surgery. Although presently very rare, VF can result from a variety of circumstances in the operating room. During induction of anesthesia, cardiac surgery patients occasionally fibrillate and are treated with external defibrillation in the usual fashion. Even when the chest has been opened, it is possible to defibrillate by external means (95,96 and 97), but internal defibrillation is usually used once the chest is opened. The most common scenario for VF requiring internal defibrillation is at the conclusion of a cardiac surgical procedure. On rewarming and unclamping of the aorta, approximately 40% to 50% of the patients experience VF (98).

Several studies have examined the optimal dose for open-chest defibrillation. Tacker and associates (99) reported that 93% of patients required 10 J or less for successful defibrillation; 48% required 5 J or less. Lake and colleagues (100) found that approximately 90% of 150 cardiac surgical patients could be defibrillated successfully with 10 J or less. Pugsley et al. (101) found similar results in a study of 168 patients showing that 98% could be defibrillated internally with less than 10 J energy.

Another less common use for open-chest defibrillation occurs during emergent circumstances in which closed-chest resuscitation efforts have failed and more aggressive open-chest measures have been used. Open-chest CPR and subsequent internal defibrillation have been shown to be more effective than closed-chest techniques in a number of circumstances (102,103). Myocardial and cerebral perfusion with open-chest CPR techniques are significantly better than those obtained with closed-chest efforts (104,105 and 106). Short-and long-term survival, in animal models, has been substantially better with open-chest resuscitation (107,108 and 109). The most difficult decision in using open-chest techniques is when to use such invasive techniques (emergent thoracotomy and open-chest resuscitation).

The University of Arizona Cardiopulmonary Resuscitation Research Group studied the time course feasibility of instituting open-chest CPR and direct defibrillation after various periods of unsuccessful closed-chest efforts and found that after a 15-minute period of ineffective closed-chest efforts, open-chest CPR resulted in improved survival (110). However, after a period of 25 or 30 minutes of ineffective closed-chest efforts, the institution of open-chest invasive resuscitation did not result in long-term benefits (109). Hence, the decision to use invasive techniques must be made relatively early, probably within 15 minutes of cardiac arrest and failed closed-chest efforts.

RISK OF DEFIBRILLATION TO THE RESCUER

Performed in an appropriate manner, defibrillation poses almost no risk to the would-be rescuer. However, precautions must be taken to assure that the procedure is safe. Gibbs et al. (111) reported on the severity of injuries to pre-hospital emergency personnel in King County, Washington. Questionnaires mailed to the paramedics in the King County emergency medical system documented only eight cases of injury to paramedics or emergency medical technicians over a 9-year period. The actual incidence was 1 in 1,700 defibrillation attempts among paramedics and 1 in 1,000 defibrillation attempts among emergency medical technicians who were trained to defibrillate. Most of the incidences resulted from contact with the cardiac arrest patient during the defibrillation shock, producing localized transmission of a portion of electrical current that culminated in extremity tingling or soreness. One equipment failure, a crack in the defibrillator paddle, resulted in a more significant shock delivered to a paramedic, resulting in frequent premature ventricular ectopic beats and localized muscle spasms that required admission to the hospital. No deaths have been reported from accidental injury to the individuals who administered the defibrillation shock. The incidence and consequences of defibrillator-associated injuries to pre-hospital emergency personnel appear to be low and the nature of the injuries minimal. However, safety must continue to be stressed and efforts made to eliminate all such injuries (111).

Cases of defibrillation hazards associated with placing defibrillating paddle electrodes over nitroglycerin patches have been reported. Wrenn (112) described a small explosion in a nitroglycerin patch during a defibrillation attempt when a paddle was placed directly on such a patch. Although no adverse effects occurred in this patient, the dangers of “arcing” during defibrillation and ineffective delivery of current in reference to patches or ointments, particularly nitroglycerin, should be considered (112).

Hummel and associates (32) reported a fire started by a defibrillation shock in an oxygen-rich environment. This occurred on the sixth defibrillation attempt in an unsuccessful 40-minute resuscitation effort. A spark generated the fire during defibrillation and ignited the bed sheets, quickly engulfing the patient’s bed. It is likely that the fire spread rapidly because of an oxygen-enriched environment created by the continued discharge of the patient’s volume-cycled ventilator, which had been disconnected from the endotracheal tube to permit manual bag-valve ventilation at the onset of the resuscitation. The patient died from his terminal illness, not as a result of the fire. However, the fire destroyed the ventilator and the bed mattress, caused minor smoke damage to the cardiac monitor attached to the patient, and forced evacuation of the remaining 11 patients in the intensive care unit (32). The major problem appeared to be that these investigators were using an electrode gel interface with high resistance (32). They reported on the spark-generating properties of electrode gels used during defibrillation. They found that low-resistance gels, such as Redux Paste or Signagel (Parker Laboratories, Inc., Orange, NJ), had little spark-generating potential, whereas high-resistance gels, such as those used for echocardiography, had high spark-generating properties (32).

CARDIOVERSION

Ventricular Tachycardia

The techniques used for cardioversion of hemodynamically stable ventricular tachycardia are the same as those advocated for elective cardioversion, except that the energy required is lower. Shock strength of 30 to 50 J can frequently cardiovert hemodynamically stable ventricular tachycardia. The exception to this rule is that the cardioversion threshold for multiform ventricular tachycardia is higher than that of monomorphic ventricular tachycardia (113).

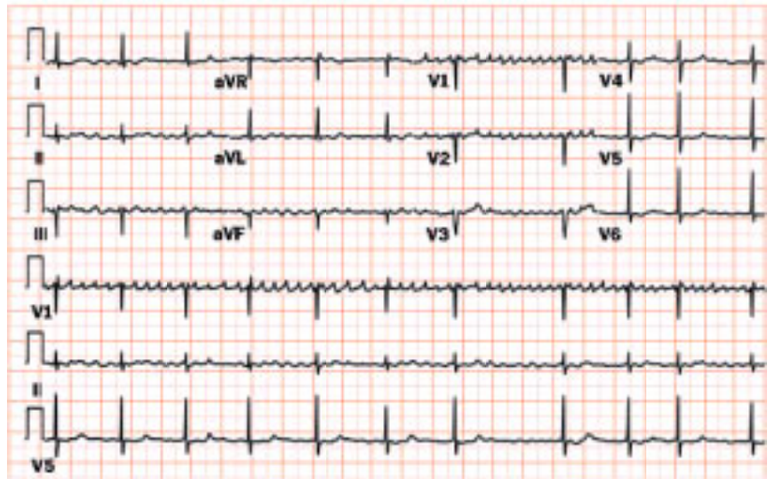
An 81-year-old male patient with ventricular tachycardia.

In hemodynamically unstable patients and perhaps in those with polymorphic ventricular tachycardia, a 200-J monophasic or 120- to 150-J biphasic shock should be given. If the initial shock is not successful, the strength of the second and third shocks, for defibrillators that deliver the monophasic sine waveform, should be 300 J and 360 J, respectively. In patients with recurrent ventricular tachycardia, shock strength on subsequent shocks should be the lowest effective dose to prevent potential cardiac damage from repeated shocks. In patients with recurrent ventricular tachycardia, consideration should be given to the placement of a temporary pacemaker for overdrive suppression or burst pace termination of the arrhythmia until an effective antiarrhythmic drug regimen has been established.

In stable patients with slower rates of ventricular tachycardia, synchronization of the cardioversion shock with the QRS complex is recommended. However, with faster rates, it is often difficult to distinguish the QRS complex from the T wave. In this situation, nonsynchronized shocks are also recommended.

Atrial Fibrillation

Lown and associates (114) developed the technique of transthoracic DC electrical cardioversion from atrial fibrillation four decades ago. Perfecting the technique, Lown reported that sinus rhythm was reinstated in 94% of the 456 episodes of atrial fibrillation (114,115). External cardioversion success rates vary (116), and as recently as 1992, a series reported only 67% success using external delivery of shocks (117). Why have cardioversion success rates been so different? One explanation is that in some series, many of the patients were in chronic atrial fibrillation for over 1 year and had failed previous pharmacologic attempts at cardioversion (117). Another possible explanation for the different success rates is the difference in techniques of external cardioversion (114,115,116,117,118,119,120 and 121).

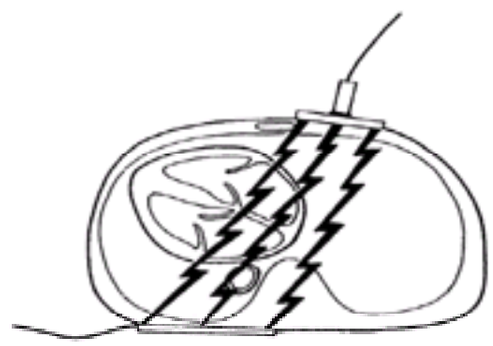


Atrial fibrillation. Narrow complex QRS with irregular RR intervals. Ventricular rate is controlled.

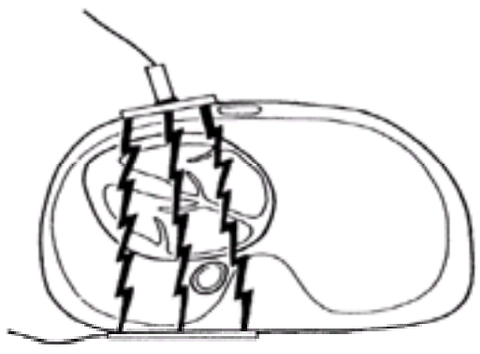
As with ventricular defibrillation, successful cardioversion of atrial fibrillation requires the delivery of adequate current density through the fibrillating chamber. The same considerations of electrode size and transthoracic impedance (see the section Factors Determining Transthoracic Impedance) apply for cardioversion as for defibrillation. However, electrode positioning should be significantly different for cardioversion of atrial fibrillation than for electrical ventricular defibrillation (see the section Electrode Positions).

Electrode Positions

Electrode position is decisive, because the current of the shock must traverse a critical mass of the atrial muscle for cardioversion to occur. Lown reported that the antero-posterior electrode position was more effective for cardioversion of atrial fibrillation than the anterior-anterior electrode position (115,116). He wrote, “The anterior paddle is held with pressure over the upper sternum at the level of the third intercostal space. . . . This antero-posterior position, compared with the previously employed antero-lateral placement, shortens the pathway between the electrodes and augments the density of the electrical field which traverses the heart, thereby diminishing by about 50% the energy required for reversion” (115). In contrast, Kerber and associates (120) reported that the electrode position or size made little difference in cardioversion success. However, in their study, the 111 patients with atrial fibrillation were divided into four groups, each with high success rates, making a statistical beta error so likely that the study is not definitive. In addition, in a study of electrode position by Kerber et al., the electrode positions recommended by Lown et al. (sternal or right parasternal anterior–left posterior) (14) (*e*Fig. 76.0.14) or Ewy (left parasternal antero-posterior) (121) (*e*Fig. 76.0.15) for cardioversion of atrial fibrillation were not tested.

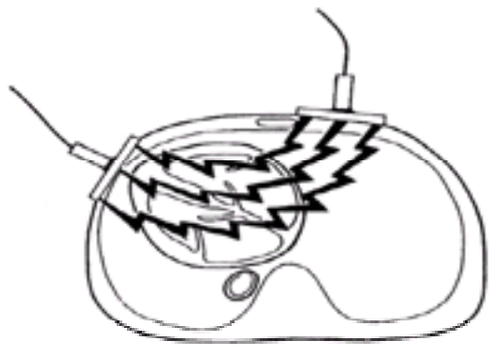


***e*FIGURE 76.0.14** Right anterior-posterior electrode position for cardioversion of atrial tachycardias. (Copyrighted and reprinted with the permission of Clinical Cardiology Publishing Company, Inc., and/or Foundation for Advances in Medicine and Science, Inc., PO Box 832, Mahwah, NJ 07430.)



***e*FIGURE 76.0.15** Left anterior-posterior electrode position for cardioversion of atrial tachycardias. (Copyrighted and reprinted with the permission of Clinical Cardiology Publishing Company, Inc., and/or Foundation for Advances in Medicine and Science, Inc., PO Box 832, Mahwah, NJ 07430.)

Cardioversion requires that the current traverse a critical mass of the atrial muscle. Analysis of computed tomographic scans of the thorax at the level of the heart provides insight into appropriate electrode positions for defibrillation of the atria. The antero-posterior positions (*e*Fig. 76.0.14 and *e*Fig. 76.0.15) fulfill this criterion the best. The right anterior–left posterior position (*e*Fig. 76.0.14) or Lown’s sternal-posterior is the position of choice if the pathology involves both atria (i.e., atrial fibrillation due to atrial septal defect or diffuse cardiomyopathy). This position has more of the right atria between the electrodes. The right antero-posterior electrode position (*e*Fig. 76.0.14) has the disadvantage of a greater interelectrode distance and more lung tissue between the electrode and the heart in the unoperated or emphysematous chest. The left parasternal antero-posterior electrode position has the advantage of smaller interelectrode distance and less lung between the electrodes (*e*Fig. 76.0.15). It is not known whether the right parasternal anterior–left posterior position (*e*Fig. 76.0.14) is better than the left parasternal antero-posterior paddle electrode position (*e*Fig. 76.0.15) that Ewy et al. (123) advocate in patients whose major pathology is left atrial enlargement. The antero-anterior (*e*Fig. 76.0.16) and the apical–left posterior position (*e*Fig. 76.0.17) are not recommended for electrical cardioversion of atrial fibrillation, as these positions probably do not provide optimal current flow through the atria.



***e*FIGURE 76.0.16** Antero-anterior electrode position for defibrillation of ventricular fibrillation or cardioversion of ventricular tachycardia. (Copyrighted and reprinted with

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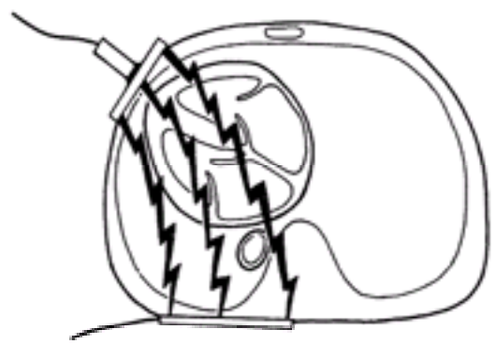
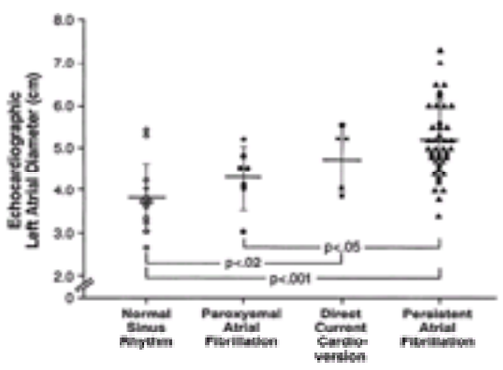


***e*FIGURE 76.0.17** Apical-posterior electrode position. (Copyrighted and reprinted with the permission of Clinical Cardiology Publishing Company, Inc., and/or Foundation for Advances in Medicine and Science, Inc., PO Box 832, Mahwah, NJ 07430.)

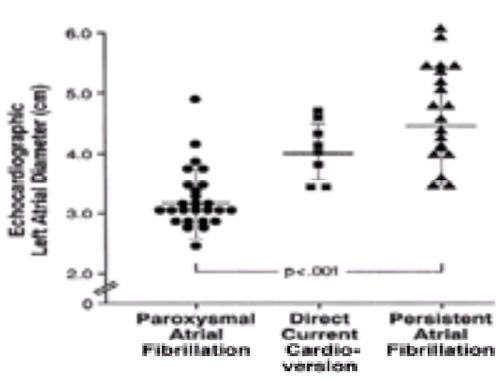
With antero-posterior electrode placement, the greater the antero-posterior chest diameter, the greater the impedance and the less likely that cardioversion will be successful (121). In a 1992 study, the only determinant of successful cardioversion was body weight (117), which usually correlates with chest diameter. Geddes and associates (28) clearly showed that the electrical dose for VF was related to body size and weight. When the impedance is low and the current delivery is high, the relationship between shock strength and body weight is difficult to show and is not clinically important in adults. However, if current delivery is marginal, this relationship is evident (117).

Predictors of Long-Term Success

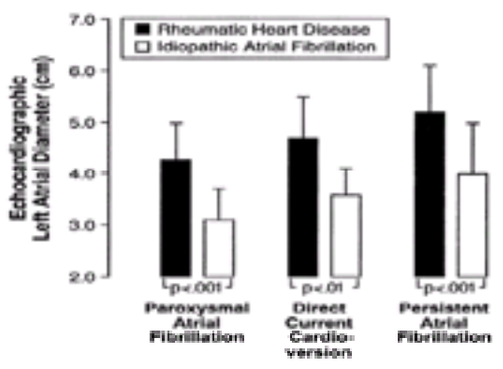
The initial enthusiasm for elective cardioversion of all patients in atrial fibrillation was somewhat dampened by the high recurrence rate in some subsets of patients. As Lown emphasized, the initiating mechanism and the sustaining mechanism of atrial fibrillation are different (114,115 and 116). If the initiating mechanism is no longer present, cardioversion should have lasting success. If, however, the initiating mechanism is still present, atrial fibrillation is very likely to recur. Some patients are not suitable candidates for cardioversion because the initiating mechanism is still present. Untreated thyrotoxicosis, significant untreated mitral valve disease, and congestive heart failure are obvious examples of situations in which the initiating mechanism is still present. Atrial fibrillation of more than 1 year's duration, first-degree heart block greater than 0.24 second before the onset of atrial fibrillation, and significant left atrial enlargement are markers that the initiating pathology is still present, because these factors predict early recurrence. Some studies have not shown a relation between left atrial size and postcardioversion atrial fibrillation recurrence rate. However, studies that looked at cardioversion success rates and recurrence rates within disease states (i.e., mitral disease, hypertrophic cardiomyopathy, idiopathic atrial fibrillation) have shown that a larger left atrium is one of the contributing factors to cardioversion failure or high recurrence rates after cardioversion (108,109,122) (*e*Fig. 76.0.18, *e*Fig. 76.0.19, and *e*Fig. 76.0.20).



***e*FIGURE 76.0.18** Relation between left atrial diameter obtained by M-mode echocardiography and the response of atrial fibrillation to therapy in patients with rheumatic mitral valve disease. The paroxysmal atrial fibrillation group converted spontaneously or with antiarrhythmic drug therapy and remained in sinus rhythm during the 3 months of follow-up. The direct current cardioversion group required electrical cardioversion and were in sinus rhythm 3 months after cardioversion. The persistent atrial fibrillation group all had electrical cardioversion but had reverted to atrial fibrillation at 3 months of follow-up. Left atrial diameter plotted as individual patients with mean ±1 standard deviation and statistical differences. (From Ewy GA, Ulfers L, Hager WD, et al. Direct current shock and transcardiac impedance. *J Electrocardiol* 1980;13:119–124, with permission.)



***e*FIGURE 76.0.19** Relation between left atrial diameter obtained by M-mode echocardiography and the response of atrial fibrillation to therapy in patients with nonvalvular atrial fibrillation. The paroxysmal atrial fibrillation group converted spontaneously or with antiarrhythmic drug therapy and remained in sinus rhythm during the 3 months of follow-up. The direct current cardioversion group required electrical cardioversion and were in sinus rhythm 3 months after cardioversion. The persistent atrial fibrillation group all had electrical cardioversion but were back in atrial fibrillation at 3 months of follow-up. Left atrial diameter plotted as individual patients with mean ± 1 standard deviation and statistical differences. (From Ewy GA, Ulfers L, Hager WD, et al. Direct current shock and transcardiac impedance. *J Electrocardiol* 1980;13:119–124, with permission.)



***e*FIGURE 76.0.20** Relation between left atrial diameter obtained by M-mode echocardiography and the response of atrial fibrillation to therapy in patients with rheumatic and “idiopathic” atrial fibrillation. In this study, patients with nonvalvular atrial fibrillation, even if they had a history of hypertension, were classified as idiopathic. The paroxysmal atrial fibrillation group converted spontaneously or with antiarrhythmic drug therapy and remained in sinus rhythm during the 3 months of follow-up. The direct current cardioversion group required electrical cardioversion and were in sinus rhythm 3 months after cardioversion. The persistent atrial fibrillation group all had electrical cardioversion but were found to have reverted to atrial fibrillation at 3 months of follow-up. Left atrial diameter plotted as individual patients with mean ±1 standard deviation and statistical differences. (From Ewy GA, Ulfers L, Hager WD, et al. Direct current shock and transcardiac impedance. *J Electrocardiol* 1980;13:119–124, with permission.)

Anticoagulation

Hemodynamically unstable patients or patients with marked ischemia secondary to recent-onset atrial fibrillation may need urgent cardioversion. In this setting, there may be no time for anticoagulation.

Otherwise, patients who are undergoing electrical cardioversion should be anticoagulated, either with heparin or with 3 weeks of warfarin (124,125,126,127,128,129,130,131,132,133,134,135 and 136). The recommendation for heparin therapy before electrical cardioversion—even if the transesophageal echocardiogram (TEE) shows no evidence of thrombus—is based in part on the observation of Fatkin et al. (131), who reported 66 patients who underwent TEE before cardioversion and 15 patients in whom TEE was performed during the cardioversion procedure. Thromboembolism occurred in four patients, none of whom had prior evidence of left atrial thrombus by TEE (131). Surprisingly, within 10 seconds of cardioversion shock, spontaneous echo contrast appeared in the left atrium in five of the patients, increased in one, and was unchanged in nine (131). These investigators concluded that transient atrial dysfunction (stunning) caused by the electrical shock of cardioversion promoted new thrombus formation (131). Grimm and associates (132) have also demonstrated the development of spontaneous echoes in the left atrium and left atrial appendage in approximately 35% of patients undergoing electrical cardioversion. These authors, in reviewing the role of TEE before electrical cardioversion for atrial fibrillation, concluded that TEE can identify left atrial clot. If clot is identified, anticoagulation for 6 weeks is indicated (132). If no clot is identified, the patient is anticoagulated with heparin and started on warfarin before the cardioversion. Heparin is continued until the international normalized ratio is therapeutic (2.0–3.0). They recommend that the warfarin anticoagulation be continued for at least 6 weeks.

Another issue is the effect of the duration of atrial fibrillation on the time of the return of atrial contractile function following cardioversion. The longer the duration of atrial fibrillation, the longer it takes for normal atrial contractile function to return (133). Manning and associates (113) found that patients with duration of atrial fibrillation of less than 6 weeks had near complete return of atrial function by 1 week. This fact argues in favor of a TEE evaluation in hospitalized patients with recent-onset atrial fibrillation and 2 days of intravenous heparin followed by cardioversion. If pharmacologic therapy does not result in cardioversion, one can proceed with electrical cardioversion. At the same time that the heparin is initiated, the patient is started on oral anticoagulation. On the other hand, the fact that it takes much longer for atrial contractions to return in atrial fibrillation of longer duration argues for longer duration of anticoagulation after cardioversion.

Cardioversion and Antiarrhythmic Drug Therapy

Lown (115) instituted quinidine therapy 1 or more days before attempted electrical reversion, stating that this antiarrhythmic (a) improves the chances of the patient who remains in normal sinus rhythm immediately after cardioversion, (b) decreases by approximately 40% the energy required for cardioversion, (c) diminishes the incidence of postcardioversion arrhythmias, and (d) helps to “obtain a small dividend of reversions which results in about 10% of patients.” Digoxin is also given to counteract the vagolytic effect of quinidine. Therapeutic digoxin dose should be halved before this antiarrhythmic is begun, as quinidine doubles the serum digoxin level. Procainamide infusion and other antiarrhythmic agents such as sotalol and propafenone have also been advocated for pharmacologic cardioversion.

A major unanswered question is the role of antiarrhythmic drugs pre- and postcardioversion. The most important drug(s) that are to be used before and after cardioversion is (are) the one(s) that treat the factor(s) predisposing to the atrial fibrillation. If the etiologic mechanism, for example, thyrotoxicosis, has been corrected, antiarrhythmic drugs may not be necessary.

Lown gave quinidine before electrical cardioversion. He thought that patients on quinidine required less energy for cardioversion (114,115 and 116). In an evaluation of antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation, patients in the Stroke Prevention in Atrial Fibrillation (SPAF) study were analyzed (137). Of the 1,330 patients in the study, 189 were taking antiarrhythmic drugs; the majority (127/189) were taking quinidine (137). No increased risk was found in patients without congestive heart failure or a history of congestive heart failure. However, with or with a history of heart failure, there was a 4.7 (1.9–11.6)-fold increase in the risk of cardiac death (137).

In the Cardiac Arrhythmia Suppression Trial (CAST), mortality was increased in patients with ventricular arrhythmias who were treated with antiarrhythmic drugs (138). The results of these studies should occasion concern about the wisdom of long-term antiarrhythmic therapy after cardioversion in patients who have congestive heart failure or a history of heart failure or who have had a previous myocardial infarction.

Beta-adrenergic blocking drugs have been used. Kuhlkamp et al. (140) reported a relapse rate of 48.7% in patients treated with beta-blocker after electrical cardioversion, compared to 59.9% in those who received placebo.

Propafenone and sotalol have both been used for cardioversion and maintenance of sinus rhythm after electrical cardioversion. De Simone and colleagues (139) reported that pretreatment with verapamil for 3 days before and 3 days after electrical cardioversion, combined with oral propafenone begun 3 days before electrical cardioversion and continued, reduced the incidence of early (3-month) recurrence of atrial fibrillation compared with propafenone therapy alone.

In the Canadian Trial of Atrial Fibrillation (CTAF), amiodarone has been reported to be twice as effective as either propafenone or sotalol in preventing recurrent atrial fibrillation (141). The recurrence of atrial fibrillation was 35% with amiodarone, 63% with propafenone, and 63% with sotalol (141).

Atrial pacing may also be important to the maintenance of sinus rhythm in those patients with the sick sinus syndrome.

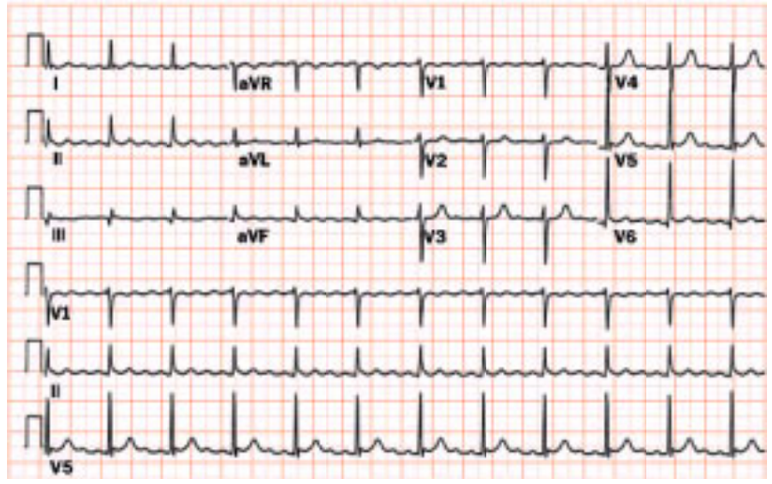
Shock Strength

The strength of the initial shock to cardiovert hemodynamically stable atrial fibrillation when one is using the monophasic waveform should be 200 J (stored energy), because only 50% of patients are cardioverted with 100 J (114,115 and 116). Approximately 85% of those who electrically cardiovert do so at 200 J (114,115 and 116). The monophasic shock should be 360 J, because almost all patients who cardiovert electrically via the external technique do so at the maximal setting (114,115 and 116). If the first 360-J shock is not successful, one should assess electrode position. If the electrode positions are to be unchanged, one should wait a full 3 minutes before delivering a final 360-J shock. This wait allows a greater decrease in transthoracic impedance from the previous DC shock than occurs with shocks delivered at 15-second or 1-minute intervals (36,63). In addition, a number of patients do not revert to sinus rhythm immediately after the shock but do so a few seconds or minutes later. This phenomenon is thought to represent depolarization of a major portion, but not all, of the atrium. The remaining rhythm does not have a large enough area for continued reentry and dies out. This “delayed” cardioversion is thought to occur in approximately 4% of electrical cardioversions.

Shock strength of biphasic waveform defibrillation is less, but the ideal shock strength for biphasic waveform cardioversion is yet to be determined.

Atrial Flutter

Multiple modalities have been used for cardioversion of atrial flutter, including antiarrhythmic drugs, atrial pacing, DC cardioversion, and catheter ablation. Although atrial flutter is usually associated with organic heart or lung disease, nearly one-third of patients have no apparent etiology. Atrial flutter with a persistently rapid ventricular response may result in the myopathy of tachycardia. These patients present with atrial flutter with a rapid ventricular response and poor ventricular function and thus are often classified as having flutter secondary to heart disease rather than having heart disease secondary to flutter (myopathy of tachycardia). This group of patients may have a marked improvement in their ventricular function after catheter ablation of their chronic atrial flutter. This same sequence of events occurs in patients with any persistent supraventricular arrhythmia, including atrial fibrillation.



Atrial flutter. Atrial rate of 300 beats/min with upright P waves inferiorly. This is consistent with atypical atrial flutter.

Atrial flutter. Inverted "saw-tooth" waves in the inferior leads suggest typical atrial flutter.

When considering cardioversion of atrial flutter, two issues are potentially different from those of atrial fibrillation. The first is the question of anticoagulation, and the second is shock strength.

Until recently, most authors and most studies recommended cardioversion of atrial flutter without anticoagulation (125). Because the incidence of systemic emboli following cardioversion of atrial flutter is small, thousands of patients would have to be studied to be sure of this approach. One is influenced by the literature, but also by one's own experience. The only fatal emboli that the author has seen after electrical cardioversion has been in a patient with hypertrophic cardiomyopathy and atrial flutter. Because of this experience, some 20 years ago, I have routinely anticoagulated patients with either atrial fibrillation or flutter of 48 or more hours in duration before elective cardioversion. Support for this approach has been published. Irani and associates (142) found atrial thrombus or spontaneous echocardiographic contrast, or both, in 34% of patients with atrial flutter. Pagadala et al. (143) studied 85 patients referred for cardioversion of chronic atrial flutter. Embolism occurred in 1 of 39 nonanticoagulated patients compared with none of 46 anticoagulated patients.

Atrial flutter can occasionally be cardioverted with very-low-energy, for example, 15- to 35-J, shocks. However, low-energy monophasic shocks often change the rhythm from flutter to atrial fibrillation, requiring a higher-energy shock. Accordingly, it is recommended that the first monophasic shock be at least 50 J (approximately 38 J delivered) for elective cardioversion of atrial flutter (118). Lower-energy shocks might be effective if biphasic shocks are delivered.

CONTROVERSIES AND PERSONAL PERSPECTIVES

It is well recognized that two of the more important determinants of survival from unexpected cardiac arrest are the speed with which basic life support is started and the interval between the onset of VF and defibrillation. Therefore, the improvement and implementation of "public access defibrillation" is critical to the success of out-of-hospital defibrillation. However, a major problem with the present AEDs is the fact that the patient cannot receive CPR while the AED is analyzing his or her rhythm. Even though the initial shock is delivered within 30 seconds, it takes 90 seconds to deliver the first three-shock cycle. This 90 seconds without CPR after a long arrest markedly increases mortality, and this delay is unacceptable.

A detailed discussion of bystander-initiated CPR is outside the context of this chapter. Nevertheless, it needs to be emphasized that presently only approximately 20% of out-of-hospital cardiac arrests are afforded bystander CPR, mainly because of the fear of infection from, or an aversion to, mouth-to-mouth resuscitation (144,145). Our experimental studies have clearly demonstrated that chest-compression-only CPR is much better than doing nothing or performing no bystander CPR (146). In the author's opinion, the other significant advance in out-of-hospital cardiac arrest, a new protocol recommending that the lay public call 911 and initiate uninterrupted chest compression CPR without pausing for assisted ventilation, is critical. Calling 911 and waiting for the emergency medical technicians or paramedics to arrive result in extremely low survival rates.

In the author's opinion, the transthoracic impedance of the majority of disposable defibrillation electrodes is too high. Therefore, one area in which my personal recommendations differ from currently accepted practice is the recommendation to use metal electrodes with Redux Paste for elective cardioversion as well as defibrillation. For elective cardioversion one needs to order special metal antero-posterior paddle electrodes so that the current passes through the atrium. After cardioversion of patients with atrial fibrillation, the author recommends anticoagulation for 3 to 6 months rather than 4 weeks because of the high incidence of asymptomatic recurrence.

Finally, this author recommends anticoagulation before cardioversion of atrial flutter as well as atrial fibrillation. The incidence of emboli with or following cardioversion of atrial flutter is rare, but it occurs.

THE FUTURE

More defibrillators will be designed to deliver biphasic or triphasic waveform shocks. AEDs will be developed that can analyze and detect VF while chest compression is in progress. Defibrillators will become lighter weight. Mass production should result in more economical defibrillators and disposable one-use AEDs. They will be used by a wide variety of individuals, including the lay public. The problem of litigation risk is being addressed by appropriate legislation.

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CLINICAL ASSESSMENT OF THE AUTONOMIC NERVOUS SYSTEM

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OVERVIEW

Disturbances of autonomic nervous system function are thought to contribute significantly to risk of ventricular arrhythmias and sudden death in patients with coronary heart disease and other cardiac diseases.

Excessive activity of the sympathetic nervous system promotes malignant ventricular arrhythmias.

The parasympathetic nervous system antagonizes sympathetically mediated malignant ventricular arrhythmias and therefore is considered to have a major protective effect against sudden death.

The autonomic nervous system can be assessed in humans by measuring RR variability, baroreflex sensitivity (BRS), or heart-rate changes during and immediately after exercise.

High-frequency (HF) cyclic fluctuations of RR intervals reflect vagal modulation of RR intervals linked to breathing.

Low-frequency (LF) cyclic fluctuations of RR intervals reflect modulation of RR intervals by baroreflexes and other cardiovascular control mechanisms.

The physiologic mechanisms responsible for ultra-low-frequency fluctuations in RR intervals are not established, but the renin-angiotensin system may be partly responsible.

Low BRS indicates inadequate vagal response to fluctuations in arterial blood pressure and results in sympathetic dominance.

Low values of RR-interval variability or BRS predict cardiac death and sustained ventricular arrhythmias.

LF or ultra-low-frequency fluctuations are the best measures of RR variability for predicting cardiac death or arrhythmic events.

RR-interval variability or BRS has a strong and independent relationship with cardiac death, sudden cardiac death, and sustained ventricular arrhythmias in coronary heart disease.

RR variability and BRS can be combined with other risk predictors [e.g., left ventricular ejection fraction (LVEF) or ventricular arrhythmias] to improve predictive accuracy for cardiac death or arrhythmic events.

Beta-blockers may improve autonomic balance; it is conceivable that in this way they improve survival in patients with coronary heart disease and chronic heart failure.

Abnormalities of autonomic nervous system function can be easily detected by measuring heart rates during and after exercise. A failure of heart rate to rise appropriately during exercise ("chronotropic incompetence") as well as a failure of heart rate to fall quickly after exercise ("impaired heart-rate recovery") are powerful, independent, and easily measured predictors of all-cause mortality.

GLOSSARY

Autoregression: A parametric statistical algorithm for resolving a complex signal into its component frequencies.

Baroreflex sensitivity: The magnitude of increase in RR intervals when systolic blood pressure increases.

Chronotropic incompetence: A failure of heart rate to rise appropriately during exercise. Chronotropic incompetence is predictive of increased mortality.

Chronotropic index: A marker of chronotropic response to exercise calculated as [(exercise heart rate) – (resting heart rate)]/[(220 – age) – (resting heart rate)]. It can also be considered as the proportion of heart-rate reserve used at peak exercise. A chronotropic index less than 0.8 at peak exercise is abnormal.

E:I ratio: Ratio of maximum RR interval during expiration to the minimum RR interval during inspiration.

Fourier transform: A nonparametric mathematical algorithm for resolving a complex signal into its component frequencies.

Heart-rate recovery (HRR): The parasympathetically mediated return toward baseline of heart rate immediately after exercise. An abnormal 1-minute HRR is less than 12. An abnormal HRR is a powerful predictor of all-cause mortality.

Heart-rate variability (HRV): Periodic fluctuations of heart rate. See *RR-interval variability*.

NN interval: Difference between adjacent normal QRS complexes.

Power spectrum: Plot of power (energy) versus frequency of a complex signal composed of oscillations at multiple frequencies.

RR interval: Difference between adjacent QRS complexes.

RR-interval variability: The periodic fluctuations of RR intervals. Information about the general health of the heart, the prognosis, and the propensity toward malignant ventricular arrhythmias may be determined from analysis of these fluctuations.

INTRODUCTION

A large body of clinical and experimental evidence indicates an important role for the autonomic nervous system in the triggering or sustaining of malignant ventricular arrhythmias. Experimentally, sympathetic stimulation reduces ventricular refractoriness and fibrillation threshold and promotes arrhythmias; it also promotes afterdepolarizations and triggered activity. Vagal stimulation opposes these effects, prolonging ventricular refractoriness and reducing the effects of adrenergic stimulation. The antiarrhythmic effects of vagal activity are much more pronounced when adrenergic activity is increased. Normally, afferent nerve impulses from the arterial baroreceptors to the brain cause inhibition of the sympathetic outflow, while increasing efferent parasympathetic activity. Lowered BRS can lead to increased sympathetic drive with decreased vagal activity, a situation promoting ventricular arrhythmias, particularly during myocardial ischemia.

There are several noninvasive or minimally invasive ways to evaluate the autonomic nervous system in intact humans. This chapter discusses three of these approaches: RR-interval variability from continuous electrocardiographic (ECG) recordings, BRS, and heart-rate changes during and immediately after exercise. RR variability measurements provide a low-cost, widely available method for assessing the status of the parasympathetic nervous system in humans and for predicting cardiovascular events, especially cardiac death and sustained ventricular arrhythmias in coronary heart disease patients. BRS also is useful for predicting cardiac death and sustained ventricular arrhythmias after myocardial infarction and adds prognostic information to RR variability.

Chronotropic incompetence during exercise and HRR immediately after exercise are important and easily obtained autonomic markers. Chronotropic incompetence may reflect excess resting sympathetic activity, and HRR reflects parasympathetic reactivation after exercise. Both have been shown to be predictive of cardiac and all-cause mortality. This chapter focuses on the mechanistic association between changes in autonomic function and sustained ventricular arrhythmias or death, and on the clinical use of the RR variability, BRS, and exercise heart-rate responses.

HISTORICAL PERSPECTIVE

In the mid-nineteenth century, Carl Ludwig recognized that the vagus nerve mediated sinus arrhythmia and that vagotomy or atropine treatment would abolish sinus arrhythmia (1). In the 1930s, Anrep determined that a direct interaction of respiratory and cardiovascular medullary centers and reflex mechanisms contributes to respiratory sinus arrhythmia (2,3). In 1970, Katona et al. (4) published direct recordings of vagus nerve activity showing that, during normal ventilation in dogs, respiratory sinus arrhythmia is due to a marked decrease of efferent vagal nerve activity during inspiration, an effect that is evident over a wide range of vagal tone. In a series of ingenious experiments on dogs, Katona and Jih (5) demonstrated that the degree of sinus arrhythmia can be used as a noninvasive, quantitative measure of parasympathetically mediated heart-rate control. They showed that the difference in the maximum and minimum RR intervals in a respiratory cycle was proportional to the average vagal activity in the cycle. When the vagus nerves were temporarily cooled, the average RR interval decreased and respiratory sinus arrhythmia was abolished; both average RR interval and sinus arrhythmia returned to control values when the vagus nerves were rewarmed. They called the change in average RR interval during cooling of the vagus nerves *parasympathetic control*. A similar result was obtained when arterial blood pressure was increased or decreased to alter vagal tone. The relationship between vagal activity and variation in RR intervals was not altered by cardiac beta-adrenergic blockade, but was abolished by atropine treatment. In 1984, Fouad et al. adapted the methods of Katona and Jih to measure parasympathetic cardiac control in humans (6).

In 1981, Hirsch and Bishop (7) reported that, in healthy human subjects, sinus arrhythmia decreased with increasing frequency of breathing and increased with increasing tidal volume. The effect of breathing frequency on respiratory sinus arrhythmia was large. At breathing frequencies of seven breaths per minute or less, respiratory sinus arrhythmia was large and constant. As breathing frequency increased above seven breaths per minute, the amplitude of respiratory sinus arrhythmia showed a steep log-linear decrease (7). In contrast to the frequency of breathing, tidal volume had a small effect; a 50% increase in tidal volume caused only a 15% increase in respiratory sinus arrhythmia (8).

Since the late 1970s, the ratio of maximum RR interval during expiration to the minimum RR interval during inspiration (E:I ratio) has been used to evaluate the autonomic nervous system in patients with diabetes mellitus (9). Smith (10) computed the E:I ratio in 174 healthy subjects aged 16 to 89 years and found no significant relation between E:I ratio and resting heart rate, but a substantial decrease in the ratio with age. Therefore, Smith recommended that age-adjusted normal values should be used to interpret the E:I ratio (10). He used the confidence intervals of the regression of E:I ratio on age to detect parasympathetic dysfunction in diabetics. The difference between maximum and minimum RR interval during a single breath or during a period of controlled deep breathing has been used extensively in humans to evaluate parasympathetic nervous system function, especially as part of a battery of autonomic function tests in patients with diabetes mellitus (11,12). The E:I ratio has not been used extensively to evaluate risk or parasympathetic nervous system function in cardiovascular diseases.

It was not until the 1980s that variability of RR intervals was evaluated with power spectral methods. Cohen's group at the Massachusetts Institute of Technology and Malliani's group in Milan performed landmark studies to define the effects of autonomic maneuvers on HRV in dogs and healthy human subjects (13,14 and 15). These workers demonstrated that noninvasive measurement of heart-rate or RR-interval variability could quantify autonomic nervous system activity in intact animals or human subjects. This methodologic advance not only made autonomic assessment easier and more precise, but also more available and less expensive. Once these tools were available, clinicians were eager to apply them in cardiovascular medicine.

The first substantial finding indicating prognostic significance for RR variability in coronary heart disease was the 1978 report by Wolf et al. in Australia (16). The definitive report in 1987 by Kleiger et al. that RR-interval variability predicted mortality after myocardial infarction catapulted RR variability into cardiovascular medicine (17). In the years since that report, there have been more than 1,000 papers on the clinical use of RR variability.

Interest in the use of heart-rate response to exercise as a prognostic marker began in the 1970s. Hinkle et al. followed 301 men for 7 years after exercise testing and noted that those men who failed to reach an expected heart rate uring exercise had an increased number of cardiac events (18). They termed the syndrome *sustained relative bradycardia*. Ellestad became interested in this area after exercise testing a 51-year-old man who had a good exercise tolerance and no ST-segment depression or pain but with maximum heart-rate response of only 110. Shortly after testing, the patient died suddenly, and an autopsy revealed significant coronary artery disease with 80% narrowing in both the anterior descending and circumflex arteries (19). Ellestad went on to examine 2,700 patients and found that a slow heart-rate response to exercise predicted an increased risk of cardiac events (20). He coined the term *chronotropic incompetence* to describe reduced heart-rate response to exercise.

In the 1980s, interest in chronotropic incompetence moved away from its prognostic properties and rather toward its adverse effect on the sensitivity of stress imaging studies (21). This led to tests showing chronotropic incompetence being labeled as *nondiagnostic*, suggesting that there was something wrong with the test, but not the patient. Beginning in the mid-1990s, however, chronotropic incompetence was rediscovered as a powerful and independent predictor of outcome in its own right (22,23,24 and 25).

HRR after exercise has been used as a marker of physical fitness since the 1940s (26,27 and 28). Several different ways of quantifying HRR have been explored. One simple method is to measure the time it takes for the heart rate to return to baseline after exercise (28). Johnson et al. were the first to notice a first-order exponential decay pattern to HRR and to calculate the time constant (T) for this equation (27). This measure was impractical due to the cumbersome calculations required until Cardus and Spencer used newly emerging computer technology to determine T (29). They demonstrated a correlation between $T_{0.63}$ and an individual's age and physical condition (29). More recently, T has been used in the correlation of HRR with parasympathetic reactivation after exercise (30,31).

The concept of HRR as a marker of physical fitness was incorporated into the Harvard Step Test (32) and later the YMCA Step Test (33). These tests prescribe physical exertion for a specified period followed by a recovery period during which the decrease in heart rate is measured. The decrease in heart rate is then compared with tables of standards (33), which provide a reference for the physical fitness of an individual. Step tests are still used today, particularly in measuring the fitness of children (34). Only relatively recently has HRR been described as a prognostic marker (35).

PHYSIOLOGIC AND PATHOPHYSIOLOGIC EFFECTS OF THE AUTONOMIC NERVOUS SYSTEM ON THE HEART

Autonomic Modulation of Heart Rate

The autonomic nervous system is the primary system for regulating heart rate in healthy persons. The intrinsic sinus node rate at rest (the rate after pharmacologic or surgical denervation of the sinus node) is 95 to 110 per minute (36). In healthy persons at rest, substantial efferent traffic on the vagus nerves suppresses the sinus node rate to 60 to 70 per minute. At rest, there is little efferent traffic on sympathetic nerves, and the concentration of circulating catecholamines is low (37). In healthy persons under resting conditions, the RR intervals fluctuate substantially to produce the familiar sinus arrhythmia. Sinus arrhythmia is caused by rhythmic fluctuations in the rate of firing on vagus nerves as modulated by the rate and depth of breathing (5,7,8). When mental or physical activity perturbs the resting state, the number of factors that modulate RR intervals increases. In particular, the average frequency of impulses on the vagus nerves decreases with mental stress (38,39,40 and 41) or physical activity (42,43,44 and 45). And, as effort increases, the sympathetic nervous system comes into play more and more intensively (37,42). During the phase immediately after cessation of exertion, HRR is almost completely driven by parasympathetic reactivation (31,45,46,47 and 48). As recovery progresses, the withdrawal of sympathetic activity plays more of a role (31).

Sympathetic Nervous System and Cardiac Arrhythmias

There is a vast literature that documents an important role for the sympathetic nervous system in the genesis of cardiac arrhythmias (49,50,51,52,53 and 54). Some of the proarrhythmic effects of increased cardiac sympathetic nervous activity can be attributed to adverse effects of tachycardia and some to heterogeneity of ventricular repolarization during intense sympathetic nervous activity. Stimulation of the hypothalamus and other areas that increase sympathetic nervous system activity cause cardiac arrhythmias, including ventricular fibrillation (VF) in healthy animals (55). Also, interruption of central pathways that inhibit sympathetic nervous system activity causes cardiac arrhythmias (56,57). Experimental situations that evoke anger or fear also can evoke cardiac arrhythmias in intact animals (58). In all of these settings, cardiac arrhythmias can be prevented by pretreatment with beta-adrenergic blockade. When the myocardium is “sensitized” to cardiac arrhythmias by acute myocardial ischemia or drug toxicity (e.g., digitalis toxicity, cocaine, or certain anesthetics), the probability of VF during increased sympathetic nervous system activity is increased substantially.

The interaction between myocardial ischemia or infarction and sympathetic nervous system activity is complex. Myocardial ischemia, especially of the anterior wall, increases the activity on afferent cardiac sympathetic nerves (59,60). The increased afferent nerve activity triggers reflexes that increase efferent cardiac sympathetic nerve activity and that decrease efferent activity on the vagus nerves (59). High extracellular K^+ concentration in the ischemic region can cause release of norepinephrine from epicardial sympathetic nerves (61). Not only is the regional concentration of norepinephrine heterogeneous, but also the response of normal and ischemic myocardial cells to norepinephrine is heterogeneous. Regional heterogeneity of depolarization and repolarization caused by acute ischemia increases the likelihood of reentrant electrical activity in the ventricles, especially VF. Damage to the epicardial sympathetic nerve by myocardial infarction can cause regional sympathetic denervation of the myocardium apical to the infarct (62). Sympathetic nerve traffic to and from denervated areas can be interrupted. Ordinarily, stimulation of cardiac sympathetic nerves causes a decrease in the effective refractory period of the ventricular myocardium, and vagal stimulation causes an increase in the ventricular effective refractory period. After experimental anterior infarction, stimulation of cardiac sympathetic or vagus nerves fails to produce these changes in the effective refractory period at epicardial sites apical to the infarct (62). The regional heterogeneity of repolarization caused by regional sympathetic denervation promotes reentrant ventricular arrhythmias for days to weeks after myocardial infarction. Preliminary studies in humans show that the extent of regional damage to cardiac sympathetic nerves 2 to 4 weeks after myocardial infarction quantified by radiolabeled meta-iodobenzylguanidine was related to the magnitude of reduction of two time domain measures of RR variability, standard deviation of normal to normal (NN) intervals over a 24-hour period (SDNN), and square root of the mean squared successive differences of NN intervals (r-MSSD) (63). Denervation of the myocardium as a consequence of infarction may be arrhythmogenic in several different ways: Areas of myocardium may become supersensitive to catecholamines, and the destruction of afferent neural fibers and receptors may result in impairment or loss of protective cardiac reflexes that promote electrical stability. Lowered BRS causes increased sympathetic drive and decreased vagal activity, promoting ventricular arrhythmias, particularly in the setting of myocardial ischemia.

Sympathetic nerves in the epicardium of the ventricle carry afferent signals to the brain when they are activated by mechanical or chemical stimuli (59,60). Epicardial application of bradykinin is used experimentally to evaluate the functional integrity of sympathetic nerves in the cardiac ventricles. Application of bradykinin to the epicardium of a dog activates afferent sympathetic nerve activity, causing a reflex increase in arterial blood pressure (64,65). Regional denervation using epicardial application of phenol blocks afferent impulses on cardiac sympathetic nerves and prevents the increase in arterial pressure. Epicardial application of bradykinin in dogs with experimental myocardial infarction has demonstrated regional epicardial denervation (65).

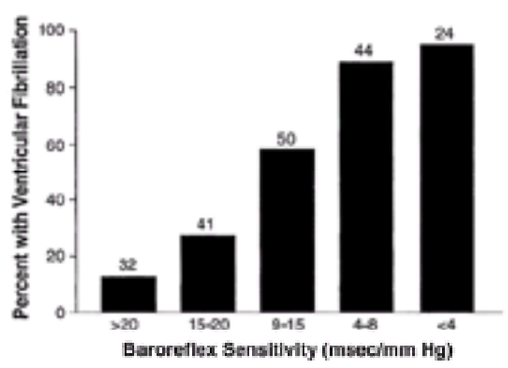
Antiarrhythmic Effects of the Parasympathetic Nervous System

The parasympathetic nervous system has pronounced antiarrhythmic properties by reducing heart rate and by counteracting the proarrhythmic effects of sympathetic nervous system activity (66). The antiarrhythmic benefit of increased parasympathetic activity is especially evident when the sympathetic nervous system plays a role in the arrhythmic activity. There are three clinical methods for quantifying parasympathetic nervous system modulation of cardiac activity: BRS, RR variability, and HRR. A number of experimental studies have attempted to define the value of these markers for assessing parasympathetic activity and for evaluating the risk of VF.

Baroreflex Sensitivity Predicts Ischemic Ventricular Fibrillation

The predictive value of BRS for ischemic VF was suggested by a series of elegant studies in an experimental model of sudden cardiac death (67,68,69 and 70). Thirty days after left anterior descending coronary artery ligation, conscious dogs with healed anterior myocardial infarctions were subjected to transient circumflex coronary artery occlusions while running on a treadmill to increase heart rate and sympathetic nervous system activity. Of 192 dogs subjected to transient ischemia during exercise, 55% developed VF during exercise and ischemia and 45% did not (69). Dogs susceptible to VF showed a substantial increase in heart rate during ischemia before the onset of VF, whereas dogs resistant to VF showed a decrease in heart rate.

In this model of sudden cardiac death, ischemic VF can be predicted with considerable accuracy by measuring BRS (69). Dogs with a lower BRS had a much higher chance of VF during the exercise ischemia challenge (eFig. 77.0.1). Unexpectedly, dogs susceptible to VF during exercise ischemia after experimental myocardial infarction already had a lower BRS before coronary artery ligation. There were large differences in BRS among healthy dogs, and those with the lowest values of BRS before myocardial infarction were most susceptible to VF after myocardial infarction when challenged with myocardial ischemia and sympathetic activation (69). This finding suggests that individuals at high risk of arrhythmic events after myocardial infarction can be identified and treated before infarction occurs. In dogs, 6 weeks of daily exercise training substantially increased BRS and markedly reduced the likelihood of VF during exercise ischemia (68). Exercise also might benefit coronary heart disease patients at high risk of VF.



***e*FIGURE 77.0.1** The probability of developing ventricular fibrillation during exercise and ischemia in dogs with previous myocardial infarction is inversely related to baroreflex sensitivity. The *x*-axis gives the categories for baroreflex sensitivity; the *y*-axis is the percent of dogs that develop ventricular fibrillation during exercise and ischemia. The numbers over the bars indicate the number of dogs in each group. (Adapted from Schwartz PJ, Vanoli E, Stramba-Badiale M, et al. Autonomic mechanisms and sudden death: new insights from the analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* 1988;78:969–973. This figure was first published as Figure 19.1 in Bigger JT Jr, Rottman JN. Spectral analysis of RR variability. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia. Mechanisms, diagnosis, and management*. Baltimore: Williams & Wilkins, 1995:280–298, with permission.)

Vagal stimulation prevented susceptible dogs from developing VF during the exercise ischemia test (71). Part of the vagal protection was due to the decrease in heart rate and part to other factors.

RR-Interval Variability Predicts Ischemic Ventricular Fibrillation

RR variability has been studied in the same dog model of sudden cardiac death that showed the value of BRS as a predictor of arrhythmic events. The study was done on dogs to test the hypothesis that low values of RR variability would predict which dogs would develop VF when challenged by exercise ischemia 1 month after myocardial infarction (72).

Immediately after infarction, RR variability decreased substantially in all dogs, but the time course of recovery of RR variability was different for dogs that were resistant and those that were susceptible to VF. In resistant dogs, RR variability recovered to pre–myocardial infarction levels within 10 days, whereas susceptible dogs had persistent attenuation of RR variability throughout the 30 days after myocardial infarction (73). Decreased RR variability 30 days after myocardial infarction had 88% sensitivity and 80% specificity for predicting VF. No sham-operated animals developed VF (72).

Chronotropic Incompetence May Reflect Baseline Sympathetic Overload

The heart-rate response to exercise can yield important prognostic information for the clinician. In the healthy individual, heart rate increases during exercise to an age-related maximum heart rate. There is a wide individual variation in peak heart rates obtained, but the maximum heart rate declines uniformly with advancing age. Age-predicted peak heart rate is commonly estimated using the formula 220 minus age. A commonly used definition of chronotropic incompetence is failure to reach 85% of the age-predicted peak heart rate, but other investigators have suggested the use of the chronotropic index as a better marker of chronotropic incompetence (22,23).

A major limitation of using a percentage of age-predicted maximum heart rate as a marker of chronotropic response is that the estimated peak heart rate has a high standard deviation and therefore may be difficult to apply to individuals, as opposed to populations (74). There are other problems with using ability to reach 85% of the age-predicted maximum heart rate as a measure of chronotropic incompetence. In addition to age, other important predictors of the heart-rate response to exercise are resting heart rate and physical fitness, both factors that themselves are predictive of coronary heart disease risk (74,75,76,77 and 78). Data from the Framingham Heart Study have shown that ability to reach a target heart rate is influenced by these two variables and even by age itself (22). Therefore, any effort to relate chronotropic incompetence of prognosis or diagnosis suffers an inherent risk of serious confounding.

Wilkoff and Miller have described a method for describing the exercise heart-rate response that takes advantage of the linear relation between exercise heart-rate increase and metabolic work (79). Before exercise, a person has a certain metabolic reserve, which is the difference between the peak oxygen consumption (or exercise capacity) and the rest oxygen consumption, which is typically 3.5 mL per kg per minute, or 1 metabolic equivalent (MET). As exercise progresses, that metabolic reserve is used up. Analogously, at rest there is a potential heart-rate reserve, which is the difference between the peak attainable heart rate (as estimated, for example, by 220 minus age) and the resting heart rate. As exercise progresses, heart-rate reserve, like the metabolic reserve, is used up as well. Wilkoff and Miller described a metabolic chronotropic relation, which we have termed the *chronotropic response index*, which is based on the long-known linear association between use of heart-rate reserve and metabolic reserve during exercise.

The mathematical derivation of the chronotropic response index is as follows: During any given stage of exercise, the percent metabolic reserve (MR) used can be expressed as

$$\%\text{MR used} = [(\text{METs}_{stage} - \text{METs}_{rest})/(\text{METs}_{peak} - \text{METs}_{rest})] \times 100$$

Similarly the percent HR reserve used at any given stage of exercise can be expressed as

$$\%\text{HR reserve used} = [(\text{HR}_{stage} - \text{HR}_{rest})/(220 - \text{age} - \text{HR}_{rest})] \times 100$$

Wilkoff and Miller have shown that among healthy adults the ratio of heart-rate reserve used to metabolic reserve used at any stage of exercise has a value of one with a 95% confidence interval of 0.8 to 1.3 (79). This ratio is the chronotropic response index (22,23) and is independent of stage of exercise considered. Thus, chronotropic incompetence can be defined as a percent heart-rate reserve used to percent metabolic reserve used ratio of less than 0.8; this is referred to as a *low chronotropic index*. The advantage of using this approach to assess chronotropic response is that it accounts for age, functional capacity, and resting heart rate; it is in fact a measure largely independent of functional capacity (22).

One problem with this method is that during routine exercise testing exercise capacity in METs is only estimated. Nonetheless, among patients who undergo symptom-limited testing, one can consider the ratio of heart-rate reserve used to metabolic reserve used at peak exercise, when by definition the proportion of metabolic reserve used has a value of one. Using this approach, the chronotropic index is based entirely on directly measured variables, namely, resting heart rate, peak heart rate, and age (80).

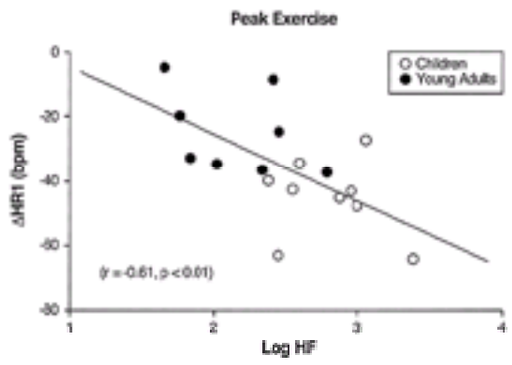
The chronotropic response to exercise has been demonstrated to be an important predictor of mortality (19,20,22,24,25,81,82). The mechanisms to explain this finding are not entirely clear, but it may be that a blunted chronotropic response is indicative of a baseline sympathetic overload (83). There is evidence to suggest that individuals with a blunted chronotropic response to exercise have a postsynaptic desensitization to beta-adrenergic receptor stimulation (83). Colucci et al. demonstrated that heart failure patients with blunted chronotropic responses had similar increments of change of norepinephrine levels from resting to peak exercise but much higher baseline levels when compared with healthy controls (83). When isoproterenol was infused the heart rate increased less in heart failure patients than in healthy controls. These data suggest that although individuals with chronotropic incompetence have an increase in sympathetic activity to maximum levels, they are unable to attain higher heart rates due to an increased baseline sympathetic level along with a decreased sensitivity to further sympathetic stimulation, leading to a blunting of the heart-rate response. This situation is analogous to an automobile that is “out of tune.” Gasoline use during idling is increased, but the car is unable to increase speed by much in response to increased gasoline delivery.

Heart-Rate Recovery Reflects Parasympathetic Reactivation

The increase in heart rate during exercise is due to the combination of parasympathetic withdrawal and sympathetic activation, whereas the recovery of heart rate back toward baseline is due to the reverse (30,42,45,46,48,74,84,85 and 86). What is less well understood is the relative contributions and timing of parasympathetic and sympathetic activity during recovery. To address this question, Imai et al. (31) measured HRR in three groups of individuals: healthy controls, trained athletes, and heart failure patients. They studied postexercise HRR under two different conditions: after parasympathetic blockade with atropine and after sympathetic blockade with propranolol. Across all groups, the decrease in heart rate during the first 30 seconds of recovery was markedly prolonged following atropine administration but not with beta-blockade. This effect was less pronounced at 2 minutes. Crouse et al. (47), Maciel et al. (46), and Perini et al. (48) obtained similar results. These findings suggest that HRR during the first minute of recovery is due almost exclusively to parasympathetic activity.

Two additional observations provide evidence that early HRR is a marker of parasympathetic activity. First, Imai et al. (31) demonstrated that HRR was accentuated in athletes, but blunted in patients with heart failure. Other investigators have also noted an increased HRR in trained individuals (87) and a decreased HRR in poorly fit persons (88). The link between these findings and the autonomic nervous system may be established by nearly identical changes in RR variability. There are data that show RR variability is decreased in poorly fit individuals and those with heart failure (89) and may be increased through exercise training (90). Arai et al. (45) found an increase in the HF power, which reflects parasympathetic activity, during early recovery that was more pronounced in individuals with higher fitness levels. Based on these studies, it may be hypothesized that parasympathetic activity is the link between fitness level and HRR.

A second observation is that HRR is known to be faster in children than in adults (87,91). A study by Ohuchi et al. (92) may shed light on this finding. They measured both HRR and RR variability in children and adults after exercise. The children had significantly higher log HF power than adults during recovery, corresponding to increased parasympathetic activity. There was a strong correlation between HRR and log HF power (eFig. 77.0.2), thus linking the two together and providing additional evidence that HRR in early recovery is primarily a function of the parasympathetic nervous system.



***e*FIGURE 77.0.2** Relationship between log high-frequency heart-rate variability (log HF) and decrease in heart rate 1 minute after peak exercise (DHR1). (From Ohuchi H, Suzuki H, Yasuda K, et al. Heart rate recovery after exercise and cardiac autonomic nervous activity in children. *Pediatr Res* 2000;47:329–335, with permission.)

MEASUREMENT OF RR-INTERVAL VARIABILITY AND BAROREFLEX SENSITIVITY

Measurement of RR Variability

Variation in RR intervals can be measured by many methods; these methods can be categorized as time domain measures or frequency domain measures (93). Table 77.1 lists the commonly used measures of RR-interval variability. Every frequency domain measure of RR variability has an equivalent time domain measure (*e*Table 77.1.1). The physiologic correlates of RR variability are discussed later (see Frequency Domain Measures of RR Variability).

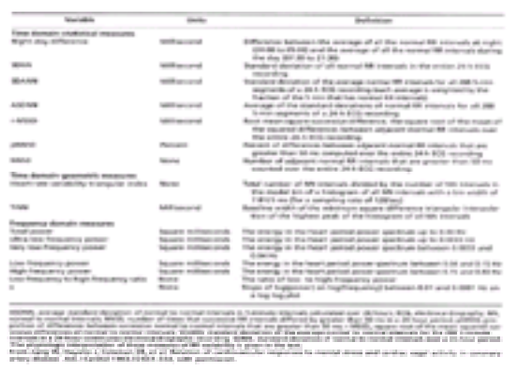


TABLE 77.1 DEFINITIONS FOR TIME AND FREQUENCY DOMAIN MEASURES OF HEART PERIOD VARIABILITY[a]

***e*TABLE 77.1.1** CORRELATIONS AMONG TIME AND FREQUENCY DOMAIN MEASURES OF RR VARIABILITY IN HEALTHY SUBJECTS (N = 274)

	Normal RR intervals	**Night–day difference**	**SDNN**	**Ln (TP)**	**Ln (ultra low frequency)**	**SDANN**	**Ln (very low frequency)**	**ASDNN**	**Ln (low frequency)**	**Ln (r-MSSD)**	**Ln (pNN50)**	**Ln (high frequency)**	**Ln (low frequency to high frequency ratio)**
Normal RR intervals	1.00												
Night–day difference	0.20	1.00											
SDNN	0.53	0.78	1.00										
Ln (TP)	0.48	0.82	**0.97**	1.00									
Ln (ultra low frequency)	0.44	0.84	**0.95**	**0.99**	1.00								
SDANN	0.42	**0.86**	**0.97**	**0.97**	**0.98**	1.00							
Ln (very low frequency)	0.65	0.41	0.73	0.73	0.65	0.63	1.00						
ASDNN	0.59	0.39	0.70	0.70	0.61	0.59	**0.95**	1.00					
Ln (low frequency)	0.28	0.27	0.49	0.52	0.43	0.41	0.79	**0.86**	1.00				
Ln (r-MSSD)	0.42	0.32	0.54	0.56	0.48	0.46	0.72	**0.83**	0.77	1.00			
Ln (pNN50)	0.46	0.28	0.51	0.53	0.49	0.44	0.74	0.78	0.73	**0.93**	1.00		
Ln (high frequency)	0.28	0.27	0.46	0.50	0.42	0.39	0.67	0.46	0.79	**0.94**	**0.88**	1.00	
Ln (low frequency to high frequency ratio)	–0.08	–0.09	–0.09	–0.12	–0.12	–0.09	–0.03	–0.13	–0.04	–0.51	–0.46	–0.58	1.00

ASDNN, average standard deviation of normal to normal intervals in 5-minute intervals calculated over 24 hours; Ln, natural logarithm; pNN50, proportion of differences between successive normal to normal intervals that are greater than 50 ms; r-MSSD, square root of the mean squared successive differences of normal to normal intervals; SDANN, standard deviation of the average normal to normal intervals for the 288 5-minute intervals in a 24-hour continuous electrocardiographic recording; SDNN, standard deviation of normal to normal intervals over a 24-hour period.
Note: Numbers in boldface indicate variables with such high correlation that they are interchangeable.
From Bigger JT Jr, Fleiss JL, Steinman RC, et al. RR variability in healthy, middle-age persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation* 1995;91:1936–1943, with permission.

Time Domain Measures of RR Variability

Time domain measures of RR variability can be used to summarize information about either short-term or long-term variation in RR intervals, and a large number of measures have been proposed. These measures attempt to estimate the influence of nervous and humoral influences on the sinus node so they usually exclude RR intervals caused by ectopic (nonsinus) beats. In a continuous ECG recording, each R wave (QRS complex) is detected and labeled as normal (N) or abnormal. The series of NN intervals is used to calculate time domain measures, which may be expressed directly as NN intervals or as instantaneous heart rate.

Statistical Measures

From a series of NN intervals, various statistical measures are calculated (93,94). Most often the NN series is recorded for an entire 24-hour period or for a short period, typically 5 minutes or 1 hour. Some of the commonly used time domain measures are summarized in Table 77.1. A commonly used and useful measure of RR variability is SDNN. This measure summarizes all sources of variation in NN intervals over the period of calculation. The longer the recording for an individual, the greater is the magnitude of SDNN. If the SDNN is calculated on an interval substantially different from 24 hours, this should always be stated clearly because the values cannot be compared with standard 24-hour values. A common time domain measure of long-term (slow) variation in NN intervals is the standard deviation of the average NN intervals for the 2885-minute intervals in a 24-hour continuous ECG recording (SDANN). A common time domain measure of short-term (fast) variation in NN intervals is the average standard deviation of NN intervals in 5-minute intervals calculated over 24 hours (ASDNN). SDANN measures fluctuations in NN intervals with cycles longer than 5 minutes, and ASDNN measures fluctuations with cycles shorter than 5 minutes.

Differences in Adjacent RR Intervals

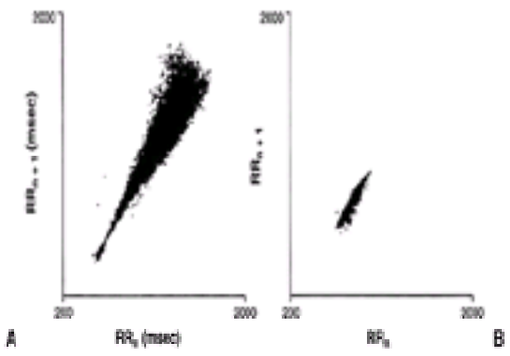
Measures calculated from differences in adjacent NN intervals measure fluctuations with very short cycles (i.e., measured in seconds). The r-MSSD and the proportion of differences between successive NN intervals that are greater than 50 ms (pNN50) are two measures that estimate HF variations in NN intervals caused by modulation of sinus node firing rate by the vagus nerves and, thus, are always highly correlated (*e*Table 77.1.1).

Geometric Methods

Geometric patterns have been used to quantify long-term RR variability (93,95). The 24-hour NN interval time series is plotted as a frequency distribution of NN intervals, and then summary measures are calculated to describe it. HRV triangular index and the triangular interpolation of NN intervals (TINN) are two geometric measures that have been used to describe the frequency histogram of NN intervals over a 24-hour period. These measures are determined by finding the length of the base of a triangle that best fits the frequency histogram (93).

The frequency histogram of NN intervals most commonly is tabulated in bins 7.8125 ms, reflecting the 128 per second sampling rate used by commercial Holter systems. The HRV triangular index is calculated by dividing the total number of NN intervals (the integral of the histogram) by the modal frequency (the number of NN intervals in the bin that contains the most NN intervals). TINN is the width of the base of the frequency histogram of NN intervals obtained by triangular interpolation and has the units of milliseconds. HRV triangular index and TINN are relatively free of errors in labeling of the RR intervals, so their values do not much depend on the quality of the recordings or the analysis.

The Lorenz or Poincaré plot is another geometric display that has been used to evaluate RR variability (95). Each RR interval is plotted as a function of RR-1, which gives a cigar-shaped distribution. The Lorenz plot for a healthy person is long and wide, and the width increases at the longer RR intervals (*e*Fig. 77.0.3A). In severe heart disease, the plot becomes short and narrow (*e*Fig. 77.0.3B). Errors in QRS detection produce characteristic patterns as well. Although certain patterns have been described and correlated with severity of disease, there are no standardized methods for quantifying Lorenz plots.



***e*FIGURE 77.0.3** Lorenz or Poincaré plots. The current RR interval (RR_n) is plotted on the *x*-axis, and the subsequent RR interval (RR_{n+1}) is plotted on the *y*-axis. Panel **A** is a plot from a healthy 52-year-old man that shows a wide range of RR intervals and shows greater dispersion of RR interval at longer RR intervals. Panel **B** is a plot from a 61-year-old man with heart failure that shows a decreased range of RR intervals and does not show greater dispersion of RR interval at longer RR intervals. (Adapted from Woo MA, Stevenson WG, Moser DK, et al. Complex heart rate variability and serum norepinephrine levels in patients with advanced heart failure. *J Am Coll Cardiol* 1994;23:565–569, with permission.)

Frequency Domain Measures of RR Variability

Analytic Methods

Both nonparametric (fast Fourier transforms; FFT) and parametric (autoregression) methods have been used to compute power spectral density of RR-interval time series (13,15,93,96). The nonparametric (FFT) method is simple, fast to compute, and does not require that a model be assumed. The parametric (autoregression) method produces a smoother spectrum and permits automatic estimation of HF and LF power and their center frequencies, but requires that the order of the model be specified (93,96). Unless there are differences in selection of beats for analysis or in signal-processing procedures, FFT and autoregression methods provide similar results.

Five-Minute Power Spectra

The Task Force on Heart Rate Variability of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology recommended that power spectral analysis of 5-minute ECG recordings be used to assess autonomic physiology and pharmacology (93). Frequencies between 0.0033 and 0.40 Hz can be estimated from a 5-minute ECG recording. Figure 77.1A shows a 5-minute power spectrum in a healthy person lying supine. Two “peaks” are present in the 5-minute power spectrum: HF power in the frequency range 0.15 to 0.40 Hz and LF power in the frequency range 0.04 to 0.15 Hz. The power spectral density usually is expressed as absolute units of power (square milliseconds), but may be expressed in normalized units (Fig. 77.2). Normalized units can be used to emphasize the reciprocal action of the parasympathetic and sympathetic limbs of the autonomic nervous system and to minimize the effect of changes in total power on the values of LF and HF components (97). HF power reflects modulation of efferent parasympathetic (vagal) activity by ventilation (respiratory sinus arrhythmia). LF power reflects modulation of efferent parasympathetic (vagal) and efferent sympathetic nervous system activity by baroreflex activity. It should be emphasized that the amplitude of LF or HF power reflects modulation of sinus node firing rate, not the average level of parasympathetic or sympathetic tone (13,98). Note that the amplitude of LF power is greater than HF power in a healthy person resting in the supine position. The LF/HF ratio is used as an index of vagosympathetic balance (15).

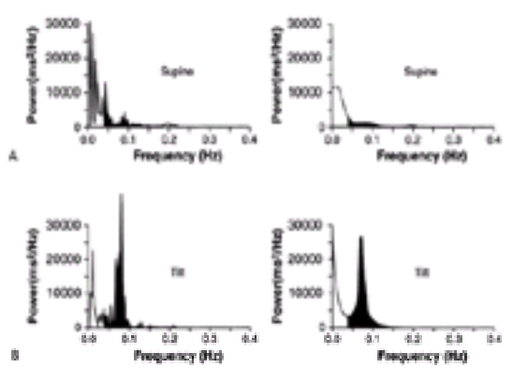


FIGURE 77.1 A,B: Power spectral analysis of RR-interval time series. The left panels show fast Fourier transform (FFT) analysis of two 5-minute recordings of RR intervals. The left panel of **A** shows the FFT of a recording made supine and resting; the left panel of **B** shows the FFT of a recording made during 60-degree head-up tilt. The right panels show the results of autoregression analysis of the same two 5-minute recordings. The autoregressive algorithm smooths the data, but gives almost identical areas under the curves as the FFT algorithm in the frequency bands of interest. In the supine recording, there is a peak at approximately 0.20 Hz in the high-frequency (HF) power band, and a peak at approximately 0.08 Hz in the low-frequency (LF) power band. More than one-half the power is in the very low-frequency power band. Both methods show a decrease in HF power and a marked increase in LF power during head-up tilt. (From Bigger JT Jr. RR variability to evaluate autonomic physiology and pharmacology and to predict cardiovascular outcomes in humans. In: Zipes DP, ed. *Cardiac arrhythmias: from cell to bedside.* Philadelphia: WB Saunders, 1995:1151–1170, with permission.)

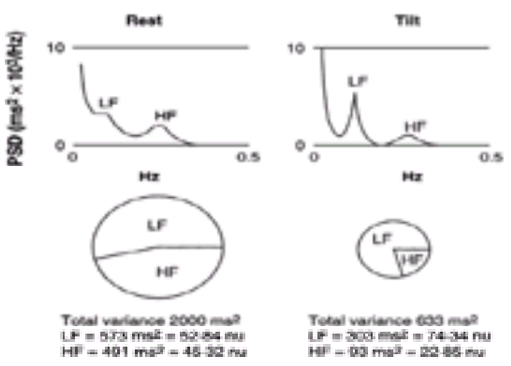


FIGURE 77.2 Use of normalized units to interpret spectral analysis (autoregressive model) of RR-interval variability in a healthy subject. The recording on the left was made while the subject was resting in the supine position; the recording on the right was made during 90-degree head-up tilt. At rest, low-frequency (LF) and high-frequency (HF) power have a similar magnitude, whereas during the head-up tilt, LF power is much greater than HF power. Total variance is markedly reduced

during tilting, so both LF power and HF power are diminished when expressed in absolute units. The use of normalized units (nu) clearly indicates the altered relation between the two spectral components induced by tilting. The pie charts show the absolute power of the two components (represented by the area of the circles) as well as the relative distribution of LF and HF power. The LF/HF ratio also quantifies the relative distribution of LF and HF power. These changes in the normalized units and LF/HF ratio are interpreted as a decrease in parasympathetic modulation and an increase in sympathetic modulation of RR intervals. PSD, power spectral density. (From Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br Heart J* 1994; 71:1–2, with permission.)

The energy between 0.0033 and 0.04 Hz is called *very low-frequency power*; the physiologic correlates of very low-frequency power are not known, but the power in this range can be influenced substantially by physical activity (99).

Dynamic Changes in the Five-Minute RR-Interval Power Spectrum

The RR-interval power spectrum is dynamic as a function of autonomic activity. For example, if breathing is synchronized to a metronome, the HF peak becomes narrow at its base and taller; if the beat of the metronome is changed, the HF peak moves to the new frequency of breathing (100). Figure 77.1B shows the dramatic changes in the NN interval power spectrum during head-up tilt to 60 degrees. HF power decreases, LF power increases, and the LF/HF ratio increases. These changes reflect the baroreflex, which causes a substantial decrease in efferent parasympathetic activity and an increase in efferent sympathetic activity.

Twenty-Four-Hour Power Spectra

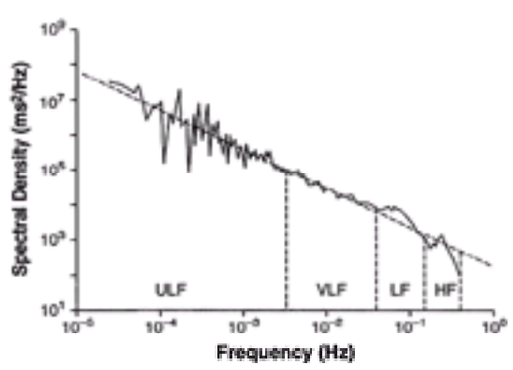
If power spectral density is calculated over a 24-hour interval, then power below 0.0033 Hz (down to approximately 0.00003 Hz) can be calculated (i.e., ultra low-frequency power) (96). Physiologic correlates of ultra low-frequency power are not established, but there is some evidence that it is modulated by activity of the renin-angiotensin system (13). Also, fluctuations of RR intervals at this very low frequency are powerful predictors of death in the years after acute myocardial infarction (101).

Power Law Behavior of RR-Interval Variability

If 24-hour power spectral density is plotted as a function of frequency on a log-log graph, the relationship is linear over a frequency range from 0.00003 to 0.04 Hz, with a slope approximately equal to –1 in healthy young people, indicating that power decreases approximately as the reciprocal of frequency, 1/*f* (102). The relationship between power and frequency is described by a power law:

$$P = Cf^{a},$$

where *P* is the power spectral density, *f* is frequency, a is a negative exponent, and *C* is a proportionality constant (eFig. 77.2.1) (103); a also corresponds to the slope of the log *P* versus log *f* relationship:



***e*FIGURE 77.2.1** The relationship between regression of the log of spectral power for RR-interval fluctuations on log frequency and traditional power spectral bands for a healthy subject. The computed power law regression line is superimposed on the data; the darkened portion of the lines is the segment between 10^{-4} and 10^{-2} Hz that is used to compute the regression line. In the region of the ultra-low-frequency (ULF) and very low-frequency (VLF) bands, the log-log graph of spectral power versus frequency is linear. In the region of the low-frequency (LF) and high-frequency (HF) bands, the log-log graph of spectral power versus frequency is nonlinear due to modulation by the autonomic nervous system. (From Bigger JT Jr, Steinman RC, Rolnitzky LM, et al. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent myocardial infarction, and patients with heart transplants. *Circulation* 1996;93:2142–2151, with permission.)

$$\log P = \log C + a \log f.$$

a usually is computed over the two-decade band from 10^{-4} to 10^{-2} Hz and then extrapolated. The slope of log power on log frequency is a fundamentally different RR-interval power spectral measure than the standard power spectral bands (e.g., ultra low frequency, very low frequency, LF, or HF). In contrast to these power spectral bands, the slope reflects not the magnitude but rather the distribution of power in this two-decade region. The average slope is close to –1 for healthy persons. Saul et al. found that a averaged –1.02 ± 0.05 in five healthy young men (102), and Bigger et al. found that a averaged –1.06 ± 0.12 in 274 healthy middle-aged subjects (103). As the heart gets sicker, the slope of log power on log frequency gets steeper, finally approaching a limit of approximately –2 found in totally denervated hearts (e.g., transplanted hearts) (103).

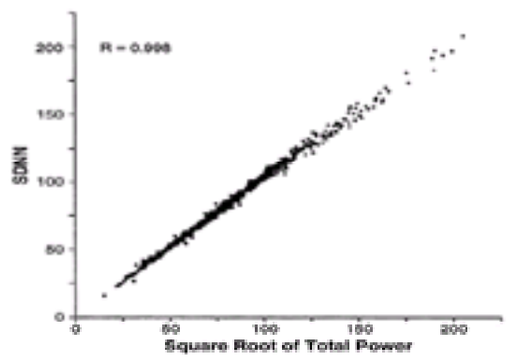
Because power is an inverse function of frequency, variance increases with the length of the ECG recording. Therefore, RR-interval variance, or its square root, SDNN, is meaningful only with respect to a particular duration of ECG recording. One implication of the power law relation between spectral power of RR-interval fluctuations and their frequency is the need to standardize the length of ECG recordings used to calculate SDNN or the need to correct SDNN for differences in the duration of Holter ECG recordings.

Nonlinear Dynamic Measures of RR Variability

RR-interval data have been analyzed using nonlinear dynamic methods, or “chaos theory” (104,105,106 and 107), which assume data are aperiodic, but not random. Nonlinear dynamic measures are less intuitive to interpret, but quantify the RR-interval time series in a different way than linear methods, including conventional power spectral analysis. Most nonlinear dynamic measures can be estimated from ECG recordings digitized at 128 samples per second, but Skinner’s correlation dimension (PD2) (106) is calculated from ECG recordings.

Correlations among the Measures of RR-Interval Variability

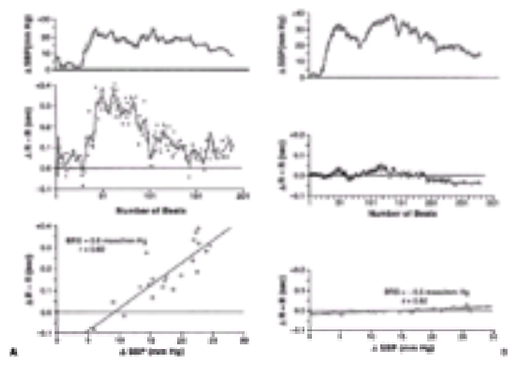
*e*Table 77.1.1 gives the correlations among the measures of RR-interval variability in 274 healthy middle-aged subjects (108). There are three natural clusters of high correlation among 10 of the 12 variables in *e*Table 77.1.1: (a) SDNN, SDANN, total power, and ultra-low-frequency power; (b) very low-frequency power, LF power, and ASDNN; and (c) HF power, r-MSSD, and pNN50. The ratio of the power in the LF band to the power in the HF band does not correlate strongly with any of the other measures of heart period variability, even those that are used to calculate the ratio. Power in each power spectral band correlates so strongly with a time domain variable (correlation coefficients approximately 0.90) that the two variables are essentially equivalent: ultra-low-frequency power with SDNN and SDANN, very low-frequency power and LF power with ASDNN, and HF power with r-MSSD and pNN50. As expected from theoretical considerations, SDNN and the square root of total power for a 24-hour interval are almost perfectly correlated (eFig. 77.2.2) (i.e., the regression line essentially has a slope of 1 and an intercept of 0). Although the absolute values of these measures of RR variability decrease markedly in patients with recent myocardial infarctions and other heart diseases, correlations between frequency and time domain measures of RR variability are preserved (94).



***e*FIGURE 77.2.2** The relationship between the standard deviation of the normal RR intervals (SDNN) and the square root of total power in the 24-hour heart period power spectrum. The unit for both variables is milliseconds. Note that the empirically observed relationship is close to the theoretically expected relationship (i.e., intercept of 0 and slope of 1). Also, the correlation coefficient is very close to 1. (From Bigger JT Jr, Fleiss JL, Steinman RC, et al. Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. *Am J Cardiol* 1992;69:891–898, with permission.)

Measurement of Baroreflex Sensitivity

Methodology to investigate the baroreflex control of heart rate was developed at Oxford University in the 1960s by measuring the reflex increase in RR intervals in response to a blood pressure increase produced by intravenous injection of an alpha-adrenergic agonist (109). Phenylephrine, a pure alpha-adrenergic receptor agonist that lacks direct effects on cardiac contractility and on the central nervous system, is most commonly used to measure BRS. Phenylephrine doses of 50 to 150 µg are injected to increase systolic arterial pressure by 20 to 30 mm Hg. In this range of blood pressure increase, a linear relationship is found between the increase in RR intervals and the initial increase in systolic blood pressure after phenylephrine injection (*e*Fig. 77.2.3). The slope of this regression line (expressed as milliseconds of increase in RR interval per 1 mm Hg rise in pressure) quantifies the sensitivity of the arterial baroreflex (eFig. 77.2.3A). Three to five injections are given at 5-minute intervals, and the individual slopes are averaged to estimate the mean slope. Variability among individual measurements can be attributed to (a) rate of the injection, (b) steepness of arterial pressure increase, and (c) selection of the time window for the analysis. The slope of RR-interval change on the increase in systolic blood pressure after phenylephrine injection is steep in healthy persons; the slope becomes less steep with increasing age and almost flat in patients with severe cardiovascular disorders (e.g., hypertension or heart failure) (eFig. 77.2.3B) (110,111). BRS is modulated by several physiologic conditions. BRS decreases whenever the autonomic balance shifts toward a sympathetic dominance and increases whenever the autonomic balance shifts toward a parasympathetic dominance. For example, BRS increases during sleep and rest (109).



***e*FIGURE 77.2.3 A:** The phenylephrine method for measuring baroreflex sensitivity (BRS). The top and middle panels show beat-to-beat changes in systolic blood pressure (SBP) and RR intervals after phenylephrine injection. Pairs of SBP and RR-interval values for regression analysis (*bottom panel*) were selected from the first major increase in blood pressure after the injection. In this patient with recent myocardial infarction, phenylephrine produced a 25-mm Hg increase in systolic blood pressure, which was accompanied by a marked increase in the RR intervals. Accordingly, the slope of the regression line reflecting BRS was steep (19 ms per mm Hg) and represents a normal response. **B:** In this patient with recent myocardial infarction, the RR intervals did not change significantly despite a clear-cut increase in SBP, indicating that BRS is extremely depressed –0.5 ms per mm Hg (*bottom panel*). (From La Rovere MT, Specchia G, Mortara A, et al. Baroreflex sensitivity, clinical correlates and cardiovascular mortality among patients with a first myocardial infarction: a prospective study. *Circulation* 1988;78:816–824, with permission.)

Two principal factors have limited the widespread clinical use of BRS by the phenylephrine method: (a) the need to cannulate an artery for beat-to-beat systolic blood pressure measurement and (b) the need for drug injection. More recently, noninvasive measurement of beat-to-beat systolic blood pressure has become practical using devices such as the FINAPRES (from *fin*ger *a*rterial *pres*sure) device. The accuracy of blood pressure measurement has been documented, in small groups of subjects, during several interventions such as Valsalva's maneuver, sustained handgrip, postural changes, and vasoactive drug administration (112,113) and in a large population of post–myocardial infarction patients as part of the Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) study (114). More recently, BRS has been quantified using spectral techniques to analyze the relationship between spontaneous beat-to-beat oscillation of blood pressure and RR intervals to obviate the need for phenylephrine injection (112,115,116). These spectral methods are promising but have not been sufficiently validated for routine clinical use.

USE OF AUTONOMIC MARKERS TO PREDICT DEATH OR ARRHYTHMIC EVENTS

Clinical Use of RR Variability for Assessment of Risk

In the opinion of the Task Force on Heart Rate Variability, there were two proven clinical uses of RR variability: (a) to predict risk of cardiac death or arrhythmic events after acute myocardial infarction, and (b) to detect and quantify autonomic neuropathy in diabetes mellitus (93). In the following sections of this chapter, we review some of the studies that have established RR variability as a predictor of cardiac death after acute myocardial infarction and in chronic coronary heart disease. Both time and frequency domain measures have been used to predict mortality, and nonfatal arrhythmic events in coronary heart disease. The measures most often used for this purpose include SDNN, SDANN, HRV triangular index, total power, ultra-low-frequency power, LF power, and power law regression parameters (Table 77.1).

Prediction of Hospital Mortality after Myocardial Infarction Using the Variance of 30 RR Intervals

In 1978, Wolf et al. published the first report of an association between RR variability and prognosis (16). These workers studied 176 patients admitted to hospital for acute myocardial infarction to evaluate the relationship between RR variability and in-hospital mortality. A 60-second ECG recording was made on the day of admission to the coronary care unit, and the variance of 30 consecutive RR intervals was calculated for each patient. Wolf et al. arbitrarily dichotomized their group using a variance of 1,000 ms^2; 73 patients (42%) had a variance greater than or equal to 1,000 ms^2, and 103 patients (59%) had a variance less than 1,000 ms^2 (eTable 77.1.2). Patients with RR variance less than 1,000 ms^2 were more likely to have anterior myocardial infarction, a Norris index greater than or equal to 10, low values for average RR interval, and admission to hospital longer after onset of chest pain.

***e*TABLE 77.1.2** RR VARIANCE AND HOSPITAL MORTALITY[a]

	Hospital death		
Variance (ms^2)	Yes	No	Total
<1,000	16 (15.5%)	87	103
³1,000	3 (4.1%)	70	73
Total	19	157	176

[a]Relative risk, 3.8 (95% confidence interval, 1.1–12.5).

From Wolf MM, Varigos GA, Hunt D, et al. Sinus arrhythmia in acute myocardial infarction. *Med J Aust* 1978;2:52–53, with permission.

The study by Wolf et al. showed that RR variability, estimated from a short ECG recording on the day of myocardial infarction, predicted mortality over the next 9 to 14 days (16). The hospital mortality of patients with RR variance less than 1,000 ms^2 was 15.5% compared with 4.1% for patients with RR variance greater than or equal to 1,000 ms^2. After adjusting for average RR interval and location of the infarct, low RR variance was still significantly associated with higher mortality.

Prediction of Long-Term Mortality after Acute Myocardial Infarction Using Time Domain Measures of RR Variability

In 1987, Kleiger et al. (17) reported that SDNN, measured at the time of hospital discharge after myocardial infarction, predicted death during the subsequent 2 to 4 years. They performed baseline studies on a group of 808 patients with acute myocardial infarction and then followed them an average of 31 months. Twenty-four-hour ECG recordings were done 11 ± 3 days after acute myocardial infarction. SDNN was calculated for the 24-hour period, and a value of 50 ms was chosen arbitrarily to dichotomize their group into 125 patients (16%) with low values and 683 patients (84%) with high values. During 2 to 4 years of follow-up, 127 deaths occurred (Fig. 77.3). The mortality of patients with an SDNN less than 50 ms was 34% compared with a 12% mortality in patients with an SDNN greater than or equal to 50 ms, a relative risk of 2.8 (95% confidence interval, 2.0 to 3.8). SDNN predicted mortality independently of other risk predictors such as LVEF or ventricular arrhythmias.

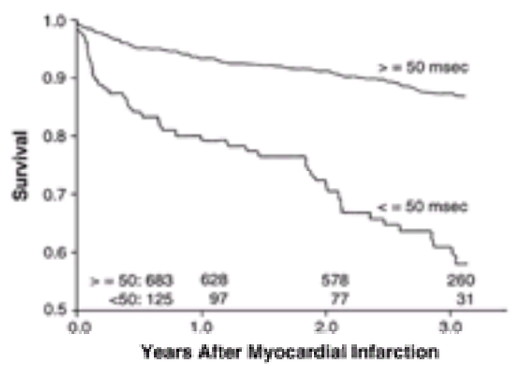


FIGURE 77.3 Survival as a function of the 24-hour standard deviation of normal RR intervals in 808 patients with myocardial infarction. Time after myocardial infarction is plotted on the *x*-axis; proportion surviving is plotted on the *y*-axis. (Adapted from data published in Kleiger RE, Miller JP, Bigger JT Jr, et al. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256–262. This figure was first published as Figure 19.6 in Bigger JT Jr, Rottman JN. Spectral analysis of RR variability. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia. Mechanisms, diagnosis, and management.* Baltimore: Williams & Wilkins, 1995:280–298, with permission.)

This study was the first to show the predictive value of RR variability for all-cause mortality during long-term follow-up after myocardial infarction. Bigger et al. showed that SDANN was strongly associated with all-cause mortality. SDNN or SDANN were better predictors of mortality than ASDNN or time domain measures of HF fluctuations in NN intervals (e.g., r-MSSD or pNN50) (94).

Farrell et al. obtained similar results using a geometric time domain measure of RR variability, the HRV triangular index (117). Farrell et al. studied 416 patients 6 or 7 days after acute myocardial infarction, 48% of whom were treated with thrombolysis (117). RR variability was quantified by triangular interpolation of the frequency distribution of normal RR intervals (TINN), a measure that is strongly correlated with SDNN, SDANN, total power, and ultra-low-frequency power. Farrell et al. arbitrarily chose a value of 20 ms for TINN to dichotomize their group into 113 patients (27%) with low values and 348 patients (73%) with high values. During an average follow-up of 20 months, 47 cardiac deaths occurred. The risk of experiencing a cardiac death during 2 years of follow-up was seven times as high in the group with a TINN less than 20 ms as in the group with a value greater than or equal to 20 ms. TINN did not predict recurrent myocardial infarction. Also, it is notable that the results of Kleiger et al. and Farrell et al. are so similar, considering that the former sample was collected before and the latter after thrombolysis was commonly used.

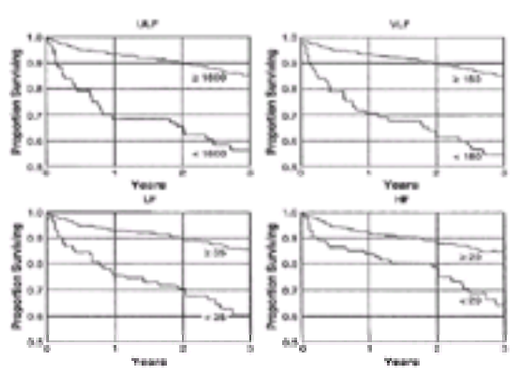
In an interesting more recent study, 185 consecutive patients who had experienced a first myocardial infarction underwent a simple deep breathing test (118). Approximately 5 days after the infarct, patients were asked to take six deep respirations during 1 minute. HRV was measured as the difference between the longest and shortest RR intervals; value difference of less than 10 beats/min was noted in 65 patients (35%). During 1 year of follow-up, decreased HRV was predictive of all-cause mortality (14% vs. 1%, p = .004) and a composite end point of death, recurrent myocardial infarction, angina, or heart failure (46% vs. 28%, p = .003).

Prediction of Long-Term Mortality after Acute Myocardial Infarction Using Frequency Domain Measures of RR Variability

Twenty-Four-Hour Power Spectral Analysis

Bigger et al. studied 715 patients with acute myocardial infarction to establish the associations between six frequency domain (power spectral) measures of RR period variability and mortality during 4 years of follow-up (101). Power was calculated for four frequency bands of the 24-hour periodogram: (a) ultra-low-frequency power; (b) very low-frequency power; (c) LF power; and (d) HF power. Also, they calculated total power and the LF/HF ratio. Calculated by this method, LF and HF power are averaged over 24 hours. Total power and all of the frequency bands were substantially reduced after acute myocardial infarction when compared with values found in healthy age- and sex-matched controls (108). The LF/HF ratio was lower early after myocardial infarction than in healthy persons, and the pattern of change suggested that the reduction in LF and HF power resulted more from reduced vagal modulation than from increased sympathetic modulation.

The six frequency domain measures of RR variability were associated with three mortality end points: death from all causes, cardiac death, and arrhythmic death (101). Each frequency domain measure of RR variability had a significant and relatively strong univariate association with all-cause mortality (eFig. 77.3.1), cardiac death, and arrhythmic death. Total power and ultra low-frequency power had the strongest associations with all three mortality end points.



***e*FIGURE 77.3.1** Kaplan-Meier survival curves. The charts show 715 patients in the high or low category for the four mutually exclusive frequency domain measures of 24-hour RR variability, ultra-low-frequency (ULF), very low-frequency (VLF), low-frequency (LF), and high-frequency (HF) power, using all-cause mortality as the end point. (From Bigger JT Jr, Fleiss JL, Steinman RC, et al. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992;85:164–171, with permission.)

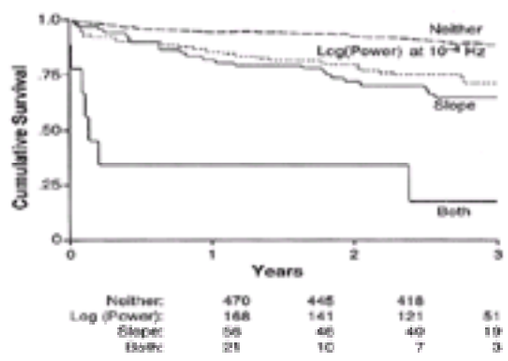
To determine how much predictive value frequency domain measures of RR variability add to previously established postinfarction risk predictors, the strength of the relationship between the RR variability measures and all-cause mortality, cardiac death, and arrhythmic death were evaluated before and after adjusting for five previously established postinfarction risk predictors: age, New York Heart Association functional class, rales in the coronary care unit, VEF, and ventricular arrhythmias quantified in a 24-hour Holter ECG recording (101). After adjustment for the five risk predictors, the association between mortality and total power, ultra low-frequency power, and very low-frequency power remained significant and strong, whereas LF power and HF power were only moderately strongly associated with mortality.

Power Spectral Measures of RR Variability Measured over a Five-Minute Interval

Bigger et al. studied 715 patients 2 weeks after myocardial infarction and showed that short-term power spectral measures of RR variability (calculated from 5 minutes of normal RR-interval data) predict all-cause mortality or arrhythmic death (119). From continuous 24-hour ECG recordings, two 5-minute segments were selected for analysis, one from the 8 a.m. to 4 p.m. interval, and one from the 12 midnight to 5 a.m. interval. The former corresponds to the time interval during which short-term measures of RR variability would most likely be obtained. The latter simulates the conditions that exist when patients have an ECG recorded while lying quietly in a laboratory. Four frequency domain measures were calculated from the daytime and nighttime 5-minute intervals: (a) very low-frequency power; (b) LF power; (c) HF power; and (d) LF/HF ratio. Mean power spectral values from 5-minute periods during the day and night were similar to 24-hour values, and the correlations between short segment values and 24-hour values were strong (most correlations were greater than or equal to 0.75). Power spectral measures of RR variability, obtained from 5-minute ECG recordings, were excellent predictors of all-cause, cardiac, and arrhythmic mortality. Patients with low values were two to four times as likely to die over an average follow-up of 31 months than were patients with high values.

Power Law Regression Parameters

In healthy persons, the slope of log(power) on log(frequency) (a) is approximately –1, and the log(power) at 10^{-4} Hz is approximately 6.90 (103). After myocardial infarction, a averages –1.15 and the log(power) at 10^{-4} Hz is 6.56. The combination of a and log(power) at 10^{-4} Hz measured soon after myocardial infarction is an outstanding predictor of death over the next 2 to 4 years (eFig. 77.3.2). Patients classified as high risk by a and log(power) at 10^{-4} Hz had a tenfold increased risk of dying during 2.5 years of follow-up compared with patients classified as low risk; the actuarial 3-year mortality was 79% for the high-risk group compared with 11% for the low-risk group. The power law regression parameters predict death of any cause or arrhythmic death better than any single power spectral band or any combination of power spectral variables (103).



***e*FIGURE 77.3.2** Predicting mortality after myocardial infarction using power law regression parameters. Kaplan-Meier survival curves for 715 myocardial infarction patients cross-classified by slope of the power law regression line (dichotomized at –1.372) and log(power) dichotomized at 10^{-4} Hz (dichotomized at 6.345). The 3-year survival rates were, for patients in neither high-risk category, labeled "Neither," 89%; for patients in the high-risk category for log(power) at 10^{-4} Hz only, labeled "Log(power) at 10^{-4} Hz," 70%; for patients in the high-risk category for slope only, labeled "Slope," 64%; for patients in the high-risk category for both variables, labeled "Both," 17%. The survival curve labeled "Log(power) at 10^{-4} Hz" is thinner than the other three curves to distinguish it from the survival curve labeled "Slope." For each of the four groups, the numbers of patients being followed at enrollment and at 1, 2, and 3 years is shown below the graph. (From Bigger JT Jr, Steinman RC, Rolnitzky LM, et al. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent myocardial infarction, and patients with heart transplants. *Circulation* 1996;93:2142–2151, with permission.)

Short-Term Fractal Scaling Exponent (a_1) and Mortality after Myocardial Infarction

Huikuri et al. studied several nonlinear dynamic measures of RR variability in a 446-patient subgroup from the Danish Investigations of Arrhythmia and Mortality on Dofetilide in Survivors of Acute Myocardial Infarction (DIAMOND-MI) trial with acute myocardial infarction and LVEF less than 0.36 (120). Time, frequency, and fractal measures of RR-interval variability were related to deaths during 2 years of follow-up. The reduced short-term fractal scaling exponent, a_1, was the strongest predictor of total mortality (n = 114), arrhythmic death (n = 75), and nonarrhythmic cardiac death (n = 28) (relative risk, 3.0; 95% confidence interval, 2.5 to 4.2). The short-term scaling exponent, a_1, remained a significant predictor of death after statistical adjustment for age, New York Heart Association functional class, ejection fraction, and use of cardiac medications.

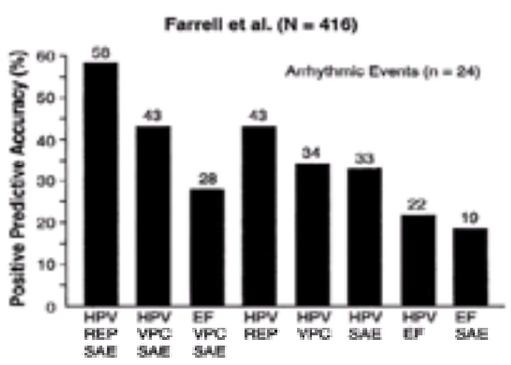
Improved Prediction of Death Using RR Variability Combined with Other Risk Predictors

All-Cause Mortality

Correlations between time or frequency domain measures of RR variability and previously identified postinfarction risk predictors, e.g., LVEF (r = 0.24) and ventricular arrhythmias (r = approximately 0.12) are remarkably weak (17). The lack of correlation between RR variability and previously established postinfarction risk predictors suggests that measures of RR variability will improve the identification of patients at high risk after myocardial infarction. Bigger et al. studied the ability of power spectral measures of RR variability to improve the accuracy of predicting all-cause mortality in 715 patients with recent myocardial infarctions (101). Adding power spectral measures of RR variability, measured approximately 10 days after myocardial infarction, to LVEF and ventricular arrhythmias quantified over a 24-hour interval, identified small subgroups with a 2.5-year mortality risk of approximately 50% (101). Total power or ultra low-frequency power increased positive predictive accuracy the most.

Arrhythmic Events

Farrell et al. studied the ability of the TINN to predict arrhythmic events (sustained ventricular arrhythmias or arrhythmic death) in 416 patients with acute myocardial infarction (117). eFigure 77.3.3 shows how combinations of risk predictors improve positive predictive accuracy for arrhythmic events during long-term follow-up after myocardial infarction. Adding the signal-averaged ECG to the TINN doubled positive predictive accuracy and adding repetitive ventricular premature complexes to the combination almost doubled positive predictive accuracy again. The best multivariate predictor for arrhythmic events was the combination of three variables: (a) TINN less than 20 ms, (b) a positive signal-averaged ECG, and (c) repetitive ventricular premature complexes quantified by 24-hour ECG recordings. The combination of these three variables had a positive predictive accuracy of 58% (113).



***e*FIGURE 77.3.3** Improving positive predictive accuracy using combinations of risk predictors after myocardial infarction. Although each risk predictor has modest (less than 20%) positive predictive accuracy for arrhythmic events when used alone, the positive predictive accuracy is 40% to 60% for some of the combinations. EF, left ventricular ejection fraction; HPV, heart period variability index; REP, repetitive ventricular premature complexes; SAE, signal-averaged electrocardiogram; VPC, ventricular premature complexes. (Adapted from data in Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events based on heart rate variability,

ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1991;18:687–697. This figure was first published in Bigger JT Jr, Rottman JN. Spectral analysis of RR variability. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia. Mechanisms, diagnosis, and management.* Baltimore: Williams & Wilkins, 1995:280–298, with permission.)

RR Variability Identifies Patients with Left Ventricular Dysfunction Who Benefit from Amiodarone Treatment

A prospective substudy of the European Myocardial Infarction Amiodarone Trial (EMIAT) tested the hypothesis that patients with recent myocardial infarctions, LVEF less than 0.41, and reduced RR variability would benefit from amiodarone treatment (121). The rationale for this substudy was that RR variability predicts more specifically arrhythmic than nonarrhythmic death; therefore, such a group would benefit from amiodarone.

In EMIAT, 1,216 patients (82%) had RR variability index calculated from 24-hour Holter recordings. The substudy consisted of the 363 (30%) patients who had an HRV index less than 21 units. In placebo-treated patients, those with reduced RR variability had a substantially higher mortality than patients with preserved RR variability (22.8% vs. 9.5%, $p < .05$). In the substudy, there was a 23% reduction in all-cause mortality in those treated with amiodarone (22.8% vs. 17.5%, $p = .24$) and a 66% reduction in cardiac mortality (12.8% vs. 4.4%, $p < .01$). The efficacy of amiodarone in patients with reduced RR variability was further evaluated in a number of patient categories. The benefit of amiodarone was large in patients with reduced RR variability and a resting heart rate greater than or equal to 75 beats/min; this subgroup had 29.0% mortality when treated with placebo compared with 19.3% when treated with amiodarone, a 33.7% reduction in mortality ($p = .075$). The EMIAT substudy is the first to demonstrate that RR variability can select a group of patients with autonomic dysfunction that will benefit from prophylactic amiodarone therapy.

Effect of Myocardial Infarction on RR Variability

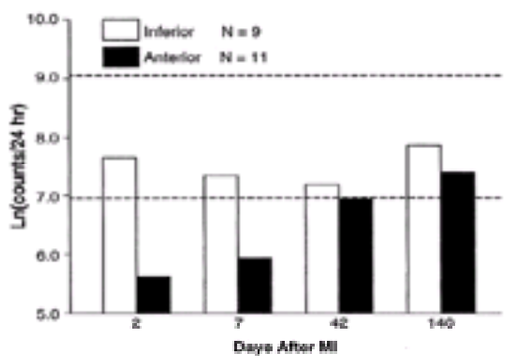
Bigger et al. showed that measures of RR variability are reduced to approximately 25% of normal 2 to 3 weeks after myocardial infarction (122). They explained the decrease in efferent cardiac vagal activity in anterior infarction by postulating an increase in afferent sympathetic nerve traffic, an effect that has been shown to decrease efferent vagal nerve traffic in experimental myocardial ischemia (123). It is not known to what extent RR variability is reduced before myocardial infarction in patients with coronary heart disease. It is known that experimental myocardial infarction created in the dog by coronary artery ligation is followed by an abrupt decrease in RR variability (72).

Recovery of RR Variability after Myocardial Infarction

Several small studies have investigated the recovery of RR variability after myocardial infarction. Both early and late phases of recovery have been studied.

Early Phase of Recovery

Flapan et al. studied 20 highly selected patients to define the time course of recovery of vagal modulation of RR intervals after a first myocardial infarction (124). This study excluded patients with previous infarction, age older than 70 years, history of diabetes, renal failure, alcohol abuse, hypertension, prior treatment with or contraindication to treatment with beta-adrenergic blocking drugs or with antihypertensive drugs. Patients with arrhythmias or heart failure on admission to the coronary care unit also were excluded. All patients were treated with streptokinase and aspirin on admission and were given atenolol and aspirin over the 3-month follow-up period. Continuous 24-hour ECG recordings were made at less than 1.5, 7.0, 42.0, and 140.0 days after myocardial infarction. Cardiac parasympathetic activity was estimated using counts of the number of times that successive RR intervals differed by greater than 50 ms in a 24-hour period (NN50). The pattern of recovery of NN50 differed depending on the site of infarction (eFig. 77.3.4). For 11 patients with anterior myocardial infarction, NN50 was 20% of normal at 1.5 days and recovered progressively to 67% of normal by 140.0 days. For nine patients with inferior myocardial infarction, NN50 was within normal limits for age at 1.5 days after infarction and did not change significantly over the 140-day follow-up. By 42 days, NN50 did not differ significantly between patients with anterior and inferior infarcts. These workers postulated that stimulation of vagal afferent nerves by ischemia and prostaglandins preserved the efferent vagal nervous activity in inferior myocardial infarction.

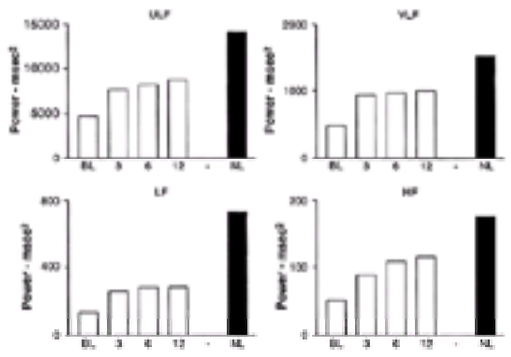


***e*FIGURE 77.3.4** Recovery of vagal modulation early after myocardial infarction (MI). The natural logarithm (Ln) of the number of times that successive normal RR intervals differ by more than 50 ms during a 24-hour period is plotted on the *x*-axis; time after MI is plotted on the *y*-axis. In this selected sample of 20 patients, vagal activity decreased markedly in patients with anterior MI, but not in those with inferior MI. By 42 days after MI, the counts had nearly recovered to a stable value. (Adapted from data in Flapan AD, Wright RA, Nolan J, et al. Differing patterns of cardiac parasympathetic activity and their evolution in selected patients with a first myocardial infarction. *J Am Coll Cardiol* 1993;21:926–931. This figure was first published in Bigger JT Jr, Rottman JN. Spectral analysis of RR variability. In: Podrid PJ, Kowey PR, eds. *Cardiac arrhythmia. Mechanisms, diagnosis, and management.* Baltimore: Williams & Wilkins, 1995:280–298, with permission.)

Late Phase of Recovery

Bigger et al. (122) studied recovery of RR variability in the placebo group of the Cardiac Arrhythmia Pilot Study (CAPS). The 68 placebo-treated patients who had 24-hour ECG recordings at baseline and at 3, 6, and 12 months after myocardial infarction were studied. The 24-hour power spectral density was computed using FFTs and divided into four components of the RR power spectrum: ultra low-frequency power, very low-frequency power, LF power, and HF power. Total power (power less than 0.40 Hz) also was calculated. The mean baseline values (25 days after myocardial infarction) for the five frequency domain measures of RR variability in the CAPS patients were similar to those found in 715 patients who participated in the Multicenter Post Infarction Program, indicating that the CAPS sample is generally representative of postinfarction patients with respect to these measures.

*e*Figure 77.3.5 shows the time course of recovery of RR variability over the year after myocardial infarction. There was a substantial increase in all measures of RR variability between 3 weeks and 3 months ($p < .001$). On average, recovery of RR variability is completed by 3 months after myocardial infarction (eFig. 77.3.5). Between 3 months and 12 months, the values were quite stable for the group as a whole, as well as for individual patients (intraclass correlation coefficients greater than or equal to 0.66). *e*Table 77.1.3 shows that, even at 12 months after infarction, the average full recovery values for the five measures of RR variability were only one-half to two-thirds the values found in the sample of 274 healthy age- and sex-matched controls (108). However, recovery of RR variability during the year after myocardial infarction is quite variable. Some patients recover to normal values of RR variability, whereas others have very little recovery or have a decrease.



***e*FIGURE 77.3.5** Recovery of RR variability during the year after myocardial infarction. Data are plotted for 68 patients in the placebo group of the Cardiac Arrhythmia Pilot Study who had a complete set of 24-hour electrocardiographic recordings. Because the distributions of RR variability measures are markedly skewed, the geometric means are plotted for baseline (BL), 3, 6, and 12 months after myocardial infarction (*white bars*). For comparison, the geometric means are plotted for a group of 95 healthy persons of similar age and sex (*black bars*). Recovery was complete by 3 months after infarction, but recovery values after infarction are lower than those found in healthy persons of similar age and sex. HF, high-frequency power; LF, low-frequency power; NL, normal; ULF, ultra-low-frequency power; VLF, very low-frequency power. (Adapted from data in Bigger JT Jr, Fleiss JL, Rolnitzky LM, et al. Time course of recovery of heart period variability after myocardial infarction. *J Am Coll Cardiol* 1991;18:1643–1649. This figure was first published in Bigger JT Jr. RR variability to evaluate autonomic physiology and pharmacology and to predict cardiovascular outcomes in humans. In: Zipes DP, ed. *Cardiac arrhythmias: from cell to bedside*. Philadelphia: WB Saunders, 1995:1151–1170, with permission.)

***e*TABLE 77.1.3** COMPARISON OF TIME AND FREQUENCY DOMAIN MEASURES OF RR VARIABILITY FOR HEALTHY MIDDLE-AGED SUBJECTS AND PATIENTS WITH CHRONIC CORONARY HEART DISEASE (CAPS), AND HEALTHY MIDDLE-AGED SUBJECTS AND PATIENTS WITH RECENT ACUTE MYOCARDIAL INFARCTION (MPIP)[a]

Measure	Healthy subjects (n = 274)	CAPS (n = 278)	MPIP (n = 684)
Duration of electrocardiographic recording (h)	23.8 ± 0.43	22.5 ± 1.62	22.9 ± 1.51
Normal RR intervals (ms)	817 ± 103	834 ± 135[b]	854 ± 138[b]
% Normal RR intervals	99.4 ± 2.00	95.0 ± 8.55	99.0 ± 2.48
Night–day difference (ms)	198 ± 89	120 ± 103[b]	84 ± 64[b]
SDNN (ms)	141 ± 39	112 ± 40[b]	81 ± 30[b]
SDANN (ms)	127 ± 35	99 ± 38[b]	70 ± 27[b]
ASDNN (ms)	54 ± 15	46 ± 18[b]	35 ± 16[b]
r-MSSD (ms)[c]	27 ± 12	28 ± 15	23 ± 12
Ln (r-MSSD)	3.24 ± 0.37	3.21 ± 0.46	3.05 ± 0.44[b]
pNN50[c]	9 ± 7	10 ± 11	7 ± 9
Ln (pNN50)	1.83 ± 0.98	1.65 ± 1.35	1.09 ± 1.58
Total (<0.40 Hz) power (ms^2)[c]	21,222 ± 11,663	14,303 ± 10,353	7,323 ± 5,720
Ln (Total power)	9.83 ± 0.51	9.31 ± 0.77[b]	8.62 ± 0.78[b]
Ultra-low-frequency (<0.0033 Hz) power (ms^2)[c]	18,420 ± 10,639	12,130 ± 9,241	6,067 ± 4,861
Ln (ultra-low-frequency power)	9.68 ± 0.54	9.13 ± 0.79[b]	8.43 ± 0.79[b]
Very low-frequency (0.0033–0.04 Hz) power (ms^2)[c]	1,782 ± 965	1,460 ± 1,090	850 ± 800
Ln (very low-frequency power)	7.35 ± 0.53	6.97 ± 0.87[b]	6.32 ± 1.02[b]
Low-frequency (0.04–0.15 Hz) power (ms^2)[c]	791 ± 563	511 ± 538	277 ± 335
Ln (low-frequency power)	6.45 ± 0.68	5.75 ± 1.07[b]	5.01 ± 1.19[b]
High-frequency (0.15–0.40 Hz) power (m/sec^2)[c]	229 ± 282	201 ± 324	129 ± 203
Ln (high-frequency power)	5.05 ± 0.83	4.69 ± 1.08[b]	4.28 ± 1.06[b]
Low-frequency power/high-frequency power[c]	4.61 ± 2.33	3.60 ± 2.43	2.75 ± 2.13
Ln (low-frequency power/high-frequency power)	1.41 ± 0.51	1.07 ± 0.67[b]	0.73 ± 0.79[b]

ASDNN, average standard deviation of normal to normal intervals in 5-minute intervals calculated over 24 hours; CAPS, Cardiac Arrhythmias Pilot Study, "washout" recordings made 404 ± 21 days after myocardial infarction; Ln, natural logarithm; MPIP, Multicenter Post Infarction Program, recordings made 11 ± 6 days after myocardial infarction; pNN50, proportion of differences between successive normal to normal intervals that are greater than 50 ms; r-MSSD, square root of the mean squared successive differences of normal to normal intervals; SDANN, standard deviation of the average normal to normal intervals for the 288 5-minute intervals in a 24-hour continuous electrocardiographic recording; SDNN, standard deviation of normal to normal intervals over a 24-hour period.
[a]Values in the table are means equal standard deviations.
[b]p <.01 after adjustment for multiple comparisons.
[c]Statistical tests were done after logarithmic transformation because of skewed distributions.
Adapted from Bigger JT Jr, Fleiss JL, Steinman RC, et al. RR variability in healthy, middle-age persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation* 1995;91:1936–1943, with permission.

Predictive Value of Power Spectral Measures of RR Variability Late after Myocardial Infarction

The substantial recovery of RR variability in the 3 months after myocardial infarction raises the question whether recovery values for RR variability predict death. To answer this question, Bigger et al. (125) studied the 331 patients in the CAPS who survived for 1 year, had a 24-hour ECG recording made after the CAPS drug was washed out, and were discharged on no antiarrhythmic drug therapy. Thirty deaths occurred in the CAPS group between 1.0 and 2.2 years after myocardial infarction. Power spectra were calculated from 24-hour continuous ECG recordings, and six power spectral measures of RR variability were evaluated: (a) ultra low-frequency power; (b) very low-frequency power; (c) LF power; (d) HF power; (e) total power; and (f) the LF/HF ratio. Because of the large increase in RR variability that takes place during the first 3 months after myocardial infarction, the optimum cutpoints for measures of RR variability in the 1-year recordings were substantially higher than those previously determined for 24-hour ECG recordings made approximately 2 weeks after infarction (*e*Table 77.1.4). Each power spectral measure of RR variability calculated from the recordings made 1 year after infarction had a strong and significant univariate association with 2.5-year all-cause mortality; the relative risks for these variables ranged from 2.5 to 5.6.

***e*TABLE 77.1.4** OPTIMAL CUTPOINTS FOR PREDICTION OF ALL-CAUSE MORTALITY AFTER MYOCARDIAL INFARCTION BY FREQUENCY DOMAIN MEASURES OF HEART PERIOD VARIABILITY

	Optimal cutpoints	
Variable	At discharge 2 weeks after myocardial infarction	After recovery from myocardial infarction
Ultra-low-frequency power (ms^2)	1,600.00	5,000.0
Very low-frequency power (ms^2)	180.00	600.0
Low-frequency power (ms^2)	35.00	120.0
High-frequency power (ms^2)	20.00	35.0
Total power (ms^2)	2000.00	6000.0
Low frequency/high frequency ratio	0.95	1.6

From Bigger JT Jr. Spectral analysis of RR variability to evaluate autonomic physiology and pharmacology and to predict cardiovascular outcomes in humans. In: Zipes DP, Jalife J, eds. *Cardiac electrophysiology from cell to bedside*, 2nd ed. Philadelphia: WB Saunders, 1995:1151–1170, with permission.

The prediction of death from the measures of RR variability made 1 year after myocardial infarction was not improved when measures of RR variability made within a month of myocardial infarction were added to the survival model (125). After adjustment for age, New York Heart Association functional class, rales in the critical care unit, LVEF, and ventricular arrhythmias, measures of RR variability still had a strong and significant independent association with all-cause mortality. It is clear from this study that RR variability, measured after full recovery from myocardial infarction, predicts death independent of other important postinfarction risk predictors. The final recovery values for RR variability are the best predictors of subsequent events (i.e., knowledge of the recovery pattern does not improve prediction significantly).

In healthy persons, RR variability is influenced significantly by age, sex, physical fitness, and drugs (126), as well as heritability (127). This naturally raises the question whether these factors confound the use of RR variability to predict death and arrhythmic events in patients with coronary heart disease. Fortunately, these factors do not confound the predictive value of RR variability in coronary heart disease because the effect of coronary disease on RR variability is much larger than the effect of

factors such as age, sex, physical fitness, and drugs.

RR Variability to Assess Prognosis in Patients with Heart Failure

Patients with heart failure often have autonomic dysfunction. The United Kingdom Heart Failure Evaluation and Assessment of Risk Trial prospectively evaluated the predictive value of RR variability in 433 patients with heart failure followed for 482 ± 161 days (128). SDNN was only weakly related to LVEF (r = 0.12). SDNN was a strong predictor of mortality: 6% of the patients had an SDNN less than 50 ms with an annual mortality of 51%, 32% had an SDNN of 50 to 100 ms with an annual mortality of 13%, and 62% had an SDNN greater than 100 ms with an annual mortality of 6%.

Significance of Low RR Variability in the Elderly

In 1948, a sample of 5,209 residents of Framingham, MA, was selected to undergo biennial examinations in a prospective study (129). In the eighteenth examination cycle (1983 to 1985), 1,028 2-hour Holter recordings were made during routine clinic examinations of 1,825 surviving participants (130).

A total of 292 were excluded, leaving 736 persons in the study. The clinical characteristics of the participants in the Holter substudy were similar to those of the nonparticipants. The average age for the study sample was 72 ± 6 years, 40% were male subjects, 9% had a history of myocardial infarction, and 2% had a history of congestive heart failure. The average heart rate for the group was 74 ± 12 beats/min, and the average blood pressure was 142/76 mm Hg. During an average follow-up of 3.9 years, 74 of the 736 participants died. Where the cause of death was known, the most common causes were coronary heart disease and cancer.

For frequency domain analysis, 100-second blocks of data were sampled at 128 samples per second, and power spectral density was calculated using an FFT method. As previously found after myocardial infarction (119), LF power was the best of eight time and frequency domain measures of RR variability for predicting death of all causes (130).

A 1 SD decrement in natural log-transformed LF power was associated with a relative risk (hazard ratio) of 1.87 (95% confidence interval, 1.55 to 2.26). After statistical adjustment for age, sex, and clinical risk factors (history of myocardial infarction, heart failure, diuretic use, and frequent or complex ventricular premature complexes), the relative risk was 1.70. These results indicate that reduced RR variability predicts mortality in a population-based sample of elderly subjects.

Significance of Low RR Variability in Patients Referred for 24-Hour Holter Recordings

Algra et al. conducted a retrospective case control study to determine whether a disturbance of autonomic nervous system activity may play a role in sudden cardiac death (131). All 6,693 consecutive patients who had 24-hour Holter ECG recordings in four Rotterdam hospitals between August 1, 1980, and December 31, 1984, were included.

The indications for the 24-hour ECG recordings were evaluation of palpitations, dizziness, syncope, or angina pectoris, 65%; evaluation of risk after myocardial infarction, 10%; evaluation of antiarrhythmic therapy, 8%; and search for a cardiac cause of transient cerebral events, 7%. Seventy-five percent of the recordings were done in outpatients. Patients were excluded for unanalyzable Holter recordings and for frequent supraventricular arrhythmias, leaving approximately 5,500 patients. During a 2-year follow-up period, 193 sudden cardiac deaths (less than 1 hour) occurred.

Three time domain measures of RR variability were used in the Rotterdam study: (a) pNN50; (b) short-term variation (mean over 24 hours of per minute standard deviations of RR intervals); and (c) long-term variation (standard deviation over 24 hours of per minute means of RR intervals). Although the latter two measures are unorthodox, the measure of short-term variation is similar to ASDNN or LF power, and the measure of long-term variation is similar to SDANN or ultra low-frequency power. Patients with low values for these three measures of RR variability had a higher relative risk of experiencing sudden cardiac death in 2 years of follow-up. The relative risks were pNN50, 1.8; short-term variation, 3.0; and long-term variation, 2.7. This study showed that RR variability had predictive value in a consecutive, heterogeneous group of patients referred to a Holter laboratory.

How to Interpret and Use RR-Variability Reports from Commercial Holter Systems

Most commercial Holter systems provide some measures of RR variability. The calculation of statistical measures of RR variability is straightforward if ectopic complexes are correctly measured. For example, measurements of SDNN made by commercial systems are comparable with those made with research systems. Power spectral measures of RR variability in most commercial systems have not been validated against research systems that establish their predictive value for cardiac death or sustained arrhythmias. Beta-blocker therapy increases RR variability somewhat in patients with recent myocardial infarctions and is known to improve survival. A careful evaluation for the sources of risk is recommended for patients with low values for RR variability after myocardial infarction, and beta-blocker therapy should be instituted if there is no contraindication.

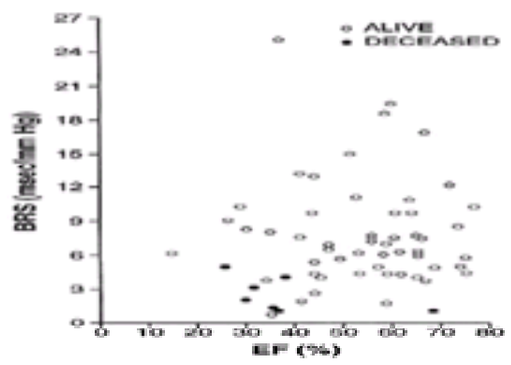
Summary of RR Variability in Coronary Heart Disease

RR variability has proven to be a remarkably effective predictor of death and arrhythmic events after acute myocardial infarction and in chronic coronary heart disease. RR variability is a better predictor than LVEF or ventricular arrhythmias. Both time and frequency domain measures of RR variability measured during 5-minute or 24-hour ECG recordings predict deaths after myocardial infarction. RR variability predicts death of all causes, cardiac death, arrhythmic death, and also nonfatal sustained arrhythmias. However, RR variability, measured soon after acute myocardial infarction, does not predict recurrent infarction. Combined with other risk predictors, RR variability has a positive predictive accuracy up to 50%. RR variability is readily available in commercial Holter equipment and is inexpensive. The EMIAT substudy indicates that patients with left ventricular dysfunction and low RR variability benefit from prophylactic amiodarone therapy.

Clinical Use of Baroreflex Sensitivity for Assessment of Risk in Coronary Heart Disease

Baroreflex Sensitivity Has a Weak Relationship with Infarct Size or Left Ventricular Ejection Fraction

To explore the correlations with other risk predictors and the predictive value of BRS in patients with recent myocardial infarction, La Rovere et al. studied 78 patients who had experienced their first infarction and were younger than age 65 years. BRS was measured with the phenylephrine method within 30 days of infarction, and patients were then followed for 24 months (132). BRS averaged 8.2 ± 4.8 ms per mm Hg in 71 patients who survived and 2.4 ± 1.5 ms per mm Hg (p = .004) in seven patients who died during follow-up. Mortality was 2.9% in the 68 patients with BRS greater than or equal to 3 ms per mm Hg compared with 40% in the ten patients with BRS less than 3 ms per mm Hg. BRS predicted total cardiac mortality as well as sudden cardiac death. The relationship between a depressed BRS and LVEF was explored in detail (eFig. 77.3.6). No association was found between the peak level of serum creatine kinase (r = 0.11) or between BRS and LVEF (r = 0.07) (132). It is clear that BRS is not just a reflection of ventricular function because there was a poor correlation between LVEF and BRS, and BRS increased the predictive accuracy for cardiovascular death after myocardial infarction. The correlation between BRS and RR variability was only modest, suggesting that BRS and RR variability might have independent predictive value for predicting death or nonfatal arrhythmic events after myocardial infarction (123).



***e*FIGURE 77.3.6** Relationships among baroreflex sensitivity (BRS), left ventricular ejection fraction (EF), and cardiovascular mortality in a group of 78 patients with a recent first myocardial infarction. All but one of the seven patients who died had a left ventricular EF below 0.50. The risk of death was 50% when left ventricular dysfunction and a BRS less than 3 ms per mm Hg were both present compared with 10% for patients with left ventricular EF less than 0.50 but BRS greater than or equal to 3 ms per mm Hg. (From La Rovere MT, Specchia G, Mortara A, et al. Baroreflex sensitivity, clinical correlates and cardiovascular mortality among patients

with a first myocardial infarction: a prospective study. *Circulation* 1988;78:816–824, with permission.)

Baroreflex Sensitivity Predicts Arrhythmic Events

Farrell et al. subsequently studied the predictive value of BRS in 122 patients with recent myocardial infarction (133). BRS, HRV, 24-hour continuous ECG recordings, exercise tests, and LVEF were measured between days 7 and 10 after myocardial infarction. During a 1-year follow-up period there were ten arrhythmic events (five sudden deaths and five admissions for sustained ventricular arrhythmias). BRS was appreciably reduced in the ten patients who experienced arrhythmic events (1.73 ± 1.49 compared with 7.83 ± 4.5 ms per mm Hg in the 112 patients who did not; p <.0001). A significant correlation was noted between BRS and age (r = –0.68, p <.001), but not with LVEF or the other tests done to identify risk. A BRS less than 3.0 ms per mm Hg carried the highest relative risk for arrhythmic events (23.1; 95% confidence interval, 7.7 to 69.2) and was similar to other prognostic variables, including LVEF (relative risk of 10.4; 95% confidence interval, 3.3 to 32.6), frequent ventricular complexes (relative risk of 20.6; 95% confidence interval, 11.0 to 37.1), or SDNN (relative risk 10.1; 95% confidence interval, 5.6 to 18.1). BRS had predictive value independent of other tests used for postinfarction risk stratification.

Baroreflex Sensitivity and Patency of the Infarct-Related Artery

Mortara et al. conducted a study to evaluate the association between patency of the infarct-related artery and BRS in 359 patients with a recent myocardial infarction who also had a coronary angiogram (134). Patients with occluded infarct-related arteries had lower values for BRS (p <.005) and LVEF (p <.001) compared with patients with patent infarct-related arteries. In different categories of LVEF, BRS was significantly lower among patients with occluded infarct-related arteries than in patients with patent infarct-related arteries. When clinical and angiographic variables were entered into a stepwise multiple regression model with BRS as the dependent variable, only age and patency of the infarct-related artery emerged as significant independent predictors of BRS (134). The correlation with age (r = –0.52) was similar in magnitude to that found by Farrell et al.

Two small studies have found that BRS was markedly reduced, whereas measures of RR variability showed only borderline reductions in patients who had arrhythmic events a year or more after myocardial infarction (135,136). These preliminary findings need to be confirmed with full-scale clinical studies. Bonaduce et al. studied a group of patients with single-vessel coronary disease who were having percutaneous transluminal coronary angioplasty (137). They measured RR variability before and 2 to 3 weeks after angioplasty. Before angioplasty, LF power and HF power were reduced only in those patients who had a regional wall motion abnormality in the distribution of the stenotic artery. Patients whose wall motion returned to normal after angioplasty showed a significant improvement in RR variability. This finding was explained by a reduction in sympathetic afferent nerve traffic when normal wall motion was restored.

Autonomic Tone and Reflexes after Myocardial Infarction Study

Based on the strong experimental evidence that BRS predicted ischemic VF, and encouraging evidence from small clinical studies, ATRAMI, a large epidemiologic study, was launched in 1991 (114). ATRAMI was designed to definitively assess the predictive value of BRS after myocardial infarction and to determine how the predictive value of BRS ranked with RR variability, LVEF, and ventricular premature complexes. A total of 1,284 patients were enrolled 6 to 28 days after myocardial infarction, had BRS measured, and were followed for greater than or equal to 12 months. The primary end point was cardiac death or nonfatal cardiac arrest.

The a priori hypotheses were that a BRS less than 3.0 ms per mm Hg would predict higher cardiac mortality and that it would add predictive power to that of SDNN less than 70 ms. The strength of association of BRS and SDNN with cardiac death and cardiac arrest with and without adjusting for LVEF and ventricular premature complexes was estimated using a Cox regression model.

The average age in ATRAMI was 57 ± 10 years and their risk was relatively low, as indicated by the mean LVEF of 0.49 ± 0.12. The average BRS for the group was 7.2 ± 4.6 ms per mm Hg and the average SDNN was 108 ± 35 ms; 17% of the patients had greater than or equal to 10 ventricular premature complexes per hour. Patients with depressed BRS or SDNN were older, were more frequently women, and had more ventricular premature complexes and lower LVEFs.

During a mean follow-up of 21 ± 8 months, cardiac death or cardiac arrest occurred in 49 patients (3.9%) (Fig. 77.4). Two-year mortality was 9% among patients with BRS less than 3 ms per mm Hg compared with 2% in patients with BRS less than or equal to 3.0 (vs. p <.0001), definitively establishing the predictive value of this autonomic marker. Similarly, patients with SDNN less than 70 ms had a 10% mortality compared with 2% in those with SDNN less than or equal to 70 ms (p <.0001), thus confirming the predictive value of SDNN. The relative risk of patients with BRS values less than 3.0 ms per mm Hg or SDNN values less than 70 ms remained strong even after adjusting for LVEF and ventricular premature complexes. BRS and SDNN both had relative risks of approximately 3.0 for cardiac death or cardiac arrest.

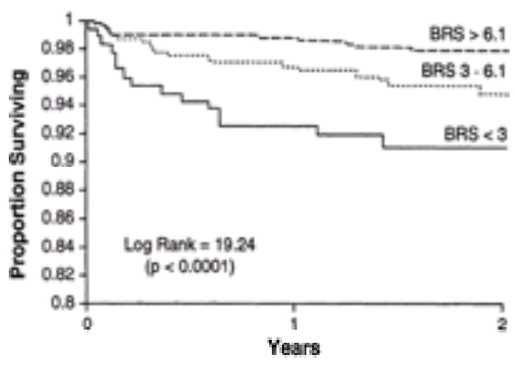


FIGURE 77.4 The ability of baroreflex sensitivity (BRS) to predict cardiac death (n = 44) or cardiac arrest (n = 5) after myocardial infarction in 1,182 patients who participated in the Autonomic Tone and Reflexes after Myocardial Infarction study and had BRS measured by the phenylephrine method. Patients were divided into three groups: 179 patients below the fifteenth percentile (BRS less than 3.0 ms per mm Hg), 414 patients from the fifteenth percentile to the median value (BRS 3.0 to 6.1 ms per mm Hg), and 589 patients above the median value (BRS greater than 6.1 ms per mm Hg). The p value refers to differences in the event rates among the three groups. [From La Rovere MT, Bigger JT Jr, Marcus FI, et al. Baroreflex sensitivity and heart rate variability in the prediction of total cardiac mortality after myocardial infarction. The results of ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction). *Lancet* 1998;351:478–484, with permission.]

Patients with depressed BRS and depressed SDNN had a 1-year mortality of 15% versus 1% (p <.0001), a relative risk of 10.9, indicating that BRS adds significantly to the predictive value of SDNN. Similarly, BRS or SDNN combined with LVEF improved predictive accuracy for cardiac mortality and cardiac arrest. When LVEF less than 0.35 was combined with an SDNN less than 70 ms, the relative risk was 7.4 (95% confidence interval, 3.1 to 17.8), and when it was combined with a BRS less than 3.0 ms per mm Hg, the relative risk was 11.9 (95% confidence interval, 5.1 to 27.4). This large prospective study provides definitive evidence that BRS is a strong and independent predictor of death after myocardial infarction. Moreover, BRS adds significantly to the predictive value of SDNN.

Clinical Use of Heart-Rate Responses to Exercise to Predict Death

Chronotropic Incompetence as a Prognostic Marker

Increase in heart-rate rise during exercise is a prognostic marker for coronary events and all-cause mortality (19,20,22,24,25,81,82). Lauer et al. examined 1,575 men from the Framingham Offspring Study who underwent exercise testing and classified their heart-rate response to exercise using three different criteria: (a) failure to reach 85% of the age-predicted maximum heart rate; (b) change in heart rate from rest to peak exercise; and (c) the percentage of the heart-rate reserve used during exercise (chronotropic response index) (22). After almost 8 years of follow-up, 55 deaths and 95 new cases of coronary artery disease accumulated. All three markers predicted total mortality and coronary artery disease. After adjustment for confounding factors, the chronotropic response index emerged as the strongest predictor of mortality.

Although chronotropic response is predictive of coronary artery disease (81), it is independent of ischemia (24,25) and coronary artery plaque burden (82). Lauer et al.

studied 2,953 patients undergoing stress thallium testing to assess the interaction between ischemic response and chronotropic response (25). Failure to achieve 85% of age-predicted maximum heart rate or a low chronotropic index was predictive of all-cause mortality outcomes even after adjusting for myocardial ischemia and other risk factors. The independence of chronotropic response from coronary artery disease was confirmed by Dresing et al. in an angiographic study (82). They looked at a cohort of patients who had undergone both exercise testing and angiography. Coronary artery plaque burden was assessed using the Duke Prognostic Weight Score. Chronotropic response remained predictive of death even after adjustment for severity of coronary artery disease. In fact, although angiographic severity of coronary disease was associated with risk of death in univariate analyses, once the chronotropic response to exercise was considered the angiographic findings had no independent predictive value.

Heart-Rate Recovery as a Prognostic Marker

Although used as a marker of physical fitness for many years, the use of HRR as a prognostic marker is a relatively recent development. In the first study to look at the predictive potential of HRR, Cole et al. (35) followed 2,428 adults who underwent symptom-limited exercise testing and single photon emission computed tomographic thallium imaging. Patients exercised to peak workload and then continued to walk at 2.4 km (1.5 miles) per hour at a grade of 2.5% for at least 2 minutes into recovery. HRR was defined as the decrease in heart rate from peak exercise to 1 minute of recovery.

$$\text{HRR} = \text{Heart rate}_{\text{Peak}} - \text{Heart rate}_{\text{1-Minute Recovery}}$$

An abnormal value for HRR was determined by finding the maximal value for the log-rank chi-square test statistic for all possible cutoff points between the tenth and ninetieth percentiles for the study cohort. This turned out to be less than 12 beats/min. The median value for HRR was 17 beats/min, with a range from the twenty-fifth to the seventy-fifth percentile of 12 to 23 beats/min. An abnormal value was found in 26% of the population.

During 6 years of follow-up, there were 213 deaths from all causes. A low value of HRR (less than 12 beats/min) was highly predictive of mortality, with a relative risk of 4.0 (mortality at 6 years, 19% vs. 5%, p <.001) (Fig. 77.5). Even after adjusting for age, fitness level, and thallium perfusion defects, HRR remained predictive of death. These data suggest that an abnormal HRR is independent of cardiac ischemia. When both an abnormal HRR and thallium perfusion defects were present, the mortality was markedly increased, with a relative risk of 7.8 (mortality at 6 years, 31% vs. 4%, p <.001). Abnormal HRR has also been demonstrated in a large population of healthy young adults undergoing routine submaximal exercise testing (138). More than 5,000 healthy adults enrolled in the Lipid Research Clinics Prevalence Study, with no known heart disease, were followed 12 years after near maximal exercise treadmill testing. Abnormal HRR was defined as less than a 42-beat fall in heart rate 2 minutes into recovery. Those with abnormal HRR were at increased risk for cardiac deaths (4% vs. 1%) and for all-cause mortality (10% vs. 4%).

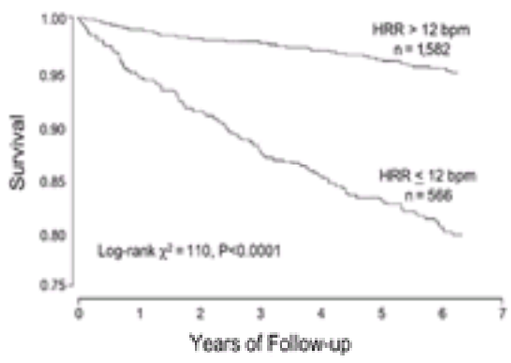


FIGURE 77.5 Kaplan-Meier plot relating heart-rate recovery (HRR) to all-cause mortality. (From Cole CR, Lauer MS. Exercise testing and risk assessment. In: Foody JM, ed. Preventive cardiology. Totowa, NJ: Humana Press, 2001, with permission. Based on data from Cole CR, Blackstone EH, Pashkow FJ, et al. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;341:1351–1357.)

There were important similarities and differences between this study and the prior study. First, the population studied was younger and at lower risk for heart disease at baseline. Second, the tests were not true maximal exercise tests but were stopped when the subjects achieved 85% to 90% of age-predicted maximum heart rate. Third, there was no cool-down period, and the subjects went directly from maximum exercise to a seated position. Last, heart rate during recovery was not measured until 2 minutes had elapsed and thus could not be directly compared with the prior study. Despite these differences, HRR was a strong, independent predictor of mortality in both populations.

To better understand the interactions that HRR has with other exercise-derived predictors of outcome, we studied HRR and the Duke treadmill exercise score in a population of 9,454 patients who underwent symptom-limited exercise ECG testing (139). The Duke treadmill exercise score incorporates exercise duration and ST-segment deviation and symptoms and has been validated as a predictor of mortality (140). Patients were divided into low-, intermediate-, or high-risk groups based on their treadmill exercise scores. For HRR a cutoff value of 12 beats/min or less after 1 minute of recovery was called an abnormal response. The primary end point was all-cause mortality.

In 5 years of follow-up, there were 312 deaths. Either an abnormal HRR or an intermediate- or high-risk treadmill exercise score predicted a fourfold increase in mortality (Fig. 77.6). If both the treadmill exercise score and HRR were normal the 5-year mortality was only 2%, but if both were abnormal mortality increased to 14%. There was no interaction between the two predictors. These findings demonstrate that HRR adds important information to the interpretation of the exercise test in addition to standard predictors.

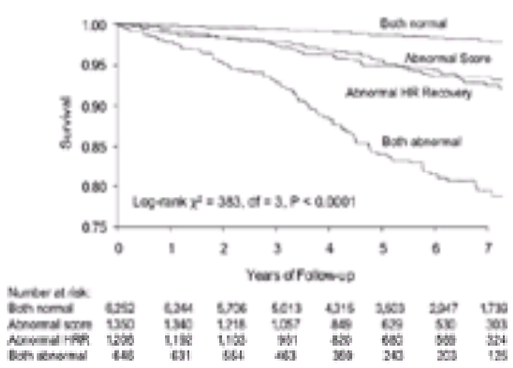


FIGURE 77.6 Kaplan-Meier survival curves according to heart rate (HR), heart-rate recovery (HRR), and treadmill exercise score. (From Nishime EO, Cole CR, Blackstone EH, et al. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA* 2000;284:1392–1398, with permission.)

CONTROVERSIES AND PERSONAL PERSPECTIVES

There is little controversy about the value of RR variability or BRS for predicting cardiac death or arrhythmic events in coronary heart disease. This new knowledge should be put to use more frequently and incorporated into practice guidelines. RR variability and BRS have positive predictive accuracy as good as any other risk predictor in coronary heart disease. After myocardial infarction, patients who have values of RR variability and BRS below the critical high-risk cut points have double the risk of cardiac death or an arrhythmic event, even if they have a good ejection fraction and lack ventricular arrhythmias. Furthermore, when combined with LVEF, ventricular arrhythmia frequency, or both, they substantially improve positive predictive accuracy and identify groups at very high risk.

The controversies with respect to diagnostic use of RR variability and BRS are when to measure these variables and what to do for patients who have critically low values for RR variability or BRS. Given what we know about the role of the autonomic nervous system in the pathophysiology of coronary heart disease, it is reasonable to measure RR variability, BRS, or both in patients with previous myocardial infarction. RR variability and BRS are best measured 6 to 21 days or greater

than or equal to 3 months after myocardial infarction. Between 3 and 12 weeks, RR variability is increasing as recovery from infarction proceeds and the values are more difficult to interpret. Many commercial Holter systems provide measurements of RR variability, making these measurements easily accessible and inexpensive. Although the RR variability measures provided by various commercial Holter systems vary, many of the measures are equivalent and can be used interchangeably (eTable 77.1.1). Thus, nearly every commercial Holter system provides one or more useful measure(s) of RR variability. Equipment to measure BRS is not widely available at the present time. However, equipment is likely to become more widely available over the coming years now that measurement of BRS has been shown to be useful and safe.

Patients categorized as high risk based on their RR variability, BRS values, or both should be evaluated carefully for reversible risk. Also, these patients should be treated with drugs proven to decrease postinfarction risk (e.g., aspirin, statins, and beta-adrenergic blocking drugs). Beta-adrenergic blocking drugs are known to be safe and effective for preventing cardiac deaths after myocardial infarction. By blocking peripheral beta-receptors, beta-adrenergic blocking drugs decrease the adverse cardiovascular effects of the sympathetic nervous system. By blocking beta-receptors in the central nervous system, beta-adrenergic blocking drugs also increase parasympathetic activity. These effects of beta-adrenergic blocking drugs increase RR variability and BRS.

Many physicians do not prescribe beta-blockers for low-risk patients with recent myocardial infarctions (i.e., patients with good left ventricular function, no ventricular arrhythmias, and a negative exercise test result). However, among such “low-risk” patients, there are some whose risk is identified only by critically low values of RR variability or BRS. These patients also should be treated with beta-adrenergic blocking drugs. Patients who have an LVEF less than 0.41 and low RR variability should be considered for prophylactic amiodarone.

The recognition that heart-rate changes during and immediately after exercise are both correlated with autonomic function and with long-term mortality now means that the exercise stress laboratory is a venue for easy, inexpensive, and prognostically meaningful assessment of autonomic disturbances. As with HRV, it might be argued that since the pathophysiology and treatment of exercise heart-rate abnormalities are not known, no practical clinical value exists. We believe that this is not the case. By combining exercise heart-rate responses with other exercise test measures, it is simple to identify a large number of very low risk patients, for whom conservative management can be confidently recommended. Although the optimal treatment of patients with abnormal heart-rate dynamics is not known, these patients can be identified as being at increased risk and therefore it is reasonable to aggressively manage all correctable disturbances for which there is evidence of benefit, such as elevated low-density lipoprotein cholesterol in the setting of known coronary disease or aggressive reduction of elevated blood pressure.

Several questions remain to be answered about HRR. The optimal time to measure the recovery rate has not been well defined. One-minute recovery heart rate has been used successfully in two studies and is also routinely measured in most exercise laboratories. However, 2-minute recovery is also predictive of outcome and may be an alternative. It is also possible that a shorter HRR, such as 30-second recovery (31), may be a better predictor of death. A cool-down period following exercise is currently routinely used except in certain situations such as stress echocardiography. HRR for the use or nonuse of different cool-down periods still needs to be defined. Last, it is unclear if HRR is a modifiable risk factor. It is possible that exercise may increase HRR (141) as may pharmacologic intervention, but this currently is unknown.

Currently, we recommend that all individuals undergoing exercise testing have 1-minute HRR measured during a cool-down period and the findings reported in the results. For those individuals whose heart rates fail to decrease by more than 12 beats/min an abnormal HRR should be reported and they should be considered at higher risk for death. Their other risk factors should be optimized, but there is no need to proceed to heart catheterization based solely on an abnormal HRR. There are no current recommendations regarding exercise or medications for an abnormal HRR.

THE FUTURE

The future will bring a clearer understanding about the physiologic systems that determine cyclic fluctuations in RR intervals. This knowledge will increase our ability to interpret alterations in RR variability in disease states or during drug therapy and to react to them appropriately. Further research will provide information on the role that the autonomic nervous system plays in cardiac death and establish treatments that target the autonomic nervous system to decrease cardiac death in patients with coronary artery disease.

We still have much to learn about how physiologic control systems determine the fluctuations of heart rate that we quantify and use diagnostically. In the future, we will learn more about the physiologic systems that determine cyclic fluctuations in RR intervals and heart-rate changes. This knowledge will increase our ability to interpret these alterations in disease states or during drug therapy and to react to them appropriately.

The predictive value of RR variability and BRS is established for death and arrhythmic events in coronary heart disease. However, the predictive value of these measures of autonomic nervous system activity for death and other important cardiovascular outcomes is yet to be firmly established for other cardiac diseases. This is an important task for the future.

Sudden cardiac death remains one of our biggest public health problems. Most out-of-hospital cardiac arrests occur in persons with coronary heart disease and are due to VF. The low salvage rate for out-of-hospital cardiac arrest motivates attempts to predict this event and to prevent it. In the 1990s, the predictive value of RR variability and BRS was established for cardiac death in coronary heart disease. These findings suggest that the autonomic nervous system is intimately involved in the pathogenesis of cardiac deaths, presumably by arrhythmic mechanisms. However, it is possible that RR variability and BRS are not responsible for cardiac death, but reflect other factors that are. It remains to be proven that the autonomic nervous system plays a major causal role in cardiac death. To establish a causal role for the autonomic nervous system, a treatment that increases RR variability and BRS must be shown to decrease cardiac death in patients with coronary heart disease. The EMIAT substudy demonstrated that amiodarone prophylaxis in patients with recent myocardial infarction and LVEF less than 0.41 was beneficial for patients who had low RR variability, but not for patients with normal RR variability. Defibrillators in Acute Myocardial Infarction Trial (DINAMIT) is recruiting patients who have reduced LVEF and low RR variability and randomizing them to implantable cardioverter-defibrillator (ICD) prophylaxis or no antiarrhythmic therapy (121).

At the present time, ICDs are the dominant treatment for coronary heart disease patients who survive out-of-hospital cardiac arrest, and beta-adrenergic blocking drugs are the dominant therapy for those at risk, but who have not had a sustained ventricular tachyarrhythmia. The dominance of implantable defibrillator therapy for cardiac arrest survivors is based several randomized trials that show ICD therapy to be superior to amiodarone therapy in patients who have survived a spontaneous cardiac arrest. For patients at risk who have not yet had a sustained ventricular arrhythmia, it remains to be proven that RR variability or BRS will predict the deaths that can be prevented by ICDs. ICD prophylaxis should be restricted in clinical practice to groups that have been shown in randomized controlled trials to benefit. The value of RR variability and BRS for identifying patients who will benefit from ICD prophylaxis is being studied in ongoing trials (e.g., DINAMIT). Also, it will be possible to conduct randomized trials of drug prophylaxis to prevent sudden cardiac death in patients who have had an ICD implant (142); before ICDs, such trials would have been unethical.

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78

CORONARY ANGIOGRAPHY

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FREDERICK A. HEUPLER, JR.

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Coronary angiography remains the clinical gold standard for the diagnosis of coronary artery disease. Approximately 2 million procedures are performed annually in the United States. More than 60% of cardiologists in the United States perform coronary angiography as part of their practice (1). Because it is an invasive procedure with potentially serious risks, it should be performed only by well-trained individuals when an appropriate clinical indication exists. Physicians who perform coronary angiography must clearly understand its limitations and possess a firm grasp of the fundamental technical aspects of catheterization (2). From gaining arterial access to obtaining adequate images of the coronary arteries, angiographers must obtain and maintain a specific set of skills.

GLOSSARY

Caudal projection: Radiographic view with the image intensifier pointing to the inferior surface of the heart.

Conus artery: A branch that variably arises either from the right coronary artery or in close proximity to it and perfuses the right ventricular outflow tract.

VIDEO

Video 78.1 Inadvertent subselective cannulation of the conus branch of the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Cranial projection: Radiographic view with the image intensifier pointing to the superior surface of the heart.

Crux: The intersection of the atrioventricular groove and the interatrial and interventricular septa on the inferior aspect of the heart.

Damping: Blunting of a recording of the arterial pressure waveform.

Diagonal artery: A branch of the left anterior descending artery that perfuses the left ventricular free wall.

Dominance: Refers to the vessel, either the right coronary artery or the left circumflex artery, that supplies the posterior part of the heart; codominance refers to the situation in which both arteries provide circulation to the posterior heart.

Image intensifier: The portion of the catheterization laboratory imaging equipment that increases the brightness of images produced by x-rays.

Internal mammary artery (IMA): An artery that runs from the subclavian artery down the chest wall, which can be harvested for use as a surgical conduit for bypass grafting; sometimes called the *internal thoracic artery*.

Left anterior descending (LAD) artery: The artery that supplies the anterior surface of the heart.

Left anterior oblique (LAO) projection: Radiographic view with the image intensifier on the left side of the patient.

Left circumflex artery (LCx): The artery that supplies blood to the lateral aspect of the heart.

Left main (LM) coronary artery: The short artery that divides into the left anterior descending artery and the left circumflex artery (and sometimes the ramus intermedius) and supplies most of the left side of the heart.

Marginal artery: A branch (acute marginal) of the right coronary artery that supplies the right ventricle; also, a branch (obtuse marginal) of the left circumflex, sometimes referred to as a *lateral branch*.

Posterior descending artery (PDA): The branch of the right coronary artery, or occasionally the left circumflex artery, that provides blood flow to the posterior aspect of the interventricular septum.

Ramus intermedius (RI): A branch of the left main artery that supplies the lateral wall of the left ventricle.

Right anterior oblique (RAO) projection: Radiographic view with the image intensifier on the right of the patient.

Right coronary artery (RCA): The artery that supplies blood to the right side of the heart and usually to the posterior aspect of the left ventricle.

Saphenous vein graft: A surgical conduit harvested from the legs, used to reroute blood from the aorta to the coronary arteries.

Scatter: Dispersion of radiation as it passes through the body; it is the source of most of the radiation exposure to the operator.

Ventricularization: Distortion of the recorded arterial pressure waveform such that the diastolic component is blunted, simulating a left ventricular pressure tracing.

GENERAL PRINCIPLES OF CORONARY ANGIOGRAPHY

Historical Perspective

The first selective coronary angiogram was performed in 1958 by Dr. F. Mason Sones, Jr., a cardiologist at The Cleveland Clinic Foundation (3). Quite accidentally, the catheter positioned in the aorta for an angiogram to assess aortic insufficiency dove into the RCA, and an image was obtained before it was fully realized what had occurred. Although the patient's heart rate slowed down transiently, there were no other untoward effects, and the era of selective coronary angiography was born. When Dr. Sones and Dr. Earl K. Shirey published their results of more than 1,000 procedures in 1962, interest in coronary angiography surged. Coronary angiography as a diagnostic tool blossomed with Dr. René Favaloro's description in 1968 of his pioneering work in performing saphenous vein coronary artery bypass grafting at The Cleveland Clinic.

Radiologists played an important role in the development of catheterization techniques in the early 1960s. New preformed catheter designs, such as those by Dr. Melvin Judkins and Dr. Kurt Amplatz, enabled selective angiography to be performed with greater ease than was previously possible with the Sones catheters. Additionally, percutaneous approaches were also now possible, and arterial cutdowns were no longer required. Improvements in radiographic imaging concomitantly led to better image quality. After Dr. Andreas Grüntzig introduced percutaneous coronary angioplasty in 1977, cardiologists were able to make the transition from being diagnosticians to becoming endovascular surgeons.

Coronary Artery Anatomy

Normal Anatomy

The LM coronary artery originates from the left sinus of Valsalva and usually bifurcates into the LAD, which supplies the left ventricle's anterior surface, and the LCx, which supplies the lateral aspect of the left ventricle (Fig. 78.1). The LAD traverses the anterior interventricular groove, giving rise to septal perforating branches to supply the interventricular septum and to diagonal branches that supply the anterolateral wall. It then bifurcates distally and tapers out as a "whale's tail" at the cardiac apex, although sometimes it "wraps around" the apex to supply part of the inferior wall. The LCx courses along the left atrioventricular groove and provides small atrial branches to the left atrium and marginal branches that supply the lateral wall of the left ventricle. The marginal branches are sometimes referred to as *lateral branches*, with the first marginal branch called the *high lateral* and subsequent lateral branches referred to as *lateral* or *posterolateral branches*. Occasionally, the LM coronary artery trifurcates to give rise also to a ramus intermedius branch that supplies the high lateral wall of the left ventricle.

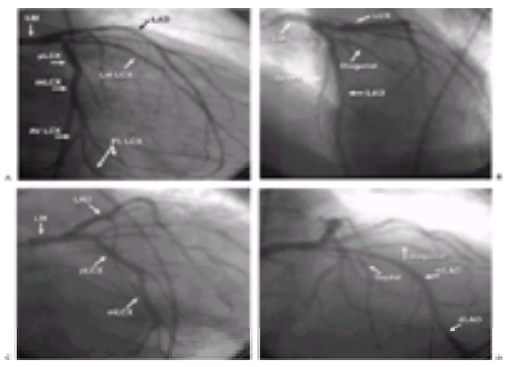


FIGURE 78.1 Normal left coronary artery with segments labeled. **A:** Shallow right anterior oblique (RAO) caudal projection. **B:** Left anterior oblique cranial projection. **C:** Posteroanterior caudal projection. **D:** RAO cranial projection. AV, atrioventricular continuation of the left circumflex artery; dLAD, distal left anterior descending artery; Lat LCX, lateral branch of the left circumflex artery; LM, left main coronary artery; mLAD, mid-left anterior descending artery; mLCX, mid-left circumflex artery; PL, posterolateral branch of the left circumflex artery; pLAD, proximal left anterior descending artery; pLCX, proximal left circumflex artery.

The RCA originates from the right sinus at a slightly more caudal level than the LM coronary artery and supplies the right ventricle and the inferior aspect of the left ventricle (Fig. 78.2). It traverses the right atrioventricular groove and provides small branches to the right atrium and marginal branches to the right ventricle. Approximately 60% of the time, the RCA atrial branches supply the sinus node; otherwise, the LCx atrial branches serve this function. Approximately 50% of the time, the first branch of the RCA is a conus branch, supplying the right ventricular outflow tract; the remainder of the time, the conus branch originates separately from an ostium near the RCA ostium. The dominant artery is generally defined as the one that provides the PDA to supply the posterior wall. In approximately 85% of patients, the RCA is dominant, with the remainder of patients having either a dominant LCx or a codominant RCA and LCx. The PDA of the RCA (or the LCx) courses along the inferior interventricular groove, providing septal perforators, a feature that may aid in its identification and differentiation from the posterolateral segment of the RCA (or LCx), which gives off branches to the posterior ventricle. More than 90% of the time, the artery to the atrioventricular node originates from the atrioventricular branch of the RCA as it passes through the crux.

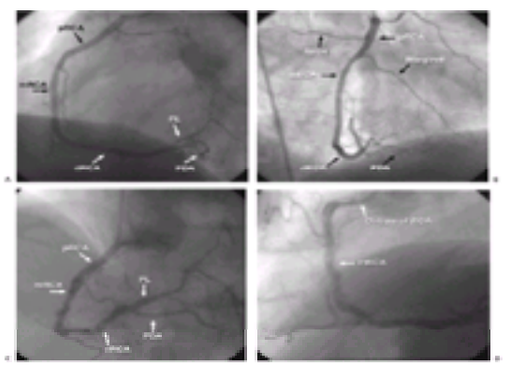
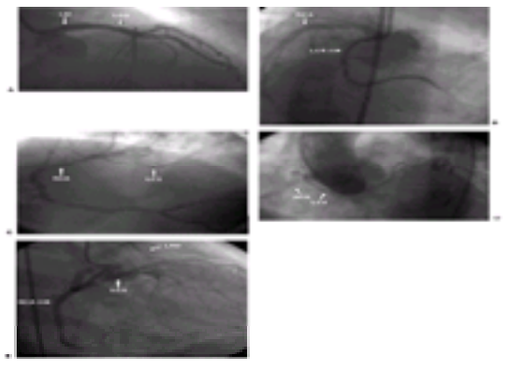


FIGURE 78.2 Normal right coronary artery with segments labeled. **A:** Left anterior oblique projection. **B:** Right anterior oblique projection. **C:** Posteroanterior cranial projection. **D:** Lateral projection. dRCA, distal right coronary artery; mRCA, mid-right coronary artery; PDA, posterior descending artery branch; PL, posterolateral branch of the right coronary artery; pRCA, proximal right coronary artery.

Coronary Anomalies

It is important for the angiographer to be alert for possible variations in normal coronary anatomy (*e*Fig. 78.2.1). In a series of 126,595 patients undergoing coronary angiography at The Cleveland Clinic Foundation, Yamanaka and Hobbs (4) found that coronary artery anomalies occur in 1.3% of patients. Of the anomalies identified, 87% involved anomalies of origin or distribution, and 13% involved the presence of coronary artery fistulae (*e*Table 78.0.1). Most coronary artery anomalies were discovered incidentally, and 81% were considered benign. Some anomalies may be potentially harmful, however, such as a coronary artery that originates from the pulmonary artery or the opposite aortic sinus. For example, most patients with an anomalous origin of the left coronary artery from the pulmonary artery (Bland-White-Garland syndrome) die as infants unless surgical repair is undertaken. In fact, surgical repair is recommended for ectopic origin of the coronary arteries from the pulmonary artery even in the asymptomatic patient.

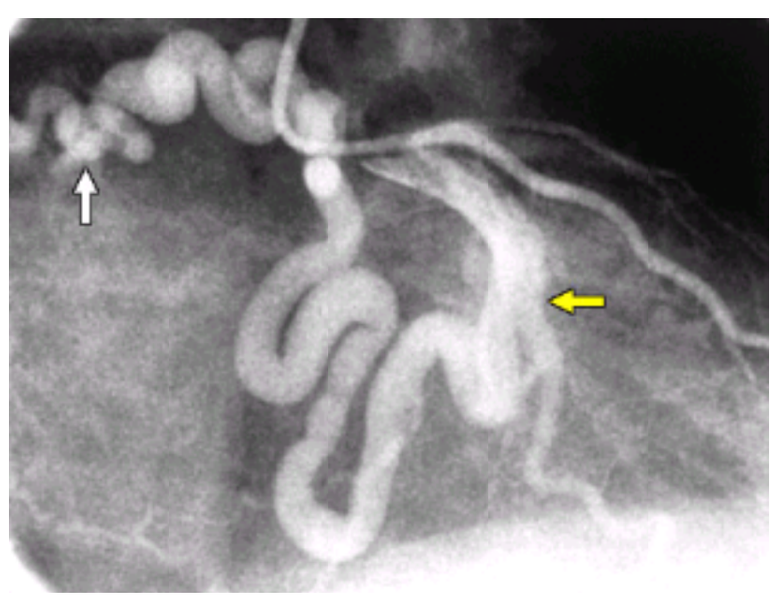


***e*FIGURE 78.2.1** Coronary artery anomalies. **A:** Angiogram of the left main (LM) coronary artery and left anterior descending artery (LAD), with no left circumflex artery (LCX), raising the suspicion of an anomalous LCX. **B:** Anomalous LCX from the right sinus (same patient as in **A**). In this right anterior oblique projection, the right coronary artery (RCA) and anomalous LCX are seen to fill from the right cusp. (Courtesy of Dr. Mark A. Robbins and Dr. Eric J. Topol.) **C:** Left anterior oblique cranial view of an anomalous LCX originating from the very proximal RCA. (Courtesy of Dr. Keith Kruithoff.) **D:** Aortogram demonstrating anomalous origins of the LCX from the right sinus. **E:** RCA, LCX, and LAD all originating from the right sinus.

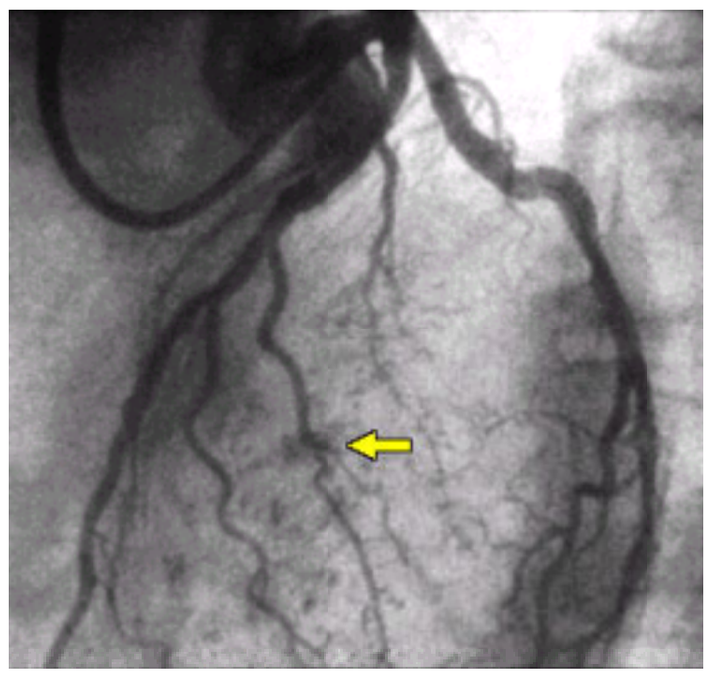
***e*TABLE 78.0.1** RELATIVE FREQUENCY OF CORONARY ARTERY ANOMALIES

Anomaly	% of total
Separate origin of the LAD and LCx	30.4
LCx from right sinus or RCA	27.7
RCA from aorta	11.2
Small coronary artery fistulae	9.7
RCA from left sinus[a]	8.1
Multiple or large fistulae[a]	3.7
LAD from right sinus[a]	2.3
Single left coronary artery[a]	1.85
Single right coronary artery[a]	1.46
LM from right sinus[a]	1.3
LM from aorta	0.95
LM from pulmonary artery[a]	0.59
Absent LCx (with very dominant RCA)	0.24
RCA from posterior sinus	0.24
Intercoronary communication	0.18
RCA from pulmonary artery	0.12
LAD from pulmonary artery[a]	0.06
LM from posterior sinus	0.06

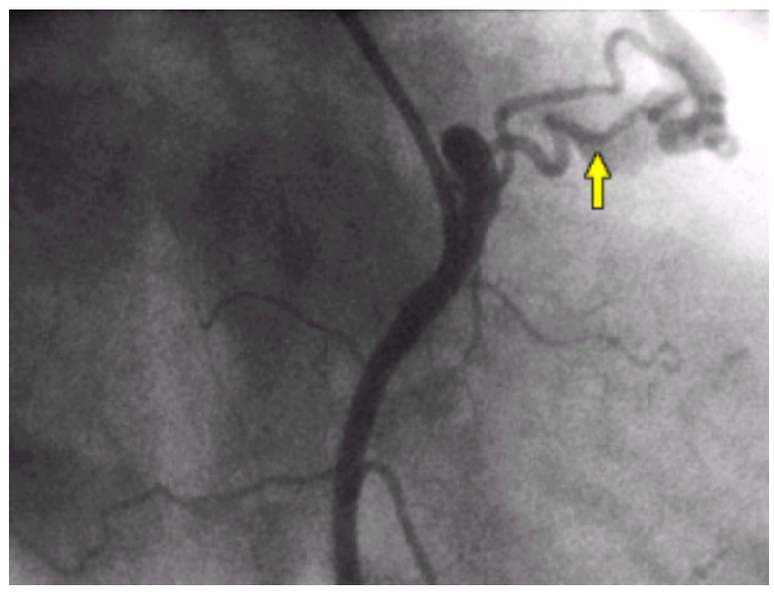
LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main coronary artery; RCA, right coronary artery.
[a]Potentially serious anomalies.
Adapted from Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary angiography. *Cathet Cardiovasc Diagn* 1990;21:28–40, with permission.



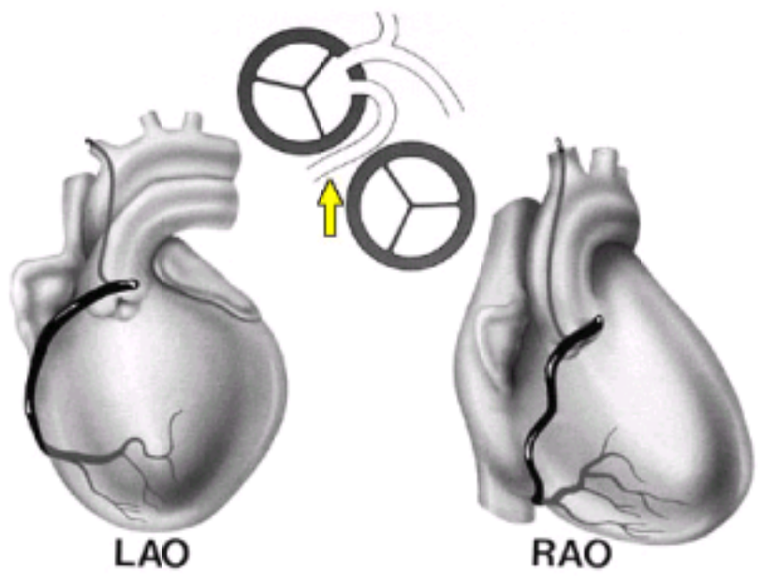
Left circumflex artery fistula to right atrium. There is a large serpiginous vessel arising from the circumflex (*yellow arrow*) that terminates in the right atrium (*white arrow*).



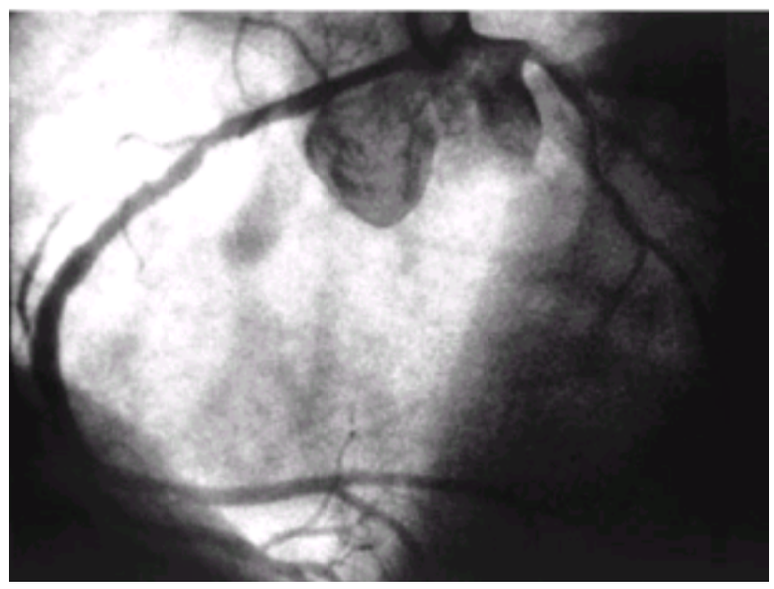
Diagonal artery fistula to the left ventricular cavity (*yellow arrow*). In this left anterior oblique projection, faint opacification of the left ventricular cavity is visible upon injection of the left coronary artery.



Fistula from the right coronary artery to the pulmonary artery (*yellow arrow*).



Fistula from the right coronary artery to the pulmonary artery (*yellow arrow*).



Angiogram showing anomalous origin of the right coronary artery. In this left anterior oblique cranial projection the right coronary artery originates from the left sinus of Valsalva and passes between the aorta and pulmonary artery.

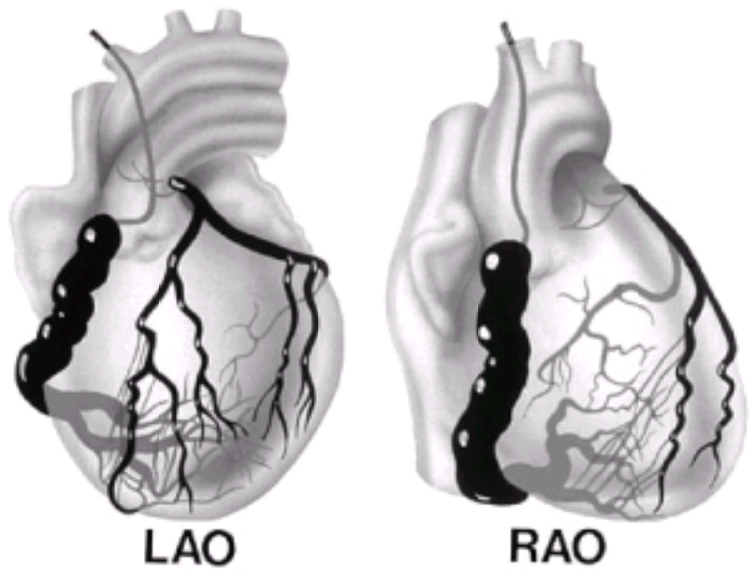
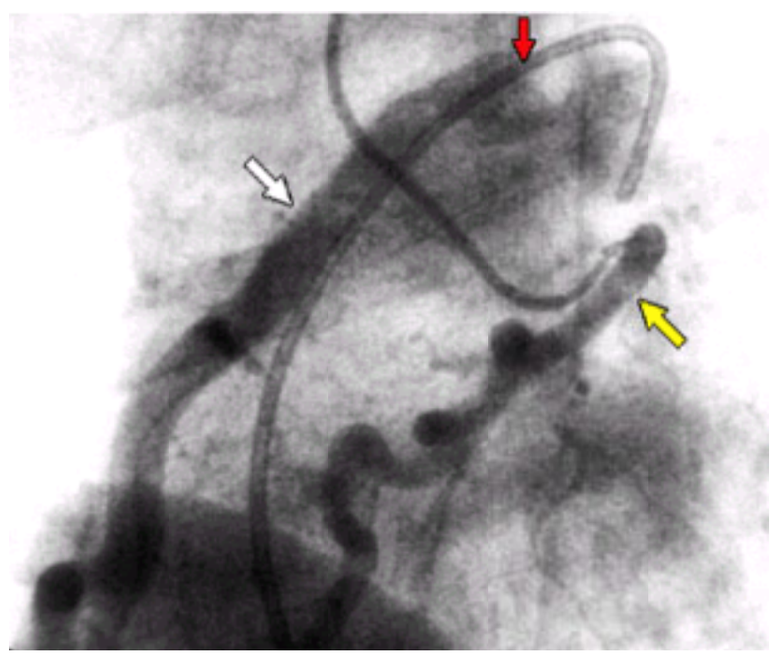
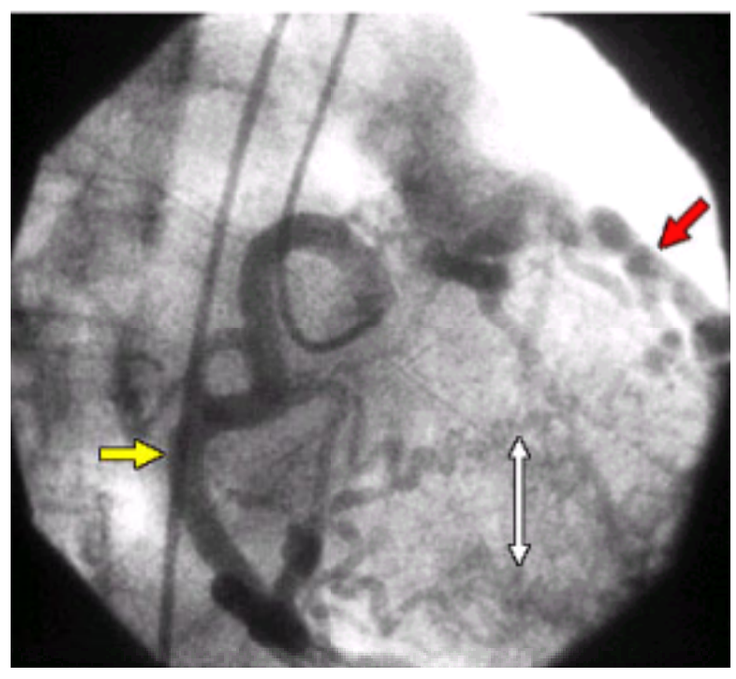


Diagram of the right coronary artery originating from the right sinus of Valsalva and providing collateral circulation to the left coronary artery, which drains directly into the pulmonary artery. This is described as the Bland-White-Garland anomaly. Left panel depicts a left anterior oblique projection of a injection of the right coronary artery arising from the right sinus of Valsalva which provides rich collateral circulation to the left anterior descending and left circumflex arteries, which fill in a retrograde fashion and drain into the pulmonary artery. The right panel depicts the right anterior oblique projection of the same.

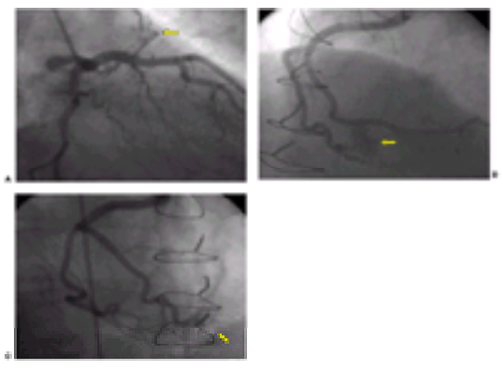


Bland-White-Garland anomaly. This left anterior oblique angiogram demonstrates injection of the right coronary artery (*yellow arrow*) originating from the right coronary sinus with return of contrast material from the left coronary artery (*white arrow*) into the pulmonary artery as demonstrated by the placement of the Swan-Ganz catheter (*red arrow*).



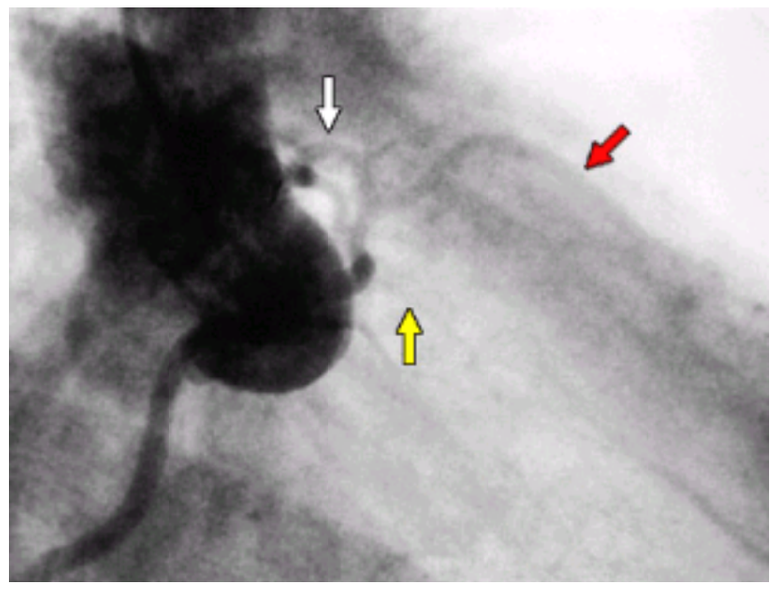
Bland-White-Garland anomaly. The right anterior oblique angiogram demonstrates injection a serpiginous and dilated right coronary artery (*yellow arrow*) that provides generous collateral circulation (*white arrow*) to the left coronary artery (*red arrow*), which originates from the pulmonary artery.

Origin of the left coronary artery from the right sinus may also lead to sudden death, depending in large part on the traversal of the anomalous artery. If the anomalous vessel travels intramyocardially through the septum (the most common variant of this anomaly), or anteriorly or posteriorly, symptoms of ischemia are less likely. If the anomalous artery courses between the pulmonary artery and aorta, however, exercise may lead to expansion of the aorta and compression of the anomalous LM coronary artery, potentially causing symptoms or leading to sudden death. In this latter variant, the LM coronary artery projects on end as a “dot” on the anterior surface of the aorta during a ventriculogram or aortogram in an RAO projection. Likewise, a single coronary artery or large coronary artery fistulae may be problematic (*e*Fig. 78.2.2). Large coronary artery fistulae may present with heart failure or ischemia, and they may also cause endocarditis; therefore, endocarditis prophylaxis is recommended (5). Small coronary artery fistulae, however, are rarely problematic. These fistulae typically originate from the LAD and drain into the pulmonary artery two-thirds of the time, with drainage into a cardiac chamber in the remainder of instances.



***e*FIGURE 78.2.2 A:** Left anterior descending artery to pulmonary artery fistula (*arrow*) in right anterior oblique caudal view. (Courtesy of Dr. Umesh Khot.) **B,C:** Right

coronary artery to right ventricular fistula (*arrows*) in two separate projections.



Left coronary artery originating from the right sinus of Valsalva and coursing intramyocardially to give rise to the left circumflex and the left anterior descending artery. Flush injection of the right coronary sinus depicts a left coronary artery originating from the right sinus of Valsalva and coursing intramyocardially and giving rise to septal perforating branches (*yellow arrow*) and ultimately giving rise to the left circumflex (*white arrow*) and the left anterior descending arteries (*red arrow*).

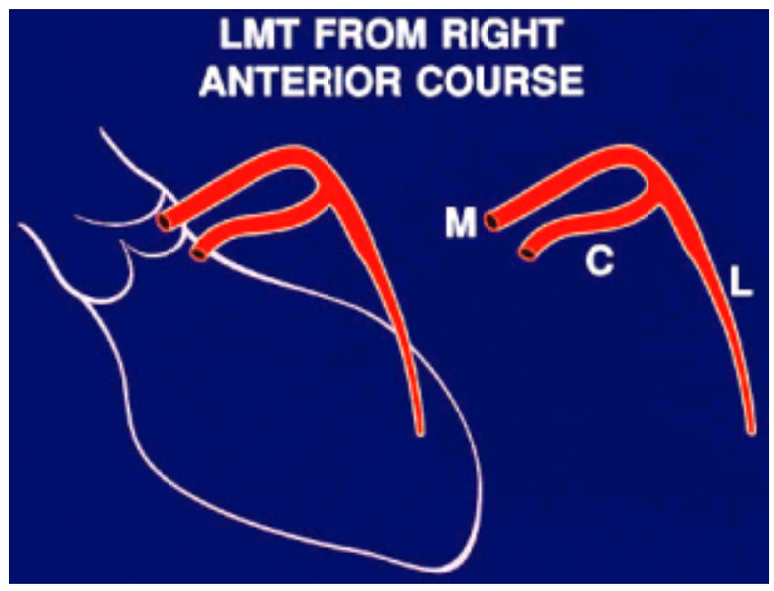
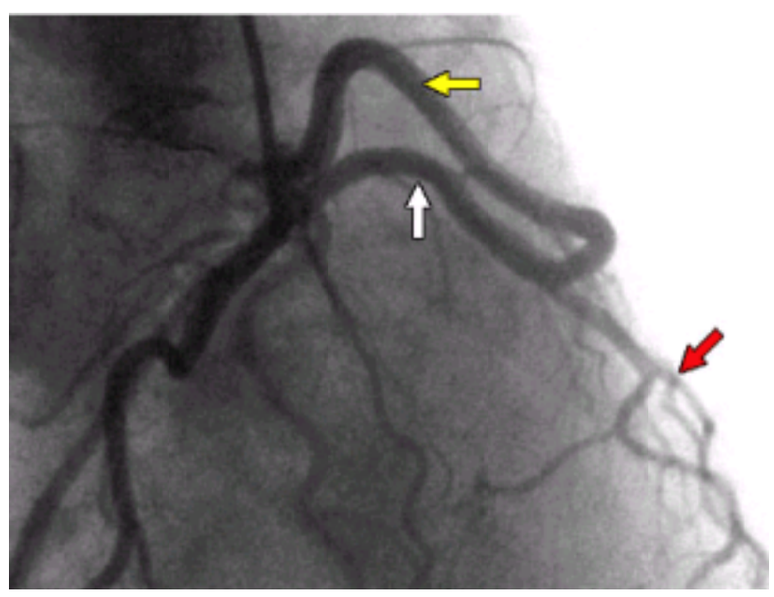
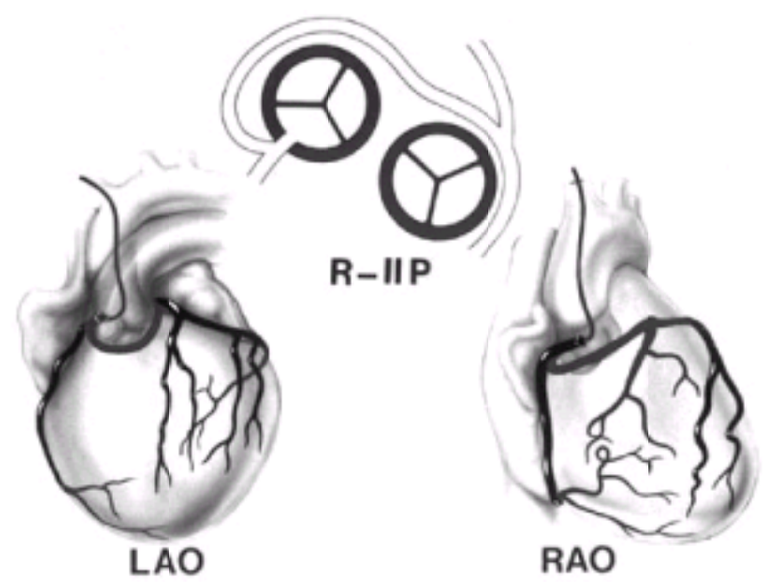


Diagram of the left coronary artery originating from the right sinus of Valsalva with an initial course anterior to the pulmonary artery. Left panel depicts a right anterior oblique projection of the geometry of the left coronary artery as it originates from the right sinus of Valsalva and coursing anterior to the pulmonary artery. The right panel depicts the geometry of the left main trunk (M) with the left circumflex (C) and the left anterior descending artery (L) as seen from the right anterior oblique projection.



Left coronary artery originating from the right sinus of Valsalva with an anterior course. This right anterior oblique projection demonstrates the diagnostic appearance and geometry of the left coronary artery originating from the right sinus of Valsalva and coursing anterior to the pulmonary artery (*yellow arrow*) and bifurcating into the left circumflex (*white arrow*) and the left anterior descending artery (*red arrow*).



Single coronary artery with the left coronary trunk originating from the right sinus of Valsalva and coursing posterior to the aorta and pulmonary artery to give rise to the left circumflex and the left anterior descending artery. Left panel depicts a left anterior oblique projection of a single coronary artery originating from the right coronary sinus of Valsalva with the left coronary trunk coursing posterior to the aorta and pulmonary artery to give rise to the left circumflex and left anterior descending artery. The right panel depicts the right anterior oblique projection of the same.

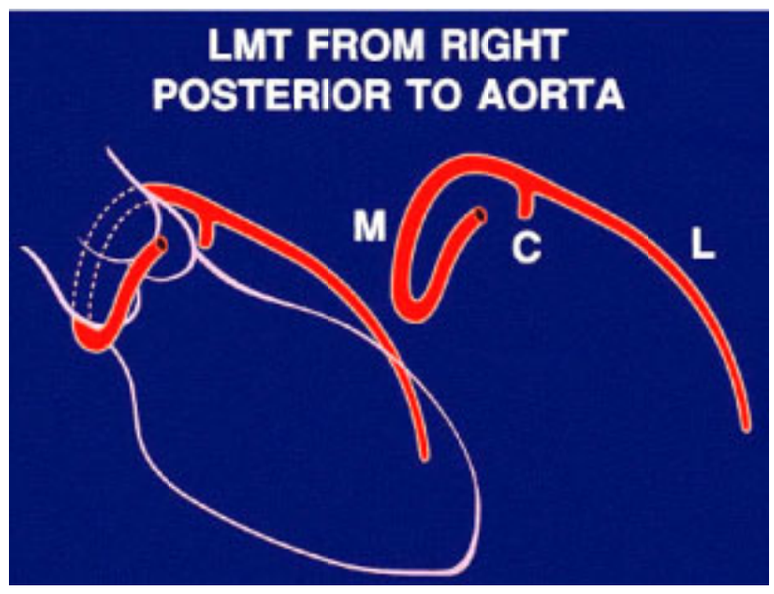
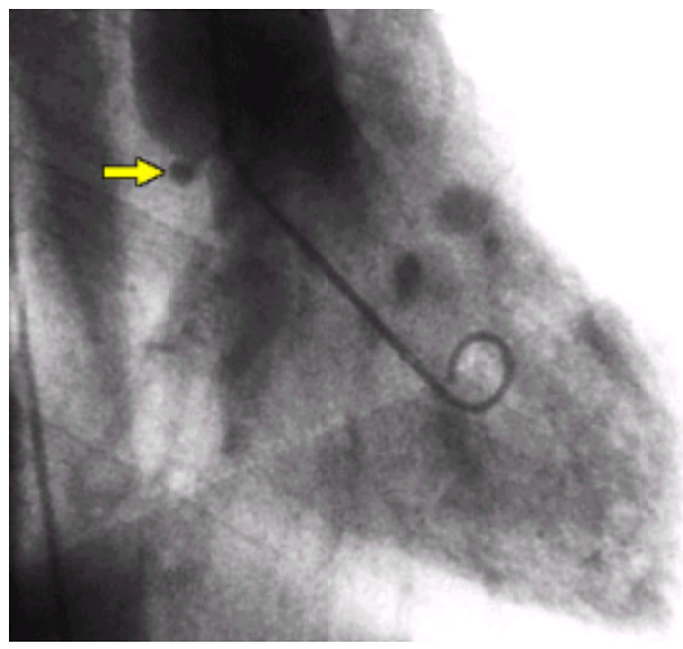


Diagram of the left coronary artery originating from the right sinus of Valsalva and coursing posterior to the aorta and the pulmonary artery to give rise to the left circumflex and the left anterior descending artery. Left panel depicts a right anterior oblique projection of the left coronary artery originating from the right sinus of Valsalva and coursing posterior to the aorta and the pulmonary artery to give rise to the left circumflex and the left anterior descending artery. Right panel depicts the diagnostic appearance and geometry of the left coronary trunk (M) originating from the right sinus of Valsalva and coursing posterior to the aorta and pulmonary artery to give rise to the left circumflex (C) and the left anterior descending arteries (L).



Left ventriculogram performed in the right anterior oblique projection demonstrating the course of a left coronary artery originating from the right sinus of Valsalva with the left coronary trunk (*yellow arrow*) coursing posterior to the aorta and pulmonary artery to give rise to the left circumflex and left anterior descending arteries.

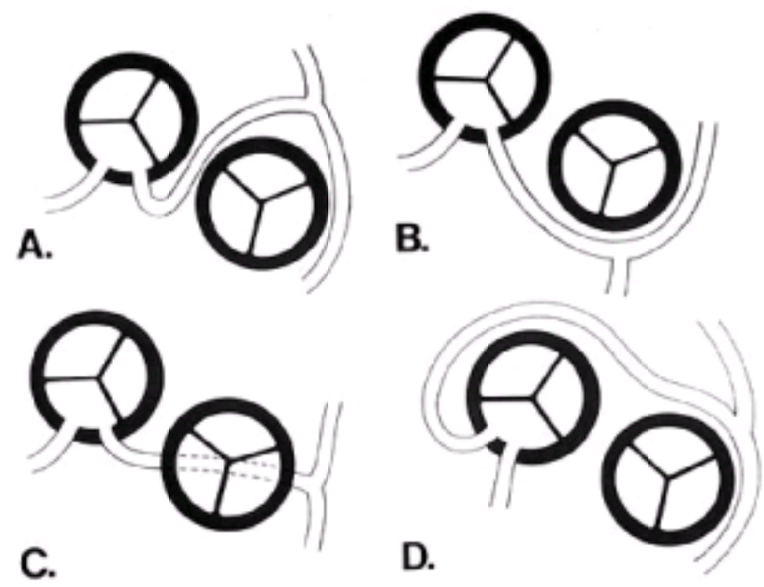


Diagram depicting the variations of the left coronary artery originating from the right sinus of Valsalva. Panel A depicts the left coronary artery arising from the right sinus of Valsalva and coursing between the pulmonary artery and the aorta. Panel B depicts origin of the left coronary artery from the right sinus of Valsalva coursing anterior to pulmonary artery. Panel C depicts the origin of the left coronary artery from the right sinus of Valsalva and coursing intramyocardially in the crista supraventricularis. Panel D depicts the origin of the left coronary artery from the right sinus of Valsalva coursing posterior to the aorta.

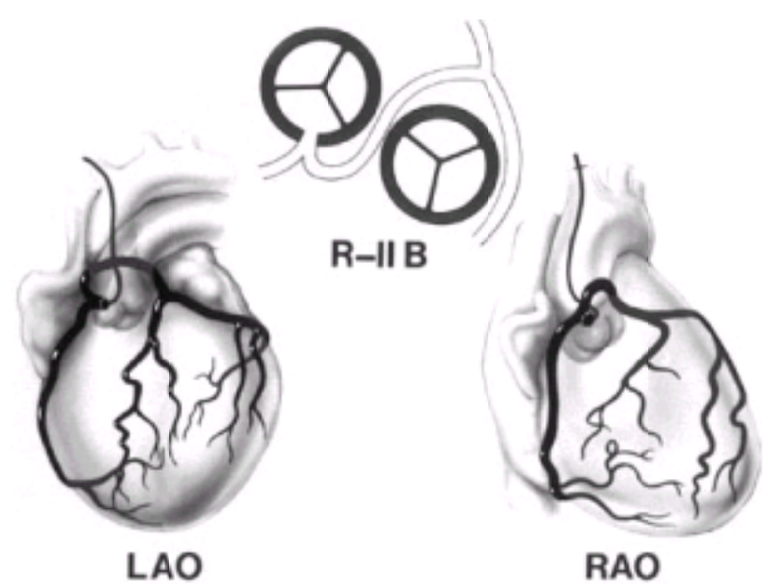


Diagram of a single coronary artery originating from the right sinus of Valsalva with the left coronary trunk coursing between the pulmonary artery and aorta. Left panel depicts a left anterior oblique projection of the single coronary artery originating from the right sinus of Valsalva with a left coronary artery trunk coursing between the pulmonary artery and aorta. The right panel depicts the right anterior oblique projection of the same.

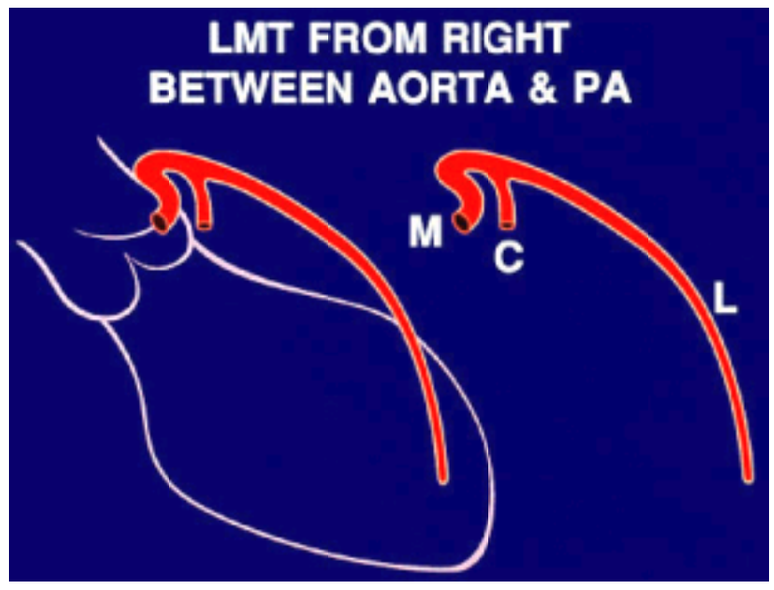
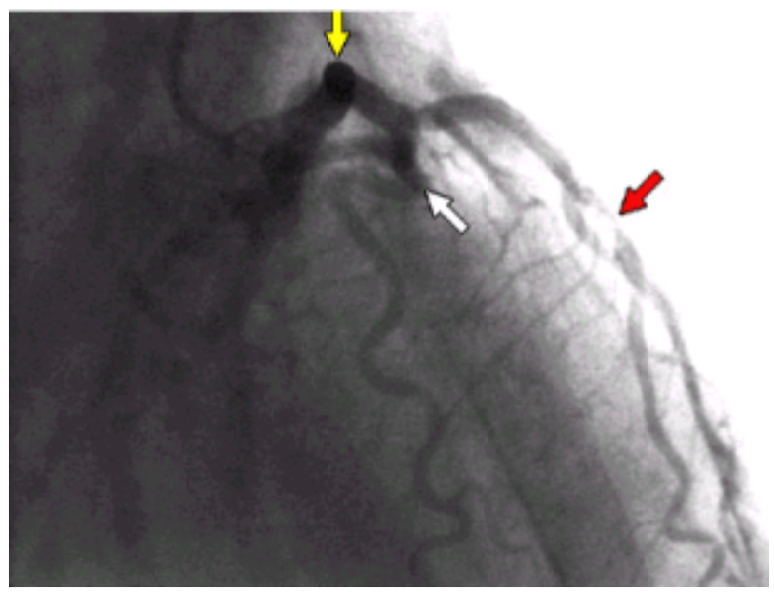
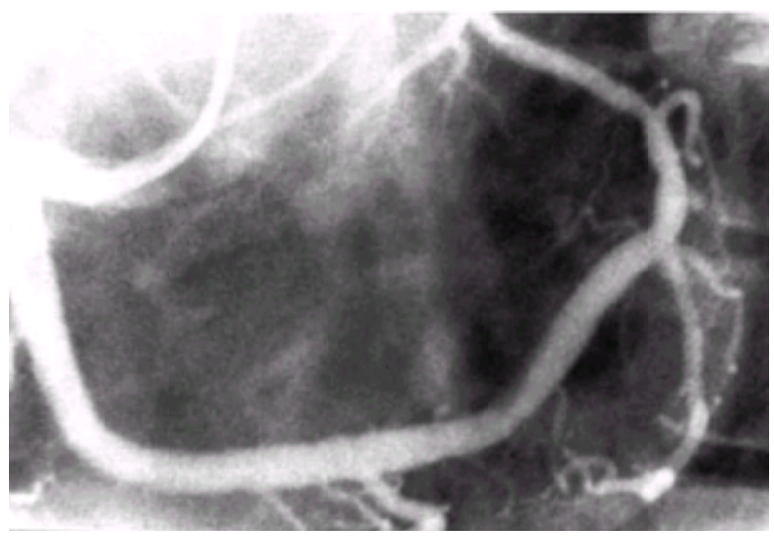


Diagram depicting left coronary artery originating from the right sinus of Valsalva and coursing between the aorta and pulmonary artery. Left panel depicts a right anterior oblique projection of the geometry of the left coronary artery originating from the right sinus of Valsalva coursing between the aorta and pulmonary artery. Right panel depicts the diagnostic appearance and geometry of the left main trunk (M) and the left circumflex (C) and the left anterior descending artery (L) as seen from the right anterior oblique projection.



Left coronary artery originating from the right sinus of Valsalva and coursing between the pulmonary artery and aorta. This right anterior oblique projection demonstrates the diagnostic appearance of the left main trunk (*yellow arrow*) originating from the right sinus of Valsalva and coursing between the pulmonary artery and aorta to give rise to the left circumflex artery (*white arrow*) and the left anterior descending artery (*red arrow*).



Single coronary artery originating from the right sinus of Valsalva. This left anterior oblique projection demonstrates an injection of right coronary artery that perfuses the entire heart.

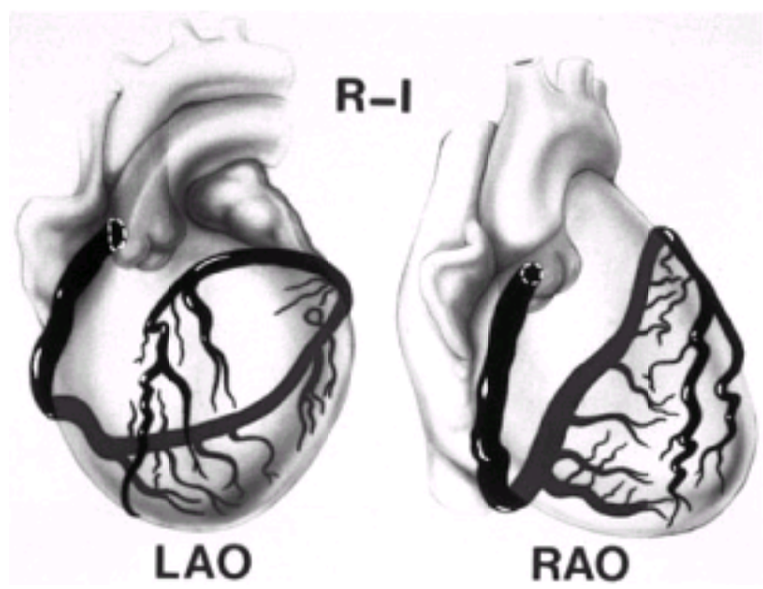
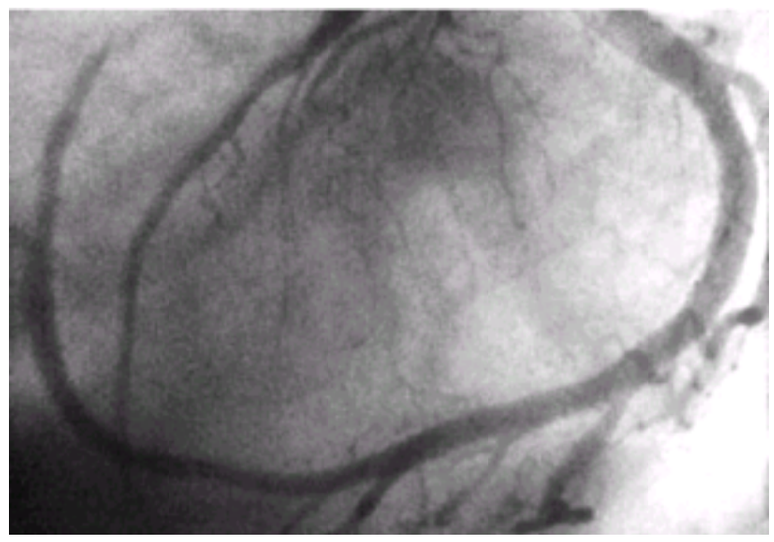
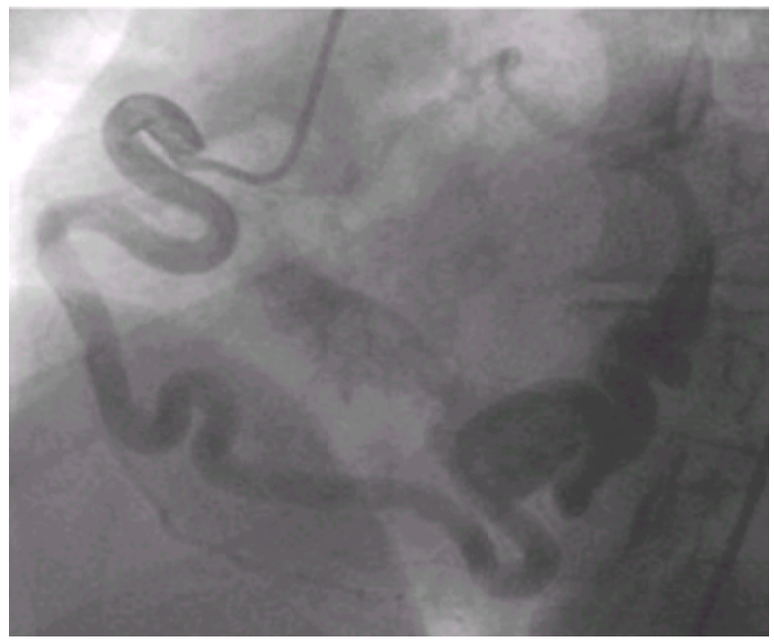


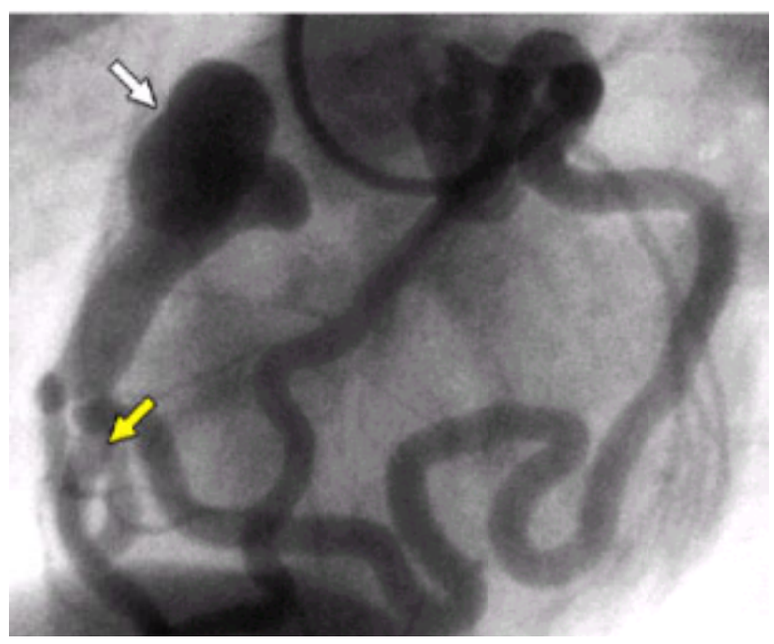
Diagram of single coronary artery originating from the right sinus of Valsalva. The left panel depicts a left anterior oblique projection of a single coronary artery originating from the right sinus of Valsalva. The right panel depicts a right anterior oblique projection of the same.



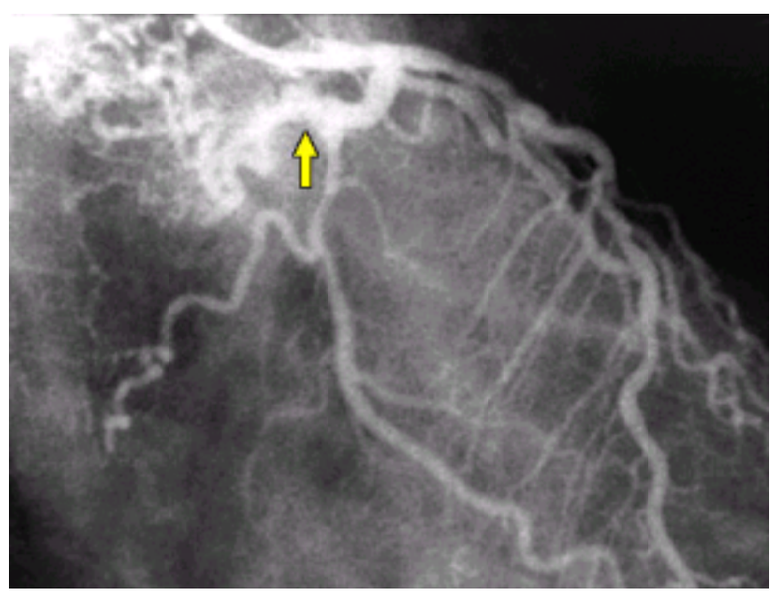
Single coronary artery originating from the left sinus of Valsalva. This left anterior oblique projection demonstrates injection of the left coronary artery that perfuses the entire heart.



A 46-year-old female patient with congestive heart failure. Coronary angiograms revealed large coronary arteriovenous fistula involving the right coronary artery. The patient underwent surgical ligation of the fistula with resolution of her symptoms.

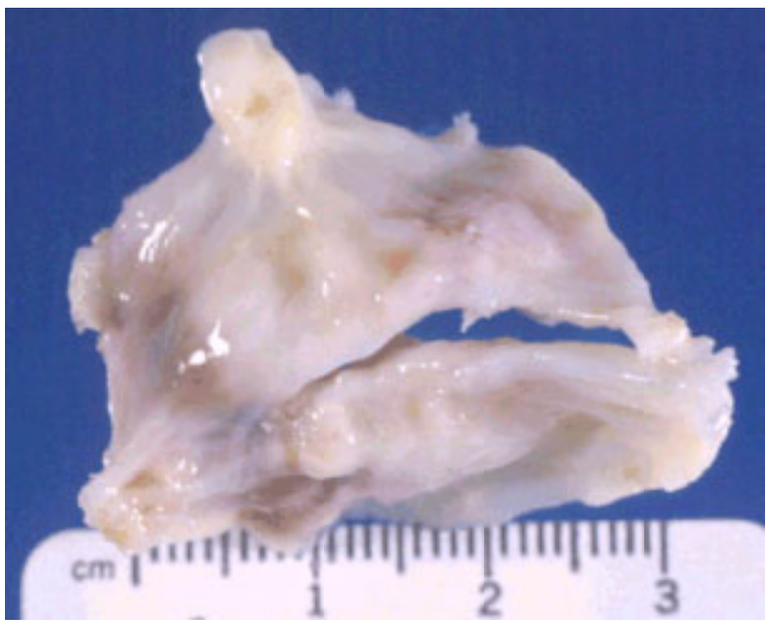


Anomalous connection of the left coronary artery to the right coronary artery with fistula to the right atrium. This left anterior oblique projection demonstrates an anomalous connection of the left circumflex to the right coronary artery (*yellow arrow*) and a fistula from the right coronary artery to the right atrium (*white arrow*).



Left coronary artery fistula to the pulmonary artery. This right anterior oblique projection demonstrates a fistula from the left circumflex to the pulmonary artery (*yellow arrow*).

The association between coronary artery anomalies and congenital heart disease is noteworthy. Approximately 10% of patients with coronary artery anomalies have some form of congenital heart abnormality, such as a bicuspid aortic valve (6). In tetralogy of Fallot, for example, the LAD sometimes originates from the right sinus, crossing the right ventricular outflow tract. Although communication between cardiologist and cardiac surgeon is always important, it is especially critical to convey the presence of any anomalies that may have an impact on the surgical approach, so as to prevent any accidental transection or ligation of anomalous coronary arteries (7).



Bicuspid aortic valve with calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 78.2 Anomalous origin of the left anterior descending artery and the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Myocardial Bridging

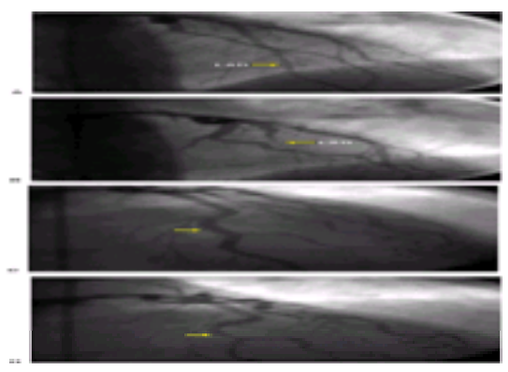
Systolic compression of a coronary artery is referred to as *bridging* (eFig. 78.2.3). Approximately 12% of normal angiograms demonstrate some degree of myocardial bridging, although only 1.7% show systolic narrowing of more than 50% (8). Bridging occurs in the mid-LAD when it courses through the septum. If this is the case, it is important to note this for the surgeon, as it makes grafting more technically challenging, especially from a minimally invasive approach. Myocardial bridging of septal perforating branches, also called *septal squeeze*, is commonly found in hypertrophic cardiomyopathy and aortic stenosis and occasionally with severe proximal LAD stenosis, but rarely in normal hearts (9). Other more unusual locations for bridging include the PDA. When a circumflex marginal branch is intramyocardial, ventricular systole usually produces little or no compression. The intramyocardial portion appears unusually straight rather than serpentine. Nitrate administration tends to make bridging more apparent angiographically. As the majority of coronary flow occurs in diastole, the systolic phenomenon of bridging rarely leads to ischemia (8). In the few instances in which it does lead to objective signs of ischemia, stenting has been performed successfully (10,11,12 and 13).

VIDEO

Video 78.3 Anomalous origin of the left anterior descending artery with a septal course. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 78.4 Severe myocardial bridging of the mid–left anterior oblique in a 30-year-old male patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 78.2.3** Posteroanterior projection of severe myocardial bridging in diastole **(A)** and systole **(B)**. (Courtesy of Dr. David Lewis.) Posteroanterior cranial projection of mild bridging in diastole **(C)** (*arrow*) and systole **(D)** (*arrow*). LAD, left anterior descending artery. (Courtesy of Dr. Tom McRae.)

Collateral Circulation

When an occlusion or severe narrowing of a coronary artery develops, collateral channels may form from a nearby artery to supply blood to the hypoperfused area of myocardium (eFig. 78.2.4). Although it may be confusing on a two-dimensional image, as a general principle, collaterals form between arteries that are situated on the same area of the heart, and such connections cannot form if a cardiac chamber is superimposed in between. For example, collateral development via septal perforators is common between the LAD and PDA when one of these vessels is occluded. Occasionally, a separate conus branch arising near the RCA supplies collaterals to the LAD; identification is important if consideration is being given to bypass surgery targets. Kugel's artery is a small vessel that arises from the proximal RCA or LCx, or both, and traverses the interatrial septum; it commonly terminates near the crux, where it may act as a source of collaterals to the distal RCA or LCx via the atrioventricular nodal artery. Just as collaterals may develop between different coronary arteries, intracoronary collaterals, so-called bridging collaterals, may form from the same coronary artery across an area of total vessel occlusion. Identification of such bridging collaterals and recognition of an underlying chronic total occlusion are important. Although rare, pericardial or bronchial arteries may provide coronary collaterals (14). When collaterals are present from more than one source, competitive flow from both sources may occur, leading to inadequate opacification of the target vessel; this may produce the false appearance of a significant luminal obstruction at the point where the two collateral flows meet.

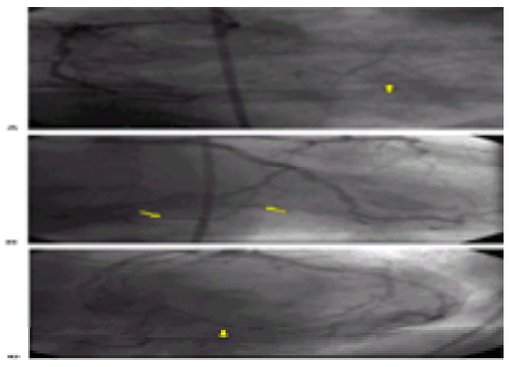
VIDEO

Video 78.5 Cine of collateral circulation from two sources **(A,B)** to a normal vessel. (Courtesy of Dr. Abdul Albirini and Dr. Irving Franco.) *This video must be viewed*

with QuickTime. If you do not have QuickTime you may download it here.

Video 78.6 Cine of collateral circulation from two sources **(A,B)** to a normal vessel. (Courtesy of Dr. Abdul Albirini and Dr. Irving Franco.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

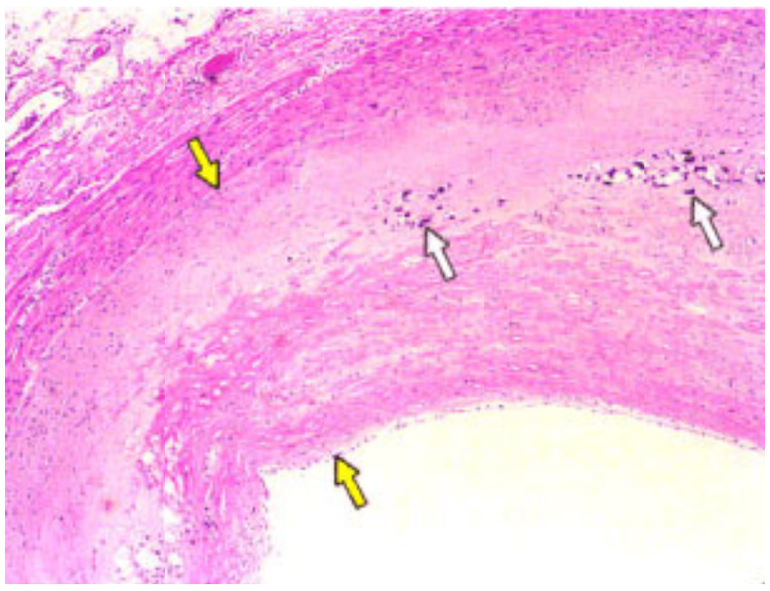
Video 78.7 Collaterals from the circumflex obtuse marginal to the posterior descending coronary. In this right anterior oblique projection, well-formed collaterals lead from the proximal obtuse marginal to the posterior descending artery. The posterior descending artery is highlighted by an arrow and can also be identified from the small septal perforators arising from this vessel. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



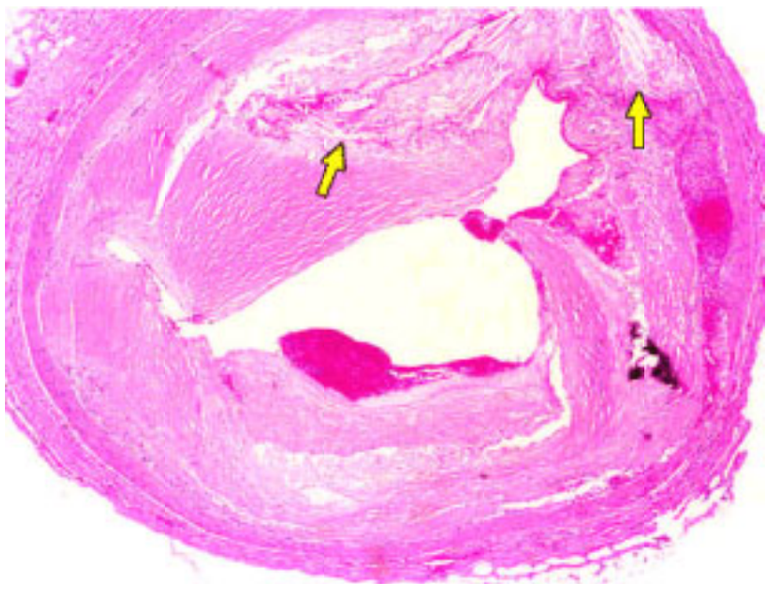
***e*FIGURE 78.2.4** Collateral circulation. **A:** Angiogram demonstrating collateral flow (*arrow*) from the right coronary artery supplying the area beyond occlusion of the left circumflex artery. (Courtesy of Dr. Mark A. Robbins.) **B,C:** Collaterals (*arrows*) from the atrioventricular left circumflex artery to the distal right coronary artery.

Lesion Assessment

An important component of coronary angiography is the description of coronary artery stenoses. Historically, lesions of at least 70% diameter stenosis of a coronary artery (50% diameter stenosis of the LM coronary artery) are considered hemodynamically significant. For the purposes of many research studies, 50% or greater stenosis constitutes significant coronary artery disease. However, the realization that the majority of myocardial infarctions are due to stenoses of less than 50% severity underscores the importance of the identification of milder degrees of atherosclerosis. Thus, the term *clean coronary arteries* is best avoided, because the absence of hemodynamically significant lesions does not preclude plaque rupture and a future ischemic event.



Advanced coronary atherosclerosis. There is fibrotic intimal thickening marked by the yellow arrows with small areas of intimal calcification (*white arrows*).

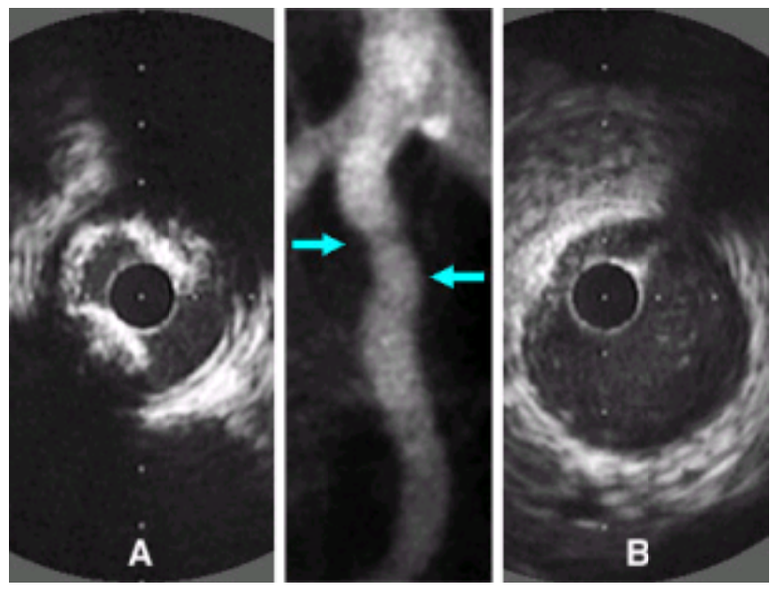


Severe fibrocalcific atherosclerosis. This is a hematoxylin-eosin stained specimen showing significant luminal narrowing with prominent cholesterol clefts within the atheromatous material (*yellow arrows*). The irregular lumen suggests remote thrombosis with recanalization.

Video 78.8 Ostial left main coronary artery disease. Contrast injection reveals severe narrowing of the ostium of the left main coronary artery. In this patient, after coronary artery bypass graft surgery there was rapid acceleration of the underlying coronary disease leading to this left main stenosis. *This video must be viewed with*

QuickTime. If you do not have QuickTime you may download it here.

Video 78.9 Left anterior oblique caudal view of the left main trunk showing severe ostial stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



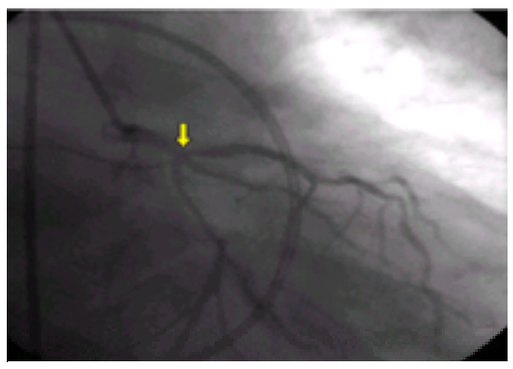
Limitations of angiography. Haziness in angiogram (*top arrow*) corresponds to lesional calcium (A). In comparison, a site just distal to the lesion (*bottom arrow*, B) remains within normal limits.

In addition to the percent diameter stenosis, the morphology and length of the lesion are important and should be described. The presence of calcification, angulation, eccentricity, or ulceration should be noted, because these characteristics may have an impact on the ability to perform percutaneous intervention (15) (eFig. 78.2.5). Any angiographically apparent thrombus should be mentioned (eFig. 78.2.6). However, the absence of thrombus on an angiogram does not mean that none is present, because angiography is a relatively crude method to detect thrombus (16). The size of the vessel should also be described, because lesions in vessels that are smaller than 1.5 mm usually do not warrant bypass surgery or angioplasty. Lesion size can be estimated by comparison with the size of the catheter. A 6-French (Fr) catheter is approximately 2 mm in external diameter (0.33 mm per Fr size). Automated quantitative coronary analysis is now commonly available and can be used to quantitate stenosis severity and length with more consistency than visual estimation (17).

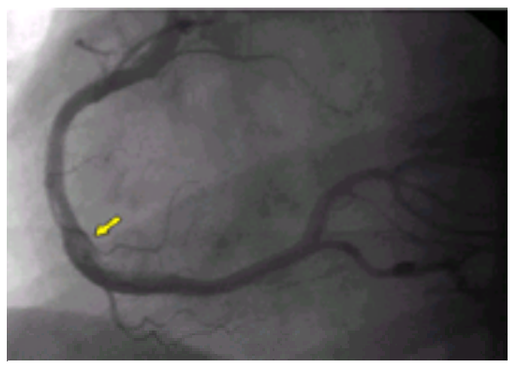
Video 78.10 A 67-year-old male patient with calcified lesion involving the left anterior descending artery and diagonal branch. Subsequent use of rotablator resulted in perforation of the left anterior descending artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.11 The angiographic characteristics of a lesion are important to characterize the risk associated with treating the lesion percutaneously. Left anterior oblique angiogram showing eccentric ulcerated lesion in a saphenous vein graft to the posterolateral branch of the left circumflex coronary artery. (Courtesy of Dr. Debabrata Mukherjee.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.12 A 59-year-old male patient with acute inferior myocardial infarction. Large angiographically visible thrombus in the mid-portion of the right coronary artery distal to a severe stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 78.2.5** The angiographic characteristics of a lesion are important to characterize the risk associated with treating the lesion percutaneously. Severe distal left main coronary artery stenosis (*arrow*) in a patient who ultimately went on to have bypass surgery.



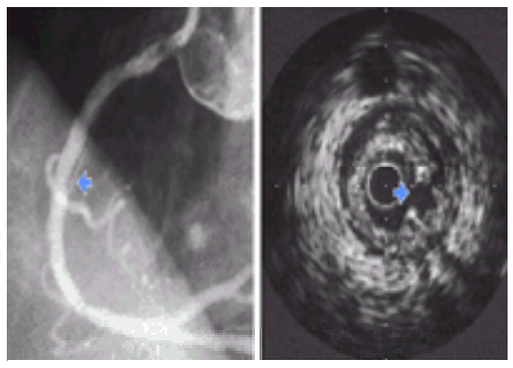
***e*FIGURE 78.2.6** Large angiographically visible thrombus (*arrow*) in the midportion of the right coronary artery distal to a stenosis in a patient with acute inferior myocardial infarction.

The modified American College of Cardiology (ACC)/American Heart Association scoring system incorporates multiple angiographic features of coronary obstructions, which helps the cardiologist stratify the risk of angioplasty (18). Lesions that are categorized as *type A* are simple lesions, *type B1* refers to moderately complex lesions, and *B2* signifies a higher degree of complexity than B1. Type C refers to complex lesions, in which angioplasty is less likely to be technically successful and more likely to be associated with complications. Even in the era of stenting, this scoring system appears to be a useful mode of categorizing lesions (19,20). The degree of flow should also be described for acute lesions using the Thrombolysis in Myocardial Infarction (TIMI) flow grade (21). In this scheme, TIMI grade 0 flow refers to no flow past the culprit lesion, and TIMI grade 1 flow refers to penetration of contrast just beyond the lesion, but not into the distal vessel and vascular bed. TIMI grade 2 flow refers to flow that reaches the distal vasculature, but at a slower than normal rate compared with nonculprit arteries. TIMI 2 flow can be further categorized into TIMI 2A, in which dye reaches the distal bed within five systolic cycles; TIMI 2B in which dye reaches the distal bed in more than five cycles; and TIMI 2C, in which inflow is normal but dye washout is slowed (22). TIMI grade 3 refers to normal angiographic flow. The corrected TIMI frame count is a newer method to describe flow, which is more reproducible than the TIMI grading system and may have incremental value (23,24 and 25). Other refinements to angiographic assessment of perfusion such as the TIMI myocardial perfusion grade, which quantifies myocardial blush, are being developed (26).

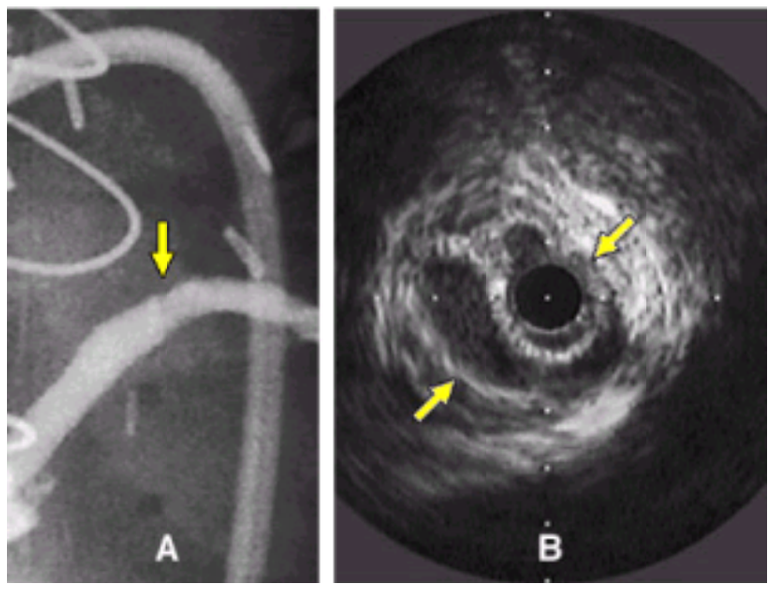
VIDEO

Video 78.13 Angiogram demonstrating TIMI 1 flow. (Courtesy of Dr. Debabrata Mukherjee.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

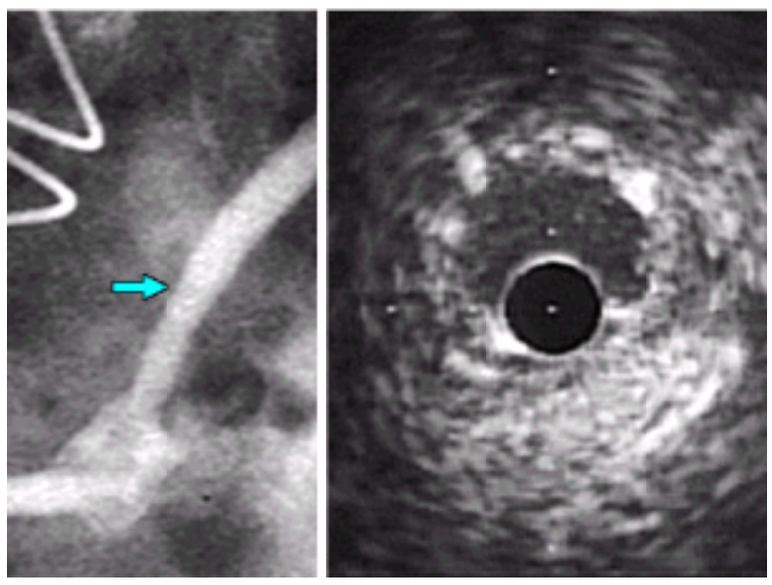
Adjunctive diagnostic modalities that should be considered for ambiguous or indeterminate coronary artery stenoses include intravascular ultrasound (IVUS) and fractional flow reserve (FFR) measurement. IVUS is able to provide a quantitative assessment of luminal dimensions in moderate angiographic lesions. Another insight that IVUS has provided is that the coronary angiogram is truly just a “luminogram” (27). Extensive atherosclerosis may be present with no obstruction detected on angiography (*e*Fig. 78.2.7). The phenomenon of outward remodeling may lead to preservation of the coronary lumen, despite significant plaque burden (28). IVUS enables the angiographer to determine whether remodeling has occurred. Although IVUS may provide better anatomic detail about coronary stenoses, the hemodynamic significance of a lesion may be better assessed by the FFR. Measurement of the FFR allows performance of stress testing in the catheterization laboratory with infusions of vasodilators such as adenosine.

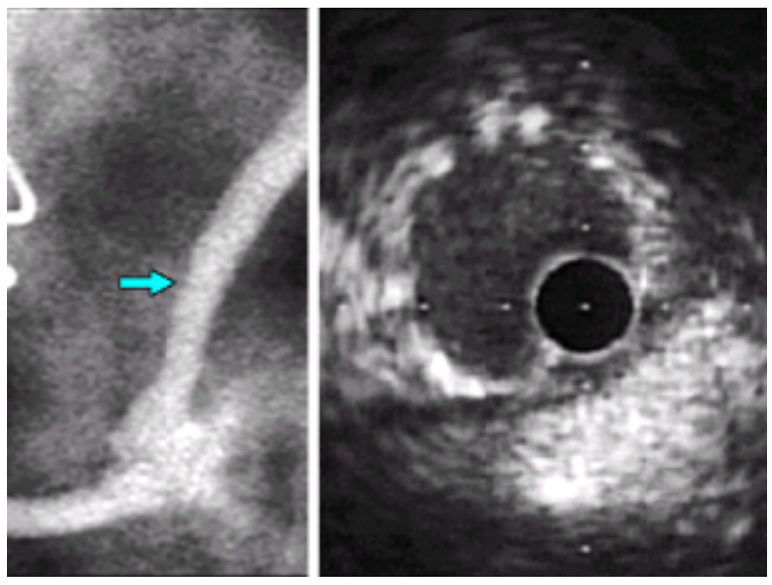


***e*FIGURE 78.2.7** Eccentric coronary artery stenosis (*arrows*). Because of the complex three-dimensional nature of this severe stenosis, single, or even multiple, two-dimensional angiograms may easily underestimate the true severity of the lesion.



Limitation of angiography: A minor angiographic luminal irregularity is present at the distal end of a stent (A, *arrow*) in a saphenous vein graft. IVUS (B) shows a dissection with two flow channels. The arrow at 2 o’clock shows the true lumen containing the imaging catheter, and the arrow at 7 o’clock indicates the false lumen.

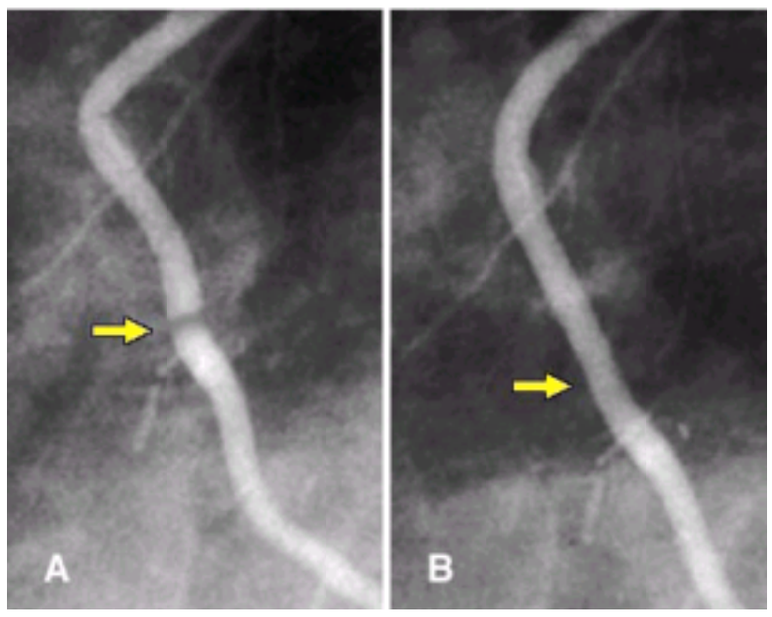




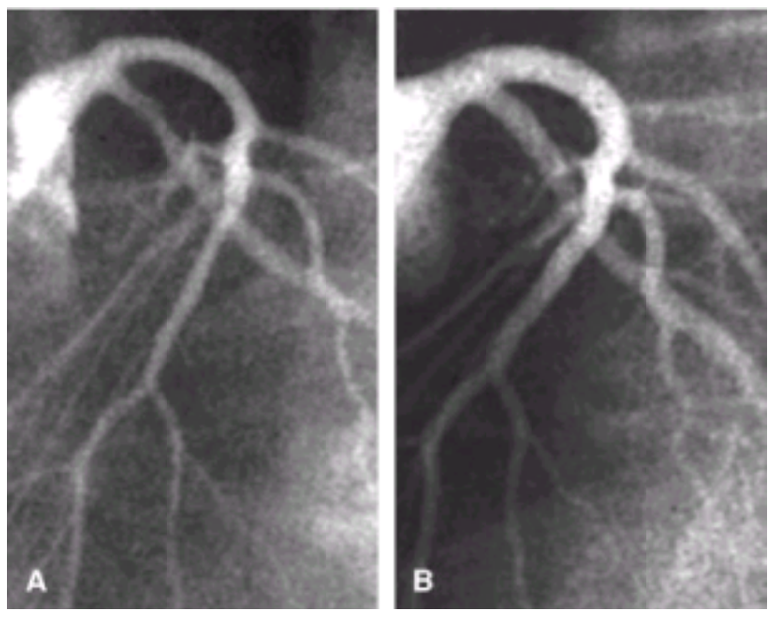
Role of intravascular ultrasound in optimizing stent deployment. Although the angiogram shows minimal residual stenosis (A), the intravascular ultrasound lumen size is small (<5 mm^2). After further dilatation (B), the lumen area increased to >7 mm^2.

Coronary Artery Spasm

Prinzmetal's angina or *variant angina* refers to the syndrome of coronary artery spasm that causes transient ST-segment elevation during angina (29,30). This may result in anginal chest pain at rest, often in the early morning, as well as syncope from heart block or ventricular arrhythmias. The coronary arteries of these patients are predisposed to spasm, often despite the absence of angiographically severe atherosclerosis. Prinzmetal's angina is rare, and it is recognized clinically even less often than in the past due to the advent of calcium channel blockers and long-acting nitrates (31). In patients with no significant atherosclerosis but a suspicion of spasm, Holter monitoring may reveal ST-segment shifts that verify the diagnosis. If angina occurs concurrent with ST-segment elevation in a patient with a "normal" catheterization, the diagnosis is made, with no need for confirmatory provocative testing.



Spasm of the left internal mammary artery after bypass surgery. In the left panel, a significant stenosis is evident that is completely resolved after administration of nitroglycerin. Spasm of the left internal mammary bypass graft can lead to ischemia in the perioperative period after coronary surgery.



Spasm of the left main coronary artery and proximal left anterior descending and left circumflex coronary arteries. The caliber of the left main, proximal left anterior descending, and circumflex arteries are smaller than the distal vessels. This can be better appreciated after administration of intracoronary nitroglycerin.

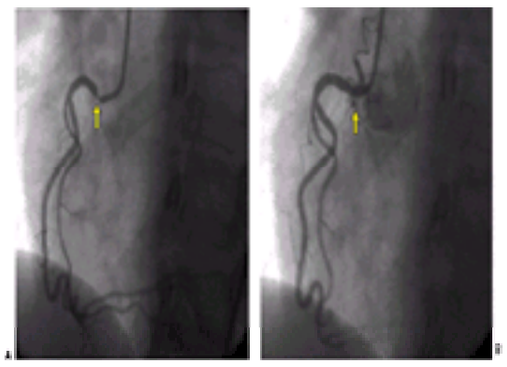
Provocative testing for coronary artery spasm is most likely to be clinically useful in the patient with no severe coronary artery obstructions, in whom it has been impossible to document the diagnosis. It is not likely to be useful in patients with fixed severe coronary obstructions, and the risk of testing is increased in these individuals. The major risk of provocative testing is unrelenting spasm, with subsequent myocardial infarction. Therefore, when this test is performed, intraarterial nitroglycerin and calcium channel blockers should be immediately available. The method to perform provocative testing involves administration of 0.05 mg intravenous (i.v.) methylergonovine while monitoring a complete electrocardiogram every minute (32,33). If typical chest pain or electrocardiographic changes develop, the coronary arteries should be reimaged immediately. The location of the ST elevation should guide which coronary artery to image first. If there is no ST elevation, the RCA should be catheterized first, because it is more likely to be the culprit. Five minutes after the methylergonovine has been administered, if there has been no chest pain or electrocardiographic changes, the coronary arteries should be reimaged. If there is no evidence of spasm, 0.2 mg methylergonovine should be administered and the above procedure repeated. Some operators prefer to omit the 0.05-mg dose to save time. If spasm does occur, 100 to 200 µg nitroglycerin should be administered intraarterially to relieve the spasm, and the diagnosis is made. Intracoronary acetylcholine is another provocative agent for coronary spasm, but it probably lacks the specificity of methylergonovine.

VIDEO

Video 78.14 Severe diffuse spasm of the right coronary artery after administration of ergonovine. In this example, the right coronary artery is significantly reduced in caliber with several areas of focal "stenosis." *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.15 Resolve spasm of the right coronary artery. This cineangiogram was obtained after administration of intracoronary nitroglycerin and shows resolution of the spasm. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Diffuse spasm that occurs without angina or ST-segment changes may be physiologic and is not diagnostic of Prinzmetal's angina. Methylergonovine-induced severe coronary spasm may recur after immediate treatment because of the longer half-life of methylergonovine compared with nitroglycerin; therefore, the patient should be observed and treated with systemic long-acting nitrates and calcium channel blockers (34). Provocative testing should be avoided in patients with severe systemic or pulmonary hypertension, as well as in patients who may be pregnant. Spasm may also be an etiology of chest pain or myocardial infarction after acute alcohol ingestion or cocaine use, in which cases the clinical history is useful in making the diagnosis (35). Nonischemic, "catheter-induced" coronary spasm, especially ostial spasm, may be triggered by the catheter tip (eFig. 78.2.8).



***e*FIGURE 78.2.8** Catheter tip spasm of the ostium (*arrows*) of the right coronary artery **(A)** before and **(B)** after intracoronary nitroglycerin. (Courtesy of Dr. Marc S. Penn.)

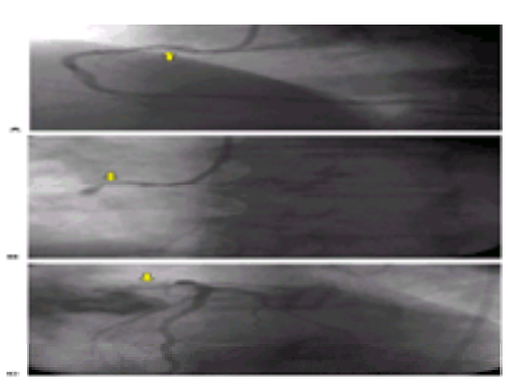
Coronary Artery Dissection

Rarely, spontaneous coronary artery dissection produces an ischemic syndrome or sudden death (36). Much of what is known about this entity is from case reports in the literature, with no one center having enough experience to make definitive statements about its etiology or natural history. Predisposing factors include pregnancy, a burst of intense physical exertion, and cocaine use (37,38). Pregnant or postpartum women are the demographic group in which spontaneous coronary artery dissection is most commonly seen, and the LAD is the vessel that is most frequently involved (39). Severe hypertension may also predispose to spontaneous dissection (40). Although not exactly spontaneous, blunt trauma, such as from a motor vehicle accident, may also lead to dissection (41). Aortic dissection may also extend into the coronary arteries, particularly the RCA. Marfan's syndrome may be complicated by coronary dissection, as may connective tissue disorders such as Ehlers-Danlos syndrome. Arteritis, such as that due to polyarteritis nodosa, may lead to dissection (42). Additionally, dissection may occur as a result of catheter trauma. It is important to recognize this entity, which may appear as a radiolucent flap in the opacified artery or as a linear persistent stain in the arterial wall after the contrast material has cleared from the true lumen (*e*Fig. 78.2.9).

Video 78.16 A 55-year-old female patient with atypical angina. JR4 catheter engagement resulted in a large spiral dissection **(A)**. The dissection was successfully treated with coronary stenting **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.17 A 55-year-old female patient with atypical angina. JR4 catheter engagement resulted in a large spiral dissection **(A)**. The dissection was successfully treated with coronary stenting **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

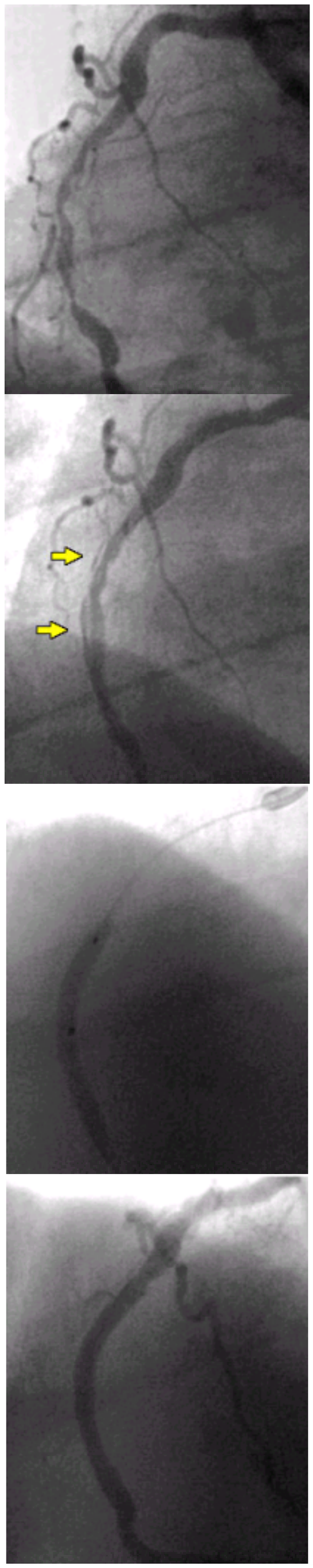
Video 78.18 Iatrogenic aortic dissection after balloon angioplasty of the ostial right coronary artery with a cutting balloon in a 77-year-old female patient. The patient needed emergent surgical repair for a type I aortic dissection. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 78.2.9** Catheter-induced coronary artery dissection. **A:** Noncoaxial alignment of catheter tip with ostial right coronary artery (*arrow*) in left anterior oblique view. **B:** Flow-limiting dissection of right coronary artery (*arrow*) (same patient as in **A**). **C:** Left anterior oblique view of left main coronary artery dissection due to noncoaxial alignment of the catheter tip (*arrow*). (Images courtesy of Dr. Leslie S. Cho.)

Regardless of the cause, dissection can often be treated percutaneously with stent deployment (43,44). Although healing of dissection with conservative treatment has been reported, this approach is less common in the interventional era (45). In some instances of postpartum dissection, immunosuppressive therapy has been used with success (46). Eosinophils appear to be present in the dissection plane in cases of peripartum dissection, similar to peripartum cardiomyopathy, suggesting an inflammatory etiology in at least some instances (47). The plane of dissection is often between the media and adventitia of the vessel, although in some cases, an

intimal tear is noted at autopsy. Some cases of spontaneous dissection, especially in older individuals at risk for atherosclerosis, are probably due to plaque rupture and intimal dissection (48).

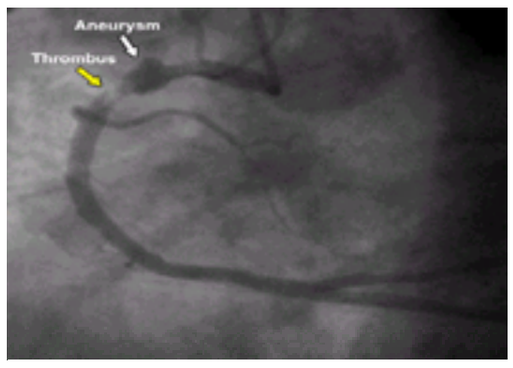


“Bailout” stent placement for a long dissection complicating balloon angioplasty. After balloon angioplasty of a long lesion of the mid-right coronary artery (A), a long linear dissection flap is apparent (B, *arrows*). A 39-mm-long AVE stent is deployed across the area of dissection (C). No residual stenosis is present after stent placement (D).

Coronary Artery Ectasia and Aneurysm

Coronary artery ectasia refers to an abnormal enlargement of the coronary arteries (eFig. 78.2.10). Arteries that are ectatic appear to be prone to thrombus formation, dissection, and spasm (49). Additionally, prior percutaneous intervention occasionally leads to development of segments of ectasia. When the area of dilatation is more than 1.5 times the diameter of the normal portion of the artery, the enlarged portion is referred to as an *aneurysm* (50). The RCA is the vessel that is most frequently involved. Atherosclerosis is the most common cause of coronary ectasia and aneurysm (51). Kawaski’s disease may lead to formation of giant coronary artery aneurysms in approximately 20% of untreated patients (52,53,54 and 55). Mycotic aneurysms of the coronary arteries occur rarely (56). Historically, large coronary artery aneurysms have been treated conservatively with antiplatelet or anticoagulant therapy, or both, but, more recently, surgery as well as intracoronary stent graft

deployment have been used (57,58). When there is an associated stenosis, invasive treatment may be indicated.



***e*FIGURE 78.2.10** Left anterior oblique view of coronary artery aneurysm (*white arrow*) in proximal right coronary artery, with angiographic lucency present just beyond the aneurysm, consistent with thrombus (*arrow*). (Courtesy of Dr. Leslie S. Cho.)

Video 78.19 Coronary ectasia. These angiograms were obtained in a 40-year-old patient with Noonan's syndrome and no coronary risk factors. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.20 Aneurysmal atherosclerotic disease involving the left main trunk, proximal left anterior descending artery, and proximal left circumflex artery in a 72-year-old male patient with a long history of smoking. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Physical features in Kawasaki's disease. These are capillary hemangiomas (*yellow arrow*).

Indications for Coronary Angiography

Coronary angiography is indicated when there is a need for delineation of coronary artery anatomy. The ACC has published guidelines to assist the clinician in appropriate use of this invasive procedure (59) (Table 78.1). Indications are listed as class I when there is general consensus that angiography is indicated, class II when there is a divergence of opinion, and class III when there is consensus that angiography should not be performed. The guidelines are useful as a starting point for discussion about evidence supporting angiography for specific indications. In a patient with anginal chest discomfort and evidence of ischemia on a functional study, coronary angiography may reveal a stenosis that is amenable to angioplasty or coronary artery bypass surgery (class I). In a patient with an acute coronary syndrome, angiography is given a class II indication. However, emerging evidence supports an invasive approach in the initial evaluation of patients with acute coronary syndromes (60,61). The development of pharmacologic adjuncts, such as the glycoprotein IIb/IIIa inhibitors, has enhanced the safety of percutaneous intervention and broadened the indications for cardiac catheterization. Thus, the ACC guidelines provide a framework for the practice of evidence-based medicine but do not substitute for clinical judgment, and they do not necessarily incorporate the most current research.

TABLE 78.1 INDICATIONS FOR CORONARY ANGIOGRAPHY

Contraindications o Coronary Angiography

The only absolute contraindication to coronary angiography is patient refusal. According to the ACC classification, indications that are labeled as class III are actually situations in which coronary angiography is contraindicated (Table 78.1). Common sense supports these recommendations. Additional relative contraindications are shown in Table 78.2. It should be emphasized that *relative* contraindications imply that in certain urgent clinical circumstances, proceeding with angiography may be appropriate, although caution must be exercised.

Renal insufficiency
Bleeding diathesis or active bleeding
Fever or active infection
Aortic valve vegetation
Anemia
Severe dye allergy
Metabolic abnormalities
Hyperkalemia
Hypokalemia
Digitalis toxicity
Uncontrolled hypertension
Decompensated heart failure
Uncontrolled tachyarrhythmia
Untreated high-grade heart block

TABLE 78.2 RELATIVE CONTRAINDICATIONS TO CORONARY ANGIOGRAPHY

Operator Proficiency

The ACC has set minimum training requirements for the performance of diagnostic angiography. During cardiology fellowship, each trainee must perform 300 diagnostic coronary angiograms while serving as the primary operator on 200. Operator and institutional procedure volumes are linked to outcomes in the catheterization laboratory (62). After training is completed, a minimum yearly volume of 150 diagnostic catheterizations per year for each angiographer has been recommended, although more recently the number has been revised to 100 (63). It is desirable to have cardiac surgical backup nearby (64). Although nonphysicians may assist in coronary angiography, they should not function as independent operators (65). Additionally, performance standards for cardiac catheterization laboratories have been established. Principally, this involves monitoring of procedural outcomes to ensure that some degree of internal review of complications occurs (66,67).

Informed Consent

The risks, benefits, and alternatives to coronary angiography should be discussed with the patient and also the family, if possible. Specifically, the risk of death, stroke, myocardial infarction, renal failure, or emergency coronary bypass surgery should be discussed. Notation of this discussion should be made in the medical record to satisfy the legal requirements for “informed consent.” In particular, consideration should be given for noninvasive assessment of coronary artery disease, if this can be substituted for initial diagnostic angiography. A discussion about percutaneous intervention and its greater level of risk should also occur at this time. Separate informed consent should be obtained for this procedure, because many patients who undergo diagnostic angiography proceed to angioplasty at the same setting.

Preprocedural Medication

Aspirin, 325 mg, should be given to eligible patients before the procedure in case an angioplasty is necessary. If the probability of percutaneous intervention seems high, a loading dose of clopidogrel, 300 mg, can also be given. Metformin (Glucophage) should be discontinued on the day of the procedure, because this medication may cause lactic acidosis if renal failure results from the procedure and if metformin is continued after the onset of renal failure (68). Warfarin should be stopped before the procedure if possible until the international normalized ratio is less than 1.8. If anticoagulation is essential, warfarin can be stopped several days before the anticipated procedure, and subcutaneous injections of the low-molecular-weight heparin, enoxaparin (1 mg per kg b.i.d.), can be substituted; the dose of enoxaparin can then be withheld the morning of the procedure.

Sedation

Conscious sedation is generally administered during cardiac catheterization procedures. Proper sedation increases the likelihood of the procedure going smoothly. This important part of the procedure is often overlooked. Lack of adequate sedation may lead to an uncooperative patient, as well as increases in blood pressure and a greater tendency to vagal reactions. Before the catheterization, the patient should be assessed for suitability for conscious sedation. Specifically, the airway should be examined. Certain patients, such as those with sleep apnea or a body habitus that suggests a predisposition to sleep apnea, should be sedated with caution. During the procedure, continuous pulse oximetry must be performed, with oxygen supplementation as necessary. Again, preprocedural assessment should include evaluation for pulmonary diseases that may predispose to hypopnea and elevations of carbon dioxide levels with oxygen supplementation. Similarly, continuous electrocardiographic monitoring and blood pressure measurement with an automated blood pressure cuff maximize the safety of conscious sedation.

A benzodiazepine or opiate can be used for initial sedation. Frequently, a combination achieves excellent patient comfort. The benzodiazepine may also provide some degree of retrograde amnesia such that the patient does not recollect any unpleasant aspect of the procedure. The benzodiazepine of choice is midazolam (Versed) because it has a rapid onset but is short-acting. An initial dose of 0.5 mg or 1.0 mg i.v., with repeat dosing every few minutes, may achieve sedation safely. Fentanyl, a short-acting agent, can be used for the opiate. A dose of 25 or 50 µg i.v. can be used initially. For more prolonged cases, morphine, at a dose of 1 to 3 mg i.v., can be substituted as the opiate if the patient has tolerated the initial fentanyl.

Radiation Principles and Safety

Most catheterization laboratories have already moved to digital image acquisition, distribution, and archiving. A major factor enabling this transition has been the widespread adoption of the Digital Imaging Communication in Medicine (DICOM) standard (69). In addition to improving image quality, digital imaging may lower radiation exposure to the operator by approximately 20%. Retrieval of angiographic information and transfer of data among physicians are also easier, because a typical catheterization study may easily fit on a single CD or be distributed rapidly on a high-bandwidth network.

Efforts to reduce radiation exposure to the angiographer and patient are important because the cumulative doses of radiation with repeated exposures can produce direct tissue injury (deterministic effects) and neoplasms (stochastic effects). Risk reduction efforts fall into two major categories: radiation protection (usually protection of the operator from radiation exposure) and radiation production. All efforts aimed at reducing radiation exposure must take into account their effects on the operator, patient, and image quality. These effects are often discordant—that is, maneuvers that decrease radiation exposure to operators and patients may degrade image quality. These effects are summarized in *e*Table 78.2.1.

***e*TABLE 78.2.1** FACTORS AFFECTING IMAGE QUALITY AND RADIATION EXPOSURE TO LABORATORY PERSONNEL AND PATIENT

Method	Operator dose	Patient dose	Image quality
Patient, operator protection			
Lead gown, thyroid collar	Lower	Same	Same
Leaded glasses	Lower	Same	Same
Lead shield above, below table	Lower	Same	Same
Increased distance from operator to table	Lower	Same	Same
Femoral vs. brachial approach	Lower	Same	Same
Operator’s fingers out of direct beam	Lower	Same	Same
Move patient’s arm out of field	Lower	Lower	Better
Radiation dose reduction			
Shorter fluoroscopy, cine times	Lower	Lower	Same
Pulsed fluoroscopy	Lower	Lower	Same
Fewer pulses/sec	Lower	Lower	Worse
Fewer cine frames/sec	Lower	Lower	Worse
Greater distance from source to patient	Variable	Lower	Better
Smaller distance from image intensifier to patient	Lower	Lower	Better
Electronic image magnification	Variable	Higher	Better
Smaller collimator opening	Lower	Variable	Better
Cranial, caudal angulation	Higher	Higher	Worse
Large patient, pleural effusion	Higher	Higher	Worse

Radiation protection for the operator is accomplished by a variety of shielding and positioning mechanisms. A thyroid collar and lead apron provide excellent protection

for the operator's thyroid (which decreases the likelihood of thyroid cancer) and trunk. Leaded glasses should be worn because radiation exposure increases the risks of cataracts; a headband may make these heavy glasses less uncomfortable. The catheterization table should be equipped with two lead shields: one for the lower body and an adjustable leaded glass shield to protect the operator's upper body and head. Doubling the distance of the operator from the x-ray entrance beam site reduces the operator's dose to one-fourth. The femoral approach, in which the operator is farther away from the site of radiation, is likely to decrease the operator's exposure compared to the brachial approach. Operators should never permit repeated or prolonged exposure of their fingers in the direct field of radiation, except for extreme emergencies.

Radiation protection for the patient can be provided by avoiding unnecessary radiation exposure to body parts that are not essential to the study. For instance, in angulated views, the patient's arm commonly enters the field of view. Displacing the arm decreases radiation dose to the patient and operator and improves image quality. If a female patient is pregnant, a lead shield placed between the x-ray source and the patient's pelvis may provide some protection, but it functions primarily as a reminder to the operator to avoid fluoroscopy in the vicinity of the pelvis. Protection of the fetus is limited because most of the radiation that the fetus receives is due to scatter radiation, and the lead shield serves only to increase the x-ray dosage to penetrate the shield if fluoroscopy is performed directly over the shielded part of the body.

Radiation production can be reduced by a variety of methods, but care must be taken to achieve adequate image quality. A trade-off is commonly made between radiation dose and image quality (eTable 78.2.1). The operator should manipulate radiation dosage to produce the minimum image quality that is required for the task at hand. For instance, high image quality is generally not needed for passage or placement of catheters, whereas it is usually required for recording of diagnostic information.

Radiation dosage to the patient and operator can be reduced with no change in image quality by shortening the fluoroscopy and cine times and by using pulsed fluoroscopy. The amount of dose reduction that is obtained with pulsed fluoroscopy depends on how the manufacturer configures the equipment. It is possible to achieve large dose reductions, but at the expense of reduced image quality. Reducing the number of fluoroscopy pulses per second and the number of cine frames per second by 50% reduces dose to the patient and operator, but the former produces flicker, and the latter reduces the information content of the study by 50%. Cineangiography leads to greater radiation exposure per second than fluoroscopy. Increasing the distance between the x-ray source and the patient not only improves image quality, but it also reduces the x-ray intensity at the patient's skin and the likelihood of skin injury. For this reason, federal regulations mandate a spacer device mounted on the x-ray tube to maintain a minimum distance of 38 cm between the x-ray source and the end of the spacing device.

Positioning the image intensifier as close as possible to the patient reduces radiation exposure to the patient and the operator, and it improves image quality. The farther the image intensifier is positioned from the patient, the larger the image becomes, because of geometric magnification, but image quality deteriorates as a result of blurring, and the dose increases with the square of the magnification. Electronic image magnification is achieved by decreasing the field-of-view size [e.g., changing from the 9-in. (23-cm) or 7-in. (17-cm) field to the 5-in. (13-cm) field]. Unless collimation is used in the larger field size, changing from the 7-in. mode to the 5-in. mode approximately doubles the entrance dose to the patient, has no major change on dose to the operator, and produces greater spatial resolution. The 5-in. mode is usually optimal for visualizing small coronary arteries.

Radiographic views obtained in LAO, lateral, or steeply angulated cranial or caudal projections result in decreased image quality and increased radiation exposure to the patient and operator. The same applies to any factor that increases the thickness or density of tissue being penetrated, such as obesity, large body size, cardiomegaly, and pleural effusion. If image quality is poor in any of these circumstances, the operator may wish to obtain most images in the RAO projection, switch from the 5-in. to the 7-in. mode, or perform a thoracentesis before the procedure. Use of shields to cover the bright areas of the lungs may decrease radiation exposure and enhance image quality. The use of collimators to minimize the field size improves image quality and decreases scatter radiation to the operator but produces a slight increase in entrance dose to the patient. However, the dose-area product (the entrance dose multiplied by the area of exposure) decreases with collimation, which reduces long-term (stochastic) effects for the patient.

The radiation exposure from a single catheterization is rarely of significance to the patient. After prolonged fluoroscopy (usually in conjunction with prolonged or multiple interventional procedures) radiation dermatitis may rarely occur. This may manifest several hours to days after the procedure as an area of erythema, although weeks or months may pass before other effects of radiation on the skin, such as dermal atrophy or telangiectasia, are manifest.

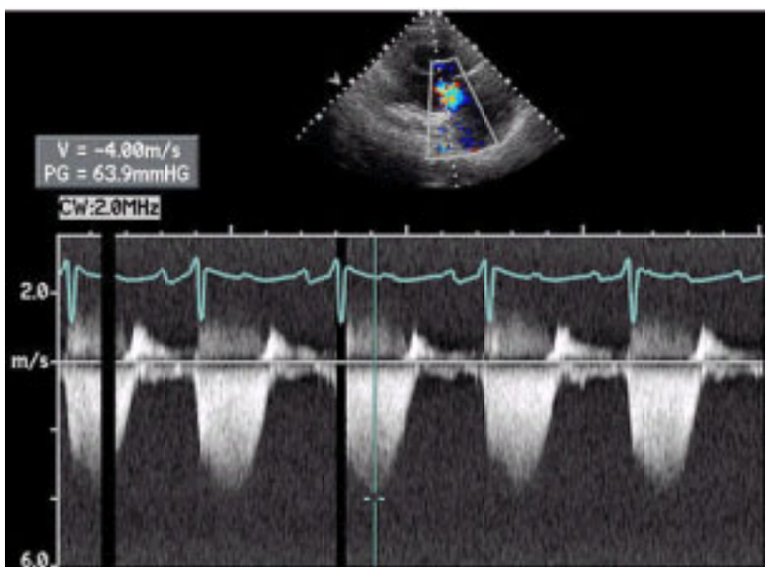
Angiographers must consider the "other side of the coin"—that is, image quality—as they reduce radiation dose. Subjective evaluation of angiographic image quality is unreliable. A new testing system has been introduced that permits standardized objective benchmarking of cardiovascular radiographic equipment performance (69a). This unique testing system permits evaluation of spatial and contrast resolution in relation to radiation dose in an anthropomorphic phantom. The clinical utility of this system remains to be validated.

Selection of Contrast Agents

Contrast agents are categorized based on their ionicity (either ionic or nonionic) and osmolality (high, low, or isosmolal). All intravascular radiopaque contrast agents contain iodine. Therefore, the iodine concentration of commonly used coronary angiographic contrast agents is within a similar range. Thus, an "allergy to iodine," likely an allergy to some other component of the contrast agent, should not influence the choice of contrast agent. The ionic, high-osmolal contrast agents include diatrizoate and metrizoate. Iogloxate is an ionic, low-osmolal agent. Iohexol, iopamidol, metrizamide, and ioversol are nonionic, low-osmolal agents. Iodixanol is a nonionic, isosmolal contrast agent. Several established factors should influence the choice of contrast agent. A major disadvantage of nonionic and low-osmolar contrast agents is their high cost. They may cost 10 to 20 times as much as ionic, high-osmolar agents, which may translate to an additional expense of a million dollars per year or more for a large-volume laboratory. There are numerous studies that contradict one another regarding purported benefits of specific contrast agents, making appropriate selection controversial in many circumstances. Complicating the issue further is the fact that many comparisons of newer contrast agents included older formulations of ionic, high-osmolal agents that are no longer in common clinical use.

Although nonionic contrast is more commonly selected by angiographers, high-osmolal, ionic contrast has been recommended as the first choice in the average patient (70). It is inexpensive and well tolerated by the majority of patients. Evidence suggests that nonionic contrast has less of an anticoagulant effect than ionic contrast and may thus be detrimental in patients with acute coronary syndromes (71,72). However, the COURT trial compared the isosmolar nonionic dye iodixanol with the low-osmolar ionic agent ioxaglate in patients with acute coronary syndromes and found a reduction in in-hospital adverse events with the nonionic agent (73). Thus, ongoing research may help determine optimal contrast agent selection.

Ionic contrast agents produce more myocardial depression than nonionic agents and also provide a greater osmotic volume load. High-osmolality ionic agents, especially in large volumes, may cause vasodilatation and hemodynamic deterioration in patients with LM coronary artery disease or aortic stenosis, and they may precipitate pulmonary edema in patients with significant left ventricular dysfunction. Thus, patients with LM coronary artery disease, severe aortic stenosis, or severe left ventricular dysfunction should receive as low a volume of nonionic contrast as possible (74). In addition to impairing contractility and affecting systolic function, contrast agents may impair ventricular relaxation, causing diastolic dysfunction and an increase in left ventricular end diastolic pressure (LVEDP). Unlike the deterioration in systolic function, which usually lasts only a few seconds to a few minutes, the diastolic dysfunction may last for more than an hour. Severe pulmonary hypertension is another situation in which nonionic agents would be preferred. Nonionic agents cause less bradycardia; therefore, the patient who experiences marked heart rate slowing with a high-osmolality ionic agent should be switched to a nonionic agent. Nonionic agents are also less likely to provoke arrhythmias such as ventricular fibrillation; however, this risk should be less than 1 in 1,000 during diagnostic angiography with high-osmolality ionic agents. Rarely, the iodine content in contrast agents may provoke thyroid storm in patients with hyperthyroidism due to thyroid nodules (75).



Continuous wave Doppler trace through the tricuspid valve of a patient with pulmonary hypertension. The maximal jet velocity of 4 m/sec corresponds to a pressure gradient of 64 mm Hg or a PA pressure of approximately 80 mm Hg.

Nonionic agents are less likely to cause minor reactions such as nausea or flushing (76). It is therefore reasonable to use them in a patient who previously had a great deal of discomfort with ionic agents. For cerebral or peripheral arterial angiography, nonionic agents are preferred for patient comfort. With cerebral angiography in particular, contrast agents may cause transient visual changes and, even more rarely, neurologic changes. This risk is greater for higher-osmolality dyes. When such changes occur, usually time and hydration result in full resolution of symptoms. Additionally, injections of the IMA may be painful if ionic agents are used; therefore, nonionic agents should be substituted.

Evidence is conflicting regarding the frequency of renal failure in relation to the type of contrast used (77,78). However, in a patient with preexisting renal insufficiency, with a serum creatinine of 2.0 mg per dL or greater before the procedure, it is reasonable to use a nonionic contrast agent. Intravenous hydration with normal saline or 0.45% saline and maintenance of adequate hydration (100 mL fluid per hour or more) during and after the procedure reduces the risk of worsening renal function in patients with baseline renal insufficiency, particularly diabetics at risk of renal failure (79). No convincing evidence has been found that mannitol, furosemide, or dopamine is useful in preventing renal dysfunction (80). Concomitant nephrotoxins should not be administered. When renal failure occurs, it may not manifest for 24 to 48 hours; hence, the creatinine measurement the morning after the procedure may be of limited value. The rise in creatinine may not occur until at least 24 hours after the procedure, peaking approximately 5 days after the procedure and, commonly, resolving by the tenth day. Acetylcysteine has been shown to reduce the occurrence of contrast nephropathy in small studies, but this approach has not yet gained widespread acceptance (81). It is important to limit the quantity of contrast agent used in patients with chronic renal insufficiency (82). Limiting the quantity of dye to less than 30 mL markedly decreases the need for subsequent dialysis (83).

Patients, such as asthmatics, with any history of atopy are at increased risk of an allergic reaction to contrast. Despite what is commonly believed, allergies to seafood, such as shellfish, are no more predictive of allergy to contrast than a history of atopy or other allergies. Previous contrast reactions increase the risk of a subsequent reaction. Anaphylactoid reaction may occur with contrast agents, although there is no difference in the incidence among agents. In patients with previous life-threatening contrast reactions, nonionic agents should be used. The patient should be premedicated with steroids and diphenhydramine. Steroids are most useful when begun the day before the procedure, preferably at least 12 hours before (84). In severe cases, premedication may include histamine (H_2) blockers such as famotidine (Pepcid), 20 mg i.v. When a life-threatening reaction has occurred in the past and catheterization is necessary, it is useful to give 1 or 2 mL contrast agent first, observe the patient for any reaction, and then proceed with the case. If a reaction to a contrast agent occurs, the treatment depends on the severity of the reaction (85). The first priority should be maintenance of the airway, ensuring ventilation, and hemodynamic resuscitation. Inhaled beta-agonists or racemic epinephrine may be useful to alleviate bronchospasm. If severe hypotension occurs, i.v. saline should be administered rapidly for volume expansion. Epinephrine should be given subcutaneously at a dose of 0.3 mL of the 1:1,000 concentration (0.3 mg), or, for severe hypotension, 10 µg per minute of the 1:10,000 concentration should be continuously infused i.v. until the patient's condition stabilizes. Diphenhydramine and steroids should also be administered, although the steroids will not produce any effect for hours. If the patient can be stabilized, it is reasonable to continue and complete the angiographic procedure (85). When severe anaphylactoid reactions to contrast agents develop, they usually occur during the procedure. Rarely, reactions occur hours to days after contrast administration (86). These more delayed contrast reactions, unlike contrast reactions in the catheterization laboratory, may be due to antibody formation (87).

Latex allergy rarely produces an anaphylactic reaction that is clinically indistinguishable from a reaction to iodinated contrast. Patients should be questioned before catheterization regarding an allergy to latex. If a latex allergy is present, the patient should be premedicated with corticosteroids, and the catheterization should be conducted in a latex-free environment, as the first case of the day before latex particles may accumulate in the catheterization suite. If latex allergy is questionable, the patient should undergo testing.

TECHNICAL ASPECTS OF CARDIAC CATHETERIZATION

Technique

Cardiac catheterization involves multiple sequential steps, each fraught with potential hazards. The first step is gaining arterial access. After this, coronary angiography is performed. Next, left ventriculography and measurement of left ventricular pressures can be done. Aortography and imaging of the cerebral or peripheral vasculature can also be performed. Sterile surgical technique should be maintained throughout the procedure (88). This includes proper preparation of the access site with hair removal and skin cleaning and sterile draping. The operator should wear a surgical cap, gown, shoe covers, and facial mask.

Anesthesia

After adequate sedation, the access site should be anesthetized with 2% lidocaine. The anesthetic should be administered slowly so as to minimize the discomfort of the injection. Once the maximum pulsation of the artery is identified, an initial skin wheal can be raised with 1 to 2 mL of 2% lidocaine administered through a 25-gauge needle. Anesthesia should be administered more deeply with a 22-gauge needle, through which an additional 4 to 8 mL can be given. In patients who are obese or in whom the pulse is difficult to locate, the volume of the local anesthetic may obliterate the pulse. In this situation, it may be useful to mark the pulse with a finger or straddle the artery with a finger on each side, administer the local anesthetic, and, without moving the finger(s), cannulate the artery. If a patient is allergic to lidocaine, which is an amide agent, procaine, which is an ester agent, can be used instead. Bupivacaine, a preservative-free amide agent, is another alternative, especially if the allergy is believed to be due to the preservative component of the local anesthetic.

Femoral Arterial Access

The most common form of arterial access for cardiac catheterization in the United States is femoral cannulation. Typically, an 18-gauge, hollow beveled needle is used. Fluoroscopy should be used to facilitate puncture of the common femoral artery at the appropriate level. Rupp et al. (89) identified the target site as 1 cm lateral to the most medial cortex of the femoral head as seen on an anteroposterior (AP) projection (Fig. 78.3). This increases the likelihood of infrainguinal puncture as well as the ability to compress the puncture site against the femoral head after sheath removal. Puncture of the artery more cranially may be associated with a greater risk of retroperitoneal hemorrhage, whereas a more caudal puncture is associated with arterial entry below the femoral artery bifurcation and with pseudoaneurysm formation (eFig. 78.3.1). Use of the skin crease to determine the arterial entry site may be misleading, especially in the obese, in whom the skin crease is often well below the desired point of entry.

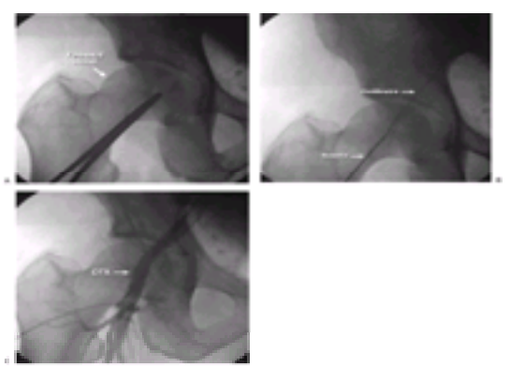
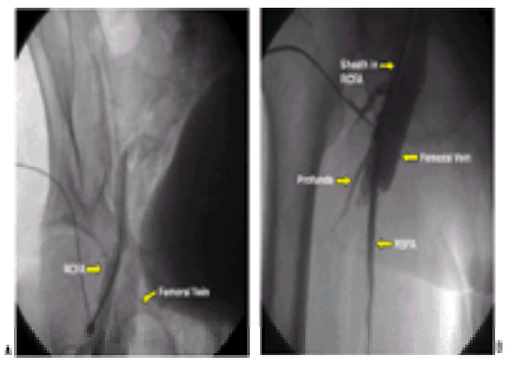


FIGURE 78.3 A: Fluoroscopic landmark for femoral artery cannulation in posteroanterior projection, marked with a hemostat. **B:** Cannulation of femoral artery and passage of guidewire. **C:** Angiogram shows the right common femoral artery and its relation to the femoral head in a posteroanterior projection. CFA, common femoral artery.



***e*FIGURE 78.3.1** Arteriovenous fistula of the femoral artery and vein, a potential complication of sheath placement. **A:** The sheath is in the right common femoral artery (RCFA). **B:** The right superficial femoral artery (RSFA) is also identified. (Courtesy of Dr. Albert W. Chan.)

The angle of entry of the needle is critical, with 30 to 45 degrees being the optimal range. A greater degree of angulation may cause problems during sheath insertion, leading to sheath kinking. Pulsatile blood flow should be obtained once the artery is effectively cannulated. Weaker degrees of blood flow could be due to subintimal position of the needle bevel or an awkward angle of the needle, with bevel abutting the vessel wall. In these situations, gentle manipulation of the needle backward or forward, or a slight change in angulation (usually a shallower angle), usually restores blood flow. In the presence of marked hypotension or severe peripheral vascular disease, blood return may not be brisk. In cases in which the pulse is not palpable, the Smart Needle, a flow needle attached to a Doppler probe, can be used to generate acoustic signals of arterial flow and facilitate puncture of the artery (90). It is helpful to use this device a few times in healthy arteries with a strong pulse before trying it for the first time on a nonpalpable one. It is relatively easy to puncture the posterior wall of the artery with this approach. Fluoroscopy can be used to locate the medial border of the femoral head, and this facilitates locating the artery. Often, with extensive peripheral vascular disease, fluoroscopic calcification is present in the vessel wall, further helping to identify the approximate location for needle entry. Old peripheral bypass grafts may also be calcified.

Once the artery is cannulated with the needle and pulsatile flow is obtained, a guidewire is passed through the needle. If resistance is encountered, fluoroscopy should be used to ensure that the wire tip is free, and undetected subintimal wire advancement is not occurring. The wire should follow a pathway to the anatomic left of the spine, unlike with venous cannulation, in which the wire follows the inferior vena cava to the right of the spine. With extensive vessel calcification or extensive scar tissue from previous procedures, resistance may be encountered during sheath advancement. Use of a small dilator, followed by progressively larger dilators, as well as a stiff wire, such as an Amplatz wire, may facilitate placement of the desired sheath size. This same technique can be used to enter Dacron grafts if they are at least 2 months old. After successful sheath placement, a blood pressure should be obtained and recorded from the sheath sidearm and correlated with the blood pressure cuff measurement. This allows detection of any aortoiliac disease, and it provides accurate documentation of the patient's arterial pressure.

Brachial or Radial Artery Access

Use of the radial artery for cardiac angiography has grown popular in certain European centers. Advantages of this technique include easy compressibility and shorter times to ambulation. Catheter manipulation may be slightly more difficult from the radial artery than from the femoral artery. Before cannulation of the radial artery, it is advisable to perform an Allen's test to ensure the adequacy of ulnar circulation to the hand. Another concern with radial artery cannulation is the possible need for this artery as a bypass graft conduit in the future.

Allen's test. To test the competence of the collateral circulation of the radial and ulnar arteries, a patient is asked to pump his or her hands after which both arteries are occluded (1). Then the pressure on one artery is released (2). Rapid return of blood flow signifies a normal response. The same steps are

repeated with the other artery (3). Final image is combined.

Although many operators attempt to cannulate the brachial artery at the level of the elbow crease, in approximately 10% of patients the brachial artery bifurcation is more proximal than this. Therefore, it is desirable to cannulate the brachial artery more proximally, a couple of centimeters above the skin crease. After sheath placement, approximately 2,000 to 3,000 units of intraarterial heparin can be given through the sheath if no pulse is palpable distal to the sheath. Some operators also give intraarterial nitroglycerin to prevent sheath spasm around the smaller-caliber radial artery. Specially designed micropuncture kits allow use of smaller equipment with the brachial or radial arteries.

Catheter Selection

The size of the catheter is largely a matter of physician choice and the size of the coronary arteries to be visualized; 6-Fr diagnostic catheters are commonly used. They provide good opacification, with easy manual injections of contrast. A 5-Fr system creates a smaller hole at the arterial access site, but adequate coronary artery opacification may be more challenging for the operator because “streaming” (incomplete mixing of contrast and blood) may occur, resulting in over- or underestimation of stenosis severity. A 4-Fr system can be used, in particular from the radial artery, but, again, coronary opacification and catheter manipulation may be problems. In certain circumstances, larger catheter sizes, up to 8 Fr, may be desirable, although this warrants a femoral approach or a brachial artery cutdown approach. If a patient has large coronary arteries or ectasia, it may be necessary to use one of the larger-bore catheters. This is also true of vein grafts, which may be quite large. Similarly, in any condition that leads to a state of increased coronary flow, such as aortic stenosis, aortic insufficiency, hypertrophic ventricular enlargement, dialysis, or tachycardia, better opacification may occur with a larger-bore catheter.

The initial catheter selected is the Judkins Left 4 (JL4) for the images of the left coronary system. The Judkins Right 4 (JR4) is next used to obtain images of the RCA. The size of the initial catheters selected depends on the aortic root. If there is a dilated aortic root or a large person, a JL5 or JR5 may be necessary. Similarly, if the aortic root is small, a JL3.5 or JR3.5 may be necessary. From the left brachial or radial artery, the standard Judkins catheters are usually adequate. However, from the right arm, multipurpose or Amplatz-type catheters are most useful. In an average-sized aorta, an AL2 is often the correct size for the LM, and an AL1 or AL2 is often appropriate for the RCA. Amplatz catheters are particularly useful if the origin of LM or RCA is more anterior, posterior, or superior than usual in the aorta. The multipurpose-A catheter is well suited for coronary artery ostia that have an inferiorly directed takeoff. Amplatz catheters are more likely than Judkins catheters to lead to ostial dissection due to their ability to engage the coronary arteries deeply. This risk can be minimized by rotating the catheter counterclockwise before disengaging from the artery.

Principles of Imaging

At least two orthogonal views should be obtained of each vessel (91). Adequate visualization of the left coronary artery commonly requires five or more views. Coronary artery visualization is commonly performed in the 5-in. (magnified) or 7-in. image intensifier mode. In the 7-in. mode, “panning” of the image intensifier is generally not necessary, but the spatial resolution of coronary arteries is less than that obtained in the 5-in. mode. Therefore, the 5-in. mode is usually preferred to obtain optimal spatial resolution, but the 7-in. mode may be preferred for the steeply angulated views and for obese patients. Use of the 5-in. mode usually requires panning of the image intensifier to visualize the distal vessels and collaterals. The process of panning is performed as follows. After waiting two or three systolic cycles after injection of contrast, the focus of the image should be moved from the proximal area, down the vessel of interest and then to the contralateral artery to observe for collaterals. If a stenosis is present, even a moderate one, multiple views may be necessary to delineate the severity of the stenosis, especially if it is eccentric.

Identification of coronary vessels and interpretation of angiograms may be difficult for the beginning practitioner (92). As a general principle, in RAO views the spine is on the left of the screen, whereas in LAO views the spine is on the right. The LCx and not the LAD is usually closer to the spine. In an RAO view, a diagonal branch of the LAD, as opposed to the LAD, forms the left heart border. However, in an LAO view, the LAD usually forms the right heart border, not the diagonal branches; it is important not to overlook an occluded LAD by mistaking a well-developed septal perforator for the true LAD.

Angulated views are generally required to prevent excessive vessel overlap that may obscure an area of interest (93). It may be helpful to use 1-mL “puffs” of dye to see if a particular view indeed adds information before filming. Cranial angulation tends to bring the shadow of the diaphragm into view at the bottom of the screen, and obtaining images while the patient takes a deep inspiration improves image quality by moving the diaphragm. Cranial angulation also tends to move posterior vessels such as the posterolateral branches of the RCA superiorly, whereas caudal angulation moves posterior vessels inferiorly.

The movement of coronary vessels provides clues to aid in differentiating them. The diagonal branches of the LAD and the marginal branches of the LCx tend to move in synchrony with cardiac contraction, as they supply the lateral aspect of the left ventricle. In the RAO projection, the LAD moves inward and the diagonal branches outward during systole if there is no anterior wall aneurysm. In patients in sinus rhythm, the portions of the RCA and LCx that lie in the atrioventricular groove move with an “atrial kick,” as do the atrial branches.

Obtaining views in different phases of respiration may also enhance image quality. An RAO cranial view performed with the patient in end expiration may help separate out the diagonal from the LAD. An RAO cranial view in end inspiration may help visualize the proximal LCx. The LAO caudal view is usually obtained in end expiration to facilitate viewing the LM coronary artery and ostial portion of the LAD, although it may be acquired at end inspiration if the objective is to view the LCx.

Historically, the frame rate for coronary cineangiographic acquisition has been 30 frames per second to minimize flicker. Many all-digital laboratories now acquire images at 15 frames per second. This practice results in a permanent 50% loss of information—a form of “lossy compression.” The clinical significance of this practice has not been established. In patients with tachycardia or high flow states such as aortic insufficiency, and in angiographic views with multiple overlapping vessels, a frame rate of at least 30 frames per second may be necessary to adequately visualize the coronary arteries.

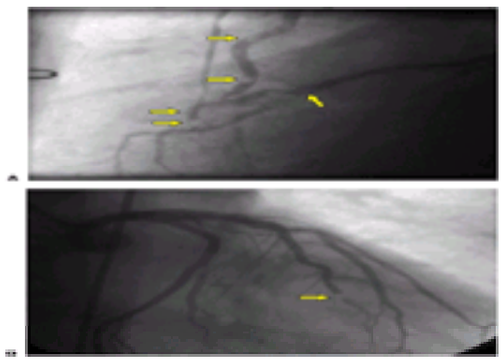
Hand injections of contrast should be “ramped,” meaning that the injection should start slowly and increase in force; this minimizes the chance of the catheter disengaging from the artery. The injection of contrast must be of adequate force to produce reflux into the sinus of Valsalva to visualize the ostium of the coronary artery. The artery should remain completely opacified throughout the cardiac cycle to prevent “washout” and “streaming” of contrast material. Extreme care must be taken to avoid injection of air into the coronary circulation (*eFig. 78.3.2*). If this does occur, an immediate attempt should be made to aspirate the air out of the vessel with the same syringe that injected the air. Unless a very large quantity of air was injected, the patient usually has only transitory chest pain and ST-segment elevation. The patient should be monitored in the catheterization laboratory until the angina and electrocardiographic changes resolve.

VIDEO

Video 78.21 Inadvertent injection of air into the left anterior descending coronary artery (right anterior oblique projection). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 78.22 Inadvertent injection of air during coronary injection for angiography. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

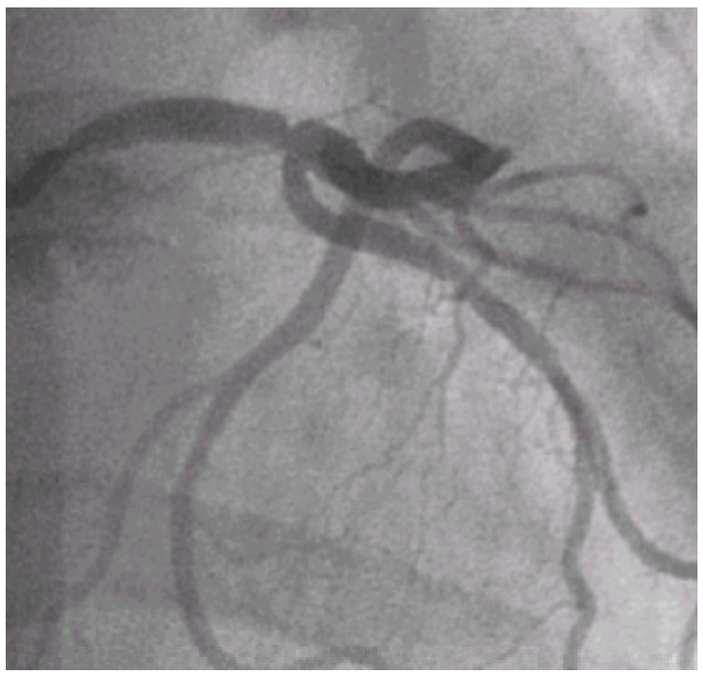


***e*FIGURE 78.3.2 A:** Inadvertent air embolus during injection of left internal mammary artery to left anterior descending (LAD) graft, shown in left anterior oblique projection. Air bubbles are seen in the left internal mammary artery, the anastomosis to the LAD, and even retrograde into the proximal LAD (*arrows*). The patient had transient, severe chest pain and ST-segment elevation but did not even develop a creatinine kinase elevation. **B:** Air bubble (*arrow*) injected down the LAD, producing transient chest discomfort without ST-segment deviation.

Coronary angiography involves integration of multiple visual cues that identify and differentiate coronary segments. With repetition, much of angiographic interpretation becomes pattern recognition. Nonetheless, a systematic approach to the evaluation of angiograms may prevent the angiographer from overlooking significant lesions that are not immediately apparent.

Left Coronary Artery

LM coronary artery disease is a serious finding that mandates proceeding with extreme caution. Clues to its presence include heavy calcification of the ostium. A stress test that demonstrates marked hypotension with exercise is another red flag. Damping or ventricularization of the pressure waveform on catheter engagement raises the possibility of LM coronary artery stenosis. Alternatively, the catheter may not be coaxial to the LM coronary artery, and slight withdrawal of the catheter tip should relieve damping in this situation; forceful contrast injection through a damped, noncoaxial catheter tip pointed upward into the LM coronary artery may lead to dissection. A contrast injection in the left coronary cusp is a reasonable first step to define the ostium of the LM coronary artery. An AP view or a shallow RAO caudal view may be useful to evaluate for mid- and distal LM coronary artery stenosis. A shallow LAO or LAO cranial view is usually best to visualize ostial LM stenosis. As soon as significant LM disease is identified, nonionic contrast should be used for the rest of the angiography. Limited injections of the left and right coronary arteries should be performed, sufficient to identify other stenoses and delineate surgical targets. A left ventriculogram should usually not be performed in the presence of severe LM coronary artery stenosis, because the contrast load and depression in cardiac contractility may prove fatal. If the patient is hemodynamically unstable, consideration should be given to intraaortic balloon pump placement.

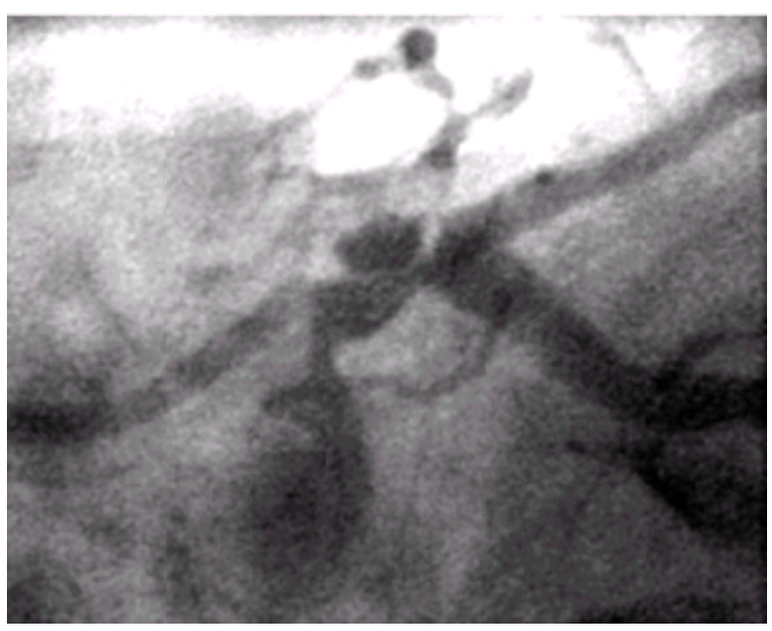


A 64-year-old male patient with severe ostial and moderate distal left main trunk stenosis.

Initial engagement of the LM coronary artery is performed in the 30-degree LAO position. If the JL4 catheter does not line up coaxially with the LM coronary artery, slight counterclockwise rotation should move the catheter tip anteriorly and engage it. If this does not work, gentle clockwise rotation, which moves the catheter posteriorly, can be applied. In a dilated aorta, the “elbow” of the JL4 catheter curve does not rest on the aortic wall, and clockwise rotation is necessary to move the catheter tip anteriorly in the aorta. Also, in the dilated aorta, larger-sized catheters such as a JL5 or JL6 may be necessary.

If Amplatz catheters are being used to engage the LM coronary artery, these are pushed down into the left cusp, with the catheter tip pointing upward until the engagement is accomplished. The catheter is then withdrawn slightly, which causes the catheter to advance into the LM coronary artery. To disengage, the catheter is advanced slightly and gently rotated counterclockwise out of the LM coronary artery. Although the JL catheters typically find the LM coronary artery with little manipulation, the Amplatz catheters are particularly useful when the orientation of this artery is unusual or anomalous. However, particular care must be used with Amplatz catheters, as the motions that are used to engage and disengage are the opposite of the Judkins catheters.

Isolated LM coronary artery disease occurs rarely (94). When there appears to be no other significant coronary artery disease, consideration should be given to LM coronary artery spasm, and intracoronary nitroglycerin should be administered before repeat angiography. Alternatively, the LM artery may just taper, and IVUS is particularly useful to document whether angiographic narrowing is due to vessel tapering or to atheroma. Additionally, whenever ostial LAD or ostial LCx stenosis, or both, are present, the index of suspicion for distal LM coronary artery stenosis should fall, and further views should be obtained to exclude this possibility.



Severe ulcerated plaque of the left main trunk discovered on diagnostic angiography.

Video 78.23 Coronary angiogram showing ostial and proximal left circumflex artery lesion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In the setting of separate ostia of the LAD and LCx, an LAO caudal view may be particularly helpful. If the catheter first engages the LAD, a larger catheter is often necessary for the engagement of the LCx, such as upsizing from a JL4 to a JL5, with clockwise rotation applied to the catheter. Alternatively, if the LCx is first engaged with the catheter, a shorter catheter is usually necessary to engage the LAD selectively, such as downsizing from a JL4 to a JL3.5, with counterclockwise rotation applied.

Several additional views of the left coronary artery should be obtained after the LM coronary artery has been evaluated. The AP cranial view is useful for evaluating the midportion of the LAD. Additional LAO or RAO cranial views may help further evaluate the mid-LAD, as well as separate the diagonal branches of the LAD, allowing the ostia to be imaged. The lateral view may further delineate the mid-LAD. The AP caudal view is useful for evaluating the body of the LCx, as well as the marginal-branch ostia. Added shallow LAO or RAO angulation may further maximize this view. For a ramus intermedius branch, an LAO caudal view is most useful to evaluate the ostium. An LAO cranial view is also useful for displaying a left-sided PDA.

Right Coronary Artery

In the 30-degree LAO projection, the JR4 is advanced to the aortic valve level and slowly withdrawn approximately 2 cm while clockwise rotation is applied to rotate the catheter anteriorly to the right sinus of Valsalva. Then the catheter should sit in the RCA ostium. If this maneuver does not work, the RCA ostium can be approached from slightly above its expected level, with clockwise rotation being applied to the catheter. With ostial disease of the RCA, if damping occurs with the catheter, it may sometimes be helpful to use a larger-sized catheter, which is less likely to engage the artery deeply. Usually, two or three views of the RCA are obtained. The LAO view is useful to evaluate the proximal and mid-RCA. The AP view with 30-degree cranial angulation is often the best for evaluating the RCA bifurcation and ostia of the PDA and posterolateral branches. A shallow RAO view is useful to lay out the entire PDA. In the RAO view, the marginal branches point to the patient's left, and the atrial branches point to the patient's right; thus, this view is useful in differentiating atrial and marginal branches that may be overlapped in an LAO view. The lateral view may be useful to evaluate the mid-RCA and the ostia of RV marginal branches. If significant LM coronary artery disease has been identified, a single view of the RCA, probably an LAO cranial to identify any needed surgical targets, may be sufficient for planning bypass surgery.

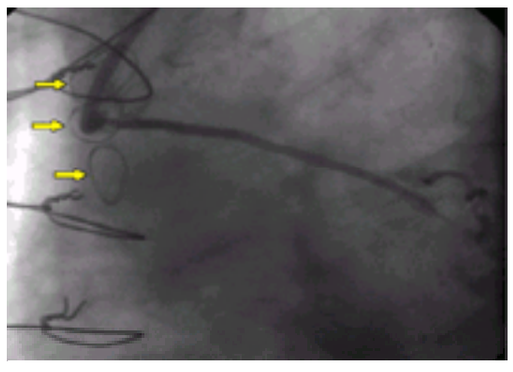
Surgical Bypass Grafts

When angiographers perform cardiac catheterization on patients with previous bypass surgery, they should obtain the operative report to know the number and types of grafts. For example, if an IMA graft has been used, is it *in situ* or is it freely anastomosed to the aorta? Are there any "Y grafts" with two limbs, or do any of the grafts have sequential anastomosis sites? The operative report may thus ensure a complete catheterization with a minimal amount of contrast expenditure. It is often helpful to review any previous postoperative angiograms. If all the vein grafts were clearly documented to be occluded on a previous study (not just the report), there would be no point in searching for them again. Additionally, any unusual anatomy of the innominate or subclavian artery could be appreciated. Furthermore, preoperative catheterization studies are also useful to ensure that all lesions were in fact bypassed. The relation of the patient's symptoms to the presence of lesions on consecutive angiograms may be revealing. For example, when a totally occluded bypass graft is detected in a patient with new-onset angina, knowledge that this vein graft was occluded 5 years ago would affect the management of this patient's current pain syndrome.

Video 78.24 A 73-year-old male patient status post coronary artery bypass grafting with right internal mammary artery (RIMA) graft to left anterior descending artery (LAD). Patient continued to have angina after coronary artery bypass grafting and stress thallium showed anterior wall ischemia. Angiography revealed arteriovenous fistula from the RIMA graft to the pulmonary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Sometimes information regarding the operative anatomy is not available. If the cardiac catheterization procedure is urgent and an operative report cannot be obtained, the patient or family may remember how many grafts were used and whether the internal mammary arteries were used. Fluoroscopic identification of the surgical clips along the course of the left or right IMA may be clues that these conduits were used. Finally, a 30-degree LAO aortogram can be performed, although adequate opacification must be ensured. At least a 50- to 60-mL aortogram is generally required; otherwise it is possible to miss grafts that are, in fact, patent. Additionally, a long cine run is sometimes necessary to view a late-filling, diseased vein graft.

Left coronary artery bypass grafts are best visualized in an RAO projection, whereas grafts to the RCA are best engaged in the LAO projection. If a graft is occluded, an injection should still be performed to confirm the presence of a stump and ensure that it is not just the catheter abutting the aortic wall. In the presence of multiple grafts from more than one bypass operation, it may be useful to visualize the stump in an RAO and an LAO projection. This allows the area to be localized more clearly and avoids multiple cannulations of the same stump or confusion with another closely located stump. Some surgeons place marker rings on the outside of the aorta at the proximal anastomosis of the graft (eFig. 78.3.3). This facilitates engagement of the graft during subsequent catheterizations. The usual sequence of proximal anastomoses of aortocoronary bypass grafts to the left coronary, going from caudal to cranial, is LAD, diagonal, ramus, first obtuse marginal, and second obtuse marginal. Grafts to the RCA are more caudal and more anterior than grafts to the left coronary artery.



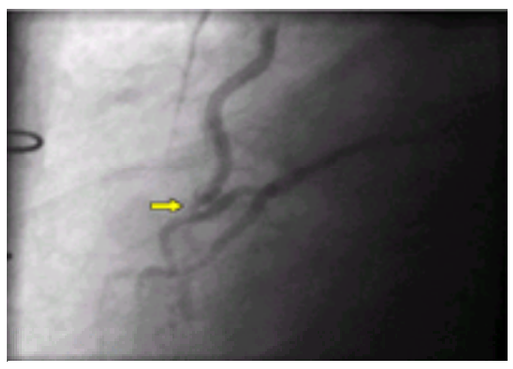
***e*FIGURE 78.3.3** Sequential marker rings (*arrows*), which denote the aortic anastomoses of saphenous vein grafts.

Before cannulating the IMA, the angiographer should visualize the proximal subclavian or innominate artery to provide a road map of the anatomy, to facilitate catheter manipulation. Importantly, the presence of a subclavian stenosis proximal to the IMA may be identified. The JR4 is well suited to cannulate the subclavian or innominate artery and is easier to use for this purpose than a preformed IMA catheter. Measurement of a pullback gradient, with a saline-filled catheter, confirms the hemodynamic significance of an angiographic stenosis.

The contralateral oblique view is useful to evaluate the ostia of the internal mammary arteries. Care must be taken on engagement of the ostia of the IMA, as dissection of an IMA–LAD conduit may be catastrophic. The IMA is more delicate in this regard than a saphenous vein graft. Although a JR4 is sometimes used to cannulate the

IMA, the curve on the catheter tip is often not sufficient to engage the IMA, which usually originates anteriorly from the subclavian artery. An IMA catheter has a more acute tip curve for selective IMA cannulation. One strategy is to use a JR4 to engage the subclavian artery, visualize this vessel, and then pass a 260-cm exchange-length J-wire or Glidewire into the distal subclavian artery and advance the IMA catheter over the exchange wire. In the presence of marked tortuosity, the Glidewire may be particularly useful, as may use of a Glide catheter; the hydrophilic coatings on these instruments may ease passage through curved vessels. Attempts to cannulate the IMA should be made while withdrawing the IMA catheter, not while advancing it, to prevent dissection. Counterclockwise torque is generally applied to turn the catheter anteriorly to engage the left IMA, or clockwise torque for the right IMA, while the catheter is withdrawn.

It is important to visualize precisely the distal anastomosis of the graft to the artery, as this is often the site of a culprit lesion. In the IMA grafts, in particular, a discrete lesion that is amenable to angioplasty may be found in this location. The lateral view is particularly useful if there is a question of a left IMA–LAD anastomosis lesion (*e*Fig. 78.3.4). The RAO and LAO cranial views are also useful. Otherwise, the views that are used to visualize grafts are similar to the views required for the native vessels. For example, the anastomosis of a graft to the distal RCA could be seen in an LAO cranial view.



***e*FIGURE 78.3.4** Lateral view of the left internal mammary artery to the left anterior descending artery anastomosis (*arrow*).

The gastroepiploic artery can be used as an *in situ* graft to the distal RCA. The gastroepiploic artery originates from the common hepatic artery, which arises from the celiac trunk in the abdominal aorta. It normally supplies the stomach but can be rerouted surgically to the inferior surface of the heart. Visualization of this graft involves cannulation of the celiac trunk with a curved catheter such as the Cobra catheter. If a selective injection is necessary for adequate opacification, a catheter can be advanced over a Glidewire into the origin of the gastroepiploic artery.

If left ventriculography is performed, opacification of vein grafts is sometimes observed. Perhaps more useful is observation of the contraction pattern of the left ventricle. For example, if the anterior wall is completely normal but the LAD is occluded and no patent graft has been found that supplies the LAD territory, it is highly likely that a graft has been overlooked.

Cerebral Angiography

A 30-degree LAO arch aortogram is performed to see the great vessels (95). A bovine arch, where the left common carotid artery arises from the innominate artery, is a relatively common anomaly. If the origins of the great vessels lie on a horizontal plane, a 5-Fr JR4 can be used to engage the great vessels. In general, 5-Fr catheters are less likely to traumatize vessels than are larger catheters. A Headhunter 1 has a shape similar to that of a JR4 and can be used to engage the common carotid arteries. If the origin of the great vessels lies in more of a vertical orientation, a curved catheter such as a Vitek is often necessary. The Simmons curved catheters may be extremely useful when the curve of the Vitek is not sufficient to engage the great vessels. However, this catheter is more difficult to use and has a tendency to jump into the vessel of interest, increasing the risk of vessel dissection. Additionally, the curved catheters by necessity scrape along the aorta, which raises the chance of embolic complications in a heavily diseased aorta. Use of these curved catheters is somewhat analogous to the use of Amplatz catheters in that the vessel is cannulated and the catheter is pulled back slightly to engage the vessel more deeply. To disengage, the catheter is not just pulled back but rather needs to be advanced and torqued. When curved catheters are used, it is easier to engage the great vessels going forward—that is, engaging the left subclavian, then the left common carotid, and then the innominate—whereas the opposite strategy is preferred when using the noncurved catheters such as the JR4.

For cerebral angiography, nonionic contrast should be used, and images should be acquired using digital subtraction angiography. The carotid arteries should be visualized in at least two views, the ipsilateral oblique and the cross-table lateral (90-degree LAO). The ostia of the vertebral arteries are best seen in the contralateral oblique. Often, a nonselective visualization of the vertebral arteries is sufficient, with the catheter tip pointed in the direction of the vertebral and a blood pressure cuff inflated above the systolic pressure in the ipsilateral arm. If selective engagement is necessary, great care must be taken with catheter manipulation so as to avoid dissection. Special vertebral artery catheters are available for selective cannulation.

Severe left internal carotid artery stenosis in a 67-year-old male patient with transient ischemic attacks (A) and after implantation of a self-expanding stent (B).

Renal Angiography

Although it is often possible to engage the left and right renal arteries with a JR4 catheter, an initial AP abdominal aortogram may be useful to identify the exact location of the renal arteries and allow visualization of accessory renal arteries. Philosophically, this sort of “drive-by” angiography, without clinical indications, is undesirable, because angiographic stenosis may be of little functional consequence to the patient in certain circumstances. However, in a patient with uncontrolled hypertension despite adequate doses of multiple antihypertensives, or when noninvasive imaging has suggested severe stenosis, renal angiography at the time of cardiac catheterization may be reasonable.

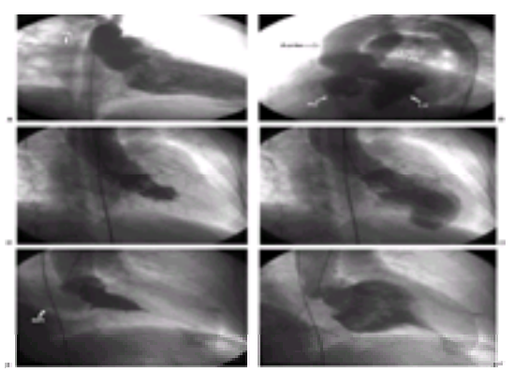
It is generally preferable to start with an abdominal aortogram. Identification of bony landmarks, such as the first lumbar vertebral body, may help position the pigtail catheter above the renal artery ostia. As the renal arteries tend to arise somewhat posteriorly, LAO or RAO angulation may help visualize the ostia. If an ostial stenosis is identified, recording of a pressure gradient may help assess the severity of the angiographic stenosis. Imaging should continue for a period of time sufficient to view the nephrograms. An abdominal aortic aneurysm may be noted on the abdominal angiogram. Even a small angiographic aneurysm may in fact be a much larger clot-filled sac, and an ultrasound or computed tomographic (CT) scan is warranted to document the exact dimensions of the aneurysm.

Left Ventriculography

Even with the refinement of several noninvasive measures, ventriculography remains a useful modality to assess left ventricular function. Before left ventriculography is performed, an assessment of LVEDP should be made with the pigtail catheter. If the pressure is markedly elevated, sublingual nitroglycerin should be administered until the pressure is reduced. If LVEDP remains elevated (e.g., LVEDP >30 mm Hg), consideration should be given to aborting the left ventriculogram.

Left ventricular hypertrophy secondary to chronic hypertension with secondary ectasia of the right ventricle.

The 30-degree RAO is the usual view for left ventriculography, although biplane ventriculography with an additional LAO or LAO cranial view may be preferable in some cases, if available. If mitral regurgitation is known to be present and an assessment of severity is required, 50 to 60 mL of dye should be used to opacify the left atrium (96). Care must be taken in positioning the catheter and ensuring that it is free, such that it does not trigger premature ventricular contractions or entwine the mitral valve apparatus, thereby artificially causing mitral regurgitation. The LAO cranial is the optimal view for a muscular ventricular septal defect, and the left lateral view is optimal for a membranous ventricular septal defect. The LAO cranial is also useful to assess for left ventricular outflow obstruction in patients with hypertrophic cardiomyopathy (eFig. 78.3.5).



***e*FIGURE 78.3.5** In addition to assessment of left ventricular function, ventriculography may diagnose several other conditions. **A:** Ventricular septal defect in a right anterior oblique (RAO) projection, showing opacification of the pulmonary artery (PA). **B:** Ventricular septal defect in a steep left anterior oblique projection, clearly showing opacification of the left ventricle (LV), right ventricle (RV), and PA. (Courtesy of Dr. Mark A. Robbins.) RAO view of hypertrophic cardiomyopathy in **(C)** systole, with cavity obliteration, and **(D)** diastole. (Courtesy of Dr. Marc S. Penn.) RAO view of hypertrophic cardiomyopathy in **(E)** systole, showing cavity obliteration and mitral regurgitation (MR) and **(F)** diastole, showing a “spade”-shaped ventricle. (Courtesy of Dr. Herb Aronow.)

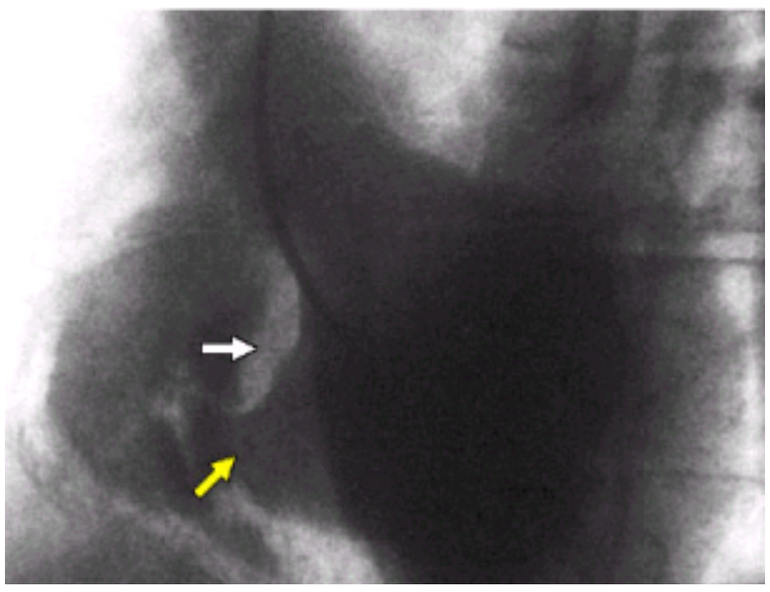
VIDEO

Video 78.25 Normal left ventriculograms in the right anterior oblique **(A)** and left anterior oblique projections **(B)**. Ventriculography only in the right anterior oblique projection may miss certain segmental wall motion abnormalities. (Courtesy of Dr. Debabrata Mukherjee.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

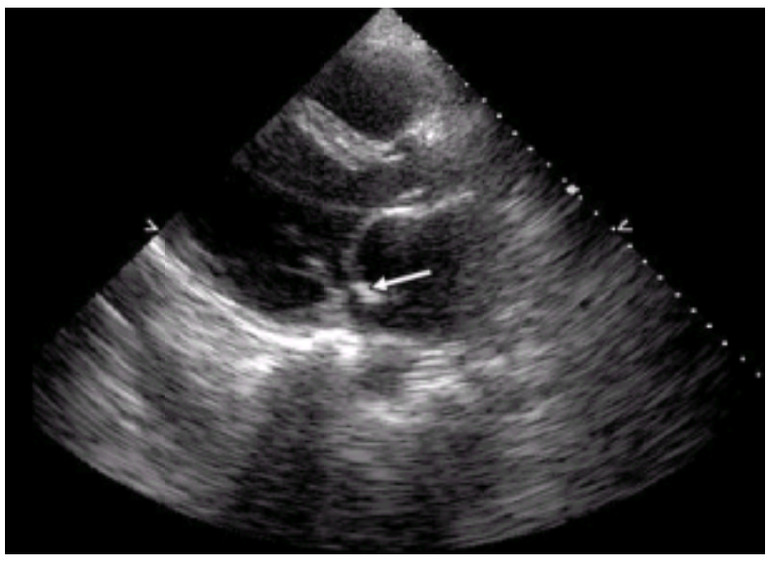
Video 78.26 Normal left ventriculograms in the right anterior oblique **(A)** and left anterior oblique projections **(B)**. Ventriculography only in the right anterior oblique projection may miss certain segmental wall motion abnormalities. (Courtesy of Dr. Debabrata Mukherjee.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.27 Left ventriculography with severe mitral regurgitation. After contrast injection in the left ventricle, the left atrium achieves the equal opacity to the left ventricular cavity indicative of severe (4+) mitral regurgitation. Before contrast injection, calcification in the mitral annulus and descending aorta is evident. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.28 Mitral valve prolapse with severe mitral regurgitation (right anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Muscular ventricular septal defect. This left anterior oblique left ventriculogram demonstrates the presence of a muscular ventricular septal defect (*yellow arrow*) with opacification of the right ventricular cavity and pulmonary outflow tract. The ventricular septum (*white arrow*) is seen to divide the right and left ventricular chambers.



Parasternal long-axis view of a papillary muscle rupture after myocardial infarction. Note the piece of papillary muscle attached to the tip of the anterior mitral leaflet as it flails into the left atrium (demonstrated by the arrow).

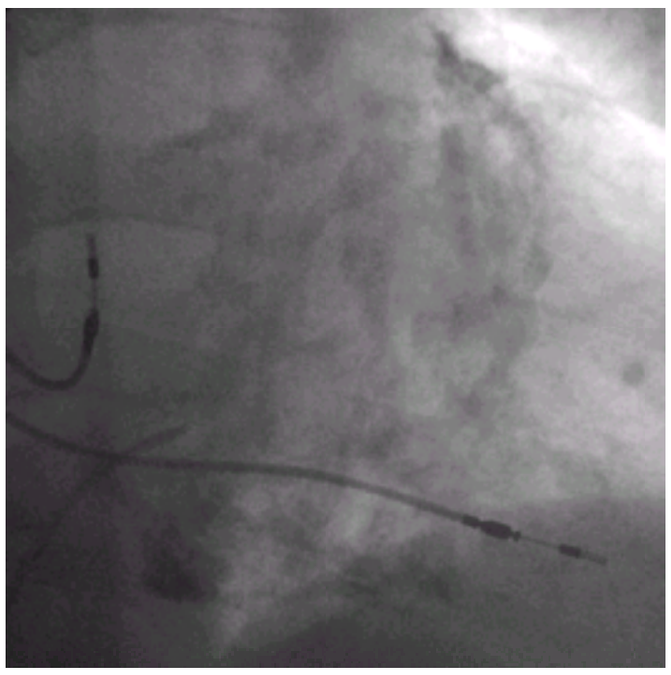
Video 78.29 Hepatoclavicular view (left anterior oblique 60, cranial 45) of a membranous ventricular septal defect in a 16-year-old male patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.30 Ventriculography in a patient with Yamaguchi's apical hypertrophy. In this syndrome there is just proportionate hypertrophy near the apex, which produces a characteristic prolongation of the left ventricular silhouette during ventriculography (right anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 78.31 Subaortic stenosis. A radiolucent membrane is visualized just below the aortic valve cusps (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In addition to angiographic assessment, the information obtained from fluoroscopy should not be overlooked. Pericardial calcification may be a clue for the presence of constrictive pericarditis, although this was much more common in the era of widespread tuberculosis (eFig. 78.3.6). Additionally, tethering of the coronary arteries during angiography may be noted in constrictive pericarditis. Fluoroscopy may also show calcification of the aortic valve or mitral annulus, perhaps indicating the presence of valvular heart disease. Fluoroscopy can also be used to assess the function of mechanical heart valve prostheses.

***e*FIGURE 78.3.6** Cine image showing severe calcification in the pericardium of a 71-year-old man with constrictive pericarditis. (Courtesy of Dr. Debabrata Mukherjee.)



Cine image showing severe calcification in the pericardium of a 71-year-old male patient with constrictive pericarditis.

VIDEO

Video 78.32 Normal-functioning Starr-Edwards prosthetic valve in the mitral position. Note the full motion of the valve pop-it within the cage. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 78.33 Normal Björk-Shiley prosthetic valve in aortic position and normal porcine valve in the mitral position. Depending on the vintage, the Björk-Shiley tilting-disc valve opens either 60 degrees or 70 degrees shown here. Prosthetic porcine valves are not radiopaque are therefore excursion cannot be ascertained fluoroscopically. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 78.34 Frozen St. Jude prosthetic valve leaflet **(A)**. Image was obtained 5 days postoperative with suspected prosthetic valve dysfunction by echocardiography. Fluoroscopy reveals only one of the two leaflets moving normally (*arrow*). St. Jude prosthetic valve after reoperation **(B)**. Both leaflets now show normal excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

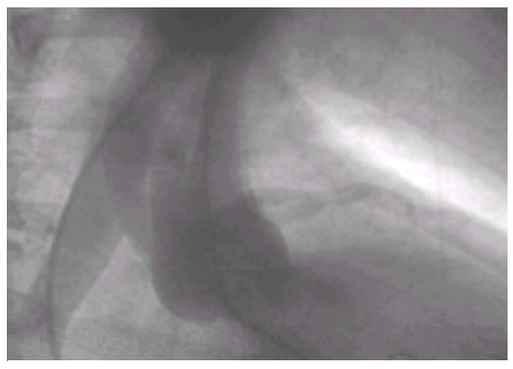
VIDEO

Video 78.35 Frozen St. Jude prosthetic valve leaflet **(A)**. Image was obtained 5 days postoperative with suspected prosthetic valve dysfunction by echocardiography. Fluoroscopy reveals only one of the two leaflets moving normally (*arrow*). St. Jude prosthetic valve after reoperation **(B)**. Both leaflets now show normal excursion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Aortography

Aortography is usually performed in a 60-degree LAO projection to assess the aortic root and determine if aortic regurgitation is present (eFig. 78.3.7). Aortic coarctation is best seen in the lateral view. If there is a suspicion of aortic dissection (which there always should be in a patient with acute chest pain), care should be taken to attempt entry into the true lumen. With a femoral approach, the stronger pulse should be used, as this also increases the likelihood of entering the true lumen if the dissection extends to involve the iliofemoral system. Entry into the true lumen may be facilitated by using a pigtail catheter or a JR4 catheter to direct the guidewire toward the medial edge of the aorta, as this increases the likelihood of avoiding the false lumen, which typically arises from the outer aspect of the aorta. A soft-tip exchange length 260-cm J-wire should be used. Entry across the aortic valve into the left ventricle is desirable to confirm entry into the true lumen. Ventriculography followed by aortography can then be performed with a pigtail catheter. An aortogram at 60 degrees LAO can be performed to assess the great vessels and ensure that these arteries are not involved. Next, over the exchange length wire, a JL5 or 6 catheter can be used to engage the LM coronary artery in what is usually a dilatated aorta. The RCA can then be cannulated with a JR4 or 5, although the dilatated aorta may necessitate the use of AL3 or multipurpose catheters for either the LM coronary artery or RCA. The initial aortogram may help guide the selection of catheter shapes and sizes for coronary engagement. Despite the conventional belief that

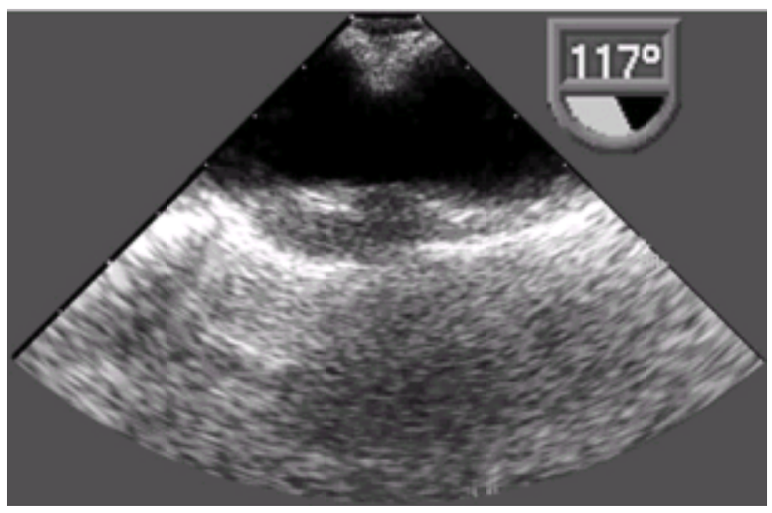
coronary angiography is necessary before a patient goes to surgery for acute aortic dissection, the data indicate that there is probably no benefit to routine coronary angiography in this setting unless the patient has had previous coronary artery bypass surgery (97).



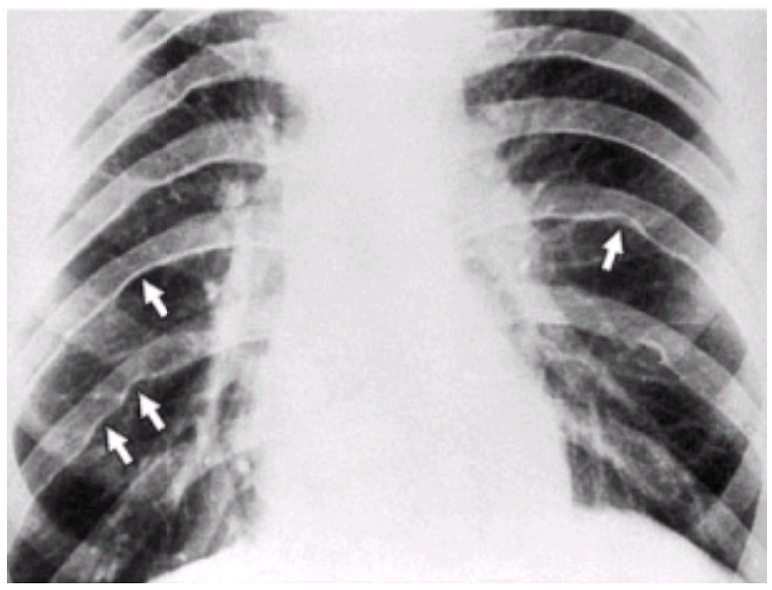
***e*FIGURE 78.3.7** Aortogram of a 77-year-old man who presented to the emergency room with severe chest pain and hypertension. Aortography revealed type A aortic dissection. (Courtesy of Dr. Debabrata Mukherjee.)

Video 78.36 Congenital bicuspid aortic valve with mild aortic regurgitation (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

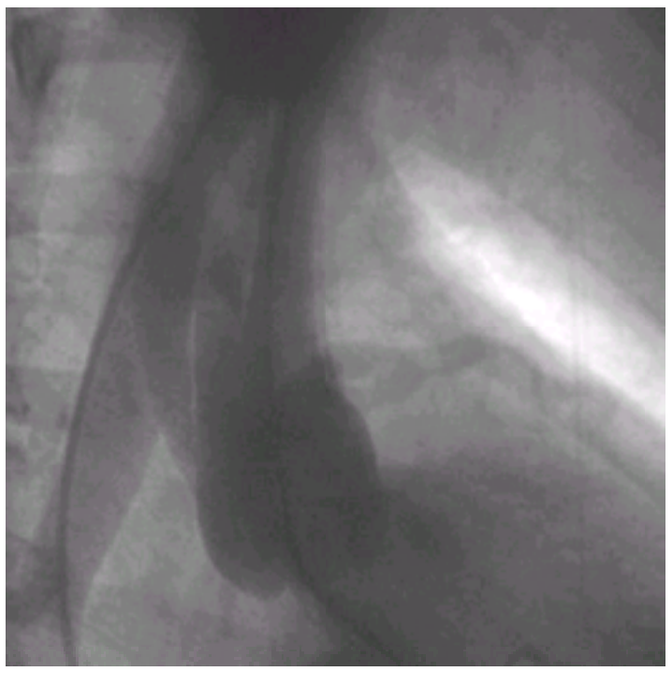
Video 78.37 Calcified sinus of Valsalva aneurysm ruptured into the right atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



A still frame of a transesophageal echo demonstrating a coarctation of the aorta. Note the local narrowing of the aorta located at the junction of the distal arch and descending aorta. There was a 100–mm Hg pressure gradient across the coarctation as determined by continuous wave Doppler.



Chest x-ray in coarctation of the aorta. There is prominent rib notching (*white arrows*).



A 77-year-old male patient presented to the emergency department with severe chest pain and hypertension. Aortogram revealed type A aortic dissection.

Ascending aortic dissection extending into the left main. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Postprocedural Care

The angiographic images should be reviewed and a plan formulated in the catheterization laboratory. Once it is certain that all necessary information has been obtained from the angiogram, the sheath can be pulled. If heparin was administered for a diagnostic coronary angiogram (e.g., when a radial/brachial approach was used or cerebral angiography was performed), an activated clotting time or activated partial thromboplastin time should be checked before the sheath is pulled. If the activated clotting time is less than 160 seconds or the activated partial thromboplastin time is under 45 seconds, the sheath can be pulled and manual pressure applied for several minutes until hemostasis is obtained. Direct compression of the artery a few fingerbreadths above the needle insertion site in the skin (above the estimated arterial entry site) with the pads of the fingertips is the most reliable method to obtain hemostasis and should be the initial approach if a closure device is not used. After a few minutes of direct manual pressure, a C-clamp can be positioned appropriately, although the patient must still be monitored. A FemoStop is an alternative to the C-clamp, but some care must be taken to ensure correct positioning over the artery. Use of smaller-sized sheaths may greatly decrease the time to ambulation. With the use of 5-Fr sheaths, ambulation has been demonstrated to be safe after 2 hours of bed rest.

Closure devices are increasingly used to obtain hemostasis. It is recommended that an oblique angiogram be performed through the sidearm of the sheath to determine the sheath insertion site. Additionally, vessel size and the presence of any plaque may be noted. If it appears that the sheath is in the bifurcation of the common femoral artery, manual pressure is best applied. If the sheath is placed in the profunda femoris or the superficial femoral artery, or if there is atherosclerotic plaque at the insertion site, it may be best not to use any closure device. Vessels of 4 mm or less in size are not well suited to current closure devices. If a slight degree of blood oozing from the skin occurs, a 10-mL solution of lidocaine hydrochloride 1% and epinephrine 1:100,000 can be injected into the skin tract.

A variety of closure devices are currently available. The Perclose is a percutaneous device used to suture the hole in the artery formed by the sheath (98). The device is placed over a wire after the sheath is removed. Then needles are deployed that pull sutures through the artery wall, and the sutures are tied to obtain hemostasis. Because the guidewire can be maintained in the artery for the entire procedure, a sheath can be reinserted if the device fails. Additionally, immediate leg movement and recannulation are possible, if necessary. The technique of “preclosing” the femoral artery involves placement of a Perclose over the guidewire after its initial placement through the cannulation needle. The sutures of the Perclose are kept to the side underneath a sterile towel until the conclusion of the procedure and the removal of the sheath. The Perclose device has been used to obtain hemostasis after brachial artery cannulation as well, although care must be taken because of the smaller caliber of the brachial artery (99).

The Angio-Seal is available in an 8-Fr device for 7- or 8-Fr sheaths and in a 6-Fr device for 5- or 6-Fr sheaths (100,101). Placement involves exchange of the sheath over a guidewire for the Angio-Seal device, which places a collagen plug external to the hole in the artery, with an anchor inside the artery to hold the plug in place. Movement of the leg should be restricted for 1 to 2 hours, and repuncture is not recommended for 3 months. The VasoSeal is an external collagen plug that is placed immediately outside the hole in the artery, as well as in the skin tract that leads to the arterial cannulation site (102). The Duett device is similar in concept to the VasoSeal except that it involves injection of thrombin external to the artery. Care must be taken to avoid intraarterial injection of thrombin. Although closure devices may decrease the time to ambulation and hasten discharge from the observation unit, there is no evidence that they decrease groin complications. Likewise, in well-trained operator hands, there is no evidence that closure devices increase groin complications, although when complications occur, they are more often immediately apparent than when manual pressure is used (103,104 and 105).

After radial artery catheterization, if the radial pulse is lost but the hand is otherwise asymptomatic (and the ulnar supply is adequate), there is no cause for action. With loss of the brachial or radial pulse after brachial artery catheterization, vascular surgical consultation ought to be obtained. Loss of distal pulses after femoral catheterization should also prompt surgical consultation or lower extremity angiography. In patients with extensive peripheral vascular disease, if pressure is being applied to the femoral catheterization site, particular care must be given to the distal extremity to ensure that ischemia is not occurring; this is best accomplished with direct visualization of the distal extremity (i.e., the foot should not be covered up with a sheet).

Elective diagnostic coronary angiography has been transformed into an outpatient procedure in most circumstances. This appears to be a safe development. However, there are patients for whom outpatient catheterization is not appropriate. Individuals with severe aortic stenosis or LM coronary artery disease should be monitored for a more extended period, as should patients who are at risk of developing renal failure. Similarly, patients with severely impaired left ventricular function or unstable coronary artery disease should remain for observation. Individuals who live alone and have no one to watch them should be monitored overnight.

Before discharge, patients should be told to notify their physician if they subsequently have any sudden drop-off in urine quantity. Any pain or swelling at the site of the catheterization should also prompt emergency care. Patients should be counseled to avoid driving for a day to allow sedation to wear off and heavy lifting for at least 2 days to allow the catheterization site to heal. Warfarin, if necessary, can be reinitiated the night of the procedure. If more immediate anticoagulation with heparin is desired, this can be started a few hours after the sheath is removed, or immediately if a closure device is used. If metformin was given, this can be resumed after 2 days if renal function appears stable.

Complications and Management

Major complications are unusual after cardiac catheterization, but the operator must be familiar with them. An analysis of 59,792 patients documented the frequency of major complications with cardiac catheterization and coronary angiography (Table 78.3) (106). Although that analysis is somewhat old, the numbers have not changed significantly, although older, sicker patients are being catheterized. Death occurs in approximately 1 in 1,000 cases. Patients with severe LM coronary artery stenosis or critical aortic stenosis are at particularly high risk. Myocardial infarction occurs in approximately 1 in 2,000 cases; stroke occurs in approximately 1 in 1,000 cases. Thus, a major complication of death, myocardial infarction, or stroke occurs in about 1 of 500 cases.

Complication	Percent
Death	0.11
Myocardial infarction	0.05
Stroke	0.07
Arrhythmia	0.38
Vascular complications	0.43
Contrast reaction	0.37
Hemodynamic complications	0.26
Perforation of cardiac chamber	0.03
Other complications	0.28
Total	**1.70**

Adapted from Noto TJ Jr, Johnson LW, Krone R, et al. Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). *Cathet Cardiovasc Diagn* 1991;24:75–83, with permission.

TABLE 78.3 INCIDENCE OF COMPLICATIONS WITH CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene (*yellow arrow*), as well as localized skin necrosis and livedo reticularis (*white arrows*).

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene, as well as localized skin necrosis and livedo reticularis (*white arrows*).

Atheroemboli. Digital necrosis resulting from severe atheroemboli.

Adapted from Noto TJ Jr, Johnson LW, Krone R, et al. Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). *Cathet Cardiovasc Diagn* 1991;24:75–83, with permission.

Hypotension and Bradycardia

Vasovagal reactions may occur, especially with initial arterial access or sheath removal. Patients should be instructed not to hold their breath, because breath-holding may predispose to a vagal reaction. Hypotension in the catheterization laboratory may be catastrophic in certain circumstances, and prompt treatment may be lifesaving. Norepinephrine (Levophed) should be administered to reverse rapidly hypotension that is due to vasovagal reactions. Dopamine is often used in catheterization laboratories; however, this is not the ideal initial agent for serious hypotension, because it takes a period of time for blood levels to reach a level at which the pressor effect occurs. At the initial low serum concentrations, dopamine acts primarily as a renal and splanchnic vasodilator and may transiently decrease blood pressure. Therefore, norepinephrine, not dopamine, is the agent of choice for prompt treatment of hypotension. Epinephrine is the treatment of choice for hypotension secondary to an anaphylactoid reaction. For hypotension that is unresponsive to i.v. fluids and vasopressors, placement of a Swan-Ganz catheter and an intraaortic balloon pump should be considered. With the availability of the lower profile 8-Fr intraaortic balloon pump systems, a balloon pump can often be placed

through an existing sheath.

Atropine, 1.0 mg i.v., should be administered for symptomatic bradycardia. dditionally, if bradycardia occurs with injections of ionic contrast, nonionic contrast should be substituted. Furthermore, if the bradycardia occurs with RCA injection, the minimum amount of dye to ensure opacification should be used. For sustained and symptomatic bradycardia, a transvenous pacemaker should be placed.

Vascular Complications

Bleeding from the arterial cannulation site with development of a hematoma is a risk of angiography. Retroperitoneal bleeding can be particularly sinister due to the difficulty in making the diagnosis. Although symptoms such as inguinal or abdominal tenderness, femoral neuropathy, and back pain may be clues to retroperitoneal hemorrhage, hypotension with a falling hemoglobin may be the only manifestation and, if undetected, may lead to death. An abdominal CT scan can confirm the diagnosis (107). The risk of vascular complications is increased in patients who are receiving anticoagulation at the time of angiography (108). Female gender, obesity, and advanced age are other risk factors for groin complications. Color duplex ultrasound is the preferred mode of assessing groin complications (109). Pseudoaneurysm and arteriovenous fistula formation are additional risks. When pseudoaneurysms are less than 3 cm in size, conservative management usually results in spontaneous closure (110). Although ultrasound-guided compression of pseudoaneurysm and arteriovenous fistula has become commonly used, surgical therapy is still necessary in a significant minority of cases, especially when anticoagulation is being administered (111). A newer method of ultrasound-guided thrombin injection has been described for the management of pseudoaneurysms that develop after catheterization (112). The success rate with this method is high, even in patients who are receiving anticoagulation, and, in experienced hands, this should likely be the first approach tried before consideration of surgical repair. Endovascular techniques have also been used successfully to treat pseudoaneurysm and arteriovenous fistula (113).

Brachial artery hematoma. Hematoma complication after brachial artery catheterization and urokinase administration.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Numerous critics of coronary angiography decry the overuse of this invasive procedure. Certainly, overuse may be a problem, especially given patient demand in fee-for-service health-care systems. Improved noninvasive screening techniques may diminish the need for angiography as a diagnostic tool in the future. As magnetic resonance imaging continues to improve, it may one day replace coronary angiography as a diagnostic tool for suspected coronary artery disease. Alternatively, newer modalities such as CT scanning may identify a larger number of people who need coronary angiography for more definitive delineation of coronary anatomy. Furthermore, percutaneous coronary intervention continues to grow as a revascularization method, necessitating coronary angiography to define stenoses. The aging of the population will further increase the need for coronary angiography. Additionally, emerging evidence suggests that an invasive strategy incorporating angiography is the ideal approach to patients with acute coronary syndromes (60,61). Individuals with unstable angina who are treated with aggressive catheterization strategies in the United States fare better than their more conservatively treated counterparts in Canada (114). For patients with acute ST-segment elevation myocardial infarction, an invasive approach, including percutaneous intervention, where available, leads to better outcomes than pharmacologic therapy (115,116 and 117). If a patient with acute myocardial infarction is in cardiogenic shock, an initial invasive approach may be lifesaving (118). Thus, the prominence of coronary angiography is likely to grow, as a diagnostic tool and as a prelude to percutaneous intervention.

THE FUTURE

Although the future of coronary angiography remains bright, limitations will be placed on who actually performs it. As minimum volume standards become more widely accepted and separate certification examinations are developed, coronary angiography will become part of a discrete invasive subspecialty within cardiology. The evolution and refinement of arterial closure devices will continue, allowing an even greater proportion of cases to be performed on an outpatient basis. Older patients with a greater degree of medical comorbidities, as in the very elderly, will undergo coronary angiography at much higher rates. Further refinements in imaging, through magnetic resonance and CT, will likely reduce radiation exposure to the operator, enhance image quality, and ultimately yield “noninvasive” coronary angiography using an i.v. injection of a contrast agent. Real-time three-dimensional reconstruction of coronary arteries will become feasible. Potentially, hybrid imaging technologies will enable the identification of vulnerable atherosclerotic plaque, the veritable “holy grail” of diagnostic angiography. Thus, although coronary angiography will probably continue to evolve, it will remain central to the evaluation of coronary artery disease.

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CARDIAC CATHETERIZATION AND HEMODYNAMIC ASSESSMENT

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Diagnostic cardiac catheterization is performed to establish the presence and to assess the severity of cardiac disease. Catheterization of the right and left sides of the heart can be accomplished by the introduction of catheters via several approaches. During routine right-sided heart catheterization, measurements of pressures and oxygen saturations in the venae cavae, right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position can be performed, and cardiac output (CO) can be quantified. The measurement of right-sided pressures helps one to evaluate the severity of tricuspid or pulmonic stenosis, to assess the presence and severity of pulmonary hypertension, and to calculate pulmonary vascular resistance. With left-sided heart catheterization, one can assess mitral and aortic valvular function, left ventricular pressures and function, systemic vascular resistance, and coronary arterial anatomy. Cardiac catheterization may be performed to assess the presence, site, and magnitude of intracardiac shunting, and injection of radiographic contrast material into various cardiac chambers (angiography) may be performed to evaluate their structure or function.

HISTORICAL PERSPECTIVE

Cardiac catheterization was first performed in the 1840s on experimental animals. In 1929, Werner Forssmann was the first to pass a catheter into the heart of a living person—himself. Guided by a fluoroscopic image projected onto a mirror, Forssmann introduced a thin urologic catheter into his left antecubital vein, advanced it to the right atrium, then climbed a flight of stairs to the radiology suite to document catheter position with a chest radiograph. Although he repeated this feat several times, concern about the utility and safety of cardiac catheterization limited its use and development until the 1940s, when Andre Cournand and Dickinson Richards systematically performed catheterization to investigate cardiac function in healthy subjects and in patients with heart disease (*e*Table 79.0.1). During its early years, catheterization was performed sparingly and with substantial risk. As time has elapsed, considerable advances have been made, and the associated morbidity and mortality have fallen precipitously. Today, diagnostic cardiac catheterization is performed with minimal risk, and therapeutic catheterization (i.e., coronary angioplasty and valvuloplasty) is performed without incident in most patients. Cardiac catheterization now plays a central role in the diagnostic evaluation of the patient with suspected or known cardiac disease, and it offers percutaneous therapeutic possibilities in many individuals.

***e*TABLE 79.0.1** HISTORICAL HIGHLIGHTS OF CARDIAC CATHETERIZATION

1929	First cardiac (right atrial) catheterization in man: Werner Forssmann
1930	Cardiac output measured by the Fick principle: O. Klein
1940s	Right-sided heart catheterization studies: Andre Cournand and Dickinson Richards
1947	Pulmonary capillary wedge measurements: Lewis Dexter
1950	Retrograde left-sided heart catheterization: H. Zimmerman, R. Limon-Lason
1953	Percutaneous catheterization technique: S. Seldinger
1956	Nobel prize awarded to Werner Forssmann, Andre Cournand, and Dickinson Richards for their work in cardiac catheterization
1959	Transseptal catheterization: John Ross, Constantin Cope
1959	Selective coronary angiography: Mason Sones
1968	Coronary artery bypass surgery: Rene Favalaro
1970	Balloon-tipped flow-directed right-sided heart catheterization: H. Jeremy Swan and William Ganz
1977	Percutaneous transluminal coronary angioplasty: Andreas Gruentzig

INDICATIONS AND CONTRAINDICATIONS

Diagnostic cardiac catheterization is appropriate in several circumstances. First, it is indicated to confirm or exclude the presence of a condition already suspected from the history, physical examination, or noninvasive evaluation. In such a circumstance, it allows one both to establish the presence and to assess the severity of cardiac disease. Second, catheterization is indicated to clarify a confusing or obscure clinical picture in a patient whose clinical findings and noninvasive data are inconclusive. Third, catheterization is performed in some patients for whom corrective cardiac surgery is contemplated to confirm the suspected abnormality and to exclude associated abnormalities that might require the surgeon's attention. Fourth, catheterization is occasionally performed purely as a research procedure.

Therapeutic catheterization is appropriate in several circumstances. Percutaneous coronary revascularization (e.g., angioplasty, directional or rotational atherectomy, or endovascular stenting) may be indicated in the patient with symptomatic atherosclerotic coronary artery disease whose coronary anatomy is suitable for the procedure. Valvuloplasty is indicated in the subject with symptomatic isolated pulmonic stenosis, and it is an acceptable alternative to surgery in the patient with mitral stenosis or aortic stenosis in whom valvular anatomy is suitable and surgery is believed to offer an unfavorable risk-benefit ratio, due, for example, to advanced age or comorbid medical conditions (i.e., chronic pulmonary, hepatic, or renal disease or an underlying malignancy).

Catheterization is absolutely contraindicated if a mentally competent individual does not consent. It is relatively contraindicated if an intercurrent condition exists that, if

corrected, would improve the safety of the procedure (*e*Table 79.0.2).

***e*TABLE 79.0.2** RELATIVE CONTRAINDICATIONS TO CARDIAC CATHETERIZATION
Decompensated heart failure (e.g., pulmonary edema)
Uncontrolled ventricular irritability
Uncontrolled systemic arterial hypertension
Acute or severe renal insufficiency
Difficulty with vascular access
Electrolyte imbalance (i.e., hypokalemia or hyperkalemia)
Digitalis intoxication
Active infection or febrile illness
Uncorrected bleeding diathesis
Severe anemia
Active bleeding from internal organ
Severe allergy to radiographic contrast material
Mental incompetence

RISKS AND COMPLICATIONS

As cardiac catheterization has been more frequently performed, the incidence of complications has diminished (*e*Table 79.0.3). However, even in skilled hands, the procedure is not without risk (1,2,3 and 4). The overall incidence of a major complication (death, myocardial infarction, or cerebrovascular accident) during or within 24 hours of diagnostic catheterization is 0.2% to 0.3%. Of these major complications, death during or within 24 hours of the procedure occurs in 0.1% to 0.2% of patients. Such deaths may be caused by perforation of the heart or great vessels, cardiac arrhythmias, acute myocardial infarction, or anaphylaxis to radiographic contrast material. Individuals with an increased risk of death include those with (a) advanced (older than 70 years) or very young (younger than 1 year) age, (b) marked functional impairment (class IV angina or heart failure), (c) severe left ventricular dysfunction or coronary artery disease (particularly left main disease), (d) severe valvular disease, (e) severe comorbid medical conditions (i.e., renal, hepatic, or pulmonary disease), or (f) history of an allergy to radiographic contrast material. Patients with significant left main coronary artery stenosis have a substantially greater risk of periprocedural death (2.8%) compared with those without left main coronary artery stenosis (0.1%) (5,6).

***e*TABLE 79.0.3** COMPLICATIONS ASSOCIATED WITH DIAGNOSTIC CARDIAC CATHETERIZATION

Complications	**Percent**
Major	
Death	0.1
Cerebrovascular accident	0.07
Myocardial infarction	0.07
Arrhythmia (life threatening)	0.5
Vascular compromise	0.5–1.5
Anaphylaxis (to contrast material)	0.007
Minor	
Hives	2.0–3.0
Nausea/vomiting	~5.0
Vasovagal reaction	3.0

Myocardial infarction during or immediately after diagnostic catheterization occurs in approximately 0.07% of patients, but most are small and uncomplicated. Cerebrovascular accidents in the pericatheterization period may be (a) embolic (from the arterial catheter, guidewire, left ventricular or atrial thrombus, or dislodged atherosclerotic plaque) or (b) thrombotic (i.e., existence of previous extensive cerebrovascular disease that, in association with the hemodynamic alterations induced by arteriography, leads to inadequate cerebral perfusion).

Numerous minor complications may cause morbidity but exert no effect on mortality. Local vascular complications occur in 0.5% to 1.5% of patients. The incidence is similar for the brachial and femoral approaches and somewhat higher for the radial approach. After arterial catheterization by the brachial or radial approach, thrombosis, dissection, intimal flap formation, or subintimal hemorrhage may compromise blood flow to the hand or arm, and the patient may require thrombectomy or surgical exploration after catheterization. With the percutaneous femoral approach, hemorrhage, hematoma formation, or both at the arterial puncture site are the most common problems and, if severe, may require limited surgical exploration. Arteriovenous (AV) fistulae or pseudoaneurysm formation may occur, especially if protracted bleeding at the puncture site occurs after sheath removal, as may result from inadequate compression of the femoral vessel, insertion of large sheaths, severe systemic arterial hypertension, prolonged heparinization, or administration of thrombolytic or antiplatelet agents. Less commonly, femoral arterial thrombosis occurs, which requires urgent thrombectomy. Compression by a large hematoma or groin clamp may cause local nerve damage. Local infection may occur at the site of catheter entrance and manipulation, but this can usually be treated effectively with meticulous wound care and antibiotics.

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene (*yellow arrow*), as well as localized skin necrosis and livedo reticularis (*white arrows*).

Atheroemboli. Digital necrosis resulting from severe atheroemboli.

Livedo reticularis. Mottled reddish discoloration of the lower extremities with accompanying multiple ulcerations associated with atheroemboli.

The injection of radiographic contrast material commonly causes nausea and vomiting as well as a transient decrease in systemic arterial pressure. Occasionally, such injections are associated with allergic reactions of varying severity, and a rare individual has anaphylaxis. Only 15% of individuals with a known allergy to contrast material have another adverse reaction with repeat administration, and most of these are minor (urticaria, nausea, vomiting) (7). In the vast majority of patients with a history of contrast allergy, angiography can be performed safely; however, premedication with glucocorticosteroids and antihistamines as well as use of a nonionic contrast agent are usually recommended. The endocardial injection of contrast material during ventriculography (so-called endocardial staining) may cause ventricular irritability. Finally, use of excessive quantities of radiographic contrast material may result in renal insufficiency, which is usually transient. This is particularly likely to occur in patients with preexisting renal dysfunction and diabetes mellitus, and its occurrence can be minimized by (a) limiting the amount of contrast material used during catheterization based on the patient's body surface area and baseline serum creatinine (8), and (b) administering sufficient oral and intravenous fluids after catheterization to ensure that the osmotic diuresis caused by the hyperosmolar contrast material does not induce intravascular volume depletion.

TECHNIQUES OF CARDIAC CATHETERIZATION

Approaches

Catheterization of the right and left sides of the heart can be accomplished by the introduction of catheters (a) by direct vision (into the brachial vein and artery) (9) or (b) by percutaneous puncture (of the radial artery or femoral or brachial vein and artery) (10). The choice of approach (brachial, femoral, or radial) for venous and arterial catheterization is determined by the preference and experience of the operator as well as the anatomic and pathophysiologic abnormalities of the patient. In general, right-sided heart catheterization is easier via the brachial approach in the patient with right ventricular or right atrial dilatation. In contrast, in the patient with a secundum atrial septal defect, a right-sided heart catheter can be passed across the defect more easily via the femoral approach. Thus, in choosing the route for right-sided heart catheterization, it is necessary to be cognizant of anatomic abnormalities and specific disease entities. In most patients, left-sided heart catheterization can be performed by the radial, brachial, or femoral approach. However, the femoral approach offers several advantages. This approach can be performed quickly and repeatedly in the same patient, allows the use of larger lumen catheters, and has a low incidence of infection or vascular injury. Certain conditions, however, render left-sided heart catheterization by the femoral approach difficult, such as extensive peripheral vascular disease, marked obesity, severe systemic arterial hypertension, bleeding diatheses, and any disorder that results in a markedly augmented arterial pulse pressure (e.g., severe aortic regurgitation). In the patient with any of these conditions, the brachial or radial approach may be safer if performed by an operator experienced with this technique. In turn, the brachial or radial approach for left-sided heart catheterization is relatively contraindicated if there is evidence of severe brachiocephalic or ulnar arterial disease.

Brachial Approach

To use the brachial cutdown approach, local anesthetic is introduced into an area 3 to 4 cm in diameter, approximately 1 cm above the flexor crease of the arm, after which a transverse cutdown is performed. If both right- and left-sided heart catheterization is planned, the incision should be wide (2 to 3 cm in length) and located over the brachial artery; if only right-sided heart catheterization is contemplated, a small incision can be made directly over a brachial vein. Once the skin incision is made, the subcutaneous tissues are separated by blunt dissection with a curved hemostat. The vein and artery are isolated with bands, separated from adjacent tissues, and cleaned. The catheters are introduced under direct vision and are advanced into the great vessels and heart.

After catheterization by the brachial cutdown approach, the catheters are removed, and the vein used for right-sided heart catheterization is ligated. The artery used for left-sided heart catheterization is rendered free of thrombi, and the arteriotomy is repaired. After blood flow has been successfully restored to the distal arm, the wound is flushed with saline, the incision is sutured, and the site of the cutdown is appropriately dressed. Alternatively, the brachial approach can be performed percutaneously in a manner similar to the femoral approach described in the next section.

Brachial artery hematoma. Hematoma complication after brachial artery catheterization and urokinase administration.

Femoral Approach

To use the percutaneous femoral approach, local anesthetic is introduced into an area 3 to 4 cm in diameter 3 to 4 cm below the inguinal ligament (the inguinal ligament extends from the anterior superior iliac crest to the symphysis pubis). The anticipated puncture site should overlie bone, thus allowing for adequate vessel compression when the sheaths are removed. A small incision (approximately $^1/_2$ cm in length) is made over the vessel(s) to be used for catheter introduction and passage, after which a "tunnel" is constructed (using a straight hemostat) at a 30- to 45-degree angle to the surface of the skin and to the approximate depth of the desired femoral vessel. An 18-gauge needle is introduced through the skin incision and tunnel into the lumen of the femoral artery or vein. Once blood flows freely through the needle, a Teflon-coated guidewire is advanced into the lumen of the punctured vessel. The wire is held firmly in place as the needle is removed, and the wire is wiped to remove blood and thrombi. Then, a sheath with a side arm port is advanced over the wire into the vessel lumen, and the wire is removed. The side arm port allows continuous pressure monitoring and infusion as catheters are advanced through the sheath to the heart. After catheterization, the vascular sheaths are

removed, and hemostasis is achieved by applying pressure over the puncture site (generally 1.0 to 1.5 cm cephalad to the skin incision) for sufficient time to ensure the cessation of bleeding. Hemostasis is generally obtained by applying direct pressure to the puncture site on the femoral vein for 5 to 10 minutes and on the femoral artery for 20 to 30 minutes. Subsequently, the patient is required to remain in bed and to immobilize the involved limb for 8 to 24 hours, depending on sheath size. The percutaneous brachial technique is performed in a similar manner by creating a tunnel 1 cm above the flexor crease of the arm.

Radial Approach

Diagnostic and interventional catheterization procedures can be performed via percutaneous cannulation of the radial artery with No. 5 or 6 Fr sheaths. Because of its small caliber, the radial artery may spasm during sheath placement or catheter manipulation, requiring treatment with intraarterial nitroglycerin or a calcium channel blocker. Bleeding is uncommon with the radial approach, but radial artery thrombosis occurs in 5% to 10% of patients, usually without sequelae provided that a preprocedure Allen's test result confirmed adequate perfusion of the hand through the ulnar artery. The major advantage of the radial approach is that it allows the patient to ambulate soon after catheterization, which is conducive to the performance of outpatient diagnostic and interventional procedures.

Allen's test. To test the competence of the collateral circulation of the radial and ulnar arteries, a patient is asked to pump his or her hands after which both arteries are occluded (1). Then the pressure on one artery is released (2). Rapid return of blood flow signifies a normal response. The same steps are repeated with the other artery (3). Combined, 4.

Transseptal Approach

In situations in which access to the left atrium is necessary, a transseptal catheterization is performed. With this technique, a long sheath is placed percutaneously in the right femoral vein and advanced to the right atrium over a guidewire. A special transseptal needle is advanced through the sheath and used to puncture the interatrial septum. The sheath is then advanced over the needle into the left atrium and the needle withdrawn from the body. Through the sheath, left atrial pressure can be measured, and catheters can be placed for therapeutic procedures, such as mitral valvuloplasty. The transseptal approach should not be attempted in the patient with (a) severely distorted or malaligned cardiac anatomy, (b) left atrial thrombus, (c) left atrial myxoma, or (d) a bleeding diathesis. In experienced hands, significant complications (cardiac perforation, pericardial tamponade, ventricular fibrillation, cerebrovascular event, or death) occur in 1% to 2% of transseptal procedures (11).

Left Ventricular Puncture

In rare circumstances, placement of a catheter in the left ventricle across the aortic (or mitral) valve is not advisable. For example, advancement of a catheter across a tilting disc prosthetic valve may result in catheter entrapment. Accordingly, direct puncture of the left ventricle through the chest wall can be performed to measure left ventricular pressure and to perform left ventriculography. With this approach, after generous local anesthesia, an 18-gauge needle is inserted at the apical impulse and directed toward the long axis of the left ventricle (toward the right shoulder). When heart pulsations or ventricular ectopy are noted, the needle is in contact with the ventricular epicardium, and it is slowly advanced until pulsatile blood flow is noted. Left ventricular pressure can be measured directly through the needle. If ventriculography is to be performed, the needle can be exchanged over a guidewire for a No. 4 or 5 Fr pigtail catheter. Significant complications (cardiac tamponade, hemothorax, pneumothorax, ventricular fibrillation) occur in 3% to 10% of these procedures, and vasovagal reactions occur in approximately 5% (12).

Endomyocardial Biopsy

Percutaneous endomyocardial biopsy may be performed to obtain pieces of myocardial tissue for microscopic examination. Most commonly, tissue is obtained from the right ventricle; however, left ventricular biopsy also can be performed. From the femoral or internal jugular vein, a long biopsy sheath with a side arm port is advanced to the right ventricle over a guidewire. Then, under fluoroscopic guidance, the bioptome is advanced through the long sheath and directed toward the interventricular septum. After it has exited the end of the sheath, its jaws are opened, and it is advanced to the septum. The jaws are then tightly closed, and the bioptome is briskly withdrawn through the sheath to tear away a small piece of tissue. This procedure is repeated until three to five tissue specimens are obtained. Local complications related to vascular access (i.e., venous thrombosis, hemorrhage, pneumothorax, recurrent laryngeal nerve injury) are the most common problems associated with this

procedure and occur in 1% to 2% of patients. Transient arrhythmias or right bundle branch block from catheter manipulation is common, but sustained rhythm abnormalities are not. Cardiac perforation is rare (13), occurring in less than 0.05% of procedures, but may lead to pericardial tamponade and hemodynamic collapse, especially if not recognized promptly and treated appropriately. Other rare complications include tricuspid regurgitation (due to chordal tear) and formation of coronary artery to right ventricular fistulae (14).

VIDEO

Video 79.1 Transesophageal echo demonstrating a flail tricuspid valve after right heart biopsy in a transplant patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Right-Sided Heart Catheterization

During routine right-sided heart catheterization, measurements of pressures and oxygen saturations in the venae cavae, right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position can be performed, and CO can be quantified (see Table 79.1 for normal values). The measurement of right-sided pressures helps one to evaluate the severity of tricuspid or pulmonic stenosis, to assess the presence and severity of pulmonary hypertension, and to calculate pulmonary vascular resistance. In the absence of pulmonary vein stenosis (a rare condition), the pulmonary capillary wedge pressure accurately reflects left atrial pressure. The determination of oxygen saturations from the various right-sided heart chambers is used to assess the presence, location, and magnitude of intracardiac left-to-right shunting, such as occurs with atrial or ventricular septal defect or patent ductus arteriosus. Occasionally, angiography is performed to define right-sided anatomic abnormalities or to evaluate the severity of right-sided valvular regurgitation.

Flows	
Cardiac index (L/min/m²)	2.6–4.2
Stroke volume index (mL/m²)	35–55
Pressures (mm Hg)	
Aorta/systemic artery	
Peak systolic/end diastolic	100–140/60–90
Mean	70–105
Left ventricle	
Peak systolic/end diastolic	100–140/3–12
Left atrium (pulmonary capillary wedge)	
Mean	1–10
'a' wave	3–15
'v' wave	3–15
Pulmonary artery	
Peak systolic/end diastolic	16–30/0–8
Mean	10–16
Right ventricle	
Peak systolic/end diastolic	16–30/0–8
Right atrium	
Mean	0–8
'a' wave	2–10
'v' wave	2–10
Resistances	
Systemic vascular resistance	
Wood units	10–20
Dynes·sec·cm⁻⁵	770–1500
Pulmonary vascular resistance	
Wood units	0.25–1.50
Dynes·sec·cm⁻⁵	20–120
Oxygen consumption (mL/min/m²)	110–150
AVO₂ difference (mL/dL)	3.5–4.5

AVO₂, arteriovenous.

TABLE 79.1 NORMAL HEMODYNAMIC VALUES

For optimal measurement of right-sided heart pressures, a relatively stiff, large-lumen, nonflotation catheter is used, which can be advanced until it “wedges” in a small pulmonary artery. The catheter’s position in the pulmonary capillary wedge location is confirmed by obtaining blood with an oxygen saturation greater than 95%. Alternatively, a softer, balloon-tipped flotation catheter can be used. With this catheter, the acquisition of a blood sample to confirm the pulmonary capillary wedge position is often difficult, and the fidelity of the pressure recordings obtained with it is less ideal than that obtained with a stiffer, large-lumen catheter; however, its ease of passage and paucity of complications make it more suitable for use by operators with limited experience. Furthermore, because it is flow directed, it often can be advanced through the right side of the heart without fluoroscopic guidance. Finally, addition of a thermistor to the flotation catheter’s distal portion allows one to measure CO by the thermodilution technique.

Left-Sided Heart Catheterization

With left-sided heart catheterization, one can assess (a) mitral and aortic valvular function, (b) left ventricular pressures and function, (c) systemic vascular resistance, and (d) coronary arterial anatomy. To perform angiography or to measure the pressure in the left ventricle, one usually advances a catheter retrograde across the aortic valve. In rare circumstances in which this is impossible (e.g., severe aortic stenosis or a tilting-disc prosthetic valve in the aortic position), transseptal catheterization is performed, and the catheter is advanced to the left ventricle antegrade across the mitral valve.

During most catheterizations, pressures are measured directly from each of the cardiac chambers except the left atrium. The left atrial pressure is generally recorded “indirectly,” that is, as the pulmonary capillary wedge pressure. To accomplish this, an end-hole catheter is placed in the pulmonary artery and advanced into the pulmonary arterial tree until it is effectively wedged. If the catheter is wedged adequately, the resultant pressure is left atrial, and the blood withdrawn from it is fully saturated. The demonstration that fully saturated blood can be withdrawn from the catheter confirms that the pressure is indeed left atrial. When a direct left atrial pressure recording is needed, a transseptal catheterization can be performed.

HEMODYNAMIC MEASUREMENTS

Cardiac Output

The role of the heart is to deliver an adequate quantity of oxygenated blood to the body. This flow of blood is known as the *CO* and is expressed in liters per minute. Since the magnitude of CO is proportional to body surface area, one person may be compared with another by means of the cardiac index (i.e., the CO adjusted for body surface area). The normal cardiac index is 2.6 to 4.2 L per minute per m^2 of body surface area (Table 79.1). The two commonly used methods of measuring CO are the Fick method and the indicator dilution technique. The latter can be performed by thermodilution or the injection of indocyanine green.

Fick Method

The measurement of CO by the Fick method is based on the hypothesis that the uptake or release of a substance by an organ is the product of the blood flow to that organ and the regional AV concentration difference of the substance (15). To measure CO in humans, this principle is applied to the lungs, and the substance measured is oxygen (O_2). By measuring the amount of O_2 extracted from inspired air by the lungs and the AVO_2 difference across the lungs, pulmonary blood flow may be calculated. Because pulmonary blood flow is similar to systemic blood flow in most people, the Fick method allows one to measure systemic blood flow. The Fick formula for the calculation of CO is:

$$\text{CO (L/min)} = \frac{O_2 \text{ consumption (mL/min)}}{AVO_2 \text{ difference across the lungs (mL/L)}}$$

The normal O_2 consumption index (O_2 consumption per m^2 of body surface) is 110 to 150 mL per minute per m^2 (Table 79.1) (16). In general, the O_2 consumption is higher for men than women and decreases gradually with age. It increases with hyperthyroidism, hyperthermia, and exercise, whereas it decreases with hypothyroidism and hypothermia. In many laboratories, the O_2 consumption is estimated from a nomogram, formula, or table. However, studies (17) have demonstrated a poor relationship between estimated and measured O_2 consumption (Fig. 79.1), in part because of the wide range of values among patients (eFig. 79.1.1) (16). Thus, to determine CO accurately via the Fick method, O_2 consumption should be measured directly.

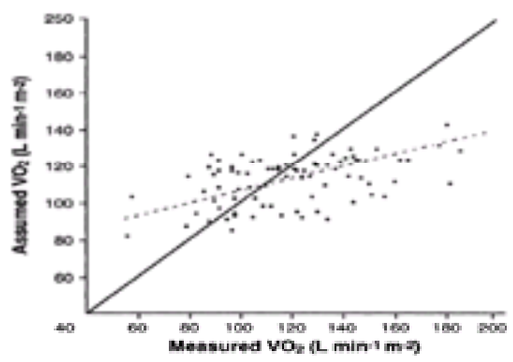
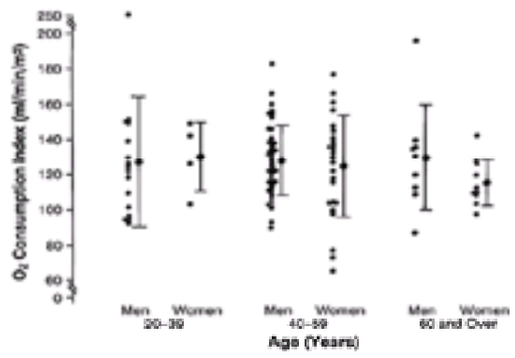
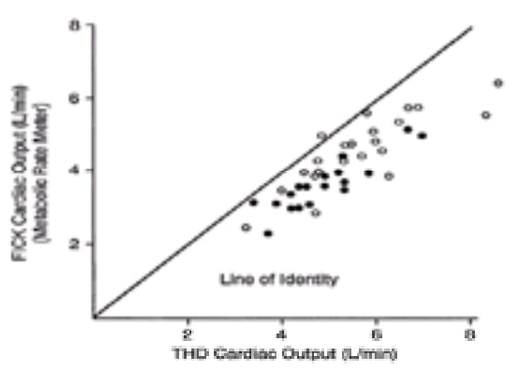


FIGURE 79.1 Comparison of measured (*x*-axis) and assumed (*y*-axis) oxygen consumption (VO_2), with the latter derived from a formula. The relationship between the measured and assumed oxygen consumptions is poor. (From Kendrick AH, West J, Papouchado M, et al. Direct Fick cardiac output: are assumed values of oxygen consumption acceptable? *Eur Heart J* 1988;9:337–342, with permission.)



***e*FIGURE 79.1.1** Oxygen consumption (indexed to body surface area) for men and women in three age groups: 20 to 39 years, 40 to 59 years, and 60 years or older. Each symbol represents the data from one patient, and the means and standard deviations for each group are displayed. Although the mean values for oxygen consumption are similar for each of the groups, the range of values is large (65 to 250 mL per minute per m^2), so that an estimate of oxygen consumption in an individual subject may be markedly inaccurate. (From Dehmer GJ, Firth BG, Hillis LD. Oxygen consumption in adult patients during cardiac catheterization. *Clin Cardiol* 1982;5:436–440, with permission.)

The O_2 consumption can be determined directly by two methods. The most reliable method involves collecting a timed sample (usually 3 to 4 minutes) of expired air in a special receptacle called a *Douglas bag*. The volume of this collection is measured, and the difference in O_2 content between inspired and expired air is calculated. From these data, the person's O_2 consumption (in mL per minute) is determined. More commonly, O_2 consumption is determined by commercially available polarographic machines (i.e., MRM-2, Waters Instruments, Rochester, MN; MedGraphics System, Medical Graphics, St. Paul, MN), which have carbon dioxide, or oxygen, or both kinds of sensors and continuously measure air flow and fractional content of carbon dioxide, oxygen, or both from expired air collected through the port of a mouthpiece or tight-fitting face mask. Because of potential inaccuracies of the polarographic systems (*e*Fig. 79.1.2) (18), laboratories that use them should regularly assess their reliability by comparing results obtained with them with other methods, such as a standard Douglas bag collection.



***e*FIGURE 79.1.2** Comparison of thermodilution (THD) cardiac output (*x*-axis) and the Fick cardiac output (*y*-axis), with the latter calculated using oxygen consumption measured with the metabolic rate meter. Open and closed circles represent data collected at two different hospitals, and the line of identity is shown. Compared with the thermodilution technique, the results of Fick using the oxygen consumption measured with the metabolic rate meter were consistently low. (From Lange RA, Dehmer GJ, Wells PJ, et al. Measurement of oxygen consumption and cardiac output: limitations of the metabolic rate meter. *Am J Cardiol* 1989;64:783–786, with permission.)

Determining the AVO_2 difference across the lungs requires that blood from the vessels entering and draining the lungs (i.e., the pulmonary artery and vein) be analyzed for O_2 content. Since the O_2 content of pulmonary venous blood is similar to that of systemic arterial blood (provided that a right-to-left shunt is not present), systemic and pulmonary arterial samples are usually obtained for the Fick determination of CO. The O_2 content of pulmonary and systemic arterial blood may be measured directly or calculated from the O_2 saturation of the blood and its hemoglobin (Hgb) concentration: O_2 content = Hgb (in g per 100 mL) × 1.36 (mL O_2 per g Hgb) × saturation, where 1.36 is the maximum O_2-carrying capacity of 1 g of Hgb. The normal AVO_2 difference is 3.0 to 4.5 vol percent (mL O_2 per dL of blood). The following is an example of the Fick calculation of CO: (a) O_2 consumption = 250 mL per minute; (b) Hgb = 14 g per dL; (c) systemic arterial O_2 saturation = 0.95 (95%); (d) pulmonary arterial O_2 saturation = 0.65 (65%); and (e) 10 = dL per L (conversion factor).

$$CO = \frac{250}{(14)(1.36)(10)(0.95) - (14)(1.36)(10)(0.65)} = 4.38 \text{ L per minute}$$

The Fick method has several potential sources of error (19). First, an incomplete collection of expired air causes an underestimation of O_2 consumption, leading to the calculation of a falsely low value for CO. This is the most common source of error. Second, incorrect timing of the collection of expired air leads to an inaccurate estimate of O_2 consumption. Third, analysis of the Douglas bag contents should be performed soon after its collection, since air may diffuse in or out of the bag if a substantial delay between collection and analysis is allowed to occur. Fourth, with commercially available polarographic systems, determination of the fractional content of oxygen or carbon dioxide may be inaccurate if the gas sensors are not calibrated regularly and correctly. Fifth, spectrophotometric determination of the O_2 saturations may be inaccurate if certain substances, such as indocyanine green, have been introduced into the blood. Finally, the mixed venous blood sample must, indeed, be *mixed venous*. It is generally obtained from the pulmonary artery; it must not be partially contaminated by pulmonary capillary wedge blood or left-to-right shunted blood.

The average error in determining O_2 consumption is approximately 6%, and that for AVO_2 difference is 5%. When the AVO_2 saturation difference is small, errors in measurement are magnified. Therefore, the Fick method is most accurate in the patient with a low CO (i.e., one with a relatively wide AVO_2 saturation difference) and least accurate in one with a high CO (i.e., one with a relatively narrow AVO_2 saturation difference) (Table 79.2).

Method	Most reliable	Least reliable
Fick	Low cardiac output	High cardiac output
Thermodilution	High cardiac output	Pulmonic regurgitation Tricuspid regurgitation Intracardiac shunting
Indocyanine green	High cardiac output	Aortic regurgitation Mitral regurgitation Low cardiac output Intracardiac shunting
Angiographic	Normal shaped ventricle	Extensive segmental wall motion abnormalities Dilated ventricle Aortic regurgitation* Mitral regurgitation*

*In these circumstances, angiographic output is greater than forward cardiac output (see text).

TABLE 79.2 METHODS FOR DETERMINING CARDIAC OUTPUT AND CONDITIONS IN WHICH THEY ARE MOST (OR LEAST) RELIABLE

Indicator Dilution Technique

The indicator dilution technique is based on the principle that the volume of fluid within a container can be determined if one adds a known quantity of indicator to the fluid and then measures the concentration of the indicator after it has completely mixed with the fluid. To determine CO, a known amount of indicator is injected into the circulation and allowed to mix completely in the blood, after which its concentration is measured over time. A time-concentration curve is generated (Fig. 79.2), and a minicomputer calculates the area of the inscribed curve.

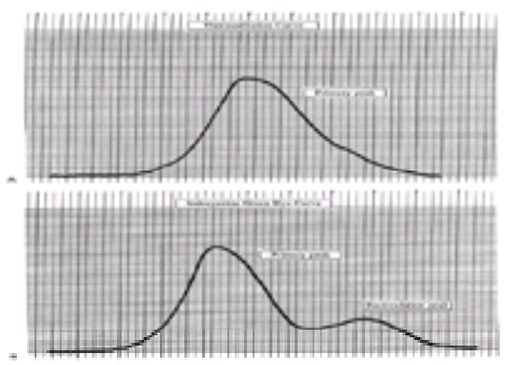


FIGURE 79.2 Time-activity curves for the indicator dilution technique for determining cardiac output: thermodilution **(A)** and indocyanine green **(B)**. With indocyanine green, a primary peak and a recirculation peak are present, whereas with thermodilution, only a primary peak is observed.

The indicator most often used to measure CO is cold saline or 5% dextrose in water. A balloon-tipped flow-directed polyvinyl chloride catheter with a thermistor at its tip and an opening 25 to 30 cm proximal to the tip is inserted into a vein and advanced to the pulmonary artery, so that the proximal opening is located in the venae cavae or right atrium, and the thermistor is in the pulmonary artery. Five to 10 mL of iced fluid is injected into the proximal port, and the change in temperature at the thermistor is recorded (20,21). CO via the thermodilution method is calculated with a computer via the equation:

$$\mathrm{CO} = \frac{(T_B - T_I)(\mathrm{vol})(60)(1.10)(0.825)}{\int \Delta T_B(t)\,dt}$$

in which T_B = body temperature, T_I = temperature of the injectate, vol = volume of the injectate (in milliliters), 60 = number of seconds in 1 minute, and 1.10 = ratio of the products of specific heat and gravity for normal saline and blood; 0.825 is an empiric factor that accounts for the warming of injectate within the catheter. The denominator of the equation is the integral of the change in blood temperature during the injection of cold and is reflected by the area of the inscribed curve (Fig. 79.2). The thermodilution technique is relatively inexpensive, easy to perform, widely available, and does not require arterial sampling or blood withdrawal. In most patients, it accurately determines pulmonary blood flow, which (in the absence of intracardiac shunting) is similar to systemic blood flow. However, certain conditions may render the results of the thermodilution technique unreliable, including (a) tricuspid or pulmonic regurgitation (22) and (b) intracardiac shunting (Table 79.2).

Indocyanine green, an easily detectable, water-soluble, nontoxic substance, can also be used for the indicator dilution measurement of CO (23). To do so, (a) a known concentration (5 to 10 mg) of indicator must be injected; (b) there must be complete mixing of the indocyanine green between the sites of injection and sampling; and (c) there must be no metabolism or disappearance of the indicator between the sites of injection and sampling. In most catheterization laboratories that use this method, CO is measured by injecting indocyanine green into the pulmonary artery as blood is withdrawn at a constant rate from a systemic artery through an optical densitometer (Fig. 79.2). The lungs, left atrium, and left ventricle act as adequate mixing sites, and there is no degradation of indocyanine green between the pulmonary and systemic arteries. The calculation of CO by the indicator dilution technique is usually done by a minicomputer, which establishes that the downslope of the inscribed curve is exponential. It then computes the area inscribed by the curve, excluding the recirculation peak. The results obtained with this method compare favorably with those of other techniques for measuring CO, but it may provide inaccurate results in circumstances in which the recirculation peak cannot be easily separated from the primary peak (e.g., low CO) or when one of the valves between the site of injection and sampling (i.e., mitral or aortic) is regurgitant (Table 79.2).

To ensure an accurate assessment of CO via the indicator dilution technique, great care must be taken to (a) inject an exact amount of indicator, (b) inject the indicator as rapidly as possible (so that, in fact, it is delivered as a bolus), (c) calibrate the densitometer and recorder systems precisely, and (d) ensure that the withdrawal of blood (in the case of indocyanine green) at the sampling site is uniform and not accompanied by air bubbles. If care is taken to eliminate these potential sources of error, the indicator dilution technique is a reliable method of measuring CO. It is most accurate in individuals with a high CO and least accurate in those with a low CO and in those with valvular regurgitation between the sites of indicator injection and sampling (24) (Table 79.2).

Angiographic Technique

From the left ventriculogram, one can determine the volume of blood ejected with each heart beat (stroke volume) and then multiply it by heart rate, yielding the angiographic CO. In patients with mitral or aortic regurgitation, a portion of the blood ejected from the left ventricle regurgitates into the left atrium or ventricle and does not enter the systemic circulation. In these patients, the angiographic CO exceeds the forward output. The measurement of CO by the angiographic method is potentially erroneous in patients with extensive segmental wall motion abnormalities or misshapen ventricles, in whom the determination of stroke volume may be inaccurate (Table 79.2).

Pressure Measurement

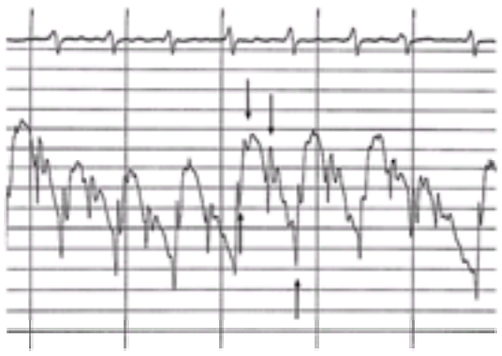
Fluid-Filled Systems

One of the most important functions of cardiac catheterization is the accurate measurement and recording of intracardiac pressures. Once a catheter has been positioned in the desired cardiac chamber, it is connected directly or through stiff, fluid-filled tubing to a pressure transducer, which transforms a pressure signal into an electrical signal (via a Wheatstone bridge). The accurate measurement of pressures requires close attention to the details of the catheter-transducer system, including proper transducer balancing as well as removing air bubbles and blood from the catheters and connections. Errors in pressure measurement may occur in several ways. First, an accurate zero reference is essential. All manometers must be referenced to the same zero level, and their position must be adjusted if the patient's position is altered. Second, pressure transducers must be calibrated frequently, preferably before each pressure recording. To allow for a meaningful interpretation of hemodynamic data, they should be collected (a) with the patient in a steady state, (b) in close temporal proximity to one another (all pressure measurements and

assessments of CO should be completed within 10 to 15 minutes), and (c) before the introduction of radiographic contrast material or other agents known to alter hemodynamic variables.

Micromanometer-Tipped Catheters

With a fluid-filled recording system, distortion of the pressure waveform (eFig. 79.2.1) occurs as a result of (a) motion of the catheter within the heart (so-called catheter whip artifact), (b) amplification of the systolic pressure in the periphery, (c) catheter movement caused by closing or opening of valves, and (d) excessive damping or augmentation of the frequency response of the system. Despite these shortcomings, the pressure recordings obtained with a fluid-filled system provide adequate information in most clinical situations. However, when it is important to obtain precise pressure recordings with undistorted contours (e.g., in the patient with suspected constrictive or restrictive physiology), such a system may be inadequate. To improve the frequency response and to decrease distortion of the pressure recordings, micromanometer pressure chips have been mounted on the end of catheters to measure intracardiac pressures directly (Millar Instruments, Houston, TX). These catheters provide undistorted high-fidelity pressure recordings, such as are necessary to assess pressure waveform contours (especially in the tachycardic patient) and to measure accurately the rate of ventricular pressure rise (dP/dT) or other sophisticated hemodynamic variables.



***e*FIGURE 79.2.1** A pulmonary arterial pressure recording obtained through a balloon-tipped flow-directed catheter. There is distortion of the pressure waveform (*arrows*) from “catheter whip” caused by motion of the catheter within the heart and catheter movement caused by closing or opening valves. Such pressure recording artifacts can be minimized by using a stiff large-lumen catheter or a micromanometer-tipped catheter to record pressures. The distance between each horizontal line represents 4 mm Hg, and the distance between each vertical time line represents 1 second.

Balloon-Tipped Flow-Directed (Swan-Ganz) Catheters

In 1970, the balloon-tipped flow-directed catheter was introduced for right-sided heart catheterization at the bedside, without the need for fluoroscopy (25). At present, it is widely used to monitor right-sided heart and pulmonary capillary wedge pressures in the critically ill patient in the intensive care unit. The catheter, which has an inflatable balloon at its tip, is made of polyvinylchloride and, therefore, is extremely soft. The standard balloon-tipped catheter has a thermistor at its tip and three lumens. One lumen allows inflation of the balloon with air; the other two lumens allow one to measure pressures and to obtain blood specimens at the catheter tip or an opening 25 to 30 cm proximal to the tip. When the catheter is inserted into a vein and advanced to the pulmonary artery, the proximal opening is located in the vena cava or right atrium, and the distal orifice and thermistor are in the pulmonary artery.

Before using the balloon-tipped catheter, the balloon should be inflated in saline to exclude air leakage, and the catheter lumen should be flushed with saline. A temporary transvenous pacing catheter should be positioned in the right ventricle in patients with a preexisting left bundle branch block before passage of any catheter from the right atrium to the pulmonary artery, because such passage may induce a transient right bundle branch block. The balloon-tipped catheter may be inserted at the bedside percutaneously (via the femoral, internal jugular, subclavian, or basilic vein) or by direct exposure of the brachial vein. When it is introduced without the use of fluoroscopy, it should be advanced 20 to 30 cm into the vasculature (depending on the site of introduction) before the balloon is inflated. The catheter is marked at 10-cm intervals to facilitate this procedure. Before advancing the catheter, blood should be aspirated through it to ensure that it is intravascular. The balloon is inflated gently with up to 1.5 mL of air to facilitate its flow-directed passage from the right atrium to the pulmonary artery. If there is resistance to balloon inflation, the catheter should be advanced or withdrawn carefully until the balloon can be inflated freely. The catheter is then connected to a pressure transducer to record right atrial pressure. It is also valuable to obtain a blood sample for oximetric analysis in each right-sided heart chamber or vessel where pressures are recorded to exclude left-to-right intracardiac shunting.

Once a blood sample and pressure have been obtained from the right atrium, the balloon is inflated and the catheter gently advanced while observing pressure and the electrocardiogram. If the catheter does not pass easily through the right ventricle to the pulmonary artery, or significant ventricular ectopy occurs, it should be withdrawn to the right atrium and the procedure repeated. Once it has passed to the pulmonary artery and the pressure has been recorded, it is advanced gently (with the balloon still inflated) until the waveform changes to that of a pulmonary capillary wedge pressure. A fully oxygenated blood specimen from this site confirms that the catheter is truly in a wedged position. When the balloon is deflated, the waveform should revert to that of pulmonary arterial pressure.

It is occasionally impossible to pass the balloon-tipped catheter without the use of fluoroscopic guidance, particularly in the patient with a large right atrium or ventricle or the subject with pulmonary hypertension. In this case, it may be necessary to introduce a 0.025-in. J-tipped guidewire into the catheter to stiffen it, after which it is advanced under fluoroscopic visualization. Passage of the catheter without the use of fluoroscopy is easier when the site of vascular entry is central (i.e., internal jugular or subclavian vein) rather than peripheral.

The balloon-tipped flow-directed catheter offers several advantages over the more traditional stiff catheter used for right-sided heart catheterization; however, it also has drawbacks. Because it is unusually soft, perforation of the major vessels or heart is virtually impossible, whereas such perforation occasionally occurs with the use of a stiff catheter. As indicated, the flow-directed catheter can be inserted and advanced without fluoroscopic control, although catheter manipulation is easier with fluoroscopic assistance. Apart from its safety, the balloon-tipped flow-directed catheter is equipped with a distal thermistor to measure CO by the thermodilution technique.

The major disadvantages of the balloon-tipped flow-directed catheter stem from the same features that are responsible for its advantages. First, because the catheter is unusually soft, the pressure recordings obtained through it may contain a good deal of “catheter whip,” that is, artifact introduced by the movement of the catheter itself within the heart. Second, since the catheter is no larger than No. 7 Fr in size and yet contains several lumens, the distal lumen is small, making the aspiration of blood difficult. Third, since this catheter is advanced in the direction of blood flow, its placement in the pulmonary artery may be impossible if flow within the right-sided heart chambers is bidirectional. For example, advancing a balloon-tipped flow-directed catheter to the pulmonary artery in a patient with severe tricuspid regurgitation may be difficult, since the jet of regurgitation directs the catheter from the right ventricle back into the right atrium. Despite these limitations, this catheter almost always allows one to measure right-and left-sided filling pressures and to make appropriate therapeutic decisions regarding fluid and drug administration.

The risks and complications of the balloon-tipped flow-directed catheter are similar to those of any catheter used for right-sided heart catheterization: ventricular irritability or transient right bundle branch block during passage through the right ventricle and local inflammation or infection at the site of entrance. In addition, because of its softness, the balloon-tipped catheter is easily knotted. Improper or prolonged inflation of the balloon can lead to rupture of a small pulmonary artery or to subsegmental pulmonary infarction, respectively. By and large, however, the balloon-tipped flow-directed catheter is extremely safe. Once it is positioned in the pulmonary artery, it may be left in place for 48 to 96 hours.

Pressure Waveforms

Right atrial systole follows the P wave of the electrocardiogram and produces the ‘a’ wave of the right atrial pressure tracing (Fig. 79.3). With atrial relaxation, there is a decline in the pressure, which is known as the *‘x’ descent*. This descent may be interrupted by a slight upward deflection, the ‘c’ wave, due to tricuspid valve closure. Filling of the right atrium from the venous circulation and retrograde movement of the tricuspid valve annulus during right ventricular systole produce the ‘v’ wave, which follows the QRS complex on the electrocardiogram. When the tricuspid valve opens, blood from the right atrium empties into the right ventricle, and the right atrial pressure declines, producing the ‘y’ descent. During diastole, the right ventricular and right atrial pressures are equal if tricuspid stenosis is absent. Typically, the peak ‘a’ wave, ‘v’ wave, and mean right atrial pressures are reported. In the normal right atrium, the peak ‘a’ wave is higher than the peak ‘v’ wave pressure.

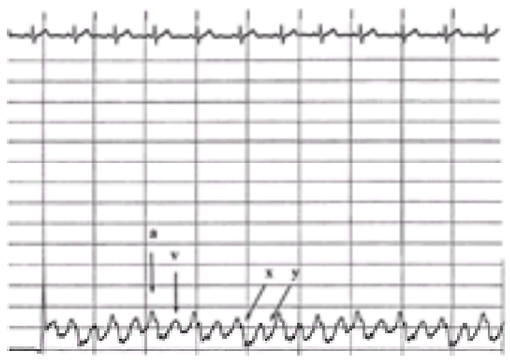


FIGURE 79.3 Typical pressure tracings from the right atrium. There is an ‘a’ wave, ‘x’ descent, ‘v’ wave, and ‘y’ descent, which correlate with right atrial systole, relaxation, filling, and emptying, respectively. The distance between each horizontal line represents 4 mm Hg, and the distance between each vertical time line represents 1 second.

In the right ventricular pressure tracing, atrial systole produces an ‘a’ wave, which occurs after the P wave of the electrocardiogram (Fig. 79.4). Right ventricular systole follows the QRS complex of the electrocardiogram and gives rise to the rapidly increasing systolic pressure waveform. With ventricular relaxation, the pressure waveform declines and reaches a nadir, after which continuous filling of the chamber from the right atrium causes a slow, steady rise in the pressure waveform. The peak systolic and end diastolic (measured at the peak of the QRS complex of the electrocardiogram) right ventricular pressures are usually reported. Similar pressures are reported for the left ventricle.

FIGURE 79.4 Simultaneous surface electrocardiogram and right ventricular pressure recordings. The right ventricular peak systolic pressure averages 45 mm Hg, and the end diastolic pressure (measured at the R-wave peak of the QRS complex) averages 16 mm Hg. The distance between each horizontal line represents 4 mm Hg, and the distance between each vertical time line represents 1 second.

The normal pulmonary arterial pressure consists of a systolic wave that coincides with right ventricular systole and follows the QRS complex of the electrocardiogram (Fig. 79.5). The decline of this pressure wave may be interrupted by a notch, the incisura, which is due to pulmonic valve closure, and the nadir of the decline represents the end diastolic pressure. The pulmonary arterial systolic, end diastolic, and mean pressures are usually reported. Similar pressures are reported for the aorta and peripheral arteries.

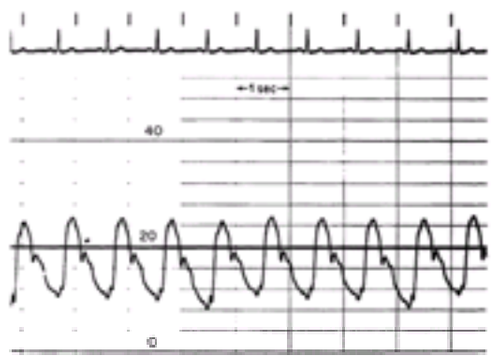


FIGURE 79.5 Simultaneous surface electrocardiogram and pulmonary arterial pressure tracings. The pulmonary arterial pressure averages 25/10 mm Hg, and the incisura, caused by closure of the pulmonic valve, is evident on the downslope of the pressure contour. The distance between each horizontal line represents 4 mm Hg, and the distance between each vertical time line represents 1 second. (From Willard JE, Lange RA, Hillis LD. Cardiac catheterization. In: Kloner RA, ed. *The guide to cardiology*, 3rd ed. New York: Wiley, 1995:145–164, with permission.)

When a catheter is advanced to the pulmonary capillary wedge position and its position confirmed oximetrically (by aspirating blood with an O_2 saturation greater than 95%), the pressure waveform obtained is a transmitted left atrial pressure (Fig. 79.6). The configuration of the waveform is similar to a right atrial pressure, in that there is an ‘a’ wave, ‘x’ descent, ‘v’ wave, and ‘y’ descent, which correlate with left atrial systole, relaxation, filling, and emptying, respectively. In the left atrium, however, the peak ‘v’ wave pressure is typically higher than the peak ‘a’ wave pressure. Transmission of the left atrial pressure through the pulmonary vasculature usually causes modest distortion of the pressure waveform (eFig. 79.6.1). To obtain the most accurate representation of left atrial pressure, the pulmonary capillary wedge pressure should be measured through a stiff catheter with a large lumen (26). Time is required for transmission of the left atrial pressure through the pulmonary vasculature. Thus, if left atrial and pulmonary capillary wedge pressures are recorded simultaneously, a 50- to 100-ms time difference is noted, with the pulmonary wedge pressure occurring later.

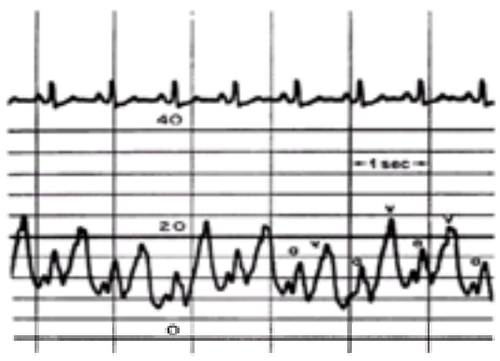
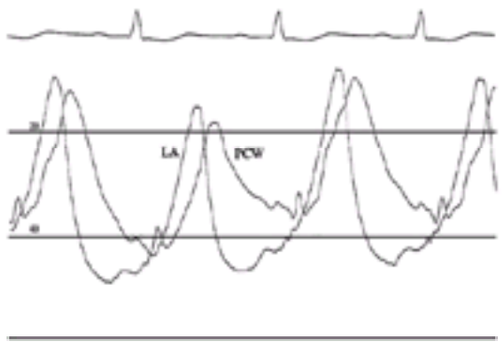
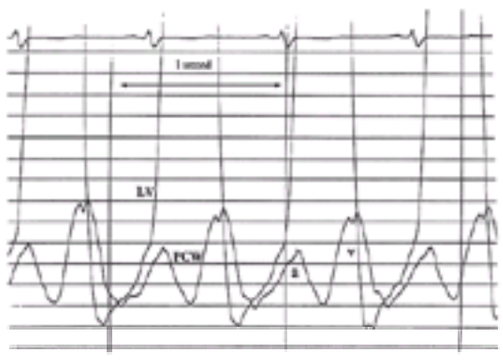


FIGURE 79.6 Pulmonary capillary wedge pressure tracing obtained through a stiff, large-lumen catheter, the position of which was confirmed oximetrically. Like the right atrial pressure tracing, there is an ‘a’ wave and ‘v’ wave, which correlate with atrial systole and filling, respectively. The distance between each horizontal line represents 4 mm Hg, and the distance between each vertical time line represents 1 second. (From Willard JE, Lange RA, Hillis LD. Cardiac catheterization. In: Kloner RA, ed. *The guide to cardiology*, 3rd ed. New York: Wiley, 1995:145–164, with permission.)



***e*FIGURE 79.6.1** Simultaneous recording of left atrial (LA) and pulmonary capillary wedge (PCW) pressures. In the absence of pulmonary vein stenosis, the PCW pressure is an accurate reflection of the LA pressure. However, there is a time delay and mild distortion of the pressure contour. The pressure peak and nadir are damped, and the 'y' descent is splayed as the LA pressure is transmitted through the pulmonary vasculature to the PCW position.

In addition to the recording of pressures from each of the cardiac chambers, it is important that the pressures from certain chambers be examined simultaneously to confirm or exclude the presence of valvular abnormalities (26,27). Thus, left ventricular and left atrial (or pulmonary capillary wedge) pressures should be recorded simultaneously to ascertain if mitral stenosis is present (*e*Fig. 79.6.2 and Fig. 79.7). Likewise, the left ventricular and systemic arterial pressures should be displayed concurrently to evaluate the presence or absence of left ventricular outflow tract obstruction (*e*Fig. 79.7.1 and Fig. 79.8). The recording of intracardiac and peripheral vascular pressures may demonstrate hemodynamic findings consistent with valvular regurgitation. For instance, large regurgitant waves in the pulmonary capillary wedge tracing may be indicative of mitral regurgitation or other causes of left atrial pressure or volume overload (Fig. 79.9) (28). Conversely, a wide peripheral arterial pulse pressure in conjunction with a greatly elevated left ventricular end diastolic pressure is suggestive of aortic regurgitation. In short, both the absolute level and the qualitative configuration of the intracardiac and peripheral vascular pressures are important in the diagnosis and quantitation of valvular heart disease. The normal intracardiac and peripheral vascular flows, pressures, and resistances are listed in Table 79.1.



***e*FIGURE 79.6.2** Simultaneous recording of left ventricular (LV) and pulmonary capillary wedge (PCW) pressures in a patient without mitral valve disease. The distance between each horizontal line represents 4 mm Hg. The PCW 'a' wave corresponds with the 'a' wave of the LV pressure trace, and the PCW 'v' wave occurs with the downslope of the LV trace. During diastole, the LV and PCW pressures are superimposed (there is no gradient between PCW and LV).

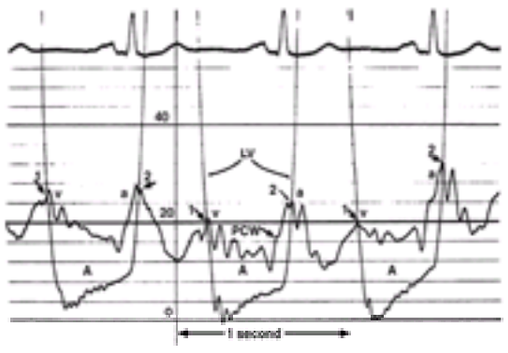
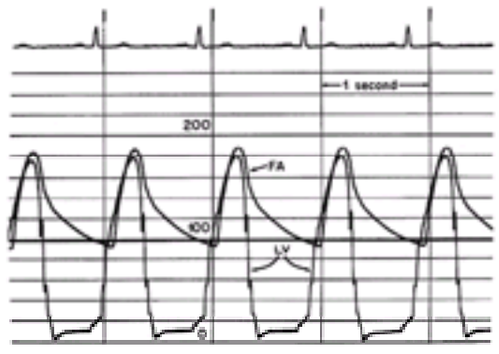


FIGURE 79.7 Simultaneous recording of left ventricular (LV) and pulmonary capillary wedge (PCW) pressures in a patient with severe mitral stenosis. Throughout diastole (from points 1 to 2), there is a pressure gradient (A) between the LV and PCW pressures. This patient had a cardiac output of 3,740 mL per minute and a heart rate of 68 beats/min. The mean diastolic filling period was 0.49 seconds per beat, and the mean pressure gradient was 13 mm Hg. Using Gorlin's equation, the mitral valve area is:

$$\frac{3{,}740/(68)(0.49)}{(38)(\sqrt{13})} = 0.8\ \text{cm}^2$$

(From Willard JE, Lange RA, Hillis LD. Cardiac catheterization. In: Kloner RA, ed. *The guide to cardiology*, 3rd ed. New York: Wiley, 1995:145–164, with permission.)



***e*FIGURE 79.7.1** Simultaneous recording of left ventricular (LV) and femoral arterial (FA) pressures in a patient without aortic stenosis. The pressure scale (in millimeters of mercury) is shown. There is no gradient during systole between LV and FA. (From Willard JE, Lange RA, Hillis LD. Cardiac catheterization. In: Kloner RA, ed. *The guide to cardiology*, 3rd ed. New York: Wiley, 1995:145–164, with permission.)

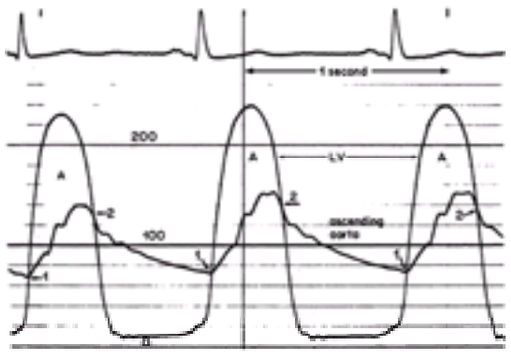


FIGURE 79.8 Simultaneous recording of left ventricular (LV) and ascending aortic pressures in a patient with severe aortic stenosis. Throughout systole, there is a pressure gradient (A) between the LV and ascending aorta. The patient had a cardiac output of 3,350 mL per minute and a heart rate of 62 beats/min. The systolic ejection period (between points 1 and 2) was 0.36 seconds per beat, and the mean systolic pressure gradient was 83 mm Hg. Thus, the aortic valve area was:

$$\frac{3{,}350/(62)(0.36)}{44.5(\sqrt{83})} = 0.4\ \text{cm}^2$$

(From Willard JE, Lange RA, Hillis LD. Cardiac catheterization. In: Kloner RA, ed. *The guide to cardiology*, 3rd ed. New York: Wiley, 1995:145–164, with permission.)

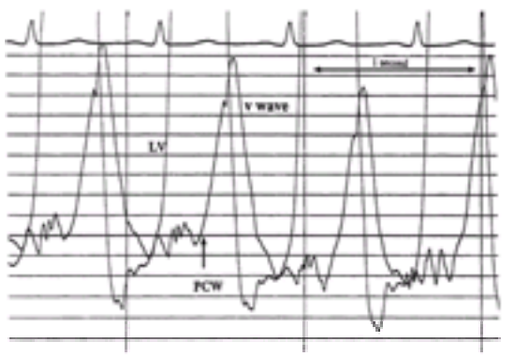


FIGURE 79.9 Simultaneous recording of left ventricular (LV) and pulmonary capillary wedge (PCW) pressures from a patient with severe mitral regurgitation. The PCW pressure tracing demonstrates large regurgitant ‘v’ waves.

Vascular Resistance

The resistance of a vascular bed is calculated by dividing the pressure gradient across the bed by the flow through it. Thus,

$$\text{Systemic vascular resistance} = \frac{\text{mean systemic arterial pressure} - \text{mean right atrial pressure}}{\text{systemic blood flow}}$$

and

$$\text{Pulmonary vascular resistance} = \frac{\text{mean pulmonary artery pressure} - \text{mean pulmonary vein pressure}}{\text{pulmonary blood flow}}$$

Since pulmonary venous pressure is not usually measured, left atrial or pulmonary capillary wedge pressure is substituted for it. Resistances are expressed in (a) resistance units (mm Hg per L per minute), (b) dynes-second-cm^{-5} (resistance units × 80), or (c) Wood units (resistance units × body surface area in m^2). The normal values for vascular resistances are displayed in Table 79.1.

An increased systemic vascular resistance is usually present in patients with systemic arterial hypertension. It may also be seen in the patient with a reduced forward CO and compensatory arteriolar vasoconstriction. In turn, a reduced systemic vascular resistance may be present in the patient with an inappropriately increased CO, the causes of which include AV fistula, severe anemia, high fever, sepsis, and thyrotoxicosis. An elevated pulmonary vascular resistance may be caused by primary lung disease, Eisenmenger’s syndrome (alterations in the pulmonary vasculature in response to increased pulmonary flow and pressure), and a greatly elevated pulmonary venous pressure due to left-sided myocardial or valvular dysfunction or both.

ASSESSMENT OF VALVULAR HEART DISEASE

Valvular Stenosis

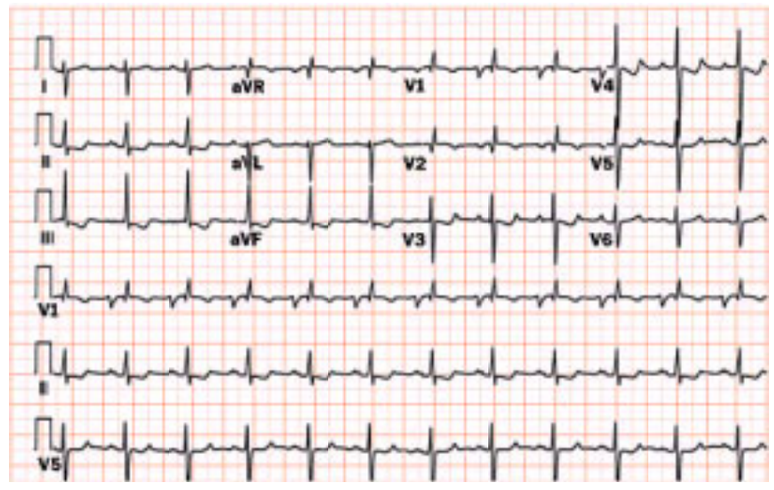
Through the application of standard fluid dynamic principles, the resistance to blood flow through a stenotic valve can be expressed as an effective valve orifice area (29). The data required for the calculation of a valve area may be obtained during cardiac catheterization. Specifically, the pressures on either side of a stenotic valve and the flow across it must be known. The Gorlin’s equation is then used to calculate the valve area:

$$\text{Valve area} = \frac{\text{CO}/(\text{DFP or SEP})(\text{heart rate})}{(\text{constant})\sqrt{\text{mean pressure gradient}}}$$

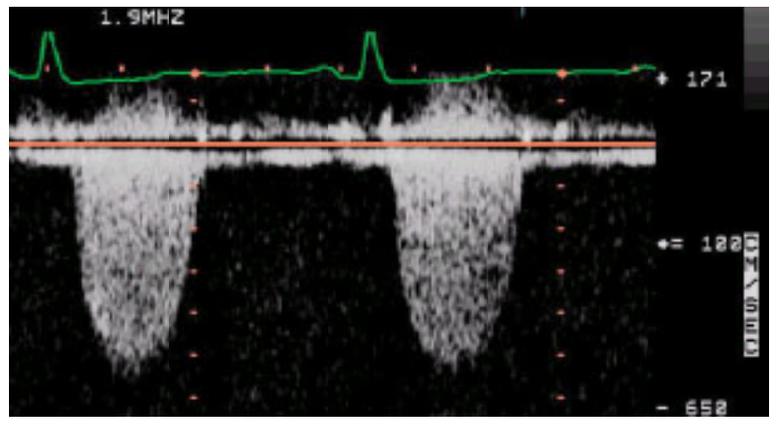
where DFP is diastolic filling period and SEP is systolic ejection period. If an atrioventricular valve (mitral or tricuspid) is being evaluated, the diastolic filling period is used; if the aortic or pulmonic valve is involved, the systolic ejection period is used. The filling periods and transvalvular gradient are measured from pressure tracings obtained simultaneously from either side of the stenotic valve. The constant used is 38.0 for the mitral valve and 44.5 for the other valves. The mean pressure gradient is the average gradient throughout systole (for aortic and pulmonic valves) or diastole (for mitral or tricuspid valves).

The normal mitral valve orifice area is 4 to 6 cm^2, and substantial stenosis may occur before a pressure gradient appears. A mitral valve with an effective orifice area less than 1.0 cm^2 is considered severely stenotic (Fig. 79.7); 1.1 to less than 1.5 cm^2, moderately stenotic; and 1.6 to less than 2.0 cm^2, mildly stenotic. A valve area greater than 2.0 cm^2 is not necessarily normal, but does not usually constitute a hemodynamically significant obstruction to flow. The normal aortic valve has a cross-sectional area of 3 to 4 cm^2, but hemodynamically important aortic stenosis does not develop until the valve orifice area falls below 1.1 to 1.3 cm^2. Specifically, an aortic valve with an effective orifice area less than 0.7 cm^2 is severely stenotic (Fig. 79.8); 0.8 to 1.0 cm^2, moderately stenotic; and 1.1 to 1.3 cm^2, mildly stenotic. The normal pulmonic valve has a cross-sectional area similar to the aortic valve. Although Gorlin’s equation can be applied to the pulmonic valve, by convention the severity of stenosis is based on the peak right ventricular systolic pressure. Pulmonic stenosis with a right ventricular peak systolic pressure of 25 to less than 50 mm Hg is termed mild; 50 to less than 100 mm Hg, moderate; and greater than 100 mm Hg, severe. Finally, the tricuspid valve is large, with a normal orifice area of 6 to 10 cm^2. The assessment of the severity of tricuspid stenosis is most accurate when right atrial and right ventricular pressures are recorded simultaneously. Patients with a tricuspid valve area less than 3.0 cm^2 in the presence of medically refractory right-sided heart failure should be considered for appropriate mechanical intervention (i.e.,

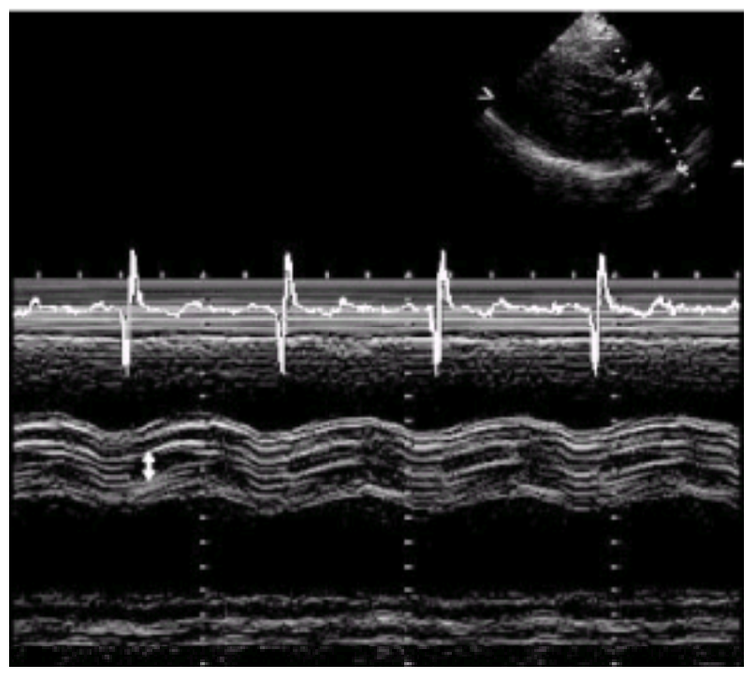
balloon valvuloplasty, open commissurotomy, or valve replacement).



Mitral stenosis. Left atrial enlargement and right ventricular hypertrophy have developed secondary to mitral stenosis, causing fixed pulmonary hypertension.



Continuous wave Doppler through a stenotic aortic valve. The maximal velocity is 5.5 m/sec, consistent with a peak pressure gradient of 121 mm Hg.



M-mode through a stenotic aortic valve. Note the thickened aortic leaflets with decreased excursion. (The small arrow designates the limited excursion of the aortic leaflets.)

It is essential that all the variables used to calculate a valve area (CO, systolic ejection period or diastolic filling period, heart rate, and pressure gradient) be measured in close temporal proximity to one another and with the patient in a hemodynamically stable state. Great care must be exercised in the acquisition of these data, since the decision for operative intervention is based on the calculated valve area.

Valvular Regurgitation

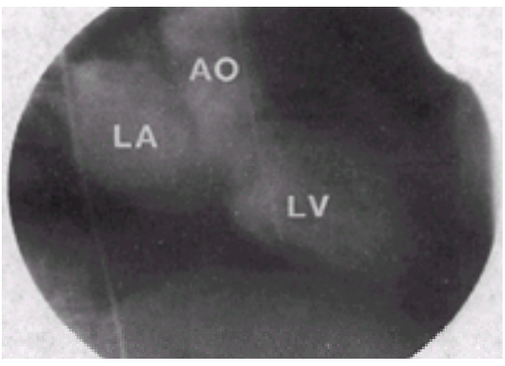
The presence and severity of mitral regurgitation may be evaluated qualitatively by observing the amount of radiographic contrast material that regurgitates into the left atrium during left ventricular systole on a standard left ventriculogram (*e*Fig. 79.9.1). The magnitude of regurgitation is estimated as trivial (1+), mild (2+), moderate (3+), or severe (4+) (see Left Ventriculography, later in this chapter). To obtain a quantitative assessment of the severity of mitral regurgitation, one can calculate the volume of blood that regurgitates from the left ventricle into the left atrium per minute (so-called regurgitant volume) by measuring the difference between the angiographic CO (determined by left ventriculography) and the forward CO (determined by the Fick method or thermodilution). The regurgitant fraction is the percentage of the total angiographic output that regurgitates into the left atrium: It is the quotient of the regurgitant volume and the angiographic output. Typically, valvular regurgitation with a regurgitant fraction 0.6 or greater is severe; 0.40 to 0.59, moderate; 0.20 to 0.39, mild; and less than 0.20, trivial.

VIDEO

Video 79.2 Mitral valve prolapse with severe mitral regurgitation (right anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 79.3 Left ventriculography with severe mitral regurgitation. After contrast injection in the left ventricle, the left atrium achieves the equal opacity to the left ventricular cavity indicative of severe (4+) mitral regurgitation. Before contrast injection, calcification in the mitral annulus and descending aorta is evident. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 79.9.1** A single plane (30-degree right anterior oblique) left ventriculogram in a patient with severe (4+) mitral regurgitation. The left atrium (LA) is opacified with radiographic contrast material that has regurgitated through an incompetent mitral valve. Ao, aorta; LV, left ventricle.

The presence and severity of aortic regurgitation may be evaluated qualitatively by observing the amount of radiographic contrast material that regurgitates into the left ventricle during ventricular diastole by aortography; it is also graded as trivial (1+), mild (2+), moderate (3+), or severe (4+) (see Aortography, later in this chapter). As with mitral regurgitation, a quantitative assessment of the severity of aortic regurgitation can be obtained by calculating the regurgitant volume and fraction.

Video 79.4 Calcified sinus of Valsalva aneurysm ruptured into the right atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 79.5 Congenital bicuspid aortic valve with mild aortic regurgitation (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

ASSESSMENT OF INTRACARDIAC SHUNTING

Left-to-Right Shunting

In the patient with known or suspected congenital heart disease, as well as the subject with unexplained heart failure, cardiac catheterization may be performed to assess the presence, location, and magnitude of intracardiac shunting. To accomplish this, several techniques may be used (Table 79.3) (30).

Method	Able to localize?	Able to quantify?	Minimal Qp/Qs reliably detected
Oximetry	Yes	Yes	1.5-1.9 at level of atrium 1.3-1.5 at level of ventricle 1.3 at level of great vessels
Indocyanine green	No	Yes	1.35
Angiography	Yes	No	Unknown

TABLE 79.3 COMPARISON OF METHODS TO DETECT, LOCALIZE, AND QUANTIFY INTRACARDIAC LEFT-TO-RIGHT SHUNTING

Video 79.6 Transesophageal echo with color Doppler flow demonstrating a secundum atrial septal defect with left-to-right flow. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Oximetric Assessment

The oximetric detection and localization of intracardiac left-to-right shunting is based on the principle that oxygenated blood shunted from the left side to the right side of the heart causes an abnormal increase (“step up”) in the oxygen content or saturation of blood in the chamber into which shunting occurs. To detect the presence and site of the left-to-right shunt, multiple blood samples are obtained from the pulmonary artery, right ventricle, right atrium, and venae cavae, and the oxygen content or saturation of each sample is evaluated for evidence of such a step up. An abnormal step up is present when the right atrial oxygen content is greater than 1.9 mL per dL higher than that of the venae cavae; the right ventricular oxygen content is greater than 0.9 mL per dL higher than that of the right atrium; or the pulmonary arterial oxygen content is greater than 0.5 mL per dL higher than that of the right ventricle (31,32). The oxygen content of blood can be measured directly or calculated from the saturation [saturation × hemoglobin (gram per deciliter) × 1.36 mL O_2 per g of hemoglobin].

The oximetric quantitation of shunting is accomplished by calculating pulmonic (Qp) and systemic (Qs) blood flows according to the Fick principle, where:

$$\text{Qp (L per minute)} = \frac{\text{Oxygen consumption (mL per minute)}}{\text{AV oxygen content difference across the lungs (mL per L)}}$$

and

$$\text{Qs (L per minute)} = \frac{\text{Oxygen consumption (mL per minute)}}{\text{AV oxygen content difference across the body (mL per L)}}$$

The AV oxygen content difference across the lungs is the difference in oxygen contents between pulmonary arterial and venous blood. The AV oxygen content across the body is the difference in oxygen contents between systemic arterial and mixed venous blood, with the latter obtained from the chamber immediately before

(proximal to) the site of shunting. For example, if a ventricular septal defect is present, the mixed venous chamber is the right atrium; if a patent ductus arteriosus is present, the mixed venous chamber is the right ventricle. An example of the calculations for a patient with an intracardiac left-to-right shunt is presented in Table 79.4.

Chamber	O_2 saturation (%)	O_2 content (mL/dL)	O_2 content difference (mL/dL)
Venae cavae	65	13.1	0.4
Right atrium	67	13.5	2.2
Right ventricle	78	15.7	0.2
Pulmonary artery	79	15.9	
Systemic artery	97		
Site of O_2 step up = right ventricle		Mixed venous chamber = right atrium	

$$Qp = \frac{250\ \text{mL/min}}{(0.97 - 0.79)\,(15\ \text{gHb/L})\,(1.36\ \text{mL}\ O_2/\text{g hemoglobin})\,(10\ \text{dL/L})} = 5.81\ \text{L/min}$$

$$Qs = \frac{250\ \text{mL/min}}{(0.97 - 0.67)\,(15\ \text{gHb/L})\,(1.36\ \text{mL}\ O_2/\text{g hemoglobin})\,(10\ \text{dL/L})} = 4.08\ \text{L/min}$$

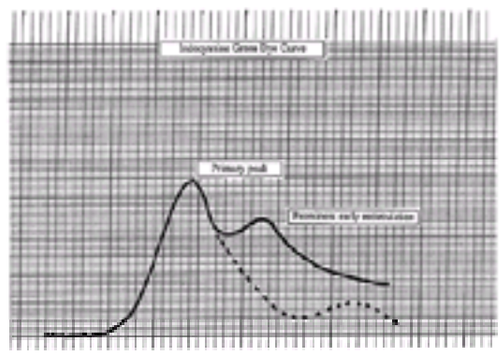
[a]Measured oxygen consumption = 250 mL per minute; Hemoglobin = 15 g per dL; Qp/Qs ratio = 5.81/4.08 = 1.3.

TABLE 79.4 OXIMETRIC ASSESSMENT OF THE PRESENCE, SITE, AND SIZE OF LEFT-TO-RIGHT INTRACARDIAC SHUNTING IN A PATIENT WITH A VENTRICULAR SEPTAL DEFECT[a]

The oximetric determination of intracardiac left-to-right shunting is highly specific but relatively insensitive, in that an oximetric assessment reliably demonstrates the presence of a moderate or large shunt but may fail to detect a small one (Table 79.3) (30).

Indocyanine Green Assessment

As described previously, when a bolus of indocyanine green is introduced into a right-sided heart chamber and its concentration measured in systemic arterial blood, a concentration-time curve is inscribed, which is characterized by a primary peak and a recirculation peak. In the patient with left-to-right intracardiac shunting, the inscribed curve demonstrates prominent early recirculation (*e*Fig. 79.9.2) due to indocyanine green's rapid recirculation to the systemic arterial system through the intracardiac shunt. Since the area of the inscribed recirculation curve is proportional to shunt flow, the magnitude of shunting can be calculated with this technique (33,34). Although this method cannot identify the site of left-to-right shunting, it can detect shunts with a Qp/Qs as small as 1.35; thus, it is somewhat more sensitive than oximetry (35).



***e*FIGURE 79.9.2** A time-concentration curve following injection of indocyanine green into the pulmonary artery, with withdrawal of blood from the aorta in a patient with a large left-to-right intracardiac shunt through an atrial septal defect. In comparison with the normal curve (*dotted line*), there is a prominent early recirculation peak.

Angiographic Assessment

When radiographic contrast material is introduced into a left-sided chamber during angiography in a subject with left-to-right intracardiac shunting, its movement into a right-sided chamber may be visualized. The reliability of any angiographic technique for detecting or localizing intracardiac left-to-right shunting depends on the location of the defect and the obliquity in which the angiogram is performed. Left-sided angiography may be used to detect and localize certain kinds of intracardiac left-to-right shunts. For example, the interventricular septum may be visualized by performing left ventriculography in a 40- to 50-degree left anterior oblique projection, allowing the diagnosis of a ventricular septal defect. A communication between the thoracic aorta and the pulmonary artery (i.e., patent ductus arteriosus or aortopulmonary window) may be identified by performing aortography in the left anterior oblique or left lateral projections. In contradistinction, atrial septal defects and anomalous pulmonary venous drainage are difficult to visualize angiographically. Although angiography can detect and localize certain intracardiac left-to-right shunts, it cannot measure the magnitude of shunting.

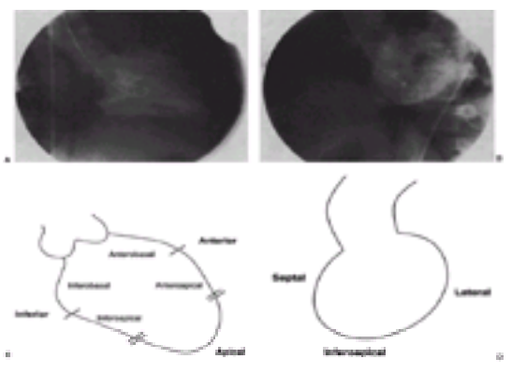
Right-to-Left Shunting

In the patient with right-to-left intracardiac shunting, passage of unoxygenated blood from the venous circulation to the systemic circulation results in arterial desaturation (less than 95%). When desaturation is due to other conditions (i.e., a ventilation-perfusion mismatch or hypoventilation), it is corrected when 100% oxygen is administered, whereas this does not happen when the arterial desaturation is due to right-to-left shunting. Thus, demonstration of a systemic arterial oxygen saturation less than 95% that does not correct with the administration of 100% oxygen (via face mask) is consistent with right-to-left intracardiac shunting.

ANGIOGRAPHY

Left Ventriculography

Cineangiocardiography of the left ventricle allows one to assess (a) global and segmental left ventricular function, (b) left ventricular volumes and ejection fraction, and (c) the presence and severity of mitral regurgitation. To achieve adequate opacification, a large bolus of radiographic contrast material must be delivered to the left ventricle over a short period of time. In the normal adult, 40 to 60 mL of contrast material is injected over 3 to 4 seconds; thus, 10 to 20 mL are injected per second. As the contrast material is injected into the left ventricle, cineangiography is performed. Ventriculography may be performed in two projections (biplane) or more commonly in one projection (single plane), which is usually performed in the 30-degree right anterior oblique projection. If biplane cineangiographic equipment is available, two projections, 90 degrees apart in obliquity (60-degree left anterior oblique and 30-degree right anterior oblique), are performed (*e*Fig. 79.9.3).



***e*FIGURE 79.9.3** With biplane ventriculography, two projections 90 degrees apart in obliquity are performed: 30-degree right anterior oblique **(A)** and 60-degree left

anterior oblique **(B)**. The segments of the left ventricle that are visualized with each obliquity are labeled **(C,D)**. With typical single-plane ventriculography, only the right anterior oblique projection is obtained.

A variety of catheters may be used for left ventriculography, but all have certain features in common. First, the catheter should be of sufficient size so that a high-pressure injection of contrast material does not cause it to recoil, with resultant ventricular ectopy. Second, the catheter should be designed so that the jet of injected contrast material exits a series of side holes rather than just an end hole; as a result, the chance of a high-pressure jet of contrast material being injected into the endocardium (endocardial staining) is minimized. Finally, although the angiographic catheter should have multiple side holes for the injection of contrast material, these holes should be confined to the distal 2 to 3 cm of the catheter to avoid contrast injection into both the left ventricle and the ascending aorta.

Left ventriculography allows for calculation of left ventricular volumes and ejection fraction using a standard area-length formula (36,37 and 38). End diastolic and end systolic volumes are measured; from these, left ventricular stroke volume is derived (end diastolic volume minus end systolic volume), and ejection fraction is calculated (stroke volume divided by end diastolic volume). The normal values for left ventricular volumes and ejection fraction are displayed in *e*Table 79.4.1. In addition to the calculation of left ventricular volumes, segmental wall motion may be assessed. A segment of the left ventricular wall with reduced systolic motion is said to be *hypokinetic*; a segment that does not move during ventricular contraction is *akinetic*; and one that moves paradoxically during ventricular systole is termed *dyskinetic*. Finally, the presence and severity of mitral regurgitation may be evaluated qualitatively during sinus beats as trivial (1+), mild (2+), moderate (3+), or severe (4+): (a) with 1+, contrast material enters the left atrium during systole and clears with each beat; (b) with 2+, contrast opacification of the left atrium does not clear with each beat and is less dense than the left ventricle; (c) with 3+, opacification of the left atrium is equal to that of the left ventricle; and (d) with 4+, the presence of one of three findings is observed—opacification of the left atrium greater than that of the left ventricle, opacification of the left atrium in one systolic ejection period, or the presence of contrast material in a pulmonary vein.

***e*TABLE 79.4.1** NORMAL ANGIOGRAPHIC VALUES

LV end diastolic volume index	50–90 mL/m^2
LV end systolic volume index	13–35 mL/m^2
LV stroke volume index	35–55 mL/m^2
LV ejection fraction	0.55–0.70%

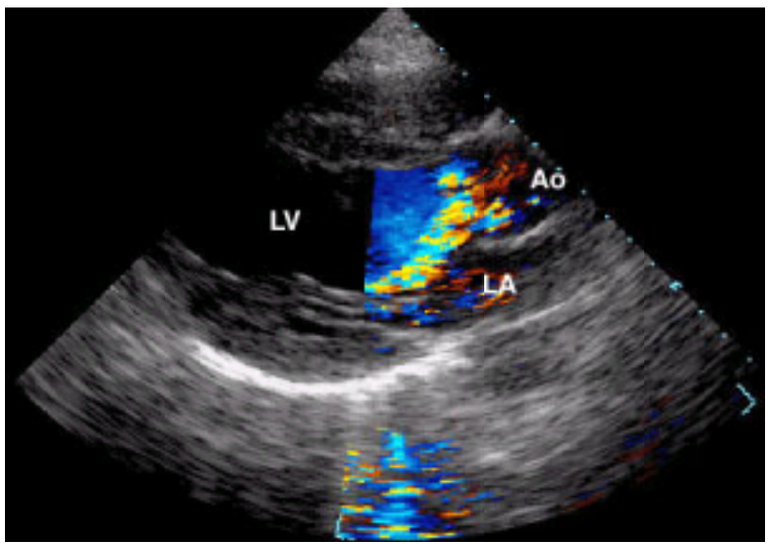
LV, left ventricular.

Right Ventriculography

Cineangiography of the right ventricle allows one to assess global right ventricular function as well as the presence and severity of tricuspid regurgitation. Right ventriculography may be performed in single or biplane projections. Single plane right ventriculography is usually performed in a 30-degree right anterior oblique projection. If biplane angiography is available, a 60-degree left anterior oblique projection is also performed. To achieve adequate opacification, a bolus of 24 to 36 mL of radiographic contrast is injected over 2 seconds as cineangiography is performed. The presence and severity of tricuspid regurgitation may be qualitatively evaluated in a manner similar to mitral regurgitation: trivial (1+), mild (2+), moderate (3+), or severe (4+). There are no reliable methods for the quantitative assessment of right ventricular volumes or ejection fraction by ventriculography.

Aortography

Aortography is performed with the rapid injection of a large amount of radiographic contrast material into the aorta. A proximal aortogram is performed to assess the competency of the aortic valve, to evaluate the anatomy of the proximal aorta and large vessels that supply the head and neck, and occasionally to assess the presence of bypass graft anastomoses that have been difficult or impossible to cannulate selectively. In turn, a distal aortogram is performed to assess the presence of vascular abnormalities (e.g., aneurysm, dissection, intraluminal thrombus, coarctation). The catheters used for aortography are similar to those used for left ventriculography. For proximal aortography, 50 to 60 mL of contrast material is injected over 2.0 to 2.5 seconds and filmed either by cineangiography or rapid cut film angiography. The standard proximal aortogram is filmed in a 45- to 60-degree left anterior oblique projection. The severity of aortic regurgitation may be qualitatively evaluated during sinus beats as trivial (1+), mild (2+), moderate (3+), or severe (4+): (a) with 1+, contrast material enters the left ventricle during diastole and clears with each beat; (b) with 2+, contrast opacification of the left ventricle does not clear with each beat and is less dense than the ascending aorta; (c) with 3+, opacification of the left ventricle is equal to that of the aorta; and (d) with 4+, opacification of the left ventricle is greater than that of the aorta, or the left ventricle is opacified in one diastolic filling period (39).



Parasternal long-axis view (transthoracic echo) with color Doppler demonstrating the posteriorly directed aortic insufficiency caused by prolapse of the anterior leaflet of a bicuspid aortic valve. Note that the jet hits the anterior mitral leaflet.

VIDEO

Video 79.7 Transgastric view (transesophageal echo) of the mitral valve in a patient with severe aortic insufficiency. Note the fluttering of the anterior mitral leaflet (*left*) due to the jet of aortic insufficiency hitting it (color flow seen on the left). (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 79.8 Long-axis 120-degree transesophageal view of a rheumatic aortic valve with central aortic insufficiency due to furled, restricted leaflets. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

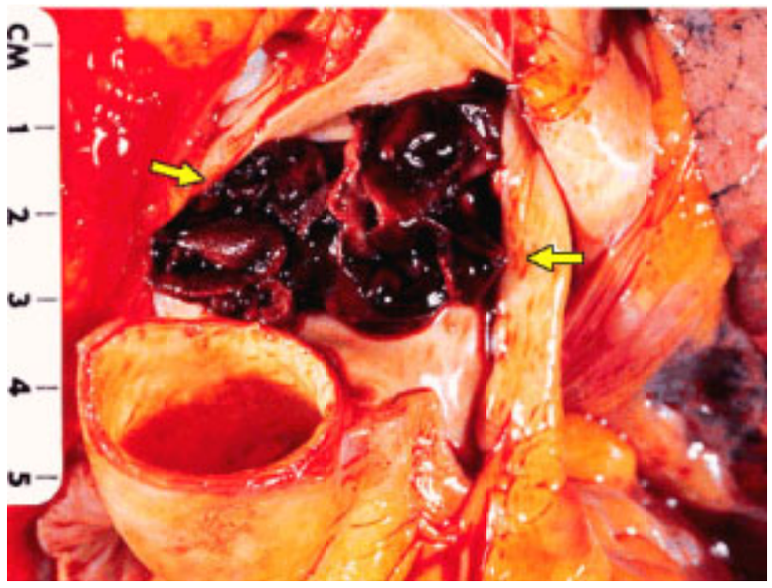
Video 79.9 Aortography in a patient with giant cell aortitis, a severely dilated aorta, and aortic regurgitation. After contrast injection, approximately 1+ aortic regurgitations are evident. The ascending and descending aorta are significantly enlarged (left anterior oblique view). *This video must be viewed with QuickTime. If you*

do not have QuickTime you may download it here.

Video 79.10 A 49-year-old male patient with bicuspid aortic valve and severe aortic regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pulmonary Angiography

Pulmonary angiography is performed primarily to confirm or to exclude the presence of pulmonary emboli (40,41). A large-bore angiographic catheter is advanced from a systemic vein to the main pulmonary artery and is positioned so that it does not recoil into the right ventricle during the injection of contrast material, with resultant ventricular irritability. A large amount of contrast material (40 to 60 mL) is injected over 2 to 3 seconds. During the injection, cineangiography or rapid cut film angiography is performed.



Saddle embolism of the pulmonary artery. The pulmonary artery has been opened via an anterior incision. Multiple fragments of thrombi protrude from the open pulmonary artery and are wedged into both the left and right pulmonary artery branches (*yellow arrows*).

Video 79.11 Pulmonary angiogram in moderately severe mitral regurgitation. In this pulmonary angiogram, several phases of contrast passage are evident. In the first phase, the pulmonary artery and its branches are seen, followed by a pacification of the pulmonary veins, the left atrium, and the left ventricle. Because much regurgitation is present, there is slow clearing of contrast from the left atrium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

If injection into the main pulmonary artery does not provide a definitive diagnosis, subselective injections are made into those segments of lung where the suspicion of pulmonary emboli is highest. These injections can be made with either a small power injection through the same angiographic catheter or a hand injection through a balloon-tipped catheter.

Analysis of the films must be meticulous, as the radiographic findings associated with pulmonary embolism may be subtle. Radiographic signs diagnostic of pulmonary embolism include a large intraluminal filling defect or an abrupt pulmonary arterial cutoff. Other radiographic signs, such as localized oligemia and asymmetry of pulmonary blood flow, are suggestive but not strictly diagnostic of embolism.

CONTROVERSIES AND PERSONAL PERSPECTIVES

There is considerable controversy regarding the value and safety of right-sided heart catheterization. In many centers, right-sided heart catheterization is performed routinely in conjunction with coronary angiography. In those with proper indications (eTable 79.4.2), it may provide valuable diagnostic and prognostic information, which influences therapy in 35% to 55% of cases (42). In contrast, right-sided heart catheterization seldom provides information that influences patient management in the absence of these indications (43). In these individuals, therefore, it should not be performed routinely.

***e*TABLE 79.4.2** INDICATIONS FOR RIGHT-SIDED HEART CATHETERIZATION
Known or suspected
Valvular heart disease
Congenital heart disease
Restrictive or constrictive heart disease
Pulmonary hypertension
Cardiac tamponade
Heart failure
Decompensated
Etiology undefined
Myocardial infarction
With hypotension
With pulmonary congestion
With mechanical complication
Unexplained right-sided heart failure

When performed by physicians experienced with the technique, right-sided heart catheterization is extremely safe. Over the past two decades, we have performed over 4,700 right-sided heart catheterizations with a stiff large-lumen (e.g., No. 8 Fr Goodale Lubin) catheter with no major complications (i.e., infection, hemorrhage, perforation, or death) and only one (0.02%) minor complication (femoral vein thrombosis).

An observational study (44) suggested that routine right-sided heart catheterization in critically ill patients is associated with an increased mortality. In such patients, physicians with limited catheterization experience often place an indwelling flow-directed pulmonary artery catheter. Complications associated with such indwelling catheters (i.e., pulmonary arterial perforation, sepsis, bacterial endocarditis, and large vein thrombosis) and placement by less experienced operators may account for the observed increased mortality. Some (45) have recommended a moratorium on routine right-sided heart catheterization in critically ill patients until properly conducted, randomized trials have assessed its utility and safety.

In our opinion, right-sided heart catheterization should not be performed in critically ill patients unless done so (a) by a physician experienced with the technique, (b) in

a patient with a clear indication, or (c) for training purposes.

Likewise, left-sided heart catheterization should be performed only for a proper indication (eTable 79.4.3) and in a facility capable of handling complications. Free-standing or mobile catheterization facilities without immediately available hospital and surgical support are ill equipped to handle serious catheterization-related complications. Patients with unstable symptoms or clinical features suggestive of an increased risk for cardiac or vascular complications (Table 79.1) should undergo catheterization in an inpatient setting (46).

***e*TABLE 79.4.3** INDICATIONS FOR THERAPEUTIC LEFT-SIDED HEART CATHETERIZATION

Angina pectoris
Unstable or rest
With exertion
Despite medical therapy
With evidence of extensive coronary artery disease by noninvasive testing
Acute myocardial infarction (for primary angioplasty)
After myocardial infarction
Evidence of extensive coronary artery disease by noninvasive testing
Postinfarction angina
Depressed left ventricular function
Failure to reperfuse following thrombolytic therapy
Cardiogenic shock
Valvular stenosis (with symptoms)
Valvular regurgitation
With symptoms
With impaired left ventricular systolic function
Congestive heart failure
Suspected congenital heart disease
Sudden cardiac death
Major noncardiac surgery and evidence of extensive coronary artery disease by noninvasive testing

THE FUTURE

Cardiac catheterization plays a central role in the diagnostic evaluation of the patient with suspected or known cardiac disease, and it offers percutaneous therapeutic possibilities in many individuals. Over the next decade, the indications for therapeutic catheterization (e.g., percutaneous coronary revascularization, endoluminal stenting, and intracardiac defect closure) will continue to increase as the techniques, equipment, and operator skill improve.

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80

PERCUTANEOUS CORONARY INTERVENTION

BERNHARD MEIER

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Percutaneous coronary intervention (PCI), traditionally known as *percutaneous transluminal coronary angioplasty* (PTCA), has emerged, predominantly as balloon angioplasty, in its first 20 years as the most common major medical intervention.

It is performed under local anesthesia, occasionally even as an outpatient procedure. For optimal performance, it requires state-of-the-art radiographic and dilatation equipment as well as a properly trained operator with an experienced crew.

It works best for single-vessel disease, but it may also be of great value for double-vessel disease and for selected triple-vessel disease, particularly in patients who are old, fragile, or have had prior coronary artery bypass grafting (CABG). It plays a dominant role in the treatment of acute myocardial infarction.

The major drawbacks are low success rates in old and long chronic total coronary occlusions, fatal outcomes in approximately 1%, acute ischemic complications in approximately 5%, and clinically significant restenosis within the first months in approximately 20% of cases. Its strong points are a greater than 90% success rate, the possibility for the patients to immediately return to a normal life, the repeatability of the procedure, and the paucity of complications after the first 24 hours or of recurrences after the first 6 months. Stents have proved to be an important complement to PCI. Although unequivocally required in less than one-half the lesions, routine stenting and even direct stenting are about to become the standard approach.

The current focus in related research is on technical advances in the crossing of chronic total coronary occlusions and on improved antiplatelet and antithrombin therapy to reduce acute occlusions. The restenosis problem, already ameliorated by stenting, is about to be further curbed by brachytherapy and drug-eluting stent coatings.

GLOSSARY

Ad hoc: Performed during diagnostic catheterization.

Culprit lesion: Lesion responsible for current event or predominant symptoms.

Fr: French, diameter unit for equipment, 1 Fr = 0.33 mm.

Guidewire: Wire over which to advance balloon catheter.

Guiding catheter: Catheter through which to introduce balloon catheter into coronary artery.

Monorail: Catheter type with side exit for guidewire in distal portion.

HISTORICAL PERSPECTIVE

Coronary balloon angioplasty is an offspring of transluminal angioplasty of peripheral arteries initiated by Dotter and Judkins in 1964 (1). Their method of dilating stenoses by successively introducing a coaxial double catheter with a diameter of 8 Fr (2.7 mm) and 12 Fr (3.7 mm), respectively, was crude. It required an access hole with a diameter equal to the target lumen. The surgically oriented care system for peripheral artery disease in the United States further impeded the development of the method. In Germany, angiology, an important subspecialty of internal medicine, provided fertile soil for such a technique.

Gruentzig had introduced the Dotter method at the University Hospital in Zurich in 1971, inspired by Zeitler from Germany. For several years, he experimented with different balloon types (2). In 1974, he performed the first balloon angioplasty in a peripheral artery using a form-constant polyvinyl chloride balloon in Zurich (3). In 1975, Gruentzig presented the double-lumen balloon catheter, which was introduced over a guidewire (4). In 1976, he presented a poster at the American Heart Association meeting in Miami demonstrating the feasibility of coronary balloon angioplasty in dogs. In 1977, the coronary dilatation balloon was used by Gruentzig in Zurich in a patient for the first time (5).

On March 22, 1976, in Zurich, a first PTCA attempt had been aborted by Gruentzig. It occurred as a last resort procedure in a patient with inoperable end-stage coronary artery disease and failed because the coronary ostium could not be engaged with the guiding catheter introduced through the arm because of iliac artery disease. On May 9, 1977, the first intraoperative balloon angioplasty procedure was performed in San Francisco jointly by Gruentzig, Myler, and Hanna, a cardiac surgeon. On September 16, 1977, in Zurich, a 38-year-old man with a single discrete stenosis of the left anterior descending coronary artery (LAD) became the first patient to undergo PTCA, or PCI as it is currently referred to (5). As the fellow in charge, I have followed the patient since. He has remained free of complications and recurrence for longer than 20 years, a living triumph of the method (6).

Primary success in the first 50 patients in Zurich was 64% without mortality. Emergency bypass operation was required in 14%, and infarction occurred in 6% (7,8).

In 1986, the Monorail principle (9) facilitated the use of guidewires (10). The shortened segment riding on the guidewire simplified exchanges over a standard length wire.

After the first clinical use of a coronary stent on March 28, 1986, by Puel in Toulouse (11), the pattern of PCI changed. The stent, first a rare and then a common ally of the balloon, matured to its Siamese twin, much in contrast to the balloon's many other short-lived companions and alternatives.

Twenty-four years after the birth of PCI, the method is thriving in spite of a tight medico-economic situation. With more than 1 million procedures performed yearly worldwide, it tops the list of major medical interventions.

In its first two decades, PCI has withstood the scrutiny of local and global peer review. It has been analyzed in numerous single-institution and multicenter registries. It has been subjected to a flurry of well-focused and meticulously monitored randomized studies. It has seen its indications expanded and then cropped again. It has turned out far from perfect but likable and extremely useful, just as Gruentzig had presaged.

MECHANISM

Dissection of intima and media, usually in thin areas of the plaque or adjacent to it, and dilatation of the vessel circumference (Fig. 80.1) constitute the key mechanisms for the luminal gain achieved by PCI (12,13 and 14). A stent prevents elastic recoil and keeps loose intimal flaps or plaque components out of the way. Reendothelialization commonly smoothes the rough surface within a few weeks. Yet, in unstented lesions together with constrictive remodeling (15), it may also cause restenosis.

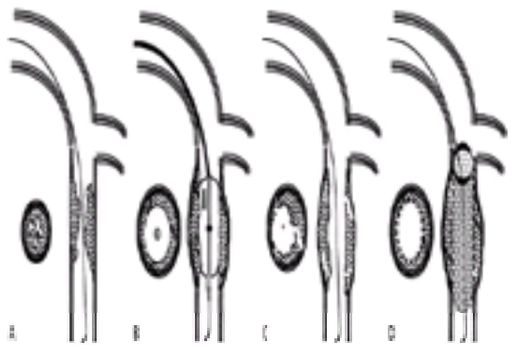


FIGURE 80.1 Schematic diagram of the primary mechanisms of balloon angioplasty and stenting. The initial gain in lumen derives from vessel dilatation and rearrangement of the noncompressible parts of the plaque made possible by an intimal dissection **(A–C)**. A stent avoids recoil and tacks flaps to the wall **(D)**.

PROCEDURE

Personnel

Primary Operator

Table 80.1 represents a reasonable compromise for a minimum curriculum to independence, considering the training facilities available and the general standard of practicing interventional cardiologists. For maintenance of skill, 50 to 75 cases per year are required. Such a low figure is only acceptable in case of a more active training period in the past and an experienced interventional environment (peers and team) as support.

General (internal) medicine (yr)	2
Clinical cardiology (yr)	3
Invasive cardiology (yr)	0.5
Diagnostic catheterization (cases)	
As assistant	50
As operator	100
Interventional cardiology (yr)	1
Therapeutic catheterization (percutaneous coronary intervention) (cases)	
As assistant	50
As operator	50
Practical courses	1

TABLE 80.1 MINIMUM CURRICULUM OF INTERVENTIONAL CARDIOLOGISTS BEFORE INDEPENDENCE

Assistants

At least one sterile person is advisable to assist the primary operator with catheter exchanges and manipulations. An additional person has to be on hand to fetch material, tend to the patient, and summon help in case of need. The more experienced the crew, the more expertly and expeditiously the case will be handled. A single physician suffices in general, but an additional physician with advanced resuscitation skills must be available within minutes and a spare angioplasty operator within the hour. An on-call 24-hour service is imposed by the unpredictable nature of coronary artery disease in general and freshly dilated coronary arteries in particular.

Surgical Standby

A surgical standby under the same roof remains the ideal setting. However, coronary angioplasty without in-house surgery is a valid option to foster ad hoc procedures and to avoid waiting periods. The risk for myocardium and life during typical PCI procedures is low (Fig. 80.2), lower than the risk of cardiac events during an extended waiting period (16).

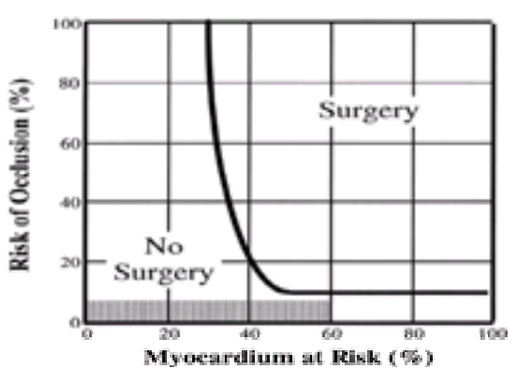


FIGURE 80.2 Chart to estimate the need for emergency bypass surgery at any stage of percutaneous coronary intervention. The hatched area encompasses the

typical percutaneous coronary intervention indications and risks in the era of stents and glycoprotein IIb/IIIa antagonists. It lies outside of the area where (emergency) surgery appears beneficial.

There are important precautions for PCI without in-house surgery. There should be no local legal objections, and the respective operators should be particularly well trained, the case selection adapted, the patient informed, and the institution fully equipped for advanced resuscitation and intensive care.

Material

*e*Table 80.1.1 lists standard and optional equipment and gear for PCI in 2001.

***e*TABLE 80.1.1** EQUIPMENT FOR PERCUTANEOUS CORONARY INTERVENTION IN 2001

Standard	**Optional**
Balloons	Atherectomy devices
Guidewires	Drills, grinders, lysers, softeners
Guiding catheters	Catchers, suckers, mashers
Digital x-ray	Laser (debulker/wire)
Stents	Local drug delivery
Covered	Angioscopy
Coated (eluting?)	Intravascular ultrasound
Adenosine diphosphate antagonists	Drugs against restenosis
Glycoprotein IIb/IIIa antagonists	Brachytherapy
Femoral plugs + sutures	Percutaneous cardiopulmonary support
Aortic counterpulsation	Percutaneous left ventricular assist device

Radiographic Equipment

Catheterization laboratories have to meet high standards to be fit for interventional cardiology. Biplane fluoroscopy is helpful but less important than digital image enhancement and automated cine loops. In the event of a breakdown of the radiographic equipment during a critical phase of a case, a spare unit providing angulated fluoroscopy should be available (17).

The storage medium is digital. Exchange is possible via data lines (local area networks or Internet), compact disk, or digital versatile disk. Still-frame hard copies are useful for the hospital chart, the patient, and the referring physician.

Monitoring Equipment

Pressure curves and electrocardiographic (ECG) tracings have to be displayed throughout the case. Pertinent ECG changes and symptoms, such as ST-segment alterations, malignant arrhythmia, and chest pain during balloon inflation, should be recorded.

Balloon Catheter

A modern balloon catheter is sleek, has a slippery coating inside (reduced guidewire friction) and outside, a low crossing profile, good “trackability” and “pushability,” inflates and deflates rapidly, tolerates pressures up to 30 bar with contained expansion (compliance), and comes in a variety of diameters and lengths.

Guiding Catheter

The coronary guiding catheters are derived from diagnostic catheters. Their walls are thinner but still torque-true and kink-resistant. Diameters of guiding catheters currently range from 5 Fr (1.7 mm) to 8 Fr (2.7 mm).

Guidewire

The guidewire has to transmit torque reliably from the stiff outside end to the floppy tip. It should provide minimal resistance during advancement but optimal support for the catheters introduced over it. Hydrophilic coating reduces friction and guarantees easy advancement but harbors the risk of occult perforations of thin-walled healthy peripheral coronary arteries with subsequent tamponade. The wire tip may be equipped with a Doppler ultrasound crystal, a pressure port, a ball tip, or an optical lens for angioscopic tissue analysis or laser transmission. A diameter of 0.014 in. (0.36 mm) is standard.

Accessories

An adjustable Y connector prevents leaking and permits contrast medium injections and pressure monitoring through a single arterial access after the introduction of the guidewire and the balloon catheter into the guiding catheter. The wire torquer ensures controlled rotation of the wire tip. The Indeflator affords effortless inflations and maintains constant negative pressure in the balloon lumen of the catheter while the balloon is not inflated.

Technique

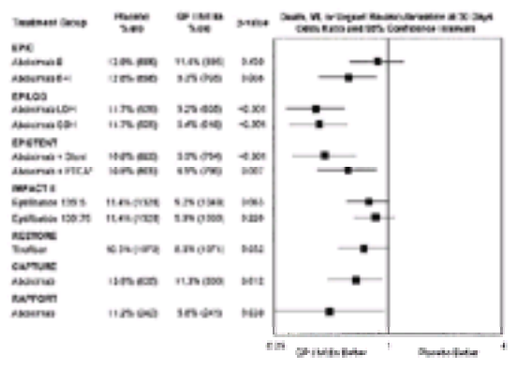
The classic point of access is the right femoral artery. Alternatives are the left femoral artery as well as either subclavian, brachial, or radial arteries. Femoral puncture site closure devices (resorbable plugs or subcutaneous sutures) shorten bed rest. The radial approach features easy hemostasis and immediate mobilization. However, it renders manipulations more painstaking, limits the selection of catheters and instruments, and carries a risk of radial artery occlusion that at the moment may be clinically silent but regretted later (e.g., on the occasion of subsequent CABG).

It is useful to observe ECG and symptomatic reaction of the patient during balloon occlusions. Marked ST-segment elevation, severe pain, malignant ectopy, or an immediate decrease in blood pressure imposes close monitoring after the intervention. Collaterals seen during the diagnostic study or documented by washout collaterometry (prompt washout of contrast medium blocked out distal to the balloon during inflation) project a low subsequent risk for the patient and allow for abridged and simplified aftercare.

Adjunctive Drug Therapy

Platelet inhibitors have to be administered at the latest at the inception of the procedure. Acetylsalicylic acid is standard except for unequivocal allergy. Clopidogrel, a thienopyridine interfering with glycoprotein IIb/IIIa receptors by reducing adenosine diphosphate activation, is advocated in addition in case of stenting. Its role in plain balloon angioplasty remains to be examined.

Intravenous direct glycoprotein IIb/IIIa receptor blockers (abciximab, tirofiban, or eptifibatide) have proved efficacious in large trials (18,19,20 and 21). Abciximab reduces death and myocardial infarction as well as the need for subsequent myocardial revascularization (*e*Fig. 80.2.1).



***e*FIGURE 80.2.1** Death, myocardial infarction (MI), or urgent repeat revascularization at 1 month for the glycoprotein (GP) IIb/IIIa interventional trials. B, bolus; B+I, bolus plus infusion; LDH, low-dose, weight-adjusted heparin; PTCA, percutaneous transluminal coronary angioplasty; SDH, standard-dose heparin; 135/.5 and 135/.75 eptifibatide doses, 135 mg per kg bolus, followed by infusions of 0.5 or 0.75 mg per kg per minute. (From Lincoff AM, Califf RM, Topol EJ. Platelet glycoprotein IIb/IIIa receptor blockade in coronary artery disease. *J Am Coll Cardiol* 2000;35:1103–1115, with permission.)

Heparin is part of the standard regimen. Doses employed vary without a clear-cut clinical difference between a bolus of 5,000 or 20,000 U (22). Low-molecular-weight heparin has not yet been tested in the setting of catheter interventions. Direct thrombin antagonists (hirudin, hirulog, and so forth) have yet to show clinical superiority to heparin worth their expense.

Heparin complication. Extensive purpura from heparin treatment.

The original contrast medium diatrizoate (ionic, high osmolar) has been largely abandoned in favor of nonionic agents for comfort reasons. Ioxaglate (ionic, low osmolar) is an alternative sharing an anticoagulant property with diatrizoate.

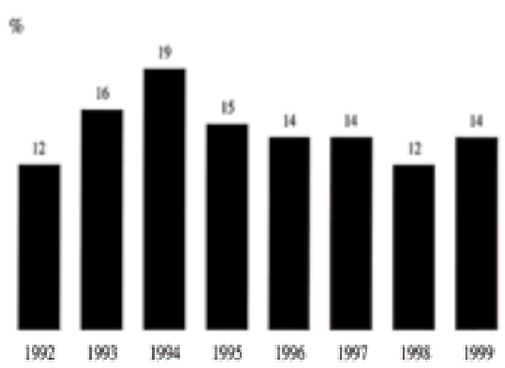
Aftercare

The level of surveillance after the procedure depends on the clinical situation and the result of PCI. ECG monitoring for a few hours is advised but not indispensable for the routine case (23). Any bleeding from the puncture site should be carefully assessed. Chest pain should prompt an immediate ECG for comparison with the baseline tracing. Patients with nonabating chest pain should be monitored for arrhythmia and reinvestigated by catheterization.

Hospital discharge of uncomplicated cases is usually the morning after the intervention. A control ECG before discharge should be standard, and cardiac enzymes should be checked in case of problems. The value of a stress test before discharge is controversial. It is safe but rarely performed.

INDICATIONS

The steady increase of yearly PCI cases was mainly due to an earlier invasive diagnosis of coronary artery disease in addition to a more aggressive attitude with elderly patients. The share of multivessel PCI did not increase over the 1990s in Europe (24) (*e*Fig. 80.2.2) or Canada (25) despite stents. Many patients undergoing PCI today would have been treated medically a decade ago. Three-vessel disease of the major branches, however, has largely remained the domain of CABG.



***e*FIGURE 80.2.2** Percentage of multivessel percutaneous coronary interventions in Europe in the 1990s. Despite the steep increase of stent use during that period, multivessel percutaneous coronary interventions in a single session did not increase. The figures are based on the official registry of the European Society of Cardiology, representing roughly 500,000 procedures per year.

Clinical Indications

Clinical indications and contraindications are listed in Table 80.2. They have to be customized to patients and situations, which requires experience. They are met by the vast majority of patients undergoing coronary angiography. Age is not as important for PCI as it is for CABG.

Indications
Acute myocardial infarction
Angina (stable or unstable)
Angina equivalent (arrhythmia, dyspnea, dizziness, and so forth)
Objective signs of reversible ischemia
Resting electrocardiogram
Stress test
Stress echocardiography
Holter monitoring
Scintigraphy
Positron emission tomography
Contraindications
Rapidly terminal cardiac or other disease (exception: uncontrollable angina)
Prolonged cardiogenic shock after myocardial infarction

TABLE 80.2 CLINICAL INDICATIONS AND CONTRAINDICATIONS

Angiographic Indications

Angiographic indications and contraindications are listed in *e*Table 80.2.1.

***e*TABLE 80.2.1** ANGIOGRAPHIC INDICATIONS AND CONTRAINDICATIONS
Indications
One to four lesions suitable for percutaneous coronary intervention
Not immediately life threatening
Vessel diameter (planned balloon size) greater than or equal to 2.5 mm
Lesion(s) subtending functional, viable, or collateral-relevant myocardium
Contraindications
Left main stem stenosis (exceptions: protected by graft or collaterals, ideal lesion, inoperable patient)
Left main stem equivalent stenoses (exceptions: staged procedures, ideal lesions, inoperable patient)
Last remaining vessel (exceptions: ideal lesion, inoperable patient)
Three-vessel disease (exceptions: ideal lesions, secondary vessels, staged procedures, inoperable patient)
Lesion characteristics
Chronic total occlusion
No collaterals to distal artery
Long and old
No stump
Extensive bridging collaterals
Thrombotic stenosis with nonsignificant underlying lesion
Diffusely diseased, small-caliber coronary artery
Diffusely diseased old venous graft

Lesion Location and Morphology

It is important but difficult to determine what makes a lesion significant enough to warrant PCI. There are different means to assess the functional significance of a stenosis. Clinical tests (exercise ECG, stress echocardiography, scintigraphy, and so forth) are not very sensitive and lack specificity for the individual lesion. Quantitative coronary angiography of the lesion is operator dependent and lacks precision almost to the degree of visual estimates (26). Intravascular ultrasound and pressure measurements (27,28) or angioscopy (29) are more objective, but they engender additional costs and risks.

To assess hemodynamic significance may mean barking up the wrong tree. The ultimate threat is not the occurrence of angina but the thrombotic occlusion of the vessel causing infarction and death. Although an individual mild stenosis has a low infarct potential, the hazard is clearly there. Collaterals are rare with mild lesions, which renders their occlusion particularly dangerous.

Restricting PCI to flow-limiting lesions ignores its potential for plaque sealing (i.e., significantly reducing the risk of subsequent thrombotic occlusion thanks to the neoendothelium overgrowing the inflicted wound) (30,31). The hypothesis about such an effect is derived from the event-free long-term course regularly observed after uncomplicated balloon angioplasty. Even restenosis is highly unlikely to produce infarction because of the different nature of the narrowing (smooth neoendothelium rather than rupture-prone atherosclerotic plaque), yet the hypothesis has not been prospectively validated and may be annihilated if a stent is implanted (small but significant risk of late infarction). Methods to elucidate the instability of a plaque seem called for (32), but they provide merely a snapshot assessment. An active plaque is meaningful, but an inactive plaque is not because it may turn active any time. Plaque passivation with statins (33) is a proved and ubiquitously applicable alternative or complement to plaque sealing by balloon angioplasty, the latter being only attractive as an ad hoc procedure for a mild lesion at a strategically important site (proximal in a large vessel).

Lesions involving branch points are technically not a particular challenge with modern equipment. However, they are fraught with a higher rate of complications and restenoses.

Thrombus-containing lesions have lost most of their ominous doom in the era of stents, glycoprotein IIb/IIIa antagonists, and protection devices.

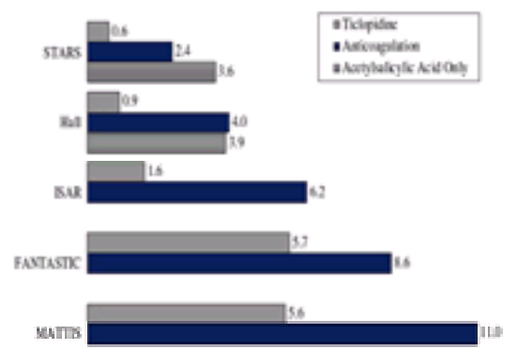
RESULTS

Results of high-volume providers show an edge over those of occasional operators (34,35). Hence, the recommended volume of 200 yearly cases per center is being challenged by some as too small (35).

Impact of Stenting

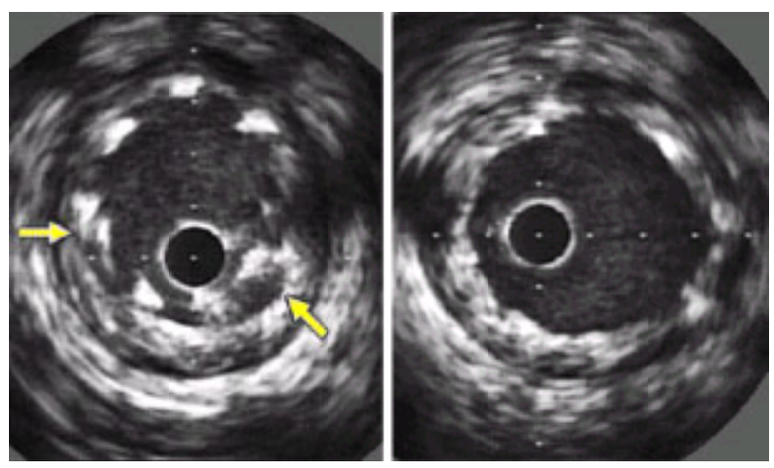
Among the various mechanical additions or alternatives to balloon angioplasty, only the stent has stood the test of time (11,36). Stenting does not complicate the procedure, some difficulties in negotiating the stent notwithstanding (compared with a naked balloon, slightly stiffer). Stenting yields an immediate result that is appealing to the eyes of the operator and the patient.

The initial problems with stent thrombosis have largely been overcome with a two-pronged antiplatelet regimen (acetylsalicylic acid and a thienopyridine). However, subacute stent thrombosis remains a concern (37) (*e*Fig. 80.2.3). The stent showed its real potential more where it was least expected, in the prevention of restenosis (38,39). Albeit highly effective in remedying impending occlusion due to obstructive dissection, routine stenting loses the advantage on balloon angioplasty over the first few weeks due to the occurrence of subacute thromboses virtually unknown to balloon angioplasty. Elective stenting has either the same or a higher (sub)acute event rate when compared with balloon angioplasty and provisional stenting. This holds true for all comers (38), diabetic patients (19), restenoses (40), small vessels (41), long lesions (42), chronic occlusions (43), LAD stenoses (44), saphenous vein grafts (45), unstable angina, or acute infarctions (46).

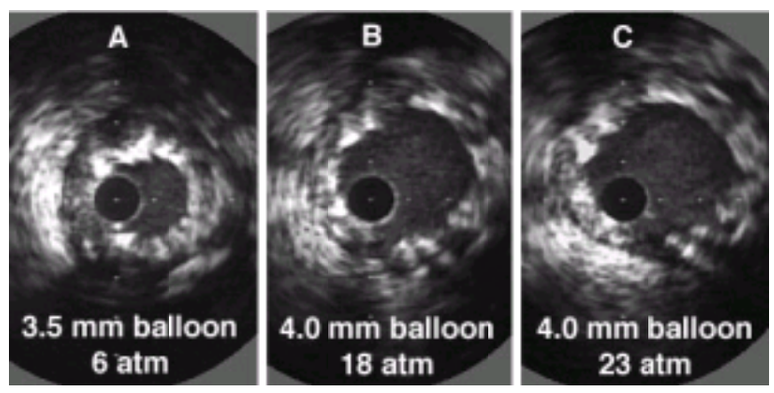


***e*FIGURE 80.2.3** Cardiac events at 30 days with different regimens of platelet inhibition or anticoagulation after stenting (37). In selected patients [Stent Antithrombotic Regimen Study (STARS), Hall, Intracoronary Stenting and Antithrombotic Regimen (ISAR) trials], ticlopidine yields much lower event rates than in less selected patients [Full Anticoagulation versus Aspirin and Ticlopidine Trial (FANTASTIC), Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS)].

The Optimal PTCA versus Primary Stenting-1 trial (47) appears to make clear that elective stenting, performed as direct stenting according to the Doppler Endpoint Balloon Angioplasty Trial Europe-II (39), is the way to go. Provisional (conditional) stenting seems to require intravascular ultrasound as a cumbersome and costly additional decisional tool to remain competitive (48). Yet the sole effect of elective stenting is that a reintervention is spared for every tenth stent implanted. Some of these reinterventions may be operator driven because a patient may be taken back for an additional intervention more readily if no stent had been implanted the first time, not to forget that an in-stent restenosis tends to be more intricate to treat than an unstented restenosis. The risk of acute occlusion in the first hours after balloon angioplasty is not really eliminated but rather deferred to the first days and weeks by stenting. Some of these stent problems fail to be brought to the attention of the operator. This makes them more dangerous, but, paradoxically, enhances the benefit of stenting as perceived by the operator.



Intravascular ultrasound assessment of stent deployment. In the left panel, incomplete stent expansion is evident, which is improved after further balloon dilatation.



Intravascular ultrasound in stent deployment. These images show the effect of both increased balloon size and pressure on the size of the in-stent lumen.

The outcome of balloon angioplasty is reliably stable for decades if not for life after a few hours of risk for acute closure and a few months of risk for restenosis. Before stents were available, approximately 70% of dilated lesions never had an acute problem or a restenosis (perfect outcome impossible to improve on). Stenting all patients means ignoring the 70% of patients whose result can be jeopardized but not improved by a stent for the benefit of the 30% with potential for improvement. Admittedly, it is impossible to accurately predict to which group the dilated lesion of the patient will belong. Yet, experienced operators do have clues and apply them to the benefit of the patient. A stenting rate of 50% to 70% could well be the trademark of an accomplished and astute interventional cardiologist.

Complications

The threat of a major acute complication haunts the operator more than the possibility of recurrence but is talked about less.

VIDEO

Video 80.1 Left anterior oblique angiogram of the right coronary artery showing coronary perforation after balloon angioplasty. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 80.2 Iatrogenic aortic dissection after balloon angioplasty of the ostial right coronary artery with a cutting balloon in a 77-year-old female patient. The patient needed emergent surgical repair for a type I aortic dissection. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 80.3 A 67-year-old male patient with calcified lesion involving the left anterior descending artery and diagonal branch. Subsequent use of rotablator resulted in perforation of the left anterior descending artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene (*yellow arrow*), as well as localized skin necrosis and livedo reticularis (*white arrows*).

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene, as well as localized skin necrosis and livedo reticularis (*white arrows*).

Atheroemboli. Digital necrosis resulting from severe atheroemboli.

Cholesterol emboli. Purpura secondary to cholesterol emboli are shown (*yellow arrows*).

Livedo reticularis. Mottled reddish discoloration of the lower extremities with accompanying multiple ulcerations associated with atheroemboli.

Embolus. Dislodged thrombus that embolized to the toes and caused gangrene (*arrows*).

Brachial artery hematoma. Hematoma complication after brachial artery catheterization and urokinase administration.

Mortality

In-hospital mortality after PCI ranges from virtually naught in young patients with single-vessel disease (49) to approximately 70% in patients with cardiogenic shock after myocardial infarction (50). Overall, it lies below 2% (51) and has remained stable during the period of general adoption of stenting (Fig. 80.3) (24,25). Mortality reduction was achieved in randomized studies with PCI compared with fibrinolysis in acute infarction (52), with stenting in conjunction with abciximab (19), with abciximab in mixed PCI cases at 3 years (pooled studies), and with PCI rather than conservative treatment in unstable angina (53).

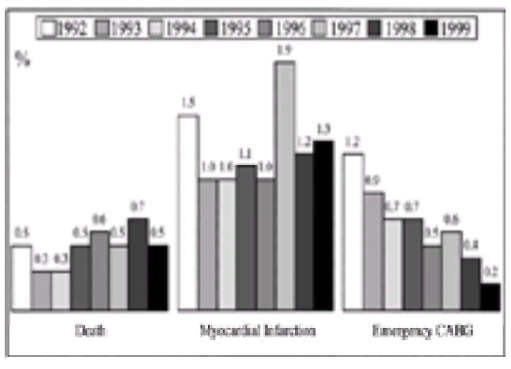


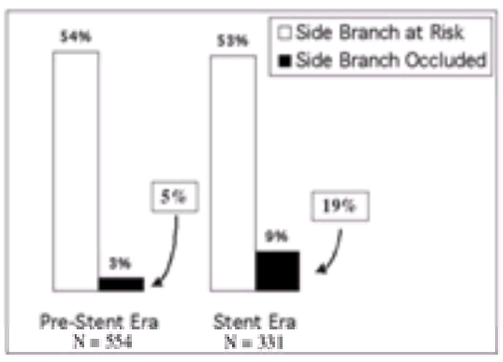
FIGURE 80.3 Evolution of adverse events in the European registry (some underreporting likely). Based on almost 500,000 percutaneous coronary intervention cases reported per year, there was no clear trend in terms of mortality or infarction rate since 1992 despite a marked increase of stenting. The reduction in need for emergency coronary artery bypass grafting (CABG) was a continuation of a trend that started 20 years ago. Yet there is an impact of stenting for the final reduction below 1%.

Myocardial Infarction

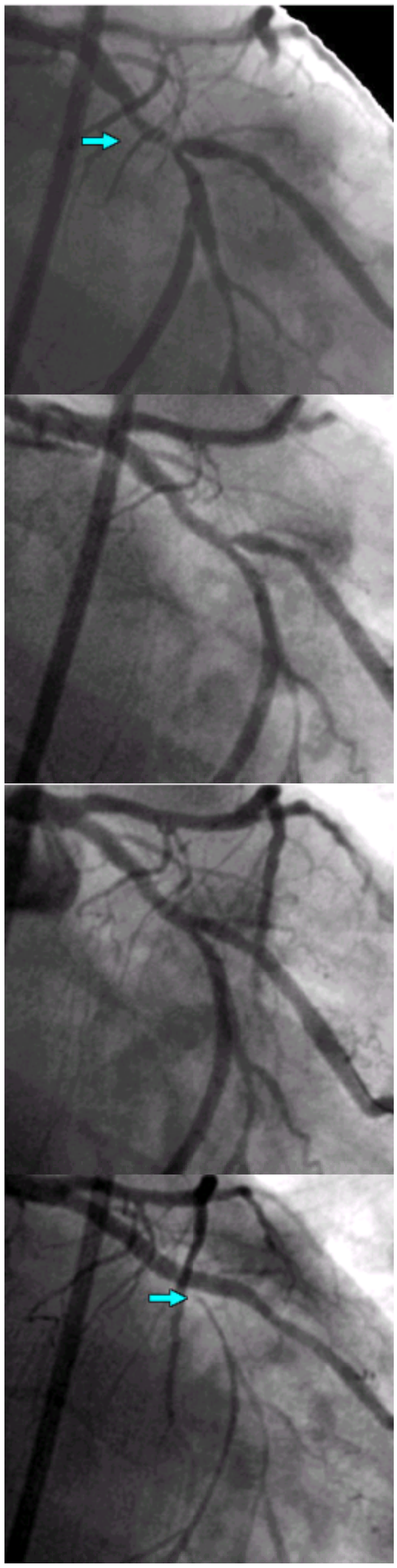
The incidence of PCI-induced myocardial infarction varies widely according to definitions used. Yet it has remained fairly stable over time (Fig. 80.3) (24,25). It is estimated that approximately 8% of patients show a creatine kinase release of greater than three times the upper limit of normal after PCI (54). This alone may be relevant to long-term outcome (54,55) [e.g., by doubling cardiac mortality from 5% to 10% over 1 year (56) and from 10% to 20% over 5 to 10 years (54,57)].

The use of perfusion balloon angioplasty to treat an acute inferior myocardial infarction. Normal antegrade flow is restored (C) beyond the area of total occlusion in the mid right coronary artery (A) after a prolonged inflation with a perfusion balloon catheter (B).

Side branch occlusions constitute the most prominent reason for creatine kinase elevations in otherwise successful procedures. Stents increase their incidence (*e*Fig. 80.3.1) (58,59) while reducing the rate of acute occlusion of the main axis. Sudden death, the dominant lethal mechanism after the first year, is probably accounted for by arrhythmogenic foci around patches of myocardial fibrosis. They may also be caused by microemboli, partially preventable by the use of abciximab or a similar drug (19).



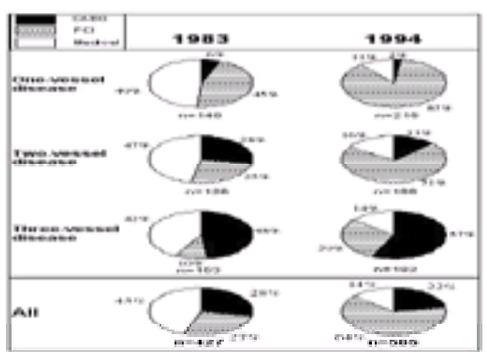
***e*FIGURE 80.3.1** Incidence of side branches at risk and actually occluded (percentages in square frames) in the pre-stent (58) and stent (59) eras.



Successfully treated side branch closure. Arrow in A demonstrates a bifurcation lesion involving the mid-left circumflex and the origin of a large-caliber obtuse marginal branch. Balloon angioplasty is performed sequentially in the mid- and then obtuse marginal (B,C). After Palmaz-Schatz stent deployment in the obtuse marginal, there is subtotal occlusion of the atrioventricular circumflex branch (D, *arrow*), which is "jailed" by the stent. A guidewire and balloon are advanced through the stent struts, and flow is restored to the distal atrioventricular circumflex and obtuse marginal branch after balloon inflation (E).

Need for Emergency Coronary Bypass Surgery

Most centers have reduced emergency CABG for failed PCI to far below 1% (Fig. 80.3). The techniques to deal with acute occlusions have evolved (stent, glycoprotein IIb/IIIa antagonists). The indications have expanded predominantly toward minor coronary heart disease (60) (*e*Fig. 80.3.2), not justifying CABG, particularly after the threshold for emergency CABG was raised because acute CABG for a small infarction was found not to be worthwhile (Fig. 80.2).

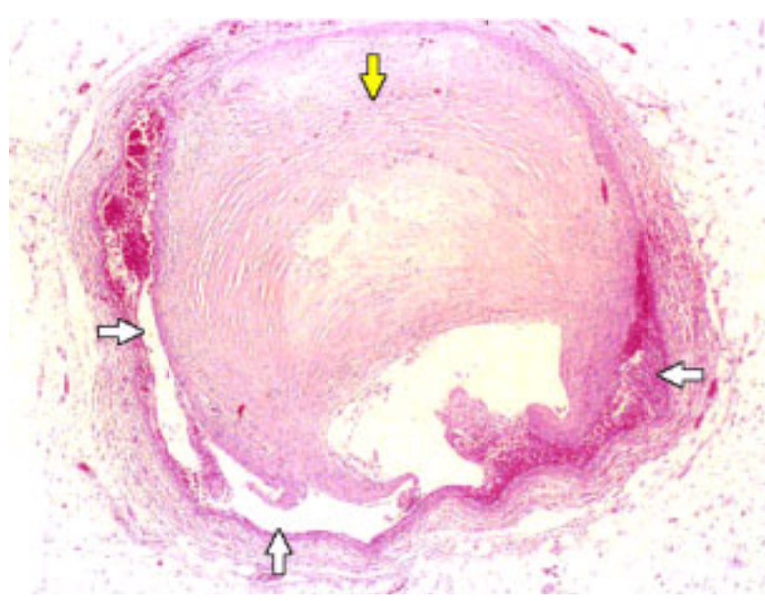


***e*FIGURE 80.3.2** Recommendations for treatment of two cohorts of consecutive patients approximately a decade apart with significant coronary artery disease. The recommendation for percutaneous coronary intervention (PCI) has increased for all stages. Coronary artery bypass grafting (CABG) has maintained its share in three-vessel disease. (From Delacrétaz E, Meier B. Use of coronary angioplasty, bypass surgery, and conservative therapy for treatment of coronary artery disease over the past decade. *Eur Heart J* 1998;19:1042–1046.)

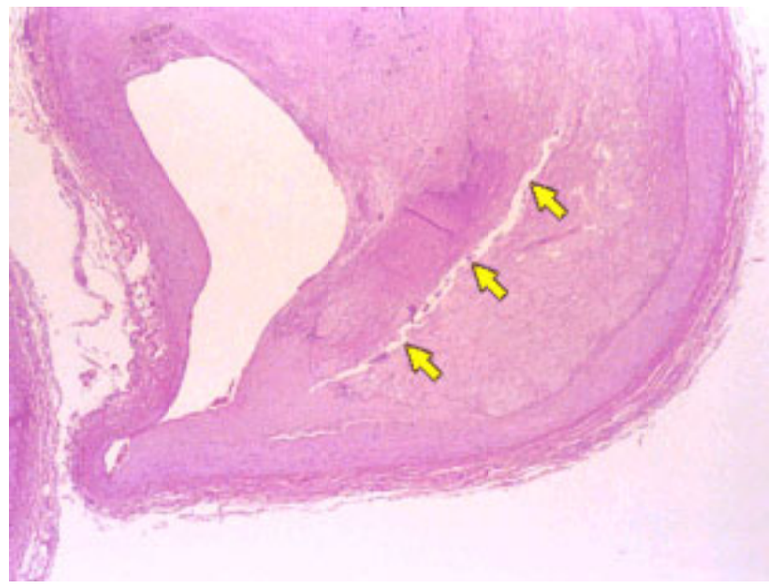
This modification in case selection for emergency CABG has led to a more dismal outcome for the few patients still referred to emergency CABG, which is not explained by their pre-PCI but by their precarious post-PCI situation.

Coronary Dissection

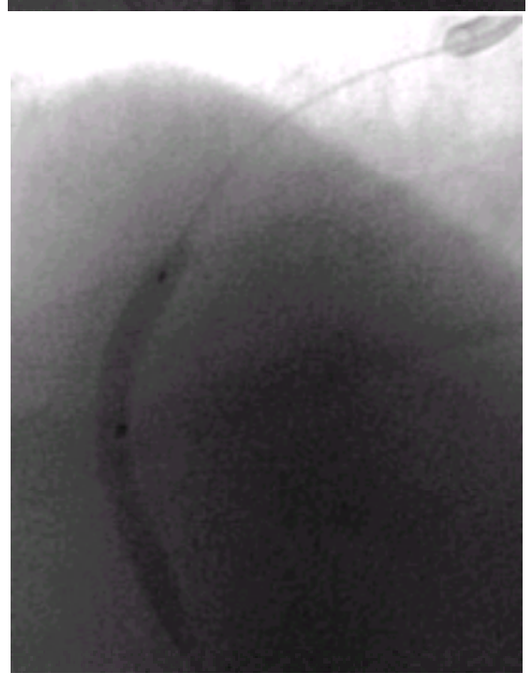
Dissections create luminal space but they may also occlude the vessel acutely if they are long, spiral, or form a cul-de-sac retaining blood bound to coagulate. The risk factors for an occlusive dissection (diffuse, tight, eccentric, tortuous, or overdilated lesions) have lost most of their importance in the wake of the liberal use of stents.



Linear, circumferential dissection 2 days after balloon angioplasty of a restenotic lesion. Note the extensive neointimal proliferation (*yellow arrow*) and dissection (*white arrows*).



Restenotic lesion. Residual tear in atherosclerotic plaque (*yellow arrows*) and large amount of neointimal proliferation 76 days after balloon angioplasty.



“Bailout” stent placement for a long dissection complicating balloon angioplasty. After balloon angioplasty of a long lesion of the mid-right coronary artery (A), a long linear dissection flap is apparent (B, *arrows*). A 39-mm-long AVE stent is deployed across the area of dissection (C). No residual stenosis is present after stent placement (D).

VIDEO

Video 80.4 A 55-year-old female patient with atypical angina. JR4 catheter engagement resulted in a large spiral dissection **(A)**. The dissection was successfully treated with coronary stenting **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

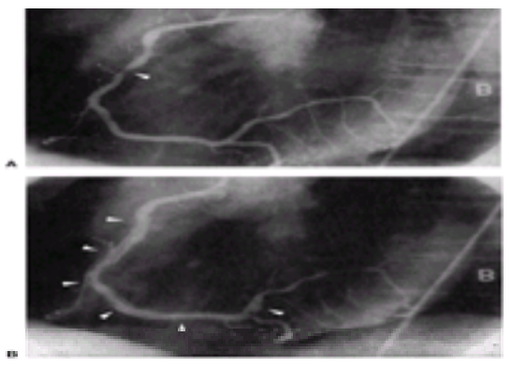
VIDEO

Video 80.5 A 55-year-old female patient with atypical angina. JR4 catheter engagement resulted in a large spiral dissection **(A)**. The dissection was successfully treated with coronary stenting **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 80.6 Coronary dissection by intravascular ultrasound. A tissue flap is seen protruding in the lumen of the vessel after high-pressure postdilatation of a Palmaz-Schatz stent in the adjacent segment. Angiographically, this flap was visualized as an area of ‘peri-stent’ haziness. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The risk of acute occlusion for nonstented lesions varies according to the degree of dissection. In the era before glycoprotein IIb/IIIa antagonists, it amounted to approximately 5% to 10% and was largely limited to the first 12 hours after the discontinuation of heparin (61). Stented dissections may have a significantly lower risk the first day, but part of this advantage is lost to subacute occlusions occurring up to several weeks after implantation. Particularly long stenoses may fare better without stenting (*e*Fig. 80.3.3), also because of the difficulty of treating long in-stent restenoses. Glycoprotein IIb/IIIa antagonists provide a valid alternative.



***e*FIGURE 80.3.3** Long spiral dissection (**B**, *arrows*) in the right coronary artery of a 60-year-old woman, resulting from angioplasty of a short stenosis (**A**, *arrow*) in a diffusely affected artery. The dissection kept obstructing flow and was therefore extended down the artery by additional distal balloon inflations until flow was again unimpeded. The dissection was not stented because of its length. The further course was uneventful.

Coronary Thrombosis

Stenting combined with novel antiplatelet agents is the preferred method of dealing with thrombosis (62,63 and 64). The place of specific antithrombin agents is still uncertain (63,64). Thrombus-extracting devices or removable embolization filters are in clinical evaluation (see Chapter 81).

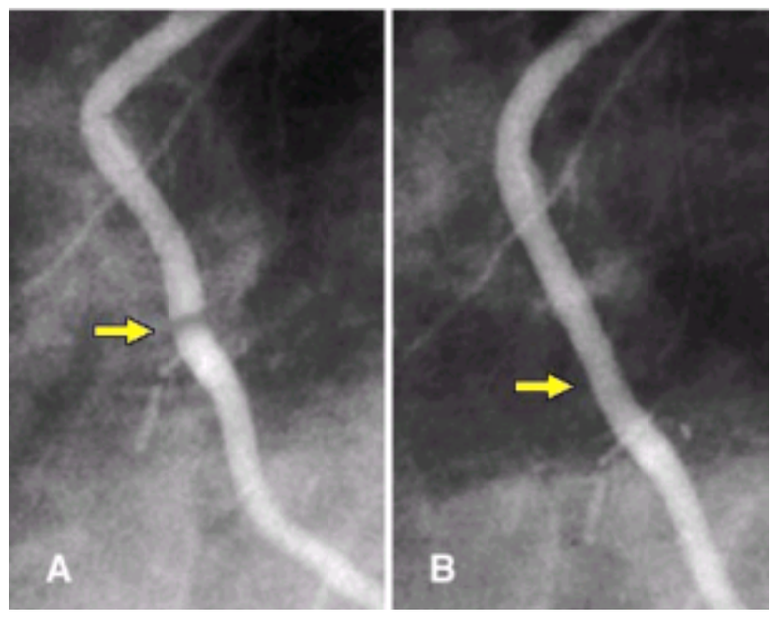
VIDEO

Video 80.7 A 59-year-old male patient with acute inferior myocardial infarction. Large angiographically visible thrombus in the mid-portion of the right coronary artery distal to a severe stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

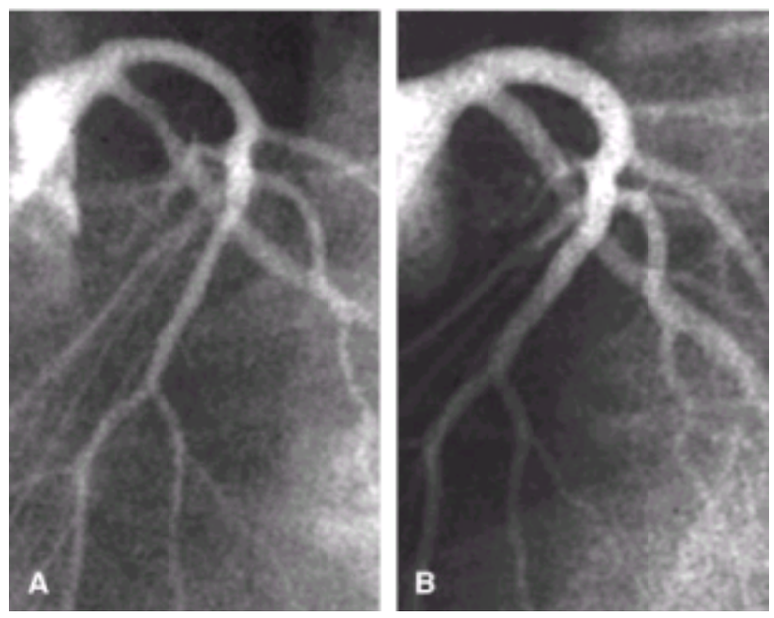
Coronary Spasm

Mechanical stimuli beget coronary spasm. Standard vasodilatory pretreatment for PCI is commonly effective. If spasm occurs just the same, reinforced nitrates or

additional calcium antagonists by the oral, intravenous, or intracoronary route are recommended.



Spasm of the left internal mammary artery after bypass surgery. In the left panel, a significant stenosis is evident that is completely resolved after administration of nitroglycerin. Spasm of the left internal mammary bypass graft can lead to ischemia in the perioperative period after coronary surgery.



Spasm of the left main coronary artery and proximal left anterior descending and left circumflex coronary arteries. The caliber of the left main, proximal left anterior descending, and circumflex arteries are smaller than the distal vessels. This can be better appreciated after administration of intracoronary nitroglycerin.

No-(Re)Flow Phenomenon

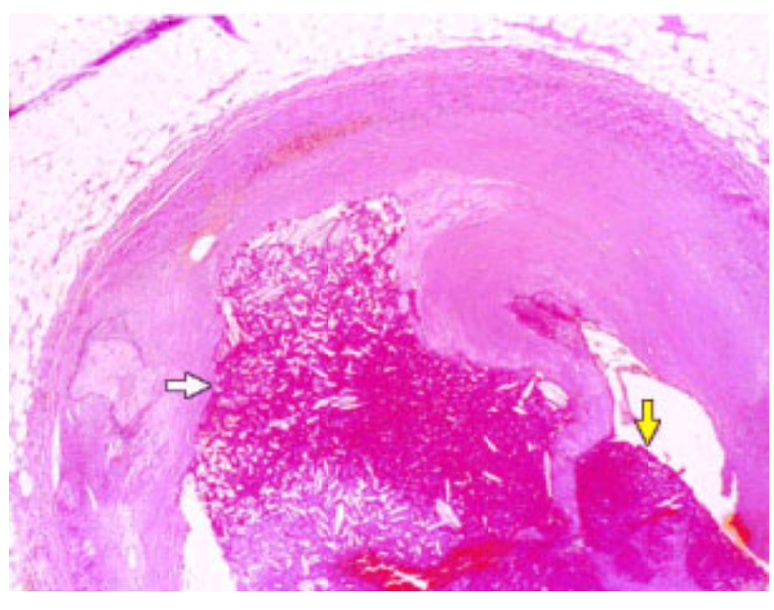
The no-(re)flow phenomenon (65) presumably originates from proximally released vasoactive substances or microembolizations producing spasm and occlusion of small intramyocardial vessels. It may be quite refractory to vasodilators and even glycoprotein IIb/IIIa antagonists and is more germane to stenting than to balloon angioplasty.

VIDEO

Video 80.8 Slow flow noted in the right coronary artery after coronary intervention. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Coronary Perforation or Rupture

Coronary perforation at the site of the lesion with a guidewire may not be rare, especially during recanalization attempts of chronic total occlusions. It is innocuous unless the perforation is enlarged by the balloon catheter. Distal perforations with hydrophilic guidewires represent a new hazard. They occur silently and perhaps multiply while balloons or stents are being introduced with the operator ignoring the wire tip (often outside the visible frame). They have a reduced tendency to seal spontaneously because the walls of normal peripheral vessels are thin.



Organized intraplaque thrombus (*white arrow*) with overlying, near-occlusive fresh thrombus (*yellow arrow*). Ruptured atherosclerotic lesion of the right coronary artery 5 days after a balloon angioplasty procedure.

Low blood pressure in the wake of a PCI involving a hydrophilic guidewire evokes suspicion of tamponade.

Coronary rupture by subintimal or oversized balloon inflation or debulking devices is a rare but serious complication with a mortality of approximately 10% (66). Coronary ruptures can be acutely plugged with a balloon inflation. This may permanently cover the defect with a tissue flap and solve the problem. Implantation of a

(covered) stent at the ruptured site or sacrifice of the vessel by embolization or exclusion (covered stent in main vessel at bifurcation) are further options short of surgery (67). Cardiac tamponade is always first treated by pericardiocentesis. The aspirated blood may be reinjected into a vein to avoid anemia.

Results with Special Indications

Elderly Patients

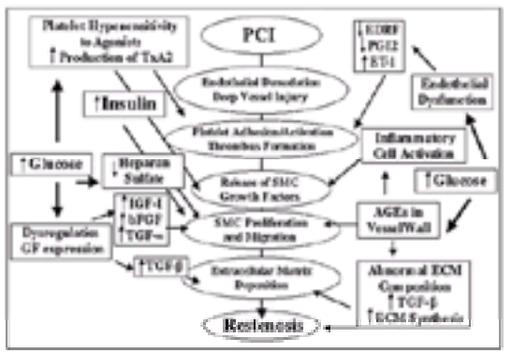
Aged patients are constituting a growing group of candidates for any medical intervention in light of the general aging of industrialized peoples. Coronary artery disease affects 20% of geriatric patients and is the reason for approximately 25% of their morbidity and more than 50% of their mortality (68).

Elderly patients should be spared CABG because of increased operative morbidity and mortality. On the other hand, they typically have diffuse disease and are difficult to catheterize. Their PCI results are less favorable than those of general PCI patients. The early results seem to be better than those with CABG. Yet, geriatric patients undergoing CABG fare better during follow-up in spite of having been sicker initially (69).

Diabetic Patients

Diabetic patients experience increased risks with virtually any major intervention. Their propensity for complications and recurrences after PCI has been highlighted (70). In-hospital mortality is 3% rather than 1% as with nondiabetics. The reintervention rate over 10 years is roughly 60% in diabetics and 50% in nondiabetics. The outcome with CABG has proved better than that with PCI in diabetics (71,72), at least in the ones on insulin (73). Glycoprotein IIb/IIIa antagonists hold potential to improve results with PCI (19).

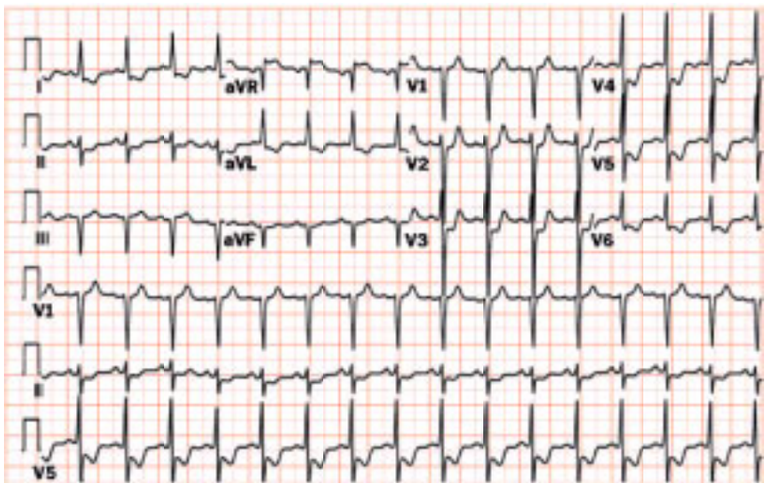
The 7-year mortality of treated diabetics in the Bypass Angioplasty Revascularization Investigation trial was 44% with PCI and 24% with CABG. Mortality in nondiabetics was approximately 14% with both therapies (72). More brittle plaques, higher blood viscosity, enhanced platelet aggregation, increased thromboxane A_2 levels, endothelial dysfunction, and impaired endogenous fibrinolysis must account for the problems of diabetics with PCI (74). Some factors explaining the high recurrence are depicted in eFigure 80.3.4 (75). Many are favorably influenced by stents and novel anticoagulant and antiaggregant compounds. Abciximab yields results in stented diabetics comparable with those of nondiabetics in terms of mortality, lumen at follow-up, or reinterventions (19).



***e*FIGURE 80.3.4** Mechanisms for (re-)stenosis formation in diabetes. AGEs, advanced glycosylation end products; bFGF, basic fibroblast growth factor; ECM, extracellular matrix; EDRF, endothelium-derived relaxing factor; ET-1, endothelin-1; GF, growth factor; IGF-1, insulin-like growth factor 1; PGI2, prostacyclin; SMC, smooth muscle cell; TGF-a, transforming growth factor–a; TGF-b, transforming growth factor–b; TxA2, thromboxane A_2. (Modified from Aronson D, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. *J Am Coll Cardiol* 1996;27:528–535.)

Unstable Angina

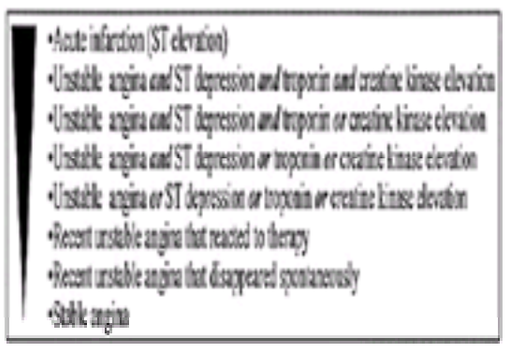
Unstable angina hints at the severity of the culprit lesion, but it does not necessarily inform about the extent of coronary artery disease.



Subendocardial ischemia. Anterolateral ST-segment depression is consistent with diffuse subendocardial ischemia versus non–Q-wave myocardial infarction.

PCI of the unstable plaque (fissured atheroma with partial thrombosis) engenders more acute occlusions than routine PCI. The stent and new antiaggregant or antithrombotic agents have improved on this (19,20,63). Pretreatment with abciximab (19) or eptifibatide (76) is recommended before stenting and the ideal time for PCI appears early (77). Postponing PCI carries the risk of an intercurrent infarction while increasing cost (53).

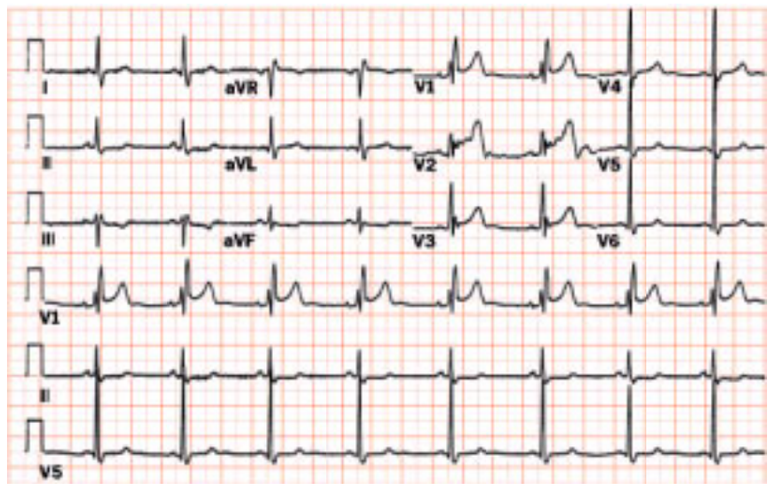
A preliminary risk assessment is recommended according to *e*Figure 80.3.5.



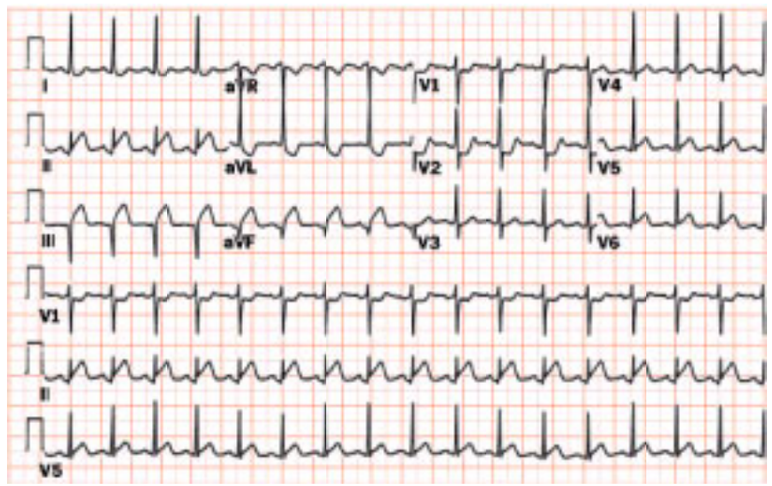
***e*FIGURE 80.3.5** Urgency of coronary angiography and percutaneous coronary intervention in various stages of coronary syndromes.

Acute Myocardial Infarction

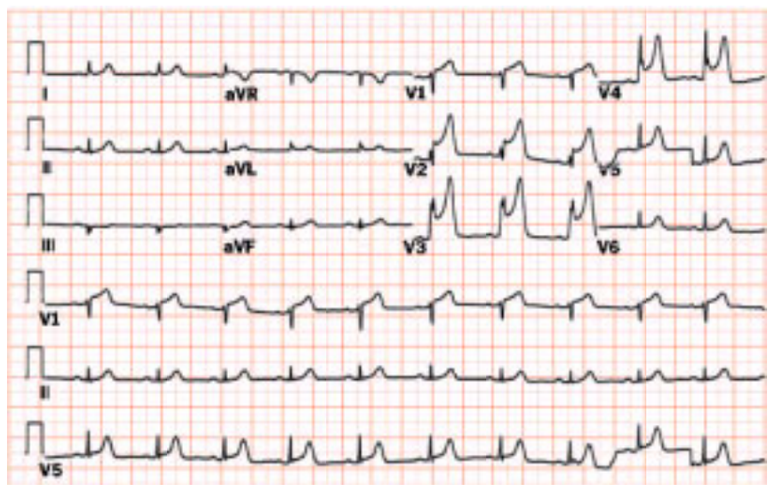
In the early 1980s, there were enthusiastic reports about PCI for failure or incomplete success of intracoronary fibrinolysis with streptokinase (78) and for prevention of reocclusion after successful fibrinolysis, in case a significant stenosis persisted (79). A first randomized trial proved the superiority of acute PCI over intracoronary streptokinase in 1986 (80). Then in the late 1980s, clot-specific fibrinolytic agents appeared, and large-scale randomized trials (81,82) seemed to push aside acute PCI for good.



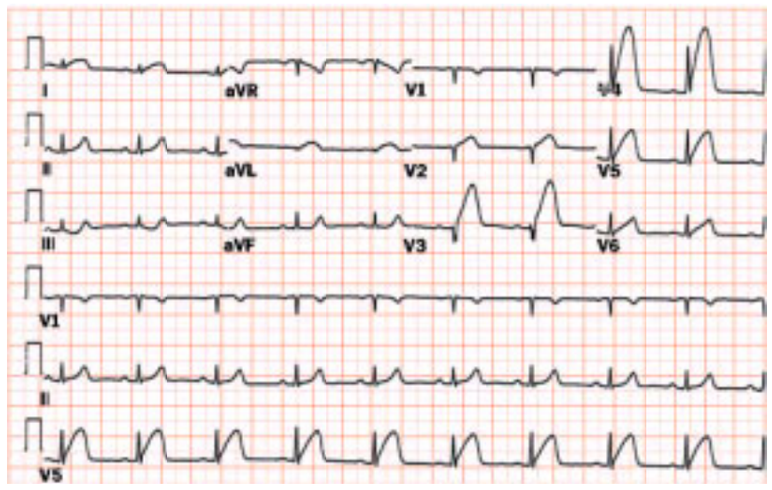
Anterior myocardial infarction in setting of right bundle branch block. ST-segment elevation in the anterior precordial leads as well as primary T-wave changes support acute anteroseptal myocardial infarction.



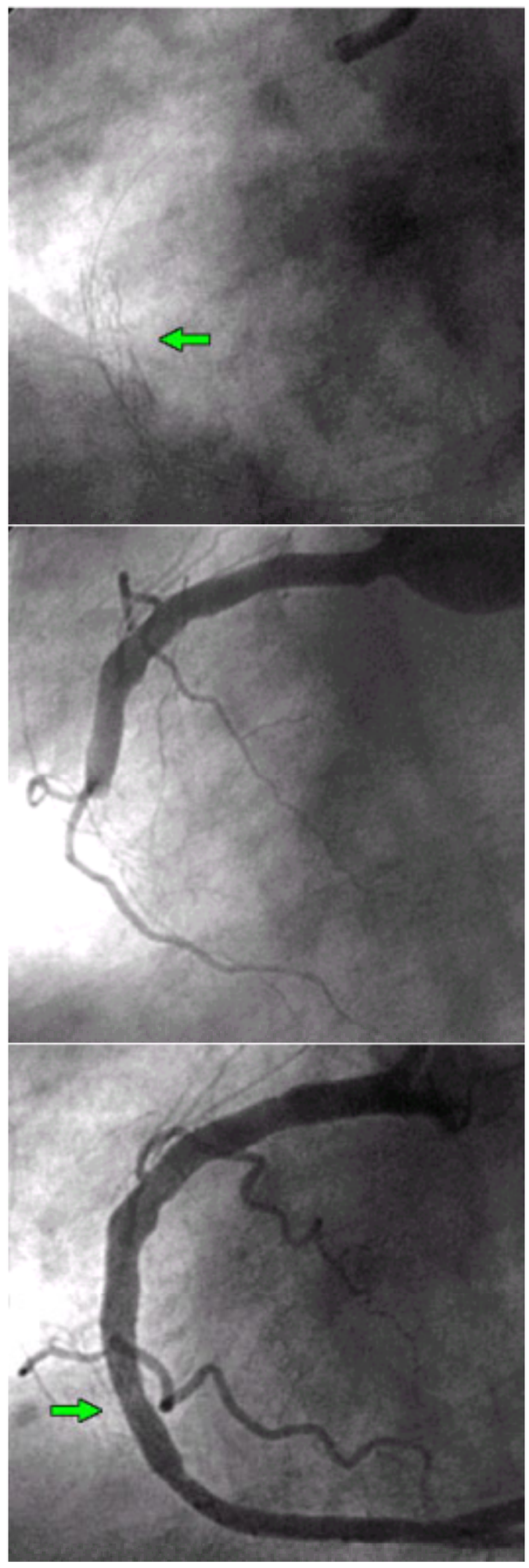
Acute inferoposterior myocardial infarction. Note ST segment elevation in leads II, III and aV_F with ST depression in leads V_1 and V_2.



Acute anteroseptal myocardial infarction. Dramatic ST segment elevations in leads V_1 through V_5 with associated hyperacute T-wave changes are noted.



Acute anterolateral myocardial infarction. Note classic “tombstoning” of ST-T waves in the anterolateral precordial leads.



Primary stent placement for an acute inferior myocardial infarction. After the administration of abciximab, a Palmaz-Schatz biliary stent (B) is deployed across the area of acute occlusion in the mid right coronary artery (A), resulting in normal antegrade flow and no residual stenosis (C).

New randomized trials (83,84 and 85) swung the pendulum back again showing that PCI was superior to fibrinolysis for the initial hours of acute infarction. However, direct angioplasty is logistically more demanding than intravenous fibrinolysis. In addition, the investment of time and money is the same whether acute angioplasty is carried out for a substantial LAD infarction, in which it may be well invested, or for a small left circumflex coronary artery infarction, in which it is unlikely to benefit the outcome (86). This explains why direct angioplasty, although regaining popularity, is still less frequently used than fibrinolysis. Primary PCI is currently the routine treatment for acute infarction only in active PCI centers.

Ongoing infarction is one of the most pressing and rewarding indications for PCI. Mortality is beneficially influenced when compared with fibrinolysis (52). Although coronary flow may be restored somewhat later with direct PCI than with fibrinolysis, particularly if the latter is aided by the dethrombotic effect of a glycoprotein IIb/IIIa antagonist (Fig. 80.4) (87,88 and 89), reperfusion is more complete and the underlying stenosis has simultaneously been taken care of (Fig. 80.5). PCI facilitated by a glycoprotein IIb/IIIa antagonist, a fibrinolytic agent, or both appears therefore as the ideal approach.

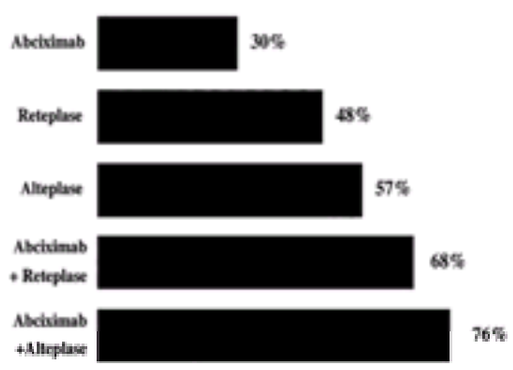


FIGURE 80.4 Flow restoration at 90 minutes by thrombolytic drugs for acute infarction. The combination of abciximab with reteplase (87,88) or alteplase (89) yields the highest patency rates.

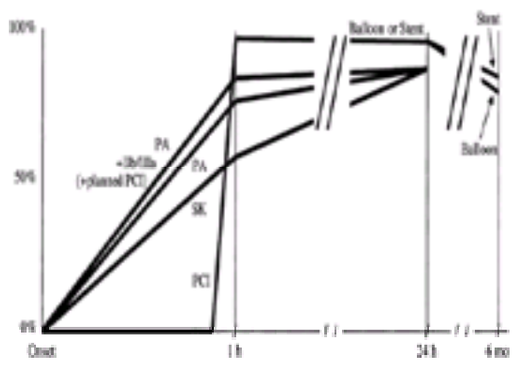


FIGURE 80.5 Percentage of normal coronary flow over time with primary percutaneous coronary intervention (PCI) or (facilitated) systemic fibrinolysis for treatment of acute myocardial infarction. The goal is to stay as high and as far to the left as possible. Up to 1 hour, the combination of a plasminogen activator (PA) with a glycoprotein IIb/IIIa antagonist (IIb/IIIa) is preferable to PA alone or to streptokinase (SK). Meanwhile, immediate percutaneous coronary intervention should be readied. The stent is clearly superior to the balloon only during follow-up that is depicted up to 6 months.

PCI for acute myocardial infarction is an exception in many respects. It dictates an ad hoc procedure and, for most, imposes restriction to the culprit vessel in multivessel disease. Although it carries a higher overall complication rate than elective PCI, it has a smaller potential to harm. The major complication of PCI, abrupt closure of the lesion, is relatively innocuous when starting with an occluded vessel.

There are data warranting stenting for all cases with PCI for infarction. Although acute results are not improved, reinterventions are reduced (Fig. 80.6) (46,90). However, the stent increases no-reflow problems and side branch occlusions. Both damage myocardium; a later restenosis does not. An experienced interventional cardiologist knows to select cases not to stent (good result with crisp flow after balloon dilatation). Direct stenting is not attractive, as the extent of the lesion cannot be anticipated in totally occluded arteries.

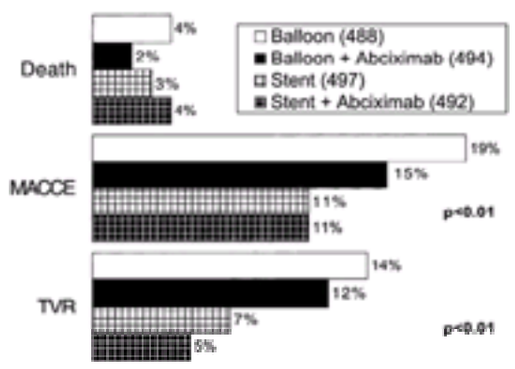


FIGURE 80.6 Randomized trial comparing balloon angioplasty for acute infarction to stenting with or without abciximab. At 6 months, there was an advantage of stenting over balloon angioplasty irrespective of the use of abciximab. It was significant only for target vessel revascularization (TVR) and remained so when major adverse cardiac and cerebral events (MACCE) were pooled. (From Stone GW. Stenting and IIb/IIIa receptor blockade in acute myocardial infarction: an introduction to the CADILLAC trial. *J Invasive Cardiol* 1998;10:36B–47B.)

PCI for cardiogenic shock is warranted unless the shock is too advanced or too long-standing or the patient is old (50,91). In 2000, a percutaneous left ventricular assist device was introduced that may aid these patients as a bridge to recovery or transplantation.

PCI should be done acutely for myocardial infarction if it can be performed within the hour. Otherwise (or perhaps in any case) modern fibrinolysis, preferably supported by a glycoprotein IIb/IIIa antagonist, should be initiated and PCI treatment appended if feasible. Only sizable infarctions (greater than or equal to three ECG leads with ST elevation) qualify for fibrinolysis or PCI.

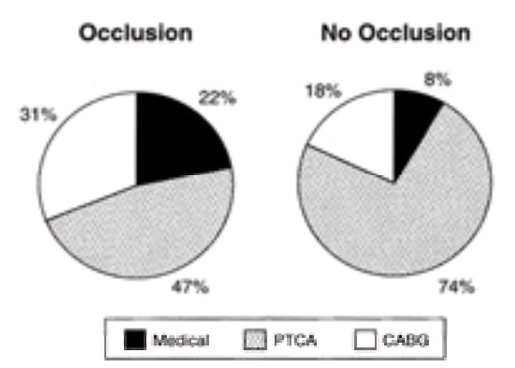
Poor Left Ventricular Function

PCI can be performed with any left ventricular function. A swift introduction of the equipment and a short dilatation is tolerated by all patients even without the use of perfusion balloons, aortic counterpulsation, or left ventricular assist devices. In case of problems, however, the possibilities of PCI to sustain life in patients with severely compromised left ventricular function are more limited than with CABG. Therefore, a markedly reduced left ventricular function tends to favor CABG as a revascularization method. PCI is a valid option in inoperable cases, however, or when only one discrete lesion is at stake, or lesions are attempted in the hope of revitalizing nonfunctional myocardium. Some operators favor the prophylactic insertion of the intraaortic balloon pump (92), but supportive randomized data are lacking. Percutaneously insertable left ventricular assist devices requiring an oxygenator (93) have been partially supplanted by a simplified approach harvesting oxygenated blood from the left atrium.

Chronic Total Coronary Occlusion

Chronic total occlusions are present in 20% to 40% of patients with angiographic documentation of coronary artery disease (94). They constitute the most frequent reason to abstain from PCI.

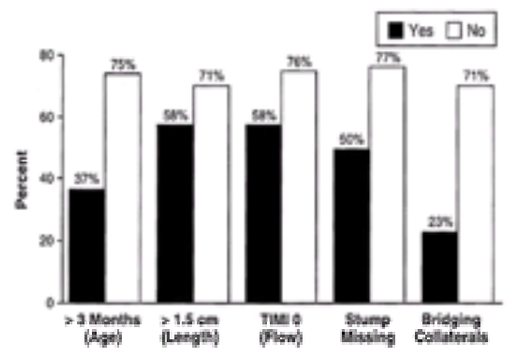
Approximately every third patient undergoing coronary angiography presents at least one total occlusion. eFigure 80.6.1 depicts that the presence of occlusions significantly sways the choice of therapy toward CABG.



***e*FIGURE 80.6.1** Recommendations for therapy in 220 consecutive patients with and 357 patients without at least one chronic total coronary occlusion at coronary angiography. The presence of occlusion favors the recommendation for coronary artery bypass grafting (CABG) rather than percutaneous transluminal coronary angioplasty (PTCA). (Adapted from Delacrétaz E, Meier B. Therapeutic strategy with total coronary artery occlusions. *Am J Cardiol* 1997;79:185–187.)

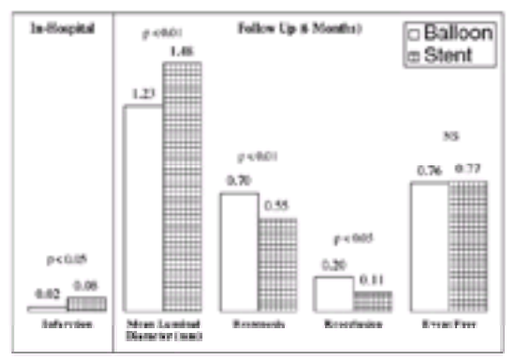
The success rates vary from below 50% to almost 90% according to the cases selected. The key determinants of success are completeness, age, and length of

occlusion; presence of local (bridging) collaterals; and absence of a stump (eFig. 80.6.2) (95). They remain instrumental even after hydrophilic and other dedicated guidewires have improved the crossing potential with this indication.



***e*FIGURE 80.6.2** Success with recanalization of chronic total coronary occlusions according to some important variables in roughly 5,000 patients from pooled reports. (Adapted from Puma JA, Sketch MH Jr, Tcheng JE, et al. Percutaneous revascularization of chronic coronary occlusions: an overview. *J Am Coll Cardiol* 1995;26:1–11.)

With recanalized chronic occlusions, as with fresh occlusions in acute infarction, there is evidence that overall results with stents are superior to those with balloons only. There may be more side branch occlusions, but restenoses and reocclusions are reduced (eFig. 80.6.3) (43). Again, judicious rather than indiscriminate use of stents is warranted.



***e*FIGURE 80.6.3** In-hospital infarction rate and 6-month follow-up in a multicenter randomized trial comparing stenting with balloon angioplasty after successful recanalization of a chronic total coronary occlusion in 410 patients. At the price of an increased in-hospital infarction rate, a better angiographic result at follow-up was achieved, without, however, reducing the overall event rate. NS, not significant. [From Buller CE, Dzavik V, Carere RG, et al. Primary stenting versus balloon angioplasty in occluded coronary arteries: the Total Occlusion Study of Canada (TOSCA). *Circulation* 1999;100:236–242, with permission.]

The high recurrence rate even after stenting is disturbing. However, only the minority of recurrences are reocclusions, and reocclusions, early or late, are unlikely to cause a myocardial infarction, thanks to the reliable recruitability of the previous collaterals (96).

The immediate and long-term clinical yield of PCI of chronic total occlusions is not as spectacular as that of PCI of stenoses, but patients with sustained patency avoid remodeling of the left ventricle (97), improve their exercise capacity (98), enjoy a drastically reduced need for CABG (99,100), and, perhaps, even live longer (99). One of the first randomized studies showing improved survival with PCI pertained to recanalization of totally occluded LADs (101).

Single- and Multivessel Disease

Single-vessel disease still represents the best indication for PCI and accounts for roughly one-half its patients (51).

The correlation between symptoms and therapy is plain. The myocardial function is usually good. The intervention is short, the risk is small and quite accurately predictable, and the rate of restenosis is acceptable. Serial stenoses in a single vessel compromise the outcome to a certain extent, but they still represent a good indication for PCI. More than 85% of PCI procedures worldwide are single-vessel interventions (24,25,51).

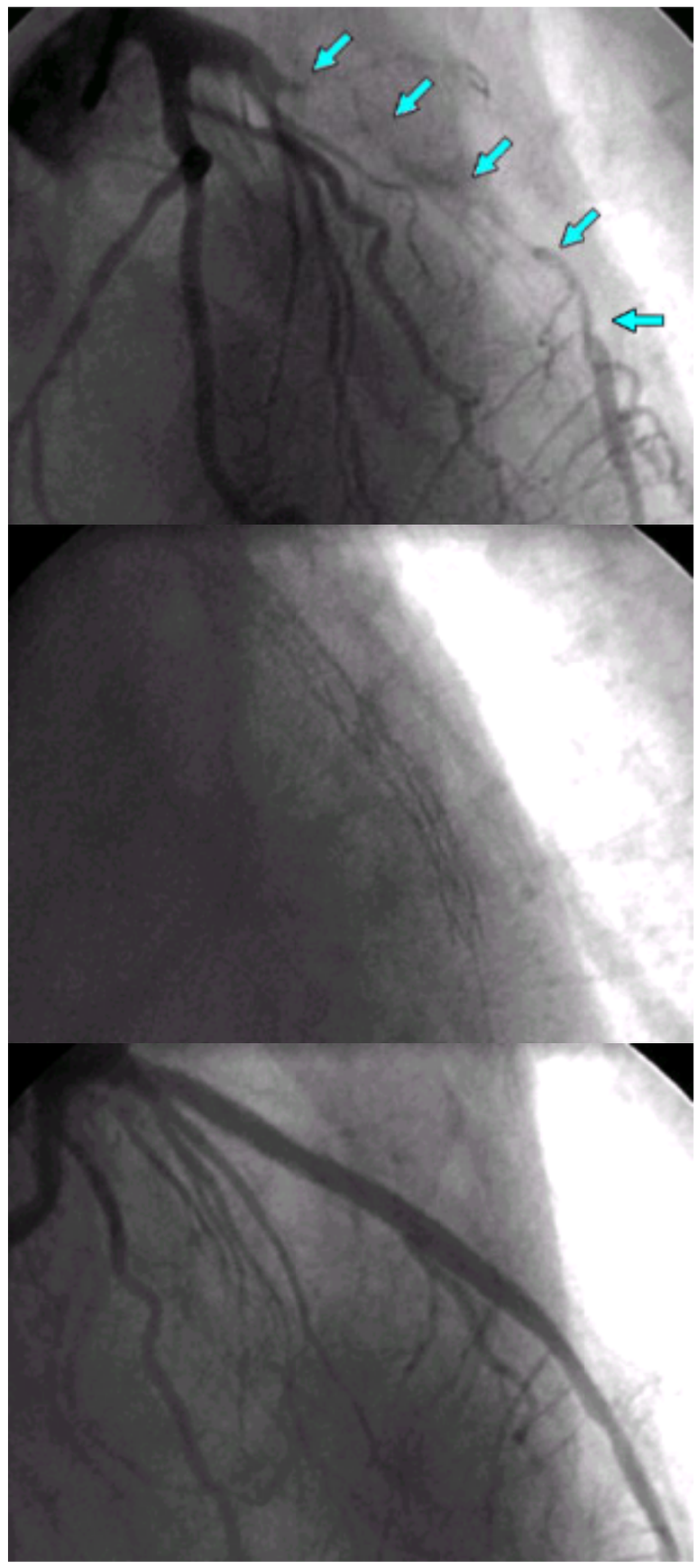
Multivessel disease can and should be considered for PCI in patients with inoperable disease or provided full revascularization at an acceptable risk is projected (for instance, if protective collaterals are present or if the patient is willing to undergo staged procedures) or a culprit lesion can be identified (particularly in the elderly or otherwise poor surgical candidate).

Multivessel disease is a risk factor for acute complications after PCI even if only one vessel is attempted (102).

If several vessels are approached, the acute risk augments further, and there is an increased likelihood of restenosis and other late cardiac events. Complete revascularization is less a prerequisite with PCI than with CABG because of the repeatability of PCI.

Proximal Left Anterior Descending Coronary Artery

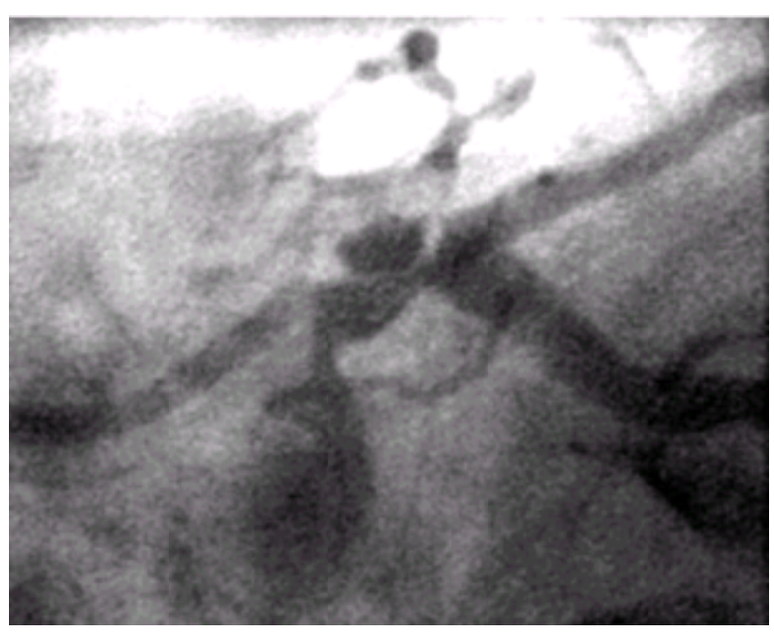
PCI of the proximal LAD has proved effective but it harbors significant jeopardy to cardiac function and survival in case of acute vessel occlusion. It has also been shown to have an increased incidence of restenosis, especially if the ostium of the LAD is involved (103). In contrast to single-vessel disease of other locations, PCI of the proximal LAD has a difficult stand against CABG with the internal mammary artery (104), even with elective stenting (105) and before minimally invasive surgical techniques have been fully exploited (106).



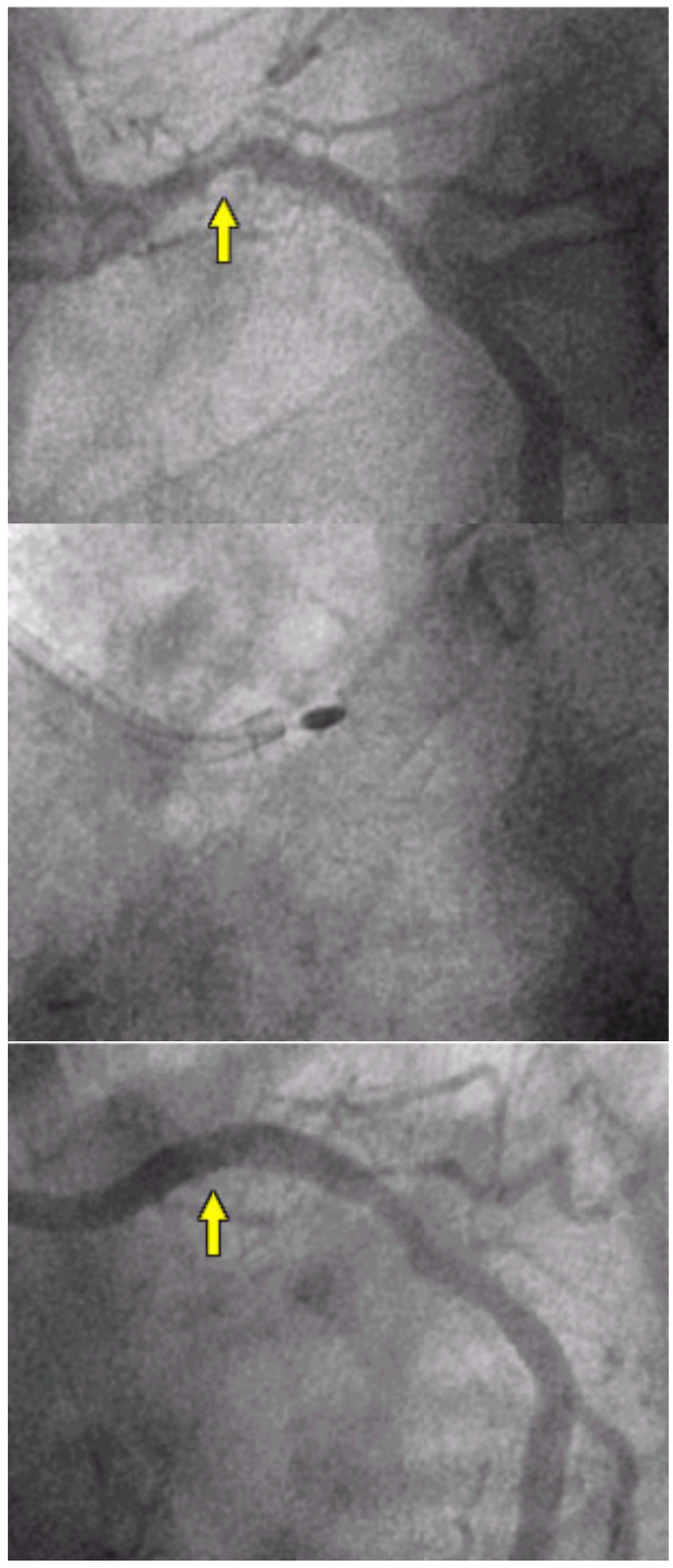
Placement of a long AVE stent in the mid-left anterior descending coronary artery. The arrows in A demonstrate a long area of severe diffuse disease involving the mid-left anterior descending artery. A 39-mm-long radiopaque AVE stent is deployed within the diseased segment (B), yielding an excellent final angiographic result (C).

Left Main Stem

PCI for left main coronary artery stenosis has been considered, tried, shunned, and retried (107). The high mortality discourages the elective use of PCI for unprotected left main stenosis (108). Stents and glycoprotein IIb/IIIa antagonists have yet to overcome this apprehension although modern PCI of a discrete left main lesion not involving the bifurcation is probably as safe and effective as CABG. Protected left main lesions (patent bypass graft or copious collaterals to at least one vessel of the left circulation) and acutely or chronically occluded left main lesions have always been a valid indication for PCI.



Severe ulcerated plaque of the left main trunk discovered on diagnostic angiography.



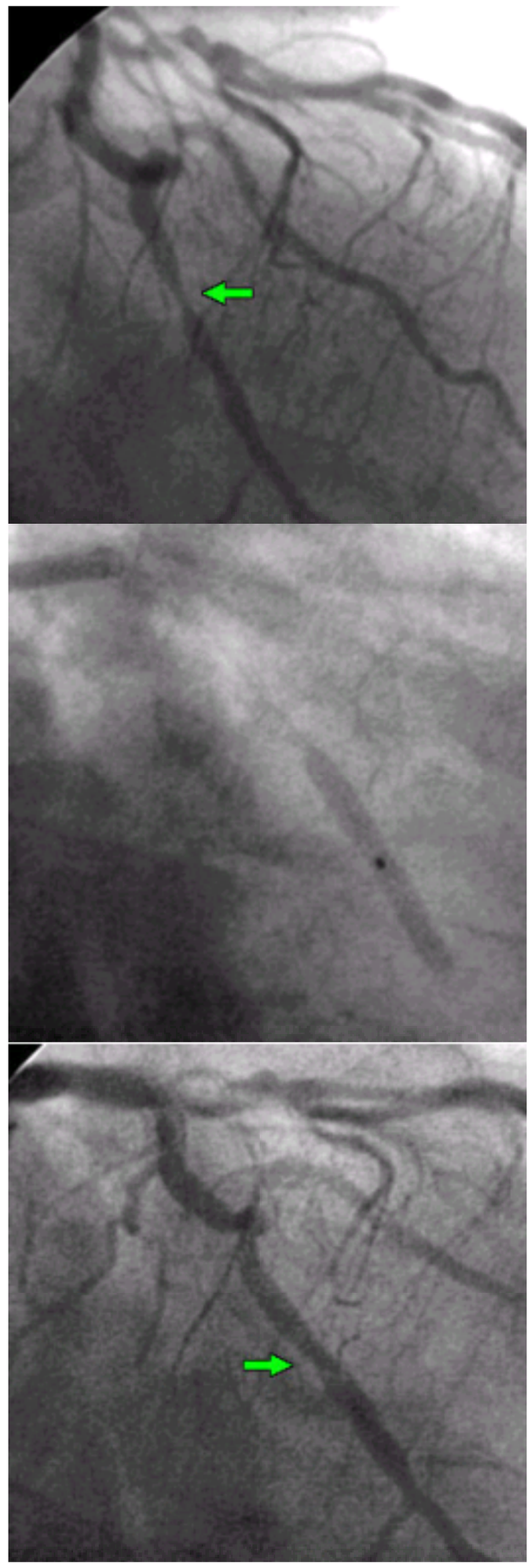
Rotational atherectomy of a "protected" left main trunk. A severe stenosis (A, *arrow*) is present in the left main trunk and compromises flow to the left circumflex. The left anterior descending artery is "protected" by a patent left internal mammary artery graft. Rotational atherectomy followed by stent implantation is successfully performed (B,C).

Video 80.9 Ostial left main coronary artery disease. Contrast injection reveals severe narrowing of the ostium of the left main coronary artery. In this patient, after coronary artery bypass graft surgery there was rapid acceleration of the underlying coronary disease leading to this left main stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

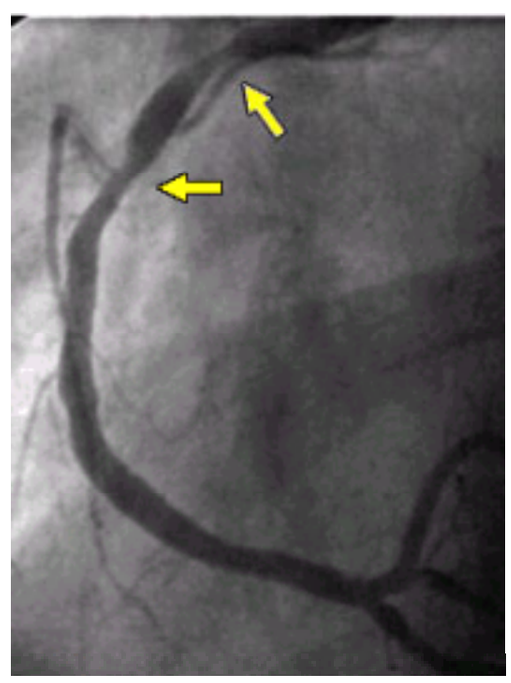
Video 80.10 Left anterior oblique caudal view of the left main trunk showing severe ostial stenosis. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

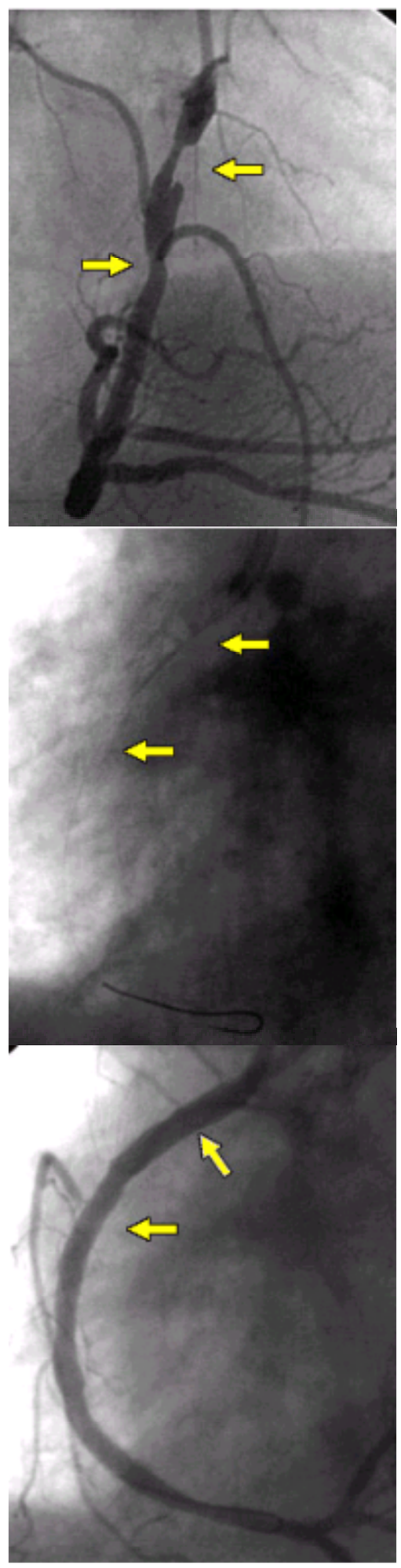
Ostial, Small, Long Diffuse, or Calcified Lesions

For many years, the search was on for a solution to the problems encountered with balloon angioplasty when dealing with ostial, small, long diffuse, or calcified lesions. Initially, it appeared that directional atherectomy might be helpful for ostial lesions and rotablation or laser for small vessels with long and diffuse lesions.



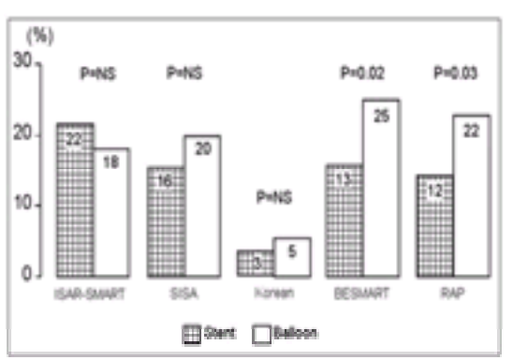
Balloon angioplasty of the lateral branch of the left circumflex (A). Stand-alone balloon angioplasty (B) resulted in substantial reduction in stenosis severity with no angiographic evidence of dissection (C).





Sequential stenosis in the proximal right coronary artery (A,B) treated with different stent types. A Palmaz-Schatz coronary stent is implanted across the more distal stenosis (C, *lower arrow*), then a Palmaz-Schatz balloon stent (more radiopaque) is used to treat the more proximal lesion (C, *upper arrow*) in a segment with a large normal reference vessel area. The postintervention result is shown in D.

The stent has replaced directional atherectomy for ostial lesions because it yields better long-term results, is more readily applicable, and produces fewer acute complications. Nice angiographic results can also be obtained in long diffuse lesions by implanting multiple or long stents, again with fewer technical or clinical problems than by using rotablation or lasing. The high recurrence rate remains a problem, however, particularly in small vessels (eFig. 80.6.4) (41,109,110).



***e*FIGURE 80.6.4** Need for reintervention in randomized trials (approximately 400 patients each) comparing stenting with balloon angioplasty in small arteries. The results are controversial. The Bestent in Small Arteries Trial (BESMART) and Restenosis en Arterias Pequeñas (RAP) trial using the same stent model showed an advantage for stenting in reduction of restenosis and reintervention. The other trials, Intracoronary Stenting and Antithrombotic Regimen-(Munich) Small Artery Stenting (ISAR-SMART) (41), Stent to Prevent Restenosis in Small Arteries (SISA), and Korean (110), using other stents, did not. NS, not significant.

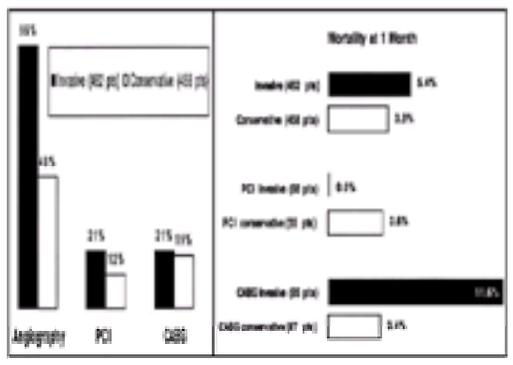
Calcifications only play a role if they are circumferential, and the stenosis fails to yield to maximal balloon pressure. These situations have all but disappeared, with balloons tolerating pressures up to 30 bar. For the few remaining cases, rotablation may be tried.

Comparison with Alternative Therapies

Medical therapy is the foremost alternative to PCI for single-vessel disease except for proximal LAD stenoses in which surgery must be considered and yields better results than PCI (104,105,111) or medical therapy (111) regarding the need for further interventions. The Angioplasty Compared to Medicine (112) and Coronary

Angioplasty versus Medical Therapy for Angina-2 (113) trials have randomized patients between PCI and medical treatment. The advantage of PCI was quite conspicuous but limited to exercise performance and quality of life.

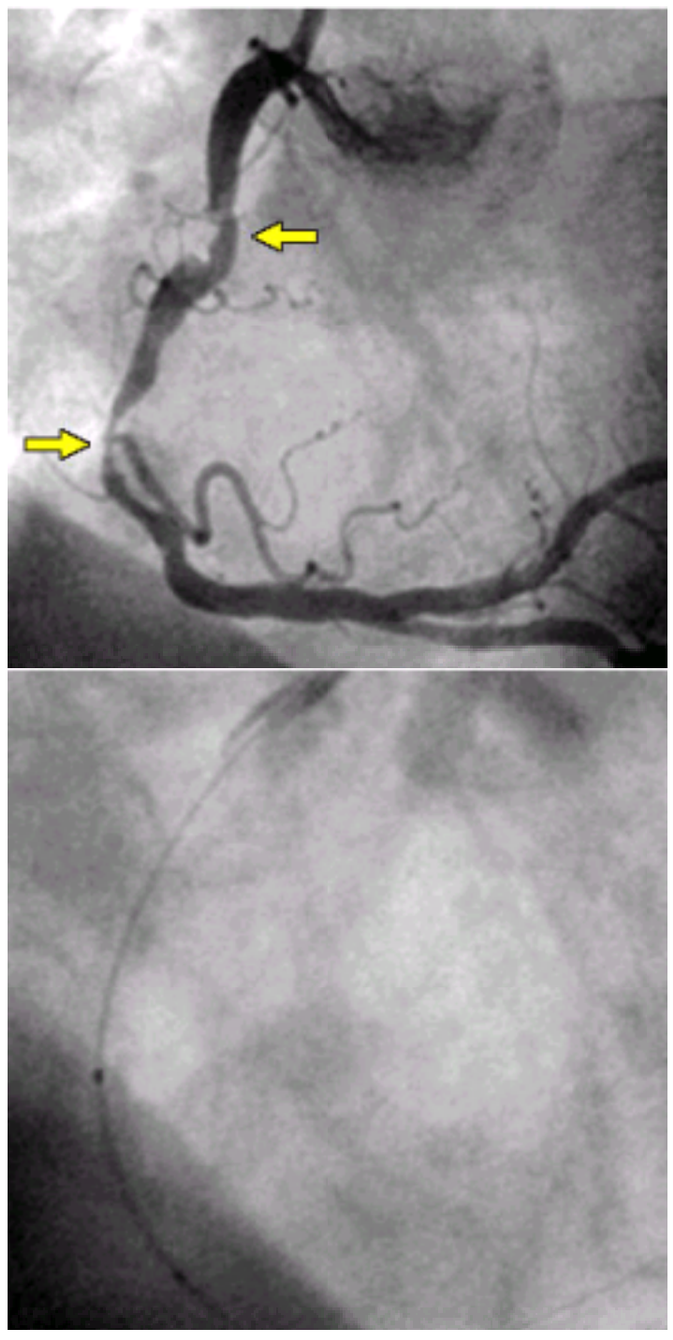
In unstable situations or after non-Q infarction, randomized trials gave mixed results. The Veterans Affairs Non-Q Wave Infarction Strategies In-Hospital Study found a negative influence of invasive workup and treatment after non-Q infarction (114). However, eFigure 80.6.5 reveals that the actual difference in invasive attitude was small, and the rather negative outcome in the invasive group was entirely due to an appalling 11.6% mortality in the patients randomized to the invasive arm and treated with CABG. Mortality in the PCI patients was nil, and the differences in outcome had disappeared at 3 years. The Fast Revascularisation during Instability in Coronary Artery Disease II trial clearly advocates an invasive attitude early in unstable angina based on a significant reduction in major cardiac events, in particular mortality at 1 year (53). The Treat Angina with Aggrastat (Tirofiban) and Determine Cost of Therapy with an Invasive or Conservative Strategy trial confirms the value of such an attitude even after pretreatment with tirofiban (77).

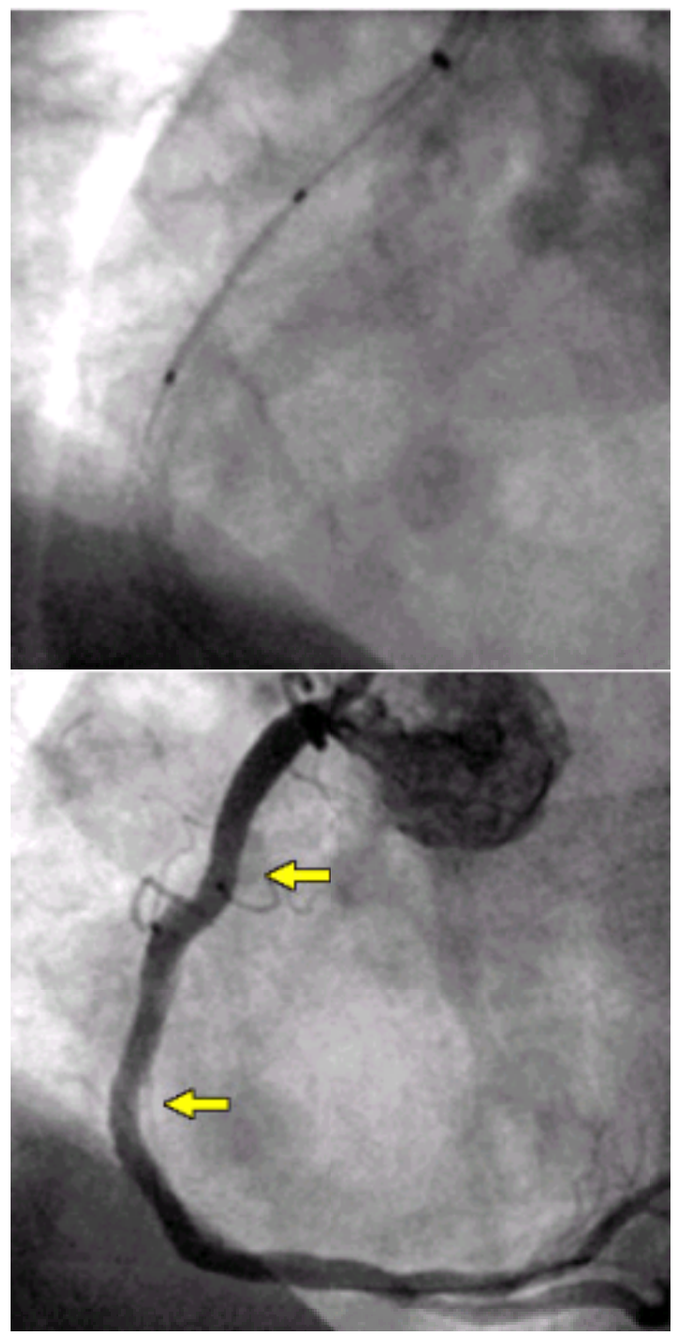


***e*FIGURE 80.6.5** Randomized trial comparing invasive with conservative therapy in 920 patients (pts) after non-Q infarction (114). The borderline significant increase in mortality with invasive strategy does not speak against percutaneous coronary intervention (PCI) because of the poor adherence to the randomized strategy (*left panel*) and the absence of lethal outcomes in patients randomized to the invasive arm and treated with PCI (*right panel*). CABG, coronary artery bypass grafting.

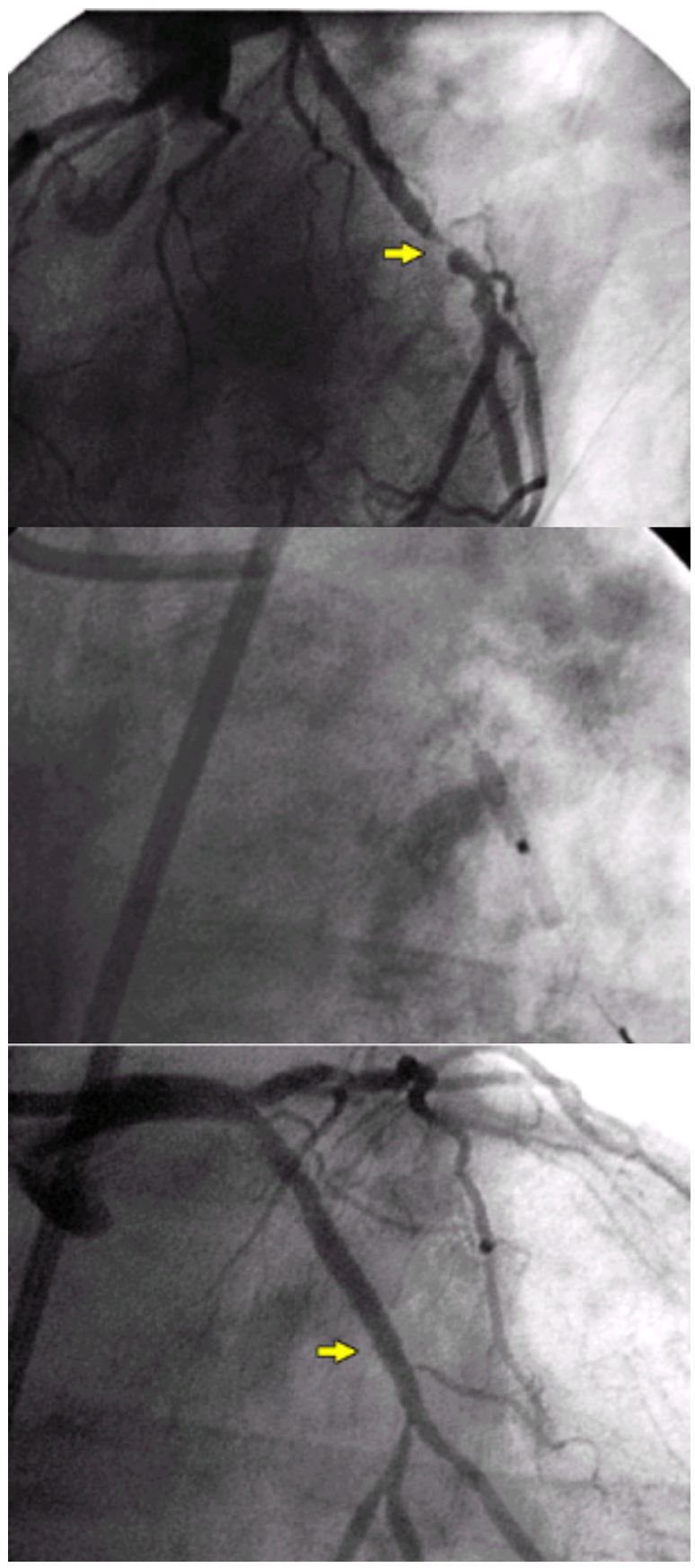
Under more stable auspices, the Atorvastatin versus Revascularization Treatment trial suggested that an aggressive treatment with a statin (80 mg of atorvastatin) for 18 months was at least equal to an invasive strategy in patients with significant coronary artery disease (115). This does not take into account that the rate of PCI in the conservative group accrues over time, manifesting that the underlying problem, the stenosis, will need to be addressed sooner or later. The same can be said for the Deferral versus Performance of PTCA Based on Coronary Pressure Derived Fractional Flow Reserve trial. It shows that a stenosis not reaching hemodynamic significance when assessed invasively by its fractional coronary flow reserve can be left undilated for at least 2 years without increasing the risk for cardiac events (116).

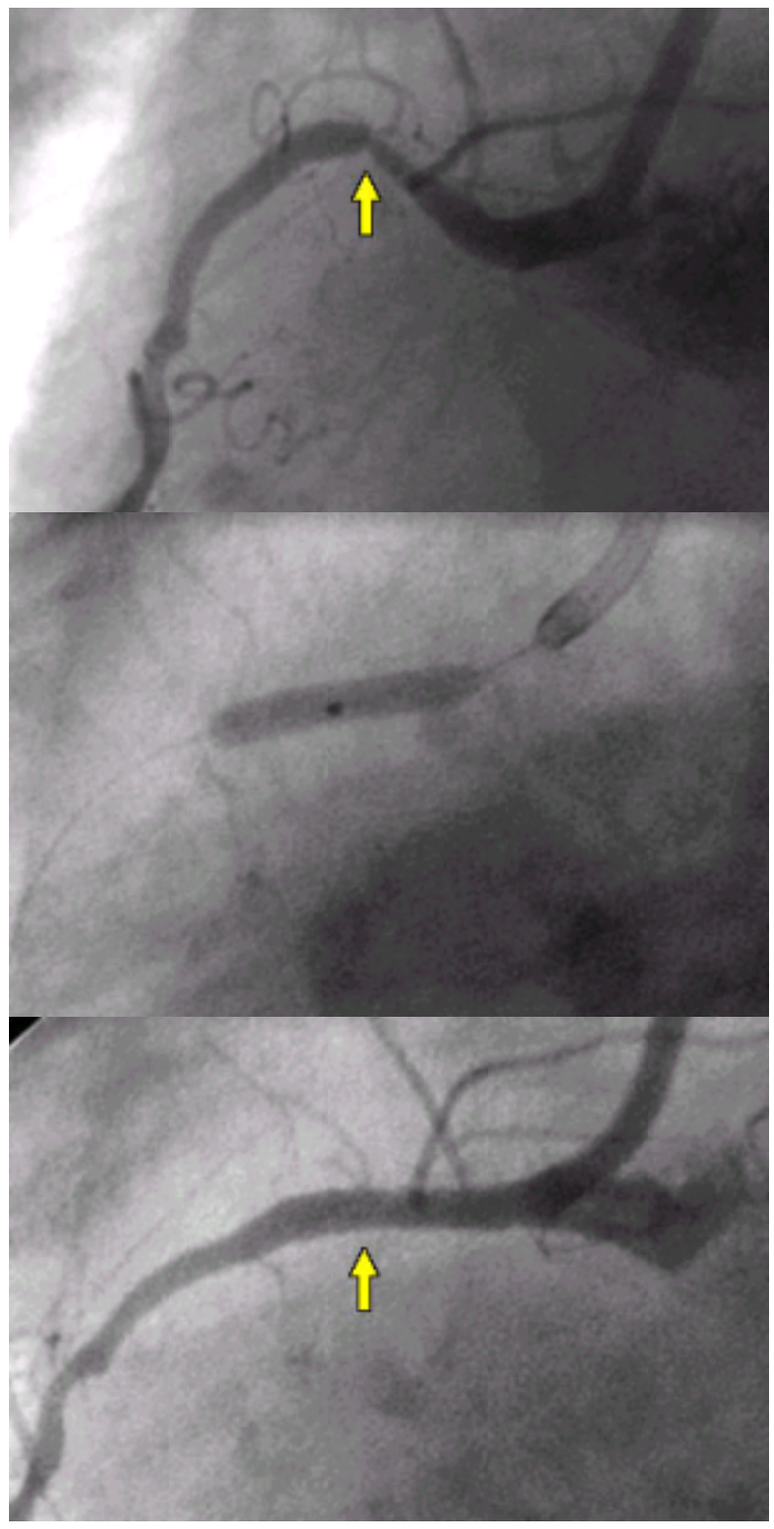
In multivessel disease, PCI has been compared with CABG in numerous randomized trials first without (72,117,118,119,120 and 121) and then with elective stenting (122,123).





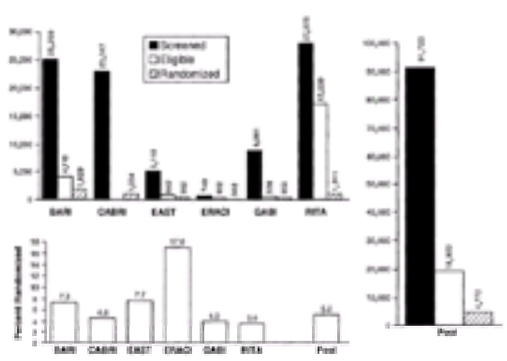
Use of multiple Palmaz-Schatz stents to treat sequential stenoses (A, *arrows*) in the right coronary artery. The first stent is deployed across the more distal lesion (B), then the second stent is deployed across the proximal stenosis (C). The result of the intervention is shown in D.





The strategy of multiple stent implantation in a patient with multivessel disease. Initially, a discrete lesion in the mid left circumflex artery (A) is successfully treated with a Palmaz-Schatz coronary stent (B,C). A second Palmaz-Schatz stent is then implanted in the proximal right coronary artery (D–F).

It has to be stressed that the inclusion rate of screened patients was minimal (*e*Fig. 80.6.6). Patients analyzed do not represent the average multivessel patient undergoing diagnostic coronary angiography.



***e*FIGURE 80.6.6** Screened, eligible, and randomized patients in various trials randomizing patients with multivessel disease between percutaneous coronary intervention and coronary artery bypass grafting. In all studies, only a small percentage of screened patients were finally randomized (*right panel*). BARI, Bypass Angioplasty Revascularization Investigation; CABRI, Coronary Angioplasty versus Bypass Revascularization Investigation; EAST, Emory Angioplasty versus Surgery Trial; ERACI, Argentine Trial of Percutaneous Transluminal Coronary Angioplasty versus CABG; GABI, German Angioplasty Bypass Surgery Investigation; RITA, Randomised Intervention Treatment of Angina (also including single-vessel disease).

The results across the board show similar mortality and infarction rates between the two methods, with a tendency to more early significant infarctions in CABG patients and more later mortality in PCI patients (124). With PCI, there is a markedly higher need for further coronary interventions than with CABG, reflecting the restenosis problem after PCI. This is somewhat mitigated by stents, according to the Arterial Revascularization Therapy Study and Stent or Surgery trials, but still remains significant with reinterventions in approximately 25% of patients after stenting versus 15% after CABG (122,123).

Patients on antidiabetic treatment were analyzed separately in some of the studies. They had a generally poor 7-year survival, but it was significantly better with CABG (76%) than with PCI (56%) (72). This difference could be blunted in the future by generous use of abciximab (125).

Rehabilitation

Return-to-work rates are not only dependent on the physical and mental ability of the patient to resume a normal life but also on the attitude of the medical professionals, on regional customs, and on the welfare system. Following a successful PCI without complications, normal physical activity can be resumed as early as 12 hours after the intervention. CABG is clearly no match for this. Only a few patients, however, take full advantage of this feature of PCI, and the average time to resume gainful activity amounts to several days to weeks in most countries.

Quality of life in the early phase after PCI is better than after CABG for obvious reasons, but at 1 year the opposite is true (126). On the other hand, quality of life after PCI is superior to that with medical treatment because of reduced symptoms and improved exercise capacity (113).

ECONOMIC ASPECTS

A procedure that prolongs life in the elderly tends to engender further medical expenses. Even with the proof for life extension by PCI pending, it is likely that the

repeated use of the method will keep coronary patients around longer than medical treatment alone. These patients are in general economically nonproductive and likely to need further costly medical care on top of general financial sustenance. Moreover, the cost of a PCI procedure is affected by a number of variables. Mostly, it is operator dependent (127). New devices tend to be more expensive (128).

It is estimated that $10,000 invested in an invasive strategy for coronary artery disease affords 1 life-year. For an additional $6,000 invested into abciximab, another year can be gained (129). This can be compared with the $6,000 to be invested into CABG for left main disease to save 1 life-year. The focus should, however, remain on the quality of life gained per investment.

The CABG package is costly during the first month (surgery, intensive care, prolonged hospital stay, rehabilitation program, and absence from work), but little additional expenditure is expected in the first year thereafter. The PCI package accrues cost over almost the entire first year (repeat interventions). A comparative cost analysis, including the first month only, will heavily favor PCI (130). Accumulated cost at 1 year seems more reasonable but may disfavor PCI. Repeat interventions in the subsequent years are virtually limited to those for disease progression after PCI while interventions for graft attrition (venous in particular) add up to those for disease progression after CABG.

In the socialized medical system of the United Kingdom, the aggregated costs of PCI at 2 years were 20% lower than those of CABG (130). Similar balances ensued from a study in Argentina (131). Some U.S. authors confirm this (132). Yet some observed a more or less rapid equalization of cost (133,134). The more systematic use of stents and glycoprotein IIb/IIIa antagonists adds cost to PCI up front. The reduced need for early or late reintervention should make up for this (129). On the surgical side, off-pump surgery has failed to show a cost benefit so far (135).

PCI is no exception to other sophisticated medical techniques. It can be used to the advantage of mankind but it is costly. Whether this luxury is offered to the entire population and how close to home and with how short a waiting period is ultimately a decision up to the local political authorities. Plenty of doctors are easily beguiled by PCI and offer it to the patients provided there are adequate logistics and reimbursement. Lastly, PCI is at the base of an entire industry spanning from manufacturing of dedicated equipment to specialized hospitals and worldwide teaching activities. These important aspects need to be factored into the economic calculations as well.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Several issues of PCI cannot be solved based on evidence and remain highly subjective and thus controversial. They have to be seen in the light of variable geographic, economic, temperamental, and philosophical backgrounds and are also subject to change as time goes by. It is difficult to deal with such topics in a way applicable to all situations, everywhere, and at any time.

The question of where PCI should be performed and by whom has been iteratively debated with high emotions. A high-volume operator working at a high-volume institution, backed up by a high-volume cardiac surgical program, is the ideal setting. However, this means that the population with coronary artery disease will have to converge at the few megacenters to receive PCI under scientifically optimal circumstances. Approximately one center for 2 million people will suffice. It will perform between 2,000 and 4,000 PCIs per year with five to ten primary operators. The operators will not be assisted by doctors because those would decrease quality while learning the trade, spread out, and dilute the high-volume scenario. Interventional cardiologists would be trained exclusively to replace retiring operators and to meet the growing demand for procedures.

But will the patients like that? Many of them prefer get the treatment at their local hospital by their familiar cardiologist. There, they find their way around. There, they know people and people come to visit. Most patients do not care so much about the theoretic variance in the quality of PCI. First, they are unable to grasp the subtle differences, and, second, most PCI results are good, anyhow, even with low-volume teams. Referring doctors like to deal with angioplasty operators they know personally, rather than sending their patients to an anonymous “superinstitution.” Smaller communities can use the business involved, too. Concentration of the facilities to PCI “hubs” hurts their economy and keeps away investors and settlers.

When respected authorities, let alone governments, set regulations, they should honor these facts to a reasonable degree. It seems unwise to set limits that “outlaw” a substantial number of current operators. It is unlikely that they will abandon their practice, as that jeopardizes their professional existence. Nevertheless, guidelines should be clear regarding what is preferable, and reasonable minimal standards must be set.

Indications for PCI are another topic in which science and the “real world” diverge. Data show that the risk of coronary lesions is related to the extent of ischemia they produce. Scientifically, one could deduct that it is unethical to dilate lesions for which objective proof of ischemia or at least hemodynamic significance is lacking. Yet, this disregards patients with lesions that at the time of an “objectively unwarranted” PCI were not significant in terms of ischemia but that would have caused an infarction under conservative treatment while waiting for them to attain a hemodynamically significant degree.

Admittedly, it is currently impossible to predict these exceptions, but it is equally impossible to predict with accuracy which lesion will adhere to the rules. Moreover, it is customary in many centers around the globe to include the eventuality of an unanticipated spontaneous occlusion of the lesion when pondering a PCI indication. Imposing a different approach with costly assessment of the functional significance of the stenosis or the instability of the plaque is difficult to enforce and may not be to the benefit of the patients overall.

THE FUTURE

PCI is currently one of the dominant assets of modern health care. It engenders abundant medical literature, occupies a significant segment of medical education programs, and is a remarkable economic factor. It produces gigantic costs but also tax revenue. It creates income, jobs, and career opportunities for countless people. It unequivocally benefits well-being and perhaps even longevity of the elder generations of industrialized countries.

Figure 80.7 reflects the past and the future of technical aspects. Stenting will be the rule before long. The approach will be direct stenting to save time and spare the predilatation balloon. The stents will be drug eluting, which will not complicate the procedure or the logistics. New gimmicks will come and go as before, but the balloon-mounted stent will reign.

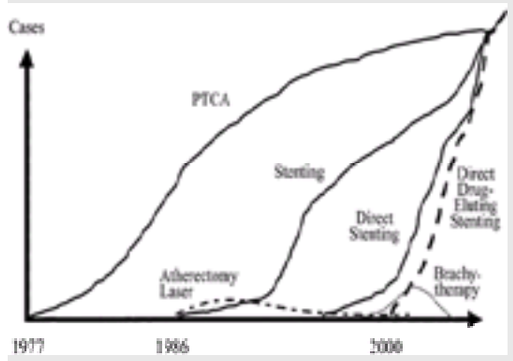


FIGURE 80.7 Past and future of percutaneous coronary intervention. The increase in cases may regain momentum once direct drug-eluting stenting has completely taken over. PTCA, percutaneous transluminal coronary angioplasty. (Modified from ideas of M. E. Bertrand and P. W. Serruys.)

The immediate future of balloon angioplasty is bright because coronary artery disease will remain the number one health problem of industrialized countries for quite some time and become increasingly prevalent in the rest of the world. It is bright because further improving technologies will expand the role of PCI for this disease, especially for its early, and perhaps for its very late, stage. The disease is increasingly discovered and documented at the early stage, and the general aging of the population creates a growing need for PCI at that end of the spectrum.

On the other hand, economic constraints increasingly frustrate those capable and willing to perform the procedure. Quality assurance activities take up more and more of the time of the interventional cardiologist. Finally, primary prevention will succeed in drastically reducing the need for PCI in middle age, stripping it of its coveted role as the most important intervention in modern medicine for people in their “best years.” Then again, there is nothing wrong with this.

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81

NEW TECHNIQUES IN INTERVENTIONAL CARDIOLOGY: RADIATION, EMBOLI PROTECTION, AND THERAPEUTIC ANGIOGENESIS

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"Indicates text or graphics that appear only in the electronic versions of this text."

Radiation
Characteristics of Radiation
Biologic Considerations
Preclinical Studies
Late Effects
Clinical Studies
Delivery Systems
Stent-Based Beta Implants
Controversies and Personal Perspectives
Emboli Protection
Pathophysiology
Clinical Evidence
Pharmacologic Approaches to Embolization
Mechanical Approaches to Embolization
Controversies and Personal Perspectives
Therapeutic Angiogenesis
Mechanical Approaches
Growth Factor Administration
Controversies and Personal Perspectives
Chapter References

RADIATION

Studies of restenosis have identified at least four mechanisms that contribute to luminal narrowing. These include elastic recoil of the artery, local thrombus formation, neointimal formation, and vascular remodeling (1,2,3,4 and 5). The relative contribution of these processes in humans is variable, with poststent restenosis dominated by neointimal hyperplasia and postballoon angioplasty restenosis primarily attributable to elastic recoil and negative remodeling of the target arterial segment (4).

VIDEO

Video 81.1 Severe in-stent restenosis involving the distal right coronary artery **(A)** and successful angioplasty **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

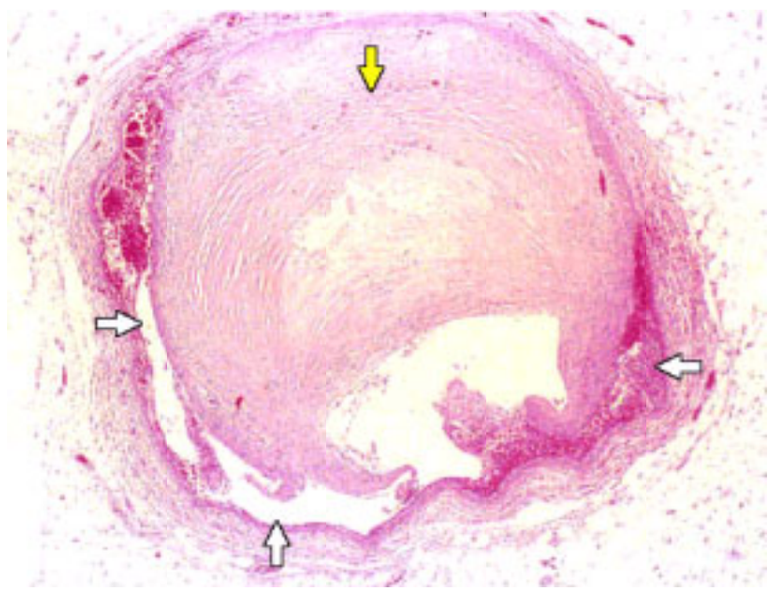
VIDEO

Video 81.2 Severe in-stent restenosis involving the distal right coronary artery **(A)** and successful angioplasty **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

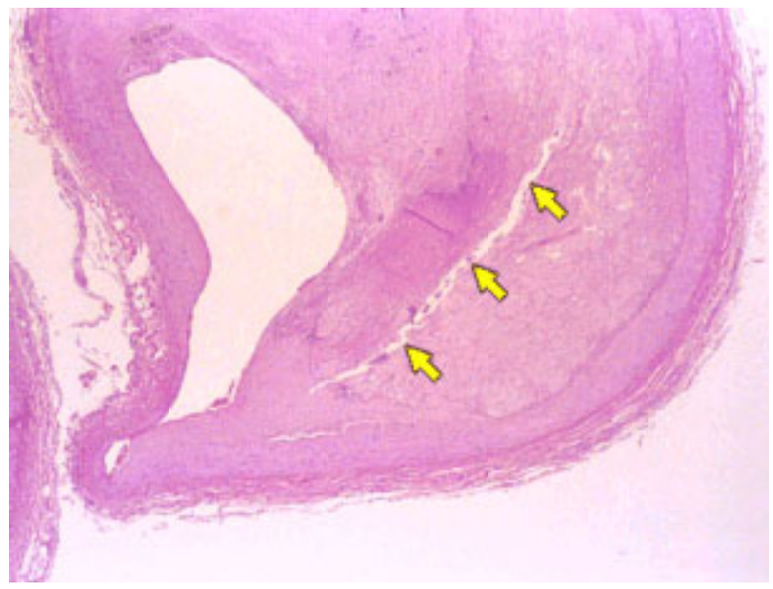
VIDEO

Video 81.3 Anomalous origin of the left circumflex coronary artery from the right sinus with in-stent restenosis 7 months post procedure. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

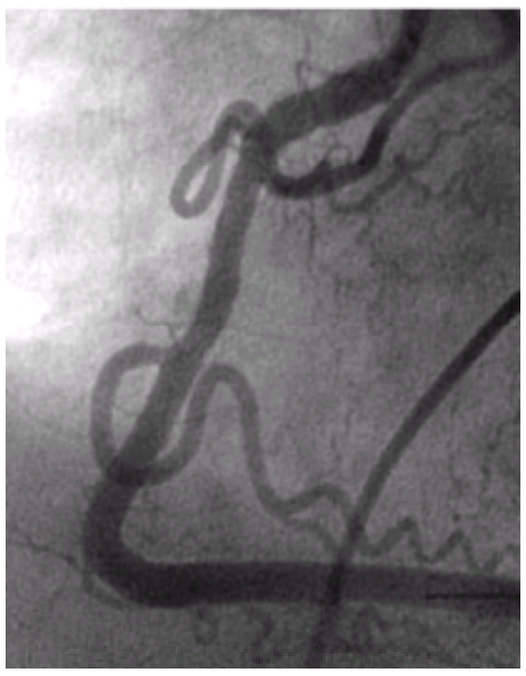
The reduction of neointimal proliferation has been the primary target of experimental and clinical restenosis efforts. The predominant cell type in the neointima has a smooth muscle phenotype; however, a significant amount of extracellular matrix is elaborated to form the bulk of the neointimal mass. More recent studies have suggested probucol (6) and tranilast (7) may both reduce restenosis rates in certain settings, although each compound has significant limitations.



Linear, circumferential dissection 2 days after balloon angioplasty of a restenotic lesion. Note the extensive neointimal proliferation (*yellow arrow*) and dissection (*white arrows*).



Restenotic lesion. Residual tear in atherosclerotic plaque (*yellow arrows*) and large amount of neointimal proliferation 76 days after balloon angioplasty.

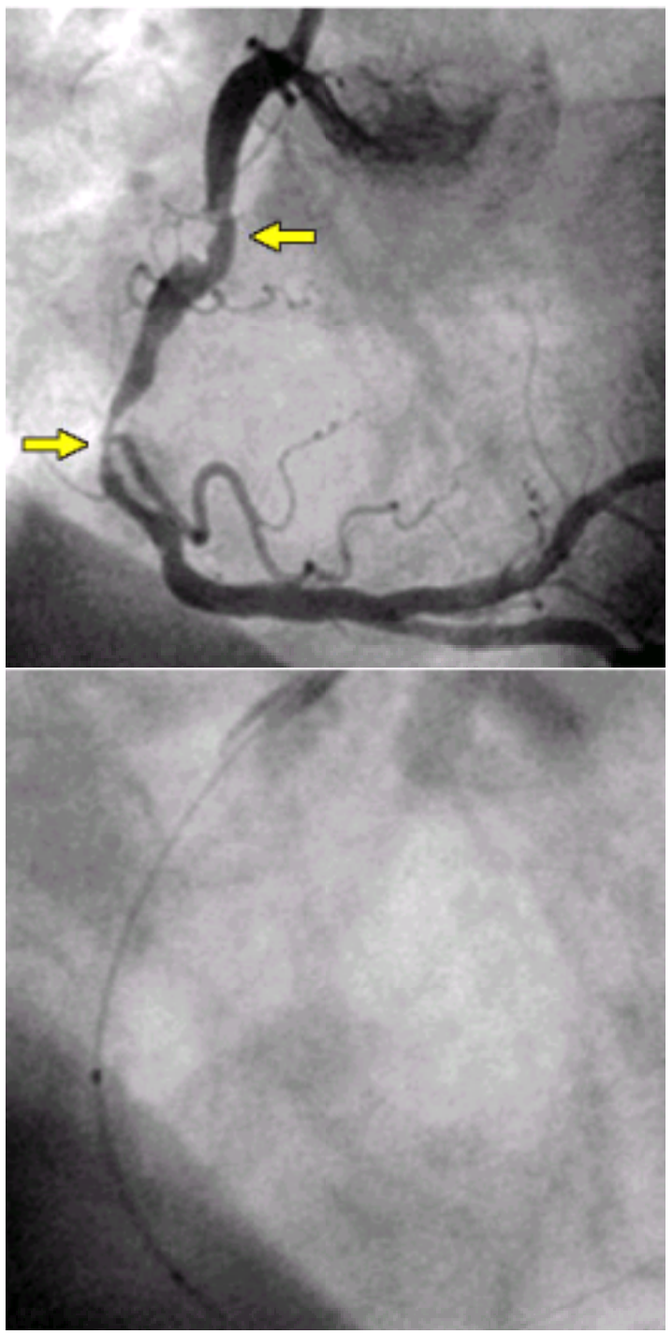


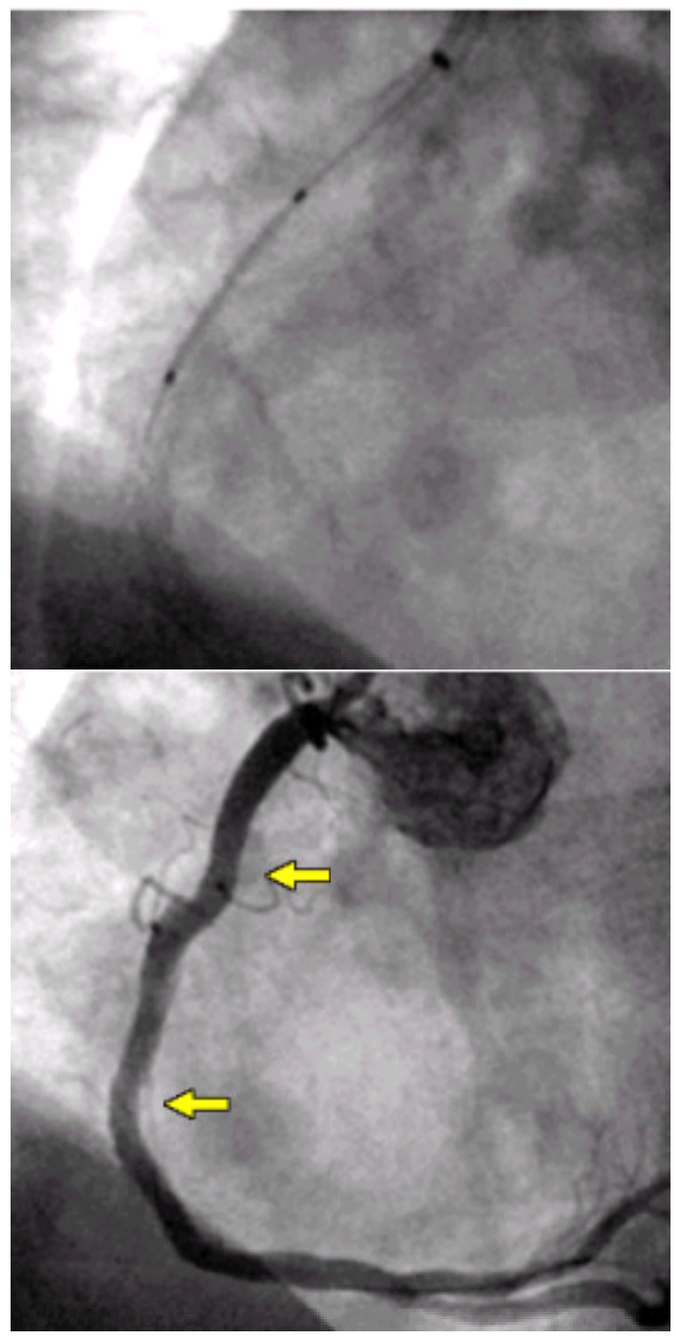
Rotational atherectomy to treat in-stent restenosis. Diffuse restenosis within a previously placed Palmaz-Schatz stent (A, *arrows*) is treated with rotational atherectomy (B), followed by adjunctive stent placement (C). The postintervention result is shown in D.

Attempts to minimize elastic recoil and remodeling using permanently deployed metallic stents have led to a decrease in restenosis rates in carefully controlled clinical trials (8,9). Even in these trials, however, the mass of neointimal tissue seen as a consequence of stent implantation is greater than the neointimal tissue seen in response to balloon angioplasty (10). Furthermore, stents are commonly used to treat lesions that deviate significantly from “ideal” lesions, as defined by these large studies. Multiple stents, newer stent designs, and intentional oversizing of stents are all associated with higher restenosis rates.

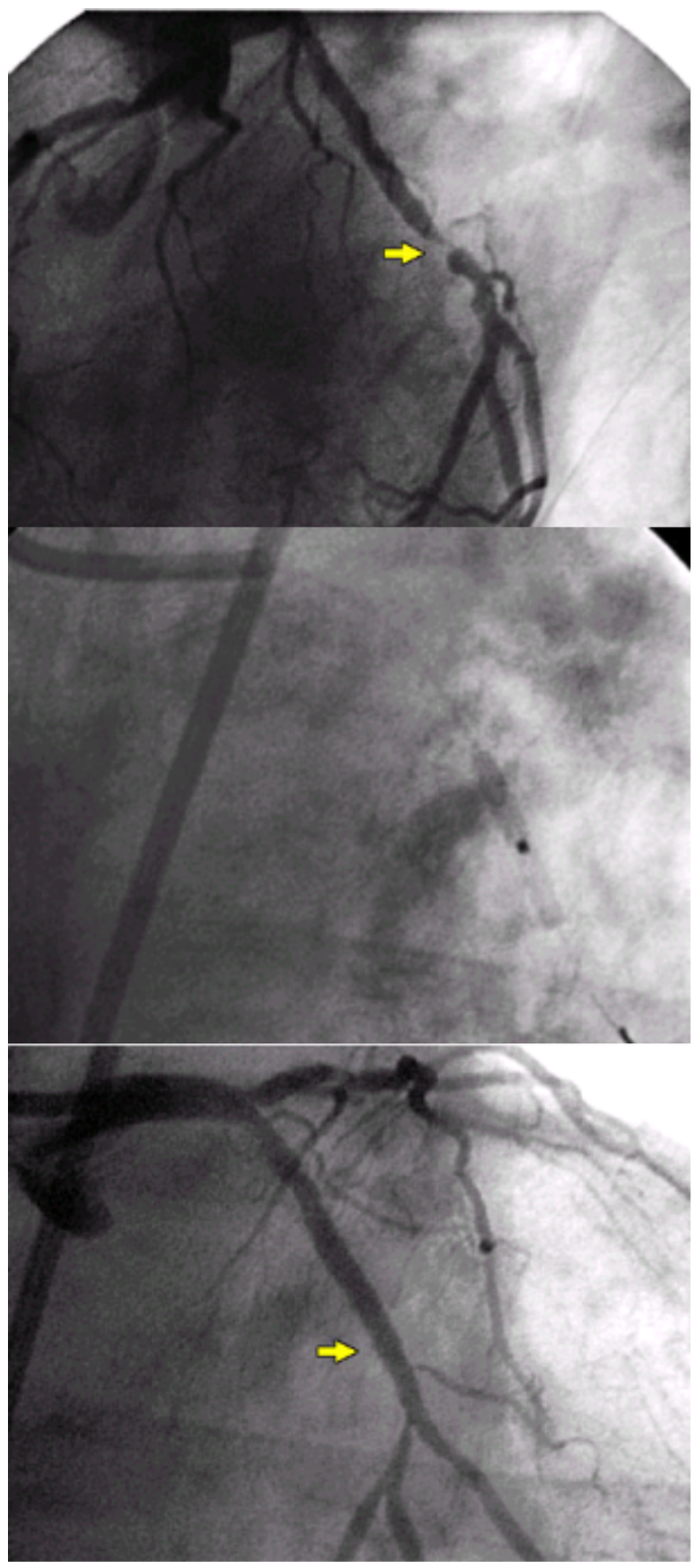
Video 81.4 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

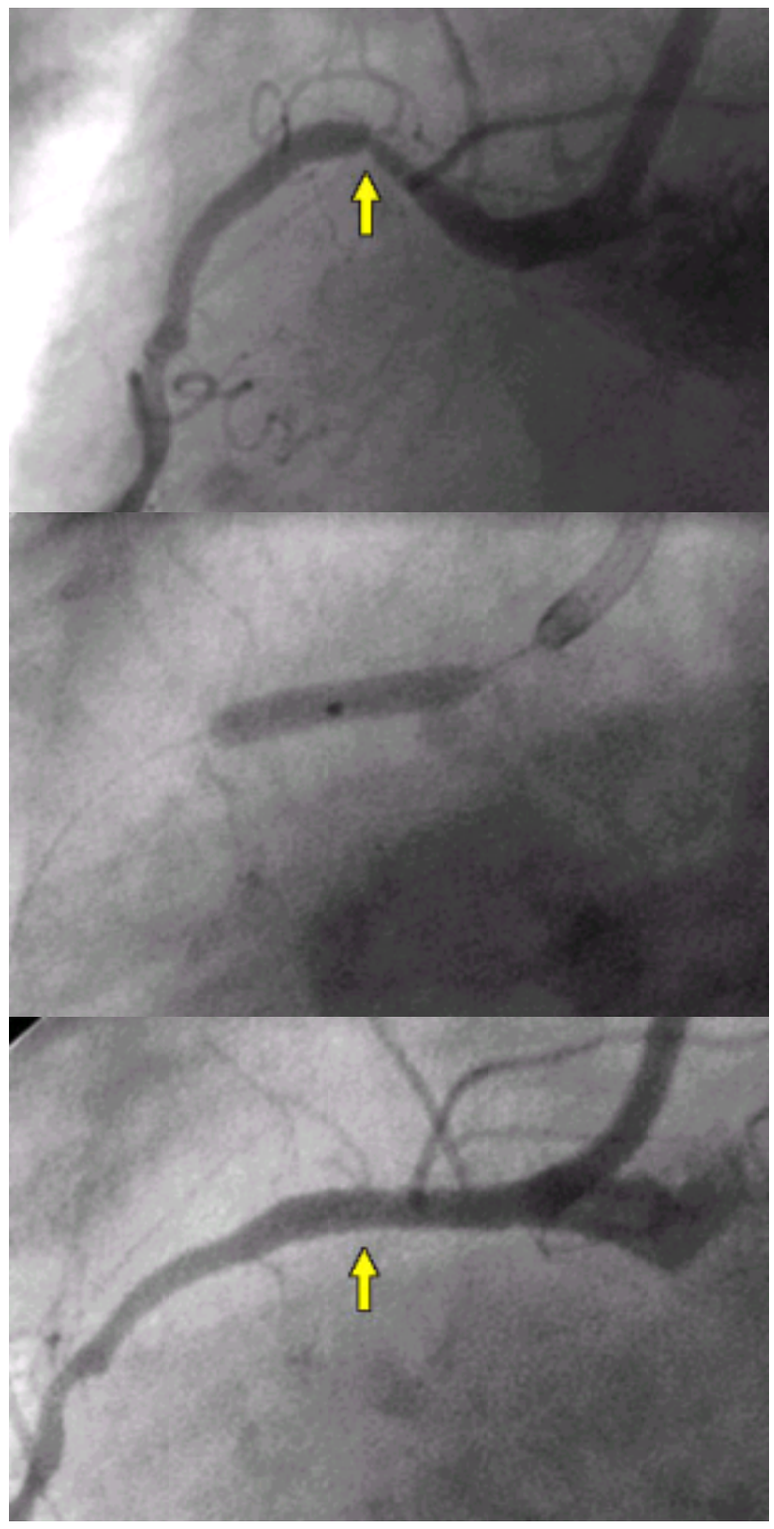
Video 81.5 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*





Use of multiple Palmaz-Schatz stents to treat sequential stenoses (A, *arrows*) in the right coronary artery. The first stent is deployed across the more distal lesion (B), then the second stent is deployed across the proximal stenosis (C). The result of the intervention is shown in D.





The strategy of multiple stent implantation in a patient with multivessel disease. Initially, a discrete lesion in the mid left circumflex artery (A) is successfully treated with a Palmaz-Schatz coronary stent (B,C). A second Palmaz-Schatz stent is then implanted in the proximal right coronary artery (D–F).

There is a long history of clinical use of ionizing radiation, both diagnostic and therapeutic. Fluoroscopic studies use x-rays in the 60- to 100-keV range; keloids, pterygia, cerebral arteriovenous malformations, heterotopic bone formation, and thyroid hyperplasia are all “benign” proliferative processes that are safely and successfully treated with ionizing radiation from external photon sources (gamma or x-rays) or systemic administration of a beta-emitting radioisotope (11). Radiation doses required to destroy function in mature nondividing cells are greater than doses required to stop the proliferative activity of dividing cells (12). Because the mass of neointima is thought to be generated by proliferating cells, therapeutic radiation treatments for prevention of restenosis have been initially studied in animal models.

Ionizing radiation, from x-rays, gamma rays, or beta particles, causes cell death at appropriate doses. Gamma radiation from an endovascular iridium-192 (^{192}I) source was first shown to inhibit intimal hyperplasia as a result of mechanical injury to the aorta of rabbits over 30 years ago (13). With the advent of clinical percutaneous revascularization several decades later, the use of ionizing radiation was extended to prevention of neointimal responses consequent to balloon-induced coronary injury using intravascular radiation sources (14,15,16 and 17). These observations were subsequently confirmed and extended by a number of groups, most notably in regard to the efficacy of beta sources of radiation in preventing experimental neointimal hyperplasia (18,19).

Clinical trials subsequently examined the effects of beta and gamma brachytherapy in treating patients with in-stent restenosis, as well as to prevent restenosis in percutaneous treatment of *de novo* coronary lesions. The initial studies suggested the expected magnitude of inhibition of subsequent restenosis events available using radiation. In addition, several surprising findings from the early rounds of clinical studies modified the technique and management of patients undergoing brachytherapy. Two important issues raised in these studies include an apparent prolonged susceptibility to stent thrombosis in patients undergoing new stent implantation at the time of brachytherapy, and the arterial response at the edges of the radiated field. This section reviews the basic science and the preclinical and clinical studies leading to release of this addition to the interventional armamentarium.

Characteristics of Radiation

The effects of a given activity (eTable 81.0.1) of a gamma or beta source on tissue vary dramatically. This difference stems from the differences in the dose of ionizing radiation absorbed from the energetic photons of gamma sources compared with the far more effective beta-mediated local energy absorption. Similar considerations account for differences in shielding requirements necessary for safe delivery of radiation.

***e*TABLE 81.0.1** GLOSSARY OF RADIATION TERMS

Becquerel (Bq)	Unit of radioactivity equal to 1 disintegration per sec (dps)
Brachytherapy	Therapeutic radiation delivered from an intravascular source
Curie (Ci)	Unit of radioactivity equal to 3.7 × 107 Bq
Gray (Gy)	Newer unit of absorbed dose of radiation, equal to 100 rad
Half-life	Time for decay of one-half of the starting amount of a radioisotope
keV	Thousand electron volts, a measure of the energy of the emitted particle
MeV	Million electron volts
Rad	Unit of absorbed radiation dose corresponding to 100 ergs/g. One centigray (cGy) equals 1 rad
Rem	Absorbed dose (in rad) corrected for the relative biologic effectiveness of the source of radiation (this weighting factor is unity for photons and electrons)
Roentgen (R)	Measure of ionizations (or exposure) produced in air by photons (e.g., x-rays or gamma rays) equal to 2.58×10^{-4} coulomb/kg
Sievert (Sv)	Absorbed dose (in Gy) corrected for the relative biologic effectiveness of the source of radiation (1 Sv = 100 rem)

Radiation dose is a measure of the amount of energy from a source of ionizing radiation deposited in a mass of a particular material. The dose of radiation absorbed by a tissue determines the biologic effect of that radiation. Dose depends on the type of radiation (e.g., beta, gamma, or neutrons), the amount of radiation, and properties of the absorbing material itself. Absorbed dose is measured in units of rad or gray, and effective and equivalent doses in rem or sievert (*e*Table 81.0.1). The relevant properties of isotopes currently in use or being studied are listed in *e*Table 81.0.2.

***e*TABLE 81.0.2** PROPERTIES OF RADIOISOTOPES

Isotope	Relevant therapeutic decay mode	Half-life	Maximum energy (MeV)	Average energy (MeV)
^{32}P (phosphorus-32)	Beta	14.262 d	1.71	0.60
^{48}V (vanadium-48)	Positron	15.9375 d	0.69	0.14

^{90}Sr (strontium-90)	Beta	28.78 yr	0.55	0.20
^{90}Y (yttrium-90)	Beta	64.10 h	2.28	0.90
^{188}W (tungsten-188)	Beta	69.4 d	0.35	0.10
^{188}Re (rhenium-188)	Beta	17.02 h	2.12	0.75
^{133}Xe (xenon-133)	Beta	5.2 d	0.35	0.10
^{192}Ir (iridium-192)	Photon (gamma)	73.83 d	0.6	0.37
^{125}I (iodine-125)	Photon (gamma, x-ray)	60.14 d	0.035	0.028
^{103}Pd (palladium-103)	Photon (x-ray)	16.97 d	0.023	0.021

Biologic Considerations

Ionizing radiation may interact with individual cells via direct ionization of DNA or other critical molecules, or indirectly by ionizing water molecules to form free radicals, which themselves are freely diffusible and can damage chromosomal DNA or critical membrane sites.

In general, the radiation dose necessary to destroy the function of a differentiated cell, such as a smooth muscle cell or endothelial cell, is far greater than the dose of radiation necessary to prevent cell division. Most lethally irradiated cells die during the mitotic process (12). It is unclear what, if any, the relative contribution of apoptosis is to postirradiation cell death seen in the arterial wall.

In radiotherapy of parenchymal organs, injury to capillaries and arterioles of normal parenchyma accounts for the majority of delayed effects of radiation. Experimental studies of large arteries (greater than 100 µm in diameter) have revealed that these vessels are less sensitive to radiation than smaller caliber vessels. Rarely, arterial perforation may occur. Large veins appear to be even more resistant to radiation than corresponding size arteries (20).

The risk of late coronary artery disease (CAD) as a consequence of radiation therapy has been best assessed in studies of patients irradiated for thoracic neoplasms. A retrospective analysis of Hodgkin's disease patients who received mediastinal radiation as part of their treatment reported a relative risk of myocardial infarction of 2.56 (21). Another retrospective study reported a relative hazard of death of 3.2 in patients who received high-dose radiation involving the heart for treatment of carcinoma of the left breast (22). Factors that were thought to be important in this increased mortality were the irradiated volume, radiation energy, fractionation (number and size of individual treatments), and total dose. Finally, a review of 2,232 Hodgkin's disease patients receiving mantel radiation reported the overall relative risk for cardiac death was 3.1 (confidence interval, 2.4 to 3.7). Mediastinal radiation of 30 Gy or less (n = 385 patients) did not increase risk; above 30 Gy (n = 1,830), relative risk was 3.5 (confidence interval, 2.7 to 4.3) (23). Interestingly, the relative risk decreased as the age at the time of treatment increased. The latency for these events in the population was as long as 5 years. The risk of secondary neoplasms because of radiation of a small volume of tissue appears to be exceedingly low.

The consequences of fibrosis at a localized coronary treatment site may be minimized in a stented vessel. Additional unexpected consequences of local radiation treatment to the coronary artery may include poor healing of localized dissection flaps, which normally seal well with time. Establishment of the late consequences of localized intravascular radiation may require collection of data on the initial patients undergoing these procedures for a period of greater than 5 years.

Preclinical Studies

A number of approaches to delivery of radiation to an arterial segment in the hope of preventing luminal compromise by neointimal tissue have been studied in various animal models. Broadly, these approaches can be categorized as external radiation source therapies, endovascular radiation delivery from a removable source (termed *brachytherapy*), or stent-based permanent radioisotope-coated stents. Intravascular radiation sources minimize the volume of tissue irradiated compared with external sources and should minimize the late complications due to unintended collateral irradiation of surrounding tissues.

Gamma radiation from an endovascular ^{192}I source was first shown to inhibit intimal hyperplasia because of mechanical injury to the aorta of rabbits in 1964 (13). With the advent of clinical percutaneous revascularization several decades later, the use of ionizing radiation in animal models of arterial injury was rediscovered (14,16,20,24,25). Subsequently, a number of investigators studied the efficacy of beta radiation, using a variety of isotopes (19,26). In addition to catheter-based radiation delivery, permanently implanted beta-emitting radioactive stents have been used as a platform to deliver vascular radiation (27,28,29 and 30). These systems apply beta (or potentially gamma) radiation locally from an endovascular source. Local radioisotope sources minimize the volume of tissue radiated. One of the guiding principles of radiation therapeutics is to minimize volume of irradiated tissue and dose to surrounding healthy tissue. It is noteworthy that the kinetics of radiation dose administration are far different in implanted stents, as compared with removable sources. In the latter, the entire dose is administered to the vessel wall in a maximum of 30 minutes, compared with the several-month time period for a phosphorus-32 (^{32}P)–coated stent. The relevant biologic parameter to consider is the time for DNA repair, and time to cell division relative to deposited dose. When a fixed dose of ionizing radiation is deposited with leisurely kinetics, the integrated dose is less effective in preventing cell division, compared with a dose delivered in a short time. Indeed, subsequent animal (31,32) and clinical (33,34) studies have borne out the more problematic nature of this sort of irradiation technique.

When a porcine coronary artery is subjected to a stretch injury by an oversized balloon, significant media and adventitia laceration may occur, leading to a proliferative neointimal response at the injury site that mimics the proliferative aspects of the response of a human coronary artery to balloon angioplasty. Between 15 and 20 Gy of gamma radiation delivered from an intracoronary ^{192}I source produced focal fibrosis of the media and markedly decreased neointima formation after overstretch balloon injury by approximately 75% in swine at both 30 days and 6 months (16,20,25,35). Similar results have been reported using endovascular beta-emitting sources, such as encapsulated yttrium-90 (^{90}Y) or strontium-90 (^{90}Sr)/^{90}Y (19,36) or rhenium-188 (^{188}Re) liquid-filled balloon sources (37,38). There was no evidence in any of these studies of perivascular, myocardial, or pericardial pathology. Further studies examining the dose-response relationship between endovascular gamma radiation and suppression of neointimal growth has shown that the minimal suppressive dose to the vessel wall lies between 1,000 and 1,500 cGy for gamma sources and approximately 18 Gy for beta sources (19,20,39).

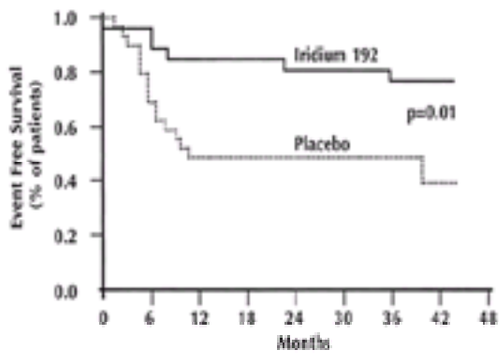
Late Effects

The administration of significant doses of therapeutic radiation has been associated with a vasculopathy, which affects vessels in the radiated region (40). In parenchymal organ radiation, the principal effect of radiation injury to blood vessels is at the level of the capillaries and arterioles. The effects on large arteries, such as the epicardial coronary arteries, analyzed in retrospective studies of patients who have received radiation for thoracic neoplasms, appear to be dose-related and inversely related to the age of the patient at the time of irradiation (23). The earliest evidence of coronary disease appears 5 years after radiation. These data are derived from studies of patients who have received fractionated doses of radiation and have had the entire heart in the radiated field. The long-term effects of single-dose (as opposed to fractionated dose) radiation of the magnitude suggested by the animal trials are not known. It is clear, however, that the risk of late complication, such as myocardial infarction or pericarditis, is related to the volume of radiated tissue (12). The late risk of radiation to the arterial wall is thus minimized when the volume of treated tissue is small, as with treatment by endovascular sources.

Clinical Studies

In-Stent Restenosis

The clinical utility of brachytherapy has been best studied for patients with in-stent restenosis, although some data exist for treatment of *de novo* lesions following native coronary angioplasty or stent placement. Animal studies initially suggested a prominent antiproliferative effect in irradiated arterial segments. Because in-stent restenosis is primarily a problem related to neointimal proliferation, with minimal vascular recoil or remodeling, the greatest benefit from radiation was hypothesized to occur in this patient population. A number of significant double-blind clinical trials using gamma sources [Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) (41,42), Washington Radiation for In-Stent Restenosis Trial (WRIST) (43), GAMMA-1 (44)] and a beta source [Sr-90 Treatment of Angiographic Restenosis Trial (START) (45) and Intimal Hyperplasia Inhibition with Beta In-Stent Trial (INHIBIT)] have been reported to show striking efficacy in preventing restenosis for patients with established in-stent restenosis (Table 81.1). SCRIPPS 3-year follow-up, reported from the most recent SCRIPPS study (42), provides evidence for continued clinical benefit for at least 3 years (*e*Fig. 81.0.1).



***e*FIGURE 81.0.1** SCRIPPS study. Kaplan-Meier curves for event-free survival in iridium-192 (^{192}Ir) and placebo groups. Event-free survival was defined as survival without myocardial infarction or repeated revascularization of target lesion. Curves diverge at 3 months, and the difference increases over the next 7 months, after which clinical events are infrequent. (From Teirstein PS, Massullo V, Jani S, et al. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. *Circulation* 2000;101:360–365, with permission.)

Trial (reference)	Patient population	Source	No. of Patients	Binary restenosis rate (%)
Gamma sources				
Verzaquella (163)	Open label, de novo PTCA	^{192}Ir	21	– 27
SCRIPPS (47)	Single-center, double-blind restenosis	^{192}Ir	55	54 57
GAMMA-1 (164)	Multicenter, double-blind, in-stent restenosis	^{192}Ir	252	56.3 34.2
WRIST (164)	Single-center, double-blind, in-stent restenosis	^{192}Ir	130	60.7 22
GAMMA-2	Multicenter, high-dose, in-stent restenosis	^{192}Ir	125	33.7
Beta sources				
GENEVA (165)	Open label, de novo PTCA	^{90}Y	15	–
BERT (166)	Open label, de novo PTCA	^{32}P/^{90}Y	23	– 15
PRESENT (48)	Open label, de novo PTCA/stent	^{90}Y	86	50 22
BRIE	Open label, de novo PTCA	^{32}P/^{90}Y	150	
Verin et al. (167)	Multicenter, dose-finding, de novo PTCA	^{90}Y	160	– 8.3
CURE (168)	Open label, native PTCA or stent	^{188}Re	47	– 27.2
BETA WRIST (49)	Registry, single-center, in-stent restenosis	^{90}Y	50	– 37
INHIBIT	Multicenter, double-blind, in-stent restenosis	^{32}P	330	52 26
START (45)	Multicenter, double-blind, in-stent restenosis	^{32}P/^{90}Y	476	45 28.8

^{192}Ir, iridium-192; ^{32}P, phosphorus-32; PTCA, percutaneous transluminal coronary angioplasty; Sr, strontium; ^{90}Y, yttrium-90.

TABLE 81.1 SELECTED BRACHYTHERAPY TRIALS

The GAMMA-1 study represents the first large, placebo-controlled, multicenter study of gamma irradiation to treat in-stent restenosis with a maximum lesion length of 45 mm. The primary end point of this study, a composite of death, myocardial infarction, or the need for repeated revascularization of the target lesion during the 9-month follow-up, occurred in 43.8% of the placebo-treated patients compared with 28.2% of the radiated patients (p <.02). The entire benefit conferred by radiation was a diminished need to revascularize. This study underlined the problems of late stent thrombosis occurring when a stent was newly implanted in the freshly radiated arterial segment (*vide infra*). These late thrombotic events only occurred after discontinuation of either ticlopidine or clopidogrel antiplatelet therapy.

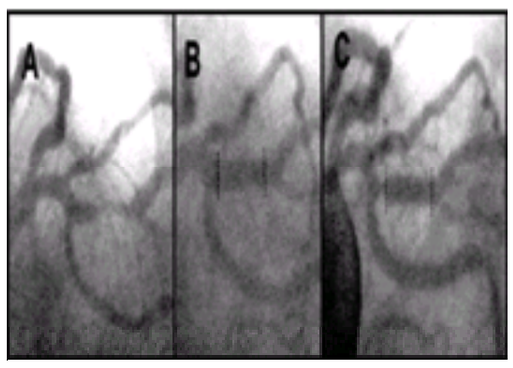
INHIBIT was a prospective, placebo-controlled, double-blind, multicenter study of 332 patients with in-stent restenosis and maximum lesion length of 47 mm, randomized to receive 20 Gy at 1 mm into the vessel wall, from a centered ^{32}P beta-emitting wire source at the time of percutaneous revascularization. The primary end point from which this study was powered was 9-month angiographic binary restenosis. There was a 33% reduction in the frequency of 9-month major adverse cardiac events (MACE), defined as death, Q-wave myocardial infarction, or target vessel revascularization, in the brachytherapy group (p <.037), due exclusively to a decrease in the rate of target vessel revascularization from 31% to 20%. There were three different antiplatelet regimens used during this trial, to minimize the concurrently appreciated risk of late thrombosis (*vide infra*).

Prolonged "Subacute" Thrombosis

Several concerns were raised by these and other early clinical trials. One predictable effect of intravascular radiation was impairment of the wound-healing response consequent to arterial injury. Indeed, intravascular ultrasound studies of coronary arteries that underwent balloon angioplasty had evidence of unhealed dissections at 6 months post–*de novo* balloon angioplasty (46). An important clinical correlate of the inhibition of the healing response is a prolongation of the course of the normal stent-healing process. Indeed, late (post–30 day) acute thromboses occurred in patients treated with brachytherapy plus either angioplasty or new stent implantation, when given standard 30-day ticlopidine/clopidogrel plus aspirin antithrombotic therapy (47). A pooled analysis of the gamma radiation trials—GAMMA-1, SCRIPPS, and WRIST—suggests a late thrombosis rate as high as 6%, particularly in patients in whom new stents were implanted in the radiated arterial segment. Preliminary evidence from trials using prolonged antiplatelet regimes (clopidogrel for greater than 3 months) suggests a marked reduction in this complication. However, it is notable that there are reports of late sudden stent thrombosis greater than 1 year after stent implantation (48), and alternative mechanisms, such as late positive vascular remodeling with stent dehiscence, may be responsible for these events.

Edge Effects

An additional problem noted first in studies of radioactive stent implants (34) (eFig. 81.0.2) is increased frequency of the occurrence of restenosis at one or both edges of the radiated field. Initially thought to be limited to radioactive stents, these events have now been seen with nonradioactive stents and with edge effects seen with removable-source brachytherapy treatments. There is significant speculation as to the cause of these observations or if these findings are even radiation related. We initially demonstrated a proliferative effect of low-dose radiation together with balloon coronary injury in a porcine model (39). Careful analysis has suggested that these edge effects may represent a "geographic miss" of radiation with regard to the zone of instrumented coronary artery (49). Alternatively, plaque shifting may account for the appearance of "new" lesions at the edge of the instrumented segment (50). A multicenter dose-finding study using ^{90}Y, a beta emitter, in which compulsive attention was directed to minimizing geometric miss, reported both a low incidence of core angiography laboratory detection of this technical problem and a notable lack of edge effects (51), together with late loss index of only 0.04 in balloon-treated *de novo* lesions. Typical late-loss indices for balloon-treated arteries are 0.50 to 0.60, depending on the prevalence of diabetics in the study. This suggests that geographic miss and the consequent propensity for edge effects may be significantly abated with careful attention to registering adequate doses of radiation throughout the instrumented segment of the coronary artery. It is important to note that the instrumented segment of the vessel is almost always significantly larger than the initially defined target lesion.



***e*FIGURE 81.0.2** Proximal edge restenosis 6 months after implantation of a radioactive stent. Baseline angiography **(A)** demonstrates a tight stenosis in the proximal obtuse marginal branch. **(B)** Final result after implantation of a 20-µCi radioactive stent. At 6-month follow-up **(C)**, there is no late loss inside the stent, but a tight stenosis exists at the proximal edge of the stent. [From Albiero R, Nishida T, Adamian M, et al. Edge restenosis after implantation of high activity (32)P radioactive beta-emitting stents. *Circulation* 2000;101:2454–2457, with permission.]

De Novo Lesions

Evidence for efficacy of brachytherapy in *de novo* lesions is less compelling and rests on small open-label groups of patients. A large, international, multicenter, double-blind, placebo-controlled trial using Sr/^{90}Y beta sources together with angioplasty to treat *de novo* coronary stenoses (Beta-Cardiac Cath) is scheduled to be reported later in 2001. The future investigation of brachytherapy clearly lies in defining high-risk subsets, such as long lesions, small-caliber reference vessels, diabetics, or chronic occlusions, which might benefit from *de novo* brachytherapy at the time of initial revascularization.

Durability of Restenosis Benefit

Radiation biologists have noted that the expected durability of the restenosis inhibition effects engendered by radiation depends on the proliferative capacity of the residual cells capable of producing the restenotic mass. In fact, theoretical studies have suggested that at the doses used currently, a recurrence of restenosis might be expected to occur at approximately 3 years. There is still a relative paucity of data regarding the durability of the brachytherapy. It is noteworthy that even after 18 months after gamma radiation, Teirstein and colleagues (42) report continued MACE events in the radiated group. In the radioactive stent population, these stents appear to simply delay rather than permanently inhibit restenosis. The ultimate value of this therapy will depend on long-term outcome studies.

Beta versus Gamma Radiation Sources

Substantial differences in handling and dwell times are required for these two classes of sources. Based on physical considerations, beta sources are more easily shielded, deposit a greater fraction of their emitted energy locally, and provide less collateral dose to nontarget tissues than do gamma sources. Because the efficiency of beta energy deposition is greater than comparable gamma sources, the intraarterial dwell time for a brachytherapy treatment for beta sources is generally substantially shorter than for available gamma sources. Because of the steep slope of their energy fall-off curve, beta-emitting isotopes obligate larger luminal and endothelial cell doses than do beta sources. The majority of the large clinical studies to date has reported on the efficacy of ^{192}I, a gamma emitter. More recently, two multicenter studies using beta sources to treat in-stent restenosis [Sr-90 Treatment of Angiographic Restenosis Trial (Sr/^{90}Y) and INHIBIT (P32)], have been announced (Table 81.1). Both studies featured significant reduction of restenosis rates and clinical event rates. The disparity between the clinical evidence for the two sorts of systems appears to be narrowing; however, no direct head-to-head clinical trial has been performed.

Delivery Systems

Currently, three systems have European CE (Conformité Européene) marks, and two of these systems have received marketing approval in the United States by the Food and Drug Administration. The Cordis Checkmate System is based on a ribbon source containing encapsulated ^{192}I gamma sources delivered via a manually operated afterloader device, which deposits the sources in a dedicated, noncentered catheter. Additional shielding is placed around the patient during the dwell time, and typically all personnel leave the room to minimize exposure to the source. Typical dwell times are 15 to 30 minutes per site treated. A variety of source train lengths are available, minimizing the necessity for stepped application. The Novoste Beta-Cath Catheterization Laboratory System is based on small canisters containing Sr/^{90}Y, which are delivered hydraulically down a dedicated, noncentered catheter. A single source length is currently available, allowing treatment of a 20 mm long arterial segment. The Guidant Galileo System, available for routine clinical use only in Europe, is based on an 0.018-in. ^{32}P beta-emitting source wire that is delivered to a dedicated spiral perfusion balloon using an automated remote afterloader. The latter two systems have typical dwell times of less than 5 minutes per treatment site. In the United States, the only currently approved indication for coronary brachytherapy is for the treatment of in-stent restenosis. Treatment of an adjacent site in the artery to ensure adequate margins of therapy by moving the source to another site and a second brachytherapy treatment are not approved.

Stent-Based Beta Implants

Despite initially exciting animal studies using beta isotope–impregnated stents (29,52), clinical trials have been decidedly disappointing. Initial studies were troubled by inadequate doses to prevent restenosis (53). As the activity on the stents increased, the absorbed radiation dose effectively prevented in-stent restenosis, but did not ameliorate the problem of edge restenosis (34). Finally, advocates of radioactive stents suggest a number of variations intended to minimize the edge effects seen. Final reports of the value of “hot end” stents, “cold end” stents, and radioactive stents deployed with attention to minimizing edge barotraumas are still awaited. A report of 1-year follow-up of moderate activity ^{32}P stents (6 to 12 µCi) by a combination of quantitative coronary angiography and integrated electrocardiographic-gated IVUS revealed delayed, rather than inhibited, neointimal proliferation. Indeed, 35% of the patients had had clinical events by 1-year follow-up (54). The latter suggests that these variations in stent dosimetry and implantation techniques are unlikely to provide long-term inhibition of restenosis using these devices.

Controversies and Personal Perspectives

Coronary brachytherapy is at the early stages of clinical adoption as a significant treatment modality for in-stent restenosis. Significant improvements in intermediate-term clinical event rates and secondary restenosis rates have been demonstrated using a variety of radiation sources and radiation delivery systems. The role of brachytherapy for preventing restenosis when *de novo* lesions undergo percutaneous revascularization remains to be defined. It is likely that certain anatomic and clinical subgroups (e.g., long lesions, small-diameter vessels, diabetics, and possibly vein graft lesions) might benefit from primary brachytherapy treatment at the time of initial intervention. The duration of antiplatelet therapy remains a controversial question. The most feared complication of coronary brachytherapy is “delayed subacute thrombosis,” which has occurred as late as 18 months after treatment. Clarification of an optimal duration and regimen of antiplatelet therapy becomes even more critical as stents are implanted into newly radiated segments of coronary arteries. Finally, the utility of brachytherapy relative to newly evolving technologies, such as drug-eluting stents (55) and alternative energy therapies (e.g., sonotherapy), will be closely scrutinized in the ensuing several years.

EMBOLI PROTECTION

Microembolization has traditionally been regarded as a relatively infrequent contributor to the major complications of percutaneous arterial revascularization or coronary acute ischemic syndromes. Although limited autopsy series demonstrate embolization of plaque and thrombotic material into the microcirculation of some patients with unstable angina or myocardial infarction who die suddenly (56), it is occlusion of the epicardial vessel that has been thought to be the important culprit leading to myocardial ischemia and infarction. Similarly, angiographically apparent distal embolization during coronary balloon or device intervention is uncommonly observed (typically in less than 2% of cases) and is usually confined to procedures performed in degenerated bypass grafts or in the presence of intraluminal thrombus, suggesting that abrupt closure of the target epicardial coronary vessel is the most frequent cause of periprocedural myocardial necrosis. In the cerebrovascular and peripheral circulations, however, emboli play a more conspicuous role in the pathogenesis of spontaneous stroke and systemic arterial ischemic events. The availability of new imaging techniques that allow demonstration of microembolization in living patients, such as myocardial contrast echocardiography, transcranial Doppler, and magnetic resonance imaging, has enhanced our appreciation of the frequency and importance of microvascular obstruction in arterial disease states and revascularization procedures. With this understanding has come the recognition that some of the clinical benefit derived from pharmacologic agents intended to treat the epicardial atherosclerotic plaque may in fact be related to suppression of distal embolization. Most recently, devices have been specifically designed to protect the microvasculature from embolization during revascularization procedures.

Pathophysiology

Erosion or rupture of the atherosclerotic plaque, occurring spontaneously in the acute ischemic syndromes or induced by percutaneous revascularization devices, exposes thrombogenic lipid and subendothelial matrix, resulting in platelet aggregation and initiation of the coagulation cascade. A growing thrombotic mass may lead to partial or complete thrombotic arterial occlusion and end-organ ischemia or infarction. Beyond the effects of *in situ* epicardial vessel thrombosis, distal embolization of plaque and thrombotic material may also occur, producing microvascular obstruction and patchy infarction. The mechanical obstruction caused by the embolized plaque and thrombus appears to be amplified by associated inflammation, which further contributes to endothelial dysfunction, microvascular spasm, impaired tissue perfusion, and end-organ necrosis. In the coronary vasculature, distal embolization may be a frequent cause of observed elevations in circulating levels of myocardial creatine kinase or troponin, which have been correlated with adverse clinical outcome during acute ischemic syndromes or after angioplasty. Interestingly, left ventricular dysfunction occurring as a result of distal embolization seems to be out of proportion to the quantity of infarcted myocardium, suggesting a particular “mechanical disadvantage from multiple microinfarcts with multiple border zones” (57). Moreover, microinfarctions may predispose to late ventricular arrhythmias and sudden cardiac death.

Clinical Evidence

Microembolization may be a relatively frequent event among patients with acute coronary ischemic syndromes or after percutaneous coronary intervention. In a series of 32 patients dying within 3 weeks of undergoing balloon angioplasty or receiving thrombolytic therapy for acute myocardial infarction, thrombotic or atheromatous emboli were observed on autopsy in 26 (81%) (58). Without the pathologic confirmation afforded by postmortem examination, however, the occurrence of

microembolization in clinical practice can only be inferred from surrogate measurements, and the frequency and consequences of this event are likely underappreciated.

“Reperfusion” therapy for acute ST-elevation myocardial infarction is directed at restoration of infarct vessel patency, based on the paradigm that recanalization of the epicardial artery translates into improved tissue-level perfusion. A dissociation may exist, however, between epicardial artery patency and the quality of myocardial reperfusion. In a pioneering study, Ito and associates (59) described 39 patients with anterior myocardial infarction in whom myocardial contrast echocardiography demonstrated absence of tissue-level reflow in 23%, despite restoration of infarct artery patency; patients without microcirculatory reflow had significantly less recovery of left ventricular function than those in whom myocardial perfusion had been achieved. Subsequent series using contrast echocardiography (60) or magnetic resonance imaging (61) confirmed the absence of microcirculatory reflow in 25% to 37% of patients following coronary recanalization, a finding that was correlated with larger infarct size, adverse remodeling, and more frequent cardiovascular complications. More recently, Gibson and colleagues have established an angiographic index of quality of myocardial reperfusion, demonstrating that mortality is lowest among patients with normalization of both epicardial artery and tissue-level blood flow following fibrinolytic therapy for acute myocardial infarction (62). Similarly, among patients undergoing primary angioplasty or stenting for acute infarction, inadequate myocardial reperfusion despite restoration of infarct vessel patency has been associated with substantially diminished mortality benefit (63). The dissociation between epicardial and microcirculatory reperfusion may in part explain why long-term mortality with primary stenting has tended to be higher than with balloon angioplasty, despite the consistent reduction in restenosis achieved with stents (64).

Embolization, visualized angiographically as a new filling defect or “cutoff” in a distal vessel, has been reported to complicate 1% to 2% of percutaneous coronary revascularization procedures. Additionally, however, “slow-reflow” or “no-reflow” phenomena may also occur in 6% or more of patients undergoing coronary intervention, characterized by profound reduction in epicardial anterograde coronary flow without evidence of vessel dissection, thrombosis, or embolization (65,66). This angiographic observation likely represents diffuse embolization and obstruction of the distal microvasculature and appears to be most frequent with revascularization of saphenous vein grafts, during acute coronary syndromes, in the presence of coronary thrombus, or with ablative device technologies (66,67 and 68). Using sensitive techniques such as technetium-99m sestamibi scintigraphy, regional myocardial hypoperfusion has been observed in as many as 87% of patients undergoing rotational atherectomy (69). The no-reflow phenomenon has been consistently associated with an increased risk for periprocedural death or myocardial infarction (66,68).

Assessment of postprocedural myocardial enzyme release (creatine kinase MB fraction or troponin) provides further insight into the prevalence of microembolization during coronary revascularization. In published reports in which enzyme determinations were made according to a systematic schedule in all patients, postprocedural rates of myocardial infarction have typically been in the range of 8% to 12% (70,71,72 and 73). Yet only a minority of these enzyme elevations can be attributed to recognized complications during the angioplasty procedure, such as target vessel or side branch closure; consequently, reported infarction rates are only 2% to 5% in studies in which enzymes were measured only in patients suspected of having an event (74,75,76 and 77). Distal microembolization represents the likely cause of many of the “silent” or unsuspected myocardial infarctions following coronary intervention. These events are clinically important in that a number of studies have demonstrated that patients who experience myocardial infarctions during and after coronary intervention are at significantly greater risk for late cardiac death than those who do not (78,79,80,81,82 and 83).

Balloon angioplasty and stenting of extracranial carotid stenoses appear to provide long-term results similar to those of surgical endarterectomy with regard to patency and stroke prevention (84). An important potential limitation of this technique, however, is dislodgement and embolization of atherosclerotic and thrombotic fragments from the carotid plaque, which may be associated with transient or permanent neurologic sequelae. Embolic load during percutaneous carotid revascularization appears to be greater than with endarterectomy (85). Plaque fragments in experimental models range in size as large as 1 mm in greatest dimension, with evidence of neuronal ischemia following embolization to the brain of particles as small as 200 µm (86). During percutaneous carotid revascularization procedures in humans, embolization of particulate material can be documented by transcranial Doppler in virtually all patients, with the maximum number of emboli signals occurring during stent deployment and balloon inflation (87).

The most compelling evidence for the ubiquitous nature of arterial microembolization during percutaneous revascularization derives from the clinical experience using distal emboli protection devices (see Mechanical Approaches to Embolization, later in this chapter). Aspirated blood or filter contents from these devices demonstrate the presence of grossly visible or microscopic embolic material in the majority of cases following stenting of carotid arteries, saphenous vein grafts, and even native coronary vessels (88). Examination of retrieved debris reveals atherosclerotic, thrombotic, and calcific particles, ranging in size as large as 2 mm or more.

Pharmacologic Approaches to Embolization

Pharmacologic approaches to prevent or treat embolization have focused primarily on vasodilators or antithrombotic agents. Vasodilators are intended to enhance clearance of microparticulate debris from the vasculature or counteract the adverse effect of vasoconstrictive mediators released from upstream plaque. Antithrombotic agents are used to enhance endogenous dissolution of thrombotic emboli, as well as to prevent amplification of the cascade of platelet activation and thrombus formation in the microvasculature. Clinical results with potent antiplatelet agents appear to be particularly promising.

Observational series have suggested that intracoronary administration of nitroglycerin or verapamil may improve distal coronary flow in many patients who experience the no-reflow state during coronary intervention (65). However, a report of 136 patients with no reflow did not show an influence of verapamil or sodium nitroprusside on death or myocardial infarction (68). In a randomized trial of 40 patients undergoing primary percutaneous intervention for acute myocardial infarction, intracoronary administration of verapamil was associated with immediate improvement in microvascular perfusion as assessed by myocardial contrast echocardiography and better recovery of left ventricular regional wall motion (89).

Adenosine exerts a protective effect during myocardial ischemia and infarction through multiple potential mechanisms. Improvements in microcirculatory flow may occur by direct vasodilation due to activation of A_2-receptors on endothelial and vascular smooth muscle cells, by prevention of neutrophil adherence and superoxide release, or by inhibition of platelet aggregation (90). In a small randomized trial of 54 patients undergoing primary angioplasty for acute myocardial infarction, administration of intracoronary adenosine was associated with improvements in coronary flow, better recovery of infarct zone regional wall motion, and lower rates of death compared with placebo (91). Similarly, patients receiving intravenous adenosine during fibrinolytic therapy for anterior myocardial infarction in a pilot study showed evidence of reduction in infarct size (92). Efficacy of adenosine in this setting has not yet been confirmed in large-scale randomized trials.

There are substantial data to suggest that part of the clinical benefit derived from intravenous platelet glycoprotein IIb/IIIa inhibitors may be through improvements in microvascular perfusion. Several randomized placebo-controlled trials have demonstrated unequivocally that administration of these agents during and after coronary intervention reduces the risk of death, myocardial infarction, or emergency repeat revascularization over 30 days by as much as 50% (93). The predominant adverse event prevented by this therapy is periprocedural myocardial infarction; as discussed previously, these infarctions are usually not associated with recognized complications in the epicardial artery but may often be due instead to microembolization.

The antiembolic effect of glycoprotein IIb/IIIa inhibitors seems particularly evident in high-risk settings and with device technologies for coronary intervention. For example, abciximab neutralized the threefold excess risk for non–Q-wave myocardial infarction seen with directional coronary atherectomy relative to balloon angioplasty in one trial (94). During saphenous vein graft interventions using transluminal extraction atherectomy (95) or other techniques (96), rates of angiographically apparent embolization were reduced from 21% to 30% with conventional therapy to 0% to 3% with abciximab.

The most compelling evidence for an effect of glycoprotein IIb/IIIa blockade on microembolization is derived from studies using imaging techniques or end points that directly assess the quality of myocardial perfusion. During rotational atherectomy, regional myocardial hypoperfusion representing diffuse microembolization was detected by Tc-99m sestamibi scintigraphy in only 33% versus 87% of patients who did or did not receive adjunctive abciximab, respectively (69). In an important mechanistic study, Neumann and colleagues randomized 200 patients with acute myocardial infarction to abciximab or conventional therapy during stenting. Despite restoration of normal epicardial artery flow by stenting in virtually all patients in both treatment groups, patients who had received abciximab had improved tissue-level perfusion as measured by Doppler peak flow velocity in the infarct-related artery or improvements in regional and global left ventricular function (97). Similarly, improvements in myocardial perfusion and coronary flow reserve have been observed during elective stenting with the glycoprotein IIb/IIIa antagonist eptifibatide (97a). Outside of the setting of percutaneous revascularization, abciximab appears to improve myocardial reperfusion during fibrinolytic therapy for acute myocardial infarction. Among a subgroup of patients who had achieved normal epicardial artery flow 90 minutes after administration of various combinations of tissue-type plasminogen activator and abciximab in a dose-ranging study, treatment with abciximab plus half-dose tissue-type plasminogen activator was associated with a substantially higher rate of complete ST-segment resolution than was tissue-type plasminogen activator alone (69% vs. 44%, respectively, $p = .0004$) (98).

Mechanical Approaches to Embolization

Although antiplatelet therapy may reduce embolization of thrombotic debris and ongoing platelet aggregation in the distal vasculature, these agents would not be expected to diminish the release of atherosclerotic and matrix material into the microcirculation. Mechanical approaches for preventing embolization were first applied to percutaneous revascularization of the carotid arteries. In 1987, Theron and colleagues described six patients in whom temporary occlusion of the internal carotid artery with a balloon catheter was used to prevent cerebral embolization during angioplasty (99). Technological advances have allowed development of low-profile

catheters or wires that can safely access the distal vasculature and retrieve embolic debris. These devices are under clinical evaluation in the carotid and peripheral circulation for revascularization of diseased saphenous vein grafts and most recently in native coronary arteries. At the time of this writing, only the PercuSurge system is approved for clinical use in the United States.

There are two major categories of emboli protection devices. Occlusion catheters employ a compliant balloon that is inflated distal or (less commonly) proximal to the site of revascularization to arrest blood flow in the treated artery. Embolic material is aspirated or flushed to a branch vessel (typically the external carotid) before the balloon is deflated and blood flow restored. Filter devices are delivered distal to the atherosclerotic lesion on a guidewire to capture emboli produced by manipulation of the plaque. Advantages of the balloon occlusion approach include the potential to capture nearly all embolic particles, regardless of size; disadvantages stem from the obligate arrest of blood flow, with resultant end-organ ischemia, unpredictable patient tolerance, and the need to perform a hasty procedure with suboptimal angiographic visualization of the revascularization site. The principal strength of filter technique is preserved blood flow, permitting longer procedures to be performed with less distal ischemia and ongoing angiographic visualization of the target lesion; disadvantages include the inability of a filter to capture particles smaller than the pore size, as well as generally larger crossing profiles.

The antiemboli device for which there is currently the most clinical experience is the occlusive PercuSurge Guardwire Balloon Protection System (Medtronic MVE, Minneapolis, MN). It consists of a hollow guidewire with its lumen connected to a compliant distal occlusion balloon and a separate aspiration catheter. The distal balloon is inflated 2 to 10 cm beyond the lesion, occluding the vessel lumen, after which standard angioplasty balloons or stents are delivered to the stenosis over the wire. The interventional procedure is performed and catheters are exchanged for the aspiration catheter, through which suction is applied to remove loose embolic material trapped behind the occlusion balloon. The occlusion balloon is then deflated and the wire removed.

In an initial feasibility report, no embolic events or ischemic complications occurred during stenting of degenerated saphenous vein grafts in 15 patients using the Guardwire Balloon Protection System (100). During the subsequent multicenter phase II registry experience of 106 patients treated for vein graft stenosis, the in-hospital MACE rate of 4.9% was approximately 70% lower than for historic controls. The efficacy of this device for saphenous vein graft interventions was convincingly demonstrated in a randomized controlled trial of 555 patients. The PercuSurge system was successfully deployed in 93% of cases; rates of in-hospital MACE were reduced from 17.3% to 8.8% (p = .001), myocardial infarction from 16.5% to 8.4%, and no-reflow from 8.0% to 3.4% (99a). Preliminary experience with this device during stenting of native coronary vessels for acute myocardial infarction produced similarly favorable results: Normal myocardial perfusion was achieved in 55% of patients, compared with only 19% to 28% of patients who had undergone stenting for acute infarction without emboli protection in previous trials (101). The Guardwire system has also been used successfully in several pilot studies of carotid stenting, with recovery of particulate material ranging in size from 50.0 µm to 1.6 mm. Approximately 5% of patients were intolerant of the occlusion balloon, however, developing transient neurologic symptoms immediately or at some point during the procedure. The number of embolic signals on transcranial Doppler was reduced by 65% to 80% as compared with unprotected carotid stenting, and rates of neurologic complications (stroke or transient ischemic attack) compared favorably with historic controls.

The Parodi Anti-Emboli System (ACT/DBI, Santa Clara, CA) uses an alternative approach to occlusive emboli protection, that of proximal balloon occlusion and passive flow reversal. It consists of a double-lumen guide catheter with a balloon at its tip; once the balloon is inflated in the common carotid artery proximal to a stenosis, flow reversal is achieved by creating a temporary artery-to-vein shunt through the lumen of the catheter connected to a sheath in the femoral vein. The stent procedure is then performed via the main lumen of the guide catheter, with embolic particles captured by a filter in the artery-to-vein connection. A favorable preliminary clinical experience has been reported (102).

A variety of filter designs are under clinical evaluation for carotid, native coronary, and vein graft interventions. Examples of “supported” filters are the Angioguard (Cordis J&J, Warren, NJ) and the TRAP (Microvena, White Bear Lake, MN), while “unsupported” designs include the EPI Filter Wire (Embolic Protection Inc., Campbell, CA). The Angioguard consists of a standard-diameter (0.014-in.) guidewire with a flexible nitinol basket covered distally with a polyurethane filter (pore size 100 µm). It is expanded distal to the stenosis by removal of a delivery sheath (1.2- to 1.5-mm diameter), then closed and removed following the interventional procedure. Early clinical experience has shown that the Angioguard can be safely tracked beyond coronary, vein graft, and carotid lesion sites, with recovery of particles as large as 2 mm (88); distal blood flow is usually maintained, although abundant embolic material may occlude the filter. The TRAP is a braided mesh, double-layered, nitinol basket mounted on a 0.014-in. guidewire. It is delivered within a 1.2-mm diameter sheath, which is withdrawn to deploy the basket beyond the stenosis. Retrieval is accomplished with a specialized sheath that employs a nitinol mesh funnel to capture the basket and prevent release of embolic debris. During the first clinical experience with this device during vein graft stenting, particles ranging in size from 10 µm to 3 mm were retrieved (103). The EPI Filter Wire is a 0.014-in. guidewire incorporating an oval nitinol wire loop supporting a polyethylene membrane (pore size 80 µm). It is deployed by withdrawal of a 1.2-mm diameter overlying sheath, but can be withdrawn into the central lumen of a standard balloon angioplasty catheter for removal. This device has undergone favorable preliminary evaluation during native coronary, vein graft, and carotid interventions (104).

Controversies and Personal Perspectives

It remains unclear in which settings emboli protection will provide the most clinical benefit. It seems likely that there will be an unequivocal indication for these techniques in the setting of carotid artery stenting, in which the consequences of distal embolization to the brain can be most catastrophic. For myocardial revascularization, certain high-risk settings are also likely to mandate an antiembolic approach. Degenerated saphenous vein grafts or thrombotic native coronary lesions have proven to be particularly difficult problems from the standpoint of embolization during percutaneous revascularization, with only marginal progress achieved with a variety of ablative devices or pharmacologic therapies. For routine percutaneous revascularization of native coronary stenoses, however, the indications for antiembolic devices will be less straightforward. Certainly, embolic debris seems to be a ubiquitous consequence of coronary intervention, even in “simple” native lesions, but the magnitude of risk for clinical consequences from such embolization remains incompletely defined, particularly relative to the potential risk of complications associated with the antiemboli devices.

What is the best approach to antiembolic therapy? There are compelling clinical data that glycoprotein IIb/IIIa inhibitors are indicated in all patients undergoing coronary intervention, but will the availability of distal protection devices render pharmacologic therapy unnecessary in many cases? I suspect this will not be so, as potent antithrombotic agents also affect other mechanisms leading to periprocedural complications as well as provide sustained suppression of embolization after a protection device has been removed. Thus, a combination of both pharmacologic and mechanical approaches will likely prove most beneficial. Which type of device, occlusion versus filter, will be the most efficacious? Although occlusion balloons may capture smaller particles, I anticipate that filters will gain more widespread acceptance due to better patient tolerance and stenosis visualization.

THERAPEUTIC ANGIOGENESIS

Despite the advances in percutaneous and surgical revascularization methods, a limited number of patients have severe ischemia but are poor candidates for conventional revascularization (105). Few options are available for these patients using conventional approaches, and the disability resulting from severe limiting angina is substantial. One potential strategy for “no options” patients is creation of new blood vessel channels in the region of ischemia or therapeutic angiogenesis.

New blood vessel growth may occur as a result of vasculogenesis, arteriogenesis, or angiogenesis (106). Although vasculogenesis is the process responsible for the growth of new blood vessels during embryonic development, its role in the formation of new blood vessels in adults is not known (106). Arteriogenesis involves the formation of new blood vessels that have a fully developed tunica media and may be manifest by the development of new collateral branches in patients with peripheral vascular disease (106). Angiogenesis relates to the development of a new blood vessel that lack a tunica media, such as capillary formation in wound healing (106). It is highly likely that neorevascularization that will benefit patients with no options results from arteriogenesis, and to a lesser extent, angiogenesis. Although the precise stimuli for therapeutic angiogenesis is not known, it likely relates to the combination of chronic ischemia and inflammation and propagation of a cascade of events that induce proliferative, chemotactic, and inflammatory factors (106).

Mechanical Approaches

Both surgical and percutaneous approaches have been used to improve regional blood flow to the ischemic myocardium by injuring the myocardium using laser energy, radiofrequency ablation, or direct myocardial injections. Each of these approaches has substantial differences with respect to the depth of myocardial injury, the laser–tissue interactions, the presence or absence of guidance, and the number of channels created. These differences may have a profound effect on the results of clinical studies in patients with refractory CAD.

Mechanism of Benefit

Three mechanisms of clinical benefit of transmyocardial revascularization (TMR) have been proposed. The first relates to the creation of channels within the myocardium to enhance blood flow into the ischemic area, although pathologic studies have demonstrated that these channels close soon after their creation (107,108,109 and 110). A second potential explanation relates to denervation of cardiac nerve fibers that cause angina (111,112). This mechanism may explain why some patients experience immediate relief after myocardial revascularization. The most likely mechanism of benefit of myocardial revascularization relates to the

stimulation of neorevascularization that improves blood supply to the ischemic myocardium (113,114).

Surgical Transmyocardial Revascularization

TMR by the creation of transmural left ventricular conduits using CO_2 laser was first reported in 12 patients with refractory angina in 1988 (115). Since then, over 3,000 patients have been treated with TMR using the CO_2 laser (116,117) or holmium:yttrium-aluminum-garnet (YAG) laser (118,119). Registry series demonstrated a marked improvement in Canadian Cardiovascular Society (CCS) angina class in these patients (116,117 and 118) and late clinical benefits after TMR has been sustained up to 5 years. One series of 78 patients treated with the CO_2 laser reported a greater than two CCS class improvement in angina status in 68% of patients 5 years after the procedure, and 17% of patients had no angina (120). Some series have also demonstrated improvements in myocardial perfusion as assessed by thallium scintigraphy (121,122) and positron emission tomographic scanning (116). The effect on left ventricular function has been variable (123,124).

Early series of TMR were associated with 5% to 9% perioperative mortality (125); overall morbidity was also high, with a 19% incidence of myocardial infarction, 52% incidence of cardiac ischemia, and a 35% incidence of noncardiac morbidity (126). Patients with adequate myocardial supply to at least one region of the heart through a native coronary artery or patent bypass graft have markedly reduced perioperative mortality (127). Patients with severe, refractory unstable angina also have a high mortality (128). More recent mortality with appropriate patient selection of patients undergoing TMR ranges from 1% to 2% (128).

Four randomized trials have been performed in patients with refractory angina randomly assigned to TMR or continued medical therapy (117,118) (eTable 81.1.1). The first of these studies randomly assigned 200 patients with CCS class III or IV angina that was refractory to medical therapy to treatment with TMR with a CO_2 laser (Heart Laser, PLC Medical Systems, Franklin, MA) or to continued medical therapy (117). In patients assigned to TMR, transmural channels approximately 1 mm in diameter were created with a single pulse of the CO_2 laser (peak power, 850 W) through the left ventricle (117). One channel was created per square centimeter of myocardial surface, resulting in approximately 36 channels per patient (117). Angina had improved by at least two CCS classes in 72% of patients assigned to TMR compared with 13% in those assigned to medical therapy at 12-month follow-up (p <.001) (117). Myocardial perfusion improved by 20% in the TMR group but worsened by 27% in patients treated with conventional therapy (p = .002) (117). The perioperative mortality was 3% with TMR, but survival was not different in the two groups at follow-up (117).

***e*TABLE 81.1.1** RANDOMIZED TRIALS USING TRANSMYOCARDIAL REVASCULARIZATION FOR MEDICALLY REFRACTORY ANGINA

Author	Laser system	No. of patients	Design	No. of channels	End point	Results
Schofield et al. (129)	PLC Medical System CO_2 laser	188	Single-center RCT	30	Mean treadmill exercise time at 3, 6, and 12 mo	Mean exercise time was 40 sec longer in the TMR group than medical management group (p = .152). Mean 12-min walk distance was 33 m longer in the TMR group than medical management group (p = .108). CCS score decreased by two classes in 25% of TMR patients compared with 4% in medical management patients (p <.001).
Burkhoff et al. (124)	CardioGenesis holmium:YAG laser	182	Multicenter RCT	18	Angina status	At 12 mo, total exercise tolerance increased by 65 sec in the TMR group and decreased by 46 sec in the medication-only group (p <.001). CCS score decreased by two classes in 48% of TMR patients and 14% in the medical only group (p <.001). All quality-of-life scores were improved in patients with TMR.
Frazier et al. (117)	PLC Medical System CO_2 laser	192	Multicenter RCT	36	Angina status	At 12 mo, CCS score decreased by two classes in 72% of patients assigned to TMR and 13% in those assigned to medical therapy (p <.001). Patients treated with TMR had a significant improvement in quality of life. Myocardial perfusion increased by 20% in patients treated with TMR and worsened by 27% in patients treated with medical therapy (p <.001). At 12 mo, 2% of patients assigned to TMR were hospitalized because of unstable angina compared with 69% of patients treated with medical therapy (p <.001).
Allen et al. (118)	Eclipse Surgical pulsed holmium laser	275	Multicenter RCT	39	Angina status	At 12 mo, CCS score decreased by two classes in 76% of patients assigned to TMR and 32% of those assigned to medical therapy (p <.001). At 12 mo, 54% of patients assigned to TMR were free of cardiac events compared with 31% of those assigned to medical therapy (p <.001). Exercise tolerance and quality-of-life scores were also higher in patients assigned to TMR.

CCS, Canadian Cardiovascular Society; RCT, randomized controlled trial; TMR, transmyocardial revascularization; YAG, yttrium-aluminum-garnet.

The second randomized trial of TMR assigned 275 patients with CCS class IV angina that was not amenable to surgical or percutaneous revascularization to TMR or to continued medical therapy (118). TMR was performed using a 20-W pulsed holmium laser (Eclipse Surgical Technologies, Sunnyvale, CA). The laser was calibrated to deliver 6 to 8 W per pulse, and the energy was delivered at a rate of 5 pulses per second. Channels were placed every square centimeter, and an average of 39 channels was created per patient. An improvement in two CCS angina classes was found in 76% of patients receiving TMR compared with 32% of patients assigned to continued medical therapy at 1-year follow-up (p <.001) (118). Patients treated with TMR also had a higher rates of freedom from late cardiac events (54% compared with 31% in medically treated patients; p <.001) and cardiac-related hospitalization (61% vs. 33% in medically treated patients; p <.001) (118). Exercise tolerance and quality-of-life scores were also better in patients treated with TMR. The perioperative mortality was 5%. There were no differences in myocardial perfusion or overall survival in the two groups (118). Two additional randomized trials demonstrated similar findings (124,129).

In aggregate, these studies demonstrate a dramatic improvement in symptoms resulting from TMR in patients with medically refractory angina. In some cases, the improvement in symptoms was associated with documented improvements in myocardial perfusion in the regions treated with TMR. The high (1% to 9%) periprocedural mortality seen in some of these studies appears to be lower in those patients who have adequate myocardial perfusion through a native coronary or arterial or venous conduit to one myocardial zone or in those patients with stable angina.

A limited number of studies has evaluated the incremental benefit of TMR performed in conjunction with conventional coronary artery bypass grafting (CABG) in patients with suboptimal surgical anatomy. Preliminary reports suggested that perioperative and late mortality and the need for postoperative left ventricular support were reduced using the combined approach (130,131). A synergistic angiogenic effect of TMR and administration of vascular endothelial growth factor (VEGF) was reported in one preclinical study (132). Whether this effect can also be demonstrated in patients with refractory CAD is the subject of ongoing study.

Percutaneous Methods of Myocardial Revascularization

Percutaneous approaches to myocardial revascularization have been developed, varying by the laser source, delivery catheter types, and use of guidance to direct placement of the laser channels (eTable 81.1.2). These methods are less invasive, can be performed from the femoral access, and have a lower periprocedural mortality than surgical approaches to myocardial revascularization. In contrast to the full-thickness myocardial channel produced with TMR, percutaneous myocardial revascularization results in partial-thickness myocardial channels, generally ranging from 3 to 5 mm in depth. Three percutaneous myocardial revascularization systems have been evaluated.

***e*TABLE 81.1.2** STUDIES USING PERCUTANEOUS MYOCARDIAL REVASCULARIZATION FOR MEDICALLY REFRACTORY ANGINA

Author	Laser source	Manufacturer	No. of patients	Study design	No. of channels	Results
Shawl et al. (133)	Holmium:YAG	Eclipse (PTMR)	27	Phase I registry	17	Mean CCS functional class decreased from 3.6 at baseline to 0.65 at 30 d (p <.01) and 0.94 at 6-mo clinical follow-up.
Whitlow et al. (134)	Holmium:YAG	Eclipse (PTMR)	335	Randomized, unblinded	19	A significant improvement in angina status and exercise time was found in those patients treated with PTMR compared with medical therapy (p = .001). An improvement in angina by two or more classes was achieved in 35% of patients treated with PTMR compared with 15% in those treated with conventional medical therapy. There was one death and five (3%) cases of cardiac tamponade.

Lauer et al. (136)	Holmium:YAG	CardioGenesis (percutaneous myocardial revascularization)	34	Phase I registry	10	Median CCS functional class was reduced from 3.0 at baseline to 1.3 at 6-mo follow-up. Exercise capacity increased from 384 min at baseline to 514 sec at 6 mo.
Oesterle et al. (135)	Holmium:YAG	CardioGenesis (percutaneous myocardial revascularization)	221	Randomized, unblinded	15	Exercise tolerance at 12 mo had increased by a median of 89 sec in patients treated with PTMR compared with 12.5 sec in patients treated with medical therapy only. Angina class was two or more lower in 34.1% of patients treated with PTMR vs. 12.0% in those patients treated with medical therapy.
Kornowski et al. (137)	Holmium:YAG	LaserStar Biosense (DMR)	77	Phase I registry	26	Exercise duration after DMR increased from 293 to 400 sec at 1 mo and 436 sec at 6-mo follow-up (p <.001). CCS angina class increased from 3.3 at baseline to 2.0 at 6-mo follow-up (p <.001). There were no changes in thallium scintigraphy.
Leon et al. (138)	Holmium:YAG	LaserStar Biosense (DMR)	298	Randomized, blinded	10–15 or 20–25	Major adverse cardiac events at 30 d were more common in patients treated with low-dose or high-dose DMR than placebo patients (p <.014). The frequency of class III or IV angina was reduced from 100% to approximately 40% in all three groups.

CCS, Canadian Cardiovascular Society; DMR, direct myocardial revascularization; PTMR, percutaneous transmyocardial myocardial revascularization; YAG, yttrium-aluminum-garnet.

Percutaneous Transmyocardial Myocardial Revascularization

A fluoroscopically guided percutaneous system for myocardial revascularization was developed for use in patients with medically refractory angina. The percutaneous transmyocardial myocardial revascularization (PTMR) technique uses a 5- or 7-cm steerable PTMR catheter (Eclipse Surgical Technologies, Sunnyvale, CA) that is positioned in the left ventricular cavity (133). A SlimFlex laser fiber is introduced and advanced under fluoroscopy to the left ventricular apex, deflected to the myocardial region to undergo laser ablation (133). The laser delivers 3.5 W through the 1-mm-diameter optical fiber in a series of three sequential pulses. The laser channels were spaced 1 cm apart and an average of 15 to 20 channels were created per patients (133).

A pilot study reported clinical benefit in 27 patients treated with the fluoroscopically guided Eclipse holmium:YAG laser system; an average of 17 channels were formed for each patient (133). Mean CCS functional class fell from 3.6 to 0.6 by 30 days after the procedure (133). There were no procedure-related deaths, pericardial effusions, or perforations. A subsequent randomized trial compared the clinical outcomes of 335 patients with CCS class III or IV angina assigned to treatment with PTMR or continued medical therapy (134). An average of 19 channels were placed per patient in those assigned to PTMR. There was one death and five (3%) cases of cardiac tamponade. There was a significant (p = .001) improvement in angina status and exercise time in those patients treated with PTMR compared with medical therapy. An improvement in angina by two or more CCS classes was achieved in 35% of patients treated with PTMR compared with 15% in those treated with conventional medical therapy (133).

Percutaneous Myocardial Revascularization

Another holmium:YAG laser system has been developed as an alternative method of myocardial revascularization in patients with medically refractory disease. The percutaneous myocardial revascularization (PMR) system (CardioGenesis Corporation, Sunnyvale, CA) consists of a 9-Fr coaxial catheter system used to deliver an optical fiber coupled to a holmium:YAG laser (135). The optical fiber, capped with a 1.75-mm lens and four nitinol pedals 3 mm from the tip to prevent full-thickness advancement during laser stimulation, was advanced through the catheter until it made contact with the endocardial surface. Each laser channel was created with four laser pulses of 2 J, and the laser channels are separated by at least 1 cm.

A phase I pilot study reported improved clinical outcomes in 34 patients with severe CAD not amenable to revascularization treated with the fluoroscopically guided CardioGenesis holmium:YAG system (136). PMR was successfully performed in all cases (136). An average of 11 channels were created per patient, and there was one death early after PMR due to a myocardial infarction in an untreated region (136). There was a significant improvement in CCS angina class from 3.0 at baseline to 1-, 3-, and 6-month follow-up. Although there was also a significant increase in exercise time, there was no improvement in myocardial perfusion found to the regions treated with PMR (136).

The Potential Angina Class Improvement from Intramyocardial Channels Trial evaluated the effect of PMR compared with medical therapy in 221 patient with medically refractory angina. Exercise tolerance at 12 months had increased by a median of 89 seconds in patients treated with PTMR compared with 12.5 seconds in patients treated with medical therapy only (135). CCS angina class improved by two or more classes in 34.1% of patients treated with PTMR compared with 12.0% of those patients treated with medical therapy. Angina scores were similarly improved in patients who received PTMR.

Direct Myocardial Revascularization

A third system uses electromechanical mapping to localize the region of myocardium treated with the Biosense Webster Holmium:YAG laser system (137). The Biosense system uses a navigational control at the tip that uses magnetic field emitters and local sensors to determine the precise location of the position of the tip of the catheter. At the conclusion of the left ventricular mapping, an 8-Fr laser catheter is advanced into the left ventricle. The laser source is a pulsed holmium:YAG laser integrated with a 300-µm fiber (LaserStar, Biosense Webster, Diamond-Barr, CA). A single laser pulse (2 J per pulse) is fired perpendicular to the endocardial surface to create 0.5-to 1.0-mm-diameter channels to a depth of 3 to 5 mm. Between 10 and 25 laser pulses are created and successive laser channels are kept greater than 5 mm between successive laser ablation zones.

In a pilot series of 77 patients with chronically refractory angina, percutaneous direct myocardial revascularization (DMR) was performed using left ventricular electromechanical guidance, delivering approximately 26 channels per patient (137). Major cardiac events occurred in 2.6% of patients; one patient required a postprocedural pericardiocentesis. Exercise duration after DMR increased from 387 seconds at baseline to 454 seconds at 30 days to 479 seconds at 6 months' follow-up. CCS angina class decreased from 3.3 at baseline to 2.0 at 6 months' follow-up (137). There were no improvements in the treated zones with dual-isotope scintigraphy at 1 or 6 months after therapy (137).

The DMR in Regeneration of Endomyocardial Channels Trial (DIRECT) evaluated the effect of DMR in 298 "no options" patients with medically refractory angina randomized to receive high-dose DMW (20 to 25 channels per zone), low-dose DMR (10 to 15 channels per zone), or a sham procedure in which the laser was positioned but not fired (138). Patients remained blinded to treatment. MACE at 30 days were more common in patients treated with low-dose or high-dose DMR than placebo patients (p = .014). All patients improved their exercise duration, but there were no incremental benefits in patients treated with low-dose or high-dose DMR (138). The frequency of class III or IV angina was reduced from 100% to approximately 40% in all three groups. All other quality-of-life measurements showed similar improvements in all groups.

Other Methods

A number of non–laser-based methods of performing myocardial revascularization have been developed. Radiofrequency energy has been used to create 1-cm-wide by 2-mm-deep divots on the endocardial surface. Other potential treatments include high-pressure saline jet drilling systems (CorMedica, Natick, MA) and use of cryotherapy to create holes in the endocardium. A rotary cutting and tissue vacuuming device that rotates at 1,000 to 2,000 rotations per minute (AngioTrax, Sunnyvale, CA) creates channels that are 1 mm wide and 5 mm deep, usually in approximately two rows of 10 to 15 channels each.

To date, percutaneous methods of myocardial revascularization have shown benefit in unblinded, randomized clinical trials. The findings in DIRECT, which was the first truly blinded clinical evaluation of patients undergoing percutaneous treatments for refractory myocardial ischemia, failed to demonstrate a clinical benefit, owing to a marked placebo effect that was demonstrated in the patients receiving the sham procedure. The smaller depth of injury and size and number of myocardial channels compared with surgical TMR may explain the reduced benefit in these patients.

Growth Factor Administration

Although a number of potential angiogenic agents have been identified to enhance the natural process of collateral development, only two growth factors, fibroblastic growth factor (FGF) and VEGF, have been developed for clinical use in patients with refractory ischemia. These agents have been developed using both protein-based and gene-based strategies, administered by intravenous, intracoronary, intramyocardial, and intrapericardial delivery. Given the potential that therapeutic angiogenesis

may stimulate vascular growth, it should not be used in patients with unstable angina or accelerated atherosclerosis, proliferative retinopathy, or suspected or confirmed malignancy.

Fibroblast Growth Factor

FGF is a member of a family of nine heparin-binding growth factors that stimulate cells of mesenchymal origin (139). FGF promotes angiogenesis by exerting its action on the endothelial cells (140), and a number of experimental studies have demonstrated the angiogenic effect of FGF (141,142 and 143) (*e*Table 81.1.3).

***e*TABLE 81.1.3** PROTEIN AND GENE-BASED ANGIOGENESIS STRATEGIES USING FIBROBLASTIC GROWTH FACTOR IN PATIENTS WITH REFRACTORY CORONARY ARTERY DISEASE

Author	Agent	No. of patients	Design	Route of administration	Dosage	Results
Schumacher (144)	FGF-1	20	Phase I	Direct i.m. injection at time of left internal mammary artery–left anterior descending	0.01 mg/kg	New capillary formation was found in all patients at the time of 12-wk follow-up angiography; new capillary networks were demonstrated in some patients.
Laham et al. (142)	bFGF	24	Phase I	Sustained release microspheres directly into myocardium at time of coronary artery bypass grafting	Placebo or 10 or 100 µg	Magnetic resonance imaging showed a trend toward a reduction in target vessel ischemia (p <.06). Stress nuclear perfusion imaging at baseline and 3 mo after coronary artery bypass grafting showed a trend toward worsening of infarct size in the placebo group, no change in myocardial perfusion in the placebo group, and a significant improvement in the 100-µg bFGF group (p = .01).
Laham et al. (145)	FGF-2	52	Phase I	Single i.c. bolus	0.33 to 48.00 µg/kg	A significant decrease in angina class, increase in exercise tolerance, and improved regional left ventricular function and perfusion by quantitative magnetic resonance imaging was found in patients receiving FGF-2. No significant improvement in the single-photon emission computed tomographic sestamibi perfusion scans.
Chronos et al. (146)	FGF-2	337	Phase I randomized controlled trial	Single i.c. infusion	Placebo or 0.3, 3.0, or 30.0 µg/kg FGF-2	After 3 mo, the treatment group had an increase in exercise duration of 65 sec compared with 45 sec in placebo-treated patients (p = NS). Older (age >63 yr) patients showed a significant improvement in exercise duration associated with FGF-2 therapy. Although there were also no differences in quality-of-life measurement or Canadian Cardiovascular Society angina class, patients with the severest symptoms had the greatest improvement in angina as a result of therapy. At 180 d, exercise tolerance remained similar in placebo and treatment arms, although there was a persistent trend in a reduction in angina frequency in patients who received treatment.
Grines et al. (150)	Adenovirus 5, FGF-4	79	Phase II randomized controlled trial	Intracoronary injection	Placebo or 5 doses of Ad5FGF-2	There was a greater increase in exercise time in patients receiving Ad5 FGF-2 than those receiving placebo There were no adverse effects in patients during the Ad5 FGF-4 infusion.

FGF, fibroblastic growth factor.

Fibroblast Growth Factor-1

The first clinical use of FGF-1 was reported in 20 patients who underwent direct intramyocardial injection of FGF-1, 0.01 mg per kg, at the time of CABG in the region of the left internal mammary artery to the left anterior descending artery anastomosis (144). Repeat angiography performed 12 weeks later demonstrated a pronounced accumulation of contrast medium in the region of the anastomosis, suggesting new blood vessel growth in FGF-1–treated patients (144).

A subsequent phase I randomized, double-blinded, placebo-controlled study of 24 patients undergoing CABG evaluated the effect of direct intramyocardial administration of basic FGF (bFGF) (142). Patients were assigned to treatment with placebo or 10 or 100 µg bFGF delivered into ischemic myocardium via sustained-release heparin-alginate microcapsules (142). Stress nuclear perfusion imaging at baseline and 3 months after CABG showed a trend toward worsening of perfusion in the placebo group and a significant improvement in the 100-µg bFGF group (p = .01) (142).

Fibroblast Growth Factor-2

Intracoronary recombinant human fibroblast growth factor-2 (rhFGF-2; Chiron Corporation, South San Francisco, CA) was administered as a single 20-minute infusion in a phase I, open-label, dose-escalating study of 52 subjects with advanced CAD (145). A single dose of rhFGF-2 (0.33 to 48.0 µg per kg) was associated with a significant decrease in angina class, increase in exercise tolerance, and improvement in regional left ventricular function and perfusion by quantitative magnetic resonance imaging and radionuclide scintigraphy (145). Adverse effects included transient renal dysfunction and hypotension with higher dose infusions (145).

A subsequent phase II FGF-2 Initiating Revascularization Support Trial compared the efficacy of placebo and three doses (0.3, 3.0, or 30.0 µg per kg) of intracoronary administration of FGF-2 in 337 patients with severe CAD (146). After 3 months, the treatment group had an increase in exercise duration of 65 seconds compared with 45 seconds in placebo-treated patients (p = not significant). Patients older than 63 years showed a significant improvement in exercise duration associated with rhFGF-2 therapy. Although there were also no differences in quality-of-life measurement or CCS angina class, patients with the severest symptoms had the greatest improvement in angina as a result of therapy. At 180 days, exercise tolerance remained similar in placebo and treatment arms (147).

The Therapeutic Angiogenesis with FGF-2 for Intermittent Claudication Trial evaluated the safety and efficacy of intraarterial injection of FGF-2 in a randomized, placebo-controlled, dose-finding phase II study of patients with severe intermittent claudication (148,149). Patients were given placebo, a “single dose” of 30 µg per kg of FGF-2 by intraarterial infusion in both legs at day 1, or a “double bolus” of 30 µg per kg of FGF-2 by intraarterial infusion rFGF-2 in both legs at day 1 and day 30 (149). Single-dose FGF-2 resulted in a significant (p = .026) improvement in the primary end point, peak walking time at 90 days, although the change in peak walking time at 90 days was not different in patients receiving a double bolus compared with those receiving placebo. By 180 days, however, there were no differences among the groups, due to a large increase in peak walking time in the placebo group (148).

Recombinant Adenovirus 5 Fibroblast Growth Factor-4

Genetic delivery of angiogenic proteins may result in higher retention rates within the myocardium when given by intracoronary injection than protein infusions. The phase I/II, dose escalation Adenovirus Gene Therapy (AGENT) trial compared the safety and efficacy of an intracoronary infusion of recombinant adenovirus 5 FGF-4 (Ad5 FGF-4; Collateral Therapeutics, San Diego, CA) in 79 patients with class II or III angina (150). Patients were randomly assigned to placebo or to one of five escalating doses of Ad5 FGF-4 (ranging from 3.2 × 108 to 3.2 × 1,010 viral particles) injected into the left or right coronary artery (150). Preliminary results reported that patients who received active therapy had a greater increase in exercise time than those receiving placebo (150), although there was a substantial improvement in placebo-treated patients. There were no adverse effects in patients during the Ad5 FGF-4 infusion. Although these results are encouraging, the sample size is small and larger studies are needed. A phase III pivotal efficacy trial is planned.

Vascular Endothelial Growth Factor

VEGF is an endothelial cell-specific mitogen that has been implicated as another potent angiogenic agent (151). Endothelial responses to VEGF include proliferation, production of proteases such as plasminogen activators and collagenases that promote capillary bed formation, and triggering migration of monocytes (151).

VEGF has been studied by numerous investigators in various *in vitro* and *in vivo* animal models (152,153). In addition to these favorable responses that promoted angiogenesis, VEGF has also been shown to be a mediator of proliferative retinopathy, age-related macular degeneration, rheumatoid arthritis, and in the formation of

atherosclerotic plaque (151). VEGF has also been shown to promote the release of nitric oxide, resulting in clinical hypotension if given in high doses.

A recombinant human VEGF (rhVEGF) phase I clinical study of 14 patients who received an intracoronary infusion of low-dose rhVEGF (Genzyme, South San Francisco, CA) (0.005 and 0.017 µg per kg) or high-dose rhVEGF (0.05 and 0.167 µg per kg) over 20 minutes demonstrated improved myocardial perfusion in a dose-dependent fashion (154) (*e*Table 81.1.4). The VEGF in Ischemia for Vascular Angiogenesis (VIVA) Trial, a phase II, double-blinded, placebo-controlled trial, randomly assigned 178 patients who were poor candidates for conventional revascularization to treatment with placebo, low-dose (17 µg per kg per min), or high-dose (50 µg per kg per min) intracoronary rhVEGF infusion over 20 minutes followed by a 4-hour intravenous rhVEGF infusion at 3, 6, and 9 days (155). All groups had a similar increase in exercise time, Canadian class angina, and quality of life at 60 days (155,156). At 120 days, the improvement in the placebo group became diminished and the high-dose infusion continued to improved, resulting in a significant improvement in CCS angina class (p = .04) and a trend toward improvement in exercise time (p = .17) in patients treated with high-dose rhVEGF compared with placebo. In a subset analysis of 107 patients who were followed for an additional 8 months, placebo-treated patients continued to worsen, whereas patients receiving high-dose rhVEGF continued to have significant improvement. The occurrence of 1-year death, myocardial infarction, revascularization, or cancer was lower in patients treated with high-dose rhVEGF (11.8%) compared with patients treated with placebo (31.6%) (p <.04) (156).

***e*TABLE 81.1.4** PROTEIN AND GENE-BASED ANGIOGENESIS STRATEGIES USING VASCULAR ENDOTHELIAL GROWTH FACTOR IN PATIENTS WITH REFRACTORY CORONARY ARTERY DISEASE

Author	Agent	No. of patients	Design	Route of administration	Dosage	Results
Hendel et al. (154)	rhVEGF	14	Phase I	i.c. Bolus	Low dose (0.005 and 0.017 µg/kg) or high dose (0.05 and 0.167 µg/kg)	An improvement in myocardial perfusion in a dose-dependent fashion was suggested.
Henry et al. (155)	rhVEGF	178	Phase II randomized controlled trial	i.c. Bolus over 20 minutes, then i.v. infusion at 3, 6, and 9 d	Placebo, or “low dose” (17 µg/kg/min) or “high dose” (50 µg/kg/min)	At the end of 60 d, all groups had a similar increase in exercise time, Canadian Class angina, and quality of life. At 120 d, the improvement in the placebo group became diminished and the high-dose infusion continued to improve, resulting in a significant improvement in Canadian Class (p = .04) and a trend toward improvement in exercise time (p = .17) in patients treated with high-dose rhVEGF compared with placebo.
Symes et al. (158)	phVEGF-165	20	Phase I	Direct i.m. injection by minithoracotomy	125 or 250 µg	Patients had significant reductions in angina, as assessed by nitroglycerin consumption (53.9 per wk at baseline and 9.8 per wk after treatment; p <.03). Improved dobutamine single-photon emission computed tomography in most patients. Improved angiographic Rentrop score in all patients.
Vale et al. (159)	phVEGF-165	13	Phase I	Direct i.m. injection via an endocardial delivery catheter	—	Improvement in single-photon emission computed tomography perfusion of the treated area. Reduction in indices of perfusion by electromechanical mapping.
Rosengart et al. (161)	Ad_{GV}VEGF121.10	21	Phase I	Direct i.m. injection at coronary artery bypass grafting	—	There was no evidence of toxicity related to the administration of the agent or vector. All patients reported an improvement in their angina class. Patients who receive Ad_{GV}VEGF121.10 as sole therapy reported an increase in exercise duration in most cases.

VEGF, vascular endothelial growth factor.

Naked Plasmid DNA Encoding the Vascular Endothelial Growth Factor–165 Gene

A phase I clinical trial demonstrated the safety of naked plasmid DNA encoding the VEGF-165 gene (Vascular Genetics, Research Triangle Park, NC) injected directly into the myocardium of patients via a minithoracotomy (157,158). Angina episodes requiring nitroglycerin therapy were reduced in most patients, and exercise tolerance improved significantly after gene transfer (158,159).

Using another approach, direct intramyocardial administration of the naked plasmid VEGF-165 was achieved using a specially designed delivery catheter that uses electromechanical mapping to localize the region of myocardial injection (160). In this series, 13 consecutive patients treated with a direct intramyocardial injection of VEGF-165 and single-photon sestamibi examinations were used to assess improvements in perfusion over a 60-day follow-up period (160). Partial or complete resolution of perfusion defects seen on the sestamibi scan were improved during the follow-up period. Improvements in the electromechanical mapping profiles were also noted.

Adenovirus Gene Transfer Vascular Endothelial Growth Factor 121.10

A phase I study used a gene-therapy strategy used an E1-E3-adenovirus (Ad) gene transfer vector expressing VEGF121 cDNA (Ad_{GV}VEGF121.10) (GenVec, Inc., Gaithersburg, MD) to induce therapeutic angiogenesis in 21 patients with symptomatic CAD (161). Ad_{GV}VEGF121.10 was administered to 15 patients as an adjunct to CABG and to six patients as sole therapy via a minithoracotomy. There was no evidence of toxicity related to the administration of the agent or vector. All patients reported an improvement in their angina class, and patients who received Ad_{GV}VEGF121.10 as sole therapy reported an increase in exercise duration in most cases (161). These effects were sustained 6 months after the procedure (162).

Candidates for Therapeutic Angiogenesis

Patients who have no options for conventional revascularization may either have a single long-standing occlusion of a proximal vessel that subtends a large amount of myocardium or have undergone one or more prior CABG surgeries, with occlusion or stenoses saphenous vein grafts in association with native CAD that is poorly suited for conventional revascularization. It is estimated that patients with no options account for approximately 4% to 12% of those undergoing coronary arteriography (105). A larger percentage of patients (20% to 30%) have incomplete revascularization due to unsuitable coronary anatomy after conventional revascularization. These patients may also be amenable to alternative approaches targeted at increasing perfusion to ischemic tissues.

It is understandable that an aggressive approach to new blood vessel formation is needed in these patients, as these individuals are “resistant” to physiologic angiogenesis that results in extensive collateral formation in some patients with long-standing occlusion (106). Resistance to therapeutic angiogenesis may occur as a result of medications, with hypercholesterolemia, smoking, and diabetes, among other factors (106).

Because of the potential that therapeutic angiogenesis may be associated with some untoward effects, patients with cancer, diabetic retinopathy, unstable angina, or protein nephropathy have not been included in studies assessing the efficacy of angiogenesis (106).

Controversies and Personal Perspectives

Patients who have refractory angina but are poor candidates for revascularization still have few options for symptom relief. Although the use of systemic and local delivery of growth factors and surgical laser revascularization to promote angiogenesis remains an active area of investigation, the clinical results obtained with these therapies have been somewhat disappointing to date. Adjunct surgical TMR appears to be the best approach to the patient who undergoes CABG but has important residual ischemic zones, and isolated TMR may also benefit patients who require symptom relief from refractory ischemia in zones not amenable to revascularization. It appears that percutaneous approaches may not provide a sufficient extent of injury to promote angiogenesis. The DIRECT trial also emphasized the importance of blinding of the treatment method to patients and their physicians, as the placebo effect may be a powerful stimulus for symptom relief in these patients. Early clinical trial results from intracoronary and intravenous protein and gene-based approaches to angiogenesis have also failed to identify a truly viable approach for the majority

of patients with refractory ischemia, although more investigation is needed.

THE FUTURE

The immediate future will see a refinement in the technology for distal protection devices, with improved flexibility, lower profiles, and reduced risk for vessel injury. The optimal device will be one that can be placed beyond distal lesions in tortuous vessels without interfering substantially with the interventional procedure itself. Clinical investigation will be directed at establishing the optimal clinical and anatomic indications for antiemboli devices, as well as critically assessing the potential complementarity between the pharmacologic and mechanical approaches.

Continued evolution of the molecular approaches to angiogenesis will likely be the next frontier for patientswith refractory CAD and no options. The encouraging preliminary results of the AGENT trial require confirmation in a larger phase III trial that will measure clinical end points in a larger number of patients. Direct intramyocardial injection of growth factors using fluoroscopically or electromechanically guided injection systems may allow more precise delivery of protein-based and gene-based factors into the ischemic myocardium. It is likely that new imaging modalities, such as functional magnetic resonance imaging, may also provide a more sensitive index to assessing the therapeutic effect of angiogenesis.

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CORONARY ARTERY BYPASS SURGERY

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"Indicates text or graphics that appear only in the electronic versions of this text."

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HISTORICAL PERSPECTIVE

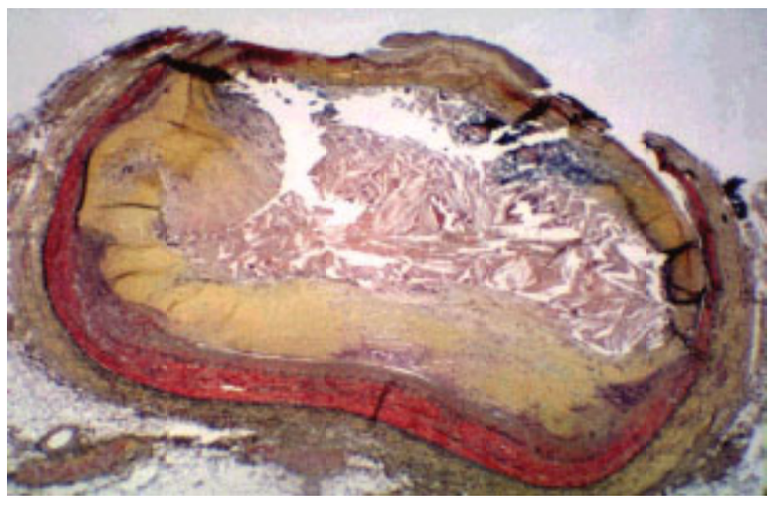
Evolution of Direct Coronary Artery Surgery

Now in its fourth decade, surgical myocardial revascularization has benefited millions of patients. Excellent early and late results are attributable to improvements in technology rather than selection of lower-risk patients. The surgical achievements relate to advances in myocardial protection, use of arterial conduits for bypass grafting, and postoperative intensive care management. The original coronary artery bypass operation as popularized by Favaloro (1) and Johnson and colleagues (2) and performed earlier by Garret and colleagues (3) involved aortocoronary saphenous vein grafts. Later, after surgeons acquired the necessary technical expertise, internal thoracic arteries (4) and other arterial conduits were successfully used. Anesthesiologists deserve a large part of the credit for advances in myocardial protection, intraoperative stabilization, and intensive care management. Improvements in anesthetic agents, afterload reduction, and ventilation management have contributed to reduction of complications, shorter hospitalization, and lower cost.

SELECTION OF CANDIDATES FOR SURGERY

Current Indications

Advanced age affects selection for surgical procedures and has stimulated risk assessment. At age 70, clinically detectable coronary atherosclerosis occurs in 15% of men and 9% of women; by age 80, this figure rises to 20% in both sexes. In addition, increasing age is associated with increasing prevalence of diabetes, peripheral vascular and cerebrovascular disease, cardiac dysfunction, and left main narrowing (5).



Severe atherosclerosis of saphenous vein graft. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

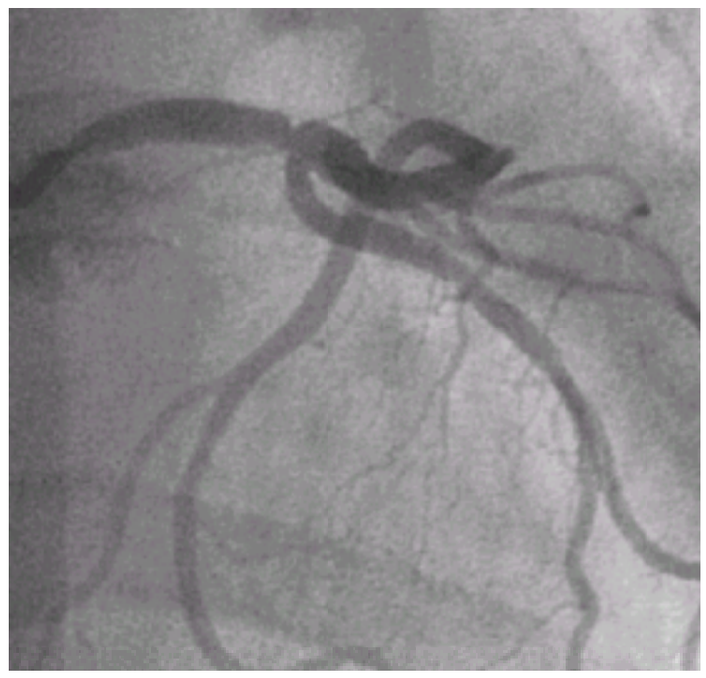
In 1967, the mean age for coronary artery surgery patients was approximately 50 years, and today it has risen to 66 years; nearly 30% of patients are older than age 70, and 10% are older than age 80. The national rate of bypass surgery in octogenarians is increasing rapidly (up 67% during a recent 4-year period), and early results are similar to those of the Medicare population overall (6), despite the complicated and frequently multisystem atherosclerosis typical in older people. In the elderly, there is a greater incidence of silent ischemia, unrecognized myocardial infarction, and diastolic dysfunction (7). Stress echocardiography with pharmacologic testing or positron emission tomographic scanning may be required to document ischemia because exercise capacity is often limited (see Chapter 50).

Age and left ventricular performance are the most important prognostic indicators for late outcome, regardless of the type of treatment (8). Men tend to manifest clinically detectable coronary atherosclerosis at a younger age than women; however, after menopause, the rates of atherosclerosis among men and women are approximately the same.

Chronologic age is a crude measure and is less important than physiologic age. Older age is fraught with the above-mentioned comorbidities, yet these do not encompass all factors in selection. Postoperative hospitalization is longer in those older than age 70 years compared with that of patients ages 65 to 70 years, and

hospital costs and charges are also greater. The four As—age, attitude, activity, and associated diseases—are helpful in assessing risk versus benefit (9).

Given that the patient is an acceptable candidate based on clinical characteristics and evidence of myocardial ischemia, the next important step is coronary arteriography. The location(s) of myocardial jeopardy influences the decision about the type of revascularization. Left main and proximal anterior descending narrowing of 50% or more of lumen diameter impacts the prognosis for adverse events and death more than lesions in other arteries. Patients with angina or ischemia and two-vessel coronary atherosclerosis with a proximal anterior descending lesion or proximal three-vessel disease should be considered for surgery (10). When viable myocardium is demonstrated, poor left ventricular function is not a contraindication to surgery, provided the target vessels are graftable.



A 64-year-old male patient with severe ostial and moderate distal left main trunk stenosis.

Lessons from Clinical Trials

The lessons learned from clinical trials of coronary bypass surgery compared with medical treatment and with angioplasty are the bases for selection of the surgical candidate. In low-risk patients (i.e., those with marginal lesions and no ischemia or with narrowing in small branch coronary arteries) medical treatment is effective. Coronary bypass surgery is indicated for patients with multivessel disease and is most appropriate in patients with left main and proximal anterior descending lesions as part of a complicated atherosclerotic pattern (Fig. 82.1) (11,12,13 and 14). As left ventricular performance worsens, survival with surgical treatment tends to be better than that with medical treatment (15). Angioplasty may yield equivalent results in single-vessel and selected two-vessel disease in the intermediate term, but more complicated atherosclerotic plaques and calcification in diffuse coronary atherosclerosis make standard balloon angioplasty less effective. In calcified vessels, rotational atherectomy combined with balloon angioplasty has been successful, as well as atherectomy performed before stent placement. Stents have reduced but not eliminated the restenosis problem.

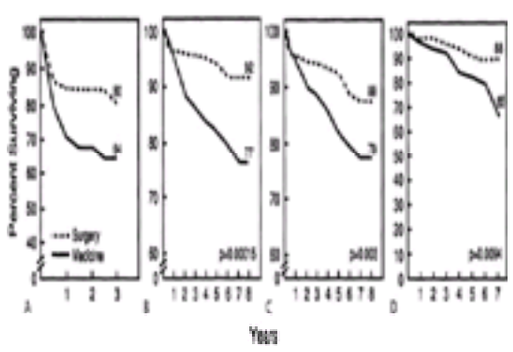


FIGURE 82.1 Survival from published randomized trials comparing coronary artery bypass surgery with medical treatment. **A:** The original Veterans Administration Coronary Arterial Disease Study, which randomly allocated 113 patients with severe left main coronary narrowing to medical or surgical treatment from 1970 to 1974. The 3-year survival was 80% for surgery and 64% for medicine. **B:** Long-term results of two- and three-vessel disease patients from the European Coronary Surgery Study Group are depicted in this panel. Actuarial survival curves for three-vessel disease patients who had an 8-year survival of 92% for surgery and 77% for medicine (p = .00015). **C:** In the subgroup of patients with more than 50% narrowing in the proximal third of the anterior descending coronary artery, there was a highly significant difference in favor of surgery in both two- and three-vessel disease subsets. **D:** Seven-year cumulative survival rates for surgery and medical patients from the randomized trial of the coronary artery surgery study. The surgical survival of 88% was significantly better (p = .012) than medical treatment when the left ventricular ejection fraction was under 0.50. (Data from Takaro T, Hultgren HN, Lipton MJ, et al. The VA Cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. *Circulation* 1976;54[Suppl III]:III107–III117; European Coronary Surgery Study Group. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982;2;1173–1180; and Passamani E, Davis KB, Gillespie MJ, et al. A randomized trial of coronary artery bypass surgery: survival of patients with a low ejection fraction. *N Engl J Med* 1985;312:1665–1671.)

Contraindications

Contraindications to coronary artery surgery are relative and include patients with no signs of ischemia, especially those with poor left ventricular function and clinical evidence of heart failure; very elderly patients who are inactive and have absent or mild symptoms; and patients who exhibit noncompliant behavior or are otherwise mentally impaired.

In patients with noncardiac conditions whose coronary atherosclerosis warrants revascularization, coronary artery surgery should precede noncardiac procedures (16). Extensive guidelines for physicians involved in preoperative, operative, and postoperative care of patients undergoing noncardiac surgery are available (17). Their purpose is to formulate a stepwise, cost-effective approach to diagnostic testing and management.

Selected Subsets

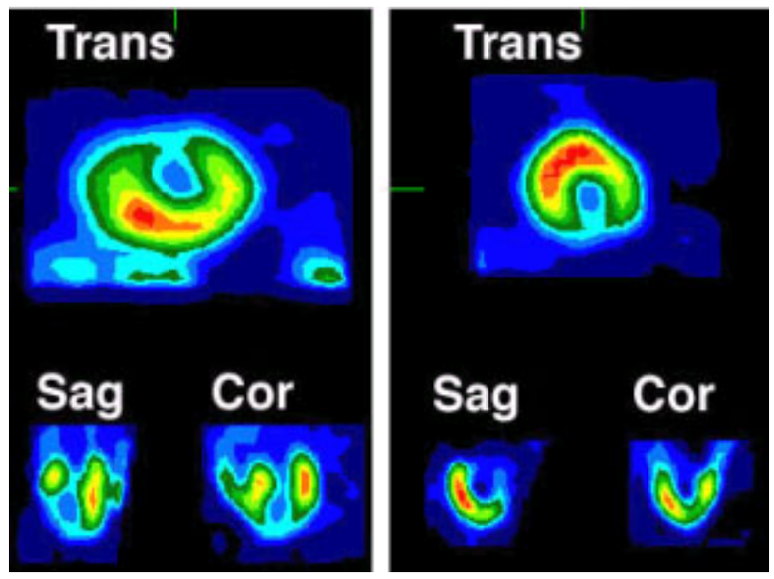
Younger Age

Young age is generally defined as age younger than 40 years. Premature atherosclerosis may be severe and require coronary artery bypass grafting followed by strict lipid modification therapy and diabetic management when indicated (18,19). Coronary risk factors tend to be more prevalent in this population. Only arterial bypass conduits should be used as grafts—that is, bilateral internal thoracic artery grafts are often used for the anterior descending and circumflex arteries, and, when the right coronary artery is small and subtotally or totally occluded, the gastroepiploic artery or other arterial conduit may be useful to revascularize the inferior wall. Larger patent but stenotic right coronary arteries may be treated with the radial artery or selectively by the *in situ* right internal thoracic artery grafted to a major branch, usually the posterior descending. The radial or inferior epigastric artery may be used as a Y or T graft for circumflex revascularization from the left internal thoracic artery or as an aortocoronary bypass graft (20).

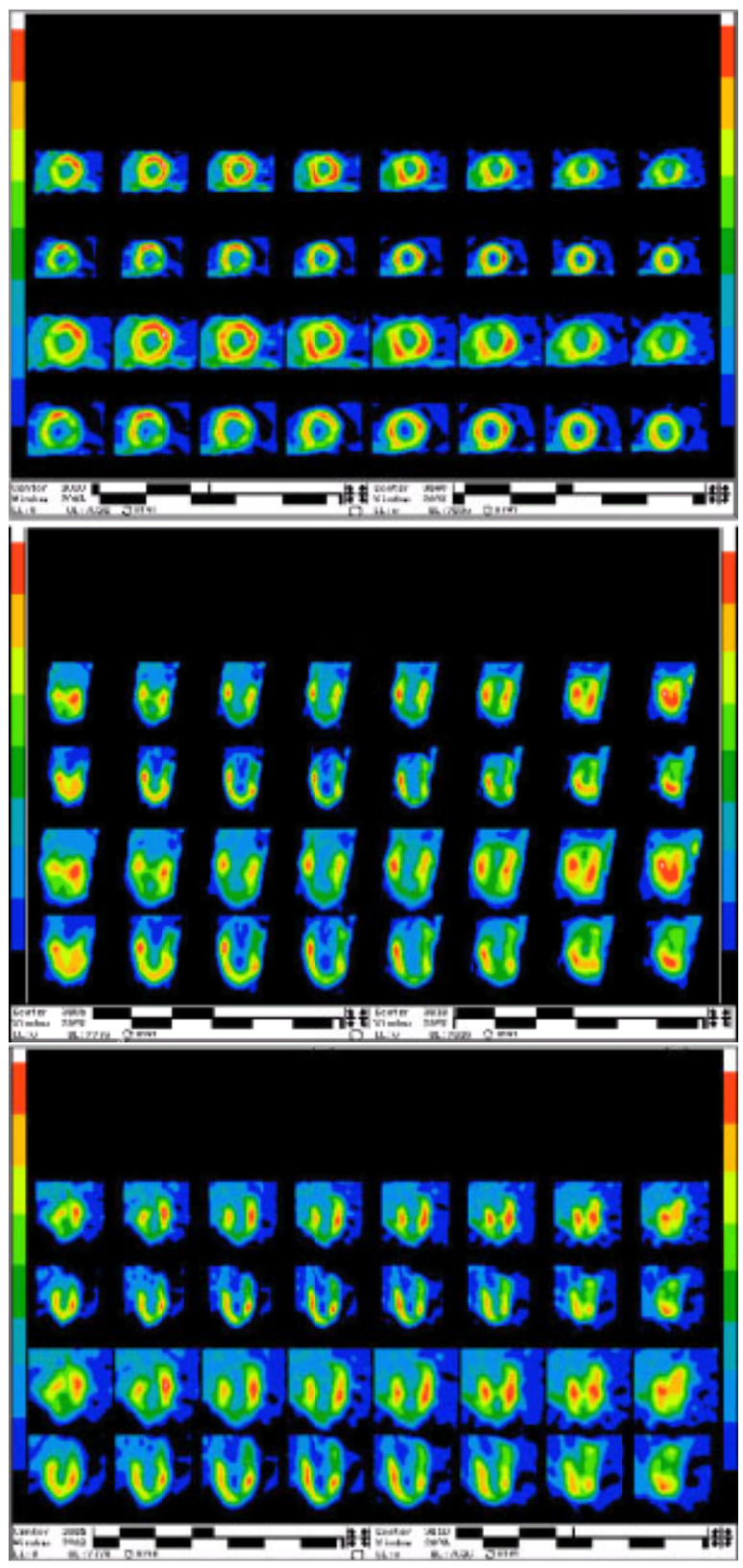
Hibernating Myocardium

Hibernating myocardium, a potentially reversible condition, indicates impaired contraction caused by chronically reduced myocardial blood flow (21). Hibernating

myocardium may be identified by demonstrating contractile reserve after administration of dobutamine, by showing preserved metabolism in abnormal regions through positron emission tomography, and by thallium uptake indicating preserved myocardial function. Of these alternatives, positron emission tomographic myocardial imaging is the most sensitive predictor of functional recovery. In contrast, stunned myocardium occurs after restoration of normal flow after a period of myocardial ischemia (22). Stunning may occur after vasospasm, myocardial infarction, angioplasty, or coronary bypass surgery. Stunning is not innocuous and may reduce contractile function to the point where the left or right ventricle is incapable of supporting the systemic circulation (see the section Reduced Left Ventricular Function). With recent technological advances, magnetic resonance imaging has become a valuable method for the detection of viable myocardium (23).



Matched resting rubidium (*left set*) and radiolabeled fluoro-deoxyglucose positron emission tomographic (*right set*) images. Transverse, sagittal, and coronal positron emission tomographic images demonstrating myocardial hibernation in the left anterior descending artery territory.

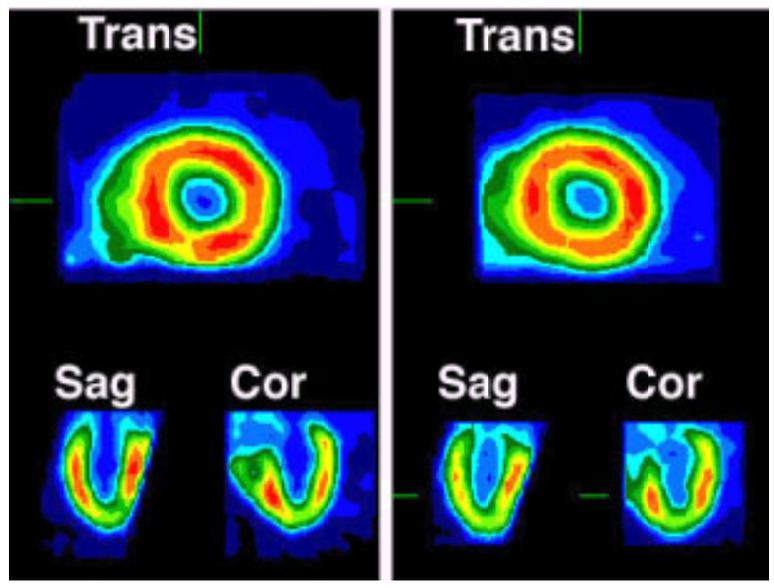


Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery.

VIDEO

Video 82.1 Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 82.2 Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



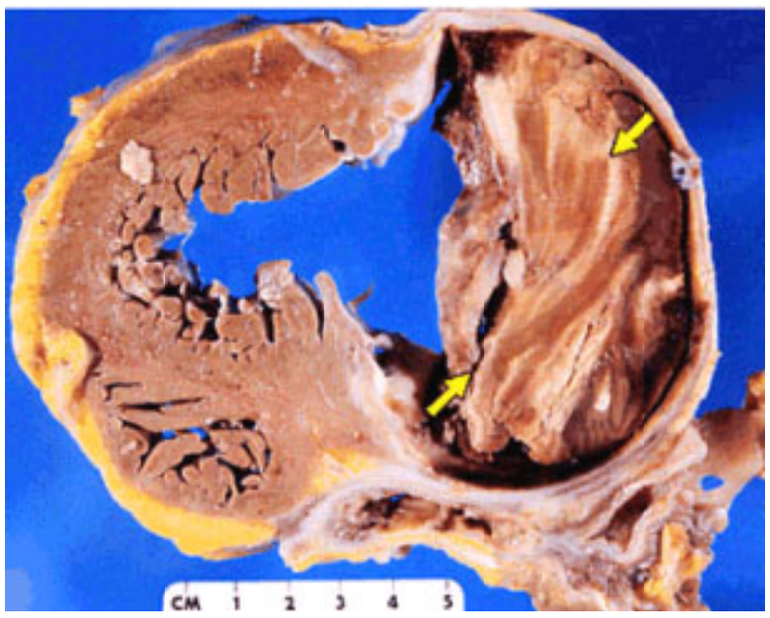
No fixed or transient changes in between stress (*left*) and resting (*right*) rubidium-82 positron emission tomographic images on transverse, sagittal, and coronal slices, demonstrating a dilated left ventricular cavity and a lack of myocardial scar or ischemia in a patient with nonischemic dilated cardiomyopathy.

Ventricular Aneurysm

Ventricular aneurysm is irreversible true scar formation that is most frequently due to anterior descending coronary artery occlusion (24). Approximately 3% to 4% of cardiac aneurysms occur posteriorly between the papillary muscles (25). The scarred region is thin-walled and frequently adherent to the pericardium. Angina, heart failure, and tachyarrhythmias are the indications for surgery. Adherent organized ventricular thrombi are seen in 50% of ventricular aneurysm cases. Embolism is rare, and left ventricular thrombus *per se* is not an indication for surgical removal. The great majority of patients have multivessel disease. Endoaneurysmorrhaphy appears more physiologic than linear repair because of a more favorable effect on measured ejection fraction and improved long-term clinical outcome (26). The best surgical treatment is to have aneurysm exclusion by ventricular patch combined with coronary bypass surgery. Several techniques for geometric preservation of the ventricle have been advanced and are characterized by a reduction in chamber volume to provide greater systolic shortening (27,28).

A 78-year-old with left ventricular aneurysm status post anterolateral myocardial infarction.

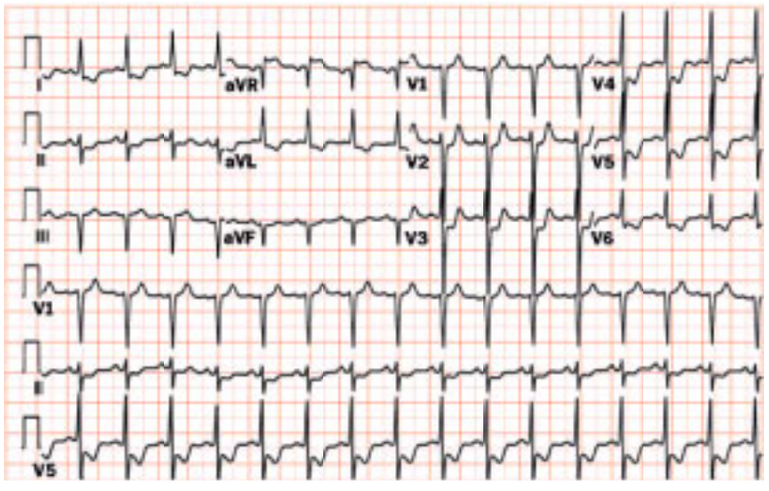
Aneurysm repair in a patient with a recent lateral wall myocardial infarction. "Packing material" is evident overlying the area of repair (*yellow arrow*).



Healed, atrophic posterolateral infarct and ventricular aneurysm containing a mural thrombosis (*yellow arrows*).

Acute Ischemic Syndromes

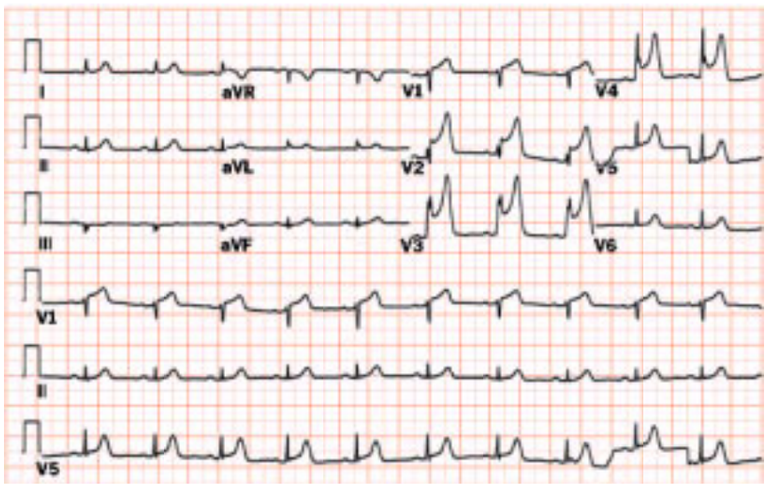
Acute ischemic syndromes include the spectrum from unstable angina to myocardial infarction. Unstable angina is a broadly interpreted condition. New and progressive angina may be categorized as unstable, but a stricter definition includes pain at rest with electrocardiographic evidence of ischemia (29). Most such patients can be stabilized, but approximately 10% experience myocardial infarction. Necropsy studies indicate that unstable angina patients frequently have severe coronary atherosclerosis. A ruptured atherosclerotic plaque has been linked to persistent instability. Refractory unstable angina may lead to early coronary arteriography and intervention. Multivessel graftable coronary atherosclerosis is an indication for coronary bypass surgery, preferably when the patient is stable. Operations in the face of acute symptoms, especially with ischemic electrocardiographic change, are associated with a higher perioperative myocardial infarction rate and associated risk (30).



Subendocardial ischemia. Anterolateral ST-segment depression is consistent with diffuse subendocardial ischemia versus non–Q-wave myocardial infarction.

Unstable angina vs. non–Q-wave myocardial infarction. ST-segment depression in leads V_2 through V_5 supports acute ischemic syndrome.

Reports on emergency surgery for acute myocardial infarction demonstrated good intermediate-term results (31); however, thrombolytic therapy and angioplasty have largely supplanted emergency surgery. Today, emergency coronary bypass surgery is generally reserved for patients who have severe left main coronary atherosclerosis, who fail angioplasty intervention, or who have mechanical defects. The greatest decrease in risks for operative mortality and perioperative myocardial infarction occurs within 48 hours of infarction, and there is little to be gained by delaying surgery longer (32). Patients with non–Q-wave infarction may, with appropriate indications, undergo bypass surgery with relative safety at any time.



Acute anteroseptal myocardial infarction. Dramatic ST segment elevations in leads V_1 through V_5 with associated hyperacute T-wave changes are noted.

Data collected from 19 Seattle hospitals showed that, among patients who underwent emergency or urgent surgery during myocardial infarction, there was no difference in mortality for patients operated on during the first 24 hours compared with those operated on later in the hospital course (8.3% vs. 7.2%) (33). Over the next 3 years, there were few cardiac events in the surgical population; the 3-year survival of 83% was better than the 66% survival rate in those treated medically. Other studies have reported a hospital mortality as low as 4% in patients operated on less than 24 hours after infarction.

As might be expected, given higher event rates among patients with left anterior descending lesions, emergency surgery for myocardial infarction is more beneficial for

anterior infarctions than for inferior infarctions (34). Multicenter trials indicate that in-hospital and 1-year results, event-free survival, angina status, and health status are similar for emergency bypass surgery and treatment by successful thrombolysis and angioplasty. Patients who have survived cardiac arrest secondary to myocardial infarction should be evaluated by electrophysiologic testing and coronary arteriography (35). Commonly, multivessel coronary artery disease is found, and surgical revascularization is considered. The result depends on preoperative left ventricular status and the potential for surgery to suppress inducible ventricular arrhythmias.

The results of emergency surgery today far surpass those of the early 1970s. Although preoperative cardiogenic shock is the leading risk factor for hospital death after emergency revascularization, techniques of controlled surgical reperfusion have reduced the mortality in that subset to 10% (36). As myocardial protection improves through better reperfusion strategies, the treatment of acute coronary occlusion should be reevaluated because ischemic muscle may be salvaged at time intervals beyond limits previously thought to cause irreversible damage.

Mechanical Complications of Myocardial Infarction

Cardiac rupture is documented at autopsy in 8% of patients after myocardial infarction. Cardiac rupture occurs more frequently in women, in the elderly, after recurrent myocardial infarction, and in patients with multivessel disease (37). Free wall rupture occurs 3 to 10 times more frequently than ruptured papillary muscle or ventricular septal defect and is a more frequent cause of acute hemopericardium than is aortic dissection (38). Rupture of the free wall, most commonly the anterior or lateral wall, usually occurs during the first week after infarction, but approximately one-third of ruptures occur in the first 24 hours. Free wall ruptures may occur after thrombolytic therapy and present subacutely. Death is often instantaneous, but in up to 40% of patients, death occurs over a matter of hours. If the rupture is contained and is recognized, surgical repair should proceed immediately (39). Conventional surgery involves bolstered primary closure or patching, and both carry high mortality due to the precarious emergency situation and necrotic muscle. Recently, patching with a biocompatible synthetic glue without direct suturing has been successful (40).

Cardiac rupture after acute transmural anteroseptal myocardial infarction. The yellow arrow indicates the site of rupture.

Recent myocardial infarction with free wall rupture of the anterior wall of the left ventricle. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

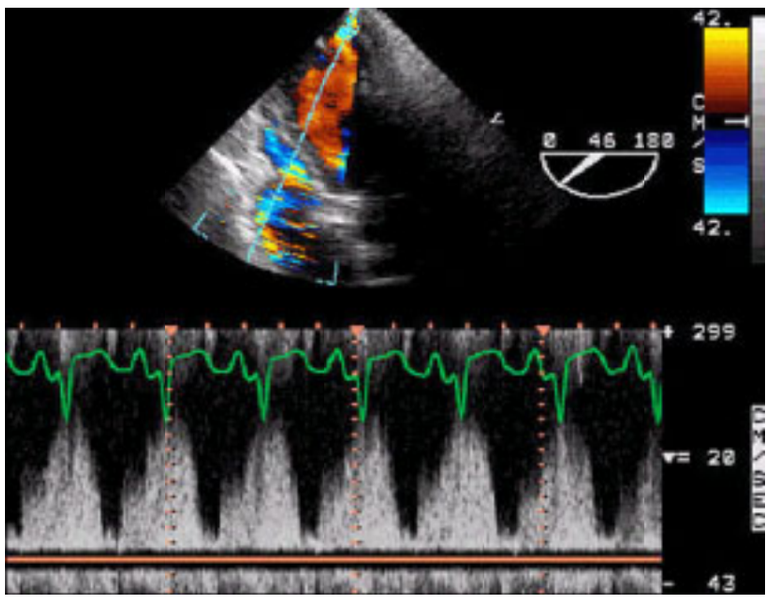
VIDEO

Video 82.3 Ventriculography of a contained rupture of the left ventricle (false aneurysm). Contrast injection reveals a noncontractile portion of the left ventricular silhouette that fills with contrast but does not clear. This is consistent with a contained rupture of the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 82.4 Post–myocardial infarction pseudoaneurysm (short-axis). Rupture of the inferolateral wall of the left ventricle due to circumflex artery occlusion. The pseudoaneurysm cavity is contained by pericardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Ventricular septal defects account for 20% of cardiac ruptures secondary to myocardial infarction. Ideally, repair is performed at 6 weeks, when the defect edges have become more fibrous and hold sutures better. However, this situation is infrequent; most patients with acute septal rupture are hemodynamically unstable and require emergency surgery. These patients should be treated expeditiously with vasopressor and intraaortic balloon pump support and should have coronary angiography before emergency surgery. The traditional surgical treatment has been infarctectomy and incorporation of septal and ventricular wall polyethylene terephthalate (Dacron) fabric patches (41).



Doppler recording of flow through an ischemic ventricular septal defect before surgical repair.

Video 82.5 Parasternal long-axis view of tetralogy of Fallot. Note the ventricular septal defect and the aorta and aortic valve overriding the interventricular septum. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 82.6 This is an intraoperative transgastric transesophageal view of an ischemic ventricular septal defect after an acute inferior myocardial infarction. Note the location of the large defect in the inferior septum. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 82.7 Color Doppler view of a post infarct ventricular septal defect in the inferior septum. Note the color flow thru the large defect. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 82.8 Transesophageal echo view of a patient following a large left anterior descending coronary artery territory infarction with an apical aneurysm. Note the spontaneous echo contrast seen within the left ventricular cavity. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

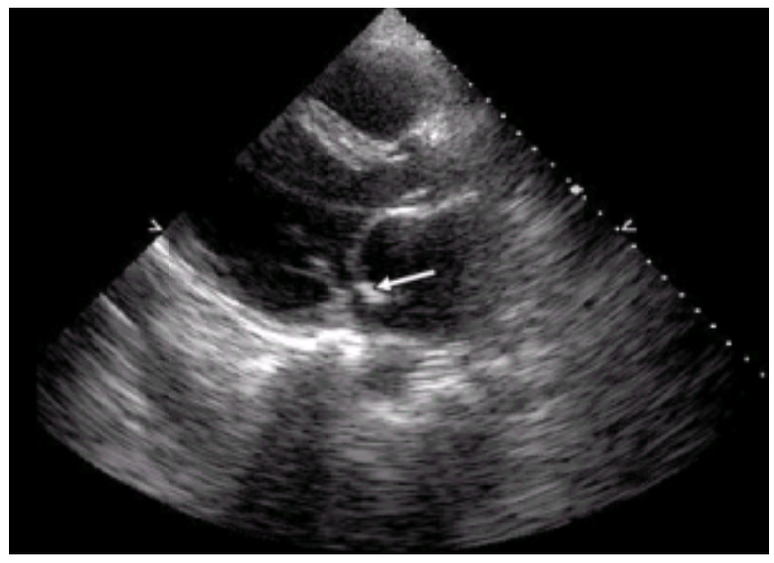
Video 82.9 Hepatoclavicular view (left anterior oblique 60, cranial 45) of a membranous ventricular septal defect in a 16-year-old male patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

More recently, introduction of a glutaraldehyde-fixed bovine pericardial patch sewn to the endocardium around the infarcted muscle has been introduced. This technique of repair by bioprosthetic endocardial patch is easy to accomplish technically and has resulted in lower operative mortality (14% operative mortality and 66% 6-year survival in the largest reported series) (42). The advantage of this approach is restoration of left ventricular geometry and preservation of right ventricular muscle. Regardless of surgical technique, the greatest risk factors in patients with postinfarct ventricular septal defects are cardiogenic shock and right ventricular dysfunction.

Ischemic Mitral Regurgitation

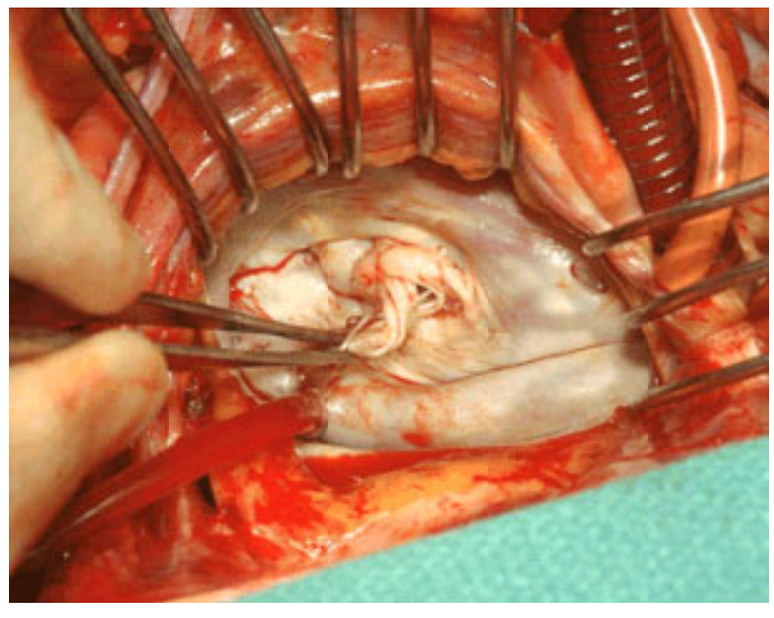
In ischemic mitral regurgitation, the mitral leaflets and chordae are normal, and the regurgitation is a consequence of ischemic disease of the myocardium. Although published classification schemes for this entity are confusing, classification by mechanism of mitral valve dysfunction is straightforward. Some patients have transient mitral regurgitation caused by intermittent ischemia. In such patients, mitral regurgitation is relieved by revascularization alone. In most cases, however, ischemic mitral regurgitation can be corrected only by mitral valve repair or replacement. In such cases, ischemic mitral regurgitation has one of three causes: (a) ruptured papillary muscle, (b) infarcted but unruptured papillary muscle, and (c) functional ischemic mitral regurgitation (43). Patients with a ruptured papillary muscle usually present with acute pulmonary edema and require urgent surgery. Patients with an infarcted but unruptured papillary muscle generally have a fibrotic, elongated papillary muscle. This causes leaflet prolapse and mitral regurgitation. The majority of patients with ischemic mitral regurgitation has functional ischemic mitral regurgitation. In such patients, alterations in ventricular and annular geometry produce restricted leaflet motion and a jet of mitral regurgitation that is frequently central or eccentric.

Video 82.10 Parasternal long-axis view of a ruptured papillary muscle after myocardial infarction. Note the bright mass (papillary muscle) attached to the tip of the anterior mitral leaflet as it flails into the left atrium. This resulted in severe mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Parasternal long-axis view of a papillary muscle rupture after myocardial infarction. Note the piece of papillary muscle attached to the tip of the anterior mitral leaflet as it flails into the left atrium (demonstrated by the arrow).

Surgical pathology specimen demonstrating a torn papillary muscle seen to the lower right of the screen, attached via chordae to a portion of the anterior mitral leaflet. Note the torn "ragged edges" at the bottom of the papillary muscle head.



Intraoperative field demonstrating a mitral valve with a torn papillary muscle prolapsing across the mitral valve into the left atrium. The surgeon has the papillary muscle in forceps demonstrating the chordae attached to the posteromedial commissure, predominantly attached to the anterior mitral leaflet. (The patient's head is to the left of the screen and feet to the right.)

Surgical treatment of ischemic mitral regurgitation consists of mitral valve repair or replacement, generally with concomitant coronary artery bypass grafting. In most patients, there is a survival advantage to mitral valve repair over mitral valve replacement (43). When mitral valve replacement is performed, the subvalvular apparatus should be preserved. Hospital mortality is 10% to 20%, and 5-year survival is approximately 50% (43). These unfavorable results are attributable to left ventricular dysfunction in this subset of patients.

Coronary Artery Aneurysms

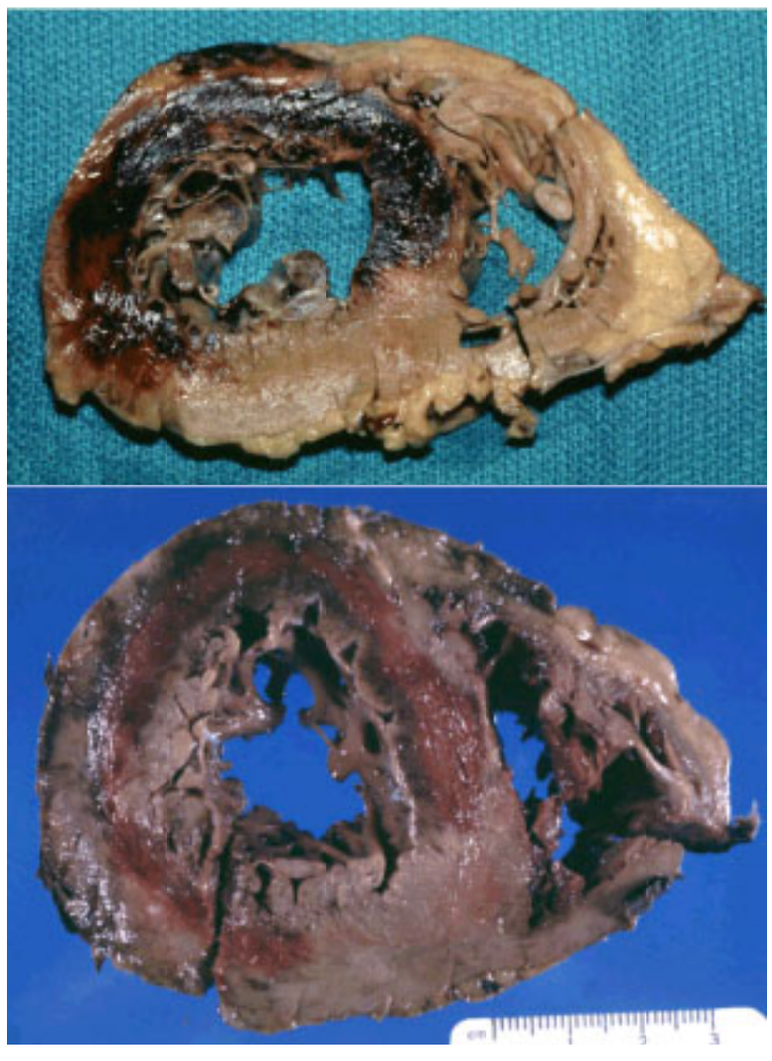
Ectasia and Kawasaki disease exhibit aneurysmal coronary arterial changes. The term *ectasia* denotes a diffuse ballooning of the coronary artery probably related to atherosclerosis, although some of these cases may be traced to past Kawasaki disease. Kawasaki coronary artery disease (also known as *mucocutaneous lymph node syndrome*) is a self-limited vasculitis of unknown etiology, occurring in children younger than 5 years of age and more commonly in males (44). Asian children are seven times more susceptible than non-Asians. The pathology is aneurysm formation, which may manifest itself 20 years or more after the acute illness. In many patients, obstructions develop at the aneurysm site. Coronary artery bypass surgery is indicated for multiple coronary artery narrowing and ischemia (45). Many of these patients are young, and extended internal thoracic artery bypass grafting is a better alternative than vein grafts, both for long-term patency and for reduction of late cardiac death. Excision of coronary artery aneurysms is rarely indicated.

Physical features in Kawasaki's disease. These are capillary hemangiomas (*yellow arrow*).

Video 82.11 Aneurysmal atherosclerotic disease involving the left main trunk, proximal left anterior descending artery, and proximal left circumflex artery in a 72-year-old male patient with a long history of smoking. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Reduced Left Ventricular Function

Poor left ventricular function is defined as a left ventricular ejection fraction of less than 0.30. Coronary bypass surgery may be indicated when such patients have angina or demonstrable ischemia coupled with critical lesions and bypassable vessels (46,47). Reversal of hibernating myocardium may be dramatic with adequate revascularization. Patients with heart failure only and poor ventricular function are rarely candidates for isolated revascularization, although selected patients may require bypass combined with ventricular aneurysmectomy. In addition to the clinical presentation, coronary pathoanatomy, and evidence of ischemia, identification of myocardial viability is important in assessing surgical candidacy of patients with impaired left ventricular function. Between 25% and 40% of patients with coronary atherosclerosis and left ventricular global dysfunction show improved contraction after revascularization. The physiologic markers used to demonstrate contractile reserve include positron emission tomographic imaging in which enhanced fluorine 18-fluorodeoxyglucose is measured relative to myocardial blood flow, thallium single-photon emission computed tomography, and dobutamine echocardiography. Each method has its proponents (see Chapter 47, Chapter 50, and Chapter 52) (48).



Hemorrhage after left main infarct (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Cardiac transplantation is reserved for younger patients who cannot be helped by catheter interventions or coronary bypass surgery. Dynamic cardiomyoplasty may be an option for patients with contraindications to transplantation (49). In cardiomyoplasty, the pedicled latissimus dorsi muscle flap is mobilized into the chest and wrapped around the ventricles of the failing heart (50). The muscle is stimulated electrically to contract synchronously with the heart. Dynamic cardiomyoplasty is still controversial, because the clinical improvement tends to be greater than the improvement in hemodynamic parameters. To date, left ventricular ejection fraction improvement has been slight (51). Only a few centers perform this operation.

Peripheral and Cerebrovascular Disease

Peripheral and cerebrovascular disease is common in patients with coronary atherosclerosis. In the evaluation of patients with peripheral atherosclerosis, history of prior myocardial infarction, congestive heart failure, angina, and age older than 70 years predicts presence or absence of coronary atherosclerosis with 94% to 96% accuracy (52). Conversely, severe carotid artery stenosis with or without neurologic symptoms is found in approximately 6% of coronary patients (53). Most reports on the efficacy of carotid endarterectomy do not take into context the occurrence of simultaneous carotid and coronary atherosclerosis. The North American Symptomatic Carotid Endarterectomy Trial found that when carotid stenosis was greater than 70% in patients who had already experienced either transient ischemic attacks or minor strokes with good functional recovery, carotid endarterectomy reduced the stroke rate by 75% over 2 to 3 years compared with nonsurgical treatment (54). Moderate symptomatic carotid stenosis is generally not treated surgically unless the patient has neurologic symptoms attributed to microemboli from an ulcerated plaque despite antiplatelet therapy (55). The Asymptomatic Carotid Atherosclerosis Study concluded that asymptomatic patients with internal carotid narrowing of more than 60% had stroke reduction after carotid endarterectomy (56). This was the first trial to reach that conclusion in asymptomatic patients.

Severe left internal carotid artery stenosis in a 67-year-old male patient with transient ischemic attacks (A) and after implantation of a self-expanding stent (B).

Doppler ultrasound (duplex) scans are used to evaluate asymptomatic cervical bruits. Angiography is reserved for those who have severe carotid stenosis, regardless of symptomatology. There are no randomized clinical studies identifying the optimal strategy for combined coronary and carotid disease. Retrospective clinical data support a strategy of combined coronary artery bypass grafting and carotid endarterectomy in two groups of patients, those with symptomatic and severe disease in both systems and those with symptomatic carotid disease and severe coronary artery disease (57,58 and 59). The approach to patients with severe coronary artery disease and asymptomatic carotid stenosis is controversial (59). Although some authors support a combined procedure in those with coronary artery disease and asymptomatic carotid stenosis of 80% or more (60,61), analysis of the available literature neither supports nor refutes this strategy (62). This subset of patients awaits randomized controlled studies to guide treatment recommendations. Pending such studies, most patients with severe asymptomatic carotid lesions are treated by staged surgical procedures.

Combined coronary artery bypass grafting and carotid endarterectomy is associated with 5% mortality and 5% stroke risk (57,58,63). These risks are higher than for either procedure alone (52). There is evidence, however, that in properly selected patients, this strategy is superior to a staged approach (57,61).

Recently, angioplasty and stenting of internal carotid stenosis have been reported. Primary stenting appears more reliable than angioplasty alone. The University of Alabama (63) reported good reduction of stenosis in 126 stents deployed in 107 patients. There were two major and seven minor strokes, one death, and a 5% recurrence rate in asymptomatic patients at 6 months. Other groups have documented similar clinical results (64,65 and 66). Furthermore, the feasibility of safe carotid stenting in patients with cardiac disease has been demonstrated (67). Because carotid stenting generally requires days to weeks of postprocedure platelet inhibitors, the strategy of carotid stenting before cardiac surgery may necessitate a delay in the treatment of the cardiac lesions. Trials comparing elective endarterectomy and stenting for symptomatic stenosis will define the role of carotid stenting in patients with carotid artery stenosis.

Radiation-Induced Atherosclerosis

In the absence of conventional risk factors, mediastinal irradiation may lead to aortic and coronary atherosclerosis and cardiac valve disease. In one report, the prevalence was 33 of 16,364 patients over a 6-year period (68). The great majority was radiated for lymphoma. The mean interval between radiation and cardiac surgery was 14 years. Pericarditis may be encountered. Calcifications of the aorta, aortic valve, and proximal coronary arteries are generally found, and radiation may damage the internal thoracic arteries. Ostial stenosis and proximal arterial calcification may require bypass surgery. Wound healing may be jeopardized, perhaps because of obliteration of lymphatic channels and effects on sternal blood supply. Despite higher risk, coronary artery surgery is not contraindicated in patients with mediastinal irradiation, and outcome of revascularization is satisfactory.

Valve Disease

Concomitant valve disease most frequently combines aortic stenosis with multivessel coronary atherosclerosis. In men, the surgical risk (1% to 2%) is approximately the same as for isolated valve replacement. However, for elderly women the risk is higher. Except in patients younger than 40 years of age who have no history of coronary artery disease, coronary arteriography is indicated for patients undergoing evaluation for valve surgery. The absence of angina does not exclude coronary atherosclerosis. Almost all aortic valve lesions are treated with valve replacement, and most cases of mitral regurgitation are treated by mitral valve repair, which carries a lower surgical risk than mitral valve replacement (69).

Advanced age, female gender, elevated creatinine, advanced New York Heart Association class, moderate to severe left ventricular dysfunction, mitral regurgitation, extensive coronary atherosclerosis, severe cardiac rhythm disorders, and prolonged intraoperative ischemia are the most important predictors of adverse clinical outcome of combined valve operation and coronary artery bypass grafting (70). Reoperative valve replacement after previous coronary artery surgery is fraught with higher hospital mortality than either primary or reoperative coronary artery surgery. Therefore, it has been suggested that liberal criteria for selection be used for valve repair or replacement in those undergoing myocardial revascularization for the first time (71).

Coronary Reoperation

Reoperation may be required for recurring symptoms (ischemia) and angiographic evidence of vein graft atherosclerosis, progressive coronary atherosclerosis, or both. Late stenosis in an anterior descending vein graft predicts a higher death and event rate than late stenosis in vein grafts to other coronary arteries and is an indication for further revascularization (Fig. 82.2) (72). For appropriately selected patients, coronary artery reoperation offers improved longevity compared with medical treatment (73).

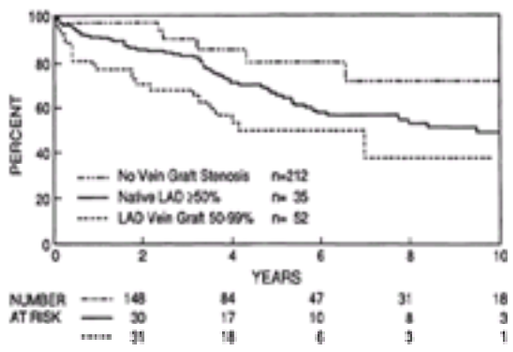


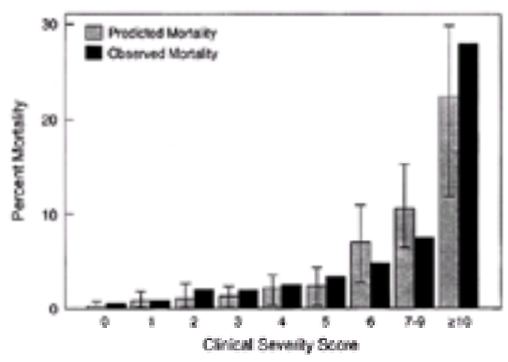
FIGURE 82.2 Patients with late stenoses and vein grafts to the anterior descending coronary artery have worse survival compared to that of either patients with native coronary anterior descending or patients with no stenotic vein grafts. LAD, left anterior descending. (From Lytle BW, Loop FD, Taylor PC, et al. Vein graft disease: the clinical impact of stenoses in saphenous vein bypass grafts to coronary arteries. *J Thorac Cardiovasc Surg* 1992;103:831–840, with permission.)

In the presence of severe diffuse coronary atherosclerosis, most patients with vein graft atherosclerosis are better served by reoperation than by catheter interventions. The exceptions are fibrous lesions or intimal hyperplasia causing graft stenosis that occurs within 18 to 36 months after the first operation. In selected cases, an isolated vein graft with a discrete lesion may be well suited for percutaneous revascularization. In general, however, angioplasty of saphenous vein grafts with or without stenting has a high rate of complications and unsatisfactory late results (74,75).

The method of revascularization hinges on the age of the graft, the location of the stenosis, the status of left ventricular performance, and overall clinical characteristics. After coronary artery surgery, four arteriographic situations warrant consideration for angioplasty or stenting: (a) progressive atherosclerosis in nonbypassed major coronary arteries when bypass grafts to other major vessels are patent; (b) distal anastomotic stricture that is less than 3 years old; (c) saphenous vein graft lesions less than 3 years old; and (d) native vessel narrowing distal to an open graft accessible via a fully patent, nondiseased graft (76). Angioplasty or stenting of early vein graft lesions or for progressive coronary artery stenoses is more successful than intraluminal dilatation of late vein graft atherosclerosis.

Risk Assessment

Preoperative risk scoring is based on clinical, angiographic, and surgical data. The scoring methodologies are more predictive of mortality than of morbidity (eFig. 82.2.1) (77). The risk factors for hospital mortality are generally considered to be advanced age, emergency surgery, elevated serum creatinine level, left main coronary artery disease, female gender, anemia, and moderate to severe left ventricular dysfunction (78,79 and 80). Adjusted for comorbid conditions, advanced age is associated with a greater risk of procedural death and complications with both coronary artery surgery and catheter-based revascularization.



***e*FIGURE 82.2.1** Clinical and angiographic risk variables are weighted by a logistic regression formula and stratified from low risk through high risk. This clinical severity score predicts mortality by the preoperative variables. This severity score ranges from 0 (lowest risk) to 10 or more (highest risk). The actual predicted and observed mortalities are shown in the bar graphs. (From Higgins TL, Estafanous FG, Loop FD, et al. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients: a clinical severity score. *JAMA* 1992;267:2344–2348, with permission.)

Smaller body size, more typical of women, is associated with increased operative mortality (81,82). Women, as bypass candidates, also tend to be older than men as bypass candidates and thus have more comorbidity. Because of generally smaller size, their coronary arteries frequently have narrower diameter. Most reports indicate women have more extensive coronary atherosclerosis but overall better preoperative left ventricular function. After adjusting for preoperative risk factors and body size, technical factors, inadequate myocardial protection, and lack of internal thoracic artery grafting contribute to higher risk in women (83) and may explain why gender remains an independent risk factor for operative mortality and low-output syndrome (84). There is recent evidence that bypass surgery mortality for women is decreasing compared with earlier reports (85).

The risk of stroke for patients who undergo cardiac surgery can also be estimated. A stroke risk index has been developed using the variables of age, history of neurologic disease, diabetes, history of vascular disease, previous coronary artery surgery, unstable angina, and history of pulmonary disease. Carotid occlusion, with or without contralateral stenosis, may be another risk factor. Of these clinical characteristics, previous stroke, vascular disease, and diabetes have the most weighted importance (86).

Prediction of risk is more complicated than simple preoperative assessment. Risk changes in response to surgery. The preoperative risk score may be affected by the type and conduct of surgery, including the volume of blood transfusion, cardiopulmonary bypass time, the type of myocardial protection, conduits used, and whether an intraaortic balloon pump is required (87). Rescoring of risk after admission to the postoperative intensive care unit indicates that two-thirds of preoperative high-risk patients are converted to low risk and 95% of those stratified in the low-risk category preoperatively remain classified as low risk in the immediate postoperative period. The contribution of the preoperative clinical and angiographic characteristics, the operating room events, and the physiologic measurements at intensive care unit admission converge postoperatively and change the predicted outcome.

Estafanous and colleagues from The Cleveland Clinic Foundation found that the prevalence of high-risk patients is increasing, and yet the surgical morbidity adjusted for preoperative risk score has fallen in the last 10 years (88). These findings are likely attributable to better myocardial protection and wider use of arterial bypass grafts.

SURGICAL PRINCIPLES

Basic Strategies

The design of the operation is based on estimated risk and a review of revascularization techniques, including availability and type of bypass conduit. The objective is to provide safe, durable, and complete revascularization with a low probability of complications. Same-day admission is safe and cost-effective and avoids at least 1 day of hospitalization (89,90). Patients may continue on beta-blockers, calcium channel blockers, antihypertensives, and nitrate therapy until the day of surgery. Aspirin should be discontinued 7 to 10 days before elective surgery. We use pulmonary artery catheters in all patients (approximately $35 total cost) to monitor hemodynamic changes and to facilitate management. An increasing number of patients have heparin-induced platelet antibodies preoperatively due to prior heparin exposure (91). These patients are at risk for thrombotic complications with additional heparin exposure.

Blood Conservation

A blood conservation protocol is important to reduce transfusion requirements and decrease the incidence of transfusion-induced complications (92). Red cell volume and patient age are the best predictors of the need for transfusion. Hematocrit levels of 20% to 25% are tolerated in young, good-risk patients intraoperatively and

postoperatively. However, in patients with impaired left ventricular function, older age, and serious preoperative comorbidities, target hematocrit levels of 28% to 30% allow better perfusion pressure and hemodynamic stability (93). As the population of surgical candidates ages, with attendant comorbidities, transfusion requirements rise.

Most intraoperative and postoperative bleeding is directly related to the surgery, but causes of bleeding are often multifactorial and relate to the use of antiplatelet drugs preoperatively, prolonged operating time, the number of transfusions of blood and blood products, previous cardiac surgery, and, very infrequently, a preoperative coagulopathy. Aspirin is associated with increased incidence of postoperative bleeding, increased use of blood and blood products, and longer intensive care unit hospitalization (94). Aspirin should be discontinued in advance, but this is not always possible in emergency situations.

Aprotinin is an effective drug for reduction of bleeding; however, there is controversy about vein graft thrombosis and increased risk of myocardial infarction (95,96). Anaphylactic reactions to aprotinin, which are infrequent, may be reduced by (a) giving a test dose (10,000 KIU) in all aprotinin patients; (b) delaying the first dose until onset of cardiopulmonary bypass; (c) prescribing H_1/H_2 blockade in reexposures; and (d) avoiding reexposure for at least 6 months (97). Preoperative and intraoperative administration of epsilon-aminocaproic acid has been reported to reduce postoperative cardiac surgical bleeding (98,99), and the cost of approximately $3 to $5 per case is small compared with $900 to $1,200 for aprotinin. Fibrin sealant has been used, largely in Europe, for small bleeding points. More than 2,000 clinical papers on its use in approximately 1 million patients attest to its safety (100).

Myocardial Protection

Current cardioprotective methods include core cooling, antegrade and retrograde cardioplegia, and continuous retrograde warm blood cardioplegia. Chemical cardioplegia initiates potassium arrest. Blood cardioplegia delivers oxygen; causes less systemic hemodilution; and provides endogenous buffers, free radical scavengers, and proteins for controlling oncotic pressure (101). Retrograde cardioplegia delivery through the coronary sinus is useful in patients with totally obstructed vessels, in patients with diffuse coronary atherosclerosis, and in reoperation cases with patent but atherosclerotic vein grafts or patent internal thoracic artery grafts.

A combination of antegrade and retrograde cardioplegia, cold or warm, provides the optimum cardioplegic distribution. Because aortic atheroma is predictive of cerebrovascular events, a single cross-clamp technique, which involves less manipulation of the ascending aorta, may reduce the stroke rate (102). Controlled reperfusion techniques of antegrade and retrograde cardioplegia using warm amino acid–enriched blood cardioplegia, combined with total vented cardiopulmonary bypass, have reduced mortality in cardiogenic shock (36). The method of reperfusion may be more important than the interval between occlusion and reperfusion. Blood cardioplegia has been correlated with a reduction of morbid events, shorter intensive care unit stay, shorter hospitalization, and reduced hospital cost (103).

Future cardioprotective strategies will be directed to the vascular endothelium rather than the myocyte. Endothelium-derived nitric oxide may prevent vasospasm and thrombus formation through its vasodilator and antiaggregant properties (104). Nitric oxide may protect against cell damage during ischemia/reperfusion by blocking hydroxyl radicals and terminating free radical chain reactions within the lipid membrane (105).

Conduits in Coronary Bypass Surgery

Vein grafts develop endothelial proliferation as soon as they are placed in arterial circulation and after a few years tend to develop atherosclerosis with thrombus formation. Low- or regular-dose aspirin therapy may prevent platelet thrombi, the release of platelet mediators, and consequent platelet aggregation in vein grafts (106). Dipyridamole has antithrombotic and vasodilating capabilities, but the addition of dipyridamole to aspirin does not improve vein graft patency (107). Also, compared with aspirin, oral anticoagulants do not improve patency. Aspirin that is begun early postoperatively and continued indefinitely does not prevent atheroma formation. Reports on serial postoperative angiograms from Montreal (108) and from The Cleveland Clinic (109) are complemented by an angiographic investigation of 1,388 Canadian military personnel operated on in the 1970s (110), in which approximately 5,000 bypass grafts were reexamined by angiography at 1 year, 5 years, and 15 years or more after surgery. These latter results are the latest available and concur with the classic studies from Montreal and Cleveland. Vein graft patency was 88% early and 81%, 75%, and 50% at 1, 5, and 15 years or more. Approximately half of the grafts showed luminal defects at 5 years, and 81% had lumen irregularities at 15 years or more (Fig. 82.3).

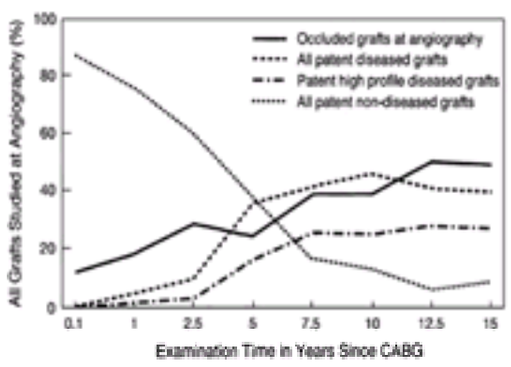


FIGURE 82.3 The latest and longest serial study of aortocoronary vein grafts has classified vein grafts through angiographic findings. High-profile lumen irregularities are defined as more than 59% graft stenosis. Note that the rate of vein graft occlusion progresses after 25 years. Vein graft occlusion rate was 2.1% per year after the first postoperative study. CABG, coronary artery bypass surgery. (From Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary bypass graft fate and patient outcome: angiographic follow up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol* 1996;28:616–626, with permission.)

Vein graft atherosclerosis is characterized by diffuse involvement of the venous conduit, circumferential atheroma instability, and fragility (111). Vein graft atherosclerosis begins as a deposition of foam cells followed by plaque formation that varies in extent of fibrosis, lipid deposition, thrombosis, and even calcification. Late thrombosis is a frequent cause of graft closure and may form slowly or suddenly after plaque rupture (112).

In diffuse native-vessel atherosclerosis wherein the artery is completely obstructed or exhibits diffuse distal involvement, coronary endarterectomy may be performed to improve arterial runoff (113,114). Endarterectomy is rarely successful in small arteries that have been completely occluded for a long time. Anterior descending endarterectomy requires an extended arteriotomy to clean out all side branches, whereas a right coronary endarterectomy is accomplished by a distal arteriotomy and dissection of the plaque from the two main branches. It is generally concluded that there is a higher rate of perioperative infarction after endarterectomy and that vein graft patency is slightly lower in endarterectomized arteries.

In the past 15 years, the internal thoracic artery graft has displaced the saphenous vein graft as the conduit of choice. There are three reasons for this change: (a) lower hospital mortality (115), (b) higher long-term patency rate (116), and (c) favorable effect on longevity (116,117). Even in patients with diffuse multisystem atherosclerosis, the internal thoracic artery is rarely affected by atherosclerosis. Metabolism in the arterial wall confers immunity compared with the more inert saphenous vein, which is prone to atherosclerotic degeneration. Coronary arteries narrowed an estimated 50% or more may be grafted with an internal thoracic artery; progression of the proximal native lesion is less after internal thoracic artery grafting than with vein grafts (118). This conduit used in young patients with Kawasaki disease has also shown growth on serial angiography (119). Competitive flow from a major coronary artery not critically narrowed may account for the infrequent internal thoracic artery “string sign” (120) on postoperative angiograms. Whether an internal thoracic artery graft with this diffuse narrowing will progress to subsequent graft closure or reopen later is not known. However, this no-flow situation was reexamined by temporary occlusion of the recipient coronary artery with a percutaneous transluminal coronary angioplasty balloon (121). The internal thoracic artery with a demonstrable string sign reopened, showing anatomic patency. Therefore, it appears that the string sign may be a reaction to reduced demand and not an intrinsic problem.

Whenever feasible, the internal thoracic artery should be the conduit of choice for anterior descending and other major arteries that supply large regions of myocardium (117,122). This recommendation is particularly important for the anterior descending artery, because severe proximal stenosis in this vessel has greater prognostic importance than stenoses elsewhere in major coronary arteries except for the left main coronary artery (123).

The relative contraindications for use of internal thoracic artery grafts include radiation-induced atherosclerosis, extensive brachiocephalic atherosclerosis, reoperation in patients who have patent large-diameter atherosclerotic vein grafts (replacement of which by a smaller-diameter internal thoracic artery may result in hypoperfusion) (124), and some unusually high-risk situations such as emergency surgery after resuscitation or other instances of cardiogenic shock. In our experience, emphysema does not constitute an absolute contraindication. In these cases of overinflated lungs, free (aortocoronary) internal thoracic grafts may be

used instead of *in situ* grafts.

The internal thoracic artery used for anterior descending grafting has consistently shown patency of greater than 90% 10 to 15 years postoperatively. Early anastomotic stenosis may be treated by angioplasty with good results (125). Late occlusions occur infrequently from progressive native-vessel atherosclerosis beyond the distal anastomosis. Rarely, a subclavian steal may occur when the proximal subclavian artery narrows or occludes proximally and blood flows from the coronary circulation retrograde through the internal thoracic artery into the distal subclavian distribution.

Increasing use of bilateral internal thoracic artery grafts has expanded arterial grafting further. Free (126), sequential, and Y or T grafts (127) increase versatility by extending graft length and by avoiding the crossing of the midline. Long-term patency of free grafts is 69% to 77%, whereas patencies of sequential and Y or T grafts are consistently 90% or greater. One series of free grafts demonstrated a 95% patency in 40 free right internal thoracic artery grafts studied an average of 40 months postoperatively (128). A study of more than 10,000 patients having primary coronary artery bypass grafting at The Cleveland Clinic has demonstrated that two internal thoracic arteries are better than one (129). This study concluded that patients who received two internal thoracic artery grafts had decreased risks of death, reoperation, and angioplasty. Although this result held for all patient subgroups, further analysis revealed that in high-risk patients, the benefit of two internal thoracic artery grafts on freedom from intervention was eroded considerably by death (130). The conclusions of these large studies support the use of bilateral internal thoracic artery grafting in most patients having primary coronary artery bypass grafting.

Some of the previous concerns about infection related to internal thoracic artery grafting have been dispelled by better techniques of internal thoracic artery dissection and wound closure. Bilateral internal thoracic artery grafting is still associated with a higher wound infection rate in diabetic patients (131). Nevertheless, the sternal blood supply in patients with diabetes is not reduced, compared with nondiabetics. Wound complications may be minimized by good surgical techniques, including a minimum of electrocautery, short operating time, blood conservation, and meticulous wound closure. Diabetes is not a contraindication to use one or both internal thoracic arteries as bypass grafts.

The gastroepiploic artery (Fig. 82.4A) may be used for revascularization of right coronary artery branches and, less frequently, the circumflex branches or the anterior descending (132,133). In addition, using the gastroepiploic artery as a composite graft by attaching it to a segment of radial artery allows grafting of two or three coronary arteries with gastroepiploic inflow (134). Previous laparotomy and severe obesity complicate procurement of this artery. The patency reported from the largest series is 80% at 5 years and 62% at 10 years (135). Once the gastroepiploic artery is perfectly anastomosed to a coronary artery with tight proximal stenosis and good runoff, late patency is good and new stenosis in both the gastroepiploic artery trunk and the anastomotic site was uncommon. The severity of the stenosis of the target artery should be high because retrograde coronary artery–to–gastroepiploic artery flow may occur if the native vessel narrowing is modest.

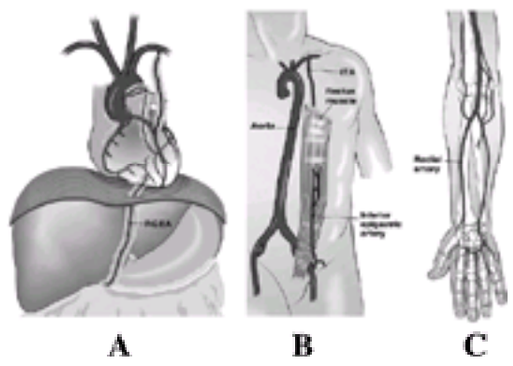


FIGURE 82.4 A: The gastroepiploic artery is mobilized from the greater curvature of the stomach and generally brought anterior to the liver through the diaphragm and grafted to one of the two branches of the right coronary artery. The conduit is small and prone to spasm. Using it to graft a large coronary artery may result in hypoperfusion. **B:** The inferior epigastric artery lies behind each rectus muscle and is removed through a midline incision. This conduit is used infrequently today but may be advantageous as a Y graft sewn proximally to an arterial conduit and distally to a secondary target. **C:** The radial artery is removed with its venae comitantes. Today, it is the second arterial graft of choice after both internal thoracic arteries, and it may be used as an aortocoronary graft or attached as a Y graft. ITA, internal thoracic artery; RGEA, right gastroepiploic artery.

The inferior epigastric artery (Fig. 82.4B), generally 10 to 12 cm in length, is located behind the rectus muscle. This artery is generally used as a Y or T graft and is often connected to secondary targets such as branch vessels (136). The intermediate-term patency of the inferior epigastric artery graft is lower (75%) than that reported for pedicled internal thoracic artery grafts. Today, it is probably the least frequently used arterial conduit (137).

The radial artery (Fig. 82.4C) has enjoyed widespread resurgence after early reports that showed a high incidence of spasm leading to focal intimal hyperplasia (138,139). Improved results in the current era have been attributed to improved harvesting technique and use of calcium channel blockers or other vasodilators to prevent perioperative spasm of the graft (139). Patients with radial artery grafts are treated today with calcium antagonists and postoperative use of aspirin. Dihydropyridine calcium antagonists are most effective at reducing radial artery spasm (140,141). Preoperative noninvasive assessment of forearm collateral flow may be accomplished by a modified Allen test, pulse volume recordings, oximetric plethysmography with calculated perfusion index, and Doppler scanning. Most agree that a modified Allen test and calculation of perfusion index suffice. Procurement is performed delicately to avoid damage of the intima, which may suffer focal endothelial damage (142). For patients undergoing unilateral radial artery procurement, the contralateral extremity is used for intravenous and arterial monitoring lines. When bilateral radial arteries are harvested, left femoral or axillary arterial lines are placed for monitoring. Intravenous nitroglycerin or calcium channel blockers are administered intraoperatively. Postoperatively, oral nitrates or calcium channel blockers are administered for 6 months or longer.

Radial artery patency is reported to be 94% at 9 months (143). Five-year patency has been reported to be 84% to 92% (144,145). Given these encouraging results, some groups have recommended performing multiple distal anastomoses with the radial artery to increase the number of arterial bypasses (146,147 and 148). Although intermediate-term results support a role for the radial artery in coronary artery bypass operations, it is premature to conclude that this conduit is equivalent to a second internal mammary artery.

REOPERATION

A number of factors influence the rate of reoperation; the single greatest determinant is the type of conduit used in the first operation. Patients with only vein grafts have a much higher and earlier reoperation rate than do patients with one or more arterial grafts. Other factors that increase the probability of reoperation include young age at the first operation, incomplete revascularization, one- or two-vessel grafting initially, and good left ventricular function. Young age, less extensive coronary disease, and normal ventricular function are markers of a good prognosis, which allows the patient to survive to eventual reoperation. The cumulative incidence of reoperation was 3% 5 years after the original surgery, 10% at 10 years, and 30% at 15 years (149).

In the past 10 years, the evolution of catheter intervention techniques has reduced the number of reoperation candidates, although the effects of angioplasty, atherectomy, and stents are not fully elucidated. Patients who are protected by patent grafts but who require native-vessel dilatation or early catheter manipulation after the original bypass operation tend to be referred for catheter intervention, whereas patients at higher risk with diffuse graft atherosclerosis or compromised left ventricular function tend to be referred for surgery rather than for angioplasty (150).

The most frequent indication for reoperation is vein graft atherosclerosis. Atherosclerosis in an anterior descending saphenous vein graft is associated with a particularly poor prognosis (72). We recommend strong consideration for reoperation in those cases. Lesions in old saphenous vein grafts are friable and are not treated consistently well by catheter intervention techniques; the restenosis rate is upward of 50% to 70%. Stenting probably results in less restenosis than does angioplasty, but stent implantation in vein grafts has not been associated with a particularly good 5-year clinical outcome, with high event rates due to infarction, repeat surgery, and repeat angioplasty (151,152). Directional, rotational, and transluminal extraction catheter atherectomy used in atherosclerotic vein grafts have been shown to cause more distal embolization than conventional angioplasty (153).

The hospital mortality for second operations is less than 5% in centers reporting large series (149,154). Emergency surgery, poor left ventricular performance, older age, and female gender influence higher in-hospital mortality. Manipulation of old vein grafts at reoperation may cause atheroembolism and myocardial infarction. Ideally, vein grafts should be replaced with arterial grafts; however, there is a risk of hypoperfusion when large patent but atherosclerotic vein grafts are replaced with *in situ* internal thoracic artery grafts. Adequacy of perfusion depends on the size of the vessel and the arterial runoff and the size of the left ventricular region perfused. In older patients, re-replacement with saphenous veins generally suffices, but younger patients should have every consideration for arterial grafting for the most critical areas of ischemia. The use of an internal thoracic artery graft at the first operation does not increase the risk of reoperation, and the use of an internal thoracic artery

graft at reoperation does not increase hospital mortality or morbidity (155).

TRANSMYOCARDIAL LASER REVASCULARIZATION

Transmyocardial laser revascularization (TMR) has been applied in patients with angina and ischemia who are not candidates for conventional revascularization techniques (156). The laser is used to create transmural channels in areas of critically ischemic tissue. Encouraging results have been reported from clinical trials using the carbon dioxide, holmium:YAG, and excimer lasers. The laser energy may be delivered to the heart via thoracotomy, thoracoscopy, or percutaneously.

VIDEO

Video 82.12 Intraoperative transesophageal echo of a patient undergoing laser transmyocardial revascularization. Note the gas production as the laser beam penetrates the myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

TMR is used solely for relief of intractable angina in patients who have failed or cannot undergo standard treatment. In several randomized trials, TMR combined with medical therapy has been shown to be superior to medical therapy alone for angina relief (157,158,159,160 and 161). These trials report similar results, with approximately 50% of TMR patients having important symptomatic improvement at 1 year. Other reported benefits include improved exercise tolerance, improved quality of life, and decrease in number of hospital admissions (157,160,161). Given these results, in August 1998 the U.S. Food and Drug Administration fully approved TMR for the sole treatment of patients with class III and IV chronic stable angina not treatable by conventional means.

TMR via thoracotomy is associated with important morbidity and mortality. Hospital mortality ranges from 1% to 9% (157,158,159,160,161 and 162). Morbidity occurs in 35% of patients (163). Morbidity and mortality are more common in patients with unstable angina (163). Therefore, TMR should be reserved for patients with disabling chronic stable angina. Although encouraging results have been reported, the efficacy and role of percutaneous laser therapy are not yet well defined (164).

TMR has also been used as an adjunct to coronary artery bypass grafting to treat ischemic myocardial regions lacking suitable targets for bypass grafting (165,166). Although the addition of TMR did not improve anginal class when compared with patients having bypass grafting alone, TMR was associated with a survival advantage in one trial (166). The reason for this is unclear, and this result requires confirmation by larger studies.

The mechanism for the improvement in angina with TMR is unclear. Both clinical and experimental work suggest that it is unlikely that the channels remain patent (167,168). Experimental models demonstrate that TMR causes increased myocardial expression of vascular endothelial growth factor (168,169). Most clinical studies, however, do not demonstrate important increases in myocardial perfusion, left ventricular function, or survival (158). Other possible mechanisms include a placebo effect, myocardial denervation, and infarction of ischemic myocardium. Further investigation will be necessary to define the precise mechanism for TMR.

In current practice, TMR is not an alternative to medical therapy, percutaneous intervention, or coronary artery bypass grafting. It is reserved for the small group of patients who cannot be treated successfully by the above means. Furthermore, it is used only for relief of chronic stable angina. It has not been demonstrated conclusively to improve ventricular function or longevity when compared with other therapies.

GENE THERAPY AND THERAPEUTIC ANGIOGENESIS

An alternative approach to inducing myocardial angiogenesis is direct myocardial injection of angiogenic genes or proteins. This approach is currently under investigation as treatment for patients with severe coronary artery disease who are unsuitable for medical therapy or traditional techniques for revascularization (170,171). There is a growing body of experimental work to support the hypothesis that injection of the gene for vascular endothelial growth factor causes angiogenesis in ischemic myocardium (170,171 and 172).

Recent reports document the safety of gene therapy to treat myocardial ischemia in humans. Rosengart performed adenovirus-mediated transfer of human vascular endothelial growth factor cDNA in 21 patients with reversible myocardial ischemia (173). In this phase I study, gene therapy was used as an adjunct to coronary artery bypass grafting or as sole therapy via mini-thoracotomy. Coronary angiography and stress sestamibi scan 30 days after therapy suggested improved perfusion in the area of vector administration (173). At 6-month follow-up, there were trends toward improvement in anginal class and xercise treadmill testing (174). In another phase I trial, Symes and colleagues injected plasmid DNA encoding vascular endothelial growth factor into the myocardium of patients with coronary artery disease (175). They demonstrated improved perfusion, as documented by angiography and single-photon emission computerized tomography sestamibi scans. In that study, all patients reported reduced angina.

As with TMR, gene therapy for myocardial ischemia is currently a therapy only for patients who fail standard medical therapy and cannot have revascularization by conventional means. The intermediate and long-term efficacy of gene therapy remains unproven. Ongoing trials are likely to clarify the role of gene therapy and therapeutic angiogenesis in the treatment of coronary artery disease.

MINIMALLY INVASIVE CORONARY ARTERY BYPASS SURGERY

Off-Pump Coronary Artery Bypass Grafting

The most dramatic change in coronary artery surgery during the last decade has been the resurgence of coronary artery bypass grafting on the beating heart. Off-pump approaches to coronary artery bypass grafting seek to eliminate morbidity and mortality associated with cardiopulmonary bypass, hasten patient recovery, and reduce cost. Initial widespread use of off-pump techniques was limited to revascularization of the left anterior descending coronary artery using the left internal thoracic artery via a small left anterior thoracotomy, so-called minimally invasive direct coronary artery bypass grafting (MIDCAB). Although technically difficult, this procedure is feasible and provides optimal revascularization of the left anterior descending coronary artery. Early concerns over graft patency using this procedure have been answered, and early patency generally exceeds 95% (176,177,178 and 179). In addition, nonocclusive early angiographic abnormalities frequently disappear during the first postoperative year (176,179). Long-term patency with this approach is superior to that attained with angioplasty (180).

MIDCAB has been used in conjunction with percutaneous interventions to offer a hybrid approach to coronary revascularization (181,182,183,184 and 185). In this approach, the left internal thoracic artery is used to revascularize the left anterior descending coronary artery, and other stenotic vessels are treated by angioplasty with or without stenting. In most cases, surgery is performed first and percutaneous intervention follows in hours to days. Advantages to the patient include a small incision and no cardiopulmonary bypass. Although initial results with this strategy have been promising, its place in coronary revascularization remains to be defined.

Although there is no demonstrable benefit in survival with MIDCAB when compared with on-pump coronary artery bypass grafting, there is some suggestion that this approach may decrease morbidity in the most seriously ill patients (186). Postoperative atrial fibrillation remains a problem with this approach (187). Costs associated with MIDCAB are less than those for standard on-pump surgery and similar to those for percutaneous coronary interventions (188,189 and 190).

Technological improvements in coronary artery stabilization and surgical advances in coronary artery exposure have enabled widespread application of multivessel off-pump coronary artery bypass grafting. Using current techniques, virtually all patients are candidates for multivessel off-pump coronary artery bypass grafting. This procedure is performed through a sternotomy but without cardiopulmonary bypass. Aortic manipulation is limited to a single application of a clamp to perform proximal anastomoses. All coronary artery targets are accessible, and conduits used may include all arterial and venous grafts used for on-pump surgery.

As with MIDCAB, the question of anastomotic patency with multivessel off-pump coronary artery bypass grafting has been answered. Studies performed before the advent of modern coronary stabilizer platforms suggested reduced anastomotic quality (191). However, in a large prospective study that involved postoperative catheterization of all patients, Puskas et al. found graft patency after off-pump surgery comparable to that documented after on-pump surgery (192). Long-term patency results are not yet available, however.

Advances in anastomotic techniques are likely to reduce the difficulty of off-pump coronary artery bypass surgery, widening its appeal to surgeons and applicability to patients. Several companies have developed anastomotic coupling devices that replace standard suturing techniques. Use of such devices for distal anastomoses will reduce the difficulty of off-pump surgery. Application of such devices for proximal anastomoses will eliminate the need to place a clamp on the aorta;

this may further reduce neurologic morbidity associated with coronary artery bypass grafting.

Although there are suggestions that off-pump surgery reduces hospital mortality in the elderly and sick (193,194), a survival advantage to this approach remains speculative (195). Nevertheless, there are several advantages to multivessel off-pump coronary artery bypass grafting when compared with conventional on-pump surgery. These include decreased cardiac damage (196), decreased inotrope requirement (196), decreased blood loss (194,197), decreased inflammation and infection (198), and decreased hospital length of stay (194,199). Most important, there appears to be decreased neurologic damage, as demonstrated by decreased cerebral edema (200), decreased cerebral microemboli (201,202), decreased serum S-100 protein (202), and decreased neurocognitive dysfunction (202). Nearly all patients experience some neurocognitive dysfunction after cardiopulmonary bypass. Occasionally, patients develop a temporary confusional state, termed “pump head.” Reduction of neurologic insults, coupled with the other aforementioned advantages, tends to result in reduced hospital costs for off-pump surgery as compared with on-pump surgery (188,203). However, atrial fibrillation still occurs with high frequency after off-pump surgery (204).

Port-Access Coronary Artery Bypass Grafting

An alternate approach to multivessel coronary artery revascularization is the port-access technique. This operation, which relies on cardiopulmonary bypass, entails a small left thoracotomy through which all coronary targets are accessible. Arterial return for cardiopulmonary bypass is attained by cannulation of the aorta or femoral artery.

Results with this approach have been comparable to those obtained using a median sternotomy and cardiopulmonary bypass (205,206,207,208 and 209). Although there may be some benefit in terms of reduced postoperative atrial fibrillation with the port-access technique (206), this remains controversial (202). The need for additional instrumentation and disposable products increases the cost of this approach by $2,000 (209). Because cardiopulmonary bypass is still used, there is some question as to whether port-access surgery is truly minimally invasive. In current practice, off-pump surgery has emerged as the preferred less-invasive surgical approach to multivessel coronary artery disease.

Endoscopic and Robotic Coronary Artery Bypass

A truly minimally invasive approach to coronary artery bypass grafting will entail a combination of endoscopic visualization, off-pump techniques, and robotic assistance. Robotically assisted endoscopic coronary artery bypass grafting has been performed in humans (210,211). Thus far, these operations require cardiopulmonary bypass. Even with cardiopulmonary bypass, these operations are technically demanding and time-consuming. Development of sutureless anastomotic techniques will greatly facilitate these efforts (212). The applicability of robotically assisted endoscopic coronary artery bypass grafting in patients with multivessel disease remains to be demonstrated.

HOSPITAL RESULTS OF CONVENTIONAL CORONARY ARTERY BYPASS SURGERY

Mortality and Morbidity

Hospital mortality varies from 1% or less in good-risk patients to approximately 5% overall in the elderly or infirm. High-risk subsets exist with mortality up to 15% to 30%, but these cases are few in number and generally are associated with cardiogenic shock or extensive, combined reoperative cardiac reconstruction and coronary bypass surgery.

Preoperative factors that prolong length of hospitalization include reoperation, combined coronary plus valve surgery, congestive heart failure, prolonged intensive care unit stay, renal failure, and insulin-dependent diabetes mellitus. Postoperatively, major complications that prolong hospitalization include perioperative myocardial infarction, bleeding requiring reoperation, respiratory insufficiency, wound infection, stroke, and renal failure. Patients who experience one or more complications have up to 10 times greater probability of mortality compared with those who sustain no complications. Patients who develop the complications of wound infection, pneumonia, respiratory insufficiency, and arrhythmias tend to remain hospitalized the longest (213).

Lower-risk patients may qualify for a fast track, with the objective of reducing cost through shorter length of stay. These patients are mobilized quickly, treated aggressively with diuretics, and started in rehabilitation early. Discharge planning is begun immediately on discharge from the recovery area or intensive care unit (214).

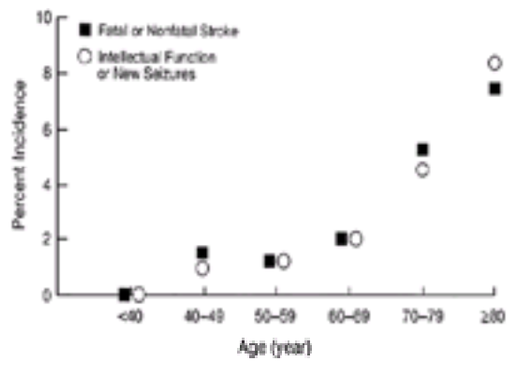
Today, perioperative myocardial infarction is infrequent. Most patients who have new Q waves along with cardiac enzyme elevation do not exhibit hemodynamic instability. The perioperative infarction rate averages 2% to 5%; the intermediate-term course of those who sustain myocardial damage is essentially the same as that of those without myocardial infarction, and the subset in which infarction affects outcome involves those who require intraaortic balloon pumping.

Balloon counterpulsation—the most frequently used form of mechanical circulatory-assist device—acts by augmenting diastolic aortic pressure and coronary blood flow while reducing the resistance (afterload) against which the heart must pump. Intraaortic balloon pumping is used in 1% to 5% of coronary bypass patients, most frequently in emergency cases and in patients requiring combined coronary artery and valvular procedures. Indications are preoperative ischemia and postoperative left ventricular failure (low cardiac output and high filling pressures). Cardiogenic shock refractory to intraaortic balloon pumping may require a ventricular-assist device. Patient selection is important, and even under the best circumstances, overall mortality in patients requiring left ventricular–assist devices for postcardiotomy cardiogenic shock is 25% to 50%. Younger patients with no underlying preoperative comorbidity and isolated left ventricular failure are the best candidates. These patients should qualify for heart transplantation if cardiac failure is not reversible.

Postoperative bleeding is most frequently surgical in origin (i.e., one or more bleeding points related to the operation). Aspirin in the immediate preoperative period is associated with a higher postoperative bleeding rate. Certain drugs such as aprotinin and epsilon-aminocaproic acid decrease postoperative bleeding. Reexploration for bleeding is an independent risk factor for mortality, renal failure, respiratory distress syndrome, sepsis, and atrial arrhythmias, and it is especially dangerous in those who have undergone complex procedures, including reoperations (215).

Wound infections are classified as superficial or deep. Deep intrathoracic or mediastinal infections are life-threatening. Most deep infections are detected during the first 10 days but may occur as late as 6 weeks postoperatively. Treatment involves sternal and mediastinal débridement, drainage, and either primary closure or rotational muscle flaps to fill any sternal defect. These infections are often associated with generalized sepsis and other complications and are fatal in 10% to 30%. Wound infections increase hospital costs more often than any other nonfatal complication because of protracted hospitalization. The infection rate in most centers ranges from a fraction of 1% to approximately 5% and depends on preoperative risk factors and length and type of operation.

Stroke is most frequently attributed to atheroemboli arising from the ascending aorta (216). The incidence of detected aortic atheromas rises with advancing age. In fact, patients who have a history of unexplained embolic events should have transesophageal echocardiography, magnetic resonance imaging, or computed tomographic scanning to evaluate the thoracic aorta (217). A multicenter study reviewed adverse neurologic outcomes after coronary artery surgery. Overall, the stroke rate was 6.1% (*e*Fig. 82.4.1) (218). Predictors of major stroke (focal injury, stupor, or coma at discharge) were proximal aortic atherosclerosis, history of neurologic disease, and older age. Other defined stroke (deterioration in intellectual function, memory deficit, and seizures) occurred more frequently with older age, systolic hypertension, pulmonary disease, and excessive use of alcohol. Stroke tends to occur more often in patients with a previously documented stroke.



***e*FIGURE 82.4.1** Incidence of different types of neurologic deficits occurring after coronary artery surgery according to age of patient. (Data from Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. *N Engl J Med* 1996;335:1857–1863.)

Atrial fibrillation is the most frequent minor postoperative complication. The prevalence of preoperative atrial arrhythmia is approximately the same for men and women but does increase with advancing age (219): Approximately 30% of patients aged 65 to 74 and approximately 45% of those older than age 75 years develop postoperative atrial fibrillation. Most patients are returned to sinus rhythm by chemical or electrical cardioversion.

The majority of patients with postoperative renal dysfunction has underlying renal disease, and most have preoperative elevation of serum creatinine. The common denominator is postoperative cardiac instability, often low cardiac output. Every effort should be made to maintain stable hemodynamics and adequate renal perfusion in the perioperative period. Progressive liver dysfunction combined with renal failure portends a uniformly poor prognosis.

Infrequent complications include the following. Peripheral nerve trauma may result from compression of the brachial plexus between the clavicle and the first rib and involve the median nerve. Horner's syndrome may result from first rib fracture. Infarction of the bowel tends to occur with multisystem failure and is associated with high mortality. Acute cholecystitis is coincidental and rare and may require cholecystectomy. Pancreatitis is also rare but may occur, especially in patients with low cardiac output, in those with a history of pancreatitis, and in those who have received large doses of calcium chloride during the surgical procedure (220). Complications related to saphenous vein procurement sites are unusual, but lower extremity cellulitis may occur in diabetic patients.

Hospital and Operator Outcomes

State and region databases periodically survey results of coronary bypass surgery. New York (221), Pennsylvania (222), and New England (223) have reported results and correlate declining mortality rates to the introduction of outcome reporting. There has been wide variation in outcomes and charges. Although the results are showing a satisfactory trend, these improvements have been attributed to coding creep and outmigration (224).

The question is whether the extra resources demanded by statewide projects are justified. The majority of physicians surveyed indicate that these consumer guides have no relevance. Recently, investigators from Massachusetts pointed out that despite absence of statewide outcome reporting, in-hospital mortality after coronary artery bypass has decreased (225). Our experience supports this view.

LATE RESULTS

Coronary artery surgery has been influenced by randomized clinical trials that were initiated during the 1970s (Fig. 82.1). Surgery has provided improved longevity in subsets of patients with left main narrowing, proximal two- and three-vessel disease (with proximal anterior descending stenosis), and multivessel disease combined with compromised left ventricular function.

The Coronary Artery Surgery Study registry followed approximately 7,000 patients operated on from 1974 to 1977. After 4 to 6 postoperative years, patients with multivessel disease and poor left ventricular function (226), patients with three-vessel disease with proximal arterial stenoses (227), patients with multivessel disease with severe angina or mild angina (228,229), and patients 65 years of age or older (230) all showed an improved survival with surgery compared with patients who received medical treatment. The disparity in the survival outcomes of the two groups widened with increasing left ventricular dysfunction (i.e., poor left ventricular function adversely affected medically treated patients more than it did surgical patients). The myocardial infarction–free survival was improved by coronary bypass surgery rather than medical treatment in patients with severe angina and in patients with mild angina (231).

Most studies show a 5-year survival rate of 90% to 95%, 10-year, 80% to 90%, and 15-year, 65% to 75% (232). Completeness of revascularization is a strong univariate and multivariate predictor of survival (233). A metaanalysis of the major clinical trials of surgery versus medical treatment indicates that surgery produced lower mortality at 5, 7, and 10 years. In pooled data from all major randomized trials of bypass surgery, Yusuf and colleagues (234) reported a risk reduction of 39% at 5 years in the bypass surgery group despite a crossover rate from medical therapy of 23%. The best differentiation in favor of surgery occurred in patients with left main and three-vessel disease with left ventricular dysfunction; however, patients with focal proximal three-vessel disease with normal left ventricular function and patients with proximal anterior descending disease also showed higher survival with surgery than with medical treatment (Fig. 82.5).

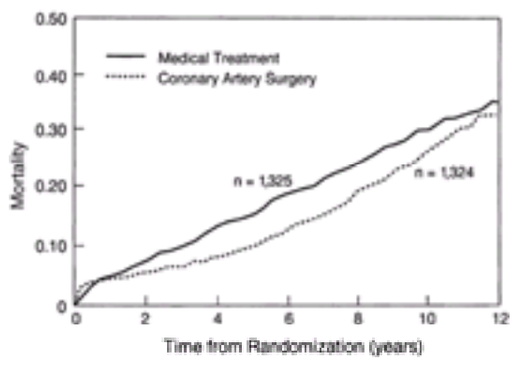


FIGURE 82.5 Results from a metaanalysis of seven randomized trials that have compared coronary artery bypass surgery with initial medical therapy. The risk reduction favored coronary surgery at 5 years, 39%; 7 years, 32%; and 10 years, 17%. The mortality curves are shown for each treatment group. The coronary artery surgery patients had significantly lower mortality than the medical group at all years surveyed. The risk reduction was greatest among left main disease patients than in those with three-vessel or one-or two-vessel disease (odds ratio at 5 years, 0.32, 0.58, and 0.77, respectively). (From Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;344:563–570, with permission.)

In 15-year studies, it has been shown that performance of the left internal thoracic artery graft to the anterior descending is a more important predictor of survival than progression of native coronary atherosclerosis (Fig. 82.6) (117). Patients who received internal thoracic artery grafting at either the first or the second operation fare significantly better than those who had vein grafts. Because internal thoracic artery grafting to the anterior descending is the single most important determinant of survival and event-free survival, it should not be withheld from any group of patients. The only relative contraindications were noted earlier.

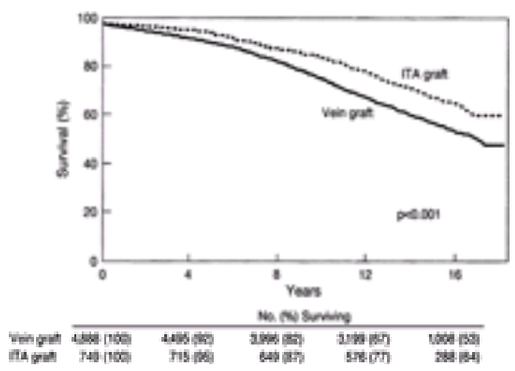


FIGURE 82.6 Actuarial survival up to 18 years comparing cohorts of patients with internal thoracic artery (ITA) bypass grafts and those with vein grafts. After 5 postoperative years, the differences in survival favor patients with ITA grafting and consistently reach statistical significance. (From Cameron A, Davis KB, Green G, et al. Coronary bypass surgery with internal-thoracic-artery grafts—effects on survival over a 15-year period. *N Engl J Med* 1996;334:216–219.)

Coronary atherosclerosis is a highly degenerative disease, and after the fifth year, the number of angina-free patients becomes progressively less due to native

coronary and conduit atherosclerosis. Typical results show 1-, 5-, and 10-year angina-free survival of 98%, 92%, and 81%, respectively (235). Recurring angina relates also to hypertension, diabetes, obesity, and other comorbidities. By the tenth to twelfth year, approximately half of the patients originally angina-free remain so. Late angina correlates with type of conduit, hyperlipidemia, and hypertension (236).

Continued cigarette smoking after surgery is the greatest determinant of early vein graft thrombosis (237). Smokers are at higher risk of myocardial infarction and reoperation compared with patients who stop smoking. Patients who continued to smoke 1 year after surgery had more than twice the risk for myocardial infarction and reoperation compared with patients who stopped smoking before surgery. Patients who were still smoking 5 years after surgery had even greater risk for myocardial infarction and reoperation and had a higher rate of recurring angina pectoris compared with patients who stopped smoking before surgery and patients who never smoked (238).

These and other older reports do not reflect the trend toward arterial grafting, nor do they compare surgery with current catheterization interventions. In general, the highest-risk patients (defined by severity of angina, extent of coronary artery disease, and left ventricular dysfunction) showed higher survival with surgery than with medical treatment. Lower-risk patients (mildly symptomatic, less extensive coronary atherosclerosis, and normal or near normal left ventricular function) showed less differentiation from medical treatment, although approximately 40% eventually underwent surgery over a 10-year period (239).

COMPARISON WITH ANGIOPLASTY AND STENTING

The nine major randomized trials comparing angioplasty and bypass surgery have shown no significant differences in intermediate-term mortality (240,241,242,243 and 244). However, the cardiac event rates, notably additional revascularization procedures and recurring angina, favor bypass surgery for multivessel disease. Patients in these trials were selected by the feasibility of either angioplasty or surgery, which excluded patients with left main narrowing, those with totally obstructed major vessels, and those with previous revascularization. Thus, these trials enrolled approximately 5% of multivessel coronary atherosclerosis revascularization candidates. Application of conclusions from these studies to all patients with multivessel coronary artery disease is problematic. Patients in the randomized angioplasty/surgery trials have tended to be of low risk; less than 10% had significant impairment of left ventricular function. Approximately half had one- or two-vessel disease, and thus those enrolled in these trials were not among those for whom a benefit from bypass surgery had previously been documented.

Most trials found that there were no differences in early mortality or combined end point of death and nonfatal myocardial infarction comparing surgery with angioplasty, but they did show repeat revascularization was more common by several-fold in patients receiving initial angioplasty (241,242,243 and 244). The angina relief, which favored surgery, abated as early as the third year, and the costs of the therapies were equivalent by the third to fifth year (241,242,243 and 244).

The Bypass Angioplasty Revascularization Investigation (BARI), the largest clinical trial with the longest follow-up, demonstrated improved survival for surgery patients at 7-year follow-up (245). This difference could be explained by the patients with treated diabetes, for whom estimates of 7-year survival were 76.4% for surgery and 55.7% for angioplasty. Among nondiabetics, survival was similar by assigned treatment (86.4% for surgery, 86.8% for angioplasty). The angioplasty group had substantially higher subsequent revascularization rates than the surgery group (59.7% vs. 13.1%). Of patients initially randomized to angioplasty, 35.5% had bypass surgery over the next 8 years.

The BARI finding that treated diabetics with multivessel coronary artery disease have excess mortality with an initial treatment strategy of angioplasty has been challenged (246,247). It is clear that diabetes is an independent risk factor for death with both strategies of revascularization (245,247,248). However, careful analysis of the BARI results (245,246) and recent reports from other studies support a strategy of initial bypass surgery in treated diabetics with multivessel disease (248,249,250 and 251).

BARI investigators analyzed medical care costs and quality of life (252). Initially, the mean cost of angioplasty was 65% of that of surgery ($21,113 vs. $32,347; p <.001), but after 5 years, the difference narrowed to only 5% ($56,225 vs. $58,889; p = .047). The cost differences favored angioplasty for two-vessel but not three-vessel disease. Surgery was especially cost-effective in diabetic patients. In the first 3 years, surgery, more so than angioplasty, was associated with improved physical function (253).

In the largest study examining death and revascularization after surgery or angioplasty, New York's surgery and angioplasty registries were used to identify nearly 30,000 people undergoing each treatment (254). Patients with single-vessel disease not involving the left anterior descending coronary artery had improved survival with angioplasty. Patients with proximal left anterior descending coronary artery disease had better 3-year survival with surgery regardless of the number of coronary vessels diseased. Also, patients with three-vessel disease had better 3-year survival with surgery than with angioplasty. These results, which reflect clinicians' decision making rather than enrollment in a randomized trial, support an initial strategy of surgery in patients with proximal left anterior descending coronary artery disease or three-vessel disease.

Other studies of one-vessel disease are noteworthy. Patients with single proximal left anterior descending stenoses were randomized to medicine, angioplasty, or surgery (255). All interventions resulted in symptom relief; however, the incidence of totally asymptomatic patients was 32% for the medically treated patients, 82% after angioplasty, and 98% after surgery. An internal thoracic artery graft to the anterior descending was associated with greater event-free probability at 3 years than was either angioplasty or medical treatment. Another study of one-vessel anterior descending revascularization found that 86% of surgically revascularized patients and 43% of angioplasty patients were free of adverse events after a mean follow-up of 2.5 years (256). Recent 5-year results of a randomized study support this, with 62% of angioplasty patients and 91% of surgery patients free of repeat revascularization (257). In each of these studies, there was no difference in cardiac death or myocardial infarction rate between surgery and angioplasty. In a study comparing different treatment modalities for isolated left anterior descending coronary artery disease, at a mean follow-up of 27 months repeat revascularization was necessary in 30% of patients having percutaneous transluminal coronary angioplasty, 24% of patients having percutaneous transluminal coronary angioplasty with stent, and 5% of patients having surgery with a left internal mammary artery (258).

Finally, a comprehensive prospective nonrandomized treatment comparison was conducted from 1984 to 1990 on 9,263 patients referred to cardiac catheterization at Duke University (Fig. 82.7) (259). In patients with three-vessel coronary atherosclerosis, coronary artery surgery provided a consistent 5-year survival advantage over angioplasty and medical treatment. For less severe coronary disease (i.e., some two- and one-vessel disease), there was a trend toward a relative survival advantage of angioplasty over medical treatment.

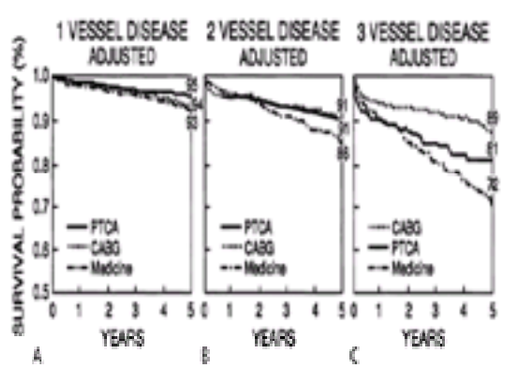


FIGURE 82.7 Survival curves for one-, two-, and three-vessel disease showing adjusted comparisons of angioplasty [percutaneous transluminal coronary angioplasty (PTCA)], coronary artery surgery [coronary artery bypass surgery (CABG)], and medicine. **A:** For one-vessel disease, there is a slight but insignificant trend toward higher survival in the angioplasty group: PTCA, 95%; CABG, 93%; medicine, 94%. **B:** Patients with two-vessel disease showed adjusted 5-year survivals of PTCA, 91%; CABG, 91%; medicine, 86%. **C:** In three-vessel disease, CABG was superior to medicine and PTCA: CABG, 89%; PTCA, 81%; medicine, 72%. (From Mark DB, Nelson CL, Califf RM, et al. Continuing evolution of therapy for coronary artery disease: initial results from the era of coronary angioplasty. *Circulation* 1994;89:2015–2025, with permission.)

How angioplasty alters the natural history of coronary arthrosclerosis depends on the selection criteria for balloon intervention. Using Rand appropriateness selection criteria, the acute success rate for angioplasty was significantly less in patients who have "necessary" revascularization compared with patients undergoing angioplasty for "uncertain" revascularization criteria. Patients undergoing angioplasty for "necessary" indications had a significantly different 5-year survival (97.8%) compared with patients who had unsuccessful, "necessary" angioplasty (85.5%). In patients classified as having "uncertain" criteria, there was no difference in survival between successful and unsuccessful cases (94.8% vs. 94.4%) (260).

Conclusions from the medical literature may be summarized as follows. Patients who have moderate to high risk of death or cardiac events, including those with diffuse

multivessel disease, are generally better off with surgery because of the high restenosis rate of angioplasty and its less consistent results. For patients who qualify for angioplasty, approximately two-thirds will avoid subsequent revascularization, including surgery within the first 3 to 5 years. In multivessel disease patients selected by angioplasty criteria, coronary bypass surgery and angioplasty have similar mortalities up to the first 7 years postprocedure. Surgery offers more complete revascularization because of the greater ability to graft totally obstructed coronary arteries; however, the morbidity is higher and hospitalization is longer. Excepting restenosis, the intermediate term after angioplasty has shown a high rate of revascularization, a higher rate of recurring angina, more use of antianginal drugs, and a trend toward higher mortality compared with surgery for multivessel disease (Table 82.1).

Coronary artery bypass grafting		Percutaneous transluminal coronary angioplasty	
Advantages	Disadvantages	Advantages	Disadvantages
Established differences			
Results in more complete revascularization	Involves major surgery (possible perioperative problems)	Major surgery avoided in 70% of patients (at 5 yr)	Results in less complete revascularization
Provides excellent relief of angina	Requires longer hospitalization and high initial costs	Associated with shorter hospitalization and lower initial costs	Angina may recur
			Associated with more subsequent procedures
Possible differences			
Possibly better long-term survival	Associated with more early infarctions	Associated with fewer periprocedural infarctions	Possibly poorer long-term survival

From Simoons ML, Myocardial revascularization—bypass surgery or angioplasty? N Engl J Med 1996;335:275-277, with permission.

TABLE 82.1 DIFFERENCES BETWEEN CORONARY ANGIOPLASTY AND SURGERY

Randomized trials comparing coronary artery surgery to angioplasty with stenting are under way (261,262). It is clear that coronary stent implantation reduces the restenosis rate associated with angioplasty in favorable lesions (263,264). Initial results of the Arterial Revascularization Therapies Study and the Stent or Surgery trials are encouraging for multivessel stenting compared with bypass surgery, but only 1-year follow-up has been reported. The addition of platelet glycoprotein-IIb/IIIa blockade to percutaneous coronary interventions has also had an important impact (265,266 and 267). As long-term results of coronary stenting become available and results of randomized trials are published, it will be important to remember that clinical results in selected patients may not apply to all patients with multivessel coronary artery disease.

LATE MANAGEMENT

All revascularization is palliative. After coronary artery surgery, lifelong attention should focus on limiting progressive disease. Patients who demonstrate progressive atherosclerosis have an increased risk of future clinical coronary events (268,269). Stabilization of the atheromatous lesion, rather than marked regression of disease, most likely determines reduction of cardiac events (270,271). Whether by diet or drugs, cardiac events and mortality related to ischemic heart disease are significantly reduced by lowering of serum cholesterol levels (272). Metaanalyses of lipid-lowering trials suggest that at least 2 years of a 10% reduction in serum cholesterol levels results in a 17% to 24% reduction in cardiac death and a 22% reduction in coronary events (273,274 and 275). These findings are consistent with those of a large, randomized, placebo-controlled study that concluded that a 25% lowering of cholesterol correlated with a 34% reduction in the combined outcome of cardiac death and onfatal myocardial infarction, a 42% reduction in coronary-related mortality, and a 37% reduction in revascularization procedures 5 years after treatment with no evidence of increased mortality from noncardiovascular causes (276). Subjects with normal serum cholesterol values (less than 240 mg per dL and a low-density lipoprotein level of 115 to 174 mg per dL) may also benefit from lipid lowering (277). In this double-blind trial, a 25% reduction in total cholesterol resulted in a 24% reduction in cardiac death and nonfatal myocardial infarctions and a 27% reduction in coronary bypass or angioplasty. Both of these most current studies revealed similar reductions in risk for those younger or older than age 60 years. Reduction in risk for women (a small percentage of participants) was approximately 25%, including approximately a 30% reduction in angioplasty and bypass surgery procedures as well as cardiac event rates over 5 years.

The above data are relevant but must be applied to patients on an individual basis. Although dietary modifications are important, more so in younger patients, a restrictive diet is less likely to benefit a very elderly patient, and compliance is less with advanced age. A lipid profile should be checked annually to monitor and adjust treatment.

Patients with aortocoronary vein bypass grafts who had low-density lipoprotein cholesterol levels between 130 and 175 mg per dL and were treated with lovastatin and, when necessary, cholestyramine showed less progression of atherosclerosis and late graft occlusion (278). The mean percentage of grafts with progressive change was 27% when low-density lipoprotein was aggressively lowered, compared with 39% with moderate treatment. Warfarin had the same effect as placebo, as documented by angiography. There was also a 29% reduction in the rate of revascularization procedures (average 4 years later) for the aggressive group compared with the moderate treatment group. However, regression does not continue at the same rate year after year. Approximately 20% to 40% of subjects treated with cholesterol-reducing drugs show some progression despite what was thought to be adequate therapy.

The wealth of data on the effects of smoking is convincing both in native-vessel and vein graft disease. Cigarette smoking is one of the greatest determinants of vein graft thrombosis. Cessation of smoking results in a 50% reduction in recurrent cardiac events and must be strongly and, if necessary, repeatedly recommended. Of all measures, smoking cessation is the most cost-effective preventive intervention (279).

Hypertension adversely affects postoperative longevity, and accurate management of diabetes is crucial for retardation of progressive coronary and peripheral atherosclerosis. Platelet antiaggregants should be continued for at least 1 year postoperatively in patients with vein or radial artery grafts. Low-dose warfarin has not been effective in reducing vein graft disease. Early recurring angina is unusual but may require full investigation. After the fifth postoperative year, surveillance should be annual, especially for those who had vein grafts. In view of the propensity for vein graft degeneration, patients with vein grafts to major vessels should have repeat angiography, in our opinion, regardless of symptoms or noninvasive test results, at 10 years.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Coronary artery revascularization is changing at an increasingly rapid pace. In the past 30 years, the operation has advanced to provide more complete revascularization, more durable conduits, and a positive effect on later survival and incidence of cardiac events. The heterogeneity of coronary atherosclerosis pathoanatomy and patient characteristics has made clinical trials difficult to design and generally not applicable to the population of patients regularly seen in practice.

Early clinical trials that compared medical and surgical treatment of unstable angina showed that conservative treatment of patients with repeated attacks of angina that ultimately required coronary artery surgery resulted in more cost than a strategy of early surgery under stable conditions. The same will be found when repeated catheter-based interventions culminate in coronary artery surgery.

In the past decade, the number of percutaneous revascularization procedures have eclipsed the number of coronary bypass procedures. Percutaneous coronary intervention has a secure place in the armamentarium of revascularization. However, there remain the problems of restenosis in stents and after angiography, the inability to approach chronic occlusions in most patients, and addressing diffuse multivessel disease.

THE FUTURE

Cardiac surgery offers a large menu of arterial conduits that can be used to provide consistent high-quality, long-lasting, biologically better conduits that are affected only by distal progression of native atherosclerosis. The whole field is moving rapidly toward minimally invasive techniques that will compete effectively for revascularization of complicated proximal anterior descending or ostial stenosis, which is often difficult to dilate or stent with consistently good results. In addition, off-pump surgery is likely to reduce the morbidity and mortality of multivessel coronary artery bypass grafting, particularly in patients with multiple comorbidities. In the near future, vein grafts, even in older patients, will be supplanted by all arterial grafting performed through small ports. Virtually every subset of coronary atherosclerosis patients in whom myocardial jeopardy and ischemia of large regions are conclusively demonstrated deserves consideration for coronary bypass surgery. In each of these subsets—even in patients with advanced age, previous coronary artery surgery, and poor ventricular function—the results have consistently shown advantages for patients receiving internal thoracic artery grafting for the anterior descending artery. More recent evidence suggests advantages of expanded arterial grafting for younger patients.

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RESTENOSIS: EPIDEMIOLOGY AND TREATMENT

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ERIC J. TOPOL

"Indicates text or graphics that appear only in the electronic versions of this text."

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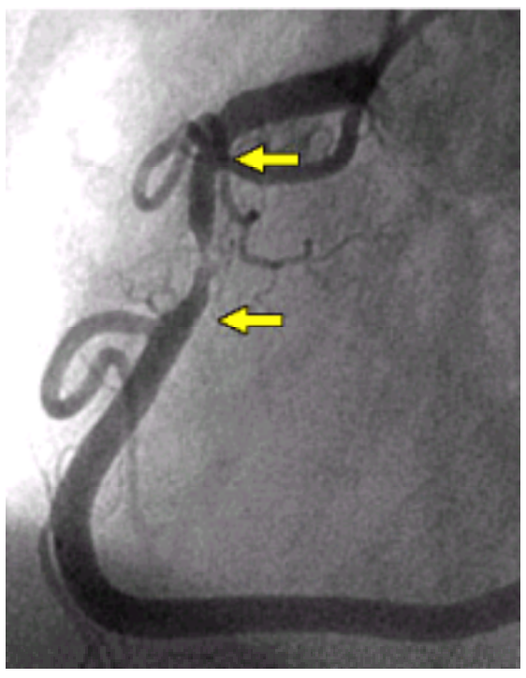
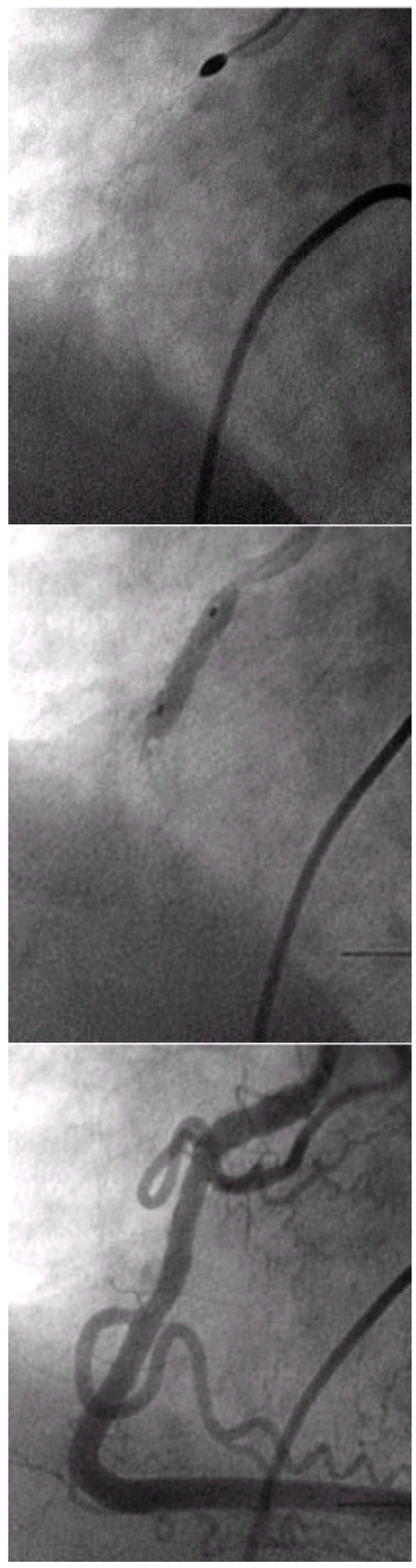
OVERVIEW

Percutaneous coronary revascularization is an increasingly attractive alternative to medical therapy and surgical revascularization for coronary artery disease. The leading drawback continues to be the occurrence of restenosis within 6 months. The epidemiology of restenosis after balloon angioplasty has been studied in many clinical trials, and several predictors of restenosis have been consistently identified: diabetes mellitus, unstable angina, preprocedural and postprocedural minimum lumen diameter, chronic occlusions, lesion length, reference vessel diameter, ostial stenoses, and lesions in saphenous vein grafts. The mechanisms of restenosis include a combination of vessel recoil, vascular remodeling, thrombus transformation, and neointimal proliferation. As indicated by intravascular ultrasonography, remodeling is the predominant mechanism after balloon angioplasty and neointimal hyperplasia dominates in in-stent restenosis. Substantial progress has been made over the past 5 years in lowering the rate of restenosis as vessel recoil and remodeling have been nearly eliminated by the use of intracoronary stents.

Restenosis occurs in one-fourth to one-third of patients within 3 to 6 months of percutaneous revascularization. Most patients with restenosis have symptom recurrence, whereas the minority have silent restenosis, and myocardial infarction is rare. Symptom status alone has weak predictive value for stenosis recurrence, so the optimal method of evaluation is stress myocardial imaging studies. For prophylaxis of restenosis, numerous pharmacologic therapies, including antithrombotics, vasodilators, lipid-lowering agents, and growth factor inhibitors, have been tested but have failed. Likewise, use of several atherectomy catheters (rotational, directional, laser) has been studied, again without consistent improvement noted in the occurrence of restenosis.

Now stents are commonly used to safely maximize postprocedural lumen diameter and decrease the incidence of angiographically identified restenosis and the need for target vessel revascularization. Compared to balloon angioplasty, intracoronary stent placement has been shown to improve the rate of restenosis in nearly all patients and for nearly all lesion subsets. On the other hand, a new disorder, in-stent restenosis, has been created, although it is less common than restenosis after balloon angioplasty. The neointimal proliferation produced by stents has required the development of agents, techniques, and equipment to address it when vessel renarrowing occurs. Radiation and cell-cycle inhibitors hold the current promise in treating in-stent restenosis.





Rotational atherectomy to treat in-stent restenosis. Diffuse restenosis within a previously placed Palmaz-Schatz stent (A, *arrows*) is treated with rotational atherectomy (B), followed by adjunctive stent placement (C). The postintervention result is shown in D.

Video 83.1 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 83.2 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HISTORICAL PERSPECTIVE

As percutaneous coronary revascularization has evolved over the past 25 years, it has become an increasingly attractive alternative to medical therapy and surgical revascularization for coronary artery disease. During this time most of the advancement in the field of interventional cardiology has been to make the procedure safer and more immediately successful while expanding the treatment to progressively more complex coronary arterial lesions. The leading drawback to percutaneous coronary intervention (PCI) has been and continues to be the recurrence of stenosis within 6 months, or restenosis. Among the first 169 patients in whom percutaneous transluminal coronary angioplasty (PTCA, balloon angioplasty) was performed by Gruentzig in Zurich, 31% of those undergoing repeat angiography at 6 months were noted to have recurrence of stenosis (1).

Currently, well over 1 million percutaneous coronary interventions are performed each year throughout the world (2,3,4 and 5). The majority of these procedures is performed in the United States and Western Europe, and the rate on both sides of the Atlantic continues to nearly double every 5 to 8 years (Fig. 83.1). Of these angioplasty cases, approximately one-fourth involve lesions previously treated by PCI. In the United States alone, restenosis still occurs in approximately 150,000 patients annually, which translates into over $3 billion of medical expenditures (6). With an increasing number of PCI procedures performed each year, the absolute number of patients who will be affected by restenosis will rise until successful treatments to prevent restenosis are discovered and implemented.

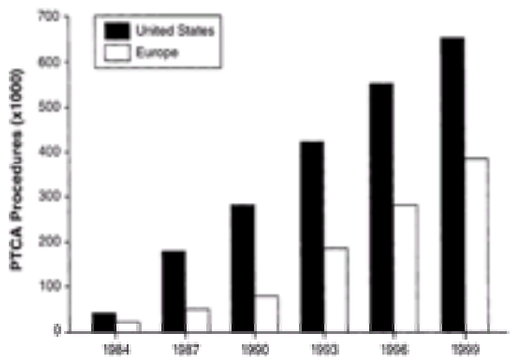


FIGURE 83.1 The number of percutaneous revascularization procedures performed in Europe and the United States has steadily increased over time, and well over 1 million procedures are now carried out each year worldwide. PTCA, percutaneous transluminal coronary angioplasty. (Data from Gruentzig AR, King SD, Schlumpf M, et al. Long-term follow-up after percutaneous transluminal coronary angioplasty: the early Zurich experience. *N Engl J Med* 1987;316:1127–1132; Bittl JA. Advances in coronary angioplasty. *N Engl J Med* 1996;335:1290–1302; Windecker S, Maier-Rudolph W, Bonzel T, et al. Interventional cardiology in Europe 1995. *Eur Heart J* 1999;20:484–495; and American Heart Association. 2001 heart and stroke statistical update. Available at: http://www.americanheart.org/statistics/index.html. Accessed September 4, 2001.)

Historically, early reports of restenosis showed a broad range in the incidence and prevalence of restenosis. This occurred because a number of arbitrary definitions existed for angiographically determined restenosis, and many early clinical studies were small and their results were confounded by problems of incomplete revascularization, withdrawal bias, and limited follow-up. Finally, the technique and technology of percutaneous revascularization have continually evolved, which perhaps limits assessments of restenosis to snapshots in time, rather than providing a dynamic perspective. This chapter reviews issues involved in the epidemiology of restenosis and contemporary efforts to prevent restenosis after coronary intervention.

PATHOPHYSIOLOGY

The response of the vessel to coronary interventions is complex (Fig. 83.2 and Fig. 83.3) (7)—with injury to the intima and media likely occurring in all patients during angioplasty, even if to a small extent—and is detailed in Chapter 105 (8). Briefly, restenosis can be broadly divided into three interrelated facets: vessel wall recoil and remodeling, thrombus formation and organization, and neointimal growth. Studies report that many patients (15% to 65%) have a 10% or greater increase in the diameter of stenosis within 2 days of balloon angioplasty (9,10,11,12,13 and 14), and some patients (10%) have a substantial early renarrowing (more than 50% acute loss) (10). This vessel wall recoil may represent elastic rebound of the arterial wall or plaque, abnormal vasoconstriction, the presence of a thrombus, or a combination of these factors. Regardless of the underlying mechanism, this very early vessel wall response affects the likelihood of subsequent restenosis. Vessel wall remodeling also occurs over the long term, and the vessel may adaptively enlarge (positive remodeling) in response to atherosclerosis or may shrink (negative remodeling) in response to the trauma of angioplasty (Fig. 83.2) (15,16 and 17).

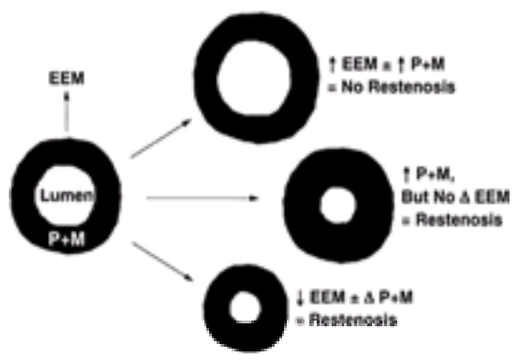
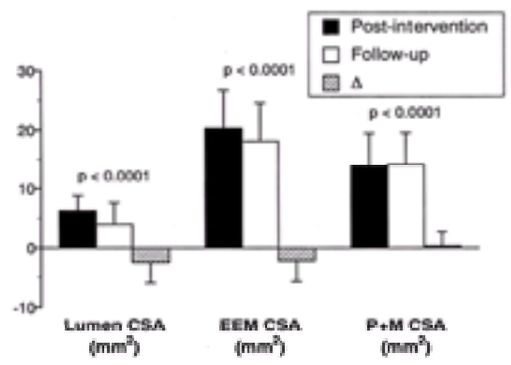


FIGURE 83.2 Restenosis can occur by several interrelated mechanisms. As shown in the schematic of the “doughnut and the hole,” neointimal proliferation can decrease lumen area by increasing the plaque plus media (P+M) cross-sectional area. If the overall vessel area (external elastic membrane, or EEM) increases adequately (compensatory arterial dilatation or favorable arterial remodeling), no restenosis will occur. Alternatively, if (a) neointimal growth is excessive, (b) arterial remodeling is inadequate, or (c) negative arterial remodeling (arterial contracture) occurs, then restenosis ensues. ↑, increase; ↓, decrease; D, change. (Adapted from Mintz G, Popma J, Pichard A, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996;94:35–43, with permission.)

FIGURE 83.3 Pathophysiologic mechanisms of restenosis after percutaneous revascularization. After balloon angioplasty, recoil occurs followed by activation of growth factors and smooth muscle cell proliferation. These lead to vessel contracture or negative remodeling in some patients. After intracoronary stent placement, the majority of lumen loss is from neointimal hyperplasia. In most cases, the mechanisms of restenosis are likely interrelated. bFGF, basic fibroblast growth factor; EDRF, endothelium-derived relaxing factor; EGF, epidermal growth factor; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); PDGF, platelet-derived growth factor; PGI_2, prostacyclin; TGF-b, transforming growth factor-b.

To directly investigate the importance of arterial remodeling in restenosis after angioplasty, Mintz and coworkers (18) performed serial intravascular ultrasonographic studies of 212 native coronary lesions. By carefully measuring changes in the vessel cross-sectional area components (lumen area and plaque plus media area) (eFig. 83.3.1), they were able to demonstrate that 73% of the loss in lumen area among those with restenosis was attributable to loss in the overall vessel wall cross-sectional area. The remaining 27% was attributable to growth of the plaque or neointimal area. Of the 212 lesions studied, 78% had some decrease in overall size (negative remodeling), whereas 22% increased in overall size. Finally, lesions that demonstrated negative remodeling were 2.4 times more likely to have angiographically identified restenosis (62% vs. 26%).



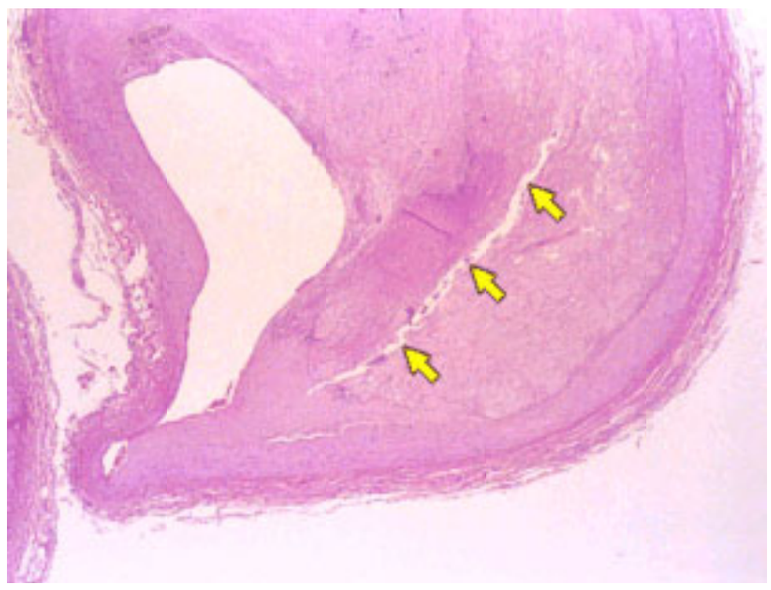
***e*FIGURE 83.3.1** Measurements of the cross-sectional areas (CSA) of the overall vessel [external elastic membrane (EEM)], plaque plus media (P+M), and lumen by serial intravascular ultrasonography demonstrated that 73% of the lumen area lost in the restenotic process was as a result of a decrease in the EEM CSA (i.e., negative remodeling). The minority of loss (27%) was from an increase in P+M (neointimal hyperplasia). (From Mintz G, Popma J, Pichard A, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996;94:35–43, with permission.)

Early Thrombus

Serial angioscopy performed in patients after elective balloon angioplasty has shown that most lesions (more than 80%) have an identifiable thrombus within the first hour (19,20). Activated platelets within the thrombus secrete a host of substances from their alpha-granules that lead to vasoconstriction, chemotaxis, mitogenesis, and activation of neighboring platelets (21,22). The released growth factors and chemokines include platelet-derived growth factor (PDGF), transforming growth factor-b (TGF-b), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and interleukin-1 (23,24 and 25). These factors are believed to be responsible for the neointimal growth after angioplasty by stimulating the migration and proliferation of smooth muscle cells (25). Thrombus contributes to restenosis directly by lumen occupation and vasoconstriction and indirectly by mediating the growth of fibromuscular tissue, or neointima.

Neointimal Hyperplasia

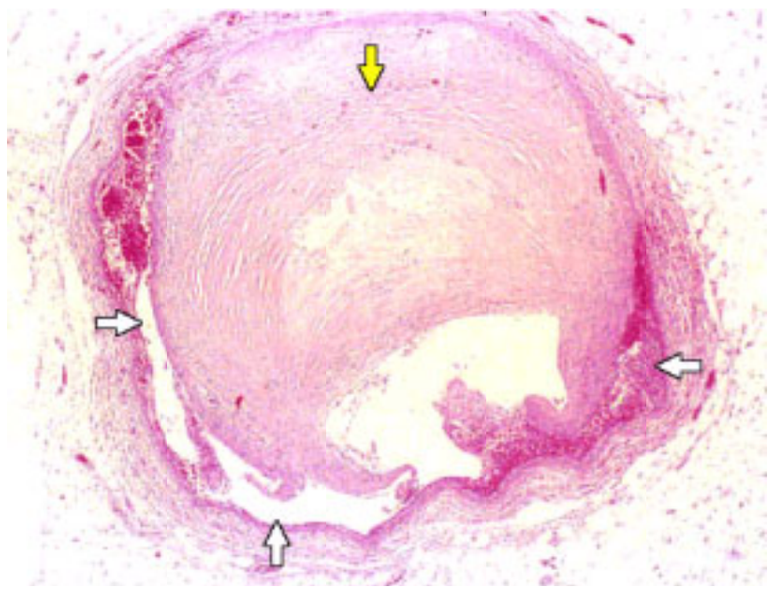
Simply stated, neointima is the new intimal tissue that develops as part of the reparative or wound healing process after vascular injury, and all angioplasty sites have some degree of neointimal formation at follow-up. These platelet-released mitogens activate surface receptors on resting medial smooth muscle cells and induce protooncogenes that stimulate the smooth muscle cells to replicate. In humans, approximately 48 hours after arterial injury, smooth muscle cells can be seen proliferating and migrating to the injured area (7,26,27). This process of replication of smooth muscle cells in the media and subsequent migration to the intima occurs during the first week after angioplasty. The final wave of neointimal growth occurs over the ensuing weeks to months as the smooth muscle cells in the intima continue to replicate and produce extracellular matrix.



Restenotic lesion. Residual tear in atherosclerotic plaque (*yellow arrows*) and large amount of neointimal proliferation 76 days after balloon angioplasty.

Restenotic Lesion

The mechanisms of restenosis—recoil, remodeling, thrombus formation, and neointimal proliferation—are dynamically interrelated (Fig. 83.3) and provide a “natural history” of the restenotic lesion. This process differs from that of *de novo* lesion formation and leads to substantial differences in lesion histology and rate of stenosis formation. *De novo* atherosclerotic lesions have a range of histologic presentations from young or “juvenile” plaques, which are often soft, lipid-laden, and covered by a relatively thin fibrous cap, to “senile,” or older, plaques, which contain more calcium and fibrous tissue in addition to the lipid component. Primary atherosclerotic lesions usually develop over years to decades, whereas restenotic lesions develop over weeks to months. Pathophysiologically, restenotic lesions (in addition to containing residual components of the original lesion) usually contain evidence of vessel wall injury, thrombus, and neointima during their development. Nobuyoshi et al. (28) studied the histopathology of 34 lesions from 20 patients who died within 2 weeks to 2 years after angioplasty. Even with this wide age range in restenotic lesions, remarkable consistency was seen in the histology. Eighty-eight percent of lesions showed intimal, medial, and adventitial tears, whereas neointimal proliferation was observed in 82%. Thrombus formation was seen most commonly among lesions treated within the prior month and was observed in 23% of all lesions studied. Neointimal proliferation was consistently present among lesions after 10 days.



Linear, circumferential dissection 2 days after balloon angioplasty of a restenotic lesion. Note the extensive neointimal proliferation (*yellow arrow*) and dissection (*white arrows*).

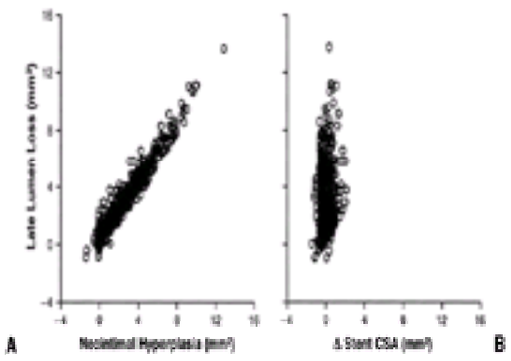
VIDEO

Video 83.3 Severe in-stent restenosis involving the distal right coronary artery **(A)** and successful angioplasty **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 83.4 Severe in-stent restenosis involving the distal right coronary artery **(A)** and successful angioplasty **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Garratt and colleagues (29) compared the histology of directional atherectomy specimens from 31 primary lesions and 30 restenotic coronary arterial lesions. Age of the restenotic lesions was 1 week to 74 months; mean age was 9 months. Among the primary lesions, 83% of the intimal tissue retrieved contained dense fibrosis and necrotic debris, and 17% of the tissue contained loose fibroproliferative (hyperplastic) tissue. In contrast, among the restenotic lesions, 55% of the intimal tissue was dense fibrosis and necrosis and 45% was hyperplastic. Likewise, foam cells were present in 32% of primary lesions but in only 3% of restenotic lesions. These two key differences—more appreciable fibromuscular hyperplasia and fewer foam cells among restenotic lesions—typify the natural history differences of restenotic lesions compared to their primary lesion predecessors. No difference in subintimal histology was seen between primary and restenotic lesions.

These histologic studies and observations have been mainly limited to restenotic lesions in native coronary arteries after balloon angioplasty, although similar findings have been reported for lesions treated by atherectomy and lesions in saphenous vein grafts (29). The contribution of the individual mechanisms of restenosis after intracoronary stent placement and the resultant histology are somewhat different from those after balloon angioplasty. The majority of lumen loss after balloon angioplasty is from remodeling, with an important but lesser component of neointimal proliferation. The converse is true of lumen loss among stented lesions that undergo restenosis. In-stent restenotic lesions have a marked hyperplastic neointimal response and very little remodeling. Hoffman et al. (30) studied 115 lesions treated with stents by serial intravascular ultrasonography and showed that late lumen loss at follow-up was strongly correlated with neointimal hyperplasia and only weakly correlated with change in stent cross-sectional area (*e*Fig. 83.3.2). Moreover, stents affected the proximal and distal segments of the arteries adjacent to the stent for at least 5 to 10 mm. Remodeling appeared progressively to increase, whereas tissue growth progressively decreased at axial distances further from the stent edge. Animal studies (31,32) and clinical investigations (30,33,34) have shown that intimal hyperplasia covers the entire stent, is exaggerated compared to that seen in lesions treated with balloon angioplasty, and results in a greater late loss. The pattern or distribution of restenotic tissue within stents is also significantly different. Volumetric intravascular ultrasonographic studies by Dussaillant et al. (35) have shown that the pattern of in-stent restenosis is more commonly focal (77% of cases), with greatest tissue growth being in the midstent articulation site, at the stent margin, or in the stent body in 45%, 30%, and 25% of cases, respectively. A more aggressive neointimal pattern within stents in which diffuse and dramatic tissue growth occurs is also well described. This growth pattern, although less common, is important because it has been associated with a high frequency of recurrent restenosis when treated by balloon angioplasty (36).



***e*FIGURE 83.3.2** When 715 segments in a total of 115 stents were analyzed by intravascular ultrasonography, the late lumen loss was found to be strongly correlated with neointimal hyperplasia **(A)** and only weakly correlated with change in the stent cross-sectional area (CSA) **(B)**. (From Hoffman R, Mintz G, Dussaillant G, et al. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. *Circulation* 1996;94:1247–1254, with permission.)

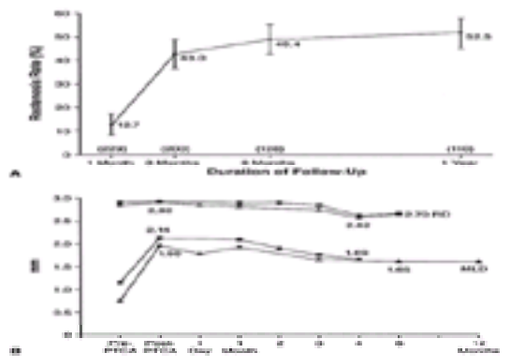
Presentation of Restenosis

The interrelated mechanisms of restenosis can translate into an anatomically or physiologically important stenosis recurrence. Depending on the predominant mechanism and its severity, as well as on characteristics of the index lesion, the timing and presentation of symptoms may vary. Restenosis can be categorized or defined angiographically or clinically, or it may be silent (asymptomatic).

Video 83.5 Anomalous origin of the left circumflex coronary artery from the right sinus with in-stent restenosis 7 months post procedure. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Timing

Three events may occur after angioplasty that can produce symptom recurrence referable to the treated lesion. The first, elastic recoil, occurs within minutes to hours after PTCA but usually does not cause symptoms. The second, abrupt vessel closure, occurs minutes to days after angioplasty in several percent of patients and produces recurrent angina or acute infarction. Finally, over the weeks to months after PTCA, restenosis due to neointimal growth and remodeling may occur. To study the time course of restenosis, Nobuyoshi and colleagues performed sequential angiography in 229 patients at 24 hours, 1 month, 3 months, 6 months, and 1 year after balloon angioplasty (10). An appreciable loss (more than 0.5 mm) in lumen diameter was detected in 15% of patients at 24 hours, consistent with lesion recoil or thrombus formation. In approximately one-half of these patients, the loss proceeded to restenosis. In the interval from 1 day to 1 month, most lesions remained unchanged or regressed, with a mean improvement in lumen diameter. During this same period, few patients (12%) were classified as having restenosis. The actuarial patient rate of restenosis increased markedly (from 12% to 43%) between 1 and 3 months, and increased only modestly thereafter (*e*Fig. 83.3.3A). This and other studies using serial angiography (*e*Fig. 83.3.3B) (37) make it evident that the majority of restenosis occurs within the first 3 months after balloon angioplasty and that restenosis after 3 to 6 months is rare (10,38,39). The time course for restenosis after intracoronary stent implantation is later by 1 to 3 months. Regardless, most patients who are free of restenosis at 6 to 8 months will have continued success for the index lesion.

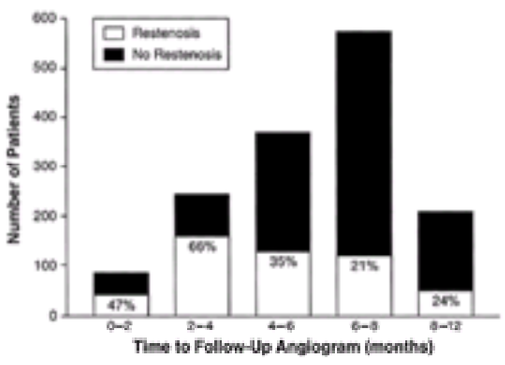


***e*FIGURE 83.3.3** By serial angiographic follow-up, restenosis after successful angioplasty can be seen to occur with highest frequency in the first 3 months in this cohort of 229 patients **(A)**. Likewise, the time-related loss in minimal lumen diameter (MLD) seen in two separate serial angiographic studies is shown to occur over this same period **(B)**. From this, the majority of restenosis can be seen to occur within the first 3 months after angioplasty. PTCA, percutaneous transluminal coronary angioplasty; RD, residual diameter. (From Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. *J Am Coll Cardiol* 1988;12:616–623; and from Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. *Circulation* 1988;77:361–371, with permission.)

Symptoms

Because restenotic lesions usually develop gradually, the recurrence of symptoms or inducible ischemia also occurs gradually over weeks to months. Although soft *de novo* lesions may rupture abruptly, causing vessel occlusion, infarction, and in some cases death, fibromuscular restenotic lesions rarely present as acute infarction (2% or fewer cases) or death (1% or fewer cases) (40,41 and 42). Rather, the majority of patients with symptomatic restenosis experience the return of their typical angina or its equivalent. The safety of restenosis was seen even among angioplasty patients at high risk for ischemic events in the Evaluation of Chimeric Monoclonal 7E3 for the Prevention of Ischemic Complications (EPIC) trial (43). At 6-month follow-up, of the 549 patients who received placebo and had no clinical event during the first 30 days, only 2.0% had myocardial infarction and 1.7% died. Although these data are from patients both with and without restenosis, Weintraub et al. (44) have reported similar results among 3,363 patients followed for 6 years. In this large cohort, those with and without angiographically identified restenosis had an annual rate of death of approximately 1.0%, and the annual rate of myocardial infarction was 2.5% and 2.0% for these groups, respectively. Among all patients undergoing intracoronary stent placement, approximately 2% die between 30 days and 1 year (45,46).

When data are pooled from several early PCI studies (47,48,49,50,51,52 and 53) including nearly 3,000 patients with midterm (3- to 6-month) follow-up, two-thirds of those with angiographically identified restenosis are found to have typical angina. Patients with typical symptom recurrence within 6 months of angioplasty are more likely to have restenosis of the index lesion, whereas development of angina at later than 6 months is often due to a different stenosis. When data from an early National Heart, Lung, and Blood Institute (NHLBI) PTCA Registry report (47) were combined with those from Emory University (54) to cover a total of 1,475 patients who presented with recurrent chest pain and underwent angiography, the highest rate of symptoms deemed related to restenosis was found to occur within the first 4 months after angioplasty. After 4 months, the majority of symptomatic patients had continued success of the treated lesion (eFig. 83.3.4). Joelson et al. (55) showed that among 102 patients, symptom persistence or recurrence within the first month after angioplasty was most often due to incomplete revascularization; symptom recurrence between 1 and 6 months was due to restenosis; and symptoms after 6 months were almost always from new lesions. In topical reviews, reports are that chest pain recurs in roughly half of patients undergoing angioplasty, although the proportion with concomitant angiographically apparent restenosis ranges widely from 48% to 92% (56). Patients who present with atypical chest pain or pain different from that which they experienced before angioplasty infrequently have restenosis (47,52). In an NHLBI PTCA Registry report, Holmes et al. (47) found that 56% of patients with definite or probable angina had angiographically identified restenosis, whereas among patients without chest pain, 14% had restenosis. Overall, the positive predictive value of chest pain for restenosis is moderate.



***e*FIGURE 83.3.4** Combined data from the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry and the Emory University registry, encompassing a total of 1,475 patients who underwent repeat angiography for chest pain, indicate that the highest rate of occurrence of symptoms deemed related to restenosis was observed within the first 4 months after revascularization. After 4 months, the majority of symptomatic patients had continued success of the treated lesion. [Adapted from Holmes DRJ, Vlietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* 1984;53:77C–81C; and Leimgruber PP, Roubin GS, Hollman J, et al. Restenosis after successful coronary angioplasty in patients with single-vessel disease. *Circulation* 1986;73:710–717, with permission.]

Angiographically Identified Restenosis

Numerous binary definitions of angiographically determined restenosis have been proposed and used in clinical reports. Serruys et al. (57) found 12 different definitions (eTable 83.0.1) in the literature. The most commonly used definition currently is stenosis of 50% or more of lumen diameter at 6-month follow-up. Likewise, the method of assessing luminal renarrowing has also varied. Some studies have used simple visual assessment of percentage diameter stenosis to assess restenosis, whereas others have used hand-held digital calipers. Computer-assisted angiographic edge-detection systems are commonly used in contemporary research protocols. Depending on the restenosis definition, assessment method, and system used to assess the angiogram, angiographically identified restenosis rates varied from under 30% to over 50% before the stent era. Among stent studies, angiographically determined restenosis rates have ranged from under 10% to over 30%.

***e*TABLE 83.0.1** CRITERIA FOR RESTENOSIS AT FOLLOW-UP ANGIOGRAPHY USED IN THE LITERATURE

Stenosis with reduction of ³30% in lumen diameter (NHLBI 1)
Immediate post-PTCA stenosis of <50% diameter that increases to ³70% at follow-up (NHLBI 2)
Return to within 10% of pre-PTCA stenosis diameter (NHLBI 3)
Loss of at least 50% of the initial gain (NHLBI 4)
Stenosis of ³50% diameter
Stenosis of ³70% diameter
Area of stenosis of ³85%
Immediate post-PTCA stenosis of <50% diameter that increases to ³50% at follow-up
Stenosis with reduction of ³20% in diameter
Loss of ³1 mm^2 in stenosis area
Loss of ³0.50 mm in minimal lumen diameter
Loss of ³0.72 mm in minimal lumen diameter

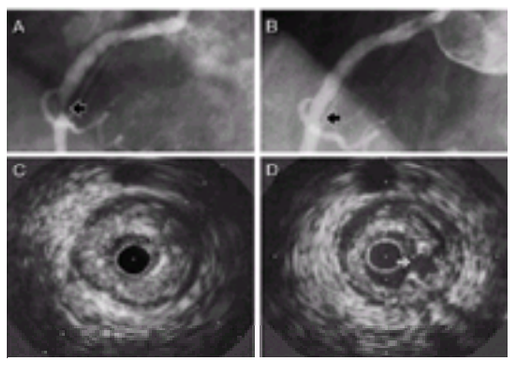
NHLBI, National Heart, Lung, and Blood Institute; PTCA, percutaneous transluminal coronary angioplasty.

From Serruys PW, Rensing BJ, Hermans WRM, et al. Definition of restenosis after percutaneous transluminal coronary angioplasty: a quickly evolving concept. *J Interv Card* 1991;4:265–276, with

permission.

Several important problems are inherent in the angiographic evaluation of restenosis. First, visual methods of assessing stenosis severity can be inaccurate, especially in the midrange of stenosis estimates (30% to 70%). Simple visual assessments underestimate lesion severity compared to direct inspection at bypass surgery or during necropsy (58,59 and 60). Second, clinically significant intraobserver and interobserver variability is found in visual interpretation, with differences in the estimation of stenosis severity approaching 50% (61,62 and 63). Computer-assisted quantitative coronary angiography (QCA) is used in most current clinical trials because it has been demonstrated to be precise, although it does show some variability due to operator- and computer program–dependent factors. Keane et al. compared ten QCA systems from North America and Europe used in major clinical trials of restenosis. When phantom coronary artery models of known diameter were used, the accuracy of the systems varied from +26% to –1% for 0.5-mm lumen diameters and from –11% to –29% for lumen diameters of 3.0 mm. Therefore, many systems showed a slight overestimation of very small diameters, and all systems consistently underestimated all other diameters tested. For models from 0.5 mm to 1.9 mm, the precision of the ten systems ranged from ±0.14 mm to ±0.24 mm. Keane et al. concluded that this marked variability among systems precludes comparison of absolute measurements from trials using different systems or performed at different centers.

The fourth important limitation to angiographic assessment of restenosis is that angiography depicts a three-dimensional structure (the coronary lumen) in two dimensions. This “luminogram” may misrepresent the true lesion geometry (64) so that important reductions in lumen cross-sectional area may be unappreciated by angiography (*e*Fig. 83.3.5). Many studies report the averaged percent diameter stenosis from two orthogonal views; others have shown the importance of distinguishing this approach from that in which only the worst view is used (65). Finally, angiographic assessment of percent stenosis requires a disease-free reference segment with which the minimal lumen diameter (MLD) of the diseased segment can be compared. Quite often, the reference segment is significantly diseased, so that the stenosis being quantified is underestimated. Using intracoronary ultrasonography, Escaned et al. (66) assessed the “disease-free” reference segment used by QCA and found that, on average, 50% of the total vessel area was occupied by plaque. Despite these limitations and the apparent dissociation between angiographic and clinical outcomes in interventional trials, angiography remains a standard for clinical trials of restenosis. These limitations should be kept in mind when considering individual angiographic reports of restenosis, and the pitfalls of comparing rates of angiographically determined restenosis across different trials should be recognized.



***e*FIGURE 83.3.5 A–D:** Angiographic and intravascular ultrasonographic (IVUS) images of a lesion before and after balloon angioplasty. As can be seen in **B**, a reasonable result by angiography was obtained with little residual stenosis. Inspection with IVUS, however, reveals that this angioplasty result was accomplished primarily by the creation of a single tear in the atheroma. A substantial stenosis remains, and this was not appreciated by angiography. (From Topol EJ, Nissen SE. Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995;92:2333–2342, with permission.)

Beyond furnishing an estimate of percent diameter stenosis, quantitative angiography is able to provide a number of indices related to the MLD of the coronary lumen. These indices (Fig. 83.4) can be helpful in understanding the mechanics of restenosis and the effect of different technologies on restenosis. The immediate gain in MLD is simply the final postprocedural MLD obtained with percutaneous revascularization minus the preprocedural MLD. Immediate gain is usually smallest for balloon angioplasty (0.7 to 1.0 mm), intermediate for rotational atherectomy (1.0 to 1.5 mm) and directional atherectomy (1.5 to 2.0 mm), and largest for intracoronary stent placement (1.5 to 2.5 mm). The late loss is the MLD at follow-up angiography minus the final postprocedural MLD. Late loss is proportional to immediate gain, so that it is greatest after stent placement and directional atherectomy, and least after balloon angioplasty. This device “taxing” is a result of the marked reparative response of the vessel wall (i.e., aggressive neointimal proliferation) to deep injury or need for extensive reendothelialization. The net gain is the follow-up MLD minus the preprocedural MLD. Because the immediate gain is so large with intracoronary stents and the late loss is moderate, the net gain is greatest with stents (approximately 1 mm). In limited series directional atherectomy has shown a net gain similar to stent placement, although in other studies has demonstrated a net gain only slightly better than that with balloon angioplasty. Balloon angioplasty and rotational and laser atherectomy usually result in a similarly moderate net gain. Finally, an important concept is the loss index, which is the late loss divided by the immediate gain and represents a “device taxing” for restenosis. The loss index is higher for new device technologies than for balloon angioplasty but may be intermediate for stents (Fig. 83.5**,** *e*Table 83.0.2) (45,67,68,69,70,71,72,73,74,75,76 and 77). If indeed the loss index is similar for different technologies and levels of aggressiveness that achieve the largest immediate gain, the theory that obtaining the largest lumen possible will give the best long-term result might hold true. This theory, called “bigger is better,” has been advanced and is discussed in the section on Procedure-Related Factors.

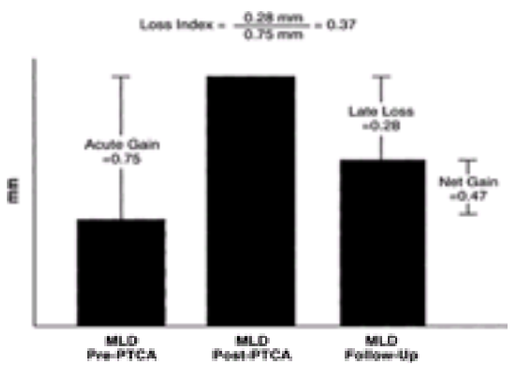


FIGURE 83.4 Indices measured and calculated during serial quantitative coronary angiography. The immediate gain is the change in minimum lumen diameter (MLD) from baseline to immediately after angioplasty. The late loss is the measured difference between the immediately postprocedure MLD and that measured at 6-month follow-up. Net gain is the difference between the follow-up MLD and the baseline MLD (immediate gain minus late loss). The loss index or “tax rate” refers to the fraction or percentage of early gain that is ultimately lost (late loss minute immediate gain). PTCA, percutaneous transluminal coronary angioplasty.

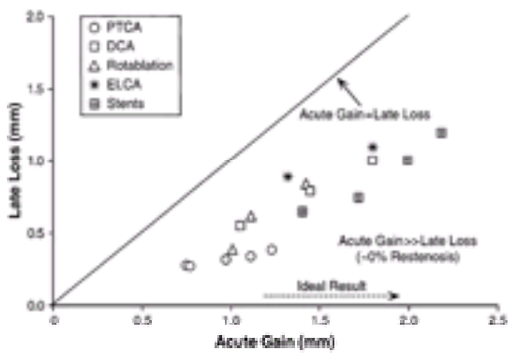


FIGURE 83.5 The loss index for angioplasty and new device technologies is represented as the relationship of late loss to immediate gain. Balloon angioplasty has the lowest loss index but produces a relatively smaller immediate gain. New technologies such as atherectomy produce a large immediate gain but have the highest loss index. Intracoronary stents also produce a large immediate gain with an intermediate loss index and, thus, a more favorable restenosis rate. The ideal revascularization procedure would produce a large immediate gain and have a low loss index. (Data are from *e*Table 83.0.2.) DCA, directional coronary atherectomy; ELCA, excimer

laser coronary angioplasty; PTCA, percutaneous transluminal coronary angioplasty.

***e*TABLE 83.0.2** LOSS INDEX (DEVICE TAX) ASSESSED BY QUANTITATIVE CORONARY ANGIOGRAPHY

Study	Lesions	Reference diameter (mm)	Restenosis rate (%)	Loss index
Balloon angioplasty				
Rensing et al. (68)	1,445	2.63	31	0.37
Serruys et al. (69)	595	2.63	28	0.35
Fischman et al. (70)	202	2.99	42	0.31
Serruys et al. (71)	257	3.01	32	0.33
Dill et al. (67)	250	2.8	51	0.39
Directional atherectomy				
Popma et al. (72)	212	3.5	44	0.55
Topol et al. (73)	512	2.90	50	0.52
Adelman et al. (74)	138	3.13	46	0.54
Rotational atherectomy				
Popma et al. (72)	152	2.39	52	0.56
Reifart et al. (77)	215	3.00	56	0.59
Dill et al. (67)	252	2.6	49	0.32
Excimer laser				
Bittl and Sanborne (76)	95	3.84	47	0.61
Reifart et al. (77)	195	2.94	61	0.67
Intracoronary stents				
Ellis et al. (75)	181	3.2	36	0.56
Fischman et al. (70)	205	3.05	32	0.43
Serruys et al. (71)	259	2.99	22	0.46
Kastrati et al. (45)	1,598	3.05	33	0.56
Kastrati et al. (45)	698	3.02	25	0.52

When data are pooled from 15 clinical trials (70,71,73,78,79,80,81,82,83,84,85,86,87,88 and 89) that defined restenosis as stenosis of 50% of luminal diameter or more and included a total of over 8,000 patients (Table 83.1), the rate of angiographically determined restenosis is found to average 40% with routine balloon angioplasty. The highest reported restenosis rate in this group (53%) is from the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT), in which the angiographic core laboratory reported data from the angiographic view demonstrating the severest stenosis, that is, the “worst view” method. Other angiographic trials have used the average of stenosis severity from several views, and this may artifactually lower the reported rate of angiographically identified restenosis. Also, more recent studies using more aggressive angioplasty techniques to obtain an optimally large final lumen diameter and relying on stenting in the case of important dissections report the lowest angiographically determined restenosis rates. The Balloon versus Optimal Atherectomy Trial (BOAT) (87) was conducted 3 years after CAVEAT and compared directional coronary atherectomy to PTCA using a more aggressive approach for both techniques. In the PTCA group, the final residual stenosis was 28%, compared to 36% in CAVEAT. Restenosis in the BOAT angioplasty cohort was 25% lower than that in CAVEAT (40% vs. 53%), and a substantial number of BOAT patients required intracoronary stents. Similarly, the Belgian-Netherlands Stent II (BENESTENT-II) trial (90) reported the lowest rate of angiographically determined restenosis for balloon angioplasty of any large-scale trial, nearly 35% lower than reported in the Belgian-Netherlands Stent I (BENESTENT-I) trial (21% vs. 32%) (71). This is likely attributable to more aggressive balloon dilation.

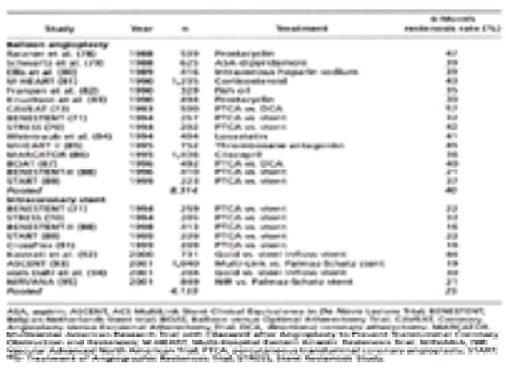
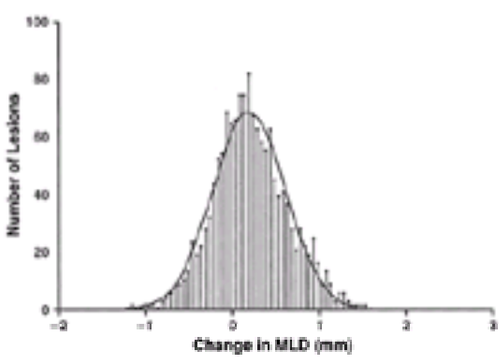


TABLE 83.1 RATES OF ANGIOGRAPHICALLY IDENTIFIED RESTENOSIS

When data are pooled from many trials studying intracoronary stents (70,71,88,89,91,92,93,94 and 95) (Table 83.1), the average 6-month angiographically determined restenosis rate is 25%. These data encompass both early and more contemporary stent designs. Early stent trial data were from studies used to approve the stent design. Because of this, cases were selected and the target lesions were “ideal” for stent placement. A more recent large study reported by Kastrati and colleagues examined 2,944 consecutively treated patients divided into subgroups with simple and complex coronary lesions. Among those with simple lesions (n = 898), the rate of angiographically determined restenosis was 25%, whereas among those with complex lesions (rated B2 and C according to the classification system of the American College of Cardiology and American Heart Association; n = 2,046), the restenosis rate was 33% (45).

Clinically Apparent Restenosis

Restenosis occurs to some extent in all individuals after coronary interventions. Given that the extent of angiographic renarrowing after balloon angioplasty follows a near normal (gaussian) distribution (*e*Fig. 83.5.1) (38,68), all angiographic definitions of restenosis are arbitrary unless they are linked to physiologic or clinically relevant parameters. The clinical return of a significant coronary stenosis most often presents as recurrent angina or a positive result on a stress test. The range of reported rates for chest pain recurrence within 6 months after angioplasty is vast: 25% to 93% (40,96), with an average rate of approximately 50% from pooled data (56). When combined with results of angiographic follow-up, this clinical information becomes difficult to interpret. The proportion of patients presenting with recurrent chest pain who have restenosis demonstrable at angiography ranges from 48% to 92% (56). The average positive predictive value of symptoms alone, therefore, is approximately 60%.



***e*FIGURE 83.5.1** Histogram of the individual changes in minimal lumen diameter (MLD) from the immediately postprocedure angiogram to that at 6-month follow-up for 1,375 lesions. Lesions that progressed to complete occlusion were not included. A positive value corresponds to a decrease in MLD or lumen loss. The curve superimposed on the distribution represents the theoretical gaussian distribution. (From van der Giessen et al. Clinical and angiographic definitions of restenosis: recommendations for clinical trials. In: Schwartz R, ed. *Coronary restenosis*. Boston: Blackwell Scientific Publications, 1993:169–191, with permission.)

Because symptoms are a weak end point or marker of restenosis, “clinical” restenosis could be defined as a clinically serious cardiac event likely related to restenosis. This would include myocardial infarction, cardiac-related death, or revascularization of the target vessel by repeat percutaneous intervention or bypass surgery. Broader definitions of clinical restenosis include a positive stress test result in the territory of the target vessel. Most contemporary clinical PCI trials use a composite end point including target vessel revascularization, myocardial infarction, and death. For example, in the placebo group in the EPIC trial, the late (1- to 6-month) rate of repeat revascularization (18.4%), when hierarchically combined with the rates for myocardial infarction (2.4%) and death (1.8%), produced a composite clinical event rate of approximately 20%. This rate increased to 35% when early postangioplasty events (1 month or less), which are likely related to poor initial outcome rather than restenosis, were included. This same composite rate from immediately postprocedure to 6-month follow-up for the placebo cohort in the Evaluation of PTCA to Improve Long-term Outcomes by c7E3 Glycoprotein Receptor Blockade (EPILOG) trial (97) was 26%. This one-fourth reduction in overall clinically apparent restenosis between the EPIC and EPILOG trials is reflected by an 18% lower target vessel revascularization in EPILOG (Fig. 83.6) and likely indicates a more aggressive revascularization strategy because 14% of the placebo group required intracoronary stents to be placed. More recently, the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT) reported an approximately 10% rate of target vessel revascularization among patients receiving an intracoronary stent (i.e., roughly half of the patients in the EPIC trial). This reemphasizes the continued change in rates of clinically apparent restenosis in contemporary practice with more aggressive percutaneous revascularization strategies. Thus, given the different ways of estimating clinical restenosis, reported rates in some studies may be as low as 10% if only target vessel revascularization is considered, 30% if all ischemic and revascularization events are considered, or over 50% if any chest pain recurrence is included.

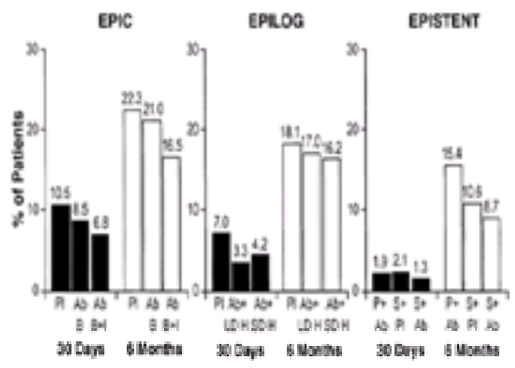


FIGURE 83.6 Target vessel revascularizations (urgent and nonurgent) performed by 30 days and by 6 months in the Evaluation of Chimeric Monoclonal 7E3 for the Prevention of Ischemic Complications (EPIC) trial, the Evaluation of PTCA to Improve Long-term Outcomes by c7E3 Glycoprotein Receptor Blockade (EPILOG) trial, and the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT). The EPILOG trial, which involved many of the same investigators as the EPIC trial, showed a reduced occurrence in target vessel revascularization compared with the latter. This may be due to evolution of a more aggressive angioplasty technique with bail-out stenting when needed. Likewise, a further reduction in target vessel revascularization was seen in EPISTENT with routine use of intracoronary stents. Ab, abciximab; B, bolus; B+I, bolus plus infusion; LD H, low-dose heparin; P, percutaneous transluminal coronary angioplasty; Pl, placebo; S, stent; SD H, standard-dose heparin.

Silent Restenosis

Asymptomatic or “silent” restenosis can be considered to occur in 10% to 15% of angioplasty patients given that, among all PTCA patients, approximately 40% have angiographically identified restenosis whereas 25% to 30% have symptoms and angiographically apparent restenosis. Specific studies of asymptomatic restenosis are limited; nevertheless, when silent restenosis is defined as stenosis of 50% lumen diameter or more at 6-month angiography and the absence of angina, the rates in individual reports range from 2% to 16% of all angioplasty patients (eTable 83.1.1) (47,48,49,50,51,52 and 53). In these trials of medium-term follow-up, 12% of all patients had silent restenosis, whereas 35% of those with restenosis were asymptomatic. One-third to one-half of asymptomatic patients with restenosis at 6 months develop symptoms in subsequent months (49).

***e*TABLE 83.1.1** RATES OF ASYMPTOMATIC RESTENOSIS

Study	Total PTCA (n)[a]	Symptomatic preprocedure (%)	Follow-up angiography (%)	Asymptomatic restenosis (%)
Popma et al. (49)	90	100	100	12.1
Levine et al. (48)	100	NA	92	2.2
Holmes et al. (47)	665	NA	84	8.1
Vetrovec et al. (50)	598	NA	85	15.5
Hernandez et al. (51)	927	90	91	15.8
Mata et al. (53)	74	97	96	3.0
Bengston et al. (52)	209	NA	96	10.0
Pooled	*2,663*		*91*	*12.1*

NA, data not available; PTCA, percutaneous transluminal coronary angioplasty.

[a]Number of successful PTCA procedures.

The reasons for lack of symptoms despite restenosis may be related to the angiographic definition of restenosis (stenosis of 50% diameter or greater). Some patients probably do not develop ischemia until the lesion is more advanced (stenosis of 70% diameter or more), and several studies have shown that those with asymptomatic restenosis have less severe cases (49,50). Alternatively, vessels that supply nonviable myocardium, along with those previously completely occluded or collateral vessels, may not develop ischemia (49,51). Patients with diabetes may also be more likely to have a silent stenosis recurrence.

NONINVASIVE METHODS FOR CLINICAL EVALUATION OF RESTENOSIS

Because the presence of symptoms is an unreliable marker for restenosis after angioplasty, results of noninvasive cardiac stress tests have been studied by a number of investigators. The attractions of noninvasive tests over repeat angiography include a more favorable procedural cost, time requirement, and risk. When reviewing trials assessing restenosis, one should remember that, to study the accuracy of noninvasive testing, a high percentage of follow-up angiograms are needed to avoid selection bias. In addition, as newer noninvasive modalities have been developed over the past decade that have improved sensitivity and specificity for detecting myocardial ischemia, the angioplasty cases being undertaken have become more complex and often involve multivessel disease, so that the possibility arises of incomplete revascularization or multiple potential sites of restenosis. Early in the evolution of coronary angioplasty, many patients were followed by routine treadmill testing. This test was soon coupled with nuclear scintigraphy, stress echocardiography, or positron emission tomography (PET).

Exercise Treadmill Electrocardiography

Myocardial stress testing with exercise electrocardiography is widely available and has moderate sensitivity for detecting myocardial ischemia. Testing in the early postangioplasty setting can be performed relatively safely within days of the PTCA procedure (98,99), although most clinicians have focused on a 4- to 6-month postprocedure interval because this is when restenosis typically becomes manifest and predictive accuracy is higher. Other factors affecting the usefulness of exercise electrocardiography include the presence of multivessel disease, history of previous myocardial infarction or baseline electrocardiographic abnormalities, and reliability of the preprocedural exercise treadmill testing (ETT). Pooled data from 14 study reports (52,98,100,101,102,103,104,105 and 106) in which restenosis was evaluated using ETT in a total of 2,103 patients indicate that the positive predictive value and negative predictive value of ETT are 55% and 73%, respectively (*e*Table 83.1.2). Although 74% of these patients had only single-vessel disease, the accuracy of ETT was mediocre and virtually the same as reported for symptom status alone. Several studies at Duke University have examined the value of postangioplasty exercise stress testing in detecting restenosis. Bengtson et al. (52) reported the results for 200 patients who had successful elective angioplasty followed by ETT and follow-up angiography approximately 6 months after PTCA without intervening cardiac events. Among clinical and ETT-related variables, only three were independent predictors of angiographically identified restenosis: recurrent angina, exercise-induced angina, and a positive result on the exercise test. In short, the positive predictive value of ETT is moderate, and the negative predictive value is higher in studies in which a greater percentage of patients have single-vessel coronary artery disease or the test is performed later than 1 month after angioplasty.

***e*TABLE 83.1.2** RESULTS OF EXERCISE TREADMILL TESTING FOR THE EVALUATION OF RESTENOSIS

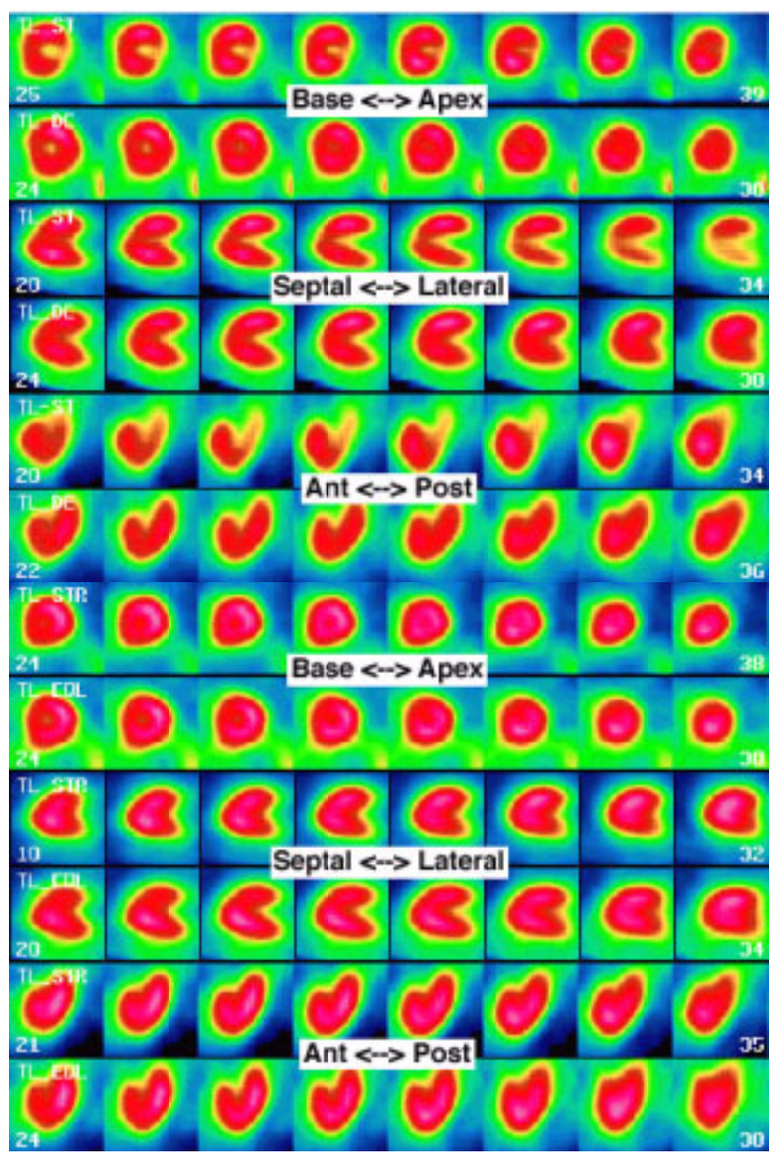
Study	Year	Single-vessel coronary artery disease (%)	No. eligible patients[a]	Interval from PTCA to exercise study	Angiographic restenosis rate (%)	Positive predictive value (%)	Negative predictive value (%)
Scholl et al. (381)	1982	83	30	6 mo	31	64	50
Ernst et al. (372)	1985	100	25	4–8 mo	16	50	95
Wijns et al. (100)	1985	96	89	1 mo	39	55	66
O'Keefe et al. (104)	1988	56	48	1 mo	27	29	73
Honan et al. (103)	1989	57	144	6 mo	40	57	63
Korzick et al. (98)	1990	46	218	3 days	46	40	48
Bengston et al. (52)	1990	67	200	6 mo	25	35	84
El-Tamimi et al. (101)	1990	100	31	1 mo	45	100	94
Pirelli et al. (106)	1991	91	75	12 mo	15	29	90
Coma-Canella et al. (105)	1992	76	58	6 mo	74	93	61
Hillegass et al. (102)	1992	NA	703	6 mo	37	65	79
Roth et al. (380)	1994	100	78	6 mo	37	37	77
Desmet et al. (371)	1995	86	191	6 mo	33	52	70
Azpitarte et al. (367)	1995	79	213	2–8 mo	39	60	72
Pooled		*74*	*2,103*		*37*	*55*	*73*

NA, data not available; PTCA, percutaneous transluminal coronary angioplasty.

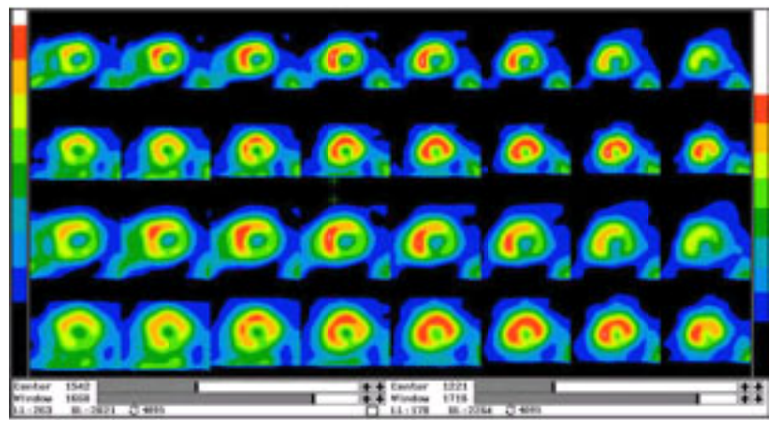
[a]Patients completing angiographic follow-up.

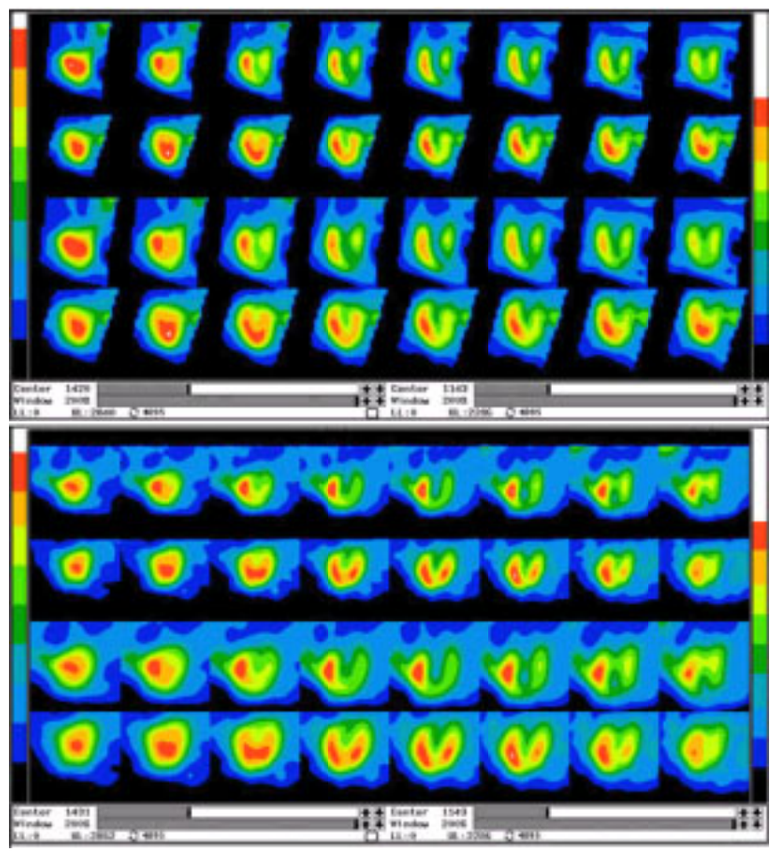
Nuclear Scintigraphic Evaluation

Adding nuclear scintigraphy to myocardial stress testing yields higher predictive values than for electrocardiography alone, and this is the case in assessment of restenosis. Radionuclide modalities used in evaluating restenosis include exercise radionuclide ventriculography, planar thallium-201 (Th-201) myocardial perfusion imaging, single-photon emission computed tomography (SPECT), and technetium-99 (Tc-99) and rubidium (Rb) PET scanning. Radionuclide ventriculography (sometimes referred to as radionuclide angiography) compares ventricular function at rest and during exercise, whereas Th-201, Tc-99, and Rb scintigraphy are used to assess regional myocardial perfusion. Although the literature contains reports of many studies evaluating the use of radionuclide scintigraphy in detecting restenosis, many are retrospective or are biased due to a low rate of angiographic follow-up.



Thallium-201 single-photon emission computed tomography stress and delayed images (A). Transverse, sagittal, and coronal plane images demonstrating lateral wall ischemia in a patient with severe proximal left circumflex artery stenosis. Thallium-201 single-photon emission computed tomography stress and equilibrium images (B). Transverse, sagittal, and coronal plane images obtained from a patient after successful intervention for severe proximal left circumflex artery stenosis (normal study).





Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery.

Video 83.6 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 83.7 Dual isotope resting thallium-201/stress technetium-sestamibi single-photon emission computed tomography transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating anterolateral, lateral, mid to distal inferolateral, distal inferior, and apical ischemia. Moderate transient left ventricular chamber dilation is seen in stress images. In the same patient, the left anterior oblique cranially angulated view (*first video*) illustrates severe obstruction of the mid left anterior descending, second diagonal, and proximal left circumflex and the left anterior oblique cranially angulated view (*second video*) illustrates severe disease in the posterior descending, posterior ventricular, and posterior lateral branches of the right coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Several small but well-designed series provide important insight. For example, DePuey and colleagues (107) studied 41 patients using radionuclide ventriculography before, 4 days after, and 4 to 12 months after coronary angioplasty. All patients underwent angiography at late follow-up and were categorized according to degree of angiographically determined restenosis: less than 20%; more than 20% but less than 50%, and 50% or more. Abnormal results of radionuclide ventriculography, defined as less than a 5% increase in ejection fraction with exercise or an exercise-induced wall motion abnormality, were found in 27% of patients with less than 20% restenosis but in 88% of patients with 50% restenosis or more. Patients with 20% to 50% restenosis had an intermediate response. From this study, the negative predictive value of radionuclide angiography in detecting restenosis of 50% or more was higher than in most electrocardiographic studies (94% vs. 74%), but the positive predictive value remained moderate (54%).

The positive predictive value of exercise Th-201 imaging is, on average, higher than that of exercise electrocardiography or radionuclide ventriculography but is still moderate (100,104,107,108,109,110,111,112,113,114 and 115) (*e*Table 83.1.3). This moderate predictive ability again may reflect the diffuse nature of coronary atherosclerosis with significant disease in small vessels or at untreated sites, which produce a false-positive result for restenosis. In addition, exercise thallium scanning abnormalities seen in patients before angioplasty frequently persist in the early days after angioplasty and are possibly attributable to depressed coronary flow reserve. Manyari et al. (116) performed sequential thallium perfusion studies in 43 patients before and at approximately 9 days, 3 months, and 6 months after successful angioplasty. Only patients with single-vessel coronary artery disease, without prior myocardial infarction, and without restenosis at 6- to 9-month follow-up angiography were included. Although symptoms and exercise treadmill results improved immediately and remained normal after PTCA, 28% of patients had persistently abnormal thallium perfusion scans 4 to 18 days after angioplasty. The perfusion defects in the distribution of the treated stenosis progressively improved from baseline in studies at 4 to 18 days, and from results at 4 to 18 days in studies at 3 months. As with exercise electrocardiographic evaluations, planar perfusion scans performed very early after PTCA may have limited usefulness, and the best course is usually to postpone assessment for restenosis to at least 1 month after angioplasty. In summary, for combined data from 12 nuclear studies assessing restenosis in approximately 700 patients, the positive and negative predictive values are 70% and 89%, respectively (*e*Table 83.1.3). The highest accuracy is for SPECT imaging (positive predictive value of 82% and negative predictive value of 92%), and this modality is therefore recommended.

***e*TABLE 83.1.3** RESULTS OF NUCLEAR AND ECHOCARDIOGRAPHIC STRESS TESTING IN THE EVALUATION OF RESTENOSIS

Study	Year	Single-vessel coronary artery disease (%)	Number of "eligible" patients[a]	Interval from PTCA to nuclear study	Angiographic restenosis rate (%)	Positive predictive value (%)	Negative predictive value (%)
RNA Tc-99							
DePuey et al. (107)	1984	98	41	4–12 mo	44	54	94
Ernst et al. (372)	1985	100	25	4–8 mo	16	44	100
O'Keefe et al. (104)	1988	56	48	1 mo	27	42	100
Planar Th-201							
Scholl et al. (381)	1982	83	36	1 mo	31	56	42
Wijns et al. (100)	1985	96	89	1 mo	39	74	83
Ernst et al. (372)	1985	100	25	4–8 mo	16	50	100
Hardoff et al. (108)	1990	45	71	1 d	32	53	86
SPECT Th-201							
Jain et al. (374)	1988	52	22	3 d	33	79	88
Breisblatt et al. (109)	1988	73	121	3–13 mo	33	93	93
Hecht et al. (110)	1990	53	116	3–9 mo	46	80	92

Marie et al. (111)[b]	1993	87	62	5–7 mo	26	68	98
SPECT Tc-99						
Milan et al. (376)	1996	68	37	NA	53	81	86
Nuclear pooled		*76*	*693*		*35*	*70*	*86*
Echocardiography						
Aboul-Enein et al. (112)	1991	79	101	6 mo	47	78	73
Hecht et al. (113)	1993	51	80	3–9 mo	56	98	70
Heinle et al. (114)	1993	40	103	6 mo	44	59	62
Hoffman et al. (373)	1994	90	60	2–9 mo	37	75	89
Takeuchi et al. (115)	1995	NA	53	5 mo	43	87	85
Crouse[c] et al. (369)	1996	NA	157	9 mo	79	95	82
Echocardiography pooled		*65*	*554*		*56*	*84*	*76*
Overall		**69**	**1,247**		**44**	**75**	**83**

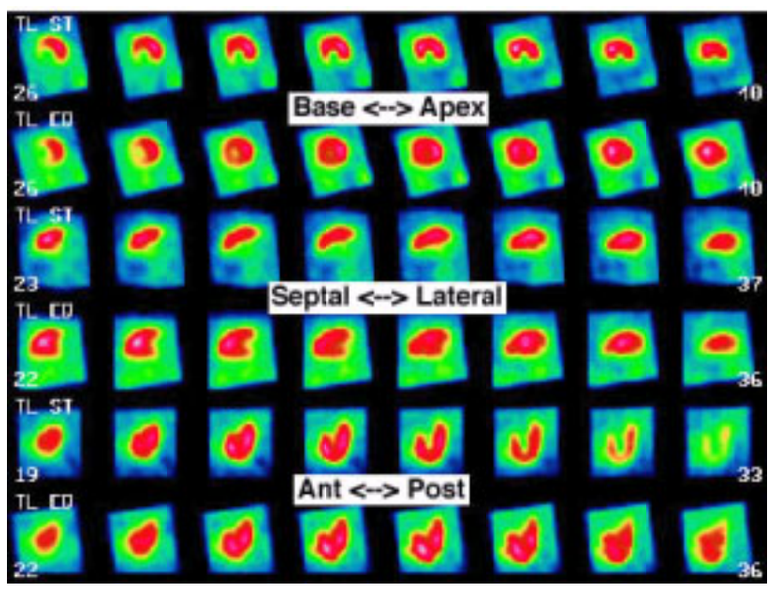
NA, data not available; RNA Tc-99, radionuclide angiocardiography with technetium-99; planar Th-201, planar thallium-201 myocardial perfusion imaging; PTCA, percutaneous transluminal coronary angioplasty; SPECT Th-201, single-photon emission computed tomography with thallium-201.

[a]Patients completing angiographic follow-up.

[b]Studied asymptomatic patients only.

[c]Studied symptomatic patients only.

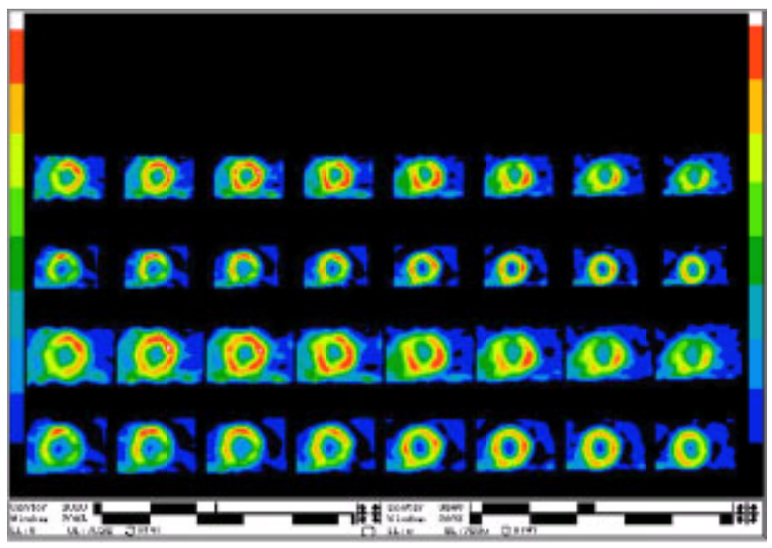
A careful prospective study of noninvasive assessment of restenosis was performed by Wijns and colleagues (100) and encompassed 89 patients who had undergone successful primary PTCA. All patients underwent exercise electrocardiography and thallium scintigraphy at 4 weeks and repeat catheterization within 6 months after angioplasty. Angiographically identified restenosis occurred in 35% of patients. The predictive accuracy of thallium perfusion scintigraphy for restenosis was 74%, compared to 50% for exercise electrocardiography alone. The authors demonstrated the insignificant contribution of electrocardiography compared with Th-201 imaging in this series. SPECT thallium imaging more effectively localizes the coronary vascular territory of ischemia than planar imaging techniques and may be advantageous in patients with known multivessel coronary artery disease or incomplete revascularization after PTCA. To study this, Hecht and colleagues (110) performed SPECT Th-201 imaging in 116 patients before performing repeat cardiac catheterization for possible restenosis. Among these patients, a similar number had had single-vessel angioplasty and multivessel angioplasty, and 77% achieved complete revascularization. Whereas exercise electrocardiography alone had a predictive accuracy of 52%, SPECT Th-201 imaging accurately identified restenosis in 86% of sites. Results were similar for patients with partial and complete revascularization. In addition, 81% of diseased nondilated vessels were correctly identified by tomographic thallium imaging.

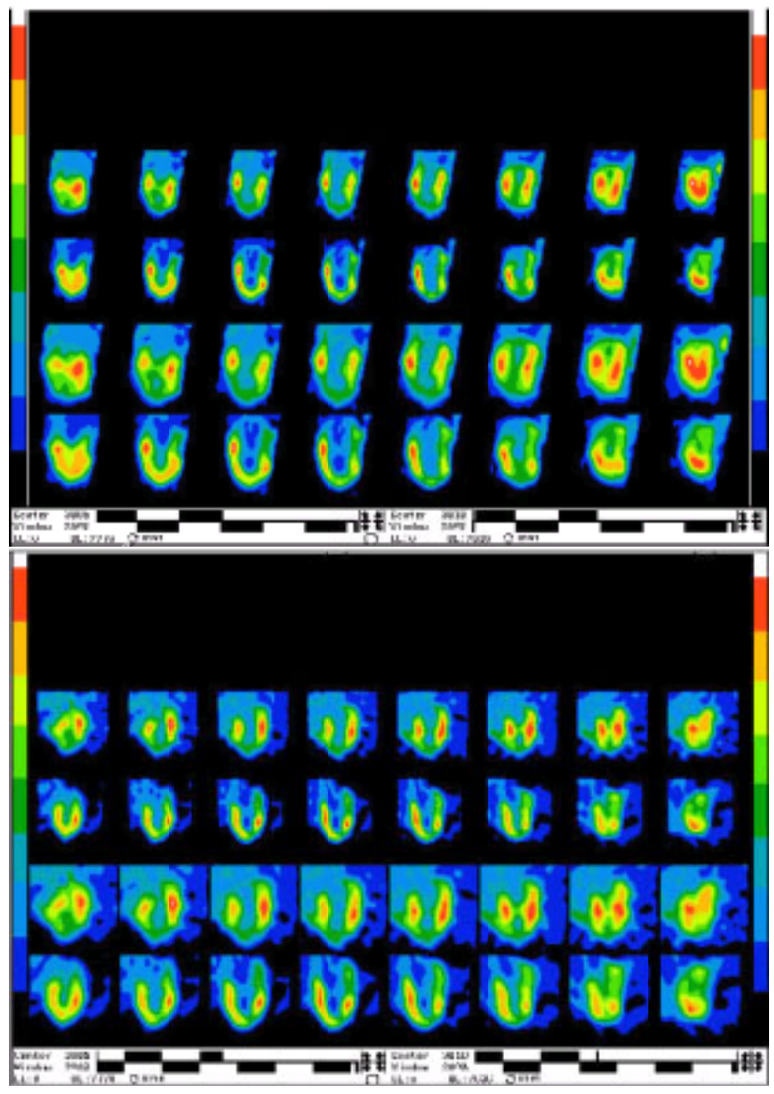


Thallium-201 single-photon emission computed tomography stress and equilibrium images. Transverse, sagittal, and coronal plane images demonstrating inferior and posterior wall ischemia in a patient with a severe proximal stenosis in a dominant right coronary artery.

Additional Noninvasive Methods

Several additional nuclear and nonnuclear imaging modalities, such as PET, isonitrile imaging, and stress echocardiography, have been studied more recently to determine their predictive ability for restenosis. Each of these modalities provides unique information or benefit. For example, by using different isotopes, PET studies can quantitate regional myocardial metabolism as well as perfusion, whereas isonitrile imaging or stress echocardiography can provide assessment of myocardial perfusion and wall motion. Several studies of exercise or pharmacologic stress echocardiography have been completed (106,112,113,114 and 115). Using supine bicycle stress echocardiography to detect restenosis in 80 patients with 129 treated sites, Hecht et al. (113) reported a sensitivity and specificity of 87% and 95%, respectively, for this test. This high sensitivity may be due, in part, to the high rate of restenosis (56%) and incomplete revascularization (32%) among patients in the study group. Overall, the positive predictive value and negative predictive value for stress echocardiography in over 500 patients are 84% and 76%, respectively (*e*Table 83.1.3).





Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery.

Video 83.8 Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 83.9 Resting rubidium-82 with fluorinated deoxyglucose viability positron emission tomographic scanning in a 63-year-old patient in the transverse (*first image*), sagittal (*second image*), and coronal (*third image*) plane images demonstrating hibernating myocardium involving the mid and distal anterior, mid and distal anteroseptal, and distal septal segments. Matched perfusion and metabolic defects are seen involving the apical and inferoapical segments. The right anterior oblique left ventriculogram (*first video*) also shows the presence of hibernating myocardium, due to occlusion of a "wrap around" left anterior descending coronary artery. The mid and distal anterior, apical, and inferior apical walls are akinetic. The anteroposterior cranially angulated angiogram (*second video*) demonstrates subtotal occlusion of a large "wrap around" left anterior descending coronary artery in the same patient with a dominant left coronary artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In summary, the predictive accuracy of symptom occurrence for restenosis is, at best, moderate and is not significantly improved by the use of exercise electrocardiography. The addition of imaging by nuclear scintigraphy or echocardiography increases both the positive and negative predictive value of testing to approximately 80%. SPECT imaging with thallium or technetium-99m sestamibi have respectably high accuracy, and more recent data show stress echocardiography to be similarly accurate. These are the leading choices for noninvasive assessment of restenosis. Testing is most reliable between 1 and 5 months after revascularization.

CLINICAL PROFILE

Although no favorable variable has been identified that assures freedom from restenosis, and none has been identified that makes restenosis inevitable, several factors clearly influence the likelihood of restenosis. A large number of clinical, anatomic, and procedural variables have been associated with restenosis in various studies. Many of these observations, however, were from retrospective or small prospective studies, so some findings have been inconsistent. Large pharmacologic or device trials with high rates of angiographic follow-up have been most helpful. Importantly, many factors that were shown to be associated with restenosis after balloon angioplasty are no longer predictive of restenosis in the stent era. Table 83.2 lists factors reported to be associated with restenosis. Factors that have been independent predictors in multivariable modeling or consistently associated in many balloon angioplasty studies are printed in italics, as are similar factors for stent procedures. Factors associated with stenosis recurrence can be categorized as related to the patient, to the lesion, or to the procedure.

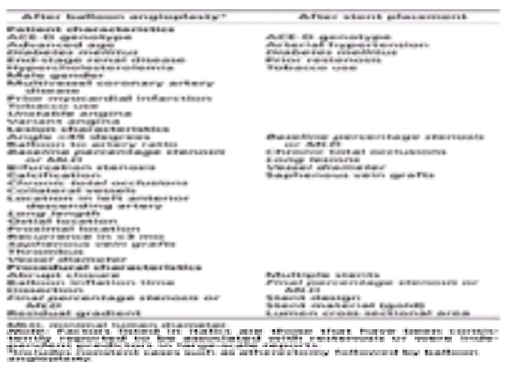


TABLE 83.2 CHARACTERISTICS ASSOCIATED WITH RESTENOSIS

Patient-Related Factors

Patient characteristics (e.g., age, race, gender, etc.) obviously have the same effect for all coronary lesions within the given individual. Weintraub et al. (117) showed that the leading predictor of restenosis for a particular lesion among patients undergoing multisite angioplasty was the occurrence of restenosis at the other treated sites. The list of patient-related variables considered in predictive models of restenosis is extensive and includes demographic characteristics, medications, concomitant medical diseases, serologic markers, and genetic polymorphisms. Large-scale clinical trials of restenosis have not revealed any consistent age-, race-, or gender-related patterns. At this time, only two patient-related risk factors have certain effects on restenosis: diabetes mellitus and unstable angina pectoris.

Demographics

Age and gender are believed not to affect restenosis, although patients of advanced age and female patients are occasionally reported to have less favorable clinical outcomes. Male gender was associated with restenosis in several older angioplasty studies (47,54), but the angioplasty equipment used in these early studies is now believed to have been undersized for the larger coronary arteries of men and thus would have left a greater residual stenosis than in female patients. More recent data have not found a gender effect in lesion recurrence. For example, among the 510 patients in the Multi-Hospital Eastern Atlantic Restenosis Trial (M-HEART) study group, restenosis was angiographically present in 39% of men and 42% of women (118). Similarly, an association between cigarette smoking and restenosis has been variably reported, but again, more recent data (56,118,119) from larger studies with greater angiographic follow-up have failed to demonstrate an association. In large-scale series of intracoronary stenting, no demographic characteristics other than the presence of diabetes mellitus has been associated with restenosis.

Diabetes Mellitus

Just as diabetes is a strong risk factor for atherosclerotic heart disease, with insulin dependency producing a higher risk, so too is diabetes an important risk factor for restenosis. This association was found first in early NHLBI PTCA Registry data (47), and a series of subsequent reports (120,121 and 122) demonstrated the relative risk of restenosis among patients with diabetes to be approximately 1.3 compared with that of patients without diabetes. Although the exact degree of risk for patient groups with type I and type II diabetes is uncertain, several studies have shown insulin-dependent diabetes to be associated more often with restenosis (123,124). Other investigations have examined this association with restenosis by studying glycosylated hemoglobin levels, insulin levels, or microalbuminuria. Regardless, the mechanisms leading to restenosis among diabetic patients are multiple (125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143 and 144) (Table 83.3) and vary in effect between those with type I and type II diabetes and among patients with type II diabetes depending on insulin use (145,146). High glucose concentrations and the presence of advanced glycosylation end products inhibit endothelial cell function in several ways, including by decreasing production of endothelium-derived relaxing factor and prostacyclin, and by retarding cellular replication during reendothelialization (Table 83.3). Because the process of endothelial cell regeneration at the site of vessel wall injury is slowed, the triggers of intimal hyperplasia linger, which may explain the greater neoproliferative response of diabetic patients (124,147). In an animal model of restenosis, Van Belle et al. demonstrated a reduction of in-stent intimal formation and restenosis by accelerating endothelialization with local delivery of vascular endothelial growth factor (148).

Endothelial dysfunction
↓ Endothelium-derived relaxing factor (EDRF) (131,144)
↓ Prostacyclin (133,138)
↓ Endothelial cell replication (134,140)
↑ Endothelin-1 production (126,135)
↑ Platelet-derived growth factor (PDGF) (128)
Heightened platelet activity
↑ Number of activated platelets (137)
↑ Platelet adhesiveness (141)
↑ Platelet aggregability (140)
↑ Thromboxane A_2 synthesis (139,140)
↑ PDGF (140)
↑ Fibrinogen levels (132)
Increased growth factors
↓ EDRF (125,136)
↑ PDGF (142)
↑ Insulin-like growth factor-1 (129,130)
↑ Endothelin-1 (125)
↑ Fibroblast growth factor (127)
↑ Transforming growth factor-β (143)

↑, increasing; ↓, decreasing.

TABLE 83.3 POSSIBLE MECHANISMS BY WHICH DIABETES AFFECTS RESTENOSIS

Platelets are known to exist more frequently in an activated state in diabetic patients despite clinical absence of vascular inflammation or injury (137). Similarly, in patients with diabetes, platelets have been shown to be more adhesive and aggregable when stimulated. These and other hypercoagulable features of diabetic patients (Table 83.3) likely contribute to the restenosis process. Finally, the endothelial and platelet abnormalities of diabetic patients allow growth factor promotion. The normally functioning endothelium and platelets serve to inhibit or suppress medial smooth muscle cell growth, and derangements in these systems enhance expression of mitogens such as PDGF, TGF-b, and bFGF (Table 83.3). Because of these multiple mechanisms leading to restenosis, the contemporary approach to treating patients with diabetes is aggressive.

The NHLBI presented a national health alert based on the findings of the Bypass Angioplasty Revascularization Investigation (BARI) study (149) showing patients with diabetes to have a worse 5-year survival rate after multivessel angioplasty than after bypass surgery (66% vs. 81%), perhaps in part due to late or silent restenosis. On the other hand, the survival curves for diabetic patients treated by angioplasty or bypass surgery in BARI separate slowly over a several-year period, so that restenosis is unlikely to be a primary explanation for the survival difference. A survival difference between diabetic patients undergoing percutaneous revascularization and those undergoing surgical revascularization has not been reported by any other prospective clinical trial (150) nor was this observed in the BARI registry of approximately 2,000 patients. A multicenter database encompassing nearly 16,000 patients undergoing a first revascularization also showed patients with diabetes to have a worse outcome after angioplasty than after bypass surgery, but on multivariable analysis of survival, no interaction of revascularization type and diabetes was present (151). Beyond balloon angioplasty, studies of directional, rotational, and laser atherectomy have shown diabetic patients to experience restenosis more often than nondiabetic patients.

The use of intracoronary stents has not ameliorated the effect of diabetes on restenosis. Combined data from four separate reports including nearly 3,300 patients (123,152,153 and 154) showed that angiographically identified restenosis occurred in 35% of diabetic patients and 23% of nondiabetic patients when contemporary stenting methods were used. Patients with diabetes were also more likely to undergo target vessel revascularization by 6-month follow-up than were nondiabetic patients (22% vs. 15%). Kastrati et al. reported diabetes to be a leading independent risk for restenosis in multivariable modeling based on data from over 4,500 consecutive patients. Diabetes was associated with an increase in rate of angiographically apparent stenosis from 31% to 35% and an odds ratio of 1.21 (155). Similarly, after directional atherectomy, diabetic patients in CAVEAT-I had greater late loss and restenosis than nondiabetic patients (156). That patients with diabetes have greater late loss after angioplasty, atherectomy, and stenting reemphasizes the biologic effects of diabetes. Using serial intravascular ultrasonography, Kornowski et al. (157) showed that the late loss after angioplasty among diabetic patients was due to exaggerated intimal hyperplasia. Interestingly, in EPISTENT, the combination of intracoronary stent placement and platelet glycoprotein IIb/IIIa inhibition did lead to clinically and angiographically determined restenosis rates that were low and similar among patients with and without diabetes (158). The rate of target vessel revascularization at 6 months was 8.1% and 8.8% for patients with and without diabetes, respectively (Fig. 83.7). Aside from this report, most data support the concept that, even with aggressive revascularization strategies, diabetic patients have restenosis and recurrent ischemic events more often than nondiabetic patients.

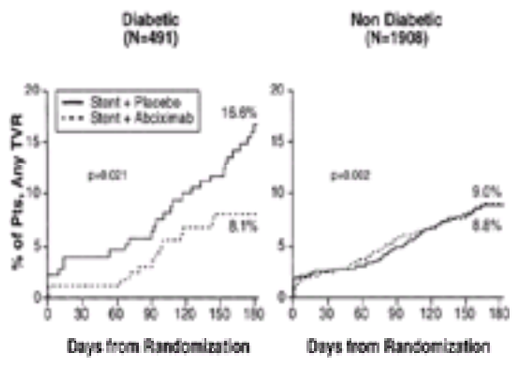
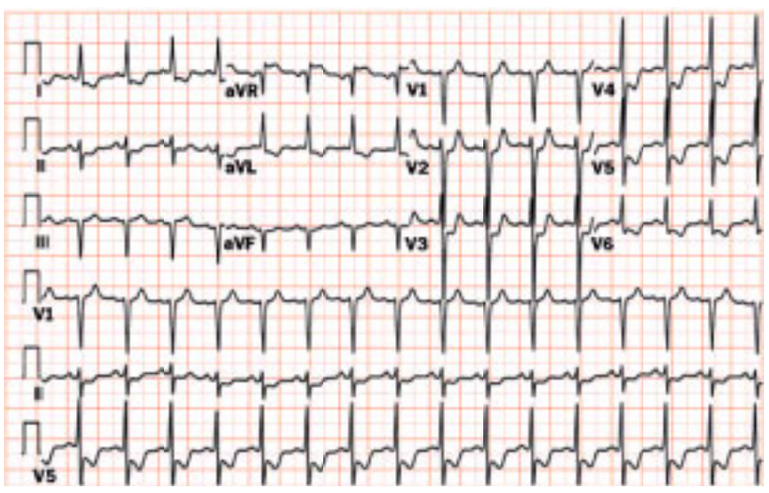


FIGURE 83.7 Kaplan-Meier distribution curves for the likelihood of restenosis among diabetic and nondiabetic patients in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT). As seen in previous stent trials, diabetic patients had a higher rate of target vessel revascularization (TVR) than did nondiabetic patients. In contrast, diabetic patients receiving abciximab during intracoronary stent placement had a low 6-month rate of target vessel revascularization similar to that of nondiabetic patients.

Unstable Angina

Like diabetes, unstable angina has been consistently associated with restenosis, especially when unstable angina is defined as pain at rest or accompanied by ischemic changes in the electrocardiogram. Because unstable angina defined in this way is often associated with thrombus-containing coronary lesions, the view that restenosis occurs acutely from clot propagation and chronically from clot transformation is plausible. Over the hours to days after angioplasty in the setting of a ruptured plaque, thrombus may propagate and organize to cause a substantial loss in lumen diameter. Thrombin present within the clot facilitates the release and heightened activity of several mitogens, including PDGF and bFGF, thereby promoting cellular proliferation and clot transformation into a neointimal thickening. The contents of the underlying plaque in unstable angina may also directly promote restenosis. Moreno and colleagues (159) studied 50 atherectomy specimens from patients with unstable angina. By careful immunocytochemical study of the tissue removed, they were able to demonstrate that lesions with subsequent restenosis had twice as large an area of macrophage-rich tissue within the plaque. In the lesions studied, the number of macrophages present was the only independent predictor for restenosis by logistic regression analysis. Macrophages are known to be increased in plaques from patients with unstable angina (160), and they release cytokines, metalloproteinases, and growth factors that may lead to neointimal growth and constrictive scarring of the adventitia.



Subendocardial ischemia. Anterolateral ST-segment depression is consistent with diffuse subendocardial ischemia versus non–Q-wave myocardial infarction.

Unstable angina vs. non–Q-wave myocardial infarction. ST-segment depression in leads V_2 through V_5 supports acute ischemic syndrome.

Clinically, several trials have reported an increased occurrence of restenosis among patients with new-onset angina (less than 2 months) (47,54), accelerating angina (161), or rest angina (162). The degree of symptom instability appears to be directly proportional to the subsequent event rate. Taken together, these and other balloon angioplasty trials (163) suggest that the relative risk of restenosis in those with unstable angina is 1.2 to 1.4 times higher than in patients with no or stable angina. Among patients receiving an intracoronary stent, unstable angina has not been consistently associated with restenosis.

Lipoprotein Levels

Several small studies reported an association between restenosis and the levels of various lipoproteins, including triglycerides (164), total cholesterol (119), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (164), and lipoprotein(a) [Lp(a)] (165,166 and 167). For each of these lipoproteins, however, a corresponding study has been carried out showing no association with restenosis (168,169). The reasons for this disparity include small sample sizes, nonnormal distributions of the levels of some lipoproteins, and changing levels of lipoproteins associated with acute coronary syndromes, hospitalization, and cardioactive medications. Moreover, dynamic changes in atherosclerotic plaque progression and regression cannot be angiographically separated from restenosis. Pooled data from the Coronary Artery Restenosis Prevention on Repeated Thromboxane-Antagonism (CARPORT) (170), Multicenter European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) (69), Multicenter American Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MARCATOR) (86), and Post-Angioplasty Restenosis Ketanserin (171) studies reported no association—either by categoric or continuous variable approaches—between serum total cholesterol or cholesterol subfractions and angiographically identified restenosis (172). Furthermore, studies targeting the reduction of lipoproteins, in particular LDL cholesterol, have shown no reduction in restenosis (84).

Lp(a) has been specifically studied in the setting of restenosis because the Lp(a) gene is among the most polymorphic genes in the human genome, and plasma levels of Lp(a) are wide ranging in the population. Desmarais et al. (166) studied 200 consecutively treated patients undergoing balloon angioplasty for whom lipoprotein fractions, including Lp(a), were simultaneously measured. Patients were evaluated 4 to 6 months after angioplasty by treadmill testing or coronary angiography when clinically indicated. Patients with clinically identified restenosis had significantly greater Lp(a) concentrations than those without restenosis. The odds ratio for clinically apparent restenosis was substantially higher for each increasing quintile concentration of Lp(a). The investigators did not genotype these patients nor did they perform consistent quantitative angiographic follow-up. Yamamoto et al. (173) and Miyata et al. (174) separately found Lp(a) to be associated with angiographically determined restenosis in small studies of Japanese patients. Lp(a) levels of 30 mg per dL or higher predicted a greater than twofold increase in restenosis. Because Lp(a) is strongly associated with the development of coronary artery disease, investigators who have not found an association between Lp(a) and restenosis have suggested that recurrent clinical ischemia is due to disease progression or new disease formation, rather than restenosis of the target lesion (175). Levels of Lp(a), as well as of HDL, LDL, and total cholesterol, were systematically studied in 671 consecutively treated patients at stent implantation and angiographic follow-up by Wehinger et al.

(176). No correlation was found between late loss or restenosis and the level of any lipoprotein. In short, although lipoproteins are clearly related to *de novo* atherosclerotic lesion progression and regression, an effect of lipoproteins on the process of restenosis is not substantiated except possibly for Lp(a).

Genetics of Restenosis

Coronary artery disease and stenosis recurrence after PTCA are likely complex processes involving multiple genes as well as interactions with many nongenetic factors. Considering balloon angioplasty cases, Berger and colleagues performed a retrospective analysis of 144 treated lesions in 113 patients and found the rate of restenosis to be 35% among patients with a history of restenosis at a different coronary site and 27% among patients without such a history (177). This observed difference did not reach statistical significance in this report but has reached significance in several others (117,178), and these findings suggest that a history of restenosis at one site increases the likelihood of restenosis at future sites. Some data also suggest that patients undergoing multivessel PTCA have a patient-specific risk of restenosis that is separate from lesion-related factors (117). Considering this concept in the stent era, Kastrati and colleagues analyzed a series of 3,370 consecutively treated patients, more than 80% of whom had follow-up angiography at 6 months. Using a multivariate model for restenosis, they found that 12% of the predictive value for restenosis was patient specific. The remaining factors were lesion related (54%) or procedure related (34%) (179). Obviously, genetic determinants of restenosis could explain some of the patient-related factors. Indeed, examining the distribution of angiographically determined stenosis diameter 6 months after stent placement, Schömig et al. (180) showed the frequency distribution curves to be bimodal, which suggests two different populations with different propensities for restenosis (Fig. 83.8).

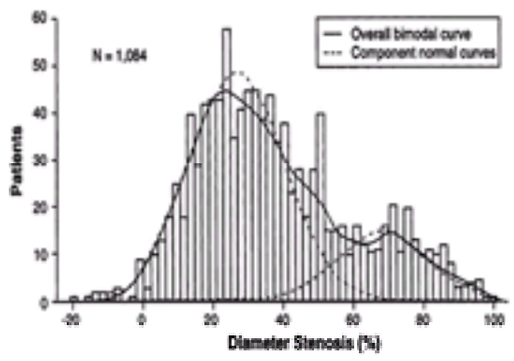


FIGURE 83.8 Distribution of percentage diameter of stenosis at follow-up angiography for 1,084 patients receiving an intracoronary stent. The overall curve appears bimodal, which suggests the existence of two separate populations or components of the normal curve. These two populations appear to have divergent propensities for restenosis, which implies a genetic or populational basis for restenosis. (From Kastrati A, Dirschinger J, Schömig A. Genetic risk factors and restenosis after percutaneous coronary interventions. *Herz* 2000;25:34–46.)

Several genomic studies have assessed the relationship between restenosis and a particular gene, locus, or combination of genes, including the angiotensin-converting enzyme (ACE) gene, HLA-C locus Cw1, apolipoprotein E (apoE) genes (181), and platelet glycoprotein IIb/IIIa polymorphisms. Experimental studies support the hypothesis that the renin-angiotensin system plays a role in the pathogenesis of restenosis (182), and ACE inhibitors have been shown to prevent neointimal thickening after angioplasty in animal models. In humans, the presence of the ACE deletion (ACE-D) allele is associated with higher tissue and plasma levels of ACE and has been identified as a potential risk factor for myocardial infarction (183). In 1993 Ohishi et al. (184) reported presence of this ACE deletion to be a potent genetic risk factor for coronary restenosis. In this relatively small study of patients undergoing emergency angioplasty for acute myocardial infarction, the investigators found a greater likelihood of angiographically identified restenosis among those with the ACE-D allele. Subsequent studies have not been consistent. Hamon et al. (185) studied 118 consecutively treated patients with single-vessel coronary artery disease after successful angioplasty. In this quantitative study, the ACE gene polymorphism had no influence or association with angiographically apparent restenosis. A similar negative finding was reported by Samani et al. (186) for 233 patients in the Subcutaneous Heparin Angioplasty Restenosis Prevention study.

Table 83.4 summarizes studies assessing the ACE polymorphism as it relates to angiographically determined restenosis (184,185,186,187,188,189,190 and 191). When data were pooled for 640 patients after balloon angioplasty, the odds ratio for restenosis for patients with the deletion genotype was 1.3 relative to patients with the insertion genotype. When this relationship was assessed among patients after coronary stenting, the odds ratio was 1.2 (95% confidence interval, 0.9 to 1.5). Important, however, is the wide variability in odds ratios among studies. This is likely due to the small sample size in most studies. As can be seen, the larger studies found the smaller odds ratios, and their results suggest no or minimal effect of ACE genotype. Addressing this issue, Koch et al. (190) prospectively studied 1,850 consecutively treated patients undergoing stent implantation. The ACE-DD genotype was not associated with angiographically apparent restenosis at 6 months (odds ratio of 0.9), nor did this genotype influence 1-year clinical outcome. In summary, the likely contribution of the ACE-deletion genotype alone to restenosis is minor.

Study	Year	n*	DD vs. II odds ratio (95% CI)
Balloon angioplasty			
Ohishi et al. (184)	1993	82	5.6 (1.6–19.8)
Samani et al. (186)	1995	233	0.8 (0.4–1.7)
Hamon et al. (185)	1995	118	0.9 (0.3–2.7)
van Bockxmeer et al. (187)	1995	207	1.8 (0.8–3.9)
Pooled		*640*	*1.3 (0.9–2.1)*
Stent			
Amant et al. (188)	1997	158	2.6 (0.8–9.1)
Ribichini et al. (169)	1998	176	16.9 (2.2–132)
Koch et al. (190)	2000	1,556	0.9 (0.7–1.3)
Gürlek et al. (191)	2000	158	6.3 (1.8–22.1)
Pooled		*1,890*	*1.2 (0.9–1.6)*

ACE, angiotensin-converting enzyme; CI, confidence interval; DD, homozygosity for ACE gene deletion; II, homozygosity for ACE gene insertion.
*Total study size.

TABLE 83.4 ACE-DD POLYMORPHISM AND RESTENOSIS

The reason for these inconsistent reports may be the multifactorial nature of restenosis, small sample sizes, or reporting bias. Although atherosclerotic coronary artery disease is believed to be a complex polygenic process, data considering restenosis as a polygenic process are limited. van Bockxmeer et al. (187) examined the combined influence of ACE and apoE genotypes on restenosis. Two hundred seven patients were systematically studied with angiographic follow-up. The distribution of the ACE genotypes did not predict restenosis, whereas the $apoEe_4$ genotype was more frequent among those with restenosis. More importantly, among those who had the combination of ACE-D and $apoEe_4$, the likelihood of restenosis was increased by 16-fold. In addition, multiple linear regression comparing the degree of lumen loss at follow-up angiography as a continuous variable revealed a significant independent effect of the ACE and apoE genotypes. These data suggest that, although the ACE genotype alone may not influence restenosis, important interactions may occur with other genes, such as the apoE gene. Understandably, advanced technologies are needed to step beyond this candidate gene approach and perform genomic studies of restenosis on a larger scale.

As genetic polymorphisms newly suspected to affect restenosis are studied, a wide variability in the predicted importance of these genes (or lack thereof) will be observed. For example, several studies have considered the association between platelet $a_{IIb}b_3$ (PI^A) polymorphism and restenosis after percutaneous coronary intervention. This particular polymorphism is associated with the gene encoding the platelet glycoprotein IIb/IIIa receptor and has been variably reported to affect the development of precocious atherosclerosis, myocardial infarction, and restenosis. As with the ACE polymorphism, not until large-scale evaluations are performed can the certainty and degree of effect for particular genes be determined.

Lesion-Related Factors

*De Novo**versus Restenotic Lesions***

The question of whether a prior restenosis portends a higher likelihood of restenosis at the same site has been the subject of great interest. Several studies have shown that the likelihood of restenosis after balloon angioplasty of a restenotic lesion (i.e., a second PTCA of the same site) is similar to that after angioplasty of a *de*

novo lesion (192,193,194 and 195). Comparing separate reports of restenosis after first and subsequent interventional procedures is difficult because the percentage of patients undergoing follow-up angiography has been low. In general, the reported rate of angiographically identified restenosis for lesions treated a second and third time by balloon angioplasty is approximately 40% (155,194,196,197,198,199,200,201,202,203,204,205,206 and 207) (eTable 83.4.1), which is similar to rates cited for *de novo* lesion balloon angioplasty in past years (Table 83.1). Bauters and colleagues, in a series of reports on a limited number of balloon angioplasty patients (196,197,208), showed that the rate of restenosis was similar after a first, second, and third angioplasty among patients within the same institution. The occurrence of restenosis does increase substantially in patients who undergo a fourth PTCA procedure or who undergo a second or third angioplasty less than 3 months after the previous procedure (197). Several studies using multivariate models to predict restenosis among those undergoing repeat angioplasty have shown time to retreatment of 3 months or less to be the strongest predictor (197,200,201). Intracoronary stents are now routinely used to treat restenotic lesions, and favorable results have been reported (155,205). Several studies comparing *de novo* versus restenotic lesions have shown 6-month target vessel revascularization and restenosis rates to be higher when stents are placed in restenotic lesions (155,209,210 and 211), increasing from approximately 30% to 36%.

***e*TABLE 83.4.1** RESTENOSIS RATE FOR RECURRENT STENOSES

Study	Year	n	Angiographic follow-up (%)	Restenosis rate (%)
				After 2nd PTCA
Kitazume et al. (206)	1996	384	92	34
Glazier et al. (202)	1989	181	NA	47
Colombo et al. (205)	1996	128	89	25
Kastrati et al. (155)	2001	974	80	39
Pooled		*1,667*		*38*
				After 3rd PTCA
Tan et al. (201)	1995	56	46	69
Joly et al. (204)	1988	33	91	37
Teirstein et al. (200)	1989	69	53	43
Glazier et al. (202)	1989	38	NA	34
Dimas et al. (203)	1992	46	61	57
Bauters et al. (197)	1993	96	86	39
Kitazume et al. (206)	1996	97	94	39
Williams et al. (194)	1984	62	48	34
Abi-Mansour (207)	1985	17	NA	24
Pooled		*514*		*43*
				After 4th PTCA
Kitazume et al. (206)	1996	23	100	48
Glazier et al. (202)	1989	8	NA	50
Teirstein et al. (200)	1989	15	40	53
Pooled		*46*		*50*

NA, data not available; PTCA, percutaneous transluminal coronary angioplasty.

Vessel

In general, saphenous vein grafts have a substantially higher rate of restenosis than native coronary arteries after balloon angioplasty and somewhat higher rates after stent placement. In the M-HEART study of 510 patients with angiographic follow-up, the highest restenosis rate (68%) was found for saphenous vein graft lesions (212). Within saphenous vein grafts, stenoses tend to recur more commonly for lesions at the proximal anastomosis or in the shaft of the conduit, although data remain limited (213,214). More recent data on saphenous vein graft intervention suggest that the predictors of restenosis are more similar to those for native coronary vessels (i.e., vessel size, residual MLD, lesion ulceration) than previously considered (215). In a randomized trial in which 220 patients with vein graft stenoses were treated with either balloon angioplasty or stent placement, the 6-month restenosis rates were 46% for the group undergoing angioplasty and 37% for the group given stents (216). For native coronary arteries, the highest rate of restenosis after balloon angioplasty has been for the left anterior descending artery (LAD). M-HEART investigators reported restenosis in 45% of LAD lesions (Fig. 83.9), compared with 31% and 32% for lesions of the left circumflex artery and right coronary artery, respectively. Considering 3,736 lesions from several large-scale trials, Foley et al. (217) found only location in the LAD to independently predict a greater loss and smaller MLD at follow-up. Similarly, Weintraub and colleagues (218) showed LAD location to be among the highest independent predictors of restenosis among 11,337 patients. The mechanism of increased restenosis after balloon angioplasty of the LAD is uncertain. Speculations include the possibility that the LAD may be undertreated because it is usually the largest coronary segment on which intervention is performed, and it has more recoil because of its course along the muscular interventricular septum.

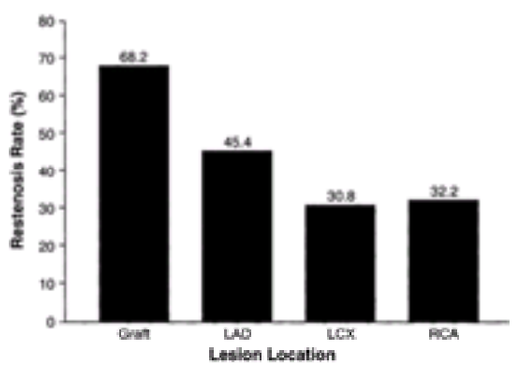


FIGURE 83.9 The vessel treated was found to be an independent predictor for restenosis for 598 treated sites in the Multi-Hospital Eastern Atlantic Restenosis Trial (chi-square *p* value for vessel = .003). The height of each column represents the restenosis rate for each group of segregated lesions. Graft, saphenous vein graft conduit; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. (Adapted from Hirshfeld JWJ, Schwartz JS, Jugo R, et al. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. *J Am Coll Cardiol* 1991;18:647–656, with permission.)

Placement of intracoronary stents likely minimizes the effect of the LAD predisposition toward restenosis, because in the Stent Restenosis Study (STRESS) the restenosis rate for stented LAD lesions was similar to that for the other coronary arteries (70). Phillips et al. (219) suggested that LAD location lowered restenosis for patients receiving an intracoronary stent, which is a plausible tenet because larger vessel size is associated with lower restenosis rates. Two separate and sizable reports have since shown that LAD location is not a predictor of restenosis with intracoronary stent placement. The pooled data from BENESTENT-I, BENESTENT-II, and Multicenter Ultrasound Stenting in Coronaries (MUSIC) studies gathered by Serruys et al. (220) showed vessel size and residual diameter of stenosis alone to be the best predictors of restenosis, whereas Schömig and colleagues (155) found no independent predictive value from LAD lesion location.

Vessel Location or Site

Within the LAD, the likelihood of restenosis after balloon angioplasty increases as the stenosis approaches the ostium and is highest for sites within 5 mm or less of the ostium (221). Boehrer et al. (222) showed that ostial LAD and proximal LAD stenoses have a similarly high rate of restenosis after directional atherectomy or balloon angioplasty, whereas other reports have shown that proximal lesions have a higher rate of restenosis than those in distal segments (54,86,223). Aorto-ostial lesions (right coronary artery, left main coronary artery, saphenous vein graft) should be considered separately from non–aorto-ostial or branch vessel stenoses, because several studies have shown that aorto-ostial lesions have a higher occurrence of complications and restenosis (224,225). That aorto-ostial lesions are more likely to undergo restenosis is probably due to elastic recoil of the aorta around the vessel ostia as well as the simultaneous presence of rigid fibrotic plaque. Similarly, bifurcation lesions and stenoses within bends have occasionally been reported to show higher restenosis rates, likely owing to the often diffuse and complex development of plaque involving a bend or ostium of a branch vessel (225). Because lesions in branch vessel ostia, bifurcations, and angled segments of arteries are generally considered to portend increased risk and worse outcome, they may be underrepresented in prospective and retrospective studies. Their independent effect on restenosis has been variably reported (218,226). Likewise, the prospective stent data are limited because most clinical trials exclude patients with ostial and bifurcation target lesions.

Vessel Size

Several large-scale studies have reported an inverse relationship between vessel size and restenosis. Separating reference vessel diameters into quartiles, the M-HEART investigators found the restenosis rate to decrease from 44% to 36% after balloon angioplasty when vessel size was greater than 2.9 mm (Fig. 83.10). Likewise, vessel diameter was one of the few variables found independently to predict restenosis in MARCATOR (86). Foley and colleagues pooled data from several large pharmacologic trials of restenosis to assess the influence of vessel size on restenosis using quantitative coronary angiography (217). Lesions from over 3,000 patients were systematically studied and, by multiple linear regression analysis, increasing coronary vessel size was noted independently to predict decreasing late lumen loss and increasing MLD. The investigators concluded that the maxim “Bigger is better” (referring to a larger postprocedural lumen) should be modified to “Bigger vessels have a better outcome.” In the large registry report from Emory University (218), the odds ratio for restenosis was 0.86 per 1-mm increase in vessel size.

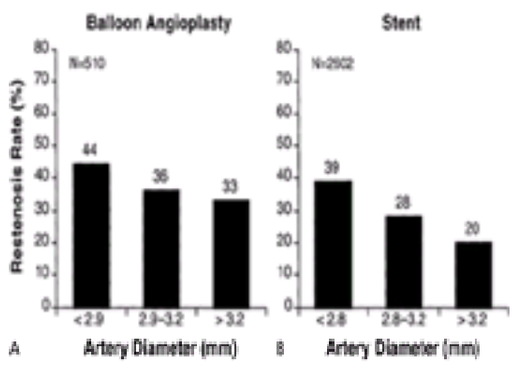


FIGURE 83.10 A: Separating reference vessel diameters into quartiles, Multi-Hospital Eastern Atlantic Restenosis Trial investigators found the restenosis rate to decrease from 44% to 36% when vessel size was larger than 2.9 mm by angiography. This inverse relationship of vessel size to restenosis has also been observed in other large-scale nonstent studies. **B:** Elezi and colleagues reported a similar pattern of restenosis in relation to vessel size among 2,602 stent patients. Vessel size is a leading predictor of restenosis regardless of method used. The benefit of stent placement over balloon angioplasty with regard to restenosis is likely lost for vessel diameters below 2.8 mm. (Adapted from Hirshfeld JWJ, Schwartz JS, Jugo R, et al. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. *J Am Coll Cardiol* 1991;18:647–656; and from Elezi S, Kastrati A, Neumann F-J, et al. Vessel size and long-term outcome after coronary stent placement. *Circulation* 1998;98:1875–1880, with permission.)

Considering the effect of vessel size on restenosis after coronary artery stenting, Kastrati and colleagues (155) have shown this to be the strongest predictor (Fig. 83.10 and Fig. 83.11) in a series of 4,510 consecutively treated patients. Vessel size accounted for 34% of all predictive value, and the risk of restenosis for a vessel of 2.7 mm was 79% higher than for a vessel of 3.4 mm. In a separate report from this group, in which 2,602 patients were systematically studied with quantitative coronary angiography and long-term follow-up, similar results were found. Vessel size was divided into terciles (less than 2.8 mm, 2.8 to 3.2 mm, and larger than 3.2 mm), and vessel size was highly significantly linked with angiographically apparent restenosis (39%, 28%, and 20% for the terciles, respectively) (p <.001) (Fig. 83.10). Interestingly, for each size tercile, the late lumen loss was similar (1.1 mm), and two associated covariates affected restenosis: namely, diabetes and lesion complexity (227). As mentioned earlier, the pooled BENESTENT-MUSIC data sets (220) systematically showed vessel size and postprocedural diameter stenosis to be the best predictors of restenosis.

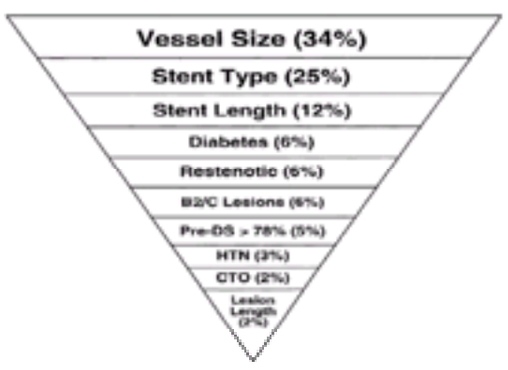


FIGURE 83.11 Pyramid of predictive factors affecting restenosis among 4,510 consecutively treated patients undergoing coronary stent placement. Percentages represent the amount of the restenosis in the model that was accounted for by the individual predictive factors. Vessel diameter and stent length accounted for nearly half of all predictive value for restenosis. CTO, chronic total occlusion; DS, diameter stenosis; HTN, hypertension. (Data from Kastrati A, Mehilli J, Dirschlinger J, et al. Restenosis after coronary stent placement of various stent types. *Am J Cardiol* 2001;87:34–39.)

Preprocedural Percent Diameter Stenosis

The preprocedural and postprocedural lesion severity or MLD has been shown to be a leading and independent predictor of stenosis recurrence in nearly every large-scale clinical study of restenosis, regardless of the revascularization device used. For example, in the CARPORT study (68), in which quantitative coronary angiography was performed on over 600 lesions before and 6 months after successful balloon angioplasty, the preprocedural MLD was directly correlated with the late loss in lumen diameter at follow-up. Specifically, as the preprocedural MLD decreased by 40%, the late loss in lumen diameter increased by nearly 70%. A similar association was also noted by the M-HEART investigators (212), who reported an increased rate of restenosis from 25% to 40% as pre-PTCA stenosis severity surpassed 73% (Fig. 83.12). Likewise, among patients receiving an intracoronary stent, preprocedural stenosis greater than 78% lumen diameter has been shown to be an independent predictor of angiographically identified restenosis (Fig. 83.11) (155). The complex interrelationship between preprocedural MLD, lumen gain, late loss, and follow-up MLD was also studied by Foley et al. (217) using the combined quantitative coronary angiography data set from several trials. In brief, the investigators showed, using mathematical models, that although smaller MLDs were associated with greater initial gain, this gain was associated with proportionally more late loss, so that larger preprocedural MLD was directly correlated with a more favorable long-term result.

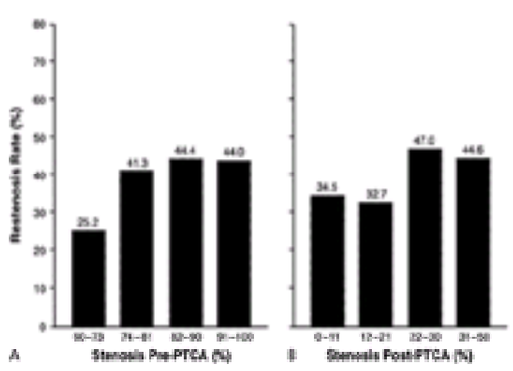


FIGURE 83.12 Relation of preprocedural **(A)** and postprocedural **(B)** stenosis severity on restenosis for 598 treated sites. In both panels, the height of each column represents the restenosis rate for each group of segregated lesions. Preprocedural stenosis severity was observed to be strongly associated with restenosis (p = .004), with higher restenosis rates for lesions with greater than 73% lumen diameter narrowing. Similarly, the postprocedural stenosis severity was independently associated with restenosis (p = .022), with a higher incidence of restenosis for lesions with a residual narrowing of more than 21%. PTCA, percutaneous transluminal coronary angioplasty. (Adapted from Hirshfeld JWJ, Schwartz JS, Jugo R, et al. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and

procedure variables to restenosis. *J Am Coll Cardiol* 1991;18:647–656, with permission.)

Lesion Length

Long lesion length has been associated with an increased rate of restenosis in several large, prospective clinical trials (161,212,228). Bourassa et al. (161), categorizing lesions in a binary fashion, reported an increase in restenosis rate from 38% to 52% for lesions greater than 10 mm long. Others have divided lesion lengths into percentiles and have reported increased restenosis for lengths longer than 4.6 mm (212) to 6.8 mm (228). Long lesions, in addition to representing greater atherosclerotic burden at the treatment site and requiring a more extensive revascularization, are associated with diffuse coronary artery disease in general. Although it is not easily quantitated, more diffuse disease such as seen in diabetic patients and those with chronic renal insufficiency has a greater restenosis potential. Intracoronary stents placed in long lesions have also been associated with an increased occurrence of restenosis. Kastrati et al. (155) reported rates of restenosis to increase from 32% to 36% for lesions longer than 10 mm. Hamasaki et al. (229) reported an increase from 20% to 31% for lesions 15 mm or longer. Yokoi et al. (230) studied several different types of stents placed in lesions longer than 20 mm and reported restenosis rates of 35% to 56%.

Degree of Occlusion

PTCA of chronically occluded coronary arteries has been estimated to comprise 10% of the total number of coronary interventions (231). The initial success rate of PTCA is lower and the incidence of restenosis is higher in cases of chronic occlusion, especially for vessels occluded 3 months or more (232). Combined data from several studies show that the recurrence of angina pectoris within months of successful balloon angioplasty of chronic occlusions is roughly 40% (233,234,235,236 and 237), whereas the rate of angiographically identified restenosis is over 60% (232,235,236,237,238,239 and 240). In the MARCATOR study, 139 patients were followed after successful angioplasty of a total occlusion and compared with 1,295 patients treated for a subtotal stenosis. The rate of angiographically demonstrated restenosis was not dissimilar in the two groups (49% in the chronic occlusion group and 42% in the subtotal stenosis group; $p = .119$), although complete vessel occlusion at follow-up was present in 19% and 7%, respectively ($p > .001$) (241). On the basis of these findings, intracoronary stent placement after successful balloon angioplasty has been advocated. The first randomized study of balloon angioplasty versus intracoronary stent placement, the Stenting in Chronic Coronary Occlusions trial, enrolled 119 patients. Restenosis occurred in 74% of the balloon angioplasty group, but in only 32% of the stent group ($p < .001$). Reocclusion was also lower in the stent group (12%) than in the balloon angioplasty group (26%). Several studies have since reported restenosis rates for stented chronic occlusions ranging from 19% to 52% depending on the rate of angiographic follow-up (238,239,242,243). In nearly every study, the rate of reocclusion and restenosis has been more favorable with stenting than with balloon angioplasty alone, yet these rates remain higher than among patients without preprocedural complete occlusions (244). Schömig and colleagues reported the rate of restenosis after coronary stent placement to increase from 33% to 48% when a chronic total occlusion was present (155). The reason for the higher predilection for restenosis among treated complete occlusions is uncertain, but these lesions may contain the highest plaque burden (i.e., the smallest possible MLD) and many have recently contained an active thrombus.

Procedure-Related Factors

Postprocedural or Residual Diameter of Stenosis

As does the severity of preprocedural stenosis, the extent of residual stenosis after successful PTCA strongly predicts restenosis. In the M-HEART study (212), the percentage of stenosis immediately after PTCA was separated into quartiles, and lesions with residual stenosis of more than 21% had a significantly higher restenosis rate than did those with a post-PTCA stenosis of 21% or less (Fig. 83.12). Similar results of reduced restenosis in the setting of least residual stenosis were reported by Bourassa et al. (161), who found that postangioplasty stenosis of 30% or more of luminal diameter was associated with a restenosis rate of 40%, compared to 28% for segments with residual stenosis of less than 30%. These studies, along with statistical models of restenosis (39), have given rise to the concept of maximizing immediate gain (i.e., the gain in lumen diameter from baseline to immediately after PTCA), or the “bigger is better” concept. Kuntz et al. (39) compared models of restenosis after balloon angioplasty, stenting, and directional atherectomy. They concluded that the loss index (late loss divided by immediate gain) was the same for all device strategies and that therefore the immediate result (procedural stenosis) was what determined the late outcome. Challenging this view, Foley and others have studied large databases of quantitative angiographic results and demonstrated different device “taxing,” with more favorable angiographic profiles found for dilating devices (balloons and stents) than for debulking procedures (atherectomy). Their findings suggest that restenosis is not only influenced strongly by vessel size and lumen gain, but also by the technique used to achieve the larger lumen (Fig. 83.5). Aside from measures obtained by quantitative angiography, perhaps the best predictor of angiographically identifiable restenosis is the percent postprocedural cross-sectional narrowing as assessed by intravascular ultrasonography (IVUS) (245). In examining numerous clinical, angiographic, and IVUS variables for 360 coronary artery lesions, Mintz et al. found IVUS cross-sectional narrowing to be the most consistent single predictor of restenosis (245,246) (Fig. 83.13). Clinically, the angiographically determined parameters of vessel size and the final percentage diameter of stenosis are primarily used to predict the likelihood of restenosis.

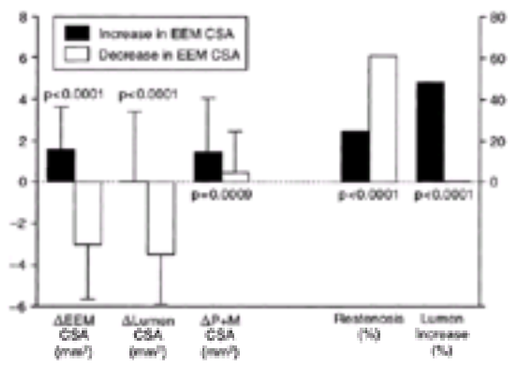


FIGURE 83.13 When numerous clinical, angiographic, and intravascular ultrasonographic variables were considered, cross-sectional narrowing as measured by ultrasonography was found to be the most consistent single predictor of restenosis. During serial study, 22% of lesions showed an increase in overall vessel size (increased external elastic membrane, or EEM, area), whereas the remainder showed a decrease. Lesions with an increased EEM had lower rates of angiographically identified restenosis than those with a decreased EEM (26% vs. 62%). D, change; CSA, cross-sectional area; P+M, plaque plus media. (From Mintz G, Popma J, Pichard A, et al. Intravascular ultrasound predictors of restenosis after percutaneous transcatheter coronary revascularization. *J Am Coll Cardiol* 1996;27:1678–1687, with permission.)

PRINCIPLES OF MANAGEMENT

When the epidemiology of restenosis is pulled together, a framework for monitoring the patient after successful angioplasty can be established. One might begin by considering the patient-, lesion-, and procedure-related factors associated with the angioplasty. Factors consistently identified as risks for restenosis after balloon angioplasty include the presence of diabetes mellitus, the presence of unstable angina, lesion location in saphenous vein grafts, lesion location in the ostium of the major epicardial arteries, long (diffuse) lesions, small vessel size, and greater severity of preprocedural and postprocedural stenosis. In the stent era, the factors consistently associated with increased rates of restenosis include the presence of diabetes, small vessel size, and larger residual diameter of stenosis (Table 83.2). Because the process of restenosis is complete within 3 to 6 months after angioplasty, clinical follow-up should take place during this interval. Depending on the patient’s initial symptoms, extent of myocardium at risk, and associated comorbidities, a tailored level of treatment aggressiveness can be established. For example, a patient initially presenting with predictable exertional angina and a small area of myocardium at risk might be followed for symptoms alone if the underlying ventricular function and overall health are good. In contrast, patients with atypical or unpredictable ischemia, a large area of myocardium at risk, or important comorbidities such as depressed ventricular function should routinely undergo stress cardiac imaging in the early months after angioplasty. Many interventional cardiologists perform cardiac stress testing for all asymptomatic patients even though most patients with restenosis have recurrent angina and not infarction. Given the poor predictive value of symptom status alone and the invasive nature of repeat angiography, this is not unreasonable. In choosing a cardiac stress test, simultaneous imaging with nuclear scintigraphy or echocardiography is worthwhile as demonstrated in *e*Table 83.1.3. If the baseline stress test results were positive and accurately located the ischemic territory, repeat testing with that particular imaging modality is logical. The positive predictive value of imaging cardiac stress testing averages approximately 80%, and this has been considered acceptable for most patients. When stress testing is believed to be unreliable and the amount of myocardium at risk is large (e.g., with ostial lesions in LAD or left-dominant left circumflex artery systems), angiography should be performed to be certain restenosis has not occurred. The need for routine or serial angiography in clinical practice is infrequent.

For patients who develop restenosis, several treatment options are available, including repeat percutaneous revascularization, which has a similar short-term and long-term success rate as with *de novo* lesions (eTable 83.4.1). Intracoronary stent placement is a prudent option for lesions not previously treated with a stent, provided the anatomy is suitable. Most patients with single-vessel restenosis undergo a second angioplasty, whereas patients with restenosis in multiple vessels may undergo percutaneous or surgical revascularization. When all patients initially treated by PTCA for multivessel disease are considered, slightly more of those with restenosis undergo a repeat angioplasty than undergo coronary artery bypass grafting. In the BARI study, nearly 70% of the cohort randomly assigned to undergo PTCA avoided surgery at 5-year follow-up (149).

Restenosis within stents is an increasing occurrence owing to the dramatic increase in stent use. In-stent restenosis usually is a diffuse proliferation of neointima (30,35), and the optimal interventional treatment is uncertain. Balloon angioplasty, perfusion balloon angioplasty, atherectomy (rotational and laser), and stent-within-stent approaches have all been tried. For focal restenotic lesions, the rate of second restenosis is 30% to 40%, whereas for diffuse restenotic lesions it is roughly 70% (36). The mainstay of current treatment is balloon angioplasty with or without intracoronary brachytherapy (local radiation). This is reviewed in the section In-Stent Restenosis.

As with most medical treatments, the best strategy for restenosis is prevention. Numerous basic scientific and clinical investigations using a wide variety of therapeutic agents (247,248 and 249) have been conducted in search of an inhibitor of restenosis. By using animal models for preclinical testing on targets of restenosis, the biology of restenosis has been advanced, although the clinical impact remains limited.

CLINICAL PREVENTION TRIALS: PHARMACOLOGIC

Many different therapeutic agents have been tested in an attempt to find a treatment that can inhibit the development of restenosis (247,248 and 249). Although thousands of patients have been enrolled in over 50 clinical trials over the past 20 years, no large-scale study has produced a pharmacologic therapy to suppress restenosis. Many animal studies targeting factors from thrombin to thromboxane, microtubules to calcium channels, and prostacyclin to platelets (i.e., factors associated with thrombus formation and cellular proliferation) have engendered hope of producing a meaningful reduction in restenosis, but these findings have been discounted by negative results from human studies, as displayed in Table 83.5 (27,79,81,83,84,86,170,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268 and 269). Given the mechanisms of restenosis, most studies have specifically targeted a factor associated with thrombus formation, vascular remodeling, or neointimal growth. An important point to be remembered when reviewing these many trials is that restenosis after balloon angioplasty is primarily a result of vessel wall remodeling as opposed to neointimal formation, and that in balloon angioplasty trials many of these agents were used in an attempt to influence neointimal proliferation.

Agent	Animal study	Year	n	Clinical trial	Year	n
Heparin sodium	Clowes et al. (27)	1983	61	Ellis et al. (80)	1989	416
Low-molecular-weight heparin	Buchwald et al. (250)	1992	18	Faxon et al. (251)	1992	459
Aspirin	Vollebergh et al. (252)	1990	18	Thornton et al. (253)	1984	248
Dipyridamole	Ingerman-Wojenski et al. (254)	1988	44	Schwartz et al. (79)	1988	249
Warfarin sodium	August et al. (255)	1980	60	Urban et al. (256)	1988	11
Thromboxane antagonist	Yokoi et al. (257)	1989	33	CARPORT (170)	1991	457
Angiopeptin	Erikson et al. (258)	1993	112	Kent et al. (259)	1995	1,246
Fish oil	Dehmer et al. (260)	1988	62	Grigg et al. (261)	1989	108
Lovastatin	Sahni et al. (262)	1991	152	Lovastatin Restenosis trial (84)	1994	404
Calcium-channel blocker	Unverdorben et al. (264)	1993	189	Whitworth et al. (265)	1986	241
ACE inhibitor	Powell et al. (266)	1989	127	MARCATOR (86)	1995	1,406
Colchicine	Currier et al. (267)	1989	24	CART (268)	1989	79
Corticosteroids	Villa et al. (269)	1994	39	Pepine et al. (81)	1990	915

ACE, angiotensin-converting enzyme; CARPORT, Coronary Artery Restenosis Prevention on Repeated Thromboxane Antagonism; CART, Colchicine Angioplasty Restenosis Trial; MARCATOR, Multicenter American Research Trial with Clazosentan after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis.

TABLE 83.5 ANIMAL STUDIES AND CLINICAL TRIALS OF AGENTS TO PREVENT RESTENOSIS

Strategies Targeting Thrombus Formation

Antiplatelet Agents

Because platelet functions (adhesion, aggregation, and release of vasoactive, mitogenic, and chemoattractant factors) are central to thrombus formation and the vascular response to injury, they are logical targets to limit restenosis. Virtually all percutaneous revascularization procedures are performed in the setting of antiplatelet therapy to prevent acute ischemic complications, although none of these therapies has shown a clear effect on angiographically identified restenosis. Aspirin, dipyridamole, thienopyridines, thromboxane antagonists, and prostacyclin analogs each has shown some promise in animal models of restenosis, although none has produced clinical benefit (Table 83.6). The most potent antiplatelet therapy, that using glycoprotein IIb/IIIa antagonists, has been studied in animal models and in several large-scale clinical trials. Animal models of restenosis demonstrated a reduction in neointimal development through blocking of either the platelet glycoprotein IIb/IIIa ($a_{IIb}b_3$) or vitronectin receptor (a_vb_3) (270,271). Matsuno et al. (270) postulated that this effect was due both to an early event such as inhibited secretion of PDGF and to a late event, possibly the interference of the smooth muscle cell a_vb_3 receptor.

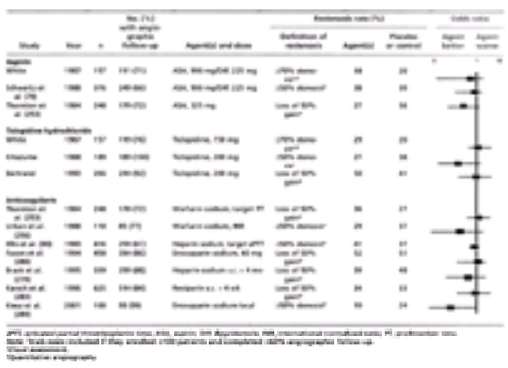


TABLE 83.6 CLINICAL TRIALS EVALUATING THE USE OF ANTITHROMBOTIC AGENTS TO LIMIT ANGIOGRAPHICALLY IDENTIFIED RESTENOSIS

By using a glycoprotein IIb/IIIa inhibitor, chimeric 7E3 Fab, and blocking the final common pathway for platelet aggregation, the EPIC (272) investigators showed the incidence of acute ischemic complications during high-risk angioplasty to be substantially reduced. At 6-month follow-up, clinically apparent restenosis was also reduced (43), but this was primarily due to a reduction in myocardial infarction. Since then, several trials have completed 6-month follow-up on patients randomly assigned to receive platelet IIb/IIIa antagonists or placebo. The Integrilin to Manage Platelet Aggregation and Coronary Thrombosis II trial, Randomized Efficacy Study of Tirofiban for Clinical Outcomes and Restenosis, EPILOG study, and Chimeric 7E3 Antiplatelet in Unstable Angina Refractory to Standard Treatment trial studied eptifibatide (Integrilin), tirofiban hydrochloride, and abciximab. Pooling of results for these 12,305 patients showed no significant reduction in target vessel revascularization at 6-month follow-up for patients given active treatment versus those receiving placebo (18.6% vs. 20.2%) (43,273,274 and 275), and no difference was seen in quantitative angiographic or neointimal tissue volume (276). The only potential exception may be for diabetic patients who received an intracoronary stent and were given abciximab, as observed in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (158) (Fig. 83.7), although this result is not confirmed in other studies.

Anticoagulants

In addition to containing activated platelets, a thrombus at the site of injury can act as a bioabsorbable matrix and also serve as a reservoir of active thrombin. Therapy with warfarin sodium, a broad-spectrum anticoagulant, did not reduce restenosis in an early angiographic study (256) but did reduce target vessel revascularization in a more recent trial of 1,058 patients (277). More specific inhibitors, such as the antithrombins heparin sodium, low-molecular-weight heparin, hirudin, and bivalirudin, have also been studied. Beyond being an anticoagulant, heparin inhibits smooth muscle cell proliferation and migration. Several small randomized trials of heparin

versus placebo unfortunately showed no salutary effect on restenosis (80,278) after nonstent procedures. Long-term heparin administration (twice-daily subcutaneous injections for 4 months) also did not favorably affect angiographic or clinical outcome (279). Low-molecular-weight (fractionated) heparin has a longer half-life than unfractionated heparin, is a more potent factor X_a inhibitor, and has been studied in several balloon angioplasty trials (280,281 and 282). Restenosis was not reduced in any of these trials, even when therapy extended for weeks postprocedure (283). More recently, a small study (n = 100) was performed using some contemporary practices: implantation of intracoronary stents, local drug delivery versus systemic administration, and therapy with low-molecular-weight heparin versus unfractionated heparin. This study, the Polish-American Local Lovenox NIR Assessment study (284), randomly assigned patients to receive locally delivered enoxaparin sodium or systemic unfractionated heparin for stent placement. At 6-month follow-up, restenosis was found in 10% of the group receiving enoxaparin versus 24% of the group given systemic heparin. Late lumen loss and target vessel revascularization were also improved by local enoxaparin delivery.

Finally, more potent antithrombins that do not require antithrombin as a cofactor (hirudin, bivalirudin, and argatroban) have been studied. The trial Hirudin in a European Trial versus Heparin in the Prevention of Restenosis after PTCA randomly assigned 1,141 patients to receive heparin during the PTCA procedure and in 24-hour infusion, hirudin during the procedure and in 24-hour infusion, or hirudin during the procedure, in 24-hour infusion, and in 3 days of subcutaneous therapy (285). Early ischemic events were reduced by the use of hirudin, but no difference in late outcome related to restenosis was observed. Similarly, the Hirulog Angioplasty Study (286) randomly assigned 4,098 patients undergoing angioplasty to receive either Hirulog (bivalirudin) or heparin. At 6 months the rate of repeat revascularization was similar for the two groups (22.9% and 23.9%). These data reveal no reduction in restenosis with anticoagulant therapies even when administered for days to weeks after angioplasty.

Vasodilators

Thromboxane Antagonists

Because the vasomotor effects of aspirin are mixed with concomitant inhibition of thromboxane and prostacyclin, specific inhibitors of thromboxane and analogs of prostacyclin have been tested for restenosis prevention after balloon angioplasty. The CARPORT trial randomly assigned 697 angioplasty patients to receive the thromboxane A_2 antagonist vapiprost or a placebo, although all patients also received aspirin. At 6-month follow-up angiography, no difference was observed in restenosis in the two groups. Similar results were found in the Glaxo Restenosis and Symptom Project (287) and M-HEART-II (85) studies using vapiprost and sulotroban, respectively. Together, these three large trials enrolled over 2,400 patients and showed no impact on restenosis (*e*Table 83.6.1).

***e*TABLE 83.6.1** CLINICAL TRIALS EVALUATING THE USE OF VASODILATORS AND ANTIPROLIFERATIVE AGENTS TO LIMIT ANGIOGRAPHICALLY IDENTIFIED RESTENOSIS

Study	Year	n	No. (%) with angiographic follow-up	Agent(s) and dose	Restenosis rate (%) Definition of restenosis	Agent(s)	Placebo or control	Odds ratio Agent better	Agent worse
Vasodilators								0	1 10
Thromboxane A_2 antagonists									
Serruys et al. (170)	1991	649	575 (89)	Vapiprost, 80 mg	Loss ³0.72 mm[a]	21	19		
Feldman et al. (287)	1992	1,192	705 (59)	Vapiprost, 40–80 mg	³70% stenosis[a]	28	31		
Prostanoids									
Knudtson et al. (83)	1990	270	224 (83)	Prostacyclin, 5 ng/kg/min	³50% stenosis	27	32		
Gershlick et al. (288)	1990	132	106 (80)	Prostacyclin, 4 ng/kg/min	³50% stenosis	31	34		
Raizner et al. (78)	1993	247	211 (85)	Ciprostene, 120 ng/kg/min	³50% stenosis[a]	26	38		
Serotonin antagonists									
Serruys et al. (171)	1993	658	592 (90)	Ketanserin, 40 mg b.i.d.	³50% stenosis	32	32		
Calcium channel blockers									
Whitworth et al. (265)	1986	241	198 (82)	Nifedipine, 40 mg/d	Loss ³50% gain	28	30		
Hoberg et al. (293)	1990	196	172 (88)	Verapamil hydrochloride, 480 mg/d	Loss ³50% gain	47	62		
O'Keefe (377)	1991	201	120 (60)	Diltiazem hydrochloride, 240–360 mg/d	Loss ³50% gain[a]	36	32		
Unverdorben et al. (264)	1992	189	170 (90)	Diltiazem hydrochloride, 180 mg/d	³50% stenosis[a]	21	38		
Antiproliferative agents									
Colchicine									
O'Keefe et al. (302)	1992	197	145 (74)	Colchicine, 1.2 mg/d	³70% stenosis[a]	22	22		
Angiotensin-converting enzyme inhibitors									
Serruys et al.	1992	735	595 (81)	Cilazapril, 10 mg/d	³50% stenosis[a]	28	28		
Faxon et al. (86)	1995	1,436	1,086 (75)	Cilazapril, 2–20 mg/d	³50% stenosis[a]	37	33		
Desmet et al. (297)	1994	509	304 (90)	Fosinopril, 40 mg/d × 6 mo	Loss ³50% gain[a]	39	37		
Angiopeptin									
Emanuelsson et al. (314)	1995	553	423 (93)	Angiopeptin, 6 mg/d	³50% stenosis[a]	36	37		
Eriksen et al. (258)	1995	112	75 (80)	Angiopeptin, 750mg/d	³50% stenosis[a]	12	40		
Kent et al. (259)	1993	1,246	917 (87)	Angiopeptin, 0.19–3.0 mg/d	³50% stenosis	37	39		
Trapidil									
Maresta et al. (308)	1994	305	254 (83)	Trapidil, 300 mg/d × 6 mo	³50% stenosis[b]	30	43		
Nishikawa	1992	160	137 (85)	Trapidil, 600 mg/d × 4 mo	Loss ³50% gain[a]	20	38		
Immunosuppressants									
Pepine et al. (81)	1990	915	510 (71)	Methylprednisolone, 1 g	³50% stenosis[a]	40	39		
Ueda	1995	205	205 (100)	Tranilast, 600 mg/d, 6 mg/d	Loss ³50% gain	22	46		

Trials were included if they enrolled ³100 patients and completed ³60% angiographic follow-up.

[a]Quantitative angiography.

[b]Visual assessment.

Prostacyclin

Prostacyclin is produced by healthy endothelium and causes vasodilation and platelet inhibition, effects opposite those of thromboxane. Prostacyclin supplementation or use of prostacyclin analogs (prostanoids) has been tried in several small studies to reduce postangioplasty neointimal formation. The largest of these trials randomly assigned 311 patients to receive ciprostene or placebo and showed an overall clinical benefit: a reduction in the composite of death, infarction, and revascularization at 6-month follow-up (263). This trial did not conduct systematic angiographic follow-up, however, and those that have done so have shown no reduction in restenosis (83,288). A large-scale trial with angiographic follow-up is needed to clarify the role of prostanoids in preventing angiographically and clinically demonstrated restenosis.

Serotonin Receptor Antagonists

Serotonin, 5-hydroxytryptamine, is able to induce vasoconstriction in the setting of abnormal endothelium and is an agonist for platelet aggregation. In addition, serotonin promotes smooth muscle cell migration and proliferation and the synthesis of extracellular matrix (289,290). Therefore, use of ketanserin, a serotonin antagonist, is a potential therapeutic approach to limit restenosis. In the Postangioplasty Restenosis Ketanserin trial, 658 angioplasty patients were randomly assigned to receive ketanserin or placebo, and 592 patients had quantitative coronary angiography at 6 months (171). No difference in angiographically identified restenosis or clinical events was observed between patients receiving ketanserin and those given placebo (*e*Table 83.6.1).

Calcium Channel Antagonists

Calcium channel antagonists have been studied in restenosis because of their potent coronary vasodilatory effects and the known role of recoil and vasoconstriction in restenosis (291,292). Although use of calcium channel antagonists is beneficial in vasoactive coronary artery disease, several small trials failed to demonstrate a

benefit for restenosis prophylaxis (265,293,294). Interestingly, one study (264) and a metaanalysis of several trials (295) showed a borderline reduction in restenosis (odds ratio of 0.5 to 0.9; p <.05) (*e*Table 83.6.1). The use of calcium channel antagonists for restenosis prevention has not been adopted because peer-reviewed data are limited, and some agents have been associated with an increased risk of ischemic events after myocardial infarction.

Angiotensin-Converting Enzyme Inhibitors

The antihypertensive and putative antiproliferative effects of ACE inhibitors are provided by blockade of angiotensin II production. Angiotensin II is a potent vasoconstrictor, and genes that encode the mitogens PDGF, TGF-b, and thrombospondin may be induced by angiotensin II (266,296). Thus, with regard to restenosis, ACE inhibitors could be categorically considered as vasodilators or antiproliferative agents. Two parallel studies, MERCATOR in Europe and MARCATOR in the United States, have shown no reduction in the incidence of restenosis after treatment with cilazapril (69). In addition, no differences were seen in clinical outcomes, including death, nonfatal myocardial infarction, coronary revascularization, and recurrence of angina, between treatment and placebo groups. Fosinopril sodium was also studied in the setting of PTCA and had no impact on restenosis (297) (*e*Table 83.6.1). Animal studies showing a restenosis benefit with ACE inhibitors used substantially higher dosages; comparable dosages in humans have been considered unacceptable because of the possibility of systemic hypotension (266,296).

Antiproliferative Agents

Immunosuppressant and Antiinflammatory Agents

The antiproliferative agents are the current hopes for reducing restenosis in the contemporary stent era. Previously tested in patients undergoing balloon angioplasty, several immunosuppressive and antimitogenic agents showed encouraging results in animal studies without demonstrating success in human trials. Corticosteroids were among the first classes of agents studied because of their known clinical effects on suppression of inflammatory response to injury and reduction in the production of smooth muscle mitogens. Specifically, corticosteroids suppress monocyte-lymphocyte interaction and lymphocyte proliferation, perhaps by decreasing platelet and macrophage-derived growth factor expression (298,299). Pepine et al. (81) performed the largest corticosteroid-angioplasty study, randomly assigning 915 patients to receive 1 g methylprednisolone or placebo the day before angioplasty. Six-month angiographic follow-up in 71% of those with successful angioplasty showed a nearly identical per-lesion restenosis rate for steroid-treated patients (40%) and placebo-treated patients (39%). Colchicine, which acts by binding to tubulin and disrupting spindle formation during cell division and inhibiting collagen formation (300,301), produced a dose-dependent reduction in neointimal formation in animal models. In clinical trials in which colchicine was used in tolerable doses alone (268,302,303), however, it was ineffective in preventing restenosis.

Finally, tranilast is an antiinflammatory agent that suppresses macrophages and fibroblasts, inhibits smooth muscle cell migration induced by PDGF, inhibits collagen synthesis in vascular smooth muscle cells, and is used to prevent keloid formation. Tranilast was initially tested in the Tranilast Restenosis Following Angioplasty Trial. Two hundred fifty-five patients were randomly assigned to receive 600 mg of tranilast, 300 mg of tranilast, or placebo for 3 months. The rate of angiographically determined restenosis for these groups at 3 months was 18%, 39%, and 39%, respectively (304). The largest clinical trial ever performed in interventional cardiology—the Prevention of Restenosis with Tranilast and Its Outcomes trial—tested the use of tranilast among 11,500 PCI patients. Tranilast was administered (300 or 450 mg twice daily) for 1 or 3 months after stent or nonstent procedures to treat *de novo* or restenotic lesions. The primary end point was the 9-month composite of death, myocardial infarction, or ischemia-driven target vessel revascularization. A 2,000-patient angiographic substudy was also performed (305).

Growth Factor Inhibitors

Trapidil

As listed in Table 83.3, several growth factors, including PDGF, bFGF, insulin-like growth factor-1, TGF-b, and EGF have been implicated in the hyperproliferative response after vascular injury. In addition to nonspecific immunosuppressant and antiinflammatory agents, specific antagonists to these growth factors have been studied in prevention of restenosis. Trapidil is a PDGF inhibitor that significantly reduces neointimal formation in animal models of restenosis (306). A small randomized clinical trial of trapidil showed a significant reduction in restenosis (from 42% to 19%) at 6 months (307). This finding was substantiated by the Studio Trapidil versus Aspirin nella Restenosi Coronarica trial (308), a multicenter, double-blind, randomized study of trapidil versus aspirin involving 305 patients. The occurrence of angiographically identified restenosis was reduced by 40% (*e*Table 83.6.1). Another study randomly assigned 97 stent patients to receive ticlopidine hydrochloride plus aspirin or ticlopidine plus trapidil (309). At 6 months, no difference was seen in angiographically determined restenosis (approximately 29% for all groups). These small studies are encouraging and indicate that further investigation is warranted.

Angiopeptin

The most widely studied growth hormone antagonist in restenosis prophylaxis is angiopeptin, a synthetic analog of somatostatin. Angiopeptin acts on the pituitary gland to reduce growth hormone secretion and may limit release of insulin-like growth factor-1 (310). In animal models of vascular injury, administration of angiopeptin before or during angioplasty reduced neointimal growth (258,311,312). Clinical results, however, have been inconsistent (259,313,314). Two trials, one using low-dose angiopeptin and the other high-dose angiopeptin, included nearly 1,400 patients and performed angiographic follow-up but showed no reduction in restenosis (259,314). Questions remain as to whether a more prolonged dosing of angiopeptin is needed to affect neointimal growth. A small placebo-controlled study in which angiopeptin was administered for hours after PTCA demonstrated angiographically determined and clinically determined restenosis rates that were 70% lower and 26% lower, respectively, with angiopeptin treatment. These discrepant findings indicate the need for further study before large-scale efforts are repeated.

Cilostazol

Acting as an antiplatelet agent by increasing levels of cyclic adenosine monophosphate, cilostazol is also an antiproliferative agent that inhibits smooth muscle cell growth by blocking synthesis of DNA. Sekiya and colleagues (315) randomly assigned 126 stent patients to receive placebo, probucol, cilostazol, or the combination of probucol and cilostazol. Drug treatment began 5 days before coronary intervention and continued until 6-month angiographic follow-up. At follow-up, restenosis was found in 32% of patients receiving the placebo, 17% of those given probucol, 13% of those getting cilostazol, and 10% of those receiving both probucol and cilostazol. Among 211 balloon angioplasty patients randomly assigned to receive either 3 months of cilostazol (200 mg per day) or a control regimen, the rate of angiographically identified restenosis at 3 months was lowered from 40% to 18% by cilostazol (316). In two more recent studies, 409 patients and 130 patients undergoing stent implantation were randomly assigned to receive either aspirin plus ticlopidine or aspirin plus cilostazol. The larger of the trials, by Park et al. (317), showed no reduction in restenosis at 6-month follow-up angiography among patients receiving cilostazol compared with those given ticlopidine (restenosis rates of 27% vs. 23%, respectively), although the smaller trial, conducted by Kozuma and colleagues (318), reported a halving of angiographically identified restenosis and target vessel revascularization rates at late follow-up among patients receiving cilostazol. Together, these trials included nearly 900 patients and showed a substantial (40%) reduction in relative risk of angiographically determined restenosis with cilostazol (32% vs. 19%).

Paclitaxel

Paclitaxel (Taxol) is a microtubule-stabilizing drug that reduces cellular functions such as migration and proliferation, which makes it a potent cytotoxic antitumor agent. Animal models of restenosis have shown delivery of paclitaxel via local catheters to be associated with reduced neointimal proliferation and increased vessel size (319). Because paclitaxel is a potent agent, local delivery is key. Linking the molecule in a polymer fashion to a stent, stent sleeve, or biodegradable stent is an option being tested (320,321). Preliminary reports of a small number of early clinical cases have reported zero restenosis rates. Although the results seem overly promising, several larger-scale clinical trials are already under way in Europe, Asia, and North America.

Rapamycin

Sirolimus (Rapamune) is a macrocyclic lactone with antibiotic, immunosuppressive, and antiproliferative actions. It is approved for use as prophylaxis for renal transplant rejection. Biologically it induces cell-cycle arrest and affects proliferation and migration of smooth muscle cells. It has been shown in animal models of restenosis to substantially reduce neointimal thickening after vascular injury (322). Sousa and colleagues (323) reported quantitative angiographic and three-dimensional intravascular ultrasonographic data on 30 patients who received sirolimus-coated stents. At 4-month follow-up, the in-stent late loss was negligible (approximately 0.1 mm) and the diameter of stenosis was virtually unchanged (approximately 5%). These remarkable results have prompted several moderate-sized (400-patient) studies in Europe and the United States, including the Rapamycin-Eluding versus Plain Polymer Stents trial and the Sirolimus-coated BX Velocity Balloon-Expandable Stent trial.

Antisense Oligonucleotides

Activation of growth factor receptors prompts gene expression in the nucleus, which leads to cytoplasmic synthesis of specific proteins. These proteins, in turn, direct the cell replication and matrix production of neointimal growth. The failure of individual antiproliferative agents to limit restenosis in clinical trials may also be related to

the existence of many different growth factors. Thus, by targeting gene expression, the final common pathway leading to cellular growth and replication, gene therapy may be particularly advantageous (324). The use of antisense agents is an approach that blocks gene expression via specific complementary DNA sequences to small segments of the messenger ribonucleic acid (mRNA). Several antisense oligonucleotides directed at protooncogenes such as c-myb and c-myc, proliferating-cell nuclear antigen, and cell-cycle regulatory genes, such as cdc2 kinase and cdk2 kinase, reduced neointimal hyperplasia in a balloon injury in the rat carotid artery model (325). Several problems still exist with antisense therapies, including agent tability, low cellular uptake, and target specificity. The development of local drug delivery systems and the efficacy of carrier systems will likely govern the future success of antisense therapies in preventing restenosis. When the intracoronary route was used, administration of c-myc antisense was shown to be safe in 16 patients undergoing percutaneous transluminal coronary revascularization (PTCR) (326).

Hypolipidemic Agents and Antioxidants

Fish Oils

Omega-3 polyunsaturated fatty acids reduce serum levels of triglycerides and very low-density lipoproteins and are associated with lower rates of atherosclerotic heart disease. In addition, because these fish oils have vasodilatory effects, show anti–platelet-aggregatory effects, alter smooth muscle cell proliferation and monocyte function (327,328 and 329), and inhibit PDGF expression from endothelial cells (330), they have been studied for restenosis prophylaxis (*e*Table 83.6.2). Five of nine studies (260,330,331,332 and 333) evaluating omega-3 fatty acids reported a beneficial effect, and a metaanalysis suggested a significant influence in reducing restenosis, with an odds ratio of 0.5 to 0.8 (56). Unfortunately, each of these studies was limited not only by small size but also by differences in dosing and definitions of restenosis. In contrast, the Fish Oil Restenosis Trial, a large multicenter study in the United States encompassing 503 patients, showed no reduction in restenosis with fish oils (334), and a large Canadian trial of fish oil and enoxaparin (2 × 2 factorial design) known as the Enoxaparin and Maxepa for the Prevention of Angioplasty Restenosis trial had negative results (281).

***e*TABLE 83.6.2** CLINICAL TRIALS EVALUATING THE USE OF LIPID-MODIFYING AGENTS TO LIMIT RESTENOSIS

Study	Year	n	No. (%) with angiographic follow-up	Agent(s) and dose	Restenosis (%)[a] Definition of restenosis	Agent(s)	Placebo or control	Odds ratio Agent better 0	Agent worse 1 10
Hydroxymethylglutaryl–coenzyme A reductase inhibitor									
Weintraub et al. (84)	1994	404	321 (79)	Lovastatin, 80 mg/d	³50% stenosis[b]	39	42		
Yui et al. (383)	1995	208	208 (100)	Pravastatin sodium, 20 mg/d	³50% stenosis[c]	41	52		
O'Keefe et al. (378)	1996	239	239 (100)	Lovastatin, 40 mg/d + probucol, 1 g/d					
Fish oils									
Grigg et al. (261)	1989	108	100 (93)	W3FA, 3.0 g	Loss of >50% gain[b]	34	33		
Reis et al. (379)	1989	18	56 (30)	W3FA, 6.0 g	³70% stenosis	34	23		
Bairati et al. (330)	1992	119	119 (100)	W3FA, 4.5 g	³50% stenosis[c]	31	48		
Bellamy et al. (368)	1992	120	113 (94)	W 3FA, 3.0 g	Loss of 50% gain[b]	21	18		
Kaul et al. (375)	1992	107	107 (100)	W3FA, 3.0 g	³50% stenosis[c]	35	27		
Franzen et al. (82)	1993	200	129 (65)	W3FA, 3.2 g	³50% steno-sis[b]	33	35		
Leaf et al. (334)	1994	551	447 (81)	W3FA, 6.9 g	³50% stenosis[b]	52	46		
Cairns et al. (281)	1996	668	625 (94)	W3FA, 5.4 g	Loss of 50% gain[b]	40	39		
Low-density lipoprotein (LDL) apheresis									
Daida et al. (370)	1994	203	203 (100)	LDL apheresis	³50% steno-sis[b]	32	38		
Antioxidants									
Watanabe et al. (342)	1996	118	118 (100)	Probucol, 500 mg/d	Loss of 50% gain[b]	20	40		
Tardif et al. (341)	1996	183	183 (100)	Probucol, 500 mg/d	³50% stenosis[b]	23	35		

W3FA, omega-3 fatty acid.

Trials were included if they enrolled ³100 patients and completed ³60% angiographic follow-up.

[a]Restenosis rate is calculated per lesion.

[b]Quantitative angiography.

[c]Visual assessment.

Hydroxymethylglutaryl–Coenzyme A Reductase Inhibitors

Hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors were reported to have a direct antiproliferative effect on endothelial and smooth muscle cells in addition to lowering lipid levels (335). In a small open-label trial (262), lovastatin reduced the restenosis rate from 45% to 15%. The unblinded method and low angiographic restudy rate, however, reduce the value of such a study. A subsequent larger multicenter, double-blind, placebo-controlled, randomized trial (84) showed that restenosis was not decreased in patients who received lovastatin, despite a greater than 40% reduction in the levels of LDL cholesterol (*e*Table 83.6.2). In addition, no significant difference in clinical outcomes was observed. Even with combination therapies or apheresis, no consistent reduction in restenosis rate has been seen despite dramatic reductions in levels of LDL cholesterol and Lp(a). Fluvastatin sodium, which reportedly has the greatest suppressant effect on neointimal growth, was studied in the large Fluvastatin Angioplasty Restenosis trial (n = 1,054) (336). Despite markedly lowering LDL cholesterol levels, fluvastatin did not lower restenosis compared with placebo (restenosis rates of 28% vs. 31%, respectively; $p = .42$). No reports of prospective large-scale trials are available that assess the use of cholesterol-lowering agents among stent-treated patients, although a retrospective analysis suggests a potential benefit (337).

Antioxidants and Combination Therapies

Antioxidants have been suggested to be useful in the prevention and treatment of several medical conditions because of their ability to remove free radicals. By preventing oxidation of LDL, reducing platelet aggregation, and modulating prostaglandin and leukotriene synthesis, antioxidants may also be efficacious in limiting restenosis (338). Probucol, ascorbic acid, and alpha-tocopherol have been shown to reduce intimal hyperplasia in various animal models (339,340). Early clinical trials of probucol combined with other therapies found no reduction in restenosis, whereas two studies that administered probucol alone for months after angioplasty have shown an overall 40% reduction in angiographically identified restenosis (341,342) (*e*Table 83.6.2). These more recent and encouraging results deserve further investigation.

CLINICAL TRIALS: TECHNOLOGIES

Atherectomy

As mentioned previously, the leading predictor of angiographically determined restenosis is the postprocedural or residual stenosis diameter. Most new technologies in interventional cardiology, such as the atherectomy devices, have targeted debulking of coronary artery lesions to produce the largest postprocedural lumen possible. Each new technology brings the hope of reducing restenosis or treating specific lesion subsets better than can balloon angioplasty. The directional coronary atherectomy (DCA) catheter allows shaving and extraction of atheroma and enables the production of a larger lumen and net gain. Data from the DCA registry and from two large multicenter trials, CAVEAT (73) and the Canadian Coronary Atherectomy Trial (74), demonstrated this; however, in combination, these studies report similar restenosis rates for DCA and balloon angioplasty. The BOAT study compared balloon angioplasty to "optimal" DCA. In BOAT, atherectomy produced larger immediate and net gain, and the rate of angiographically identified restenosis at the specific enrolling centers able to perform optimal atherectomy (15% mean residual stenosis) was lower for DCA (32%) than for balloon angioplasty alone (40%) (87). This occurred without an increase in "major" adverse events, although patients undergoing DCA were nearly three times more likely to have a significant periprocedural rise in levels of myocardial muscle creatine kinase isoenzyme. Target vessel revascularization rates at 6-month and 1-year follow-up were similar for the groups undergoing PTCA and optimal DCA.

Excimer laser and rotational atherectomy have been assessed in the Excimer Laser Rotational Atherectomy Balloon Angioplasty Complications study (77), the Study to Determine Rotablator and Transluminal Angioplasty Strategy, the Amsterdam Rotterdam (AMRO) trial (343), and the Comparison of Balloon Angioplasty versus

Rotational Atherectomy in Complex Coronary Lesions study (67). Compared with balloon angioplasty, these atherectomy devices used to debulk the lesion before balloon dilation have yielded higher procedural success rates and greater immediate gain. No significant outcome differences have been found during clinical or angiographic follow-up, however, with restenosis rates approximating 50% in all treatment groups in each trial. Like DCA, these debulking devices facilitate balloon angioplasty but cause a greater late lumen loss, or device taxing, which implies that remodeling and neointimal proliferation are not favorably reduced.

Intracoronary Stents

Stent Placement Compared with Balloon Angioplasty

The increasingly popular intracoronary stents address restenosis from the perspective of plaque persistence, recoil, and remodeling (Fig. 83.3) by compressing the plaque and scaffolding the vessel lumen to safely maximize diameter. Early stent registry data indicated that restenosis rates were similar to those with balloon angioplasty unless the lesion treated was “ideal,” in other words, was a short, *de novo* lesion in a vessel 3 mm or more in diameter. With this in mind, two randomized trials of stent implantation versus stand-alone balloon angioplasty in *de novo* native coronary artery lesions were undertaken: the BENESTENT trial (71,344,345) and the STRESS trial (344,346). The BENESTENT investigators reported a restenosis rate of 22% in the stent group and 32% in the balloon angioplasty group. A decreased incidence of cardiac events—mainly repeat percutaneous coronary revascularization—was noted for the stent group at 6-month follow-up. The STRESS trial (70) also demonstrated an absolute 10% lower occurrence of restenosis among subjects receiving a Palmaz-Schatz coronary stent than among those undergoing balloon angioplasty (32% and 42%, respectively). Similarly, at 8-month follow-up, the STRESS stent group had a better event-free survival and had undergone fewer revascularization procedures. Comparison of angiographically determined restenosis rates in past balloon angioplasty trials and in more recent stent trials confirms this 10% to 15% lower rate of restenosis after stent implantation (Table 83.1).

Since completion of the BENESTENT and STRESS trials, many other stent-versus-angioplasty trials have been performed (Table 83.1) to assess the effect of contemporary stenting techniques (high-pressure deployment, IVUS, reduced anticoagulation), characteristics of patient and clinical subgroups (presence of diabetes or acute myocardial infarction), features of specific lesions (restenotic lesions, chronic occlusions, long lesions), and new stent designs. Although restenosis rates have been somewhat lowered with more aggressive balloon angioplasty, intracoronary stenting has proven superior in nearly every study. In BENESTENT-II, for example, in which aggressive balloon angioplasty was tested against placement of heparin-coated stents with high-pressure delivery, the restenosis rate after angioplasty was only 31%, but the rate was an impressively low 16% in the stent group. Other studies using different stents or more contemporary practices than in STRESS-I and BENESTENT-I confirm this impressively low restenosis rate (347).

Important points to be remembered regarding restenosis in the current stent era include the exception in which stent placement has not been proven superior to balloon angioplasty—in small vessels. Several studies showed comparable rates of restenosis for balloon angioplasty and stent placement when vessel size was 2.8 mm or less (155). For small vessels, the rate of restenosis approximates 40% regardless of treatment assignment. In addition, the rates of restenosis initially published for nearly all stent designs were for ideal lesions, and large-scale observational studies have reported higher overall rates than in those trials used to gain U.S. Food and Drug Administration approval of particular stent designs. In summary, target vessel revascularization rates in contemporary stent practice can approximate the single digits (i.e., less than 10%). When angiographically determined restenosis is considered, the rates increase to 20% to 25%, and when the nonideal end of the spectrum is included, this rate may double.

In-Stent Restenosis

With the exponential increase in stent use over the past few years and the increased rate of percutaneous revascularization overall, in-stent restenosis has become a new epidemic in medicine. Angiographically identified restenosis (stenosis of 50% or more lumen diameter) occurs in one of four stent patients, and repeat revascularization of the target lesion is needed in roughly 10% of patients receiving an intracoronary stent. Because stents stimulate more neointimal proliferation than other interventional methods (balloon angioplasty and atherectomy), antiproliferation strategies are the main therapeutic consideration. Results of the conventional mechanical treatment of in-stent restenosis using balloon angioplasty, cutting balloon angioplasty, repeat stenting, or atherectomy have been disappointing, with recurrent rates of restenosis averaging 30% to 50% for focal disease and approximately 70% for diffuse in-stent restenosis (348,349,350 and 351). Current treatment options include gamma and beta radiation, and antiproliferative drugs are being studied.

Vascular Brachytherapy for In-Stent Restenosis

Gamma and beta radiotherapy have been studied for the treatment of in-stent restenosis over the past several years. Radiation is emitted during the spontaneous decay of the nuclei of certain elements. This radiation can be gamma radiation (electromagnetic energy carried by photons, which may penetrate more than 10 mm of human tissue) or beta particles (electrons carrying a wide range of energy levels and traveling 2 to 3 mm in human tissue). By affecting DNA in the actively dividing cells in the vascular media and intima, brachytherapy inhibits smooth muscle proliferation and neointima formation. Isotopes studied for clinical brachytherapy include iridium-192 (Ir-192, gamma emitter), phosphorus-32 (P-32, beta emitter), strontium-90 (Sr-90, beta emitter), yttrium-90 (Y-90, beta emitter), and rhenium-188 (Re-188, beta emitter). Three types of radiation delivery systems have been tested: balloon-filled catheters, radioactive stents, and catheter-based delivery of radioactive seeds. Only the last one has been examined in randomized clinical trials and approved by U.S. Food and Drug Administration.

Gamma Radiation

Several randomized clinical trials have reported the efficacy of Ir-192 gamma radiation in preventing restenosis in patients with in-stent restenosis (352,353,354 and 355) (Fig. 83.14). Teirstein and colleagues have reported the 1-year and 3-year results of the Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting trial, which randomly assigned 55 patients with restenosis (both in-stent restenosis and post-PTCA restenosis) to receive gamma radiation or placebo after undergoing a successful angioplasty procedure. Late luminal loss was significantly lower in the Ir-192–treated group than in the placebo group (1.85 ± 0.89 mm vs. 2.43 ± 0.78 mm, p = .02) in the first year of follow-up, and adverse ischemic events remained lower at 3 years (352) (Table 83.7). In the GAMMA-1 trial (353) Ir-192 was administered after a successful PTCA and was associated with less target lesion revascularization (24% vs. 42%; p <.01) (Fig. 83.14) and less binary angiographically determined restenosis (32% vs. 55%; p = .01) than was delivery of a placebo. In the Gamma Washington Radiation for In-Stent Restenosis Trial (WRIST), patients who were assigned to receive ^{192}Ir also had less target lesion revascularization (23% vs. 63%; p <.001) (Fig. 83.14) and less angiographically identified restenosis (19% vs. 58%; p = .001) than did those in the placebo group at 6 months. For long lesions (mean stent length 70 mm), the Long WRIST study reported a 50% reduction of target lesion revascularization (p = .001) (Fig. 83.14). A significant reduction in the composite of death, myocardial infarction, and target vessel revascularization was noted in each study at 6-month to 1-year follow-up (352,353,354 and 355) (Table 83.7).

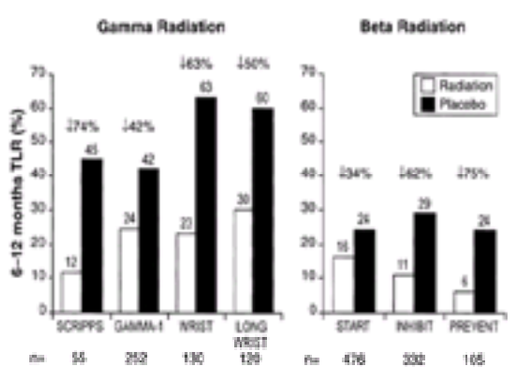


FIGURE 83.14 Rates of target lesion revascularization (TLR) after intracoronary brachytherapy for in-stent restenosis. Compared with results after placebo administration, target vessel revascularization was relatively reduced by 43% to 74% after gamma radiation therapy and by 34% to 63% after beta radiation at 6 to 12 months of follow-up. INHIBIT, Intimal Hyperplasia Inhibition with Beta In-stent Trial; PREVENT, Proliferation Reduction with Vascular Energy Trial; SCRIPPS, Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting trial; START, ^{90}Sr Treatment of Angiographic Restenosis Trial; WRIST, Washington Radiation for In-stent Restenosis Trial.

Study	n	Dosimetry	Follow-up period (mo)	MACE (%)		p Value
				Radiation	Control	
Gamma radiation (Ir-192)						
SCRIPPS (352)	55	8-30 Gy, IVUS guidance	12	15	48	.01
			24	23	55	.01
GAMMA-1 (353)	252	9-30 Gy, IVUS guidance	9	28	44	.02
WRIST (354)	130	15 Gy, 2 mm from the source	12*	35	68	<.001
LONG WRIST (355)	120	15 Gy, 2.0 mm from the source	12	38	62	.01
Beta radiation (Y-90, Sr-90, P-32)						
START (358)	476	Sr-90/Y-90: 16-20 Gy, 2.0 mm from center	8	18	26	.009
INHIBIT (357)	332	P-32: 20 Gy, 1 mm from center	9	22	33	.007
PREVENT (356)	105	P-32: 16-24 Gy, 1 mm in artery wall	12	16	24	NS

INHIBIT, Intimal Hyperplasia Inhibition with Beta In-stent Trial; Ir-192, iridium-192; IVUS, intravascular ultrasonography; MACE, major adverse cardiovascular events (death, myocardial infarction, target lesion revascularization); NS, not significant; P-32, phosphorus-32; PREVENT, Proliferation Reduction with Vascular Energy Trial; SCRIPPS, Scripps Coronary Radiation to Inhibit Proliferation Post Stenting trial; Sr-90, strontium-90; START, Sr-90 Treatment of Angiographic Restenosis Trial; WRIST, Washington Radiation for In-stent Restenosis Trial; Y-90, yttrium-90.
*Death, myocardial infarction, target lesion revascularization.

TABLE 83.7 CLINICAL TRIALS OF INTRACORONARY RADIATION FOR TREATMENT OF IN-STENT RESTENOSIS

Beta Radiation

Initially studied as an adjunctive treatment to prevent restenosis in *de novo* lesions in native coronary arteries, beta radiation has been demonstrated to effectively lower recurrent stenosis after PCI for in-stent stenosis (356,357 and 358). The Beta WRIST (359), a registry of Y-90 beta radiation in treating in-stent restenosis, first reported the safety of Y-90 administration. At 6 months, target lesion revascularization was 26%, which compared favorably with the previous results of the placebo cohort in Gamma WRIST. The Sr-90 Treatment of Angiographic Restenosis Trial (358), in which 476 patients were randomly assigned to undergo either Sr-90 brachytherapy or a placebo procedure for in-stent restenosis, demonstrated a marked reduction in favor of the group receiving beta radiation in both clinically determined restenosis (Sr-90 24% vs. placebo 34%; risk reduction, 34%; $p = .008$) and angiographically determined restenosis (Sr-90 14% vs. placebo 42%; $p < .001$) at 8 months (356,358,359) (Table 83.7; Fig. 83.14). The Intimal Hyperplasia Inhibition with Beta In-Stent Trial is a moderately sized (332-patient) multicenter, randomized, placebo-controlled trial that has preliminarily observed a 63% reduction in target vessel revascularization (11% for the radiation group vs. 29% for the placebo group) at 8 months through treatment with a P-32 beta radiation source (Table 83.7; Fig. 83.14).

Parallel to the development of catheter-based brachytherapy, stent-based brachytherapy using a beta-emitting P-32 radiation source has been investigated (360,361). Advantages of this technique include the fact that it does not require the presence of radiation oncologists, additional shielding in the catheterization laboratory, or particular additional equipment. Although in-stent restenosis is essentially eliminated, stent-edge hyperplasia due to the stimulating effect of low-dose radiation (geographic miss) and balloon injury is a major limitation of this technique.

Late Restenosis and Late Thrombosis

Although intracoronary radiotherapy has been proven to attenuate restenosis overall, its effects are not always consistent or curative. At the extremes of outcomes are patients who have divergent late effects of either thrombosis (perhaps due to inadequate reendothelialization) or restenosis (possibly from paradoxical neointimal stimulation of adjacent vessel segment), although such occurrences are infrequent. In the Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting trial, late luminal loss was observed in some patients between the 6-month and 3-year follow-up. This suggests that a time course–modified restenosis model may be needed when considering brachytherapy. Although not reported in any of the trials mentioned earlier, mitotic changes (carcinoma) or aneurysmal changes in coronary arteries are potential late sequelae, and observing such potential events may require many years of follow-up. More important concern about the safety of radiation was raised when late thrombosis and myocardial infarction occurred months after radiotherapy. After intracoronary radiation, endothelial repair is delayed due to the same inhibiting effect of radiation in attenuating tissue proliferation. Late thrombosis is thought to be due either to delayed reendothelialization of stents or to late positive arterial remodeling that causes separation of the stent from the arterial wall. The reduction in the composite primary end points with radiation therapy in these clinical trials is driven mainly by the reduction in target vessel revascularization. For example, in GAMMA-1 (353) a trend was seen in the ^{192}Ir arm toward increased death (3.1% vs. 0.8% for the placebo arm; $p = .17$) and increased myocardial infarction (4.6% vs. 2.5% in the placebo arm; $p = .09$) at 9 months. When data for the brachytherapy trials are combined, late thrombosis is found to occur in 9.1% of the radiation-treated group versus 1.2% of the placebo group ($p < .0001$). By multivariate logistic regression analysis, new stent implantation and long lesions were found to be the major predictors of late thrombosis. Current recommendations, therefore, include either the avoidance of new stent placement or long-term therapy with thienopyridine. The GAMMA-V and Plavix WRIST registries are intended to study the efficacy of a 6-month course of clopidogrel bisulfate and aspirin for prevention of subacute thrombosis after Ir-192 radiotherapy (362). In beta radiation trials, prolonged clopidogrel and aspirin therapy (3 to 6 months) was associated with low (less than 2%) incidence of late thrombosis (357,358).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Despite extensive basic scientific and clinical research, the epidemiology, prophylactic measures, and treatment of restenosis after angioplasty are still surrounded by controversy. For example, for many years the working hypothesis of restenosis pathophysiology focused on neointimal hyperplasia. Thus, pharmacologic and mechanical therapies targeted thrombus formation, intimal dissection, and smooth muscle cell proliferation in keeping with this hyperplastic paradigm. Subsequent histologic investigations in animal models (363) and serial intravascular ultrasonographic data from clinical studies (18), however, suggested that the majority of lumen loss after balloon angioplasty was due to negative arterial remodeling or vessel contracture, not neointimal growth. These new findings may explain why some final lumen diameters have been reported to increase in the months after angioplasty, whereas in other cases lumen diameters remain the same or restenosis develops (Fig. 83.2) (38). They would also explain why early pharmacologic therapies did not improve restenosis after balloon angioplasty. Hence, reevaluation of those therapies that limited neointimal growth but were not successful in halting the remodeling-induced restenosis of balloon angioplasty is reasonable. Used in association with intracoronary stents, these agents may prove to be particularly useful. Agents for which results currently appear hopeful include probucol, cilostazol, paclitaxel, and rapamycin.

Although the effect of remodeling was being elucidated in the balloon angioplasty population, intracoronary stent placement increased in frequency to become the leading procedure, and in-stent restenosis is almost entirely due to neointimal hyperplasia. This has necessarily led to reevaluation of the epidemiology of restenosis. Regarding predictors of restenosis, most of the previously described anatomic and demographic risk factors still apply to contemporary balloon angioplasty procedures. On the other hand, data on intracoronary stents show that these well-entrenched restenosis predictors have decreased in importance (Table 83.2). For example, unstable angina, chronic total occlusion, vessel treated, and lesion length—all strong predictors of restenosis after balloon angioplasty—have little or no predictive value for restenosis after stent placement.

The rapid replacement of balloon angioplasty by intracoronary stent placement has also introduced several other important controversies. First, despite several focused studies comparing balloon angioplasty to stent placement, much of the rush to use stents in the interventional laboratory has not been evidence based. For example, although few controlled data are available, stents are being placed in gradually smaller vessels, in longer lesions, and in lesions already containing a restenotic stent. Although these practices may be the treatment of choice in the future, current practice remains ahead of prospectively collected evidence and technology. Several studies are continuing to elucidate when a “stent-like” result obtained with balloon angioplasty or other techniques alone provides a restenosis rate similar to that achieved with stent placement.

A second area of current interest created by the rapid flux of stent use includes both the prophylaxis and treatment of in-stent restenosis. Despite the relatively low rate of restenosis within stents, the actual number of patients with in-stent restenosis now exceeds the number with nonstent restenosis. For the prophylaxis of in-stent restenosis, radiation therapy and use of platelet glycoprotein IIb/IIIa inhibitors continue to be studied. Because diabetic patients account for approximately 20% of all patients undergoing intervention, the suggestion that abciximab may reduce target vessel revascularization among diabetic patients needs to be further explored. The 6-month data from the Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial (364) and Enhanced Suppresion of the Platelet IIb/IIIa Receptor with Integrilin Therapy (365) trials may give additional insight. Administration of gamma and beta radiation has proven successful in attenuating recurrent in-stent restenosis. Data must accumulate before the factors that predict benefit from radiation therapy can be understood (366). Likewise, one hopes that the several unattractive features of radiation delivery and safety will be improved. Although controversies do abound, the future will undoubtedly continue to supply new pharmacologic and mechanical therapies targeting restenosis. Given the complex and interrelated mechanisms of restenosis, a combination of therapies will most likely provide the optimal preventive strategy.

THE FUTURE

With new information regarding the mechanisms of restenosis and the application of strategies to limit recurrence of stenosis, the future for interventional cardiology is bright. The spectrum of patients and coronary anatomy that can be successfully treated with percutaneous revascularization will continue to broaden. At the same time, the occurrence of restenosis should be further reduced as novel techniques and agents, such as intracoronary stents incorporating radiation or antiproliferative agents, are applied.

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84

APPROACHES TO THE PATIENT WITH PRIOR BYPASS SURGERY

JOHN S. DOUGLAS, JR.

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

The important issues in the postbypass patient who has recurrent angina or ischemia are providing relief of symptoms and ischemia with the least morbidity and cost and doing it in a manner that provides durable benefit. It takes considerable judgment to make the best decision in these patients because there are frequently many options, most of which have substantial baggage (complications and short-term benefit).

HISTORICAL PERSPECTIVE

Advent and Maturation of Surgical Revascularization

As was later true of percutaneous transluminal coronary angioplasty (PTCA) (1,2 and 3), surgical coronary revascularization began more than 30 years ago with attempts to revascularize a single coronary artery. The result of these efforts was a dramatic change in cardiologic practice as surgical techniques adequate to palliate multivessel obstructive disease evolved. Within a decade, the growth of coronary bypass surgery was exponential (Fig. 84.1). Hundreds of thousands of patients were operated on annually, creating a large population of several million postbypass patients in the United States alone. Owing to the progressive nature of the atherosclerotic process and the limited durability of venous conduits and in spite of widespread use of arterial grafts and antiplatelet agents, recurrent ischemia after surgical revascularization is a problem all cardiologists face with increasing frequency. Recurrence of angina in the first year alone was reported in 24% of patients in the Coronary Artery Surgery Study (4), and by the fifth postoperative year, almost one-half of the broad spectrum of postoperative patients have recurrent symptoms (4,5 and 6).

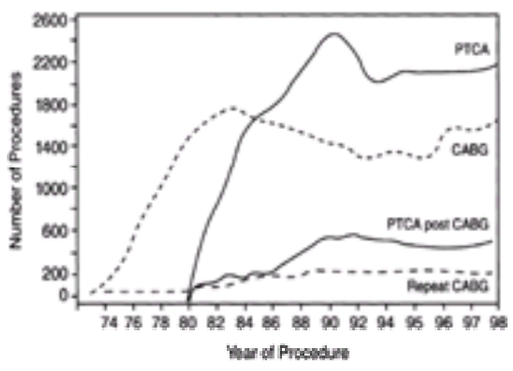


FIGURE 84.1 Coronary artery revascularization procedures at Emory University Hospitals from 1973 to 1998. CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

Recurrent angina sufficient to require reoperation occurred in 12% to 15% of patients within one decade of a first coronary operation at Emory University and at The Cleveland Clinic, and by the twelfth to fifteenth year, 30% required reoperation (7,8). Reoperative coronary surgery when compared with initial operation proved to be more costly, two to three times more likely to lead to in-hospital death or myocardial infarction (MI), and less effective in achieving angina relief (7,9,10 and 11). Among 2,030 patients who underwent reoperation at Emory University, in-hospital mortality was 7.0% (4.6% younger than 60 years, 8.2% aged 60 to 69, 10.0% 70 years or older). Five- and 10-year survival was 76% and 55%, respectively (10). Reported outcome data confined to patients who underwent reoperation in the 1990s confirmed the high operative mortality noted previously (7.4%) and reported a higher rate of Q-wave infarction, a longer length of stay, and higher costs than initial operations (11). The increase in complications and reduced efficacy of reoperative coronary surgery are probably related to the more extensive disease present, the requirement to use second-line venous conduits in many cases, and the technically more difficult and operator-dependent nature of reoperative heart surgery.

Percutaneous Intervention Postbypass

Percutaneous catheter revascularization in patients who had prior coronary bypass surgery (Fig. 84.2) was first described by Gruentzig, who treated eight patients, six successfully, among the first 50 patients he reported. Seven of the eight postbypass patients had angioplasty of saphenous vein graft (SVG) lesions, and three of five treated successfully had recurrences, leading Gruentzig to make the following insightful comments based on such limited observations: "The different kind of disease may explain the high incidence of recurrence in graft stenosis. Further experience will show whether we should eliminate this lesion from consideration" (12).

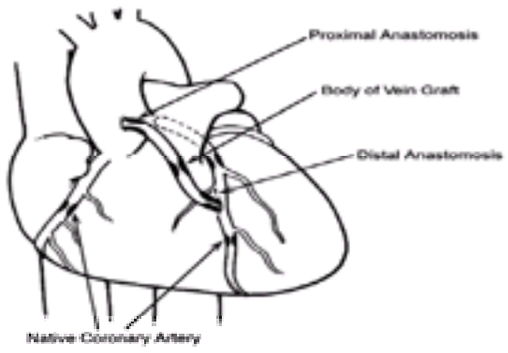


FIGURE 84.2 Targets for percutaneous coronary intervention include saphenous vein grafts and native coronary artery sites in unbypassed and bypassed vessels. In addition, internal mammary artery, radial, subclavian, innominate, and gastroepiploic artery grafts are potential targets. (Adapted from Douglas JS Jr, Gruentzig AR, King SB III, et al. Percutaneous transluminal coronary angioplasty in patients with prior coronary bypass surgery. *J Am Coll Cardiol* 1983;2:745–754, with permission.)

Among the first 1,116 patients treated with coronary angioplasty in the National Heart, Lung, and Blood Institute PTCA Registry, 62 patients had had previous bypass surgery. The in-hospital mortality in these patients, 8.1%, was significantly higher than in patients without prior surgery, 0.7%, causing concern about the safety of the procedure in this group of patients (13). The early experience at Emory University was reassuring, however; 116 patients were treated with no procedural death, three emergency operations, and one Q-wave MI (Fig. 84.2). One late death occurred during an 8.3-month mean follow-up. Gruentzig's observation of higher restenosis rates for SVGs was reaffirmed for mid- and proximal graft sites, but an acceptable restenosis rate for distal anastomosis lesions of 18% (4 of 22) was first reported (Fig. 84.3) as well as the initial report of attempted internal mammary artery (IMA) graft angioplasty (14). In subsequent experience with more than 34,000 coronary angioplasty procedures at Emory University, a history of prior bypass surgery was not associated with increased risk of death or Q-wave MI and was negatively correlated with need for in-hospital coronary artery bypass graft (CABG) surgery (15).

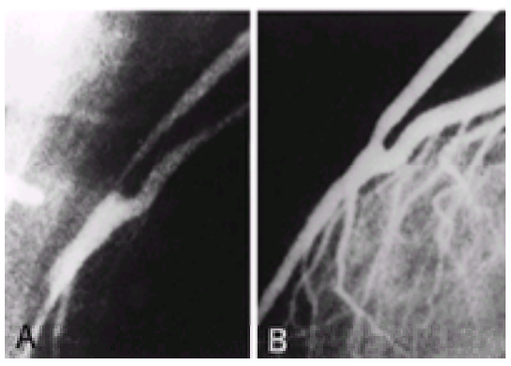


FIGURE 84.3 A 57-year-old man underwent saphenous vein bypass grafting to the distal left anterior descending (LAD) artery in July 1981; coronary arteriography a few months later **(A)** revealed high-grade stenosis at the junction of the saphenous vein graft to the LAD artery (left lateral view). Percutaneous transluminal coronary angioplasty was successful (residual stenosis, 13%), and recatheterization 9 months later showed a widely patent anastomosis **(B)**. The patient subsequently remained completely asymptomatic, and at last follow-up 19 years later (July 2000), he had a negative stress thallium scan result. (From Douglas JS Jr, Gruentzig AR, King SB III, et al. Percutaneous transluminal coronary angioplasty in patients with prior coronary bypass surgery. *J Am Coll Cardiol* 1983;2:745–754, with permission.)

Percutaneous coronary intervention (PCI) became a less invasive revascularization alternative for many symptomatic postbypass patients (Fig. 84.1), including an increasing number who, because of contraindications (pulmonary and renal failure, old age, malignancy), were not candidates for reoperative coronary artery surgery. Patients with patent arterial grafts that would be jeopardized by reoperation, patients with relatively small amounts of ischemic, symptom-producing myocardium, and patients with no available venous or arterial conduits for grafts underwent percutaneous revascularization at an acceptable risk. At many centers, patients with prior bypass surgery account for up to 25% of the PCI procedures performed (Fig. 84.1).

In 4,174 postbypass patients who underwent coronary revascularization at Emory University, 2,613 (63%) underwent PTCA, and 1,561 (37%) underwent CABG, with 1.2% and 6.8% (p <.0001) in-hospital mortality, respectively, and with in-hospital costs of $8,500 ± $7,300 for PTCA compared with $24,200 ± $17,000 ($p$ <.0001) for CABG (16). The initial cost advantages of PTCA over CABG may, however, be moderated by the current increasing use of multiple devices, especially stents, in postbypass patients, a group of patients in whom coronary interventional strategies have the broadest application and by subsequent reinterventions. It is the goal of this chapter to focus on the cause and treatment, emphasizing percutaneous revascularization strategies, of recurrent angina after bypass surgery.

ANATOMIC CONSIDERATIONS

Among the anatomic factors influencing revascularization decisions (Table 84.1), the status of the left anterior descending coronary artery (LAD) and its graft is paramount. Placement of an IMA, a conduit immune to atherosclerosis, as a graft to the LAD has been shown to enhance survival and reduce ischemic events 10 to as long as 20 years later (17,18 and 19). In a patient with a patent IMA graft to the LAD, reoperative surgery to treat non-LAD ischemia has been reported to offer no survival benefit (20,21), may jeopardize the arterial graft, and, in our experience and others, more frequently leads to percutaneous intervention. Multivessel involvement, small number of patent grafts, severe vein graft disease (especially if to LAD), and a damaged left ventricle are factors more likely to lead to reoperative surgery (22,23).

Often leads to percutaneous transluminal coronary angioplasty	Often leads to coronary artery bypass grafting
Patent arterial graft (especially left anterior descending coronary artery)	Diseased saphenous vein graft to left anterior descending
≤2 patent grafts	Bulky saphenous vein graft atheroma
1–3 culprit lesions	>3 culprit lesions
Difficult surgical access	Multiple saphenous vein graft lesions
Mediastinal scarring secondary to radiation, infection, or pericarditis	Available arterial conduits
Prior muscle transfer closure of unhealed sternotomy	Ejection fraction 25% to 35%
Posterior lateral target vessel	
Inadequate conduits	
Near normal left ventricle	
Future cardiac surgery anticipated	
In situ prosthetic valve	
Mild to moderate aortic or mitral valve disease	

P>**TABLE 84.1** ANATOMIC FACTORS INFLUENCING REVASCULARIZATION DECISIONS IN POSTBYPASS PATIENTS

PATHOPHYSIOLOGY: BASIS FOR RECURRENT ISCHEMIA

Incomplete Revascularization

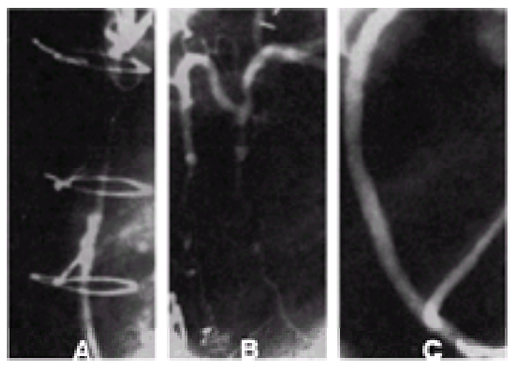
In many patients, complete surgical revascularization was not achieved due to the presence of distal coronary disease, whereas less common causes include the following: an inadequate amount of venous or arterial conduit, inadequate conduit lumen due to small vessel size (IMA especially) or injury, intramyocardial location of target coronary vessel, placement of grafts to the wrong coronary artery or to a coronary vein, creating an arterial venous fistula (24), use of an IMA in the presence of significant stenosis of the subclavian or innominate arteries (25,26), or coronary steal phenomenon attributed to large arterial graft side branches (27), a cause that has been questioned (28). Intentional incomplete surgical revascularization is an increasingly frequent phenomenon in patients selected for "beating heart" operations because of the technical difficulty of bypassing posteriorly located coronary arteries. In some patients, this strategy has resulted in subsequent percutaneous revascularization because of inadequate relief of symptoms. In others, incomplete surgical revascularization has been dealt with up front with adjunctive percutaneous

revascularization during the same hospitalization, the so-called hybrid approach. In addition to less complete revascularization with beating heart surgery, there is some evidence that less precise anastomoses may compromise graft patency, especially in the surgical learning curve (see Venous Graft Attrition and Arterial Graft Compromise, later in this chapter).

Loss of Revascularization Benefit

Venous Graft Attrition

In patients with recurrent ischemia and infarction after bypass surgery, stenosis, occlusion, or both stenosis and occlusion of SVGs is the most common cause of venous graft attrition (6,21,29,30,31,32,33,34,35,36,37,38,39 and 40). Thrombotic occlusion related to surgical technical problems or slow graft flow secondary to a small or compromised distal coronary arterial bed results in closure of 10% to 15% of SVGs within the first month (29,30 and 31), and even with aspirin therapy, 7% of vein grafts were shown to be occluded by 9 days, with up to 17% of patients having a closed graft at that time (29). Subsequently 15% to 20% of vein grafts occlude by 1 year, 1% to 2% per year from years 1 to 6, and 4% per year from 6 to 10 years after surgery (eFig. 84.3.1) (29,30 and 31,41). After 10 years, a minority of vein grafts were free of significant occlusion disease (32,45).



***e*FIGURE 84.3.1** A 66-year-old man with unstable angina and two prior bypass operations, the first to the right coronary artery 15 years ago and the last to the right and left anterior descending arteries 10 years ago, was found to have a long stenosis of the saphenous vein graft to the right coronary artery **(A)**. The left internal mammary artery graft to the left anterior descending was patent. Recanalization of the old right coronary artery occlusion **(B)** was successful using a stiff hydrophilic-coated guidewire and conventional balloon angioplasty followed by placement of 3.5-mm stents **(C)**. The patient was treated for right coronary artery in-stent restenosis 2 years later, and at 5 years the patient was asymptomatic and fully active.

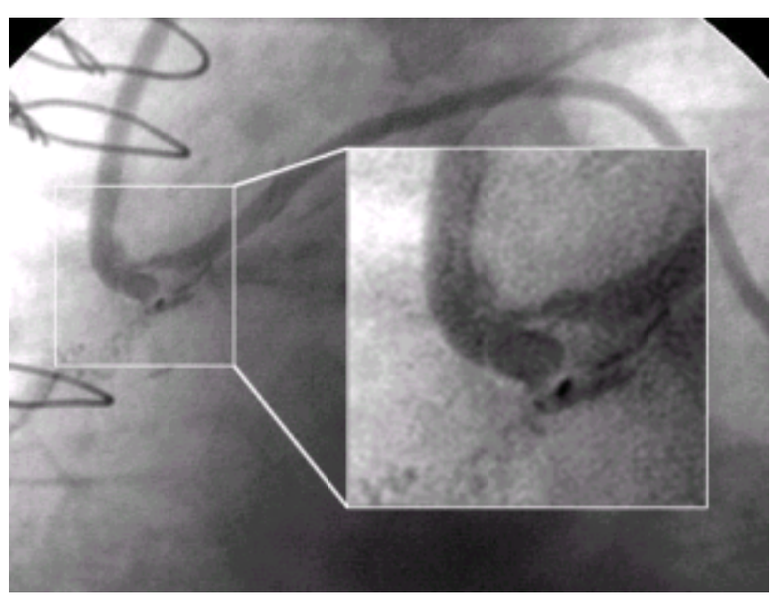
The morphologic changes occurring in arterialized saphenous veins that lead to stenosis and occlusion have been described in detail (42,43 and 44). Diffuse intimal thickening universally present in vein grafts in place longer than 1 month infrequently causes high-grade focal narrowing but may account for the following: perianastomotic lesions, stenoses where vein branches have been ligated and clipped, and diffuse narrowing throughout a graft (43,45). Use of beating heart surgical techniques has resulted in more frequent anastomotic problems, probably related to learning curve issues and the currently evolving technology that is used to assist the surgeon by stabilizing the heart. Beginning approximately 3 years after surgery, atherosclerotic vein graft lesions become increasingly frequent. Vein graft atheroma contain foam cells, cholesterol clefts, blood elements, and necrotic debris with less fibrous tissue and calcification than is present in native coronary arteries (44,46). Atheroma in older vein grafts are frequently larger, softer, and more friable than native coronary lesions and are more likely to lack a fibrous cap and have associated thrombus (47,48,49 and 50), all features with ominous prognostic implications for subsequent cardiac events and for atheroembolic complications of percutaneous intervention. Information from surgical and angioplasty series are concordant, indicating that even mild stenoses of vein grafts are associated with significant risk of recurrent ischemic events (stenosis 41% to 50%, recurrent ischemic events 45%; stenosis 31% to 40%, recurrent ischemic events 18%; stenosis less than or equal to 30%, recurrent ischemic events 2%) (21,51). Extrinsic focal compression of SVGs by mediastinal scar is infrequently recognized by development of stenosis at a fixed graft flexion point, and high balloon pressure is frequently required to dilate such stenoses.

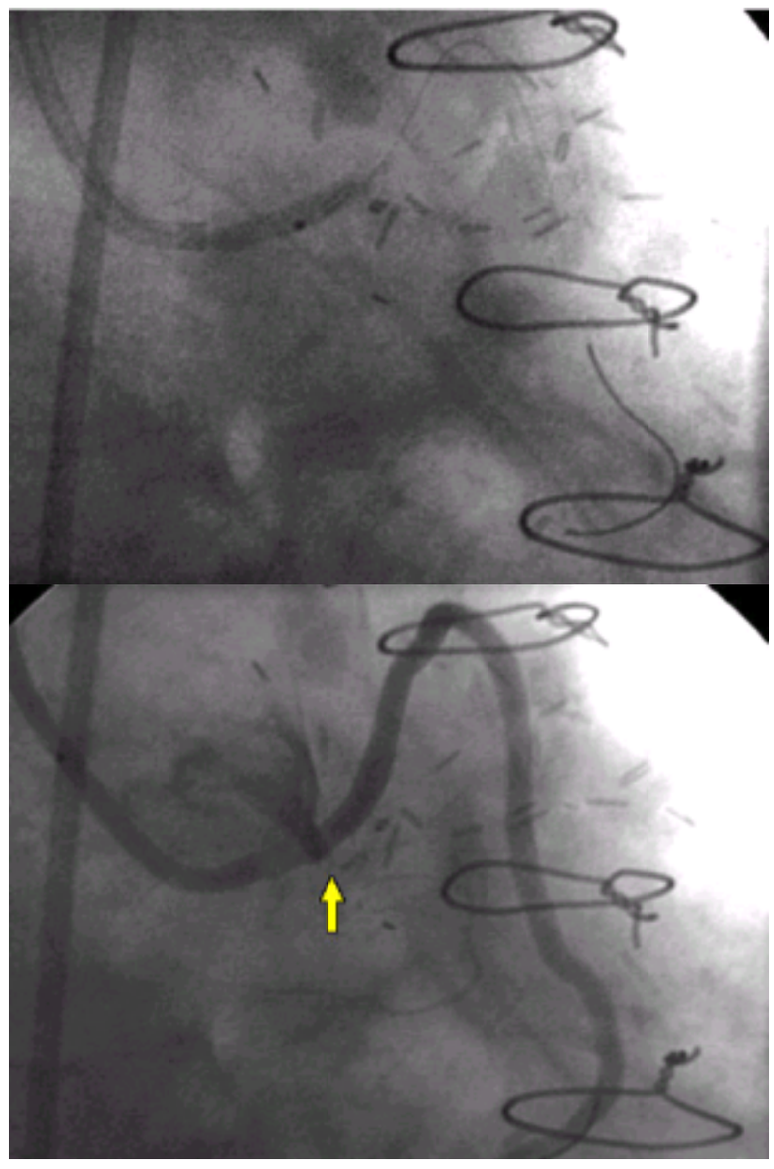
Native Coronary Artery Progression

Worsening of native coronary artery disease after bypass surgery has been reported in approximately 5% of patients annually (52,53 and 54). Frequency of disease progression at native vessel sites at 5 years was reported as follows: proximal to graft insertion (70%), unbypassed artery (15%), and distal to graft insertion (0%) (55). Loop and colleagues noted that progression of disease distal to grafts was uncommon and that at 2 years progression of disease proximal to grafts was more common for SVG than for IMA grafts (67% vs. 39%) (18). Progression of native coronary disease proximal to grafts has implications for coronary intervention when graft disease or occlusion occurs and is an important cause of ischemia due to poor perfusion of side branches (such as diagonal coronary arteries).

Arterial Graft Compromise

Although numerous publications attest to the excellent long-term patency of arterial grafts, several hundred patients have been reported who required IMA, radial artery, or subclavian artery intervention (25,26 and 27,56,57,58,59,60,61 and 62). In most instances IMA interventions were needed for anastomotic lesions, but proximal and midgraft sites have been treated (see Arterial Graft Intervention). The technical difficulty of performing an anastomosis in beating heart surgery probably accounts for more anastomotic problems after this type of surgery.



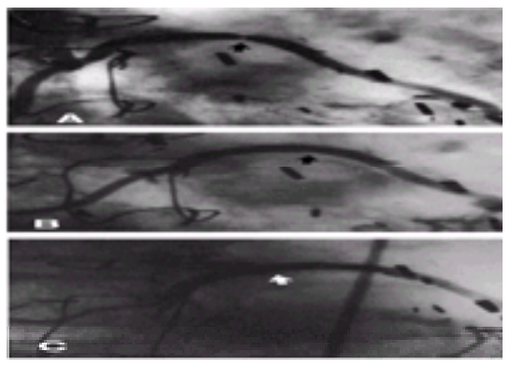


Palmaz-Schatz coronary stent placement in the ostium of a free right internal mammary artery graft to an obtuse marginal branch of the left circumflex (A). The stent is positioned so that the proximal 1 to 2 mm of the stent protrudes into the ascending aorta to guarantee coverage of the ostium (B). The postintervention result is shown in C.

CLINICAL PROFILE

Early Postoperative Ischemia (within the First Year)

Recurrent ischemia presenting as unstable angina or MI within a few hours or days of surgery is usually due to venous graft thrombosis, but coronary arteriography may reveal a compromised proximal or distal anastomosis, narrowing in the midportion of a graft due to graft torsion, IMA spasm, incomplete revascularization, or other surgical technical problems (injured IMA, and so forth), and in 25% of patients, the cause of ischemia is not apparent (61,62 and 63). Occlusion of an important graft may produce cardiogenic shock (64). Recurrent angina between 1 month and 1 year postoperation is most often due to perianastomotic stenosis (Fig. 84.3), graft occlusion, or mid-SVG stenoses due to fibrous intimal hyperplasia (eFig. 84.3.2) and only rarely due to progression of native coronary artery disease. Recurrence of angina at approximately 3 months postoperatively is highly suggestive of a distal graft anastomosis lesion and should, in most cases, lead to coronary arteriography.

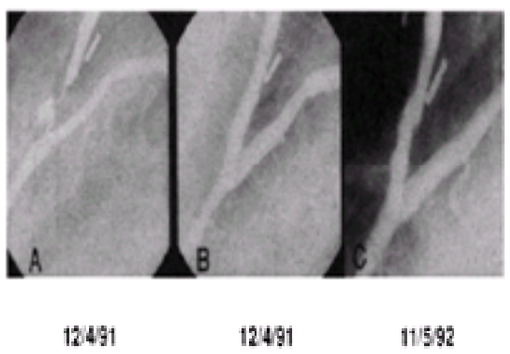


***e*FIGURE 84.3.2** A 74-year-old man developed unstable angina within 5 months of bypass surgery (left internal mammary artery to left anterior descending and saphenous vein graft to obtuse marginal). The right coronary artery was occluded and not grafted. Balloon angioplasty of a stenosis of the midportion of the vein graft to the circumflex was twice followed by restenosis within 6 weeks. Because of severe recurrent angina, a focal stenosis of 88% **(A)** (*arrow*) was dilated and stented with a 3.5-mm Palmaz-Schatz stent in July 1991 with an excellent initial result **(B)** (*arrow*). Protocol-driven recatheterization 7 months later revealed a widely patent stent site **(C)** (*arrow*). The patient has remained completely asymptomatic and fully active for over 5 years (last follow-up, July 1996).

Late Postoperative Ischemia (Greater Than 1 Year)

When ischemia develops more than 1 year following bypass surgery, culprit lesions are commonly present in graft conduits and in native coronary arteries. In 95 postbypass patients with unstable angina or non–Q-wave infarction, culprit lesions were identified in 51 vein grafts, 17 ungrafted coronary arteries, and 9 grafted arteries; in 18 patients a culprit lesion could not be determined. One-half of the vein grafts and 25% of unbypassed coronary arteries were totally occluded (33).

Approximately 3% of postbypass patients experienced acute MI annually (65), and mortality related to reperfusion strategies was relatively high, presumably due to the presence of multivessel disease and prior MI (34,35 and 36). In two-thirds of patients with evolving infarction, the culprit lesion was in a vein graft (*e*Fig. 84.3.3) (34,35 and 36,49), and this may have contributed to the low reperfusion rate of 25% reported by some (37) but not all investigators (39) with intravenous thrombolytic therapy.



***e*FIGURE 84.3.3** A 74-year-old man presented in December 1991 with unrelenting chest pain, left bundle branch block, and hypotension. There was a history of bypass surgery (1981) and prior percutaneous transluminal coronary angioplasty to the circumflex coronary artery, a saphenous vein graft to the left anterior descending coronary artery (LAD), and an occluded right coronary artery. Coronary angiography revealed a complex stenosis of the saphenous vein graft to the LAD (**A**, left lateral view). Balloon angioplasty and deployment of a 3.5-mm stent yielded an excellent angiographic result **(B)**. Follow-up angiography 1 year later revealed only mild narrowing **(C)**. At last follow-up 6 years later, the patient was asymptomatic and had had no cardiac events. Younger patients with such complex saphenous vein graft lesions of left anterior descending grafts are commonly referred for reoperation in our hospital. (From Douglas JS Jr. Percutaneous strategies for the management of angina pectoris after bypass surgery. In: Ventrovec GW, Carabello BA, eds. *Invasive cardiology: current diagnostic and therapeutic issues*. Armonk, NY: Futura Publishing, 1996:489, with permission.)

PRINCIPLES OF MANAGEMENT

Preventive Measures

Patients who have had coronary bypass surgery are at substantial risk for subsequent cardiac events related in large part to progressive arteriosclerosis. Recurrence of angina, angiographic progressions of vein graft atheroma, and pathologic changes at autopsy have been correlated with increased serum lipids and smoking, and lipid lowering has been shown to be beneficial (4,9,41,48,66,67 and 68). Given the increased effectiveness of current strategies for lipid lowering and smoking cessation, and reduced cardiac events that accrue, an aggressive approach to risk factor modification is mandatory in all postbypass patients. An aggressive lipid-lowering strategy resulted in a 30% reduction in revascularization (p = .0006) and a 24% reduction in a composite clinical end point (p = .001) during 7.5 years of follow-up in the post-CABG trial (67,68). The place of more aggressive antiplatelet therapy in the post-CABG patient is not clear, but more recently reported mortality benefits with clopidogrel are provocative and suggest that the use of this or other adjunctive agents may become routine in the future (69).

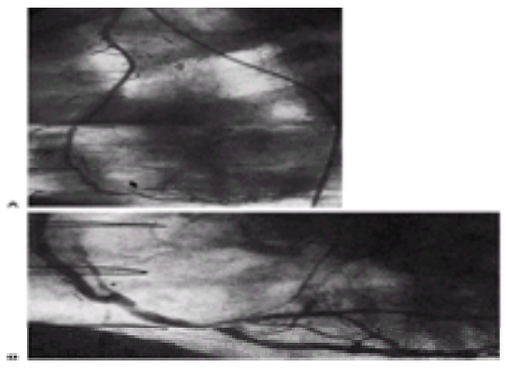
Treatment of Ischemia in the Postoperative Patient

Patients with recurrent symptoms or signs of ischemia after bypass surgery constitute an extremely heterogeneous group (Fig. 84.2). Treatment strategies must be based on a careful analysis of multiple factors (many angiographically based) including anatomic factors (Table 84.1), the likelihood of a successful percutaneous intervention, risk of complications, probability of long-term symptomatic benefit, and resource consumption compared with other viable options (7,14,70,71,72,73,74 and 75). Patient preferences must be considered since reinterventions are common with percutaneous intervention in postbypass patients, occurring in approximately 50% of patients at 5 years (72). In the postbypass patient, the ability to effect ischemia relief percutaneously is influenced by the time that has lapsed since surgery, the type of conduit (SVG vs. native vessel vs. IMA graft), and location of the stenotic segment.

Native Coronary Intervention

Technical Strategy

Although SVG attrition is the most common cause of ischemia postbypass, native vessel intervention frequently offers the most durable percutaneous revascularization and should be considered whenever possible. Approaches to native vessel sites in the postbypass patient present unique challenges including treatment of very old, calcified stenoses including left main coronary disease, recanalization of old total occlusions (eFig. 83.3.1), and treatment of native vessel sites via grafts. Treatment of native coronary sites via IMA grafts or SVGs may require even better guide catheter support and longer balloon catheters (or shorter guide catheters) than are necessary for graft angioplasty (eFig. 84.3.4), especially if catheters must be passed retrograde into native vessel sites proximal to graft insertion (see Saphenous Vein Graft Intervention and Arterial Graft Intervention). Retrograde passage to proximal coronary artery sites may require special guidewire strategies and high-performance catheters to traverse the sharp angles involved (73).



***e*FIGURE 84.3.4** A 57-year-old man developed disabling angina 7 years following bypass surgery. Cardiac catheterization revealed normal left ventricular function, a patent left internal mammary artery to the left anterior descending, and a patent right internal mammary artery to the right coronary artery, but severe stenosis of the continuation of the right coronary beyond the posterior descending **(A)**. Black arrow indicates site of lesion. Angioplasty was successful **(B)** from the femoral approach using a 145-cm balloon catheter. Four and a half years postangioplasty, the patient developed mild angina, and recatheterization showed no significant changes, with only mild narrowing at the percutaneous transluminal coronary angioplasty site, and medical therapy was advised.

Results of Native Coronary Intervention

The procedural outcome of angioplasty for native coronary intervention after CABG was reported for the first 372 such patients treated at Emory in 1987 (74). Most were men (81%), and 78% had multivessel disease. Angiographic success was achieved in 91%, and in-hospital complications were infrequent: mortality, 0.3%; Q-wave MI, 2%; non–Q-wave infarction, 4%; bypass surgery, 6%. At Mid-America Heart Institute, 1,543 postbypass patients underwent angioplasty of native coronary arteries; 21% were older than 70 years, 47% had unstable angina, and 74% had triple-vessel disease. Angiographic success was 94%, in-hospital mortality 0.8%, Q-wave MI 1.5%, and emergency bypass surgery 1.0% (75). At Emory University between 1980 and 1995, 2,246 postbypass patients underwent coronary intervention of native arteries with favorable outcome: procedural success 89%, in-hospital mortality 1%, Q-wave MI 1%, non–Q-wave infarction 4% (creatine kinase greater than three times normal), and emergency or elective surgery 2.8%. Although the definitions of outcomes were slightly different in these series, the overall procedural results were favorable, with a trend toward less need for in-hospital bypass surgery for failed percutaneous intervention. These outcomes were largely that of conventional balloon angioplasty. The Mayo Clinic experience with 937 post-CABG patients treated between 1995 and 1998 reflected a dramatic increase in stent use to 76% of patients and a reduction in use of atherectomy and laser strategies. Patients who underwent interventions in native vessels were younger, more likely female, had less severe coronary disease (70), and had a more favorable long-term outlook than those who underwent venous bypass graft intervention (71).

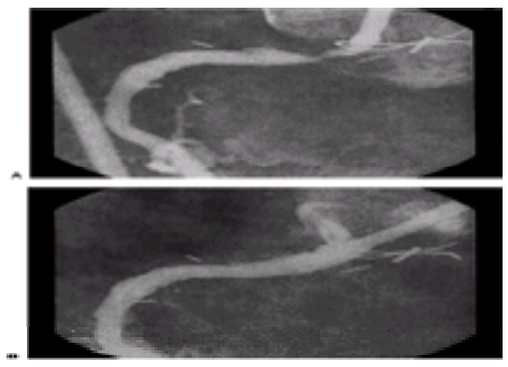
Saphenous Vein Graft Intervention

Technical Strategy

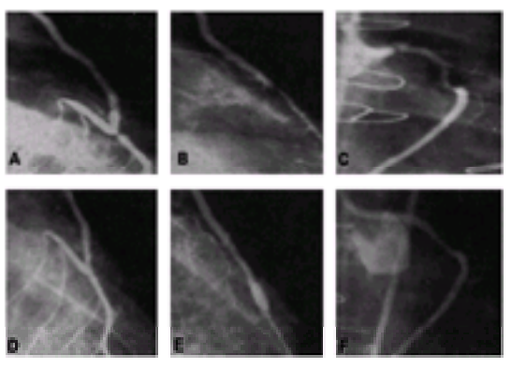
Guide catheters for SVG interventions are selected to achieve coaxial alignment and excellent backup support. For grafts arising from the outer curve of the aorta (usually to the right coronary), the multipurpose shape is best; for grafts arising anteriorly (LAD and diagonal), many shapes are adequate (right Judkins, left venous bypass, hockey stick), but for grafts arising in the inner curve (to the circumflex), guide catheter selection is critical, and the hockey stick and Amplatz left shapes are used most often. Side-hole guide catheters are sometimes used to avoid flow interruption with catheter engagement (i.e., with small grafts and ostial lesions).

Video 84.1 The angiographic characteristics of a lesion are important to characterize the risk associated with treating the lesion percutaneously. Left anterior oblique angiogram showing eccentric ulcerated lesion in a saphenous vein graft to the posterolateral branch of the left circumflex coronary artery. (Courtesy of Dr. Debabrata Mukherjee.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Balloon angioplasty is performed frequently at Emory University for focal lesions at the distal anastomosis occurring within a year of surgery. Almost all other SVG interventions include stent implantation with a balloon to graft diameter ratio of unity. Slight oversizing of the stent is usually safe when dealing with restenotic lesions. Inflation pressures exceeding 15 atm are used only to achieve complete stent expansion due to data from the Stent Versus Angioplasty in Saphenous Vein Graft (SAVED) trial, suggesting higher pressure had a deleterious effect on 6-month angiographic outcome in vein grafts (76). Although based only on clinical experience, many operators use a slightly longer stent than might be selected for a native vessel lesion (due to longitudinal extrusion of the plaque material) and prefer to use a high scaffolding stent placed without predilation to trap as much atheroma as possible. Directional atherectomy is not currently used for mid-SVG lesions due to increased complications and lack of long-term benefit (see Results of Saphenous Vein Graft Intervention, later in this chapter). Aortoostial vein graft lesions (*e*Fig. 84.3.5) are most often treated with placement of stents (77,78,79 and 80). Debulking before stenting aortoostial lesions is probably unnecessary based on results of observational studies (79). Nondilatable aortoostial or distal anastomotic lesions have been successfully treated with rotational or directional atherectomy (80) (*e*Fig. 84.3.6). Techniques to achieve protection from distal embolization of graft atheroma are currently evolving and will become an integral part of vein graft intervention (see Results of Saphenous Vein Graft Intervention, later in this chapter, and Chapter 81). Whether filters, covered stents, or occlusion-aspiration techniques are used depends on the location of the lesion and the availability of appropriate distal protection devices currently undergoing evaluation.

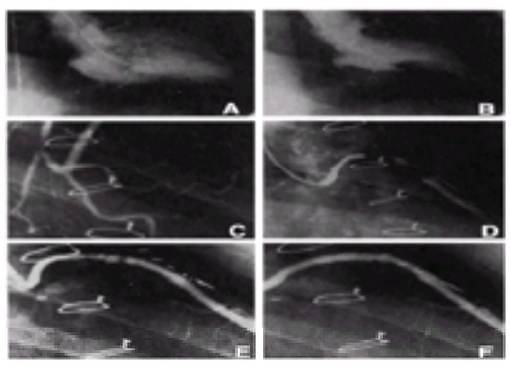


***e*FIGURE 84.3.5** Right anterior oblique view of a severe aortoostial stenosis of the saphenous vein graft to the right coronary artery in a 77-year-old woman with disabling angina that was refractory to medical therapy 4 years after coronary artery bypass grafting **(A)**. A vein graft to the left anterior descending was patent. Directional coronary atherectomy of the stenosis was successful using a JR 4.0 inferiorly directed guide catheter and 7-G AtheroCath without predilating **(B)**. The patient developed restenosis 3 months later with recurrence of unstable angina. Directional coronary atherectomy was repeated with a similar angiographic result, and 7 years postatherectomy, the saphenous vein graft to the right coronary artery was widely patent. Unfortunately, restenosis is relatively common at this site with directional coronary atherectomy, stents, and laser angioplasty. Most patients are currently treated with stent implantation without debulking procedures.



***e*FIGURE 84.3.6** A 53-year-old non–insulin-dependent diabetic secretary developed unstable angina and was found to have severe left main coronary disease with a dominant circumflex artery and underwent bypass surgery [left internal mammary artery to left anterior descending, saphenous vein graft to posterior lateral obtuse marginal (PLOM), saphenous vein graft to anterior lateral obtuse marginal (ALOM)] in September 1995. Angina recurred in February 1996, and a stenosis of the saphenous vein graft to ALOM was dilated successfully. In June 1996, unstable angina recurred, and cardiac catheterization revealed left ventricular hypokinesis with an ejection fraction of 30%, 80% stenosis of the left anterior descending artery just beyond insertion of the left internal mammary artery graft **(A)**, severe stenosis at the junction of the saphenous vein graft with ALOM **(B)**, closed saphenous vein graft to PLOM, severe stenosis of the ostium of the left main coronary, and moderately severe proximal circumflex stenosis **(C)**. The left anterior descending artery was successfully dilated **(D)**. The stenosis at the junction of the saphenous vein graft with ALOM failed to respond to 26-atm inflation of a 2.5-mm balloon catheter, and this site was successfully treated with rotational atherectomy (1.5- and 1.75-mm burrs) followed by a 2.5-mm balloon inflation with excellent result **(E)**. The left main coronary artery was dilated and stented with a Palmaz-Schatz 3.0-by 7-mm stent that was postdilated to 15 atm, and the proximal circumflex was dilated with a 3.0-mm balloon **(F)**. Intravascular ultrasound revealed excellent stent and proximal circumflex results. The patient was asymptomatic and working full-time at last follow-up 5 years later.

SVG lesions with associated thrombus are considered to be high-risk lesions and are treated with percutaneous intervention only if there are no better alternatives. Most such lesions are treated with mechanical thrombectomy followed by stenting (*e*Fig. 84.3.7) or by pretreatment with heparin and a IIb/IIIa platelet receptor inhibitor for a few days before intervention (81,82,83 and 84). Infusions of a thrombolytic agent into the graft have been carried out before intervention to reduce thrombus (85,86 and 87), and thrombolytic agents or IIb/IIIa inhibitors have been delivered locally (88,89 and 90). Ultrasound thrombolysis is an interesting strategy currently being evaluated (91,92). Completely occluded SVGs are rarely recanalized unless there are both recent occlusion and ongoing ischemia.



***e*FIGURE 84.3.7** A 61-year-old woman with a history of bypass surgery 9 years earlier was hospitalized with prolonged chest pain and anterior T-wave changes. A thallium scan revealed a large anterior septal perfusion abnormality with almost complete redistribution (large ischemic defect, small scar?). Left ventricular angiography showed minimal anterior hypokinesis and a normal ejection fraction **(A,B)**. A saphenous vein graft to the circumflex was patent **(C)**. The right coronary artery and proximal left anterior descending (LAD) were occluded. The saphenous vein graft to the LAD had no effective flow, and a large thrombus was present. There was no antegrade or collateral flow to the distal LAD. Intragraft urokinase was given, and after 3 days of heparin, there was no change in the LAD graft **(D)**. Transluminal extraction catheter atherectomy followed by a 12-hour infusion of abciximab (ReoPro) removed much of the thrombus **(E)** and restored flow into a large distal LAD that appeared suitable for bypass surgery, but there were no donor veins, both internal mammary arteries were inadequate by angiography, and the gastroepiploic artery was unavailable due to previous gastric surgery. Two 4-mm Palmaz-Schatz stents were deployed in the vein graft with excellent angiographic

results **(F)**.

In the presence of thrombus or bulky vein graft lesions, there is an increased incidence of slow or no reflow and MI due to distal embolization and microvascular spasm (50,93,94), and calcium channel blocking agents have been helpful in prevention and relief of this phenomenon (verapamil or diltiazem, 100-µg doses intracoronary to a total of 900 µg) (94,95); adenosine and nitroprusside have also been used in this setting (96,97).

The place of glycoprotein IIb/IIIa inhibitors in SVG PCI has not been clearly established (see below). Because the use of these agents is intuitively appealing in SVG PCI, many PCI operators administer them even though the limited published data do not support their use (98).

Results of Saphenous Vein Graft Intervention

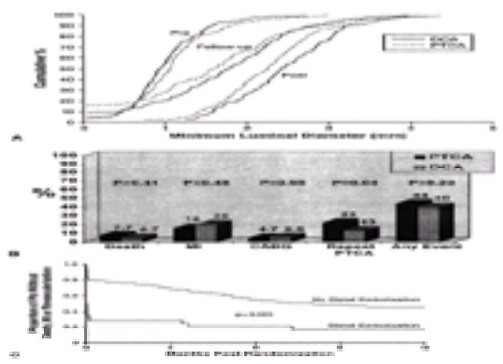
A number of reports have described the results of balloon angioplasty in SVG disease (eTable 84.1.1) (14,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117 and 118), indicating that in selected patients success rates of approximately 90% were achieved with mortality of approximately 1%, Q-wave MI of less than 2%, and in-hospital CABG in approximately 2% of patients. Many of these patients had relatively favorable anatomy with focal lesions free of obvious thrombus. Non–Q-wave MI, the most frequent complication, occurred in 78 (13%) of 599 patients at Emory University (105). The length of time since surgery was an important predictor of restenosis (less than 6 months, 32%; 6 months to 1 year, 43%; 1 to 5 years, 61%; and 64% for those older than 5 years, $p < .02$) as was the location of the lesion (proximal anastomosis, 68%; midgraft, 61%; distal anastomosis, 45%; $p < .06$). The lowest restenosis rate, 22%, was noted for lesions that occurred at the distal anastomosis within 1 year of surgery, and these patients had excellent event-free survival (Fig. 84.3).

***e*TABLE 84.1.1** BALLOON ANGIOPLASTY OF AORTOCORONARY SAPHENOUS VEIN GRAFTS: REPORTS OF MORE THAN 50 PATIENTS

Author (yr)	Reference	Successful percutaneous transluminal coronary angioplasty (%)	Coronary emboli	Emergency coronary artery bypass grafting	Death	Acute myocardial infarction
Douglas et al. (1983)	14	58/62 (94)	0	1	0	1
Douglas et al. (1986)	99	216/235 (92)	7 (3%)	3 (1.3%)	0	1
Cote et al. (1987)	100	86/101 (85)	2 (2%)	1	0	1
Pinkerton et al. (1988)	118	93/100 (93)	—	—	—	—
Dorros et al. (1988)	101	44/53 (83)	3 (6%)	—	1	1
Reed et al. (1989)	102	47/52 (90)	0	—	0	0
Platko et al. (1989)	103	92/101 (92)	—	4 (4%)	2%	6%
Webb et al. (1990)	106	371/442 (84)	—	2.4%	0.2%	3.1%
Plokker et al. (1991)	104	409/454 (90)	—	6 (1.3%)	3 (0.7%)	—
Reeves et al. (1991)	107	47/57 (83)	7%	2%	2%	9%
Douglas et al. (1991)	105	539/599 (90)	—	21 (3.5%)	7 (1.2%)	15 (2.5%)
Miranda et al. (1992)	75	410/440 (93)	—	[a]	5 (1.1%)	[a]
Morrison et al. (1994)	108	70/75 (93)	0	1%	3%	3%

[a]A total of 19 patients (5%) had acute myocardial infarction.

Directional atherectomy, the first nonballoon procedure approved by the U.S. Food and Drug Administration, was used in SVGs with the hope that debulking would reduce complications and restenosis. A multicenter, randomized comparison of directional atherectomy and balloon angioplasty in SVGs [Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT II)] was performed in 305 patients, 86% with midvein lesions (111). The results paralleled CAVEAT I: higher angiographic success with atherectomy, a trend toward more non–Q-wave MIs with atherectomy (16.0% vs. 9.6%), and similar restenosis at 6 months (45.6% for atherectomy and 50.5% for angioplasty, $p = .491$) (eFig. 84.3.8). There was a trend toward more target lesion revascularization at 6 months with angioplasty (22% and 13% for atherectomy, $p = .04$) (eFig. 84.3.8B). There was, however, no difference in the frequency of experiencing any cardiac event at 6 months. Angiographic evidence of distal embolization noted twice as frequently with atherectomy (13.5% vs. 5.1%) was a predictor of adverse events in-hospital and at 12 months (112) (eFig. 84.3.8C). An increased awareness of the importance of non–Q-wave infarction combined with an absent restenosis benefit and increased cost led to decreased use of this approach for midvein lesions. Performance of directional atherectomy for treatment of aortoostial SVG lesions (eFig. 84.3.5) has been reported only in relatively small observation series with angiographic success in 94.0%, major complications in 5.9%, and repeat target lesion revascularization in 42.0% at 12 months (compared with 33% with stenting, $p = .05$) (113). Results from Emory suggest similar high subsequent cardiac event rates of approximately 50% at 1 year with balloons, directional atherectomy, and stents at proximal and midvein sites (114).



***e*FIGURE 84.3.8 A:** Graph showing preprocedure, postprocedure, and follow-up minimal luminal diameter by treatment group in the Coronary Angioplasty Versus Excisional Atherectomy Trial II (CAVEAT II), a randomized comparison of directional coronary atherectomy (DCA) and balloon angioplasty (percutaneous transluminal coronary angioplasty, PTCA) in saphenous vein graft intervention. At follow-up angiography, there was no significant difference in the minimum lumen diameter achieved by directional coronary atherectomy and PTCA. **B:** Major cardiac events at 6 months in CAVEAT II. MI, myocardial infarction. (**A** and **B** from Holmes DR, Topol EJ, Califf RM, et al. A multicenter, randomized trial of coronary angioplasty versus directional atherectomy of patients with saphenous vein graft lesions. *Circulation* 1995;91:1966–1974, with permission.) **C:** Kaplan-Meier plots of freedom from the composite end point of death, myocardial infarction, repeat intervention, or coronary artery bypass grafting for patients with or without distal embolization in CAVEAT II. (From Lefkovits J, Holmes DR, Califf RM, et al. Predictors and sequelae of distal embolization during saphenous vein graft interventional from the CAVEAT-II trial. *Circulation* 1995;92:734–740, with permission.)

Excimer laser angioplasty has been applied to treatment of SVG lesions with 495 patients reported in a multicenter registry (115). At least one in-hospital complication occurred in 6.1%: death (1.0%), bypass surgery (0.6%), and Q-wave (2.4%) or non–Q-wave (2.2%) MI. The use of a saline flush technique aimed at bloodless laser ablation for prestent debulking of high-risk vein graft lesions yielded favorable results (100% procedural success, 8.7% non–Q-wave MI, 0% no reflow, and 0% major ischemic complications in 81 patients) (116,117). However, the lack of definitive data supporting incremental benefit relative to the increased cost and complexity of laser technology has resulted in little use of lasers in SVG PCI in most centers.

Stenting of SVGs, which has become the dominant percutaneous strategy, was carried out for more than a decade, initially with mixed results. The first vein graft

implantations were with the Wallstent (Schneider, Zurich, Switzerland) (119), and subsequent reports (Table 84.2) indicated a 99% to 100% deployment success rate, a 4% to 10% rate of early thrombosis, and restenosis in 34% to 47% (125,126,127,128,129 and 130). In follow-up of 62 patients with 93 stents (90% were Wallstents) out to 5.9 years (median, 2.5 years), there was a high cardiac event rate: 8% died, 23% had MI, 20% underwent bypass surgery, and 23% underwent angioplasty. The estimated 5-year survival and event-free survival rates were 83% ± 5% and 30% ± 7% (127). Of potential importance is the fact that optimal Wallstent expansion with high-pressure balloons was not routinely used in the reported patients.

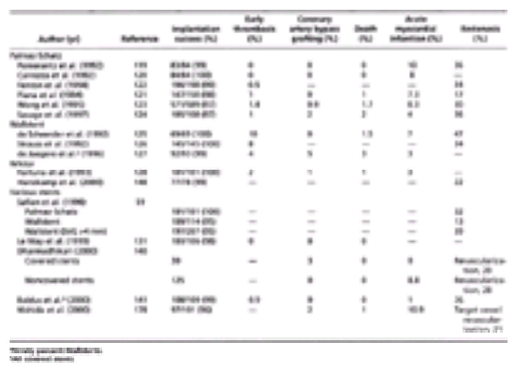


TABLE 84.2 RESULTS OF STENTING OF AORTOCORONARY SAPHENOUS VEIN GRAFTS (SVG): SELECTED REPORTS OF GREATER THAN OR EQUAL TO 50 PATIENTS

The largest experience in vein graft stenting has been with the Palmaz-Schatz stent (Johnson & Johnson Interventional Systems) (Table 84.2). Deployment success rates were high, and in-hospital complications were low, including a lower rate of stent thrombosis than was observed in native coronary artery use at that time. Six-month restenosis rates in the Multicenter U.S. Palmaz-Schatz Registry were a surprisingly low 18% for *de novo* lesions and 46% for restenotic lesions. The 12-month actuarial event-free survival was 76% (123). When used in the treatment of aortoostial vein graft disease in 29 patients, stents proved effective with 100% deployment success, and at 11 months, 24 (82%) were free of death, MI, and repeat revascularization (131). In a report of 20 patients who underwent stenting of aortoostial lesions, seven (35%) restenosed (132).

The first randomized multicenter comparison of the use of balloon angioplasty and stents in SVGs (the SAVED trial) was carried out with the Palmaz-Schatz coronary stent in 215 patients with focal *de novo* stenosis (124). Patients were excluded who had MI within 7 days, thrombus, ejection fraction less than 25%, and contraindications to coumadin anticoagulation. Graft age (mean, 10 years), lesion characteristics, and patient characteristics in the balloon (n = 107) and stent (n = 108) groups were similar except for an increased incidence of diabetes in the balloon group (36% vs. 23%, p = .03). In the stent group, 105 (97%) had successful stent deployment, two patients were treated with balloon angioplasty alone, and one with bypass surgery. In the balloon group, 96 patients (90%) were treated with balloons, seven (7%) received bailout stenting, two had bypass surgery, and two were treated medically. Procedural technical success (less than 50% stenosis with assigned therapy) was therefore higher with stenting (95% vs. 75%, p <.001). In-hospital complications of death, Q-wave MI, bypass surgery, and abrupt closure were similar, but there was a trend toward more non–Q-wave infarctions in the balloon group (7% vs. 2%, p = .10), and more stent patients required transfusions (10% vs. 1%, p = .003). At 6 months, restenosis occurred in 36% of stent patients versus 47% of balloon patients (p = .11) (Fig. 84.4A), and the minimal luminal diameter of stent patients was significantly larger (1.75 vs. 1.47 mm, p = .05) (Fig. 84.4B) as was the net gain in lumen diameter (0.87 vs. 0.52 mm, p = .015). Cumulative cardiac events (death, Q-wave MI, non–Q-wave infarction, CABG, and repeat PTCA) were significantly less frequent in stent patients (26% vs. 38%, p = .05) (Fig. 84.4C). A number of single-center and multicenter observational reports of stenting in SVGs have been reported (Table 84.2).

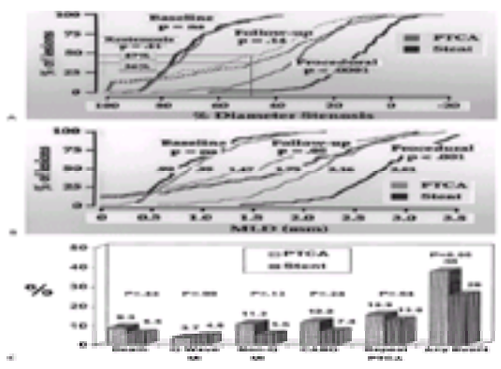


FIGURE 84.4 A: Cumulative frequency of percent diameter stenosis determined by quantitative coronary angiography before, immediately after, and at 6 months after stent or balloon angioplasty in the Stent Versus Angioplasty in Saphenous Vein Graft (SAVED) trial. **B:** Cumulative frequency of minimal luminal diameter (MLD) before, immediately after, and 6 months after stenting or balloon angioplasty in the SAVED trial. **C:** Major cardiac events experienced by patients 6 months after randomization to balloon angioplasty or stent in the SAVED trial. CABG, coronary artery bypass grafting; MI, myocardial infarction; ns, not significant; PTCA, percutaneous transluminal coronary angioplasty.

In one of the most recent publications, 106 consecutive patients who underwent SVG stenting at the Ottawa Heart Institute were reported; in-hospital success was 98%, and before discharge, no patient died, required bypass surgery, or had repeat PCI of the same graft (131). With complete follow-up at a median of 18 months, only 44% experienced event-free survival emphasizing the high late event rate after SVG stent implantation (15% died, 17% had MI, 20% had repeat CABG, and 37% had repeat PCI). Factors that have been reported to have the strongest predictive value for late adverse events after SVG stenting include unstable angina, diabetes, previous PTCA, and number of stents (132).

Several other studies of contemporary SVG stenting indicated that even with mostly single-lesion, single-stent procedures, the incidence of clinically important myocardial necrosis (creatine kinase greater than three times normal) was approximately 20%. In the Reduced Anticoagulation Vein Graft Study, 22% of patients had Q-wave or non–Q-wave MI (133), and in more than 400 patients treated in two high-volume centers from 1995 to 1997, 17% had creatine kinase MB greater than three times normal, and among these patients the 30-day mortality was 14% (134). As the lesion complexity, length, and plaque volume increased, so did the rate of myonecrosis and procedure risks (93). Procedural MI also affected long-term outcomes. In a study of 1,056 consecutive SVG PCI procedures, procedural creatine kinase MB elevation was the strongest independent predictor of late mortality (135). A heightened appreciation of the importance of atheroembolic MI in SVG PCI dovetailed with the development of strategies for distal protection generating enormous interest in its potential for improving outcomes of SVG PCI (136). Webb and colleagues, using the PercuSurge system (distal occlusion balloon and aspiration, Medtronic-AVE, Santa Rosa, CA) in 45 patients, reported aspiration of atherosclerotic debris in more than 80% of patients and an MI rate of less than 4% (137). Carlino et al. used this device in 15 patients with degenerated SVGs with no evidence of atheroembolic infarction (138). In a randomized trial comparing SVG PCI outcomes with and without PercuSurge (SAFER trial) in 551 patients, in-hospital major adverse cardiac events were reduced by 50% (17.3% to 8.8%, p <.001) with distal protection (139). Q-wave MI was reduced from 2.2% to 1.1%, and non–Q-wave MI from 14.4% to 7.3%. It seems likely that some form of distal protection will be used in many, perhaps all, SVG PCI procedures in the future. Other strategies currently being evaluated include the use of filters to catch atherosclerotic debris liberated during PCI procedures and using covered stents to trap debris, excluding it from the circulation. Both of these strategies avoid the need to routinely occlude blood flow in the SVG for several minutes. Randomized trials are currently testing these approaches. Observational reports of the use of a polytetrafluoroethylene (PTFE)-covered stent in SVG PCI by Colombo and colleagues suggested that both immediate and long-term outcomes were better than with conventional stents or balloon angioplasty (140) (Fig. 84.5). In a multicenter study Baldus et al. reported 6-month outcomes from 109 consecutive patients who received PTFE-covered stents for *de novo* stenoses in SVG, noting periprocedural increase in creatine kinase MB in 5%, angiographic evidence of in-stent restenosis in 8%, vessel occlusion in 9%, and an 8% mortality (141). In five consecutive patients who received a PTFE-covered stent in one SVG and a conventional stent in another SVG, Baldus et al. reported that four of five conventional stents developed restenosis, but all five covered stents remained patent, with only a 9% decrease in lumen diameter at 5 months (142). A variety of filter devices also appear promising for “distal protection” in SVG procedures (136,143,144). In an initial experience with a porous membrane filter (80- to 100-µm holes) mounted in a 0.014 PTCA wire and supported by a nitinol basket, it was possible to successfully deploy the filter in 23 of 24 patients, and no in-hospital death, MI, or CABG occurred; one patient experienced a small creatine kinase elevation, and visible debris was removed in more than 80% of patients (144) (eFig. 84.5.1).

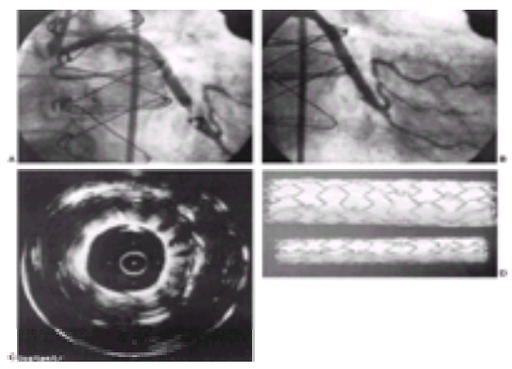
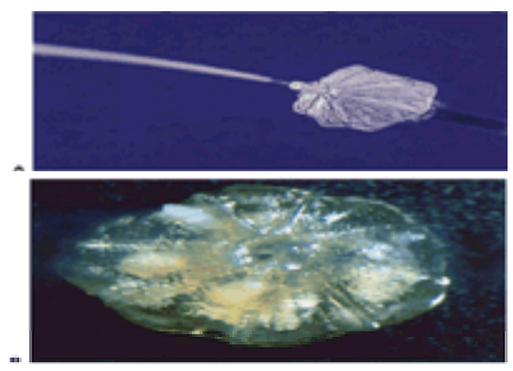


FIGURE 84.5 Severely diseased saphenous vein graft with large filling defect consistent with thrombus **(A)** successfully treated **(B)** with a 4.0-by 16.0-mm Jostent coronary stent graft (Jomed, Rangendingen, Germany), a polytetrafluoroethylene-covered stent. Intravascular ultrasound revealed a widely patent site **(C)**. (Courtesy of Dr. Fausto Feres.) **D:** Jostent coronary stent graft. (From Douglas JS Jr. Diffuse saphenous vein graft disease. In: Ellis SG, Holmes DR, eds. *Strategic approaches in coronary intervention*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:355, with permission.)



***e*FIGURE 84.5.1 A:** Investigational filter device for embolic protection (Angioguard, Cordis-Johnson & Johnson, Miami, FL). **B:** Filter with trapped atherosclerotic debris.

The large amount of atheroembolic debris filtered or aspirated during SVG stent procedures (137,139,144) provides insight into the failure of IIb/IIIa platelet receptor inhibitors to reduce periprocedural ischemic events during SVG PCI. Ellis et al. found degenerated SVG to be the only lesion type not to benefit from abciximab when data from the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial and the Evaluation of PTCA to Improve Long-Term Outcome with Abciximab GPIIb/IIIa Receptor Blockade (EPILOG) trial were pooled (145). Similarly when data from five trials [EPIC, EPILOG, Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT), Integrelin to Minimize Platelet Aggregation and Coronary Thrombosis in Stenting II (IMPACT II), and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT)] totaling 627 patients with SVG PCI and the Cleveland Clinic registry of 278 patients with SVG PCI were analyzed, there was no benefit from IIb/IIIa inhibitors or stents with respect to 30-day outcome, and a trend was present toward increased MI with stenting (p = .09) (146,147). The lack of any acute benefit with SVG stent deployment is consistent with the SAVED trial (124) and the VENESTENT Study (148), each of which randomized patients to balloon angioplasty or stent implantation and demonstrated an improved major adverse cardiac event-free survival at 6 months, but no early difference in major adverse cardiac events.

The transluminal extraction catheter (Interventional Technologies, San Diego, CA) and the rheolytic thrombectomy catheter (Angiojet; Possis Medical, Inc., Minneapolis, MN) have been used for the treatment of thrombus-associated lesions in SVGs (81,82,83 and 84,116) (*e*Fig. 84.3.7). Although both devices were shown to be relatively effective in clearing thrombus from the treatment site as judged by angioscopy (83,149), distal embolization remained a problem, occurring in 15% with transluminal extraction catheters, associated with a 36% mortality (150), and resulting in non–Q wave in 27% with the Angiojet (151,152).

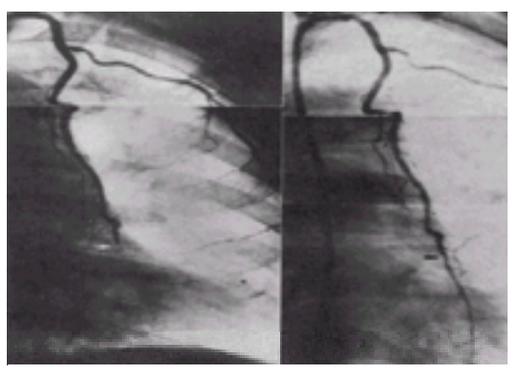
Recanalizing totally occluded SVGs not in the setting of acute MI has tempted interventional cardiologists for years in spite of low long-term patency and significant procedural complications (91,92,153,154,155,156,157,158,159,160,161 and 162). In a multicenter trial of 107 patients with total vein graft occlusion who received an intragraft infusion of thrombolytic agent for a mean of 25 hours, 74 (69%) achieved initial patency. Adverse acute events included MI (22.0%), emergency CABG (4.0%), stroke (3.0%), transfusion (19.0%), and death (6.5%) (161). Of 40 patients who underwent recatheterization at 6 months, 16 had a patent graft. In a single-center report of 77 consecutive patients with intervention to occluded vein graft, angiographic success was achieved in 71%, 5% died, and 8% underwent bypass surgery within 30 days (162). Three-year survival, event-free survival, and freedom from severe angina were not different in patients with angiographic success and failure. Whether new strategies of mechanical thrombectomy or ultrasound thrombolysis will alter the risk-benefit relationship in these difficult patients remains unclear.

On a brighter note, intravascular radiation for the prevention of recurrence of restenosis yielded promising results in the Washington Radiation for In-Stent Restenosis Trial for Saphenous Vein Grafts. This was a double-blind, randomized trial in 120 patients with diffuse in-stent restenosis (less than 47 mm in length) in SVGs, which compared iridium-192 versus placebo. Of the first 78 patients who completed 6-month angiographic evaluation, 48 (62%) had restenosis, 14 (29%) from the radiation arm and 34 (71%) from the placebo group (163). It is, therefore, anticipated that the final results of Washington Radiation for In-Stent Restenosis Trial for Saphenous Vein Grafts will demonstrate effectiveness of intravascular radiation in this setting.

Arterial Graft Intervention

Technical Strategy

Although arterial grafts are resistant to arteriosclerosis, percutaneous intervention has been used to relieve ischemia, most often in the IMA via a femoral approach using 6- to 8-Fr guide catheters. A radial or brachial approach may be necessary if guide catheter support is poor and if severe graft tortuosity or a difficult distal lesion is present. A novel catheter shape for a right brachial approach to IMA angioplasty has been reported (164). In patients with severe stenosis or occlusion of the subclavian or innominate arteries, dilation, stenting, or both have been performed before bypass surgery to permit use of the mammary artery and after surgery to relieve ischemia in patients with a patent IMA graft or to treat a dissection complicating IMA angioplasty (165,166,167,168,169 and 170). Conventional balloon angioplasty is used for most IMA lesions, and an over-the-wire system is favored for tortuous grafts, or if a total occlusion must be recanalized (*e*Fig. 84.5.2), or if retrograde passage into the native coronary artery is necessary. Hydrophilic steerable guidewires are also helpful in the presence of severe graft tortuosity. Prophylactic nitroglycerin is usually given before intervention. Balloon-mounted stents have been used to treat dissections in both mammary arteries (171,172). Use of a low-osmolar contrast agent is recommended; a blinded study reported that there was less discomfort with ioxaglate, a low-osmolar ionic dimer, than with iopamidol, a nonionic monomer (173). Care must be taken to ensure that there is sufficient catheter length to reach distal sites through tortuous mammary grafts. Extra long (145 cm) balloon catheters or short (80 cm) guide catheters can provide the additional length required, or the guide catheter can be shortened and capped by a flared, short sheath one size smaller (174). Intervention to relieve stenosed radial artery and gastroepiploic artery grafts has also been required (175).



***e*FIGURE 84.5.2** A 52-year-old man developed recurrent angina 5 months after coronary bypass surgery. Coronary arteriography revealed occlusion of the left internal mammary artery graft 1 to 2 cm proximal to insertion into the left anterior descending coronary artery (*left*). The graft was recanalized by balloon angioplasty (*right*) after using an intermediate wire to punch across the resistant total occlusion. At last follow-up 5 years after bypass surgery, the patient was totally asymptomatic and the left internal mammary artery was widely patent.

Results of Arterial Graft Intervention

Procedural success in IMA graft intervention was approximately 90% and highly dependent on the presence of excessive graft tortuosity and lesion location (Table 84.3). The most common complication was dissection, which occurred in 3.5%, rarely resulting in infarction or bypass surgery. In a published report of 68 consecutive patients, angiographic follow-up at a mean interval of 8 months was available in 78% of successful procedures. Restenosis occurred in 15% (6 of 40) of distal anastomotic sites and 43% (3 of 7) in the midportion of the graft (176). At a mean follow-up of 14 months, 76% of patients had class I or II angina, and event-free survival was 86%. The favorable results at the distal anastomosis parallel those of vein graft lesions at that site (176,177,178 and 179). Gruberg et al. reported outcomes in 174 consecutive patients, 63% with anastomotic lesions treated predominantly with balloon angioplasty (116 of 128, 91%), whereas ostial lesions were treated more frequently with stents (11 of 16, 69%) (61). Procedural success was 97% and 1-year target lesion revascularization was 7.4%. Long-term results of radial and gastroepiploic artery graft intervention have not been reported.

Author (yr)	Reference	No. of patients	Success	Complications	Restenosis
Webb et al. (1990)	106	18	12	1 dissection and coronary artery bypass graft	–
Dorros et al. (1991)	56	31	28	2 dissections	1
Sketch et al. (1992)	57	14	13	–	1
Shimshak et al. (1988)	58	26	24	3 dissections	1
Hill et al. (1988)	25	11	9	0	2
Shimshak et al. (1991)	60	86	81	1 Q-wave myocardial infarction	4 late deaths
Hearne et al. (1995)	176	68	60	2 dissections	5 (19%)
Ishizaka et al. (1995)	177	46	34	1 spasm	30%
Gruberg et al. (2002)	61	174	168	1 death, 1 coronary artery bypass graft, 15 non–Q-wave myocardial infarction	1-yr target lesion revascularization, 7.4%

TABLE 84.3 RESULTS OF INTERNAL MAMMARY ARTERY GRAFT PERCUTANEOUS CORONARY INTERVENTION: SELECTED SERIES

CONTROVERSIES AND PERSONAL PERSPECTIVES

Value of Saphenous Vein Graft Intervention

After successful SVG intervention, there is a high cardiac event rate for most patient subgroups. Distal anastomotic lesions are an exception. The restenotic process in vein grafts does not plateau as it does in native coronary arteries, and mild to moderate nontarget vein graft lesions are associated with recurrent ischemic events in approximately one-third of patients (51). Even with careful selection of patients, emphasizing focal disease and absence of thrombus as was the case in the SAVED trial, the 6-month major cardiac event rate was 26% for SVG stenting, and restenosis occurred in almost 40% of patients (124). At Emory, 5-year event-free survival for vein graft intervention was 31% (105), and survival was less favorable than that with native coronary intervention (Fig. 84.6). If one moves from these relatively ideal candidates to the treatment of diffuse vein graft disease, recent total occlusions, or even to chronic occlusions, the prospects for long-term patency and clinical stability diminish, while the acute risk of thromboembolic MI and bleeding and costs escalate. Although continued study is needed to develop methods to prolong the functional life of degenerating venous grafts, day-to-day application of percutaneous strategies to these difficult problems must be done with caution.

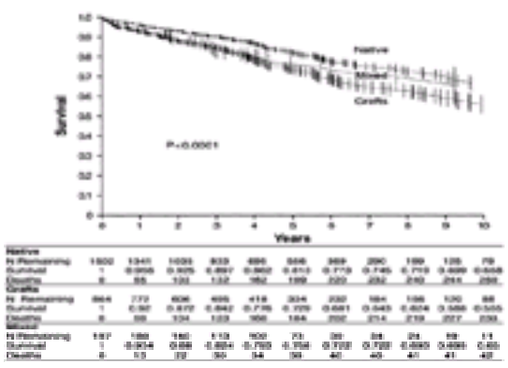


FIGURE 84.6 Ten-year survival of postbypass patients who underwent percutaneous coronary intervention of a native coronary artery (native), saphenous vein grafts (grafts), or both (mixed) at Emory University Hospitals (Kaplan-Meier method).

Repeat Interventions

Andreas Gruentzig envisioned coronary angioplasty as a strategy that could be used over the years to prevent patients from moving from low-risk categories (nil or single-vessel disease) to high-risk coronary disease. In the postbypass patient, percutaneous intervention is more often performed in an attempt to control symptoms and preserve quality of life. If the patient can be palliated safely by repeat interventions, even for periods as short as a year, this may be reasonable (179,180). However, thoughtful cost-conscious consideration of risks and benefits and of resource consumption must take place.

THE FUTURE

In the next decade, there will be an increasing number of postbypass patients who have begun to have recurrent angina requiring hospitalization. Because of the enormous cost, morbidity, and impracticality of surgical revascularization, it will be important to palliate these patients by percutaneous means as much as possible. We expect improved technology (especially better, coated, and covered stents) to help, but a major problem is the inadequacy of strategies to treat old, degenerated SVGs. Perhaps with the development of reliable methods of distal protection, techniques to renew (pave?) old grafts and prevent restenosis will evolve.

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INTRAVASCULAR ULTRASONOGRAPHY, ANGIOSCOPY, DOPPLER FLOW, AND PRESSURE MEASUREMENTS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Recent technical advances have enabled intraluminal evaluation of the coronary arteries using ultrasonographic imaging, Doppler probes, small pressure sensors, and angioscopy. Data from miniaturized intravascular devices are increasingly used to supplement angiographic data. The rationale for these new imaging devices is based on multiple studies showing limited accuracy and reproducibility of coronary arteriography in determining the morphologic changes and associated physiologic disturbances in the coronary arteries. Intracoronary ultrasonography enables visualization of the full 360-degree circumference of the vessel wall with high spatial resolution.

Normal ultrasonographic morphology of coronary arteries consists of an echogenic intimal leading edge, a sonolucent media, and an echogenic adventitia, although not all of the normal arteries show all three layers. Atherosclerotic lesions consist of lipid-laden plaques of low echogenicity, more echogenic fibrous lesions, and calcified plaques that produce acoustic shadowing. Angiography and ultrasonography are frequently discrepant in the assessment of atheroma eccentricity. Angiography also exhibits poor sensitivity in detection of coronary calcification. Important artifacts in ultrasonographic images include nonuniform rotational distortion and the ring-down phenomenon. Patients with "normal coronary arteries" frequently have abnormal ultrasonographic findings. False-negative angiograms often result from coronary remodeling and diffuse disease. In cases of ambiguous angiographic stenosis, ultrasonography often permits lesion quantification. Ultrasonography is useful for measuring intimal proliferation in cardiac transplant recipients. After angioplasty, studies usually reveal plaque fissuring or dissection. Ultrasonography and angiography correlate poorly in assessing residual stenosis after interventions. Ultrasonography has refined the understanding of restenosis, suggesting, although not proving, the relative importance of "negative remodeling" and neointimal proliferation. Intravascular ultrasonography (IVUS) has been used to guide directional atherectomy and rotational ablation. IVUS has significantly influenced the development of coronary stenting.

Coronary angioscopy uses visible light conducted through fiberoptic filaments to directly visualize the luminal surface. Thrombus is frequently seen in unstable syndromes. The technique is cumbersome as it requires temporary interruption of blood flow imaging and is limited to proximal straight segments of the coronary arteries. A miniaturized Doppler-equipped guidewire has made assessment of coronary blood flow feasible during catheterization. Doppler flow measurements are used to confirm or exclude the functional severity of angiographically identified intermediate stenoses and to assess the results of percutaneous interventions.

Normal flow reserve as measured by Doppler devices is typically greater than 3:1 with large individual variability. Hemodynamically significant stenosis reduces flow reserve below 1.8:1, increases the proportion of flow during systole, and increases the ratio of proximal to distal flow velocity. Microvascular disease and transplant vasculopathy can also reduce flow reserve. False-positive findings are common, particularly in patients with increased basal flow, for example, those with ventricular hypertrophy.

Measurement of fractional coronary flow reserve is a new method for determining the functional significance of coronary stenosis. Using very small sensors, intracoronary pressures are measured during maximal pharmacologic vasodilatation to calculate the ratio of flow in a stenotic vessel and flow in the same vessel if no stenosis were present. Careful systematic studies demonstrated the reproducibility and reliability of this method in a wide range of clinical settings.

All of the new intracoronary imaging modalities are contributing to clinical practice and research. Several of these methods, especially ultrasonographic imaging and fractional flow reserve measurement, are likely to have a larger role in the catheterization laboratory in the future.

INTRODUCTION

Since its introduction by Sones in 1958, contrast angiography has served as the predominant imaging technique used to guide therapy for coronary artery disease. Technical advances in the last decade in ultrasonographic imaging, Doppler flow devices, small pressure sensors, and associated microelectronics have enabled development of miniaturized catheter systems capable of real-time intraluminal interrogation of the coronary arteries (1,2,3,4,5,6,7,8,9 and 10). Each of the new intravascular modalities offers certain unique capabilities that expand the diagnostic armamentarium. The incremental value of IVUS originates principally from two key features: its tomographic perspective and the ability to directly image coronary atheromas (2). Although angiography depicts the cross-sectional coronary anatomy as a planar silhouette of the lumen, ultrasonography directly images the atheroma within the vessel wall, allowing measurement of atheroma size, distribution, and, to some extent, composition. The principal value of angioscopy is derived from its ability to directly visualize the surface anatomy of the arterial wall, particularly the presence or absence of thrombus (8). The guidewire-size Doppler flow wires and miniaturized pressure-sensing devices provide useful data regarding coronary blood flow and the hemodynamic effects of stenosis (9,10).

New coronary imaging devices are rapidly altering conventional paradigms in the diagnosis and treatment of coronary artery disease. Despite the independent and incremental value of these new imaging modalities, however, intracoronary application usually requires fluoroscopy and angiographic road mapping. Accordingly, these new techniques should be considered supplemental and complementary to angiography and not an alternative to conventional radiographic methods. This chapter reviews the status of each of the technologies and defines its role in assisting percutaneous coronary revascularization. The implications of these findings for understanding the pathogenesis and optimal management of coronary pathophysiology are discussed.

INTRACORONARY ULTRASONOGRAPHY

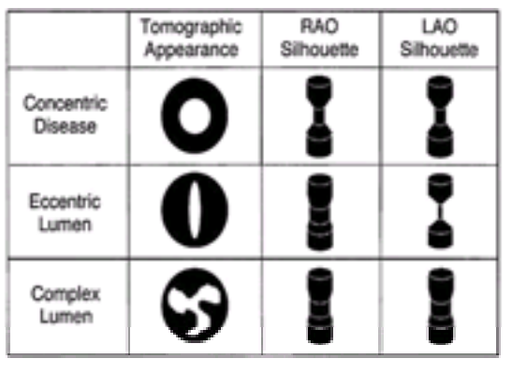
Rationale and Technique

Limitations of Angiography

The well-established limitations of angiography represent an important component of the rationale for intraluminal coronary imaging (11,12,13,14,15,16 and 17). Visual interpretation of angiograms exhibits clinically significant intra- and interobserver variability (15,16). Importantly, comparisons of angiographic information to postmortem histology have documented major discrepancies between the apparent angiographically determined severity of lesions and results of postmortem histologic examination (11,12,13 and 14). Nearly all necropsy studies demonstrate that angiography significantly underestimates the extent of atherosclerosis. Location of the lesion, lumen irregularity, angle of the x-ray beam, diffuse nature of the disease, tortuosity, and overlapping vasculature all contribute to this discrepancy.

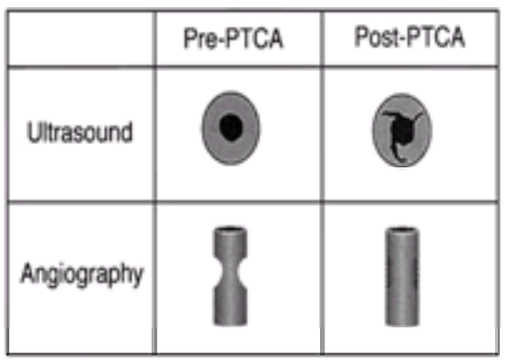
Angiography provides no direct information on the hemodynamic effects of coronary stenosis. This limitation is particularly important in evaluating angiographically identified intermediate lesions in the range of 40% to 75% diameter stenosis. Making a clinical decision between a recommendation for medical therapy versus a recommendation for percutaneous or surgical revascularization is particularly difficult. Using functional testing, investigators have demonstrated a striking discordance between angiographically determined lesion severity and measurements of the physiologic effects of the stenosis (17). Accordingly, most patients with ischemic disease require one or more functional tests, in addition to angiography, to enable appropriate clinical decision making.

Several inherent properties explain the limitations of coronary angiography. Angiography is a two-dimensional imaging modality, depicting the complex coronary cross-sectional anatomy as a planar silhouette of the contrast-filled lumen. Both necropsy and IVUS studies, however, demonstrate that coronary lesions are often highly complex, exhibiting markedly distorted or eccentric luminal shapes (6,18,19). Accordingly, any arbitrary angle of view may misrepresent the true extent of luminal narrowing (*e*Fig. 85.0.1). Although orthogonal angiograms should accurately reflect the severity of many complex lesions, optimal imaging angles are frequently unobtainable because the vessel may be obscured by side branches, disease at a bifurcation, or foreshortening.



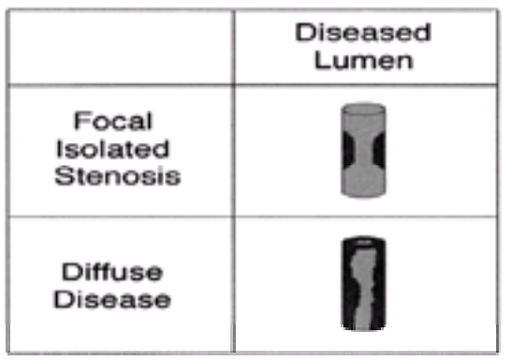
***e*FIGURE 85.0.1** Theoretical differences between intravascular ultrasonography and angiography. **Top:** For a concentric coronary narrowing, the right anterior oblique (RAO) and left anterior oblique (LAO) angiograms accurately depict the severity of the obstruction. **Middle:** If the lumen is eccentric, angiography will show major differences between the RAO and LAO silhouettes. **Bottom:** If the lumen exhibits a complex shape, no angle of view may adequately reflect the severity of the narrowing.

Percutaneous coronary interventions increase the complexity and irregularity of lumen shape, further impairing the ability of a luminal silhouette to accurately depict coronary anatomy (6,20,21,22 and 23). After balloon angioplasty, the angiographic appearance of a dissected postintervention vessel often consists of an enlarged, frequently hazy lumen (22) (*e*Fig. 85.0.2).



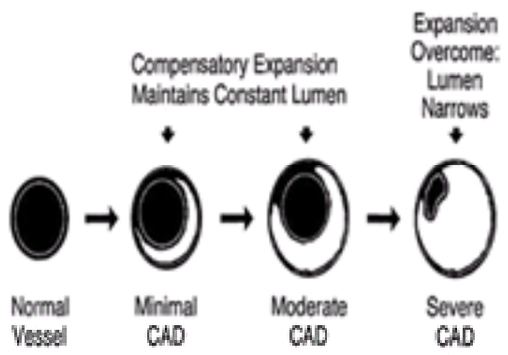
***e*FIGURE 85.0.2** Schematic representation of angiography and ultrasonography before and after balloon angioplasty (PTCA). **Bottom:** The angiogram may show an enlarged, although hazy, silhouette. **Top:** Ultrasonography will frequently show a lesser degree of luminal enlargement with multiple cracks or dissections in the atheroma that are opacified by iodinated contrast, which produces the appearance of an enlarged silhouette.

The method most commonly used to assess the severity of angiographic lesions uses visual or computer measurements to determine the percent diameter of the stenosis. This approach compares the luminal diameter within the lesion to the caliber of an adjacent, “normal” reference segment. Necropsy examinations have demonstrated that coronary atherosclerosis is often diffuse, involving long segments of the diseased vessel. Therefore, in many patients, no truly normal reference segment exists, which precludes accurate calculation of the percent diameter reduction. In the presence of diffuse vessel involvement, determination of percent diameter stenosis predictably underestimates true disease severity (18,19,22). In the most dramatic circumstances, diffuse, concentric, and symmetrical coronary disease can affect the entire length of the vessel, which results in an angiographic appearance of a small artery with minimal luminal irregularities (*e*Fig. 85.0.3).



***e*FIGURE 85.0.3** Underestimation of stenosis severity due to diffuse disease. **Top:** Measurement of percent stenosis assumes that a narrowing consists of a focal isolated stenosis. **Bottom:** In many clinical settings, however, the coronary obstruction consists of a focal stenosis superimposed on a diffusely diseased vessel. In such cases, percent stenosis will predictably underestimate disease severity.

Accurate assessment of the severity of coronary disease by angiography is further confounded by the phenomenon of coronary arterial remodeling, first described by Glagov et al. (24). This process consists of outward displacement of the external vessel wall in segments with atherosclerosis (eFig. 85.0.4). In the early stages of coronary disease, this adventitial enlargement prevents the atheroma from encroaching on the lumen and thereby conceals the presence of a lesion on angiography. Although such lesions do not restrict blood flow, observational studies demonstrate that minimal, nonobstructive angiographically identified lesions represent an important substrate for acute coronary syndromes (25,26).



***e*FIGURE 85.0.4** Coronary remodeling (compensatory enlargement). As originally proposed by Glagov et al. (24), coronary artery disease (CAD) in its earliest stages results in compensatory enlargement of the adventitia, which opposes luminal encroachment. In the later stages of coronary disease, the luminal encroachment overcomes the luminal expansion, which results in an angiographic stenosis.

Advantages of Ultrasonography

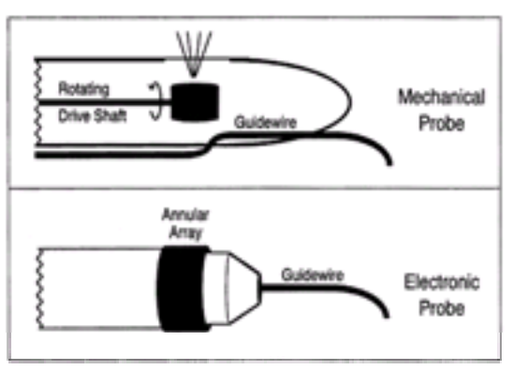
Several characteristics inherent in IVUS imaging have potential value in the precise quantitation of atherosclerotic coronary artery disease. The tomographic orientation of ultrasonography enables visualization of the full 360-degree circumference of the vessel wall, rather than a two-dimensional projection of the lumen, which allows accurate assessment of the plaques residing in the vessel wall. Measurement of lumen area uses direct planimetry performed on a cross-sectional image, which, unlike angiography, is not dependent on the projection angle. In angiographic stenosis sizing, careful calibration of the analysis system is required to correct for radiographic magnification. Ultrasonographic devices, however, rely on an electronic distance scale, internally generated and overlaid on the image. Because the velocity of sound within soft tissues is nearly constant, ultrasonographic measurements are inherently accurate and require no special calibration methods.

Ultrasonographic Catheters

The equipment required to perform intracoronary ultrasonography consists of two major components, a catheter incorporating a miniaturized transducer (20 to 50 MHz) and a console containing the electronics necessary to reconstruct the image. In the currently available ultrasonographic systems, axial and lateral resolution approach 80 to 100 µm and 250 µm, respectively. Two different transducer systems are in use. Mechanical systems use a rotating transducer. Electronic systems use a multielement solid-state nonmoving transducer.

Because the transducer is placed in close proximity to the vessel wall, high ultrasonic frequencies are used for intravascular imaging, typically, centered at 20 to 50 MHz for coronary imaging. The use of high frequencies provides excellent theoretical resolution because the ultrasound wavelength, which determines the theoretical maximum resolution, is inversely proportional to the frequency. Spatial resolution of an ultrasonographic image is expressed in two directions: axial resolution (parallel to the sound beam) and lateral resolution (perpendicular to the beam). At 30 MHz, the wavelength is approximately 50 µm (0.05 mm), which permits axial resolution to approach 80 to 100 µm. Determinants of lateral resolution are more complicated and depend on imaging depth and beam shape determined by not only wavelength but also by aperture. Typically, lateral resolution for a 30-MHz device averages approximately 250 µm at the typical distance of 2 to 4 mm most prevalent in coronary imaging. Although higher frequency catheters may be desirable for better resolution, significant trade-offs may exist in moving beyond the current 25- to 40-MHz frequency range. For example, although high-frequency probes enable better axial and lateral resolution, penetration is likely to be impaired in comparison to that of more conventional devices. In addition, greater backscatter from blood cells at high frequencies may interfere with discrimination of the interface between lumen and vessel wall. As the demand for catheter miniaturization becomes more intense, however, use of a shorter wavelength becomes more important in preserving near-field image quality. Use of a center frequency of 40 to 50 MHz, for example, would allow discrimination of small fatty deposits or zones of fibrous tissue separated by as little as three to four times the size of a red blood cell.

Initial efforts to develop miniaturized transducers for intraluminal examination were begun some three decades ago by Bom et al. (1). Practical applications, however, required major improvements in the physical properties of imaging catheters. Reductions in catheter sizes and improvements in image quality resulted in the reintroduction of modern coronary ultrasonographic devices in 1989 (2). Two dissimilar technical designs for transducers have emerged: mechanically rotated devices and multielement electronic arrays (eFig. 85.0.5).



***e*FIGURE 85.0.5** Two types of intravascular ultrasonography catheter designs. **Top:** Mechanical devices use a drive shaft that rotates a single transducer element located near the catheter tip. A short monorail allows positioning of the device over a guidewire. **Bottom:** Electronic probes use an annular array of transducer elements near the catheter tip. The absence of a mechanical drive shaft allows a traditional over-the-wire approach.

Mechanical probes use a drive cable running the length of the catheter that rotates a single piezoelectric transducer element mounted near the distal catheter tip. For most mechanical ultrasonographic systems, a rotation rate of 1,800 rpm is used, which corresponds to 30 full revolutions per second, yielding 30 images per second.

In the electronic systems, an annular array of multiple piezoelectric transducer elements (currently up to 64) is activated sequentially to generate a tomographic image. The electronic signals are processed and multiplexed by several ultraminiaturized integrated circuits near the catheter tip. Accordingly, only two flexible conductive wires are required within the catheter shaft, which yields a flexible catheter with a central lumen, which can accommodate a guidewire. For image generation, this device uses a reconstruction algorithm known as a “synthetic aperture array,” which has different operational principles from the “phased-array” devices used in conventional ultrasonography. In a synthetic aperture approach, radial scan lines are reconstructed from data derived from multiple transducer elements, using a smaller number of elements for pixels near the catheter surface and a larger number for pixels in the far field. This approach yields a variable aperture, which provides a consistent focus and more uniform image quality throughout the near and far fields.

Early devices available for IVUS were relatively large, ranging from 4.3 Fr to 5.5 Fr (1.43 to 1.67 mm), which limited examination to proximal and occasionally midvessel segments. Currently available ultrasonographic catheters for intracoronary applications have an outer diameter at the tip of approximately 3 Fr (0.96 to 1.17 mm).

The smaller ultrasonographic catheters (3 Fr) can be delivered through a large-lumen 6-Fr guide catheter and are suitable for examination of the most stenotic lesions

before intervention, even if they are located distally within the coronary artery. The mechanical ultrasonographic catheters for coronary arteries use a distal sheath (telescopic shaft) system, which allows the safe and free movement of the ultrasonic transducer mounted on a central cable. The ultrasonographic catheter is advanced over a guidewire using a short monorail segment (15 mm in length) located at the tip of the sheath beyond the most distal point that the transducer can be advanced. Thus, the tip of the ultrasonographic catheter should be placed 2 cm beyond the most distal site that needs to be imaged by ultrasonography. Once the operator places the ultrasonographic catheter in the coronary artery, the transducer can be advanced or retracted within the sheath to interrogate the vessel freely. Mechanical catheters should be flushed with saline carefully; otherwise, even microbubbles of air trapped near the transducer can markedly degrade the image quality. The catheters using the electronic solid-state systems have no moving parts. They are designed as over-the-wire as well as monorail catheters. In these systems the ring-down artifact around the transducer is minimized by subtraction before catheter insertion into the coronary artery.

Regardless of the design of the catheter delivery device, most systems contain an integrated videotape recording system for archival storage of imaging studies on super-VHS tape. Digital image-recording technology has now been introduced to IVUS imaging, and the most recent commercially available systems permit digital recording of up to 60 seconds of an ultrasonographic pullback. Newer systems can display the acquired “cine loop” at variable playback rates, provide digital freeze frames, and permit writing of the sequence to a recordable CD-ROM disk. They also allow on-line reconstruction of the individual tomographic images into longitudinal two- or three-dimensional images.

Examination Technique

Standard interventional techniques for intracoronary catheter delivery are used for intraluminal ultrasonographic examination. Intravenous heparin sodium and intracoronary nitroglycerin are routinely administered before imaging. Most practitioners use a 6- or 7-Fr guiding catheter and a steerable 0.014-in. angioplasty guidewire. A stable guiding catheter position with good support is desirable, because current ultrasonographic catheters have less trackability and a larger profile than modern balloon angioplasty catheters. After placing the catheter into the distal coronary artery, the operator carefully retracts the imaging core or the catheter to examine the vessel in real time, recording images on videotape for subsequent quantitative or qualitative analysis.

Settings of the ultrasonographic system should be carefully adjusted before imaging, using the controls on the machine. Time gain compensation controls are for optimization of the signal amplitude at different depths. Overuse of these adjustments may result in loss of real information from near field or far field. Gradations of gray are adjusted using compression and adjustment controls. These adjustments are not found in solid-state systems.

Most operators use a motorized pullback device to withdraw the catheter at a constant speed (between 0.25 and 1.00 mm per second, most frequently 0.5 mm per second). Pullback at a constant speed allows the registration of the location of a given cross section along the vessel (27). Side branches, visualized with both angiography and ultrasonography, and extraarterial structures such as veins and pericardial shadows are useful as landmarks to facilitate interpretation and comparison of sequential examinations. Automatic pullback is also useful in measuring the length of a given arterial segment. Length measurement is a prerequisite for volumetric analysis. The advantages provided by automatic pullback are particularly useful in serial ultrasonographic studies.

A number of combination devices incorporating both an imaging and a therapeutic device have been developed. An angioplasty balloon with an ultrasonic transducer, a transducer combined with a directional atherectomy device, and a combined ultrasonographic and brachytherapy catheter could provide on-line guidance during revascularization procedures (28,29 and 30).

Safety of Coronary Ultrasonography

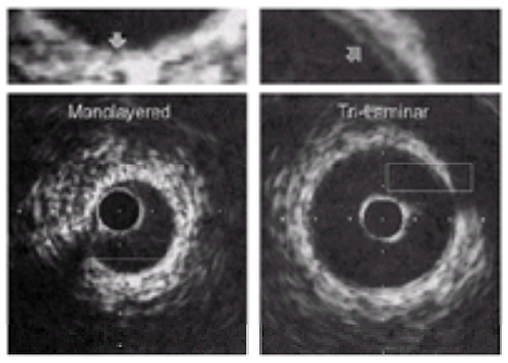
IVUS has been performed safely in a wide variety of clinical situations with few serious untoward effects. In interventional practice, coronary ultrasonography has been performed safely after most types of revascularization procedures, including balloon angioplasty, directional coronary atherectomy (DCA), rotational ablation, and stent deployment. Focal coronary spasm is the most frequent complication of ultrasonographic imaging but is usually transient and responds rapidly to intracoronary administration of nitroglycerin (100 to 300 g). Multicenter registries indicate that complications other than spasm occur in less than 1% of patients (31,32). Additional care is required when imaging small distal vessels or tight stenosis, because the imaging transducer can partially or totally occlude the blood vessel and lead to ischemia.

Although the safety of intracoronary ultrasonography is well documented, any device placed subselectively in the coronary arteries carries the potential risk of vessel injury. Isolated incidents of a new or worsening coronary dissection after ultrasonographic examination have been reported. Because of the inherent risk, many centers that use IVUS during diagnostic catheterization limit credentialing for intraluminal examination to personnel with interventional training. This safety measure ensures that the necessary personnel and equipment are immediately available in the unlikely event of an intimal disruption.

Image Interpretation

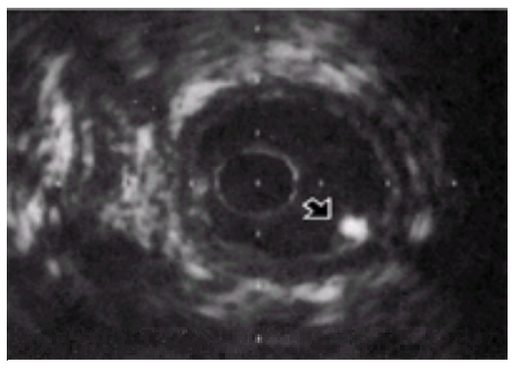
Standards for applications, image interpretation, measurement, and nomenclature have been published by the European Society of Cardiology, American College of Cardiology, and the American Heart Association (33,34).

Ultrasonographic studies performed either *in vivo* or using excised, pressure-distended vessels have characterized the appearance of normal and abnormal coronary artery wall by IVUS (6,35,36,37,38,39,40 and 41). Important determinants of the vessel wall appearance include both the normal arterial structure and the inherent properties of ultrasound. An abrupt change in acoustic impedance between adjacent tissue layers is the most important factor responsible for the ultrasonographic appearance of the vessel wall. The leading edge of the intima (at the interface between the blood-filled lumen and the endothelium) and the outer border of the media (at the junction of media and external elastic membrane) are two particularly strong acoustic interfaces. As a result, both boundaries are typically well visualized by ultrasonography in human coronaries and are described as trilaminar (trilayer) in appearance except in younger individuals in whom intima is too thin to be detected by ultrasonography (eFig. 85.0.6).



***e*FIGURE 85.0.6** Normal coronary wall morphology by intravascular ultrasonography. **Left:** A monolayered arterial structure is evident (*arrow*). **Right:** A trilaminar structure is observed (*arrow*). In both examples, the inset at the top of the panel shows a magnified portion of the image that is indicated by the white rectangle.

The two classical interfaces are not well visualized in all normal subjects (37). Theoretically, at 30 MHz, the maximal axial resolution for IVUS devices is approximately 80 µm, although actual clinical performance is usually less, typically 100 to 150 µm. The normal intima is thin and consists principally of a superficial layer of endothelial cells and connective tissue, which results in a relatively small impedance difference between blood and intima. Accordingly, in young subjects, ultrasonographic imaging frequently cannot distinguish the intima from deeper wall layers, which results in a single rather than trilayer appearance. In older subjects, progressive intimal thickening or the development of pathologic intimal changes results in an ultrasonographic pattern consisting of two distinct echogenic layers sandwiching a sonolucent intermediate layer (three-layered appearance; eFig. 85.0.7). A clear delineation of the inner border of the media (internal elastic membrane) is frequently difficult or impossible, so that only two layers are normally distinguished with ultrasonography. The inner layer, often described as *intima* or *intimal plaque*, should be more correctly described as *intima-media complex*. Whether the artery is trilaminar or monolayered, the deepest layers representing the adventitia and periadventitial tissues exhibit a characteristic “onionskin” pattern. The outer border of the vessel is usually indistinct, primarily because no acoustic differences exist between the adventitia and other encasing tissues. Accordingly, total wall thickness cannot be measured using ultrasonography, except in vessels with a distinct outer border such as aorto-coronary saphenous vein grafts.

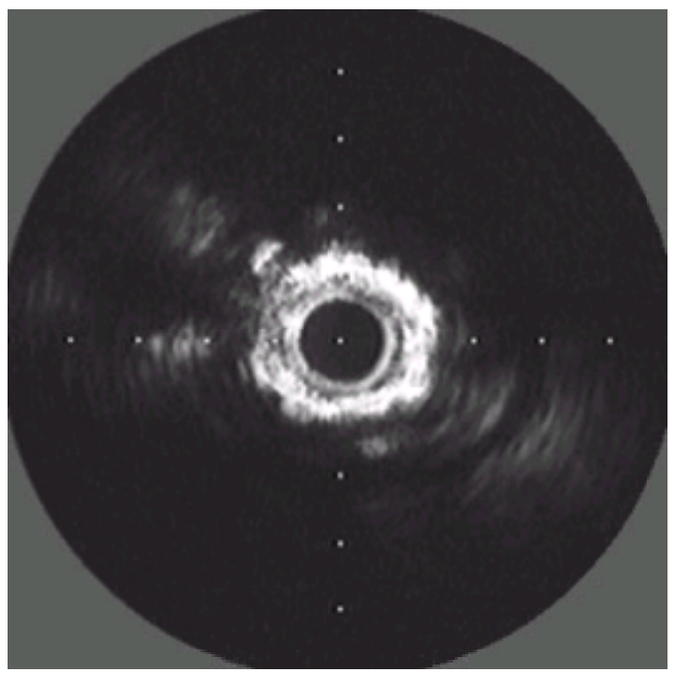


***e*FIGURE 85.0.7** Minimal circumferential intimal thickening. In this example, the intima is slightly thickened, but no luminal encroachment is seen. The bright circular object indicated by the arrow is a 0.014-in. guidewire.

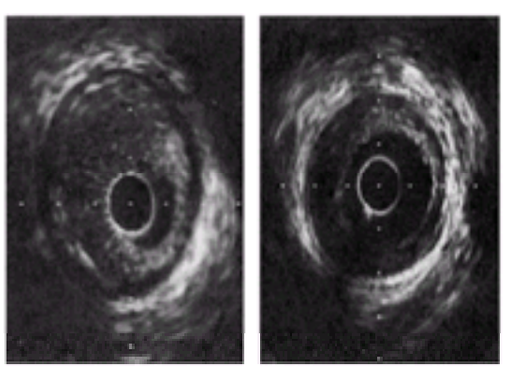
The blood within the vessel lumen exhibits a characteristic pattern of echogenicity in IVUS examinations. At frequencies greater than 25 MHz, the lumen is characterized by subtle, finely textured, specular echoes that move in a characteristic swirling pattern during blood flow. The echogenicity within the lumen arises from reflection of acoustic energy by circulating blood elements, although the precise origin of this effect remains uncertain. In many clinical situations, the presence of blood "speckle" can assist image interpretation by confirming the communication between dissection planes and the lumen. The pattern of blood speckle is dependent on the velocity of flow, exhibiting increased intensity and a coarser texture when flow is reduced. This latter property can represent a confounding variable in some examinations because the increased echogenicity of blood may interfere with delineation of the blood tissue interface.

Classification of Atheromas

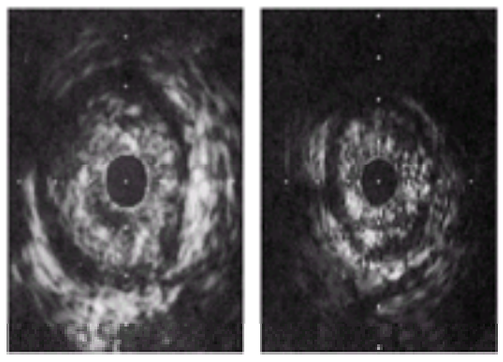
The subtle changes observed by histology early in the development of coronary atherosclerosis, such as fatty streaks, are not visible using currently available 30-MHz ultrasonographic devices. Vessels with classical atherosclerosis exhibit a diversity of abnormal features that reflect the severity, composition, and distribution of the atheromas (6,23,34,35,36,37,38,39,40,41 and 42) (*e*Fig. 85.0.8, *e*Fig. 85.0.9, and *e*Fig. 85.0.10). Sites with limited disease often exhibit generalized or focal thickening of the intimal leading edge, whereas advanced lesions appear as large echogenic protrusions encroaching on the lumen. Three basic types of lesions are distinguished: (a) highly cellular fibromuscular lesions or lesions with diffuse lipid infiltration, which have a low echogenicity (*e*Fig. 85.0.8); (b) dense fibrous lesions, which produce bright echo reflections (*e*Fig. 85.0.9); and (c) calcified lesions, which produce intensely bright reflections with acoustic shadowing (*e*Fig. 85.0.10).



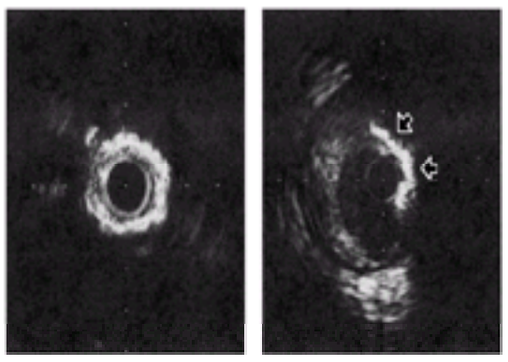
Severe coronary calcification. In this example, there is dense shadowing due to 360 degrees of lesional calcification.



***e*FIGURE 85.0.8** Soft, lipid-laden coronary atheromas. In both panels, the atherosclerotic plaque is relatively sonolucent, which indicates a high lipid content.



***e*FIGURE 85.0.9** Fibrotic coronary atheromas. In both panels, the atheroma approaches the egocentricity of the adventitia, which indicates a high content of fibrous tissue.

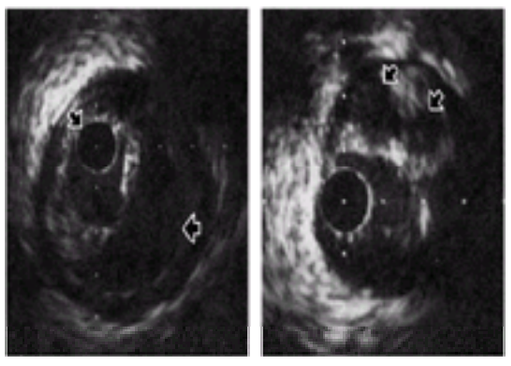


***e*FIGURE 85.0.10** Calcified coronary atheromas. **Left:** Calcification extends throughout the 360-degree circumference of the vessel ("napkin-ring" calcification). **Right:** A more focal area of calcification is shown (*gray arrows*).

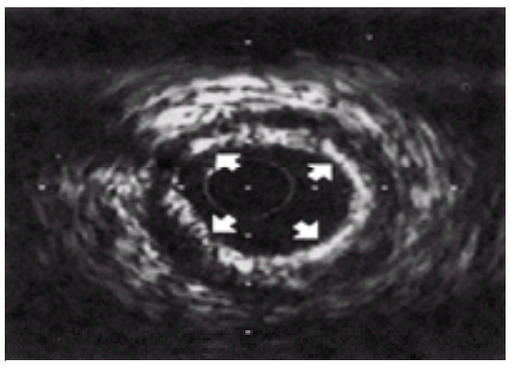
No standardized method exists for analysis of atheroma composition. Most classification schemes differentiate atheromas into one of three categories (soft, fibrous, or calcified) according to plaque echogenicity. The echogenicity of the atheroma is dependent not only on the acoustic properties of tissue, however, but also on the acquisition settings (gain, compression, etc.) of the ultrasonographic system. Accordingly, most classification methods compare the echo intensity of the plaque to that of the surrounding adventitia to correct for differences in ultrasonographic technique. When this approach is used, atheromas are termed "soft" if they are less echogenic than the adventitia and "fibrous" or "hard" if echodensity is similar to that of the adventitia. Most plaques are mixed, however, with elements of lipid, fibrosis with or without calcification, and necrosis.

Calcified atheromas exhibit a characteristic morphology by IVUS. Calcium attenuates transmission of high-frequency ultrasound and thereby obscures deeper layers of the vessel wall, a phenomenon known as *acoustic shadowing*. Obstruction of ultrasound transmission, not merely a high degree of echogenicity, is a requisite for identification of calcium. Except for detection of multiple scattered microcalcifications, ultrasonography can be considered highly specific and sensitive for the detection of calcified plaque. Because of the importance of calcium for the selection of coronary interventional devices, most interpretation schemes further classify calcified atheromas (43,44 and 45). Additional descriptors indicate whether deposits are single or multiple, the circumferential extent of calcium expressed in degrees of arc, and the length in millimeters. Most approaches also determine the depth of the calcification, described as "superficial" or "deep" depending on whether tissue is found between the calcium deposit and lumen.

The appearance of unstable or degenerating atheromas by ultrasonography remains incompletely characterized (46,47) (eFig. 85.0.11). Some plaques contain a zone of reduced echogenicity within the central core of the atheroma. Current methods cannot distinguish whether these represent areas of lipid deposition or necrotic degeneration, both of which can appear as zones of low density. Often, an echolucent zone within the atheroma is covered by a distinct "cap" of greater echogenicity, which presumably represents the classical fibrous cap described by histology (eFig. 85.0.12). Spontaneous plaque rupture associated with unstable coronary syndromes is sometimes evident in ultrasonographic examination of the culprit lesions (hours to days after the event) (48). These lesions often show single or multiple channels within the plaque that communicate with the lumen. The ultrasonographic appearance of angiographic "pseudoaneurysms" typically consists of crevices within the atherosclerotic plaque, most likely due to emptying of the lipid-rich necrotic plaque core. In a serial study, ultrasonographic characteristics of vulnerable plaques that subsequently ruptured included presence of an echolucent core and a relatively thin echogenic cap (49).



***e*FIGURE 85.0.11** Features of unstable coronary lesions. **Left:** The ultrasonographic catheter is located within the "true" lumen (*top arrow*). The bottom arrow points to a secondary flow channel within the body of the atheroma, which has been recanalized. **Right:** The arrows point to a secondary flow channel within the body of the atheroma in a patient recovering from an episode of unstable angina.



***e*FIGURE 85.0.12** Thickened fibrous cap. An atheroma of low echogenicity is covered by a more echogenic fibrous cap (*arrows*).

The presence of mobile intraluminal masses suggests the presence of thrombi, but at 30 MHz, organizing thrombus appears visually indistinguishable from other types of plaques. In several small observational studies, the IVUS appearance of a coronary thrombus was defined as low echogenic material within the lumen demonstrating slight synchronic pulsation. This entity has significantly different acoustic impedance at the interface between the thrombus and the more echogenic plaque (50,51). Analysis of the unprocessed radiofrequency signals is a promising technique in differentiating the intracoronary thrombus from the atherosclerotic plaque (52,53).

Despite extensive research regarding assessment of plaque morphology by IVUS, some caution is warranted in interpretation of images. Although contemporary devices produce remarkably detailed views of the vessel wall, interpretation must rely on simple visual inspection of acoustic reflections to determine plaque composition. In echogenicity and texture, different histologic features may exhibit comparable acoustic properties and therefore appear quite similar by IVUS. Furthermore, the pictures displayed on the monitor are the result of multiple processing steps in the scanner that influence the ultrasonographic texture of the plaque in a variety of ways.

IVUS can delineate the thickness and echogenicity of vessel wall structures but does not provide actual histology. Validated methods do not yet exist for objective or automated classification of atheromatous lesions. One must also emphasize that classification of the plaque morphology uses common terms that are not precise indicators of the mechanical characteristics of the atheroma. For example, the definitions of "soft" and "fibrous" are potentially misleading, because some plaques classified as "soft" may not necessarily be mechanically soft and show a high resistance to dilatation (54).

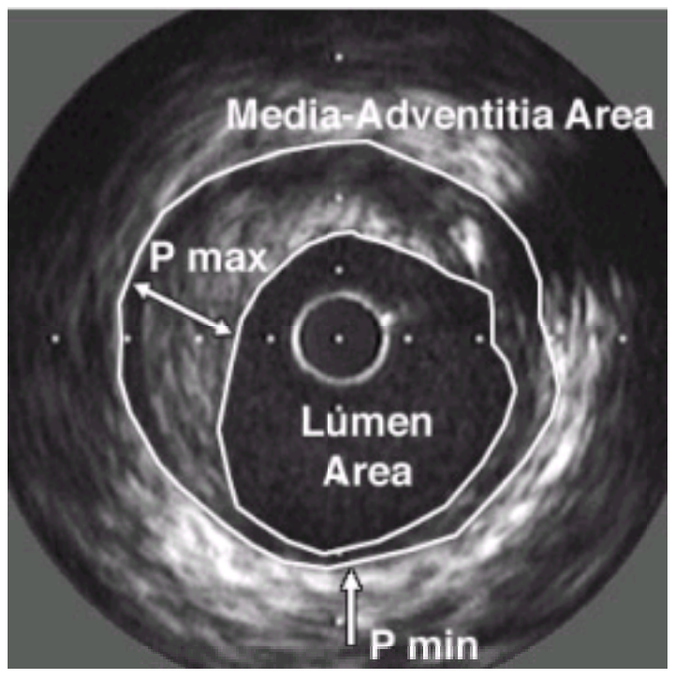
Despite these limitations, the general classification of coronary plaques into the categories of soft, fibrous, or calcified has significant clinical implications. Initial experience suggests that the three different categories often respond differently to interventional devices (55,56). For example, very dense fibrotic or calcified plaques often resist removal with DCA devices (57,58). The presence of heavily calcified or fibrotic plaques can prevent full expansion of stents. Armed with this information, the

interventionalist may choose an alternative revascularization technique, such as rotational atherectomy, for such lesions. Further refinement of interventional strategies based on ultrasonographic lesion morphology is likely and may permit improved results or reduction in complications.

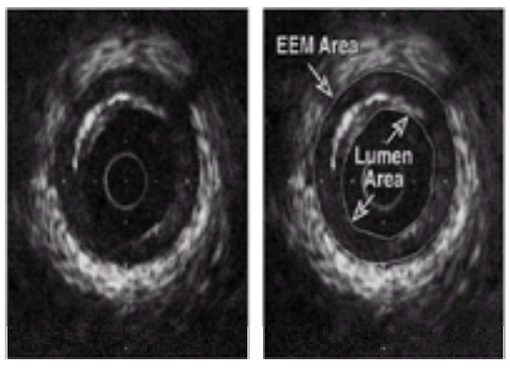
Ultrasonographic Measurements

Lumen Area

The lumen cross-sectional area (CSA) is determined by tracing the circumference of the leading edge of the blood-intima interface (*e*Fig. 85.0.13). Maximum and minimum lumen diameters are measured over a line crossing the center of the lumen. Lumen area stenosis is analogous to percent diameter stenosis on the angiogram and is calculated using the following formula: (reference lumen CSA – minimum lumen CSA)/reference lumen CSA.



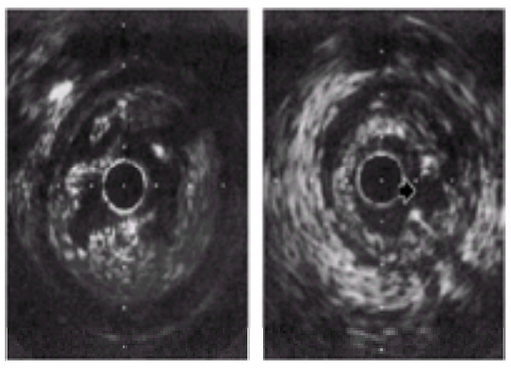
Method of intravascular ultrasonography measurement. Plaque area is the area between the external elastic membrane border and the lumen. Minimum and maximum plaque thicknesses are often reported in the literature (P max and P min).



***e*FIGURE 85.0.13** Intravascular ultrasonographic measurements of the areas of the lumen and external elastic membrane (EEM). The area of the atheroma is the EEM area minus the lumen area. In both cases, planimetry is performed on the leading edge of the structure to be measured.

Because of the speckled nature of ultrasonographic images, individual frames of the video recording may not contain a continuous intimal leading edge. Accordingly, review of the videotape with the vessel in motion may assist in accurate edge detection by allowing the moving display of images to fill in discontinuous portions of the vessel circumference. This process is also facilitated by differentiating the dynamic speckle pattern characteristic of flowing blood from the more static pattern of adjacent tissue. The injection of contrast dye or saline into the vessel temporarily clears the echogenic blood signals and may facilitate border delineation.

After coronary interventions, particularly balloon angioplasty, the shape of the lumen may be extremely complex, exhibiting plaque fissures or deep wall dissections (18,20,21 and 22,43) (*e*Fig. 85.0.14). These extraluminal channels contribute little to blood flow capacity, which raises the question of whether such structures should be included in tracing the luminal contour. A commonly applied solution to this conundrum distinguishes the true lumen area (in general, the lumen in which the ultrasonographic catheter is positioned) from the "dissection area," which is separated from the true lumen by a dissection flap.



***e*FIGURE 85.0.14** Complex dissections after balloon angioplasty. **Left:** A complex stellate-like lumen is evident. **Right:** A single curvilinear split in the plaque is apparent (*arrow*).

Relative location of the lumen in the vessel cross section is expressed by lumen eccentricity: (maximum lumen diameter – minimum lumen diameter)/maximum lumen diameter. This calculation yields an index of 1.0 if the lumen is perfectly round, with values less than unity indicating increasing luminal eccentricity.

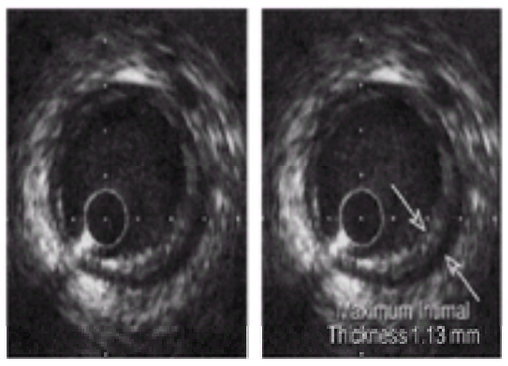
External Elastic Membrane Area

The total cross-sectional area of the vessel is defined as the area enclosed by the interface between the media and adventitia—the leading edge of the external elastic membrane (EEM). The terms *total vessel area*, *EEM area*, and *external elastic lamina area* are used interchangeably.

As previously discussed, measurement of the area within the external elastic lamina does not allow calculation of true plaque or intimal area because the *internal* elastic membrane is not well delineated with ultrasonography. Calcium-induced acoustic shadowing can obscure a large portion of the vessel wall, which requires interpolation of missing portions of the vessel circumference. Coronary stent implantation compresses the plaque, media, and surrounding adventitia and, together with the variable degree of acoustic shadowing produced by stent struts, may also give rise to difficulties in quantitating the EEM area.

Atheroma Area and Thickness

In addition to cross-sectional area measurements, most laboratories also routinely measure atheroma area and thickness (eFig. 85.0.15). All atheroma measurements include the media thickness and area. Thus, the terms *atheroma area* and *plaque plus media area* are used. Maximal atheroma thickness is defined as the longest distance between the intimal and adventitial leading edges, whereas the minimum thickness is the shortest distance between these two interfaces. The difference between maximum and minimum atheroma thickness represents a useful measure of plaque eccentricity, usually expressed by the following calculation: (maximum plaque plus media thickness – minimum plaque plus media thickness)/maximum plaque plus media thickness.



***e*FIGURE 85.0.15** Measurement of maximal intimal thickness. In this example, the distance from the leading edge of the intima to the external elastic membrane reaches a maximum valve of 1.13 mm (*arrows*).

Plaque area or plaque plus media (or atheroma) is calculated by the following formula: EEM CSA – lumen CSA.

The circumferential extent of disease is also commonly classified by determining whether abnormal intimal thickening involves the entire circumference of the vessel. Longitudinal extent of atherosclerosis can be expressed in millimeters if automatic pullback is used or reported using the qualitative terms *diffuse* and *focal*.

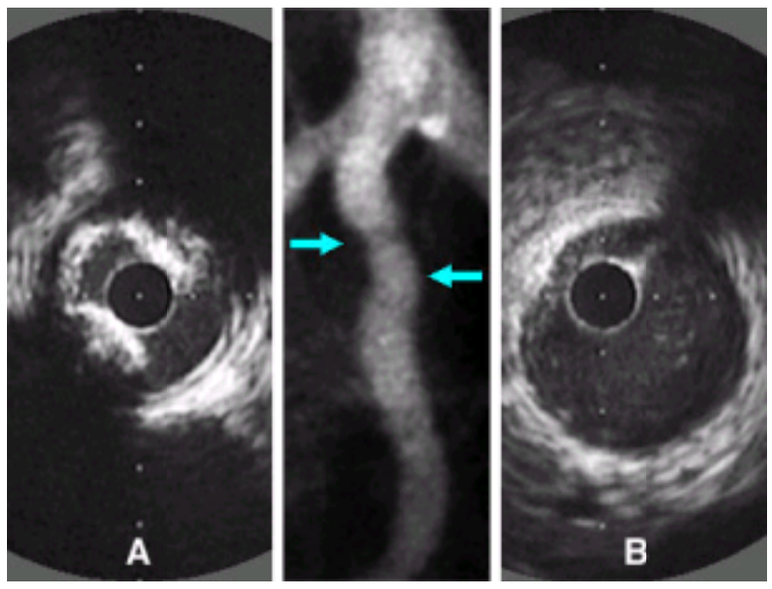
Percent Vessel Area Stenosis

The calculated value of percent vessel area stenosis is different than lumen area stenosis because it represents the atheroma or plaque burden and cannot be measured with angiography. This parameter has been referred to as *percent vessel area stenosis*, *plaque area stenosis*, or simply *percent stenosis*. This measurement, however, is not equivalent to angiographically determined percent stenosis, which represents an expression of luminal narrowing at the stenosis relative to the reference segment. The percentage of the vessel area occupied by atheroma is calculated using the following formula: [(EEM CSA – lumen area)/EEM CSA] × 100.

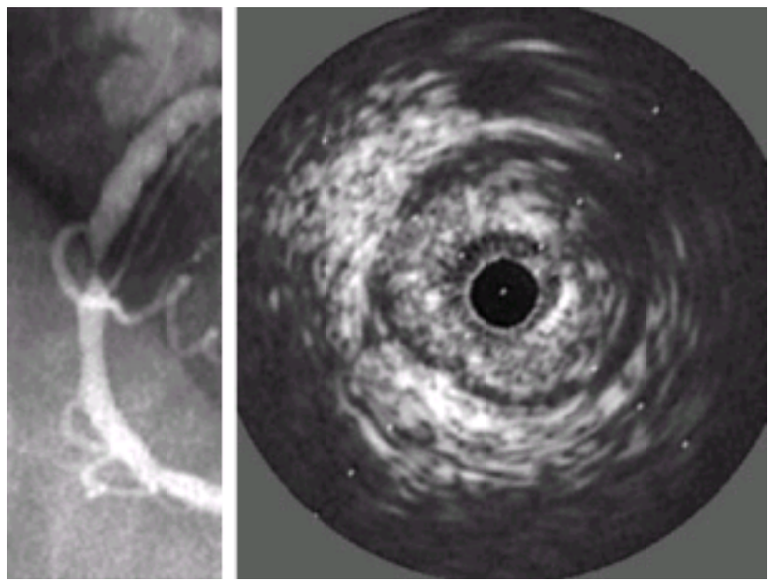
Discrepancies with Angiography

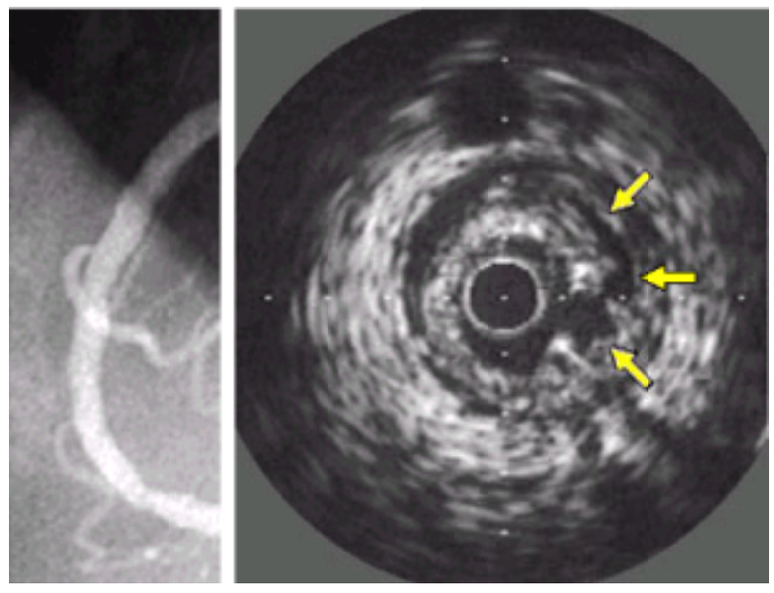
Percent Stenosis

The percent vessel area stenosis determined by ultrasonography is greater than the percent diameter stenosis evident by angiography (22). This phenomenon is a consequence of two major factors: (a) the diffuse nature of coronary atherosclerosis, which frequently affects the angiographically normal “reference” vessel (eFig. 85.0.16); and (b) the presence of adaptive enlargement of the vessel, which opposes luminal encroachment and thereby keeps the lumen constant during the early phases of atherosclerosis (24) (eFig. 85.0.17).

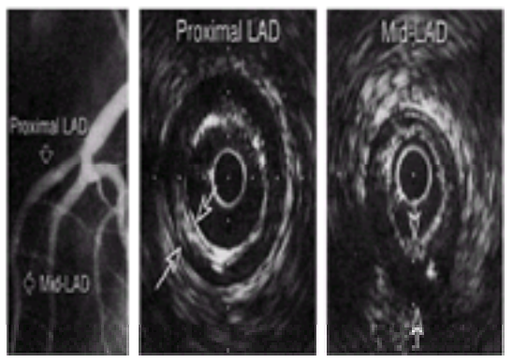


Limitations of angiography. Haziness in angiogram (*top arrow*) corresponds to lesional calcium (A). In comparison, a site just distal to the lesion (*bottom arrow*, B) remains within normal limits.

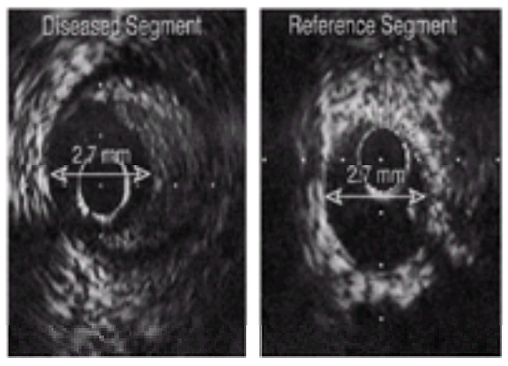




Limitation of angiography. In this example, A shows a preinterventional view of a tight distal right coronary artery stenosis. Due to intimal tears and irregular lumen shape after an angioplasty, it may be difficult to assess the lumen gain by angiography. In B, what appears to be a good result on angiogram is actually less favorable with intimal dissection evident on intravascular ultrasound examination.



***e*FIGURE 85.0.16** Diffuse disease resulting in false-negative angiography. **Left:** Two sites, one in the proximal left anterior descending artery (LAD) and another in the mid-LAD, are indicated by arrows. **Middle:** Ultrasonography at the proximal LAD site shows extensive atherosclerosis with increased intimal thickness (*arrows*). **Right:** A mid-LAD site with a similar degree of atherosclerosis is illustrated. Intimal thickness is significantly increased at both sites, which leads to false-negative angiography (*arrows*).

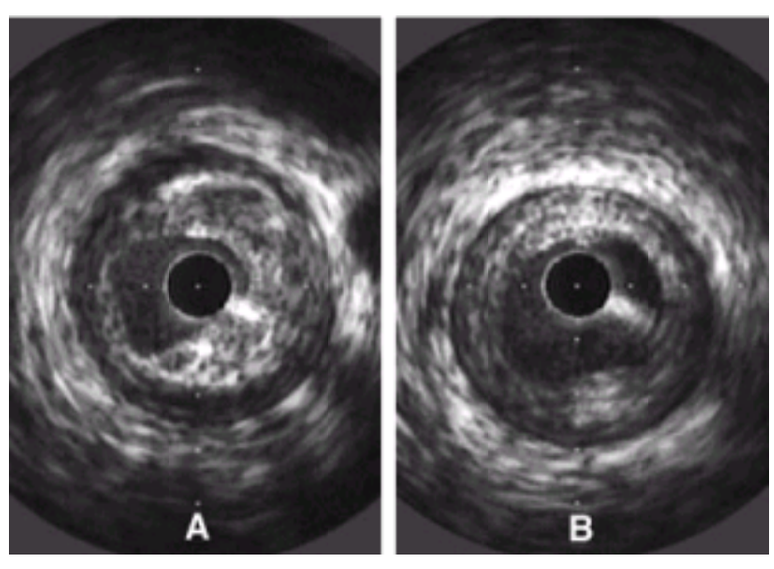


***e*FIGURE 85.0.17** Coronary remodeling. **Left:** In the diseased segment, the lumen is 2.7 mm and round, with lumen size maintained by outward displacement of the adventitia overlying a large atherosclerotic plaque. **Right:** Lumen size is nearly identical, although no atheroma is present. Because lumen size is identical in the diseased and reference segments, the angiogram is normal.

As previously discussed, angiography, a planar technique, has major limitations in measuring the size of vessels with complex luminal geometry. Accordingly, studies comparing angiographic and ultrasonographic assessment of luminal narrowing show close correlation for arteries with a nearly circular cross section and progressively lower correlation with increasing luminal eccentricity (5,6,22).

Atheroma Distribution

A second frequent area of discrepancy concerns the eccentricity of the atheromas. In patients with coronary disease, the circumferential distribution of the atheroma varies from symmetric, circumferential plaques to highly eccentric lesions in which the entire atheroma is located on only one side of the artery. The majority of plaques is eccentric by IVUS, with a maximum atheroma thickness more than twice the minimum plaque thickness. Comparative studies have demonstrated a poor correlation between the apparent plaque distribution by angiography and the actual circumferential pattern revealed by ultrasonographic examination. In 267 of 651 lesions (41%) deemed concentric by angiography, ultrasonography revealed a ratio between maximum and minimum plaque thickness greater than or equal to 3.0 (59). Conversely, only 126 of 795 plaques deemed eccentric by angiography (15%) had a segment of completely normal vessel wall. Such studies demonstrate the inaccuracy inherent in determining plaque distribution from projected two-dimensional silhouettes of the lumen (angiography). This observation has important implications for guidance of coronary interventions, particularly techniques for selective plaque removal such as DCA.

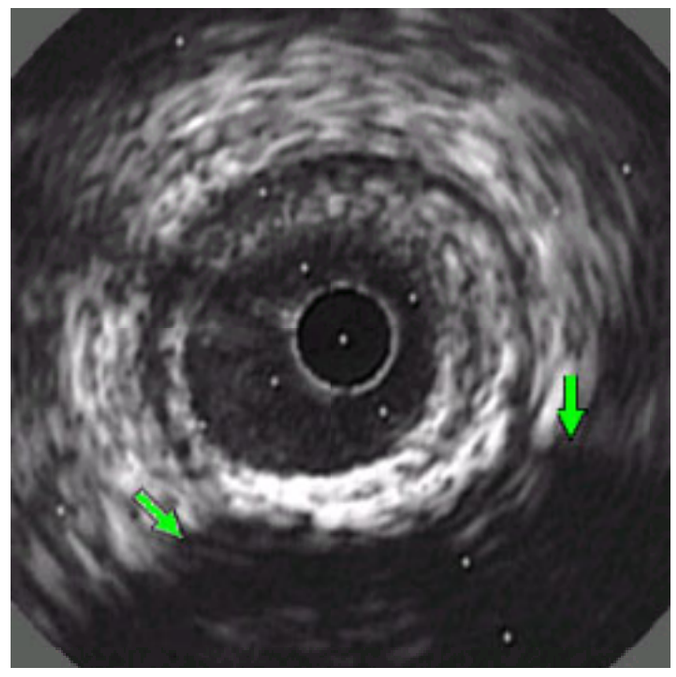


Atheroma distribution patterns. Eccentric plaque has a significant difference between the maximum and minimum plaque thickness (A). A concentric

lesion shows similar plaque thickness throughout the entire circumference of the vessel (B).

Atheroma Calcification

Extensive atheroma calcification represents an important sequela of coronary atherosclerosis, generally associated with disease of long duration. The traditional approach to identifying calcification uses cinefluoroscopy to visualize moving opacities in proximity to the vessel silhouette. This approach is limited by many factors, including the moderate spatial and contrast resolution of fluoroscopy and the confounding effects produced by the overlap of other calcium-containing structures. Studies comparing ultrasonography and angiography demonstrate poor sensitivity for angiography in detection of coronary calcification. Among 1,155 coronary lesions, Mintz et al. detected calcium in 73% of the lesions by ultrasonography and in only 38% by angiography (44). In interventional target lesions, Tuzcu et al. reported that angiography identified less than half (45%) of cases in which calcification was detected by ultrasonography (45). Even in the presence of more extensive calcification, the sensitivity of angiography remains poor, with angiography correctly identifying only 52% of lesions with calcium subtending more than 90 degrees of vessel circumference and only 63% of lesions with more than 180 degrees of involvement.



Lesional calcification. The arrows identify the calcified portion of the vessel circumference, which impedes transmission of the 30-MHz ultrasound signal, a phenomenon known as acoustic shadowing.

Although the sensitivity of angiography in detecting calcification is low, the specificity remains high. In 183 patients examined before coronary interventions, the presence of calcium identified by angiography at the target stenosis was almost invariably associated with greater than 90 degrees of arc of calcium (45). Visualization of calcium by fluoroscopy at a site remote from the target stenosis is also associated with target lesion calcification. Ultrasonographically detected calcification was evident in 35% of lesions with remote angiographic calcification. Conversely, when calcium was not present by fluoroscopy anywhere in the coronary arterial tree, the likelihood of severe target lesion calcification was low.

Arterial Remodeling

The phenomenon of coronary remodeling, originally described by Glagov from necropsy examinations, represents another important mechanism underlying false-negative angiography (24,60,61). It is also an important factor that confounds the angiographic estimation of the true size of the coronary artery, which is crucial to the technique and result of percutaneous coronary revascularization. IVUS with its tomographic perspective contributed substantially to the understanding of the remodeling phenomenon. The findings of Glagov et al. were validated *in vivo* by intracoronary ultrasonographic imaging (eFig. 85.0.17). In some of the IVUS studies and most histologic investigations, the presence and extent of remodeling are inferred from the comparison of plaque and EEM area in groups of lesions of differing severity (60). Positive remodeling is defined by a positive correlation between plaque and EEM area. In this type of analysis, remodeling can be described for a large group of lesions but not for individual lesion sites.

To assess the extent and direction of remodeling in individual lesions, one must compare vessel size at the lesion site to vessel size at an adjacent reference site. Positive and negative remodeling are defined as larger or smaller EEM area at the lesion site than at an adjacent reference site. Angiographically “normal” reference segments frequently contain mild to moderate atherosclerosis and remodeling, however. If serial ultrasonographic images are available, the changes in plaque and EEM areas can be assessed over time, which eliminates the confounding variable of reference segment remodeling.

Changes in the vessel wall in response to atherosclerosis are not always in the form of outward expansion but can manifest as a shrinkage. The phenomenon of negative remodeling was demonstrated in peripheral as well as coronary atherosclerosis (62,63). At diseased sites, the artery may actually shrink in size and contribute to, instead of compensate for, the degree of luminal stenosis.

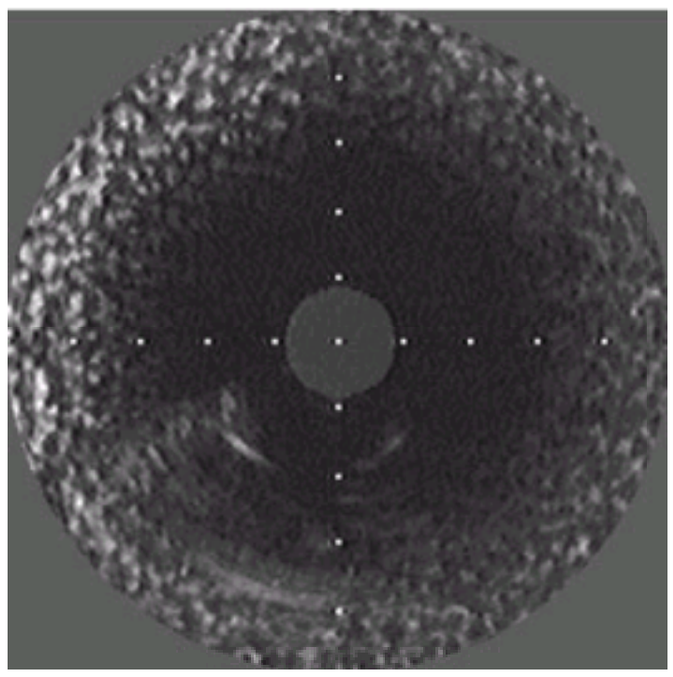
Intriguing IVUS and histopathologic studies provided new insights into arterial remodeling by shedding new light on the relationship between remodeling and the clinical presentation of coronary artery disease. In one study, positive remodeling was more prevalent in patients who presented with unstable angina (51% vs. 18%; $p = .002$), and negative remodeling was more prevalent in patients with stable angina (58% vs. 33%; $p = .002$) (64). A similar relationship between the direction of remodeling and clinical presentation was also shown in the setting of myocardial infarction (65). In a combined IVUS-angioscopy study, unstable lesions were more commonly characterized by positive than by negative remodeling (58% vs. 17%). Also, angioscopically complex lesions more often had positive than negative remodeling (57% vs. 14%) (66). These studies support the hypothesis that plaque vulnerability and positive remodeling have some common pathophysiologic mechanisms.

The pathophysiologic mechanisms underlying plaque vulnerability and remodeling are not well known. However, inflammation may represent a common link. An IVUS and histologic study of the human femoral arteries showed an association between histologic markers associated with plaque inflammation and positive arterial remodeling (67). Comparative analysis of the preatherectomy ultrasonographic images and histology of the plaque tissue obtained by DCA demonstrated an association between intense matrix metalloprotein staining and positive remodeling, which suggests that degradation of the extracellular matrix plays a role in arterial remodeling (68).

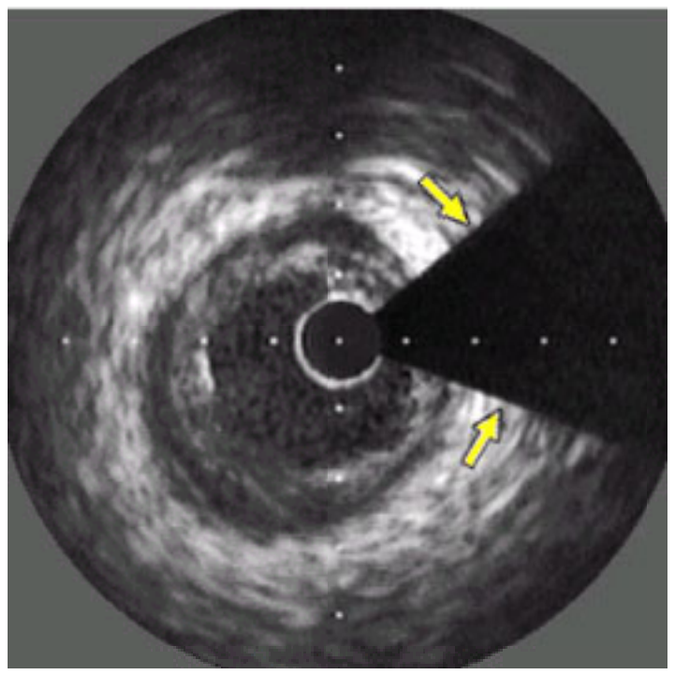
Changes in the geometry of the vessel and tissue changes leading to the geometric alteration probably affect the response of the vascular segment to balloon angioplasty. Immediate and long-term outcomes of various percutaneous coronary interventions have been correlated with direction and extent of remodeling (69,70,71 and 72).

Limitations and Artifacts

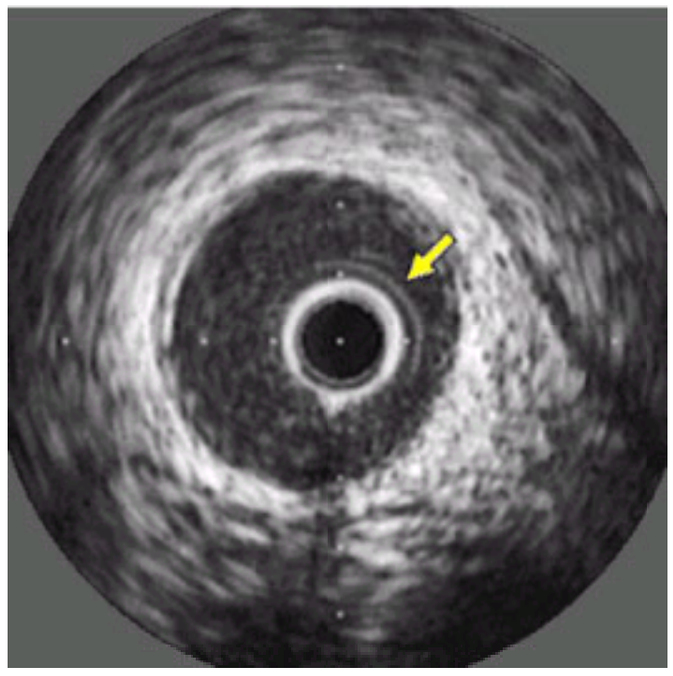
Important artifacts are often present in images generated by contemporary IVUS devices. These artifacts can have wide-ranging consequences and may adversely affect image quality, increase interpretation difficulty, or reduce the accuracy of quantitative measurements (73). Imaging of small coronary arteries or preinterventional assessment of target lesions with severe stenosis requires imaging close to the transducer surface. *Ring-down artifact*, however, a defect that appears in virtually all medical ultrasonographic devices, impairs the ability to image structures adjacent to the transducer surface (eFig. 85.0.18). The size of the catheter itself can be the cause of artifact by disrupting the severely stenotic plaque. Geometric distortion, which influences area and diameter measurements, is the result of noncoaxial alignment of the ultrasonographic catheter.



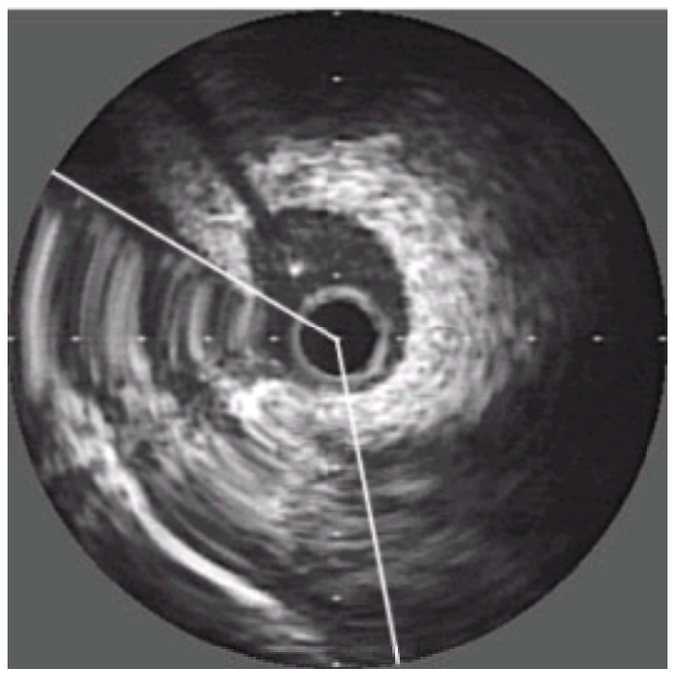
Appearance of an imaging artifact. Air within the catheter surrounds the transducer, resulting in absence of an interpretable image.



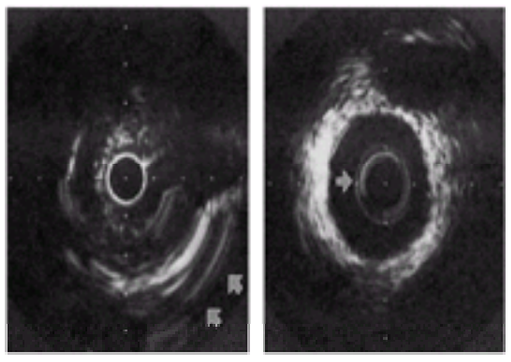
Imaging artifacts. An incomplete connection between the catheter and patient interface results in missing image information from a portion of the vessel circumference.



Imaging artifacts. "Ring-down" artifact consists of high amplitude echo signals in the near field (*arrow*).



Intravascular ultrasound artifacts. Nonuniform rotational distortion (NURD) results from variability in rotational velocity in mechanical intravascular ultrasound catheters (zone between lines).



***e*FIGURE 85.0.18** Two types of intravascular ultrasonographic imaging artifacts. **Left:** The ultrasonographic image exhibits nonuniform rotational distortion, which can be recognized by a circumferential "stretching" of the image (*arrows*). **Right:** A large "near-field" artifact (ring-down) is evident (*arrow*).

Ring-down artifacts are produced by acoustic oscillations in the piezoelectric transducer material, which results in high-amplitude ultrasonic signals that preclude near-field imaging. Inability to image structures immediately adjacent to the transducer results in an acoustic catheter size that is slightly larger than its physical size. Current designs use carefully chosen transducer materials, ultrasound-absorbent backings, specialized coatings, and electronic filtering to suppress ring-down artifacts. In the electronic array design, the transducers are surface mounted, and ring-down must be reduced by digital subtraction.

The physical size of ultrasonographic catheters (currently approximately 1.0 mm) constitutes an important limitation in certain clinical applications. Although the operator may be able to reach many critical stenoses with a 1-mm device, lesional morphology and quantitative measurements are distorted by the distending effect of the catheter. Reductions in transducer size are feasible, but finite physical limitations exist to further transducer miniaturization. A smaller transducer reduces the "aperture" of the device, which limits available acoustic power, significantly reduces lateral resolution, and impairs the signal-to-noise ratio. The resolution limits at small apertures may be partially compensated by using higher frequency transducers (40 to 50 MHz).

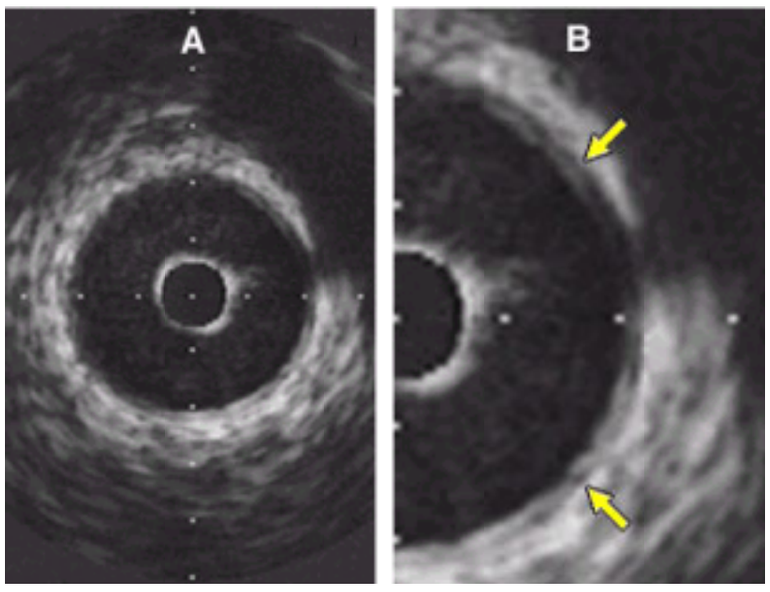
Geometric distortion can result from imaging in an oblique plane (not perpendicular to the long axis of the vessel). Noncoaxial alignment of the transducer within the artery results in an elliptical rather than circular cross-sectional imaging plane (74). This phenomenon can represent a significant confounding variable in the application of IVUS for quantitative plaque and lumen measurements. During data acquisition, the operator often can recognize a nonorthogonal catheter position and manipulate the device to a more coaxial position. The maximum extent of obliquity is influenced by the relative sizes of imaging catheter and lumen. Accordingly, this artifact can be more troublesome when larger vessels such as the aorta or the peripheral vasculature are imaged.

A very important artifact, known as *nonuniform rotational distortion* (NURD), is present in all mechanical IVUS systems (*e*Fig. 85.0.18). This artifact arises from uneven mechanical drag on the catheter drive shaft during the various portions of its rotational cycle, which results in cyclical oscillations in rotational speed. Nonuniform speed variation, when severe, produces visible distortion of the ultrasonographic image. During the portion of the rotational cycle when velocity is high, the image exhibits circumferential "stretching" with "compression" of the contralateral vessel wall (*e*Fig. 85.0.18). NURD is most evident when the drive shaft is deformed into a small radius of curvature either by external manipulation or vessel tortuosity. One preventable cause of NURD is excessive tightening of the hemostasis valve at the hub of the guiding catheter. Improvements in the mechanical precision of ultrasonographic devices have reduced the impact of this artifact, but it remains a troublesome problem during some examinations.

Diagnostic Clinical Applications

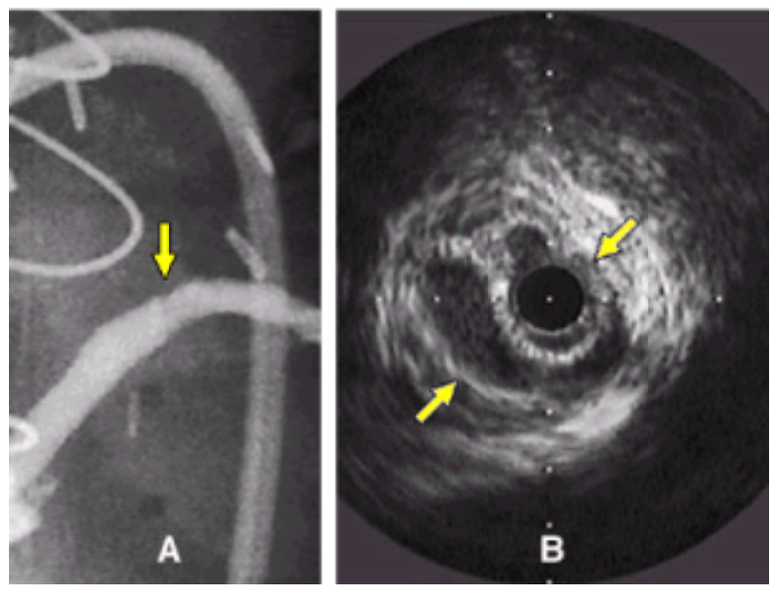
Angiographically Normal Coronary Arteries

Normal angiograms are obtained in 10% to 15% of patients undergoing coronary angiography for suspected coronary artery disease. In these patients with clinical symptoms of coronary disease, IVUS commonly detects atherosclerosis at angiographically normal sites (6,75,76,77 and 78). Erbel et al. observed atherosclerotic abnormalities in 21 of 44 patients (48%) with suspected coronary artery disease and a normal coronary angiogram (75). Combining ultrasonography with methods for functional assessment (measurement of coronary flow reserve and endothelium-mediated vasodilator response) reduced the proportion of completely normal results to only 36%. Other studies demonstrate that, if any luminal irregularity is present by angiography, ultrasonography usually demonstrates disease at nearly all other examined sites (6). The prevalence of disease at angiographically normal sites confirms the finding, previously reported from necropsy studies, that coronary disease is more extensive than apparent by angiography (19).



Normal coronary wall morphology by intravascular ultrasound. A trilaminar appearance is apparent with distinct layers representing the intima, media, and adventitia (B, *arrows*).

IVUS studies have revealed several important mechanisms by which angiography may underestimate the presence, extent, or severity of atherosclerosis. Angiography compares the interrogated site to an adjacent uninvolved segment to detect a focal stenosis. The diseased vessel may be reduced in caliber along its entire length, however, containing no truly normal segment for comparison (*e*Fig. 85.0.16). Accordingly, the angiographer could erroneously conclude that the vessel is simply "small in caliber." The ability to obtain optimal radiographic projections is limited in some patients. For example, at certain angles, overlapping structures such as adjacent vessels can obscure some segments of the coronary artery. Mechanical radiograph positioners have finite limits in the available projection angles. Accordingly, an eccentric lesion may not be visualized adequately by angiography.



Limitation of angiography: A minor angiographic luminal irregularity is present at the distal end of a stent (A, *arrow*) in a saphenous vein graft. Intravascular ultrasonography (B) shows a dissection with two flow channels. The arrow at 2 o'clock shows the true lumen containing the imaging catheter, and the arrow at 7 o'clock indicates the false lumen.

As previously discussed, compensatory enlargement (remodeling) of the vessel wall overlying the plaque preserves lumen diameter, which results in an angiographic diameter similar to that of adjacent, uninvolved coronary segments (eFig. 85.0.17). Finally, vessel foreshortening can conceal short "napkin-ring" lesions (usually less than 1 to 2 mm in length) from angiographic detection, which results in false-negative angiography.

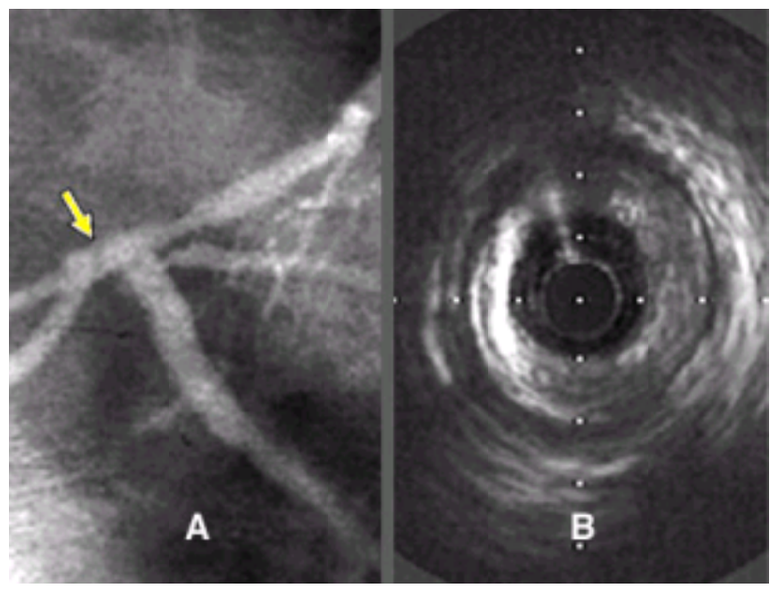
Intermediate Stenosis

Angiographers commonly encounter lesions that elude accurate characterization despite thorough examination using multiple radiographic projections. Difficult lesions include ostial lesions, bifurcation lesions, and moderate stenoses (angiographic severity ranging from 40% to 75%) in patients whose symptomatic status is difficult to evaluate. Occasionally, insufficient quality of the angiogram results from extreme obesity, emphysema, or chest deformities. For ambiguous lesions, ultrasonography provides a tomographic perspective, independent of the radiographic projection that often permits lesion quantification. In reports from two centers, intracoronary ultrasonography changed the management strategy in more than 20% of cases in which examinations were performed immediately before coronary intervention (treatment of angiographically insignificant lesions after imaging or vice versa) (55,56). In both studies, however, the selection of patients for ultrasonographic examination may have resulted in an overestimation of the true impact of ultrasonographic imaging on clinical decision making. Furthermore, the retrospective nature of these studies limits the applicability of their results to routine clinical practice.

No consensus exists regarding the criteria that would allow the application of ultrasonographic measurements to the functional assessment of the coronary blood flow and clinical decision making. The lesion lumen area and ultrasonographically derived stenosis indices such as luminal area showed sensitivities and specificities ranging between 80% and 90% when myocardial perfusion imaging is used as the gold standard (79).

The role of IVUS in clinical decision making has been assessed in two single-center retrospective clinical studies. In one of the studies, intervention was deferred in 300 patients based on ultrasonographic information. At 1-year follow-up, the rate of adverse events (death, myocardial infarction, or target lesion revascularization) was low, particularly in patients with a minimum lumen area greater than 4.0 mm (80). In another study that used IVUS and fractional flow reserve measurements, a minimum lumen area of greater than 3 mm^2 was recommended as the threshold for deferring intervention in native coronary artery obstructions other than left main coronary artery (81).

Angiographic quantification of the severity of left main coronary artery obstruction represents a particularly vexing clinical problem (13). Because the left main artery is short, no normal segment may exist that can be used as a reference. Furthermore, contrast in the aortic cusp often obscures the ostium, which requires the operator to engage the vessel with the angiographic catheter and "reflux" dye to visualize the proximal vessel. The angle between the catheter and the left main coronary artery and the take-off angle of this vessel may give the false impression of severe ostial stenosis. Sometimes, streaming of contrast material from the injection vortex may also result in pseudostenosis. Furthermore, overlapping vessels at bifurcation or trifurcation often conceal the distal left main coronary artery. Accordingly, IVUS is commonly used to quantify left main coronary artery obstruction when angiographic interpretation is uncertain (82). No consensus yet exists regarding the cutoff at which the left main obstruction is considered to require surgical treatment. Although stenosis of greater than 50% of the vessel area is proposed as a cutoff for consideration for revascularization, no data exist to support such a critical measure (83,84).

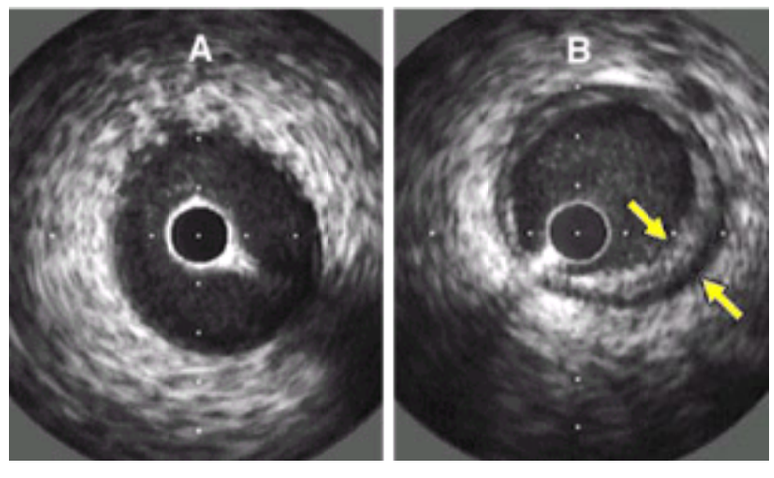


Limitation of angiography. The concentric plaque in the left main trunk (A) was not clearly defined by angiography because of the diffuse nature of the disease. Intravascular ultrasound examination demonstrates a major area reduction by concentric plaque (B).

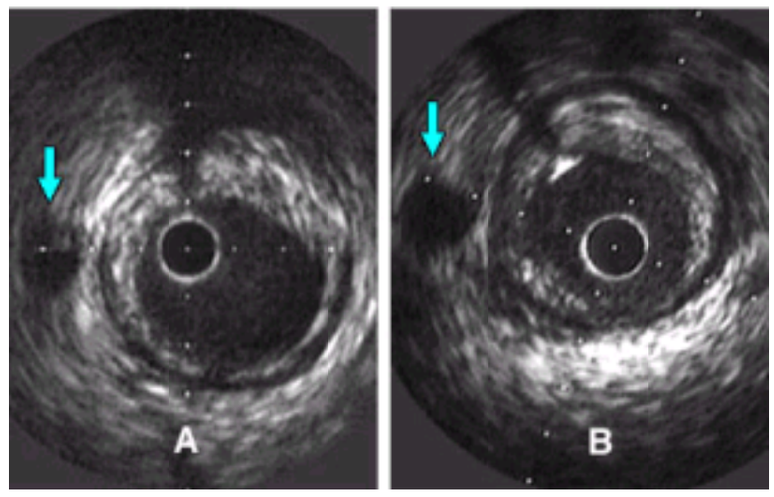
Morphologic information provided by IVUS is valuable in decision making in the catheterization laboratory, particularly at angiographically poorly defined sites such as ostia, bifurcations, and tortuous segments. Ultrasonography, however, unlike physiologic measurements such as Doppler coronary flow reserve and fractional flow, does not give physiologic information. Thus, a physiologic rather than a morphologic method should be used as the first choice in the assessment of borderline lesions (angiographically determined severity ranging from 40% to 75%).

Cardiac Allograft Vasculopathy

Accelerated coronary vasculopathy is the leading cause of mortality in cardiac transplant recipients beyond the first year after transplantation (85). Because cardiac allografts are functionally denervated, major clinical events such as myocardial infarction, congestive heart failure, and sudden death may occur without prodromal angina. Although most transplant centers perform coronary arteriograms annually for screening, these surveillance studies often fail to detect atherosclerosis before a clinical event (77,86). Intracoronary ultrasonography is an accurate and reproducible method. It provided valuable insights to the understanding of transplant coronary artery disease and demonstrated that the incidence of transplant coronary disease is much higher than previous angiographic studies had documented (77,87,88 and 89).



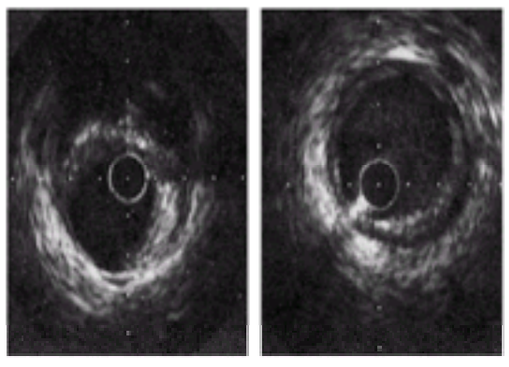
Serial intravascular ultrasound study in a cardiac transplant patient. The baseline intravascular ultrasound study (A), 1 month after transplantation, shows a normal left anterior descending artery. After 1 year (B), there is obvious thickening of intima with a concentric distribution pattern.



Serial intravascular ultrasound study in transplant recipient. The baseline study (A, 2 months after cardiac transplant), shows an eccentric plaque in the left anterior descending artery. One year later (B), the same site is identified with the help of anatomic and angiographic landmarks (a branch vessel, *arrow*). This permits repeated imaging of the same site, which reveals no change over 1 year.

Studies performed in patients soon after transplantation have helped define the normal appearance of young healthy arteries but have also shown that advanced atherosclerotic changes can be present in apparently normal donor hearts (77,87). Several studies, however, showed that preexisting donor disease detected by IVUS did not accelerate the progression of transplant vasculopathy within the first few years after cardiac transplantation (90,91). Serial studies starting a few weeks after transplantation led to differentiation of allograft vasculopathy from donor-transmitted atherosclerosis, which would be impossible in cross-sectional studies done one or more years after transplantation (91,92 and 93).

In contrast to the histologic paradigm of transplant coronary artery disease, large ultrasonographic studies have demonstrated a heterogeneous distribution of coronary lesions (92,93) (eFig. 85.0.19). In early allograft vasculopathy, focal and eccentric lesions were common in the proximal segments. Fibrous intimal proliferation occurs mostly during the first 2 years after transplantation, whereas calcification of plaques occurs to a significant extent only later in the process. Detection of early vasculopathic changes has significant clinical implications. Development of intimal thickness is an independent predictor of overall and cardiac survival and of freedom from retransplantation (94,95).



***e*FIGURE 85.0.19** Concentric and eccentric patterns of disease in a transplant recipient. **Left:** The atheroma involves approximately 270 degrees of the circumference of the artery with sparing of the opposite wall. This pattern is typical of disease grafted from the donor heart. **Right:** A more circumferential pattern is evident, consistent with acquired immune-mediated transplant vasculopathy.

Studies have shown a correlation of multiple immunologic and metabolic recipient factors as well as donor characteristics with intimal thickness, a finding which suggests a multifactorial etiology for transplant vasculopathy. Lipid values, particularly marked change in levels of low-density lipoprotein cholesterol, were shown to play a role in the development of severe vasculopathy (96). A small randomized study that used serial ultrasonographic imaging demonstrated reduction in the progression of transplant coronary disease with pravastatin sodium therapy (97). Introduction of IVUS imaging to the follow-up of posttransplant patients improved the understanding of transplant coronary disease and led to the development of new treatment strategies.

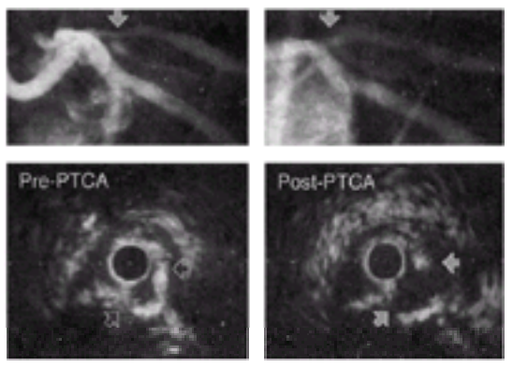
Interventional Clinical Applications

Preintervention Device Selection

The small diameter of contemporary ultrasonographic imaging catheters permits interrogation of most coronary lesions before mechanical intervention. Occasionally, severe calcific stenosis precludes passage of the imaging catheter, so that the operator must dilate before ultrasonographic examination. Intracoronary imaging offers several potential advantages for selection of the most appropriate treatment modality for a particular lesion. However, prospective randomized studies examining the utility of ultrasonographically directed revascularization strategies are essentially nonexistent. In the absence of controlled trials, interventional operators commonly use a variety of morphologic features to assist in selection of the optimal interventional approach. These include the extent of calcification, the degree of lesional eccentricity, and the amount of vessel remodeling. Despite the absence of strong data, useful observations regarding application of specific devices have emerged from initial research. These observations offer useful insights into the mechanisms of benefit and risk for many interventional approaches.

Balloon Angioplasty

Postmortem examination of the coronary arteries in patients who expired within a few days after balloon angioplasty reveal plaque fracturing or dissection as the most common mechanism of successful balloon dilatation (18,20). Ultrasonographic studies performed both *in vitro* and *in vivo* have confirmed that plaque fissuring or dissection is the most common mechanism of luminal enlargement after conventional balloon angioplasty (21,23,98,99) (eFig. 85.0.20). The diagnosis of dissection requires the visualization of blood flow in a newly created lumen or behind an intraluminal “flap.” In some cases, injection of saline or iodinated contrast through the guiding catheter can be helpful to opacify structures and aids in confirming the diagnosis. The severity of wall disruptions can be defined by measuring the circumferential extent, length, and maximal depth of the dissection.

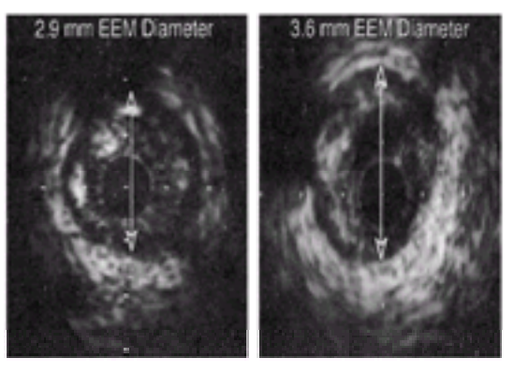


***e*FIGURE 85.0.20** Angiographic and intravascular ultrasonographic images before and after balloon angioplasty. **Top left:** An angiographic narrowing is indicated by the gray arrow. **Top right:** After balloon angioplasty, this narrowing appears improved (*gray arrow*). **Bottom left:** A dense fibrocalcific lesion is shown before intervention (*arrows*). **Bottom right:** After percutaneous transluminal coronary angioplasty (PTCA), the ultrasonographic image shows two areas of plaque fracture with extensive dissection (*arrows*).

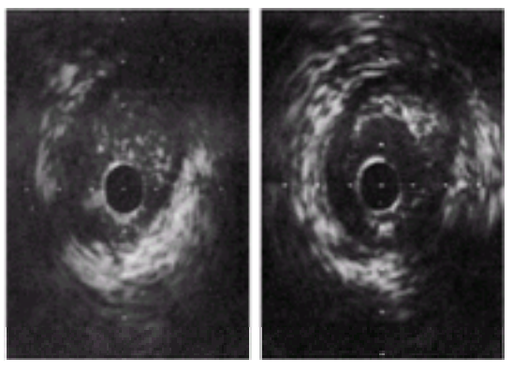
Although dissection is the most common finding, ultrasonography often reveals alternative mechanisms of luminal enlargement after balloon angioplasty that cannot be appreciated by angiography (98,99,100 and 101). For example, systematic comparison of pre- and postangioplasty ultrasonographic measurements shows that "stretching" of the external elastic lamina occurs in many patients (*e*Fig. 85.0.21). In other patients, an apparent reduction of the atheroma area ("compression") is evident, although studies using automatic pullback devices have shown that "compression" actually represents longitudinal redistribution of plaque in the vessel (101) (*e*Fig. 5.0.22).

VIDEO

Video 85.1 Coronary dissection by intravascular ultrasound. A tissue flap is seen protruding in the lumen of the vessel after high-pressure postdilatation of a Palmaz-Schatz stent in the adjacent segment. Angiographically, this flap was visualized as an area of 'peri-stent' haziness. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

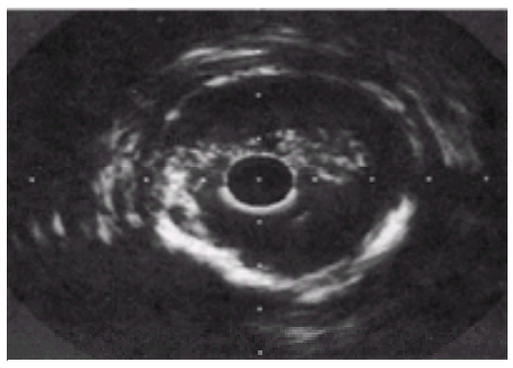


***e*FIGURE 85.0.21** Luminal enlargement by stretching of the vessel during percutaneous transluminal coronary angioplasty. **Left:** The external elastic membrane (EEM) diameter is 2.9 mm before balloon angioplasty and increases to 3.6 mm after the intervention. Thus, lumen gain is almost exclusively secondary to stretching.



***e*FIGURE 85.0.22** Luminal enlargement by plaque redistribution. **Left:** Ultrasonographic image before intervention shows a sonolucent, eccentric, bulky atheroma. **Right:** After intervention, the lumen is enlarged, and the plaque area appears to be reduced. Serial sections demonstrate that the plaque has actually been redistributed within the vessel.

Preinterventional assessment of lesions offers the potential to modify the dilatation strategy through selection of the length and size of the balloon. For example, ultrasonography may reveal a more diffuse atherosclerotic involvement than that expected from angiography, which suggests the use of a longer balloon. Ultrasonographically guided balloon sizing considers measurements not only of the lumen diameter but also of the total vessel diameter (EEM diameter). In the multicenter Clinical Outcomes with Ultrasound Trial (CLOUT) study, investigators addressed the question of how ultrasonographic information could be used in the guidance of balloon angioplasty. IVUS was performed after a satisfactory angiographic result was obtained by standard intervention. A weighted average of the lumen and EEM diameters obtained by ultrasonography was used for balloon size selection. Following this strategy led to selection of larger balloons for 73% of the patients. This ultrasonographically guided strategy led to further increase in minimal luminal diameter from 1.95 to 2.21 mm and in lumen area from 3.2 to 4.4 mm^2 (102). In contrast to previous angiographic studies, which have shown that a balloon to artery ratio greater than 1.1 leads to more severe dissections, procedures with a balloon to artery ratio of 1.3 in the CLOUT study did not result in excess dissections (103). These data suggest that with discriminate ultrasonographically guided balloon upsizing, the results of balloon angioplasty can be improved. Nonrandomized studies from two centers provide further support for ultrasonographically guided balloon sizing. Aggressive balloon sizing (based on the media to media dimension determined by ultrasonography) led to stent-like procedural results and complication and target vessel revascularization rates (104,105 and 106). Most operators experienced in IVUS believe that the presence, depth, and circumferential extent of calcification have predictive value in estimating the risk of complications after balloon angioplasty (43). Dissections frequently occur at the junction between soft tissue and calcium due to the different stress modulus of these two plaque components (*e*Fig. 85.0.23). Contrary to these observations, in a series of 197 patients who underwent ultrasonographic imaging before and after angioplasty, lesion morphology was not a predictor of severe coronary dissections (107). Whether knowledge of coronary calcification can be used in planning interventional procedures to reduce dissections has not yet been adequately tested in clinical trials.



***e*FIGURE 85.0.23** Large dissection after intervention. A large peninsula of plaque nearly bisects this vessel after coronary intervention. Because such lesions are surrounded by contrast, they may be inapparent on angiography.

The most important information obtained by IVUS concerns assessment of the procedural results. After angioplasty, ultrasonography can detect the circumferential and longitudinal extent of dissection. Several studies report a poor correlation between ultrasonography and angiography in assessing residual stenosis after angioplasty (108,109). Measurements of luminal cross-sectional area after angioplasty are generally smaller by ultrasonography than by angiography. These differences likely represent enhancement of the apparent angiographic diameter of the vessel produced by extraluminal contrast within cracks or splits in the intima or media, or both, of the vessel. Because balloon dilatation distorts the vessel lumen and wall, the reported differences between angiographic and ultrasonographic measurements probably reflect the differences between silhouette and tomographic imaging of complex eccentric lumen shapes after angioplasty.

Two factors influence the tendency of angiographic imaging to yield overly optimistic results after balloon angioplasty. Because of the frequent presence of unrecognized atherosclerosis at the reference site, angiography tends to underestimate the diameter of the normal reference vessel. At the lesion site, angiography tends to overestimate the actual gain in luminal diameter, because contrast material penetrates into complex cracks and fissures produced by the intervention, which gives the appearance of a more enlarged lumen. To calculate a postprocedure percent diameter stenosis, the diameter at the target site (an overestimate) is divided by the reference diameter (an underestimate), which results in a more favorable impression of the actual gain in luminal dimensions. Accordingly, when quantitative angiography reports a residual diameter of stenosis of 10% to 15%, ultrasonography not uncommonly reports that 60% to 80% of the vessel is still occupied by atheroma (percent vessel area stenosis).

Intravascular Ultrasonography and Restenosis

IVUS provides a unique perspective to better understand the mechanisms and characteristics of restenosis, which continues to be the Achilles' heel of percutaneous coronary intervention. Angiographic parameters, including quantitative angiographic measurements, are limited predictors of the long-term results after balloon angioplasty (110). Preliminary ultrasonographic studies have shown conflicting data concerning the factors predictive of restenosis after balloon angioplasty (111,112). A more complete understanding of restenosis has evolved from serial ultrasonographic measurements of plaque and lumen areas at follow-up studies after balloon angioplasty and DCA (113,114).

IVUS provided valuable insight about the mechanism and characteristics of the restenosis phenomenon. In the Post Intra-Coronary Treatment Ultrasound Restenosis Evaluation study, ultrasonography was used to assess lesion composition, mechanism of luminal enlargement, and quantitative measurements of the lumen and plaque after final balloon inflation (111). In this small prospective trial enrolling 200 patients, clinical and angiographic results could not be predicted by ultrasonographic findings. However, lack of blinding of interventional operators and the relatively small patient population were important limitations of this study.

A single-center observational study demonstrated that the residual cross-sectional area stenosis measured by ultrasonography was an independent predictor of restenosis (114). Plotting of the residual cross-sectional area stenosis versus the probability of restenosis at 6 months demonstrated a curvilinear relationship, with restenosis occurring in more than 50% of the lesions showing more than 70% residual area stenosis immediately after intervention.

The Guidance by Ultrasound Imaging for Decision Endpoints II trial was a multicenter study assessing the factors predictive of restenosis after balloon angioplasty and DCA based on a final ultrasonographic examination (112). The analysis, performed without discriminating between balloon angioplasty and DCA, demonstrated that two ultrasonographic parameters were predictive of long-term recurrence of symptoms: residual plaque burden and luminal cross-sectional area after intervention. The results of these studies suggest that ultrasonography may be useful whenever angiography shows diffuse haziness or intraluminal defects in the treated segment, suggestive of the presence of suboptimal results associated with a high risk of persistence or recurrence of symptoms.

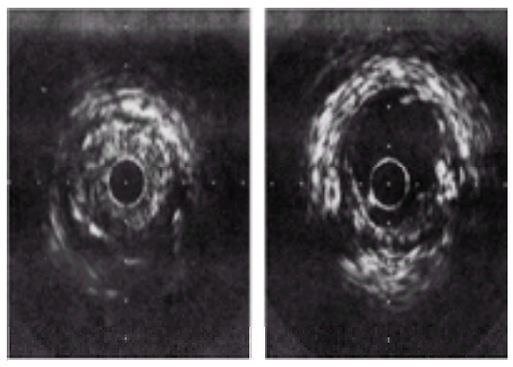
Until recently, neointimal proliferation was thought to be the predominant mechanism of restenosis after angioplasty and atherectomy. Studies of the peripheral arteries using IVUS imaging demonstrated that negative remodeling, or localized shrinkage of the vessel wall, was the primary mechanism of restenosis (62,115). Observations in patients who underwent repeat percutaneous coronary angiography supported this concept. In follow-up ultrasonographic examinations, a decrease in EEM area and an increase in plaque area were observed at the site of intervention. Decrease in EEM area caused 70% of lumen loss, whereas neointimal proliferation contributed to only 23% of the loss after percutaneous transluminal coronary angioplasty (PTCA). Late loss was correlated more strongly with the change in EEM area than with the change in plaque area (63). In a unique systematic serial study, 57 patients were examined by IVUS before and immediately after balloon angioplasty or atherectomy, and again after 24 hours, 1 month, and 6 months (114). The lumen area continued to enlarge during the first month after the intervention but decreased significantly at 6 months. The changes in EEM area or vessel area corresponded to those in the lumen area, with EEM area increasing in the first month and decreasing at 6 months. Plaque area, on the other hand, steadily increased from the immediately postintervention image to the 6-month follow-up image. The changes in lumen area correlated strongly with the changes in EEM area (r = .72, p = .0001). Correlation of the change in the plaque area with lumen loss was less impressive (r = .34, p = .0008). The findings of these studies indicated a complex remodeling response after nonstent percutaneous coronary interventions. Bidirectional changes of the vessel (EEM) area and intimal hyperplasia contributed to the late lumen loss.

Unlike restenosis after angioplasty or atherectomy, restenosis after stenting is primarily due to neointimal proliferation. In a serial ultrasonographic study, late lumen loss correlated strongly with the degree of in-stent neointimal growth (r = 0.98) (116,117). In another serial ultrasonographic study, the area within the stent did not change over time, which indicates that stented segments are not affected by recoil or negative remodeling over time (116). Resistance to constricting forces combined with the greater initial lumen expansion accomplished with stenting results in a lower net restenosis rate than occurs with angioplasty or atherectomy. The severity of intimal proliferation correlated with the preinterventional plaque burden (118). Although positive remodeling was associated with in-stent intimal hyperplasia, other studies demonstrated no such correlation (71,119). New insights into the mechanism of restenosis provided by IVUS explain the lower restenosis rate observed in randomized multicenter studies comparing balloon angioplasty and stent implantation (120,121). Other phenomena observed by ultrasonography may also play a role in determining the outcome after coronary interventions. The relatively poor correlation between angiographic and ultrasonic dimensions after angioplasty raises a provocative issue.

Response to various percutaneous interventions and development of restenosis have been correlated with remodeling. The response of the coronary segment to balloon dilatation appears to be linked to the direction of remodeling. The absolute lumen gain achieved with balloon angioplasty did not differ significantly for lesions with positive and negative remodeling, but differences were seen in the mechanism of lumen gain. Stretch of the EEM area was significantly larger in the group with wall shrinkage than in the group with compensatory enlargement. Subsequent lumen loss secondary to elastic recoil was not significantly different for the two groups (69). The direction of remodeling also affects outcome after percutaneous interventions. Target vessel revascularization after nonstent interventions was more frequently observed in lesions with positive remodeling (70). This effect of positive remodeling on target lesion remodeling was not observed in one report of stented segments (71). Conflicting reports have been published regarding the relationship between extent of remodeling and neointimal proliferation after coronary stenting (72).

Guidance of Directional Atherectomy

Although vessel stretch contributes to lumen enlargement, in DCA plaque removal is the primary aim of luminal enlargement (57,58) (*e*Fig. 85.0.24). Ultrasonographic studies, however, revealed that despite a successful angiographic result after atherectomy, 40% to 60% or more of the cross-sectional vessel area at the target site was still occupied by atheroma (122,123). Pre-DCA ultrasonography provides information about location, eccentricity, and calcium content of the plaques. Repeated ultrasonographic examinations during the procedure allow the operator safely to maximize plaque removal. However, only limited data are available suggesting that ultrasonographically guided DCA leads to stent-like results with comparable long-term outcome.



***e*FIGURE 85.0.24** Intravascular ultrasonographic images taken before and after directional coronary atherectomy. **Left:** A bulky plaque is illustrated. **Right:** Greater than 70% of the atheroma has been removed using a directional coronary atherectomy device.

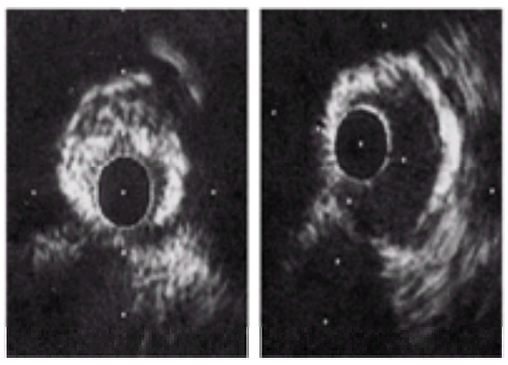
Angiographically guided DCA was not proven superior to conventional balloon angioplasty in two large prospective trials conducted in the early 1990s (124,125). Studies of “optimal” atherectomy showed superiority of DCA in achieving larger lumens (122). Ultrasonography can define plaque location and circumferential distribution, potentially improve preprocedural planning, and aid intraprocedural decision making, which results in maximal plaque removal (59). Preinterventional ultrasonographic imaging is the most sensitive method for detecting, localizing, and quantifying calcium deposits (44,45). Subendothelial plaque calcium has been shown to be an important factor that limits tissue retrieval and increases the incidence of procedural complications (57,59). Efficacy of new titanium cutters in ablating calcium has been anecdotally reported, but controlled studies are not yet available. Preinterventional ultrasonographic information also helps the operator target the cutter to the plaque using anatomical landmarks and side branches. Studies demonstrate that the use of ultrasonography during atherectomy results in a more aggressive strategy and leads to greater plaque removal and a larger final lumen diameter (126). The results of the Optimal Atherectomy Restenosis Study registry support the hypothesis of an improved immediate result (angiographically determined residual diameter of stenosis of 8 11%) and a high initial procedural success with aggressive ultrasonographically guided atherectomy (122). Despite these stent-like immediate results, however, a relatively large residual plaque area (mean of 58%) was still observed by ultrasonography after atherectomy. Some investigators have proposed that a larger lumen after atherectomy would in turn result in a lower restenosis rate. In the Adjunctive Balloon Angioplasty After Coronary A therectomy Study, which compared DCA alone to DCA plus PTCA, ultrasonographic guidance allowed operators to perform very aggressive atherectomy with residual plaque occupying 46% of the vessel area with stand-alone DCA (127). Similarly, in the Stent versus Directional Coronary Atherectomy Randomized Trial, operators used serial ultrasonographic imaging and achieved a residual plaque burden of 52%. In this randomized study, restenosis was significantly lower in the group receiving aggressive IVUS-guided atherectomy (16%) than in those undergoing stenting (33%) (128).

Despite the promising results from preliminary studies of a novel device that combines an ultrasonographic transducer with an atherectomy catheter, no commercially available devices enable the operator to visualize the plaque located directly in the path of the atherectomy cutter (29).

Guidance of Rotational Ablation

Rotational ablation is effective in the treatment of heavily calcified coronary arteries. IVUS is helpful in detecting and quantifying the extent of calcification. It is also useful in the assessment of outcome and in determining type and size of other interventional devices that need to be used.

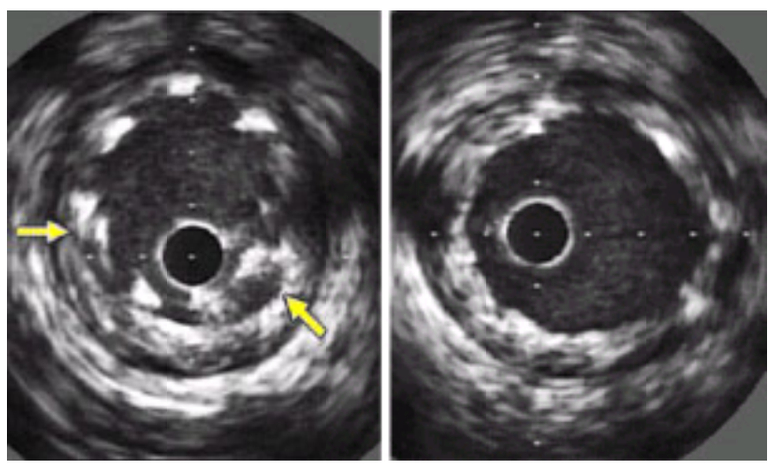
Rotational ablation uses a high-speed diamond-coated burr to debulk atheromas within coronary stenosis. Angiographically and ultrasonographically guided studies have demonstrated the efficacy of this approach at removing calcium from stenotic vessels (129,130 and 131). As noted previously, however, a poor correlation exists between ultrasonography and fluoroscopy in assessment of the presence and extent of calcification. Angiography cannot distinguish subendothelial from deep calcium. Accordingly, the demonstration of heavy vessel calcification by ultrasonography permits the operator to use rotational ablation in settings in which it may be particularly efficacious (eFig. 85.0.25). Precise guidelines for ultrasonographically directed rotational ablation have not been defined. In centers performing preinterventional IVUS, rotational ablation is commonly used if the arc of superficial calcium exceeds 180 degrees in multiple cross sections along the stenotic segment. Vessels revascularized using rotational ablation frequently have diffuse disease, and the “normal” dimension can be difficult to determine angiographically. Ultrasonography can be performed to size the vessel and determine the largest burr that can be safely used. The residual lumen after rotablation is usually round or ellipsoid, and the resulting lumen may have a 15% to 20% greater area than the largest burr used, presumably due to lateral movement of the burr during the procedure. Rotational atherectomy is also effective in treating “soft” plaques such as the hyperplastic response within stents observed in diffuse restenotic lesions (130).



***e*FIGURE 85.0.25** Intravascular ultrasonographic images taken before and after rotational ablation. **Left:** A heavily calcified lesion is illustrated. **Right:** The lumen is enlarged by removal of calcium using the Rotablator. The dark oval structure at 6 to 7 o’clock is a diagonal side branch of this left anterior descending coronary artery.

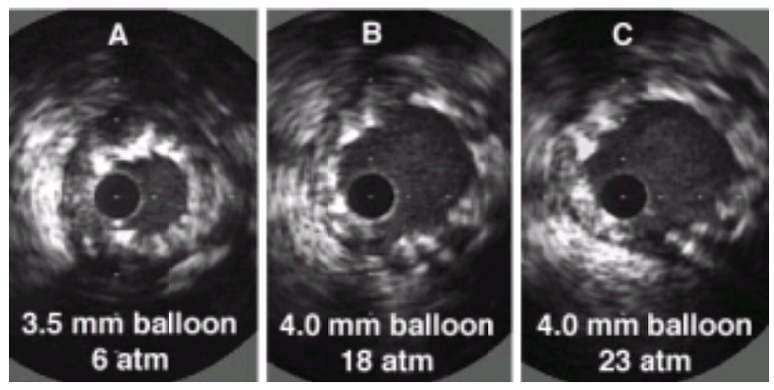
Coronary Stent Deployment

IVUS has significantly influenced the application of stenting in the treatment of coronary disease (132,133,134 and 135). The studies leading to U.S. Food and Drug Administration approval of the articulated slotted-tube stents were performed using conventional balloon pressures of 6 to 10 atm (120,121). To prevent subacute stent thrombosis, patients received aggressive anticoagulation therapy during and immediately after the procedure using both antiplatelet and antithrombotic agents. Although these preapproval studies demonstrated a reduction in the restenosis rate compared to balloon angioplasty, a high prevalence of hemorrhagic complications, longer hospital stays, and sometimes fatal subacute stent thrombosis were important obstacles to widespread acceptance of stent implantation in the treatment of coronary artery disease.

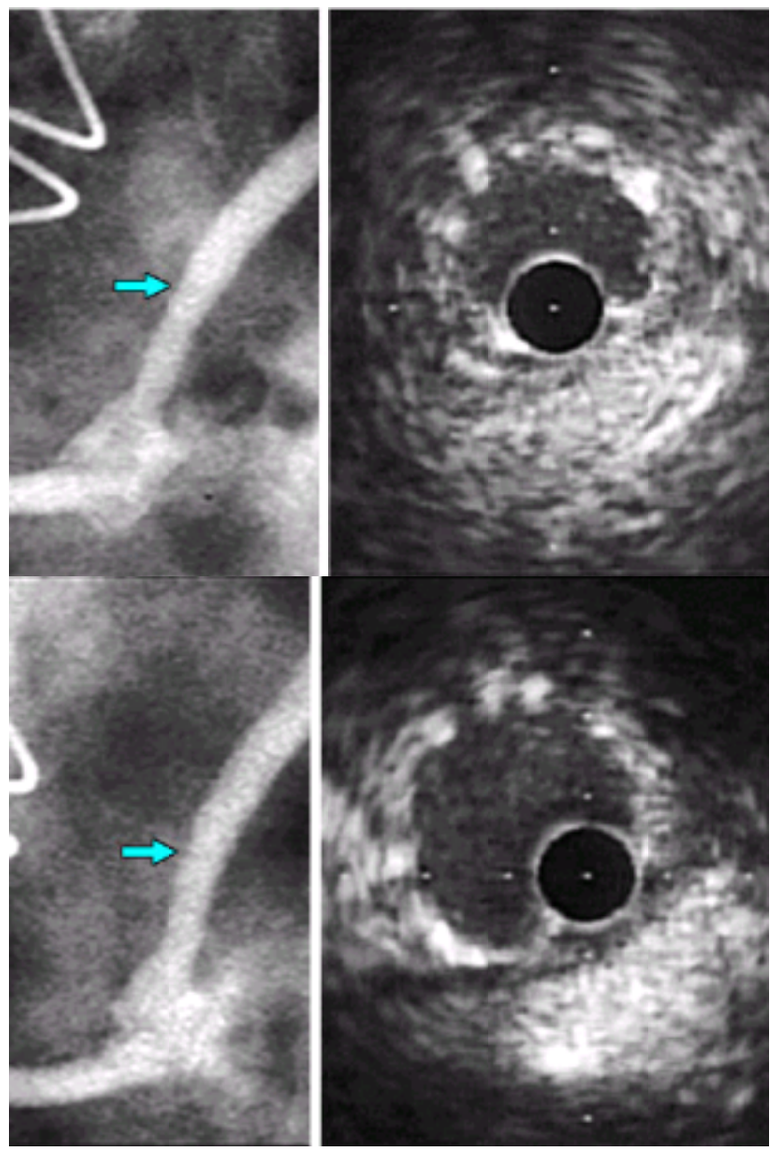


Intravascular ultrasound assessment of stent deployment. In the left panel, incomplete stent expansion is evident, which is improved after further balloon

dilatation.

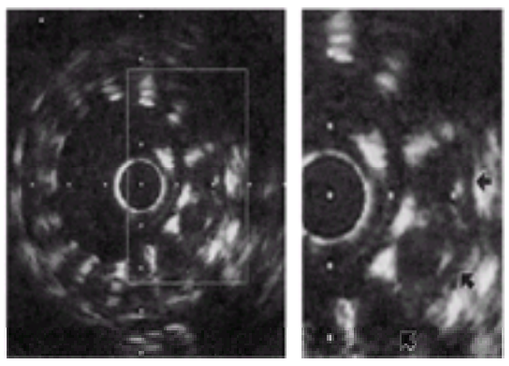


Intravascular ultrasound in stent deployment. These images show the effect of both increased balloon size and pressure on the size of the in-stent lumen.



Role of intravascular ultrasound in optimizing stent deployment. Although the angiogram shows minimal residual stenosis (A), the intravascular ultrasound lumen size is small (<5 mm^2). After further dilatation (B), the lumen area increased to >7 mm^2.

IVUS studies in the early 1990s demonstrated that the standard technique of stent deployment used in the pivotal randomized Stent Restenosis Study and Belgian-Netherlands Stent trial often resulted in failure of stent expansion or presence of unopposed struts or both (132,133). In all these studies inadequate expansion or strut apposition was observed in the majority of patients despite the excellent results shown on angiography. Because stents are porous structures, angiographic contrast can flow outside of a partially deployed stent and result in the angiographic appearance of full deployment, despite the presence of incomplete apposition (*e*Fig. 85.0.26). A pioneering IVUS study detailing the experience of Colombo et al. significantly altered the understanding of the optimal technique for stent deployment and prevention of subacute thrombosis (134). This large but nonrandomized study used routine IVUS imaging after angiographically guided stent placement and revealed an average ultrasonographically derived 51% residual lumen area stenosis. The authors frequently observed an absence of complete stent contact with the vessel wall (incomplete apposition) after angiographically guided low-pressure deployment. When apposition was incomplete, operators performed additional balloon inflations at higher pressures (typically 18 to 20 atm) or used a larger balloon (or both), which resulted in a larger in-stent lumen area. Interestingly, the final angiographic percent stenosis was negative (–7.0%). Using ultrasonography to guide deployment, this study reported a subacute thrombosis rate of only 0.3% when patients were given aspirin and ticlopidine hydrochloride but not warfarin sodium. It is now widely accepted that high-pressure deployment of the stents dramatically reduces the incidence of subacute thrombosis and obviates the need for immediate and long-term administration of antithrombotic agents.



***e*FIGURE 85.0.26 Left:** Incomplete apposition of a Palmaz-Schatz stent. **Right:** Enlargement of the area contained within the white rectangle. A false channel deep to the stent struts is evident (*black arrows*).

In the era of high-pressure stent deployment, the number of cases in which further interventions are triggered by ultrasonographic findings is certainly lower than initially reported. On the other hand, some observers have advocated routine high-pressure deployment without ultrasonographic imaging to achieve excellent procedural results and low subacute thrombosis rates (135). In the French registry, a subacute thrombosis rate of 1.6% in 1,156 patients is compelling evidence that high-pressure dilatation, supported by effective antiplatelet therapy (aspirin, ticlopidine), can achieve a substantial decrease in subacute stent thrombosis without ultrasonographic guidance (135). Despite the application of high-pressure balloon dilatation, however, ultrasonography frequently leads to further refinements of the result, most importantly an increase in the in-stent lumen area and decrease in residual stenosis at stent edges (136).

The additional lumen gain achieved with these further ultrasonographically driven interventions should be considered potentially useful, not only to eliminate subacute thrombosis but also to reduce stent restenosis. In the Milan experience, despite the high incidence of restenotic lesions, long lesions, small vessels with diffuse

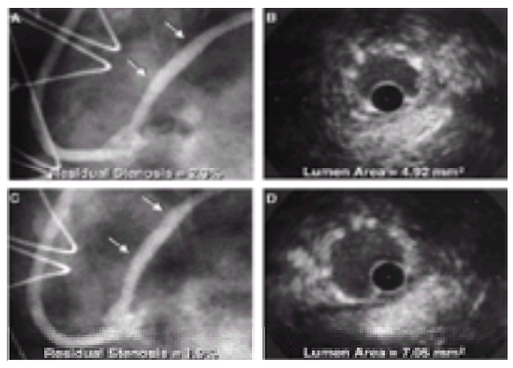
disease, and total occlusions, the overall angiographic restenosis rate was 21% and repeated interventions were required in 13% of patients (134).

Restenosis after stent implantation is strongly related to the in-stent lumen area. Achieving the largest lumen area in the stented segment within the confines of the vessel size is probably the most important antirestenosis strategy. Even after the routine use of high-pressure postdilatation, additional ultrasonographically guided inflations increase immediate lumen gain. The resultant larger lumen area may help to reduce restenosis rates. In a case-control study, patients who had optimum stent expansion according to predefined ultrasonographic criteria had an angiographically determined restenosis rate of 13.0% compared with 28.3% for those with suboptimal expansion (137). In another nonrandomized trial (Can Routine Ultrasound Influence Stent Expansion study) investigators assigned eight centers to perform ultrasonographic guidance and ten centers to perform angiographic guidance (138). In-stent lumen area was 0.9 mm larger in the ultrasonographically guided group and target vessel revascularization was reduced by 38%, from 14.9% to 8.9%.

Three multicenter randomized trials tested the hypothesis that increased in-stent lumen areas resulting from ultrasonographic guidance actually translate to lower target vessel revascularization rates. In the Optimal Coronary UltraSound trial, 550 patients were randomly assigned to procedures using either ultrasonographic or angiographic guidance. No significant difference was seen in restenosis rates for the two groups (139). The differences in stent dimensions between the IVUS and angiographically guided groups were smaller than in other trials, however. A smaller randomized trial (Restenosis after IVUS-Guided Stenting) enrolled 155 patients. An absolute reduction in target vessel revascularization rate of 6.3% was seen, but this difference did not reach statistical significance, mainly due to small sample size (140). In a larger randomized trial (Angiography versus IVUS-Directed Stent Deployment), 759 patients were randomly assigned to undergo procedures with either IVUS or angiographic guidance (141). Overall, a trend was seen toward improved 12-month target lesion revascularization rates in all groups in which IVUS guidance was used, but this trend did not achieve statistical significance (8% vs. 12%). A statistically significant difference in favor of IVUS guidance was seen in vessels with a reference diameter of less than 3.25 mm, in more severe lesions, and, in particular, in saphenous vein grafts.

Despite the improved understanding of stent deployment using IVUS, no consensus exists regarding the optimal procedural end points for ultrasonographically guided stenting. The goal of complete apposition of the stent struts to the wall is generally accepted. The criterion for optimal expansion is controversial, however. In their initial experience, Colombo et al. aimed to achieve 60% or more of the average reference lumen area, but later revised their target to 100% or more of the distal reference vessel area (134). The criteria developed in the pilot Milan experience have been revised and tested in the multicenter trial Multicenter Ultrasound Guided Stent Implantation in the Coronaries (142). Using optimal expansion criteria of 100% or more of the distal and 80% or more (for large vessels) or 90% or more of the average proximal and distal reference lumen areas, and a lumen symmetry index greater than 0.7, investigators achieved a subacute thrombosis rate of only 0.6% and restenosis rate of less than 10% in this trial. Other criteria based on the comparison of the smallest in-stent area to the areas of proximal or distal reference segments or to their average have been proposed. Interestingly, these procedural end points are not easy to achieve in most cases (134,137,141,142 and 143). In the Optimal Stent Implantation Trial investigators serially dilated each stent at 12, 15, and 18 atm and evaluated the result at each pressure level by quantitative angiography and IVUS. Ultrasonographic imaging documented gradual and marked increase in stent expansion with higher pressures, but these changes often were not apparent by angiography. In this study, end points of more than 90% of the average reference or more than 100% of the smaller reference were not achieved in half of the patients at an inflation pressure of 15 atm. At a pressure of 18 atm, these end points were attained in only 60% of patients (144). In the preliminary results of the Angiography versus Intravascular Ultrasound–Directed Stent Placement trial, the target end point of 90% or more of the distal reference was not achieved in two-thirds of the patients, and 27% of the patients required further intervention because of inadequate dilatation (141).

The predictive value of the stent-to-reference area ratio as an end point for stenting has been studied. In a study of 165 patients receiving one or two Palmaz-Schatz stents, the target vessel revascularization rate was 11% after 8 months (136). This adverse clinical outcome was best predicted by the value of the in-stent lumen area achieved at the end of the procedure (odds ratio, 1.4; 95% confidence interval, 1.1 to 1.9) and not by the ratio of stent to reference lumen area (odds ratio, 1.1; 95% confidence interval, 0.85 to 1.60). Revascularization procedures were required in more than 30% of patients with a minimum in-stent lumen area of less than 5 mm^2 but in only 3% of cases with a minimum area exceeding 9 mm^2. In other studies with larger cohorts of patients the conclusions were similar: Incidence of restenosis was inversely related to the absolute minimum in-stent lumen area (145,146). Most of the studies indicate that the end points of a predefined stent-to-reference area ratio are difficult to achieve and correlate weakly with stent thrombosis and restenosis rates. In-stent restenosis is mainly due to the extent of the neointimal proliferation, which can be measured accurately only by IVUS (147). The degree of intimal hyperplasia during the 9 months after stent implantation is independent of the final stent lumen size (148). Accordingly, in a given lesion restenosis occurs when immediate lumen gain is inadequate to accommodate the neointimal proliferation. Therefore, higher restenosis rates are common in smaller vessels and inadequately expanded stents. Although larger absolute in-stent lumen area is correlated with lower target vessel revascularization rates, the extent of stent expansion is limited by the size of the coronary artery. When the size of the vessel is taken into account, the incremental predictive value of ultrasonographic criteria diminishes (136). Nevertheless, the experience of the last decade demonstrated that IVUS is helpful in optimizing the assessment of the true vessel size and maximizing stent expansion safely (eFig. 85.0.27).

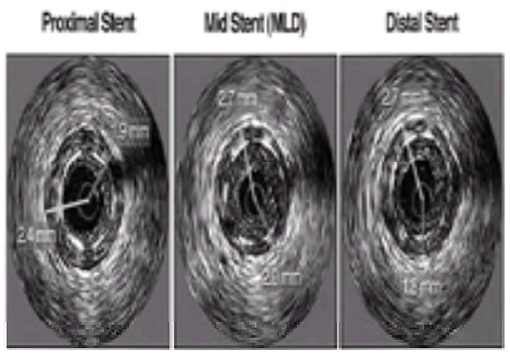


***e*FIGURE 85.0.27** Angiographic findings after stent placement can sometimes be deceiving. **A:** After stent placement, angiography shows excellent results with no residual stenosis of the stented segment (*arrows*). **B:** On interrogation by intravascular ultrasonography (IVUS), however, the stent is seen to be underexpanded with a suboptimal lumen area. **C:** When the stent was postdilated with a noncompliant balloon, the angiographic appearance did not change. **D:** On IVUS imaging, however, the lumen area is significantly increased.

In addition assessing final lumen area, stent expansion, symmetry, and strut apposition, IVUS is useful in evaluating the morphologic changes in the vessel wall at the edges of the stented segment, such as tissue prolapse, dissections, and so on. Some of these poststent morphologies partially obstruct the lumen and may increase the risk of stent thrombosis (134). Axial redistribution of plaque from the lesion into the reference segments contributes to lumen enlargement after stenting (149). To see a step down or areas of haziness at the edges of the stents is not uncommon. In a study of 201 stent patients, 31 segments of peristent angiographic haziness were detected. Of those, ultrasonographic imaging revealed an occult, moderately severe obstructive lesion in 15, a peristent wall injury in 14, and mild intimal thickening in the remaining two segments (150). The extent of neointimal hyperplasia at the stent margins has been linked to preexisting reference segment disease (151) (eFig. 85.0.17). Peristent wall injury and dissections are frequently seen by ultrasonographic imaging after high-pressure inflations. The natural history of the ultrasonographically detected edge tears, which are angiographically silent, appears to be benign, and they do not require further intervention (152).

Analysis of Brachytherapy Results

Intracoronary radiation is a promising therapy to decrease restenosis after percutaneous coronary interventions. Animal studies showing inhibition of neointimal formation were followed by randomized clinical trials demonstrating the reduction of restenosis by treating restenotic lesions with intracoronary brachytherapy (153,154). IVUS has been critical in understanding the effects of brachytherapy on the vascular wall. IVUS analysis of patients treated for in-stent restenosis corroborated angiographic data showing that intravascular brachytherapy is associated with a reduction in late lumen loss mainly through reduced neointimal hyperplasia (155). Serial ultrasonographic studies demonstrated that radiation treatment led to larger lumen areas after balloon angioplasty of *de novo* lesions (156). This gain was mainly due to vessel enlargement rather than plaque reduction. IVUS was pivotal in understanding the impact of radiation on neointimal growth and vessel size in different lesions (157). Ultrasonography has been helpful in documenting potential adverse effects of brachytherapy, particularly edge restenosis after radioactive stent implantation (158). Delivered dose homogeneity is an important issue when treating coronary segments with variable degrees of curvature, tapering, remodeling, and plaque extent, particularly with the application of beta radiation, which shows a rapid dose fall-off (eFig. 85.0.28). The difficulty in achieving adequate doses when treating long restenotic segments may explain the persistence of high rates of recurrences in these lesions (159). Dose-volume histograms obtained by ultrasonography have been implemented as a tool for dosimetry. Accordingly, a study involving 18 patients showed a wide range of dose distribution in the irradiated coronary segments and, in general, a lower than prescribed dose to the adventitia (160). Serial IVUS has also been used to study a phenomenon that has led to the withdrawal of radioactive stents due to a prominent reduction in lumen area at the stent edges, mainly due to intimal hyperplasia (161,162).

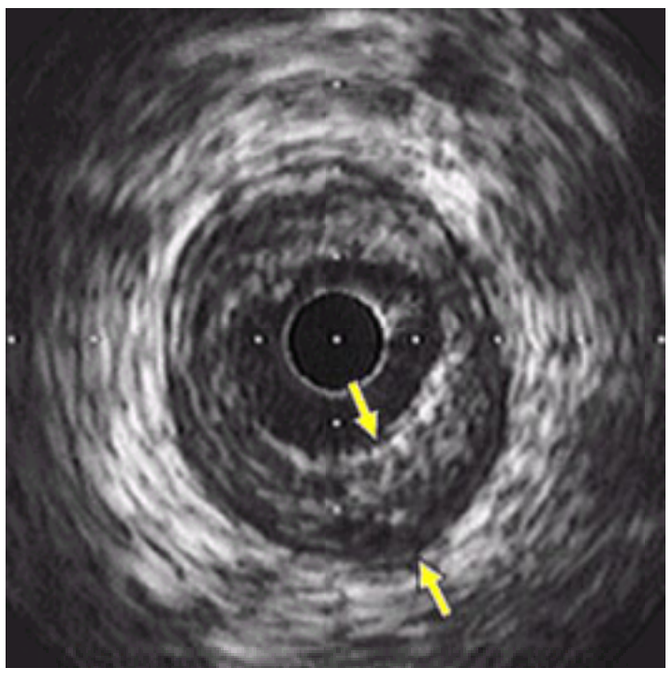


***e*FIGURE 85.0.28** An example of dose calculations for iridium-192 coronary brachytherapy based on intravascular ultrasonography. A survey of the treated segment is performed. At a minimum, the proximal, middle, and distal portions are measured. The example shows the minimum three images needed for prescription. The minimum radius from the center of the catheter to the external elastic lamina (EEL) (*blue lines*) and the maximum radius from the center of the catheter to the EEL (*gold lines*) are measured. The absolute maximum and minimum radii (2.7 mm and 1.8 mm, respectively, in this example) across the entire segment are noted. A prescription is calculated so that the dose at the maximum distance (radius) is 8 Gy, whereas that at the minimum does not exceed 30 Gy. If this is not possible, the dose at the minimum distance (radius) is prescribed to be 30 Gy and that at the maximum distance is less than 8 Gy. This latter circumstance arises when the ratio of the dose rate at the shortest radius to the dose rate at the longest radius exceeds 3.75. MLD, minimal lumen diameter.

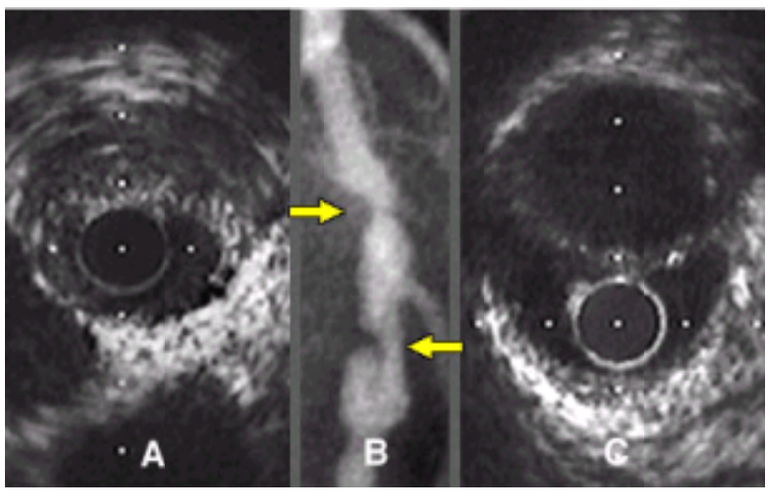
Future Directions

Tissue Characterization

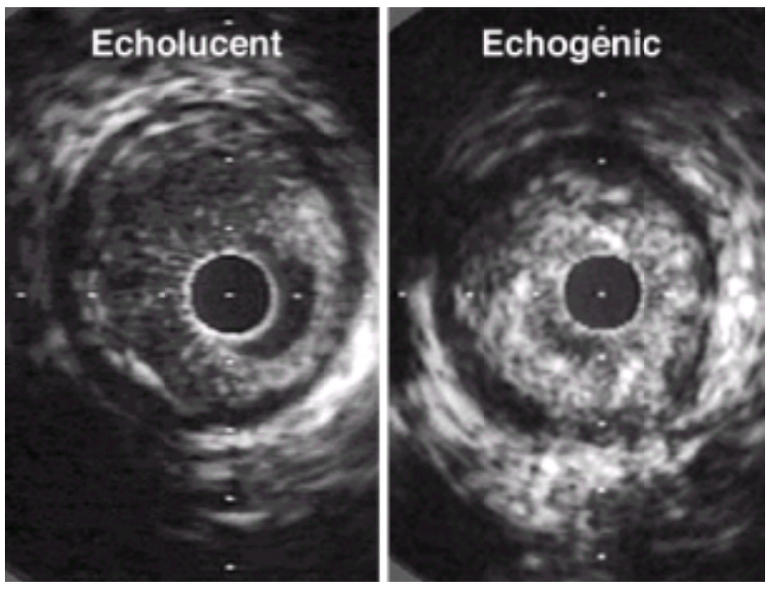
Accurate characterization of the atheroma contents *in vivo* will enhance the understanding of atherosclerosis and its complexity and heterogeneity. Conventional IVUS, although a powerful tool for tomographic imaging, is limited in delineating the plaque contents accurately. Analysis of backscattered ultrasonographic signals obtained directly from the ultrasonographic catheter before they are subjected to postprocessing has been used to perform “tissue characterization” of coronary plaques. Intrinsic characteristics of the backscattered ultrasonographic signals, including the amplitude distribution, frequency response, and power spectrum of the signal, convey specific information about tissue types (163). The use of computer-based analysis of the unprocessed radiofrequency backscatter to differentiate the histologic layers of the normal vessel wall remains investigational.



Plaque morphology. This image demonstrates a soft echolucent plaque.



Intravascular ultrasound interrogation of a complex coronary lesion. The proximal part of the lesion shows an eccentric soft plaque (A), whereas the distal end of the lesion (B) demonstrates rupture of the plaque with a double lumen.



Differences in lesion composition. Intravascular ultrasonography can characterize lesions into soft (echolucent) and fibrous (echogenic). Available evidence demonstrates that sonolucent lesions exhibit a high lipid content, whereas more echogenic lesions have greater fibrous tissue content.

In a study addressing the question of whether spectral analysis of unprocessed radiofrequency signal offers advantages over standard video densitometric analysis in identifying the morphology of coronary atherosclerotic plaques, regions of interest were imaged at 30 MHz from postmortem, pressure-perfused coronary arteries in saline baths. The analysis of the digitized radiofrequency data revealed parameters of spectral slope, *y*-axis intercept, mean power, and maximum power over a given bandwidth of 17 to 42 MHz. Lipid-rich areas, moderate and dense fibrotic tissue, and calcified deposits were differentiated (164). In an animal model of allograft rejection, conventional video images and radiofrequency signals were acquired from cross sections of the recipient and the allograft aortas. Radiofrequency attenuation measurements were more sensitive than visual or quantitative gray-scale analysis in differentiating the vessel wall changes of transplant vasculopathy (165). In another *in vitro* study, impedance as well as spectral analysis was used to differentiate lipid-rich plaques from fibrotic ones (166). In an attempt to better characterize the atheroma contents, mechanical properties of vasculature were assessed. In an *in vitro* study, IVUS elastography has been proposed as a technique capable of reflecting the mechanical properties of the vessel wall and characterizing different plaque components (167).

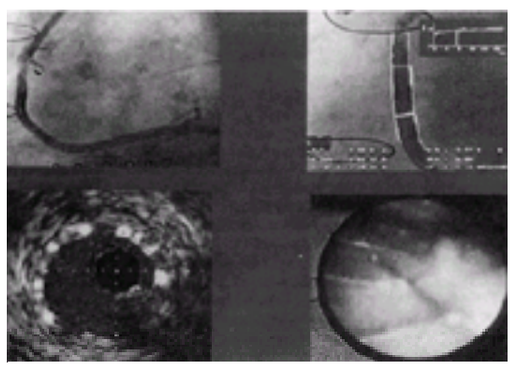
Three-Dimensional Reconstruction

Quantitative studies using IVUS require the identification of the luminal and medial-adventitial borders in image sequences. Traditional methods of border detection involve manual tracing of many IVUS images. Automated and semiautomated segmentation techniques have been developed to replace the tedious and time-consuming method of manual tracing (168). Three-dimensional reconstruction using automated pullback systems and electrocardiographic gating have been partially successful. However, tortuosity of the coronary arteries, limitations of automatic pullback and border detection, and the additional time needed prevent it from being a widely used clinical tool.

Segmenting borders manually in three-dimensional image sequences is laborious; therefore, automated or semiautomated techniques can reduce not only observer variability but also the time needed for analysis. The development of three-dimensional segmentation techniques, which take advantage of the similarity of borders between frames, is a recent development in the movement toward routine automatic quantitative analysis in catheterization laboratories (169,170). Three-dimensional reconstruction of IVUS data has been proposed as a means to facilitate understanding of the spatial relationship between the structures within different tomographic cross sections, particularly after percutaneous interventions (171). A prerequisite for most three-dimensional reconstruction techniques is the use of a motorized pullback, which allows the acquisition of successive cross sections separated by known distances. Other three-dimensional IVUS reconstruction techniques, however, track the transducer as it passes through the vessel. This procedure negates the requirement of a pullback device (168). Electrocardiographic gating was proposed to improve accuracy of volumetric assessment by registering similar points of the cardiac cycle in every image (172). Despite the promise of three-dimensional reconstruction, many unresolved problems remain. The algorithms applied for three-dimensional reconstruction do not consider the presence of curvatures of the vessel and assume that the catheter passes in a straight line through the center of consecutive cross sections. The systolic expansion of the coronary vessel and the movements of the catheter within the vessel during the cardiac cycle also generate characteristic artifacts. Despite these limitations, this technique remains the best method for volumetric plaque determination and has become the gold standard for assessment of the efficacy of interventions aimed at reducing the progression of atherosclerosis and preventing restenosis (173). Simultaneous digitization of biplane fluoroscopic tracking of the radiopaque transducer and catheter tip has the potential to overcome some of these limitations but at present is practical only for small-scale research studies (174,175 and 176). A novel technique of blood flow measurement simultaneous with IVUS imaging has been described. Color mapping of flow velocities and decorrelation of the radiofrequency signals were used for volumetric blood flow measurements (177).

CORONARY ANGIOSCOPY

Coronary angioscopy uses visible light conducted through fiberoptic filaments to obtain direct visual information of the surface characteristics and intraluminal morphology of the human coronaries *in vivo*. The images appear in full color on a television monitor, which enables detailed examination of the hue of the target lesion and associated plaques. Angioscopy allows the differentiation of platelet-rich thrombus from fibrin-rich thrombus and provides evidence of atheroma rupture, intraplaque hemorrhage, and coronary dissection. Accordingly, this diagnostic modality yields information on the pathogenesis of acute coronary syndromes not obtainable by any other technique (eFig. 85.0.29).



***e*FIGURE 85.0.29** Angiographic, ultrasonographic, and angioscopic appearance of a Palmaz-Schatz stent implanted in a saphenous vein graft. Both angioscopy and ultrasonography confirm the full apposition of the stent struts to the vessel wall.

Equipment and Technique

Development of an effective coronary angioscope is technically challenging. It should be small and flexible to steer easily and safely over a guidewire through tortuous coronary segments. A daunting challenge to device design and profile is the necessity for a multitask catheter. All angioscopes require a blood-free field for visualization of the arterial wall. The coronary lumen must be cleared of residual blood by continuous irrigation.

A variety of design iterations were used in initial animal and human investigations. One angioscope uses an occluding balloon to clear the examination field. Another type of angioscope uses a probing catheter to introduce the device. A multifiber imaging bundle and the light source provide surface images in the blood-free coronary segments.

The procedural aspects of coronary angioscopy are similar to those of other interventional techniques. After heparin administration, the operator places a conventional guidewire subselectively in the distal portion of the target coronary through a standard angioplasty-guiding catheter. The angioscope is attached to the light source, camera, and irrigation system and then advanced over the guidewire or through the probing catheter until it is just proximal to the target segment. The balloon is gently inflated to occlude the lumen while clear irrigation solution is infused distal to the balloon or through the catheter. The longitudinal axis of the vessel is examined by advancing and withdrawing the fiberoptic bundle. Because no coronary flow is permitted during examination, the operator must complete the examination quickly to minimize ischemia. Despite the inherent difficulties of maneuverability and induced ischemia, the monorail design and the moderate size of the angioscope allow the operator to obtain high-quality images with reasonable speed and safety.

Clinical Applications

Coronary angioscopy enhances the understanding of the atherosclerotic process by showing the surface characteristics of the atheroma. Angioscopy provides the opportunity to directly observe the unstable plaque, saphenous graft lesions, and different types of thrombi and lesions of the allograft vasculopathy. It has also been used in the setting of percutaneous coronary interventions.

Plaque Characterization

Coronary angioscopy was first performed during cardiac surgery and demonstrated important differences in the intraluminal appearance of stable versus unstable coronary atheromas (8). Later studies that used percutaneous angioscopy also demonstrated the high prevalence of thrombus-containing lesions in patients with unstable angina but not in those with stable angina (178). On the other hand, plaque disruption and thrombus were absent in a considerable number of patients with unstable angina who underwent imaging with angioscopy (179).

In addition to identifying the presence of thrombus, studies have documented the ability of angioscopy to differentiate grayish-white platelet-rich thrombus from red fibrin-rich thrombus, depending on the color assessment by the operator (180). This differentiation, however, is confounded by the hardware-induced chromatic

distortions and the subjectivity of human color perception. Quantitative colorimetric angioscopic analysis was proposed as a more objective and reproducible analytical tool (181).

Angioscopy can distinguish other surface features of coronary atheromas. Stable plaques are recognized by their elevated contour, smooth configuration, and yellowish-white color. In a study of 199 patients, those with predominantly yellow plaques were found to have higher levels of low-density lipoprotein cholesterol and apoprotein B lipoprotein (182). In a multivessel angioscopic study of patients with myocardial infarction, all three major epicardial coronary arteries were found to be diffusely diseased with multiple yellow, although nondisrupted, plaques (vulnerable plaques) (183). These findings suggest that acute myocardial infarction may represent the pan-coronary process of vulnerable plaque development. In an interesting study by Van Belle et al., 56 patients underwent angioscopic imaging between 24 hours and 4 weeks after myocardial infarction. Their findings suggest that healing of the infarct-related lesion requires more than 1 month and that “unstable” yellow plaques and thrombus are common within the first month after infarction (184).

Angioscopy can also identify morphologic features of degenerative saphenous vein grafts. In such vessels, angiography often reveals complex lesions with irregular borders and multiple filling defects. Necropsy studies have shown that such lesions often contain friable and sometimes frankly necrotic atheromatous material, intraluminal thrombus, or both. Angioscopic studies demonstrated that vein grafts frequently contained friable plaques even when angiography did not reveal the complexity. These studies suggest that surface morphology of the atherosclerosis of the native coronary arteries and saphenous vein grafts are similar except that a high incidence of friable plaque is seen in the latter group (185).

Observations during Coronary Interventions

Assessment of lesions before or after coronary intervention represents the most commonly reported application of coronary angioscopy. Angioscopy after balloon angioplasty demonstrates that dissections and thrombus are present in almost all cases, although angiography often shows neither luminal irregularities, tears, nor filling defects (178). In a comparative study of angiography and angioscopy, the specificity of angiography for identifying thrombus was high (100%), but the sensitivity of angiography (compared to angioscopy) was only 19.4% (186). Acute closure after angioplasty may be secondary to dissection, thrombus formation, coronary spasm, vessel wall hematoma, or elastic recoil, or combinations of these mechanisms. Several small studies have reported that, once acute closure has occurred, angioscopy can correctly identify whether thrombus or dissection is the primary mechanism of early abrupt closure (178,186,187).

Angioscopy has been used after other types of transcatheter procedures, including DCA and rotational ablation. After plaque removal by DCA, angiography often reveals an enlarged lumen with a smooth contour. Angioscopy has demonstrated, however, that the intimal surface is often very irregular with pieces of atheromatous material protruding into the lumen. Finally, angioscopy has provided information about the human endothelial response to implanted stents. Ueda et al. performed angioscopy in 14 patients immediately after stent deployment, at 8 to 45 days after the procedure, and again at 65 to 142 days (188). These investigators found that completion of neointimal coverage required approximately 3 months in the majority of patients.

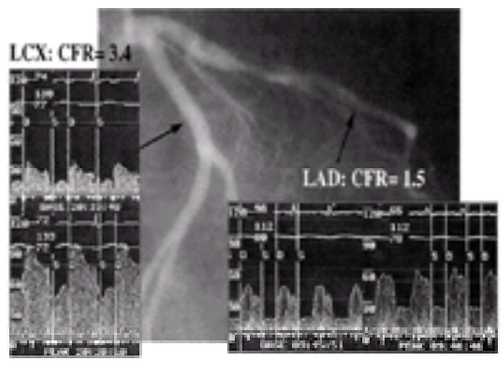
Limitations of Coronary Angioscopy

Despite recent technical advances, angioscopy is still limited to the proximal and mid-portion of relatively straight coronary arteries. Due to the present limits of size and flexibility, advancing angioscopic catheters through tortuous coronary arteries into small distal branches remains difficult. Furthermore, the development of ischemia in some patients during balloon inflation limits the time of examination. Angioscopy shows only the surface characteristics of plaques and cannot discern the underlying atheroma morphology. Accordingly, whether visualization of surface anatomy alone warrants the time, expense, and risk of angioscopy remains unproved. Lastly, the occlusion of coronary flow may produce important imaging artifacts. Angioscopy frequently observes flaps or fronds of tissue protruding into the lumen. This appearance, however, may represent an artifact produced by depressurization of the coronary by the occlusion balloon and may not reflect actual *in vivo* pathophysiology. Another important issue in the application of coronary angioscopy is interobserver variability. Interpretation of the angioscopic images may vary among observers. A study of the European Working Group on Coronary Angioscopy demonstrated that, although interobserver agreement is acceptable in the identification of red thrombus and dissection, wide interobserver variability is seen in other angioscopic diagnoses (189).

ASSESSMENT OF CORONARY CIRCULATION

The myocardium is supplied by an extensive network of vascular channels. Epicardial coronary arteries originate from the aorta as large trunks and decrease in size as they give branches. Epicardial coronary arteries do not create any significant resistance to coronary blood flow. They act as conduit vessels. The smaller arteries, arterioles, and capillaries constitute the distal vascular bed or microvasculature and act as resistance vessels. In contrast to epicardial coronary arteries, smaller arteries and arterioles change in size—dilate or constrict—in response to a variety of stimuli. This characteristic makes the microvasculature the regulator of coronary blood flow. Coronary blood flow is influenced by various structural, humoral, neural, and hemodynamic factors. In this environment of multiple interactions and continuously changing demands, coronary blood flow is kept at an adequate level in a wide range of driving pressures. Coronary vasculature maintains optimum myocardial perfusion through autoregulatory mechanisms.

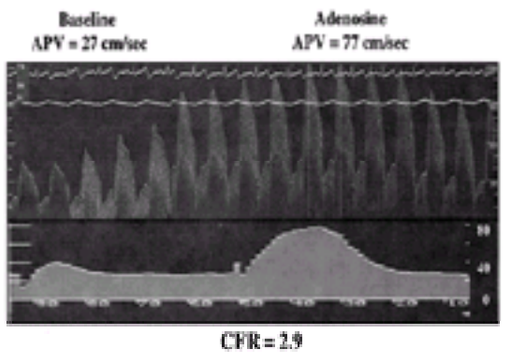
Flow patterns differ substantially within different coronary branches (eFig. 85.0.30). Under normal conditions, flow in the left coronary and its branches occurs primarily in diastole, whereas the right coronary exhibits a more homogeneous distribution with more continuous flow throughout the cardiac cycle (190). A predominant diastolic component is observed only in the most distal branches of the right coronary artery (posterolateral and descending posterior arteries) (191). Pulsatile flow is presumed secondary to the presence of a “reservoir” that is compressed during the systolic phase of the cardiac cycle and refills during the after diastole.



***e*FIGURE 85.0.30** Flow velocity measurements during baseline and hyperemia in the mid left anterior descending coronary artery (LAD) and in the proximal left circumflex artery (LCX). Note the blunt flow velocity response in the LAD, with a coronary flow reserve (CFR) of 1.5, and the normal flow increase in the left circumflex (CFR of 3.4). Relative flow reserve can also be calculated.

Coronary Flow Reserve

The principle of flow reserve was established originally by the work of Gould et al. (192). In the normal coronary artery, the distal arteriolar bed actively dilates in response to increased metabolic demands (e.g., exercise), producing a two- to sixfold increase in coronary blood flow (eFig. 85.0.31). In the presence of a hemodynamically significant epicardial coronary stenosis, vasodilatation of the microvasculature occurs in a progressive fashion to compensate for the flow limitation created by the stenosis. The vasodilatation maintains a stable level of coronary blood flow. Eventually, increasing epicardial narrowing exhausts the vasodilatory capacity of the microvasculature and leads to inducible myocardial ischemia (eFig. 85.0.30). The term *coronary flow reserve* (CFR) refers to the maximum vasodilatory capacity of the coronary vasculature in response to demand (hyperemic stimulus). This capacity is usually expressed as the ratio of maximum hyperemic blood flow to basal flow. If all measurements are obtained after maximum vasodilatation of the epicardial coronary arteries by nitroglycerin, the cross-sectional area of the epicardial vessels does not change any further. Thus, the ratio of velocities is equal to the ratio of coronary flows, and the terms *coronary flow reserve* and *coronary velocity reserve* can be used interchangeably.



***e*FIGURE 85.0.31 Top:** Progressive flow increase after injection of adenosine, 18 g, into the left main coronary artery. Note the rapid peak and the short duration of action, which make adenosine the ideal drug for repeated measurements. **Bottom:** Velocity trend, showing the stability of the basal flow velocity and the duration of the peak effect (approximately 30 seconds). APV, average peak velocity; CFR, coronary flow reserve.

The presence of a flow-limiting stenosis in a major epicardial vessel generates a pressure drop across the stenotic lesion, which is the result of viscous and turbulent resistances. In the presence of moderate or severe narrowings, the resting flow remains unchanged. Only very severe stenoses (greater than 90% diameter reduction) produce a pressure drop reduction in blood flow during normal resting conditions. Less severe stenoses (40% to 90% diameter stenosis) limit the maximum increase in blood flow in response to demand, which results in a reduction in coronary flow reserve (3,4).

Maximal Hyperemia

Maximal hyperemia can be induced by transient coronary occlusion or pharmacologic agents (193). Iodinated contrast media, which was used in the past, does not produce maximal vasodilatation. Likewise, the nitrates predominantly affect large-conductance vessels and do not consistently induce maximal flow increase. Continuous intravenous infusion of an adequate dose of dipyridamole results in maximal coronary vasodilation, but it has the disadvantage of having a relatively long duration of action. An 8- to 12-mg dose of intracoronary papaverine hydrochloride is equivalent to an intravenous infusion of dipyridamole in a dose of 0.56 to 0.84 mg per kg of body weight (194). In dogs, a high-rate infusion (600 g per minute) or a large intracoronary bolus of adenosine triphosphate (ATP) or papaverine has been shown to induce the same flow increase as a 15-second occlusion of the coronary artery (195) (eFig. 85.0.31). These results have not been confirmed using similarly large, clinically applicable doses of ATP or adenosine (100-g bolus) (196). Intracoronary adenosine or ATP does not induce significant changes in heart rate or blood pressure and does not prolong the QT interval, so that the potentially dangerous ventricular arrhythmias occasionally observed after papaverine are avoided (197). However, the time from intracoronary injection of adenosine to peak effect and the total duration of the hyperemic response is much shorter (198). A continuous intravenous infusion of 140 g per kg per minute of adenosine also induces maximal coronary vasodilatation but may produce mild hypotension, bradycardia, flushing, chest discomfort, headache, dyspnea, or atrioventricular block (199). In view of the high safety profile, absence of side effects, and ease of use, low-dose intracoronary adenosine is the most frequently used agent to induce maximal hyperemia. The intra coronary dose of adenosine is 18 to 48 g for the left coronary artery. A lower dose (12 g) should be used initially for the right coronary artery to reduce the risk of sinus node or atrioventricular node depression. If a guiding catheter with side holes must be used, only a fraction of the total dose can be delivered into the coronary artery. Intravenous adenosine administration is the best alternative in this setting, although some investigators have recommended increasing the intracoronary dose threefold (200).

DOPPLER CORONARY FLOW MEASUREMENTS

The development of small intracoronary devices incorporating a Doppler flow transducer has made *in vivo* physiologic assessment of coronary blood flow feasible during diagnostic or therapeutic catheterization. Doppler flow probes are commonly used to evaluate ambiguous lesions and to determine the success of coronary interventions at restoring normal flow reserve.

Equipment and Technique

A change in frequency occurs when a source and receiver of electromagnetic radiation or sonic energy move relative to each other, a phenomenon known as the *Doppler effect*. This change in frequency due to the relative motion between source and receiver is called the *Doppler shift*. Motion that reduces the distance between the energy source and receiver raises the frequency, whereas motion that increases the gap lowers the frequency. The magnitude of the Doppler shift is proportional to the velocity and direction of motion. Electronic processing of signals can precisely measure this effect and thereby determine the velocity at which the two objects move relative to each other. The principles of Doppler flow measurement are further described in Chapter 51.

The first probe designed to measure intracoronary flow velocity consisted of a transducer mounted on a Sones-type angiographic catheter. Subsequently, technical developments yielded probes designed for subselective intracoronary placement. The initial devices were relatively large (3 Fr) and used a transducer mounted either on the side or at the tip of the catheter. Because of size considerations, these devices could sample flow velocities only in the largest portions of the proximal coronary artery. The Millar device (Millar Instruments, Houston, TX) was the most widely used due to its flexibility and compatibility with a guidewire. It was designed to minimize the angle between the ultrasonic beam and the centerline of the intravascular flow profile, which thus allowed a close approximation of the maximal velocity.

Commercial development has led to the introduction of a miniaturized Doppler-equipped guidewire, called the JOMETRICS FloWire (JOMED). This device consists of a 0.014-in. steerable, 175-cm-long, flexible guidewire with handling characteristics similar to those of angioplasty wires and a 12-MHz piezoelectric transducer integrated into the tip. The smaller profile allows the operator to advance the device into distal coronary segments and beyond stenoses. In addition, the guidewire device accommodates over-the-wire or monorail balloon angioplasty systems and thus enables diagnostic and therapeutic procedures to be performed without exchanging the wire. The FloWire transducer uses a pulsed waveform Doppler system that samples at 5.2 mm beyond the guidewire tip. It samples a relatively large blood volume by using an ultrasonic beam that diverges at an angle of 14 degrees on either side of the centerline of flow. The sample volume is approximately 0.65 mm thick and 2.25 mm in diameter. In contrast to earlier catheter-mounted probes, the Doppler guidewire system uses fast Fourier transform signal processing (201), generating approximately 90 spectra per second. The Doppler guidewire is attached via a sterile cable to a console that displays the flow signal pattern and generates a superimposed envelope tracing that depicts the relative contributions of systolic and diastolic flow and continuously updates the measurements of peak velocity, averaged over two consecutive beats.

This system has been validated in *in vitro* and *in vivo* models by comparison with electromagnetic quantitative volumetric analysis (202). This study has shown that in vessels of less than 7.5 mm, the blood flow velocity measurements by the Doppler guidewire system had a close correlation (r^2 = 0.85 to 0.99) to measured flow volumes. The safety of using this device to obtain Doppler flow measurements has been demonstrated in a study involving 906 patients. Most of the complications (bradycardia, atrioventricular block) resolved rapidly without sequela. They were largely due to the concomitant use of adenosine (203).

Coronary Flow: Normal and Abnormal

Pulsatile Coronary Flow

The pulsatile pattern of flow is altered in the presence of a hemodynamically significant narrowing, which depresses the diastolic component. Experimental and intraoperative human studies have demonstrated the change in the diastolic flow in the presence of a significant epicardial stenosis (190,204,205). Unfortunately, the applicability of this phenomenon in clinical practice is limited because of the large variability of this index. The diastolic to systolic velocity ratio is influenced by changes in myocardial contractility, site of measurement, and artifacts. The flow patterns in other vascular structures of the heart are variable. The venous flow pattern consists mostly of a systolic component. Saphenous vein grafts and the arterial conduits behave according to the pattern of flow in the native artery to which they are anastomosed (206). Changes in cardiac function may affect the flow pattern, for example, left bundle branch block may delay left ventricular relaxation and impair early diastolic blood flow (207).

Characteristic flow patterns have been described in particular clinical settings. A predominantly negative systolic flow velocity and rapid flow velocity deceleration have been identified as a typical flow pattern in patients with slow flow or no reflow phenomena after percutaneous coronary interventions (208,209). A specific flow pattern has been described in patients with myocardial bridging. It consists of accelerated flow velocity and rapid deceleration in early diastole (fingertip phenomenon) with reduced systolic antegrade flow or retrograde flow in the proximal segment, more evident after administration of nitrates (210). The Doppler guidewire device can also identify reverse coronary flow, such as collateral flow from other vessels (211).

Proximal versus Distal Coronary Flow

The normal coronary arterial tree maintains relatively constant flow velocities despite the presence of multiple branches originating from the main coronary artery throughout its length (212). A marked difference in the flow velocities across a stenosis was thought to have hemodynamic significance. A high proximal to distal velocity ratio (greater than 1.7) has been proposed as a marker of severe flow-limiting epicardial stenoses (190). Basal and hyperemic flow velocity in “normal” arteries, however, shows large variability leading to inconsistencies in the proximal-to-distal velocity ratio (213). In clinical studies, this index was shown to have no predictive value for post-PTCA outcome.

Continuity Equation

The continuity equation that is most frequently used in the calculation of the valve areas is based on the concept that the volume of blood in the proximal vessel must reach the distal segment, so that the velocity measurements in a reference segment and across the stenosis can be used to estimate the percent area stenosis and even to calculate the absolute minimal cross-sectional area at the site of the stenosis provided the reference area is known. The following equation is used:

$$APV_L \times A_L = APV_D \times A_D$$

where *APV* = average peak velocity at the lesion (L) and distally (D)

A_L = area within the lesion

A_D = area distal to the lesion

Thus, by measuring the peak velocity both within and distal to the target lesion, the area of the lesion and the percent diameter stenosis can be calculated. The value obtained is subject to the limitations of velocity measurements and reflects the functional arterial dimension rather than the actual minimal lumen diameter. The calculated diameter reflects more the actual channel through which blood flows, rather than the anatomic dimensions. Nevertheless, this value can be useful in evaluating the functional stenosis before and after intervention, particularly in segments poorly visualized angiographically (such as bends, superimposed vessels, etc.).

The continuity equation was initially used in studies employing Millar catheters, but the size and characteristics of these transducers did not allow assessment of more severe lesions (214,215). The use of Doppler guidewire systems with high repetition frequency allows measurement of flow velocity up to 4 m per second and interrogation of severe stenoses without inducing flow impairment. Lumen area calculations based on flow velocity measurements correlate well with angiographic measurements (216). A similar method has been proposed for measurement of the residual cross-sectional narrowing after stent implantation (217). However, difficulties associated with optimal alignment of the Doppler wire with the centerline of flow in segments with severe flow disruption and recording of high-quality signals limit the applicability of this method.

Flow Reserve: Normal Range

Intracoronary papaverine was found to increase coronary blood flow velocity four- to sixfold in subjects with normal coronary arteries (218). In this study, however, a highly selected patient population was examined, and patients with myocardial hypertrophy, previous myocardial infarction, or other conditions known to increase the basal coronary flow (anemia, hyperthyroidism, etc.) were excluded. Intracoronary adenosine was used as the hyperemic agent in a large study of 490 subjects without coronary artery stenosis in the target arteries. The study population included patients with chest pain and angiographically normal arteries, patients with known coronary artery disease in whom the vessels measured were without stenoses, and cardiac transplant recipients without significant coronary disease. Coronary flow rate (CFR) was similar in the three major epicardial coronary arteries and in men and women. The lowest values were observed in the group with significant atherosclerotic involvement of other arteries (2.50 0.95) (219). Also, after coronary interventions, even with a complete elimination of the epicardial stenosis with successful stent implantation, similar values of CFR are observed (final CFR of 2.59 0.87 in 132 patients) (220). This large individual variability and the low average values measured in arteries without significant epicardial stenoses in patients with coronary artery disease are due to the presence of many other variables that affect CFR in this patient population. For example, left ventricular hypertrophy is associated with abnormal CFR due to the increased resting demands of the greater muscle mass (221). Factors to correct for basal flow velocity and age have been proposed and have been calculated from measurements performed in 141 patients with angina-like symptoms and angiographically unobstructed coronary arteries [corrected CFR for the left anterior descending artery = 2.85 × CFR × 10 × (0.48 × log basal average peak velocity) + (0.025 × age in years) – 1.16] (222). The possible usefulness of these proposed correction factors to improve the specificity of CFR has not been tested in large clinical studies. Interpretation is further complicated if abnormal myocardium is present in the territory subtended by the vessel in question, as scarred myocardium tends to have an abnormal vasodilatory response due to structural damage to the vascular bed.

Despite these limitations, various groups have demonstrated a close correlation between coronary flow reserve measured with the Doppler flow wire and thallium-201 or technetium-99m sestamibi SPECT. A cutoff value between 1.7 and 2.0 for CFR identifies more than 90% of the patients with abnormal scintigraphy (223,224,225,226,227 and 228).

In a large patient population with single-vessel disease, distal CFR was the only Doppler index predictive of the presence and severity of ST-segment depression. It correlated with minimal luminal diameter, the functionally relevant quantitative angiographic index of stenosis severity (229). To improve the diagnostic accuracy and identify false-positive flow reserve measurements (normal scintigraphy with less than 2.0 flow reserve), the determination of flow reserve in a second artery without significant stenoses has been advocated. The ratio between CFR in a normal control artery and CFR in the artery under evaluation is called *relative flow reserve* (230). Relative flow reserve of less than 0.65 was associated with reversible perfusion defects in a relatively small study (228). Although relative flow reserve is used in the evaluation of low CFR measurements, particularly after percutaneous interventions, several factors limit its routine use (231). Measurement of CFR in a second coronary artery requires additional time, intracoronary manipulation, and a suitable normal or near-normal coronary artery. Furthermore, the presence of a severe stenosis in an artery can affect flow in other arteries as well. The presence of collateral flow may increase basal velocity in the contralateral artery and lead to a falsely low CFR. CFR increases (on average by 0.8) after the dilatation of the stenotic artery that was the recipient of the collateral flow. This phenomenon is less evident but is still present (average increase of 0.3) in the absence of angiographically visible collaterals (232).

Clinical Applications

Assessment of Intermediate Lesions

In clinical practice, the lesions that pose the greatest diagnostic dilemmas fall in the intermediate range, typically a 30% to 70% diameter reduction. Gould et al. have shown in their classic work in dogs that myocardial perfusion reserve gradually becomes abnormal over this intermediate range of stenoses (192). Noninvasive assessment of intermediate coronary lesions has relied mainly on the demonstration of an abnormal response to exercise, in the form of characteristic electrocardiographic changes, nuclear scintigraphic perfusion defects, or segmental wall motion abnormalities on echocardiography. Noninvasive detection of ischemia, however, faces many confounding variables related to the ability to exercise, pretest probability of the disease, and the presence of ischemia in multiple territories. Moreover, because of a widespread trend to perform angiography and angioplasty in the same session to reduce cost and patient discomfort (233), a significant proportion of patients undergo coronary angioplasty without a preceding functional test (234).

Doppler flow measurements correlated with thallium stress test results in patients with angiographically intermediate stenosis. Accordingly, intracoronary Doppler measurements were proposed as a functional test for selection of patients requiring percutaneous revascularization without leaving the catheterization laboratory. In two studies, patients were observed after revascularization was deferred based on the Doppler flow velocity measurements. At 1-year follow-up, the target-lesion–related event rate, including the need for revascularization, was less than 10% (235,236). These findings support the concept that Doppler flow parameters can be used in selection of patients for percutaneous coronary interventions.

Chest Pain and Normal Angiography

The presence of normal or near-normal coronary arteries in patients with typical angina or evidence of ischemia during noninvasive tests is observed in 10% to 20% of the patients undergoing coronary angiography. After vasospasm or angiographically occult significant lesions (e.g., ostial or bifurcation lesions) are excluded, the cause of the symptoms or signs of ischemia remain to be investigated. Abnormal responses can be elicited at an epicardial and at a microvascular level, and the combination of morphologic and functional techniques described in this chapter (quantitative angiography, IVUS, and Doppler flow measurements) allow the calculation of flow velocity, absolute coronary flow, and flow resistance after different pharmacologic stimuli. Acetylcholine produces epicardial and microvascular vasodilatation by stimulating a normally reacting endothelium when concentrations of 10^{-8} to 10^{-6} mol per L are obtained with subselective intracoronary infusion. Paradoxical

vasoconstriction of the epicardial arteries or inadequate flow increase may reveal the presence of a significant endothelial dysfunction (237). In patients with diffuse atherosclerosis or transplant vasculopathy, the response to adenosine or nitrates can possibly be normal, but an abnormal reaction to acetylcholine can reveal impaired endothelial function in these patients (238,239). In patients with chest pain and angiographically normal arteries, microvascular disease with flow reserve impairment has been reported (240). Other studies, however, have found contradictory results, which may be explained by differences in inclusion criteria and methodology (241,242). More recent studies with Doppler flow wires indicate that the flow velocity response in this population is heterogeneous and may reflect either impairment of response to endothelium-independent vasodilators such as adenosine, or an endothelium-mediated response (243,244,245 and 246). Initial reports suggest that these results may have relevance for prognostic stratification (247) and for guidance of aggressive risk factor modification that is able to restore endothelial function and improve symptoms (248). Furthermore, with serial measurements the method can be used to study the effect of drugs on endothelium-dependent and endothelium-independent flow changes (249,250 and 251).

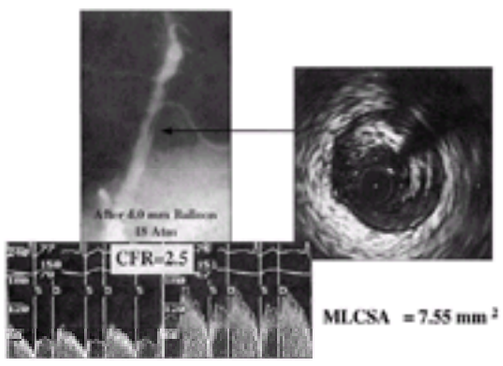
Transplant Vasculopathy

Necropsy studies describe transplant vasculopathy as a diffuse disease involving vessels smaller than 400 µm and resulting in a reduction of maximal coronary blood flow. The initial experience with Doppler catheters documented a normal flow reserve in these patients (252). More recent studies using Doppler guidewire systems suggest that the maximal hyperemia in these patients is frequently impaired. These studies also demonstrate a dissociation between degree of flow impairment and severity of the intimal thickening of the epicardial vessels as assessed with intracoronary ultrasonography (253,254).

The prognostic value of an impaired CFR after cardiac transplantation is still controversial. Wolford and Kern documented that angiographic abnormalities and elevated coefficient of variation of CFR were predictive of death, heart failure, or development of significant coronary stenoses (255). On the other hand, Spes et al. found no correlation between coronary flow measurements and ultrasonographically detected intimal thickening or abnormal stress test results (256). In the experience of this group, only left ventricular hypertrophy and donor age were correlated with higher resting flow velocity and low CFR (257).

Flow Alterations after Angioplasty

Doppler flow measurements can be used instead of noninvasive functional tests in the evaluation of angiographically intermediate lesions to save time and reduce cost by allowing intervention to proceed immediately after coronary angiography. During interventions, however, noninvasive methods of functional assessment are not applicable. Doppler flow measurements have the potential to become an indispensable functional parameter in the assessment of the results of percutaneous coronary interventions. Unfortunately, especially during coronary interventions, the use of intracoronary Doppler flow measurements is challenged by the development of major hemodynamic changes and the presence of microvascular dysfunction that may interfere with the ability of Doppler flow sensing to detect the effect of percutaneous coronary interventions on epicardial stenoses. Coronary revascularization deemed successful by angiography is usually associated with restoration of normal Doppler flow characteristics (205,258,259) (eFig. 85.0.32). On the other hand, abnormalities in CFR may persist after PTCA due to the limitations of angiography in detecting the true lumen gain after treatment (260). CFR impairment may persist even after truly successful angioplasty. The discrepancy between the adequately enlarged lumen and the depressed CFR may be due to procedure–related hemodynamic changes, microembolization, or transient or persistent changes in the distal vasculature. Later normalization of CFR in some of the lesions is probably due to these transient alterations (261).



***e*FIGURE 85.0.32** Basal and hyperemic flow velocity after percutaneous transluminal coronary angioplasty with a 4.0-mm balloon at 18 atm selected based on the media-to-media diameter measured with intracoronary ultrasonography. Note the restoration of a normal coronary flow reserve (CFR) despite the large residual dissection. Ultrasonography shows a large residual fibrous plaque and a minimal lumen cross-sectional area (MLCSA) of 7.55 mm^2.

Large studies have demonstrated that a postintervention impairment in flow reserve is more frequently associated with persistent or recurrent angina and that such patients are more likely to have a positive exercise test result at 1 month or to require target lesion revascularization by 6 months, or both (262,263). In the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) study, the combination of an optimal result by angiography (less than 35% diameter residual stenosis) and a CFR of greater than 2.5 was associated with a favorable clinical outcome at 6 months (16% incidence of major adverse cardiac events) (264). In the DEBATE trial the patients were also monitored for 15 minutes after the last balloon inflation: If CFR remained stable and no cyclic flow velocity variations were observed, a rare but ominous phenomenon related to recurrent platelet emboli (264,265), no abrupt closure was observed in the 24 hours after PTCA (266).

Based on these results, three randomized trials were performed to test the hypothesis that angiographic and Doppler parameters can identify postangioplasty results that have a relatively low restenosis risk similar to that observed after stent placement (267,268 and 269). In the DEBATE II study, only patients with discrete lesions in relatively large arteries (larger than 2.75 mm) were included. Patients underwent an unbalanced randomization: 97 patients were treated with elective stenting; 523 patients were categorized according to whether they fulfilled a predetermined criterion of residual stenosis of less than 35% lumen diameter and CFR of more than 2.5 and then underwent a second randomization to stenting or PTCA. The study confirmed the high risk of major adverse cardiac events in the patients undergoing PTCA who did not reach the angiographic and Doppler criteria. Overall event-free survival rate was similar in patients treated with elective and provisional stenting (86.6% and 85.6%, respectively). The separate analysis of the subgroup that achieved the optimal end points after PTCA demonstrated that stenting could further improve 1-year event-free survival (93.5% vs. 84.1%; p = .066). This difference was not statistically significant but casts doubts on the provisional stenting strategy, especially when the higher cost of this strategy after 1 year of follow-up is considered (EUR 6573 vs. EUR 5885; p = .014). The other two trials, the French Randomized Optimal Stenting Trial (FROST) and the Doppler Endpoints Stent International Investigation (DESTINI), enrolled 251 and 723 patients, respectively. These trials, which compared elective stenting and guided angioplasty strategies, differed from the DEBATE II trial in several ways. Both of these studies used a simple 1:1 randomization protocol. The CFR threshold to define success was lower (2.0 in DESTINI and 2.2 in FROST), and inclusion criteria were less restrictive. For example, in DESTINI patients with multivessel disease were included, provided that all lesions were suitable for stent implantation. Both studies showed a similar clinical outcome at 1 year. In DESTINI, the incidence of major adverse cardiac events was 17.8% in the elective stenting group and 18.9% in the guided PTCA group, and the incidence of repeat target lesion revascularization at 1 year was 14.9% in the elective stent group and 15.6% in the guided PTCA group. In FROST a follow-up angiogram was also performed, which demonstrated that the groups with provisional and elective stenting had similar minimal luminal diameters (1.90 0.79 mm vs. 1.99 0.70 mm, respectively; p = 0.39) and similar binary restenosis rates (27.1% vs. 21.4%, respectively; p = 0.37). In the DESTINI trial, possibly because of the greater complexity of the lesions treated, cost was higher and procedure duration was longer in the elective stenting arm (270).

Two reviews on provisional stenting (271,272) have stressed the fact that in these trials only a minority of the patients in a provisional stenting strategy guided by Doppler flow measurements and quantitative angiography were treated with balloons only, and that 50% to 60% of these patients required a stent after balloon angioplasty. Under these circumstances, this strategy is unlikely to lead to cost and time savings compared to elective stenting, which, with modern stents, can be performed in 30% to 60% of cases without predilation (273).

Acute Myocardial Infarction

Flow velocity measurements do not fully correlate with angiographically determined flow [as graded based on the results of the Thrombolysis in Myocardial Infarction (TIMI) trial] or frame count. In particular, a very low flow velocity is observed in the majority of patients with TIMI grade 2 flow that is not significantly different from that in patients with TIMI grade 1 flow. These findings suggest that incomplete recanalization is responsible for the limited recovery of ventricular function in these cases (274,275). Continuous monitoring of flow velocity with the Doppler guidewire device allows confirmation of flow restoration after thrombolysis and can document the persistence of antegrade flow in the hours after thrombolysis (276). An abnormal pattern of early systolic retrograde flow and prolonged diastolic flow velocity has been shown to be associated with the presence of a “no reflow” phenomenon (209,277). A more sophisticated index calculated from the slope of the instantaneous relationship between coronary flow velocity and pressure in diastole during maximal hyperemia (278) has also shown good correlation with recovery of regional wall motion (279). Besides having prognostic value, the measurement of CFR can also detect the protective effect of pharmacologic interventions to prevent myocardial damage during reperfusion: A higher maximal hyperemic velocity and an improved regional and global left ventricular function were observed in patients undergoing

PTCA after treatment with the IIb-IIIa platelet receptor inhibitor abciximab (280).

Limitations of Doppler Techniques

The blood volume sampled by the transducer in Doppler devices is small and may not accurately reflect the velocity of the whole bloodstream at the interrogated location. This problem is particularly important in zones of turbulent flow (such as areas distal to severe stenoses) or lumen segments with odd geometric configuration, in which different strata of the bloodstream may move at different velocities. The blood flow velocity measured in coronary arteries is a surrogate for the actual volumetric flow. The Doppler guidewire device is significantly dependent on positioning within the coronary, and this may explain the variability of serial measurements made during the same procedure and in repeated studies (251). In many cases, artifacts related to wall motion and signals from adjacent venous structures can be eliminated by repositioning the device to a more central location or by adjusting the J curve of the tip. Considerable care, patience, and time are often required to obtain accurate and reproducible blood flow velocity measurements, however, particularly during an operator's initial experience.

Although the concept of coronary flow reserve can be applied in optimal situations in humans, one must recognize that flow reserve is influenced by several factors that are independent from the hydrodynamic characteristics of the stenotic lesion. Because flow reserve is a ratio, the occurrence of changes in resting flow without changes in hyperemic flow considerably influences the result. Furthermore, factors such as heart rate, preload, myocardial hypertrophy, and disease of the microvasculature alter the hyperemic pressure flow relationship and modify the flow reserve (281). The experience gained with intracoronary Doppler devices is important because these limitations also apply to new techniques able to measure coronary velocity and CFR noninvasively (282,283,284 and 285).

INTRACORONARY PRESSURE MEASUREMENTS

Fractional Flow Reserve

Fractional coronary flow reserve (FFR) represents one of the most recent additions to the intracoronary diagnostic armamentarium for evaluation of coronary disease severity. Although the mathematical derivation of this approach shown later is complex, the principles can be easily understood. The flow to an area of myocardium providing resistance is determined by the pressure drop across that resistance. In the myocardial vasculature, this resistance can be located in the epicardial conduit, representing a coronary artery stenosis, or in the small vessels, the "resistance" vessels of the microcirculation. Because FFR is used to determine the functional significance of an epicardial stenosis, the resistance of the microcirculation must be minimized and maintained constant using maximal pharmacologic vasodilatation. Further, the second component of the pressure drop, the right atrial pressure, can be neglected (if venous pressure is not increased) as it is too small to affect results under normal conditions. In the presence of a stenosis, the ratio between the actual driving pressure (poststenotic pressure) and the arterial (aortic or prestenotic) pressure is compared with the driving pressure in the hypothetical situation of absence of stenosis, which defines FFR (286). This measurement must be done under maximal hyperemic flow to minimize resistance of the microcirculation. Under these circumstances, the flow is limited solely by the epicardial resistance, which makes FFR a specific index for the determination of epicardial stenosis. FFR is equal to 1.0 for a normal vessel and falls progressively below 1.0 for stenoses of increasing severity.

The variables required to calculate FFR include mean arterial pressure, P_a; central venous pressure, P_v; coronary pressure distal to the stenosis, P_d; and coronary wedge pressure (pressure in the distal coronary with the vessel occluded), P_w. Q is the total blood flow through the supplying coronary artery (sum of Q_s, antegrade flow in the coronary, plus Q_c, collateral flow). If no stenosis is present, Q and Q_s are called Q^N and Q_s^N and are assumed to be equal. From these variables, FFR_{cor}, fractional coronary flow reserve, and FFR_{myo}, fractional myocardial flow reserve, can be calculated:

$$FFR_{cor} \quad \frac{Q_s}{Q_s^N} = \frac{P_d - P_v}{P_a - P_w}$$

$$FR_{myo} \quad \frac{Q}{Q^N} = \frac{P_d - P_v}{P_a - P_v}$$

The difference between coronary and myocardial FFR represents the contribution of collateral blood flow (287). The technique for measuring the variables and computing FFR has been validated in a sophisticated *in vitro* model of pulsatile flow (288) and in an animal model using a Doppler flow meter surgically implanted on the epicardial vessel (289).

FFR is a measure of the maximum flow capacity for a stenotic vessel compared to flow capacity for the same vessel without the stenosis. Unlike measurements with Doppler methods, FFR measurements are unaffected by any increase in basal flow because all measurements are performed in a pharmacologically induced state of maximum vasodilatation; they are also unaffected by changes in the hemodynamic conditions at the time of assessment (arterial pressure, inotropic state, heart rate) (281). Uniquely, the FFR method allows calculation of both the antegrade and collateral components of flow (290).

Equipment and Technique

Available Systems

To avoid the effects of placing large catheters across the stenosis, pressure is measured using a 0.014-in. micromanometer-tipped guidewire. Currently, two systems approved by the U.S. Food and Drug Administration are commercially available (PressureWire, Radi Medical Systems, Uppsala, Sweden; and WaveWire, Endosonics-Jomed, Rancho Cordova, CA) (286,291,292). Both wires can be disconnected and used as primary angioplasty wires. The steerability is comparable to that of a regular floppy guidewire and is continuously improving. Both systems must be calibrated before use, and the operator must ensure that equal pressures are recorded by both the guide catheter and the pressure wire at the ostium of the vessel at the beginning of the procedure. Pressure signal drift can be observed during the procedure on occasion (depending on the quality of the particular wire and the duration of the procedure) and can be accounted for by comparing the pressure obtained by the guidewire with the guide catheter pressure at the end of the procedure. The pressure sensor is mounted 3 cm from the tip of the wire, which allows the operator to advance and retract the wire across the stenosis without losing position and confirm the exact location of the lesion by the pressure drop. More importantly, when a complete pullback through the entire vessel is performed at maximal hyperemia (either by a continuous infusion of adenosine or by intracoronary papaverine) the physiologic significance of all lesions within the vessel can be studied and potential interventions can be planned accordingly. Sometimes, the presence of diffuse disease can be revealed by a gradual decrease in the hyperemic pressure gradient; this makes a focal intervention unfeasible and medical treatment the therapy of choice.

Induction of Hyperemia

Once the pressure sensor has passed the stenosis, a maximum hyperemic stimulus is required to eliminate the microcirculatory resistance and allow evaluation of the hemodynamic significance of the epicardial lesion. Intravenous adenosine was initially recommended to achieve a stable steady-state poststenotic pressure drop. The simplicity and lower cost of intracoronary bolus injection of adenosine has prompted studies to compare the two methods. These studies showed that a clinically relevant overestimation of FFR (and thus underestimation of lesion severity) occurred in 8% of lesions when intracoronary adenosine was given (293). Larger adenosine boluses can be safely used after the initial test dose, especially in the left coronary artery, and are recommended to exclude a suboptimal hyperemic response in cases with borderline results (slightly above the cutoff criteria) (196). Intracoronary administration of adenosine has several advantages over intravenous infusion, including easier and faster administration, rapid onset of action and an ultrashort half-life (ideal for repetitive measurements), fewer side effects, and a significant reduction in cost. However, a pressure pullback curve as described earlier cannot be performed with intracoronary adenosine because of its short half-life. For that purpose, a continuous intravenous infusion of adenosine or intracoronary papaverine (which has a half-life of 30 to 45 seconds) can be used. Further, if guide catheters with side holes are used, intracoronary adenosine should be avoided, because part of the intracoronary bolus will be delivered into the aorta and the precise amount of drug reaching the microcirculation cannot be determined reliably.

Clinical Applications

Assessment of Intermediate Lesions

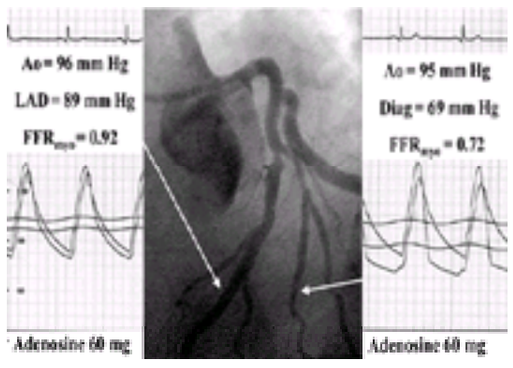
At present, the best-established and most widely used applications of intracoronary pressure measurements and calculation of the FFR is the diagnosis of hemodynamically significant coronary artery lesions found at angiography. Several carefully conducted studies have confirmed the clinical usefulness of FFR measurements in the setting of "intermediate" or undetermined degree of stenosis. In the first clinical validation study, a closer correlation was observed between FFR and relative flow reserve obtained from positron emission tomography than between relative flow reserve measured by positron emission tomography and various

angiographic parameters; these results illustrate the usefulness of FFR measurements in physiologic lesion assessment (294). These findings were confirmed in other studies assessing lesions of intermediate severity by angiography with nuclear perfusion imaging (295,296). Another study, which included 60 patients with single-vessel disease who had positive stress test results that became normal after PTCA, established that an FFR cutoff value of 0.75 can distinguish patients with and without ischemic changes in the distribution area of the assessed artery (297). Similar cutoff criteria were derived from the comparison with other noninvasive methods of detection of regional ischemia, such as dobutamine stress echocardiography (298). Pijls et al. compared FFR measurements with conventional noninvasive methods, performing bicycle exercise testing, thallium scintigraphy, stress echocardiography, and quantitative angiography in 45 patients with single-vessel disease, angiographically identified intermediate stenoses, and chest pain of uncertain origin (10). In all 21 patients with an FFR of less than 0.75, reversible myocardial ischemia was demonstrated in at least one of the noninvasive tests. Of the remaining 24 patients with an FFR greater than 0.75, 21 had negative results on all of the noninvasive tests. None of the 24 patients with an FFR greater than 0.75 was treated, and all remained free of cardiac events for a mean follow-up of 14 months. The mean stenosis diameters by quantitative angiography were similar in both groups, which demonstrates the lack of sensitivity of angiography in discriminating lesions capable of producing ischemia.

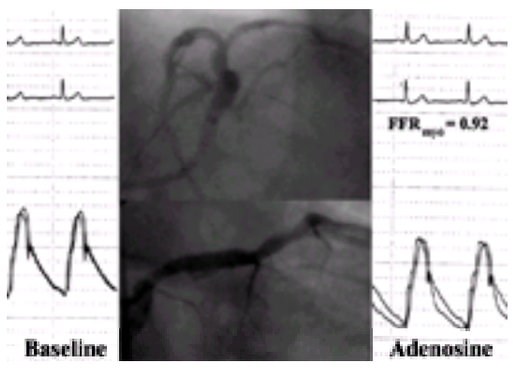
After establishing these cutoff values for myocardial ischemia, a retrospective analysis evaluated the clinical outcome of patients with single-vessel disease and angiographically intermediate stenosis who were referred for PTCA but in whom the intervention was deferred based on an FFR value of more than 0.75 (299). Of the 100 patients included in the study, 90 patients remained free of any coronary events at a mean follow-up of 18 months, with most patients asymptomatic or minimally symptomatic. Based on these encouraging results, a large prospective randomized study tested the hypothesis that percutaneous coronary intervention can be safely deferred based on FFR measurements (300). Patients referred for angioplasty underwent FFR measurement, and all patients with FFR above the ischemic threshold were randomly assigned to intervention or deferral of the intervention. Although results have not yet been reported in full detail, no statistically significant difference was seen in event-free survival between the two groups at 1 and at 2 years. Furthermore, a significant increase in functional status was observed in both groups independent of the performance of the intervention.

A more complex set of equations is used to determine the individual relevance of serial stenoses within the same artery. An animal study has validated this concept (301), and an elegant clinical study of 32 patients with two stenoses in the same artery demonstrated that the predicted FFR of one stenosis derived from the pressure measurements made before treatment was confirmed by a second measurement performed after the elimination of the second stenosis (302).

In summary, the main application for FFR measurements lies in the arena of angiographically ambiguous lesions whose hemodynamic significance is unclear. FFR can be used to justify coronary revascularization but also to safely avoid intervention for nonsignificant lesions (*e*Fig. 85.0.33 and *e*Fig. 85.0.34). Further, pressure gradient measurements help to unmask angiographically occult lesions, to determine the exact location of the lesion, and to evaluate multiple lesions within one vessel.



***e*FIGURE 85.0.33** Angiogram in the left anterior oblique view of the left coronary artery with two intermediate lesions in the middle segment of the left anterior descending coronary artery (LAD) and proximal segment of the major diagonal branch (Diag). Arrows indicate the position of the pressure transducer in the distal LAD and diagonal branch. Note the small gradient in the LAD and the large pressure gradient in the diagonal branch after a relatively large dose of intracoronary adenosine. The fractional flow reserve is within the normal range in the LAD (0.92); however, it is abnormal in the diagonal branch (0.72). Ao, aorta; FFR_{myo}, fractional myocardial flow reserve.

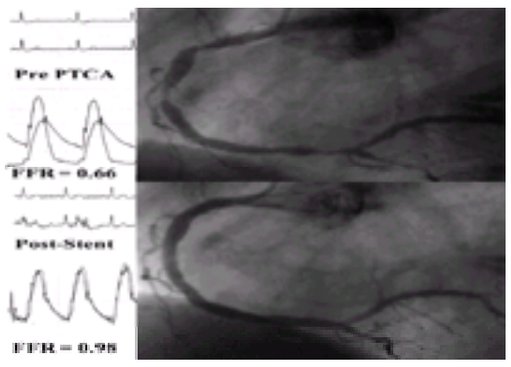


***e*FIGURE 85.0.34** Left coronary angiogram of a patient who was referred for coronary artery bypass surgery because of severe left main coronary ostial stenosis. Minimal gradient is seen between the aorta and the mid left anterior descending artery in the hyperemic state induced by intravenous adenosine infusion. Fractional myocardial flow reserve (FFR_{myo}) is greater than 0.90.

Coronary Interventions

The value of FFR for guidance of coronary interventions has been assessed in multiple studies. FFR measurement has been shown to be useful in evaluating PTCA results, and the complementary value of FFR and angiography in this setting has been demonstrated. In a study involving patients treated with PTCA, those who had an FFR above the cutoff value of 0.90 in combination with a residual diameter stenosis of less than 35% showed a significantly more favorable outcome at 24 months of follow-up, with an event rate of only 12% among this group compared with 41% in the group not meeting these criteria (303). Further studies are warranted to confirm these data in a prospective analysis and to evaluate this strategy for provisional stenting.

An important potential application of FFR measurements is the evaluation of coronary stenting. The hypothesis has been put forward that, after optimal coronary stenting, FFR should return to normal in the absence of concomitant disease within the same vessel, or that at least the hyperemic gradient across the stented segment should be diminished in the presence of disease elsewhere in the vessel (*e*Fig. 85.0.35). FFR in normal subjects without coronary stenosis varies from 0.94 to 1.00 (289), so that 0.94 is the lower limit of normalcy after an optimal stent result. In one study, 81 paired observations were made comparing FFR measurements after stent deployment to the current gold standard, IVUS (304). An excellent correlation was found, with 91% concordant results between FFR values and ultrasonographic findings, which demonstrates the usefulness of FFR in poststent assessment. Quantitative coronary angiography, on the contrary, showed a low concordance rate with both IVUS results and FFR. Despite the good correlation found, the pressures and type of stent used do not reflect current practice and suggest that the method may be applicable only in cases of rather severe residual stenosis. More recently, a multicenter study investigated the relationship between FFR measurement and IVUS after coronary stenting and found that an FFR of less than 0.96, measured after stent deployment, predicts a suboptimal result based on IVUS imaging, whereas an FFR higher than 0.96 does not reliably predict an optimal stent result (305). The use of FFR measurement in coronary stenting is therefore not yet established.



***e*FIGURE 85.0.35 Top:** A large right coronary artery with three lesions in series. Fractional flow reserve (FFR) is very abnormal. **Bottom:** After implantation of three stents, the FFR normalized completely. PTCA, percutaneous transluminal coronary angioplasty.

The coronary collateral circulation represents an alternative source of blood supply to a myocardial area that is not adequately perfused due to a stenotic or occluded vessel. Until recently, few modalities were available to assess coronary collateral flow, and a precise quantitative assessment was not possible. With the development of pressure-sensitive guidewire devices, the coronary wedge pressure distal to a balloon-occluded vessel can now be studied and the functional variables for coronary collateral flow calculated (306). Use of this method in humans during coronary interventional procedures allows investigation of the pathophysiology and therapeutic promotion of collateral flow *in vivo*. Studies have demonstrated an association between collateral flow and intracoronary concentration of vascular endothelial growth factor in patients with coronary artery disease (307). Moreover, patients with well-developed collaterals have been shown to have a better increase in collateral flow after adenosine administration (308) but to be prone to restenosis after PTCA compared to patients with little collateral supply, possibly due to increased competitive flow (309). Further work in this area is expected to greatly expand the knowledge and understanding of collateral circulation in health and disease.

Limitations of Fractional Flow Reserve Measurement

FFR predictably underestimates the severity of the flow impairment due to epicardial stenosis when conditions other than the stenosis restrict the increase in flow and pressure gradient after pharmacologic vasodilation. Known conditions that impair accuracy of this method include left ventricular hypertrophy, diffuse or small-vessel coronary disease, and previous myocardial infarction. In left ventricular hypertrophy, vascular supply is inadequate for the increase in muscle mass, which affects the natural physiologic reserve and pushes up the cutoff value indicating myocardial ischemia. Currently, no study has established the ischemic threshold, which makes the interpretation of FFR in the presence of left ventricular hypertrophy difficult. Microvascular disease cannot be detected by coronary pressure measurements alone. Small-vessel disease may influence FFR, however, as only submaximal flow can be achieved with hyperemic stimuli alleviating the pressure gradient across the epicardial conduit. In those cases, FFR may be artificially high, so that the severity of the stenosis is underestimated. The same is true for FFR measurements taken after previous myocardial infarction. In such cases, only a small gradient and a high FFR may be present despite a severe angiographically identified stenosis (310). This represents only a theoretical limitation of FFR, however. In clinical practice, FFR still reliably indicates the degree to which myocardial blood flow is restored by revascularization of the epicardial conduit. In the presence of severe small-vessel disease or myocardial necrosis after myocardial infarction, revascularization of even a severe stenosis may not improve distal perfusion. Two small studies indicate the potential application of FFR measurement in this setting (311,312). Simultaneous assessment of pressure and flow may overcome these limitations, but the use of two sensor-tipped wires makes this assessment impossible in clinical practice (313), and methods to derive CFR from pressure measurements in basal and hyperemic conditions still lack clinical validation (314).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Additional information obtained with IVUS, angioscopy, Doppler flow, and pressure measurements can improve the routine care of patients presenting with acute and chronic coronary syndromes. The valuable pathophysiologic and mechanistic observations provided by these diagnostic modalities shaped our understanding of coronary atherosclerosis and have had considerable impact on catheter-based interventions. Although these techniques have been used since the 1980s, they are currently not used routinely during either diagnostic or interventional catheterization. The existing data are not sufficient to recommend use of these techniques in every patient who is studied in the catheterization laboratory. In our clinical practice, we therefore use these techniques when coronary angiography does not provide adequate answers to the clinical question. We carefully choose between an additional morphologic test such as IVUS (e.g., unclear left main lesion, assessment of post-interventional lumen) or a functional test such as the FFR (e.g., intermediate lesions with positive stress test) or Doppler flow measurement (e.g., microvascular angina). In these situations, the potential benefit for the individual patient is large enough to justify the added risk, time, and cost of these exciting modalities.

Techniques assessing the coronary morphology and physiology will continue to help us to advance atherosclerosis research. Several ongoing, randomized pharmacologic trials assessing progression and regression of atherosclerosis use serial IVUS. Combined use of these techniques will shed new light on the interaction between coronary anatomy and physiology. Furthermore, emerging techniques using intracoronary thermometers, infrared imaging catheters, optical coherence tomography wires, and others will open new windows to this research.

THE FUTURE

The four modalities—IVUS, angioscopy, Doppler flow measurements, and FFR measurements—each provide important new opportunities to study the coronary circulation in health and disease. IVUS will play an increasingly important role in arteriosclerosis research. As new pharmacologic interventions targeting the atherosclerotic plaque are developed, ultrasonography will be used in assessing the efficacy of these interventions. Automatic border detection and measurement, three-dimensional reconstruction, and volumetric measurements will probably be used more frequently in future studies. Tissue characterization by IVUS is an important element in the assessment of various plaque types. Further research is needed to establish the accuracy and reproducibility of this technique before it can be used in the histology-like examination of the plaque. IVUS will continue to be an indispensable tool for optimizing the application of new therapeutic devices such as coated stents. (Angioscopy equipment is currently not available in the United States.)

Measurement of FFR will continue to be a useful tool for the assessment of borderline lesions. Combination devices are in development that will allow pressure and velocity measurements to be made by a single device.

Over time, the most developed of these techniques, IVUS and FFR measurement, will likely be integrated into the state-of-the-art practice of interventional cardiology, particularly in complex diagnostic situations. Although coronary angiography will not be replaced, these new modalities will provide critical ancillary information in selected patients for many years to come.

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86

VALVULOPLASTY

ALEC SYLVAIN VAHANIAN

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Fifteen years of experience with percutaneous valve dilatation for acquired valve stenoses has shown the following:

- Percutaneous mitral valvuloplasty is an effective treatment in a wide range of patients with mitral stenosis. Its risk is low when it is performed by experienced teams, and follow-up at more than 10 years demonstrates excellent durability of the procedure. The prediction of immediate and midterm results is multifactorial and based on clinical and anatomic variables.
- Percutaneous aortic valvuloplasty for degenerative calcified aortic stenosis provides short-term palliation of symptoms at the cost of high periprocedural risk. Its role is in question.
- Percutaneous tricuspid or multivalve dilatation is used in exceptional cases.
- Percutaneous dilatation of a bioprosthesis has no future.

HISTORICAL PERSPECTIVE

Until the early 1980s, surgery was the only possible treatment for severe valvular stenoses; thereafter a new alternative appeared: percutaneous balloon valvuloplasty.

HEART SOUNDS

Audio 86.1 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm^2. Note the loud S1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border **(A)** and apex **(B)**. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics, Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

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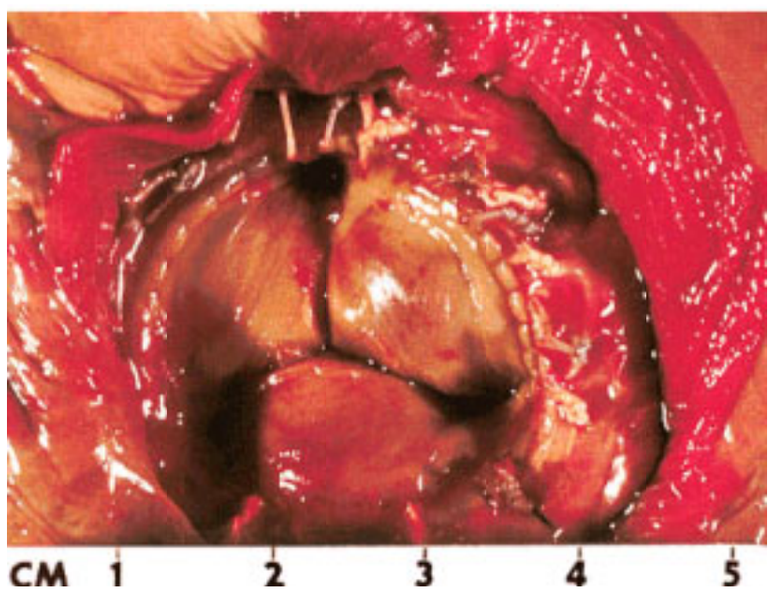
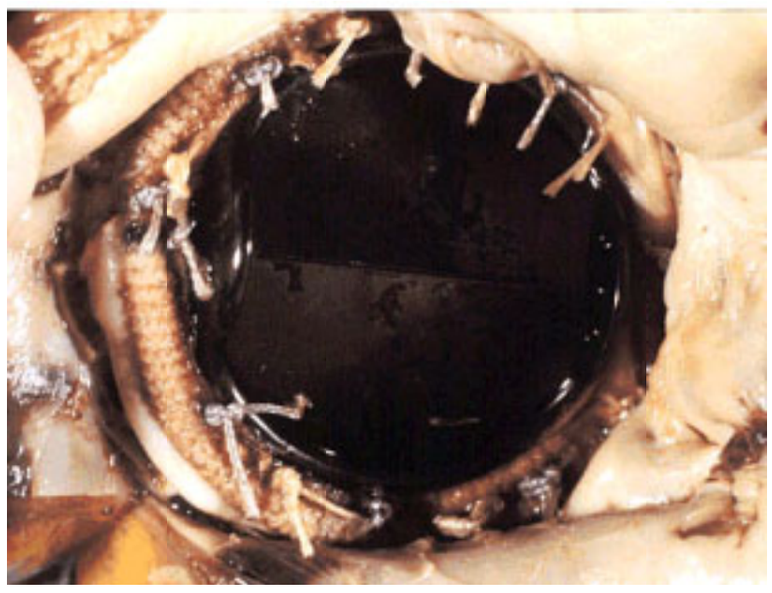


Porcine prosthetic mitral valve. In this example, the valve is normal and the suture line is intact.



Normal St. Jude valve in the mitral position.

A 62-year-old female patient with mitral stenosis.

The first to perform balloon valvuloplasty as an alternative to surgery in the treatment of mitral stenosis was K. Inoue in 1982 during open-heart surgery. The initial report of percutaneous balloon valvuloplasty was published in 1984 (1); most subsequent reports concerning the technique have been published since 1986. As was to be expected from earlier experience with closed surgical commissurotomy, the good immediate and midterm results obtained during this period led to increasing worldwide use of the technique, which became the second most important in the field of interventional cardiology.

In the field of aortic stenosis, percutaneous valvuloplasty was used for the first time by Cribier et al. in 1985 in an elderly patient with severe calcific aortic stenosis (2). Despite great initial enthusiasm related to encouraging preliminary immediate reports, the technique has largely lost favor because of the lack of midterm benefit, and today it has a very limited role, if any.

Percutaneous balloon valvuloplasty is therefore still a recent innovation that, despite marked changes in practice during the first decade of its use, will continue to be refined and subjected to long-term surveillance.

This chapter deals with percutaneous balloon valvuloplasty for acquired valvular stenoses in the fields of mitral stenosis, aortic stenosis, and the less frequent lesions of tricuspid, bioprosthesis, and multivalve stenoses.

Mitral stenosis. Left atrial enlargement and right ventricular hypertrophy have developed secondary to mitral stenosis, causing fixed pulmonary hypertension.

PERCUTANEOUS MITRAL VALVULOPLASTY

Rheumatic fever continues to be endemic in developing countries where mitral stenosis is the most common valve disease. Although the prevalence of rheumatic heart disease has greatly decreased in Western countries, it continues to represent an important clinical entity because of out-migration from developing countries and the presence of restenosis after previous surgical commissurotomy (3).

Mechanisms

Balloon dilatation acts in the same way as surgical commissurotomy by opening the fused commissures (4); therefore, a more appropriate term for the procedure is probably *percutaneous mitral commissurotomy* rather than *percutaneous mitral valvuloplasty*. Balloons are also able to enlarge the valve area by fracturing nodular deposits in patients with calcified valves (5).

Technique

The techniques and devices used have varied over time and from group to group.

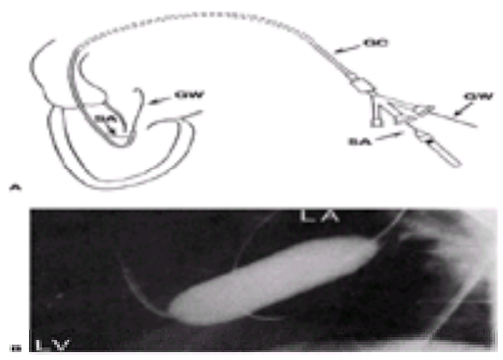
Approaches

At the present time, two approaches are used: transarterial and transvenous.

The *transvenous* or *antegrade approach* is the most widely used. Transseptal catheterization, which allows access to the left atrium, is the first step in the procedure and one of the most crucial. It is performed through the femoral vein or, in exceptional circumstances, through the jugular vein (6).

The *retrograde approach* using transseptal catheterization, described by Babic, has now been abandoned. In the retrograde technique without transseptal catheterization (eFig. 86.0.1) described by Stefanadis (7), the balloon is introduced through the femoral artery or, less frequently, the brachial artery. The passage from

the left ventricle to the left atrium is achieved using preshaped, steerable catheters, by which exchange guidewires are positioned in the left atrium. The specific advantage to this approach is that it avoids transseptal catheterization. Retrograde left atrial catheterization is not always easy, however, and it carries the risk of inserting the guidewire between the chordae tendineae and damaging the subvalvular apparatus on balloon inflation, which causes severe mitral regurgitation. It has been used with single, double, or Inoue balloons with good results and no serious complications. The number of patients treated in this way has been limited, however, and further studies are needed to evaluate its place. Knowledge of this approach does provide an alternative in the rare cases in which use of the transseptal approach is contraindicated.



***e*FIGURE 86.0.1** Mitral valvuloplasty: retrograde technique. **A:** Schematic representation of the steerable catheter. GC, guiding catheter; GW, guidewire; SA, steering arm. **B:** Inflation of a balloon in left anterior oblique projection. LA, left atrium; LV, left ventricle. (From Stefanadis C, Toutoutzas P. Retrograde nontransseptal mitral valvuloplasty. In: Topol EJ, ed. *Textbook of interventional cardiology.* Philadelphia: WB Saunders, 1994:1253, with permission.)

Devices

Currently, two main techniques are used: balloon commissurotomy and metallic commissurotomy.

Balloons

In the double-balloon technique (8,9 and 10), a floating balloon catheter is used to catheterize the left ventricle; then two long exchange guidewires are positioned in the apex of the left ventricle or, less frequently, the ascending aorta. The interatrial septum is dilated. Finally, the balloons are positioned across the mitral valve. The balloons used are two round conventional balloons or a combination of the trefoil balloon and a conventional balloon. The double-balloon technique is effective but demanding and carries the risk of left ventricular perforation by the guidewires or the tips of the balloons.

The Multi-Track system is a refinement of the double-balloon technique, as it uses a monorail system that requires the presence of only one guidewire and eases the performance of the dilatation in comparison with the standard double-balloon technique. Clinical experience with this device is still limited. Preliminary results indicate that the efficacy is good but a risk remains of perforation with the guidewire or the tips of the balloons in the apex (11).

The Inoue technique (Fig. 86.1) was the first to be developed (1,12,13 and 14). The Inoue balloon, made of nylon and rubber micromesh, is self-positioning and pressure extensible. Because the balloon has three distinct parts, each with a specific elasticity, each part can be inflated sequentially. This sequence allows fast and stable positioning across the valve. The Inoue balloon comes in four sizes (24, 26, 28, and 30 mm), and each is pressure dependent, so that its diameter can be varied by up to 4 mm as required by circumstances. Inoue recommends the use of a stepwise dilatation technique under echocardiographic guidance: the first inflation is performed to the minimal diameter of the balloon chosen. The balloon is then deflated and withdrawn into the left atrium. If mitral regurgitation has not increased and valve area is insufficient, the balloon is readvanced across the mitral valve, and inflation is repeated with the balloon diameter increased by 1 to 2 mm.

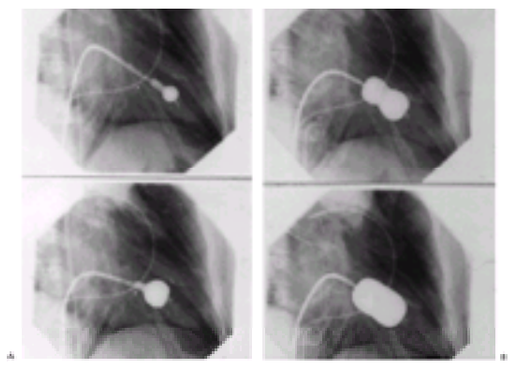


FIGURE 86.1 Mitral valvuloplasty: Inoue technique. **A:** Inflation of the distal portion of the balloon, which is thereafter pulled back and anchored at the mitral valve. **B:** Subsequent inflation of the proximal and middle portions of the balloon. At full inflation, the waist of the balloon in its midportion has disappeared.

Although a number of retrospective studies have compared the efficacy of the two balloon techniques, comparison is still difficult because only a few small randomized studies are available (15). They suggest, first, that the Inoue technique makes the procedure much easier. The suggestion has even been made that experienced operators can avoid an arterial line, which decreases the risks and allows the procedure to be performed on an outpatient basis (16). Second, these studies suggest that the Inoue technique has grossly similar efficacy to that of the double-balloon technique, although the latter may result in a slightly larger valve area. Furthermore, long-term results are equivalent (17). Finally, these studies suggest that the Inoue technique carries a lower risk because the risk of ventricular perforation is avoided and the stepwise technique allows early diagnosis of mitral regurgitation and could decrease the development of severe regurgitation.

Whatever balloon is used, the *preselection of balloon size* remains controversial. The desire for greater improvement in valve area must be balanced against the risk of producing severe mitral regurgitation. Balloon size is usually chosen according to patient characteristics: height (12), body surface area (18), or diameter of the mitral annulus (19).

Metallic Dilator

In the late 1990s, Cribier introduced the metallic commissurotomy (Fig. 86.2), which uses a device similar to the Tubb dilator used during closed commissurotomy (20). The performance of the technique is similar to performance of the previous single-balloon technique, as it requires the positioning of a guidewire in the left ventricle using a floating balloon catheter. The septum is dilated using an 18-Fr dilator. Then the metallic dilator is introduced. It is made of stainless steel, is shaped like a cylinder, and is 5 cm long. The metallic head is screwed on the distal end of the catheter and is detachable. Manual pressure allows the dilator to be opened up to 40 mm. The experience with this device is only preliminary and comprises approximately 1,000 cases, mainly in developing countries; it is reported almost exclusively by the promoter of the method (20,21). The initial results suggest that this method is similar in efficacy to the balloon commissurotomy, but the risk of hemopericardium seems higher due to the type of device and the presence of a stiff guidewire in the left ventricle. In addition, this technique is more demanding for the operator than the Inoue technique. The potential advantage of the metallic commissurotomy is that the dilator is reusable, which reduces the cost of the procedure.

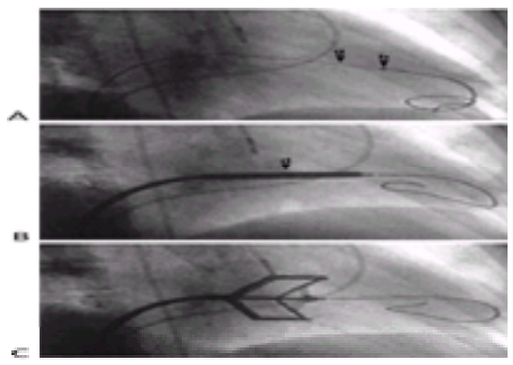


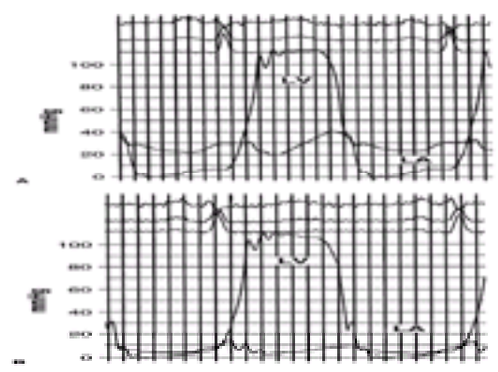
FIGURE 86.2 Percutaneous metallic commissurotomy. **A:** Guidewire (g) is placed in left ventricle after transseptal catheterization. Metallic bead (b) is positioned at midventricle, beyond mitral valve. **B:** After dilation of septal puncture site, device is pushed over guidewire and metallic dilator (d) is positioned across mitral valve. Metallic bead is placed in contact with distal end of dilator. **C:** Commissurotomy is performed by opening dilator to its maximum extent of 40 mm. (Adapted from Cribier A, Eltchaninoff H, Koning R, et al. Percutaneous mechanical mitral commissurotomy with a newly designed metallic valvotome: immediate results of the initial experience in 153 patients. *Circulation* 1999;99:793–799.)

Monitoring of the Procedure and Assessment of Immediate Results

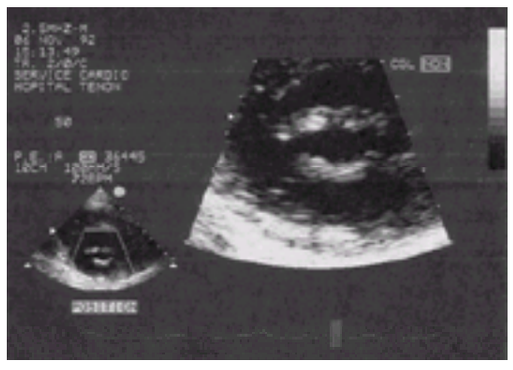
Two means are used to assess immediate results in the catheterization laboratory: hemodynamics and echocardiography. Although echocardiography may be difficult to perform in the catheterization laboratory for logistic reasons, it provides essential information. First, echocardiography enables detection of early complications such as a pericardial hemorrhage or severe mitral regurgitation. Second, it may facilitate puncturing the interatrial septum and also perhaps crossing the valve. This has been accomplished primarily with the transesophageal approach (22), which is superior to the transthoracic approach in imaging the interatrial septum. Nevertheless, echocardiography using the transesophageal approach is not easy to perform in the catheterization laboratory, and its use should probably be restricted to cases in which technical difficulties such as severe anatomic distortion are encountered. Intracardiac echocardiography has been used in such cases (23). Third, echocardiography provides essential information on the course of the mitral opening, which is of utmost importance when using the stepwise Inoue technique (12,14).

Assessment of the following parameters has been suggested for the guidance of the procedure:

- Mean left atrial pressure and mean valve gradient (eFig. 86.2.1). These measures can be criticized because of variations that may occur, particularly with respect to change in heart rate or cardiac output.
- Hemodynamic measurements of the valve area. Repeated evaluation of the valve area during the procedure by hemodynamic measurements lacks practicality and may be subject to error because of the instability of the patient's condition and the inaccuracy of Gorlin's formula in the presence of atrial shunts or in cases of mitral regurgitation. The accuracy of Doppler measurements during valvuloplasty is low (24), so that planimetry from two-dimensional echocardiography appears to be the method of choice when it is technically feasible.
- Changes in the degree of regurgitation. Color Doppler ultrasonography assessment is the method of choice for sequential evaluation.
- Commissural morphology. This can be assessed by two-dimensional echocardiography using the short-axis view (eFig. 86.2.2).



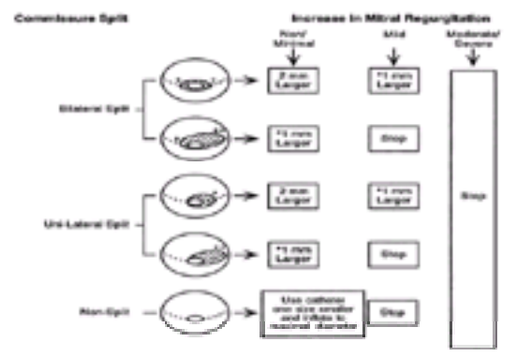
***e*FIGURE 86.2.1** Hemodynamic changes before **(A)** and after **(B)** mitral valvuloplasty. LA, left atrium; LV, left ventricle.



***e*FIGURE 86.2.2** Transthoracic echocardiogram (parasternal short-axis view) showing bicommissural opening.

The following criteria have been proposed for the desired end point of the procedure: (a) mitral valve area greater than 1 cm^2 per square meter of body surface area, (b) complete opening of at least one commissure, or (c) appearance or increment of regurgitation greater than 1 in the Sellers 0 to 4 classification.

Tailoring the strategy to the individual circumstances is vital; clinical factors as well as anatomic factors and the cumulative data of periprocedural monitoring should be taken into account. For example, balloon size, increments of size, and expected final valve area are smaller in elderly patients; in cases of very tight mitral stenosis or extensive valve and subvalvular disease; and in cases of nodular commissural calcification (25). A summary of decision making in the stepwise dilatation technique using the Inoue balloon under echocardiographic guidance is provided in eFigure 86.2.3.



***e*FIGURE 86.2.3** Decision making in the stepwise dilation technique based on echocardiographic findings after each balloon dilation. +, incomplete split; ++, complete split; *, stop in cases of severely diseased valve or age older than 65 years. (Adapted from Inoue K, Hung JS. Percutaneous transvenous mitral commissurotomy: the Far East experience. In: Topol EJ, ed. *Textbook of interventional cardiology.* Philadelphia: WB Saunders, 1994:1226–1243.)

The strong predictive value of the quality of the immediate results for long-term outcome stresses the importance of a careful evaluation of the immediate results. After the procedure, the most accurate evaluation of valve area is provided by echocardiography (26). To allow for the slight loss occurring during the first 24 hours, echocardiography should be performed 1 or 2 days after mitral valvuloplasty (27), when calculation of the valve area may be done by planimetry, the half-pressure time method, or the continuity equation method. The final assessment of the degree of regurgitation may be made by angiography or by Doppler color flow imaging. Transesophageal examination is recommended in cases of severe mitral regurgitation to determine the mechanisms involved. The most sensitive method for the assessment of shunting is Doppler color flow imaging, especially when transesophageal examination is used, which shows the importance of the defect and detects shunting in a more sensitive way than does assessment of hemodynamics.

Immediate Results

The technique of mitral valvuloplasty has now been evaluated in several thousand patients with different clinical conditions and valve anatomy (7,10,11 and 12,14,21,28,29,30,31,32 and 33).

Hemodynamics

The results shown in Table 86.1 demonstrate the efficacy of mitral valvuloplasty, which usually provides an increase of over 100% in valve area.

Study	Number	Valve area (cm^2)	
		Before PMV	After PMV
Tuzcu et al. (10)	311	0.9	2
Ben Farhat et al. (29)	463	1	2.1
Arora et al. (30)	600	0.75	2.2
Chen and Cheng (31)	4,832	1.1	2.1
NHLBI (32)	738	1	2
Iung et al. (33)	1,514	1.1	2
Stefanadis et al. (7)	893	1	2.1
Cribier et al. (21)	882	0.9	2.1
Bonhoeffer et al. (11)	153	0.7	2

NHLBI, National Heart, Lung, and Blood Institute.

TABLE 86.1 VALVE AREA AFTER PERCUTANEOUS MITRAL VALVULOPLASTY (PMV)

The improvement in valve function results in an immediate decrease in left atrial pressure and a slight increase in cardiac index. A gradual decrease in pulmonary arterial pressure and pulmonary vascular resistances is seen. High pulmonary vascular resistances continue to decrease over the first 24 hours after the procedure and decrease further later in the absence of restenosis (34).

Valvuloplasty has a beneficial effect on exercise hemodynamics and exercise capacity, which improves further in the following weeks because of structural and metabolic alterations in skeletal muscle (35,36). The procedure also improves right ventricle function (37) and, to a lesser extent, left ventricle function (38). In addition, studies have shown that this technique improves left atrial and left atrial appendage (39,40) pump function and decreases left atrial stiffness. It also results in a decrease in the intensity of spontaneous echo contrast in the left atrium (41) and improves local hemostasis in the left atrium (42).

Failures

The failure rates range from 1% to 17% (7,14,21,28,29,30,31,32 and 33). Most failures occurred in the early part of the investigators' experience. Others were due to unfavorable anatomy, such as severe left atrial enlargement or cardiothoracic deformity.

Risks

Procedural mortality ranges from 0% to 3% in most series (18,28,29,30,31,32 and 33,43) (Table 86.2). The main causes of death are left ventricular perforation or the poor general condition of the patient. The incidence of hemopericardium varies from 0.5% to 12%. Pericardial hemorrhage may be related to transseptal catheterization or to apex perforation by the guidewires or the balloon itself when exaggerated movement occurs. Embolism is encountered in 0.5% to 5% of cases. It is rarely the cause of permanent incapacitation and even more rarely of death. Embolism may be cerebral or coronary in location, and it may be due to fibrinothrombotic material from a thrombus that was preexistent or developed during the procedure (44), less frequently to gas, and very seldom to calcium. In most cases, the degree of mitral regurgitation remains stable or increases slightly after valvuloplasty. In a few cases, however, the degree of mitral regurgitation may decrease. Severe mitral regurgitation is rare; its frequency ranges from 2% to 19% (45,46,47,48 and 49). Surgical findings (46,47 and 48) have shown that it is related to noncommissural leaflet tearing, which is often associated with chordal rupture. In these cases, one or both commissures are often too tightly fused to be split. Severe mitral regurgitation may also be due to excessive commissural splitting or, in very rare cases, rupture of a papillary muscle. In the majority of cases, severe mitral regurgitation occurred in patients with unfavorable anatomy. The suggestion has been made that the development of severe mitral regurgitation after percutaneous mitral commissurotomy depends more on the distribution of morphologic changes than on their severity (5,49). Severe mitral regurgitation may be well tolerated, but more often it is not, and surgery on a scheduled basis is necessary. In most cases, valve replacement is required because of the severity of the underlying valve disease. Conservative surgery has been successfully performed in cases of less severe valve deformity (47). The frequency of atrial septal defect reported after valvuloplasty varies from 10% to 90% depending on the technique used for its detection (50,51). These shunts are usually small. Right to left shunts can occur on rare occasions in patients with elevated right heart pressures and pulmonary hypertension (52). The incidence of transient, complete heart block is 1.5%, and it seldom requires implantation of a permanent pacemaker (53). After the transvenous approach, vascular complications are the exception. Finally, endocarditis is extremely rare (54). Although urgent surgery (within 24 hours) is seldom needed for complications, it may be required for massive hemopericardium resulting from left ventricular perforation intractable to treatment by pericardiocentesis or, less frequently, for severe mitral regurgitation leading to hemodynamic collapse or refractory pulmonary edema (47).

Study	Number	Mortality (%)	Hemopericardium (%)	Embolism (%)	Severe mitral regurgitation (%)
Tuzcu et al. (10)	311	1.7	–	–	8.7 (>2+ increase)
Ben Farhat et al. (29)	463	0.4	0.7	2	4.6
Arora et al. (30)	600	1	1.3	0.5	1
Chen and Cheng (31)	4,832	0.12	0.8	0.5	1.4
NHLBI (32)	738	3	4	3	3
Iung et al. (33)	1,514	0.4	0.3	0.3	3.4
Stefanadis et al. (7)	893	0.3	0	0	3.1
Cribier et al. (21)	882	NA	1.4	NA	2.1

NA, not available; NHLBI, National Heart, Lung, and Blood Institute.

TABLE 86.2 MAJOR COMPLICATIONS OF MITRAL VALVULOPLASTY

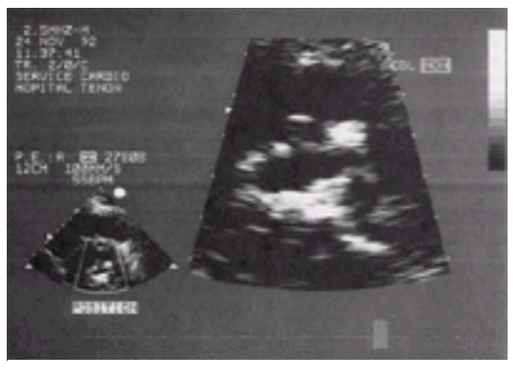
Predictors of Immediate Results

The results from multicenter studies (21,31,55) and large single-center studies (29,30,33), which include a wide population of patients with varied characteristics, enable us to identify predictors of the results to be identified and the strength of these predictors to be evaluated.

Evaluation of the immediate results is based mainly on anatomic criteria. The definition of good immediate results varies from series to series. The two definitions usually used are a final valve area larger than 1.5 cm^2 and an increase in valve area of at least 25%, or a final valve area larger than 1.5 cm^2 without mitral regurgitation greater than 2/4.

Valve anatomy was initially considered (56,57) to be the main predictor of the results, but later it appeared to be only a relative predictor (33,55,58,59). In fact, prediction of results is multifactorial (33,57). Several studies have shown that, in addition to morphologic factors, preoperative variables such as age, history of surgical commissurotomy, functional class, small mitral valve area, presence of mitral regurgitation before valvuloplasty, atrial fibrillation, high pulmonary artery pressure, and presence of severe tricuspid regurgitation, as well as procedural factors such as balloon type and size, are all independent predictors of the immediate results.

The identification of variables linked to outcome enabled the development of predictive models, from which it appears that the sensitivity of prediction is high. Nevertheless, specificity is low, which indicates insufficient prediction of poor immediate results. This latter finding is particularly true with regard to the lack of accurate prediction of severe mitral regurgitation (33,60). This low specificity is related to the intrinsic limitations of the prediction of immediate results, that is, to the possibility of good results in patients who are at high risk for poor results. The possibility of good results in theoretically unsuitable cases has been demonstrated in experimental studies (5) and confirmed clinically (33,59) (*e*Fig. 86.2.4).



***e*FIGURE 86.2.4** Transthoracic echocardiogram (parasternal short-axis view) after valvuloplasty: bicommissural opening, including a calcified commissural area where the balloon has cracked the calcium nodulus, located in the anterior commissure.

Long-Term Results

Data from follow-up at more than 10 years can now be analyzed. In clinical terms, which are the most widely used, the overall long-term results of valvuloplasty are good in a large population of patients comprising a variety of patient subsets (61,62,63,64,65,66,67,68,69 and 70) (Table 86.3). As shown for surgical commissurotomy (71,72 and 73), late outcome after valvuloplasty differs according to the quality of the immediate results (Fig. 86.3).

Study	Number	Mean age (y)	Length of follow-up (y)	Survival (%)	Freedom from operation (%)	NYHA class III (%)
Delimaris et al. (7)	441	44	9	–	–	75
Meneveau et al. (57)	532	54	7.5	80	–	52
Hernandez et al. (58)	561	53	7	95	84	69
Iung et al. (69)	1,024	49	10	85	61	56
Orsinger et al. (65)	132	44	7	95	65	–

NYHA, New York Heart Association.

TABLE 86.3 FOLLOW-UP AFTER MITRAL VALVULOPLASTY

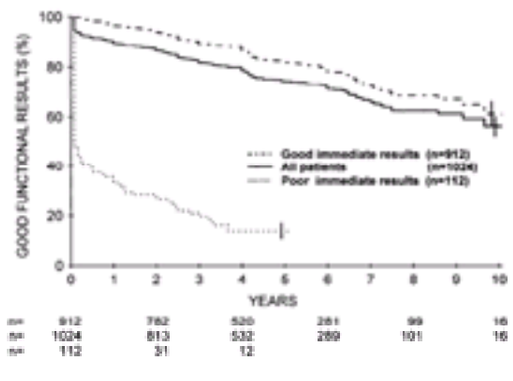


FIGURE 86.3 Long-term results of mitral valvuloplasty. “Good functional results” refers to survival considering cardiovascular-related deaths with no need for mitral surgery or repeat dilatation and in New York Heart Association functional class I or II. (Adapted from Iung B, Garbarz E, Michaud P, et al. Late results of percutaneous mitral commissurotomy in a series of 1024 patients: analysis of late clinical deterioration: frequency, anatomic findings, and predictive factors. *Circulation* 1999;99:3272–3278.)

When the immediate results are unsatisfactory, patients experience only transient or no functional improvement. In these cases, late symptomatic deterioration may be related to lasting poor initial results. In cases of severe mitral regurgitation, the prognosis after surgical commissurotomy or balloon valvuloplasty is usually poor, with lack of improvement in symptoms and secondary objective deterioration; surgical treatment is usually undertaken during the following months. In cases of insufficient initial opening, delayed surgery is usually performed when the extracardiac conditions allow. Here, valve replacement is necessary in almost all cases because of the unfavorable valve anatomy responsible for the initial poor results. In some patients, however, moderate initial improvement in valve function provides functional improvement for several years, although such patients must be carefully followed to allow for a timely operation.

Conversely, if valvuloplasty is initially successful, then survival rates are excellent, functional improvement occurs in the majority of cases, and the need for secondary surgery is infrequent (69). When clinical deterioration occurs in these patients, it is late and mainly related to mitral restenosis.

Determining the incidence of restenosis by echocardiography is compromised by the absence of a uniform definition. It has generally been defined as a loss of more than 50% of the initial gain with a valve area less than 1.5 cm^2. After a successful procedure, the incidence of echographically identified restenosis is usually low,

ranging from 2% to 40% at time intervals of 3 to 5 years (29,31,68,69,74,75). The possibility of repeating valvuloplasty in cases of recurrent mitral stenosis is one of the potentials of this nonsurgical procedure. Repeated valvuloplasty can be proposed if recurrent stenosis leads to symptoms, if it occurs several years after an initially successful procedure, and if the predominant mechanism of restenosis is commissural refusion. At the moment, results of only a small number of series on revalvuloplasty are available; these show good immediate and midterm outcome in patients with favorable characteristics (76). Although the results are less favorable in patients presenting with worse characteristics, repeat valvuloplasty has a palliative role in patients who are not surgical candidates (77). These preliminary results are encouraging; however, defining the exact role of revalvuloplasty must await larger series with longer follow-up.

Predictors of Long-Term Results

Prediction of long-term results is also multifactorial (62,63,64,65,66,67,68 and 69,78,79) and is based on clinical variables such as age; valve anatomy as assessed by different echocardiography scores [one study has shown the negative prognostic value of the presence of commissural calcification (80)]; factors related to the evolutional stage of the disease, that is, a higher New York Heart Association class before valvuloplasty; history of previous commissurotomy; severe tricuspid regurgitation; cardiomegaly; atrial fibrillation; high pulmonary vascular resistances; and the results of the procedure, that is, final valve area, final gradient, and degree of regurgitation. The quality of the late results is generally considered as independent of the technique used (69).

The identification of these predictors provides important information for patient selection and has a relevance to follow-up: patients who have good immediate results but who are at high risk of further events must be carefully followed to detect deterioration and allow for timely intervention. Awareness of these predictors explains the discrepancies in the follow-up results from studies that included patients with different characteristics: late results are clearly less satisfactory in North American or European series (25,62,64,65,67,68 and 69), in which patients are older and frequently have severe valve deformities, than in studies from developing countries, where the patients studied have more favorable characteristics (29,30,61).

Despite interpatient variability, the degree of mitral regurgitation generally remains stable or slightly decreases during follow-up (46,48,51). Atrial septal defects are likely to close over time in the majority of cases because of reduction in the interatrial pressure gradient. The persistence of shunts is related to their magnitude or to unsatisfactory relief of the valve obstruction (81). Finally, clinical series of surgical and balloon commissurotomy suggest that intervention reduces the risk of embolism even if it does not eliminate it (69,82).

Indications

The decision to perform valvuloplasty must be based on both clinical and anatomic variables.

Clinical Variables

Clinical evaluation of patients concentrates mainly on functional disability and the alternative risk with surgery.

For symptomatic patients, the indication for valvuloplasty is perfectly clear. Truly asymptomatic patients, however, are not usually candidates for the procedure because of the small but definite risk inherent in the technique. For patients in the latter group, balloon commissurotomy may be considered in the following cases: patients at high risk of thromboembolism, for example, patients with a previous history of embolism or with heavy spontaneous contrast in the left atrium; and patients with recurrent atrial arrhythmias. Pulmonary hypertension is an adverse prognostic indicator, and patients with pulmonary hypertension are likely to become symptomatic in the near future. Guidelines recommend balloon valvuloplasty for patients with systolic pulmonary pressures higher than 50 mm Hg at rest or 60 mm Hg on exercise (83). Finally, balloon valvuloplasty can be considered for patients requiring major extracardiac surgery or to allow for pregnancy.

Valvuloplasty is the only solution when surgery is contraindicated. It is also preferable to surgery, at least as a first attempt, in patients with an increased risk for surgery of cardiac origin, as in patients with restenosis after surgical commissurotomy. Available data show that the results of the procedure are good in such cases, even if slightly less satisfactory than those obtained in patients without previous surgery (33,84,85 and 86). This suggests that valvuloplasty may well postpone reoperation in selected patients, provided anatomy is still suitable and restenosis is due mainly to commissural refusion. The same reasoning applies in cases of patients who have undergone aortic valve replacement. Preliminary reports have suggested that valvuloplasty can be performed safely and effectively in patients with pulmonary hypertension (87). In cases of coexistence of mitral stenosis and moderate aortic valve disease (88), balloon valvuloplasty can be performed as a means of postponing the inevitable later surgical treatment of both valves.

In Western countries, many patients with mitral stenosis have concomitant noncardiac disease, which may also increase the risk of surgery. Valvuloplasty can be performed as a lifesaving procedure in critically ill patients (89,90 and 91)—as the sole treatment in case of absolute contraindication to surgery or as a bridge to surgery in the other cases. In elderly patients, valvuloplasty results in moderate but significant improvement in valve function at an acceptable risk, although subsequent functional deterioration is frequent (92,93 and 94). In such cases valvuloplasty may be an effective treatment in patients with favorable characteristics. It is also a useful palliative procedure for those who are unsuitable for surgery. In pregnant patients the procedure is efficacious in terms of improving the mother's hemodynamic status; it is also well tolerated by the fetus if performed after the twentieth week. Due to the ever-present risk of complication, use of valvuloplasty should be limited to patients who remain symptomatic despite appropriate other treatment (95,96 and 97).

Anatomic Aspects

The assessment of anatomy has several aims with respect to establishing indications and prognostic considerations. Assuring that no anatomic contraindications exist to use of the technique is very critical (Table 86.4). The first contraindication is the presence of left atrial thrombosis, which must be excluded by the systematic performance of transesophageal echocardiography a few days before the procedure. A contraindication to valvuloplasty is self-evident if the thrombus is floating, localized in the cavity, or on the atrial septum. Second, mitral regurgitation greater than grade 2 in the Sellers classification contraindicates valvuloplasty. Third, in cases of combined mitral stenosis and severe aortic disease, the indication for surgery is obvious in the absence of contraindication for surgery. Fourth, the existence of tricuspid regurgitation is not a contraindication for the procedure even though it represents a negative prognostic factor (98). On the other hand, the presence of combined severe tricuspid stenosis and tricuspid regurgitation with clinical signs of heart failure is an indication for surgery on both valves.

Left atrial thrombosis
Mitral regurgitation greater than 2/4
Massive or bicommissural calcification
Severe aortic valve disease, or severe tricuspid stenosis + regurgitation associated with mitral stenosis
Severe concomitant coronary artery disease requiring bypass surgery

TABLE 86.4 CONTRAINDICATIONS FOR MITRAL VALVULOPLASTY

For prognostic purposes, echocardiographic assessment allows the classification of patients into anatomic groups with a view to predicting the results. Most investigators use the Wilkins score (Table 86.5) for categorization, whereas others, such as our group, use a more general assessment of valve anatomy (Table 86.6). In fact, today none of the scores available has been shown to be superior to the others, and all echocardiographic classifications have the same limitations: (a) technical factors; (b) the difficulty of reproducibility, as they are only semiquantitative; (c) underestimation of the lesions, especially regarding the assessment of subvalvular disease; and (d) the inability of scores describing the degree of overall valve deformity to identify localized changes in very specific portions of the valve apparatus (leaflets, commissures) that may increase the risk of severe mitral regurgitation. Therefore, the use of the system with which one is most familiar and at ease is recommended. More recently, scores that take into account the uneven distribution of the anatomic deformities of the leaflets or the commissural area have been developed (49,99). Preliminary results for their use are promising (100,101) but disputed (102); therefore, further studies are needed to determine their exact value (*e*Table 86.6.1).

Leaflet mobility
1. Valve is highly mobile, with restriction of only the leaflet tips.
2. Midportion and base of leaflets have reduced mobility.
3. Valve leaflets move forward in diastole mainly at the base.
4. No or minimal forward movement of the leaflets occurs in diastole.
Valvular thickening
1. Leaflets near normal (4–5 mm).
2. Midleaflet thickening, marked thickening of the margins.
3. Thickening extending through the entire leaflets (5–8 mm).
4. Marked thickening of all leaflet tissue (≥8–10 mm).
Subvalvular thickening
1. Minimal thickening of chordal structures just below the valve.
2. Thickening of chordae extending up to one-third of chordal length.
3. Thickening extending to the distal third of the chordae.
4. Extensive thickening and shortening of all chordae extending down to the papillary muscle.
Valvular calification
1. A single area of increased echo brightness.
2. Scattered areas of brightness confined to leaflet margins.
3. Brightness extending into the midportion of leaflets.
4. Extensive brightness through most of the leaflet tissue.

Note: The final score is found by adding the scores for each of the components.
From Wilkins GT, Gillam LD, Weyman AE, et al. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J 1988;60:299–308.

TABLE 86.5 ANATOMIC CLASSIFICATION OF THE MITRAL VALVE (MASSACHUSETTS GENERAL HOSPITAL, BOSTON): ECHOCARDIOGRAPHIC EXAMINATION

Echocardiographic group	Mitral valve anatomy
Group 1	Pliable noncalcified anterior mitral leaflet and mild subvalvular disease (i.e., thin chordae ≥10 mm long)
Group 2	Pliable noncalcified anterior mitral leaflet and severe subvalvular disease (i.e., thickened chordae <10 mm long)
Group 3	Calcification of mitral valve of any extent, as assessed by fluoroscopy, any condition of subvalvular apparatus

From Iung B, Cormier B, Ducimetiere P, et al. Immediate results of percutaneous mitral commissurotomy. Circulation 1996;94:2124–2130.

TABLE 86.6 ANATOMIC CLASSIFICATION OF THE MITRAL VALVE

***e*TABLE 86.6.1** CALCULATION OF ECHOCARDIOGRAPHIC SCORE TO PREDICT MITRAL REGURGITATION AFTER PERCUTANEOUS MITRAL VALVULOPLASTY

A/BCalcification/fibrosis of leaflets

*(Score anterior***and***posterior leaflet)*

1. Thickening normal (4–5 mm) or only one thick segment.
2. Evenly fibrotic/calcified without thin areas.
3. Uneven distribution of calcification/thickening. Thinner segments are mildly thickened (5–8 mm).

Uneven distribution of calcification /thickening. Thinner segments are near normal (4–5 mm).

C Fibrosis/calcification of commissures

1. Only one commissure affected.
2. Both commissures mildly affected.
3. Calcification of both commissures: one severely affected.
4. Marked calcification of both commissures.

D Subvalvular disease

1. Minimal chordal thickening just below valve.
2. Chordal thickening to one-third of length.
3. Thickening to distal one-third of chordae.
4. Shortening/fibrosis of all chordae to papillary muscle.

Adapted from Padial LR, Freitas N, Sagie A, et al. Echocardiography can predict which patients will develop severe mitral regurgitation after percutaneous mitral valvulotomy. *J Am Coll Cardiol* 1996;27:1225–1231.

Thus, even if it is not the sole criterion, anatomy is a simple and practical way of selecting patients for valvuloplasty. In patients with good anatomy—that is, pliable valves and moderate subvalvular disease (echocardiographic score of 8 or less)—results of valvuloplasty are generally excellent. Results of several randomized studies with follow-up comparing valvuloplasty and surgical commissurotomy are available (103,104 and 105). They show that valvuloplasty is at least comparable to surgical commissurotomy as regards immediate and long-term results and is no doubt more comfortable for the patient. Valvuloplasty would thus appear to be the procedure of choice for these patients, provided that it is affordable. In addition, if restenosis occurs, patients treated by valvuloplasty could undergo repeat balloon procedures or surgery without the difficulties and inherent risk resulting from pericardial adhesions and chest wall scarring (eTable 86.6.2).

***e*TABLE 86.6.2** COMPARISON BETWEEN VALVULOPLASTY AND SURGICAL COMMISSUROTOMY

	PMC (n = 50)	Open commissurotomy (n = 50)	Closed commissurotomy (n = 50)
Age (yr)	29	28	27
Echocardiographic score	6	6.1	6
Valve area (cm^2)			
Before	0.9	0.9	0.9
After	2.1	2.2	1.6[a]
7 years	1.8	1.8	1.3[b]
Restenosis (%)	6.6	6.6	37[a]

PMC, percutaneous mitral commissurotomy.
[a]p <.0001.
[b]p <.001.
Adapted from Ben Farhat M, Ayari M, Maatouk F. Percutaneous balloon versus surgical closed and open mitral commissurotomy. *Circulation* 1998;97:245–250.

On the other hand, much remains to be done in refining the indications for valvuloplasty in other patients, especially those with unfavorable anatomy (106,107,108 and 109), who are more common in Western countries. For this group, some favor immediate surgery because of the less satisfying results of valvuloplasty, whereas others prefer valvuloplasty as an initial treatment for selected candidates and reserve surgery for cases in which this treatment fails.

PERCUTANEOUS AORTIC VALVULOPLASTY

As reviewed in Chapter 22, Aortic Valve Disease, severe degenerative calcified aortic stenosis is the most frequent valve disease in Western countries, which accounts for the initial interest in its potential treatment by interventional cardiology.

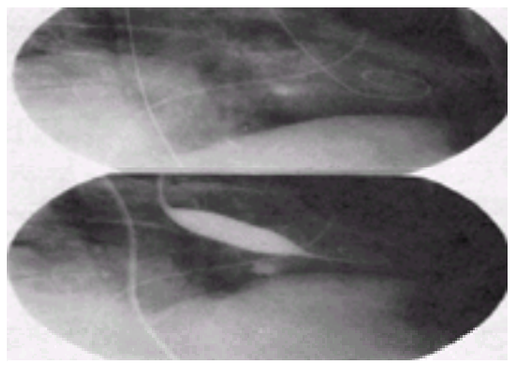
Mechanisms

In degenerative calcific aortic stenosis, calcium deposits are located at the base of the aortic cusps and commissural fusion is rare. These anatomic findings explain why dilation by a balloon has a very limited and transitory effect; results show little macroscopically and are only detectable by microscopic or radiologic studies (110,111). The mechanisms of action proposed are the cracking of the calcified nodulus, which may increase the flexibility of the leaflets, and the stretching of the aortic wall. These mechanisms easily explain the loss of effect that occurs in the hours or days after the procedure; this is secondary to valvular and aortic wall elastic recoil. In addition, later loss may be due to organization and collagenization of scar tissue, which results in fibrosis and ossification (112,113). In rheumatic aortic stenosis, in which commissural fusion does occur, valvuloplasty, which creates commissural splitting, may be theoretically more effective (114).

Technique

Approaches

The femoral retrograde approach is most frequently used (115,116). After placement of an introducer sheath, the aortic valve is crossed (eFig. 86.3.1); this represents the most difficult technical part of the procedure. Then, a stiff wire is inserted into the apex of the left ventricle to stabilize the balloon during inflation (115,116 and 117).



***e*FIGURE 86.3.1** Aortic valvuloplasty: retrograde technique. **Upper panel:** Crossing of the valve with a stiff guidewire with a preshaped tip. **Lower panel:** Dilatation of the valve with a conventional balloon (23 mm).

The alternative is the anterograde approach, which necessitates a transseptal catheterization. This latter technique is a difficult procedure but constitutes a recourse in case of inaccessibility of the femoral approach (117).

Balloons

Valvuloplasty is performed with balloons from 15 mm to 25 mm in diameter, from 3 cm to 5 cm in length, and of variable form: conventional, bifoil, trefoil, or, more recently, double size, which has the advantage of a low profile.

Selection of the balloon size is controversial. The ratio between the size of the balloon and the diameter of the aortic ring must not exceed 1.2 to 1.3 to obtain satisfactory results without increasing risk.

Monitoring of the Procedure and Assessment of Immediate Results

Methods for evaluating immediate results during the procedure include the monitoring of the transaortic gradient and cardiac output, which enables repeated calculation of the valve area. Nevertheless, because of the hemodynamic instability of the patient during the procedure and very early loss in valve area after the procedure, the most viable method is measurement of the valve area by Doppler echocardiography in the days after the procedure (118). Aortography before and after the procedure evaluates any change in the degree of aortic incompetence.

Immediate Results

The technique has been used in several hundred patients, and the results from single-center (115,116 and 117) and multicenter registries (119) can be evaluated. The series reported concern essentially aortic stenosis in older subjects. Any analysis of the results must take into account the severity of the cardiac disease and comorbidities found in such an aged population.

Hemodynamics

Immediately after the procedure the transvalvular pressure gradient is reduced; cardiac output is little modified. Overall, percutaneous aortic valvuloplasty (PAV) reduces tight stenosis to moderate stenosis with a final area between 0.7 and 1.1 cm^2 (115,116,117 and 118,120,121). These results are clearly inferior to those obtained with a valvular prosthesis, which usually provides a valve area over 1.5 cm^2(eTable 86.6.3).

***e*TABLE 86.6.3** AORTIC VALVE AREA AFTER PERCUTANEOUS AORTIC VALVULOPLASTY (PAV)

		Valve area (cm^2)	
Study	**n**	**Before PAV**	**After PAV**
Cribier et al. (115)	506	0.6	1.0
Safian et al. (120)	170	0.6	0.9
Mansfield registry (121)	492	0.5	0.8
NHBLI (119)	674	0.5	0.8
Block and Palacios (124)	375	0.5	0.9

NHLBI, National Heart, Lung, and Blood Institute.

Risks

Mortality and morbidity of the procedure are high (115,116 and 117,119,120,121,122,123 and 124) (Table 86.7). Hospital mortality varies from 3.5% to 13.5%, and 20% to 25% of the patients have at least one serious complication within the first 24 hours. The most frequent complications are vascular complications at the puncture site, which necessitate an intervention in nearly half of the cases. Ventricular perforations are responsible for tamponade. Acute aortic incompetence is rare. Embolic complications are also rare. Two complications are exceptional but can be fatal: mitral regurgitation and the rupture of the aortic ring.

	NHBLI (119) (n = 674)	Mansfield registry (121) (n = 492)	Cribier et al. (115) (n = 368)	Safian et al. (120) (n = 170)
Hospital mortality (%)	10	7.5	4	3.5
Tamponade (%)	0.5	1.8	1	1.8
Severe aortic regurgitation (%)	1	1	0	1.2
Stroke (%)	3	2.2	1.4	0
Myocardial infarction (%)	2	0.2	0.3	0.6
Vascular events[a] (%)	7	5.5	5	10

NHLBI, National Heart, Lung, and Blood Institute.
[a]Vascular events requiring surgical treatment.

TABLE 86.7 IMMEDIATE COMPLICATIONS OF AORTIC VALVULOPLASTY

Predictors of Immediate Results

The immediate outcome is linked to the clinical status of the patient (age, New York Heart Association class, and presence of congestive heart failure) or to procedural complications. Depressed left ventricular function, low cardiac output, and the existence of diffuse coronary lesions are all important covariates associated with worse outcome (115,120,124). Finally, a final valve area smaller than 0.7 cm^2 carries a negative prognosis (124).

Long-Term Results

Despite a relatively modest improvement in valve function, a degree of functional improvement is commonly noted during the first weeks or months. This is of short duration, however. PAV seems to improve survival rates at 1 year and especially improves the quality of life. The benefit decreases, however, and finally disappears after 2 years (115,124,125,126,127 and 128) (Table 86.8). In selected patients, an aortic valve replacement has been subsequently performed with good results (129); on the other hand, the prognosis of the other patients is particularly poor (129,130 and 131) (Fig. 86.4). Overall, the opinion is now that PAV alone does not change the natural course of the disease (132). These poor long-term results are mainly due to the clinical status of the patients and to the moderate and transient improvement in valve function obtained by PAV.

Study	n	Survival (%)				Survival without intervention (%)			
		1 yr	2 yr	3 yr	5 yr	1 yr	2 yr	3 yr	5 yr
Lieberman et al. (127)	165	80	48	35	–	48	15	6	–
Otto et al. (128)	674	55	35	25	–	–	–	–	–
Bernard et al. (136)	46	75	47	–	33	70	25	–	7

TABLE 86.8 RESULTS OF CLINICAL FOLLOW-UP AFTER AORTIC VALVULOPLASTY

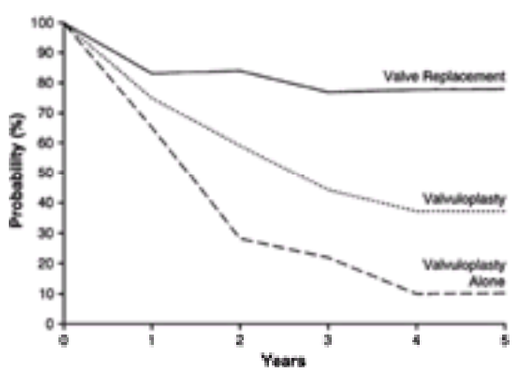


FIGURE 86.4 Long-term survival rate after aortic valve replacement or balloon valvuloplasty. (From Bernard Y, Etievent J, Mourand JL, et al. Long-term results of percutaneous aortic valvuloplasty compared with aortic replacement in patients older than 75 years. *J Am Coll Cardiol* 1992;20:796–801.)

Indications

Comparison with surgical results is difficult because the patients included in the dilatation series are older, are in a more precarious clinical condition, and very frequently have associated comorbidities. After the operative period, surgical results are good, and most of the survivors have good functional status and closely resemble other populations of the same composition of age and gender in terms of life expectancy and quality of life (133,134 and 135). In the absence of randomized studies, the comparison between surgery and PAV is based on retrospective studies such as that of Bernard and colleagues (136), which compared surgical results and results of balloon valvuloplasty in patients over 75 years of age, comparable in age, functional status, and hemodynamics. Therefore, the indications should take into account the excellent results of surgery when it is possible and the poor results of PAV.

In practice, aortic valve replacement is the treatment of choice for symptomatic patients with tight aortic stenosis. Valvuloplasty can be considered only in the following circumstances:

- For critically ill patients with cardiogenic shock with multivisceral failure. Good midterm results have been obtained in limited series if surgical intervention was possible secondarily (137). For this group of patients, valvuloplasty can be considered a bridge to surgery, permitting the secondary operation with less risk.
- For patients with severe, poorly tolerated aortic stenosis who require significant emergency noncardiac surgery.
- For patients who have an absolute, but not life-threatening, short-term contraindication to surgery and have a significant functional disability.
- For patients who refuse surgery.

OTHER PERCUTANEOUS VALVE DILATATIONS

Unlike percutaneous valvuloplasty for mitral and aortic stenosis, other applications of percutaneous valve dilatation have been used only sparingly. The few interventions performed show that the procedures are feasible, but the cases are insufficient in number to allow evaluation of results and establishment of indications.

Percutaneous Tricuspid Valvuloplasty

The indications of tricuspid valvuloplasty are rare. The procedure is reserved for symptomatic patients presenting with tight tricuspid stenosis, pure or associated with mild regurgitation (138,139 and 140). In all other cases in which the tricuspid stenosis is accompanied by significant or moderate regurgitation, or is associated with another valvular disease necessitating surgical treatment, the treatment must be surgery.

Percutaneous Dilatation of Bioprostheses

Anatomic findings and experimental dilatations lead one to conclude that dilatations of bioprostheses do not produce good results (141,142,143,144,145 and 146). They may give rise to severe immediate complications at the level of the left heart (145) and give poor midterm results in the tricuspid position. Percutaneous dilatation may in certain rare cases be performed as a palliative treatment for stenotic degeneration of a bioprosthesis in the tricuspid position (146,147 and 148).

Multiple Dilatations

Actual experience allows one to say only that multiple dilations are technically feasible in selected patients (149,150 and 151). One application that might be imagined in the field of rheumatic pathology is in cases of contraindication to surgery or high surgical risk, such as during pregnancy.

Percutaneous Valve Dilatation and Coronary Angioplasty

Because of the aging of the population in Western countries, the association of calcified aortic stenosis and coronary pathology is frequently encountered; however, the association of a tight mitral stenosis and obstructive coronary lesions is observed much less frequently. Few cases of percutaneous valve dilatations for calcified aortic stenosis and coronary angioplasty in either one or two sessions have been reported (152). In addition, a single case was reported in which dilation for mitral stenosis and coronary angioplasty with stent placement was performed with success (153). The rarity of the indications for aortic dilatation suggests that such a combined procedure has little practical application.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Mitral valvuloplasty is the valvuloplasty technique used most frequently, if not exclusively (154). Because of the good results that have been obtained with mitral valvuloplasty, currently this technique has an important place in the treatment of mitral stenosis. The main objects of controversy and the main questions still to be solved concern economic aspects, the technique itself, and the respective indications for treatment by balloon valvuloplasty or surgery.

Further developments of the technique depend on the possibilities for application in countries where mitral stenosis is endemic and where means are lacking. In such countries, limitations in finances restrict the use of the Inoue balloon or leads to its reuse, with the attendant risks. With this in mind, the price of the devices must be reduced by making them reusable, as with the metallic commissurotome, or by simplifying them, as with the Multi-Track system.

Regarding the choice of technique, the Inoue technique has become the most popular in the world and has been used in more than 30,000 patients with good and reproducible results. The experience with the metallic commissurotome is only preliminary and almost exclusively reported by the promoter of the method. Comparison of the respective merits of this new technique and the Inoue technique requires accumulation of further data concerning the metallic commissurotome and randomized comparisons of the two techniques. In the author's opinion, the efficacy, safety, and applicability of the Inoue technique are clearly established, whereas those of the metallic commissurotome are yet to be fully proven. This new device is unlikely to replace the Inoue balloon in Western countries because safety is probably decreased and the technique is more demanding. On the other hand, a potential exists for the application of the metallic commissurotome in developing countries.

The considerable simplification resulting from use of the Inoue balloon could lead to a false sense of security in the application of the technique and should not overshadow the importance of training. In the author's opinion, performance of percutaneous valvuloplasty should be restricted to groups whose experience with transseptal catheterization has been positive and who have been able to carry out an adequate number of procedures and thus improve their technical performance and ability to select patients. This recommendation carries even more weight in Western countries, where mitral stenosis is infrequent. In particular, valvuloplasty should be performed only in centers with sufficient experience, in cases where patients have minimal symptoms, during pregnancy, or in cases of cardiothoracic deformity. The decision to perform valvuloplasty also depends on the results of surgery at the institution concerned. The potential for valve repair in case of traumatic regurgitation is an important incentive in favor of performing valvuloplasty at an earlier stage of the disease.

The debate on how best to perform the technique must not overshadow other, probably more important matters such as the selection of candidates. Regarding indications, no problems are presented in cases in which surgery is contraindicated or for "ideal candidates," such as young adults (155) with favorable characteristics. On the other hand, much remains to be done in refining the indications for other patients, especially those with minimal symptoms and those with unfavorable anatomy (156).

The level of evidence for performing valvuloplasty in asymptomatic patients is low because no data exist comparing the results of valvuloplasty and medical therapy for such patients. For these patients, the goal is not to prolong life or to decrease symptoms but rather to prevent thromboembolism. The efficacy of valvuloplasty for the specific problem of embolism is not established, but the different findings previously mentioned consistently show the beneficial effect of valvuloplasty on the causes of thromboembolism: intensity of left atrial echocardiographic contrast, size of the atrium, left atrial function, and coagulation activity in the left atrium. No direct evidence exists that valvuloplasty reduces the incidence of atrial fibrillation, even if its favorable influence on predictors of atrial fibrillation, such as atrial size or degree of obstruction, seems to indicate that this is indeed the case. In such patients, valvuloplasty should be performed only by experienced interventionists and when valve anatomy is favorable, in which case a safe and successful procedure can be expected.

Among patients with less favorable valve anatomy (echocardiographic score higher than 8) as a result of extensive subvalvular disease or mild valve calcification, the comparison between the results of valvuloplasty and of surgery is much more difficult. Unfortunately, no randomized study has been performed examining this issue, and comparison of the results of balloon commissurotomy with those of surgical series is difficult due to differences in the patient populations and the fact that the surgical alternative can include surgical commissurotomy, in practice seldom, and also valve replacement in most cases. Valve replacement has its drawbacks: namely, operative mortality, particularly in the elderly, and prosthesis-related complications whose cumulative incidence compromises late outcome, particularly in young patients who are most exposed to the risk of long-term deterioration.

The indications in this subgroup of patients must take into account their heterogeneity with respect to anatomy, especially the extent and location of calcification. The clinical status is even more vital because this subgroup includes patients in good clinical condition and others who are not surgical candidates because of an associated comorbid condition. For this group of patients, an individualistic approach is favored that allows for the multifactorial nature of prediction (Fig. 86.5). The possibility of good results in poor candidates cannot be excluded; consequently, wider indications are proposed for valvuloplasty as an initial treatment in selected patients. Current opinion is that surgery can be considered the treatment of choice in patients with bicommissural or heavy calcification. On the other hand, in the author's opinion, balloon valvuloplasty can be attempted as a first approach in patients with extensive lesions of the subvalvular apparatus or moderate or unicommissural calcification, the more so because their clinical status argues in favor of this. Surgery should be considered reasonably early after unsatisfactory results or secondary deterioration. Extending knowledge regarding this group requires evaluation of new anatomic scores that may be developed in the future using new echocardiographic methods such as three-dimensional imaging (157), predictive models that take into account the multifactorial aspect of the prediction, and, ideally, the conduct of randomized studies on an "intent-to-treat" basis that compare balloon valvuloplasty with surgery. Such studies should include follow-up and should simultaneously be cost-effective.

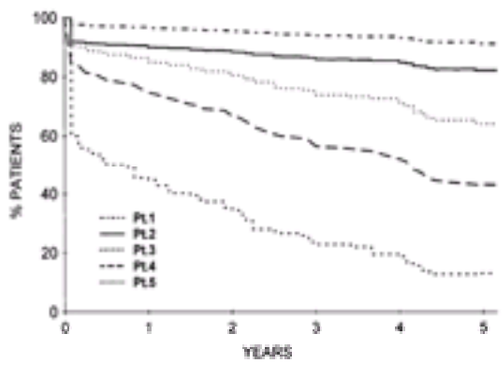


FIGURE 86.5 Multifactorial nature of the prediction of the results of mitral valvuloplasty. Predicted probability of good immediate results (valve area at least 1.5 cm^2 without regurgitation, Seller's grade greater than 2) and good late functional results [survival with no intervention and in New York Heart Association (NYHA) class I or II] according to patient characteristics. Values are given for a procedure using an Inoue balloon with an effective balloon dilating area of at least 5.5 cm^2 (i.e., a final diameter greater than or equal to 27 mm). Pt. 1, less than 50 years, NYHA class II, sinus rhythm, calcium grade I, valve area 1.25 to 1.5 cm^2; Pt. 2, less than 50 years, NYHA class II, sinus rhythm, calcium grade 2, valve area 1 to 1.25 cm^2; Pt. 3, 50 to 70 years, NYHA class III, sinus rhythm, calcium grade 2, valve area 1.25 to 1.5 cm^2; Pt. 4, 50 to 70 years, NYHA class III, atrial fibrillation, calcium grade 2, valve area 1.25 to 1.5 cm^2; Pt. 5, at least 70 years, NYHA class III, atrial fibrillation, calcium grade 3, valve area 0.75 to 1 cm^2. (Adapted from Iung B, Garbarz E, Doutrelant L, et al. Late results of percutaneous mitral commissurotomy for calcific mitral stenosis. *Am J Cardiol* 2000;85:1308–1314.)

In addition, no consensus has been reached regarding indication for valvuloplasty in patients with left atrial thrombosis located in the left atrial appendage and in patients with moderate stenosis.

A number of small series have reported that valvuloplasty is feasible for patients with thrombosis localized in the left atrial appendage (158,159). However, these studies have not satisfactorily shown that even use of the Inoue technique under transesophageal echocardiographic guidance precludes a risk of embolism. In such cases, the indications for valvuloplasty are limited to patients with contraindications to surgery or those without urgent need for intervention, when oral anticoagulation

can be given for at least 2 months and provided a new transesophageal echocardiographic examination shows the disappearance of the thrombus.

The suggestion has been made that valvuloplasty be performed in patients with moderate stenosis in the hope of delaying the natural course of the disease (160). These patients are usually candidates for medical treatment, however, and the risks of valvuloplasty probably outweigh the benefits. To define a threshold of valve area above which valvuloplasty should not be performed is somewhat arbitrary because, besides measuring valve area, one must take into account functional disability and pulmonary pressures at rest and on exercise. The author's current practice is usually to avoid valvuloplasty in patients with a valve area over 1.5 cm^2 or greater than 1 cm^2 per square meter of body surface area for unusually large patients.

Finally, the comparison between percutaneous valvuloplasty and surgery in the future will need to include minimally invasive surgery. In comparison with traditional surgery, these new techniques seem promising from an aesthetic point of view, because they lower potential risk by obviating or limiting the sternotomy, and because they use new videoscopic techniques. Few patients have so far been treated in this way, however, and data are still insufficient to evaluate the efficacy and the safety of the method; moreover, the expectation is that such methods will be reserved for surgeons of wide experience in the field of conservative surgery.

The question today is whether aortic valvuloplasty still really has a place (161,162). Most groups have abandoned the technique, but others see some role for it, albeit a very limited one. The remaining indication is mainly cardiogenic shock, with multivisceral failure if secondary operation is not definitely contraindicated. The use of valvuloplasty to treat rheumatic aortic stenosis should be better evaluated, however, because this might ultimately be an attractive application of the method.

Other percutaneous valve dilatation techniques will probably be used in exceptional cases in tricuspid stenosis or multiple valve disease. Percutaneous dilatation of bioprostheses seems to have no future.

Publication of a report of the first case of percutaneous valve replacement leaves the door open for the future (163).

THE FUTURE

After nearly 15 years of extensive clinical evaluation, the technique of percutaneous valve dilatation, which for practical purposes can be summed up as percutaneous mitral valvuloplasty, is now here to stay. This is because of its proven efficacy in the treatment of mitral stenosis as a substitute for surgical commissurotomy (164) and as a complement to valve replacement.

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CATHETER INTERVENTIONS IN CONGENITAL HEART DISEASE

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OVERVIEW

Transcatheter therapy is routinely performed in many centers for treatment of a wide variety of congenital cardiac defects. These techniques are appropriate for children and adults with congenital heart disease. This chapter describes current interventional therapies available to the practitioner for treating common congenital heart defects. A brief history, technical aspects, indications and contraindications, and early and long-term outcome data, where available, are reviewed for the more common interventions. The uses of implantable devices, such as embolization coils, endovascular stents, and septal occluders, are also examined. Newer technologies representing major advances in transcatheter therapy for congenital heart disease are also discussed.

GLOSSARY

Aortopulmonary shunt: Direct surgical anastomosis or tube-graft (usually Gore-Tex) interposition between the aorta or one of its branches (carotid, innominate, subclavian) and the ipsilateral pulmonary artery that augments pulmonary flow in patients with anatomic limitations to flow. Examples of this type of shunt include Blalock-Taussig shunt, Waterston shunt, and Potts shunt.

Balloon atrial septostomy: Palliative technique pioneered by William Rashkind by which pulling an inflated balloon-tipped catheter through the atrial septum (from left atrium to right atrium) produces an atrial septal defect (ASD) that affords improved mixing of oxygenated and deoxygenated blood.

End-to-end anastomosis: Surgical technique for repair of aortic coarctation by which stenotic aortic segment is resected and the two ends of the nonstenotic aorta are anastomosed.

Fontan operation: Operation used in patients with single ventricle anatomy. Total anastomosis of superior and inferior venae cavae to the pulmonary arteries redirects systemic venous return to the lungs, bypassing the single ventricular chamber.

Glenn procedure: Anastomosis between superior vena cava and pulmonary artery. It may be *bidirectional* (anastomosis to continuous pulmonary arteries) or *unidirectional* ("classic") (anastomosis to single right pulmonary artery).

Modified hepatoclavicular position: Camera angulation during angiography. Position is approximately 40 degrees left anterior oblique/30 degrees cranial in the lateral plane.

Paradoxical hypertension: Acute hypertensive crisis after either surgical correction or rarely after balloon angioplasty for aortic coarctation. These hypertensive episodes are postulated to be secondary to damage to the sympathetic and parasympathetic innervation of the aorta. It is treated with intravenous antihypertensive

drugs.

Prostaglandin E_1: A naturally occurring prostaglandin that can be administered intravenously to induce reopening (or continued patency) of the ductus arteriosus, to permit continued ductal shunting when physiologically advantageous. Used in neonates with severe semilunar valvular obstruction or as palliation in the cyanotic newborn before surgical or transcatheter intervention.

Restrictive patent ductus arteriosus (PDA): PDA internal diameter small enough to restrict flow and pressure from aorta to the pulmonary artery.

Shone's complex: Complex of multiple left-sided heart lesions, usually valvular, subvalvular, or both aortic stenosis; mitral stenosis; and aortic coarctation. In some cases, this complex may also include a ventricular septal defect.

Static balloon dilation: Inflation of the balloon valvuloplasty catheter across the valve annulus, leading to tearing of the fused commissures.

Transposition: D-transposition of the great arteries (pulmonary artery arising from left ventricle, aorta from right ventricle, with atrioventricular concordance).

INTRODUCTION AND HISTORICAL PERSPECTIVE

Pediatric interventional cardiac catheterization was first described by Rashkind (1) in 1966 when he reported the technique of balloon atrial septostomy in infants with transposition; the procedure now carries his name. The field of pediatric interventional cardiology then remained quiescent until 1982 when Kan (2) described percutaneous balloon dilation in children with pulmonary valve stenosis. From 1983 to 1987 a number of centers explored the use of transcatheter therapy for a wide variety of congenital cardiac defects. These included pulmonary valve stenosis, pulmonary artery stenosis, aortic valve stenosis, coarctation of the aorta (i.e., postoperative recurrent stenosis, or native stenosis), PDA, and ASD. By the late 1980s, the field of pediatric interventional cardiology was established as a new subspecialty within pediatric cardiology.

At present, transcatheter therapies are available for 30% to 40% of children with congenital heart disease. Percutaneous balloon dilation is widely regarded as the treatment of choice in children with congenital pulmonary valve stenosis, aortic stenosis, pulmonary artery stenosis, postoperative recurrent coarctation, and PDA. Balloon expandable stent implantation has proven invaluable for treating children with pulmonary artery stenosis, whether it occurs as an isolated lesion or in association with tetralogy of Fallot. Newer data regarding stent therapy for aortic coarctation are encouraging. Promising clinical trials are under way to evaluate the effectiveness of transcatheter occlusion devices as alternatives to surgery in children with a secundum ASD or a muscular ventricular septal defect. Even more novel interventions are being evaluated, the most recent being transcatheter implantation of stent valves in the right ventricular (RV) outflow tract.

This chapter provides an overview of the field of interventional pediatric cardiology. The most common transcatheter therapies currently in use are discussed, with a focus on their indications, contraindications, acute and long-term results, as well as associated complications. Because interventional pediatric cardiology embodies a large number of procedures for a wide variety of cardiac defects, discussion of each procedure is brief.

BALLOON DILATION FOR CONGENITAL AORTIC VALVE STENOSIS

Historical Perspective

Balloon dilation of a congenitally stenotic aortic valve was first described by Lababidi et al. (3,4) in 1983. The procedure was subsequently evaluated in numerous centers (5,6,7,8,9,10 and 11). It soon became apparent that percutaneous balloon dilation provides good short-and intermediate-term relief of aortic valve obstruction in patients with congenital valve stenosis. Initial concerns regarding iliofemoral artery injury in children have diminished with the introduction of small-caliber balloon dilation catheters. To date, there are no prospective trials comparing the outcomes of balloon dilation with those of surgical valvotomy in patients with congenital aortic valve stenosis. Nevertheless, there is widespread agreement that the results of balloon dilation, specifically regarding gradient relief and the occurrence of important valve regurgitation, compare favorably with those of surgery. Thus, percutaneous balloon dilation has been widely adopted as the treatment of choice in this group of patients.

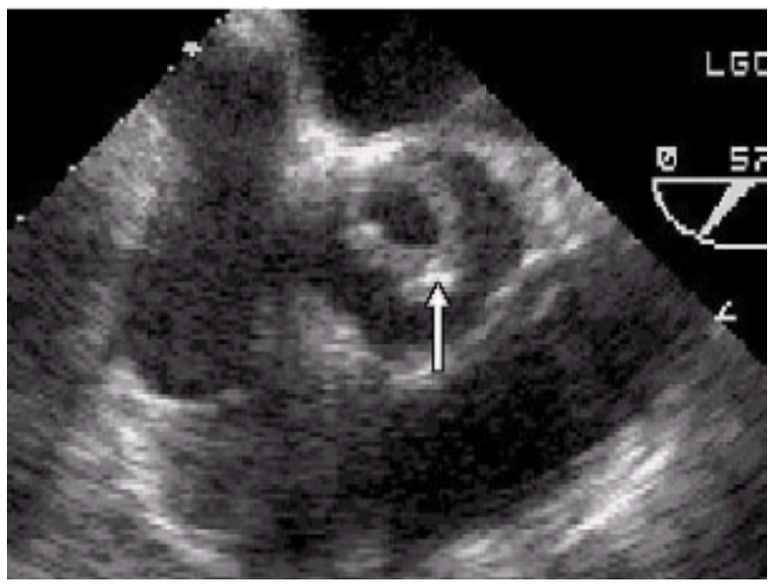
Video 87.1 A 60-degree intraoperative transesophageal echo of a patient with aortic stenosis due to a unicuspid valve (seen in short axis). Note the single commissure at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Unicuspid aortic valve (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Video 87.2 Congenital bicuspid aortic valve with mild aortic regurgitation (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Indications and Contraindications

Indications for percutaneous balloon aortic valvotomy have generally paralleled those previously adhered to for surgical valvotomy. In more recent years, some centers have relaxed their clinical indications due to the perception that the risk-benefit ratio of a percutaneous procedure is probably superior to that of open heart surgery. Currently in our practice, the indications for performing balloon valvotomy in patients with congenital valvar aortic stenosis are (a) peak systolic gradient greater than or equal to 65 mm Hg in an asymptomatic child; (b) peak systolic gradient 45 to 65 mm Hg in a child with electrocardiographic evidence of myocardial ischemia (at rest or during exercise), or with symptoms attributable to myocardial ischemia; and (c) the presence of critical aortic stenosis in an infant with low cardiac output, regardless of gradient.

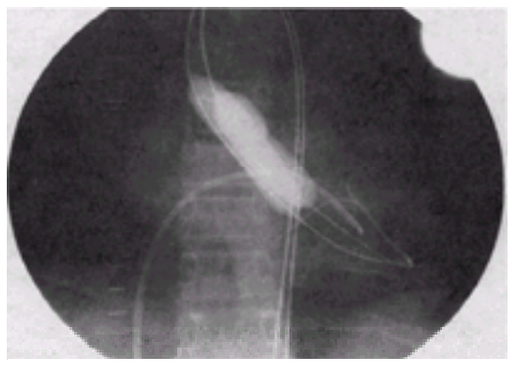


Short-axis transesophageal view of a unicuspid aortic valve with aortic stenosis. The arrow designates the single commissure present in this aortic valve. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)

The contraindications currently adhered to at our institution include (a) mild to moderate aortic valve stenosis in an asymptomatic child, (b) the presence of associated severe aortic regurgitation (of sufficient severity to warrant valve replacement), (c) important hypoplasia of the aortic valve annulus (e.g., less than 5 mm in a newborn), and (d) calcific aortic valve stenosis.

Technique

The technique of percutaneous balloon dilation for congenital aortic valve stenosis has been previously reported in detail. The procedure is most often performed using a retrograde transarterial approach, although an antegrade transvenous route has been used in some centers. In newborns, we often use a transumbilical arterial approach (12), thus sparing the newborn femoral artery. A carotid artery cutdown has also been described by Fischer et al. (13) to minimize femoral complications in neonates. This approach has been used in newborns as small as 1,600 g (14). The transcarotid approach also has an additional advantage in patients with associated coarctation of the aorta, which may make catheter manipulation around the arch difficult. Once arterial access is obtained, the stenotic valve is crossed in a retrograde fashion. A soft-tipped wire must be used in newborns and with extreme caution to avoid perforating an aortic valve cusp. A balloon with an inflated diameter of 90% to 100% of the measured diameter of the aortic valve annulus is used (eFig. 87.0.1). Balloons with an inflated diameter that is wider than that of the aortic annulus are avoided because they increase the risk for important valve regurgitation. Throughout the procedure, left ventricular (LV) pressure is monitored in infants by an antegrade catheter placed across the foramen ovale or by a transseptal puncture in older patients. Patients are fully heparinized, and the activated clotting time is monitored (target, 250 to 300 seconds), with the exception of critically ill acidotic newborns. The balloon (or balloons, in the case of a double-balloon technique) is inflated briefly by hand one to four times, with care taken to observe the waist of the stenotic valve near the midportion of the balloon. After dilation, repeat hemodynamic measurements are obtained, and an aortic root angiogram is performed to document the presence and severity of any aortic regurgitation that may have been produced.



***e*FIGURE 87.0.1** Double-balloon aortic valve dilation in a 9-year-old boy with congenital aortic valve stenosis. A 12-mm balloon and a 15-mm balloon are used in tandem to effectively dilate an aortic valve annulus measuring 21 mm in diameter.

Acute and Long-Term Results

The largest study describing the acute outcome after balloon dilation in children with congenital aortic stenosis was reported by the Valvuloplasty and Angioplasty of Congenital Anomalies Registry (11) in 1990. The Valvuloplasty and Angioplasty of Congenital Anomalies Registry reported data from 240 children whose short-term data were submitted to the registry after balloon dilation procedures performed between 1986 and 1992. It should be noted that the registry made no attempt to standardize the dilation procedure itself or data analysis practices. The patients in this report ranged in age from newborn to young adult, with a mean age of 10.1 years. All patients had congenital valvular aortic stenosis of a moderate to severe degree. Balloon dilation of congenital aortic valve stenosis can generally be expected to decrease peak systolic gradient to a range of 25 to 35 mm Hg (i.e., mild), with a 10% incidence of increase in aortic valve regurgitation. Less satisfactory gradient relief typically indicates either a suboptimal technical procedure or the presence of complex LV outflow tract disease (i.e., annulus hypoplasia, subvalvular stenosis, or calcific stenosis).

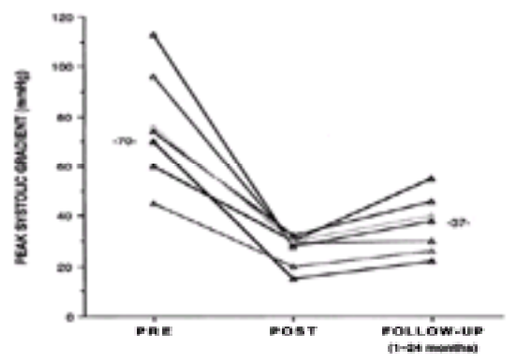
The longer-term results of aortic valve balloon dilation for congenital stenosis indicate that, as with surgery, the procedure is palliative. Several studies (15,16 and 17) have shown satisfactory gradient relief for a period of 2 to 5 years, and longer-term benefits can be expected. Shim et al. (18) noted that successful balloon aortic valvuloplasty was effective in decreasing LV mass in children with isolated aortic stenosis. In this study, the decrease in LV mass was gradual and was not statistically

significant until the second year after successful valvuloplasty.

As with surgical valvotomy, balloon dilation can only be expected to palliate patients with congenital valvular aortic stenosis (19). It is to be expected that a substantial proportion of patients experience progressive restenosis or important valve regurgitation on late follow-up after aortic valve dilation. Repeat balloon dilation is effective in most patients who experience restenosis after aortic balloon valvotomy (20), as it is with restenosis after surgical valvotomy (21).

Neonates

Neonates with critical aortic stenosis constitute a high-risk complex subgroup that deserves special mention. Newborns with critical aortic stenosis present with severe LV dysfunction and shock. Often these patients must be resuscitated with prostaglandin E_1 and inotropic support. As with older children, balloon dilation has been shown to be an effective palliative therapy in newborns with critical aortic valve stenosis (12,22,23 and 24) (*e*Fig. 87.0.2). Egito et al. (24) described the results of balloon dilation in 33 neonates ranging in age from 1 to 33 days. Twenty-seven of these newborns had LV dysfunction, and most were receiving prostaglandin E_1 infusions and were intubated. The procedure was performed from the umbilical artery in 11, from the femoral artery in 20, and antegrade across a patent foramen ovale (PFO) in two children. A second valve procedure was required in 12 children during the follow-up period, underscoring the palliative nature of this procedure in newborns. Mosca et al. (25) compared the results of neonatal balloon dilation with those of surgical valvotomy for critical aortic stenosis and found no significant difference between the procedures in the degree of gradient reduction, aortic regurgitation, or patient survival.



***e*FIGURE 87.0.2** Peak systolic aortic valve gradient in seven newborn infants with critical aortic valve stenosis. Measurements are made immediately before (PRE), immediately after (POST), and at 1 to 24 months after transumbilical aortic valve dilation. In these patients the peak systolic gradient was reduced from 70 to 37 mm Hg at follow-up.

Complications

Beyond the newborn period, balloon aortic valvotomy is a relatively safe procedure. Immediate postoperative complications that have been reported include aortic valve regurgitation, iliofemoral artery injury, hemorrhage, ventricular rrhythmia, endocarditis, valve leaflet or ventricular perforation, injury to the anterior mitral leaflet, and death. Death has been exceedingly uncommon after elective balloon dilation in childhood. The complications of greatest concern have been valve regurgitation and arterial injury. In the Valvuloplasty and Angioplasty of Congenital Anomalies Registry (11), aortic regurgitation reportedly occurred in only 10% of the children studied. More recent experience (15) suggests that balloon dilation produces new aortic insufficiency in 25% to 30% of patients, in most of whom it is mild. Severe aortic insufficiency is detected in approximately 5% to 6% of patients after the procedure. The occurrence of aortic insufficiency may relate to a balloon-annulus ratio that exceeds 1.0 (11) or to valve morphology (7).

Injury to the iliofemoral artery most frequently occurs in infants younger than 12 months. For this reason, the authors advocate use of the transumbilical route whenever possible for balloon dilation in newborns with critical aortic stenosis (12). Infants are at particular risk for iliofemoral artery injury because of the relatively large profile of the balloon catheters required in transfemoral arterial procedures. Although important clinical consequences of such vascular injury appear to be uncommon, subsequent transarterial procedures may be difficult or impossible to perform. Development in the future of lower profile valvuloplasty balloon catheters may well help to alleviate this problem.

Complications are substantially more frequent and more severe in neonates. The mortality in newborns with critical aortic stenosis is high and ranges from 10% to 20% after balloon dilation in this patient population (24,25). Other important complications in the newborn include LV perforation with the wire or catheter, aortic valve leaflet perforation and subsequent dilation producing severe valvular insufficiency, arrhythmia, hemorrhage, sepsis, and endocarditis. To avoid perforating the valve, retrograde entrance into the LV must be performed with a soft wire; perforation of a leaflet may be recognized if the wire does not pass freely through the subvalvular area and into the LV apex. To avoid sepsis or endocarditis, vancomycin should be administered for all transumbilical dilation procedures.

BALLOON DILATION OF CONGENITAL PULMONARY VALVE STENOSIS

Historical Perspective

Balloon valvotomy was first performed for pulmonary stenosis. The rationale for this technique was provided by early surgical experience that demonstrated the efficacy of transventricular dilation of stenotic pulmonary valves. In 1979 Semb et al. (26) reported a dynamic technique in which a gas-filled balloon was withdrawn across a stenotic pulmonary valve. In 1992, Kan et al. (2) reported the first static balloon dilation in children with pulmonary valve stenosis; this technique is still used today. After these early reports, many institutions confirmed the safety and efficacy of percutaneous balloon dilation for pulmonary valve stenosis. The technique can be expected to reduce the peak systolic valve gradient to approximately 20 to 30 mm Hg, which represents mild clinically insignificant pulmonary stenosis. With the exception of neonates, pulmonary valve dilation is associated with few complications. The procedure has clearly replaced surgical valvotomy as the treatment of choice in congenital pulmonary valve stenosis (27,28,29,30,31 and 32).

Indications and Contraindications

Balloon dilation effectively treats typical, congenital valvular pulmonary stenosis. Indications for such therapy at our institution include (a) a peak systolic gradient greater than or equal to 35 mm Hg; and (b) critical pulmonary valve stenosis in an infant regardless of gradient (pressure gradient may be diminished by right-to-left atrial shunt, a patent ductus, or both).

HEART SOUNDS

Audio 87.3 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 87.4 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 87.5 Pulmonic valve stenosis. Auscultation in a 24-year-old female patient with repaired tetralogy of Fallot and homograft pulmonic valve replacement. There is mild pulmonic valve stenosis with mean gradient of 9 mm Hg. Left upper sternal border (*first clip*), left lower sternal border (*second clip*), and apex (*third clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The only contraindication to this procedure in a child with valvar pulmonary stenosis is the presence of mild asymptomatic stenosis having a peak systolic gradient less than 35 mm Hg. Conditions under which balloon dilation often fails to provide definitive therapy, and which therefore may be considered relative contraindications, include (a) a dysplastic pulmonary valve (e.g., in Noonan's syndrome); and (b) a hypoplastic pulmonary valve annulus (less than 7 mm in newborns).

It should be noted, however, that children with these two relative contraindications may derive significant palliation from balloon dilation despite a dysplastic or hypoplastic valve.

Technique

Percutaneous balloon pulmonary valvotomy can be performed using a relatively straightforward technique. Once baseline hemodynamics and valve annulus diameter are measured, an end-hole catheter is advanced across the valve and positioned in the left pulmonary artery. Using an exchange length wire, the catheter is then exchanged for a balloon dilation catheter of appropriate size (i.e., a balloon with a diameter that is approximately 25% to 30% wider than that of the valve annulus). A double-balloon technique is used in patients whose annulus diameter is greater than 15 to 18 mm. The balloon(s) are inflated and deflated rapidly by hand, with careful attention to ensure that the waist created by the stenotic valve occurs in the midportion of the balloon. After one to four inflations, the deflated balloons are withdrawn and repeat hemodynamics are measured. An RV angiogram may be obtained after dilation to document the site of any residual stenosis (particularly dynamic infundibular stenosis) and to assess any possible resultant increase in tricuspid valve regurgitation (rare).

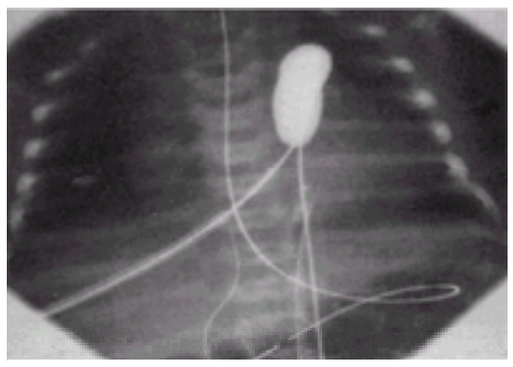
Acute and Long-Term Results

The immediate and long-term effectiveness of balloon dilation for congenital pulmonary valve stenosis has been documented by many institutions (27,28,29,30,31,32,33,34 and 35). The procedure generally decreases the systolic gradient to levels consistent with mild stenosis. An oversized balloon (i.e., one that is approximately 25% to 30% wider than the annulus diameter) is required for optimal dilation outcome (33). In some patients, an important element of the residual gradient is due to a transient dynamic subvalvar (infundibular) stenosis. The data indicate that balloon dilation is less effective in patients with dysplasia of the pulmonary valve, with or without Noonan's syndrome.

Thus far, longer-term results have been excellent (32,34,35). A report of late results (4 to 5 years) after balloon dilation in children with congenital pulmonary stenosis compared with those in a matched control group of children who had undergone surgical pulmonary valvotomy was encouraging (35). Noninvasive evaluation at follow-up documented excellent gradient relief in both groups. The Doppler peak instantaneous gradient at follow-up was 24.0 ± 2.7 mm Hg in the balloon dilation group compared with 16.0 ± 2.0 mm Hg in the surgical valvotomy group. At late follow-up, children who had undergone balloon dilation had no or only mild pulmonary valve insufficiency. In contrast, the surgical control group had substantially more valve insufficiency. The increase in ventricular arrhythmias at follow-up may relate to the greater prevalence and severity of pulmonary valve insufficiency and RV volume overload in the surgical group, although the duration of follow-up was also longer in these children. These data support the currently and generally accepted practice of using balloon dilation as the therapy of choice in children with pulmonary valve stenosis.

Neonates

Balloon dilation in neonates with critical pulmonary valve stenosis represents a special, more complex, and higher-risk subgroup. In most centers percutaneous transcatheter therapy has become the preferred mode of treatment for these children; however, it requires substantially more technical expertise in neonates than in older children (36,37,38,39 and 40). Newborns with critical pulmonary stenosis typically present with cyanosis (due to a right-to-left atrial shunt) and require prostaglandin E_1 infusion for medical palliation. A PDA is clearly advantageous during the dilation procedure. An open ductus arteriosus not only provides a reliable source of pulmonary blood flow during balloon inflation, but also provides a stable wire course (RV to pulmonary artery to ductus to descending aorta), which facilitates catheter exchanges (eFig. 87.0.3). The effectiveness of balloon dilation is related to right-sided heart anatomy, specifically the diameters of the pulmonary and tricuspid valves and the RV volume. In infants with an adequate right heart (i.e., with a tricuspid valve greater than 11 mm, a pulmonary valve annulus greater than 7 mm, and an RV volume greater than 30 mL per m^2), balloon dilation provides definitive long-term therapy (39). In infants with more hypoplastic right-sided heart structures, balloon dilation does not usually provide sufficient long-term therapy; in these children an early aortopulmonary shunt or an RV outflow tract patch may be required.



***e*FIGURE 87.0.3** Transhepatic balloon dilation of critical pulmonary valve stenosis in a newborn. The guidewire has been advanced down the ductus and is positioned in the descending aorta. There was no residual gradient measured immediately after the dilation procedure.

Complications

Outside of the newborn period, percutaneous balloon dilation for congenital pulmonary valve stenosis is quite safe (31). Complications, especially in newborns, include perforation of the RV outflow tract while attempting to cross a severely stenotic valve, important systemic hypotension during balloon inflation (in children without intracardiac shunting), arrhythmias, and pulmonary valve insufficiency. Pulmonary valve insufficiency is generally well tolerated, although severe valve insufficiency may be problematic in infants, particularly those who also have tricuspid insufficiency, who subsequently require an aortopulmonary shunt.

BALLOON DILATION FOR CONGENITAL MITRAL STENOSIS

Historical Perspective

Congenital mitral stenosis is a rare congenital heart lesion constituting less than 2% of autopsy-delineated congenital cardiac defects. Worldwide, most cases of mitral stenosis are still acquired as a result of rheumatic heart disease. Initial attempts at percutaneous mitral valvuloplasty were made by Reifart et al. and Inoue et al. in 1984 and 1985 in adult rheumatic heart disease (41,42,43 and 44). In 1985, Lock et al. (45) reported use of this technology in children with rheumatic mitral stenosis. Subsequently, there have been increasing numbers of single center reports in the pediatric literature (46,47).

Access to the mitral valve is secured by a transseptal approach after balloon dilation of the atrial septal perforation using an 8- to 10-mm angioplasty balloon. If large

12- to 14-Fr sheaths are used, no septal dilation is recommended. Grifka et al. (48) have shown that double-balloon or double-transseptal techniques result in no significant atrial shunts and fewer vascular problems in younger patients. A more secure wire position is initially achieved in children by passage of the exchange wire antegrade through the aortic valve into the descending aorta, which differs from the technique in adults. Some investigators (49) have described snaring of the exchange wire from the femoral artery and passage of the dilation balloons in a retrograde fashion. Once the dilation catheters are securely across the stenotic mitral valve, the guidewires are retracted into the LV apex and the balloons are inflated for 10 to 15 seconds.

Indications and Contraindications

As in older patients, symptoms of dyspnea, heart failure, pulmonary artery hypertension, or failure to thrive are indications for intervention. The patient's body size and requirements for large introducer sheaths may limit transcatheter intervention in children. The presence of valve calcifications may also limit the effectiveness of this procedure in some patients. Leaflet calcifications have proven to be a major hindrance to success in the adult population (50). Valve morphology also affects the outcome of balloon dilation therapy. Significant short-term restenosis and poor short-term gradient reduction are common in infants with asymmetric papillary muscles or a hypoplastic mitral valve annulus. A parachute mitral valve is not amenable to balloon dilation.

Acute and Long-Term Results

Early reports revealed 40% to 50% long-term success after the procedure in children (45,48,50,51). More recent single-center studies have demonstrated acute procedural success in more than 90% of patients (47) with long-term follow-up to greater than 4 years. This compares with data after surgical valvotomy, which provides 70% survival, 71% freedom from further surgeries, and 6% freedom from mitral valve replacement (52,53 and 54). Obviously, outcome data are affected by patient selection because valve morphology is such an important variable.

Complications

Balloon mitral valvuloplasty is relatively safe in the majority of children. Unlike adults, there are few instances of postdilation hemoptysis, pulmonary edema, or thromboembolic events reported in children. The incidence of acute severe mitral insufficiency due to torn or flail mitral leaflets varies from 3.3% to 6.3% in different series (46,47). Arrhythmias, particularly second- and third-degree atrioventricular block, have been reported in as many as 20% of children after mitral balloon dilation. Pericardial effusions from ventricular perforations and transient ischemic attacks have also been reported to occur rarely in children.

BALLOON DILATION FOR PULMONARY ARTERY STENOSIS

Historical Perspective

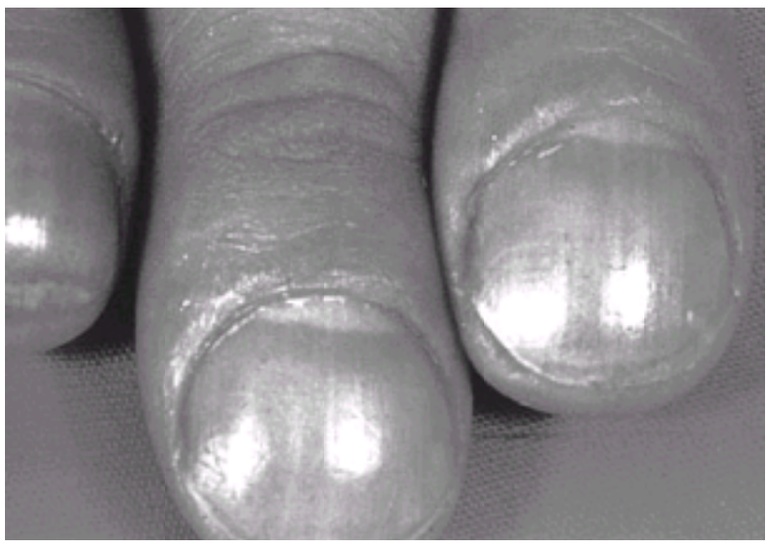
Isolated peripheral pulmonary artery stenosis represents 2% to 3% of congenital heart lesions, but has a high (20% to 40%) association with other forms of congenital RV outflow tract obstruction (i.e., tetralogy of Fallot, with or without pulmonary atresia). Acquired peripheral pulmonary artery stenosis also frequently occurs after surgical procedures. A significant association exists between peripheral pulmonary artery stenosis and maternal rubella syndrome, Williams syndrome, and Alagille syndrome, with a reported prevalence of 50% to 90% of these children. The initial report demonstrating the utility of balloon angioplasty in this condition appeared in 1980 (55), and data were reported from an experimental model of peripheral pulmonary artery stenosis by Lock et al. in 1981 (56). Transcatheter therapy for pulmonary artery stenosis plays an important role in staged therapy for many children with complex congenital heart disease.

HEART SOUNDS

Audio 87.6 Tetralogy of Fallot. Auscultation performed in a 25-year-old male with newly diagnosed tetralogy of Fallot. Note the mid-systolic ejection murmur probably related to right ventricular outflow tract obstruction. Left lower sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 87.7 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Clubbing. There is bullous enlargement of the distal portion of the digit as a result of increased soft tissue. This may be associated with cyanotic heart disease.

VIDEO

Video 87.8 Parasternal short-axis view of tetralogy of Fallot. Note the ventricular septal defect just beneath the right coronary cusp of the aortic valve. The infundibular pulmonic stenosis can be seen superiorly while the pulmonary valve with its vegetation can be seen to the upper right of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 87.9 Parasternal long-axis view of tetralogy of Fallot. Note the ventricular septal defect and the aorta and aortic valve overriding the interventricular septum. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 87.10 Color Doppler in the apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect by color flow and the overriding aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

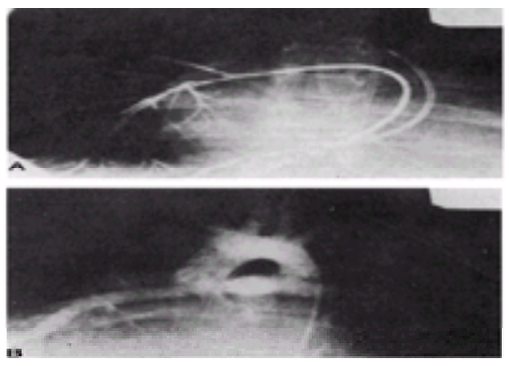
Video 87.11 Apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect, the overriding aorta, and the right ventricular hypertrophy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Indications and Contraindications

Isolated balloon angioplasty without concomitant endovascular stent implantation is primarily used in the very young child or in individual patients in whom stent implantation may be technically challenging. Clinical indications for intervention include (a) evidence of RV strain or hypertrophy, (b) RV failure, or (c) significant RV systolic hypertension of greater than 60% of systemic systolic pressure. In addition, because of the value of nuclear perfusion scanning in defining flow disturbances due to obstruction, evidence of significantly diminished perfusion to one lung has been used as an additional indication.

Acute and Long-Term Results

There have been numerous reports (57,58,59,60,61,62 and 63) of the acute and long-term results after balloon angioplasty. Although technical success (e.g., increased vessel diameter greater than 75%, decreased systolic pressure gradient and RV systolic pressure less than 50% systemic, increase of greater than 25% in pulmonary blood flow, increased ipsilateral lung perfusion) has been reported in more than one-half of patients (eFig. 87.0.4), sustained improvement beyond 6 months is less common. Syndromic patients (Williams or Alagille) tend to have the poorest outcomes after balloon angioplasty, probably as a result of significant vessel elastic recoil. In light of these mediocre results, Gentles et al. (64) have recommended using higher-pressure balloons (i.e., maximal inflation pressure of 17 to 20 atm). Nevertheless, because of intrinsic vessel elasticity, endovascular stenting is preferred to balloon angioplasty alone in many patients (65).



***e*FIGURE 87.0.4** Shown here are selective pulmonary angiograms before successful balloon angioplasty **(A)** and after successful balloon angioplasty **(B)**. There is marked improvement in the right pulmonary artery diameter. A patency of the ductus arteriosus is shown **(B)** with left-to-right shunting. (From Beekman RH, Rocchini AP, Rosenthal A. Therapeutic cardiac catheterization for pulmonary valve and pulmonary artery stenosis. *Cardiol Clin* 1989;7:331, with permission.)

Complications

Angioplasty of peripheral pulmonary artery stenosis is accompanied by relatively high morbidity (5% to 16%) and mortality (3.0% to 4.5%) compared with other transcatheter procedures for congenital heart disease. Major complications include wire perforation of the distal pulmonary artery, vessel tear by the dilation itself, need for surgical repair, and, rarely, death. Significant aneurysm formation of the dilated vessel occurs in 0.5% to 5.0% of patients, although smaller aneurysms have reportedly been detected by intravascular ultrasound in greater than 80% of patients undergoing the procedure (66). Segmental pulmonary edema distal to the dilated segment occurs in 0.5% to 3.0% of patients (67).

BALLOON DILATION: COARCTATION OF THE AORTA

Historical Perspective

Surgical therapy for coarctation of the aorta was first described in 1945 by Gross and Hufnagel (68) and by Crafoord and Nylin (69). The multitude of surgical and transcatheter therapies that have subsequently been reported for coarctation suggests that the optimal form of treatment is not yet clearly identified. Nevertheless, currently balloon angioplasty is widely regarded as the treatment of choice for discrete recurrent coarctation that develops late after surgical repair. In contrast, the role of angioplasty in the treatment of native (unoperated) aortic coarctation remains controversial. Early *ex vivo* human and *in vivo* animal experiments (70,71 and 72) revealed 1-to 3-mm intimal tears with variable but nontransmedial extension into the media that healed within 8 weeks and no significant aneurysm formation.

Video 87.12 Color Doppler interrogation of the coarctation demonstrating the high-velocity, turbulent flow across the focal narrowing in the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Audio 87.13 Coarctation of the aorta. Auscultation performed in a 54-year-old female patient with coarctation of the aorta, status post Dacron graft replacement of the proximal descending aorta and persistent severe graft stenosis. The mid-systolic ejection murmur is a result of residual high-grade coarctation. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 87.14 Coarctation of aorta (oblique). A signal-void jet is visible in the proximal descending aorta due to a short-segment narrowing representing a coarctation.

Left ventricular hypertrophy is also present. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The technical approaches to balloon angioplasty of coarctation vary. Aortography is performed to visualize the coarctation and to obtain measurements for selecting the appropriate balloon catheter. Most cardiologists use a standardized aortic measurement (i.e., the aortic isthmus diameter above the coarctation, approximately three times the coarctation diameter itself, or the descending aortic diameter at the level of the diaphragm) to determine balloon size. There are no data to support that using any one method of choosing balloon size is better than another. Most agree, however, that the balloon diameter should not exceed by more than 1 to 2 mm the aortic diameter at the diaphragm. Pressure measurements and aortography are obtained after angioplasty to evaluate residual systolic gradients and to visualize acute intimal dissections or early aneurysm formation. Importantly, postangioplasty manipulation across the coarctation region with unguided wires or catheters must be avoided to prevent vessel perforation. Early data (73,74 and 75) suggest that stent implantation may avoid the early aortic recoil that is noted relatively often after naked balloon angioplasty.

Indications and Contraindications

Indications for intervention include an anatomically discrete stenosis in association with a resting systolic pressure gradient of greater than or equal to 20 mm Hg. Some consider intervention for smaller resting gradients if they are associated with significant upper extremity hypertension at rest or with exercise. Tubular nondiscrete coarctations are not as amenable to balloon angioplasty alone (78) as more discrete lesions (although stenting may offer promise in these more complex lesions). Balloon angioplasty of native coarctations in the neonate or young infant is almost invariably complicated by early restenosis, and therefore most centers do not perform angioplasty in this age group.

Acute and Long-Term Results

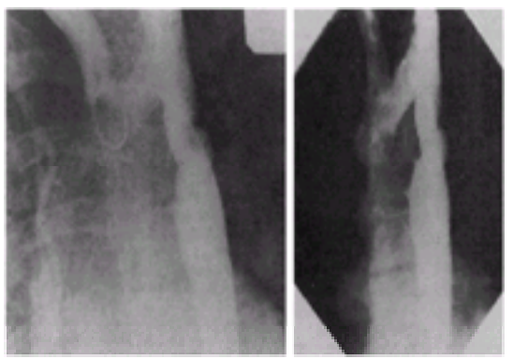
Many centers have reported their short-term results after balloon angioplasty for native coarctation (76,77,78,79,80 and 81). In the majority of patients, the resting gradient is reduced to less than 20 mm Hg. Early studies that compared older patients with younger patients demonstrated similar acute results in neonates and infants, but significantly worse long-term results in these younger children (82,83,84,85 and 86). Complete relief of hypertension (i.e., blood pressure less than 140/90 mm Hg, no requirement for medications) has been reported in approximately 40% of older children (78); however, in the adult population, the need for antihypertensive medications postprocedure remains significant (76). Interventions performed at younger age (younger than 1 year) may reduce late-onset systemic hypertension (87). More recent studies (88) have demonstrated an inverse relationship between procedural success and higher predilation and postdilation gradients, degree of transverse arch hypoplasia, or both, whereas a direct relationship exists between insufficient tearing of the intima and media and procedural failure. The incidence of late aneurysm formation at the dilation site is 5% to 10% in patients with a native coarctation, similar to that reported in patients with recurrent postoperative coarctation.

Good clinical results have been reported in more than 300 patients with recurrent aortic coarctation (89,90,91,92,93,94 and 95). More recent studies of balloon angioplasty in postsurgical recoarctation reveal an equivalent 16% restenosis rate between younger and older patients at mean 56-month follow-up (96). The incidence of aneurysm formation postangioplasty in the patient with recurrent coarctation is 5% to 10%. As with patients with native coarctations, long-term success of this procedure may be related to arch anatomy and balloon size. Anjos et al. (93) observed that if the ratio of aortic isthmus diameter to diaphragmatic aortic diameter was less than 0.8, 80% of patients had a poor result at follow-up, whereas if the ratio was greater than 0.9, 81% had sustained improvement. The type of previous surgical repair, age at surgery, and predilation systolic pressure gradients did not affect long-term outcomes.

Complications

Aneurysms

The reported incidence of late aneurysm formation after coarctation angioplasty varies from 4.5% to 13.4% (82,85) (*e*Fig. 87.0.5). It is postulated that aneurysms develop after the creation of intimal and transmedial tears in an intrinsically abnormal aortic wall. Isner et al. (97) demonstrated cystic medial necrosis of varying degrees in 80% of excised human coarctation specimens. Similar problems of aneurysm formation, spontaneous aortic dissection, and rupture have been reported in 17% to 23% of untreated patients with aortic coarctation (98,99). Postangioplasty aneurysms appear to be less common in infants and younger children than in older adolescents and young adults. More follow-up data are needed to better define the risk for aortic aneurysms after coarctation angioplasty.



***e*FIGURE 87.0.5** In this figure, spot cineangiograms are shown 2 years **(left)** and 8 years **(right)** after coarctation balloon angioplasty. The small, saccular aneurysm at the coarctation site remains stable in size and configuration at long-term follow-up. (From Mendelsohn AM, Lloyd TR, Crowley DC, et al. Late follow-up of balloon angioplasty in children with a native coarctation of the aorta. *Am J Cardiol* 1994;74:696, with permission.)

Restenosis

In contrast to aortic aneurysms, restenosis or recurrent coarctation after balloon angioplasty appears to be much more common in younger patients (*e*Fig. 87.0.6). In neonates and infants, 12-month follow-up restenosis rates vary from 30% to 70% (83,84), whereas restenosis occurs in only 7% to 11% of older patients (84,85 and 86). If additional intervention is required, standard surgical techniques or repeat balloon angioplasty (and possibly stenting) generally yield excellent results.

***e*FIGURE 87.0.6 A:** Serial spot cineangiograms are shown from a 4-month-old child before balloon angioplasty (*left*) and after balloon angioplasty (*right*). Systolic gradient balloon angioplasty decreases from 54 to 8 mm Hg. **B:** Within 9 months there was angiographic evidence of recurrent coarctation (*left*). Coarctation was retreated successfully with angioplasty (*right*), and systolic gradient decreased from 45 to 15 mm Hg. (From Mendelsohn AM, Lloyd TR, Crowley DC, et al. Late follow-up of balloon angioplasty in children with a native coarctation of the aorta. *Am J Cardiol* 1994;74:696, with permission.)

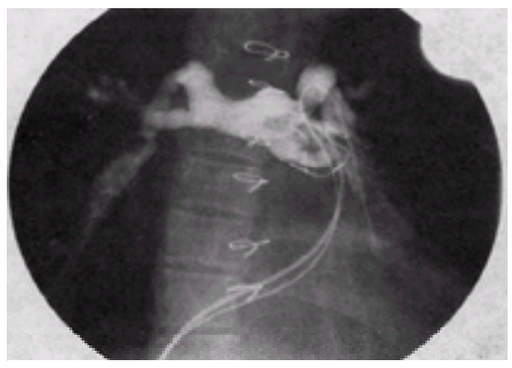
Paradoxical Hypertension

Episodes of paradoxical hypertension occur rarely after balloon angioplasty (100) and less frequently in patients after angioplasty than in patients after surgical repair (101,102). This may potentially be due to lower serum renin and catecholamine levels in the postangioplasty patients, disruption of the afferent thoracic sympathetic fibers with surgical coarctectomy, or both (101).

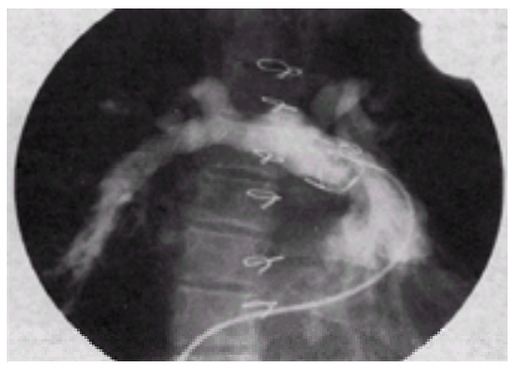
ENDOVASCULAR STENTS IN CONGENITAL HEART DISEASE

Historical Perspective

Balloon expandable stents have rapidly assumed an important role in interventional pediatric cardiology. For patients with congenital or acquired vascular stenosis, balloon angioplasty alone or surgery often fail to provide adequate relief of obstruction. By providing an endovascular buttress to maintain vessel patency, balloon expandable stents have radically improved the treatment options for children with these lesions. Stenting is particularly useful in pulmonary artery stenosis or hypoplasia occurring as an isolated lesion, in tetralogy of Fallot, or pulmonary atresia and ventricular septal defect, often after initial palliative surgical procedures (*e*Fig. 87.0.7 and *e*Fig. 87.0.8). Stenting has also proven valuable in patients with systemic venous obstructions such as superior vena cava stenosis or systemic venous baffle obstruction after the Mustard procedure. Data have appeared indicating that stenting is also an effective intervention for selected patients with coarctation of the aorta.



***e*FIGURE 87.0.7** A pulmonary arteriogram is shown from a 13-year-old girl with pulmonary atresia and ventricular septal defect demonstrating severe right pulmonary stenosis.



***e*FIGURE 87.0.8** A Palmaz P308 stent has been implanted in the lower right pulmonary artery, effectively relieving all obstruction at that level. The patient subsequently underwent successful surgical ventricular septal defect closure.

Dotter and Judkins (103) proposed stenting in 1964 when they described an endovascular splint to maintain vascular patency. In 1969, Dotter (104) reported the first animal experiments that clearly identified the exciting potential of stent therapy. The stainless steel balloon expandable stent most commonly used in pediatric cardiology was developed by Palmaz and Schatz (105) in the mid-1980s. Investigations at several pediatric centers (106,107 and 108) using experimental animal models demonstrated the effectiveness of stents in treating pulmonary artery and systemic venous stenosis. Shortly thereafter, clinical trials (109,110,111 and 112) documented excellent short-term results with balloon expandable stents in children with these vascular stenoses. Endovascular stenting with the Palmaz stainless steel stent (Johnson & Johnson Interventional Systems, Warren, NJ) is now the treatment of choice at many centers for patients with pulmonary artery or systemic venous obstruction. More recent intermediate follow-up data (113,114) have documented the favorable effect of pulmonary artery stenting on patient management, noting that restenosis is relatively infrequent when stents are implanted in large pulmonary arteries or systemic veins (112,113,114,115 and 116), and that pulmonary artery stents can be redilated safely after a child has grown (112,116,117 and 118). Data have also demonstrated that stenting is more cost effective than balloon dilation alone in patients with pulmonary artery stenosis (119).

Indications and Contraindications

Indications for endovascular stents are rapidly evolving; however, stenting is now considered a primary therapeutic modality for many children. The size of the patient is an important consideration for several reasons. A stent implanted in a small child may well require redilation once the child has grown, and there is minimal long-term experience with stent redilation. We therefore prefer to implant a stent initially to the largest diameter appropriate for the child. Larger stents with an outside diameter of 3.4 mm must be delivered through an 8- to 10-Fr sheath; thus, percutaneous implantation in children smaller than 8 kg may be difficult. We have used the transhepatic approach in some patients to overcome limitations of traditional peripheral venous access. Intraoperative implantation of large stents may prove useful in some small children, particularly if such implantation can be incorporated into another surgical procedure (111). The indications for endovascular stents in children are (a) pulmonary artery stenosis or hypoplasia of moderate to severe degree; (b) stenotic RV to pulmonary artery conduits; (c) superior vena cava stenosis; (d) stenosis of the systemic venous baffle (superior or inferior limb) after atrial repair of transposition; (e) stenotic aortopulmonary collaterals in selected patients with tetralogy of Fallot or pulmonary atresia; and (f) recurrent postoperative coarctation, and possibly native coarctation, in patients able to safely accept 8- to 9-Fr arterial sheaths.

Contraindications to endovascular stenting include (a) a stenosis that is not balloon dilatable; (b) small patient size precluding use of a large delivery sheath (transhepatic or intraoperative delivery may be considered); and (c) pulmonary venous obstruction (pulmonary venous stenting is invariably unsuccessful).

Technique

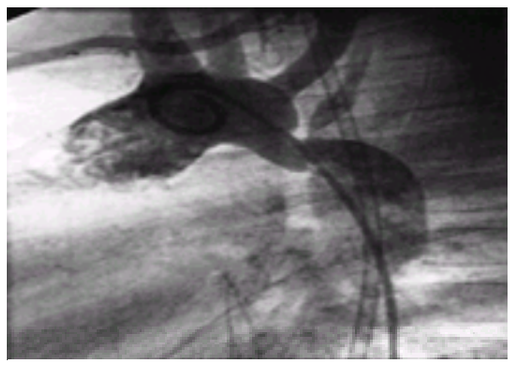
The Palmaz stainless steel balloon expandable stent is the stent most often used in congenital cardiovascular disease. Self-expanding stents limit future redilation when a child has grown and are therefore rarely used in children. The Palmaz P308 stent has a length of 30 mm and an outer diameter of 3.4 mm and can be expanded to a maximal diameter of 19 to 20 mm; it requires an 8- to 10-Fr delivery sheath. The Palmaz 204 stent has a length of 20 mm and an outside diameter of 2.4 mm, and it can be dilated to a maximum diameter of 9 to 10 mm; it requires a 6- to 7-Fr delivery sheath. Stent implantation is performed after a complete hemodynamic and angiographic evaluation. The diameter of the stenosis is carefully measured, as is the vessel proximal and distal to the stenosis to determine the stent and balloon size most appropriate for the lesion. We typically do not predilate vascular stenoses, but do predilate conduits to assess whether the stenosis is dilatable. With a 0.035- to 0.038-in. stiff exchange wire positioned across the stenosis, an appropriate delivery sheath is advanced across the area to be stented. The stent is mounted and tightly hand crimped on the balloon to ensure that the stent does not strip off within the sheath. We often use a front-loaded, or modified front-loaded, technique to minimize the need to advance the stented balloon through the delivery sheath; this is especially important with tortuous catheter and sheath courses. Once the stent is positioned within the delivery sheath at the site of stenosis, the sheath is carefully withdrawn to a point just proximal to the balloon. Contrast is injected through the side arm of the sheath or through a second catheter to document that the stent is properly positioned. The balloon is inflated using an inflation manometer, and the stent is implanted. The deflated balloon is then withdrawn through the sheath, leaving the exchange wire in place. The stent can then be dilated with a larger balloon if

necessary. Angiography is performed again to document the position of the stent, its diameter, the status of side branches that may originate through the stent, and to rule out any important vessel tear or perforation. Patients are discharged on low-dose aspirin or warfarin when stents are implanted in the venous circulation of patients with a univentricular heart (after the Glenn or Fontan procedures).

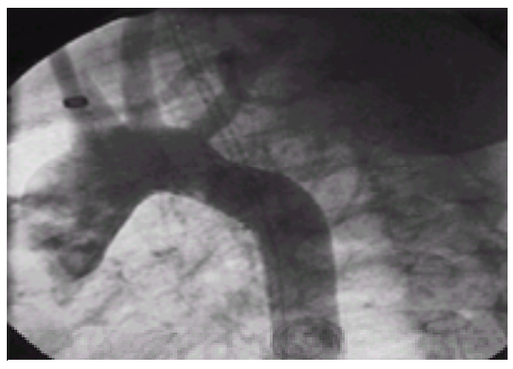
Acute and Long-Term Results

In pediatric cardiology, stenting is most often used to treat pulmonary artery stenosis or hypoplasia. Several centers (109,110,111,112,113 and 114) have reported favorable short- and intermediate-term results. Angiographic evidence of modest 1- to 2-mm neointimal ingrowth is commonly observed, but is rarely physiologically important in large vessels. Data indicate that endovascular stenting provides important intermediate-term clinical benefits to many patients with pulmonary artery stenosis. Pulmonary artery stents can be safely redilated to larger dimensions, if necessary, in growing children up to 3 years after stent implantation (112,113,117); longer-term studies of redilation are needed to document that stents can be safely enlarged more than 3 years after implantation.

Recent data suggest that stenting also provides effective treatment for coarctation of the aorta (73,74 and 75,120). In patients with postoperative recurrent coarctation (*e*Fig. 87.0.9 and *e*Fig. 87.0.10) or native unoperated coarctation, stenting generally reduces the resting gradient to less than 5 mm Hg. In addition to typical discrete coarctation, transverse arch hypoplasia may also respond favorably to stenting (121). Limited follow-up data suggest that restenosis and aneurysm formation are uncommon. However, before coarctation stenting is widely accepted as routine, longer-term follow-up data are needed regarding restenosis, aneurysm formation, safety of late stent redilation, and blood pressure response to exercise after this novel therapy.



***e*FIGURE 87.0.9** Lateral angiogram showing a moderate arch stenosis in a 7-month-old child with hypoplastic left ventricle, after a Norwood reconstruction.



***e*FIGURE 87.0.10** After implantation of a Palmaz 308 stent (through a right carotid cutdown because of the patient's small peripheral vessels). There is no residual stenosis. Same patient as in *e*Figure 87.0.9.

Complications

Complications of endovascular stenting include (a) stent embolization, (b) vessel tear or perforation, (c) in-stent thrombosis, (d) side branch compromise, (e) transient distal reperfusion injury after pulmonary artery stenting, and (f) stent fracture at redilation (112). In a multiinstitutional study, O'Laughlin et al. (112) reported one possible stent-related death after the Fontan procedure in a patient who had embolization of a preexisting right atrial clot to the stented lung. Six stents embolized or were positioned incorrectly and were removed either at surgery or through a large percutaneous sheath. Stents placed in pulmonary arteries of patients with a univentricular heart after Fontan or Glenn procedures are at increased risk for thrombosis, particularly if postoperative events such as atelectasis diminish pulmonary arterial flow to the ipsilateral lung. To avoid these complications, aggressive anticoagulation is advocated in such patients for a minimum of 6 months after stent implantation.

PERCUTANEOUS COIL EMBOLIZATION OF PATENT DUCTUS ARTERIOSUS

Historical Perspective

PDA is a relatively common condition that, with the exception of newborns, is usually treated electively. For decades pediatric cardiologists have pursued a method for nonsurgical closure (122,123,124,125,126,127 and 128). It was not until 1992, however, that the technique of percutaneous coil embolization of the PDA was first reported (129). Coil occlusion of the PDA has rapidly become the treatment of choice in many institutions for small to moderate restrictive PDA (130,131,132,133,134,135,136 and 137).

The Gianturco coil (Cook Incorporated, Bloomington, IN) is the most frequently used embolization device for closing PDA. This coil is made of a stainless steel wire with Dacron strands to promote thrombus formation (138,139). Vascular occlusion occurs after coil implantation as the result of thrombus formation and subsequent organization (140). The Gianturco coil has been used since the 1970s for transcatheter occlusion of a variety of arterial vessels and venous channels. Percutaneous coil embolization with the Gianturco coil is widely regarded as safe and effective transcatheter therapy for PDA. There have been several modifications to the Gianturco coil, which may make them more suitable for PDA coil occlusion. These modifications include the shape of the coil (e.g., Tornado coil), which allows itself to more readily conform to the shape of the PDA, and ampulla, which may decrease the likelihood of residual shunting. Also, detachable coils have made coil occlusion technically easier with less chance of embolization. However, all these modifications increase the cost of the coil, and for the small (less than 2.5 mm) PDA, standard Gianturco coil embolization remains the procedure of choice.

Indications and Contraindications

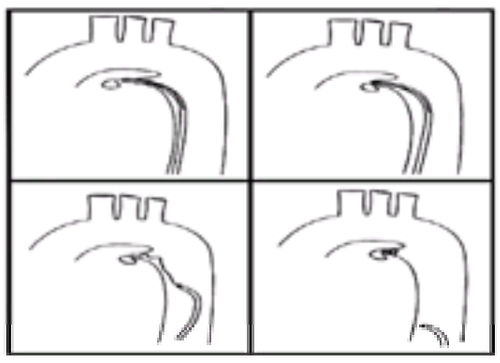
Percutaneous coil embolization provides effective nonsurgical treatment for the restrictive PDA. Here, the clinical objective usually is to diminish the long-term risk for infective endarteritis, and much less frequently, to treat the physiologic consequences of a significant left-to-right shunt. In our program, the most common indication for this procedure is a restrictive PDA with a minimal angiographic diameter of less than 4 mm.

Conditions that are currently considered to be contraindications to coil occlusion include (a) a large nonrestrictive PDA (e.g., a PDA in a neonate); (b) pulmonary vascular obstructive disease with a right-to-left ductus shunt; and (c) associated heart disease requiring surgical intervention.

Technique

Occlusion coils can be delivered to a PDA either retrogradely using a transarterial approach or antegradely from the venous circulation. The transarterial approach is preferred, because it requires only a single catheter for coil delivery and angiography. A 4- to 5-Fr pigtail catheter is introduced percutaneously through an arterial sheath, and the patient is given heparin (100 U per kg; maximum dose, 3,000 U). The pigtail catheter is then used to obtain complete left-sided heart hemodynamics.

An aortic angiogram is filmed in the anteroposterior and lateral projections, and the minimum ductus diameter is measured from the lateral image. A Gianturco coil with a helical diameter two to three times that of the minimum angiographic ductus diameter is used. The length of the coil must be sufficient to allow three or four loops of coil to form on implantation (two or three loops in the aortic ampulla). We prefer to use a 0.038-in. Gianturco coil. Using a 4- to 5-Fr Judkins right coronary catheter (a Bernstein catheter is also frequently used), the ductus is crossed in a retrograde fashion. Pulmonary artery pressure is then measured and a blood sample is obtained to measure oxygen saturation. The Gianturco coil is then advanced to the tip of the delivery catheter and approximately two-thirds of one complete loop is extruded in the main pulmonary artery (eFig. 87.0.11). The catheter-coil unit is then withdrawn until the distal coil engages the narrowest portion of the ductus. The pushing wire is then held steady so as not to push more coil into the pulmonary artery while the delivery catheter is withdrawn off the intraaortic portion of the coil. When the coil is released from the catheter its intrinsic elasticity causes it to seat within the aortic ampulla. A repeat aortogram is then filmed 10 to 15 minutes after coil delivery to document the degree of occlusion (eFig. 87.0.12 and eFig. 87.0.13). If more than a trivial shunt persists, a second, usually smaller, coil is implanted. We have not found it necessary to enter the right side of the heart unless there is significant associated intracardiac disease or the coil has to be retrieved. Patients are discharged after 4 to 6 hours of observation.



***e*FIGURE 87.0.11** Schematic illustration of the transarterial method for patent ductus arteriosus coil occlusion. This technique differs from the method used to occlude aortopulmonary collaterals. Approximately three-fourths of one coil loop is advanced into the pulmonary artery. The delivery catheter is then withdrawn into the aorta, releasing two or three coil loops in the ductus ampulla. (From Hijazi ZM, Lloyd TR, Beekman RH, et al. Transcatheter closure with single or multiple Gianturco coils of patent ductus arteriosus in infants weighing < or = 8 kg: retrograde versus antegrade approach. *Am Heart J* 1996;132:827, with permission.)

***e*FIGURE 87.0.12** This figure shows a lateral aortogram demonstrating a small conical patent ductus arteriosus.

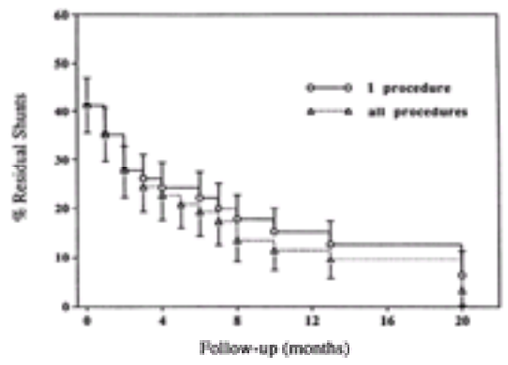
***e*FIGURE 87.0.13** In this figure, there is no residual shunt noted on angiography immediately after percutaneous coil occlusion.

A number of modified PDA coil occlusion techniques have been described. Some investigators have delivered coils antegradely from the venous circulation; however, this usually also requires an arterial line to perform arteriography after occlusion. Using a wire snare to hold the pulmonary artery end of the coil during transarterial delivery has proved helpful in some centers (133) to diminish the incidence of coil embolization to the pulmonary artery. Besides the Gianturco stainless steel coil, other coils have also been used, including platinum microcoils for a tiny ductus and, more recently, detachable coils that may decrease the risk for extraductal coil embolization.

Acute and Long-Term Results

Acute and intermediate-term results of coil embolization for small to moderate PDAs have proved to be excellent (141,142). The PDA Coil Registry (141) has reported the results of its first 535 procedures performed in 38 cardiology centers. Complete early occlusion was shown to be significantly related to ductus diameter. In those patients with complete and immediate occlusion, the minimum ductus diameter was 1.9 mm, compared with 2.4 and 2.9 mm in patients who experienced partial occlusion or in whom coil implantation failed, respectively. The data also indicated that failure to successfully implant a coil was significantly more frequent in patients with a short angiographic type B ductus. A more recent study (142) has also shown that percutaneous coil retrograde or antegrade occlusion may well prove successful in a high proportion of infants weighing less than 8 kg.

There are few longer term follow-up data available for coil occlusion of the PDA. The available data indicate, however, that intermediate-term effectiveness of this technique is excellent and that complications are few. In a series of 75 patients (136), the prevalence of residual shunts was high (41%) immediately after percutaneous coil embolization, a manifestation of ignoring small residual shunts early on. Follow-up Doppler-echocardiography documented a high incidence of spontaneous closure of these small residual shunts. Actuarial analysis estimated that the prevalence of residual shunts at 20 months after a single coil procedure was 6% (eFig. 87.0.14). When analysis included five patients who had undergone a second coil procedure for residual shunting, the prevalence of residual shunting dropped to 3% at 20 months. The relationship of ductus diameter to outcome was similar to that reported by the PDA Coil Registry (141). The minimal angiographic diameter was 1.2 mm in those patients with immediate and complete occlusion after a single coil implantation, 1.9 mm in patients who had a small residual shunt that closed spontaneously during follow-up, and 2.5 mm in patients who required two coils for immediate and complete occlusion of the ductus.



***e*FIGURE 87.0.14** A Kaplan-Meier analysis demonstrates the relationship between proportion of patients with residual ductal shunting and duration of follow-up in months. After single-coil procedures, the actuarial estimate of the prevalence of residual shunt is 15% at 10 months and 6% at 20 months of follow-up. These data document the high incidence of spontaneous closure of small residual shunts after coil occlusion of patent ductus arteriosus. (From Shim D, Fedderly RT, Beekman RH, et al. Follow-up of coil occlusion of patent ductus arteriosus. *J Am Coll Cardiol* 1996;28:207, with permission.)

Complications

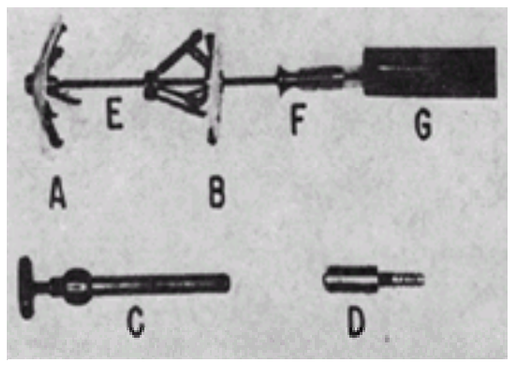
The most common complications reported with coil embolization for a PDA are failure to successfully implant the coil and extraductal coil embolization. The PDA Coil Registry currently contains data regarding 817 PDA coil occlusion procedures in 800 patients from 46 institutions. In 5% of patients, a coil could not be implanted in the ductus because of technical or patient-related issues (e.g., patients with a ductus that was too large). In another 11%, a coil embolized to an extraductal vascular structure, most frequently a distal pulmonary artery branch. Ninety-five coils embolized to a distal pulmonary artery in 75 patients. Seventy-five coils were percutaneously retrieved, but 20 were left in the pulmonary artery without evident clinical complications. One coil was left in a small splenic artery branch, and no clinical consequence was reported. Other complications occurred in 29 patients and were regarded as general complications of cardiac catheterization procedures. A femoral hematoma was reported in 2.0% of patients, fever in 0.5%, oversedation in 0.4%, and drug allergy in 0.4%, and transfusions were required in 0.2% of patients. There were no deaths attributable to coil occlusion. Significant hemolysis relating to residual shunting across a PDA has also been reported after coil implantation (143). Because a portion of the coil is positioned in the proximal left pulmonary artery, some investigators have expressed concern as to whether pulmonary artery stenosis may develop after this procedure; however, preliminary studies suggest that this is not the case (144).

Radiation exposure associated with coil occlusion of PDA has been shown to be comparable with those undergoing standard diagnostic catheterization and pulmonary balloon valvuloplasty (145). Total fluoroscopy time was 10.1 ± 1.8 minutes in patients receiving coil occlusion of their PDA. This was also comparable with the patients receiving diagnostic catheterization and was significantly less than patients undergoing pulmonary balloon valvuloplasty.

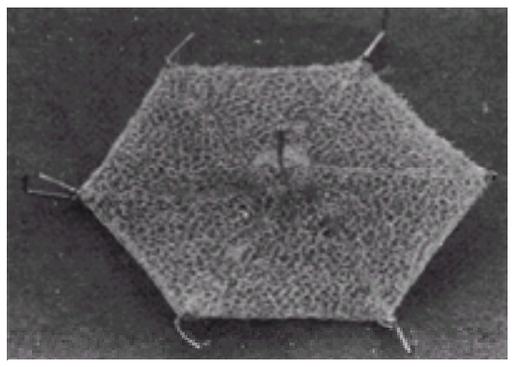
TRANSCATHETER CLOSURE OF ATRIAL SEPTAL DEFECTS

Historical Perspective

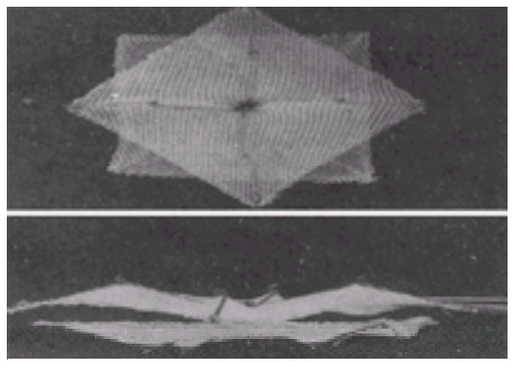
Surgical repair (146) is the conventional method for closing the secundum ASD, but this is about to change. Over the past 20 years, design improvements have led to significant progress in the transcatheter approach to ASDs. Initial attempts at device closure of ASDs were first reported in 1959 by Hufnagel and Gillespie (147), who implanted plastic buttons in ASDs at the time of thoracotomy. In 1974, King and Mills (148) created the first ASD occlusion device suitable for transcatheter implantation (*e*Fig. 87.0.15). This was closely followed by the single-disk Rashkind ASD occlusion device (*e*Fig. 87.0.16) (149,150). The Clamshell occluder (now CardioSEAL) has been under evaluation since 1989 (*e*Fig. 87.0.17) (151,152 and 153). The Sideris buttoned device is now in its fourth generation (*e*Fig. 87.0.18) (154,155 and 156). Unlike the previous devices described, this device is manufactured as two separate components that are physically connected (or buttoned together) during cardiac catheterization. The Das Angel Wings device was introduced into clinical trials in 1993 (*e*Fig. 87.0.19) (157,158 and 159). Most recently, promising experience with the Amplatzer Septal Occluder device have been reported (*e*Fig. 87.0.20) (160,161 and 162).



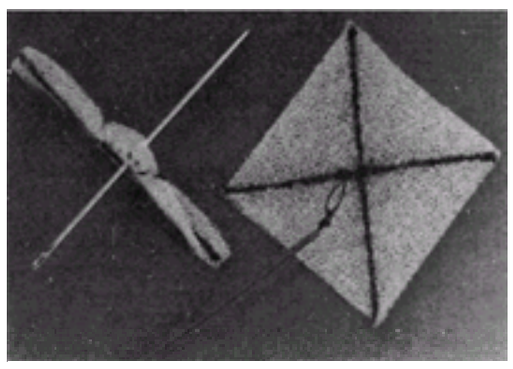
***e*FIGURE 87.0.15** King and Mills device. Teflon-coated, stainless steel skeleton composed of two interlocking disks with central connecting pin on which a Dacron patch was mounted. (From King TD, Mills NL. Nonoperative closure of atrial septal defects. *Surgery* 1974;75:383, with permission.)



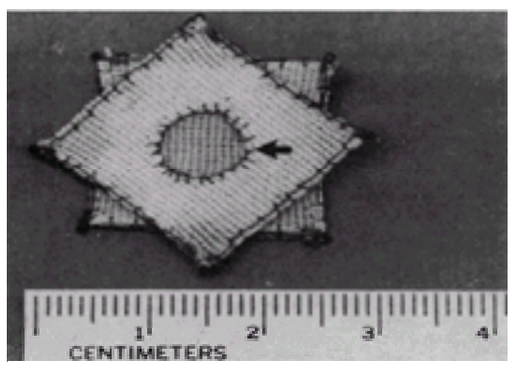
***e*FIGURE 87.0.16** Rashkind occlusion device. A single disk of polyurethane foam mounted on a stainless steel skeleton. The hooks are designed to appose firmly to left atrial septal surface. (From Rashkind WJ. Interventional cardiac catheterization in congenital heart disease. *Int J Cardiol* 1985;7:1, with permission.)



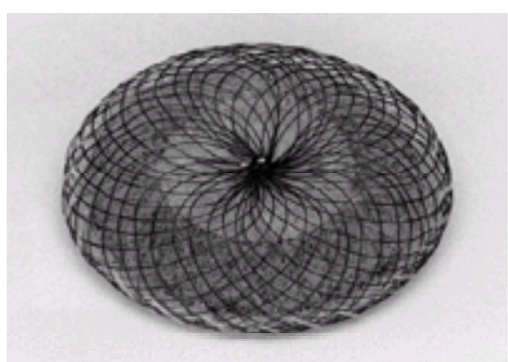
***e*FIGURE 87.0.17** Clamshell occluder. This occluder is composed of two stainless steel frames with multiple articulated arms and Dacron fabric overlay. (From Rome JJ, Lock JE, Davis R, et al. Transcatheter closure of atrial septal defects: experimental studies. *Circulation* 1989;79:1091, with permission.)



***e*FIGURE 87.0.18** Sideris "button" occluder. A two-component system comprised of an occluder, an X-shaped stainless steel wire frame with polyurethane fabric, and counteroccluder, a rhomboid-shaped wire of polyurethane construction with a central rubber grommet through which the knotted button is passed. (From Sideris EB, Sideris SE, Thanopoulos BD, et al. Transvenous atrial septal defect occlusion by the buttoned device. *Am J Cardiol* 1990;66:1524, with permission.)



***e*FIGURE 87.0.19** Das Angel Wings occluder. This occluder consists of two square frames of nitinol covered by polyester fabric. A central hole removed from right atrial disk allows two disks to be sewn together. (From Das GS, Voss G, Jarvis G, et al. Experimental atrial septal defect closure with a new transcatheter, self-centering device. *Circulation* 1993;88:1754, with permission.)



***e*FIGURE 87.0.20** The Amplatzer atrial septal occluder device is composed of nitinol wire mesh woven into a left and right atrial disk, connected by a central waist whose diameter corresponds to the atrial septal defect size. The disks are filled with thin polyester patches. This figure shows the left atrial side of an Amplatzer device.

Technique

Indications and contraindications to transcatheter therapy are similar to those for standard surgical repair. The devices are appropriate only for the secundum-type ASD, and then only when there is sufficient septal rim surrounding the defect. At present, there are no age limitations precluding device implantation, although the large introducer sizes necessary for implantation of some devices limit applicability to patients who weigh greater than 8 to 10 kg. A reported advantage of the Amplatzer device is the smaller introducer system needed for device implantation (6 to 7 Fr).

Preliminary measurements of the ASD and atrial septum length are made in multiple planes by transthoracic or transesophageal echocardiography (TEE). Procedures are usually performed under general anesthesia to minimize patient movement and to allow for transesophageal monitoring. Patients are heparinized to maintain an activated coagulation time greater than 250 seconds throughout the procedure. Standard right-sided heart catheterization is performed to document hemodynamic data and to determine the magnitude of the interatrial shunt. Continuous TEE monitoring is used during device deployment. The defect is balloon sized using occlusion balloon catheters of known dimension to assess defect size and septal compliance. Balloon occlusion with guidance from TEE is also helpful to detect additional smaller septal defects. Rao et al. (163) found that the balloon-stretched diameter of the ASD correlates fairly well with the echocardiographically determined ASD diameter (stretch diameter of defect = 1.05 × echocardiographic diameter + 5.49 mm; p <.01).

After ASD sizing, the delivery system is advanced across the atrial septum, and the left atrial component of the device is deployed. After the left side is properly aligned by echocardiographic guidance, the right atrial component (if applicable) of the device (i.e., right atrial disk in Amplatzer, Clamshell, and Das devices, counteroccluder in Sideris device) is deployed. Once echocardiography confirms the position and stability of the device, it is released from its wire or cable. TEE is used to evaluate residual shunts and the relationship of the device to nearby structures (e.g., right upper pulmonary vein, superior vena cava, mitral valve). The degree of residual shunt may also be measured by repeat hemodynamic study.

Results

King and Mills Device

The clinical applicability of this device to children was limited by the need for a 23-Fr introducer sheath requiring saphenofemoral cutdown for access (*e*Fig. 87.0.15). It is no longer in use.

Rashkind Single-Disk Device

Use of the Rashkind device (*e*Fig. 87.0.16) has been examined by several investigators (149,150) with mixed results. A large (15 Fr) introducer sheath was required, and the device could not be retrieved because of the presence of hooks. It is no longer under investigation.

Clamshell/CardioSEAL Device

Latson et al. (164) reported a multicenter trial of 400 patients in whom the Clamshell device (eFig. 87.0.17) was implanted. This device requires an 11-or 12-Fr sheath. Implantation failed or embolization occurred in 7 and 17 patients, respectively. In the 376 patients in whom the device was implanted, there was a 33% rate of residual shunts on echocardiography at follow-up, a 7% complication rate, and one late death. There have been reports of fractures of the device arms at follow-up in more than one-half of patients; the clinical significance of these fractures has been questioned. At present, the newer CardioSEAL design is being evaluated. Early single center experiences have reported similar defect closure rates (46% residual shunt at mean 9.9 months) and a reduced incidence (14%) of arm fractures (153).

Sideris Button Device

In the initial multicenter trial (155), 57 patients underwent implantation of the Sideris button device (eFig. 87.0.18), with successful implantation in 81%. There was an 8% unbuttoning rate, requiring surgical removal of the device and closure of the defect. Total, long-term follow-up results have been encouraging with lower rates of unbuttoning (0.9%) and similar degrees of occlusion (90%) with the fourth-generation model (156).

Das Angel Wings Device

Das Angel Wings device (eFig. 87.0.19) (157,158 and 159) represents a modification of previous concepts, incorporating a self-centering design. Initial clinical results appeared promising (158). In the first 24 patients who underwent closures in the United States, devices were deployed with either no shunting or trivial residual shunting in 92% of patients. The novelty of this device was reported to be the ability to implant devices with a smaller device-to-defect ratio than reported for other devices (diameter ratio, 1.1:2.0). A 12- or 13-Fr sheath is required for implantation of the device. At present, further clinical trials have been postponed as attempts at design improvement continue.

Amplatzer Septal Occluder

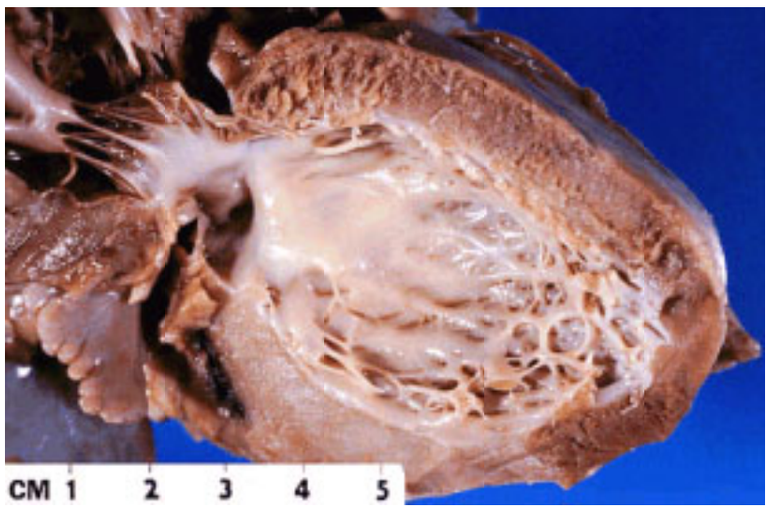
The Amplatzer Septal Occluder (eFig. 87.0.20) is the newest of the devices currently under investigation. It is gaining international popularity, as evidenced by multiple single center and multicenter reports constituting over 1,000 device implantations (160,161 and 162). The advantages of the Amplatzer device relate to its ease of implantation and maneuverability, retrievability, smaller introducer systems (6 to 7 Fr), highly effective defect closure rates (greater than 95%), and low complication rates.

Complications

Typical cardiac catheterization complications have been reported after transcatheter ASD occlusion, including arrhythmias and vascular injury. A low incidence of cerebrovascular events also has been reported. Mild regurgitation of an atrioventricular valve may occur if a device impinges on the valve. Device embolization after deployment has also been reported in a small minority of patients. The need for surgical intervention after device implantation has been reported in up to 8% of patients, primarily for repair of residual shunts (165), but this is expected to decrease with newer devices. The mortality for transcatheter ASD closure is extremely low.

TRANSCATHETER CLOSURE OF PATENT FORAMEN OVALE

One of the more controversial uses of transcatheter ASD occlusion technology is closure of a PFO after presumed paradoxical embolic stroke or transient ischemic attack. In multiple studies (166,167) of patients with transient ischemic attacks and stroke but with no clinical evidence of cardiovascular disease, a PFO was noted in up to 12% of patients. The association of the anatomic combination of PFO and atrial septal aneurysm with strokes is quite high (odds ratio, 4.96), particularly in patients younger than 55 years. In patients with a PFO alone, the odds ratio is also increased (odds ratio, 1.83) (168). This has been borne out by long-term studies demonstrating a rate of recurrent neurologic events of 3.3% to 12.5% per year without defect closure (169,170). Similar associations have been reported between the presence of PFO and symptomatic migraine headaches, orthodeoxia/platypnea syndrome, or both. Some have advocated transcatheter PFO closure as a curative procedure for these conditions (171). Others, however (172,173), believe that the association between a PFO and neurologic symptoms may not be causal, and that the etiology of stroke in these patients may be related to rheumatic mitral valve disease or thrombus formation within the atrial appendage exacerbated by atrial dysrhythmias. In a multicenter trial, Bridges et al. (174) reported 36 patients with documented right-to-left atrial shunting and presumed paradoxical emboli who underwent PFO closure with a Clamshell device. Of the 34 patients in whom devices were implanted, no recurrent strokes occurred during a mean follow-up period of 8.4 years. More recent studies have revealed the risk of recurrent stroke or other neurologic events after transcatheter PFO closure to vary from 3.2% to 3.4% per year (175,176), possibly lower than the recurrence risk without closure. Additional investigation is needed to elucidate the interplay between idiopathic strokes, congenital atrial septal patencies, and outcome after closure of such defects.



Fibroelastosis and hypertrophy of the left ventricle. This specimen was obtained from a 3-month-old child with incomplete closure of the foramen ovale.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Advances in imaging technologies (particularly echocardiography and magnetic resonance imaging) have permitted surgical intervention in many patients with simple (e.g., ASD, ventricular septal defects, PDA, aortic coarctation) or complex (e.g., D-transposition of the great arteries, hypoplastic left-sided heart syndrome) lesions to proceed based solely on noninvasive studies. This, in turn, has led to changes in the patterns of cardiac catheterization in children. At our institution, for example, approximately 80% of the cardiac catheterizations performed in the late 1980s were for diagnostic purposes. With smaller catheters and our ability to perform interventional procedures safely in neonates and children, the ratio has reversed, with 60% to 70% of patients currently entering the catheterization suite for interventional procedures. We anticipate that this trend will continue and grow over time.

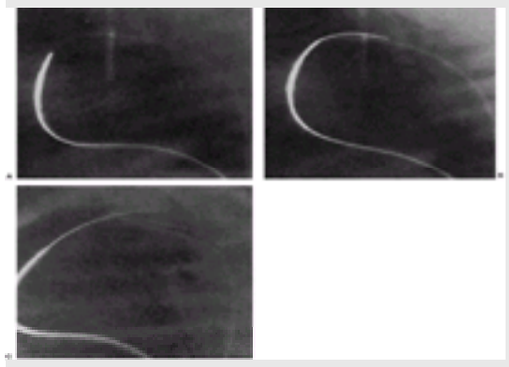
In this chapter, we have described most of what is available to the interventional cardiologist for the transcatheter treatment of congenital heart disease. However, not all of the interventions described have met with universal acceptance. In most centers, but not in all, balloon valvuloplasty is considered the treatment of choice in children with valvar pulmonic or aortic stenosis. However, many cardiologists still refrain from transcatheter treatment of native aortic coarctation out of concern for the development of aneurysms or restenosis; in the future, coarctation stenting may effectively address these issues. Other device implantation procedures such as coil embolization for PDA and endovascular stenting for pulmonary artery stenosis are now widely accepted as the treatment of choice for these lesions. Development of effective transcatheter technology for intracardiac lesions such as ASDs and ventricular septal defects has proceeded rapidly, but unfortunately, in 2001, U.S. Food and Drug Administration approval for these devices lags far behind their general acceptance worldwide.

THE FUTURE

Because of advances in interventional catheter design, particularly miniaturization of catheters and devices, and the development of laser-tipped catheters, a number of new technologies, as described here, are being applied in a novel fashion to congenital cardiac lesions.

Laser-Assisted Valve Dilation

Bommer et al. (177) first demonstrated the applicability of laser ablation technology to creation of experimental ASDs. Riemenschneider et al. (178) later reported the application of lasers to other forms of congenital heart disease. Qureshi et al. (179,180) first reported the use of 0.018-in. neodymium:yttrium-aluminum-garnet laser guidewires to perforate atretic pulmonary valves. Passage of the laser wire in pulmonary atresia was performed after adequately aligning catheters in the infundibulum and main pulmonary artery through the PDA (eFig. 87.0.21). Standard balloon valvuloplasty techniques are used after perforation with the laser wire (3 to 5 seconds, 3.5 W).



***e*FIGURE 87.0.21** Shown here are fluoroscopic images demonstrating alignment of catheters before laser catheter perforation of the pulmonary valve **(A)**, passage of the laser wire into the main pulmonary artery **(B)**, and snaring of the wire through the ductus arteriosus **(C)**. (From Rosenthal E, Qureshi SA, Kakadekar AP, et al. Technique of percutaneous laser-assisted valve dilation for valvar atresia in congenital heart disease. *Br Heart J* 1993;69:556, with permission.)

Stent Valves

Bonhoeffer and colleagues reported the percutaneous transcatheter implantation of functional valves into the RV outflow tract. Initially in a lamb model (181) and later in a 12-year-old child (182), a stent-mounted valve was implanted and shown to be nonstenotic and competent on follow-up. Larger trials with longer-term data are needed, but this technique promises to greatly improve the care available to patients (e.g., postoperative tetralogy of Fallot patients), who currently require reoperations for pulmonary valve insufficiency.

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PATHOPHYSIOLOGY OF THE HEART FAILURE CLINICAL SYNDROME

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Heart failure continues to emerge as an enormous public health problem in the new millennium. The aging population continues to grow around the world, and the incidence of heart failure continues to climb commensurate with the graying of the world population. It is estimated that 10% of patients older than 75 years have heart failure. Because it is a syndrome and not a specific disease, heart failure has many forms and faces. This has led to persistent controversy and lack of agreement regarding the definition. The confusion regarding the definition stems in part from the differences between historical bedside observations (e.g., cardiomegaly, third heart sound gallop, rales, fluid retention, oliguria, breathlessness, and fatigue) and elaborations emanating from careful laboratory exercises performed from 1950 to 2000 (e.g., measurement of contractile abnormalities, isolated papillary muscle function, identification of key molecular abnormalities). The clinical definition of *heart failure*, a syndrome readily diagnosed by a careful history and physical examination, is considered in very broad terms to be an abnormality of the heart with a characteristic pattern of hemodynamic and neuroendocrine responses. The clinical picture is dominated by secondary organ abnormalities in the lungs (shortness of breath), the kidneys (salt and water retention), and the skeletal muscles (fatigue), but the central problem is always in the heart. The syndrome of heart failure is the expression of the final common pathway by which many etiologic factors can damage the heart, including acute myocardial infarction, inflammatory myocarditis, gene mutations with abnormal contractile function, valvular heart disease, severe undertreated hypertension, and so forth. Virtually any form of heart disease can culminate in the syndrome of heart failure.

We now understand that chronic systolic heart failure is often characterized by progressive remodeling of the left ventricular (LV) chamber. The other three chambers are also frequently involved and can progressively dilate as well. The LV becomes larger and more spherical over months to years, obligating a reduction in LV ejection fraction. The process of remodeling is highly complex and is addressed in detail later in this chapter. However, the remodeling process is central to the pathophysiology of heart failure and is now the prime target for two major effective forms of treatment—angiotensin-converting enzyme (ACE) inhibitors and beta-adrenergic blockers. The observation by clinicians that treatment designed to block various neuroendocrine responses can result in inhibition and, in some cases, reversal of LV remodeling has been an epiphany. Although there are many gaps in our knowledge of pathophysiology, especially in cellular biology, we are beginning to recognize complex but coherent patterns that develop in the pathogenesis of heart failure. The purpose of this chapter is to feature the most current thinking as it relates to the pathophysiology.

HISTORICAL PERSPECTIVE

Although heart failure has been recognized in retrospect by medical historians to have been evident throughout history, the timing of when the medical concept of heart failure first arose is difficult to be confident about. In 1832, Hope put forth both the term *cardiac failure* and attempted to explain the idea of edema on the basis of increased filling pressure of the heart (1). He presumed that increased heart pressure was subsequently transmitted back to the veins and the capillaries, where it was associated with extravasation of fluid. At the time, Hope was aware of the even now popular belief that heart failure is associated with an abnormal mechanical load, which leads to adaptive hypertrophy of the myocardium. He also recognized that at a certain point, the hypertrophy becomes insufficient to overcome the loading impediments and is associated with the clinical onset of heart failure. Of interest, the very same concept is now considered to be one of the foremost questions in contemporary cardiology and the subject of intense research in recent years. The transition from adaptive hypertrophy to heart failure remains poorly understood but is fundamental to our understanding of heart failure.

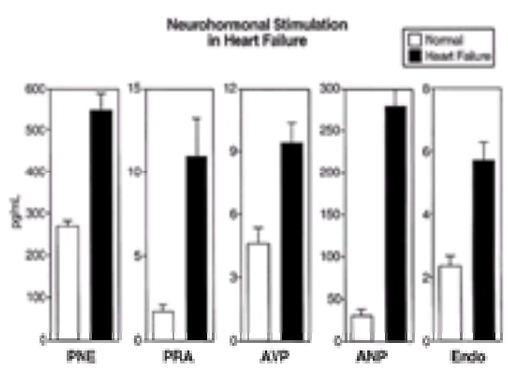
Hope's concepts persisted throughout the nineteenth century. It was Starling in 1886 who developed his now famous equation explaining the movement of fluid across the capillary bed (2). Starling also instilled fluid into the pericardial sac of anesthetized dogs to produce "heart failure," what we now consider to be cardiac tamponade. However, he incorrectly concluded that "in heart disease the capillary pressure is not higher, but rather lower, than in a normal animal." Starling believed that extravasation of fluid was a fundamental defect in heart failure.

Starling's preeminence in the field perpetuated the concept that heart failure was associated with an increased capillary permeability. Even the master clinician Mackenzie suggested, in 1913, that blood was passing through the capillaries at such a slow rate in heart failure so as to impair nutrition and allow transudation (3). At the time of Mackenzie the condition of heart failure was referred to as "dropsy."

By the turn of the century there were rival theories about heart failure, including the so-called backward theory and forward theory. The backward theory of heart failure eventually emerged to explain the traditional concepts of heart failure, but the theory failed to take into account the concept of systemic edema and anasarca. Moreover, blood volume was noted to increase during heart failure and not diminish, as might be expected from the backward theory. It was Starr who challenged the current dogma and carried new ideas from the laboratory to the bedside (4,5). He proposed the opposite idea that “static pressure” in patients dying from heart failure is higher than normal. Subsequent clinical studies by Warren and Stead (6) demonstrated that as patients develop edema, their weight increases even before there is any detectable change in venous pressure, suggesting tremendous potential for the venous capacitance to increase its volume.

A clear shift in the thinking about heart failure occurred after the studies of Merrill (7). These important studies demonstrated that there was diminished renal blood flow in patients with heart failure. It was assumed that patients with heart failure had a reduced cardiac output, but this concept had to await the introduction of cardiac catheterization to be confirmed. About this time (1950s), in the early days of cardiac catheterization, it was popular to define heart failure as a condition whereby the heart fails to maintain adequate circulation for the needs of the body. The implication of this definition was that entry of oxygen into the circulation was dependent on the cardiac output, and therefore the needs of the body for oxygen could not be met during heart failure. However, this concept is flawed, as it has been known since at least 1948 that the uptake of oxygen at rest is normal in patients with heart failure (8).

The definition of heart failure became further complicated when it was recognized that some patients suffered from “high-output heart failure.” Such patients also had peripheral edema and lung congestion and typically presented with conditions such as thyrotoxicosis, severe anemia, cor pulmonale, arterial-venous shunts, beriberi, and Paget’s disease of bone. Patients with high-output heart failure often have cardiac outputs two or three times normal, thus casting doubt on the whole concept of “forward heart failure.” In the 1950s, the work of Barger and others emphasized the fact that retention of sodium by the kidney was due not only to abnormal renal blood flow but also to systemic activation of the renin-angiotensin-aldosterone system (9,10). The primary stimulus for the release of renin was discovered to be a reduction in the “effective circulating volume” and reduced blood pressure. Subsequently, a long series of studies was performed substantiating the fact that heart failure was characterized by many neuroendocrine abnormalities that we now appreciate as highly important in the pathogenesis of the syndrome (11,12,13,14,15,16,17,18 and 19). It is now clear that the sympathetic nervous system is activated in heart failure (20). There is an incremental change in plasma renin activity (PRA) (21) and a host of other vasoactive substances, including arginine vasopressin (AVP) (22), natriuretic peptides, and endothelin (*e*Fig. 88.0.1) (23). Presumably these neurohormones are increased in an attempt to maintain blood pressure in the face of a falling cardiac output. It is as if blood pressure is being “protected” by endogenous vasoconstrictors, presumably a major evolutionary advantage (24,25). The vasodilator/natriuretic peptides are released as heart failure progresses and include atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), and prostaglandins. These are presumed to affect the local control of blood volume, arteriolar tone, baroreceptor reflex control mechanisms, and excretion of salt and water (26,27,28,29 and 30). BNP has recently emerged as a marker of elevated cardiac filling pressure (31,32 and 33). The recognition of neuroendocrine activation as an important component of heart failure has culminated in the development of a currently popular hypothesis—the neurohumoral hypothesis—which implies that neuroendocrine abnormalities are responsible for much of the disturbed pathophysiology and progression of abnormalities common to the syndrome of heart failure.



***e*FIGURE 88.0.1** Patients with chronic heart failure are known to have increased plasma levels of plasma norepinephrine (PNE), plasma renin activity (PRA), arginine vasopressin (AVP), atrial natriuretic peptide (ANP), and endothelin (Endo). (Courtesy of Dr. J.N. Cohn.)

Recently there has been the development of a plethora of transgenic mouse models of heart failure, usually created by overexpression or “knockout” of specific genes, sometimes with cross-breeding to create specific molecular lesions. The phenotypes produced by these models are somewhat similar and include myocardial hypertrophy, reduced myocardial function, LV dilation, and edema formation. Although these studies have shed much light on underlying molecular mechanisms of heart failure, there are now more than 40 models, and the number is rapidly growing. Although these animal models may phenotypically resemble dilated or hypertrophic cardiomyopathy, direct extrapolation to the human condition of heart failure has remained speculative for the most part. In some cases, genes unheard of by cardiovascular researchers have been found to have a profound effect on cardiac development. Altered contractile proteins, calcium regulatory proteins, receptors, transcription factors, and signal transduction molecules all can lead to experimental mouse heart failure. However, one can be confident that no single molecule or group of genes causes heart failure. Moreover, there are some shortcomings to the transgenic model strategy. These models allow little control over the time course of transgene expression, and the levels of expression are difficult to control. Many proteins implicated in the pathogenesis of heart failure have different functions during development than in mature, adult heart cells. Although many of these models will undoubtedly be useful, some transgenics will be overexpression artifacts or physiologically irrelevant. The transgenic work so far serves only to emphasize the enormous complexities of the molecular basis of disease. Much more work is required.

We then return to the question—what is heart failure? It is probably best to define *heart failure* as a complex clinical syndrome manifested by shortness of breath, fatigue, and abnormal heart function. The syndrome must be characterized by an abnormality of cardiac function to distinguish it from the syndrome of “circulatory congestion,” as might occur in a patient with a normal heart and acute renal failure.

Systolic Heart Failure

Abnormalities of systolic and diastolic function frequently coexist in the syndrome of heart failure, although today patients are somewhat arbitrarily determined to have either systolic heart failure or diastolic heart failure. The former condition is associated with a reduction in systolic performance of the heart, circulatory congestion, and progressive activation of various neuroendocrine systems (34,35,36 and 37). In the late stages, systolic heart failure is characterized by excessive sympathetic nervous system activity, tachycardia, a gallop rhythm, peripheral edema, ascites, and oliguria. Classically, patients with systolic failure have enlargement of the left ventricle with hypertrophy and remodeling of the chamber and markedly diminished LV performance. In most circumstances there is an increase in LV end diastolic and end systolic volume and a marked reduction in ejection fraction, a standard method of measuring cardiac systolic performance.

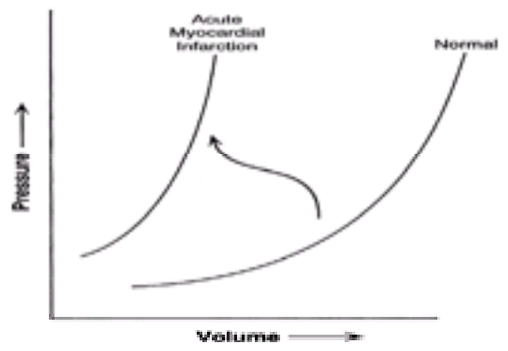
The heart adapts to diminished performance from any acute or chronic injury by altering its shape and size (i.e., remodeling). Cardiac output is temporarily maintained in the face of reduced stroke volume by chamber hypertrophy and dilatation. Hypertrophy tends to reduce wall stress via the Laplace relation (tension = pressure × radius/wall thickness), thereby maintaining systolic performance. However, when the heart is severely dilated, the tension in the walls of the heart is so great that it essentially outstrips the increase in wall thickness, leading to a decrease in systolic performance. The ventricles are designed so that the upper limit of normal filling pressure is achieved at the optimal length of the heart’s basic contractile unit—the sarcomere. A sarcomere length below 2.2 μ provides reserve for the Starling mechanism, whereas a sarcomere length above 2.2 μ does not further enhance systolic performance. The sarcomeres normally do not elongate beyond 2.2 μ (although the myocyte may increase the number of sarcomeres in series, thus elongating the cell and increasing the chamber diameter). When stretched beyond 2.2 μ, “slippage” may occur, leading to mitral regurgitation. Although there is no true descending limb to the Starling curve in the intact circulation, a continuously increased volume of the heart leads to mitral and tricuspid insufficiency. From this discussion it should be clear that LV remodeling with new sarcomeres in series, although initially adaptive, if progressive becomes very maladaptive and greatly contributes to diminishment in LV function. A clear understanding of this principle allows one to understand why treatment designed to reduce remodeling is so effective.

Diastolic Heart Failure

The syndrome of diastolic heart failure implies normal systolic function of the heart in the presence of clinical heart failure. It is now well documented that many patients with heart failure have normal LV systolic function. Diastolic heart failure may account for one-third or more of patients referred to specialty centers for the management of heart failure. Often, such patients are elderly women with severe systemic hypertension and LV hypertrophy (38). Characteristically, patients with diastolic heart failure present with the usual signs and symptoms of pulmonary vascular congestion but have a small heart or normal internal chamber diameter and a normal LV ejection fraction by echo or radionuclide left ventriculography (39). As with systolic heart failure, diastolic heart failure may, in many cases, be complicated by mitral regurgitation. Although the clinical manifestations of heart failure due to diastolic dysfunction are very similar to those of systolic dysfunction, the pathogenesis,

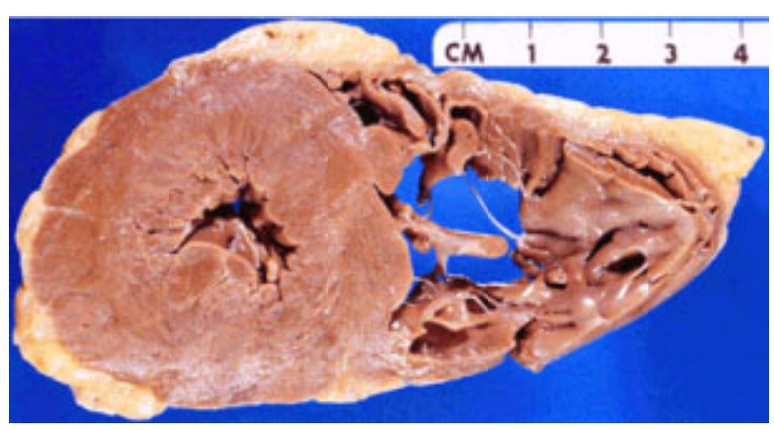
prognosis, and treatment of the two syndromes are different.

The clinical features of diastolic heart failure are virtually identical to those of systolic heart failure, but the fundamental causes are impaired diastolic function. The LV chamber is stiff, leading to an abnormal diastolic pressure–volume relationship (eFig. 88.0.2). The factors that raise LV filling pressure in diastolic heart failure may be due to a variety of active and passive processes that affect chamber and muscle stiffness. In marked contrast to systolic heart failure, patients with pure diastolic heart failure frequently have normal or, in many cases, enhanced contractile function of the left ventricle. A classic example is hypertrophic cardiomyopathy. Such hearts are characterized by marked hypertrophy, heightened ejection phase indices, and concomitant mitral regurgitation. Diastolic filling of the left ventricle is very impaired, leaving the patient with elevated LV filling pressures. It is presumed that the elevated filling pressures contribute to the sensation of breathlessness, although the mechanism of shortness of breath is more complex than this. Diastolic heart failure can also be caused by acute coronary insufficiency, which tends to increase chamber stiffness and decrease compliance of the left ventricle. In general, there is a shift of the pressure–volume relationship to the left, producing a higher pressure for any given diastolic volume.



***e*FIGURE 88.0.2** The fundamental consequence of diastolic heart failure is a shift in the pressure-volume relationship of the left ventricle so that for any given volume, there is a much higher left ventricular end diastolic pressure.

Other etiologic considerations of diastolic heart failure include long-standing systemic hypertension with LV hypertrophy, chronic coronary artery disease with excessive scar formation, and infiltrative cardiomyopathies such as cardiac amyloidosis and sarcoidosis. Despite the fact that patients may become markedly disabled by diastolic heart failure, the prognosis of these patients appears to be somewhat better than those with pure systolic heart failure (40). Still, such patients have a fourfold mortality risk compared with control subjects who are free of heart failure.



Left ventricular hypertrophy secondary to chronic hypertension with secondary ectasia of the right ventricle.

New criteria for diastolic heart failure have been proposed (41). The history, physical examination, and chest x-ray may well point toward a clinical diagnosis of diastolic heart failure, but the diagnostic test of choice is echocardiography (42). Doppler assessment of diastolic function by echocardiography provides information relevant to the patient's functional class, management, and prognosis. A continuum of Doppler patterns of diastolic function exists, including normal diastolic function, impaired relaxation, pseudonormal filling, restriction, constriction, and tamponade (42). These patterns evolve from one to another with changes in disease evolution. However, it has become clear with many years' experience that the Doppler abnormalities are sensitive to heart rate, loading conditions, age, and treatment. They can be lacking in specificity. Defining diastolic heart failure is not simple (43). It usually coexists with systolic dysfunction and may have multiple etiologies with various treatments. It is not a single, homogeneous entity.

Diastole has classically been divided into four phases: isovolumic relaxation, a rapid filling phase, a slow filling phase, and atrial systole. Isovolumic relaxation is the interval between aortic valve closure and mitral valve opening. During this phase, ventricular pressure rapidly declines without a significant change in ventricular volume. This process is energy dependent and may be susceptible to myocardial ischemia. Isovolumic relaxation is followed by the rapid filling phase, which also is energy dependent. As the rapid filling continues, an increase in LV size is limited by passive elements affecting stiffness of the myocardium. A slow filling phase of diastole is then primarily dependent on the stiffness of the heart, which may increase as LV volume increases. Passive stiffness of the heart will also be increased by fibrosis related to previous myocardial infarction, or from various infiltrative processes. The last phase of diastole is the result of atrial contraction, which actively propels blood into the left ventricle and produces a final increase in LV volume and pressure. Normally the atrium contributes approximately 15% to 25% of the ventricular diastolic volume. Actual contribution from atrial contraction relates to underlying ventricular compliance and chamber stiffness, the contractile function of the atria, and the ventricular diastolic pressure at which point atrial contraction begins.

Most patients with diastolic heart failure have abnormal active and passive diastolic function. Varying disease states may be associated with different aspects of diastolic function. For example, LV hypertrophy is associated with slowing of both active relaxation and increased passive chamber stiffness. Acute myocardial ischemia causes a transient reduction in the ability of the left ventricle to completely relax, and infiltrative cardiomyopathies cause increased passive chamber stiffness due to the deposition of material in the interstitial spaces. It is also important to remember that ventricular diastolic properties of the heart are altered by age. Relaxation is prolonged with increased age, and older patients are more likely to often have concomitant myocardial fibrosis and LV hypertrophy.

Although there is no uniformly agreed-on therapy for pure diastolic heart failure, control of blood pressure is seemingly critical to the patient's well-being. Beta-adrenergic–blocking drugs may be useful in that they slow the heart rate and prolong diastole. In principle, prolongation of diastole should improve filling. Calcium channel blockers and ACE inhibitors are also useful treatment for the management of chronic diastolic heart failure (44). More recently, nitric oxide (NO) donors, or drugs that enhance NO release, have been shown to improve diastolic function in humans (45).

Circulatory Congestion Is Not Synonymous with Heart Failure

Over the years it has become clear that the two major features of heart failure are circulatory congestion and reduced flow to vital organs. Congestion behind the right ventricle, principally as a result of elevated right ventricular filling pressures, produces the characteristically distended neck veins, enlarged liver, and edema. Heightened LV filling pressures are responsible in part for dyspnea, orthopnea, and pulmonary rales, although exercise intolerance in patients with chronic heart failure does not always relate directly to the degree of elevated LV filling pressure (46).

It is somewhat unfortunate that over the years the presence of circulatory congestion, regardless of the circumstances under which it appears, has traditionally become accepted as tantamount to the diagnosis of heart failure (47). It is likely that this traditional concept is incorrect. Administration of excessive intravenous infusions to a patient with a normal heart results in a state of circulatory congestion. The blood volume is artificially increased and venous distention occurs. Indeed, the clinical picture can be indistinguishable from that of heart failure. However, one must question whether the heart has truly failed. In fact, the hemodynamic disturbance that occurs as a result of excessive administration of fluids in the face of a normal heart is a consequence of noncardiac circulatory congestion. It is now clear that both systemic and pulmonary vascular congestion can arise from noncardiac causes to produce a clinical syndrome that simulates that of heart failure. Examples might include acute renal failure, constrictive pericarditis, and pure mitral stenosis. In each of these cases, LV performance remains intact, and circulatory congestion ensues as a consequence of factors other than those due to reduced myocardial performances. Characteristically, in circulatory congestion the heart size is normal, as opposed to the cardiomegaly that occurs in the condition of true systolic heart failure. Circulatory congestion from noncardiac causes rarely responds to inotropic stimulation, whereas patients with systolic heart failure usually respond quickly to inotropic stimulation with drugs such as dobutamine. It is therefore important to

recognize that circulatory congestion is a nonspecific hemodynamic disturbance that may arise even when the heart is not failing as a pump. The term *congestive heart failure* should be reserved for those patients with circulatory congestion due to inadequate myocardial pump function. Because many patients today with severe chronic heart failure fail to demonstrate circulatory congestion, in part because of the common usage of potent loop diuretics and other therapies, the term *heart failure* is preferred by some over the previously fashionable term *congestive heart failure*.

DIAGNOSIS AND EVALUATION OF HEART FAILURE

History and Physical Examination

Perhaps the most predominant symptom of heart failure is breathlessness. The medical term for breathlessness, *dyspnea*, is the awareness by the patient of increased respiratory effort. This may occur at rest or with minimal physical activity. The patient is aware of an uncomfortable sensation, not being able to get enough air. It is somewhat surprising that to this day the mechanism of dyspnea is poorly understood. In patients with acute pulmonary edema, hypoxemia probably contributes to the sensation of dyspnea. However, patients with more chronic forms of heart failure have dyspnea that bears no direct relationship to hypoxemia, elevated pulmonary capillary wedge pressure, or other central hemodynamics (46). Likewise, the level of dyspnea is not related in a simple manner to dead space inhalation. It is likely that chronic shortness of breath at rest or with minimal activity is due to multiple peripheral mechanisms, including fatigue of the respiratory muscles, increased physiologic dead space, reduced pulmonary compliance, increased airway resistance, endothelial dysfunction, abnormal skeletal muscle metabolism, and perhaps signals from the pulmonary J receptors and respiratory muscles (48,49).

Orthopnea and paroxysmal nocturnal dyspnea occur in the more advanced stages of heart failure. Neither orthopnea nor paroxysmal nocturnal dyspnea is specific for heart failure and can occur in other conditions. Patients with more advanced and chronic heart failure frequently have Cheyne-Stokes respirations. This type of periodic breathing in patients with heart failure, characterized by repeated episodes of apnea and hypopnea during sleep, is associated with severe nocturnal arterial blood saturation. It also carries a poor prognosis (50) and is correlated with an elevated pulmonary capillary wedge pressure (51). Central sleep apnea is common in patients with heart failure (52) and may be related to enhanced sensitivity to carbon dioxide (53). Continuous positive airway pressure improves cardiac function in patients with heart failure who demonstrate Cheyne-Stokes respiration or central sleep apnea (54). Coughing and wheezing can also occur in patients with heart failure and may be the predominant symptoms.

The second cardinal feature of heart failure is chronic fatigue. Fatigue is also a very nonspecific symptom and, like dyspnea, is rather poorly understood. In the past, fatigue was attributed to low cardiac output, but we now know that the mechanism is far more complex. Drugs that improve blood flow to exercising muscles in heart failure do not necessarily improve exercise tolerance or reduce fatigue (55,56). It is likely that abnormalities of skeletal muscle histology and biochemistry contribute to poor exercise tolerance and chronic fatigue (57,58,59 and 60).

Circulatory congestion is responsible for many of the physical signs of heart failure. Occasionally patients with new-onset heart failure present with severe right-upper-quadrant pain and abdominal fullness. This may be accompanied by nausea and vomiting and is probably due to engorgement of the liver and bowel from high venous pressure. Rarely, heart failure can even present as an acute surgical abdomen. However, peripheral edema and pulmonary rales are not invariably present in heart failure, even when cardiac filling pressure is markedly increased (61).

The physical findings in heart failure span the spectrum from very unimpressive to highly remarkable. In the current era of loop diuretics and ACE inhibitor therapy, patients frequently have an absence of the traditional findings, such as pulmonary rales, gallop rhythm, hepatomegaly, ascites, and peripheral edema. Even jugular venous distention may be absent in the face of severe LV dysfunction if the patient is well compensated. On the contrary, the presence of neck vein distention, a third heart sound, pulmonary rales, and peripheral edema is highly characteristic of the syndrome of heart failure. During the sequential follow-up of patients in the clinic over time, particular attention should be focused on examination of venous pressure. Sequential examination of the patient is most important, and examination of the neck veins is perhaps the single most useful physical finding. The presence or absence of venous distention is also most helpful in determining the dose of diuretic therapy.

The cardiac examination itself should be carried out with the patient in both the supine and the left lateral decubitus position. Often the cardiac apex impulse is displaced and sustained. A third heart sound gallop, when present, may be palpable. Patients with heart failure frequently have a murmur of mitral regurgitation that radiates to the axilla. Tricuspid regurgitation is also common in patients with heart failure, although sometimes more difficult to auscultate.

Routine Laboratory Tests

A number of routine laboratory tests useful in the evaluation of patients with heart failure are suggested in Table 88.1. Evaluation of a new patient with heart failure should also include a chest x-ray to assess the size of the heart and the pulmonary vascular markings. Occasionally the cardiac silhouette is normal in size, which should signal the possibility of pure diastolic heart failure. Enlargement of the cardiac silhouette can be due to either right, left, or biventricular enlargement. Heart failure is characterized by roentgenographic perihilar engorgement of the pulmonary vasculature with cephalization of lung vascular markings. Pleural effusions may be present and are more likely to occur on the right.

Test recommendation	Finding	Suspected diagnosis
Electrocardiogram	Acute ST-T-wave changes	Myocardial ischemia
	Atrial fibrillation, other tachyarrhythmia	Thyroid disease or heart failure due to rapid ventricular rate
	Bradyarrhythmias rate	Heart failure due to low heart rate
	Previous myocardial infarction (e.g., Q waves) left ventricular performance	Heart failure due to reduced contractile tissue
	Low voltage	Pericardial effusion
	Left ventricular hypertrophy	Diastolic dysfunction
Complete blood cell count	Anemia	Heart failure due to or aggravated by decreased oxygen-carrying capacity
Urinalysis	Proteinuria	Nephrotic syndrome
	Red blood cells or cellular casts	Glomerulonephritis
Serum creatinine	Elevated failure	Volume overload due to renal dysfunction
Serum albumin	Decreased	Increased extravascular volume due to hypoalbuminemia
T4 and TSH (obtain only if atrial fibrillation, evidence of thyroid disease, or patient age >65 yr)	Abnormal T4 or TSH	Heart failure due to or aggravated by hypo/hyperthyroidism

TSH, thyroid stimulating hormone.
From Konstam M, Dracup K, Baker D, et al. Heart failure: management of patients with left ventricular systolic dysfunction. Quick reference guide for clinicians No. 11. AHCPR Publication No. 94-0613. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Human Services, June 1994, with permission.

TABLE 88.1 RECOMMENDED TESTS FOR PATIENTS WITH SIGNS OR SYMPTOMS OF HEART FAILURE

The cornerstone of evaluation remains the echocardiogram. Every new patient with heart failure should have an echocardiogram performed with Doppler interrogation to assess LV size, cardiac performance, as well as valvular architecture and function. The echocardiogram can be used to distinguish systolic from diastolic heart failure. It is also useful in diagnosing pericardial effusion, hypertrophic cardiomyopathy, regional wall motion abnormalities, and unsuspected valvular heart disease.

Although the radionuclide ventriculography can provide very precise information regarding ejection fraction, most laboratories prefer to use echocardiographic data because they provide a more comprehensive observation, are simpler to obtain, and are less costly. The use of transthoracic Doppler is also helpful. The features of both echocardiography and radionuclide left ventriculography are compared in Table 88.2.

Test	Advantages	Disadvantages
Echocardiogram	Permits concomitant assessment of valvular disease, left ventricular hypertrophy, and left atrial size	Difficult to perform in patients with lung disease
	Less expensive than radionuclide ventriculography in most areas	Usually only semiquantitative estimate of ejection fraction provided
	Able to detect pericardial effusion and ventricular thrombus	Technically inadequate in up to 10% of patients under optimal circumstances
	More generally available	
Radionuclide ventriculogram	More precise and reliable measurement of ejection fraction	Requires venipuncture and radiation exposure
	Better assessment of right ventricular function	Limited assessment of valvular heart disease and left ventricular hypertrophy

From Konstam M, Dracup K, Baker D, et al. Heart failure: management of patients with left ventricular systolic dysfunction. Quick reference guide for clinicians No. 11. AHCPR Publication No. 94-0613. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Human Services, June 1994, with permission.

TABLE 88.2 ECHOCARDIOGRAPHY AND RADIONUCLIDE VENTRICULOGRAPHY COMPARED IN EVALUATION OF LEFT VENTRICULAR PERFORMANCE

The electrocardiogram continues to be useful in the evaluation of new patients with heart failure. It is inexpensive and provides information about the rhythm and conduction of the heart. The presence of old myocardial infarction, LV hypertrophy, left atrial enlargement, and underlying ischemic heart disease can also be suggested by a careful examination of the 12-lead electrocardiogram. Patients with advanced heart failure frequently have arrhythmias, which are usually diagnosed by simple electrocardiography. The presence of new atrial fibrillation on the electrocardiogram may provide a clue as to why a patient may have suffered acute decompensation. Approximately 20% to 30% of patients with heart failure have atrial fibrillation. In general, the electrocardiogram remains part of the standard initial evaluation but is probably not indicated for routine follow-up visits.

All new patients should have a complete blood count and urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, blood glucose, and, in some cases, an assay for thyroid-stimulating hormone. Measurement of the levels of plasma norepinephrine, plasma ANF, and PRA, although increased in patients with heart failure, is not considered routine or clinically necessary. Plasma neurohormone levels are primarily research tools. This may change with the emerging data on BNP (31,32 and 33). This peptide tracks with LV filling pressure and is an excellent tool to aid in the diagnosis of heart failure. It may also be useful in confirming vague physical findings, making decisions about hospital admission, and determining the response to therapy (62,63). The availability of a quantitative bedside “point-of-care” kit may facilitate the use of BNP for the diagnosis of heart failure.

Exercise Testing

Ambulatory patients with heart failure should always be considered for exercise testing. When available, gas exchange measurements should be made to assess anaerobic threshold and maximal oxygen consumption at peak exercise (53,64,65). Submaximal exercise end points such as anaerobic threshold are much less subjective motivational factors, which limits the utility of maximal exercise tolerance and the 6-minute walk test. Symptom-limited exercise testing is safe in patients with heart failure (66) and provides valuable information regarding the patient’s ability to withstand physical stress. Occasionally the exercise test is highly enlightening with regard to the patient’s perceived extent of disability. In addition to measurement of the heart rate and blood pressure, the duration of exercise should be noted, as well as the electrocardiographic response to exercise. The reasons for stopping the test should always be thoroughly explored. Patients with advanced heart failure usually discontinue exercise because of leg fatigue, although generalized fatigue and dyspnea are almost always also present. We now know that patients with a peak oxygen consumption of less than 14 mL per kg per minute and/or who exercise less than 50% of that expected for their age and size have a very poor prognosis and may be candidates for heart transplantation (67). In some cases, exercise testing will provide evidence of unsuspected myocardial ischemia. Such patients frequently have coronary angiography and in some cases improve with revascularization.

Cardiac Catheterization and Coronary Angiography

The need to do a right heart catheterization and coronary angiogram as part of the routine evaluation of patients with heart failure remains contentious (68). If the patient is being considered for heart transplantation, hemodynamic and coronary angiographic assessments are mandatory. In general, patients who are ill with advanced heart failure who demonstrate refractoriness to conventional therapy should be considered for hemodynamic evaluation. The acute response to therapy will, in some cases, predict the patient’s longer-term prognosis (69). Nevertheless, invasive investigation of the hemodynamic profile remains highly dependent on local customs and prerogatives of the individual attending physician. This issue is currently the subject of a large randomized trial. In general, there is no need to perform a right heart catheterization to diagnose heart failure. Rather, hemodynamic monitoring is used to help make judgments to aid in the management of patients with acute hemodynamic decompensation. Knowing whether there is underlying severe coronary disease is valued by some physicians and not by others. In general, it is useful to know the extent of underlying coronary disease and whether the patient may be a candidate for bypass graft surgery or other revascularization techniques. This is particularly true if the patient has angina or demonstrates myocardial ischemia. It is less clear in patients with no clinical evidence of coronary artery disease.

Myocardial Dysfunction Due to Chronic Ischemia and Its Reversibility by Revascularization

Severe LV regional dysfunction can result from myocardial necrosis, myocardial stunning (70), or hibernating myocardium (71). If enough regional dysfunction is present, global LV ejection fraction can be markedly depressed. We now know that simple assessment of LV function by contrast ventriculography or echocardiography cannot distinguish among these three mechanisms of reduced systolic function (i.e., necrosis, hibernation, and stunned myocardium). On the other hand, it is vitally important to be able to accurately and noninvasively assess myocardial viability to know whether severe cardiac dysfunction is due to irreversible cellular injury, stunning, or hibernation (72). This decision-making process permits the selection of patients for coronary artery bypass revascularization and is important in reassuring both the patient and the surgeons that a technically successful bypass operation can result in improved global LV function (73,74,75 and 76).

A number of strategies have been used to determine myocardial viability. Thallium-201 (Tl-201) imaging has been extensively studied in this regard (77,78,79,80 and 81). Irreversibly damaged myocardial cells cannot extract Tl-201 intracellularly, even after coronary reflow. Various approaches have been used in the assessment of Tl-201 imaging.

Often the clinical question is simply whether there is viability in a zone of severely reduced myocardial function. In such cases, early and delayed Tl-201 imaging performed in the resting state may be adequate.

New technetium-99m–labeled perfusion techniques have emerged in recent years and may be useful in assessing regional myocardial perfusion and viability. Technetium-99m sestamibi uptake is comparable to delayed Tl-201 uptake (82,83). The two imaging agents appear to be comparable for predicting enhanced regional systolic function after revascularization.

Positron emission tomography has also been used to differentiate viable from nonviable myocardium in patients with poor LV function (84,85,86 and 87). Noninvasive positron emission tomographic imaging with N-13 ammonia or fluorine 18-fluorodeoxyglucose is helpful in distinguishing patients with severe LV dysfunction secondary to coronary artery disease from those with nonischemic cardiomyopathy (88). Multiple metabolic tracers have been developed to define fatty acid metabolism (C-11 palmitate), glucose metabolism (fluorine 18-fluorodeoxyglucose), and overall oxidative metabolism (C-11 acetate). With the development of these isotopes, positron emission tomographic scanning has the potential for clearly distinguishing ischemic from nonischemic cardiomyopathy and is considered by many to be the gold standard. Unfortunately, it is expensive and not readily available.

Echocardiography is gradually replacing thallium perfusion tests in the determination of myocardial viability. Evaluation of wall thickening by echo during low-dose dobutamine infusion can be used to determine reversible LV dysfunction in patients with chronic coronary artery disease (89,90 and 91). Recent studies using dobutamine echocardiography have reported an 88% sensitivity and an 87% specificity in identifying viable but hypoperfused dysfunctional myocardial segments before revascularization (92). Dobutamine stress echocardiography is now the preferred method of assessing myocardial viability in patients with heart failure at many centers. However, it remains relatively nonquantitative. More recently, contrast-enhanced magnetic resonance imaging has emerged as an excellent tool to identify reversible myocardial dysfunction (92a,92b).

The determination of viable from nonviable myocardium is important for physicians caring for patients with severe heart failure. Those patients with reversible severe LV dysfunction will often respond favorably to coronary artery bypass surgery, whereas patients with nonviable tissue are perhaps more suitable for heart transplantation. This is an emerging field, and various centers rely more or less on the laboratory techniques that have served them best. Regardless of how one determines myocardial viability, the sensitivity and specificity of the test within each laboratory should be determined to provide a certain level of confidence for both the referring physician and the surgeon.

FACTORS KNOWN TO PRECIPITATE HEART FAILURE

Chronic heart failure is characterized by a waxing and waning of the signs and symptoms of circulatory congestion, sometimes culminating in severe pump dysfunction leading to death. It now seems apparent that approximately one-third to one-half of patients die suddenly and unexpectedly from a presumed arrhythmic death, whereas remaining patients appear to die from progressive pump dysfunction. However, recent experience with clinical trials has suggested that this distinction with regard to the mechanism of death in patients with heart failure is not a simple matter (93). Nevertheless, an undulating course characterized as compensation and decompensation is familiar to all physicians who care for these patients on a long-term basis. When patients acutely deteriorate, specific reasons for this acute deterioration should always be explored (Table 88.3).

Acute myocardial ischemia
Uncorrected high blood pressure
Obesity
Superimposed infection
Atrial fibrillation and other arrhythmias
Excessive alcohol consumption
Endocrine abnormalities (e.g., diabetes mellitus, hyperthyroidism, hypothyroidism)
Negative inotropic drugs (e.g., verapamil, nifedipine, diltiazem, beta-adrenergic blockers)
Nonsteroidal antiinflammatory drugs
Treatment and Na^+ noncompliance; lack of information given to patient about diet, medications, etc.

TABLE 88.3 CAUSES OF ACUTE DECOMPENSATION OF CHRONIC HEART FAILURE

Among the causes of acute decompensation of previously stable heart failure is the syndrome of acute myocardial ischemia. Although classic angina pectoris is not usually a prominent feature of patients with heart failure, we now know that approximately half or more patients with heart failure harbor severe underlying coronary artery disease. It is important to consider this etiologic factor when seeing patients with heart failure and acute decompensation. A 12-lead electrocardiogram should always be performed and compared with previous electrocardiograms. If there is any evidence for acute myocardial ischemia, patients should be considered for hospitalization, and acute myocardial infarction should be excluded. The importance of acute coronary events as a trigger for sudden death in patients with heart failure has likely been underappreciated (94).

Superimposed infections are well known to provide the nidus for acute decompensation. Even so-called simple viral illnesses can present a severe stress to the already compromised cardiovascular system of patients with advanced heart failure. Bronchial pneumonia is still a common cause of death in patients with chronic heart failure, and any infectious process occurring in the setting of decompensated heart failure may well be an indication for hospitalization and more aggressive therapy.

The onset of atrial fibrillation is well known to precipitate decompensation of previously stable heart failure. Although it is still not entirely clear if atrial fibrillation predicts an overall worse prognosis, ample anecdotal experience would suggest that the onset of new atrial fibrillation is often accompanied by worsening heart failure. With the loss of atrial contribution, cardiac output may be further reduced. Additionally, an excess ventricular response to the atrial fibrillation and inadequate filling of the left ventricle can both be contributory factors toward acute decompensation. When the atrial fibrillation is of 48 hours or more in duration, chronic anticoagulation with warfarin is usually indicated. Aggressive attempts toward restoration of normal sinus rhythm are sometimes in order, including the need for hospitalization and electrical cardioversion. In some cases, atrial fibrillation becomes chronic and is resistant to preventive antiarrhythmic therapy. In such cases, control of the heart rate may be the best strategy for the patient's well-being. Although digoxin has long been used to control heart rate in this setting, it may not be particularly effective in patients with heart failure who demonstrate excessive sympathetic activity. Agents with negative inotropic properties, such as beta-adrenergic blockers and diltiazem, are sometimes required as adjunctive therapy to digitalis. Low-dose amiodarone is sometimes highly effective in preventing recurrent atrial fibrillation in patients with advanced heart failure. A rapid ventricular response to atrial fibrillation that is sustained can cause heart failure, and atrioventricular node ablation should be considered in such patients (95).

Patients who acutely decompensate should always be queried on the excessive use of alcohol. Many patients are unfamiliar with the concept of alcoholic cardiomyopathy and need intensive education with regard to potential detrimental effects of alcohol in the setting of advanced heart failure. For patients with severe heart failure, it is probably prudent to recommend complete abstinence, although recently this has been called into question (96). It should be remembered that there is an epidemiologic link between chronic alcohol use and systemic hypertension, a situation to be clearly avoided in the patient with advanced heart failure. Patients with chronic alcoholism may have a tendency early to have abnormal ejection with a dilated ventricle, LV hypertrophy, and impaired LV relaxation (97).

Poorly controlled diabetes mellitus, hyperthyroidism, or hypothyroidism can all lead to acute decompensation of heart failure. Signs and symptoms of hypothyroidism can be difficult to elicit and/or can even be masked by episodes of depression and chronic fatigue. Poorly controlled diabetes mellitus can lead to substantial abnormalities in fluid and electrolyte balance and must always be aggressively corrected. In each case of acute decompensation of heart failure, possible endocrine or metabolic causes should be pursued.

Perhaps one of the commonest causes of worsening heart failure is noncompliance with drug therapy and dietary indiscretion. In general, medication compliance is approximately 75% in patients with heart failure, somewhat better than with hypertension. Nevertheless, patients must continually be educated about their medications and the need to take them on a regular basis. The importance of diet should be continually stressed. The most common cause for "diuretic resistance" is excessive dietary sodium, which can easily go unnoticed by the patient.

It is extremely important that the physician caring for the patient with heart failure be aware of the patient's full medication repertoire, including prescribed drugs and over-the-counter agents. Medications that are knowingly associated with negative inotropy, such as the first-generation calcium channel blockers and beta-adrenergic blockers, should be reduced or sometimes discontinued in the face of worsening heart failure. Nonsteroidal antiinflammatory agents are frequently a cause of excessive sodium and water retention and may offset the use of potent loop diuretics. Patients with advanced heart failure should be discouraged from using either prescribed or over-the-counter nonsteroidal antiinflammatory drugs. Such agents are well known to be associated with hemodynamic compromise (98).

MECHANISMS OF LEFT VENTRICULAR DYSFUNCTION

Abnormalities at the Molecular Level

Our current understanding of the mechanisms by which the myocardial cell fails to supply power for ventricular contraction is most uncertain. Despite extensive investigation into the fundamental properties of the failing heart, the precise molecular mechanisms responsible for diminished myocardial cell function, particularly at the molecular level, remain poorly defined. Undoubtedly, multiple mechanisms are operative. For many patients with congestive heart failure, the clinical problem is simply a loss of sarcomeres subsequent to myocardial infarction and replacement fibrosis. Nevertheless, the cellular counterpart of myocardial tension development in heart failure has been a subject of intense study for many years by many investigators. From the standpoint of normal physiologic responses, the cardiac power output is regulated by alterations of the molecular interactions between myosin cross-bridges and actin. The maximum intrinsic velocity for any one muscle type is dictated by the intrinsic characteristics of the myosin adenosine triphosphatase (ATPase). Under normal physiologic conditions, the primary regulator of contractility on a moment-to-moment basis in the normal cardiac cell is calcium flux. The sarcoplasmic reticulum is the internal membrane organelle that primarily functions in cardiac muscle to accumulate calcium and allow relaxation and subsequent release of calcium to initiate contraction.

Work in the 1960s indicated a reciprocal relationship between sodium and calcium exchange in cardiac muscle, suggesting that a sodium-calcium interaction may be important in providing incremental changes in intracellular calcium concentration. Although the mechanisms by which myocardial contractile abnormalities occur have been studied assiduously for the past 25 years, no general agreement has emerged regarding specific molecular, biochemical, or physiologic abnormalities associated with heart failure. In fact, there are frequent conflicts in the literature regarding potential biochemical abnormalities. Divergent results, which have stemmed from excellent laboratories, suggests that a number of methodologic problems in the study of cardiac tissue remains. For example, there is no consensus on identification of high-energy phosphate-level abnormalities during contractile failure. Although some studies have suggested abnormal sarcoplasmic reticulum abnormalities of calcium accumulation, the mechanism by which the sarcoplasmic reticulum function is altered in heart failure has yet to be clearly defined. More recently, isoform changes in cardiac muscle have been identified, but their role, if any, in human heart failure remains uncertain. Phospholamban is normally associated with regulation of sarcolemma Ca^{2+} transport and is reduced in heart failure due to dilated cardiomyopathy, coronary artery disease, and primary pulmonary hypertension; the expression level is inversely correlated with the myocardial ANF mRNA level (99). This has also been noted for Ca^{2+}-ATPase (99). It is possible that these changes are secondary to primary alterations in cardiac hypertrophy rather than heart failure, but this remains unclear. Protein levels of calcium-transporting ATPase, phospholamban, and calsequestran are not consistently diminished in failing human LV myocardium (100). It has been suggested that in dilated cardiomyopathy there is no alteration of contractile and regulatory proteins, but that the gating mechanism of calcium release from the sarcoplasmic reticulum is abnormal (101,102). Although mRNA expression of the calcium release channel or ryanodine receptor of the sarcoplasmic reticulum may be abnormal in end-stage human heart failure (103,104 and 105), it remains unclear whether these changes are mechanistically linked to abnormal contractile function or are simply epiphenomena related to the transition from normal to hypertrophy to failure (106).

Approximately 80% of the calcium flux involved in excitation-contraction coupling occurs across the sarcoplasmic reticulum membrane, but 20% of the calcium is moved across the cell membrane or sarcolemma by two transport systems. These sarcolemma transport systems include the sodium-calcium exchanger and the plasma membrane calcium pump. The sodium-calcium exchanger may be important in activation of contraction by providing a source of calcium to trigger the release of additional calcium from the cardiac sarcoplasmic reticulum. Recent data have indicated that the sodium-calcium exchanger gene expression is actually upregulated

in the failing human heart, suggesting that there is a compensation for depressed sarcoplasmic reticulum function (107). Membrane-bound Na^+-K^+-ATPase is also reduced in the failing heart (108). The decrease in the sarcoplasmic reticulum calcium ATPase mRNA in the myocardium may play an important role in the regulation of calcium movements. For example, impaired sarcoplasmic reticulum function may retard the removal of calcium in diastole, thereby contributing to diastolic dysfunction (109,110).

Abnormalities of Cellular Function

In addition to putative abnormalities in calcium-transporting ATPase, phospholamban, calsequestran, and myocardial ryanodine receptors, there remains the possibility that the production of intracellular cyclic adenosine monophosphate is deficient and hence an important cause of contractile dysfunction in patients with end-stage heart failure (111). It is well known that the time course of contraction and rate of relaxation are greatly prolonged in heart failure, and these abnormalities can be corrected when intracellular cyclic adenosine monophosphate is replenished by forskolin. Myocytes isolated from the left ventricles of patients with failing hearts demonstrate reduced contraction and slowed relaxation (112). At the cellular level, these findings suggest that abnormalities of myocyte function can contribute to both systolic and diastolic abnormalities in the failing human heart (113). Although no single chemical or molecular abnormality likely accounts for these abnormalities, it is of some interest to know that at physiologic frequencies, abnormalities of both contraction and relaxation can be detected at the level of the cardiac cells (96).

It has long been known that the failing heart adapts to the adverse circulatory conditions through a process of myocyte hypertrophy. However, fundamental knowledge regarding the transition from hypertrophy to failure is very incomplete. Adding new sarcomeres diminishes the rate of mechanical energy expenditure. Architectural changes in the hypertrophied heart can further exacerbate the imbalance between energy expenditure and energy production (114). For example, there may be an increase in the distance between capillaries that impairs the diffusion of substrates and oxygen essential for the production of energy by the hypertrophied heart. Long-standing hypertrophy may increase cell volume and myofibrils, thereby increasing the number of ATP-consuming myofibrils, thus further exacerbating an energy deficit. Although myocyte hypertrophy is a complex process that may be both adaptive and detrimental, the long-term effects of cellular enlargement may be deleterious to organ function. Abnormal protein isoforms may occur in response to hypertrophy due to well-known changes in gene expression. Although many of these changes are unique for various animal models, there is also a diminishment in the proportion of alpha-myosin heavy chain in the atria in patients during the development of left atrial pressure overload and enlargement.

As individual cardiac myocytes adapt to changing environmental conditions by increasing in size, a host of additional abnormalities occur. LV hypertrophy is associated with arrhythmias, some of which may be lethal (115). Abnormalities of relaxation occur, resulting in altered diastolic function of the heart. There is also a dynamic alteration in the connective tissue matrix of the heart during its response to injury or circulatory overload, leading to a rapid increase in collagen synthesis (116). The replacement of myocytes with connective tissue may additionally contribute to both systolic and diastolic abnormalities of organ function. Cardiac myocytes from failing hearts have a reduced responsiveness to sympathetic neurotransmitters (117). Not only do the cells become desensitized to beta-adrenergic receptor agonists through a downregulation of the $beta_1$-receptor, but there is also an uncoupling between the $beta_2$-receptor and the guanine nucleotide–binding (G) protein and an upregulation of the Gia subunit (118). Although such changes may be adaptive in the short term, protecting the heart from excessive sympathetic and inotropic drive, in the long term it is certainly possible that these changes contribute to the exacerbation of circulatory abnormalities well described in patients with congestive heart failure.

Abnormalities of Chamber Function

Heart failure is a very common clinical syndrome, but the pathophysiologic factors that affect chamber function vary considerably among patients. In my experience, coronary artery disease remains the most common cause of heart failure, although systemic hypertension continues to be the most common risk factor for heart failure in the Framingham studies (119). Differences between clinical trial patients and population-based cohorts may explain such differences, as well as difficulties with defining heart failure. Dilated cardiomyopathy and valvular heart disease also continue to be common causes of chronic heart failure.

The fundamental abnormality of the heart in the syndrome of heart failure is a diminished ability of the failing muscle to develop force and shorten at a given velocity and at specified loading conditions. The decreased velocity of shortening is conceptually related to the observed decrease in the maximal rate of force development. In general, there is little or no change in the passive length–tension relations of isolated failing heart muscle. Despite this, there can be dramatic changes in the passive pressure–volume relationship of the intact ventricle. Another elastic property of the heart muscle, the series elastic element, also does not appear to be grossly changed in the failing heart muscle. However, the failing left ventricle is exquisitely sensitive to afterload conditions (Fig. 88.1).

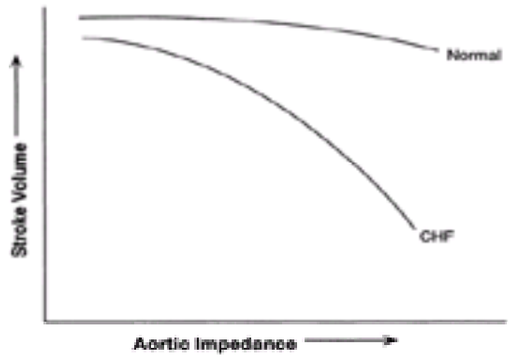


FIGURE 88.1 A hallmark of heart failure is the exquisite sensitivity of the left ventricle to an afterload stress. As impedance to ejection is raised, there is an impressive reduction in left ventricular performance. CHF, congestive heart failure.

To improve myocardial performance, several compensatory mechanisms are activated. One of these (previously discussed briefly) is the Frank-Starling mechanism, in which an increased preload enhances contractile force. The relationship between muscle length and the development of tension in cardiac muscle represents the basis of Starling's law of the heart. The dependence of the development of tension on muscle length arises from several observations, the most important of which is length-dependent activation of cardiac myofibrils by calcium. This effect is believed to be due to a change in the calcium sensitivity of the myofibrils. The failing heart does not generate a normal increase in force development when preload is enhanced (Fig. 88.2). Thus, Starling's mechanism fails to improve myocardial performance as much as normally expected in the failing heart (120). This becomes apparent clinically when it is noted that diuretic treatment, which reduces preload, is not necessarily accompanied by a diminishment in stroke volume. Experimentally, it has also been noted that the Frank-Starling mechanism is exhausted in dogs with rapid pacing–induced chronic dilation (121). In these animals, the application of an acute volume load fails to elicit a further increase in cardiac output or stroke volume, further substantiating a reduction in the Frank-Starling mechanism. Difference in the length-dependent force development in the failing heart may be due to either a change of calcium sensitivity in the myofibrils or an altered amount of calcium supplied to the myofibrils. Because contractile proteins are basically unchanged in severe heart failure, alterations in filament-regulatory proteins such as troponin T or troponin I and other isoform changes may play some role (122).

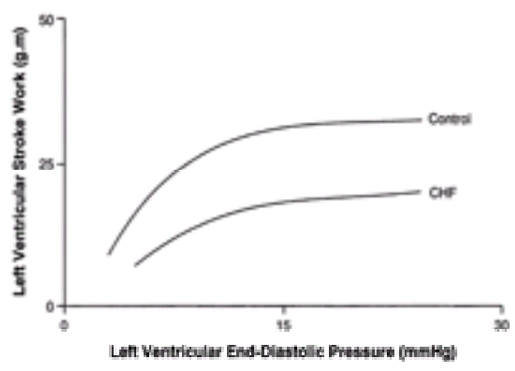


FIGURE 88.2 The Frank-Starling mechanism is altered in heart failure. The failing ventricle is unable to respond to an increase in preload with a normal increase in left ventricular stroke work. CHF, congestive heart failure.

It seems extraordinary that despite decades of investigations into the mechanism of heart failure, there still is not a coherent understanding of the precise sequence of events whereby LV performance is progressively diminished. Undoubtedly, multiple mechanisms are operative, including abnormalities of phenotypic gene expression, as yet imprecisely understood metabolic changes, and critically important peripheral adaptations, including activation of various neurohormones. The complexities inherent in the syndrome of heart failure make it unlikely that any single therapy is likely to emerge as solely effective. Current therapeutic strategies using polypharmacy to treat heart failure are consistent with this observation.

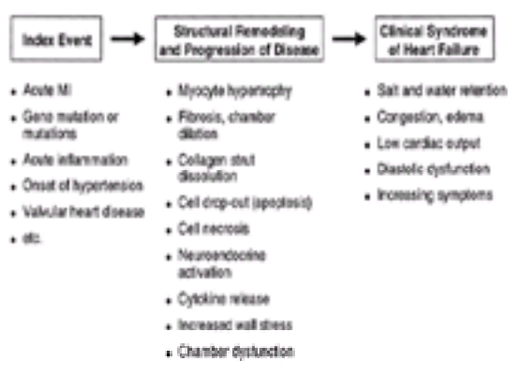
LEFT VENTRICULAR REMODELING

Ventricular remodeling is an alteration in the contour or volume of the ventricular cavity that is not attributed to acute changes in distending pressure (123). Cardiomegaly occurs and leads to a dilated and thinned-out left ventricle, a common but very complex finding in patients with congestive heart failure. The mechanism whereby LV remodeling occurs has been the subject of intensive study during the past decade (124,125). Multiple mechanisms drive this process, including myocyte loss, replacement scarring, and reactive growth mechanisms in the remaining viable cells. Although the early sequence of events at the molecular level are still not unraveled, much clinical and experimental data support the old concept that ventricular dilatation after myocardial infarction is a most accurate predictor of an unfavorable long-term prognosis (126,127).

The classic setting of LV remodeling occurs after an acute myocardial infarction. The infarcted territory may exhibit abnormal contraction patterns during systole, and this may ultimately lead to a progressive alteration in the shape of the ventricle. Although many investigators have suggested that LV remodeling represents an adaptive process serving to preserve stroke volume and cardiac output, it is now clear that the enlargement process has very deleterious long-term effects (123). With acute myocardial infarction, the extent of LV remodeling is very dependent on the size of the infarction as well as the location and depth of the acute myocardial injury. Immediately after myocardial infarction, sometimes within hours, there can be “infarct expansion,” which is an important complication and is associated with increased mortality. Infarct expansion is caused by acute dilatation and thinning of the area of infarction that is not explained by additional myocardial necrosis (128). Although the process of infarct expansion is still incompletely understood, it is believed that wall thinning occurs due to slippage between myocyte bundles as well as loss of intracellular space (129). This process can be detected clinically by echocardiogram and is more common in patients experiencing acute transmural infarction of the anterior apical left ventricle (130). In long-term studies, it is the extent of LV end systolic volume that has the most important prognostic power, even more so than the extent of underlying coronary artery disease.

Mechanisms of Progressive Left Ventricular Remodeling

Unlike infarct expansion, LV remodeling is the slowly progressive increment in volume of the heart that occurs over a prolonged period after acute myocardial injury (eFig. 88.2.1) (131). Stroke volume may be preserved by augmenting cavity size, but this occurs at a significant cost. According to the Laplace principle, LV enlargement is accompanied by an increase in wall stress. Wall stress then serves as a stimulus for compensatory myocardial hypertrophy. In addition to mechanical stresses that drive the remodeling process, there are probably also important neuroendocrine signals that act in an autocrine or a paracrine fashion to augment myocardial cellular hypertrophy (132,133,134 and 135). Experimentally, and in human dilated ventricles, it is now clear that cardiac myocytes increase in length shortly after acute myocardial injury (136,137). This increase in the length of the myocyte cell is largely due to so-called eccentric hypertrophy, or an increase in the number of sarcomeres in series. A suggestion has been made that the elongated cell is structurally inadequate and may contribute to the heart failure syndrome (138), although direct proof in support of this hypothesis is still lacking. Factors that contribute to LV remodeling are shown in Table 88.4.



***e*FIGURE 88.2.1** Working hypothesis of heart failure. After an index event, there is neuroendocrine activation leading to a progressive change in the size and the shape of the left ventricle. Further neuroendocrine activation occurs, leading to excessive vasoconstriction and ultimately to reduced organ perfusion. Eventually signs and symptoms of overt heart failure ensue. MI, myocardial infarction.

Neurohormones and cytokines
Increased left ventricular volume and pressure
Myocardial cell elongation
Replacement and reactive collagen deposition (i.e., increased collagen turnover)
Myocyte slippage secondary to dissolution of collagen struts
Apoptosis
Necrosis
Myocardial infarct expansion
Dilation and reshaping of left entricle

TABLE 88.4 FACTORS THAT CONTRIBUTE TO LEFT VENTRICULAR REMODELING

Patency of the infarct-related artery is also important in protecting against LV enlargement (139,140). The presence of antegrade blood flow through the infarct-related artery, either by collaterals or by reperfusion therapy, tends to protect against the development of LV wall motion abnormalities and progressive dilatation of the left ventricle (141,142 and 143).

The fundamental mechanisms that cause the LV remodeling are under intensive study by both basic scientists and clinical investigators. We now know that the increase in heart size is not due to a change in sarcomere length but rather is due to changes in the number of sarcomeres and change in cell size (144,145). Additionally, it is very likely that the process of apoptosis, or programmed cell death, is amplified in the setting of acute myocardial infarction (146). It is not simply loss of cells due to coagulation necrosis, but perhaps also the presumed loss of cells due to apoptosis, that makes an important contribution to the remodeling process. Myocytes may slip away from each other due to dissolution of the collagen struts that normally hold cells in a syncytial pattern. Cells enlarge both concentrically and eccentrically, but it is the increase in length that is most striking. Lastly, and very importantly, there are both replacement fibrosis of necrotic myocardial cells and enhanced growth of the interstitial matrix interstitium (147) during myocardial remodeling. It has long been known that there is a transition from the hypertrophied myocardium to the failing myocardium, but how and when this occurs are still not very clear.

Many of the changes of hypertrophy and remodeling are related not solely to altered mechanical forces, which are clearly important, but also to activation of neurohormones and various cytokines. The renin-angiotensin system is particularly important in this regard (148). It has repeatedly been shown in experimental studies, as well as in clinical trials, that the early use of ACE inhibitors retards LV remodeling after acute myocardial infarction (149,150,151,152 and 153). However, it remains unclear how much of this antiremodeling effect is simply due to betterment of loading conditions, or whether there is an important direct effect via inhibition of the renin-angiotensin system and the incremental increase in local concentrations of bradykinin. ACE inhibitors have multiple pharmacologic actions, including reduction of the sympathetic nervous system, and these actions may also contribute to their antiremodeling properties. Nitroglycerin has also been shown to reduce LV remodeling both experimentally (154) and clinically (155), but as with ACE inhibitors, the antiremodeling effects of nitrates are also not entirely understood. Although nitrates tend to reduce filling pressures and thereby may attenuate LV wall stress, it is also possible that the incremental change in local concentrations of NO associated with nitrates may retard cellular growth and hypertrophy (156). Beta-adrenergic blockers, which do not have immediate effects on loading conditions, also

attenuate progressive LV remodeling (157,158,159,160 and 161) and improve survival (162,163,164 and 165), suggesting that neuroendocrine overactivity is critical in the pathogenesis of heart failure.

What seems clear is that modification of abnormal mechanical forces and excessive neuroendocrine activity can importantly influence LV enlargement. Progressive increases in LV end systolic volume are a very important prognostic marker for a poor outcome, regardless of the cause of heart failure (127). Judicious use of agents such as nitrates and ACE inhibitors, which can favorably alter loading conditions of the left ventricle, may reduce progressive ventricular enlargement and improve survival. The combination of ACE inhibitor therapy, beta-adrenergic blockers, and maintaining patency of the infarct-related artery even beyond the time of myocardial necrosis may powerfully influence the ultimate size and shape of the ventricle. Clinical studies cited above have already led to a very aggressive change in the management of patients in the early stages after acute myocardial infarction. Therapies that limit the size of the infarction, prevent infarct expansion, reduce LV wall stress, and attenuate neuroendocrine activity are likely to favorably alter topographic changes of the ventricle and thus improve prognosis. It is entirely possible that surgical reduction of heart size (the Dor procedure) may some day play a role in the treatment of heart failure. Surgical reduction of marked cavity expansion is currently under intense study as a rational form of therapy (see Chapter 95).

NEUROENDOCRINE ABNORMALITIES

It has been known for many years that heart failure is characterized by activation of a number of neuroendocrine systems (Table 88.5) (12,14). Activation of neurohormones in heart failure has long been considered to be an “adaptive” process, perhaps a response to a fall in cardiac output and an attempt to maintain blood pressure. The perceived threat to circulatory homeostasis is similar to that of volume depletion, even though blood volume is usually increased in patients with heart failure. The sympathetic nervous system is activated, there is activation of the systemic renin-angiotensin-aldosterone system, and in many patients there is a release of AVP. The extent of neuroendocrine activations varies widely from patient to patient, but in general there appears to be a gradual incremental change during the evolution from LV dysfunction to overt heart failure (21) (Fig. 88.3). For many years, and to some extent still today, there has been a serious question as to whether these neuroendocrine changes represent simple markers (epiphenomena) or whether they actually contribute to the pathogenesis of the heart failure syndrome. In all likelihood, neuroendocrine activation makes an important contribution to the pathogenesis of heart failure. This statement is based on the fact that activation occurs very early in the course of the illness, even in the asymptomatic stage (21), and therapies designed to block neuroendocrine activation, such as ACE inhibitors and beta-adrenergic blockers, have had a favorable effect on the natural history of the illness (160).

Norepinephrine	Endothelin
Epinephrine	Beta-endorphins
Renin activity	Calcitonin gene–related peptide
Angiotensin II	Growth hormone
Aldosterone	Cortisol
Arginine vasopressin	Tumor necrosis factor-α
Neuropeptide Y	Neurokinin A
Vasoactive intestinal peptide	Substance P
Prostaglandins	Adrenomedullin
Atrial natriuretic factor	Brain natriuretic peptide

TABLE 88.5 NEUROENDOCRINE FACTORS KNOWN TO BE INCREASED IN PATIENTS WITH HEART ufailure

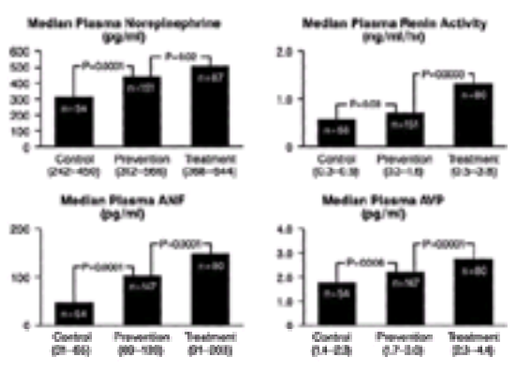


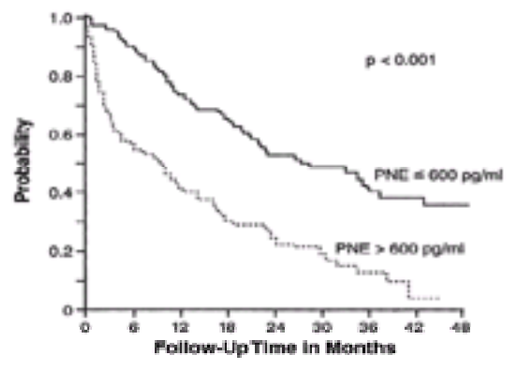
FIGURE 88.3 Data from the Studies of Left Ventricular Dysfunction substudy of baseline neurohormones. There is a progressive incremental rise in neurohormones as patients pass from the asymptomatic left ventricular dysfunction phase (prevention) to overt heart failure (treatment), suggesting that neurohormone activation may precede the onset of symptomatic heart failure. ANF, atrial natriuretic factor; AVP, arginine vasopressin. (From Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. *Circulation* 1990;82:1724–1729, and the American Heart Association, with permission.)

It is generally believed that a number of vasopressor/sodium-retaining peptides or hormones dominate the end stages of heart failure. These include norepinephrine (marked activation of the sympathetic nervous system), angiotensin II and aldosterone, AVP, and endothelin. There are also counterregulatory vasodilators/natriuretic peptides that are released in a presumed attempt to offset excessive peripheral vasoconstriction and salt and water retention. These natriuretic peptides include ANF, BNP, and adrenomedullin. Prostaglandins are also increased, at least locally within the kidney, to maintain homeostasis of renal blood flow and intraglomerular hydraulic pressure. On balance, however, there appears in most cases a dominance of heightened peripheral vascular resistance with sodium and water retention. In all likelihood, the increase in ventricular afterload, coupled with the inability to normally excrete salt and water, contributes importantly to worsening pump failure and circulatory congestion.

The mechanisms responsible for neuroendocrine activation in the syndrome of heart failure have been the subject of numerous studies. It is still unclear how the sympathetic nervous system is activated, although some investigators have suggested that altered reflex control mechanisms are at least partly responsible for excessive sympathetic drive. However, the fundamental signals that are responsible for altered reflex control mechanisms and the incremental change in sympathetic activity remain poorly understood. This lack of insight has impaired, to some extent, our therapeutic attempts to directly block neuroendocrine activation, forcing therapists to rely on drugs that inhibit neuroendocrine responses.

Abnormalities of the Sympathetic Nervous System

There is now direct evidence that increased central sympathetic nerve outflow occurs in patients with heart failure and is associated with an increase in plasma norepinephrine (20). In general, the greater the activation of the sympathetic nervous system, the worse the prognosis (eFig. 88.3.1). A single resting venous blood sample of plasma norepinephrine concentration provides a better guide to prognosis than many of the other commonly measured indexes of cardiac performance (18,166). Because hemodynamic abnormalities do not correlate well with levels of plasma norepinephrine, a direct causal link between heightened sympathetic activity and LV dysfunction has been difficult to substantiate. Moreover, there is a relatively loose correlation between plasma norepinephrine and PRA, suggesting that the two systems are independently activated in heart failure (167). However, it is well known that sympathetic stimulation may be one factor contributing to renin release.



***e*FIGURE 88.3.1** The probability of survival in patients with heart failure who have modest elevation of plasma norepinephrine (PNE) (600 pg per mL or less) and marked elevation of plasma norepinephrine (600 pg per mL or more). In general, elevated plasma norepinephrine has been consistently associated with a poor prognosis. (From Rector TS, Olivari MT, Levine TB, et al. Predicting survival for an individual with congestive heart failure using the plasma norepinephrine concentration. *Am Heart J* 1987;114:148–152, with permission.)

It is now believed that both increased neuronal release of norepinephrine and decreased efficiency of neuronal norepinephrine reuptake contribute to decreased cardiac adrenergic drive in congestive heart failure (168). Diminished norepinephrine stores in the failing heart are likely due to chronically increased norepinephrine turnover and reduced efficiency of norepinephrine reuptake in storage. In the short term, the adrenergic nervous system is important in supporting the failing circulation in patients with heart failure. However, in the long term, excessive sympathetic activity is likely making a major contribution to progressive LV dysfunction. It is well known that high levels of catecholamines are directly toxic to the myocardium (169,170). Cardiac norepinephrine spillover rate is perhaps the single most powerful prognostic neuroendocrine marker for patients destined to do poorly (171). It is the marked increase in norepinephrine spillover from the heart, or excessive sympathetic nerve firing, that is the dominant mechanism of heightened sympathetic activity, rather than faulty neuronal reuptake of norepinephrine (172). Adrenal medullary activity is also increased in patients with heart failure leading to increased plasma epinephrine concentrations, particularly toward the end stages of the disease. The fact that skin sympathetic nerve activity (in contrast to muscle sympathetic nerve activity) is not increased in heart failure supports the concept that altered reflex systems (which have nonuniform effects on muscle and skin sympathetic activity) may underlie much of the sympathoexcitation found in patients with heart failure (173). There is also increased central nervous system turnover of both norepinephrine and epinephrine in patients with heart failure (174), perhaps related to epinephrine neurons in the brain. The fact that norepinephrine kinetics return to normal after heart transplantation would suggest that many of the abnormalities of the sympathetic nervous system in heart failure are functional and to some extent reversible (175).

It is now believed that excessive sympathetic drive to the heart in patients with heart failure is responsible for downregulation of the $beta_1$-receptor and perhaps uncoupling of the $beta_2$-receptor (118). Isolated papillary muscles from pretransplant patients have been demonstrated to be nearly devoid of membrane beta-adrenergic receptors but respond normally to calcium. It has been hypothesized that receptor downregulation of the $beta_1$-receptor and uncoupling of the $beta_2$-receptor is more likely due to excessive local concentrations of norepinephrine and not due to high circulating levels of catecholamines.

The fact that excessive sympathetic stimulation has been repeatedly demonstrated in patients with heart failure and that patients respond to agents that knowingly inhibit excessive neuroendocrine activity would support the contention that neurohormonal activation is a critical factor in the pathogenesis of heart failure. These observations have stimulated a change in thinking away from drugs designed to have direct positive inotropic effects to those that secondarily improve cardiac function via inhibition of the sympathetic nervous system and the renin-angiotensin-aldosterone system.

Renin-Angiotensin-Aldosterone System

As with the sympathetic nervous system, it has been known for many years that the renin-angiotensin-aldosterone system is activated in patients with heart failure (Fig. 88.4) (7,12,14,176). Unlike the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system is less obvious in patients with minimally symptomatic LV dysfunction (21). However, as heart failure progresses, there are profound incremental changes in circulating renin, angiotensin II, and aldosterone (177,178). Moreover, there are now substantial data to support the concept of a tissue renin-angiotensin-aldosterone system, which may play a critical role in both myocardial and vascular remodeling (179,180). A number of factors are responsible for the release of renin (Table 88.6). Decreased perfusion to the kidney with an accompanying reduction in the renal tubular concentrations of sodium and chloride ions in the macula densa can activate the renin-angiotensin-aldosterone system. Increased activity of the sympathetic nervous system is also a potent stimulus for renin-angiotensin-aldosterone system activation. The institution of a low-sodium diet, vasodilator therapy, and diuretics are all known to further activate the renin-angiotensin system.

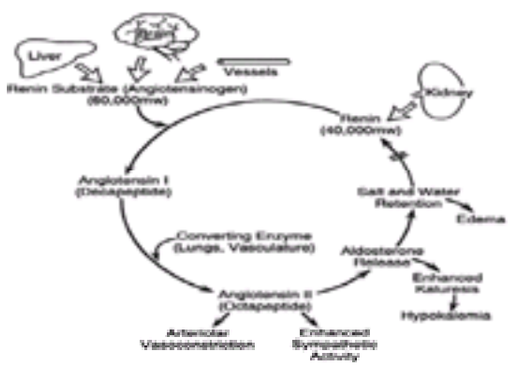


FIGURE 88.4 The circulating renin-angiotensin-aldosterone system. Angiotensinogen and renin produce a small decapeptide, angiotensin I, which is cleaved to angiotensin II by a converting enzyme. Angiotensin II, in turn, causes vasoconstriction, enhanced sympathetic nervous system activity, and aldosterone release. Increased salt and water retention expands circulating volume, which normally reduces renin release.

Renal artery baroreceptor activity
Renal hypoperfusion
Hyponatremic perfusate to the macula densa
Volume contraction secondary to diuretics and salt restriction
Stimulation of beta-adrenergic receptors in the kidney

TABLE 88.6 FACTORS THAT RELEASE RENIN

Angiotensin II is known to be a potent vasoconstrictor substance and also acts on the adrenal cortex to release aldosterone, a mineralocorticoid with potent sodium retentive properties (Fig. 88.5). Hypokalemia and hypomagnesemia often occur in the setting of heart failure, in part induced by the use of powerful diuretics. The combination of excessive adrenergic nervous system drive and hypokalemia is believed to predispose patients to lethal cardiac arrhythmias, from which nearly 30% to 50% of patients with severe heart failure die suddenly. The effectiveness of ACE inhibitors is in part related to their ability to block excessive angiotensin II activity, thus reducing some of the pathoexcitatory drive and diminishing the hypokalemic and hypomagnesemic effects of aldosterone in the kidney. Converting enzyme inhibitor

therapy also increases local concentrations of bradykinin, which in principle may have antiremodeling effects on the heart and contribute to vasodilation. Both excessive adrenergic nervous system activity and an overly active renin-angiotensin-aldosterone system are believed to contribute to progressive remodeling of the left ventricle and may form the underpinnings of the important transition from myocardial hypertrophy to myocardial failure. The precise molecular and cellular abnormalities that are operative in this important transition have yet to be elucidated.

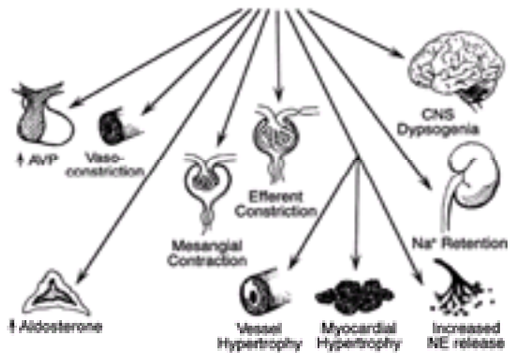


FIGURE 88.5 Angiotensin II has a vast array of biologic activities. These include release of arginine vasopressin (AVP) from the posterior pituitary, peripheral arteriole vasoconstriction, release of aldosterone from the adrenal cortex, mesangial contraction, constriction of the efferent glomerular arterioles, vascular hypertrophy, myocardial hypertrophy, facilitation of norepinephrine (NE) release from sympathetic neurons, sodium retention, and thirst sensation. CNS, central nervous system. (From Francis GS. The relationship of the sympathetic nervous system and the renin-angiotensin system in congestive heart failure. *Am Heart J* 1989;118:642–648, with permission.)

Arginine Vasopressin

Although plasma AVP has been demonstrated to be increased in patients with heart failure (22), these findings have not been highly consistent (178). Nevertheless, there is a trend for a gradual, incremental rise in plasma AVP as patients develop progressive LV dysfunction and overt heart failure (21). Synthesis and release of AVP from the posterior hypothalamus in both normal and pathologic states are regulated by osmotic and nonosmotic stimuli. The primary osmotic stimulus to AVP release is hyponatremia, whereas excessive diuresis, hypotension, and angiotensin II, as well as certain reflex control mechanisms, can act as nonosmotic stimuli. Patients with heart failure primarily have nonosmotic stimuli for AVP release (181,182), although this aspect has not been carefully studied. Although diuretics tend to stimulate AVP release, digitalis may reduce AVP levels by sensitizing cardiac baroreceptors.

AVP may act to constrict peripheral vessels, thus further raising systemic vascular resistance and myocardial afterload. AVP also acts via V_2 receptors in the kidneys to reduce the clearance of free water. V_2 receptors are also found in vascular tissue, where they subserve vasodilation in response to AVP (183,184). The level of AVP does not correlate with serum sodium, plasma norepinephrine, or hemodynamic variables (22). There is a weak correlation between plasma AVP and PRA (22). Patients with high circulating levels of AVP may be responsive to AVP antagonists (185,186), and there currently is an aquaretic AVP antagonist under study in clinical trials for the treatment of heart failure.

Endothelin

Endothelin-1 (ET-1) is a 21–amino acid peptide first reported as a potent vasoconstrictor produced by cultured porcine endothelial cells (187). There are now known to be three isoforms that share common receptors with somewhat different affinities. Only ET-1 is synthesized by vascular endothelial cells. In addition to very potent vasoconstrictive and mitogenic effects on vascular smooth muscle cells, ET-1 acts on endothelial cells in an autocrine fashion to induce the release of NO and prostacyclin. Furthermore, ET-1 has numerous effects on various tissues, including stimulation of the secretion of ANF and aldosterone, as well as inhibition of renin release and potent positive inotropic effects on the heart. Based on these findings, it has been suggested that endothelin has a role in maintaining the homeostasis of the circulatory system and may be important in the pathogenesis of various cardiovascular disorders, such as hypertension, heart failure, vasospasm, and atherosclerosis (188). Mice deficient in ET-1 developed elevated blood pressure and craniofacial abnormalities (189).

Because endothelin is associated with pressure overload hypertrophy (190,191), there is reason to believe that it may be important in the development of progressive LV remodeling. ET_A receptor blockers prevent cardiac hypertrophy in the face of hemodynamic overload (190). Plasma levels of endothelin are known to be increased in experimental heart failure (192) and in patients with dilated cardiomyopathy and heart failure (193,194,195,196 and 197). Evidence now suggests that circulatory endothelin concentrations in the range of 5 to 40 pg per L are vasoactive (198). Consequently, the endothelin concentrations found in patients with heart failure may be of pathophysiologic significance.

In addition to their effects on circulatory homeostasis, endothelins may have important functions in the regulation of contractility when released from the endothelial lining of the heart (199,200). There is growing evidence to support the existence of a dynamic interaction *in vivo* between cardiac myocytes and the adjacent microvascular endothelial cells in the regulation of both cardiac myocyte and possibly endothelial phenotype and function. The endothelium regulates the inotropic response of subadjacent cardiac myofibrils *in vitro* to changes in extracellular calcium. In healthy people, endothelin can induce a rise in blood pressure and in serum potassium concentration. Elevated plasma levels of endothelin are characteristic of severe heart failure and are not usually associated with asymptomatic or mild heart failure. The degree of plasma elevation of endothelin correlates with the magnitude of alterations in cardiac hemodynamics and functional class.

As our understanding of synthesis and release of endothelin in heart failure has expanded, there is great interest in exploring pharmacologic techniques that may alter its plasma concentration. For example, an enzymatic step is responsible for converting proendothelin to the mature peptide. As with angiotensin II, it is conceivable that an enzyme blocker will eventually be developed to inhibit this step. Neutral endopeptidases (NEPs) are known to inactivate endothelin (201,202 and 203), and several NEP inhibitors are now being widely studied as potential therapy for heart failure and hypertension. Perhaps most important, the acute administration of the endothelin receptor antagonist bosentan has been demonstrated to improve hemodynamics in patients with advanced heart failure (204). As with the renin-angiotensin system, it is likely that further research of endothelins will give way to potentially important new forms of therapy designed to block these peptides (205). A single dose of an ET_A blocker given to patients with heart block improves hemodynamics, does not activate other neurohormones, and is well tolerated (206). ET_A blockers may also improve pulmonary hypertension (207) and show promise as antiremodeling agents (208).

Atrial Natriuretic Factor

ANF is a naturally occurring hormone that has been demonstrated to be increased in several pathologic states, including hypertension and heart failure (26). Several different molecular forms of ANF have been isolated, but it is alpha-ANF that represents the major circulating form in humans. Synthesis of ANF occurs predominantly in the atria, where right atrial stretch appears to be an important stimulus for release. The peptide has also been identified in several other tissues, including ventricular myocardium. It is now known that the ANF gene is not expressed fully until late in embryonic life and after birth. However, there is heightened expression of the ANF gene in ventricular myocardium during hypertrophy and cardiomyopathy (209). It is believed that the reemergence of the fetal capacity to synthesize ANF in the setting of ventricular overload in hypertrophy represents an adaptive response to maintain volume homeostasis in response to the failing circulation. As with many other neuropeptides, ANF is progressively released into the circulation during the transition from asymptomatic LV dysfunction to overt heart failure (21). The peptide has vasodilatory properties and can thereby potentially improve cardiac function. It also may inhibit aldosterone secretion in patients with heart failure (210). Although it is a potent natriuretic, the renal effects of ANF appear to be attenuated during progressive heart failure. NEPs, which are highly concentrated in the proximal tubule brush border of the kidney, are responsible for degradation of ANF. This concept has driven the development of NEP inhibitors, some of which are hybrid molecules that include ACE inhibitors, of which omapatrilat is now in clinical trials for treatment of hypertension and heart failure.

In addition to the cardiovascular, renal, and neuroendocrine effects of ANF, the peptide may also have a moderating effect on cell growth (211). Unlike vasoconstrictor peptides, which tend to increase afterload, promote cell growth, and promote retention of salt and water, ANF appears to have important vasodilator properties, may be antigrowth *in vitro*, and has the ability to attenuate neuroendocrine activation and promote natriuresis. It is therefore part of a counterregulatory system that to some extent offsets excessive sympathetic nervous system and renin-angiotensin system activity. Although ANF has not itself become established as a therapeutic drug for heart failure, NEP inhibitors are potentially very important therapy for heart failure and hypertension, particularly when combined with ACE inhibitors (212).

Brain Natriuretic Peptide and C-Type Natriuretic Peptide

BNP was first isolated from the brains of pigs and forms a peptide family with ANF that is involved in the regulation of blood pressure and fluid volume (213). Plasma levels of BNP mainly reflect the degree of LV overload, and the secretion patterns of ANF and BNP vary with underlying cardiac disorders. BNP has been isolated from both brain and heart, whereas C-type natriuretic peptide is purified from porcine brain (214,215). Like ANF, both CNP and BNP can elicit vasorelaxant activity. All three natriuretic peptides share a common structural motif consisting of a 17-amino-acid loop formed by an intermolecular disulfide linkage bridge. When BNP is infused into humans with heart failure, urine volume significantly increases, excretion of sodium is enhanced, and plasma levels of BNP are increased (216). As with ANF, BNP causes a decrease in plasma aldosterone concentrations. Hemodynamic changes with BNP include an increase in heart rate, a decrease in blood pressure, as well as reduction in pulmonary capillary wedge pressure with little or no change in stroke volume index (217). Nesiritide, a human synthetic BNP, is currently approved as an infusion therapy for acute heart failure (218,219). Like ANF, BNP appears to be predominantly synthesized and secreted from the heart. BNP infusion also causes beneficial hemodynamic and neuroendocrine effects during exercise in patients with diastolic heart failure (220). It has been suggested that BNP, when persistently elevated, is a marker for poor long-term prognosis after acute myocardial infarction (184) and may serve as an important marker for ventricular dysfunction and myocardial hypertrophy. Perhaps the most exciting development is the use of BNP as a diagnostic marker for elevated LV filling pressures (31,32 and 33) and the potential to use bedside kits to quantitatively measure the response of circulating BNP to therapy. If successful, this strategy may obviate the need for invasive monitoring in some patients.

Growth Hormone

Patients with untreated heart failure are reported to have serum growth hormone levels more than 10 times the normal values (178). However, because in humans growth hormone secretion occurs mainly at night, random samples taken during the day may be less meaningful. At least one report has suggested that the severity of cardiac failure in patients with dilated cardiomyopathy is correlated with a decrease in circulating growth hormone levels at night (221). Even more intriguing are recent suggestions that recombinant human growth hormone may be useful as therapy for dilated cardiomyopathy. Many of the biologic effects of growth hormone on the heart appear to be mediated by local production of insulin-like growth factor I, which in turn regulates tissue growth by paracrine and autocrine mechanisms. Fazio and colleagues have reported that when administered at a dose of 14 IU per week, recombinant human growth hormone doubled the serum concentration of insulin-like growth factor I, and there were associated increases in LV wall thickness and reduced chamber size (222). In this small uncontrolled study, growth hormone also improved clinical symptoms, exercise capacity, and the quality of life. It has been known for many years that patients with acromegaly may present with cardiomyopathy and myocyte hypertrophy. In rats with acute myocardial infarction due to ligation of the left coronary artery, growth hormone improves cardiac index, stroke volume index, and LV dP/dT (223). The combination of insulin-like growth factor I given with growth hormone to rats with LV failure is associated with diminished vascular resistance and improved cardiac output (224). Severely dysfunctional hearts with evolving myocardial infarction may still be capable of undergoing additional hypertrophy in response to growth factor and may demonstrate evidence of improved function, suggesting a potentially beneficial effect (225). Clearly, this is an area where further basic and clinical studies are needed; however, work in this area has slowed, and there are no clinical trials in progress.

Tumor Necrosis Factor-a

Tumor necrosis factor (TNF)–a is a cytokine produced mainly by macrophages but has also been found in vascular smooth muscle and heart. It is a proinflammatory cytokine that has been consistently identified in virtually all forms of cardiac injury (226,227). It may play an important role in mediating and integrating the myocardial response to stress. As with other neurohormones, TNF-a may have a maladaptive role in long-term LV remodeling and heart failure. It has been suggested that TNF-a may produce inducible NO synthase (iNOS), leading to enhanced local concentrations of NO (229), which is known to exert a negative inotropic effect in the myocardium. TNF-a has also been implicated as a systemic mediator of septic shock and has been isolated from rat myocardium under conditions of acute ischemia and reperfusion (227). TNF is expressed in cardiac tissue of patients with heart failure (226,228). The observation that failing hearts express increased levels of TNF-a suggests that overexpression of the cytokine may have some biologic role in the progressive dysfunction that characterizes the failing heart.

It has been suggested that heart failure is characterized by the progressive loss of cardiac cells. The mechanism of cell dropout is not entirely clear, but apoptosis has been suggested as a potential mechanism. TNF-a is associated with apoptosis (230) and may play a role in the cell dropout associated with ventricular remodeling and heart failure. Ligand family members of the TNF receptor superfamily can induce pleiotropic biologic responses, including differentiation, proliferation, activation of enzymes, and cell death. Levine and colleagues were the first to demonstrate that TNF-a is increased in patients with heart failure (231). In high concentrations, TNF-a can cause pulmonary edema and LV dysfunction. It has also been suggested to stimulate catabolism and cardiac cachexia (232). Soluble TNF-a receptors may be shed from cells and can bind circulating TNF-a, thereby prolonging its half-life and biologic functions (233). In the aggregate, TNF may be an important contributor to the syndrome of progressive heart failure through a vast array of mechanisms, including increased expression of iNOS, deactivation of protooncogenes, and stimulation of apoptosis, and perhaps through as yet not fully identified mechanisms. The development of anti–TNF-a as treatment for heart failure has progressed rapidly, and a large, randomized, controlled trial in patients with heart failure has been conducted with etanercept, a fusion molecule consisting of the p75 receptor linked to the Fc portion of human immunoglobulin G (234). Etanercept and infliximab (a monoclonal antibody to TNF-a) are now being widely used to treat inflammatory conditions such as rheumatoid arthritis and Crohn's disease. Early experience in clinical trials has, however, been disappointing.

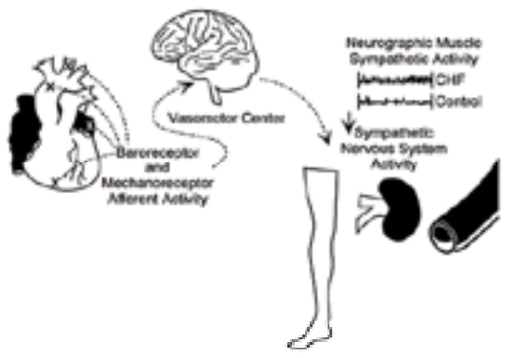
Adrenomedullin

Adrenomedullin is a newly discovered vasodilating and natriuretic peptide that may have some role in the regulation of cardiorenal homeostasis. Plasma concentrations of adrenomedullin are increased in patients with heart failure (235,236), and the peptide is known to be present in the human heart through immunoactive staining. Plasma adrenomedullin levels correlate with pulmonary artery pressure and pulmonary capillary wedge pressure. The precise role, if any, that adrenomedullin plays in the pathogenesis of heart failure has yet to be elucidated.

REFLEX CONTROL ABNORMALITIES IN HEART FAILURE

Human patients and animals with experimental chronic heart failure have abnormal reflex control mechanisms. Both arterial baroreflexes and cardiac reflexes are abnormal and can have profound effects on the patient with low cardiac output (237,238). Eckberg and colleagues first reported in 1971 that patients with heart disease had depressed baroreflex responses when given intravenous phenylephrine (239). Patients with advanced heart failure were subsequently demonstrated to have a blunted baroreceptor response to orthostasis (240).

Abnormal reflex control of the circulation is due to a combination of factors, including changes in end-organ responsiveness, as well as abnormalities in the synthesis, storage, and release of neurotransmitters. Left atrial stretch receptor discharge sensitivity is depressed in animals with heart failure (241). Under normal conditions, increases in atrial and ventricular filling pressures, as well as increased mean arterial pressure or pulse pressure, lead to stimulation of cardiopulmonary and arterial baroreceptors. Baroreceptor activation, in turn, sends inhibitory signals to the medullary vasomotor center in the brain, which in turn suppresses sympathetic efferent activity (*e*Fig. 88.5.1). There is also accompanying increased vagal efferent activity. For reasons that are still not entirely understood, heart failure is characterized by blunting of the normal baroreflex inhibition. This results in increased activation of the sympathetic nervous system and enhanced renin-angiotensin activity. It is as if the normal breaking of inhibitory signals of the medullary cardiovascular control region is lost in heart failure, presumably due to decreases in cardiopulmonary and the aortic baroreceptor sensitivity.



***e*FIGURE 88.5.1** Normal reflex control mechanisms sense changes in heart and vascular fullness and send afferent signals to the vasomotor center of the brain medulla, where they are processed to send out inhibitory efferent traffic that normally reduces sympathetic drive. In heart failure, this inhibitory "breaking" mechanism is defective, leading to enhanced efferent sympathetic activity (as measured by neurographic sympathetic activity to the skeletal muscles), affecting skeletal muscles, the kidney, and peripheral vascular tissue. CHF, congestive heart failure.

Abnormal sensitivity of the reflex control mechanisms can be restored to some extent by pharmacologic interdiction with drugs such as digitalis or ACE inhibitors. Although cardiopulmonary baroreflex control of sympathetic nerve activity is clearly less responsive in heart failure, there is less confidence about abnormalities of baseline arterial baroreflex control of sympathetic nerve activity. However, recent data suggest that reduced inhibitory signals from arterial baroreceptors also contribute to heightened sympathetic activity in heart failure (242). It does seem clear, however, that arterial and cardiac reflex abnormalities are not the sole cause of enhanced sympathetic tone in patients with heart failure. Increases in plasma norepinephrine are similar in baroreceptor-denervated and baroreceptor-intact dogs paced to heart failure (243). It is therefore unlikely that depression of baroreflex sensitivity in heart failure is the only cause of augmented sympathetic tone. It is also unlikely that abnormal baroreflex sensitivity seen in heart failure is due to structural alterations of the baroreceptors (244). Abnormalities of reflex control have been shown to reverse after orthotopic cardiac transplantation (245).

DISTURBANCES OF SALT AND WATER CONTROL

It has been understood by generations of physicians that heart failure is characterized by excessive sodium and water retention, but the mechanisms that underlie this observation continue to be elusive. It is unlikely that any single mechanism accounts for the maintenance of normal sodium balance. Patients with very severe heart failure have glomerular filtration reduced to approximately one-half of normal and renal blood flow reduced to approximately one-fifth of normal, suggesting that there is a considerable diversion of blood away from the kidney. As a result of the lowered filtration rate, a smaller quantity of sodium is probably delivered to the renal tubular cells. However, glomerular filtration rate is not invariably reduced in patients with heart failure, and its preservation is dependent by activation of the renin-angiotensin system (246).

Vasoconstriction and sodium retention are appropriate responses to loss of circulating volume. In heart failure, the kidney is responding to a perceived loss of extracellular fluid and plasma volume. The kidney, therefore, is not the culprit, but the victim. Glomerular filtration may be maintained by the vasoconstrictor effects of angiotensin II on glomerular efferent arterials. In the later stages of heart failure, salt and water retention are enhanced due to the effects of aldosterone and angiotensin II on the kidney. In some cases, vasopressin is released, leading to further reabsorption of free water. Eventually, heightened systemic resistance, circulatory congestion, edema, and hyponatremia become clinically manifested.

The primary signal that the kidney receives to initiate salt and water retention has remained elusive. It is not known what initiates the signal, nor is it understood where the signal is processed. Early studies by Barger observed that sodium excretion alterations are detected even in the mildest forms of experimental heart failure, before venous pressure is even changed (247). Abnormalities of cardiac output may not necessarily precede the increase in salt and water retention. These findings would suggest that sodium excretion abnormalities occur very early in the syndrome of heart failure, perhaps before there is a major reduction in maximal LV performance (248). Clearly, a reduction in cardiac output alone is not sufficient to cause sodium retention.

One of the major determinants of sodium retention is activation of the renin-angiotensin system. But there is only a rough correlation among hemodynamic measurements, the renin-angiotensin system, and urinary sodium excretion in patients with heart failure. Undoubtedly, neural and humoral pathways involve physical adjustments in renal microvascular hemodynamics, tubule fluid composition, flow rate, and tubular ion gradients, but these interactions are highly complex and difficult to precisely characterize (249).

Despite the lack of a penetrating understanding of how the initiation of salt and water retention occurs in heart failure, it does seem rather clear that the kidney perceives, in some way, a threat to the arterial blood pressure. There is a very consistent response to this perceived threat, with activation of baroreceptor reflexes, increases in sympathetic nervous system activity, and enhanced activity of the renin-angiotensin-aldosterone system. Ultimately, the increase in sympathetic nervous system activity may be coupled to reduced renal blood flow, thus leading to the nonosmotic release of vasopressin and other neurohormones. The net effect of these changes is an expansion of the extracellular volume, which helps to maintain blood pressure. Increased blood volume, in turn, acts as a negative feedback message to reduce the renin-angiotensin-aldosterone response, thus accounting for some of the observed heterogeneity in the renin-angiotensin-aldosterone system in patients with early heart failure.

To some extent, the expanded blood volume and intracardiac pressures lead to counterregulatory steps, including the release of ANF and other natriuretic peptides that have important endogenous natriuretic and vasodilator properties. However, the effects of the various natriuretic peptides on the kidney seem to be diminished as the syndrome of heart failure progresses. Ultimately, the effects of the natriuretic peptides are overwhelmed by opposing influences, and the overall effect is one of salt and water retention. It seems fortunate for the patient that our knowledge of how to treat salt and water retention has probably surpassed our understanding of the fundamental mechanisms that cause edema formation (250).

ABNORMALITIES OF THE PERIPHERAL CIRCULATION

It is now recognized that the maladaptive changes in the peripheral vasculature and skeletal muscle of patients with heart failure are largely responsible for symptoms of exercise intolerance. In the peripheral vasculature, impaired vasodilator capacity results from enhanced vessel wall stiffness, endothelial dysfunction, and other structural abnormalities. Blood vessels of patients with heart failure are generally more vasoconstricted. Initially, the vasoconstriction is minimal and somewhat selective as the body strives to redistribute blood flow between organs to maintain circulatory efficiency (Fig. 88.6) (251). However, over time, vasoconstriction becomes excessive in an attempt to protect blood pressure. Only the coronary and cerebral circulations are spared. The vasoconstriction ultimately becomes inappropriate and increases aortic impedance, thus placing a further burden on the already failing heart.

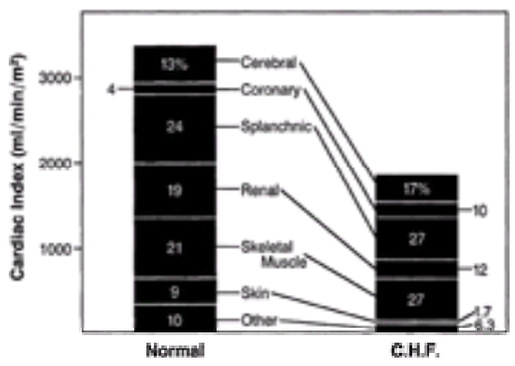


FIGURE 88.6 Cardiac output at rest. The normal distribution of cardiac index and the distribution of flow in heart failure. Renal and skin blood flow are markedly reduced in heart failure, whereas flow to the brain, heart, splanchnic bed, and skeletal muscles is preserved. CHF, congestive heart failure. (From Zelis R, Nellis SH, Longhurst J, et al. Abnormalities in the regional circulations accompanying congestive heart failure.*Prog Cardiovasc Dis* 1975;18:181–199, with permission.)

Although the cause of the heightened vasoconstrictor tone in heart failure is not entirely clear, it appears to be related to increased circulating catecholamines, particularly norepinephrine, as well as to other vasoconstrictors, including angiotensin II, vasopressin, and possibly endothelin. The abnormal redistribution of blood flow that occurs at rest is accentuated by exercise in patients with heart failure (251). Maximum metabolic vasodilation is significantly reduced. The increased sodium content of the vessels accounts for some of the vascular stiffness observed in heart failure. There is also heightened venous tone. Ultimately, the limited arteriolar dilator capacity results in a relative skeletal muscle hypoxia that may, through a reflex arc, lead to further sympathetic tone.

Although the increase in vascular resistance in heart failure is obvious, it is only partially explained by neurogenic and humoral stimuli. More recently, interest has focused on endothelial function, which is well known to be impaired in heart failure (252). Endogenous NO is known to be increased in patients with heart failure (253,254) and correlates with the severity of the syndrome as measured by the New York Heart Association functional class (255). It is believed that increased NO production in heart failure may compensate to some extent for the excessive vasoconstrictor adaptation. Despite an elevated basal release of NO and its role in depressing cardiac function, there is evidence to suggest that the peripheral vasculature has impaired release of NO on stimulation, which may play a role in inadequate vasodilator responses to exercise (256). In support of this hypothesis, there are data to suggest that oral L-arginine, when given in a supplemental fashion to patients with heart failure, has a beneficial effect by increasing forearm blood flow, improving the distances as walked during the 6-minute walk test, and improving quality of life as measured by a questionnaire (257). Dysfunction of the endothelium may persist and worsen as heart failure progresses, as evidenced by diminished vasodilator responses to acetylcholine and attenuated hyperemic responses to exercise and ischemia, both of which are largely endothelium-dependent. Of interest,

heart transplantation results in some reversal of impaired vasodilation, but it is delayed and incomplete (258).

In summary, congestive heart failure is characterized by abnormal peripheral vascular blood flow distribution with diminished hepatic, renal, and limb flow. The changes in peripheral blood flow are proportional and linearly related to the reduction in cardiac output. Vascular resistance is increased and is related to circulating catecholamines, angiotensin II, and AVP. Additionally, there appears to be significant impairment of NO release due to endothelial dysfunction, which probably accounts for some of the exercise intolerance noted in patients with heart failure. A generalized inability to maximally dilate a response to various stimuli characterizes the abnormal circulatory response, which may be corrected to some extent by medical therapy and heart transplantation.

EXERCISE INTOLERANCE IN HEART FAILURE

One of the hallmarks of the syndrome of heart failure is exercise intolerance. Although exercise tolerance is associated with LV systolic dysfunction, numerous studies have suggested that the extent of LV dysfunction bears little correlation to it (259,260,261,262 and 263). Moreover, it has been demonstrated that short-term administration of positive inotropic agents and vasodilators, which acutely improve LV performance, do not improve maximal exercise capacity in patients with heart failure (264). Even agents that are knowingly effective for the long-term therapy of heart failure, such as ACE inhibitors, have failed to consistently demonstrate improvement in exercise tolerance. The reasons for this are not entirely understood but may be related to inadequate methodology. The maximal exercise test may not be very representative of the daily activities of patients suffering from advanced heart failure (264). Maximal exercise testing is also somewhat subjective in that motivational factors and the experience of the operator/investigator can influence the end point. Because of this, the anaerobic threshold may be a more objective end point, but it is sometimes difficult to demonstrate, even with sophisticated gas exchange techniques. The simple 6-minute walk test is highly correlated to overall prognosis and seems to be emerging as an important measurement of exercise tolerance (265).

Maximal oxygen consumption is characterized by a plateau in oxygen uptake despite an increasing work rate (64). It is highly reproducible in normal subjects but can be difficult to determine in patients with advanced heart failure. The regional distribution of cardiac output during exercise is regulated by a complex interaction between the sympathetic nervous system, regional vasoactive factors including metaboreceptors, and endothelial-derived vasoactive substances including NO. The extent of widening of the arteriovenous oxygen difference is determined by increasing oxygen extraction in the exercising skeletal muscles. This in turn is somewhat dependent on capillary density, the number of open capillaries, and the transit time of the red blood cells through the capillaries. These complexities, coupled to the notorious difficulty in making accurate measurements during maximal exercise, have made it difficult to understand the precise mechanism of exercise intolerance in patients with heart failure.

In contrast to normal subjects, patients with heart failure do not achieve a plateau in oxygen uptake at the end of exercise. Rather, a “peak” oxygen uptake is determined in patients with heart failure that can be somewhat less reproducible. Whereas normal subjects distribute close to 90% of their total output to exercising skeletal muscle during maximal exercise, patients with heart failure distribute only 50% to 60% of the total cardiac output to exercising muscle. It has been presumed that the maximum caliber of the resistance arterioles is decreased in patients with heart failure due to changes in structure or perhaps vascular remodeling. When blood flow is chronically reduced, as occurs in advanced heart failure, the maximal vasodilator capacity of the peripheral circulation is markedly diminished through a complex sequence of events. These events include neurohormonal activation, diminished endothelial function related to impaired synthesis of NO, increased synthesis of endothelin, and possibly activation of cytokines and local factors that may further reduce arteriolar diameter. Patients with heart failure compensate for the reduced perfusion by widening their arteriovenous oxygen difference. Complete oxygen extraction can occur in the exercising skeletal muscle beds of patients with heart failure. This compensatory increase in oxygen extraction by skeletal muscles is similar to that observed in highly trained athletes. The mechanism of hyperextraction of oxygen is not understood very well. Unlike in well-trained athletes, increased capillary density has not been observed in patients with heart failure. In fact, there may well be diffuse atrophy of the lower extremities with diminished oxidative skeletal muscle fibers and oxidative enzyme content. This paradox remains poorly explained.

The exercise response in heart failure is very complex. Pump function is poorly related to exercise tolerance. Factors in the peripheral musculature, not the central hemodynamics, largely determine shortness of breath and fatigue. These peripheral factors include endothelial function, vasodilator capacity, distribution of cardiac output, heightened chemoreceptor and ergoreceptor sensitivity, skeletal muscle histology, and oxidative enzyme activity. Minute ventilation is markedly increased. There is a higher ventilation for any given carbon dioxide production (VE/VCO_2 slope), which reflects the severity of heart failure and the prognosis. Enhanced ergoreflexes and chemoreceptor responses drive hyperventilation and heightened sympathetic outflow, leading to increased peripheral resistance and a decrease in muscle perfusion.

Reduced muscle endurance can be improved with chronic exercise training in patients with heart failure (266,267 and 268). Although drugs such as ACE inhibitors may not improve maximal exercise tolerance in patients with heart failure, they can redistribute blood flow to the skeletal muscles during exercise and thereby improve submaximal exercise tolerance. Changes in skeletal muscle structure and function in heart failure may be related in part to deconditioning (266). Therefore, it is reasonable to recommend that all patients with heart failure continue to be physically active, at least with regard to isotonic activity. On the other hand, isometric activities such as work against gravity, are to be discouraged, because such activities impose an immediate afterload stress on the left ventricle. Reduced physical activity alone, however, does not easily explain the genesis of the skeletal muscle changes observed in heart failure (269). Clearly, we still have much to learn regarding the problem of exercise intolerance in heart failure.

TRANSITION FROM ASYMPTOMATIC LEFT VENTRICULAR DYSFUNCTION TO CLINICALLY OVERT HEART FAILURE

There is perhaps no more intriguing concept in the pathophysiology of heart failure than the transition from silent LV dysfunction to overt congestive heart failure. This transition is poorly understood but very important. Available experimental data would suggest that the initial response to an index event, such as acute myocardial infarction, includes a form of adaptive hypertrophy of myocardial cells. Eventually, there is remodeling of the left ventricle with replacement fibrosis, growth of the interstitium, and cell dropout due to apoptosis. Among the host of counterregulatory vasodilator mechanisms set into play is enhanced basal NO production (253,254 and 255). The expression of iNOS is enhanced in the failing human heart (270). iNOS is likely part of a primitive but evolutionary conserved inflammatory response. NO has been shown to have a negative effect on cardiac performance both experimentally (271) and clinically (272). NO may contribute to beta-adrenergic hyporesponsiveness in patients with LV dysfunction (271). Thus, in a purely speculative sense, the overexpression of cardiac NO may contribute to the transition to overt clinical heart failure.

Another mechanism perhaps responsible for the transition from clinically silent dilated cardiomyopathy to overt heart failure is dropout of myocardial cells. Although apoptosis is currently a feature of intense laboratory investigation, its role in the development of heart failure remains somewhat undefined. Nevertheless, there seems to be a commonality of interaction between TNF-a and iNOS. Cytokines such as TNF-a are increased in patients with heart failure (231,232 and 233) and are known to produce apoptosis through a receptor-mediated mechanism (273). TNF-a is also known to stimulate the production of iNOS (270). It is possible that as TNF-a increases over time, it has the dual propensity to induce local myocardial NO release (which in turn hampers LV function) while at the same time mediating cell dropout. In principle, such a mechanism would be a powerful factor in the pathogenesis of transition from clinically silent LV dysfunction to overt heart failure. More study of the complex interaction between TNF-a, iNOS, and progression of heart failure will be required to unravel this potentially very important mechanism.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Heart failure remains a problem of growing magnitude in the Western world. It primarily afflicts the older population and is a major drain on scarce medical resources. Although great strides have been made in the past two decades regarding the management of this complex syndrome, much work remains to be done (274,275,276 and 277).

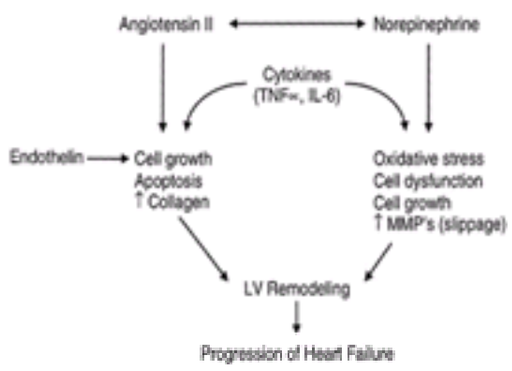
Heart failure is a prime example whereby a clearer understanding of the basic pathophysiology has led to highly specific therapies that are uniformly effective, such as ACE inhibitors and beta-adrenergic blockers. As we delve further into the neuroendocrine and cytokine disturbances in the syndrome, it becomes clear that other potential therapeutic targets are worth developing. Over the years there has been a rather direct course away from drugs designed to stimulate the inotropic state to agents that block excessive neuroendocrine activation pathways. In the future, we can look forward to drugs that are designed to more specifically inhibit the sympathetic nervous system, perhaps through mechanisms other than beta-adrenergic blockade. Drugs designed to block specific ET_A receptors have recently become available in an oral form (278). Preliminary data would suggest that endothelin blockers may have a primary role in the management of patients with heart failure by causing both a reduction in systemic vascular resistance and by stimulating vasodilator counterregulatory mechanisms. Augmentation of these vasodilator counterregulatory mechanisms is also possible through hybrid molecules that contain both NEP inhibitors and ACE inhibitors. Short-term infusion of peptides such as BNP may also find a role.

It will be useful, perhaps, to clinically screen for asymptomatic LV enlargement. Identification of markers in such patients might enable the early introduction of pharmaceutical interdiction. It is also possible that surgical reduction of a markedly expanded LV cavity will prove to be a valuable adjunct form of therapy. If cell dropout via apoptosis is found to be a dominant mechanism in the transition of LV dilation to overt heart failure, research in this arena may allow for the development of agents that block TNF-a receptor activity, thereby reducing iNOS synthase and blocking apoptosis. Until such agents are available, it is perhaps important to recognize that most cases of heart failure are due to coronary artery disease and hypertension. Many of the consequences of long-term high blood pressure can now be prevented with early identification and aggressive treatment. All physicians need to recognize that LV hypertrophy is a powerful risk factor for heart failure and

premature death and should be prevented or controlled when possible. Although the prevention of coronary artery disease is still not fully within our grasp, identification and aggressive control of risk factors are now certainly possible. In the long run, it is through the prevention of heart failure that measurable strides will be made in curbing what is now described as an emerging epidemic. Despite obvious progress, many controversies and uncertainties remain. The role of anticoagulation, especially aspirin, is still debated. The role of myocardial reperfusion on outcome is not entirely clear. The role and costs of polypharmacy remain a challenge. Controversy and uncertainty remain the driving force behind additional study, however, and will continue to serve us well.

CONCLUSIONS

Heart failure is a complex disorder that is still rather poorly understood. An index event occurs, such as acute myocardial infarction or onset of cardiomyopathy, and a host of “adaptations” are staged. Abnormal LV function from any cause appears to stimulate the release of a number of neurohormones and cytokines in an attempt to provide presumed circulatory homeostasis. However, over time neuroendocrine and cytokine activity may become highly maladaptive, contributing to LV remodeling, heightened systemic vascular resistance, and ultimately, worsening heart failure (*e*Fig. 88.6.1). To date, the most impressive long-term effective therapy has been designed to limit excessive neuroendocrine activation, and this is likely where future and more imaginative therapies will also reside.



***e*FIGURE 88.6.1** The neurohumoral hypothesis. Heart failure is characterized by activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and specific cytokines, including tumor necrosis factor-a (TNF-a). Endothelin, a potent vasoconstrictor and mitogenic peptide, is also released, and there are counterregulatory natriuretic peptides, which to some extent offset the vasoconstrictor-enhanced growth milieu. Presumably these systems are activated in response to various signals stemming from deranged circulatory homeostasis to provide short-term support to the circulation. However, their long-term or persistent effects are ultimately maladaptive, and their chronic, excessive activity favors a pathway for left ventricular (LV) remodeling, hypertrophy, and progressive heart failure. These changes are facilitated by oxidative stress, apoptosis, increased collagen turnover, and excessive matrix metalloproteinase (MMP) activity. Drugs designed to block the adrenergic nervous system and the renin-angiotensin-aldosterone system are among the most effective therapies we have for the treatment of heart failure. IL, interleukin.

THE FUTURE

Heart failure is a common and highly disabling clinical syndrome. Although advancements have been made in our understanding of the pathogenesis and management of this complex disorder, we are still lacking substantial information regarding fundamental abnormalities, particularly at the cellular level. The mechanisms whereby neurohormones are activated and released are still not explained, but we have the means to abrogate their excessive activity. The underlying myocyte contractile abnormalities that occur on a molecular level are still poorly defined. The precise mechanism leading to exercise intolerance is still debated. Despite these misgivings, it is likely that continued research at both the basic and clinical level will afford clinicians the opportunity to better understand and manage this common clinical syndrome, provided there is sufficient support for basic science as well as clinical investigation. It is likely we will be able to better screen for heart failure via biochemical markers such as BNP, thereby initiating therapy at an earlier stage and thus preventing onset of the full-blown syndrome.

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HEALTH CARE IMPACT OF HEART FAILURE

RANDALL C. STARLING

"Indicates text or graphics that appear only in the electronic versions of this text."

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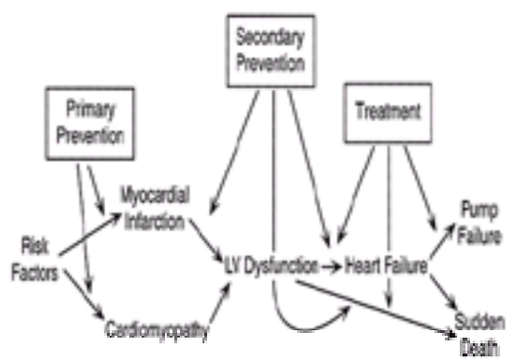
OVERVIEW

Congestive heart failure is an increasing, global epidemic, particularly in the elderly, that results in significant health care expenditure, disability, and mortality. Coronary artery disease, hypertension, and diabetes mellitus are the major etiologic risk factors. Ironically, advances in the treatment of coronary artery disease and acute ischemic syndromes, which have saved lives, have resulted in a growing population of survivors with left ventricular dysfunction destined to develop the heart failure syndrome. Preventive measures that have evolved over the last 25 years, including hypertension management, have not reduced the incidence of heart failure. Congestive heart failure is the leading indication for hospitalization in the United States for patients older than 65 years. The majority of health care dollars spent on heart failure is for inpatient care. Heart failure is a chronic disease amenable to an intensive multidisciplinary care model (disease management program) designed to prevent hospital admissions through patient education, focused outpatient initiatives, and adherence to management guidelines that should enhance cost effectiveness and improve quality of life. Patients with advanced heart failure represent approximately 10% of the total heart failure population, have the highest short-term mortality, and consume the greatest percentage of resources (labor and dollars). Regionalized centers with expertise in the management of advanced heart failure patients (through pharmacotherapy, circulatory support devices, surgical procedures, and transplantation) are necessary to deliver sophisticated care for this expanding population.

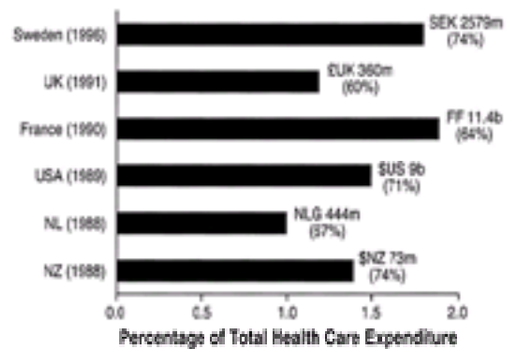
INTRODUCTION

Fifty years ago, chronic heart failure was considered primarily an edematous disorder. Hypertension and valvular heart disease were the most frequent predisposing causes (1). Physicians attempted to control pulmonary and peripheral congestion with diuretic therapy. Heart failure was a slowly progressive disease until patients succumbed with biventricular failure, anasarca, and renal insufficiency. Today, symptomatic heart failure is most often characterized by effort intolerance (dyspnea) and fatigue.

The most common causes of heart failure are coronary artery disease and hypertension. In the United States, incidence is twice as high in hypertensives and five times greater in persons who have had a myocardial infarction (2). Current treatments are judged by their ability to (a) reduce mortality, (b) reduce cardiovascular morbidity, (c) improve functional capacity, (d) improve quality of life, and (e) retard disease progression. As shown in eFigure 89.0.1, the natural history of heart failure has five key stages. The opportunities for medical interventions include primary prevention, secondary prevention, and treatment. An example of primary prevention is the use of pravastatin sodium to retard the progression of coronary artery disease and the incidence of myocardial infarction in a high-risk patient (3). The treatment of hypertension and the reduction in the vectoral transmission of Chagas' disease are also primary prevention efforts (4). A secondary prevention measure would be the use of captopril in a patient after an anterior myocardial infarction to retard left ventricular remodeling and the development of congestive heart failure (5). The mainstay of heart failure therapy today is "treatment" for established and symptomatic disease. Certainly the health care impact of heart failure for our society will continue to grow until effective primary and secondary prevention strategies are adopted and used. Therapeutic strategies can be assessed by determining the expenditure per quality-adjusted life-year (QALY) achieved with the treatment (6,7). A ratio of less than $20,000 per QALY is considered excellent, a ratio of $20,000 to $60,000 acceptable, and a ratio in excess of $100,000 per QALY unattractive (7). Examples for each year of life gained include renal dialysis, $40,000; cardiac transplantation, $25,000 to $44,300; and heart failure treatment with carvedilol, $12,800 to $29,000 (7,8). The cost of treating advanced symptomatic heart failure is high and represents a growing economic burden for industrialized nations. An analysis of six countries revealed that 1% to 2% of total health care expenditures were for treatment of heart failure (eFig. 89.0.2) and approximately 70% of this was consumed by hospital costs (9). The rapidly increasing prevalence of heart failure represents the most important public health problem in cardiovascular medicine (1,9,10).



***e*FIGURE 89.0.1** Stages in the natural history of heart failure, from the presence of risk factors to the syndrome of heart failure and its sequelae. Points for primary and secondary prevention and treatment are shown. LV, left ventricular. (Adapted from the Task Force on Research in Heart Failure, National Heart, Lung, and Blood Institute report Heart Failure. Washington, DC: U.S. Department of Health and Human Services, 1994.)



***e*FIGURE 89.0.2** Costs of chronic heart failure care in relation to the total annual health care expenditure in six industrialized nations. The component for hospital costs, quoted in the local currency, and the percentage of total expenditures on chronic heart failure care consumed by hospital costs are shown to the right of the bars. (Adapted from McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. *Heart* 2000;83:596–602.)

Heart failure is a chronic disease that may evolve over years and progress from minimal to severe impairment. Successful heart failure management requires lifestyle modifications and impinges on the activities and lives of family members and caregivers as well. Patients may live a limited but reasonable lifestyle for years. Most are disabled, however, and thus are not productive members of society. Aside from the economic burden from a health care resources standpoint, the disability and long-term nature of the condition that limit a patient's ability to be gainfully employed are significant. The components of cost to be considered from a public health perspective include hospitalization costs, outpatient care costs, and disability costs (11). Management of a chronic disease requires a multidisciplinary continuum of care designed to improve quality of life, reduce hospitalizations, and decrease costs (12,13). Thus, heart failure is not an isolated encounter, such as acute pharyngitis or bacterial pneumonia. Rather, it is an "epic of care," and patients, their families, and health care providers must develop relationships. Optimal outcomes can be achieved when physicians have the expertise to care for the patient through the various phases of his or her illness, effect lifestyle changes through education, and use a multidisciplinary team for effective chronic disease management (14).

EPIDEMIOLOGY

Heart failure is a widespread epidemic affecting 2 to 4 million Americans and nearly 15 million people worldwide (10,15,16). The American Heart Association estimated that, in 2001, 4.7 million Americans were alive with congestive heart failure (11). Although mortality rates are declining for cardiovascular disease in the United States, hospitalizations for heart failure have increased substantially (17). In 1990, more than 700,000 hospital discharges had heart failure as the primary diagnosis in the United States (15). This represents a fourfold increase since 1971. Hospital discharges of patients with congestive heart failure in the United States rose from 377,000 in 1979 to 978,000 in 1998, a 155% increase (11). In 1990, there were 708,000 new heart failure patients and 280,000 deaths, which represents a net increase of 428,000 patients or a 12% growth per year (18). Estimates are that approximately one-half of patients with heart failure are age 65 years or older.

A cohort of 2,000 persons aged 25 to 74 years living in Scotland underwent a detailed assessment of cardiac status including echocardiography (9). The overall prevalence of left ventricular systolic dysfunction (ejection fraction of 30% or less) was 2.9%. Concurrent symptoms of heart failure were found in 1.5%, whereas the remaining 1.4% were asymptomatic. Prevalence was greater with increasing age and in men, reaching 6.4% in men aged 65 to 74 years.

The criteria for the diagnosis of the syndrome of congestive heart failure are not standardized. Measures used in population-based studies and cardiovascular drug research rely on a composite of signs, symptoms, and diagnostic findings. Heart failure is a clinical diagnosis, and measures such as ejection fraction do not always identify patients with congestive heart failure (e.g., diastolic dysfunction). Attempts to validate the Framingham clinical heart failure score against a measure of ejection fraction showed that, in patients with a low left ventricular ejection fraction (0.40 or less), 20% met none of the criteria for congestive heart failure (19).

The crude incidence (unadjusted for age) ranges from one to five cases per 1,000 population per year and increases sharply with advancing age to as high as 40 cases per 1,000 population over age 75 years in some studies (20). An indication of the incidence of heart failure in the United States can be obtained from the Framingham study and the Framingham Offspring Study, which represent a population of over 10,000 (15). The incidence of heart failure rises with age in both men and women, as shown in Figure 89.1. In the Framingham study, the annual incidence increased from 3 per 1,000 in men aged 50 to 59 to 27 per 1,000 in men aged 80 to 89 years, and from 2 per 1,000 in women aged 50 to 59 to 22 per 1,000 in women aged 80 to 89 years. The incidence of congestive heart failure after adjustment for age is one-third lower in women than in men. Crude prevalence, unadjusted for age, ranges from 3 to 20 cases per 1,000 and, for those older than 65 years, from 30 to 130 cases per 1,000 population (20). Based on the increasing age of the U.S. population, estimates are that the prevalence of congestive heart failure will nearly double to 5.7 million cases by the year 2030 (21).

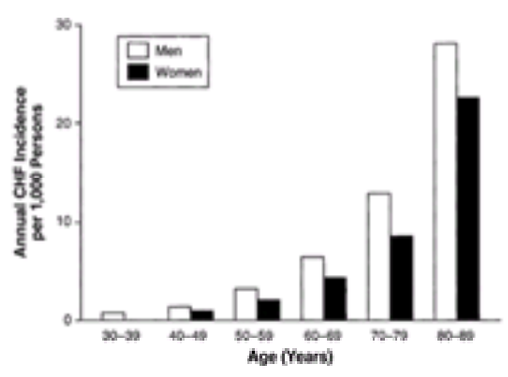


FIGURE 89.1 The annual incidence of congestive heart failure (CHF) among subjects in the Framingham Heart Study, shown by age in decades for men and women. (Adapted from Ho KKL, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham study. *J Am Coll Cardiol* 1993;22[Suppl A]:6A–13A, with permission.)

Etiologic Risk Factors

The prevalence of certain causes of and risk factors for congestive heart failure among Framingham Heart Study subjects is shown in Figure 89.2. The Framingham study documented the relative risk for the development of heart failure in the presence of specific risk factors, including hypertension, hypercholesterolemia, cigarette smoking, electrocardiographically identified left ventricular hypertrophy, and diabetes mellitus, in a population-based cohort study (15). Among 331 men and 321 women in the Framingham study who developed congestive heart failure during follow-up, hypertension and coronary artery disease were the two most common preexisting conditions (15). Only 11% of men and 15% of women had no antecedent history of coronary artery disease or hypertension. Interestingly, in the 40-year period from 1948 to 1988, the age-adjusted prevalence of coronary disease in men with new congestive heart failure increased by 46% per calendar decade (p <.05). However, the age-adjusted prevalence of coronary heart disease among all males in the Framingham Heart Study decreased by 8% per calendar decade (p <.05) (15).

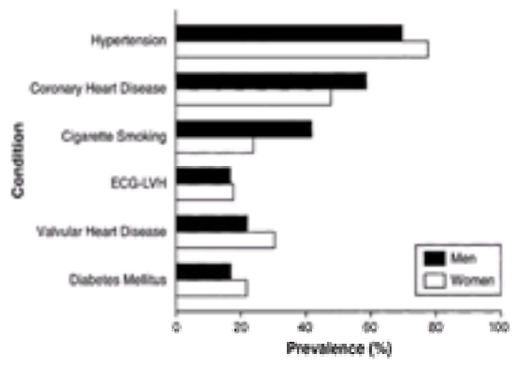


FIGURE 89.2 Prevalence of causes and risk factors for the development of congestive heart failure by gender in the Framingham Heart Study cohort. ECG-LVH, electrocardiographically identified left ventricular hypertrophy. [Adapted from Ho KKL, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham study. *J Am Coll Cardiol* 1993;22(Suppl A):6A–13A, with permission.]

The incidence of heart failure is twice as high in persons with hypertension, and the incidence can be stratified based on severity of hypertension as shown in Figure 89.3 (2). Similarly, when followed prospectively, persons with a history of prior myocardial infarction are found to have a fivefold greater incidence of heart failure over a 5-year period (2) (Fig. 89.4).

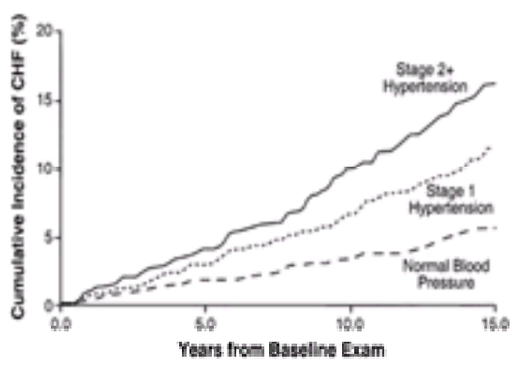


FIGURE 89.3 Incidence of congestive heart failure (CHF) in men and women aged 50 to 79 years by hypertension status. Stage 1 hypertension is defined as systolic blood pressure of 140 to 159 mm Hg or diastolic blood pressure of 90 to 99 mm Hg in people not receiving antihypertensive medication; stage 2 or higher hypertension is defined as systolic blood pressure of 160 or greater, diastolic blood pressure of 100 or greater, or current use of antihypertensive medication. (Adapted from National Heart, Lung and Blood Institute. Congestive heart failure in the United States: a new epidemic. Bethesda, MD: U.S. Department of Health and Human Services, 1996.)

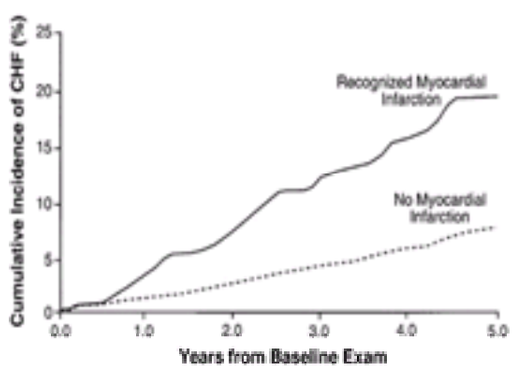


FIGURE 89.4 Incidence of congestive heart failure (CHF) by myocardial infarction status. (Adapted from National Heart, Lung and Blood Institute. *Congestive heart failure in the United States: a new epidemic*. Bethesda, MD: U.S. Department of Health and Human Services, 1996.)

Mortality

Although a significant decline in mortality due to coronary heart disease and hypertension has occurred over the past 40 years, no significant decline was observed in age-adjusted mortality in patients diagnosed with congestive heart failure in the Framingham cohort (15). Heart failure remains a lethal condition, with 5-year survival rates of less than 40% from the time of diagnosis, as shown in Figure 89.5. Data obtained from the National Center for Health Statistics in 1988 show that 267,356 deaths due to heart failure occurred. At all ages, the death rates from heart failure are greater for the African-America population, as shown in Figure 89.6, and the mortality rate from heart failure increases precipitously after age 65 years (15). Since 1968, the incidence of heart failure as the primary cause of death has increased fourfold (15). The most dismal prognosis for patients with severe symptoms [New York Heart Association (NYHA) class IV] and coronary artery disease was a survival rate of 43% and 18% at 1 and 3 years, respectively (22). Patients with dilated, nonischemic cardiomyopathy who are symptomatic with medical therapy have a better prognosis than patients with underlying coronary artery disease (22).

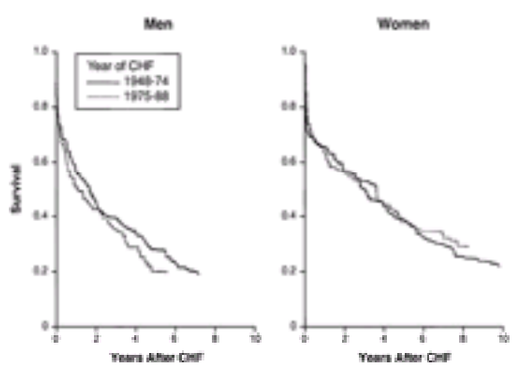


FIGURE 89.5 Age-adjusted survival rates by calendar year after the first diagnosis of congestive heart failure (CHF) for men and women in the Framingham Heart Study. No significant change in survival over 40 years of follow-up was found despite a considerable decline in coronary artery disease mortality. [Adapted from Kannel WG, Ho K, Thom T. Changing epidemiological features of cardiac failure. *Br Heart J* 1994;72(Suppl 2):S3–S9, with permission.]

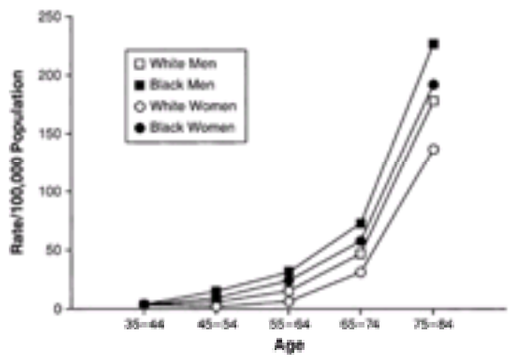


FIGURE 89.6 U.S. heart failure death rate in 1988 by age, gender, and race. Compiled from data from the National Center for Health Statistics. [Adapted from Kannel WG, Ho K, Thom T. Changing epidemiological features of cardiac failure. *Br Heart J* 1994;72(Suppl 2):S3–S9, with permission.]

Although major advances in pharmacologic therapy have occurred in the past decade, cardiac transplantation remains the only therapy that has a major, positive impact (reduced mortality and improved functional class) for patients with class IV symptoms refractory to medical therapy. The primary limitation of heart transplantation is the low availability: only 2,184 heart transplantations were performed in 1999 in the United States (see Chapter 94). Thus, a very small minority of the population at risk is served with this life-sustaining form of therapy. Therefore, most patients with class IV disease, comprising 10% to 15% of the total population with heart failure, remain at highest risk for hospital admission, require frequent outpatient monitoring, and consume a high percentage of the total dollars spent on heart failure care. In 1999, the estimated first-year cost for a heart transplant was $303,400, and the estimated annual follow-up cost was $39,700 (11).

Hospitalization Rates

Congestive heart failure represents America's largest diagnosis-related group, with an annual inpatient volume of more than 600,000, almost double the number of all other cardiovascular disorders (21). As the U.S. population ages, heart failure is a rapidly increasing indication for hospitalization, as depicted in Figure 89.7 (17). A sharp increase in the rates of hospital admission for heart failure in the elderly cohort older than 65 years was observed from 1972 to 1990, with the rate tripling from 55 per 10,000 to more than 150 per 10,000 population (17). The National Hospital Discharge Survey, which analyzed data from 1973 to 1986, identified a dramatic increase in hospital discharges for congestive heart failure in the population older than 74 years (23). Data for persons aged 35 to 54 years showed a significant gender and race differential (nonwhite men and white men have the highest hospitalization rates). With advancing age, however, the gender and race differential for hospitalization attributable to heart failure disappears (23). Overall, since 1971, a fourfold increase has occurred in hospital admissions for which congestive heart failure was the primary diagnosis, rising from 165,000 to 722,000 in 1990 (17). In 1997, 957,000 Americans were discharged from short-stay hospitals with a primary diagnosis of heart failure; of these, 79% were age 65 and older (11).

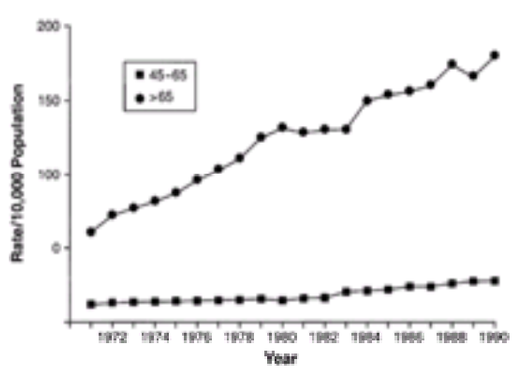


FIGURE 89.7 Hospital admissions per 10,000 population per year for congestive heart failure in the United States. [Adapted from Kannel WG, Ho K, Thom T. Changing epidemiological features of cardiac failure. *Br Heart J* 1994;72(Suppl 2):S3–S9, with permission.]

Reasons for Increasing Prevalence of Heart Failure

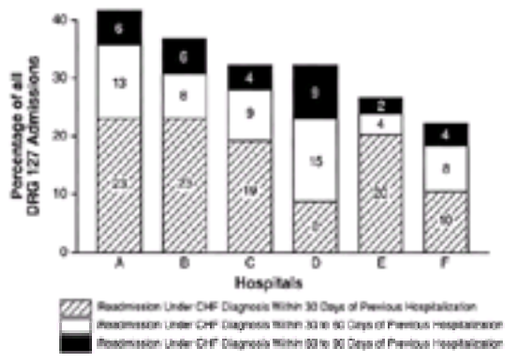
The prevalence of heart failure increases with age. Furthermore, advances in the pharmacologic and surgical management of coronary artery disease, arrhythmias, valvular heart disease, and hypertension have resulted in an ever-enlarging, aging pool of patients who are likely to develop worsening systolic or diastolic function and ventricular remodeling leading to the syndrome of heart failure. Effective medical and surgical interventions have resulted in a reduction in premature deaths. The prevalence of heart failure is rising, however, because predisposing conditions (coronary artery disease and diabetes mellitus) are palliated but not cured. The population of "survivors" with chronic coronary heart disease and left ventricular dysfunction who eventually develop the syndrome of congestive heart failure is growing. Similarly, the advent of implantable cardiac defibrillators has further reduced the incidence of sudden cardiac death. Thus, patients now live longer with left ventricular dysfunction and progressive congestive heart failure. Successful strategies aimed at the primary prevention of coronary artery disease will result in a major decline in the prevalence of congestive heart failure.

ECONOMICS AND THE HEALTH CARE IMPACT OF HEART FAILURE

Medical economics and heart failure are reviewed in Chapter 42. Health care reform in the United States has led to the reexamining, restructuring, and reengineering of all aspects of health care delivery in America. Because congestive heart failure represents the number one public health problem in cardiovascular medicine, its economic impact is tremendous. Projections attempting to estimate the total health care costs of heart failure are performed using indirect measures, extrapolations, and assumptions. Statistics, including those from the National Disease and Therapeutics Index, National Hospital Discharge Survey, and National Ambulatory Medical Care Survey, are used (18,24). Recent estimates of total annual health care expenditures for heart failure in America have ranged from $10.3 billion to $37.8 billion (18,24). The disparity of these figures demonstrates the unavailability of accurate economic data, but the cost to American society per year is at least $10 billion and may be as high as $40 billion. The American Heart Association estimated $21.0 billion for direct and indirect costs of congestive heart failure in the United States in 2001 (11). The breakdown included: $14.3 billion for hospital and nursing home care, $1.5 billion for physician and professional services, $1.6 billion for medications, $1.5 billion for home health care, and $1.6 billion for lost productivity and mortality. Hence, 68% of the total expense is for inpatient care, very similar to the estimates for inpatient care (73% and 62%) in the other two reports cited earlier (18,24). Considering the rates of hospitalization (including readmissions) for heart failure, the fact that 1% to 2% of total health care expenditures is consumed by treatment of heart failure in a number of industrialized countries is not surprising (9) (eFig. 89.0.2). Actual health care expenditures for treatment of heart failure can only be estimated. All estimates assume the accuracy of discharge summaries, death certificates, prescription use, and physician surveys in coding heart failure events.

The frequency of hospitalizations for congestive heart failure accounts for much of the economic burden. A conservative estimate of cumulative care costs during hospitalization ranges from $6,000 to $12,000 per admission. Approximately 35% of the population diagnosed with heart failure become hospitalized on an annual basis (10). Multiple hospitalizations, particularly of elderly patients with multiple comorbid conditions (50% have three or more), are especially common. Indeed, the 3-month readmission rate after an index hospitalization for congestive heart failure was found to be as high as 47% of discharges (25). A demonstration project showed that, in six medical centers, congestive heart failure patients are most likely to require readmission in the first 30 days after hospital discharge, as shown in eFigure 89.7.1, and that 22% to 42% of all patients classified into diagnosis-related group 127 at admission are readmitted within 90 days of a previous hospitalization (21). Many factors are related to the high rates of hospitalization for heart failure patients, including progression of underlying disease, inappropriate treatment plans, lack of patient compliance with prescribed regimens or diet or both, and use of detrimental drug therapy in certain heart failure settings. Many patient- and physician-specific issues that contribute to "heart failure decompensation" are potentially reversible (26). An analysis in Germany of 179 patients admitted to the hospital with acute decompensation of preexisting heart failure concluded that 54% of admissions could be regarded as preventable (27). Noncompliance with drug regimens or diet was the leading cause of acute decompensation and was present in 42%. The importance for practitioners of using pharmacologic agents proven to be effective in multicenter clinical trials (e.g., lisinopril in the Assessment of Treatment with Lisinopril and Survival trial; see Chapter 92) at target doses when managing chronic heart

failure must be reinforced (28).



***e*FIGURE 89.7.1** Rates of readmission under the diagnosis of congestive heart failure (CHF) [diagnosis-related group (DRG) 127] at six hospitals. (Adapted from Field JL. *Beyond four walls: research summary for clinicians and administrators on CHF management.* Washington, DC: Cardiology Preeminence Round Table, Advisory Board Company, 1994, with permission.)

Methods of reducing the high frequency and acuteness of hospitalization, prolonged length of hospital stays, and frequent emergency room visits are essential to reduce costs. Outpatient care is much less expensive. Thus, the costs to intensify the outpatient delivery of care are trivial and are offset by the major reduction in total health care costs if hospital days are reduced. One goal should be to improve the “effectiveness” of inpatient stays so that readmission rate declines. Up to 25% of Medicare expenditures for hospitalizations are for readmissions (29). A demonstration project performed in the United States showed that initiatives to reduce readmissions resulted in a 43% greater reduction in total hospital days than did initiatives to reduce length of stay (21). A study was conducted of 748 patients hospitalized for heart failure in 12 Veterans Administration hospitals. Patients were scored according to ten criteria believed to define readiness for discharge (30). A readiness-for-discharge score below the twenty-fifth percentile was associated with a twofold increase in the risk for readmission. The criteria used are intuitive and simple (stable renal function, compensated congestive heart failure, no change in cardiac medications in 24 hours, patient or family or both understand dietary regimen, etc.). Thus, in heart failure, improving the “quality” of the hospitalization may be the most cost-effective approach. Initiatives to reduce length of stay are important but should not compromise efforts to decrease the risk of hospital readmission.

SEVERITY OF HEART FAILURE AND RESOURCE USE

Patients with advanced heart failure represent approximately 10% of the total heart failure population, experience the highest short-term mortality, and consume tremendous resources (labor and dollars). Because of better pharmacotherapy and management, an increasing number of patients is expected to survive with severe left ventricular dysfunction who will ultimately die from refractory heart failure. Before the era of angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and improved treatment for arrhythmias, approximately 50% of patients with left ventricular dysfunction died of presumed arrhythmias. Information now indicates that approximately 20% of patients with compensated heart failure and preserved exercise capacity die from sudden cardiac death (31,32). Despite meticulous management to reduce exacerbations of congestive heart failure, these patients ultimately deteriorate, develop worsening heart failure, and require advanced therapies. Patients with refractory heart failure are the consumers of expensive, technologically sophisticated options, including cardiac transplantation, mechanical circulatory assist devices, automatic implantable cardiac defibrillators, outpatient intravenous inotropic therapy, and frequent high-acuteness admissions (intensive care unit stays and hemodynamic monitoring). A European analysis has shown that treating severe heart failure is more expensive than treating mild heart failure, primarily due to the high rate and costs of hospitalization over the 6- to 12-month period before death (33). An admission for cardiac transplantation and postoperative care averages $303,400. Cost for implantation and care associated with a left ventricular assist device averages $175,000, and implantation of a cardiac defibrillator, $50,000. As discussed in Chapter 42, the cost for 1 year of care for a patient with advanced heart failure is approximately $20,000. Specialized regional heart failure centers will play a critical role in the delivery of cost-effective high-quality care to this group of patients, who consume a high percentage of the total health care dollars spent.

ECONOMIC IMPACT OF PHARMACOTHERAPY

ACEIs reduce mortality, progression of symptomatic disease, and hospitalizations in patients with symptomatic and asymptomatic left ventricular dysfunction (34,35). In the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial, a 26% reduction in risk of death or hospitalizations for heart failure was seen among patients treated with enalapril maleate (34). In the SOLVD prevention trial, which enrolled asymptomatic patients with left ventricular systolic dysfunction, enalapril-treated patients experienced a 36% risk reduction for first hospitalizations and a 44% risk reduction for multiple hospitalizations for heart failure (35). Based on results of published randomized trials with hydralazine hydrochloride/isosorbide dinitrate and enalapril, the incremental cost-effectiveness ratio per year of life saved was calculated (36). The cost per year of life saved is an additional $5,600 for a patient receiving hydralazine and isosorbide and an additional $9,700 for a patient receiving enalapril above the costs for patients receiving no vasodilator therapy (Table 89.1). In comparison, when this modeling technique is used, the cost for a year of life saved by treatment of moderate hypertension is $25,000 and for a year of “useful life saved” by renal dialysis is $35,000 (36). A study in the United Kingdom found that only 17% of patients with heart failure were prescribed ACEIs by their general practitioner (37). In the United States, surveys have indicated that cardiologists are more likely to prescribe ACEIs than are general practitioners and internists (38). Furthermore, “heart failure specialty cardiologists” are more likely to use the documented efficacious dosage of studied drugs and to avoid concomitant use of potentially deleterious medications.

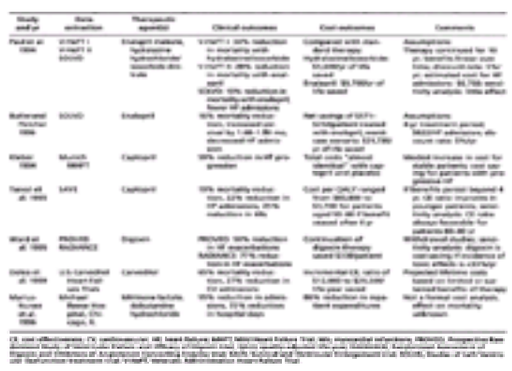


TABLE 89.1 COST EFFECTIVENESS OF PHARMACOLOGIC AGENTS FOR THE TREATMENT OF HEART FAILURE

The use of multiple agents for the treatment of heart failure is becoming state of the art as all randomized trials now include background ACEI therapy (see Chapter 92). In the prospective randomized trial of carvedilol, patients with heart failure receiving background treatment with digoxin, diuretics, and an ACEI were randomly assigned to receive carvedilol or a placebo. Compared with placebo, carvedilol therapy was accompanied by a 27% reduction in the risk of hospitalization for cardiovascular causes (19.6% vs. 14.1%; $p = .036$) as well as a 38% reduction in the combined risk of hospitalization or death (24.6% vs. 15.8%; $p < .001$) (39). Subsequent trials of beta-blocker therapy have consistently shown that the addition of beta-blockers reduces need for hospitalization and can result in considerable reduction in cost of care ($800 per patient over 2 years) (33). The economic outcomes of withdrawal of digoxin therapy for American adults with stable heart failure have been examined (see Chapter 42) (40). When a decision-analytic model is used to estimate the impact of digoxin withdrawal in patients with NYHA class II and III heart failure and a left ventricular ejection fraction of 35% or less, based on hospital Medicare data, an annual savings of over $400 million is anticipated. The proper use of medications thus saves lives, improves quality of life, reduces the need for hospitalizations, and can reduce the cost of treating patients with heart failure.

Heart Failure Guidelines

Clinical practice guidelines have been developed by carefully evaluating the world’s literature, with emphasis on well-controlled randomized clinical trials of solid scientific validity and expert opinion of prominent clinicians. Guideline documents for the evaluation and management of heart failure have been published (41,42,43,44

and 45). Heart failure experts believe that the pharmacologic treatment of patients remains suboptimal, which is explained in part by provider inexperience and the lack of definitive management recommendations. These documents, with acknowledged deficits, represent ambitious efforts to fill the void and communicate state-of-the-art guidelines. The guidelines emphasize the importance of appropriate pharmacologic therapy (target dosages and ACEI use for asymptomatic left ventricular dysfunction) and nonpharmacologic treatment (counseling, education, and lifestyle modifications) in the management of heart failure (42). The economic and quality-of-care ramifications related to the dissemination of and improved adherence to these guidelines are enormous. The publication of guidelines has led to the development of disease care management algorithms that can be implemented within health care systems (14,46).

Cardiac Transplantation and Alternatives

The fiduciary involvement of the U.S. government in the field of heart transplantation began in 1986. Criteria for approval as a Medicare-designated heart transplant center were developed, and reimbursement for treatment of Medicare patients is restricted to centers that have met the stipulated approval criteria (47). Transplant center volume and the experience of key personnel (e.g., transplant cardiologist) may influence a center's results (48,49). With the advent of managed care and capitation, insurance carriers are defining organ-specific transplant centers ("designated centers") based on volume, outcomes, and cost, and are providing coverage for transplantation only at the designated centers. The designated-center approach to the provision of cardiac transplantation tends to favor high-volume, cost-efficient centers with excellent outcomes. The Prudential Institutes of Quality program has reported savings ranging from 9% to 28% and 1-year patient survival rates for patients treated at designated centers that were 4% to 12% higher than average national survival rates (50).

Few accurate data are available detailing the actual cost expended for a heart transplant procedure, and much attention has focused on the total charges ("list price"). The National Cooperative Transplantation Study revealed a wide range of hospital charges, from $8,173 to $1,290,033 (51). The average price (e.g., capitated reimbursement) for a heart transplant procedure reported by national health care provider networks in the United States in 1997 was approximately $98,500. In 1999 in the United States, the estimated first-year cost for a heart transplant was $303,400 and the estimated annual follow-up cost was $39,700 (11). Wide variability exists nationwide. For example, the average hospital charge for a heart transplantation in Pennsylvania in 1991 was $233,276, and the maximum charge approached $1 million (50). In Ohio the breakdown for third-party coverage is 73% covered by a private carrier and 27% by government carriers, including 8% by Medicare and 13% by Medicaid (52).

High-cost procedures are often performed on mortally ill patients with complicated disease, a "no win" practice from a financial viewpoint in an environment of capitation. Thus, transplant professionals must increasingly face the ethical and economic dilemmas posed by high-risk/high-cost patients. Transplant programs are under increasing pressure to be economically efficient. As programs strive to increase their volumes (economy of scale), patient selection policies may actually become more prudent relative to the demands of managed care (50). Transplant professionals must scrutinize and justify the costs and benefits of their patient selection criteria and patient outcomes and must be responsive to the managed care programs with which they contract. Liberal patient selection criteria with regard to high-risk patients will jeopardize a program's competitiveness in an environment of capitation. Current trends suggest that more regionalization of heart transplant centers will occur, driven by managed care contracts and the demands of price and quality considerations. The transplant professional faces complex intertwined ethical and economic challenges and must carefully balance the issues of patient selection, cost containment, patient outcomes, and responsiveness to one's competition in the health care market.

Alternatives to transplantation are discussed in Chapter 94. Mechanical circulatory support, cardiac xenograft transplantation, dynamic cardiomyoplasty, and cardiac reduction surgery are all unproven experimental techniques. Cardiac reduction surgery, highly touted to provide a cost-effective alternative for a discrete subset of patients with dilated cardiomyopathy, has proven largely ineffective (53).

ECONOMIC STRATEGIES FOR TREATMENT OF HEART FAILURE

Principles

Imperative for effective treatment is correctly diagnosing the heart disease and, hence, facilitating definition of the best therapy. Already acknowledged was the fact that heart failure specialists believe that many patients receive suboptimal pharmacotherapy. Perhaps more problematic is the failure to recognize and apply an effective surgical or medical treatment. Regional heart failure centers evaluate many patients referred for consideration of heart transplantation (54). Only approximately 30% of patients referred are listed for transplantation initially. Treatable forms of heart failure must be identified. The expert opinion of a heart failure specialist may often identify an appropriate treatment other than cardiac transplantation. Examples would include the treatment of an arrhythmia that leads to improvement in ventricular function, successful surgical revascularization of a patient with hibernating myocardium, and careful observation of a patient with new-onset dilated cardiomyopathy who ultimately has spontaneous improvement in ventricular function. Transplantation in these situations would be medically inappropriate and expensive and would deprive another patient of a potential donor organ. A positive spin-off of the creation of regional heart failure/transplantation centers has been the exposure of referred patients to heart failure specialists who can make definitive diagnostic and treatment plans (55). These observations are most relevant to patients with advanced heart failure, who have the highest short-term mortality. Patients with stable NYHA class I or II heart failure are generally cared for very appropriately by the primary care physician or general cardiologist. Patients with problematic refractory heart failure may benefit from evaluation by a heart failure specialist (14).

Risk Factors and High-Risk Patients

Elderly patients represent a high-risk population. Readmissions can be reduced in the elderly patient population with a multidisciplinary interventional scheme (25). One study involving a group of geriatric heart failure patients used intensive education on the treatment of heart failure, dietary education, social services evaluation, review of medications and follow-up care by a geriatric cardiologist, intensive outpatient home visits, and telephone contact as interventional techniques. The number of readmissions for heart failure was significantly reduced by 56% in the treatment group (from 39% to 17%) (25). These findings support the tenet of using a nurse-directed multidisciplinary treatment strategy to significantly reduce hospital admissions and improve quality of life in elderly patients with heart failure (25). An analysis of elderly patients (65 years or older) with heart failure in Connecticut identified four predictors of hospital readmission: prior admission within 1 year, prior heart failure, diabetes, and creatinine level higher than 2.5 mg per dL at discharge (56).

Similar conclusions were reached in a study conducted in Israel, in which 42 patients with functional class III or IV heart failure, whose mean age was 78 years, were studied before and after the implementation of a general home care surveillance program (57). Cardiovascular-related hospital admissions decreased 72% from a mean of 2.9 ± 1.5 admissions per patient per year to 0.8 ± 1.1 admission per patient per year (p <.001). The duration of hospitalization for cardiovascular disease fell sharply from 23 ± 13 to 4 ± 4 days, an 83% reduction (p <.001). A significant improvement in the global functional status index was also observed. Resource allocation to fund interventions designed to reduce hospitalizations in high-risk patients (elderly patients and those with NYHA class IV congestive heart failure or a history of frequent hospital admissions for congestive heart failure) is cost effective and improves quality of life. These strategies will play an important role in the management of the expanding elderly population with heart failure (see Chapter 42).

Educational Programs

The heart failure guidelines stress the importance of education in the treatment of heart failure. Education must extend beyond the patient to the family members and care providers who assist in the necessary dietary and lifestyle modifications (42,58). Educational initiatives improve quality of life for the patient and prevent hospitalization. Hence, the cost-savings potential is tremendous. Educational interventions designed to improve dietary compliance and reduce hospital admissions in heart failure patients have been found to be highly successful (59,60). A physician-supervised, nurse-managed, home care program for heart failure management that implemented pharmacologic and dietary therapy with frequent monitoring via telephone contact was conducted in northern California (59). Three generic problems in the outpatient management of heart failure were addressed: cognitive (what to do), executive (who should do it), and organizational (when and where it should be done). Consensus guidelines (of the American College of Cardiology/American Heart Association consensus report and Agency for Health Care Policy and Research) were embedded in the clinical algorithms. The nurse-manager was responsible for obtaining essential information from the patient and laboratory and carrying out the therapeutic program. Fifty-one patients with moderate to severe heart failure were followed for over 4 months, and hospitalization rates for heart failure declined significantly by 87%. Other key findings included a reduction in dietary sodium by 38% and a significant increase in dosages of lisinopril and hydralazine (59). Although this was not a randomized trial, nonetheless it emphasizes the health care impact of adherence to heart failure guidelines and dietary and educational programs in the management of heart failure. Eight studies (Table 89.2) without a pharmacologic component have shown the benefit of multidisciplinary education-based therapy for heart failure (7).

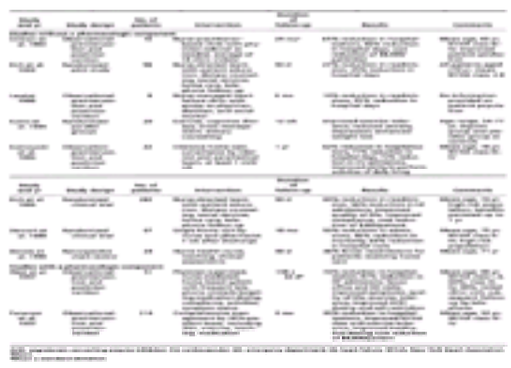
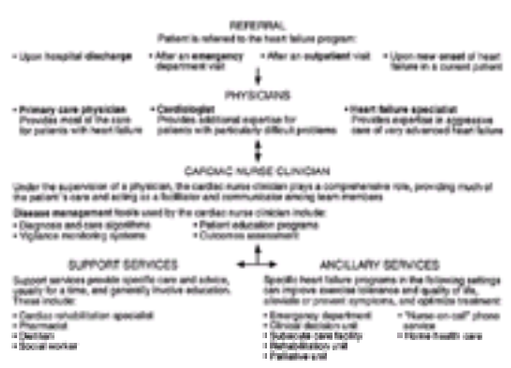


TABLE 89.2 COST EFFECTIVENESS OF NONPHARMACOLOGIC INTERVENTIONS FOR THE TREATMENT OF HEART FAILURE

Management of Chronic Disease

Disease management programs are designed to reduce net costs and improve patient outcomes. The primary care model includes a primary care physician as the gatekeeper. Medical care is scheduled and episodic, and the focus is on reducing specialist referrals. In contrast, the chronic care model emphasizes more liberal access to specialized physician and nursing care, disease management, patient monitoring and proactive interventions, and reduction of acute hospital admissions. Disease management is a concept aimed at patient populations with a discrete clinical problem and proposes that tertiary care provided by specialists can be more cost effective and of higher quality than care given in the primary care setting (61). Heart failure is a specific clinical condition that is amenable to treatment by means of a disease management program using specialized physicians and intensive nursing and education programs (14,21,59). A typical heart failure disease management program consists of inpatient consultation and care, treatment at an outpatient heart failure clinic, cardiac home care, and compliance monitoring (62).

A multidisciplinary heart failure disease management program used at The Cleveland Clinic Foundation is shown in eFigure 89.7.2 (14). The cornerstone of a heart failure disease management program is the use of pharmacologic therapy in accordance with evidence-based heart failure guidelines and development of a mechanism to monitor compliance by both patients and physicians. Multidisciplinary heart failure disease management programs have proven efficacy (they are cost effective and improve clinical outcomes) and should be a standard component of routine heart failure care (13). Further research is required to define which patients with heart failure are most likely to benefit from multidisciplinary disease management programs; however, intuitively the elderly, socially deprived, and patients at high risk for readmission appear to require and derive the greatest benefit (56).



***e*FIGURE 89.7.2** Heart failure disease management program used at The Cleveland Clinic.

Heart failure ranks second only to essential hypertension as a cardiovascular reason for an outpatient visit. In 1990, 11.4 million outpatient visits were made, with 3.5 million patients making an average of 3.4 visits per year (18). New algorithms to shift more patient care to the outpatient setting are being implemented at a furious pace. Implementation of cost-effective strategies for the outpatient management of congestive heart failure is mandated. The cornerstone of cost reduction in heart failure care is the reduction of emergency room visits and the frequency and length of hospitalization. The question for the future is how this can be accomplished most effectively. The three components of outpatient care, emergency care, and inpatient care should be addressed. In the chronic care model, the optimal outpatient delivery of care should include (a) a heart failure clinic staffed by heart failure physicians and nurses, (b) home health heart failure nursing specialists, (c) immediate communication between patient and center via telephone or telecommunications, and (d) heart failure–specific cardiac rehabilitation. Insurers do not currently reimburse for cardiac rehabilitation for “heart failure” patients. However, exercise training has been shown to improve exercise tolerance (63). Heart failure centers should provide emergency room–based, 24-hour observation units with algorithms for care designed to reduce hospital admissions. Heart failure–specific subacute care facilities can provide a transition from the hospital to the outpatient setting, reduce the length of hospital stay, and facilitate education and implementation of home health nursing follow-up care (21).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Many heart failure patients are treated suboptimally with pharmacotherapy and receive medical regimens that do not comply with published guidelines for heart failure management (41,44,45). A U.S. survey showed that cardiologists are more likely to prescribe ACEIs than are general practitioners and internists (38). Furthermore, a survey comparing the practice patterns of cardiologists and heart failure specialists showed general conformity but concluded that a portion of heart failure patients may be managed more optimally by heart failure specialists (64). The conclusion was that the improved outcomes observed in heart failure clinics was attributable to the optimal management provided by cardiologists with additional experience in treating heart failure.

These observations indicate that specialist care is cost effective and improves outcomes. Efforts to contain health care costs have attempted to limit patients’ access to specialists, including cardiologists. As discussed previously, the experience of the cardiologist has been shown to be linked to the outcome of patients after cardiac transplantation (48). Few data are currently available to prove that heart failure specialists provide superior care for heart failure patients. An observational study at a single institution showed that hospitalized heart failure patients cared for by a cardiologist were sicker, had a longer length of stay, and underwent more diagnostic studies; however, the incidence of 6-month readmission was lower than that for patients cared for by generalists (65). An analysis of all New York State hospital discharges in heart failure cases (44,296 patients) in 1995 showed that 23% received care from cardiologists, 63% from internists, 11% from family physicians, and 3% from other physicians (66). Care by cardiologists was not associated with longer stay or higher hospital charges, a result that belies the tenet that specialist care is more costly. Conclusions cannot be drawn at present, but the question of who should deliver care to heart failure patients in a manner that is cost effective while maintaining good-quality outcomes requires investigation. Patients with advanced heart failure represent a subpopulation for which specialist treatment seems clearly justified, and the multidisciplinary care model of disease management appears cost effective with superior clinical outcomes.

The a priori end point in most randomized heart failure trials is mortality. Pharmacologic agents that improve quality of life and reduce hospitalizations but increase mortality are unlikely to obtain approval from the U.S. Food and Drug Administration. Initial reports on the use of outpatient dobutamine hydrochloride therapy showed that functional class improved significantly, but mortality was high in this uncontrolled study (67). Outpatient inotropic therapy appears to be cost effective and is reimbursed by many third-party payers despite the lack of randomized trials showing efficacy or a U.S. Food and Drug Administration–approved indication. An uncontrolled study followed 36 patients with intractable heart failure on intermittent inotropic therapy for a mean duration of 294 days (68). The number of emergency room visits, hospital admissions, and days hospitalized all decreased significantly compared to the pretreatment period, and no adverse events were reported. The results of a randomized controlled study evaluating the use of weekly milrinone lactate infusions in treating refractory heart failure over 6 months of follow-up [Randomized Outpatient Assessment of Milrinone Efficacy in Heart Failure (ROME) trial] remain unpublished. No conclusions or projections can be drawn from these uncontrolled studies; nonetheless, many heart failure clinics with outpatient infusion programs have been established throughout the United States. Outpatient inotropic infusions are likely vastly overused in patients who could be readily managed by experienced heart failure specialists with conventional oral medications (69). Outpatient inotropic infusions administered as palliative treatment for refractory heart failure in patients who are not candidates for transplantation may facilitate a return to the home setting with an improved quality of life. In a fatal chronic illness such as heart failure, the quality-of-life benefits of a therapy must be considered, as they may outweigh any mortality effects.

THE FUTURE

Potential economic strategies to face the epidemic of heart failure should include the following initiatives: (a) targeted reduction of inpatient costs, (b) investment in outpatient care and development of chronic disease management programs for heart failure, (c) prevention of admissions (more important than reduction in length of stay), (d) concentration of efforts and resources on high-risk patients (those with a history of frequent readmissions), (e) use of specialized heart failure treatment providers (physicians, nurses, dietitians, rehabilitation specialists), and (f) provisions for extensive patient education. The establishment and implementation of regional specialized heart failure centers should include the following to help achieve these initiatives: (a) detailed patient evaluation to stage disease and ensure appropriate diagnosis and treatment, (b) close patient monitoring at intervals tailored to the individual patient's needs (direct and telephone or electronic contact), (c) immediate access of patients to heart failure team staff and timely responses to patient crises, and (d) comprehensive and continuing patient education concerning heart failure. Regional heart failure centers will provide expertise in the medical and surgical management of heart failure (54,70). Surgical therapy [high-risk standard cardiac surgical procedures, transplantation, connection to mechanical circulatory assist devices, ventricular remodeling procedures (partial left ventriculectomy, Dor procedure, Acorn device, Myosplint), transmyocardial laser revascularization, etc.] has become an essential component and now extends far beyond transplantation. Increasing numbers of high-risk patients will benefit from standard surgical procedures, with a safety net of mechanical support and transplantation available at specialized heart failure centers.

Developing and perfecting a health care delivery system for heart failure should help achieve these goals and result in improved survival, better quality of life, and reduction in cost. Primary prevention is the solution to the challenge. Secondary prevention strategies to alleviate morbidity should be an immediate focus, however, to reduce the economic burden of this devastating epidemic.

The development of health care delivery systems incorporating specialized heart failure centers with systemwide disease management programs will provide the infrastructure to achieve cost-effective improved clinical outcomes for the rapidly expanding heart failure patient population. Efforts and resources will be concentrated on high-risk patients so that overall costs are reduced. Increased emphasis on education of patients and care providers is required. The role of the heart failure nurse-practitioner will expand in heart failure patient management. Emphasis will continue to be on primary prevention as the seminal solution to the increasing cost of heart failure management.

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CARDIOMYOPATHY AND MYOCARDIAL FAILURE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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Löffler's Endocardial Fibrosis
Right Ventricular Cardiomyopathy
Arrhythmogenic Right Ventricular Cardiomyopathy
Uhl's Anomaly
Unclassified Cardiomyopathies
Endocardial Fibroelastosis
Noncompacted Myocardium
Mitochondrial Cardiomyopathy
Systolic Dysfunction with Minimal Dilatation
Specific Cardiomyopathies
Ischemic
Valvular
Hypertensive
Obesity
Inflammatory
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OVERVIEW

The current World Health Organization definition and classification of cardiomyopathy have been revised to reflect the recent insight gained into the pathogenesis of the heart muscle disorders. Cardiomyopathies are categorized into dilated, restrictive, hypertrophic, and unclassified based on the predominant pathophysiologic characteristics. A new category has been added to include right ventricular abnormalities. The disorders that are associated with systemic or certain cardiac diseases are called *specific heart muscle diseases* and include, for example, ischemic cardiomyopathy, diabetic cardiomyopathy, and alcoholic cardiomyopathy. Dilated cardiomyopathy (DCM) is characterized by myocyte hypertrophy and ventricular chamber dilation with diminution of systolic function. This is the most common of the cardiomyopathies. Hypertrophic cardiomyopathy (HCM) is a syndrome that results in heart failure due to left ventricular outflow tract obstruction, diastolic cardiac dysfunction, global cardiac ischemia, dysrhythmias, and sudden cardiac death syndrome in a setting of hyperactive autonomic states. Myocardial hypertrophy and mitral valve abnormalities are gross characteristics of the difficulty with myocardial histology, revealing cellular hypertrophy and disarray with substantive interstitial fibrosis. Inheritance is seemingly in an autosomal dominant fashion, due to mutations in multiple and different contractile protein genes. Restrictive cardiomyopathy is a primarily diastolic disorder, with impairment of ventricular relaxation and filling, usually resulting from an infiltrative or fibrotic process. The myocyte and its surrounding interstitium can be affected. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a fascinating disorder that primarily involves the right ventricle and may be the result of uncontrolled apoptosis. The unclassified cardiomyopathy category includes disorders such as fibroelastosis, noncompacted myocardium, and systolic dysfunction with minimal dilation. These diseases either have features that overlap the other classifications or do not readily fit any category. Ischemic cardiomyopathy is a common disorder, and one of the most important aspects of its management is identifying areas of viable, but not contracting, myocardium and restoring adequate blood flow if possible. A cardiomyopathy that is associated with infection with the human immunodeficiency virus (HIV) has many possible mechanisms; gaining a better understanding of them will improve treatment of this cardiomyopathy and others. This disorder will certainly be encountered with increasing frequency in the future. Identification of toxins that are associated with left ventricular dysfunction is important because often, if the offending agent is withdrawn, ventricular function returns to near normal levels. Finally, peripartum cardiomyopathy occurs in young women in the last trimester of pregnancy or shortly after delivery. Because its signs and symptoms may resemble some of the normal findings in pregnancy, awareness is key. No reliable methods are available to predict which patients will improve and which will progressively deteriorate. The identification of the etiology of any patient who presents with cardiomyopathy is very important, because specific treatment may reverse cardiac dysfunction. Endomyocardial biopsy is indicated in select situations: to diagnose a specific disease, as part of a clinical trial, to differentiate between restrictive and constrictive disorders, and to monitor anthracycline toxicity. Routine biopsies for idiopathic DCM are of little benefit. Future directions in the diagnosis and management of cardiomyopathies include elucidating genetic and molecular mechanisms and examining the roles of proinflammatory cytokines and apoptosis in the pathogenesis of heart failure.

HISTORICAL PERSPECTIVE

In 1891, one of the earliest descriptions of heart muscle diseases appeared (1). Unfortunately, little more about these "obscure disorders" was gleaned in the six decades that followed. In 1957, Brigden highlighted the ignorance and confusion that existed regarding "noncoronary cardiomyopathies," their terminology, and clinicians' reluctance to diagnose them (2). Since then, medical science has amassed considerable insight regarding the pathophysiology and treatment of these prevalent disorders. Although remarkable progress has been made, there is considerable need for further investigation. Currently, there is tremendous excitement about the field, fueled by clarification of the molecular biodynamic processes and the potential role of apoptosis in cardiomyopathy.

To understand more fully the current nomenclature relating to myocardial failure, it is helpful to review the original working terminology of heart muscle disorders. In 1980, the World Health Organization and International Society and Federation of Cardiology task force met in Paris to clarify this area. They defined the cardiomyopathies as "heart muscle diseases of unknown cause" and divided them into three broad classifications based on characteristic anatomic findings of the heart: dilation, hypertrophy, and restriction (3) (*e*Table 90.0.1). For instance, the dilated and restrictive categories were based on left ventricular dimensions and volume. The reasoning behind creation of these divisions was that they had distinct natural histories, pathophysiologic mechanisms, and medical treatments. A fourth group, "unclassified cardiomyopathies," was also listed to include cases that did not easily fit into one of the other three general categories. Unclassified cardiomyopathies were sometimes referred to as *latent cardiomyopathies*. Completely separate from the cardiomyopathies were specific heart muscle diseases, characterized as diseases of known cause or associated with specific disorders of other systems. They were further divided into infective, metabolic, general system diseases, heredofamilial, hypersensitivity, and toxic reactions categories. Myocardial dysfunction as a result of systemic or pulmonary hypertension, coronary artery disease, valvular heart disease, or congenital anomalies was excluded.

***e*TABLE 90.0.1** ANATOMIC DESCRIPTION OF THE CARDIOMYOPATHIES[a]

Classification	EDV	ESV	EF	Mass	Mass/volume	Primary mechanism of failure
Dilated	↑↑	↑↑	↓↓	↑	–	Systolic
Restrictive	↓, –, ↑	↓	↓, –, ↑	↑↑	↑	Diastolic
Hypertrophic	↓, –, ↑	↓	↓, –, ↑↑	↑↑↑	↑↑	Diastolic
ARV	↑	↑	↓	↓	↓	Systolic

ARV, arrhythmogenic right ventricular; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; LV, left ventricle; ↑, increased; ↓, decreased; –, no change.
[a]Values reported for the left ventricle except ARV, which corresponds to the right ventricle.

Some debate has taken place regarding which diseases should be included in the category of cardiomyopathy. Etymologically, *cardiomyopathy* refers to a disease that arises from the heart itself (4). When clinical heart failure syndromes are diagnosed, it is the functional integrity of the circulatory network, including the heart, that is important for characterization of heart failure. Many agreed that the term *cardiomyopathy* should refer to a dynamic cardiac muscle process that evolves after myocyte injury of any sort, regardless of whether the injury was rooted in heritable molecular biodynamic aberration or was the result of exogenous muscle injury. Thus, patients with heart failure associated with Duchenne's muscular dystrophy would correctly be labeled as having cardiomyopathy, just as would a patient with ischemic heart disease caused by coronary atherosclerosis. Others have limited use of the term to situations in which the heart itself was the primary problem. Obviously, all cardiomyopathies have some etiologic factor. Many times, the specific reason for the cardiac malfunction and subsequent remodeling cannot be precisely characterized. The term *idiopathic* is used to describe this clinical situation. It is not a specific disease entity but likely represents a wide spectrum of difficulties and is a term that largely reflects our ignorance regarding the etiology of heart failure in many given instances. Over time, the distinction between cardiomyopathy and specific heart muscle disease has became blurred. Furthermore, many previously ill-characterized abnormalities have been better elucidated. As more became known about the individual disorders, it was apparent that new definitions and classifications were needed, and in 1996, a revised categorization was released (5) (*e*Table 90.0.2). Cardiomyopathies were generally more simply defined as diseases of the myocardium associated with cardiac dysfunction. As in the previous scheme, dilated, hypertrophic, restrictive, and unclassified divisions remained. However, ARVC was added. Further, specific heart muscle diseases were referred to as specific cardiomyopathies that included myocardial dysfunction associated with distinct cardiac or systemic disorders.

***e*TABLE 90.0.2** WORLD HEALTH ORGANIZATION CLASSIFICATION OF CARDIOMYOPATHIES

Dilated
Idiopathic
Familial/genetic
Viral and/or immune
Alcohol/toxic
Certain specific cardiomyopathies
Hypertrophic
Restrictive
Idiopathic myocardial fibrosis
Endomyocardial and Löffler's endocardial fibrosis
Certain specific cardiomyopathies
Right ventricular
Arrhythmogenic
Uhl's anomaly
Unclassified
Fibroelastosis
Noncompacted myocardium
Systolic dysfunction with minimal dilatation
Mitochondrial myopathies
Specific
Ischemic
Valvular
Hypertensive
Inflammatory or infectious
Tachycardia induced
Metabolic
General system disease
Muscular dystrophies
Neuromuscular disorders
Sensitivity and toxic reactions
Peripartal

DILATED CARDIOMYOPATHY

DCM is characterized by ventricular remodeling that produces chamber dilation, with normal or decreased wall thickness, and diminution in systolic function (Fig. 90.1). The impairment of systolic function can involve the left, right, or both ventricles, with the ejection fraction traditionally being defined as less than 40% (6). Although the total mass of the heart is increased, the ratio of left ventricular volume to ventricular wall thickness is much greater than for patients with HCM or diastolic dysfunction due to hypertensive heart disease (7). This eccentric hypertrophy provides a unifying concept for many different disease processes, ultimately resulting in dilation of the heart. It is important to note that remodeling of this sort is caused by diseases that are, for the most part, distinct from those causing hypertrophic and restrictive cardiomyopathy, problems that generally do not result in chamber dilation. Myocardial remodeling is associated with altered hemodynamics characterized by diminished ejection fraction, reduced stroke volume, increased chamber volumes, and, therefore, increased chamber pressures. This triggers the multiple neurohormonal aberrations that are characteristic of the heart failure milieu.

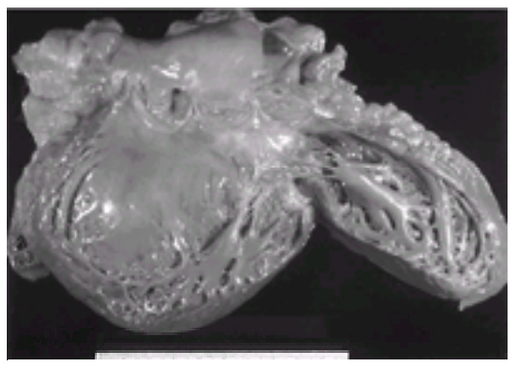


FIGURE 90.1 Dilated cardiomyopathy. The cardiomegaly, globular shape of the heart, dilated ventricular chambers, and flattened trabeculae, which are characteristic of this disease, are all evident in this photograph. No significant endocardial fibrosis is present.

Often, if the toxic or injurious agent can be identified and removed before a cell mortality program is triggered (apoptosis), further detrimental chamber remodeling can be blocked and systolic function returned to a more normal state. However, DCMs generally pass through an early and late evolutionary period. The stages parallel pathophysiologic events triggered by whatever myocardial insult initiated the heart failure process in the first place. At some point, injury produces myocyte and myocardial dysfunction that antedates clinically apparent disease. As progression occurs and decompensation develops, symptoms begin to appear that are characteristic of heart failure in general. Cardiac and extracardiac signs and symptoms that are disease specific may provide insight to the etiology of the heart failure and cardiomyopathy. If the process is not interdicted, later stages will appear and manifest with profound eccentric hypertrophy and, ultimately, marked reduction in systemic flows accompanying elevation of intracardiac pressures. Figure 90.2 conceptually presents the relationship of the heart failure clinical syndrome to molecular and organ-specific physiology.

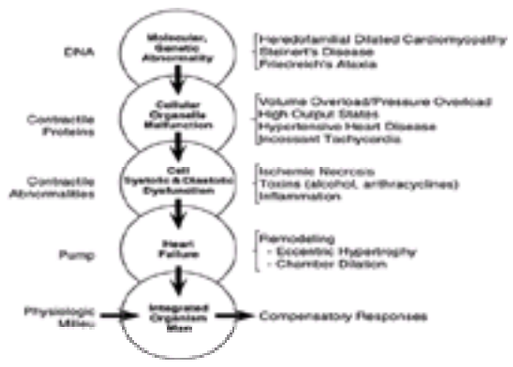


FIGURE 90.2 The milieu of dilated cardiomyopathy from molecular biodynamics to a clinical syndrome.

DCM was previously referred to as *congestive cardiomyopathy*; however, this term is no longer applied because congestion is not consistently present, particularly in the milder and earlier stages or after therapy. DCM is the most common of the cardiomyopathies, comprising more than 90% of all cases that are referred to specialized centers (8), and represents the end result of more than 50 distinct diseases (9,10). When diagnosing DCM, it is important to review the major etiologic and pathophysiologic classes that are responsible for this disorder, as detailed in eTable 90.0.2. By and large, DCMs include those that can be familial or genetic in origin, secondary to infection or inflammation, toxic substance exposure, metabolic derangements, and idiopathic. Examples of genetic disorders that cause cardiomyopathies include Friedreich's ataxia, myotonic dystrophy, Duchenne's muscular dystrophy, and certain mitochondrial dysfunction syndromes. DCM can also be ischemic in origin, particularly when microvascular disease complicating diabetes mellitus is present. A category sometimes referred to as *hyperergopathic* DCM includes heart failure caused by high cardiac output states as noted with certain vitamin deficiencies (beriberi), thyrotoxicosis (particularly Graves' disease), severe anemia, arteriovenous fistulae, osteitis deformans (Paget's disease), chronic liver disease with cirrhosis (intrahepatic arteriovenous shunts), pregnancy, and hypernephroma. Hypertensive heart disease, valvular insufficiency or stenosis, and incessant tachycardia are also examples of DCM due to an "overworked" ventricle (11). Pathogenic factors to consider when evaluating patients with DCM are the potential for substance abuse (alcohol and cocaine in particular), coronary artery disease or atherosclerotic risk factors, family history of DCM, presence of systemic arterial hypertension, history compatible with significant viral illness, presence of diabetes mellitus, cardiotoxin exposure (anthracyclines, for example), malnutrition, and valvular heart disease.

Some progress has been made in characterizing the molecular genetics of DCM (12,13). Perhaps as many as 30% of DCM cases are inherited or familial, with a significant percentage of the remaining being acquired as alluded to above. Inherited forms of DCM may have autosomal dominant, autosomal recessive, X-linked, or mitochondrial transmission, and, to date, genes for X-linked DCM and autosomal dominant DCM have been mapped with genetic heterogeneity documented. The genes for two X-linked cardiomyopathies have been identified, specifically, the dystrophin gene, also responsible for Duchenne's and Becker's muscular dystrophy, and G4.5 in Barth's syndrome, which is X-linked cardioskeletal myopathy with neutropenia and aciduria. Dystrophin is a large cytoskeletal protein that is noted in myocyte sarcolemma. The protein attaches at its N-terminal domain to F-actin in the sarcolemma matrix region and to the dystrophin-associated glycoprotein complex at its C-terminal domain. Although the protein encoded by the G4.5 gene has been identified and referred to as *Tafazzin*, its function is not presently known. Autosomal dominant DCM genes have been noted at six different loci, with "pure" DCM localized to 1q32, 2p31, 9q13, and 10q21–10q23, in contrast to DCM, with conduction defects that have been mapped to 1p1, 1q1, and 3p22–3p25 (12). Mutations in cardiac actin located on chromosome 15q14 have also been identified. Indeed, it has been suggested that DCM is, ultimately, a consequence of defective transmission of force in cardiac myocytes that leads to heart failure.

Idiopathic Dilated Cardiomyopathy

Background and Prevalence

Idiopathic DCM is a primary global myocardial disorder of unknown cause. Because it is the pathophysiologic model for other specific DCMs, this section focuses on the idiopathic type, with distinguishing characteristics of other specific disorders discussed subsequently. Idiopathic DCM alone accounts for 36 cases per 100,000 population, 10,000 deaths in the United States per year (14,15), and approximately 25% of all cases of cardiomyopathy.

Pathophysiology

eTable 90.0.1 compares the anatomic description of the cardiomyopathies, emphasizing that DCM has marked enlargement of left ventricular end diastolic and end systolic volumes, usually with profound reduction of the ejection fraction. This is in contrast to restrictive and hypertrophic cardiomyopathies, which have more normal end diastolic volumes and, sometimes, supernormal ejection fractions. The left ventricular mass-volume ratios (eTable 90.0.1) reflect the fact that muscular hypertrophy is seen in all cardiomyopathies, but to a more significant degree in patients who have HCM. With DCM, the mitral and tricuspid annuli are frequently enlarged from ventricular dilation, with resultant valvular regurgitation. By definition, idiopathic DCM is not caused by coronary artery disease, and therefore the coronary arterial tree is usually normal. It is possible to have some plaque formation; however, the degree of systolic impairment is out of proportion to atherosclerotic involvement. The histology is usually nonspecific, but certain features are present. Under the light microscope, the myocytes are commonly quite hypertrophied, with areas of myocyte necrosis. The nuclei may be very large with bizarre shapes. The areas of interstitial fibrosis are frequently underappreciated. Occasionally, small clusters of lymphocytes in the interstitium or perivasculature can be present. By electron microscopy, the mitochondria may be abnormal, the T tubules dilated, and lipid vacuoles present.

Investigations into the pathogenesis of idiopathic DCM have centered around four potential areas to gain additional insight into this disease: familial and genetic factors, viral myocarditis and cytotoxic damage, abnormal immune responses, and metabolic, energetic, and contractile abnormalities (16). Exogenous injury or internal myocyte perturbation can cause alterations in the cell's genetic program. Reversion to a fetal genotypic program occurs, with resultant cell hypertrophy and malfunction. This ultimately produces ventricular chamber enlargement and dilation. Poisoning the cells with alcohol or doxorubicin can incite cell injury, giving rise to detrimental myocardial remodeling. With idiopathic DCM, the inciting factor is unknown. Patients with idiopathic DCM frequently (5% to 10%) have a positive family history of signs and symptoms that are suggestive of a myocardial disorder, and consequently these individuals have been labeled as having familial idiopathic DCM. Certain gene expressions have been identified as being associated with idiopathic DCM, such as the angiotensin-converting enzyme (ACE) DD genotype (17), human leukocyte antigen (HLA) class II DR4 and Dqw4 antigens (18), and Xp21 locus of the dystrophin gene, which may explain some of these cases (19). The presumption of an underlying viral myocarditis as the cause of idiopathic DCM remains to be proven. Clearly, viral genomic sequences have not been detected in the myocardium to support this theory (20). An abnormal autoimmune response (again possibly inherited), perhaps initiated by a viral infection, may also initiate a cardiomyopathy. Several abnormalities with the immune system have been recognized in idiopathic DCM, including cellular and humoral alterations, decreased natural killer cell and suppressor T-cell activities, and increased levels of many autoantibodies reacting with various cardiac antigens. It is unclear whether these changes are part of the pathogenesis of the disorder or a result of the dysfunction. Finally, as mentioned earlier, neurohormonal activation occurs as a consequence of the disease and may propagate additional injury. Many irregularities occur in cellular energy metabolism (21), calcium interactions and uptake, guanine nucleotide-binding regulatory proteins, and beta-adrenergic receptors, which again may contribute to the heart failure decline or merely be a consequence of it.

Clinical Profile and Management

Most patients initially present with signs and symptoms of fluid overload or low cardiac output. Usually, by the time of diagnosis, they have severe ventricular dysfunction and New York Heart Association (NYHA) class III and IV symptoms (22). Chest pain is surprisingly common and affects up to 35% of patients with normal coronaries (22,23). This angina, in part, may be because of limited coronary vascular reserve (24). The electrocardiogram (ECG) may complicate the picture by having unexplained Q waves, and this has led to the term *pseudoinfarction*. Occasionally, patients present with more right- than left-sided heart failure symptoms, mesenteric congestion more than pulmonary edema, which can be mistaken for a gastrointestinal disorder. Arrhythmias and sudden death are common and may occur at any level of dysfunction and disability. Pulmonary and systemic thromboembolism occur at a variable rate of approximately 1% to 6% per year without anticoagulation (25,26). It is difficult to predict the natural history of idiopathic DCM, and in the past the average 5-year survival rate was approximately 50% (27). With the increasingly aggressive use of ACE inhibitors and other therapies, survival has improved. Predictors of poor outcome are listed in Table 90.1 and parallel prognostic indicators for adverse events in patients with heart failure generally. Various ventricular size and function parameters, laboratory tests, clinical features, and cardiac studies may all be helpful in assessing prognosis. Chapter 91 and Chapter 92 discuss in full detail the treatment of acute and chronic heart failure. Management options include supportive therapy (diet, sodium, toxin and fluid restriction, exercise, etc.), medications (diuretics, digoxin, ACE inhibitors, angiotensin II receptor blockers, inotropes, anticoagulants, antiarrhythmics, and beta-blockers), ventricular assist devices, and novel surgical procedures (cardiomyoplasty, mitral and tricuspid valve repair, and partial left ventriculectomy and cardiac transplantation).

Ventricular size and functioning	
	Increased left ventricular end diastolic volume
	Increased right ventricular end diastolic volume
	Low ejection fraction
	Decreased ventricular mass-volume ratio
	Global rather than segmental wall motion abnormalities
Clinical features	
	New York Heart Association class IV symptoms
	Older age
	Male sex
	History of syncope
	Right-sided heart failure symptoms
	Persistent S_3
	Symptomatic ventricular tachycardia
Laboratory tests	
	Hyponatremia
	Increased norepinephrine levels
	Increased atrial natriuretic factor
	Hyperreninemia
Hemodynamic monitoring	
	Pulmonary capillary wedge pressure >20 mm Hg
	Cardiac index <2.5 L/min/m^2
	Systemic hypotension
	Pulmonary hypertension
	Elevated central venous pressure
Cardiac tests	
	Chest x-ray–increased cardiothoracic ratio
	Electrocardiographic–1- or 2-degree atrioventricular blocks, left bundle branch block
	Stress test–maximal systemic oxygen uptake <10–12 mL/kg
	Endomyocardial biopsy–loss of intracellular myofilaments

TABLE 90.1 PREDICTORS OF POOR OUTCOME IN DILATED CARDIOMYOPATHY

Hyperergasic Dilated Cardiomyopathy

Hyperergasia refers to an increased or excessive functional activity. Hyperergasic or hyperergopathic cardiomyopathy is cardiac remodeling and heart failure that develop secondary to chronically increased myocardial workload. This cardiomyopathy of overwork produces all of the characteristics of DCM. It is this process that is important, additionally, in settings such as acute myocardial infarction whereby well-perfused and remaining healthy myocytes are forced to tote greater workloads to compensate for the loss of neighboring contractile elements and maintain reasonable cardiac output. Situations that produce increased chronic workload with resultant myocardial hypertrophy and dilation include incessant tachycardias, high-output states that accompany anemia, thyrotoxicosis, beriberi, arteriovenous fistulae, cirrhosis of the liver, osteitis deformans, pregnancy, hypernephroma, and hypertensive heart disease. Valvular stenoses that produce significant afterload increase (aortic stenosis and pulmonic stenosis, for example) or valvular insufficiency with volume overload (aortic regurgitation and mitral regurgitation) are examples of hyperergopathic cardiomyopathies. Diagnosis and treatment of these conditions focus on the clinical link between heart failure and each of these specific disease processes. It is important to diagnose this condition because some of the most gratifying treatment responses in heart failure patients are associated with eliminating the primary process that causes the cardiomyopathy and heart failure in the first place. For example, complete normalization of profoundly depressed cardiac contractile activity has been well described after control of tachycardia, resolution of anemia, and repair of arteriovenous fistulae.

HYPERTROPHIC CARDIOMYOPATHY

Prevalence and Background

HCM is addressed in detail in Chapter 29. However, it is important to consider some of the contrasts between hypertrophic, dilated, and restrictive cardiomyopathies (28). The contemporary definition of HCM focuses on the fact that this disorder is characterized by disproportionate and remarkable left, and sometimes right, ventricular hypertrophy. Typically, the septum is more involved than the free left ventricular wall, although on occasion the hypertrophy can be completely concentric in nature (Fig. 90.3). HCM, which may develop at any age, is associated with marked left ventricular volume reduction, and systolic left ventricular outflow tract gradients are common. Up to 70% of cases have a familial pattern of occurrence, with autosomal dominant inheritance.

VIDEO

Video 90.1 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy **(A)**. Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy **(B)** for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 90.2 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy **(A)**. Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy **(B)** for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

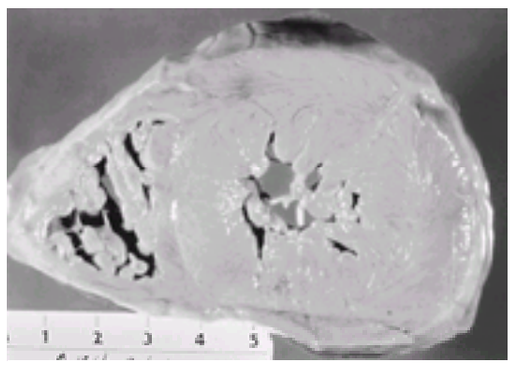


FIGURE 90.3 Severe concentric left ventricular hypertrophy: The left ventricle and interventricular septum are severely and concentrically hypertrophied, with a marked reduction in the size of the ventricular cavity.

Pathophysiology

Some reports have emphasized that variable degrees of myocyte ultrastructural, myofibrillar, and muscle bundle disorganization can be detected, often with substantial degrees of interstitial fibrosis (28,29,30 and 31) (Fig. 90.4). Identification of specific gene mutations associated with HCM has led to the suggestion that the severity of hypertrophy is associated with cardiac troponin t-gene mutations and also mutations at the loci that are responsible for alpha-tropomyosin formation. Intense study of the molecular biodynamics and genetic characteristics of this syndrome is now under way. It is likely that many genetic abnormalities are associated with this pathologic hypertrophy. Indeed, HCM can be a component of many inheritable disease states, such as Noonan's syndrome, Friedreich's ataxia, Fabry's disease, and Hunter's and Hurler's syndromes.

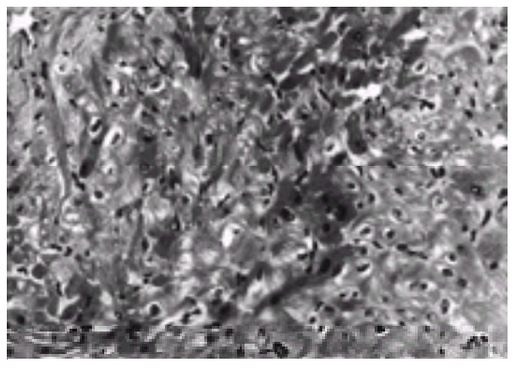


FIGURE 90.4 Hypertrophic cardiomyopathy: In this light micrograph, the myocyte disarray, characteristic of hypertrophic obstructive cardiomyopathy, is evident.

Clinical Profile and Management

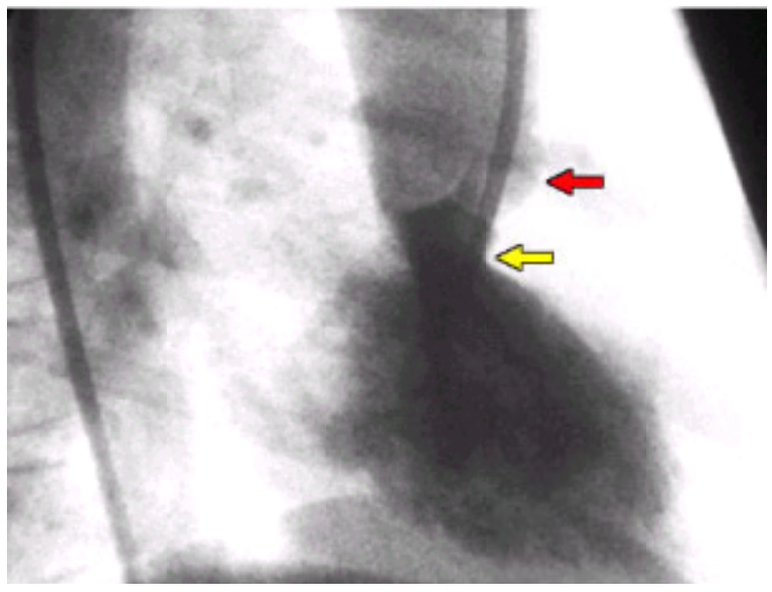
From a hemodynamic standpoint, most patients with HCM have hyperdynamic systolic function with high ejection fraction. This “supernormal” systolic function sets the stage for increased myocardial oxygen consumption, which, in conjunction with a relative myocardial blood flow derangement, can cause ischemia. Diastolic dysfunction is virtually universal in the syndrome and likely arises from factors that decrease the lusitropic properties of the chamber, such as myocyte hypertrophy, interstitial fibrosis, and myocyte disarray. The stiff ventricle requires high filling pressures to operate, and this often translates into pulmonary hypertension and subsequent dyspnea, particularly during exercise. It is the combination of diastolic dysfunction with outflow tract obstruction that likely is responsible for most of the symptoms related to HCM.

VIDEO

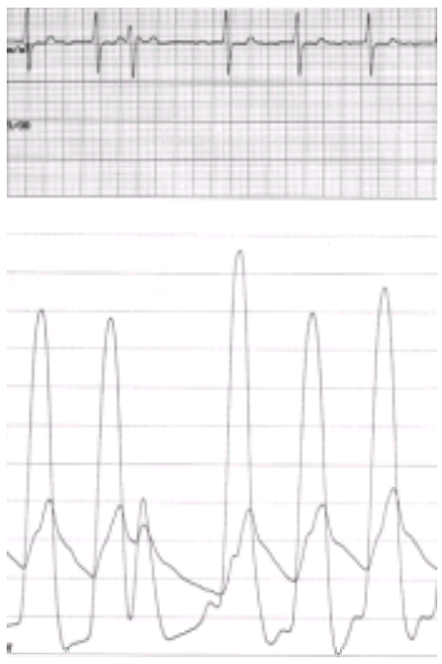
Video 90.3 Intraoperative transesophageal echo of a patient with hypertrophic obstructive cardiomyopathy and left ventricular outflow tract (LVOT) obstruction. The septum is hypertrophied, and the mitral leaflets show some systolic anterior motion of the mitral valve leaflets. An accessory mitral leaflet is located on the left ventricular septum. Note the independent motion of this leaflet in the LVOT. The pressure gradient across the LVOT/AV was greater than 100 mm Hg; however, the aortic valve opens freely. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

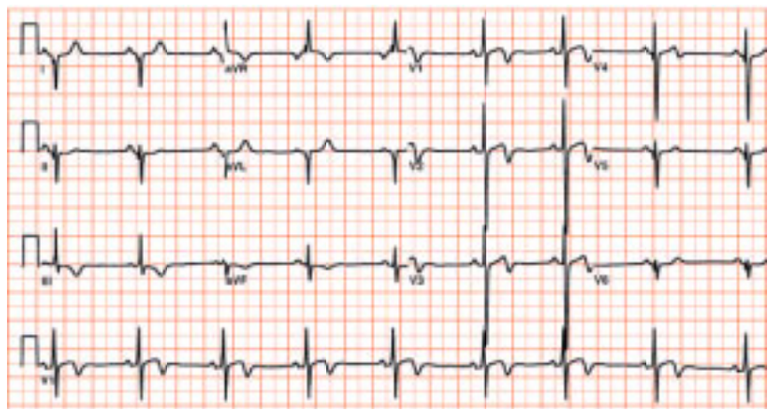
Video 90.4 Subaortic poststenotic flow in hypertrophic cardiomyopathy (long-axis). Asymmetric hypertrophy is noted, resulting in dynamic narrowing of the left ventricular outflow tract with a signal-void jet in the subaortic region. In addition, a signal-void jet in the left atrium is also seen, representing mitral regurgitation due to systolic anterior motion of the anterior leaflet of the mitral valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Subaortic stenosis. This right anterior oblique left ventriculogram demonstrates the presence of a stenosis in the left ventricular outflow tract (*yellow arrow*) just below the level of the aortic valve (*red arrow*).



A 57-year-old female patient with hypertrophic cardiomyopathy. This figure shows the Brockenbrough response after a ventricular premature beat. The Brockenbrough response includes an increase in left ventricular systolic pressure, a decrease in aortic systolic pressure, an increase in left ventricular–to-aortic gradient, and diminished aortic pulse pressure.



A 28-year-old Caucasian male patient with hypertrophic obstructive cardiomyopathy.

Audio 90.5 Hypertrophic cardiomyopathy. Auscultation performed in a 60-year-old male patient. The systolic gradient across the left ventricular outflow tract was 55 mm Hg at rest and increased to 121 mm Hg after amyl nitrate inhalation. The mid-systolic, crescendo-decrescendo ejection murmur is observed. Valsalva maneuver and sudden squatting are helpful in distinguishing this from fixed aortic valvular stenosis. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

RESTRICTIVE CARDIOMYOPATHY

The restrictive cardiomyopathies, sometimes referred to as *nondilated, nonhypertrophic cardiomyopathies*, are described in Chapter 26. Several points deserve reiteration to aid in understanding specific restrictive disorders, as well as to contrast this myopathy with the others. Generally, this is the least common of the major myopathies and is characterized by a normal or only slightly enlarged heart, decreased diastolic volumes, and, early in the disease, normal systolic function. The main pathologic disorder is one of impaired diastolic functioning, resulting from decreased ventricular compliance and filling. This dysfunction may result from a process that involves, primarily, the endocardium, myocardium, or both. The most commonly encountered myocardial disorders are amyloid heart disease and idiopathic myocardial fibrosis, which are fully discussed in the sections Idiopathic Myocardial Fibrosis and Amyloidosis. Other specific myocardial forms include metabolic storage disorders such as Fabry's disease and hemochromatosis, sarcoid heart disease, radiation fibrosis, and various tumor infiltrations, many of which are also addressed under the section Specific Cardiomyopathies. The endocardial disorders, less common in the United States, include entities such as endomyocardial fibrosis, Löffler's endocardial fibrosis (endocarditis parietalis fibroplastica), and, even more rarely, endocardial fibroelastosis. Endocardial fibroelastosis is typically placed in the unclassified cardiomyopathy category. Another restrictive cardiomyopathy is frequently encountered after cardiac transplantation (32). Immediately after transplant and for up to a year, restrictive hemodynamics may exist. Later on, restriction is associated with acute and with chronic rejection (33). Restrictive cardiomyopathy should be considered when patients present with signs and symptoms of myocardial failure but normal cardiac size. Frequently, right-sided findings of increased jugular venous pressure, ascites, and peripheral edema predominate, although left-sided failure does occur. The differential diagnosis includes constrictive pericarditis, which is a more readily treatable condition. Echocardiography and right heart catheterization may help differentiate these disorders. The hemodynamic findings usually demonstrate elevation of left and right ventricular end diastolic pressures, and a characteristic early ventricular diastolic dip and rapid rise to a plateau (square-root sign). Early diastolic pressure typically does not fall to 0 mm Hg, however. Endomyocardial biopsy should also be considered if other historical and physical clues to the diagnosis are not present. The treatment of restrictive cardiomyopathy is also reviewed in Chapter 26 and generally remains quite unsatisfactory.

Idiopathic Myocardial Fibrosis

Idiopathic myocardial fibrosis results in a restrictive physiology; however, no specific histopathologic changes are present to account for the extensive fibrosis (34). Grossly, the heart is increased in weight, with normal ventricular cavity size and wall thickness. By light microscopy, there is patchy endocardial and interstitial fibrosis that ranges from mild to quite severe. The disorder is frequently associated with distal skeletal myopathies, atrioventricular blocks, and possibly an autosomal dominant inheritance. It may occur in children or adults but carries a worse prognosis in children. No specific therapy is present, except that heart blocks frequently necessitate pacemaker insertion. Atrial fibrillation is readily controlled with digoxin. Some have proposed that the etiology of this disorder is related to an abnormality in a calcium-dependent phase of cardiac relaxation. Therefore, calcium antagonists may have a role in therapy, but this has yet to be proven.

Endomyocardial Fibrosis

Endomyocardial fibrosis, also known as *tropical eosinophilic endomyocardial fibrosis*, is common in South and Central America and tropical and subtropical Africa. Surprisingly, it accounts for 15% to 25% of the cardiac deaths in equatorial Africa (35). Endomyocardial fibrosis is characterized by thickening and scarring of the endocardium (Fig. 90.5), which can be so extensive that the ventricular cavity is obliterated. Thrombi may overlie these lesions, increasing the risk of thromboembolism. Frequently, the subendocardial myocardium is also affected. In 50% of cases, the left and the right ventricles are involved, whereas another 40% of cases have lesions isolated to the left ventricle. The mitral and tricuspid valves may become fibrotic as well, leading to valvular regurgitation. Many believe that this disease is a form of, if not the same as, Löffler's endocardial fibrosis, perhaps at a different stage (36,37). Although the overall prognosis is poor, palliative treatment with surgical endocardiectomy and valvular repair/replacement may alleviate some symptoms (38).

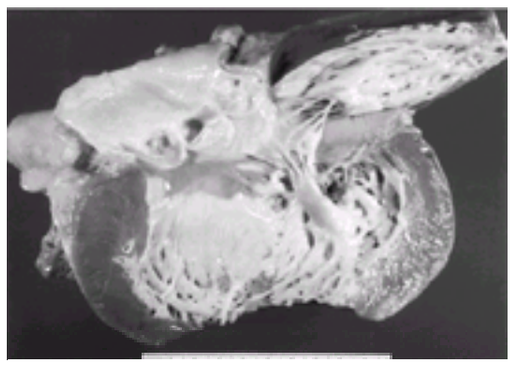


FIGURE 90.5 Endocardial fibrosis. The left ventricle is markedly dilated and hypertrophied. The endocardium, including the papillary muscles, is covered by thick, white, shiny, fibrotic endocardium.

Löffler's Endocardial Fibrosis

Löffler's endocardial fibrosis is also associated with eosinophilia, giving it its other names: eosinophilic cardiomyopathy and nontropical eosinophilic endomyocardial fibrosis. The severity of cardiac dysfunction seems to parallel the degree and duration of the eosinophilia, leading to the belief that the eosinophil itself is responsible for the dysfunction. Compared to normal eosinophils, the cells in endocardial fibrosis have fewer granules and contain vacuoles and may represent an abnormal cell line producing a type of autoimmune disorder (39). The contents of the intracytoplasmic granules of the eosinophils can cause direct myocardial necrosis. It has also been observed that the eosinophils bind immunoglobulin G and increase peroxidase, which can have further direct toxic effects. The cardiac manifestations of this eosinophilic disorder are similar, if not identical to, those produced by eosinophilic leukemia and the eosinophilia-myalgia syndrome, which has been associated with tryptophan. Treatment with corticosteroids and cytotoxic agents (hydroxyurea) can improve symptoms and survival (40).

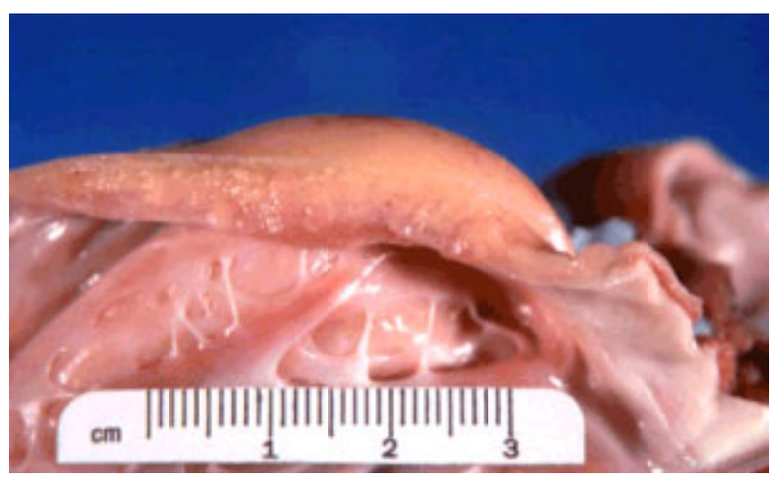
RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic Right Ventricular Cardiomyopathy

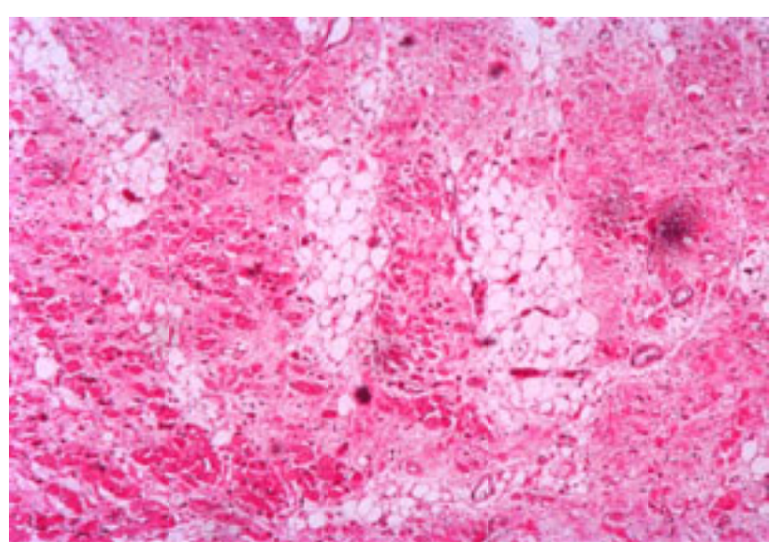
Prevalence and Background

ARVC, also known as *arrhythmogenic right ventricular dysplasia*, is a rare disorder that occurs in adolescence and young adulthood. It has a male-female ratio of approximately 2 to 3:1 (41). Interestingly, similar to HCM, the disorder was initially described anatomically, but it has been discovered to have a genetic basis. The true incidence of ARVC remains unknown, partly because of difficulties with its diagnosis, as described below.

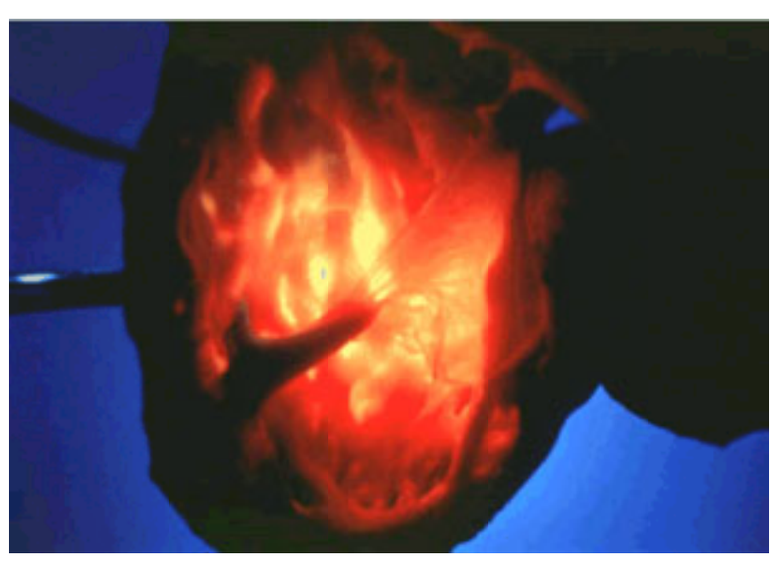
Muscular hypertrophy of the arterial wall in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



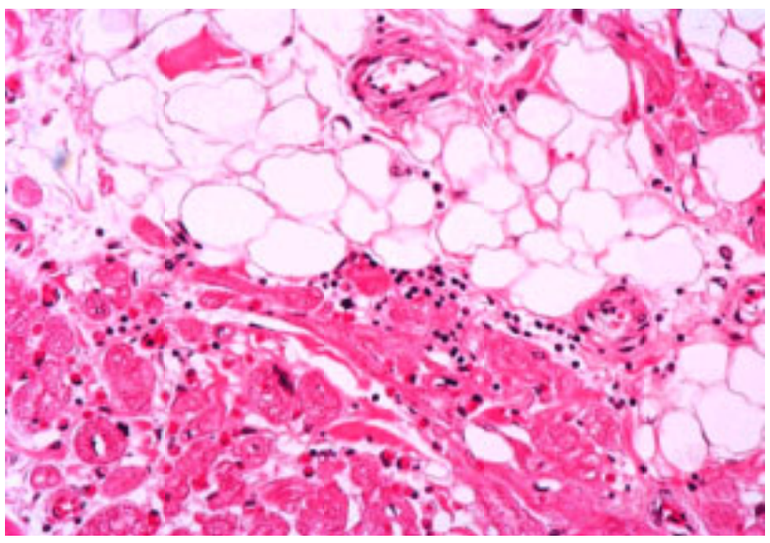
Right ventricle completely replaced by fat in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Arrhythmogenic right ventricular dysplasia with transmural fatty infiltration. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Arrhythmogenic right ventricular dysplasia. Illumination reveals thinned right ventricular wall. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Focal chronic inflammation in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)

VIDEO

Video 90.6 Arrhythmogenic right ventricular dysplasia (transaxial). Thinning the right ventricular wall with dyskinesia of the right ventricular free wall during systole is due to fibrous replacement of the myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pathophysiology

The abnormalities of ARVC are limited to the right ventricle, although in rare instances, the left ventricle is involved (42,43 and 44). Grossly, the ventricle is mildly dilated and thinned. The characteristic feature is the segmental, progressive, noninflammatory loss of myocytes and their replacement by nonhyalinized collagen and adipose tissue (39,45). This fibrofatty infiltration is transmural in nature and can be confirmed either at autopsy or with surgical biopsy. Transvenous endomyocardial biopsies are sometimes helpful but have limitations (46). First, full-thickness specimens are not obtained, preventing a definitive diagnosis. Second, ARVC is focal and segmental in nature; therefore, the likelihood of false-negative tests increases. Also, the septum, the usual area of endomyocardial biopsy sampling, is rarely, if ever, involved. Finally, adipose tissue in the right ventricle can be a normal finding. Despite this, finding extensive fibrofatty replacement of myocytes in the right ventricle is concerning. Cine–magnetic resonance imaging has the potential to aid diagnosis by being able to differentiate normal myocardium from adipose tissue, assess morphologic alterations, and detect areas of regional and global ventricular dysfunction (47,48 and 49). Because so much remains unknown about the exact pathogenesis of ARVC, a possibility is that the fibrofatty infiltrate may represent the end result of several different diseases rather than one specific process (see Uhl's Anomaly).

Evidence has been found for a familial pattern of autosomal dominant inheritance, with variable penetration (50). At least three different gene loci have been identified (51,52 and 53). It is unclear at this time, however, how abnormalities in each of these genes affect the disease process and phenotype. Apoptosis has been described in ARVC and may be the cause of the degenerative process (54). Apoptosis is a highly regulated and active process that leads to programmed cell death. It differs significantly from cell necrosis, which is normally considered the mechanism for myocyte loss. Most notably, the apoptotic cells are quickly phagocytosed by adjacent cells or macrophages, without releasing toxic substances and causing an inflammatory reaction (55). In a study by Mallat and colleagues, not only was apoptosis demonstrated in ARVC, but high levels of expression of CPP-32, a cysteine protease that is required for the initiation of apoptotic cell death (56), were also present (52). Further, apoptotic cells were seen in areas with little fibrofatty replacement, suggesting that the myocyte loss preceded the infiltration. Possibly, the triggering events and pathways that led to the cell death can be identified and favorably manipulated in the future. It is possible that the three genes that have been recognized to be associated with ARVC control various steps in myocyte apoptosis.

Clinical Profile and Management

Because of the difficulties and risks of obtaining tissue to confirm the diagnosis of ARVC, as well as inaccuracies in assessing right ventricular structure and function with many of the noninvasive tests, a task force from the European Society of Cardiology and the International Society and Federation of Cardiology met and released criteria to assist in this process. The diagnosis can be made by meeting any of the following: two major criteria, one major plus two minor, or four minor criteria (57) (Table 90.2). These criteria are based on the clinical manifestations of the disease, family history, endomyocardial biopsy, and electrophysiologic abnormalities. Other diagnoses can mimic ARVC: atrial septal defects, abnormal pulmonary venous return, congenital absence of the left pericardium, Ebstein's anomaly, right ventricular outflow tract tachycardia, and pulmonic insufficiency.

Category	Major criteria	Minor criteria
Global and/or regional dysfunction and structural alterations	Severe dilatation and reduction of RV ejection fraction	Mild global RV dilatation and/or EF reduction with normal LV
	Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)	Mild segmental dilatation of the RV
	Severe segmental dilatation of the RV	Regional RV hypokinesia
Tissue characterization of walls	Fibrofatty replacement of myocardium on endomyocardial biopsy	—
Repolarization abnormalities	—	Inverted T waves in right precordial leads (V_2 and V_3)[a]
Depolarization/conduction abnormalities	Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1–V_3)	Late potentials on signal-averaged ECG
Arrhythmias	—	LBBB-type ventricular tachycardia (sustained and nonsustained)
		Frequent ventricular extrasystoles (>1,000/24 h)
Family history	Familial disease confirmed at autopsy or surgery	Family history of premature sudden death (<35) due to suspected RV dysplasia
		Family history (clinical diagnosis based on present criteria)

ECG, electrocardiogram; EF, ejection fraction; LBBB, left bundle branch block; LV, left ventricle; RV, right ventricle.
[a]The diagnosis of arrhythmogenic right ventricular myocardium is based on meeting two major, one major plus two minor, or four minor criteria as outlined in the table. These criteria are based on the known structural and functional abnormalities of the right ventricle, family history, and repolarization/depolarization and electrical conduction disturbances.
[b]Patient must be ≤17 yr old, in the absence of right bundle branch block.
From Wichterle H, Thiene G, Basso C, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 1994;71:215–218.

TABLE 90.2 CRITERIA FOR THE DIAGNOSIS OF ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY[a]

Severe ventricular dysrhythmias and, less frequently, supraventricular dysrhythmias are a common presentation for ARVC. Patients may also present with right heart failure, asymptomatic cardiomegaly, syncope, or sudden death syndrome. Polymorphic ventricular tachycardia originating from the right ventricle, with a left bundle branch morphology, is often associated with exertion. In patients who have ventricular tachycardia, the signal-averaged ECG is almost always abnormal, with a very long duration of the low-amplitude signals (58). Premature death results from right-sided congestive heart failure or sudden death. In fact, ARVC is one of the most common causes of juvenile sudden death.

The clinical course of ARVC is unknown, and patients may live to be quite old, whereas others die in early childhood. Treatment of ARVC is aimed at the specific manifestations of the disease. The ventricular dysrhythmias can be treated with antiarrhythmics such as amiodarone and sotalol but may be quite refractory. Radiofrequency ablation of severe refractory tachycardias may be successful, although it is possible to have recurrence of the dysrhythmias but from a different area within the right ventricle. Not uncommonly, automatic cardioverter defibrillators are necessary. Because of conduction abnormalities, pacemakers may be required. Right-sided heart failure should be treated with sodium restriction, diuretics, digoxin, and afterload reducers. Cardiac transplantation also has been successfully performed for this syndrome. In the future, the identification of ARVC carriers by linkage analysis in affected families (50) may allow for earlier treatment with more standard therapies such as automatic defibrillators or even with the administration of agents that can prevent further apoptosis.

Uhl's Anomaly

Prevalence and Background

Uhl's anomaly, first described in 1952, is similar to ARVC (59). It is rare, tends to occur in infancy and early childhood, and has a more equal male-female sex distribution. Primarily, it affects the right ventricle but has much more extensive loss of the myocytes, with severe dilatation. Unlike ARVC, which tends to be focal and episodic in nature, Uhl's anomaly is an incessant disease that frequently results in complete destruction of the entire ventricle.

Pathophysiology

In Uhl's anomaly, the entire right ventricular wall can be paper thin, with apposition of the endocardium to the epicardium, explaining its other moniker: parchment heart. Apoptosis has been described in Uhl's anomaly (60,61). At birth, when the pressure in the right ventricle decreases with pulmonary flow, appropriate apoptosis may occur as fewer myocytes are needed. Uhl's anomaly may represent a case in which the triggering signals for apoptosis do not stop or for some other reason escape appropriate regulation. Indeed, massive apoptosis has been reported in other systems, including the central nervous system and bone marrow (62,63).

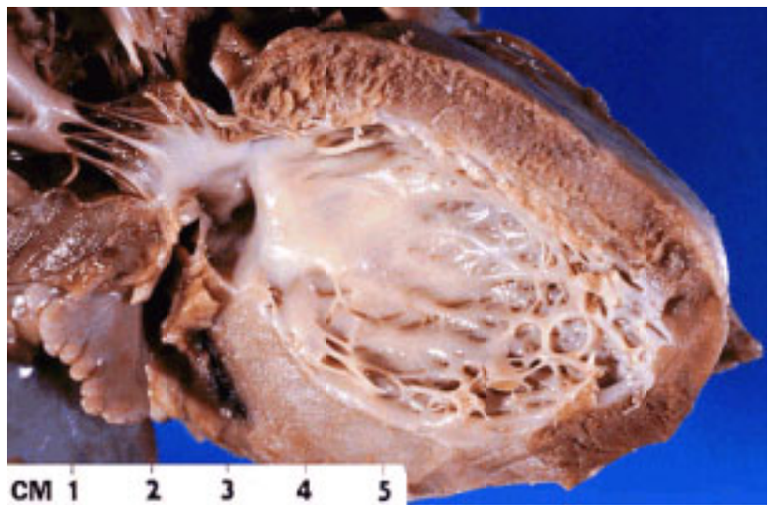
Clinical Profile and Management

The manifestations of Uhl's anomaly are quite similar to those of ARVC and include right heart failure, supraventricular and ventricular dysrhythmias, and conduction abnormalities. The right-sided failure tends to be more common and severe. The treatment of Uhl's anomaly is the same as for ARVC. Unfortunately, because of the progressive, more extensive nature of this disease, patients tend to be refractory to treatment. Cardiac transplantation has been successfully performed in these cases, but the timing of listing for transplant can be exceedingly difficult because there is a high risk of sudden cardiac death on the one hand and patients who live for several years with ventricular dysrhythmias on the other. Many investigators have contemplated whether Uhl's anomaly and ARVC are the same or different entities (64,65 and 66). It is best explained, at this time, that they share the common pathogenesis of apoptosis, but they remain separate clinical diseases.

UNCLASSIFIED CARDIOMYOPATHIES

Endocardial Fibroelastosis

Endocardial fibroelastosis is an abnormal thickening of the endocardium of the left ventricle and aortic and mitral valves. It occurs in infancy and early childhood. The fibrosis leads to decreased compliance of the myocardium and diastolic dysfunction. Typically, a DCM occurs frequently with significant mitral regurgitation, but a restrictive cardiomyopathy can also occur. The exact genetic defect has not been identified; autosomal recessive, autosomal dominant, and X-linked recessive patterns of inheritance have been reported. The X-linked forms demonstrate mitochondrial abnormalities that are similar to those of Barth's syndrome. Endocardial fibroelastosis has also been associated with tissue carnitine deficiency (67), and there is evidence that it may be related to a defect in the plasma membrane carnitine transporter (68). Other theories of its pathogenesis include inadequate subendocardial blood flow, pre- or postnatal inflammation, and infections. The diagnosis is one of exclusion, with diseases such as hypertrophic obstructive cardiomyopathy, myocarditis, anomalous pulmonary origin of the left coronary artery, and glycogen storage diseases needing to be ruled out. The ECG frequently shows features of left ventricular hypertrophy, with occasional pseudoinfarction patterns and atrioventricular block. The echocardiogram is remarkable for dense echoes along the left ventricular endocardium. The treatment consists of prolonged administration of digoxin. In one study, up to 74% of children were cured, with the remainder having either persistent ventricular dysfunction or dying. Prolonged treatment with high doses of digoxin seemed to be a determining prognostic factor, with relapses demonstrated with cessation of therapy (69). Cardiac transplantation has been successful in select cases.



Fibroelastosis and hypertrophy of the left ventricle. This specimen was obtained from a 3 month old child with incomplete closure of the foramen ovale.

Endofibroelastosis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

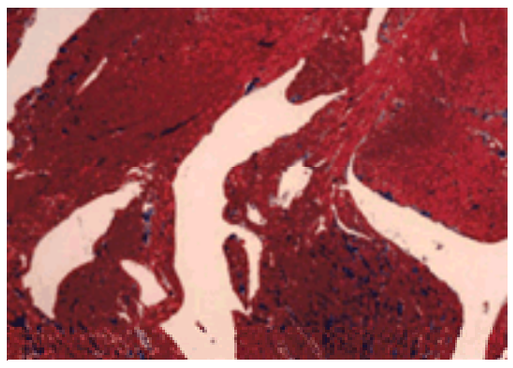
Noncompacted Myocardium

Noncompaction of the myocardium, also known as *spongy myocardium* or *persisting myocardial sinusoids*, is a relatively rare disorder that is encountered mainly in pediatric patients and young adults. This disorder is characterized by numerous, excessively prominent ventricular trabeculations and deep intertrabecular recesses and is readily diagnosed by echocardiography (70,71). The intertrabecular recesses extend approximately two-thirds of the way through the walls of the involved ventricles and may be lined by thickened, fibrotic endocardium. The deep intertrabecular recesses and prominent trabeculae are features of embryonic or "spongy" myocardium, which normally develops into the compact myocardium that is characteristic of the mature mammalian heart (eFig. 90.5.1). Presumably, this entity is from an arrest in endomyocardial morphogenesis (72) and may involve either both ventricles or the left ventricle alone. It has never been reported as involving only the right ventricle. Noncompaction is almost always associated with other cardiac congenital defects, such as anomalous origin of the left coronary artery, and a characteristic facial dysmorphism. Isolated noncompaction of the myocardium is a similar disorder except that it is even rarer and is not associated with other congenital abnormalities (73). Both diseases have an increased incidence of familial cardiomyopathies, but no specific genetic locus has been identified. In pediatric and adult patients, embolic events occur because of the deep intertrabecular recesses. Ventricular dysrhythmias have been the most common presenting complaint. Left ventricular systolic dysfunction also occurs, although the etiology is uncertain. Restrictive physiology and endocardial fibrosis have also been noted (74). No definitive therapy is available, and many patients die from dysrhythmias.

Video 90.7 Apical two-chamber view of a patient with noncompaction with the inferior wall to the left of the screen and the anterior wall to the right. Again, note the thickened, heavily trabeculated myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 90.8 Apical four-chamber view of a patient with noncompaction with the right ventricle to the left of the field and the left ventricle to the right. Note the thickened, heavily trabeculated myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 90.9 Apical long-axis view of a patient with noncompaction. Isolated ventricular noncompaction is a rare idiopathic cardiomyopathy characterized by abnormal structure of the myocardium caused by intrauterine arrest of compaction of the myocardial fibers without any coexisting congenital lesions. The typical echocardiographic appearance includes segmental thickening of the myocardium consisting of two layers: a thin compacted epicardial and an extremely thickened endocardial layer with prominent trabeculations and deep recesses. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 90.5.1** Noncompacted myocardium. This is a typical example of the microscopic appearance of noncompaction of the myocardium. This section, taken from the left ventricle and stained with Masson's trichrome, could just as easily have come from the right ventricle or interventricular septum. The characteristic feature of this congenital abnormality is the deep, endocardial-lined invaginations in the myocardium, reminiscent of the sinusoidal lining of reptilian ventricles.

The largest series to date of noncompaction cardiomyopathy was reported by Oechslin et al. (75,76). Thirty-four adults, all aged greater than 16 years (25 men) demonstrated echocardiographic criteria for noncompaction cardiomyopathy that included, in the absence of significant heart lesions, segmental thickening of the left ventricular myocardial wall consisting of two layers, a thin compacted epicardial and an extremely thickened endocardial layer with prominent trabeculations and deep recesses. The mean age of the cohort was 42 ± 17 years, and 35% of the patients were in NYHA class III or IV. The left ventricular end diastolic diameter was 65 ± 12 mm and ejection fraction was 33% ± 13%. The apex or midventricular segments, or both, of the inferior and the lateral wall were involved in more than 80% of the patients. Mean follow-up was 44 ± 40 months with major complications noted during follow-up, including worsening heart failure in 53%, thromboembolic events in 24%, and ventricular tachycardia in 41%. Twelve deaths occurred; six were sudden, and four were related to worsening congestive heart failure. Four patients underwent heart transplantation, and automatic implantable cardioverter-defibrillator devices were implanted in four other individuals. This large case series emphasizes the mortality and morbidity of noncompaction cardiomyopathy and points out the risks of worsening heart failure, thromboembolic events, and ventricular arrhythmias. This group suggested that patients receive "heart failure therapy," oral anticoagulation, and consideration for heart transplant or automatic implantable cardioverter-defibrillator implantation. It should be pointed out, however, that no specific recommendations can be made regarding these tactics.

Mitochondrial Cardiomyopathy

Mitochondrial cardiomyopathy is defined as ventricular dysfunction caused by mitochondrial DNA mutations, which are maternally inherited. These mutations are not limited to the heart mitochondria and may also be demonstrated throughout the liver, kidney, pancreas, central nervous system, skeletal muscles, and thyroid gland. The mitochondria are typically irregular, vary in size, and have a very abnormal cristae structure (Fig. 90.6). Within the myocardium, there may be focal fibrosis and myofibrillar disarray, closely resembling idiopathic HCM. Mitochondrial cardiomyopathy may also present with signs, symptoms, and features of DCM. Progressive hypertrophy and dilation of the heart with cardiac dysrhythmias are characteristics of these mitochondrial abnormalities. DNA defects frequently result in cytochrome c oxidase deficiency and abnormalities in the mitochondrial respiratory chain. Research is active in identifying these mutations by endomyocardial biopsy (77). Several systemic diseases are associated with mitochondrial dysfunction. For example, the MELAS syndrome (*m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*troke-like episodes) is complicated by cardiomyopathy and generalized microangiopathic occlusive disease.

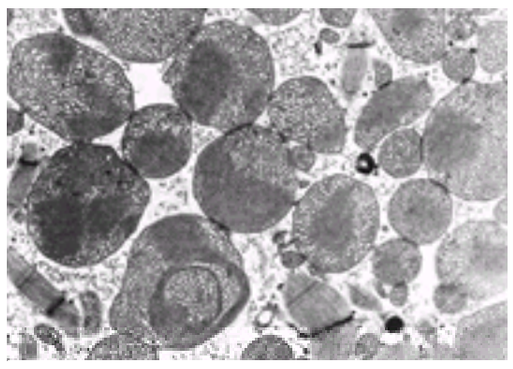


FIGURE 90.6 Mitochondrial myopathy. In this electron micrograph, the bizarre mitochondria, which are characteristic of a mitochondrial myopathy, are evident. All of the mitochondria illustrated here are abnormal. The normal mitochondria in a myocyte are filamentous and branching with regular cristae. The mitochondria in this myopathy are predominantly spherical. The extreme variation in size and structure of the cristae is distinctly abnormal. Within individual mitochondria, two distinct conformations of cristae can be seen. One of the mitochondria has ring-shaped cristae. Other abnormalities, too numerous to illustrate, were noted in this patient.

Systolic Dysfunction with Minimal Dilatation

Patients with DCM have ventricular dysfunction with enlarged ventricles. However, there is an entity in which ventricular dysfunction that is similar to DMC occurs but with minimal or no dilation (78). Furthermore, there are no signs of restrictive physiology to suggest that it is a restrictive or early HCM. This variant of DCM is termed *mildly dilated congestive cardiomyopathy* (MDCM) or *systolic dysfunction with minimal dilatation cardiomyopathy*. MDCM is defined as end-stage heart failure of unknown etiology (NYHA class IV), with an ejection fraction of less than 30%, without significant ventricular dilation (<15% above the normal range of ventricular size

for body surface area) (79). Additionally, the ventricular hemodynamic waveforms should not suggest restriction, such as with an early diastolic dip and plateau. MDCM can be differentiated from early stages of DCM, because early DCM does not have severe dysfunction clinically by echocardiogram or with right heart catheterization. On endomyocardial biopsy, the light microscopic findings demonstrate myocyte hypertrophy, bizarre-shaped nuclei, and interstitial fibrosis. Little to no myofibrillar loss occurs by electron microscopy, despite severe ventricular impairment. This preservation of myofibrils may explain the lack of dilation. Vitamin and nutritional element deficiencies must be ruled out before this diagnosis can be made, because these processes can cause profound reduction in systolic performance with preserved heart size as well. The etiology of this disorder is unknown; however, a positive family history of DCM can frequently be elicited. The prognosis overall is similar to that of DCM, but it appears more related to the hemodynamic impairment than to ventricular size. This is in contrast to DCM, in which increasing ventricular size denotes a poorer survival. For this reason, cardiac transplant should be considered if congestive symptoms persist after medical therapy.

SPECIFIC CARDIOMYOPATHIES

Ischemic

Ischemic cardiomyopathy, defined as an ejection fraction of less than 40%, with multifocal wall motion abnormalities due to coronary artery diseases, is the most common DCM in the United States (Fig. 90.7 and Fig. 90.8). It carries with it significant disability and mortality. In the past, a 5-year survival rate of only approximately 40% has been reported (80). Adequate perfusion of the myocardium is essential for appropriate cellular aerobic respiration, and heart failure due to ischemic cardiomyopathy is caused by at least four distinct mechanisms. The predominant mechanism is ischemic necrosis, owing to myocardial infarction (81). It is vital to determine the amount of stunned myocardium in these ischemic cardiomyopathy patients, particularly in the periinfarction phase, as well as the extent of hibernating tissue, because they may play significant roles in contractile dysfunction (82). Stunned and hibernating myocardial tissue are viable, with potential for improvement in functioning with better perfusion. Differentiation of ischemia, scar, and hibernating myocardial tissue is discussed fully in Chapter 50 and Chapter 55 and includes methods such as positron emission tomography, dobutamine and myocardial contrast echocardiography, and rest-redistribution thallium-201 scintigraphy (83). The final mechanism of ischemia that causes cardiomyopathy is related to pathologic remodeling after acute myocardial infarction. Nonischemic myocytes are subjected to increased workloads as infarcted cardiac tissue drops out of the contractile scene. Pathologic hypertrophy is induced in these remaining myocytes, as well as other molecular biodynamic characteristics of remodeling. Additional important factors include the development of ventricular aneurysm, dysrhythmias, and mitral regurgitation from papillary muscle ischemia and dysfunction. It is the combination of these factors that contributes to progression from normal cardiac function to cardiac dilation and heart failure.

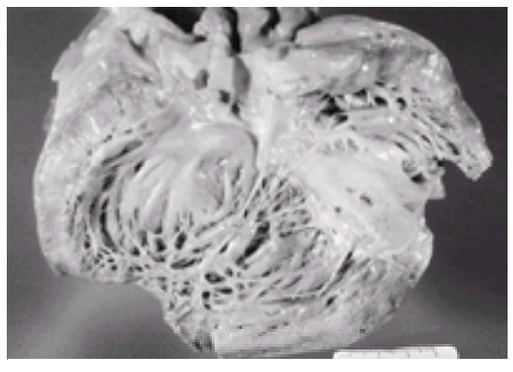


FIGURE 90.7 Ischemic cardiomyopathy. Photograph shows a heart that has been sectioned through the mitral and aortic valves, exposing the left ventricle. The heart is dilated, round, and globular, with an overall appearance much like that of an idiopathic dilated cardiomyopathy. However, in the cut surfaces of the left ventricle, visible here, the extensive white scar tissue of remote myocardial infarcts can be appreciated.

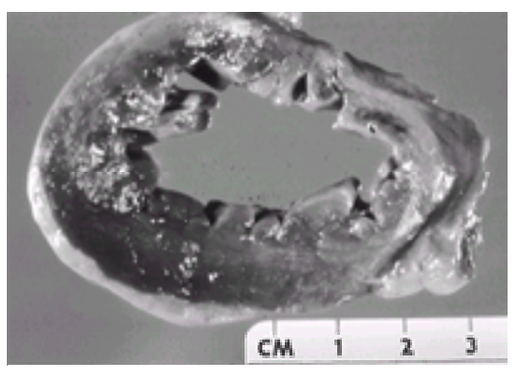
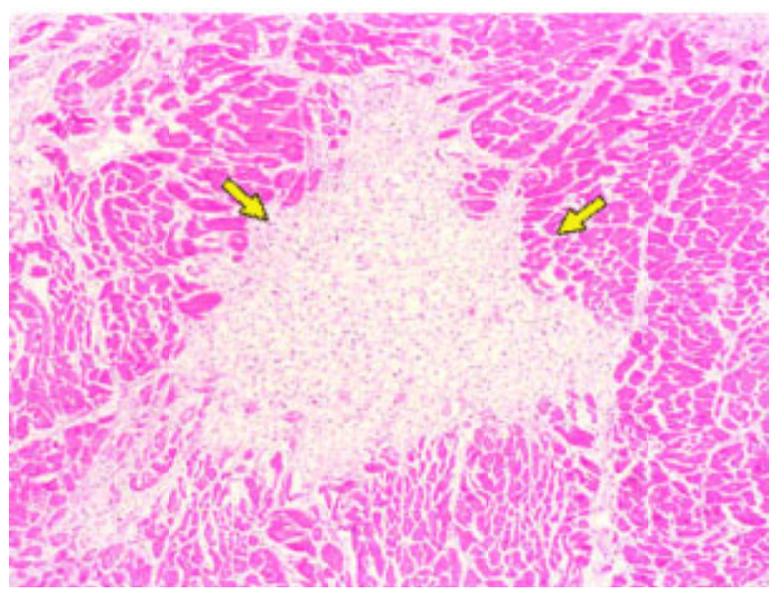


FIGURE 90.8 Ischemic cardiomyopathy. In this cross section from a heart with a remote myocardial infarct, many of the features of ischemic cardiomyopathy are demonstrated. A remote infarct is at the top of the picture. The portion of the left ventricular wall involved by this transmural infarct is notably thinner than the remainder of the ventricle, reflecting stretching and distention of the infarcted area. The left ventricular cavity is substantially enlarged, a reflection of the overall dilatation of the left ventricle.



Histology showing the early stages of healing following myocardial infarction. These changes are typical in the second week after the acute event. This is a hematoxylin-eosin stain showing removal of the necrotic myocytes and early ingrowth of vascular tissue and fibroblasts, particularly evident at the edges of the lesion (*yellow arrows*).

This characterization of ischemic cardiomyopathy is more generally related to the traditional large-vessel epicardial coronary artery disease that is seen in most patients with atherosclerotic heart disease. However, diffuse small-vessel atherosclerosis can also produce ischemic-related malfunction of the cardiac myocyte. Indeed, the cardiomyopathy of diabetes mellitus may be due, in part, to epicardial vessel disease as well as diffuse, small-vessel subendocardial atherosclerosis. Syndrome X, systemic lupus erythematosus, and other autoimmune chronic inflammatory disease states produce, on occasion, similar findings. The allograft arteriopathy noted in patients after cardiac transplantation is also an example of diffuse small-vessel coronary artery disease that can produce myocyte contractile dysfunction that leads to cardiac remodeling and heart failure. These diseases are difficult to address because of the limited ability to restore adequate myocardial perfusion.

Differentiation of ischemic cardiomyopathy from nonischemic processes is extraordinarily important. Patients with ischemic cardiomyopathy frequently, but not

always, have histories of chest discomfort, myocardial infarctions, or abnormal ECGs, suggesting previous infarction. Restoring adequate perfusion of the heart is key to reversing the progression of a clinical heart failure state. Coronary angiography is key, although often lesions are seen that are not producing ischemia, and, on the other hand, diffuse small-vessel disease may not be well appreciated. Coupling angiographic findings to perfusion, viability, and functional studies of the heart differentiates contributions of ischemia, scar, hibernation, and periinfarction stunning to the pathologic remodeling process of heart failure.

Valvular

Valvular cardiomyopathy is a hyperergopathic DCM produced by valvular defects of numerous etiologies, discussed in Chapter 21, Chapter 22, Chapter 23, and Chapter 24. Typically, defects that produce volume-overloaded states (regurgitation) are more likely to cause cardiomyopathy than are lesions associated with pressure overload (valvular stenosis). The etiologies of valvular cardiomyopathy have changed considerably over the past several decades. The aggressive treatment of rheumatic fever and the earlier and more successful valvular repairs and replacements being performed are leading to a decreased incidence of more common causes. Further, the identification of nonrheumatic disorders are increasing the documented frequency of other problems. The clinical presentation of valvular cardiomyopathy is similar to that of any of the other dilated cardiomyopathies. The prominent signs and symptoms of failure depend on what valve or valves are dysfunctional and on what side of the heart they are located. It may be difficult to evaluate fully the severity of some disorders when myocardial dysfunction is present. For example, the degree of aortic stenosis can be underestimated by echocardiography, because the ventricle may be too weak to generate a large gradient across the valve. The use of dobutamine may help to clarify this. Another area in which physicians frequently struggle is mitral regurgitation in the setting of a very dilated ventricle. Unless a good history is available, it may be difficult to ascertain whether the insufficiency caused the dilation and dysfunction or whether the regurgitation is a result of ventricular dilation with stretching of the annulus. Medical treatment is the same as with the other DCMs. Frequently, the issue of corrective valvular surgery in the setting of severe myocardial dysfunction is raised, with the hope of promoting myocardial recovery if the lesion is fixed. For instance, attempts at reducing mitral regurgitation have been performed in patients with severe cardiomyopathy, either as an isolated surgery or in conjunction with partial left ventriculectomy, with some symptomatic success and at least early improvement in certain cases (84,85).

Hypertensive

Hypertensive cardiomyopathy is discussed in detail in Chapter 5.

Obesity

Obesity is recognized as a specific separate disorder that can result in a cardiomyopathy. This is a condition distinct from other entities that can cause heart failure and are also associated with obesity, such as hypertension, coronary atherosclerosis, sleep apnea, and diabetes. It is believed that the severity of the cardiomyopathy is associated with the duration and the severity of the obesity and initially is a type of high-output failure. Obesity cardiomyopathy results in systolic and diastolic dysfunction, left ventricular hypertrophy, and elevations in left ventricular filling pressure. Substantial weight loss has been correlated with improvement in the ventricular function.

Inflammatory

Inflammatory cardiomyopathies are addressed specifically in Chapter 93. They are generally divided into idiopathic, autoimmune, and infectious categories and are listed in Table 90.3. The cardiomyopathies that are associated with systemic autoimmune disorders include the collagen-vascular disease syndromes and many of the mixed connective tissue diseases. Numerous viral infections are associated with DCM, including viral (enterovirus, adenovirus and cytomegalovirus, Coxsackie), rickettsial, bacterial (diphtheria), mycobacterial, fungal, parasitic (toxoplasmosis, trichinosis, Chagas' disease), and spirochetal (see Chapter 39). One particular cardiomyopathy, associated with HIV, warrants further mention here because it will, unfortunately, be encountered more and more frequently in clinical practice.

Idiopathic
Autoimmune
Collagen-vascular and mixed connective tissue diseases
Churg-Strauss syndrome
Systemic lupus erythematosus
Polyarteritis nodosa
Progressive systemic sclerosis
Infectious
Bacterial
Fungal
Parasitic
Schistosomiasis
Trichinosis
Toxoplasmosis
Trypanosoma cruzi
Rickettsial
Leptospirosis
Spirochetal
Viral
Adenovirus
Coxsackie virus
Cytomegalovirus
Echovirus
Human immunodeficiency virus

TABLE 90.3 CAUSES OF INFLAMMATORY CARDIOMYOPATHY

Human Immunodeficiency Virus

Background and Prevalence

The first mention of a cardiac manifestation of the acquired immunodeficiency syndrome (AIDS) occurred in 1983, when a woman with cardiac Kaposi's sarcoma and heart failure was described (86). Since then, several cardiac pathologies associated with HIV infection have been identified, including pericardial diseases, valvular lesions with or without endocarditis, lymphocytic myocarditis and myocardial necrosis, neoplasms, right ventricular failure, and DCM (87,88 and 89) (see also Chapter 39). The actual incidence of cardiac abnormalities in HIV-infected patients remains unknown; however, it has been estimated to be approximately 50% in cases when confirmed at autopsy (90,91 and 92). About 20% of these had DCM, although many were not clinically apparent. The presence of a cardiomyopathy is strongly associated with CD4 cell counts of less than 100 H 10^6 per L (93). Cardiac complications may be the cause of death in approximately 5% of all AIDS cases (94), with patients who manifest signs and symptoms of heart failure having a 6-month mortality that approaches 50%. With the currently increasing number of HIV-infected individuals worldwide, HIV cardiomyopathy will clearly become a more commonly seen clinical entity.

Pathophysiology

Many theories have been advanced proposing possible etiologies of HIV cardiomyopathy. No single mechanism has been accepted as the cause, and probably several different factors contribute to the dysfunction. First, the presence of an underlying mononuclear cell infiltrate/myocarditis is frequently present and may chronically lead to myocyte necrosis with resultant myocardial failure (88). Many of the opportunistic organisms that are common in HIV-infected patients, including bacterial, fungal, viral, and protozoal infections, are already known to cause myocarditis in otherwise healthy individuals. The mononuclear infiltrate may also be the result of an autoimmune process. In one study, immunoglobulin G antibodies directed against myosin and cardiac mitochondrial adenine nucleotide translocators were identified in HIV-positive patients with cardiomyopathy (95).

Several substances that are present in HIV patients may be directly or indirectly toxic to the myocardium. Catecholamines, found in higher levels in this group, can induce myocyte death. Further, it has been postulated that there may be focal areas of catecholamine-induced microvascular spasm, leading to areas of chronic ischemia or even infarction. Many of the drugs that are commonly used to treat AIDS or one of its associated problems have been implicated in the cardiomyopathy, including zidovudine (AZT), interferon-a, and doxorubicin. For instance, a correlation between antiretroviral therapy, such as with AZT, and the degree of cardiomyopathy has been identified (96). Additionally, AZT has been shown to cause myocyte mitochondrial DNA chain replication termination *in vitro*. This may eventually lead to impaired cellular energy production and myocyte death. It has been demonstrated that tumor necrosis factor-a (TNF-a), present in increased amounts in HIV-positive patients, can directly induce significant myocardial depression (97,98). It also promotes the release of other harmful substances, such as nitric oxide and oxygen-free radicals, which can in turn cause additional depression of function (99,100). The AIDS virus itself can directly infect myocytes and may be directly toxic by a cytolytic effect (101,102). Additionally, when the virus replicates in interstitial lymphocytes and macrophages, destructive enzymes can be released (103). It has been suggested that nutritional deficiencies can lead to heart failure (104,105). For example, low selenium levels are common in HIV-positive patients, especially in more severe cases. Glutathione peroxidase activity is diminished with selenium deficiency, which may lead to the accumulation of myocardial toxins.

Other factors that can contribute to cardiomyopathy in AIDS are the same causes of cardiac failure in non-HIV–positive patients (106,107). It is always possible that

underlying coronary artery disease can lead to ischemic cardiomyopathy, hypertension resulting in hypertensive cardiomyopathy, or a secondary viral infection, such as Coxsackie B virus, with subsequent viral cardiomyopathy. Similarly, patients with a history of drug abuse may have a higher incidence of alcoholic cardiomyopathy or cocaine-induced failure that is unrelated to their HIV status.

Clinical Profile and Management

The clinical presentation of heart failure is frequently misinterpreted to be one of the other more common illnesses in HIV-positive patients. For example, shortness of breath and dyspnea with exertion immediately raise the suspicion of an opportunistic pulmonary infection. It is important to consider also the possibility of heart failure when these patients present with new complaints. The chest x-ray is insensitive, but it may be helpful by demonstrating cardiomegaly or pulmonary edema. ECGs are usually nonspecific with HIV cardiomyopathy, although they could exclude other possibilities such as ischemia or infarction. The most helpful diagnostic test is an echocardiogram, which assesses ventricular size and contractility and valvular function and detects pericardial effusions.

In addition to the conventional treatment of heart failure with digoxin, diuretics, and ACE inhibitors, several other therapies have been suggested. Selenium supplementation has been documented to improve left ventricular function in a few cases (108). If AZT or another drug is suspected of causing or contributing to the ventricular dysfunction, the risk-benefit ratio of discontinuing therapy warrants examination. Some clinicians have supported the use of immunosuppressive agents, such as corticosteroids with or without azathioprine, especially if an inflammatory or autoimmune mechanism is responsible (85,109). No randomized trials have validated this approach, however, and the use of immunosuppressants in an already compromised host requires careful consideration. In the future, as more is understood about TNF-a and similar compounds, antioxidants and oxygen-free radical scavengers may play a pivotal role.

Tachycardia Induced

One of the more important cardiomyopathies is that related to chronic tachyarrhythmia. In many senses this form of cardiomyopathy is a classic hyperergasic cardiomyopathy. If substantive ventricular dysfunction and heart failure are due to this difficulty, response to treatment can be gratifying. Severe dropsical states can resolve quickly, for example, by simply slowing the ventricular heart-rate response in patients with heart failure due to rapid atrial fibrillation. In fact, William Withering's (110) description of patients who are likely to respond to his foxglove herbal tea therapy were characterized as having pale countenances with weak, thready, and irregular pulses accompanying their dropsical state. It is very likely, in retrospect, that these individuals had atrial fibrillation with rapid ventricular response rates. Although ventricular and atrial tachycardias are very common in patients with heart failure, whether or not they are the primary etiology of the difficulty or simply an added complication that contributes to decompensation varies from patient to patient. This is of little consequence, however, because control of dysrhythmia, with slowing of the heart rate, is mandatory in either circumstance. Further, it is often difficult to know whether tachyarrhythmias that are seen in heart failure patients caused or are the result of ventricular chamber dilatation, hypertrophy, and heart failure. Indeed, in 1913, Gossage and Braxton Hicks (111) first suggested that atrial fibrillation might have been the etiology of left ventricular dilation and hypertrophy. This report did not, however, document reversal of the cardiac remodeling with control of the "auricular fibrillation." Many reports in the 1930s and 1940s did, however, describe resolution of congestive heart failure syndromes after termination of atrial fibrillation and cardioversion to normal sinus rhythm (112,113 and 114). Because atrial fibrillation frequently complicates hypertension and coronary heart disease, with both difficulties also contributing to ventricular dysfunction and possibly precipitating heart failure, it is difficult to determine precisely the degree of contribution that the dysrhythmia is making to the cardiomyopathy in some patients. On the other hand, descriptions of heart failure syndromes associated with reentrant atrial tachyarrhythmias with resolution of the syndrome after control of the arrhythmia are convincing that heart rate alone contributes to contractile dysfunction (115,116 and 117). As electrophysiologic techniques became more sophisticated and pathophysiologic clarification of atrial tachycardias emerged, it became even more apparent that rapid heart rates alone could cause heart failure and cardiomyopathy. Restoration of systolic function, manifest by normalization of ejection fraction, has been reported for accessory pathway–reciprocating tachycardias (118,119) and atrial ventricular nodal reentry tachyarrhythmia (120,121). In children, control of incessant ventricular tachycardia has also been noted to reverse dilated myopathic ventricles (122,123).

In an attempt to mimic tachycardia-induced heart failure clinically, an experimental model was proposed by Whipple et al. (124) in 1962 that demonstrated that cardiomyopathy could be produced in large mammals if the heart was stimulated to incessantly beat very fast. Furthermore, this model of low-output biventricular failure demonstrated that termination of the pacing stimulation with slowing of the heart rate reversed the heart failure syndrome. Tachycardia-pacing animal models of heart failure have been invaluable during characterization of heart failure syndromes in general. Overall, they have served to stress the importance of controlling tachycardia in managing clinical heart failure (125). The reasons for the development of ergopathic myocyte contractile impairment in patients with incessant tachyarrhythmias or rapid pacing–induced cardiomyopathy are complicated. Decompensation of cardiac performance may be due to myocardial energy depletion or impaired energy use, regional ischemia (usually subendocardial), abnormalities of myocyte organelle calcium flux, and acute leading to chronic cardiac myocyte and interstitial matrix remodeling. Chronic tachypacing in animals has been demonstrated in some studies to reduce creatine, phosphocreatine, and adenosine trisphosphate (126). Furthermore, mitochondrial structural injury and functional abnormalities have been noted. Particularly intriguing is the observation that altered subendocardial-subepicardial blood flow ratios impair coronary flow reserve states when tachycardia is induced in animals and might contribute to myocyte dysfunction by promoting a relative ischemic setting. This is an important observation because many patients have concomitant coronary heart disease or substantive hypertension-induced left ventricular hypertrophy and could be quite susceptible to myocardial flow changes. A considerable amount of attention has focused on abnormalities of calcium channel activity and sarcoplasmic reticulum calcium transport in paced heart failure models. The downregulation of calcium cycling, which ultimately decreases availability of this ion to the myocyte contractile machinery, may be a unifying hypothesis to explain the failure that develops in this syndrome. Observations of myocyte hypertrophy and extracellular matrix deposition with resultant stiffening could explain the more chronic abnormalities noted in paced cardiac models. Collectively, these pathophysiologic effects translate into low cardiac output and, ultimately, high cardiac filling pressures with dilatation and hypertrophy of the heart. Concomitant aberration in neurohumoral characteristics of the clinical heart failure syndrome subsequently occurs.

Controlling rapid ventricular responses is, therefore, paramount in attempting to ameliorate heart failure states that are associated with tachycardia. Because atrial fibrillation is so common in patients with heart failure, control of the ventricular rate needs to be emphasized. Focus should first be on attempts to convert the patient, either with pharmacologic therapy or direct current cardioversion, to sinus rhythm. Should this not be possible, consideration of pharmacologic strategies to control ventricular rate is important, as might be atrioventricular junction nodal ablation with permanent ventricular pacemaker insertion. Other types of supraventricular tachycardias might respond to more focused electrophysiologic arrhythmia-track ablation techniques or insertion of electronic arrhythmia-termination pacing devices. Likewise, incessant, but not necessarily sustained, ventricular arrhythmias need to be addressed in similar fashion with consideration of pharmacologic treatment strategies, ablation therapeutics, or use of electronic arrhythmia-termination and control devices. Finally, the Maze operation is a surgical alternative that might assist in controlling the dysrhythmia and ameliorate heart failure. The procedure involves making several intertwining incisions in the atria to interrupt the fibrillation circuits.

Metabolic

Many metabolic disorders are known to induce myocardial dysfunction and can be categorized into endocrine, familial storage disease and infiltrations, deficiency states and nutritional disorders, and amyloidosis. Endocrine diseases, such as adrenocortical insufficiency, thyrotoxicosis, hypothyroidism, acromegaly, and pheochromocytoma, are covered in detail in the endocrine section of Chapter 35. Because diabetes mellitus and diabetic heart disease are so frequently encountered, they are further explored here. Additionally, amyloidosis and its unique nature deserve additional description.

Diabetic

Heart failure in the setting of diabetes is multifactorial and can be due to epicardial atherosclerotic coronary artery disease, small-vessel subendocardial disease, or the diabetes itself (127). Patients with diabetes mellitus are well known to be prone to silent myocardial ischemia and infarction. Furthermore, hypertension often complicates diabetes and can also contribute to the detrimental remodeling of the heart. It is disturbing to note that almost half of asymptomatic diabetics experience a reduction in left ventricular ejection fraction during stress.

The hearts of diabetic patients at autopsy demonstrate the characteristic findings of DCM, with widespread regions of myocardial fibrosis, intimal proliferation of small myocardial arterioles, and accumulation of interstitial glycoprotein and collagen, all leading to decreased ventricular compliance and contractility (128). In laboratory animals, alterations in myocytes occurred before any damage to the intramural arteries, suggesting other derangements in cellular metabolism (129). It has been presumed that some of the resultant dysfunction may be related to abnormal processing of lipids and decreased lysosomal activity (130). Many additional theories have been postulated and explored to explain the ventricular failure, including the possible role of increased circulating catecholamines (131). It has also been observed that the concentration of collagen increases when diabetes is poorly controlled (132), and other studies have documented improvement in left ventricular functioning and reversal of biochemical abnormalities with the administration of insulin (133). In addition to the more standard treatments for DCM, tighter control of glucose levels may be beneficial to cardiac functioning in diabetics. Finally, the chronic addition of propionyl-L-carnitine to the diets of diabetic rats in one study overcame the induced myocardial dysfunction (134), raising the potential of testing this treatment in humans.

Familial Storage Disease and Infiltrations

Many of the familial storage diseases and infiltrations cause various substances to be deposited within the myocardium, either intracellularly (frequently interfering with cellular metabolism and functioning) or extracellularly (resulting in a restrictive cardiomyopathy). Many of these disorders, such as Hurler's syndrome, Niemann-Pick

disease, Hand-Schüller-Christian disease, and Morquio-Ullrich disease, are more fully reviewed in the neurology section of Chapter 35. A few of the more understood and common disorders are further discussed here.

Hemochromatosis

Hemochromatosis is a metabolic storage disorder, associated with HLA-A3 and HLA-B14 autosomal recessive inheritance, leading to iron deposition in the sarcoplasmic reticulum of many organs (Fig. 90.9). It results clinically in the classic description of the bronzed diabetic with heart failure due to skin, pancreatic, and cardiac iron deposition. The cardiac deposits tend to be in the subepicardial and subendocardial regions and in the papillary muscles. Cardiac hemochromatosis may present as either a restrictive cardiomyopathy early on or, more commonly, a dilated one, with impressively enlarged ventricles. In addition to the iron deposition, an interstitial fibrosis that is unrelated to the degree of iron overload may occur independently. Endomyocardial biopsy is useful in demonstrating the iron deposits and important in establishing the diagnosis because the most common form of death in hemochromatosis is cardiac. Treatment consists of repeated phlebotomy or possibly chelation therapy, with the cardiomyopathy often reversible when the iron load is decreased.

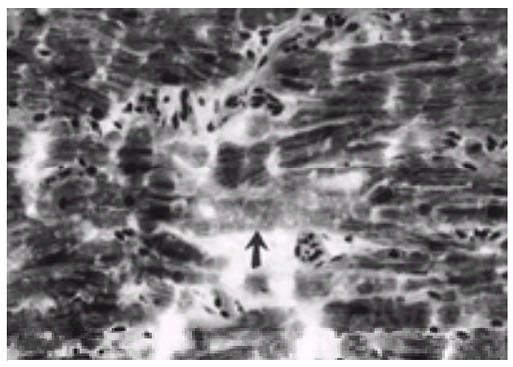


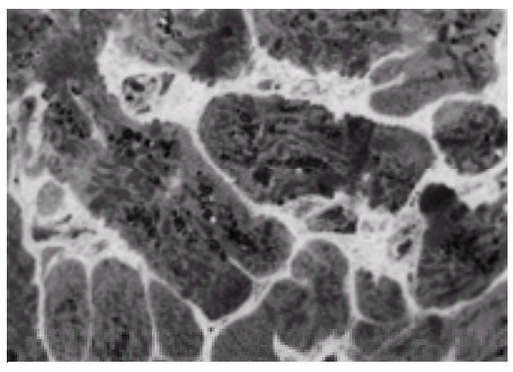
FIGURE 90.9 Cardiac hemochromatosis. This longitudinal light microscopic section of myocardium has been stained for iron. It has been specially stained blue for iron, but in black and white print all of the dark material seen within the myocytes is iron, with one large aggregate of iron in the center (*arrow*). This particular area does not have any overlying cardiac structures and appears lighter than other iron-laden areas in this picture. In the normal heart, there should be virtually no stainable iron.

Refsum's Syndrome

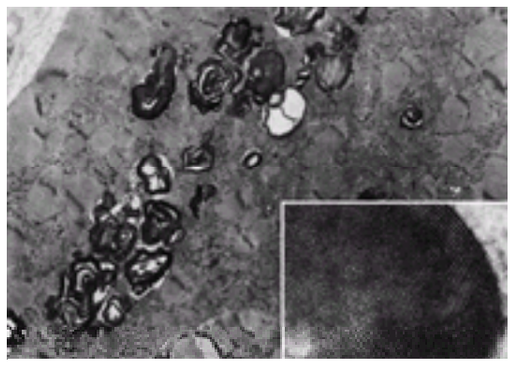
Refsum's syndrome is an autosomal recessive disorder caused by the absence of the enzyme alpha-hydroxylase, which metabolizes dietary phytol and phytanic acid. This results in an accumulation of intracellular phytanic acid. The syndrome is characterized by cerebellar ataxia, peripheral neuropathies, retinitis pigmentosa, and cardiac disorders. A cardiomyopathy may result and can be either dilated or hypertrophic, depending on the stage of the disease. Wide-ranging conduction disturbances may occur, as well as dysrhythmias and sudden cardiac death. Current treatment consists of dietary modifications. Plasmapheresis has been shown to remove the accumulated phytanic acid.

Anderson-Fabry's Disease

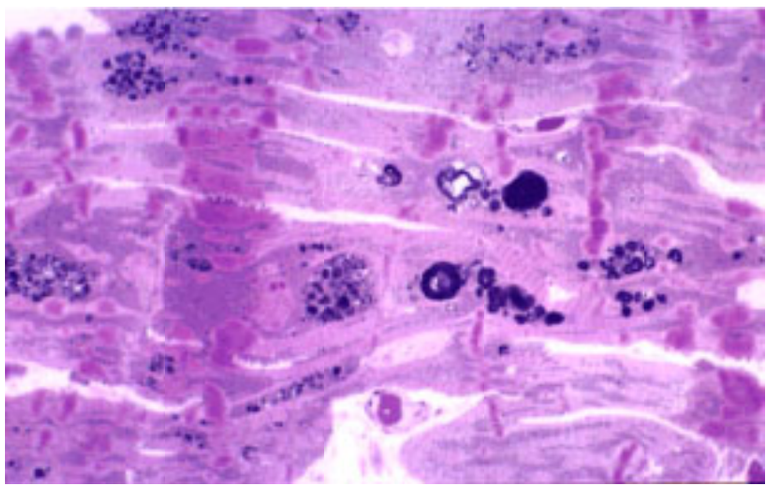
Fabry's disease, formally known as *angiokeratoma corporis diffusum universale*, is an X-linked disorder of glycosphingolipid metabolism and is present in 1 in 40,000 live births. It is due to a deficiency of the lysosomal enzyme alpha-galactosidase A, which normally degrades the neutral glycolipid ceramide trihexoside. The disorder is characterized by the intracellular lysosomal accumulation of this glycolipid, with prominent involvement of the skin, glomerular, and tubular cells of the kidneys, and the heart (eFig. 90.9.1 and eFig. 90.9.2). Within the heart, the myocytes, vascular endothelium, conducting system, and valves can all be affected (135). Storage of the lipid in the blood vessels, with eventual occlusion on the small arterioles, leads to most of the clinical manifestations. Mostly males are affected, whereas the female carriers are usually asymptomatic or have only mild symptoms. Patients are generally diagnosed in childhood, when they present with burning pains, fevers, multiple angiokeratomas, corneal opacifications, and strokes; however, they do not present with renal and cardiac failure until their third or fourth decade of life. An atypical form of Fabry's disease exists, in which there is retention of some residual alpha-galactosidase activity, probably from partial gene deletions and point mutations (136,137 and 138). These patients present late with a cardiomyopathy but no other systemic complaints.



***e*FIGURE 90.9.1** Fabry's disease. High-magnification light micrograph of a semithin plastic section. With dual fixation in glutaraldehyde and osmium tetroxide, the globular dark-staining glycolipids within the cytoplasm of the myocytes, which are characteristic of Fabry's disease, have been preserved. When biopsies from Fabry's disease are processed by standard light microscopic methods with paraffin sections, the appearance is that of a vacuolar myopathy.



***e*FIGURE 90.9.2** Fabry's disease. Electron micrograph illustrating the accumulation of dark, electron-dense membrane profiles of accumulated glycolipids within myocytes. **Inset:** High-magnification electron micrograph revealing the characteristic "fingerprint" of the membrane accumulations within the cytoplasm of the myocytes.



Fabry's syndrome exemplified in cardiac muscle. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Cardiovascular manifestations include renovascular and systemic hypertension, aortic root dilatation, mitral valve prolapse, and congestive heart failure. Patients may additionally have severe vasospastic angina and myocardial infarctions, perhaps from endothelial cell damage (139). The ECG may show left ventricular hypertrophy, P-wave abnormalities, conduction defects, and ventricular dysrhythmias. The echocardiogram typically shows marked increases in wall thickness and ventricular dilatation later in the disease process. The diagnoses may be confused with other disorders, such as HCM, hypertensive cardiomyopathy, and amyloidosis (140). Magnetic resonance imaging may help differentiate this from amyloid (141). Endomyocardial biopsy is remarkable, showing the lipid vacuoles creating a lacework (fingerprint) appearance, with increased levels of ceramide trihexosidase. The muscle fibers demonstrate an irregular degree of hypertrophy. Definitive diagnosis requires showing decreased alpha-galactosidase activity in leukocytes. No specific therapy exists for Fabry's disease. Unfortunately, renal transplantation, by attempting to replace the missing enzyme, does not prevent further cardiac deterioration (142). Lately, encouraging preclinical studies have been performed in corrective gene transfer for enzyme replacement. By using high-titer recombinant retroviral vectors to transduce and correct target cells, a continuous source of alpha-galactosidase may ultimately be available for uptake by unmodified patient cells (143).

Selenium Deficiency

Selenium deficiency is a form of DCM that has been primarily reported in northeast China, where it is known as Keshan disease. It has, however, been demonstrated in HIV-positive patients with cardiomyopathy and in individuals who are receiving chronic parenteral nutrition. Selenium is an essential mineral, and deficiency results in the decreased activity of glutathione peroxidase. This causes an increase in free radicals that can be directly toxic to myocytes. Selenium replacement can reverse the ventricular dysfunction.

Thiamine Deficiency (Beriberi)

The Sinhalese word *beriberi* translates into "I cannot," meaning the patient is too ill to do anything. Thiamine (vitamin B_1) is a necessary coenzyme for carbohydrate metabolism, and patients with this deficiency can present with edema, polyneuritis, and cardiac pathologies for at least 3 months. *Dry beriberi* refers to the constellation of flaccid paralysis, muscular atrophy, areflexia, and cardiac enlargement with tachycardia. Wet beriberi is similar in terms of the cardiac failure, except it has extensive edema. The extensive nervous system involvement is not present. Patients with beriberi have high-output failure, with a cardiac presentation similar to that of the other dilated cardiomyopathies. The mechanism of this failure is uncertain. Lesions in sympathetic nuclei have been observed (144) and may lead to decreased peripheral resistance with compensatory increases in cardiac workload, eventually resulting in ventricular failure. The cardiac dysfunction can rapidly return to near normal with thiamine replacement, although if the deficiency has been long-standing the dysfunction may be irreversible.

Carnitine Deficiency

In carnitine deficiency, the oxidation and mitochondrial transport of fatty acids are impaired, leading to lipid accumulation in the cytoplasm. The deficiency may be familial (145). Carnitine deficiency may result in a dilated or occasionally restrictive cardiomyopathy or a worsening of a preexisting cardiomyopathy of another cause. The cardiac lesions are often associated with endocardial fibroelastosis. Oral therapy with L-carnitine can be quite effective (146).

Amyloidosis

Background and Prevalence

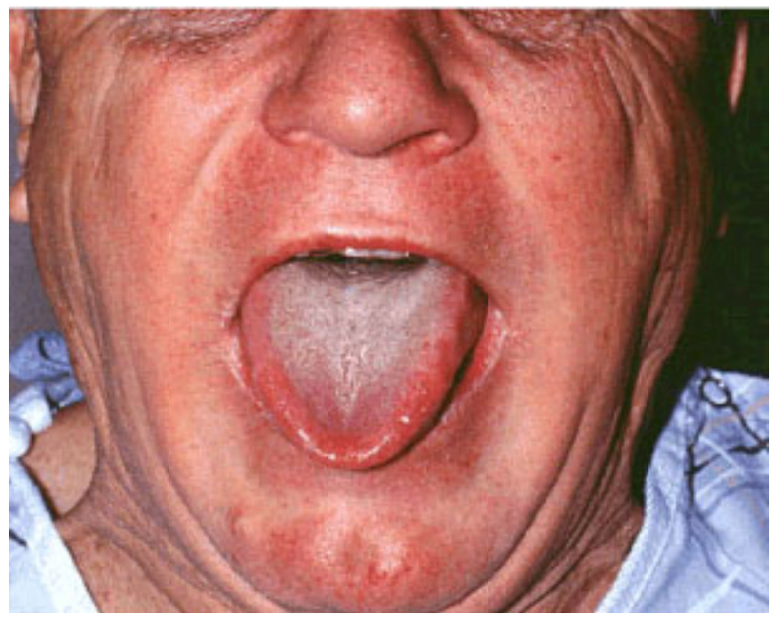
Amyloid restrictive cardiomyopathy is caused by the abnormal deposition of various proteins into the interstitium of the myocardium. The four general categories of amyloid heart disease are primary systemic, secondary, familial or hereditary, and senile. These are summarized in Table 90.4. Primary systemic amyloidosis is also known as *myeloma-associated* or *amyloid AL*. It is caused by the uncontrolled production of an amyloid protein subunit, the ammonia terminal portion of an immunoglobulin light chain (kappa or lambda), from a monoclonal population of plasma cells. It is usually, but not always, the consequence of multiple myeloma, is more common in men, and rarely presents before age 30. Secondary amyloidosis results from the production of a nonimmunoglobulin protein, termed *AA*. It is frequently encountered with chronic inflammatory disorders, such as rheumatoid arthritis, tuberculosis, and Crohn's disease, and in familial Mediterranean fever. Familial and hereditary cardiac amyloidosis consists of six different forms. They result from the production of amyloid AF, a prealbumin protein component known as transthyretin. They are autosomally dominant disorders, unlike familial Mediterranean fever, which is autosomal recessive. Senile cardiac amyloid, also known as *amyloid SSA*, is also due to the production of an abnormal transthyretin and is seen in older individuals (147). The three forms of this disorder are amyloid IAA, which only affects the atria; senile systemic amyloidosis, which may involve other organs; and a third form that is limited to the aorta. Each of the four main categories of amyloid heart disease has varying degrees of cardiac involvement, clinical significance, and survival rates. For instance, cardiac failure is the most common cause of death in primary amyloidosis. At autopsy, nearly 100% of systemic amyloid cases have demonstrable cardiac infiltration, although only 25% to 33% have clinically apparent disease (148,149). In contrast, fewer than 10% of secondary amyloid cases are associated with clinically significant cardiac derangement. Even when present, the deposits are typically small and perivascular in location and do not result in considerable ventricular dysfunction. Familial amyloidosis rarely has cardiac involvement, and then only very late in the disease. Senile amyloidosis is much more variable than the other types. Almost all individuals over the age of 60 have scattered deposits of amyloid in locations such as the aorta, and one-fourth have some cardiac infiltration (150). This ranges from small atrial deposits to extensive ventricular involvement with severe congestive failure. The survival with senile amyloidosis is much longer than with primary amyloid. In one study, the median survival was 60.0 months and 5.5 months, respectively, from the time of diagnosis (151).

Name	Designation	Other names	Amyloid deposit
Primary	AL	Myeloma-associated, idiopathic*	Immunoglobulin light chain, kappa or lambda
Secondary	AA	Associated with other inflammatory disorders, familial Mediterranean fever	Nonimmunoglobulin protein A
Familial	AF	Hereditary	Transthyretin
Senile	SSA	Senile systemic amyloid	Transthyretin

*This term is outdated and should no longer be used.

TABLE 90.4 CLASSIFICATION OF AMYLOIDOSIS

Amyloidosis. Infiltration of the skin results in raised waxy papules or plaques that are usually in clusters.



Amyloidosis. Infiltration of the tongue occasionally leads to macroglossia. Cardiac manifestations include cardiomegaly, congestive heart failure, and arrhythmias.

Pathophysiology

The myocardium in amyloidosis is usually firm, thickened, and noncompliant, with the amyloid being present extracellularly. The deposits occur in the interstitium in a pericellular or focal nodular pattern and can result in systolic and diastolic impairment (Fig. 90.10 and Fig. 90.11). Nodular deposits and thick perimyocyte layers of amyloid are associated with shorter survival (152). Mild atrial enlargement is generally present, usually without significant ventricular dilatation. Besides the myocardial infiltration, there can also be deposition in the papillary muscles, the sinoatrial and atrioventricular nodes, the bundle branches, and the endocardium. Amyloidosis can incite focal thickening of all four valves, especially the mitral; however, it rarely interferes with overall valve function and competence. Finally, the intramural arteries and veins can contain deposits in the media and adventitia, occasionally compromising blood flow. Rarely, deposits can also occur directly in the lumen of the vessels. The different types of amyloid vary in their vascular encroachment. Only 4% of senile amyloidosis has vascular involvement, whereas it is found in up to 90% of primary amyloid cases (153).

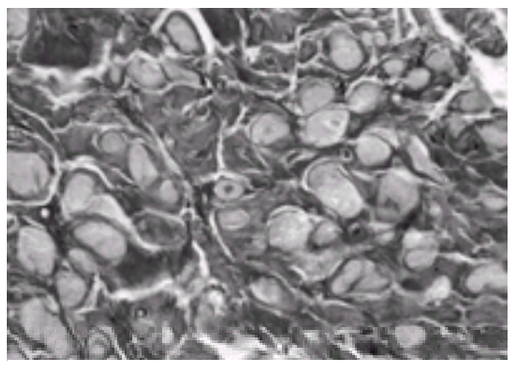


FIGURE 90.10 Cardiac amyloid. Light microscopic section from an endomyocardial biopsy stained with sulfonated alcian blue. Although the color cannot be appreciated, the myocytes are the lighter-shaded cells. The darker-colored amyloid closely surrounds each myocyte and isolates it.

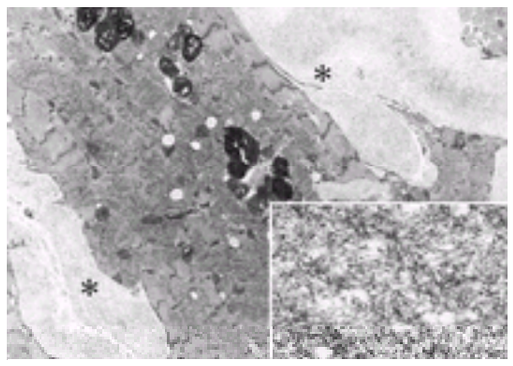
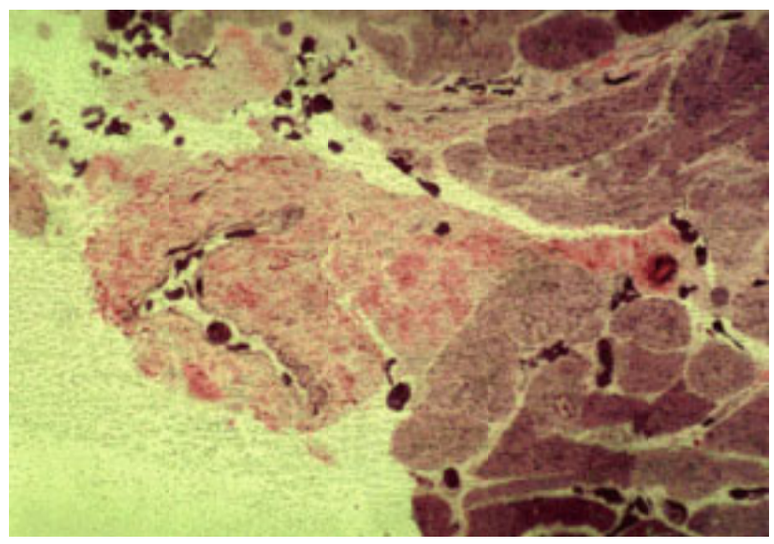
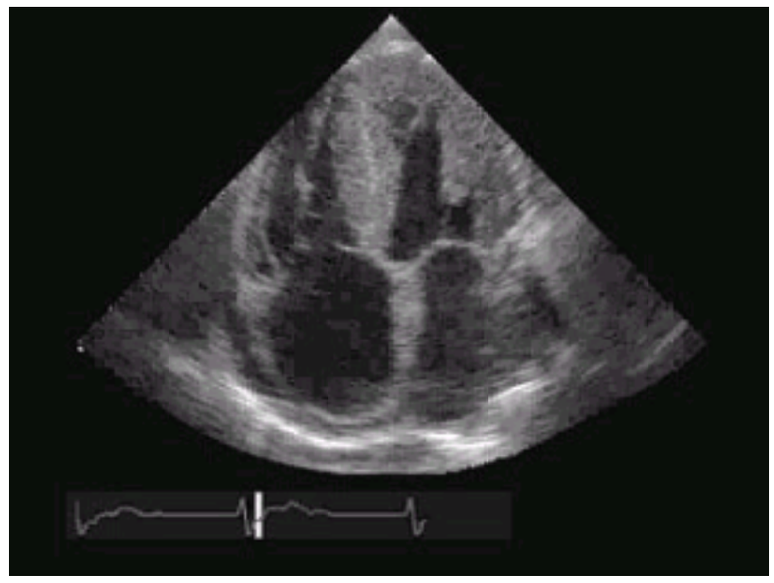


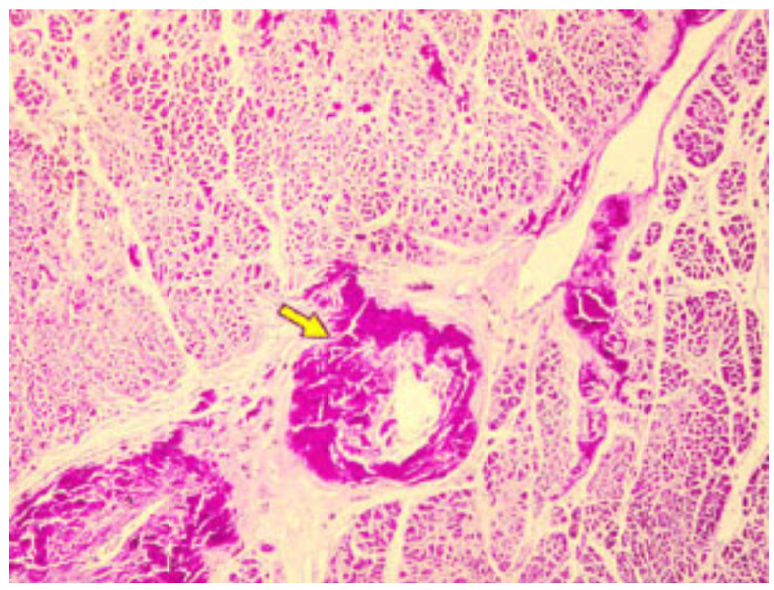
FIGURE 90.11 Amyloid. Electron micrograph showing a dense accumulation on amyloid fibrils (*asterisks*) hugging the myocyte. **Inset:** At high magnification, 10-nm nonbranching straight filaments, which are characteristic of amyloid, are revealed.



Amyloid deposition. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

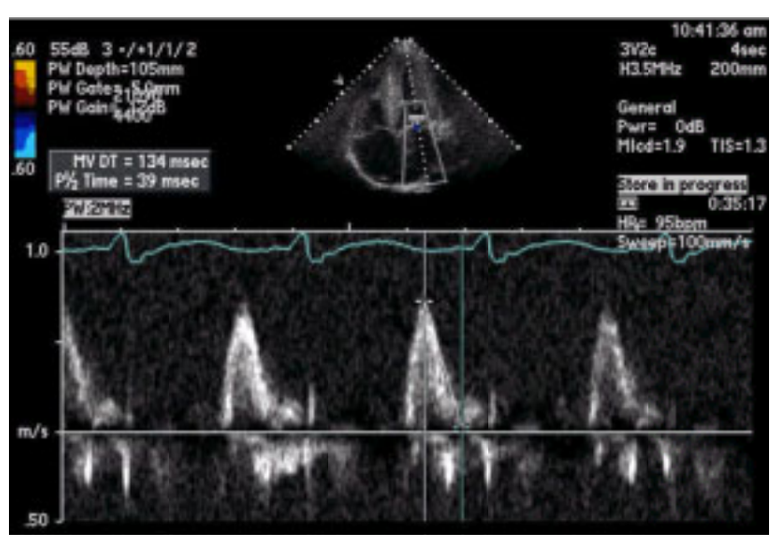


Apical four-chamber view of amyloid heart disease. Note the significant thickening of the left ventricle and right ventricle walls due to infiltration. There is also characteristic thickening of the valves and biatrial enlargement. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)



Amyloidosis of the heart. This is cresyl violet stain of the left ventricular myocardium. The yellow arrow indicates a metachromatic red-violet homogenous deposit around an intramyocardial arteriole with similar interstitial deposits.

A 68-year-old male patient with amyloidosis.



Pulsed wave Doppler of the mitral valve inflow in a patient with amyloidosis demonstrating a short deceleration time (134 ms) consistent with restrictive physiology.

Video 90.10 Transthoracic apical four-chamber view of a patient with amyloidosis. Note the thickened “sparkling” walls of the right and left ventricles. Both the mitral and tricuspid valves are mildly thickened and there is biatrial enlargement and a trivial pericardial effusion. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Clinical Profile and Management

Cardiac amyloidosis can manifest itself in one of four general ways; however, it is important to realize that by the time symptoms appear there is generally quite extensive myocardial infiltration. The first presentation is that of a restrictive cardiomyopathy, with primarily diastolic dysfunction and right-sided heart failure findings. These include peripheral edema, jugular venous distention, and hepatic congestion. A fourth heart sound is uncommon, because atrial infiltration can decrease pumping ability. Right-heart catheterization can demonstrate a restrictive physiology, including the characteristic diastolic dip and plateau in the ventricular pressure waveform. The second presentation is one of more typical congestive heart failure symptoms from systolic dysfunction. In this case, hemodynamic restriction may not be as prominent. Systolic ventricular impairment, when present, is an ominous sign, with a generally poor response to treatment and a progressive decline. Patients may have angina, either from involvement of the coronaries with amyloid deposition or from unrelated coronary atherosclerosis (154). Third, orthostatic hypotension may be the initial presenting complaint in approximately 10% of patients. Amyloid infiltration of the autonomic nervous system, blood vessels, or the adrenal glands may be partially responsible. Finally, because there may be amyloid deposits within the conduction system, various abnormalities of impulse formation and conduction may occur. Patients may have bradycardia and varying degrees of blocks, including complete heart block and atrial and ventricular dysrhythmias. In such patients with conduction system involvement, sudden death, unfortunately, is relatively common.

Cardiac studies range in usefulness for the diagnosis of amyloidosis. The chest x-ray is nonspecific and can show cardiomegaly, pulmonary congestion, and pleural effusions. The classic description of amyloid heart disease seen on the ECG is diffuse low voltage in all leads, which is present in approximately 50% of patients. Pericardial effusions, chronic obstructive lung disease, and obesity can also cause low voltage. Other findings on the ECG include left-axis deviation, ventricular dysrhythmias, and atrioventricular conduction delays and blocks. The echocardiogram can display small cardiac chambers with symmetric thickening of the left ventricle, dilated atria, thickened valves, pericardial effusions, and impaired left ventricular contractility. A characteristic finding is a granular sparkling appearance of increased echogenicity of the myocardium. Increasing myocardial wall thickness is a predictor of poor survival. Diastolic dysfunction, with impaired relaxation, is manifested by a reduction in the rate and volume of the rapid diastolic filling phase. A Doppler-derived index of combined systolic and diastolic myocardial performance has been described. This index is the sum of isovolumetric contraction and relaxation times divided by the ejection time and was found to be another independent predictor of survival (155). Amyloid infiltration can cause the technetium-99m (Tc-99m)–pyrophosphate and gadolinium-diethylenetriaminepentaacetic acid–enhanced magnetic resonance imaging scans to be strongly positive (156,157 and 158). Finally, endomyocardial biopsy can demonstrate amyloid if other laboratory tests and areas of biopsy are negative or equivocal. Special stains, including immunoperoxidase stains for kappa and lambda immunoglobulin chains and prealbumin, may help to distinguish subtypes of the amyloid infiltrate, guiding management decisions and prognosis.

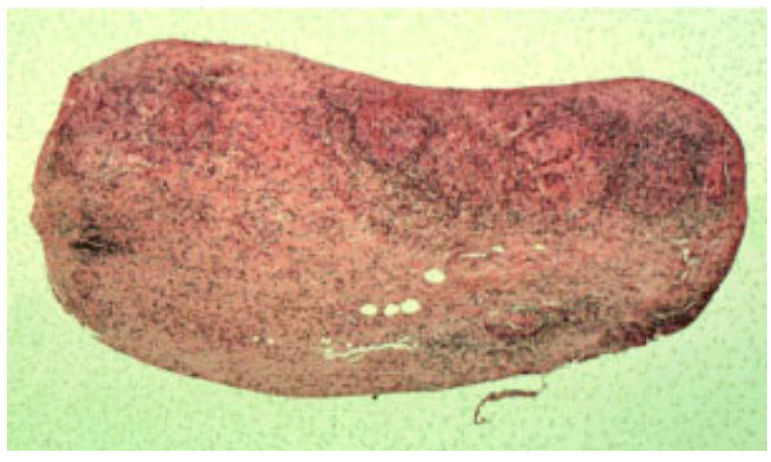
The management of amyloid cardiomyopathy is exceedingly difficult and typically ineffective. Low doses of diuretics and vasodilators are the most useful of the drug options but require careful supervision. Patients with nephrotic syndrome from the amyloid, for example, may have a considerable amount of extravascular fluid, but they may be intravascularly depleted. Vasodilators can easily cause orthostatic symptoms, especially in patients who already have amyloid-induced autonomic dysfunction. ACE inhibitors have been reported to be of benefit, although no controlled trials have confirmed this. Unfortunately, calcium channel blockers, which have been of benefit in other disorders that cause diastolic dysfunction, have been disappointing in the treatment of amyloid cardiomyopathy. Nifedipine is bound by the amyloid fibrils and its use, as well as that of other calcium channel blockers, and may exacerbate congestive heart failure symptoms by a local, enhanced, negative inotropic mechanism (159,160 and 161). Digoxin, which controls supraventricular dysrhythmias, is similarly relatively contraindicated because the drug may also be selectively bound to the fibrils, resulting in increased sensitivity and toxicity (162,163). It is unknown whether other antiarrhythmics share this same potential for toxicity. Beta-blockers can be detrimental by promoting heart blocks. Pacemakers are helpful for the treatment of severe and symptomatic conduction disease. Various drugs, including colchicine, dimethyl sulfoxide, and prednisone, have anecdotal reports of improving amyloidosis, but these have not been validated with prospective randomized trials. Early studies with interferon-a and TNF antagonists have been encouraging. Dose-intensive intravenous melphalan followed by autologous growth factor–mobilized stem cells for primary amyloidosis may result in improvement, with reversal of the cardiomyopathy symptoms and reductions in ventricular wall thickness (164). Finally, cardiac transplantation is generally believed to be contraindicated in most cases of amyloidosis because of the propensity for recurrence of the disease in the transplanted heart and progression of systemic problems (165).

General System Diseases

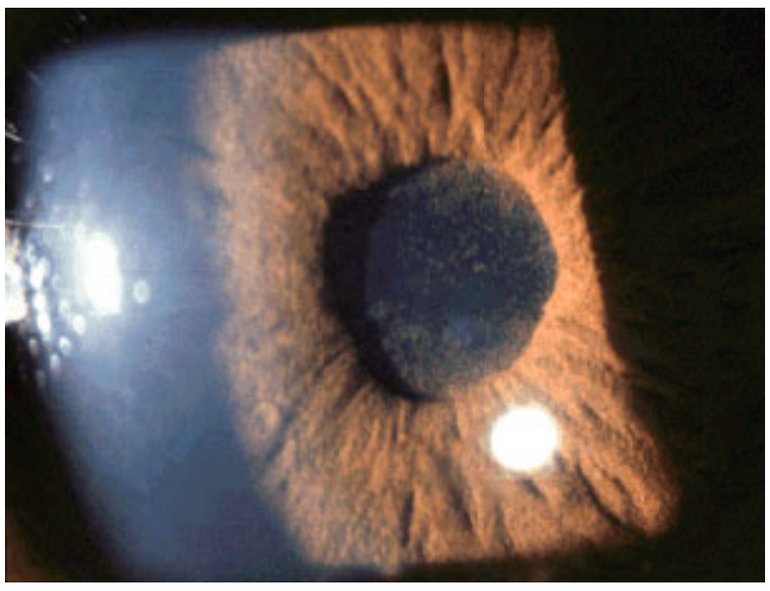
The connective tissue and collagen-vascular disorders, such as systemic lupus erythematosus, polyarteritis nodosa, and rheumatoid arthritis, are covered in Chapter 35E. A few entities warrant additional description.

Sarcoidosis

Sarcoidosis is a systemic disease that is typified by noncaseating granulomas infiltrating the lungs, skin, and reticuloendothelial system. Cardiac sarcoidosis results in a restrictive cardiomyopathy, although rarely it more closely resembles a DCM. Interstitial lymphocytic inflammation and fibrosis may be present, in addition to the myocardial granulomas, which early on cause diastolic dysfunction but preserve systolic function. Later on, further fibrosis and infiltration can lead to systolic impairment as well. Cardiac sarcoid is often present with systemic sarcoidosis but clinically remains silent approximately 95% of the time (166). The initial cardiac presentation may be with high-degree atrioventricular blocks, syncope, or sudden cardiac death. Gallium-67, thallium-201, and Tc-99m–pyrophosphate myocardial imaging have been useful in localizing segmental myocardial involvement (167,168). Endomyocardial sampling can be helpful in confirming the diagnosis; however, the false-negative rate is high, even when numerous pieces are obtained. One explanation for this is that the granulomas have a predilection for the basal and free wall portions of the myocardium, areas where sampling does not usually occur. The cardiac granulomas occasionally respond to treatment with steroids. Pacemakers may help with symptomatic conduction disturbances.



Endomyocardial biopsy demonstrating multiple granulomas in a case of sarcoidosis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Iridocyclitis in a patient with sarcoidosis. There is inflammation of the iris and there may be associated lacrimal gland enlargement (not shown here).

Scleroderma

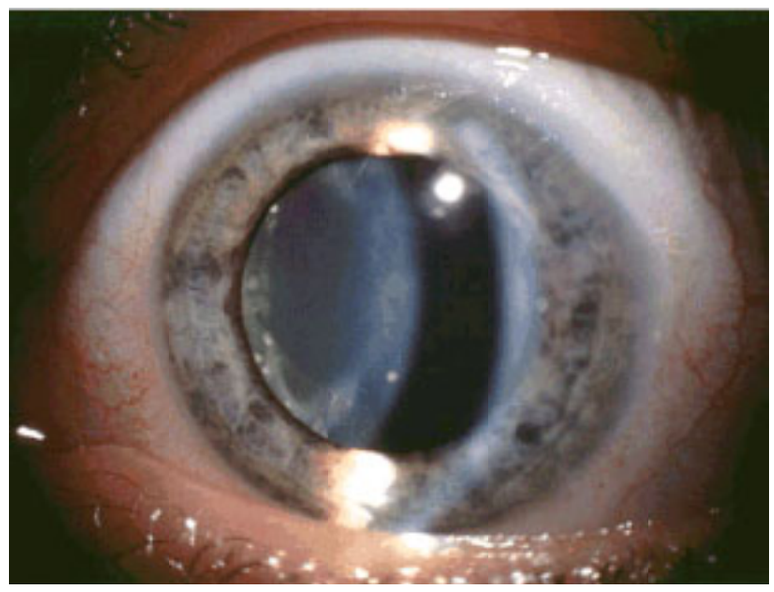
The cardiac manifestations of scleroderma include a slowly progressive fibrosis that involves the pericardium, myocardial interstitium, and conduction system. Small-vessel coronary artery disease may also occur. These patients can present with either dilated or restrictive cardiomyopathies.

Scleroderma. In scleroderma, there is swelling of the fingers and hands, later becoming firm, thick, and tight with flexion contractures. On the second panel, digital ulcers are shown (*arrows*). Cardiac manifestations include cardiac fibrosis, abnormality of the conduction system, and pericarditis.

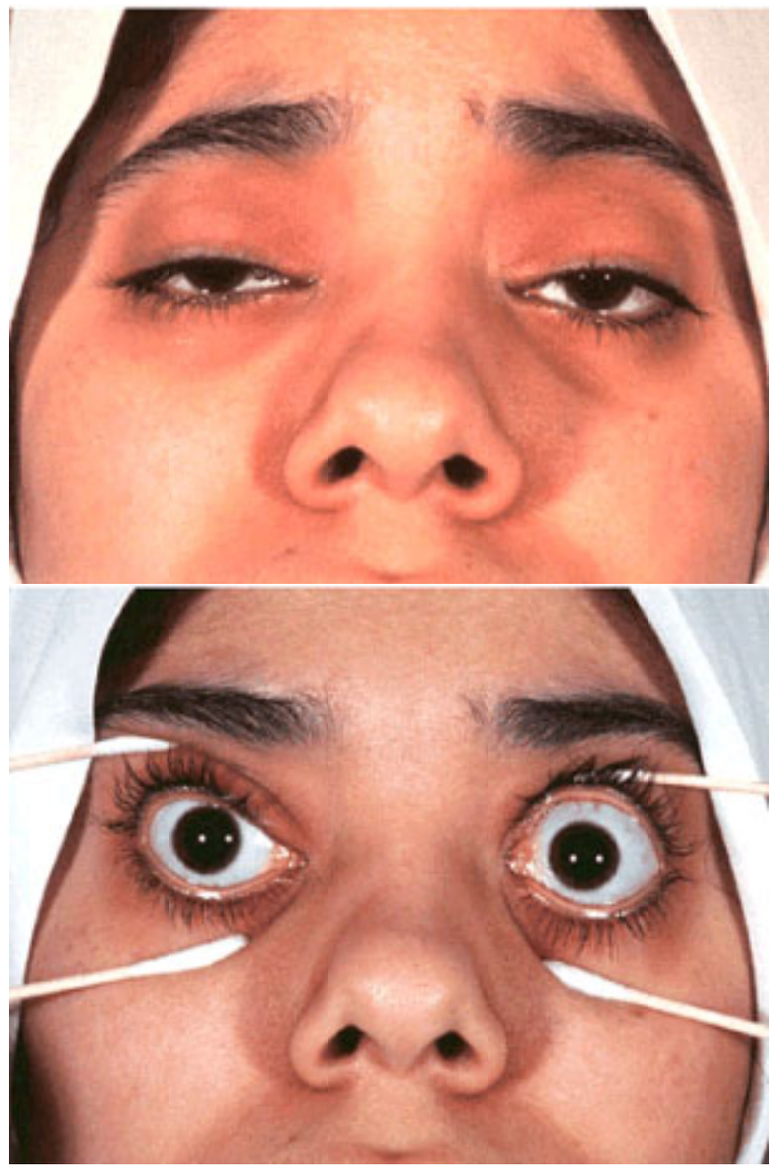
Scleroderma. Calcific deposit in subcutaneous tissue in the olecranon bursa (*arrows*).

Muscular Dystrophies

Many cases of DCM are familial (169). Pedigree analysis of families with suspected heredofamilial cardiomyopathy suggest a polygenic inheritance pattern, which in turn suggests that environmental factors such as infections or other toxins play a role in precipitating the detrimental remodeling process. A variety of neuromuscular diseases are associated with cardiomyopathy as part of their syndrome complex. Disorders of oxidative phosphorylation have been identified that are associated with these neuromuscular disorders (170), and linkage analysis has demonstrated that these difficulties are related to DNA mutations of mitochondrial protein function. Many of the muscular dystrophies and neuromuscular disorders are covered in Chapter 35D.



Premature cataract in myotonic muscular dystrophy.



Ocular findings in the Kearns-Sayre syndrome (A,B). There is ptosis and external ophthalmoplegia (not shown) secondary to muscular dystrophia.

Duchenne's Muscular Dystrophy

Duchenne's muscular dystrophy, also known as *pseudohypertrophic muscular dystrophy*, is an X-linked, proximal muscle dystrophic disease that is frequently associated with cardiac involvement manifesting as DCM (166). Indeed, death usually results either from respiratory infection due to cardiorespiratory failure or from the development of congestive heart failure with sudden cardiac death syndrome. Specific point mutations have been identified for this particular muscular dystrophy, and sometimes a DCM may be the only manifestation of the dystrophin gene mutation (171). Becker-type muscular dystrophy, similar to Duchenne's, is also X-linked recessive in inheritance. Its onset is later in life, but it is slowly progressive once it manifests signs and symptoms.

Erb's Limb-Girdle Dystrophy

Limb-girdle muscular dystrophy, Erb's disease, is an autosomal recessive condition, with DCM as a potential complicating factor (172). Like myotonic dystrophy it appears toward the middle years. It is a slowly progressive disorder that can affect either sex.

Myotonic Dystrophy

Myotonic dystrophy, also known as *Steinert's disease*, is an autosomal dominant disorder that demonstrates incomplete penetrance and variable expressiveness. The defect has been located to chromosome 19, with the production of a protein kinase that may be associated with receptor signal transduction. Myotonic dystrophy is the most common inherited dystrophy in adults. This slowly progressive and insidious dystrophic process frequently manifests symptoms between the ages of 20 and 50 years. Patients present with ptosis, cataracts, hypogonadism, and a mask-like expression from atrophy of the face and neck muscles. Cardiac involvement occurs in up to 90% of patients, and it typically presents as a DCM or with conduction disturbances. Replacement of the myocytes and Purkinje system with fibrofatty tissue occurs. Indeed, these patients are at extremely high risk of sudden cardiac death syndrome due to either a malignant ventricular arrhythmia or sudden-onset high-degree atrioventricular heart block. Cardiac transplantation is generally not an option because of the systemic nature of the disease. Often the respiratory muscles are involved, and general anesthesia should be avoided if at all possible.

Neuromuscular Disorders

X-Linked Cardioskeletal Myopathy

Barth's syndrome is an X-linked recessive condition characterized by cardiomyopathy, accompanied by a variety of neuromuscular abnormalities (proportionate short stature) and recurrent neutropenia (173). Some patients exhibit carnitine deficiency, although this is an inconsistent finding. Contrary to most cardiomyopathies, this syndrome tends to improve with age. It is proposed that the primary defect in this disorder rests in the mitochondrial electron transport chain (174).

Friedreich's Ataxia

Friedreich's ataxia is a spinocerebellar degenerative disorder that has an autosomal recessive form of inheritance, with the genetic defect located to chromosome 9. It is characterized by a broad-based gait, impaired vibration, position and joint sense, dysarthria, pes cavus, and incoordination. Childhood onset has a high likelihood of also developing diabetes, although the reasons for this are unclear (175). Interestingly, Friedreich's ataxia is commonly associated with HCM, either with concentric or

asymmetric left ventricular hypertrophy (176). More rarely, this neuromuscular syndrome can present as a DCM, with myocardial fibrosis, at times apparently transformed from an initially hypertrophic ventricle. Death from cardiac origin occurs in 5% of cases. Histologic findings include diffuse interstitial fibrosis, myocellular hypertrophy, and necrosis. Abnormalities of large and small coronary arteries can also occur. One theory of the etiology of the dysfunction suggests that myocardial calcium overload may have a role. Verapamil treatment, effective with other forms of HCM, has had no effect on patients with established hypertrophy (177).

Sensitivity and Toxic Reactions

A variety of toxins can cause myocyte injury, with subsequent dysfunction leading to actual cell death with fibrotic replacement or, simply, more transient contractile dysfunction. *e*Table 90.4.1 lists many cardiotoxic agents that have been reported to cause heart muscle disease. Discontinuing some of these drugs has led to substantive improvement in cardiac function on occasion. Specific examples of this include lithium, phenothiazines, and tricyclic antidepressants. One should always be particularly sensitive to the possibility that these drugs are producing cardiomyopathy in patients who receive them for psychiatric conditions. Some other specific toxins are discussed in the following sections.

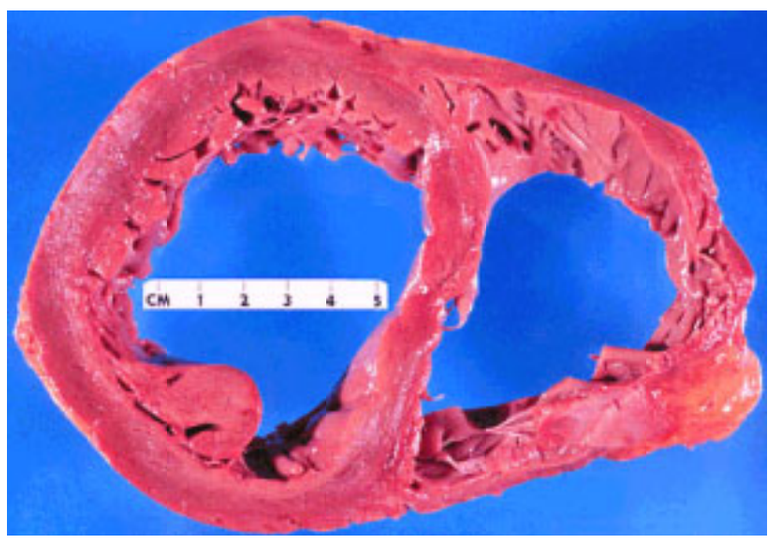
***e*TABLE 90.4.1** TOXINS KNOWN TO CAUSE CARDIOMYOPATHY

Alcohol
Antibiotics
Chloroquine
Didanosine
Sulfonamides
Zidovudine
Antipsychotics
Lithium
Phenothiazines
Carbon monoxide
Catecholamines
Chemotherapeutic agents
Bleomycin
Amsacrine
Busulfan
Cisplatin
Cytosine arabinoside
Doxorubicin
Etoposide
5-Fluorouracil
Methotrexate
Mitomycin
Mitoxantrone
Vincristine
Cobalt
Cocaine
Irradiation
Lead
Mercury

Alcoholic Cardiomyopathy

Background and Prevalence

An association between alcohol and cardiac dysfunction was first reported in Wood's treatise of 1855 (178). However, it was not until the 1950s that clinicians began to realize that alcohol and its major metabolite, acetaldehyde, could cause direct toxicity to the myocardium (179,180 and 181). Until that time, the cardiomyopathy had been presumed to be due solely to nutritional deficiencies. Currently, alcohol consumption is increasing, and, therefore, the incidence of alcohol-related cardiomyopathy is increasing as well. It is estimated that at least 15 million people in the United States alone are at risk for development of cardiac trouble from excessive alcohol use (182). Interestingly, it is a cardiomyopathy that is quite difficult to produce in animals, and substantive DCM develops in only a small proportion of ethanol drinkers who meet diagnostic criteria for alcoholism. On the other hand, 60% to 80% of patients with "idiopathic" dilated congestive cardiomyopathy report a history of substantive alcohol intake. Furthermore, individuals with DCM who continue to imbibe to excess have continued and progressive ventricular function deterioration. Currently, alcoholic cardiomyopathy accounts for approximately one-third of all nonischemic dilated cardiomyopathies (183). If alcohol consumption continues, 40% to 50% of patients will die within 3 to 6 years (184). The effects of alcohol on the cardiovascular system are fully explored in Chapter 9.



Dilated congestive cardiomyopathy. Both the left and right ventricles are significantly enlarged. In this example, the left ventricular wall thickness falls within normal limits.

Pathology

The pathologic findings of alcoholic cardiomyopathy are nonspecific and similar to, if not indistinguishable from, idiopathic DCM. The electron microscopic study of endomyocardial biopsies suggest that an accumulation of intracellular lipid droplets within the cardiac myocytes, too small to be seen with the light microscope, is a common finding in patients with alcoholic cardiomyopathy (185). Additionally, edema of the vascular wall and perivascular fibrosis of intramyocardial coronaries have been seen. Three basic mechanisms may explain the cardiac dysfunction that results from alcohol exposure. The first, and most important, is the direct toxicity that alcohol and its metabolites can have on the heart (186). Second, various additives in alcohol may produce dysfunction. The most widely recognized was the cobalt additive in beer in Quebec and Milwaukee that was used to stabilize the foam before its identification as a cardiac toxin. Finally, alcohol may lead to select deficiencies in magnesium, potassium, and thiamine, which may further exacerbate existing dysfunction. When the cardiovascular system is exposed to ethanol, there are acute and chronic changes, with the most significant being a depression in contractility.

Ethanol has been shown to depress the force of contraction acutely through inhibition of the calcium-myofilament interaction (187). Compensatory mechanisms such as vasodilation or sympathetic stimulation (catecholamines) may mask this direct depression. Experimentally, the electromechanical alteration can be reversed by increasing the amount of calcium available to the myofilament or by removing the ethanol. Because catecholamines can modulate intracellular calcium transport, this may explain why the acute negative inotropic effects of alcohol can be reversed by catecholamine administration. Alcohol and acetaldehyde have also been shown to interfere with a number of other membrane and cellular functions that involve mitochondrial respiration, myocardial lipid metabolism, and myocardial protein synthesis.

Clinical Profile and Management

The stereotyped profile of a patient with alcoholic cardiomyopathy is a man, aged 30 to 55, who has consumed whiskey, wine, or beer for more than 10 years. In reality, however, it has been virtually impossible to quantitate the amount of alcohol consumption that is required to produce cardiomyopathic effects. The diagnosis of alcoholic cardiomyopathy is likely best made in the setting of an idiopathic DCM accompanied by the traditional psychosocial characteristics of a chronic alcoholic (blackouts, marital discord, excessive work absenteeism, business failures, misdemeanor driving citations, and high blood-alcohol concentrations while appearing not to be intoxicated). Besides the more common presentation of congestive heart failure with right- and left-sided findings, atrial fibrillation and other supraventricular dysrhythmias may be the initial manifestation of the disorder. On physical examination, a narrow pulse pressure may be present, signifying the elevated diastolic pressure from excessive compensatory vasoconstriction. The ECG findings are nonspecific and numerous, including first-degree atrioventricular block, bundle branch block, left ventricular hypertrophy, repolarization abnormalities, and prolongation of the QT interval. Frequently, there will be rapid normalization of the ST-T changes after alcohol cessation. Complete abstinence may stop the progression or even allow for reversal of the failure (188,189) in early stages (usually in the first 2 to 6 months); however, severe heart failure may have little improvement. Continued consumption leads to further damage and fibrosis. It may also be prudent to give thiamine in case of underlying beriberi. The risk of anticoagulation is tremendously increased in alcoholic patients for several reasons and warrants use in only very select individuals and situations. For instance, the risk of bleeding in the alcoholic is elevated due to noncompliance, high likelihood of significant trauma, and overanticoagulation due to concomitant hepatic dysfunction.

Anthracycline-Induced Cardiomyopathy

Chronic anthracycline toxic cardiomyopathy is a dose-dependent DCM that is seen after therapy with agents such as doxorubicin (190). It is believed that anthracyclines cause myocyte cell death by increasing oxygen-derived free radical molecules, activating platelets, increasing histamine secretion, and producing C-13 hydroxymetabolites. This ultimately inhibits enzymatic activity within the sarcoplastic reticulum, mitochondria, and sarcolemma such that energy production by adenosine triphosphate cleavage is altered. Doxorubicin can cause the release of TNF-a and interleukin-2, which may create further toxicity. Myocyte destruction is associated with characteristic histopathologic findings, and this is one of the cardiomyopathies that is readily diagnosed by specific electron microscopic changes noted at the time of endomyocardial biopsy sample analysis (191) (Fig. 90.12 and Fig. 90.13). Evaluation of anthracycline cardiotoxicity requires semithin (1 to 2 μ) plastic sections with electron microscopy to ensure an adequate evaluation of the severity of cardiotoxicity. Therefore, it is essential that this information be conveyed to the pathologist before the endomyocardial biopsy specimens reach the histology laboratory. Doxorubicin has been associated with this cardiomyopathy, with cumulative doses under 400 mg per m^2 having a trivial incidence, but dose levels over 700 mg per m^2 have resulted in a nearly 20% incidence of cardiomyopathy. Why some patients who receive very low doses of doxorubicin still get cardiomyopathy and others who receive extraordinarily high doses do not remains unclear. Some of the risk factors identified for the development of toxicity include higher rates of administration and a history of previous cardiac irradiation. Patients can present either acutely or several years after exposure to this chemotherapeutic agent. Most patients who are exposed to this drug have a determination of the baseline ejection fraction with serial studies performed to follow ventricular performance indexes during treatment. Some data suggest that using continuous infusion of doxorubicin rather than bolus dosing, coadministering antioxidants or free radical scavengers, or treating patients with concomitant beta-adrenergic or calcium channel blocking drugs reduces the incidence of anthracycline cardiotoxicity. Unfortunately, this form of DCM does not usually improve with time.

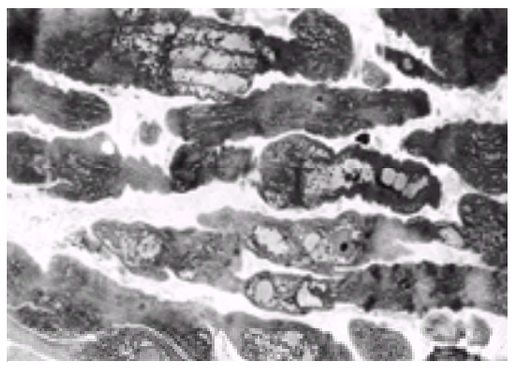


FIGURE 90.12 Severe doxorubicin cardiotoxicity. This light micrograph of a semithin plastic section illustrates the swollen sarcoplasmic reticulum, appearing as cytoplasmic vacuoles by light microscopy, and the loss of contractile elements.

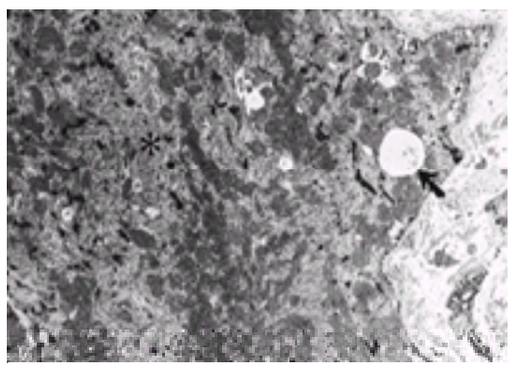
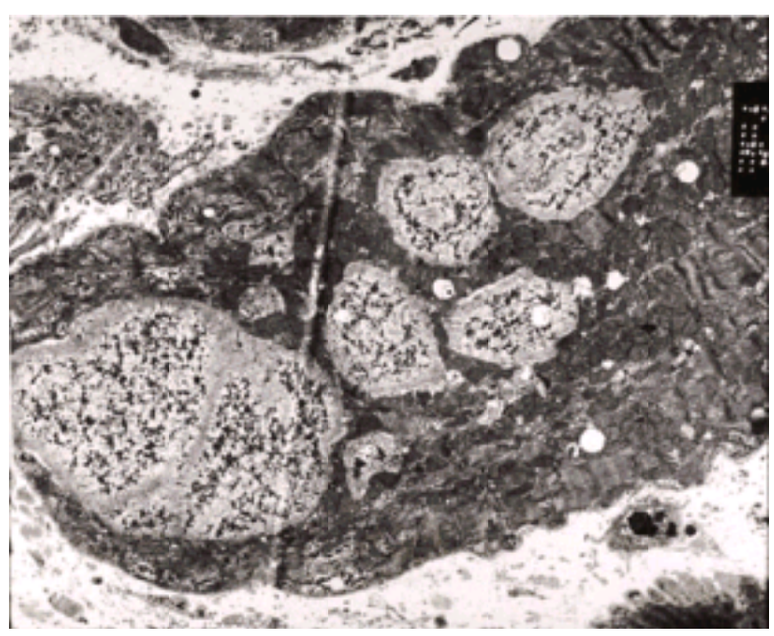
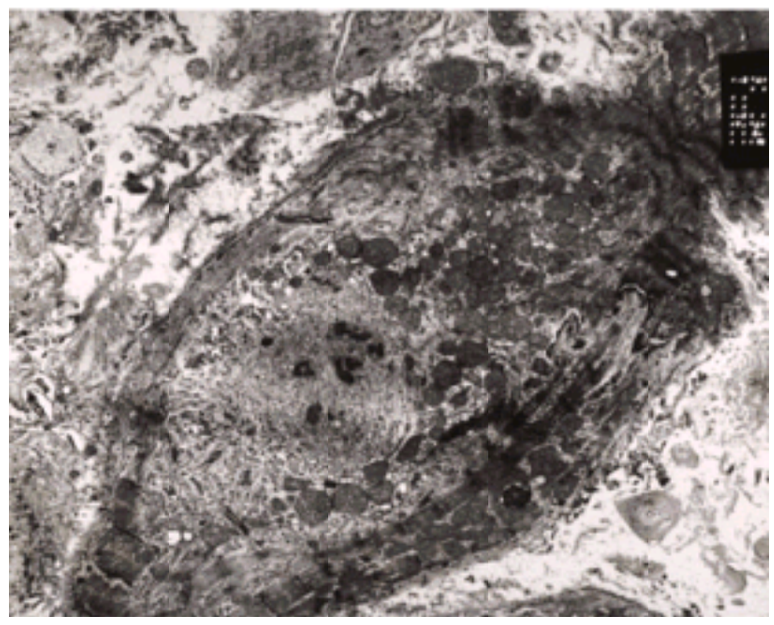


FIGURE 90.13 Doxorubicin cardiotoxicity. This electron micrograph illustrates the dilation of the sarcoplasmic reticulum (*arrow*) and the loss of contractile elements (*asterisk*), which are characteristic of doxorubicin cardiotoxicity.

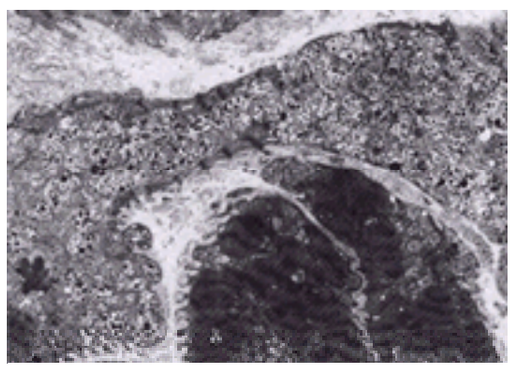




Electron microgram of 3+ doxorubicin (Adriamycin) toxicity (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Cocaine

Cocaine-related heart disease is increasing in frequency, with myocardial infarction sometimes noted after acute cocaine intoxication (192,193). An acute DCM has been described, as well as DCM occurring after long-term use of this drug (*e*Fig. 90.13.1). Cocaine produces central and peripheral nervous system adrenergic stimulation by inhibiting the presynaptic uptake of catecholamine. Therefore, this cardiomyopathy is likely due to excessive or excessively long myocyte exposure to adrenergic stimulation. In addition, cocaine can have direct effects on myocardial contractility and coronary resistance. Finally, vasospasm may cause chronic focal ischemia, leading to segmental wall motion abnormalities.



***e*FIGURE 90.13.1** Cocaine cardiomyopathy. This electron micrograph shows a myocyte in which the contractile elements have been virtually replaced by accumulations of large, dark-staining secondary lysosomes. The accumulation of these lysosomes seems to be characteristic of certain forms of drug toxicity. Compare this with chloroquine cardiomyopathy. This image could represent other drug toxicities as well, and the diagnosis rests on the history of cocaine abuse in this patient.

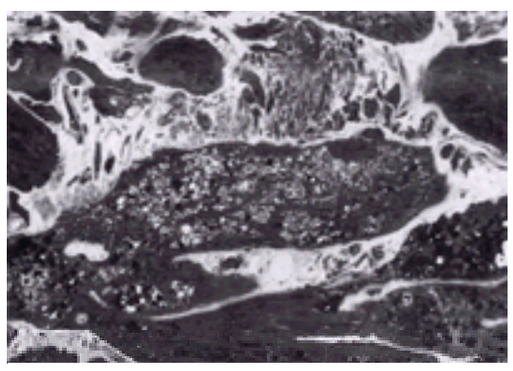
Irradiation

Radiation therapy, especially when used to treat Hodgkin's disease, may induce acute and chronic ventricular dysfunction and is an increasingly common entity as more and more patients are receiving radiation. Acutely, radiation may cause a pancarditis and arteritis, producing a transient decrease in ventricular function, which usually resolves over 48 hours (194). Chronically, radiation may induce several cardiac disorders, each of which can lead to ventricular failure (195,196). First, endocardial and myocardial fibrosis, sometimes massive in nature, result causing a restrictive cardiomyopathy (197). The fibrosis is usually more prominent in the right ventricle, because it is more anterior and therefore receives a higher dose of radiation. The fibrosis is typically very dense, nearly acellular, and primarily perivascular in location. Second, the vascular endothelium is particularly sensitive to the effects of radiation. Loss of endothelial alkaline phosphatase activity has been demonstrated and may be another factor in the pathogenesis of the myocardial dysfunction (198). Third, the clinical picture may be confused by concomitant radiation-induced constrictive pericarditis, which may also be present years after the therapy was administered. Next, radiation may also cause valvular fibrosis, resulting in either regurgitant or stenotic lesions (199). Finally, accelerated atherosclerosis usually manifests 6 to 12 years after exposure and may cause more of a DCM picture (200). If endomyocardial biopsy is performed to evaluate chemotherapeutic cardiac toxicity, radiation heart disease may complicate the interpretation. Further, radiation injury to the heart may be compounded by certain chemotherapeutic agents, especially the anthracyclines and cyclophosphamide (201). Additionally, some drugs, particularly doxorubicin, may "recall" the radiation effects even years after the administration of radiation. Risks for cardiac mortality from irradiation therapy increase with higher mediastinal doses, minimal protective cardiac blocking, and younger age at irradiation (202). No specific therapy is available.

Chloroquine Cardiomyopathy

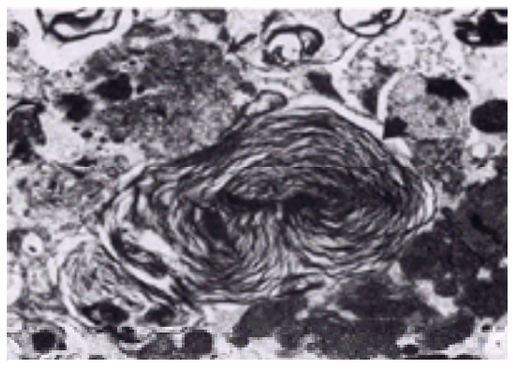
Chloroquine is a 4-aminoquinoline compound, which was widely used during World War II as an antimalarial drug. It was subsequently found to be useful in the treatment of a variety of collagen-vascular diseases, including rheumatoid arthritis, systemic lupus erythematosus, and certain dermatologic disorders. Hydroxychloroquine was found to be less toxic than chloroquine and equally effective for the treatment of rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine contains a single hydroxyl group at the end of the side chain—its only difference from chloroquine.

It has been known for some time that the long-term administration of chloroquine could result in a vacuolar myopathy of skeletal muscle. More recently, it has been recognized that hydroxychloroquine can produce a similar myopathy and that both drugs can also induce a severe toxic cardiomyopathy (203) (*e*Fig. 90.13.2 and *e*Fig. 90.13.3). Biventricular hypertrophy, congestive heart failure, and heart block have all been reported with chloroquine cardiomyopathy. Some, but not all, of the patients with chloroquine cardiomyopathy have a concomitant skeletal muscle myopathy. Biopsy findings in cardiac muscle are similar to those in skeletal muscle and are diagnostic of the disease (204). The light microscopic findings in semithin plastic sections are highly suggestive, with striking accumulation of large lysosomes and membrane profiles within the myocytes. The diagnostic changes of curvilinear bodies can only be visualized in biopsies that have been fixed according to an electron microscopy protocol and embedded in plastic. On cessation of the drug, patients begin a slow but progressive recovery over months from the skeletal and cardiac myopathies.

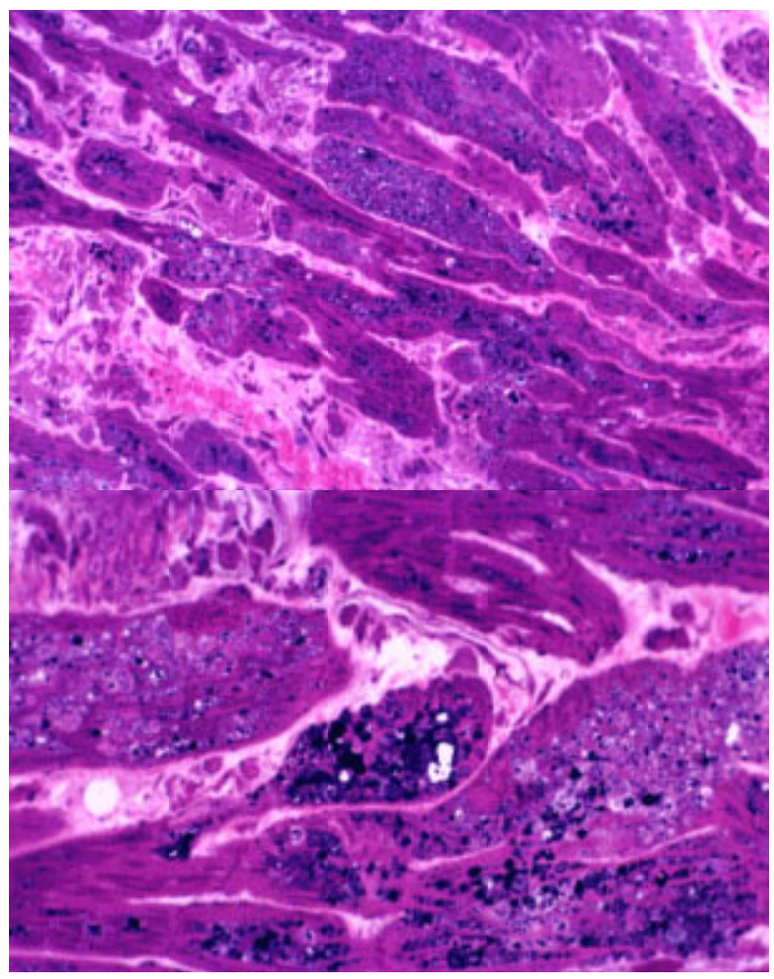


***e*FIGURE 90.13.2** Chloroquine cardiomyopathy. This is a high-magnification light micrograph of a semithin plastic section, which has been fixed with glutaraldehyde

and osmium tetroxide by an electron micrograph protocol. This preserves the secondary lysosomes that are filling the cytoplasm of the myocytes. The large, complex secondary lysosomes vary in size, shape, and staining intensity, from pale gray to black. By standard light microscopy, this would appear as a vacuolar myopathy, with the center of the myocytes appearing largely empty.



***e*FIGURE 90.13.3** Chloroquine cardiomyopathy. This higher-magnification electron micrograph reveals, side by side, a curvilinear body (*thin arrow*), characteristic of chloroquine cardiomyopathy, and a large myelin figure (*thick arrow*), a common feature of this disease but one that is not diagnostic. Chloroquine cardiomyopathy may be the prototype of the toxic myopathies. Note the resemblance to cocaine cardiomyopathy.



Chloroquine cardiomyopathy (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Peripartum Cardiomyopathy

Background and Prevalence

Peripartum DCM is defined as left ventricular systolic dysfunction without other apparent causes or underlying heart disease, occurring in the peripartum period. The onset must occur during the last month of pregnancy or within the first 5 months after delivery, although it is most common (75%) during the first 2 months postpartum (205). Because of differences in precisely defining this cardiomyopathy and aggressiveness in searching out other causes, the incidence has been reported to be anywhere between 1 in 1,300 to 1 in 15,000 pregnancies (206,207 and 208). Several risk factors have been identified, including twin pregnancy, age greater than 30, multiparity, a family history of peripartum cardiomyopathy, African descent, and prolonged therapy with tocolytic agents. The natural history differs from other forms of DCM. If recovery is going to occur, there is usually some sign of improvement within the first 6 weeks. Approximately 50% of patients spontaneously recover, usually in the first 6 months, with improvement after that time unlikely. The initial severity of heart failure or ventricular dysfunction is not predictive of long-term outcome (209). Death or deterioration to the point of requiring transplantation occurs in 25% to 50% of patients (210). Progressive congestive heart failure, dysrhythmias, and embolic events are the usual immediate causes of death. However, identifying patients who are likely to improve is not usually possible. A notable exception: In one small report, women who appeared to have peripartum cardiomyopathy associated with prolonged b-sympathomimetic tocolysis had full recovery (211).

Pathophysiology

The actual mechanism that causes ventricular dysfunction remains unknown, although several explanations have been offered. Numerous series have reported a higher incidence of myocarditis diagnosed by endomyocardial biopsy compared to idiopathic DCM (212,213,214 and 215). The cases of confirmed myocarditis may represent one of two distinct possibilities. It may be that these patients should not be labeled as having peripartum cardiomyopathy at all but rather an inflammatory cardiomyopathy. Indeed, in one study, the incidence of myocarditis by biopsy with “peripartum cardiomyopathy” did not differ from age- and sex-controlled matches that had idiopathic DCM (216). Alternatively, cases in which myocarditis is not confirmed by biopsy may represent a false-negative test. Diagnostic tissue may not have been obtained either because of insufficient tissue sampling or because the timing of the biopsy was not during the acute phase when inflammation was present. To some extent, perhaps all peripartum cardiomyopathies represent a pregnancy-induced, abnormal, immune-mediated response with myocarditis. It is known that T-cell suppressor activity is decreased during pregnancy. This may make patients more susceptible to certain viral infections such as Coxsackie virus, or perhaps maternal exposure to fetal or placental antigens may result in the production of antibodies that cross-react with the myocardium.

Clinical Profile and Management

The diagnosis of heart failure in the last month of pregnancy may be difficult to make, because many of the early signs and symptoms of ventricular dysfunction mimic those of normal pregnancy. These include fatigue, dyspnea on exertion, pretibial edema, and an increase in baseline heart rate. Orthopnea, chest discomfort, cough, gallops, and rales are also suggestive of heart failure. After delivery, these findings should quickly resolve, and failure to do so may indicate an underlying cardiomyopathy. Other diseases can have a presentation similar to that of heart failure and should therefore be considered in the differential diagnosis. Some of these disorders are listed in *e*Table 90.4.2. Echocardiography, the most helpful study, typically shows four-chamber enlargement, biventricular hypokinesia, and a small, hemodynamically insignificant pericardial effusion. Strong opposing views have been presented regarding the necessity of performing endomyocardial biopsies. Some have suggested that the biopsy may give prognostic information, because individuals with mild interstitial changes have a better prognosis than patients with dense fibrosis (217). This may encourage more aggressive treatment and earlier referral for transplantation. Biopsy may also identify active myocarditis, for which some have advocated immunosuppressive therapy. This has never been shown to be effective therapy, and it is our recommendation that biopsy not be performed unless the patient is enrolled in a specific trial addressing this issue or if one is concerned that a different diagnosis would have an impact on the treatment strategy.

***e*TABLE 90.4.2** DIFFERENTIAL DIAGNOSIS OF NONCARDIAC DISORDERS MIMICKING PERIPARTUM CARDIOMYOPATHY
Anemia (profound)
Amniotic fluid embolism
Hypertension
Pulmonary embolism
Sepsis
Thyrotoxicosis
Toxemia of pregnancy

The treatment of peripartum cardiomyopathy is different from that of the more traditional DCMs in several aspects. First, ACE inhibitors are contraindicated during pregnancy because of the risks of fetal anuria and death. They are also relatively contraindicated in nursing women. Hydralazine can be safely used in place of ACE inhibitors if afterload reduction is required. It should be recalled that during pregnancy the systemic vascular resistance is already low because of the placenta, and further afterload reduction may not be necessary or may not be well tolerated. Digoxin is a U.S. Food and Drug Administration (FDA) class C drug, and its risks and benefits should be considered. Digoxin can pass into the placenta and is secreted in breast milk. Similarly, diuretics are also FDA class C drugs. Frequently, strict sodium restriction diminishes fluid overload and can avert the need for diuretics. Beta-blockers may be helpful if the patient is not volume overloaded. Strong consideration for anticoagulation is important because of the marked increased incidence of thromboembolic events, which has been reported to be as high as 53% (218,219). As reviewed in Chapter 32, pregnancy is a hypercoagulable state, with demonstrated increases in coagulation factors II, VII, VIII, and X and plasma fibrinogen. Coagulation slowly returns to normal by approximately 6 weeks postpartum (220), and after this time anticoagulation becomes less critical. Warfarin is contraindicated (FDA class D) and should not be used prenatally because of severe teratogenic effects. Short-term unfractionated or low-molecular-weight heparin use is easily stopped just before delivery. If symptoms and ventricular function do not improve or if the clinical condition deteriorates, referral for cardiac transplantation should be contemplated. Some of these patients may even require a left ventricular assist device for stabilization while awaiting a suitable donor (221,222). A compatible donor may be more difficult to identify, because postpartum women tend to have higher panels of reactive antibodies from fetal antigen exposure. Some have advocated the use of immunosuppressants or intravenous immunoglobulin (223) for the treatment of peripartum cardiomyopathy based on small, retrospective, nonrandomized trials and observations. No large, prospective, randomized controlled trials have demonstrated a benefit for any of these therapies.

If full recovery of left ventricular function does not occur, the mother should be warned to avoid future pregnancies, because the rate of maternal and fetal morbidity and mortality is unacceptably high. The recommendation to the patient who is clinically completely recovered and contemplating another pregnancy is controversial. In general, the woman should be advised that recurrence is certainly possible, is usually more severe the second time, and is fatal approximately 10% of the time (224). One group has suggested performing dobutamine stress testing on apparently recovered hearts. Evidence of impaired contractile reserve may identify a subset of patients who have inducible abnormalities, which may become significant with the increased hemodynamic load of pregnancy (225). Finally, it has been demonstrated that there is increased activity of calcium-independent inducible nitric oxide synthetases (iNOS) in peripartum cardiomyopathy (226). The generation of nitric oxide by iNOS may be responsible for some of the dilation and impaired contractility of the heart. In the future, nitric oxide or iNOS antagonists may play a critical role in the early treatment of peripartum as well as some of the other dilated cardiomyopathies.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Even with the most recent revisions in the World Health Organization classification scheme of cardiomyopathy, it remains difficult to categorize certain disease states. At times there can be overlap because of changing ventricle characteristics. For example, hypertensive cardiomyopathy may initially best fit classification as an HCM, but when end-stage dilation occurs, it may be better defined as a DCM. Similarly, a patient may present with numerous risk factors that, alone or in combination, could be responsible for the ventricular dysfunction. Consider, for instance, how a gentleman who had diabetes, coronary artery disease, and hypertension would be classified if he were found to have an ejection fraction of 30% and a mildly dilated ventricle. Further complicating the issue would be a history of a flu-like illness with fever developing 2 months before presentation with a low ejection fraction.

When such a patient presents with signs and symptoms that are suggestive of ventricular dysfunction, one of the first steps in devising a management plan is obtaining an accurate diagnosis. With the desire to provide exemplary care, while at the same time maintaining cost effectiveness, the provider must choose tests carefully. One should not overlook the importance of a detailed history and physical examination, which can often provide insight into the disease process. Specifically important is looking for onset and duration history, a positive family history of heart failure, evidence of systemic diseases, and a history of other illnesses or toxin exposure. If a specific cardiomyopathy is suggested, the evaluation usually proceeds along a fairly demarcated path. However, when an illness appears obscure, idiopathic in origin, or due to a number of different possibilities, one must decide critically which of the multiple tests will lead one to a more definite diagnosis. A rational approach is imperative. Echocardiography is extremely helpful and can, for example, determine which chambers are involved (and to what degree), differentiate a focal from a global process, determine if the major dysfunction is systolic or diastolic, and detect valvular abnormalities. It is the single most important test to obtain, because it is necessary to determine a cardiomyopathy etiology that might respond to medical or surgical therapies or elimination of toxins. These patients with heart failure usually have a gratifying response, with, at times, dramatic reversal of their failure syndrome. Stopping ethanol consumption in the face of alcoholic cardiomyopathy, for example, can effect substantial improvement in ventricular function in more than 50% of patients. If a DCM is present, often a viral myocarditis is suspected. It is tempting to order large panels of acute and convalescent viral titers; however, the clinician should refrain from doing so because it is extremely expensive and the tests' conclusiveness is questionable. (Consider the current general public incidence of cytomegalovirus or Epstein-Barr virus seroconversion evidence.) Further, patient management would not generally change. The question of whether to perform right ventricular endomyocardial biopsy for a diagnosis frequently arises. Currently, if a specific disease process is strongly suggested and cannot be diagnosed by a less invasive manner, a biopsy is reasonable. *e*Table 90.4.3 lists some specific cardiomyopathies that can be diagnosed by biopsy. A second reason for biopsy is to monitor the effects of anthracycline cardiotoxicity, guiding further chemotherapy. Third, if a patient will be participating in a randomized trial to evaluate a specific therapeutic intervention, a biopsy might be useful to document entry criteria. The Intervention in Myocarditis and Acute Cardiomyopathy with Intravenous Immunoglobulin (IMAC) multicenter trial is such a study (see below). Fourth, in patients in whom it is unclear, after other noninvasive studies, that a restrictive process (as opposed to constrictive pathology) is responsible for the syndrome, the prognosis and treatment can be considerably different. Routine endomyocardial biopsy in patients with idiopathic DCM serves little purpose.

***e*TABLE 90.4.3** SPECIFIC CARDIOMYOPATHIES DETECTABLE BY BIOPSY
Amyloidosis
Carcinoid heart disease
Chagas' disease
Drug toxicity
Alcohol
Chloroquine
Cocaine
Doxorubicin
Endocardial fibroelastosis
Endocardial fibrosis
Fabry's disease
Gaucher's disease
Giant-cell myocarditis
Hemochromatosis
Hyperthyroidism
Löffler's endocarditis
Sarcoidosis
Wilson's disease

The treatment of cardiomyopathy is covered in Chapter 91 and Chapter 92; however, one area that remains unsettled regards diseases for which transplantation may not be indicated because of an increased likelihood of primary disease recurrence in the transplanted heart. Although early- and intermediate-term follow-up reports of patients with cardiac amyloid indicated that transplantation could be successfully performed (227,228 and 229), long-term results suggest a high incidence of failure due to recurrent amyloid (230,231). Transplantation in sarcoidosis, when other end-organ involvement is present, is also unwise. When the only manifestation of sarcoid is cardiac infiltration, transplantation has been performed and can be successful (232). It is, however, possible to have recurrence of noncaseating granulomas in the heart in as short a time as 6 months (233). Inflammatory cardiac conditions, such as lymphocytic myocarditis, may have an increased incidence of rejection after heart transplant as compared with control groups, and they may have a significantly higher mortality. Although this diagnosis does not represent an absolute contraindication to transplant, this therapy should be considered with caution.

Importantly, in a controlled trial of intravenous immunoglobulin in recent-onset DCM (234), 62 patients with recent onset (less than 6 months of symptoms) of DCM and left ventricular ejection fraction of less than 40% were randomized to receive 2 g per kg intravenous immunoglobulin or placebo. The mean age of the group was 43.0 ± 12.3 years, with 37 men and 25 women participating. All underwent an endomyocardial biopsy before randomization, which revealed cellular inflammation (lymphocytic myocarditis) in 16%. The primary outcome was change in left ventricular ejection fraction at 6 and 12 months after randomization, with the ejection fraction improving from 25% to 41% at 6 months (p <.001) and 42% (p <.001 vs. baseline) at 12 months. The increase was the same for patients who received intravenous

immunoglobulin and placebo. Overall, 56% of patients at 1 year had an increase in ejection fraction of greater than 10% from study entry, and 36% normalized their ejection fraction (greater than 50%). The transplant-free survival rate was 92% at 1 year and 88% at 2 years. Thus, the IMAC trial suggests that for patients with recent-onset DCM, intravenous immunoglobulin does not augment the improvement in left ventricular ejection fraction and, as an overall cohort, ejection fraction is likely to improve significantly during follow-up, with short-term prognosis remaining favorable in patients who meet this trial's entry criteria. The debate about treating these patients will likely continue.

Further highlighting the issues is the European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID) (235). Initial epidemiologic results have been published from this registry. By adding immunohistochemical parameters, the World Heart Federation Task Force for the Definition of Acute and Chronic Myocarditis expanded the light microscopy "Dallas" criteria of myocarditis, referred to in previous sections. Polymerase chain reaction molecular biologic techniques and *in situ* hybridization have improved our understanding of the underlying etiologic and pathophysiologic mechanisms in inflammatory heart disease. Because of this, patients in ESETCID are screened not only for infiltrating cells but for the presence of persisting viral genomes and, specifically, footprints of enterovirus, cytomegalovirus, and adenovirus. ESETCID investigated endomyocardial biopsies from 3,055 patients but could find an ongoing inflammatory process in the heart in only approximately 17%. Of these patients, only 182 showed a reduced ejection fraction below 45%, fulfilling the entrance criteria for the ESETCID trial. The observations suggest that in symptomatic patients, inflammatory heart disease muscle has to be considered regardless of left ventricular function and that endomyocardial biopsy can in fact be an important tool for diagnosis. However, virus could be detected in only approximately 12% of patients (enterovirus in 2%, cytomegalovirus in 5%, and adenovirus in 4%). This exercise was the first epidemiologic study to demonstrate that viral persistence may contribute to the pathogenesis of inflammatory heart muscle disease and that in chronic myocarditis, viral persistence occurs in a small percentage of patients compared to previous studies that were performed on highly selected individuals. The implications of this study are that, perhaps, more specific viral treatment therapeutics will be useful in the future to attenuate ventricular function deterioration.

THE FUTURE

Every day, new insight is gained in all areas of basic research addressing the pathophysiology of cardiomyopathy. Clarification and elucidation of genetic and molecular biodynamic mechanisms that are important to the development of cardiomyopathy are anticipated. The time when recognition of genetic markers that can identify susceptible or asymptomatic patients, thereby allowing preventive and early-treatment strategies to be instituted, is rapidly approaching. Clinical trials are under way that examine the role of various humors, including proinflammatory cytokines (TNF-a, interleukin-1, interleukin-6) and nitric oxide, in the cardiomyopathic process and may allow identification of new, specific treatment modalities such as anticytokine agents and antioxidants. Likewise, the use of cell transplants and gene-vector therapy is actively being pursued. Finally, we are entering a new era of examining mechanisms that mediate apoptosis. Inappropriate apoptosis has been associated with arrhythmogenic right ventricular cardiomyopathy, and already more than 30 inducers of programmed cell death have been discovered. Apoptosis in end-stage heart failure, for example, has been suggested to be the result of TNF-a exposure, amyloidosis, incessant tachycardia syndromes, pressure overload states, ischemia-reperfusion injuries, hypertension, situations with increased mechanical stretch, and chemotherapeutic and radiation injuries (236,237,238,239,240,241,242 and 243).

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ACUTE HEART FAILURE MANAGEMENT

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Acute heart failure is a complex syndrome that is often a direct result of myocardial systolic dysfunction caused by underlying ischemia or infarction. Although atherosclerotic heart disease is the most common cause of acute heart failure in Western societies, a broad spectrum of other potential causes exists, including such diverse conditions as acute valvular abnormalities, pericardial disease, acute myocarditis, and pulmonary embolism. The management of acute heart failure requires rapid identification of the underlying mechanism, with specific treatment directed at reversing the associated abnormal pathophysiologic state. The support of patients while the diagnostic evaluation is pursued can range from therapy with intravenous nitrates and diuretics to full pharmacologic support with combinations of inotropic, vasodilator, and vasopressor agents. In complicated situations, hemodynamic monitoring is essential. In circumstances in which a reparable lesion has been identified or in which cardiac transplantation is considered an option, mechanical circulatory support may be required until definitive treatment can be instituted. Because of the complexity and diverse nature of the acute heart failure syndrome, treatment must be individualized.

The ultimate success of acute heart failure management depends heavily on the rapid institution of effective pharmacologic support to relieve symptoms and reverse hemodynamic derangement with simultaneous pursuit of definitive diagnostic studies. The inability to identify or correct an underlying lesion or condition is associated with significant short-term mortality.

INTRODUCTION

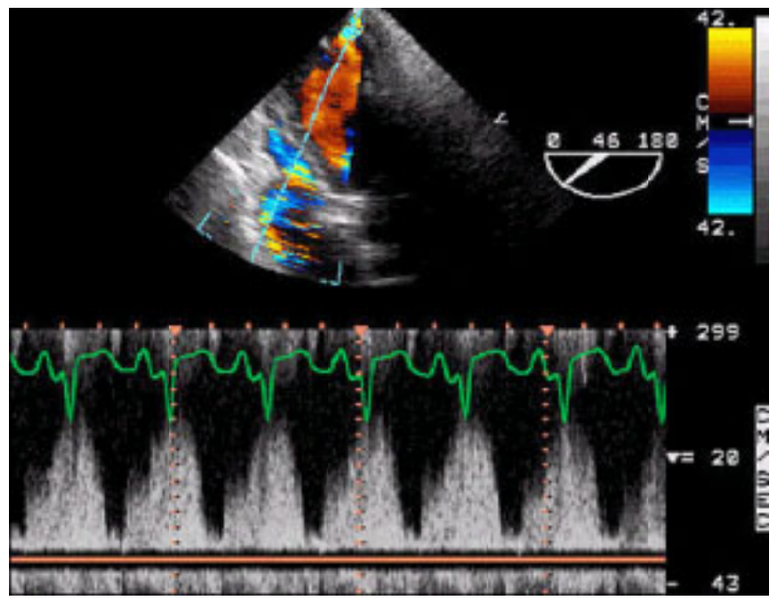
The syndrome of acute heart failure represents a true medical emergency that warrants an expedient diagnostic and therapeutic approach by the clinician. If appropriate treatment is not instituted within a reasonable period of time, irreversible cardiac decompensation may ensue, leading to a progressive syndrome of shock, multiorgan failure, and death. The complexity of acute heart failure and the diversity of its potential causes make a precise definition difficult. But in clinical practice, it is generally recognized when symptoms develop within hours to days in patients without a history of cardiac decompensation (1). A history of previous treatment for heart disease may be elicited, however, because many patients will have experienced symptoms (i.e., angina, exertional dyspnea) related to myocardial ischemia. In fact, atherosclerotic heart disease and the complications of myocardial ischemia and infarction are the most common causes of acute heart failure in Western societies. A multitude of other potential causes must also be considered, however, including acute valvular dysfunction, pericardial disease, acute myocarditis with left ventricular dysfunction, uncontrolled severe hypertension, and pulmonary embolism (Table 91.1). Many of the conditions resulting in acute heart failure may be definitively treated, which results in a favorable impact on the patient's short- and long-term course. Although the majority of patients presenting with acute heart failure suffer from some degree of myocardial systolic dysfunction, diastolic heart failure with preserved systolic function may also occur in those with underlying restrictive or hypertrophic myocardial diseases. When acute pulmonary edema is the presenting problem, consideration must also be given to possible noncardiac causes. A brief history and directed physical examination, electrocardiogram, and possibly echocardiography usually suffice to differentiate cardiogenic from noncardiogenic pulmonary edema.

Myocardial ischemia or infarction
Complications of myocardial infarction
Acute mitral regurgitation (papillary muscle rupture)
Ventricular septal rupture
Cardiac free wall rupture and pericardial tamponade
Acute valvular catastrophe (mitral or aortic)
Severe, poorly controlled hypertension
Myocarditis
Sustained cardiac arrhythmias
Acute pulmonary embolism
Decompensation of chronic heart failure or cardiomyopathy
Acute aortic dissection with myocardial ischemia or infarction

TABLE 91.1 MAJOR CAUSES OF ACUTE HEART FAILURE

Guidelines published by a task force of the American College of Cardiology and American Heart Association have categorized presentations of acute heart failure into three major clinical groups: acute cardiogenic pulmonary edema, cardiogenic shock, and acute decompensation of chronic left heart failure (2). Treatment strategies differ for these groups, but in general, rapid evaluation, diagnosis, and therapy are imperative. The 1-year mortality rate for patients presenting with acute pulmonary edema may exceed 50% when an underlying lesion or condition is not defined and treated (3). In certain life-threatening conditions, such as acute ischemic myocardial injury or complications thereof (i.e., acute valvular regurgitation, ventricular septal defect, cardiac tamponade), immediate evaluation and specific, directed therapy are indicated for stabilization and treatment of the acute heart failure syndrome. In these emergency situations, definitive therapy should not be delayed by prolonged efforts to achieve a stabler clinical situation. Without correction of the underlying lesion, such efforts are often unsuccessful and commonly result in further clinical deterioration with the development of irreversible myocardial dysfunction. When the disorder precipitating acute heart failure does not appear to be one requiring urgent therapy, definitive diagnostic studies and consideration for specific forms of therapy can be delayed until clinical and hemodynamic stabilization have been achieved. In patients with decompensated chronic heart failure, an urgent diagnostic evaluation is often unnecessary because the underlying cause of myocardial dysfunction is

usually known.



Doppler recording of flow through an ischemic ventricular septal defect before surgical repair.

This chapter focuses on patients presenting with predominantly acute systolic heart failure. Because management strategies differ for different clinical groups across the spectrum of acute heart failure (e.g., acute myocardial infarction is managed differently from acute valvular insufficiency or right ventricular infarction), specific therapeutic principles for the treatment of patients presenting within the major clinical subsets of acute cardiogenic pulmonary edema, cardiogenic shock, and decompensated chronic heart failure are addressed. Individualization of the therapeutic strategy is always necessary. The standard intravenous pharmacologic agents used to manage acute heart failure are discussed in detail, as are some of the more promising investigational drugs currently being evaluated in clinical trials. For those situations in which pharmacologic stabilization of the patient is not achieved, selection criteria for mechanical support are reviewed. The initial assessment of the patient with acute heart failure is reviewed with an emphasis toward disease-specific treatment. One must recognize that the evaluation process (determination of cause) and the initial management and stabilization of the patient occur nearly simultaneously.

HISTORICAL PERSPECTIVE

Significant advances in the pharmacologic support of acute heart failure have been made over the past four decades. In the 1960s, only digitalis and diuretics were available for heart failure management, and furosemide was the mainstay of drug therapy for acute heart failure. The intravenous inotropic, vasopressor, and vasodilator therapies introduced in the 1970s proved to be effective in the stabilization of many patients presenting with acute cardiac decompensation. The development of dobutamine by Tuttle and Mills was an important step in the refinement of inotropic support for acute heart failure and cardiogenic shock, and this drug has largely replaced agents with unacceptable toxicity such as isoproterenol and epinephrine (4). The use of hemodynamic monitoring in intensive care units now allows for the appropriate titration of inotropic and vasodilator medications and provides a means for more effective assessment and correction of hemodynamic abnormalities. This methodology also provides a means for investigating the effectiveness of new and perhaps novel experimental agents that may be beneficial for treating acute heart failure. In those situations in which significant hemodynamic instability unresponsive to pharmacologic intervention is present, circulatory support with intraaortic balloon counterpulsation or extracorporeal membrane oxygenation serves as a temporary measure to allow for completion of the diagnostic work-up and institution of the appropriate therapeutic intervention (5). More recently, the development of ventricular assist devices has provided a means for prolonged support until definitive treatment, such as cardiac transplantation, can be offered (see Chapter 95).

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF ACUTE HEART FAILURE

Acute left ventricular failure usually occurs as a result or complication of coronary artery disease, valvular disease, or, less commonly, primary myocardial disease such as myocarditis. An acute exacerbation of chronic heart failure or cardiomyopathy may also manifest as pulmonary edema and cardiogenic shock. The majority of patients presenting with acute heart failure has suffered significant injury to or ischemia of the myocardium, producing a substantial degree of regional and global myocardial systolic and diastolic dysfunction. This leads to a progressive deterioration in central hemodynamics that usually results in elevated left ventricular filling pressures and a variable reduction in stroke volume and cardiac output with subsequent circulatory failure. Often concomitant valvular dysfunction secondary to increased ventricular volumes and annular distention is found, which further exacerbates the hemodynamic abnormality (6). If immediate intervention with the goal of stabilizing the patient and definitively treating the underlying condition is not pursued, progressive left ventricular dysfunction and hemodynamic compromise may ensue.

Acute Cardiogenic Pulmonary Edema

The accumulation of extravascular fluid in the pulmonary interstitium or alveolar space resulting in pulmonary edema is caused by an imbalance in the equilibrium that normally exists between the opposing hydrostatic and oncotic forces of the pulmonary capillaries and the pulmonary interstitium (Starling forces). Under normal conditions, the balance of forces favors a continuous transudation of fluid from the capillaries to the interstitial space of approximately 500 mL per day, which is removed by the lymphatics (7). If the pulmonary capillary wedge pressure (PCWP) acutely exceeds 20 to 25 mm Hg, as may occur in acute left ventricular dysfunction, the increase in capillary hydrostatic pressure results in increased filtration of fluid and protein across the vascular endothelium, which leads to interstitial or alveolar pulmonary edema (7). As a result, the patient experiences breathlessness and increased work of breathing due to a drop in pulmonary compliance and hypoxia.

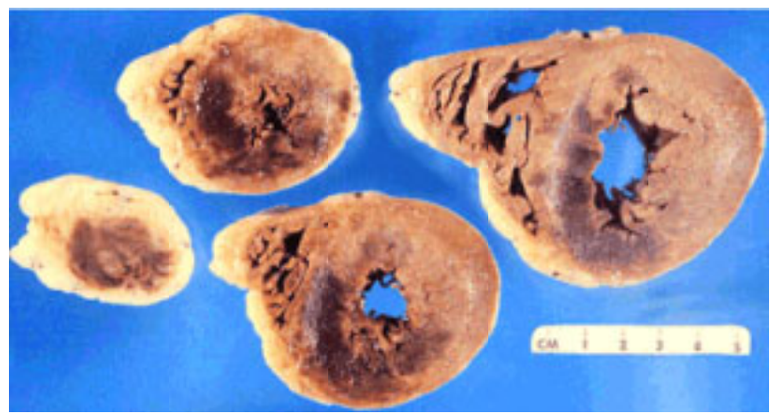
Few conditions in clinical practice generate the degree of alarm and sense of urgency for both the patient and clinician that acute pulmonary edema does. Patients present in acute distress with extreme breathlessness and increased respiratory effort. They may have a cough with hemoptysis and are often diaphoretic and demonstrate a variable reduction in peripheral perfusion manifest as cool extremities and poor capillary refill (8). This results not only from a possible diminution in cardiac output but also from a markedly elevated sympathetic tone and redistribution of blood flow away from the skin. Unlike in the patient with chronic heart failure and cardiomyopathy, the pulmonary examination usually demonstrates course rales and diffuse rhonchi. Conducting the cardiac examination in this setting may be difficult because of patient distress, but specific findings (or the absence thereof) can provide important clues to the cause of heart failure.

Pulmonary edema may occur in the setting of high, normal, or low cardiac output. Treatment initially is directed toward “unloading” the ventricle with the goal of reducing pulmonary capillary hydrostatic pressure, pulmonary edema, and dyspnea. In treating this condition, one should be aware that correction of the hemodynamic abnormality precedes the clearance of excess pulmonary fluid as assessed by either physical examination or chest radiography (7,9,10). Therefore, the detection of pulmonary rales on physical examination would not necessarily warrant further diuretic administration if the hemodynamic abnormality has been reversed. Failure to recognize this phase lag could result in inappropriate diuretic use, intravascular volume depletion, and hypotension in the patient with acute myocardial infarction.

When evaluating acute pulmonary edema, one must always be aware of noncardiac causes that are seen in the clinical setting of normal to low PCWP and most often result from injury to the alveolar-capillary membrane due to any of a number of reasons (7,11). Edema formation by this mechanism often occurs more rapidly and to a greater degree than cardiogenic pulmonary edema.

Cardiogenic Shock

The often catastrophic condition of cardiogenic shock (see Chapter 19) is usually the result of myocardial damage resulting either from a single acute event or as the culmination of multiple events resulting in extensive (greater than 40%) ischemic myocardial injury. Cardiogenic shock most commonly occurs as a consequence of left ventricular dysfunction resulting from coronary occlusion. Data from the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?) Trial Registry identified predominant left ventricular failure as the cause of shock in 78.5% of all cases (12). Complications of myocardial infarction, including severe mitral regurgitation and ventricular septal rupture, were identified as the primary cause of shock in 6.9% and 3.9% of cases, respectively (12).



Massive acute transmural anteroseptal myocardial infarction. Cross sections from multiple levels are shown in this chemical fixed preparation. The dark brown area represents the zone of infarction. In this example, approximately 50% of the myocardium is involved.

Several additional cardiovascular causes may also produce cardiogenic shock, including acute myocarditis, primary valvular catastrophe, and acute decompensation of end-stage cardiomyopathy (13). The shock syndrome may also result from predominant right ventricular infarction, which generally has a better prognosis than shock due to left ventricular failure and is treated primarily with volume resuscitation and inotropic support.

Right ventricular infarction. ST-segment elevation in leads V_{4R} and V_{5R} reveals right ventricular involvement complicating the inferior infarct.

The incidence of cardiogenic shock in patients suffering acute myocardial infarction is approximately 7.5% (14,15). The cardiogenic shock syndrome is often accompanied by severe hypotension with diminished pulse pressure and tachycardia, low cardiac output, and signs and symptoms of reduced tissue and organ perfusion, including renal dysfunction, cool and clammy extremities, lethargy and confusion due to cerebral hypoperfusion, and metabolic acidosis resulting from elevated blood lactate levels. In the absence of prompt reperfusion and pharmacologic or mechanical support to correct the profound hemodynamic derangement associated with shock, progressive deterioration will occur, resulting in a high probability of continued cardiac dysfunction and circulatory failure (Fig. 91.1) (13). Although significant progress has been made in the short-term support of the cardiovascular system in shock, if the ischemic myocardium is not reperfused, the mortality rate remains high and in excess of 70% (14,16). In the SHOCK Trial Registry, in-hospital mortality was approximately 60% in patients with shock after myocardial infarction (12).

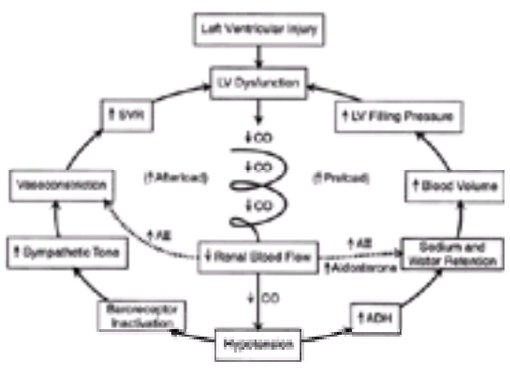


FIGURE 91.1 Depicted are the factors in cardiogenic shock perpetuating continued left ventricular (LV) dysfunction and progressive deterioration in cardiac output (CO). As CO falls, renal blood flow is reduced, which thus activates the renin-angiotensin-aldosterone system. Angiotensin II (AII) directly results in vasoconstriction and indirectly increases blood volume by enhancing aldosterone release. Hypotension resulting from a further fall in CO activates the central nervous system release of antidiuretic hormone (ADH). Inactivation of baroreceptors enhances sympathetic tone and vasoconstriction. As CO, renal blood flow, and hypotension remain reduced, preload and afterload continue to increase, which leads to further LV dysfunction. ↑, increased; ↓, decreased; SVR, systemic vascular resistance.

The neurohormonal compensatory mechanisms activated to acutely support the cardiovascular system in shock are similar to those activated in chronic heart failure (see Chapter 88). As shown in Figure 91.1, a dramatic and often acute reduction in cardiac output leads to the perception that intravascular volume is reduced. Baroreceptor inactivation results in increased sympathetic tone with consequent vasoconstriction and increased heart rate and myocardial contractility. Diminished renal perfusion causes activation of the renin-angiotensin-aldosterone axis, which causes further vasoconstriction (mediated by angiotensin II) and sodium and water reabsorption mediated by elevated aldosterone levels. Hypotension induces the central release of antidiuretic hormone, which serves to further increase renal water resorption and intravascular volume. Peripheral autoregulation and local production of vasoactive metabolites cause redistribution of blood flow away from skin, intestines, and skeletal muscle in favor of the brain, heart, and kidneys (13). These compensatory mechanisms may support the cardiovascular system for a brief period of time, but without appropriate intervention, they are soon overwhelmed, which results in continued hypoperfusion and myocardial dysfunction. Pharmacologic intervention is directed toward supporting the blood pressure and systemic perfusion with inotropic and possibly vasopressor therapy. If an adequate systemic blood pressure can be sustained, vasodilators may also be considered in an attempt to lower filling pressures and decrease pulmonary congestion and valvular regurgitation. Mechanical support will likely be necessary to allow for definitive diagnostic studies and therapeutic interventions.

Acute Decompensation of Chronic Heart Failure

Acute decompensation and clinical deterioration in a patient with previously documented chronic heart failure represent a different pathophysiologic state than the acute heart failure syndrome in patients without prior left ventricular dysfunction. These patients have a marked reduction in left ventricular systolic function at baseline due to a previous substantial injury to the myocardium. In approximately 50% of cases, the underlying disease is ischemic in etiology. In the remainder, a variety of causes may be identified, such as valvular disease or long-standing hypertension. The majority of cases of nonischemic chronic heart failure, however, is idiopathic (17). The typical patient with chronic heart failure is likely receiving some rational combination of oral therapy (angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, vasodilators, diuretics, digoxin) in an attempt to maintain stability and adequate functional capacity. Despite this treatment, however, these patients generally have mild to moderate symptoms of heart failure and exhibit some degree of total volume overload even in the compensated state. Left ventricular wall stress, because of left ventricular dilatation, is usually elevated, and compensatory neurohormonal mechanisms are activated (see Chapter 88). When acute decompensation occurs, these baseline abnormalities become further deranged. This is in contrast to the patient without significant myocardial dysfunction who suffers an acute insult to the myocardium leading to acute heart failure. Before the precipitating event, these patients generally have normal heart size and total body volume and do not exhibit baseline neurohormonal perturbation.

Table 91.2 outlines some of the important clinical and pathophysiologic characteristics of acute and chronic heart failure (18). Patients with decompensated chronic heart failure usually present with low output and congestive symptoms. They may describe worsening exertional dyspnea or dyspnea at rest, orthopnea, paroxysmal

nocturnal dyspnea, and fatigue. Findings of the physical examination often reflect volume overload with peripheral edema and jugular venous distention. Pulmonary rales may be present but are certainly not as impressive as in the patient with acute myocardial injury and pulmonary edema. In fact, pulmonary findings may be relatively unremarkable in cases of decompensated chronic heart failure even when cardiac filling pressure is markedly elevated. A gallop rhythm and murmur of mitral regurgitation are typically audible, and the cardiac impulse is enlarged, sustained, and laterally displaced (8). Again, this is in contrast to the findings in acute pulmonary edema, in which cardiac size is usually normal and mitral regurgitation is less audible due to rapid equilibration of pressures between the left ventricle and normal left atrium.

Feature	Acute heart failure	Decompensated chronic heart failure	Stable chronic heart failure
Symptom severity	Marked	Marked	Mild to moderate
Pulmonary edema	Frequent	Frequent	Rare
Peripheral edema	Rare	Frequent	Frequent
Weight gain	None to mild	Marked	Frequent
Total body volume	No change or mildly increased	Markedly increased	Increased
Cardiomegaly	Uncommon	Usual	Common
Left ventricular systolic function	Hypo-, normo-, or hypercontractile	Reduced	Markedly reduced
Wall stress	Elevated	Markedly elevated	Elevated
Activation of sympathetic nervous system	Marked	Marked	Mild to marked
Activation of RAAS	Acutely abnormal	Marked	Mild to marked
Acute ischemia	Common	Occasional	Rare
Hypertensive crisis	Common	Occasional	Rare
Reparable, remediable causative lesions[a]	Common	Occasional	Occasional

RAAS, renin-angiotensin-aldosterone system.
[a]Coronary thrombosis, acute mitral regurgitation, etc.
From Leier CV. Unstable heart failure. In: Colucci WS, ed. Heart failure: cardiac function and dysfunction. St. Louis: Mosby, [illegible], and Braunwald E, ed. Atlas of heart disease, vol 4, with permission.

TABLE 91.2 COMPARISON OF ACUTE AND CHRONIC HEART FAILURE

A broad range of variability exists, however, and specific physical findings are often dependent on the underlying lesion and duration of cardiac dysfunction. The factors leading to acute decompensation in chronic heart failure may be obvious or subtle and include such diverse conditions as myocardial ischemia, hypertension, new-onset atrial fibrillation, poorly controlled diabetes, hyper-or hypothyroidism, dietary sodium indiscretion, and medication noncompliance. In many cases, however, the cause is not as obvious clinically as are the events causing acute cardiogenic pulmonary edema (see Chapter 92). In both conditions, a concerted effort must be made to identify the precipitating factor, but a reparable lesion amenable to definitive treatment is less likely to be discovered in those with decompensated chronic heart failure.

PHARMACOTHERAPEUTICS OF ACUTE HEART FAILURE

Goal of Acute Pharmacologic Therapy

The objectives of the pharmacologic management of acute heart failure are to relieve disabling symptoms and discomfort rapidly, to reverse hemodynamic derangement, to preserve myocardial blood flow and energetics, and to stabilize the patient while further definitive diagnostic evaluation and therapy are pursued. Acute intravenous therapy is directed toward improving overall ventricular performance by favorably affecting the major determinants of ventricular function, including ventricular preload, afterload, and myocardial contractility. Acute intravenous pharmacologic support merely serves as a bridge to a more definitive treatment (i.e., myocardial revascularization, valve replacement) in most situations of acute heart failure and therefore should be viewed as a temporary means of support. The medications commonly used to stabilize the patient presenting with acute heart failure are usually administered intravenously, exhibit pharmacokinetic properties that allow for rapid titration to hemodynamic effect, and have a short plasma half-life so that any untoward effect can be quickly terminated. The medications commonly used to initially support the patient with acute heart failure are discussed in detail.

Acute Vasodilator Therapy

Nitroglycerin

Nitroglycerin is often effective in the early management of acute heart failure. The major hemodynamic effect of nitrates is to evoke a reduction in ventricular filling pressure and volume by increasing venous capacitance through venodilation (19,20,21,22,23,24,25,26,27,28 and 29). This shifts central blood volume to the venous capacitance vessels, which causes a decrease in pulmonary congestion and often a dramatic improvement in the symptoms of breathlessness associated with acute heart failure and elevated ventricular filling pressures. This vasodilating action is mediated through relaxation of vascular smooth muscle resulting primarily from a nitrate-induced production of *S*-nitrosothiols, which cause an increase in intracellular cyclic guanosine monophosphate (30,31). Nitrates may also elicit vasodilation by other mechanisms, including stimulation of the endothelial production and release of prostacyclin or prostaglandin E (32,33 and 34). Although these agents are predominantly considered for venodilation, higher doses of nitrates produce arterial dilatation and therefore reduce systemic vascular resistance (SVR) and ventricular impedance (35).

This effect is variable, however, and is not nearly comparable to the potent afterload-reducing properties of sodium nitroprusside (see the following section, Nitroprusside). For this reason, nitrates are less effective in reducing and treating acute mitral or aortic regurgitation, which require aggressive afterload reduction to augment forward stroke volume. If nitrates are to improve valvular regurgitant volume, they must be given in dosages that not only lower ventricular filling pressure but, most important, also reduce SVR (36).

Nitrate therapy may also favorably affect myocardial blood flow and energetics. Although not studied extensively in acute heart failure, this benefit is secondary to significant reductions in ventricular filling pressures and volume that reduce wall stress, a major determinant of myocardial oxygen consumption (MVO_2). Nitrates reduce coronary vascular resistance and lengthen diastolic perfusion time (by lowering heart rate in heart failure), and thus favorably affect subendocardial perfusion and oxygenation (37,38). An improvement in diastolic function has also been described, particularly in patients with ischemic heart disease and subendocardial ischemia (38,39,40 and 41).

Nitrates are effective therapy in the urgent treatment of acute heart failure, acute cardiogenic pulmonary edema, and acute decompensation of chronic heart failure (21,42,43,44,45,46 and 47). Nitroglycerin therapy can generally be instituted rapidly when it is evident that pulmonary congestion is present and therefore preload reduction is desired. Intravenous nitroglycerin is the preparation most commonly used. However, sublingual tablets and lingual-buccal spray may occasionally be used until an intravenous preparation is available to be infused (48,49). Sublingual nitrates have rapid onset of action (3 to 6 minutes) and can be administered in 0.4- to 0.8-mg doses every 5 to 10 minutes as necessary to reduce the severe dyspnea and elevated ventricular filling pressures commonly associated with acute heart failure, particularly if myocardial dysfunction is secondary to ischemia or infarction. A 0.4-mg sublingual tablet given every 4 to 5 minutes is approximately equivalent to a 1.5-µg-per-kg-per-minute continuous infusion (50). The sublingual preparation is often used at the authors' institution to reverse high pulmonary artery pressures in patients with chronic heart failure who are undergoing transplant evaluation (51). Therefore, its potency should not be underestimated.

Intravenous nitroglycerin (typically starting at a dosage of 0.2 µg per kg per minute) may be rapidly titrated upward in increments of 0.1 to 0.2 µg per kg per minute to improve symptoms and reduce pulmonary and systemic venous pressures and resistance, ventricular filling pressures, and, to a variable degree, SVR. As noted previously, however, the ability of nitrates to augment stroke volume and cardiac output by decreasing left ventricular afterload is often dose dependent and usually requires an initial intravenous dosage of at least 0.4 µg per kg per minute (21). One must also consider the propensity for the development of pharmacodynamic tolerance during continuous intravenous infusions, which necessitates an intermittent increase in dose to maintain the desired hemodynamic effect (52).

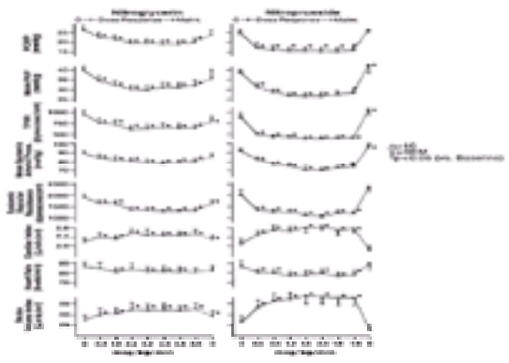
Careful attention should also be given to intravascular volume and the need for diuretic therapy because this may also affect pharmacodynamic tolerance (21,53). Resistance to the hemodynamic effects of nitrates has also been described in patients with elevated right atrial pressures (53). Institution of diuretic therapy may reverse nitrate resistance. Patients already on long-term nitrate therapy may require a higher initial dose of intravenous nitroglycerin. If the desired clinical response has not been achieved after reaching a dosage of 5 to 6 µg per kg per minute, use of an alternative or additional vasodilating agent is generally required. In this setting, further intravenous therapy is often most optimally tailored with the guidance of hemodynamic monitoring. An added advantage of intravenous nitroglycerin administration in the unstable patient is that its hemodynamic effects resolve rapidly once the infusion is stopped.

Nitroprusside

Sodium nitroprusside is a powerful venous and arterial vasodilator with potent afterload-reducing properties (54). It is the agent most frequently used early in the treatment of acute heart failure, particularly when a rapid and substantial reduction in SVR is necessary. Common clinical conditions for which it is used include

complications of myocardial infarction such as acute mitral regurgitation secondary to papillary muscle dysfunction or rupture, ventricular septal defect, and acute aortic regurgitation. Nitroprusside relaxes arterial and venous smooth muscle via the production of nitric oxide and nitrosothiols, which leads to an increase in cyclic guanosine monophosphate and smooth muscle relaxation (23). As with nitroglycerin, nitroprusside causes preload reduction by diminishing heightened venous tone and increasing venous capacitance with a concomitant shift in central blood volume to the periphery (24). This causes a reduction in right ventricular pressure and volume. Unique to nitroprusside is its rapid and powerful effect on afterload. This agent reduces the major components of aortic impedance (mean and hydraulic vascular load), which results in an improved and often dramatic increase in forward stroke volume and cardiac output with reductions in left ventricular filling pressure, volume, and valvular regurgitation (19,21,24,55,56,57 and 58). Fortunately, this decrease in afterload occurs without major changes in aortic pressure (56).

In most patients with heart failure, judicious titration of nitroprusside can result in decreased aortic impedance, increased cardiac output, and reduced ventricular filling pressures without the undesirable effects of a decrease in systemic blood pressure or rise in heart rate. The combined balanced vasodilator effect of nitroprusside can therefore rapidly improve the hemodynamic abnormalities associated with acute heart failure when preload and afterload reduction is desired. eFigure 91.1.1 compares the hemodynamic response to intravenous nitroglycerin and nitroprusside in chronic heart failure. Although both medications produce desirable effects on cardiac filling pressures and cardiac output, the magnitude of the response to nitroprusside appears to be significantly greater, particularly with respect to afterload reduction (21).



***e*FIGURE 91.1.1** The hemodynamic responses to intravenous nitroglycerin and sodium nitroprusside are depicted in ten patients with moderately severe congestive heart failure. The baseline control period (C) is followed in sequence by a dose response, a 90-minute constant maintenance dose (Maint), and a discontinuation point. The changes in hemodynamic parameters evoked by nitroglycerin and nitroprusside are directionally similar, but the magnitude of change is greater with nitroprusside. Note the dramatic rebound effect after discontinuation of nitroprusside. PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SEM, standard error of the mean; TPVR, total pulmonary vascular resistance. (Adapted from Leier CV, Bambach D, Thompson MJ, et al. Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin, and nitroprusside in patients with congestive heart failure. *Am J Cardiol* 1981;48:1115–1123, with permission.)

Generally, by improving ventricular wall stress and reducing MVO_2, nitroprusside has a favorable effect on myocardial energetics (59,60). Nitroprusside may also improve coronary blood flow and myocardial perfusion by directly reducing coronary vascular resistance and by increasing coronary perfusion pressure (61). The latter will occur as long as the reduction in ventricular diastolic pressure is greater than aortic coronary diastolic pressure. In patients with occlusive coronary artery disease, care must be taken to avoid excessive reductions in systemic pressure or elevations in heart rate that would reduce coronary perfusion and increase myocardial oxygen demand. Unlike nitroglycerin, nitroprusside may cause “coronary steal” whereby arteriolar dilatation in nonischemic zones diverts coronary flow away from areas of ischemia (60,62). The frequency with which this occurs in heart failure is not well documented.

Nitroprusside is administered intravenously with an infusion pump and is usually initiated at a dosage of 0.10 to 0.20 µg per kg per minute. Its effects are evident within 60 to 90 seconds after initiation of the infusion, and, should an adverse effect such as symptomatic hypotension occur, the vasodilating properties usually abate within 20 to 30 minutes after discontinuation (19). Continuous monitoring of central hemodynamics with an indwelling flow-directed thermodilution pulmonary artery catheter is mandatory to safely and effectively achieve the optimal dosage. In acute heart failure, insertion of an arterial catheter for continuous systemic blood pressure recording and monitoring and frequent blood gas determinations is also recommended. One should recognize, however, that during nitroprusside infusion, the pressure measured in a peripheral artery (i.e., radial artery) may not reflect a reduction in central aortic pressure because of nitroprusside-induced changes in the amplitude and timing of reflected waves within the central aorta (63). One must remain cognizant of this when the clinical findings are consistent with systemic hypoperfusion despite a seemingly acceptable peripheral arterial pressure.

Nitroprusside can be rapidly titrated to achieve the desired clinical and hemodynamic end points, including a reduction in PCWP to 18 to 20 mm Hg, a decrease in SVR to 1,000 to 1,200 dynes per second per cm^5, a reduction in valvular regurgitation, and an improvement in stroke volume, cardiac output, and systemic perfusion, while avoiding significant hypotension and tachycardia. Although the target blood pressure is variable depending on the individual patient, a systolic blood pressure of 80 mm Hg or greater is usually acceptable. A higher systolic blood pressure may be required in the elderly or in patients with a recent history of hypertension or cerebrovascular disease. The target PCWP is usually higher in patients with acute heart failure than in patients with decompensated chronic heart failure. In the latter condition, the stroke volume of the dilated ventricle is not preload dependent, and therefore relatively normal left ventricular filling pressures can be targeted. In acute heart failure, particularly when myocardial ischemia is present, attention to Starling mechanisms with respect to preload and augmentation of stroke volume remains important. Although nitroprusside is titrated to achieve hemodynamic goals, rarely are dosages greater than 4 to 5 µg per kg per minute required to maintain adequate vasodilation in the acute heart failure setting, and dosing this high for prolonged periods (greater than 72 hours) should generally be avoided due to the risk of thiocyanate and cyanide toxicity (64,65).

The most common serious adverse effect of nitroprusside administration in acute heart failure is systemic hypotension (54,62,66). One should be particularly cautious when initiating nitroprusside therapy in a patient with ischemia or infarction and a systolic arterial pressure of less than 100 mm Hg. An increase in heart rate during the infusion is an ominous finding and usually presages hypotension. This typically occurs when stroke volume has not increased appropriately, often because of ongoing or worsening ischemia, valvular regurgitation, and inadequate cardiac reserve. A reduction or cessation of the nitroprusside infusion is usually warranted. Alternatively, the addition of a positive inotropic agent such as dobutamine hydrochloride is often advantageous and may allow for the continuation of nitroprusside. Such a combination is commonly used to stabilize particularly severe, low-output heart failure until more definitive therapy can be instituted (see the section Combination Pharmacologic Therapy later in this chapter). When systemic hypotension and poor peripheral perfusion are present at the outset, nitroprusside should generally be avoided as initial treatment.

As noted earlier, thiocyanate toxicity is a potentially serious side effect of prolonged nitroprusside infusion and is manifest clinically by nausea, disorientation, psychosis, muscle spasm, and hyperreflexia when plasma thiocyanate concentrations exceed 6 mg% (64,65). Such toxicity is uncommon in the management of acute heart failure in which nitroprusside therapy is usually a temporary means of support while the patient awaits definitive therapy. Cyanide toxicity is extremely rare in heart failure management and occurs only during prolonged high-dose infusion, usually in the setting of significant hepatic dysfunction.

The rationale for intravenous vasodilator therapy in acute heart failure is based on correction of hemodynamic derangement and stabilization of the patient while a therapeutic plan is devised. The necessity for prolonged treatment (longer than 72 hours) often portends a poor prognosis, particularly in the absence of a reversible underlying disorder.

Positive Inotropic Therapy

Dobutamine

Dobutamine hydrochloride is a synthetic catecholamine and positive inotropic agent that is useful in the acute management of systolic heart failure associated with systemic hypoperfusion. Along with intravenous diuretics, it is used commonly in patients with acute decompensation of chronic heart failure or myocardial infarction presenting with pulmonary congestion and low cardiac output symptoms. Dobutamine exists as a racemic mixture of dextro-and levoisomers, which are potent beta- and alpha-adrenergic agonists, respectively (67). Therefore, dobutamine produces its positive inotropic effect via stimulation of myocardial $beta_1$ and probably $alpha_1$ receptors (68). Theoretically, the opposing forces of $alpha_1$ and $beta_2$ stimulation on the peripheral vasculature should result in a negligible change in vascular resistance. Binkley and colleagues have shown, however, that in a total-artificial-heart model, dobutamine improves ventricular performance through direct modulation of arterial and venous tone (69). Dobutamine also has a favorable effect on aortic impedance, which allows for more efficient transfer of ventricular work and energy into stroke volume, cardiac output, and systemic perfusion. This maximizes the blood volume ejected by the ventricle for any augmentation in myocardial contractility (70,71). This is in contrast to the inotropic/vasopressor agent dopamine hydrochloride, which does not decrease aortic impedance and therefore limits the amount of

blood ejected for any given increase in contractility (70,71) (Table 91.3). These differences in ventricular-vascular coupling explain why dobutamine augments cardiac output and improves ventricular performance whereas dopamine, at moderate to high doses, is a vasopressor and ultimately worsens cardiac function in heart failure (71,72 and 73) (Fig. 91.2, eFig. 91.2.1). Thus, these inotropic and vascular effects of dobutamine account for its favorable hemodynamic profile in acute heart failure. Dobutamine increases stroke volume and cardiac output, reduces ventricular volume and mitral regurgitant fraction, and lowers left ventricular diastolic pressure without producing a significant increase in heart rate (72,74). This cardiocirculatory response to dobutamine results from its potent inotropic and substantial vasodilator effects, which are linearly related to dose and plasma concentration (74,75).

	Dobutamine hydrochloride	Dopamine hydrochloride
Systemic vascular resistance	↓	→ or ↑
Characteristic aortic impedance	↓	→ or ↑
Ventricular-vascular coupling	↑Systolic ejection ↑Stroke volume ↑Cardiac output	→ or ↓Ejection ↑Systemic blood pressure
Transfer of ventricular work-energy	Systemic blood flow	Systemic pressure

↑, increased; ↓, decreased; →, unchanged.
Adapted from Leier CV. Positive inotropic therapy: an update and new agents. *Curr Probl Cardiol* 1996;21:558, with permission.

TABLE 91.3 SYSTEMIC VASCULAR PROFILES OF DOBUTAMINE AND DOPAMINE IN HEART FAILURE

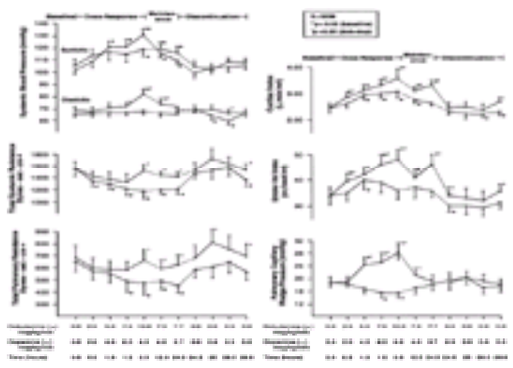
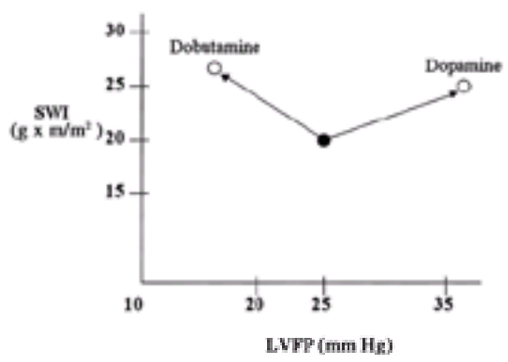


FIGURE 91.2 Comparison of dopamine hydrochloride (*filled circles*) and dobutamine hydrochloride (*open triangles*) on central hemodynamics in patients with low-output congestive heart failure. Infusions for both medications followed a baseline period, with titration of each drug to peak effect. The maximal dosage of dobutamine was 10 µg per kg per minute and of dopamine was 8 µg per kg per minute. The data illustrate that dopamine given at infusion rates that exceed 2 to 4 µg per kg per minute does not have a favorable effect on total systemic vascular resistance. This results in a reduction in stroke volume and cardiac index compared to those of dobutamine. Dopamine at moderate dosages also increases pulmonary capillary wedge pressure. Dobutamine produces a mild increase in systemic blood pressure, with reduction in total systemic resistance and improvement in cardiac filling pressure and cardiac index. SEM, standard error of the mean. (From Leier CV, Heban PT, Huss P, et al. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. *Circulation* 1978;58:466–475, with permission.)



***e*FIGURE 91.2.1** Comparison of effects of dopamine hydrochloride and dobutamine hydrochloride on left ventricular filling pressure (LVFP). Doses of dopamine and dobutamine that produce a similar augmentation in stroke work index (SWI) have opposite effects on LVFPs in patients with heart failure. (From Loeb HS, Bredakis J, Gunnar RM. Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. *Circulation* 1977;55:375–381, with permission.)

The safety of inotropic therapy in patients with occlusive coronary artery disease and active myocardial ischemia is often questioned in clinical practice. Often dobutamine therapy is withheld from patients with low cardiac output and coronary artery disease for fear of aggravating ischemia or precipitating arrhythmias. Although the positive inotropic effect of dobutamine increases MVO_2, which could be detrimental in acute ischemia or infarction, this is balanced by other factors that decrease MVO_2 and improve coronary blood flow and myocardial perfusion (76). Dobutamine, when carefully administered to the patient with heart failure, systemic hypoperfusion, and elevated filling pressures, reduces MVO_2 by decreasing ventricular volume and wall tension. Dobutamine may increase coronary blood flow by increasing coronary perfusion pressure (increase in arterial diastolic pressure and decrease in ventricular diastolic pressure) and coronary perfusion time, and possibly by causing mild coronary vasodilation (76,77,78 and 79). These factors tend to offset any increase in MVO_2 evoked by positive inotropy. In fact, standard dosages of dobutamine have been shown to improve cardiac function in patients with heart failure and significant coronary obstruction without undue risk of worsening ischemia or infarction (76,80,81). In a controlled study of patients with myocardial infarction, dobutamine use did not increase infarct size or the frequency of arrhythmia (82). Avoiding significant increases in heart rate during dobutamine infusion is imperative, however, because this would serve to increase MVO_2 and reduce coronary perfusion time (76). Also, dobutamine administration should be avoided when ventricular filling pressures are not significantly elevated. Therefore, the titration of dobutamine dosage in the patient with occlusive coronary artery disease mandates careful attention to multiple parameters, including heart rate, systolic and diastolic blood pressures, central hemodynamics, presence of arrhythmias, acid–base balance, and clinical signs of improved systemic perfusion. Failure to follow these parameters closely may result in an adverse response to dobutamine therapy, particularly when occlusive coronary artery disease is present.

In acute heart failure, dobutamine therapy is usually initiated when an augmentation in cardiac output and systemic perfusion is desired in patients with elevated filling pressures. The infusion is started at 2.5 to 5.0 µg per kg per minute and is titrated in increments of 1 to 2 µg per kg per minute at 20- to 30-minute intervals until the desired clinical and hemodynamic response is attained. Rarely is it necessary to exceed a dosage of 15 µg per kg per minute in treating acute heart failure, although dosages this high are sometimes necessary for a brief time while more definitive therapy is pursued. Sustained dosing at this level or greater may be detrimental, however, because of a higher MVO_2 and reduced myocardial perfusion, primarily related to the increased chronotropic response to dosages greater than 15 to 20 µg per kg per minute. In addition, the ideal body weight of the patient should be considered when initiating therapy.

The pharmacokinetic profile of dobutamine makes this agent ideal for the critical care setting. It has an extremely short half-life (less than 5 minutes), and a full pharmacodynamic response to a particular dose and its steady-state phase is attained within 10 to 15 minutes (71). Importantly, any adverse effect of dobutamine is also eliminated within only 10 to 15 minutes of stopping the infusion. Additional side effects that may occur during dobutamine infusion include headache, anxiety, and tremor. Dobutamine must also be used cautiously in patients with atrial arrhythmia such as atrial fibrillation or atrial flutter. Dobutamine has been reported to increase atrioventricular conduction in atrial fibrillation (83). Due to the excessive dosing required to achieve hemodynamic benefit in patients who are receiving long-term

beta-blocker therapy, dobutamine should generally not be used for inotropic support in these patients (see the next section, Milrinone) (*e*Table 91.3.1).

***e*TABLE 91.3.1** HEMODYNAMIC EFFECT OF MILRINONE COMPARED WITH DOBUTAMINE IN PATIENTS TREATED WITH CARVEDILOL

	Milrinone lactate	**Dobutamine hydrochloride**
Cardiac index	↑	↑
Heart rate	→	↑
Mean arterial pressure	↓	↑
PCWP	↓	→
Mean PAP	↓	↑
LVSWI	↑	↑↑
LVSVI	↑	→

↑, increased; ↑↑, markedly increased; ↓, decreased; →, unchanged; LVSVI, left ventricular stroke volume index; LVSWI, left ventricular stroke work index; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.

From Bristow MR. Enhancing contractile function pharmacologically may improve natural history of heart failure. *Cardiol Rev* 2000;17[Suppl]:3.

Milrinone

Milrinone lactate, a bipyridine analog of amrinone, is a second-generation phosphodiesterase inhibitor that exhibits both direct inotropic and vasodilator properties (71,76,84). Milrinone is approved by the U.S. Food and Drug Administration (FDA) for parenteral use in the treatment of congestive heart failure. The parent compound, amrinone, is also available parenterally but because of its substantial side-effect profile and weak inotropic properties, it has largely been supplanted by milrinone.

Through inhibition of the phosphodiesterase III isoenzyme located primarily in cardiomyocytes and vascular smooth muscle, milrinone increases the concentration of cyclic adenosine monophosphate (cAMP) in these tissues. Elevated cAMP levels, via phosphorylation of several cellular proteins, increase intracellular calcium, which is the final common pathway to enhanced inotropy and vasodilatation. Although dobutamine and milrinone exert their effects through the cAMP-dependent pathway, important differences are found. Dobutamine actually increases cAMP production via beta receptor activation, whereas milrinone raises cAMP levels by preventing its degradation. This mechanistic difference is important with respect to the potential for both drugs to act synergistically to enhance myocardial contractility in patients with heart failure (see the section Combination Pharmacologic Therapy) (81).

The acute hemodynamic effects of milrinone in patients with chronic heart failure have been well described (85,86,87,88 and 89). The hemodynamic profile is one that would be expected from a drug with potent inotropic and balanced vasodilator properties. Once therapeutic plasma levels are achieved, milrinone elicits a reduction in right and left ventricular filling pressures and increases cardiac output without producing significant changes in the heart rate–blood pressure product. Because of its potent vasodilator properties, however, milrinone has the potential to worsen preexisting systemic hypotension. A reduction in pulmonary vascular resistance is usually observed and is primarily secondary to the reduction in left ventricular filling pressure rather than a direct pulmonary vasodilator effect. Even though milrinone may be expected to increase MVO_2 via its direct positive inotropic effect, its substantial vasodilator properties usually offset any detrimental increase in MVO_2 (87). This favorable effect is further enhanced by mild coronary vasodilatation (90). Compared with dobutamine, milrinone tends to evoke a greater reduction in left ventricular filling pressure and SVR while producing an equivalent increase in cardiac output (88) (Fig. 91.3). For the same reduction in SVR, milrinone produces a greater increase in stroke work index than nitroprusside, which reflects its additional inotropic properties (88,89).

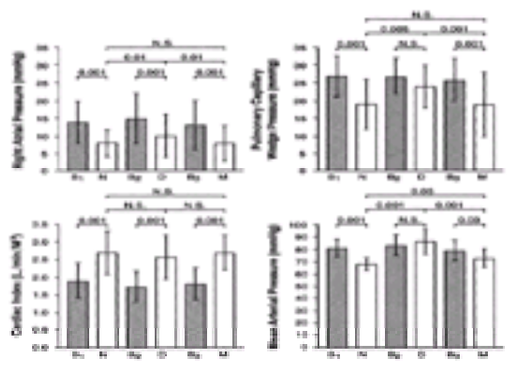


FIGURE 91.3 Effects of sodium nitroprusside (N), dobutamine hydrochloride (D), and milrinone lactate (M) on cardiac index, mean arterial pressure, right atrial pressure, and pulmonary capillary wedge pressure in patients with severe heart failure (B_1, B_2, and B_3 = baseline measurements). At dosages evoking a similar increase in cardiac index, all agents significantly reduced right atrial pressure, with nitroprusside and milrinone also producing a significant reduction in mean arterial pressure compared to baseline. The effect of milrinone and nitroprusside on pulmonary capillary wedge pressure was greater than that observed with dobutamine. N.S., not significant. (Adapted from Monrad ES, Baim DS, Smith HS, et al. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986;73[Suppl III]:168–174.)

Based on its hemodynamic profile in heart failure, milrinone would appear to be advantageous in the treatment of the patient with acute pulmonary congestion and low cardiac output. Unfortunately, the pharmacokinetic properties of milrinone may make it less desirable as an acute, first-line therapy in some patients. Milrinone has a long half-life (20 to 45 minutes) compared to nitroglycerin, nitroprusside, and dobutamine (50,71,76). To rapidly achieve a therapeutic plasma level, a bolus administration of 50 µg per kg is given over a 10-minute period followed by a constant infusion at a rate of 0.375 to 0.750 µg per kg per minute. This requirement for an initial bolus or high infusion rate to elicit a significant inotropic response places the unstable patient at greater risk for hypotension. The elimination half-life of 1.7 hours is also much longer than that of dobutamine or nitroprusside, and more time would be required to eliminate the drug should an undesirable side effect occur (76). Therefore, milrinone should generally not be used as first-line therapy in the management of acute heart failure but should be reserved for situations in which hemodynamic instability continues despite maximal support with dobutamine, nitroprusside, or nitroglycerin. These drugs are favorable first-line agents because of their short half-lives and ease of titration to inotropic and vasodilator effects. Milrinone may be more appropriate for treating chronic decompensated heart failure or during combination therapy with dobutamine or beta-blockers.

The choice of inotropic agent for treating decompensated heart failure will likely be affected by the growing numbers of patients receiving long-term beta-blocker therapy. Beta-blockers have now been shown to dramatically improve survival in chronic heart failure and play an integral role in the pharmacotherapy of this condition. Therefore, patients presenting with acute decompensation are increasingly likely to be receiving some form of long-term beta-blocker treatment. If inotropic support is necessary, milrinone is currently the agent of choice given that it acts beyond the level of the beta receptor and its inotropic effect is not altered by beta-receptor blockade (91,92) (*e*Table 91.3.1 and *e*Table 91.3.2). Depending on the degree of decompensation and hemodynamic compromise, the dose of beta-blocker should generally remain unchanged or gradually reduced during institution of inotropic support. If prolonged inotropic support is likely to be necessary or an inadequate hemodynamic response is observed, then the beta-blocker should be stopped.

***e*TABLE 91.3.2** CARDIOVASCULAR EFFECTS OF BETA-ADRENERGIC BLOCKING AGENTS (BB), PHOSPHODIESTERASE INHIBITORS (PDEI), OR THEIR COMBINATION IN PATIENTS WITH HEART FAILURE

Effect	**BB**	**PDEI**	**BB + PDEI**
Heart rate	↓	→ or ↑	↓
Systolic function	↓ then ↑	↑	↑↑
Diastolic function	→	↑	↑
Arterial vasodilation	↑, →, or ↓	↑	↑
Venodilation	↑, →, or ↓	↑	↑
LV filling pressure	→ or ↑, then ↓	↓	↓
MVO_2	↓	→ or ↑	↓
Exercise capacity	→ or ↓	↑	↑
Proarrhythmia	↓	→ or ↑	→ or ↓

↑, increased; ↑↑, markedly increased; ↓, decreased; →, unchanged; LV, left ventricle; MVO_2, myocardial oxygen consumption.

From Lowes BD, Simon MA, Tsvetkova TD, et al. Inotropes in the beta blocker era. *Clin Cardiol* 2000;23[Suppl III]:III-11–III-16.

Vasopressor Therapy

Dopamine

Dopamine hydrochloride is a drug that exhibits complex pharmacologic properties. This agent mediates its effects through either direct activation or indirect activation (via norepinephrine release) of multiple pre- and postsynaptic receptors (93,94). Receptors that are activated are extremely sensitive to dopamine concentration, and this contributes further to the complexity of drug administration (94). The positive inotropic and chronotropic effect of dopamine is mediated through activation of postsynaptic myocardial $beta_1$ receptors. This effect is most evident clinically at dosages greater than 5 µg per kg per minute. At low doses, the primary effect of dopamine is one of vascular relaxation and sodium excretion by stimulation of specific dopaminergic receptors located postsynaptically on vascular smooth muscle cells (primarily in renal and mesenteric vascular beds) and renal tubular cells (95,96). Dopamine receptors may also be found in cerebral, coronary, skeletal muscle, and cutaneous vessels (93). Low-dose dopamine (0.5 to 2.0 µg per kg per minute) is often used to treat patients with heart failure and renal insufficiency to selectively activate renal dopaminergic receptors, induce renal vasodilatation and improve renal blood flow, and provoke natriuresis (97). As the dopamine dosage is progressively increased above 5 µg per kg per minute, postsynaptic $alpha_1$ and $alpha_2$ receptors are activated, and this mediates vasoconstriction and produces blood pressure elevation.

Dopamine does not stimulate postsynaptic $beta_2$ receptors, so the predominant effect of higher dosing is one of vasoconstriction. On the presynaptic membrane, dopamine activates $alpha_2$ and $dopaminergic_2$ receptors, both of which inhibit the release of norepinephrine (98). By another mechanism, however, dopamine directly increases the release of norepinephrine, which further enhances peripheral vasoconstriction via alpha-adrenergic receptor activation (94,96).

Because dopamine selectively affects multiple receptors in a dose-dependent manner, a variety of hemodynamic effects can be achieved with careful titration (72). In the setting of acute heart failure, its primary use is to elevate systemic blood pressure and improve renal perfusion through activation of $beta_1$, alpha, and dopaminergic receptors. In patients with cardiogenic shock and significant hypotension, dopamine is usually the drug of choice and may be used either alone or in combination with dobutamine to elevate blood pressure and improve systemic and renal perfusion (99,100).

Prolonged use at high dosages, however, will ultimately cause worsening of myocardial function because of the increase in aortic impedance and the negative influence of dopamine on ventricular-vascular coupling (Table 91.3) (70). This is reflected in significant increases in PCWP and systemic blood pressure when dopamine is administered at dosages of 5 µg per kg per minute and greater (72). As the dopamine dosage is progressively increased, peripheral vasoconstriction is the predominant clinical feature similar to that seen with norepinephrine infusion. Upward titration of dopamine is usually limited by tachycardia, ischemia, and arrhythmia, particularly in the presence of occlusive coronary artery disease. At low to moderate dosages, coronary blood flow increases in parallel with increased myocardial work and a mild dopamine-induced coronary vasodilator effect (93,101,102). At high dosages, dopamine further increases MVO_2; however, coronary vascular resistance also increases because of alpha-mediated vasoconstriction (102).

To summarize, dopamine is the drug of choice in acute heart failure when significant hypotension is present despite adequate intravascular volume and ventricular filling pressures. In addition to evoking peripheral vasoconstriction and elevating blood pressure, it also has the unique property of enhancing renal blood flow through dopaminergic receptor activation, although this effect is probably negligible at doses in excess of 10.0 to 12.5 µg per kg per minute. Because of undesirable effects on myocardial function and hemodynamics, dopamine at high doses should be used only until more effective and definitive treatment is available.

Norepinephrine and Epinephrine

Norepinephrine is a potent alpha-adrenergic agonist that also possesses mild $beta_1$-agonist properties. It elicits a cardiovascular vasopressor response through dose-related vasoconstriction (76,103,104). This drug is not used for positive inotropic therapy because any increase in myocardial contractility is offset by increased afterload. During norepinephrine infusion, the combination of high preload and afterload markedly increases MVO_2 to the point at which the myocardial oxygen demand to supply ratio is threatened (76). Its primary indication in acute heart failure is to improve blood pressure and coronary perfusion in the setting of shock and persistent hypotension when dopamine and dobutamine are ineffective.

Norepinephrine can be infused starting at a rate of 0.02 to 0.04 µg per kg per minute and the dose can be advanced every 10 to 15 minutes until the desired blood pressure response is achieved (76). The target blood pressure should be that which is considered minimally acceptable in the individual patient to maintain adequate coronary perfusion and avoid serious side effects. Dopamine or dobutamine may be used in combination with norepinephrine to allow for lower dosing.

Epinephrine, like norepinephrine, is a catecholamine with potent alpha- and beta-agonist properties. Unlike norepinephrine, epinephrine also exhibits mild $beta_2$-agonist properties, which offsets some of the alpha effect and thereby mildly reduces its pressor response in comparison to norepinephrine (105). Epinephrine may be used in intensive care units for hemodynamic support in patients with severe heart failure and shock. It may be used in conjunction with other catecholamine inotropic and pressor drugs. Infusions of 0.1 to 1.0 µg per minute are commonly used.

The adverse effects seen during norepinephrine and epinephrine infusions are those usually observed with catecholamine administration, including ischemia and serious arrhythmia. Prolonged use may result in problems associated with reduced organ and tissue perfusion. The plasma half-life of these agents is short (less than 10 minutes), so undesirable pharmacologic effects generally resolve by 10 to 20 minutes after discontinuation of the infusion (76,105). As with high-dose dopamine therapy, the duration of treatment with any potent vasopressor should be as brief as possible, because prolonged use leads to continued myocardial dysfunction, decreased organ perfusion, and metabolic derangement. The need for prolonged catecholamine vasopressor infusions to maintain an acceptable systemic blood pressure would warrant proceeding to mechanical assistance such as intraaortic balloon counterpulsation in the appropriate patient.

Vasopressin

In the critical care setting, some centers advocate the use of vasopressin (antidiuretic hormone) for systemic pressure support when catecholamine infusions have failed to improve hemodynamics or when serious adverse responses to catecholamine infusions have occurred (105). Vasopressin, by activation of vascular smooth muscle V1 receptors, is a potent vasoconstrictor of skeletal muscle vascular beds at high dosages, but importantly, it produces less intense vasoconstriction of the renal and coronary vasculature (105).

Interestingly, vasopressin seems to produce vasodilation of the cerebral vasculature, which results in an improvement in cerebral blood flow during infusions (105,106 and 107). This selective vasodilatory response may be mediated by nitric oxide (107). In the absence of direct myocardial stimulation through beta-receptor activation, vasopressin may result in lower MVO_2 compared to catecholamines. Also, unlike catecholamines, the pressor response to vasopressin remains intact during severe metabolic acidosis.

Diuretic Therapy

Intravenous furosemide is the loop diuretic most commonly used to treat the patient presenting with acute heart failure and pulmonary congestion. The major objective of diuretic therapy in this circumstance is to decrease excessive lung water through natriuresis and diuresis with a reduction in intravascular volume. Intravenous administration is necessary to rapidly achieve adequate furosemide levels at its site of action, the renal tubules.

The most important effect of furosemide in the acute management of heart failure probably relates to its substantial hemodynamic effects. Although both vasodilator and vasoconstrictor properties have been attributed to intravenous furosemide (108,109,110 and 111), most data support the view that furosemide evokes a reduction in cardiac filling pressures, and this likely results from an early vasodilator effect. A vasoconstrictor effect with reduction in cardiac output has also been reported, however, and may be a consequence of diuretic-induced neurohormonal activation (110,111). Furosemide, by decreasing systemic and pulmonary venoconstriction, has been shown to reduce left ventricular filling pressure in acute heart failure associated with myocardial infarction (112,113).

Diuretic therapy must be used judiciously in acute heart failure secondary to myocardial infarction because intravascular and total body volume is usually normal (Table 91.2). Excessive diuresis can result in hypotension with progression of myocardial ischemia by further compromise of coronary perfusion. In fact, subgroup analysis of data from two large post–myocardial infarction treatment trials suggests that diuretic therapy may be detrimental in this patient population (114,115).

The effective dosage of intravenous furosemide is variable but is usually in the range of 20 to 40 mg in the patient not previously receiving diuretic therapy and exhibiting normal renal function. On the other hand, patients with acute decompensation of chronic heart failure often present with substantial volume overload and

usually require much larger dosages to achieve an adequate diuresis. This is because of prior chronic oral diuretic use and activation of renal compensatory mechanisms to counteract natriuresis in the chronic heart failure milieu. In patients exhibiting volume overload and diuretic resistance, a continuous infusion of furosemide (5 to 20 mg per hour) may prove advantageous (50,116). An attempt to enhance renal perfusion by increasing cardiac output (with dobutamine or nitroprusside) or by reducing renal vascular resistance (with low-dose dopamine) should also be considered. In patients with massive volume overload unresponsive to these therapeutic maneuvers, ultrafiltration may be effective (117).

Combination Pharmacologic Therapy

The use of multiple agents to support the failing circulation may provide certain advantages over treatment with a single agent (76,118). This is because acute heart failure or acute decompensation of chronic heart failure is associated with several hemodynamic abnormalities that cannot be entirely addressed by a single drug. The administration of an inotrope treats systolic dysfunction by improving contractility and stroke volume, but cardiac filling pressures and SVR (and associated valvular regurgitation) may not be substantively altered. A pure vasodilator alone may not be sufficient to support the circulation, and in fact may be detrimental when myocardial contractility is severely diminished and systemic blood pressure is unacceptably low. Using only a vasopressor drug to raise blood pressure in a patient with hypotension would increase afterload, ventricular wall stress, and filling pressures, which would inhibit the desired increase in cardiac output and potentially worsen ischemia.

Several combinations of intravenous drugs are theoretically appealing in the setting of severe acute heart failure. The simultaneous administration of dobutamine and a vasodilator such as nitroglycerin or nitroprusside augments stroke volume and lowers cardiac filling pressures more effectively than either agent alone (119,120). This combination is particularly useful in treating patients with cardiogenic shock resulting from a complication of myocardial infarction such as ventricular septal or papillary muscle rupture. As noted previously, the phosphodiesterase inhibitors also offer the advantage of potent vasodilation and positive inotropy; unfortunately, their pharmacokinetics and long half-life make these agents less than ideal in managing acute, unstable heart failure (71,76).

Using dobutamine (a beta-agonist), and milrinone (a phosphodiesterase inhibitor) simultaneously also offers possible advantages (85,118,121,122). The rationale behind this approach is based on the different mechanisms by which these drugs increase inotropy. Both agents, by different and complementary mechanisms, increase inotropy by elevating cAMP levels in cardiomyocytes (71,76,89). Studies in patients with stable heart failure have shown an added effect of combination therapy on major hemodynamic parameters (122) (Fig. 91.4).

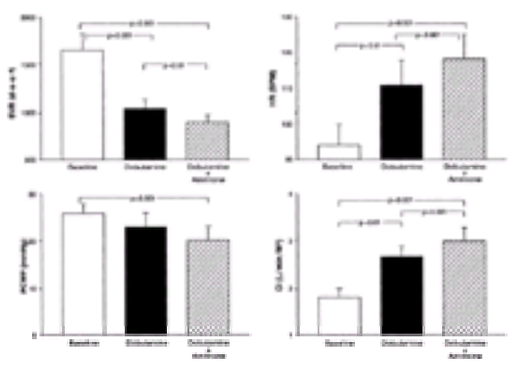


FIGURE 91.4 Effects of dobutamine hydrochloride and amrinone in ten patients with severe congestive heart failure. Dobutamine at peak dose increases cardiac index and reduces pulmonary wedge pressure (PCWP) and systemic vascular resistance (SVR). Dobutamine also increases heart rate (HR) above baseline. The addition of amrinone to dobutamine results in further augmentation in cardiac index (CI) and reduction in pulmonary wedge and SVR. Amrinone added to dobutamine further elevates the HR. (Modified from Uretsky BF, Lawless CE, Verbalis JG, et al. Combined therapy with dobutamine and amrinone in severe heart failure. *Chest* 1987;92:657–662.)

Dobutamine plus low-dose dopamine is one of the most commonly used combinations. The goal of this therapy is to achieve the inotropic effect of dobutamine with the concomitant renal vasodilator effect of low-dose dopamine (72,84,118). This combination is usually considered for the patient exhibiting marginal urine output and poor responsiveness to diuretics despite seemingly adequate central hemodynamics and systemic blood pressure.

Combination pharmacologic therapy is usually reserved for conditions associated with severe hemodynamic derangement, such as cardiogenic shock or severely decompensated chronic heart failure. It is rarely indicated in acute pulmonary congestion alone, for which a diuretic and vasodilator (or inotrope) often suffice. Combination therapy would be indicated for conditions in which its use would allow more immediate and prolonged stabilization of the circulation while definitive therapy is pursued. Another potential advantage of combination therapy is to enable the use of lower dosages of drugs so that significant untoward effects can be avoided. Again, the success of this therapy, as with any treatment of acute heart failure, is highly dependent on the cause and potential for myocardial recovery (118). In the patient in whom combination therapy is deemed potentially useful, hemodynamic monitoring should be used to guide treatment.

Investigational Agents for Acute Heart Failure

The current management of stable, chronic heart failure is guided by data from numerous large clinical trials, and several sets of guidelines have been published. Unfortunately, similar guidelines for the management of acute heart failure or acutely decompensated chronic heart failure do not exist. All of the therapies previously discussed may play a role in treating a particular patient with decompensated chronic heart failure; however, no consensus exists regarding the relative role of each therapeutic class. This uncertainty in selecting the appropriate treatment strategy is compounded by the fact that more than a decade has passed since the introduction of a new drug (milrinone) for acute heart failure. Thus, interest is now growing in several promising acute heart failure therapies.

Positive Inotropic Drugs

Levosimendan (levo-OR-1259) and toborinone (OPC 18790) are two compounds that are presently undergoing evaluation in clinical trials and are nearing final review by the FDA. Both agents have positive inotropic properties and other unique features that set them apart from dobutamine and milrinone. Their role in clinical practice, if they are approved by the FDA, remains to be determined.

Levosimendan evokes a positive inotropic response primarily by increasing the sensitivity of myofilaments (specifically troponin C) to intracellular calcium (123,124). This action is independent of cAMP mechanisms and thus elicits inotropy while avoiding many of the adverse effects commonly associated with cAMP-dependent agents (125,126). Levosimendan also exhibits vasodilator properties through its mild inhibition of phosphodiesterase III and by activation of potassium-dependent adenosine triphosphate channels (126,127). *In vitro*, it does not impair myocardial relaxation and, in fact, has lusitropic actions in the failing myocardium (123). These multiple mechanisms of action result in the expected hemodynamic changes during short-term intravenous administration to patients with severe heart failure. Investigators have reported a significant improvement in cardiac index (primarily as a result of increased stroke volume), reduction in systemic and pulmonary vascular resistance, and reduced filling pressures with only a small increase (approximately 8%) in heart rate (126).

As with most cardiotonic medications, increased heart rates and ventricular arrhythmia were more likely to be evident at the higher infusion rates. Preliminary studies suggest that this favorable hemodynamic response may translate into a survival benefit in those with severe heart failure (128). Large clinical trials are currently under way to better define the value of this agent in the management of decompensated heart failure.

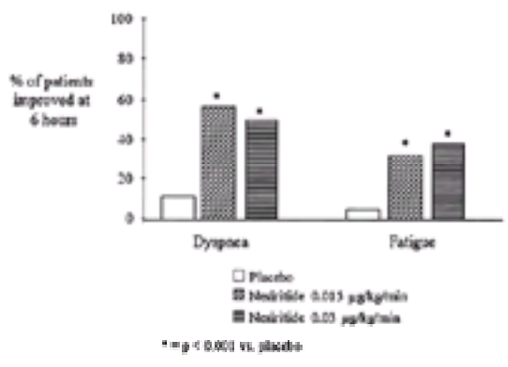
Toborinone exerts positive inotropic activity and balanced vasodilation primarily through phosphodiesterase III inhibition (129,130). Clinical evaluations of this compound have identified favorable hemodynamic benefits in heart failure during short-term intravenous administration, including improvements in cardiac output and reductions in ventricular filling pressure and vascular resistances coincident with reductions in MVO_2 (129,130 and 131). Unlike most other cardiotonic medications, toborinone does not appear to increase heart rate at hemodynamically effective doses.

Toborinone seems to act primarily as a venodilator at low dosages (similar to nitrates), whereas at higher infusion rates, conductance vessels are dilated, which produces a balanced vasodilator effect (132). As with other phosphodiesterase III inhibitors, the inotropic and vasodilating properties of toborinone are cAMP dependent and thus may be associated with similar adverse effects.

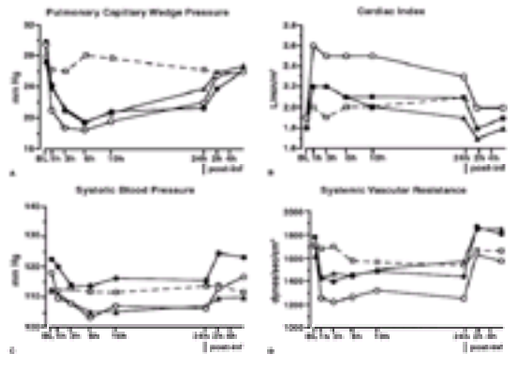
Natriuretic Peptides

The concentrations of circulating endogenous natriuretic peptides are known to be increased in patients with heart failure. These peptides are produced by the myocardium in response to increased myocyte stretch and wall tension resulting from an elevation in ventricular pressure. Elevated circulating levels appear to correlate with disease severity (133). The physiologic actions of endogenous natriuretic peptides only partially counteract the harmful effects of other neurohormones that are elevated in heart failure, specifically renin, aldosterone, and norepinephrine. By targeting various biologic sites, natriuretic peptides act as balanced vasodilators while also producing a mild degree of natriuresis and lusitropy.

Because of these beneficial hemodynamic effects, the postulation has been that the intravenous administration of natriuretic peptides may be beneficial in managing patients with decompensated heart failure. Nesiritide, a recombinant human brain natriuretic peptide, is currently being evaluated in clinical trials of acute and decompensated heart failure. The intravenous administration of this agent has been shown to produce favorable hemodynamic effects, including balanced vasodilation associated with a rapid improvement in heart failure clinical symptoms (*e*Fig. 91.4.1). Several trials have identified a dose-related reduction in ventricular filling pressures and augmentation in left ventricular stroke volume after both bolus administration and continuous infusion of nesiritide (134,135). These effects appear to be sustained during continuous administration over 24 hours (136) (*e*Fig. 91.4.2). Nesiritide compares favorably to standard inotropic and vasodilator therapy for heart failure with a trend toward fewer side effects (137). Clinical trials have identified the following adverse reactions to nesiritide:



***e*FIGURE 91.4.1** Effect of nesiritide and placebo on dyspnea and fatigue. Compared to placebo, nesiritide evoked a dose-related improvement in the symptoms of dyspnea and fatigue after 6 hours of infusion in hospitalized patients with decompensated heart failure. (From Colucci WS, Elkayam U, Horton DP, et al., for the Nesiritide Study Group. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure*. N Engl J Med* 2000;343:246–253.)



***e*FIGURE 91.4.2** Mean observed hemodynamic values from baseline (BL) through 24 hours and 4 hours postinfusion (post-inf) of nesiritide in patients with symptomatic heart failure. As early as 1 hour after initiation of nesiritide infusion, the pulmonary capillary wedge pressure **(A)** was significantly reduced below baseline. A dose-related decrease in cardiac index **(B)**, systolic blood pressure **(C)**, and systemic vascular resistance **(D)** was also observed. Importantly, no evidence was seen of a rebound effect after infusion in any of the treatment groups. Open squares: placebo; filled circles: 0.015 µg per kg per minute; filled triangles: 0.03 µg per kg per minute; open circles: 0.06 µg per kg per minute. [From Mills RM, LeJemtel TH, Horton DP, et al., on behalf of the Natrecor Study Group. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure. *J Am Coll Cardiol* 1999;34:155–162, with permission.]

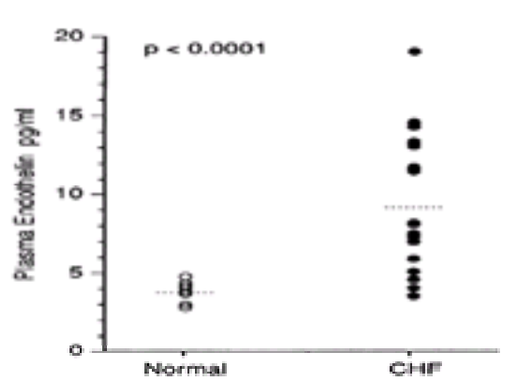
- Hypotension (symptomatic or asymptomatic)
- Nausea
- Bradycardia
- Nervousness
- Confusion
- Headache

The most common of these are dose-related hypotension, which is usually asymptomatic, and nausea. Significant proarrhythmia, a common concern during positive inotropic therapy, has not been observed during nesiritide infusion.

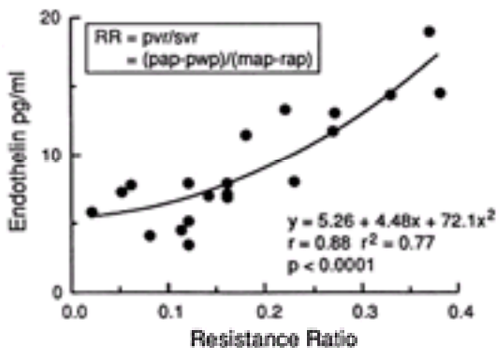
The Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial has been completed and the preliminary results have been presented. This trial was conducted in response to the FDA's request for additional clinical data concerning the efficacy of nesiritide compared with standard vasodilator therapy using intravenous nitroglycerin. The VMAC trial was a multicenter, randomized, double-blind comparison of the hemodynamic and clinical effects of nesiritide, intravenous nitroglycerin, and placebo when added to standard therapy (including dobutamine, dopamine, and diuretics) in patients with acutely decompensated congestive heart failure. Preliminary results indicate that nesiritide achieved a greater hemodynamic and clinical benefit than did intravenous nitroglycerin with fewer adverse effects.

Endothelin Receptor Antagonists

Endothelin (ET-1) is a potent vasoconstrictor, the level of which is elevated in patients with congestive heart failure (138,139) (*e*Fig 91.4.3). This endogenous peptide, which activates endothelin type A and B receptors (located on vascular smooth muscle and vascular endothelium, respectively), is yet another neuropeptide that is likely a significant contributor to the pathophysiology of heart failure (see Chapter 88). ET-1 levels have been shown to correlate strongly with pulmonary vascular resistance in severe congestive heart failure, which suggests that ET-1 mediates the reactive pulmonary hypertension seen in this condition (138) (*e*Fig. 91.4.4). Therefore, clinical trials are under way to evaluate the potential benefit of endothelin receptor antagonists in treating both acute and chronic heart failure as well as pulmonary hypertension.

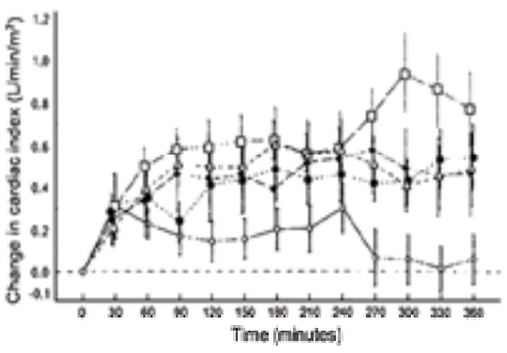


***e*FIGURE 91.4.3** Comparison of levels of plasma immunoreactive endothelin-1 in healthy subjects and patients with congestive heart failure (CHF). A threefold increase in mean levels of endothelin-1 was seen in the patients with heart failure compared with healthy subjects. (From Cody RJ, Haas GJ, Binkley PF, et al. Increased plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. *Circulation* 1992;85:504–509, with permission.)

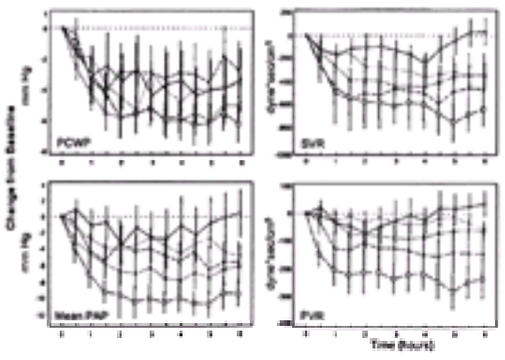


***e*FIGURE 91.4.4** Correlation of the resistance ratio (RR) with plasma endothelin level in patients with heart failure. A strong relationship is seen between endothelin plasma activity in heart failure and the degree of secondary pulmonary hypertension. map, mean arterial pressure; pap, pulmonary artery pressure; pvr, pulmonary vascular resistance; pwp, pulmonary wedge pressure; rap, right atrial pressure; svr, systemic vascular resistance. (From Cody RJ, Haas GJ, Binkley PF, et al. Increased plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. *Circulation* 1992;85:504–509.)

Tezosentan is a short-acting, parenteral dual endothelin receptor antagonist. This drug, because of its water solubility and short plasma half-life, seems particularly promising and is undergoing phase III clinical trials targeting the acute heart failure population (140). A study comparing tezosentan to placebo in the treatment of severe heart failure identified a dose-dependent increase in cardiac index during tezosentan administration (141) (*e*Fig. 91.4.5). A significant reduction in PCWP and systemic and pulmonary vascular resistances also resulted from endothelin receptor blockade (*e*Fig. 91.4.6). Importantly, heart rate remained unchanged. Tezosentan did not produce significant hypotension or proarrhythmia (141). These findings support a potential role for tezosentan in the treatment of acute heart failure; however, further studies may be necessary before final FDA consideration.



***e*FIGURE 91.4.5** Effect of endothelin receptor blockade with tezosentan on cardiac index in patients with severe heart failure. Depicted are the changes in cardiac index over the course of treatment with placebo (*open circles*) or tezosentan at 5 mg per hour (*filled circles*), 20 mg per hour (*open triangles*), 50 mg per hour (*filled diamonds*), and 100 mg per hour (*open squares*). Dose-trend analysis of the change from baseline to the end of treatment (hour 6) in cardiac index with the four tezosentan dosages showed a significant dose relationship (*p* = .038). (From Torre-Amione G, Young JB, Durand JB, et al. Hemodynamic effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients with class III to IV congestive heart failure*. Circulation* 2001;103:973–980, with permission.)



***e*FIGURE 91.4.6** Acute hemodynamic changes during tezosentan infusion. Change from baseline in pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (mean PAP), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) over the treatment period with placebo (*open circles*) or tezosentan at 5 mg per hour (*filled circles*), 20 mg per hour (*open triangles*), 50 mg per hour (*filled diamonds*), and 100 mg per hour (*open squares*). Tezosentan produces favorable acute hemodynamic changes during short-term infusion in patients with severe heart failure. (From Torre-Amione G, Young JB, Durand JB, et al. Hemodynamic effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients with class III to IV congestive heart failure*. Circulation* 2001;103:973–980, with permission.)

HEMODYNAMIC MONITORING IN ACUTE HEART FAILURE

Catheterization with a flow-directed thermodilution pulmonary artery catheter (Swan-Ganz catheter) is often indicated for optimal management of acute heart failure. Although hemodynamic monitoring is rarely necessary in uncomplicated cases of acute pulmonary edema, it is often helpful in the patient who does not respond initially to standard therapy (usually nitroglycerin and diuretics) and is vital in managing those with persistent hypotension and preshock or shock syndromes (2) (Table 91.4). These patients have evidence of hypoperfusion on examination, including a narrow pulse pressure, cool skin, reduced urine output, and mental obtundation. Continuous assessment of cardiac output and ventricular filling pressure is essential to appropriately guide and determine the effectiveness of pharmacologic therapy or assess the need for mechanical support. Other indications for hemodynamic monitoring include acute heart failure in which volume status is in question and pulmonary edema in which a cardiac cause has not been definitely determined (2,142,143). As discussed previously, some patients presenting with acute cardiogenic pulmonary edema may have only mild elevation of PCWP. This is typically a result of reduced plasma volume from extravasation of water outside of the pulmonary capillaries further complicated by diuretic therapy. Hemodynamic monitoring may also be diagnostically helpful in further defining the severity of hemodynamic compromise due to specific lesions or conditions such as pericardial tamponade, right ventricular infarction, ventricular septal rupture, or circulatory collapse secondary to various shock syndromes (Table 91.5) (143).

Acute pulmonary edema
- After poor response to initial treatment
- To exclude noncardiogenic pulmonary edema

Cardiogenic shock or preshock syndrome not responsive to initial fluid challenge

Acute decompensation of chronic heart failure (to allow tailored therapy)

Questionable volume status

TABLE 91.4 INDICATIONS FOR PULMONARY ARTERY CATHETERIZATION AND HEMODYNAMIC MONITORING IN ACUTE HEART FAILURE

	CO	RAP	PAP	PCWP	SVR	SvO_2
Acute pulmonary edema	Variable	→	Variable	Variable	Variable	Variable
Cardiogenic shock	↓	↑	↑ or →	↑ or →	↑↑	↓↓
Decompensated heart failure	↓	↑	↑↑	↑↑	↑	↓
Acute right ventricular failure	↑	↑↑	→ or ↓	→ or ↓	↑	↓
Massive pulmonary embolism	↓	↑	↑	→	↑	↓
Acute aortic/mitral valve insufficiency	↓	→	↑	↑↑	↑	↓
Tamponade	↓	↑*	↑*	↑*	↑	↓
Hypovolemic shock	↓	↓	↓	↓	↑	↓

↑, increased; →, normal; ↓, decreased; ↑↑, markedly increased; ↓↓, markedly decreased; CO, cardiac output; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance
*Equalization of pressure is characteristic.

TABLE 91.5 COMMON HEMODYNAMIC PATTERNS IN LOW CARDIAC OUTPUT STATES

The major parameters measured during hemodynamic monitoring are cardiac output, PCWP, systemic arterial pressure (usually measured with an indwelling arterial catheter), heart rate, and the calculated SVR (mean arterial pressure minus mean right atrial pressure, divided by cardiac output). The measurement of mixed venous oxygen saturation is also important (143,144), particularly when the thermodilution cardiac output may not be reliable (i.e., in cases of tricuspid regurgitation). By repeated assessment of these parameters, pharmacologic therapy using the agents previously discussed can be more effectively tailored to achieve the optimal hemodynamics for the individual patient (145). The therapeutic approach must take into account not only the presenting hemodynamics but also the cause of the underlying condition. For example, the optimal PCWP for patients with acute myocardial injury is higher (18 to 20 mm Hg) (9,146) than that for patients with acutely decompensated chronic heart failure in which a normal PCWP (10 to 12 mm Hg) is often the goal (147). Even when the underlying condition is known and general hemodynamic goals have been defined, individualization of therapy is important. Metabolic demand may be significantly different among individuals, and often significant variability exists in individual peripheral oxygen extraction ratios and oxygen use. Because of these differences, some patients tolerate a much lower cardiac output than others. Therefore, parameters in addition to hemodynamics must be considered when treating severe heart failure, and assessment should include a physical examination with attention to peripheral perfusion, urine output, and mentation. The blood lactate level is an important prognostic indicator in shock and is also useful in guiding therapy (148,149).

The use of hemodynamic monitoring in the management of critically ill heart-failure patients has come under scrutiny since the publication of data from the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (150). In this study, patients undergoing right heart catheterization had a significantly lower survival at 30 days than did those not undergoing this invasive monitoring approach. Drawing conclusions from this trial is difficult, however, because only 11% of patients had heart failure as the primary reason for admission to the intensive care unit and multisystem failure was present in the majority (150). Greater insight into the utility of invasive hemodynamic monitoring in the management of decompensated heart failure should be available after completion of an ongoing randomized, controlled trial [Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE)] sponsored by the National Institutes of Health.

GENERAL APPROACH TO THE MANAGEMENT OF ACUTE HEART FAILURE

Acute Cardiogenic Pulmonary Edema

The patient presenting with acute pulmonary edema is often in great distress, and the diagnosis is usually not in question because of the dramatic nature of the clinical presentation. Although the ultimate management strategy is dictated by the precipitating factor or factors causing pulmonary edema, initial therapy must be guided by the early clinical findings until a definitive diagnostic evaluation can be completed. As mentioned previously, the evaluation for precipitating factors and the initial therapeutic intervention usually occur simultaneously.

The management strategy for the patient with acute cardiogenic pulmonary edema is outlined in Table 91.6. Nitroglycerin, administered by the sublingual route, is a rational first step in the treatment of most patients (2). This preload-reducing agent, which can be administered every 5 minutes, often relieves a significant amount of the sensation of breathlessness and can provide a bridge for preparation of the patient for further treatment and diagnostic procedures. Sublingual nitroglycerin is an effective means of immediately reducing preload and afterload until the intravenous preparation can be infused (49,51). If afterload reduction is the most important objective, as in a patient with pulmonary edema, acute valvular insufficiency, or hypertension, or if the response to nitroglycerin is suboptimal, nitroprusside should be substituted or added for its balanced vasodilator effect. An indwelling arterial catheter for continuous monitoring of systemic blood pressure is optimal but not mandatory for initiation of treatment. Intravenous furosemide should also be administered early in the clinical course but with care to avoid overdiuresis. In acute heart failure, intravascular volume is often normal or low; judicious diuretic therapy is useful primarily for its early vasodilator effect (108,109 and 110). The patient's failure to respond within a reasonable period to these measures should warrant strong consideration of hemodynamic monitoring and the addition of inotropic therapy (Table 91.4; also see the section Cardiogenic Shock and Decompensated Heart Failure).

Sublingual nitroglycerin
- 0.4 mg every 5 min

Intravenous nitroglycerin
- Start at 0.2 to 0.4 μg/kg/min

Intravenous furosemide
- 20 to 40 mg i.v.
- Follow volume status closely

Sodium nitroprusside if further afterload reduction required

Supplemental oxygen/mechanical ventilation as guided by arterial blood gas analysis

Consider intravenous morphine sulfate (2 to 6 mg) if no pulmonary contraindication

Electrocardiogram
- Exclude myocardial infarction

Echocardiography
- Evaluate ventricular function, valvular status

Proceed with urgent coronary angiography if reperfusion therapy indicated

TABLE 91.6 INITIAL MANAGEMENT OF ACUTE CARDIOGENIC PULMONARY EDEMA

In the acute setting, patients with pulmonary edema may also benefit from morphine sulfate 2 to 6 mg given intravenously (50). This medication may have an immediate hemodynamic effect through its preload-reducing properties. It may also alleviate anxiety and blunt the catecholamine response to the acute illness. Caution must be used, however, in patients with evidence of respiratory or metabolic acidosis or in those with significant underlying obstructive lung disease.

Supplemental oxygen is traditionally administered to patients with acute pulmonary edema regardless of arterial oxygen saturation. This is essential in the patient with hypoxemia; however, its utility in those with normal oxygen saturation is questionable, and typically therapy is empiric. Although patients may receive a subjective benefit, supplemental oxygen administration may have an adverse effect on central hemodynamics in patients with chronic heart failure (151). Optimally, one should obtain information from arterial blood gas analysis before administering supplemental oxygen. When severe respiratory distress or acidosis is present, the threshold for proceeding to mechanical ventilatory support should be low. This not only corrects hypoxemia but also may reduce metabolic demands and therefore favorably affect the relationship between oxygen delivery and utilization (144).

Early in the treatment of the patient with acute heart failure, a directed history and physical examination, electrocardiography, and usually transthoracic two-dimensional echocardiography should be performed to determine the presence of myocardial injury and assess the severity of cardiac dysfunction (2). Evidence of acute myocardial infarction would warrant proceeding to cardiac catheterization with consideration of urgent reperfusion therapy. A diligent effort must be made to identify the cause of acute heart failure, because without correction of a reversible lesion, the long-term prognosis is poor (3).

Cardiogenic Shock and Decompensated Heart Failure

Patients with acute unstable heart failure (preshock or shock syndromes) require an expedient diagnostic evaluation and therapeutic plan. They usually exhibit severe cardiac dysfunction and hemodynamic compromise, and often present with symptoms and signs of organ hypoperfusion (cyanosis, cool extremities, altered mentation) (13). If the high mortality associated with this syndrome is to be avoided, a rapid diagnostic evaluation and institution of supportive therapy (pharmacologic and mechanical) is necessary.

In patients with acute decompensation of chronic heart failure, the underlying heart disease is often known. In this setting, the therapeutic strategy incorporates a search for factors precipitating acute decompensation. Patients are usually receiving standard medical therapy for chronic heart failure, and a reparable lesion is less likely to be identified. Nevertheless, one must always consider the possibility of correctable ischemic myocardial dysfunction if a prior assessment for coronary artery disease has not been performed.

When cardiogenic shock occurs or when standard therapy fails to stabilize decompensated chronic heart failure, hemodynamic monitoring to guide pharmacologic support is essential (142,143,145). In addition, hemodynamic evaluation, along with the physical examination and echocardiography, can assist in the identification of common shock syndromes requiring specific forms of therapy (e.g., right ventricular infarction) (143,152) (Table 91.5).

Figure 91.5 provides a general approach to the selection of specific intravenous pharmacologic agents based on hemodynamic profile. The initial therapeutic decision is influenced primarily by systemic arterial pressure. Although the optimal systolic or mean arterial pressure for the individual patient is variable, a systolic arterial pressure of less than 80 to 85 mm Hg would be classified as significant hypotension when accompanied by evidence of organ hypoperfusion, such as renal dysfunction and altered central nervous system activity. When this clinical situation presents, arterial pressure must be rapidly augmented to the level at which myocardial perfusion is not jeopardized. General hemodynamic goals would include increasing the cardiac index above 2.2 L per minute per m^2, reducing the PCWP below 20 mm Hg (15 mm Hg or less in chronic heart failure), maintaining SVR at 1,000 to 1,200 dynes per second per cm^5, and reducing right atrial pressure to 7 mm Hg or less (Table 91.7) (153). For the individual patient, these goals will vary depending on the nature and acuteness of the cardiac dysfunction. The optimal PCWP would be the lowest pressure that can be maintained without a preload-related decline in systolic arterial pressure or cardiac index. In dilated cardiomyopathy and severe systolic dysfunction, stroke volume is primarily afterload-dependent and is affected minimally by manipulation of preload (19,154). Therefore, relatively normal PCWP can be targeted (147). The optimal SVR would be the lowest that one could achieve while maintaining adequate systemic perfusion.

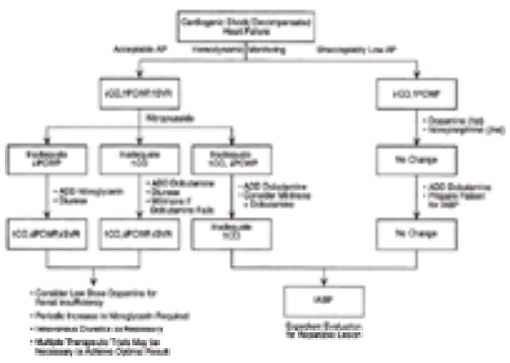


FIGURE 91.5 Algorithm for hemodynamics-directed pharmacologic support of cardiogenic shock and decompensated heart failure.↑, increased; ↓, decreased; AP, arterial pressure; CO, cardiac output; IABP, intraaortic balloon pump; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

TABLE 91.7 HEMODYNAMICS-DIRECTED PROTOCOL FOR TREATMENT OF DECOMPENSATED HEART FAILURE

When significant systemic hypotension is present, therapy with vasopressor doses of dopamine (more than 5 µg per kg per minute) should be used (99,100). Failure to achieve an acceptable blood pressure response with high-dose dopamine would warrant consideration of switching to another vasopressor, such as norepinephrine or vasopressin, or adding dobutamine (71,76). In either case, preparations should be made for proceeding to mechanical assistance if appropriate (see the section Circulatory Support Devices). In refractory hypotension and shock, the mortality is extremely high if a surgically correctable lesion is not identified or if mechanical support (as a bridge to transplantation) is not an option (2).

Unstable or decompensated heart failure with low cardiac output but acceptable arterial pressure may initially be treated with nitroprusside to augment stroke volume and reduce the quantity of valvular regurgitation (19,21). A failure to augment cardiac output with this approach would warrant consideration of dobutamine or milrinone to enhance inotropy and vasodilation (71,74,79,86,87,89,118). If cardiac output increases appropriately with nitroprusside but left ventricular filling pressure remains elevated, then nitroglycerin can be added for further preload reduction (21,26,28,29). If both cardiac output and PCWP remain unacceptable, the option of changing to or adding milrinone should be considered (86,88,118,121). Other therapeutic considerations would include the addition of low-dose dopamine to augment renal blood flow, frequent assessment of volume status and appropriate intravenous diuretic administration, and upward titration of intravenous nitroglycerin when hemodynamic tolerance develops (52,95,96 and 97,108,110,116).

The approach to the pharmacologic support of the patient with cardiogenic shock or severely decompensated heart failure must be individualized. Evaluation of multiple clinical variables is often necessary for appropriate drug selection. Even then, several therapeutic trials may be required. When pharmacologic support obviously will not be sufficient to avoid progressive circulatory failure, then mechanical assistance must be considered.

CIRCULATORY SUPPORT DEVICES

Overview of Available Devices

In cardiology, few situations are as dramatic as observing the successful use of circulatory-support-device technology in an individual about to succumb to acute heart failure with cardiogenic shock and devastating hemodynamic profiles. A wide spectrum of mechanical circulatory assistance devices is now available and can provide extended hemodynamic support for patients showing acute deterioration while awaiting definitive therapy (see Chapter 95). Implantable ventricular assist devices successfully provide extended support for patients hemodynamically deteriorating to the degree that they are unlikely to survive until transplantation. This observation served as a major impetus for the successful development of many circulatory support systems (155,156 and 157). Many types of ventricular assist devices have also been used as a bridge to recovery. In select individuals suffering shock after acute myocardial infarction or myocarditis, timely insertion of mechanical support can allow for recovery of the injured heart so that primary responsibility for hemodynamic support can ultimately once again be carried by the heart. Indeed, relieving pressure and stress-load burdens from the injured myocardium might be therapeutic in and of itself.

Many devices are available that can provide one degree or another of circulatory support. These range from the intraaortic balloon counterpulsation pump (IABP), extracorporeal membrane oxygenation (ECMO) systems, and univentricular and biventricular nonpulsatile and pulsatile devices to the total artificial heart. *e*Table 91.7.1 lists the various options currently available. Many of these devices are commercially available for routine use (the IABP, nonpulsatile extracorporeal centrifugal pump, ECMO, extracorporeal pulsatile devices, and the pneumatic intracorporeal pulsatile HeartMate device). Others must be used according to FDA-monitored research protocols.

***e*TABLE 91.7.1** CIRCULATORY SUPPORT DEVICES

Intraaortic counterpulsation balloon
Nonpulsatile extracorporeal pumps
BioMedicus (centrifugal)
Nonpulsatile intracorporeal centrifugal pumps
Nimbus Hemopump (axial flow)
DeBakey-NASA (axial flow)
Extracorporeal membrane oxygenator
Extracorporeal pulsatile devices
Pierce-Donachy Thoratec
Abiomed BVS 5000
Intracorporeal pulsatile devices
Novacor
HeartMate
Total artificial heart
CardioWest
Penn State Pneumatic

Ventricular-assist-device implantation today is playing a greater role in heart transplantation (158). At some centers as many as 30% to 50% of patients undergoing cardiac transplantation are being bridged to that procedure with a ventricular assist device. Posttransplant outcome in these patients is now excellent, with survival rates at some centers exceeding 90% for patients successfully bridged to transplantation. Approximately three-fourths of patients undergoing ventricular-assist-device insertion with this intention survive.

Patient Selection

Table 91.8 summarizes many considerations that come into play when ventricular assist devices or other circulatory-support machinery is considered for the individual patient. Devices capable of being used as a short-term bridge to cardiac transplantation can be singled out. Devices used to “bail out” a patient from acute shock (such as might occur after myocardial infarction) or used for a more subacute insertion in a patient with “preterminal” heart failure and hemodynamics are in this category. Furthermore, some patients undergo device insertion with the idea of bridging to recovery. These patients are those likely to be suffering acute inflammatory conditions of the heart or shock syndromes rooted in difficulties with stunned or hibernating myocardium. The reality and implications of using ventricular-assist-device insertion long term as an alternative to cardiac transplantation are just beginning to be explored. Obviously, mechanical circulatory support and, more specifically, ventricular-assist-device insertion, attenuates the multifactorial difficulties apparent in circulatory decompensation. Pump dynamics are important, as is flow. That ventricular-assist-device insertion can dramatically reverse the neurohumoral perturbation characteristic of heart failure states has been elegantly demonstrated. These devices are capable of returning catecholamine levels, for example, to near normal (159).

Patient selection
Short-term bridge to heart transplantation
Acute insertion: bailout from acute shock (after myocardial infarction)
Subacute insertion: insertion in patients with "preterminal" heart failure
Short-term bridge to recovery
Long-term alternative to transplantation
Ventricular-assist device interdiction of circulatory decompensation
Pump dynamics
Flow dynamics
Impact on neural-humoral perturbation
Troublesome circumstances
Small patient size
Cachexia
Infection (particularly sepsis)
Fixed pulmonary hypertension
Substantive right heart failure
Significant hepatic or renal dysfunction
Malignant tachyarrhythmias (atrial and ventricular)
Hypercoagulable states
Consumption coagulopathy
Acute/chronic pulmonary emboli
Challenging acute clinical situations
Myocardial infarction with shock
Cardiac arrest with ongoing cardiopulmonary resuscitation
Failure to wean from cardiopulmonary bypass after open heart surgery

TABLE 91.8 CONSIDERATIONS FOR VENTRICULAR-ASSIST DEVICE INSERTION IN CASES OF ADVANCED HEART FAILURE

Indications for emergency mechanical support vary. Patients with long-standing heart failure deteriorate more slowly than those with the recent onset of ventricular dysfunction, but patients with both acute and chronic heart failure can be saved with this technology. One must remember that exacerbation of chronic heart failure frequently reverses after aggressive adjustment of tailored medication and resolution of concomitant difficulties such as acute ischemia or infection (145). Such patients do not require mechanical circulatory support. In general, the indication for the use of circulatory-support devices is evidence of critical organ hypoperfusion despite aggressive and adequate medication therapies, including infusion of inotropic drugs such as milrinone and dobutamine, as previously discussed.

Hemodynamic parameters that characterize severe end-stage heart failure vary from patient to patient, and these indicators should be analyzed over long periods of time rather than at any one given moment. Generally, an inability to maintain a systolic blood pressure greater than 75 to 80 mm Hg, cardiac index greater than 1.5 to 2.0 L per minute per m^2, and mixed pulmonary venous saturation of more than 50% on aggressive oral and parenteral pharmacotherapeutic support defines a patient who might benefit from use of a support device. When analyzing hemodynamics, one should ensure that adequate ventricular filling pressures are present but not inordinately elevated. Invariably, reduction of left ventricular filling pressures below 25 to 30 mm Hg leads to improvement in cardiac output, because high ventricular filling pressures are frequently causing significant mitral regurgitation (160). Persistently elevated high right atrial pressures (mean pressure greater than 20 mm Hg) despite reduction in PCWP identifies a patient population not likely to be easily stabilized with long-term drug therapy. Unfortunately, this characteristic hemodynamic pattern also identifies individuals who might be at risk for right ventricular failure after support-device implantation. A goal should be to attempt to lower pulmonary vascular resistance below 5 Wood units and to maintain SVR at 1,000 to 1,200 dynes per second per cm^5. Deterioration during pharmacologic bridge to cardiac transplantation is generally manifest by an insidious drop in urine output, rising creatinine levels, and tachycardia (161).

Contraindications to circulatory-support-device insertion relate largely to device choice and therapeutic goal. For implantable left ventricular assist devices, technical contraindications include a body surface area less than 1.5 m^2 or greater than 2.5 m^2 or a weight greater than 150% of the patient’s ideal body weight. Currently, most implantable devices are large and will not fit into very small patients. Obese patients can have problems with percutaneous access sites and are at higher risk for comorbid events such as pulmonary embolism. A highly calcified aorta, particularly at the proposed site of outflow conduit anastomoses, can be problematic, as can substantive aortic insufficiency. Presence of a prosthetic aortic valve is considered to be a contraindication to ventricular-assist-device insertion because frequently the aortic valve closes permanently as blood is pumped during diastole into the ventricular assist device. This sets the stage for thromboembolism. Some device controllers that regulate the circulatory pressure/electrocardiography/device interphase react adversely in electrical fields in which pacemakers or defibrillating units are present. Therefore, pacemaker dependence or presence of an implanted defibrillating device may be a contraindication to the use of certain ventricular assist devices. Certainly, the inability to deliver long-term anticoagulation therapy to a patient is also cause for great concern. As suggested, hemodynamic contraindications to device insertion

might include significant right heart failure as reflected by right atrial pressures higher than 20 mm Hg despite aggressive medical therapy. Likewise, patients with a PCWP below 15 mm Hg and a cardiac index of more than 2 L per minute per m^2 without the use of parenteral inotropes represent a population that might, although very sick, do reasonably well without insertion of a circulatory support device.

Pulmonary contraindications to device insertion might include long-term ventilator dependency, recent pulmonary embolism, or the presence of markedly impaired pulmonary function, particularly that characteristic of chronic obstructive pulmonary disease (forced expiratory volume in 1 second less than 50% of predicted, for example). As mentioned, fixed pulmonary hypertension can lead to right heart failure and set the stage for low systemic flows during left ventricular-assist-device insertion. Generally, those patients with systolic pulmonary artery pressures greater than 70 mm Hg, transpulmonary gradient greater than 17 mm Hg, and pulmonary vascular resistance greater than 5 Wood units while on intensive vasodilator therapy are poor candidates for ventricular-assist-device insertion or the use of circulatory-support devices in general. Peripheral vascular disease can produce complications after device insertion as well. Significant abdominal aortic aneurysm (larger than 4.5 cm) carries the risk for rupture at the higher pulsatile flows generated by these devices. Peripheral vascular disease in general, with significant limb claudication or limb risk due to low flow states, can arise from device insertion. Cerebrovascular disease can also be a contraindication to ventricular-assist-device insertion, and, in particular, a prior stroke or transient ischemic episode in the presence of internal carotid artery plaque or lesion is considered a contraindication. Active infection is a great concern, because these devices are susceptible to microbial organism seeding and may give rise to chronic endocarditis. Often, the organisms cannot be eliminated with antimicrobial therapy with the device still in place. Irreversible end-organ dysfunction is also associated with high mortality after device insertion. Hepatic cirrhosis must be ruled out, and a liver biopsy should be performed when questions arise. Liver enzyme levels greater than three times the upper limit of normal or a bilirubin level greater than 3 mg per dL should be of great concern and prompt serious consideration of postponing device insertion. Patients with platelet counts of less than 50,000, primary coagulopathy, prothrombin time with an international normalized ratio greater than 1.8, or activated partial thromboplastin time greater than twice the control value in patients not on an anticoagulant do not make good candidates for mechanical circulatory support. Likewise, a serum creatinine level of more than 3 mg per dL or creatinine clearance of less than 30 mg per hour predicts poor outcome. Finally, psychosocial issues that might impair compliance with prescribed regimens after device insertion represent contraindications. Alcohol dependency or abuse, major psychiatric illness, and inadequate social support matrixes will likely be associated with failure to survive device implantation (*e*Table 91.8.1). The choice of a particular circulatory-support device (*e*Table 91.7.1) is based on patient presentation characteristics. Potentially reversible difficulties requiring only short-term support would be best treated by an IABP or extracorporeal pulsatile device. Sometimes the IABP is used as a “bridge to a bridge,” that is, this device is inserted to stabilize a patient long enough to make definitive decisions regarding ventricular-assist device insertion. Patients not likely to improve solely with this limited form of support might be considered candidates for insertion of intracorporeal pulsatile devices that can be used over the long term. Sometimes patients receiving left ventricular assist devices require temporary right ventricular assistance with a separate pump that can be subsequently removed.

***e*TABLE 91.8.1** FACTORS TO CONSIDER WHEN EVALUATING PATIENTS FOR VENTRICULAR-ASSIST DEVICE INSERTION
Technical contraindications
Body surface area <1.5 m^2 or >2.5 m^2
Weight greater than 150% of ideal
Highly calcified aorta (particularly at proposed site of outflow conduit anastomosis)
Moderate to severe aortic insufficiency
Prosthetic aortic valve
Pacemaker dependence or presence of an implantable defibrillating device
Contraindication to anticoagulation
Hemodynamic contraindications
Right atrial pressure >20 mm Hg despite aggressive diuresis and vasodilator therapy
Pulmonary capillary wedge pressure generally <15 mm Hg when treated
Cardiac index generally >2.0 L/min/m^2 without use of parenteral inotropes
Pulmonary contraindications
Long-term ventilator dependency
Recent pulmonary embolism
Substantively impaired pulmonary function (forced expiratory volume in 1 sec <50% predicted)
Fixed pulmonary hypertension (systolic pulmonary artery pressure >60 mm Hg, transpulmonary gradient >17 mm Hg, pulmonary vascular resistance >5 Wood units while on intensive pulmonary vasodilator therapy)
Peripheral vascular contraindications
Significant abdominal aortic aneurysm (>4.5 cm)
Peripheral vascular disease with limb claudication
Cerebrovascular disease (prior stroke or transient ischemic episode in the presence of internal carotid artery plaque/lesion)
Active systemic infection (fever >38°C)
Irreversible end-organ dysfunction
Hepatic cirrhosis
Liver enzymes >3× upper limit of normal or bilirubin >3.0 mL/dL
Platelet count <50,000
Primary coagulopathy
Prothrombin time with international normalized ratio >1.8 or activated partial thromboplastin time more than twice control value in patients not on anticoagulant therapy
Serum creatinine >3.0 mg/dL or creatinine clearance <30 mL/h
Psychosocial issues that might impair compliance
Alcohol dependence or abuse
Major psychiatric illness
Inadequate social support systems

CONTROVERSIES AND PERSONAL PERSPECTIVES

The complexity and significant mortality associated with the acute heart failure syndrome have served to generate a broad spectrum of potential therapeutic modalities, as has been discussed. Potent intravenous vasodilator and inotropic drugs, designed to correct specific hemodynamic abnormalities, are now available for use alone, or in combination, to support patients with acute pulmonary edema as well as those with severe cardiac dysfunction and cardiogenic shock. New drug therapies targeting more specific hemodynamic and neurohormonal perturbations are promising. Advancements in medical technology have improved the ability to monitor and evaluate continuously the patient with severe hemodynamic compromise so that medical therapy can be appropriately tailored. For those not responding to aggressive pharmacologic management, short- and long-term mechanical assist devices can now be used to support the sickest of patients until further therapeutic options are explored. These advances in the ability to treat and support the patient with acute heart failure allow for a more thorough and aggressive diagnostic evaluation in many instances. As emphasized throughout this chapter, the finding of a treatable condition has important prognostic implications, and the ability to uncover a reparable lesion in an individual with heart failure continues to improve. The continued advancements in reperfusion strategies (thrombolysis, angioplasty, antithrombotic therapy) as well as improved outcome after high-risk coronary bypass surgery provides a means potentially to avoid irreversible myocardial injury and its sequela of severe heart failure. These therapeutic options also offer some encouragement that the high mortality of cardiogenic shock may be favorably altered in the future. Various reperfusion strategies continue to undergo clinical investigation.

The advances in technological support and treatment options for acute heart failure, however, have not simplified its management. The significance of the initial clinical assessment and treatment plan cannot be overemphasized. Due to the complexity and diverse nature of the acute heart failure syndrome, diagnostic and therapeutic strategies must be individualized and a “cookbook” approach to pharmacologic therapy or other modes of support cannot be advocated. Certainly, the patient presenting with acute pulmonary edema and hypertension is treated differently from the patient with a large anterior myocardial infarction presenting with congestion and hypotension. Within these two extremes lies a great diversity of acute heart failure presentations, each with subtle differences requiring a different diagnostic and therapeutic approach. Therefore, the basics of patient care cannot be ignored but must be used in conjunction with advanced monitoring capabilities.

The algorithm for the pharmacologic management of heart failure presented in this chapter should be viewed as a generalized approach to therapy in which various treatment trials may be necessary. Even when one uses specific drugs with known hemodynamic profiles, close observation and monitoring are essential because the response of a given patient is not always predictable. For example, dobutamine administration is often avoided in the setting of myocardial ischemia and marginal cardiac output because of the perceived potential for inducing worsening ischemia and myocardial dysfunction or arrhythmia, or both. As has been discussed, dobutamine may also evoke hemodynamic effects that are favorable, even in the setting of ongoing ischemia. Some individuals, however, experience untoward effects if the drug is not judiciously administered. (For instance, one should not administer dobutamine to those with normal or low left ventricular filling pressures, and rapid titration or initiation at a dosage greater than 5 µg per kg per minute should also generally be avoided.) The identification of an excessive heart-rate response during dobutamine titration would also identify the patient with marginal cardiac reserve and potential for adverse effects. Therefore, repeated clinical evaluation in conjunction with appropriate medication adjustment is necessary.

Hemodynamic monitoring should be used in concert with, but should not replace, the overall clinical assessment. Unfortunately, major alterations in therapy based solely on hemodynamic parameters are often seen in intensive care settings. For example, a cardiac index of 2.2 L per minute per m^2 might lead to an increase in

inotropic therapy even though no evidence of organ hypoperfusion otherwise exists. This pharmacologic manipulation based only on hemodynamics without account taken of other important clinical variables is often not necessary and potentially detrimental.

At the other end of the spectrum are patients who continue to exhibit clinical deterioration despite maximal pharmacologic support. In this scenario an early decision to proceed with mechanical assistance is imperative. Failure to recognize this and proceed to mechanical assistance in an expedient manner, unfortunately, is common. Often, excessive delays are incurred in an attempt to stabilize a condition that is clearly unstable and nonresponsive to medical therapy. The greater the delay when significant organ hypoperfusion is evident, the less effective mechanical support will be, and this translates into fewer definitive therapeutic options. At the present time, options primarily include surgical approaches such as coronary bypass surgery, valvular repair or replacement, and cardiac transplantation.

A tremendous amount of progress has occurred in the management of acute heart failure over recent years, particularly with respect to mechanical circulatory support systems that can bridge patients from devastating hemodynamic decompensation to more clinically acceptable stages. The beginning of the century is an exciting time in which smaller and more reliable devices with fewer complications will become available for implantation. Even then, individualization of therapy and careful, repeated clinical assessment will be important.

THE FUTURE

Although a decade has passed since the introduction of a new pharmacologic treatment for the management of acute heart failure, important progress has been made recently toward the development of novel, more directed, and perhaps safer therapies. As with the pharmacologic approach for treating chronic heart failure, the treatment of acute hemodynamic compromise may also follow the neurohormonal paradigm. One or more drugs directed toward specific neurohormonal abnormalities of acute heart failure likely will be approved in the near future. Certainly, the continued development of aggressive myocardial reperfusion strategies will be important for the majority who present with acute ischemia and infarction to minimize ventricular remodeling and left ventricular dysfunction. Advances toward smaller, totally implantable mechanical devices will also continue.

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CHRONIC HEART FAILURE MANAGEMENT

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OVERVIEW

Treatment of heart failure is a challenging task that depends on making the proper diagnosis, staging the syndrome severity, and choosing interventions that are likely to diminish suffering while decreasing an exceptionally high mortality. Contemporary insight into the pathophysiology of heart failure has set the stage for designing and implementing a large number of clinical trials, whose results give guidance when planning medical therapies and surgical adventures. No longer is treatment of heart failure the simple dispensation of a diuretic and digitalis preparation. Therapies are now very complicated, and an appreciation of the sometimes subtle nuances of the heart failure syndrome is mandatory if greater strides are to be made with treatment paradigms. Medications for heart failure have evolved from diuretics to digoxin to vasodilators to angiotensin-converting enzyme (ACE) inhibitors to angiotensin II receptor blockers to beta-adrenergic receptor blockers, and they have included a vast variety of drug combinations. A greater focus has more recently been placed on surgical treatment of heart failure. Implantable arrhythmia management devices and biventricular cardiac resynchronizing pacemakers are presently undergoing intense study. Equally important has been clarification of therapeutic strategies that have proved detrimental in heart failure patients, such as use of certain inotropic and antiarrhythmic agents. Much can be done today to ameliorate heart failure's devastating natural course, and familiarity with treatment options is essential. We are now seeing another paradigm shift occurring in heart failure treatment: the early diagnosis of cardiac failure such that "preventive" strategies can be implemented in an attempt to forestall ventricular function deterioration and manifest congestive heart failure. Furthermore, it is now well established that use of agents capable of countermanding the complicated neurohumoral cascade characteristic of heart failure (ACE inhibitors and beta-blockers) is the primary focus when considering therapeutic options. Greater understanding of the molecular dynamics, humoral perturbation, and circulatory insufficiency characteristic of heart failure will lead to even newer and more radical heart failure treatments.

HISTORICAL PERSPECTIVES ON THE TREATMENT OF HEART FAILURE

Evolution of Heart Failure Therapies Related to Pathophysiologic Insight

Treating patients with heart failure is no longer the simple matter of prescribing concoctions of digitalis and primitive diuretics. Largely because of insight gained from well-designed and meticulously performed clinical trials undertaken to define better strategies with new drugs, therapeutic schemes have become very complicated. Substantive evolution of treatment paradigms has occurred (Table 92.1). Therapies have moved from crude attempts to relieve dropsy toward the amelioration of hemodynamic and, subsequently, neurohormonal perturbation characteristic of the syndrome (1,2 and 3). Today, strategies that block or ameliorate adverse remodeling seem most important (4,5 and 6). Future treatment paradigms will shift toward attenuation of inflammatory processes important in the pathophysiology of heart failure and toward blocking, at the molecular signaling level, necrotic or apoptotic events that lead to cell death. A wide array of surgical, electrophysiologic, and pharmacologic treatment options are now available, and prescribing safe and effective therapies requires a sophisticated understanding of the etiology and pathophysiology of the syndrome as well as drug effects, arrhythmia management, and anticipated surgical results.

Heart failure is a dropsical condition.
Lymphatic drainage tubes
Primitive diuretic therapies
Foxglove tea
Heart failure is central cardiac pump inadequacy.
Cardiac glycoside preparations
Alternative inotropic therapies
Cardiac transplantation
Mechanical ventricular assist devices and total artificial hearts
Heart failure is caused by decompensated ventricular hypertrophy.
Antihypertensive therapy
Surgical repair of valvular defects
Heart failure is circulatory dysfunction.
Vasodilator therapy
Heart failure is an endocrinopathy.
Angiotensin-converting enzyme inhibitor therapy
Angiotensin II receptor blockade
Beta-blocker use
Heart failure is a fever.
Development of cytokine-modulating agents
Heart failure is a complicated milieu of pump dysfunction, myocardial remodeling, humoral perturbation, and subsequent circulatory insufficiency.
Angiotensin-converting enzyme inhibitor therapy
Digoxin therapy
Diuretic therapy
Beta-blocker therapy
Surgical therapies (revascularization, remodeling, valve repair, transplantation)

TABLE 92.1 PROGRESS OF UNDERSTANDING OF HEART FAILURE RELATED TO THERAPIES

Today's spectrum of options should be placed in the perspective of the limited strategies previously available. Before the seminal publication of William Withering's marvelously accurate monograph on the Shropshire maid's remedy for dropsy, *An Account of the Foxglove*, in 1785 (7), Thomas Sydenham (in 1683) suggested bleeding, purges, vomiting, blistering, garlic, and wine or good ale as therapies (8). Although there had been a tenuous intellectual link between the heart and certain dropsical conditions at the time of Withering's publication, it would be many decades before clear-cut relationships would be described. Withering, however, knew the implications of giving foxglove preparations to the wrong patients or in improper dosages (7). He cautioned against treating dropsical patients who had robust and regular pulses, indicating that these individuals simply became toxic with the potion and, seemingly, did not achieve effective diuresis. Excessive or excessively concentrated foxglove tea would, Withering pointed out, precipitate a spectrum of nausea, vomiting, visual disturbances, and cardiovascular collapse. In responders to his therapy, it is likely that the prescient Withering was observing dropsical states with atrial fibrillation; the weak and thready pulse, coupled with pale countenance, characterized patients he thought would likely respond to the herb. Dropsical patients with nephrotic syndrome, tuberculosis, peritonitis, myxedema, or cirrhosis of the liver (conditions common in Withering's day) would be more likely to have robust and regular pulses with ruddy complexion and not be expected to diurese with a foxglove preparation. These observations hold true today and follow more contemporaneous and important tenets of heart failure therapeutics, which emphasize the necessity of ensuring that a given patient's symptomatology and physical findings, are, in fact, due to heart failure and not some other disease that produces edematous states.

Treatment paradigms for dropsical conditions due to heart failure shifted slowly. In 1812, Corvisart, in *Essay on the Organic Diseases and Lesions of the Heart and Great Vessels* (9), continued to suggest purges, bleeding, leaches, squill (a glycoside preparation), physical removal of ascites and pleural effusions, puncture of

edematous legs, and nitrated drinks for dropsy. The mid-nineteenth century saw more aggressive use of diuretics, although the agents were rather primitive and weak, being primarily mercurial preparations (calomel) and potassium bitartrate. Subcutaneous morphine sulfate injections came into use in the late 1860s. The Karrell diet, which was primarily skimmed milk (relatively low in sodium), was proposed in 1866. In Austin Flint's 1873 edition of *A Treatise on the Principles and Practice of Medicine* (10), dropsy due to decompensated ventricular hypertrophy was said to respond to digitalis, ether, dry cupping, opiates, cathartics, incisions, and organ-cavity space puncture. Southey tubes inserted into leg lymphatics were introduced in 1877, and bromides for sedation were also urged at that time. Diuretics used in that period included theophylline, theobromine, and urea salts. Catharsis and venesection were still much practiced in the late 1800s. Supplemental oxygen therapy was urged in the early 1900s, and in James MacKenzie's 1910 edition of *Diseases of the Heart* (11), amyl nitrate was suggested as therapy as well as digitalis, oxygen, purgatives, and venesection. Mercurial diuretics were used with increasing frequency in the 1920s and 1930s, as was thyroidectomy in severe cases. The cardiac chair was introduced about this time, and diet therapies began to focus seriously on water and salt restriction. Bed rest was virtually always a component of therapies, culminating in the late 1950s and early 1960s with recommendations of Birch and colleagues for complete and compulsive long-term bed rest for patients with cardiomyopathy (12). In Arthur Fishberg's 1937 *Heart Disease* (13), recommendations can be found to treat atrial fibrillation and flutter with quinidine and digitalis. Fishberg also proposed thyroidectomy as an alternative, albeit aggressive, therapy. The carbonic anhydrase inhibitor acetazolamide (Diamox) was introduced in 1950 and hexamethonium in 1956. Ligation of the inferior vena cava was a treatment used in 1952. Friedberg continued to suggest thyroidectomy and radioactive iodine ablation of the thyroid gland for severe heart failure in his second edition of *Diseases of the Heart* (1956) (14). Intraaortic balloon counterpulsation for hemodynamic collapse secondary to severe heart failure was proposed in 1961 (15), and Lillehei and coworkers introduced left ventricular aneurysmectomy as a surgical treatment of heart failure in 1962 (16). Lown and colleagues promoted electrical cardioversion for atrial fibrillation complicating heart failure in 1962 (17), and the era of cardiac valvular surgery as therapy for heart failure due to valvular stenosis or insufficiency began in earnest. Thiazide diuretics were introduced in 1962, furosemide in 1965, and ethacrynic acid (Edecrin) in 1966. The first human-to-human cardiac transplant was performed in 1967 (18). The 1970s were characterized by use of vasodilator therapies (19), in general, and new inotropic preparations were pursued in earnest as the Holy Grail of heart failure therapeutics (20). Dopamine was introduced by Goldberg in 1972, nitroprusside by Guiaha in 1974, dobutamine by Tuttle in 1975, and hydralazine in 1977. J. Willis Hurst and colleagues' 1978 textbook, *The Heart* (21), recommended decreasing physical and emotional stress, low-salt diet, digitalis, diuretics (including thiazide, furosemide, ethacrynic acid, spironolactone, and mercurials), and vasodilators (including nitroprusside, isosorbide dinitrate, and hydralazine) in certain heart failure states. Captopril was introduced in 1980 and enalapril in 1984. Indeed, the decade of the 1980s can best be characterized as the era of the ACE I inhibitor in heart failure (4,5,22,23 and 24). Many landmark clinical trials were performed beginning in the late 1970s (extending through today) that promoted better definitions and modern therapies for the syndrome. These trials focused on pharmaceutical strategies as well as operative intervention. The 1980s and 1990s also were decades characterizing heart failure treatment practices that, although intuitive, ended up actually increasing mortality. Several inotropic agents with varying degrees of vasodilating properties seemingly improved heart failure symptoms, but at the cost of higher death rates (20,25,26). Certain antiarrhythmic agents were found detrimental in the face of left ventricular dysfunction, even though heart failure patients frequently die of malignant ventricular arrhythmias, and it seemed logical to eliminate the arrhythmias (27,28). Trials suggested that calcium channel blockers, despite being potent arteriolar dilators, as a group seemed to produce more problems than benefits in heart failure cohorts.

The 1990s have been marked by continued paradigm shift with better, but still incomplete, clarification of the role of digitalis (29,30 and 31) and beta-blockers (4,32,33) and with heart failure assuming a more prominent profile. Professional and public awareness of the heart failure pandemic increased, and it became clear that strategies should focus more on the asymptomatic patient with left ventricular dysfunction. An awareness that heart failure was not solely a "congestive" state, but, rather, a complicated spectrum of cardiac dysfunction seen in patients entirely asymptomatic as well as those with fulminant pulmonary edema or shock. Although beta-blockers were first given to heart failure patients in the 1970s, two decades of drug package inserts have warned of their use in patients with heart failure. The 1990s appeared to be an the era of clarifying the importance of this strategy. Indeed, as we enter the twenty-first century, the treatment paradigm shift continues, with a focus now on interdiction of the alpha- and beta-adrenergic cascades known to be important in heart failure (32,33,34 and 35) and more recently identified inflammatory components of the syndrome (36,37,38,39 and 40). More complete blockade of the renin-angiotensin-aldosterone pathway has been attempted with specific angiotensin II receptor antagonists. The past decade has also seen mechanical left ventricular assist devices emerging as lifesaving options in seriously ill patients with cardiogenic shock, and they have become frequently used tools to "bridge" patients to recovery or cardiac transplantation (41). Programs began to evaluate use of these machines as long-term heart failure treatment options as well (42).

Prescription Practice in Heart Failure

To set the stage for contemporary heart failure treatment recommendations, it is important to mark more recent practice patterns (43,44,45,46,47 and 48). Studies of Left Ventricular Dysfunction (SOLVD) and the Studies of Patients Intolerant to Converting Enzyme inhibitors (SPICE) trial registries were two of the most extensive evaluations of patterns of medication use in patients with heart failure (44,47) undertaken to date. They are important data sets to review because they document the change in prescription practice with regard to heart failure over the last decade. In SOLVD, drug use was analyzed in almost 6,000 patients participating in a registry running concurrently with the two SOLVD clinical trials from 1986 through 1989. The SOLVD Registry comprised a broad spectrum of patients with heart failure, including some with predominantly diastolic dysfunction. Drug use was determined in a population cross-section manner at the time patients were identified as having "heart failure." Almost three-fourths of the patients were evaluated during a hospitalization. The median number of cardiovascular drugs used per patient was four (Fig. 92.1), with diuretics taken by 62%, digitalis by 45%, ACE inhibitors by 32%, calcium channel blockers by 36%, antiarrhythmics (nonamiodarone) by 22%, and beta-blockers by 18%. At that time (data were compiled between January 1988 and February 1989), only 18% were on the combination of ACE inhibitor, diuretic, and digitalis. Stratification for diagnosis, heart failure symptoms, and ejection fraction demonstrated that triple-drug therapy (digitalis, diuretic, and ACE inhibitor) was common only in patients with ejection fraction less than 20% and several concomitant signs or symptoms of heart failure. "Preventive" strategies in individuals with a few symptoms did not appear to be common practice. Older patients were taking diuretics frequently (73% of patients older than 70 years).

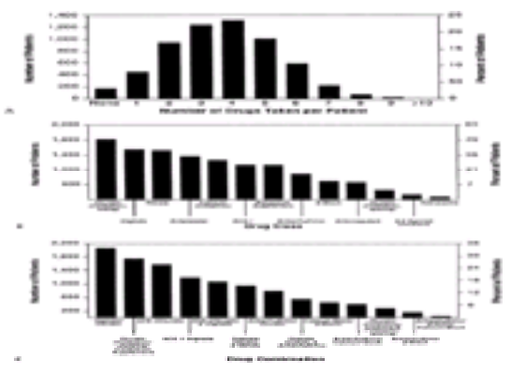


FIGURE 92.1 Data from 5,999 patients in the Studies of Left Ventricular Dysfunction (SOLVD) Registry indicated that the median number of cardiac drugs taken per patient with heart failure was four **(A)**. The rank-order histographic plot of drugs most commonly used by registry participants **(B)** and the most common drug combinations **(C)**. These data were compiled in 1988 and, therefore, represent the prescription practice to which we should compare contemporaneous habits. In 1988, more calcium antagonists were used than angiotensin-converting enzyme (ACE-I) inhibitors in patients with heart failure, and antiarrhythmic therapies (generally Vaughn Williams class I agents) were noted in approximately one-fifth of patients. Triple therapy (i.e., ACE inhibitor, diuretic, and digitalis) were used in less than 20% of patients with heart failure at that time. [Modified from Young JB, Weiner DH, Yusuf S, et al. Patterns of medication use in patients with heart failure: a report from the registry of Studies of Left Ventricular Dysfunction (SOLVD). *South Med J* 1994;88:514–523.]

The SPICE Trial Registry was designed to evaluate heart failure treatment practices, and, more specifically, determine the incidence of ACE inhibitor intolerance in an "optimal" practice situation (48). Between 1996 and 1997, study centers located in eight American and European countries retrospectively reviewed the medical records of 100 consecutive patients with heart failure and an ejection fraction less than or equal to 35%. There were 9,580 subjects studied, and the mean age was 66 years with 26% women and a median ejection fraction of 27%. Ischemic heart disease was the primary cause of the heart failure in 63% of the population. ACE inhibitors were used in 80% of the patients, and this likely represents an ideal circumstance because the study was conducted at largely academic medical centers with education and interests in this issue. The most common reason for not using ACE inhibitors was intolerance, and of these patients, 80% were said to be intolerant because of cough. Figure 92.2 compares the use of medications, generally, in the SPICE and SOLVD Registries, giving insight into the changing prescription practices in heart failure evolving over the last decade. The difference in the prevalence of ACE inhibitors was the most obvious difference, with 30% of the SOLVD Registry population on these agents compared with 80% in SPICE. This likely reflects the acceptance of clinical trial results into day-to-day clinical practice. Other descriptive differences between the groups merit commentary as well. The higher use of diuretics among SPICE Registry patients may reflect more advanced heart failure symptoms as the prevalence of New York Heart Association (NYHA) class III or IV in the SPICE Registry was 43% compared with 32% in the SOLVD Treatment Trial and 17% in the SOLVD Registry. The increase in the use of beta-blockers in SPICE may be related to the growing acceptance of the important role these agents play in ameliorating perturbed neurohormonal activation in patients with heart failure. Of course, today, it is known that these agents are essential. The increase in the use of digoxin and warfarin in the SPICE Registry probably relates to the higher prevalence of atrial fibrillation (27% vs. 14% in the SOLVD Registry). Interestingly, the use of calcium channel antagonists and antiarrhythmic drugs in SPICE was less than that noted in SOLVD. This is not surprising given the results of several clinical trials that were published in the intervening period that showed increased mortality in post–myocardial infarction patients with left ventricular dysfunction treated with class I antiarrhythmic agents (49). As well, several intervening studies suggested that calcium channel antagonists (particularly short-acting dihydropyridines) may increase mortality in patients with heart failure (50,51). Perhaps the differences in the use of certain cardiovascular medications as noted in the SOLVD-SPICE Registry

comparison indicate that so-called evidence-based medicine has had an effect on routine clinical practice (52).

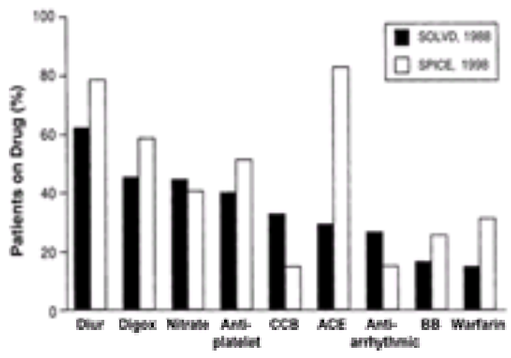


FIGURE 92.2 Comparison of Studies of Left Ventricular Dysfunction (SOLVD) Registry medication use (1988) to the Studies of Patients Intolerant to Converting Enzyme Inhibitors (SPICE) Registry (1998). More angiotensin-converting enzyme (ACE) inhibitors and beta-blockers (BB) are used today, with fewer calcium channel blocker (CCB) and class I antiarrhythmic medications prescribed. Nonetheless, optimal treatment prescription practices have not generally been met. Digox, digoxin; Diur, diuretics.

It is accepted today that congestive heart failure patients should be treated with combinations of ACE inhibitors, diuretics, and digoxin (22,53,54,55,56,57,58 and 59). This should be compared with patterns of practice identified by the Clinical Quality Improvement Network Investigators (45). Perhaps giving a more real world assessment of ACE inhibitor use in heart failure, this audit of 4,606 consecutive hospitalized patient charts between 1992 and 1993 demonstrated that diuretics were used in 86% of heart failure patients, ACE inhibitors in 53%, long-acting nitrates in 49%, digoxin in 46%, potassium supplements in 40%, aspirin in 36%, calcium channel antagonists in 20%, warfarin in 17%, beta-adrenergic blockers in 15%, and magnesium supplements in 10%. Hospital mortality was high in this cohort (19%), with 30% of the deaths due to noncardiovascular causes. More data accumulated in 1994 and 1995 in Ohio also suggest that ACE inhibitors are underused in at-risk heart failure patients (46). The Ohio Peer Review Project analyzed the records of 760 patients in 21 hospitals admitted with a principal diagnosis of congestive heart failure. In those having objective measurements of left ventricular ejection fraction less than 40%, with serum creatinine less than 3.0 mg per dL, serum potassium less than 5.5 mEq per L, and systolic blood pressure greater than 90 mm Hg (n = 381), an assessment of admission and discharge medications was made with respect to ACE inhibitor use. Patients in both rural (n = 280) and urban (n = 480) hospitals were evaluated. Mean patient age was approximately 75 years, and 55% were men. In cases eligible for ACE inhibitors at hospital discharge, 16% were said to have contraindications to ACE inhibitors at hospital admission. No difference with respect to hospital type or location was noted with respect to ACE inhibitor use. Although only 37.7% of patients with documented systolic dysfunction were on ACE inhibitors at admission, 73% were prescribed this drug class at discharge.

Now that beta-blockers are also considered important adjuncts to a heart failure patient's polypharmacy protocol, new approaches to educating care givers and patients about the importance of compliance with consensus statement recommendations are needed. Perhaps implementation of heart failure disease management protocols will be helpful (58,59). Although the observations regarding the increasing number of heart failure patients being treated with ACE inhibitors is reassuring in some senses, it is obvious that a large cohort of patients who would likely benefit from this class of drugs is not being so treated. Also troublesome is the fact that patients were often noted to be on medication doses lower than those generally used in the ACE inhibitor heart failure trials. What dose of beta-blocker and ACE inhibitor to prescribe to patients with heart failure has become contentious, with some suggesting that aggressive dosing of these drugs is best, whereas others are content to see patients simply on, at the least, the combination of any dose of the agents (60,61).

CREATING A CHRONIC HEART FAILURE MANAGEMENT STRATEGY

Therapeutic Philosophy

*e*Table 92.1.1 addresses the contemporary definition of heart failure and summarizes important considerations during patient evaluation that emphasize treatment strategies (1,2 and 3,61,63). A variety of injurious processes can cause acute or chronic myocardial dysfunction (diastolic or systolic and right-sided or left-sided heart dysfunction). Injured myocytes, because of inotropic and lusitropic dysfunction, are exposed to passive tension and workload demand changes that translate, ultimately, into increased preload and afterload. This sets the stage for detrimental cardiac remodeling (2,64,65,66 and 67). Therapies designed to normalize these hemodynamic perturbations seem logical. Less easy to address is myocyte interstitial matrix deposition, which occurs in heart failure and causes stiffening of the myocardium, with all its diastolic dysfunction implications (67,68 and 69). Strategies (not yet clearly defined) that prevent inflammation and fibrosis may become important with respect to this issue. The aforementioned mechanical alterations produce peripheral vascular bed flow decrement in either subtle or more obvious fashion (70,71). Therein lies the attraction of using agents that increase stroke volume (vasodilators or inotropic agents, for example). The combination of mechanical cardiovascular and peripheral vascular blood flow changes triggers a variety of humoral, neurohormonal, and inflammatory responses, which initially appear to create systemic organ flow compensation. Ultimately, these factors intertwine to precipitate detrimental remodeling of the heart (cardiac hypertrophy and chamber dilation) and provide targets for therapies that can block molecular factors leading to this remodeling. Because these processes vary in degree from patient to patient, individuals may present without symptoms or suffer from a variety of fatigue, dyspnea, or fluid retention states that fluctuate based on treatment protocols, diet, physical conditioning, and diseases that caused the problem in the first place. Obviously, findings such as valvular heart disease, coronary artery occlusions, cardiac conduction disturbances, and ventricular or atrial arrhythmias important in the pathophysiology of heart failure need to be surgically or electrophysiologically addressed as well.

***e*TABLE 92.1.1** A CONTEMPORARY DEFINITION OF HEART FAILURE RELATED TO THERAPIES
Myocardial injury causes acute or chronic myocyte dysfunction (systolic or diastolic or both).
Prevent injury to the heart
Myocyte passive tension and workloads change.
Preload and afterload reduction
Myocyte interstitial matrix stiffens.
Prevent inflammation and fibrosis
Peripheral vascular bed blood flow is altered (generally decreased in subtle fashion).
Increase cardiac output and organ perfusion
Subsequent mechanical, humoral, neurohumoral, and inflammatory responses appear in an attempt to create systemic organ flow compensation.
Block adverse humoral factors
Compensatory mechanisms ultimately produce a maladaptive circulatory state.
Reverse remodeling of the heart and vascular network
Patients may present without symptoms or suffer from a variety of fatigue, dyspnea, or dropsical states that fluctuate in severity based on treatment protocols, diet, physical conditioning, and diseases that precipitate the heart failure syndrome.
Design therapies based on syndrome stage
In addition to ameliorating symptoms with tailored treatment strategies, early identification of patients with insidious hemodynamic and hormonal perturbation is critical so that therapy can attenuate heart failure morbidity and decrease mortality.

Figure 92.3 links an overview of heart failure therapy to prevention and treatment strategies. Besides ameliorating symptoms with tailored therapeutic programs, identifying individuals with insidious hemodynamic and hormonal perturbation early on is critical so that therapy can be given early in the syndrome's course to prevent development of symptomatic heart failure. It is imperative that treatment of asymptomatic ventricular dysfunction begin early to interdict harmful remodeling. Obviously, treatment strategies are designed to ameliorate symptoms when present, maintain functional capacity at maximal levels, keep patients out of the hospital, reduce mortality, and reverse remodeling.

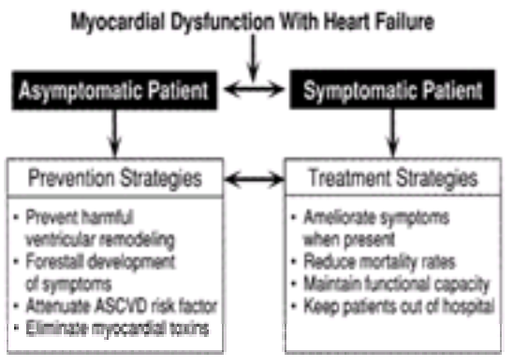


FIGURE 92.3 This diagram emphasizes the importance of a philosophy of heart failure therapy that focuses on practices revolving around *prevention* strategies for the asymptomatic patient and *treatment* strategies for the symptomatic patient. Obviously, one would like to identify myocardial dysfunction in asymptomatic or minimally symptomatic individuals early on so that intervention has the greatest likelihood of preventing ventricular function deterioration and subsequent symptoms. When symptoms are present, treatment protocols should move patients into an asymptomatic position. ASCVD, arteriosclerotic cardiovascular disease.

Table 92.2 summarizes important questions to ask when designing protocols for patients with chronic heart failure (62,63). Does the patient actually suffer from heart failure and are symptoms or physical findings related to this difficulty? Many patients with weakness, fatigue, dyspnea, and dropsical states do not have heart failure. Furthermore, patients with heart failure may present with these symptoms and physical findings, but the symptoms are related to ancillary comorbidities rather than cardiac dysfunction. What is the etiology of the syndrome? This question forces consideration of diseases that can be treated and eliminated or, at the least, ameliorated, such that progression of the heart failure milieu is halted. Following this is questioning what evaluation is needed to confirm the diagnosis and stage the syndrome severity. Indeed, it is important to note what precipitated the patient's deterioration. Frequently, medication noncompliance, excessive sodium or fluid consumption, worsening ischemic syndromes, atrial and ventricular arrhythmias, intercurrent infection, uncontrolled chronic obstructive pulmonary disease, diabetes mellitus, and hypertension plunge patients into the realm of symptomatic congestive heart failure. Staging the syndrome severity is critical to answering the question of what a patient's short- and long-term prognosis might be. A question that often goes unasked is whether the patient takes medications that can be detrimental in the heart failure setting, such as nonsteroidal antiinflammatory agents, certain calcium channel blockers, and Vaughn Williams class I antiarrhythmic drugs. Obviously, designing a treatment protocol is intimately linked to the question of how the patient should be treated acutely as well as chronically (22,53,57,72,73,74,75 and 76). Often, we neglect social factors that play a significant role in morbidity, and we should always ask what social support mechanisms that can be considered adjunctive nonpharmacologic treatments are available to the patient (73). Again, it is critical to remember that patients with heart failure have varied clinical presentations as they move from asymptomatic cardiac dysfunction to symptomatic heart failure. Complicating this issue further is the fact that patients make this transition over highly variable time intervals.

Does the patient actually suffer from heart failure, and are presenting symptoms or physical findings related to this difficulty?
What is the etiology of the syndrome?
What evaluation is needed to confirm diagnosis, clarify etiology, and stage syndrome severity?
What precipitated the patient's deterioration?
How severe is the heart failure syndrome, and what are the patient's short- and long-term prognoses?
Is the patient on medications that are potentially detrimental in the heart failure milieu?
How should the patient be treated acutely?
How should the patient be treated chronically?
Can the precipitating disease process be cured, or can the state of heart failure be ameliorated?
What social factors played a role in morbidity, and what social support mechanisms should be considered as adjunctive therapeutic measures?

TABLE 92.2 INTEGRATION OF DIAGNOSTIC EVALUATION INTO A MANAGEMENT STRATEGY: QUESTIONS TO ASK WHEN DESIGNING THERAPEUTIC PROTOCOLS FOR CHRONIC HEART FAILURE PATIENTS

Guidelines for Heart Failure Patient Evaluation and Management

The Agency for Health Care Policy and Research (AHCPR) published the first guidelines for evaluating and treating heart failure patients in 1994 (72,73,74,75 and 76). Subsequently, guidelines have emerged from several groups as our knowledge base increased (see Table 92.3 for a listing). Diagnosis and treatment algorithms subsequently have been based largely on experience gained during the performance of carefully controlled clinical trials evaluating a variety of strategies. These trials are subsequently reviewed. In general, a well-constructed practice guideline specifies the types of professionals involved in developing the guideline, defines the methods of primary evidence analysis, and provides a grading of one sort or another to characterize the strength of data the recommendations are based on. There are several problems with clinical practice guidelines, however. Generally, the guidelines do not emphasize the importance of risk stratification with regard to syndrome severity (particularly in asymptomatic or minimally symptomatic patients and more advanced, decompensated patients), and, therefore, largely ignore the issue of tailoring therapies to patients in the mildly or severely ill categories. Furthermore, guidelines cannot possibly address all relevant clinical situations (76). Often, consensus cannot be reached because evidence is not always available regarding certain therapeutic strategies. Guideline development can be a slow, politically charged, and ponderous process with guidelines being slow to respond to new knowledge and therapies. It is also difficult to educate clinicians regarding guidelines, and many practitioners perceive guidelines as being intrusive and excessively regulatory. Nonetheless, practice guidelines are, arguably, the best method of defining treatment practices that continuing quality improvement programs can use to grade any health care provider's practice.

Guidelines	Year published
U.S. Department of Health and Human Services, Agency for Health Care Policy and Research (Clinical Practice Guideline no. 11, publication 94-0612)	1994
American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Heart Failure (*Circulation* 1995;92:2764)	1995
World Health Organization Heart Failure Guidelines (*J Card Fail* 1996;2:153)	1996
European Society of Cardiology Heart Failure Guidelines (*Eur Heart J* 1997;18:736)	1997
ACTION Heart Failure Treatment Guidelines [*Am J Cardiol* 1999;83(2A):1]	1999
Heart Failure Society of America Guidelines for the Management of Heart Failure (*J Card Fail* 1999;5:358)	1999

TABLE 92.3 CLINICAL HEART FAILURE GUIDELINES

The commonest themes of all of these guidelines are summarized in Table 92.4. All guidelines support an aggressive approach to diagnosing and treating patients with active ischemia and left ventricular dysfunction. The guidelines are unanimous in recommending ACE inhibitors in all patients with left ventricular systolic dysfunction. The more recent guidelines address use of beta-blockers in stable patients with mild to moderate heart failure symptoms and no significant congestion. All guidelines suggest avoiding agents with incomplete benefit-risk profiles and reminding clinicians about diagnosing and treating underlying and precipitating difficulties. Furthermore, most of the guidelines emphasize the importance of prescribing nonpharmacologic therapy such as exercise and salt and fluid restriction while addressing patient education about heart failure. Largely ignored in present guidelines are patients with congestive heart failure but preserved left ventricular systolic function and management of advanced heart failure (particularly the acutely decompensated chronic heart failure patient who requires hospitalization and the terminal "hospice-type" patient with heart failure).

Identify and aggressively treat ischemia in patients with heart failure (revascularization)
Use angiotensin-converting enzyme inhibitors in all tolerant patients with left ventricular systolic dysfunction
Use beta-blockers in stable patients with mild to moderate symptoms and no significant congestion
Avoid agents with incomplete benefit-risk profiles
Diagnose and address underlying and precipitating disorders
Prescribe nonpharmacologic therapies
Exercise
Salt and fluid restriction
Educate patient, family, and care givers

TABLE 92.4 MOST COMMON THEMES OF HEART FAILURE GUIDELINES

The AHCPR algorithm (72) specifically suggests evaluation of all patients with symptoms suggestive of heart failure, such as paroxysmal nocturnal dyspnea, orthopnea, dyspnea on exertion, lower-extremity edema, decreased exercise tolerance, unexplained confusion, altered mental status or fatigue in an elderly patient, and abdominal complaints associated with ascites and hepatic engorgement (nausea or abdominal pain). The algorithm stresses the importance of a physical examination to elicit findings supportive of congestive heart failure, such as elevated jugular venous pressure or positive abdominal jugular reflex, a third heart sound, a laterally displaced apical cardiac impulse, pulmonary rales not clearing with cough, and peripheral edema not due to simple venous insufficiency. In individuals with symptoms and physical findings suggestive of heart failure, determination of left ventricular function is mandated. Echocardiographic and radionuclide ventriculographic studies are important to quantify the degree of systolic left ventricular dysfunction. Echocardiography was thought to be more advantageous because it permitted concomitant assessment of valvular heart disease, left ventricular hypertrophy, chamber dimension, and left atrial size. Furthermore, this technique is generally less expensive and more readily available than radionuclide ventriculography. Ancillary tests suggested included electrocardiography, a complete blood cell count, urine analysis, serum creatinine, serum albumin, and thyroid function tests. To broaden the scope of catchment populations and assist in characterization of patient-specific therapies, AHCPR and other guidelines should be amended to include a category that refers patients at high risk of having occult left ventricular systolic dysfunction for an estimation of left ventricular ejection fraction. It is probably prudent to perform echocardiography, for example, in every patient suffering an acute myocardial infarction, particularly if more than one has occurred in the past. Additionally, elderly patients having had chronic hypertension, prior coronary artery bypass graft surgery, or percutaneous coronary interventions (particularly in the setting of comorbid conditions, such as diabetes mellitus, cerebrovascular accidents, or peripheral vascular disease) should have echocardiography performed at some intermittent screening interval that has yet to be optimally characterized.

VIDEO

Video 92.1 Apical long-axis view of a patient with severe left ventricular dysfunction and annular dilatation causing 4+, centrally directed mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 92.2 Multiple gated acquisition scan illustrating a normal study in the anterior **(A)** and left anterior oblique **(B)** projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 92.3 Multiple gated acquisition scan illustrating a normal study in the anterior **(A)** and left anterior oblique **(B)** projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 92.4 Standard anterior view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating global hypokinesis and a reduced left ventricular ejection fraction of 25% in a patient with nonischemic dilated cardiomyopathy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 92.5 Standard lateral view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating global hypokinesis and a reduced left ventricular ejection fraction of 25% in a patient with nonischemic dilated cardiomyopathy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

CLINICAL TRIAL INSIGHTS

Certainly, clinical trials cannot answer all questions about heart failure therapeutics. Anecdotal experience as well as more detailed, but small, uncontrolled experimental paradigms can offer guidance. Clinical trials performed in heart failure cohorts are limited by certain design difficulties. There is a tremendous winnowing of patients screened for these studies, for example, and it is not unusual to see a 10:1 or 20:1 ratio of patient screening to trial entry. Figure 92.4 and Figure 92.5 depict mortality end points in a variety of clinical heart failure trials and emphasize, by reviewing placebo group death rates, the tremendous heterogeneity of populations included in the trials. To be successful, clinical trials require that specific questions be asked in well-characterized and relatively homogeneous patient populations; therefore, the most challenging patient to manage (the aged patient, female in particular, with multiple comorbidities) is often not allowed into clinical trials. Unfortunately, there is a large underrepresentation of women, minority races, the elderly, and youth in clinical trials. Furthermore, end points used to evaluate potentially beneficial or detrimental treatment strategies are sometimes imprecise or not necessarily clinically relevant. Another difficulty is that the studies are performed on varying “background” pharmacotherapeutic strategies. It is extremely important to assess clinical trials with respect to their analyzed end points and the power with which the study was designed to answer the questions asked. It must be emphasized that the success of a clinical trial is not rooted solely in demonstration of a positive result. Trials that do not support a priori hypotheses are sometimes more important than those that do because they can clarify what should be done in these populations as well as strategies that should not be pursued.

FIGURE 92.4 An algorithm for diagnosis and pharmacologic management of heart failure (HF) patients that focuses largely on symptomatic out-of-hospital patients with suspected congestive HF. In these patients, initiating diuretic, angiotensin-converting enzyme (ACE) inhibitor therapy, and beta-blockers is initially recommended, with addition of digoxin and other vasodilating agents suggested for cases with persistent symptomatology. BMI, body mass index; CAD, coronary artery disease; CPK-MB, creatine phosphokinase-MB; ECG, electrocardiography; ED, emergency department; ETOH, ethanol; NSAIDs, nonsteroidal antiinflammatory drugs; NYHA, New York Heart Association; Tx, treatment.

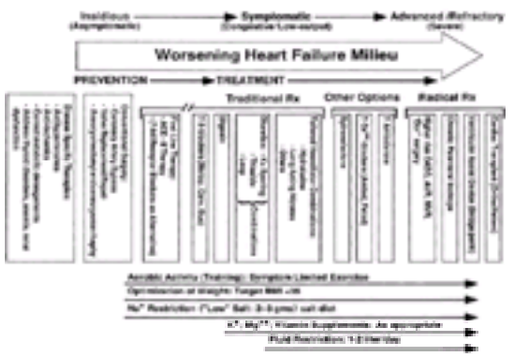


FIGURE 92.5 This figure graphically plots a scheme for tailoring therapies to individual heart failure patients. It is based on the fact that treatments change as the heart failure milieu worsens. Preventive strategies are recommended for individuals with insidious and asymptomatic or minimally symptomatic heart failure, with treatment strategies accelerating in intensity as congestive or low-output states worsen. At the root of all treatment protocols, however, is disease-specific therapy. Also important is a variety of lifestyle changes, including aerobic activity training, optimization of weight, and dietary restriction of salt use. ACE, angiotensin-converting enzyme inhibitor; AVR, aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass grafting; MVR, mitral valve replacement.

Despite these issues, the clinical trial remains an excellent method for fashioning rational protocols and identifying their cost effectiveness by exploring schemes that are effective, neutral, or detrimental with respect to endpoint impact. Because of the multiple drugs heart failure patients take and the complicated interrelationship of comorbidities, it is important to create algorithms that include only advantageous strategies. Those that are neutral or disadvantageous should be avoided.

*e*Table 92.4.1 lists select clinical trials that provide important insight into treatment of patients with a wide range of heart failure. Highlighting a few specific trials allows the stage to be set for proffering contemporary heart failure treatment recommendations. The first Veterans Administration Cooperative Vasodilator Heart Failure Trial (V-HeFT-I) (77) was made up of men with moderate congestive heart failure and was a landmark study because it was the first to suggest that vasodilators beneficially affected mortality in patients with congestive heart failure. At the time it was performed, the trial was controversial because conventional wisdom dictated that diuretics and inotropic agents were the most logical approach to congestive heart failure. Insight into detrimental ventricular remodeling in heart failure was not great at that time, but the beneficial effects of direct-acting vasodilators, such as hydralazine and isosorbide dinitrate, on cardiac output and ventricular filling pressures gave rise to the so-called hemodynamic hypothesis of heart failure therapy and led to the design of V-HeFT-I. Specifically, this hypothesis speculated that drugs that lowered impedance to ventricular ejection, with subsequent reduction of diastolic pressures and augmentation of forward flow (or reduction of venous blood return after venodilation with nitrates), was beneficial and decreased mortality and morbidity. This study was also important because it demonstrated disparity among vasodilating drugs. Although the combination of hydralazine and isosorbide dinitrate, prescribed in addition to digoxin and a diuretic, arguably improved morbidity and mortality (the study was relatively small, and its statistical analysis has been criticized), V-HeFT-I showed that the peripherally acting alpha-adrenergic blocking agent prazosin, known to effectively reduce both preload and afterload in heart failure, was no better than placebo. Thus, the conclusion was reached that all vasodilators may not be alike with respect to long-term morbidity and mortality effects. Since V-HeFT-I, we have seen drugs that improve heart failure hemodynamics significantly but produce higher mortality in clinical trials (67,68,69,70,71,72,73,74,75,76,77,78,79,80,81 and 82) (*e*Table 92.4.1).

***e*TABLE 92.4.1** SELECT CLINICAL TRIALS, REGISTRIES, AND EXPERIENCES RELEVANT TO HEART FAILURE

Acronym	Full title	Study design	Findings	Therapeutic implication
AIRE	Acute Infarction Ramipril Evaluation	Effect of ramipril on morbidity and mortality of survivors of acute MI with clinical evidence of heart failure.	Significant reduction in mortality noted with ramipril; findings complement SAVE, SMILE, TRACE, GISSI-III, ISSIS-IV.	ACE inhibitor therapy should be routinely started postinfarct when CHF or left ventricular systolic dysfunction present.
AIREX	Acute Infarction Ramipril Evaluation—Extension Study	Long-term (mean, 59 mo) follow-up of AIRE study patients.	Average duration of “masked” trial drug 12 mo but even poststudy differences in mortality were 39% for placebo vs. 28% for ramipril groups (RR = 36%; 95% CI, 0.15–0.52; *p* = .002).	Ramipril post-MI with heart failure has large and sustained benefit.
ALLHAT	Anti-Hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial	Randomized, double-blind, active drug controlled clinical trial of chlorthalidone, doxazosin, amlodipine, or lisinopril with composite end point of fatal CAD event or nonfatal MI (prevention of CHF) secondary end point (n = 24,335).	Doxazosin arm discontinued early because the diuretic produced equal mortality to the alpha-blocker, but there were fewer strokes and combined CVD events with the risk of CHF doubled with doxazosin at 4 yr (RR = 2.04; 95% CI, 1.79–2.32; *p* <.001).	Doxazosin appears inferior to at least a thiazide diuretic for hypertension for the prevention of CVD events, particularly heart failure (chlorthalidone, amlodipine, and lisinopril arms still running).
APRES	Angiotensin-Converting Enzyme Inhibition Post Revascularization Study	After revascularization, angina patients with EF 0.30–0.50 (asymptomatic) were randomized (double-blind) to ramipril or placebo for mean of 33 mo (n = 159).	ACE inhibitor reduced composite end point of cardiac death, acute MI, CHF, or recurrent angina (RR = .58; 95% CI, 0.07–0.80; *p* = .031).	More evidence for benefits of ACE inhibitor for broad spectrum of LVD/heart failure patients.
ATLAS	Assessment of Treatment with Lisinopril and Survival	Survival study of high- (approximately 35 mg) vs. low-dose (approximately 5 mg) lisinopril in moderate to severe CHF (n = 3,164).	No mortality benefit with high ACE inhibitor dose, but hospitalizations and morbidity diminished.	High target ACE inhibitor dose likely wise.

AVID	Antiarrhythmics Versus Implantable Defibrillators Trial	Randomized comparison in resuscitated (near fatal ventricular fibrillation or symptomatic ventricular tachycardia) patients with EF <0.40 of AICD vs. antiarrhythmics (amiodarone or sotalol) (n = 1,016).	Survival greater in AICD group (75.4% vs. 64.1% at 3 yr; *p* <.02; a 39% ± 20% reduction in mortality).	In survivors of ventricular fibrillation or symptomatic ventricular tachycardia with low EF, AICDs appeared superior to antiarrhythmic drugs for improving survival.
BASIS	Basel Antiarrhythmic Study of Infarct Survival	Randomized, open, clinical trial of antiarrhythmic (amiodarone) therapy in post-MI patients with asymptomatic complex arrhythmias (frequent multiform or repetitive ventricular arrhythmias); control group, “individualized” antiarrhythmic treatment (drug titrated to eliminate arrhythmia), routine low-dose amiodarone (200 mg daily) (n = 312).	Probability of “survival” (combined end point of mortality and sudden death, sustained ventricular tachycardia/fibrillation) increased with routine amiodarone prescription (10 group 1 vs. 5 group 2 vs. 15 control deaths).	Low-dose amiodarone appears to decrease mortality the first yr after MI when certain asymptomatic ventricular arrhythmias are present; although not a “heart failure” trial, mean EF was 0.43 ± 0.16.
BEST	Beta-Blocker Evaluation Survival	Patients receiving standard treatment randomized to placebo or bucindolol to determine a mortality benefit in moderate to severe heart failure.	No benefit noted in class III and IV CHF patients with bucindolol.	Either bucindolol is a beta-blocker not associated with benefit in heart failure or population studied was resistant to benefit.
CABG-Patch	Coronary Artery Bypass Graft Patch Trial	CAD patients undergoing CABG with EF <0.36 and abnormal SAECG randomized to patch-ICD vs. control with mortality primary end point (n = 1,055).	At mean follow-up of 32 ± 16 mo, the hazard ratio for death was 1.07 (95% CI, 0.81–1.42; *p* = .64); no significant interaction between ICD and baseline variables).	Survival not improved with ICD during CABG in patients with depressed EF and abnormal SAECG.
CAMIAT	Canadian Myocardial Infarction Amiodarone Trial	Patients (n = 120) 6–45 d postinfarction without EF entry criteria but electrocardiographic ventricular arrhythmia followed for combined end point of arrhythmic death or resuscitated ventricular fibrillation; all-cause mortality and cardiac mortality secondary end point.	Primary end point benefitted with amiodarone but toxicity great (42.3% of treatment group stopped amiodarone by 2 yr), all-cause mortality not reduced.	Although not a heart failure trial per se, some patients obviously had LVD; amiodarone may benefit select post-MI patients, but difficult to tolerate.
CAPPP	Captopril Prevention Project	Prospective, randomized, open label trial of captopril vs. conventional (diuretics/beta-blockers) antihypertensive therapies with composite end point of fatal/nonfatal MI, stroke, other CVD deaths (n = 10,985).	No difference in events was observed (RR = 1.05; 95% CI, 0.90–1.22; *p* = .52).	Captopril and conventional therapy did not differ in hypertensives for CVD end points, but captopril dosing did.
CARVEDILOL PROGRAM	The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure	Combined analysis of four distinct studies with varied patient enrollment criteria and outcome measures analyzing safety data regarding mortality events (n = 1,094).	Carvedilol reduced mortality from 7.8% to 3.2% (*p* <.001); findings and analysis controversial because this was not a prospective mortality endpoint trial; rather, a pooled analysis.	More data supporting use of beta-blocker (this one with alpha-blocking properties as well) in CHF; there may be important differences between selective and nonselective beta-blockers in CHF.
CASH	Cardiac Arrest Study Hamburg	Prospective, randomized trial of AICD vs. antiarrhythmics (amiodarone, propafenone, metoprolol) in SCD survivors (n = 349, 61 with AICD).	With a mean follow-up of 57 ± 34 mo survival was only slightly higher in the AICD group (*p* = .081; RR = .766; 97.5% CI, 1.112).	This study only suggested AICD therapy slightly better (in nonsignificant sense) in SCD survivals; although not a heart failure trial, the mean EF was approximately 45%.
CASS	Coronary Artery Surgery Study	Survival endpoint randomized study of CABG vs. best medical therapy of ischemic heart disease with 10-yr follow-up (n = 780) performed over a decade ago.	CABG did not prolong life or prevent infarcts compared with medical therapy except when EF <50%.	One of several studies to suggest that coronary revascularization is important in patients with heart failure and ischemia.
CAST	Cardiac Arrhythmia Suppression Trial	Mortality endpoint trial of encainide and flecainide post-MI in patients with premature ventricular contractions and, generally, LV dysfunction.	Potent class I antiarrhythmic agents increase mortality in MI patients with LVD.	Avoid Vaughn Williams class I antiarrhythmics in CHF if possible.
CATS	Captopril and Thrombolysis Study	Double-blind, placebo-controlled clinical trial of captopril in patients receiving streptokinase post-MI with remodeling LV function end points (n = 298).	Occurrence of LV dilation significantly lower (*p* = .018) and development of CHF less (*p* = .04) with captopril.	Early post-MI remodeling study showing ACE inhibitor benefits.
CHARM	Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity	Placebo-controlled, blinded, mortality endpoint trial of the angiotensin II receptor blocker candesartan in three types of heart failure patients: those with EF >40%, those with EF <40% and ACE inhibitor intolerance, and those with EF <40% and on ACE inhibitor (add-on therapy).	Trial ongoing.	Will help clarify role of an angiotensin II blocker in a wide spectrum of heart failure patients.
CHF-STAT	Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy	Survival study of amiodarone vs. placebo in CHF patients with 10 PVCs/h.	Amiodarone overall did not improve survival compared with placebo.	Did not support hypothesis that amiodarone was helpful generally in CHF.
CIBIS	Cardiac Insufficiency Bisoprolol Study	Bisoprolol (a selective beta-blocker) added to diuretics/vasodilator with mortality end point.	Trend toward morbidity reduction without statistically significant reduction in mortality.	Added to portfolio suggesting beta-blockers beneficial in some CHF patients.
CIBIS-II	Cardiac Insufficiency Bisoprolol Study-II	Placebo-controlled mortality endpoint trial of 2,647 patients given bisoprolol for 16 mo.	Significant reduction in mortality.	Longer trial than CIBIS-I with more ill population and higher dose of bisoprolol; 34% reduction in mortality, particularly sudden death.

CIDS	Canadian Implantable Defibrillator Study	Sudden cardiac death survivors randomized to either AICD or amiodarone (n = 659).	There was a nonsignificant 20% relative risk reduction (95% CI, –0.07–0.40; *p* = .142) in total mortality with a stronger trend toward reduction of “arrhythmic death” (relative risk reduction of 33%; 95% CI, –0.07–0.58%; *p* = .094). The study was stratified for EF < or >0.35 with mean EF of 0.33 and 12% with EF <0.20.	Dofetilide appears to be a risky drug to use in CHF patients with a long-term neutral effect on mortality but significant proarrhythmia problem.
COMET	Comparison of Metoprolol/Carvedilol Trial	Active drug control design with metoprolol compared with carvedilol in 4,000 stable CHF patients.	Trial ongoing.	Study will give important insight into possible superiority of nonselective, vasodilating beta-blocker in mild to moderate CHF.
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study	Enalapril added to digoxin and diuretic in severe heart failure (NYHA IV).	Dramatic reduction in mortality at 6 mo.	ACE inhibitor an important addition in CHF.
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival Trial	Carvedilol vs. placebo in 1,800 NYHA class IIIB/IV CHF with mortality end point.	Significant reduction in mortality.	Most ill CHF group yet studied with beta-blocker.
DIAMOND-CHF (1999)	Danish Investigations of Arrhythmia on Dofetilide Study (Congestive Heart Failure)	Double-blind, placebo-controlled clinical trial of dofetilide in symptomatic congestive heart failure and severe LV dysfunction with mortality the primary end point (n = 1,518).	During a median follow-up of 18 mo there was no difference in mortality (approximately 41%) with the hazard ratio 0.95; 95% CI, 0.81–1.11; but dofetilide decreased CHF hospitalization and converted atrial fibrillation more but with a 3.3% incidence of torsade in the dofetilide group.	Dofetilide appears to be a risky drug to use in CHF patients with a long-term neutral effect on mortality but significant proarrhythmia problem.
DIAMOND-MI (2000)	Danish Investigations of Arrhythmia on Dofetilide Study (Myocardial Infarction)	Double-blind, placebo-controlled mortality endpoint clinical trial of dofetilide in MI survivors with severe LV dysfunction (n = 1,510).	Morbidity and mortality no different in dofetilide and placebo groups.	No antiarrhythmic agent post-MI reduces mortality unlike ACE inhibitor and beta-blockers.
DIG	Digoxin Investigation Group	Survival evaluation to assess the mortality effect of digoxin vs. placebo in stable CHF when used with ACE inhibitor and diuretics (n = 7,000).	No survival benefit with digoxin but morbidity (CHF hospitalizations) reduced.	Digoxin is an important agent in CHF to reduce morbidity but likely has no mortality effect.
DIMT	Dutch Ibopamine Multicenter Trial	Double-blind digoxin and placebo-controlled trials of ibopamine in mild to moderate CHF with exercise capacity, neurohormonal measurements, and function class end points (n = 161).	Digoxin increased exercise time after 6 mo compared with placebo (*p* = .008), whereas ibopamine effective only in patients with EF >0.30. Plasma norepinephrine and renin decreased by both.	Digoxin likely clinically beneficial, whereas ibopamine results need to be placed into the perspective of the other prematurely stopped trials showing detriment (PRIME-II).
ELITE	Evaluation of Losartan in the Elderly	Tolerability and morbidity and mortality study of 722 patients over age 65 with class II, III, IV CHF assigned to either losartan or captopril.	Losartan better tolerated and had lower mortality than captopril.	The angiotensin II receptor blocker losartan may be a reasonable substitute for ACE inhibitor in CHF.
ELITE-II	Evaluation of Losartan in the Elderly-II	Comparison of losartan with captopril with mortality end point in 3,152 NYHA II/IV CHF with EF <40% and age >60.	No mortality difference between ACE inhibitor and angiotensin II blocker in this trial; however, trial not powered to demonstrate equivalence.	Role of angiotensin II blockers in CHF still not clear. One should not substitute an angiotensin II blocker for an ACE inhibitor routinely.
ELVD	Exercise in Left Ventricular Dysfunction Trial	Patients post non–Q-wave MI with EF <0.40 randomized to 6-mo exercise training or control groups with LV volumes and function end points (n = 77).	Exercise training decreased LV volumes and increased EF.	Long-term exercise in post-MI CHF prevents remodeling.
EMIAT	European Myocardial Infarction Amiodarone Trial	Patients 5–21 d post-MI with EF <40% randomized (n = 1,486) with mortality primary end point.	Primary end point, death, not reduced by amiodarone but combined end point of arrhythmic death/resuscitated cardiac arrest reduced slightly.	No definite benefit with amiodarone in post-MI LVD and toxicity of drug significant in this study.
ENOXIMONE	Oral Enoximone in moderate to moderately severe CHF	Randomized placebo-controlled trial of enoximone in combination with digoxin/diuretics with exercise and symptoms primary end points (n = 102).	Enoximone did not improve exercise tolerance or symptoms during 16 wk of therapy, with significantly more dropouts (46% vs. 25%) and more deaths (10 vs. 3; *p* <.05).	Worse survival and questionable benefits raise serious questions about this PDE inhibitor.
ESCAPE	Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness.	Randomized trial designed to test the long-term safety and efficacy of CHF hospital therapy guided by hemodynamics vs. clinical assessment. Primary end point is number of days patients hospitalized or death during 6-mo follow-up (n = 500).	Trial ongoing.	Study will likely demonstrate utility of “hemodynamically” guided CHF therapy.
FACET	Flosequinan ACE-Inhibition Trial	Exercise and QOL endpoint trial with flosequinan, 100 or 75 mg, added to digoxin, diuretic, and ACE inhibitor.	100-mg dose improved patients clinically.	Subsequent mortality trial demonstrated increase in death rates; drug may make patient feel better but at a cost of higher mortality.
FIRST	Flolan International Randomized Survival Trial	Mortality study of conventional therapy vs. continuous i.v. epoprostenol (prostacyclin) in end-stage CHF.	This study was terminated prematurely due to increased mortality and clinical deterioration in the epoprostenol group.	Prostacyclin not an option for chronic parenteral infusion in heart failure; mortality is increased.
GESICA	Group Study of Heart Failure Argentina	Placebo-controlled study of amiodarone in moderate to severe CHF assessing mortality as a primary end point.	Mortality was significantly reduced with amiodarone (42%), compared with placebo (53%).	Suggested amiodarone can be used in some CHF patients.

GROWTH HORMONE	Preliminary Study of Growth Hormone in the Treatment of Dilated Cardiomyopathy	Open label, case series of growth hormone given to IDCM patients with LV function, QOL, clinical class as end points (n = 7).	All parameters improved during 3-mo treatment period (including the development of hypertrophy).	Small pilot study suggesting growth hormone may be beneficial but hypertrophy concerning.
HOPE	Heart Outcomes Prevention Trial	Randomized 2-by-2 factorial design of ramipril and vitamin E in approximately 9,500 patients at high risk of cardiovascular events, including development of CHF.	Impressive reductions in cardiovascular events, including development of CHF, particularly in diabetics with ACE inhibitor but not vitamin E.	ACE inhibitors (ramipril) are powerful agents when given early to patients at risk of cardiovascular events with benefit not entirely due to blood pressure reduction.
HY-C	Hydralazine versus Captopril: Effect on Mortality in Patients with Advanced Heart Failure	Comparison of captopril or hydralazine tailored to hemodynamic goals with respect to mortality in NYHA III/IV CHF (n = 117).	Captopril survival at 1 yr 81% vs. hydralazine (51%; *p* = .05).	Early study demonstrating ACE inhibitor better than hydralazine/nitrates despite achieving same hemodynamics.
IMAC	Intervention in Myocarditis and Acute Cardiomyopathy with i.v. Immunoglobulin	Randomized, double-blind, multicenter trial in 61 patients with new-onset cardiomyopathy who received i.v. immunoglobulin or placebo.	No differences in outcomes, with LVEF being primary end point.	i.v. immunoglobulin likely plays no role in benefiting patients with new-onset cardiomyopathy presumed to be inflammatory in etiology.
IMPRESS	Comparison of vasopeptidase inhibitor omapatrilat and lisinopril on exercise tolerance and morbidity in patients with CHF	Randomized, double-blind, clinical trial with omapatrilat or lisinopril in NYHA II–IV CHF, with exercise primary end point (n = 573).	Exercise tolerance improved similarly in two groups but few CVD events with omapatrilat (7% vs. 12%; *p* = .04) and trend toward fewer deaths plus CHF admissions (RR = .53; 95% CI, 0.28–0.96; *p* = .035).	Pilot trial suggesting omapatrilat could have some advantages over ACE inhibitor in CHF; angioedema question needs to resolved.
LIDO	Levosimendan Infusion vs. Dobutamine	Randomized, double-blind, multicenter comparison of the efficacy and safety of 24-h levosimendan infusion vs. dobutamine in severely decompensated CHF patients (n = 200).	Both drugs hemodynamically active, with fewer deaths in group exposed to levosimendan at 180-d follow-up (concomitant medications not specified/controlled).	Study raises the important question of long-term effects of short-term vasoactive drug infusion.
MACH-I	Mortality Assessment in Congestive Heart Failure	Mibefradil, a T-type calcium channel blocker compared with placebo in 2,390 patients with NYHA II/III CHF on ACE inhibitor, diuretics, digoxin.	Mibefradil increased mortality compared with placebo by 11%.	Calcium channel blockers remain concerning in CHF, with mibefradil likely adversely interacting with drugs that prolong the QT interval.
MADIT	Multicenter Automatic Defibrillator Implantation Trial	Randomized trial of AICD vs. conventional therapy in post-MI patients with EF <35%, nonsustained ventricular tachycardia, and nonsuppressible ventricular tachycardia on EPS.	AICD leads to better survival in this high-risk arteriosclerotic cardiovascular disease population with heart failure; beta-blockers and amiodarone did not appear to have significant effect on hazard ratio.	Provides an alternative strategy for treatment of select patients with heart failure and life-threatening ventricular arrhythmias.
MDC	Metoprolol in Dilated Cardiomyopathy	Effect of metoprolol vs. placebo on survival in dilated cardiomyopathy.	Compared with placebo, metoprolol patients had improved symptoms and cardiac function; 34% fewer primary end points of death or transplant listing with metoprolol.	Provided some support for beta-blocker use in CHF patients but study design criticized.
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Heart Failure	Tested efficacy of adding beta-blocker metoprolol to standard therapy in NYHA II/IV CHF (n = 3,991), morbidity and mortality end points.	Highly significant (35%) decrease in mortality with metoprolol. Trial stopped early.	Additional evidence supporting beta-blocker use in mild to moderate CHF. Metoprolol properties different from carvedilol and bisoprolol.
MEXIS	Metoprolol and Xamoterol in Ischemic Syndromes	Double-blind, active drug controlled evaluation of beta-blockers (one with significant ISA) in MI patients with heart failure with exercise, QOL, and symptoms primary end points (n = 210).	Generally little difference between drugs, but mortality 4.7% at 1 yr for metoprolol and 5.8% for xamoterol, with more withdrawals from xamoterol (22% vs. 17%).	Findings are concerning when juxtaposed to adverse events noted in the xamoterol heart failure trial.
MICRO-HOPE	Microvascular Outcomes in Heart Outcomes Prevention Trial	Substudy of HOPE trial assessing development of nephropathy in diabetics (n = 3,577).	In diabetics, ramipril lowered cardiovascular events by 25% (95% CI, 0.12–0.36; *p* = .0004) and over nephropathy by 24% (95% CI, 0.03–0.04; *p* = .027).	Ramipril reduces CVD events, nephropathy in high-risk diabetics.
MIRACLE	Multicenter InSync Randomization Clinical Evaluation	Randomized exercise and QOL endpoint clinical trial of atrial biventricular pacing in NYHA III/IV CHF patients with wide QRS but no indications for a pacemaker.	Trial ongoing.	Study may justify mechanical approach to CHF that will improve efficiency of cardiac contraction resynchronization and decrease mitral regurgitation.
MIRACLE-ICD	Multicenter InSync Randomization Clinical Evaluation Implantable Cardioverter Defibrillator	Randomized exercise/QOL endpoint clinical trial of atrial biventricular pacing, with device having ICD capabilities in patients with indication for ICD but not a pacemaker.	Trial ongoing.	Extends concepts being evaluated in MIRACLE, but CHF patient applicability being broadened by coupling ICD capabilities to cardiac resynchronization.
MOXCON	Moxonidine in Congestive Heart Failure	Mortality endpoint trial planned for approximately 4,000 NYHA II/IV CHF patients with EF <40%.	Study terminated early because moxonidine associated with increase in mortality.	Reasons for adverse outcomes not clear. Concept of central alpha-blockade in heart failure deserves more scrutiny.
MUNICH MHFT	Munich Mild Heart Failure Trial	Class II CHF patients randomized to captopril, 25 mg b.i.d. vs. placebo, with progression of heart failure major end point (n = 170).	Fewer patients progressed to class IV in the captopril group (11% vs. 26%; *p* = .01).	Early study suggesting ACE inhibitor benefit even at low dose.
MUSTIC	Multi-site Stimulation Cardiomyopathy Trial	Randomized heart failure patients with no pacer indications to biventricular pacer on or off in crossover single-blind design with 6% walk primary end point (n = 58).	Biventricular pacer “on” group had greater increase in 6% walk, peak VO_2, and QOL.	Small clinical trial suggesting biventricular pacing might be helpful in some CHF patients, but observations limited by design problems (crossover).

MUTTI	Multicenter Unsustained Tachycardia Trial Investigators	Randomized trial of EPS-guided antiarrhythmic therapy or simple heart failure treatment in CAD patients with EF <0.40 and asymptomatic unsustained ventricular tachycardia. Outcomes were SCD or cardiac arrest (n = 2,202 with 1,397 in a registry).	Mortality after 5 yr was 48% with inducible ventricular tachycardia vs. 44% without (p = .005).	Study suggests that EPS testing identifies a high-risk group of CAD heart failure patients.
MYOCARDITIS	A Clinical Trial of Immunosuppressive Therapy for Myocarditis	Patients with biopsy-proven “myocarditis” and EF <0.45 randomly assigned (open label) to “standard” care vs. immunosuppression for 24 wk with EF primary end point (n = 111).	No improvement noted with prednisone plus either cyclosporine or azathioprine therapy.	Results did not support routine treatment of myocarditis with immunosuppressive drugs.
OPTIME	Outcomes of a Prospective Trial of Intravenous Milrinone	Randomized milrinone vs. dobutamine study in which patients (n = 950) admitted for CHF management but not decompensation to the point of requiring inotropes were studied to see if length of stay could be shortened.	No impact on length of stay outcomes; more adverse events with milrinone.	Routinely prescribed inotropes in CHF patients generally likely not beneficial and could be associated with an increase in adverse events (new atrial fibrillation and sustained hypotension, p <.05).
PIAF	Pharmacological Intervention in Atrial Fibrillation	Randomized trial of atrial fibrillation patients to diltiazem vs. amiodarone (rhythm control) with symptomatic improvement the primary end point; 17% had cardiomyopathy with symptoms primarily of palpitations, dyspnea (66%), and dizziness observed (n = 252).	23% of amiodarone group converted with 6% walk better, but hospitalizations more frequent (69% vs. 24%; p = .001) and more adverse drug events (25% vs. 14%; p = .036).	Not many symptomatic differences between rate vs. rhythm control with exercise tolerance better, but more hospitalizations and problems with amiodarone (note few “CHF” patients).
PICO	Pimobendan in Congestive Heart Failure	Randomized, double-blind, placebo-controlled trial of the PDE inhibitor pimobendan in CHF, with exercise as primary end point (n = 317).	Pimobendan added to ACE inhibitor/diuretic improved exercise duration with effect on MVO_2 or QOL with more deaths seen in the pimobendan group (RR = 1.8; 95% CI, 0.9–3.5).	Only slight improvement with this oral PDE inhibitor, and potential for proarrhythmia of concern.
PRAISE	Prospective Randomized Amlodipine Survival Evaluation	Effect of amlodipine, a long-acting calcium antagonist, vs. placebo on survival against background of digoxin, diuretic, ACE inhibitor.	Benefits seemed confined to dilated cardiomyopathy group; overall, drug seemingly well tolerated.	Suggested at least one calcium channel blocker might be safe and possibly advantageous in select nonischemic CHF patients.
PRAISE-II	Prospective Randomized Amlodipine Survival Evaluation-II	Randomized, multicenter, placebo-controlled add-on amlodipine therapy in 1,800 patients with dilated, nonischemic cardiomyopathy, with mortality primary end point.	No harm nor benefit detected with amlodipine therapy.	In a properly powered mortality endpoint clinical trial, the calcium channel blocker amlodipine did not confer benefit and negated suggestion of benefit in PRAISE-I.
PRECISE/MOCHA	Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise/Multicenter Oral Carvedilol Heart Failure Assessment	Patients randomized to placebo vs. carvedilol in three distinct subgroups to accommodate mild, moderate, or severe CHF. Ascending carvedilol dose as tolerated (PRECISE) vs. fixed dose carvedilol (MOCHA).	Trials combined with two others to suggest mortality reduction; effects on exercise tolerance minimal; clinical CHF improved.	Carvedilol may be first beta-blocker (with alpha-blocking properties) to be given regulatory approbation for heart failure therapeutics.
PRIME-II	Prospective Randomized Studies of Ibopamine on Mortality and Efficacy	Placebo-controlled mortality endpoint trial of a novel dopaminergic-1 active agent in 2,200 advanced CHF patients.	Trial stopped prematurely after 1,906 patients because of excessive treatment group mortality.	Although drug has primary effects of peripheral and renal vasodilation without significant inotropic or proarrhythmia, there was a negative mortality impact; drug will likely not be developed.
PROFILE	Prospective Randomized Flosequinan Longevity Evaluation	Effect of flosequinan vs. placebo on survival, against background of digoxin, diuretic, ACE inhibitor.	A higher mortality rate in the flosequinan group (100 mg/d) was observed compared with placebo.	Forced withdrawal of flosequinan from the market in May 1993.
PROMISE	Prospective Randomized Milrinone Survival Evaluation	Survival evaluation of milrinone vs. placebo against digoxin, diuretic, ACE inhibitor background.	Milrinone produced decreased survival and increased side effects compared with placebo.	PDE inhibitors used chronically in heart failure likely to improve symptoms at the risk of higher mortality.
PROVED	Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin	Efficacy evaluation in patients with stable heart failure, on digoxin and diuretics, randomized to continued digoxin or withdrawal onto placebo (same design as RADIANCE).	Digoxin withdrawal group demonstrated significant deterioration of exercise and increased treatment failure.	Small trial support for digoxin use in CHF (and caution against stopping drug).
RADIANCE	Randomized Digoxin and Inhibitor of Angiotensin Converting Enzyme Inhibitor	Patients with moderate to severe heart failure were randomized to remain on digoxin or be withdrawn on placebo (same design as PROVED).	Patients withdrawn to placebo had deterioration of exercise performance and worsening symptoms compared with individuals maintained on digoxin.	Triple therapy with ACE inhibitor, diuretic, digoxin likely is best baseline approach to CHF treatment.
RALES	Randomized Aldactone Evaluation Study	Randomized, multicenter, placebo-controlled mortality endpoint trial in 1,663 NYHA class III/IV CHF patients older than 60 yr.	30% reduction in risk of death (p <.001) with low doses of spironolactone (Aldactone).	Older patients with more advanced CHF may benefit with Aldactone added on to other agents to more completely block the adverse neurohormonal milieu associated with heart failure. Hyperkalemia could be a problem.
REFLECT	Randomized Evaluation of Flosequinan on Exercise Tolerance	Randomized, double-blind, exercise tolerance trial of the vasodilator flosequinan in class II/III patients (EF <0.40) on ACE inhibitor/diuretics (n = 193).	After 12 wk, patients exercised better and symptomatically improved on flosequinan.	Although flosequinan improved CHF symptoms, the excess mortality noted in the PROFILE study killed drug.

RENAISSANCE	Randomized Etanercept North American Strategy to Study Antagonism of Cytokines	Randomized, composite endpoint, placebo-controlled, multicenter trial with 2 times weekly injections of tumor necrosis factor modulator added on to standard therapies in NYHA II/IV CHF patients with EF <30%.	Trial ongoing.	Results will give insight into the role of cytokines in heart failure.
RESOLV	Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity	Randomized, placebo-controlled, international, multicenter mortality endpoint trial of candesartan in 6,500 patients with NYHA II/IV CHF. Three groups assessed: ACE inhibitor intolerant, EF >40%, EF <40%, and on ACE inhibitor.	Trial ongoing.	Tests angiotensin II blocker across the broad spectrum of CHF. Only ongoing trial evaluating this strategy in ACE inhibitor–intolerant and “diastolic dysfunction” patients.
RESOLVD	Randomized Evaluation of Strategies for Left Ventricular Dysfunction	Double-blind pilot study in which CHF patients randomized to candesartan (several doses), candesartan plus enalapril, or enalapril for a mean of 43 wk with exercise, remodeling and LV function, neurohormones, and safety/tolerability of drugs end points (n = 768).	No differences noted in exercise, functional class, or QOL with LV volumes better and BNP lower with combination therapy.	Candesartan as effective, safe, and tolerable as enalapril in CHF, with candesartan/enalapril seemingly more beneficial for preventing remodeling than either drug alone.
RESOLVD-Beta-blocker	Randomized Evaluation of Strategies for Left Ventricular Dysfunction-Beta-blocker	During RESOLVD Metoprolol-CR given in double-blind factorial design fashion after initial uptitration of candesartan/enalapril with same RESOLVD end points (n = 426).	No differences in exercise, functional class, or QOL but significant improvement of LV function and attenuation of remodeling with greater decrease of angiotensin II and renin (p = .036 and .032), but increase of BNP (p <.01) with metoprolol-CR.	When added to an ACE, ARB, or ACE/ARB combination, metoprolol-CR improves LV function and renin-angiotensin activation.
SAVE	Survival and Ventricular Enlargement	Effect of placebo vs. captopril on survival and ventricular enlargement in LV dysfunction patients following MI.	Captopril improved survival, functional status, and reduced repeat MI compared with placebo.	Even in asymptomatic ventricular dysfunction, postinfarct ACE inhibitor beneficial.
SCD-HeFT	The Sudden Cardiac Death-Heart Failure Trial	CHF patients without AICD indications randomized to amiodarone, AICD, or routine CHF therapy with total mortality end point (n = 2,500).	Trial ongoing.	Study will likely clarify role of routine AICD or amiodarone therapy in CHF patients.
SHOCK	Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock	Randomized, open study of early revascularization strategies (percutaneous and surgical) in patients with post-MI shock (86% on IABC) (n = 302).	Mortality at 30 d no different between medical and revascularized groups, but 6-mo mortality lower in later (50% vs. 63%, p = .027).	Early revascularization should be considered for MI patients with shock.
SOLVD (Treatment and Prevention Trials)	Studies of Left Ventricular Dysfunction Trial	Patients with symptomatic heart failure and decreased EF (treatment trial) or asymptomatic LV dysfunction (prevention trial) were randomized to placebo vs. enalapril.	Enalapril improved survival and symptoms in the treatment trial and delayed onset or progression of heart failure in the prevention trial.	Taken together, trials established concept that ACE inhibitor is first-line therapy in all heart failure patients (not just CHF).
SPICE	Studies of Patients Intolerant of Converting Enzyme Inhibitors	Registry to determine true incidence of ACE inhibitor intolerance in CHF patients with EF <40% and randomized, double-blind, placebo-controlled pilot study of 75 ACE inhibitor patients.	In registry of approximately 10,000 patients, 80% successfully uptitrated on ACE inhibitor. True intolerance noted in a little over 10%, with cough being greatest problem. Candesartan well tolerated in ACE inhibitor–intolerant patients.	Reasonable to say 80% of CHF patients with low EF can be on ACE inhibitor, and the angiotensin II blocker candesartan was well tolerated when ACE inhibitors were not.
SPICE-Registry	Study of Patients Intolerant to Converting Enzyme Inhibitors (clinical registry)	Multinational registry of patients with CHF to determine medication use patterns and reasons for so-called ACE inhibitor intolerance.	Under optimal situations it seems that approximately 80% of CHF patients with depressed EF tolerate ACE inhibitor. In the 20% who do not, cough is the major reason for intolerance.	Under optimal circumstances, we should anticipate being able to get 80% of CHF patients with LV systolic dysfunction on ACE inhibitor.
SPICE-Trial	Study of Patients Intolerant to Converting Enzyme Inhibitors (clinical trial)	Double-blind, placebo-controlled, randomized clinical trial of candesartan to determine tolerability of an ARB in ACE inhibitor–intolerant patients (n = 270).	Over 12 wk of study, statistically equivalent numbers of candesartan and placebo were continued (83% vs. 87%).	ACE inhibitor–intolerant CHF patients seemingly tolerate the ARB candesartan over 80% of the time, with discontinuations being no more frequent than placebo.
STRETCH	Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure	Multicenter, double-blind, parallel group study of CHF patients on either candesartan or placebo for 16 wk with exercise, functional class, and dyspnea/fatigue index. ACE inhibitor, Ca^{2+} blockers, beta-blockers, and antiarrhythmics not permitted (n = 844).	In a CHF setting with mostly dig/diuretic/vasodilator background therapy, the ARB candesartan was well tolerated and improved heart failure symptoms.	Candesartan appears effective in heart failure patients off of standard ACE inhibitor/beta-blocker therapies.
SUPPORT	Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatment	Case-matching and propensity score analysis done to evaluate right heart catheterize use in critically ill patients (n = 5,735).	Observational study suggesting right heart catheterization associated with increased mortality in all but CHF patients.	Difficult to extrapolate results to “tailored” hemodynamic management of CHF groups.
SWORD	Effect of D-Sotalol on Mortality in Patients with Left Ventricular Dysfunction after Recent and Remote Myocardial Infarction	Randomized, placebo-controlled, multicenter trial in patients with EF below 40% and recent (6–42 d) or remote (>42 d) infarction (n = 3,121).	Study stopped prematurely because of excess treatment mortality (5% vs. 3% death rate, p <.008) in sotalol group.	Even an antiarrhythmic agent with only pure K^+ channel blocking effects has adverse outcome in heart failure patients.
VAL-HeFT	Valsartan Heart Failure Trial	Double-blind, placebo-controlled, multicenter trial of valsartan added on to ACE inhibitor (92% of patients) with approximately 35% on beta-blocker, with all-cause mortality and combined mortality/morbidity end points (n = 5,010).	Largest ARB trial reported to date with ARB/ACE inhibitor combination tested. No mortality benefit, seeming morbidity benefit, but this mostly limited to 7% net on ACE inhibitor. Possible adverse interaction with patients on beta ACE inhibitor and beta-blockers.	Question of ARB’s role in CHF remains unanswered.

VALIANT	Valsartan Post Myocardial Infarction	Double-blind, placebo-controlled comparison of valsartan, captopril, and their combinations after acute MI.	Trial ongoing.	—
VEST	Vesnarinone Survival Trial	Large-scale mortality endpoint trial of 60- and 30-mg doses in NYHA III/IV patients on digoxin, diuretic, and ACE inhibitor.	Increased mortality noted in contrast to prior study, which suggested dramatic benefit.	Role of vesnarinone in CHF now in question; certain subgroups may benefit, but this is yet to be determined.
V-HeFT-I	Veterans Administration Cooperative Vasodilator Heart Failure Trial I	Parallel study of the effects of placebo, prazosin, and hydralazine on survival.	Hydralazine isosorbide dinitrate improved survival; prazosin was no different than placebo.	First study to confirm that vasodilators could save lives in CHF.
V-HeFT-II	Veterans Administration Cooperative Vasodilator Heart Failure Trial II	Parallel study of enalapril vs. hydralazine/isosorbide dinitrate on survival in moderate heart failure.	Enalapril significantly improved survival; hydralazine/isosorbide dinitrate improved EF and exercise.	First to demonstrate incremental benefit of vasodilators with endocrinologic effects.
V-HeFT-III	Veterans Administration Cooperative Vasodilator Heart Failure Trial III	2-by-2 factorial design study evaluating the efficacy of felodipine, digoxin, and placebo.	No mortality reduction noted; felodipine seemingly well tolerated.	Felodipine possibly another calcium channel blocking drug that can be used safely in CHF, although not beneficial.
VMAC	Vasodilation in the Management of Acute Congestive Heart Failure	Randomized, multicenter, nitroglycerin-controlled, symptom/hemodynamic endpoint, clinical trial (n = 500) of Natrecor (BNP) infusion in severe CHF in patients.	BNP superior to TNG, better tolerated and easier to use.	Vasodilating efficacy of BNP in severe CHF demonstrated; VMAC designed to evaluate safety of different infusion strategies, including those not using ICU/PAP pressure monitoring.
WATCH	Warfarin Anticoagulation Trial in CHF	Multicenter, randomized, placebo-controlled trial of anticoagulation vs. platelet inhibition to reduce CHF morbidity/mortality.	Trial ongoing.	Study will clarify wisdom of routine anticoagulation strategies in CHF patients.
Xamoterol	Xamoterol in Severe Heart Failure	Survival endpoint evaluation in 516 CHF patients; placebo-controlled, multicenter, European.	Xamoterol associated with higher mortality at 90-d point.	Inotropic agents with beta-agonist effects increase mortality in CHF patients.

ACE, angiotensin-converting enzyme; AICD, automatic implantable cardioverter-defibrillator; ARB, angiotensin receptor blocker; BNP, b-natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; EF, ejection fraction; EPS, electrophysiologic testing; IABC, intraaortic balloon counterpulsation; ICD, implantable cardioverter-defibrillator; ICU/PAP, intensive care unit/pulmonary artery pressure; IDCM, idiopathic dilated cardiomyopathy; ISA, intrinsic sympathomimetic activity; LV, left ventricular; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVO_2, peak oxygen consumption; NYHA, New York Heart Association; PDE, paroxysmal dyspnea on exertion; PVC, premature ventricular contraction; QOL, quality of life; RR, relative risk; SAECG, signal-averaged electrocardiogram; SCD, sudden cardiac death; TNG, nitroglycerine; VO_2, oxygen consumption per unit time.

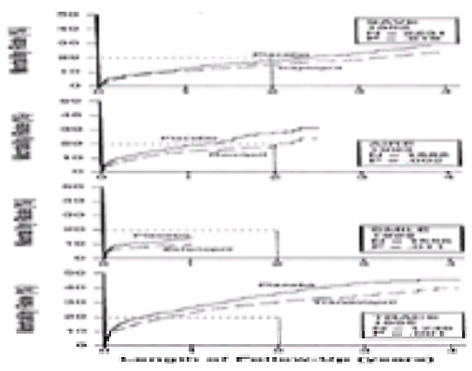
The Cooperative Scandinavian Enalapril Survival Study (CONSENSUS) (83) used an agent that was not only an effective vasodilating antihypertensive drug but one that also blocked certain neurohormonal characteristics of heart failure and demonstrated a profound mortality reduction in severely ill heart failure patients (NYHA class IV). The dramatic CONSENSUS results supported yet a new hypothesis in the treatment of heart failure: the *neurohumoral interdiction hypothesis*. Clinical benefit with respect to mortality reduction could be achieved by blocking certain aspects of neurohormonal compensatory systems characteristic of heart failure, and, specifically, the renin-angiotensin-aldosterone cascade.

Subsequently, V-HeFT-II (84) compared the combination of hydralazine and isosorbide dinitrate to the ACE inhibitor enalapril and demonstrated that enalapril effected greater mortality reduction than did the direct-acting vasodilator combination. This raised the question of whether agents primarily blocking humoral factors were better in heart failure than those with only hemodynamic actions. It is logical that both types of drugs might be important. The syndrome stage in any given patient may have great bearing on outcome with respect to drugs chosen, but this is not entirely clear now. It is interesting to note that the combination of direct-acting vasodilators and ACE inhibitors might be even more effective, but this has not directly been addressed. Some information from the Prospect of Randomized Amlodipine Survival Evaluation (PRAISE) (85) and the V-HeFT-III (86) provide insight into this hypothesis. PRAISE demonstrated mortality reduction, but only in patients with no coronary heart disease. Amlodipine was prescribed as adjunctive therapy to ACE inhibitors and digoxin. V-HeFT-III was a 2-by-2 factorially designed protocol that studied the combination of felodipine, digoxin, and placebo on a background of angiotensin-converting therapy. In this study, felodipine demonstrated no benefit in any group, but harm was not suggested either. PRAISE and V-HeFT-III are also important because they focus on calcium channel blockers in heart failure, which are generally found to be detrimental in this setting. Studies performed with first- and second-generation calcium antagonists usually showed increased morbidity and mortality when prescribed in a heart failure milieu.

The SOLVD program (87,88) evaluated enalapril in asymptomatic or minimally symptomatic patients (the prevention trial) (87) and in patients with mild to moderate congestive heart failure (the treatment trial) (88). Baseline medications generally included diuretics and digoxin. In patients with ejection fraction less than 35% and symptomatic heart failure, enalapril significantly reduced mortality, morbidity, and, importantly, major ischemic events, such as acute myocardial infarction or hospital admission for unstable angina. In fact, the reduction in major ischemic events was more impressive than reduction of any other single morbid event, including hospitalization for heart failure. The SOLVD prevention trial demonstrated significant decrement in the combined end point of congestive heart failure morbidity (hospital admission for heart failure) and mortality. This trial was the first to suggest that a preventive intervention strategy with ACE inhibitors could attenuate progression toward clinically manifest heart failure when used as first-line drug therapy in asymptomatic or minimally symptomatic patients with systolic left ventricular dysfunction. Observations from SOLVD shift the paradigm of therapy from simply a diuretic and digoxin prescription, begun when patients develop congestive heart failure, to instituting ACE inhibitor therapy first even in noncongested, asymptomatic, or minimally symptomatic patients.

In an attempt to finally put to rest the controversy surrounding digoxin use in heart failure, the Digoxin Investigators Group (DIG) Trial (89) followed 7,788 patients with congestive heart failure for 5 years. DIG suggested that digoxin did not significantly affect mortality one way or another but substantially diminished the likelihood that patients would develop worsening heart failure requiring hospitalization. The DIG Trial was performed on a background of diuretic and ACE inhibitor and thus supports the contention that triple therapy is likely the best strategy in congestive heart failure patients. An important result was that a large subset of patients having only diastolic dysfunction with congestive heart failure also saw substantive benefits with digoxin. Some have suggested that a subset analysis in this trial increased risk of “arrhythmic death,” but this conclusion may not be completely justified.

The Survival and Ventricular Enlargement Trial (90) demonstrated that captopril improved survival, functional status, and reduced repeat myocardial infarction rate compared with placebo when this ACE inhibitor was begun the first week after acute myocardial infarction when left ventricular systolic dysfunction in the absence of substantive congestion (ejection fraction less than 40%) was observed. Several other clinical trials after acute myocardial infarction (91,92,93 and 94) (*e*Fig. 92.5.1) have confirmed that ACE inhibitors begun shortly after the event were associated with significant benefit when either asymptomatic systolic left ventricular dysfunction or mild clinical congestive heart failure was present. Captopril, ramipril, zofenopril, and trandolapril, therefore, have been used in this setting, and it is suggested that long-term benefit accrues when a variety of ACE inhibitors are used. Furthermore, several “megatrials” of ACE inhibitors after myocardial infarction conclude that ACE inhibitors given routinely after myocardial infarction (i.e., irrespective of presence or absence of left ventricular systolic dysfunction or congestive heart failure) produce short-term reduction in mortality. The International Study of Infarct Survival IV (95) and Gruppo Italiano Della Infarto Miocardial III trial (96) included patients with a wide spectrum of ejection fractions. Their positive findings suggested that early administration of ACE inhibitors would translate more generally into postinfarct benefit.



***e*FIGURE 92.5.1** Plotted in this figure are the mortality and lengths of follow-up for four trials of angiotensin-converting enzyme inhibitors used in the acute post–myocardial infarction patient with either clinical heart failure (signs and symptoms of congestion) or left ventricular systolic dysfunction that was asymptomatic or mildly symptomatic. The mortality and follow-up periods have been normalized so that the trials can be better compared. Panel I is the Survival and Ventricular Enlargement (SAVE) trial evaluating captopril, panel II the Acute Infarction Ramipril Efficacy (AIRE) study evaluating ramipril, panel III the Survival of Myocardial Infarction: Long-Term Evaluation (SMILE) trial evaluating zofenopril, and panel IV the Trandolapril Cardiac Evaluation (TRACE) trial evaluating trandolapril. The total number of patients included is listed in each box as well as the *p* value for total mortality outcome. Placebo is always the solid line. Marked for convenience of comparison are the 20% mortality and 2-year follow-up points. Mortality reduction was seen with all these angiotensin-converting enzyme inhibitors in a fairly similar population, suggesting that benefits are class related. Still, it is important to note that the patient population did have varying risk profiles: the TRACE placebo group crossed the 20% actuarial mortality between 6 and 12 months, whereas this mark was crossed in AIRE between 12 and 18 months, and in SAVE only after 2 years of follow-up. Use of an angiotensin-converting enzyme inhibitor should be strongly encouraged in patients with heart failure after an acute myocardial infarction and, generally, started within the first week. Obviously, a wide spectrum of post–myocardial infarction patients benefit from this strategy.

Although small clinical trials attempting to evaluate beneficial effects of beta-blockers in heart failure had been published with disparate results, the Metoprolol in Dilated Cardiomyopathy (97) study was the first larger-scale trial to resolve some of the controversy about this strategy. The $beta_1$-selective beta-blocker metoprolol versus placebo was studied in dilated cardiomyopathy patients. Compared with placebo, patients in the active drug limb had improved symptoms with a decrement in the combined end point of survival and need for heart transplant. Many design issues were raised, however, such as the reasonability of including heart transplant as an end point. Although conclusions were tenuous, the observations added some support to the growing portfolio of heart failure therapy benefits with beta-blockers. Subsequently, the Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (98) and the Multicenter Oral Carvedilol Heart Failure Assessment (99) trials were completed. These studies demonstrated improvement in patients with mild to moderate heart failure receiving this beta-blocker and vasodilator on top of digoxin, diuretic, and ACE inhibitors. More interesting was the pooled analysis of four large carvedilol treatment protocols, which indicated that mortality was reduced substantially (100). More recently, other studies with different beta-blockers support the contention that these agents should be used, albeit carefully, in patients with heart failure. Cardiac Insufficiency Bisoprolol Studies I and II using bisoprolol (101,102 and 103) and Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (104) using sustained-release metoprolol (104) were also positive beta-blocker studies. The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study has also been completed, and one aspect of this clinical trial evaluated the effects of sustained-release metoprolol in an aggressive heart failure protocol in which an angiotensin II receptor antagonist (candesartan) and the beta-blocker were added to ACE inhibitors and other heart failure medications (generally diuretics and digoxin) (105). Although not a mortality trial by design, when added to ACE inhibitors, angiotensin II receptor antagonists, or both, the use of metoprolol improved ventricular function, reduced activation of the renin-angiotensin system, and resulted in fewer deaths. Perhaps the most ill heart failure patients yet studied with beta-blockers were in the Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS) (106,107 and 108). This mortality endpoint study extended observations of benefit noted in prior trials with carvedilol to more ill NYHA class IV patients. This study did not, however, include patients who could not reach some degree of compensation (euvolemic at trial entry). Nonetheless, COPERNICUS markedly broadened the patient population likely to benefit from these agents, demonstrating that, when carefully titrated, even very ill individuals could tolerate beta-blockers. Interestingly, in the Beta-blocker Evaluation and Survival Trial (BEST), bucindolol, a nonselective beta-adrenergic blocker with mild vasodilating properties, did not show significant overall survival benefit in a demographically diverse group of patients with NYHA class III and IV congestive heart failure (109). Perhaps important was the fact that in BEST the point estimate of mortality reduction favored bucindolol, but the confidence intervals were wide and not statistically significant compared with placebo, yet when white participants only were included in the analysis, benefits were noted (107). In the United States, then, two beta-adrenergic blocking drugs now have approval by the Food and Drug Administration for use in heart failure patients, carvedilol (Coreg) and long-acting metoprolol (Toprol XL).

Antiarrhythmic drugs have not generally fared well in clinical trials evaluating their effects in heart failure patients (27,28,110,111,112,113,114,115,116,117,118,119 and 120). This has been tremendously disappointing. Many patients with substantive ventricular dysfunction have malignant or potentially malignant ventricular arrhythmias. Furthermore, sudden cardiac death (frequently presumed due to ventricular tachycardia and fibrillation) often accounts for this difficulty. It seems logical that efforts to eliminate these arrhythmias should translate into mortality reduction. Many agents studied are potent with respect to elimination of ventricular dysrhythmia. The Cardiac Arrhythmia Suppression Trial (113,114,120) studied encainide, flecainide, and moricizine post–myocardial infarction in patients with multiple premature ventricular contractions and, generally, left ventricular dysfunction. Indeed, in many senses, the patient population resembled the populations of several other trials (90,91,92 and 93). This study was terminated prematurely, however, because of excessive mortality in the treatment groups. All three drugs seemed to exhibit detriment more than benefit when used routinely in post–myocardial infarction patients with ventricular arrhythmias. The Survival with Oral D-Sotalol (115) trial evaluated the effect of D-sotalol on mortality in patients after recent and remote myocardial infarction [again, populations similar to several other trials, including SOLVD (87,88,90,91,92 and 93)] with ejection fraction less than 40%. This trial was stopped prematurely because of excessive treatment group mortality. Even with an antiarrhythmic agent with only pure potassium channel blocking effects, adverse outcome has been demonstrated. Amiodarone may be, arguably, the one exception to this observation. The Group Study of Heart Failure in Argentina (121) was a placebo-controlled (but unblinded) study of amiodarone in moderate to severe congestive heart failure having mortality end points. Mortality was significantly reduced in the amiodarone group compared with placebo (42% vs. 53%), which suggested that amiodarone could be used safely in congestive heart failure patients and might provide benefit. The European Myocardial Infarction Amiodarone Trial (122) randomized patients 5 to 21 days after myocardial infarction who had an ejection fraction less than 40% and evaluated total mortality as a primary end point. Although the primary end point was not affected by amiodarone, the combined end point of presumed arrhythmic death and resuscitated cardiac arrest was reduced slightly. The Canadian Myocardial Infarction Amiodarone Trial (123,124) evaluated patients 6 to 45 days after myocardial infarction and had no ejection fraction entry criteria, but electrocardiographic ventricular arrhythmias, for combined end points of arrhythmic death or resuscitated ventricular fibrillation. All-cause mortality and cardiac mortality were secondary end points. Although this study demonstrated that amiodarone reduces the incidence of ventricular fibrillation or arrhythmic death among survivors of acute myocardial infarction having frequent or repetitive ventricular premature depolarizations, 42% of the treatment group had stopped the drug by year 2 because of toxicity. The Canadian Myocardial Infarction Amiodarone Trial was not a heart failure trial, per se, but many of its subjects had left ventricular dysfunction. Concern has been raised about making strong conclusions from end points such as “presumed” ventricular tachyarrhythmic death and, therefore, use of amiodarone routinely in heart failure patients is still open to question (125). The Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (126) studied amiodarone versus placebo in congestive heart failure patients generally who had ten premature ventricular contractions per hour on ambulatory monitoring. Amiodarone in this study did not improve survival compared with placebo. Thus, the routine use of amiodarone in patients with heart failure, whether it be manifest as congestive heart failure or left ventricular dysfunction after myocardial infarction, remains highly controversial. Furthermore, it is an expensive therapy in both cost and toxicity. Two large studies of the newest available antiarrhythmic drug, dofetilide, Danish Investigations of Arrhythmia and Mortality on Dofetilide—Congestive Heart Failure (127) and Danish Investigations of Arrhythmia and Mortality on Dofetilide—Myocardial Infarction (128), have now been published. Both trials were primary mortality endpoint studies with the heart failure study assessing mortality in symptomatic congestive heart failure patients with severe left ventricular dysfunction and the myocardial infarction study randomizing patients with severe left ventricular dysfunction after an acute infarct. The heart failure study did show that dofetilide decreased heart failure hospitalizations and converted atrial fibrillation more frequently but with a significant incidence of torsades de pointes in the antiarrhythmic group. In patients with severe left ventricular dysfunction and recent myocardial infarction, treatment with dofetilide did not decrease all-cause mortality, cardiac mortality, or total arrhythmic deaths. However, dofetilide was effective in treating atrial fibrillation and atrial flutter.

Other mortality endpoint heart failure trials have suggested that intervention with certain drugs might actually increase mortality. Studies of flosequinan, milrinone, and prostacyclin (Flolan) are examples. These studies include the Prospective Randomized Flosequinan on Longevity Evaluation (80), the Prospective Randomized Milrinone Survival Evaluation (81), the Xamoterol in Severe Heart Failure (Xamoterol-CHF) (129), and the Flolan International Randomized Survival Trial (78). Milrinone is a potent phosphodiesterase inhibitor demonstrating both inotropic and vasodilating properties. It is an effective drug when used parenterally in acute heart failure patients and may, in fact, be helpful during treatment of chronic and refractory heart failure when given in either chronic or pulsed parenteral infusion fashion (130). However, chronic oral treatment with this drug increased mortality (131). Flosequinan is also likely an “inodilator,” exhibiting inotropic and vasodilating properties, yet it demonstrated increased mortality. Prostacyclin is quite different from phosphodiesterase inhibitors in action and, specifically, does not elicit inotropic effects. Prostacyclin is a potent pulmonary and peripheral arteriolar dilator, yet it was associated with higher mortality than placebo when given chronically to severely ill heart failure patients.

Again, although not a heart failure trial per se, the Multicenter Diltiazem Reinfarction Trial (132) was important because of its demonstration that diltiazem, when routinely administered after myocardial infarction, significantly increased adverse cardiac events in patients with heart failure. Generally, results with calcium channel blocking agents in heart failure have been disappointing, particularly post infarct.

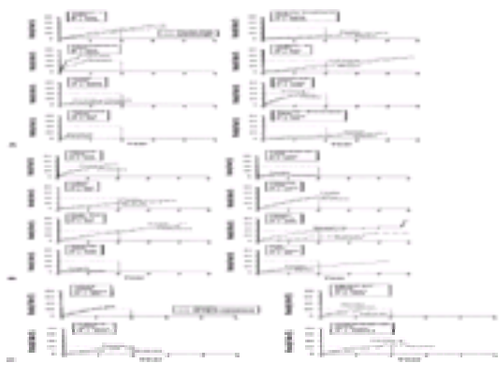
More recently, the Vesnarinone Survival Trial (82) demonstrated a 24% increase in total mortality with the 60-mg dose of vesnarinone ($p < .05$) and a 12% mortality increase with the 30-mg dose (p = not significant). This should be counterposed to a previous vesnarinone study that indicated that this drug reduced mortality substantially at the 60-mg dose, whereas 120 mg increased death rates (133). The lower vesnarinone doses do not, for the most part, produce clinically measurable inotropic or hemodynamic changes in heart failure. Vesnarinone is an interesting proposed heart failure therapy because it may interdict the inflammatory (cytokine or tumor necrosis factor) components of heart failure. Observations are incomplete at this time, but the disparity between outcomes noted in two well-designed, well-controlled, compulsively performed mortality endpoint clinical trials is troubling. One wonders whether vesnarinone may have specific beneficial effects in only a well-defined subset patient population that is yet to be characterized.

Studies with calcium channel blockers generally have demonstrated increased morbidity and mortality in heart failure. PRAISE I and II and V-HeFT-III are the only clinical trials to date that suggest that specific calcium channel blocking agents (amlodipine and felodipine) might not carry such concerns for heart failure patients

(134,135). The calcium channel blocker mibefradil studied in Mortality Assessment in Congestive Heart Failure I actually increased morbidity. This drug is no longer available (136).

Other pharmacologic approaches in heart failure have been studied including the use of human growth hormone, but concern has been raised about the induction of ventricular hypertrophy and diastolic dysfunction with this agent (137). Spironolactone proved quite efficacious in the Randomized Aldactone Evaluation Study trial when added to diuretics, digoxin, and ACE inhibitors in NYHA class II and III patients (138).

*e*Figure 92.5.2 graphically presents selected mortality endpoint clinical trials that have greatly shaped our philosophy regarding best approaches to the patients with heart failure. The figure is arranged so that all of the trials are comparable with respect to total mortality end points and length of patient follow-up. These trials were well performed and therefore provide credible information regarding therapeutic algorithms. Important to note is the fact that a wide spectrum of placebo mortality can be observed, implying that different patient populations have been studied. It is also likely that, over time, patient management strategies have improved more generally.



***e*FIGURE 92.5.2 A–C:** Actuarialized total mortality end points are plotted for select multicenter clinical heart failure trials. The mortality and follow-up periods have been normalized for each study so that placebo mortality can be compared among the different populations. It is important to note that placebo group mortality is quite different from trial to trial, emphasizing that different populations with heart failure were studied. Furthermore, different therapeutic adventures have produced widely disparate results, with some being highly beneficial and others detrimental. Trial results are ordered from top to bottom and right column to left based on their historic sequence of publication. The total number of patients included is listed in each box as well as the *p* value for total mortality outcome. Placebo is always the solid line. Marked for convenience (*dotted line*) of comparison are the 40% mortality and 2-year follow-up points.

SPECIFIC THERAPIES FOR CHRONIC HEART FAILURE

It is important to reemphasize that the principles of chronic heart failure therapeutics are rooted in making the appropriate diagnosis, staging the syndrome (different therapies are warranted for asymptomatic vs. symptomatic patients), addressing diseases causing or precipitating the difficulty, and using strategies that prevent disease progression (e.g., appropriate treatment of hypertension and atherosclerotic cardiovascular risk factors). Patient counseling and general education of family and home care givers is also important but is often ignored.

Suggested Topics for Patient, Family, and Care Giver Education

Table 92.5 presents topics for patient, family, and care giver education and counseling that have been modified from the AHCPR guidelines (72,73). Central to therapy is an explanation to the patient of heart failure and the reason for symptoms, if the patient is symptomatic. Discussion of the cause or probable cause of heart failure is important, as are expected symptoms, symptoms that herald worsening heart failure, and strategies to pursue if symptoms worsen. Instruction with regard to self-monitoring of daily weights, blood pressure, pulse rate, and blood sugar in diabetics is helpful. Explicit explanation of treatment and care plans is important to gain acceptance of therapeutic strategies. One should be specific when discussing patient responsibilities with regard to cessation of tobacco and alcohol use, salt restriction, and fluid intake reduction. The important role of family members or other care givers in the treatment plan should be stressed. Atherosclerotic risk factor intervention is essential, as is the need for obtaining vaccinations at appropriate intervals against influenza and pneumococcal disease. Prognosis should be frankly discussed, and advanced directives elicited when appropriate. This is particularly important for those patients suffering with advanced or end-stage heart failure. Advice should be given to family members with regard to resuscitation efforts should sudden cardiac death syndrome occur. Activity recommendations need to focus on benefits of exercise-based cardiac rehabilitation programs. Recreational, leisure, work, and exercise activities can be frankly addressed, and patients should be encouraged to perform aerobic activities that are symptom limited. Exercise should not necessarily be banned in patients with heart failure. Generally, patients “can do what they can, and can’t do what they can’t.” Dietary recommendations are essential and focus on restriction of salt and excessive fluid intake. Alcohol might be proscribed in certain situations. The effects of medications on quality of life and survival should be frankly addressed, and schemes designed to optimize compliance with treatment and care plans are important. One must emphasize the necessity of taking medications in timely fashion, and it is good practice to provide forms to record medication consumption, pulse rate, blood pressure, and daily weights so that the patient can take an active part in the therapeutic program. One should not ignore the importance of education with regard to atherosclerotic cardiovascular disease risk factor modification. Because ischemic heart disease is the major reason for patients developing heart failure, it makes sense to halt progression of atherosclerosis.

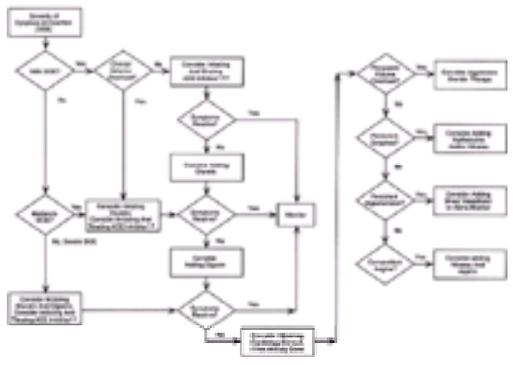
TABLE 92.5 SUGGESTED TOPICS FOR PATIENT, FAMILY, AND CARE GIVER EDUCATION AND COUNSELING

Surgical Therapeutics

When appropriate, surgical therapies can provide dramatic symptomatic relief in patients with congestive heart failure (53,72,74,139). Particularly important is identifying individuals who might benefit from coronary revascularization with percutaneous coronary interventional strategies or coronary artery bypass surgery (74,140,141).

*e*Figure 92.5.3 presents the AHCPR guidelines regarding evaluation and treatment of coronary artery disease in patients with heart failure. This algorithm was included in the AHCPR recommendations because most data support revascularization strategies in coronary disease patients having left ventricular dysfunction. Revascularization is thought to be important in those having significant myocardial ischemia when targeted lesions can be addressed. Although procedure-related morbidity and mortality increase as left ventricular systolic function worsens, substantive benefit can be noted in individuals with profoundly reduced ejection fraction and concomitant ischemia. Provocative tests should be performed to characterize and quantify the relative contribution of nonviable myocardial scar, ischemia, or “hibernation” to the heart failure milieu (139). Atrioventricular valve repair or replacement, even when ejection fraction is significantly reduced, may be an option. Particularly important is the relief of left ventricular outflow tract obstruction. Aortic valve replacement, repair, or valvuloplasty should be seriously considered in all individuals with substantive valve orifice reduction and diminished ejection fraction. It is a challenge to separate patients likely to benefit from aortic valve replacement from those who are not, when ejection fraction is depressed. Factors that may negatively affect outcomes in these patients appear to be substantive myocardial fibrosis and scar, particularly in the setting of ischemic heart disease. Therefore, patients with concomitant coronary artery disease need to be evaluated carefully. Obviously,

repair of congenital defects can be beneficial. Volume and pressure loads created by intracardiac shunts can be quite detrimental in patients with ventricular dysfunction. Assessment of the degree of fixed pulmonary hypertension is essential in separating patients likely to benefit from repair of congenital lesions from those not likely to benefit.



***e*FIGURE 92.5.3** The Agency for Health Care Policy and Research algorithm for evaluation and treatment of coronary artery disease patients with heart failure emphasizes the importance of determining if ischemic myocardium is present so that it can be addressed with revascularization of one sort or another. ACE, angiotensin-converting enzyme.

Relatively recently, an innovative surgical procedure has been proposed as an additional treatment option for select patients with advanced heart failure (142). Partial left ventriculectomy (or volume reduction surgery) in patients with severely dilated hearts due to cardiomyopathy may make some patients better. Ventricular remodeling involves removal of a wedge of cardiac tissue from the enlarged heart to relieve myocardial wall stress and reshape the cardiac chamber. This operation is usually performed concomitantly with attempts to reduce mitral and tricuspid valve leakage. However, outcomes after this procedure were not optimal, with only one-third of patients seeing long-term improvements. The operation has largely been abandoned (143,144). On the other hand, resection of myocardial scar tissue or aneurysm formation after myocardial infarction appears to be a more rational procedure in the sense that patients undergoing this later remodeling operation have myocardial scar tissue removed rather than actual muscle (145). More traditional left ventricular aneurysmectomy is effective in select ischemic heart disease patients with significant focal dyskinesia of the left ventricle (particularly when mitral regurgitation is present and substantive). Cardiac transplantation can play an extraordinarily dramatic role in truly end-stage patients without contraindications to this operation. The problem is that donor organ supply is inadequate, and, at best, only 2,000 to 3,000 of these operations can be performed annually around the world. Dynamic cardiomyoplasty is a procedure that involves mobilization of a latissimus dorsi muscle into the chest, wrapping the heart, and then training the skeletal muscle to become fatigue resistant with an electrical stimulating device that is coupled to a pacemaker (146,147 and 148). Anecdotal experience suggests that this procedure can effect symptomatic improvement in some class II and III patients and has an acceptable mortality risk. Unfortunately, the cardiac myostimulating device is no longer available. Other even more innovative surgeries include the insertion of a variety of endomyocardial splinting devices and epicardial wraps designed to extrinsically reshape the heart into a more normal configuration. Clinical trials are ongoing with the so-called MyoSplint and Acorn devices (145).

Pharmacotherapeutic Approaches

Figure 92.5 presents an overview algorithm for drug management of patients with heart failure. Again, drug therapy needs to be linked to staging the heart failure syndrome severity and determining whether the problem is due to left ventricular systolic dysfunction or so-called diastolic dysfunction (meaning, generally, that the left ventricular systolic ejection fraction is greater than approximately 45%). At the core of therapy for systolic dysfunction are ACE inhibitors, with digoxin and diuretics added when congestive heart failure is present. Beta-blockers are also critical drugs to use, generally added to the triple-therapy core. Long-acting nitrate preparations may be important for dyspnea relief. If an ACE inhibitor cannot be used because of intolerance or undesirable pharmacologic effects, one should consider the combination of hydralazine and isosorbide dinitrate or, alternatively, angiotensin II receptor blocking agents. As has been repeatedly emphasized, if coronary artery disease is present, consideration of revascularization is important. In patients with atherosclerosis generally, use of lipid-lowering drugs should also be considered. For patients with diastolic dysfunction, treatment options are less well defined. In individuals with congestive heart failure but relative preservation of left ventricular systolic function, one should first attempt to make a diagnosis of an infiltrative cardiomyopathy and base treatment on symptoms. Perhaps the most important drugs in diastolic dysfunction are nitrates and vasodilating agents, with diuretics used to control fluid retention states, but this is contentious. *e*Table 92.5.1 lists alternatives to diuretics, beta-blockers, and ACE inhibitors that might be useful in patients with hypertension or high normal blood pressure who have heart failure associated with either systolic or diastolic left ventricular dysfunction.

***e*TABLE 92.5.1** MEDICATIONS OTHER THAN DIURETICS, BETA-BLOCKERS, AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS TO TREAT HYPERTENSION OR HIGH NORMAL BLOOD PRESSURE IN PATIENTS WITH HEART FAILURE

Drug dose (mg)	Initial dose (mg)	Maximum dose (mg)	Major adverse reactions
Direct vasodilators			
Hydralazine	10 t.i.d.	75 t.i.d.	Headache, nausea, dizziness, tachycardia, lupus-like syndrome
Minoxidil	2.5 q.d.	80 q.d.	Fluid retention, hair growth, thrombocytopenia, leukopenia
Alpha$_1$-adrenergic blockers			
Doxazosin	1 q.d.	16 q.d.	Postural hypotension, dizziness, syncope, headache
Terazosin	1 q.d.	20 q.d.	Similar to doxazosin
Prazosin	1 t.i.d.	10 t.i.d.	Similar to doxazosin
Centrally acting alpha-blockers			
Clonidine tablets	0.1 b.i.d.	0.6 b.i.d.	Sedation, dry mouth, blurry vision, headache, bradycardia
Clonidine patch	0.1 weekly	0.3 weekly	Same as clonidine; contact dermatitis
Guanabenz	4 b.i.d.	64 b.i.d.	Similar to clonidine
Guanfacine	1 q.d.	3 q.d.	Similar to clonidine
Angiotensin II receptor blockers			
Candesartan	16 q.d.	32 q.d.	Hypotension, hyperkalemia, rash, renal insufficiency
Irbesartan	150 q.d.	300 q.d.	Hypotension, hyperkalemia, rash, renal insufficiency
Losartan	25 q.d.	50 b.i.d. or 100 q.d.	Hypotension, hyperkalemia, rash, renal insufficiency
Telmisartan	40 q.d.	80 q.d.	Hypotension, hyperkalemia, rash, renal insufficiency
Valsartan	80 q.d.	320 q.d.	Hypotension, hyperkalemia, rash, renal insufficiency

Specific Strategies

Positive Inotropic Agents

Pharmacologic effects that make digitalis attractive in heart failure include its positive inotropic action and negative chronotropic effects, as well as the agent's ability to modulate neurohormonal factors (by increasing baroreceptor sensitivity), to attenuate sympathetic nervous system tone, to decrease norepinephrine concentration, and to diminish renin-angiotensin levels (30,31,149). Controversy about using digoxin has centered around proper patient selection and drug dosing (29,31). Little debate exists regarding its utility in congestive heart failure patients with atrial fibrillation. In this situation, it is not clear whether digoxin is more helpful by controlling heart rate or by precipitating other beneficial effects, such as positive inotropy or baroreceptor readjustment. In a survey regarding physician practice in the management of congestive heart failure published in 1986, among 2,700 physicians actively treating patients with heart failure, approximately two-thirds of respondents considered digitalis effective in improving exercise tolerance, but fewer than one-third believed this drug could prolong life. Indeed, only approximately 30% reported that they would use digitalis as first-line therapy in patients with congestive heart failure with normal sinus rhythm. In the SOLVD Registry, 65% of patients with an ejection fraction of less than 20% were receiving digoxin compared with only 29% with ejection fractions of 36% to 45% (47).

Two clinical trials have placed the contemporary role of digoxin in patients with heart failure and normal sinus rhythm into better perspective. The Prospective Randomized Study of Ventricular Failure and the Effect of Digoxin (PROVED) (150) and the Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) (151) were designed to assess the contribution of digoxin therapy to a patient's clinical status when used in a setting of either diuretic (PROVED) or combination diuretic and ACE inhibitor therapy (RADIANCE). These trials are particularly important because they clarify the role of triple heart failure therapy in patients with congestive heart failure. Both trials were simultaneously performed and identical in design, with the exception of baseline drugs permitted. Patients were required to have mild to moderate congestive heart failure with ejection fraction less than 35%. They were treated with digoxin and diuretics in

PROVED and digoxin, diuretics, and ACE inhibitors in RADIANCE. In both studies, a blinded randomization schedule determined which patients were to have digoxin replaced by placebo. Patients were required to be quite stable on their existing therapies. End points of the trials included maximal exercise capacity, incidence and probability of treatment failure with and without digoxin, control of signs and symptoms of congestive heart failure, and changes in certain parameters of ventricular function. Patients were all in sinus rhythm. Both studies demonstrated that withdrawal of digoxin therapy led to significant increase in the probability that heart failure would worsen over time with reduction in exercise tolerance. Digoxin therapy also was related to improved ventricular performance manifest by increasing ejection fraction. Importantly, pooled analysis of outcome in patients from both trials demonstrated that the lowest probability of treatment failure was seen in patients treated with the triple-drug combination (31). Although the combination of digoxin and a diuretic was far better than a diuretic alone, and the combination of diuretic and ACE inhibitor was similar to the digoxin and diuretic combination, triple-drug therapy clearly was best. Furthermore, this trial suggested that withdrawal of digoxin in stable congestive heart failure patients was associated with higher adverse event rates, and that stopping this drug should be avoided.

Gaining insight into the effect of digitalis on survival has been more difficult. In 1981, Moss et al. evaluated the effect of digitalis therapy on 4-month postdischarge cardiac mortality in 812 patients after acute myocardial infarction (152). Overall, there was an insignificant difference in mortality among treatment cohorts, but in the group with combined ventricular dysfunction and arrhythmias, digitalis was associated with increased mortality. In 1983, Ryan et al. evaluated the effects of digitalis on survival in high-risk patients with coronary artery disease using the Coronary Artery Surgery Study data bank (153). This report failed to confirm the observation of Moss et al. A year later, Madsen et al. analyzed 1,599 patients discharged from the hospital after acute myocardial infarction who were also on digitalis therapy (154). This drug was not an independent predictor of late mortality. Bigger et al. (155) evaluated another set of patients after myocardial infarction, but, in contradistinction to Ryan and Madsen, suggested that postinfarction survival was inversely and significantly related to serum digoxin concentration, with higher serum digoxin levels (and, generally, dose) associated with reduced long-term survival. After adjusting for the presence of atrial fibrillation and left ventricular dysfunction, however, serum digoxin concentration was not significantly related to survival. In 1985, Byington et al. (156) evaluated the Beta-Blocker Heart Attack Trial (BHAT) database and found that 250 (13%) of the 1,921 placebo-treated patients were receiving digitalis at the time of randomization. These patients experienced a higher incidence of in-hospital complications, such as pulmonary edema, persistent hypotension, atrial fibrillation, and heart failure, as well as demonstrated a greater frequency of complex ventricular arrhythmias. Multivariable logistic regression analysis adjusting for many independent factors usually predictive of mortality demonstrated that the use of digitalis was no longer independently associated with mortality. It is likely that patients receiving this drug had more extensive cardiovascular disease and greater morbidity than those not receiving digitalis and that their higher mortality was more related to the severity of underlying disease than to digitalis administration. Mueller et al. evaluated the experience in the Multicenter Investigation of the Limitation of Infarct Size (157) and reached the same conclusion as did the inquiry of the BHAT database.

The DIG Trial seemingly has given a definitive answer regarding digoxin's effect on mortality (89). This trial evaluated almost 8,000 patients with digoxin added to a background of ACE inhibitor and diuretics. Approximately 1,000 patients had congestive heart failure but preserved left ventricular systolic function (ejection fraction greater than 45%). The trial was relatively nonselective, with inclusion criteria being a history of clinical heart failure with current or previous evidence of low output (manifest by historic limitation of physical activity), normal sinus rhythm, chest radiograph, and ejection fraction performed within 6 months of trial entry, and evidence at some time of congestion (i.e., peripheral or central edema, jugular venous distention, pulmonary rales, or chest radiographic pulmonary edema). The primary end point was total mortality in patients with left ventricular ejection fraction less than 45%, and secondary end points included reduction in hospitalization for worsening congestive heart failure, cardiovascular mortality, death due to progressive heart failure, all-cause hospitalization, and quality of life. In this trial, 93% of patients were maintained on ACE inhibitors long term, with diuretics being used in 82% and long-acting nitrates in 42%. Outcome of this trial demonstrated that digoxin had a completely neutral effect on mortality. Still, digoxin reduced hospitalization and favorably affected the combined end point of death or hospitalization due to worsening congestive heart failure. There was a trend toward increased death due to arrhythmic events in analysis of certain subgroups, which has led some investigators to urge caution with prescription of this drug (29). However, the most appropriate interpretation of study results may be that digoxin has been shown safe, with substantive reduction in clinically significant morbid events, and that the effects are incremental to ACE inhibitor and diuretic therapy in patients with congestive heart failure. Analysis of the diastolic dysfunction subset demonstrated the same beneficial outcome results noted in the trial more generally. Digoxin appears effective in this group of patients as well. Routine digoxin prescription will, no doubt, become a more contentious issue.

Use of plasma digoxin levels to monitor therapy has been common. The diagnosis of digoxin toxicity seems to be related to elevated plasma levels, but few data are available concerning the relationship of plasma levels to their physiologic effects. In 1972, Redfors first explored the relationship between plasma digoxin concentration and clinical effects using the reduction in heart rate in patients with atrial fibrillation as an end point (158). Some observations on systolic time intervals suggested that higher digoxin doses and levels produced more inotropic effects. Slatton et al. have demonstrated no significant differences between 0.125-mg and 0.25-mg doses of digoxin with respect to echocardiographic ventricular contractility parameters (159). A significant difference was observed between 0.125 mg and placebo. This should be coupled to an analysis of the pooled PROVED and RADIANCE trial database, which split patient cohorts into tertiles of serum digoxin concentration (0.5 to 0.9 ng per mL; greater than 0.9 to 1.2 ng per mL; greater than 1.2 ng per mL) (160). The difference between the median change in exercise time when digoxin and placebo groups were compared was significantly different for each tertile of digoxin level. Patients receiving placebo did worse in every respect. The placebo group with a baseline digoxin level greater than 1.2 ng per mL had the largest decrement in exercise time after placebo was substituted for digoxin, but the fact that a statistically significant difference was noted in all groups suggested that, even at lower serum concentrations, digoxin is effective. A similar observation was made when the percentage of patients was determined in whom clinical congestive heart failure was developing. Low levels of digoxin and low doses were equally beneficial when this end point was considered. Thus, it appears that digoxin was superior to placebo regardless of plasma concentration. It is likely that high doses and levels of digoxin are unnecessary for efficacy in congestive heart failure patients.

Newer Inotropic Agents

As mentioned, few inotropic agents have met the challenge of both morbidity and mortality reduction in patients with heart failure (20,26,130). Although some (e.g., Xamoterol, milrinone, and flosequinan) have seemingly improved patient symptomatology, this has occurred generally in a setting of increased mortality. It is important to distinguish chronic therapy with these oral drugs from the use of inotropic agents, such as dobutamine and milrinone, in the acute heart failure setting or as last ditch attempts to control symptomatology when given parenterally to advanced heart failure patients on a long-term basis.

A great deal of attention has been directed toward vesnarinone (82,133). This drug is an orally active quinolinone preparation that exerts its positive inotropic effect not only by inhibiting phosphodiesterase, but also by decreasing the delayed outward and inward rectifying potassium current, increasing intracellular sodium by prolonging opening of sodium channels, and prolonging the action potential on a rate-dependent basis. Initial studies demonstrated that, in patients with heart failure, vesnarinone improves quality of life and exercise capacity and was well tolerated, without a seeming proarrhythmic effect. One large survival endpoint clinical trial of nearly 500 patients with left ventricular ejection fraction less than 30% who were treated with digoxin and an ACE inhibitor had a remarkable 62% reduction in risk of all-cause mortality and a 50% reduction in combined morbidity and mortality with the 60-mg dose (133). These results were highly significant, but they should be balanced against the dosage of 120 mg per day, which significantly increased mortality in this study. One side effect of vesnarinone is neutropenia, which occurs in 1% to 5% of patients exposed to the compound. The results of this clinical trial were particularly intriguing. Although vesnarinone has some phosphodiesterase activities, the mechanism of action is not entirely clear. Of interest, the drug attenuates certain aspects of cytokine activation in patients with heart failure. Vesnarinone appeared to offer benefits that apparently may have little to do with inotropic properties. Indeed, lower doses of the drug did not demonstrate significant inotropic or hemodynamic effects. All these conclusions, however, have been tempered by the more recently completed Vesnarinone Survival Trial, which was also a large-scale, placebo-controlled, multicenter, mortality endpoint study (82). Vesnarinone Survival Trial demonstrated an excess of mortality in the 60-mg dose group. This dose was associated with an increase in sudden cardiac death without favorable effect on secondary end points of quality of life, hospitalization, or worsening heart failure.

Ibopamine is an inotropic drug once considered for use in heart failure patients because of its dopaminergic activity (20). Ibopamine is the prodrug of epinine and stimulates dopamine-1 and dopamine-2 receptors as well as the $beta_1$-and $beta_2$-adrenergic receptors. There is a dose-related hemodynamic and inotropic response with this drug, and patients with heart failure had beneficial hemodynamic and renal blood flow changes, without inotropic effects, at lower doses. Several trials have suggested that the drug is beneficial when exercise performance end points were used to judge efficacy; however, the multicenter Prospective Randomized Ibopamine Trial of Mortality and Efficacy II trial was prematurely stopped because of increased mortality (79,161). Subgroup analysis of this study has revealed that the increased mortality was associated with concomitant use of the antiarrhythmic amiodarone.

Many explanations have been proposed to explain the rather dismal performance of inotropes in more recent clinical trials, but evidence-based explanations remain elusive. It is interesting to note the contemporary shift toward greater use of beta-blocker therapy in congestive heart failure patients as opposed to drugs affecting beta-receptor augmentation. Still, there remains the belief, fueled by the intuitive logic of positive inotropic agents in this setting, that these drugs will have a role in the management of heart failure. A preferred pharmacologic profile for inotropic drugs likely includes the requirements that neurohormonal activity should be attenuated or at least not exacerbated, heart rate should not be increased, and pharmacologic effects should not promote propagation of ventricular arrhythmias or increase myocardial oxygen consumption. One new drug, levosimendan, may represent an emerging inotropic compound that could prove beneficial in heart failure patients (162). This drug is available for intravenous use in Europe, and the oral formulation is now in clinical trials. In experimental models, levosimendan has demonstrated an antiischemic effect and has an action independent of traditional cyclic adenosine monophosphate pathways. It appears to be a "calcium-sensitizing" drug. It will be interesting to see if this compound is but one more inotropic drug failing to keep its promise.

Diuretics

Long the mainstay of congestive heart failure treatment, diuretics continue to play an important role (136). It is essential, however, that their utility be placed into proper perspective. Diuretics, for example, have never been studied in large-scale mortality trials in patients with heart failure but no overt congestion. There is no question

that they are essential agents to relieve the volume-overload states associated with congestive heart failure, but congestion is not necessarily always present in the majority of patients with heart failure. Furthermore, patients may develop congestive states that resolve with pulsed or intermittent diuretic therapy (163,164). As can be seen in *e*Table 92.5.2, substantive difficulties are possible, including hyponatremia, hypokalemia, metabolic alkalosis, and increased uric acid levels, setting the stage for overt gout or worsening renal function. Carbohydrate metabolism is frequently disturbed, with resultant hyperglycemia, insulin resistance, decreased insulin secretion, and nonketotic hyperosmolar states. Lipid perturbation is also a problem, but its significance is not well understood. Diuretic-specific side effects include the ototoxicity of furosemide, gynecomastia, and galactorrhea with spironolactone, metabolic acidosis caused by carbonic anhydrase inhibitors, and hyperkalemia caused by potassium-sparing diuretics, such as triamterene, spironolactone, and amiloride. When treating congestive heart failure, generally the least toxic drug (thiazides, such as hydrochlorothiazide or chlorthalidone) is prescribed in the lowest dose necessary to induce effective diuresis (*e*Table 92.5.3). As congestion worsens, longer-acting loop diuretics (such as furosemide, bumetanide, or torsemide) are prescribed. Occasionally, for particularly refractory edematous states, combinations of diuretic classes may be necessary. It should be emphasized that failure to mobilize salt and water is often due to inadequate sodium and fluid restriction, particularly in individuals recently diuresed and at risk of rebound sodium retention. Ensuring low sodium consumption is essential to success with these compounds. Acute resistance is generally overcome with an increased single diuretic dose. Chronic resistance can be addressed with the coadministration of thiazide or potassium-sparing diuretics with a loop diuretic. Using combinations of agents active at different points of the nephron is essential. From a pharmacokinetic standpoint, overcoming diuretic resistance by simply increasing diuretic dose is important. Altered bioavailability may account for some aspects of diuretic resistance, and there are different absorption kinetics associated with furosemide, bumetanide, and torsemide. Switching among these oral loop diuretics may be helpful. Alternatively, giving diuretics intravenously may accomplish the same end point.

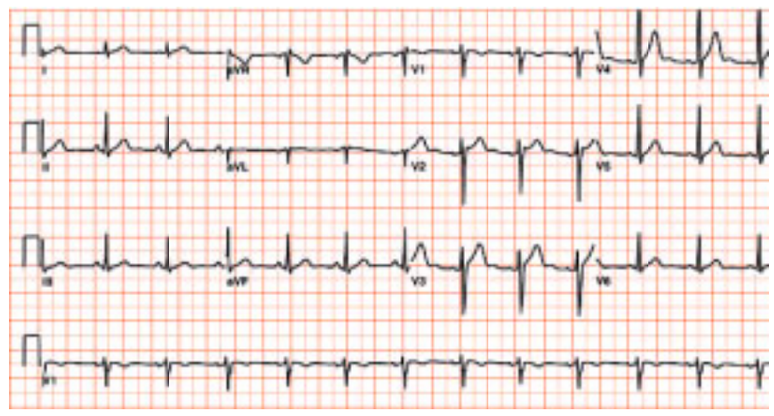
***e*TABLE 92.5.2** COMMON PROBLEMS WITH DIURETICS

Electrolyte disturbances
Hyponatremia
Hypokalemia
Hypomagnesemia
Hypocalciuria
Hyperuricemia
Metabolic alkalosis
Carbohydrate metabolism perturbation
Hyperglycemia
Insulin resistance
Decreased insulin secretion
Nonketotic hyperosmolar state
Lipid abnormalities
Increased low-density lipoprotein
Increased very-low-density lipoprotein
Increased total cholesterol
Increased triglycerides
Diuretic-specific side effects
Furosemide: ototoxicity
Spironolactone: gynecomastia and galactorrhea
Acetazolamide: metabolic acidosis
Potassium-sparing diuretics: hyperkalemia

***e*TABLE 92.5.3** MEDICATIONS COMMONLY USED IN CHRONIC HEART FAILURE TREATMENT PROTOCOLS

Drug	Initial dose (mg)	Target dose (mg)	Recommended maximum dose (mg)	Major adverse reactions
Thiazide diuretics				
Hydrochlorothiazide	25 q.d.	As needed	50 q.d.	Postural hypotension
Chlorthalidone	25 q.d.	As needed	50 q.d.	Hypokalemia, hyperglycemia, rash; rare severe reaction includes pancreatitis, bone marrow suppression, and anaphylaxis
Thiazide-related agents				
Metolazone	2.5 q.d.	As needed	10 b.i.d.	Same as thiazide diuretics
Loop diuretics				
Furosemide	10–40 q.d.	As needed	240 b.i.d.	Same as thiazide diuretics
Torsemide	10 q.d.	As needed	200 q.d.	Same as thiazide diuretics
Bumetanide	0.5–1.0 q.d.	As needed	10 q.d.	Same as thiazide diuretics
Ethacrynic acid	50 q.d.	As needed	200 b.i.d.	Same as thiazide diuretics
Potassium-sparing diuretics				
Spironolactone	25 q.d.	As needed	100 b.i.d.	Hyperkalemia, gynecomastia (spironolactone only)
Triamterene	50 q.d.	As needed	100 b.i.d.	—
Amiloride	5 q.d.	As needed	40 b.i.d.	—
Select angiotensin-converting enzyme inhibitors[a]				
Enalapril	2.5 b.i.d.	10 b.i.d.	20 b.i.d.	Hypotension, hyperkalemia, renal insufficiency, cough, skin rash, angioedema, neutropenia, nausea, dysgeusia
Captopril	6.25–12.50 t.i.d.	50 t.i.d.	100 mg t.i.d.	—
Lisinopril	5 q.d.	20 q.d.	40 q.d.	—
Quinapril	5 q.d.	20 q.d.	40 q.d.	—
Beta-blockers				
Bisoprolol	1.25 b.i.d.	5 q.d. (£85 kg); 10 q.d. (>85 kg)	20 q.d.	Same as carvedilol (plus vivid dreams)
Carvedilol	3.125 b.i.d.	25 b.i.d. (£85 kg); 50 b.i.d. (>85 kg); (minimally effective dose 6.25 b.i.d.)	25 b.i.d. (£85 kg); 50 b.i.d. (>85 kg)	Bradycardia, hypotension, atrioventricular block, worsening congestive heart failure, bronchospasm, fatigue
Metoprolol	12–25 b.i.d.	100 b.i.d.	100 b.i.d.	Same as carvedilol (hypotension may be less)
Metoprolol-CR/XL	12–25 q.d.	200 q.d.	200 q.d.	Same as carvedilol (hypotension may be less)
Angiotensin II receptor blocker				
Losartan	25 q.d.	50 q.d.	100 q.d.	Diarrhea, dyspepsia, orthostatic dizziness
Candesartan	16 q.d.	32 q.d.	32 q.d.	—
Valsartan	80 q.d.	160 q.d.	320 q.d.	—
Digoxin	0.25 q.d.	As needed	As needed	Cardiotoxicity, confusion, nausea, anorexia, visual disturbances
Hydralazine	10–25 t.i.d.	75 t.i.d.	100 t.i.d.	Headache, nausea, dizziness, tachycardia, lupus-like syndrome
Isosorbide dinitrate[b] (Isordil)	10 t.i.d.	40 t.i.d.	80 t.i.d.	Headache, hypotension, flushing
Isosorbide mononitrate				
Imdur	30 q.d.	As needed	240 q.d.	Same as isosorbide dinitrate
ISMO	20 b.i.d.	As needed	40 q.d.	Same as isosorbide dinitrate

[a]Angiotensin-converting enzyme inhibitors available, with dosages known to reduce mortality.
[b]Mortality benefit noted when given in combination with isosorbide dinitrate.
Modified from Konstam M, Dracup K, Baker D, et al. *Heart failure: evaluation and care of patient with left-ventricular systolic dysfunction. Clinical practice guideline.* AHCPR publication no. 94-0612. Rockville, MD: Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, June 1994.



A 30-year-old male patient with U waves secondary to hypokalemia.

An 83-year-old female patient with hyperkalemia.

A 41-year-old with hyperkalemia.

A 9-year-old male patient with hyperkalemia and QRS widening.

It must be remembered that by reducing blood volume, diuretics lower cardiac filling pressures, with subsequent reduction in wall stress, pulmonary edema, and peripheral congestion. All these effects are advantageous, but reduction in plasma volume might adversely activate the renin-angiotensin-aldosterone and sympathetic nervous systems, paradoxically promoting further sodium and water retention while increasing impedance to left ventricular ejection. This effect could eventually contribute to the progression of heart failure remodeling. For this reason, diuretic therapy alone is not justified during heart failure treatment. The one exception might be the use of diuretics for treatment of hypertension (165,166). Long-term studies assessing major disease-specific outcomes in hypertensive patients receiving diuretics have demonstrated reduction in the incidence of stroke, congestive heart failure, coronary disease, and total mortality. This should be contrasted to outcomes noted with calcium channel blockers, which are meager with respect to similar benefits in hypertensives. Beta-blocker therapy in hypertensive patients is also effective in preventing stroke and congestive heart failure. When used primarily as antihypertensive agents or as adjuncts to control blood pressure, diuretics likely provide substantial benefits (166). Still, compulsive attention to the serum electrolyte profile is necessary.

The best method for initiating diuretic prescription is controversial. Some patients may respond to transient pulses of diuretics with resolution of the congestive state; with a low-salt diet, these patients do not require long-term diuretic therapy. This seems a wise tactic to take but is underused. Other patients might need intermittent, but regular, oral pulses of diuretics, whereas some require continuous administration of diuretics in large doses or combinations. Stopping diuretics entirely or creating an interval drug holiday should be considered in patients who have been on diuretics for chronic congestive heart failure but resolved their fluid retention state (164).

Direct-Acting Vasodilators

Elegant studies of pressure volume curves generated from echocardiographic study of normal and failing hearts have given additional insight into how the ventricle might best be manipulated to allow an effective transfer of the mechanical energy of ventricular contraction to cardiac output (37). Reducing the operating end systolic pressure toward a more energetically optimal level without changing contractility might give the energy-starved failing heart a better chance of healing. Care must be taken, however, that this energetically optimal position is not exceeded, because this might reflexively activate the sympathetic nervous system and renin-angiotensin-aldosterone axis. That is why concomitant use of beta-blockers, ACE inhibitors, or specific angiotensin II–receptor blockers might be a wise strategy, although it is not yet well characterized.

It is now well accepted that preload and afterload diminution in patients with heart failure reduces short-term morbidity and, with certain agents, long-term mortality (167). Relaxing venous capacitance vessels diminishes preload, whereas peripheral arteriolar dilation drops afterload and impedance to ventricular emptying. Venous capacitance vessels can be dilated by nitrates, such as nitroglycerin, nitroprusside, isosorbide dinitrate, and mononitrate preparations. Arterial resistance vessels are dilated by hydralazine. *e*Table 92.5.3 summarizes dosages and major adverse reactions for select agents. The combination of arterial and venous dilation occurs with ACE inhibitors and some alpha-adrenergic blockers (e.g., guanabenz and clonidine). Calcium channel blocking drugs are arteriolar dilators as well, but, as mentioned, concern exists about their use in the heart failure setting. Dilation of the arteriolar bed alone, without concomitant venous dilation, may fail to achieve sustained morbidity and mortality benefit. Likewise, although sudden dyspnea can be alleviated with acute administration of short-acting sublingual nitroglycerin, long-term attenuation of neurohormonal or mechanical responses by the failing ventricle may not be observed. Remember, it was the combination of hydralazine and isosorbide dinitrate in doses that provided balanced vasodilatory effects that were suggested as beneficial in the V-HeFT-I trial (77). Although isolated use of long-acting oral nitrates in congestive heart failure patients is thought to be useful at times, there are significant issues surrounding the development of nitrate tolerance, and no current preparation has regulatory labeling indicating this use (168,169 and 170). The nitrovasodilators, as a group, induce nitric oxide within vascular smooth muscle cells. This results in guanylate cyclase activation, which causes increases in cyclic guanosine monophosphate with subsequent vasodilation. Particularly in the setting of

atherosclerosis, endothelial dysfunction is associated with decreased nitric oxide availability, and nitrate supplies exogenous nitric oxide to the vascular wall and improves the vasodilator state. When nitrates are given, endothelium-dependent stimulation causes relaxation rather than constriction, which is characteristic of endothelial dysfunction. Evidence also suggests that nitrites have antiplatelet effects that might be important in patients with ischemic heart disease with respect to platelet aggregation and thrombosis. Nitrate tolerance develops, however, when blood levels are constantly elevated. Hemodynamic effects, as well as antianginal activity, are lost with chronic exposure to these agents. There is some suggestion that enhancement of vascular superoxide production secondary to exposure to nitrates may be an important mechanism in the development of tolerance (169,170). *In vitro* studies suggest that hydralazine, which has an antioxidant effect, prevents the nitrate-mediated formation of vascular superoxide and thus prevents nitrate tolerance. This observation may provide an explanation for benefits seen in V-HeFT-I with the combination of isosorbide dinitrate and hydralazine (77). By virtue of its capability to become a sulfhydryl donor, captopril is another drug that might combat nitrate tolerance. Alternatively, nitrate tolerance can be reversed after a washout period of 10 to 12 hours with thrice-daily administration patterns of isosorbide dinitrate (rather than every 4-, 6-, or 8-hour dosing schedules). Alternatively, isosorbide mononitrate preparations given once daily (Imdur) or in an asymmetric twice-daily fashion (ISMO) can obviate tolerance. If nitroglycerin patches are used, they should be limited to 8- or 12-hour administration periods, either at night to combat nocturnal dyspnea or during the day to treat exercise intolerance and dyspnea (169,170).

Angiotensin-Converting Enzyme Inhibitors

As might be anticipated from reviewing heart failure clinical trials (*e*Table 92.4.1 and Fig. 92.1 and Fig. 92.2), ACE inhibitors have now assumed the role of first-line drug in patients with heart failure. The reason for this is their multifactorial benefits, including interdiction of the renin-angiotensin-aldosterone system and balanced arterial and venous vasodilation. Significantly, a broad spectrum of heart failure patients have been studied with respect to ACE inhibitor use. Clinical trials that included asymptomatic patients with systolic left ventricular dysfunction (e.g., SOLVD prevention trial) (87) as well as extremely ill NYHA class IV congestive heart failure patients (e.g., CONSENSUS) (83) justify their use in such a wide spectrum. Every effort must be made to get patients with heart failure on a drug of this class at a proper dose. *e*Table 92.5.3 lists selective ACE inhibitors that have been evaluated extensively with mortality endpoint clinical trials so that the proper target dosages can be defined. It is important to remember that many smaller double-blind, placebo-controlled clinical trials have demonstrated the ability of ACE inhibitors to relieve dyspnea, improve exercise tolerance, and decrease the incidence of hospitalization for patients with mild to moderate heart failure. Furthermore, these drugs appear to prevent development of symptomatic congestive heart failure in many patients with asymptomatic left ventricular systolic dysfunction. In patients without symptoms, ACE inhibitors should be considered first-line drug therapy (even as monotherapy), with digoxin, diuretics, and possibly beta-blockers becoming important additive components as congestive symptoms develop. Although the beneficial effects of ACE inhibitors are likely related to “class” actions, regulatory labeling has been based on the types of clinical trials performed. For example, some agents have been suggested as useful in the postinfarct setting, and others have been given labeling approbation for mortality as well as morbidity reduction in heart failure patients. *e*Table 92.5.4 describes a reasonable ACE I dose-titration sequence for hospitalized patients. The prescription of these drugs in dosages similar to those used during clinical trial performance and in similar patient populations appears to be important (144). It has been suggested, for example, that underdosing of captopril is common. This may be fueled by fear of causing unacceptable reduction in blood pressure or worsening renal function. As discussed previously, defining optimal blood pressure in patients with ventricular dysfunction and heart failure is a contentious issue, and no precise target pressure can easily be identified. It appears, however, that the lowest blood pressure a patient can tolerate without significant orthostatic symptoms or renal dysfunction is the best in any specific clinical setting. *e*Table 92.5.4 proposes a schema for initiating ACE inhibitor therapy when patients are hospitalized with substantive congestive states. This schema is based on using the shorter-acting agent captopril acutely and avoiding it during aggressive diuretic administration. Although low doses are used initially, higher doses should be mandated (171). After patients have been exposed to the short-acting drug, switching to a longer-acting preparation such as enalapril or lisinopril seems reasonable so that compliance can be increased by decreasing multiple dosing points. Reasonable target dosages are 150 mg daily for captopril, 20 mg daily for enalapril, and 20 mg for lisinopril. Patients who are at risk for developing orthostatic hypotension after ACE inhibitor exposure include those with hyponatremia, azotemia, volume depletion, and orthostatic dizziness or syncope (172,173). Problems can be avoided with simple dosage adjustment techniques or reduction of aggressive diuretic therapies. It is important to remember ACE inhibitors are likely more important than diuretics in the heart failure patient long term, and therefore, when congestive states are relieved, it is more appropriate to sacrifice diuretic administration so that ACE inhibitors can be begun or maintained rather than continuing high diuretic dosages (or continuing diuretics at all). Still, ACE inhibitors can be challenging to administer. In the SOLVD study analysis of adverse effects of enalapril in 6,797 patients (double-blinded and placebo-controlled) followed over a 40-month average period, 28% of participants randomized to drug compared with 16% in the placebo group reported side effects (172). Enalapril use was associated with a higher rate of orthostatic hypotension (15% vs. 7%), azotemia (4% vs. 2%), cough (5% vs. 2%), fatigue (6% vs. 4%), and hyperkalemia (1.2% vs. 0.4%). All these observations were statistically significant. Angioedema occurred in 0.4% of patients exposed to the ACE inhibitor. Side effects resulted in discontinuation of blinded therapy in 15% of the treatment group compared with 9% in the placebo group. One must put the benefits of ACE inhibitors in perspective, however, and stopping the drug for a mild but troublesome cough might not be in the best long-term interests of the heart failure patient.

***e*TABLE 92.5.4** INITIATING ANGIOTENSIN-CONVERTING ENZYME I THERAPY IN HOSPITALIZED PATIENTS: RAPID TITRATION SCHEME

Captopril incremental increase: 6.25 mg → 12.5 mg → 25.0 mg → 50.0 mg t.i.d.
Hold diuretic 1 h before and 1 h after initial dose
Begin 12.5 mg orally (6.25 mg in labile[a] patient)
After 2 h, increase dose (if tolerated) to 25 mg orally
After 6 h, increase dose (if tolerated) to 50 mg t.i.d.
Target dose is 150 mg/d
Enalapril incremental increase: 2.5 mg → 5.0 mg → 10.0 mg b.i.d.
Hold diuretic 1 h before and 1 h after initial dose
Begin 5 mg orally (2.5 mg in labile patient)
After 6 h, increase dose (if tolerated) to 10 mg orally
After 12 h, increase dose (if tolerated) to 10 mg b.i.d.
Target dose is 20 mg/d
Chronic maintenance angiotensin-converting enzyme I targets[b]
Captopril, 50 mg t.i.d.
Enalapril, 10 mg b.i.d.
Lisinopril, 20 mg q.d.
Ramipril, 20 mg q.d.

[a]Labile patients are those with hyponatremia, azotemia, volume depletion, and orthostatic hypotension.
[b]Other angiotensin-converting enzyme I inhibitors have labeling approbation for heart failure therapy, but those selected are representative of short-, medium-, and long-term agents.

More recently, attention has been directed toward the question of differential effects of drugs based on race. Indeed, African-American patients with heart failure seemingly have a worse prognosis than Caucasians. To address this issue with respect to ACE inhibitors, an analysis of the SOLVD database has been published (174). Using a matched cohort design in which up to four white patients were matched with each black patient, a total of 1,196 white patients were compared with 800 black patients. The average duration of follow-up was approximately 34 months. The black and white patients had similar demographic and clinical characteristics, but the black patients had higher rates of death from any cause (12 vs. 10 per 100 person-years of follow-up) and of hospitalization for heart failure (13 vs. 8 per 100 person-years of follow-up). Despite similar doses of drug in the two groups, enalapril therapy, as compared with placebo, was associated with a 44% reduction (95% confidence interval, 27% to 57%) in the risk of hospitalization for heart failure among the white patients (p <.001), but with no significant reduction among black patients (p = .74). At 1 year, enalapril therapy was associated with significant reductions from baseline and systolic blood pressure and diastolic blood pressure among the white but not among the black patients. No significant change in the risk of death was observed in association with enalapril therapy in either group. The conclusion of this study was that enalapril therapy is associated with a significant reduction in the risk of hospitalization for heart failure among white patients with left ventricular dysfunction, but not among similar black patients. It is important, however, to note that this observation simply underscores the need for additional research on the efficacy of therapies for heart failure in black patients. It does not mean that ACE inhibitors should not be prescribed in this cohort. Furthermore, it must be pointed out that this was a retrospective analysis that was not prespecified. Furthermore, this type of observation has not been recapitulated with at least one beta-blocker, carvedilol, in clinical trials (see Beta-Adrenergic Blocking Agents, later in this chapter).

Angiotensin II Receptor Blockers

An alternative to ACE inhibitors might be a specific angiotensin II receptor antagonist (146,147). Such drugs might induce similar benefits to those observed in heart failure patients on ACE inhibitors, without some of the side effects seen with these agents (172,173,176). On the other hand, these compounds do not affect potentially beneficial cyclooxygenase pathways, which are activated by ACE inhibitors (176). Small clinical trials have demonstrated that the first commercially available angiotensin II receptor blocking agent, losartan, when given to patients with symptomatic heart failure, produced beneficial hemodynamic effects in the short term as well as after 12 weeks of therapy (173). There was a dose-related response, with 50 mg daily of losartan effecting the most significant changes, but higher doses likely not helpful. Hemodynamic effects are similar to ACE inhibitors with respect to reducing preload and afterload and increasing cardiac output. Furthermore, these agents are effective in preventing left ventricular hypertrophy in animals.

The first large-scale clinical trial with mortality endpoint data to give some insight into use of specific angiotensin II receptor blockade in patients with heart failure was the Evaluation of Losartan in the Elderly study (177,178). This multicenter, international clinical trial was a prospective, double-blind, randomized, parallel-group, captopril-controlled study performed in 722 ACE I–naïve patients (1:1 group randomization) age 65 years or older (66% older than 70 years) with mild to moderately symptomatic heart failure (primarily NYHA class II and III) and left ventricular ejection fraction of 40% or less. Mean ejection fraction was approximately 30%, and

patients primarily had heart failure due to coronary heart disease (68%). The primary end point was development of renal dysfunction after drug titration, defined as an increase in serum creatinine by 0.3 mg per dL from baseline. Secondary end points were combined mortality from all causes and heart failure hospitalization and mortality and hospitalizations for heart failure individually. Tertiary end points included drug tolerability and focused on symptomatic hypotension, potassium increase (greater than 0.5 mmol per L), cough, or other side effects prompting drug discontinuation. Drug administration protocol gives some insight into losartan dosing. After a 2-week placebo run-in, patients received either captopril (6.25 mg titrated to 12.5 mg, 25 mg, and then 50 mg three times daily) or losartan (12.5 mg titrated to 25 mg and then 50 mg daily). Dose increases generally occurred at 7-day intervals, as tolerated. Patients were followed for 48 weeks. The incidence of persistent renal dysfunction was the same (10.5%) in losartan and captopril cohorts. Losartan did appear to be better tolerated in this trial, with 27 patients stopping captopril because of dysgeusia, rash, or angioneurotic edema compared with none in the losartan group. It is interesting that the secondary mortality end point (composite of death and heart failure hospital admissions) demonstrated less all-cause mortality in the losartan group. This benefit was observed early and persisted throughout the 48-week observation period. This study prompted the Evaluation of Losartan in the Elderly II trial, which was a larger clinical trial having mortality as the primary end point (179,180). In contrast to Evaluation of Losartan in the Elderly trial, the second trial had no beneficial effect on mortality according to initial data analysis.

Still, the hypothesis that angiotensin II receptor antagonists might be beneficial in heart failure is intriguing because ACE activity may not be completely suppressed by traditional ACE I therapy because angiotensin II can also be formed by non-ACE or tissue chymase-dependent pathways (181,182 and 183). The more complete blockade of angiotensin II activity is theoretically more beneficial, but one reason to think these drugs might not be as effective as ACE I in heart failure is their lack of effect on bradykinin. As alluded to previously, bradykinin actions seem related to nitric oxide, and prostacyclin release, which may mediate vasodilation, is thought to be beneficial in these patients. On the other hand, bradykinin might account for some of the ACE I adverse reactions, such as cough, angioneurotic edema, and dysgeusia (173,175). Losartan could therefore provide more complete blockade of the tissue-active ACE systems without increasing bradykinin, which, in addition to being associated with certain mediators of vasodilation, can also precipitate norepinephrine spill.

Other studies addressing angiotensin II receptor blocking drugs in heart failure include the RESOLVD, Valsartan Heart Failure Trial, and Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity projects. RESOLVD focused on candesartan and was a double-blind (pilot) study (with 768 patients) in which congestive heart failure patients were randomized to candesartan in several doses, candesartan plus enalapril, or enalapril, for a mean of 43 weeks with exercise tolerance, ventricular function, quality of life, neurohormone levels, and tolerability of drug treatment protocol as end points (184). No differences were noted in exercise, functional class, or quality of life measurements, but left ventricular volumes decreased with natriuretic peptide and aldosterone levels significantly lower with the combination of an ACE inhibitor and angiotensin II receptor blocking drug. Perhaps more important was the fact that candesartan was as effective, safe, and tolerable as enalapril in congestive heart failure patients, with seemingly more beneficial effects when the drugs were combined than when used alone.

A second RESOLVD report details the addition of long-acting metoprolol to ACE inhibitors and candesartan (105). In this portion of the RESOLVD pilot program, metoprolol-CR was given in double-blind factorial designed fashion after the initial uptitration of candesartan or enalapril or their combination in 426 patients. The primary reason for this trial was to determine tolerability of extensive neurohormonal blockade with the combination of an ACE inhibitor, angiotensin II receptor blocker, and beta-blocker. No differences in exercise, functional class, or quality of life were noted between any of the groups, but significant improvement of left ventricular systolic function and attenuation of detrimental remodeling with a greater decrease of angiotensin II and renin levels was noted when metoprolol was added. Particularly impressive was the reduction in heart size and improvement in left ventricular systolic dysfunction in the group receiving an ACE inhibitor, candesartan, and the beta-blocker metoprolol.

Exploring the potential for added benefit with an angiotensin II receptor blocking drug was the Valsartan Heart Failure Trial (185). This study was a double-blind, placebo-controlled multicenter clinical trial of valsartan generally added onto an ACE inhibitor (92% of patients concomitantly on ACE inhibitors) with approximately 35% of the population on beta-blockers. All-cause mortality and combined mortality and morbidity were end points in this trial of over 5,000 patients. Results were preliminarily reported at the November 2000 American Heart Association meeting. This was the largest angiotensin II receptor blocking drug trial reported to date, and no mortality reduction was noted. Patients were, however, less likely to be hospitalized for worsening congestive heart failure when taking valsartan. Interestingly, perhaps there was an adverse interaction with patients on both ACE inhibitors and beta-blockers when valsartan was added. This is somewhat at odds with the previously summarized RESOLVD beta-blocker observations. We will have to await further clarification of this issue.

Perhaps the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity program will help resolve some of these issues (186). Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity is actually three independent international parallel placebo-controlled mortality endpoint trials of candesartan in patients with congestive heart failure. The first trial of over 2,300 patients is in patients with left ventricular systolic ejection fraction less than 40% and treated with concomitant ACE inhibitors. The second trial is in patients with a similar degree of left ventricular systolic dysfunction but deemed “ACE intolerant.” Almost 2,000 patients will be entered into this trial. Finally, a third trial of over 2,500 patients will evaluate candesartan in individuals with congestive heart failure and ejection fraction greater than 40%. This program obviously will be testing the angiotensin II receptor blocking agent candesartan across the broad spectrum of chronic congestive heart failure and is the only ongoing trial of these agents evaluating this strategy in ACE-intolerant and “diastolic dysfunction” heart failure patients.

Calcium Channel Antagonists

Calcium channel blockers, as a group, are an example of agents that may create significant problems in patients with heart failure. Although these drugs are very effective in lowering systemic vascular resistance, they generally have negative inotropic effects. Granted, newer drugs in this class seem to have less negative inotropic activity and more potent selective peripheral vasodilatory effects. Still, to date, no sustaining symptomatic or mortality benefit, overall, has been demonstrated for these drugs when used in patients with congestive heart failure. At best, effects seem to be neutral for a few select compounds (amlodipine and felodipine) (85,86). Indeed, in patients who have had acute myocardial infarction complicated by left ventricular systolic dysfunction, calcium channel blockers have proved detrimental more often than not, with a greater chance of adverse effects seen in patients randomized to drugs such as nifedipine and diltiazem. Because patients with heart failure frequently have concomitant ischemic heart disease or hypertension, calcium channel blockers are frequently found as therapies in heart failure patients. Indeed, in the late 1980s, more patients in the SOLVD registry were on calcium channel blockers than on ACE inhibitors (47). Although this has changed somewhat more recently, it has been suggested that significant numbers of patients with heart failure (probably around 20%) are still taking these drugs. This strategy might best be reassessed on an individual patient basis. In the patient with heart failure, for example, control of hypertension with ACE inhibitors, diuretics, beta-blockers, angiotensin II receptor blockers, or other agents summarized in Table 92.6 may be preferred strategies. Treatment of angina pectoris with nitrates can be considered a substitute for treatment with calcium channel blockers. It should also be emphasized that, although ACE inhibitors are not acutely antiischemic in their actions, clinical trials have consistently demonstrated long-term diminution in major atherosclerotic heart disease end points (187,188). Patients with heart failure and angina pectoris should have aggressive attempts at percutaneous or surgical revascularization or medication therapies refocused on long-acting nitrates and beta-blockers.

TABLE 92.6 COMMON PITFALLS IN THE TREATMENT OF HEART FAILURE: FACTORS PREDISPOSING TO HEART FAILURE DECOMPENSATION

To date, amlodipine (85) and felodipine (86) have been the only two agents studied with reasonably designed clinical trials to suggest no detriment with the drugs. Because of the importance of this issue, details of these two studies should be reviewed. The PRAISE (74) trial randomly assigned 1,153 patients with severe chronic congestive heart failure (NYHA class III or IV) and ejection fraction less than 30% to either placebo or amlodipine for 6 to 33 months, while their usual therapy (digoxin, diuretics, and ACE inhibitors) was continued. Prerandomization stratification occurred based on a diagnosis of ischemic versus nonischemic heart disease etiology. Primary end point was all-cause mortality and hospitalization for major cardiovascular events. The primary end point was reached in 42% of placebo and 39% of the amlodipine group, an insignificant 9% reduction in the combined mortality and morbidity events (p = .07). In coronary artery disease patients, there was no difference between the amlodipine and placebo groups in the occurrence of a prior end point. On the other hand, among patients with nonischemic heart failure, amlodipine reduced the combined risk of fatal and nonfatal events by 31% (p = .04) and the risk of death by 46% (p <.001). Amlodipine, therefore, did not increase cardiovascular morbidity or mortality in patients with symptomatic and relatively severe heart failure and may actually decrease mortality in patients with nonischemic dilated cardiomyopathy. PRAISE II is critically evaluating this specific issue. V-HeFT-III (75) studied 451 male patients with NYHA class II or III symptoms, with chest radiographic cardiothoracic ratio greater than 0.66, echocardiographic left ventricular internal diastolic diameter greater than 2.7 cm per m^2, and ejection fraction less

than 45%. Background therapy was enalapril. Patients were randomized in factorial fashion to digoxin or placebo and then to felodipine or placebo. The cohort mean age was 63 years, approximately 53% had coronary heart disease accounting for their heart failure, and the mean ejection fraction was 30%. At the end of the 18-month follow-up period, total mortality was 31 deaths in the felodipine and 29 in the placebo groups (*p* = NS). Cardiovascular mortality also was not significantly different. Subgroup (coronary artery disease vs. nonischemic, NYHA class II or III, ejection fraction greater or less than 30%, norepinephrine levels, exercise time, or digoxin use) mortality risk ratios did not suggest that any particular set was benefited or harmed by felodipine. At the 27-week follow-up point, ejection fraction was significantly increased by felodipine compared with placebo, as was exercise time. The group on felodipine noted a decrease in atrial natriuretic peptide levels compared with placebo. In the early dosing phase, felodipine seemed associated with worsening heart failure. Conclusions from this trial are that felodipine, in ACE inhibitor–treated patients with mild to moderate heart failure, improves left ventricular function and certain humoral factors but does not produce any apparent effect on long-term morbidity or mortality. Although the small number of deaths in V-HeFT-III does not exclude an increase or decrease of mortality from felodipine, the overall experience suggests that this drug may be safe when used for other indications in mild to moderate heart failure. Still, this conclusion has to be balanced by the fact that these other conditions are usually hypertension or angina pectoris. There are many alternative strategies. It is interesting that the observations in V-HeFT-III were somewhat discordant with those of PRAISE in that no mortality benefit was seen in nonischemic veteran patients. Possible explanations for this difference include the fact that PRAISE enrolled NYHA class III and IV patients, whereas V-HeFT-III enrolled class II and III subjects and turned out to be underpowered with respect to mortality end points (too few events occurred). Other explanations might be that the nonischemic stratification scheme was flawed (no stress test was done in PRAISE to exclude ischemia, and neither study required coronary angiography). Alternatively, one could postulate that the PRAISE subgroup finding was a chance occurrence or that amlodipine really is quite different from felodipine.

Beta-Adrenergic Blocking Agents

As suggested earlier, the portfolio supporting beta-blocker use in patients with heart failure is rapidly expanding, with information suggesting that, although these agents may be difficult to use at times, significant benefit can accrue (189,190,191 and 192). The clinical trials Cardiac Insufficiency Bisoprolol Study, BEST, Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise/Multicenter Oral Carvedilol Heart Failure Assessment, Multicenter Oral Carvedilol Heart Failure Assessment, Metoprolol CR/XL Randomized Intervention Trial in Heart Failure, and COPERNICUS (*e*Table 92.4.1) have evaluated a variety of heart failure subsets. These trials should be compared with older, classic clinical trials evaluating the routine use of beta-blocker therapy after myocardial infarction. The BHAT (192) and Timolol Post-Infarction Trials (193) both demonstrated positive impact with beta-blockers after myocardial infarction with respect to survival and major ischemic events. Indeed, the group seemingly having the greatest beneficial impact with propranolol (Inderal) in BHAT was the one with heart failure during hospitalization. It has been difficult to sort through some of the issues regarding beta-blocker benefits, possibly because of the major differences between these drugs despite their all being classed in the same group. Beta-blockers generally can be categorized with regard to their ability block the different beta- and alpha-adrenergic receptors. Some are relatively $beta_1$ selective, and others are not. Additionally, some agents have intrinsic sympathomimetic activity. Finally, some agents, such as the drug carvedilol, combine $beta_1$- and $beta_2$-adrenergic receptor blocking activity, with alpha-blocking capabilities as well. In trials involving $beta_1$-selective beta-blockers in patients with left ventricular dysfunction, with or without acute myocardial infarction, no effect on sudden cardiac death was generally found. This may be due to interdiction of only one beta-receptor, with the second beta-receptor still permitting active signal transmission to the myocyte, which could perpetuate risk of arrhythmic death. It is interesting that trials using nonselective agents after myocardial infarction (propanolol and timolol) noted diminution in sudden cardiac death rates.

In a series of four randomized, placebo-controlled multicenter trials (100) of the nonselective beta-blocker carvedilol (remembering that alpha-blocking activity is also present with this drug), pooled analysis showed a 33% risk reduction for death. Analysis of each individual carvedilol trial demonstrated an interesting disparity: Although the studies, for the most part, had primary end points of exercise tolerance, they were generally not affected by carvedilol. Other data from these trials indicated that congestive heart failure symptomatology and NYHA functional classification and general patient well-being were significantly improved by carvedilol. These individual trial results, as well as the combined analysis, suggested a significant reduction in mortality.

As alluded to in the discussion of clinical trials, bisoprolol and long-acting metoprolol were demonstrated to be quite effective in patients with mild to moderate congestive heart failure secondary to broad-ranging difficulties and having depressed systolic left ventricular dysfunction (101,102,103 and 104). In contradistinction to the positive mortality trial endpoint results noted in the carvedilol trials, Cardiac Insufficiency Bisoprolol Study II and Metoprolol CR/XL Randomized Intervention Trial in Heart Failure, BEST, studying bucindolol, did not suggest mortality or morbidity benefit. Bucindolol is a nonselective beta-blocker with mild vasodilating properties. BEST focused, perhaps, a bit more on women, African Americans, and advanced heart failure patients. A total of 2,708 patients with NYHA class III (92%) or IV (8%) and left ventricular systolic dysfunction were evaluated. The trial was stopped after the seventh interim analysis because of no significant difference in mortality between the two groups. No harm was noted, and the point estimate for mortality was lower in the bucindolol group, but in a demographically diverse group of patients with NYHA class III or IV heart failure, bucindolol appeared not to be associated with significant survival benefit (109). This observation should not, however, taint the case of beta-blocker therapy for heart failure. As has been pointed out, the confidence intervals for this study overlap those of other trials, and the point estimate for mortality reduction did favor benefit with bucindolol. Furthermore, a significant improvement in survival with bucindolol was actually observed in nonblack patients who made up the majority of individuals enrolled in this and previous beta-blocker trials. Additionally, many of the secondary end points were favorably affected by bucindolol (107).

Nonetheless, this observation of a potential difference between black and nonblack patients in BEST should be counterposed to a report suggesting that benefits of carvedilol prescription in the United States carvedilol heart failure trials program were of similar magnitude in black and nonblack patients (194). As with the question raised previously regarding ACE inhibitor responsiveness based on race in heart failure cohorts, one should temper opinions about this issue until more definitive evidence comes available. These observations in BEST and with carvedilol may simply be the play of chance. Still, there may well be racial differences in the response to drugs that are likely to be characterized (195).

The COPERNICUS trial studied a quite ill population with heart failure (106). Carvedilol was evaluated in a double-blinded mortality endpoint trial of 2,289 patients with, generally, NYHA class IV heart failure manifest by symptoms at rest or on minimal exertion. Importantly, the patients were clinically euvolemic but had an ejection fraction of less than 25%. Patients were observed for almost 1 year during which standard therapies were continued. There was a 35% decrease in the risk of death with carvedilol and a 24% decrease in the combined risk of death or hospitalization. The favorable effects on end points were seen consistently in all subgroups examined and, particularly, in those most ill as reflected by multiple prior congestive heart failure hospitalizations. This study suggests that the previously reported benefits of carvedilol with respect to morbidity and mortality in patients with mild to moderate congestive heart failure were also found in patients with severe heart failure who met trial entry criteria (primarily, euvolemic with severe heart failure). As with other patients started on beta-blockers, cautious and slow uptitration of drug dosage seems the most prudent approach (34).

Perhaps third-generation beta-blocking compounds may be more advantageous in heart failure than selective beta-blocking drugs. It is interesting to note that carvedilol has also been said to have potent antioxidant properties that might provide additional, favorable pharmacologic effects in the heart failure patient. It appears that the ideal beta-blocker for treating heart failure is a compound that is nonselective with regard to beta-receptor blockage, induces vasodilation (generally by alpha-receptor blockade), does not downregulate $beta_1$-receptors, lowers systemic adrenergic activity, decreases cardiac sympathetic tone, causes minimal myocardial depression via negative inotropic effects, and reduces mortality and morbidity associated with the heart failure syndrome.

A few trials comparing metoprolol with carvedilol in heart failure patients are available. Based on these observations, some have suggested that carvedilol with its significant vasodilating and antioxidant properties might be a superior agent (195a). This is, however, a contentious issue, with patients seemingly best served by receiving one of the agents shown undisputedly in clinical trials to have benefited from beta-blocker prescription (196).

Antiarrhythmic Drugs and Implantable Defibrillating Devices

One of the more difficult issues to address in patients with heart failure is how to treat arrhythmia. The incidence of atrial and ventricular dysrhythmia in this patient population is high, and the temptation to use antiarrhythmic drugs is great. As indicated, class I antiarrhythmic agents are problematic in patients exhibiting clinical heart failure, particularly in the setting of an acute myocardial infarction. As reviewed, the Cardiac Arrhythmia Suppression Trial and Survival with Oral D-Sotalol trials (*e*Table 92.4.1) indicated that encainide, flecainide, moricizine, and D-sotalol actually increased mortality. These observations are troublesome because the patient at highest risk of sudden cardiac death seems to be the individual who would benefit most from arrhythmia control. However, this is also the patient likely to have proarrhythmic events associated with antiarrhythmic drug prescription. Indeed, there is a fairly clear-cut relationship between ejection fraction and antiarrhythmic drug efficacy, as well as a direct relationship between heart failure severity and adverse proarrhythmic effects with most compounds. The lower the ejection fraction, the less likely potent antiarrhythmic drugs are to control potentially malignant arrhythmias. Beta-blockers and amiodarone may be possible exceptions to this generalization, but clinical trials have produced disparate results. Amiodarone use is, indeed, more controversial (197,198,199,200 and 201). Amiodarone does seem to be a valuable adjunct during therapy for atrial fibrillation. Unfortunately, amiodarone is expensive and sometimes poorly tolerated, with toxicities that include pulmonary fibrosis, thyroid function disorders, and photosensitization syndromes. It is intriguing, however, to note that low-dose amiodarone may be better tolerated and still have apparently beneficial hemodynamic effects (199). Indeed, any beneficial effects amiodarone may have in the heart failure syndrome might be independent of antiarrhythmic drug action.

Because antiarrhythmic drug therapy has been so problematic in the heart failure patient, use of implantable electronic arrhythmic termination devices may be preferable in patients with potentially malignant ventricular arrhythmias and heart failure. Still, however, it should be realized that many patients who have these devices continue to be on antiarrhythmic therapies. A relatively recently completed clinical trial has given some insight into this issue. The Multicenter Automatic Defibrillator

Implantation Trial (202) was a randomized trial of defibrillating devices versus conventional therapy in post–myocardial infarction patients with ejection fraction less than 35%, nonsustained ventricular tachycardia, and then nonsuppressible ventricular tachycardia at the time of electrophysiologic study. This trial suggested that device implantation led to better survival in this high-risk atherosclerotic cardiovascular disease population with ventricular dysfunction and heart failure. Beta-blockers and amiodarone use did not appear to have a significant effect on the risk reduction ratio in patients assigned to the device group.

Several additional clinical trials have prospectively evaluated the value of antiarrhythmic drugs or defibrillating devices in a setting of ischemic heart failure (coronary heart disease with an ejection fraction of less than 40%) and ventricular tachycardia. Three secondary prevention trials have suggested that an implantable cardioverter defibrillator was superior to antiarrhythmic drugs (generally amiodarone) in reducing mortality. Some have argued that the major benefit of implantable defibrillating devices occurred in those with lower ejection fractions. The Antiarrhythmics vs. Implantable Defibrillators Trial (203), the Canadian Implantable Defibrillator Study (204), and Cardiac Arrest Study—Hamburg trial (205) were secondary prevention trials and should be compared with the Multicenter Automatic Defibrillator Implantation Trial discussed previously and an additional primary prevention trial, Multicenter Unsustained Tachycardia Trial (206).

These observations provide an alternative strategy for treatment of selective patients with heart failure and life-threatening arrhythmias. It must be emphasized that often the best treatment of ventricular arrhythmias in the heart failure milieu is careful attention to relieving the congestive state and optimizing ventricular performance with vasodilators, diuretics, and ACE inhibitors. Correction of fluid balance and electrolyte disorders may be quite helpful. Addressing atrial fibrillation in heart failure is also sometimes critical to improving patients' symptoms. Obviously, care must be taken in these patients to ensure that risk of thromboembolism is as low as possible with anticoagulants. Because of the known adverse outcome of heart failure patients treated with Vaughn Williams class I antiarrhythmic drugs, consideration of the relative risk of using quinidine, procainide, and other similar agents is challenging.

Indeed, it should be emphasized that the American College of Cardiology/American Heart Association guidelines regarding heart failure therapeutics caution against aggressive pharmacologic or mechanical treatment of asymptomatic ventricular arrhythmias (53). To consider either pharmacologic strategies or implantation of arrhythmia-termination devices, patients should have significantly symptomatic ventricular tachycardia (not simply palpitations) or an episode of syncope or sudden cardiac death syndrome.

Ventricular Resynchronization

Because patients with heart failure, systolic left ventricular dysfunction, and wide QRS complexes have dyssynergic contractility, using multisite atrial right and left ventricular pacing strategies has been proposed. So-called biventricular cardiac resynchronization pacing for heart failure is being actively studied, with some trials focusing solely on resynchronization pacing for severe congestive heart failure [Multicenter InSync Randomization Clinical Evaluation (North America); *e*Table 92.4.1], whereas others include defibrillator insertion or antiarrhythmic therapies (Sudden Cardiac Death—Heart Failure Trial, Multicenter InSync Randomization Clinical Evaluation Implantable Cardioverter Defibrillator; *e*Table 92.4.1). Some trials are secondary prevention studies (secondary prevention with heart failure treatment) or primary sudden cardiac death prevention (primary sudden cardiac death prevention with heart failure therapy). Completion of these studies will clarify best strategies regarding defibrillator implantation or coupling defibrillator implantation to resynchronization pacing therapeutics. More recently published data do, however, suggest that patient quality of life and exercise capacity are improved with resynchronization mode pacing. The Multisite Stimulation Cardiomyopathy Trial was the first such study to be reported (207). Particularly interesting is the fact that patients appear to have reduction in mitral regurgitation when undergoing biventricular pacing.

Anticoagulants

Routine anticoagulation in patients with heart failure may not be necessary (75). Patients with substantive congestive heart failure frequently have significant hepatic congestion, and, because of this, anticoagulation can be difficult to achieve safely. Furthermore, with the large number of drugs taken by patients with heart failure (Fig. 92.1 and Fig. 92.2), an important tenet is to continue only those medications with demonstrated effectiveness. This practice helps ensure compliance with drug treatment regimens. Routine anticoagulation in heart failure patients has never been convincingly demonstrated to be beneficial in well-designed clinical trials despite the fact that heart failure patients have relative hypercoagulable states (208). Some studies have suggested a lower incidence of pulmonary and peripheral emboli in patients on warfarin (209), but, on the whole, the data are not overwhelmingly persuasive. It may be prudent to anticoagulate heart failure patients with a history of systemic or pulmonary embolism or when left or right ventricular thrombi are noted on echocardiography. Certainly, atrial fibrillation is a clear-cut indication for careful anticoagulation. Candidates for anticoagulation should be monitored carefully, with a goal of achieving an international normalization ratio for prothrombin times of 2 to 4.

Video 92.6 This 45-degree transesophageal echo view demonstrates the pulmonary artery bifurcation in the center of the screen and the aorta in cross section to the left. This can be useful to see a large saddle pulmonary embolus at the bifurcation. However, smaller, more distal emboli would be missed. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Atheroemboli. Digital necrosis resulting from severe atheroemboli.

Embolus. Dislodged thrombus that embolized to the toes and caused gangrene (*arrows*).

Video 92.7 Subcostal view of a patient with severe left ventricular dysfunction and multiple mobile thrombi within the left ventricular cavity. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

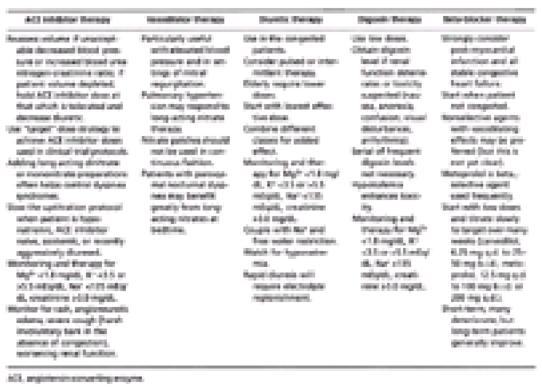
Video 92.8 A 54-year-old male patient with filling defect of the left ventricular apex consistent with left ventricular apical thrombus. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

PITFALLS IN TREATING HEART FAILURE

Table 92.6 lists many of the common pitfalls that trap clinicians when evaluating and treating heart failure patients. Inadequate recognition of the syndrome, or symptoms that are related not to cardiac dysfunction but to other conditions, makes any therapeutic adventure a challenge. Starting late in a patient's disease course makes failure to beneficially affect long-term morbidity and mortality more likely. A focus on preventive therapeutics is necessary. Ignoring the patient's underlying disease state and focusing only on symptomatic elements of heart failure sets the stage for recurring difficulties. Granted, some disease processes, such as advanced ischemic heart disease, are difficult to ameliorate. However, it is a mistake to not consider therapies to reverse myocardial ischemia. Obviously, unrecognized hyperthyroidism, hypothyroidism, poorly controlled diabetes mellitus, and inadequate control of hypertension contribute to making the heart failure state worse. Atrial arrhythmias can be quite problematic, and an attempt should be made, if at all possible, to keep patients in normal sinus rhythm. Chronotropic incompetence or certain arrhythmias might respond to pacemaker therapy. Inadequate salt and water restriction sets the stage for hyponatremia, hypokalemia, and dropsical states despite aggressive diuretic use. Excessive alcohol consumption, particularly in patients with dilated cardiomyopathy, is likely harmful and can contribute to worsening heart failure states. Concomitant use of potentially harmful medications (such as Vaughn Williams class I antiarrhythmic drugs and nonsteroidal antiinflammatory agents) might be part of a therapeutic protocol and should be stopped, if possible. Excessive intravascular volume depletion with diuretics can be counterproductive by producing orthostatic symptoms and further activating adverse neurohumoral factors important in the pathophysiology of heart failure. On the opposite side of this spectrum is ineffective diuretic prescription, which does not mobilize fluid adequately: diuretic doses that are too low, combinations that are not rational (e.g., combining two loop diuretics, such as furosemide and torsemide), or failure to switch from oral to parenteral diuretic administration when necessary. Use of inadequate ACE inhibitor doses or failure to start ACE inhibitor therapy is a major difficulty. Every attempt should be made to get patients on target ACE inhibitor doses, and, rather than sacrificing the ACE inhibitor in an aggressively diuresed patient, the diuretic dose should be decreased. Likewise, use of suboptimal doses of vasodilators because of "relative hypotension" can produce a clinical scenario in which high afterload negatively affects cardiac systolic performance. Sometimes we see the reflex prescription of parenteral salt solutions for orthostatic hypotension or hyponatremia. A cycle of aggressive diuretic administration, low blood pressure, parenteral fluid administration, then congestion often develops in hospitalized patients, and this is counterproductive to appropriate long-term therapy. Only patients with shock and clear-cut intravascular volume depletion should have volume-expanding fluids administered. It is best to allow hyponatremia to correct on its own, with salt and water restriction and, possibly, concomitant parenteral loop diuretic administration. Orthostatic hypotension generally responds to bed rest with a reduction in diuretics or, possibly, vasodilators. When the situation becomes confusing and volume status is difficult to clinically assess, failure to use hemodynamic monitoring simply perpetuates the inability to resolve the challenging situation. Ponderosity with cardiovascular deconditioning and poorly compliant patients are difficult situations, but sometimes aggressive counseling and cardiac rehabilitation programs help to ameliorate these challenges. Because of the cytokine liberation that infections produce, not recognizing or treating intercurrent infections in patients with heart failure allows the syndrome to worsen. Furthermore, some difficulties, such as hypoventilation sleep apnea syndromes, when treated with theophylline preparations or nocturnal positive pressure breathing devices, dramatically improve the heart failure syndrome. This is particularly the case in individuals with pulmonary hypertension and right-sided heart failure.

CONSIDERATIONS DURING IMPLEMENTATION OF HEART FAILURE TREATMENT GUIDELINES

Table 92.7 summarizes important issues to consider when initiating heart failure therapy. Assuming that the proper diagnosis has been made, etiology identified, and precipitating causes of clinical decompensation eliminated, clinicians can strive to create effective therapeutic programs. With regard to institution of ACE inhibitor therapy, one must assess and intermittently reassess volume status if unacceptable hypotension or azotemia is present. Decreasing ACE inhibitor dose or adjusting the use of diuretic therapies often allows uptitration of the ACE inhibitor so that optimal doses can be taken. One should use a target dose strategy. These ACE inhibitor doses were chosen for evaluation in the many clinical trials carried out in heart failure populations. When patients are hyponatremic, ACE inhibitor–naïve, azotemic, or have recently been diuresed aggressively, slow upward titration of drug after starting with low doses is reasonable. Serum magnesium levels should be kept above 1.8 mg per dL, potassium levels between 3.5 and 5.5 mEq per dL, sodium greater than 135 mEq per L, and creatinine greater than 3.0 mg per dL if at all possible. Administering magnesium often helps to control hypokalemia. One should monitor patients for development of rash, angioneurotic edema, worsening renal function, and severe cough, which can be blamed on the ACE inhibitor use. This troublesome cough is frequently described as a harsh involuntary bark in the absence of congestion. One must be cautious about the inappropriate discontinuation of the ACE inhibitor, however, because many patients cough due to pulmonary hypertension, pulmonary congestion, or chronic obstructive pulmonary disease that accompanies the heart failure syndrome. It may be inappropriate to discontinue the ACE inhibitor for the latter reasons. Rather, attention to ameliorating these difficulties seems more appropriate. Often, when patients are told of the importance of ACE inhibitor effects, they are willing to continue taking these drugs. Some have proposed substituting angiotensin II receptor blocking drugs, such as losartan, for ACE inhibitor–intolerant patients.



ACE inhibitor therapy	Vasodilator therapy	Diuretic therapy	Digoxin therapy	Beta-blocker therapy
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

ACE, angiotensin-converting enzyme.

TABLE 92.7 ISSUES TO CONSIDER WHEN INITIATING HEART FAILURE THERAPY

When initiating diuretic therapy as part of the treatment algorithm, make certain that the focus is on either congestion or hypertension. Consider the use of pulsed or intermittent diuretic therapy, use lower doses in elderly patients, and, generally, start with the lowest effective dose of the class chosen. For more intense diuresis, consider combinations of different classes of diuretics. Strive for substantive sodium and free water restriction, and monitor serum solutes to keep the magnesium, potassium, and sodium greater than 135 mEq and creatinine levels reasonable. Remember that thiazide and thiazide-type diuretics and the combination of thiazide diuretics with a loop diuretic can precipitate hyponatremia easily. This is generally the case when free water and sodium consumption is excessive. Again, sodium and water restriction is important to prevent this difficulty. Also important is the fact that a rapid diuresis generally requires electrolyte replenishment.

When digoxin is prescribed for heart failure, it should be used in lower doses than previously suggested. Frequent digoxin levels are not necessary. Serum concentration should be determined if the heart failure syndrome worsens, if absorption problems or patient noncompliance are suspected, if renal function deteriorates, or if toxicity is possible. As with ACE inhibitor and diuretic therapy, it is important to monitor patients intermittently for serum magnesium, potassium, sodium, and creatinine levels.

The use of non–ACE inhibitor vasodilator therapy in heart failure patients can be particularly useful when the systemic blood pressure is elevated (sometimes despite ACE inhibitors) and in the setting of mitral regurgitation. Of course, the combination of hydralazine and isosorbide dinitrate is more frequently used because this combination was the first to suggest that mortality could be attenuated in heart failure populations with vasoactive compounds. When used as mortality-reducing therapies, the drugs should be combined. Pulmonary hypertension often responds nicely to long-acting nitrate therapy. One should be careful to administer these drugs in a fashion that does not produce continuous serum levels of nitrate such that tachyphylaxis might occur. Often, troublesome paroxysmal nocturnal dyspnea or orthopnea improves greatly when chronic long-acting nitrates are administered at bedtime.

Major issues to consider when initiating beta-blocker therapy include considering them in every patient who has had an acute myocardial infarction, particularly in combination with an ACE inhibitor when left ventricular systolic dysfunction is present. Beta-blocker therapy should be begun when patients are stable and not overtly congested. Some suggest that nonselective agents with vasodilating effects (e.g., carvedilol) are preferred. Still, metoprolol is one $beta_1$-selective agent used frequently in heart failure settings, including post–myocardial infarction left ventricular systolic dysfunction. Therapy should be begun with low drug doses and a titration time period of many weeks.

STRATEGIES FOR PERSISTENT CONGESTION

*e*Table 92.7.1 addresses several strategies to consider when there is apparent failure of chronic oral outpatient treatments. One should review the pitfalls listed in Table 92.6 in an attempt to identify ancillary or extraneous issues that might account for this decompensation and then move toward the strategies outlined. Of course, many patients simply have progression of their disease.

***e*TABLE 92.7.1** STRATEGIES TO CONSIDER WHEN CONGESTION PERSISTS DESPITE OPTIMIZED DIGOXIN, DIURETIC, AND ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR VASODILATOR THERAPY

Placement of pulmonary artery catheter capable of measuring capillary occlusive pressure (cardiac output determination and oximetric mixed venous saturation measurement capabilities also helpful)
Hemodynamically guided
Parenteral vasodilator therapy (nitroglycerine, nitroprusside)
Parenteral inotrope therapy (dobutamine, milrinone)
Continuous parenteral loop diuretic infusion
Infusion of “dopaminergic” or “renal” doses of dopamine (<5 µg/kg/min)
Hemofiltration or ultrafiltration
Peritoneal dialysis

Placing pulmonary artery catheters and objectively measuring hemodynamics is at the root of clarifying confusing or challenging situations. With objective flow and pressure measurements, as well as the frequent determination of mixed venous oxygen saturation, tailoring therapeutics to each patient’s clinical situation becomes possible. Parenteral vasodilator therapy (generally nitroglycerin and nitroprusside) alone or in combination with inotrope infusion (usually dobutamine or milrinone) can be dramatically effective. Continuous diuretic infusions, generally with a loop diuretic, such as furosemide, are an alternative strategy to consider in the patient with refractory edema. Although controversial, infusion of dopaminergic or so-called renal doses of dopamine (less than 5 µg per kg per minute) has been said to be helpful in patients refractory to diuretics and in those with worsening renal function. When substantive dropsy persists despite all of these recommendations, hemofiltration ultrafiltration, or, possibly, peritoneal dialysis frequently removes substantial quantities of volume and improves the patient’s symptoms rather dramatically.

TREATMENT OF ADVANCED OR REFRACTORY HEART FAILURE

*e*Table 92.7.1 lists options to consider for the patient with advanced heart failure. In patients who have progressive and steadily worsening heart failure syndromes, therapeutic tracks become narrowed, but many still exist. When all attempts fail to create an adequate pharmacotherapeutic program that is successful in keeping patients symptom free over the long term, parenteral drug infusion protocols (which generally use dobutamine, dopamine, or milrinone or sometimes combinations of these drugs) can dramatically reduce symptoms. There is a suggestion, however, that these infusion therapies actually increase mortality. One must weigh carefully the risks and benefits of this approach. It may be an entirely acceptable trade-off in the truly end-stage patient suffering greatly from refractory congestive states. Furthermore, the necessity of indwelling central venous catheter line access creates many challenges with respect to provision of skilled care givers and provision of support for administering the drugs. Obviously, infections and catheter malfunction are major difficulties. Whether chronic infusion of these drugs is necessary, or if they can be given in pulsed parenteral fashion once weekly or monthly over shorter periods (6 to 24 hours), is not known. Also unknown is the best strategy to attempt long-term drug weaning. One practice is to infuse these drugs continuously for a 4- to 6-week period and then attempt to wean as an outpatient over several days or weeks.

One should always consider higher-risk standard operative or percutaneous coronary interventional procedures in the patient with advanced heart failure. Although they are not always options, some patients with substantive ischemia or repairable valvular heart lesions have responded rather dramatically. Coronary artery bypass graft surgery, mitral and aortic valve repair or replacement, left ventricular aneurysmectomy, and endoaneurysmorrhaphy can all be effective options. Percutaneous transluminal coronary angioplasty also likely plays a role when objective evidence of ischemic myocardium related to target coronary lesions is apparent. The main challenge is to identify patients with viable and salvageable myocardium, who are likely to benefit from procedures of this sort. Individuals with extensive scarring of their ventricles may not be the best candidates. Several alternative operative approaches are currently being evaluated. These include dynamic cardiomyoplasty, ventricular remodeling surgery, ventricular assist devices, and total artificial heart implantation.

VIDEO

Video 92.9 Batista procedure. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 92.10 DOR procedure. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Dynamic cardiomyoplasty involves mobilization of the latissimus dorsi muscle into the chest, encircling the heart, and inserting pacing and myostimulating devices to train the skeletal muscle to become a fatigue-resistant contractile force. Anecdotal experience and some aspects of clinical trial data suggest that patients with moderately severe heart failure may benefit from this procedure. Innovative strategies, which include using the latissimus dorsi to wrap extra cardiac pumps or the aorta to provide counterpulsation, are also intriguing, but not yet well studied. Ventricular reduction or remodeling surgery generally accompanies repair of mitral and tricuspid valve regurgitation and may be an option for certain individuals with ischemic cardiomyopathy. Ventricular assist devices have proved to be lifesaving in acute cardiogenic shock states when they are inserted as an attempted “bridge to recovery” or “bridge to cardiac transplantation.” These devices, as well as cardiac transplantation, are addressed in detail in other chapters.

SUMMARY OF APPROACH TO HEART FAILURE THERAPEUTICS

Table 92.8 summarizes a rational approach to heart failure therapeutics. Tailored therapeutic protocols are based on the progression of patients from insidious to symptomatic to advanced or refractory heart failure settings. It relates the philosophy of prevention to treatment strategies. Also important is the coupling of efforts to address underlying diseases with medication prescription and lifestyle issues, which include increased aerobic activity, optimization of weight, dietary restriction of sodium and fluid, and appropriate vitamin and electrolyte supplementation.

TABLE 92.8 SUMMARY OF APPROACH TO HEART FAILURE THERAPEUTICS

Making an appropriate diagnosis is paramount, as is staging the heart failure syndrome severity. Stopping potentially detrimental drugs, or those of unproved benefit, is as important as beginning appropriate therapeutic regimens designed to prevent functional deterioration, reduce mortality, or control symptoms when symptomatic heart failure (particularly congestive heart failure) is present. Underlying these important principles is the concept that rational polypharmacy is mandatory because these patients are on multiple drugs and combinations of drugs. The fewest drugs possible should be prescribed and dispensed in such a way that the fewest side effects appear and compliance can be high. Finally, the period is over in which chronic bed rest is an important component of heart failure therapy. It is likely that the medications used today achieve the same results of yesteryear’s bed rest prescriptions. We now know it is quite important that patients with all except the severest end stage of heart failure attempt to exercise aerobically. Patients with heart failure should be referred to supervised cardiac rehabilitation programs, if at all possible, to become schooled in aerobic training exercises. This is an adjunctive opportunity for more general patient education as well.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Obviously, individuals frequently managing patients with heart failure have had different experiences and interpret anecdotal or clinical trial data in many ways. Controversy exists. It should be apparent from the foregoing discussion that heart failure treatment protocols are broad and complex. This is because the syndrome is, in fact, a difficult milieu. Much has been learned about designing heart failure treatment protocols, but perhaps most important is the necessity of beginning early in the difficulty to prevent deterioration to advanced stages. Therefore, tailoring therapeutics to each individual’s particular clinical situation seems most important. ACE inhibitors are now first-line treatment for heart failure. Beta-blockers have emerged as rational options, and an argument is even made that they provide greater opportunity for benefits than ACE inhibitors. Still, it is apparent that despite the fact that ACE inhibitors and beta-blockers are now considered first-line therapy, they are frequently not prescribed, are underdosed, or prematurely discontinued. Whether angiotensin II receptor blocking agents are effective substitutes for ACE inhibitors in intolerant patients or, more generally, better than ACE inhibitors is not yet known, although initial data are encouraging. Combining these two drug classes is an intriguing thought. It seems that beta-blocker benefits are most notable over the long term and that, during the short term, patients frequently feel worse. Many argue that digoxin should be prescribed in all congestive heart failure patients for morbidity reduction, and that triple therapy with digoxin, diuretics, and ACE inhibitors is the best basic heart failure treatment protocol in those with congestive states. Antiarrhythmics should be avoided if at all possible, particularly Vaughn Williams class I antiarrhythmic drugs. Alternative strategies might include arrhythmia ablation techniques, implantation of electronic arrhythmia-terminating devices, and, possibly, amiodarone. Amiodarone is one antiarrhythmic agent that may actually be beneficial in some heart failure patients, and it is possible that the toxicity of this drug can be controlled with prescription of much lower doses. Cardiac resynchronization with multisite pacing is emerging as an attractive strategy.

It is not clear if chronic parenteral inotrope infusion reduces end-stage heart failure morbidity and mortality, although most believe that symptoms are substantively reduced at the cost of higher sudden cardiac death rates. Arguably, chronic parenteral inotropic infusion is preferred to intermittent or periodic pulsed infusions. In general, positive inotropic drugs that do not ameliorate adverse neurohormonal profiles seem detrimental to long-term prognosis in heart failure patients, although they may attenuate morbidity. Diuretics should only be used in congestive states or as an antihypertensive agent. It seems that we pay inadequate attention to electrolyte and solute replenishment in many heart failure patients. Furthermore, aerobic exercise is good for heart failure patients, not detrimental, and should be encouraged.

THE FUTURE

Emerging pharmacotherapeutic strategies will likely influence the direction heart failure treatment paradigms take in the future. Preliminary reports using growth hormone in patients with substantive left ventricular dysfunction are intriguing (210). Administration of this humor might beneficially remodel the heart. On the other hand, growth hormone might induce undesired levels of interstitial matrix deposition that results in diastolic dysfunction and unnatural myocyte hypertrophy. Endothelin has been recognized as a paracrine humor important in increasing vascular bed resistance. Endothelin-blocking agents are being studied with respect to their hemodynamic, humoral, and clinical effectiveness (211,212 and 213). A variety of natriuretic peptides have been identified and found useful in characterizing severity of heart failure as well as having some potential therapeutic benefits (214). B-type natriuretic peptide blood concentration measurement now available as a “point of care” test appears to be a sensitive and specific test to diagnose congestive heart failure in the urgent care setting (215). Indeed, this test may become the “CBC” of heart failure as it has been shown to reliably predict the presence or absence of left ventricular dysfunction on echocardiography. This test may be an excellent screening tool for left ventricular dysfunction and may preclude the need for echocardiography in many patients (216). Furthermore, in patients admitted with decompensated congestive heart failure, changes in B-type natriuretic peptide levels during treatment are strong predictors of mortality and morbidity and have been successfully used to guide treatment of patients admitted for decompensated congestive heart failure (217). B-type natriuretic peptide produced by recombinant DNA techniques is now available for parenteral infusion in severe congestive heart failure (218). With the realization that heart failure has inflammatory elements characterizing the milieu, methods to attenuate cytokine trafficking with antibodies or anticytokine agents may prove beneficial. Intriguing studies are ongoing to clarify this issue (19). Simple, durable, and reliable permanent ventricular assist device pumps will become available and will be used as both alternative treatments versus transplantation or bridges to recovery with subsequent pump removal (145). Myoblast implants (219,220) may serve a similar purpose. Even more futuristic is the likelihood that therapies can be designed to interdict the apoptotic signaling loops at a molecular biodynamic level. This would be the ultimate in reversing adverse remodeling (221,222,223,224,225,226,227 and 228).

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93

INFLAMMATORY CARDIOMYOPATHY

DENNIS M. MCNAMARA

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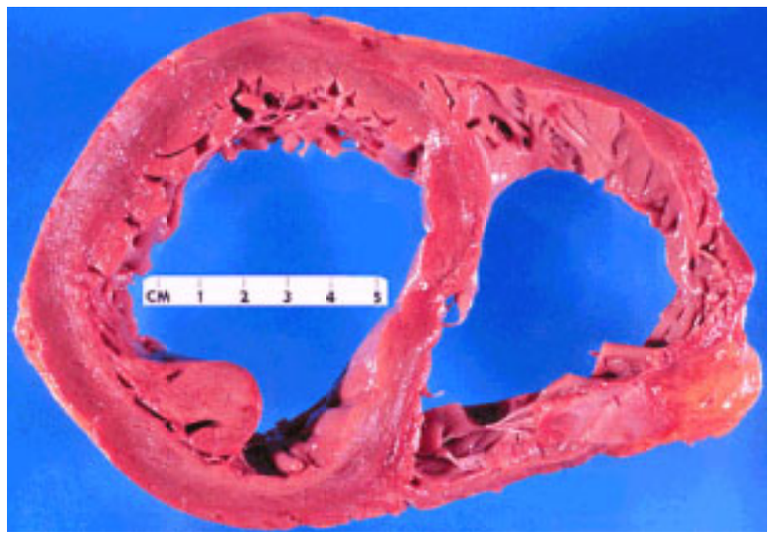
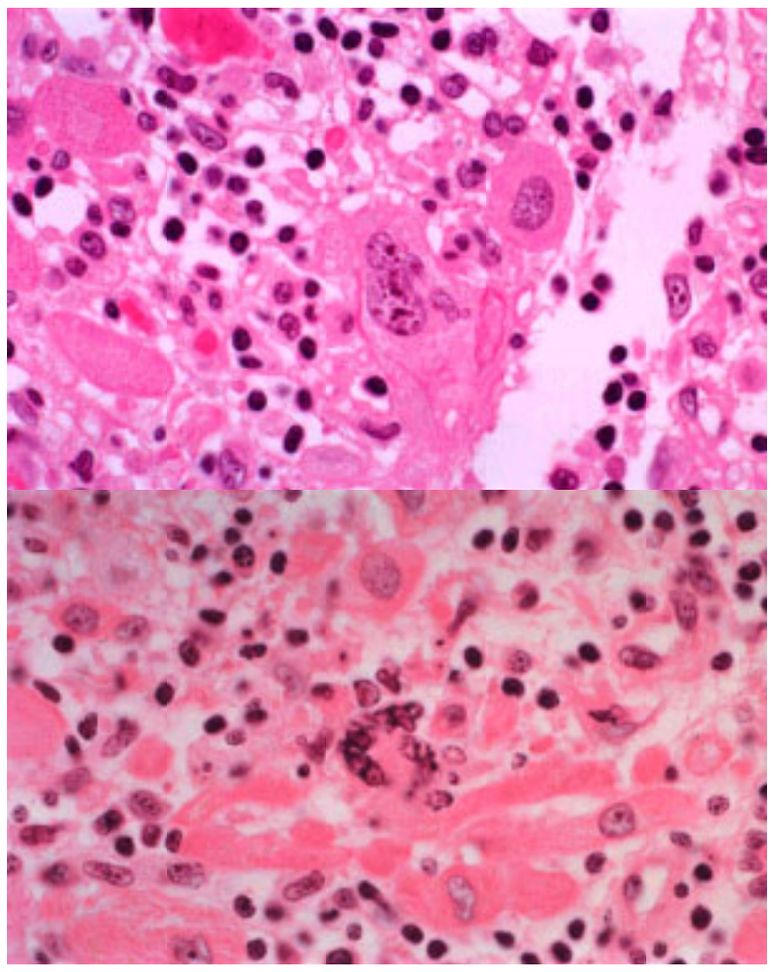
OVERVIEW

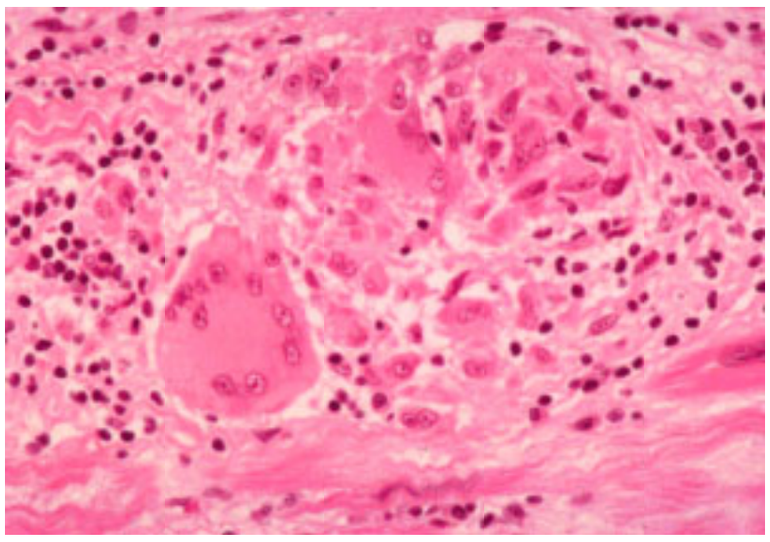
Myocardial inflammation underlies cardiac dysfunction in a wide spectrum of disorders, from lymphocytic myocarditis (1,2) to idiopathic dilated cardiomyopathy (IDC) (3). Animal models and clinical studies support viral etiologies in the majority of cases, although specific infectious agents are documented in only a fraction. Therapy remains supportive because, despite this inflammatory pathogenesis and scores of anecdotal series that suggest a therapeutic role for immunosuppression, controlled trials have consistently failed to demonstrate clinical benefit (4,5 and 6). Endomyocardial biopsy, once widely used for diagnosis, is currently not recommended for the majority of cases given the absence of specific biopsy-guided therapies (7). Giant-cell myocarditis remains one exception, as biopsy confirmation of this aggressive disorder may assist in therapeutic decisions, including the consideration of immunosuppressive therapy (8). The potential future role for immune modulatory therapy remains an intense area of investigation.



Dilated congestive cardiomyopathy. Both the left and right ventricles are significantly enlarged. In this example, the left ventricular wall thickness falls within normal limits.



Giant cell myocarditis with apoptosis (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Giant cell myocarditis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

INTRODUCTION

Primary dilated cardiomyopathy or IDC is a leading cause of congestive heart failure in the United States, particularly among young people (9). Although cardiac inflammation is postulated as an important early pathologic event, signs of systemic inflammation are rarely seen at presentation. Myocarditis, an often suspected but infrequently diagnosed disorder of primary cardiac inflammation, is believed to be an early precursor of IDC (10). Whether these two diagnoses are distinct entities or merely separate time points in a pathologic progression remains a matter of significant controversy. Over the last two decades, the search for mechanistic-based therapies for primary dilated cardiomyopathy has focused on the inflammatory pathogenesis. This current intensive period of investigation can be seen as the culmination of nearly two centuries of broad clinical interests in this common and mysterious form of cardiac disease.

HISTORICAL PERSPECTIVE

Clinicians in the early nineteenth century, guided by introduction of the stethoscope by Laënnec, divided cardiac disorders into valvular and nonvalvular (11). “Carditis” was a subset of nonvalvular disease that included vascular and inflammatory forms of cardiac dysfunction and was believed to have a particularly grave prognosis. Although the term *carditis* was gradually replaced by *myocarditis*, this continued for the remainder of the century to be a broad category of nonvalvular forms of myocardial dysfunction.

In the early part of the twentieth century, two important clinical breakthroughs led to an evolution of the concept of “myocarditis” to the modern application. Studies of rheumatic fever by Ashoff demonstrated that cellular inflammatory lesions played an important role in myocardial dysfunction. In addition, coronary artery disease became increasingly recognized as an important etiology for myocardial dysfunction, distinct from primary myocardial inflammation. By the mid-twentieth century, the search for infectious etiologic agents for inflammatory heart disease intensified, with increased recognition of the importance of viral pathogens (12,13 and 14).

The introduction of transvenous endomyocardial biopsy in the latter part of the twentieth century (15) heralded a new age of understanding for primary dilated cardiomyopathy, in which an apparent heterogeneous group of disorders could now be divided into distinct pathologic subsets. With the widespread growth in cardiac transplantation in the 1980s, it was recognized that the common form of cellular inflammation in native hearts, lymphocytic myocarditis, was histologically similar to cardiac allograft rejection. This supported a hypothesized autoimmune pathogenesis and led to a randomized clinical trial of immunosuppression, the Myocarditis Treatment Trial (MTT) (5). The clinical use of endomyocardial biopsy reached its zenith by the early 1990s and has subsequently declined in the absence of biopsy-guided therapeutic interventions. Over the last decade, molecular genetic techniques have been used in an attempt to enhance the diagnostic power of endomyocardial biopsy, in particular, for the detection of viral genomes (16). In addition, an increasing role has been noted for myocardial and systemic inflammatory mediators, including cytokines (1), chemokines (17), and autoantibodies (18) as potential surrogate markers for cardiac inflammation.

INFLAMMATORY CARDIOMYOPATHY: TERMINOLOGY AND CLINICAL SUBSETS

With the increasing use of endomyocardial biopsy for diagnosis, the term *myocarditis* gradually became synonymous with left ventricular (LV) dysfunction with histologic evidence of cellular inflammation. Indeed, as recently as 1995, the World Health Organization task force defined *inflammatory cardiomyopathy* as “myocarditis in association with myocardial dysfunction. Myocarditis is an inflammatory disease of the myocardium and is diagnosed by established histologic, immunologic, and immunohistochemical criteria” (19). In the current age in which biopsy data are infrequently obtained, reliance on histologically defined criteria may be impractical. From the standpoint of clinical practice, myocarditis can be defined more simply and literally as inflammation of the myocardium or heart muscle as assessed by a number of clinical criteria.

The risk of broadened clinical criteria remains that the pathologic and clinical distinction between inflammatory myocarditis and IDC can become somewhat obscured. As stated by eminent cardiac pathologist Michael Davies, “Cardiomyopathy and myocarditis are terms used with an expectation that they are generally understood. In practice, once their definition is attempted, difficulties emerge and their meaning seems less clear” (20). In its broadest definition, *inflammatory cardiomyopathy* includes a heterogeneous set of disorders in which myocardial inflammation plays the primary role in the pathogenesis of cardiac dysfunction. This heterogeneous grouping can be subdivided into more distinct subsets based on the clinical setting of presentation (e.g., pregnancy) or diagnostic histopathology (Table 93.1).

Myocarditis
Biopsy defined: lymphocytic, eosinophilic
Clinically defined
Giant-cell myocarditis
Systemic autoimmune disorders with myocarditis
Systemic lupus erythematosus
Polymyositis
Sarcoid
Peripartum cardiomyopathy
Subsets of idiopathic dilated cardiomyopathy

TABLE 93.1 INFLAMMATORY CARDIOMYOPATHY: CLINICAL SUBSETS

For many patients with the clinical syndrome of myocarditis, endomyocardial biopsy is either not obtained or is uninformative. Approximately 30% to 40% (6,21,22) of patients with new-onset, unexplained LV dysfunction have dramatic recovery of systolic function during subsequent follow-up. Myocarditis is the suspected etiology for most cases; however, this conclusion is generally only reached retrospectively. Only a fraction of patients who undergo biopsy have evidence of cellular myocardial inflammation (6).

Among those patients with biopsy evidence of cellular inflammation, most are classified as having “lymphocytic myocarditis” based on lymphocyte predominance in the myocardial cellular infiltrates (23). An eosinophilic predominance can be seen in myocarditis that is associated with an allergic reaction or with peripheral eosinophilia (24,25,26 and 27). Although lymphocytic myocarditis is seen in roughly 10% of biopsied patients (5), only 1% to 2% are diagnosed with giant-cell myocarditis, defined by the presence of multinucleated giant cells in the myocardium (28). The distinction between this disorder and lymphocytic myocarditis is critically important, as

giant-cell myocarditis is a much more aggressive pathologic process with a distinct natural history (8,28).

Myocarditis can also be seen as part of systemic autoimmune disorders such as sarcoidosis (29) or systemic lupus erythematosus (30). These disorders are defined by their respective systemic syndromes in terms of their clinical course and treatment. The histologic appearance of myocarditis as part of a systemic disorder is similar to that seen in isolated myocarditis. The granulomas of cardiac sarcoid in particular can be difficult to distinguish from its histologic mimic, giant-cell myocarditis (31).

IDC may be the most common form of “inflammatory” heart disease despite the fact that IDC endomyocardial biopsy is generally uninformative (3). Peripartum cardiomyopathy, the form of primary dilated cardiomyopathy that is seen as a complication of pregnancy, also likely has an inflammatory pathogenesis, and cellular inflammation is frequently seen on endomyocardial biopsy (32).

PREVALENCE

The prevalence of primary “idiopathic” dilated cardiomyopathy has been estimated at 0.4 per 1,000, with an annual incidence of 0.08 per 1,000 (33). This correlates to approximately 120,000 cases within the United States alone, with 24,000 new cases each year. The prevalence of histologic myocarditis, defined specifically as cellular inflammation on endomyocardial biopsy, varies widely in published series (Table 93.2) but can be best estimated from multicenter studies at approximately 10% to 20% of patients with new-onset IDC (5,6,34). The MTT noted biopsies that were positive for inflammation in only 10% of 2,233 screened patients (5). In a similar fashion, the ongoing European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases has reported positive biopsies in 17.2% of the first 3,055 patients screened (34). Evidence of myocarditis may be found in 1% to 9% of routine autopsy cases (35,36 and 37) and up to 20% of those that are performed for unexplained sudden cardiac death in young people (38). Although autopsy series and multicenter trials provide estimates for myocarditis with major cardiac consequences (LV dysfunction or sudden death), most cases of myocarditis are likely self-limited and never present to medical attention. The true prevalence of these subacute forms of myocarditis is difficult to determine, as is their role in initiating the pathway that leads to IDC.

Author (reference)	Years	Percent with positive biopsy	Patient group
Dec et al. (21)	1975–1983	67 (16/27)	Recent-onset cardiomyopathy with <6 mo of symptoms
Parillo et al. (4)	1982–1988	38 (38/102)	Patients referred to the National Institute of Health for randomized trial of prednisone in idiopathic dilated cardiomyopathy
Mason et al. (5)	1986–1989	10 (214/2,233)	Patients screened for the Myocarditis Treatment Trial
McCarthy et al. (162)	1984–1997	14 (25/21,757)	Large single-center series from Johns Hopkins
McNamara et al. (6)	1996–1998	16 (10/62)	All recent-onset dilated cardiomyopathy enrolled in the NIAC trial
Drucker et al. (122)	1985–1991	51 (20/39)	Children referred with the clinical syndrome of suspected myocarditis
Mabie et al. (82)	1983–1988	78 (14/18)	Patients with peripartum cardiomyopathy from a single center, Johns Hopkins
Bozkurt et al. (124)	1996–1998	9 (1/11)	Patients with peripartum cardiomyopathy from a single center, University of Pittsburgh

From Feldman AM, McNamara D. Myocarditis. N Engl J Med 2000;343:1388–1398; with permission.

TABLE 93.2 PREVALENCE OF MYOCARDITIS IN PUBLISHED SERIES

PATHOGENESIS: LESSONS FROM ANIMAL MODELS

The murine models of myocarditis are the most extensively studied, particularly those initiated with the cardiotropic ribonucleic acid virus Coxsackie virus group B (39,40 and 41) or encephalomyocarditis virus (42). After uptake by receptor-mediated endocytosis, viral proteins are translated, and replication of viral particles is initiated in the cytoplasm of the myocyte (41). Direct virally induced myocyte necrosis can be seen within 3 days, before any inflammatory infiltrates. Viral particles are subsequently released into the interstitium, where they are taken up by phagocytosis by macrophages. Subsequently, macrophage activation leads to cytokine expression, including interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factor-a (TNF-a), and interferon-g (10).

Cytokine expression, particularly IL-2, results in the activation of natural killer (NK) cells (43). NK cells interact specifically with virally infected myocytes and induce necrosis through the release of perforin and granzymes (44,45). Through this cytotoxic mechanism, NK cells play an important role in viral clearing, as murine models that are deficient in NK cells show a marked increase in viral titers and in the severity of the virally induced myocarditis. Endogenous interferons likely also play a direct role in limiting viral replication. In addition, cytokines induce the expression of inducible nitric oxide synthase in myocytes (46). The subsequent nitric oxide production serves to kill infectious agents directly and to modulate the host immune response.

The activation of cell-mediated immunity initiates the second phase of viral clearing. Within 7 days of viral inoculation, infiltrates of antigen-specific T-lymphocytes are seen throughout the myocardium. These cells can be subclassed based on surface antigens and function into T-helper (CD4+) cells and cytotoxic T-lymphocyte (CD8+) cells (10). Cytotoxic T-lymphocytes, in particular, play an important role in the necrosis of virally infected cells, which results in viral clearing. Viral antigens are reduced to peptides placed in the cell membrane of target cells bound to the major histocompatibility complex (MHC) for presentation to T-cell receptors. The recognition by cytotoxic T-lymphocyte receptors of viral peptide presented by MHC class I antigens initiates myocyte damage of virally infected cells (47). This interaction is dependent on cell contact. The induction of intracellular adhesion molecule-1 as well as MHC class I molecules by interferon-g and TNF-a plays an important facilitatory role (48).

Of the mononuclear cells in the myocardium, 10% to 20% are B-lymphocytes (49). T cell–depleted murine strains inoculated with encephalomyocarditis virus have less myocardial damage and overall less severe myocarditis than do T cell–competent strains (49,50 and 51). In this model, viral titers, the development of neutralizing antibody titers, and viral clearing were similar in T cell–competent and T cell–depleted strains. Although it does not participate directly in cytotoxicity, B cell–mediated humoral mechanisms play an important role in the overall elimination of viral particles.

Although the pathologic processes that are involved in the acute and subacute phases of myocarditis are well defined, there is less certainty regarding the mechanisms of the chronic phase. Approximately 15 days after viral inoculation, culturable virus is no longer detected. By 90 days after inoculation, inflammatory cell infiltrates are no longer seen; however, ventricular enlargement and myocardial fibrosis become prominent (42). This chronic postviral phase closely replicates the clinical presentation of patients with IDC. Viral nucleic acid can be detected by polymerase chain reaction in only a small percentage of mice at 90 days after inoculation (52) and, in a similar fashion, is only seen in a minority of patients with dilated cardiomyopathy (53,54 and 55). The importance of this carrier state for the persistence of myocardial injury and LV dysfunction remains unknown. The absence of detectable virus for the majority of subjects (murine or human) has powered speculation that this phase of chronic insidious myocardial injury is driven by persistent autoimmune pathologic mechanisms.

The potential of cytokine-mediated immune injury to persist long after the resolution of inflammation is supported by findings in transgenic mice. Murine strains that overexpress TNF-a in the myocardium develop lymphocytic myocarditis that is histologically similar to that seen in the virally induced model (56). Although the histologic evidence of myocarditis subsequently resolves, mice go on to develop a dilated cardiomyopathy and die prematurely from heart failure. The ability of TNF-a overexpression to produce progressive LV dysfunction demonstrates that the cytokine response to injury may be as important as the initiating stimulus itself in the subsequent development of dilated cardiomyopathy.

Immunization with cardiac myosin in a murine model elicits a T cell–mediated myocarditis that replicates the histology of the Coxsackie model in a virus-free system (57). In addition, inoculation of susceptible strains with murine cytomegalovirus induces an acute and chronic myocarditis as well as sera that cross-react with murine cytomegalovirus isolates and cardiac myosin (58). These findings support the hypothesis that antigenic similarity between viral and native myocardial peptides (cardiac myosin in particular) perpetuates the chronic inflammatory response.

ETIOLOGY

As in animal models, clinical studies of myocarditis suggest that a viral trigger initiates an immune pathogenesis involving cellular and humoral mechanisms. In serologic studies, enteroviruses, in particular Coxsackie B, are the most common viral agents (59). Adenovirus, influenza A and B, and hepatitis C have also been implicated as important viral pathogens (60,61,62 and 63) (*e*Table 93.2.1). In addition, advanced human immunodeficiency virus (HIV) infection has been associated with myocarditis and dilated cardiomyopathy (64,65 and 66). Whether this reflects a manifestation of HIV infiltration itself or opportunistic systemic infections with myocardial involvement in an immunocompromised host remains uncertain. Additional viral genomes, cytomegalovirus and adenovirus in particular, have also been detected in the myocardium of HIV-positive patients with lymphocytic myocarditis (67).

***e*TABLE 93.2.1** VIRAL ETIOLOGIES OF INFLAMMATORY CARDIOMYOPATHY[a]

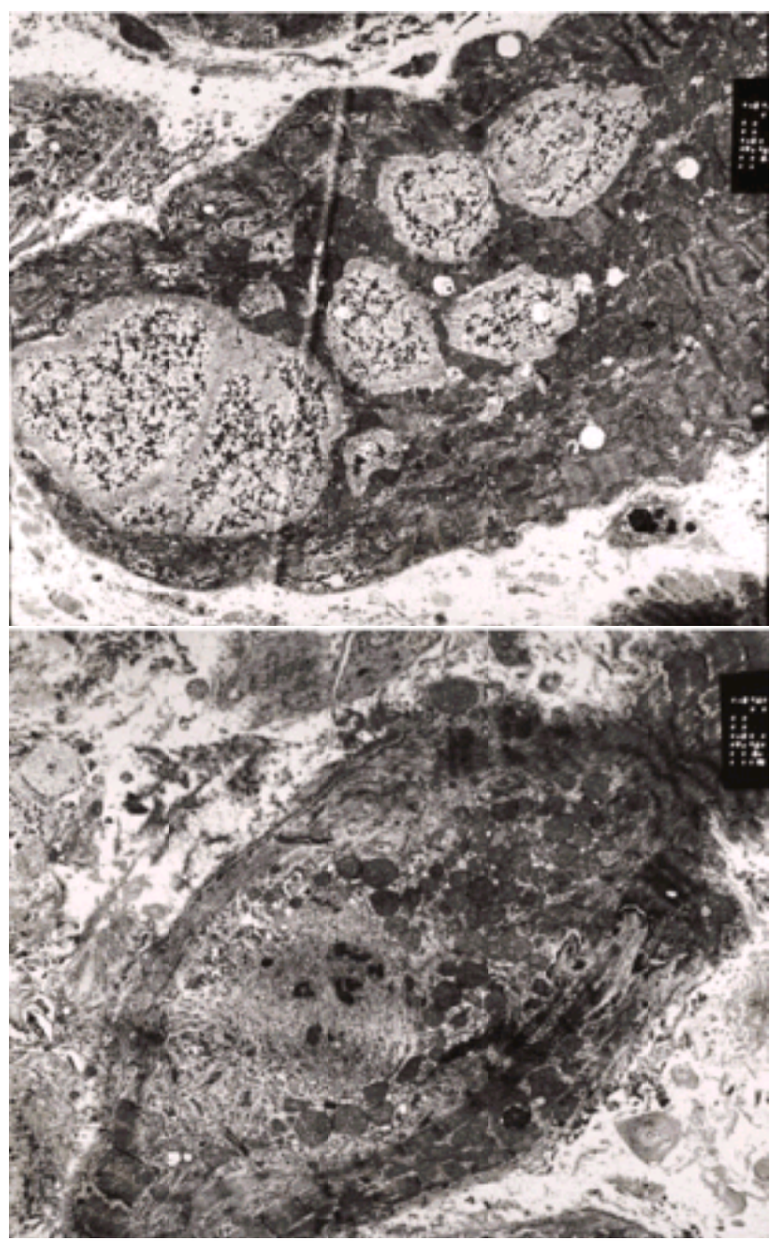
Enteroviruses
Coxsackie A and **B**
Influenza A and B
Echovirus
Polio
Herpesviruses
Herpes simplex
Varicella-zoster
Epstein-Barr
Cytomegalovirus
Adenovirus
Mumps
Rubella
Rubeola
Vaccinia
Rabies
Hepatitis B and **C**
Arbovirus
Human immunodeficiency virus

[a]Most common etiologic agents in boldface.
Data from references 59–67,174.

Nonviral infectious pathogens have also been implicated as the causative agent in myocarditis. Chagas' disease caused by parasitism with the protozoa *Trypanosoma cruzi* is endemic in parts of South America (68). Serologic epidemiology studies indicate that between 15 and 20 million people are infected in Central and South America, with more than 60 million people at risk (69). The infection causes an acute inflammatory cardiomyopathy and in animal models produces elevation in myocardial expression of TNF-a, IL-1b, and IL-6 (70). In its chronic stage, it can develop to progressive dilated cardiomyopathy and is associated with alterations in circulating T-cell subsets (71). This disorder is not seen among U.S. patients in the absence of a significant travel history to endemic areas. Among immunocompromised hosts, myocarditis associated with toxoplasmosis (72,73) or aspergillus (74,75) has been reported, but generally only with signs of other systemic infestation and only rarely as an isolated myocarditis.

Noninfectious triggers can also initiate myocardial inflammation, as demonstrated by peripartum cardiomyopathy, the syndrome of dilated cardiomyopathy that affects women in their last trimester of pregnancy or in the first few months postpartum (76,77 and 78). This disorder follows a similar clinical progression to the virally initiated syndrome, with the exception that the initiating stimulus is likely fetal or placental antigen. Modulation of the maternal immune system is an important aspect of fetal tolerance during routine pregnancy (79,80). Exacerbations of other autoimmune disorders such as multiple sclerosis typically decline during pregnancy because of this modulation, with a subsequent rebound increase generally noted in the postpartum period (81). The period of autoimmune "rebound" phenomenon postpartum is also the most common time for women to present with peripartum cardiomyopathy. Lymphocytic infiltrations of the myocardium can be seen in peripartum cardiomyopathy (82), particularly in patients who are biopsied soon after delivery. Multiparity is a risk factor for the development of peripartum cardiomyopathy (83), suggesting that previous exposure to fetal paternal antigens is important in the development of the pathologic immune response.

Toxins, namely alcohol and chemotherapeutic agents such as doxorubicin (84,85 and 86), can also initiate a progression to dilated cardiomyopathy. In contrast to the virally initiated and peripartum syndrome, these agents appear to act through direct myocardial toxicity. In these syndromes, myocardial inflammation may be more the result rather than the cause of myocardial injury. In addition, up to 25% of primary dilated cardiomyopathies may be familial in etiology (87). Responsible genetic loci have been delineated for several pedigrees and mutations identified in several cytoskeletal proteins, including dystrophin (88), cardiac actin (89), and the myosin heavy chain itself (90). Although inherited abnormalities of the inflammatory response may be important in some pedigrees (91,92,93 and 94), in general, the mechanism of cardiac dysfunction in familial cardiomyopathy appears quite distinct from that evident in the more common sporadic cases.



Electron microgram of 3+ doxorubicin (Adriamycin) toxicity (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

IMMUNOPATHOLOGY OF PROGRESSION

Whether virally initiated, peripartum, or idiopathic, the most common histologic appearance of myocardial cellular inflammation, lymphocytic myocarditis, is indistinguishable from the appearance of acute allograft rejection in the transplanted heart (95), with a predominance of T-lymphocytes. In murine models, whether the initial immune response is self-limited or results in progressive inflammation and cardiomyopathy is strain dependent (96), supporting a strong role of genetic background in determining outcome. In clinical studies, specific human leukocyte antigen genotypes appear to confer an increased risk of the development of dilated cardiomyopathy (97), suggesting that genetic susceptibility may be equally important in the human perpetuation of immune-mediated injury. Genetic predisposition to autoimmune pathology may be particularly important in giant-cell myocarditis, as a high percentage of patients who present with this disorder also have previously had other autoimmune diseases such as thyroiditis and colitis (8). Perpetuation of myocardial inflammatory disease requires not only antigenic similarity of myocardial and

viral peptides, but also a genetic “background” that facilitates the continuation of the pathologic immune response (98,99).

Increasing evidence over the last decade points toward myocardial expression of cytokines in general and TNF-a in particular as being important driving forces in the development of the end-stage cardiomyopathy phenotype (100,101). Myocardial expression and plasma levels of TNF-a and IL-6 increase as functional status worsens (102,103). The explanted heart from patients who are undergoing transplantation frequently demonstrates inflammatory myocardial infiltrates (104), even in those with coronary artery disease as the primary etiology of their heart failure. This demonstrates that in the end-stage ischemic heart, expression of inflammatory mediators can elicit cellular infiltration of the myocardium and contribute to the decline in cardiac function. The role of myocardial cytokine expression in the progression of heart failure from the compensated to the end-stage phenotype has broadened our appreciation of the inflammatory nature of chronic heart failure and led many investigators to focus efforts at immune modulation on chronic or end-stage disease (105,106).

Circulating cytokines, in particular TNF-a, are markedly elevated in the plasma of patients with acute cardiomyopathy and myocarditis. In contrast to its negative prognostic role in chronic end-stage cardiomyopathy, in acute myocarditis high circulating TNF-a levels may be a marker of a potentially reversible immune injury. In the multicenter Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study of patients with new-onset cardiomyopathy and myocarditis, higher plasma TNF-a at entry was associated with a higher probability of eventual recovery of LV function (107). The association of high plasma TNF-a at presentation with a higher left ventricular ejection fraction (LVEF) at follow-up closely parallels the earlier findings of the MTT that patients with evidence of active cellular autoimmunity tended to have less severe impairment of LV function (5). Increasingly, investigators are evaluating the role of “surrogate markers” of immune activation as potentially useful diagnostic and prognostic tools (108).

The role of autoantibodies and humoral immunity in clinical disease remains controversial. Antigenic specificity of circulating autoantibodies against myocardial proteins has been demonstrated for the adrenergic beta-receptor (18), myosin (109), and other myocardial peptides (110,111,112 and 113). The presence of autoantibodies in asymptomatic relatives of patients with familial cardiomyopathy supports an autoimmune pathogenesis for these particular pedigrees (92). However, whether autoantibodies are pathogenic or nonspecific epiphenomena associated with myocardial injury remains to be determined.

IMMUNOSUPPRESSIVE AND IMMUNE MODULATORY THERAPIES: LESSONS FROM CLINICAL TRIALS

The immune hypothesis for the progression of myocarditis to dilated cardiomyopathy has led to intense clinical interests over the years in improving ventricular function by blunting or modulating the pathologic aspects of the immune response. The challenge in studying the impact of therapeutic interventions in this disorder has been the clinical heterogeneity and a high spontaneous recovery rate in small subsets of patients. In addition, given the relative infrequency of patients who present with myocarditis and LV dysfunction, single-center anecdotal series are generally quite small, and a multicenter format is required to evaluate therapeutic interventions. Three major prospective randomized trials of immune suppression or modulation have been reported over the last decade, and all three controlled studies failed to confirm the therapeutic benefits that were suggested by anecdotal reports (4,5 and 6) (Table 93.3).

Author (reference)	Agent studied	No. randomized	Primary outcome measure	Result
Parillo et al. (4)	Prednisone	102	Change in EF at 3 mo	Modest benefit (4 EF units vs. 2 EF units in the placebo)
Mason et al. (Myocarditis Treatment Trial) (5)	Prednisone and cyclosporine	111	Change in EF at 6 mo	No significant effect (increase of 10 EF units vs. 7 EF units with placebo)
McNamara et al. (IMAC Trial) (6)	Immune globulin	62	Change in EF at 6 mo	No treatment effect (increase of 14 EF units in both groups)

EF, ejection fraction.
From Feldman AM, McNamara D. Myocarditis. *N Engl J Med* 2000;343:1388–1398, with permission.

TABLE 93.3 RANDOMIZED CLINICAL TRIALS OF IMMUNE MODULATION IN MYOCARDITIS AND DILATED CARDIOMYOPATHY

The first major randomized trial of immunosuppressive therapy in inflammatory heart disease was conducted by the National Institutes of Health and enrolled patients from 1982 through 1988 (4). One hundred two patients with an evaluation that was consistent with either IDC or myocarditis were randomized to high-dose prednisone therapy (60 mg per day) or standard therapy. All patients underwent endomyocardial biopsy; however, no strict biopsy inclusion criteria were used. Fifty percent of those enrolled were classified as “reactive” due to either cellular infiltrate in the myocardium, myocardial deposition of immunoglobulins or complement, elevation in the erythrocyte sedimentation rate, or positive myocardial gallium scans.

Overall, a modest increase in ejection fraction (EF) in the treatment group was noted at 3 months (4.3 EF units vs. 2.1 EF units, $p = .054$). Most of the improvement was seen in patients who were classified by these prespecified criteria as being “reactive.” However, despite maintenance therapy for reactive patients with 60 mg prednisone every other day, at subsequent 6-month follow-up, the small therapeutic benefit that was seen at 3 months was no longer evident. The investigators concluded that given the modest, transient nature of the improvement and the significant risk of steroid therapy, prednisone should not be standard therapy for dilated cardiomyopathy.

With the development and wide acceptance of the Dallas criteria, investigators focused therapeutic efforts in this subset of patients when an immune pathogenesis was more clearly evident. The histologic similarity of lymphocytic myocarditis with cardiac allograft rejection led to the belief that a combined immunosuppressive approach, similar to that used to prevent transplant rejection, would be more effective than prednisone alone. This hypothesis was evaluated in the MTT, which randomized 111 patients with a histopathologic diagnosis of myocarditis and an LVEF of less than 0.45 to conventional therapy alone or 24 weeks of prednisone combined with either cyclosporine or azathioprine. The primary outcome that was measured was the change in LVEF at 28 weeks (114).

Recruitment for the MTT was challenging due to the strict biopsy criteria. Local pathologists found evidence of myocarditis on endomyocardial biopsy for only 214 of 2,233 screened patients. Of these individuals, 111 met the other entry criteria and were randomized. Overall, LV function improved significantly over time from a mean of 0.25 at baseline to 0.34 at 28 weeks. No treatment effect was evident with immunosuppressive therapy, as the improvement in LVEF was similar in the two groups (0.10 with immunosuppressive therapy vs. 0.07 in the control group) (Fig. 93.1). No long-term difference in survival was seen ($p = .96$), with an overall mortality of 20% at 1 year and 56% at 4.3 years (Fig. 93.2). In current practice, the absence of therapeutic benefit for immunosuppression in the MTT has all but eliminated its use in adults with suspected myocarditis.

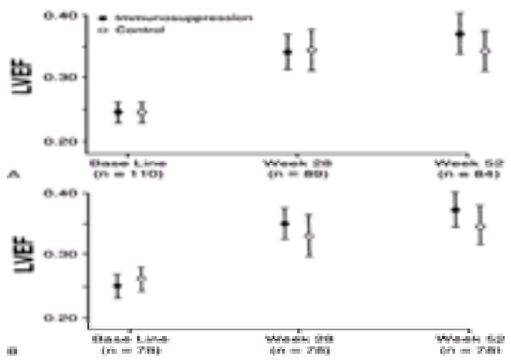


FIGURE 93.1 Serial change in left ventricular ejection fraction (LVEF) for all patients enrolled in the Myocarditis Treatment Trial **(A)** and only those who had paired studies **(B)**, showing comparable improvement in LVEF in the two groups. (From Mason JW, O’Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med* 1995;333:269–275, with permission. Copyright © 1995 Massachusetts Medical Society. All rights reserved.)

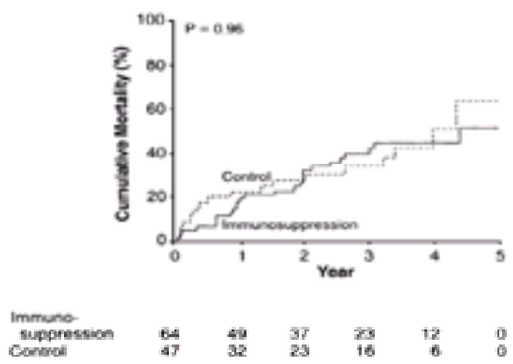


FIGURE 93.2 Cumulative mortality in subjects receiving immunosuppression and controls from the Myocarditis Treatment Trial, showing no difference between the groups. (From Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med* 1995;333:269–275, with permission. Copyright © 1995 Massachusetts Medical Society. All rights reserved.)

Recent research has focused on the use of intravenous immunoglobulin (IVIG) as an immune modulating agent (115,116 and 117). High-dose IVIG has been used in a number of autoimmune disorders, including idiopathic thrombocytopenic purpura (118), Guillain-Barré syndrome (119), and dermatomyositis (120). Based on effectiveness in Kawasaki's disease (121), a coronary vasculitis in children, pediatricians began investigating its use in myocarditis and reported significant improvement in LV function compared to that of historical controls (122). Subsequently, two small series were reported in adults with new-onset dilated cardiomyopathy and myocarditis (123) and peripartum cardiomyopathy (124) that suggested enhanced improvement in LVEF compared to historical controls.

The therapeutic role of immunoglobulin for adults with recent-onset inflammatory cardiomyopathy was evaluated in the IMAC trial (6). This multicenter study randomized 62 patients to 2 g per kg IVIG or a placebo infusion at the time of initial presentation with new-onset heart failure. All enrolled patients had evaluation that was consistent with a primary dilated cardiomyopathy or myocarditis, had an LVEF of 0.40 or less, and were randomized within 6 months of their onset of cardiac symptoms. All underwent an endomyocardial biopsy; however, patients with and without cellular inflammation on biopsy were included. Overall, the clinical characteristics of the IMAC and MTT study populations were quite similar (*e*Table 93.3.1). The primary end point was the change in LVEF at 6 months after randomization. Overall, LVEF improved significantly from 0.25 at baseline to 0.42 at 12 months. No treatment effect was evident, as the improvement at 6 months was 14 EF units in both groups and at 12 months was 16 EF units with IVIG versus 15 with placebo (Fig. 93.3). Overall event-free survival [events defined as death, transplantation, or need for LV assist device (LVAD)] was 91% at 1 year and 88% at 2 years (Fig. 93.4), and there were no significant differences between treatment groups.

***e*TABLE 93.3.1** CLINICAL CHARACTERISTICS OF MYOCARDITIS TREATMENT TRIAL (MTT) VERSUS INTERVENTION IN MYOCARDITIS AND ACUTE CARDIOMYOPATHY (IMAC)

	MTT	**IMAC**
n	111	62
Age	42 ± 14	43 ± 13
Gender (% male)	62%	60%
Antecedent viral syndrome	59%	62%
Fever	19%	N/A
Elevated creatine kinase	12%	N/A
Elevated erythrocyte sedimentation rate	60%	40%
Leukocytosis	24%	13%
Autoantibody present	62%	74%
Chest pain	35%	22%
Biopsy-positive inflammation	64%	16%
Symptoms £1 mo	46%	45%
Pulmonary capillary wedge pressure	19 ± 9	16 ± 10
New York Heart Association class % entry		
Class I	15	10
Class II	35	45
Class III	40	35
Class IV	10	10
LVEF entry	0.24 ± 0.10	0.25 ± 0.08
LVEF 1 yr	0.34 ± 0.02[a]	0.42 ± 0.14

LVEF, left ventricular ejection fraction; N/A, not available.
[a]Mean ± standard error; all other values mean ± standard deviation.
From Myocarditis Treatment Trial (5,114); Intervention in Myocarditis and Acute Cardiomyopathy trial (6).

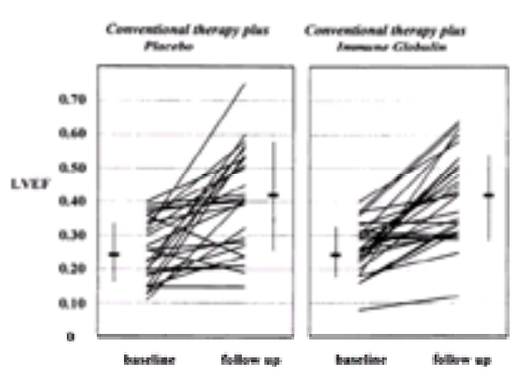


FIGURE 93.3 Left ventricular ejection fraction (LVEF) over time by treatment. LVEF by radionuclide scan at baseline and 12 months postrandomization in patients randomized to placebo and immunoglobulin. Overall, LVEF improved significantly over time (12 months LVEF significantly higher than baseline, p <.001). However, no differences by treatment group were evident (p = not significant for comparisons by treatment). (From McNamara DM, Holubkov R, Starling RC, et al., for the IMAC investigators. A controlled trial of intravenous immune globulin for recent onset dilated cardiomyopathy. *Circulation* 2001;103:2254–2259, with permission.)

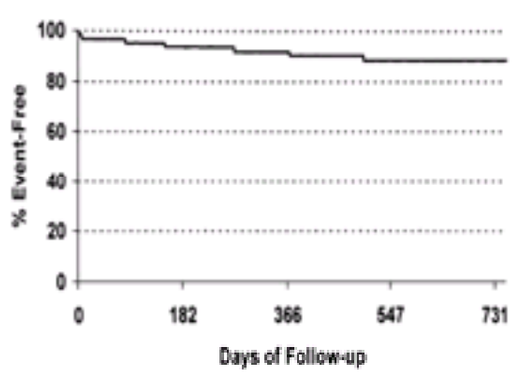


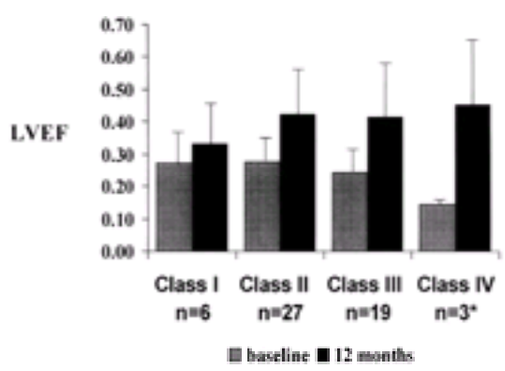
FIGURE 93.4 Event-free survival for patients with new-onset dilated cardiomyopathy and myocarditis enrolled in the IMAC trial (events defined as death, cardiac transplantation, or need for left ventricular assist device). Event-free survival 91% at 1 year and 88% at 2 years.

The IMAC trial provides important insights into the current natural history of new-onset dilated cardiomyopathy and myocarditis. At 1 year follow-up, an improvement in LVEF of at least 10 EF units was noted in more than 50% of patients, including nearly one-third (20 of 62) who normalized their EF (greater than or equal to 0.50). The high rate of spontaneous recovery in the IMAC control group represents a significant challenge for future clinical studies in myocarditis, as the marked heterogeneity of clinical outcomes limits the statistical power to evaluate interventions. Notably, the findings on endomyocardial biopsy (presence or absence of cellular inflammation, fibrosis, or myocyte hypertrophy) were of little prognostic value and did not predict the subsequent LVEF at 1 year (eTable 93.3.2). Higher New York Heart Association functional class at presentation was associated with an increased risk of events during follow-up, but with a trend toward greater LV recovery in survivors (eFig. 93.4.1). The absence of LV enlargement was the best clinical predictor of potential LV recovery. Patients with an LV end diastolic diameter of 6 cm or less at presentation (by transthoracic echo) had an average improvement of nearly 20 EF units during subsequent follow-up.

***e*TABLE 93.3.2** BASELINE, 12-MONTH LEFT VENTRICULAR EJECTION FRACTION, AND INCREASE IN LEFT VENTRICULAR EJECTION FRACTION (LVEF) AT 1 YEAR, ACCORDING TO BIOPSY STATUS[a]

	Baseline LVEF	**12-Mo LVEF**	**D LVEF at 1 yr**
Cellular inflammation			
Absent (n = 52)	0.25 ± 0.09	0.41 ± 0.14	0.15 ± 0.14
Present (n = 10)	0.25 ± 0.08	0.49 ± 0.19	0.21 ± 0.14
Fibrosis			
Absent (n = 23)	0.26 ± 0.08	0.43 ± 0.13	0.16 ± 0.12
Present (n = 39)	0.25 ± 0.09	0.41 ± 0.15	0.15 ± 0.15
Myocyte hypertrophy			
Absent (n = 31)	0.26 ± 0.09	0.44 ± 0.14	0.17 ± 0.14
Present (n = 31)	0.24 ± 0.08	0.40 ± 0.15	0.13 ± 0.14

[a]No statistically significant differences based on biopsy status were found between the subgroups with respect to LVEF at entry, at 1-year follow-up, or at the change at 1 year.
From McNamara DM, Holubkov R, Starling RC, et al., for the IMAC investigators. A controlled trial of intravenous immune globulin for recent onset dilated cardiomyopathy. *Circulation* 2001;103:2254–2259, with permission.



***e*FIGURE 93.4.1** Natural history of left ventricular ejection fraction (LVEF) recovery in acute cardiomyopathy and myocarditis. LVEF at baseline and 12 months by New York Heart Association class at presentation: Patients with baseline and 12-month multiple gated acquisition data only. Higher New York Heart Association functional class at entry was significantly associated with a lower LVEF at baseline (p = .02) but a nonsignificant trend toward a higher LVEF at 12 months. *A fourth class IV patient, excluded from this analysis, had an LVEF of 0.69 at 1 year. (From McNamara DM, Holubkov R, Starling RC, et al. for the IMAC investigators. A controlled trial of intravenous immune globulin for recent onset dilated cardiomyopathy. *Circulation* 2001;103:2254–2259, with permission.)

More recently, investigators of immune modulatory therapies have focused on more chronic populations (i.e., histories of dilated cardiomyopathy greater than 6 months), in which spontaneous recovery is generally rarer. Current therapies under investigation include interferon-g (125,126 and 127), TNF-a soluble receptor (105), and immunoadsorption (128). Immunoglobulin has also been studied in a more chronic population of dilated cardiomyopathy (129) and appears to be more efficacious in this subset than in the acute population of the IMAC study. Although these results in small single-center series suggest benefit, larger multicenter trials are needed to confirm therapeutic efficacy.

A unique approach to the diagnosis and treatment is currently being evaluated by the large multicenter European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (130). This study combines conventional histology and molecular genetics in an effort to enhance the ability of myocardial biopsy to delineate distinct patient subsets and guide more individualized treatments, including antiviral therapies. Patients in this trial are randomized to several different treatment arms based not only on the presence or absence of cellular inflammation but also on the basis of myocardial immunoglobulin or complement deposition and the presence of viral genomes. Given the complexity of this randomization design, enrollment is ongoing, with no therapeutic outcomes yet reported.

CLINICAL MANAGEMENT: EVALUATION

Presentation

The classic presentation for a patient with myocarditis is symptoms of chest pain or dyspnea in the setting of an acute febrile illness. However, subacute myocarditis (inflammation with mild or no LV dysfunction) may present without any cardiac symptoms. Occasionally, these cases are surreptitiously diagnosed in the setting of an acute viral syndrome by the incidental finding of electrocardiographic (ECG) abnormalities (131) or elevations of cardiac enzymes (132,133). Just as cardiac symptoms are not necessarily part of the presentation with myocarditis, neither is an acute febrile illness. Fever was present in only a minority of patients in the MTT (5) (eTable 93.3.1).

In patients who present with LV dysfunction, the most common cardiac symptoms are those of congestive heart failure (dyspnea, fatigue, and chest discomfort) (134). In general, heart failure symptoms are more left sided, although signs of right-sided failure, in particular peripheral edema, or symptoms of hepatic congestion (abdominal discomfort or nausea) can be seen. Palpitations are a common presenting complaint and may represent atrial or ventricular arrhythmias (135,136 and 137). Atrial arrhythmias generally reflect left atrial hypertension or irritation from associated pericarditis. Ventricular dysrhythmias, although usually associated with heart failure and significant LV dysfunction, are occasionally seen with relatively preserved LV function and presumably originate from an inflammatory focus within the ventricle (138).

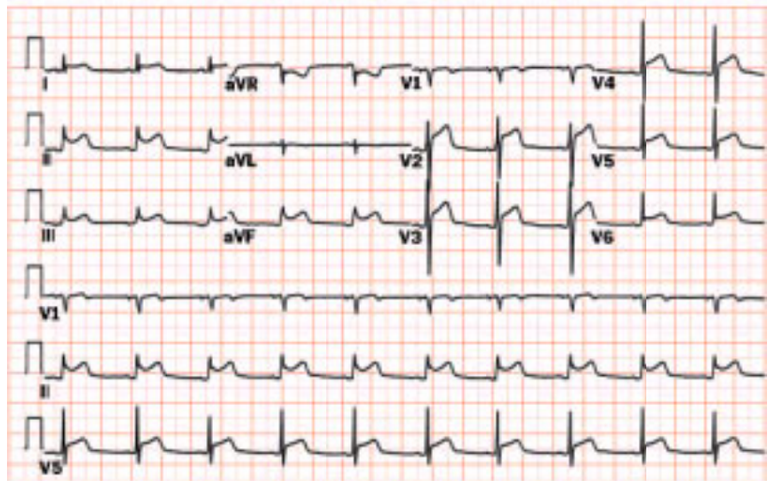
Adult patients who present with symptoms of heart failure due to myocarditis typically do so with no signs of systemic inflammation (5,6) and come to medical attention months after the initial symptom complex began. In this regard, the presentation in young children is distinctly different from that of adults, perhaps reflecting differences in the pediatric viral milieu. Children are more likely to present within days of the onset of symptoms (122) and have more systemic signs of an acute inflammatory state. As patients who present earlier generally have a higher probability of spontaneous recovery once systemic inflammation has resolved, this may lead to a higher probability of significant LV recovery in children.

Diagnostic Evaluation

The clinical examination of patients with suspected myocarditis should focus on signs of ventricular dysfunction. Although tachycardia and borderline hypotension may reflect an acute febrile syndrome, they may also be the first signs of significant hemodynamic compromise. In acute cases, rales on the pulmonary examination provide evidence of left-sided failure; however, in patients with a more insidious presentation a clear lung examination can be heard despite significant dyspnea and marked elevations in left-sided filling pressure. Elevated jugular venous pressure, hepatic tenderness, or peripheral edema is consistent with right-sided failure and suggests right ventricular involvement.

The ECG remains an important clinical tool in evaluating cases of suspected myocarditis (131). Common findings are diffuse and nonspecific ST- and T-wave abnormalities. In cases of fever and acute chest pain, PR depression and diffuse global ST elevation may allow a rapid diagnosis of pericarditis. Low voltage may be evident, particularly in those with an associated pericardial effusion. Occasionally, myocarditis presents with ECG findings suggestive of myocardial infarction in a specific vascular territory. Although this form of myocarditis that mimics the presentation of myocardial infarction has been well described (139,140,141 and 142), it

remains important in such cases to rule out an acute ischemic event and to have a low threshold for proceeding with rapid coronary angiography.



Acute pericarditis. Note diffuse, marked ST-segment elevation with PR-segment elevation in lead aV_R.

Pericardial tamponade. Low QRS voltage and electrical alternans are characteristic findings of tamponade.

Serum analysis for patients with a suspected myocarditis should include creatine phosphokinase (CPK) with appropriate fractionation or, alternatively, cardiac troponin. Elevations of CPK tend to be moderate, in the range of 200 to 1,000, even in cases of fulminant myocarditis. In young men who present with dilated cardiomyopathy with a persistent chronic elevation of CPK, a detailed family history should be obtained, as chronic elevations in CPK may reflect not persistent myocarditis but dystrophinopathy, a familial X-linked disorder (88).

For patients who present with an acute febrile illness, acute and convalescent sera against most common viral pathogens should be performed. Such a panel should include Coxsackie B, influenza A and B, cytomegalovirus, and appropriate adenoviral forms (59). A mild leukocytosis may be seen, particularly with a lymphocyte predominance. Marked leukocytosis should elicit a thorough evaluation for a systemic bacterial infection in which LV dysfunction may be secondary to septicemia. Peripheral eosinophilia should suggest the possibility of eosinophilic myocarditis, a syndrome that is frequently related to drug or other allergies. Serologic testing should include antinuclear antibody and rheumatoid factor, looking for occult connective tissue disease or other systemic autoimmune disease. Testing for other cardiac-specific autoantibodies, for example, those directed against cardiac myosin or the adrenergic beta-receptor, remains investigational and is not part of clinical screening.

In young patients with chronic cough or dyspnea, chest x-ray findings of cardiomegaly or interstitial edema often initiate the cardiac consultation. Usually, marked cardiomegaly is associated with a more insidious progressive course. In these patients, as in chronic dilated cardiomyopathy, findings on chest x-ray of pulmonary edema may be minimal despite markedly elevated left-sided filling pressures. In contrast, acute fulminant myocarditis can present with florid alveolar edema and acute respiratory failure, but, given the short time course of the illness, a relatively normal-sized cardiac silhouette.

In any patient with suspected myocarditis, an echocardiogram should be performed. This one test gives clinicians the maximum information about LV size and function and right ventricular involvement (143,144). The presence of a pericardial effusion, relatively small chamber size with decreased systolic function, and increased LV wall thickness are essentially diagnostic of an active process of myocardial inflammation. In general, decrease in LV systolic function is global, although marked segmental wall motion abnormalities can be seen. However, the echogenicity of the myocardium itself does not change with active inflammation, and therefore the echo images of the myocardium itself do not help in the specific diagnosis of cardiac inflammation. Despite this limitation, echocardiography remains clinically the most useful tool for clinical management and should be a part of any diagnostic evaluation.

In patients with LV systolic dysfunction and significant hemodynamic impairment, consideration should be given to invasive hemodynamic assessment by right heart catheterization. Persistent tachycardia may be compensatory for a decrease in stroke volume and a resultant decrease in cardiac output. As acute myocardial inflammation can affect systolic and diastolic properties, pulmonary capillary wedge and right atrial pressures are frequently elevated out of proportion to the apparent decrease in systolic function. In addition, in any adult patient with cardiac risk factors, coronary artery disease should be ruled out either by angiography or by appropriate noninvasive evaluation given the distinctly different treatment pathway engaged by this diagnosis.

Endomyocardial Biopsy

In the 1960s, the development of techniques for transvenous endomyocardial right ventricular biopsy made possible the antemortem diagnosis of myocardial inflammation (15,145). By the mid-1980s, its critical role in managing patients after cardiac transplant led to increased use in the evaluation of native myocardial disease (146). Infiltrates of inflammatory cells invading the myocardium on biopsy rapidly became the gold standard for the diagnosis of myocarditis, which previously had relied on more indirect clinical assessment. However, the sensitivity of endomyocardial biopsy has historically been limited by sampling error. Biopsy samples are taken from the apical portion of the right ventricular septum, as limiting sampling to this region lessens the risk of complications, namely, acute tricuspid regurgitation or cardiac perforation and tamponade. Autopsy studies of patients who are known to have myocarditis have estimated the sensitivity of endomyocardial biopsy at no better than 60% to 70% because of regional sampling error (147).

In addition, the finding of cellular inflammation as indicative of myocarditis is dependent on interpretation. In an effort to have more consistent pathologic guidelines, a group of leading cardiac pathologists met in Dallas in 1986 to establish a consensus for the definition of myocarditis (148). The Dallas criteria defined “borderline myocarditis” as the presence of mononuclear cell infiltrates without myocyte necrosis (Fig. 93.5A and *e*Fig. 93.5.1) and “myocarditis” as cellular infiltration with myocyte necrosis (Fig. 93.5B and *e*Fig. 93.5.2). Despite this widely accepted consensus, interpretation remains problematic and physician dependent (149). After review by the study pathology panel of the endomyocardial biopsies from patients enrolled in the MTT (all of whom were believed by their local pathologists to have histologic myocarditis), 36% were not thought to have Dallas criteria myocarditis or borderline myocarditis (5). Conversely, a “negative” biopsy does not rule out myocarditis, as patients without cellular inflammation on biopsy may still follow a clinical course that is suggestive of myocarditis. In the IMAC study, 16 of 20 patients who normalized their EF (greater than or equal to 0.50) during follow-up had biopsies that were interpreted as negative for cellular inflammation at entry. Most such cases of reversible LV dysfunction in retrospect had a clinical syndrome that was strongly suggestive of transient myocardial inflammation.

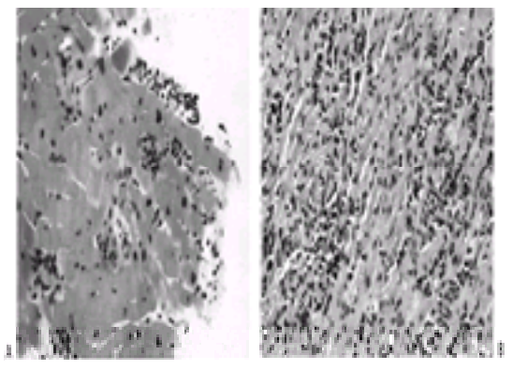
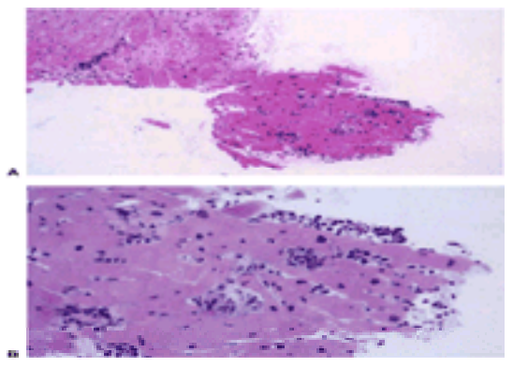
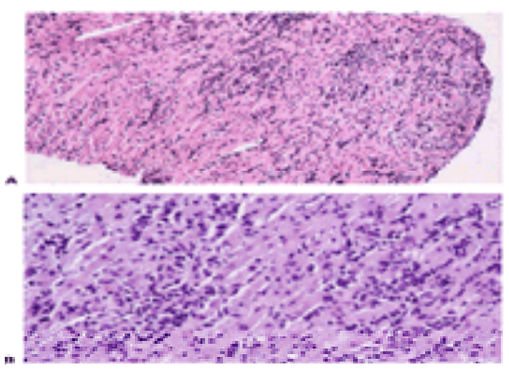


FIGURE 93.5 Histopathologic appearance of borderline myocarditis (lymphocytic infiltrates *without* myocyte necrosis) **(A)** and myocarditis (lymphocytic infiltrates *with* myocyte necrosis) **(B)**. **A:** ×350 magnification; **B:** ×300 magnification. (From Feldman AM, McNamara D. Myocarditis. *N Engl J Med* 2000;343:1388–1398, with permission. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)



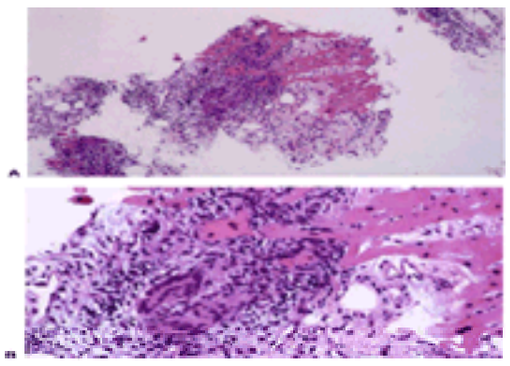
***e*FIGURE 93.5.1** Histopathologic appearance of borderline myocarditis (lymphocytic infiltrates *without* myocyte necrosis). **A:** ×100 magnification; **B:** ×350 magnification. (From Feldman AM, McNamara D. Myocarditis. *N Engl J Med* 2000;343:1388–1398, with permission. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)



***e*FIGURE 93.5.2** Histopathologic appearance of myocarditis (lymphocytic infiltrates *with* myocyte necrosis). **A:** ×100 magnification; **B:** ×300 magnification. (From Feldman AM, McNamara D. Myocarditis. *N Engl J Med* 2000;343:1388–1398, with permission. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

Two additional considerations are important in determining the role of endomyocardial biopsy in the workup of suspected myocarditis. First, for endomyocardial biopsy in native hearts the risk of a major complication, in particular cardiac tamponade, approaches 1% (150,151), significantly higher than in cardiac transplant patients. In addition, currently there are few histologically guided therapies; therefore, biopsy findings of cellular inflammation usually do not change therapeutic plans and are of minimal prognostic value (6,152). This absence of specific biopsy-guided therapy has led the American College of Cardiology to classify endomyocardial biopsy for the evaluation of heart failure due to unexplained myocardial dysfunction as a “class II procedure . . . acceptable but of uncertain efficacy and may be controversial” (7).

In patients with fulminant myocarditis, endomyocardial biopsy may have more clinical utility than in the compensated patient. Patients with fulminant disease and hemodynamic compromise are more likely to have giant-cell myocarditis (*e*Fig. 93.5.3). Although it remains investigational, data from the Giant Cell Registry (8,153) suggest that immunosuppression therapy may be appropriate in patients with giant-cell myocarditis. In addition, biopsy evidence of a dynamic destructive process may help guide the timing of therapeutic interventions such as LVAD placement or cardiac transplantation. Although in this very-high-risk subset biopsy may assist in these therapeutic decisions, it should be performed at a tertiary referral center where such end-stage supportive therapies are readily available.



***e*FIGURE 93.5.3** Histopathologic appearance of giant-cell myocarditis (multinucleated giant cell in the center of the specimen). **A:** ×100 magnification; **B:** ×350 magnification.

MEDICAL MANAGEMENT OF MYOCARDITIS

In the absence of proven benefit in prospective clinical trials, immunosuppressive therapy is not recommended for adult patients with isolated myocarditis. For individuals with myocarditis as part of a systemic autoimmune disorder, such as sarcoid, systemic lupus erythematosus, or polymyositis, immunosuppressive therapy may be beneficial but is generally directed against the systemic disorder (e.g., prednisone for active sarcoid). The need for therapeutic intervention is determined by systemic markers of inflammation (serum CPK from skeletal muscle in polymyositis) and not on measures of myocardial function or findings on biopsy.

The medical therapy of patients with suspected myocarditis is therefore supportive and is dependent on the degree of LV dysfunction. In general, patients with myocarditis can be divided into three broad categories based on the severity of LV compromise: (a) myocarditis and preserved LV function; (b) myocarditis with LV

dysfunction and class I–III heart failure; and (c) myocarditis with LV dysfunction and class IV heart failure, or fulminant myocarditis.

Patients with Myocarditis and Preserved Left Ventricular Function

This group of patients frequently present in a setting of an acute febrile illness with ECG abnormalities or chest pain due to associated pericarditis. Therapy in this case consists of observation and partial restriction of activities. Although chest pain due to isolated pericarditis can be treated with indomethacin or nonsteroidal antiinflammatory agents, these agents should be avoided in cases with myocarditis, as they potentiate myocyte necrosis in murine viral models (154,155 and 156). In the absence of LV dysfunction, there is no indication for beta-adrenergic receptor antagonists or angiotensin-converting enzyme (ACE) inhibitors. In general, it is recommended that aerobic activities or heavy lifting be avoided for at least 6 to 8 weeks (157). Cardiac assessment, generally ECG and echocardiography, should be repeated roughly 6 to 8 weeks after presentation to guard against progressive cardiac involvement. Endomyocardial biopsy is of limited clinical utility and is not recommended. In general, cases of myocarditis with either mild or no LV dysfunction are self-limited and carry an excellent prognosis.

Myocarditis Associated with Left Ventricular Dysfunction and Class I–III Heart Failure

Recommended therapy is similar to that for patients with LV dysfunction in the absence of myocarditis. ACE inhibitors or angiotensin-receptor blockers are recommended for all patients. Pulmonary congestion or symptoms of fluid overload should be treated with a loop diuretic, generally at the lowest effective dose. Digoxin should be added in patients with New York Heart Association class III heart failure; however, given potential proarrhythmic and proinflammatory (158) effects it should be maintained at a low dose and avoided entirely in minimally symptomatic (class I or II) subjects.

Consideration should be given to beta-adrenergic antagonists. Caution should be used, however, in the use of such agents in individuals with relatively small chamber size and tachycardia. In such acute patients with systolic dysfunction without a compensatory increase in LV chamber size, tachycardia is compensatory for low stroke volume, and slowing of the heart rate precipitously can exacerbate a low-output state. Although caution must be exercised, given the potential beneficial effects of blocking adrenergic overstimulation in such patients, low-dose beta-blockade can still be considered.

In the absence of atrial fibrillation or a clinical embolic event, anticoagulation in patients with myocarditis and low EF remains controversial, as in noninflammatory dilated cardiomyopathy. Echocardiography is recommended, and if a mural thrombus (159) is detected, 6 to 12 months of low-dose warfarin with an international normalized ratio of 2 to 3 is recommended. In the absence of a mural thrombus or history of embolic event, warfarin is not universally recommended, and there exists much variation in standard practice.

Video 93.1 Subcostal view of a patient with severe left ventricular dysfunction and multiple mobile thrombi within the left ventricular cavity. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

In patients with myocarditis and LV dysfunction, ventricular arrhythmias are frequently seen. Although their management is similar to that of other patients with nonischemic cardiomyopathy, it should be noted that the potential stimulus for ventricular arrhythmias, myocardial inflammation, may resolve. In patients who present with cardiac arrest or aborted sudden death, an implantable defibrillator should be considered, given the potential risk of recurrence. However, in patients with symptomatic nonsustained ventricular tachycardia, amiodarone therapy can be considered an alternative. Multicenter studies in congestive heart failure (160,161) have shown that low-dose amiodarone therapy can be used without significant hazard and may actually improve survival in nonischemic cardiomyopathies. Therefore, amiodarone may offer some protection during the acute inflammatory period, with the potential benefit that it can be gradually withdrawn once the inflammatory period has resolved, particularly if systolic function improves. Amiodarone therapy should also be considered for treatment of symptomatic atrial dysrhythmias.

In general, in patients with LV dysfunction, strenuous physical activity is limited for a period of several months. Follow-up evaluation of LV dysfunction in 3 to 6 months and at 12 months after presentation is recommended. In patients with severe LV dysfunction and class II–III heart failure, we generally defer listing for cardiac transplantation for a period of at least 6 to 12 months, as a significant percentage of patients, from 30% to 50%, exhibit substantial improvement in LV dysfunction in the first year after presentation (6,21,22). In patients with persistent severe LV dysfunction at 12-month follow-up and significant functional limitations, metabolic stress testing should be performed to determine if further evaluation for transplant listing is indicated.

Fulminant Myocarditis: Myocarditis Associated with Hemodynamic Compromise and Class IV Heart Failure

Reports from the single-center registry at Johns Hopkins suggest that for patients with acute lymphocytic myocarditis and severe hemodynamic compromise, long-term prognosis (and the probability of LV recovery) may be better than for patients who present with more insidious chronic disease (162). In addition, dramatic recovery of LV function has been reported in patients with fulminant myocarditis that is maintained with LVAD support and has led to renewed interest in the use of assist devices as “bridges to recovery” rather than transplantation (163,164,165,166,167 and 168). Hemodynamic unloading should theoretically rest inflamed myocardium; however, the role of mechanical support in facilitating recovery is difficult to determine, and the use of LVADs is currently reserved for patients who are failing despite maximal inotropic therapy. For patients with cardiogenic shock and aggressive myocarditis, consideration should be given to referral to a tertiary center where both cardiac transplantation and device support are more accessible.

Giant-Cell Myocarditis

In patients with fulminant disease, evaluation for possible giant-cell myocarditis is the primary indication for endomyocardial biopsy. Patients with giant-cell myocarditis were excluded from the Johns Hopkins study, as their prognosis and potential for recovery are significantly worse than for those with lymphocytic myocarditis (8,28). Anecdotal reports (153,169) and the Giant Cell Registry (8) suggest that immunosuppressive therapy, in particular the combination of cyclosporine and the anti–T-lymphocyte antibody muromonab-CD3, may improve transplant-free survival. Given the grim prognosis of giant-cell myocarditis with conventional therapy, immunosuppression should be considered. This remains investigational as the subject of an ongoing multicenter trial.

Postrecovery

For patients whose LV size and systolic function completely normalize, ACE inhibitor therapy and beta-receptor antagonists can gradually be discontinued. In many such patients, subjective limitations in functional capacity and objective limitations in metabolic stress testing may persist, potentially because of a slower recovery of diastolic function (170). Overall prognosis of such patients remains excellent. Although a chance of recurrence of myocarditis exists, most investigators believe that this is seen only in a minority of patients.

Peripartum Cardiomyopathy

For women who are diagnosed with cardiomyopathy during pregnancy, ACE inhibitors and angiotensin-receptor antagonists are contraindicated given potential harmful effects to the developing fetus. Recommendations for management of cardiomyopathy postpartum are similar to those for inflammatory heart disease that is not associated with pregnancy. ACE inhibitors or angiotensin-receptor antagonists are recommended for all postpartum patients. Beta-blockers should be considered but used with caution in patients with small LV chamber size and reflex tachycardia. In general, small LV diameter at presentation predicts a better chance at ventricular recovery, whereas functional class does not. Strenuous exercise should be avoided for 3 to 6 months. Breast-feeding is generally to be avoided given the potential increased metabolic demands on the mother and the potential for certain therapies such as ACE inhibitors to be passed to the child through breast milk. Substantial recovery of LV function is seen in roughly 50% of cases (82,124). In patients with persistent LV dysfunction, subsequent pregnancy should clearly be avoided. In patients with recovered LV function, a risk of LV decompensation with subsequent pregnancy exists, and patients should be monitored carefully.

Pediatric Myocarditis

Children are more likely than their adult counterparts to present with an acute febrile illness and with a positive endomyocardial biopsy (122). As they present more acutely, they appear to have a higher likelihood of ventricular recovery (171,172). ACE inhibitors are recommended for all patients with LV dysfunction (173). Less

experience has been gained with the use of beta-adrenergic receptor antagonists in children, and the use of such agents must be individualized.

A study of pediatric patients with myocarditis suggests that immunoglobulin improves LV function (122). However, this study relied on historical controls, and no randomized trial has evaluated the efficacy of immunoglobulin for this indication in children. Indeed, all previous multicenter trials of immunosuppressive therapy for myocarditis have enrolled only adults, and few controlled data exist to guide therapy for the pediatric patient. In the absence of randomized prospective data, anecdotal reports (169,171) will continue to have a strong influence on practice. Although the benefits of immunoglobulin and steroid therapy remain speculative, they are used more frequently in the management of children with inflammatory heart disease, and randomized trials are clearly needed.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Despite the absence of proven benefit in both the IMAC (6) and MTT trials (5), the search for an immune modulatory therapy which improves patient outcome remains the elusive “Holy Grail” of current myocarditis research. Interestingly, in both trials, patients with more active systemic inflammation actually appeared to have a better prognosis, leading some investigators to question whether suppression of inflammation is the appropriate goal of acute therapy. In the IMAC study, patients with higher initial plasma TNF-a levels tended to have more LV recovery and a higher LVEF at 12-month follow-up (107). In the MTT, patients with an active systemic inflammatory response at presentation (higher white-cell count or autoantibody titer) had less initial impairment of left ventricular function (5). Taken together, these data support the hypothesis that it is not the initial inflammatory event per se, but the myocardial response and subsequent transition to chronic disease that is the true culprit of this pathologic process. For many patients with acute myocarditis, supportive therapy is all that is needed. It is those patients with persistent inflammation who appear to progress toward cardiomyopathy, and identifying and targeting this subset should be the subject of future investigations. Indeed, recent trials in more chronic heart failure suggest a potentially more beneficial therapeutic role for immune modulation than has been seen in previous studies of acute new onset disease (174).

An additional point of controversy remains about whether newer molecular techniques will improve the clinical utility of endomyocardial biopsy and lead to a renaissance of its use in general practice. As important as investigations of gene expression are to the understanding of basic pathogenesis, the same factors which have limited the clinical utility of conventional histology, in particular sampling error, limited tissue availability, and the potential procedural morbidity, will remain significant obstacles despite molecular advances. It is likely that systemic markers of inflammation will be of increasing diagnostic importance, and that future innovations in noninvasive imaging techniques will continue to diminish the current clinical role of endomyocardial biopsy.

THE FUTURE

Primary dilated cardiomyopathy remains an important cause of morbidity. Although myocarditis and cardiac inflammation clearly play a role in its early pathogenesis, the clinical heterogeneity of its natural history remains an enigma. Two similar patients who present with LV dysfunction and myocarditis can embark on distinctly different courses, one to complete recovery and the other to chronic cardiomyopathy, cardiac transplantation, or death. The major challenge in the treatment of inflammatory heart disease is to distinguish at presentation those patients who are destined for recovery from those on the path to end-stage heart failure. In current clinical practice, most tools including endomyocardial biopsy are of limited use in this regard. Future investigations that focus on circulating cytokines or other inflammatory mediators, or on additional molecular techniques to enhance the role of biopsy, are needed to decipher these very distinct subsets.

One added untapped resource for the future will be provided by the ongoing research of the human genome project. Genetic background exerts a powerful influence on outcomes with myocarditis, but the genetic loci that are responsible for modulating recovery remain unknown. The human genome project will provide a wealth of information on human genetic variants for scores of genes of interest over the next decade. Studies of the impact of genetic background on the natural history of the disorder and on the efficacy of therapeutic intervention will be of critical importance. It is extremely likely that the current revolution in human genetics will have a significant impact on how we treat patients with inflammatory heart disease within the next decade.

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94

CARDIAC TRANSPLANTATION

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"Indicates text or graphics that appear only in the electronic versions of this text."

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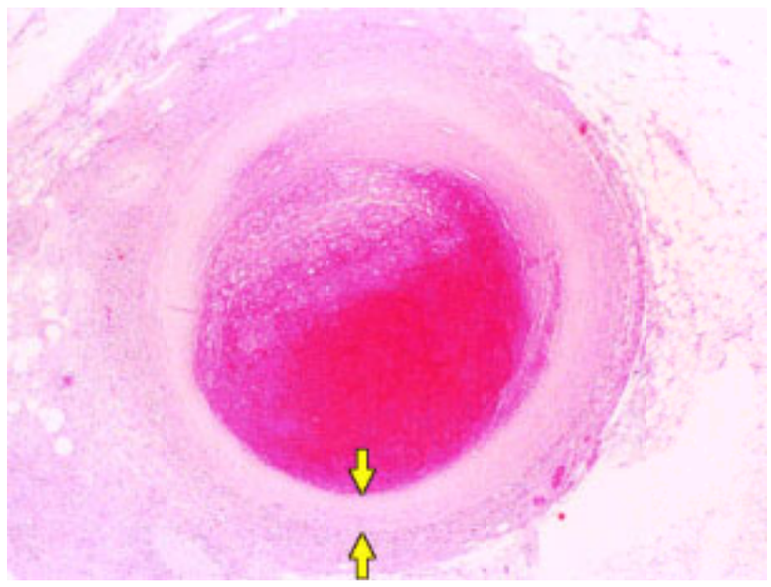
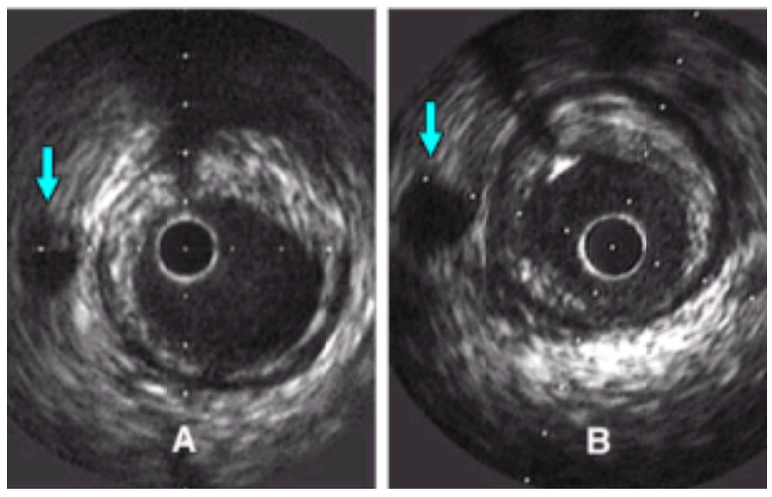
OVERVIEW

Despite major pharmacologic advances in the management of heart failure, cardiac transplantation is the most effective treatment for selected patients with end-stage heart failure. Sound, evidence-based immunosuppressive strategies have decreased morbidity and mortality, enabling the successful transplantation of even less than ideal candidates. Most infections and rejections are either preventable or treatable, and 1-year and 3-year survival rates exceed 85% and 80%, respectively. Cardiac allograft vasculopathy limits long-term survival and is the major cause of death after the first few years. Nonetheless, approximately 50% of recipients are alive 10 years after transplantation. Because of this success, the number of patients who could potentially benefit from cardiac transplantation is even greater than previously thought, which results in an ever-increasing donor to recipient disparity. Not only must every effort be made to increase the number of donors and use every appropriate donor heart, but care must be taken to ensure that individuals listed as candidates for cardiac transplantation are those who are likely to benefit the most. Potentially suitable candidates should be referred early in the course of their end-stage disease to heart failure and transplant specialists so that transplantation can be appropriately timed or alternative treatment options implemented. After transplantation, the care of recipients should be directed, at least in part, by transplant physicians.



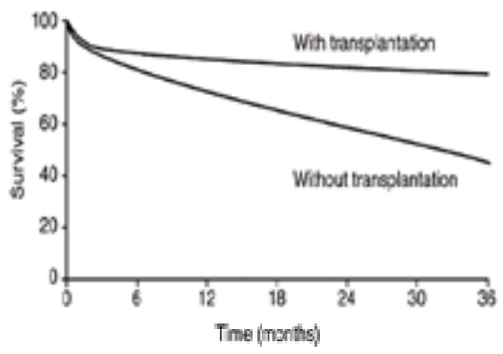
Acute thrombosis of the coronary artery in a transplant heart. The concentric thickening of the vessel wall is consistent with transplant associated vascular disease (*yellow arrows*).



Serial intravascular ultrasound study in transplant recipient. The baseline study (A, 2 months after cardiac transplant), shows an eccentric plaque in the left anterior descending artery. One year later (B), the same site is identified with the help of anatomic and angiographic landmarks (a branch vessel, *arrow*). This permits repeated imaging of the same site, which reveals no change over 1 year.

HISTORICAL PERSPECTIVE

Although much progress has been made in pharmacologic therapy for heart failure, the most effective treatment for selected patients with end-stage heart disease is cardiac transplantation. Patients with severe heart failure have a 1- to 2-year mortality approaching 50% despite appropriate and advanced medical treatment (1). Heart transplantation alters the course of end-stage heart disease, with 1-year, 3-year, and 10-year survival rates exceeding 85%, 80%, and 50%, respectively (2) (*e*Fig. 94.0.1). More than 55,000 procedures have been performed in over 330 centers worldwide, and nearly 3,000 additional procedures are performed each year (2). Although certain demographic variables influence the likelihood of survival after cardiac transplantation (e.g., retransplantation, older recipient and donor age, higher pulmonary vascular resistance, and longer duration of ischemia) (2) (*e*Table 94.0.1), survival and quality of life continue to improve (3,4,5 and 6). Heart transplantation is not experimental.



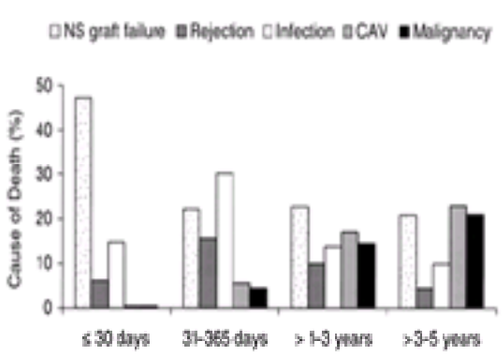
***e*FIGURE 94.0.1** Survival of cardiac transplant recipients. Moderate and severe congestive heart failure is associated with a poor prognosis. Without transplantation, candidates would likely survive as depicted in the lower curve. The poor prognosis contrasts with the survival achieved with transplantation, depicted in the upper curve, as reported to the International Society for Heart and Lung Transplantation, 1996–1999 (n = 11,844). (Adapted from Hosenpud JD, Bennett LE, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report—2000. *J Heart Lung Transplant* 2000;19:912, with permission.)

***e*TABLE 94.0.1** RISK FACTORS FOR SURVIVAL AFTER HEART TRANSPLANTATION IN ADULTS

	1 Yr (n = 37,257)		**5 Yr (n = 23,684)**	
Variable	**Odds ratio**	***p* Value**	**Odds ratio**	***p* Value**
Repeat heart transplantation	2.27	<.0001	2.36	<.0001
Ventilator use	1.94	<.0001	1.28	.01
Congenital heart disease	1.47	.001	—	—
Non-CAD, non-IDC diagnosis	1.25	<.0001	1.22	<.0001
VAD implanted	1.25	.0003	1.35	.002
Female donor	1.23	<.0001	1.14	.0002
Recipient age (linear analysis)	1.0 + 0.025/yr for each year over age 50	<.0001	1.0 + 0.025/yr for each year over age 50	<.0001
Donor age (linear analysis)	1.0 + 0.025/yr for each year over age 30	<.0001	1.0 + 0.02/yr for each year over age 30	<.0001
PVR (linear analysis)	1.0 + 0.13/Wood unit for each Wood unit over 1.0 Wood unit	<.0001	1.0 + 0.07/Wood unit for each Wood unit over 1.0 Wood unit	.03
Ischemic time (linear analysis)	1.0 + 0.26/h for each hour over 3 h	<.0001	1.0 + 0.26/h for each hour over 3 h	<.0001

CAD, coronary artery disease; IDC, idiopathic dilated cardiomyopathy; PVR, pulmonary vascular resistance in Wood units (mean pulmonary artery pressure in mm Hg minus mean pulmonary capillary wedge pressure in mm Hg divided by the cardiac output in L/min); VAD, ventricular assist device.
Adapted from Hosenpud JD, Bennett LE, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report—2000. *J Heart Lung Transplant* 2000;19:913.

During the first month after cardiac transplantation, donor heart dysfunction predominates as a cause of death. The propensity to reject the transplanted heart decreases over time. Consequently, the first few months after transplantation present not only the highest risk of rejection but also the highest risk of infection because of the higher doses of immunosuppressive agents used. Between 1 and 12 months after transplantation, not surprisingly, infection and acute rejection predominate as causes of death. After the first few years, cardiac allograft vasculopathy (CAV) and malignancy become the leading causes of death, the former accounting for a quarter of the deaths in transplant recipients (2,3 and 4) (*e*Fig. 94.0.2).



***e*FIGURE 94.0.2** Causes of death after heart transplantation: influence of time. Although infection, acute allograft rejection, and nonspecific (NS) cardiac allograft failure remain significant causes of mortality after heart transplantation, cardiac allograft vasculopathy (CAV) and malignancy become the leading causes of death after the first few years after heart transplantation. (Adapted from Hosenpud JD, Bennett LE, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report—2000. *J Heart Lung Transplant* 2000;19:918, with permission.)

The quality of life achieved after transplantation is generally good (5). By 5 years, approximately 55% of survivors are employed or retired (2,6). Many of those who are not employed could be, but are prevented from working because of various societal factors. Hospitalization rates among survivors decrease over the first 5

years from approximately 40% in the first year to 20% in the fifth year (2).

The care of potential transplant patients and posttransplant patients is important to internists and cardiologists alike. Given the success of heart transplantation, knowing when to refer a patient to a heart failure and transplant specialist for evaluation is of paramount importance. Early referral of any patient who has persistent significant left ventricular dysfunction (ejection fraction <25%) despite appropriate medical therapy is warranted, not only for evaluation of the potential need for cardiac transplantation, but also for determination of whether alternative therapies might delay or even prevent the need for transplantation. In addition, many patients awaiting cardiac transplantation (more than 4,000 in the United States alone) and many cardiac transplant recipients are cared for, at least in part, by their primary physicians. Management of end-stage heart failure and cardiac transplant patients is challenging and requires vigilance and attention to detail.

CLINICAL PROFILE

Recipient Selection

Indications

Cardiac transplantation is indicated for one of the many reasons listed in Table 94.1 (1,7,8 and 9). Cardiac transplantation is not indicated, however, simply because of an ejection fraction of less than 20%, a past history of functional class III or IV symptoms of heart failure, or a previous history of ventricular arrhythmias. Also, before transplantation is considered, a thorough search for reversible or surgically amenable cardiac disease must be completed and optimal medical management implemented. Patients should either have failed to improve with a trial of beta-blocker therapy or have clear contraindications to beta-blocker use. Confidence that the medical therapy is optimal is increased when the therapy is directed or administered by heart failure specialists.

TABLE 94.1 INDICATIONS FOR CARDIAC TRANSPLANTATION CANDIDACY

Patients who require continuous intravenous inotropic support (e.g., dobutamine hydrochloride or milrinone lactate) or mechanical circulatory support (intraaortic balloon pump or left ventricular assist devices) despite maximal medical therapy for heart failure are likely to benefit from transplantation and should be evaluated. Whether less ill, ambulatory patients with heart failure will benefit from transplantation is more difficult to determine. Identifying all patients at high risk for death during continued medical therapy remains challenging. Individuals whose predicted chance of survival for 1 year is less than 80% without heart transplantation warrant consideration for transplantation. Most patients being considered for cardiac transplantation usually have New York Heart Association class III to IV symptoms despite receiving best medical therapy. Ambulatory candidates usually have peak oxygen consumption (VO_2) values of 14 mL per kg per minute or less when assessed by maximal exercise tolerance testing. Unless the test is terminated because of myocardial ischemia or ventricular arrhythmias, anaerobic threshold occurs at 50% to 70% of peak oxygen uptake. The effects of age, gender, and conditioning effects on maximal oxygen uptake must be considered in interpreting VO_2 data.

Assessment of Risk of Mortality and Morbidity after Transplantation

Patients meeting indications for cardiac transplantation are evaluated to determine whether they are at higher than acceptable risk for a poor outcome after transplantation (7,10,11,12,13 and 14). Anecdotal experience of successfully overcoming isolated risk factors should not justify ignoring known risks in the majority of situations. Table 94.2 lists characteristics that increase the risk of morbidity and mortality after cardiac transplantation. These risk factors do not necessarily represent absolute exclusionary criteria. For example, combined heart-liver or heart-kidney transplantation is feasible in selected patients with both end-stage heart and liver disease or end-stage heart and kidney disease (12,13).

TABLE 94.2 CHARACTERISTICS INCREASING THE RISK OF MORBIDITY AND MORTALITY AFTER CARDIAC TRANSPLANTATION

The use of standardized indications and risk assessment procedures assists physicians in (a) selecting appropriate transplant recipients by ensuring that transplantation is avoided or delayed for patients who are functioning well, (b) encouraging optimal medical or surgical management before considering transplantation, and (c) helping to avoid the transplantation of patients who are at high risk of a poor outcome. For high-risk patients, the use of a donor heart may not be justifiable, given the scarcity of donor hearts and the abundance of lower-risk patients. Older patients can be successfully transplanted, and any age limitation is obviously arbitrary (14). Even though, for recipients older than 50 years, increasing age increases the risk of mortality after transplantation, the effect is moderate, with a mortality risk 50% greater in a 70-year-old than in a 50-year-old candidate (2). Therefore, patients are probably best considered individually using criteria that contain as few arbitrary guidelines as possible.

Management of the Patient while Awaiting Transplantation

While the patient awaits transplantation, his or her general health and hemodynamic compensation must not be allowed to deteriorate without intervention. A low threshold for hospitalization and more intensive heart failure treatment are mandated for any hemodynamic deterioration that may manifest as significant azotemia, refractory salt and water overload, persistent hypotension, altered mental status, or even gastrointestinal distress. Signs and symptoms of low cardiac output should prompt escalation in therapy from intravenous diuretics to intravenous inotropic agents, and from intravenous inotropic agents to intraaortic balloon pump or left ventricular assist devices (see Chapter 95). Heart transplant candidates who nonetheless develop irreversible end-organ failure in other organ systems or who are likely to die despite transplantation are not transplanted. Therapeutic approaches to the prevention of sudden death, including the use of an implantable cardioverter defibrillator, as appropriate, are considered. The routine placement of an implantable cardioverter defibrillator in heart transplant candidates in the absence of standard indications for use has not been proven.

All patients awaiting transplantation are routinely tested and evaluated to insure that indications and risk assessments remain valid. Every 3 to 6 months, even stable patients undergo repeat right heart catheterization to insure acceptable pulmonary vascular resistance. Levels of panel-reactive antibodies (PRA) are periodically

monitored, particularly after any blood transfusions. If blood transfusions are needed, leukocyte-removing filters are used to minimize anti-HLA antibody formation. Various therapies may be used to decrease elevated PRA levels in sensitized patients, for example, administration of intravenous immunoglobulin, plasmapheresis, administration of immunosuppressive agents, or some combination of these. Patients are monitored for recovery of left ventricular function that would obviate or at least postpone the need for transplantation. Peak VO_2 is reassessed every 6 months and left ventricular ejection fraction is reassessed every 6 to 12 months. Peak VO_2 measurements of 15 mL per kg per minute or more generally allow deferment of transplantation. Transplantation is postponed if indications are no longer met.

Donor Selection

Donor selection is influenced by many factors, including ABO blood type compatibility, donor-recipient size disparity, presence of intrinsic cardiac disease, and presence of transmissible infectious or malignant diseases (15,16,17 and 18). The risk of using a specific donor heart is always balanced against the risk one is willing to take with regard to a particular recipient. A decision to use a marginal donor heart may sometimes be made if the condition of the potential recipient warrants the risk and the potential recipient consents.

The lowest donor weight deemed compatible is usually considered to be 80% of the recipient's weight. In adults, upper weight limits are only rarely needed, and then only in situations in which the size disparity is large. In recipients with significant (but acceptable) pulmonary hypertension, the lower donor weight limit is often increased in hopes of preventing acute right ventricular failure in the transplanted heart.

To avoid intrinsic cardiac disease, electrocardiography, echocardiography, and (at times) coronary angiography are used. Electrocardiographic abnormalities that generally preclude the use of a donor heart include evidence of myocardial infarction and significant ventricular arrhythmias. Echocardiographic abnormalities that generally preclude the use of a donor heart include significant global hypokinesis, significant valvular abnormalities, and moderate to severe left ventricular hypertrophy. In addition, evidence of a significant cardiac contusion with a significantly elevated troponin level generally precludes use of the donor heart. Although older donor hearts are associated with a higher risk (eTable 94.0.1), many have been successfully used (2,19). Even in the absence of risk factors for coronary artery disease, coronary angiography is recommended in male donors older than 45 years and in female donors older than 50 years. The presence of risk factors for coronary artery disease prompts coronary angiography in even younger donors. Some donor hearts with significant coronary artery or valvular disease have been transplanted successfully with simultaneous bypass surgery or valve replacement, but doing so is not yet standard care. Brain death can cause time-dependent changes in left ventricular function (20) that may be related to catecholamine release. Donor heart dysfunction may be reversible, and thyroid hormone is frequently administered to improve donor heart function. Clearly using an irreversibly damaged donor heart is to be avoided.

To avoid transmitting infectious disease with the donated heart, a series of tests are performed to determine the suitability for transplantation. A history of behaviors, especially recent, that predispose to human immunodeficiency virus (HIV) infection or viral hepatitis (e.g., intravenous drug use); positivity for HIV, hepatitis B surface antigen (HB_SAg), or hepatitis C; and uncontrolled gram-negative sepsis generally preclude donor use. The use of a heart from an HB_SAg-positive donor could be considered, however, if the recipient is also HB_SAg positive. Due to the differences in virulence of various hepatitis C subtypes, the use of hepatitis C–positive donors' hearts in hepatitis C–positive recipients remains controversial. Generally, if the donor has a malignancy not confined to the cranium, the donor heart is not used (16,17 and 18,21). The final decision to transplant a particular heart is made at the time of visual inspection.

An additional donor-related factor affecting survival after cardiac transplantation is the degree of HLA matching between donor and recipient. Time constraints affecting donor cardiectomy and implantation generally preclude prospective HLA matching. Retrospective evaluations suggest that improved matching would in fact lead to improved outcomes.

Donor Allocation

Given the increasing donor to recipient disparity, the procurement and methods of allocation of all solid organs are frequently debated. Of course, everything should be done to decrease candidate waiting time, increase the use of suitable donor hearts, and increase the willingness of the population at large to donate (16,21,22). Hearts are allocated based on mandated guidelines. In the United States, hearts are allocated to specific patients based on blood type, size, proximity of the donor to the candidate's transplant center, and the disease severity and waiting time of the candidate (23).

Flexibility in organ allocation is at odds with predictability and societal accountability. Flexibility in matching donors to recipients maximizes the use of donor hearts. For instance, marginal donor hearts can be transplanted into less than ideal candidates, which increases the use of altruistically donated hearts. Many older patients might be more than willing to accept a heart with less than normal coronary arteries or even a heart that requires bypass surgery. Granting unlimited flexibility to transplant surgeons and physicians is not socially acceptable, however, because the public generally requires predictability and accountability.

ANATOMIC CONSIDERATIONS

Donor Cardiectomy

In donor cardiectomy and transplant surgery, one key to successful transplantation is the minimization of donor heart ischemic time (24,25). Ischemic time (from the time of aortic cross-clamping in the donor to release of aortic cross-clamp in the recipient) of less than 4 hours is generally acceptable, although some risk is conferred by every hour of donor heart ischemia (risk = 1.0 + 0.26 per hour for each hour over 3 hours) (2) (eTable 94.0.1).

In multiorgan donor procurement procedures, a midline incision is extended from the sternal notch to the pubis. The sternum is incised longitudinally and the pericardium is opened. The superior and inferior venae cavae within the pericardium are dissected free, and the superior vena cava is encircled with transfixion sutures. Because the sinoatrial node is located at the atrial-caval junction, care is taken to avoid this area to minimize the risk of injury. The aorta and pulmonary artery are separated, and the pulmonary artery is dissected free to its bifurcation. A purse-string or horizontal mattress suture is placed in the adventitia of the aorta as far distal as possible. Heparin is administered (10,000 to 20,000 U intravenously), and the inferior vena cava is divided at or slightly cephalad to the diaphragm. Bleeding is allowed into the pericardium and the ascending aorta is cross-clamped as far cephalad as possible. Cardioplegic solution is infused through an angiocatheter placed through the purse-string suture. The superior vena cava is double-ligated by tying the transfixion sutures and dividing the cava between them. The right and left pulmonary veins are divided at their entrance into the pericardium. The left and right pulmonary arteries distal to the bifurcation of the main pulmonary artery are divided. The aorta is transected distal to the cardioplegic needle but proximal to the aortic cross-clamp. The excised donor heart is rinsed in saline at 4°C, placed into two concentric sterile plastic bags, and packed beneath crushed ice in a portable ice chest for transport.

Implantation Techniques

Lower and Shumway Technique

Three implantation techniques are available: the traditional Lower and Shumway technique, the bicaval technique, and the rarely used heterotopic technique (24,25,26,27 and 28). Concern about the loss of normal atrial anatomy using the Lower and Shumway technique has led to the more frequent use of the bicaval technique. The bicaval technique may result in a longer donor heart ischemic time but is associated with lower right atrial pressure, lower incidence of atrial tachyarrhythmias, lower diuretic dose, less need for pacing, less tricuspid valve incompetence, and shorter hospital stay. An improved atrial kick contribution to cardiac output may also decrease the incidence of thrombus formation in the left atrium (29). Heterotopic cardiac transplantation can be performed with the donor heart placed in the right lower thorax in parallel to the recipient heart, which is left in place.

In the traditional Lower and Shumway technique, the recipient is placed on cardiopulmonary bypass and cooled to 30°C as the diseased heart is removed. Atria are incised on the atrial side of the atrioventricular groove and the atrial septum is incised, with a large remnant left posteriorly. The great arteries are divided cephalad to the commissures of the aortic and pulmonic valves. The left atrium of the donor heart is opened by connecting the orifices of the pulmonary veins and trimming residual tissue to fit the remnant of the excised left atrium of the recipient. The left atria are connected with continuous suture. The right atrium of the donor heart is opened by incising the lateral wall beginning at the orifice of the inferior vena cava and continuing in the direction of the atrial appendage. The right atria are then connected. End-to-end anastomoses are made for donor and recipient aortae and donor and recipient pulmonary arteries. Air is evacuated from the heart and great vessels, and the aortic cross-clamp is released after rewarming. Cardiopulmonary bypass is discontinued, and temporary pacing wires are attached to both the right atrium and the right ventricle.

Bicaval Technique

In the bicaval technique, the right atrium of the recipient is excised, with a 2- to 3-cm cuff left around each cava (cavo-atrial cuff). The left atrial size and structure are

more or less normal because the recipient's atrial septum is resected, so that only the atrial roof is left *in situ*. This contrasts with the standard technique in which the atrial septum, as well as a large remnant of the recipient atrial mass, is left behind. The donor heart is excised with the right atrium intact and with long cavae. The donor left atrium is sutured to the recipient left atrium with continuous suture. Cardiac rewarming is avoided by venting the left atrium. The inferior vena cava opening is then sutured to the inferior vena cava cuff with continuous suture. The donor superior vena cava is similarly sutured to the recipient superior cavo-atrial cuff. The great arteries are then anastomosed in the usual fashion.

Heterotopic Technique

In heterotopic transplantation, anastomoses are made between donor left atrium and recipient left atrium, donor and recipient aortae, donor superior vena cava and recipient right atrium or superior vena cava, and donor pulmonary artery and recipient pulmonary artery or right atrium. Heterotopic heart transplantation accounts for less than 0.3% of all procedures. The indications for heterotopic cardiac transplantation include severely elevated pulmonary hypertension, a small donor heart, and a donor heart with anticipated poor initial function.

PATHOPHYSIOLOGY OF THE TRANSPLANTED HEART

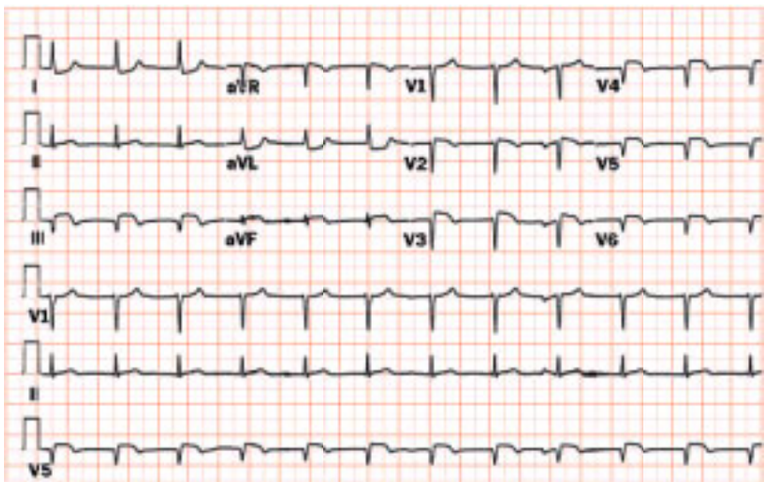
Cardiac Allograft Function and Inotropic Support

The function of the newly transplanted cardiac allograft is influenced by preexplant variables (e.g., degree of inotropic support, cardiopulmonary resuscitation, and trauma), the ischemic insult during explant and implantation, effectiveness of cardioplegia, and total denervation. Inotropic support (using isoproterenol, dobutamine, or milrinone) is usually required for 2 to 5 days, depending on donor heart function.

Ischemia induces diastolic noncompliance, which necessitates higher than normal filling pressures (right atrial pressures of 10 to 15 mm Hg and left atrial pressures of 15 to 20 mm Hg). Failure to maintain adequate preload results in increasing inotropic requirements and hemodynamic deterioration. Early on, impaired contractility and depressed systolic function may also be seen. Even with adequate preload, inotropic support is generally necessary to obtain sufficient cardiac output.

Agents such as isoproterenol (0.25 to 5.00 µg per minute) or dobutamine (2.5 to 20.0 µg per kg per minute) are indicated. In most adults, inotropic support with these agents maintains the heart rate between 110 and 120 beats/min, enhances diastolic relaxation, and insures adequate cardiac output. If further inotropic support is needed beyond isoproterenol or dobutamine, the agents may be combined, or milrinone (0.25 to 0.75 µg per kg per minute), epinephrine (1 to 10 µg per minute), or other inotropic agents may be used. Dopamine hydrochloride can be used to reverse moderate systemic vasodilation or to enhance renal blood flow. Profound systemic vasodilation, which may rarely be seen with the disruption of central aortic reflexes or with severe muromonab-CD3 monoclonal antibody (OKT3) first-dose reactions, responds well to phenylephrine or arginine vasopressin.

One of the most serious hemodynamic problems that can occur early after transplantation is acute distention and failure of the right ventricle. Right ventricular failure nearly always results from excessive right ventricular afterload. This may be due to preexisting pulmonary hypertension or severe reactive pulmonary vasoconstriction, caused by cardiopulmonary bypass or the administration of protamine sulfate or both. Although isoproterenol, nitroglycerin, sodium nitroprusside, milrinone, or amrinone may each dilate the pulmonary vasculature, the most effective agents are prostaglandin E_1, administered in incremental doses of 30 to 50 ng per kg per minute, or nitric oxide. Should prostaglandin E_1 or nitric oxide be ineffective, mechanical right ventricular support is indicated.



Right ventricular infarction. ST-segment elevation in leads V_4R and V_5R reveals right ventricular involvement complicating the inferior infarct.

If global ischemia is the cause of poor allograft function, recovery is likely. Even poorly functioning cardiac allografts can return to normal function after as little as 1 week. In most cardiac transplant recipients, measures of left ventricular function, such as ejection fraction, are normal within 1 to 2 weeks after transplantation. Resting hemodynamics tend to normalize over time as well.

Denervation and Reinnervation

Although the cardiac allograft is totally denervated at the time of transplantation, over a period of months to years it reinnervates at least partially in the majority of recipients (30,31,32,33 and 34). When totally denervated, the heart responds differently to many common cardiovascular medicines. The response to direct beta-adrenergic agonists (isoproterenol, dobutamine, epinephrine, norepinephrine) is qualitatively unchanged. The sympathomimetic amines that act indirectly by releasing catecholamines from nerve terminals (dopamine, ephedrine, metaraminol bitartrate, and mephentermine sulfate) are likely diminished, and supersensitivity to adenosine is occasionally seen.

Because of denervation, norepinephrine-induced hypertension does not cause reflex bradycardia. Oxymetazoline hydrochloride (Neo-Synephrine) would not be expected to cause reflex bradycardia. Similarly, atropine sulfate, edrophonium chloride, digoxin, and quinidine would not be expected to affect atrioventricular conduction.

Exercise Capacity

Despite demonstrably normal left ventricular function, most patients do not achieve a normal exercise capacity (32). Many patients are inadequately rehabilitated (33). In others, concomitant pulmonary or vascular disease limits exercise tolerance. Administered immunosuppressive agents, particularly corticosteroids, undoubtedly take their toll and likely affect even the structure of skeletal muscle in transplant recipients (34). Nonetheless, all recipients are encouraged to rehabilitate to the extent possible, preferably, at least early on, in organized cardiac rehabilitation programs.

Cardiac Arrhythmias

Sinus node dysfunction is common early after transplantation and appears to be more common when the traditional Lower and Shumway technique is used than when the bicaval technique is used. Transient bradycardia can be treated with temporary pacing or administration of theophylline. Permanent bradycardia, which can occur late after transplantation, eventually necessitates use of an electronic pacemaker in approximately 5% of patients.

A 55-year-old African-American male patient status post cardiac transplant. Note the accessory atrial rhythm as evidenced by the extra P waves in the inferior leads.

As with many other types of cardiac surgery, postoperative atrial tachyarrhythmias may occur and are generally approached as usual. Cardiac allograft rejection, however, is considered in the differential diagnosis, and the pharmacologic interventions need to take into account the denervation (35). Late after transplantation, recipient remnant atrial to donor atrial conduction (across the suture line) has been observed (36). Early on, postoperative ventricular ectopy can be seen, but it usually resolves without the need for long-term treatment. After the postoperative period, electrophysiologic disease may become manifest or may develop. Generally, traditional approaches are appropriate, including the use of antiarrhythmic agents, devices, or interventions.

CARDIAC ALLOGRAFT REJECTION

Pathophysiology of Cardiac Allograft Rejection (the Immune System)

Transplantation of an organ between members of the same species is known as allotransplantation; hence, the use of the term *cardiac allograft*. Alloantigens are molecules recognized as foreign (or nonself) by the recipient immune system. In the absence of immunosuppression, destruction of the organ bearing alloantigens occurs (37,38,39,40,41,42 and 43).

HLA antigens are serologically identified alloantigens that have been shown to correspond to the human major histocompatibility complex (MHC). These cell surface antigens are subclassified as MHC class I (HLA-A, HLA-B, and HLA-C) or MHC class II (HLA-DP, HLA-DQ, and HLA-DR) and have distinctly different roles in the rejection process.

The sequence of events leading to cardiac allograft rejection encompasses antigen recognition (Fig. 94.1A), primary and secondary (costimulatory) signals for T-cell activation (Fig. 94.1B), and T-cell proliferation and differentiation (Fig. 94.1C).

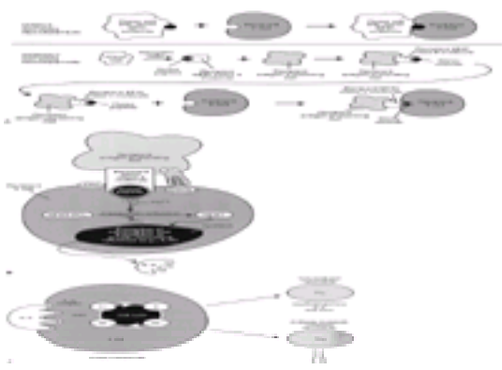


FIGURE 94.1 Sequence of events leading to cardiac allograft rejection, encompassing antigen recognition **(A)**, primary and secondary (costimulatory) signals for T-cell activation **(B)**, and T-cell proliferation and differentiation **(C)**. **A:** Antigen recognition. Direct recognition of alloantigen occurs when recipient T lymphocytes recognize major histocompatibility complex (MHC) molecules on the surface of foreign cells. Indirect allorecognition involves intermediate steps before T-cell recognition. Recipient cells take up foreign MHC molecules, degrade the protein into peptide antigens, and complex the resulting peptide with recipient MHC class II molecules. The recipient MHC class II molecule and the foreign peptide antigen complex are displayed on the cell surface of recipient antigen-presenting cells (macrophages, dendritic cells, or B cells), which enables recipient T-cell recognition of the foreign peptide and binding at the T-cell receptor. **B:** Primary and secondary (costimulatory) signals for T-cell activation. T-cell activation requires two signals. The first is the binding of the foreign peptide to the T-cell receptor (TCR). The second signal, shown here as a CD28/B7 receptor/ligand interaction, is an independent costimulatory signal. Together, the first and second signals trigger a series of calcium-dependent steps that lead to calcineurin dephosphorylation of a transcription factor, nuclear factor of activated T-cells (NFAT). NFAT binds to DNA elements in the promoter regions of many key cytokine genes [e.g., interleukin-2 (IL-2), interferon-g, and tumor necrosis factor (TNF)-a], which leads to the transcription and translation of growth-promoting cytokines. **C:** T-cell proliferation and differentiation. When growth-promoting cytokines (e.g., IL-2) bind to receptors on the surface of T lymphocytes, intracellular signaling occurs that allows the cell to enter the cell cycle and undergo mitosis (M) and clonal amplification. Undifferentiated T cells differentiate into Th_1 (cell-mediated cytotoxicity) or Th_2 [antibody (humorally)-mediated cytotoxicity] subsets depending on the influences of various cytokines. Both cell-mediated and humorally mediated cytotoxic immune responses may cause allograft destruction. G_1 and G_2, growth phases; S, synthesis phase; TOR, target of rapamycin.

Without an interaction of the T-cell receptor and antigen, T cells remain quiescent. The interaction with the T-cell receptor can be aided by a series of accessory molecules that alter the affinity, stability, and duration of the interaction. A number of intracellular signaling pathways are activated, which results in *de novo* expression of a range of genes, including those encoding cytokines [e.g., interleukin-2 (IL-2)] and new cell surface proteins.

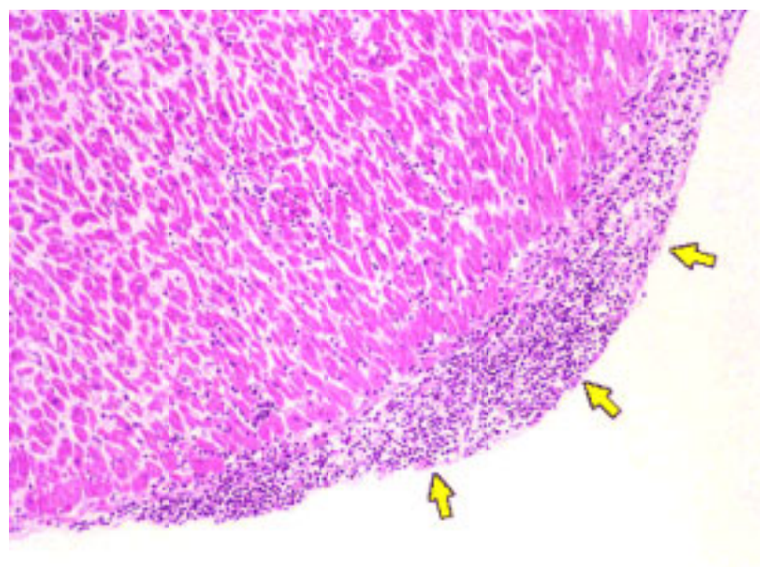
Once the primary signal is received, the destiny of a T cell depends on whether it receives a second signal (37). Without a second signal, a T cell may become apoptotic, anergic, or unresponsive, failing to progress through the cell cycle. Such a cell may inhibit the growth or activation of neighboring T cells in an antigen-specific fashion. Together, the first and second signals trigger a series of calcium-dependent steps that lead to calcineurin dephosphorylation of a transcription factor, nuclear factor of activated T-cells (NFAT). NFAT binds to DNA elements in the promoter regions of many key cytokine genes (e.g., IL-2, interferon-g, and tumor necrosis factor-a), which leads to the transcription and translation of growth-promoting cytokines.

When growth-promoting cytokines (e.g., IL-2) bind to their respective receptors on the surface of lymphocytes, intracellular signaling occurs via a number of tyrosine- and cyclin-dependent kinases, which allows the cell to enter the cell cycle and undergo mitosis and clonal amplification. Depending on the influences of various cytokines, undifferentiated T cells differentiate into T_H1 or T_H2 subsets. T_H1 cytokines (interferon-g, IL-2, tumor necrosis factor-b) are believed to promote cell-mediated and cytotoxic responses, and T_H2 cytokines (IL-4, IL-5, IL-6, IL-10, IL-13) promote humoral immune responses. Both cell- and humoral-mediated cytotoxic immune responses may then cause allograft destruction.

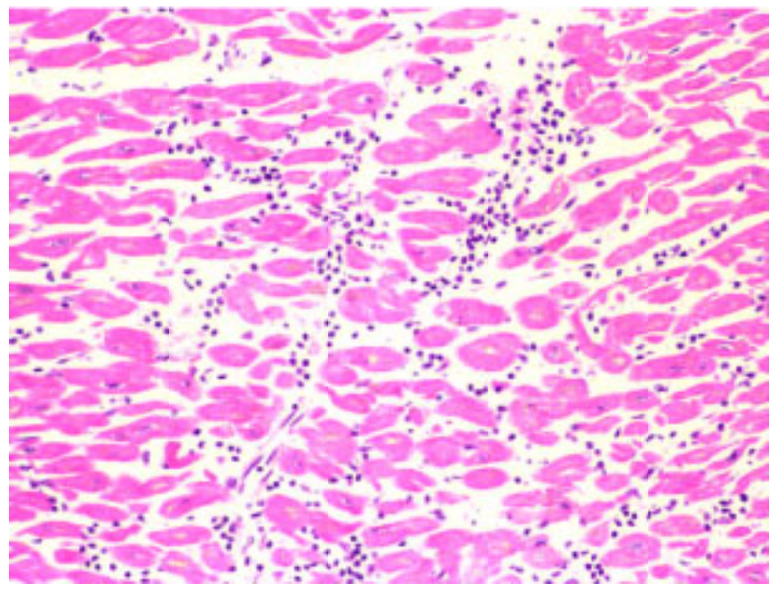
In brief, after the heart is transplanted, proinflammatory cytokines are elaborated and recipient inflammatory cells (e.g., macrophages) are recruited into the cardiac allograft. Donor passenger leukocytes migrate from the allograft into host lymphoid tissue, and recipient leukocytes enter the allograft. T-cell stimulation occurs via a T-cell receptor signal and a necessary costimulation signal. Cytokine production leads to the generation of effector cells for cell-mediated and antibody (humoral)-mediated immunity. Destruction of the allograft occurs via involvement of antibody, cytotoxic T lymphocytes, macrophages, and cytokines.

Types of Cardiac Allograft Rejection

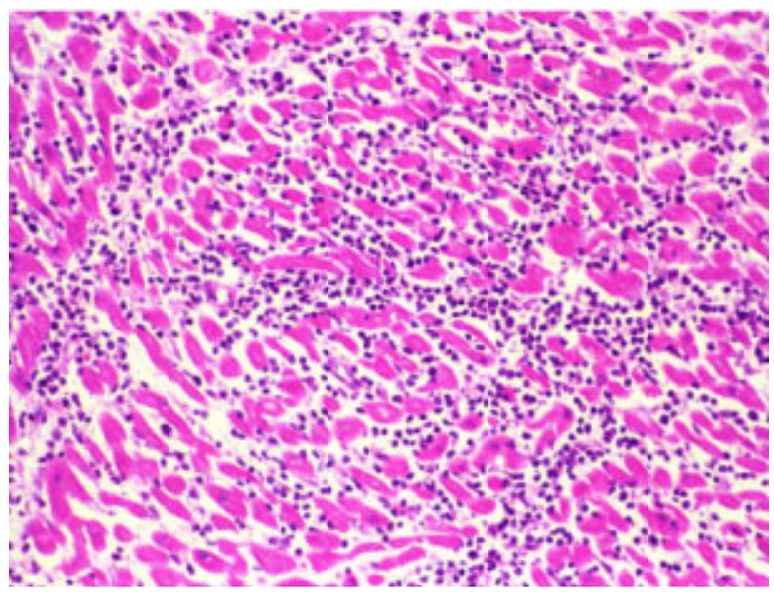
Cardiac allograft rejection is an immunologic process that, left unchecked, leads to allograft destruction. Rejection has been variously classified but may be defined histologically, functionally, or clinically. The most generally recognized categories are hyperacute, acute cellular, and acute vascular (humoral) rejection. In cardiac transplantation, the term *chronic rejection* generally refers to CAV.



“Quilty” lesion in a transplant heart. A benign infiltration of the endocardium (*yellow arrows*) with small lymphocytes can be seen in this section. The adjacent myocardium shows interstitial infiltration with lymphocytes, which is part of a multifocal acute rejection process seen elsewhere in the heart.



Mild acute rejection (grade 1A). Interstitial infiltration of lymphocytes with no myocyte damage in a transplanted heart.



Moderate acute rejection (grade 3A). Interstitial inflammatory infiltrate of large, aggressive lymphocytes in a transplanted heart.

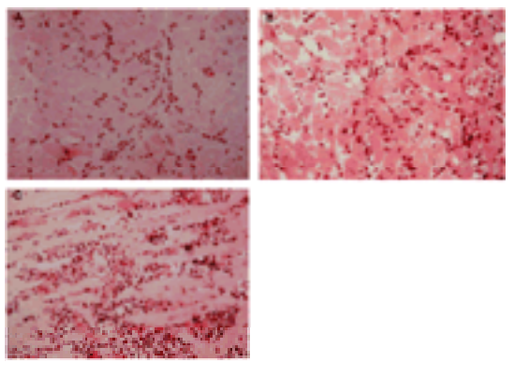
Although hyperacute rejection is due to preformed, donor-specific antibodies in the recipient, the presence of such antibodies does not always result in hyperacute rejection. When it occurs, hyperacute rejection is a vigorous immune response that takes place within minutes to hours. The outcome, without repeat transplantation or total artificial heart support, is uniformly fatal. The best method for avoiding hyperacute rejection is to avoid transplanting a donor heart into a patient who is sensitized to the donor (a positive donor-specific cross-match). Screening PRA is useful because prospective cross-matching is frequently impractical (44). PRA screening is performed by exposing recipient serum to lymphocytes from 50 or more random individuals. A normal result of 0% reactivity suggests a low risk that a retrospective cross-match would be positive. For PRA reactivity greater than 10%, prospective cross-matching is generally warranted (45,46).

Even a positive cross-match that does not result in hyperacute rejection may be associated with a more vigorous immune response (45). Patients with a positive cross-match generally require an increased intensity of immunosuppression or the initial use of plasmapheresis or both. Long-term survival, however, can be achieved with positive cross-match results in the absence of hyperacute rejection. Strategies for decreasing pretransplant PRA levels include use of intravenous gamma globulin or cyclophosphamide and plasmapheresis (46). Even in the absence of a positive cross-match, an elevated PRA level might by itself indicate a more challenging posttransplant course.

Acute cellular rejection is the most common form of rejection and occurs at least once in approximately half of heart transplant recipients (47). Even though the propensity toward allograft rejection decreases over time and nearly half of the rejection episodes occur in the first 2 to 3 months, late rejection can and does occur. Rejection occurring early after transplantation tends to be more aggressive and life-threatening than late-occurring rejection. Acute cellular rejection is most frequently diagnosed by endomyocardial biopsy graded in accordance with the International Society for Heart and Lung Transplantation (ISHLT) criteria (48) (Table 94.3 and *e*Fig. 94.1.1). Certain factors increase the risk for rejection. For instance, both increasing age and male gender appear to be associated with decreased cardiac allograft rejection (49,50). All patients are at risk for rejection, however, and are carefully followed regardless of demographic variables.

Grade	Finding	Rejection severity
0	No infiltrate, normal myocytes	None
1A	Focal perivascular or interstitial infiltrates without necrosis	Borderline mild
1B	Diffuse but sparse infiltrates without necrosis	Mild
2	One focus only with aggressive infiltrate and/or myocyte damage	Mild or focal moderate
3A	Multifocal aggressive infiltrates and/or myocyte damage	Moderate
3B	Diffuse inflammatory infiltrates with necrosis	Borderline severe
4	Diffuse aggressive polymorphous infiltrate with edema, hemorrhage, and vasculitis, with necrosis	Severe

TABLE 94.3 ENDOMYOCARDIAL BIOPSY GRADING SCALE USED BY THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION



***e*FIGURE 94.1.1** Lymphocytic infiltrate in endomyocardial biopsy specimens. Progressing from panel **A** to panel **C**, an increasing degree of lymphocytic infiltration is seen, indicative of worsening cardiac allograft rejection. These changes correspond to International Society for Heart and Lung Transplantation grades 1B **(A)**, 2–3A **(B)**, and 4 **(C)**.

Vascular rejection may be manifest by otherwise unexplained cardiac allograft dysfunction with or without histologic evidence. Histologic evidence is scant cellular infiltrate but abundant colocalized immunoglobulin and complement components in the allograft microvasculature seen on one or more biopsy specimens. In addition, vascular rejection may be manifest only histologically in the absence of allograft dysfunction (47).

Vascular rejection has been associated with a positive cross-match, the development of sensitization to OKT3, prolonged use of OKT3, female gender, and younger recipient age. Vascular rejection is more difficult to treat than acute cellular rejection and is more often accompanied by hemodynamic compromise or instability. As a result, vascular rejection is associated with a worse prognosis and appears to increase the risk of CAV nearly tenfold (47).

Diagnosis of Cardiac Allograft Rejection

Surveillance for allograft rejection generally centers on the routine use of endomyocardial biopsy (51). Endomyocardial biopsy is initially performed weekly (for the first 4 to 8 weeks) and then at gradually increasing intervals. Twelve to 24 months after transplant, biopsies are performed every 3 to 6 months. Over time, some patients are managed without routine endomyocardial biopsies (52). After the diagnosis of rejection, the endomyocardial biopsy interval is, of course, altered.

To perform an endomyocardial biopsy, venous access is obtained and an intravascular sheath is placed. A bioptome (either a disposable or a reusable Scholten bioptome) is directed under fluoroscopic or echocardiographic guidance to the right atrium with the tip pointing to the lateral wall. The handle is turned 180 degrees toward the interatrial septum and advanced through the tricuspid valve. Once the bioptome is in the right ventricle, the handle is rotated directly posteriorly, which directs the bioptome toward the right ventricular side of the interventricular septum. Only the septum is biopsied to prevent ventricular perforation. Biopsy specimens are obtained by opening the handle, advancing to the point of slight resistance or ventricular ectopy, closing the handles, and withdrawing the endomyocardial tissue. Four good specimens are usually required for adequate pathologic evaluation. Endomyocardial biopsy may also be performed via right subclavian vein and femoral vein approaches. Acute complications are rare but include cardiac perforation and pneumothorax. Inadvertent carotid puncture occurs occasionally and is generally benign. Long-term complications include occlusion of the jugular vein and damage to the tricuspid apparatus, which requires tricuspid valve replacement in some situations.

VIDEO

Video 94.1 Transesophageal echo with color Doppler showing tricuspid regurgitation after a myocardial biopsy of the right ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 94.2 Transesophageal echo demonstrating a flail tricuspid valve after right heart biopsy in a transplant patient. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Clinically, most rejection episodes are detected by surveillance endomyocardial biopsies and manifest no signs or symptoms. If the episode is symptomatic, the most frequent symptom is fatigue. Later in the rejection process, exercise intolerance or frank heart failure symptoms may occur. Physical findings, if present, may include relative hypotension (decrease in systolic blood pressure of more than 20 mm Hg from baseline), elevated jugular venous pressure, or a third heart sound gallop. Symptoms or signs such as those mentioned prompt an urgent endomyocardial biopsy. An enlarging pericardial effusion or worsened indices of systolic or diastolic function determined by echocardiography may herald rejection. Fever is an infrequent manifestation of rejection. Atrial or ventricular arrhythmias are considered indicative of allograft rejection until proven otherwise. Clearly, if the patient has significant allograft dysfunction, signs of heart failure may be present.

VIDEO

Video 94.3 Apical four-chamber view demonstrating a large pericardial effusion causing tamponade. Note the inability of the right side to fill. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Many noninvasive strategies for the early diagnosis of cardiac allograft rejection have been evaluated in an attempt to decrease the dependence on endomyocardial biopsy (53,54,55,56 and 57). Generally, sensitivities of 85% to 90% can be achieved with fair specificity. No technique has as yet eliminated the clinical practice of routine endomyocardial biopsy surveillance.

In infants, echocardiography almost completely supplants endomyocardial biopsy (53). In adults, echocardiographically derived indices, myocardial relaxation velocities determined by Doppler tissue imaging, integrated backscatter techniques, nuclear and magnetic resonance imaging, paced epimyocardial electrography, heart rate variability, measurement of immunologic markers, and many other methods have been evaluated (54,55,56 and 57).

Pharmacology of Immunosuppressive Agents

Suppression of the recipient immune system (Fig. 94.1) is necessary to prevent and treat cardiac allograft rejection. The pharmacology of currently available agents is summarized in Table 94.4. Polypharmacy is almost always used to minimize the toxicity of individual agents and to block the immune system in multiple locations (58,59,60,61,62,63,64,65,66,67,68,69,70,71 and 72). Immunosuppression is conveniently considered in three phases: early rejection prophylaxis (perioperatively and for the first several weeks after transplantation), long-term maintenance prophylaxis (immunosuppression in the absence of allograft rejection), and the augmentation in immunosuppression after the diagnosis of allograft rejection.

TABLE 94.4 PHARMACOLOGY OF IMMUNOSUPPRESSIVE AGENTS

Prevention and Treatment of Cardiac Allograft Rejection

Early Rejection Prophylaxis

To prevent cardiac allograft rejection perioperatively and for the first several weeks after transplantation, multiple agents are administered. Generally, “triple therapy” is used, consisting of (a) cyclosporine or tacrolimus; (b) azathioprine, mycophenolate mofetil, or sirolimus; and (c) corticosteroids (61,62,63,64,65,66,67,68,69,70,71 and 72). Although not perfect, triple therapy has proven to be simple and effective for most patients. In some patients with marginal renal function, early administration of cyclosporine or tacrolimus can lead to significant transient renal dysfunction and volume retention. To avoid the early use of cyclosporine or tacrolimus in patients at high risk of renal dysfunction (serum creatinine level higher than 2.0 mg per dL before transplant), OKT3, one of a variety of antilymphocyte globulins, or even IL-2 receptor blockers may be used perioperatively (67,68 and 69). Antilymphocyte antibody-based early rejection prophylaxis can safely delay cyclosporine or tacrolimus administration until after cardiac and renal function have stabilized. Disadvantages to using antilymphocyte antibody-based early rejection prophylaxis include first-dose reactions, greater expense, more complicated immunosuppression, and potentially more immunosuppressive side effects.

After binding to an intracellular binding protein (cyclophilin in the case of cyclosporine, FK binding protein in the case of tacrolimus), both cyclosporine and tacrolimus interfere with calcineurin and thus block the production of IL-2 in T lymphocytes (70). Disparate experience with the efficacy and tolerability of cyclosporine compared with tacrolimus is reported. In a U.S. multicenter trial, no clear advantage was seen with the use of tacrolimus (62). Rejection frequency, mortality, and degree of renal dysfunction were no different than with cyclosporine. In other trials tacrolimus has been found to be superior, especially when combined with mycophenolate mofetil (71). Tacrolimus therapy is associated with less hypertension, hirsutism, hyperlipidemia, and gingival hyperplasia but may have a higher incidence of neurotoxicity and glucose intolerance.

Both azathioprine and mycophenolate mofetil inhibit lymphocyte proliferation, but by different mechanisms. Azathioprine is metabolized to 6-mercaptopurine, which blocks DNA replication. Mycophenolate mofetil blocks the *de novo* pathway for purine biosynthesis by inhibiting the action of inosine monophosphate dehydrogenase. Lymphocytes rely almost exclusively on *de novo* biosynthesis for purines. Whether to use azathioprine or mycophenolate mofetil in early rejection prophylaxis depends on the interpretation of the findings of a multicenter trial comparing the two agents (64). However, interpretation of the results of the study is difficult. Eleven percent of transplant recipients in the study never received study medicine but were counted in the intent-to-treat analysis, and those in the group randomly assigned to receive mycophenolate mofetil experienced a higher mortality rate. No difference in rejection frequency, mortality, or morbidity is seen in the intent-to-treat analysis. On the other hand, if one analyzes data only for the patients actually taking at least one dose of study medicine, survival is better and rejection less frequent in the group randomly assigned to receive mycophenolate mofetil.

Trials with sirolimus and derivative of sirolimus (SDZ RAD) (72) are under way. Usually, these agents are substituted for the azathioprine or mycophenolate mofetil as part of triple therapy. After binding to the intracellular binding protein FK binding protein, they abrogate IL-2–driven effects by interfering with mitosis. Trials are also under way of basiliximab and daclizumab, monoclonal antibodies that block the IL-2 receptor (68,69). In cases of renal transplantation, both decrease rejection episodes by approximately one-third.

Long-Term Maintenance Immunosuppression

The majority of patients is maintained long term on triple therapy. Because the propensity to reject decreases over time, dosages of all three drugs may be decreased accordingly. Cyclosporine and tacrolimus are usually maintained long term at levels less than half of those used early after transplant. Similarly, although azathioprine may have been used early after transplant to target white blood cell counts in the 4,500 to 5,500 per mm^3 range, long-term doses larger than 2 mg per kg per day are generally not used. Long-term doses of mycophenolate mofetil generally decrease from 3,000 mg per day to 2,000 mg per day. Prednisone can safely be withdrawn in patients who demonstrate a low propensity to reject (73). Advantages of corticosteroid-free maintenance immunosuppression include reversal of most corticosteroid-induced side effects.

Treatment of Established Cardiac Allograft Rejection

The treatment of cardiac allograft rejection depends on several factors: severity of rejection (ISHLT grade of endomyocardial biopsy specimens), time since transplant, rejection and immunosuppressive history, and hemodynamic status of the patient. Even “mild” rejection (ISHLT grades IB and II) may warrant augmentation of immunosuppression in the setting of allograft dysfunction. In treating rejection, one generally optimizes or increases the dosages of maintenance immunosuppressors and markedly increases corticosteroid dosages. In corticosteroid-refractory rejection or in rejection episodes associated with hemodynamic instability, antilymphocyte antibodies such as OKT3 or one of a variety of antithymocyte globulins are added. Mild rejection in hemodynamically stable patients, those without evidence of allograft dysfunction, is not treated. Some data, however, suggest that occurrence of even mild rejection may increase the likelihood of CAV. Moderate rejection in the absence of hemodynamic instability is usually treated initially with a several-day course of either intravenous or high-dose oral corticosteroids. If a subsequent biopsy specimen shows resolution, the maintenance dosages are continued. If a subsequent biopsy specimen does not show resolution, however, then intravenous corticosteroids are used. Failure of a second course of corticosteroids to resolve the rejection episode generally leads to the use of antilymphocyte antibodies (*e*Fig. 94.1.2).

***e*FIGURE 94.1.2** Algorithm for the treatment of cardiac allograft rejection in patients taking cyclosporine and azathioprine as maintenance immunosuppression. Early: less than 3 months from transplant; hemodynamic instability: decrease in ejection fraction, elevated filling pressures, or hypotension; prednisone: oral corticosteroids, usually given as prednisone 1 to 2 mg per kg per day for 3 to 5 days followed either by an immediate return to maintenance doses or with a 1- to 2-week gradual

tapering to maintenance doses; methylprednisolone: intravenous corticosteroids, usually given as methylprednisolone 500 to 1,000 mg daily for 3 days followed either by an immediate return to maintenance dosages or by a 1- to 2-week gradual tapering to maintenance doses; MMF: mycophenolate mofetil; OKT3: muromonab-CD3 monoclonal antibody given for 7 to 14 days; ATG: antithymocyte globulin given for 7 to 10 days; thymoglobulin: thymoglobulin given for 7 to 10 days.

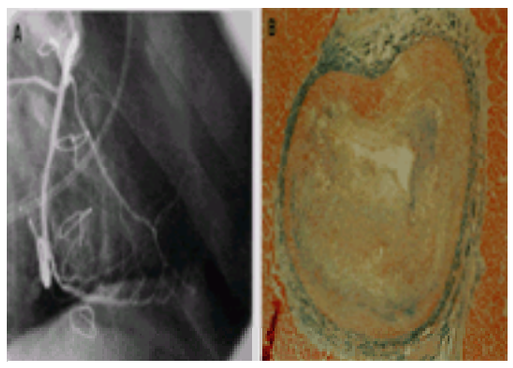
Rejection frequently may be treated by changing the maintenance immunosuppression. For instance, mycophenolate mofetil may be substituted for azathioprine, or tacrolimus for cyclosporine, or both substitutions may be made (74). Sirolimus may be added to or substituted into the regimen. The most vexing problem in immunosuppressive management is treating recurring or refractory rejection. Patients who require high dosages of maintenance immunosuppressive agents are at high risk of developing untoward, life-threatening immunosuppressive side effects. In difficult situations, one can add an agent to the treatment regimen (e.g., methotrexate sodium or sirolimus), consider the substitutions mentioned earlier, or even consider total lymphoid irradiation (75). An interesting new approach to dealing with rejection is photopheresis, which has been shown to decrease rejection when given as early rejection prophylaxis and may be able to treat ongoing rejection (76).

CARDIAC ALLOGRAFT VASCULOPATHY

Pathophysiology of Cardiac Allograft Vasculopathy

After the first few years posttransplantation, CAV is the leading cause of death and the cause of significant morbidity (2,77,78). The prevalence of angiographically detectable disease approaches 50% to 60% at 5 years. The prevalence of disease detected by intravascular ultrasonography or at autopsy is greater. Thus far, the improvements in immunosuppression have not greatly affected the incidence and morbidity associated with CAV development. CAV is not a homogeneous disease; rather, it changes over time. Early, CAV is characterized by diffuse and distal involvement, whereas later-onset coronary artery disease is more proximal, focal, and eccentric. Because the vasculopathy is localized to the vascular bed of the transplanted heart, CAV cannot be totally explained by any property of the medications used after cardiac transplantation.

Histologically, CAV is characterized by proliferation and migration of smooth muscle cells, proliferation and migration of macrophages, intact elastic lamina, increased ground substance and foam cells, and macrophage-engulfed cholesterol (*e*Fig 94.1.3) (79). Angiographically, several types of lesions have been described, as shown in Figure 94.2 (80).



***e*FIGURE 94.1.3** Right coronary artery 3.5 years after cardiac transplantation. **A:** Angiograph of the right coronary artery, taken 1 week before explantation for retransplantation in a 35-year-old man with unexplained allograft dysfunction, was relatively normal. **B:** Trichrome stain of the midportion of the right coronary artery of the explanted heart shows extensive allograft coronary artery disease.

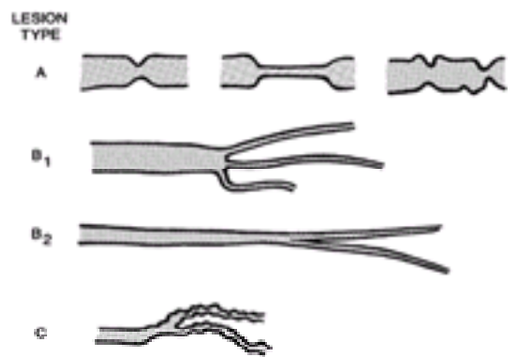


FIGURE 94.2 Types of lesion seen in cardiac allograft vasculopathy. Cardiac allograft vasculopathy can present with a variety of lesions, most of which are not amenable to revascularization. (From Gao SZ, Alderman EL, Schroeder JS, et al. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings. *J Am Coll Cardiol* 1988;12:334–348, with permission.)

P>Various risk factors have been identified for the development of CAV diagnosed by angiography, intravascular ultrasonography, or angioscopy (2,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94 and 95). Although older donor hearts are associated with an increased risk of the development of CAV at 3 years after transplantation [risk = 1.0 + 0.073 per year for each additional year of donor age above 30 years; p <.0001 (2)], given the significant and growing donor to recipient disparity, older donor hearts will likely continue to be used with even greater frequency. Not surprisingly, coronary artery disease leading to the need for cardiac transplantation is associated with a 33% increased risk of developing CAV at 3 years (2). The influence on CAV of the more common risk factors for native coronary artery disease (e.g., hypertension, diabetes, cigarette use, hyperlipidemia, hyperhomocysteinemia, low folate and vitamin B_6 concentrations) is likely greater later after transplantation (82,83).

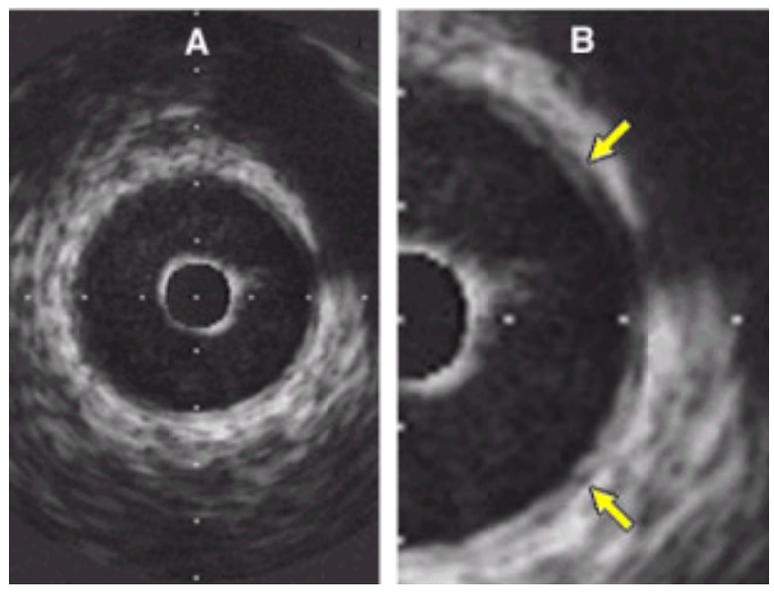
Many other possible risk factors for CAV have been evaluated. The frequency and type of rejection; the degree of HLA matching; increased levels of endothelin; the presence of endothelial cell–derived mesenchymal growth factors; cytomegalovirus (CMV) infection; the expression of various chemokines, cytokines, or serum cardiac troponin-T concentrations; the quantity of various apolipoproteins; MHC class II expression; gene polymorphisms for plasminogen activation factors; the quantity of various anticoagulation factors; and even race and ethnicity have been assessed as being potentially contributive (84,85,86,87,88,89,90,91,92,93,94 and 95).

Diagnosis of Cardiac Allograft Vasculopathy

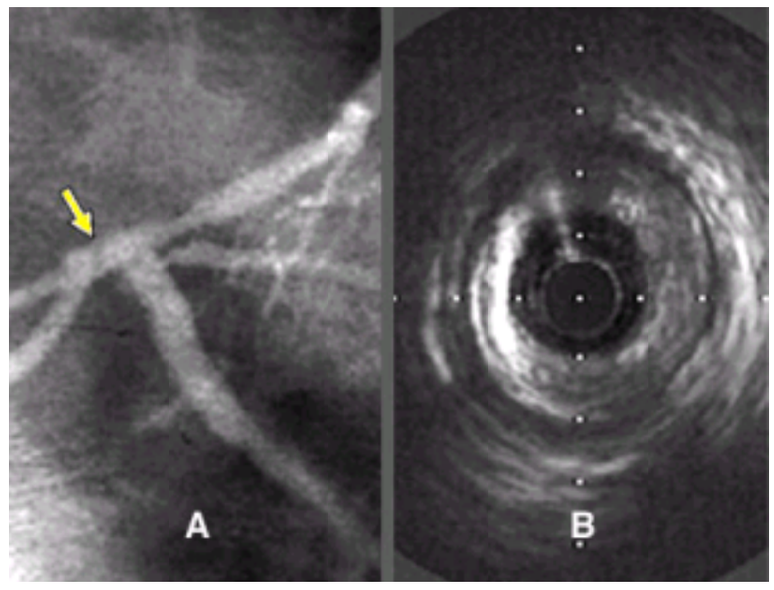
The clinical presentation of CAV early after transplant may be silent, manifesting as acute myocardial infarction, congestive heart failure, arrhythmias, wall motion abnormalities, or sudden death. Later, typical angina pectoris may occur due to focal, albeit incomplete, reinnervation. Most CAV is diagnosed by routinely scheduled yearly surveillance angiography, although many noninvasive techniques have been evaluated in an attempt to decrease the need for invasive testing (96,97 and 98).

Exercise or dobutamine stress echocardiography is frequently used to screen for disease and at times replaces routine surveillance angiography. Dobutamine stress echocardiography may also be able to track the progression of established CAV (96). A negative dobutamine stress echocardiogram is associated with a low risk of cardiac events. Nuclear techniques, for example, stress thallium scintigraphy and positron emission tomography, may also be used (97,98). Some characteristics of the endomyocardial biopsy specimen may predict the presence of CAV.

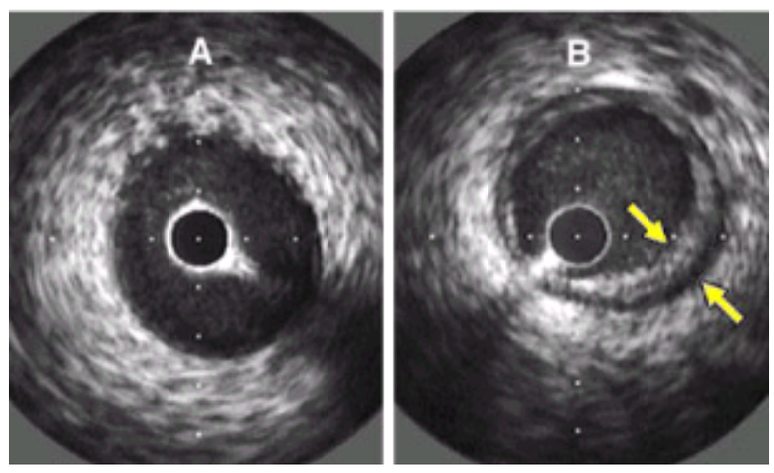
Regrettably, angiography is insensitive in detecting CAV (eFig. 94.1.3). Compared with angiography, intravascular ultrasonography (or other techniques, see Chapter 85) is more sensitive, detecting disease in a much larger percentage of patients (99,100). Intravascular ultrasonography predicts the development of angiographic coronary artery disease and is predictive of morbidity and mortality (99). However, early diagnosis of CAV has not been shown to affect long-term outcomes.



Normal coronary wall morphology by intravascular ultrasound. A trilaminar appearance is apparent with distinct layers representing the intima, media, and adventitia (B, *arrows*).



Limitation of angiography. The concentric plaque in the left main trunk (A) was not clearly defined by angiography because of the diffuse nature of the disease. Intravascular ultrasound examination demonstrates a major area reduction by concentric plaque (B).



Serial intravascular ultrasound study in a cardiac transplant patient. The baseline intravascular ultrasound study (A), 1 month after transplantation, shows a normal left anterior descending artery. After 1 year (B), there is obvious thickening of intima with a concentric distribution pattern.

Treatment of Cardiac Allograft Vasculopathy

Treatments need to be developed that prevent disease, halt disease progression, and effectively ameliorate significant CAV. For both primary prevention and the prevention of progression of established disease, conventional risk factors for coronary disease should be eliminated, minimized, or controlled. Although such risk factor reduction may not affect the early aggressive form associated with intimal hyperplasia, the later form may be impacted.

The treatment of established disease appears to be limited to retransplantation and revascularization techniques, because augmented immunosuppression has not been conclusively shown to prevent progression. Retransplantation is the only option for patients with type B and C lesions, especially because transmyocardial laser revascularization is unlikely to be beneficial in the long term with current techniques (101). Retransplantation for CAV can, if performed years after the initial transplantation, result in survival rates of nearly 80% at 1 year after retransplantation (2).

Percutaneous revascularization in the presence of distal disease, even for type A lesions, is associated with a poor outcome, whereas revascularization in the presence of angiographically normal distal coronary arteries is associated with better outcomes. The use of coronary artery bypass grafting is considered in some situations. Given the results seen with retransplantation and the current donor to recipient disparity, aggressive use of interventional or surgical treatment or both to prolong the life of the cardiac allograft, if possible, seems prudent.

COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

The complications encountered after cardiac transplantation are legion. Recipients are at risk for cardiac, immunosuppression-related, and other complications. Although largely not preventable, most problems can be mitigated, at least in part. The cardiac complications have been addressed earlier in this chapter.

Immunosuppression-Related Complications

Infectious Complications

Infection is common in organ transplant recipients (102). The types of infections expected in cardiac transplant recipients vary depending on the time from transplantation. This is because the intensity of immunosuppression administered varies directly with the propensity for rejection, and the propensity to reject decreases over time. Figure 94.3 depicts the changing frequencies of bacterial, viral, protozoal, and fungal infections after transplantation (103).

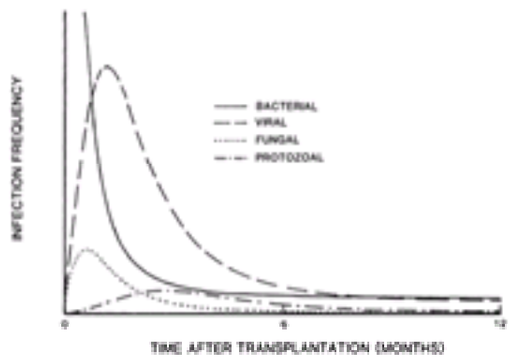


FIGURE 94.3 Risk of infection after cardiac transplantation. The risk of infection from various etiologic agents peaks at different times after cardiac transplantation. (Adapted from Miller LW, Naftel DC, Bourge RC, et al. Infection after heart transplantation: a multiinstitutional study. *J Heart Lung Transplant* 1994;13:384, with permission.)

Bacteria and viruses account for more than 80% of infections after transplantation. The most common bacterial infections early after transplantation are nosocomial, due to infected intravascular catheters or lines, or gram-negative pneumonias. As can be seen in Figure 94.3, the risk decreases rapidly over time. The most common viral infections are caused by herpes viruses, CMV, and herpes simplex. Although CMV infection used to be associated with significant morbidity and mortality, the use of ganciclovir has significantly improved the prognosis (104,105). However, ganciclovir-resistant CMV is occasionally seen. Patients who are CMV seronegative who receive a heart from a seropositive donor are at greatest risk for aggressive disease. Attempts to prevent CMV disease in these patients have been less fruitful than in patients who are seropositive before transplantation. Although fungi and protozoa account for less than 15% of infections after transplantation, such infections can be associated with the worst prognosis (106). Fungal infections occur in patients who require intensive treatment over a prolonged period before transplantation or in whom significant rejection occurs in the setting of a bacterial infection that requires the use of broad-spectrum antibiotics.

The overall incidence of infection is approximately 0.5 infections per patient, although as many as two-thirds of patients remain free from serious infections during the first year. The most common site of infection is the lung, accounting for up to one-third of all infections. Although most serious infections are treated successfully, infection remains a leading cause of death during the first year (103).

Given the potential morbidity and mortality associated with infections during the first posttransplant year, infection prophylaxis is common. This has reduced the morbidity and mortality after cardiac transplantation for CMV infection, *Pneumocystis carinii* pneumonia, and toxoplasmosis (107,108). Prophylactic regimens are commonly used against CMV (if either recipient or donor is seropositive), toxoplasmosis (especially if the recipient tests negative and the donor tests positive), *P. carinii*, *Candida albicans*, and herpes simplex (*e*Table 94.4.1). Whether or not influenza vaccines should be given is not entirely clear. Concern exists about administering them early after transplantation; however, they are given to recipients who are at high risk (109).

***e*TABLE 94.4.1** INFECTION PROPHYLAXIS AFTER CARDIAC TRANSPLANTATION

Organism	**Regimen**
Cytomegalovirus (recipient seropositive)	Ganciclovir 5 mg/kg i.v. b.i.d. for 2–4 wk, then 1,000 mg p.o. t.i.d. until 1 mo posttransplant, then acyclovir 800 mg p.o. q.i.d. until 2–3 mo posttransplant
Cytomegalovirus (recipient seronegative and donor seropositive)	Ganciclovir 5 mg/kg i.v. b.i.d. for 2–4 wk, then 1,000 mg p.o. t.i.d. until 3 mo posttransplant
Herpes simplex	Acyclovir 200 mg p.o. q.i.d. until corticosteroid dosage <20 mg prednisone/d
Epstein-Barr virus (recipient seronegative and donor seropositive)	Acyclovir 800 mg p.o. q.i.d. for 12 mo, then 200 mg p.o. q.i.d.
Toxoplasma gondii (donor or recipient seropositive)	Pyrimethamine 25 mg p.o. q.d. for 6 wk and leucovorin calcium 5–10 mg p.o. q.d. for 6 wk
Pneumocystis carinii	Trimethoprim maleate/sulfamethoxazole 160 mg/800 mg p.o. 3–7 times per wk or dapsone 75–100 mg p.o. q.d. if sulfa allergic
Candida albicans	Nystatin 10 mL swish and swallow q.i.d. or clotrimazole troche p.o. q.i.d. until corticosteroid dosage (prednisone) <20 mg/d

Renal Insufficiency

Five years after heart transplantation, 8.5% of recipients have a serum creatinine level higher than 2.5 mg per dL, and 1.9% require long-term dialysis (2). Although some renal dysfunction is related to preexisting renal disease, most is acquired. Cyclosporine and tacrolimus are nephrotoxic and probably account for the majority of renal problems (110,111,112 and 113). Minimizing the dosages of these and other nephrotoxins, avoiding dehydration, and searching carefully for nonimmunosuppression-related reversible causes are warranted (111).

Whether some individuals are at greater than usual risk for cyclosporine- or tacrolimus-related nephrotoxicity is not known (112). Once renal dysfunction occurs, the course is variable. Some patients progress quickly to dependence on dialysis, whereas others do not. Costs are likely increased and prognosis worsened in heart transplant patients with significant renal dysfunction (113).

Hypertension

After transplantation, hypertension occurs in approximately two-thirds of recipients (2). Hypertension is more prevalent in cyclosporine-treated recipients (70% to 90%) than in tacrolimus-treated recipients (30% to 50%). In nontransplant patients, hypertension is a significant risk factor for vascular disease and to assume otherwise in transplant recipients is unwise. The role of hypertension in the development of renal dysfunction and CAV among long-term survivors is not known.

Even though most hypertensive cardiac transplant recipients require pharmacologic treatment, moderate limitation of salt intake, maintenance of ideal body weight, and moderate exercise are encouraged. Generally, blood pressures consistently greater than 140/90 mm Hg are treated. Either angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers in conventional dosages are effective monotherapy for many patients (114,115). Some patients are prone to hyperkalemia due to the combined effect of cyclosporine and ACE inhibition on the kidney. Due to decreased metabolism of cyclosporine and tacrolimus, the use of either diltiazem or verapamil necessitates lowering of the dosages of cyclosporine or tacrolimus and initially more frequent cyclosporine or tacrolimus level monitoring. Use of both an ACE inhibitor and a calcium channel blocker is effective in many patients in whom neither class of drugs alone is sufficient. Diuretics are effective in some patients, although rarely as monotherapy. Dehydration should, of course, be avoided with the concomitant use of cyclosporine or tacrolimus.

In some patients, hypertension is inadequately controlled despite the use of maximally tolerated dosages of both calcium channel blockers and ACE inhibitors. Clonidine, beta-blockers, hydralazine, prazosin, or even minoxidil may be effective. In some patients, changing from cyclosporine to tacrolimus or minimizing the dosage of cyclosporine may be helpful.

Osteoporosis

By the time most patients undergo cardiac transplantation, the risk of osteoporosis and other skeletal complications is high. Prolonged inactivity and, in some cases, prolonged heparin administration can demineralize bone and put the patient at risk for complications. Further bone loss occurs due to high-dose corticosteroid therapy. Bone loss is rapid in the first 6 months after transplantation and is most marked in the lumbar spine. Vertebral compression fractures and aseptic necrosis of the femoral head are among the most common skeletal problems after heart transplantation. Due to the morbidity associated with osteoporosis, patients at risk are treated (116,117 and 118). Postmenopausal women are generally prescribed estrogen replacement therapy. Postmenopausal women and all patients with evidence of pretransplant osteoporosis receive calcium salts (e.g., calcium carbonate 1,000 to 1,500 mg per day in divided doses) and upwardly titrated doses of calcitriol (beginning at 0.25 µg every other day) while awaiting transplantation and indefinitely thereafter (116). Alendronate sodium (10 mg per day) may effectively increase bone density and can be safely added to calcium salts and calcitriol (117).

Treatment of bony complications of the spine is supportive. Clearly, maintaining physical activity and ideal body weight are important measures (118). Physical

therapy is helpful. Joint replacement is successful in the vast majority of posttransplant patients and should be recommended as indicated.

Hyperlipidemia

After cardiac transplantation, hyperlipidemia is common (119) and requires treatment in as many as 50% of recipients (2). All patients are encouraged to limit intake of cholesterol and other fats, maintain ideal body weight, and exercise. Minimization of corticosteroid dosage, when possible, is also generally helpful. Serum cholesterol levels greater than 200 mg per dL (or levels of low-density lipoprotein cholesterol above 100 mg per dL) are treated. If levels are not successfully lowered with dietary and other behavior modification, pharmacologic treatment is instituted. Although use of gemfibrozil (in doses up to 600 mg twice daily) can be successful is some patients with mild to moderate hyperlipidemia, particularly in the setting of hypertriglyceridemia, moderate to severe hypercholesterolemia generally requires the use of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (119,120). The combination of cyclosporine or tacrolimus and an HMG-CoA reductase inhibitor increases the risk of rhabdomyolysis over that for the HMG-CoA reductase inhibitor alone. When used, HMG-CoA reductase inhibitors should be started at low dosage and the dosage should be increased periodically while levels of creatine kinase and liver enzyme are monitored. Combining an HMG-CoA reductase inhibitor with gemfibrozil or nicotinic acid in lipid-lowering doses (1 g per day or more) can cause rhabdomyolysis, and these combinations are used cautiously in transplant patients. Bile acid sequestrants, probucol, and fish oil (omega-3 free fatty acids) are infrequently used to treat hyperlipidemia after transplantation.

Preexisting hyperlipidemia, corticosteroid therapy, and the use of cyclosporine or tacrolimus play a role in the development of hyperlipidemia. Because it is a risk factor for vascular disease in nontransplant patients, hyperlipidemia could also be a risk factor for cerebrovascular and peripheral vascular disease in transplant patients. Hypertriglyceridemia has frequently been shown to be a risk factor for the development of CAV and hypercholesterolemia has occasionally been shown to be a risk factor, and aggressive treatment seems to lead to regression of existing disease.

Malignancy

After transplantation, cardiac allograft recipients have an increased risk of malignancy compared with the general population. The overall degree of immunosuppression may be more important than any intrinsic property associated with a particular drug. Care is taken to avoid overimmunosuppression. By 5 years after transplantation, nearly 10% of survivors have experienced a malignancy (2). Fortunately, nearly half are skin cancers, occurring predominantly in those who would otherwise be at risk (121). Because locally invasive skin cancer can be fatal if not treated promptly and adequately, routine screening is performed. Posttransplant lymphoproliferative disease (PTLD) occurs in less than 2% of patients (122). PTLD can be refractory to any treatment or relatively localized and benign, responding simply to reduction in immunosuppression (123). The Epstein-Barr virus (EBV), a lymphotropic virus that infects more than 90% of the population by adulthood, is thought to be the etiologic agent responsible for most cases of PTLD (123,124).

Among patients who are seropositive for EBV before transplantation, the incidence of PTLD is low, approximately 1%. The incidence of PTLD in patients who are seronegative for EBV before transplant and who receive an organ from an EBV-seropositive donor may be as high as 50%. Preemptive antiviral therapy may be helpful (124). Treatment of PTLD usually involves reduction of immunosuppression, administration of acyclovir, and chemotherapy for widespread disease.

Although other malignancies occur in heart transplant recipients, the behavior of prostate, breast, and cervical cancer and of other solid tumors seems no different than in the general population.

Glucose Intolerance

Although nearly 20% of cardiac transplant survivors develop frank diabetes within the first year, by 5 years after transplantation, only 15% would be classified as diabetic (2). This is likely related to the use of decreasing dosages of immunosuppressive agents, in particular, corticosteroids. No evidence exists that cardiac transplant recipients should be treated differently with regard to diabetic control in terms of target levels of blood glucose and glycosylated hemoglobin and the agents used to treat them.

Other Age-Related Complications

Other diseases that are associated with aging that likely have nothing to do with the events surrounding the management of transplantation should not be ignored. Usual health maintenance measures need to be carried out. Breast cancer, cervical cancer, and prostate cancer screening is recommended.

Biliary Disease

The incidence of biliary disease is greater in cardiac transplant recipients than in nontransplant patients (125). The incidence may be as high as 8%, which represents a 17-fold increase over the incidence in the general population.

During transplantation, the vagus nerve is transected. Because gallbladder emptying is controlled by both neural and humoral factors, the resulting gallbladder denervation increases the risk of cholelithiasis. Thus, after transplantation, patients depend solely on cholecystokinin to stimulate gallbladder contraction. Cyclosporine increases the risk of cholelithiasis because of its lithogenic and cholestatic properties.

Generally, presence of any abdominal symptoms coupled with cholelithiasis warrants surgical intervention. Laparoscopic cholecystectomy is the procedure of choice in uncomplicated situations (126).

Pregnancy

Successful pregnancies after heart transplantation have been reported (127). Maternal and fetal risk is undoubtedly higher than in the general population and transplant recipients are so counseled. Once the recipient is pregnant, close collaboration with an obstetrician knowledgeable with regard to high-risk cases is warranted to avoid teratogenic drugs and manage the pregnancy. Immunosuppressive drug levels are monitored frequently, as volume changes and metabolic changes occur during pregnancy. Radiation exposure can be minimized by using echocardiographically guided endomyocardial biopsies.

Management of the Cardiac Transplant Recipient Undergoing Surgery

Due to bone complications, biliary disease, and other surgically amenable problems, many cardiac transplant recipients undergo noncardiac surgery. In general, antibiotic prophylaxis is used for dental procedures and other procedures in which the risk of septicemia is high. The risk associated with noncardiac surgery depends on the status of the allograft. In patients without ongoing rejection, significant coronary disease, or left ventricular dysfunction, the risk is low. Before all elective procedures, an endomyocardial biopsy is performed, and the most recent angiogram is reviewed. Patients receiving corticosteroids within the preceding 9 months receive stress doses of corticosteroids. If intravenous immunosuppressants are to be needed due to prolonged ileus, appropriate dosage adjustments are made.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Controversies in Recipient Selection

The impact of cardiac transplantation on the mortality of patients with end-stage heart failure should not obfuscate the fact that the need for transplantation generally represents a failure of heart muscle disease prevention or early detection and treatment. Viewed simplistically, decreasing the number of patients who could benefit from cardiac transplantation by preventive and early treatment measures is of greater importance than perfecting cardiac transplantation for those who need it.

Medical advances have made it possible to successfully transplant patients who were previously considered inappropriate candidates. Although individual patient advocacy is admirable, physicians bear a responsibility in their stewardship over donor hearts. Physicians must balance two competing interests—those of individual patient advocacy and societal responsibility—to ensure that appropriate candidates are given donor hearts.

Controversies in Transplant Center Restriction

The United States currently has over 150 heart transplant centers. Given that just over 2,000 heart transplants are performed in the United States each year, the average is a little over one transplant per center per month. Data suggest that centers performing a low number of transplants do so with increased risk to recipient

survival. Therefore, reason suggests that the number of centers should be limited to improve overall patient survival, to ensure continued expertise, to further develop the science and art of transplantation, and to minimize cost.

Cost of Transplantation: Who Should Pay?

An unstated consideration in selecting a transplant candidate is the ability to pay. Many heart transplant centers will not list a patient unless funding for the procedure is secure. Patients from lower socioeconomic classes are not afforded the same opportunity for transplantation as others. The answer to the question of who should pay is not unique to transplantation but underlies much of the policy that governs health economics (128). The only resource scarcer than funding is donor hearts.

THE FUTURE

During the next decade, the induction of donor-specific tolerance will be furthered, which will decrease the need for pharmacologic immunosuppression. Because both xenotransplantation and permanent mechanical circulatory support systems will emerge as clinically appropriate, the donor to recipient disparity will stabilize as alternatives to allotransplantation are provided for selected patients with end-stage heart disease.

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SURGICAL TREATMENT OF HEART FAILURE

NICHOLAS G. SMEDIRA

"Indicates text or graphics that appear only in the electronic versions of this text."

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INTRODUCTION

Heart failure is a major epidemic. Patients who would have otherwise died after acute coronary events or patients with chronic ventricular dysfunction are surviving, albeit with reduced left ventricular (LV) function and diminished quality of life. Medical therapies for these patients have improved dramatically, but survival in patients with advanced heart failure remains poor. Similar to medical therapies, great strides have been made in the surgical treatment of patients with cardiac disease. Currently, the mortality for primary and reoperative coronary artery bypass grafting (CABG) at The Cleveland Clinic Foundation is less than 2%. Improvements in preoperative medical care, anesthetic management, perfusion technology, myocardial protection, inotropic agents, intensive care unit care, and postoperative medical therapy all have played important roles. These advances have encouraged the application of surgical techniques to patients with severe heart failure resulting in similarly low morbidity and mortality.

The goal of this chapter is to review the current state of surgical interventions for chronic heart failure. The focus is on surgical risk assessment, management of ischemic cardiomyopathy with revascularization and remodeling, mitral valve procedures, and LV assist devices (LVADs). Acute cardiogenic shock and mechanical complications of acute myocardial infarctions (MIs) are addressed in Chapter 19. Because the field is rapidly changing, an effort was made to summarize information published in the last decade, and references are limited to important contributions in each area during this time period. Surgical videos and illustrations of the various procedures described are present on the CD-ROM that accompanies this textbook.

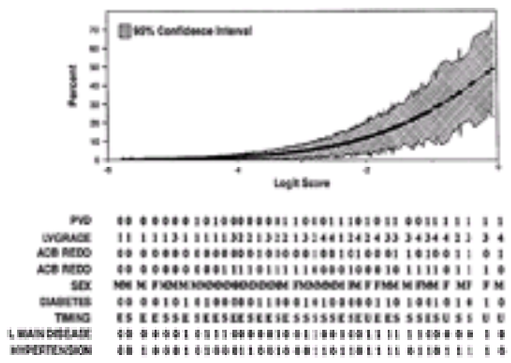
RISK ASSESSMENT

Patients at the highest risk for surgical morbidity and mortality are often the patients most likely to gain some improvement in quality of life or a survival benefit. Solid data are now available to estimate the risk of coronary revascularization and valvular intervention. What is often much more difficult is determining whether functional recovery of the ventricle will occur postoperatively and whether this is in fact a prerequisite for symptom resolution or has a survival advantage.

Series evaluating this early risk of coronary revascularization have concluded that the degree of LV dysfunction is no longer important. This is probably incorrect and reflects the practice of defining LV dysfunction at some arbitrary relatively high level of ejection fraction (EF). Rao et al. reviewed the Toronto General Experience in 4,558 CABG patients (1). The strongest predictor of mortality was LVEF less than 20%. When compared with patients with EFs between 20% and 40%, the mortality for patients with EF less than 20% increased from 3% to 11% (Table 95.1). The addition of advanced age, reoperation, and the need for emergency operation significantly increases the risk of revascularization. Using the equation generated by the analysis, an institution can input the variables and arrive at the patient's estimated risk (eFig. 95.0.1).

Variable	Odds ratio	95% Confidence interval
Left ventricular ejection fraction		
40–60%	1.62	(0.93–2.83)
20–40%	2.02	(1.11–3.68)
<20%	8.10	(3.91–16.80)
Repeat operation	4.86	(2.97–7.95)
Age ≥70 yr	2.79	(1.85–4.19)
Emergency operation	2.69	(1.25–5.79)

TABLE 95.1 ODDS RATIO FOR MORTALITY AFTER CORONARY REVASCULARIZATION



***e*FIGURE 95.0.1** Logit score for mortality after coronary artery bypass grafting as determined by Rao et al. ACB, arterocoronary bypass; E, elective; LV, left ventricular; PVD, pulmonary valve disease; S, semielective; U, urgent. (From Rao V, Ivanov J, Weisel RD, et al. Predictors of low cardiac output syndrome after coronary artery bypass. *J Thorac Cardiovasc Surg* 1996;112:38–51, with permission.)

Other risk factors in patients with ischemic cardiomyopathy include obesity, poor target vessels for revascularization, need for intraaortic balloon pump, and severity of congestive heart failure (CHF) symptoms or New York Heart Association (NYHA) functional class (2,3,4,5 and 6).

The presence of clinical heart failure deserves attention. In general, there is a poor correlation between EF and functional class. From the Duke database, approximately 20% of patients were in NYHA class IV in each quintile of EF below 55% (7) (Table 95.2). Olhshansky et al. reviewed data from the CABG Patch trial, which shows that when corrected for degree of CHF, EF failed to predict outcome across EF quartiles (eTable 95.2.1) (8). If they arbitrarily selected EFs above and below 0.27, then CHF predicted mortality in each group (eTable 95.2.2). These data support clinical experience that has found that the EF is at best a rough indicator of clinical well-being and that therapy to eliminate or reduce heart failure signs and symptoms before intervention may significantly affect early survival.

	Congestive heart failure class				
Ejection fraction (%)	0	I	II	III	IV
<0.25	1.1	10.8	5.0	6.0	18.2
0.25–0.35	6.5	14.9	15.0	26.5	29.5
0.36–0.45	15.8	29.7	21.7	22.9	22.8
0.46–0.55	28.0	20.3	25.8	26.5	22.8
>0.55	47.0	24.3	32.5	18.1	6.8

From Wechsler AS, Junod FL. Coronary bypass grafting in patients with chronic congestive heart failure. *Circulation* 1989;79(Suppl I):I-92–I-96, with permission.

TABLE 95.2 RELATIONSHIP BETWEEN EJECTION FRACTION AND CONGESTIVE HEART FAILURE CLASS

***e*TABLE 95.2.1** RELATIVE RISK OF LEFT VENTRICULAR EJECTION FRACTION FOR DEATH: UNADJUSTED AND ADJUSTED FOR CONGESTIVE HEART FAILURE[a]

Quartile	Left ventricular ejection fraction	Unadjusted	Adjusted
1	<0.24	1.69[b]	1.39
2	0.24–0.28	1.68[b]	1.62
3	0.29–0.32	1.30	1.22
4	>0.32	1.00	1.00

[a] Before adjustment, left ventricular ejection fraction predicts death. After adjustment for degree of congestive heart failure, ejection fraction is a poor predictor of mortality.
[b] $p = .001$.
From Olshansky B, Telfer EA, Curtis AB, et al. Predictive value of preoperative left ventricular ejection fraction and functional class for mortality and morbidity after high-risk coronary artery bypass grafting. *Am J Cardiol* 2000;85:1489–1491, with permission.

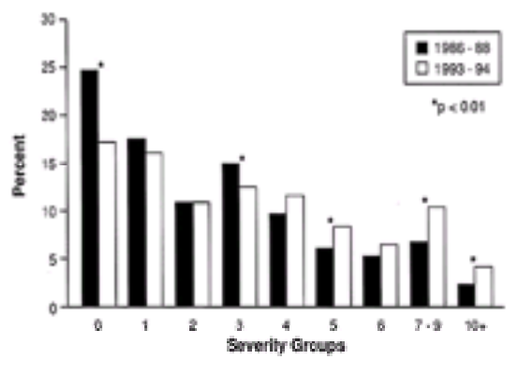
***e*TABLE 95.2.2** RELATIONSHIP BETWEEN LEFT VENTRICULAR EJECTION FRACTION (LVEF) AND CONGESTIVE HEART FAILURE (CHF) SYMPTOMS AND MORTALITY[a]

Quartile	LVEF <0.27	LVEF ³0.27
CHF present	2.72	2.06
CHF absent	1.31	1.00

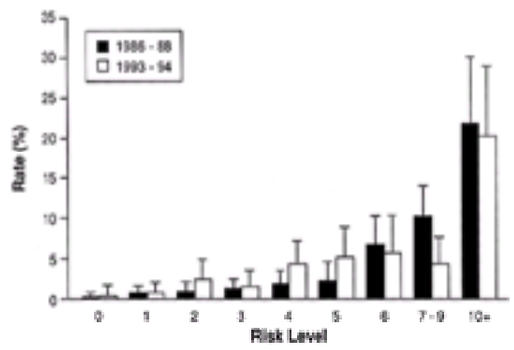
[a] Values represent relative risk.
From Olshansky B, Telfer EA, Curtis AB, et al. Predictive value of preoperative left ventricular ejection fraction and functional class for mortality and morbidity after high-risk coronary artery bypass grafting. *Am J Cardiol* 2000;85:1489–1491, with permission.

Some data are available to assess the risk of valve interventions in patients with reduced LV function. In 257 patients with a mixture of aortic and mitral interventions, predictors of hospital mortality mirrored those of coronary revascularization and included lower EF, reoperations, ischemic mitral disease, and emergency surgery (9). Predictors of decreased 10-year survival were age greater than 60 years, aortic regurgitation, and diuretic use. The authors suggest that the more advanced the heart failure, as reflected by the diuretic use, the worse the prognosis. For patients with severe aortic stenosis and low gradients secondary to severe LV dysfunction, surgery has a relatively high published mortality with few defined risk factors except older age (10,11).

At The Cleveland Clinic Foundation, we have used a severity scoring system that uses many of the variables identified as risk factors after coronary bypass surgery. Compared with the early 1980s, the patients undergoing surgery a decade later are in higher risk groups, yet have lower risk adjusted morbidity and mortality. It is noteworthy that stroke mortality has declined substantially. This reflects use of a single cross-clamp technique, frequent use of transesophageal echocardiography, and avoidance of aortic manipulation if ascending atheroslerosis is present (*e*Fig. 95.0.2 and *e*Fig. 95.0.3, *e*Table 95.2.3) (12). Currently, isolated mitral valve operations at The Cleveland Clinic Foundation are now consistently performed with a less than 2% operative risk of death (Fig. 95.1).



***e*FIGURE 95.0.2** Ever-increasing risk profile of patients undergoing coronary bypass grafting at The Cleveland Clinic Foundation. (From Estafanous FG, Loop FD, Higgins TL, et al. Increased risk and decreased morbidity of coronary artery bypass grafting between 1986 and 1994. *Ann Thorac Surg* 1998;65:383–389, with permission.)



***e*FIGURE 95.0.3** Mortality and preoperative risk profiles. Vertical bars indicate 95% confidence intervals. (From Estafanous FG, Loop FD, Higgins TL, et al. Increased risk and decreased morbidity of coronary artery bypass grafting between 1986 and 1994. *Ann Thorac Surg* 1998;65:383–389, with permission.)

***e*TABLE 95.2.3** RISK-ADJUSTED MORBIDITY AND MORTALITY HAS BEEN DECLINING DESPITE THE INCREASING RISK PROFILE OF PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

	Risk-unadjusted rates			Risk-adjusted rates		
Complications	1986–1988 (%)	1993–1994 (%)	*p*	1986–1988 (%)	1993–1994 (%)	*p*
Hospital mortality	2.47	3.44	.013[a]	2.79	2.94	.149
Overall morbidity	13.48	9.95	<.001[b]	14.46	8.82	<.001[b]
Myocardial infarction	4.79	3.37	<.003[b]	4.98	3.22	<.001[b]
Cardiac assist devices	3.21	7.88	<.001[a]	3.59	6.86	<.001[a]
Ventilatory support	5.23	7.41	<.001[a]	5.80	6.49	.023[a]
Neurologic	4.08	2.43	<.001[b]	4.44	2.20	<.001[b]
Renal[c]	1.41	1.58	.55	1.84	1.58	.57
Serious	2.71	2.58	.28	2.99	2.29	.48

[a] The 1986 to 1988 rate exceeds the 1993 to 1994 rate.
[b] Indirect standardization procedure used to adjust for risk.
[c] The 1993 to 1994 rate exceeds the 1986 to 1988 rate.
From Estafanous FG, Loop FD, Higgins TL, et al. Increased risk and decreased morbidity of coronary artery bypass grafting between 1986 and 1994. *Ann Thorac Surg* 1998;65:383–389, with permission.

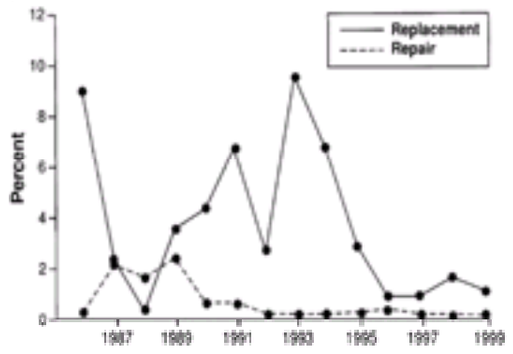
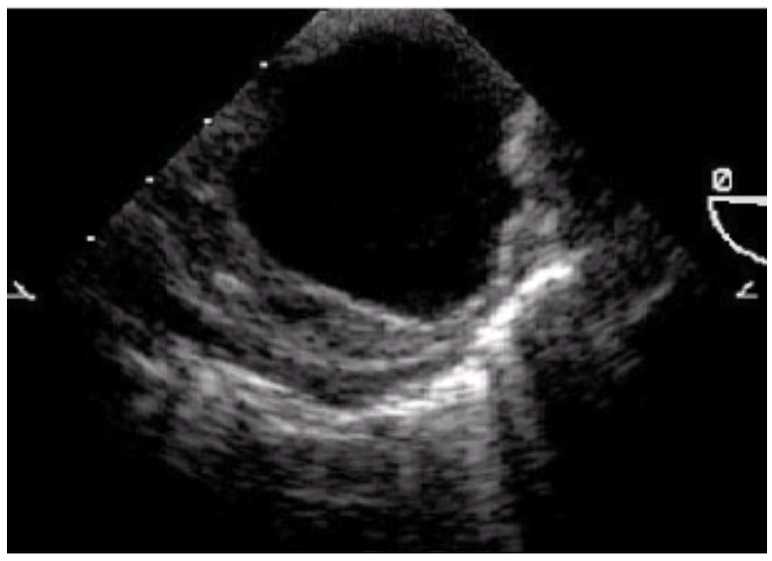


FIGURE 95.1 Operative mortality for isolated mitral valve operations at The Cleveland Clinic Foundation.



Transesophageal echo view of the descending aorta in short axis demonstrating significant atheromatous plaque.

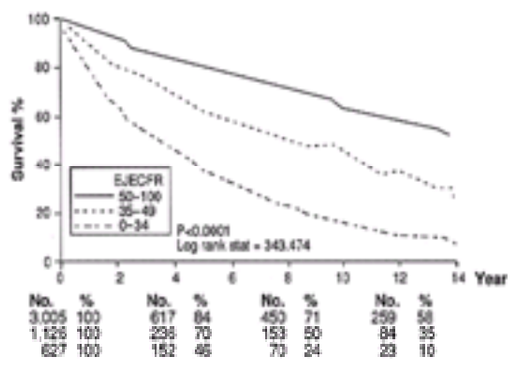
Severe calcific atherosclerosis of aorta. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

There lies the quandary. Surgical risk has been reduced substantially for even the highest risk subgroups, a result that is undoubtedly multifactorial and reflects improvements in preoperative preparation and management of heart failure, surgical techniques and myocardial protection, and intraoperative and postoperative care. Most patients survive the operation, but the real dilemma is identifying the patient most likely to benefit from the procedure.

ISCHEMIC CARDIOMYOPATHY: ROLE OF SURGICAL REVASCULARIZATION

The rationale behind revascularization is based on the concept that a chronically ischemic ventricle contains hibernating myocardium that will improve functionally with improvement of myocardial blood flow. This concept was first introduced by Rahimtoola (13,14). In a busy heart failure surgical section, the question of which patient with ischemic cardiomyopathy is a candidate for revascularization arises daily. The only randomized study to help with this decision is the Coronary Artery Surgery Study (CASS) study (15,16). It is important to note that the patients enrolled in this study had mild angina and were excluded if heart failure was present and if the EF was below 0.36. In the medically treated cohort excluded from surgery because of a low EF, survival was quite poor (17). It is true that these studies are nonrandomized, but it suggests that the subgroup of patients with the lowest EF have the poorest survival (*e*Fig. 95.1.1). Data supporting the value of surgical

revascularization in this subgroup of patients was presented by Alderman and colleagues (18). They reviewed these patients who were evaluated for the CASS study but excluded because the EF was less than 36%. Surgically treated patients had more angina, more left main stenosis, and less heart failure (18). In addition to these differences, there was crossover into the surgical group. Medically treated patients with severely reduced LV function and three-vessel disease had dismal survival over 8 years. Overall they showed that surgically treated patients did better and the greatest benefit was seen in the patients with the lowest EFs (Fig. 95.2).



***e*FIGURE 95.1.1** Medically treated CASS registry patients with three-vessel disease by ejection fraction (EJECFR). [From Emond M, Mock MB, Davis KB, et al. Long term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994;90:2645–2657, with permission.]

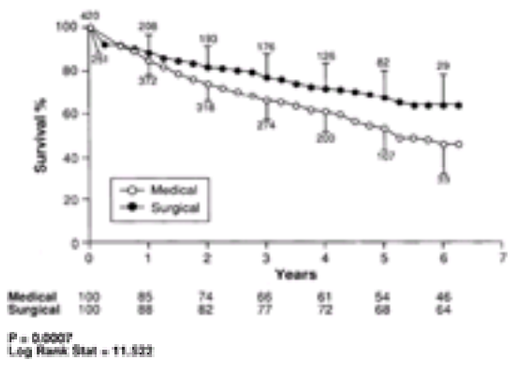
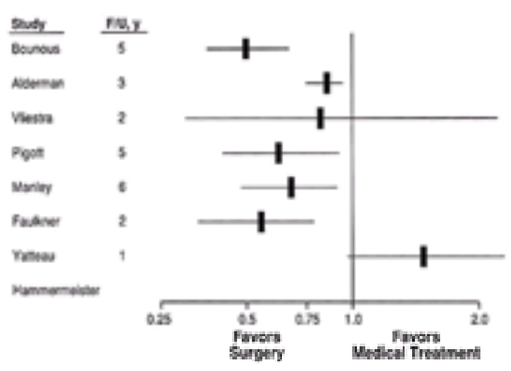


FIGURE 95.2 Comparison of medically and surgically treated CASS registry patients excluded from the study because of an ejection fraction less than 36%. [Alderman EL, Fisher LD, Litwin P, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 1983;68:785–795, with permission.]

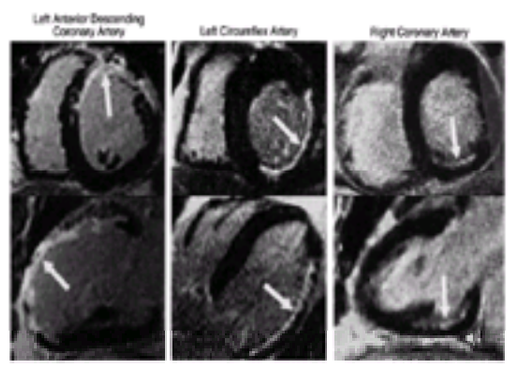
Patient Selection

Patients with angina and severe LV dysfunction are candidates for surgical therapy assuming adequate targets for revascularization (19,20). Baker et al. concluded that this approach is favored by review of the literature, improves EF and angina by 30% to 50%, and reduces NYHA functional class by one (19). It must be noted, however, that these are nonrandomized trials, somewhat outdated, and with small numbers. However, clinical experience supports these findings (eFig. 95.2.1). The more difficult question is when to intervene in patients without angina. It is primarily in this group of patients in which viability and functional studies have their greatest impact. It is beyond the scope of this chapter to detail the utility of functional studies. In general, the greater the number of viable myocardial segments, the greater the increase in postoperative EF and exercise capacity. However, improvement in quality of life and functional class has not correlated with the volume of hibernating myocardium (21).

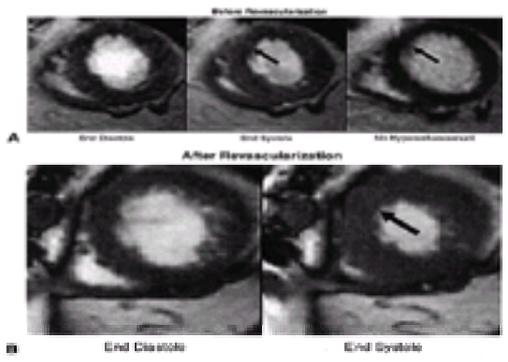


***e*FIGURE 95.2.1** Review of published papers supporting surgical or medical therapy for ischemic cardiomyopathy. F/U, follow-up; y, years. (From Baker DW, Jones R, Hodges J. The role of revascularization in the treatment of patients with moderate or severe left ventricular systolic dysfunction. *JAMA* 1994;272:1528–1534, with permission.)

To assess myocardial viability in patients with ischemic cardiomyopathy and heart failure, the author relies primarily on positron emission tomography (PET) and magnetic resonance imaging (MRI) scans. MRI has the advantage of assessing wall motion and perfusion, identifying scar distribution, and determining chamber volume and valve function. The study has its limitations, however. Approximately 10% of patients cannot tolerate the confined spaces of the MRI scanner and another 10% to 20% are excluded from the study because of the presence of pacemakers or internal defibrillators. The patient receives intravenous gadolinium, which is taken up by myocardial scar (eFig. 95.2.2 and eFig. 95.2.3). Kim et al. have shown that the absence of enhancement of the myocardium by gadolinium predicts improvement in wall motion after revascularization, whereas greater than 75% transmural uptake of gadolinium is indicative of scar and irreversible segmental dysfunction (22).



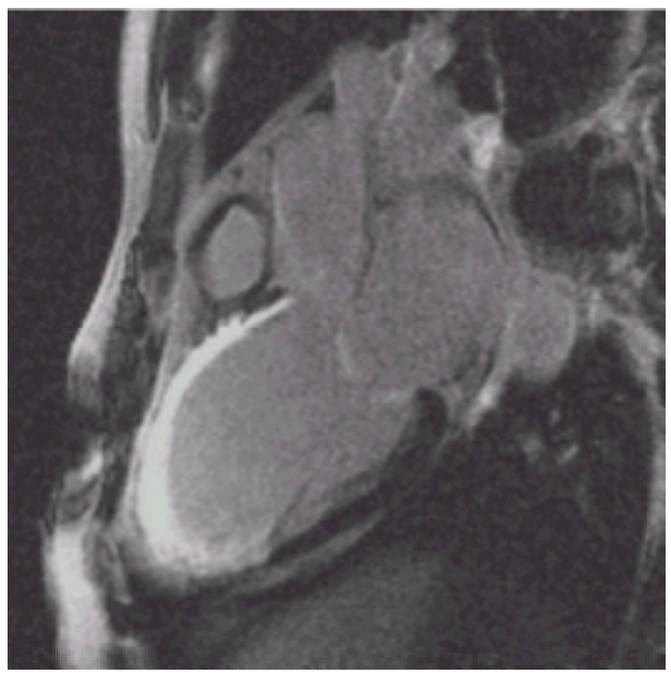
***e*FIGURE 95.2.2** Myocardial wall enhancement with gadolinium (*arrows*). The extent of wall enhancement predicts functional recovery after revascularization.



***e*FIGURE 95.2.3** Magnetic resonance imaging showing regional dysfunction before grafting **(A)** and improvement after revascularization **(B)**. Arrows in **A** show absent wall thickening before revascularization that is present **(B)** after revascularization. The absence of gadolinium enhancement predicts recovery. (From Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;343:1445–1453, with permission.)

Video 95.1 Post–myocardial infarction true aneurysm (long-axis). Dyskinesia and thinning of the left ventricular apex due to an occlusion of left anterior descending artery. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 95.2 Impaired systolic function and necrosis delineation in a chronic myocardial infarction region (long-axis). The SPAMM (spatial modulation of magnetization) image **(A)** demonstrates contraction of the left ventricular inferior wall but akinesia of the anterior, apex, and infero-apical segments. The delayed-enhancement image **(B)** demonstrates transmural hyperenhancement of the segments with impaired systolic function. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Impaired systolic function and necrosis delineation in a chronic myocardial infarction region (long-axis). The SPAMM (spatial modulation of magnetization) image (A) demonstrates contraction of the left ventricular inferior wall but akinesia of the anterior, apex, and infero-apical segments. The delayed-enhancement image (B) demonstrates transmural hyperenhancement of the segments with impaired systolic function.

DiCarli and colleagues have evaluated the utility of PET scans in conjunction with clinical symptoms. Patients with PET mismatch (greater than 5% of myocardium, which is a low percentage), with and without angina, have a survival advantage over medical therapy. Sudden death was a common event in the medically treated patients, supporting the thesis that hibernating myocardium is a more unstable substrate than scar. In patients without angina, the use of PET matching of low perfusion and no metabolic activity predicts no survival benefit with revascularization (23). Other studies confirm this but suggest that quality of life and exercise capacity increase in this group. Because the number of patients assessed is small, further studies are necessary to define the role of revascularization in patients with heart failure and limited amounts of viable myocardium.

The size or volume of the ventricle is another important variable predicting outcome. Yamaguchi et al. showed that in patients with EFs less than 30%, if the LV end systolic volume index was greater than 100 mL per m^2, those patients did not have an increase in EF postrevascularization and had significantly worse 5-year survival and event-free survival (Fig. 95.3, Fig. 95.4, and Fig. 95.5) (24). It is likely that, in the future, some assessment of ventricular volume will be used to determine the likelihood of functional recovery of the revascularization.

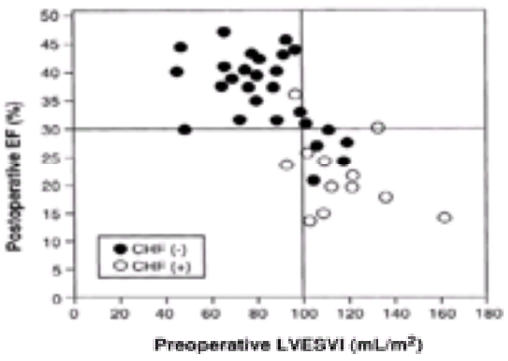


FIGURE 95.3 For patients with ischemic cardiomyopathy, ejection fraction (EF) less than 30% and left ventricular end systolic volume index (LVESVI) greater than 100 mL per m^2functional recovery was unlikely after revascularization. CHF, congestive heart failure. (From Yamaguchi A, Takashi I, Adachi H. Left ventricular volume predicts postoperative course in patients with ischemic cardiomyopathy. *Ann Thorac Surg* 1998;65:434–438, with permission.)

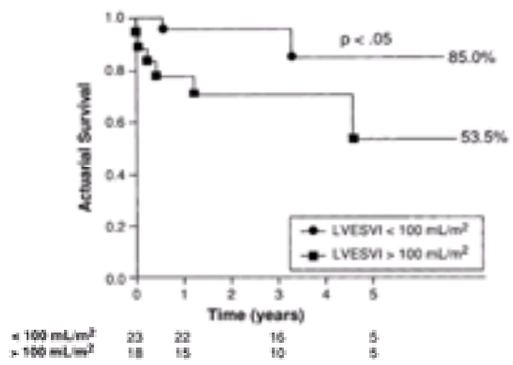


FIGURE 95.4 Ischemic cardiomyopathy and ventricular enlargement greater than 100 mL per m^2 is associated with reduced survival after revascularization. LVESVI, left ventricular end systolic volume index. (From Yamaguchi A, Takashi I, Adachi H. Left ventricular volume predicts postoperative course in patients with ischemic cardiomyopathy. *Ann Thorac Surg* 1998;65:434–438, with permission.)

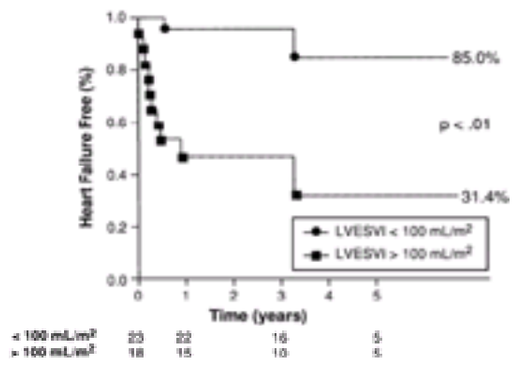


FIGURE 95.5 Event-free survival after revascularization is significantly reduced in the larger ventricle. LVESVI, left ventricular end systolic volume index. (From Yamaguchi A, Takashi I, Adachi H. Left ventricular volume predicts postoperative course in patients with ischemic cardiomyopathy. *Ann Thorac Surg* 1998;65:434–438, with permission.)

Current Practice

Given the critical shortage of donor organs for transplantation, all patients with ischemic cardiomyopathy are assessed for nontransplant alternatives. For patients with angina, multivessel disease, and normal to mild chamber enlargement, revascularization can be expected to improve function and survival. A common clinical practice rarely described in the literature is to base revascularization decisions on target vessel quality. Langensburg et al. showed that in a small series of patients with ischemic cardiomyopathy, patients with vessels rated as poor had 100% mortality after revascularization (2). For patients with only heart failure symptoms, markedly enlarged ventricles, and previous operations (all predictors of increased operative risks), functional studies are obtained to help support surgical intervention. A PET scan showing mismatch of greater than 15% of the myocardial mass supports intervention. If PET corroborates extensive scarring, then isolated revascularization is not considered. A combination of anterior scar, ventricular enlargement, and lateral and inferior ischemia or hibernation directs the surgeon toward revascularization and a remodeling procedure.

Patients with a markedly enlarged ventricle, fair to poor targets, and limited viability, especially if the procedure is a reoperation, are at high risk for postcardiotomy pump failure and are assessed preoperatively for transplant candidacy. If postcardiotomy pump failure occurs, then an LVAD may be used to bridge the patient to transplantation.

SURGICAL TECHNIQUES

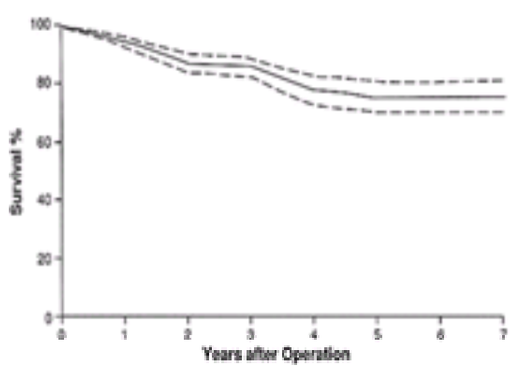
The goal of intervention is complete revascularization and meticulous myocardial protection. Because antegrade and retrograde blood cardioplegia provide outstanding protection of these marginal ventricles, an effort should be made to graft all bypassable targets. The approach of “get in and get out” is no longer supportable. The left internal thoracic artery should be used to bypass the left anterior descending artery and not avoided because it is a high-risk case. In fact, Leavitt et al. have shown in a large series of 21,873 consecutive patients that the use of the internal thoracic artery reduced in-hospital mortality and adverse events, especially in the higher risk patients (25). During reoperations the greatest risk is atheroembolization from diseased vein grafts. This would be potentially fatal in patients with marginal LV function. Gentle dissection, use of retrograde cardioplegia, and early ligation of diseased vein grafts all help minimize this problem.

For patients with more diffuse disease, coronary endarterectomy or laser transmyocardial revascularization have been employed. The efficacy and safety of these techniques are not known at this time.

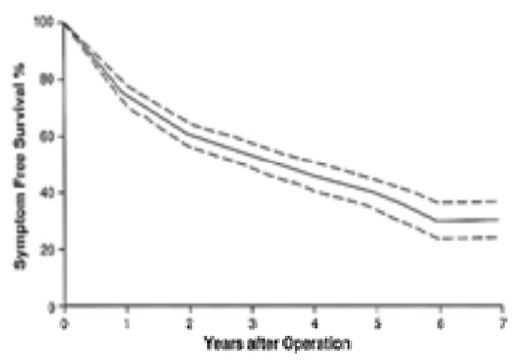
Results

Most published results have focused on early mortality. In one series, mortality was been quite respectable at 1.8% to 6.9% (26,27,28,29 and 30). However, these results are published from centers with expertise in treating patients with reduced LV function, and patients are often carefully selected.

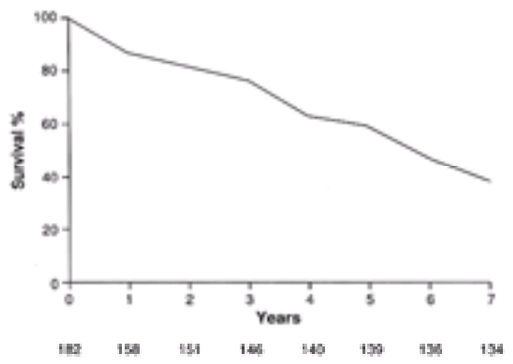
Longer term results also are quite good in patients with and without angina and match that of transplantation. Most studies have shown a 1-year survival of 75% to 80% with a 5-year (5) survival of 50% (*e*Fig. 95.5.1, *e*Fig. 95.5.2, and *e*Fig. 95.5.3) (29,30). These patients’ conditions are improved but not cured. Given the fixed number of donor hearts available, any reduction in the number of patients awaiting transplant or delaying transplantation is an important benefit of the procedures. Survival is good, but cardiac events continue to occur, indicating that medical therapy for heart failure must be diligently maintained. In the future, patients will be stratified by the volume of the ventricle, degree of dysfunctional myocardium, angina, and heart failure class, and results should assess, in addition to survival, quality of life, exercise capacity, and cause of death. Once these data are available, we will be able to better identify the patient with severe, chronic ventricular dysfunction most likely to benefit from surgical revascularization.



***e*FIGURE 95.5.1** Long-term survival after revascularization in patients with ischemic cardiomyopathy. (From Luciani GB, Montalbano G, Casali G, et al. Predicting long term functional results after myocardial revascularization in ischemic cardiomyopathy. *J Thorac Cardiovasc Surg* 2000;120:478–489, with permission.)



***e*FIGURE 95.5.2** Symptom-free survival after coronary artery bypass grafting for ischemic cardiomyopathy. (From Luciani GB, Montalbano G, Casali G, et al. Predicting long term functional results after myocardial revascularization in ischemic cardiomyopathy. *J Thorac Cardiovasc Surg* 2000;120:478–489, with permission.)



***e*FIGURE 95.5.3** Survival after coronary revascularization in patients with ischemic cardiomyopathy and heart failure without angina. (From Anderson WA, Ilkowski DA, Mahan VL, et al. Coronary artery bypass grafting in patients with chronic congestive heart failure: a 10-year experience with 203 patients. *J Cardiol Surg* 1997;12:167–175, with permission.)

DIRECT VENTRICULAR REMODELING

Partial Left Ventriculectomy and Aneurysmorrhaphy

LV chamber enlargement is a compensatory response commonly seen after many forms of myocardial injury. Despite concomitant hypertrophy, wall stress remains excessive when compared with normal-sized ventricles. After infarction the progressive enlargement of the akinetic or dyskinetic segment places additional stress or afterload on the normal segments of the myocardium, which eventually fail, especially if ischemia is present. Early after acute MI a ventricular end systolic volume of more than 40 mL per m^2 is associated with significantly increased 1-year mortality, and massive ventricular enlargement significantly worsens survival in patients with chronic heart failure (*e*Fig. 95.5.4) (31,32). It is interesting that the volume of the ventricle early after the MI is predictive of future mortality. This also seen in patients with chronic CHF, although the size of the ventricle is much larger (*e*Table 95.2.4 and *e*Fig. 95.5.5). As is discussed later, this raises the question of at what size should surgical intervention be considered? Options in the future will include active remodeling of the ventricle as with the Dor procedure or passive restraints such as with the Acorn CS device. As discussed in the previous section, Yamaguchi et al. have shown that patients with LV end systolic volume index greater than 100 mL per m^2 do not respond to revascularization, and overall and event-free survival are poor (24). These findings support the concept of surgical remodeling to reduce the chamber volume and to decrease wall stress with the goal of improving overall cardiac performance, which then, it is hoped, will translate into improvement in functional status and long-term outcomes.

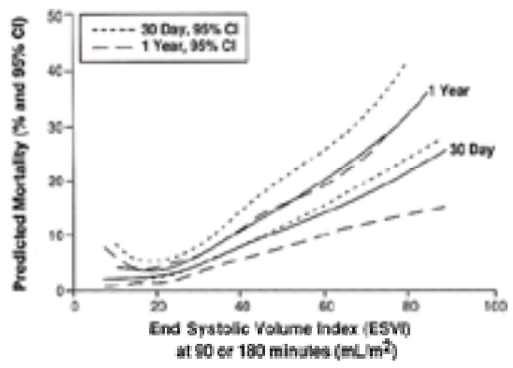
Video 95.3 Apical left ventricular aneurysm in a 69-year-old female patient with history of anterior myocardial infarction. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 95.4 Standard left anterior oblique view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating apical dyskinesis and a reduced left ventricular ejection fraction of 40% secondary to ischemic heart disease. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 95.5 Standard anterior view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating apical dyskinesis and a reduced left ventricular ejection fraction of 40% secondary to ischemic heart disease. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 95.6 Standard lateral view of a 16-frame nuclear ventriculogram (multiple gated acquisition scan) demonstrating apical dyskinesis and a reduced left ventricular ejection fraction of 40% secondary to ischemic heart disease. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 95.7 DOR procedure. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

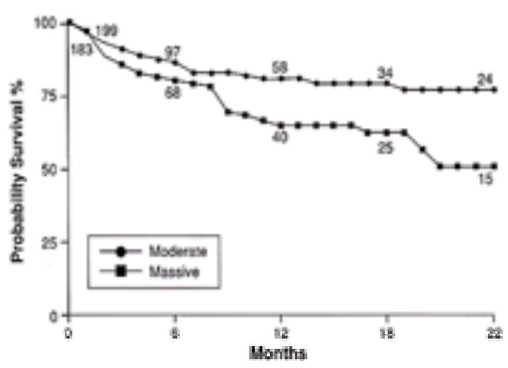


***e*FIGURE 95.5.4** Survival at 30 days and 1 year based on chamber volume measurements at 90 or 180 minutes after thrombolytic therapy for acute myocardial infarction. CI, confidence interval. (From Migrino RQ, Young JB, Ellis SG, et al. End-systolic index at 90 to 180 minutes into reperfusion therapy for acute myocardial infarction is a strong predictor of early and late mortality. *Circulation* 1997;96:116–121, with permission.)

***e*TABLE 95.2.4** ADJUSTED ODDS RATIOS OF VARIABLES INDEPENDENTLY PREDICTIVE OF 30-DAY AND 1-YEAR MORTALITY[a]

Variable	30-Day odds ratio[b]	Mortality, 95% confidence interval	1-Yr odds ratio[c]	Mortality, 95% confidence interval[b]
Age[d]	4.6	4.1–5.1	3.4	3.0–3.8
Prior coronary artery bypass grafting	1.4	1.2–1.7	1.9	1.6–2.3
Prior myocardial infarction	1.5	1.4–1.7	1.9	1.7–2.1
Anterior myocardial infarction	1.7	1.6–1.9	1.4	1.3–1.6
ESVI ³30 mL/m^2	2.4	1.4–4.1	2.5	1.1–5.9
ESVI ³35 mL/m^2	3.0	1.8–5.2	2.5	1.2–5.6
ESVI ³40 mL/m^2	3.4	2.0–5.8	3.8	1.7–8.5

ESVI, end systolic volume index.
[a] In addition to age, ESVI greater than or equal to 40 mL per m^2 at 90 or 180 minutes after thrombolytic therapy predicted reduced survival after acute myocardial infarction.
[b] Only patients who survived >30 days were included in the analysis.
[c] All p <.001.
[d] Per 20 years of age.
From Anderson WA, Ilkowski DA, Mahan VL, et al. Coronary artery bypass grafting in patients with chronic congestive heart failure: a 10-year experience with 203 patients. *J Cardiol Surg* 1997;12:167–175, with permission.



***e*FIGURE 95.5.5** Effect of left ventricular cavity size on survival in patients with congestive heart failure. Moderate enlargement averaged less than or equal to 4 cm per m^2, whereas massive enlargement averaged greater than 4 cm per m^2. (From Lee TH, Hamilton MA, Stevenson LW. Impact of left ventricular cavity size on survival in advanced heart failure. *Am J Cardiol* 1993;72:672–676, with permission.)

Partial Left Ventriculectomy

Randas Batista introduced partial left ventriculectomy (PLV) in late 1995 based on the law of LaPlace and the reduction of wall stress with a decrease in chamber radius. The procedure and its promoter drew a great deal of attention and interest from heart failure physicians and patients with end-stage heart disease. This procedure offered an alternative to patients who were not candidates for transplant or LV assist devices or preferred to avoid or delay transplantation. More important, it encouraged physicians to look for more unconventional approaches to end-stage heart failure, and along with the contemporaneous success with mitral valve repair in patients with end-stage cardiomyopathy, surgeons were emboldened to attempt surgery in these high-risk patients.

VIDEO

Video 95.8 Transgastric short-axis view of a mitral valve after the Batista left ventricular remodeling procedure. Note the Alfieri stitch placed in the mitral leaflet tips creating the characteristic figure-of-eight appearance of the mitral valve. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 95.9 Batista procedure. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Patient Selection and Technique

In most published series, patients undergoing PLV had idiopathic dilated cardiomyopathy with or without mitral regurgitation. LV dimensions needed to be greater than 7.0 cm; at The Cleveland Clinic Foundation, all patients were transplant candidates (33).

A wedge of ventricular myocardium weighing an average 96 g (range, 30 to 290 g) was resected in the coronary distribution of the lateral circumflex artery. This removed the muscle between the papillary muscles. If this was thought to be insufficient for radius reduction, the papillary muscles were detached, more myocardium was resected, and the papillary muscles reattached. Mitral valve repair or replacement was performed in most patients. An incremental but potentially significant advance in patient selection was described by Suma et al. (34). Early in The Cleveland Clinic experience, the preoperative MRI scans suggested that the lateral wall was functioning the best and the anterior wall and septum were akinetic and scarred. After lateral wall resection, the anterior and septal walls sometimes had improvement in function, but often they did not. Suma et al. intraoperatively looked at regional wall motion of the decompressed ventricles (on partial bypasses) with transesophageal echocardiography. If all walls show improved motion while decompressed on partial cardiopulmonary bypass, the patient is not a candidate for PLV and undergoes mitral valve surgery alone. If the anterior wall and septum are akinetic with good lateral wall function, a modified endoventricular circular patch plasty is performed even for idiopathic dilated ventricles. For lateral wall akinesis, the standard PLV is done (34).

Results

There were astonishing successes and dismal failures after PLV, with an inability to predict outcomes (35) (Table 95.3). In general, ventricular volume and wall stress were reduced, EF increased, but central hemodynamics were unchanged. Surgical mortality was high, and longer-term results were poor (36,37,38,39,40 and 41). The experience of Suma et al. suggests that a more selective approach to resection in elective patients can be done safely with good results (Table 95.4).

Operative mortality	3–20%
Early left ventricular assist device (The Cleveland Clinic Foundation)	15%
2-year survival	50–60%
3-year event-free survival	30%

TABLE 95.3 PARTIAL LEFT VENTRICULECTOMY RESULTS

		Group I		Group II	
	EVOW + CABG/valve	LV reduction + valve	LV reduction + valve	Valve alone
No.	33	24	16	13
Mortality	3/33	12/24	1/16	2/13
Hospital + late (%)	21.2	50.0	6.3	15.4
IABP/LVAD	10	60	10	11
Return to heart failure	3	4	3	2
Follow-up (d)	377 ± 228	365 ± 323	273 ± 109	316 ± 156
Median (d)	362	278	262	368

CABG, coronary artery bypass grafting; EVOW, endoventricular circular patch plasty; IABP, intraaortic balloon pumping; LV, left ventricular; LVAD, left ventricular assist device.
<Group I patients underwent standard partial left ventriculectomy. In Group II, ventricular remodeling was done after the dysfunctional walls were identified by partial decompression on cardiopulmonary bypass; otherwise they underwent valve repair alone if there was no evidence of regional dysfunction.
From Suma H, Isomura T, Horii T. Non-transplant cardiac surgery for end-stage cardiomyopathy. *J Thorac Cardiovasc Surg* 2000;119:1220–1249, with permission.

TABLE 95.4 RESULTS OF TARGETED VENTRICULAR REDUCTION[a]

The reason for the unpredictability of PLV remains unclear. Computer analysis has shown that volume reduction by wall segment resection improves end systolic elastance but worsens diastolic compliance (Fig. 95.6 and Fig. 95.7) (42,43 and 44). The net effect is a decreased slope of the Starling relationship and worse cardiac pump function. Additional factors such as coronary artery injury in the resection closure further compromise cardiac function.

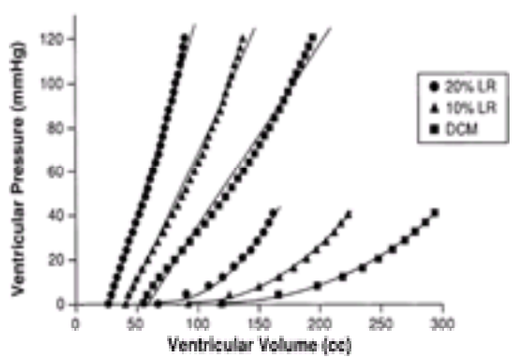


FIGURE 95.6 Finite element analysis predicting improvement in elastance with deterioration in compliance after lateral partial left ventriculectomy. DCM, dilated cardiomyopathy; LR, lateral resection. (From Ratcliffe MB, Hong J, Salahieh A, et al. The effect of ventricular volume reduction surgery in the dilated, poorly contractile left ventricle: a simple finite element analysis. *J Thorac Cardiovasc Surg* 1998;116:566–577, with permission.)

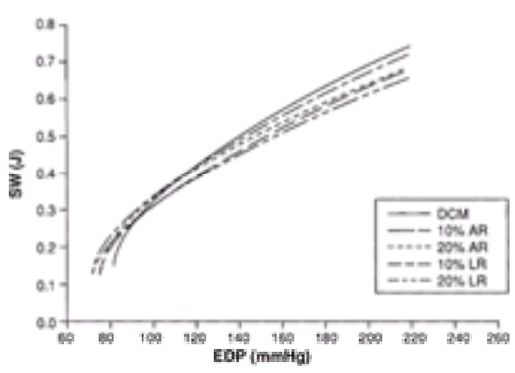


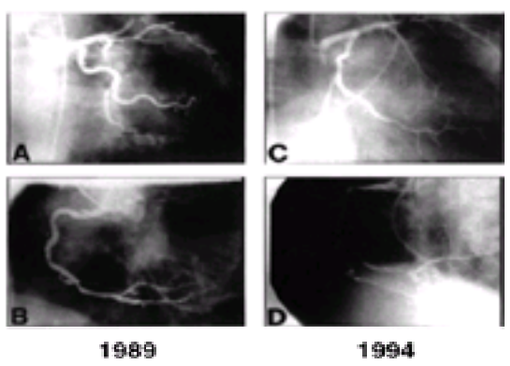
FIGURE 95.7 Overall result of partial left ventriculectomy with worsening of the Starling relationship. AR, apical resection; DCM, dilated cardiomyopathy; EDP, end diastolic pressure; LR, lateral resection; SW, stroke work. (From Ratcliffe MB, Hong J, Salahieh A, et al. The effect of ventricular volume reduction surgery in the dilated, poorly contractile left ventricle: a simple finite element analysis. *J Thorac Cardiovasc Surg* 1998;116:566–577, with permission.)

Currently, most centers have abandoned PLV as a therapy for idiopathic dilated cardiomyopathy. However, some European and Asian centers continue to pursue this approach in both ischemic and dilated cardiomyopathies. In general, early operative mortality is high (approximately 20%), and long-term results are not known. New devices such as the Myosplint (Myocor, Inc., Plymouth, MN) may accomplish the same stress reduction without the high morbidity and mortality (see New Surgical Therapies for Congestive Heart Failure).

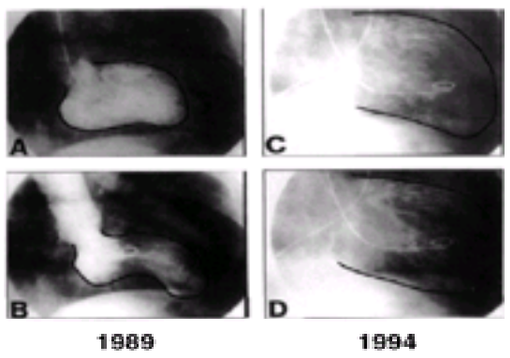
Apical asymmetric septal hypertrophy after the Batista procedure. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

REMODELING THE ISCHEMIC VENTRICLE

The deleterious effects of a large dyskinetic ventricular wall have been known for over 50 years. Increased attention has been directed toward preventing ventricular enlargement and managing the enlarged ventricle with akinetic anterior walls. Traditionally, surgical intervention was reserved for symptomatic patients (angina, CHF, thromboemboli) with large aneurysms. Dor and colleagues directed attention to the deleterious effects aneurysmal segments have on the adjacent normal walls (45,46) and have argued for a more aggressive and early approach to akinetic segments to prevent irreversible damage. In some patients, over a relatively short time period after an acute anterior MI, patients remodel and enlarge the ventricle but also develop myocardial wall motion dysfunction remote from the area of infarct (*e*Fig. 95.7.1 and *e*Fig. 95.7.2). It is unknown how common this is. We have seen patients present with severe heart failure within months of an acute anterior MI from single-vessel disease and others who are followed for decades with large anterior and apical aneurysms before the signs and symptoms of CHF arise. It is worthwhile to note that in the review by Alderman et al. of the patients excluded from the CASS study for EF less than 36% that an LV aneurysm was present in 30% of the medical and surgical treatment groups. Most surgically treated patients had some form of aneurysmectomy (18). There was no surgical benefit in survival in this subgroup when adjusted for the degree of heart failure and wall motion scores. This does not negate the value of aneurysmectomy but supports the notion that early intervention is beneficial before heart failure and remote wall motion dysfunction is advanced.



***e*FIGURE 95.7.1 A–D:** Stable coronary anatomy over 5 years after an anterior infarct. (From Cox JI. Left ventricular aneurysms: pathophysiologic observations. *Semin Thorac Cardiovasc Surg* 1997;9:113–122, with permission.)



***e*FIGURE 95.7.2 A–D:** Marked deterioration in left ventricular function despite stable coronary anatomy. (From Cox JI. Left ventricular aneurysms: pathophysiologic observations. *Semin Thorac Cardiovasc Surg* 1997;9:113–122, with permission.)

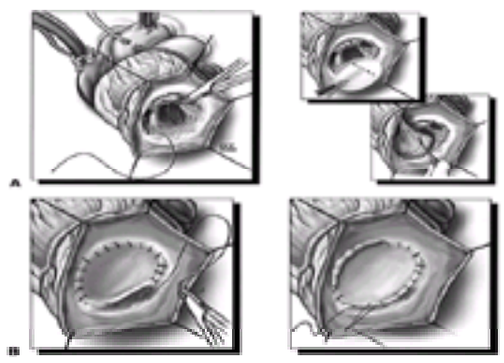
Indications for Ventricular Remodeling

As mentioned previously, traditionally patients have presented with symptoms of cardiac failure and have undergone aneurysm repair at this stage. Currently, asymptomatic patients with ventricular enlargement after an anterior MI should be considered for remodeling. Recommendations vary, but an end diastolic volume greater than 150 to 200 mL, end diastolic dimension of greater than 6.0 to 6.5 cm, or LV end systolic volume index of greater than 60 to 70 mL per m^2 are reasonable guidelines. In our ischemic remodeling group, the average end diastolic volume was 240 mL (end diastolic volume index = 97 mL per m^2) by three-dimensional echo or MRI, whereas Dor's patients had end diastolic volumes ranging from 205 to 246 mL by biplane cineangiography for akinetic and dyskinetic ventricles, respectively (47,48 and 49). We use MRI to assess regional wall motion abnormalities in conjunction with clinical status to exclude patients from remodeling. In patients with massively enlarged ventricles or those with extensive wall thinning with class IV symptoms and patients on inotropes, ventilators, or balloon pumps are considered for transplantation or LVAD.

Aneurysm repair in a patient with a recent lateral wall myocardial infarction. "Packing material" is evident overlying the area of repair (*yellow arrow*).

Techniques

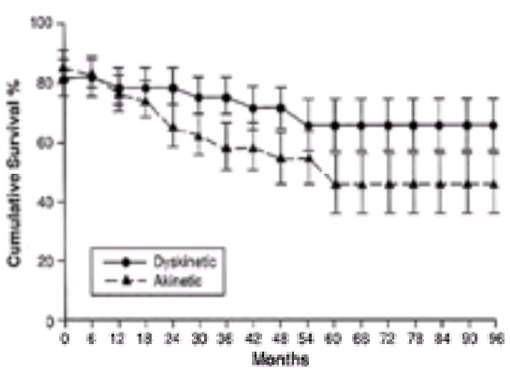
Cooley is credited with performing the first open aneurysm resection in 1958. After 2,000 cases, he has modified the technique from linear closure to internal patch technique. Jatene and Dor nearly simultaneously described an internal remodeling technique that has the theoretical advantage of excluding the infarcted and nonfunctional septum from chamber pressures (45). This is our preferred technique. In brief, the operation consists of differentiating the infarcted or akinetic muscle from contractile muscle and placing two concentric purse strings to reapproximate the normal geometry of the ventricle (eFig. 95.7.3). An additional series of purse strings or a patch is used to exclude the remainder of the nonfunctional wall. CABG is performed in 98% of Dor's patients and 93% in our series, whereas mitral valve procedures were necessary in 54%.



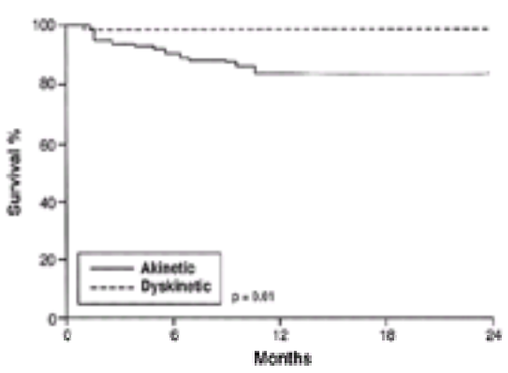
***e*FIGURE 95.7.3 A,B:** Dor procedure: The border zone between scar and muscle is identified and encircled by two purse-string sutures. This excludes the infarcted anterior wall and septum. A patch of either mobilized scar or Dacron is used to close the defect.

Results

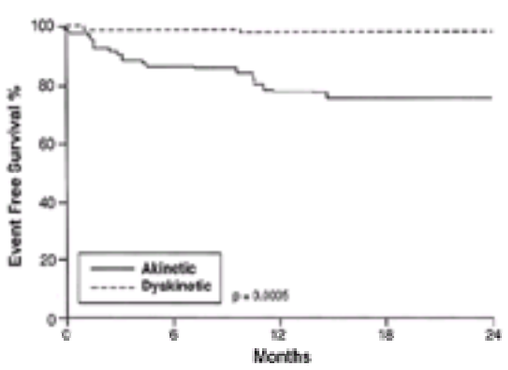
Operative mortality is 12.0% in Dor's experience and 1.5% at The Cleveland Clinic Foundation. Dor has shown that patients with akinetic ventricles do not do as well as those with dyskinetic aneurysms, and this is corroborated in our experience. Both survival and event-free survival are reduced in patients with akinetic anterior walls (eFig. 95.7.4, eFig. 95.7.5, and eFig. 95.7.6). The exact reason for this is not clear. It may be that, in general, the akinetic ventricles are larger and, if compared by size outcomes, would not be so different. Overall, the patients do quite well, and the results support the argument for an aggressive approach to ventricular reduction and preventing remodeling (see Acorn Cardiac Support Device, later in this chapter).



***e*FIGURE 95.7.4** Dor's results after endoventricular patch plasty separated by "function" of anterior wall. (From Dor V, Sabatier M, Di Donato M. Efficacy of endoventricular patch plasty in large postinfarction akinetic scar and severe left ventricular dysfunction: comparison with a series of large dyskinetic scars. *J Thorac Cardiovasc Surg* 1998;116:50–59, with permission.)



***e*FIGURE 95.7.5** Survival after the Dor procedure at The Cleveland Clinic Foundation.



***e*FIGURE 95.7.6** Event-free survival after the Dor procedure at The Cleveland Clinic Foundation.

MITRAL VALVE SURGERY IN REDUCED LEFT VENTRICULAR FUNCTION

Historically mitral valve surgery in the setting of reduced LV function was thought to be associated with prohibitive perioperative mortality. The oft quoted mortality of

greater than 30% arose from papers published in the 1980s (50). Significant advances have been made since those series in the understanding of the mechanism of mitral insufficiency, the need to preserve papillary annular continuity, and improvements in myocardial protection and surgical techniques that have resulted in substantial improvement in survival. Currently, mitral valve interventions of all types including ischemic mitral regurgitation have an operative mortality of less than 10% (51,52 and 53).

Mechanism

Surgical dogma stated that replacement of the mitral valve in the setting of reduced ventricular function would eliminate the pop-off mechanism for the failing ventricle and result in deterioration in LV function (54). In fact, the mechanism for LV dysfunction was the common practice of excising both the anterior and posterior leaflets and chordal attachments. This loss of the papillary annular connection immediately worsened LV function and resulted in a more spherical ventricular shape with increased wall stress. As experience with mitral valve repair grew, it was demonstrated that when compared with mitral replacement LV function was maintained by repair. This led to the expansion of repair techniques in patients with LV dysfunction. It is worthwhile to note that mitral valve replacement that spares the subvalvular apparatus may be as useful as mitral replacement (55).

In patients with dilated cardiomyopathy, the mitral valve leaflets are usually normal and the mitral regurgitation is related to annular dilatation and apical displacement of the papillary muscles as the chamber enlarges. In ischemic cardiomyopathy, the pathology is much more varied (*e*Table 95.4.1) (56).

Video 95.10 Apical long-axis view of a patient with severe left ventricular dysfunction and annular dilatation causing 4+, centrally directed mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

***e*TABLE 95.4.1** POTENTIAL CAUSES OF ISCHEMIC MITRAL REGURGITATION

Leaflet(s) prolapse
Transient ischemia
Papillary muscle rupture
Papillary muscle trunk
Papillary muscle head
Chordal avulsion
Papillary muscle elongation
Lack of coaptation of leaflets[a]
Transient ischemia
Annular dilation
Dyskinetic/akinetic wall with apical displacement of papillary muscle and leaflets
Distortion of papillary muscles

[a] Due to apical displacement of the papillary muscle.

From David TE. Techniques and results of mitral valve repair for ischemic mitral regurgitation. *J Cardiol Surg* 1994;9[Suppl]:274–277, with permission.

Ischemic injury to the papillary muscles results in regional wall motion abnormalities; muscle elongation and fibrosis lead to leaflet prolapse centrally and at the commissures. Postinfarction ventricular enlargement apically displaces the papillary muscles yet infrequently results in annular dilatation. Ischemic injury to the valve may cause morphologic changes similar to those seen with myxomatous valve disease. This results in reduced leaflet coaptation and restricted leaflet motion. These distinctions are important for determining repair techniques.

In general, patients with restricted leaflet motion have more severe reduction in LV function and significantly worse survival at 3 years (Fig. 95.8). Acute severe mitral regurgitation is usually seen after a limited transmural infarct with a ruptured papillary muscle head or an acutely torn chorda. These patients usually have preserved LV function (*e*Fig. 95.8.1). Patients with intrinsic mitral valve pathology usually have fairly normal LV function as compared with patients who have normal valves and poor LV function. Patients with normal mitral valves do well after interventions on the mitral valve (*e*Fig. 95.8.2).

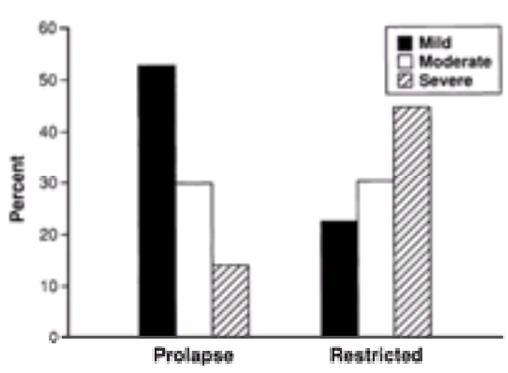
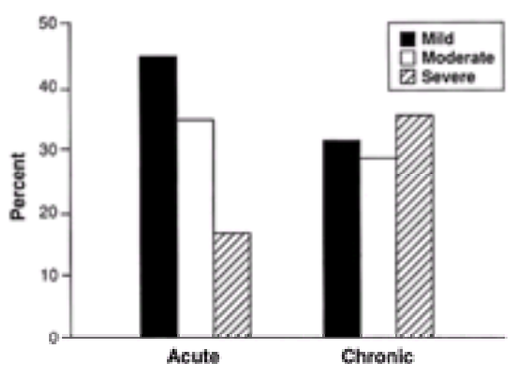
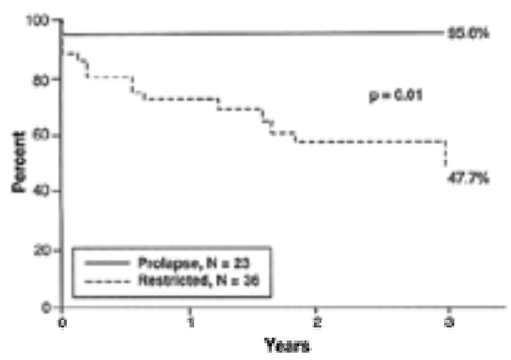


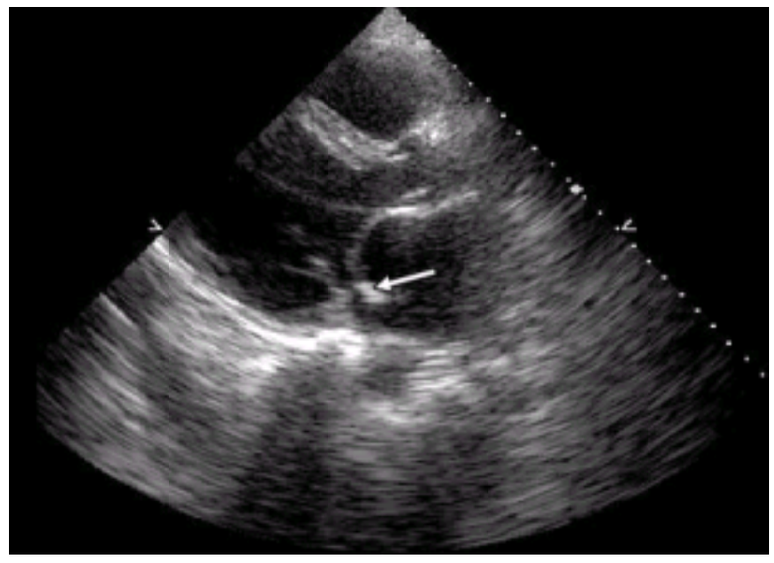
FIGURE 95.8 Relationship of valve pathology and ventricular function. *Mild*, *moderate*, and *severe* refer to ventricular dysfunction. (From Hendren WG, Nemec JJ, Lytle BW, et al. Mitral valve repair for ischemic mitral insufficiency. *Ann Thorac Surg* 1991;52:1246–1252, with permission.)



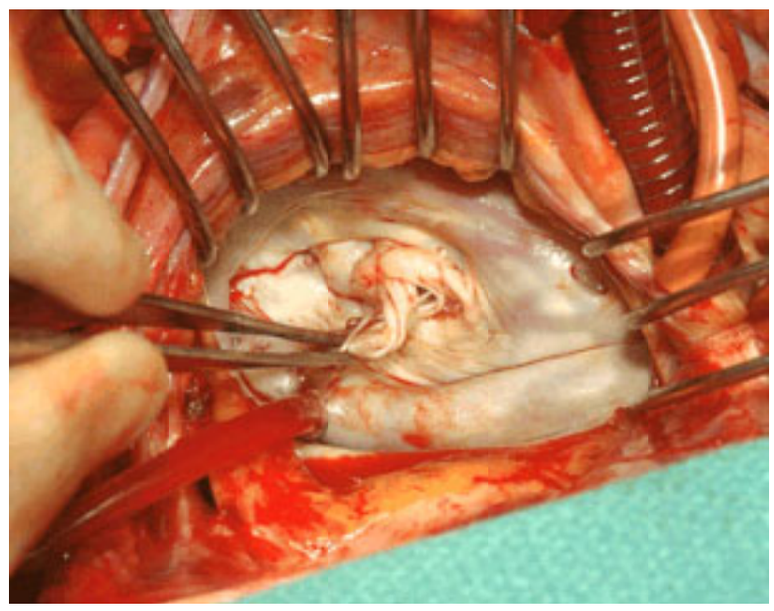
***e*FIGURE 95.8.1** Chronicity of mitral regurgitation and severity of left ventricular dysfunction. *Mild*, *moderate*, and *severe* refer to ventricular dysfunction. (From Hendren WG, Nemec JJ, Lytle BW, et al. Mitral valve repair for ischemic mitral insufficiency. *Ann Thorac Surg* 1991;52:1246–1252, with permission.)



***e*FIGURE 95.8.2** Survival after mitral valve repair for ischemic mitral regurgitation, depending on the pathology of the valve. This, in reality, reflects the severity of left ventricular dysfunction. (From Hendren WG, Nemec JJ, Lytle BW, et al. Mitral valve repair for ischemic mitral insufficiency. *Ann Thorac Surg* 1991;52:1246–1252, with permission.)



Parasternal long-axis view of a papillary muscle rupture after myocardial infarction. Note the piece of papillary muscle attached to the tip of the anterior mitral leaflet as it flails into the left atrium (demonstrated by the arrow).



Intraoperative field demonstrating a mitral valve with a torn papillary muscle prolapsing across the mitral valve into the left atrium. The surgeon has the papillary muscle in forceps demonstrating the chordae attached to the posteromedial commissure, predominantly attached to the anterior mitral leaflet. (The patient's head is to the left of the screen and feet to the right.)

Surgical pathology specimen demonstrating a torn papillary muscle seen to the lower right of the screen, attached via chordae to a portion of the anterior mitral leaflet. Note the torn "ragged edges" at the bottom of the papillary muscle head.

VIDEO

Video 95.11 Parasternal long-axis view of a ruptured papillary muscle after myocardial infarction. Note the bright mass (papillary muscle) attached to the tip of the anterior mitral leaflet as it flails into the left atrium. This resulted in severe mitral regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 95.12 Intraoperative 0-degree transesophageal echo showing a flail posterior mitral leaflet from a patient with myxomatous valve disease. Note the movement of the torn chordae attached to the tip of the leaflet (see color Doppler assessment). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Indications for Mitral Valve Repair or Replacement with Reduced Left Ventricular Function

Clinically, there are no published data available to separate out patients with heart failure and mitral regurgitation so advanced that the patients would be better served by heart transplantation. In general, patients requiring continuous intravenous inotropes are not considered for mitral valve surgery. Patients weaned from inotropes have been successfully operated on. On the other side of the coin, the best approach for patients with 2 to 3+ mitral regurgitation remains unclear. In general, if preoperative echoes have shown 3+ mitral regurgitation and revascularization is unlikely to eliminate the regurgitation, valve repair should be considered.

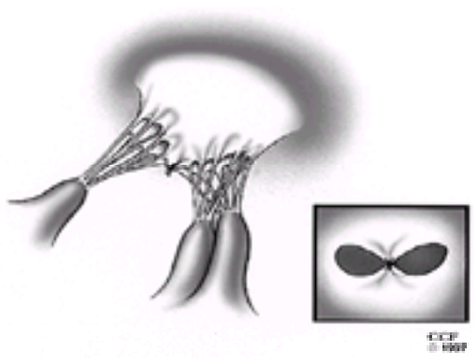
Techniques

For successful surgical results when operating on ventricles with severe reduction in LV function, meticulous attention to myocardial protection, complete revascularization, and knowledge of valve repair techniques is paramount.

Chapter 21 focuses on valve repair techniques, and details can be found elsewhere in this text. Annuloplasty is the main technique for patients with dilated mitral annuli (*e*Fig. 95.8.3 and *e*Fig. 95.8.4). The addition of a stitch to approximate the leaflets (Alfieri) (*e*Fig. 95.8.5) may help reduce late mitral regurgitation from apical displacement but this remains to be proven. Repair techniques such as leaflet resection for prolapse and flail segments, chordal transfer and shortening, papillary muscle plication, and commissural plication are used as necessary. In general, ischemic mitral regurgitation tends to be multifactorial and repairs more difficult. Chordal-sparing mitral valve replacement may be simpler, more effective, and result in similar short- and long-term outcomes.

***e*FIGURE 95.8.3** Operative photograph of a posterior annuloplasty band. By undersizing the band, the coaptation zone of the leaflets increases substantially. In some cases, it converts the mitral into a monocuspid (anterior leaflet) valve.

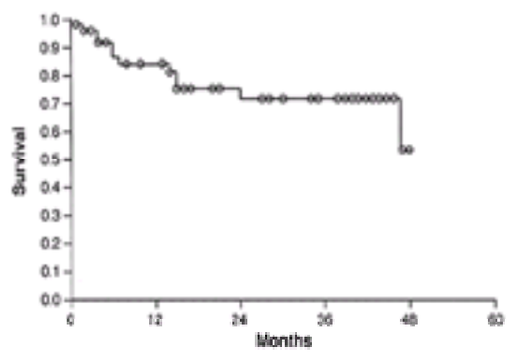
***e*FIGURE 95.8.4** A Carpentier's annuloplasty band. In degenerative mitral disease, only the posterior annulus dilates. The entire annulus dilates in patients with ventricular enlargement.



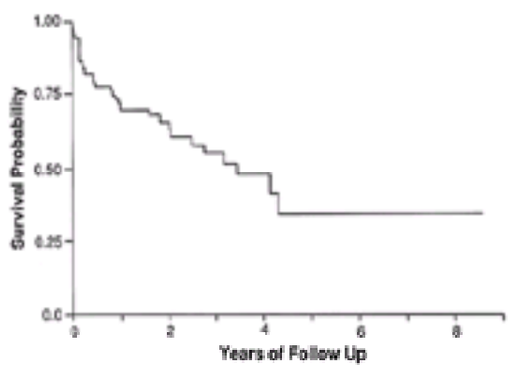
***e*FIGURE 95.8.5** An Alfieri's or bow-tie stitch directly increases leaflet coaptation. In large degenerative valves, there is little concern for causing mitral stenosis. However, in patients with apical displacement of the papillary muscles without annular enlargement, an undersized annuloplasty band along with this stitch may cause mitral stenosis.

Results

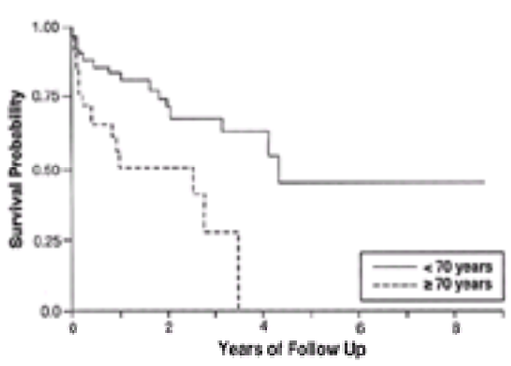
Early reports of mitral valve surgery for ischemic cardiomyopathy showed relatively poor results. Currently at The Cleveland Clinic Foundation, the overall mortality for mitral valve replacement and CABG has decreased over the past decade to less than or equal to 10%. Similar results have been published by Gangemi from the University of Virginia. In their experience, 16 patients with a mean EF of 23% and 4+ mitral regurgitation underwent CABG with mitral valve repair with a 6.3% operative mortality and a 87% 1-year survival (57). Bolling et al. studied 100 elderly patients with ischemic mitral regurgitation (52). There were four early deaths with six late deaths. NYHA class improved significantly with a reduction in hospital admissions for CHF. For patients with profound end-stage LV dysfunction (mean EF = 16%) and severe mitral regurgitation, Bolling et al. have successfully repaired the valve in 130 patients, with one death and a 1-year survival of 82%. Five-year survival is 56% (58,59) (*e*Fig. 95.8.6). Patients less likely to do well have an ischemic etiology of the mitral regurgitation, larger ventricles, and pulmonary hypertension. Chen et al. have reported similar results (*e*Fig. 95.8.7). Survival is much worse in patients over 70 years of age and those with preoperative CHF (*e*Fig. 95.8.8 and *e*Fig. 95.8.9) (51).



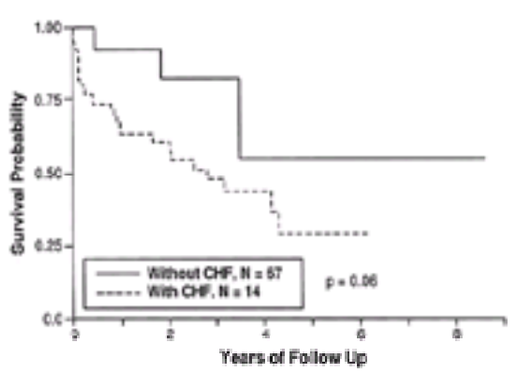
***e*FIGURE 95.8.6** Survival (*p*) after mitral valve repair in patients with end-stage cardiomyopathy. (From Bolling SF, Pagani FD, Deeb GM, et al. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;115:381–388, with permission.)



***e*FIGURE 95.8.7** Survival after mitral valve repair for cardiomyopathy. (From Chen FY, Adams DH, Aranki SF, et al. Mitral valve repair in cardiomyopathy. *Circulation* 1998;98:II-124–II-127, with permission.)

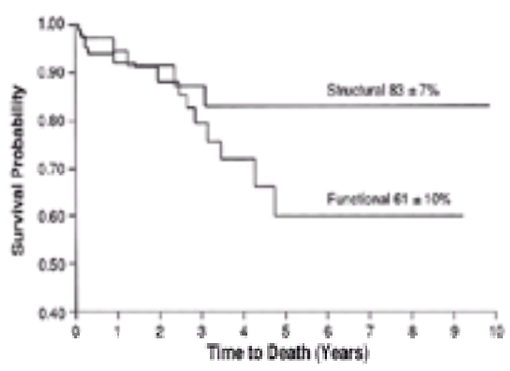


***e*FIGURE 95.8.8** Age again is associated with reduced survival after mitral valve repair in patients with cardiomyopathy. (From Chen FY, Adams DH, Aranki SF, et al. Mitral valve repair in cardiomyopathy. *Circulation* 1998;98:II-124–II-127, with permission.)

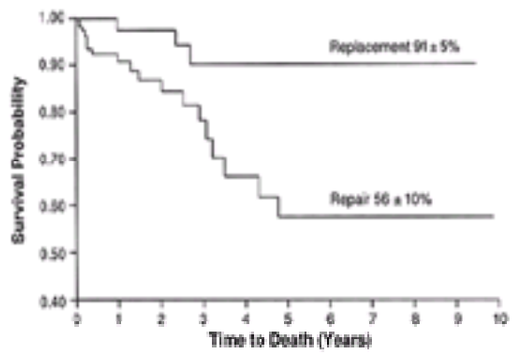


***e*FIGURE 95.8.9** Preoperative heart failure symptoms are associated with decreased survival after mitral repair for cardiomyopathy. CHF, congestive heart failure. (From Chen FY, Adams DH, Aranki SF, et al. Mitral valve repair in cardiomyopathy. *Circulation* 1998;98:II-124–II-127, with permission.)

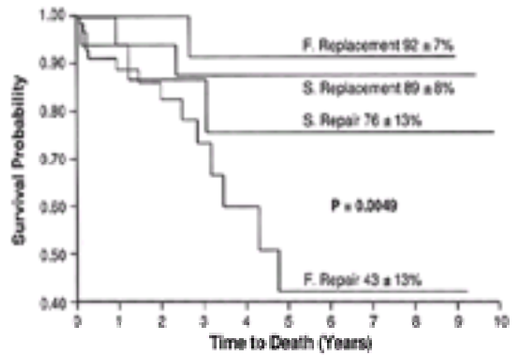
The documented superiority of mitral valve repair over replacement in patients with degenerative disease is thought to apply to patients with advanced ventricular dysfunction. However, this may not be the case, especially in patients with functional ischemic mitral regurgitation (eFig. 95.8.10). Patients who undergo valve repair, often with an annuloplasty only, have significantly worse survival than valve replacement (eFig. 95.8.11). This reflects the functional state of the ventricle (worse with valve repair) and not the technique. However, for patients with functional mitral regurgitation (normal valves; apical displacement of papillary muscles), Cohn et al. have shown better survival and less morbidity and mortality in the valve replacement groups (eFig. 95.8.12) (55). These authors believe that chordal-sparing mitral valve replacement is likely to be as efficacious as valve repair, especially in patients with mitral regurgitation that has a multifactorial complex basis and may not be amenable to easy and durable repair techniques.



***e*FIGURE 95.8.10** Decreased survival in patients undergoing valve repair or replacement when the mitral regurgitation is based on ventricular dysfunction. *Structural* refers to valve abnormality as a mechanism for mitral regurgitation, whereas *functional* refers to normal valves with left ventricular dysfunction. (From Cohn LH, Rizzo RJ, Adams DH, et al. The effect of pathophysiology on the surgical treatment of ischemic mitral regurgitation: operative and late risks of repair versus replacement. *Eur J Cardiothorac Surg* 1995;9:568–574, with permission.)



***e*FIGURE 95.8.11** Reduced survival in the repair group reflects the poor left ventricular dysfunction in this group. (From Cohn LH, Rizzo RJ, Adams DH, et al. The effect of pathophysiology on the surgical treatment of ischemic mitral regurgitation: operative and late risks of repair versus replacement. *Eur J Cardiothorac Surg* 1995;9:568–574, with permission.)



***e*FIGURE 95.8.12** Surprising survival advantage after mitral replacement for functional regurgitation. F, functional; S, structural. (From Cohn LH, Rizzo RJ, Adams DH, et al. The effect of pathophysiology on the surgical treatment of ischemic mitral regurgitation: operative and late risks of repair versus replacement. *Eur J Cardiothorac Surg* 1995;9:568–574, with permission.)

MECHANICAL CIRCULATORY SUPPORT

A detailed discussion of mechanical circulatory support is beyond the scope of this chapter, but it is extremely important in the surgical management of patients with end-stage heart disease. Mechanical support can be categorized in multiple ways depending on the duration of support (acute or chronic), type of pump (pulsatile vs. continuous flow), completely implantable, implantable or external, total heart replacement, or ventricular assist devices (Table 95.5).

Device	Pulsatile	Short and long-term	Internal
Extracorporeal membrane oxygenation	No	Short	No
ABIOMED	Yes	Short	No
AB-180	No	Short	Yes
HeartMate	Yes	Long	Yes
Novacor	Yes	Long	Yes
Thoratec	Yes	Short/long	Yes
LionHeart	Yes	Long	Completely
Debakey	No	Long	Yes
Jarvik 2000	No	Long	Yes
ABIOCOR	Yes	Long	Completely

TABLE 95.5 CHARACTERISTICS OF MECHANICAL SUPPORT DEVICES

Currently, mechanical support is indicated for postcardiotomy pump failure, acute MI with cardiogenic shock, as a bridge to transplantation, and for patients with the potential for myocardial recovery. Permanent implant or destination therapy is the ultimate goal of mechanical support but has yet to be realized. The REMATCH trial may help define the role of implantable LVADs as an alternative for patients with end-stage cardiomyopathy (60).

Postcardiotomy Support

The need for postcardiotomy mechanical support is declining, despite increasing numbers of high-risk operations (61). To date, all short-term support devices have had equivalent outcomes with approximately 30% of patients surviving the hospitalization (62,63,64 and 65). Despite numerous advances in caring for these patients over the past 20 years, only the ability to convert these patients to an implantable LVAD has improved survival to nearly 50% (66,67). Samuels et al. have recommended that earlier initiation of mechanical support in the operating room to avoid the toxic effects of high doses of inotropes could improve outcome (68).

Bridge to Transplant

The largest collective experience worldwide with mechanical support has been in the group of patients bridged to transplant. The three most common devices are the TCI HeartMate (Fig. 95.9) (Thermo Cardiosystem, Woburn, MA), Novacor (WorldHeart Corp., Ottawa, Canada), and Thoratec VAD (Thoratec Laboratories, Berkeley, CA). A much smaller experience has accumulated with the Cardiowest (Cardiowest Technologies, Tucson, AZ) total artificial heart.

HEART SOUNDS

Audio 95.13 Left ventricular assist device. Auscultation performed in a 48-year-old male patient with end-stage cardiomyopathy after implantation of a Novacor pneumatic left ventricular assist device as a bridge to transplantation. Left lower sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

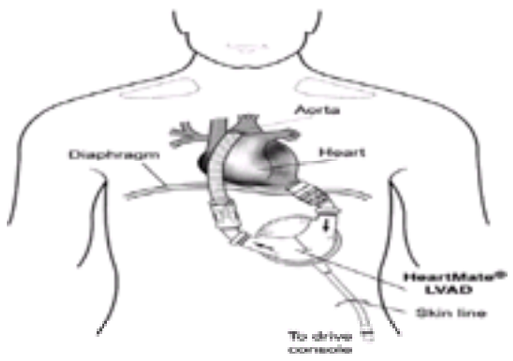


FIGURE 95.9 HeartMate left ventricular assist device (LVAD). (From Slaughter MS, Pappas PS, Tatooles AJ. Modified implant technique for the pneumatic HeartMate left ventricular assist system. *Journal of Congestive Heart Failure and Circulatory Support* 2000;1:123–125, with permission.)

In general, these pumps have worked quite well, with 60% to 75% of patients surviving to transplant (66,69,70). Complications are frequent, including thromboemboli, pump-related infections, and mechanical and valve dysfunction. It is hoped that the smaller axial flow pumps will reduce or eliminate some of these problems as the implantation is much simpler and the pumps are smaller so infection may be less (Fig. 95.10). There are no valves, which may reduce the risk of thromboemboli and eliminates the problem of valve failure.

FIGURE 95.10 A,B: Jarvik axial flow pump. The metal portion is inserted into the apex of the ventricle with the graft anastomosed to the descending thoracic aorta. (From Katsumata T, Westaby S. Implantable axial flow impeller pumps. *J Circ Support* 1998;1:13–19, with permission.)

Ventricular Recovery

It was noticed early in the LVAD bridge to transplant that many hearts had decreased in size, remodeled, and improved in function. Some worked so well that the pump was removed and transplant avoided.

In addition to macroscopic changes, neurohormonal and histologic changes supported the concept that unloading the ventricle may promote recovery. It has been more difficult to characterize ventricles and patients who may recover on support. Hetzer et al. reported the largest experience with 23 patients weaned from LVAD support (71). In general, only patients with idiopathic dilated cardiomyopathy, younger patients, those with shorter durations of heart failure symptoms, and those with greater and earlier remodeling while on support had lasting recovery. It is estimated that of the patients supported with LVADs for long-standing ischemic or dilated cardiomyopathies less than 10% will be recoverable. Given the declining number of donor hearts, identifying even a small group of potentially weanable patients is critical. Additionally, the best support parameters that rest the ventricle but also load it to promote recovery and avoid atrophy and fibrosis remain to be determined. Finally, adjuvant pharmacology, gene therapy, or myoblast transfer may be needed to increase the number of weanable patients.

Destination Therapy

The original purpose of mechanical support funding was to develop a permanent cardiac substitute. That dream remains elusive. Current LVADs work well as a temporary bridge to transplantation but are unlikely to provide the durability and quality of life necessary for more widespread application. The REMATCH trial will provide some insight into how close to the goal we are (60).

Future Devices

The next generation of devices will be the continuous flow pumps (72). These are either axial (straight) or centrifugal (right angle inflow and outflow relationship) miniature pumps that generate flow through high-speed revolution of an impeller blade (Fig. 95.10). The advantages of these pumps are they are much smaller and can be used in pediatric patients and small adults, limited dissection is needed to create a pump pocket, they are quiet, they work without valves, and they are technically easier to convert to a completely implantable design. They currently are in trial in Europe, and trials will begin soon in the United States. It is hoped that the smaller continuous flow pumps will have fewer complications with greater durability and provide an alternative for nontransplant candidates.

NEW SURGICAL THERAPIES FOR CONGESTIVE HEART FAILURE

Acorn Cardiac Support Device

Cardiomyoplasty was developed with the idea that the trained muscle would augment systolic function of the ventricle. Research showed this augmentation was infrequent and the major advantage was a result of a passive girdling of the LV that reduced wall stress, decreased future LV enlargement, and occasionally reversed remodeled the ventricle. This led to the development of a simple mesh-like jacket (Fig. 95.11 and Fig. 95.12) that is slipped around the heart with the hopes of preserving or improving myocardial properties.

FIGURE 95.11 Acorn mesh.

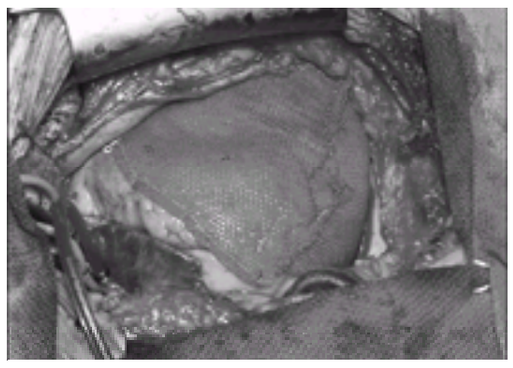


FIGURE 95.12 Acorn after placement around the left ventricle and right ventricle.

Animal studies are quite promising. In an ischemic heart failure model in dogs, the CSD after 3 to 6 months resulted in lower end systolic and end diastolic volumes, improved adrenergic reserve, and showed no evidence of constricting the myocardium. These investigators showed that the CSD attenuates cardiomyocyte stretch, limits cardiomyocyte hypertrophy, and improves sarcoplastic reticulum Ca^{2+} ATPase cycling (73).

In two small series published as abstracts, the Acorn CSD (Acorn Cardiovascular, St. Paul, MN) appears to reduce LV size and improve functional class. Currently, a randomized trial is under way that has two arms: CSD alone versus medical therapy, and CSD plus mitral valve surgery versus mitral valve surgery alone. The cardiomyoplasty experience has helped guide the selection of patients. This device will likely be most beneficial in retarding progression of chamber enlargement. This requires its application in patients with class II to III symptoms and moderate (6.0 to 7.5 cm) chamber enlargement. More advanced stages of heart failure are unlikely to benefit from the CSD and operative mortality will be substantially higher. An interesting application of this technology would be in patients after a large acute MI to prevent remodeling. Identifying patients at high risk for remodeling after an acute MI remains to be completely defined.

Myosplint

Unlike the Acorn CSD, which passively remodels the ventricle, the Myosplint (Myocor Inc., Plymouth, MN) actively and acutely reshapes the LV. Conceived after the Batista principle that geometric reduction in LV size should improve wall stress, the Myosplint is a transventricular splint with epicardial pads that reduce the LV radius by creating a bilobular or two-chamber LV (Fig. 95.13 and Fig. 95.14).

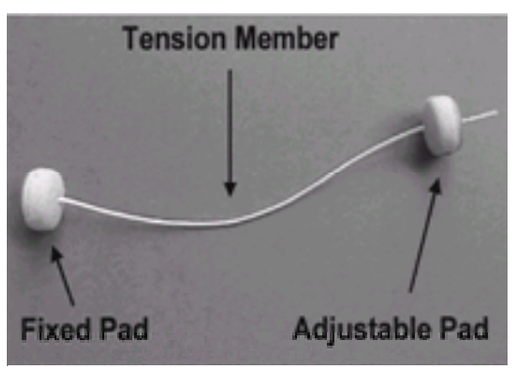


FIGURE 95.13 Myosplint tension member. This metal wire traverses the left ventricle in three spots from base to apex.

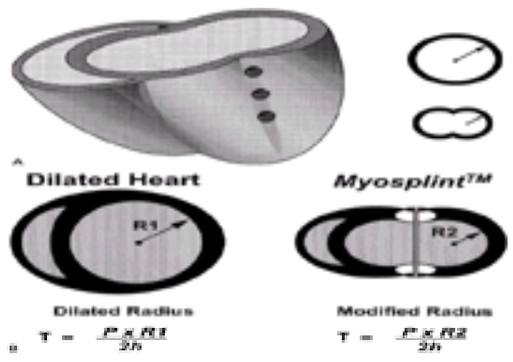


FIGURE 95.14 A,B: Myosplint concept. Stress reduction through ventricular shape change **(A)**.

In early animal studies, LVEF increased from 19% to 38% with significant decreases in end systolic volume (75). It is anticipated that this device will be applied to patients with more advanced heart failure symptoms and larger ventricular volumes.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The statistics speak for themselves. An ever-growing pool of patients with heart failure, limited biologic replacement therapy, and an enlarging armamentarium of surgical therapies and devices suggest that surgery for heart failure will continue to play an important role in treating these patients.

The greatest difficulty in choosing a therapy is the rapidly changing landscape of heart failure medicine. In addition to angiotensin-converting enzyme inhibitors and beta-blockers, angiotensin-receptor blockers, anti–tumor necrosis factor, and other immunotherapy, biventricular pacing, automatic internal cardiodefibrillators, and gene and myoblast therapy are all being assessed in these patients and may affect ventricular remodeling, ischemia, arrhythmias, and mitral regurgitation such that they compete favorably with a surgical procedure. Conversely, waiting until the patient's disease is so far advanced before considering surgical therapy significantly increases the operative risk and most certainly diminishes the benefit. As this chapter outlines, operations for heart failure can be done with low mortality and the concerns that these are high-risk procedures and should be avoided are no longer true. The real question is whether they provide an improvement in the quality of life of the patient and, secondarily, whether they prolong survival at a reasonable cost.

Uncertainty remains as to the benefit of procedures with advanced heart failure. Patients with extensive myocardial ischemia or hibernation by functional studies should undergo revascularization. There is no justification to consider these patients for inclusion in a randomized trial. On the other hand, there is a great deal of uncertainty and conflicting information about the value of revascularization in patients with only heart failure symptoms, no ischemia or hibernation, and markedly enlarged ventricles. This group should and likely will be evaluated in a randomized trial that includes remodeling and revascularization versus medical therapy.

Other randomized trials are investigating the role of mitral valve repair in end-stage patients compared with medical therapy and the benefit of repair valves with lesser degrees of mitral regurgitation to prevent remodeling.

Assist devices are seen as the answer to end-stage heart disease. Some people say no one should die from heart failure without a trial on an assist device, probably with an AICD to reduce the risk of sudden death. It is hoped that the smaller rotary pumps will make the implant easier, be totally implantable, and run forever. The REMATCH trial may give us some insight into these issues. The profession and society as a whole will need to decide what cost we are willing to expend to improve

the quality of and, it is hoped, extend the duration of life in these patients. This undoubtedly will assume greater urgency in the next few years.

THE FUTURE

The lines between heart failure medicine and surgery will grow less distinct. Operations will be performed earlier to prevent the deleterious effects of remodeling and long-standing valve insufficiency. Adjuvant gene or myoblast therrapy along with tissue engineering may allow us to rebuild segments of damaged myocardium. Assist devices will get smaller, more durable, completely implantable, and less expensive, justifying a wider application of this technology.

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GENERAL TECHNIQUES IN MOLECULAR CARDIOLOGY

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"Indicates text or graphics that appear only in the electronic versions of this text."

Historical Perspective
Models Used in Cardiovascular Research
Cell Culture
In Vivo Models
Analysis of Gene Expression
RNA (Northern) Blot Analysis
Ribonuclease Protection Assays
Polymerase Chain Reaction
In Situ Hybridization
New Directions: Laser Capture Microdissection
Analysis of Transcription
Nuclear Run-on (or Run-off) Analysis
Promoter Analysis
Protein Identification
Molecular Cloning
Screening Libraries
Constructing and Screening Complementary DNA Libraries
Constructing and Screening Genomic Libraries
Functional (Expression) Cloning
Use of DNA Libraries for Comparing Expression of Multiple Genes
Subtraction Techniques
Differential Display of Messenger RNA
Yeast Two-Hybrid System
Recent Advances in Molecular Cloning
Molecular Methods for Altering Gene Expression
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Chapter References

HISTORICAL PERSPECTIVE

A series of critical experiments in the 1950s and early 1960s established what has come to be known as the central dogma of molecular biology. These experiments demonstrated that deoxyribonucleic acid (DNA) is the genetic material responsible for transmitting heritable information, that DNA is "transcribed" into messenger ribonucleic acid (mRNA), and that mRNA is then "translated" into proteins. However, several crucial discoveries were required before detailed analyses of these processes could be routinely made. One of these was the identification of a series of DNA-processing enzymes from bacteria and bacteriophages. These enzymes included restriction endonucleases, which cleave DNA at sequence-specific sites; polymerases, which synthesize new DNA from a DNA template; and ligases, which can join two pieces of DNA together. This technology ushered in the era of recombinant DNA, allowing small pieces of DNA to be isolated, sequenced, ligated to other pieces of DNA, radiolabeled, and used as molecular probes.

The discovery of the enzyme reverse transcriptase had a particularly great impact on the field of molecular biology. Reverse transcriptase synthesizes DNA from an RNA template, thus allowing one to make a strand of DNA that is complementary to the mRNA. The ability to synthesize complementary DNA (cDNA) from mRNA isolated from a specific tissue was critical to the development of cDNA libraries, ushering in the era of molecular cloning. Other important technical advances included the development of nucleic acid and protein gel electrophoresis to separate different species by size, systems for "blotting" nucleic acids and proteins on filters so that they can be subjected to a variety of analyses, the development of "hybridization" techniques to identify specific DNA and RNA molecules, and the advent of DNA sequencing. The development of viral and plasmid "vectors" that are designed to introduce DNA into a variety of cells where it can be transcribed into mRNA and then translated into proteins has provided powerful tools for the functional analysis of specific genes as well as the generation of recombinant proteins, a number of which are now routinely used in clinical medicine.

The development of appropriate experimental models was critical to the application of molecular techniques to basic investigation in cardiovascular disease. A critical breakthrough was the establishment of culture systems for studying the individual cellular components of the cardiovascular system. The ability to study each cell type as an essentially "pure" culture provided the initial stimulus for a vast array of studies that examined cell surface receptors, transmembrane signals, gene regulation, and the pathways involved in growth, migration, and control of shape. A variety of "coculture" models have been developed to examine interactions among cell types. The breakthroughs in tissue culture techniques have been paralleled by the development of a variety of animal models of cardiovascular disease. These include models of vessel injury, congestive heart failure, and dyslipidemia, as well as animals with genetic preponderance toward hypertension, atherosclerosis, and other cardiac diseases. These *in vivo* models have been complementary to cell culture and have allowed investigators to verify findings in culture using a more clinically relevant setting. The ability to generate "transgenic" animals—animals whose genetic makeup has been altered using recombinant DNA techniques—has allowed investigators to examine the functions of specific *in vivo* models and to develop small animal models that more closely mimic human pathology.

This chapter is designed as an overview of some of the major molecular and cellular techniques that are used in contemporary cardiovascular research. The revolution in molecular biology over the previous century has provided the tools to examine biologic processes at their most basic level. As is evident throughout this text, the application of molecular techniques to cardiovascular research has led to major advances in our understanding of the pathobiology of cardiovascular disease. Although the techniques described are widely used in many areas of biologic investigation, our focus is on their application to cardiovascular investigation; as such, we hope that it provides a frame of reference for understanding the experiments described in the other chapters of this book. The following sections of this chapter describe the cell culture and *in vivo* models that were developed to allow the application of basic molecular techniques to the study of cardiovascular diseases, the major methods used in the study of gene expression, the techniques for molecular cloning, and the methods used to alter gene expression.

MODELS USED IN CARDIOVASCULAR RESEARCH

The development of appropriate experimental models was critical to the application of molecular techniques to cardiovascular research. Hundreds of models have been developed over the past few decades to help further our understanding of cardiovascular pathology. This section provides an overview of some of the models that are most commonly used.

Cell Culture

Cardiovascular diseases involve complex interaction among multiple cell types. As is discussed in later sections, state-of-the-art techniques are being increasingly refined to allow gene expression to be monitored in individual cells in their natural milieu. In spite of these advances, the ability to examine pure populations of cells in

an environment that can be experimentally controlled has provided a wealth of information about the biologic properties of each cell type and continues to be a powerful approach. The relevance of data obtained from cell culture systems to the intact organism must be established experimentally. Hence, the ability to move rapidly from cell culture, to animal models, to clinical studies, and back is an important feature of contemporary molecular cardiology. The following paragraphs outline some of the procedures that are used to study cells in culture, the problems inherent in such cell culture systems, and more recent approaches to addressing cell-cell interactions.

Smooth Muscle Cell Culture

Smooth muscle cells have been cultured from a number of vascular beds (1), including aorta, carotid, mesenteric, pulmonary, and coronary arteries, as well as from veins. Although the most used system has been that of the rat, smooth muscle cells have been cultured from rabbit, bovine, primate, human, and, most recently, murine sources. The availability of explanted hearts from human cardiac transplant recipients has also led to a marked increase in studies that use human smooth muscle cell culture. The general approach to smooth muscle cell culture is to grow cells in plastic dishes in the presence of culture medium and 10% to 20% serum (usually fetal bovine serum). Two approaches have been used to obtain smooth muscle cells. For smaller animals and vessels, such as rat aorta or human coronaries, collagenase/elastase digestion accompanied by fine dissection has provided a means of obtaining essentially pure cultures of smooth muscle cells (1). For larger vessels with extensive media, such as human aorta, the use of explants (2) has proved to be more successful than enzymatic disruption. In this technique, the vessels are dissected free of adventitia and endothelium and cut into small chunks, and the cells are allowed to proliferate and migrate onto the culture dish. These preparations tend to have lower degrees of purity than enzyme digests but provide ample supplies of smooth muscle cells.

Although both techniques provide high yields of smooth muscle cells, they contain mixed populations of smooth muscle cell types. In most cases, the cells grow rapidly to cover the surface of the tissue culture plates and can then be passaged. In this process, the cells are removed from the plastic surface by trypsin digestion, diluted at ratios of 1:5 to 1:10, and transferred to an expanded number of new plates. This allows for large-scale and complex experiments that involve dozens, and sometimes hundreds, of plates. Cells can also be grown on slides or cover slips for specialized procedures. In addition, cells can be grown on or in a variety of matrices, such as those comprised of collagen, vitronectin, or mixtures of matrix proteins. Such matrices often affect the properties of the cultured cells (3). Ultimately, normal smooth muscle cells develop senescence and can no longer be passaged. Therefore, they are characterized as strains, rather than cell lines, which can be grown indefinitely.

A major drawback to the use of cell culture is the phenomenon characterized as *phenotypic modulation*. In the normal vessel, smooth muscle cells maintain a contractile phenotype in which their cytoplasm is largely comprised of actin and myosin filaments, and they do not divide in response to growth factors. In cell culture, smooth muscle cells quickly lose their filaments and modulate to a synthetic phenotype in which they no longer contract but divide rapidly in response to growth factors (4,5 and 6). To date, attempts to identify the genes for altering smooth muscle cell phenotype have proved unsuccessful, and the switch from the synthetic back to the contractile phenotype has not been observed. The two phenotypes described in cell culture mimic those seen in atherosclerosis, in which the medial smooth muscle cells modulate to a synthetic phenotype, migrate to the intima, and grow rapidly. In contrast to cell culture, these synthetic smooth muscle cells appear to be able to modulate back to the contractile phenotype under certain conditions. It should thus be stressed that studies that involve smooth muscle cell cultures focus on cells whose phenotypes are decidedly different from those of normal vessels but may be more representative of those found in injured or atherosclerotic vessels. This remains an important limitation in interpreting studies using cultured smooth muscle cells. Despite these limitations, considerable information has been obtained from the use of cell culture systems, and they remain a mainstay of smooth muscle cell biology. The use of smooth muscle cell culture has been extensively reviewed in a two-volume set edited by the Campbells (7).

Endothelial Cell Culture

Studies on vascular endothelium have also extensively availed themselves of cell culture. Unlike smooth muscle cells, endothelial cells are present as a single layer lining the intima. Therefore, smaller amounts of endothelial cells can be obtained from blood vessels. These cells also tend to develop senescence more quickly than smooth muscle and therefore provide a greater challenge in obtaining large numbers of cells. A favorite choice for endothelial cell culture has been the human umbilical vein endothelial cell. This cell can usually be passaged four to five times, and a large number of cells can be obtained from individual placentas (8). The ready availability of placentas has been instrumental in the popularity of these cells. Other sources include arterial endothelial cells from bovine, rat, and human sources. Unlike smooth muscle cells, endothelial cells grow poorly on plastic or glass and are usually grown on a matrix of gelatin, collagen, or fibronectin.

Two particularly important properties of cultured endothelial cells have received considerable attention. The first is the ability of endothelial cells to respond directly to shear or turbulence (9). This has led to the development of a variety of cell culture systems to study endothelial cell biology under various flow conditions. The second property is the ability of microvascular endothelial cells to form capillaries under appropriate cell culture conditions (10). This has allowed investigators to use cell culture to model capillary formation, such as that seen in tumor angiogenesis and in angiogenesis associated with ischemia.

Cardiac Myocyte Culture

Cardiac myocytes that are isolated by explant or enzymatic digestion of fetal and adult hearts maintain their contractile phenotype in culture on plastic and have been particularly useful for electrophysiologic as well as molecular biologic studies (reviewed in reference 11). Because they are at or near terminal differentiation, cardiac myocytes that are isolated from late stages of development do not divide in culture and, therefore, can only be used as primary cultures. Isolation of relatively pure populations of myocytes requires dissection to isolate the chamber of interest, mechanical and enzymatic disruption, and serial plating or density centrifugation to remove fibroblasts (which grow rapidly in culture and would quickly outnumber the myocytes). The passage of cardiac myocytes in serial culture has thus far been limited to transformed or cardiac tumor–derived cells that show varying degrees of differentiation in culture. The ability to expand large quantities of fetal cardiac myocytes in culture to repopulate damaged myocardium *in vivo* remains a major goal.

Coculture Techniques

As noted previously, a rational approach to vascular biology has been to use “pure” cell culture systems to study the biologic properties and responses of individual cell types. The next step in the process is to examine the effects of one cell type on another. A variety of systems have been used to raise the level of complexity and to address cell-cell interactions. The simplest has been the use of “conditioned” medium. In this approach, the culture medium that is collected after incubation with one cell type is added to another. The use of conditioned medium has been particularly important in examining stable humoral factors synthesized by one cell that have effects on the other. A second approach is to culture two cell types in chambers separated by a semiporous membrane. The rationale for this approach is to prevent direct cell contact but to allow humoral effects involving molecules with shorter half-lives. This approach also allows for cross talk, in which one cell may induce the other to synthesize a molecule, which then acts on the original cell. The third approach is to allow for direct cell contact, either by plating one cell on top of another or by plating one cell on plastic monolayers and the other on beads (12). The use of beads allows ready separation of one cell type from the other at the end of the experiment. The use of cocultures has provided important information on endothelial–smooth muscle cell interactions and has led to the discovery of a large number of important molecules that regulate endothelial and smooth muscle cell phenotype. In addition to endothelial–smooth muscle cell coculture, attention has focused on cocultures of endothelial cells and leukocytes. These studies have been stimulated by the discovery of families of molecules that mediate the interaction of leukocytes with the vessel wall and, specifically, with the endothelium. These studies have been reviewed (13).

Other Cell Types

The cell types described previously in this section represent some of the more commonly studied in the cardiovascular literature. The list is by no means exhaustive. Most of the cells types involved in the pathogenesis of cardiovascular diseases, including fibroblasts, lymphocytes, macrophages, and circulating stem cells, can be grown in culture.

In Vivo Models

Despite the invaluable contribution of cell culture, the utility of molecular cardiology to improve the treatment of human disease is dependent on the development of animal models that accurately mimic these diseases. Although naturally occurring animal models of cardiovascular disease have been exploited, many of the common human diseases are rarely seen in animals. In recent years, the increasing application of transgenic technology to cardiovascular research has allowed the development of more sophisticated mouse models of cardiovascular pathology. Although the small size of the mouse presents challenges, a variety of diagnostic techniques have been adapted for its use, including echocardiography (14), micromanometry (15), and *in vivo* magnetic resonance imaging (16).

Atherosclerosis

One model that is commonly used to study atherosclerosis and arterial injury involves the use of balloon catheters to denude the endothelium and to injure the media (17). The approach to catheterization is similar to that used in human angioplasties, involving cannulation of a distal artery and passage of a balloon-tipped catheter into the area to be injured. Injuries can range from gentle endothelial denudation to injuries that tear the internal elastic lamina and damage the media. Alternative approaches include external injury to the artery, for example, using a forceps to crush the artery (18,19), or internal injury using air (20) or electrical stimulation (21).

Such models have been used in rats, rabbits, transgenic mice, dogs, pigs, and nonhuman primates. The hallmark of this model is the development of intimal hyperplasia, characterized by the migration and proliferation of smooth muscle cells in the intima. An example is shown in Figure 96.1.

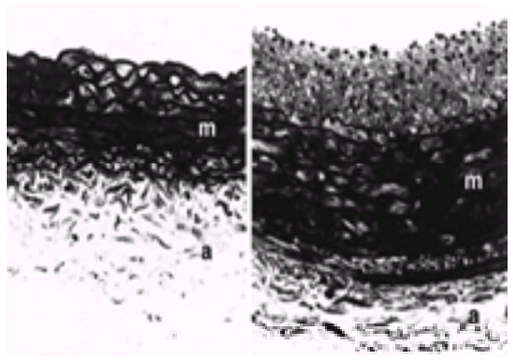


FIGURE 96.1 Intimal hyperplasia following balloon injury of the rat aorta. Cross section of a normal rat aorta **(left)** stained with hematoxylin and eosin and a rat aorta 2 weeks after balloon catheter injury **(right)** showing the development of a thickened intima (i). a, adventitia; m, media.

Balloon injury models have been instrumental in elucidating the early molecular and cellular events following vessel injury and have also been used widely for studying approaches to inhibit intimal hyperplasia. Because intimal hyperplasia is a major component of the atherosclerotic plaque and is thought to play a role in restenosis after angioplasty, balloon injury models have received considerable attention. One criticism of most models is that they involve the use of normal vessels, whereas atherosclerosis occurs and angioplasty is performed in the setting of abnormal vessels that contain lipid-rich, calcified plaques. Studies that use injury to normal vessels have contributed greatly to understanding cell biology *in vivo* but have been less useful for predicting the effects of pharmacologic interventions in human disease.

An alternative to injuring normal vessels is the use of double-injury models in which a second injury is performed several weeks after an initial injury (22). In rodents, double injury is associated with a more thrombotic response than that seen after single injury. Whether this model is more representative of human atherosclerosis remains to be determined.

In addition to acute arterial injury, a variety of *in vivo* systems have been used to model the more chronic development of atherosclerosis, such as that seen in human disease. These have included the use of high-fat/high-cholesterol diets in rabbits (reviewed in reference 23), pigeons (24), pigs (25), and nonhuman primates (26,27 and 28). Although these diets are often associated with the types of lesions that are seen in early atherosclerosis, they are not as severe as those seen in human disease (29). A variety of genetically engineered hyperlipidemic transgenic mice that more closely resemble the complex lesions of human atherosclerosis have been developed (30). The study of genetically altered mice has led to dramatic advances in the study of lipoprotein metabolism and atherosclerosis. (See reference 31 for an in-depth review.) In spite of these advances, challenges still remain. A critical feature of human unstable coronary syndromes is the rupture of atherosclerotic plaques, and the lack of plaque rupture is a shortcoming of the dyslipidemic animal models.

Congestive Heart Failure

A variety of large animal models that were developed to study the hemodynamic aspects of congestive heart failure have been modified for use in small rodents. Aortic banding is a well-established model of left ventricular (LV) hypertrophy due to pressure overload. The progression of LV hypertrophy to progressive LV dysfunction and overt heart failure has been documented in guinea pigs and rats. Similar effects have been observed following renal artery ligation (32) and after the administration of a high-salt diet to Dahl salt-sensitive rats (33). Surgical procedures are more technically challenging in mice because of their small size, but aortic banding can be accomplished via microsurgical techniques (34). Aortic banding leads to cardiac decompensation in mice that express specific transgenes (35,36) and in mice treated with cyclosporin (37). Coronary artery ligation as a model of myocardial infarction with subsequent LV failure has a long history in cardiovascular research and has been adapted to the mouse (38). Murine models of viral myocarditis with cardiac failure have been extensively studied (well reviewed in reference 39). A hereditary form of dilated cardiomyopathy occurs in a strain of Syrian hamsters (40); the underlying genetic defect has been identified (41,42). Although naturally occurring inherited cardiomyopathy models are lacking in the mouse, an array of transgenic models has been generated (see reference 43 for review). In addition to the models of dilated cardiomyopathy, an important model of hypertrophic cardiomyopathy has been developed by introduction of a missense mutation analogous to a mutation that causes familial hypertrophic cardiomyopathy into the murine alpha-cardiac myosin heavy-chain gene (44).

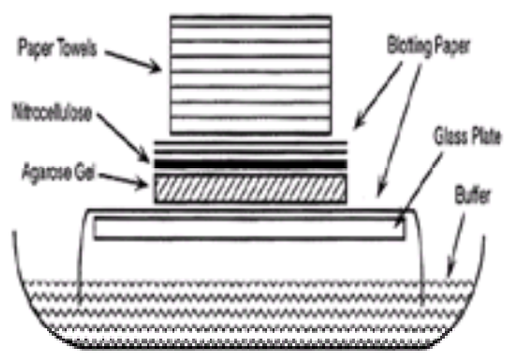
ANALYSIS OF GENE EXPRESSION

The central dogma in molecular biology is that the genetic information stored in DNA is transcribed to RNA and then translated to proteins. In strictest terms, *gene expression* refers to the process by which a gene is “turned on” to produce mRNA. However, it often is used to describe the entire process by which activation of a gene leads to an increase in its protein. This section describes approaches that are used to examine mRNA and protein.

RNA (Northern) Blot Analysis

RNA blot analysis (45) has been the most popular method for identifying and quantifying specific mRNAs. It is particularly useful for identifying mRNAs that are abundant (i.e., that are present in large enough quantities to be easily measured). This process involves size fractionation of RNA on formaldehyde/agarose gels, followed by transferring the RNA to filters and then hybridizing the filters with probes that recognize a specific mRNA.

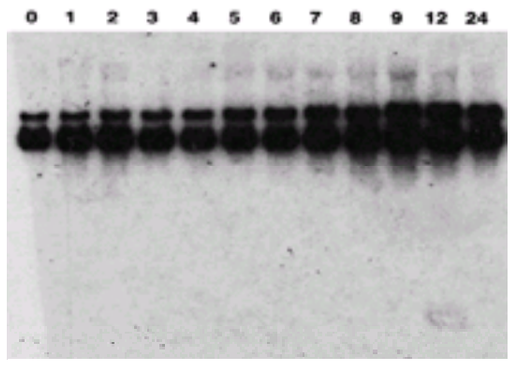
The basic principle underlying RNA blot analysis is that under denaturing conditions, in response to an electric current, RNA moves through an agarose gel at a rate inversely proportional to its size; that is, the largest RNA moves the least. This allows one to isolate total RNA from cells or tissues, apply small amounts (~10 µg) to the lanes of an agarose gel, and then separate the various RNA species by size. Because the vast majority of RNA is ribosomal RNA, the individual mRNA species cannot be seen directly. However, the RNA can be transferred to filters (usually composed of nitrocellulose or nylon) by the process of “blotting” (eFig. 96.1.1). The RNA is then baked onto the filter, where it can remain stable for months to years.



***e*FIGURE 96.1.1** Schematic representation of the blotting apparatus used to transfer RNA (or DNA) from agarose electrophoresis gels to nitrocellulose. Buffer placed in the bottom of the apparatus is drawn up through the layers of material to the paper towels by capillary action. RNA moves with the stream of buffer and becomes immobilized when it reaches the nitrocellulose membrane.

Specific mRNAs can be identified on the filters using the technique of hybridization. This is based on the ability of RNA to form hydrogen bonds with complementary strands of DNA (cDNA) or RNA (cRNA). The binding between mRNA and its exact complement is extremely tight, and therefore high-affinity probes can be designed to detect a specific mRNA. Various approaches have been used to label the probes, including phosphate-32 (P-32) nucleotides, fluorescent or biotinylated compounds, or

digoxigenin (46). The most common approach is to label cDNA with P-32 deoxynucleotides using either the technique of “nick translation” (47) or random oligomer priming (47,48 and 49). he hybridization protocol is carried out by incubating the blotted filter in a buffer containing the labeled probe. The filter is washed several times to remove the labeled probe and then processed based on the type of label used. The specific mRNA is detected as a band (eFig. 96.1.2). Most typically, radiolabeled bands are identified by autoradiography on x-ray film or using a phosphoimager.



***e*FIGURE 96.1.2** RNA blot analysis. To examine the effects of basic fibroblast growth factor (FGF) on the expression of messenger ribonucleic acid (mRNA) for the rat protein osteopontin, total RNA was isolated from cultured vascular smooth muscle cells following treatment with 50 ng/mL basic FGF. 10 µg per lane was loaded on a 1% agarose, 7.5% formaldehyde electrophoresis gel, and, following electrophoresis, the RNA was transferred to nitrocellulose using the apparatus depicted in *e*Figure 96.1.1. The nitrocellulose “blot” was hybridized with P-32–labeled complementary DNA probes for rat osteopontin and myosin light chain. Because myosin light chain is known to be constitutively expressed under these conditions, it was used as an internal control. The higher band in the autoradiogram above demonstrates hybridization to osteopontin mRNA, and the lower band demonstrates hybridization to myosin light-chain messenger RNA (mRNA). Levels of osteopontin mRNA rise after exposure to basic FGF, whereas levels of myosin light chain remain constant.

The specificity with which the cDNA or cRNA probes hybridize to the mRNAs contained on the filter is determined by the conditions of hybridization and of the washing, referred to as the *stringency*. Homologous probes (i.e., probes that correspond exactly to the specific mRNA being examined) bind most tightly to the target mRNA. As the degree of similarity between the probe and the target mRNA decreases (e.g., when probes from one species are used to identify mRNA from another, or when probes represent related but not identical molecules), the tightness of binding decreases. The higher the temperature of washing and the lower the salt concentration of the wash buffer (i.e., the higher the stringency), the more closely related the probe and mRNA must be to remain bound. The advantage of RNA blot hybridization is the ability to identify related but not identical signals by hybridizing and washing at low stringencies. The disadvantage is that the technique only identifies signals if the mRNA is abundant. Another disadvantage is that even under high stringency, a single probe can hybridize to several highly related mRNA species of similar size. Several alternative techniques have been designed to identify less abundant mRNAs and to provide a higher degree of specificity. One approach is to perform RNA blot hybridizations with poly A^+ RNA. Because mRNAs contain large tracts of poly A at their 3' ends, they can be purified from the ribosomal RNA on columns that contain oligo dT (47) or poly U. This purification results in an approximately 50- to 100-fold enrichment for mRNA and therefore allows for substantially more mRNA to be loaded on the agarose gels.

Ribonuclease Protection Assays

Ribonuclease (RNAse) protection assay uses a sequence-specific labeled cRNA molecule as a probe to hybridize with RNA in solution (50,51). Base pairing between the labeled probe and the mRNA of interest results in double-stranded cRNA-RNA hybrids that are resistant to digestion by RNAse. Following hybridization, samples are digested with RNAse to destroy the unhybridized, single-stranded probe and mRNA. The products of digestion are then run on a polyacrylamide gel. The gel is dried, and the “protected” bands are detected by autoradiography (Fig. 96.2). One advantage of this technique is the extremely high degree of base pairing that is needed to prevent RNAse from digesting the cRNA-RNA hybrids. Even two consecutive base pair mismatches are sufficient to allow the RNAse to digest the hybrid at the point of the mismatch. This technique thus allows for the identification of mRNA that is virtually 100% complementary to the cRNA probe. The area that corresponds to the alternative spliced exon is degraded by the RNAse. RNAse protection assays are usually more sensitive than RNA blot analysis and can therefore be used to detect lower levels of mRNA. Kits are commercially available to generate specific probes for the detection of multiple mRNAs in a single sample at one time.

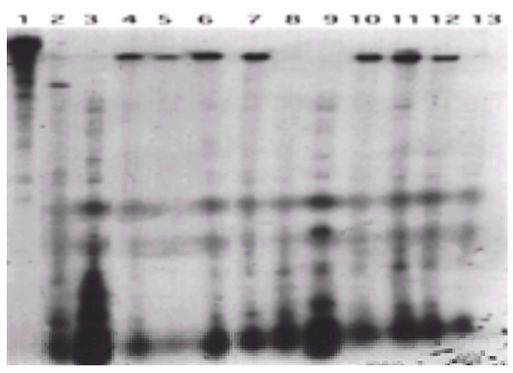


FIGURE 96.2 Ribonuclease (RNAse) protection. To examine the expression of the rat gene SM-20, an antisense P-32–labeled RNA probe was synthesized by *in vitro* transcription using a plasmid containing the rat SM-20 complementary DNA and the recognition site for T3 polymerase. The 420–base pair (bp) probe contained a 40-bp sequence from the plasmid vector and a 384-bp sequence complementary to SM-20 messenger RNA (mRNA). Total RNA, 10 µg per lane, from a variety of tissues was hybridized with the rat probe, incubated with RNAse, and then analyzed by polyacrylamide gel electrophoresis. Lane 1 of the autoradiogram shows the undigested probe. When the probe was hybridized to RNA from mouse heart (lane 2), part of the probe was protected from RNAse digestion, implying that there is partial sequence identity between the rat and mouse SM-20 mRNA. Rat tissues that express the SM-20 mRNA (lanes 4–7, 10–12) showed full protection of the complementary region of the probe. Yeast transfer RNA (lane 13) and RNA from tissues that do not express SM-20 (lanes 3, 8, 9) failed to protect the probe.

Unlike RNA blot hybridization, RNAse protection assays do not usually identify highly related isoforms unless they are generated by the process of alternative splicing, in which identical exons, representing regions of 100% identity, are spliced to different exons. This results in partial protection of the cRNA probe, corresponding to the area that contains the shared exon.

Polymerase Chain Reaction

The most sensitive approach for identifying and amplifying specific DNA or mRNA sequences is polymerase chain reaction (PCR) (Fig. 96.3). Standard PCR involves the synthesis of a set of primers (sense and antisense) that correspond to the 5' and 3' ends of the segment of DNA to be amplified. DNA (genomic DNA, or plasmid DNA) is used as a template. To amplify sequences from mRNA, a cDNA copy of the mRNA is generated by reverse transcription and used as a template in the PCR reaction. To begin the PCR, template DNA is incubated in solution with the primers, all four deoxyribonucleotides, and a temperature-stable DNA polymerase. Three reactions are performed in a thermocycler that allows for very rapid changes of temperature. The initial step is the denaturation of the double-stranded DNA template by heating to approximately 95°C. The next step is annealing (performed between 37°C and 65°C) of the primers to the denatured template. This is followed by synthesis of complementary DNA strands by the heat-stable DNA polymerase (performed at ~72°C). At the beginning of the next cycle, the newly synthesized DNA is denatured (at ~95°C) to produce new single-stranded templates. This cycle is repeated 20 to 40 times to achieve greater than 1 million–fold amplification of the sequence of interest. The products are then resolved on agarose or polyacrylamide gels. PCR can be used to identify and amplify a single molecule of viral DNA from a single cell. It can also be used to identify DNA that contains a specific mutation.

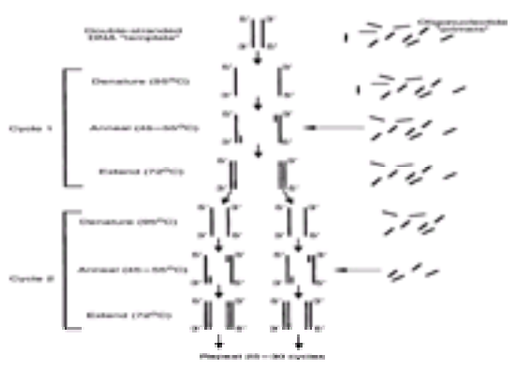
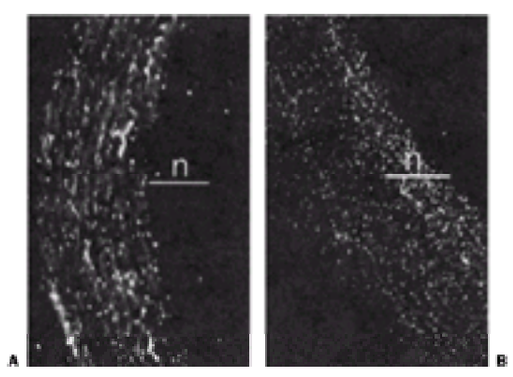


FIGURE 96.3 Polymerase chain reaction for amplification of DNA. The schematic shows two complete cycles of polymerase chain reaction. The procedure is repeated for a total of 25 to 30 cycles.

The sensitivity of reverse-transcription (RT)–PCR enables one to amplify from just a few molecules of mRNA. RT-PCR can therefore be used to examine mRNA from a single cell or from small tissue samples, such as those obtained from cardiac biopsies or coronary arthectomies. One disadvantage of RT-PCR is that it is difficult to use for quantitation. During the early cycles, there is exponential amplification and a direct relationship between the amount of original DNA template and the amount of product. As the number of cycles increases, the reagents in the reaction tube cannot sustain the continued exponential amplification. The rate of accumulation of PCR product falls off in an unpredictable way. Once this occurs, the final yield of product may have little relationship to the original amount of starting material. A variety of procedures involving the use of internal standards and varying cycle lengths have been used to allow “semiquantitation” of RT-PCR, but these techniques can be cumbersome. Real-time quantitative PCR is designed to circumvent these problems (reviewed in references 52 and 53). In this technique, the reaction is carried out in a thermocycler equipped with fluorescence detection and specialized software. The incorporation of dyes that are specific for double-stranded DNA or the release of fluorescence from specially designed primers is continuously monitored. The numbers of cycles that are required to permit fluorescence detection are then correlated to the quantity of starting material.

In Situ Hybridization

The above techniques involve the identification and measurement of mRNA from samples extracted from cells or tissues. *In situ* hybridization provides a method for identifying mRNA in intact cells or tissue samples (54). The general strategy is similar to that used for RNAse protection assays and involves the generation of single-stranded, labeled cRNA probes. Rather than being hybridized in solution, the probes are incubated with cells or tissue sections fixed on slides or cover slips. After hybridization, the slides are washed at high stringency. In the case of radiolabeled probes, the slides are covered with photographic emulsion for several weeks and then developed. For digoxigenin-labeled probes, the slides are analyzed using antibodies to digoxigenin and colorimetric detection. They are then examined by light- or dark-field microscopy. After detection of radiolabeled probes, mRNA appears as grains associated with cell bodies. After detection with digoxigenin-labeled probes, it appears as colored staining. With either labeling technique, slides can be counterstained such that the normal cellular architecture can be determined. This procedure thus allows one to identify specific cells that express mRNA. In the early stages of murine development, embryos are small enough to allow penetration of cRNA probes without sectioning. This allows intact embryos to be examined by light microscopy to determine the expression of developmentally regulated genes. Although *in situ* hybridization is excellent for localizing sites of mRNA expression, it is not ideal for quantitation. Nevertheless, semiquantitative approaches have been used based on the number of grains seen. The availability of increasingly sophisticated imaging systems should allow for more reliable quantitation. An example of the use of *in situ* hybridization to examine gene expression in an animal model of balloon arterial injury is shown in *e*Figure 96.3.1.



***e*FIGURE 96.3.1** *In situ* hybridization. Localization of messenger RNA (mRNA) expression for the rat gene SM-20 in balloon-injured rat aorta using ^{35}S–complementary RNA (cRNA) probes. **A:** The sense cRNA probe used as a negative control did not hybridize to an mRNA species. **B:** The antisense cRNA probe hybridized to SM-20 mRNA and was detected as small grains seen throughout the specimen, most strikingly in the neointima (n). (From Wax SD, Tsao L, Lieb ME, et al. SM-20 is a novel 40-kd protein whose expression in the arterial wall is restricted to smooth muscle. *Lab Invest* 1996;74:797–808, with permission.)

New Directions: Laser Capture Microdissection

As discussed in the section Models Used in Cardiovascular Research, cardiovascular diseases involve complex interaction among multiple types of cells, and the ability to culture pure preparations of these cells has been critical to work in molecular cardiology. Still, each of the cell culture models has inherent limitations. It would be ideal to be able to study the individual cell types within pathologic lesions. *In situ* hybridization and immunostaining allow gene expression to be examined in tissue sections but are of limited sensitivity and do not permit comprehensive analysis of gene expression. Laser capture microdissection (LCM) is a technique developed at the National Cancer Institute that allows pure cell populations to be microscopically dissected from tissue sections so that their DNA, RNA, and proteins can be analyzed (55). Briefly, a glass slide with a routine tissue section is overlain with a transparent thermal polymer film and placed on a microscope. Once the investigator visualizes the cells of interest, a brief burst of infrared laser light is directed at the area, causing the cells to adhere to the thermoplastic film. The cells can then be recovered from the film and subjected to molecular analysis, including RT-PCR followed by gene-array screening (56). The National Cancer Institute maintains a website devoted to LCM (http://dir.nichd.nih.gov/lcm/lcm.htm) to distribute information regarding the rapidly evolving uses of LCM. Figure 96.4 shows an application of LCM to isolate macrophages from an atherosclerotic plaque.

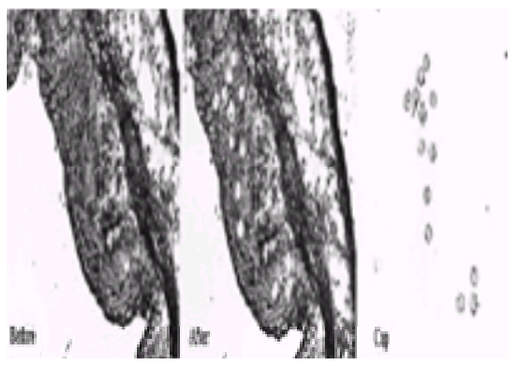


FIGURE 96.4 Laser capture microdissection (LCM) of atherosclerotic plaque. Sections of atherosclerotic plaque were immunostained to detect macrophage-derived foam cells and then covered with a thermoplastic film. Short bursts of infrared laser light were used to attach 15-µm circular fragments of macrophage-rich tissue to the film. Tissue section is shown before LCM **(left)** and after LCM **(middle)**. Thermoplastic film with adherent 15-µm specimens **(right)**. (Photo courtesy of Eugene Trogan, Hayes M. Dansky, and Edward A. Fisher, Mount Sinai School of Medicine.)

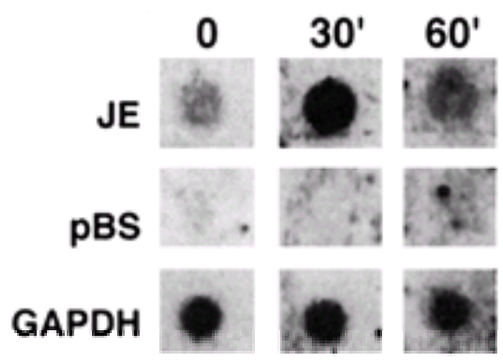
Analysis of Transcription

The above techniques measure steady-state levels of mRNA and can be used to assess the accumulation of mRNA in response to a particular stimulus, for example, arterial balloon injury or treatment with agonists. Steady-state mRNA levels represent a balance between transcription of new mRNA and changes in the stability of the transcribed message. It should be noted that the term *induction* has been most typically used to describe mRNA transcription. However, it is sometimes used to describe any increase in mRNA levels, whether it be due to changes in transcription, mRNA stability, or a combination of both. Several approaches have been used to examine specifically the transcriptional component.

Nuclear Run-On (or Run-Off) Analysis

Nuclear run-on (or run-off) analysis (57) has been the gold standard for examining mRNA transcription. This technique is based on the principle that isolated nuclei contain RNA that is in the process of being transcribed. One can complete this process (elongation) in a test tube by adding ribonucleotides. In contrast, transcription cannot be initiated in a test tube under the same conditions. By including a radiolabeled ribonucleotide in the reaction, one can measure the level of transcription that occurs at the moment that the nuclei were collected.

The technique for measuring transcription of specific mRNAs is essentially the reverse of RNA blot hybridization. The unlabeled specific probe is blotted onto the filter, and the filter is hybridized to the reaction mixture that contains the radiolabeled transcripts, representing all of the mRNAs being elongated in the *in vitro* reaction. Because one can blot dozens of probes on a single filter, it is possible to analyze levels of transcription for many different mRNAs at the same time (*e*Fig. 96.4.1).



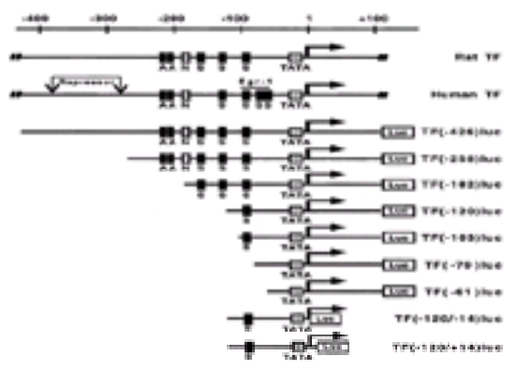
***e*FIGURE 96.4.1** Nuclear run-off analysis. Nuclear RNA was isolated and labeled as described in the text from quiescent VSMC and at 30 and 60 minutes after exposure to 10 ng per mL platelet-derived growth factor (PDGF). Linearized plasmid DNA containing complementary DNA (cDNA) from the rat called *JE*, empty plasmid vector (pBS), and plasmid containing the cDNA encoding glyceraldehyde phosphate dehydrogenase (GAPDH) were spotted onto a nitrocellulose filter (10 µg DNA per spot), and the filter was hybridized with the labeled nuclear fractions. The experiment demonstrates that there is a marked increase in *JE* messenger RNA (mRNA) transcription 30 minutes after PDGF exposure, whereas GAPDH mRNA is transcribed at a constant rate.

Because the elongation reaction is performed in a cell-free system for a short period of time, it should not be affected by changes in mRNA stability, most of which are mediated by cytoplasmic factors and occur over a longer time frame. Although nuclear run-on analysis remains the most rigorous approach for assessing the role of new transcription in the accumulation of mRNA, it is limited by the need to isolate nuclei from large numbers of cells and is poorly suited to examine transcription *in vivo* or in cell cultures, where only limited numbers of cells are available such as those derived from human coronary arteries. The advantage of the procedure is that it is measuring transcription of the target gene in its original environment in the chromosome.

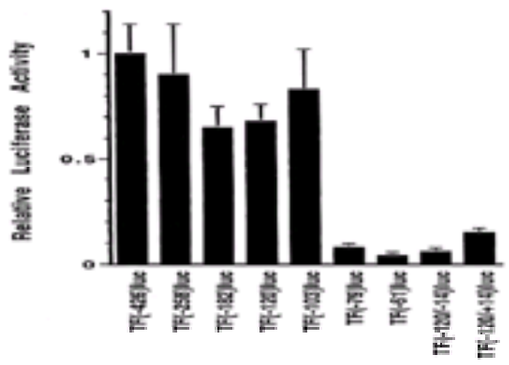
Promoter Analysis

A second approach to analysis of transcription is to isolate the transcriptional unit of the specific gene of interest and to examine its regulation in cell culture. This approach, referred to as *promoter analysis*, has been a major focus of research in molecular biology and has provided a wealth of information on the molecular events that are required for gene transcription. Transcription begins when RNA polymerase attaches to the promoter area of the gene being transcribed. In the presence of ribonucleotides, the polymerase then moves along the gene, linking ribonucleotides together in a pattern that is complementary to the antisense strand of DNA. In general, transcription begins 25 bases downstream from the promoter. Binding of the RNA polymerase to the promoter requires a very small amount of DNA sequence. However, regulation of polymerase binding and subsequent transcription involve a variety of sequences located apart from the promoter. Many of these sequences are found within 200 to 300 bases of the promoter. However, others can be located thousands of bases away.

Regulatory sequences may convey tissue specificity, developmental specificity, or agonist specificity to transcription. The sequences, referred to as cis-*acting elements*, can either be positive or negative regulators of transcription. A particular class of regulators, known as *enhancers* or *suppressors*, has the property of being able to act in an orientation- and position-independent fashion. For example, an enhancer can be turned around or placed thousands of bases away from the promoter (upstream or downstream) and still regulate transcription. For a *cis*-acting element to function in regulating transcription, it must be bound by a humoral "*trans*-acting" factor, usually a protein. Substantial progress has been made in identifying the *cis*-acting elements and *trans*-acting factors that are involved in gene regulation in a variety of cell systems. An example of the regulatory region of the human tissue factor promoter is shown in *e*Figure 96.4.2. This figure demonstrates binding sites for some of the most well-studied transcriptional factors in vascular biology, including NFkB, AP-1, and SP-1.



***e*FIGURE 96.4.2** Comparison of the known transcriptional elements in the proximal rat and human tissue factor (TF) promoters. The presumed transcription start site was assigned the number 1. Nucleotides located upstream of the transcription start site were assigned negative numbers, and nucleotides downstream of the start site were assigned positive numbers. The luciferase (Luc) reporter constructs used in *e*Figure 96.4.3 to examine the basal activity of the rat tissue factor promoter are also shown. A, AP-1 site; Egr-1, Egr-1 binding site; N, NFkB site; S, SP-1 site; TATA, TATA box. (From Taby O, Rosenfield C-L, Bogfanov V, et al. Cloning of the rat tissue factor cDNA and promoter: identification of a serum-response region. *Thromb Haemost* 1996;76:697–702, with permission.)



***e*FIGURE 96.4.3** Basal activity of the rat tissue factor (TF) promoter–luciferase constructs. Rat aortic vascular smooth muscle cells were transiently transfected with each of the luciferase constructs shown in eFigure 96.4.2. Luciferase activity was measured and expressed relative to the activity of the longest construct [TF(–426)luc]. Minimal activity was seen for constructs lacking the region between –79 and –103 and in constructs lacking the region between the transcription start site and the luciferase reporter [TF(–120/–14)luc and TF(–120/+14)]. (From Taby O, Rosenfield C-L, Bogfanov V, et al. Cloning of the rat tissue factor cDNA and promoter: identification of a serum-response region. *Thromb Haemost* 1996;76:697–702, with permission.)

The general approach to promoter analysis is to isolate the promoter region and "flanking sequences" (those that contain the putative *cis*-acting elements) from a genomic library. The entire region is then ligated to a "reporter gene," a gene whose product can be easily measured. Among the most common reporters are those that encode the bacterial enzyme, chloramphenicol acetyl transferase (58), or the firefly enzyme, luciferase (59). The activity of these enzymes can be easily measured (60,61) and used to monitor promoter activity. For these studies, the constructs that contain the promoter region and the reporter are ligated into a plasmid vector and transfected into cultured cells. Levels of the reporter gene product are measured and used to assess the rate of transcription of the promoter. Once the level of transcription has been assayed for the entire promoter region, serial deletions can be made in the promoter construct to identify specific areas that contain the *cis*-acting positive and regulatory elements. An example of deletion analysis is shown in eFigure 96.4.3.

The technically straightforward method for promoter analysis involves transient transfections (by any of the methods discussed in the section Functional (Expression) Cloning) of the construct into cultured cells followed by measurement of promoter activity. Although this *in vitro* approach has allowed the identification of regulatory elements in a multitude of genes, the elements that regulate transcription of a particular gene *in vivo* may be quite different, emphasizing the importance of confirming cell culture findings in the intact animal. Most often, this is accomplished by creating transgenic mice with a promoter construct driving expression of the beta-galactosidase gene as a reporter (used because it produces a blue color when the appropriate substrate is added). This approach has been used to identify the elements that are responsible for tissue-specific expression of smooth muscle alpha-actin (62) and to identify sequences responsible for the transcriptional regulation of smooth muscle genes following balloon angioplasty (63).

Protein Identification

A variety of approaches are used to identify proteins. In some cases, functional assays can be used, particularly in the case of specific enzymes. More often, antibodies are used to identify specific proteins.

Immunoprecipitation

For immunoprecipitation, extracts that contain the desired protein are incubated with a specific antibody. An antibody-binding reagent, complexed to beads, is then used to precipitate the complex by centrifugation. Two approaches can be used for quantitation. In the first, the protein is labeled *in vivo* using radiolabeled amino acids. Most commonly, sulfate-35 (S-35)–methionine is used. The labeled material can then be counted using liquid scintillography. To provide maximum specificity, the precipitated complex can be run on a sodium dodecyl sulfate polyacrylamide gel that separates proteins by size in a fashion similar to that described for mRNA. The gel is then subjected to autoradiography. After this, the protein of interest can be verified by its position relative to known-sized markers and the amount of protein assayed either by densitometric analysis of the autoradiogram, by cutting out the band and measuring radioactivity in a scintillation counter, or by the use of a phosphoimager. An example of autoradiography is shown in Figure 96.5.

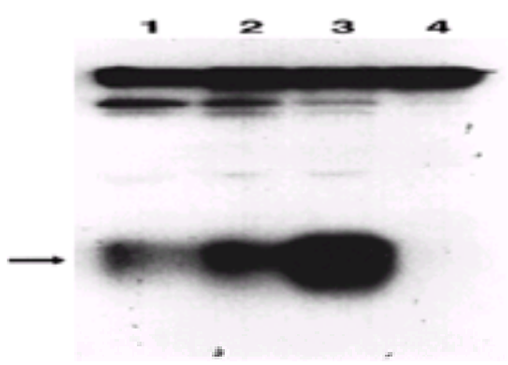


FIGURE 96.5 Immunoprecipitation. VSMC proteins were labeled *in vivo* by incubating cultured cells for 4 hours with sulfate-35–methionine. Protein lysates were isolated from cells that did not receive further treatment (lane 1) and cells labeled in the presence of 1 µM angiotensin II (lane 2) or 20 ng per mL platelet-derived growth factor (PDGF; lanes 3 and 4). Samples were precipitated with anti-JE antiserum (lanes 1–3) and preimmune serum (lane 4) and then analyzed by polyacrylamide gel electrophoresis followed by autoradiography. JE protein (*arrow*) was precipitated by the immune serum and showed elevated levels in cells exposed to angiotensin II or PDGF. [From Taubman M, Rollins B, Poon M, et al. JE mRNA accumulates rapidly after aortic injury and in platelet derived growth factor–stimulated vascular smooth muscle cells. *Circ Res* 1992;70(2),314–325, with permission.]

Western Blot Analysis

An alternative to immunoprecipitation is Western blot analysis (Fig. 96.6). In this technique, the protein extract is first run on a polyacrylamide gel. The proteins in the gel are then transferred to a membrane, and the membrane is incubated with an antibody that is specific for the protein in question. A variety of approaches can then be used to identify the antibody, most often involving the use of a secondary antibody, followed by enzymatic detection (see the section Enzyme-Linked Immunosorbent Assay). Western blot analysis has the same advantage as running immunoprecipitates on gels: It allows for confirmation of the desired protein by comparison with either size markers or by using purified protein as a control. In addition, it does not require prior labeling of the protein. Thus, Western blot analysis can be used to identify proteins in animal models of arterial injury, from cardiac biopsies, or from atherectomy samples.

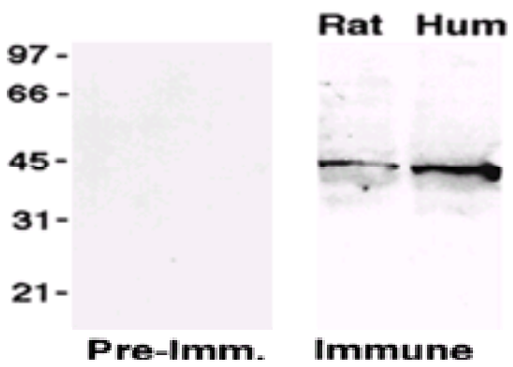


FIGURE 96.6 Western blot analysis. Protein lysates (25 µg per lane) of rat and human cultured vascular smooth muscle cells were loaded onto a 12% polyacrylamide gel. After electrophoresis and transfer to nitrocellulose, the blots were incubated with preimmune rabbit serum (Pre-Imm.) and antiserum against the rat protein SM-20. The blots were washed and then incubated with horseradish peroxidase–conjugated donkey antirabbit antibody. Detection of bound antibody was accomplished by exposing the blots to photographic film immediately after incubation with a chemiluminescent substrate for horseradish peroxidase. (From Wax SD, Tsao L, Lieb ME, et al. SM-20 is a novel 40-kd protein whose expression in the arterial wall is restricted to smooth muscle. *Lab Invest* 1996;74:797–808, with permission.)

Enzyme-Linked Immunosorbent Assay

Several approaches have been used for rapid large-scale quantification of protein. These approaches have been of particular import in clinical laboratories, where large-scale and rapid quantitation is required and very small amounts of protein need to be measured. The most common techniques involve enzyme-linked immunosorbent assay (ELISA). In one approach, samples coat the bottom of 96-well immunosorbent plates. Nonspecific binding is blocked by incubating wells with normal horse serum and albumin. Wells are then rinsed and incubated with specific antibody. The wells are washed and the antibody detected using a variety of enzyme-based procedures. A commonly used method involves incubating with a biotinylated secondary antibody (e.g., horse antimouse or antirabbit immunoglobulin G) followed by avidin-conjugated horseradish peroxidase and then a developing solution that contains the chromogenic substrate *O*-phenylenediamine dihydrochloride. Protein concentrations are determined by comparison of light absorption of the samples to a standard curve that is generated using purified protein. A variety of kits are commercially available, as are automated ELISA readers.

Radioimmunoassay

Radioimmunoassay requires the availability of purified protein and a specific antibody. The purified protein is radiolabeled, usually with iodine-125, and the radiolabeled protein is immunoprecipitated with a specific antibody and counted in a gamma counter. To quantify levels of the target protein from a solution, such as a cell extract, culture medium, or human serum, increasing amounts of the solution are incubated with a fixed amount of iodinated protein. If the solution contains significant amounts of the target protein, it will compete away the radiolabeled protein. A competition curve can be generated and compared to a standard curve made with purified protein. This is a particularly sensitive and reliable means for quantifying protein. Its one potential drawback is the ability of a closely related but not identical protein to compete effectively with the target protein.

Immunohistochemistry

Immunohistochemistry uses antibodies in a fashion analogous to that described for *in situ* hybridization. Specific antibodies can be used to identify proteins in cell culture or in tissue sections. These techniques have been particularly useful for localizing proteins in tissue sections from experimental animal models or human specimens. Like *in situ* hybridization, they are less useful for quantitation. Immunohistochemistry can be used with light microscopy, confocal microscopy, or electron microscopy, the latter allowing for precise cellular localization of proteins. Double- and triple-labeling techniques are available to colocalize proteins. In addition, immunohistochemistry can be performed together with *in situ* hybridization. Examples of immunohistochemistry of cultured cells and tissue are shown in Figure 96.7.

FIGURE 96.7 Immunohistochemistry. **A:** Immunohistochemical detection of tissue factor in cultured vascular smooth muscle cells. **B:** Immunohistochemical detection of the protein SM-20 in a section of an injured rat artery. Strongest immunostaining is seen in the intima (I) but is also seen in the media (M).

MOLECULAR CLONING

In molecular cloning, genetic information from a species or cell type of interest is expanded in bacteria (or other simple hosts) to allow the isolation of DNA containing a single sequence of interest. Foreign DNA is introduced into bacteria most commonly in the form of plasmids (small pieces of circular DNA that replicate within bacteria) or bacteriophage (viruses that infect bacteria). The plasmids or phage that are used have been extensively engineered to facilitate the process of molecular cloning and are referred to as *cloning vectors*.

To begin the process of cloning, known quantities of DNA and of the cloning vector are digested with a restriction endonuclease and joined together by the enzyme DNA ligase. The result is a collection of millions of copies of the vector, each containing a single DNA fragment, referred to as the *insert*. This collection is called a *DNA library*; a high-quality library is one in which all of the DNA sequences that are present in the starting material are represented in the final pool of ligated vector.

If the starting material for the library is genomic DNA, the library is referred to as a *genomic library*. Because each somatic cell in an organism contains a complete copy of the genome, the tissue chosen for generating a genomic library is based on convenience. Genomic libraries contain exons and introns and thus may not provide direct information about the sequence of the mRNA or the protein. They are particularly valuable for isolating the promoter and associated regulatory sequences involved in gene transcription. Most of the information that has been obtained on the regulation of gene transcription has required cloning the regulatory regions from genomic libraries. Fragments that are isolated from genomic libraries are also necessary for generating transgenic animals.

Often, the sequence of interest is the mRNA that encodes a particular protein. In this case, the library is designed to represent the unique set of mRNA species that are expressed in a specific tissue or cell type at the moment of isolation. To allow mRNA sequences to be cloned using the same powerful techniques as genomic DNA, a DNA copy is made of the single-stranded mRNA using the enzymes reverse transcriptase and DNA polymerase. The resulting library is known as a *cDNA library*. The cDNA represents a faithful copy of the mRNA and therefore can be used to determine the sequence of the mRNA and to deduce the sequence of the protein encoded by the mRNA. A high-quality cDNA library contains copies of all of the mRNA transcripts that are present in the starting material; a high proportion of the copies will be full length, and the number of cDNA copies of a particular transcript will be directly proportional to the mRNA transcript's abundance.

Screening Libraries

Once an appropriate library has been constructed, the actual cloning process takes place. In its simplest form this involves "screening the library" with a radioactive probe that has a sequence similar to that of the clone of interest. Briefly, the phage or plasmid library is introduced into bacteria and spread out on agar plates so that the individual clones are physically separated from each other. The bacteria are allowed to grow overnight, greatly amplifying the amount of plasmid or phage DNA that is present in each colony on the plates. The next day, sheets of nitrocellulose filter are briefly layered on top of the plates so that some of the DNA from each colony adheres to the nitrocellulose. The DNA that sticks to the filters is then denatured and "hybridized" by incubation with a solution that contains the radioactive probe. The nitrocellulose filters are washed and then subjected to autoradiography. Hybridizing clones are identified as spots on the autoradiogram and then recovered from the original agar plates by lining up the filters with the plates. The recovered clone is then amplified and spread onto agar plates, and the process is repeated until the clone is purified to homogeneity. The probe can be labeled to allow nonradioactive detection. Alternatively, the probe may be an antibody. In this case, the library can be introduced into bacteria that can express the protein sequences encoded by the cDNA. In cases in which no DNA or antibody probe exists, the cloning process is adapted to screen the library using a functional assay.

Constructing and Screening Complementary DNA Libraries

Although a plethora of cDNA libraries are now commercially available, the methodology for generating these libraries merits discussion. Total RNA is first isolated from the tissue or cell of interest. In the cellular processing of eukaryotic mRNA, long repetitive stretches of the ribonucleotide adenosine are added to the 3' end. To purify this poly A+ mRNA from total RNA in the laboratory, chromatography resins with synthetic oligonucleotides (short stretches of single-stranded DNA or RNA) that are complementary to this poly A tail are used. Single-stranded cDNA is generated using reverse transcriptase and either oligonucleotides to prime the poly A tail of the 3' untranslated end of the molecule or random oligonucleotides that may prime from anywhere along the mRNA, or primers designed for a specific mRNA or class of mRNAs. Double-stranded cDNA is then generated with DNA polymerase. After this, the cDNA is ligated into an appropriate cloning vector, usually derived from bacteriophage lambda. These vectors allow for the cloning of large pieces of cDNA that correspond to the full-length mRNA transcript. The bacteriophage is then used to infect *Escherichia coli* that is grown as lawns on large agar dishes. Infection of the *E. coli* results in plaques that contain large amounts of the bacteriophage bearing the cDNA inserts.

Screening of cDNA libraries is analogous to the techniques used for blot hybridization. Large nitrocellulose filters are placed on the bacterial lawns. DNA from each plaque will stick to the nitrocellulose, which is then lifted from the plates, washed, and baked. The filters can then be hybridized to labeled cDNA, cRNA, or oligonucleotide probes. After washing at appropriate stringencies, hybridizing plaques are identified as round dots after autoradiography on x-ray film. The appropriate plaques are then isolated from the original plate and purified.

When appropriate nucleotide probes do not exist, antibodies can also be used to identify plaques that contain the desired cDNA. To do this, the bacteriophage-infected *E. coli* must be induced to produce the protein that corresponds to the cDNA insert. Specific strains of *E. coli* are available for this procedure. Bacteriophage "expression vectors" contain an inducible promoter, such as the beta-galactosidase promoter, to drive the transcription of the cloned cDNA insert. If the insert contains the protein-coding region and is in the correct reading frame and orientation, induction of the promoter enables the bacteria to synthesize and accumulate large amounts of the protein that is encoded by the cDNA insert. Using procedures similar to those described for hybridization, filters impregnated with material to induce the promoter can be placed on the bacterial lawns and, after lifting, can be incubated with specific antibodies to identify the desired protein. The plaque that produces this protein can then be purified and the cDNA isolated and characterized.

An alternative to using bacterial systems is to generate cDNA libraries in baculovirus and to express them in insect Sf9 cells. Because these cells are more closely related to mammalian cells, they are more likely than simple bacteria to modify the synthesized peptides in ways that are similar to those of mammalian cells (e.g., by attaching sugar molecules) to produce mature proteins that can be recognized by mammalian antibodies.

It should be noted that because cDNA libraries are generated by reverse transcriptase from mRNA, the cDNA inserts represent the relative amounts of mRNA in a particular cell under particular conditions, for example, after treatment with a growth factor. Therefore, libraries that are made from different cells or in response to different treatments contain different cDNAs. The mRNAs expressed in a particular cell usually correspond to only 10% to 20% of the total number of genes.

Constructing and Screening Genomic Libraries

Genomic libraries are generated by isolating total DNA and mechanically or enzymatically disrupting it to generate 8,000 to 100,000 nucleotide fragments and ligating the fragments into bacteriophage vectors, cosmids, or bacterial artificial chromosomes. Genomic libraries from many species are commercially available. Unlike cDNA libraries, because each cell contains the same DNA, a high-quality genomic library generated from any cell type should contain inserts that are representative of all of the genomic material of a particular species. Genomic libraries are usually screened using labeled cDNA probes. In mammals, the genomic inserts contain exons (which encode mRNA) and introns (which are spliced out before the mRNA is generated). Therefore, genomic libraries cannot usually be used for expression cloning. As noted previously, genomic libraries are used for isolating the regulatory regions of genes (not present in the mRNA), for genome sequencing projects, and for generating transgenic animals.

Functional (Expression) Cloning

Many cloning projects involve isolating a cDNA encoding a protein of known function that has not been purified and whose sequence is unknown. Such cDNA cannot be isolated using antibodies (because they do not exist) or nucleotide probes (because the sequence is not known). Several approaches have been used to identify cDNA clones by expressing the protein in mammalian cells or frog (*Xenopus laevis*) oocytes and then assessing protein function. Examples of this have been the cloning of angiotensin II and thrombin receptors.

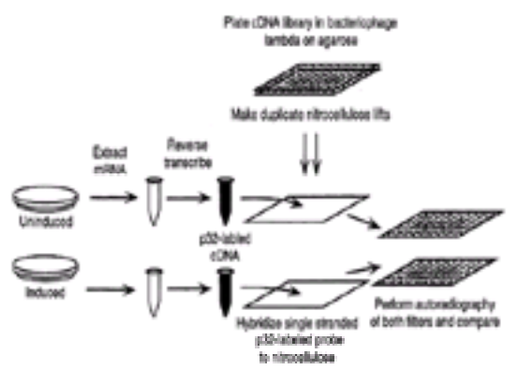
For expression cloning in mammalian cells, cDNA libraries are constructed in plasmid vectors containing a promoter that is active in mammalian cells. Examples of particularly active promoters include those derived from cytomegalovirus, SV40 virus, and adenovirus. The plasmids are then introduced into the mammalian cells by the process that is referred to as *transfection*. Approaches used for transfection include those using calcium phosphate precipitation, cationic liposomes, diethyl aminethyl–dextran, and electroporation. The most widely used cell lines for expression studies have been COS cells, derived from African green monkey kidneys, and Chinese hamster ovary cells. Once transfected, the cells are split into a large number of pools and assayed for the desired function. For example, in the cloning of the angiotensin II receptor, pools of transfected COS cells were assayed for their ability to bind radiolabeled angiotensin II (64). Once a pool was identified, it was split into smaller pools until a single clone of COS cells was isolated that bound radiolabeled angiotensin II. The plasmid was then isolated and the cDNA sequenced.

An alternative to expression cloning in mammalian cells is to use *Xenopus* oocytes. In this procedure, a cDNA library is generated in a plasmid vector, as has been described for mammalian expression studies. mRNA is then transcribed *in vitro* from pools of cDNA and microinjected into the oocytes. Next, oocytes are assayed for the biologic activity of interest. For example, in the cloning of the thrombin receptor (65), oocytes were injected with cRNA generated from pools from a plasmid library and assayed for mobilization of calcium in response to thrombin. Once a positive oocyte was found, the cDNA pool from which the cRNA was synthesized was split into smaller pools until a single cDNA clone was isolated (64,65).

Use of DNA Libraries for Comparing Expression of Multiple Genes

The above strategies all involve screening libraries for "known" genes or genes that encode known proteins or specific functions. A number of strategies have been designed to find novel genes or to identify sets of genes that have been induced by specific circumstances, for example, genes activated by treatment with platelet-derived growth factor or genes induced during muscle differentiation. Technical innovations have made these types of comparisons increasingly robust.

The earliest approach to large-scale comparisons of gene expression was differential screening of cDNA libraries (*e*Fig. 96.7.1). This was an extension of the standard methods described previously for screening libraries by hybridization. A cDNA library was generated from mRNA that was isolated from the cells or tissues of interest. After the library was plated, duplicate nitrocellulose lifts were made from the same bacterial lawn. The duplicate filters were then hybridized to labeled cDNA or cRNA probes made from RNA that was isolated under different conditions and subjected to autoradiography. If the duplicate membranes were nearly identical, a transcript present at high levels in one probe and at low levels in the other probe would be expected to show a corresponding difference of intensity after annealing to its corresponding clone on the two membranes. This somewhat crude technique has largely been supplanted by the use of arrayed libraries (discussed in the section Recent Advances in Molecular Cloning).



***e*FIGURE 96.7.1** Differential screening. Complementary DNA (cDNA) probes generated from cells or tissues grown under two different conditions are used to screen duplicate nitrocellulose lifts from a cDNA library. Hybridizing clones from genes that are more highly expressed under one of the two conditions show a stronger signal

on autoradiography (see text for details). mRNA, messenger RNA.

Subtraction Techniques

A limitation of the differential cloning approach outlined previously is that transcripts present at low levels may be difficult to detect because of their low signal intensity and may also be underrepresented in the cDNA library used for the screening or for the array. An alternative is to use “subtractive” strategies to enrich for differentially expressed genes. Single-stranded cDNA is synthesized from mRNA isolated under the condition in which the genes of interest are presumed to be induced. This cDNA is then hybridized in solution to an excess of mRNA isolated from the uninduced condition. The double-stranded DNA-RNA hybrids are then removed by hydroxyapatite column chromatography. The remaining cDNA should be enriched for transcripts that are present in the induced state. This enriched cDNA can be used either to generate a library for screening or to generate a probe for screening a more conventional cDNA library. This technique was used to identify the myogenic factor MyoD1 by using fibroblast mRNA to subtract cDNA from proliferating myoblasts (66). A variety of novel techniques are commercially available as kits to provide a similar type of enrichment with smaller amounts of starting material.

Differential Display of Messenger RNA

This is a PCR-based method used for identifying differentially expressed mRNAs. The basic strategy for this is to use RT-PCR (described in the section Polymerase Chain Reaction) to produce short cDNA fragments that correspond to every mRNA present. Because of the sensitivity of RT-PCR, even the least abundant mRNAs can theoretically be amplified. The amplified products from mRNA isolated from multiple different conditions can be separated on polyacrylamide gels and compared. Products that appear to be differentially regulated are recovered and sequenced.

Yeast Two-Hybrid System

The yeast two-hybrid system is a sophisticated expression cloning technique designed to identify genes encoding unknown proteins that interact with a protein of interest. The system takes advantage of the yeast protein GAL4, a transcriptional activator. The GAL4 protein has a binding domain that interacts with DNA and an activation domain that initiates transcription. These domains are structurally distinct and do not activate transcription unless they are associated. The yeast two-hybrid system exploits this property by separating the two domains in two different expression plasmids. One plasmid contains DNA encoding the known protein (referred to as the *bait*). The second plasmid contains a cDNA library generated from cells or tissues hypothesized to express proteins that bind to the bait. Both plasmids are introduced into yeast, where they generate “fusion proteins,” one containing the GAL4-binding domain fused to the bait, the others containing the activation domain fused to proteins encoded by the cDNA library. For example, if one wanted to clone genes encoding proteins that bind to the intracellular domain of a particular receptor, one could use DNA encoding the intracellular domain as the bait and generate a cDNA library from cells hypothesized to contain the binding proteins. When these plasmids are cotransfected into yeast, if a fusion protein from the library binds to the bait, the two GAL4 domains are brought together and the complex is able to activate the promoter of a reporter gene. cDNA encoding potential binding proteins is then isolated from yeast colonies that express the reporter gene.

Recent Advances in Molecular Cloning

Automation and new resources associated with the large-scale genome sequencing efforts have dramatically changed the common approach to molecular cloning. A limitation to the library screening approach is that each time the library is spread out onto agar plates, the identity of the millions of randomly dispersed clones is unknown. The only clones that are identified are those that are being specifically probed. In addition, the nitrocellulose filters can only be screened several times before new plates must be generated, creating a new array of millions of isolated colonies. Automation can improve this situation by arraying the library in a known configuration. Individual clones are picked off the plates and transferred to numbered wells on multiwell microtiter plates. The library is now “arrayed” and can be duplicated as many times as needed in this configuration. One way of screening an arrayed library is by having a robot “spot” an aliquot of each clone in an identifiable location on a membrane and then hybridizing the membrane with a labeled probe. Alternatively, the spots can be placed in a microscopic array for hybridization and detection using one of the microarray (“gene chip”) technologies. In either case, the location of the hybridizing signal tells the investigator which well of the microtiter plate contains the clone of interest. Taking this one step further, the array can be constructed entirely of sequenced clones so that after identifying the location on the membrane by hybridization, the investigator can immediately have access to information about the clone’s identity. When screening commercially available membranes (or microarrays), it is unnecessary for an investigator to actually possess the library—the individual clones of interest can be obtained from the vendor after their location is identified by screening.

In theory, hybridizing a gene array with a probe derived from the mRNA of a specific tissue identifies all of the arrayed genes that are actively expressed in the tissue. Thus, hybridizing duplicate arrays with probes derived from normal and diseased tissues can identify genes that are regulated in pathologic conditions. For example, a DNA array containing 6,000 genes was used to identify genes activated in a transgenic mouse model of lethal cardiomyopathy (67). Hybridization of identical arrays with probes derived from different tissues is essentially a modern version of the differential cloning strategy discussed previously except that now the identity of the clones has been established beforehand and there is no limit on the number of conditions that can be compared (other than the expense associated with acquiring the arrays).

Two types of resources generated through the publicly funded genome projects are particularly useful and, in many cases, can make the traditional techniques for molecular cloning unnecessary. The first applies to genomic cloning and the second to cDNA cloning. Each of the genome projects generates a library of overlapping, large genomic clones that are used in the sequencing process. In the early stages of a genome project, arrayed membranes produced from these libraries are usually available commercially. As the project progresses, vast amounts of sequence information from the individual clones is deposited in the public databases and is freely accessible via the Internet. By the time the genome project is completed, genomic library screening can be effectively accomplished “*in silico*” by searching the databases for the sequence of interest. If the actual genomic material is needed (e.g., for a promoter analysis or making a transgenic animal), a phone call or e-mail can replace the actual cloning process. The second resources are the expressed sequence tag libraries. These are cDNA libraries from a wide variety of tissues that are being systematically arrayed. Each clone is partially sequenced, and the sequence is deposited in the public databases. After an expressed sequence tag of interest is identified through a search of the public database, the actual clones can be obtained from a number of vendors. Certainly, these resources are evolving too rapidly for any printed source of information to be current. The National Center for Biotechnology Information maintains the public sequence databases in the United States, and its website is an excellent source of further information (http://www.ncbi.nlm.nih.gov/).

MOLECULAR METHODS FOR ALTERING GENE EXPRESSION

A major approach for studying protein function is to either overexpress a protein that is normally not present at high levels in a particular cell type or to decrease the expression of the protein. Many of the techniques are similar to those described previously, and studies that use these techniques are described in detail in subsequent chapters.

Overexpression in Cell Culture

The basic strategies are similar to those described in expression cloning. Plasmid vectors are constructed containing promoters that are active in mammalian cells. The cDNA that encodes the protein to be overexpressed is then ligated into the vector, and the vector is transfected into the cells. Two types of promoters are used. Constitutive promoters, such as the cytomegalovirus promoter, are always active and thus continually generate large amounts of the target protein. Inducible promoters, such as the metallothionein or mouse mammary tumor virus promoter, are relatively inactive until the cells are treated with specific inducers, such as divalent cations or glucocorticoids, respectively. The plasmids are introduced into the cells using a variety of techniques, including transfection with calcium phosphate, DEAE-dextran, cationic liposomes, or electroporation. A second approach is to use viral vectors, such as retroviruses or adenoviruses. These “infections” have higher efficiencies of DNA transfer into cells than transfections. Expression can either be transient or stable. In the latter, transfections or infections are performed with vectors that contain a selectable marker, such as neomycin or hygromycin resistance, and stable clones are isolated in the presence of high levels of the appropriate antibiotic. Stable overexpressing lines can be used to generate high levels of recombinant proteins for a variety of studies.

Overexpression in Animals

Two general approaches have been used to overexpress proteins in animals. The first mimics cell culture and requires the introduction of expression vectors into animals. Like cell culture, these studies can use transfections with liposomes or, more typically, viral vectors. A particular target for such work has been the arterial wall, where DNA can be introduced locally using catheters. Plasmids have also been injected directly into cardiac muscle, to overexpress proteins and to perform *in vivo* promoter analyses.

The second approach to overexpression uses transgenic animals. In this technique, a gene that encodes a desired protein is injected into embryos at the earliest stages of development. Animals that incorporate the gene into their germline transmit it to their offspring. The gene's product is expressed by the "transgenic" animal during development and at maturation. For such studies, the choice of promoters is critical. Nonspecific promoters drive the expression of the gene in virtually all types of cells and tissues. However, many tissue-specific promoters exist that target expression to a particular organ. For example, the cardiac myosin heavy-chain promoter directs expression largely to the heart. In this way, one can overexpress a particular protein in heart muscle.

Underexpression in Cell Culture

The inhibition of specific protein expression is more problematic than overexpression, although many of the techniques are analogous. One approach is to transfect or infect cells with plasmids that contain cDNA in the antisense orientation. On transcription, antisense mRNA is produced that specifically binds to the normal ("sense") mRNA. The double-stranded RNA either remains as a stable complex, unable to be translated into protein, or is rapidly degraded. An example of this approach was the generation of smooth muscle cell lines with abnormal adhesion properties because of decreased expression of the matrix protein, osteopontin (68). The technique depends on generating levels of antisense mRNA that are significantly in excess of the normal sense mRNA. It often results in decreased levels of specific protein synthesis but does not completely inhibit synthesis of the target protein. Such studies usually require stable transfections to analyze the results of protein inhibition adequately and to provide an environment in which all of the cells display lower levels of the target protein.

The use of antisense oligonucleotides has provided an important alternative to transfection of antisense cDNAs. These small fragments can bind to the target mRNA, destabilizing the mRNA or preventing it from binding to the ribosome and being translated. Antisense oligonucleotides may also affect transcription by binding to nuclear DNA. The advantage of this approach is that oligonucleotides can be easily synthesized and are taken up by cells in culture with much higher efficiency than large plasmids. Therefore, they can be used in transient transfection studies. Oligonucleotides can also be used in animal models and have been used extensively in attempts to inhibit gene expression in the arterial wall, where they can be delivered by catheters or by absorption from the adventitial surface. One concern about the use of antisense oligonucleotides is nonspecific effects that are unrelated to their binding to mRNA and the potential for more than one species of mRNA to be inhibited. Nevertheless, the use of antisense oligonucleotides, particularly in cell culture, has provided many insights into the importance of specific proteins in a variety of cell processes.

Alternatives to antisense oligonucleotides are ribozymes, RNA molecules with enzymatic activity (see reference 69 for review). Like protein enzymes, ribozymes cleave RNA at specific sites. However, because of the ability of RNA to form complementary base pairs with other RNA, ribozymes can be synthesized to cleave a particular mRNA species. Ideally, this cleavage is catalytic, thereby allowing a small number of ribozyme molecules to cleave, and thus inactivate, a large number of mRNA molecules. In most cases, ribozymes are believed to act catalytically as well as like antisense oligonucleotides. Ribozymes are usually synthesized in the form of their corresponding cDNAs and introduced into cells via plasmids. Their uptake into cells thus follows the same rules as those of transfection or infection of vectors that contain sense or antisense cDNAs. Like other antisense strategies, ribozymes can often decrease levels of protein synthesis but do not fully "knock out" gene expression.

Underexpression in Animals

As noted previously, antisense oligonucleotides have been used to reduce gene expression in animal models. However, the most effective way to inhibit gene expression is to generate transgenic animals in which the gene of interest has been knocked out (reviewed in reference 70). In this approach, the gene is first isolated from a genomic library. It is then altered to produce a nonfunctioning gene, usually through the introduction of a premature stop codon, resulting in a truncated nonfunctioning protein. The gene, coupled to a selectable marker, is then introduced into embryonic stem (ES) cells; by the process of "homologous recombination," a small number of stem cells replace their native gene with the genetically altered one. This process of recombination is not significantly different from that which occurs in nature during meiosis, leading to genetic variation and sometimes serious abnormalities. By growing cells in the selection medium, the appropriate ES cells can be isolated. These are then used to generate mosaic animals whose germ cells contain one chromosome that lacks a functioning gene. After mating, these animals transmit the targeted allele to their offspring, who then are heterozygous for the targeted allele. By crossing these heterozygotes, one can generate mice that are homozygous for the nonfunctioning gene. The generation of knockout mice has produced a revolution in molecular biology, in that it has created hundreds of different animals that lack a specific gene product. Unlike all of the previously mentioned approaches, these animals can potentially be completely deficient in the target gene. In addition, one set of knockout mice can be bred with another to examine the interactions between two specific gene products. Although current work has used mice (because of the ease of generating mouse ES cells and of injecting mouse oocytes), knockout strategies are now being applied to other mammals as well and offer great promise for examining gene expression *in vivo*.

Disrupting a gene by homologous recombination in the manner described removes the gene from all tissues throughout the entire life of the organism. Knocking out a gene that is required at an early stage of development is likely to cause lethality at the earliest point in development that its protein product is required, eliminating the opportunity to determine the protein's function in tissues that appear at later points in development. To circumvent this problem and to allow the function of a gene to be examined in a specific tissue, conditional knockouts can be generated using the Cre/lox site-specific recombination system (reviewed in reference 71). In this technique, a gene encoding the site-specific recombinase "Cre" is attached to a promoter that drives expression in the tissue to be studied and is introduced into a mouse by transgenic techniques. Another mouse, in which the gene to be disrupted is flanked by specific recognition sequences for the recombinase ("lox" sites), is generated by homologous recombination in ES cells. The mice are crossed to produce offspring that carry the Cre recombinase transgene and the targeted gene (flanked by lox sites). When the tissue-specific promoter is turned on during development, the recombinase is expressed and causes the gene between the two lox sites to be efficiently removed. The resulting animal is a genetic mosaic in which the majority of cells that express the Cre recombinase are missing the targeted gene.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Mouse Models of Cardiovascular Disease

The powerful techniques for targeted gene disruption that have been described are critical to contemporary biomedical research. Because knockout mice have phenotypes that closely resemble a number of human cardiovascular diseases, they are widely used as models. This is particularly true of mice with targeted disruptions of genes involved in lipoprotein metabolism that develop arterial lesions very similar to those seen in human arteriosclerosis. Despite the utility of these powerful models, there are several theoretical and practical considerations that should be kept in mind.

When targeting a gene by homologous recombination, there is an assumption that targeting will result in specific loss of the gene's product and will not directly affect the expression of other genes. Although the loss of the gene's product can be verified, the upregulation of another gene in the vicinity of the targeting can occur (72) and may readily escape detection. Such upregulation could have an important effect on the observed phenotype. In addition, the genetic background of the mice may have a profound effect on the observed phenotype. A particularly striking example is the vast difference in the extent of atherosclerosis observed in apolipoprotein E knockout mice based on their genetic background (73). To circumvent these concerns, one would ideally disrupt a gene using several different targeting strategies and then test the mutants to see if they are allelic (or use a transgene to "rescue" the mutant phenotype). The resultant knockouts could then be crossed onto several different genetic backgrounds. However, the time and expense of generating a mouse knockout are considerable, and seldom are different knockouts intentionally made for the same gene. Where they exist, subtle differences in the mutant phenotypes are not uncommon.

The standard approach to gene targeting by homologous recombination involves targeting the gene of interest in ES cells derived from one mouse strain and then transferring the targeted allele into a specific inbred strain by mating. Multiple rounds of backcrossing the targeted allele into the inbred strain are repeated until (after more than ten generations) the resulting mice are considered to be *congenic*, meaning identical to the inbred strain at all loci except for the targeted allele. Although the initial generations of targeted animals may be useful as experimental subjects, background genetic heterogeneity is high, and littermates must be used as controls. From a practical viewpoint, the investigator must be able to genotype the animals readily and to maintain a large enough colony of animals to ensure that adequate numbers with each genotype are available. In congenic strains the genetic background is uniform, but it is important to recognize that this "identity" is transient. Carrying a deleterious mutation in the homozygous state for multiple generations will favor the accumulation of new mutations over time that will tend to mitigate the severity of the mutant phenotype. Thus, even when using congenic strains, the "cleanest" experiment from a genetic perspective is one in which the homozygotes have had minimal opportunity for genetic drift from the control animals.

Gene Expression and Molecular Cloning

A major focus of cardiovascular research (and of this chapter) is the analysis of gene expression in normal and diseased tissues and the cloning of individual genes. Until recently, technical constraints limited most studies to the examination of only a few genes at a time. In the "postgenome era," there has been a shift toward performing far more comprehensive analysis of arrays that may include thousands of genes at one time. When studying such large sets of genes, each experiment produces a wealth of information that is then subjected to computational analysis. In previous investigations that focused on a single gene at a time, there was a natural tendency to study those genes that demonstrated the greatest difference in expression among conditions. In the large data sets generated by array screening, large numbers of genes with relatively modest degrees of regulation will be identified. If these robust analyses are to live up to their full promise, a major challenge for investigators will be to identify the underlying patterns and biologic significance of these more subtle forms of gene regulation. The rapidly developing field of

proteomics should help provide rapid ways of determining whether subtle changes in mRNA are translated into important changes in protein levels and activity. Undoubtedly, exciting new approaches will be developed to combine experimental and computational biology.

THE FUTURE

The complete sequencing of the human genome is a critical milestone in the history of molecular biology, not only for the wealth of information that it provides but as a stunning example of how high-throughput techniques can be used to tackle basic problems in biology. As these technologies continue to evolve, the same trends toward miniaturization, increased speed, and decreased cost that are seen in other industries can be anticipated in molecular biology. The ability to characterize gene expression extensively in progressively smaller samples will permit wider application of these techniques to clinical medicine, further narrowing the gap between the clinical and basic sciences.

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MOLECULAR GENETICS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Finding the gene(s) for a disease is considered a breakthrough discovery because it defines the genetic pathway and molecular basis underlying the pathogenesis of the disease and raises hopes that knowledge of the disease-causing genes and their functions may soon lead to accurate genetic testing, effective therapy, and prevention or cure for the disease. Identification and characterization of disease-causing genes is the central theme in the field of human molecular genetics. It usually starts with definition of the chromosomal location (disease locus) of a disease gene by cytogenetic analysis or gene mapping studies. Genes located within that chromosomal region can then be identified or cloned and become candidate genes for the disease. Mutation analysis of the candidate genes is then performed. Identification of disease-causing mutations in one of the genes implicates that gene in the disorder. Functional characterization of the mutations using transgenic/knockout mouse technology as well as biochemical, cell biologic, and molecular biologic studies can reveal pathogenic mechanisms underlying the disorder. The use of DNA microarrays and other related new technologies to determine genome-wide expression profiling of a disease offers a new avenue for identification of disease genes and is providing a wealth of new information for diagnosis and ultimate prevention or cure of cardiovascular disease.

GLOSSARY

Bioinformatics: Computational molecular biology.

Contig: A stretch of overlapping genomic clones such as yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), and cosmids that provide a continuous representation of a genetic locus or a genomic region defined by markers, sequence tagged sites (STSs), or genes.

Embryonic stem cells: The preimplanted embryo-derived pluripotent cells that maintain an unlimited differentiation potential and normal karyotype during the cell culture.

Expressed sequence tag (EST): A partial single-pass sequence from either end of a cDNA clone.

Functional cloning: A technique used for cloning human disease genes based on the availability of information on the target gene and its corresponding protein product.

Genome: All of the genes in an organism.

Genotype: Genetic makeup of an individual, often at a single locus.

GRAIL: Gene Recognition and Analysis–Internet Link software used to predict genes embedded in genomic DNA sequence.

Heterogeneity: If diseases or other phenotypes have multiple causal factors, they are considered heterogeneous. Allelic or intragenic heterogeneity refers to different genotypes at the same genetic locus that cause a similar phenotype. Locus heterogeneity refers to a situation in which a disease is caused by defects at different genetic loci.

Linkage analysis: Analysis to determine whether alleles at two or more genetic loci (usually a disease locus and one or more marker loci) are cosegregating within a pedigree.

Pedigree: Illustration of the relationships among family members.

Penetrance: Probability that a genotype will yield the predicted phenotype.

Phenotype: An observable biochemical, cellular, or clinical characteristic that is associated with the expression of a gene.

Polymorphisms: If there are at least two identifiable alternative gene forms (alleles) at a locus and none with frequency greater than 0.99, the locus is considered polymorphic. Commonly, any allele with a population frequency greater than 0.01 is termed a *polymorphism*. Any allele with a population frequency less than 0.01 is often called a *mutation*.

Positional cloning: A technique used to identify the underlying genetic cause of a disease based primarily on finding the location of the defective gene.

Segregation analysis: Analysis to determine the most likely genetic model for an observed trait in a pedigree: autosomal dominant, autosomal recessive, X-linked, or polygenic.

Sequence tagged site: A unique site in the genome defined by two oligonucleotide primers for polymerase chain reaction. STSs have become the common currency of physical mapping.

Simple tandem repeat markers: Polymorphic microsatellite markers that are ideal for genotyping and linkage studies. Simple tandem repeat markers can be dinucleotide, trinucleotide, or tetranucleotide repeats. Simple tandem repeat markers are widely and evenly distributed across the human genome and can be typed using polymerase chain reaction amplification.

Single nucleotide polymorphisms (SNPs): SNPs are single nucleotide changes or substitutions that are highly abundant and are perceived as the basis for the high-density genetic marker maps required for unraveling complex genetic traits.

Transcriptome: A set of genes that are expressed or transcribed from genomic DNA.

INTRODUCTION

Genetic factors have long been recognized to contribute to human phenotypes and disease. As the incidence of nutritional and infectious diseases markedly decreases, there has been an increasing awareness of the role of genes in the pathogenesis of human disease. Some human diseases, such as long QT syndrome and hypertrophic cardiomyopathy, are strongly determined by genes. Other diseases, such as infectious diseases, are strongly determined by nongenetic or environmental factors, although it is now realized that host defense protein factors encoded by genes play an important role in susceptibility to infection (1). Many of the most prevalent diseases, such as coronary artery disease, hypertension, diabetes mellitus, and cancer, are determined in varying degrees by both genetic and environmental factors. Therefore, all diseases are to some extent genetic.

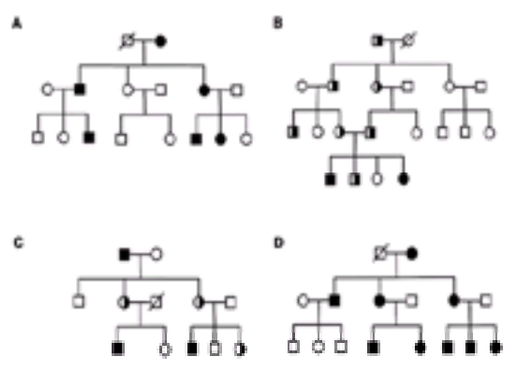
Advances in human molecular genetics, coupled with exponential growth in genomic research, have led to the development of a variety of technologies for identification of human disease genes. Positional cloning, a primary tool used for finding disease genes, has become far easier over the years. Newly developed DNA microarray technology offers a new alternative for identification of disease genes. Transgenic and knockout mice and other technologies have been developed to assess how a mutation in a given gene affects the function of the protein product and so defines the functional role of a novel gene. The new discipline of bioinformatics, or functional genomics, has become an important tool for the rapid computer-based screening of DNA and protein databases, identification of novel genes from genomic DNA sequences, and the prediction of gene function. The purpose of this chapter is to review the theory and practice of these key molecular genetic technologies.

MAJOR TYPES OF GENETIC DISEASES

Genetically determined diseases can be broadly classified into four groups: chromosomal disorders, single gene disorders, polygenic or multifactorial diseases, and mitochondrial disorders (2).

Chromosomal disorders are the result of deletions, duplications, or other alterations of entire chromosomes or large segments of them. These disorders include Down syndrome and DiGeorge syndrome.

Single gene disorders are caused by single mutant genes. Human diseases caused by single genes are inherited in a simple mendelian fashion and are often referred to as *mendelian disorders*. More than 4,000 mendelian disorders are now known that are inherited in autosomal dominant, autosomal recessive, or X-linked fashion (eFig. 97.0.1). The characteristics of autosomal dominant inheritance include vertical transmission of the disease phenotype, a lack of skipped generations, and approximately equal numbers of affected male and female subjects. Father-to-son transmission may be observed, which is a feature that can be used to exclude X-linked inheritance. Autosomal recessive inheritance is characterized by clustering of affected individuals in the same generation, absence of disease among parents of the affected, and approximately equal numbers of affected male and female subjects. Consanguinity is often a factor in recessive diseases. A major distinction between dominant and recessive disorders is that heterozygotes are clinically affected in most cases of dominant diseases, whereas they are clinically normal in the case of recessive disorders.



***e*FIGURE 97.0.1** Inheritance patterns of genetic disease. **A:** Autosomal dominant inheritance. **B:** Autosomal recessive inheritance. **C:** X-linked recessive inheritance. **D:** Mitochondrial inheritance. Affected individuals are shown as filled circles (female subjects) or squares (male subjects), and unaffected individuals as empty symbols. Heterozygous carriers in **B** and **C** are shown as half-filled symbols.

The first human gene to be mapped was the color blindness gene, deduced to be on the X chromosome by the distinct features of X-linked inheritance. In a pedigree with X-linked recessive inheritance, father-to-son transmission is absent; affected individuals are more frequently of the male gender; and the disease phenotype skips generations when genes are passed through female carriers. Approximately 50% of sons from the female carrier with a mutant X chromosome develop the disease phenotype.

Polygenic or multifactorial diseases such as coronary artery disease, heart failure, and hypertension result from the joint action of multiple genes and environmental factors. They are the most common human genetic diseases and pose a major challenge to contemporary human geneticists owing to their complex nature in which additive, interactive, or both effects of many genes and environmental factors create predisposition to the disease.

Mitochondrial diseases are caused by mutations on the mitochondrial genome. This group of diseases is inherited in a maternal fashion [i.e., only affected female subjects can transmit the disease mutation (phenotype) to their offspring] (eFig. 97.0.1).

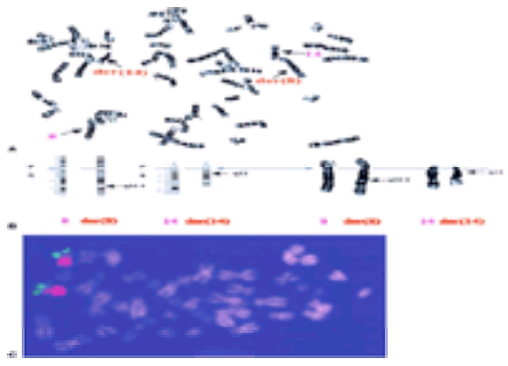
All the diseases discussed previously are associated with genetic abnormalities in the DNA of all cells in the body and can be transmitted to future generations. However, a new paradigm of diseases called *somatic cell genetic disorders* caused by mutations in specific somatic cells has been recognized. Examples of such diseases include cancer and some vascular disorders.

CYTOGENETICS IN GENETIC RESEARCH AND MOLECULAR DIAGNOSTICS

Chromosomal (or cytogenetic) abnormalities account for at least 50% of spontaneous abortions or miscarriages and cause congenital malformations, mental disability, infertility, and certain cancers (3). Chromosomal abnormalities involving one chromosome include a deletion or duplication of a portion of a chromosome, a pericentric (involving the centromere) inversion or paracentric (not involving the centromere) inversion, or the formation of a ring chromosome or isochromosome. When two or more chromosomes are involved, a translocation or exchange of chromosomal materials between the chromosomes occurs. The chromosomal abnormalities associated with cardiovascular disease include Down syndrome, DiGeorge syndrome or velocardiofacial syndrome, congenital heart defects, and Williams syndrome.

Karyotype Analysis

Karyotyping from peripheral blood is a standard technique used for examining human chromosomes and for identifying chromosomal abnormalities (4). A small amount of anticoagulated blood is centrifuged to isolate white blood cells, to which are added tissue culture medium containing plant lectins such as phytohemagglutinin to stimulate them to divide. The dividing cells are then arrested at metaphase with mitotic spindle inhibitors such as colchicine and lysed in hypotonic buffers to prepare metaphase chromosomes. Preparations of metaphase chromosomes are then stained with dyes such as Giemsa (G-banding) and examined under a microscope. G-banding involves a series of acid, heat, or gentle trypsin treatment of chromosome preparations followed by staining with Giemsa. The alternation of chromosomal regions with high or low G/C content results in a pattern of light and dark bands that is unique for each human chromosome (*e*Fig. 97.0.2A). The unique pattern for each human chromosome allows the unequivocal definition of each chromosome, and any deviations from this typical pattern may indicate occurrence of chromosomal abnormalities (*e*Fig. 97.0.2B). Other chromosome banding techniques producing quinacrine (Q) bands, reverse (R), or centromeric (C) bands can be used to examine special chromosomal domains.



***e*FIGURE 97.0.2** Examples of karyotype analysis **(A,B)** and fluorescence *in situ* hybridization analysis **(C)**. **A:** A metaphase spread prepared from blood samples of a patient with Klippel-Trenaunay syndrome and stained by Giemsa banding. A translocation involving chromosomes 8 and 14 (*arrows*) was identified. **B:** Translocation t(8;14)(q22.3;q13) with centromeres at the solid line and breakpoints marked. Ideograms of normal chromosomes 8 and 14 and derivative chromosomes 8 and 14 are shown at the left, and G-banded chromosomes are shown at the right. **C:** Fluorescence *in situ* hybridization analysis to map the human myotrophin gene to chromosome 7q36. The painting probe (*red*) is for the short arm (p) of chromosome 7. The signals from the test probe, a bacterial artificial chromosome containing the myotrophin gene, are in green. (**A** and **B**, unpublished data from Azita Sadgephour and Qing Wang; **C**, unpublished data from Ayse Anil Timur and Qing Wang.)

Fluorescence *In Situ* Hybridization

Fluorescence *in situ* hybridization (FISH) technology is a major tool for gene mapping and for identifying chromosomal abnormalities (5,6). In FISH analysis, DNA probes (any cloned DNA sequences, genes, microdissected fragments, or flow-sorted chromosomes) are labeled by incorporation of chemically modified nucleotides (e.g., BrdU) that fluoresce directly or can be labeled by incorporation of reporter molecules (e.g., DIG or Biotin). The DNA probes are then hybridized to metaphase or interphase chromosomes. Chromosomes are then counterstained with 4,6-diamino-2-phenyliodole (DAPI) to provide high-definition banding of the chromosomes, and hybridization signals are detected by binding a fluorescently tagged molecule to reporter molecules (e.g., anti-DIG-FITC). Chromosomes are then photographed under a fluorescence microscope (*e*Fig. 97.0.2C). FISH can allow rapid mapping of any gene or DNA sequence cloned into cosmids, BACs, or YACs to a particular chromosome (*e*Fig. 97.0.2C). FISH can also be used to detect numerical chromosomal abnormalities, including the small deletions involved in DiGeorge syndrome and supravalvular aortic stenosis and Williams syndrome.

Advances in FISH technology include chromosome painting, which allows the entire chromosome to fluoresce with the chosen color (*e*Fig. 97.0.2C), and multicolor FISH, which allows each human chromosome to be painted in up to 12 different colors (5). Both chromosome painting and multicolor FISH can be used to identify complex chromosomal rearrangements or abnormalities rapidly.

In conclusion, both karyotype analysis and FISH are powerful technologies that can be implemented in many research and diagnostic fields of human genetics.

OVERVIEW OF STRATEGIES FOR DISEASE GENE DISCOVERY

Functional Cloning

Until the mid-1980s, the primary approach to identify the gene responsible for a human disease was through careful analysis of biochemical and physiologic differences between healthy and affected individuals. The deficient protein or enzyme from patients can be purified, and partial amino acid sequences can be obtained or antibodies against the protein can be raised. The antibodies, degenerate oligonucleotides derived from the partial amino acid sequences, or tagged fusion proteins, can then be used to screen various cDNA libraries to identify the disease gene. The approach moving from the basic biochemical defect to the disease gene is referred to as *functional cloning*. Sickle cell anemia caused by mutations in the hemoglobin gene was the first human disease characterized by human molecular genetics. Initially, red blood cells from affected individuals were noticed to be abnormally shaped. Later, it was found that hemoglobin from patients was electrophoretically different from normal hemoglobin, and this difference was due to the substitution of valine for glutamic acid at the sixth amino acid position of the beta chain of hemoglobin (7). Subsequently, the gene for beta-hemoglobin was cloned and the mutation of a single base substitution of A to T was identified at the nucleic acid level (8). However, the genetic etiology of most diseases cannot be tackled using functional cloning due to lack of information on biochemical defects.

Candidate Gene Approach

With the candidate gene approach, potential known candidate genes for a disease are chosen based on the assumption of physiologic mechanisms of the disease and are assessed using mutation analysis to verify the candidacy of the gene. The candidate gene approach was used to establish that mutations in the cardiac sodium channel gene *SCN5A* cause idiopathic ventricular fibrillation with right bundle branch block and ST-segment elevation (known as *Brugada syndrome*) (9).

POSITIONAL CLONING

The development of genetic markers, together with the availability of efficient and accessible statistical methods for analyzing the segregation of markers and disease genes, made it possible to locate and clone the gene responsible for a human disease solely on its map position, without any prior knowledge of the function of its protein product. This approach is referred to as *positional cloning* (originally referred to as *reverse genetics*) (10). The first disease gene cloned by positional cloning was chronic granulomatous disease in 1986 (11) (*e*Table 97.0.1). By 1989, positional cloning had led to cloning of only four disease genes. A similar approach was used to clone *KvLQT1* on chromosome 11p15.5 that causes long QT syndrome (12). By 1998, more than 100 disease genes had been cloned by positional cloning (*e*Table 97.0.1). Although positional cloning has become much easier, it is still a difficult and time-consuming approach.

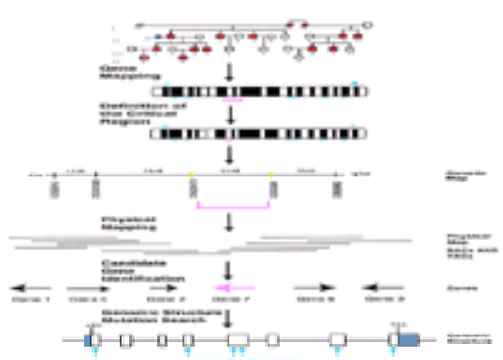
***e*TABLE 97.0.1** NOVEL DISEASE GENES IDENTIFIED BY POSITIONAL CLONING FROM 1986 TO 1998[a]

1986	1996
Chronic granulomatous disease (*NCF1*)	Anhidrotic ectodermal dysplasia (*EDA*)
Duchenne's muscular dystrophy (*DMD*)	Barth's syndrome (*BTHS*)
Retinoblastoma (*RB1*)	Basal cell nevus syndrome (*BCNS*)

1989	
Cystic fibrosis (*CFTR*)	
1990	
Choroideremia (*CHM*)	
Gonadal dysgenesis (*SRY*)	
Neurofibromatosis, type 1 (*NF1*)	
Wilms' tumor (*WT1*)	
1991	
Adenomatous polyposis coli (*APC*)	
Amyotrophic lateral sclerosis (*SOD1*)	
Aniridia (*PAX6*)	
Fragile-X syndrome (*FMR1*)	
Kallmann's syndrome (*KAL*)	
1992	
Lowe oculocerebrorenal syndrome (*OCRL*)	
Myotonic dystrophy (*DM*)	
Norrie's disease (*NDP*)	
1993	
Adrenoleukodystrophy, X-linked (*ALD*)	
Agammaglobulinemia, X-linked (*BTK*)	
Epidermolytic palmoplantar keratoderma (*KRT9*)	
Glycerol kinase deficiency (*GK*)	
Huntington's disease (*HD*)	
Menkes syndrome (*MNK*)	
Miller-Dieker lissencephaly (*PAF*)	
Neurofibromatosis, type 2 (*NF2*)	
Spinocerebellar ataxia 1 (*SCA1*)	
Tuberous sclerosis (*TSC*)	
von Hippel-Lindau syndrome (*VHL*)	
Wilson disease (*WND*)	
1994	
Aarskog-Scott syndrome (*FGD1*)	
Achondroplasia (*FGFLR*)	
Breast cancer, type 1 (*BRCA1*)	
Chondrodysplasia punctata (*ARSE*)	
Congenital adrenal hyperplasia (*CYP21*)	
Dentatorubral pallidoluysian atrophy (*DRPLA*)	
Diastrophic dysplasia (*DTD*)	
Emery-Dreifuss muscular dystrophy (*STA*)	
Machado-Joseph disease (*MJD1*)	
McLeod syndrome (*XK*)	
Polycystic kidney disease, type 1 (*PKD1*)	
Wiskott-Aldrich syndrome (*WASP*)	
1995	
Alzheimer's disease (chromosome 1) (*AD4*)	
Alzheimer's disease (chromosome 14) (*AD3*)	
Ataxia telangiectasia (*ATM*)	
Bloom's syndrome (*BLM*)	
Breast cancer, type 2 (*BRCA2*)	
Hereditary multiple exostoses, type 1 (*EXT1*)	
Hereditary multiple exostoses, type 2 (*EXT2*)	
Hypophosphatemic rickets (*XLH*)	
Limb-girdle muscular dystrophy (*LGMD2A*)	
Ocular albinism (*OA1*)	
Spinal muscular atrophy (*SMA*)	
Chediak-Higashi syndrome (*CHS*)	
Dementia, hereditary multiinfarct (*CADASIL*)	
Diabetes of the young, maturity-onset (*MODY3*)	
Fanconi's anemia A (*FAA*)	
Friedreich's ataxia (*FRDA*)	
Hemochromatosis (*HFE*)	
Hermansky-Pudlak syndrome (*HPS*)	
Long QT syndrome (*KvLQT1*)	
Myotubular myopathy 1, X-linked (*MTM1*)	
Polycystic kidney disease, type 2 (*PKD2*)	
Progressive myoclonic epilepsy (*PME*)	
Retinitis pigmentosa, X-linked (*RP3, RPGR*)	
Rieger's syndrome, type 1 (*RIEG1*)	
Simpson-Golabi-Behmel syndrome (*SDYS*)	
Spinocerebellar ataxia 2 (*Sca2*)	
Treacher Collins syndrome (*TCS*)	
Werner syndrome (*WRN*)	
1997	
Alagille's syndrome (*AS*)	
Angelman's syndrome (*AGS*)	
Deafness (*DFNA1*)	
Dystonia (*GCH1*)	
Familial Mediterranean fever (*MEFV*)	
Holt-Oram syndrome (*HOS*)	
Juvenile glaucoma (*GLC1A*)	
Multiple endocrine neoplasia, type 1 (*MEN1*)	
Niemann-Pick disease, type C (*NPC1*)	
Opitz syndrome (*OS*)	
Pendred's syndrome (*PDS*)	
Situs inversus (*HTX1*)	
Spinocerebellar ataxia 7 (*SCA7*)	
Stargardt's disease (*STGD1*)	
Tuberous sclerosis 1 (*TSC1*)	
1998	
Best's macular dystrophy (*BMD*)	
Congenital nephrotic syndrome (*NPHS1*)	
Congenital night blindness, X-linked (*CSNB*)	
Cystinosis (*CTNS*)	
Deafness (*DFNA5*)	
Fukuyama-type congenital muscular dystrophy (*FCMD*)	
Lafora's disease (*MELF*)	
Limb-girdle muscular dystrophy, type 2B (*LGMD2B*)	
Lissencephaly, X-linked (*LISX*)	
Neuronal ceroid-lipofuscinosis, late infantile (*CLN2*)	
Nijmegen's breakage syndrome (*NBS1*)	
Oculopharyngeal muscular dystrophy (*OPMD*)	
Peutz-Jeghers syndrome (*PJS*)	
Retinitis pigmentosa 2, X-linked (*RP2*)	
Wolfram's syndrome (*WFS*)	

[a] Based on information from http://genome.nhgri.nih.gov/clone/. Genes identified by a (positional) candidate gene approach are excluded.

The overall strategy for positional cloning is illustrated in eFigure 97.0.3. Positional cloning includes five major steps: gene mapping, definition of the critical region, physical mapping, identification of candidate genes, and mutation analysis. Each step is discussed in detail later in this chapter.



***e*FIGURE 97.0.3** Positional cloning. The five major steps are shown schematically. BAC, bacterial artificial chromosomes; YAC, yeast artificial chromosomes.

Positional Candidate Gene Approach

This approach is a shortcut to positional cloning. When a disease gene is mapped by linkage analysis or cytogenetic abnormalities, known genes located near the disease gene become candidate genes for the disease. Mutation analysis is then used to verify the candidacy of each gene. The positional candidate gene approach was used to identify the chromosome 7–linked long QT gene (*HERG*) and the chromosome 3–linked long QT gene (*SCN5A*) (13,14 and 15). The completion of the Human Genome Project will make the positional candidate gene approach the predominant method to identify disease genes in the coming decade.

Genetic Mapping

The first step in positional cloning is to determine the map position of the disease gene of interest by linkage analysis (*e*Table 97.0.2). Occasionally, a cytogenetic abnormality associated with the disease can provide the first clue. However, increasingly, disease genes are mapped by performing genome-wide linkage analysis.

***e*TABLE 97.0.2** STRATEGIES FOR MAPPING DISEASE GENES

Strategy	Disease
Model-based linkage analysis	Single gene disease (e.g., long QT syndrome, dilated cardiomyopathy)
Model-free linkage analysis	Complex genetic disease (e.g., coronary artery disease, hypertension)
Variance component linkage analysis	Polygenic disease (e.g., coronary artery disease, hypertension)
Cytogenetic abnormalities (chromosomal breakpoints)	Single gene disease

Linkage is the location of two loci sufficiently close together on a pair of homologous chromosomes that they do not segregate independently. Linkage occurs because alleles on the same chromosome at loci that are close to each other tend to be transmitted together. Consider two diallelic loci, one with alleles *A* and *a*, the other with alleles *B* and *b*. Suppose a person inherited *A* and *B* from one parent and *a* and *b* from the other parent. We denote the person's genotype *AB/ab*, where the slash separates the two parental contributions. If this person transmits a gamete with haplotype *Ab* or *aB*, a recombination has occurred. The proportion of gametes in which a recombination has occurred, q, is known as the *recombination fraction* between the two loci. The four different haplotypes that a person with genotype *AB/ab* can transmit, together with their probabilities, are given in eTable 97.0.3. If q = 1/2, these four probabilities are each equal to 1/4, and the alleles at the two loci segregate independently.

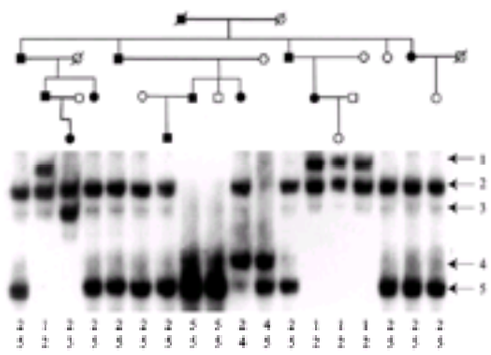
***e*TABLE 97.0.3** THE FOUR POSSIBLE GAMETES, AND THEIR PROBABILITIES, TRANSMITTED BY A PERSON WITH GENOTYPE AB/AB

Gamete	Probability
AB	1/2(1–q)
Ab	1/2q
aB	1/2q
ab	1/2(1–q)

Linkage leads to an intrafamilial association between the two phenotypes determined by the genotypes at the two loci. Furthermore, unless the two loci are so close together that recombination has not destroyed the association formed between them at the time a mutant allele first appeared at one of the loci, the two phenotypes are not associated in a random sample of unrelated persons from the population. It is difficult to conceive of any environmental factor that could simulate the typical result of genetic linkage between the two traits: lack of association at the population level, but association within families. This is especially the case if one of the two traits is known to be genetically determined. For this reason, evidence of linkage between a known genetic marker and a putative gene for a disease is usually taken to be the "ultimate" statistical evidence for the existence of that disease gene.

Markers

A genetic marker is a polymorphic trait that is genetically determined in a simple mendelian manner. The first markers were the blood cell antigens, red cell antigens such as the ABO and Rhesus blood groups and the HLA white cell antigens. About 40 years ago, enzyme polymorphisms were discovered that could be determined as bands on electrophoresis. In 1980 (16) the era of DNA polymorphisms began. At first, the DNA polymorphisms were restriction fragment length polymorphisms, but these were soon followed by variable number tandem repeat polymorphisms and short tandem repeat polymorphisms, or microsatellites (*e*Fig. 97.0.4), easily typed by use of the polymerase chain reaction (PCR). The newest markers are diallelic SNPs.



***e*FIGURE 97.0.4** Genotyping analysis using a simple tandem repeat marker. The pedigree is shown above, and the actual results of genotyping are shown below. Each of the alleles (1 to 5) for this simple tandem repeat or microsatellite marker carries a different number of copies for the simple repeated sequence, GATA. The marker was amplified using polymerase chain reaction as described (13), and products were separated by electrophoresing through 6% denaturing polyacrylamide. Each family member has two alleles at this locus, which are scored as 2/5, 1/2, 2/3, and so on.

Genetic Map

To use linkage analysis to place trait genes on the genome, we need a genetic map, a linearly arranged set of loci with known distances between them. Whereas a physical map gives the distances between loci in physical units (numbers of base pairs), a genetic map gives the distances in genetic units. At the beginning of meiosis, the pairs of homologous chromosomes line up alongside each other, and each chromosome duplicates into two identical sister strands, or chromatids. At this stage, crossing over between nonsister chromatids occurs at one or more points along the chromosome; crossing over is a reciprocal event resulting in each of two chromatids switching their DNA from being maternal to paternal in origin, or vice versa. It follows that a recombination occurs whenever there is an odd number of crossovers between the two loci on a particular gamete. The genetic map distance is measured in Morgans: 1 Morgan is the distance in which we expect exactly one crossover event to occur. The unit usually used is the centiMorgan (cM) (i.e., one-hundredth of a Morgan). Between loci that are separated by a small distance, only 0 or 1 crossover can occur; it follows that map distance and the recombination fraction are then the same. For loci that are far apart, the distance between them in centiMorgans will be larger than the recombination fraction expressed as a percentage, because only an odd number of crossovers leads to recombination between the two loci. The recombination fraction depends on the sex and other characteristics of the transmitting parent; on average, the human autosomal genome is approximately 3,600 cM long (17), and so approximately 180 markers are required to span it at 20-cM intervals.

Methods of Linkage Analysis

There are two main types of linkage analyses, model-based and model-free (18). Every statistical analysis requires a probability model to make inferences, and in both types of analyses the marker's mode of inheritance is specified. The terms *model-based* and *model-free*, when used to describe linkage analysis, refer specifically to the trait one is trying to map. In model-based analysis, the genetic model for the mode of inheritance of the trait must be completely specified, whereas in model-free linkage analysis, it does not have to be specified. We focus first on classical model-based linkage analysis. This is often called *parametric*, or *lod score*, linkage analysis, but these terms are equally applicable to model-free linkage analysis.

Model-Based Linkage Analysis

Given the trait and marker modes of inheritance, one can calculate the likelihood for a particular set of pedigree data that have been randomly sampled from a population. In general, to do this we need to specify (a) founder genotypic frequencies, (b) transmission probabilities, and (c) penetrance functions.

The founders of a pedigree are those members who have neither parent in the pedigree, and it is usually assumed that their genotypes are sampled at random from a particular population. If we consider two alleles at each of two loci, say *A* and *a* at one locus and *B* and *b* at the other locus, then four haplotypes, those indicated in eTable 97.0.3, are possible. When these are paired, they give rise to (5 × 4)/2 = 10 distinct unordered pairs that can be called *diplotypes*. eTable 97.0.4 shows what are often called the nine two-locus genotypes formed by two-diallelic loci, but genetically the double heterozygote *AaBb* corresponds to two different genotypes: *AB/ab* and *Ab/aB*. These are different two-locus genotypes, but they are often called the two phases of the same two-locus genotype. Use of the word *diplotype* (which unfortunately is not yet in common usage) avoids the ambiguity that often occurs whenever the term *multilocus genotype* is used.

***e*TABLE 97.0.4** THE NINE GENOTYPES AT TWO DIALLELIC LOCI, CORRESPONDING TO TEN TWO-LOCUS GENOTYPES, OR DIPLOTYPES

Genotypes at the first locus	Genotypes at the second locus		
	BB	*Bb*	*bb*
AA	*AABB*	*AABb*	*AAbb*
Aa	*AaBB*	*AaBb*	*Aabb*
aa	*aaBB*	*aaBb*	*aabb*

Unless all founder diplotypes are known, their relative frequencies in the population must be specified. It is usually assumed that the genotype frequencies at each locus are in Hardy-Weinberg equilibrium proportions, that the genotype distributions at the two loci are independent, and that each phase is equally frequent in the population.

The transmission probabilities (19) determine, conditional on the genotypes of their parents, the genotype probabilities of all nonfounders (i.e., of those individuals who have both parents in the pedigree). Transmission is usually assumed to be mendelian at each locus individually. The transmission of haplotypes from each double

heterozygote diplotype depends on the recombination fraction. The transmission probabilities from the double heterozygote *AB/ab* are the probabilities listed in *e*Table 97.0.3. Those from the double heterozygote *Ab/aB* are the same except that 1 – q replaces q.

Each penetrance function is a probability distribution, the distribution of phenotype given a particular genotype. In model-based linkage analysis we usually assume

P(trait phenotype, marker phenotype | diplotype) = P(trait phenotype | trait genotype) P(marker phenotype | marker genotype)

The second factor is usually assumed to be 0 or 1 for all phenotypes and genotypes, corresponding to a marker whose alleles are all codominant and at which there are no genotyping errors. The first factor is taken to follow a model estimated by segregation analysis or guessed, and, except as noted in the following discussion, is assumed to be known without error.

Calculation of Likelihoods and Lods

In terms of the three kinds of probability functions just described, the probability of observing the phenotypes Y on pedigree members can be expressed as a function of the recombination fraction q. This probability is calculated for various values of q, and each resulting probability is divided by the probability that results when we set q = 1/2. The ratio of these two probabilities, considered as a function of the unknown recombination fraction q, is a likelihood ratio. The logarithm to base 10 of the likelihood ratio is called a lod (20), or lod score, and is denoted *Z(q)*. The calculation of the likelihood ratio usually requires a computer. The value of q that maximizes Z(q), $\hat{\theta}$, is the maximum likelihood estimate of the recombination function, and Z($\hat{\theta}$) is the maximum lod.

Interpretation of Lods

Traditionally, when a single recombination fraction is estimated, a maximum lod Z($\hat{\theta}$) greater than or equal to 3 has been taken to be good evidence for linkage, whereas Z($\hat{\theta}$) less than or equal to –2 has been taken to exclude linkage within a recombination fraction of q (21). If there is no linkage, P(Z($\hat{\theta}$) ³3) £10^{-3}, so 10^{-3} is an upper bound for the probability of type I error, or *p* value. Furthermore, as the number of informative meioses becomes large, the corresponding *p* value becomes equal to 10^{-4}. The original reason for requiring a lod greater than or equal to 3 (in large samples equivalent to *p* £10^{-4}) before concluding that a linkage exists was to control to approximately 5%, not the probability of a type I error when there is *no* linkage (the null hypothesis), but rather the *posterior* probability of type I error when concluding that there *is* linkage (21). This follows from the fact that two loci picked randomly from the genome have a small prior probability, approximately 1/20, of being linked. It has been argued that this is an unsatisfactory assumption in the case of a complex trait for which the very existence of genetic involvement may be in doubt. Lander and Kruglyak (22) have therefore advocated a somewhat more stringent criterion, reasoning that, because we are testing for linkage at all locations along the genome when performing multipoint linkage analysis (i.e., using the information from multiple markers spread out over each chromosome), we must allow for the multiple tests being performed. However, they state that this same more stringent criterion should be met whether a part or whole genome scan is actually performed. This is illogical, if the reason for the criterion is based on a need to correct for multiple testing, for then the criterion should depend on how many tests are performed. Morton (23) has pointed out that the very fact that a linkage study is being performed indicates that one has a prior belief that a gene must be involved and that the criterion for accepting linkage must logically depend on how many data are available, which determines the power of the analysis.

When more than one parameter is estimated, it is common to derive the (larger) lod that then corresponds in large samples to a *p* value of 10^{-4} and require that the observed lod be this large to have good evidence for linkage.

Robustness

When using model-based linkage analysis, errors in the assumed trait model (the number of loci involved, the number of alleles at each locus, the allele frequencies, and the penetrances) can lead to inconsistent estimates, invalid tests, or lack of power. Furthermore, the pedigree data analyzed are not usually obtained by randomly sampling pedigrees, and in general the appropriate likelihood depends on the mode of ascertainment of the families in the study. However, provided any assumption errors concern only one of the variables involved, trait *or* marker, the results will be validity robust (i.e., the probability of coming to an erroneous conclusion when the null hypothesis of no linkage is true will not be inflated; and by the same token, lod scores do not depend on the mode of ascertainment if ascertainment is through only one of the variates, trait *or* marker) (24,25). Furthermore, in the case of a rare disease, the disease allele frequency assumed in the analysis, provided it is less than 0.01, is not critical; and provided all founder genotypes are known without error (or can be deduced without error from their relatives), the likelihood ratios, and hence also the lods, do not depend on the marker allele frequencies assumed for the analysis.

Model-Free Linkage Analysis

If a trait locus is linked to a marker locus, relatives such as siblings who have similar trait phenotypes tend to have similar marker phenotypes, whereas relatives who have dissimilar trait phenotypes tend to have dissimilar marker phenotypes. All methods of model-free linkage analysis test for a correlation between two such measures of similarity among relatives, because in the absence of linkage there is no reason for such a correlation to exist. The relatives may be chosen to be similar (e.g., they may all have a particular disease), in which case the test is to determine whether their marker phenotypes are more similar than expected by chance; they may be chosen to be dissimilar (e.g., discordant sibling pairs), in which case the test is to determine whether their marker phenotypes are less similar than expected by chance; or they may be chosen to include both these types, in which case we test whether their degree of similarity or dissimilarity is correlated with their marker similarity or dissimilarity. The most powerful of such tests measure marker similarity in terms of identity by descent (ibd). Two alleles at a marker locus are ibd if they are copies of the same ancestral allele. In a random sample from a random mating population, unrelated persons share no alleles ibd, parent–offspring pairs share one allele ibd, and monozygotic twins share two alleles ibd, at every autosomal locus.

The earliest model-free method of linkage analysis based on marker ibd is that of Haseman and Elston (1972) (26). In this method, the probabilities that two siblings share zero, one, or two alleles ibd at a marker are calculated, using parental marker information, population marker allele frequencies, or both, if how many alleles they share ibd cannot be determined exactly. The proportion of marker alleles each sib pair shares ibd is estimated as the probability they share two alleles ibd plus one-half the probability they share one allele ibd. Then the sib pair squared trait difference is linearly regressed on this estimate, $\hat{\pi}_j$ for the *j*th sib pair. A significantly negative regression coefficient is taken as evidence for linkage. If markers spanning the whole genome have been typed, ibd sharing can be calculated in a multipoint fashion and a test performed at every point in the genome (27).

In the case of a dichotomous disease trait, most of the information often comes from affected sib pairs. This has led to a sampling design in which only affected sib pairs are collected and model-free methods of affected sib pair analysis used. (It should be noted that the same sample can undergo model-based linkage analysis, but the term *affected sib pair analysis* is usually used to denote model-free methods). This design is analogous to performing an experiment without controls, which in this case would be discordant sib pairs. Especially when parental genotypes are not known, a comparison between affected sib pairs and discordant pairs is advisable because the estimates of marker allele sharing are then dependent on the marker allele frequencies, which may be only poorly known, and are assumed in the analysis.

Another type of model-free linkage analysis, which may be thought of as a hybrid between model-based and model-free analysis, is variance component linkage analysis. This method is model-free in that it does not require one to specify the allele frequencies and penetrance functions at the trait locus, but a model is built in which the trait variance is decomposed into components due to individual marker locations and residual polygenic and environmental components. In particular, the trait covariance between a pair of relatives is modeled, assuming multivariate normality of the trait across family members, as a function of locus-specific trait variance components. In this type of analysis the assumption of multivariate normality can be critical if the resulting lods are to be interpreted in large samples as *p* values (28). Elston et al. (29) have proposed changing the Haseman-Elston regression procedure in a manner that makes it analogous to the usual variance component method of linkage analysis in that it models the sib covariance, rather than the squared sib-pair difference; but the fact that it is done by linear regression makes it much less dependent on any assumption of normality.

Finally, it should be pointed out all methods of linkage analysis depend critically on correct knowledge of the relationships among the pedigree members whose data are being analyzed. When the results of a whole genome marker scan are available, it is possible to detect, for example, unrelated persons or half-sibs who have been misclassified as full sibs (30).

DEFINITION OF THE CRITICAL REGION

After an initial linkage is obtained, multiple new markers in the region of interest are genotyped to assign the target gene to a critical interval by identifying two flanking genetic markers. The flanking markers are markers at either side of the critical interval (region) that demonstrate recombination events with the disease phenotype. In genetically homogeneous populations, the critical region for a disease gene can be narrowed with the study of linkage disequilibrium (LD) (i.e., the identification of a specific haplotype segregating with the disease in affected individuals). For diseases with cytogenetic abnormalities, the landmarks of the critical region for the target disease gene are chromosome breakpoints. The chromosome breakpoints can be defined using FISH analysis or somatic hybrid analysis, thus providing the precise

location of the disease gene.

PHYSICAL MAPPING

After the critical region for a disease gene is narrowed to the order of 2 cM or less, the next critical step in positional cloning is the characterization and cloning of large segments of human DNA from the critical region in specialized vectors such as the YAC cloning system (31) and the BAC system (32). This is achieved by the construction of an overlapping series of genomic YAC and BAC clones (a clone contig) across the critical region. YACs contain DNA inserts up to 1 Mb and are the best currently available tool for cloning large genomic regions. For many chromosomes, large uninterrupted YAC contigs with few gaps have been constructed, and the YAC contig information is available from http://www-genome.wi.mit.edu/. The relevant YAC clones can be purchased from commercial suppliers such as Research Genetics or Incyte, Inc. The YAC system is an excellent tool to construct physical maps and YAC contigs provide a framework on which to map other sequences or candidate genes. However, owing to difficulty in isolating and purifying YAC DNA and the chimerical nature of most YAC clones, YAC contigs are not ideal for identifying all genes across the critical region. Therefore, the YAC contigs are usually converted into BAC/PAC/P1 or cosmids contigs. The cloning capacity for the bacteriophage P1 system, the PAC system, the BAC system, and cosmid are 70 to 100 kb, 60 to 300 kb, 120 to 300 kb, and 40 kb, respectively (31,32,33 and 34). The high-density STSs on the YAC contigs can be used to screen BAC, PAC, P1, or cosmid libraries that are commercially available.

Identification of Candidate Genes (General Techniques)

Based on the high-resolution physical maps, novel genes in the region can be identified using several strategies. The principles of each gene identification method are discussed here. The technical details can be found in *Current Protocols in Human Genetics* (34a).

Exon Trapping

The exon-trapping technique was used to identify the chromosome 11–linked long QT gene, *KVLQT1* (12). Exon trapping relies on functional sequences required for RNA splicing and flank exon-coding sequences (35,36). Cloned genomic DNA fragments in BACs, PACs, P1s, or cosmids are ligated into a plasmid vector that contains consensus-splicing sequences. If the genomic fragment insert ligated in the vector contains an exon, then the exon can be spliced properly into the mature mRNA after expression in mammalian cells in culture. Trapped exons can then be amplified by reverse transcription PCR with primers flanking the consensus splice sites and used to screen cDNA libraries to identify the full-length cDNA corresponding to the new gene.

Complementary DNA Selection

The cDNA selection method captures cDNA sequences directly on the basis of their hybridization to target genomic DNA (37). The cDNA molecules are amplified from a cDNA library and hybridized to biotinylated genomic DNAs (YACs, BACs, PACs, P1s, cosmids) after suppression of repeated sequences. The cDNAs are then captured using streptavidin-coated magnetic beads. The cDNAs that specifically hybridize to genomic DNAs are then eluted and amplified by PCR; this process is repeated two or three times before cloning the selected cDNAs and sequencing them. This method is dependent on the choice of cDNA sources and the predicted pattern of expression of the target gene.

Cloning CpG Islands

The CpG islands are the GC-rich regions in the genome that are usually located at the 5' end of genes, somewhere around the first exon, and act as signposts for the 5' end of genes (38). Thus, finding CpG islands can lead to identification of novel genes. The CpG islands can be identified by analyzing results from digestion of genomic clones with restriction endonucleases recognizing CG sequences for clustering of CpG-rich sites.

Testing for Cross-Species Conservation

The rationale for cross-species conservation is that protein-coding sequences (genes) rather than intronic sequences are conserved to varying degrees across species (39). The evolutionary conservation of DNA fragments can be identified by hybridizing radioactively labeled DNA fragments from genomic clones to Southern blot filters containing genomic DNA from multiple species (“zoo” blot). If a DNA fragment demonstrates cross-hybridizing bands in several distantly related species, it may indicate that the DNA fragment contains coding sequences.

Identifying Expressed Sequence Tags

ESTs are partial, single-pass sequences from either end of clones (representing individual genes) that are randomly selected from cDNA libraries. Extensive databases of ESTs exist for finding ESTs or genes mapped to a disease locus (http://www.ncbi.nlm.nih.gov/UniGene; http://corba.ebi.ac.uk/RHdb/species/HUMAN/gm99.html). The National Center for Biotechnology Information also provides a map viewer that provides displays of the human genome sequence data and the location of genes, STSs, and SNPs on finished and draft sequences (http://www.ncbi.nlm.nih.gov/). ESTs located within the disease locus are then characterized as candidate genes for the disease.

Direct Screening of Complementary DNA Libraries

Screening cDNA libraries is the final step required to identify the corresponding genes and to obtain the full-length cDNA for most gene identification strategies. Screening cDNA libraries can also be used as a direct approach to find novel genes from genomic DNA fragments. DNA inserts in genomic clones such as BACs, PACs, P1s, and cosmids can be radioactively labeled and hybridized directly to cDNA libraries blotted on nylon filters after suppression of repetitive sequences. Positive cDNA colonies are then picked up and sequenced to find the novel genes.

Strategies for Sequence-Based Gene Discovery and Mapping (Bioinformatics)

Genomic sequencing, coupled with bioinformatics that allows for faster and more accurate recognition of coding sequences in long stretches of genomic DNA sequences, is becoming the ultimate gene identification method. Advances in automation and robotics for faster and cheaper long-range sequencing have made it possible to sequence the genomic clones (YACs, BACs, or cosmids) isolated from the critical disease region. Moreover, a “working draft” of sequences covering 90% of the human genome has been determined and is freely available to the community via the Internet. Thus, a significant number of sequencing data for the critical disease gene region may be already available or obtainable quickly. All sequence data from a project can be used to explore the GenBank or other databases (discussed in the next section) for new genes with bioinformatics tools.

Databases

Entrez ties together several linked databases (http://www.ncbi.nlm.nih.gov/):

- Nucleotide sequence database (GenBank): National Center for Biotechnology Information maintains and updates GenBank, a comprehensive repository of sequence data and associated annotation. GenBank contains sequences from GenBank, European Molecular Biology Laboratory Data Library, and DNA Database of Japan.
- PubMed database: The biomedical literature (PubMed) contains bibliographic information and journal abstracts indexed from more than 4,300 biomedical journals.
- Protein sequence database.
- Structure: A database for three-dimensional macromolecular structures.
- Genome: The genomes of over 800 organisms, both completely sequenced organisms and those for which sequencing is in progress.
- PopSet: A set of DNA sequences that have been collected to analyze the evolutionary relatedness of a population.
- Taxonomy: The names of all organisms that are represented in the genetic databases with at least one nucleotide or protein sequence.
- Online Mendelian Inheritance in Man database: A catalog of human genes and genetic disorders.

Information on the human genetic map (primer sequences, chromosomal locations, PCR profiles of polymorphic markers) and the physical map (contigs, YACs, BACs, genes, STSs, ESTs) can be obtained at the following locations: http://www.gdb.org//; http://www.genlink.wustl.edu/genethon_frame/; http://www.genethon.fr/genethon_en.html; http://www-genome.wi.mit.edu/; http://research.marshfieldclinic.org/genetics/; http://www.chlc.org/; and http://www.sanger.ac.uk/.

Bioinformatics Tools

Bioinformatics (computational molecular biology) has become a major research tool to identify and characterize genes implicated in human diseases. Putative genes in stretches of raw genomic DNA sequences can be identified by two primary approaches: homology-based methods [searching for related sequences in GenBank using computational programs such as Basic Local Alignment Search Tool (BLAST)] and feature-recognition methods [finding regions with protein-coding potential using tools such as Gene Recognition and Analysis–Internet Link (GRAIL)].

Homology-Based Methods (Basic Local Alignment Search Tool)

Database sequence similarity searching has become a valuable research tool for all molecular biologists and can be accomplished with the BLAST programs (40,41). In brief, users can access the National Center for Biotechnology Information Web page, click “BLAST” to open the program, input a nucleotide or amino acid query sequence, and search a nucleotide or amino acid sequence database. The program returns a list of sequences that are identical or homologous to the query sequence. The BLAST programs consist of BLASTP, BLASTN, BLASTX, TBLASTN, and TBLASTX, which differ on the query sequence and database sequence (*e*Table 97.0.5).

***e*TABLE 97.0.5** BASIC LOCAL ALIGNMENT SEARCH TOOL PROGRAMS

Program	Query sequence	Database sequence
BLASTP	Protein	Protein
BLASTN	Nucleotide (both strands)	Nucleotide
BLASTX	Nucleotide (six-frame translation)	Protein
TBLASTN	Protein	Nucleotide (six-frame translation)
TBLASTX	Nucleotide (six-frame translation)	Nucleotide (six-frame translation)

BLAST, Basic Local Alignment Search Tool.

If input is a genomic DNA sequence, and returned sequence hits are ESTs, other mRNA sequences, or protein sequence motifs or profiles, it suggests that the genomic DNA sequence contains the new gene(s) and the EST hits highlight the location of exons.

Feature-Recognition Methods (Gene Prediction)

Computer programs have been developed to predict and identify a DNA sequence that is likely to encode a protein by identifying patterns that exist in protein coding DNA sequences such as splice-donor and splice-acceptor junctions. The GRAIL software package is the most widely used system for recognizing portions of a sequence that have the potential to encode a protein (42). Besides GRAIL, a number of other programs have been developed. All these programs are available as stand-alone programs or via e-mail or the World Wide Web listed here, and instructions for using them are easily accessible via the Internet.

- GRAIL: http://compbio.ornl.gov/tools/index.shtml
- GeneID: http://www1.imim.es/geneid.html
- GeneParser: http://beagle.colorado.edu/~eesnyder/GeneParser.html
- FGENEH: http://genomic.sanger.ac.uk/gf/gf.shtml
- GENSCAN: http://genes.mit.edu/GENSCAN.html
- MZEF: http://www.cshl.org/genefinder
- PROCRUSTES: http://www-hto.usc.edu/software/procrustes

DNA sequences predicted to encode proteins are further characterized using Northern analysis or reverse transcription PCR to verify whether they are true protein-coding sequences. If positive, the DNA sequences are used as probes to screen cDNA libraries to isolate the full-length cDNA.

Sequence Motifs and Profiles

Sequence motifs or profiles are derived from the statistical analysis of amino acid residue conservation in aligned families of sequences with a particular biologic function. Identification of sequence motifs is usually indicative of the potential function of proteins encoded by novel genes. The sequence motifs can be identified by using a target sequence to query key databases providing collections of motifs such as BLOCK (http://www.blocks.fhcrc.org/), PROSITE (http://www.expasy.ch/prosite/), PRINTS (http://www.bioinf.man.ac.uk/dbbrowser/PRINTS), PFAM (http://www.sanger.ac.uk/Pfam), and TRANSFAC (http://transfac.gbf.de/TRANSFAC/).

Mutation Detection

Once a candidate gene has been identified, mutational analysis is performed to determine whether this gene, when mutated, causes a mutant phenotype or disease state. The presence of multiple mutations in the same gene in different families or patients is generally accepted as evidence that the mutant gene causes the disease. This section discusses types of mutations and several methods for detecting mutations.

Overview of Mutations

A *mutation* is defined as a change in DNA sequence. Mutations can occur in germline cells (germline mutations) or somatic cells (somatic mutations). Some mutations alter the number or structure of chromosomes. These major chromosomal abnormalities, such as aneuploidy, deletions, duplications, inversions, and translocations, have been discussed earlier. Here we list mutations that are not microscopically observable and affect single genes.

1. Base pair substitutions may or may not result in amino acid changes. Base pair substitutions can be divided into missense mutations that result in a change in a single amino acid, and nonsense mutations that produce a stop codon.
2. Deletions or insertions of one or more base pairs can result in extra or missing amino acids as well as frameshift mutations when the number of missing or extra base pairs is not three.
3. Mutations can occur in promoters (promoter mutations), enhancers (enhancer mutations), or intron-exon boundaries (splice site mutations or splicing mutations).
4. Trinucleotide repeat expansions have been shown to cause anticipation (earlier age of onset, more severe expression, or both in more recent generations of a pedigree) in some genetic diseases such as Huntington’s disease, myotonic dystrophy, and fragile X syndrome (43).

Methods for Detecting Mutations

Many techniques have been developed to detect or identify mutations (*e*Table 97.0.6). Here we discuss only a few of the most commonly used techniques.

***e*TABLE 97.0.6** TECHNIQUES FOR DETECTING MUTATIONS

Category (mechanisms)	Method	Reference
Gel electrophoresis mobility alteration techniques	Single strand conformation polymorphism analysis	44
	Denaturing gradient gel electrophoresis	93
	Heteroduplex analysis	45
	Restriction enzyme fingerprinting	94
	ddNTP fingerprinting	95
	Southern analysis	93
	Constant denaturant gel electrophoresis	96
Sequencing techniques	Direct sequence analysis of uncloned polymerase chain reaction products	—
	Sequence analysis of cloned polymerase chain reaction products	—
Mismatch cleavage/recognition techniques	RNAse A cleavage	93
	Chemical mismatch cleavage	93
	Bacteriophage T4 endonuclease VII cleavage	97
	MutY cleavage	98
	Mismatch repair detection	99
Cytogenetic techniques	Fluorescence *in situ* hybridization	93

High-performance liquid chromatography	Transgenomic WAVE DNA fragment analysis	47
DNA chip–based techniques	Oligonucleotide microarray hybridization	46
Protein truncation technique	Protein truncation analysis	100

Fluorescence *In Situ* Hybridization

Large deletions or insertions (greater than 300 kb) can be detected by the use of FISH analysis. FISH is particularly useful for detecting aneuploidy, deletions, duplication, complex arrangements, or loss of heterozygosity.

Southern Blot Hybridization or Restriction Fragment Length Polymorphism Analysis

Large deletions or insertions can be identified by the presence of junction fragments. Point mutations, microdeletions, or insertions (less than 300 bp) can be identified by altered restriction sites.

Single-Strand Conformation Polymorphism Analysis

Single-strand conformation polymorphism is the most commonly used method for identifying mutations. The single-strand conformation polymorphism method relies on the fact that single-strand DNA in solution, under certain conditions, has a defined secondary structure (44). This secondary structure can be altered when one of the bases is changed; the alteration in secondary structure can be detected by electrophoresis in nondenaturing polyacrylamide gels because normal and mutant strands have different mobilities (9,12,13,14 and 15).

Heteroduplex Analysis

Heteroduplex analysis relies on the fact that heteroduplex molecules, hybrids between wild-type and mutant DNA fragments, may show differential mobility from homoduplexes through polyacrylamide (45) or other gel matrices such as MDE (BioWhittaker Molecular Applications).

Sequencing Methods

PCR products used to be cloned into a bacterial vector, and multiple clones were then sequenced from each individual. Development of cycle sequencing eliminates the cloning step and makes it possible to directly sequence uncloned PCR products. Direct sequencing of uncloned PCR fragments has become a common technique for searching for mutations in candidate genes.

DNA Chips

DNA chips are high-density arrays of oligonucleotides. The labeled test DNA probe is hybridized to one or more DNA chips. Mutant and wild-type oligonucleotides may show differential intensity of hybridization to the test DNA (46). The DNA chip method is ideal for genetic diagnosis to detect known mutations in new patients.

Transgenomic WAVE DNA Fragment Analysis System

The Transgenomic WAVE System is a rapid and automated scanning method to detect mutations. It separates heteroduplexes from homoduplexes using denaturing high-performance liquid chromatography (47). The running time per sample in the Transgenomic WAVE System is short (approximately 10 minutes), and the method is automated; thus, the potential to analyze many samples rapidly is high. Although the Transgenomic WAVE System can be used to identify novel mutations, it is best suited for genetic diagnosis to detect known mutations in new patients.

GENE IDENTIFICATION FOR COMPLEX DISEASE

Many of the genes causing mendelian diseases have been identified, but genetics has yet to make a significant impact on common multifactorial disorders such as coronary artery disease, hypertension, and heart failure. It is thought that the availability of highly polymorphic markers and dense linkage maps will enable genetics to identify the constituent genes of complex diseases on the basis of their genomic locations. Once linkage analysis has identified these locations, the genetic dissection of a complex disease can be accomplished with one of the following approaches.

Association Studies (Case-Control Studies)

In association studies, affected individuals (cases) and matched controls are genotyped at test loci, and the resultant genotypes are analyzed. An allele is associated with the disease if it occurs in a collection of patients with a frequency significantly higher than that in a control population. If the disease-associated allele is within the coding sequence or promoter region and affects the physiologic function and expression of the coded protein, it may directly cause susceptibility to the disease. However, it is equally possible that the association occurs because of LD between the marker locus and the disease susceptibility locus. In this case, further studies are required to identify the susceptible gene near the marker. Until now, population-based association studies have been limited to a few candidate genes with disease. Associations can also occur because of population stratification and confounding, and care must be taken to avoid such ‘‘spurious’’ associations.

Linkage Disequilibrium Mapping Using Single Nucleotide Polymorphisms

On average, sequence variants occur every 1,000 bp in the human genome (48). Approximately 90% of sequence variants are single-base substitutions, referred to as *SNPs* (49,50). SNPs that occur within genes or in regulatory elements may affect the function or expression of a gene, which in turn may be responsible for disease susceptibility or drug response. Construction of human SNP maps is currently under way. The SNP Consortium Ltd. has identified and mapped more than 100,000 SNPs (http://snp.cshl.org/) and aims to expand the number to 300,000 at the beginning of 2001. High-throughput genotyping technologies (e.g., Affymetrix microarrays) have been developed for SNP genotyping. The advantages of SNPs have attracted attention for their use in whole-genome LD analysis to map common disease genes (50). The primary objective of LD analysis is to use a dense map of SNPs to detect association between an SNP and disease. If the disease-associated SNP identified is a functional variant, it becomes a mutation causing susceptibility to disease. Otherwise, the disease-associated SNP acts as a marker that allows mapping of a disease-susceptible gene. Positional cloning focusing on the disease-susceptible region can then lead to identification of the causative gene, a situation analogous to the use of linkage analysis to identify disease-related genes in families. Computer simulations (but not empirical evidence) have predicted that LD is unlikely to extend beyond 3 kb in the general human population, and approximately 500,000 SNPs will be required for whole-genome LD analysis. Because many types of LD analyses merely detect association, which is then assumed to be due to LD, they leave open the possibility of spurious results.

PHARMACOGENOMICS

The genetic study of drug response is referred to as *pharmacogenomics*. It is a newly developed field, and its principal objective is to understand the genetic basis of patients’ responses to medicines so that treatments can be targeted to those most likely to benefit.

SNPs that occur within genes or in regulatory regions may affect the function or expression of the gene. These functional SNPs may be responsible for the genetic component of phenotypic variables, including drug response. A major goal of pharmacogenetics is to identify the functional SNPs and then to determine how a specific allele contributes to patients’ responses to medicines (50). Novel drug target candidate genes can also be identified using transcriptome and proteome analysis (51). In summary, pharmacogenomics aims to identify multiple susceptible genes that are involved in determining a patient’s response to a given drug. These studies will eventually allow physicians to determine a patient’s likely response to a medicine before it is prescribed.

Gene Chip Technology and DNA Arrays (Transcriptional Profiling)

One of the most powerful and versatile tools developed for functional genomics is the high-density DNA or oligonucleotide arrays or gene chip technology. As previously mentioned, DNA arrays can be used both to perform mutational analysis and also to measure levels of gene expression (mRNA abundance). In this section, we focus on this latter use. A set of genes expressed or transcribed from genomic DNA is referred to as the *transcriptome* (52), the expression profile or transcriptional profile. Transcriptional profiling allows massively parallel analysis of gene expression. Here we use a study on heart failure using oligonucleotide arrays to demonstrate the principles and applications of this approach.

The basic premise for using this type of high-throughput approach to measure changes in gene expression is that each protein within the cell functions as part of an extended network with other proteins (i.e., each protein is part of a “functional module”) (53). It is rare that a particular cell function can be ascribed to a single molecule; much more likely, a functional effect is due to a collection of proteins that make up a functional group. Thus, to truly understand the complex changes in gene expression that occur during development of heart failure, we need to measure the expression of a large number of genes, and then cluster the results into functional gene families (54). The benefits of this approach have been succinctly stated by Weinstein (1998) (55): “We will have to understand our favorite biological molecule in the context of many thousands of others . . . a wide net must be cast to be sure that we have, in fact, found the important ones. . . .”

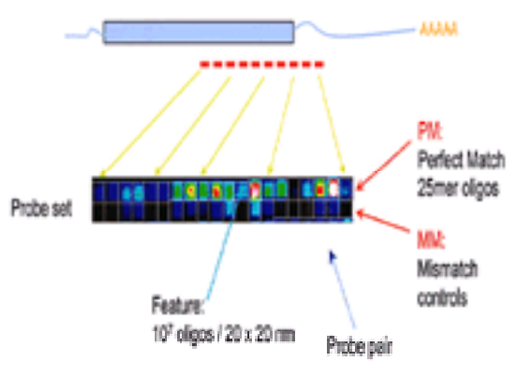
High-Throughput Methods of Gene Expression Analysis

With the working draft of the human genome now complete, the rate at which we identify new human genes is rapidly accelerating. Out of a total of approximately 30,000 to 40,000 genes predicted to make up the human genome, more than 12,000 full-length human genes (open reading frames) have already been sequenced. Partial DNA sequences of many more thousands of genes are represented by ESTs. As a result of the rapid increase in our knowledge of the repertoire of human genes, we now have the unprecedented opportunity to analyze the expression levels of thousands of genes by high-throughput gene-profiling technologies. These approaches permit an unbiased assessment (i.e., no preselection of genes is required) of expression levels of thousands of full-length genes, ESTs, or both. By simultaneously measuring changes in expression of hundreds or even thousands of genes, we can for the first time identify changes in whole classes or clusters of genes that do not function normally in failing hearts. This represents a giant leap forward in our ability to sort out all the different pathways in the heart muscle cells where changes in gene expression, and thus, most likely, changes in protein expression, have occurred.

The earlier methods that permitted simultaneous analysis of expression levels of large numbers of cDNAs included differential display, subtractive hybridization, and serial analysis of gene expression. More recently, microarray technologies have rapidly achieved popularity. These may consist of cDNAs printed or spotted onto a solid support, often called *spotted arrays* or *cDNA arrays* (56,57). Commercially available cDNA arrays may include large numbers of cDNAs within a gene family (e.g., genes involved in apoptosis) or members of cytokine gene families. Alternatively, arrays customized by robotic array makers can now be produced in house or purchased from a vendor. A variant of this approach, pioneered by Affymetrix, is to synthesize short oligonucleotides directly onto a glass substrate using photolithography techniques. We discuss in greater detail the use of oligonucleotide arrays and provide an example of the power of microarray technology to shed light on the large number of changes in gene expression that take place in the failing heart (58). Detailed information on methods of array manufacture, sample preparation, and data analysis can be found in original publications (46,59).

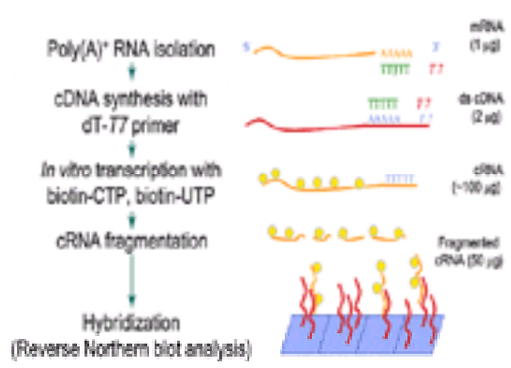
Oligonucleotide Arrays

An oligonucleotide array consists of a gene chip with many thousands of oligonucleotides synthesized on its surface using a photolithographic mask, as used in the semiconductor industry. Each of the cDNA sequences on the array is represented by one probe set containing approximately 20 different 25-mer oligonucleotides, chosen from unique regions of the nucleotide sequence of the gene. Each of these “perfect match” probes has a mismatch control (59) that serves to control for nonspecific hybridization to the chip (eFig. 97.0.5).

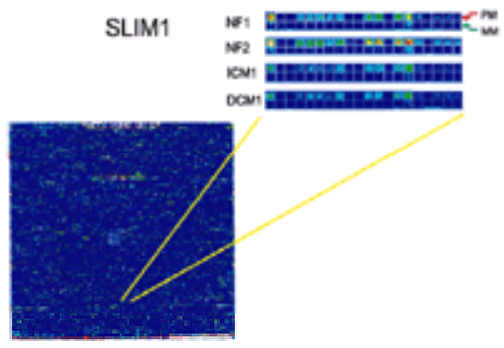


***e*FIGURE 97.0.5** Example of a probe set on a gene chip representing one particular gene. Each feature on the chip represents approximately $10^7$25-mer oligonucleotides, representing a unique region of the sequence of that gene (PM, perfect match oligonucleotides) or the same sequence but with a mismatch nucleotide (MM, mismatch) to control for nonspecific hybridization. Together, each PM and MM pair makes up a probe pair. A probe set represents a set of probe pairs that should uniquely identify a particular gene. Thus, when complementary RNA prepared from myocardium hybridizes to the probe set, after subtracting the nonspecific hybridization to the MM oligonucleotides, the relative extent of hybridization is a quantitative indication of the expression level of that gene (or, for some chips, of an expressed sequence tag). (Figure prepared by Jiacheng Yang, PhD.)

From a starting material of approximately 2 g of myocardium from the ventricular free wall, the main steps involved in sample preparation for analysis by oligonucleotide arrays or gene chips are (a) preparation of total RNA from tissue or cell homogenate, (b) purification of poly(A)$^+$ RNA, (c) double-stranded cDNA synthesis using poly(A)$^+$ RNA as a template and a *T7*-(dT)$_{24}$ oligonucleotide as initial primer; then (d) amplification by *in vitro* transcription to produce biotin-labeled cRNA; and (e) approximately 50 µg of fragmented cRNA plus control cRNAs hybridized to the chips (eFig. 97.0.6). More recent protocols eliminate the poly(A)$^+$ RNA step. After subtracting nonspecific hybridization due to cRNA binding to mismatch oligonucleotides, the intensity of fluorescence averaged over all of the probe pairs representing each gene is then determined. This is proportional to the level of expression of the gene in the tissue being assayed. An example of a gene chip showing a sample of cRNA from a human heart hybridized to a gene chip, highlighting hybridization to the probe set representing the gene *SLIM1*, is shown in eFigure 97.0.7.



***e*FIGURE 97.0.6** Sequence of steps to isolate complementary RNA (cRNA) from heart homogenate for hybridization to a gene chip. The initial starting material is total RNA. Either poly(A)+ RNA is then isolated from the total RNA, or, more commonly, total RNA is used as the starting material. Single-chain complementary DNA (cDNA) and then double-stranded (ds) cDNA is prepared by reverse transcription using a dT-T7 primer. The amplification step is next: This involves *in vitro* transcription performed in the presence of biotinylated CTP and UTP. The cRNA obtained is then fragmented to optimize hybridization to the oligonucleotides on the chip. The final step is fluorescent labeling of the hybridized biotinylated sample to quantitate the extent of hybridization. mRNA, messenger RNA. (Figure prepared by Jiacheng Yang, PhD.)



***e*FIGURE 97.0.7** Fluorescent image of biotinylated complementary RNA (cRNA) hybridized to high-density oligonucleotide arrays (gene chips). This demonstrates the result of hybridization of biotinylated cRNAs prepared from failing and nonfailing human hearts (NF1, NF2) to Affymetrix gene chips. The entire image of the chip (1.3 cm × 1.3 cm) containing oligonucleotides representing approximately 7,000 full-length human genes is shown at left. Magnified images compare the fluorescent intensity of biotin-labeled cRNAs hybridized to the perfect match (PM) and mismatch (MM) oligonucleotide probes specific for the striated muscle LIM protein-1 (*SLIM1*) gene. Expression of *SLIM1* was decreased in the failing human hearts. DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy. (From Yang J, Moravec CS, Sussman MA, et al. Decreased SLIM1 expression and increased gelsolin expression in failing human hearts measured by high-density oligonucleotide arrays. *Circulation* 2000;102:3046–3052, with permission; figure by Jiacheng Yang, PhD.)

The Next Step

A unique problem that DNA array studies present is sorting out the vast array of data obtained. Sophisticated computer programs and advances in the burgeoning field of bioinformatics are needed to facilitate the data analysis and help identify the gene families that show altered expression in heart failure. We also need to determine whether the changes that we identify are initial triggering events or compensatory changes; the latter may be good for the failing heart, whereas the former changes may be bad. The next step is to go back to animal models of heart failure, manipulate the expression level of these same genes shown to have altered expression levels in failing hearts, and find out if, by mimicking the changes in the failing human heart, we either exacerbate disease development or ameliorate impaired cardiac function.

How will gene chip technology ultimately find its way into the heart clinic? There is potential for gene chip technology to help people who demonstrate an increased likelihood of developing heart failure, or it could be of use even earlier in the disease process (e.g., to forewarn of increased risk of ischemic cardiomyopathy as a result of an early triggering event, blockage of coronary arteries with secondary ischemic damage to the heart muscle cells). In the one instance, the goal would be to help identify that subset of genes that shows altered expression in groups of people with an increased risk of heart disease; in the second case, in view of the range of successful surgical and medical treatments now available, it may be even more timely to use gene chip technology to identify people who are “good responders” to a particular therapy versus poor responders. What differences in gene expression distinguish these people? Gene chip arrays could help to predict these individual differences.

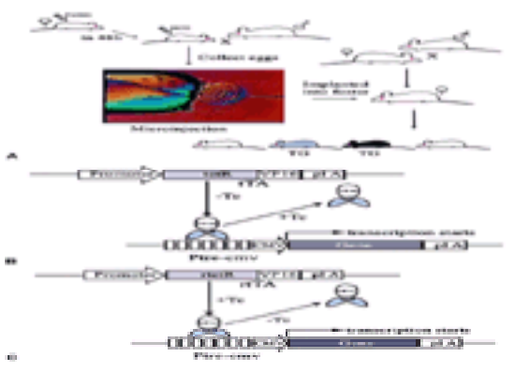
ANIMAL MODELS (TRANSGENIC AND EMBRYONIC STEM CELL TECHNOLOGIES)

Transgenic and embryonic stem (ES) cell (gene-targeting) techniques have become essential tools in modern molecular genetics to define normal physiologic function of new genes, to assess how a mutation can affect its protein functions, and to create animal models for human genetic diseases. Here we review the principles and applications of transgenic and ES cell technologies.

Transgenic Animal Technology

In 1980, the first transgenic mouse was generated by microinjecting DNA into the pronucleus (60). The foreign DNA could be transmitted into the descendants. The animal carrying the foreign DNA (transgene) in its genome is referred to as the *transgenic animal*. The transgene, which can be integrated as a cluster (head to head, head to tail, or tail to tail) at a single site and rarely at multiple sites on the chromosome(s) (61), can function as an endogenous gene (62). To date, besides transgenic mice, transgenic rats, rabbits, sheep, pigs, goats, and cows have been successfully generated (63,64,65,66 and 67).

The transgenic animals can be generated by various methods. The conventional procedure is to microinject DNA into the pronuclei of the fertilized eggs at the one-cell stage (*e*Fig. 97.0.8A) (67,68). Other methods include the infection of blastocysts with retrovirus vectors (69), sperm-mediated DNA transfer (70), and ES cell–mediated DNA transfer (71).



***e*FIGURE 97.0.8 A:** Generation of transgenic (TG) animals by microinjection. Different colors in TG represent the fact that the TG founders carry various copies of the transgene, and they are usually chimeric to different degrees. **B,C:** Tet-off and tet-on systems, respectively. CMV, human cytomegalovirus promoter; HCG, human chorionic gonadotropin; pl A, poly A adding signal; PMSG, pregnant mare serum gonadotropin; Tc, tetracycline; VP16, herpes simplex virus VP16 activation domain.

Design of Transgenic Constructs

A transgene consists of three parts: a promoter region, a structural gene (target gene), and a poly A adding signal.

Overexpression

The transgene can be overexpressed in the specific tissues (organs), in the whole body, or in the tissues where it is natively expressed. The tissue overexpression can be achieved by using a tissue- or organ-specific promoter to direct the expression of the transgene. There are many tissue-specific promoters available, such as cardiac myosin heavy chain-a promoter specific for cardiac tissues (both ventricles and atria) (72), cardiac myosin light chain-2 promoter specific for ventricles (73), and *TIE* (*TIE1* and *TIE2*) promoters specific for endothelial cells (74,75).

Some promoters, such as the CMV and RSV promoters, are strong but of less selectivity in tissue expression, and give high expression levels in most parts of the body. The high expression of a gene in various tissues or organs can allow one to investigate a spectrum of functions of the gene.

The enhanced expression of a gene in its natively expressed tissues can be accomplished by using its genomic DNA, including BACs, PACs, and YACs (76) or its natural promoter-directed cDNA as the transgene.

Inducible Expression

The tetracycline-resistance operon was modified and used in the regulation of a transgene's expression, a system referred to as *tet-off/tet-on*. In the tet-off system (eFig. 97.0.8B), the tTA, a fusion protein that consists of the tet repressor (tetR) protein (1-207 aa) and the C-terminal region (127 aa) of the herpes simplex virus VP16 activation domain (VP16), activates transcription by binding to the adapted tet operator (Ptre-cmv, tet response element plus the minimal CMV promoter) (77). The tetracycline (Tc or doxycycline, Dc) can remove tTA from the binding site, and therefore turn off the Ptre-cmv–directed transcription.

In the tet-on system (eFig. 97.0.8C), the tTA has been modified, and the modified tTA (rtTA) reverses the binding property of tTA, and therefore permits binding only in the presence of Tc or Dc. When Tc or Dc is present, rtTA binds to the Ptre-cmv and turns on the transcription (78).

The transgenic animals with the tet-on/tet-off system carry two transgenes: one is the tissue-specific promoter-directed rtTA/tTA, and the other is the Ptre-cmv–directed transgene. The expression of the transgene can be initiated when the animal is treated with Tc or Dc (79).

Reporter Gene

The spatial and temporal expression pattern of a given gene during embryogenesis as well as adulthood can be analyzed by using its promoter to drive the expression of a reporter gene, such as *Lac Z* or *GFP* in transgenic animals. The expression pattern of the interest gene can be mapped by determining the expression of reporter genes (73).

Dominant Negative and Antisense

The functions of an interest gene can be arrested if a dominant negative mutant is used as the transgene. The dominant negative mutant is usually a truncated fragment of the interest gene that can antagonize the normal function of the endogenous gene (80). In addition, the function of a gene can also be suppressed by using an antisense construct as the transgene (81).

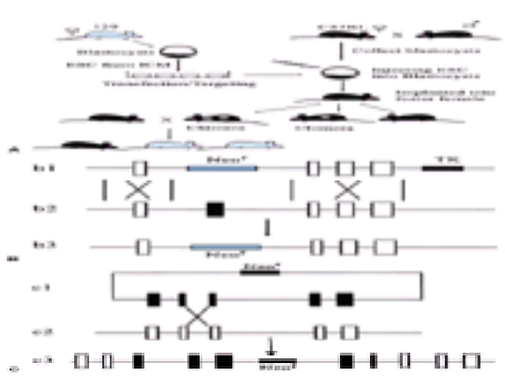
Embryonic Stem Cell Technologies

Embryonic Stem Cell

The ES cells are the preimplanted embryo-derived pluripotent cells that maintain an unlimited differentiation potential and normal karyotype during cell culture (82,83). Several ES cell lines have been generated from various mouse strains. The ES-like cell lines have been isolated from other species, but the murine species is currently the only laboratory animal whose ES cells can be genetically manipulated both *in vivo* and *in vitro*.

Gene Targeting

By homologous recombination, a specific gene can be modified in ES cells when they are transfected with a proper construct. This process is referred to as *gene targeting* (84,85). The genetically manipulated ES cells are injected into blastocysts, and the blastocysts are then transferred into the uteri of the foster female mouse where they develop into chimeric mice. The chimeric mice can transmit the ES cell genotype if the modified gene is integrated into the germline cells (eFig. 97.0.9A) (68).



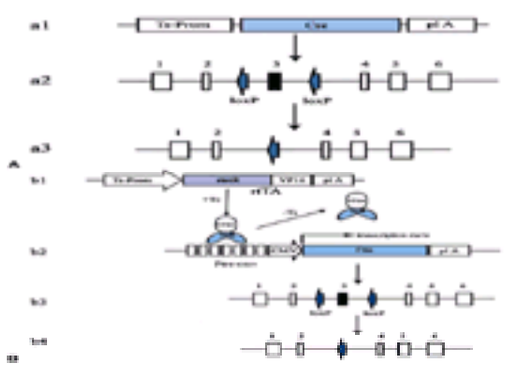
***e*FIGURE 97.0.9 A:** Scheme for gene targeting. Spots on the animals' coats indicate that the animals have different degrees of chimerism. Gray indicates that the animals are homozygous. **B,C:** Replacement and insertion vectors, respectively. The vertical open or filled bars are the exons of a gene. b1 and c1, targeting vectors; b2 and c2, wild-type alleles; b3 and c3, targeted alleles; ESC, embryonic stem cell; ICM, inner cell mass.

Targeting Vectors

Replacement vectors are used to replace a certain region of an endogenous gene with the DNA fragment from a targeting vector. The DNA fragment can be a reporter gene, the selective marker such as a neomycin-resistant gene (Neo^r), or the same endogenous gene, but with subtle mutations. The replacement vector usually has positive and negative markers, such as Neo^r and the herpes simplex virus-1 thymidine kinase gene (*HSV-1tk*), allowing the selection of correctly targeted ES clones (eFig. 97.0.9B).

Insertion vectors are used to introduce the subtle mutations or to duplicate the gene *in vivo* (eFig. 97.0.9C). Several targeting systems have been designed, respectively, for these purposes: gap-repair gene targeting (86) as well as hit-and-run gene targeting (87).

The *Cre-loxP system* is developed for tissue-specific targeting. Two components are needed in the Cre-loxP system: bacteriophage P1 Cre recombinase and loxP sites. The loxP site is a 34-bp DNA sequence consisting of two 13-bp inverted repeats, the binding sites for the Cre, and an 8-bp asymmetric core sequence. The core sequence determines the orientation of the loxP. When Cre is present, the DNA sequence between two loxP sites that are in the same orientation can be efficiently excised (eFig. 97.0.10A) (88,89). For example, if the target gene is to be deleted in cardiac ventricles, two types of mice are needed; one is the transgenic mouse in which the Cre is specifically expressed in the ventricles, and the other is the knockout mouse in which certain exons of the target gene are flanked by the loxP sites (but the gene's function is still normal) by means of regular gene targeting. Because the Cre is specifically expressed in ventricles, it deletes the targeted gene (locked exons of this gene) only in the ventricles in their offspring when the two strains are bred together (90).



***e*FIGURE 97.0.10 A:** Cre-loxP system. The vertical open or filled bars are the exons of a gene, and the arrows are the loxP sites. Cre produced by a1 acts on a2, and exon 3 is then removed in a3. **B:** Inducible gene-targeting system. The fusion protein, rtTA, is expressed under the control of a tissue-specific promoter (b1). If Tc exists, rtTA can bind to Ptre-cmv, leading to the expression of CRE (b2). CRE then removes the loxed exon 3 in the gene of interest (b3 and b4). CMV, human

cytomegalovirus promoter; pl A, poly A adding signal; Ts-Prom, tissue-specific promoter; VP16, herpes simplex virus VP16 activation domain.

In combination with the tet-on/tet-off system, the Cre-loxP system has been used to create inducible gene targeting that deletes the target gene only when the animals are treated with tetracycline or doxycycline (eFig. 97.0.10B) (91,92). The inducible targeting strategy is particularly useful in characterizing genes that cause embryonic lethality when deleted in mice.

Transgenic and ES cell technologies have been widely used to characterize the genes causing cardiovascular diseases. In addition, gene trapping, the other ES cell–based technique, has been developed to identify the novel genes involved in developmental processes, such as the formation of the heart. As the majority of human genes is identified in the near future, transgenic and ES cell technologies will remain the major tools in genetic research over the next decade.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The Human Genome Project has already led to a rapid acceleration in the pace of disease gene discovery. Linkage analysis is still the key to positional cloning. The physical mapping phase of positional cloning will eventually be eliminated. Candidate gene identification will rely on ESTs and genes available in the critical disease region, and on bioinformatic programs that can predict genes from raw genomic DNA sequences. The current mutation detection methods are sufficient for finding novel mutations in candidate genes.

Gene chip technology and transgenic and gene-targeting technologies will remain predominant approaches in finding the physiologic function of human genes, all of which will be identified in the next few years. However, gene chip studies create an enormous number of data. Sophisticated computer programs and advances in the burgeoning field of bioinformatics are needed to sort out this vast array of data. We also need to determine whether the changes that we identify are initial triggering events or compensatory changes. The next step is to go back to animal models, manipulate the expression levels of these same genes, and find out if the changes in human disease can be mimicked. At the present time, the ES cell–based gene-targeting technique can only be performed in mice, but it is expected that the same technique will be developed for other species that may serve as better animal models to study cardiovascular disease. Transgenic congenic animals may become particularly useful in characterizing complex cardiovascular diseases.

The genetic studies of cardiovascular disease will go through four paradigm shifts: disease gene identification, genetic testing, pharmacogenomics, and therapy. We are currently at the peak of the gene discovery phase. In 5 to 10 years, genetic testing will start to truly benefit many patients by providing risk assessment and allowing implementation of medical surveillance and lifestyle planning programs to reduce risks. Many policy issues need to be resolved for genetic testing. Current mutation detection technologies are not sufficient for fast and low-cost genetic testing because many genes are usually involved in the pathogenesis of a disease, and most of the mutations are isolated or individual mutations. High-throughput and low-cost technologies need to be developed to make massive genetic testing possible. The field of pharmacogenomics has just started, and therapies based on disease gene discoveries may take an unpredictably long time to reach and benefit patients. The future challenge will be to develop new technologies for pharmacogenomics and better therapies.

THE FUTURE

Positional cloning will remain as a dominant strategy for genetic dissection of human disease over the next 5 to 10 years. Many genes for single gene disorders will be quickly identified, and some susceptibility genes for complex diseases will be discovered. The completion of the Human Genome Project, coupled with increasingly more powerful bioinformatic tools, will speed up positional cloning significantly. The focus of genetic research in human disease is gradually shifting from single gene disorders to complex diseases and pharmacogenomics. Sib pair linkage analysis, case-control studies with candidate genes, and LD analysis with SNPs will be the key technologies used in finding genes for complex diseases and drug response. Another focus of research in the next decade will be functional genomics. The goal of functional genomics is to assign a function to each human gene. Ultimately, individual genes will be integrated together to form networks, thus forming networks of proteins that regulate genes. Transgenic and ES cell technologies (gene targeting), as well as finding human disease genes, will be the most informative approaches to identify or assign functions to genes. However, we expect that the main strategy to accumulate functional information for all human genes will be the whole genome approaches, in the form of expression profiles (gene chip technology), computational molecular biology, protein–protein interactions, proteomics, and comparative genomics.

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GENETICS OF ATHEROSCLEROSIS

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GLOSSARY

Allele: One alternative form of a gene.

Candidate gene: A gene that, by virtue of its known properties, could contribute to a genetic disease.

Dominant: A trait that is expressed in a heterozygote (such as familial hypercholesterolemia).

Genotype: Either the genetic constitution of an individual or the alleles that are present at a particular locus.

Heritability: The proportion of variance of a trait (such as blood pressure or myocardial infarction) explained by genetics.

Linkage: The tendency of genes that reside near one another on a chromosome to be inherited together.

Locus: A unique chromosomal location that defines the position of a gene.

Modifier gene: A gene whose expression can modulate a phenotype.

Multifactorial: A trait determined by multiple factors, usually including genetic and environmental factors.

Phenotype: The physical characteristics of an individual determined by his or her genetic constitution (e.g., the phenotype of high levels of plasma cholesterol result from low-density lipoprotein receptor mutations).

Polymorphism: A genetic variation that occurs relatively frequently (>1%) in the population.

Restriction fragment length polymorphism: A polymorphism recognized by a difference in the size of hybridizing fragments following digestion of deoxyribonucleic acid.

INTRODUCTION

Atherosclerosis, the primary cause of heart disease and stroke, is a disorder with multiple genetic and environmental contributions. Epidemiologic studies have identified a surprisingly long list of genetic and nongenetic risk factors (eTable 98.0.1). Within populations, genetic differences appear to be of primary importance in determining those in whom significant atherosclerosis will and will not develop clinically. Between certain populations, particularly those with different levels of dietary fat consumption, environmental influences predominate. A number of mendelian disorders that are associated with atherosclerosis, such as familial hypercholesterolemia (FH), have been characterized, but such genetic disorders explain only a small fraction of disease susceptibility (less than a few percent). The vast majority of cases of coronary artery disease (CAD) and stroke result from the interactions of multiple genetic and environmental factors, none of which is able to cause disease by itself. As yet, we have little understanding of the genes that are involved in such "complex" or "multifactorial" forms of atherosclerosis. Many association studies and linkage studies for CAD and its risk factors have been reported, but most such studies have been able to provide only suggestive evidence for the involvement of certain candidate genes, and our understanding is very incomplete. New approaches for the dissection of complex genetic traits, including novel analytic methods, large-scale sequencing of candidate genes, and the use of animal models, are being applied to atherosclerosis and its risk factors. The Human

Genome Project, now nearing completion, is a crucial resource for such studies. The identification of genes involved in common forms of atherosclerosis should lead to improved prevention, control, and cure of the disease. In this chapter we present a geneticist's perspective of atherosclerosis and review the current state of knowledge of the simple and the complex forms of the disease and its risk factors. Several previous reviews of the genetics of atherosclerosis are available (1,2,3,4,5 and 6).

***e*TABLE 98.0.1** GENETIC AND ENVIRONMENTAL RISK FACTORS ASSOCIATED WITH ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

Factors with strong genetic component	
Elevated levels of LDL/VLDL	Associations have been demonstrated by numerous epidemiologic studies and are supported by studies of genetic disorders and animal models. Small, dense LDL particles are particularly strongly associated with CAD. Clinical trials have shown benefits of cholesterol reduction.
Reduced levels of HDL	Associations have been demonstrated by numerous epidemiologic studies, studies of genetic diseases, and studies of animal models. The relationship is complex, however, because HDL is heterogeneous and exhibits different functional states.
Elevated levels of Lp(a)	Associations with CAD have been observed in many but not all epidemiologic studies. Animal studies have yielded positive as well as negative results.
Elevated blood pressure	Associations with CAD and stroke have been observed in numerous epidemiologic studies. Clinical trials have demonstrated benefits of blood pressure reduction, with a particularly strong effect on stroke.
Elevated levels of homocysteine	Associations have been observed in epidemiologic studies, and homocystinuria results in severe occlusive vascular disease. Animal studies have been inconclusive.
Family history	When all known risk factors are controlled for, family history remains a very significant, independent factor in nearly all studies reported.
Diabetes and obesity	Associations have been observed in epidemiologic studies and in studies with animal models. Atherosclerosis is accelerated in part through interactions with other risk factors.
Elevated levels of hemostatic factors	Significant independent associations have been observed with elevated levels of fibrinogen, plasminogen activator inhibitor type 1, and platelet reactivity.
Depression and other behavioral traits	Associations have been observed in several studies. The results are complicated due to associated traits; for example, depressed people are more likely to smoke.
Gender (male)	Under age 60 yr, CAD develops in men at more than twice the rate of women. A recent trial has raised concerns about the benefits of postmenopausal estrogen replacement.
Systemic inflammation	Elevated levels of inflammatory molecules such as C-reactive protein are associated with CAD, as are inflammatory diseases such as rheumatic arthritis.
The "metabolic syndrome"	This cluster of metabolic disturbances, with insulin resistance as a central feature, is strongly associated with CAD.
Environmental factors	
High-fat diet	Population migration studies have revealed very strong associations with lifestyle, and diet appears to be the most significant factor. High-fat, high-cholesterol diets are usually required for development of atherosclerosis in experimental animals.
Smoking	Strong associations have been observed in numerous epidemiologic studies. It has been estimated that approximately 30% of CAD deaths are due to smoking. Clinical trials have demonstrated benefits of cessation of smoking.
Low antioxidant levels	Results of clinical trials with antioxidants have yielded mixed results and are as yet inconclusive. However, fat-soluble antioxidants protect against atherosclerosis in experimental animals.
Lack of exercise	This is associated with many other risk factors, such as diabetes, obesity, and smoking, but a significant independent relationship has been observed.
Infectious agents	Epidemiologic studies have provided suggestive evidence for associations with various infectious agents, such as *Chlamydia pneumoniae*. Preliminary animal studies have supported the relationship.

CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); VLDL, very-low-density lipoprotein.
Adapted from Lusis AJ. Atherosclerosis. *Nature* 2000;407:233–241, with permission.

An understanding of the genetic aspects of CAD and stroke is becoming increasingly important to the clinician who is concerned with the management of patients with CAD. For example, an appreciation of the nature of genetic-environmental interactions that are involved in the disease is essential in assessing risk and advising patients of lifestyle changes. Moreover, knowledge of the genetics of CAD allows optimal use of the family history for counseling patients and other family members who may be at risk for CAD later in life. Genetically based classifications for various risk factors for atherosclerosis—including plasma lipid variations, hypertension, and diabetes—will become possible as our knowledge of the genetic factors that underlie these traits expand.

OVERVIEW: GENETICS OF ATHEROSCLEROSIS

Atherosclerosis Has an Important Genetic Component

With the exception of rare mendelian forms, CAD does not exhibit obvious genetic patterns of inheritance. Because the disease is so common, with an incidence of more than 50% in some populations, it is not surprising that in some families there are multiple affected individuals. How, then, can we estimate the influence of genetic factors on disease susceptibility or even be sure that atherosclerosis has an important genetic component?

First, family studies have clearly shown a clustering of atherosclerosis, and there is a very significant increase in mortality in first-degree relatives of men and women with CAD compared to control subjects. The familial effect of CAD appears to be particularly strong for early-onset disease, approximately 50 years of age or less (1,2,7). For example, one study analyzed first-degree relatives of 121 men and 96 women with CAD and an approximately equal number of control subjects. When deaths in men under 55 years and in women under 65 years were considered, the relatives of female patients showed a sevenfold increased risk and the relatives of male patients showed a fivefold increased risk (8).

Second, twin studies strongly support a genetic component, because monozygotic twins, who share 100% of their genes, have a much higher concordance rate for CAD and stroke than do dizygotic twins, who share approximately 50% of their genes (1,4,9). *e*Table 98.0.2 shows concordance data from a Norwegian twin study. A very large twin study, which included 21,004 Swedish twins, yielded similar results. Among men, the relative hazard of death from CAD when the twin died of CAD before the age of 55 years, as compared with the hazard when the twin did not die of CAD before the age of 55 years, was 8.1 for monozygotic twins and 3.8 for dizygotic twins. Among women, when the twin died of CAD before age 65, the relative hazard was 15.0 for monozygotic twins and 2.6 for dizygotic twins (10). Family studies and twin studies are both confounded by the effects of common environmental factors. Although it seems that monozygotic and dizygotic twins should share the environment to about the same extent, there are likely to be subtle differences.

***e*TABLE 98.0.2** NORWEGIAN SAME-SEX TWIN PAIRS: CONCORDANCE RATES FOR CORONARY ARTERY DISEASE

Category	Monozygotic pairs	Dizygotic pairs
All affected pairs	0.66[a]	0.25
Affected pairs, 60 yr or younger	0.83	0.22

[a]Concordance rates are expressed as correlation coefficients. Individuals were determined to be affected if they experienced myocardial infarction or angina pectoris.
Data from Berg K. Genetics of coronary heart disease. In: Steinbert AG, Bearne AG, Motulsky AR, Childs B, eds. *Progress in medical genetics.* Philadelphia: WB Saunders, 1983:35–90.

The fact that certain atherosclerosis risk factors (*e*Table 98.0.1) are clearly heritable provides additional strong evidence for a genetic component in atherosclerosis (11). For example, *e*Table 98.0.3 shows the heritability of plasma lipoprotein levels and blood pressure in one study. Many other studies have revealed similar results, and other atherosclerosis risk factors, such as obesity and type II diabetes, also exhibit high degrees of heritability as evidenced by higher concordance rates in monozygotic twins compared to dizygotic twins (*e*Table 98.0.4). In addition to heritability estimates from family and twin studies, candidate gene studies have identified a number of genes contributing to various risk factors. Some examples are shown in *e*Table 98.0.5.

***e*TABLE 98.0.3** HERITABILITY OF BLOOD LIPIDS AND RELATED TRAITS FROM MULTIGENERATIONAL UTAH PEDIGREES[a]

	Correlation coefficients (*r*)		Heritability estimates (%)		
Trait	MZ	DZ	Twin H^2	Pedigree H^2	Pedigree C^2
Total cholesterol	0.80	0.49	61	42	8
Total triglycerides	0.68	0.28	81	37	6
High-density lipoprotein cholesterol	0.75	0.39	74	45	15
Body mass index	0.68	0.41	54	24	0
Diastolic blood pressure	0.46	0.16	60	22	3

[a]Shown are correlation coefficients in monozygotic (MZ) and dizygotic (DZ) twins, gene heritability (H^2) calculated from twins or pedigrees, and percentage of variance attributable to common household (C^2).

Data from Ma J, Stampfer MJ, Hennekens CH, et al. Methylenetetrahydrofolate reductase polymorphism, plasma folate, homocysteine, and risk of myocardial infarction in US physicians. *Circulation* 1996;94:2410–2416.

***e*TABLE 98.0.4** CONCORDANCE RATES IN MONOZYGOTIC (MZ) AND DIZYGOTIC (DZ) TWINS FOR SELECTED TRAITS RELEVANT TO ATHEROSCLEROSIS

	Concordance rates		
Trait or disease	MZ twin	DZ twin	Heritability
Blood pressure (diastolic)	0.58	0.27	0.62
Blood pressure (systolic)	0.55	0.25	0.60
Body fat percentage	0.73	0.22	>1.0
Diabetes mellitus (type II)	0.70–0.90	0.25–0.40	0.9–1.0
Myocardial infarction (men)	0.39	0.26	0.26
Myocardial infarction (women)	0.44	0.14	0.60

From Jorde LB, Carey JC, Bamshad MJ, White RL. *Medical genetics*. St. Louis: Mosby, 1999:249.

***e*TABLE 98.0.5** COMMON GENETIC VARIATIONS CONTRIBUTING TO CORONARY ARTERY DISEASE AND ITS RISK FACTORS[a]

Trait	Gene	Variation
LDL/VLDL	ApoE	Three common missense alleles explain ~5% of variance of cholesterol
	ApoAI-CIII-AIV-AV cluster	Multiple polymorphisms
HDL levels	Hepatic lipase	Promoter polymorphism
	ApoAI-CIII-AIV cluster	Multiple polymorphisms
	ApoAII	Multiple polymorphisms
	Cholesteryl ester transfer protein	Common null mutations (Japanese); missense polymorphisms
	Lipoprotein lipase	Missense polymorphisms
Lp(a)	Apo(a)	Many alleles of apo(a) explain >90% variance
Homocysteine	Methylenetetrahydrofolate reductase	Missense polymorphism
Coagulation	Fibrinogen B	Promoter polymorphism
	Plasminogen activator inhibitor type 1	Promoter polymorphism
	Factor VIII	Common missense
Blood pressure	Angiotensinogen	Missense and promoter polymorphisms
	$Beta_2$-adrenergic receptor	Missense polymorphism
	Alpha-adducin	Missense polymorphism; support from studies in rats
CAD	Angiotensin-converting enzyme	Insertion-deletion polymorphism
	Serum paraoxonase	Missense polymorphism affecting enzymatic activity; animal studies support
	Hemochromatosis-associated gene	Missense polymorphism
	Endothelial nitric oxide synthase	Missense polymorphism
	Factor XIII	Missense polymorphism
	Fibrinogen cluster	Various polymorphism
	Interleukin-1 receptor antagonist	Missense polymorphism
	P-selectin	Missense polymorphism
	CD14	Promoter polymorphism
	Mannose-binding lectin	Missense polymorphism
	Plasminogen-activated inhibitor type 1	Insertion/deletion polymorphism

Apo, apolipoprotein; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); VLDL, very-low-density lipoprotein.
[a]Only genes exhibiting evidence of linkage or association in two or more studies are cited. See text for discussion.
Adapted from Lusis AJ. Atherosclerosis. *Nature* 2000;407:233–241.

The strongest evidence for a genetic component in CAD is the identification of genes that contribute to the disease. Striking progress has been made in characterizing the mendelian forms of the disease (*e*Table 98.0.6), but few genes have been conclusively implicated in the common forms of CAD (*e*Table 98.0.5).

***e*TABLE 98.0.6** MENDELIAN DISORDERS RELEVANT TO ATHEROSCLEROSIS

Trait	Disease (gene)	Characteristics
Elevated LDL/VLDL levels	Familial hypercholesterolemia (LDL receptor)	Dominant disorder characterized by very high LDL-cholesterol levels and early CAD
	Familial defective apoB-100 (apoB)	Dominant disorder due to apoB mutations that affect binding to LDL receptor; less severe than FH
Low HDL levels	ApoAI deficiency (apoAI)	In the homozygous state, null mutations of apoAI result in the virtual absence of HDL and early CAD
	Tangier disease (ABCA1 transporter)	This recessive disorder results in the inability of cells to properly efflux cholesterol and phospholipids, resulting in very low levels of HDL
Coagulation	Various genetic disorders of hemostasis	Unlike rare disorders of lipid metabolism in which atherosclerotic disease is a primary manifestation, genetic disorders of hemostasis usually present either as increased risk of bleeding or thrombosis (usually venous), with no outstanding effect on atherogenesis
Elevated homocysteine	Homocystinuria (cystathionine beta-synthetase)	Recessive metabolic disorder resulting in very high levels of homocysteine and severe occlusive vascular disease
Diabetes, type II	MODY1 (hepatocyte nuclear factor 4a), MODY2 (glucokinase), MODY3 (hepatocyte nuclear factor 1a)	MODY1, 2, and 3 are characterized by the development of non–insulin-dependent diabetes mellitus in young adults
Hypertension	Glucocorticoid-remediable aldosteronism (hybrid gene from crossover of 11-b-hydroxylase and aldosterone synthase)	Dominant disorder with early-onset hypertension and stroke
	Liddle's syndrome (epithelial sodium channel)	Dominant disorder with hypertension and metabolic alkalosis

Apo, apolipoprotein; CAD, coronary artery disease; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MODY, maturity-onset diabetes of the young; VLDL, very-low-density lipoprotein.
Adapted from Lusis AJ. Atherosclerosis. *Nature* 2000;407:233–241.

Atherosclerosis Is Etiologically Very Complex

The number of different genetic factors that contribute to the common forms of atherosclerosis is unknown, but it is likely that dozens of different genes, each acting on the background of important environmental influences, are involved. It is evident from the numerous genetic risk factors associated with the disease that the number of genes involved must be large (*e*Table 98.0.1). With the exception of gender and lipoprotein(a) [Lp(a)] levels, each genetic risk factor is multifactorial. Studies with animal models indicate that traits such as plasma cholesterol levels, diabetes, obesity, and blood pressure are genetically very complex. It is also clear that atherosclerosis can result from different sets of genetic factors. Classically, such "genetic heterogeneity" has been found to result from mutations of genes that encode either different enzymes in the same metabolic pathway or different proteins in a multiprotein complex. The heterogeneity of atherosclerosis is probably due in large part to the fact that many different processes contribute to the disease (e.g., pathways for cholesterol homeostasis, blood pressure regulation, and artery wall cell interactions). Furthermore, the heterogeneity of atherosclerosis is also evidenced by the numerous different transgenes or gene knockouts that influence lesion formation in mouse models (see the section Dissection of Genetic Factors in Atherosclerosis).

Atherosclerosis Involves Genetic-Environmental Interactions

Atherosclerosis is not a function of genetics alone or environment alone but, rather, the interaction of the two. Between certain populations, environmental factors predominate; for example, the Japanese have a much lower incidence of CAD than do Americans, but Japanese-Americans who have adopted an American lifestyle, including diet, have about the same incidence of disease as European-Americans. On the other hand, within populations, genetic factors are likely to be most important; thus, numerous twin studies and family studies in the United States and in Europe argue that genetic factors outweigh environmental influences. In populations that consume low-fat diets, CAD tends to be relatively uncommon, irrespective of genetics, although rare individuals with very strong genetic predisposing

factors, such as FH, still have a high probability of developing the disease. In populations that consume high-fat diets, CAD is very common (up to approximately 50% of the population), but a large fraction of the population remains resistant to the disease or at least to its clinical consequences. Within a population, whether premature CAD does or does not develop in an individual is determined in large part by genetic factors, presumably because within a population most people experience a similar environment. The environmental factor that appears to be of greatest importance is dietary fat, although smoking, stress, lack of exercise, and other factors are clearly involved as well (*e*Table 98.0.1).

Genetic-environmental interactions have been studied in most detail for lipoprotein metabolism. The influence of environmental factors on lipoprotein metabolism and CAD has been most dramatically revealed by studies of different populations. The Seven Countries study (12,13) demonstrated strong positive correlations between the consumption of saturated fats, serum cholesterol levels, and CAD mortality among different populations. Migration studies suggested that such differences between populations are due primarily to environmental rather than genetic factors (although important genetic differences undoubtedly do exist between populations). For example, one study compared Japanese individuals living in Japan, Hawaii, and the mainland United States with total fat consumption progressively increasing among the three groups. Corresponding to the increases in fat consumption were increases in serum cholesterol levels and the incidence of CAD and stroke (14,15). Nevertheless, hereditary factors are primarily responsible for the plasma lipid differences within populations (1,16). This is most likely due to the fact that most individuals in a population tend to consume relatively similar diets and lead similar lifestyles.

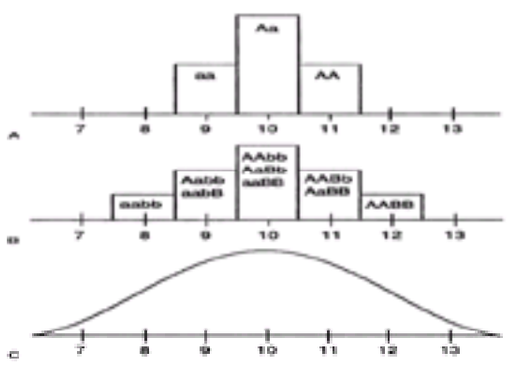
In some instances, genetic-environmental interactions are also known for certain other atherosclerosis risk factors. For example, a common polymorphism of the fibrinogen gene appears to influence myocardial infarction (MI) primarily in individuals who smoke (17,18). In addition, a common polymorphism of methylenetetrahydrofolate reductase (MTHFR), an enzyme in the folate cycle that precedes methionine synthetase, appears to cause high levels of homocysteine if the intake of folate is low (19,20). This latter polymorphism provides a potential paradigm for genetic screening and risk assessment for CAD; thus, if individuals who exhibit the polymorphism could be identified, they could be advised about the importance of folate intake.

An important but poorly understood aspect of the genetics of atherosclerosis involves how genes contribute to the *response* to dietary, or other environmental, changes. It is well known, for example, that different individuals respond very differently to challenge with a high-fat diet. Some striking ethnic differences are also seen in dietary responses. For example, the Masai, a Nilo-Hamitic tribe of East Africa, have extremely high fat intake, with their diet consisting almost entirely of animal products, but they appear to maintain low blood cholesterol levels by unusually efficient negative feedback regulation of cholesterol synthesis (21). On the other hand, Arctic Eskimos have relatively poor repression of cholesterol synthesis in response to dietary cholesterol, and their serum cholesterol levels are roughly proportional to their daily intake (22). Berg (4) has distinguished between “level” genes, which set the level of expression of a protein irrespective of environment, and “variability genes,” which influence how the expression of a protein changes in response to an environmental challenge. Using pairs of identical twins who exhibit various alleles of certain candidate genes, such as apolipoprotein (apo) B, he has obtained suggestive evidence for variability genes. For example, certain alleles of apoB resulted in larger differences in low-density lipoprotein (LDL) levels *within* a pair of twins than did other alleles. Because the twins are genetically identical, the alleles of apoB presumably determined the response to the environment.

Genetic-environmental interactions are very difficult to study in detail in humans. In particular, it would be very difficult to determine the relationship between a quantifiable phenotype, such as blood cholesterol, and various environments. One problem relates to our inability to control the environment carefully. However, the major problem is that a genotype cannot be replicated in humans (except in identical twins), and, therefore, it is almost impossible to examine the effect of a number of different environments on a phenotype while holding the genotype constant. Consequently, the data that are available for humans represent average results over many different genotypes. An excellent potential model for detailed studies of genetic-environmental interactions is the mouse, because many different inbred strains, each representing a unique gene pool, have been derived by brother-sister mating. Numerous differences in dietary responsiveness have been observed among strains of mice, affecting traits such as plasma lipoproteins and lesion development (23,24).

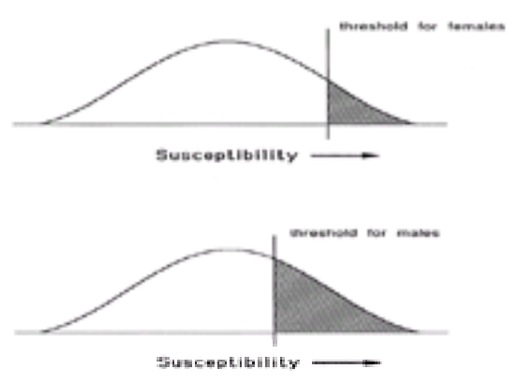
Models for the Inheritance of Atherosclerosis

As discussed in the Introduction, most forms of atherosclerosis are multifactorial, being governed by the simultaneous action of numerous gene loci. Traits that are controlled by a small number of loci yield discontinuous distributions, although the various classes may be obscured by environmental influences. Traits that are determined by the additive actions of a large number of different loci are distributed in a normal, or Gaussian, distribution in the population (*e*Fig. 98.0.1). Height is an example of such a trait. The smooth normal distributions of various risk factors for CAD, such as plasma cholesterol levels or blood pressure, suggest the involvement of a large number of loci. Such distributions are specified by two parameters—the *mean* and the *variance*. The variance is a statistic to quantify the dispersion about the mean. When variances are due to independent causes, they are additive. Thus, the overall variance of a phenotype (V_P), such as cholesterol levels or blood pressure, is the sum of the individual causes. These can be divided into the environmental variance (V_E) and the genetic variance (V_G). The heritability (h^2) of a trait is the proportion of total variance that is genetic (V_G/V_P). Heritabilities of human traits can be estimated from family studies or twin studies (e.g., *e*Table 98.0.3). The genetic variance V_G can be partitioned into components with additive, dominant, and epistatic influences (9,25). The mathematical modeling of complex traits has provided information about the existence of “major genes,” with relatively large effects on a trait and their modes of inheritance (26,27). For very complex traits such as atherosclerosis, or even blood pressure or cholesterol levels, it is very difficult to construct realistic models, because the observed phenotypes depend on so many unknowns, including the number of genes involved, the number of alleles of each gene and their frequencies, the impact of each allele on the trait, gene-environment interactions, and gene-gene interactions.



***e*FIGURE 98.0.1** Distribution of quantitative traits determined by one, two, or many additive gene loci. The graph shows the distribution in a population of a hypothetical trait determined by the effect of one **(A)**, two **(B)**, or many **(C)** loci. In this example, the trait has a mean value of 10; each lowercase allele subtracts 0.5 units, and each uppercase allele adds 0.5 units. (Modified from Strachen T, Read AP. *Human molecular genetics.* New York: Wiley-Liss, 1996.)

Unlike cholesterol levels and blood pressure, CAD and stroke are not continuously variable, or even quantitative, traits (although the area or size of atherosclerotic lesions in the population is continuously variable and may even have a Gaussian distribution). Traits such as MI or stroke are discontinuous: They are either present or not. The theory of polygenic inheritance was extended to discontinuous non-mendelian traits by postulating a continuously variable *susceptibility* and the existence of a threshold, beyond which the development of the disease would occur (28) (*e*Fig. 98.0.2). Thus, affected people would have inherited an unfortunate combination of susceptibility genes, pushing them beyond the threshold. The relatives of affected people would, on average, also tend to inherit genes that raise susceptibility, explaining the inheritance of the trait. The greater susceptibility of men to early CAD can be explained by a higher threshold in women than in men (*e*Fig. 98.0.2). A corollary of this is that, because a woman requires more susceptibility alleles for development of the disease than does a man, the children of an affected woman (or other first-degree relatives) have a higher likelihood of developing the disease than do the children of an affected man.



***e*FIGURE 98.0.2** A threshold model for coronary artery disease and stroke. See text for discussion.

The heritability of CAD can be estimated from twin studies and family studies. For example, using twin studies, the heritability *h* can be estimated using the simple formula

$$h = 2(C_{MZ} - C_{DZ})$$

where C_{MZ} is the concordance of the disease among monozygotic twins and C_{DZ} is the concordance among dizygotic twins. *e*Table 98.0.4 lists heritabilities for CAD and a number of related traits. The formula provides only a very rough estimate, however, because it assumes additive inheritance and the absence of genetic interactions (neither of which is realistic). The heritability of atherosclerosis, examined in numerous studies, frequently exceeded 50% but varies depending on the age (heritability tends to be larger for "early" CAD) and the sex of the subjects.

Dissection of Genetic Factors in Atherosclerosis

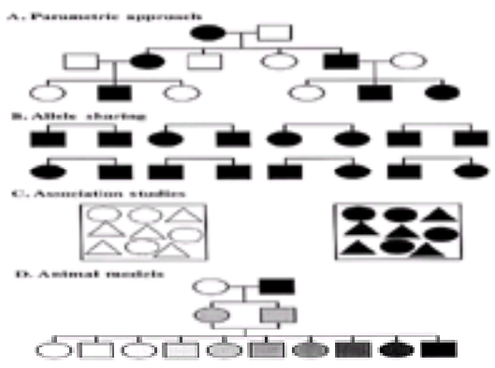
Very rapid progress is being made in identifying the genes in mendelian traits that are relevant to heart disease, using candidate gene and positional cloning approaches (*e*Table 98.0.6). Such studies often have relevance to understanding the complex forms of heart disease. The most outstanding example of this is FH. The genetics of FH were first elucidated in the 1930s by Carl Miller, a physician at a county hospital in Oslo. Miller's studies showed that the triad of very high plasma cholesterol, tendon xanthomas, and early heart disease tended to segregate together in a dominant fashion in families. This conclusively established the link between cholesterol and atherosclerosis. The classic studies of Brown and Goldstein, beginning in the early 1970s and continuing to the present day, have established the basis of the disease and, more important, have defined mechanisms that govern cholesterol homeostasis. This knowledge has formed a scientific cornerstone for further understanding of the common forms of hypercholesterolemia, and it has contributed to the development of powerful new therapies, such as the family of statins. Mendelian forms of high-density lipoprotein (HDL) deficiency, hypertension, and cardiomyopathies have similarly clarified the common complex forms (*e*Table 98.0.6).

A starting point for the dissection of atherosclerosis, as is the case for most other complex diseases, is genetic epidemiology (27). Epidemiology reveals associations between subclinical traits and clinical disease, and it can help divide complex diseases into different forms. A list of genetic and environmental risk factors identified by epidemiologic studies is presented in *e*Table 98.0.1. A classic example of the utility of epidemiology in revealing disease heterogeneity is diabetes. Diabetes used to be considered a single disease, characterized simply by high blood sugar. Epidemiologic studies, however, revealed that one form of diabetes, termed *type I*, tended to occur in early childhood and was associated with a lean body mass, whereas another form, termed *type II*, tended to occur in adulthood and was associated with obesity. It is now clear that type I and type II diabetes are separate diseases, resulting from very different genetic and environmental contributions. This is, of course, crucial for further understanding of the diseases. When a complex disease process such as atherosclerosis is considered as a single disease entity, genetic and biochemical dissection is enormously complicated. Just as in diabetes, various forms of hypertension and hypercholesterolemia and CAD have different causes, and defining the various forms is an important step toward deeper understanding.

Genetic dissection of atherosclerosis has built on the foundations provided by epidemiology, focusing on the various risk factors that are known to contribute to the disease. By analyzing the genetics of plasma lipoprotein levels, blood pressure, and other risk factors, we are dissecting the resulting diseases, CAD and stroke. Clearly, it is much simpler to analyze such quantitative traits that underlie atherosclerosis than the disease itself, particularly because the clinical disease is difficult to diagnose and to quantitate. On the other hand, the known systemic risk factors for atherosclerosis explain only part of its genetic component. To understand genetic factors that act at the level of the artery wall, it is necessary to assess the disease itself. Markers of the disease, such as C-reactive protein (CRP) or various noninvasive techniques for measuring lesion development, should be useful in such efforts.

Most of the genetic studies related to atherosclerosis that have been performed thus far have tested for associations between polymorphisms of "candidate genes" (known genes likely to contribute to processes involved in atherosclerosis) and various risk factors, such as lipoprotein phenotypes (29). Systematic searches for polymorphisms of hundreds of candidate genes for atherosclerosis, hypertension, and related disorders have been reported (30), and a complete catalog of all known human polymorphisms (variations with frequency >1%) is expected in the next few years. Because most deoxyribonucleic acid (DNA) polymorphisms are unlikely to be functionally relevant (i.e., the cause of differences in gene expression), associations in general depend on the phenomenon of "linkage disequilibrium." This refers to the fact that various polymorphisms of a particular gene are nonrandomly associated with one another as a result of the evolutionary history and population genetics of a gene. Thus, when a mutation of a gene that results in an altered phenotype occurs, it tends to remain associated with whatever polymorphisms were present at the ancestral locus as it spreads through the population. Only fragmentary data are available, but such linkage disequilibrium should in many cases be detectable in the general population for markers as far away as approximately 10 kilobases or more (31). Association studies are subject to various artifactual problems, such as the ethnic composition of the populations being examined. Thus, if the population consists of two or more ethnic groups, one of which differs from the others in a phenotype and also the frequency of a particular polymorphism, an association could be detected between the phenotype and the polymorphism. In such a case, the association would reflect population admixture rather than linkage. One means of controlling for admixture is to examine associations within families using "transmission distortion" (27). Hundreds of association studies have been reported for traits that are relevant to atherosclerosis, but almost all of these require further confirmation.

With the development of thousands of informative genetic markers, linkage studies involving complete genome scans are being performed for traits that are relevant to atherosclerosis. Classic linkage analysis, involving the construction of a model for the transmission of the trait, has proved useful for certain complex diseases, such as breast cancer, but has not been applied to complex forms of CAD. Linkage analysis with complex traits has been performed primarily using robust sib-pair analysis (32) (*e*Fig. 98.0.3), although other methods, including the variance component approach, have also proved useful (26,27,33,34). The advantage of allele-sharing approaches, such as sib-pair analysis, is that they make no assumptions about the mode of inheritance and the types of gene interactions. Sib-pair analysis suffers from relatively low power as compared to parametric methods, perhaps explaining in part the relatively disappointing results of genome scans for hypertension and other atherosclerosis-related risk factors (31). One study that involved a genome scan of families from the Finnish isolate identified several suggestive loci for CAD (34). Many other genome scans have been conducted for CAD risk factors (see the section Metabolic Syndrome).



***e*FIGURE 98.0.3** Four approaches to the dissection of complex genetic traits. Lander and Schork (Genetic dissection of complex traits. *Science* 1994;265:2037–2048) have critically reviewed the four approaches to the mapping and identification of genes that contribute to complex genetic traits such as atherosclerosis, hypertension, and diabetes. The first, classic linkage analysis **(A)**, involved the construction of a model for the segregation of genes that contribute to the trait. The model includes parameters such as the number of genes, the mode of inheritance (recessive, dominant, codominant, X-linked, etc.), the distance between genetic markers and the gene, and nongenetic contributions. Such models are straightforward to construct for mendelian traits but have proved difficult to devise for most multifactorial traits. Allele-sharing methods **(B)** provide a model-free approach for linkage analysis of complex traits. Usually, pairs of siblings are studied, although the method can be extended to various relations. The basic concept of the method is that affected pairs tend to have increased sharing of chromosomal regions (as recognized by genetic markers) that contain genes contributing to the trait. Allele-sharing methods have much less power to detect linkage than does classic linkage analysis. The third approach is association **(C)**. This involves testing whether particular polymorphisms occur more frequently in affected individuals than in controls. As discussed by Risch (31), association is more powerful than allele-sharing methods, but it is dependent on the identification of candidate genes. A complete catalog of all common polymorphisms in the human genome will be generated within the next year or two, and it may be possible to conduct whole-genome studies, but some important issues must still be resolved (31). The fourth approach uses animal models, which provide much greater power to detect linkage than do human studies **(D)**. Rats and mice are the most useful mammals of genetic studies, and different strains of these rodents exhibit many variations relevant to atherosclerosis, including differences in susceptibility to arterial lesions in the presence of hyperlipidemia and variations in lipid metabolism, blood pressure, obesity, insulin resistance, and artery wall functions (7). Genetic crosses of such strains can produce hundreds of unique progeny that inherit different parental alleles contributing to the trait. In the case of complex quantitative traits, the progeny would exhibit a continuum rather than discreet groupings, as in the case of a mendelian trait. The regions that contain genes contributing to the trait can be recognized using statistical methods. For such regions, progeny inheriting marker alleles from one parent would differ in phenotype from progeny

inheriting alleles from the other parent.

Because of the difficulty of assessing lesion development in humans, animal models have been especially important for understanding the biology of atherosclerosis. During the last 15 years, the mouse has been developed as a particularly important model for identifying genetic factors in atherosclerosis and for examining pathways that lead to the disease (35,36 and 37). Rats are also useful genetic models, particularly for studies of hypertension and insulin resistance. Because the environment can be controlled and large numbers of animals can be studied, genetic mapping of the underlying genes is much simpler with mice or rats than with humans. Perhaps most importantly, the individual genetic loci that contribute to the complex traits can be isolated as congenic strains, making fine structure mapping and gene identification feasible. Finally, the pathways involved can be examined through the use of transgenic and gene-targeted animals (38). *e*Table 98.0.7 summarizes some results from studies with transgenic and gene-targeted mice for various candidate genes. Of course, mice differ in a number of respects from humans, and studies with mice cannot lead to a complete understanding of the genetics of the human disease. Nevertheless, many processes and genetic factors that are relevant to atherosclerosis are likely to be shared between the two species. Thus, studies in mice will elucidate a subset of genes involved in the human disease. Fixing on these will in turn simplify the analysis of the remaining human genes.

***e*TABLE 98.0.7** *IN VIVO* ANALYSIS OF CELLULAR AND MOLECULAR INTERACTIONS IN ATHEROSCLEROSIS USING TRANSGENIC AND GENE-TARGETED MODELS IN MICE[a]

Process in atherogenesis	Gene: transgene (tg) or knockout (KO)	Effect on lesion size: decrease (↓), increase (↑), or no change (↔)
Lesion initiation	Apo-I tg	↓
	Apo-II tg	↑
	ApoE KO	↑
	ApoB tg	↑
	ApoAIV tg	↓
	LDL-receptor KO	↑
	Lp(a) tg	↑
	Cholesteryl ester transfer protein tg	↑
	12,15-Lipoxygenase KO	↓
	Serum paraoxonase KO	↑
	Endothelial nitric oxide synthase KO	↑
Inflammation	P-selectin KO	↓
	E-selectin KO	↓
	ICAM KO	↓
	MCP-1 KO	↓
	MCP-1 receptor KO	↓
	Macrophage colony-stimulating factor KO	↓
	Secretory phospholipase A2 tg	↑
	Streptozotocin-induced diabetes	↑
Foam cell formation	Scavenger receptor type A KO	↓
	CD36 KO	↓
	Tumor necrosis factor-a receptor KO	↑
	Acyl cholesterol acyltransferase-1	↓
	Sphingomyelinase KO	↓
	Myeloperoxidase KO	↑
	Inducible nitric oxide synthase KO	↔
Fibrous plaques	Immunodeficiencies of T and B cells	↔
	CD40 ligand KO	↓
	CD40 ligand receptor KO	↓
	Angiotensin-converting enzyme	↔
	p53 KO	↑
	Interferon-g receptor KO	↓
	Interleukin-10 tg	↓
Advanced lesions and thrombosis	Fibrinogen KO	↔
	Plasminogen KO	↔
	Plasminogen activator inhibitor type 1 KO	↔

Apo, apolipoprotein; ICAM, intercellular adhesion molecule; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MCP, monocyte chemotactic protein.
[a]Reviewed in Lusis AJ. Atherosclerosis. *Nature* 2000;407:233–241, and references therein. Mice are relatively resistant to the development of atherosclerosis. When fed a high-fat, high-cholesterol diet containing cholic acid, certain strains, such as C57BL/6J, develop fatty streak lesions of the proximal aorta. More advanced lesions develop in mice with null mutations of apolipoprotein (apo) E or the low-density lipoprotein (LDL) receptor, because these result in extreme hyperlipidemia. Many of these studies tested the effect of the transgenes or null mutations in the presence of null mutations of the apoE gene or the LDL-receptor gene.

LIPOPROTEIN METABOLISM

The most significant risk factors for CAD and stroke are related to lipoprotein metabolism. Twin studies and family studies indicate that the heritability of most lipoprotein traits within populations is greater than 50%, indicating that genetic rather than environmental factors are of primary importance. A number of rare mendelian disorders affecting lipoprotein metabolism have been characterized (*e*Table 98.0.8 and *e*Table 98.0.9). However, most forms of hyperlipidemia or low HDL levels are due to a combination of multiple genetic and environmental factors.

***e*TABLE 98.0.8** RARE MUTATIONS AFFECTING APOLIPOPROTEIN B–CONTAINING LIPOPROTEINS AND CELLULAR CHOLESTEROL METABOLISM

Sitosterolemia	A rare, autosomal recessive disorder that results in greatly increased absorption of plant sterols and an increase in cholesterol absorption. Total plasma cholesterol levels are elevated in the disease; tendon xanthomas develop in affected individuals by 10 yr of age and severe atherosclerosis as early as age 5. The genes underlying sitosterolemia have been identified.
Abetalipoproteinemia	Characterized by the failure to secrete either chylomicrons or VLDL, resulting in fat malabsorption, retinitis pigmentosa, and ataxic neuropathy. It is due to a defect in the expression of microsomal triglyceride transfer protein, which appears to be involved in the assembly of triglycerides and cholesteryl esters into growing triglyceride-rich lipoproteins in hepatocytes and enterocytes.
Anderson's disease	Also termed *chylomicron retention disease*, it is characterized by the failure of intestinal mucosal cells to secrete chylomicrons. The genetic defect is unknown, although the apoB gene appears normal.
Chylomicronemia	Due to LPL or apoCII deficiencies. Recessive mutations of the LPL gene lead to massive accumulation of chylomicrons (and VLDL) in the circulation. Interestingly, the incidence of CAD is not strikingly elevated in LPL deficiency, although one study suggests that LPL deficiency can cause premature CAD. ApoCII is an essential cofactor for LPL, and recessive mutations of the apoCII gene produce symptoms very similar to those of homozygous LPL deficiency.
Hypobetalipoproteinemia	A relatively rare disorder, characterized by low levels of VLDL, IDL, and LDL resulting from defects of the apoB gene. If the mutations affect the expression of apoB48, chylomicron expression is also decreased. Many of the mutations of the apoB gene that occur in hypobetalipoproteinemia result in truncated forms of the protein. In contrast to abetalipoproteinemia, hypobetalipoproteinemia shows additive inheritance.
Hepatic lipase deficiency	A very rare, recessive disorder resulting in the accumulation of triglyceride-rich LDL and HDL particles. Some forms of the deficiency result from HTGL gene mutations.
CESD and Wolman's disease	Very rare autosomal recessive diseases resulting from mutations of lysosomal acid lipase, leading to the intracellular accumulation of cholesteryl esters and triglycerides. CESD patients are characteristically hypercholesterolemic, and premature CAD develops before the fourth decade of life.
Cerebrotendinous xanthomatosis	A rare, autosomal recessive disorder resulting in deposition of cholesterol and cholestanol in multiple tissues, including the central nervous system. The disorder is caused by mutations of sterol-27-hydroxylase, an enzyme that hydroxylates a variety of sterol substrates, and the disorder impairs the ability to convert cholesterol to bile acids. Early diagnosis of the disorder is important, because treatment with chenodeoxycholic acid reduces the progression of the disease.
Smith-Lemli-Opitz syndrome	Caused by a block in the last reaction in the cholesterol biosynthetic pathway, catalyzed by 7-dehydrocholesterol delta 7-reductase. This results in low plasma and tissue cholesterol in homozygotes, who show mental retardation and facial dysmorphism. Feeding of cholesterol to homozygotes appears to improve symptoms.

apo, apolipoprotein; CAD, coronary artery disease; CESD, cholesteryl ester storage disease; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.
Adapted from Lusis AJ, Ivandic B. Lipoprotein and lipid metabolism. In: Rimoin DL, Connor JM, Pyeritz RE, eds. Emery and Rimoin's principles and practice of medical genetics. New York: Churchill Livingston, 1996:1945–1976.

TABLE cellSpacing=0 cellPadding=0 width="100%" border=0> ***e*TABLE 98.0.9** RARE MUTATIONS AFFECTING HIGH-DENSITY LIPOPROTEIN (HDL) Familial hypoalphalipoproteinemia Although most individuals with low HDL levels simply reflect the low end of the normal distribution, certain pedigrees appear to exhibit an apparent autosomal dominant factor determining low HDL levels, termed *familial hypoalphalipoproteinemia*. Some such families appear to have mutations in the ABCA1 transporter that is mutated in Tangier disease. ApoAI deficiency Several mutations of the apoAI gene resulting in greatly diminished or totally absent plasma apoAI levels have been characterized. All result in the virtual absence of HDL, and the affected individuals exhibited a high prevalence of premature CAD, although the clinical manifestations are highly heterogeneous. ApoAI structural variants Approximately 20 different mutations affecting the structure of apoAI have been reported. Some significantly reduce HDL-cholesterol levels, several are defective in LCAT cofactor activity, and one results in lethal amyloidosis. It is noteworthy that individuals with certain apoAI structural defects resulting in very low HDL-cholesterol levels (in some cases, <10 mg/dL) do not exhibit premature CAD. The explanation is probably related to HDL functional heterogeneity or to compensatory genetic variations. Tangier disease Characterized by very low levels of plasma HDL cholesterol, apoAI, and apoAII. It results from the inability of cells to donate cholesterol to apoAI and other acceptors, producing very small HDL particles that are rapidly catabolized. The gene for Tangier disease has been identified and shown to be an ABC transporter. LCAT deficiency LCAT is responsible for the esterification of HDL cholesterol, and deficiencies result in lamellar HDL particles containing primarily unesterified cholesterol, low HDL-cholesterol levels, and abnormalities of other lipoprotein classes. Although LCAT deficiencies are accompanied by large reductions in HDL cholesterol (<10 mg/dL), they do not appear to accelerate CAD dramatically. The explanation is unclear but is probably related to HDL functional heterogeneity. Hyperalphalipoproteinemia due to CETP deficiency CETP transfers cholesteryl esters from HDL to very-low-density lipoprotein and IDL, with a reciprocal transfer of triglycerides to HDL. CETP deficiency results in substantial elevations of HDL-cholesterol levels, often exceeding 150 mg/dL. Such mutations are rare in white populations but relatively common in Japanese. ApoAII deficiency A family with total apoAII deficiency due to a splice junction mutation of the apoAII gene exhibited unremarkable lipoprotein profiles, indicating that apoAII is not required for HDL assembly and that its absence does not profoundly affect other aspects of plasma lipid transport. Nevertheless, several independent studies indicate that common variations of the apoAII gene influence apoAII levels and HDL composition (67,70).

Apo, apolipoprotein; CAD, coronary artery disease; CETP, cholesteryl ester transfer protein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyl transferase; VLDL, very-low-density lipoprotein.
Adapted from Lusis AJ, Ivandic B. Lipoprotein and lipid metabolism. In: Rimoin DL, Connor JM, Pyeritz RE, eds. Emery and Rimoin's principles and practice of medical genetics. New York: Churchill Livingston, 1996:1945–1976.

Genetic Classification of Lipoprotein Variations

The clinical classification of lipoprotein disorders has been based largely on the plasma lipid and lipoprotein phenotypes. For example, an early classification of hyperlipidemias, known as the *Frederickson classification* (39), is based on electrophoretic lipoprotein phenotypes. With the exception of type III hyperlipidemia, each of the classes is now known to include multiple, genetically distinct disorders. Similarly, HDL deficiencies have been lumped together as "hypoalphalipoproteinemia," although they clearly result from different genetic factors. We have suggested that an alternative classification, based on the underlying genetic factors, provides a more useful subdivision of lipid disorders, because it allows the targeting of therapies based on mechanisms and it facilitates assessment of risk to the patient and his or her relatives (40). The inheritance patterns include "simple" (or mendelian) and "complex" disorders. The mendelian disorders can be further subdivided into those that exhibit recessive, dominant, or codominant patterns of inheritance. As yet, analysis at the level of DNA is of little value for the screening or classification of common dyslipoproteinemias, although in some cases, such as apoE alleles in type III hyperlipidemia, genotype analysis can be useful for family studies and genetic counseling (40).

Common Hyperlipidemias and Other Variations Affecting Metabolism of Apolipoprotein B–Containing Lipoproteins

Complex Hyperlipidemias

Most moderate hyperlipidemias are multifactorial in nature and simply reflect the high end of the normal population distribution. Some are associated with other conditions, such as type II diabetes, obesity, alcoholism, hypothyroidism, pregnancy, renal failure, or drug use, and hence are termed *secondary*. Primary and secondary hyperlipidemias can have a strong genetic component. Many of the genes for apolipoproteins, lipoprotein receptors, and enzymes in plasma lipoprotein metabolism have been examined as "candidate" genes to test for possible associations or linkages with levels of plasma lipoproteins and lipids (38). Most of the observed effects on lipoprotein metabolism are relatively small and require confirmation. Three common variations of apoE, however, exhibit marked effects on plasma cholesterol levels as well as contributing to type III hyperlipidemia (*e*Table 98.0.10). In Western populations, it has been estimated that the apoE alleles explain 4% or more of total plasma cholesterol levels (41).

***e*TABLE 98.0.10** EFFECT OF COMMON APOLIPOPROTEIN E (APOE) ALLELES ON PLASMA CHOLESTEROL LEVELS IN TWO POPULATIONS

ApoE isoforms	U.S. population		German population	
Frequency (%)	Mean cholesterol (mg/dL)	Frequency (%)	Mean cholesterol (mg/dL)	
4/4	0.9	207	2.8	197
4/3	23.9	193	22.9	189
3/3	59.5	192	57.4	184
4/2	3.2	183	—	—
3/2	12.7	182	4.9	166
2/2	0.5	133	0.2	140

Data for U.S. population from Sing CF, Davignon J. Role of the apolipoprotein E polymorphism and determining normal plasma lipid and lipoprotein variation. *Am J Hum Genet* 1985;37:268–285; and data for German population from Utermann G. The apoE-system: genetic control of plasma lipoprotein concentration. *Adv Exp Med Biol* 1986;201:261–272.

Familial Combined Hyperlipidemia

Familial combined hyperlipidemia (FCH) is a common disorder (approximately 1% of the European population but also common in other populations) that is characterized by elevations of very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL. FCH can best be distinguished from other forms of primary hyperlipidemia by family studies, because it exhibits an apparent dominant mode of inheritance. Among survivors of premature MI (<60 years), FCH is the most common familial lipid disorder, with a frequency of approximately 10% to 20% (42,43). The primary defect in FCH appears to involve an increased production of apoB and VLDL (44). Population association and family linkage studies have suggested that certain alleles of the apoAI-CIII-AIV gene cluster may contribute to familial forms of hypertriglyceridemia (45), and this cluster is also associated with FCH (46). Hypertriglyceridemia develops in transgenic mice that overexpress apoCIII (47). Heterozygosity for null mutations of lipoprotein lipase (LPL) may also contribute to certain forms of FCH (48). None of the candidate genes that have been studied thus far is likely to be the primary cause of FCH. One possible explanation for FCH is a "double hit" hypothesis. This hypothesis states that the primary defect in FCH is an increased production of apoB and VLDL and that a variety of secondary defects that inhibit lipolysis (apoCIII overexpression, LPL deficiency, certain apoE alleles) add to the burden, resulting in dramatic elevations in VLDL and IDL. This might appear to be inconsistent with the apparent dominant mode of FCH inheritance, but the hypothesis could explain the observed inheritance patterns if the secondary defects are quite common (49).

Familial Hypercholesterolemia

FH is caused by mutations of the LDL-receptor gene that affect receptor function. FH is extremely heterogeneous at the molecular level, and dozens of mutations of the LDL-receptor gene with variable effects on plasma cholesterol levels have been characterized. Because of the heterogeneity of LDL-receptor mutations, molecular diagnosis of the disorder is difficult. Certain populations, including French-Canadians, Afrikaners, and Lebanese, exhibit an increased incidence of FH due to a high frequency of specific mutations in each population. This is the result of a founder effect involving the rapid expansion of a population, and in such populations, molecular screening for FH is probably feasible (50).

Analysis of a large pedigree that exhibits FH has revealed the existence of a dominant, mendelian genetic factor capable of suppressing FH (51). Thus, obligate FH individuals who carried the factor exhibited relatively normal LDL-cholesterol levels, whereas other FH family members not carrying the factor had the highly elevated LDL-cholesterol levels that are typically associated with heterozygous FH. The factor does not significantly influence lipoprotein metabolism in non-FH individuals. The identity of the genetic factor is unknown, but a number of candidate genes (including the LDL receptor) have been excluded. Presumably, the factor is rare, and the fact that it can only be observed on the background of FH makes its study difficult.

Familial Defective Apolipoprotein B100

Familial defective apoB100 is due to a mutation in the coding sequence of apoB100 that substitutes glutamine (Gln) for arginine (Arg) at amino acid 3,500 of the polypeptide. This region serves as the ligand for binding to the LDL receptor, and the mutant form exhibits only a few percent of normal receptor-binding activity. Heterozygous familial defective apoB100 individuals exhibit cholesterol levels of approximately 300 mg per dL because of defective LDL clearance (52,53). The frequency of the disorder is approximately 1 in 500 to 1,000 in white populations.

Familial Dysbetalipoproteinemia or Type III Hyperlipidemia

Familial dysbetalipoproteinemia or type III hyperlipidemia is a relatively rare (approximately 1 in 5,000 in white populations) recessive disorder that is characterized by the accumulation of chylomicron remnants and IDL due to impaired clearance, resulting in cholesterol levels of greater than 300 mg per dL and even higher triglyceride levels. In the majority of cases (approximately 90%), type III is associated with homozygosity for a common allele of apoE, designated *E2*. The properties of various apoE alleles are given in *e*Table 98.0.11. Homozygosity for the E2 allele is, in most cases, necessary but not sufficient for the development of type III, because the vast majority (approximately 95%) of individuals who are homozygous for E2 do not exhibit the disorder and, in fact, tend to have low cholesterol levels (*e*Table 98.0.10). Thus, there are additional genetic or environmental predisposing factors, possibly relating to obesity or type II diabetes (approximately 50% of patients have glucose intolerance).

***e*TABLE 98.0.11** MUTATIONS AND COMMON VARIATIONS OF APOLIPOPROTEIN E

Phenotypic designation (charge)	Structure	Frequency[a] (%)	LDL receptor–binding activity (%)	Association with hyperlipidemia
Common alleles				
E3	“Wild type”	77	100	No
E4	Cys_{112}→Arg	15	100	Multigenic hypercholesterolemia
E2	Arg_{158}→Cys	8	2	Type III
Rare alleles				
E1	Arg_{158}→Cys, Gly_{127}→Asp		4	Type III
E2	Arg_{136}→Ser		n.d.	Type III
E2	Arg_{145}→Cys		45	Type III
E2	Lys_{146}→Gln		40	Type III
E3	Cys_{112}→Arg, Arg_{142}→Cys		<20	Type III
$E3_{Leiden}$	No Cys		~50	Type III
Null	No protein			Type III

LDL, low-density lipoprotein; n.d., not determined.
[a]Approximate frequencies of common variants in white populations; the rare alleles were identified in a variety of populations.
Adapted from Rimoin DL, Emery AEH, eds. *Principles and practice of medical genetics*, 2nd ed. New York: Churchill LIvingstone, 1990:1239–1262.

The utility of a genetic classification for lipoprotein disorders is nicely illustrated by type III hyperlipidemia. Because the disorder overlaps with several other hyperlipidemias in terms of cholesterol and triglyceride levels, definitive classification is best made by characterizing inheritance patterns and testing for apoE alleles. The latter is now widely performed using polymerase chain reaction amplification of DNA, although it should be noted that apoE genotyping can have some ethical considerations, because a relatively common allele of apoE (E4) is strongly associated with late-onset Alzheimer’s disease. A definitive classification of type III is important in at least two respects. First, because the disorder is highly responsive to diet and, if untreated, strongly predisposes to clinical disease, the diagnosis significantly influences therapy. Second, knowledge of the genetic nature of the disease allows determination of other family members at risk.

Lipoprotein(a)

Like LDL, Lp(a) contains a cholesteryl ester–rich core surrounded by a single molecule of apoB100, but it contains an additional polypeptide, termed *apo(a)*, that is disulfide bridged to apoB. The levels of Lp(a) differ greatly among individuals, ranging from undetectable to approximately 200 mg per dL. Significant differences are also found between populations; for example, Chinese and whites exhibit highly skewed distributions, with most individuals having relatively low levels (less than approximately 10 mg per dL), whereas black populations have more normal distributions with higher mean levels. Since the discovery of Lp(a) (59), numerous epidemiologic studies have indicated an association between high Lp(a) levels and CAD (60,61). Several prospective studies with Lp(a) and CAD have, however, yielded negative results. Most likely, these are related in part to differences in methodologies or the cohorts studied. Structurally, the apo(a) polypeptide exhibits remarkable sequence homology with plasminogen, and it is very likely that apo(a) evolved by a duplication and modification of the plasminogen gene. A striking characteristic of apo(a) is the presence of numerous repeats (in somewhat different versions) of the plasminogen kringle IV domain. The number of these repeats differs among individuals and results in genetic variation in the length of the apo(a) polypeptide. More than 30 different alleles of apo(a) have been identified, each differing by a single kringle IV repeat. Analysis of Lp(a) levels using the sib-pair method indicated that more than 90% of the variance of Lp(a) levels is determined by genetic variations of the apo(a) gene (62,63 and 64).

Common Genetic Variations of High-Density Lipoprotein

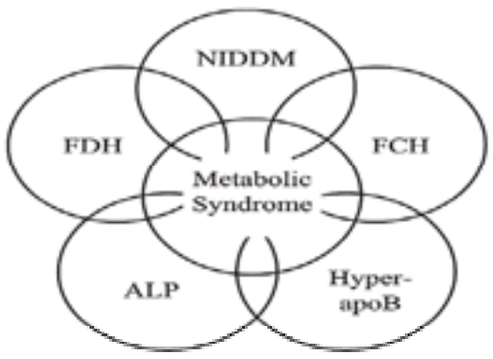
The majority of variation in HDL levels and structures is multifactorial in nature. Included in this are most forms of *hypoalphalipoproteinemia*, arbitrarily defined as HDL concentrations of less than the tenth percentile. Thus far, a variety of candidate genes have been examined in various populations, and several have been confirmed in multiple studies (*e*Table 98.0.5). High triglyceride levels and low HDL levels are frequently associated with abdominal obesity and type II diabetes (16). The mechanisms involved are unclear but may be related to changes in the expression of LPL (positively correlated with HDL) and hepatic lipase (negatively correlated), because both are altered in obesity.

It is clear that HDL is structurally and functionally heterogeneous. The levels of the various-sized classes of HDL differ among individuals, and this is determined in part by genetic factors (65,66). Polymorphisms of the apoAII gene in humans and in mice influence the ratio of apoAII to apoAI in HDL and the levels of plasma free fatty acids and triglycerides (67,68,69 and 70).

The composition of HDL can also be dramatically altered as the result of infections or various chronic inflammatory processes. In particular, acute or chronic inflammatory processes can cause hepatic serum amyloid A expression to increase to the point at which it becomes a major protein component of HDL. Such HDL, termed *acute-phase HDL*, has altered functional properties and, with respect to atherosclerosis, is likely to be proinflammatory rather than antiinflammatory (71).

METABOLIC SYNDROME

The metabolic syndrome, also called the *insulin resistance syndrome*, is in reality not a single disease but a combination of several disorders. It is characterized by the presence of hyperinsulinemia; obesity; decreased HDL-cholesterol levels; small, dense LDL particles; hypertriglyceridemia; hypertension; and hypofibrinolysis, all of which contribute to an increased risk of heart disease (72,73). Genetic studies of pedigrees from Utah defined a similar condition, termed *familial dyslipidemic hypertension*, involving a clustering of central obesity, lipid abnormalities, hypertension, and elevated fasting insulin levels (74). In addition, there is considerable phenotypic overlap between the metabolic syndrome and other disorders, such as non–insulin-dependent diabetes mellitus (NIDDM), FCH, and ALP (75,76) (*e*Fig. 98.0.4). Diabetes and obesity are risk factors for premature CAD, and it appears that they accelerate the atherosclerotic process, in part through interactions with other risk factors (77,78 and 79). It is not certain whether these disorders are different entities or just different definitions of the same underlying metabolic defect. Although the aggregate of the abnormalities in the metabolic syndrome clearly results in an unfavorable atherogenic risk profile, the mechanistic link with atherosclerosis is not entirely understood. Evidence from familial aggregation, twin studies, ethnic predilection, and animal studies suggests that genetic and environmental factors contribute to the abnormalities observed (80). Because the metabolic syndrome and the diseases with which it overlaps are complex, there will most likely be multiple genes, but it is not certain whether there will be specific susceptibility genes or an overlapping set of genes. Identification of the genetic factors that underlie the component abnormalities of the metabolic syndrome may elucidate the mechanism by which there is an increased risk for development of CAD.



***e*FIGURE 98.0.4** Overlap of the metabolic syndrome with other disorders. See text for discussion. ALP, atherogenic lipoprotein phenotype; apoB, apolipoprotein B; FCH, familial combined hyperlipidemia; FDH, familial dyslipidemic hypertension; NIDDM, non–insulin-dependent diabetes mellitus. (Adapted from Kwiterovich PO. Genetic and molecular biology of familial combined hyperlipidemia. *Curr Opin Lipidol* 1993;4:133–143.)

Low-Density Lipoprotein Particle Size

Small, dense LDL particles, as characterized by either a low ratio of LDL cholesterol to apoB, a plasma LDL apoB above 130 mg per dL but an LDL-cholesterol level below the ninetieth percentile (termed *hyperapobetalipoproteinemia*), or rapid polyacrylamide gel electrophoretic mobility [termed *atherogenic lipoprotein phenotype* (ALP)] are commonly associated with increased CAD, FCH, low HDL levels, and elevated triglyceride levels (54). The size of LDL is determined by environmental as well as genetic influences, and whether it contributes to atherosclerosis or is simply associated with other aspects of lipoprotein metabolism is unclear. Some studies have suggested that small, dense LDL particles are particularly susceptible to oxidation, providing a potential causal link to atherosclerosis (55). Family studies suggested linkage of the ALP to the LDL-receptor locus on chromosome 19 (56), and more recent studies with pedigrees enriched for heart disease suggested a complex pattern of inheritance with contributions from several loci, including a locus on chromosome 6 linked to the manganese superoxide dismutase (MnSOD) gene, a locus on chromosome 11 linked to the apoAI-CIII-AIV gene cluster, a locus on chromosome 16 linked to the cholesteryl ester transfer protein gene, and a locus on chromosome 19 linked to the LDL-receptor gene (57). In a subsequent study, the AI-CIII-AIV, MnSOD, and cholesteryl ester transfer protein gene loci were also found to segregate with ALP in FCH families, supporting the previous results (58). Interestingly, this latter study also demonstrated that small, dense LDL particles were tenfold more prevalent in FCH probands than in control subjects, lending support for the association between FCH and ALP (58).

Non–Insulin-Dependent Diabetes Mellitus

NIDDM (type II) is associated with obesity and is characterized by the presence of peripheral insulin resistance or a relative decreased insulin secretory capacity, or both. Diabetes is discussed in Chapter 7, and we review here only certain genetic aspects. Studies in monozygotic twins have demonstrated concordance rates of up to 90%, indicating a strong genetic determinant of susceptibility (81,82). Physiologic and genetic studies indicate heterogeneity in the pathogenesis of NIDDM and are most consistent with a multifactorial mode of inheritance. Several inbred rat and mouse strains exhibit NIDDM (83), providing useful models for identifying susceptibility genes. A large number of candidate genes have also been tested in population association studies and in linkage studies. Among those that have shown significant associations to NIDDM or glucose and insulin levels are the following: insulin and insulin-receptor genes (84), the glycogen synthase gene (85), the glucokinase gene (86), the $beta_3$-adrenergic receptor gene (81), and the apoAI and apoB genes (81). The gene for the intestinal fatty acid–binding protein (FABP2) on chromosome 4q exhibited linkage in Mexican-Americans and in Pima Indians (87,88). Mutations in the glucokinase, hepatocyte nuclear factor-4a, and hepatocyte nuclear factor-1a genes cause different forms of maturity-onset diabetes of the young (MODY), in which the NIDDM phenotype develops in young adults and segregates in a dominant fashion within families (89,90 and 91). However, it appears that these genes are not the cause of the more common forms of diabetes. Point mutations and deletions within the mitochondrial genome have been shown to result in specific maternally transmitted syndromes in which diabetes is a significant element (92). Several syndromes of marked insulin resistance are caused by mutations in the insulin-receptor gene (93). Finally, a common polymorphism in the peroxisome proliferator-activated receptor gamma gene has also been associated with diabetes, although the effect does not appear to be very strong (94).

As with other complex diseases, the use of genome-wide searches for NIDDM is proving to be an important tool in identifying additional genetic loci. Numerous genome scans have now been conducted in a variety of ethnic populations, including European whites, Mexican-Americans, and Pima Indians (95,96,97,98,99 and 100). The first genome scan identified a major NIDDM susceptibility locus, designated *NIDDM1*, on chromosome 2q in a Mexican-American population from Texas with a high rate of diabetes (95). Using high-resolution linkage disequilibrium mapping, the critical region was narrowed and an intronic polymorphism in the calpain-10 gene was identified that was more frequent in affected individuals than in normal control subjects (101). Calpain-10 is a cysteine protease and is ubiquitously expressed in all tissues. Although the intronic polymorphism is associated with NIDDM, it is not clear how it plays a functional role in the development of diabetes. Studies in the Pima Indians suggest that this variant alters expression of calpain-10 in muscle and leads to lower glucose oxidation rates, lending support for its role in glucose metabolism (102). Ultimate proof of whether this is an NIDDM susceptibility gene will rely on more detailed functional experiments and the development of animal models. Although the NIDDM1 locus has been identified in Mexican-Americans, it does not appear to contribute significantly to diabetes in other ethnic populations.

A locus for diabetes was identified on the long arm of chromosome 1, near the apoAII gene, in the Pima Indian population of Arizona (96). Subsequently, this locus was also linked to diabetes in two independent sets of white pedigrees from Utah and France (98,100). Of particular interest is the fact that the chromosome 1 locus was originally linked to the FCH phenotype in a set of Finnish families (103). This locus is also syntenic to a region on mouse chromosome 3, where a gene for combined hyperlipidemia was mapped (104). Thus, given the phenotypic overlap between NIDDM and FCH, the results from these studies raise the possibility that the same gene in this locus contributes to the development of FCH and NIDDM. Identification of the gene should be easier in the mouse. Whether the same gene gives rise to hyperlipidemia or diabetes, or both, remains to be determined.

Obesity

Obesity exhibits considerable metabolic overlap with the abnormalities that are present in diabetes and is associated with hypertension. Numerous family studies have shown that measures of obesity such as body mass index are significantly correlated between parents and their children (105), and concordance rates in monozygotic twins are much greater than those in dizygotic twins, supporting a strong genetic component contributing to these phenotypes. Adoption studies have confirmed these results. Furthermore, obesity is a characteristic feature of several genetic syndromes (106).

A variety of candidate genes have shown associations with various measures of obesity in human populations (107). These include the sodium–potassium–adenosine triphosphatase genes on chromosome 1, the $alpha_2$-adrenergic receptor on chromosome 10, the beta-hydroxysteroid dehydrogenase gene on chromosome 1, and the brown adipose tissue uncoupling protein gene on chromosome 4. A mutation within the coding region of the $beta_3$-adrenergic receptor may be associated with the propensity to gain weight in a French population (108). Last, obesity in Pima Indians has been linked to a marker near the tumor necrosis factor-a gene on chromosome 6 (109).

Genetic studies in mutant mouse strains have led to the identification of several genes that contribute to obesity (110). These include the dominant Agouti (*A*) gene on chromosome 2 and several recessive genes, including diabetes (*db*) on chromosome 4, obese (*ob*) on chromosome 6, tubby (*tub*) on chromosome 7, and fat (*fat*) on chromosome 8. The *ob* and *db* genes have proved to be particularly interesting, contributing directly to an understanding of body fat homeostasis. The *ob* gene is expressed in adipocytes and encodes the hormone leptin, which plays a role in regulating metabolism and satiety (111,112 and 113). The *db* gene encodes the leptin receptor (Ob-R), which is expressed in many tissues including the hypothalamus (114). The Ob-R gene undergoes alternative splicing, and only one of the splice products, expressed primarily in the brain, is capable of signal transduction following leptin binding. These findings demonstrate that the regulation of fat metabolism involves an important feedback loop between adipocytes and the hypothalamus. Leptin mutations in obese humans are extremely rare, however, suggesting that leptin resistance may cause obesity. Additional genetic loci that contribute to obesity and body fat measures have been identified in humans and mice through the use of quantitative trait locus mapping, although the underlying genes are unknown (107,115,116,117,118,119,120,121 and 122).

Hypertension

A number of studies have revealed associations between elevated blood pressure, hyperlipidemia, insulin resistance, and coronary atherosclerotic disease (123). Thus, identification of genes that contribute to blood pressure variation will also increase our understanding of the relationship between hypertension and atherosclerosis.

Significant progress has been made in elucidating the genetic basis for certain mendelian forms of hypertension, but the genetic factors that contribute to essential hypertension are largely unknown (124,125). Ample evidence from twin studies and family studies has shown that the patterns of familial aggregation of the common

forms of hypertension have a very significant genetic component (126). A number of candidate genes, particularly members of the renin-angiotensin system, have been investigated in humans and animal models. Linkage and association studies have provided relatively strong evidence for the role of the angiotensinogen gene in hypertension in white and African-Caribbean populations as well as in pregnancy-induced hypertension (127,128,129 and 130). The angiotensin-converting enzyme (ACE) gene has been found to be associated with coronary heart disease, but this appears to be a mechanism that is independent of the effects on blood pressure (131). In addition to candidate gene studies, several genome scans for essential hypertension and blood pressure have now been reported in various populations (132,133,134,135 and 136). However, unlike the results of the NIDDM genome scans discussed above, there is no overlap between the loci identified in these genome scans for hypertension/blood pressure. One explanation for the variation in these results could be the different racial makeup of the study populations. Another potential reason is the underlying genetic heterogeneity, because numerous genetic factors contribute to variation in blood pressure. One strategy for reducing this confounding factor may be to stratify the study population. For example, gene-finding efforts for blood pressure may yield better results if they are conducted in a study sample that is restricted to hypertension within the context of other pathophysiologic processes. In this manner, a more homogeneous hypertensive group can be selected, potentially reducing the problem of genetic heterogeneity. This strategy is exemplified by one study in which a genome scan for blood pressure was conducted in families with insulin-resistant dyslipidemia (136). In that study, systolic blood pressure and free fatty acid levels were mapped to the same locus on the short arm of chromosome 4. Although it is possible that there are two different genes in the region, a more attractive hypothesis is that there is a single gene at that locus contributing to blood pressure and to free fatty acids, supporting the notion that common loci underlie the clustering of traits in the metabolic syndrome.

Conclusions

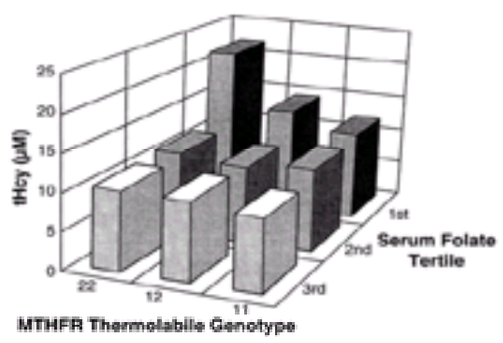
In summary, the strong clustering of insulin resistance, hyperlipidemia, and hypertension in the metabolic syndrome (and other related disorders) suggests that these traits have common genetic determinants. Some studies support this hypothesis, but genes that are specific to each component most likely exist as well. How the abnormalities in the metabolic syndrome exacerbate the atherosclerotic process is poorly understood. Metabolic derangements in diabetes consist of hyperglycemia, hyperinsulinemia, insulin resistance, and lipid abnormalities. Hyperglycemia has been shown to cause increased nonenzymatic glycation of proteins, resulting in the production of advanced glycation end products and the formation of reactive oxygen species (137). Such advanced glycation end products may damage the artery wall, perhaps contributing to the accelerated atherosclerosis that is observed in diabetics. The role of hyperinsulinemia and cellular insulin resistance on atherosclerosis development is less clear but may potentially involve its association with blood pressure (138). For example, it has been shown that insulin resistance (defined by hyperinsulinemia) in Mexican-Americans not only precedes the development of hypertension but also is predictive of it and that insulin resistance and blood pressure cosegregate in hypertensive families (139,140). Furthermore, elevated insulin levels may result in increased expression of endothelin, a vasoconstrictive protein produced by the endothelium (141). Insulin also appears to suppress C-type natriuretic peptide, an endothelial-derived vasodilatory molecule, and has been shown to decrease plasma vitamin E levels (142,143). Although these latter effects need to be examined in the hyperinsulinemic state, they provide potential mechanisms that could accelerate the atherosclerotic process.

HOMOCYSTEINE METABOLISM

The consideration of homocysteine as a risk factor for atherosclerosis derives from elucidation of the autosomal recessive disorder homocystinuria, characterized by the presence of highly elevated levels of homocysteine in plasma and a high frequency of occlusive vascular disease accompanying other manifestations. Subsequent studies have established that total plasma homocysteine (tHcy), at levels present in the general population, is an independent and significant risk factor for coronary artery, cerebrovascular, and peripheral arterial atherosclerotic disease.

Highly elevated levels of tHcy are found in patients with homocystinuria, which most commonly results from homozygosity for cystathionine beta-synthase (CBS) and much less often from homozygous deficiency of MTHFR or enzymes in cobolamin metabolism. Homocystinuria is relatively uncommon, with incidence rates varying from 1 in 50,000 to 1 in 1,000,000 in different countries (it is approximately 1:400,000 in the United States). Heterozygosity for classic homocystinuria due to CBS deficiency is typically associated with disproportionate elevation of plasma tHcy after a methionine load, but fasting levels are near normal in most individuals (144). Whether the heterozygous state is also associated with an increased risk of atherosclerotic or thrombotic disease is not established, as limited data are available from studies of obligate heterozygotes. A survey of such individuals found no increased incidence of vascular disease (although relative risk of <5 could not be excluded), and two reports of carotid ultrasound assessment of intima-media thickening found no increases compared to those of normal control subjects (145,146 and 147).

Individuals whose plasma tHcy levels exceed the ninetieth or ninety-fifth percentile of the population for fasting or postmethionine load are defined as having moderate (sometimes termed *mild*) hyperhomocysteinemia. General evidence for a genetic basis comes from family studies that have shown an increased frequency of moderate hyperhomocysteinemia among relatives of affected individuals (148,149 and 150). Genetic analyses have clearly shown that heterozygosity for classic CBS deficiency does not account for any significant fraction of moderate hyperhomocysteinemia in the general population (151,152), contradicting earlier reports suggesting that it did (153,154 and 155). However, substantial data have accumulated indicating that a common mutation in the MTHFR gene is the underlying cause of moderate hyperhomocysteinemia in approximately half the cases. In 1988, Kang and colleagues (156) described a biochemically variant form of MTHFR, which was unstable at elevated temperatures (thermolabile), and later noted an increased frequency in CAD patients (157). This phenotype has subsequently been shown to be due to homozygosity for a point mutation ($C_{677}T$) in the coding region of MTHFR that decreases enzyme activity (158,159). The frequency varies among different ethnic groups, being relatively common in various white populations (10% to 15%) but less so in some others (160). Although the majority of individuals who are homozygous for the thermolabile mutation do not have hyperhomocysteinemia, half or more of individuals with basal plasma tHcy concentrations that exceed 20 µM are homozygous for the mutation. The most important known factors in determining whether the presence of the mutation will result in elevated homocysteine levels are the intake and availability of folic acid (19,20). When plasma levels of folate are above 4 µM, homocysteine levels in patients with the mutation are no different on average from those of unaffected individuals. At lower concentrations of folate, the likelihood of having increased basal homocysteine goes up in all persons, but to much higher levels in individuals with the mutation (*e*Fig. 98.0.5). The mutation has no effect on postmethionine load tHcy concentrations. Although the thermolabile mutation clearly is associated with moderate hyperhomocysteinemia, the frequency of homozygotes is not increased in most atherosclerotic disease populations compared with that of control subjects (161). This may be because most individuals have adequate folate intake, nullifying the potential atherogenic effect of the mutation and leaving too few individuals to contribute sufficiently to the risk of being detected statistically. An alternative interpretation is that elevated plasma homocysteine is not a causative factor in atherosclerosis but rather a marker of another as yet unidentified process.



***e*FIGURE 98.0.5** Gene-environment interaction in the determination of plasma homocysteine levels. Homozygosity for the methylenetetrahydrofolate reductase (MTHFR) thermolabile mutation has a significant effect on plasma homocysteine levels, but only among individuals with relatively low folate levels (unpublished data). tHcy, total plasma homocysteine.

Additional genetic determinants of plasma tHcy remain to be identified. Up to half of the cases of moderate hyperhomocysteinemia are not associated with the MTHFR thermolabile mutation, and the underlying cause is not known (162). Within the normal range of basal plasma tHcy, several twin and family studies, although not all, have shown a fairly strong hereditary component that is unlikely to be due to the MTHFR $C_{677}T$ mutation (163,164 and 165). This has stimulated the search for additional common mutations/polymorphisms in the MTHFR, CBS, and methionine synthase genes. Although a number has been identified in each of these, their effects on plasma tHcy or association with disease are negative or, at best, inconsistent (166,167,168,169 and 170).

HEMOSTATIC FACTORS

Thrombosis triggered by atherosclerotic plaque rupture is the proximate cause of the majority of morbidity and mortality associated with atherosclerotic vascular disease. Nonocclusive thrombosis with organization of the thrombus is also believed to be an important mechanism of plaque enlargement. Thus, factors that are involved in thrombus formation and persistence must be considered as potential risk factors and, correspondingly, the genetic regulation of these as a part of the genetic basis of atherosclerotic vascular disease. Epidemiologic studies have evaluated a number of the blood hemostatic factors. Of these, fibrinogen, plasminogen activator inhibitor type 1 (PAI-1), and factor VII (FVII) have shown significant independent associations with arterial vascular disease, most consistently for fibrinogen

and PAI-1; platelet hyperactivity has also been observed (171). Substantial data have accumulated showing that each of these is regulated in part by common genetic variations in the population (172).

The hemostatic system encompasses the multitude of cellular and fluid phase constituents, which interact to prevent bleeding and limit intravascular fibrin formation. In pathologic settings, this same system is responsible for thrombosis. It can be viewed as a tripartite system composed of (a) fibrin as the central structural molecule of the thrombus and fibrinogen, from which fibrin is formed by the proteolytic action of thrombin; (b) a procoagulant protease cascade resulting in thrombin generation, composed of a series of cellular and fluid phase molecules; and (c) a fibrinolytic cascade resulting in plasmin generation that proteolytically degrades fibrin, composed of another series of cellular and fluid phase molecules. The procoagulant and the fibrinolytic arms have constituents that promote or participate in thrombin or plasmin generation and constituents that inhibit the processes. Endothelial cells and platelets (and in some cases monocytes) participate in both systems by either the cell surface expression or release of constituents. Fibrinogen, in addition to its central role as the precursor of fibrin, is a multifunctional molecule that contributes to blood viscosity and cell adhesion phenomena. Thus, the levels of hemostatic factors that are present in blood represent only one compartment of the hemostatic system, which almost certainly does not reflect the full activity of the system. The fact that elements from each of these arms are independently associated with arterial disease suggests that vessel wall components in each of them that have not been accessible to study may ultimately contribute as well.

Mendelian disorders that affect fibrinogen and most of the plasma constituents of the procoagulant and fibrinolytic systems have been described. These are all relatively rare, and for most there is little information concerning their effects on atherosclerotic disease risk. Unlike the rare disorders of lipid metabolism in which atherosclerotic disease is a primary manifestation of the disease, genetic disorders of hemostasis present either as increased risk of bleeding or thrombosis (usually venous), with no outstanding effect on atherogenesis. In general, the little evidence there is suggests that mutations manifesting as increased bleeding risk do not absolutely protect against atherosclerotic disease. Conversely, the mutations that manifest as increased venous thrombotic risk (prothrombin 20210, factor V Leiden, antithrombin III deficiency, and protein C deficiency) do not appear to predispose significantly to increased arterial thrombotic risk in the general population (171,172 and 173).

Fibrinogen

A genetic effect on plasma fibrinogen levels has been found in linkage and association studies. Heritability estimates from twin and family studies range from approximately 20% to 50% (174,175,176,177 and 178). One family-based study found that the impact of heritability varied with age, decreasing from approximately 50% at age 20 to 20% at age 60 and over (176). Most studies of plasma fibrinogen levels in offspring of CAD patients compared with control subjects have been consistent with this, showing increased levels in offspring of affected parents (179,180 and 181). Similar findings are observed in offspring of persons with essential hypertension or with NIDDM, conditions that are also associated directly with higher plasma fibrinogen levels (182).

A number of studies have examined the association of specific common polymorphisms in the fibrinogen genes with plasma fibrinogen levels, and the majority have found significant associations (17,18,183,184,185,186,187 and 188). Fibrinogen is composed of two identical subunits, each consisting of three polypeptide chains (alpha, beta, and gamma). These are encoded for by separate genes (FGA, FGB, and FGG) that are clustered adjacent to one another on chromosome 4. Because transcription of the beta chain is the rate-limiting step in fibrinogen biosynthesis, interest has focused on polymorphisms in FGB, and in particular on those in the promoter region of the gene. At present none of the polymorphisms has been documented to be functionally significant. The HaeIII polymorphism in the FGB promoter region (G/A at –455) has been studied most thoroughly and is associated with modest differences in plasma fibrinogen levels, ranging from 1% to 10% in different studies. This allele has a frequency of 20% to 25% in white populations but is less common in some others such as the Japanese (189). *e*Table 98.0.12 shows representative findings of the effect of the HaeIII genotype on plasma fibrinogen from a relatively large, European multicenter study of patients with MI (Etude Cas-Temoins de l'Infarctus du Myocarde; ECTIM), with comparable data in the same population for polymorphisms of the FVII and PAI-1 genes, discussed in the section Plasminogen Activator Inhibitor Type 1. Several studies have observed that the effect of the polymorphism is only, or more noticeably, present in individuals who smoke (17,18). This is consistent with a proposed biologic process of fibrinogen synthesis being responsive to smoking-induced mediators such as interleukin (IL)-6, as is well demonstrated in acute-phase reactions. Support for this comes from studies showing that the HaeIII genotype influenced the acute-phase fibrinogen response (190,191). The other FGB polymorphisms are in close linkage disequilibrium with the HaeIII polymorphism, and some may provide an additive effect (18,192,193). Because the overall heritable contribution is estimated to be 20% to 50%, additional genes beyond the fibrinogen gene itself are likely to be involved in determining plasma fibrinogen concentrations.

***e*TABLE 98.0.12** FREQUENCY OF HEMOSTATIC GENE POLYMORPHISMS IN MYOCARDIAL INFARCTION PATIENTS (ECTIM STUDY) AND THEIR EFFECT ON CIRCULATING LEVELS OF RESPECTIVE HEMOSTATIC PROTEINS

Fibrinogen beta	**HaeIII (G/A-455)**		
Genotype	H1H1	H1H2	H2H2
Frequency (n = 533)	0.66	0.30	0.04
Fibrinogen (mg/dL)	338	351	380
PAI-1	**4G/5G (–675)**		
Genotype	4G4G	4G5G	5G5G
Frequency (n = 476)	0.31	0.48	0.21
PAI-1 (AU/mL)	14.2	12.2	12.1
FVII	**Arg/Gln 353**		
Genotype	Arg/Arg	Arg/Gln	Gln/Gln
Frequency (n = 461)	0.80	0.19	0.01
FVIIc (%)	116	103	78

Arg, arginine; FVII, factor VII; Gln, glutamine; PAI-1, plasminogen activator inhibitor type 1.

Results of studies that attempt to establish a direct association of fibrinogen polymorphisms with clinical disease have been mixed (172). The largest study to date that has examined this is the ECTIM study, which found no difference in allele frequency overall between MI patients and control subjects (187,192). Similar findings were obtained in a Swedish study of men with MIs before age 45 (184). However, a separate case-control study of individuals undergoing coronary angioplasty found patients to have the HaeIII polymorphism significantly more frequently than did the control population (194), and in a prospective study of patients with established CAD, this polymorphism was more common in those patients who showed progression (195). Similarly, two studies of patients with peripheral vascular disease reported a positive association with disease (196,197), as have several studies of stroke patients (198,199 and 200). Several studies have examined the relationship of genotype with severity of CAD, assessed angiographically, with mixed results. A positive association was observed in the French arm of the ECTIM study, but none was found in an Australian arm (192,201). Given the numbers of patients studied and the fact that these polymorphisms contribute to only a portion of fibrinogen variability (which, in turn, contributes a small portion to vascular disease risk), these data are not unexpected or inconsistent with the hypothesis that one or more common mutations in the fibrinogen gene(s) contribute incrementally to overall cardiovascular disease risk.

Plasminogen Activator Inhibitor Type 1

Genetic regulation of PAI-1 is supported by twin studies, suggesting a moderate degree of heritability (202,203). Additionally, two family studies found a significant correlation of PAI-1 activity among first-degree relatives, with one showing strong correlation with lipid and body mass phenotypes (204,205). A large European cooperative study of offspring of men with premature CAD found no evidence of increased PAI-1 compared with control subjects (179).

Several polymorphisms have been described in the PAI-1 gene, one of which appears to be functionally significant (206,207 and 208). The latter is an insertion/deletion polymorphism in the promoter region, consisting of either four or five guanine nucleotides (4G/5G). The 5G allele has been shown to bind a repressor protein, whereas the 4G allele does not, thus reducing transcriptional activity. Clinical studies are consistent, finding that individuals who are homozygous for the 4G allele have increased PAI-1 in plasma (ranging from 15% to 50% greater than that of individuals with the 5G5G genotype; *e*Table 98.0.12) (208,209,210,211 and 212). Several of these have found evidence that the polymorphism affects the relationship of PAI-1 to triglycerides (209,210 and 211). These two traits are positively correlated in all genotypes, but among individuals with the 4G4G genotype, the slope of the regression curve is much steeper. Thus, the extent to which PAI-1 is elevated secondary to genetic or environmental influences acting on triglycerides is regulated in part by PAI-1 genotype. This is consistent with the observation that PAI-1 concentrations increase significantly after a fat tolerance test in individuals who have at least one 4G allele compared to 5G/5G homozygotes (213). However, association studies with the 4G/5G PAI-1 polymorphism and clinical disease have been mixed. Several large studies in which the risk of MI was examined (the European collaborative ECTIM study and the U.S.-based Physicians Health Study) found no significant association, whereas other studies have (208,210,212,214,215).

Factor VII/VIIa

The information that is available on the heritability of FVII is limited. One study of monozygotic twins with NIDDM reported a significant twin intrapair correlation coefficient (*r*) of 0.69 for FVII levels. Two studies of offspring of parents with premature CAD examined FVII levels, but opposing conclusions were reached (179,180).

Nevertheless, there is direct and convincing evidence that a moderately common MspI polymorphism in the FVII gene (causing a Gln substitution for an Arg) is

associated with plasma levels of FVII in men and in women (216,217,218,219,220 and 221) (*e*Table 98.0.12). Numerous studies have demonstrated a consistent decrease in FVII activity with the Gln allele, ranging from 11% to 38% for Gln heterozygosity compared with the homozygous Arg genotype. The relative frequency of the Gln allele ranges from 0.06 to 0.25, being less common in some nonwhite populations (222). Homozygous Gln individuals had levels of FVII activity that were 32% to 62% of standard and FVII antigen levels that were approximately 50% of normal. Subsequently, a 10–base pair insertion polymorphism in the FVII promoter region has been found that is in close linkage disequilibrium with the Arg/Gln polymorphism (223,224). In at least one study, this shows even stronger association with FVII levels. Studies of the functional consequences of these polymorphisms are in progress. FVII, like PAI-1, is strongly correlated with plasma triglyceride levels, and one group has observed an effect of FVII genotype on the relationship between FVII activity and triglycerides (223). Association of FVII gene polymorphisms with CAD incidence has not been demonstrated in the several studies, but a relatively large study would be required due to the high prevalence of the genotypes that are associated with higher FVII levels (201,218,221).

Platelets

Platelet function has been evaluated in fewer epidemiologic studies than plasma coagulation proteins, although enhanced platelet reactivity has been observed in several cross-sectional studies of CAD patients (171,225). This is a complex phenotypic trait with many possible causes. No data on traditional heritability measures are available, and there are no established syndromes of hereditary thrombotic disease caused by intrinsic platelet defects.

Because of the key role that platelets play in thrombosis, the potential functional and clinical consequences of common polymorphisms in the major platelet surface receptors have been investigated. These include the glycoprotein (Gp) IIb/IIIa complex, critical for platelet aggregation; the Gp Ib-V-IX complex, involved in adhesion; and the Gp Ia/IIa complex, involved in collagen binding. For each of these, there are studies that show functional and clinical associations and others that show no such associations.

The most thoroughly studied of these is the PI^{A2} polymorphism of the platelet Gp IIIa gene, which in white populations has an allele frequency of approximately 20%. Some *in vitro* studies have shown that the presence of the PI^{A2} allele is associated with a prothrombotic phenotype (226). Overall, clinical studies with relatively large numbers of subjects have not confirmed the initial observation of an association with MI or other manifestations of atherosclerotic disease, although it may play a role in some clinical settings (172,227,228 and 229).

Assessment of polymorphisms in other platelet-receptor proteins is an active area of research (172). Several polymorphisms have been identified in the gene for Gp Ia that are associated with altered Gp Ia/IIa receptor complex density. However, it is unclear whether these influence platelet functional properties. Likewise, polymorphisms are described that affect the Gp Iba gene. Although one or more clinical studies suggest an association with atherosclerotic disease for each of these, they have yet to be confirmed in larger prospective study sets (172).

Conclusions

Fibrinogen, PAI-1, and FVII are implicated as risk factors for CAD, and there is strong evidence that genetic factors moderately contribute to the overall interindividual variability in levels. Common polymorphisms in each gene have been identified that influence levels to varying degrees. Because these account for only a portion of the estimated genetic contribution to variability, it is likely that common polymorphisms in other genes will be identified. A common theme, shared with the thermolabile mutation of MTHFR affecting homocysteine levels, is that these mutations influence the response to, or their effects are potentiated by, environmental factors (fibrinogen and smoking, PAI-1 and triglycerides, MTHFR and folate) (230). Individually, these appear to contribute only a relatively small fraction to overall disease risk, such that statistical association with disease incidence or severity is frequently not observed when sought. This is an active area of research, and preliminary studies of other hemostasis-related genes have been reported in addition to those discussed here (see reference 172 for a detailed review). Genes that determine the expression and function of hemostatic elements of the vessel wall compartment also likely contribute to vascular disease, and genetic-epidemiologic studies to test for these are needed. With the advent of the complete human genome sequence and the intense search for clinically significant polymorphisms, there will undoubtedly be many more candidate polymorphisms to be evaluated. As demonstrated by the divergent results obtained in studies of the platelet PI^{A2} allele as well as those of the fibrinogen polymorphisms, these should be evaluated in multiple, large-scale, and preferably prospective studies. However, it may be premature to discount the importance of polymorphisms that have equivocal associations with disease despite confirmed functional effects. Inability to identify relevant patient subsets or the presence of as yet unrecognized gene-gene or gene-environment interactions may be reasons for false-negative results, even in large clinical studies.

INFLAMMATION

Inflammation and the immune system have been identified as important contributors to the pathogenesis of atherosclerosis. For example, premature atherosclerosis is recognized as the one disease-related complication in systemic lupus erythematosus (231). The inflammatory and immune system proteins can be classified into the acute-phase proteins, cytokines, cell adhesion molecules, and autoantibodies. In addition, an increasing role for T cells has been identified (232). Thus, the genes that encode these inflammatory and immune mediators can be considered as potential candidate genes for atherosclerosis. The focus of this section is on heritable features of these inflammatory and immune system proteins.

Acute-Phase Proteins

C-Reactive Protein

CRP is an acute-phase pentameric protein synthesized by the liver and lymphocytes that was initially identified as a protein able to bind the somatic C-polysaccharide of the pneumococcus (233). It can bind to various infectious agents, damaged cell membranes, lymphocyte Fc receptors, and LDL/VLDL particles. Hepatic synthesis can increase its concentration 1,000-fold during inflammation (234), and CRP appears to play a role in complement activation, antigen clearance, tissue factor production by macrophages, and platelet aggregation (235,236). These properties of CRP can result in damage to the endothelium, thereby contributing directly to atherosclerosis.

Many studies have examined the relationships between CRP levels and cardiovascular disease (237,238,239 and 240). Elevated CRP levels are associated with an increased risk of unstable angina in individuals with underlying CAD, an increased risk of CAD development in healthy subjects with CAD risk factors, and an increased risk for peripheral vascular disease development. Whether CRP is a marker for inflammation in atherosclerosis or plays a direct role in its pathogenesis is unclear. CRP has been shown to induce the expression of cellular adhesion molecules on human endothelial cells *in vitro*, suggesting a more direct pathogenic role (241).

The genetic determinants of CRP levels and function are poorly understood. CRP levels are increased in first-degree relatives of CAD patients who have had an MI. Although these individuals tended to be older, hypertensive, and homozygous for the 4G allele of the PAI-1 gene, elevated CRP levels (>0.33 mg per L) were still independently associated with a family history of MI (242). This association may represent an inherited predisposition to elevated CRP levels but may also represent shared atherosclerotic risk factors within families. To date, only one variation in the coding region has been identified (243). Because IL-6 increases the production of CRP (244), it is possible that polymorphisms within the IL-6 promoter, which increase IL-6 expression (245), could result in an inherited predisposition to elevated CRP levels. If CRP plays a direct role in atherosclerosis, inherited differences in its interaction with the FcgRIIa receptor on human monocytes and neutrophils may also be important. For example, CRP was found to bind to a much greater extent to monocytes and neutrophils from individuals who were homozygous for the R-131 allele of FcgRIIa compared to cells from individuals homozygous for the H-131 allele. As monocyte FcgRII receptors have been shown to play a role in LDL uptake and foam cell formation (246), the binding of CRP to monocyte receptors could influence the development of foam cells.

Mannose-Binding Lectin

Mannose-binding lectin binds to mannose and *N*-acetylglucosamine carbohydrates on infectious organisms, playing a role in opsonization and complement activation (247). Three polymorphic sites have been associated with decreased levels of expression and increased risk of infection (248,249). In a small Norwegian study, homozygosity for the rarer alleles at these three polymorphic sites was associated with patients who require coronary artery bypass surgery (250). In a study of white Canadian patients (men <55 years of age, women <60 years of age) with clinical CAD (angina, MI, coronary revascularization), heterozygosity for one of the alleles at these three sites was associated with increased carotid plaque area (251). This relationship remained significant when controlled for age, hyperlipidemia, hypertension, and smoking. The association of mannose-binding lectin polymorphisms with atherosclerosis is of particular interest given the postulated role that infectious agents, such as *Chlamydia pneumoniae*, may play in atherosclerosis.

CD14

CD14 is expressed on the surface of macrophages, monocytes, and activated neutrophils (252). Two soluble isoforms are also found in the serum (253). Binding of bacterial lipopolysaccharide to the membrane and the soluble forms of CD14 leads to cellular activation. The soluble form of CD14 is responsible for endothelial and smooth muscle cell activation (254,255). As inflammation secondary to bacterial infection has been postulated to be a mechanism that contributes to the pathogenesis of atherosclerosis, polymorphisms in the CD14 gene that may affect responsiveness to lipopolysaccharide have been tested for association with CAD. The T allele of a

T-C transition polymorphism at position –159 in the CD14 promoter region was found to be associated with MI in patients older than 62 years of age who did not have smoking or a history of hypertension as a risk factor. Homozygosity for the T allele at this locus resulted in an odds ratio of 3.8 for MI in this group (256). In another study, the frequency of the T allele at position –260 in the CD14 promoter region was found to be elevated in subjects who had experienced an MI. It was also shown in the study that healthy volunteers who were homozygous for the T allele had higher levels of CD14 on the surfaces of their monocytes (257). Similarly, in a Japanese population, the T allele of the –260 polymorphism was associated with MI (258). Thus, these studies suggest a role for CD14 in plaque stability.

Cytokines, Growth Factors, and Adhesion Molecules

Transforming Growth Factor-b

The transforming growth factor-b (TGF-b) family consists of three genes, each encoding a distinct isoform (TGF-b1, TGF-b2, and TGF-b3). With respect to atherosclerosis, TGF-b1 is of particular interest, because it is expressed in endothelial cells, connective-tissue, and hematopoietic cells. TGF-b1 exists as a latent complex that is proteolytically activated and plays an immunosuppressive role in the inflammatory process by inhibiting proliferation and activation of leukocytes. It can promote apoptosis of T and B cells, and it also plays a role in chemotaxis and cell localization through adhesion molecule regulation (reviewed in reference 259). TGF-b1 exerts antiproliferative and antimigratory effects on endothelial cells, smooth muscle cells, and macrophages (reviewed in reference 260); thus, functional polymorphisms may play a role in atherosclerosis. The TGF-b1 gene has eight known polymorphisms. A leucine-to-proline substitution at position 10 within the signal sequence of the TGF-b1 protein was examined for its association with MI in a Japanese population (261). The polymorphism was found to be associated with MI in men and with altered serum concentrations of TGF-b1. In a similar study performed in populations from France and Northern Ireland, a polymorphism that resulted in an Arg-to-proline substitution was found to be associated with MI, but the position 10 polymorphism failed to show any association (262). In contrast to the above-mentioned studies, five polymorphisms in the TGF-b1 gene failed to show any association with angiographically identified CAD or hypertension in an English population (263). Differences in the background genes of the study populations may also account for the differences in these results.

Interleukin-1 and Interleukin-1–Receptor Antagonist

IL-1 is an inflammatory mediator with a wide range of effects, including leukocyte chemotaxis, T- and B-cell activation, increased endothelial cell adhesion molecule expression, increased prostaglandin E_2 production, increased metalloproteinase production, and fever (264). In addition to playing a role in infection and autoimmune/inflammatory diseases, these mechanisms are important in the pathogenesis of atherosclerosis. The IL-1 genes (IL-1a and IL-1b) and the IL-1–receptor gene (IL-1RN) are located in a cluster on the long arm of chromosome 2. Several polymorphisms have been identified in these genes (265), and some are associated with differences in IL-1 production in response to lipopolysaccharide and with differences in IL-1–receptor antagonist levels (266,267). Polymorphisms of IL-1b and IL-1RN were found to be associated with angiographically demonstrated CAD (268,269). In a study that examined carotid artery wall intimal-medial thickness in African-Americans, an IL-1RN allele exhibited altered frequency in subjects with increased wall thickness (270). The same IL-1RN allele was also found to be associated with angiographically confirmed single-vessel CAD in an English population from Sheffield (271). Last, an Italian study demonstrated that the same IL-1RN allele was associated with MI in patients under 40 years of age (272).

Cellular Adhesion Molecules

Adhesion molecules mediate interactions between leukocytes and endothelium that result in the binding and diapedesis of leukocytes. Given the role that monocytes and lymphocytes play in atherosclerotic plaque development, these molecules could have an important role in genetic susceptibility to atherosclerosis. Polymorphisms have been identified in several of the cellular adhesion molecules, including E-selectin, P-selectin, L-selectin, VCAM-1, and ICAM-1 (273). Genetic studies in mice have shown that deficient expression of P-selectin, ICAM-1, and $beta_2$-integrin (CD18) resulted in atherosclerotic fatty streak reduction of 50% to 75% in mice fed a high-fat diet (274). In another study, P-selectin deficiency in apoE-deficient mice resulted in a decrease in monocyte recruitment into lesions, delayed plaque formation, and smaller and less calcified lesions in the aortic sinus (275). Similarly, P- and E-selectin–deficient mice bred onto an LDL receptor–deficient background exhibited delayed fatty streak development and smaller lesions in the aortic sinus (276). These results indicate that variations in expression or function of cellular adhesion molecules can affect the development of atherosclerosis.

E-selectin is expressed on activated endothelial cells, contributing to leukocyte adherence in inflammatory states. An association of a Ser-to-Arg substitution at position 128 in the epidermal growth factor–like domain of E-selectin was found to be associated with angiographically confirmed severe CAD in patients aged 50 years or younger (277). This Arg substitution was found to result in decreased adhesion strength in COS cells and in stimulated human umbilical vein endothelial cells *in vitro* (278).

P-selectin is expressed primarily on activated platelets and endothelial cells. In a study involving populations from France and Northern Ireland, a P-selectin allele with a proline substitution at position 715 (pro715) was found less frequently in patients with MI (279), suggesting a protective effect of this allele. The protective effect of this pro715 allele was confirmed in a Northern Irish population, although the effect was modest (280).

Conclusions

Most of the current human studies are preliminary, requiring confirmation in larger independent studies. The role of genetic susceptibility to infection and risk for atherosclerosis development will be an important area of investigation given the postulated mechanisms of infection in the pathogenesis of atherosclerosis. The ability to identify patients who carry functional polymorphisms in inflammatory genes that increase their risk of developing atherosclerosis or MI may permit such patients to be targeted for antiinflammatory therapy.

GENETIC FACTORS: THE VESSEL WALL

As atherosclerosis involves an interaction of arterial cells with blood elements, it stands to reason that genetic factors acting at the level of the artery wall play an important role in genetic control of susceptibility to CAD and stroke. Evidence for the existence of such factors is based in part on the finding by some, but not all, studies that the known risk factors do not fully account for the familial clustering of CAD (2,7). An interesting study bearing on this point showed that intimal thickening of coronary arteries in infants who had died before 1 year of age was significantly associated with a family history of CAD (281). As yet, little is known of such putative genetic factors, although a large number of candidate genes for processes such as cellular growth, inflammation, and oxidative stress have been identified. The genetic complexity of atherosclerosis, however, makes it difficult to test the role of these genes directly, because only relatively major genes are likely to be identified in population association and family studies. Moreover, the difficulty of quantitating lesions in humans presents a problem for human genetic studies, and the end points that are most often used, such as MI, are relatively crude. For these reasons, studies in animal models have proved particularly informative. Animal studies have provided conclusive evidence that genetic variations in vascular cell functions can profoundly influence susceptibility to atherosclerosis (282,283). In this section, we discuss some of the processes and candidate genes that may influence atherogenesis at the level of the vessel wall.

Lipoprotein Entry and Retention

Vascular permeability is increased at anatomic sites of atherosclerosis predilection, and the composition of the intimal matrix can influence LDL binding and retention (284). These processes suggest various candidate genes that could be examined in genetic studies, such as matrix proteins, but no definitive reports have been published. In studies of mice, it is clear that genetic factors can influence not only the development and size of lesions but also the sites of lesion development. For example, when fed a high-fat diet, certain strains of mice develop fatty streak lesions predominantly in the proximal aorta, whereas others develop lesions in the coronary arteries (285).

Oxidation

Abundant evidence has been found that oxidation within the vessel wall is central to at least the early stages of atherogenesis (286), but the evidence that genetic factors contribute to such oxidation is derived largely from studies with animal models (282,287,288). Molecular studies and studies with transgenic mice have suggested a variety of processes and candidate proteins that could contribute to lipoprotein oxidation (*e*Table 98.0.7). These include the levels of metal ions, thiols, superoxide, lipoxygenase, glucose, nitric oxide, myeloperoxidase, antioxidants, and HDL-associated enzymes that protect against oxidation. It is likely that some of these processes are determined in part by common genetic variations. Polymorphisms of some genes that are likely to influence oxidative stress or lipoprotein oxidation, including serum paraoxonase (PON1), nitric oxide synthase, and the hemachromatosis-associated gene, have been associated with CAD in population studies (*e*Table 98.0.5).

The evidence that PON1, a protein carried on HDL that inhibits the accumulation of oxidized lipids, plays an important role in genetic susceptibility to atherosclerosis is particularly convincing (reviewed in reference 289). Stimulated by observations that PON1 could inhibit the oxidation of LDL *in vitro*, a large number of association studies of PON1 gene polymorphisms have been conducted. Two common missense polymorphisms, a leucine-to-methionine substitution at amino acid 55 and a

Gln-to-Arg substitution at amino acid 192, have been most extensively studied. At present, more than 40 PON1 association studies with many different populations, including many European groups, Japanese, Chinese, Asian Indians, and American Indians, have been conducted. As expected for a trait as complex as CAD, results have differed between studies. However, taken together, the data are quite impressive, as more than half of the studies yielded significant results. In particular, studies that involved the Gln-to-Arg polymorphism, which clearly affects the activity of the enzyme, have consistently shown that the Arg allele is associated with increased risk. Some studies also suggest that PON1 could contribute to diabetes (reviewed in reference 289). Supporting the human data are studies in PON1 knockout mice that have conclusively shown that the enzyme can inhibit the development of atherosclerotic lesions (290,291).

Inflammation

In response to lipoprotein oxidation or other influences, monocytes are recruited to the artery wall. This involves the expression of adhesion molecules, chemotactic proteins, and growth factors for monocyte-macrophages. A number of inflammatory genes have been shown to contribute to atherogenesis in studies with transgenic mice (*e*Table 98.0.7). Among the many potential candidate genes that could contribute to vascular inflammation, several have been examined in human association studies (discussed earlier in the section Inflammation). Results with some, including TGF-b1 and IL-1–receptor antagonist, are at least suggestive.

Foam Cell Formation

Foam cells, the hallmark of early atherosclerosis, are also of importance in advanced lesions, because they contribute to lesion growth and possibly lesion stability. The growth and differentiation of macrophages appear to be importantly influenced by macrophage colony-stimulating factor (M-CSF), and much smaller lesions develop in mice with a null mutation of the M-CSF gene than in their normal littermates (292). A key process in foam cell formation is the uptake of oxidized lipoproteins, mediated by cell surface receptors that recognize oxidatively modified LDL. One study with two rabbit strains selected by breeding for either resistance or susceptibility to atherosclerosis revealed an association between the expression of receptors for modified lipoproteins and lesion susceptibility (293). Null mutations of CD36, an important receptor for uptake of oxidized lipoproteins, occur commonly in the Japanese population, but the effect on atherosclerosis has not been investigated (294). However, CD36-deficient mice exhibit smaller lesions compared to control mice, suggesting that CD36 could play a role in the development of CAD (*e*Table 98.0.7).

Smooth Muscle Proliferation

Many growth-promoting molecules for vascular smooth muscle cells have been recognized as possible contributing factors in atherosclerosis, including platelet-derived growth factor and angiotensin II (295). Inhibitors of smooth muscle cell proliferation, such as TGF-b, have also been considered in the context of atherosclerosis (296), discussed in the section Inflammation. Studies also suggest that apoptosis of human vascular smooth muscle cells may be significant in the development of fibrous plaques (297). Polymorphisms of the ACE gene have been associated with CAD in several populations (298,299 and 300). Certain common alleles of the ACE gene are associated with differences in plasma levels of ACE, which converts angiotensin I to angiotensin II and also degrades the vasodilator bradykinin. Angiotensin II promotes smooth muscle cell proliferation, whereas bradykinin is a growth inhibitor. It is likely that the ACE variation contributes to artery wall metabolism, because it is not associated with differences in blood pressure. An insertion/deletion polymorphism of the ACE gene was also strongly associated with CAD in NIDDM, providing a possible link between diabetes and CAD (301).

Monoclonal Proliferation

One possible explanation for the proliferation of smooth muscle cells in atherogenesis is a nonmalignant transformation of the cells, resulting from mutations of genes that are involved in growth control. Such a mechanism would predict that atherosclerotic lesions would show monoclonal proliferation; that is, all the smooth muscle cells in a lesion would be derived from the same transformed cell. Benditt and Benditt (302) tested this hypothesis more than 25 years ago, making use of females who were heterozygous for a genetic marker on the X chromosome. As a result of X-chromosome inactivation, women are chimeric with respect to the active X chromosome. Some cells have the paternal copy of the X chromosome active, and other cells have the maternal copy of the X chromosome active. Furthermore, because X-chromosome inactivation is stable during mitosis, all the progenitors of a particular cell have the same X chromosome active. Surprisingly, Benditt and Benditt (302) observed that small sections of coronary atherosclerotic lesions taken from deceased women who were heterozygous for the X-chromosome marker glucose 6-phosphate dehydrogenase expressed predominantly one allele of the marker or the other. More recent studies, however, have indicated that this monoclonal proliferation results from normal development (303).

Some evidence has been found that cells in lesions may undergo elevated mutation rates. In the mid-1980s, it was reported that DNA extracted from human atherosclerotic lesions exhibited the ability to transform NIH/3T3 cells (304), consistent with the activation of an oncogene, but a subsequent study failed to confirm those results (305). More recently, evidence for loss of heterozygosity and microsatellite instability in human atherosclerotic plaques has been reported (306). The significance of these findings is unknown.

Calcification

Arterial calcification is a very common occurrence in advanced human atherosclerotic lesions, and such calcification may contribute to lesion rupture (307). Because of the complexity of arterial calcification, which is clearly age and gender dependent and strongly promoted by atherosclerosis, it has been difficult to examine the genetics of the process in humans, and as yet familial clustering of calcification has not been demonstrated. Cell biology studies have suggested that arterial calcification is an active process akin to bone formation, suggesting potential candidate genes. Studies with mice have confirmed that arterial calcification is promoted by atherosclerosis, and they have also revealed the existence of distinct genetic factors (i.e., factors not involved in atherosclerotic lesion development) that contribute to the occurrence of arterial calcification and the sites of arterial calcification (285,292). Genetic studies in mice indicate that one mechanism that contributes to arterial calcification involves chondrocyte metaplasia. Some evidence also suggests that M-CSF, involved in the development of osteoclasts as well as macrophages, may contribute to arterial calcification (292). Genetic studies in mice have also resulted in the mapping of loci contributing to myocardial cell calcification (308), and these genes may also be involved in arterial calcification.

Lesion Rupture and Thrombosis

As discussed in the section Hemostatic Factors, association studies have shown that levels of various proteins involved in hemostasis, such as fibrinogen, are associated with polymorphisms of genes encoding the proteins. Epidemiologic studies have, in turn, correlated the levels of some such proteins with CAD and MI. Thus, we can conclude that common variations of certain genes for hemostasis contribute to the genetic component in CAD. Undoubtedly, this correlation is due in part to thrombosis following plaque rupture. Genetic factors may also influence the likelihood that a plaque will rupture. Clearly, the composition of a plaque, particularly whether it is primarily fibrous or fatty in nature, influences the probability of rupture. Fatty lesions are much more likely to rupture, and rupture frequently occurs at the lesion edges that are fatty in nature and contain foam cells, suggesting that the same factors that contribute to early atherosclerosis may promote rupture as well (309). It has also been suggested that certain metalloproteinases expressed in lesions, and produced in part by macrophages, may weaken lesions and increase the probability of rupture (310). One study produced suggestive evidence that a polymorphism of the gene for stromelysin-1, a metalloproteinase with broad substrate activity and expressed in atherosclerotic plaques, is associated with CAD (311). Some evidence has also been shown that polymorphisms of genes for proteins involved in host defense (such as CD14) may influence plaque stability (258).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Identification of the genes that contribute to atherosclerosis will help to unravel its complex nature and may provide insights into the interrelationship between the component traits. The successful discovery of these genetic factors will rely on the use of complementary approaches with animal models, large-scale human genetic studies, and functional experiments.

Genetic approaches are likely to have far-reaching effects on the diagnosis and treatment of heart disease and stroke. Molecular-genetic studies of mendelian disorders, such as FH, have contributed greatly to our understanding of disease processes, and the resulting knowledge has been important to the development of therapeutic strategies. For example, the knowledge of pathways for cholesterol homeostasis from studies of FH has contributed to the development of drugs such as bile acid chelators and statins (50). An outstanding example of the value of a genetic approach is the cloning of the mouse *ob* gene, which encodes the hormone leptin (111). This discovery has virtually revolutionized the field of obesity research. Clearly, understanding the underlying etiology of a disease is the best means of prevention and cure. The power of a genetic approach in providing an understanding of complex as well as simple diseases is that it leads to the identification of the primary causes. This contrasts with biochemical approaches, which frequently reveal only secondary consequences.

As yet, most of the primary causes of common forms of atherosclerosis, and of its associated risk factors, are totally unknown. Even for a process as carefully studied as lipoprotein metabolism, genetic studies suggest that many of the important genes and pathways have not yet been identified (312). Common forms of atherosclerosis present a particularly challenging problem because they are due to multiple genetic factors in combination with specific environmental contributions. Although many formidable problems remain, powerful new approaches and resources, such as those developed as part of the Human Genome Project, have created

optimism about the possibility of identifying the individual contributing genes in multifactorial diseases.

Although there is no guarantee that the identification of pathways that contribute to atherosclerosis will rapidly translate into useful new forms of pharmacologic intervention, the prospects seem excellent. Unlike most mendelian diseases, common forms of atherosclerosis depend heavily on environmental interactions. The fact that atherosclerosis progression can be modified by environmental factors, such as diet, suggests that pharmacologic intervention may be developed more readily than in the case of diseases such as sickle cell anemia, cystic fibrosis, and cancer. Although excellent pharmacologic interventions for hypercholesterolemia and hypertension are available, no effective treatments for any of the other risk factors have been developed. Of particular interest would be intervention at the level of the artery wall, perhaps complementing interventions directed at systemic factors such as cholesterol levels. Although not discussed here, genetic approaches may also be useful in dissecting pathways that contribute to restenosis, atherosclerosis following heart transplantation, plaque formation in coronary artery bypass grafts, or calcification of bioprosthetic valves. In addition to traditional drug intervention, gene therapy efforts for atherosclerosis have already been initiated, and several promising strategies have been developed. With the fundamental advances in gene delivery and gene expression that are likely to occur during the next decade, mendelian and complex forms of CAD and stroke are likely to be important targets. It may seem that gene therapy for complex forms of the disease would not be effective because there are so many contributing factors. This need not be the case, however. Even though a disease has multiple causes, altering just one can, in some cases, have a significant clinical effect. For example, simply lowering blood lipids, despite the presence of other risk factors, has proved to be very beneficial. The generation of mouse models has created many excellent opportunities for developing such therapies.

Another important consequence of understanding the genetics of atherosclerosis in more detail will be the ability to distinguish different forms of the disease for purposes of targeting pharmacologic intervention. Atherosclerosis is heterogeneous with respect to genetics and to environment. Different patients have, in a sense, different diseases, and the most appropriate therapy will differ depending on the particular variety of disease. Such classification is already used clinically, where patients are grouped according to the variety of risk factors that they display. A patient with high cholesterol is treated with a statin, whereas an individual with high blood pressure is given another drug. However, understanding the genetics of atherosclerosis, and the development of protein- or gene-based diagnostic tests, may greatly expand the possible subdivision of disease. It may also make it possible to help decide between different pharmaceuticals for treatment of a particular risk factor. For example, the differences in the responses of patients to various blood pressure medications are undoubtedly due to the fact that the patients have high blood pressure caused by different sets of genetic and environmental factors. If the patients could be classified according to genetic causes, effective medications could be identified with less trial and error. In summary, genetic approaches are likely to lead to more individualized therapy for CAD, stroke, and other common diseases.

A potential long-term benefit of genetic approaches is susceptibility testing for CAD and stroke. Cholesterol testing has been advocated for a number of years as a means of identifying individuals at increased risk, and more recently components such as HDL levels, Lp(a) levels, and homocysteinemia have emerged as indicators of risk. Once the genes that contribute to common forms of the disease have been identified, along with the specific nucleotide changes involved, DNA-based tests may greatly add to our ability to assess risk. It is clear that complexity of the genetic etiology of CAD and stroke will make it difficult to implement efficient screening procedures, and the development and validation of comprehensive test panels to assess risk profiles represent a very large challenge. Nevertheless, the potential benefits are great. Because CAD and stroke are disorders of adult onset, knowledge of disease propensity could be available many years before the development of clinical disease, permitting early intervention.

THE FUTURE

Although as yet we have relatively little understanding of the genetic causes of the common complex forms of atherosclerosis, rapid progress is now being made. This progress is dependent on new technologies, such as rapid genotyping, new analytic approaches, new information about the genome (generated in large part by the Human Genome Project), and the development of genetic animal models, particularly the mouse. Genetic approaches, by their nature, will reveal the underlying etiology of the disease. This knowledge will translate into new forms of intervention and new diagnostic tests that are capable of distinguishing different forms of the disease, allowing better targeting of intervention. A potential long-term benefit of genetic studies of the disease is risk assessment.

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GENETICS OF HYPERTENSION

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OVERVIEW

Ever since blood pressure could first be reliably measured, studies have been carried out on the population distribution and hereditary nature of hypertension. Blood pressure is a quantitative trait that varies continuously throughout the whole population, and its regulation is controlled by a variety of mechanisms that involve several genetic loci and environmental factors in conjunction with unmodifiable parameters such as age and sex. Despite this complexity, several genetic approaches have been used to unravel the molecular mechanisms responsible for arterial hypertension in the population. The first one, called the *candidate gene approach*, corresponds to the analysis of genes coding for enzymes, receptors, and proteins known to be involved in blood pressure regulation and genes shown to be involved in blood pressure level in experimental animal models. Numerous candidate genes have been investigated in different settings such as case-control and sibling pair studies. Among genes encoding the renin-angiotensin system, interesting polymorphisms of the angiotensinogen (AGT), angiotensin I–converting enzyme (ACE), and angiotensin II type 1 receptor (AT_1) genes have been identified and have been suggested to increase the activity of the renin-angiotensin system and to play a role in human hypertension. Other important results have been found with other candidate genes such as the a-adducin, the G-protein b3 subunit, the adrenergic receptors, and the subunits of the epithelial sodium channel.

Thanks to the progress made in mapping the human genome and to several groups of clinicians who have collected data from large samples of families characterized with regard to blood pressure, the genome-wide scan strategy has been used in the recent years. This approach aims at identifying loci involved in blood pressure regulation or arterial hypertension without any a priori hypothesis as to the pathophysiologic pathway(s) that might be involved. Although no major gene has been found that could explain a large part of hypertension, several loci have been suggested. Among them, a locus on the long arm of chromosome 17 seems one of the most promising.

Finally, genes responsible for several rare mendelian forms of hypertension have also been identified. Most of them correspond to defects related to increased renal salt reabsorption and volume expansion. This is especially the case for glucocorticoid-remediable aldosteronism, due to an abnormal production of aldosterone in the adrenal zona fasciculata caused by a chimeric 11-b-hydroxylase/aldosterone synthase gene; for Liddle syndrome, due to mutations leading to increased activity of the epithelial amiloride-sensitive sodium channel; and for the syndrome of apparent mineralocorticoid excess, which is caused by a defect in 11-b hydroxysteroid dehydrogenase type 2, the enzyme inactivating cortisol in the kidney. Two genes responsible for pseudohypoaldosteronism type 2 (or Gordon syndrome) have also been identified, opening the possibility of new molecular pathways regulating renal ionic exchange and blood pressure.

GLOSSARY

Association studies: The concept behind association studies is the presence of susceptibility alleles for a given disease, which is reflected by a linkage disequilibrium with a polymorphism or a series of polymorphisms (haplotype). The statistics are based on the comparison of genotype frequencies for affected and unaffected individuals (cases and controls) either in retrospective or in prospective studies. These studies, which do not require any genetic model, are in principle able to detect susceptibility alleles—even those with a minor role on the disease. They have numerous pitfalls, however. Negative results can be the consequence of insufficient power or insufficient molecular analysis of the locus—failure to test the right polymorphism—and no conclusion can be drawn from a negative result. Positive study results can be due to a true positive association, an epigenetic effect, or a false-positive finding arising from the incorrect choice of cases and controls. This last possibility is probably the main problem raised by association studies, which too often are performed using inadequate controls (small number, population admixture). The second problem involves the choice of statistical significance level in populations in which the testing of multiple loci enhances the probability of detecting, by chance, a positive result. Results obtained by association studies need to be replicated and complemented by family-based association studies and by linkage studies.

Candidate gene approach: Most of the studies conducted so far concerning human complex traits are based on the candidate gene strategy. Due to the difficulty of mapping the gene, the idea is to test genes whose products have been proven to be important in the pathophysiology of the trait or that have been identified in animal experimental models as linked to the disease. This method has the advantage of maintaining maximal statistical power for the studies, with zero recombination between the marker and the locus tested.

Complex inherited disease: A disease arising due to a trait or phenotype that does not exhibit a classic mendelian transmission (autosomal, X-linked, recessive, dominant) is known as a *complex inherited disease*. At the opposite end of the spectrum from mendelian diseases, which are usually the consequence of alterations at a single gene locus, complex diseases such as essential hypertension are the consequences of the interaction of both environmental and multiple genetic influences.

Genome-wide scan: The strategy of genome-wide scan relies on the tremendous power of linkage analysis and the very impressive progress made in human genome mapping. The genes involved in a large number of monogenic diseases have been mapped by this method, once informative families have been collected. Mapping the locus involved in a complex trait is a much more difficult task, based on more robust but less powerful methods, such as the affected sibling pair method. The density of polymorphic genetic markers and the connections between the genetic and physical human genome maps, however, make such a genetic approach feasible, as has been already demonstrated with regard to diabetes and asthma.

Sibling pair linkage analysis: For complex traits, one cannot expect a simple cosegregation of a gene locus and a disease within a large multigenerational pedigree. There are several reasons: in particular, the age-related phenotype, the effect of the environment, the multiplicity of the susceptibility loci, and their high frequency in the population. Linkage analysis based on a specified genetic model and applied to large pedigrees is therefore problematic. Affected sibling pair analysis is a nonparametric method that is based on the number of alleles shared by affected siblings. If a locus is linked to the disease, the affected pairs will share more than the 50% distribution expected from mendelian inheritance. This methodology offers several advantages: (a) it does not assume any specific mode of inheritance at the test locus and looks only for a distortion of segregation between a genetic marker and the disease; (b) the use of a single adult generation decreases problems due to the age-related increase in blood pressure; and finally, (c) analysis of hypertensive sibling pairs can partly resolve the problem of genetic heterogeneity generated by the analysis of extended multigenerational families. The method has low statistical power, however, and requires highly polymorphic markers and a large number (several hundred) of affected sibling pairs. Increased power can be obtained by selecting individuals at the extreme (i.e., in the highest and lowest deciles of a continuous trait

such as blood pressure). This type of analysis has been widely used, with some success, in identifying loci involved in complex diseases.

BACKGROUND

A number of epidemiologic studies have shown that individual blood pressure levels result from both genetic predisposition and environmental factors. The heritable component of blood pressure has been documented in familial and twin studies and in studies such as those performed in Montreal, where blood pressure levels were documented in families with natural and adopted children (1). That approximately 30% of the variance of blood pressure is attributable to genetic heritability and 50% to environmental influences is generally accepted (2) (eTable 99.0.1).

***e*TABLE 99.0.1** MECHANISMS IMPLICATED IN BLOOD PRESSURE VARIANCE

Genetic heritability	30%
Allelic effect on a single gene	
Gene-gene interactions	
Gene-environment interactions	
Environmental influences	50%
Cultural heritability	10%
Residual variance	10%

From Ward R. Familial aggregation and genetic epidemiology of blood pressure. In: Laragh JH, Brenner BM, eds. *Hypertension: pathophysiology, diagnosis and management.* New York: Raven Press, 1990:81–100.

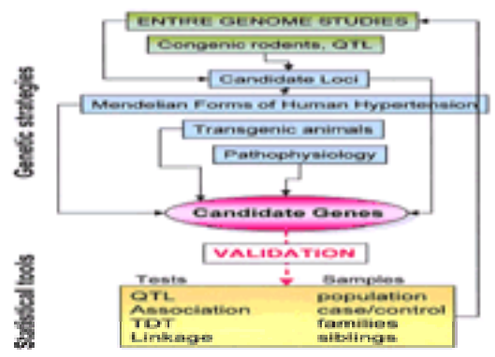
The familial component of high blood pressure can also be estimated by the use of self-questionnaires answered by hypertensive patients. Although this approach is recognized as having limited value (3), it allows screening of hypertensive patients with a putative family history of hypertension. Review of the Artemis data bank from the Hypertension Clinic of the Broussais Hospital showed that 13% of hypertensive patients reported at least one parent and one sibling with hypertension (4). Interestingly, a family history of hypertension was associated with a marked increase in the incidence of cardiovascular death of both parents before the age of 65 years and also with an increase in the prevalence of cardiovascular accidents in both parents, again before the age of 65 years. High blood pressure was detected at a younger age in patients without an apparent genetic component.

A positive family history of hypertension has a practical clinical application in identifying persons at high risk of hypertension. As reported by Williams et al. (5) in a Utah epidemiologic study, normotensive persons aged 20 to 49 years with at least two hypertensive first-degree relatives, who were observed for 7 years, had a four times higher risk of developing high blood pressure than persons without a family history of hypertension. In older adults, the relative risk of high blood pressure depends less on a positive family history of hypertension, probably because of the more prominent role of environmental factors at this age. Therefore, the finding of a strong positive family history of hypertension, especially in a young hypertensive patient, should encourage physicians to search for high blood pressure in first-degree relatives and to strongly advocate risk-factor treatment.

With the notable exception of a few autosomal forms of hypertension for which the molecular basis has been elucidated, no indication has been found regarding the number of genetic loci involved in the regulation of blood pressure, the frequency of deleterious alleles, their mode of transmission, and the quantitative effect of any single allele on blood pressure. The unimodal distribution of blood pressures within each age group and in each sex strongly suggests, but does not definitively prove, that several loci are involved. Because of the likely etiologic heterogeneity of the disease, a single biochemical or DNA genetic marker cannot be expected to help the clinician in the management of most hypertensive patients. However, genetic markers, alone and in combination, will probably be useful indicators for elucidating the various genetic loci linked to high blood pressure through intermediate phenotypes and for predicting the sensitivity to antihypertensive agents.

ANALYSIS OF CANDIDATE GENES IN ESSENTIAL HYPERTENSION

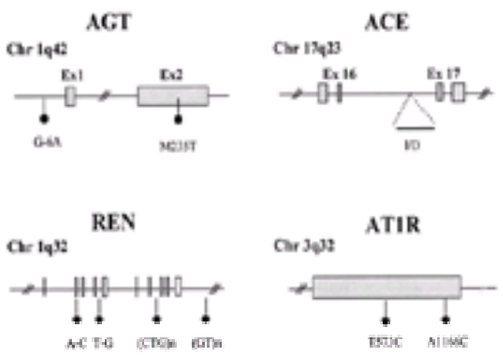
For studying the genes that might be involved in common forms of familial hypertension, the first logical approach used by researchers in the field has been to investigate genes that likely contribute to the variance of blood pressure because of their well-known effect on the cardiovascular system (eFig. 99.0.1). These candidate genes have been selected on the basis of the well-known physiologic effects of the corresponding encoded proteins or experimental results, especially in rodent models, due to their location within a quantitative trait locus or their effects on blood pressure in transgenic animals (6,7,8 and 9).



***e*FIGURE 99.0.1** Schematic diagram of the candidate gene approach. QTL, quantitative trait loci; TDT, transmission disequilibrium test.

Renin-Angiotensin System

The genes of the renin-angiotensin-aldosterone system are a good illustration of the use of the candidate gene approach because this system is well known to be involved in the control of blood pressure and the pathogenesis of several forms of experimental and human hypertension. This system consists of four main proteins: renin, AGT, ACE, and angiotensin II receptors. During the past years, considerable progress has been achieved, since all these genes have been cloned for humans and informative genetic markers have been identified (eFig. 99.0.2). Since very complete reviews on that matter by the authors' group (10) and others (11,12 and 13) have already been published, only the main findings that concern essential hypertension and blood pressure regulation are summarized here.



***e*FIGURE 99.0.2** Main polymorphisms of the renin-angiotensin system genes. ACE, angiotensin I–converting enzyme gene; AGT, angiotensinogen gene; AT1R, AT_1 receptor gene; Chr, chromosome; EX, exon; REN, renin gene.

Renin Gene

Activation of the renin system depends on the renin-AGT reaction, which is the first and rate-limiting step leading to angiotensin II production. Numerous studies have linked renin to some degree with experimental forms of hypertension and human hypertension. A fulminant hypertension develops in transgenic rats harboring the mouse Ren 2 gene (14). Even more interesting was the pioneering observation by Rapp et al. (15) of a cosegregation between a renin gene polymorphism and blood pressure level in an F2 population issued from crosses between inbred salt-sensitive and salt-resistant Dahl rats. In humans, approximately 30% of subjects with essential hypertension have higher renin levels than do normotensive subjects of the same age when examined under the same metabolic conditions (16). Interestingly, renin levels seem at least partly heritable, as observed by Grim and colleagues (17) in twins submitted to well-standardized conditions of posture and sodium diet, and more recently by Rossi et al. (18). The analysis of 175 sibling pairs and trios who participated in a multicenter trial showed very significant correlations between a familial aggregation of low-renin hypertension and plasma renin levels on either a high-salt diet (r = .36, p <.001) or a low-salt diet (r = .46, p <.001) (X. Jeunemaitre, N. D. L. Fisher, A. Vuagnat, and G. H. Williams, *unpublished data*, 1998).

The human renin gene is located on the short arm of chromosome 1 (1q32–1q42) (19). Several restriction fragment length polymorphisms (RFLPs) have been located throughout the renin gene: *Taq*I and *Bgl*I polymorphisms in the 5' region, *Hind* III in the 3' region, and *Hinf* I in the first intron. In a single large Utah human pedigree with high prevalence of coronary disease and hypertension, no significant association was found between the renin RFLPs and blood pressure or plasma renin activity (20). Interpretation was limited, however, by the very low number of patients studied. In another preliminary report, Morris and Griffiths (21) compared the renin RFLPs of 29 subjects under antihypertensive treatment with those of 202 adult patients. No association was found between hypertension and the renin gene allele but, again, no definite conclusion could be drawn because only a few patients with hypertension were studied, clinical data were not available, and the renin gene polymorphism was defined by a single and weakly informative RFLP.

Soubrier et al. (22) reported a study comparing the frequency of renin RFLPs in a large and contrasted population of normotensive and hypertensive subjects. A group of 102 hypertensive patients was selected according to strict criteria of age (between 20 and 60 years), established essential hypertension, and familial history of hypertension (defined as hypertension occurring before age 65 years in at least one parent and one sibling). A group of 120 normotensive subjects without a personal history of high blood pressure or a family history of hypertension was matched for age, sex ratio, and body mass index. In all cases, patients presenting other hypertensive risk factors such as elevated body mass index, excessive alcohol use, oral contraceptive use, or diabetes mellitus were excluded. Renin gene allele and haplotype frequencies were similar in the hypertensive and the normotensive groups.

To explore further the potential role of the renin gene as a genetic determinant of hypertension, the hypertensive sibling pairs approach was used (23). When the same clinical criteria and the same renin gene haplotypes as in the association study were used (22), no linkage was found between the renin gene and hypertension, which suggests again that the renin gene does not have a frequent or important role in the pathogenesis of essential hypertension. The definitive exclusion of a contribution of the renin gene in the heritability of essential hypertension, however, would require more powerful linkage studies, such as the use of a reliable renin intermediate phenotype and a more polymorphic marker of the renin locus. Of interest, some of the genome scans conducted since then have found the chromosome 1q32 region to be a possible hypertension-related locus.

Angiotensin I–Converting Enzyme Gene

ACE is a zinc metalloproteinase whose main functions are to convert angiotensin I into angiotensin II and to inactivate bradykinin. This step of the renin-angiotensin system is assumed not to be limiting in plasma, and indeed no indication exists that plasma ACE levels are directly related to blood pressure levels. The local generation of angiotensin I and the degradation of a bradykinin, however, might depend on the level of ACE expressed in tissues.

The enzyme consists of two highly homologous and functionally active domains resulting from a gene duplication (24). Two ACE promoters are found, a somatic promoter localized on the 5' side of the first exon of the gene and a germinal, intragenic promoter located on the 5' side of the specific testicular ACE messenger RNA (25,26 and 27). The two alternate promoters of the ACE gene exhibit highly contrasting cell specificities: the somatic promoter is active in endothelial, epithelial, and neuronal cell types, whereas the germinal promoter is active only in a stage-specific manner in male germinal cells (27). Plasma ACE concentration is thought to reflect the level of the synthesis of the somatic enzyme.

Relationship between Plasma Levels of Angiotensin I–Converting Enzyme and Genotype

From a geneticist's point of view, plasma ACE concentration is an interesting marker, as it varies considerably between individuals (from 1 to 8 at the extremes of the distribution) but remains remarkably constant when measured repeatedly in a given subject (28). This important variability is due, in large part, to a major genetic effect, as shown by Cambien et al. (29) in a family population study in which an intrafamilial resemblance was found between plasma ACE levels. This effect accounted for approximately 30% and 75% of the ACE variance in parents and in offspring, respectively.

The role of the ACE gene in the genetic control of plasma ACE was assessed using several genetic polymorphisms. The most studied is an insertion/deletion (I/D) of a 287–base pair DNA fragment in intron 16 of the gene, which corresponds to an Alu sequence. In their seminal observation of 80 healthy subjects, Rigat and colleagues showed that the serum ACE concentration of DD subjects was almost twice as high as that observed in patients homozygous for the I allele, whereas heterozygous patients were intermediate (30). In this study, the ACE I/D polymorphism accounted for 47% of the total variance of serum ACE level. As are serum ACE levels, T-lymphocyte ACE levels are significantly higher in patients homozygous for the D allele than in the other subjects (31). Another study combining segregation and linkage analysis in 98 healthy nuclear families showed that the ACE I/D polymorphism is only a neutral marker in strong linkage disequilibrium with the putative functional variant (32). Soubrier's group performed an extensive analysis of eight new polymorphisms in 95 healthy nuclear families (33). After adjustment for the I/D polymorphism, all polymorphisms of the 5' group remained significantly associated with ACE levels, which suggests the existence of two quantitative trait loci that act additively on ACE levels and account for 38% and 49% of the ACE variance in parents and offspring, respectively. More recently, Rieder and colleagues determined the complete genomic sequence of the ACE gene from 11 individuals, which represents the longest contiguous scan (24 kilobases) for sequence variation in human DNA (34). They identified 78 varying sites in 22 chromosomes that resolved into 13 distinct haplotypes. Seventeen were in absolute linkage disequilibrium with the ACE I/D polymorphism, producing two distinct and distantly related clades. The investigators suggested that the causal variant should be located within the 3' part of the gene. Despite these efforts, the causative variant or variants responsible for the increase in ACE has yet to be found, which might foreshadow the difficulty of identifying causal molecular variants in complex traits.

Angiotensin I–Converting Enzyme Gene Polymorphism and Hypertension

The observation that plasma ACE levels are under the direct control of an ACE gene variant, coupled with the linking of the ACE enzyme to two main enzymatic cascades (renin-angiotensin system and kallikrein-kinin system) implicated in cardiovascular physiology, rapidly made the ACE I/D polymorphism one of the most popular markers tested in cardiovascular diseases. The first genome scans performed in genetically hypertensive rats from an F2 rat population generated from stroke-prone spontaneously hypertensive rats (SHR/SP) and normotensive (WKY) rats rendered this hypothesis even more attractive: two groups of investigators found a significant linkage between sodium chloride–increased blood pressure and a gene locus on rat chromosome 10 (35,36). This locus—which contains ACE—contributed as much as 20% of the blood pressure variance of SHR/SP rats compared to WKY rats under conditions of high salt intake. A very large number of reported and unreported studies have been performed since then (11,12 and 13). Only some of the main findings of studies using the ACE gene as a candidate gene for human essential hypertension are summarized here.

One association study comparing a normotensive Australian population with a population of hypertensive individuals who had two hypertensive parents showed an association of hypertension with ACE gene polymorphism (37). In fact, the significant difference among the I/D genotype originated only from a subgroup of patients aged 50 years or older, in whom the D genotype was less frequent than in normotensives. This finding was interpreted as due to an increased risk of cardiovascular events in hypertensive patients carrying the D allele (38). Harrap et al. (39) investigated the distribution of the ACE I/D gene polymorphism described earlier in young adults with contrasting genetic predispositions to high blood pressure (40), using a "four corners" approach: young adults with high blood pressure and two parents with high blood pressure did not show any significant difference in frequencies of the I/D allele of the ACE gene compared to adults of the same age who had low blood pressure and no genetic predisposition to high blood pressure. Other association studies also yielded negative results (41,42). In a large series of hypertensive sibling pairs from Utah, no evidence was found of a linkage between hypertension and a growth hormone gene polymorphic marker in complete linkage disequilibrium with the ACE gene (43). Taken together, these results suggest that the ACE gene does not play a major role in blood pressure variance in these populations.

Some positive results, however, suggest that the ACE locus might influence blood pressure variability in a sex-specific manner. In a logistic regression analysis of 3,095 participants in the Framingham Heart Study (44), the adjusted odds ratios for hypertension among men with the DD and DI genotypes versus the II genotype were 1.59 and 1.18, respectively, whereas no effect was observed in women. Positive results were also reported by Fornage et al. in the analysis of a large population-based sample of 1,488 siblings having a mean age of 15 years and belonging to the youngest generation of 583 randomly ascertained three-generation pedigrees from Rochester, Minnesota (45). In sex-specific analyses, genetic variation in the region of the ACE gene explained as much as 35% of the interindividual blood pressure variation—again in males but not in females. Finally, Julier et al. (46) conducted an affected sibling pair analysis in families of France and the United Kingdom and explored chromosome region 17q23–32, based on the location of the ACE locus and on the quantitative trait loci observed in rats on the homologous region of chromosome 10. Significant evidence of linkage was found near two closely linked microsatellite markers, D17S183 and D17S934, that reside 18

centimorgans (cM) proximal to the ACE locus in the homology region.

Taken together, these results suggest that the ACE gene does not play a major role on blood pressure variance in the overall population. It may influence it in a sex-specific manner, however, in combination with other polymorphisms (47). Its role in the function of different organs (kidney, heart, vessels) has been suggested in different studies (10,11,12 and 13). Its influence on physical endurance and exercise, left ventricular mass, and renal and cardiovascular diseases has also been suggested, and excellent reviews of this topic are available (48,49,50 and 51).

Angiotensinogen Gene

Angiotensinogen, the renin substrate, is mainly synthesized by the liver and is the unique substrate for renin. In humans, AGT plasma concentration is within a range in which variations of concentration directly affect the angiotensin I production rate. Indeed, AGT levels are around the Michaelis-Menten dissociation constant of renin, and therefore to suspect that a chronic state of increased plasma AGT might increase angiotensin I levels and facilitate hypertension or cardiovascular diseases is logical. The role of AGT in human hypertension had been suspected in an epidemiologic study in which a strong correlation was found between plasma AGT concentration and blood pressure (52) as well as in another study in which offspring of hypertensive patients had elevated plasma AGT levels (53).

Angiotensinogen and Essential Hypertension

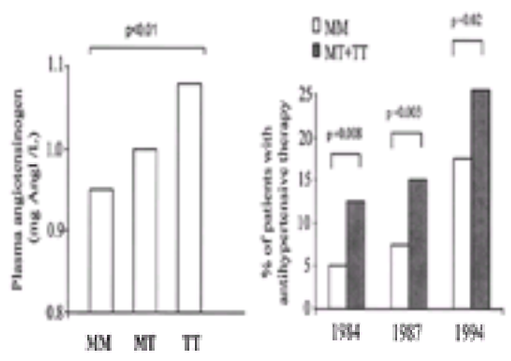
The human AGT gene belongs to the superfamily of serpins (54) and is localized to chromosome region 1q42.3, in the same region as human renin (55). With the group of J. M. Lalouel, the authors reported discovery of the first molecular elements suggesting a role for the AGT gene in human essential hypertension (56). An extensive study was performed involving two large series of hypertensive sibships yielding a total of 379 sibling pairs (Salt Lake City, UT, and Paris, France) and using a highly polymorphic microsatellite marker at the AGT locus. An excess of AGT allele sharing was found mainly in severely hypertensive sibling pairs and in men. Other linkage studies have since been reported with controversial results. Caulfield et al. showed a strong linkage and an association of the AGT gene locus to essential hypertension in a set of British families (57,58). To the contrary, no evidence for linkage was found in a large European study involving 630 affected sibling pairs, either in the whole panel or in family subsets selected for severity or early onset of disease (59). Linkage of the AGT gene to essential hypertension was also found in 63 affected African Caribbean sibling pairs (60). Similarly, positive albeit modest significant excess of AGT allele sharing was found in 46 extended Mexican-American families (61). No linkage was found between the AGT locus and hypertension in 310 hypertensive Chinese sibling pairs (62).

A strong effect of race is seen on the allele frequency of most of the polymorphisms found at the AGT locus. For example, the 235T allele frequency varies from 40% in whites to 80% in the Asian and African-American population and was even 93% in Nigerians (63). This high prevalence of the 235T allele may explain why no relation between 235T or 174M allele frequencies and hypertension was observed in a study of African-Americans (63). In the Japanese population, a significant association between this allele and high blood pressure was found in several separate case-control studies (64,65,66 and 67). These differences in allele frequencies might also facilitate false-positive results in case of admixture in case-control studies.

The association between the M235T polymorphism and essential hypertension has been tested in a large number of case-control studies that have been reviewed (68). A metaanalysis of case-control studies representing 5,493 white patients showed that the 235T allele was significantly but mildly associated with hypertension (odds ratio, 1.20; 95% confidence interval, 1.11 to 1.29; p <.0001), an association that increased in studies of individuals with a positive family history (odds ratio, 1.42; 95% confidence interval, 1.25 to 1.61, p <.0001) (69). Another metaanalysis that included 10,720 white individuals showed a 32% increase in the risk of elevated blood pressure associated with the 235T allele (70). More recently, Sethi et al. studied 9,100 men and women from the Danish general population (71). On multifactorial logistic regression analysis, women homozygous for the 235T allele, when compared to noncarriers, had an odds ratio for elevated blood pressure of 1.29, which increased to 1.50 if they were also homozygous for the T174 allele. No significant association was found in men. Altogether, these results probably highlight the modest effect of the AGT locus in the overall population and the difficulty of identifying susceptibility genes by linkage analysis for complex diseases.

Angiotensinogen Gene and Plasma Angiotensinogen

Among the 15 polymorphisms initially identified (56), two leading to amino acid changes, 174M and M235T, were found to be associated with hypertension and plasma AGT concentration. This association between plasma AGT level and the M235T genotype was further confirmed in white children (72). In this study, a strong and independent relationship of serum AGT level with body mass index (p = .0001) and race (p = .0003) was also observed. In young African-American individuals, Pratt's group showed an association between a haplotype containing the T235 allele and a polymorphism located in the promoter region of the gene (73). In a large sample of the MONICA Augsburg cohort, a mild codominant and significant increase of plasma AGT concentration associated with the M235T polymorphism was also observed (74) (*e*Fig. 99.0.3). In the Danish general population, homozygosity for both the 235T and T174 alleles was associated with a 10% increase in plasma AGT level (71). Because of the intra- and interassay variability of the plasma AGT measurement and the mild association with the M235T polymorphism, a large number of individuals are required to detect this relation.



***e*FIGURE 99.0.3** Relationship of the M235T polymorphism of the human angiotensinogen gene, plasma angiotensinogen level, and need for antihypertensive therapy in the Monica Augsburg cohort. AngI, angiotensin I. (Adapted from Schunkert H, Hense HW, Gimenez-Roqueplo AP, et al. The angiotensinogen T235 variant and the use of antihypertensive drugs in a population-based cohort. *Hypertension* 1997;29:628–633.)

Confirmation of the impact of an increased expression of AGT on blood pressure was obtained by Smithies and colleagues, who performed genetic manipulations in mice that resulted in animals with several functional copies of a given gene (9). Mice bearing one, two, three, or four functional AGT copies displayed a gene-dosage effect on plasma AGT concentration and blood pressure level that paralleled the M235T variant effect observed in humans (9,75). The amino acid residue at position 235 is not conserved across species and is in complete linkage disequilibrium with another nucleotide substitution at position –6 in the promoter of the gene with the same allele frequency (76). Lalouel's group was able to show that this variant is associated *in vitro* with an increased expression of the AGT gene, and this probably explains the association with increased plasma AGT levels (77). The true biologic effect may be more complex, however, because other polymorphisms such as C-532T, C-18T, A-20C, T+31C that are also in linkage disequilibrium with G-6A and M235T might play a role in the variation of transcription of the gene (68,78,79 and 80).

Angiotensinogen and Pregnancy-Induced Hypertension

One of the possibilities is that molecular variants of AGT might also represent a susceptibility allele for pregnancy-induced hypertension, for which a familial tendency has been documented (81,82). Two reports have suggested that the AGT locus could play an important role in the occurrence of pregnancy-induced hypertension. Ward et al. (83) found a significant association between the AGT 235T variant and preeclampsia in both white and Japanese samples. Using another strategy, analysis of the allelic inheritance of the GT repeat in 52 sibling pairs of preeclamptic sisters, Arngrimsson et al. (84) showed a significant linkage between the AGT locus and preeclampsia in Icelandic and Scottish families. Thus, although different mechanisms have been proposed for preeclampsia and essential hypertension, these results suggest that some common variants of the AGT gene could predispose to both diseases. Other studies, however, found no indication of association or linkage between preeclampsia and the AGT gene, and genome-scan studies have reported possible loci on chromosome arms 4q (85) and 2p (86,87).

Some of the contradictory results of the case-control studies could be explained by the difficulty of distinguishing between preeclampsia and other hypertensive disorders of pregnancy, which are likely to be caused by different mechanisms. The AGT gene could predispose to hypertension in only one subset of the women with pregnancy-induced hypertension. Two molecular mechanisms could explain this relationship. First, in heterozygous women, AGT expression of the T235 allele seems higher than that of the M235 allele in decidual spiral arteries (88), and nulligravid women homozygous for T235 have a lower plasma volume during the follicular phase of the menstrual cycle than those bearing the MT or MM genotype (89). Among normal volunteers receiving 50 mg of ethinyl estradiol for 1 week, homozygous TT

subjects had higher peak plasma AGT concentrations than MM subjects, a finding that confirms the influence of the genotype on the estrogen-induced stimulation of the renin substrate (90). Second, research has shown that the presence of a Met or Thr at position 235 could interact with the Cys at position 232 of the mature protein and thus favor or inhibit the formation of a disulfide bond with pro–major basic protein (91). Because hydrolysis of the AGT–pro–major basic protein complex is approximately seven times slower than that of the monomeric form of AGT and the proportion of the latter was found to be higher with the T235 recombinant AGT *in vitro*, women bearing this allele could therefore possess a more active renin substrate in the amniotic fluid and placenta. Both mechanisms acting together, an increased AGT expression due to the G-6A variant and an increased proportion of the active monomeric form of AGT, could increase the local formation of angiotensin II and facilitate hyperplasia of the spiral arteries and thus a reduction of the uteroplacental blood flow.

Other studies have tested the influence of the AGT gene on various pathologic conditions, such as coronary heart disease and diabetic nephropathy, of which reviews are available (9,13,68,92,93).

Angiotensin II Type 1 Receptor Gene

Angiotensin II receptors that mediate all the biologic and physiologic effects of the renin-angiotensin system are also candidate genes for essential hypertension. The AT_1 subtype is a G-coupled receptor inserted into the plasma membrane of angiotensin II target cells, vascular smooth muscle cells, renal vasculature and mesangial cells, adrenal gland, and brain. The human gene has been cloned and is located on chromosome region 3q21–3q25 (94,95).

No evidence was seen of linkage between a microsatellite marker of the AT_1 receptor gene and hypertension in a hypertensive sibling pair study, but an informative diallelic marker A1166C present in the 3' untranslated region of the AT1R gene was found significantly more frequently in 206 hypertensive subjects than in 298 normotensive control subjects, which suggests that a variant of AT_1 receptor exerts a small effect on blood pressure (96).

Other polymorphisms have been described, especially at the promoter region of the AT1R gene. None of these newly characterized polymorphisms has shown evidence for association with hypertension in a large white population-based sample (97). Results of studies performed in Finland, however, favor linkage between hypertension and the AT1R locus and an association with the A1166C polymorphism (98,99). In 218 white hypertensive patients, a positive relationship was found between the acute blood pressure response to angiotensin II and the AT1R locus (100). Of interest, the A1166C polymorphism of the AT1R gene has also been associated with aortic stiffness (101), left ventricular mass (102), coronary vasoconstriction (103), increased response to angiotensin II in isolated human arteries (104), and myocardial infarction in interaction with the ACE I/D polymorphism (105). These associations have been disputed in other studies, however; for example, no relation was found between AT1R density in platelets and the A1166C genotype (79).

Other Candidate Genes in Human Hypertension

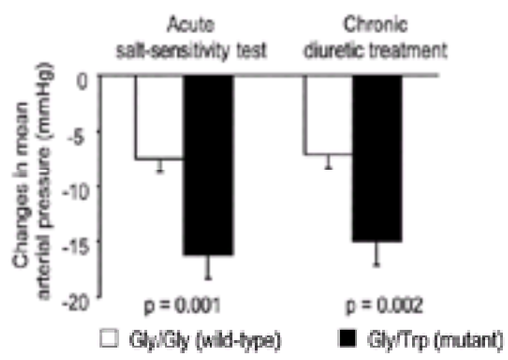
Several candidate genes have been evaluated in human hypertension using the affected sibling pair methodology or the case-control approach or both. Three of these are discussed here.

a-Adducin Gene

For more than 10 years, Bianchi's group in Milan has extensively studied the possible role of a- and b-adducin genes in rat and human hypertension (106,107). Adducin is a ubiquitously expressed membrane-skeletal protein that binds calmodulin and favors the association between spectrin and actin. Thereby, it interacts with membrane cytoskeletal proteins that affect ion transport across the cell membrane and may also be involved in cell motility. Adducin is a tetramer comprised of either a/bor a/gheterodimers (108). Each of the a,b,and g subunits is composed of two distinct domains: an N-terminal globular hydrophobic domain and a carboxy-terminal tail responsible for its interaction with actin and spectrin. The a-adducin gene is located at human chromosome band 4p16 and was originally identified due to its proximity with the gene responsible for Huntington disease. The a-adducin is widely expressed but predominates in brain and kidney. The b-adducin gene is 50% identical and is expressed with different tissue-specific isoforms. Thus, quantitative and qualitative physiologic differences exist in assembly of these subunits according to the tissue in which they are expressed.

Bianchi and co-workers put forward the hypothesis that variations in adducin could lead to variations in the activity of ionic transporters or channels, especially the Na-K-Cl cotransporter in the thick ascending limb and the Na-K–adenosine triphosphatase cotransporter all along the renal tubule, and thus lead to increased salt reabsorption and hypertension. The Milan strain of hypertensive rat (MHS) has characteristics that suggest a renal abnormality of sodium handling: increased glomerular filtration rate during the first weeks of life, low renin level, and greater sensitivity to furosemide than the normotensive strain (MNS) (106). ifferences in the amino acid sequence of the adducin genes between the MHS and the MNS strains could explain a significant part of the blood pressure difference between these two strains (107). Indeed, two amino acid changes were found in the a (F316Y) and b (Q529R) adducin genes. The transfection of wild or mutant subunits in renal epithelial cells showed that these mutations induce an increased activity of the Na-K pump, which provides a possible pathophysiologic link with increased renal sodium handling and with high blood pressure.

In humans, several studies have provided evidence in favor of a relationship between the a-adducin gene, salt sensitivity, and blood pressure level, even though the effect is probably mild at the population level. In a study involving French and Italian hypertensive sibling pairs, significant linkage was found between several markers surrounding the a-adducin locus and essential hypertension (109,110). A positive association was also found when the genotype frequencies of the G460W polymorphism of the a subunit of the adducin gene was studied in 190 hypertensive patients and 126 controls. Among 822 white and 572 African-American subjects participating in the HyperGEN Network in the United States, the 460W allele was associated with an increased risk of hypertension only in white subjects (odds ratio, 1.73; p <.01) and appeared particularly important for subjects older than 60 years (111). The blood pressure response to the long-term administration of hydrochlorothiazide was also significantly more important in subjects bearing the G460W allele, which suggests that this variant could predispose to salt sensitivity and hypertension (110) (eFig. 99.0.4). Since then, other studies have been performed that yielded negative results. This was the case, for example, in the linkage and association study examining the white population of Rochester, Minnesota (112), and the association study involving two large U.S. samples, one from an urban African-American population (Maywood, IL) and another from a rural white population (Tecumseh, MI) (113). Conversely, the association with low-renin status was confirmed in a multicenter international study investigating intermediate phenotypes in hypertension (114). Determination of the exact importance of the adducin locus in human hypertension will probably require large-scale studies as well as a search for interaction with other genes and sodium status (115).



***e*FIGURE 99.0.4** Blood pressure effect of acute and chronic salt depletion in hypertensive subjects by a-adducin G460W polymorphism. (Adapted from Cusi D, Barlassina C, Azzani T, et al. Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension. *Lancet* 1997;349:1353–1357.)

Protein b3 Subunit Gene

Several studies have suggested an increased activity of the sodium-proton exchanger in approximately 50% of the subjects with essential hypertension. Increased ion transport activity has also been found in immortalized lymphoblasts and in fibroblasts from hypertensive subjects, which might be due to altered intracellular signal transduction and enhanced activation of pertussis toxin–sensitive G-proteins (116). The heterotrimeric G-proteins are formed by the assembly of several subunits a,b and g. After excluding mutations of several of these subunits, Siffert et al. (117) found a very interesting genetic polymorphism (C825T) in exon 10 of the gene coding for the b3 subunit (GNB3). This polymorphism is not a missense mutation but favors the use of an alternative splicing of exon 9 of the gene and thus the expression of a protein with a deletion of 41 amino acids. The expression of the deleted protein in insect cells showed that it was functional but that it presents an enhanced reactivity to pharmacologic activators. Finally, in this pioneering study, the 825T allele was found to be present more frequently in 426 hypertensive subjects (0.31) than in 427

controls (0.25), which suggests a role as a susceptibility factor for essential hypertension.

This association with essential hypertension has since been debated, however. In a population-based study at Augsburg, Germany, selected from the Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA) survey (118), the C825T polymorphism showed a weak, albeit significant, association with diastolic blood pressure (CC, 88.6 mm Hg; CT, 90.1 mm Hg; TT, 91.8 mm Hg; p <.02). Interestingly, plasma renin levels were lower in individuals bearing the 825T allele, which suggests that it might be associated with a low-renin profile. An association study involving 110 Australian white hypertensive individuals, each of whom was the offspring of two hypertensive parents, and 189 controls whose parents were both normotensive beyond the age of 50 years, found a significant difference in frequency of the 825T allele (0.43 vs. 0.25; p <.001), a finding which supports a role for this variant (119).

Results of several subsequent studies failed to confirm the association of this polymorphism with essential hypertension. Brand et al. (120) analyzed the GNB3 variant in two large case-control studies in which patients were selected for essential hypertension (Projet d'Etude des Gènes de l'Hypertension Artérielle Severe à Modérée study) and myocardial infarction (Etude Cas-Témoins de l'Infarctus du Myocarde study). The odds ratios for hypertension and myocardial infarction associated with presence of the T allele were 1.23 (95% confidence interval, 0.94 to 1.62; p = .13) and 1.11 (95% confidence interval, 0.88 to 1.39; p = .37), respectively. No association was found between the GNB3 polymorphism and early onset of hypertension, familial history of hypertension, or blood pressure. In a German case-control study involving 479 hypertensive persons and 1,000 sex- and age-matched controls, presence of the 825T allele was associated with an odds ratio for the qualitative trait of "hypertension" of 1.5 (95% confidence interval, 1.1 to 2.2) (121). In both the group as a whole and the untreated group, however, blood pressure levels were virtually identical for all genotypic groups. In a study involving 447 Indians of the Oji-Cree tribe in Canada, the frequency of the 825T allele was found to be 0.50, much greater than the frequency usually observed in whites (122). Surprisingly, the 825T allele was associated with a lower mean systolic blood pressure (CC, 126.7 mm Hg; CT, 123.5 mm Hg; TT, 119.6 mm Hg; p <.05) and was not associated with a significant difference in diastolic blood pressure. A Japanese study confirmed these negative results (123). In this study, the frequency of the 825T allele was very similar (0.49) in 718 subjects with confirmed essential hypertension, 191 subjects with borderline hypertension, and 515 controls, all from the Tokyo area.

In conclusion, the impact of the genetic polymorphism of the GNB3 subunit on blood pressure in the general population needs be assessed in large epidemiologic prospective studies. The hypothesis is attractive because of the possible ubiquitous effect of this protein, especially on vascular tone and renal sodium handling. If the role of this genetic polymorphism is confirmed, it may have some therapeutic implications, because the genotyping of 197 African-Americans and 190 non-Hispanic whites who underwent monotherapy with hydrochlorothiazide for 4 weeks revealed that 825TT homozygotes showed a greater response of both diastolic and systolic blood pressure than did the CC homozygotes (124).

Genes for Subunits of the Epithelial Sodium Channel

The amiloride-sensitive epithelial sodium channel (ENaC) is the rate-limiting step of Na^+ reabsorption by the kidney distal tubule. As discussed in the subsection on Liddle syndrome, the presence of gain-of-function mutations in the genes coding for the b and g ENaC subunits suggests the possibility of more subtle polymorphisms at those genes that might modify ENaC activity, especially in salt-sensitive patients or those with a low-renin profile. Several groups have therefore extended the screening for mutations in essential hypertension to bENaC and gENaC. In a series including more than 400 hypertensive subjects, seven missense mutations were found at the gene coding for the bENaC subunit, almost all of them in patients of African descent (125). Whereas these variants led to no significant increase in Na^+ current after expression of the corresponding complementary DNAs in *Xenopus* oocytes, data obtained in human B lymphocytes (126) suggest that at least one of them (T594M) could have an effect on Na^+ reabsorption. In a case-control study involving black residents of London, Baker et al. (127) found a significantly greater frequency of T594M in 206 hypertensive patients (8.3%) than in normotensive subjects (2.1%); the statistical significance persisted after adjustment for sex and body mass index. In the subset of patients in whom plasma renin activity was measured, the T594M polymorphism was also associated with a low renin profile, which suggested that it could raise blood pressure in affected people by increasing renal tubular sodium reabsorption. However, the impact of this polymorphism is still debated.

Several polymorphisms have also been detected on gENaC. The authors found four neutral polymorphisms, three in the third exon of the gene (T387C, T474C, C549T) and one in the last exon (C1990G) (128). These four variants occurred with similar frequencies in 453 hypertensive and 245 normotensive white subjects as well as in patients with a low renin profile. In three hypertensive subjects, two rare mutations, 594insP and R631H, were also found that produced no significant increase in Na^+ current in *Xenopus* oocytes. Together with the results obtained by other groups (129), these data suggest that this subunit is not frequently involved in essential hypertension.

The analysis of aENaC showed an interesting missense polymorphism (W493R) located in the extracellular loop of the subunit and in a rather well-conserved sequence not far from the amino acids responsible for the sensitivity to amiloride. In whites, however, this polymorphism was found at similar allele frequencies in hypertensive and normotensive individuals and did not change the amiloride-sensitive current when expressed in *Xenopus* oocytes (130). Other polymorphisms, G442V at bENaC and T663A at aENaC, have been shown to be associated with changes in the ratio of aldosterone to potassium in urine and with essential hypertension (131). Also of interest, a sibling pair linkage study involving 286 white Australian families showed significant linkage between systolic blood pressure and microsatellites at chromosome band 16p12, located in the vicinity of the genes encoding the b and g subunits of ENaC (132).

Other Candidate Genes

Many other genes can be considered as attractive candidates for essential hypertension. In large projects aimed at systematic investigation of genes that may act directly or indirectly on blood pressure, a list of more than 100 genes can be easily established. Among them are genes coding for proteins of the adrenergic systems (dopamine receptors, alpha-and beta-adrenergic receptors, in particular), proteins involved in salt-water homeostasis (natriuretic peptides and their receptors, subunits of the epithelial sodium channel, renal transporters, kallikrein-kinin system, etc.), proteins involved in hormonal regulation of blood pressure (enzymes and receptors of the mineralocorticoid and glucocorticoid pathways), and proteins involved in the structure or the regulation of vascular tone (endothelins and their receptors, adrenomedullin).

Of course, to summarize here the studies that have been performed for all these candidate genes is impossible, except to mention that none of the polymorphisms found within or near these genes has been definitively associated with significant changes in blood pressure in the general population. For example, the gene coding for endothelial cell nitric oxide synthase was very attractive because nitric oxide plays an important role in regulating blood flow and pressure, and because several reports have suggested that hypertensive subjects have a blunted endothelium-dependent vasodilatation that might be secondary to decreased nitric oxide production. Linkage and case-control studies involving French hypertensive and normotensive subjects, however, failed to show association or linkage with essential hypertension (133), which suggests that common variants of this isoform of nitric oxide synthase are not involved in common hypertension. Similar negative results were obtained in humans for the SA locus (134), which has been linked to blood pressure levels in several crosses involving different strains of genetically hypertensive rats (135).

The CYP 11B2 gene coding for aldosterone synthase is also an attractive candidate gene. It has been tested for its possible association with essential hypertension (136,137 and 138) and primary aldosteronism (139). A polymorphism in the promoter region of the gene (C-344T) is located at a steroidogenic transcription factor SF-1 binding site and could play a role in the expression of the gene. Despite the fact that the angiotensin II, K^+, and cyclic adenosine monophosphate signaling pathways *in vitro* use a cAMP-responsive element–like *cis* element and another SF-1 binding site that is located closer to the transcription start to regulate human CYP 11B2 expression (140), the C-344T polymorphism has been associated with variations in plasma aldosterone (136,141), which suggests that it could favor sodium retention and high blood pressure. Contradictory results have been obtained depending on the populations and the clinical and biochemical parameters studied (138,142,143,144 and 145).

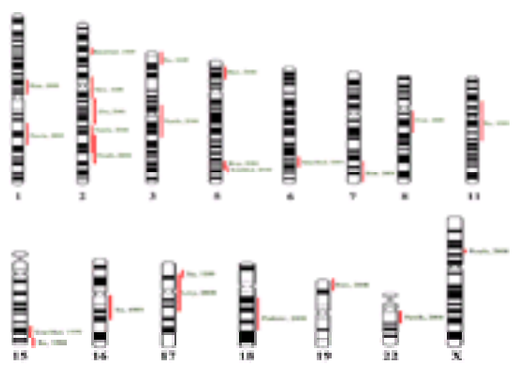
Finally, one should note that most of the studies performed so far on candidate genes have been conducted using a very simple design, by testing the role of each candidate one by one. However, several genes are recognized to control blood pressure level in an additive or interactive manner, together with environmental factors. A more integrated approach needs to be developed in which several genes and some environmental factors can be tested with or without a specific *a priori* hypothesis (146). In that regard, the study performed by Staessen and colleagues (47) showed the combined effect of the ACE I/D, the a-adducin Gly460Trp, and the aldosterone synthase C-344T polymorphisms on blood pressure level.

GENOME-WIDE SCANNING

Given the major advances over the last few years in developing the genetic and physical map of the human genome, the genome-wide scan (GWS) approach has become another important strategy for identifying major loci implicated in complex traits. Once the regions of interest are identified, a positional candidate gene approach can be used initially on the most promising genes (147). Because it does not make any *a priori* assumption regarding the genes to identify, this strategy appears very promising for discovering new pathways involved in blood pressure regulation.

This approach has strong statistical limits, however, that have been well delineated by several authors (148,149,150 and 151). Among them are (a) the problem of insufficient power to identify loci that have only a small influence on blood pressure level; (b) the use of nonparametric methods that require inclusion of hundreds of sibling pairs or the use of particular study designs, such as discordant sibling pairs, or both; (c) the need to adjust the statistical significance for multiple testing to

prevent the identification of genes with mild effects on the trait; (d) the requirement of replication of any positive result in another sample with the same characteristics using either the same design or a complementary approach such as family-based association studies or case-control studies; (e) the low power of replication for loci with only a small effect on blood pressure; and (f) the possible heterogeneity of genes causing essential hypertension depending on ethnic background and confounding factors such as obesity or associated diseases like dyslipidemia and diabetes. Finally, one must be aware that GWS, at least in the first stage, does not take into account the interaction between genes and between genes and the environment, which are the mechanisms at work in determining blood pressure level. Thus, negative results can be obtained for a locus with a true biologic and clinical effect that would have been detected only if analyzed in combination with other loci or with environmental factors. Despite these limitations, several GWS studies have been reported that provide interesting although contradictory results. A nonexhaustive summary of these studies is given below and in eFigure 99.0.5.



***e*FIGURE 99.0.5** Schematic representation of the susceptibility loci found in human hypertension. Each quantitative trait locus is represented as a vertical line, and the corresponding source is indicated.

White Individuals

One of the first published GWS studies was that performed by the group of Boerwinkle based on the Family Heart Program in Rochester, Minnesota, which included 3,974 subjects from 583 families. A first study (152) was based on the selection of 69 sibling pairs highly discordant with regard to blood pressure level (above the 80th percentile or below the 20th percentile). Four genomic regions (2p22, 5q33, 6q23, 15q25) were suggested to be linked with systolic blood pressure. In a second study (153), the investigators analyzed the candidate genes contained in the most promising region (5q33), among them those for dopaminergic receptor type 1A, the $alpha_{1B}$-adrenergic receptor, and the $beta_2$-adrenergic receptor. For each of those, an extensive search for polymorphisms was performed followed by the genotyping of the population. Most data did not show any consistent association between these polymorphisms and blood pressure. The polymorphism (Arg16Gly) of the $beta_2$-adrenergic receptor was the most interesting because of its association with significant although minor changes (2 to 3 mm Hg) of systolic blood pressure.

Another study was performed in the United Kingdom involving 119 white families selected for the presence of at least three hypertensive subjects in the same sibship (154). The genome scan used 262 markers and pointed out a suggestive region on chromosome arm 11q. An analysis of 124 additional families, however, did not confirm that location. A statistical simulation confirmed the genetic complexity of essential hypertension with a multipoint exclusion-linkage analysis showing that at least three genetic loci were necessary to explain the familial aggregation of the trait.

The Amish population may appear ideal for genetic studies examining blood pressure because of the size of the families and the standardized environment that largely prevents alcohol consumption and obesity. A study reported by Hsueh et al. (155) examined 694 subjects from 28 Amish families, each containing from 3 to 69 individuals. A total of 357 microsatellite markers were genotyped in 436 parent-sibling couples, 1,326 sibling pairs, 1,342 first-degree relatives, and 1,311 first cousins. In these families, blood pressure heritability was 0.23 for systolic pressure and 0.29 for diastolic pressure, estimates similar to those generally reported in the literature. The only chromosomic region that was linked to the trait was located in 2q31–34, with lod scores of 1.64 for systolic and 3.36 for diastolic blood pressure.

One of the most recently published GWS studies is also probably one of the most convincing (156). It involved 1,702 subjects from 332 families selected from the Framingham survey. For each individual, blood pressure was averaged on measurements taken at least three times over at least 10 years and adjusted for age and body mass index. A 10-cM genome scan was performed that allowed the analysis of the following relative pairs: 1,545 sibling pairs, 933 parent-offspring pairs, 742 cousin pairs, and 468 pairs of other first-degree relatives. The statistical analysis showed only one region of interest—chromosome 9—for diastolic blood pressure. For systolic blood pressure, a suggestion of linkage was found for several regions on chromosomes 5, 10, and 17. On this last chromosome, two regions were suggested, with the one located on 17q12–21 giving the most promising multipoint lod score (4.7).

This chromosome 17 region corresponds to one also found earlier by Julier et al. (46). In this study involving French hypertensive sibling pairs, French diabetic pairs with hypertension, and United Kingdom families, significant linkage and association were found using markers of the same region that contains the ACE locus at its telomeric end. No particular gene has yet been shown to be the one responsible for this statistical association, however, because the ACE gene seems excluded. Other arguments make this region of interest. First, it corresponds to the main quantitative trait loci found in the rat genome (35,36). Second, this region also contains one of the genes responsible for Gordon syndrome [pseudohypoaldosteronism (PHA2B)] (157). Finally, a missense polymorphism (Gly40Ser) at the glucagon receptor gene located at this locus has been shown to be associated with hypertension. This association, however, was detected in a limited set of white hypertensive patients with two hypertensive parents, with an allele frequency of 0.08 compared to only 0.01 in normotensive controls (158). It was not detected in a sample of 741 French hypertensive subjects who were compared with 412 controls (159). One might argue that this chromosome 17 region contains several important genes for blood pressure control that are not sufficient individually but could predispose to hypertension in the presence of several interacting molecular variants.

The Finnish Twin Cohort Study has also been used for a GWS analysis of blood pressure (99). The strategy was to study a limited number of pairs with an early-onset phenotype (mean age at discovery of 38.3 years) and to diminish the effect of possible confounding factors (at least one sib with body mass index less than 27, exclusion of diabetes). Only 47 sibling pairs were studied in stage 1 of the analysis, 36 dizygotic twins and 11 nontwin siblings. In stage 2, genotyping was densified for the regions suggestive of linkage with the addition of all available family members of the 47 probands (total of 138 subjects). Despite these relatively small numbers, several regions gave a maximum likelihood score higher than 1.5 (1q, 2q, 22q, and Xp). The most significant result was obtained on 3q21–25 (maximum lod score = 3.38 on the entire sample). This region contains the AT_1 receptor gene, and the stronger result was obtained with the intragenic CA repeat at this locus. An analysis of candidate genes in a German population, using blood pressure as a quantitative trait, also suggested linkage with the AT_1 receptor gene (160).

A GWS was also performed of 125 randomly selected and 81 obese families participating in the Québec Family Study (161). Multiple linkage regions were suggested for systolic blood pressure, especially on chromosome arms 1p, 2p, 5p, 7q, 8q, and 19p. One of the main aims of this study was to show the importance of gene–gene and gene–environment interactions, because most of the regions that were suggested in lean families did not show any linkage when analyzed in families in which one or more members had a body mass index greater than 32.

Finally, the GWS analysis of pulse pressure in 10 families (440 individuals) in the San Antonio Family Heart Study showed a heritability of 0.21 of this trait and suggested four regions of importance on chromosomes 21, 7, 8, and 18 (162). Suggestive evidence for linkage on chromosome arm 18q was found with postural systolic blood pressure in 498 white sibling pairs from the Hypertension Genetic Epidemiology Network (163). Using creatinine clearance measurements for a large biracial sample of hypertensive siblings from the same network (466 African-American subjects and 634 white subjects), DeWan et al. (164) showed that a locus on chromosome arm 3q may contribute to the degradation of renal function.

Asian Individuals

A remarkable effort has been made by Xu and colleagues to characterize a large population from the Anqing region in China (165). A GWS using 367 markers was performed for sibling pairs (207 discordant, 258 high concordant, and 99 low concordant) selected from a blood pressure screen of more than 200,000 Chinese adults (166). Although no regions achieved a 5% genome-wide significance level, maximum lod score values were over 2.0 (unadjusted p <.001) for five markers (D3S2387, D11S2019, D15S657, D16S3396, and D17S1303). Of interest, the suggestive regions identified depended on the design of comparisons and were different for systolic and diastolic blood pressure. By refining the trait definition and genotyping additional markers, the investigators highlighted a region on chromosome arm 15q with a maximum lod score of 3.8 near D15S203 in sibling pairs at the lower extreme of diastolic blood pressure (166).

A three-stage GWS study was carried out with 240 microsatellite markers, initially in 283 Chinese sibling pairs with hypertension, then in 637 pairs, and finally in 777 pairs (167). Multipoint linkage analysis showed lod score higher than 2.0 throughout a 5-cM region on chromosome band 2q14–2q23 (D2S112–D2S2370).

Nonparametric analysis also revealed positive linkage to this region (maximum Z-score = 3.27; p = .00086).

MONOGENIC FORMS OF HYPERTENSION

The molecular basis of several rare mendelian forms of hypertension has been elucidated. These forms are usually characterized by an early onset of hypertension, a frequent familial history of cerebrovascular accidents, and a strong penetrance. Most are related to abnormal sodium retention, which leads to volume expansion accompanied by suppression of plasma renin activity.

Glucocorticoid-Suppressible Hypertension

Glucocorticoid-suppressible hypertension (GSH; also called *dexamethasone-suppressible aldosteronism* or *glucocorticoid-remediable aldosteronism*) is characterized by a variable degree of hyperaldosteronism and an increased urinary excretion of 18-hydroxylated and 18-oxo-cortisol metabolites, 18-hydroxycortisol, and 18-oxocortisol. These abnormalities, including hypertension, can be corrected by the suppression of adrenocorticotropic hormone (ACTH) by dexamethasone. The proposal had been made that the disease was due to an abnormal expression in the zona fasciculata of aldosterone synthase, CYP 11B2, the enzyme responsible for the conversion of corticosterone into aldosterone. Lifton et al. (168) showed that this disorder was linked to an abnormal aldosterone synthase gene. They studied a large affected kindred and found a gene duplication arising from an unequal crossing over, resulting in a fusion of the 11b-hydroxylase (CYP 11B1) promoter with the coding sequence of aldosterone synthase. The chimeric gene encodes a protein that can hydroxylate cortisol (the steroid substrate present in the zona fasciculata) in the 18 position. This gene is under the control of the 11b-hydroxylase gene regulatory region, whose expression is under ACTH control and can be downregulated by exogenous glucocorticoid administration. All the phenotypic abnormalities of GSH can be explained by this mutation.

Since this original description, several other families affected with this syndrome have been identified. In a patient with GSH with an adrenal tumor, the chimeric gene was found to be expressed in the tumoral tissue and in the zona fasciculata of the surrounding adrenal tissue, and sensitivity of the corresponding adrenal cells to ACTH was observed (169). In all families reported so far, the chimeric gene derives from unequal homologous recombination between exons 2 and 4 of the 11b-hydroxylase and aldosterone synthase genes, respectively. It has been shown by site-directed mutagenesis that such hybrid genes expressed in heterologous eukaryotic cells are able to encode chimeric proteins that hydroxylate cortisol in the 18 position (170). More recently, the transfection into COS-7 cells of a series of CYP 11B1 complementary DNAs containing various regions of CYP 11B2 sequence showed that two amino acid changes, Ser288Gly and Val320Ala, are sufficient to convert CYP 11B1 into an efficient aldosterone-producing enzyme (171). Although these results suggest that a gene conversion involving exons 5 and 6—in which these residues are encoded—could cause a novel form of GSH, no such molecular abnormality has yet been found in a series of patients with essential hypertension and primary aldosteronism (172).

GSH is probably very rare. The possible locations of the unequal crossover between the CYP 11B1 and CYP 11B2 genes allow its molecular diagnosis by a simple Southern blot analysis or a long-range polymerase chain reaction assay (173). In the authors' own hypertension clinic, no case of GSH could be found in a systematic analysis of more than 200 patients with primary aldosteronism without overt tumoral primary aldosteronism (X. Jeunemaitre et al., *unpublished data*, 2000), and only four French families have been diagnosed with GSH up to now. One of the major interests of this diagnosis is its therapeutic implication, however, because low dosages of dexamethasone improve the clinical and biologic features of this syndrome (173,174).

Gordon's group described another form of familial primary aldosteronism, called *type II* (FH-II), that is found in a few families. Approximately 30% of the affected patients present with an aldosterone-producing tumor. The inheritance pattern is probably autosomal dominant (175,176). The screening of the entire genome in a large family with FH-II showed linkage with chromosome 7p22 (177).

Liddle Syndrome

In 1963, Liddle et al. (178) described a family with hypertension and an abnormality of Na^+ reabsorption at the level of the renal distal tubule that simulated primary aldosteronism but showed negligible basal and stimulated aldosterone secretion. Blood pressure and hypokalemia were not influenced by spironolactone treatment but triamterene, a specific inhibitor of the distal renal epithelial sodium channel, corrected these abnormalities. The authors proposed that the primary abnormality was a constitutive activation of the epithelial sodium channel. Some 30 years later, this hypothesis was reinvestigated in the proband and in the originally described pedigree. The index case developed renal failure. Renal transplantation corrected the aldosterone and renin responses to salt restriction, which demonstrated the involvement of the kidney in the disease (179). Thus, the gene for the ENaC located in the collecting cortical tubule is a logical candidate gene for this disease. This channel constitutes at least three homologous subunits, a,b and g which act together to confer its low sodium conductance and its high selectivity for sodium and amiloride (180).

Analyzing the original Liddle pedigree, Shimkets et al. (181) showed complete linkage of the gene encoding the b subunit of this channel, located at 16p13–12. In this pedigree and in other unrelated kindreds, a premature stop codon, a frameshift mutation, and other deleterious mutations were found, all located in the last exon of the gene encoding for the intracellular carboxy-terminal domain of the b subunit (181). These mutations were shown to be gain-of-function mutations, with an increased amiloride-sensitive Na^+ current after transfection of the corresponding mutant subunits together with a and g wild-type subunits. In a Portuguese family affected with this syndrome, a 32–base pair deletion was found leading to a premature termination of the carboxy end of the same subunit (182). Investigation of the epithelial nasal sodium-chloride conductance instead of the kidney conductance showed the presence of an increased amiloride-sensitive conductance in the three affected patients but not in their unaffected sister (183). A point mutation affecting the same region of the g subunit has also been found to cause Liddle syndrome (184), but no mutation of aENaC has been discovered in this syndrome as yet.

Comprehensive studies (185,186 and 187) have shown that the mechanism by which the truncation of the carboxy terminus of the b and g subunits alters the function of the epithelial sodium channel corresponds to an alteration of a conserved motif (PPxxY) in the carboxy terminus of all three subunits of the sodium channel. Normally, a specific interaction between this PY motif and cytosolic proteins (Nedd4 isoforms 1 and 2, and other related WW proteins) leads to ubiquitination and then degradation of part of the newly synthesized subunits (188). Both truncation or punctual mutation of this PY motif increase surface expression of the mutant proteins and thus increase the number of sodium channels in the apical membrane (189), which favors renal sodium absorption and hypertension.

Gain-of-Function Mutation in the Mineralocorticoid Receptor

One case of a new monogenic form of hypertension, which could be called *pseudoaldosteronism type II*, has been reported by Geller et al. (190). It is characterized by an early onset and severe form of hypertension associated with low plasma levels of renin and aldosterone. It is caused by an activating missense mutation (Ser810Leu) of the human mineralocorticoid receptor. This mutation is located within the hormone-binding domain and results in a constitutive mineralocorticoid receptor activity and in an alteration of the receptor specificity. The receptor becomes abnormally activated by progesterone and other steroids lacking 21-hydroxyl groups that normally act as antagonists. In the family described by Geller and coworkers, all women bearing the mutation had severe pregnancy-induced hypertension with hypoaldosteronism, which was caused by the massive increased production of progesterone during pregnancy. These original findings open the possibility of discovering other cases of similar types of mutations in pregnancy-induced hypertension.

Apparent Mineralocorticoid Excess (Ulick Syndrome)

The syndrome of apparent mineralocorticoid excess is a rare autosomal recessive form of hypertension diagnosed in children and characterized by a very early and severe hypertension associated with hyporeninism and hypoaldosteronism (191). It corresponds to a defect of the 11b-hydroxysteroid dehydrogenase type 2 enzyme that is expressed in the kidney. This enzyme inactivates glucocorticoids by converting cortisol into cortisone and corticosterone into 11-dehydrocorticosterone. Deleterious mutations have been found in affected patients, who are either homozygous for the mutation, especially in consanguineous families, or composite heterozygous (192,193 and 194).

The enzymatic defect leads to increased renal concentrations of cortisol and corticosterone, which are themselves powerful agonists of the human mineralocorticoid receptor, contrary to cortisone and 11-dehydrocorticosterone. Thus, affected patients are characterized by high ratios of cortisol to cortisone in plasma and urine, and by arterial hypertension, which mimics a primary aldosteronism (195). The genetic diagnosis can be obtained rapidly by direct sequencing of the five exons of the gene.

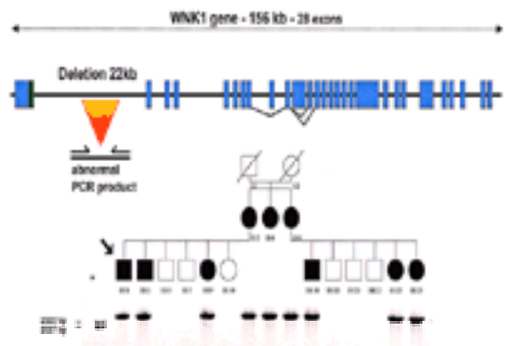
Pseudohypoaldosteronism Type 2 (Gordon Syndrome)

Pseudohypoaldosteronism type 2 (PHA2), also known as *Gordon syndrome*, is an autosomal dominant form of volume-dependent hypertension characterized by hyperkalemia and hyperchloremic acidosis without glomerular insufficiency (196). The low renin levels are thought to be the consequence of volume expansion, whereas plasma aldosterone levels are variable depending on the opposite influences of low renin and high potassium levels. At least two features suggest a primary renal tubular defect along the convoluted distal tubule: affected patients are highly sensitive to small doses of thiazide diuretics, and the clinical and biochemical features of PHA2 are the mirror image of those of Bartter-Gitelman syndrome, in which inactivating mutations in the thiazide-sensitive sodium-chloride cotransporter (SLC12A3) gene have been demonstrated (197). The pathophysiology of PHA2 is certainly more complex, however, as in some cases an associated reduced proximal

reabsorption, a chloride reabsorption defect, and an altered sensitivity to mineralocorticoids have been shown (198).

Examining eight affected but limited families, Mansfield et al. (157) have identified two loci on the long arm of chromosomes 1 and 17 named, respectively, PHA2A and PHA2B. The locus on chromosome 17 was confirmed in another Australian kindred (199). The direct implication of SLCA12A3 was excluded by genetic linkage analysis. The selection and genetic analysis of a large French pedigree led to identification of a third chromosomal region on chromosome arm 12p, designated PHA2C (200). Exclusion of linkage for these three chromosomal regions in two additional affected pedigrees suggests further genetic heterogeneity (201). Thus, the molecular genetics of this syndrome is expected to lead to a variety of molecular defects revealing the role of either several new components of the same pathway or of direct or indirect partners of the sodium-chloride cotransporter.

Lifton's laboratory and the authors' own group identified the genes corresponding to the PHA2C (chromosome 12) and PHA2B (chromosome 17) loci (202). Both genes are members of a particular family of serine-threonine kinases, called *WNK1* and *WNK4*, and the corresponding proteins localize to the distal nephron. Disease-causing mutations in the WNK1 gene are large deletions in the first intron, which lead to increased gene expression of the kidney isoform (eFig. 99.0.6). Mutations in the WNK4 gene are missense mutations clustering in a highly conserved domain among these types of kinases. Altogether, these findings implicate these kinases in a previously unrecognized signaling pathway likely to be involved in the control of sodium reabsorption in the distal nephron and blood pressure regulation.



***e*FIGURE 99.0.6** Mutation of the WNK1 gene in one family affected with Gordon syndrome. The mutation corresponds to a deletion of 22 kilobases (kb) in intron 1 of the WNK1 gene. An abnormal amplification product can be generated from peripheral DNA of affected patients. bp, base pairs; PCR, polymerase chain reaction. (Adapted from Disse-Nicodème S, Achard JM, Desitter I, et al. A new locus on chromosome 12p13.3 for pseudohypoaldosteronism type II, an autosomal dominant form of hypertension. *Am J Hum Genet* 2000;67:302–310; and Wilson FH, Disse-Nicodème S, Choate KA, et al. Human hypertension caused by mutations in WNK kinases. *Science* 2001;293:1107–1112.)

As already discussed, the WNK4 gene lies within the largest genetic linkage peak for blood pressure variation observed in the Framingham Heart Study population (156). Two studies of European hypertensive sibling pairs have also found evidence of linkage to this region (46). Searching for polymorphisms of that gene that might be implicated in essential hypertension is therefore of interest.

Syndrome Associating Arterial Hypertension and Brachydactyly

A rare form of autosomal dominant syndrome associating arterial hypertension and brachydactyly has been reported in a few families, especially one extended Turkish pedigree (203,204). In 100% of the affected patients, hypertension is accompanied by a short stature and brachydactyly but with no other special biologic or hormonal phenotype (205). A particular defect of cerebral vascularization—loops in the posterior inferior cerebellar artery—has been discussed as the possible origin of neurovascular compression and high blood pressure (206). In addition, abnormalities of autonomic function tests suggest an alteration of the baroreflex (207). The locus responsible for the disease has been mapped to chromosome arm 12p (208), in a region that is more centromeric than the PHA2C locus, but the gene has not yet been identified.

THE FUTURE

Several strategies have been used to identify genes involved in hypertension, from experimental models of rodent hypertension to multiple studies involving various human populations. These investigations have now shown that not a single gene but, rather, combinations of several susceptibility genes are involved in blood pressure regulation, although no clear picture emerges as to precisely which ones. The most remarkable results so far have been obtained in the rare cases of monogenic forms of hypertension. The attractive hypothesis that some genes directly implicated in monogenic forms of hypertension may also be involved in essential hypertension has not yet been confirmed. The discovery that WNK1 and WNK4 are responsible for two genetic forms of Gordon syndrome, however, leaves open the possibility that this family of genes may be implicated in essential hypertension.

Future directions might take advantage of the analysis of the present data:

1. An important effort needs to be made to define more accurate phenotypes than just hypertension per se. When possible, blood pressure (systolic, diastolic, pulse pressure) should be considered as a quantitative trait. Many variables that affect blood pressure should be taken into account, such as age and sex of the patient, the presence or absence of a documented family history of hypertension, and precisely estimated environmental factors (tobacco smoking, obesity, alcohol consumption, estrogen treatment). Better clinical and biochemical descriptions of hypertensive (and normotensive) populations should allow the description of intermediate phenotypes and the study of more homogeneous populations providing increased statistical power. A detailed investigation of the physiologic and biochemical parameters of well-characterized patients, in relation to gene variants, might thus provide evidence for a functional link between genotypes and phenotypes. Such studies could reveal unsuspected and interesting relationships between gene variants and intermediate phenotypes.
2. Ongoing genetic studies in hypertensive rodents should further contribute to the analysis of human genetic hypertension. GWS analyses revealed that several genetic loci are linked to hypertension or to hypertensive phenotypes in various strains of rats and mice. Although no candidate gene has yet been discovered using this approach, one hopes that in the near future several genes will be identified and will be tested for their potential contribution to human genetic hypertension.
3. A large effort has already begun on the systematic search for common molecular gene variants likely involved in blood pressure regulation and in cardiovascular diseases. Essential hypertension is a complex phenotypic trait that is influenced by several (or many) genetic factors and several (or many) environmental stresses. Thus, one cannot expect a restricted number of gene variants to influence blood pressure in individuals of different ages, in different environments, and of different ethnic origins in the same manner. As reported in the present review, some limited studies have already shown that a combination of gene variants is associated with an increased risk of cardiovascular complications. A systematic search for polymorphisms at candidate genes should be extremely useful for the identification of susceptibility genes through association and linkage studies. One must emphasize that testing hundreds of different genetic markers on large sample populations is now feasible. Two comments must be made, however: (a) because the allele frequencies may vary considerably by population, the frequency of the allelic variants in each ethnic group must be determined. To minimize the difficulty of obtaining strictly homogeneous patients with regard to ethnicity, several genetic-epidemiologic studies have been performed in well-defined and limited geographic areas such as Iceland, Finland, and other genetically isolated areas to obtain maximal control of this parameter. (b) Analysis of the effect of the combination of several gene polymorphisms might require very large population samples, especially because some of them may have a low allelic frequency. Such studies will require national and international collaboration.
4. Thanks to the tremendous efforts of the laboratories involved in the human genome project, a complete gene map of approximately 30,000 genes should be available within the next 5 years. This will have important consequences in the search for the genes of interest. In particular, a positional candidate cloning approach is now more and more feasible, with a test of different candidate genes once a chromosomal region has been determined to influence the level of blood pressure. Therefore, a strategy of positional cloning using random markers evenly distributed all along the genome appears increasingly as one of the strategies that can bring new insights into the primary causes of essential hypertension. The first attempts in that direction, however, have shown its limits and difficulties. The absence of replication from one sample to another demonstrates the importance of the type of population analyzed and possibly the fact that there is no major gene regulating the trait but rather many genes with mild effects that may play a role in determining basal blood pressure or its evolution with age, reactivity to different stimuli, or complications.
5. The time is too early to propose dietary recommendations and specific drug treatment according to a patient's genotype, although a few preliminary reports have been published suggesting relationships between a given polymorphism and the blood pressure response to antihypertensive therapy. Clearly, defining the subset of individuals in whom a gene or a combination of genes might play a role is one of the important tasks for the near future.

6. Finally, clinicians working in the field should be aware of the potential of molecular genetics and thus of the discovery of new genetic syndromes associated with hypertension. The exact prevalence of the mendelian forms of hypertension might have been underestimated due to the difficulty of establishing the diagnosis by classical biochemical approaches. It should be facilitated by further clinical attention and genetic testing. In this regard, the fact that the authors were able to collect more than 15 independent PHA2 families within the last 4 years in France is of interest.

Using these different approaches, our knowledge of the molecular defects involved in different forms of hypertension is likely to be improved. This should have a large impact on the strategies aimed at preventing and treating this common and complex disease.

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GENETIC STUDIES OF MYOCARDIAL AND VASCULAR DISEASE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Genetic factors contribute to the pathogenesis of a wide variety of disorders that affect cardiac and vascular structure and function. Advances in molecular genetics since the 1980s have provided remarkable insights into the genes responsible and pathogenic mechanisms of cardiovascular disease. Disease-causing genes have been identified for cardiac arrhythmic disorders [e.g., long QT syndrome (LQT), idiopathic ventricular fibrillation (IVF)], congenital heart disease [e.g., Holt-Oram syndrome, Ellis-van Creveld syndrome, atrial septal defect (ASD) with atrioventricular (AV) block, cardiac myxoma], hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, and familial vascular anomalies [e.g., Marfan syndrome (MFS), patent ductus arteriosus, supravalvular aortic stenosis, lymphedema]. Genetic studies of human cardiovascular disorders continue to provide insight into molecular mechanisms underlying morphogenesis, development, and physiologic function of the cardiovascular system. Molecular genetic analysis of cardiovascular disease permits DNA-based diagnosis, which will promote new approaches to risk stratification and therapy. These exciting molecular discoveries have raised the hope of genetic testing, drug development, and gene-based therapies for a variety of cardiovascular disorders. In this chapter, we discuss major advances in the genetics of myocardial and vascular disease.

GLOSSARY

Allele: Alternative forms of a gene or a genetic locus.

Allelic: A condition in which two phenotypically different traits are the result of different mutations in the same gene.

Compound heterozygote: An individual with one mutation in one allele of a given gene and a different mutation in the other allele of the gene. Compound heterozygous mutations are usually associated with autosomal recessive disease.

Heterogeneity: *Allelic* or *intragenic heterogeneity* is different genotypes at the same genetic locus that cause a similar phenotype. *Locus heterogeneity* refers to a situation in which a disease is caused by defects at different genetic loci.

Heterozygote: An individual with a mutation in one copy of a given gene but without a mutation in the other copy. Heterozygous mutations are usually associated with autosomal dominant disease.

Homozygote: An individual with the identical sequence in both alleles of a given gene. Homozygous mutations are usually associated with autosomal recessive disease.

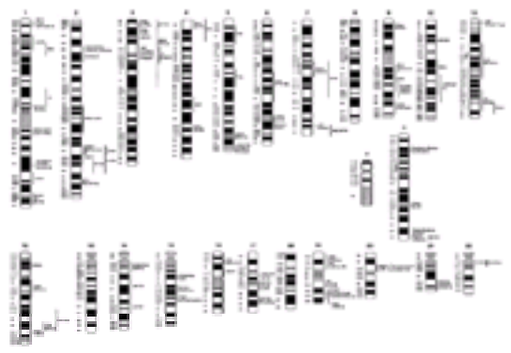
Linkage analysis: Analysis to determine whether two or more genetic traits (a marker locus and a disease trait) are cosegregating within a pedigree.

Positional cloning: A technique used to identify the underlying genetic cause of a disease based primarily on finding the location of the defective gene.

INTRODUCTION

Cardiovascular disease is the leading cause of death in developed countries. Genetic factors play an important role in the pathogenesis of cardiovascular disease. Each human being is variably estimated to have at least 30,000 to 40,000 different genes (1,2 and 3). Mutations in single or multiple genes can cause cardiovascular disease. The revolutionary advances in molecular genetics over the past 15 years have provided new insights into the responsible genes and pathogenic mechanisms of cardiovascular disease (eFig. 100.0.1). Some of these diseases are individually quite prevalent. Many of the most common diagnoses, such as "stroke," "heart attack," "hypertension," or "heart failure," subsume several distinct disorders. Other cardiovascular conditions are quite rare but have proven instructive in terms of the etiology and pathogenesis of common disease processes, such as atherosclerosis, aneurysms, and dysrhythmia. Mendelian disorders may be rare and can be caused by mutations in a single gene with profound consequences. Many of the more common disorders are not simply inherited, yet have a few or perhaps many genes that

stochastically interact with each other and the environment to produce pathology.



***e*FIGURE 100.0.1** Inherited disorders of the cardiovascular system. Ideograms of the 22 autosomes and the X and Y chromosomes are shown with their Giemsa banding patterns. Bands are numbered to the left of each ideogram. Known loci for autosomal dominant, autosomal recessive, and X-linked cardiovascular disorders are shown to the right of each ideogram. When disease-causing mutations have been identified in specific genes at a given locus, the gene is written in parentheses below the locus name. AF, familial atrial fibrillation; ARLK1, activin receptor-like kinase 1; ARVD, arrhythmogenic right ventricular dysplasia; AT, ataxia-telangiectasia; ATM, ataxia-telangiectasia mutated gene; AVSD, atrioventricular septal defect; beta-MHC, beta-myosin heavy chain; CACNL1A4, calcium channel, L type, alpha-1 polypeptide, isoform 4; CCM, cerebral cavernous malformations; COL3A1, collagen type III alpha 1 gene; DCM, dilated cardiomyopathy; EDIV, Ehlers-Danlos type IV; EDVI, Ehlers-Danlos type VI; EvC, Ellis-van Creveld syndrome; FHC, familial hypertrophic cardiomyopathy; FHM, familial hemiplegic migraine; FrA, Friedreich's ataxia; HERG, human ether-a-go-go-related gene; HMID, hereditary multi-infarct dementia; HOS, Holt-Oram syndrome; JAG1, Jagged-1 gene; JUP; plakoglobin; KVLQT1, potassium voltage-gated long QT syndrome 1 channel; LQT, long QT syndrome; MYBPC, myosin binding protein C; MYL2, regulatory ventricular myosin light chain; MYL3, essential ventricular myosin light chain; NF1, neurofibromin; ORW, Osler-Rendu-Weber syndrome; PPH, familial primary pulmonary hypertension; RyR2, ryanodine receptor; SCN5A, sodium channel, voltage-gated, type V, alpha polypeptide; SVAS, supravalvular aortic stenosis; TAPVR, total anomalous pulmonary venous return; TBX5, T-box 5 transcription factor; TIE2, endothelial cell specific receptor tyrosine kinase; VCFS, velocardiofacial syndrome; VHL, von Hippel-Lindau syndrome/gene; WH, Wolf-Hirschhorn syndrome; WPW, Wolff-Parkinson-White syndrome.

Monogenic cardiovascular disorders can be inherited as autosomal dominant, autosomal recessive, or X-linked traits. A rapidly increasing number of the genes responsible for such disorders have been mapped to specific chromosomal regions by linkage analysis and identified by candidate gene or positional cloning approaches (eFig. 100.0.1) (4,5). The "working draft" of the human genome sequence will greatly facilitate identification of additional genes. A recent tabulation of genes that have been mapped and are associated with human phenotypes numbers just more than 1,000; just over one-fourth involve the cardiovascular system (5).

Analysis of the genetics of common disease is far more complicated, whether in terms of populations, families, or molecules, than that for simply inherited conditions. Nonetheless, considerable progress has been made, both in experimental animals and in humans, in identifying genes that contribute to the cause, pathogenesis, or both of common diseases such as coronary artery disease and hypertension. In many instances, specific genetic variations that confer an increased risk of developing a condition can now be identified before symptoms develop. The challenge is to devise approaches to modulating the risk in those so identified.

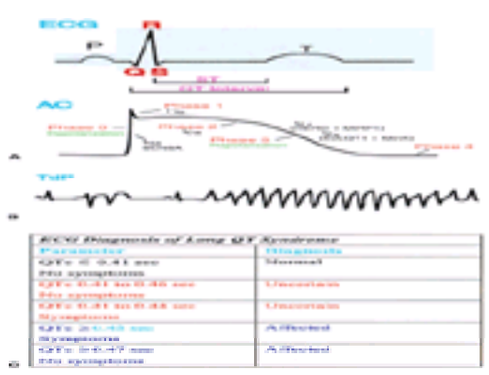
This chapter reviews the major advances in the molecular genetics of single gene disorders of the cardiovascular system. The genetics of complex diseases, such as coronary artery disease and hypertension, is covered in other chapters in this textbook.

DISORDERS OF CARDIAC RHYTHM AND CONDUCTION

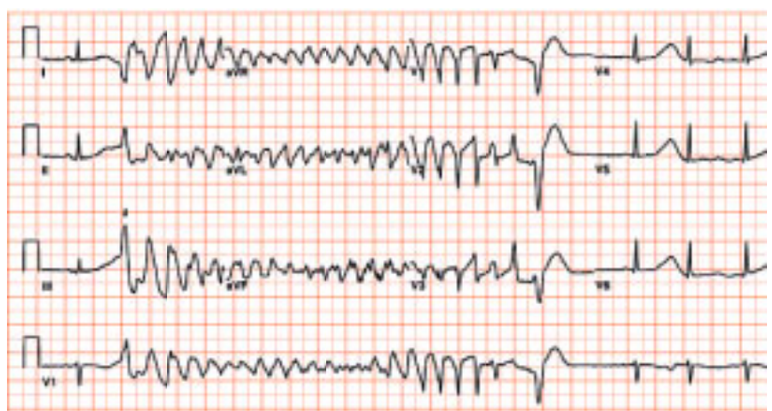
Cardiac arrhythmias are a common cause of morbidity and mortality, accounting for 300,000 to 400,000 sudden deaths each year in the United States alone (6,7). A number of mendelian conditions account for an unknown but clearly underestimated fraction of this mortality.

Long QT Syndrome

LQT is characterized by prolongation of the QT interval and T-wave abnormalities on electrocardiograms (ECGs) and symptoms of syncope, seizures, and sudden death, usually from a specific ventricular arrhythmia, *torsades de pointes* (8,9 and 10). Two inherited forms of LQT have been reported: autosomal dominant LQT (Romano-Ward syndrome) with normal hearing (8,9) and the much rarer autosomal recessive LQT (Jervell-Lange-Nielsen syndrome) associated with congenital deafness (9,11). It appears that patients with Jervell-Lange-Nielsen syndrome have a more adverse course and higher rate of sudden death. The primary defect at the tissue level involves cardiac repolarization, and the prolonged QT interval, when corrected for heart rate, is usually (but not always) evident on standard 12-lead ECG (*e*Fig. 100.0.2). Autosomal dominant LQT has an incidence of approximately 1 per 10,000, without apparent ethnic or geographic predilection (12,13). A set of clinical criteria to assist in diagnosis has been developed (*e*Fig. 100.0.2) (14). Although most clinical events are "triggered" by excitement, exercise, emotional upset, and the like, sudden death can occur during sleep. Some have suggested LQT as a cause of sudden infant death syndrome (15,16 and 17).



***e*FIGURE 100.0.2 A:** Temporal relationship between the electrocardiogram (ECG) and the cardiac action potential (AC). **B:** A representative ECG pattern for torsades de pointes (TdP). **C:** A conservative diagnostic criterion for long QT (LQT) syndrome. This diagnostic system has been successful in identification of LQT genes (18).



A 51-year-old female patient with torsades de pointes.

Molecular Genetics

The first LQT gene was mapped to chromosome 11p15.5 (*LQT1*) in 1991 (18). Since then, at least five other genetic loci for LQT have been identified on chromosome 7q35–36 (*LQT2*) (19), 3p21–24 (*LQT3*) (19), 4q25–27 (*LQT4*) (20), 21q22 (*LQT5*) (21), and 21q22 (*LQT6*) (22), and further locus heterogeneity exists. Five disease genes have been cloned or identified, and mutations have been described in each gene. *KVLQT1* (*LQT1*), *HERG* (*LQT2*), *KCNE1* (*LQT5*), and *KCNE2* (*LQT6*) all encode potassium channel subunits. *SCN5A* (*LQT3*) encodes the cardiac sodium channel protein. Heterozygous mutations in these genes cause autosomal dominant LQT. Homozygous or compound heterozygous mutations in *KVLQT1* and *KCNE1* cause Jervell-Lange-Nielsen syndrome. The LQT gene on chromosome 4q25–27 has been mapped in one family, but it has not been cloned yet.

Cardiac Potassium Channel Gene KVLQT1

KVLQT1, the LQT1 gene on chromosome 11p15.5, is the first novel gene cloned for LQT (23). This gene encodes a potassium channel alpha-subunit with a conserved potassium-selective pore-signature sequence flanked by six transmembrane-spanning segments (S1 to S6). People who are heterozygous for mutations in *KVLQT1* are at risk for autosomal dominant LQT. However, people who have mutations in both of their *KVLQT1* alleles have the more severe disease, autosomal recessive LQT with congenital deafness (24,25). Mutations in *KVLQT1*, when heterozygous, cause loss of channel function, altered channel gating, and/or a dominant-negative effect (26) in which the mutant form of the channel subunit interferes with the function of the normal form. The KVLQT1 protein normally functions by interacting with MinK, a short potassium channel subunit with a mere 130 amino acids and only one transmembrane-spanning segment (27,28). The physical interaction between KVLQT1 and MinK produces the slowly activating potassium current (I_{Ks}) in cardiac myocytes.

Various ion currents such as I_{Ks} are responsible for the different phases of the cardiac action potential (CAP) (eFig. 100.0.2). One CAP corresponds to one heart beat. The time course of one CAP can be divided into five phases: upstroke of rapid depolarization (phase 0); rapid repolarization following the peak (phase 1); a plateau (phase 2); rapid repolarization (phase 3); and the period between the maximum negativity (maximum diastolic potential) and the upstroke of the next action potential (phase 4) (eFig. 100.0.2) (29,30). The I_{Ks} potassium current acts at the repolarization phase (phase 3). KVLQT1 mutations reduce the repolarizing cardiac I_{Ks} current, causing delayed repolarization and prolongation of the CAP duration, and prolongation of the QT interval on ECG.

Cardiac Potassium Channel Gene *HERG*

The *LQT2* gene on chromosome 7q35–36 was identified as *HERG*, which encodes a cardiac potassium channel core–forming subunit with six transmembrane segments (31). This channel ordinarily generates the rapidly activating delayed rectifier potassium current (I_{Kr}) in the heart. LQT-associated mutations in *HERG* act through either a loss-of-function or a dominant-negative mechanism (32). The I_{Kr} potassium current is a major current at the repolarization phase of CAP. HERG mutations reduce the repolarizing cardiac I_{Kr} current, thus causing prolongation of the CAP duration, leading to prolongation of the QT interval on ECG.

Cardiac Sodium Channel Gene *SCN5A*

The gene associated with LQT3 on chromosome 3p21–24 is the cardiac sodium channel gene, *SCN5A* (12,33). It encodes a large protein of 2,016 amino acids with a putative structure of four homologous domains (DI-DIV), each of which contains six membrane-spanning segments (S1 to S6) (34). The sodium current I_{Na} generated by this channel is responsible for the depolarization phase of the CAP and contributes some current at the plateau phase. LQT-causing mutations in *SCN5A* act through a gain-of-function mechanism, in which the mutant channel functions, but with altered properties. Four *SCN5A* mutations (DKPQ, N1325S, R1644H, E1784K) generate the persistent noninactivated sodium current in the plateau phase of the CAP (35,36,37,38 and 39). One *SCN5A* mutation (D1790G) shifts steady-state inactivation by –16 mV in the presence of the $beta_1$-subunit (40). The E1784K mutation shifts the voltage dependence of steady-state inactivation toward more negative potentials (5 mV), and coexpression with the $beta_1$-subunit exaggerates the negative shift. The mutation R1623Q increases the probability of long openings and causes early reopenings, producing a threefold prolongation of sodium current decay (41,42). Although the LQT-causing mutations in *SCN5A* produce variable degrees of altered channel function, they all lead to the increase of inward plateau sodium current, prolonging the action potential duration and the QT interval on ECG.

Cardiac Potassium Channel Gene *KCNE1* (*MinK*)

As in *KVLQT1*, heterozygous mutations in *MinK* cause autosomal dominant LQT, but homozygous or compound heterozygous mutations in *MinK* cause autosomal recessive LQT (21,43). MinK interacts with KVLQT1 and HERG, recapitulating I_{Ks} with KVLQT1 and augmenting the amplitude of I_{Kr} generated by HERG (44). Different MinK mutations appear to have different effects on KVLQT1 and HERG (44). Mutation V47F alters I_{Ks} currents, and increases the HERG current. W87R alters I_{Ks} currents only. D76N suppresses both KVLQT1 and HERG currents. Mutant L51H channels are processed improperly and interact with neither KVLQT1 nor HERG.

Cardiac Potassium Channel Gene *KCNE2*

This gene, also called *MiRP1*, for minK-related peptide 1, encodes an integral component of a potassium channel. This gene has high homology with KCNE1; their close linkage (70 kb apart on chromosome 21q22) suggests that one arose as a result of gene duplication of the other. Mutations in *KCNE2* cause LQT6 (22). MiRP1 is a small integral membrane subunit that assembles with HERG to form I_{Kr}. Recently, MiRP1 was shown to interact with KVLQT1, resulting in a great change of the amplitude and gating properties of the KVLQT1 current (45).

The KCNE family includes another member, *KCNE3* (46), but no mutations in *KCNE3* were reported in LQT patients.

Potassium Channel Gene *Kir2.1* and Andersen's Syndrome

Mutations in the Kir2.1 inward rectifier potassium channel were recently identified in patients with Andersen's syndrome, which is characterized by QTc prolongation, periodic skeletal muscle paralysis, and mild dysmorphic features (46a). Kir2.1 mutations act by either loss-of-function mechanism or a dominant negative mechanism. Kir2.1 consists of only two transmembrane segments, M1 and M2, flanking a pore region and may generate the I_{K1} potassium current at the terminal repolarization phase (phase 3) and for maintenance of the cardiac resting potential.

Genotype-Phenotype Correlation in Long QT Syndrome

Mutations in *KVLQT1* and *HERG* cause approximately 40% of LQT cases, respectively, whereas mutations in *SCN5A* are associated with 10% of cases (47). Mutations in *KCNE1* and *KCNE2* are rare. Patients with LQT1 tend to have frequent exercise-related cardiac events, whereas most with LQT3 experience cardiac events during sleep or at rest. Patients with LQT2 may experience cardiac events both at rest and during exercise. The risk of cardiac events is higher in LQT1 and LQT2 than in LQT3; however, the likelihood of dying during a cardiac event is significantly higher among LQT3 patients (48). LQT1, LQT2, and possibly LQT3 genotypes are associated with different but typical ST-T–wave patterns on ECG (49).

Diagnosis, Genetic Testing, and Treatment

LQT can be diagnosed with reasonable certainty if QTc is 0.47 second or longer for asymptomatic individuals or if QTc is 0.45 second or longer for symptomatic individuals (29,30). LQT is not likely if QTc is less than 0.41 second in males and less than 0.43 second in females. Many mutation carriers as well as normal people have QTc ranging from 0.41 second to 0.46 second, which significantly limits the power of ECG diagnosis of LQT patients. Sudden death occurs in 10% to 30% symptomatic LQT patients (13), and it may occur with the first syncope. These factors make genetic testing extremely important. Current genetic testing for LQT patients is carried out only in research laboratories. Only positive results—that is, identification of a mutation—confirm the diagnosis.

The identification of LQT genes has led to the development of gene-specific therapies for LQT patients (30). Sodium channel–blocking agents such as mexiletine and flecainide can shorten QTc for LQT3 patients (50,51). Raising the serum potassium concentration shortens QTc for LQT2 patients (52). Potassium channel–opening agents and verapamil may be beneficial to patients with potassium channel mutations (13). All these therapies are at the investigational stage, and it is not clear whether these therapies can eliminate life-threatening ventricular arrhythmias.

All symptomatic patients as well as all asymptomatic children require treatment (13). For most LQT patients, administration of a beta-blocker is the initial choice of therapy. Beta-blockers are effective in patients with KVLQT1 and HERG mutations. Other therapeutic options include pacing and implantation of a cardioverter-defibrillator in combination with beta-blockers.

Idiopathic Ventricular Tachycardia and Ventricular Fibrillation

Idiopathic Ventricular Fibrillation with Right Bundle Branch Block and ST-Segment Elevation ("Martini"-Brugada Syndrome)

IVF is ventricular fibrillation without underlying structural heart disease and other electrolyte disorders such as LQT. IVF can be classified into two types: IVF with normal ECG and IVF with an ECG feature of right bundle branch block and persistent ST-segment elevation (STE) in leads V1 to V3 (IVF with STE) (Fig. 100.1), which was first described by Martini et al. and is now often referred to as *Brugada syndrome* (53,54 and 55). In a small percentage of patients with IVF, a family history of sudden death or even IVF can be found, with inheritance as an autosomal dominant pattern (56).

FIGURE 100.1 Twelve-lead electrocardiograms (ECGs) showing typical features of idiopathic ventricular fibrillation with right bundle branch block and ST-segment elevation (STE) ("Martini"-Brugada syndrome). **A:** ECG recorded immediately after the patient arrived at the emergency room because of an episode of syncope and seizures. The episode was triggered by cold-related fever. Note the presence of STE and development of polymorphic ventricular tachycardia (VT) after a ventricular premature contraction. **B:** ECG recorded 11 hours after the syncopal episode. The patient recovered after a cardioversion. Note the typical STE (mainly in lead V2). After the episode, a defibrillator was implanted in the patient. (Unpublished data, Carlos Oberti, Palmira Vanzini, Alvaro Rivara, and Qing Wang.)

In 1998, the first gene for IVF with STE (Brugada syndrome) was identified as *SCN5A*, the cardiac sodium channel gene (56). *SCN5A* mutations were also identified in IVF patients without STE on ECG (56,57). The IVF mutations are functionally different from *SCN5A* mutations associated with LQT. The IVF mutations act by a loss-of-function mechanism (16,56,58,59). *SCN5A* mutations may account for 15% to 35% of IVF patients (56,60), and other genes are involved and remain to be identified.

Catecholaminergic Ventricular Tachycardia

Families with stress-induced ventricular tachycardia [catecholaminergic ventricular tachycardia (CVT)] occurring in the structurally intact heart have been reported (61). Clinical symptoms of CVT include a family history of juvenile sudden death and stress-induced syncope. The inheritance pattern appears to be autosomal dominant, and a genetic locus for CVT was mapped to 1q42–q43 (61). The gene for CVT has recently been identified as the cardiac ryanodine receptor gene (*RYR2*) (62,63). Mutations in *RYR2* (62,63) were identified in autosomal dominant families presenting with bidirectional ventricular tachycardia that was reproducibly induced by exercise stress testing and/or isoproterenol infusion without structural heart abnormalities. As discussed later, *RYR2* mutations also cause arrhythmogenic right ventricular dysplasia (ARVD).

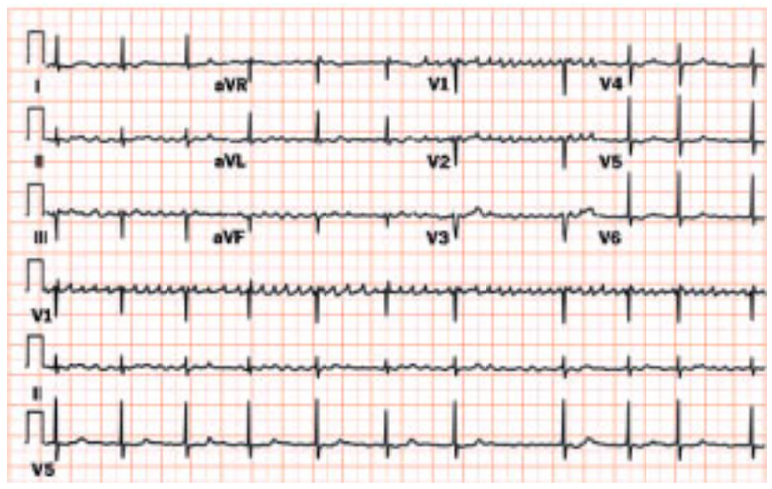
Polymorphic ventricular tachycardia can segregate in families as an autosomal recessive trait, and an autosomal recessive polymorphic ventricular tachycardia gene was mapped to 1p13–21 (64); however, the gene remains to be cloned.

Right Ventricular Outflow Tract Tachycardia

Right ventricular outflow tract (RVOT) tachycardia is a paroxysmal IVT with the focal origin localized to the RVOT. A functional mutation of F200L in the guanosine triphosphate binding protein inhibitory subunit alpha-i2 gene (GNAI2) on chromosome 3p21 was identified in a patient with RVOT tachycardia (65). Mutation F200L is a somatic mutation because it was identified in a biopsy sample from the arrhythmogenic focus but not from peripheral lymphocytes or the sample distant from the arrhythmogenic focus. This finding raises the possibility that common RVOT tachycardia is a somatic cell genetic disorder caused by mutations in specific somatic cells.

Atrial Fibrillation

In atrial fibrillation (AF), the atrial rate is very fast, typically more than 400 beats per minute; intermittent conduction across the AV nodes leads to an irregular ventricular rhythm. The characteristic ECG features include irregular atrial activation and a lack of a repetitive pattern of coordinated atrial activity. The overall prevalence rate of AF is 0.89% in the United States, but the rate increases to 5.9% among individuals older than age 65 (66). The clinical manifestations of AF range from thromboembolism, reduced left ventricular function, palpitations, dizziness, breathlessness, and chest pain to cardiac failure and stroke. AF is the cause of stroke for 30% of victims older than age 65 years (67). AF is associated with changes in distribution of ion channels such as reduction of calcium current I_{CaL} and transient outward potassium current I_{TO}, loss of atrial myocytes, and increasing fibrosis (68). Familial instances of AF are rare. An autosomal dominant AF gene has been mapped to chromosome 10q22–24 (69), but the gene remains to be cloned.



Atrial fibrillation. Narrow complex QRS with irregular RR intervals. Ventricular rate is controlled.

Conduction Defects

Interference with conduction across the AV block results in delayed, intermittent, or absent conduction of electrical impulses from the atria to the ventricles. AV conduction can be impaired in either the AV node or His-Purkinje system (AV bundle and bundle branches). If complete heart block (third-degree AV block) occurs, the ventricles can no longer be activated by impulses propagated from the atria, leading to syncopal episodes, Stokes-Adams seizures, or sudden death. The first gene for progressive familial heart block (PFHBI) was mapped to chromosome 19q13.2–13.3 (70), but the gene remains to be cloned. PFHBI is characterized by right bundle branch block and/or left anterior hemiblock with broad QRS complexes and progression to complete heart block. Inheritance is autosomal dominant. The second genetic locus for progressive familial heart block or progressive cardiac conduction defect was mapped to 16q23–24 (71), but the gene remains to be cloned.

Two *SCN5A* mutations (a splicing mutation at the splice donor site of intron 22 and a 1-bp deletion at position 5280 that creates a premature stop codon) were

identified in two separate families with progressive cardiac conduction defect, also referred to as *Lenègre* or *Lev disease* (72). Close examinations of the reported ECGs revealed mild STE in two of the patients and suggest the possibility that the two mutations reported by Schott et al. (72) may be associated with a variant of IVF with STE (Brugada syndrome).

Wolff-Parkinson-White Syndrome

The Wolff-Parkinson-White syndrome (WPW) is cardiac conduction defect characterized by a short PR interval, an increased duration of QRS complex, and a delta wave on ECG, and supraventricular tachyarrhythmias. A single mutation (R302Q) in the gamma$_2$-subunit of AMP-activated protein kinase was identified in two families with WPW, establishing a molecular basis for WPW (72a).

CONGENITAL STRUCTURAL HEART DISEASE

Many structural congenital cardiac anomalies have anatomic and physiologic manifestations that can be diagnosed at birth or even prenatally. Such anomalies occur in more than 5% of all live births and 10% of stillborns (73,74). Although some of these are sporadic events that result from somatic or *de novo* germline mutations, a significant portion represent familial transmission of disease. The increased risk of structural congenital heart disease in the first-degree relatives of patients with structural cardiac anomalies has long been recognized (75), and autosomal dominant, autosomal recessive, and X-linked modes of transmission have all been reported (5,75).

Mendelian patterns of inheritance can also vary in some disorders with a recognized heritable genetic basis. For instance, situs inversus can occur as an isolated heritable finding or as a component either of visceral heterotaxy syndromes (X-linked or autosomal recessive) or of autosomal recessive Kartagener syndrome. Molecular genetic analysis of such disorders has been limited by kindred size and low penetrance. Insights may be gleaned, however, from murine models (e.g., mutations in the *iv* and *inv* genes can produce murine *situs inversus*) (76,77). Macroscopic chromosomal aberrations and rearrangements (including trisomies of chromosomes 13, 18, and 21) have been associated with variable forms of congenital structural heart disease in the context of complex extracardiac abnormalities. Subtle mutations occur more often, however, and can cause discrete congenital cardiac malformations as well as syndromes with cardiac components. Recent advances in molecular biology have begun to elucidate the fundamental genetic mechanisms underlying such heritable cardiac disorders.

Septation Defects

Defects in the atrial and ventricular septa are the most commonly reported congenital cardiac anomalies. Studies have reported an incidence of greater than 5% of live births (74,78), and this is likely to be an underestimate given that both ventricular septal defects (VSDs) and ASDs may occur in isolation and may close spontaneously during infancy. Many VSDs as well as ASDs occur in the setting of other cardiac and extracardiac anomalies and can have grave physiologic consequences such as the development of Eisenmenger syndrome.

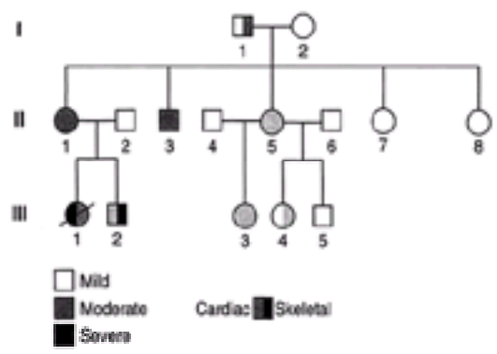
Holt-Oram Syndrome

Clinical Manifestations

Holt-Oram syndrome is characterized by cardiac septation defects in the setting of upper limb deformity (79). It is the most common form of “heart-hand syndrome” and occurs in at least 0.95 per 100,000 individuals (80). All individuals affected by Holt-Oram syndrome exhibit some degree of malformation of the arms or hands (*e*Fig. 100.1.1); such malformation is frequently asymmetric and may be unilateral. Although the initial descriptions of this syndrome focused on abnormalities of the thumb (typically triphalangism or aplasia) (*e*Fig. 100.1.1A), the most common manifestations are carpal bone malformations or fusions (5,79,80). These may be evident only radiographically and in fact may be the only clinical evidence of Holt-Oram syndrome in a given patient. On the other hand, limb malformation may be sufficiently severe for individuals to present with phocomelia (*e*Fig. 100.1.1B), and the syndrome has been called a “pseudo-thalidomide syndrome.”

***e*FIGURE 100.1.1** Skeletal manifestations of Holt-Oram syndrome. **A:** This individual exhibits a minimally deforming triphalangeal thumb on her right hand. Her left thumb is mildly displaced because of carpal bone malformation. Note the bilateral acrocyanosis secondary to her Eisenmenger’s syndrome from her uncorrected ventricular septal defect. **B:** This individual exhibits severe bilateral skeletal deformity. Such phocomelia found in individuals affected by Holt-Oram syndrome prompted some clinicians to call it a “pseudo-thalidomide” syndrome.

Approximately 75% of Holt-Oram syndrome patients (81) have some cardiac abnormality (*e*Fig. 100.1.2). In most cases, these defects are ASD or VSD, which range in size, number, and location. Most ASDs are ostium secundum defects, and most VSDs are muscular. Severely affected individuals may present with multiple VSDs (sometimes termed “Swiss cheese septum”) as well as ASDs, and rare individuals with AV canal defects have been reported. Many Holt-Oram syndrome patients will present with conduction disease (ranging from sinus bradycardia and first-degree AV block to AF and high-grade AV block). Conduction disease occurs independent of the presence or size of septation defects in a given patient. Other cardiac anomalies, including anomalous pulmonary venous drainage, abnormal isomerism, mitral valve prolapse, as well as persistent left superior vena cava and more rarely hypoplastic left heart syndrome and tetralogy of Fallot, have all been reported to occur in some patients with Holt-Oram syndrome (5).



***e*FIGURE 100.1.2** Variable expression of a TBX5 mutation in the Holt-Oram syndrome. Holt-Oram syndrome in Family F is caused by a premature stop codon in the TBX5 gene (2). Despite all individuals being affected by the same DNA mutation in TBX5, the manifestations of the disease vary considerably from individual to individual. Square symbols denote males, and circles females. A slash denotes a deceased individual. Symbols are filled on the left to denote the cardiac manifestations and on the right to denote the skeletal manifestations of the TBX5 mutation in the particular individual. Severity of the cardiac or skeletal malformations are shown by the density of shading as indicated in the key. Note that the severity of cardiac and skeletal malformations are often not equivalent in any individual. Moreover, a particular individual’s phenotype severity does not predict how his or her offspring will be affected.

Genetic Studies

Holt-Oram syndrome is an autosomal dominant disorder. Sporadic disease may represent a *de novo* germline mutation—that is, individuals who present with sporadic disease usually can transmit the disorder to their offspring. Despite its highly variable pattern of expression, Holt-Oram syndrome is highly penetrant in affected families.

Initial linkage analysis studies (82,83) revealed that the gene defect for Holt-Oram syndrome resides on the long arm of chromosome 12 (although this locus does not account for all other heart-hand syndromes). Recent studies (84,85) have demonstrated that Holt-Oram syndrome is caused by mutations on chromosome 12q24.1 that inactivate the *TBX5* gene. TBX5 is a member of the T-box family of transcription factors, and it is expressed in the embryonic human heart and forelimb (86,87). Atrial expression is much greater than ventricular expression in humans, mice, and chicks (86,87,88,89 and 90). It is currently unknown which genes are activated by this transcription factor, and the precise mechanism whereby *TBX5* haploinsufficiency causes cardiac and limb malformation is under active investigation. Studies correlating *TBX5* genotypes with Holt-Oram syndrome phenotypes suggest that mutations that produce truncation of the TBX5 protein have a higher incidence of both severe cardiac and severe limb malformation than less common missense mutations, which only alter a single amino acid (91). In the case of missense mutations, their location within the T-box appears to mediate the severity of cardiac versus limb malformations (91,92 and 93). The role of *TBX5* mutations in isolated septation defects and common atria syndromes also remains to be demonstrated. Detection of *TBX5* mutations in the families of Holt-Oram syndrome patients now permits accurate diagnosis of the syndrome even in subtly affected individuals (eFig. 100.1.2). In the future, delineation of TBX5-mediated regulation of cardiac development may provide new approaches to gene therapy for septation defects.

Ellis-van Creveld Syndrome

Like Holt-Oram syndrome, Ellis-van Creveld syndrome represents an association of cardiac septation defects with skeletal abnormalities (94). Transmitted in an autosomal recessive pattern, Ellis-van Creveld syndrome is most obviously characterized by dwarfism with particularly evident shortening of the distal extremities. Other features include polydactyly, carpal bone abnormalities, nail dystrophy, upper lip deformity, and premature dental eruption. Cardiac abnormalities typically include ASDs and common atrium. Linkage analysis (95) of interrelated Amish families and unrelated Hispanic kindreds affected by Ellis-van Creveld mapped the genetic defect to a locus at chromosome 4p16. More recently, positional cloning studies have identified disease-causing mutations in the novel *EVC* gene, whose function remains unknown (96). Cytogenetic abnormalities of distal chromosome 4p have been associated with ostium secundum ASDs in the setting of craniofacial abnormalities in the Wolf-Hirschhorn syndrome (97). The relationship (if any) of the chromosome 4p Ellis-van Creveld locus to this syndrome is as yet unknown.

Familial Atrial Septal Defects with Atrioventricular Block

In the syndrome of familial ASD with AV block, ASDs occur without associated skeletal malformation, as seen in Holt-Oram or Ellis-van Creveld syndrome. Some individuals exhibit conduction delay manifest as progressive AV block. This condition is transmitted in families as an autosomal dominant trait. Schott et al. (98) used linkage analysis to study families with this disorder and demonstrated that the disease gene mapped to chromosome 5q35. They subsequently applied a candidate gene strategy to identify the disease gene as the *NKX2.5* gene at this locus. *NKX2.5* is a member of the large NK homeobox transcription factor gene family. The prototypical member of this family is the *Drosophila* tin man gene, without which the fly heart fails to develop.

Schott et al. (98) and Benson et al. (99) demonstrated a number of mutations in the *NKX2.5* gene that cause familial ASD with AV block. These mutations include not only nonsense and other mutations that are predicted to result in *NKX2.5* haploinsufficiency but also a number of missense mutations. Recently, Kashahara et al. (100) studied a number of truncated forms of NKX2.5 as well as mutant NKX2.5 isoforms resulting from missense mutations observed in humans. They observed decreased NKX2.5 activity in all cases not only via NKX2.5 haploinsufficiency but also through impaired DNA binding or defective protein-protein interactions with essential cofactors.

Of note, although Lyons et al. (101) had initially noted that knockout mice who were homozygous null for *NKX2.5* died during embryogenesis with a failure of cardiac looping, subsequent analyses (101,102) have demonstrated both ASDs and conduction disease in mice heterozygous null for *NKX2.5*. Benson et al. (99) noted a number of protean manifestations of *NKX2.5* mutations in human patients. Not only do individuals with *NKX2.5* mutations exhibit ASDs, but also they may be affected by a number of other forms of congenital structural heart disease, including VSDs, tetralogy of Fallot, subvalvular aortic stenosis, pulmonary atresia, double-outlet right ventricle, and Ebstein's anomaly. However, no genotype-phenotype correlations have been observed (98,99,103) to allow the association of any particular form of congenital heart disease with any given single or group of *NKX2.5* mutations. Thus, the mechanism whereby *NKX2.5* mutations result in ASDs versus other forms of congenital heart disease remains unknown.

Familial Atrioventricular Defects

Isolated AV canal defects may also occur as sporadic or familial disease. These defects have most commonly been associated with trisomy of chromosome 21 in Down syndrome. From a cardiac perspective, Down syndrome frequently manifests as an AV septal defect in association with a cleft mitral valve. Although fertility is often impaired in such individuals, the disorder is heritable. Moreover, somatic mosaicism is the rule, and thus there is considerable tissue-to-tissue variation in the effects of the trisomy 21. Although investigators have tried to identify "cardiac critical" regions on chromosome 21, no consensus has been reached; it is generally accepted that the syndrome reflects the effect of abnormalities in the copy number of multiple genes (104).

Familial AV defects can occur without trisomy 21. The disorder can be transmitted in pedigrees in an autosomal dominant fashion, and linkage analysis (105) of some such pedigrees has excluded the presence of any gene defect on chromosome 21. A genetic locus for this disorder on chromosome 1p has been described (106), but no specific gene mutation has yet been identified.

McKusick-Kaufman Syndrome

Only females express the full spectrum of abnormalities in autosomal recessive McKusick-Kaufman syndrome: postaxial polydactyly, cardiac septation defects, and hydrometrocolpos (a congenital vaginal web) (5). Originally identified in Old Order Amish, the locus for McKusick-Kaufman syndrome was mapped to 20p12 (107). The disease-causing gene (*MKKS*) was a previously unknown gene and encodes a protein homologous to the chaperonins (108). These proteins are involved in determining the three-dimensional structure of other proteins and could play important roles in development.

Total Anomalous Pulmonary Venous Return

Total anomalous pulmonary venous return (TAPVR) may occur in the setting of isolated or complex septation defects and isomerism as in Holt-Oram syndrome or cat-eye syndrome (see below). However, TAPVR can present as an isolated finding. Incidence of TAPVR may be as high as one per 15,000 live births (109). If the anomalous pulmonary venous drainage is total (vs. partial), unrepaired TAPVR can lead to progressive heart failure and pulmonary hypertension during the first year of life, with a consequent high mortality rate.

Nonsyndromic familial TAPVR can be transmitted as an autosomal dominant trait. Its expression is highly variable, and the disease penetrance is low, confounding genetic analysis. Nevertheless, genetic analysis (110) has demonstrated that the gene defect in some families localizes to the pericentromeric region of chromosome 4. A founder effect appears to account for the common locus in at least some of these families. However, the specific mutated gene has yet to be identified. In addition, it is clear that the disorder is genetically heterogeneous, and gene defects at other as-yet unidentified loci can also cause TAPVR. In one case, TAPVR in the setting of a variety of extracardiac malformations has been associated with a chromosome 2q31–q33 deletion (111).

Conotruncal Abnormalities

Conotruncal abnormalities may account for more than 15% of congenital heart disease (112) and include malformation of the ventricular outflow tracts or the developing branchial arches. On the basis of animal studies in which neural crest cells have been experimentally ablated, defects in neural crest cell function/migration in the primitive contruncus are thought to be at the root of these abnormalities. Despite reports of autosomal dominant and recessive transmission (5), genetic investigation of many human conotruncal disorders has generally been limited by the impaired survival of affected individuals. With the advent of modern surgical repair of such disorders, however, improved survival of individuals affected by conotruncal malformations, including transposition of the great vessels, truncus arteriosus, and double-outlet right ventricle, has aided molecular genetic studies of these disorders, particularly velocardiofacial syndrome (VCFS) and tetralogy of Fallot.

Velocardiofacial Syndrome

Clinical Features

Individuals affected by VCFS or Shprintzen-Goldberg syndrome present with characteristic abnormal facies (including an elongated nose and face with almond-shaped eyes and low-set ears) in the setting of cleft palate and velopharyngeal incompetence. Many VCFS patients exhibit developmental delay as well as a variety of axial skeletal abnormalities, genitourinary defects, gastrointestinal motility disorders, and ophthalmologic difficulties. Approximately one-third of VCFS patients present with structural cardiac disease (5), including tetralogy of Fallot, VSDs, and right-sided aortic arch. When individuals present as well with hypocalcemia and immunologic impairment (particularly T cell–mediated immunodeficiency) secondary to absent or hypoplastic thymus and parathyroid glands, the disorder is referred to as *DiGeorge syndrome*. DiGeorge syndrome and VCFS are now thought to represent variation within a single clinical disorder. The reported incidence is on the order of 1 per 4,000 births (113).

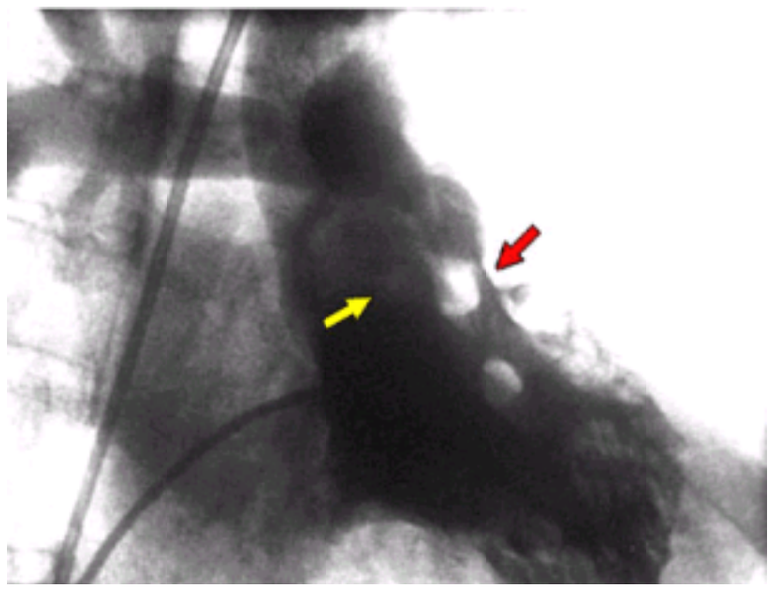
Genetic Studies

VCFS is an autosomal dominant disorder with both variable expression and decreased penetrance. Cytogenetic analyses of VCFS/DiGeorge syndrome patients led to its association with chromosome 22q11.2 deletions (114,115). Subsequent investigation demonstrated that even affected individuals without obvious cytogenetic abnormalities had microscopic deletions when they were evaluated by fluorescent *in situ* hybridization (FISH) with DNA probes specific to this region (114,115). A number of genes have been isolated from the 22q11.2 locus, but no single gene defect has yet been identified to cause VCFS. In fact, VCFS may reflect deletion of several contiguous genes at this locus, and the variation in the chromosomal abnormalities between patients may account for the differing clinical presentations. Recent efforts have sought to identify genes at chromosome 22q11.2, whose defect may specifically account for the cardiac versus the cranial malformations in VCFS. Deletion analyses of this region in mouse models (116) identified several critical genes that may contribute to the VCFS phenotype, including *Tbx1*, a T-box transcription factor gene with homology to the TBX5 gene mutated in Holt-Oram syndrome. Recent mouse knockout models of *Tbxl* haploinsufficiency have demonstrated that a 50% reduction in the *Tbxl* gene dose is sufficient in the mouse to produce aortic arch defects similar to VCFS in humans (116a,116b and 116c). Ongoing human analyses seek to identify TBXl-specific human mutations that might cause VCFS.

Establishment of densely spaced DNA probes at the 22q11.2 locus has made FISH an important diagnostic modality in this disorder (115). FISH analysis can be applied not only to blood samples from adults with equivocal diagnoses, but also to amniocentesis samples to provide prenatal diagnosis. Given the inability of current knowledge to predict structural disease manifestations from a given genetic defect, it will remain important, as with other DNA-based diagnoses, to follow FISH analysis with careful imaging studies of the affected adult or fetus.

Tetralogy of Fallot

Tetralogy of Fallot was initially thought to be a multicomponent disorder including a malalignment VSD with pulmonic stenosis, overriding aorta, and right ventricular hypertrophy. More recent nosology has considered tetralogy of Fallot a “monology”: failure of right ventricular infundibulum development with the other anatomic abnormalities secondary to this embryonic defect. This concept has been supported by experimental manipulation of the conus in chick embryos, which suggests that tetralogy of Fallot is one form of aberrant conotruncal development (117). Tetralogy of Fallot accounts for approximately 10% of congenital heart disease (118) and may occur in isolation or in association with other cardiac anomalies—for example, ASDs, AV septal defect, and persistent left superior vena cava, as well as complex syndromes such as Holt-Oram, Noonan’s, and Down. Tetralogy of Fallot frequently occurs in patients with noncardiac malformations that comprise the CHARGE association (*c*olobomata, *h*eart defects, cho*a*nal atresia, *r*etardation, *g*enital hypoplasia, and *e*ar abnormalities). Tetralogy of Fallot has been suggested to be transmitted in families in both autosomal dominant and recessive patterns (5).



Tetralogy of Fallot. This right anterior oblique right ventriculogram demonstrates some of the findings of tetralogy of Fallot with subpulmonic or infundibular stenosis (*red arrow*) and overriding aorta (*yellow arrow*) and prominent trabeculation of the right ventricle consistent with right ventricular hypertrophy.

VIDEO

Video 100.1 Parasternal short-axis view of tetralogy of Fallot. Note the ventricular septal defect just beneath the right coronary cusp of the aortic valve. The infundibular pulmonic stenosis can be seen superiorly while the pulmonary valve with its vegetation can be seen to the upper right of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 100.2 Parasternal long-axis view of tetralogy of Fallot. Note the ventricular septal defect and the aorta and aortic valve overriding the interventricular septum. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 100.3 Color Doppler in the apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect by color flow and the overriding aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 100.4 Apical five-chamber view of tetralogy of Fallot. Note the ventricular septal defect, the overriding aorta, and the right ventricular hypertrophy. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Evaluation of patients with tetralogy of Fallot and/or CHARGE association by a variety of investigators has shown that a variable but significant portion of these individuals has chromosome 22q11 microdeletions like VCFS patients (119). In one series, chromosome 22q11 microdeletions were present in 15% of tetralogy of Fallot patients as well as in 50% of interrupted aortic arch patients, 35% of truncus arteriosus patients, and 33% of posterior malalignment VSD patients (120). Although these microdeletions may be *de novo* events, they may be inherited from parents, and they can certainly be transmitted to offspring in an autosomal dominant fashion. In addition, individuals affected by the rare cat-eye syndrome (abnormal facies, inferior iris coloboma, preauricular pits or tags, anal deformity, and renal malformation), which shares features of the CHARGE association, also exhibit abnormalities of chromosome 22q that usually include a duplication of the 22q11 region (121,122 and 123). Cat-eye syndrome patients more often exhibit TAPVR than tetralogy of Fallot. Although 22q abnormalities certainly do not account for all conotruncal abnormalities, their high prevalence in this patient population mandates FISH evaluation of chromosome 22 in such individuals and their first-degree relatives for diagnostic and counseling purposes.

Single gene mutations have occasionally been identified in tetralogy of Fallot patients. As described above, *NKX2.5* mutations may be associated with tetralogy of Fallot (98,99,103). Additionally, mutations in the *JAG1* gene have also rarely been observed (124,125) in tetralogy of Fallot even in the absence of findings of Alagille syndrome, more commonly caused by *JAG1* mutations (see the section Pulmonic Stenosis). Mutational analysis of these genes in tetralogy of Fallot remains available only through research laboratories (see http://www.genetests.org/).

Cardiac Looping Defects (Heterotaxy, or Left-Right Malformations)

Many genes implicated in defining the left-right plan have been identified. Seminal discoveries were made by exploring two mouse mutants, *iv* (*inversus viscerum*) and *inv* (*inversion of embryonic turning*) (126). Homozygous *iv* mice display randomized left-right development of heart and viscera, whereas in mice homozygous for the *inv* mutation, the reversal of left-right asymmetry and cardiac looping is nearly 100% (*situs inversus*), and cysts are formed in the kidneys. The *iv* gene was cloned and named as *lrd* (left-right dynein), which encodes a protein homologous to the sea urchin axonemal dynein heavy chain, a minus-end directed microtubule-based motor protein (127,128). The *inv* gene encodes inversin, which contains 15 consecutive repeats of an Ank/Swi6 motif at its amino terminus (129).

Humans born with altered left-right asymmetry are said to have heterotaxy. Randomization (*situs ambiguus*) and complete reversal (*situs inversus*) of the normal left-right position of the organs (*situs solitus*) are forms of heterotaxy. *Situs inversus* is often not associated with any pathologic abnormalities, but *situs ambiguus* is almost always associated with abnormal visceral organs. Familial heterotaxy can occur as autosomal dominant, autosomal recessive, and X-linked disorders. Several genes have been identified for heterotaxy. In 1995, mutations in connexin 43 (*cx43*), a gap junction gene, were proposed in six patients associated with *situs ambiguus*, but these findings have not been confirmed (130). Mutations were also identified in the human *EBAF* (*LEFTY A*, chromosome 1q42.1) gene coding for a protein with homology to the members of transforming growth factor-b superfamily, the *ACVR2B* gene (chromosome 3p22–21.3) encoding the type II receptor for activins, gonadal polypeptide hormones (131,132), and EGF-CFC encoding a cofactor for Nodal-related signals among some left-right malformation cases (4,133). Mutations in the *ZIC3* gene, located on Xq24–27.1, cause X-linked heterotaxy. *ZIC3* codes for a putative zinc-finger transcription factor (134).

Familial Valvular Disease

Abnormalities of the aortic, pulmonic, mitral, and pulmonic valves are common associations of a variety of complex cardiac malformation syndromes. These syndromes exhibit all modes of transmission. Examples of heritable entities of which valvular abnormalities are major components are highlighted below.

Bicuspid Aortic Valve

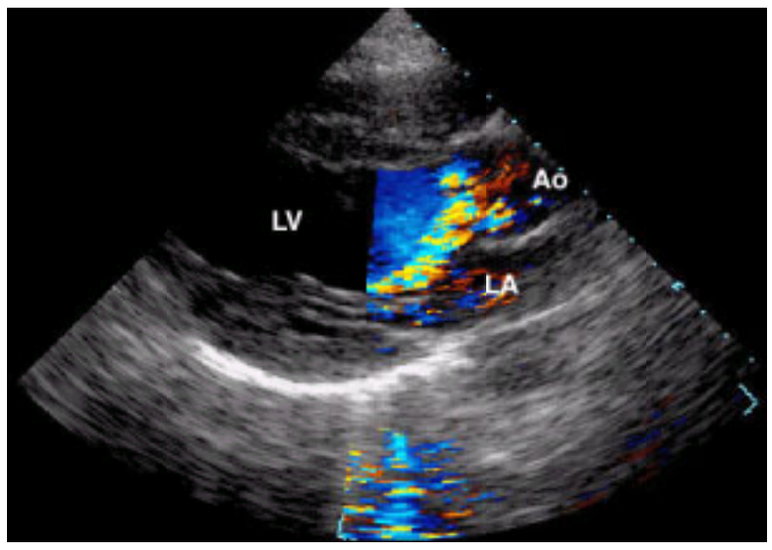
Bicuspid aortic valve is a common isolated finding; one series reported an incidence of 0.9% in 1,440 autopsies (135). In addition, this congenital malformation is an important cause of progressive aortic stenosis. At least 17% of cases of isolated bicuspid aortic valve have a familial occurrence (136). A reduced penetrance (particularly in females) for this heritable disorder has confounded genetic analysis. Nevertheless, identification of some families affected by bicuspid aortic valve has suggested an autosomal dominant mode of transmission (135). No autosomal chromosomal locus or gene defect has been associated with this disorder. Bicuspid aortic valve is, however, an important cardiac manifestation of Turner's syndrome (characterized by karyotype 45,XO), which affects approximately 3% of female fetuses (although few of these survive to term). As many as 50% of Turner's syndrome patients have bicuspid aortic valve and are at high risk for progressive aortic root dilatation and aortic valvar stenosis. Approximately 20% of Turner's syndrome patients also present with coarctation of the aorta (137).

VIDEO

Video 100.5 Congenital bicuspid aortic valve with mild aortic regurgitation (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

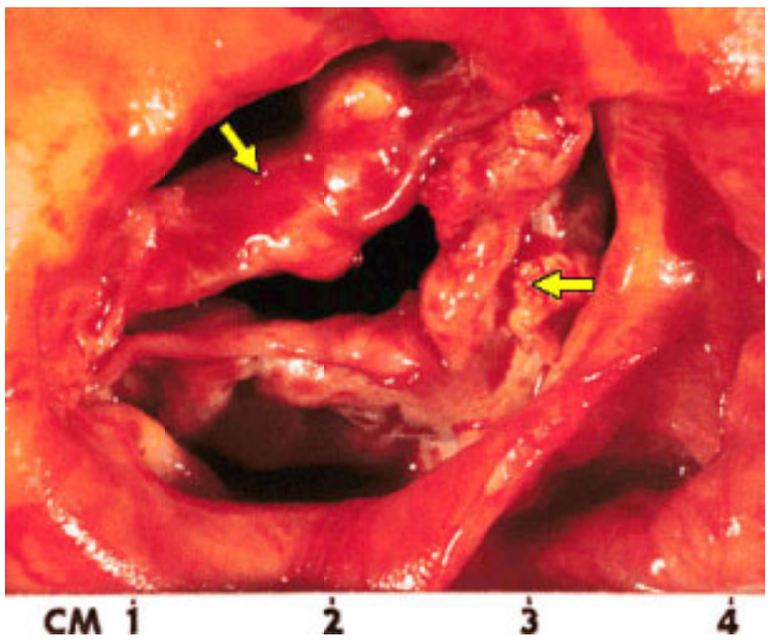
VIDEO

Video 100.6 Intraoperative transesophageal echo of a bicuspid aortic valve. There is fusion between the right coronary cusp (RCC) and left coronary cusp (LCC) with a raphe at 4 o'clock. This is the most common combination of leaflets to be fused. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

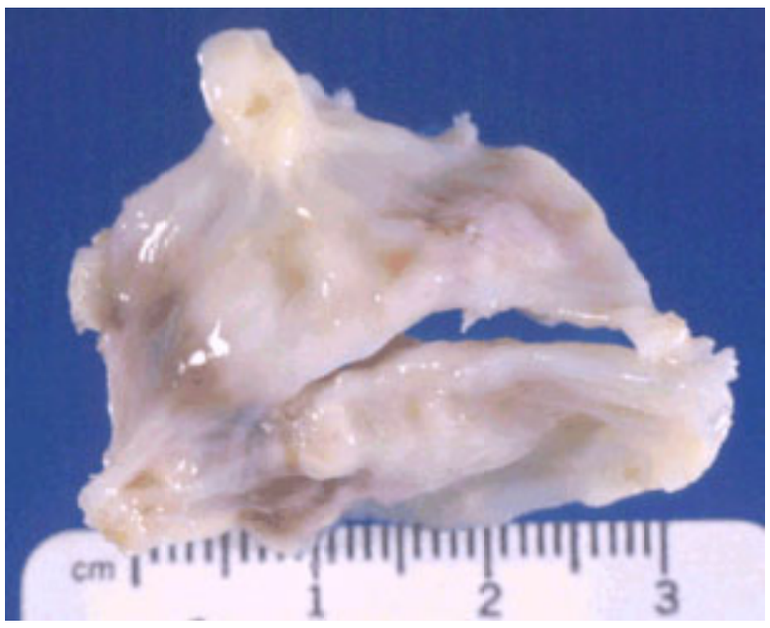


Parasternal long-axis view (transthoracic echo) with color Doppler demonstrating the posteriorly directed aortic insufficiency caused by prolapse of the anterior leaflet of a bicuspid aortic valve. Note that the jet hits the anterior mitral leaflet.

Parasternal long-axis view of a prolapsing anterior cusp (right coronary cusp + left coronary cusp fusion) of a bicuspid aortic valve (The prolapsing leaflet is demonstrated by the short arrow). The posteriorly directed aortic insufficiency that is produced causes the posterior deformation of the anterior mitral leaflet (designated by the long arrow) as the aortic insufficiency jet hits this leaflet.



Bicuspid aortic valve with calcific stenosis. The yellow arrows identify each of the valve leaflets.



Bicuspid aortic valve with calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Pulmonic Stenosis

Several examples of isolated familial pulmonic stenosis have been reported without a clear pattern of inheritance. However, valvular pulmonic stenosis is an important component of Noonan's syndrome. Noonan's syndrome, which like Turner's syndrome presents with lymphedema as well as skeletal and facial abnormalities, also presents with a variety of congenital cardiac abnormalities, most important, myxomatous degeneration of the pulmonic valve, causing stenosis and abnormal left ventricular hypertrophy (5). Noonan's syndrome is an important cause of infantile hypertrophic cardiomyopathy. Recent evidence (138) has demonstrated that this autosomal dominant syndrome is caused by a genetic defect that maps to chromosome 12q2. Tartaglia et al. (138a) have now demonstrated that mutations in the *PTPN11* gene, which encodes the protein tyrosine phosphatase SHP-2, cause Noonan's syndrome. *PTPN11* mutations account for approximately half of Noonan's syndrome.

VIDEO

Video 100.7 Transesophageal echo of a patient with congenital pulmonary stenosis. Note the severe hypertrophy of the right ventricular outflow tract, causing infundibular pulmonary stenosis as well as valvular pulmonary stenosis. The pulmonic leaflets are thin and pliable; however, there is marked doming caused by tethering of the leaflet tips. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 100.8 Coronary ectasia. These angiograms were obtained in a 40-year-old patient with Noonan's syndrome and no coronary risk factors. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

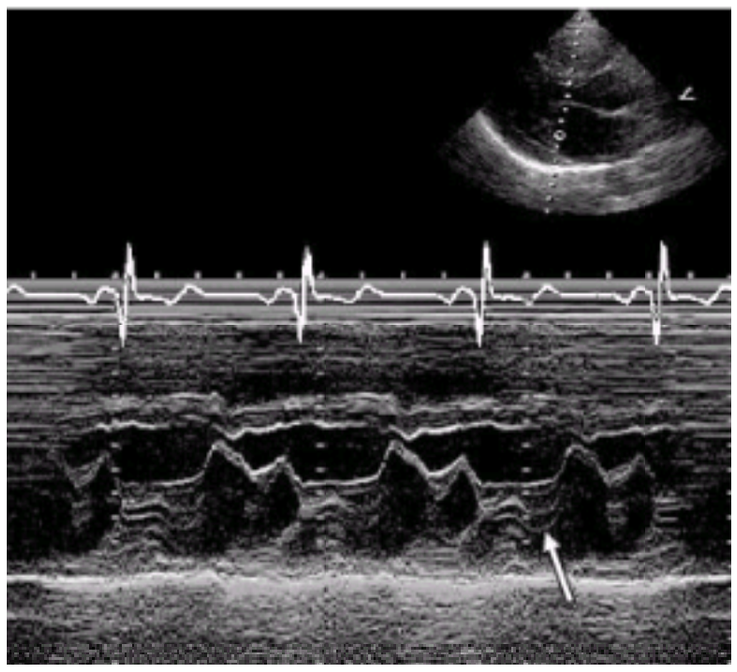
Some patients with pulmonic stenosis present with café au lait spots, short stature, and decreased intelligence, and this syndrome has been given the eponym of Watson syndrome. Watson syndrome is an autosomal dominant disorder. Despite the absence of neurofibromata in patients with Watson syndrome, this syndrome is allelic to neurofibromatosis and has been associated with both deletions and duplications within the neurofibromin (NF1) gene on chromosome 17q11.2 (139,140 and

141).

Pulmonic valvular and peripheral pulmonic arterial stenosis are also major components of Alagille syndrome, which is also characterized by abnormal facies, anterior chamber ocular abnormalities, and bile duct hypoplasia with resultant cholestasis. Cytogenetic analysis of chromosomal rearrangements in sporadic patients (142), as well as analysis of families that transmit Alagille syndrome in an autosomal dominant fashion (143), have demonstrated that the gene defect resides on chromosome 20p11.2. Recent investigation has mapped the human homologue of the Jagged-1 gene (*JAG1*) to this 20p locus, and mutations secondary to submicroscopic rearrangements in JAG1 have been shown to cause Alagille syndrome (144,145). The JAG1 protein is thought to be a ligand for Notch1, a member of a transmembrane receptor gene family shown to be important in cell fate commitment in a variety of species. As described above *JAG1* mutations have also rarely been associated with tetralogy of Fallot (124), but no specific genotype-phenotype correlations have been observed.

Familial Mitral Valve Prolapse

Although mitral valve prolapse is an extraordinarily common finding in the general population and is associated with a variety (5) of complex congenital syndromes [e.g., Holt-Oram syndrome (see above), MFS and MASS phenotype (see below), as well as pseudoxanthoma elasticum], familial isolated mitral valve prolapse and myxomatous degeneration are rare. Nonetheless, familial occurrence is an important observation because it is the only known significant predictor (146) of the rare but devastating sudden death events in isolated mitral valvular abnormalities. Although some investigators have reported an autosomal dominant mode of transmission (146,147), a low and age-related penetrance of familial mitral valve prolapse has made thorough genetic analyses difficult. In some cases, concomitant abnormalities of other valves (especially the tricuspid valve) have given rise to the diagnosis of a multiple floppy valve syndrome.



M-mode tracing of posterior leaflet mitral valve prolapse. Note the posterior displacement of the posterior mitral leaflet after the leaflets close in systole.

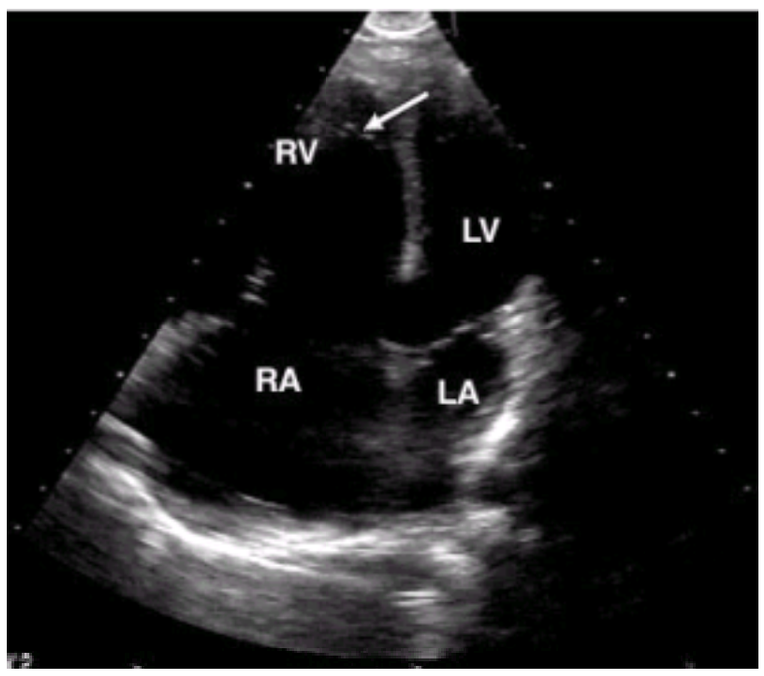
VIDEO

Video 100.9 Intraoperative transesophageal echo with color Doppler of a mitral valve with severe prolapse of the posterior mitral leaflet with 4+, anteriorly directed mitral regurgitation. A very prominent proximal convergence zone is seen in the left ventricle. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

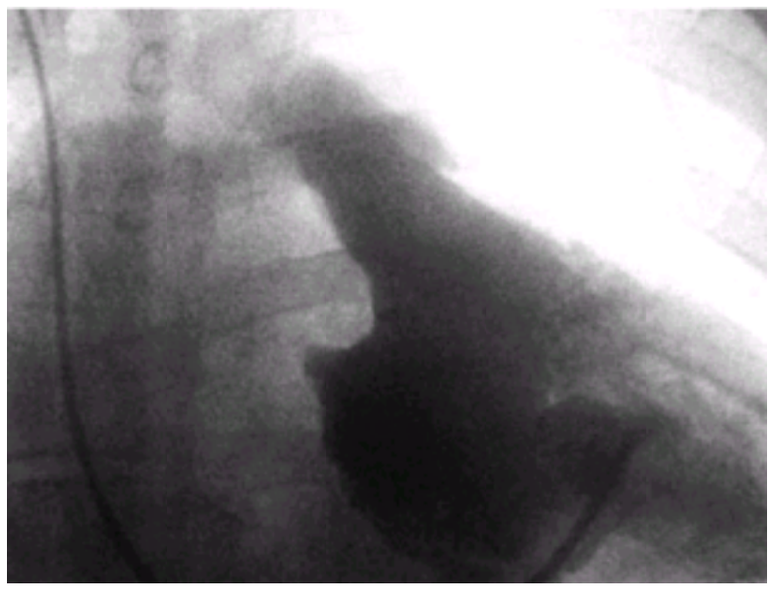
Recently, genetic analysis of families with myxomatous valvular disease has begun to shed light on the bases of mitral valve prolapse. Kyndt et al. (148) studied a large family affected by X-linked myxomatous valvular disease, sometimes referred to as *cardiac valvular dysplasia*, most commonly manifest as mitral valve prolapse, and mapped the as-yet unidentified gene defect to chromosome Xq28. Disse et al. (149) studied four families with autosomal dominant myxomatous mitral valve prolapse and mapped that as-yet unidentified gene defect to chromosome 16p11.2–p12.1. The etiology of sudden death in mitral valve prolapse remains controversial, and both exercise testing and electrophysiologic study are important diagnostic modalities for individuals with a diagnosis of familial mitral valve abnormalities. In the future, identification of the specific gene defects on chromosomes X, 16, and others that lead to mitral valvular defects may assist in risk stratification of individuals with mitral valve disease.

Ebstein's Anomaly

Ebstein's anomaly is characterized by an apical displacement of the tricuspid valve leaflets with an "atrialization" of the right ventricular myocardium superior to the deformed valve leaflets. Although the atrialized right ventricular myocardium is part of the atrium from a hemodynamic perspective, this region of myocardium retains ventricular electrophysiologic properties. An ASD is often present as well. Approximately 0.5% of congenital heart disease patients have Ebstein's anomaly, and there is no obvious gender predilection (150,151). Familial cases have been reported, but no mode of transmission has been documented, although male-to-male transmission has been noted. Most recently, Benson et al. (99) have observed *NKX2.5* mutations in rare individuals with Ebstein's anomaly, but the applicability of this finding to Ebstein's patients in general remains to be determined. Conduction abnormalities, including right bundle branch block, AF, and preexcitation, have been associated with Ebstein's anomaly; active investigation of the genetics of preexcitation syndromes such as Wolff-Parkinson-White syndrome (see the section Wolff-Parkinson-White Syndrome) may eventually contribute to our understanding of the genetic etiology of Ebstein's anomaly.



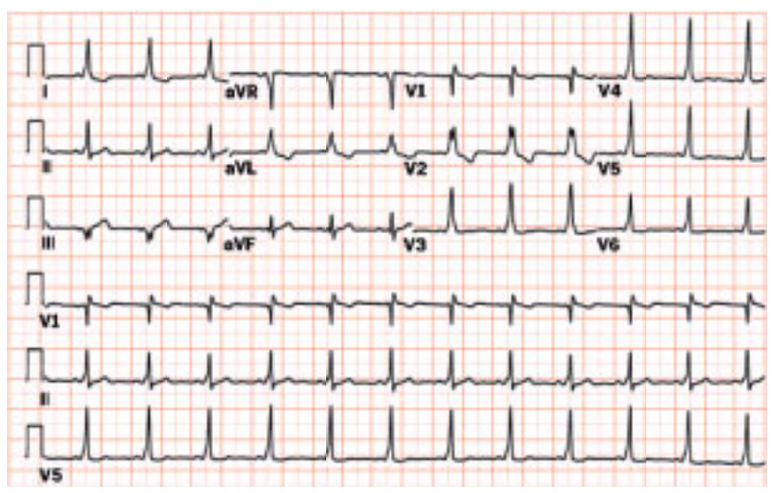
Ebstein's anomaly of the tricuspid valve. Note marked apical displacement of the tricuspid leaflets, especially the septal leaflet. The arrow designates the septal leaflet of the tricuspid valve.



Epstein's anomaly. Right anterior oblique projection of a right ventriculogram demonstrating Epstein's anomaly.

A 47-year-old male patient with Ebstein's anomaly.

A 19-year-old male patient with Ebstein's anomaly.



Wolff-Parkinson-White syndrome. Note short PR interval with classic delta wave due to accessory pathway conduction.

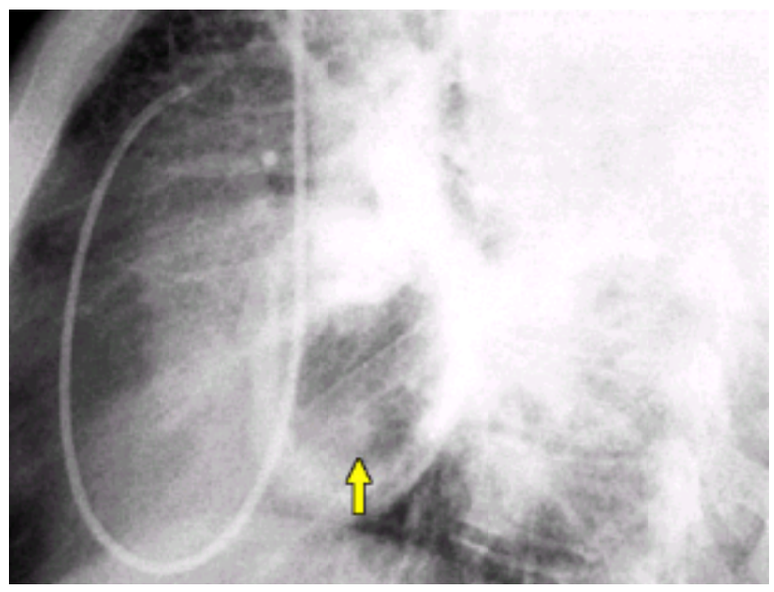
Familial Cardiac Myxoma

Clinical Manifestations

Intracardiac tumors are themselves rarely evident at birth, although they may be features of complex syndromes whose signs and symptoms can be observed immediately postpartum. Intracardiac myxomas account for one-third to one-half of all primary cardiac tumors and are generally regarded as isolated benign tumors of the left atrium of middle-aged women; they are amenable to surgical resection and rarely recur or metastasize. Approximately 7% of individuals with intracardiac myxomas have a familial history of intracardiac myxoma (Fig. 100.2), and these individuals are often young and as likely to be male as female. Tumors in such individuals may occur in any cardiac chamber (although atrial involvement is more common than ventricular), may be multicentric, and frequently recur at intracardiac sites distant from the original tumor despite complete surgical resection (152,153). Moreover, familial atrial myxomas (Fig. 100.2A) usually occur as part of a complex syndrome. Previously referred to by acronyms such as *NAME* (*n*evi, *a*trial myxoma, *m*yxoid neurofibromata, *e*phelides) and *LAMB* (*l*entigines, *a*trial myxoma, *m*ucocutaneous myxoma, *b*lue nevi), these syndromes are encompassed by the eponym Carney complex. Carney complex is characterized by not only intracardiac myxomas, but also by extracardiac myxomas in the setting of lentiginosis (Fig. 100.2B) and endocrine dysfunction. This syndrome is transmitted in an autosomal dominant fashion, and although it is highly penetrant, disease manifestations are highly variable even among individuals within a given family (153). Although at least one-third of individuals will ultimately present with an intracardiac tumor, diagnosis is facilitated by the fact that almost all individuals will exhibit some abnormal form of hyperpigmentation even in infancy (154,155).

FIGURE 100.2 Cutaneous and cardiac involvement in the Carney complex. **A:** An apical four-chamber, two-dimensional echocardiographic view of the heart from an individual affected by Carney complex. Although the ventricular myocardium is structurally normal, a large mass arising from the interatrial septum can be seen in the

left atrium. Histopathology of this mass after surgical removal demonstrated that it was an atrial myxoma. Cutaneous findings in this individual were similar to those seen in **B**. **B:** This child, a cousin of the individual illustrated in **A**, exhibits the typical cutaneous hyperpigmentation of the Carney complex. His face illustrates the excessive and atypical freckling pattern in this syndrome, including freckles on his lips. Note, as well, the large nevi on his right ear and between his right ear and right eye. In adulthood, he developed an atrial myxoma. Individuals in this family carry the haploinsufficient DFSterGly208 mutation in the PRKAR1a gene.



Left atrial myxoma. This left anterior oblique projection depicts the left atrial filling phase of a pulmonary angiogram performed via a pulmonary artery catheter inserted into the right jugular vein. A large contrast free space (*yellow arrow*) depicts a space occupying mass within the left atrial cavity, which surgical pathology confirmed to be a myxoma.

Video 100.10 Atrial myxoma (long-axis). A myxoma attached to the interatrial septum is seen. During diastole, the myxoma moves through the mitral orifice into the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 100.11 An 80-year-old male patient with weight loss, fever, and dyspnea for 2 months. Angiography revealed vascular tumor, which received blood supply from the right coronary artery. Echocardiograph confirmed location of the tumor in the left atrium with appearance consistent with myxoma. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Genetic Studies

Linkage analyses (155) demonstrated that a gene defect at a locus on chromosome 17q caused Carney complex in several families. Subsequent candidate-positional cloning studies (156,157) demonstrated that mutations in the gene encoding the R1a regulatory subunit of cyclic adenosine monophosphate–dependent protein kinase A (*PRKAR1*a) cause Carney complex. All of the *PRKAR1*a mutations identified to date (156,157,158 and 159) result in haploinsufficiency. Although development of some tumors may be associated with loss of heterozygosity at the *PRKAR1*a locus (157), other tumors (156) maintain the wild-type allele and continue to synthesize the PRKAR1a subunit. Thus, *PRKAR1*a may function as a tumor suppressor gene in the heart, but tumorigenesis may be the result of a constitutional mutation in *PRKAR1*a along with acquired mutation of other tumor suppressor genes as has been demonstrated for the NF1 gene in neurofibromatosis (160,161).

Carney complex is likely genetically heterogeneous (158,162). A minority of families have been described in whom mutational analysis has failed to demonstrate *PRKAR1*a mutations and in which potential recombination exists between the Carney complex phenotype and the *PRKAR1*a gene. A second locus (154) has been described on chromosome 2p, but thus far, the statistical significance of this locus remains unclear. Ongoing investigation will likely identify at least one other Carney complex disease gene. In the interim, for those families in whom linkage can be demonstrated of Carney complex to chromosome 17, DNA-based testing may help identify individuals at risk for cardiac myxoma formation and who will benefit from annual surveillance echocardiography (156,163).

CARDIOMYOPATHIES: ADULT-ONSET DEFECTS OF CARDIAC STRUCTURE

Cardiomyopathies are a heterogeneous group of primary myocardial disorders characterized by impaired ventricular function. These are traditionally classified as dilated, hypertrophic, or restrictive, based on anatomic and hemodynamic features. With an estimated prevalence of 36.5 per 100,000 individuals, dilated cardiomyopathies occur most commonly (164,165) and are associated with cardiac chamber dilation and depressed ventricular contractility. Hypertrophic cardiomyopathies are defined by an increase in myocardial mass with myocyte and myofibrillar disarray and abnormalities of both diastolic and systolic function (164). Although the incidence of familial hypertrophic cardiomyopathy (FHC) is unknown, an echocardiographic survey demonstrated unexplained hypertrophy in 1 of 500 young adults (166). Restrictive cardiomyopathies are the least common of these disorders; these are characterized by normal cardiac dimensions and abnormal ventricular diastolic function with preserved systolic function.

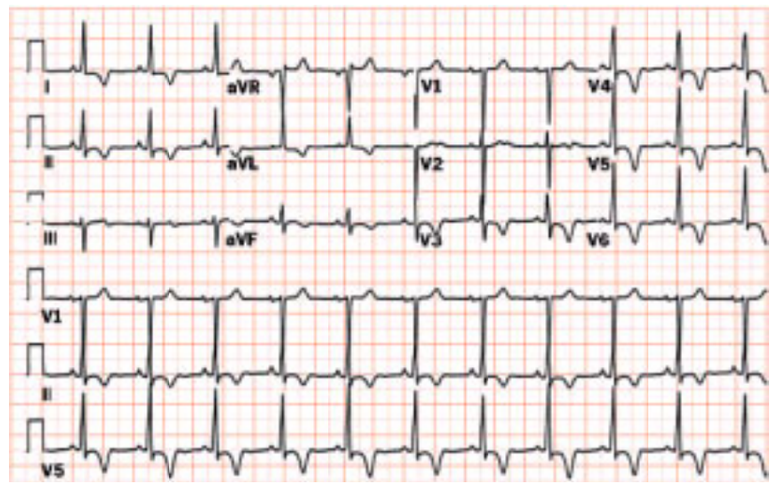
Clinical and research efforts have demonstrated that both dilated and hypertrophic cardiomyopathies are often familial. By contrast, restrictive cardiomyopathies are rarely inherited. Familial cardiomyopathies have been reported to be inherited as autosomal (dominant or recessive), X-linked, and matrilinear (presumably mitochondrial) disorders (167,168). Combined with recent advances in human molecular genetics, these observations have permitted significant progress toward identifying the genetic etiology of inherited cardiomyopathies. These endeavors will have a substantial impact on clinical medicine, including the immediate opportunity for accurate diagnosis. Such gene-based diagnosis also creates a scaffolding for ongoing analyses of clinical outcomes and therapies. In the future, understanding genetic mechanisms of cardiomyopathies may provide optimally targeted therapy instead of the currently available palliative therapy or cardiac transplantation. In this section, we explore in more detail current understanding of genetic etiologies of each form of cardiomyopathy and how they may relate to clinical presentation and management.

Familial Hypertrophic Cardiomyopathy

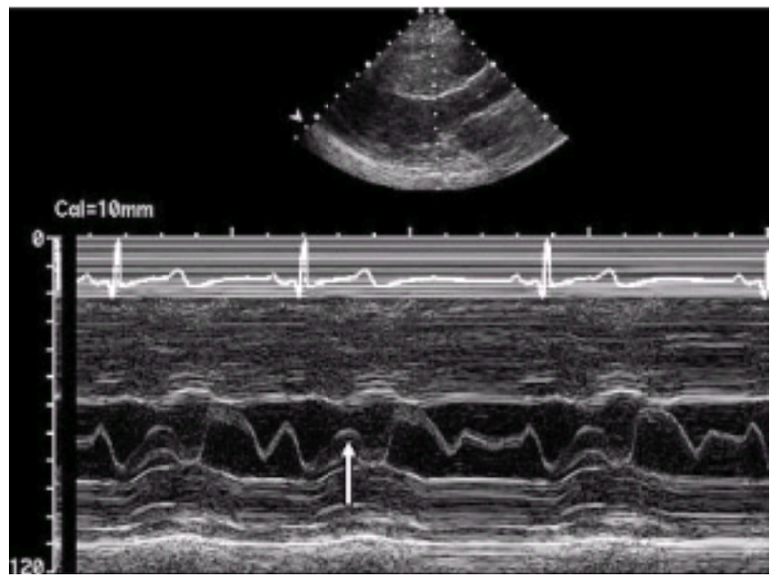
Clinical Features

FHC is an autosomal dominant disorder characterized by increased ventricular mass, hyperkinetic systolic function, and impaired diastolic relaxation. The cardiac hypertrophy found in this inherited disorder may affect either ventricle but usually involves the left ventricle and is often predominant in the interventricular septum (169,170). Histologic examination of affected myocardium reveals myocyte and myofibrillar disarray, which, if extensive, is pathognomonic (170). Symptoms of FHC are diverse and variable, including exertional dyspnea, angina pectoris, and sudden death, which can occur even in asymptomatic individuals (169). Hypertrophic cardiomyopathy is clinically significant because it is one of the most commonly recognized causes of sudden death in apparently healthy young adults (169,171,172). Hypertrophic cardiomyopathy can occur as a sporadic disease, but affected individuals can be shown to have familial disease with echocardiographic features of cardiac hypertrophy in first-degree relatives. Penetrance in familial disease is age-related, with the clinical manifestations of the disease typically developing in adolescence. In adults, penetrance may not be complete, although estimates of penetrance depend on the diagnostic criteria used. Although several studies of the natural history of FHC have demonstrated an annual mortality rate of 2% to 4% from sudden death (171), reports on ambulatory FHC patients suggest a more benign prognosis (169). The mechanism for sudden death is often unknown, and both primary arrhythmias and hemodynamic factors have been proposed. Atrial

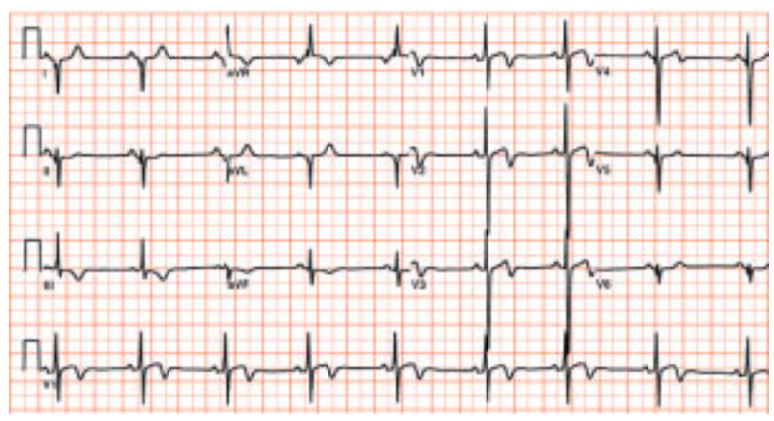
dysrhythmias, particularly fibrillation, are frequently problematic in FHC patients independent of their history of sudden death.



Yamaguchi's disease. Note anterior precordial T wave inversion in this Asian patient with apical hypertrophy.



M-mode tracing of hypertrophic cardiomyopathy with severe septal hypertrophy seen at the top of the trace and systolic anterior motion (SAM) of the mitral valve in systole seen in the middle of the trace (designated by the arrow).



A 28-year-old Caucasian male patient with hypertrophic obstructive cardiomyopathy.

Physical findings (particularly a systolic murmur that increases with maneuvers that decrease preload) or ECG abnormalities (e.g., inferior Q waves and left ventricular hypertrophy) may suggest FHC. However, the mainstay of diagnosis in the adult is the observation by two-dimensional echocardiography of left ventricular hypertrophy (*e*Fig. 100.2.1) without obvious explanation (e.g., aortic stenosis or long-standing hypertension). Associated echocardiographic findings include asymmetric hypertrophy (particularly of the interventricular septum), a dynamic left ventricular outflow tract pressure gradient, and systolic anterior motion of the anterior mitral valve leaflet. With the discovery of genetic causes of hypertrophic cardiomyopathy, the natural history of disease has been expanded to include a preclinical stage. Most often this occurs in the young because hypertrophy may not develop until after adolescent growth has been completed (173). However in some adults, development of the morphologic features of disease may not be manifest until late in life. Although echocardiograms are, by definition normal throughout this preclinical stage, these individuals sometimes show ECG abnormalities.

***e*FIGURE 100.2.1** Echocardiographic manifestations of familial hypertrophic cardiomyopathy. A parasternal long-axis two-dimensional echocardiographic view of the heart from this individual with familial hypertrophic cardiomyopathy is shown. Note the marked thickening of the left ventricular walls, particularly the interventricular septum.

Video 100.12 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy **(A)**. Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy **(B)** for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 100.13 A four-chamber transesophageal echo (TEE) of a patient with hypertrophic obstructive cardiomyopathy before myectomy **(A)**. Note the mitral regurgitation due to systolic anterior motion of the mitral valve leaflets. Intraoperative TEE after myectomy **(B)** for hypertrophic cardiomyopathy. Note that there is no longer mitral regurgitation from systolic anterior motion of the mitral valve leaflets, and the left ventricular outflow tract is opened up compared with the preoperative TEE. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 100.14 Intraoperative transesophageal echo of a patient with hypertrophic obstructive cardiomyopathy and left ventricular outflow tract (LVOT) obstruction. The septum is hypertrophied, and the mitral leaflets show some systolic anterior motion of the mitral valve leaflets. An accessory mitral leaflet is located on the left ventricular septum. Note the independent motion of this leaflet in the LVOT. The pressure gradient across the LVOT/AV was greater than 100 mm Hg; however, the aortic valve opens freely. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Genetic Studies

Molecular genetic analyses have demonstrated that FHC is a disease of the sarcomere. Linkage analyses and positional cloning studies of kindreds with FHC have demonstrated that hypertrophic cardiomyopathy is a genetically heterogeneous disorder; a mutation in one of many sarcomeric genes can produce a clinically indistinguishable phenotype. To date, studies have demonstrated that mutations in genes for beta-myosin heavy chain (MHC) (chromosome 14q1) (174), cardiac troponin T (chromosome 1q31) (175), alpha-tropomyosin (chromosome 15q2) (175), myosin-binding protein C (chromosome 11p13–q13) (176), ventricular myosin regulatory light chain (chromosome 12q2) (177), ventricular myosin essential light chain (chromosome 3p) (177), cardiac actin (chromosome 15q14) (178), and titin (chromosome 2q31) (179) can all produce FHC.

Beta-cardiac MHC mutations are detected in approximately 35% to 40% of FHC patients, and extensive analyses of FHC patients have led to the identification of more than 50 mutations in the beta-cardiac MHC gene (180,181 and 182). The gene defects that cause FHC are typically family-specific—that is, unique mutations are found in different families (termed *allelic* or *intragenic heterogeneity*). All mutations are missense; the nucleotide change results in the replacement of the normally encoded amino acid with a different residue. Mutations are all localized to the globular head or head-rod junction in the molecule (183).

Different beta-cardiac MHC gene mutations appear to correlate with survival in patients with FHC (181,183,184). Several mutations have been identified that are associated with a significant risk of sudden and/or premature death (malignant mutations), whereas other mutations correlate with long-term survival (benign mutations). Kaplan-Meier curves for survival with FHC illustrate these different profiles (Fig. 100.3). For instance, near-normal survival is found in individuals with the Val606Met (benign) beta-MHC mutation. In contrast, approximately half of individuals with the Arg403Gln (malignant) beta-MHC mutation are dead by age 50 years. Because there are no good clinical predictors of risk for premature death in hypertrophic cardiomyopathy, acquisition of more survival data from the full spectrum of sarcomere mutations may be extremely useful for stratifying patient risk and allowing appropriate intervention.

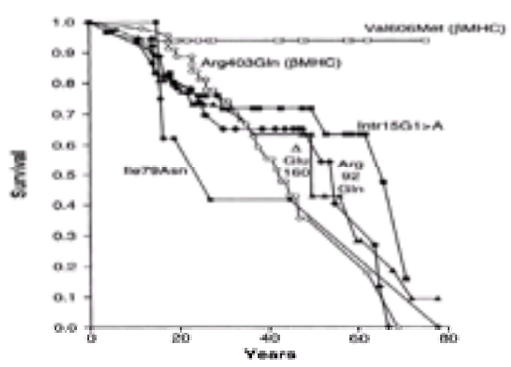


FIGURE 100.3 Kaplan-Meier product-limit curves for survival in patients with hypertrophic cardiomyopathy caused by different mutations. Survival data are plotted for all persons carrying a given mutation. The survival of individuals with hypertrophic cardiomyopathy caused by cardiac troponin T mutations [Intron 15 $G_1 \rightarrow A$ (■), Ile79Asn (●), DGlu160 (▲), and Arg92Gln (✚)] is similar to that in persons with a malignant beta-cardiac myosin heavy chain mutation (Arg403Gln) but significantly shorter than that in persons with a benign myosin mutation (Val606Met). (p <.03 for the comparison with each troponin T mutation and p = .006 for the comparison with all troponin T mutations.) Myosin mutations are shown in □ and ○. (From Watkins H, McKenna W, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* 1995;332:1058, with permission.)

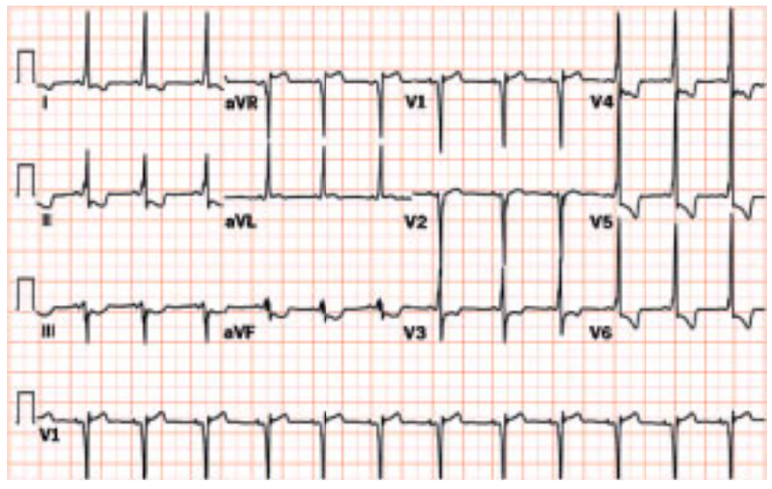
Despite this correlation between survival and alteration in charge of the mutated amino acid, considerable variation remains in the extent and distribution of hypertrophy even within a given family, all of whom have the same genetic basis for FHC. Recent analyses (185) of the anatomic features of FHC categorized according to different genetic etiologies have confirmed earlier work, thereby suggesting that other factors (genetic or environmental, or both) are important in modulating the hypertrophic phenotype. In addition, such factors undoubtedly also modulate the frequency of sudden death in FHC. Studies that correlate the clinical features of FHC in individuals with distinct genetic etiologies are an area of active research, and assessing various factors' impacts in light of the genetic background on which they occur will, it is hoped, improve risk stratification in patients.

In addition to beta-cardiac MHC mutations, mutations in other sarcomere components can also produce FHC (175,177,186). Defects in cardiac troponin T (175,187) and myosin-binding protein C (188,189) each account for approximately 15% of all cases of FHC. A wide range of different defects cause FHC in these genes, including missense mutations, insertions, deletions, and defects in splice signals. FHC caused by mutations in cardiac troponin T often has reduced penetrance, and the hypertrophic phenotype associated with these mutations can be subtle—that is, affected individuals appear to have modest increases in the maximum left ventricular hypertrophy (detected by echocardiography). Despite this, survival of individuals with FHC caused by cardiac troponin T mutations is often quite poor and comparable to that seen with malignant beta-cardiac MHC gene mutations. These findings suggest that genetic diagnosis may be particularly important in families with mutations in cardiac troponin T. A very different clinical profile is produced by cardiac myosin-binding protein C mutations (188,189). Hypertrophic cardiomyopathy caused by these defects can exhibit delayed expression, such that hypertrophy does not become manifest until middle age. Survival with myosin-binding protein C mutations is variable; some defects have near normal survival, whereas others have a poorer prognosis.

Other gene mutations are rarer causes of hypertrophic cardiomyopathy. Alpha-tropomyosin mutations account for approximately 5% (175), and a few mutations have been defined in the genes encoding the ventricular myosin regulatory and essential light chains (177), cardiac actin (178), and titin (179) in patients with FHC. Individuals with mutations in alpha-tropomyosin appear to have a variable presentation of FHC; severity of hypertrophy among families with unique mutations differs. Nonetheless, survival among such individuals is good, with only rare sudden death. Ongoing evaluations are needed to better assess the disease phenotype in individuals with mutations in ventricular myosin regulatory and essential light chains, cardiac actin, and titin.

Current research also centers on identification of other genetic causes of cardiac hypertrophy. For instance, clinicians have recognized an association between cardiac hypertrophy and electrical abnormalities, including Wolff-Parkinson-White syndrome and progressive atrioventricular block (190). Recent investigations (72a,190a) have established that defects in the gene encoding the $gamma_2$ regulatory subunit of AMP-activated protein kinase (*PRKAG2*) on chromosome 7q3 cause this phenotype. Although this disorder was initially felt to be a variant of hypertrophic cardiomyopathy, histopathology and biochemical features of *PRKAG2* defects indicate this to be a novel glycogen storage disease of the heart (190b). Similarly, hypertrophic cardiomyopathy has been associated with the autosomal dominant Noonan's syndrome (craniofacial malformation, axial skeletal abnormalities, pulmonic stenosis, and hypertrophic cardiomyopathy) as well as the neuromuscular disorder Friedreich's ataxia (191). Mutations have recently been identified (192) in the novel frataxin gene on chromosome 9q from individuals with Friedreich's ataxia. At this time, however, no physiologic function has yet been ascribed to the frataxin gene, and the mechanism by which these mutations cause the cardiac manifestations of

this syndrome are unclear. A hypertrophic cardiomyopathy occurs also in the context of multisystem neuromuscular disease. These disorders result from mutations in mitochondrial proteins encoded within the nuclear and mitochondrial genomes (reviewed in reference 172 and not discussed further in this chapter).



Wolff-Parkinson-White syndrome. Eleven-year-old patient with manifest preexcitation consistent with Wolff-Parkinson-White.

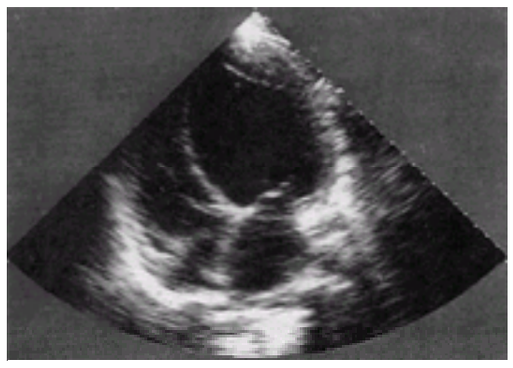
Strategies for understanding how sarcomere mutations result in cardiac hypertrophy are an avenue of active investigation. Mutated sarcomeric proteins are generally thought to produce disease via a dominant negative effect—that is, the mutated protein directly alters sarcomeric function. *In vitro* analysis of mutated myosins has suggested altered biochemical and biophysical properties of the protein. Although early data suggested that mutations in myosin caused a loss of function (193), more recent data indicate the opposite. *In vitro* analyses (194) of single molecule mechanics of Arg403Gln myosin showed supranormal actin-activated adenosine triphosphatase activity, increased generated force, and accelerated sliding with respect to actin filaments. These data indicate a gain in function resulting from this missense mutation. Ongoing evaluation of models (195,196,197,198 and 199) in which human mutations have been engineered into the mouse or rabbit genomes has helped define the physiologic and cellular consequences of FHC-causing mutations. These models also provide the opportunity to define intracellular signals and pathways that respond to perturbation in sarcomere structure or function, or both. Such data may provide a new framework for the rational design of therapeutic agents.

More immediately, the definition of distinct genetic etiologies for FHC permits gene-based diagnosis in some families. As noted, FHC is an autosomal dominant disorder that is equally inherited by men and women. Because only one mutated gene is sufficient to cause autosomal dominant diseases, 50% of the offspring of an affected individual will inherit the disease-causing mutation. In individuals for whom a sarcomere mutation has been identified, gene-based diagnosis of all family members is now possible. Gene-based diagnosis can be particularly beneficial to families with a high incidence of sudden death. Not only can this information target longitudinal evaluation to children who are genotype positive (200,201), but in addition these data can prevent unnecessary restrictions on children who are not at risk of developing FHC.

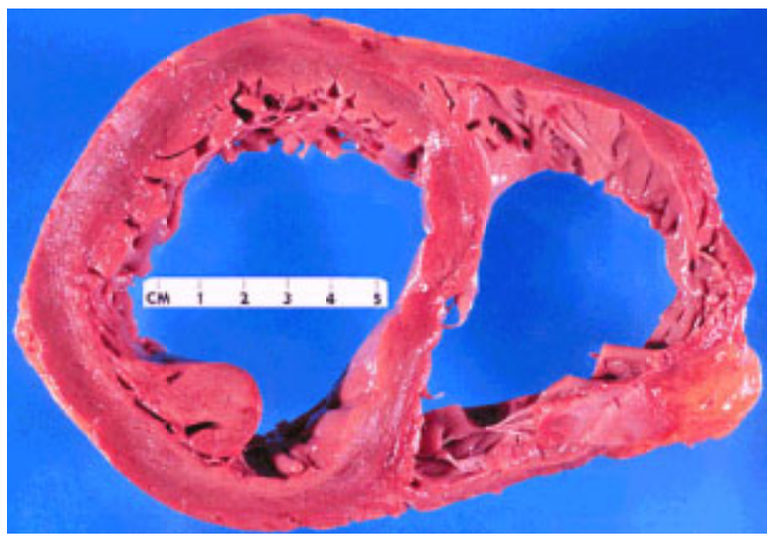
Familial Dilated Cardiomyopathies

Clinical Features

Dilated cardiomyopathy occurs as a primary disorder of the myocardium characterized by cardiac dilation (eFig. 100.3.1) and impaired ventricular function or secondary to toxic, metabolic, or infectious agents (reviewed in reference 164). The incidence of dilated cardiomyopathies is approximately 37 per 100,000 individuals (164,202), and these prevalent disorders contribute substantially to overall incidence of heart failure in the United States (164,165,202). Indeed, dilated cardiomyopathy accounts for up to one-third of heart failure in individuals between the ages of 25 and 65 (164,202), and is the most common indication for heart transplantation. In addition to signs and symptoms of congestive heart failure, pericardial effusion and conduction disturbances are often observed. Thromboembolic events, syncopal episodes, and unexplained sudden death further contribute to substantial morbidity and mortality associated with dilated cardiomyopathy.



***e*FIGURE 100.3.1** Echocardiographic manifestations of familial dilated cardiomyopathy. In this apical four-chamber, two-dimensional echocardiographic view of the heart from an individual affected by a familial dilated cardiomyopathy, the left ventricle chamber can be seen to be markedly enlarged without change in wall thickness.



Dilated congestive cardiomyopathy. Both the left and right ventricles are significantly enlarged. In this example, the left ventricular wall thickness falls within normal limits.

Pathologic findings also suggest that familial dilated cardiomyopathy is heterogeneous. Myocyte necrosis in the absence or presence of inflammation, fibrosis, and/or conduction system disease have all been noted (203). Cellular studies have identified a variety of physiologic defects (172,204) in dilated cardiomyopathy, including impaired sarcoplasmic reticulum calcium handling, atypical myocyte potassium currents, and autoantibodies to a variety of cardiomyocyte antigens, but have not provided a unified pathophysiologic or molecular mechanism (205). These data suggest that multiple gene defects individually or together may cause myocardial dysfunction that results in chamber dilation and dysfunction.

Genetic Studies

Primary dilated cardiomyopathy occurs as sporadic disease. Although elucidation of the initiating cause for idiopathic dilated cardiomyopathy in a single affected individual is often impossible, several studies have demonstrated that more than 25% of affected probands have an affected relative (202,206). Familial dilated

cardiomyopathy can be inherited as a matrilinear, X-linked, autosomal recessive, or autosomal dominant trait (167,168). Dilated cardiomyopathy due to mitochondrial mutation is one component of multisystem disease (164); these disorders are not discussed further. Autosomal dominant transmission is the most prevalent mode of transmission that has fostered application of molecular genetic approaches to identify gene defects that cause dilated cardiomyopathy. Premature morbidity and mortality in familial dilated cardiomyopathy initially hindered genetic studies of this disorder but with advances in the genome project, issues such as small family size have become less significant obstacles. Increasingly genetic loci and disease genes have been defined. Identification of the full complement of mutations that cause familial dilated cardiomyopathy is also likely to provide insights into the causes of sporadic disease; in some instances these may be due to *de novo* mutations in genes that also cause heritable disease.

Familial dilated cardiomyopathy (5,204,206) can be associated with a variety of cardiac findings, including atrial cardiomyopathy, conduction system abnormalities (particularly AV block), valvular disease, and ventricular tachycardia. Extracardiac manifestations are sometimes present; the coexistence of subclinical or overt skeletal myopathy is particularly common (167).

Mutations in three X-linked genes cause dilated cardiomyopathy. In addition to cardiac disease, these defects cause muscular dystrophy (Duchenne's or Becker's muscular dystrophy and Emery-Dreifuss muscular dystrophy) or the complex phenotype of Barth's syndrome.

In Duchenne's/Becker's muscular dystrophy, proximal muscular atrophy is the most striking feature, but most patients will exhibit some degree of cardiac involvement (207). Ninety-five percent of Duchenne's patients will exhibit some manifestation of dilated cardiomyopathy by the end of their lives, and in many, signs and symptoms appear before the age of 6. Cardiomyopathy tends to present after puberty in Becker patients. In some Duchenne's/Becker's patients, dilated cardiomyopathy is the dominant clinical finding. These cardiomyopathies result from deletions of the 5' muscle promoter of the dystrophin gene (208). Such individuals exhibit pathologic findings of dystrophy on skeletal muscle biopsy, but they may remain subclinical. A similar phenotype has been demonstrated in a recently described family with a premature stop codon and consequent dystrophin protein truncation (209). However, when the dystrophin promoter region in a large series of patients with idiopathic cardiomyopathy was examined, no mutations were identified (210). Thus, it is thought that this is a relatively rare etiology for adult-onset sporadic dilated cardiomyopathy.

Emery-Dreifuss muscular dystrophy often presents with dilated cardiomyopathy and AV conduction abnormalities in the setting of progressive skeletal muscle dysfunction and contractures. Although atrial dysrhythmias (paralysis, fibrillation, and flutter) are common, infranodal disease with slow junctional rhythms and AV block frequently causes symptoms. Mutations in the emerin gene cause this disorder (211), but the precise function of this protein as well as the contribution of emerin mutations to more common adult-onset cardiomyopathy remains unknown.

Barth's syndrome is a frequently lethal infantile disorder in which patients exhibit dilated cardiomyopathy associated with short stature and neutropenia. Although the genetic locus established by linkage analyses overlaps with the Emery-Dreifuss locus, recent positional cloning studies (212) have demonstrated that Barth's syndrome is caused by mutations in a distinct gene called *tafazzin*. Investigation of alternative splicing of tafazzin transcripts is an area of active research and may help explain the variable phenotypes in Barth's syndrome.

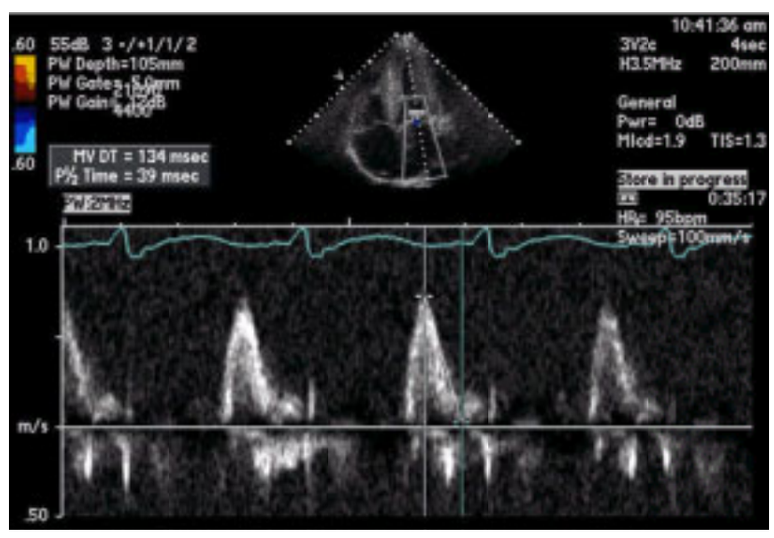
Autosomal dominant dilated cardiomyopathy is the most common form of hereditary primary dilated cardiomyopathy. To date, 17 distinct chromosomal loci have been reported (5) and more will likely be identified in the future. Disease genes that map to chromosomes 1q32, 2q31, 6q12–16, 9q13–q22, 14q11, and 15q14 cause isolated cardiac disease. Loci on chromosomes 1q21, 2q11–q22, 3q22–p25, 6q23, and 19q13.2 cause dilated cardiomyopathy in association with conduction system disease (5,70,213,214,215,216 and 217). Dilated cardiomyopathy that is caused by a mutated gene encoded on chromosome 10q21–q23 (216) is associated with mitral valve prolapse, whereas dilated cardiomyopathy due to mutation on chromosome 6q23–24 (218) is associated with sensorineural hearing loss. In several instances, these genomic locations have been defined by analyses of a single family, and in many instances specific gene defects have not yet been identified. In addition to the considerable variation in associated clinical manifestations, the age of onset of ventricular dilatation, systolic dysfunction, and frank heart failure can vary considerably. Early-onset disease that affects children and young adults characterizes some gene mutations, whereas others often present in middle-aged and older adults.

Conduction abnormalities are particularly prevalent in some families with autosomal dominant dilated cardiomyopathy. Individuals typically present early in life (before overt chamber dilatation) with sinoatrial node dysfunction, which may progress to supraventricular tachyarrhythmias and His-Purkinje system conduction delay. Pacemaker implantation is often required. Although mutations at three distinct loci are known to produce this phenotype, only one disease-causing gene has been identified. Mutations in the gene encoding lamin A and C isoforms (on chromosome 1q21) can cause this disease (219). Missense mutations that perturb the structure of the alpha-helical domain of these peptides usually cause dilated cardiomyopathy and conduction disease. Other mutations (missense and nonsense) in lamin can produce two different diseases, Emery-Dreifuss syndrome (220) or familial partial lipodystrophy (221). Emery-Dreifuss is a childhood-onset muscular dystrophy with contractures and adult-onset cardiac conduction abnormalities. Familial partial lipodystrophy (Dunnigan-type) is a metabolic disorder characterized by abnormal deposition of fat, insulin-resistant diabetes, and cardiac conduction system disease. The mechanisms by which distinct mutations in lamins cause these three different clinical phenotypes is unknown. Lamins are components of the nuclear envelope and may both contribute to the integrity of the nucleus; these may also participate in nuclear-cytoplasmic trafficking and in transcriptional regulation.

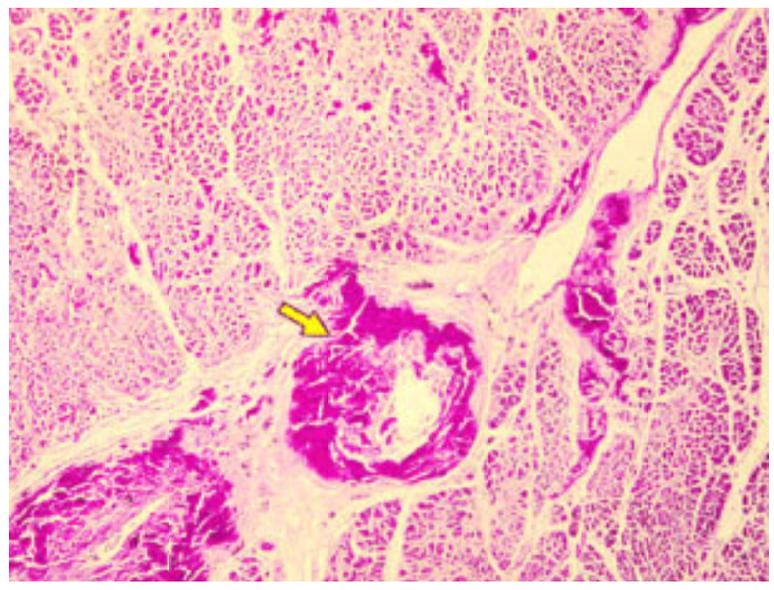
Dilated cardiomyopathy that occurs in isolation can be due to mutations in sarcomere protein genes. Although most mutations in these proteins cause hypertrophic cardiomyopathy, some missense mutations in cardiac actin (222) or the beta-cardiac MHC gene (223) and a deletion in cardiac troponin T (223) cause cardiac dilatation and dysfunction. Presumably these have distinct effects on the biophysical properties of the sarcomere than do mutations that result in cardiac hypertrophy. Although understanding the mechanisms by which different mutations produce these different cardiac morphologies is an area of active research, an important clinical observation came from this genetic research. The onset of cardiac failure occurs early in those individuals with dilated cardiomyopathy due to sarcomere gene mutations. Signs and symptoms of heart failure and even sudden death may present during childhood.

Restrictive Cardiomyopathy

Restrictive cardiomyopathies are a rare group of disorders characterized by abnormal diastolic function resulting from impaired ventricular filling and preserved systolic function. Restrictive cardiomyopathy often accompanies genetic conditions, such as amyloidosis, hemochromatosis, and Fabry's disease, and eosinophilic disorders, including myeloproliferative, vasculitic, and parasitic disease. Familial restrictive cardiomyopathy is exceedingly rare (5), and although one report (224) suggests dominant transmission, virtually nothing further is known about the genetic etiology of this condition.



Pulsed wave Doppler of the mitral valve inflow in a patient with amyloidosis demonstrating a short deceleration time (134 ms) consistent with restrictive physiology.



Amyloidosis of the heart. This is cresyl violet stain of the left ventricular myocardium. The yellow arrow indicates a metachromatic red-violet homogenous deposit around an intramyocardial arteriole with similar interstitial deposits.

Arrhythmogenic Right Ventricular Dysplasia

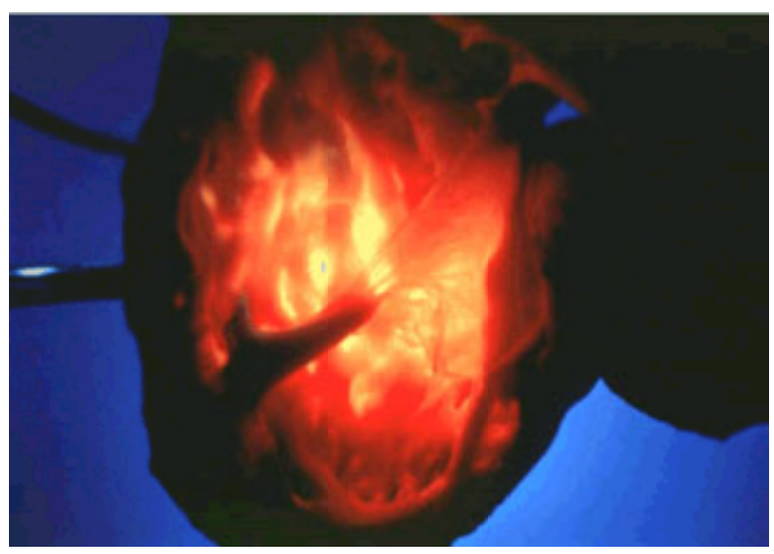
Clinical Features

ARVD refers to a condition of progressive atrophy of the myocardium with fatty or fibrofatty tissue replacement (225,226 and 227). Although this primary myocardial disorder typically involves the right ventricle and pathologic findings are initially found there, left chamber involvement is not uncommon. The pathology can be segmental or diffuse and transmural. Right ventricular wall thickness can be normal or increased by fatty infiltration, but replacement of myocardium by fibrofatty tissue usually results in marked thinning of the right ventricular wall, often with aneurysmal dilatation. Histologic features include myocardial necrosis and focal inflammation (lymphocytic infiltrates). Pathologic specimens that demonstrate greater than 3% fat and greater than 40% fibrosis tissue have been considered pathognomonic for suggested ARVD.

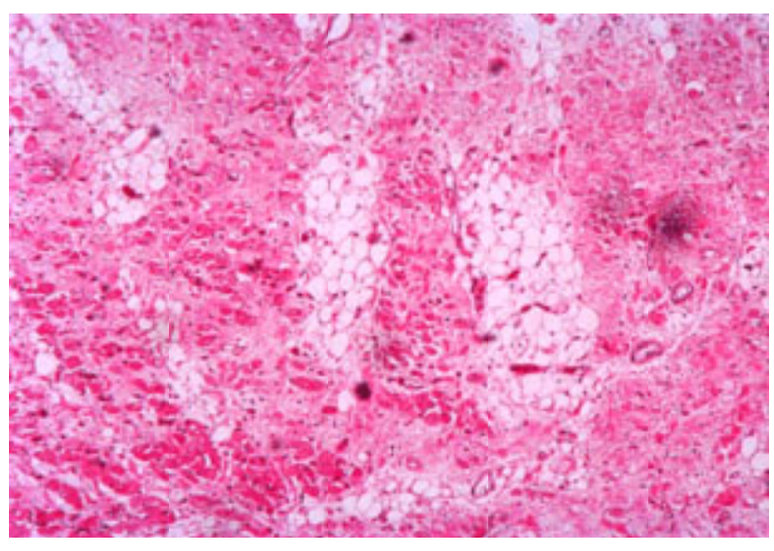
VIDEO

Video 100.15 Arrhythmogenic right ventricular dysplasia (transaxial). Thinning the right ventricular wall with dyskinesia of the right ventricular free wall during systole is due to fibrous replacement of the myocardium. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

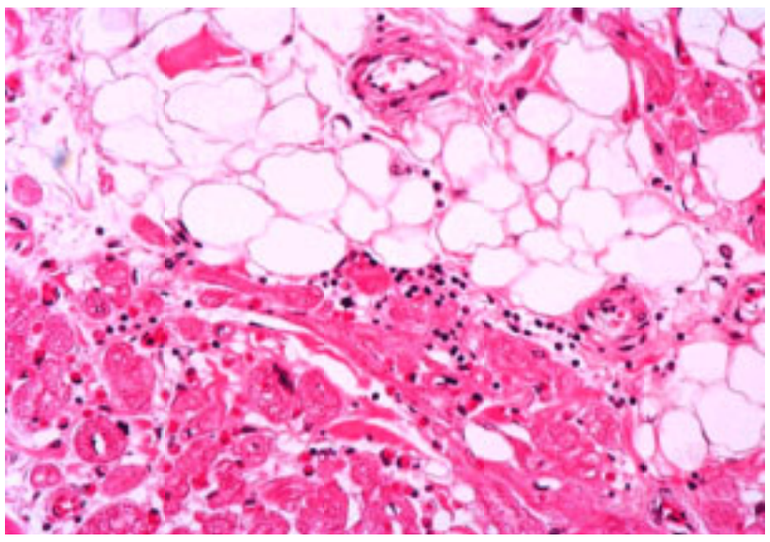
Muscular hypertrophy of the arterial wall in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Arrhythmogenic right ventricular dysplasia. Illumination reveals thinned right ventricular wall. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Arrhythmogenic right ventricular dysplasia with transmural fatty infiltration. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)



Focal chronic inflammation in a case of arrhythmogenic right ventricular dysplasia. (Courtesy of Norman Ratliff, M.D., and Marc Smith, M.D., Cardiac Pathologists at The Cleveland Clinic Foundation.)

Clinical recognition of the disease involves demonstration of perturbed structure and function. Endomyocardial biopsy should evidence the histopathology discussed above. Angiography and magnetic resonance imaging can be particularly helpful for defining right ventricular dilatation and/or aneurysm and diminished function (segmental or global dyskinesis/akinesis). Two-dimensional echocardiography has limited sensitivity in defining right ventricular abnormalities and may therefore be most helpful in longitudinal assessment rather than initial diagnosis. ECG findings of ARVD include right ventricular T-wave inversion, an epsilon wave, ventricular conduction delays, and ventricular tachycardia with left bundle branch block morphology (5).

Symptoms in ARVD can be absent during childhood and young adulthood, and in these ages the first manifestation of disease is often sudden death (228,229). Life-threatening arrhythmias characterize the disorder and appear to increase with disease duration. Affected adults can also develop symptoms of heart failure.

Genetics

Seven genetic loci have been mapped for autosomal dominant ARVD (230): *ARVD1* on chromosome 14q23–24 (231), *ARVD2* on 1q42–43 (232), *ARVD3* on 14q12–22 (233), *ARVD4* on 2q32.1–32.2 (234), *ARVD5* on 3p23 (235), *ARVD6* on 10p14–12 (236), and *ARVD7* on 10q22.3 (237). Recently, the ARVD2 gene has been identified as the cardiac ryanodine receptor gene (*RYR2*) (238). Tiso et al. (238) identified four missense mutations in *RYR2* in four ARVD families. The RYR2 protein induces the release of calcium from the sarcoplasmic reticulum into the cytosol and is involved in excitation-contraction coupling of myocardial cells. As discussed previously, mutations in RYR2 also cause catecholaminergic polymorphic ventricular tachycardia (62,63). Therefore, catecholaminergic polymorphic ventricular tachycardia and ARVD are allelic disorders. Other causative genes for autosomal dominant ARVD remain to be cloned or identified.

ARVD with an autosomal recessive inheritance pattern has also been reported in the setting of Naxos disease. Naxos disease was first reported in families on the Greek island of Naxos (239), and it is the triad of autosomal recessive ARVD, palmoplantar keratoderma, and woolly hair. The genetic locus for autosomal recessive ARVD (Naxos disease) was mapped to chromosome 17q21 (240). Recently, a homozygous 2-bp deletion in the plakoglobin gene was identified in patients with Naxos disease (241). The 2-bp deletion is located at the 3' end of the plakoglobin gene and causes a frameshift and creates a premature stop codon, leading to truncation of the plakoglobin protein by 56 amino acids. Plakoglobin is a major protein in the desmosomes and the intermediate junctions. Plakoglobin interacts with other desmosomal proteins, such as desmoglein I (242), and cell-cell adhesion proteins, such as E- and N-cadherin (243), linking it to the actin-based cytoskeleton. As discussed previously, mutations in the cardiac actin gene cause both dilated and hypertrophic cardiomyopathies. Thus, ARVD, dilated cardiomyopathy, and hypertrophic cardiomyopathy may share the same genetic pathogenic pathway—that is, mutations in a network of proteins in the cytoskeleton.

VASCULAR DISEASE

The vascular system is composed of four types of vessels based on anatomic and functional differences: arteries, capillaries, veins, and lymphatics. Blood vessels are composed of two cellular layers: an inner layer of endothelial cells lining the lumen and an outer layer of smooth muscle cells. During embryogenesis, blood vessels are formed via two processes: vasculogenesis and angiogenesis [reviewed by Risau (244)]. *Vasculogenesis* is defined as the process in which mesoderm cells are induced to differentiate into angioblasts (vascular endothelial cells that have not yet formed a lumen), which then assemble into a reticulum of primitive blood vessels called the *primary capillary plexus*. The primary capillary plexus later undergoes a remodeling and sprouting process called *angiogenesis*, which involves the sprouting, branching, and differential growth of blood vessels to form the more mature-appearing vascular patterns within almost all tissues of the mammalian body. In addition, during angiogenesis, the endothelial cells recruit smooth muscle cell precursors from mesenchymal and neural crest cells to ensheathe them. These precursor cells eventually differentiate into the smooth muscle cell layers of blood vessel walls. Further development accompanied by changes in size and mural structure leads to the formation of arteries, capillaries, veins, and lymphatics, each with its own function and characteristics. Studies in transgenic mice have established that vascular endothelial growth factor and its receptors, angiopoietin-1 and angiopoietin-2 and their receptors (Tie1, Tie2), the endothelin receptor-A, and the ephrin-B2 ligand and the Eph-B4 receptor are involved in the cascade of developmental processes leading to the formation of the vascular network (245).

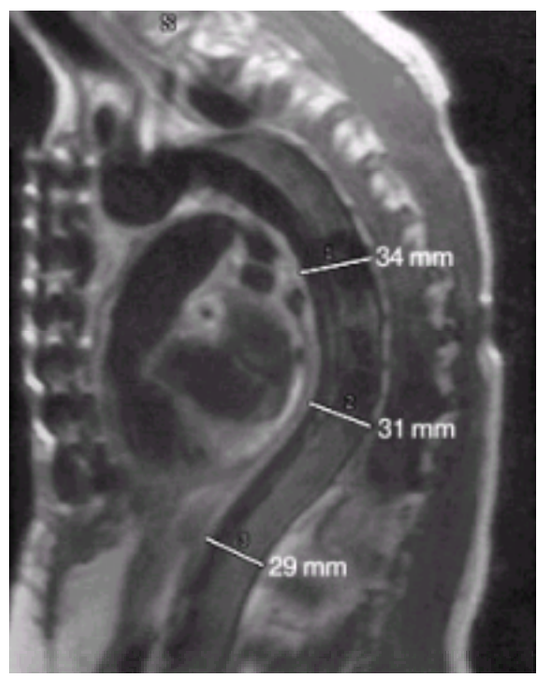
Marfan Syndrome

MFS is an autosomal dominant disorder of fibrous connective tissue with manifestations in the cardiovascular, skeletal, and ocular systems (246). Cardiovascular features include mitral valve prolapse, mitral regurgitation, dilatation of the aortic root, and aortic regurgitation (Fig. 100.4). The major life-threatening cardiovascular complications are aneurysm of the aorta and aortic dissection (4). The gene for MFS was mapped to chromosome 15q21.1 and identified as *FBN1*, which encodes fibrillin-1, the principal component of the extracellular microfibrils (247,248 and 249). Microfibrils are present in extracellular matrices in early mammalian development and later throughout the body, which helps explain the extensive pleiotropic features of MFS. Life expectancy in MFS, which previously averaged in the third to fourth decades, has been considerably extended by a combination of advice against vigorous exertion, chronic beta-adrenergic blockade, and prophylactic aortic root repair when the diameter reaches 50 to 55 mm in the adult (250,251). More than 300 distinct mutations in *FBN1* have been found in MFS patients, but clinical utility of mutation searching is limited (252,253). Mutations in this gene also cause related conditions, such as MASS phenotype and familial aortic aneurysm (FAA) (4).

FIGURE 100.4 Aortic root dilatation in Marfan syndrome. A parasternal long-axis two-dimensional echocardiographic view of the heart from an individual affected by Marfan syndrome is shown. Note the marked dilatation of the aortic root, particularly at the sinuses of Valsalva (*dashed line*). The maximal measurement of the width of the aortic root at the sinuses in this individual was 5.09 cm.

Ectopia lentis. This lens dislocation is associated with Marfan syndrome.

Arachnodactylia in Marfan syndrome. The ratio of finger length to hand size is markedly increased.

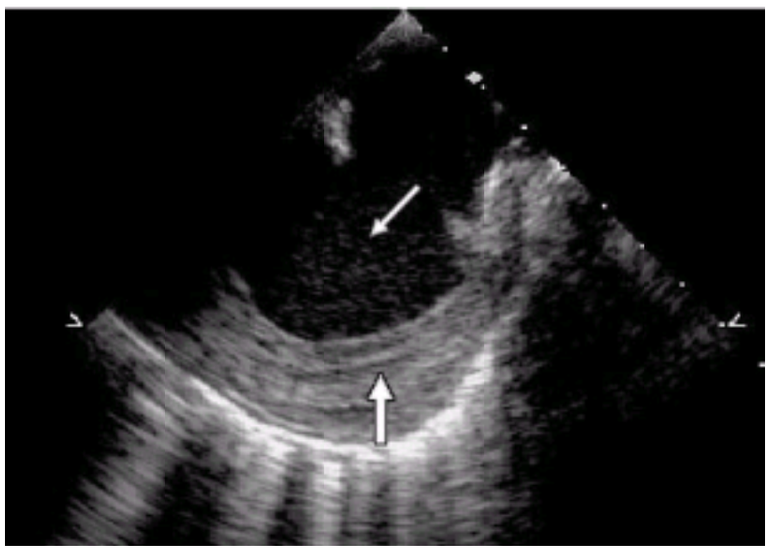


Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

Mutations in the gene encoding fibrillin-2 (*FBN2*) on chromosome 5q23 have been identified to cause congenital contractural arachnodactyly, which shares skeletal abnormalities with MFS but is less commonly associated with cardiovascular abnormalities (254). Another gene has been mapped to chromosome 3p24.2–25 in a single family with marfanoid skeletal and vascular features (255,256).

Familial Aortic Aneurysm

Approximately 20% of aortic aneurysms have primary heritable etiologies, including the rare Marfan or type IV Ehlers-Danlos syndromes. Such FAA disease often presents with dissection and arterial pathology consistent with cystic medial necrosis. The disorder can affect all aortic segments—thoracic and abdominal—as well as other large arteries. Although thoracic aortic dilatation may be associated with bicuspid aortic valve, FAA also occurs in the absence of valvular abnormalities. In some cases, isolated thoracic aortic aneurysms (257) and FAA (258,259) have been associated with mutations in the FBN1 gene, although affected individuals have no other stigmata of MFS. These findings suggest that aortic aneurysms can represent a fibrillinopathy distinct from MFS. A number of families have now been identified and studied who inherit aortic aneurysms in an autosomal dominant fashion but who do not meet clinical criteria of MFS and have no molecular evidence of fibrillin abnormalities. Vaughan et al. (259) identified one genetic locus for this disorder (FAA1) on human chromosome 11q23.2–q24. Similarly, Guo et al. (260) described a genetic locus for a more restricted form of this disorder that affects only the thoracic aorta at human chromosome 5q13–q14. Although specific gene defects at these loci remain to be identified, these clinical and molecular genetic studies highlight the necessity of procuring a careful family history and screening of first-degree family members of patients when probands with aortic aneurysms are identified.



Transesophageal view of the aortic arch demonstrating an arch aneurysm (*thin arrow*) with layering of thrombus inferiorly (*thick arrow*).

Patent Ductus Arteriosus

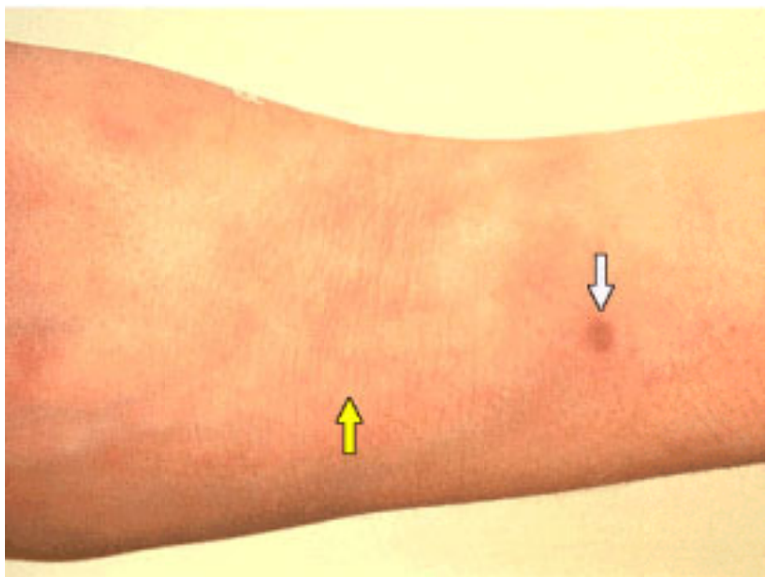
Failure of the ductus arteriosus to close at birth occurs in approximately 0.05% of all full-term infants; patent ductus arteriosus comprises approximately 10% of all congenital heart defects (5). A small fraction of patent ductus arteriosus occurs in variable association with abnormal facial and hand development in the autosomal dominant Char syndrome. This condition was mapped to 6p12–p21, and the gene was recently shown to be a transcription factor, *TFAP2B*, that is expressed in neural crest cells (261).

Supravalvular Aortic Stenosis and Williams Syndrome

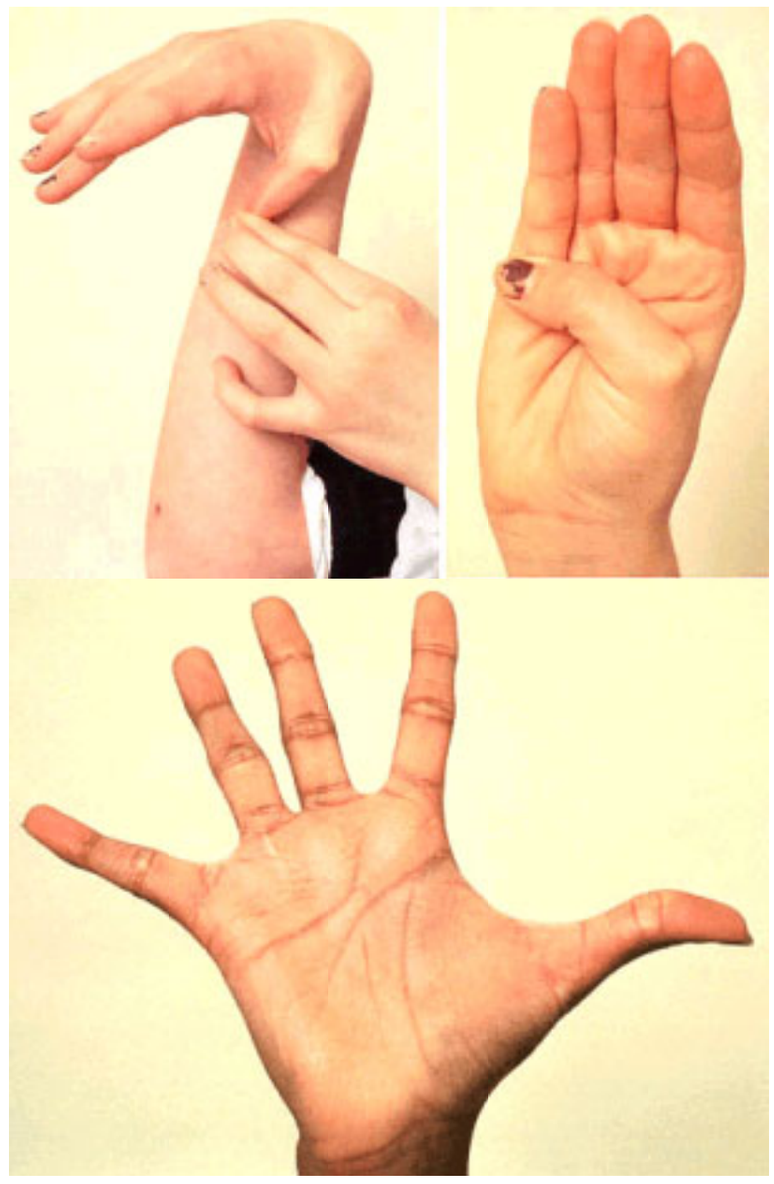
Supravalvular aortic stenosis is characterized by localized or diffuse congenital narrowing of the ascending aorta most pronounced just distal to the aortic valve (262). This is a common finding in Williams syndrome but can occur as an isolated autosomal dominant trait (263). In both instances, the supravalvular aortic stenosis is due to defects (often deletion) of one copy of the tropoelastin gene (*ELN*), which maps to chromosome 7q11.2 (262). Williams syndrome is characterized by infantile hypercalcemia, a face reminiscent of an elf, mental retardation but a gregarious personality, and dental abnormalities (264). The additional defects in Williams syndrome are due to deletion of genes surrounding *ELN*, making this condition a “contiguous gene deletion syndrome” (263). The cardiovascular defects in Williams syndrome, which include peripheral pulmonic stenosis, tend to be severer in males for unclear reasons (265). In both supravalvular aortic stenosis and Williams syndrome, the arterial constriction is not limited to the proximal aorta. Over time, a diffuse arteriopathy develops, which predisposes to stroke, myocardial infarction, and hypertension. The developmental impact of deletion of one *ELN* allele has been examined in mice made hemizygous at this locus. A loss of 50% of normal tropoelastin mRNA and protein was compensated by a 35% increase in the number of elastic lamellae and smooth muscle in arteries (266).

Ehlers-Danlos Syndrome

The Ehlers-Danlos syndrome group of conditions shares features in the skin and joints. Patients with all of the various types have hyperelastic skin and hyperextensible joints (267). The one form with high mortality was previously termed *Ehlers-Danlos syndrome type IV* and is now termed the *vascular type* (268). This condition is due to mutations in *COL3A1*, the gene that encodes type III collagen (269). Arterial walls ordinarily contain both types I and III collagen. In the vascular form of Ehlers-Danlos syndrome, muscular arteries are susceptible to spontaneous rupture, usually without preceding dilatation or dissection. Other organs, such as the bowel and uterus, are also prone to potentially catastrophic rupture (268).



Skin changes of Ehlers-Danlos syndrome. There is thin, velvety appearance of the skin (*yellow arrow*), as well as easy bruisability (*white arrow*).



Ehlers-Danlos syndrome. There is severe joint laxity and hypermobility that may produce joint dislocations (A–C).

Mucocutaneous Venous Malformations

Mucocutaneous venous malformations is a vascular anomaly associated with gastrointestinal bleeding. A gene for mucocutaneous venous malformations was mapped to chromosome 9p21 and cloned (270). The mutated gene codes for the receptor kinase *TIE2*, which is expressed specifically in endothelial cells. The *TIE2* mutations caused a six-to tenfold increase in the phosphorylation activity or ligand-independent hyperphosphorylation of the receptor (270), suggesting a gain-of-function mechanism for development of venous malformations.

Cutaneous Venous Malformations with Glomus Cells

Glomus tumors, or glomangiomas, are benign cutaneous neoplasms derived from specialized arteriovenous shunts (5). Glomus tumors are a clinical and radiologic subtype of venous malformations. The distinctive feature is the presence of undifferentiated smooth muscle cells (glomus cells) surrounding convoluted venous channels. A genetic locus for cutaneous venous malformations with glomus cells was mapped to chromosome 1p22–21 (271), and the specific mutated gene has been identified as a novel gene named glomulin (271a).

Lymphedema

Hereditary primary lymphedema is a developmental disorder of the lymphatic system that leads to a chronic tissue swelling resulting from deficient lymphatic drainage (5,272). A gene for hereditary lymphedema was mapped to chromosome 5q35.3 and identified (273,274). The mutated gene, the *FLT4* gene, encodes vascular endothelial growth factor receptor-3, a receptor for the vascular endothelial growth factor C (274).

An autosomal dominant condition of lymphedema of variable age of onset coupled with a double row of eyelashes (distichiasis) is due to mutations in a gene, *FOXC2*, that encodes a transcription factor (275).

Lymphedema. There is edema of the entire leg with induration and fibrosis of tissues, creating a woody texture.

Cerebral Cavernous Malformations

Cerebral cavernous malformations, or cavernous angiomas, are vascular malformations that may involve any part of the central nervous system and sometimes cause seizures, hemorrhage, or focal neurologic deficit (5). Three genetic loci for cerebral cavernous malformations have been identified: CCM1 on chromosome 7q11.2–21 (276,277), CCM2 on 7p15–13 (278), and CCM3 on 3q25.2–27 (278). The *CCM1* gene has been identified, and it encodes KRIT1, a protein that interacts with RAP1A (KREV1), which is a member of the RAS family of GTPases (279). The CCM2 and CCM3 genes remain to be identified.

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HTT), or Rendu-Osler-Weber syndrome, is a vascular dysplasia leading to telangiectases and arteriovenous malformations of skin, mucosa, and viscera (the lung, liver, and brain) (5). The frequent complications of mucosal involvement are epistaxis and gastrointestinal bleeding. Two genes for

HHT have been identified: the endoglin gene on chromosome 9q34.1 and the *ACVRL1* gene on 12q11–14 (280,281). The endoglin gene encodes a transforming growth factor-b binding protein, its mutations cause HHT1, which is associated with a high frequency of pulmonary arteriovenous malformations (280). The *ACVRL1* gene codes for an activin receptor–like kinase, also a transforming growth factor-b binding protein. The *ACVRL1* mutations cause HHT2, which rarely have pulmonary arteriovenous malformations (281).

Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia). Multiple dark red and slightly elevated telangiectasia in the back (*left panel*) and hands (*right panel*) are shown. These represent arteriovenous malformations of dermal microvasculature.

CONTROVERSIES AND PERSONAL PERSPECTIVES

As increasing numbers of genes associated with cardiovascular diseases are identified, accurate adult and prenatal diagnoses of these conditions become technically feasible. Although few such tests are currently available on a routine clinical basis, we can certainly anticipate commercial application of such testing in the future. In addition, although most research efforts have in the past focused on less common monogenic disorders, more recent studies have begun to identify genetic abnormalities that confer risk for common polygenic cardiovascular disorders such as hypertension and atherosclerosis. Clearly, definition of DNA-based diagnosis for both monogenic and polygenic disorders will be of great interest to patients and their physicians.

As with any clinical test, however, guidelines need to be developed for when to conduct and how to apply DNA testing. In some cases, preliminary genotype-phenotype studies have shown that certain mutations can predict an increased risk of mortality (e.g., sudden death in FHC and the beta-MHC Arg403Gln mutation) or morbidity (e.g., severe cardiac and limb malformation in Holt-Oram syndrome and *TBX5* mutations, which produce protein truncation). However, such DNA-based pre- and postnatal prognostication is limited by the variable expression of disease gene mutations; even within families that inherit “malignant” mutations, there are individuals who show minimal disease manifestations. Moreover, management options (including both currently available standard pharmacologic therapy and anticipated gene manipulation therapy) derived from DNA-based risk stratification have yet to be elucidated. Although studies (282) of at least one disease gene, huntingtin, have demonstrated that there are few significant negative psychological consequences to preclinical diagnosis, outcomes of studies demonstrating a universal benefit to such testing are not yet available.

Thus, we believe that at this time, DNA-based diagnosis should be selectively applied. Frequently, establishment of familial disease patterns by history is more than adequate for diagnosis and management when coupled with routine physical examination and imaging modalities. In fact, because a thorough family history and noninvasive evaluation may often be sufficient, they should always be carefully performed. Thorough consideration must be given to each patient’s cultural, social, and financial situation, as well as his or her medical condition. In addition, before DNA-based testing, the physician should conduct a careful discussion with each patient regarding the reliability, medical risks, and clinical, social, and financial implications of both positive and negative test results and how they might have an impact on the patient’s medical and personal decision making. To facilitate the appropriate application of DNA-based diagnoses, all candidate patients should be counseled both before and after testing by a physician with experience in both clinical genetics and the disease state in question.

In summary, genetic studies will have far-reaching effects on the diagnosis, treatment, and prevention of heart disease. They will lead to precise and definitive genetic diagnoses (including prenatal diagnosis), early detection of persons at high risk for disease development (even in the absence of symptoms), ore rational and specific therapeutic intervention, and ultimately, prevention of many cardiovascular disorders.

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THE FUTURE

The genetic studies of cardiovascular disease will go through multiple phases, including disease gene identification, diagnostic genetic testing, pharmacogenomics, and therapy. We are currently at the peak of the gene discovery phase. Genes for many rare monogenic cardiovascular disorders have been identified. Study of common diseases is progressing, both in animals and in humans. Future studies will continue to identify new genes for the monogenic forms of cardiovascular diseases as well as the primary genetic causes for complex and polygenic disorders such as coronary artery disease, heart failure, and hypertension. Ultimately, genetic testing will benefit many patients by providing risk assessment and allowing implementation of medical surveillance and lifestyle planning programs to reduce risks. The novel field of pharmacogenomics has just started, and therapies based on disease gene discoveries may take an unpredictable length of time to reach and benefit patients. The completion of the sequencing of the human genome and the development of new bioinformatic tools promise rapid progress in all these four fields in the near future.

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GENE THERAPY

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Gene transfer is the introduction and expression of recombinant genes in mammalian cells. Although the field of human gene therapy is young, having its origins in the mid-1980s, major advances in the past 20 years have been in scientific principles, vectors, and delivery systems, development of animal models, and applications to specific diseases. Genetic models of human disease have been created using gene transfer techniques, and these models have been used to understand the pathophysiology of cardiovascular diseases as well as to develop new therapies. The concept that one might use a recombinant gene, rather than a drug, to treat a cardiovascular disease is relatively straightforward. However, the technical difficulties of selecting the appropriate gene and expressing it in a sufficient number of cells to achieve the appropriate biologic effect have been the major challenges in the field. In this chapter, the field of gene transfer in relation to cardiovascular disease is reviewed. The principles of gene therapy are defined. Viral and nonviral vectors used for cardiovascular gene transfer are reviewed. Animal models of cardiovascular disease based on gene transfer approaches are discussed. Finally, prospects for gene therapy of cardiovascular diseases are critically analyzed.

GLOSSARY

Antisense RNA: A single strand of RNA that is complementary to RNA sense strand. Binding of antisense to sense strand creates a double-stranded RNA hybrid that is not translated into protein.

Coding region: The portion of the gene or messenger RNA (mRNA) that contains the base pair sequences that are translated into protein.

Complementary DNA (cDNA): A single-stranded DNA sequence that is synthesized from the RNA strand by reverse transcriptase and is complementary to an mRNA coding region.

Electroporation: A method to transfect cells that employs an electrical field to affect the entry of DNA into cells.

Episomes: Genetic sequences that exist in stable form separate from the chromosome.

Exons: The segments of a gene that remain after splicing of the primary RNA transcript and make up mature mRNA, which in turn encodes protein.

Expression, stable: Expression of a gene that has been transfected into cells and is maintained long term in the target cell.

Expression, transient: Expression of a gene that has been transfected into target cells and is maintained short term in the cell.

Homologous: Common structural features found in two separate genes, which suggest a common ancestor gene.

Intron: Noncoding gene sequences. The segments of a gene that are transcribed into the primary nuclear RNA transcript but are excised during RNA splicing.

Oligonucleotides: A short polymer of DNA that is synthesized to perform studies of gene expression and function.

Plasmids: Naturally occurring circular DNA molecules that replicate in bacteria, which can be modified for use as vectors.

Promoter: The region of a gene that binds RNA polymerase and initiates gene transcription. Promoters can be constitutive-active in all cell types, cell-specific-active only in a specific cell type, or inducible switched on or off.

Recombination: The joining together of different segments of identical DNA sequence into a single continuous piece of nucleic acid sequence.

Reporter gene: A gene that is employed to assess the relative activity of a promoter or to encode a protein that is normally not found in the target cell, thereby allowing assessment of the promoter or gene expression in a target cell.

Reverse transcriptase: An enzyme that catalyzes the synthesis of DNA from an RNA template.

Sense strand: The single strand of DNA that gives rise to the RNA from which protein can be translated.

Transcription: The synthesis of mRNA from a DNA template by RNA polymerase.

Transfection: A technique that is used to transfer naked DNA to the nside of the cell, resulting in the expression of the gene in the target cell.

Translation: The synthesis of protein from the mRNA template by ribosomes.

Vector: A genetic carrier used to deliver exogenous DNA fragments into a host cell.

HISTORICAL PERSPECTIVE

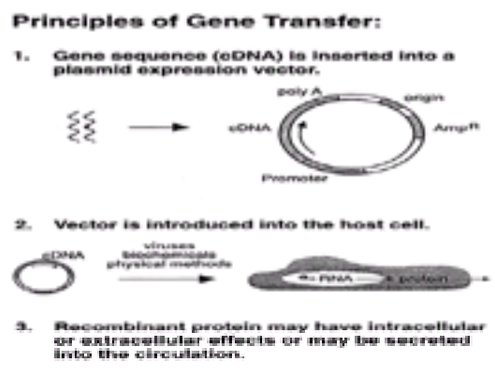
The field of human gene therapy has its origin in molecular biology and recombinant DNA technology. Major discoveries in molecular biology since 1950 have laid the foundation for the scientific basis for current molecular approaches to studying human disease. DNA was first discovered in 1944 as the genetic material in bacterial

cells (1). Watson and Crick determined the double helical structure of DNA in 1953 (2). Nirenberg and Leder elucidated the genetic code by 1964 (3), and the first recombinant DNA molecules were synthesized using molecular biology techniques by 1972 (4,5). The scientific basis for gene therapy was developed in the 1970s, based on knowledge of the mechanisms of cell transformation by tumor viruses (6). The principles of gene transfer are based on the entry of foreign recombinant DNA into a host cell. Cells are resistant to the uptake of foreign genes, and viruses have adapted methods to gain entry into the cell. Early gene transfer methods adapted viruses (modified to be replication incompetent) to carry recombinant genes into cells (7,8). Basic investigations of tumor viruses, particularly retroviruses, laid the scientific foundation for the development of gene therapy in the 1980s. In the early 1990s, investigators used their knowledge of viral vectors and gene delivery to develop animal models of human disease (9,10,11 and 12). These experimental models evolved into the development of human gene therapy protocols in the United States. The first approved trial of gene transfer in humans was performed in May 1989 (13). A human gene therapy trial was initiated in 1990 for adenosine deaminase deficiency, which used *ex vivo* delivery of retroviral vectors encoding the human *ADA* gene into lymphocytes (14). In the early to mid-1990s, the approval process for human gene therapy trials consisted of two components: first, approval by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH); and second, approval by the U.S. Food and Drug Administration (FDA). The RAC was established to review the risks and benefits of the use of recombinant DNA in institutions receiving support from the NIH. Approval from the RAC was required since recombinant genes were being used in human subjects. Through 1996, more than 100 protocols were presented for approval to the RAC and FDA (11). The majority of these protocols was directed toward treating cancer, acquired immunodeficiency syndrome, and single-gene inherited disorders. In 1995, Dr. Harold Varmus, then Director of the NIH, appointed an ad hoc committee to assess the current status and promise of gene therapy. The report of this committee, chaired by Drs. Orkin and Motulsky, led to a general review of the field of gene therapy in the United States. Many of their recommendations are discussed later in this chapter in the section Controversies and Personal Perspectives. One outcome of their report was reconfiguration of the RAC, since in its role as evaluating risk, it was not judging scientific merit of the proposals. The FDA now must approve all proposals for human gene therapy trials in the United States. In addition, the tragic death of a young man in a gene therapy trial has appropriately led to a critical reevaluation of the conduct of clinical gene therapy studies in the United States.

PRINCIPLES AND CONCEPTS OF GENE TRANSFER

Gene therapy is a set of approaches to the treatment of human disease based on the transfer of genetic material into an individual. Gene delivery can be achieved either by direct introduction of vector or DNA to blood or tissues, or indirectly through the modification of cells that have been transduced to carry the foreign DNA. Gene therapy treats a disease in an individual by the administration of DNA rather than a drug. Somatic cells, not germ cells, are the target of these efforts. Therefore, gene therapy affects only individuals and not their offspring.

An initial step in the delivery of genes to individuals is the construction of gene transfer vectors (eFig. 101.0.1). A vector carries the recombinant gene (or DNA or RNA) into cells within a tissue. Vectors are used to transfer genes into cells because most cells are resistant to the uptake of foreign DNA. Vectors penetrate host cells with varying efficiency, depending on the cell type and the vector. Current viral vectors include retroviral vectors, adenoviral vectors, adeno-associated vectors, and herpes simplex viruses. Nonviral vectors include plasmid DNA, cationic liposomes, and biolistics (15).



***e*FIGURE 101.0.1** Delivery and expression of a recombinant gene within an individual. The complementary DNA (cDNA) is ligated into a plasmid expression vector. This vector may be introduced into the host cell alone or with a shuttle vector, such as a virus or lipid. Once within the cell, the recombinant gene is expressed and may exert autocrine or paracrine effects. (From Nabel EG, Pompili VJ, Plautz GE, et al. Gene transfer and vascular disease. *Cardiovasc Res* 1994;28:445–455, with permission.)

After construction of a vector, the vector is generally tested in the laboratory in cultured target cells. If the gene is adequately expressed in these target cells, then animal models are developed *in vivo*. Gene delivery can be achieved by two methods: *ex vivo* and *in vivo* approaches. *Ex vivo* gene transfer involves the removal of autologous cells from the individual, genetically modifying or transducing the cells in culture, and returning the genetically modified autologous cells to the individual (16,17). *Ex vivo* gene transfer permits the introduction of recombinant genetic material into a particular cell type (e.g., a smooth muscle cell), and analysis of gene expression within that cell type (18). *Ex vivo* gene transfer, however, is a cumbersome and costly procedure, requiring the establishment and modification of cells in the laboratory. *In vivo* gene transfer, on the other hand, is a relatively straightforward approach by which the vector harboring the foreign DNA is directly inserted into host cells *in vivo*. This might be achieved by direct injection (19) or catheter-mediated gene delivery (20). After *in vivo* gene transfer, recombinant genes are generally expressed in multiple cell types. Both *ex vivo* and *in vivo* gene transfer approaches have been used to develop animal models of cardiovascular disease (21). *In vivo* approaches using catheter-mediated gene delivery have gained attention more recently (22,23).

The fate of recombinant DNA, once inside host cells, has been difficult to regulate and control. Considerable efforts have been devoted to developing methods for retaining the correct function of the gene and for regulating the gene so that the physiologic effects of gene expression can be evaluated.

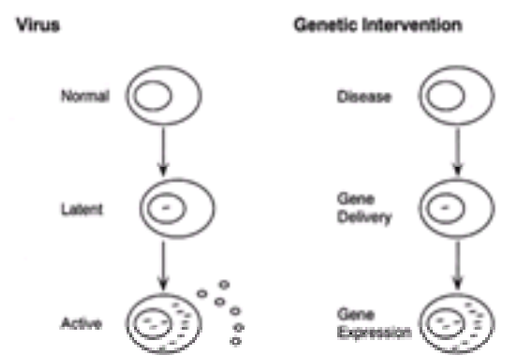
As the field of gene therapy has grown and seasoned, several important concepts have emerged. First, genetic defects contribute to the pathophysiology of many human diseases. Alterations or mutations in human genes result in abnormal phenotypes and disease. For example, an inherited mutation in the cystic fibrosis transmembrane regulator gene (*CFTR*) results in the disease cystic fibrosis (24). There are many acquired diseases in which genetic mutations contribute to the pathophysiology of the disease. Colon cancer is one example in which many individuals have inherited mutations in a gene that regulates cell growth and DNA repair, known as *p53* (25). Likewise, an individual can acquire genetic changes within cells due to viral infections, which in turn lead to serious disease. For example, infection of T-lymphocytes by human immunodeficiency virus results in alterations in T-cell genome and abnormal T-cell function (26,27). Many acquired diseases are characterized by normal genetic structure but abnormal expression of genes. For example, in atherosclerosis, normal repair of an injured artery leads to abnormal expression of cytokine and growth factor genes (28). Therefore, many human diseases, both inherited and acquired, are characterized by genetic mutations that result in abnormal gene expression and pathophysiology.

Second, the fields of genetics and gene therapy, in the past, have developed in parallel, but there is increasing recognition of the interdependence of the two areas. The human genome has been mapped (29). The fields of genomics and proteomics are emerging. Studies of gene expression and protein mapping will influence the diagnosis and treatment of cardiovascular diseases. Genomics, proteomics, and gene therapy do indeed go hand in hand and must be developed together.

Third, DNA is a drug that is being used to treat human disease. Therefore, the evolution of DNA as a drug is analogous to traditional drug development in the pharmaceutical industry. However, there are unique features that require special attention, including a greater understanding of the introduction and expression of genes within cells, host–cell interactions, and dose-response studies to determine the optimal concentrations of DNA that will achieve maximal biologic effect with minimal toxicity.

VECTORS FOR GENE THERAPY

Gene transfer vectors have relied on normal mechanisms of viral infection of human cells. For example, viruses have evolved mechanisms for receptor-mediated entry into human cells (6,30). Once within a cell, a virus, such as human immunodeficiency virus, may reside latent for long periods of time. On viral activation by cytokines or other host genes, active viral replication occurs. In a similar manner, researchers have modified viruses to become vectors that carry a recombinant gene into a cell, but cannot replicate within the cell (eFig. 101.0.2). The recombinant gene resides within the nucleus where it either integrates into host genome or undergoes episomal replication.



***e*FIGURE 101.0.2** Viral infection as a paradigm for gene therapy. Genetic interventions are modeled after viral infection of human cells, in which a virus gains entry into a cell and is expressed using host cellular factors.

An increasing number of vectors have been developed and evaluated for cardiovascular gene therapy. These vectors are summarized in *e*Table 101.0.1. Viral vectors (retroviruses, adenoviruses, adeno-associated viruses, and herpes simplex viruses) have been the predominant methods for delivery of genes into cells. In response to growing concerns about the safety of viral vectors, considerable effort has been expended to optimize nonviral vectors (plasmid DNA, DNA liposome complexes, and biolistics). These endeavors have succeeded in providing a safer alternative for a number of applications. There are advantages and disadvantages to each vector, dependent in part on the particular application, including cell type and organ system. These vectors differ in efficiency, integration, stability, and potential for immunogenicity (*e*Table 101.0.2). As each of these vectors is discussed, several concepts should be kept in mind. When selecting a suitable vector, certain features are desired. First, specificity to target tissues is critical. The vector should achieve local gene expression within an organ without systemic shedding and widespread toxicity. The vector should be delivered to host cells in sufficient quantity to result in high-level gene expression. Expression of the gene should persist for a sufficient period of time to treat the disease. Gene expression preferably is regulated through tissue-specific promoters or inducible or repressible promoters, or both. Finally, regulatory concerns about possible vector and gene toxicity should be kept in mind.

***e*TABLE 101.0.1** SOMATIC GENE TRANSFER VECTORS

Vector	Advantages	Disadvantages	Applications
Viral			
Retrovirus	Biology well understood	Low titer	Marker studies
	Stable integration into host cells	Infection limited to dividing cells	*Ex vivo* treatments
	Efficient entry	Expression difficult to control and stabilize	Vaccines
	No viral genes in vector	Expensive and complex to prepare	
Adenovirus	High titers	Vectors contain viral genes	Localized *in vivo* treatments: cystic fibrosis, short-term treatments such as cancer and cardiovascular disease
	Efficient entry into most cell types	Immunogenic, stimulating T- and B-cell responses	
	High level of expression	Generation of replication-competent virus	
	Infection of nondividing cells	Factors controlling tropism not well understood	
Adeno-associated virus	Integration at specific sites	Requires replicating adenovirus to grow	Similar to adenovirus
		No helper cell line	
		Limited insert size	
Herpesvirus	High titers	Complex construction	Neurologic diseases
	May be neurotropic	No packaging cell lines	
Pseudotyped retrovirus	High titers	Similar to retrovirus	Not established; may be similar to retrovirus
	Higher efficiency of retrovirus infection		
	Broader host range		
Nonviral			
Naked DNA	Easy to prepare	Inefficient entry and uptake	Topical or mechanical applications, or both, including skin and vasculature
	No size constraints	Limited persistence and lack of stability	
	High level of safety		
	No viral genes		
	Lack of integration		
DNA liposomes	Same as naked DNA	Limited persistence and lack of stability	Direct *in vivo* applications, cancer, cardiovascular disease, cystic fibrosis
	More efficient uptake of DNA		
Adenoviral polylysine DNA conjugate	Same as DNA liposomes	Requires adenovirus	Same as DNA liposomes
	Targetable to specific cell types	Complex to construct	

Modified from Nabel EG. Introduction to vectors for gene therapy. *Curr Protocols Hum Gene* 1996;[Suppl 10]:Unit 12.0.

***e*TABLE 101.0.2** COMPARISON OF GENE TRANSFER VECTORS

Vector	Efficiency	Integration	Stability	Immunogenicity
Viral				
Retrovirus	+	+	+	±
Adenovirus	+++	–	–	++
Adeno-associated virus	+	±	±	–
Herpes simplex virus	++	±	±	++
Nonviral				
Plasmid DNA	+	–	±	–
Cationic liposomes	+	±	±	–
Microparticle DNA	+++	+	+	–

Several approaches have been developed to achieve site-specific gene expression. These include ligand-directed vectors, targeted gene expression using cell-specific promoters, catheter-mediated gene delivery, and direct injection (31). In the cardiovascular system, catheter-mediated gene delivery has been used most often to achieve site-specific gene expression within focal segments of blood vessels (20,21). Direct injection may be a feasible approach for gene delivery into the myocardium (32). Cell-specific gene expression may be desirable for selected approaches to vascular gene transfer, such as inhibition of inflammatory cells or smooth muscle cell proliferation. Although a number of laboratories have identified smooth muscle (33,34) and endothelial (35) cell-specific promoters, these promoters have not been extensively evaluated yet in gene transfer vectors.

Viral Vectors

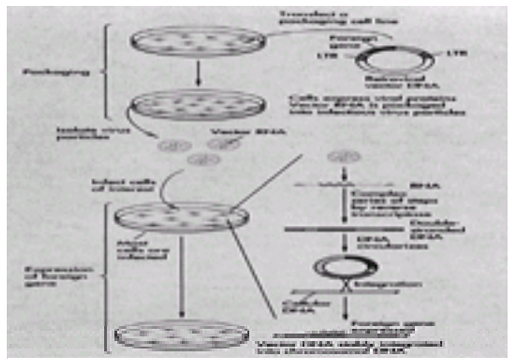
Retroviral Vectors

Retroviral vectors were the first viral vectors developed for gene transfer (9,36). These vectors promote efficient gene transfer and expression in cultured primary cells from humans and other animals. The transferred genes are integrated at random sites in the host cell genome with minimal alteration of host cell genomic DNA. Retroviral vectors, however, are replication defective (i.e., they do not encode any viral proteins, and hence, they do not replicate within the host cell) (37,38). Therefore, when using a replication-deficient viral vector, the process of gene transfer and expression is called *transduction*, as opposed to infection, to differentiate this

process from viral infection, which implies further viral replication and spread.

The advantages of retroviral vectors include a well-understood biology (6). They produce stable integration into host cell genome. Entry into host cell is sufficient via receptor-mediated uptake. No viral genes within the vector result in enhanced safety for human use (39). Disadvantages of these vectors include low titer production (40). Transduction is limited to dividing cells, thus lowering the number of applications to human diseases (41). Gene expression after retroviral transduction is difficult to control and stabilize. Finally, retroviral vectors are expensive and complex to prepare.

Production of the retroviral vector consists of two steps, the construction of the vector in plasma DNA form, followed by production of the virus from cultured cells that express proteins required for viral replication (42). An overview of this process is shown in eFigure 101.0.3. Construction of replication-defective retroviral vectors relies on the use of retrovirus packaging cells that synthesize all of the retroviral proteins but do not produce a replication-competent virus. Many packaging cell lines have been constructed for mammalian cell gene transfer (43). The range of cells transduced by retroviral vectors depends on the retrovirus used to make the packaging cell line. Amphotropic retroviral vectors are the most commonly used packing cell line because of their wide host range. A detailed protocol for the construction of retroviral vectors is reviewed elsewhere (42).



***e*FIGURE 101.0.3** Construction of a retroviral vector. The recombinant gene is cloned into a retroviral plasmid, which lacks viral replication genes. The retroviral plasmid is transfected into a packaging cell line that contains a provirus with replication genes. Vector RNA is packaged into virions, capable of infecting target cells. LTR, long terminal repeat. [From Watson JD, Gillman M, Witkowski J, et al., eds. *Recombinant DNA.* New York: Scientific American Books (WH Freeman Co), 1992:227, with permission.]

The current applications of retroviral vectors include marking studies in which autologous cells are removed from an individual, transduced to express a reporter or marker gene *in vitro* using a retroviral vector, and given intravenously back to the individual. The fate of these cells *in vivo* can then be traced (13). In addition, retroviral vectors are also useful for other *ex vivo* treatments involving T cells (14), hematopoietic stem cells (44), and endothelial cells (45,46 and 47). Finally, retroviral vectors are being evaluated for use in cancer vaccines (48).

All packaging lines still have the potential to produce helper virus by recombination events between the vector, helper virus sequences in the packaging cells, and endogenous retroviral elements, but fortunately, the frequency of helper production in currently used packaging cells is low (39). No viral proteins are synthesized during viral entry and integration into target cells; thus all viral protein-coding regions can be removed from the retroviral vectors without altering gene transfer efficiency. Transient transfection of retroviral vectors in murine packaging cell lines generally results in viral titers of less than 10^5 units per mL. Stable cell lines typically produce viral titers in the 10^5 to 10^7 range. Generation of stable vector-producing clones usually takes 1 month.

Pseudotype Retroviral Vectors

A pseudotyped retrovirus is defined as a retrovirus that incorporates the envelope protein of a second virus. The host range of the pseudotype is that of the virus donating the envelope protein. The envelope glycoprotein (G) of the vesicular stomatitis virus (VSV), a member of the rhabdovirus family, can be efficiently incorporated into a retroviral particle. VSV-G pseudotype retroviral vectors have an increased host range, because VSV infects cells ranging from insects to primates, unlike the amphotropic virus. The VSV-G pseudotype vectors are also able to infect mammalian cells more efficiently than conventional amphotropic vectors. VSV-G pseudotyped retroviral vectors can be concentrated to titers greater than 10^9 CFU per mL. Therefore, VSV-G pseudotype retroviral vectors have gained favor because they extend the use of retroviral vectors for stable gene transfer into species not previously accessible to retroviral infection. Also, they allow more efficient gene transfer into mammalian cells for possible treatment of human diseases. The production of pseudotyped retroviral vectors is similar to retroviral vectors (49). The applications of pseudotype retroviral vectors are not well established, but may be similar to retroviruses (50,51).

Adenoviral Vectors

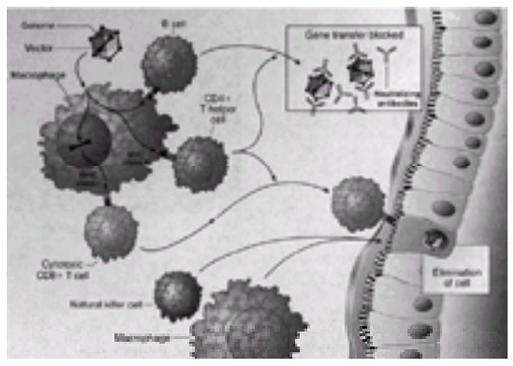
Viral vectors based on human adenoviruses have shown considerable promise for *in vivo* gene delivery compared with retroviruses, because they can transfer recombinant genes efficiently into a wide variety of dividing and nondividing cells. Adenoviral vectors are also attractive because large amounts of highly purified recombinant virus, 10^{12} particles per mL, can be produced from expansion of viral plaques. Human adenoviruses were initially evaluated as vectors to treat cystic fibrosis because of their tropism for pulmonary endothelial cells (52). The human adenovirus is a double-stranded DNA virus with a 36-kb linear genome that contains four early transcription units (E1 to E4), which are active at early time points after infection (3 to 12 hours), and five late transcription units (L1 to L5), which are active after 12 hours and produce the structural genes of the virus. Further details on the human adenovirus and its life cycle are reviewed elsewhere (53).

Adenoviral vectors are propagated in packaging cell lines, such as 293, which supply E1 function in trans. The final vector, however, is replication defective. Adenoviral vectors are constructed using a plasmid that contains the recombinant gene of interest and flanking adenoviral sequences. This adenoviral transfer plasmid is cotransfected with an adenoviral backbone into 293 cells. Recombination occurs in the region of overlap, in the E1 region between the restricted viral DNA or viral backbone and the plasmid. Viral plaques are produced, which then can be expanded. After further rounds of plaque purification, a stock of the adenoviral vectors is produced (54).

Transduction of host cells by adenoviral vectors follows the principles of adenoviral infection of epithelial cells. When the viral genome enters the cell, the early immediate genes (E1) are expressed. They activate other important regulatory early genes, E2 to E4. In the second phase of replication, late genes, L1 to L5, are expressed, leading to the production of more virus and cell death. The adenovirus has been engineered to be replication defective by deleting the early adenovirus genes that activate other viral genes (55). In the absence of these regulatory genes, the virus should not replicate *in vivo*, and the late viral genes should remain dormant. The first-generation adenoviral vectors have deletion of E1 genes and partial deletion of E3 genes, which renders them replication defective.

There has been extensive experience with first-generation adenoviral vectors in many cell types. Several themes have emerged. Concerns about the hazards of viral recombination, replication, and shedding have not been realized (56). Inflammation occurs with first-generation adenoviral vectors in a dose-dependent manner at the site of gene transfer, but there are differences among species and tissues within species in the quality and quantity of the inflammation (57). A consistent finding is that the expression of genes after adenoviral transduction is transient (58,59,60 and 61). Attempts to restore expression by the administration of a second dose using the same serotype of the vector are usually not successful. These limitations have tempered the initial enthusiasm for first-generation adenoviral vectors (56,62,63 and 64).

Transient expression of the therapeutic gene has been a major limitation of first-generation adenoviral vectors for application to many human diseases. Studies have elucidated possible mechanisms (65,66). There are humoral and cellular immune responses to the vector and vector-infected host cells (*e*Fig. 101.0.4). To overcome these immune problems, second-generation adenoviral vectors have been engineered to minimize the expression of viral antigens. Another approach is to prevent activation of T-helper cells by transient immunosuppression during the delivery of the adenoviral vector. Combining these approaches may prove useful in minimizing the immune reaction to adenoviral vectors. Current applications of adenoviral vectors include localized *in vivo* treatments, such as vascular diseases (67,68 and 69) and cystic fibrosis (57). Short-term treatments requiring transient expression of the gene are also likely approaches, including vascular diseases and cancer (70,71).



***e*FIGURE 101.0.4** Humoral and cellular immunity to adenoviral vectors. Vectors are taken up by macrophages where viral proteins are presented by class I major histocompatibility complex molecules to $CD8^+$ T cells. $CD4^+$ T cells also stimulate cytotoxic T-lymphocytes that destroy the genetically modified target cell and produce inflammation. In addition, B cells are activated to secrete humoral antibodies that neutralize the vector. These neutralizing antibodies then prevent subsequent administration of the same viral serotype. (From Wilson JM. Adenoviruses as gene-delivery vehicles. *N Engl J Med* 1996;334:1185–1187, with permission.)

The early experience with adenoviral vectors has been useful in defining many principles of *in vivo* gene transfer that are of general importance to other vector systems, including host responses to the vector and transgene. Broader applications of adenoviral vectors will require modifications that improve efficiency and promote targeting of vector uptake. Modifications in the vector to reduce viral antigen presentation, combined with transient immune suppression, may prove useful.

Adeno-Associated Viral Vectors

Adeno-associated viral (AAV) vectors have been explored for gene transfer. Recombinant AAV (rAAV) vectors are based on nonpathogenic human parvovirus, an adeno-associated virus (72). rAAV have two important advantages: their physical stability, which allows *in vivo* administration, and their ability to maintain stable gene expression.

rAAV can infect many cell types, including quiescent cells. Wild-type AAV infection results in integration into host chromosomes where it exists as a stable provirus. Wild-type AAV has preferences for insertion into certain chromosomal locations (73). If latently infected AAV-infected cells are subsequently infected with adenovirus, the AAV genome is rescued or excised from the chromosome, replicated, and packaged to produce progeny virions. This is the principle behind construction of rAAV vectors (74). The production of rAAV involves cotransfection of a rAAV-vector plasmid and the AAV-helper plasmid into 293 cells. These cells are subsequently infected with adenovirus to produce progeny virions. The rAAV virions are then separated from the adenovirus on cesium chloride gradients. rAAV stocks with titers as high as 10^{10} particles can be produced.

Transduction performed *in vivo* using rAAV factors has shown long-term gene expression; furthermore, the level of gene expression does not decrease substantially over time. Studies are in progress to evaluate the application of this vector to the vasculature and myocardium. There has been greater initial success in the myocardium (75), and limited to no success in the vasculature (76). The major advantage of rAAV is integration at specific sites in host cell genome as well as persistent expression (73). Major disadvantages of rAAV include the lack of helper cell lines, size limitation of the recombinant genome that can be packaged (4,681 bases), and a requirement for replicating adenovirus to grow. Eventual applications of rAAV vectors may be similar to adenovirus, including localized *in vivo* treatments.

Nonviral Vectors

Nonviral vectors offer safety advantages for a number of applications to human gene therapy. Nonviral vectors currently in development include plasmid DNA, DNA liposome complexes, and biolistics or particle-mediated DNA delivery.

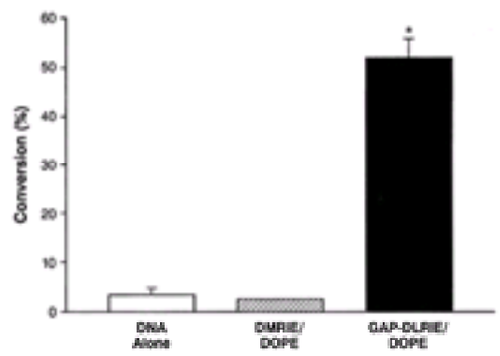
Plasmid DNA

Plasmid DNA can be delivered to cells, under certain conditions, in the absence of a vector shuttle. The use of plasmid DNA alone offers several advantages, including ease of preparation. There are no size constraints for insertion of the transgene into the plasmid backbone. Experience with laboratory preparation and use of plasmid DNA in human trials has demonstrated considerable safety and lack of toxicity (77). There are no viral genes within the plasmid backbone. Expression of plasmid DNA within host cells does not require integration into host genome. Disadvantages of plasmid DNA include inefficient entry and uptake into cells, as well as limited persistence and a lack of stability. The major applications of plasmid DNA include topical or mechanical applications, or both, including catheter-mediated gene delivery (78), direct injection into tumors (77), and vaccination by direct injection into skeletal muscle (79). Several human gene therapy trials have used direct injection of DNA to treat cancer (77), as well as catheter-mediated gene delivery of plasmid DNA to the vasculature (80).

DNA Liposome Complexes

Cationic liposomes are positively charged lipid molecules that complex with negatively charged DNA and facilitate entry into cells. The mechanisms by which cell entry occurs are not well worked out, but receptor-mediated endocytosis or fusion with cell membranes is most likely. Several generations of cationic lipid formulations have been constructed and tested (81,82 and 83). In general, newer formulations have improved uptake by cells and increased gene expression (84). After entry into the cell, the lipid DNA complex is engulfed by lysosomes. Dissociation of lipid from DNA occurs with escape of plasmid DNA that is transported by unknown mechanisms to the nucleus (85). A limitation of DNA liposome complexes has been endosomal degradation; current research on liposome technology has focused on mechanisms to enhance cell entry and reduce degradation in the cytoplasm.

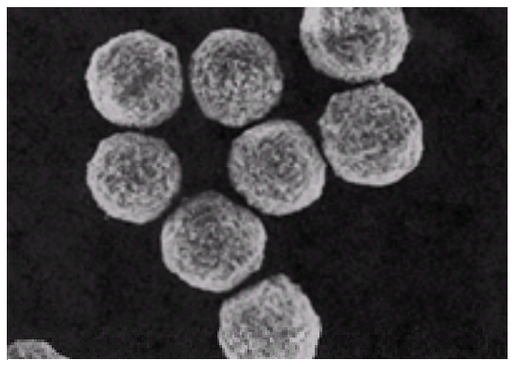
There are multiple advantages to using cationic DNA liposome complexes as a gene-delivery vehicle. These complexes are easy to prepare, and there are no constraints on the size of the transgene. Because no viral genes are present within the plasmid, these complexes are safe for human use. However, limited persistence and lack of stability are major concerns. More recently, a newer cationic liposome has been evaluated that results in 15-fold higher levels of gene expression in arteries *in vivo* compared with previous generations (eFig. 101.0.5) (84). Current applications for DNA liposomes include direct *in vivo* use in cardiovascular diseases (84), cancer (77), and cystic fibrosis (86).



***e*FIGURE 101.0.5** Comparison of gene expression with a newer formulation of cationic liposomes. Porcine arteries were transfected *in vivo* with a CAT reporter gene alone (DNA alone) or complexed with two lipids, DMRIE/DOPE or GAP-DLRIE/DOPE. Percent CAT conversion was measured 2 days later. Gene transfer with GAP-DLRIE/DOPE resulted in a 15-fold increase in gene expression. (From Stephan DJ, Yang ZY, San H, et al. A new cationic liposome DNA complex enhances the efficiency of arterial gene transfer *in vivo. Hum Gene Ther* 1996;7:1803–1812, with permission.)

Biolistics

Particle-mediated or gene gun technologies have been developed as a nonviral method for gene transfer into various experimental systems. A physical force is used to introduce plasmid DNA coated onto microscopic gold particles into target cells. This technology was initially developed in the agricultural industry for plant cell wall biology. More recently, there have been applications to human systems, such as the skin. Gene delivery is achieved by generating a strong shock wave to accelerate DNA-coated gold particles to high speeds, providing the momentum to penetrate the target cells. This concept has now been extended to the delivery of other molecules, including RNA and proteins. Before transfection, the plasmid DNA must be attached to the gold particles (eFig. 101.0.6). This is accomplished by precipitation of the DNA from solution in the presence of the gold particles by addition of polycations, spermidine, and $CaCl_2$. The particles are then resuspended in ethanol and coated onto the inner wall of tenzeo tubing. The DNA gold-coated tubing is cut into $^1/_2$-in. length cartridges, which are inserted into the cylinder of the gene gun device. Physical energy is generated by helium gas to shoot the particles into the tissue (87). The size of the gold particles is approximately 2.0 µm in diameter.



***e*FIGURE 101.0.6** DNA-coated gold particles. DNA is coated onto microscopic gold particles (2.0 µm), and the particles are shot into the target cell using a gun device driven by pressure from helium gas.

The major uses for particle-mediated gene delivery include epidermal skin and surgically exposed internal organs, such as the liver, pancreas, and skeletal muscle. *Ex vivo* applications include transduction of primary T cells, which are then returned to the patient for treatment of acquired immunodeficiency syndrome (88). With a helium pulse gene gun device, DNA-coded gold bead penetration and transgene expression has been detected 20 to 40 cell layers deep.

ANIMAL MODELS OF GENE TRANSFER

One of the major applications of gene transfer has been the development of animal models of cardiovascular diseases. This progress has been made in parallel with development of animal models of human disease created by germline manipulation of the mouse. Indeed, transgenic technology, including knockout of genes by homologous recombination, has gone hand in hand with gene transfer technology. The combination of these two methods has allowed for the development of powerful genetic models of complex cardiovascular disease. However, these models have largely been limited to the mouse. Due to the complexities of transgene technology, transgenics have been performed primarily in the mouse, with notable exceptions in the rat for studies of hypertension and the rabbit for studies of lipoprotein metabolism. Somatic gene transfer has been used in larger animal models, such as the rat, rabbit, and pig, to model focal vascular disease.

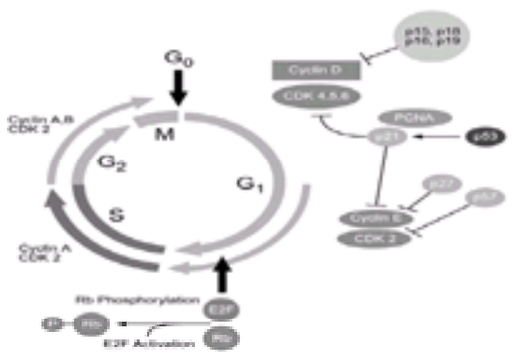
The initial animal models of cardiovascular disease emphasized *ex vivo* approaches, particularly in the vasculature (91). In these models, autologous endothelial cells (6,45,90) or smooth muscle cells (8,46,91) were derived from the host, genetically modified in culture, and then returned to intact blood vessels *in vivo*, where recombinant gene expression was monitored. Other applications included the seeding of vascular prostheses (17). Although these techniques were useful in the vasculature, to establish the principles and feasibility of gene transfer from a practical perspective, they proved to be complex and cumbersome, offering little short-term clinical applicability.

Direct *in vivo* transfer of genes has proven more useful for development of animal models of vascular and myocardial diseases. In the vasculature, these approaches have been used to study growth regulation, angiogenesis, lipoprotein metabolism, and thrombosis. The feasibility and principles of gene transfer have been well worked out in the vasculature by many investigators. These studies have generally used reporter genes to mark gene expression. Different animal models have been studied, including the rat, rabbit, dog, pig, and sheep, using primarily retroviral, liposome, and adenoviral vectors (89). Several themes have emerged. Initial studies of retroviral and liposome-mediated gene transfer in healthy arteries demonstrated low levels of gene expression, generally less than 0.01% of intimal and medial cells (20,92,93). Balloon injury of arteries increased gene expression (94). Gene transfer efficiency was improved after adenoviral-mediated gene transfer in many species (59,60 and 61,95,96). Adenoviral-mediated gene transfer of injured rat (96) and pig (67) arteries resulted in reporter gene expression in intimal endothelial and smooth muscle cells and medial smooth muscle cells, with an efficiency ranging from 10% to 75% (59). Gene expression after adenoviral delivery is transient, generally peaking at 1 to 2 weeks and lost by 1 month (60,61,95). Simple infusion of vector into an intact blood vessel generally results in transfection of endothelial cells (95,97). Manipulation of the artery, by mechanical stretch or pressure, results in gene expression in deeper layers of the vessel and mimics an angioplasty procedure (67,94,98). Several local delivery catheters have been tested for gene administration, each with its own unique features, advantages, and disadvantages (78,99,100).

Cell Cycle and Regulation of Cell Proliferation

Gene transfer is an approach to investigate the *in vivo* function of growth factor, receptor, signal transduction, and cell-cycle proteins. For example, several studies have examined the effects of overexpression of growth factor genes in normal arteries *in vivo*. These growth factor genes include platelet-derived growth factor-b, a secreted form of acidic fibroblast growth factor (FGF-1), and an active secreted form of transforming growth factor-b. Expression of these molecules produced intimal hyperplasia of smooth muscle cells, but the nature of the intimal lesions was different for each molecule. Overexpression of platelet-derived growth factor-b led to smooth muscle cell proliferation (101,102), FGF-1 produced intimal angiogenesis (103), and transforming growth factor-b stimulated procollagen synthesis (104).

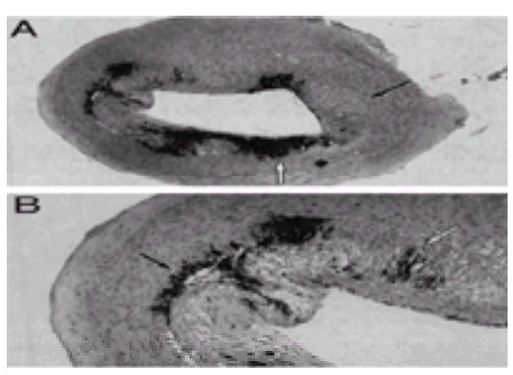
Because expression of multiple growth factor and cytokine genes can all lead to a common end point, intimal hyperplasia, a single inhibitor of one growth factor or its receptor, is likely not to have significant effects on limiting intimal size after arterial injury. Instead, many investigators have pursued regulators of the cell cycle as potential inhibitors of cell growth during vascular repair. When vascular cells are stimulated by mitogens to proliferate, they enter the cell cycle (eFig. 101.0.7) (105,106). The mammalian cell cycle consists of several sequential phases: G_1 or gap 1, S, during which DNA synthesis occurs, G_2 or gap 2, and M, when cells undergo mitosis. Progression through the cell cycle is tightly regulated by the sequential assembly and activation of cyclins and cyclin-dependent kinases (cdks). There are naturally occurring inhibitors of the cyclin-cdk complexes, called the *cyclin-dependent kinase inhibitors*, which arrest cells in G_1 and prevent cell proliferation. Several strategies have been devised to overexpress natural inhibitors of the cyclins and cdks, such as p21 (107,108) or to inhibit the cyclins or cdks directly by antisense oligonucleotides (109,110). Additional approaches include inhibition of protooncogenes, such as c-*myb* (111) and c-*myc* (112), or other cell-cycle proteins, such as proliferating cell nuclear antigen (113,114). These gene products have been tested in balloon-injured rat and pig arteries where they have resulted in a significant reduction in intimal smooth muscle cell proliferation and in intima to media area ratios. Whether these gene products are effective in the treatment of human vascular diseases awaits further testing.



***e*FIGURE 101.0.7** Regulation of the cell cycle. Progression of the cell cycle through G_1 is regulated by the assembly and activation of cyclins and cyclin-dependent kinases (CDKs). Naturally occurring inhibitors of cyclin-CDK complexes, termed the *cyclin-dependent kinase inhibitors*, arrest cells in G_1 and prevent proliferation.

(From Boehm M, Nabel EG. Cell cycle and cell migration: new pieces to the puzzle. *Circulation* 2001;103:2879–2881, with permission.)

Other cell inhibitors have relied on the secretion of cytotoxic molecules, which have paracrine effects on surrounding vascular cells. These approaches offer several advantages over the direct inhibitors of the cell cycle. A major advantage is that the gene product is secreted, and hence a greater number of cells are treated, compared with gene products that remain intracellular. Gene transfer efficiency is less critical when the gene product is secreted. Second, the timing of cell killing can be regulated by the administration of a prodrug. Third, these strategies are selective for dividing cells, and nondividing cells are not affected. Finally, local gene transfer without systemic toxicities can achieve high local concentrations. Two such strategies have been employed to inhibit vascular cell proliferation: a herpes simplex thymidine kinase gene (*HSV-tk*) and a cytosine deaminase gene (*CD*) gene, both of which are converted to active forms by the administration of a prodrug, ganciclovir (a nucleoside analog). *HSV-tk* gene transfer has been tested using adenoviral vectors in injured rat (69,115) and pig (67) arteries as well as injured atherosclerotic rabbit arteries (98) (eFig. 101.0.8). These treatments have been associated with 40% to 60% reduction in intimal cell proliferation and intimal area. A cytosine deaminase gene has also been evaluated in a rabbit model of restenosis in which effects on cell proliferation similar to those of *HSV-tk* were observed (116).



***e*FIGURE 101.0.8** Recombinant gene expression in atherosclerotic rabbit arteries. Peripheral arteries were denuded of endothelium, and the rabbit was lipid-fed for 3 weeks. A second angioplasty was performed, and adenoviral vectors encoding a marker gene were delivered to the injured vessel. Five days later, recombinant marker gene expression was observed in the atherosclerotic intima and media. **A:** Magnification ×100. **B:** Magnification ×250. The black arrows indicate the internal elastic laminae. The white arrows point to areas of recombinant gene expression in the media. (From Simari R, San H, Rekhter M, et al. Regulation of cellular proliferation and intimal formation following balloon injury in atherosclerotic rabbit arteries. *J Clin Invest* 1996;98:225–235, with permission.)

The role of growth inhibitors in the treatment of vascular proliferative diseases has yet to be established. These approaches are likely to be most effective in those settings in which cell proliferation plays a major role in the pathophysiology of the disease. For example, multiple components contribute to the pathophysiology of restenosis, including elastic recoil, thrombosis, and cell proliferation. Although the treatment of restenosis has improved with the use of stents (117,118), it is possible that the combination of a stent, a cell proliferation inhibitor, and an antithrombotic might be the optimal therapy. Stents coated with antiproliferative and antimitotic proteins are in clinical trials; if successful, the next generation of coated stents is likely to include DNA plasmid–coated stents.

Angiogenesis

Angiogenesis for peripheral vascular disease and myocardial insufficiency has been a focus of research efforts. Several candidate molecules have been identified, particularly vascular endothelial growth factor (VEGF) and FGF. VEGF is an endothelial cell-specific mitogen with a signal sequence, resulting in secretion of the active molecule. Plasmid DNA has been applied to an angioplasty catheter (the balloon is coated with a hydrogel polymer) and transferred to iliac arteries of rabbits with ischemic hind limbs. Significant improvements in angiographically proven collaterals, blood flow, and capillary density were observed (22,119). In additional studies, similar results have been obtained with a single intramuscular injection of plasmid DNA-encoding VEGF (120). These animal studies form the basis for a human gene therapy trial for therapeutic angiogenesis in patients with peripheral vascular disease (80). The improvement in collateral vessel formation and limb perfusion achieved with the VEGF gene is comparable with results achieved with a single infusion of recombinant VEGF protein (121). Whether one agent is preferable to another (the gene vs. the protein) will await further studies in humans. Continuous production of protein from a transgene, even in low doses, may be preferable than one or multiple larger doses of recombinant proteins from several perspectives, including safety, systemic toxicity, and production costs.

Methods have also been developed for intracoronary gene transfer of angiogenic genes to enhance coronary blood flow to ischemic myocardium. In a model of stress-induced myocardial ischemia, intracoronary (left anterior descending) infusion of an adenoviral vector encoding FGF-5 resulted in expression of FGF-5 mRNA and protein in ischemic and nonischemic regions of the left anterior descending territory. Expression of this angiogenic factor was associated with regional improvements in myocardial contractility and blood flow (122). Intracoronary infusions of recombinant basic FGF (123,124) and VEGF (125) protein have also enhanced myocardial collateral blood flow in ischemic myocardium of dogs.

Despite these notable results in animals, further evaluation is required. Whether these animal models faithfully reproduce the human disease is not known. The difference between the canine models and human peripheral, myocardial, or both kinds of ischemia may be significant, such that the duration of gene expression that was sufficient to induce collaterals in the animal model may not be so in human disease. Finally, whether these newly formed collaterals have vascular integrity to maintain significant improvements in blood flow and relief of clinical symptoms remains to be tested.

Lipoprotein Metabolism

The development of transgenic mouse technologies has provided a powerful animal model system for studies of the molecular and cellular pathophysiology of human atherosclerosis. Mice have now been produced that overexpress human apolipoprotein (apo)-E (126), human apoA-I (127), human and murine apoAII (128,129), human cholesterol ester transport protein (130), human lecithin-cholesterol acyltransferase (131), and human apoC-III (132). The results of these studies have provided important information on lipoprotein metabolism and atherosclerosis (133). In parallel with these transgenic models, a number of groups have demonstrated that adenoviral vectors can be used to program gene expression to hepatocytes in these animals. Specifically, the efficacy of adenoviral vectors encoding apolipoproteins and lipid-modifying molecules to alter lipid profiles and atherogenesis have been tested (134,135 and 136). For example, injection of adenoviral vectors encoding human lecithin-cholesterol acyltransferase into transgenic mice expressing human apoA-I resulted in elevation of plasma high-density lipoprotein-C levels and human apoA-I levels, which were associated with an increase in cholesterol efflux from serum (137). This study suggested that modifications of high-density lipoprotein composition by overexpression of apolipoproteins, for example, might prove useful as a gene therapy approach to modify atherosclerotic risk. Again, the therapeutic potential of this approach for inherited lipid disorders is unknown and awaits further study.

Thrombotic Disorders

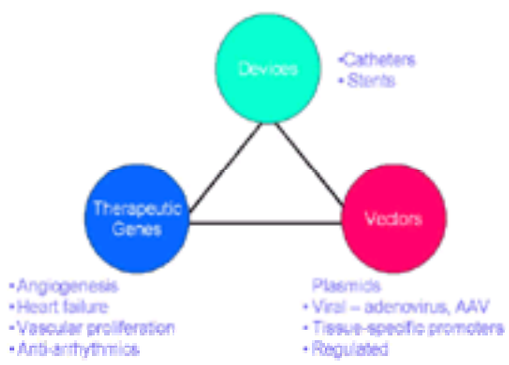
Transgenic technology, including knocking out of genes by homologous recombination, has also been a powerful tool for the analysis of thrombotic disorders and their role in the development of atherosclerosis and other vascular diseases. Murine models for a number of defects in the fibrinolytic and coagulation systems have been constructed, including mice deficient in plasminogen (138), urokinase plasminogen activator and tissue-type plasminogen activator (139), plasminogen activator inhibitor 1 (PAI-1) (140,141), a thrombin receptor (142), and thrombomodulin (143). These studies have provided important and surprising results. For example, mice deficient in thrombomodulin are embryonic lethal (143). Mice lacking a thrombin receptor have variable outcomes; approximately 50% die during embryonic development, whereas 50% survive to birth (142).

These animal models are currently being used to explore the genetic contributions to complex traits, such as atherosclerosis, and to dissect the pathophysiology of vascular diseases, such as the role of protease inhibitors to cell migration and proliferation. Adenoviral vectors have also been constructed to express fibrinolytic proteins, and the feasibility of these vectors infused into knockout mice to rescue the phenotype can be tested. For example, mice deficient in PAI-1 demonstrate accelerated intimal hyperplasia, whereas mice deficient in urokinase plasminogen activator have reduced neointimal formation after arterial injury. Adenoviral-mediated gene transfer of PAI-1 to PAI-1–deficient mice reverses the phenotype (i.e., neointimal formation is reduced) (144). Adenoviral gene transfer may also play a role in gene therapy approaches for the treatment of thrombotic disorders (145).

CLINICAL TRIALS

Cardiovascular diseases are ideal targets for gene therapy. Arterial lesions are focal, facilitating delivery of recombinant gene or protein directly into the site of disease. Devices can be adapted for delivery of gene products to the vasculature or myocardium. Short-term expression is sufficient to treat the disease, and this avoids systemic side effects.

Cardiovascular gene therapy can be thought of as a “three-legged” stool (eFig. 101.0.9). Three components are required: therapeutic genes, delivery device, and vectors. Considerable work by many investigators has identified a number of therapeutic candidate genes for angiogenesis and cell-inhibitor therapies. Only relatively recently has the need for delivery devices that are compatible with vectors been identified (146). Since the 1995 NIH review of the gene therapy field, many basic investigators have successfully improved viral and nonviral vectors, achieving tissue-specific expression and regulated expression.



***e*FIGURE 101.0.9** The three essential components to successful cardiovascular gene therapy. A successful clinical product must integrate a therapeutic gene with a vector and a delivery device. AAV, adeno-associated virus.

In the past 5 years, there has been an explosion in recombinant gene and protein phase I and II trials for cardiovascular diseases. Angiogenesis and cell-inhibitor therapies have been the major focus. VEGF and basic FGF are the two dominant growth factors delivered by recombinant gene or protein approaches for peripheral vascular disease and coronary artery disease. Recombinant genes have been delivered via adenoviral vectors or plasmid DNA. Direct injection into skeletal muscle or cardiac muscle, infusion into femoral coronary arteries, or injection into the left ventricle are the three major delivery approaches. This field is clearly in its infancy; however, there are several major lessons learned from the clinical trials to date: (a) VEGF and basic FGF delivered as plasmid DNA are safely tolerated in the peripheral and coronary vasculature and muscle; (b) the full safety profile on adenoviral vectors is not yet known; (c) after direct injection into skeletal and cardiac muscle, recombinant genes are expressed, although the duration of gene expression in human tissues is not known; (d) direct comparisons of recombinant protein and genes have not been made, and hence, we do not know whether one approach is preferable to the other; (e) demonstration of intact functional collaterals has not been made in any trial to date; and (f) therapeutic effectiveness has not yet been demonstrated and awaits randomized, controlled, multicenter phase III trials.

Cell-inhibitor therapies have been initiated to treat vascular proliferative diseases. Cell-cycle inhibitors, cytostatic and cytotoxic compounds, and secreted multifunctional proteins such as NOS have been tested in preclinical animal models and now are moving forward to phase I studies. The major indication is restenosis in the coronary and peripheral vasculature and in-stent restenosis. However, in the future, indications will be expanded to include bypass grafts, atrioventricular fistulas, transplant arteriopathy, and native lesions in the coronary and peripheral vasculature. A phase I and II trial to inhibit smooth muscle cells’ replication in saphenous vein bypass grafts has been reported (147). Cell-cycle progression was prevented by disrupting the E2F transcription factor by use of antisense oligonucleotides to E2F. Saphenous veins were incubated in the operating room with a solution containing E2F transcription decoys before placement as a bypass graft for peripheral artery stenosis. This trial demonstrated the safe delivery of a genetic factor in a lipid preparation into vessels before operative insertion. Clinical end points will need to be tested in a randomized, controlled, multicenter trial.

Several key issues must be resolved before broad implementation of cardiovascular gene therapies. Transfection efficiencies with most vectors remain low, and improvements in vector design are required. These vectors must be delivered by catheters to sites of disease. Many local delivery catheters have been designed, yet there is no consensus on the optimal configuration of a gene transfer catheter. Finally, interactions of host cells and vectors must be examined, and the risk of vectors must be sufficiently low to warrant use in cardiovascular diseases.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Tremendous early progress was made in the field of gene transfer and gene therapy in the late 1980s. Multiple new vectors were developed, including viral and nonviral vectors. These vectors were tested in cell lines *in vitro*, and recombinant gene expression was measured. The feasibility of expressing recombinant genes in many cell lines from multiple organs led to tremendous enthusiasm and speculation that gene therapy would have a ready-made niche in the therapeutic armamentarium of physicians. Based on these promising *in vitro* results, *in vivo* animal models of gene therapy were created. Although there were specific challenges related to vector, delivery, and expression for each organ system tested, the feasibility of expressing recombinant genes *in vivo* was established in the vasculature, heart, brain, lung, liver, skeletal muscle, bone marrow, skin, and tumors. The number of investigators in the field grew and so did the number of published studies. The number of applications to conduct human gene therapy trials also rose exponentially. More than 150 clinical protocols for gene therapy have been reviewed and approved by the FDA. The majority of the protocols involve cardiovascular diseases, cancer, inherited diseases, and infectious diseases (acquired immunodeficiency syndrome). Many of the early studies were gene-marking studies. Retroviruses have been employed in the majority of protocols, but quickly, phase I and II trials were initiated as well. Several observations were made on studies conducted up to the mid- to late 1990s: Recombinant genes are expressed in human cells *in vivo* in different organ systems; adverse side effects from the vectors vary, depending on the nature of the vector, the patient, and where it is administered; assessment of the results of gene therapy trials has been difficult because of the relatively low frequency of gene delivery to cells and often the lack of biochemical or other measurable end points; and efficacy has not been clearly established (nor was it explicitly tested).

There are several general goals for human gene therapy protocols. The appropriate disease target must be identified. A gene delivery system that programs temporal and spatial patterns of recombinant gene expression must be developed. Sufficient gene delivery and gene expression must be achieved within targeted cells to achieve long-term therapeutic benefits. Finally, little to no toxicity from the vector recombinant gene must be demonstrated in human studies *in vivo*. The *Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy*, prepared by Drs. Orkin and Motulsky, shaped the field in the mid-1990s. This panel has recommended that greater focus be placed on the basic science aspects of gene transfer, including improving vectors for gene delivery, increasing and maintaining high levels of gene expression, directing genes to specific cell types using cell- or tissue-specific promoters, and further developing animal models of gene transfer to study disease pathogenesis.

The field of gene therapy was turned upside down in the fall of 1999 when the first gene therapy–related death occurred in a young patient at the University of Pennsylvania. Further examination of this protocol revealed a lack of clinical oversight and financial disclosure. Public hearings ensued, followed by issuance of new regulations by the FDA. Investigators have responded appropriately with intensified efforts to improve vectors, thoroughly testing the efficacy and toxicity of vectors and genes in animals before proceeding to human trials, carefully weighing the nature and likelihood of clinical benefit against the risks, and explaining these benefits and risks to patients and family. Informed consent must be clear with oversight and monitoring by a data safety and monitoring board. Conflict of interest must be disclosed.

Improvements in vectors and gene delivery systems will play an increasingly important role in the further development of human gene therapies. Animal models of cardiovascular disease will be based on transgenic and gene transfer techniques. The initial limitations of low-efficiency vectors and inefficient delivery systems, it is hoped, will be overcome through focused research efforts. The most useful strategies will integrate refinements in vectors with improved delivery systems. For gene therapy to realize its clinical potential, there must be efficient and safe strategies for delivering therapeutic genes to somatic cells *in vivo*. Gene therapy is a unique case of drug delivery in which the therapeutic gene constitutes the drug. Although traditional drug development can take 10 years or more to market, human gene therapy products may require an equivalent amount of time, if not more. Yet the promise remains great.

THE FUTURE

Improvements in vectors and gene delivery systems will play an increasingly important role in the further development of human gene therapies. Future basic research in cardiovascular disease will be based on genetic technology. Clinical trials are proceeding, and it is likely that a gene therapy product for angiogenesis will reach the marketplace within the next 3 to 5 years.

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102

MYOCYTE STRUCTURE AND FUNCTION

ARNOLD M. KATZ

"Indicates text or graphics that appear only in the electronic versions of this text."

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Myocyte Structure
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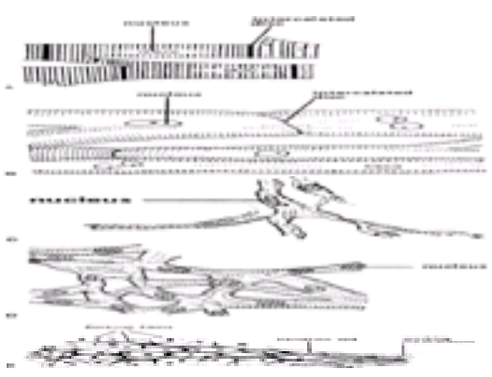
WHAT THE CARDIAC MYOCYTE DOES

The pumping action of the heart depends on interactions between the contractile proteins in its muscular walls. These interactions transform the chemical energy derived from adenosine triphosphate (ATP) into the mechanical work that moves blood under pressure from the great veins into the pulmonary artery, and from the pulmonary veins into the aorta. The contractile proteins are activated by a signaling process called excitation-contraction coupling, which begins when the action potential depolarizes the cell and ends when ionized calcium (Ca^{2+}) that appears within the cytosol binds to the Ca^{2+} receptor of the contractile apparatus. Movement of Ca^{2+} into the cytosol is a passive (downhill) process mediated by Ca^{2+} channels, whereas the heart relaxes when ion exchangers and pumps transport Ca^{2+} uphill, out of the cytosol. This chapter describes the mechanisms responsible for excitation-contraction coupling, contraction, and relaxation by the working cells of the atria and ventricles (for general reviews, see references 1,2,3,4 and 5).

MYOCYTE STRUCTURE

Several cell types are found within the myocardium. Most important are the *working myocardial cells* of the atria and ventricles, which are specialized for contraction (eFig. 102.0.1). *Nodal cells* of the sinoatrial and atrioventricular nodes are responsible for pacemaker activity and the atrioventricular conduction delay, respectively, whereas *Purkinje fibers* effect rapid conduction through the ventricular septum and throughout the ventricles. All of these myocardial cell types make up a functional syncytium in which cells are linked both electrically and mechanically by the *intercalated discs*. The latter contain low-resistance gap junction channels made up of connexin molecules that allow electrical current and small molecules to flow freely from one cardiac myocyte to another (6,7). Granules in the atrial myocardium contain biologically active atriopeptides; the latter, which are key regulators of vascular volume released in response to atrial stretch, promote smooth muscle relaxation and have natriuretic and diuretic effects.



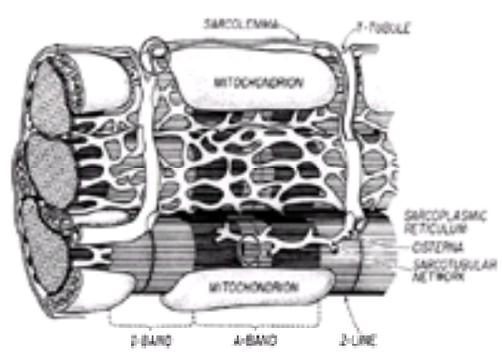
***e*FIGURE 102.0.1** Cells comprising the human heart. **A:** Working myocardial cell of the ventricle, showing intensely staining cross striations, central nuclei, and intercalated discs. **B:** Purkinje fiber, showing large, faintly staining cells with sparse cross striation. **C:** Sinoatrial node. **D:** Atrioventricular node. Both nodes have a network of small, sparsely cross-striated cells. **E:** Point of impingement of Purkinje fibers (*left*) on the working myocardium (*right*), showing transition cells. The scale for **E** is approximately half that for **A–D**. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

Specialized Myocytes

The *His-Purkinje cells*, which are specialized for rapid conduction, are large, pale cells that contain more glycogen and many fewer contractile filaments than the cells of the working myocardium (eFig. 102.0.1). These cells make up the atrioventricular bundle and bundle branches, and course along the ventricular endocardium where they synchronize ventricular systole. Fast conduction by the His-Purkinje cells is made possible by the many large Na^+ channels in their plasma membranes (for review, see reference 8). The sinoatrial and atrioventricular nodes are made up of small *nodal cells* (eFig. 102.0.1), which, like the His-Purkinje cells, are rich in glycogen and contain few contractile filaments. Slow conduction by nodal cells reflects the dependence action of their potentials on Ca^{2+} channels (for review, see references 8 and 9). *Transition cells*, intermediate in appearance between the His-Purkinje cells and ordinary working myocardial cells, are found between these two cell types in the ventricles. They are also scattered in the atria, where they contribute to preferential atrial conduction pathways (the "internodal tracts"). The heterogeneity among these histologically different cell types is also apparent at a molecular level.

Working Myocardium

The cells of the working myocardium are filled with cross-striated *myofibrils* (eFig. 102.0.2). Excitation-contraction coupling and relaxation are regulated by the *plasma membrane*, which separates the cytosol from the extracellular space, and the internal membranes of the *sarcoplasmic reticulum*. As the latter is a specialization of the endoplasmic reticulum, the generic term for these internal membranes is *sarco(endo)plasmic reticulum*. The *mitochondria*, which generate ATP, contain enzymes responsible for aerobic metabolism and oxidative phosphorylation; the latter are located on the inner mitochondrial membrane, whose surface is increased by infoldings called *cristae*.



***e*FIGURE 102.0.2** Ultrastructure of the working myocardial cell. Contractile proteins are arranged in a regular array of thick and thin filaments (seen in cross section at left). The A-band represents the region of the sarcomere occupied by the thick filaments, whereas the I-band is occupied only by thin filaments that extend toward the center of the sarcomere from the Z-lines, which bisect each I-band. The sarcomere, the functional unit of the contractile apparatus, is defined as the region between a pair of Z-lines and contains two half I-bands and one A-band. The sarcoplasmic reticulum, a membrane network that surrounds the contractile proteins, consists of the sarcotubular network at the center of the sarcomere and the subsarcolemmal cisternae, which abut the T-tubules and the sarcolemma. The transverse tubular system (T-tubule) is lined by a membrane that is continuous with the sarcolemma, so that the lumen of the T-tubules carries the extracellular space toward the center of the myocardial cell. Mitochondria are shown in the central sarcomere and in cross section at the left. (From Katz AM. Congestive heart failure: role of altered myocardial cellular control. *N Engl J Med* 1975;293:1184–1191. Copyright 1975, Massachusetts Medical Society. All rights reserved.)

Myofibrils

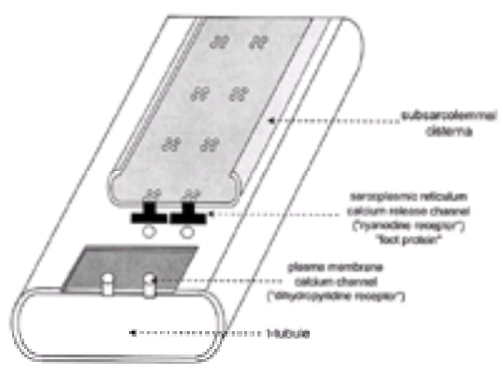
The organization of the *contractile proteins* gives rise to the characteristic pattern of light and dark striations (*e*Fig. 102.0.2). The more darkly staining bands are called *A bands*, whereas the lightly staining striations are called *I bands*. Each I band is bisected by a narrow, darkly staining *Z line*; a broad, dense *M band* is found in the center of the A band. The morphologic unit is the *sarcomere*, which lies between two Z lines (10); each sarcomere therefore consists of a central A band plus the two adjacent half I bands.

The A bands contain thick filaments that are composed largely of myosin, whereas the lightly staining half I bands at either side of the A band contain only thin filaments. The latter, which are strands of actin polymers, contain the regulatory proteins tropomyosin and the troponin complex. At physiologic sarcomere lengths in the resting heart, the thin filaments extend from the Z lines almost to the center of the A band, so that as the muscle shortens the extent of overlap between the thick and thin filaments increases. At short sarcomere lengths, double overlap is found between the thin filaments from the two adjacent I bands in the center of the sarcomere.

Sarcomere shortening occurs when the thin filaments are pulled toward the center of the A band by motion of the myosin *cross-bridges*, which project from the thick filaments to establish links with adjacent thin filaments. Like the oars of a racing shell, cross-bridge motion sweeps the thin filaments toward the center of the sarcomere in a reaction that is powered by energy released by ATP hydrolysis.

Membrane Structures

Contraction and relaxation in the adult human heart are regulated by the plasma membrane and sarcoplasmic reticulum (*e*Fig. 102.0.2). The plasma membrane is divided structurally into the *sarcolemma*, which surrounds the cell to separate the cytosol from the extracellular space, and the *transverse tubular (T-tubular) system* that penetrates the cell interior. The T tubules, whose lumens open to the extracellular space, rapidly transmit action potentials to the cell interior. Dyads, formed by the plasma membrane and sarcoplasmic reticulum (*e*Fig. 102.0.3), are composite structures that regulate the release of activator Ca^{2+} during excitation-contraction coupling.



***e*FIGURE 102.0.3** Schematic diagram of a dyad showing the Ca^{2+} release channels through which this cation leaves the subsarcolemmal cisternae of the sarcoplasmic reticulum, and their close approximation to the plasma membrane Ca^{2+} channels. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

The heart's sarcoplasmic reticulum, which takes up, stores, and releases Ca^{2+}, can be divided into two regions. The *subsarcolemmal cisternae* contain Ca^{2+}-binding proteins that store this activator cation and Ca^{2+} release channels that release this activator cation into the cytosol to initiate systole. The more extensive *sarcotubular network*, which surrounds the contractile proteins in the center of the sarcomere, contains a densely packed array of Ca^{2+} pump adenosine triphosphatase (ATPase) proteins that transport Ca^{2+} out of the cytosol into the lumen of the sarcoplasmic reticulum to relax the heart.

MYOCYTE FUNCTION

Contractile Proteins

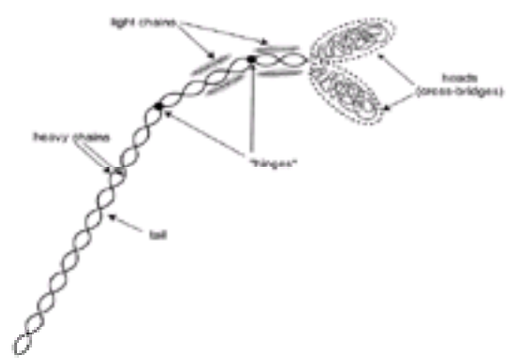
Myocardial contraction and its control can be understood in terms of the interactions between six proteins (1,10,11 and 12) (*e*Table 102.0.1) that, when assembled *in vitro*, hydrolyze ATP, undergo physicochemical changes that develop tension and cause shortening, and are controlled by Ca^{2+} in a manner that mimics physiologic excitation-contraction coupling.

***e*TABLE 102.0.1** CONTRACTILE PROTEINS OF THE HEART

Protein	Location	Salient properties
Myosin	Thick filament	Hydrolyzes adenosine triphosphate, interacts with actin
Actin	Thin filament	Activates myosin adenosine triphosphatase, interacts with myosin
Tropomyosin	Thin filament	Modulates actin-myosin interaction
Troponin C	Thin filament	Binds Ca^{2+}
Troponin I	Thin filament	Inhibits actin-myosin interactions
Troponin T	Thin filament	Binds troponin complex to the thin filament

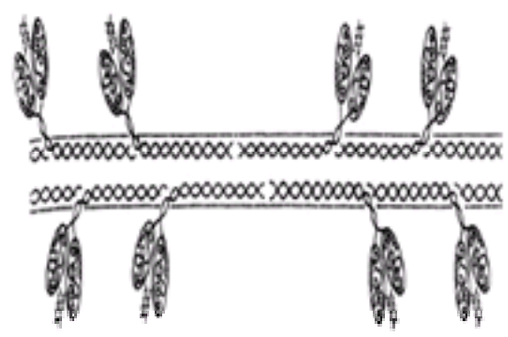
Myosin

Myosin, the major protein of the thick filament of muscle, is a large, elongated molecule with a filamentous "tail" and a globular "head" (*e*Fig. 102.0.4) that is able to hydrolyze ATP. When myosin interacts with actin, chemical energy is transduced into the mechanical energy used during contraction. Each myosin molecule contains two heavy chains and four light chains. The heavy chains extend into the cross-bridge and contain the sites responsible for both ATPase activity and the ability to interact with actin, whereas the light chains mediate responses of the contractile proteins to various signaling cascades. The myosin heavy chains and light chains differ among different muscle types, among different regions of the heart, and even among adjacent cells.

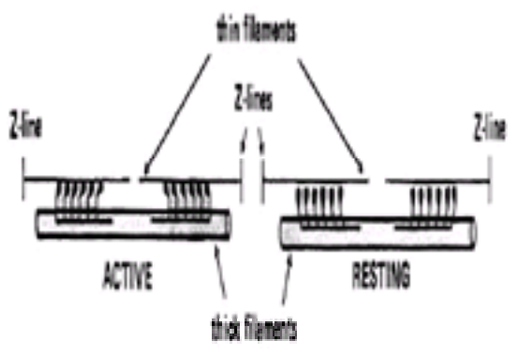


***e*FIGURE 102.0.4** Myosin is an elongated molecule consisting of two heavy chains and four light chains. The “tail” of the molecule, which is made up of a-helical regions of the heavy chains, extends into a paired globular “head” that makes up the cross-bridge. The hinges represent points of flexibility that allow for cross-bridge movement. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

Myosin in the living muscle is aggregated in the *thick filament* in which the tails are wound together as a rigid backbone, and the heads project as the cross-bridges that effect contraction when they interact with actin (eFig. 102.0.5). In resting muscle the cross-bridges are perpendicular to the long axis of the thick filament, whereas in active muscle their tips shift toward the center of the sarcomere so as to “row” the thin filaments toward the center of the sarcomere (eFig. 102.0.6).



***e*FIGURE 102.0.5** Organization of the thick filament, in which the backbone—delineated by dashed lines—is made up of the tails of myosin molecules that have opposite polarities in the two halves of the sarcomere. The cross-bridges represent the heads of the individual myosin molecules, which project from the long axis of the thick filament. A bare area in the center of the thick filament, which is devoid of cross-bridges, occurs because of the tail-to-tail organization of myosin molecules unique to the center of the thick filament. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

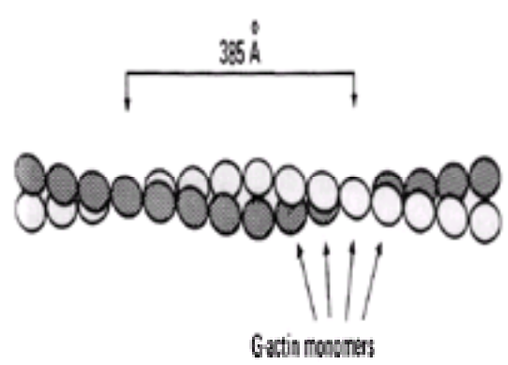


***e*FIGURE 102.0.6** In resting muscle (*right*), the cross-bridges project almost at right angles to the longitudinal axis of the thick filament. In active muscle (*left*), motion of the myosin cross-bridges pulls the thin filaments toward the center of the sarcomere. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

The myosin heavy chains determine muscle-shortening velocity and myocardial contractility. A higher ATPase myosin heavy chain (called a) is associated with a rapid muscle-shortening velocity, high contractility, and efficient contraction against light load, whereas a lower ATPase myosin heavy chain (called b) is associated with lower contractility but greater efficiency of tension development at heavy loads. In the human heart, atrial myosin heavy chains are mostly a high-ATPase isoform, whereas the human ventricle contains only a small amount of the fast myosin heavy chain (13).

Actin

Actin is a globular protein that forms a double-stranded macromolecular helix which serves as the backbone of the thin filament (eFig. 102.0.7). Human hearts contain mainly a-cardiac actin, along with a smaller amount of a-skeletal actin.



***e*FIGURE 102.0.7** The F-actin polymer is composed of two strands of G-actin monomers (*ovals*) wound around each other. The G-actin monomers in the two strands are identical; one strand is shaded here only to illustrate the two-stranded structure of F-actin. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

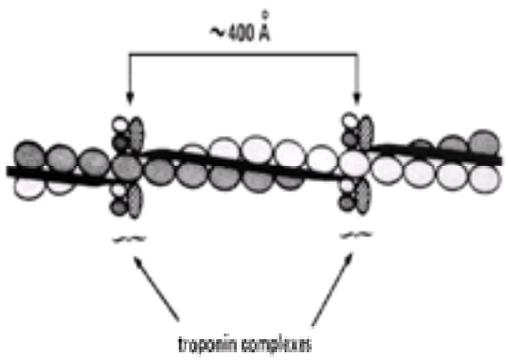
Tropomyosin

Tropomyosin is an elongated molecule made up of two helical peptide chains that is found along with actin in the thin filament, where one tropomyosin molecule lies in each of the two longitudinal grooves between the two strands of actin. Tropomyosin, which can contain either or both of two isoforms, a and b, regulates the

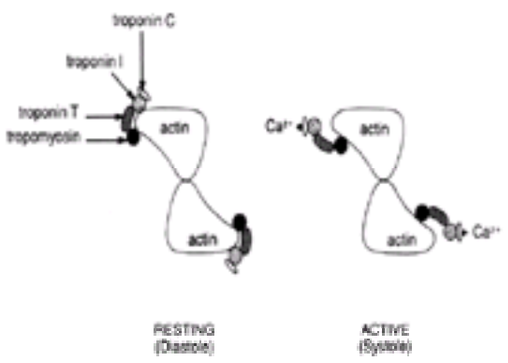
interactions between myosin, actin, and the troponin complex.

Troponin Complex

Troponin includes three discrete proteins (eFig. 102.0.8 and eFig. 102.0.9). *Troponin I*, in concert with tropomyosin, reversibly inhibits the interactions between actin and myosin; *troponin T* binds the troponin complex to tropomyosin; and *troponin C* contains the high-affinity Ca^{2+}-binding sites that recognize the appearance of Ca^{2+} in the cytosol as a signal to initiate contraction.



***e*FIGURE 102.0.8** Troponin complexes are distributed at approximately 400-Å intervals in the thin filament, along with actin and tropomyosin (dark lines in the grooves between the two actin strands). (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)



***e*FIGURE 102.0.9** Cross section of a thin filament in resting (*left*) and active (*right*) muscle. At rest, the troponin complex holds the tropomyosin molecules toward the periphery of the groove between actin strands in a manner that prevents actin from interacting with the myosin cross-bridges. In active muscle, Ca^{2+} binding to troponin C weakens the bond linking troponin I to actin, which causes a structural rearrangement of the regulatory proteins that shifts the tropomyosin deeper into the groove between the strands of actin. This rearrangement exposes active sites on actin for interaction with the myosin cross-bridges. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

Troponin C is a member of a family of Ca^{2+}-binding proteins that includes the myosin light chains and calmodulin, a ubiquitous intracellular Ca^{2+}-mediated regulator. Troponin I, which inhibits actin-myosin interactions in resting muscle, allows actin to interact with the myosin cross-bridges when Ca^{2+} binds to troponin C. When phosphorylated by cyclic adenosine monophosphate–dependent protein kinase (PK-A), cardiac troponin I reduces the Ca^{2+} sensitivity of troponin C, which contributes to the lusitropic effect of beta-adrenergic stimulation. Troponin T binds the troponin complex to tropomyosin. Although troponin T itself does not bind Ca^{2+}, isoform switches can modify the Ca^{2+} sensitivity of tension development.

Interactions between the Contractile Proteins

The interactions of the contractile proteins are modified by the effects of Ca^{2+} described earlier, by changes in muscle length, and by an allosteric effect of ATP. The major determinant of contractility is the level of cytosolic Ca^{2+} achieved during excitation-contraction coupling. At the low Ca^{2+} concentrations found in resting muscle, actin-myosin interactions are inhibited by a blocking action of tropomyosin and the troponin complex. Ca^{2+} binding to troponin C reverses this inhibitory effect by initiating a series of cooperative interactions in the thin filament that shift the position of tropomyosin in the grooves between the double-stranded F-actin polymer (eFig. 102.0.9). In resting muscle, tropomyosin lies toward the outside of the grooves between the two actin chains, where it blocks the development of actin-myosin interactions. Ca^{2+} binding to troponin C shifts the elongated tropomyosin molecules toward the center of the groove between the actin chains, which initiates systole by allowing the myosin cross-bridges to interact with active sites on actin. The muscle returns to its resting state when Ca^{2+} dissociation from troponin C returns tropomyosin to its inhibitory position in the thin filament.

Regulation of cardiac performance by end diastolic volume (the Frank-Starling relationship) is due mainly to sarcomere length–dependent changes in both the Ca^{2+} sensitivity of the contractile proteins (14) and Ca^{2+} release from the sarcoplasmic reticulum (15). ATP, in addition to supplying energy for the interactions between myosin cross-bridges and actin, has important allosteric effects. At levels between 0.1 and 10.0 µM, ATP provides the substrate for energy-consuming reactions. The allosteric effects, which are seen at concentrations above 100 µM, facilitate relaxation by dissociating actin and myosin. ATP concentration in the living heart is well above 1 mM, more than three orders of magnitude higher than needed to saturate the catalytic site of myosin, so that the initial effect of energy starvation is to blunt this allosteric effect.

Excitation-Contraction Coupling and Relaxation

Excitation-contraction coupling in working myocardial cells begins when an inward Na^{+} current depolarizes the plasma membrane and ends when Ca^{2+} released from intracellular stores binds to troponin C. Relaxation, which is much more than reversal of the processes involved in excitation-contraction coupling, is brought about when energy-dependent Ca^{2+} pumps and exchangers lower cytosolic Ca^{2+} concentration.

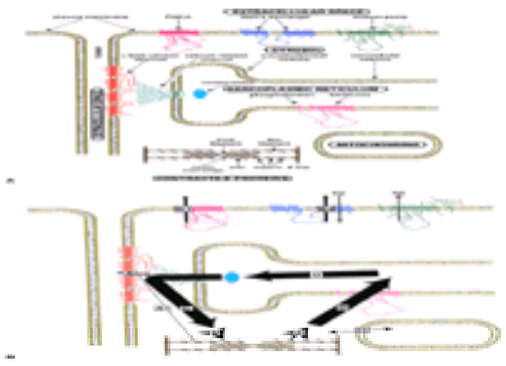
Energetics of Excitation-Contraction Coupling and Relaxation

Although energy is needed for both contraction and relaxation, energy is used in different ways and by different structures. During systole, energy released from ATP is used by the contractile proteins for tension development and muscle shortening, whereas the heart relaxes when energy-dependent ion pumps and exchangers remove Ca^{2+} from the cytosol. The Ca^{2+} concentration in the extracellular space and sarcoplasmic reticulum is approximately 1 mM, whereas much lower Ca^{2+} concentrations, approximately 10 µM, saturate troponin; both are much higher than the cytosolic Ca^{2+} concentration in the resting heart, approximately 0.2 µM. For this reason, the Ca^{2+} fluxes that activate contraction are passive, whereas those involved in relaxation require the expenditure of energy.

Ca^{2+} Cycles in Excitation-Contraction Coupling and Relaxation

The entry and removal of Ca^{2+} from the cytosol of working cardiac myocytes are effected by two distinct Ca^{2+} cycles (eFig. 102.0.10). In the extracellular cycle, Ca^{2+} enters and leaves the cytosol by crossing the plasma membrane from what is, in effect, an unlimited store of Ca^{2+} in the extracellular space. In the intracellular cycle, Ca^{2+} is pumped into and out of limited stores within the sarcoplasmic reticulum. Most of the Ca^{2+} that activates contraction by the adult human heart is derived from the sarcoplasmic reticulum (the intracellular cycle). Although Ca^{2+} derived from the extracellular space makes only a small contribution to the intracellular pool of activator Ca^{2+}, this Ca^{2+} flux plays a major role in triggering Ca^{2+} release from the sarcoplasmic reticulum and in determining the Ca^{2+} content of the internal stores. Both Ca^{2+} cycles are regulated by channels through which Ca^{2+} diffuses into the cytosol and by Ca^{2+} pumps and exchangers that actively transport this cation into the extracellular

space and lumen of the sarcoplasmic reticulum.



***e*FIGURE 102.0.10** Schematic diagram showing key structures **(A)** and Ca^{2+} fluxes **(B)** that control cardiac excitation-contraction coupling and relaxation. Ca^{2+} "pools" are in bold capital letters **(A)**. In **B**, the thickness of the arrows indicates the magnitude of the Ca^{2+} fluxes, whereas their vertical orientations describe their "energetics": downward arrows represent passive Ca^{2+} fluxes and upward arrows represent energy-dependent active Ca^{2+} transport. Most of the Ca^{2+} that enters the cell from the extracellular fluid via L-type Ca^{2+} channels (*arrow A*) triggers Ca^{2+} release from the sarcoplasmic reticulum; only a small portion directly activates the contractile proteins (*arrow A1*). Ca^{2+} is actively transported back into the extracellular fluid by the plasma membrane Ca^{2+} pump adenosine triphosphatase (PMCA; *arrow B1*) and the Na^+/ Ca^{2+} exchanger (*arrow B2*). The Na^+ that enters the cell in exchange for Ca^{2+} (*dashed line*) is pumped out of the cytosol by the Na^+ pump. Two Ca^{2+} fluxes are regulated by the sarcoplasmic reticulum: Ca^{2+} efflux from the subsarcolemmal cisternae via Ca^{2+} release channels (*arrow C*) and Ca^{2+} uptake into the sarcotubular network by the sarco(endo)plasmic reticulum Ca^{2+} pump adenosine triphosphatase (SERCA; *arrow D*). Ca^{2+} diffuses within the sarcoplasmic reticulum from the sarcotubular network to the subsarcolemmal cisternae (*arrow G*), where it is stored in a complex with calsequestrin and other Ca^{2+}-binding proteins. Ca^{2+} binding to (*arrow E*) and dissociation from (*arrow F*) high-affinity Ca^{2+}-binding sites of troponin C activate and inhibit the interactions of the contractile proteins. Ca^{2+} movements into and out of mitochondria (*arrow H*) buffer cytosolic Ca^{2+} concentration. The extracellular Ca^{2+} cycle consists of arrows A, B1, and B2, whereas the intracellular cycle involves arrows C, E, F, D, and G. (Modified from Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

The plasma membrane Ca^{2+} channels (extracellular Ca^{2+} cycle) and the sarcoplasmic reticulum Ca^{2+} release channels (intracellular Ca^{2+} cycle) are members of two distinct protein families (*e*Table 102.0.2), whereas the ATP-dependent Ca^{2+} pumps in the plasma membrane and sarcoplasmic reticulum belong to a single family of ATPases that also includes the Na^+ pump (Na^+-K^+ ATPase). The Na^+/Ca^{2+} exchanger, which transports Ca^{2+} uphill out of the cytosol in exchange for extracellular Na^+, belongs to a different class of membrane proteins.

***e*TABLE 102.0.2** STRUCTURE-FUNCTION RELATIONSHIPS IN EXCITATION-CONTRACTION COUPLING OF WORKING CARDIAC MYOCYTES

Structure	Role in systole	Role in diastole
Plasma membrane		
Sarcolemma		
Na^+ channel	Depolarization	
	Opening of Ca^{2+} channels	
Ca^{2+} channel	Action potential plateau	
	Ca^{2+}-triggered Ca^{2+} release	
Ca^{2+} pump (PMCA)		Ca^{2+} removal
Na^+/Ca^{2+} exchanger	Ca^{2+} entry	Ca^{2+} removal
Na^+ pump		Repolarization
		Na^+ gradient for Na^+/Ca^{2+} exchanger
Transverse tubule		
Na^+ channel	Action potential propagation	
Ca^{2+} channel	Ca^{2+}-triggered Ca^{2+} release	
Sarcoplasmic reticulum		
Subsarcolemmal cisternae		
Ca^{2+} release channel	Ca^{2+} release	
Sarcotubular network		
Ca^{2+} pump (SERCA)		Ca^{2+} removal
Myofilaments		
Actin and myosin	Contraction	
Troponin C	Ca^{2+} receptor	
Other proteins	Allosteric regulation	

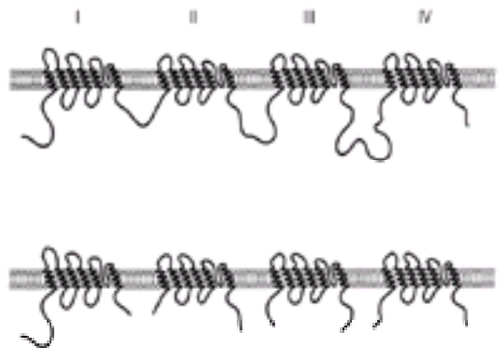
PMCA, plasma membrane Ca^{2+} pump adenosine triphosphatase; SERCA, sarco(endo)plasmic reticulum Ca^{2+} adenosine triphosphatase.

The functional link between plasma membrane depolarization (the action potential) and the opening of intracellular Ca^{2+} release channels in the heart is provided by L-type plasma membrane Ca^{2+} channels. When membrane depolarization opens the latter, a localized increase in cytosolic Ca^{2+} concentration, called a "Ca^{2+} spark" (16), opens nearby intracellular Ca^{2+} release channels. This causes a much greater Ca^{2+} release from the sarcoplasmic reticulum by a process that is often referred to as "Ca^{2+}-induced Ca^{2+} release" (17,18).

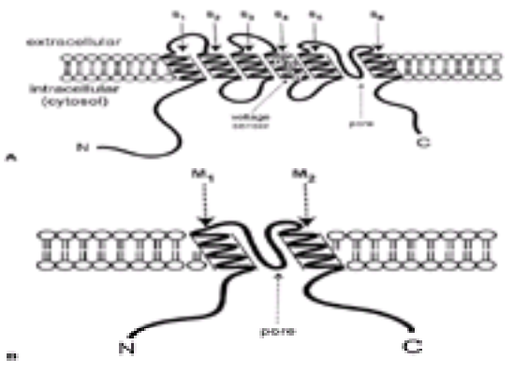
Structures Involved in Excitation-Contraction Coupling and Relaxation

Plasma Membrane Ion Channels

Plasma membrane channels, which are generally named for the ions that they carry (*e*Table 102.0.2), are oligomers that can contain as many as five subunits, called a_1, a_2, b, g, and d (for review, see references 1 and 8). Central to their physiologic function are large proteins (called a or a_1 in different channels) that make up and surround the channel pores, which determine ion specificity and which contain the activation and inactivation gates that open, close, and inactivate the channels. The a and a_1 subunits of Na^+ and Ca^{2+} channels, and outwardly rectifying K^+ channels, are tetramers (*e*Fig. 102.0.11), each of whose four domains contains six a-helical transmembrane segments (*e*Fig. 102.0.12). The S_4 transmembrane segment, which is rich in charged amino acids, provides the "voltage sensor" that mediates the voltage-dependent conformational changes that open (activate) the channel. Several of these channels are inactivated by the intracellular peptide chain that links domains III and IV. The "pore" region of the channel is made up of the S_5 and S_6 a-helical transmembrane segments and the intervening sequence of amino acids. The major subunits of inwardly rectifying K^+ channels, which are closed by depolarization, are smaller peptides that consist of only the pore region of the ancestral channel domain (19,20). The four domains of the a and a_1 subunits of most plasma membrane Na^+ and Ca^{2+} channels are linked covalently (*e*Fig. 102.0.11), whereas the K^+ channel domains are not covalently linked; as a result, K^+ channel domains can exchange among each other so as to generate a large number of channel subtypes (21,22 and 23).



***e*FIGURE 102.0.11** Schematic representation of two types of voltage-gated ion channels. **Top:** Na^+ and Ca^{2+} channels are covalently linked tetramers made up of four homologous domains (numbered I through IV), each of which contains six a-helical transmembrane segments. **Bottom:** The major class of K^+ channels is also made up of four homologous domains, except that unlike the channels shown at top, these domains are not linked covalently. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

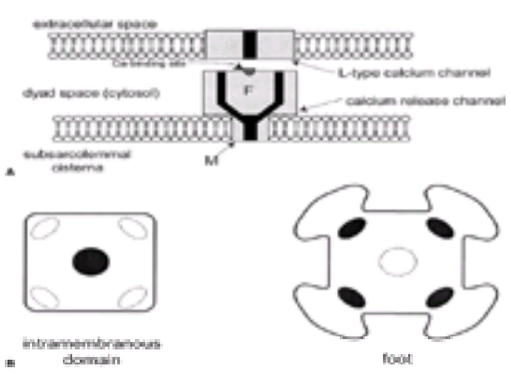


***e*FIGURE 102.0.12** Schematic representation of two types of ion channel domains. **A:** The domains in Na^+ and Ca^{2+} channels, and in the major class of K^+ channels, contain six transmembrane a-helices. The positively charged S_4 transmembrane segment in each of these domains provides the voltage sensor that responds to membrane depolarization by opening the channel. The "pore region" is made up of the S_5 and S_6 transmembrane segments and the intervening loop that "dips" into the membrane bilayer. **B:** Inward-rectifying K^+ channels are made of smaller domains that are homologous to the S_5 and S_6 transmembrane segments of the larger domain shown in **(A)**. This domain is largely a pore, composed of the M_1 and M_2 transmembrane segments along with the intervening loop. The absence of a charged transmembrane segment homologous to S_4 explains why the response of inward-rectifying channels to membrane depolarization differs from that of channels made up of the larger domains depicted in **(A)**. C, C terminus; N, N terminus. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

Several classes of the plasma membrane Ca^{2+} channels are found (for review, see references 9, 24, and 25). In the heart, the most important members of this family are the L-type Ca^{2+} channels, which bind the familiar classes of Ca^{2+} channel blockers (*dihydropyridines* such as nifedipine, *phenylalkylamines* such as verapamil, and *benzothiazepines* such as diltiazem). These are sometimes called *dihydropyridine receptors* because of their high-affinity binding to this class of Ca^{2+} channel blockers. A second class, the T-type Ca^{2+} channels, opens only transiently and plays an important role in the sinoatrial node pacemaker; these channels may also participate in proliferative signaling.

Intracellular Ca^{2+} Release Channels

Intracellular Ca^{2+} release channels, whose structure differs considerably from that of the plasma membrane Ca^{2+} channels, include at least two classes of related proteins (for review, see references 26,27 and 28). The larger *ryanodine receptors*, so named because they bind to this plant alkaloid, mediate excitation-contraction coupling by releasing Ca^{2+} from the sarcoplasmic reticulum. A smaller class of Ca^{2+} channels, called *$InsP_3$ receptors*, are activated by inositol triphosphate ($InsP_3$). Both the ryanodine receptors and the $InsP_3$ receptors are tetrameric structures in which the four subunits surround a central pore through which Ca^{2+} is released when the channel is opened (*e*Fig. 102.0.13).

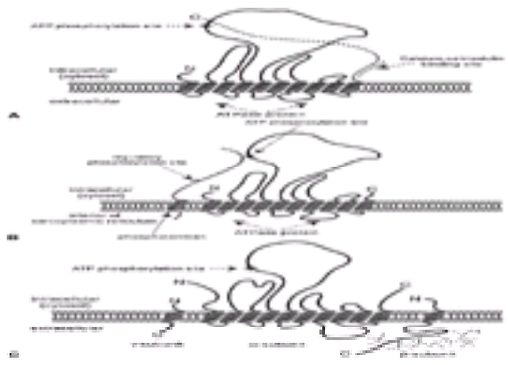


***e*FIGURE 102.0.13** Schematic representation of a single Ca^{2+} release channel (foot protein or ryanodine receptor) in a dyad. **A:** View through the plane of the bilayer showing the plasma membrane (*above*) and the subsarcolemmal cisterna (*below*). The former contains an L-type Ca^{2+} channel that delivers Ca^{2+} to a binding site on the sarcoplasmic reticulum Ca^{2+} release channel. Each of the latter is a tetrameric structure that contains an intramembranous domain (M) and a large foot (F). Opening of the sarcoplasmic reticulum channel opens pores (*dark areas*). **B:** Intracellular Ca^{2+} release channel viewed from within the lumen of the subsarcolemmal cisterna, which faces the intramembranous domain (*left*), and from the cytosolic space within the dyad, which faces the foot. The intramembranous domain contains a central channel, whereas four radial channels are found within the foot (*right*). (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

The explosive contractile responses of cardiac and skeletal muscle are initiated by the opening of the ryanodine receptors, whereas the smaller $InsP_3$ receptors initiate the slower contractile responses in smooth muscle (29). In the heart, slow Ca^{2+} release by the $InsP_3$ receptors may, like Ca^{2+} entry through T-type Ca^{2+} channels, regulate proliferative responses, such as cell growth, differentiation, and programmed cell death (apoptosis).

Ca^{2+} Pump Adenosine Triphosphatases

The Ca^{2+} pump ATPases are members of a family called *P-type ion pumps* that contains ten membrane-spanning a-helices and a large "head" that projects into the cytosol (*e*Fig. 102.0.14) (for review, see reference 30). All use a similar reaction mechanism to couple the hydrolysis of the high-energy phosphate bond of ATP to ion transport. The cardiac plasma membrane Ca^{2+} pump (31,32) is larger than that of the sarcoplasmic reticulum, called *SERCA* [sarco(endo)plasmic reticulum Ca^{2+} ATPase]; both share a similar reaction mechanism, but they are regulated differently.



***e*FIGURE 102.0.14** Molecular structure of three P-type adenosine triphosphatase pump proteins. The plasma membrane Ca^{2+} pump **(A)**, sarcoplasmic reticulum Ca^{2+} pump **(B)**, and major a-subunit of the Na^{+} pump **(C)** contain ten membrane-spanning a-helices within the plane of the membrane bilayer. In all three proteins, a large cytosolic loop between the fourth and fifth membrane-spanning helices contains the active site that is phosphorylated by adenosine triphosphate (ATP) to provide energy for active transport. In the plasma membrane Ca^{2+} pump **(A)**, a portion of the C-terminal peptide chain provides a regulatory site that binds the Ca^{2+}-calmodulin complex. Phospholamban, which regulates the sarcoplasmic reticulum Ca^{2+} pump **(B)**, has a sequence similar to the C-terminal portion of the plasma membrane Ca^{2+} pump. The Na^{+} pump has three subunits; the larger a-subunit contains the Na^{+}-, K^{+}-, ATP-, and cardiac glycoside–binding sites. The glycosylated b-subunit and small g-subunit regulate Na^{+} pump activity. C, C terminus; N, N terminus. (From Katz AM. *Physiology of the heart*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

The sarcoplasmic reticulum Ca^{2+} pump is stimulated when cyclic AMP stimulates PK-A to catalyze the phosphorylation of phospholamban that, when phosphorylated, accelerates Ca^{2+} uptake by SERCA (for review, see reference 33). The result is accelerated relaxation and increased Ca^{2+} stores in the sarcoplasmic reticulum that contribute to the lusitropic and inotropic effects of beta-adrenergic stimulation (34). Phospholamban can also be phosphorylated by a Ca^{2+}-calmodulin–dependent protein kinase, which helps rid the cytosol of excess Ca^{2+}. The plasma membrane Ca^{2+} pump ATPase is stimulated when the Ca^{2+}-calmodulin complex binds to an inhibitory site located on the C-terminal domain of the molecule (31), which promotes Ca^{2+} efflux from Ca^{2+}-overloaded cells.

Na^{+}/Ca^{2+} Exchanger

A second mechanism that transports Ca^{2+} out of the cytosol is the Na^{+}/Ca^{2+} exchanger, which uses the osmotic energy of the Na^{+} gradient across the plasma membrane for the uphill transport of Ca^{2+} (for review, see references 35,36 and 37). The Na^{+}/Ca^{2+} exchanger is a large membrane protein that contains 12 a-helical transmembrane segments and so differs structurally from the Ca^{2+} pump ATPases.

Ca^{2+} efflux via the Na^{+}/Ca^{2+} exchanger occurs when one cytosolic Ca^{2+} ion is exchanged for three Na^{+} ions that enter the cytosol, so that Na^{+}/Ca^{2+} exchange generates a small ionic current. These currents are small, and probably contribute less than a few millivolts to membrane potential. The electrogenicity also allows membrane potential to influence ion exchange. In resting cells, the negative intracellular potential tends to pull Na^{+} into the cell, so that during diastole the exchanger favors Ca^{2+} efflux, whereas reversal of membrane potential during systole, when the cell interior becomes positively charged, has the opposite effect and favors Ca^{2+} influx. The ultimate energy source for Ca^{2+} transport out of the cell via the exchanger is the Na^{+} gradient established by the Na^{+}-K^{+} ATPase (Na^{+} pump).

Na^{+} Pump

The Na^{+} pump serves several functions in the myocardium (for review, see reference 38). Most important are to exchange the small amount of Na^{+} that enters the cell during each action potential for K^{+} lost during repolarization and to generate a Na^{+} gradient across the plasma membrane that can be coupled to the active transport of several molecules, notably Ca^{2+} (see earlier). Because three Na^{+} ions are exchanged for only two K^{+} ions, the Na^{+} pump is electrogenic, generating a small, repolarizing current.

Ca^{2+} Retention within the Sarcoplasmic Reticulum

Although some of the Ca^{2+} stored in the sarcoplasmic reticulum is free (ionized), much of this cation is associated with Ca^{2+}-binding proteins that include *calsequestrin*, *calreticulin,* and a *histidine-rich calcium-binding protein* (39). These Ca^{2+}-binding proteins, which are concentrated in the subsarcolemmal cisternae, store Ca^{2+} for release through the Ca^{2+} release channels.

Mitochondria

Mitochondria, although serving primarily to regenerate ATP, can also take up Ca^{2+}. Because of the low Ca^{2+} affinity of mitochondrial Ca^{2+} uptake, little mitochondrial Ca^{2+} transport occurs at physiologic cytosolic Ca^{2+} concentrations. For this reason, these energy-producing structures do not normally play a role in excitation-contraction coupling. Under conditions of Ca^{2+} overload, the mitochondria can “buffer” cytosolic Ca^{2+} and so protect the myocardium from the detrimental effects of excess Ca^{2+}.

SUMMARY

Contraction of the working cells of the myocardium involves interactions among six proteins: myosin of the thick filament, actin, tropomyosin, and the three components of troponin in the thin filament. These interactions are controlled by the downhill movement of Ca^{2+} into the cytosol (excitation-contraction coupling) and active Ca^{2+} transport out of the cytosol. All of these Ca^{2+} fluxes are highly regulated, which provides for the changes in cardiac muscle chemistry that give rise to changes in myocardial contractility.

THE FUTURE

As knowledge of the biochemistry of myocardial contraction, excitation-contraction coupling, and relaxation have become clarified, new questions as to molecular alterations in the contractile machinery have come into focus. Important advances can be expected in areas that relate alterations in the mechanical behavior of muscle to changes in the composition of the myocardial cell. Links between these aspects of functional signaling and the proliferative signal transduction pathways that control cell differentiation, growth, and death (apoptosis) should provide new insights into the mechanism—and treatment—of heart disease.

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103

MOLECULAR BASIS OF HEART DEVELOPMENT

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MAHESH P. GUPTA

"Indicates text or graphics that appear only in the electronic versions of this text."

Overview
Molecular Basis of the Developing Heart
Cardiac Progenitors
Formation of the Tubular Heart and Looping
Chamber Formation
Role of Neural Crest Cells
Molecular Regulation of Cardiac Myogenesis
Determination of Cardiogenic Muscle Lineage
Differentiation and Activation of Cardiac Genes
Modulation of Gene Transcription by Extrinsic Factors
Genetic Basis of Congenital Heart Defects
Marfan Syndrome
Supravalvular Aortic Stenosis
Duchenne's Muscular Dystrophy
DiGeorge Syndrome
Long QT Syndrome
Down Syndrome
Holt-Oram Syndrome
Familial Hypertrophic Cardiomyopathy
Controversies and Personal Perspectives
Acknowledgment
Chapter References

OVERVIEW

Heart development results from a complex but highly integrated series of interactions involving various cell types of diverse origins. These are carried out in a strictly regulated environment at both genetic and epigenetic levels. This chapter focuses on the molecular control of the sequential processes involved in heart development, from cardiac progenitors through the fully developed four-chambered heart. Recent advances in cardiomyogenesis, including commitment, differentiation, and modulation of cardiac muscle lineage, are described. The critical role of the neural crest to cardiac development and the genetic basis for cardiac malformations are also presented.

The heart is a unique organ. Its development begins shortly after the onset of embryogenesis, and it is functional long before other parts of the embryo are discernible. It comprises diversified cell types of different embryonic lineages, including myocyte of the myocardium, endothelial cells of the endocardium, and cells of the neural crest that participate in the formation of the outflow tract. Each cell type has distinct inherent potential for proliferation, growth, cell migration, and cell death. Accordingly, the process of heart development follows a complex series of events involving highly integrated and programmed morphogenetic interactions among the cells of various origins. To understand heart formation at the very early stages of development, it is imperative to analyze the basic cell biology of the constituent cells and identify the key factors that regulate their development. Recent advances in molecular biology, such as gene cloning, immunohistochemistry, *in situ* hybridization, and targeted mutagenesis, have introduced new insights. This chapter is divided into three main parts: (a) molecular changes during heart development, (b) regulation of cardiac myogenesis, and (c) current concepts on cardiac malformations.

MOLECULAR BASIS OF THE DEVELOPING HEART

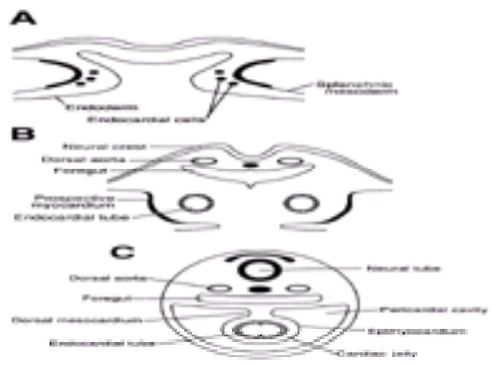
In this section, we briefly describe the molecular changes at various morphologic stages, starting from cardiac primordia through the fully developed four-chambered heart. *e*Table 103.0.1 summarizes the important genes and their functions in vertebrates.

***e*TABLE 103.0.1** ROLE OF DIFFERENT GENE PRODUCTS IN DIFFERENT STAGES OF HEART DEVELOPMENT

Morphologic changes/developmental stages	Genes	Gene function
Cardiac progenitors	Adhesion molecules (cadherins, catenins)	Show restricted expression in cell clusters that subsequently form splanchnic mesoderm.
	Bone morphogenic protein	Expressed in endoderm, induces expression of Nkx2-5 in the overlying cardiogenic mesoderm.
	GATA-6	Reduction in GATA-6 is required for cardiac progenitors to proceed in development.
Cardiac tube	Tinman/Nkx2-5/Csx	Essential for heart development.
	GATA-4, retinoic acid receptor signaling	Participates in ventromedial migration and eventual fusion of cardiac progenitors.
Cardiac looping	Signaling molecules (activin receptors, Shh, nodal, cSnR, Pitx-2)	Asymmetric expression along left-right axis is essential for looping.
	Gap junction protein connexin 43	Mutations are associated with left and right atrial isomerism.
Septae formation	Bone morphogenetic protein 4, transforming growth factor-b, Msx-1,2	Show regional expression in atrioventricular canal and conotruncus.
	N-CAM, tenascin	Involved in transformation of endocardial cells to mesenchymal cells.
Valves	Fibrillin, fibulin, transforming growth factor-b	Involved in remodeling of cushion to valvular tissue.
	NFATC, Sox 4	Transcription factors show restricted expression, mutations result in defective semilunar and possibly atrioventricular valves.
	Smad6	Gene disruption leads to hyperplasia of cardiac valves and outflow tract.
	Epidermal growth factor receptors (ErbB2, ErbB4)	Signaling between myocardial receptor and endocardial ligand is essential for trabeculae growth.
Trabeculation	Neuregulins	Ligand for ErbB2 and ErbB4 expressed in the endocardium, mutations in either receptors or ligand result in aborted trabeculations.
Conduction system	MSX-2	A homeobox gene expressed in the central portion of conduction system.

Cardiac Progenitors

In all vertebrates, the heart is derived from the splanchnic mesoderm and the endoderm situated in the anterior region of the developing embryo. Cardiac primordia appear as bilateral thickenings of the splanchnic mesoderm. In avians, heart specification occurs at about the time of Hamburger Hamilton (H-H) stages 3 to 4 (1); in humans, it occurs during the third week of embryogenesis, right after gastrulation when three germ layers are formed and simple diffusion alone is no longer adequate for the nutritional requirements of the embryo. These precardiac areas situated on either side of the embryonic midline contain splanchnic mesodermal cells, the preendocardial cells, and associated extracellular matrix (*e*Fig. 103.0.1). In chick embryos (H-H stages 5 to 9), expression of certain adhesion molecules such as N-cadherin and catenins is restricted to specific cell clusters that subsequently develop into cardiac splanchnic mesoderm, suggesting their important roles in early heart specification (2).



***e*FIGURE 103.0.1** Diagram illustrating paired cardiac primordia undergoing fusion to form a single heart tube. **A:** Endocardial cells appear between the endoderm and splanchnic mesoderm. The prospective myocardium is seen as bilateral thickenings of splanchnic mesoderm. **B:** The prospective myocardium is bending toward the embryonic midline enwrapping both endocardial tubes. **C:** The two endocardial tubes have undergone fusion, and the unfused mesodermal layer remains as dorsal mesocardium.

Studies in avians and amphibians have demonstrated that endodermal cells play an inductive role in cardiogenesis and in the subsequent beating of the primitive heart. In chick embryos, removal of the endodermal cells at H-H stage 4 prevented heart formation (3). A recent study involving cultured explants of chick embryo at H-H stage 6 further emphasized the role of endodermal cells (4). In this study, explants from anterior endoderm/mesoderm underwent terminal differentiation, whereas those from anterior ectoderm/mesoderm or posterior endoderm/mesoderm did not, suggesting the role of anterior endoderm in providing the inducers. One such molecule includes bone morphogenetic protein (BMP-2), which is expressed in the endoderm and is able to induce expression of transcription factor Csx/Nkx2-5 (*c*ardiac-*s*pecific homeob*x*/*n*eurenberg *k*im homeob*x*) in the overlying (cardiogenic) mesoderm (5). Nkx2-5 is a homologue of *Drosophila tinman* and shows conserved expression in many species including humans (6). Targeted disruption of *NKX-2.5* results in abnormal morphogenesis, growth retardation, and even embryonic death (7). These studies underscore the important role of homeobox genes in specifying heart mesoderm and during cardiogenesis.

Lineage-labeling studies suggest that mesoderm and endoderm cells arise from a common progenitor. The two germ layers of cardiac primordia retain certain properties in common, as for example, expression of certain key transcription factors belonging to NKX and GATA families of proteins. Some of these factors such as GATA-6 maintain heart cells in precursor state, and reduction in GATA-6 is required for the progenitors to proceed in development (8).

Formation of the Tubular Heart and Looping

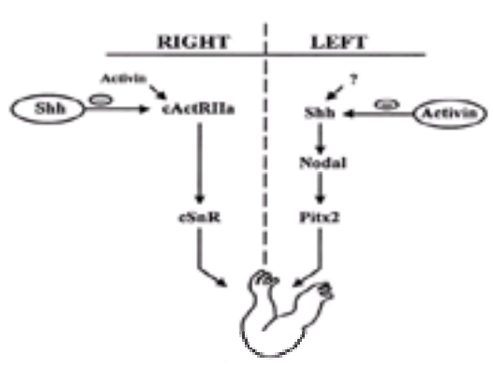
As development proceeds, after closure of the neural tube and subsequent folding of the embryo, the cardiogenic area is pulled forward and rotated approximately 180 degrees along a transverse axis. This results in the two lateral endothelial/mesodermal primordia approximating each other and eventually fusing to form the cardiac tube. Fusion of the mesodermal layers begins at the cephalic end and progresses toward the caudal end. Although the molecular events during these changes have not been fully characterized, several studies implicate the role of retinoic acid receptor signaling pathways. Treatment with retinoic acid in chicks inhibited embryonic folding, resulting in persistence of the cardiac progenitors at their posterior and medial positions and failure of primordial fusion at the midline (9). In addition, injection of antibodies against N-cadherins (to block the actions of cadherins) into cultured chick embryos (stages 5 to 12) blocked the fusion (10).

Transcription factor GATA-4 has also been emphasized to play a role in heart tube formation in two separate studies using gene targeting to produce GATA-deficient mice in which cardiac primordia failed to migrate ventrally (11,12). Because GATA-4 is expressed both in the endoderm as well as in the cardiogenic mesoderm, it is the endodermal expression that contributes to the heart development (13). More recently a cofactor of GATA (FOG-2) has been cloned (14) and shown to repress GATA-4–dependent transcription (15). FOG-2–deficient mice die of heart failure at E13 and show several septal defects (16).

After fusion of the paired primordia at the midline, a straight heart tube located inside the pericardial cavity shows an outer mesenchymal layer, or *myocardium*, and an inner endothelial layer, or *endocardium*. A gelatinous substance, the cardiac jelly, which is later invaded by cells derived from the endothelium, separates the two layers. Eventually, the wall of the heart tube consists of three layers: the endocardium, the myocardium, and the epicardium. At this stage, the cardiac tube can be divided into a bulboventricular portion located inside the pericardial cavity, an atrial portion, and a paired sinus venosus lying outside the pericardium. Subsequent development results in elongation and bending of the cardiac tube in such a manner that the cranial portion of the tube bends in a ventral and caudal direction to the right, whereas the caudal atrial portion shifts in a dorsocranial direction to the left.

Looping of the heart toward the right provides the first indication of programmed left-right asymmetry. The direction of looping is conserved within the vertebrate phyla, suggesting that it is an evolutionary conserved course of events (17). Asymmetric looping of the cardiac tube is essential for the proper spatial orientation of the future right and left cardiac chambers. Understanding the mechanisms for the dominant right-sided heart looping is crucial, because several syndromes display laterality defects, including a laterality mutation that was mapped to the X chromosome in humans (18).

Asymmetric expression of several signaling molecules mainly belonging to transforming growth factor-b (TGF-b) family is essential to cardiac looping. Experimental perturbation of their expression pattern results in randomized looping (19,20 and 21). These molecules include activin; activin receptor protein (cAct RIIa); Shh, a vertebrate homologue of *Drosophila melanogaster* hedgehog protein; and nodal. Analysis of these transcripts during and after gastrulation showed transient asymmetric expression along the left-right axis of the chick embryo just before the onset of cardiac looping (19,20 and 21). At H-H stage 4, the cAct RIIa is expressed in the ectodermal layer near the right side of Hensen's node. Shortly thereafter, Shh is expressed on the left side in the same germ layer, and in subsequent hours, nodal is expressed on the left side but in the mesodermal layer. These molecules regulate the expression of one another in a sequential pathway such that activin stimulates cAct RIIa and suppresses the expression of Shh along the right axis (eFig. 103.0.2). Absence of cAct RIIa allows Shh to be expressed and stimulates nodal gene expression along the left axis. Manipulation of the sidedness of these molecules by ectopically expressing either activin or Shh protein also results in randomized cardiac looping (20). A putative transcription factor encoded by a snail-related gene *cSnR* also is implicated in the process of cardiac looping (21). In the chick embryo, the mRNA for this gene was expressed in the right lateral plate mesoderm in a domain that roughly mirrored that of nodal on the left. Antisense disruption of this transcript before heart formation randomized cardiac looping (21). The expression of another transcription factor, Pitx2, is induced by nodal and Shh in the left lateral plate mesoderm and, subsequently, on the left side of the developing heart. Forced expression of Pitx2 on the right side of the developing embryo was sufficient to reverse cardiac looping and heart isomerisms (22). Thus, these studies collectively suggest that asymmetric expression of some of the signaling molecules and certain transcription factors is crucial for the normal cardiac looping to the right.



***e*FIGURE 103.0.2** Signaling molecules implicated in the process of cardiac looping. Activin molecule induces cAct RIIa and cSnR on right; Shh induces expression of nodal on the left side of the embryo. Signal for the induction of Shh's expression on left is not known (?). Ectopic expression of Shh on the right, or of activin on the left, randomizes asymmetric expression of these molecules as well as of cardiac looping. —, inhibitory effect on the expression of target protein.

Other embryologic manipulations, such as stimulation of the $alpha_1$-adrenergic receptor subtype in rat neurula-stage embryos, result in randomization of cardiac asymmetry (23). A gap junction protein, connexin 43, also plays an important role in defining left-right asymmetry. In a clinical study, patients with visceroatrial heterotaxia syndrome and complex cardiac malformations (including right or left atrial isomerism) showed mutations in the coding region of the connexin 43 gene (24).

In addition, transgenic mice embryos with homozygous mutation in the connexin 43 gene showed a laterality defect (25).

Chamber Formation

Septa and Valve Formation

The transformation of the developing heart from a simple tube to a four-chamber structure containing valves and septa is accomplished through highly integrated and sequential processes of cell proliferation and cell migration. The heart tube is subdivided into segments that give rise to the outflow tract (*conotruncus*), the ventricle, the atrioventricular (AV) canal, and the atrium. Segmentation of heart tube is accomplished by regionally restricted changes surrounding two regions: the AV canal site and the outflow tract. Endocardial cells in the two regions extend pseudopodia and filopodia and eventually migrate into the cardiac jelly, where they become mesenchymal cells. As cell density progressively increases, the previously acellular cardiac jelly becomes transformed into mesenchymal outgrowths known as *endocardial cushions*.

Why is transformation of endocardial cells to cushion-forming mesenchymal cells restricted regionally to the AV canal region and to the outflow tract? This process was studied extensively in chicks by Runyan et al. (26) and Eisenberg and Markwald (27). It has been suggested that a regional induction signal emanating from the myocardium acts on the endocardium to initiate this transformation. Regional specificity is provided by the ability of the myocardium to produce the inducer(s) and endocardial endothelial cells to respond. Alterations in the expression of several genes have been demonstrated during AV canal morphogenesis. In particular, members of the TGF-b family (BMP-4, TGF-b_1, and TGF-b_2), homeobox genes (*Msx*-1, *Mox*-1), and Es antigens (adherons) show restricted expressions in the AV canal and conotruncal regions. The cell adhesion molecule N-CAM, initially expressed throughout the endocardium, is greatly downregulated after transformation of endocardial to mesenchymal cells. On the other hand, the substrate adhesion molecule, tenascin, is upregulated in the transformed cells. Tenascin disrupts cell substrate adhesion, thus allowing cells to migrate more freely. Abnormalities or arrests in these processes may result in developmental abnormalities of the AV canal and conotruncal regions.

The interatrial septum originates as an invagination from the dorsocephalic wall of the atrium between the openings of the sinus venosus and pulmonary veins to form a thin myocardial partition between the atria. Formation of the interventricular septum is intimately related to myocardial trabeculation.

The primordia of the semilunar valves are three pairs of small tubercles of the cushion tissue, whereas the primordia of the AV valve leaflets consist of cushion as well as muscular tissues. In mammalian embryos, the muscular tissues are soon replaced by connective tissue, and only occasionally are muscle fibers found at the base of the leaflets in the mature heart. It is now clear that cushion mesenchymal cells differentiate into fibrous connective tissue of both the semilunar and AV valves and that this process correlates with the expression of two microfibrillar proteins, fibrillin and fibulin (28,29). Sulfated proteoglycans (another matrix protein) have also been implicated in this remodeling process (30). Furthermore, several regulatory molecules may participate in valvulogenesis, including TGF-b_1, which maintains high expression levels throughout valve formation (26). More recently, transcription factors NF-ATc and Sox 4 have been shown to play important roles in valve formation (31,32 and 33). In normal embryos, Sox 4 has specific expression in the endocardial cushion and ridges, and NF-ATc has restricted but transient expression in endocardial cushion, followed by outflow tract and developing valves (32,33). Targeted disruption of NF-ATc and Sox 4 gene products in mice has resulted in embryonic death before day 14.5 due to circulatory failure. These mutants showed defective development of the semilunar valves and ventricular septum; the mitral and tricuspid valves had normal development (32) or restricted development (31). Nuclear localization of NF-ATc involves Ca^{2+}/calicineurin–signaling pathway; however, the ligand and receptor involved, and their downstream targets, are not known. Smad6 involved in signaling of TGF-b family (activins and BMPs) shows restricted expression in the developing heart, and its disruption leads to hyperplasia of cardiac valves and outflow tract (34).

Myocardial Trabeculation

At the final stages of loop formation, the myocardium is a compact epithelial tissue layer formed exclusively of myocytes. In the ventricular region, wide intercellular spaces start appearing between the myocardial cells, separating the myocardium into two distinct zones: a compact outer layer and an inner spongy layer. Simultaneously, the endocardium evaginates at discrete points, forming outpocketing that is directed toward the myocardium. When the endocardial outpocketing establishes contact with the myocardial basal surface, the myocardial cells separate to form little gaps. Subsequently, the endocardium penetrates the myocardial wall through these gaps and expands laterally into the previously formed intercellular spaces, resulting in primitive trabecular formation, which later assumes a more complex pattern. Most of the primitive trabeculae eventually disappear, but some coalesce to form papillary muscles or trabecula carneae of the mature heart. Continued trabeculae formation has an important developmental impact. It prevents unrestricted myocyte growth during cardiogenesis and at the same time ensures potential chamber cavity preservation. The net result is a ventricular structure that is not solid or excessively thick-walled and, consequently, able to perform the fundamental pump function during all stages of cardiac development and thereafter.

Signaling events between the endocardium and the myocardium are important for ventricular growth. Recent studies have demonstrated that cell surface receptors ErbB2 and ErbB4, both members of the epidermal growth factor receptor family, are involved in ventricular trabeculae formation. Transcripts of these receptors have been detected in the myocardium but not in the endocardium of the developing heart (35). The endocardium expresses neuregulins, which are ligands for these receptors. Mice deficient in receptors or their ligands die during mid-embryogenesis and show aborted development of myocardial trabeculae in the ventricle (36).

Conduction System

Establishment of the cardiac conduction system represents another cellular diversification of the developing myocardium. It is not precisely known when this system develops; however, experiments suggest that the conduction system is already functional during the final stages of cardiac loop formation. The cells of the future conduction system are found mostly in the vicinity of arterioles and show distinct morphologic features such as higher glycogen content and lesser myofibrils. The cells of the conduction system probably have dual origin because both muscle- and neuron-specific genes are coexpressed in these cells (37).

Molecular signals that promote and regulate the development of the conduction system from specialized cardiomyocytes have not been identified. The homeobox gene *Msx-2* is expressed in central portions of the conduction system (38). The peripheral Purkinje fibers appear with the coronary arterial bed, suggesting participation of a blood-derived factor in the transformation of myocardial cells to Purkinje fibers (39).

Role of Neural Crest Cells

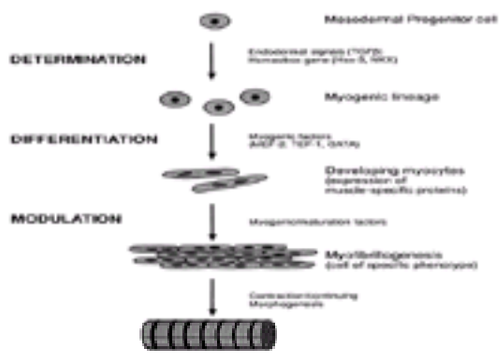
The neural crest exists only briefly during early embryonic development and constitutes a population of cells contained initially in the neural folds. As the neural plate closes to form the neural tube, neural crest cells are released from the neural folds. The neural crest is anatomically divided into two parts: a cranial region and a trunk region. A portion of the cranial region extending between midotic placodes and somite 3 is known as the *cardiac neural crest*. Cells of the cardiac neural crest play crucial roles in cardiac development. Ablation of the cardiac neural crest, either surgically or chemically, resulted in predictable cardiac malformations that include persistent truncus arteriosus and double-outlet right ventricle (reviewed in reference 40). More recently, neural crest cells, which contribute to the formation of the aorticopulmonary septum, have been directly visualized by specific cell-labeling techniques (41). The cardiac neural crest cells migrate to and populate pharyngeal arches 3, 4, and 6 to participate in the development of the major branches of the aortic arch.

Despite the critical role of the neural crest to cardiovascular development, little is known about its contribution at the molecular level. Suggested molecules include retinoic acid, vitamin A, endothelin-1, or endothelin-A receptor (42). Mice deficient in these molecules display similar cardiovascular abnormalities to those seen after neural crest ablation. Endothelin-3 has been shown to promote neural crest cell proliferation in a cell culture model (43). Candidate genes for neural crest origin belong to the homeodomain family of transcription factors such as Pax 3, Msx1, and Msx2 (reviewed in reference 44). Besides neural crest, these genes are also expressed in the outflow tract region and in the endocardial cushion of the developing heart. Transgenic mice deficient in one of these regulatory molecules display normal cardiovascular development, but double homozygous-deficient mice show cardiac defects (44), suggesting that these transcription factors may cooperate in the regulation of as yet unidentified target genes. Other genes of cardiac neural crest origin include the *bHLH* gene products dHAND and eHAND, which are expressed in crest-derived tissue structures (45).

MOLECULAR REGULATION OF CARDIAC MYOGENESIS

Myogenesis of cross-striated muscle consists of three basic developmental stages: (a) commitment (also known as *determination*), (b) differentiation, and (c) modulation (or *maturation*). During *commitment*, the mesodermal cell is specified to a muscle lineage such that the committed cell, unlike the noncommitted ones, will have restricted potential. *Differentiation* consists of expression of cardiac-specific proteins such as myosins, actins, troponins, tropomyosins, and channel proteins. Some investigators refer to “terminal differentiation” as either a state when a battery of cell-specific genes becomes turned on, resulting in the cells exhibiting morphologic and functional characteristics of their specific phenotype, or to a terminal pathway culminating in an irreversible phenotype. It has been argued, however, that terminal differentiation has little meaning because in many instances the differentiated state is not irreversible but requires continuous maintenance (46). *Modulation* is characterized by sequential changes in the pattern of gene expression whereby genes coding for some of muscle proteins are induced, whereas others become repressed. This stage of muscle maturation takes place during the fetal and neonatal periods when muscle cells begin to assume morphologic features

required for contractile function. The regulatory aspects of these various stages are summarized in *e*Figure 103.0.3.



***e*FIGURE 103.0.3** Schematic illustration of molecular events during cardiac myogenesis. Stages of myogenesis are represented by (1) determination, conversion of progenitor cells to myogenic lineage; (2) differentiation, conversion of lineage-specific cells to myocytes that now express muscle-specific proteins, and (3) modulation, the process of maturation resulting in a specific phenotype. Regulatory factors involved in different stages of myogenesis are shown. MEF-2, myocyte enhancer factor 2; TEF, transcription enhancer factor; TGFb, transforming growth factor-b.

Determination of Cardiogenic Muscle Lineage

Determination of lateral mesodermal cells to cardiac muscle lineage is an early event. In chick embryos, it occurs at the late primitive stage (47). The cardiogenic area shows regional differences along an anteroposterior axis such that the posteriorly positioned cardiac precursors express atrial-specific, but not ventricular-specific, myosin heavy chain (MHC). Thus, atrial and ventricular lineages are separately specified, and their determination is primarily based on the anteroposterior polarity of the heart progenitors in the very early embryo (reviewed in reference 48).

Our understanding regarding regulation of the determination stage of myogenesis is still fragmentary. Current theories predict two types of regulation. One consists of signals derived from neighboring endodermal cells because mesodermal cells cultured alone fail to express cardiac-specific muscle proteins. The role of endodermal inducers and other signaling mechanisms in lineage specification has been described above. The other type of regulation assumes an existing determination gene(s) coding for lineage-restricted factors that play an important role in commitment and differentiation of cardiogenic cells and are regulated by signals derived from the neighboring cells. These molecules fall into the category of transcription factors, which are DNA-binding proteins and regulate gene expression through interaction with regulatory elements in the target genes. Most of these regulators exist as multimember families, with each member sharing extensive sequence homology in their DNA binding domain, often providing redundancy to their function.

The well-described class of transcription factors that play important roles in cardiac muscle commitment and differentiation belong to homeobox proteins. Homeobox-containing genes were first defined in *Drosophila* to possess a 180–base pair conserved sequence motif that encodes a helix-turn-helix DNA-binding domain called a *homeodomain*. Mammalian homeobox genes may be divided into two classes: hox-class genes and non–hox-class genes. Hox-class genes exist in four clusters in the mammalian genome and appear to convey positional information rather than specification of cell type. Members of hox-class genes, such as *Mox-1* and *Mox-2*, are expressed in the posterior mesoderm during early mouse embryogenesis before extensive mesoderm patterning is apparent. Other members, such as *Hox-7*, *Hox-3.1*, and *Hox-1.5*, display different but overlapping patterns of expression. The interplay of these proteins is considered to have major roles in both early and late embryonic and fetal heart development (reviewed in reference 49). The importance of non-hox proteins (Nkx family) in cardiac lineage (progenitors) specification has been described. There are at least six different Nkx-2 genes, but the expression pattern of only a few genes has been characterized (50). In Nkx2-5 knockout mice, the expression of several cardiac muscle genes was not affected, most likely due to genetic redundancy of Nkx-2 loci during cardiogenesis (50).

Differentiation and Activation of Cardiac Genes

Once committed, the precursor myogenic cells have the potential to express muscle genes through the process of differentiation, resulting in a cardiac-specific phenotype. Differentiation proceeds in a highly ordered anterior-to-posterior manner within the cardiogenic mesoderm. MHC mRNA has been detected in the cardiac primordia, suggesting that differentiation of lineage-specific cells occurs much before the primitive heart tube is formed. In the newly formed cardiac tube, the expression of different contractile proteins varies along the antero-posterior axis (51). In the developing heart, all cardiac myoblasts undergo differentiation, and further increase in number occurs strictly through mitosis of differentiated myocytes. Mitotic potential is lost once cardiomyocytes attain their adult phenotype during development. Regulation of muscle cell differentiation is provided by transcription factors that belong to the basic helix-loop-helix (bHLH) proteins, transcription enhancer factor 1 (TEF-1) proteins, and myocyte enhancer factor 2 (MEF-2) and GATA family of factors. A list of these factors, target genes, and their role in muscle gene regulation is provided in *e*Table 103.0.2.

***e*TABLE 103.0.2** IMPORTANT FACTORS INVOLVED IN CARDIAC MUSCLE GENE TRANSCRIPTION

Transcription factor	Target sequence	Name	Gene regulation
MEF-2	CT (A/T)(A/T) AAATAG	AT-rich	Expressed in cardiac precursors; regulate cardiac and skeletal muscle genes
TEF-1	CATTCCT	M-CAT	Muscle-specific expression of cardiac troponin-T and a- and b-MHC genes; protein kinase C–induced expression of b-MHC gene
Myc family	CANNTG	E-box	Cardiac-specific expression of a-MHC
GATA family	GATA	GATA	Expressed in cardiac precursors; involved in cardiac tube formation
TEF-1 and MAX	CACGTGGAATG	EM	Cyclic adenosine monophosphate– and contractility-induced regulation of a-MHC
T_3 receptor (c-erbA)	C (T/A) GGAGG (T/A)	TRE	T_3-induced expression of a-MHC

EM, E-box/M-CAT element; M-CAT, muscle CAT element; MEF-2, myocyte enhancer factor 2; MHC, myosin heavy chain; TEF-1, transcription enhancer factor 1; TRE, thyroid response element; T_3, thyroid hormone.

Basic Helix-Loop-Helix Proteins

Many, but not all, sarcomeric proteins are expressed in cardiac as well as in skeletal muscle cells, suggesting that overlapping as well as divergent regulatory pathways must be involved in their expression. Of the known factors in skeletal muscle gene transcription, members of the *MyoD family* (MyoD, Myf-5, myogenin, and MRF-4) are the best understood. They share a high degree of homology in their DNA-binding domain, referred to as *bHLH domain*. Proteins of the bHLH class mediate their effects by forming heterodimers with other ubiquitously expressed proteins known as *E-proteins* (52). The MyoD family of bHLH proteins has not been detected in cardiac myocytes, and double-mutant (Myf-$5^{-/-}$MyoD$^{-/-}$) mice develop normally functioning hearts (52,53). However, the MyoD inhibitor Id is present in cardiac cells and, similar to skeletal muscle, is regulated by alpha-adrenergic agonists and by serum (54). In addition, forced expression of Id downregulates transcription from both skeletal and cardiac actin promoter constructs in neonatal cardiac myocytes (55). These findings suggest that the cardiac cell context is permissive to the E-box–dependent pathway and must involve a separate class of transcription factors for the regulation of cardiac-specific genes. Recently, such a role has been assigned to the bHLH-LZ class (myc family) of factors, which mediate their effects through E-box (56). Transgenic studies involving knockouts of the N-*myc* gene resulted in embryonic death around embryonic day 11, accompanied by multiple developmental defects of the myocardium and interventricular septum and consequent pump failure. N-myc, like other myc proteins, is able to transactivate target genes by binding to specific DNA sequences as a heterodimer with another protein, Max. Nevertheless, the downstream target genes in cardiomyocytes are not known (reviewed in reference 57).

Transcription Enhancer Factor 1 Proteins

Another class of factors necessary for muscle-specific gene expression in both the cardiac and skeletal muscle cell context binds to the muscle CAT (M-CAT) (CATTCCT) element originally identified in the regulation of cardiac troponin-T gene. The factor binding to the M-CAT element is related to TEF-1 (58), which belongs to a family of factors having TEA/ATTS DNA-binding domain. Transcripts of TEF-1 family members are abundant in many tissues, and cardiac- and neuronal cell–specific isoforms have recently been reported. Knockout experiments of TEF-1 resulted in fetal death from cardiac malformation, including thinning of the ventricular wall (59). One interesting feature in many TEF-1–regulated muscle genes relates to the TEF-1 binding site, M-CAT, located at an overlapping site or in close

proximity to a canonical E-box binding consensus. Such a hybrid motif located immediately upstream to the TATA box sequence was identified in the rat cardiac a-*MHC* gene responsible for muscle-specific as well as contraction-induced gene expression in cultured cardiac myocytes (60,61). Similar motifs have been described in the human b-*MHC* gene and in the avian cardiac troponin-T genes, where both the E-box and M-CAT elements are functionally important in determining promoter specificity of the gene (61). Two factors, Max and TEF-1, bind this hybrid motif in the rat cardiac a-*MHC* gene. These two factors physically interact with each other both *in vitro* and *in vivo,* and transactivate the a-*MHC*/*CAT* gene. Thus, a cooperative synergism exists between TEF-1 and Max for cardiac muscle gene regulation (56). Recently TEF-1 has been shown to be a substrate for protein kinase A–dependent phosphorylation, which enhances the activation potential of TEF-1 for a-*MHC* gene transcription (62).

MCM1, Agamous, Deficiens, and Serum Response Factor Proteins

The MADS [name derived from four of the originally identified members: *M*CM1, *a*gamous, *d*eficiens, and *s*erum response factor (SRF)] family of transcription factors share a conserved DNA-binding domain (MADS-box). The majority of MADS-box proteins binds to consensus sequence $CC(A/T)_6GG$ and recruits other transcription factors into multicomponent regulatory complexes with subtly different DNA-binding specificities (63 and references therein). Until recently, SRF has been considered as a ubiquitous transcription factor involved in regulation of growth factor–responsive genes; however, preferential expression of SRF has been demonstrated in chick myogenic lineages, in adult murine skeletal and cardiac muscle, and in the embryonic heart. SRF promoter activity is also higher in muscle cell background (64). Further, SRF physically interacts with Nkx-2.5 and results in strong transcriptional activation of the cardiac alpha-actin promoter via serum response element (65). Additionally, effect of SRF is enhanced by TEF-1 for the activation of rat a-skeletal actin promoter (66). Thus, through cooperative interaction, SRF controls muscle gene expression. Recent gene knockout studies have shown an obligatory role of SRF in mesoderm differentiation (67).

MEF-2, another member of MADS proteins, comprises a subfamily of transcription factors that also participate in muscle gene regulation. Four MEF-2 isoforms (MEF-2A through D) are expressed in the precursors of cardiac muscle lineage, have the ability to physically interact with the MyoD family of factors, and together can activate muscle gene promoters. Mutations in the MEF-2 gene in *Drosophila* blocked differentiation of all muscle cell types in the embryo (68 and references therein). This family of transcription factors is regulated by non–hox-class determination factors, as the MEF-2D gene has recently been shown to be a target for Nkx activation (69). A homozygous mouse with null mutation of MEF-2C has shown failure of the cardiac tube to undergo looping and nonexpression of muscle genes (70), demonstrating the importance of these factors in cardiogenesis.

GATA Proteins

The GATA family of transcription factors binds to GATA-rich sequences in various cardiac gene promoters. Expression of GATA-4 and GATA-5 has been detected in the splanchnic mesoderm and subsequently in endocardial and myocardial layers of the developing heart. These factors were originally thought to play roles in cardiac muscle cell differentiation. However, studies in transgenic mice deficient in GATA-4 have demonstrated normal development of splanchnic mesoderm, its differentiation into primitive cardiomyocytes, and normal expression of contractile proteins. Thus, in spite of their crucial role in early morphogenesis, GATA proteins are not essential for the induction of the cardiac myogenic program (11,12).

Modulation of Gene Transcription by Extrinsic Factors

Differentiation, as described previously, is due to the activation of muscle gene transcription, followed by sequential changes in gene expression, resulting in replacement of some isoforms by others. In some cases, this diversity is generated at the transcriptional level (e.g., MHCs); in others it is achieved by alternative splicing of gene transcripts as seen in tropomyosin or troponin T. From a pool of various isoforms, only a subset is expressed at any given time. Some of these changes follow an intrinsic program, whereas others require hormonal input.

Among the isoform families, the MHCs have been studied most extensively. In rodents, the two isoforms of MHC (a and b) are already coexpressed in the newly formed cardiac tube. As trabeculation begins, selective downregulation of a-MHC expression occurs in the ventricle; however, a-MHC expression in the atria remains unchanged. After a-MHC mRNA has decreased to the lowest level in the developing ventricular myocardium, it begins to increase just before birth and ultimately replaces all b-MHC mRNA postnatally (71). The well-described hormonal signals involved in this transition are thyroid hormones (THs) and catecholamines. This dynamic state of muscle phenotypes (also known as *phenotypic plasticity*) is noticeable not only during embryonic and fetal development but also postnatally, and even in adult animals.

Thyroid Hormone

TH exerts a variety of effects on gene transcription of several muscle genes. Its role in modulating cardiac muscle gene transcription is complex because the same gene responds to the hormone differently in different chambers of the heart or in different cell backgrounds. For example, TH influences a-MHC expression in the ventricle but the atria remain unresponsive. Likewise, b-MHC is repressed by the TH in the ventricle but remains almost unaffected in slow-type skeletal muscle (72).

The molecular mechanism of the TH action is mediated through its binding to a TH receptor, which is a nuclear protein product of the *c-erbA* protooncogene (73). These receptors are hormone-dependent transcription factors and exert their effects by binding to a hormone-responsive DNA element thyroid response element (TRE) in the target gene. The TH effect on a-*MHC* gene expression is mediated by TRE present in the 5' promoter region of both the human and rat a-*MHC* genes. This TRE is responsive to TH even on a heterologous promoter, suggesting that TRE of the a-*MHC* gene acts as an enhancer element (73). The mechanism for the TH-dependent repression of b-*MHC* gene expression is not yet fully understood.

Adrenergic System

In recent years, several studies have documented the importance of alpha- and beta-adrenergic receptor pathways in the regulation of cardiac MHC gene transcription. These studies suggest that $alpha_1$-adrenergic receptor agonists activate b-*MHC* gene transcription through protein kinase C, whereas beta-adrenergic receptor agonists activate a-*MHC* gene transcription via protein kinase A–dependent pathway (reviewed in reference 74). In each case, the hormone-responsive sequence is identified in the promoter region of the respective genes. The protein kinase A pathway involves E-box/M-CAT hybrid motif in the a-*MHC* gene promoter that interacts with TEF-1. The protein kinase C mediates its effect via the M-CAT element of b-*MHC* gene promoter, which also recognizes TEF-1 (75). Thus, these observations implicate that TEF-1 binding is a functional end point for both alpha- and beta-adrenergic–regulated expression of cardiac *MHC* genes. The precise mechanism on how phosphorylation of TEF-1 by two different signaling pathways regulates expression of a- and b-*MHC* genes remains to be defined.

Recent studies have demonstrated the presence of cell clusters capable of synthesizing and releasing catecholamines in the atrial and ventricular chambers of the fetal heart at a developmental stage before the onset of sympathetic innervation (76). In addition, targeted disruption of enzyme genes of catecholamine synthesis (77) and of the beta-adrenergic receptor kinase (78) resulted in embryonic death and severe anomalies of the heart. These observations indicate an important contributory role of the adrenergic pathway to the development and maintenance of the cardiac muscle phenotype.

GENETIC BASIS OF CONGENITAL HEART DEFECTS

Recent advances in cardiac molecular biology provide noteworthy insights into our understanding of congenital heart disease. Despite these advances, our knowledge remains fragmentary. In most cases, the abnormalities are linked to a specific locus, and only in a few cases have the gene abnormalities been identified. The role of a single gene product in the overall pathogenesis of the cardiac abnormality remains to be established. In this section, we briefly review the relevant literature pertaining to the genetic basis for congenital heart disease (summarized in *e*Table 103.0.3).

***e*TABLE 103.0.3** MOLECULAR BASIS OF HERITABLE CONGENITAL MALFORMATIONS

Disorder	Mode of inheritance	Chromosome location	Gene	Cardiovascular manifestation
Marfan syndrome	Autosomal dominant	15q21.1	Fibrillin-1	Aortic root dilation, elongated chordae, atrioventricular prolapse plus regurgitation, aortic dissection
Supravalvular aortic stenosis	Autosomal dominant	7q11.23	Elastin	Discrete or diffuse narrowing of ascending aorta
Williams syndrome	Sporadic	7q11.23	Elastin	Same as above plus other symptoms
Duchenne’s muscular dystrophy	X-linked	Xp21	Dystrophin	Dilated cardiomyopathy
CATCH 22 (DiGeorge, velocardiofacial syndrome, conotruncal heart defects)	Sporadic	22q11 deletion	Contiguous gene disorder	Interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, double-outlet right ventricle
Long QT syndrome	Autosomal dominant	11p15.5	Na and K channel	Ventricular arrhythmias

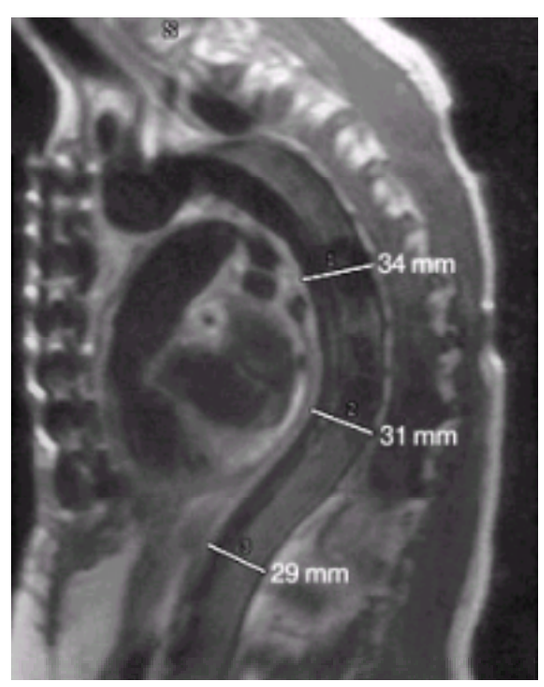
Holt-Oram syndrome	Autosomal dominant	12q2	TBX5	Atrial septal defects
Down syndrome	Autosomal dominant	21q22 (trisomy)	?	Atrioventricular canal defects
Familial hypertrophic cardiomyopathy	Autosomal dominant	14q11,15q21q3,11p13–q13, 7q3	b-MHC, cTnT, a-tropomyosin	Asymmetric cardiac hypertrophy and subaortic stenosis

Marfan Syndrome

Marfan syndrome is a pleiotropic, autosomal dominant, connective tissue disorder with prominent manifestations in the cardiovascular, skeletal, and ocular systems. The molecular genetic defect is linked to abnormalities in the *FBN1* gene, which is located on chromosome 15 and codes for fibrillin-1 protein. It is a microfibrillar protein that is a part of a multiprotein complex involving elastin and other extracellular matrix proteins. This protein has several epidermal growth factor-like repeats, suggesting an important role of these domains in its function. There are at least 30 different mutations described in the fibrillin gene in association with Marfan syndrome. These mutations result in truncated protein or affect its functional properties (reviewed in references 79 and 80). The mechanism by which abnormal fibrillin produces the Marfan syndrome phenotype is not known.

Ectopia lentis. This lens dislocation is associated with Marfan syndrome.

Arachnodactylia in Marfan syndrome. The ratio of finger length to hand size is markedly increased.



Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

Supravalvular Aortic Stenosis

Supravalvular aortic stenosis (SVAS) is a congenital localized or diffuse narrowing of the ascending aorta that may occur sporadically, as a familial defect, or in relation with Williams syndrome (WS). WS is a contiguous gene syndrome associated with neurodevelopmental and multisystemic manifestation caused by hemizygous microdeletion of 1.4 MB at chromosomal 7q11.23. Genetic linkage analysis showed that alteration in elastin, an extracellular matrix component, may result in SVAS. The first evidence that elastin is defective in SVAS was provided by mapping studies on the long arm of chromosome 7 (81). Using positional cloning, three genes were identified at this locus, namely, collagen 1A2, laminin B1, and elastin. A truncated elastin protein was demonstrated in a family due to translocation of part of chromosome 6 to the elastin locus of chromosome 7 on one allele (82).

Monosomy at the elastin locus (7q11.23) has been demonstrated in many patients with WS and also may harbor mutations in nearby genes located near elastin (83). These additional mutations may account for the psychological and behavioral abnormalities associated with WS. More recently, six novel point mutations were identified in the elastin gene in patients with nonsyndromic SVAS from a total of eight unrelated families. These mutations resulted in selective elimination of the mutant

transcript and an overall decrease of the steady-state levels of elastin mRNA (84).

Duchenne's Muscular Dystrophy

Duchenne's muscular dystrophy is a common X-linked heritable form of muscle disease and is one of the most severe forms of muscular dystrophy, causing progressive muscle wasting and death in adolescence or early adulthood. Cardiac dysrhythmias and dilated cardiomyopathy are common features at the late stages of the disease. An X-linked dilated cardiomyopathy linkage has been provided to the locus of the dystrophin gene at Xp21 (85). Mutations in the dystrophin gene have been described as the genetic basis of Duchenne's muscular dystrophy. The gene codes for a cytoskeletal protein anchoring membrane proteins and may be involved in maintaining intracellular calcium levels. This protein is present widely, and multiple isoforms of dystrophin RNA are identified in the brain and skeletal and cardiac muscle. These isoforms show developmentally regulated expression in different tissues (86).

DiGeorge Syndrome

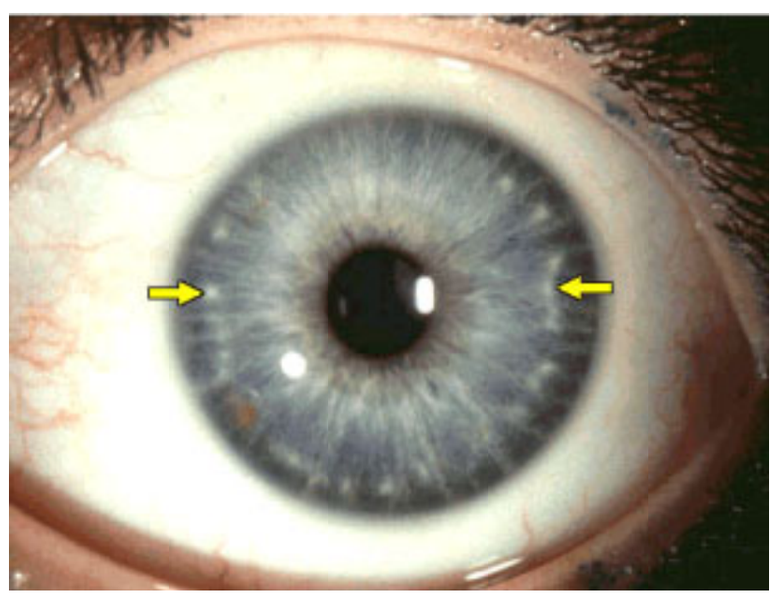
Both microdeletions and rearrangements in chromosome 22 are linked to DiGeorge syndrome. This condition, along with conotruncal face anomaly syndrome and Shprintzen syndrome, displays a group of cardiovascular defects that have several etiologic bases and are known collectively as CATCH 22 (for *c*ardiac, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate, *h*ypocalcemia, and chromosome *22*). Velocardiofacial syndrome also shares some of these abnormalities, namely, cleft palate and cardiac and cognitive defects. Cardiovascular defects in these syndromes include persistent truncus arteriosus, tetralogy of Fallot, double-outlet right ventricle, interrupted aortic arch, and ventricular septal defect. A variable percentage of patients with one of these defects or syndromes have deletion in the long arm of one of the chromosomes 22 close to the centromere, resulting in a 22q11.2 monosomy that is either through a large interstitial deletion or through an unbalanced translocation in a 500-kb region (87). Extensive analysis of this region led to the cloning of the translocation breakpoint and isolation of several candidate genes. Some of these genes are transcribed as nontranslatable RNA (88) or as translatable RNA such as a cDNA (IDD) encoding a transmembrane protein, mapped within 10 kb of the break-point (89). A human analog of *Drosophila* segment-polarity gene (*dsh*) was cloned and its deletion was reported in DiGeorge syndrome (90). How these genes fit into the pathogenesis of DiGeorge syndrome remains to be clarified.

Long QT Syndrome

Long QT syndrome is an autosomal inheritance disorder characterized by syncope, seizures, and sudden death resulting from episodic ventricular dysrhythmia. Linkage analyses indicate that this syndrome is genetically heterogeneous, involving at least three distinct loci in different families: LQT1 on chromosome 11p15.5, LQT2 on 7q35–36, LQT3 on 3p21–24, LQT5, and LQT6. Mutations in a putative potassium channel are identified in LQT2, whereas mutations in the cardiac sodium channel gene are linked to LQT3 (for a recent review, see reference 91).

Down Syndrome

Down syndrome, which is caused by trisomy of chromosome 21, is associated with congenital heart disease in approximately 50% of patients, most often with AV canal defects. Although the defect has not been mapped to a specific gene, candidate genes include a tetratricopeptide repeat sequence located within the Down syndrome region on chromosome 21 (92). Similarly, *CAF1P60* gene, also located on chromosome 21, is overexpressed in this syndrome (93). Other candidate genes include a transcription factor, GABPA, belonging to the E26 transformation–specific family of DNA-binding proteins (94). The role of these factors in the pathogenesis of Down syndrome remains to be identified.



Brush field spots in association with Down syndrome. The yellow arrows indicate grayish-white spots in the iris, which are associated with trisomy 21.

Holt-Oram Syndrome

Holt-Oram syndrome is a prototypical heart-hand disorder characterized by atrial septal defect and radial ray limb deformity with autosomal dominance. Genetic mapping studies in two large families revealed the linkage on the long arm of chromosome 12 at 12q2 (95) and suggest it to be a genetically heterogeneous disorder (96).

Recent studies have implicated many different mutations in a transcription factor TBX5 to be responsible for this syndrome (97). Introduction of specific missense mutations in the TBX5 gene in mice resulted in either heart or skeletal abnormalities that resembled the clinical phenotype of Holt-Oram syndrome (98). Expression studies also suggest an essential role for TBX5 in early heart development and chamber-specific gene expression (99).

Familial Hypertrophic Cardiomyopathy

Familial hypertrophic cardiomyopathy is an autosomal dominant disorder manifesting as primary cardiac hypertrophy. It is phenotypically and genotypically a heterogeneous disease. So far, hypertrophic cardiomyopathy has been mapped to five different loci, of which three genes have been identified to be mutated. All three genes encode contractile proteins of the thick and thin filaments of the sarcomere: the b-*MHC* gene on chromosome 14q11, the a-tropomyosin gene on chromosome 15q2, and the cardiac troponin-T gene on chromosome 1q3. Other disease loci have been mapped to chromosome 11p13–q13 and 7q3, but the candidate genes at these two additional loci have not been identified. A number of missense mutations have been found in each of the three genes coding for sarcomere proteins. These mutations result in alteration of the peptide structure, causing abnormal myofibrillar formation and alignment, which in turn impair cross-bridge cycling and contractile function of the myocardium. Identification of the mutations in these genes is extremely useful for screening or preclinical diagnosis in high-risk patients (i.e., with a family history of hypertrophic cardiomyopathy). In addition, specific mutations are associated with increased disease severity and shortened life span, providing prognostic information not available from clinical assessment (100).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Future investigations will complete our information on the molecular regulatory mechanisms involved in normal cardiogenesis. Genetic screening of many types of heart defects will be available. With the development of effective delivery systems, gene therapy *in utero* will be possible for certain types of cardiac anomalies, such as hypoplastic right or left ventricle complexes, ventricular septal defects, and AV canal defects.

THE FUTURE

Rapid advances in molecular biology continue to enhance our understanding of normal heart development and to provide insights into fundamental mechanisms that may lead to cardiac malformations. Molecular regulatory mechanisms involved in normal cardiogenesis have been identified, but important informational gaps still must be clarified in future investigations. The critical role of the neural crest to cardiovascular development, specifically, the outflow tract and great vessels of the developing heart, is well recognized; nevertheless, its embryogenetic contributions at the molecular level still need to be defined. A few candidate genes have been suggested, but more definitive investigations are needed to characterize gene expression by the neural crest cells and their interactions with other regulatory factors. Identification of these genes will allow us to screen families of children with certain types of heart defects and will help to identify alterations in human genomes that may be responsible for the neural crest–related cardiac defects.

The study of regulatory mechanisms that maintain cardiac cells in terminally differentiated states and the ability to manipulate muscle gene transcription will greatly facilitate efforts to regenerate heart muscle in patients with myocardial cell loss. There is a need for more studies in this field to expand current knowledge and discover new ones to pave the way for future therapeutic interventions, such as gene therapy *in utero* for certain types of cardiac anomalies that are currently diagnosed by fetal echocardiography. Potential therapy includes direct delivery of genes into the myocardium or introduction of genetically altered cells into the heart, but effective delivery systems must be developed. This potential for genetic manipulation in congenital heart disease, as is the case for many other cardiovascular disorders, remains a distant possibility. The combined advances in molecular biology, genetics, and gene therapy will not only improve our basic understanding of cardiovascular disease processes but also create new diagnostic and therapeutic programs.

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PATHOBIOLOGY OF HYPERTENSION

GARY H. GIBBONS

"Indicates text or graphics that appear only in the electronic versions of this text."

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INTRODUCTION

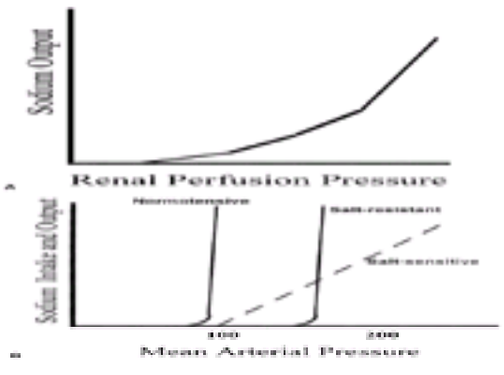
Although the clinical problem of hypertension is relatively well defined, its etiologic basis remains an enigma. A century has passed since the discovery of renin by Tigerstedt and Bergman, and more than 60 years have elapsed since the first animal model of hypertension was created by Harry Goldblatt (1). During the intervening period, students of hypertension have attempted to elucidate the causes of hypertension by characterizing the factors that regulate blood pressure and creating animal models that simulate the human disease. This chapter reviews our current understanding of the pathobiologic basis of hypertension in the hope that these principles will further advance the treatment of this disorder.

BLOOD PRESSURE AND THE KIDNEY

Any attempt to define the etiologic basis of human hypertension must begin by understanding the normal homeostatic regulatory mechanisms that control blood pressure. Moreover, a distinction must be made between short-term regulatory systems that buffer changes in blood pressure *around* a set point and long-term regulatory systems that *establish* the blood pressure set point. Short-term blood pressure buffering systems such as arterial baroreceptors are important homeostatic mechanisms in contexts such as acute hemorrhage but play relatively minor roles as long-term determinants of blood pressure. In an elegant series of experimental studies using integrative physiology as well as computer modeling, Guyton and his colleagues systematically characterized the relative contributions of various regulatory systems as long-term determinants of blood pressure (2,3). These analytical models based on extensive experimental studies have clearly established that the kidney plays an overarching role as the dominant long-term determinant of blood pressure.

An Intrinsic Antihypertensive Mechanism: Pressure-Natriuresis

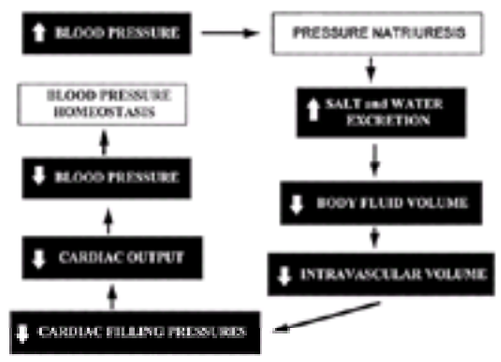
Perhaps one of the earliest clues about the pathogenesis of hypertension was derived from the observation that it is actually difficult to create an animal model of the disease. The normal function of the kidney serves as an intrinsic antihypertensive mechanism. The phenomenon of pressure-natriuresis, illustrated schematically in *e*Figure 104.0.1A, functions to prevent a chronic hypertensive state (3,4 and 5). This response creates a strict and intimate relationship between blood pressure and a control mechanism that governs the body fluid volume.



***e*FIGURE 104.0.1 A:** Pressure-natriuresis curve. The relationship between renal perfusion pressure and kidney sodium output observed in an isolated kidney preparation is illustrated. **B:** The renal function curve. The curve illustrates the maintenance of the normotensive state by the kidney at the equilibrium set point over a wide range of sodium intakes. The hypertensive state is characterized by a rightward shift in the equilibrium set point pressure. The salt sensitivity of the hypertensive state is a function of the slope of the renal function curve.

Although the mechanistic basis of the pressure-natriuresis phenomenon is not entirely clear, it is postulated that hemodynamic and humoral changes within the renal medullary circulation are involved (4,5). Although controversial, this working hypothesis predicts that factors that induce an increase in vascular resistance within the renal medullary bed and/or the afferent arteriole will modify the pressure-natriuresis curve and thereby promote a hypertensive state. The relative balance of factors such as nitric oxide (NO), reactive oxygen species, angiotensin II (Ang II), and arachidonic acid metabolites appear to play an important role in defining the pressure-natriuresis curve and thereby exert a long-term influence on systemic blood pressure (4,5 and 6).

Implicit in the renal function curve is an intrinsic antihypertensive mechanism that maintains the blood pressure at a certain set point (*e*Fig. 104.0.1B). At this set point, or equilibrium blood pressure, the net intake of salt and water equals the urinary fluid output. When the systemic pressure rises above a certain set point, a sequence of antihypertensive processes is activated: The kidney increases its excretion of salt and water in proportion to the elevation of the blood pressure such that the loss of salt and water promotes a decline in cardiac output and a decrease in blood pressure (*e*Fig. 104.0.2). Thus, the kidney is strategically poised to regulate blood pressure by mediating the pressure-natriuresis phenomenon and regulating body fluid volume in accordance with the renal function curve.



***e*FIGURE 104.0.2** The body fluid volume–blood pressure homeostatic mechanism. The sequential steps linking pressure natriuresis with the maintenance of blood pressure homeostasis at the equilibrium set point are illustrated.

Body Fluid Volume–Blood Pressure Relationship

The clinical observation that primary hypertension is characterized by an increase total peripheral resistance raises the question: How does an initial increase in body fluid volume result in a chronic increase in peripheral resistance?

Experimental studies have established that volume expansion results in an increase in cardiac output and therefore blood pressure. Over the course of time, the etiology of the blood pressure elevation shifts from a high cardiac output hypertension to a high total peripheral resistance form of hypertension. This shift in the hemodynamics of hypertension occurs as a result of a phenomenon described as *whole body autoregulation* (2,3,7). The delivery of excess oxygen and/or the enhanced removal of vasodilatory metabolic end products (e.g., adenosine) combined with the intrinsic myogenic properties of the vasculature cause the blood vessels to constrict in response to the increase in flow and pressure. This autoregulatory increase in vascular resistance effectively maintains the hypertensive state as cardiac output returns toward normal.

Causes of Hypertension: Insights from the Renal Function Curve

The fundamental thesis of the guytonian model is that all causes of chronic hypertension must modify the relationship between blood pressure and salt–water balance defined by the renal function curve. In general, the shape of the renal function curve can be modified by three basic mechanisms: (a) an alteration in the transmission of systemic pressure to the glomerulus, (b) a change in the ultrafiltration properties of the glomerulus, and (c) modifications in the sodium absorptive capacity of the tubules. This conceptual framework suggests a list of potential causes of hypertension (*e*Table 104.0.1).

***e*TABLE 104.0.1** SHIFTING THE RENAL FUNCTION CURVE: MECHANISMS OF HYPERTENSION
I. Renal resistance
Renal artery stenosis
Increased preglomerular vascular tone (increased vasoconstrictors/decreased vasodilators)
Increased preglomerular vascular reactivity (alterations in vasoactive receptor expression)
Increased vasoconstrictive ion fluxes (changes in ion channel expression/sensitivity)
Structural decrease in lumen dimensions (vascular remodeling)
II. Glomerular filtration
Alteration in glomerular ultrafiltration characteristics (glomerulosclerosis)
Decreased glomerular number
III. Tubular reabsorption
Increased sodium reabsorption (increased sodium channel activity/sensitivity)
Increased antinatriuretic factors (aldosterone)
Increased mineralocorticoid receptor activity (11b-hydroxylase)
Decreased natriuretic factors (atrial natriuretic peptide)
Dysfunctional natriuretic factor receptor pathways

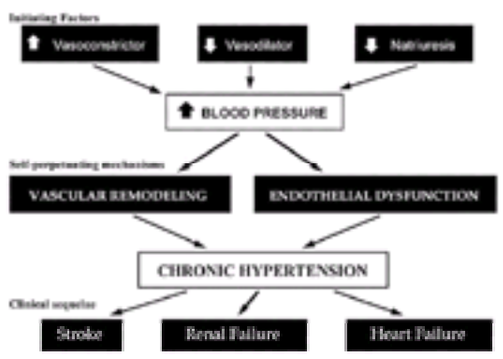
As we seek to understand the interaction between genetic and environmental factors that cause hypertension, it is readily apparent that this may involve a dynamic interplay between several variables that influence vascular tone and body fluid homeostasis. Moreover, this model predicts that hypertensives will be a heterogeneous population in which the relative mediator role of each of these factors will vary. Furthermore, it predicts that the hypertensive phenotype will include relatively simple etiologies such as single gene defects of sodium reabsorption (e.g., Liddle's syndrome) as well as more complex multifactorial forms of hypertension. Similarly, the model accommodates either congenital or genetic developmental determinants such as nephron number as well as age-related changes such as nephron loss (8). This guytonian model provides a unifying paradigm in which a large body of experimental evidence derived from a wide variety of model systems can be integrated into a powerful working hypothesis. It is anticipated that characterizing the molecular basis of shifts in the renal function curve will provide new insights into the fundamental causes of hypertension.

Clinical Implications of the Renal Function Curve

In addition to providing a framework for using a reductionist approach to characterize the etiology of hypertension, the guytonian model is also a useful paradigm in the clinical context. For example, the renal function curves defined in human hypertensives are strikingly similar to those characterized in genetically hypertensive rats (9,10). In some cases, analyses have documented that this shift is related to an increase in renal vascular resistance (*e*Fig. 104.0.1B). Clinical studies have documented that "salt-sensitive" hypertensive patients also exhibit the reduced slope of the renal function curve observed in animal models. Moreover, it is this patient subset that appears to have the greatest clinical response to diuretic treatment. Furthermore, it is apparent that many of the effective pharmacologic interventions used to treat hypertension modulate the renal function curve. For example, angiotensin-converting enzyme inhibitors and calcium channel blockers appear to be particularly effective in altering the pressure-natriuresis relationship (9,10,11 and 12). Finally, the pivotal role of the kidney as the critical determinant of the hypertensive state is most definitively demonstrated by studies in humans that have established that implanting a kidney from a normotensive donor into a hypertensive individual can induce the remission of hypertension (13,14,15 and 16). Thus, a substantial body of evidence has confirmed that the guytonian model is equally applicable to the clinical problem of primary hypertension.

CHRONIC HYPERTENSION: MALADAPTIVE SELF-PERPETUATING MECHANISMS

It is clear that a myriad of factors may initiate the pathogenesis of hypertension. It is important to recognize, however, that the development of chronic hypertension involves a complex cascade of pathobiologic processes. The set of factors that initiates the hypertensive state may be quite distinct from the factors that perpetuate the elevation of blood pressure. This postulate is illustrated schematically in *e*Figure 104.0.3. These intermediate processes appear to function as a common pathogenic pathway observed in a variety of animal models as well as in human hypertension.



***e*FIGURE 104.0.3** The pathogenic cascade of chronic hypertension. The sequence of pathophysiologic events linking initiating factors and self-perpetuating

mechanisms with the clinical course of hypertensive vascular disease.

It is important to recognize that the vasculature is itself a complex, integrated organ capable of modulating its tone and structure in accordance to its microenvironment. The chronic nature of the hypertensive state is dependent in part on self-perpetuating mechanisms that involve these intrinsic properties of the vasculature. During the pathogenesis of hypertensive vascular disease, these self-perpetuating mechanisms become maladaptive and appear to predispose to the common clinical sequelae of hypertension: stroke, myocardial infarction, and renal failure.

Vascular Remodeling: A Final Common Pathway

The intrinsic capacity of the vasculature to modify its geometry has been described as vascular remodeling. The experimental basis for the concept of vascular remodeling in hypertension has been established over many years (17,18,19 and 20). *Vascular remodeling* can be broadly defined as an alteration in vessel architecture that includes changes in overall vessel dimensions, the outer circumference, lumen dimensions, or the wall thickness–lumen ratio. Morphometric studies of hypertensive vessels in various animal models as well as in humans have documented several forms of vascular remodeling including (a) medial layer hypertrophy due to an increase in cellular mass, (b) medial layer hypertrophy due to expansion or alteration of the extracellular matrix without changes in cellular mass, (c) decreased vessel or lumen diameter (shrinkage remodeling), and (d) vessel rarefaction (microvessel occlusion).

In many cases of hypertension, vascular remodeling involves a structural decrease in lumen diameter that promotes a chronic increase in vascular resistance. These changes in vessel architecture reduce the overall vasodilatory capacity of the hypertensive vessel. Moreover, the structural increase in the wall–lumen ratio confers an increase in vascular reactivity that amplifies the effect of vasoconstrictors on vessel tone (17). Thus, structural changes in vessel lumen size and vascular reactivity may explain why relatively normal levels of circulating neurohumoral vasoconstrictors may be associated with a chronic increase in peripheral resistance and target organs are predisposed to tissue ischemia.

Another important form of vascular remodeling characterized in all species involves the process of rarefaction in which the number of microvessels becomes reduced by an occlusive process. This reduction in the arborization network of the microcirculation appears to be potentiated by a high salt diet (21) and is an important component of the overall increase in systemic resistance in hypertension (22). Bioengineering models suggest that this process of microvessel occlusion serves as an adaptive response to maintain the autoregulation of tissue blood flow in the setting of increased arterial pressure while normalizing wall stress (23).

These structural responses of the vasculature to chronic elevations in blood pressure, blood flow, or salt intake provide a long-term mechanism for the process of whole body autoregulation described previously. The guytonian model predicts that maladaptive remodeling (i.e., medial hypertrophy, shrinkage remodeling, or rarefaction) involving the afferent arteriole of the kidney, the renal medullary bed, or the glomerulus will be sufficient to alter the renal function curve. Thus vascular remodeling appears to be a common, self-perpetuating mechanism that resets the renal function curve and thereby contributes to maintaining the chronic hypertensive state (24,25).

Vascular Remodeling: Mechanisms and Mediators

The process of vascular remodeling involves the modification of four basic cellular functions within the blood vessel: cell growth, programmed cell death (apoptosis), migration, and extracellular matrix modification. Several studies have documented that the balance between cell proliferation and apoptosis accompanies the process of vascular remodeling in hypertension (25,26 and 27). Similarly, the architecture of the vessel is critically dependent on the scaffolding provided by the extracellular matrix. The matrix that is fashioned by a homeostatic balance of synthesis, cross-linking, reshaping, and degradation. The activation of metalloproteinases appears to play an important role in the process of vascular remodeling in response to hemodynamic stimuli (28).

The signaling pathways and factors that mediate the process of vascular remodeling during the pathogenesis of hypertension have not been fully characterized. It is clear that hemodynamic stimuli play an important role in promoting changes in vessel architecture. *In vitro* model systems that simulate the hypertensive state by imposing biomechanical forces such as mechanical strain and shear stress on vascular cells have documented alterations in ion channel activity, G-protein coupling, redox state, and signaling cascades of tyrosine kinase activation in response to mechanical stress (29,30). Recent studies incorporating DNA microarray technology have shown that mechanical stress activates signaling cascades that are coordinately coupled to subsets of genes (e.g., growth factors and matrix proteins) that can mediate changes in vessel structure (31,32). This pathobiologic insight may explain why simply lowering blood pressure is effective in reversing maladaptive changes in vessel structure and preventing the clinical sequelae of hypertensive vascular disease.

In addition to the effects of hemodynamic stimuli, it is clear that vasoactive factors produced locally within the vessel wall may play a critical role in the remodeling process. Many vasoactive substances (e.g., Ang II) that were originally defined as regulators of vessel tone are now recognized as pleiotropic factors capable of modulating vascular cell growth, cell death, migration, and extracellular matrix composition. Ang II serves as a useful archetype of a vasoactive substance that can modulate the cellular processes of vascular remodeling. Experimental studies have documented that blockade of Ang II effectively reverses the changes in vascular structure associated with hypertension in both animal models as well as in patients with hypertension (33,34). Stimulation of the Ang II type I receptor activates signaling molecules such as c-Src and mitogen-activated protein kinase in a manner similar to classic mitogens such as platelet-derived growth factor. Recent studies indicate that Ang II–induced vascular cell growth is mediated in part by reactive oxygen species generated by the NADPH oxidase (35). Ang II also induces the expression of growth factors such as platelet-derived growth factor and transforming growth factor-b_1 by vascular cells (35,36). These studies indicate that activation of a local paracrine systems such as the vascular angiotensin system (37,38) can induce the vascular remodeling characteristic of hypertensive vessels independent of changes in systemic hemodynamics.

Ang II may also mediate remodeling by altering extracellular matrix composition via its effect on thrombospondin, collagen, fibronectin, osteopontin, tenascin, and plasminogen activator activity (25,35,37,39,40 and 41). Similarly, there is a growing body of evidence that Ang II is a proinflammatory and procoagulant factor that promotes the generation of mediators such vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, tumor necrosis factor-a, and tissue factor that may predispose to atherogenesis and acute thrombotic syndromes (37,42,43 and 44). Finally, there is emerging evidence that the Ang II–mediated stimulation of aldosterone production is not simply a mechanism to promote sodium retention. In addition to its effects on the adrenal gland, Ang II also stimulates local aldosterone production within the heart and vasculature. Moreover, aldosterone activates a transcription factor that is coupled to the expression of genes regulating vascular cell growth and tissue fibrosis (45,46 and 47).

Thus, Ang II is a pleiotropic local mediator capable of modulating cell growth, apoptosis, migration, inflammation, hemostasis, and matrix modulation—all of the biologic mechanisms of vascular remodeling and acute vascular complications. Although Ang II serves as a useful example, similar pleiotropic effects on vascular smooth muscle cell behavior have been described for other vasoconstrictors such as norepinephrine and endothelin-1 (48,49). These mechanisms are consistent with the recent clinical findings of the Heart Outcomes Prevention Evaluation trial demonstrating that blockade of Ang II generation is associated with the prevention of vascular complications in high-risk patients either with or without hypertension (50).

Endothelial Dysfunction: An Imbalance in Reactive Nitrogen and Oxygen Species

The endothelium is a multifunctional determinant of tissue function based on its capacity to regulate vessel tone, thrombosis, inflammation, and structure. A large body of evidence indicates that the normal endothelium functions as an intrinsic mechanism that prevents vascular disease. However, an impairment of endothelial function manifested as abnormal endothelium-dependent vasorelaxation has been documented in a wide variety of vascular diseases, including hypertension (51). In fact, this perturbation has been described in normotensive subjects who merely have a positive family history of hypertension (52). In most cases, this reflects a decrease in the bioactivity of endothelium-derived NO due to catabolism by reactive oxygen species. Studies involving pharmacologic blockade of NO generation in normotensive humans have documented that NO inactivation is sufficient to induce marked increases in vascular resistance (53). Moreover, the demonstration that mutant mice that lack the endothelial cell–type NO synthase gene are spontaneously hypertensive indicates that NO is an important long-term determinant of blood pressure (54). Thus, endothelial dysfunction manifested as a deficiency in NO bioactivity may represent a self-perpetuating mechanism that promotes the progression of hypertensive vascular disease.

Endogenous vasodilators such as NO and natriuretic peptides appear to have a countervailing influence on vascular architecture relative to vasoconstrictors. In general, the vasodilators inhibit vascular smooth muscle cell growth (55,56). Moreover, NO appears to counteract the process of shrinkage remodeling that characterizes the hypertensive vasculopathy (57). Thus, impairment of endothelial NO generation may predispose to vascular complications. Recent evidence suggests that the mechanism of the decreased NO bioactivity is related to increased generation of reactive oxygen species by the NADPH oxidase in response to vasoconstrictors such as Ang II as well as the mechanical stress imposed by elevations in blood pressure (58,59).

Overall, these data indicate that an imbalance between vasoconstrictors versus vasodilators and the alteration in the vascular redox state can initiate the hypertensive

state by increasing vessel tone and perpetuate the elevation in blood pressure by inducing long-term changes in vessel structure.

Vascular Remodeling and Lesion Formation: Clinical Implications

Microvascular Disease

One pathologic role of vascular remodeling involves its participation in the vicious cycle of events that promote the clinical complications of hypertension. Studies of animal models have documented that hypertensive states associated with impaired NO generation develop occlusive coronary microvascular disease that promotes myocardial ischemia or glomerulosclerosis that results in renal failure (12,42,60). Similarly, analyses of the stroke-prone spontaneously hypertensive rat have documented that stroke susceptibility is related to alterations in cerebral microvascular structure that can be reversed by antihypertensive treatment (60). In the clinical context, arteriovenous nicking due to arteriolar hypertrophy is a clinical manifestation of remodeling in the brain microvasculature that correlates with progressive hypertension and its complications (61). This remodeled cerebral microvasculature may be the mechanistic basis for the clinical associations between hypertension, subcortical white matter disease, lacunar infarction, and vascular dementia (62,63). In accord with this postulate, recent clinical trials have documented that blockade of angiotensin generation is associated with the amelioration of vascular lesions and the prevention of microvascular complications such as renal failure and stroke (64,65).

Insulin Resistance

The coincidence of obesity, insulin resistance, and hypertension is a common clinical scenario. There is evidence to suggest that endothelial dysfunction and hypertension-induced vessel rarefaction in skeletal muscle beds may promote the phenomenon of insulin resistance in hypertension by compromising the delivery of insulin and glucose to skeletal muscle (54). The provocative observation that blockade of angiotensin may be associated with retarding the onset of diabetes is of interest in this regard (50). An exciting recent study in human genetics has provided evidence that a transcription factor, peroxisome proliferator–activated receptor-g, is a molecular link between hypertension and insulin resistance (66). In the clinical context, it is noteworthy that glycemic control with peroxisome proliferator–activated receptor-g agonists (e.g., the thiazolidinediones) is associated with improvements in vascular function and a regression of hypertensive vascular remodeling (67).

Vascular Compliance

The capacity for the conduit vasculature to absorb each ejected stroke volume diminishes as a function of age, and this decline is accelerated by hypertension. An imbalance between vasoconstrictors versus vasodilators coupled with a structural decrease in the elastin–collagen ratio promotes this decline in vascular compliance. This increase in vascular “stiffness” predisposes to an increase in systolic blood pressure and a widened pulse pressure common among the elderly. Indeed, epidemiologic studies suggest that the increase in vascular stiffness and the widened pulse pressure may be more sensitive indices of a poor prognosis than the mean arterial pressure alone (68,69). This decrease in vascular compliance promotes an increased afterload that predisposes to left ventricular hypertrophy, maladaptive remodeling, and worsening heart failure (69,70). Thus, many of the clinical sequelae of hypertension (i.e., heart failure, stroke, and renal failure) may result from vascular remodeling within conduit vessels as well as the microcirculation.

ANIMAL MODELS OF GENETIC HYPERTENSION: WHAT CAN WE LEARN?

Innumerable studies have been performed over the years comparing the physiologic, hormonal, biochemical, and morphometric differences between genetically hypertensive animals and normotensive animals. However, it remains to be demonstrated how closely the characterization of the genetic basis of hypertension in these animal models will mirror the characterization of the genetic basis of primary hypertension or intermediate phenotypes (e.g., salt sensitivity) in humans (71,72 and 73).

Well-defined models of genetic hypertension include the spontaneously hypertensive rat (SHR); Dahl salt-sensitive strains; the Fawn-hooded model; and rat strains derived in Lyon, Milan, and New Zealand as well as the spontaneously hypertensive BPH mouse. The detailed characteristics of various genetic models of hypertension have been previously reviewed (71,72 and 73). A host of experimental studies have documented a myriad of differences between the hypertensive and normal animals as well as distinctions between the various strains of hypertensive models. Perhaps what is most remarkable are the *similarities* between the models derived from various founder strains and breeding regimens. For example, it is remarkable that many of the models recapitulate the common clinical complications observed in human hypertension—left ventricular hypertrophy, stroke, and nephrosclerosis. Moreover, nearly all of the models studied exhibit the self-perpetuating mechanisms of hypertension—vascular remodeling, endothelial dysfunction, and vascular stiffness. All of these pathogenic processes participate in the maintenance of hypertension as well as the vascular complications such as stroke, heart failure, and renal failure. Thus, the pathobiologic principles that have emerged from these studies reemphasize the pivotal importance of the kidney in hypertension and the ubiquity of critical self-perpetuating mechanisms.

Despite this understanding of broad pathobiologic principles, we lack a fundamental understanding of the molecular basis of hypertension and its complications. The fact that blood pressure is a continuous variable probably reflects the integrated effects of alleles at multiple genetic loci that have either positive or negative effects on blood pressure. It is a complex matter to dissect out the links between the multiple genes that promote hypertension, the cellular processes controlled by these genes, as well as the integrative physiology induced by these cellular processes that eventuates in the hypertension phenotype.

The characterization of quantitative trait loci by genomic scanning coupled with the creation of congenic and consomic animals has begun to enable investigators to narrow down the regions within the genome that contribute to the hypertensive phenotype. Although there are many pitfalls in this rather daunting task, the power and usefulness of this approach are already evidenced in recent studies (74,77). This experimental strategy will not only identify genes that may initiate hypertension but also genes that predispose to the clinical complications of the disease. For example, morphometric studies of the Fawn-hooded strain have noted a particularly high incidence of nephrosclerosis and renal dysfunction in this particular model of genetic hypertension. Genomic scanning studies have begun to identify loci that predispose to renal dysfunction yet are distinct from genetic loci that promote the hypertensive state per se (74). Similarly, there appear to be discrete genetic loci that increase the susceptibility to complications such as left ventricular hypertrophy (75) and stroke (76) that are distinct from the loci that determine blood pressure in genetically hypertensive rats. Conversely, this approach can also lead to the identification of genes that may be protective against salt-sensitive elevations in blood pressure and the development of target organ injury such as proteinuria (77). Eventually, it is hoped that the genes that predispose or prevent the clinical complications of hypertension can be identified and cloned as a novel approach to drug target discovery.

One emerging technology that may enhance the identification of hypertension susceptibility genes is the use of gene expression profiling techniques such as DNA microarrays and serial analysis of gene expression (78). A recent series of experiments has provided an exciting demonstration of the usefulness of this strategy and has provided new insights into the mechanistic links between hypertension and insulin resistance (79). The use of DNA microarrays enabled investigators to rapidly assay thousands of transcripts and define the subset of genes that were differentially expressed in the tissues of spontaneously hypertensive rats compared with normotensive controls. These experiments established that the hypertensive, insulin-resistant phenotype observed in SHR was associated with a decreased expression of CD36, a membrane fatty acid transporter. To further establish a causal relationship between genotype and phenotype, these investigators generated SHR transgenic rats with upregulated expression of CD36 and documented changes in fatty acid metabolism and amelioration of the insulin resistance (80). Thus, this combination of genomic strategies that includes systematic mapping of genetic loci associated with disease phenotypes, the incorporation of gene expression profiling, and the creation of novel congenic or transgenic models has great potential for identifying factors that cause hypertension and predispose to its complications. To the extent that these animal models simulate human hypertension, the characterization of these susceptibility loci may also accelerate the identification of genes involved in human hypertensive vascular disease.

PHYSIOLOGIC GENOMICS OF BLOOD PRESSURE: NEW INSIGHTS INTO AN OLD PROBLEM

One of the challenges to defining the molecular basis of human hypertension is to recreate the state of chronic hypertension that simulates what is observed in the clinical context. The revolution in molecular genetics and genomic technologies has made it possible to create animal models by genetic engineering and analyzing changes in gene expression profiles of thousands of genes at a given time point. The creation of new models has proceeded at such a fast rate that any list that includes published descriptions of models becomes out of date within months (*e*Table 104.0.2). In general, the predictions of the guytonian model based on physiologic principles have been validated by the use of genetic engineering approaches.

***e*TABLE 104.0.2** GENETIC ENGINEERING OF BLOOD PRESSURE

Gene knockout	Phenotype
Angiotensinogen	Hypotension, abnormal kidney
Angiotensin-converting enzyme	Hypotension, abnormal kidney
Angiotensin type I receptor	Hypotension
Angiotensin type II receptor	Normotensive
Endothelin-1	Normotensive, craniofacial abnormalities
Endothelial cell–type nitric oxide synthase	Hypertension
Large conductance K^+ channel	Hypertension

Atrial natriuretic peptide	Hypertension, salt-sensitive
Brain natriuretic peptide	Normotensive, cardiac fibrosis
b-Adducin	Hypertension
Glomerular epithelial protein phosphatase	Hypertension, abnormal glomerulus, decreased renal ultrafiltration

Despite all of the compensatory and countervailing mechanisms that determine blood pressure, it is noteworthy that the ablation of a single gene encoding a component of the renin-angiotensin system has profound long-term effects on blood pressure. Smithies and colleagues conducted a series of elegant studies using homologous recombination techniques to ablate the expression of the substrate angiotensinogen, angiotensin-converting enzyme, and the Ang II type I receptor (81,82 and 83). In the studies involving angiotensinogen, a gene duplication construct was created such that mice exhibited a range of zero to four copies of the angiotensinogen gene. There was a linear relationship between angiotensinogen gene copy number, plasma angiotensinogen levels, and blood pressure increases of approximately 8 mm Hg per gene copy. The homozygous null mutants that lacked angiotensinogen, angiotensin-converting enzyme, or the angiotensin-type IA receptor exhibited a substantial decrease in blood pressure that could not be compensated for by alternative homeostatic mechanisms. Taken together, this series of observations suggests that inactivation of the renin-angiotensin-aldosterone system resets the renal function curve and exerts long-term influences on blood pressure.

The use of genetic engineering techniques has also shed light on the mechanisms by which the renin-angiotensin-aldosterone system regulates cardiovascular function and structure. For example, an ongoing controversy relates to the relative roles of the circulating versus tissue renin-angiotensin-aldosterone systems as determinants of cardiovascular homeostasis. To address this issue, Bernstein and colleagues generated genetically engineered mice with two different forms of the angiotensin-converting enzyme such that animals had relatively normal levels of circulating plasma angiotensin-converting enzyme but were deficient in tissue angiotensin-converting enzyme (84). Of note, the animals deficient in tissue angiotensin-converting enzyme exhibited a hypotensive phenotype similar to those in which the entire angiotensin-converting enzyme gene was deleted (84). These findings are consistent with the concept that local generation of angiotensin within tissues may be as important as the circulating system as a long-term determinant of blood pressure. Another clinical controversy relates to the fact that enzymes such as chymase are capable of generating Ang II but are not inhibited by conventional angiotensin-converting enzyme inhibitors. Although the physiologic significance of chymase remains to be further defined, it is noteworthy that vascular-selective, conditional overexpression of chymase is sufficient to promote hypertension in transgenic mice (85). These animal model studies may have implications for achieving effective blockade of Ang II in the clinical context.

It could be argued that the results of gene deletion experiments targeted at the renin-angiotensin system were predictable given the potency of Ang II as a vasoactive agent. However, it is interesting that gene knockout experiments involving endothelin and its receptors failed to document significant effects of gene ablation on blood pressure despite the fact that it is a more potent vasoconstrictor than Ang II (86). It is also noteworthy that several models have documented that hypertension is readily induced by the deletion of certain vasodilators such as NO, natriuretic peptides, prostaglandin E_2, dopamine, and calcitonin gene-related peptide (54,87,88,89,90 and 91). In addition to receptor-mediated vasodilation, recent studies have also shown that disruption of large-conductance potassium channels modulates calcium metabolism, promotes increased vasoconstriction, and results in sustained hypertension (92). Overall, these findings are consistent with the postulate that the balance of vasoconstrictors versus vasodilators is an important determinant of the renal function curve and thereby exerts long-term influences on blood pressure homeostasis.

It is also noteworthy that the generation of gene ablation models can provide insights into less obvious candidate genes for hypertension susceptibility. For example, disruption of the glomerular epithelial protein, a receptor tyrosine phosphatase, is associated with a hypertensive phenotype. In retrospect, this finding is consistent with the guytonian model because ablating the gene perturbs glomerular podocyte structure such that ultrafiltration is compromised and the renal function curve is altered (93). Similarly, the adducin gene became a candidate susceptibility gene for hypertension based on genome scanning in the Milan hypertensive rat model (94). Genetic association studies of human hypertensives have yielded suggestive but equivocal results (95). However, the mechanism by which a cytoskeletal protein such as adducin is coupled to long-term control of blood pressure was not readily apparent. Recent experimental findings have provided a mechanistic basis for these associations and linkage studies by documenting a causal relationship between ablation of the b-adducin gene and a hypertensive phenotype (96). Thus, genome scanning may generate hypotheses about novel mediators of hypertension that can be tested by the creation of genetically modified animals.

Finally, it is anticipated that the use of genetically engineered models will provide important clinical insights into the molecular basis of hypertensive complications or the potential usefulness of certain therapeutic options. For example, studies involving mice that lack the brain natriuretic peptide have documented substantial cardiac fibrosis despite the fact that the animals are normotensive at baseline (97). These studies in knockout mice indicate that brain natriuretic peptide (BNP) not only serves as a marker of ventricular dysfunction but may also be a key mediator in the process of ventricular remodeling. The clinical implications of this observation have become more profound with the advent of a new class of drugs, the vasopeptidase inhibitors, that block both angiotensin-converting enzyme and a neutral endopeptidase that degrades peptides such as BNP. It is conceivable that pharmacologic interventions that prevent BNP degradation may not only promote vasodilation and natriuresis but may also have direct salutary effects on cardiovascular structure. However, a cautionary approach is suggested by the observation that genetic ablation of the neutral endopeptidase is associated with a phenotype in which the mutant mice exhibit increased microvascular permeability and tissue edema (98). It remains to be determined whether clinical trials will document whether the beneficial effects of vasodilation and natriuresis induced by pharmacologic inhibitors of the neutral endopeptidase counterbalance a potentially adverse effect on microvascular permeability.

In summary, the capacity to target, mutate, ablate, or conditionally regulate a gene that is transmitted through the germline has become a powerful tool for elucidating the fundamental basis of pathophysiologic processes such as hypertension (99). The studies performed to date are consistent with the pathobiologic principles that emphasize the role of the kidney as a critical long-term determinant of the blood pressure. In addition, they have proved to be useful in defining the molecular basis of hypertensive vascular complications as well as characterizing the mechanisms of effective therapeutic interventions. Finally, these models have provided a very important link between the molecular genetics that identify susceptibility genes and physiologic experiments that establish causality.

CONTROVERSIES AND PERSONAL PERSPECTIVES

As detailed above, a great deal has been learned about the pathobiology of hypertension during the past century. The advent of powerful new experimental technologies continues to reinforce the time-tested concept that the kidney is the predominant long-term determinant of blood pressure and that neurohumoral systems such as the renin-angiotensin system and the sympathetic nervous system are major modulators of this function.

It is anticipated that advances in rodent molecular genetics, genetically engineered model systems, microarray technology, and human molecular genetics will begin to provide important new insights into the factors that predispose individuals to elevations in blood pressure. In addition to defining these etiologic factors, the incorporation of genomic technologies into molecular cardiology holds promise for elucidating the variances in the susceptibility to complications such as stroke, renal failure, or heart failure among hypertensive patients.

THE FUTURE

With the completion of the Human Genome Project, we stand on the threshold of an unprecedented opportunity to discover the molecular basis of hypertension and its clinical complications. The capacity for large-scale assays of RNA and protein levels by genomic and proteomic technologies should provide a means for investigators to characterize the molecular basis of the physiologic phenomena defined in the guytonian models. It promises to be an exciting second century of discovery in which we embrace the challenge of translating new pathobiologic insights into ameliorating the course of the disease.

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THE BIOLOGY OF RESTENOSIS

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Neointimal thickening, also referred to as *neointimal hyperplasia*, occurs in response to experimental arterial injury with a balloon catheter. This process, which is mainly the consequence of a growth response of the smooth muscle cells (SMCs), is maximal 1 to 4 weeks after the initial injury. It occurs in different vascular beds (coronary arteries, peripheral arteries) and in various animal species, including rats, rabbits, and pigs. A marked hyperplastic response can be observed after a single injury performed in normal vessels but also in animal models in which a first injury combined with a hypercholesterolemic diet has induced a stenosis that can then be dilated with an angioplasty balloon catheter. Neointimal formation involves the activation, proliferation, and migration of SMCs, and the production of extracellular matrix (ECM).

The factors that control neointimal thickening include growth factors, hormonal factors, and mechanical factors. Growth factors released at the site of injury play a major role in the response of SMCs to balloon injury and include platelet-derived growth factor (PDGF), basic fibroblastic growth factor (bFGF), transforming growth factor-b (TGF-b), and insulin-like growth factor-1 (IGF-1). Hormonal factors include angiotensin II, serotonin, and endothelin. Mechanical factors include trauma related to interventional devices and the mechanical events that comprise plaque rupture.

Experimental evidence is increasing that neointimal hyperplasia is not the sole mechanism leading to lumen renarrowing after angioplasty, namely, that arterial remodeling also plays a major role in this process. Studies performed in animals and human subjects have established the potential for "constrictive remodeling" to reduce vessel wall area after angioplasty, which indirectly narrows the vessel lumen and thus contributes to restenosis.

Delinquent reendothelialization has been shown to have a permissive, if not facilitatory, impact on SMC proliferation. This inverse relationship has been attributed to certain functions of the endothelium, including barrier regulation of permeability, thrombogenicity, and leukocyte adherence, as well as to growth-inhibitory molecules. More recent studies have confirmed this notion by demonstrating that administration of endothelial cell mitogens may facilitate endothelial cell regeneration, reduce neointimal thickening, and promote recovery of endothelial dysfunction after balloon injury.

Histologic findings after stent deployment in animal models and analyses of specimens retrieved from patients with in-stent restenosis have established that this complication of endovascular stents is due to intimal hyperplasia. Application of endothelial cell mitogens to promote endothelialization of the stent struts seems to reduce the thickness of the stent neointima in animal models.

Studies have also shown that endovascular brachytherapy might interfere with the various mechanisms involved in the restenosis process, and this new approach is currently under investigation in humans to treat or to prevent restenosis.

INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA) has become a well-established technique for myocardial revascularization of patients with coronary artery disease (1,2 and 3). The use of PTCA remains limited by restenosis, however, which occurs in 30% to 60% of patients despite performance of a successful procedure (4,5,6,7,8 and 9). If one assumes that 500,000 PTCA procedures are performed per year in the United States (10), then more than 150,000 patients develop restenosis every year.

During the last decade, numerous agents have been used in an attempt to prevent restenosis (5,11,12 and 13). Despite positive results in animal models, no pharmacologic therapy has been found to significantly decrease the risk of restenosis in humans. These apparent discrepancies between animal models and the clinical situation were probably related mainly to an incomplete understanding of the mechanisms of restenosis in humans as well as in animal models. During the last few years, important experimental and clinical studies have allowed a better understanding of the various processes that occur after PTCA and that may lead to restenosis. The purpose of this chapter is to review the available information relevant to the response of the vascular wall to injury. The focus is on four major processes: neointimal hyperplasia, vessel remodeling, thrombosis, and endothelial regeneration. The mechanisms of these processes, as well as their relative contributions to lumen renarrowing in animals and humans, are reviewed in an attempt to reconcile results for animal models of restenosis with the clinical situation.

NEOINTIMAL HYPERPLASIA

Neointimal Hyperplasia after Experimental Arterial Injury

During the past 10 to 15 years, multiple studies have described the process of neointimal thickening—also known as *neointimal hyperplasia*—that occurs in response to experimental arterial injury with a balloon catheter (6,14,15,16,17,18,19,20,21 and 22) (Fig. 105.1). This process is due largely to growth of the SMCs and is maximal 1 to 4 weeks after the initial injury (Fig. 105.2). Neointimal thickening occurs both in coronary arteries and in peripheral arteries and is found in various animal species, including rats, rabbits, and pigs (14,22,23,24,25 and 26). A single injury performed in a normal vessel can produce a marked hyperplastic response (14,22,27). Neointimal hyperplasia is also observed in animal models fed a hypercholesterolemic diet after a first injury to induce a stenosis that can then be dilated with an angioplasty balloon catheter (double-injury model) (17,18). Neointimal formation involves several steps: SMC activation, proliferation, and migration, and the production of ECM.

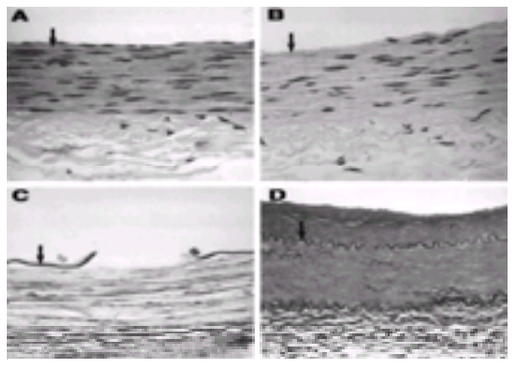


FIGURE 105.1 Experimental balloon denudation of rabbit aorta. **A:** Noninjured artery. **B:** Immediately after balloon denudation, complete deendothelialization is apparent. **C:** Immediately after balloon denudation, a break is also seen in the internal elastic membrane. **D:** Twenty-eight days after balloon denudation, neointimal thickening is observed. Arrow indicates the internal elastic lamina.

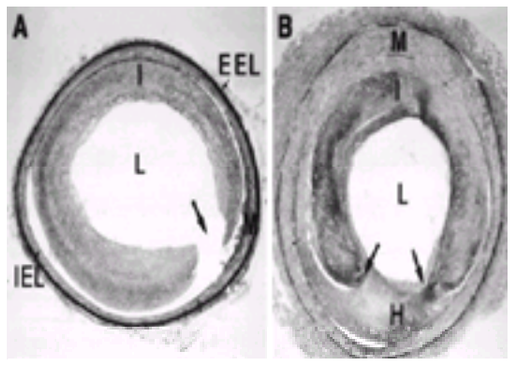


FIGURE 105.2 Experimental balloon angioplasty of an iliac artery in the hypercholesterolemic rabbit model. **A:** Immediately after balloon angioplasty, rupture (*arrow*) of the atherosclerotic lesion is seen. **B:** Twenty-eight days after balloon angioplasty, site of plaque rupture is "grouted in" by neointimal hyperplasia (H), maximal at the site of plaque rupture (elastic tissue stain). EEL, external elastic lamina; I, intima; IEL, internal elastic lamina; L, lumen; M, media.

The Early Phase: Smooth Muscle Cell Activation

Immediately after experimental arterial injury with a balloon catheter, multiple factors (see later) lead to the activation of SMCs. Early markers of SMC activation, such as expression of nuclear oncogenes, are detectable as soon as 30 minutes after injury (22,28,29,30 and 31). Induction of c-*fos*, c-*jun*, and c-*myc* protooncogenes is one of the earliest transcriptional events associated with growth factor stimulation (32), and the increased expression of these genes is a transient response to mitogenic stimulation persisting at most for a few hours after exposure to growth factors (33). The distribution of c-*fos* and c-*jun* products after arterial injury is concentrated in SMC nuclei (28). The corresponding oncoproteins bind to specific DNA sequence of target genes to stimulate their transcription and are involved in the G_1 phase of the cell cycle (32). Experiments involving cell culture models have shown that the use of antibodies or antisense RNA against nuclear oncogenes prevents cell entry into the S phase and the subsequent synthesis of DNA (34,35). That this expression of nuclear oncogenes in the hours after angioplasty is associated with the early G_1 events preceding DNA synthesis in SMCs is therefore plausible. The use of antisense oligonucleotides against nuclear oncogenes was shown to inhibit neointimal thickening *in vivo* in various animal models (36,37); these results suggest that the inhibition of this early phase can significantly affect the cascade of events leading to neointimal hyperplasia a few weeks later.

Interestingly, some genes expressed early after vascular injury may also be downregulated during the process of SMC activation. One of these genes is the homeobox transcription factor gax, which has now been cloned. Gax is unique among homeobox factors in that it is expressed in quiescent SMCs but rapidly downregulated when the SMCs are stimulated to proliferate (38). *In vivo*, gax expression is rapidly reduced in rat aorta after balloon denudation. Furthermore, an adenoviral vector expressing gax was shown to efficiently inhibit SMC growth by blocking the cell cycle in the G_0 phase (39).

The activation of SMCs is thus a very early response after experimental balloon denudation. Changes in gene expression can be detected very soon after arterial injury; some genes are switched on whereas others are downregulated. These early events are likely to be of major importance for the occurrence of the next steps of the vascular wall response.

Proliferation and Migration of Smooth Muscle Cells

Activation of SMCs is associated with a shift from a contractile to a synthetic phenotype (40,41 and 42) and leads to proliferation, migration, and synthesis of ECM. Proliferation of medial SMCs is evident 24 hours after experimental balloon injury and continues for at least 2 weeks (16). At least 20% to 40% of medial SMCs are activated and enter the cell cycle between 24 hours and 3 days after balloon denudation (43). *In vivo* animal studies have demonstrated the extent to which cell-cycle events are temporally coordinated after balloon injury (44). These cells then migrate to the intima through breaks in the internal elastic membrane. SMCs are observed on the luminal side of the internal elastic lamina 4 days after injury to rat arteries (14). Many of these neointimal cells continue to proliferate for several cycles, but nearly half of the migrating cells do not synthesize DNA (43). Proliferation and migration should thus be considered as two distinct mechanisms leading to neointimal thickening; as discussed later, some factors may affect SMC migration but have no effect on SMC proliferation, and vice versa (15).

Synthesis of Extracellular Matrix

In animal models, the degree of intimal thickening is maximal after 3 months (14). The additional volume that accumulates after 2 to 4 weeks reflects the adjunctive synthesis of ECM by synthetic SMCs. Experimental balloon denudation is followed by a marked increase in expression of the genes that code for ECM proteins such as collagen and elastin in the arterial wall (45). Similarly, the reexpression of embryonic forms of fibronectin occurs in the media and adventitia of rabbit arteries 24 to 48 hours after injury. Two weeks after balloon denudation, when the neointima is formed, fibronectin messenger RNAs (mRNAs) as well as the fibronectin protein accumulate in the luminal layers of the neointima (46). Fibronectin, as well as other matrix constituents characterized by the presence of an RGD amino acid sequence such as osteopontin (47) and vitronectin, is likely to facilitate SMC migration by interaction with certain integrins expressed by activated SMCs (48). As pointed out by Schwartz et al. (49), cellular components constitute only approximately 11% of neointimal volume, and the remainder is ECM. After 2 to 3 months, SMCs return to a contractile phenotype, and no further significant increase in intimal thickening occurs (50).

Potential Regulators of Neointimal Formation

Although the process of neointimal formation has been relatively well described, the factors that control it are still under intense investigation. The candidates for this regulation include growth factors, hormonal factors, and mechanical factors.

Growth Factors

Growth factors released at the site of injury play a major role in the response of SMCs to balloon injury. Platelets are an important source of PDGF, but endothelial cells, macrophages, and SMCs may themselves secrete PDGF after arterial injury (40,51,52 and 53). PDGF may be critical for SMC migration from media to intima; however, its absence does not limit SMC proliferation (23,54). Indeed, using an antibody to PDGF, Ferns et al. (54) were able to reduce neointimal SMC accumulation after experimental angioplasty without affecting mitogenic activity.

Basic fibroblast growth factor, an *in vivo* angiogenic factor (55) that is mitogenic for SMCs as well as endothelial cells through specific receptors (56,57), may also play a role in restenosis. SMCs within the tunica media, when damaged by an oversized balloon, may release bFGF due to stretch or crush injury. The liberated bFGF can

then mediate the initial wave of cell division within this layer of the blood vessel. Infusion of an antibody that neutralizes bFGF reduces the first cycle of SMC replication by up to 80% in the arterial media after balloon denudation but has no effect on the resulting neointimal thickening (58).

Additional growth factors that have been implicated in the development of restenosis include TGF-b and IGF-1. TGF-b mRNA is increased in SMCs after arterial wall injury and reaches a maximum before the phase of ECM synthesis (59,60). TGF-b is known to modulate fibronectin expression (61) and may be important in the control of ECM synthesis (62,63). TGF-b is produced by SMCs, platelets, and endothelial cells (51,64). The main source of IGF-1 is SMCs, and its mRNA expression undergoes a tenfold increase in the weeks after balloon denudation (65).

Hormonal Factors

Work by Dzau and colleagues has suggested a role for the renin-angiotensin-aldosterone axis in the pathogenesis of restenosis (66,67,68 and 69). Angiotensin II may modulate SMC growth *in vitro* (70,71); *in vivo* studies have demonstrated that angiotensin II infusion in rats is followed by marked SMC proliferation in the intima (72). Rakugi et al. (67) have reported that after balloon injury the rat abdominal aorta expresses increased levels of angiotensin-converting enzyme (ACE) activity as well as increased immunoreactivity for ACE in the neointima. Powell et al. (73) and others (74) have reported that inhibitors of ACE suppress myointimal proliferation after vascular injury. Intimal thickening can also be prevented by angiotensin II type 1 receptor antagonists (75). The actions of ACE inhibitors are probably not related solely to an effect on angiotensin II levels, however, but may in part be due to an effect on bradykinin metabolism (76,77). Farhy et al. (77) have reported that *N*(*G*)-monomethyl-L-arginine (L-NMMA), a blocker of nitric oxide (NO) generation, can partially counteract the suppressive effect of the ACE inhibitor ramipril on neointimal thickening after balloon injury in rat arteries. As bradykinin is a potent stimulator of NO production and is itself normally degraded by ACE, they speculated that the decrease in neointimal thickening observed with ACE inhibitors may be a result of elevation in the level of bradykinin. Similarly, in a rabbit model of balloon denudation the reduction in neointimal thickening observed with the ACE inhibitor perindopril erbumine was reversed by cotreatment with *N*(*G*)-nitro-L-arginine methyl ester (76).

Serotonin and other vasoactive hormones (catecholamines, vasopressin) released at the angioplasty site are also able to induce SMC proliferation (78,79,80 and 81). Considerable interest has been focused on endothelin, a potent vasoconstrictor peptide produced by vascular endothelial cells (82). Endothelin binds specifically to human SMCs in culture and can induce nuclear oncogene expression (83,84). Endothelin has been shown to have mitogenic activity for rat aortic SMCs (85), and use of endothelin antagonists reduces neointimal thickening after vascular injury *in vivo* (86,87).

Mechanical Factors

Mechanical factors may also play a role in determining the magnitude of the restenotic lesion generated in experimental models. Large areas of endothelial denudation without trauma to the media lead to mild neointimal thickening despite late endothelial regeneration (88). In contrast, focal endothelial denudation with substantial medial trauma, including rupture of the internal elastic lamina, is associated with marked neointimal proliferation, despite prompt endothelial regeneration (89). These results suggest that endothelial denudation alone is not sufficient to produce major neointimal thickening and that direct stimulation of SMCs is also an important factor. Direct injury of SMCs may induce a greater neointimal response by (a) increasing the local release of growth factors from necrotic SMCs and (b) activating intracellular pathways leading to proliferation of residual viable SMCs (90,91).

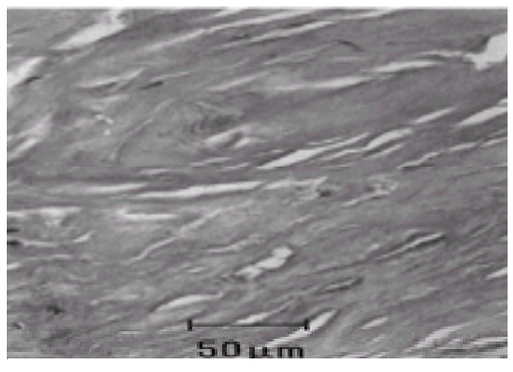
Besides acute mechanical factors, chronic mechanical factors may also play a role. Blood flow in the injured vessel may be a determinant of subsequent restenosis. Experimental studies by Kohler et al. (92,93) have demonstrated greater neointimal hyperplasia when blood flow is reduced after angioplasty.

Neointimal Formation after Percutaneous Transluminal Coronary Angioplasty in Humans

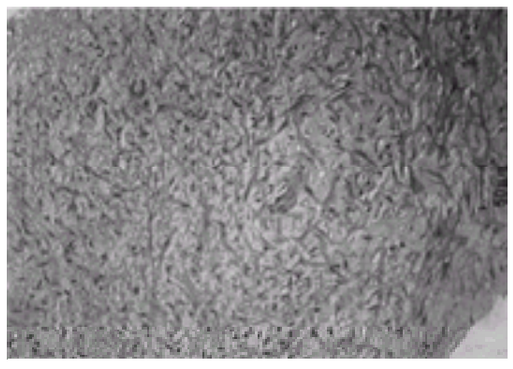
An important issue is to determine whether evidence for certain pathophysiologic mechanisms of restenosis demonstrated in experimental models can be supported by clinical observations in humans. Although angiographic studies have exhaustively detailed the incidence and time course of restenosis after PTCA, the arterial wall response in humans has been less well documented than responses in experimental animal models. Nevertheless, necropsy studies and contemporary diagnostic tools of invasive cardiology such as directional atherectomy, intravascular ultrasonography (IVUS), and angioscopy have allowed a better description and understanding of neointimal formation after PTCA in humans.

Proliferation and Restenosis

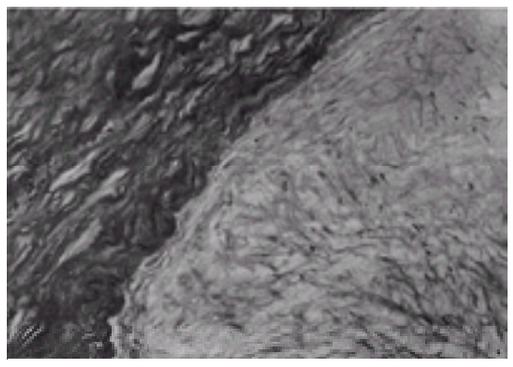
Light-microscopic features of atherectomy specimens retrieved from coronary arteries of patients undergoing percutaneous revascularization (94,95 and 96) have confirmed observations made in smaller numbers of patients at necropsy (97,98). Primary and restenotic lesions can often be distinguished from each other on the basis of certain light-microscopic findings (99). Primary lesions (*e*Fig. 105.2.1) appear typically hypocellular, consisting predominantly of well-organized collagen and ground substance. In contrast, restenotic lesions (*e*Fig. 105.2.2) typically include a focus of hypercellularity. Cells within these foci have phenotypic characteristics of proliferative SMCs, and the ECM surrounding these cells has a distinctive hue and less compact appearance than does the ECM of primary plaque (*e*Fig. 105.2.3).



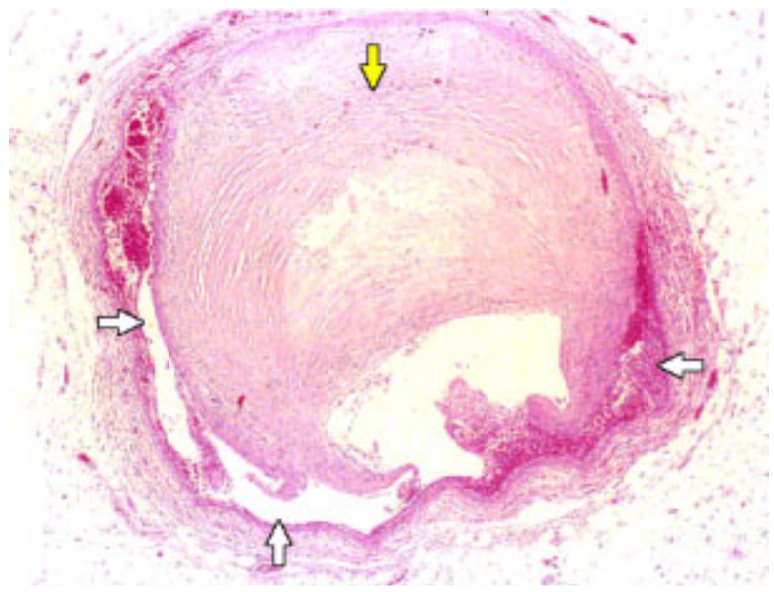
***e*FIGURE 105.2.1** Typical histologic appearance of primary atherosclerotic lesion. The specimen consists principally of collagenous extracellular matrix with a paucity of cellular elements (hematoxylin and eosin stain).



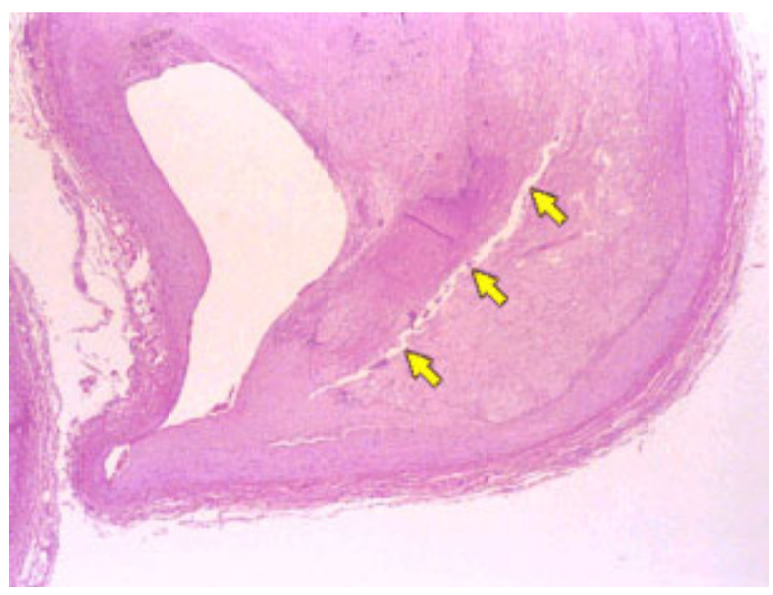
***e*FIGURE 105.2.2** Classic hyperplastic response in a human restenotic lesion comprised of smooth muscle cells with “activated” phenotypic appearance (hematoxylin and eosin stain).



***e*FIGURE 105.2.3** Bilayer appearance illustrating contrasting features of primary lesion and superimposed restenosis aspect. Primary lesion is hypocellular, and extracellular matrix has a blue-green hue. Restenosis component is hypercellular, including cells with phenotypic features of “activated” smooth muscle cells, embedded in loose, less compact matrix with a distinctive, light-staining hue (elastic tissue stain).

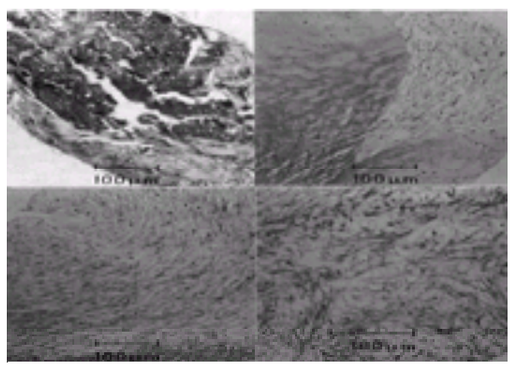


Linear, circumferential dissection 2 days after balloon angioplasty of a restenotic lesion. Note the extensive neointimal proliferation (*yellow arrow*) and dissection (*white arrows*).



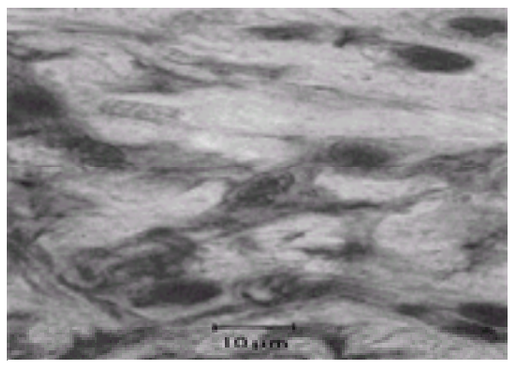
Restenotic lesion. Residual tear in atherosclerotic plaque (*yellow arrows*) and large amount of neointimal proliferation 76 days after balloon angioplasty.

These contrasting findings between primary and restenotic lesions are perhaps best illustrated in a group of 18 patients studied in the authors’ laboratory (100), in whom directional atherectomy had been performed both as the primary intervention and again at the time that the patient returned with restenosis (*e*Fig. 105.2.4). These 18 patients thus offered a unique opportunity to study the same lesion site in the same artery of the same patient at two different times. Light-microscopic examination documented distinctive features, including hypercellular foci consisting of proliferative vascular SMCs surrounded by a loose neomatrix, in 13 (72%) of 18 cases. In five patients, neither the primary nor the restenotic specimen demonstrated such a “restenotic focus.” A similar restenotic focus has been observed in 165 (65%) of 253 restenotic specimens retrieved by directional atherectomy in the authors’ laboratory. Acknowledgment must be made, however, that the hypercellular lesion is not altogether specific for restenosis: In *de novo* directional atherectomy specimens, a similar lesion was observed in 7% of primary specimens (99).



***e*FIGURE 105.2.4** Sequential specimens retrieved by directional atherectomy from same patient. **Top left:** Thrombotic primary lesion. **Top right:** Restenotic lesion no. 1, demonstrating bilayer appearance with hypocellular primary component and hypercellular restenosis portion. **Bottom left:** Restenotic lesion no. 2. **Bottom right:** Restenotic lesion no. 3.

Pathologic analyses of specimens retrieved from restenotic lesions by directional atherectomy have been performed to determine the extent of ongoing cellular proliferation (101). Pickering et al. (101) have analyzed the expression of the proliferating-cell nuclear antigen (PCNA) (restenosis) (*e*Fig. 105.2.5) and found that the proliferative index (percentage of PCNA-positive cells) was higher in restenotic than in primary lesions. Proliferating cells were detected by *in situ* hybridization and immunohistochemistry in 15% to 20% of cells of specimens retrieved from restenotic lesions. These findings thus indicate that, among patients referred for percutaneous revascularization, SMC proliferative activity is still ongoing at the time the patient presents with symptoms requiring interventional therapy. One must underscore, however, that based on animal studies (102) in which the histopathology of restenosis could be systematically examined at a number of arbitrary—including early—time points, peak proliferative activity occurs soon after the initial injury; thus, the proliferative activity seen at the time of intervention represents a fraction of the proliferative activity responsible for generating hyperplastic lesions typical of restenosis.



***e*FIGURE 105.2.5** Restenotic lesion double immunostained with antibody to proliferating-cell nuclear antigen (red nuclear reaction product) and a-actin (yellow-brown cytoplasmic stain).

Apoptosis and Restenosis

Previous studies have suggested that development of restenosis represents the net outcome of SMC proliferation and programmed cell death, or apoptosis (103,104,105 and 105a), and that cellular proliferation is associated with apoptosis rates that are higher than those observed in primary lesions; this is true for coronary as well as peripheral vascular sites (104) (Fig. 105.3).

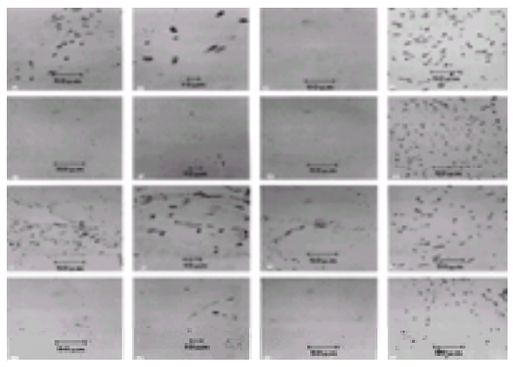


FIGURE 105.3 Apoptosis in human vascular lesions retrieved by directional atherectomy and identified by immunostaining of primary atherosclerosis. This composite photograph illustrates the use of terminal deoxytransferase (TdT)–mediated deoxyuridine 5-triphosphate–biotin nick end labeling to immunostain sections from specimens representative of the four groups of lesions studied: peripheral restenosis **(A–D)**, peripheral primary **(E–H)**, coronary restenosis **(I–L)**, and coronary primary **(M–P)**. Negative control was incubated in the absence of the TdT enzyme. One section of each tissue was processed as a positive control by pretreatment with deoxyribonuclease.

The possibility, if not the likelihood, exists that proliferation and apoptosis are temporally dissociated. Specifically, the contribution of SMC proliferation to the genesis of the restenotic lesion may peak relatively early after angioplasty, as has been repeatedly demonstrated in various animal models (106,107,108,109,110,111 and 112) studied at early time points seldom sampled in human subjects. Apoptosis, in contrast, may become more frequently recognizable at a later time. This latter concept is in fact consistent with previous animal studies reported by Clowes et al. (113) in the balloon-injured rat carotid artery. They found that proliferative activity of vascular SMCs, as determined by use of tritiated thymidine, persisted at relatively high levels (3.8%) for up to 12 weeks after balloon injury. Total arterial SMC content at 12 weeks, however, was unchanged from that measured at 2 weeks. In the absence of cell death, Clowes et al. calculated that this level of ongoing proliferation should have led to a 36% increase in cell number. Because this increase was not observed, they made the clairvoyant deduction that “cell death must account for our finding.”

Extracellular Matrix and Restenosis

Although vascular SMC proliferation and the resulting hypercellular nature of the fibroproliferative tissue have been the focus of most studies of restenosis, it is the ECM that in fact accounts for the bulk volume of these lesions (Fig. 105.4). Together with activated SMCs, ECM having a distinctively lighter hue on histochemical staining comprises the classic restenotic focus (114). Various collagen subtypes and proteoglycans have been demonstrated to comprise the ECM of atherectomy specimens (115), and certain constituents, particularly collagen, are derived from adventitial fibroblasts (116). The contribution of two proteoglycans in particular, biglycan and decorin (Fig. 105.5), known to be differentially modulated during ECM elaboration and differentially regulated by TGF-b_1 (Fig. 105.6), have been found to be differentially distributed in primary versus restenotic lesions (115). Extracellular deposits of biglycan were found to be characteristic of the loose, rich ECM typical of restenosis, whereas staining for decorin was limited to weak staining intensity in the more compact transition zone between loose ECM and dense connective tissue typical of advanced lesions composed of hypocellular fibrous plaque. More recently, the glycosaminoglycan hyaluronic acid (Fig. 105.7) has been shown to be a characteristic constituent of the loose myxoid ECM of human restenotic arteries (117). The presence of hyaluronic acid may be a marker for an initial phase of the ECM remodeling that occurs during the development of a fibroproliferative lesion and could facilitate biologic processes such as cell migration. Furthermore, because hyaluronic acid is heavily hydrated, the proposal has been made that (a) this hydrated feature of restenotic lesions may be responsible for the distinctive hue of the restenotic lesion; and (b) gradual loss of water or replacement of hyaluronan by collagen, or both, converts the restenotic lesion into a compact scar, with the resulting cicatrization then pulling in the arterial wall, which leads to constrictive remodeling (Fig. 105.8).

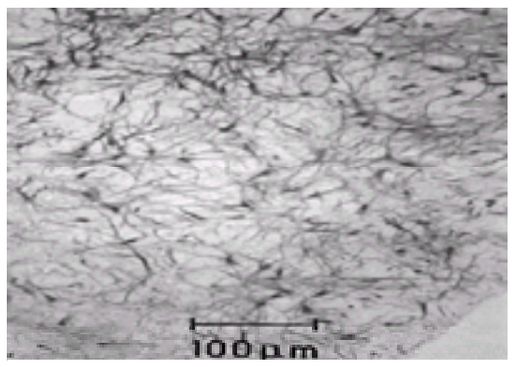


FIGURE 105.4 Restenosis specimen with abundant extracellular matrix. Note characteristic light-hued area in which are embedded stellate-shaped, synthetic smooth muscle cells (elastic tissue stain).

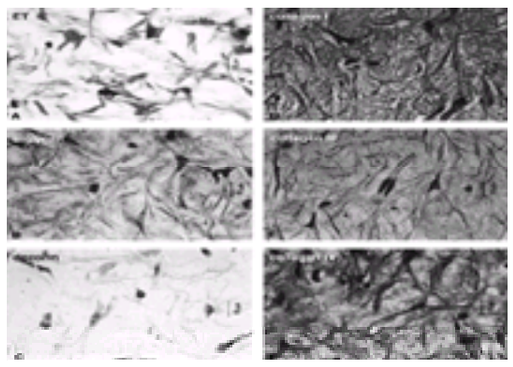


FIGURE 105.5 High-magnification photomicrographs taken from serial sections of a restenotic lesion (6 months after angioplasty) showing a fibroproliferative focus. Stellate-shaped a-actin–positive smooth muscle cells (not shown) are embedded in a loose extracellular matrix (elastic tissue trichrome stain) **(A)**. Immunostaining shows disseminated biglycan deposits **(B)**, no decorin **(C)**, and a loose network of collagen type I **(D)** and type III **(E)**. Staining for collagen type IV **(F)**, although also present in an interstitial distribution, is most intense around the perimeter of the cells.

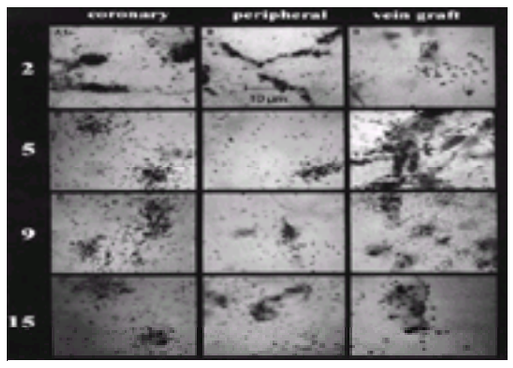


FIGURE 105.6 *In situ* hybridization performed on specimens retrieved by directional atherectomy from restenotic lesions in coronary and peripheral arteries and vein grafts. Numbers on the left refer to the time interval (months) between previous intervention and atherectomy procedure. Dark black silver grains overlying smooth muscle cells denote messenger RNA for transforming growth factor-b.

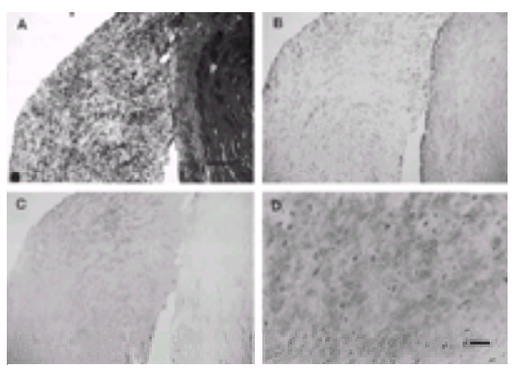


FIGURE 105.7 A: Low magnification of the elastic tissue trichrome staining of a restenotic lesion retrieved 7 months after angioplasty. A large restenotic focus (fibroproliferative tissue, FPT) is clearly demarcated from dense, compact matrix typical of primary plaque (*P*) (bar = 10 µm). **B:** In this adjacent section, the restenotic focus shows patchy staining for collagen type III, whereas collagen staining in areas of primary plaque is much more homogeneous. **C:** Staining for hyaluronic acid (HA) is inversely related to that for collagen, with dense, homogeneous staining for HA in the restenotic regions and only focal deposits of HA in primary plaque. **D:** High-power view of restenotic portion of previous specimen, double-stained for HA and proliferating-cell nuclear antigen (PCNA). The numerous PCNA-positive smooth muscle cells in this tissue are surrounded by an HA-rich matrix (bar = 10 µm).

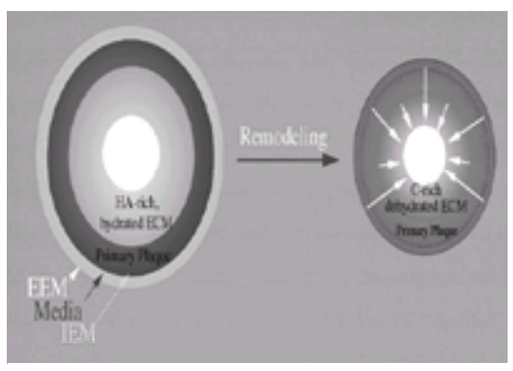


FIGURE 105.8 As hyaluronic acid (HA), heavily hydrated, is replaced by collagen (C), resulting dehydration of the extracellular matrix (ECM) may exert a cicatrizing effect on the arterial wall, retracting the dimensions of the artery wall, much as a contracting scar pulls in skin. This process is proposed to contribute to constrictive remodeling of the vessel wall. EEM, external elastic membrane; IEM, internal elastic membrane.

Angioscopic Findings

Evidence for neointimal formation after PTCA in humans can also be obtained from angioscopic studies (118,119) (Fig. 105.9). Although the angioscopic appearance of a primary lesion is extremely variable in terms of color, shape, and presence of superimposed thrombus, the angioscopic appearance of a lesion that was dilated a few months earlier is almost unvaryingly that of a stable smooth white plaque without thrombus (119). These differences reflect the magnitude of the changes occurring at the lesion site during the months after PTCA. The smooth concentric white aspect of the plaque is likely to be a consequence of neointimal hyperplasia that leads to a remodeling of the inner part of the vessel. Interestingly, this angioscopic aspect is not limited to restenotic lesions (greater than 50% stenosis by angiography) but is also observed in vessels that are widely patent at 6-month angiographic follow-up. This suggests that a significant healing process of the inner part of the vessel (probably related to neointimal hyperplasia) may occur without deleterious effects in terms of lumen size.

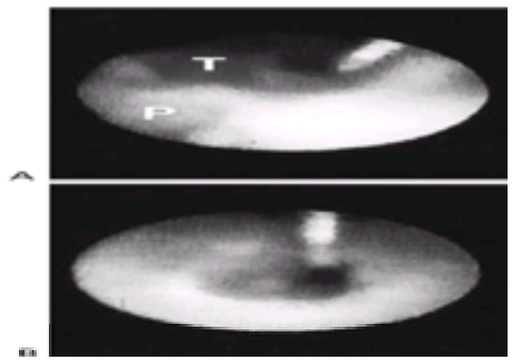


FIGURE 105.9 Serial images before angioplasty and 6 months after angioplasty. **A:** Angioscopic appearance of a lesion before angioplasty in a patient with unstable angina discloses a yellow plaque (*P*) with a superimposed red thrombus (*T*). **B:** Angioscopy of the same lesion 6 months after successful angioplasty; angioscopy now discloses a white, smooth, concentric lesion without thrombus.

Rotational atherectomy to treat in-stent restenosis. Diffuse restenosis within a previously placed Palmaz-Schatz stent (A, *arrows*) is treated with rotational atherectomy (B), followed by adjunctive stent placement (C). The postintervention result is shown in D.

Vessel Remodeling

Experimental evidence is increasing that neointimal hyperplasia is not the sole mechanism leading to lumen renarrowing after angioplasty, namely, that arterial remodeling also plays a major role in this process (17,18,120,121 and 122). Arterial remodeling is a well-recognized feature of *de novo* atherosclerosis. Glagov et al. (123) observed that human coronary arteries undergo adaptive enlargement in response to progressive plaque expansion and maintain the lumen area until the plaque occupies 40% of the area circumscribed by the internal elastic lamina. *In vivo* confirmation of the "Glagov hypothesis" was reported by Losordo et al. (124). This compensatory enlargement may thus obviate the effect of plaque development on lumen narrowing.

Studies involving animals and human subjects have established the potential for an alternative form of remodeling, constrictive remodeling. In contrast to the compensatory dilatation described by Glagov et al., constrictive remodeling after angioplasty results in reduced vessel wall diameter, indirectly narrowing the vessel lumen and thus contributing to restenosis.

Post et al. (120) observed a consistent deficit between the magnitude of late lumen loss measured by serial quantitative angiography and the diameter reduction that could be attributed to histologically identifiable intimal thickening. They concluded that "the deficit appeared to be due predominantly to reduction in the area circumscribed by the internal elastic membrane." Because the internal elastic membrane demarcates the native arterial lumen, any reduction in lumen area unassociated with plaque growth must, by default, be due to "constriction" of the lumen by a "shrinking" arterial wall. Post et al. estimated that remodeling accounted for 52% to 89% of the late loss in their *in vivo* experiments. Conversely, neointimal proliferation seemed to be responsible for an insignificant fraction of the late lumen loss in most cases.

Subsequently, double-injury models (i.e., models in which a first injury has been combined with a hypercholesterolemic diet to induce a stenosis that can be dilated with an angioplasty balloon) were used to study the impact of neointimal formation on lumen size a few weeks after angioplasty. Using this model, Kakuta et al. (18) showed that compensatory enlargement of the vessel (increase in internal elastic lamina area) occurs in the weeks after experimental angioplasty. This process seemed to compensate for nearly 60% of neointimal thickening in response to balloon injury and to prevent lumen narrowing. In this model, restenosis is not related to neointimal thickening but to a lack of compensatory enlargement or some degree of vessel constriction or both. The vessel size (area circumscribed by the internal elastic lamina) increased with increases in intimal area. In restenotic arteries, the slope of this correlation was less than one, which showed inadequate compensatory enlargement for neointimal formation. In nonrestenotic arteries, the slope was greater than one, which indicates limited effects of neointimal formation on luminal narrowing. Vascular remodeling thus acts to offset the effect of neointimal formation on chronic luminal narrowing, and differences in vascular remodeling seem to constitute a key element leading to restenosis in this model.

Mintz et al. (125) analyzed the contribution of neointimal formation to restenosis in human subjects studied by serial IVUS imaging after successful coronary angioplasty and again at the time of late angiographic follow-up. They observed that the change in lumen area between post-PTCA and late angiographic follow-up were more strongly correlated with the change in vessel size (area circumscribed by the external elastic lamina) than with the change in plaque plus media area (125,126). In the study by Mintz et al. (125), the changes in vessel size were bidirectional: Some lesions showed an increase in vessel size (enlargement), whereas others showed a decrease in vessel size (constriction). Lesions that exhibited an increase in vessel size had no change in lumen area (–0.1 ± 3.3 mm^2 versus a decrease in lumen area of 3.6 ± 2.3 mm^2 for lesions with a decrease in vessel size; p <.0001). Seventy-three percent of the late lumen loss was explained by the decrease in vessel size. They concluded that restenosis was determined primarily by the direction and magnitude of the vessel wall remodeling (change in external elastic lamina). An increase in the area circumscribed by the external elastic lamina is adaptive, whereas a decrease contributes to restenosis.

The precise mechanisms responsible for arterial remodeling after balloon injury remain uncertain. Proposed mechanisms for compensatory enlargement in *de novo* arteriosclerosis include increased flow with concomitant increase in shear stress and modulation of the ECM support structure with protrusion of the lesion outside the original contour of the artery (123). After balloon angioplasty, compensatory enlargement in response to neointimal growth may occur as a result of high flow velocity or as a consequence of ECM degradation (18). Chronic constriction, on the other hand, may be related to collagen deposition and reorganization of a hyaluronan-rich matrix (127). This is accentuated by low flow and may be secondary to stimulation of PDGF and TGF-b expression by low shear (127a,127b).

Studies have also suggested a role for the adventitia in the remodeling process (128,129). In the porcine model, injury leads to sequential changes in the adventitial layer, including cell proliferation, myofibroblast formation, and fibrosis (128). Associated significant focal adventitial thickening may play a role in the remodeling process.

THROMBOSIS

Immediately after experimental balloon injury, endothelial denudation induces platelet adhesion and aggregation, which results in release of the constituents of their alpha granules within a few minutes (6,23). Numerous mitogenic substances, including PDGF, are thus released at the site of injury and may be involved in the process of SMC activation (130). Experiments performed in thrombocytopenic animals have demonstrated the fundamental role of platelets in determining the extent of neointimal thickening after arterial injury (131). Experiments involving a canine model of endothelial injury have demonstrated that the intensity of cyclic flow variations related to platelet accumulation constitutes a major determinant of neointimal thickening (132). Thrombocytopenia has been shown to inhibit migration of activated SMCs from the media to the intima but to have no effect on the initial cycle of cell proliferation (23). Coagulation proteins such as thrombin may also be implicated in the response of SMCs (133). Thrombin has mitogenic properties for SMCs (134) and has been demonstrated to induce multiple growth-related signals in SMCs, including the expression of the c-*fos* protooncogenes (135). Finally, the volume of thrombus at the PTCA site may also play a role in the subsequent restenosis process; Schwartz et al. (49), based on observations made in the porcine coronary injury model, proposed that the volume of intracoronary thrombus resulting from PTCA may serve as a scaffold that determines the subsequent volume of neointima.

Clinical studies have suggested that thrombus formation may play a role in restenosis after PTCA in humans. The contribution of thrombosis to lumen renarrowing may be especially marked when PTCA is indicated for an unstable coronary syndrome. High restenosis rates have been observed, for example, in patients in whom angioplasty was performed at an infarct-related lesion (136,137) or in patients with severe unstable angina (138,139). The impact of local versus systemic factors on restenosis after PTCA of patients with unstable angina was studied (139). To assess these factors, a group of patients was identified who had unstable angina with a clearly defined culprit lesion and who underwent successful double-vessel angioplasty during a single catheterization session. Using quantitative angiography, the incidence of restenosis at culprit and nonculprit lesions was compared. The late loss at culprit lesions (0.87 ± 0.75 mm) was significantly greater than the equivalent value for nonculprit lesions (0.33 ± 0.69 mm; p <.01). Restenosis occurred at 67% of culprit lesions and at 32% of nonculprit lesions (p <.01). These results suggest that the increased rate of restenosis in patients with unstable angina predominantly reflects the influence of local lesion-related factors.

Because the pathophysiology of unstable angina or acute myocardial infarction, or both, involves episodes of plaque rupture associated with platelet aggregation and thrombus formation (140,141 and 142), studies have been designed to examine the relationship between thrombus and restenosis (118,143). Coronary angioscopy is

to date the reference technique for the detection of intracoronary thrombus in humans. More than 50% of the thrombi detected by angioscopy are not detected by angiography (144,145). Ninety-nine consecutively treated patients who underwent coronary angioscopy before and immediately after a successful PTCA procedure and who had angiographic follow-up 6 months later were studied (118). To assess the role of an angioscopically visible thrombus at the PTCA site on the risk of restenosis, patients were classified into three groups: no thrombus, lining thrombus, and protruding thrombus. An angioscopic protruding thrombus at the PTCA site was associated with significantly greater loss in luminal diameter (late loss: no thrombus, 0.47 ± 0.52 mm; lining thrombus, 0.59 ± 0.67 mm; protruding thrombus, 1.07 ± 0.77 mm; p <.05). The restenosis rate (greater than 50% stenosis at follow-up) was also higher in the case of an angioscopic protruding thrombus (no thrombus, 38%; lining thrombus, 47%; protruding thrombus, 65%).

The mechanisms by which an intraluminal thrombus may increase the risk of restenosis after PTCA are not known specifically, but at least two hypotheses may be invoked. First, as discussed earlier, thrombosis may stimulate neointimal formation (49,131,132). However, a significant proportion of the restenoses observed after PTCA of lesions with superimposed thrombus are in fact due to total occlusion of the vessel at follow-up (118,143). These occlusions may occur as a final step in severely restenotic lesions but also may be the consequence of a thrombotic event occurring early after PTCA.

ENDOTHELIAL REGENERATION

Endothelial Regeneration after Experimental Arterial Injury

Endothelial Regrowth

In the hours after experimental angioplasty, endothelial cells rapidly enter the replication cycle to restore endothelial continuity. Proliferation and migration can be initiated either by loss of contact inhibition, stretch, or growth factors secreted by endothelial cells, SMCs, and circulating cells (15,56). Endothelial regeneration starts from the leading edge of the denuded area and from the ostia of collateral or branch arteries or both (146). Reendothelialization begins within the first 24 hours of arterial denudation and ceases 6 or 10 weeks later, depending on animal species (19). The rate and extent of endothelial regrowth are related to animal models and experimental conditions, but the most important factor seems to be the severity of the initial injury. Indeed, although complete reendothelialization can be achieved after small denuding injuries (147,148), endothelial cells have been found to be incapable of sustained regrowth after widespread denudation (19,20,149). Even if complete reendothelialization occurs, the regenerated endothelium often displays abnormal morphologic characteristics. In contrast to normal endothelial cells, regenerating endothelial cells grow as a sheet with close cell-to-cell contacts, no longer aligned with blood flow, and are both polygonal in shape and irregular in size, with cytoplasm bulging toward the lumen (19,146,148,149 and 150).

Studies have emphasized the important role of endothelial cell growth factors in the reendothelialization process. Lindner et al. (56) have shown that systemic administration of bFGF (120 µg over an 8-hour period) after balloon catheter denudation of the rat carotid artery induces a highly significant increase in the replication rate of endothelial cells at the leading edge of the regrowth process. In this study, when bFGF was given over a longer period of time (12 µg daily for 12 days), a significant increase in the extent of endothelial outgrowth onto the denuded surface was observed. A study of the effect of much lower dosages of bFGF (systemic administration of 2.5 µg twice a week for 2 weeks) on the extent of endothelial regrowth after balloon denudation of rabbit iliac arteries found that animals in the bFGF group had a significantly greater degree of reendothelialization than did controls (151). Similar results have been observed with the use of acidic fibroblast growth factor in the same model (152). Stimulation of endothelial regrowth can also be achieved with vascular endothelial growth factor (VEGF). Asahara et al. (153) have demonstrated that a single local administration of VEGF (100 µg) immediately after balloon injury of the rat carotid artery is sufficient to significantly increase carotid artery reendothelialization at 2 and 4 weeks after injury. More recently, gene transfer of a plasmid encoding VEGF was associated with accelerated endothelial regrowth in a rabbit model (154) (Fig. 105.10). Taken together, these results demonstrate that both bFGF and VEGF are powerful stimuli of endothelial regrowth *in vivo* and suggest that they may participate in the spontaneous reendothelialization that occurs after injury.

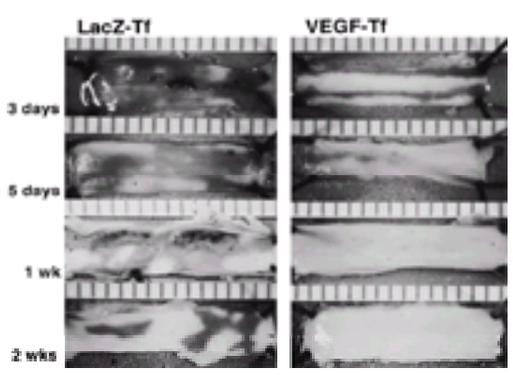


FIGURE 105.10 Representative macroscopic appearance of intimal surface of balloon-injured arteries transfected with control gene encoding b-galactosidase (LacZ-Tf) and gene encoding vascular endothelial growth factor (VEGF-Tf) at 3 days, 5 days, 1 week, and 2 weeks after gene transfer. Animals received systemic injection of Evans blue dye before sacrifice. Stained areas denote absent endothelium; reendothelialized areas, not stained by dye, appear white. Reendothelialization is accelerated in animals given VEGF-Tf.

Role of Progenitor Endothelial Cells in Reendothelialization

Work by Asahara et al. (155) has established that circulating mononuclear cells isolated from peripheral blood using antibodies to CD34 or Flk-1 can differentiate into endothelial cells *in vitro*. *In vivo*, such circulating endothelial cell progenitor cells were shown to incorporate into sites of angiogenesis, and more recent studies have indicated that such cells may contribute to reendothelialization at sites where balloon angioplasty has resulted in endothelial denudation. These findings thus suggest the need to reevaluate the conventional paradigm in which endothelial cells responsible for reendothelialization are considered to proliferate and migrate from intact endothelium at the proximal and distal boundaries of the balloon-injured segment, or from branch vessels. Some as-yet-undefined proportion of these endothelial cells may in fact be derived from circulating endothelial cell progenitor cells. Still to be determined is whether primary alterations in the proteoglycan “landing pad” that constitutes the denuded segment—for example, expression of osteopontin or fibronectin beginning at the wound edges and progressing to the center of the denuded segment—determine the sequence in which such circulating progenitor cells may attach, differentiate, migrate, and proliferate.

Endothelial Dysfunction

The functional properties of regenerated endothelium have also been shown to be abnormal (27,148,156). After vascular injury, endothelium-dependent relaxation to vasodilator agonists is depressed in arteries with regenerated endothelium at a time when the ability of underlying vascular SMCs to relax or contract is unchanged. The severity of the endothelial dysfunction seems to be dependent on the nature of the initial injury. In a rabbit iliac artery model of angioplasty, impaired endothelium-dependent relaxation was found 4 weeks after the procedure only if animals experienced severe injury (148). Similarly, studies performed after coronary angioplasty in humans have demonstrated abnormal responses of previously dilated sites to endothelium-dependent agonists such as serotonin (157) and acetylcholine (158).

Endothelial dysfunction may be related to a reduction in the ability of endothelial cells to produce endothelium-derived relaxing factors (159,160 and 161). Indeed, enhancing the production and release of NO may reverse endothelial dysfunction. In a rabbit model of balloon-injured iliac arteries, L-arginine, given in animal drinking water, restored acetylcholine-induced relaxations 4 weeks after vascular injury when these responses were depressed in the control group (27). This finding is in agreement with a reported study in which a constant intravenous infusion of the NO donor SPM-5185 significantly accelerated the functional recovery of the regenerating endothelium (162).

Importantly, the function of the endothelium that regenerates in response to exogenous administration of bFGF or VEGF seems to be normal (151,154). This demonstrates that endothelial cell growth factors are not only associated with a beneficial anatomic effect but also with an improvement in endothelial cell function. Similar results have been reported in other models of endothelial dysfunction. For example, the administration of angiogenic growth factors has been demonstrated to restore endothelium-dependent responses in arterial beds perfused via collaterals (163,164 and 165) and in hypercholesterolemic rabbits (166,167).

Impact of Endothelial Regeneration on Restenosis

Effects on Neointimal Hyperplasia

Previous investigations have underscored the principle of cross talk between endothelial cells and SMCs (149,168,169 and 170). Neointimal thickness is closely related to the presence of a regenerated endothelium. Indeed, intimal areas that are rapidly covered by continuous endothelium are protected from the accumulation of intimal SMCs, whereas typical intimal hyperplasia occurs in areas where reendothelialization is delayed.

Endothelium, in addition to its well-known role in regulating vessel tone and platelet aggregation, seems to modulate proliferative activity of the underlying SMCs. *In vitro* studies have emphasized a possible role for NO in controlling SMC growth (171,172). NO donors inhibit DNA synthesis in cultured SMCs, and similar effects achieved by administration of the analog 8-bromo-cyclic-guanosine monophosphate implicate the cyclic guanosine monophosphate pathway, physiologically activated by NO, in SMC growth regulation. Endothelial cells may maintain SMC quiescence through the growth-inhibitory effect of NO (172). Dysfunctional regenerating endothelium in which NO production is compromised may thus contribute to the development of a thickened intima due to reduced inhibition of platelet aggregation as well as SMC proliferation. Intriguingly, animal experiments have in fact documented that endothelial cell recovery is slower over damaged media than over normal media (173). On the basis that NO synthase catalyzes the synthesis of NO after oxidation of terminal guanidine-nitrogen atoms of L-arginine (174,175), several authors have administered this precursor locally or systemically and confirmed *in vivo* the efficacy of NO in preventing intimal hyperplasia (21,176,177).

Investigational experience with endothelial cell mitogens has yielded similar results. As discussed earlier, Asahara et al. demonstrated that a single local application of the endothelial cell–specific mitogen VEGF, either as a recombinant protein (153) or as naked DNA (154) (Fig. 105.10), is sufficient to facilitate endothelial repair after balloon injury (153). In these studies neointimal thickening was correspondingly attenuated to a statistically significant degree in VEGF-treated animals (Fig. 105.11). Somewhat different results have been observed in the case of FGF-induced reendothelialization. Lindner et al. (55), using high dosages of bFGF (12 µg daily for 12 days in a rat model), found a significant increase in neointimal thickening. By contrast, Bjornsson et al. (152), using low dosages of acidic FGF [a mitogen for SMCs *in vitro* (178)] in the same model, observed an inhibition of neointimal thickening. The present authors found that administration of 2.5 µg of bFGF twice a week for 2 weeks in a rabbit model was associated with a very significant increase in endothelial regrowth but with no change in neointimal thickening (151). As bFGF is also a growth factor for SMCs, its final effect on neointimal thickening may be the consequence of a balance between stimulatory and inhibitory mechanisms on SMC growth. Factors such as the dosage used, the duration of the treatment, and the animal model studied may explain discrepancies between studies. On the other hand, the results obtained with VEGF are probably mainly the consequence of reendothelialization, without detrimental effect on SMC—that is, proliferation—because VEGF high-affinity binding sites are limited to endothelial cells.

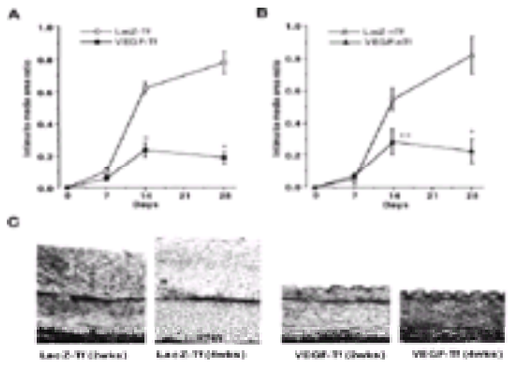


FIGURE 105.11 A: Arteries transfected with control gene encoding b-galactosidase (LacZ-Tf) showed progressive neointimal thickening through 4 weeks. Significantly less intimal thickening was observed among arteries transfected with gene encoding vascular endothelial growth factor (VEGF-Tf), including regression of intimal thickening between 2 and 4 weeks (*, p <.01 vs. LacZ-Tf). **B:** Contralateral balloon-injured, nontransfected arteries in VEGF group (VEGF-nTf) developed less intimal thickening and displayed no progression during weeks 2 to 4 compared with those in LacZ-nTf group (*, p <.01 vs. LacZ-nTf; **, p <.05). **C:** Representative effect of transfection on intimal thickening for LacZ-Tf and VEGF-Tf at 2 and 4 weeks posttransfection.

Effects on Vessel Remodeling

Several studies have also suggested a potential role for the endothelium in modifying the remodeling process. Previous studies have shown that adaptive enlargement, that is, increase in the lumen area of the vessel, occurs in response to a long-term increase in flow velocity (179). Conversely, a structural decrease in the lumen diameter is associated with a long-term decrease in blood flow. A functional endothelium seems to be essential for the compensatory arterial response to long-term changes in luminal flow rates (180). Thus, the absence of endothelium or the presence of a regenerated dysfunctional endothelium after arterial injury may impair the shear stress–induced remodeling response and may be an important factor in restenosis (181).

Antithrombotic Effects

In addition to the effects on the vascular wall described earlier, endothelial regeneration may also exert beneficial antithrombotic effects. Endothelium-derived relaxing factors such as NO and prostacyclin act synergistically to inhibit platelet aggregation and leukocyte adhesion (182,183). Aggregating platelets can initiate the coagulation cascade with the production of thrombin.

IMPACT OF ENDOVASCULAR STENTS ON THE BIOLOGY OF RESTENOSIS

Coronary stenting is emerging as an effective treatment for patients with coronary artery disease (184,185 and 186). Changes in antithrombotic regimens and in the technique of implantation have allowed coronary stenting to be performed with excellent immediate outcome (187,188 and 189). As a result, the proportion of patients receiving a stent as an adjunct to conventional balloon angioplasty is increasing exponentially. Studies have shown that implantation of permanent metal prosthetic stents results in significantly lower rates of clinically and angiographically determined recurrence than with conventional balloon angioplasty (190,191). Even if restenosis is less frequent, however, it remains a significant problem after coronary stenting. Rates of angiographically identified restenosis varying between 13% and 32% have been reported after successful coronary stenting (190,191 and 192). Importantly, the mechanisms of restenosis within coronary stents differ very significantly from those of restenosis after conventional balloon angioplasty.

Stent and Vessel Remodeling

Serial intravascular ultrasonographic studies have indicated that stents do not recoil over the long term (193,194). Implantation of an intracoronary stent seems to eliminate any component of arterial remodeling, either enlargement or constriction. As vessel remodeling is the major mechanism of restenosis after conventional balloon angioplasty (125), its elimination is probably the main explanation for the decrease in restenosis rate after coronary stenting.

In-Stent Restenosis

Because stents are considered to neutralize geometric effects, including remodeling (121), development of restenosis after stent implantation has been attributed principally to SMC proliferation. Successful application of intravascular radiation to limit thickening of stent neointima in a variety of animal models (195,196 and 197), on the premise that proliferating cells display enhanced sensitivity to ionizing radiation, constitutes indirect support for this notion. Likewise, accelerated endothelialization of stents after catheter delivery of the gene encoding VEGF has been shown to markedly reduce SMC proliferation and thereby reduce luminal narrowing due to thickening of the stent neointima (198).

VIDEO

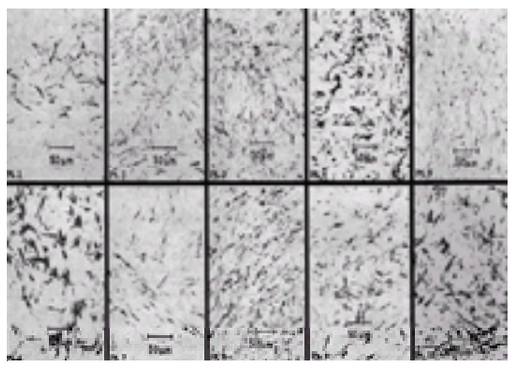
Video 105.1 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)** *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 105.2 Chronic total occlusion of the mid-portion of the right coronary artery **(A)** and subsequent successful recanalization **(B)**. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

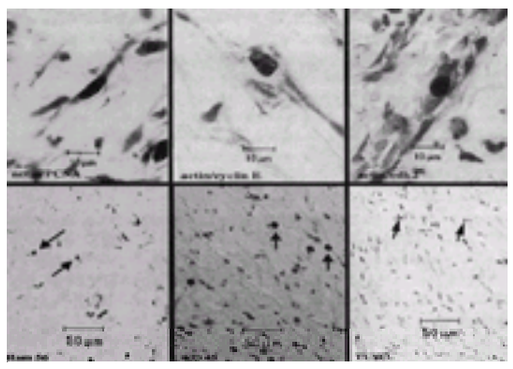
Histologic findings reported for a limited number of patients have suggested that in-stent restenosis is characterized by SMC hyperplasia. Pathologic analysis of graft segments surgically retrieved from two patients described by Anderson et al. (199) revealed "smooth muscle cells with abundant eosinophilic cytoplasm and minimal interstitial tissue" in the tissue overlying the stent wires. Among four patients with in-stent restenosis described by van Beusekom et al. (200), "tissue that narrowed the vessels always consisted of SMCs (often with a 'dendritic' appearance) within an extensive extracellular matrix." The extent of residual proliferative activity among these hypercellular foci was not specifically investigated in either series of patients.

Strauss et al. (201) identified foci of intimal hyperplasia, defined as a proliferative cellular response associated with a matrix of loose connective tissue, in eight of ten specimens retrieved from sites of in-stent restenosis. SMCs were identified as the principal cell type within the lesion by the presence of alpha-actin. In none of the seven cases, however, did they observe positive staining for PCNA. Unfortunately, all of the specimens studied by Strauss et al. had been fixed in 10% buffered formalin, a preservative that has been shown to attenuate or eliminate positive staining for PCNA (96,202).

Kearney et al. (203) analyzed a series of ten atherectomy specimens retrieved from stents deployed in patients undergoing lower-extremity percutaneous revascularization. Each of the ten specimens contained extensive foci of hypercellularity, predominantly SMCs (eFig. 105.11.1). Moreover, when these tissues were preserved in fixative specifically intended to preserve the antigenicity of three different cell-cycle regulatory proteins, immunostaining performed with the corresponding monoclonal (PCNA) or polyclonal (cyclin 2, cdk2) antibodies (204) disclosed that proliferative activity was abundant in all such specimens (eFig. 105.11.2). Double immunostaining with cell-specific markers confirmed that SMCs accounted for most proliferative activity. These findings thus constitute direct evidence that SMC proliferation contributes to in-stent restenosis in human subjects and implies a potential role for adjunctive therapies intended to reduce in-stent restenosis by inhibiting SMC proliferation.



***e*FIGURE 105.11.1** Photomicrographs showing representative hypercellular foci in tissue retrieved from sites of in-stent restenosis in ten patients. Low-power photomicrographs of a-actin–immunostained sections show abundant cells with phenotypic characteristics of activated smooth muscle cells. In methanol-preserved specimens (patients 1, 4, 6, 7, 8, 9, and 10), immunostaining for proliferating-cell nuclear antigen disclosed evidence of abundant proliferative activity.



***e*FIGURE 105.11.2** Cell-specific, cell-cycle, and apoptotic immunostaining. Hematoxylin and eosin staining shows typical hypercellular focus. Three top photomicrographs illustrate proliferating smooth muscle cells, double-immunostained for a-actin and either proliferating-cell nuclear antigen (PCNA), cyclin E, or cdk2. Bottom left two panels show sparsely distributed macrophages [human alveolar macrophage 56 (HAM 56)] and leukocytes (CD45). Terminal deoxytransferase–mediated deoxyuridine 5-triphosphate–biotin nick end labeling (TUNEL) stain applied to eight specimens preserved in paraformaldehyde-identified evidence of abundant apoptosis in all eight cases. Arrows identify representative positive staining.

Foci of apoptosis were relatively abundant among these ten cases of in-stent restenosis, a finding that is consistent with observations made in restenosis specimens retrieved from native vessels (204). Cardiovascular and noncardiovascular studies have typically disclosed a relationship between cellular proliferation and apoptosis, a finding that is consistent with the proliferative activity demonstrated in the restenosis specimens.

Inflammatory cells, including foreign body granulomata formation, have been described in at least one previous animal study of endovascular stents (205). Although neither giant cells nor granulomata were observed in these specimens, occasional inflammatory cells were identified by CD45 immunostaining. A relatively small human alveolar macrophage-56 population was identified as well, but the contribution of both cell types to restenosis in these ten cases seems limited.

The role of thrombus in restenosis, including in-stent restenosis, is unclear. Schwartz et al. (206) have suggested that mural thrombus may constitute the primordial infrastructure that is subsequently colonized by activated SMCs. Thrombus was in fact observed in 60% of ten specimens in the cohort described and thus cannot be excluded as a factor contributing to the genesis of in-stent restenosis.

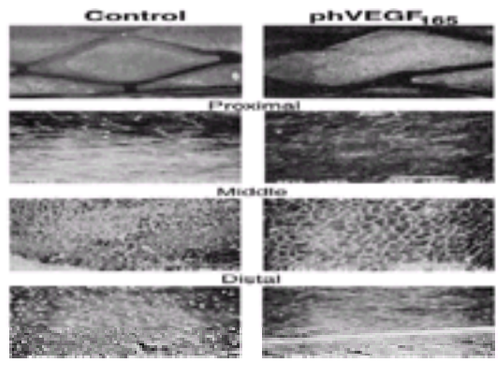
Stents and Thrombosis

As discussed earlier, thrombosis may contribute to restenosis. Stent implantation per se may increase the thrombotic response of the vessel wall. Thrombosis, however, may be significantly reduced by new antithrombotic regimens (189) and the use of heparin-coated stents (192).

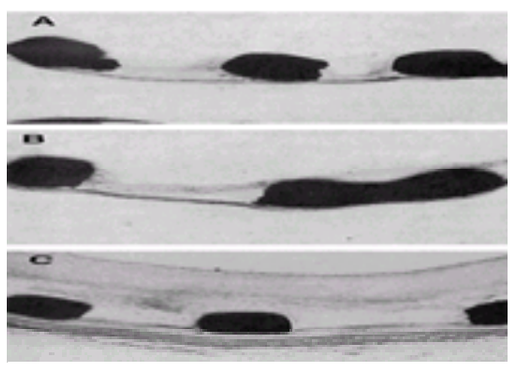
Stent Reendothelialization

Discordant results have been published regarding the process of stent reendothelialization. In rabbit aorta the process has been described as "completed" after 1 week (207); for rabbit iliac arteries, arteries were observed to "begin to endothelialize" after 1 week (195); and in dog and pig coronary models endothelialization was evaluated as "incomplete" (208) or "advanced" (209) after 1 week. In a series in which stents were implanted in human venous bypass grafts, no significant endothelialization was observed in three specimens retrieved within 14 days of implantation (200). In the only published series of human coronary stents examined at necropsy, endothelialization was observed in one of three specimens retrieved 3 weeks after implantation (199).

Reendothelialization was studied after Palmaz-Schatz stent implantation in iliac arteries of New Zealand White rabbits (210). Planimetric time-course analysis disclosed less than 20% stent endothelialization at 4 days, less than 40% at 7 days, and near-complete endothelialization at 28 days. When VEGF (100 µg) was delivered from a local catheter after stent implant, however, stent endothelialization was nearly complete by day 7 (92 ± 4%; p <.001 vs. no local delivery). In addition, a dramatic reduction in mural thrombus on the luminal surface of stents treated with VEGF was observed. Similar results were achieved with arterial gene transfer of naked plasmid DNA encoding for VEGF ($phVEGF_{165}$) (211) (eFig. 105.11.3 and eFig. 105.11.4). These findings may ultimately have important implications for preservation of stent patency.



***e*FIGURE 105.11.3** Representative examples of spontaneous stent endothelialization at day 7 (*left*) or after site-specific gene transfer of $phVEGF_{165}$ (*right*). Top left panel shows a macrophotograph of the silver-stained surface of the middle portion of the stent (×8.5). Stent endothelialization is incomplete (*bottom*), and mural thrombus is visible at the stent struts. Scanning electron photomicrographs from the proximal (×500), middle (×300), and distal portions (×300) of the stent confirm incomplete stent endothelialization of the proximal and distal portions of the stent with blood cell deposition in areas of nonconfluent endothelial cells (*Distal*), as well as thrombus along a nonendothelialized strut segment (*Middle*). Top right panel shows a macrophotograph of the silver-stained surface of the middle portion of the stent (×8.5). Stent endothelialization is virtually complete; no mural thrombus is visible. Scanning electron photomicrographs from the proximal (×300), middle (×300), and distal portions (×300) of the stent confirm that a confluent endothelial cell monolayer completely covers the stent (see *Distal*). The endothelial cells appear arranged in the direction of the flow in the proximal part of the stent. No foci of blood cells are visible.



***e*FIGURE 105.11.4** Effect of $phVEGF_{165}$ on intimal hyperplasia. **A,B:** Cross sections of transfected arteries 2 and 4 weeks, respectively, after stent implantation and site-specific delivery of 800 µg of $phVEGF_{165}$. Note limited intimal hyperplasia. **C:** Cross section of artery transfected with pCMV-luciferase (control) at 4 weeks posttransfection.

IMPACT OF ENDOVASCULAR BRACHYTHERAPY ON THE BIOLOGY OF RESTENOSIS

Endovascular brachytherapy is currently under investigation in humans to treat or prevent coronary restenosis after standard balloon angioplasty or coronary stenting. Although preliminary results are encouraging and suggest that this strategy may be effective in reducing restenosis rates at 6 months in selected patients (212,213), several issues are still unresolved. For example, the optimal dosage, the nature of the source (beta vs. gamma), and the ideal mode of administration (external irradiation vs. catheter-based irradiation, stent-based vs. wire-based delivery) are unknown. In addition, although long-term results of radiation are still uncertain, the suggestion has been made that endovascular brachytherapy may be harmful and may increase the rate of restenosis at the edge of stents (214) or increase the rate of thrombotic events (215,216). The effects of radiation on the restenotic process and on the cellular components involved in vascular healing are discussed in the following sections.

Brachytherapy and Vessel Remodeling

Animal and IVUS studies have shown that brachytherapy may alter vessel remodeling. In porcine coronary arteries (217,218), administration of intravascular irradiation at the time of balloon injury was associated with a larger external diameter of coronary vessels at 14 days than in animals receiving balloon injury alone. Consistent with this observation, a serial IVUS study (219) involving patients treated with balloon angioplasty and receiving beta irradiation found that 16 of 22 patients (76%) had vessel enlargement at 6 months. Similarly, Condado et al. (220) reported a negative late loss by angiography at 6 months in 10 of 22 patients (45%) treated with gamma radiation. This effect seems to be related to inhibition of adventitial fibrosis as suggested by the decrease in the number of adventitial cells expressing alpha-actin immunostaining after intravascular irradiation (218,221).

One must also point out, however, that animal experiments using external beam radiation have shown that irradiation may induce vessel constriction rather than vessel enlargement at 4 weeks (217). These effects were related to fibroblast proliferation and inflammation in the myocardium and to an increase in interstitial and perivascular fibrosis.

Brachytherapy and Intimal Hyperplasia

Studies have shown that intravascular radiation using a beta or gamma source may reduce intimal hyperplasia after balloon angioplasty at 14 days and 6 months in pigs (222,223 and 224) and at 6 weeks in rabbits (225). Similar results were found in animal models using beta-emitting stents (226,227 and 228). Results of preliminary trials showing that intravascular irradiation associated with stent implantation may reduce restenosis at 6 months suggest that this is also the case in humans (212). IVUS studies performed in humans are also consistent with a reduction of intimal hyperplasia at 6 months (229). Whether these results may last over the long term is not clear, however. Indeed, endovascular irradiation has also been associated with delayed arterial wound healing, including delayed endothelialization and persistent fibrin deposition in the intima 3 months after the implantation of beta-emitting stents in rabbits (230). In addition, smooth muscle cells with a synthetic rather than contractile phenotype produced large amounts of collagen 6 months after endovascular radiotherapy (217). Reports showing that intimal hyperplasia may continue to increase beyond the 6-month point in patients treated by endovascular brachytherapy are also consistent with these observations (231,232). Finally, some reports suggest that radiation may increase, rather than decrease, intimal hyperplasia. This has been observed with beta-emitting stents in animal models (233,234 and 235) as well as in humans at the stent edges (214).

Radiation inhibits proliferation and migration of endothelial and vascular smooth muscle cells and inhibits proliferation of myofibroblasts as demonstrated *in vitro* and *in vivo* (218,236,237). *In vitro*, the effects of radiation on endothelial cells and vascular SMCs relate to induction of G_0/G_1 arrest, without evidence of cell viability alteration, apoptosis, or ultrastructural changes (237,238). The absence of an effect of radiation on apoptosis was confirmed *in vivo* (218).

The apparently contradictory results observed in animal models and in humans seem to depend on the dosage, the method of delivery, and the timing of follow-up. The increase in intimal hyperplasia is thought to be secondary to insufficient direct inhibitory effect of radiation on proliferation and migration of vascular SMCs associated with stimulation of the production of collagen (6), a key component of ECM and intimal hyperplasia. The lack of the endothelial barrier may also indirectly stimulate the

growth of vascular SMCs (239).

Brachytherapy and Reendothelialization

Balloon angioplasty and stent implantation induce disruption of the endothelial lining. Radiation, by inhibiting endothelial cell proliferation and migration (236), may delay the reendothelialization process. Endothelialization remains incomplete 2 to 3 months after implantation of beta-emitting stents in animals (230), and analysis of human coronary artery specimens also shows limited endothelialization at 2 months (230). Delayed reendothelialization may have some impact on endothelial function and may explain the impaired endothelium-dependent relaxation observed at 6 weeks after endovascular brachytherapy and balloon injury in animals (240). Endothelial function seems to have returned to normal at 6 months, however, as observed in patients treated with endovascular brachytherapy (241). Delayed endothelialization may also partly explain some of the side effects that have been reported in some circumstances with endovascular brachytherapy, such as increased thrombus formation (242,243) and increased intimal hyperplasia (243,244 and 245). A study showing that the combination of agents able to stimulate reendothelialization may reduce thrombus formation after endovascular brachytherapy provides additional support to this hypothesis (244).

Brachytherapy and Thrombosis

A high rate (approximately 9%) of late total occlusion 1 to 6 months after endovascular gamma or beta radiotherapy was reported in the early experience of endovascular brachytherapy. This was more frequently observed in patients receiving a new stent (14.6%) than in patients receiving radiation but no new stenting (3.8%). This complication is usually observed after the first month and the discontinuation of ticlopidine hydrochloride or clopidogrel bisulfate (245).

As discussed earlier, delayed healing of the intima and lack of endothelial coverage for several months (242,243) are probably key factors leading to coronary thrombosis after endovascular brachytherapy combined with stent implantation.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Certain issues pertaining to the biology of restenosis have generated some controversy. Four, in particular, merit comment. The first issue is the extent to which SMC proliferation contributes to restenosis. All animal studies, without exception, have shown that when tissue sampling can be performed at arbitrary, including early, times, evidence of SMC proliferation is abundant. Most, indeed nearly all, human studies of tissues obtained at necropsy or surgery (including atherectomy) have shown evidence of SMC hyperplasia. The controversy has been generated largely because of one study in which proliferative activity was observed (using PCNA staining) in 15% to 20% of atherectomy specimens, whereas in a subsequent study PCNA staining was infrequent. The difference between these two studies may be explained largely by differences in methodology: In the latter study, a PCNA stain was identified as positive only if the staining intensity corresponded to that of control tissues colabeled for PCNA and the S-phase–specific marker bromodeoxyuridine. Such an analysis tests SMCs in S phase, as opposed to proliferating SMCs stained by PCNA in G_1 and G_2 as well. Because proportionately far more cells are in G_1 and G_2 at any given time, this methodology severely underestimates proliferative activity. Furthermore, because animal studies indicate that peak proliferative activity occurs soon after the initial injury, the extent of cellular proliferation seen at the time of intervention represents a fraction of the proliferative activity responsible for generating hyperplastic lesions typical of restenosis.

A second issue is the role of constrictive remodeling in the pathogenesis of restenosis. No controversy exists that constrictive remodeling, first demonstrated by the laboratory of Cornelius Borst, contributes to restenosis. This has been inferentially confirmed by the clinical experience with endovascular stents, in which the reduction of restenosis is assumed to represent successful inhibition of remodeling. What is controversial is the extent to which remodeling contributes to restenosis in general. Clinical studies performed using high-resolution IVUS to follow patients treated by angioplasty without stents may clarify this issue; the authors' own personal perspective, however, is that remodeling accounts for proportionately fewer cases of restenosis than does SMC proliferation. Parenthetically, published data regarding stenosis that develops within a stent has unequivocally indicated that SMC proliferation is the culprit.

A third issue also relates to the pathogenesis of restenosis, namely, the role of postangioplasty mural thrombus. Some have held the view that such mural thrombus forms the infrastructure of the restenotic lesion; indeed, good data are available from animal models of stent restenosis to support this interpretation. Others have questioned this view, based on patients studied by angiography and particularly angioscopy postangioplasty, in whom evidence of such mural thrombus has been difficult to identify. Suffice it to say that even if mural thrombus does not itself comprise a precursor scaffold for neointimal thickening, the possibility remains that elements derived from transient thrombus formation—for example, thrombin—contribute to neointimal thickening via their mitogenic effect on SMCs.

Finally, what is perhaps the most controversial issue of all relates not to restenosis per se but instead to one principal means used to study its pathogenesis: the use of animal models. Species that have been used for this purpose include mouse, rat, rabbit, pig, and primate. Although certain of these models have gained favored status at one time or another, none has been shown to be uniquely predictive of what happens when a certain intervention is performed in human species. Each has certain advantages and liabilities. No basis exists, however, for considering any one, two, or combination of these to be uniquely valid in a scientific sense. At best, each offers only the opportunity to establish proof of concept, and when considered in such context, each may be instructive.

SUMMARY

Restenosis is clearly a multifactorial entity. SMC proliferation, elaboration of ECM, thrombosis, and vascular remodeling all contribute to its pathogenesis. The contribution of these individual elements does not seem to be consistently proportional from one patient to another, or even from one lesion to another in the same patient. Similarly, the mechanisms of restenosis after coronary stent implantation are different from those of restenosis after conventional balloon angioplasty.

In the absence of a single therapy that effectively addresses all of these pathogenic elements, the capability to routinely preempt restenosis will likely require accurate clinical identification and understanding of the principal factor governing the biology of a given restenotic lesion.

THE FUTURE

Subsequent studies may further disclose the extent to which SMC proliferation, vessel remodeling, and thrombosis proportionately contribute to restenosis. Much of this may come with investigation of stented arteries, because the remodeling component should be minimal and SMC is currently considered to represent the key pathogenetic mechanism of in-stent restenosis.

Current studies focusing on the interaction of key integrins and their respective ligands may also clarify the extent to which upregulation of specific integrins in SMCs contributes to restenosis and, correspondingly, whether this represents a suitable target for antirestenosis strategies.

The role played by progenitor endothelial cells in passivating the site of balloon injury should be clarified by ongoing studies. Resolution of this issue will determine the extent to which conventional concepts regarding the source of endothelial cells responsible for reendothelialization need to be modified. These studies may also offer insights into the potential for such precursor cells, with or without administration of endothelial cell mitogens, to constitute a novel therapy for expediting reendothelialization and thereby inhibiting restenosis.

Identification of genotypes that predispose to restenosis will receive increasing attention. Successful execution of such investigations will not only assist in management decisions regarding percutaneous revascularization but may also provide clues to restenosis prevention.

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ANGIOGENESIS

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"Indicates text or graphics that appear only in the electronic versions of this text."

Overview
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OVERVIEW

The development of blood vessels can be considered in several contexts. Vasculogenesis and angiogenesis are the processes that are responsible for the development of the circulatory system, the first functional unit in the developing embryo (1). Therapeutic angiogenesis includes the development of collateral blood vessels that supply ischemic tissues, either endogenously or in response to administered growth factors. Pathologic angiogenesis includes the role of postnatal neovascularization in the pathogenesis of arthritis, diabetic retinopathy, and, most notably, tumor growth and metastasis (2).

Because recapitulation of the embryonic paradigm forms the basis for therapeutic, as well as pathologic, angiogenesis, this chapter addresses selected aspects of embryonic blood vessel development. Therapeutic angiogenesis represents a natural response to myocardial ischemia in particular and tissue ischemia in general, and, along with novel strategies that have been devised to augment this response, is discussed in detail. Although pathologic angiogenesis is beyond the scope of the current chapter, certain principles that have emerged from studies of pathologic neovascularization are considered for the implications that they may have for cardiovascular disease.

VASCULOGENESIS AND ANGIOGENESIS

Vasculogenesis refers to the *in situ* formation of blood vessels from progenitor endothelial cells (ECs), or angioblasts (3). It is necessary to distinguish between vascular development that takes place in the yolk sac of the embryo from that which occurs in the embryo proper. Extraembryonic vasculogenesis begins as a cluster formation, or blood island (Fig. 106.1). Growth and fusion of multiple blood islands in the yolk sac of the embryo ultimately give rise to the yolk sac capillary network (4); after the onset of blood circulation, this network differentiates into an arteriovenous vascular system (5). The integral relationship between the elements that circulate in the vascular system—the blood cells—and the cells that are principally responsible for the vessels themselves—ECs—is implied by the composition of the embryonic blood islands. The cells that are destined to generate hematopoietic cells are situated in the center of the blood island and are termed *hematopoietic stem cells* (*HSCs*). Endothelial progenitor cells (EPCs), or angioblasts, are located at the periphery of the blood islands. In addition to this spatial association, HSCs and angioblasts share certain antigenic determinants, including Flk-1, Tie-2, and CD34. These progenitor cells have consequently been considered to derive from a common precursor, putatively termed a *hemangioblast* (6, 7 and 8).

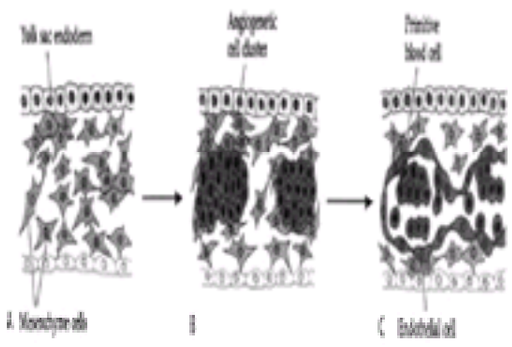


FIGURE 106.1 Blood islands. Blood vessel formation is first seen in the wall of the yolk sac, where **(A)** undifferentiated mesenchyme condenses to form **(B)** angiogenic cell clusters. **C:** The centers of these clusters form the blood cells, and the outside of the clusters develop into blood vessel endothelial cells. (From Gilbert SF. *Developmental biology*, 4th ed. Sunderland, MA: Sinauer Associates, 1997:342, with permission.)

Vasculogenesis that occurs within the embryo proper is currently considered to involve differentiation of so-called solitary angioblasts—that is, angioblasts that are not intimately associated with concomitantly differentiating HSCs (3). The sole exception to this is a small region in the aorta, termed *paraaortic clusters*. *In situ* differentiation of such solitary angioblasts occurs primarily from mesodermal cells in contact with endoderm. These angioblasts may migrate and fuse with other angioblasts and capillaries or form vessels *in situ*. Blood elements that circulate within the blood vessels of the embryo proper are believed to derive from the yolk sac

or paraaortic clusters.

In contrast to *in situ* differentiation of progenitor cells that are required to establish the primordial vascular network, extension of the primitive vasculature involves angiogenesis—that is, sprouting of new capillaries from the preexisting network; by definition, this implicates differentiated ECs as the responsible cellular element. Full development of the circulatory system involves recurrent remodeling, as some vessels regress, presumably by apoptosis, and others branch or are invested with a multilayer architecture characteristic of medium to large arteries and veins, or both. The extensive EC proliferative activity, which constitutes the basis for angiogenesis in the embryo, contrasts with extraordinary EC quiescence in the adult, in whom the interval for EC turnover is estimated to be more than 1,000 days (9).

Classic Paradigm for Angiogenesis

Until recently, vasculogenesis was considered to be restricted to the embryo, and new blood vessel formation in adult species was inferred to be the exclusive consequence of angiogenesis. The full paradigm for angiogenesis has been suggested to begin with “activation” of ECs within a parent vessel, followed by disruption of the basement membrane and subsequent migration of ECs into the interstitial space, possibly in the direction of an ischemic stimulus (10) (Fig. 106.2). Concomitant and/or subsequent EC proliferation, intracellular-vacuolar lumen formation, pericyte “capping,” and production of a basement membrane complete the developmental sequence.

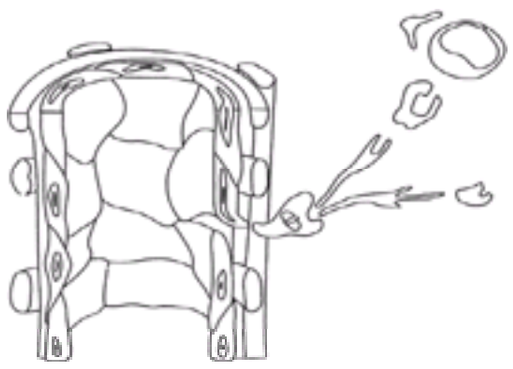


FIGURE 106.2 Classic paradigm for angiogenesis. Endothelial cells break free from their basement membrane and surrounding extracellular matrix, migrate, proliferate, and remodel (i.e., form a lumen), thus generating new blood vessels or “sprouts” from the parent vessel. (From D’Amore PA, Thompson RW. Mechanisms of angiogenesis. *Annu Rev Physiol* 1987;49:453–464, with permission.)

During angiogenesis, migration always precedes proliferation by approximately 24 hours (11). This principle was best demonstrated in classic experiments performed by Sholley et al. (12). Using a model of inflammation-induced angiogenesis of the rat cornea, initiation of vascular sprouting was shown to occur in the absence of EC proliferation. EC proliferation in this model was suppressed by X-irradiation with 2,000 or 8,000 rads before application of the inflammatory stimulus. In irradiated corneas displaying no cellular proliferation, vascular sprouting at 2 days was similar to that seen in contralateral shielded corneas. Although neovascular growth was subsequently blunted and ultimately ceased by 4 to 7 days, these experiments documented the critical if not exclusive roles of migration and redistribution of preexisting ECs in the commencement of neovascularization. Similar implications resulted from work by Nicosia et al. (13): Fibronectin was shown to promote, in a dose-dependent fashion, the elongation of microvessels that sprout from explants of rat aorta placed in serum-free collagen gel—despite the fact that neither deoxyribonucleic acid (DNA) synthesis nor mitotic activity was increased in comparison to fibronectin-negative gels. Fibronectin was therefore inferred to promote angiogenesis *in vitro* by migratory recruitment of preexisting ECs. Subsequent studies have established the critical role played by plasmin and other proteases in promoting migration through preexisting matrix (14,15).

In contrast to these *in vivo* inflammatory and *in vitro* organ culture models, angiogenesis that develops in response to experimental vascular obstruction, that is, collateral vessel development, has been shown by several previous investigators to involve proliferation of not only ECs but smooth muscle cells (SMCs) as well. Several important principles were elucidated by these studies.

First, evidence of EC proliferation is nearly absent in normal arteries (16,17), a finding that is consistent with an estimated EC turnover time of “thousands of days” in quiescent microvasculature (9). Even a relatively low percentage of EC proliferation observed in response to arterial occlusion or exogenous growth factors may therefore represent considerable enhancement of EC proliferative activity and, when considered in relation to a denominator of thousands of ECs, is clearly sufficient to provide the basis for new blood vessel formation. Second, peak EC proliferation that contributes to naturally occurring collateral development in the setting of vascular occlusion varies from 2.6% to 3.5% in the canine coronary circulation (16,18), from 5% to 6% in the rodent renal vasculature (19), and less than 1% in swine coronaries (20). The contrasting rates of EC proliferation between the canine and swine coronary circulations are indeed representative of the contrasting propensity for natural collateral artery development in these two species. Third, proliferation of SMCs, the additional requisite cell type for the formation of larger blood vessels, is an implicit component of angiogenesis, regardless of animal species or circulatory site. In fact, Schaper et al. (21) speculated more than 30 years ago that “it is tempting to assume that EC proliferation not only serves the purpose of forming the endothelium of a finally larger artery but rather actively participates in the development of the tunica media.” Fourth, proliferative activity—for SMCs as well as ECs—is highest at the level of the smallest-diameter collateral vessels, the so-called midzone collateral segments (16,18,22,23). Fifth, although evidence of EC and SMC proliferation alone does not necessarily distinguish new vessel development from an increase in the size of preexisting vessels, adjunctive data regarding increased capillary density (24,25) support the notion that proliferative activity does in fact reflect true angiogenesis.

Ligand-Receptor Systems Modulate Vasculogenesis and Angiogenesis

A series of gene-targeting studies has elucidated the role of certain ligands or their receptors, or both, in vasculogenesis and angiogenesis. The phenotypic characteristics of these “knockout” mice are relevant to adult cardiovascular disease because of the implications they may have for the role played by these same ligand-receptor systems in promoting postnatal angiogenesis.

As indicated previously, KDR (the murine equivalent is known as *Flk-1* or *VEGFR-2*), the principal receptor for vascular endothelial growth factor (VEGF), is expressed by angioblasts and HSCs. It is perhaps not surprising, therefore, that mice deficient in this gene die *in utero* between 8.5 and 9.5 days postcoitum as the result of an early defect in the development of hematopoietic cells and ECs. Yolk sac blood islands were absent at 7.5 days, organized blood vessels could not be observed in the embryo and yolk sac at any stage, and hematopoietic progenitors were severely reduced (26). Markers of early endothelial precursors, such as Flt-1, Flt-4, and Tie-2, were expressed, but a marker of later endothelial development, Tie-2, could not be detected, indicating a deficiency of mature ECs (26). Expression of CD34, a marker of HSCs, was greatly reduced as well. The absence of blood islands and blood vessels in these mice established that the Flk-1 signaling pathway is required very early in the development of endothelial lineage and may be important for blood cell development as well.

Findings in the Flk-1 knockout mouse predicted what was to be found when the ligand, VEGF, was deficient. Mice that were deficient in even one of two VEGF alleles died *in utero* between days 10.5 and 12. Blood island formation (vasculogenesis) and vascular sprouting from preexisting vessels (angiogenesis) were again impaired (27,28). The failure of blood vessel ingrowth was accompanied by apoptosis and disorganization of neuroepithelial cells. The heterozygous lethal phenotype was interpreted as evidence for tight dose-dependent regulation of embryonic vessel development by VEGF. Parenthetically, the aortas of VEGF-deficient mice have been noted to be hypoplastic, similar to those observed in mice deficient in endothelial nitric oxide (NO) synthase (P. Huang, *personal communication*, 2001). It is interesting to speculate that this may reflect the role of NO in VEGF-modulation of EC function.

The tyrosine kinase Flt-1 receptor (VEGF-R1) constitutes a second high-affinity binding receptor for VEGF. Mouse embryos that are homozygous for a targeted mutation in the Flt-1 locus formed fully differentiated ECs in embryonic and extraembryonic regions but assembled these cells into abnormal vascular channels and died *in utero* (29). Blood islands, for example, were disorganized, consisting of intermixed angioblasts and HSCs. In the head mesenchyme, instead of progressive development of individual small vessels, large fused vessels were seen that contained internally localized groups of ECs. These findings were interpreted as evidence that the Flt-1 signaling pathway may regulate normal EC cell-cell or cell-matrix interactions during vascular development.

Tie-1 and Tie-2 (30) comprise a second family of receptor tyrosine kinases, other than the VEGF family, in which expression is nearly specific for ECs. Mice embryos that are deficient in Tie-1 fail to establish structural integrity of otherwise differentiated ECs (31); consequently, erythrocytes extravasate through the blood-vessel EC (but not between ECs), leading to death immediately after birth with widespread hemorrhage. Embryos that are homozygous mutant for Tie-2 die earlier (day 10.5 *in utero*), with dilated vessels lacking distinction between small and large vessels; absence of ordered branching has been inferred as evidence of disordered

angiogenesis. Vasculogenesis *per se* was not disrupted.

Successful disruption of the ligand for Tie-2, angiopoietin-1 (32,33), resulted in embryonic lethality by day 12.5, with defects similar to those seen in the Tie-2 receptor knockout. These included defects in organized branching, so that vessels remained dilated and almost syncytial. No change occurred in the total number of ECs, however.

The critical roles played by VEGF and its receptors in governing vasculogenesis and angiogenesis, and the Tie receptor/ligand family in maturation of the vascular network, have implications for the roles of these EC mitogens in promoting angiogenesis under circumstances of tissue ischemia in adults. In contrast to the lethal consequences of VEGF and Tie deficiencies, it is interesting to note that mice in which gene targeting has been used to disrupt the gene for basic fibroblast growth factor (bFGF) survive to maturity with no apparent phenotypic abnormalities of either the vascular or hematopoietic systems (G. Dorn and T. Deutschman, *personal communication*, 2001).

Remodeling

Remodeling in angiogenesis refers to the formation of a vascular lumen. Whereas multiple cell types, including ECs, grown *in vitro* on a collagen-matrix gel form cords, the presence of a lumen distinguishes vessels, or tubes, from solid cords. The presence of a lumen is clearly fundamental to the function of the circulatory system; however, the mechanisms that are responsible for tube formation are perhaps the least well understood aspect of angiogenesis (34). As Risau has pointed out, because isolated ECs may combine to form a lumen *in vitro* (35), lumen formation must represent an intrinsic feature or differentiation program of these cells (3). Mechanisms that have been discussed include the joining of polarized ends of capillary ECs in a ring-like fashion or, alternatively, simple deletion of a portion of the cell (vacuole formation) (36). Adding further to the complexity is the requirement to form qualitatively differing luminal and abluminal surfaces. Finally, it is inferred that remodeling comprises a coordinated process of lumen formation and vessel extension, with fusion of individual cells and their lumina via cell-cell adhesion molecules. The specific molecules that are responsible for vessel extension remain ambiguous. It is presumed that this aspect of vessel formation is subject to the regulatory factors that are responsible for vascular development in the embryo, as discussed above. In this respect, it is interesting to note that VEGF, for example, upregulates gap junction expression (specifically connexin 43) in ECs (37).

Nascent Vessels

Capillary growth rates (i.e., the velocity of neovascularization) range from 0.23 to 0.80 mm per day, depending on the experimental system used or the type of tumor, or both (38). The light microscopic features of newly formed vessels have been distinguished from those of native vessels (39). Whereas a histologic section of a capillary blood vessel in the normal brain reveals one or two ECs per lumen, in a brain tumor such as a glioblastoma, five to ten ECs may occupy one lumen. Tumor-induced vessels often appear dilated and saccular. Moreover, tumors may contain giant capillaries and arteriovenous shunts without intervening capillaries, so that blood may even flow from one venule to another.

Ultrastructural analysis of newly formed vessels has focused on features that are potentially responsible for augmented permeability. Dvorak et al. (40,41), for example, found that vascular leakage could not be attributed to passage of molecules through inter-EC junctions or injured tumor endothelium but instead involved transendothelial transport via a novel cytoplasmic organelle that they termed the *vesicular-vacuolar organelle*. Others (42) have reported VEGF-induced ultrastructural features that are consistent with endothelial fenestration.

Matrix-Integrin Interactions

Activated or proliferative ECs have been shown to express high levels of anb_3 (43,44). In nonhuman primates that were subjected to focal cerebral ischemia, for example, microvascular expression of anb_3 was noted in ischemic, but not nonischemic, tissues (45). Ligation of anb_3 on proliferating ECs promotes a critical adhesion-dependent cell survival signal, leading to inhibition of p53 activity, decreased expression of $p21^{WAF1/CIP1}$, and suppression of the bax cell death pathway (46). The intracellular molecular conflict that results from blocking anb_3 thus leads to unscheduled apoptosis and the abrogation of angiogenesis (44,46,47). Failure to ligate anb_3 may therefore inhibit the ability of actively cycling cells to ligate extracellular matrix proteins, including fibronectin, vitronectin, fibrinogen, and osteopontin, thereby influencing adhesion, migration, and, ultimately, survival of these cells (48).

Consistent with this notion, the integrin anb_3 has been shown to be required for angiogenesis *in vivo* (43), and antagonists of this integrin have been shown to inhibit angiogenesis by inducing apoptosis (44). Basic FGF, which has been shown to protect ECs from apoptosis (49), is known to modulate integrin expression by ECs (50,51 and 52). VEGF, by upregulation of the b_3 integrin and fibronectin, may similarly inhibit apoptosis by enhancing EC adhesion to matrix proteins (53). This notion is thus consistent with the concept that VEGF may exert a survival effect on ECs (43,44,54,55 and 56). These findings suggest that the net increase in EC viability after VEGF administration is not limited to the mitogenic effects of VEGF on ECs but is supplemented by the potential for VEGF to inhibit apoptosis.

Vasculogenesis in the Adult

Postnatal neovascularization was previously considered to result exclusively from the proliferation, migration, and remodeling of fully differentiated ECs derived from preexisting blood vessels, that is, angiogenesis (3,9,16). The formation of blood vessels from EC progenitors, or angioblasts (i.e., vasculogenesis), has been considered to be restricted to embryogenesis (5,57). However, the use of HSCs derived from peripheral blood in lieu of bone marrow to provide sustained hematopoietic recovery can be reasoned to constitute inferential evidence for circulating stem cells (58). Given the common ancestry of HSCs and angioblasts, the hypothesis that stem cells circulating in peripheral blood might under selected circumstances differentiate into ECs was investigated (59,60). Flk-1 and a second antigen, CD34, shared by angioblasts and HSCs (26,61,62,63,64,65,66,67,68,69,70 and 71), were used to isolate putative angioblasts from the leukocyte fraction of peripheral blood. *In vitro*, these cells differentiated into ECs (Fig. 106.3). In animal models of ischemia, heterologous, homologous, and autologous EC progenitors are incorporated into sites of active angiogenesis (Fig. 106.4). These findings thus suggest that circulating EC progenitors may contribute to neoangiogenesis in adult species, consistent with vasculogenesis.

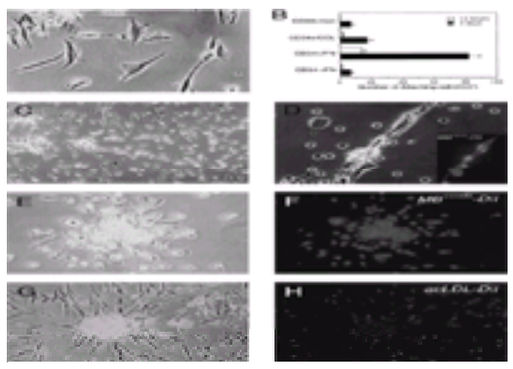


FIGURE 106.3 Attachment, cluster formation, and capillary network development by progenitor endothelial cells *in vitro*. **A:** Spindle-shaped attaching cells (AT^{CD34+}) 7 days after plating CD34+ mononuclear peripheral blood cells (MB^{CD34+}) (5 × 10 per mm^2) on fibronectin with standard medium. **B:** Number of AT^{CD34+} 12 hours and 3 days after single culture of MB^{CD34+} on plastic alone (CD34+/non), collagen coating (CD34+/COL), or fibronectin (CD34+/FN) and MB^{CD34-} on fibronectin (CD34–/FN). AT^{CD34+} yielded a significantly higher number of cells at 12 hours and 3 days when plated on fibronectin. Network formation **(C)** and cord-like structures **(D)** were observed 48 hours after plating coculture of MB^{CD34+}, labeled with DiI fluorescent dye, and unlabeled MB^{CD34-} (ratio of 1:100) on fibronectin-coated dish. These cords consisted principally of DiI-labeled MB^{CD34+}-derived cells (AT^{CD34+}). Beginning 12 hours after coculture, MB^{CD34+}-derived cells demonstrated multiple foci of cluster formation **(E,F)**. AT^{CD34+} sprout from the periphery, whereas round cells remain in the center and detach from the cluster several days later. After 5 days, uptake of DiI-labeled acLDL was seen in AT^{CD34+} at the periphery but not the center of the cluster **(G,H)**. (From Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997;275:964–967, with permission.)

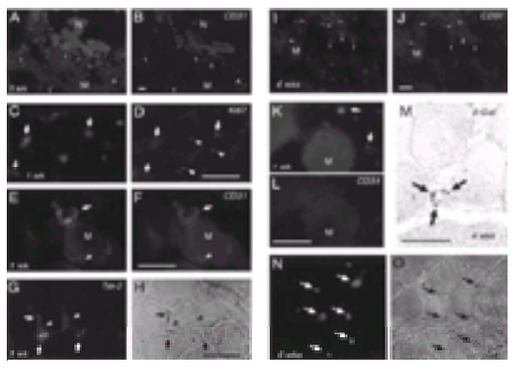


FIGURE 106.4 Heterologous **(A–L)**, homologous **(M)**, or autologous **(N and O)** endothelial cell (EC) progenitors incorporate into sites of angiogenesis *in vivo*. **A,B:** CD34+ mononuclear peripheral blood cells (MB^{CD34+}; *arrows*), labeled with the fluorescent dye DiI, between skeletal myocytes **(M)**, including necrotic **(N)** myocytes 1 week after injection; most are colabeled with CD31 (*arrows*). Note preexisting artery (a), identified as CD31 positive but DiI negative. **C,D:** Evidence of proliferative activity among several DiI-labeled MB^{CD34+}-derived cells (*arrows*), indicated by coimmunostaining for Ki^{67} antibody. Proliferative activity is also seen among DiI-negative, Ki^{67}-positive capillary ECs (*arrowheads*); both cell types comprise neovasculature. **E:** DiI and CD31 in capillary ECs (*arrows*) between skeletal myocytes, photographed through double filter 1 week after DiI-labeled MB^{CD34+} injection. **F:** Single green filter shows CD31 expression in DiI-labeled capillary ECs, integrated into capillary with native (DiI-negative, CD31-positive) ECs (*arrowheads*). **G:** Immunostaining 1 week after MB^{CD34+} injection showing capillaries comprised of DiI-labeled MB^{CD34+}-derived cells expressing Tie-2 receptor. Several MB^{CD34+}-derived cells (*arrows*) are Tie-2 positive and are integrated with some Tie-2–positive host capillary cells (*arrowheads*) identified by the absence of red fluorescence. **H:** Phase-contrast photomicrograph of same tissue section shown in **G** indicates corresponding DiI-labeled (*arrows*) and -unlabeled (*arrowheads*) capillary ECs. **I,J:** Six weeks after administration, MB^{CD34+}-derived cells colabel for CD31 in capillaries between preserved skeletal myocytes. **K,L:** One week after injection of MB^{CD34-}, isolated MB^{CD34-} derived cells (*arrows*) are observed between myocytes but do not express CD31. **M:** Immunostaining of b-galactosidase (b-gal) in tissue section harvested from ischemic muscle of B6,129 mice 4 weeks after administration of MB^{Flk-1+} isolated from transgenic mice constitutively expressing b-gal. (Flk-1 cell isolation was used for selection of EC progenitors due to lack of a suitable antimouse CD34 antibody.) Cells overexpressing b-gal (*arrows*) have been incorporated into capillaries and small arteries; these cells were identified as ECs by anti-CD31 and anti-BS-1 lectin. **N,O:** Sections of muscles harvested from rabbit ischemic hindlimb 4 weeks after administration of autologous MB^{CD34+}. Red fluorescence indicates localization of MB^{CD34+}-derived cells in capillaries, seen (*arrows*) in phase-contrast photomicrograph **(O)**. Each scale bar indicates 50 mm. (From Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997;275:964–967, with permission.)

Parenthetically, these findings may have implications for augmenting collateral vessel growth to ischemic tissues (see Therapeutic Angiogenesis) and for delivery of anti- or proangiogenic agents, respectively, to sites of pathologic or utilitarian angiogenesis. A potentially limiting factor in strategies designed to promote neovascularization of ischemic tissues (72) is the resident population of ECs that is competent to respond to administered angiogenic cytokines (73). This issue can be successfully addressed with autologous EC transplants (74,75 and 76) (Fig. 106.5). The fact that progenitor ECs are home to foci of angiogenesis suggests potential utility as autologous vectors for gene therapy. For antineoplastic therapies, CD34+ mononuclear peripheral blood cells (MB^{CD34+}) could be transfected with or coupled to antitumor drugs or angiogenesis inhibitors. For treatment of regional ischemia, angiogenesis could be amplified by transfection of MB^{CD34+} to achieve constitutive expression of angiogenic cytokines or provisional matrix proteins, or both (77).

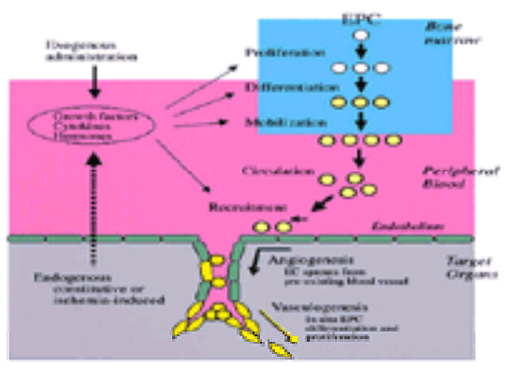


FIGURE 106.5 Neovascularization encompasses angiogenesis and vasculogenesis. Angiogenesis represents the classic paradigm for new vessel growth, as mature, differentiated endothelial cells (ECs) break free from their basement membrane and migrate as well as proliferate to form sprouts from parental vessels. Vasculogenesis involves participation of bone marrow–derived endothelial progenitor cells (EPCs), which circulate to sites of neovascularization, where they differentiate *in situ* into mature ECs. Growth factors, cytokines, or hormones released endogenously in response to tissue ischemia, or administered exogenously for therapeutic neovascularization, act to promote EPC proliferation, differentiation, and mobilization from bone marrow, via the peripheral circulation, to neovascular foci.

Angiogenesis within Blood Vessels: the Special Case of the Vasa Vasorum

The vasa vasorum consist of blood vessels that vary in size from vessels with single or multiple SMC layers to simple endothelial channels (78). In all but large or atherosclerotic vessels, the vasa vasorum are confined essentially to the adventitia of the blood vessel wall (79). This microcirculatory system presumably exists for the purpose of nourishing large and medium-sized blood vessels, including the aorta and epicardial coronary arteries. The vasa vasorum constitute a reservoir for postnatal angiogenesis that has been studied for its potential contribution to the growth and development of neointimal thickening.

Examination of human atherosclerotic specimens obtained by directional atherectomy (80,81 and 82) or at necropsy (83), together with studies performed in a variety of animal models (84,85,86 and 87), has clearly documented that extension of the vasa vasorum typically accompanies plaque growth and by inference “nourishes” the developing vascular lesion (Fig. 106.6). The ultimate extension of this principle is evidence suggesting that balloon injury to the arterial wall stimulates proliferation of vasa vasorum in conjunction with intimal thickening (88).

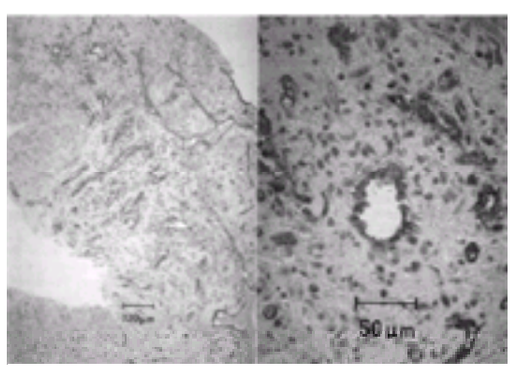


FIGURE 106.6 Identification of vasa vasorum in low-power (*left*) and higher-power (*right*) photomicrographs of atherosclerotic specimen obtained by directional atherectomy. Yellow-brown reaction product of Ulex immunostain identifies the endothelium of the vasa vasorum.

Experiments performed by Shweiki et al. (89) have identified hypoxia and glucose deprivation as the elements that are responsible for stimulating microangiogenesis in underperfused tissues. As indicated previously, EC mitogens, including VEGF (89), bFGF (90,91 and 92), and acidic fibroblast growth factor (aFGF) (93), have been

implicated in mediating such neovascularization. In the case of aFGF, Nabel et al. (94) have reported that arterial gene transfer of complementary DNA encoding aFGF to the arterial wall may result in neointimal microangiogenesis. It is thus intriguing to consider the developing primary or restenotic lesion as relatively underperfused and, as is the model for tumor development (95), dependent for continued growth on triggering augmented vascularization. Given the established association between diabetes and restenosis, it is further intriguing to consider that neointimal or medial cells, or both, that are relatively deprived of intracellular glucose and capable of elaborating angiogenic cytokines may facilitate combinatorial growth of vessel and plaque.

These findings have begun to undergo reevaluation for possible implications that they may have in designing novel treatment strategies for atherosclerosis and restenosis. Conceptually, this is not unrealistic. More than two decades of research aimed at elucidating the role of angiogenesis in tumor growth and metastases have led to the identification of several classes of agents that are capable of interfering with angiogenesis (95). From the standpoint of drug delivery, even if the agent were not preferentially targeted to the neovessels of the plaque or wall, or both, a variety of interventional devices (96) are now clinically available to execute local delivery to selected segments of the human vasculature.

With regard to primary atherosclerosis, there are at least two potential applications to consider. The first is restriction, including inhibition as well as regression, of plaque mass. As primary prevention, an inhibitory strategy targeted specifically at the vasa vasorum assumes that retardation of microangiogenesis secondarily inhibits plaque growth. Although it is true that wall (including plaque) thickness is a critical determinant of growth of the vasa (97), the extent of microvascular perfusion that is required to permit continued plaque expansion is uncertain. In the case of tumor growth, angiogenesis is regarded as “necessary but not sufficient” (95); in the case of plaque, whether angiogenesis is even necessary remains to be shown.

As secondary prevention, the ability to reduce established plaque mass medically represents the holy grail of preventive cardiology. It is encouraging to note that work performed by Brooks et al. (44) has demonstrated that antibodies targeted to adhesion integrins expressed by activated ECs can cause EC apoptosis, regression of tumor vasculature, and associated reduction in tumor mass. It is similarly provocative to note that studies performed in primates have documented a reduction in vasa vasorum *pari passu* with regression of atherosclerotic plaque (97). Whether any significant reduction in plaque mass could be achieved consequent to antiangiogenic therapy, however, remains to be demonstrated.

Acute stabilization of the so-called vulnerable lesion (98) constitutes a second potential application of therapies targeted at the vasa vasorum. Rupture of the vasa vasorum has been previously proposed (99) as the basis for plaque rupture and hemorrhage, the pathologic substrate that is considered to underlie most cases of acute myocardial infarction. Whether because of the lack of an animal model of plaque rupture or the complexities of establishing with certainty specific microvessels as the source of specific sites of intraplaque hemorrhage identified at necropsy, this proposed relationship remains currently intuitive. Nevertheless, given the limited options that are available for passivating destabilized lesions in patients with preinfarction angina, the logic of choking the putative microvascular source of intraplaque instability is appealing.

Studies of the vasa vasorum of the arterial wall also have therapeutic implications for local drug delivery *per se*. The network of transmural neovasculature may well be responsible for transport of agents from the intimal site of local delivery to the neointimal, medial, and adventitial layers of the arterial wall (96).

Although the catalogue of existing observations thus supports a number of logical strategies for targeting the vasa vasorum to develop novel therapeutic paradigms, the complexity of these proposals should not be underestimated. First, timing—when to initiate and how long to treat—is a difficult issue generic to any preventive therapy. More problematic, however, are certain inherent paradoxes that are peculiar to vasa vasorum and their presumed growth stimulus. For example, previous studies have demonstrated that adventitial injury may stimulate neointimal thickening; intimal ischemia resulting from injury to the vasa vasorum has been implicated in the development of such lesions. Similar consequences have been reported after thrombosis of the vasa (100). These observations suggest that interfering with the blood supply to the neointima to stabilize a vulnerable lesion or prevent further intimal thickening, or both, may constitute a “catch 22.” Moreover, experimental applications of bFGF (101), aFGF (102), and VEGF (103) to the injured arterial wall have all been shown to expedite reendothelialization and thus reduce intimal thickening; in the case of VEGF, no evidence of plaque neovascularity was observed (103). These findings are noteworthy, given the results of animal studies in which angiogenesis inhibitors have been shown to promote modest degrees of atherosclerosis in the ascending aorta in apoprotein $E^{-/-}$ mice (104). The consequences of exposure to an EC mitogen are thus likely to vary depending on the duration of cytokine expression and the circumstances of arterial wall pathology. Again, the “necessary but not sufficient” analogy to the tumor paradigm appears to apply to plaque angiogenesis as well.

ANGIOGENIC CYTOKINES

Beginning a little over a decade ago (105), a series of polypeptide growth factors (Table 106.1) was purified, sequenced, and demonstrated to be responsible for natural as well as pathologic angiogenesis. These angiogenic cytokines all share in common the ability to act as mitogens for ECs.

Cytokine	Protein	Gene Ph	Gene Ad	EC specific	Pleiotropic	Secretory sequence
$VEGF_{165}$	✓	✓		✓		✓
$VEGF_{121}$			✓	✓		✓
VEGF-2 (VEGF-C)		✓		✓		✓
HIF-1a			✓			
FGF-1 (aFGF)	✓				✓	
FGF-1 modified		✓			✓	✓
FGF-2 (bFGF)	✓				✓	
FGF-4			✓		✓	✓

a, acidic; Ad, adenoviral vector; b, basic; EC, endothelial cell; FGF, fibroblast growth factor; HIF, hypoxia inducible factor; Ph, plasmid human; VEGF, vascular endothelial growth factor.

TABLE 106.1 ANGIOGENIC CYTOKINES AND GENES USED IN CLINICAL ANGIOGENESIS TRIALS

Among the various growth factors that have been shown to promote angiogenesis, VEGF (106), also known as *vascular permeability factor* (107) and *vasculotropin* (108), is an EC-specific mitogen. Moreover, a plethora of studies have documented upregulation of VEGF in various cell types after exposure to other angiogenic cytokines. VEGF can thus be considered a prototypical angiogenic cytokine and for this reason is discussed here in further detail. Specific aspects of the remaining angiogenic cytokines in Table 106.1 can be found in the accompanying lists of citations.

At least five VEGF genes have now been identified: VEGF-1 (or VEGF-A), VEGF-2 (or VEGF-C), VEGF-3 (or VEGF-B), VEGF-D, and VEGF-E. In turn, four homodimeric species of VEGF-1 have been identified, with each monomer having 121, 165, 189, or 206 amino acids, respectively (109). The secretion pattern of the four isoforms differs markedly. $VEGF_{121}$ is a weakly acidic polypeptide that does not bind to heparin and is freely soluble in the conditioned medium of transfected cells. The heparin-binding capabilities of the remaining three isoforms are progressively augmented as the result of a stepwise enrichment in basic residues. Thus, $VEGF_{165}$, the predominant form secreted by a variety of normal and transformed cells (40), is a basic heparin-binding glycoprotein with an isoelectric point of 8.5; while secreted, a significant portion remains bound to the cell surface or extracellular matrix. The $VEGF_{189}$ isoform includes 24 additional amino acids and has been shown not to be freely secreted but instead remains nearly completely bound to the cell surface or extracellular matrix, or both (110). $VEGF_{206}$ is a rare isoform that has so far been identified only in a human fetal liver complementary DNA library.

The teleologic basis for the 121, 165, and 189 isoforms that result from alternative splicing of the VEGF-1 transcript has remained enigmatic. It has been proposed (111) that the heparin-binding feature of angiogenic growth factors such as VEGF may explain in part their protracted efficacy due to binding of the growth factor by heparan sulfate proteoglycans present on the luminal surface of the vascular endothelium or within the extracellular matrix, or both. Although $VEGF_{121}$ lacks heparin-binding ability, all three isoforms bind to the Flk-1 receptor, which transduces the mitogenic signal (112), including $VEGF_{121}$, which binds exclusively to Flk-1 (113). Plate et al. (114) speculated that the three principal isoforms might mediate distinct EC functions. We considered that angiogenesis induced by VEGF may be differentially dependent on the extent to which each particular isoform used is freely secreted and soluble. The magnitude of freely secreted $VEGF_{121}$ isoform that reaches the ischemic focus from the site of synthesis, for example, might be superior to that achieved with the $VEGF_{165}$ isoform; alternatively, avid binding of the $VEGF_{189}$ isoform to the basement membrane or extracellular matrix, or both (115), might result in more protracted bioavailability and thereby yield an outcome superior to that of $VEGF_{165}$.

Because it has proved difficult to express affinity-purified recombinant $VEGF_{189}$ protein from mammalian and bacterial systems, we investigated the possibility of

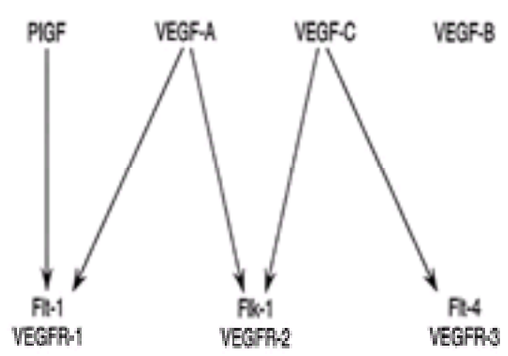
hierarchical efficacy among these three isoforms by performing arterial gene transfer of plasmid human (ph) $VEGF_{121}$, $phVEGF_{165}$, and $phVEGF_{189}$ in the rabbit ischemic hindlimb model (116). Remarkably, no differences with regard to anatomic or physiologic evidence of angiogenesis could be demonstrated, although all three isoforms yielded statistically significant improvement in every parameter measured compared to the LacZ controls. Moreover, separate experiments performed using 100, 200, and 400 µg of each plasmid failed to disclose a differential dose-response curve among the three isoforms with respect to angiographic score, calf blood pressure ratio, resting/maximum flow, or capillary-myocyte ratio (Y. Tsurumi, *unpublished data*, 2001).

These findings suggested biologic equivalency among the three principal VEGF-1 isoforms for *in vivo* angiogenesis in adult species and can be interpreted to support the observation made previously by Houck et al. (110) regarding the proteolytically clipped VEGF-1 species that result from the action of plasmin on the 165 and 189 isoforms. The size of the resulting monomers, which in each case are mitogenic for ECs and enhance vascular permeability in a Miles assay (117), is similar to the size of the intact 121 isoform. It is therefore possible that the proteolytic cascade of plasminogen activation, a key step during angiogenesis (14), cleaves the longer forms of VEGF-1, releasing a soluble $VEGF_{121}$-like species that is the final common mediator of angiogenesis *in vivo*. Although future experiments using conditional knockout genetically engineered mice will clarify the issue of isoform-dependent function, there is evidence that, at least during embryonic development, deletion of the 165 and 189 isoforms—but not the 121 isoform—results in ischemic cardiomyopathy (118).

Although the three principal VEGF-1 isoforms differ markedly with regard to heparin avidity, all include the secretory signal sequence. This contrasts with other angiogenic cytokines such as aFGF and bFGF, which lack such a signal peptide and thus are not typically secreted from intact cells. This feature has been critical to the use of naked DNA for gene therapy (116,119).

VEGF-2 or VEGF-C (120) and VEGF-3 or VEGF-B have been shown to be particularly abundant in heart and skeletal muscle (121). VEGF-C has now been demonstrated to promote angiogenesis *in vivo*, in experimental animal models (122,123), and in human subjects with ischemic heart disease (124). VEGF-C also promotes lymphangiogenesis. In contrast to the widespread distribution of these VEGFs, placenta growth factor (PlGF) (125), another VEGF family member, appears to be restricted *in vivo* to placenta and certain tumors (126,127). All four proteins share structural homology among themselves as well as with the platelet-derived growth factor A and B polypeptides (PDGF-A and -B), in particular a conserved motif, including eight cysteine residues in the putative receptor-binding domain (115). Similar to the A and B chains of PDGF, VEGF-1/VEGF-A and PlGF can form heterodimers with biologic activity (128,129 and 130). VEGF-3/VEGF-B is also able to heterodimerize with VEGF-1/VEGF-A in cells that express both factors (121). Although not shown thus far, it seems reasonable to assume that VEGF-2/VEGF-C, by virtue of its shared homology to the other members of the VEGF family, can form heterodimers in a similar manner, therefore adding another level of complexity to processes that are related to angiogenesis.

Whereas VEGF-1/VEGF-A is a high-affinity ligand for the receptors Flt-1 and KDR/Flk-1, VEGF-2/VEGF-C was shown to bind to another endothelial-specific receptor tyrosine kinase, Flt-4, as well as to Flk-1/KDR, but not to Flt-1 (120,131) (*e*Fig. 106.6.1). PlGF was shown to bind with high affinity to Flt-1, but not to Flk-1/KDR (129) or Flt-4 (132). The receptor(s) for VEGF-3/VEGF-B (121) have not yet been characterized. The constitutive coexpression of multiple VEGF types in many adult tissues (120,121,133) suggests an interactive or at least redundant capacity of the VEGF members to regulate angiogenesis and modulate EC function.



***e*FIGURE 106.6.1** Ligand-receptor relationships for placental growth factor (PlGF) and proteins encoded for by the three vascular endothelial growth factor (VEGF) genes (alternative receptor nomenclature is shown directly above). (From Carmeliet P, Collen D. Molecular analysis of blood vessel formation and disease. *Am J Physiol* 1997;273:H2091–H2104, with permission.)

Autocrine Loop as a Feature of Angiogenic Cytokines

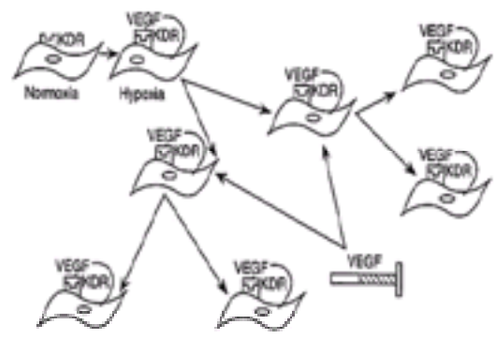
Certain angiogenic cytokines, notably aFGF and bFGF, lack a secretory signal sequence (134,135). This prompted previous investigators to study the possibility that these cytokines act via an alternative pathway. Several groups established evidence to support the notion that aFGF and bFGF can indeed modulate EC behavior via an autocrine pathway (136,137,138 and 139).

Evidence for a similar autocrine pathway in the case of VEGF was established by Namiki et al. (140). Under quiescent conditions, VEGF messenger ribonucleic acid (mRNA) was not detected in either human umbilical vein endothelial cells (HUVECs) or human microvascular ECs. In contrast, hypoxia provoked VEGF expression in HUVECs and human microvascular ECs. The response of human ECs to hypoxia was not limited to expression of VEGF mRNA but involved production of VEGF protein as well. Immunoreactive VEGF was distributed abundantly in the cytosol of hypoxic ECs. Because the VEGF antibody used recognizes all alternatively spliced VEGF isoforms (141,142), the specific VEGF species produced by HUVECs in response to hypoxia remain uncertain. The fact that media conditioned by hypoxic HUVECs augmented uptake of tritiated thymidine, however, implies a freely or relatively freely secreted (121 or 165) VEGF isoform.

Previous studies have indicated a variable requirement for new protein synthesis before hypoxic induction of erythropoietin and VEGF mRNA (143,144,145 and 146). We observed that cycloheximide pretreatment augmented VEGF expression induced by hypoxia as well as Co^{2+}, suggesting that a factor induced by hypoxia may modulate stability of VEGF mRNA, in part by inhibition of translation of ribonucleases responsible for degradation of mRNA. Similar regulatory influences have been previously demonstrated for other growth factors (147) and oncoproteins (148).

These findings thus establish that macrovascular and microvascular ECs, under hypoxic conditions, are capable of expressing VEGF mRNA and protein. Furthermore, thymidine incorporation was increased in ECs after application of media conditioned by hypoxic HUVECs, indicating that the magnitude of protein secreted is sufficient to drive mitogenesis. Because ECs also express the high-affinity VEGF receptors, Flt-1 and KDR, these cells in humans appear to include the requisite elements for an autocrine pathway. The finding that hypoxia induces activation of KDR in HUVECs is consistent with an external autocrine pathway (149), given that all VEGF isoforms include a secretory signal sequence.

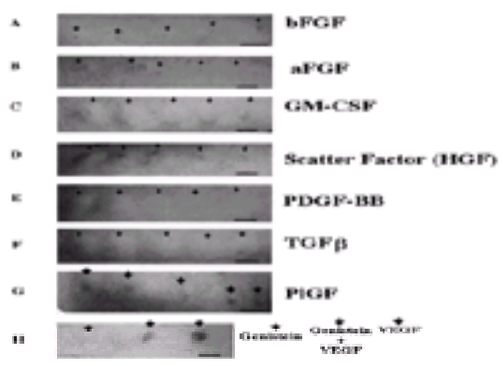
The extent to which such an autocrine pathway may complement endogenous production of VEGF from SMCs, macrophages, and tumor cells or facilitate the response to exogenous administration of VEGF remains to be determined. With regard to the latter, it has been recognized that single-bolus administration of VEGF may stimulate development of new collateral vessels over a period of several days, despite the fact that the circulating half-life of VEGF is less than 3 minutes. One explanation for this observation is that, as VEGF is rapidly cleared from the circulation, it binds avidly to heparan sulfate proteoglycans that are present on the luminal surface of the vascular endothelium. Experimental evidence to support this concept in the case of bFGF has been reported by Fuks et al. (49). Alternatively, an autocrine loop, activated under hypoxic conditions that are known to stimulate angiogenesis, might also serve to amplify and thereby protract the response in ECs stimulated by exogenously administered VEGF (*e*Fig. 106.6.2). Such autocrine amplification may in fact represent a common motif shared by angiogenic cytokines in general.



***e*FIGURE 106.6.2** Under conditions of hypoxia, endothelial cells upregulate vascular endothelial growth factor (VEGF), which, once secreted, may then interact with its receptor. Such an autocrine loop provides the basis for amplification of any given VEGF secreted or administered into an ischemic territory. Endothelial cells stimulated to proliferate in response to VEGF may then serve as additional sources of VEGF synthesis, thus amplifying the effect of the initial dose of VEGF.

Angiogenic Cytokines and Vascular Permeability

Vascular permeability often precedes and/or accompanies angiogenesis, particularly tumor-associated angiogenesis (40,77,150,151). As suggested by the designation *vascular permeability factor* (107), VEGF increases vascular permeability when assessed by the Miles assay (*e*Fig. 106.6.3). Angiogenic cytokines other than VEGF, including bFGF, aFGF, scatter factor (hepatocyte growth factor), granulocyte-macrophage colony-stimulating factor, transforming growth factor-b (TGF-b), PlGF, and PDGF-BB all fail to increase permeability in the Miles assay (117) (*e*Fig. 106.6.3).



***e*FIGURE 106.6.3 A–G:** Angiogenic cytokines other than vascular endothelial growth factor (VEGF)/vascular permeability factor failed to increase vascular permeability. aFGF, acidic fibroblast growth factor; bFGF, basic fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor/scatter factor; PDGF-BB, platelet-derived growth factor-BB; PlGF, placenta growth factor (all 8, 16, 32, 64, and 128 ng in 0.1 mL saline); TGF-b, transforming growth factor-b. **H:** VEGF/vascular permeability factor (128 ng)–induced vascular permeability was reduced by previous intradermal injection of the tyrosine kinase inhibitor genistein (100 mM). Scale bar = 10 mm.

These findings have several possible interpretations. First, most of these angiogenic cytokines have been shown to increase VEGF expression (152,153,154,155,156 and 157). The failure of other angiogenic cytokines to result in a positive Miles assay might then be interpreted to indicate not that angiogenesis and permeability are disassociated but that other angiogenic cytokines stimulate permeability indirectly via VEGF. Because this depends on protein synthesis, however, the required time course (hours) is insufficient to explain the acute (minutes) response that is characteristic of the Miles assay. Second, VEGF, identified initially as a tumor-secreted protein (158), has been more tightly linked with tumor angiogenesis than other angiogenic cytokines (2). Perhaps, then, increased vascular permeability is more particularly a function of tumor-associated angiogenesis. Third, increased vascular permeability may not in fact be a common feature of angiogenesis that is mediated by growth factors but rather may be most specifically associated with VEGF-induced angiogenesis.

The mechanism of action by which VEGF augments permeability has remained enigmatic. NO has been previously implicated as a factor in regulating vascular permeability (159,160 and 161). Nguyen et al. (160) demonstrated that substance P, a potent endothelium-dependent vasodilator, increases microvascular permeability via NO-dependent pathways. More recent findings suggest that NO-mediated alteration of vascular permeability may depend on its local concentration (161).

Prostaglandins have similarly been suggested to regulate angiogenesis and vascular permeability (162,163). Yamamoto's group (162) reported that a stable prostacyclin analog, SM-10902, accelerated wound healing in a murine model of diabetic skin ulcers. Fujii et al. (163) have demonstrated that lipopolysaccharide-induced vascular permeability is significantly attenuated by either an NO synthase inhibitor or indomethacin. These results collectively support the notion that prostaglandins that are produced from arachidonic acid via cyclooxygenase can regulate vascular permeability.

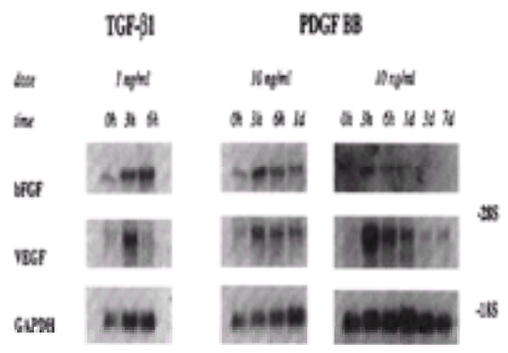
The author's group used the Miles assay to study the putative mediators of VEGF-induced permeability. VEGF (8 to 128 ng) and positive controls (platelet-activating factor and bradykinin) increased vascular permeability. Prior administration of the tyrosine kinase inhibitor, genistein, prevented VEGF-induced permeability. PlGF, which binds to Flt-1/VEGF-R1 but not Flk-1/KDR/VEGF-R2 receptor tyrosine kinase, failed to increase permeability. VEGF-induced permeability was significantly attenuated by the NO synthase inhibitors N^{w}-nitro-L-arginine (10 mg per kg) or N^{w}-nitro-L-arginine methyl ester (20 mg per kg) or the cyclooxygenase inhibitor indomethacin (5 mg per kg). *In vitro* studies confirmed that VEGF stimulates synthesis of NO (164) and prostaglandin metabolites in microvascular ECs. NO donors and the prostacyclin analog taprostene administered together, but not alone, reproduced the increase in permeability that was observed with VEGF. These results implicate NO and prostaglandin(s) produced via the interaction of VEGF with its Flk-1/KDR/VEGF-R2 receptor as mediators of VEGF-induced vascular permeability. Moreover, this property appears unique to VEGF among angiogenic cytokines. Given the conceptual link between permeability and angiogenesis, these findings can be interpreted to suggest a role for NO in VEGF-induced angiogenesis.

Direct versus Indirect Cytokines

Certain stimuli that are capable of inducing the development of neovessels *in vivo*, specifically certain cytokines (165,166,167 and 168) and hypoxia, fail to stimulate EC proliferation *in vitro*, suggesting a role for additional mediators or cell types, or both. The author's group considered whether these so-called indirect angiogenic growth factors might stimulate vascular SMCs to express genes that encode direct EC mitogens. Such a sequential cascade would provide a mechanism by which growth factors that are otherwise nonmitogenic or frankly inhibitory for EC proliferation *in vitro* could instead stimulate angiogenesis *in vivo*.

Although PDGF-BB, for example, can directly stimulate proliferation of selected populations of microvascular ECs *in vitro* (169,170 and 171), ECs from most vascular districts do not respond to treatment with PDGF-BB (172). Nonetheless, *in vivo* PDGF-BB has been clearly demonstrated to induce supportive angiogenesis in a wound-healing model (167) and chorioallantoic membrane assay (168). Furthermore, microvascular ECs that are isolated from rat epididymal fat pads and not directly responsive to PDGF-BB stimulation, when cocultured with myofibroblasts from the same tissue source, form capillary chords in the presence of PDGF-BB (166). The angiogenic action of PDGF-BB documented in this way was attributed to production of soluble EC mitogen(s) by myofibroblasts in response to stimulation with PDGF-BB.

PDGF-BB treatment of human vascular SMCs was demonstrated to induce VEGF and bFGF mRNA species concurrently (152) (*e*Fig. 106.6.4). This finding indicates that PDGF-BB, a known mitogen for SMCs, could also stimulate SMCs to produce direct angiogenic factors and thereby promote angiogenesis.



***e*FIGURE 106.6.4** Transforming growth factor-b1 (TGF-b1) and platelet-derived growth factor-BB (PDGF-BB) induce vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) gene expression in vascular smooth muscle cells (SMCs). Northern analysis of SMCs treated with TGF-b1 (0.1 or 1 ng per mL) or PDGF-BB (10 ng per mL) in serum-free medium to detect VEGF (3.7- and 4.2-kb bands) and bFGF (7.0-kb band) mRNA. Unstimulated SMCs contained low basal levels of VEGF or bFGF mRNA species. Levels of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA demonstrate similar loading of lanes. TGF-b1 stimulation of SMCs induced VEGF and bFGF mRNA. Accumulation of VEGF transcripts is evident at 3 hours and increase of bFGF mRNA at 8 hours of treatment. The dose of 1 ng per mL was the most effective for inducing VEGF and bFGF gene expression. PDGF-BB stimulation induced VEGF and bFGF mRNA species, with simultaneous peak at 3 hours. VEGF mRNA transcripts are still evident at 7 days of treatment. (From Brogi E, Wu T, Namiki A, et al. Indirect angiogenic cytokines upregulate VEGF and bFGF expression in vascular smooth muscle cells, while hypoxia upregulates VEGF expression only. *Circulation* 1994;90:649–652, with permission.)

Likewise, the plurality of mechanisms that contribute to the angiogenic activity of TGF-b1 (173) has been the subject of controversy. Although clearly inhibiting growth and migration of subconfluent ECs *in vitro* (174), TGF-b1 facilitates capillary formation *in vivo* (173). Furthermore, TGF-b1 modulates the composition of the extracellular matrix (175) and may therefore act in part by locally creating a proangiogenic environment. Although TGF-b1 directly inhibits EC proliferation (174), it may nevertheless direct organization of ECs into tube-like structures, depending on the conditions of culture tested (176). TGF-b1 in high concentrations was found to inhibit the formation of capillary-like structures in an *in vitro* model of angiogenesis, whereas low doses were observed to potentiate VEGF- or bFGF-induced neovessel formation in the same assay system (174). This phenomenon was interpreted by Pepper et al. (174) as an example of “contextual” angiogenesis to indicate that the angiogenic response to a given cytokine is dependent on the presence and concentration of other mediators in the pericellular environment of the target ECs. Winkles et al. (177) have also observed that TGF-b1 stimulates bFGF expression by SMCs, thus supporting the notion that direct angiogenic mediators might contribute in part to TGF-b1–induced angiogenesis. The finding (152) that TGF-b1 stimulation induces VEGF as well as bFGF gene expression, in concert with the above-described mechanisms, suggests that both EC mitogens are likely instrumental for mediating the indirect angiogenic effects of TGF-b1 *in vivo*. More recently, the notion of indirect angiogenic growth factors has been shown to extend to morphogens, such as sonic hedgehog, inducing angiogenesis via upregulated expression of VEGF as well as angiopoietin and possibly scatter factor from fibroblasts (178).

Subsequently, this same motif has been demonstrated for insulin-like growth factor (157), bFGF (153), and scatter factor (hepatocyte growth factor) (156). bFGF and scatter factor, however, are further distinguished by the fact that they exert a direct effect on EC proliferation and migration, in addition to upregulating VEGF synthesis in vascular SMCs.

In the context of factors that upregulate VEGF expression, it is important to emphasize the critical role played by hypoxia, because this explains at least in part the clinical observation that tissue ischemia is a fundamental stimulus for angiogenesis. Increased expression of VEGF has been documented at the periphery of necrotic foci of certain neoplasms, as well as hypoxia-stimulated induction of VEGF in cultured cells from glial tumor and rat skeletal muscle (144). Low oxygen tension has been shown to selectively modulate VEGF but not bFGF in vascular SMCs (152). This observation is intriguing in light of homology between a sequence in the VEGF promoter (109) and a nucleotide sequence in the erythropoietin promoter identified as a binding site for a hypoxia-specific transcription factor (179). It is now clear that, although transcriptional as well as posttranslational (146,180,181 and 182) upregulation of VEGF occurs in response to hypoxia and is mediated via hypoxia-specific growth factor-1 (183), VEGF expression may be upregulated by non–hypoxia-inducing mechanisms (184,185) as well.

Synergism of Angiogenic Cytokines

Studies from several groups have disclosed evidence for a synergistic effect of growth factors on angiogenesis *in vitro*. Pepper et al. (174) demonstrated that, whereas EC migration and capillary lumen formation were inhibited by TGF-b1 alone, a lower concentration of TGF-b1 potentiated the effect of bFGF- and VEGF-induced migration. Furthermore, these same authors (186) showed that adding VEGF or bFGF to microvascular ECs grown on the surface of three-dimensional collagen gels induced the cells to invade the underlying matrix and form capillary-like tubules. When these same two mitogens were added simultaneously, however, they induced an angiogenic response that was far greater than additive and occurred with greater rapidity than the response to either cytokine alone. Goto et al. (187) measured the combined effect of VEGF and bFGF on the proliferative and morphologic changes exhibited by bovine capillary ECs cultured in a gel of type I collagen; when the two factors were added simultaneously, the number of cells and the number of cord-like structures were greater than the sum of those that were stimulated with either growth factor alone. Results of *in vivo* studies performed in the author’s laboratory (188) are in agreement with these previous *in vitro* experiments. Necropsy examination documented an increase in vascularity at the capillary level, consistent with the classic definition of angiogenesis that was formulated by Klagsbrun and Folkman (189). Moreover, the angiographic luminal diameter of the stem artery was significantly greater in the group treated with VEGF + bFGF than VEGF or bFGF alone.

The potential therapeutic benefit of stimulating formation of larger, more “mature” collaterals is suggested by the physiologic evidence of increased downstream perfusion that was documented on serial measurements of the lower limb blood pressure ratio. The dramatic increase in blood pressure ratio in rabbits treated with VEGF + bFGF between day 0 and day 10 compared with that seen after administration of either growth factor alone is likely to be a consequence of better arterial reconstitution in the combined therapy group. This conclusion is further supported by findings in the author’s laboratory in which the combination of VEGF and bFGF was found to have a synergistic effect on maximum flow reserve in this same animal model, compared to bFGF or VEGF alone (C. Bauters, *unpublished observations*, 2001).

The fundamental basis for the synergistic effect of VEGF and bFGF *in vivo* remains to be elucidated. Although VEGF is EC specific, bFGF is also a potent mitogen for a variety of other cell types, including SMCs. Direct stimulation of SMCs by bFGF might be responsible for certain of the *in vivo* effects that have been observed, such as the increase in the angiographic luminal diameter of the stem artery.

Conversely, the increase in capillary density and capillary-muscle fiber ratio in the ischemic muscles is more likely to be a consequence of a synergistic effect on ECs similar to that observed in the previously cited *in vitro* experiments. It is important in this regard to underscore the independent receptor systems that are responsible for signaling the mitogenic effects of VEGF and bFGF in ECs (67,190,191). Thus, amplification of the endothelial response to these mitogens is feasible based on their independent receptor systems alone.

Park et al. (129) proposed another possible basis for synergism among angiogenic growth factors. They demonstrated that the 152–amino acid isoform of PlGF potentiates the action of low, marginally efficacious concentrations of VEGF on EC growth *in vitro* and *in vivo* potentiates Evans blue dye extravasation observed in a Miles assay. Although PlGF binds with high affinity to Flt-1, it does not bind to the KDR receptor. The latter receptor appears to account for most of the bioactivity induced by VEGF. These authors thus suggested that potentiation in this case might be the result of the Flt-1 receptor behaving as a “decoy,” that is, binding either ligand but having little or no transducing activity. PlGF might therefore act to release VEGF from Flt-1 and increase its availability to the more relevant KDR receptor. Because PlGF failed to potentiate low doses of bFGF, these findings were interpreted to be specific for VEGF. Whether an as-yet-unidentified high-affinity receptor for VEGF/bFGF could similarly contribute to the synergism we observed remains to be investigated.

Site-Specific Effects of Angiogenic Cytokines

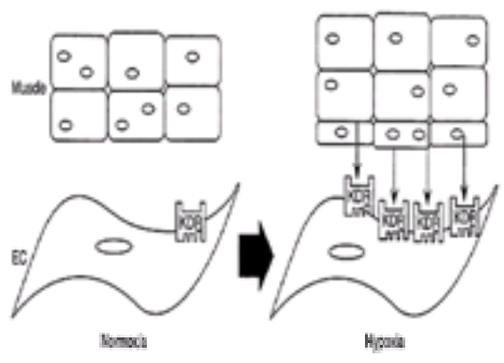
From a teleologic perspective, it appears critical that EC mitogens not promote angiogenesis in an indiscriminate fashion; it is clearly preferable for the survival of the organism that angiogenesis be limited to sites of wound healing and tissue ischemia, where it may have facilitatory effects. In fact, there is evidence to indicate that this is the case. Studies in a variety of animal models using aFGF (192), bFGF (188,193), VEGF (25,194,195), and scatter factor (156) have shown that systemic administration of angiogenic cytokines selectively produces neovascularization in the ischemic limb (196); neither in the contralateral normal limb nor in any other organs were foci of neovascularization observed. In fact, when recombinant human vascular endothelial growth factor (rhVEGF) was injected into the normal or ischemic limb of rabbits with unilateral hindlimb ischemia, angiogenesis was observed only in the ischemic limb.

Furthermore, although patients with peripheral vascular disease have been shown to have detectable levels of circulating bFGF (197), evidence of angiogenesis appeared limited in these individuals to collateral vessel development in the ischemic lower extremities. More recently, after intramuscular injection of the gene that encodes VEGF, circulating levels of VEGF have been documented (198); nevertheless, again, evidence of angiogenesis was limited to the ischemic limb.

Evidence suggests that regional ischemia is the principal factor that is responsible for localization of angiogenesis. For example, in rabbits treated with rhVEGF, the magnitude of augmented collateral development is inversely related to the extent of hindlimb collateral arteries seen before rhVEGF therapy (25). The same is true for blood flow in the ischemic limb (199). Thus, if a paucity of angiographically visible collaterals and reduced blood flow is indicative of limb ischemia, it appears that the extent to which angiogenesis is enhanced is related to the severity of ischemia.

Experiments performed on ECs *in vitro* suggest that the basis for localized bioactivity of angiogenic cytokines such as VEGF is due to upregulation of the VEGF receptor in response to hypoxia. In certain types of ECs, notably bovine retinal ECs, this may occur as a direct response to hypoxia (200); in our experience, direct upregulation of receptor expression does not occur in HUVECs or microvascular ECs. The difference in these observations may be due to the fact that bovine retinal ECs possess threefold more VEGF receptors (200).

In the case of HUVECs and microvascular ECs, receptor upregulation appears to occur indirectly in response to hypoxia (eFig. 106.6.5). Specifically, we observed an increase in KDR mRNA levels in HUVECs that were treated for 3 hours with conditioned medium from hypoxic myoblasts, as compared to KDR mRNA levels of HUVECs treated for the same time with conditioned medium from normoxic myoblasts (201). Such increase suggests new receptor synthesis, in conjunction with mobilization of preformed receptors from the cellular pool. Scatchard analysis of iodine-125 VEGF binding indicated no substantial change in affinity of the KDR receptor in HUVECs that were treated with myoblast medium conditioned either in normoxia or hypoxia. Thus, increased binding observed using hypoxia-CM was due to a 13-fold increase in the number of KDR receptors. These data suggest that a “factor” secreted from hypoxic myocytes in ischemic tissues upregulates VEGF receptor expression on adjacent ECs; consequently, the ECs in these ischemic tissues act as a magnet for circulating VEGF.



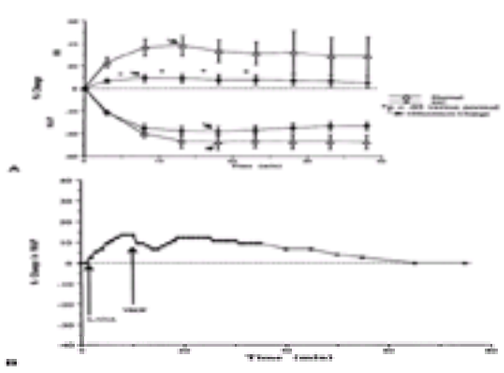
***e*FIGURE 106.6.5** Factors secreted by hypoxic myocytes upregulate vascular endothelial growth factor receptor expression on endothelial cells (ECs) within the hypoxic milieu. Such localized receptor expression may explain the finding that angiogenesis does not occur indiscriminately but rather at sites of tissue ischemia.

Role of Nitric Oxide in Mediating Effects of Angiogenic Growth Factors

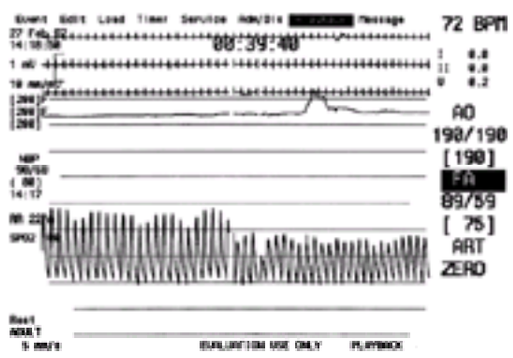
To elucidate the mechanisms by which VEGF may modulate EC biology, Brock et al. (202) used Fura-2, a Ca^{2+}-sensitive fluorescent dye, to monitor changes in $[Ca^{2+}]_i$ in suspensions of human ECs. They observed a three- to fourfold increase in $[Ca^{2+}]_i$ associated with an increase in inositol triphosphate in response to VEGF. Although an influx of extracellular Ca^{2+} appeared to constitute the predominant source of $[Ca^{2+}]_i$, a blunted but reproducible increase in $[Ca^{2+}]_i$ was obtained even in the absence of extracellular Ca^{2+}, suggesting that the VEGF-induced $[Ca^{2+}]_i$ increase was due to release of Ca^{2+} from internal as well as extracellular pools.

Evidence that the VEGF-induced increase in $[Ca^{2+}]_i$ was sufficient to stimulate production of NO was subsequently published by Ku et al. (203). They observed that VEGF-induced dose-dependent relaxation of isolated canine coronary arteries could be abolished by prior endothelium disruption or pretreatment with N^G-monomethyl-L-arginine, or both. The findings of Brock and of Ku suggest that VEGF-receptor binding is associated with tyrosine kinase–mediated phosphorylation of phospholipase C-g-1, release of inositol triphosphate from phosphoinositide, a consequent increase in $[Ca^{2+}]_i$, and ultimately increased EC production of NO. More recently, measurements performed in the author’s own laboratory have confirmed that application of VEGF to freshly excised arterial segments with intact endothelium results in a dose-dependent increase in the production or release, or both, of NO (164).

Cuevas et al. (22) successfully dissociated the mitogenic and hypotensive effects of aFGF, using a truncated form of the protein, mitogenically inactive due to loss of the nuclear translocation sequence but nevertheless capable of producing hypotension equivalent to that observed with the full-length wild type. Work from the author’s own laboratory has documented endothelium-dependent hypotension following intracoronary and intravenous administration of rhVEGF (eFig. 106.6.6 and eFig. 106.6.7). Leibovich et al. (204) found that the angiogenic activity of monocytes stimulated with lipopolysaccharide was L-arginine dependent and inhibited by inhibitors of NO synthase. Similarly, we have shown that dietary supplements of L-arginine enhance angiogenesis in the rabbit model of hindlimb ischemia and that genetically engineered mice lacking the eNOS gene fail to develop mature collaterals after iatrogenic ischemic injury (205), consistent with a role for NO in promoting angiogenesis *in vivo*.



***e*FIGURE 106.6.6 A:** Administration of recombinant human vascular endothelial growth factor (VEGF) to normal and hypercholesterolemic (HC) rabbits leads to prompt reduction in mean arterial pressure (MAP), with compensatory increase in heart rate (HR). The magnitude and duration (40 minutes) of hypotension are not significantly different in HC versus normal rabbits. **B:** MAP does not drop below baseline when administration of VEGF is preceded by administration of an inhibitor of nitric oxide synthase (L-NNA).



***e*FIGURE 106.6.7** Mild reduction in systemic blood pressure after injection of recombinant human vascular endothelial growth factor into saphenous vein graft of patient receiving recombinant protein therapy for myocardial angiogenesis.

THERAPEUTIC ANGIOGENESIS

The therapeutic implications of angiogenic growth factors were identified by the pioneering work of Folkman and colleagues more than two decades ago (206). Their work documented the extent to which tumor development was dependent on neovascularization and suggested that this relationship might involve angiogenic growth factors that were specific for neoplasms.

More recent investigations have established the feasibility of using recombinant formulations of such angiogenic growth factors to expedite and/or augment collateral artery development in animal models of myocardial and hindlimb ischemia. This novel strategy for the treatment of vascular insufficiency has been termed *therapeutic angiogenesis* (25).

Rationale for Therapeutic Angiogenesis in Patients with Occlusive Vascular Disease

Although ischemia from vascular occlusion upregulates expression of angiogenic growth factors, the fact that certain patients present with disabling angina indicates that such natural compensatory processes are not always sufficient. This can be explained in two possible ways: Either the production of angiogenic cytokines is inadequate or patients' response to them is attenuated. It has been shown that angiogenesis is impaired in older versus younger animals (207), secondary to reduced VEGF expression. Similar reductions in VEGF expression were observed in nonobese diabetic mice (208) and in hypercholesterolemic mice (209). These limitations in VEGF expression can be overcome in part by VEGF supplementation (208,209). Patients with advanced coronary disease are often older and may have diabetes, hypercholesterolemia, or other undetermined characteristics, limiting their capacity to upregulate angiogenic cytokines in response to ischemia, but may nevertheless respond to exogenous angiogenic cytokines. Significantly higher VEGF production in response to hypoxia was demonstrated in monocytes harvested from patients with angiographically visible collaterals, compared to those with reduced collaterals, suggesting that individual differences in cytokine expression may constitute yet another basis for variations in the magnitude of collateral development (210).

Reduced expression of angiogenic cytokines is not the only factor that contributes to the heterogeneous response to collateral vessel development. Marked genetic heterogeneity in the response to growth factor–stimulated angiogenesis has been observed in different strains of inbred mice (211). Age-related reduction in EC viability has also been demonstrated (207). Endothelial dysfunction accompanies many of the known coronary risk factors and may reduce endothelial responsiveness to angiogenic growth factors. Also, the responsiveness of EPCs to hypoxic stimuli may well be deficient and potentially limit therapeutic angiogenesis. Strategies to increase EC responsiveness and to enhance EPC production or availability are therefore reasonable targets for therapeutic angiogenesis (212,213 and 214).

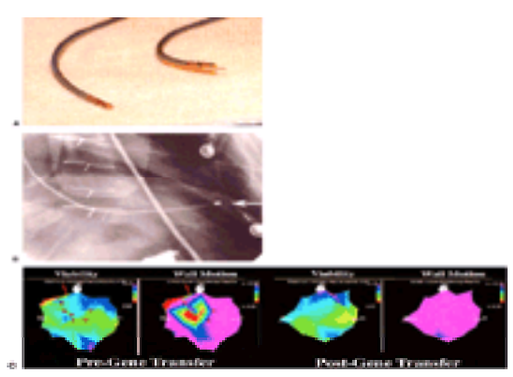
Angiogenic Protein versus Gene Therapy

Angiogenic cytokines can be administered as the natural recombinant human protein or by gene transfer. Recombinant protein is a more conventional approach and typically displays a more precise dose-response relationship than gene transfer. Recombinant protein is usually administered systemically and is therefore limited by potential adverse effects of the high plasma concentrations that are required to achieve adequate myocardial uptake. These include hypotension and edema with VEGF (215,216) and anemia, thrombocytopenia, and renal toxicity for FGF (217,218). Data regarding the kinetics of recombinant protein circulation suggest that intravenous delivery is unlikely to result in sufficient myocardial uptake or residence time to achieve important biologic effects; intracoronary delivery constitutes an alternative route of parenteral administration (219).

The ideal regimen for therapeutic angiogenesis is a single administration that provides a sustained but transient (2–3 weeks) increase in local angiogenic protein concentration at foci of myocardial ischemia. A limited rise in systemic VEGF levels would be expected to reduce the potential for distant unwanted side effects. Currently available gene therapy strategies approach this ideal. Naked DNA and adenoviral vectors produce only transient transfection, ideal for the time scale that is required for angiogenesis. The principal challenge is that optimal transfection in the case of naked DNA is best achieved by intramyocardial injection, although intracoronary administration may be sufficient for adenoviral gene transfer (220). Unlike viral vectors, plasmid DNA does not induce inflammation. Although naked DNA gene transfer is less efficient than viral-mediated transduction, uptake of naked DNA is augmented in muscle (221), particularly ischemic or inflamed muscle (119,222).

Routes of Administration

Angiogenic cytokines and genes have been administered via a wide variety of routes. Injection sites include intravenous, selective pulmonary artery, left atrium, intracoronary, selective intracoronary, transepicardial intramyocardial at time of bypass surgery or via thoracotomy, transendocardial intramyocardial by electromechanical catheter, periadventitial at time of bypass surgery or by thoracotomy, and intrapericardial. Because local delivery of recombinant protein or gene can be considered ideal (223), trials in patients have favored the intracoronary (adenovirus) or intramyocardial (naked DNA or adenovirus) route. Although not an issue if performed as a part of a coronary bypass procedure, the attendant risk of surgery is otherwise a limitation of the transepicardial route; in the future, this may be averted by the catheter-based transendocardial approach (*e*Fig. 106.6.8).



***e*FIGURE 106.6.8** Composite illustration of gene transfer of vascular endothelial growth factor-2 (VEGF-2). **A:** Catheter on the left, with the 27-gauge needle advanced on the right. **B:** Position of the catheter tip (*arrow*) in the left ventricle. A combination of electromechanical mapping and fluoroscopy is used to guide catheter positioning within the ventricle. **C:** Four electromechanical maps: two before and two after VEGF-2 gene transfer. Pregene transfer, the left map ("viability"), comprises the maximum unipolar voltage electrical endocardial map, with viable areas color coded from green through blue to purple, indicating that hypocontractile areas were viable. The points chosen for gene transfer are marked in brown. The next panel ("wall motion") shows the linear local shortening map before gene transfer, with an area of hypocontractility, indicated by the red, yellow, green, and blue colors in the anterolateral wall. Surrounding areas have normal contractility color-coded purple. Hypocontractile areas were inferred to be either ischemic or hibernating. The follow-up maps in this patient, on the right, performed at 12 weeks after gene transfer, show no change in the unipolar voltage map (viability unchanged); the far right panel of linear local shortening shows complete normalization of contraction in the previously hypocontractile area as indicated by the uniform purple color after gene transfer. LV, left ventricular.

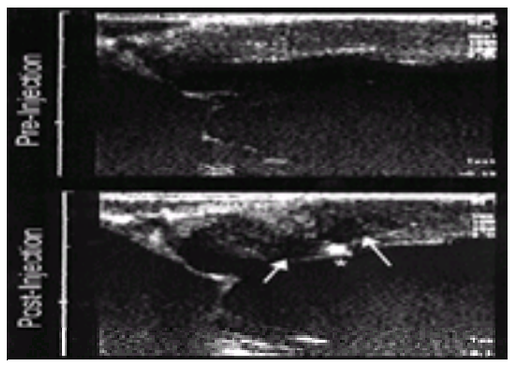
Experimental Studies in Animal Models of Myocardial Ischemia

The most widely studied animal model of focal myocardial ischemia involves application of an ameroid constrictor to produce gradual occlusion of the left circumflex coronary artery over 10 to 20 days. The choice of animal is important, as species differ from one another and from humans in the number of preexisting arteriolar connections: Pigs and rabbits have few, whereas dogs have many. Acute coronary ligation produces transmural infarction in the pig, compared to smaller nontransmural infarcts in dogs (224). In these models, angiogenic proteins or encoding genes have been administered successfully via a wide variety of routes. The effectiveness of angiogenesis has been documented by histologic assessment of capillary or vessel number and size, quantitation of EC markers, measures of resting or vasodilated coronary blood flow, angiography, and measures of left ventricular function at rest or during stress.

Most, but not all, of the studies have demonstrated evidence of enhanced angiogenesis after the intervention. FGF-2 increased collateral flow in the dog when given by the intracoronary route for 2, 7, or 28 days (225,226,227 and 228), with effects that were measurable for up to 5 weeks, but not at 6 months (229). Central venous administration in the same model was ineffective (228), presumably due to lung sequestration (219). Beneficial effects on collateral flow and left ventricular function were also seen with FGF-2 in the pig after single doses administered perivascularly or into the pericardium (230,231 and 232). FGF-1 recombinant protein was ineffective in the dog (233,234), probably because of rapid inactivation of this protein, which can be prevented by altering its structure (235). Experience with FGF gene transfer is more limited. Single-dose intramuscular injection of naked DNA encoding FGF-1 and intracoronary adenoviral transfer of the FGF-5 gene have each been shown to improve flow in the rabbit hindlimb (236) and porcine myocardium (220), respectively.

The effect of $VEGF_{165}$ protein has been studied in dog and in porcine models. Single intracoronary doses were effective in the pig (215,237), as was a series of two local injections via a balloon catheter, 3- or 4-week periadventitial infusions via minipump (237,238), and intramyocardial injection (239). Collateral perfusion improved after VEGF, and endocardial-epicardial flow ratios were improved. Intravenous administration, however, was ineffective (239). In the dog, $VEGF_{165}$ protein injected by the intracoronary route over 28 days was reported to improve collateral flow (240).

Genes that encode $VEGF_{165}$ and $VEGF_{121}$ as well as VEGF-2 have been transfected in a number of animal studies using either naked plasmid DNA or adenoviral vectors. Intramyocardial injection of plasmid DNA encoding $VEGF_{165}$ (241,242) (eFig. 106.6.9), VEGF-2 (243), or adenovirus encoding $VEGF_{121}$ (244,245) via thoracotomy in a pig ameroid model improved collateral perfusion and function. Intracoronary adenoviral gene delivery produced much lower gene and VEGF levels in the myocardium with poor localization, which would favor the intramyocardial route (245). Pericardial delivery of adenovirus encoding $VEGF_{165}$ in a dog model did not increase collateral flow (246). Intramyocardial injection of the entire dose of plasmid $VEGF_{165}$ at a single site in a rat model of myocardial infarction induced angiogenesis with angioma formation at the injection site, without enhancing regional blood flow (247); subsequent studies suggested that this was a dose-related event, in that a 50% reduction in dose of plasmid DNA did not induce angiomas (R. A. Kloner, *personal communication*, 2001). Similar results were observed with local massive overexpression of VEGF achieved with transformed myoblasts (248).



***e*FIGURE 106.6.9** Transepicardial two-dimensional echocardiogram demonstrating distribution of vascular endothelial growth factor DNA solution injected directly into ischemic porcine myocardium. **Top:** Anterolateral free wall is shown superiorly, with the mitral valve plane at the left of the image. **Bottom:** Bright needle artifact (*asterisk*) is seen in the anterolateral wall near two echolucent zones (*arrows*); the echolucency is the result of injected fluid containing the plasmid vascular endothelial growth factor DNA.

Studies have suggested that catheter-based intramyocardial injection of plasmid $VEGF_{165}$ is effective in the pig (242). This less invasive approach to intramyocardial gene transfer has been shown to achieve suitable gene expression (242,249,250 and 251) and is currently being investigated in a double-blind, randomized, prospective placebo-controlled trial of VEGF-2 gene transfer (124) (eFig. 106.6.8).

Translation of Therapeutic Myocardial Angiogenesis from Bench to Bedside

The species differences in myocardial collateralization and the relatively small area of ischemia that is produced in the pig model underscore the difficulty in taking the results from animal models of myocardial ischemia directly to the clinical arena for myocardial angiogenesis. In addition, the heart is a difficult organ to access directly for either vascular or intramyocardial administration of angiogenic factors, and assessment of neovascularization and blood flow is not trivial. Consequently, to investigate therapeutic angiogenesis in human subjects, a strategy was adopted of first studying patients with peripheral artery disease, specifically critical limb ischemia. The rationale for this included consideration of two issues. First, in patients with critical limb ischemia, the risk (limb loss)-benefit (limb salvage) ratio is appropriate for a novel therapeutic, due to the absence of any effective medical therapy (252). Second, access to ischemic skeletal muscle is straightforward, requiring only a superficial, nearly painless injection with a 27-gauge needle.

The effects of VEGF gene transfer were initially studied in patients with critical limb ischemia by delivering the gene to a patent arterial site in the ischemic limb upstream from the site of occlusion (72,253). Subsequently, however, this approach was replaced by direct intramuscular injection (198,254). Clinical benefit, including abolition of rest pain, limb salvage, and healing of ischemic ulcers, was associated with objective findings of improved perfusion (Fig. 106.7, Fig. 106.8, Fig. 106.9, and Fig. 106.10), including increase in ankle-brachial index, angiographic evidence of new collaterals, and improved leg blood flow on magnetic resonance angiography. Having established proof of the concept for therapeutic angiogenesis in human subjects, extrapolation of these findings to patients with myocardial ischemia were sought (255).

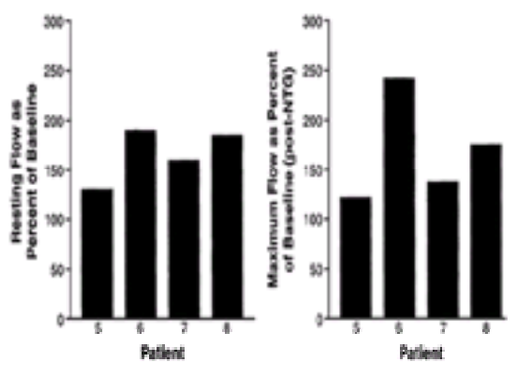


FIGURE 106.7 Resting flow (*left*) and maximum flow stimulated by intraarterial administration of nitroglycerin (NTG) (*right*) are augmented by 100% to 250% above baseline measurements in four patients undergoing gene therapy with 1,000 µg (patients 5, 6, 7) or 2,000 µg (patient 8) naked DNA encoding vascular endothelial growth factor. Blood flow was measured with intraarterial Doppler wire (FloMap, Cardiometrics).

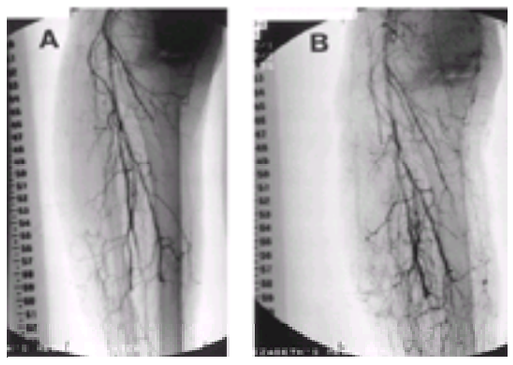


FIGURE 106.8 Selective digital subtraction angiograms performed in patient with critical limb ischemia due to occlusion of all three infrapopliteal vessels at midcalf level. Immediately before **(A)** and 1 month after gene therapy with 2,000 µg naked DNA encoding vascular endothelial growth factor **(B)**. The latter angiogram disclosed a plethora of new collateral vessels in the ischemic limb.

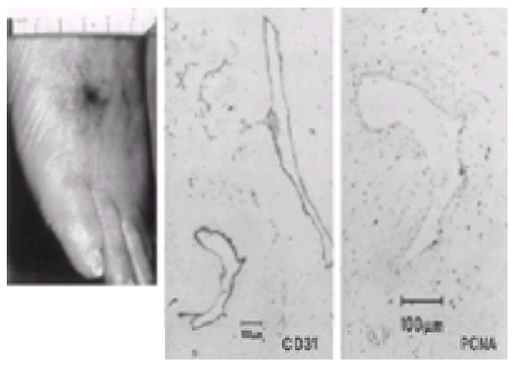


FIGURE 106.9 One of three spider angiomas that developed approximately 1 week after gene therapy in the distal portion of the ischemic limb of a patient whose angiograms are shown in Figure 106.8. Photomicrographs of tissue sections immunostained with antibody to endothelial antigen CD31 indicate the vascularity of the lesion, and immunostain of the adjacent section for proliferating cell nuclear antigen (PCNA) indicates the extent of proliferative activity among endothelial cells in the lesion.

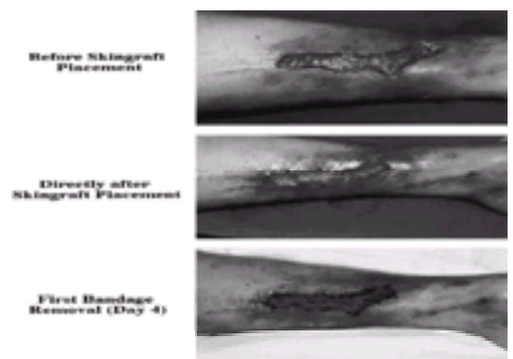


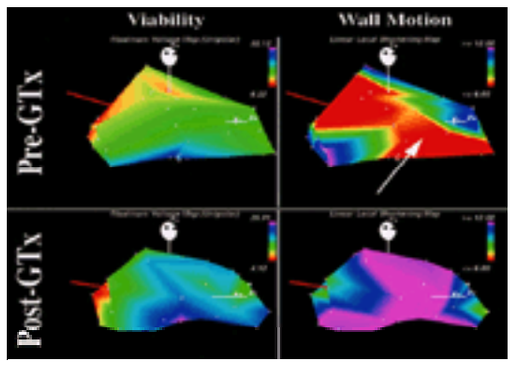
FIGURE 106.10 Successful placement of split-thickness skin graft in first patient treated with intramuscular administration of naked DNA encoding plasmid human vascular endothelial growth factor (phVEGF$_{165}$). After two intramuscular injections of 2,000 µg phVEGF$_{165}$, the patient's ankle-brachial index increased from 0.28 to 0.55, angiography disclosed new collateral vessels in the ischemic limb, and a 9 × 3–cm wound at the site of vein harvest in the medial calf healed sufficiently to permit successful grafting.

Evaluating Clinical Results of Myocardial Angiogenesis

No consensus has been reached regarding how best to evaluate the efficacy of therapeutic angiogenesis in patients with coronary heart disease. Most clinical studies have focused on the clinical end points that were used historically to evaluate new antianginal drugs, namely, angina class, exercise time, and quality of life. Each of these, however, is potentially subject to placebo and training effects, which cannot be eliminated in phase I trials and may limit the power of smaller phase II studies to detect a meaningful difference. Although these parameters may ultimately prove useful for establishing efficacy in larger phase II/III trials, additional objective evaluations may help to establish evidence of biologic effects that are attributable to therapeutic angiogenesis.

Rest and stress single-photon emission computed tomography (SPECT) perfusion imaging with thallium-201 or technetium-99m sestamibi provide objective estimates of relative myocardial blood flow and are used widely and routinely in clinical practice. As such, evidence of improved relative myocardial perfusion on images recorded before and after gene transfer may constitute inferential evidence of angiogenesis.

Percutaneous catheter-based electromechanical mapping (256,257) is a novel technique that provides concurrent imaging of myocardial viability and endocardial wall motion (*e*Fig. 106.6.8 and *e*Fig. 106.10.1); analysis of the two resulting maps can be used to identify foci of hibernating myocardium, which can be serially evaluated before and after gene transfer (258).



***e*FIGURE 106.10.1** NOGA (Biosense Webster) left ventricular (LV) electromechanical mapping performed in a 48-year-old man. NOGA images in the right anterior oblique projection before gene transfer (GTx) show the unipolar voltage map **(upper left panel)**, with normal voltages suggestive of viable myocardium (*purple/pink/blue/green*) and the linear local shortening (LLS) map **(upper right panel)** with a large zone of abnormal wall motion (*red, arrow*) representing electromechanical uncoupling that suggests ischemic or hibernating myocardium predominantly involving the septum. Unipolar voltage and LLS maps in the right anterior oblique projection 60 days after GTx (**lower left and right panels**, respectively) demonstrate almost complete resolution of the ischemic zone (ischemic area 9.57 cm^2 pre-GTx vs. 0.39 cm^2 post-GTx). Changes in LLS correspond to changes observed on single-photon emission computed tomographic scan (Fig. 106.6). Red line represents long axis through the apex.

Positron emission tomography using $^{13}NH_3$ or $H_2{}^{15}O$ can quantify regional coronary blood flow at rest and during vasodilation and has been used to demonstrate increased flow after a variety of interventions (259), but the technique is not widely available. Novel modifications of magnetic resonance perfusion imaging to detect foci of neovascularization (260,261) may prove useful for evaluation of angiogenesis after confirmation of reproducibility, sensitivity, and specificity by other centers.

Serial measures of left ventricular function have not proved consistently useful in animal or clinical studies to date. Angiographic studies have likewise failed to depict consistently reproducible evidence of neovascularization, even in animal or clinical studies with evidence of improved myocardial perfusion. This is likely due to the fact that the diameter of most collaterals formed in response to arterial occlusion or therapeutic angiogenesis, or both, is less than 200 µm (20)—that is, beyond the resolution of conventional angiography and certainly beyond the spatial resolution of magnetic resonance angiography. Consistent with this notion is the fact that the increased resolution achieved by synchrotron radiation imaging has disclosed new collateral vessels in preclinical studies that could not be identified by conventional angiographic techniques (262).

Initial Results of Therapeutic Myocardial Angiogenesis in Patients with Coronary Disease

Table 106.2 and Table 106.3 list completed and ongoing clinical trials of recombinant proteins and genes used for therapeutic angiogenesis, although data regarding the major end points have been published in only five, with two currently in press. Patients in these trials generally have severe angina that is unresponsive to medical therapy and are unsuitable for conventional revascularization. Many of the studies have been small phase I trials without control groups, designed primarily to establish safety or to evaluate dose-related effects, or both. Nevertheless, almost all have reported encouraging reductions in angina and nitroglycerin consumption and, in certain cases, improvement in exercise time and/or improvement in objective measures of left ventricular perfusion or function, or both.

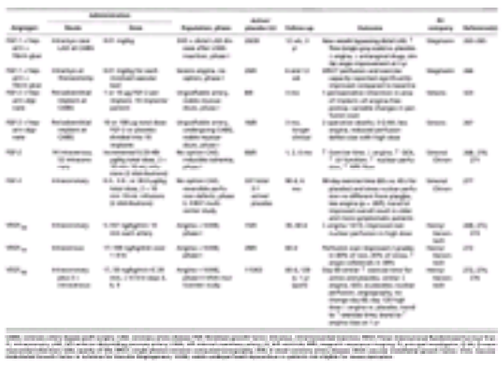


TABLE 106.2 CLINICAL STUDIES OF RECOMBINANT PROTEINS FOR MYOCARDIAL ANGIOGENESIS—COMPLETED AND IN PROGRESS

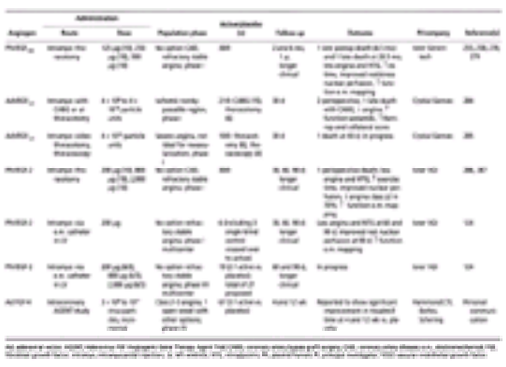


TABLE 106.3 CLINICAL STUDIES OF GENE TRANSFER FOR MYOCARDIAL ANGIOGENESIS—COMPLETED AND IN PROGRESS

Clinical Studies Using Recombinant Proteins

The first clinical study of recombinant protein for myocardial ischemia used intramyocardial injections of FGF-1 (aFGF) with heparin in patients who were undergoing left internal mammary bypass of the left anterior descending coronary artery (263,264) (Table 106.2). Twenty patients received active drug, and 20 received heat-denatured protein as placebo. The authors used a novel form of imaging to suggest improved collateralization of the distal left anterior descending coronary artery in comparison to placebo. This effect was maintained at 3-year follow-up (265). At 3 years, 16 of 17 patients who were given FGF were in Canadian functional class I compared to 12 of 16 control subjects, and only 1 of 17 given FGF required nitrates compared to 12 of 16 controls (p <.01). In addition, fewer patients given FGF were on calcium channel blockers (1 of 17 vs. 10 of 16) or beta-blockers (5 of 17 vs. 10 of 16). The same group completed an uncontrolled study of FGF-1 injected transepicardially via minithoracotomy in patients with severe angina that was unsuitable for conventional revascularization (266). Compared to baseline preoperative values, SPECT perfusion and exercise capacity were reported to be improved at 6 and at 12 weeks.

Periadventitial implantation of FGF-2 (bFGF) administered intraoperatively in heparin alginate beads at the site of a nonbypassable artery has been evaluated in a placebo-controlled trial of patients who were undergoing concomitant bypass surgery (267). Despite a relatively high perioperative mortality and morbidity attributed to the advanced nature of coronary artery disease in the patient cohort, the investigators reported less angina in the active treatment group. Trends to less severe stress nuclear perfusion defects and less evidence of ischemia by magnetic resonance imaging were noted as well in the high-dose FGF-2 group.

Three uncontrolled phase I studies of intravenous or intracoronary FGF-2 or VEGF recombinant protein have been completed (Table 106.2). These studies overall reported less angina and improved exercise time and improvements in either nuclear or magnetic resonance imaging perfusion or left ventricular function (268,269,270,271,272 and 273).

Results of phase I studies, designed by definition to assess safety, must be interpreted with caution. Typically, the number of patients who are enrolled in such trials is relatively small, and for those lacking a control group, a placebo effect cannot be excluded. For studies in which recombinant protein or gene is administered in conjunction with conventional revascularization, it may be difficult to determine the relative contributions of the angiogenic agent versus bypass surgery to the symptomatic response.

Two larger placebo-controlled phase II studies of intracoronary ± intravenous recombinant protein have been completed. The Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis (VIVA) study compared two doses of VEGF-1 protein to placebo in 178 patients who were given a single intracoronary infusion followed by three separate intravenous infusions (274,275 and 276). The primary end point of exercise duration was not different from placebo in the VIVA study; in each of the three groups, the increase in exercise time at 60 days, approximately 45 seconds, was similar. At 120 days, the high-dose group maintained the improvement, with an increase of 47 seconds over baseline, whereas the placebo group showed only a 14-second improvement. Although this difference was not significant, given the relatively small numbers and the large placebo effect, the possibility of a type II error cannot be excluded. No significant differences from placebo were found in angina grade or quality-of-life measures at 60 days, although there was a significant reduction in angina grade at 120 days in the high-dose group. Angiographic and nuclear perfusion studies were interpreted to show no differences between active therapy and placebo at 60 days.

Perhaps the most striking finding in the VIVA trial was that, in spite of exclusion of patients with evidence of a malignancy, three patients were diagnosed and one died of cancer within the 120-day follow-up period, and worsening retinopathy developed in one patient. Remarkably, all of these individuals had been fortuitously randomized to the placebo group.

The Flolan International Randomized Survival Trial (FIRST) compared a single intracoronary dose of FGF-2 (bFGF) with placebo in 337 patients. The 90-day results (277) failed to show significant differences from placebo in the primary end point of exercise time (65 vs. 45 seconds' improvement, p = .64) or in rest or stress nuclear

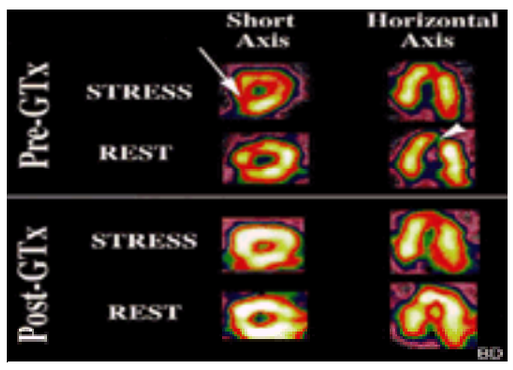
perfusion. Angina frequency determined by the Seattle Angina Questionnaire was less in the FGF group, although this did not achieve statistical significance. In a *post hoc* analysis, a significant improvement in exercise time was seen in patients who were older than 63 years (80 vs. 40 seconds, $p = .03$). The otherwise negative primary endpoint results of the VIVA and FIRST studies using intracoronary ± intravenous protein administration underscore the concern that the pharmacokinetics of recombinant protein administered into the vascular space may lead to inadequate local delivery of angiogenic growth factor within the ischemic myocardium, as suggested by studies reported previously using labeled ligand (219,223).

Clinical Studies Using Gene Transfer

Published studies of gene transfer for therapeutic angiogenesis in human subjects have thus far been limited to phase I dose-escalating, nonrandomized trials (Table 106.3). The largest of these trials with the longest follow-up to date involved 30 patients with refractory angina that was unsuitable for conventional revascularization, in whom naked DNA encoding the 165 isoform of the VEGF-1 gene as sole therapy was administered intraoperatively by direct intramyocardial injection via a minithoracotomy (255,258,278,279). A technical aspect of the procedure worthy of note was the use of intraoperative multiplane transesophageal echocardiography with test injections of agitated saline to ensure that the DNA injectate was not delivered into the left ventricular cavity (280). Intracavitary microbubbles that necessitated needle repositioning were seen in 20% of needle placements, underscoring this aspect of transepicardial gene transfer.

The patients experienced a remarkable reduction in angina frequency, with weekly nitroglycerin consumption falling from an average of 60 per week to 3.5 per week at 90 days. Exercise time for the group at 90 days improved by an average of 47 seconds, and exercise time to angina improved by almost 2 minutes; the improvements in symptoms were maintained at 1 year, and there was further improvement in exercise time (increase of 98 seconds over baseline) and time to angina (increase of 2.5 minutes). Two late deaths [4.5 (278) and 28.5 months] occurred, and one patient underwent a cardiac transplant at 13 months.

An important objective evaluation in the final 13 consecutive patients was the use of electromechanical endocardial maps of left ventricular shortening before and 60 days after gene transfer (258). Foci of electromechanical uncoupling (reduced endocardial shortening with persistent evidence of electrical viability) were identified preoperatively in all patients, with significant improvement in these endocardial wall motion abnormalities in the repeat study at 60 days (*e*Fig. 106.6.8 and *e*Fig. 106.10.1). These findings corresponded to improved perfusion scores calculated from SPECT-sestamibi myocardial perfusion scans recorded at rest and with pharmacologic stress. Perfusion defects on the SPECT rest images were associated with ischemic characteristics on the endocardial maps. Sequential SPECT scans (*e*Fig. 106.10.2) recorded before and after gene transfer demonstrated partial or complete resolution of fixed defects in four (33%) and five (43%) patients, respectively, in whom defects were present on the initial rest images. Partial or complete resolution of these rest defects after gene transfer is consistent with the notion that these preexisting defects constitute foci of hibernating viable myocardium (281,282 and 283), which have resumed or improved contractile activity as a result of therapeutic neovascularization.



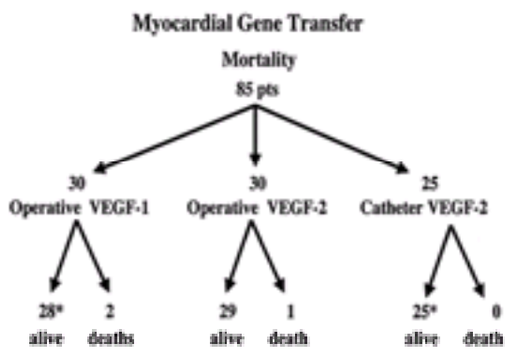
***e*FIGURE 106.10.2** Persantine single-photon emission computed tomographic–sestamibi myocardial perfusion scanning. Selected short and horizontal axis stress and rest images taken before and after plasmid human vascular endothelial growth factor165–gene transfer (GTx) in the same patient as shown in *e*Figure 106.10.1. White/yellow color depicts maximal uptake of radionuclide, and red depicts impaired uptake. Pre-GTx scans **(upper panel)** show a fixed anteroapical defect (*arrowhead*) and a partially reversible inferoseptal defect (*arrow*). Post-GTx scans **(lower panel)** show complete normalization of resting perfusion with a small, persistent, reversible anteroapical defect after pharmacologic stress.

A second phase I study of intramyocardial gene transfer was reported by Rosengart et al. (284). In that study, a first-generation adenoviral vector was used to deliver the 121 isoform of the VEGF-1 gene to 15 patients who were undergoing bypass graft surgery and as sole therapy to 6 patients via minithoracotomy. Symptoms improved in bypass surgery and in sole-therapy groups, although stress-induced nuclear perfusion images remained unchanged. The same group has since injected adenoviral $VEGF_{121}$ transepicardially, using video-assisted thoracotomy or thoracoscopy in ten patients (285), with one late death. Symptomatic outcomes in these latter patients have not yet been reported.

Our initial experience with intramyocardial naked DNA gene transfer was subsequently reproduced in a multicenter, consecutive series, dose-escalating study of transepicardial VEGF-2 gene transfer in 30 patients with class 3 or 4 angina. Once again, angina frequency and nitroglycerin consumption were reduced, and exercise time was increased by more than 2 minutes (*unpublished data*); improvement in nuclear perfusion studies and NOGA maps (Biosense Webster) similar to those described for naked DNA gene transfer of VEGF-1 (286,287) were documented as well. Among the 30-patient cohort, 29 are alive at a minimum of 12 months' follow-up, and none has undergone cardiac transplantation. A single postoperative death occurred 20 hours after gene transfer.

More recently, the first clinical study of percutaneous, catheter-based myocardial gene transfer was completed (124). This single-blind pilot study, designed to establish the safety and feasibility of nonsurgical needle injection, involved a total of six patients who were randomized to gene transfer or a mock procedure; each of the three patients assigned to the mock group ultimately required crossover to gene transfer for persistent symptoms. The number of anginal episodes fell similarly in the active and control groups over the first 30 days after gene transfer, suggesting an initial placebo effect (33 ± 5 to 14 ± 5 episodes per week for active therapy vs. 40 ± 5 to 15 ± 5 episodes per week for control, p = not significant). Longer follow-up, however, disclosed that angina continued to decrease at 90 days only in the active group, whereas patients in the mock group regressed toward their initial symptomatic status (3 ± 6 episodes per week vs. 22 ± 4, $p = .002$), suggesting that the late reduction in angina was not a placebo effect. The symptomatic improvement was again accompanied by noninvasive evidence of improved myocardial perfusion and electromechanical evidence of improved myocardial function (124). This study served as the basis for a multicenter, randomized, double-blind, placebo-controlled trial of catheter-based VEGF-2 gene transfer that has thus far enrolled 19 patients. No complications have been associated with a total of 150 injections among the 25 patients who were given either VEGF-2 or placebo in these two studies.

With specific regard to mortality, it should be noted that the cumulative mortality for the 85 patients with class 3 or 4 angina, all of whom were refused for conventional revascularization, undergoing operative or percutaneous naked DNA gene transfer of VEGF-1 or VEGF-2, has been 3 of 85, or 3.5%, at up to 33 months' follow-up (*e*Fig. 106.10.3). This compares favorably with an average 11% to 13% 1-year mortality for a similar group of almost 1,000 patients who received laser myocardial revascularization (see Transmyocardial Laser Revascularization) or continued medical therapy in five contemporary controlled studies (288,289,290,291 and 292).



***e*FIGURE 106.10.3** Mortality outcome data for all clinical trials using plasmid human (naked DNA) vascular endothelial growth factor (VEGF)-1 or VEGF-2 gene transfer in patients with disabling angina and severe coronary artery disease that was unsuitable for revascularization. Cumulative overall mortality in all 85 patients in the combined studies, with follow-up ranging from 10 to 33 months, was 3.5%, with 1 patient requiring cardiac transplantation at 13 months for symptoms (*asterisk*). No

mortality has occurred in the catheter-based gene transfer studies.

Potential Risks of Inducing Angiogenesis

The risks associated with therapeutic angiogenesis include those that are specific to the growth factor *per se* and those generic to strategies of promoting angiogenesis. With regard to the former, risks thus far recognized clinically in association with VEGF depend on the mode of administration. Administration of recombinant protein can lead to hypotension (215,293), because VEGF upregulates NO synthesis (164,205); this complication, however, has never been described after gene transfer in either animals or humans. Although experiments performed in transgenic mice that were engineered to overexpress VEGF ± angiopoietin have been interpreted to suggest lethal permeability-enhancing effects of VEGF (294), evidence of enhanced permeability in humans has been limited to transient lower extremity edema (Fig. 106.11) in patients with critical limb ischemia following VEGF gene transfer (216). A third issue concerns the development of angiomas in mice (295) or rats (247) that were treated with transduced myoblasts or supraphysiologic doses of plasmid DNA, respectively. Importantly, in the latter study, no angiomas were observed when the dose of administered plasmid DNA was reduced by 50% (R. A. Kloner et al., *unpublished data*, 2001). Except for these studies, no other preclinical or clinical reports, including those that used adenoviral vectors, have described this complication. With bFGF, hypotension may also result from the use of recombinant protein—again mediated via augmented NO release—but has not been described after gene transfer. Use of recombinant protein has also been associated with proteinuria (218).

FIGURE 106.11 Representative examples of lower extremity edema (*asterisk*) according to clinical grade in four patients after intramuscular plasmid human vascular endothelial growth factor$_{165}$ gene transfer. **A:** Grade 1. **B:** Grade 2. **C:** Grade 3. **D:** Grade 4.

More generic safety issues concern the potential to stimulate tumor vascularity and growth in the case of occult neoplasms, as well as the potential to exacerbate proliferative or hemorrhagic retinopathy, or both, in patients with diabetes, in view of the high VEGF levels that are demonstrated in the ocular fluid of patients with active proliferative retinopathy (296). With regard to carcinogenesis, there are neither *in vitro* nor *in vivo* data to date to suggest that VEGF increases the risk of neoplastic growth or metastases, or both, although longer-term follow-up will be required to address this issue in clinical trials. With regard to retinopathy, more than 100 patients who received VEGF-1 or -2 have now been treated at the author's institution and undergone serial funduscopic examinations before and after gene transfer by an independent group of retinal specialists; none to date (up to 4 years follow-up) has shown evidence of new retinopathy, despite the fact that nearly one-third had a history of diabetes or remote retinopathy, or both (297).

Another concern stems from the demonstration that inhibitors of angiogenesis tested in an apolipoprotein E–deficient mouse model of atherosclerosis inhibited plaque growth and intimal neovascularization (104). It is important to underscore the fact that these experiments were designed to test the hypothesis that inhibition of plaque angiogenesis would reduce the growth of atherosclerotic lesions; the experiments were not designed to test the hypothesis that administration of agents that promote angiogenesis would enhance atherosclerosis. To this end, several animal studies (103,298,299 and 300) and clinical studies of human subjects (301,302) (Table 106.4) fail to support the notion that accelerated atherosclerosis is a likely consequence of administering angiogenic cytokines; the outcome, in fact, is quite the opposite, in that administration of VEGF led to a statistically significant reduction in intimal thickening due to accelerated reendothelialization. The data available to date thus do not support the notion that acceleration of atherosclerosis is a consequence of VEGF-induced stimulation of angiogenesis.

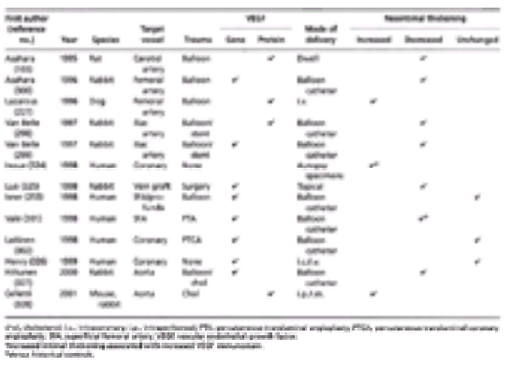


TABLE 106.4 STUDIES REGARDING VASCULAR ENDOTHELIAL GROWTH FACTOR AND NEOINTIMAL THICKENING

Transmyocardial Laser Revascularization

Transmyocardial laser revascularization (TMR) was investigated initially by Mirhoseini in 1982 (303) as a means of augmenting blood flow to the myocardium by creating sinusoidal tracts that are typical of amphibian ventricles. The past decade has witnessed renewed interest in this strategy, particularly for patients who are not suitable candidates for conventional revascularization. Indeed, the U.S. Food and Drug Administration approved two systems for commercial use, and the costs of TMR are now coded for reimbursement by the Health Care Financing Administration. As interest in TMR was renewed during the past decade, it was suggested that putative benefit from the procedure might be the result of angiogenesis (304,305 and 306), as multiple pathologic studies failed to show evidence that the lased channels remained patent (307,308 and 309). This issue remains unresolved because of the difficulty in distinguishing neovascularization that is associated with wound healing in response to laser injury from nutrient angiogenesis (310,311).

Mechanisms aside, TMR as sole therapy has now been compared to maximum medical therapy for severe angina in just under 1,000 patients with coronary artery disease that is not amenable to standard revascularization in five randomized trials (288,289,290,291 and 292). One-year mortality was high in this patient group (11.5% for laser and 12.7% for medical controls). The trials were concordant in showing reduced angina compared to control subjects, but quite variable in comparisons of treadmill time. No consistent pattern of change in SPECT nuclear perfusion was found, with three of four studies showing no improvement in reversible SPECT defects. In two uncontrolled studies in which perfusion was determined by positron emission tomography (312,313), no increase in regional blood flow was observed in the laser-irradiated regions. These findings have been interpreted by some to suggest that reduction in angina may result from either denervation or the placebo effect of thoracotomy. Denervation as a mechanism of symptom relief is supported by the predominance of silent ischemia in the perioperative period (314) and by evidence of denervation in canine models of TMR (315,316), as well as in patients who showed reduced hydroxyephedrine uptake with positron tomography (313).

More recently, several trials have tested the potential to perform TMR percutaneously using catheter-based fiberoptic delivery of laser light to multiple left ventricular endocardial sites. The first of these trials (317) showed a significant improvement in exercise capacity and reduction in anginal symptoms at 6 months, but thallium perfusion scintigraphy was unchanged. The Direct Myocardial Revascularization In Regeneration of Endomyocardial Channels Trial (DIRECT), a stringent multicenter, double-blind, placebo-controlled study in which patients received either holmium:YAG (yttrium-aluminum-garnet) or mock laser irradiation, failed to show improvement in anginal symptoms or exercise time compared to placebo; at 6 months, the treated and control groups reported an almost identical reduction in angina symptoms and

a similar improvement in exercise time (27- and 35-second increases in high- and low-dose laser, respectively, vs. 31 seconds in placebo) (318).

CONCLUSIONS

The immediate goal of clinical research in therapeutic myocardial angiogenesis with either protein administration or gene transfer is to demonstrate efficacy in larger-scale, placebo-controlled trials. To be sure, the rate at which regulatory agencies have permitted clinical trials of gene therapy, as opposed to recombinant protein or TMR, to progress has delayed achieving this objective. In addition, it should be acknowledged that clinical evaluation of therapies designed to promote collateral development would benefit from improvements in imaging capabilities that permit routine, high-resolution imaging of vessels less than 200 µm in diameter, typical of synchrotron radiation (262) but not possible with current angiographic imaging suites. Given the goal of optimizing tissue exposure to growth factor, it remains to be demonstrated that this can be achieved with single or even multiple injections of recombinant protein; recognizing this, certain groups are currently investigating sustained-release formulations of recombinant protein (N. Ferrara, *personal communication*, 2001). In contrast, sustained release is an inherent feature of gene transfer, at least over a period of 2 to 4 weeks in the case of naked plasmid or adenoviral gene transfer (119,319), and thus constitutes a potential advantage for gene therapy. Subsequent studies will be required to confirm preliminary suggestions that the levels and duration of gene expression achieved with naked plasmid DNA are of sufficient magnitude to achieve therapeutic angiogenesis while avoiding adverse effects and to optimize the choice, dose, and route of administration of angiogenic growth factor. Similarly, clinical trials will ultimately be required to test combinations of growth factors (188,320) in an attempt to reproduce the cascade evolved by nature to elaborate vascular networks.

Finally, complementary strategies that are not limited to supplying the growth factor, but instead enrich the cellular population capable of responding to the ligand, may be required for optimally robust vascularity. A number of studies (207,208 and 209,212,214,321,322) have suggested that the viable population of ECs capable of responding to angiogenic cytokine replacement may represent a limiting factor in trials of angiogenesis. Preliminary attempts to address this by a strategy of “supply side” angiogenesis, administering expanded populations of endothelial progenitors harvested from the patient’s own circulating blood volume, have successfully augmented hindlimb (74) and myocardial (75) angiogenesis. Clinical implementation of such a strategy will require further research into techniques for harvesting and separating cells and stimulation of their growth *ex vivo* before reinfusion at the time of cytokine stimulation. Implicit in this approach is the development of paradigms capable of identifying which patients are likely to have inadequate cytokine (21) or cellular responses to ischemia, so that therapy can be tailored and therapeutic angiogenesis targeted appropriately.

CONTROVERSIES AND PERSONAL PERSPECTIVES

The most daunting controversy in the clinical field of therapeutic angiogenesis is the task of executing a definitive clinical trial with regard to efficacy of either recombinant protein or gene transfer. Federal regulatory agencies have thus far been more permissive with regard to the more conventional of these two options, namely, recombinant protein. Unfortunately, the short half-life and greater difficulty of establishing site-preferential delivery have constituted recognized liabilities of this approach, and, not surprisingly, clinical trials to date have established limited evidence that recombinant proteins are efficacious for therapeutic angiogenesis.

Clinical trials of gene therapy for therapeutic angiogenesis have come under far greater scrutiny by federal regulatory agencies, and, thus, available clinical data regarding the efficacy of this delivery strategy to date are less robust than those for recombinant protein. The ability to extend the half-life of the angiogenic agent considerably as well as optimize local concentrations while minimizing systemic exposure is an inherent advantage of gene transfer; evidence of efficacy in the limited clinical investigations carried out thus far indeed suggests that these conceptual features translate into clinical advantages for therapeutic angiogenesis.

It is hoped that the clinical evidence to date that gene transfer for therapeutic angiogenesis is safe and well tolerated will now permit larger-scale, appropriately randomized trials to be performed at the more accelerated pace necessary to establish definitive evidence of therapeutic utility. In particular, it is noteworthy that many of the potential toxicities raised by experiments involving a variety of genetically engineered mice have not been borne out in clinical trials of either protein or gene therapy performed to date. Specifically, clinical trials to date do not suggest that the use of angiogenic cytokines accelerates atherosclerosis; indeed, the preclinical and more limited clinical data now available suggest that certain angiogenic cytokines, such as VEGF, may have utility for preventing restenosis; this strategy is parenthetically being tested clinically (using gene transfer) for patients with lower extremity vascular disease and will soon begin for patients with coronary artery disease, as catheter and as stent delivery of the transgene.

Finally, the potential to use cell therapy as an adjunct or even independent mode of therapeutic angiogenesis has now been established in preclinical studies and is about to be tested in human subjects. This therapeutic approach has great appeal, as it constitutes a “supply side” approach to replacing senescent ECs with robust precursors that may integrate into neovascular foci and at the same time delivers with each cell a “payload” of angiogenic cytokines that may facilitate neovascularization. It is likely that this approach will emerge as an effective option for promoting lower extremity and myocardial revascularization.

THE FUTURE

The identification of angiogenic growth factors has generated the opportunity for novel therapies in the treatment of a variety of diseases. This includes pathologic angiogenesis, such as diabetic retinopathy, rheumatoid arthritis, and cancer. In these cases, antibodies or naturally occurring angiogenesis inhibitors, or both, are being investigated clinically to antagonize key angiogenic factors. The strategy is designed to eliminate the vascular infrastructure and thereby minimize the extent of pathologic consequences to the patient.

A complementary strategy is now emerging for the treatment of cardiovascular diseases. Clinical trials of therapeutic angiogenesis have already been initiated in patients with myocardial ischemia and peripheral vascular disease and are imminent for patients with heart failure. These include trials of recombinant protein therapy as well as gene transfer. Protein and gene transfer have thus far been shown to be safe in human subjects. Preliminary trials of recombinant protein have shown limited evidence of efficacy. Preliminary applications of gene therapy have established proof of concept that angiogenic growth factors can augment myocardial perfusion. Subsequent clinical trials will determine the relative advantages of protein versus gene therapy, in terms of bioactivity and cost and safety; the maximum extent of clinical improvement that can be expected; and how the therapeutic outcome may be affected by certain features of the host.

It is also likely that future investigations may clarify the impact on established risk factors for vascular disease, such as lipid dyscrasias and diabetes, on native angiogenesis; thus, risk factor modifications may be useful for indirectly aiding natural angiogenesis in ischemic territories. It is intriguing to consider the possibility that one may be able to identify certain genotypic characteristics that may indicate why some patients form robust collateral networks whereas others fail to do so.

The role of EC progenitors in natural as well as therapeutic angiogenesis will be clarified by future studies. Recent studies have forced us to modify the classic concept that collateral development occurs solely by migration of fully differentiated ECs. It is now clear that circulating stem or progenitor cells, or both, contribute to such neovascularization. What remains to be determined is the proportion of new vessel growth that results from circulating stem cells versus parent vessel ECs. Finally, clinical trials will soon investigate the possibility that EC progenitors may be used in strategies of “supply side” therapeutic angiogenesis, specifically, whether administration of enriched or mixed populations of EC or less lineage-defined progenitors, including cells that are engineered to secrete proangiogenic agents, complement the impact of angiogenic cytokines on collateral vessel growth.

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DISEASES OF THE PULMONARY VASCULATURE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Perturbations in pulmonary vascular development *in utero* associated with lesions such as pulmonary atresia and ventricular septal defect (VSD), absence of the pulmonary valve, or diaphragmatic hernia lead to major difficulties in clinical management. Understanding cellular and molecular mechanisms governing early endothelial and smooth muscle cell differentiation, hypertrophy, and proliferation will affect our ability to reverse and overcome the hemodynamic consequences of these aberrations.

The mechanisms that lead to the severe structural remodeling observed in pulmonary arteries have many common features at the cellular and molecular levels regardless of the initiating cause. Experimental *in vivo* and *in vitro* studies suggest that this is due to induction of elastase activity and the consequent sequelae, including the release of growth factors, smooth muscle cell proliferation, induction of fibronectin, and smooth muscle cell migration.

In the setting of patients with congenital heart defects, pulmonary artery medial hypertrophy will cause increased vasoreactivity, particularly in the early postoperative period, which will likely be responsive to dilators such as nitric oxide (NO) phosphodiesterase inhibitors or endothelin receptor blockers. The more advanced changes of neointimal formation, combined with the patient's age at intracardiac repair (older than 8 months), will be the major determinants of hemodynamic reversibility.

Increased production of endothelin and altered potassium channel activation appear to be responsible for hypoxia-induced pulmonary vasoconstriction. The development of chronic hypoxia-induced pulmonary vascular abnormalities is characterized by dense accumulation of connective tissue proteins. Return to normoxia or improvement in the parenchymal lung disease results in regression of hemodynamic and structural abnormalities.

Immune/inflammatory mechanisms are likely responsible for the pulmonary vascular disease that accompanies autoimmune disorders, and therapy targeted at altering lymphocyte-endothelial interaction and activation will likely prove useful. The discovery of mutations in the bone morphogenetic protein receptor underlying unexplained or primary pulmonary hypertension will allow for new approaches to diagnosis and treatment. Currently, introduction of chronic intravenous prostacyclin or NO therapy and a variety of analogs including oral prostaglandin is proving of benefit in inducing regression in some patients and in retarding the progression of the changes in others.

INTRODUCTION

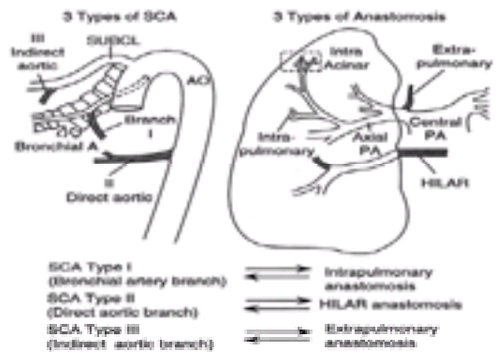
This chapter addresses the structural basis and functional sequelae of diseases of the pulmonary vasculature. The embryology of the pulmonary arterial tree is presented and the etiologic basis of developmental and genetic aberrations discussed. The structural changes associated with the altered pulmonary hemodynamics observed in congenital heart defects and alveolar hypoxia are described, as is the pulmonary vascular pathophysiology associated with thromboembolic disease, portal hypertension, and immune/inflammatory states. Unexplained (primary) pulmonary hypertension and associated vascular lesions also are considered, and recent genetic studies are discussed. Experimental studies addressing mechanisms leading to the structural lesions that cause pulmonary hypertension are discussed. Particular emphasis is placed on the degradation and synthesis of connective tissue proteins and the impact this has on vascular cell–extracellular matrix interactions, leading to cellular differentiation, hyperplasia, hypertrophy, and migration and culminating in occlusive neointimal formation. Current thinking is presented with regard to the roles of growth factors and their receptors and inflammatory and vasoactive mediator pathways. Treatments that are currently being instituted to control pulmonary vascular disease and future therapies aimed at preventing progression and inducing regression are discussed.

DEVELOPMENTAL BIOLOGY OF THE PULMONARY VASCULATURE

Macroscopic Features

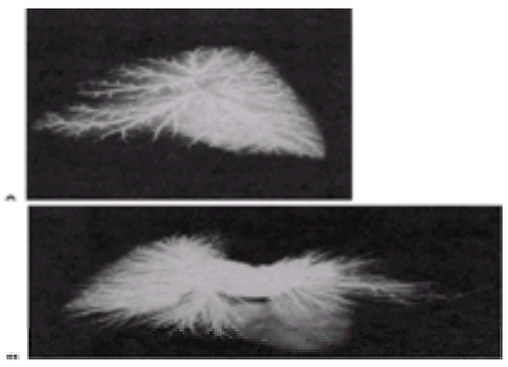
In the fifth-week human embryo, primitive pulmonary vessels from the sixth aortic arch supply the upper "poles" of the right and left lung, whereas the lower poles are supplied by a pair of intersegmental arteries arising from the dorsal aorta and penetrating upward through the diaphragm. The developing lung parenchymal blood vessels are largely localized to the interlobular septae. Between the fifth and eighth weeks of gestation, numerous paired dorsal intersegmental arteries supply the emerging blood vessels that are developing alongside the branching bronchi in the lung parenchyma. As the true central pulmonary arteries form from the aortopulmonary trunk and anastomose with the intrapulmonary arteries, the primitive pulmonary arteries arising from the aorta, as well as the primitive intersegmental arteries, involute. Formation of the bronchial system occurs only at the ninth week of gestation. With each airway generation, there is an accompanying artery in addition to numerous supernumerary arteries. By the sixteenth week of gestation, the number of preacinar airways and accompanying arteries is complete. Thereafter, as the acini (terminal bronchioli, respiratory bronchioli, alveolar ducts, and alveoli) develop, so do the accompanying and supernumerary arteries (reviewed in references 1 and 2).

Abnormal maturation or maturational arrest in pulmonary arterial development is reflected in functional derangement, which can present in the newborn period. Persistent pulmonary hypertension of the newborn has been reported in association with pulmonary arterial maturational arrest at the fifth week of gestation (3). Infants with pulmonary atresia and VSD frequently have persistence of the intersegmental arteries (aortopulmonary collaterals) (*e*Fig. 107.0.1) (4). These vessels can serve as the sole source of blood supply to a lobe or lobar segment; alternatively, they can form a dual circulation with intersegmental arteries anastomosing to arteries that can be traced back to a central pulmonary artery origin. There also can be multiple "indirect" aortopulmonary collaterals arising from aortic branches (e.g., from subclavian, intercostals, coronary arteries) and observed in the absence of direct collaterals, suggesting that they develop as a consequence of pulmonary atresia when it occurs later in development. Finally, in some cases of pulmonary atresia, there is supply by anastomotic vessels that arise from true bronchial arteries.



***e*FIGURE 107.0.1** The collateral anatomy in ventricular septal defect with pulmonary atresia. The three types of systemic collateral arteries (SCA) and the three types of anastomoses with the pulmonary artery (PA) are generally observed. The characteristic pattern of anastomosis for each type of SCA is given. AO, aorta; SUBCL, subclavian. (Reproduced from Rabinovitch M, Herrera-DeLeon V, Castaneda AR, Reid L. Growth and development of the pulmonary vascular bed in patients with tetralogy of Fallot with or without pulmonary atresia. *Circulation* 1981;64:1234–1249, with permission.)

A striking pulmonary vascular abnormality is observed with absence of the pulmonary valve (5). In patients who present with severe respiratory problems from birth, we have observed abnormal branching morphogenesis. Tufts of intersegmental pulmonary arteries are seen arising in “weeping willow” or “squid-like” fashion, encircling and compressing the intrapulmonary airways (*e*Fig. 107.0.2).

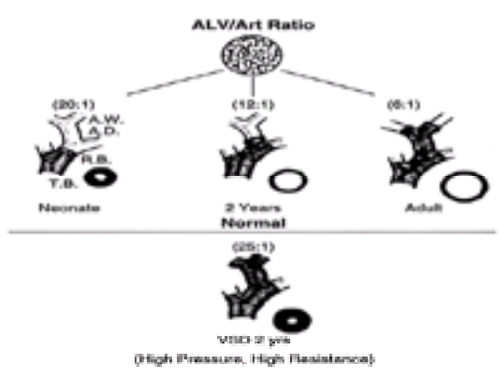


***e*FIGURE 107.0.2** Postmortem arteriograms. **A:** Arteriogram from a 4-day-old healthy infant. **B:** From a 4-day-old patient with absent pulmonary valve syndrome associated with a ventricular septal defect and D-transposition of the great arteries (*right*) showing tufts of vessels in both lungs. (Reproduced from Rabinovitch M, Grady S, David I, et al. Compression of intrapulmonary bronchi by abnormally branching pulmonary arteries associated with absent pulmonary valves. *Am J Cardiol* 1982;50:804–813, with permission.)

Microscopic Features

In the fetus, the preacinar arteries and those at the terminal bronchiolus level are muscular, whereas the intraacinar arteries (i.e., those accompanying respiratory bronchioli) are partially muscular (surrounded by a spiral of muscle) or nonmuscular. Arteries at alveolar duct and wall levels are nonmuscular. The preacinar arteries are thick-walled, and wall thickness changes little relative to external diameter throughout the fetal period. Experimental studies (6) suggest that the immediate postnatal period is characterized by rapid recruitment of small alveolar duct and wall vessels, which appear to be functionally and structurally closed in the prenatal period. Progressive dilatation of muscular arteries also occurs—that is, the smallest muscular arteries (less than 250 µm) dilate, and their walls thin to adult levels within a few days, and by the age of 4 months, this process has included the largest pulmonary arteries at the hilum. As the external diameter of the intraacinar arteries at the various airway levels increases with age, muscle appears to extend peripherally in that it is observed in arteries located more distally within the acinus. Nonmuscular arteries become partially muscular and later fully muscularized. For example, in infancy, vessels at the alveolar duct level are still largely nonmuscular, but in childhood they become partially muscularized and in the adult are fully muscularized (7). Alveolar wall arteries remain largely nonmuscular even in the adult. The muscularization of these peripheral pulmonary arteries may be related to the differentiation of pericytes as well as to the recruitment of fibroblasts (8,9).

Arteries proliferate through the neonatal period and early infancy, accompanying the proliferation of alveoli; the ratio of alveoli to arteries can therefore be used as a measure of numerical arterial growth. The ratio of alveoli to arteries actually decreases from the newborn value of 20:1 to the value of 6:1 to 8:1, which is achieved first in early childhood and persists (*e*Fig. 107.0.3). The growth and development of the pulmonary circulation are also likely influenced by the trophic effects of neuropeptides (10) released from nerve endings as well as from neuroendocrine bodies (11) associated with accompanying airways.



***e*FIGURE 107.0.3** Schema showing peripheral pulmonary arterial development through morphometric changes: extension of muscle into peripheral arteries, percent wall thickness, and artery number (alveolar-arterial ratio), as they relate to age. **Upper panel:** Normal development. **Lower panel:** Abnormalities in all three features in a 2-year-old child with a hypertensive ventricular septal defect (VSD). A.D., artery accompanying an alveolar duct; A.W., artery accompanying an alveolar wall; ALV/Art, alveolar-arterial ratio; R.B., artery accompanying a respiratory bronchiolus; T.B., artery accompanying a terminal bronchiolus. (Reproduced from Rabinovitch M, Haworth SG, Castaneda AR, et al. Lung biopsy in congenital heart disease: a morphometric approach to pulmonary vascular disease. *Circulation* 1978;58:1107–1122, with permission.)

Experimental studies indicate that the normal adaptation to postnatal life is regulated by remodeling of the smooth muscle cell actin cytoskeleton (12) changes in the production and distribution of connective tissue, especially elastin and collagen (13,14) and by consequent cellular rearrangement (15). It also has been shown experimentally that there are smooth muscle cells with differing proliferative potential (16,17). For example, metavinculin-positive smooth muscle cells are relatively resistant to proliferation, and the variability in proliferative potential is reflective of differences in activation of protein kinase C intracellular signaling pathways (18).

Cellular Mechanisms of Vascular Development

Current studies by several groups (reviewed in reference 19) are addressing specific cellular and molecular mechanisms that might regulate fetal growth and development of the pulmonary vasculature. These mechanisms include expression of cell adhesion molecules, such as vascular cell adhesion molecule 1 (20) and platelet endothelial cell adhesion molecule (21), in addition to the b_1 (22) and, more recently, the b_3 family of integrin receptors, especially $a_v b_3$ (23). The b_1 family of integrins binds fibronectin, and the b_3 family also binds fibronectin, as well as a host of matrix molecules, but especially tenascin, osteopontin, and vitronectin, some of

which have been shown to govern vascular cell migration (e.g., fibronectin) (24,25,26 and 27) or proliferation (e.g., tenascin) (28). Because these molecules mediate direct interactions between vascular cells and the extracellular matrix, perturbations can be expected to lead to malformation of the pulmonary and systemic arteries. A variety of growth factors, including vascular endothelial growth factor (29) and acidic and basic fibroblast growth factor (FGF-1 and FGF-2) (30), are also responsible for the orderly growth and branching morphogenesis of blood vessels. These factors are regulated through their interaction with specific cell-surface tyrosine kinase receptors, such as flt-1 and flk-1, tek, and tie (31,32 and 33). The balance between proteases and antiproteinases also controls growth factor interaction with cell-surface molecules. Plasmin, thrombin (34,35), and elastases, including leukocyte and endogenous vascular elastase (36), release growth factors from storage sites in the extracellular matrix in an active form. In addition, a variety of endogenously expressed inhibitors of proteinases and elastases, such as plasminogen activator inhibitor (37) and elafin (38), likely control growth and development. Other classes of molecules are known to control angiogenesis, such as angiostatin, a molecule that appears to be derived from plasminogen (39) and endostatin (40). Production of matrix proteins, specifically elastin and collagen, in blood vessels, is regulated by insulin-like growth factor I (41) and transforming growth factor-b (TGF-b) (42).

Vasoactive peptides also regulate pulmonary vascular development—for example, endothelin production is associated with cell proliferation and NO with the suppression of cell growth (reviewed in references 43 and 44). Transcription factors are being identified that control vascular smooth muscle cell differentiation (45,46) and the programming of constellations of genes involved in pulmonary vascular morphogenesis.

Abnormal Pulmonary Vascular Development *In Utero*

Underdevelopment of the lung parenchyma and associated pulmonary vasculature (reviewed in reference 1) is associated with congenital diaphragmatic hernia (47), hypoplastic or dysplastic lungs, scimitar syndrome, and oligohydramnios secondary to renal agenesis and dysplasia. Pulmonary hypoplasia is also a feature of prematurity, the absence of the phrenic nerve, asphyxiating thoracic dystrophy, rhesus isoimmunization, and, experimentally, amniocentesis (48) and smoking (49).

Reversible or irreversible pulmonary artery hypertension and right-to-left shunting from birth can be a direct result of derangement or hypoplasia of the pulmonary vascular bed. Heightened pulmonary vascular resistance can be attributed to the impaired gas exchange (hypoxia, hypercapnia) in addition to the structural changes in the vessels. In infants with congenital diaphragmatic hernia, reversal of the pulmonary hypertension was achieved by using vasodilators (50), extracorporeal membrane oxygenation (or high-frequency oscillation) (51), and NO alone or in combination with phosphodiesterase inhibitors (52). Some infants with hypoplastic lungs who had been refractory to NO before extracorporeal membrane oxygenation demonstrated a beneficial effect of NO after extracorporeal membrane oxygenation. The expectation is that the reduction in pulmonary artery resistance will stimulate regression of vascular changes and maturation in growth of the pulmonary arteries. In our studies of infants who died after an attempt at repair of congenital diaphragmatic hernia, a striking decrease in the number of alveoli and associated arteries (47) was the major determinant of mortality, explaining why attempts to reverse severe pulmonary hypertension with NO have been less successful in this group of patients. Dysplasias of the lung associated with persistent pulmonary hypertension of the newborn [e.g., alveolar capillary dysplasia (*e*Fig. 107.0.4) (53)] are currently so refractory to treatment that a biopsy should probably be done to guide clinical management.

***e*FIGURE 107.0.4 A–C:** Lung micrographs from an infant with alveolar capillary dysplasia. Barium distends the lumen of a preacinar artery (A) but does not enter the anomalous vein to the left of the artery. Intraacinar arterial branches that contain barium are identified, but intraacinar veins and venules are distended with red cells, presumably forced ahead of the barium by the postmortem angiogram. Air spaces are lined by cuboidal epithelium, and no luminal capillaries are seen; all vessels lie centrally in the air-space walls (hematoxylin and eosin, ×90). **B:** Intraacinar pulmonary arteries show medial muscular thickening that forms a continuous layer even in the smallest branch, which is 20 µm in external diameter. Media is demarcated by external and internal elastic laminae, stained black in this elastic stain. A bronchiole is identified (B). Elastin–van Gieson, ×220. (Reproduced from Cullinane C, Cox PN, Silver MM. Persistent pulmonary hypertension of the newborn due to alveolar capillary dysplasia. *Pediatr Pathol Lab Med* 1992;12:499–514, with permission.)

Structural studies of the lung at postmortem in fatal cases of meconium aspiration suggest that antecedent pulmonary vascular abnormalities exacerbated the postnatal pulmonary hypertension (54). The most striking feature is the presence of muscle in arteries that are small and peripheral in location and normally nonmuscular. The muscle cells are surrounded by darkly stained elastic laminae, suggesting that they formed several weeks before death and therefore *in utero*. Clinical studies suggest in some cases a relationship between maternal ingestion of prostaglandin synthetase inhibitors and subsequent persistent pulmonary hypertension (55). Chronic hypoxia in pregnant rats will produce structural changes in the pulmonary vascular bed of the newborn (56). In lambs, the clinical syndrome was produced by administration of a cytokine associated with inflammation (i.e., tumor necrosis factor- a) (57). Relatively short periods of hypoxia in the fetal lamb will result in sustained elevation of pulmonary artery pressure and structural changes in the pulmonary arteries. *In utero* closure or constriction of the ductus arteriosus simulates the structural changes and the initial hemodynamic profile of persistent pulmonary hypertension (58,59). Pulmonary hypertension can be created *in utero* by prolonged endothelin receptor blockade (60) and by chronic lung injury (61). The sequelae of experimental pulmonary hypertension that is established *in utero* include decreased potassium channel gene expression (62), which could contribute to heightened vasoreactivity and impaired endothelium-dependent relaxation (63), reduced cyclic guanosine monophosphate, and reduced soluble guanylate cyclase (64).

Recent experimental studies carried out in newborn lambs and rabbits showed that heparin can stimulate remodeling of the pulmonary circulation. Accelerated maturation of the pulmonary circulation was achieved by inducing an increase in he number of peripheral pulmonary arteries relative to alveoli (unpublished), and clinical studies have supported this strategy (65). Therapy with phosphodiesterase inhibitors (66) as well as with estradiol (67) has been shown to positively influence vascular remodeling associated with pulmonary hypertension. There is experimental evidence that NO therapy impairs the endogenous production of NO synthase in lambs with pulmonary hypertension induced *in utero* (68), which is in keeping with clinical data that show profound rebound effects in some patients on withdrawal of therapy. A positive feedback mechanism was, however, observed in cultured endothelial cells, suggesting that there may be other contributing factors (69). One study suggests that brief *in utero* exposure to hypoxia may aggravate the response to pulmonary hypertension–producing stimuli later in life (70).

Perinatal stress (e.g., hemorrhage, hypoglycemia, aspiration, hypoxia) may result in failure of dilatation of normally muscular vessels and left ventricular dysfunction, both of which contribute to persistent pulmonary hypertension. The use of inhaled NO in clinical studies (71,72), the use of L-arginine in experimental studies (73), and strategies to maximize dilator effects with phosphodiesterase inhibitors (66,74) proved effective in lowering pulmonary artery pressure. Because increased production of endothelin may underlie the pathophysiology (75,76), the use of endothelin receptor blockade or endothelial-converting enzyme inhibition (77,78) may prove beneficial, especially if specificity could be controlled to maximize dilatory activity.

ALTERED POSTNATAL PULMONARY VASCULAR DEVELOPMENT

Alterations in pulmonary blood flow associated with congenital heart defects, hypoxia, hyperoxia or toxins also affect the postnatal structural development of the pulmonary vascular bed in infancy and childhood.

Congenital Heart Defects and Pulmonary Vascular Disease

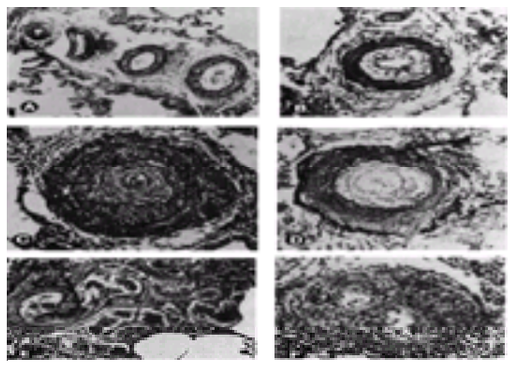
High Flow and Pressure and Structural Abnormalities

In clinical studies, it has been shown that high flow and pressure induce increasing pulmonary hypertension related to progressive vascular abnormalities (79) associated with impaired growth of the pulmonary arteries as assessed morphometrically. The first abnormality detected is extension of muscle into peripheral normally nonmuscular arteries (morphometric grade A) (*e*Fig. 107.0.3). Meyrick and Reid (8) showed from ultrastructural studies of lung biopsy tissue that this change is due to precocious differentiation of precursor cells (i.e., the pericyte in the nonmuscular region of the artery and the intermediate cell in the partially muscular region) to mature smooth muscle cells. Because arteries become more muscular as they increase in size, it is tempting to speculate that, in the altered hemodynamic setting of chronic

high flow and high pressure, “stretch” is the stimulus for smooth muscle cell differentiation from precursor cells.

With grade B, as in grade A, there is increased extension of muscle, but in addition, there is more severe medial hypertrophy of normally muscular arteries. When medial wall thickness is greater than 1.5 but less than 2 times normal (mild grade B), pulmonary hypertension is usually present; when medial wall thickness is more than twice normal (severe grade B), pulmonary hypertension is invariably present and usually has a pressure value greater than half that of the systemic level. The medial thickness is due to hypertrophy as well as hyperplasia of preexisting smooth muscle cells and also to an increase in the intercellular connective tissue proteins.

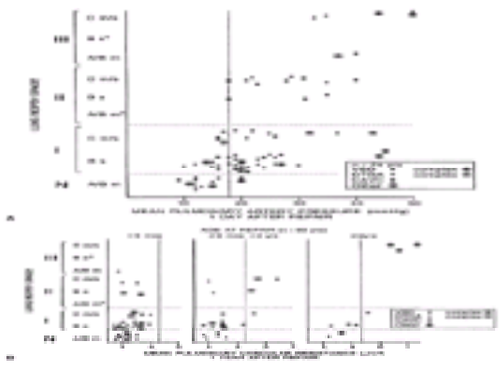
With grade C, in addition to the findings of “severe grade B,” arterial concentration and, usually, artery size are reduced. Patients with these changes usually have a pulmonary vascular resistance of greater than 3.5 U•m^2. When the artery number is less than half of normal (severe grade C), pulmonary vascular resistance values are often greater than 6 U•m^2. The basis for grade C is likely the failure of new vessels to grow normally, although some loss of arteries also may occur. Morphometric grades A and B are refinements of Heath-Edwards grade I (medial hypertrophy) (eFig. 107.0.5). Grade C may be found with Heath-Edwards grade I, is common with grade II (cellular neointimal formation), and is invariable with grade III (occlusive neointimal formation with fibrosis). In fact, when grade III is seen, arterial concentration is generally half of normal or less. In general, features of grade III C or more severe abnormalities such as Heath-Edwards grade IV (dilatation complexes), grade V angiomata formation, or grade VI (fibrinoid necrosis) correlate with severe elevation in pulmonary vascular resistance of greater than 8 U•m^2, which is refractory to vasodilators such as oxygen, prostacyclin, or NO.



***e*FIGURE 107.0.5** Heath-Edwards classification of pulmonary vascular changes. **A:** Grade I: medial hypertrophy. Elastin–van Gieson stain (EVG), ×150. **B:** Grade II: cellular intimal proliferation in an abnormally muscular artery. EVG, ×250. **C:** Grade III: occlusive changes. Medium is thickened due to fasciculi of longitudinal muscle, and vessel is all but occluded by fibroelastic tissue. EVG, ×150. **D:** Grade IV: dilatation. Vessel is dilated, and muscular media is abnormally thin. Lumen is occluded by fibrous tissue. EVG, ×150. **E:** Grade V: plexiform lesion. There is cellular intimal proliferation; clustered around are numerous thin-walled vessels that terminate as capillaries in the alveolar wall. EVG, ×95. **F:** Grade VI: acute necrotizing arteritis. A severe reactive inflammatory exudate is seen through all layers of the vessel. Hematoxylin and eosin stain, ×250. (Reproduced from Wagenvoort CA, Health D, Edwards JE. *The pathology of the pulmonary vasculature*. Springfield, IL: Charles C Thomas, 1964, with permission.)

We correlated the quantitative features of abnormal growth and remodeling of the pulmonary arteries and the qualitative changes described by Heath and Edwards with the hemodynamic behavior of the pulmonary circulation in the immediate postoperative period in the intensive care unit, 1 day after repair, and at the time of routine cardiac catheter study (i.e., 1 year later). Patients with grade A or mild grade B changes have normal pulmonary artery pressures in the early postoperative period or only a minimal degree of elevation. Most patients with more severe medial hypertrophy (i.e., severe grade B and Heath-Edwards grade I) have elevated values (8). The observed pulmonary hypertension is frequently labile and almost always can be controlled, and the mechanism and treatment are discussed in the next section. Both the presence and the severity of pulmonary hypertension in the early postoperative period are increasingly predictable when there are more advanced changes on lung biopsy (i.e., reduced artery number, grade C) and intimal hyperplasia (Heath-Edwards grades II and III).

One year after repair, however, patients operated on within the first 8 months of life tend to have normal pulmonary hemodynamics regardless of the severity of vascular changes on lung biopsy, as do all patients with severe grade B (Heath-Edwards grade I) abnormalities, regardless of their age at repair. Patients surgically corrected between 9 months and 2 years of life with grade C and Heath-Edwards grades II or III structural changes may have persistent elevation in pulmonary vascular resistance; this appears inevitable in those operated after 2 years of life (eFig. 107.0.6) (80).



***e*FIGURE 107.0.6 A:** Lung biopsy grade is correlated with mean pulmonary arterial pressure recorded the day after surgical repair. Dashed vertical lines separate normal from abnormally elevated pressure values, and the dotted horizontal lines separate the biopsy grades. Note that with the more severe Heath-Edwards changes on lung biopsy tissue, there is a trend toward a greater proportion of patients with elevated pulmonary arterial pressures and higher values. **B:** Graph correlating lung biopsy grade with pulmonary vascular resistance 1 year after cardiac repair. Patients who underwent repair within the first 8 months of life, but not those operated on later, had normal pulmonary vascular resistance regardless of the severity of their structural changes. *, no patients in this group; A, B, and C, morphometric grades; CAVC, complete atrioventricular canal; complex, associated abnormality; DTGA, D-transposition of the great arteries; m, mild; N, I, II, III, Heath-Edwards grades; n, normal; s, severe; VSD, ventricular septal defect. (Reproduced from Rabinovitch M, Keane JF, Norwood WI, et al. Vascular structure in lung tissue obtained at biopsy correlated with pulmonary hemodynamic findings after repair of congenital heart defects. *Circulation* 1984;69:655–667, with permission.)

A variety of physiologic factors appears to contribute to the severity and rate at which vascular disease develops in patients with congenital heart defects (eTable 107.0.1). It is recognized that certain lesions, such as transposition of the great arteries with intact septum (81) but especially with a large VSD (82) or a patent ductus arteriosus (83), are at high risk. Curiously, there have been reports of the progression of pulmonary vascular disease in infants with transposition of the great arteries, even after successful surgical correction (84). Infants with a large VSD (85), and especially an atrioventricular septal defect (86,87), also develop pulmonary vascular disease in early infancy, and in the latter, there are advanced changes observed even within the first 6 months of life. Patients with cyanotic heart defects who have large surgically created systemic-to-pulmonary artery shunts are also at risk for pulmonary vascular disease (88).

***e*TABLE 107.0.1** FACTORS DETERMINING THE DEVELOPMENT OF PULMONARY VASCULAR DISEASE IN PATIENTS WITH COMMON VARIETIES OF CONGENITAL HEART DISEASE

	Major factors			**Minor factors**				
	↑P_{PA}	**↑P_{PV}**	**↑Q_{PA}**	**↑Po_{2PA}**	**↓ Po_{2SA}**	**↓ pH_{SA}**	**Hematocrit ↑**	**PVD**
ASD, secundum	–	–	+	+	–	–	–	Unlikely
ASD, primum	–	±	+	+	–	–	–	Possible
TAVC	+	+	+	+	±	±	±	Highly probable
Large VSD	+	±	+	+	–	–	–	Probable
With mitral disease	+	+	+	+	–	–	–	Virtually certain

TF	–	–	–	–	+	+	+	Unlikely until late
With Potts	+	±	+	+	±	–	±	Probable
TGA	±	±	+	+	+	±	+	Virtually certain
With VSD	+	+	+	+	+	±	+	Certain

–, absent; +, present; ±, may or may not be present; ASD, atrial septal defect; P, pressure; PA, pulmonary artery; pH_{SA}, pH in systemic artery; Po_{2PA}, oxygen pressure in pulmonary artery; Po_{2SA}, oxygen pressure in systemic artery; P_{PA}, mean pulmonary artery pressure; P_{PV}, mean pulmonary venous pressure; PV, pulmonary vein; PVD, pulmonary vascular disease; Q, flow; Q_{PA}, flow in pulmonary artery; SA, systemic artery; TAVC, total anomalous venous connection; TF, tetralogy of Fallot; TGA, transposition of the great arteries; VSD, ventricular septal defect.
Adapted from Nades AS, Fyler DF. *Pediatric cardiology.* Philadelphia: WB Saunders, 1972:684.

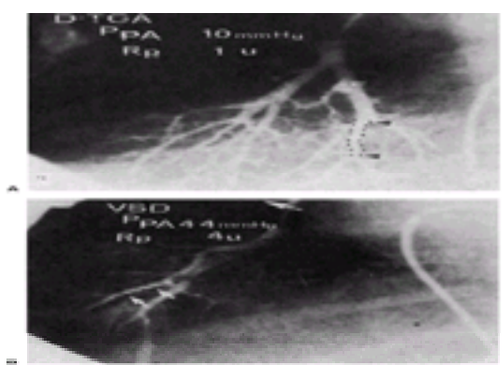
Application of Wedge Angiography

Techniques of wedge angiography have been developed to assess preoperatively the structural state of the pulmonary vascular bed. Changes that can be evaluated quantitatively (i.e., sparsity of arborization of the pulmonary tree, abrupt termination, tortuosity and narrowing of small arteries, reduced background capillary filling) generally reflect advanced changes in the preacinar arteries of at least Heath-Edwards grade III severity (89). A technique has been described that allows quantitative assessment of abnormalities in a pulmonary wedge angiogram (90). A balloon catheter is directed to the origin of the axial artery of the posterior basal segment of the right lower lobe; contrast material is injected, and the injection is filmed on biplane cine. The rate of tapering of the arteries is assessed by measuring the length of a segment over which the lumen diameter narrows between 2.5 mm and 1.5 mm. More abrupt arterial tapering is suggestive of more severe changes in the intraacinar arteries, assessed both morphometrically and by the Heath-Edwards classification (*e*Table 107.0.2 and *e*Fig. 107.0.7).

***e*TABLE 107.0.2** CORRELATION OF THE PATHOLOGY, PHYSIOLOGY, AND ANGIOGRAM IN PULMONARY VASCULAR DISEASE

		Physiology			
Grade	**Pathology**	**Q_P**	**P_{PA}**	**R_P**	**Wedge angiogram**
A	Abnormal extension of muscle into small arteries	↑	N	N	Shows tapering of axial arteries
	mild medial hypertrophy	↑	N	N	
B	A and severe medial hypertrophy	↑	↑	N	Abrupt tapering
C	B and reduced artery, number, and size	±	↑	↑	Very abrupt tapering

↑, increased; ±, may or may not be increased; N, normal; P_{PA}, mean pulmonary artery pressure; Q_P, pulmonary blood flow; R_P, pulmonary vascular resistance.



***e*FIGURE 107.0.7 A:** A wedge angiogram shows slow tapering of the axial artery in a child with D-transposition of the great arteries (D-TGA) and normal pulmonary artery pressure (P_{PA}) and resistance (R_P). Approximate segment length between 2.5- and 1.5-mm internal diameter is marked off (*arrows*). **B:** A wedge angiogram in a child with a ventricular septal defect (VSD) shows rapid tapering of the artery when there is increased pulmonary artery pressure and resistance. An approximate segment length of 2.5- to 1.5-mm internal diameter is marked off (*arrows*). Large arrow denotes takeoff to the right pulmonary artery. (Reproduced from Rabinovitch M. Quantitative structural analysis of the pulmonary vascular bed in congenital heart defects. In: Engle MA, ed. *Pediatric cardiovascular disease.* Philadelphia: FA Davis, 1981:149–169, with permission.)

There are, however, pitfalls and limitations in the interpretation of the pulmonary wedge angiogram. Pulmonary stenosis or previous placement of a pulmonary artery band, owing to poststenotic dilatation, will give the impression of rapid tapering. With advanced vascular disease, there is sometimes such extensive intimal hyperplasia that the vessel appears narrowed all the way from the hilum so that abrupt tapering is no longer apparent. In that situation, however, the background haze is absent, and the pulmonary circulation time usually is prolonged. Technical abnormalities also can result in difficulties in interpretation. If the injection of contrast fails to fill the vessels all the way out to the pleura, the background will appear dark, and if the balloon does not completely occlude the vessel, the false impression of a dense background will be created, owing to filling of capillaries and veins. The circulation-time assessment depends on exclusion of pulmonary vein stenosis and intrapulmonary shunting.

When pulmonary vascular-resistance calculations (based on measured oxygen consumption) are elevated (>8 U•m^2 and nonreactive) and wedge angiography supports extensive structural abnormalities, lung biopsy evaluation has not, in our experience, provided other than confirmatory evidence of severe pulmonary vascular disease. If, however, discrepancies are found or if the patient is in the first 2 years of life, the analysis of lung biopsy tissue, even prepared by frozen section, will help decide on a corrective procedure (91). The ability to predict from biopsy tissue whether even mild elevation in pulmonary vascular resistance will be present postoperatively is also of increasing importance, particularly in the consideration of patients who require a Fontan procedure (92). Patients with tricuspid atresia who have had previous systemic-to-pulmonary artery shunts and those with single ventricle and previous pulmonary artery bands are a particular problem. We currently consider a biopsy showing severe grade C (less than one-half the normal number of arteries) and grade III or greater changes in 20% of vessels to indicate severe vascular disease that is unlikely to regress postoperatively and may preclude a successful result from closure of a VSD; severe grade B, medial wall thickness greater than twice normal, and grade II changes in any vessels may preclude a favorable result from a Fontan procedure. Further studies showed that even minor vascular changes on lung biopsy tissue (mild grade B) are associated with increased morbidity after Fontan procedure, as gauged by prolonged hospitalization because of the need for increased ventilator support and drainage from chest tubes (our unpublished data).

Intravascular ultrasound may hold new promise for estimating the severity of pulmonary vascular disease (93). Noninvasive methods may help estimate the level of pulmonary artery pressure, in addition to pulsed Doppler echocardiography (94), high-resolution computed tomography (95), magnetic resonance imaging (96), and fractal analysis (97).

Postoperative Increased Pulmonary Vascular Reactivity

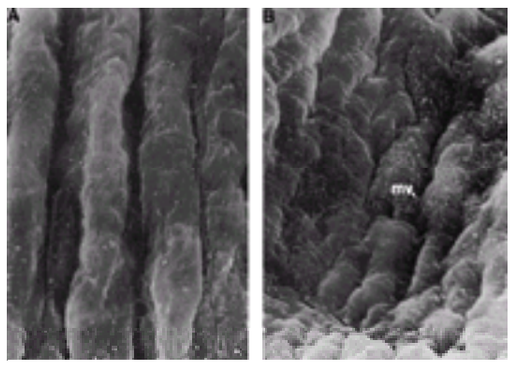
Various methods of managing postoperative increased pulmonary vascular reactivity have been proposed, including prolonged anesthesia with fentanyl (98) and vasodilators such as prostacyclin or, more recently, atrial natriuretic peptide or inhaled NO, which has proven to be particularly useful (99,100 and 101). Infusion of L-arginine also may hold promise (102), as do endothelin receptor antagonists (77,103,104). Adenosine (105,106) and amrinone (107) also have been used effectively to dilate the pulmonary vascular bed. Recent studies have shown beneficial effects with inhaled NO (108) or aerosolized prostacyclin (iloprost) (109). In our own unit, we have benefited from continuous monitoring of pulmonary artery and left atrial pressure. To maintain the pulmonary artery pressure at less than or equal to half systemic level, we institute hyperventilation (carbon dioxide tension 25 to 30 mm Hg) for the first 24 hours. We are currently assessing whether weaning from the ventilator can be accomplished more effectively using NO or phenoxybenzamine. Usually, the use of the extracorporeal membrane oxygenator (110) or ventricular assist devices is necessary only when there is severe ventricular dysfunction. Experimentally, cardiomyoplasty has been successful in providing hemodynamic support during acute pulmonary hypertension (111). Experimental studies with left-to-right shunts have related the pulmonary hypertension to increased production of endothelin, reduced “dilator” endothelin B receptors (112), and impaired endothelial-dependent relaxation (113,114). In addition, NO can suppress the pulmonary vascular remodeling associated with pulmonary hypertension (115). There is experimental evidence that reduction in pulmonary artery pressure per se will induce regression of even advanced pulmonary vascular disease induced by high flow and endothelial injury (116).

A few patients, however, maintain a high level of pulmonary vascular resistance and are refractory to vasodilator therapy despite what appear to be mild vascular

changes on light microscopy (medial hypertrophy), and there are other patients who develop rapidly progressive pulmonary vascular disease despite early diagnosis and timely intervention. For these patients, the prognosis may not be much better than those with unexplained pulmonary hypertension (117). Therapies for the patient with Eisenmenger's have included chronic oxygen (118), anticoagulants (119), and palliative surgical procedures, including atrial septal defect creation (120,121), and intravenous (122), aerosolized (123), or oral prostacyclin (124), although the results from nonintravenously administered prostacyclin are less encouraging. Generally, these measures are taken to gain time in anticipation of a heart-lung transplantation, a heterotopic heart transplantation, or surgical correction along with single-or double-lung transplantation (125,126,127 and 128).

Mechanisms Underlying the Reactive Pulmonary Circulation

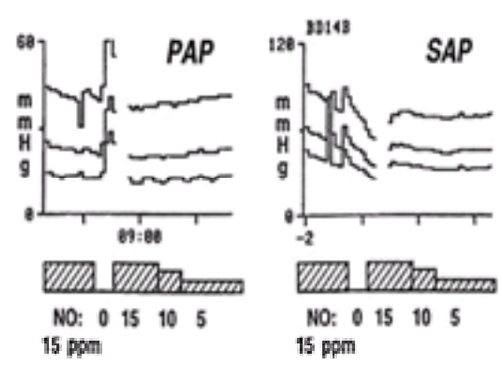
Many factors could contribute to the hyperreactive pulmonary circulation. We observed endothelial changes on scanning and transmission electron microscopy, suggesting a potential for altered function, as well as increased interaction with circulating blood elements, such as platelets and leukocytes (*e*Fig. 107.0.8) (129,130,131,132 and 133), through the release of thromboxanes (131) and other vasoactive mediators such as angiotensin II. In fact, angiotensin II elevation is attributed to an elevation in both angiotensin-converting enzyme (134) as well as mast cell chymase, which can also produce endothelin-1 (135). In addition, alterations in the subendothelium reflected in fragmentation of elastin suggest that an elastolytic enzyme might be stimulating the remodeling process as well as altering the functional response of the vessel. On scanning electron microscopy, the endothelial surface of normal thin-walled pulmonary arteries has a "corduroy-like" appearance in that the cells form narrow, even ridges. In contrast, the endothelial surface of hypertensive thick-walled pulmonary arteries has a "cable-like" texture in that the cells form deep, twisted ridges. In patients with advanced pulmonary vascular changes, the endothelial surface exhibits a chenille pattern in which high ridges alternate with narrow, twisted, misshapen ones. If this abnormally contoured endothelium is more likely to interact with marginating blood cells (platelets and leukocytes), the result might be the release of pulmonary vasoconstrictor substances, such as thromboxanes and smooth muscle mitogens. Platelet-activating factor also may be important, although its effect is likely local, as an increase in circulating levels of this agent has not been documented in patients after repair of a congenital heart defect (133). On transmission electron microscopy, an increased density of microfilament bundles and rough endoplasmic reticulum are seen. The former suggests an altered cytoskeleton, which may affect endothelial permeability, and the latter is associated with increased protein synthesis and metabolic activity.



***e*FIGURE 107.0.8** Scanning electron photomicrographs of pulmonary artery endothelial surfaces. **A:** Normal pulmonary artery shows "corduroy" pattern, closely aligned ridges. **B:** Hypertensive pulmonary artery shows "cable" pattern, deep knotted ridges, and numerous microvilli (mv). ×810. (Reproduced from Rabinovitch M, Bothwell T, Hayakawa BN, et al. Pulmonary artery endothelial abnormalities in patients with congenital heart defects and pulmonary hypertension: a correlation of light with scanning electron microscopy and transmission electron microscopy. *Lab Invest* 1986;55:632–653, with permission.)

We showed by immunohistochemistry that hypertensive endothelial cells produce increased von Willebrand factor (factor VIII). The factor VIII:Ag levels were significantly higher in patients with congenital heart defects and elevated pulmonary artery pressure than in those with normal pressure, but the molecule being secreted was lacking in biologic activity. Under conditions that aggravate the endothelial dysfunction (e.g., cardiopulmonary bypass), von Willebrand factor biologic activity is markedly increased (132), which could account for the development of platelet fibrin microthrombi in the postoperative period and for the abnormal release of vasoactive compounds, causing increased vascular reactivity. In recent studies, an increased density of neuroepithelial bodies has been observed in the airways of patients at risk for this complication as well as an elevation in vasoconstrictor neuropeptide-containing nerves (10). The neuroendocrine cells, which are also oxygen sensors (11), contain bombesin and serotonin, agents known to be potent vasoconstrictors. Because most of the pulmonary hypertensive crises occur on weaning from the ventilator, it is tempting to speculate that "swings" in airway pressure might lead to degranulation of the neuroepithelial cells and release of the vasoconstrictor substances. To support this, we observed a striking decrease in lung compliance accompanying the pulmonary hypertensive crisis (136).

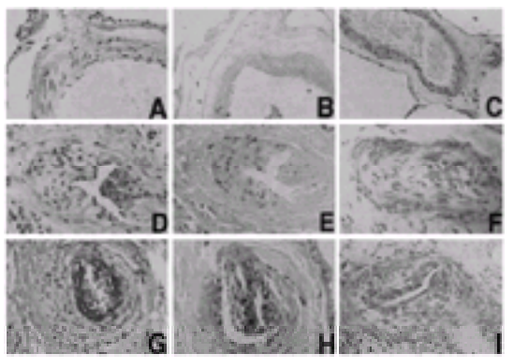
There is now very convincing evidence that endothelial-dependent relaxing factor, or NO, is lacking in hypertensive pulmonary arteries of patients with Eisenmenger's syndrome and the production of endothelial-dependent relaxing factor is impaired beginning at an early time in patients with congenital heart defects (137,138,139 and 140). Injury to the endothelium after cardiopulmonary bypass likely explains the further decrease in endothelial-dependent relaxing factor production, which has prompted the successful use of NO in the postoperative patient (*e*Fig. 107.0.9). There is also evidence that production of the vasoconstrictor endothelin might be increased in patients with pulmonary hypertension and congenital heart defects (141,142). Because endothelin is proproliferative as well as vasoconstrictive, it is tempting to speculate that mechanical factors may mediate the increase in DNA associated with cell proliferation (143) through release of endothelin. Receptors for growth factors such as platelet-derived growth factor are increased in response to mechanical forces as well (144).



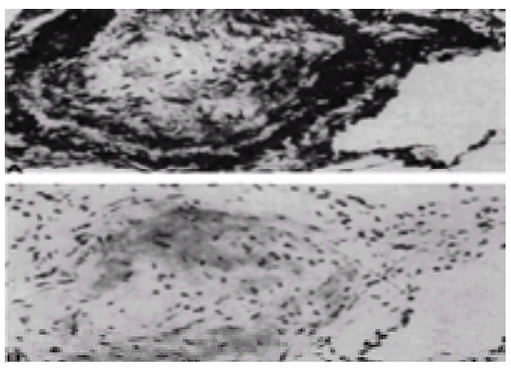
***e*FIGURE 107.0.9** Systemic (SAP) and pulmonary (PAP) artery recordings from the bedside monitor in a 1-day-old patient immediately after repair of obstructed total anomalous pulmonary venous connection. Systolic, mean, and diastolic pressures are recorded each minute. Stable SAP and PAP are noted on 15 ppm of nitric oxide (NO). When the NO is transiently stopped, there is a prompt increase in PAP and decrease in SAP. With reinstitution of NO, recovery occurs. (Reproduced from Adatia I, Wessel DL. Diagnostic and therapeutic uses of inhaled nitric oxide in congenital heart disease. In: Zapol WM, Bloch KD, eds. *Nitric oxide and the lung.* New York: Marcel Dekker, 1995:365–392, with permission.)

Nature of the Vascular Lesions

Our recent immunohistochemical studies carried out in lung biopsy tissue from patients with congenital heart defects showed that the deposition of tenascin and fibronectin in the media and neointima increases progressively with the severity of the lesion (*e*Fig. 107.0.10) (145). We related increased expression of tenascin to vascular smooth muscle cell proliferation (146) in cultured smooth muscle cells, and in fact, there is colocalization of tenascin with proliferating smooth muscle cells, as judged by the proliferating cell nuclear antigen and with expression of growth factors such as epidermal growth factor in human lung tissue. We also related fibronectin to increased smooth muscle cell migration in the context of neointimal formation (147). Studies by other investigators found evidence that the neointimal lesions in the context of primary pulmonary hypertension are associated with increased expression of TGF-b (148) and procollagen (*e*Fig. 107.0.11) (149) in addition to fibronectin (150). It is also proposed that endothelial cell proliferation and a form of angiogenesis are observed with plexiform lesions (151).



***e*FIGURE 107.0.10** Representative photomicrographs showing immunoperoxidase staining for tenascin-C (TN) **(A,D,G)**, proliferating cell nuclear antigen (PCNA) **(B,E,H)**, and epidermal growth factor (EGF) **(C,F,I)** in graded lung biopsy tissue sections. **A–C:** Vessel showing a typical grade I^A lesion. **D–F:** Vessel showing a typical grade I^C lesion. **G–I:** Vessel showing a typical grade III^C lesion. In low-grade lesions **(A)**, modest TN immunostaining was evident in the adventitia. With medial hypertrophy, TN immunoreactivity became more prominent in the periendothelium **(D)**, with the most intense immunostaining being apparent within the neointima of high-grade lesions showing occlusive neointimal formation **(G)**. In the lowest grade of lesion, PCNA was negative **(B)**, despite foci of EGF in the media. With medial hypertrophy, PCNA was expressed in the media **(E)**, together with foci of EGF **(F)**. With the development of higher grade occlusive lesions, TN **(G)**, PCNA **(H)**, and EGF **(I)** colocalized to the neointimal cell layers. Note that TN and PCNA staining was performed on serial sections, whereas EGF detection was carried out on similar vessels within the same biopsy. ×40. (Reproduced from Jones PL, Cowan KN, Rabinovitch M. Progressive pulmonary vascular disease is characterized by a proliferative response related to deposition of tenascin-C and is preceded by subendothelial accumulation of fibronectin. *Am J Pathol* 1997;150:1349–1360, with permission.)



***e*FIGURE 107.0.11** Immunohistochemistry was performed on formalin-fixed, paraffin-embedded parenchyma obtained from patients with severe primary pulmonary hypertension at the time of single-lung transplantation. Tissue sections then were stained with antibodies to the aminoterminal end of the procollagen type 1 propeptide **(B)**. This antibody identifies newly synthesized a-I(I) procollagen before cleavage of the aminoterminal propeptide after secretion and therefore can identify sites of active collagen deposition. An elastin–van Gieson stain demonstrates vascular structures **(A)**. Procollagen immunoreactivity **(B)** is present only within the neointima of this occluded artery. ×10. (Reproduced from Botney MD, Liptay MJ, Kaiser LR, et al. Active collagen synthesis by pulmonary arteries in human primary pulmonary hypertension. *Am J Pathol* 1993;143:121–129, with permission.)

Experimental Studies

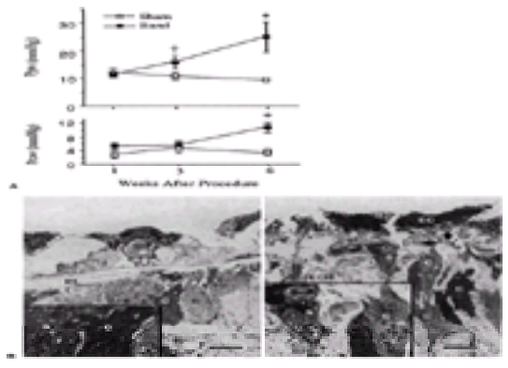
In experimental studies, high pulmonary blood flow alone produced by pneumonectomy (152), single pulmonary artery banding, or ligation (153,154 and 155) results in minimal, if any, elevation in pulmonary artery pressure and structural changes in the vessels. Slight elevation in pulmonary artery pressure is accompanied by extension of muscle into peripheral arteries. Aortopulmonary shunts surgically created in growing piglets are associated with a progressive increase in pulmonary artery pressure and with the development of structural changes, specifically, extension of muscle into peripheral arteries, medial hypertrophy of muscular arteries, and reduced arterial number (155). Takedown of the shunts during the period of rapid lung growth results in regression of the structural changes and of pulmonary hypertension (156). However, even reduction in pressure in adult animals results in regression of vascular disease (116). Creation of large aortopulmonary shunts in dogs, particularly into a single pulmonary artery, results in rapidly progressive pulmonary vascular changes (157,158). Several additional experimental models of high-flow congenital heart defects have been created, including lambs with a VSD (159) or placement of an aortopulmonary shunt in fetal lambs *in utero* (104), in sheep (158), or in calves (160). In addition to abnormalities in endothelial-dependent relaxation and in the production of vasoconstrictors previously discussed, many common features link the cellular and molecular pathophysiology of pulmonary vascular disease regardless of etiology; this subject is discussed at the end of the chapter.

High Pulmonary Venous Pressure–Pulmonary Vascular Disease

Advanced pulmonary vascular disease is unlikely to occur rapidly in patients with congenital heart defects related to increased pulmonary venous pressure. Collins-Nakai et al. (161), however, reported changes greater than Heath-Edwards grade III in most older children with congenital mitral stenosis in their series. In patients with total anomalous pulmonary venous connection, abnormal muscularization of the small arteries and veins has been observed from birth, and more severe structural changes (i.e., Heath-Edwards grade III) have been described in infants as young as 1 month (162). In infants with hypoplastic left heart syndrome, medial hypertrophy of the small arteries and veins from birth is so severe that it must have developed *in utero* (163,164). The presence of pulmonary vascular changes in defects and the capacity for these abnormalities to regress with improvement in hemodynamics may be of relevance because the Norwood staged surgical procedure for the treatment of hypoplastic left heart syndrome ultimately depends on the success of a bidirectional cavopulmonary shunt and a right atrial-to-pulmonary artery anastomosis or tunnel. Recent studies showed that manipulation of oxygen and carbon dioxide can successfully control pulmonary blood flow and resistance in managing infants with hypoplastic left-sided heart syndrome preoperatively and postoperatively (165). In both adults and children with rheumatic mitral stenosis, Wagenvoort and Wagenvoort (166) observed increased medial wall thickness of the pulmonary arteries; in children, this is due to hyperplasia of smooth muscle cells, but in adults, only hypertrophy is present.

Experimental Studies

Pulmonary venous hypertension has been reproduced experimentally by banding the pulmonary veins (167,168), by elevating left atrial pressure (169), or by creating coarctation of the aorta *in utero* in fetal lambs (170). In studies from our laboratory, LaBourene et al. (168) banded the pulmonary veins in newborn piglets and observed a striking decrease in compliance of the pulmonary veins after 1 week but no change in pulmonary hemodynamics. By 3 weeks, there was pulmonary arterial hypertension without elevation in pulmonary venous pressure; by 6 weeks, further progression of pulmonary hypertension was associated with elevated pulmonary venous pressure (*e*Fig. 07.0.12). Ultrastructural changes in the veins were seen at 1 week, consisting of fragmentation of elastin and a phenotypic switch in medial smooth muscle cells in which they appeared to be more synthetic and to be migrating toward the subendothelium (*e*Fig. 107.0.12). By 3 weeks, there was already evidence of intimal proliferation; by 6 weeks, collagen had increased in the walls of the pulmonary veins. This study suggests that pulmonary hypertension may be the first sign of pulmonary venous obstruction and that elevation of pulmonary venous pressure is associated with considerable structural remodeling. This may explain the frequent failure of surgical therapy in correcting pulmonary vein stenoses and suggests that it should be undertaken at the earliest suggestion of this disease and with a novel approach minimizing suture lines (171).



***e*FIGURE 107.0.12 A:** Pulmonary artery pressure (Ppa) (*upper panel*) and pulmonary capillary wedge pressure (Pcw) (*lower panel*) in banded and sham-operated piglets 1, 3, and 6 weeks after banding. Values are averages of mean ± SEM (n = 6 piglets per group at each time point). At 1 week, there was no change. At 3 weeks, there was a significant increase in P_{pa}, which preceded the rise in P_{cw} at 6 weeks and a further increase in P_{pa} (**p* <.01; †*p* <.05). **B:** Transmission electron photomicrographs of representative pulmonary veins (PVs) from banded (*right panel*) and sham-operated (*left panel*) piglets at 3 weeks after banding (×14,131) (inset, ×28,263). Both pulmonary veins show apparent injury and lifting of endothelial cells and subendothelial spaces due to poor preservation during handling. Sham-operated PV displays on intact internal elastic lamina (IEL) and predominantly contractile-appearing smooth muscle cells (C) in media. In contrast, PV from banded piglet depicts complete breakdown of IEL into elastin fragments (Efg), a thickened subendothelium composed of collagen, extracellular matrix (ECM), and smooth muscle cells that appear to have migrated in from the media, many of which have a synthetic-appearing phenotype (S) exemplified by a large amount of endoplasmic reticulum and a corresponding paucity of contractile filaments. C and S smooth muscle cells are better appreciated in insets. Bar = 1 µm. (Reproduced from LaBourene JI, Coles JG, Johnson DJ, et al. Alterations in elastin and collagen related to the mechanism of progressive pulmonary venous obstruction in a piglet model: a hemodynamic, ultrastructural, and biochemical study. *Circ Res* 1990;66:438–456, with permission.)

Decreased Pulmonary Blood Flow

In patients with congenital heart defects causing low pulmonary blood flow, hypoplasia of the pulmonary arterial musculature is observed; in those in whom the hematocrit is particularly elevated, thromboembolic changes occur (172,173,174,175,176,177 and 178). The creation of systemic to pulmonary artery shunts may improve the hypoplasia, but secondary to abnormally high flow and pressure, medial hypertrophy and intimal hyperplasia soon occur. Recent studies suggest that the potential for growth of the central pulmonary arteries is correlated with the proportion of elastin in the media, and the same may be true for the intrapulmonary vessels (178).

On the postmortem arteriograms in patients with decreased pulmonary blood flow, the axial arteries are abnormally narrow in lumen diameter (4). On microscopic examination of the lung, the intraacinar pulmonary arteries are abnormally thin-walled, small, and few. Alveolar development is impaired in patients with decreased pulmonary blood flow. Patients with tetralogy of Fallot and associated pulmonary atresia form a special subgroup in which the relative distribution of central pulmonary arteries and aortopulmonary collaterals determines peripheral pulmonary vascular structure (4,176).

Experimental Studies

Levin et al. (179) also created low pulmonary blood flow by banding the main pulmonary artery of fetal lambs. The changes in the lung resembled those seen clinically in that there was diffuse hypoplasia of the musculature of the peripheral pulmonary vessels. Haworth et al. (180) ligated the left pulmonary artery in newborn piglets and demonstrated normal development of the intraacinar arteries owing to extensive anastomoses with bronchial arteries and occlusive fibrosis in the preacinar vessels.

CHRONIC HYPOXIA-INDUCED PULMONARY VASCULAR DISEASE

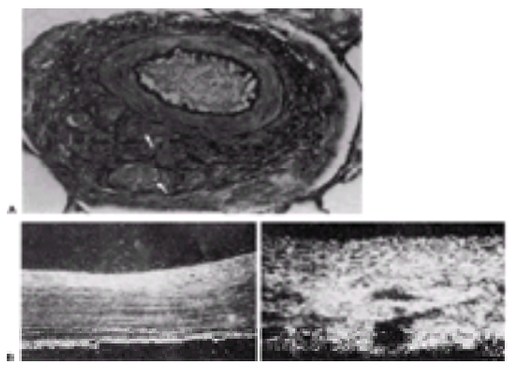
High-Altitude Hypoxia

In those living at high altitude, there is chronic elevation of pulmonary artery pressure present, only a small portion of which is reversible with administration of oxygen (181,182). The peripheral arteries are more muscular than normal and have a decreased lumen diameter. The severity of pulmonary hypertension is variable and almost always improves on return to sea level, at least at rest. In response to exercise, it may increase markedly, suggesting limited functional reserve, owing to persistent structural abnormalities (183).

Experimental Studies

The degree of reactivity to hypoxia or the level of pulmonary hypertension with chronic hypoxia may be a function of the amount of smooth muscle in the pulmonary vascular bed, the llama having the least muscle and being the least reactive (184). In the rat, the development of structural changes and sustained pulmonary hypertension appears to occur after 3 days of chronic hypoxia (air at half atmospheric pressure, oxygen partial pressure = approximately 40 mm Hg). Over the ensuing 2 weeks, pulmonary artery pressure progressively doubles and is associated with progressive extension of muscle into peripheral normally nonmuscular arteries, medial hypertrophy of normally muscular arteries, and reduction in arterial number, and right ventricular hypertrophy is evident. The hemodynamic and structural responses progress slowly thereafter. The structural changes induced by hypoxia appear to be less severe in mature female experimental animals, and those of both sexes exposed to hypoxia through the period of development may show less potential for regression (185,186). Regression of smooth muscle hypertrophy may be accompanied by a relative increase in the amount of elastin and collagen (187), so the vessel, although less muscular, nonetheless may be abnormally noncompliant (188). Collagen increases in hypertensive pulmonary arteries, and stretch may be the stimulus (189,190 and 191); inhibition of collagen synthesis decreases chronic hypoxic pulmonary hypertension and vascular changes (192). Recent work suggests that increased activity of metalloproteinases may be evident in the regression of vascular disease (193), but inhibition of metalloproteinases appears to aggravate experimental pulmonary hypertension in rats (194). Loss of small arteries may not, however, be recoverable, explaining why the pulmonary vascular bed may have limited functional reserve.

Stenmark et al. (195) took newborn calves to a simulated high altitude of 4,300 m and observed severe pulmonary hypertension with right-to-left shunting owing to the rapid development of suprasystemic levels of pulmonary artery pressure. There was striking medial hypertrophy and remarkable proliferation of a dense adventitial sheath that, in large vessels, was sometimes seen to exhibit neovascularization (eFig. 107.0.13). Hypoxia-induced adventitial fibroblast proliferation has been related to protein kinase C (zeta isoform) (196). Further studies have shown striking synthesis of elastin in the pulmonary arteries of these neonatal calves (eFig. 107.0.13) (13,14). There may be a role for insulin-like growth factor I, as increased expression of this growth factor stimulates elastin synthesis in cultured vascular cells (197), as does TGF-b (198). Studies in the piglet by Allen and Haworth (199) showed that when the animal is subjected to hypoxia from birth, the fetal medial musculature does not regress, but connective tissue synthesis is not stimulated. When hypoxic exposure begins at 3 days of age, however—that is, after the fall in pulmonary vascular resistance and the regression of the fetal musculature—neosynthesis of elastin is apparent.



***e*FIGURE 107.0.13 A:** An artery from the lung of a 2-week-old calf raised at a simulated altitude of 4,300 m from birth. Pulmonary artery systolic pressure was 100 mm Hg. There is marked medial hypertrophy and adventitial thickening with neovascularization (*arrows*). Elastin tissue stain, ×400. (Reproduced from Rabinovitch M. Pathophysiology of pulmonary hypertension. In: Emmanouilides GC, Allen HD, Thomas AR, Howard PG, eds. *Moss and Adams heart disease in infants, children, and adolescents including the fetus and young adult*, 5th ed. Baltimore: Williams & Wilkins, 1995:1659–1695, with permission.) **B:** *In situ* hybridization localization of

tropoelastin messenger RNA (mRNA) in control and hypertensive vessels from neonatal calves. White staining over areas indicates tropoelastin mRNA labeling. In normotensive vessels (*left*), labeled cells (^{35}S-labeled T66-T7) were confined to the inner media. Minimal signal is noted in the outer vessel wall. In vessels from hypertensive animals (14 days of hypoxia) (*right*), intense autoradiographic signal was observed throughout the media, albeit in a patchy distribution. (Reproduced from Prosser IW, Stenmark KR, Suthar M, et al. Regional heterogeneity of elastin and collagen gene expression in intralobar arteries in response to hypoxic pulmonary hypertension as demonstrated by in situ hybridization. *Am J Pathol* 1989;135:1073–1088, with permission.)

A variety of studies attempted to show how acute vasoconstriction or a direct hypoxic "injury" initiates the structural changes observed in the pulmonary arteries. Angiotensin II appears to be unimportant as a hypoxic vasoconstrictor but nonetheless is critical to the mechanism responsible for inducing vascular disease because of its biologic properties in stimulating vascular smooth muscle cell hypertrophy and proliferation (200). Chronic hypoxia is also associated with an increase in angiotensin I and II receptors (201). On the other hand, we showed that chronic infusion of angiotensin II by releasing prostacyclin is actually protective of the pulmonary hypertension and vascular changes that develop during exposure to chronic hypoxia (202). Fetal and neonatal lamb pulmonary artery smooth muscle cells in culture show a decrease in the production of prostacyclin in response to acute hypoxic exposure (203), as do bovine endothelial cells (204). Although a variety of vasoactive blockers will lower pressure, endothelin receptor blockade appears to be most promising as a selective strategy in reversing acute hypoxia-induced pulmonary vasoconstriction as well as the remodeling associated with chronic exposure. These studies have provided convincing evidence that the high endothelin levels observed are causally related to hypoxic vasoconstriction (205,206). In addition, hypoxia inhibits endothelin receptor B–mediated NO synthesis (207). Impaired NO synthesis and vasodilatation in chronic hypoxia are also associated with impaired cyclic guanosine monophosphate–dependent mechanisms (208). Agents also shown to be effective in the treatment of chronic hypoxic pulmonary hypertension in rats include inhibitors of 5-lipoxygenase activating protein (209) as well as of cyclic 3',5' guanosinemonophosphate-specific phosphodiesterase (210) and continuous inhalation of NO (211). Additional strategies are aimed at preventing acute hypoxic vasoconstriction by blocking potassium channels (212,213). Recent studies in transgenic mice suggest that genetic factors might modulate the response to chronic hypoxia. For example, in the absence of hemoxygenase 1, there is reduced production of CO and its associated vasodilatory effects (214). Prostacyclin synthetase overexpression is protective against the hemodynamic and vascular changes of pulmonary hypertension (215). Serotonin has been implicated in the increased vasoreactivity of the fawn-hooded rat (216), and there is attenuated severity of pulmonary vascular disease in mice lacking the serotonin transporter gene (217). We also showed that endogenous or exogenous (unpublished) serine elastase inhibitors will effectively reduce chronic hypoxia-induced pulmonary hypertension (218).

In addition, experimental studies of Thompson et al. (219) and Benitz et al. *in vitro* (220) suggest that vascular smooth muscle growth inhibitors may be useful in preventing vascular disease. Heparin infusion will decrease the severity of hypoxia-induced vascular changes, presumably by decreasing smooth muscle hyperplasia. The influence of the Na/H antiporter in the mechanism of heparin-induced inhibition of smooth muscle cell growth is currently being addressed (221). Recent studies have also shown that calcitonin gene–related peptide administered by gene transfer not only attenuated hypoxia-induced vasoconstriction and remodeling but also enhanced the effects of phosphodiesterase inhibitors (222).

Lung Disease

Clinically, lung disease is the most common cause of hypoxia-induced pulmonary vascular disease. The pulmonary hypertension may be the result of hypoxic vasoconstriction-induced abnormalities described above, compounded by the adverse effects of long-standing polycythemia (microthrombi) and elevated pulmonary venous pressure secondary to dysfunction of the hypoxemic left ventricle. Treatment of the lung disease will decrease the level of pulmonary artery pressure and hence allow some regression of the structural changes. It is of interest that the severity of the vascular lesions and associated elevation in pulmonary vascular resistance, even with extensive lung disease, is usually so much more manageable than that observed with congenital heart disease. Cor pulmonale is discussed in detail in Chapter 27. Pulmonary vascular disease is rare with obstructive lung disorders, such as asthma (223), and more common with parenchymal disorders associated with loss of tissue, such as cystic fibrosis (224), in which it is more likely a late complication. Restrictive lung disease also may be associated with pulmonary hypertension. Restrictive lung disorders include diffuse interstitial fibrosis (Hamman-Rich) (225), radiation fibrosis and chemotherapy toxicity (226), and infiltrative lung tumors (227). Neuromuscular disorders affecting the chest wall [e.g., Duchenne's muscular dystrophy (228) and Werdnig-Hoffmann disease] also can cause pulmonary hypertension, as can diseases affecting the vertebrae and rib cage, such as severe scoliosis (229,230).

Upper Airway Obstruction

Severe upper airway obstruction from a variety of causes may be complicated by the development of pulmonary hypertension. Obstructive sleep apnea may be associated with the pickwickian syndrome (231,232). Obesity, through the increased work of breathing and carbon dioxide production, stresses the respiratory control system, and depending on its inherent sensitivity, hypoventilation may result, causing further carbon dioxide retention and hypoxia, which contribute to the lethargy and cor pulmonale. Damage to the respiratory center is rarely a primary disorder (Ondine's curse) or secondary to trauma or other neurologic disease. Although removal of the airway obstruction often results in a prompt return to normal pulmonary artery pressure and resolution of the heart failure, these symptoms can persist for some time due to slow regression of hypoxia-induced structural changes in the pulmonary vascular bed or persistent impairment of ventilatory drive.

THROMBOEMBOLIC DISEASES

Diagnosing thromboemboli as a cause of pulmonary hypertension requires a high index of suspicion in patients who have disorders in which the former are likely to occur. Deep vein thrombosis (233), right-sided endocarditis, and right atrial myxoma also may be sources of emboli (234). Patients with sickle cell anemia may develop pulmonary thromboses and infarctions (235), and thromboemboli occur in children with ventriculoatrial shunts for hydrocephalus (236). In endogenous areas, ova emboli resulting from schistosomiasis have been described (237), and fatal emboli may occur secondary to trauma or in association with collagen vascular disease (238). Tumor emboli may carry metastatic disease from the kidneys or other abdominal organs or may be present in association with infiltrative carcinomatous disease of the lung (239), and thromboembolic pulmonary hypertension is associated with tumor chemotherapy as well as steroids (240). There is little direct evidence that oral contraceptives alone will cause the development of pulmonary vascular disease in women; these compounds probably should be avoided, however, particularly in susceptible women, such as those with congenital heart defects and pulmonary hypertension. Diagnosis of the nature and severity of embolic phenomena may be established by chest radiographs and lung scans, although occasionally angiography is necessary. Recent advances have been made in treatment by thromboendarterectomy (241).

The pulmonary hypertension of thromboembolic disease is likely related to both the structural damage and occlusion as well as to the concomitant release of vasoactive substances from degenerating platelets. The microscopic features of thromboembolic disease reflect both the patchy nature of the abnormalities and the eccentricity of the fibrotic lesions (242)—that is, some vessels show evidence of having been completely occluded and later recanalized, but in other areas, vessels are increased both in size and concentration, suggesting compensatory dilatation and recruitment.

PORTAL HYPERTENSION

Intrahepatic portal hypertension resulting from severe liver disease causing cirrhosis and extrahepatic portal hypertension due to portal vein thrombosis have been associated with pulmonary hypertension (243,244,245,246 and 247). The pulmonary vascular changes include medial hypertrophy, occlusive cellular intimal hyperplasia, plexiform lesions, and dilatation complexes (246,247). It has been postulated that the "toxic liver" is unable to degrade a certain vasoconstrictor or toxin that circulates through the lung in high concentration, inducing structural changes in the vessels. In some patients with liver disease, however, there is generalized vasodilatation of the vessels in the lung (247), and there are also cases in which large vascular fistulae between pulmonary and hepatic arteries are observed, suggesting abnormal production of a different metabolite or a different end-organ response. Severe pulmonary hypertension should not, however, be considered a contraindication to liver transplantation, because regression of the hemodynamic abnormalities has been described (248).

GRANULOMATOUS AND COLLAGEN VASCULAR DISEASE

Pulmonary hypertension may occur with sarcoidosis as a result of the presence of obstructive granulomas within the pulmonary arteries (249). It is also a complication of certain collagen vascular diseases (e.g., commonly scleroderma); the CREST syndrome (*c*alcinosis cutis, *R*aynaud's phenomenon, *e*sophageal dysfunction, *s*clerodactyly, and *t*elangiectasias) (250,251); and, more rarely, systemic lupus erythematosus (252,253), rheumatoid arthritis (254,255), Takayasu's arteritis (256), polymyositis (257), and dermatomyositis (258). Most recently, severe pulmonary hypertension has been associated with acquired immunodeficiency syndrome, even in the absence of lung parenchymal disease (259,260), and has been reproduced experimentally (261). Moreover, the development of pulmonary hypertension in the subset of patients with human immunodeficiency virus infection may be a function of the immunogenetic background (i.e., human leukocyte antigen class II alleles) (262).

The structural basis for the pulmonary hypertension of collagen vascular disease is usually a vasculitis believed to be immune/inflammatory in origin and usually observed in the absence of or with minimal evidence of parenchymal lung disease. Thromboembolic phenomena also have been described, particularly in association with the antiphospholipid syndrome (263). There is also high circulating endothelin-1 described in subsets of patients with systemic sclerosis (264). There may be many

pathophysiologic similarities between the immune/inflammatory–mediated postcardiac transplant coronary artery disease, which we and others have studied, and collagen vascular disease–associated pulmonary hypertension. We showed experimentally that the neointimal formation seen in the coronary arteries is mediated by an increase in serine elastase activity (265), which together with an increase in cytokine release (266) induces the production or release of gene products, such as vascular cell adhesion molecule 1, inflammatory cell adhesion molecule 1, and fibronectin (267,268). These molecules are associated with neointimal formation related to smooth muscle cell proliferation and migration. In our studies, cytokine blockade with the tumor necrosis factor-a–soluble receptor (269), the VLA-4 integrin inhibitor CS-1 (270), which prevents interaction between fibronectin and T cells, and the elastase inhibitor elafin (271) all can serve to reduce markedly the incidence and severity of coronary artery neointimal lesions in rabbits after heterotopic transplant. These same strategies might be relevant to the treatment of pulmonary vasculitis–associated pulmonary hypertension. Recent studies have shown good results from intravenous epoprostenol in the treatment of pulmonary hypertension associated with immune inflammatory diseases such as lupus (272).

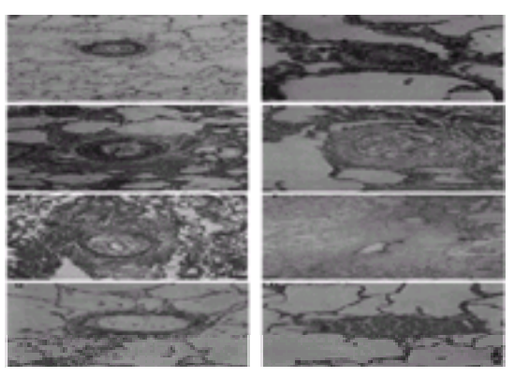
DRUGS

The ingestion of various substances is known to be associated with pulmonary hypertension (273). These substances include aminorex, which resembles epinephrine in its chemical structure, suppresses appetite, and causes symptoms of right-sided heart failure in 10% of patients within 6 to 12 months of initial administration (274), and the fenfluramine compounds, most recently, dexfenfluramine, a serotonin antagonist (275). The mechanism whereby these compounds induce progressive pulmonary hypertension is uncertain, but there is no evidence that they are vasoconstrictors (276), although they can be responsible for the release of intracellular calcium (277). Pathophysiologic studies have also suggested that there are similarities to primary pulmonary hypertension in terms of monoclonal expansion of endothelial cell populations (278). The toxic oils, such as rapeseed oil, also have been implicated in the development of malignant pulmonary hypertension (279). Ingestion of pyrrolizidine alkaloids, such as bush tea, causes hepatic venoocclusive disease, and a similar compound, monocrotaline, when ingested by animals, causes pulmonary vascular disease (280). In many cases, there has been regression on termination of the treatment, but in other cases, the disease presumably was detected at a very advanced stage or persisted in a malignant course. Microscopic changes in the lung were similar to those in patients with end-stage pulmonary vascular disease, regardless of etiology (i.e., medial hypertrophy and intimal fibroelastosis), including the presence of plexiform and dilatation lesions (279).

UNEXPLAINED PULMONARY HYPERTENSION

After all known causes of pulmonary hypertension have been ruled out, the diagnosis becomes that of idiopathic pulmonary hypertension. This unexplained disease, in which a structural abnormality is always found either in the arteries or in the veins, occurs both in children and adults and sometimes with a familial tendency (281,282,283,284,285 and 286). Recently a breakthrough has been made in the discovery of the locus and more recently the mutation in the gene associated with 40% of familial cases of pulmonary hypertension (282,283,284,285 and 286). The mutation discovered was in the gene for bone morphogenetic protein receptor II (285,286), a receptor for growth factors of the TGF-b receptor family. More recently, mutations in this pathway have been described in sporadic cases of primary pulmonary hypertension (287,288). Many studies are currently addressing the pathophysiologic mechanism involved, but bone morphogenetic protein receptor II signaling might suppress intracellular mechanisms responsible for the proliferative response associated with pulmonary hypertension. Other studies using cDNA array technology have suggested that there might be mutations in the genes for TGF-b receptor II, *Bax* (antiapoptosis) (289), and a homeobox gene *HOXA5* (290).

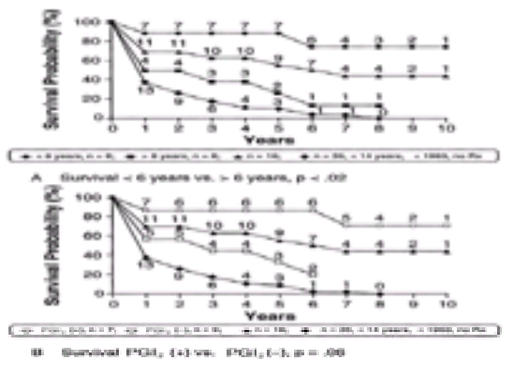
By the time the patient becomes symptomatic, the disease is usually advanced. In the absence of treatment, it is usually rapidly progressive and invariably fatal, although rare cases of spontaneous regression have been reported (291,292). The preponderance of affected females ranges in some studies from a ratio of 4:1 to 2:1 (117). In general, there is an inverse relationship between the age of onset of symptoms and the duration of illness until death. In young children, the pathobiology suggests failure of the neonatal vasculature to open and a striking reduction in arterial number (293). In older children, intimal hyperplasia and occlusive changes are found in the pulmonary arteries as well as plexiform lesions. In adults, in addition to the latter changes, “ghost” arteries also have been reported. An electron microscopic study by Meyrick et al. (294), performed on a lung biopsy of an adult patient, showed severe endothelial injury, which they speculated to be the initial site of damage. In some patients, defective von Willebrand factor (295) and fibrinolysis (296) have been described. Additional features most recently described include thickening of the pulmonary adventitia and venous hypertrophy as well as endothelial cell hyperplasia (*e*Fig. 107.0.14) (297). Immunohistochemical changes have been described and include increased expression of TGF-b matrix proteins and macrophages (298).



***e*FIGURE 107.0.14** Micrographs of pulmonary arteries from patients with primary pulmonary hypertension. **A:** Concentric intimal thickening with whorls of cells with elastin and collagen deposition in an artery, approximately 180-µm diameter. The thickness of the medial wall also is increased ×100. **B:** Obliteration of lumen of artery, approximately 80 µm in diameter. ×260. **C:** Eccentric intimal thickening (*arrow*), approximately 220-µm diameter. The medial and adventitial layers are also thickened. ×130. **D:** Recanalization of an artery, approximately 120 µm in diameter. **E:** Note the numerous small vessels containing red blood cells in the thickened intima. The adventitial and medial coats also are thickened. ×120. **F:** A plexiform lesion (*arrow*) associated with a muscular pulmonary artery. Note the absence of elastic laminae in the wall of the artery where the plexiform lesion arises. ×110. **G:** Pulmonary vein, approximately 100 µm in diameter, from a patient with primary pulmonary hypertension showing a thickened intimal and adventitial layer. ×210. **H:** Control vein, approximately 100 µm in diameter. ×210. Sections were stained with Verhoeff’s elastin stain followed by van Gieson’s stain. (Reproduced from Chazova I, Loyd JE, Zhdanov VS, et al. Pulmonary artery adventitial changes and venous involvement in primary pulmonary hypertension. *Am J Pathol* 1995;146:389–397, with permission.)

In the venous form of unexplained pulmonary hypertension (299), the clinical presentation differs somewhat from the arterial in that orthopnea is a characteristic feature and changes suggesting pulmonary edema are apparent on the chest radiograph despite a normal pulmonary wedge pressure. Structural abnormalities in the lung are most striking in both large and small veins and consist of loose fibrous intimal hyperplasia with dilated lymphatics. There are secondary changes in the arteries of mild medial hypertrophy and intimal hyperplasia. There is evidence that pulmonary venous occlusive disease might also occur *in utero* (299).

Studies of the National Registry of Primary Pulmonary Hypertension (300) showed some relationship between advanced disease and outcome. An intimal area of 18% had an 85% predictive value for patients who did poorly during the first 3 years of follow-up. Some studies (301) suggest that the acute response to vasodilators may have some predictive value in assessing the long-term response, but this is not a uniform finding (302). Intravenous prostacyclin has been given, even without evidence of a favorable acute hemodynamic effect (303,304). In many patients, stabilization of their clinical condition has allowed time for lung transplantation. In other patients, particularly in children, the beneficial effects have so improved their clinical condition and hemodynamics that they have been removed from the transplant list (*e*Fig. 107.0.15), and some patients have been successfully weaned from this therapy onto calcium channel blockers (unpublished).



***e*FIGURE 107.0.15 A:** Prolonged vasodilator therapy improved long-term survival in children with primary pulmonary hypertension (n = 16) compared with historical controls (n = 35) who never received vasodilator treatment (5-year survival 55 vs. 9%, respectively; *p* <.005). Long-term survival was further increased in the children

diagnosed early in life. Five-year survival for the younger children was 88% compared with 25% for patients diagnosed at 6 years of age or older (p <.02). **B:** Improved long-term survival in children with primary pulmonary hypertension who had a positive response to acute prostacyclin (PGI_2) testing. Five-year survival for children with a positive response to acute prostacyclin testing was 86% compared with 33% for patients who did not respond favorably to such testing (p = .06). (Reproduced from Barst RJ. Primary pulmonary hypertension in children. In: Rubin LJ, Rich S, eds. *Primary pulmonary hypertension*. New York: Marcel Dekker, 1997:179–225, with permission.)

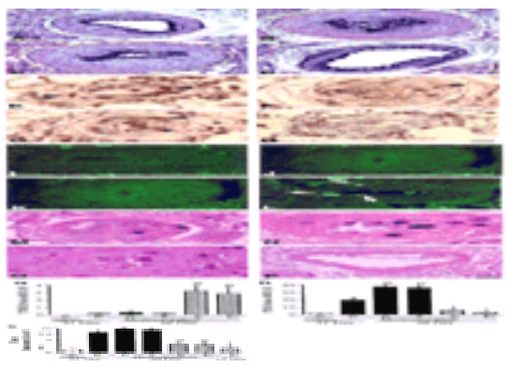
The use of chronic aerosolized or oral prostaglandin agents may, of course, prove more convenient than the constant intravenous infusion but may also be less efficacious (305). In addition to its vasodilating properties (306), the lack of expression of NO synthase (307) coupled with increased expression of endothelin (308) in the vessels of patients with unexplained pulmonary hypertension suggests that treatment with NO, L-arginine, phosphodiesterase inhibitors such as sildenafil (309), or endothelin receptor blockers (310) may be beneficial. Because inflammatory mediators are elevated (311), it could be suggested that cytokine blockade may also be beneficial. Although a variety of treatments have been tried (see reference 312), the calcium channel blocker diltiazem and oxygen therapy remain mainstays of initial therapy. Studies aimed at the identification of coagulation disturbances (313) also have suggested that anticoagulants could be of benefit, and clinical trials indicate that this treatment may rarely induce regression of disease.

Review of the literature reveals that approximately one-third of patients with unexplained pulmonary hypertension will show a decrease in pulmonary artery pressure or resistance with vasodilators. In approximately a third of those, the response will be sustained, however temporarily, although the data are more encouraging in the pediatric population. Whereas blade septostomy has been used in isolated cases (314), most patients will ultimately require a lung transplant (315,316,317 and 318). Our approaches to the diagnosis of pulmonary hypertension might be feasible because pulmonary artery pressure is elevated in carriers of the primary pulmonary hypertension gene (319). Studies addressing endothelial cell phenotype on biopsy tissue (320) or altered potassium channel function in isolated smooth muscle cells might prove useful (321), as might detection of antifibrillin 1 antibodies (322). Experimental studies indicate that exposure to dexamethasone in neonatal rats correlated with lung hypoplasia and increased pulmonary hypertension in adults (323). The studies using long-term prostacyclin suggest that this agent may have direct effects in suppressing smooth muscle cell proliferation (324), and studies suggest that interfering with smooth muscle cell contractility may provide new therapeutic possibilities (325). Particularly promising are experimental studies with elastase inhibitors to be described, which have shown reversibility of advanced disease in rats (326).

Experimental Models

Rats that ingest the toxin monocrotaline develop pulmonary arterial changes that can be correlated with hemodynamic evidence of progressive pulmonary hypertension and increased pulmonary vascular resistance (327,328,329,330,331 and 332). Initially, there is an increase in cardiac output associated with extension of muscle into peripheral arteries that are normally nonmuscular. After a few weeks, when there is an increase in pulmonary artery pressure, medial hypertrophy of normally muscular arteries is apparent. After 3 weeks, when an increase in pulmonary vascular resistance occurs secondary to both a further rise in pulmonary artery pressure and a drop in cardiac output, there is a reduction in the number of peripheral pulmonary arteries, and “ghost,” or disappearing, vessels can be seen. Ultrastructural studies have shown injury to the vascular endothelium within several hours of monocrotaline injection; inflammatory cells and edema are apparent after 1 week. Studies carried out in our laboratory comparing the response to monocrotaline in neonatal, infant, and adult rats suggested that, in the neonate, transient inflammation causes a severe decrease in alveolar number. The development of vascular changes is similar in the three groups. In the infant rat, however, the abnormalities regress between 2 and 4 weeks after injection, whereas in the adult animal, they progress (327). Our studies showed that increased elastase activity not only initiated but also contributed to the progression of the vascular changes (330). Similar to pulmonary hypertension secondary to chronic hypoxia, there is an early increase in enzymatic activity only 2 days after injection of the toxin, but there is also a further increase in elastase activity observed with malignant progression of the disease in adult rats.

Furthermore, we demonstrated that elastase inhibitors are effective in reducing the pulmonary hypertension and vascular changes (330) in association with decreasing the elastase activity in the pulmonary arteries. Even when infusion of elastase inhibitors is delayed, they are still effective in retarding the progression of the hypertensive process. The pulmonary artery endogenous vascular elastase was localized to the smooth muscle cells of the arterial wall and appeared to be related to the serine proteinase adipsin (331). The mechanism of induction of vascular disease is likely related to the endothelial injury (332), and perhaps parenchymal lung injury as well (333), and is reflected in Na/K adenosine triphosphatase activity (334), metabolism of ornithine decarboxylase (335), and expression of growth factors (336) and interleukin receptors (337). In addition, there is evidence that cytokine blockade may prevent monocrotaline-induced pulmonary vascular changes (337), as might L-arginine (338) or endothelin receptor A–selective and nonselective endothelin A/B receptor antagonists (339). Expression of growth factors, such as (basic) FGF-2, has been implicated in the pathophysiology of monocrotaline-induced pulmonary vascular disease (336), and we have shown that elastase will induce release of (basic) FGF-2 in a mitogenically active form from the extracellular matrix (340). Other strategies to prevent monocrotaline-induced pulmonary hypertension have included inhaled NO (341) as well as cell-based delivery of NO synthase (342). In addition, reduction in monocrotaline-induced pulmonary vascular disease has been achieved with serotonin receptor antagonists (343) as well as with a Chinese herbal medicine called *triptolide* (344), which has been used in inflammatory conditions. As alluded to previously, we have shown that elastase inhibitors will not only retard progression of pulmonary vascular disease but will also induce regression by blocking b_3 integrin–mediated signal transduction and inducing programmed cell death, or apoptosis, of vascular smooth muscle cells (*e*Fig. 107.0.16) (345).



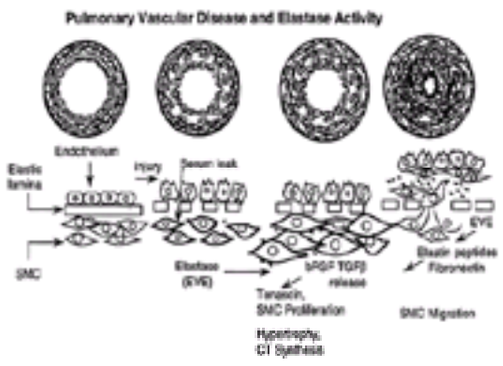
***e*FIGURE 107.0.16** Cellular mechanism responsible for reversal of pulmonary artery muscularity. Elastase inhibition arrests tenascin-C accumulation and proliferation and induces apoptosis and loss of extracellular matrix (such as elastin). **A–P:** Days refer to time after injection of monocrotaline: **A,E,I,M**, day 21; **B,F,J,N**, day 28; **C,G,K,O**, day 28; **D,H,L,P**, day 28. **A–D:** Saline-perfused pulmonary arteries stained with Movat pentachrome stain. **E–H:** Pulmonary arteries after tenascin-C immunohistochemistry. Arrows indicate positive brown peroxidase staining. **I–L:** *In situ* TUNEL assays identifying apoptosis. Arrows indicate TUNEL-positive vascular cells. **M–P:** Proliferating vascular cells, shown by immunohistochemistry for proliferating cell nuclear antigen (PCNA); dark nuclei are PCNA-positive cells. **Q, R:** Percent of smooth muscles cells (SMCs) that are TUNEL-positive **(Q)** or PCNA-positive **(R)**. **S:** Densitometric quantification of elastin. I, inhibitor-treated (I^Z, ZD0892; I^M M249314); TUNEL, *in situ* DNA nick end labeling; u, untreated; v, vehicle-treated. Graphed data represent mean + standard error of the mean of n = 4; scale bars represent 5 µm; *, p <.05, compared with †, p <.05, compared with results on day 21 in rats treated with monocrotaline.

Our studies showed that with progressive pulmonary vascular disease, there is increased expression of the matrix glycoprotein tenascin, where there is also increased cellular proliferation, as judged by expression of proliferating cell nuclear antigen (146). Growth factors such as FGF-2 (released by elastases) can stimulate the production of tenascin, and elastin peptides released by elastase can induce fibronectin synthesis (346,347). Based on our previous studies, increased fibronectin in the subendothelium appears to form a favorable environment for smooth muscle cell migration, and increased tenascin has been shown in our pulmonary artery smooth muscle cell culture systems to be a prerequisite for epidermal growth factor–dependent proliferation and to enhance FGF-2–induced proliferation (146). The mechanism involves the clustering of $a_v b_3$ integrins, the subsequent alteration in the actin cytoskeleton, clustering of epidermal growth factor receptors, and their subsequent rapid phosphorylation and nuclear signal on ligation with epidermal growth factor (28).

Other models of chronic inflammation, such as repeated injections of endotoxin (348) and tumor necrosis factor (349), also have been associated with the development of pulmonary vascular changes. Whereas in these models there is at least a transient inflammatory response, in models of chronic air embolization (350) and thoracic irradiation (351) in which pulmonary hypertension and vascular changes are produced, endothelial injury is the common observation, as it is in the monocrotaline model. Increased elastin peptides also are observed in lung lymph early after induction of chronic air embolism, suggesting increased elastolytic activity in this model of pulmonary hypertension (350). Serine leukoproteinase inhibitor proved beneficial in alleviating the pulmonary hypertension (352). Increased expression of TGF-b has been described but not specifically targeted therapeutically to determine its pathophysiologic significance (353,354). It also was shown that repeated injections of indomethacin will induce pulmonary hypertension and structural changes (355).

CONTROVERSIES AND PERSONAL PERSPECTIVES

Based on experimental and clinical observations, we propose the following hypothesis with regard to the pathophysiology of pulmonary hypertension (eFig. 107.0.17). A mechanical stimulus such as the high flow and pressure of a congenital heart defect with a left-to-right shunt, hypoxic vasoconstriction, or a toxin will injure the pulmonary vascular bed, and the first casualty will be the endothelial cell. We propose that endothelial perturbation results in a “serum leak” owing to loss of barrier function. In cell culture studies, we showed that both serum and endothelial factors increase smooth muscle cell elastase activity and that elastase releases biologically active mitogens by degrading extracellular matrix proteoglycans that “store” these growth factors in an inactive form. We showed that serum-induced smooth muscle cell elastase activity releases FGF-2, whereas others have shown that TGF-b also can be released from proteoglycan storage sites by proteolytic enzymes, including elastases. These growth factors will induce smooth muscle cell hypertrophy and proliferation and stimulate connective tissue protein synthesis, leading to hypertrophy of the arterial wall. Breakdown products of elastin and collagen, as well as TGF-b, stimulate neosynthesis of collagen elastin and fibronectin. The increase in elastin and collagen synthesis observed with pulmonary hypertension also may be related directly to the increase in pressure. Continued release of elastase will lead to smooth muscle cell migration by inducing further changes in matrix that signal the smooth muscle cells to produce a new constellation of gene products, including fibronectin, that change their shape and confer on them the properties of motility.



***e*FIGURE 107.0.17** We speculated as to how a stimulus could induce activity of an elastolytic enzyme and how this might stimulate the remodeling process. The process of progressive pulmonary hypertension involves a series of switches in the smooth muscle cell (SMC) phenotype (i.e., differentiation of muscle from nonmuscle precursor cells, SMC hypertrophy and proliferation accounting for medial hypertrophy, and SMC migration resulting in neointimal formation). In response to a stimulus, such as high flow and pressure, the first “casualty” is the endothelial cell. As a result of structural and functional alterations in endothelial cells, some of the barrier function would be lost, allowing a leak into the subendothelium of a serum factor normally excluded from this region. The serum factor could induce activity of an endogenous vascular elastase (EVE). This enzyme released from precursor or mature SMCs would activate growth factors normally stored in the extracellular matrix in an inactive form, such as basic fibroblast growth factor (bFGF) and transforming growth factor-b (TGF-b), which are known to induce smooth muscle hypertrophy and proliferation and increases in connective tissue (CT) protein (e.g., collagen and elastin) synthesis. bFGF also induces tenascin, a matrix glycoprotein that amplifies the proliferative response as described in the text. This also results in the differentiation of precursor cells to mature smooth muscle related to the muscularization of normally nonmuscular small peripheral arteries. In the muscular arteries, the release of growth factors would also result in hypertrophy of the vessel wall. Continued elastase activity would cause migration of SMCs in several ways. The elastin peptides or degradation products of elastin can stimulate fibronectin, a glycoprotein that is pivotal in altering smooth muscle cell shape and in switching them from the contractile to motile phenotype. [Reproduced from Rabinovitch M. It all begins with EVE (endogenous vascular elastase). *Isr J Med Sci* 1996;32:803–808, with permission.]

The mechanism of induction of elastase by serum factors involves engagement of integrins, binding of elastin to smooth muscle cell surfaces, tyrosine kinase activity, and phosphorylation of focal adhesion kinase and extracellular-related kinase 1 and extracellular-related kinase 2 of the mitogen-activated protein kinase family, culminating in transactivation of the transcription factor for elastase, AML-1 (338).

THE FUTURE

We are making progress in understanding critical gene products involved in the development of the pulmonary vasculature and in the initiation of abnormalities as a result of injurious stimuli. Many more gene products remain to be discovered that are likely also to be key players in the mechanisms causing pulmonary vascular disease. With advanced microsequencing capability, more sophisticated understanding, and application of candidate gene approaches, we will determine the predisposing profile of the patient who develops pulmonary vascular disease or in whom the course is rapidly progressive. The future is aimed not only at retarding progression but also at preventing the development of vascular disease and inducing regression of advanced structural abnormalities. We have made important inroads in this regard with elastase inhibitors and with b_3 integrin blockers, but a continuous armamentarium will be necessary given the varied etiologies and pathogeneses of this condition. The development of highly targeted approaches aimed at introducing genes or gene products in a tissue- and time-specific manner will allow the future development of “biologic interventional cardiology” to address the pulmonary vascular complications and abnormalities associated with congenital and acquired heart disease.

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108

DISEASES OF THE AORTA

PETER C. SPITTELL

"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

Increased awareness of the clinical features of acquired diseases of the thoracic and abdominal aorta and familiarity with currently available diagnostic techniques are basic to their effective treatment. Acute dissection of the thoracic aorta, one of the most common fatal aortic conditions that is encountered clinically, is commonly misdiagnosed and has a markedly increased mortality during the first 48 hours after the onset of symptoms. Aortic dissection should always be included in the differential diagnosis of a patient with unexplained syncope, stroke, congestive heart failure, acute arterial occlusion, or an abnormal aortic contour on chest radiography, even in the absence of chest pain. In suspected acute aortic dissection, institution of beta-adrenergic blockade followed by rapid diagnosis with transesophageal echocardiography (TEE) is indicated. If ascending aortic dissection is present, emergent surgical therapy is indicated. Indications for surgical resection of a thoracic aortic aneurysm include symptomatic aneurysm and an aneurysm diameter of 6 cm or greater (>5.0 cm in diameter in patients with Marfan syndrome). Unless there are contraindications, elective surgical resection of thoracic aortic aneurysm that results from trauma, even when asymptomatic, is indicated because of the unpredictability of these aneurysms and the low risk of elective surgical repair. Surgical repair of an abdominal aortic aneurysm (AAA) is indicated when aneurysm diameter reaches 5 cm. In good-risk patients, selective repair of an AAA is indicated when the diameter reaches 4.5 cm. Surgical resection is the treatment of choice in patients with an inflammatory AAA, regardless of diameter. All patients with Marfan syndrome should be placed on a beta-adrenergic blocking agent if no contraindications exist. When an uncommon type of aortic disease is suspected (i.e., Takayasu's disease or giant-cell aortitis), invasive diagnosis should be pursued (angiography and/or arterial biopsy).

INTRODUCTION

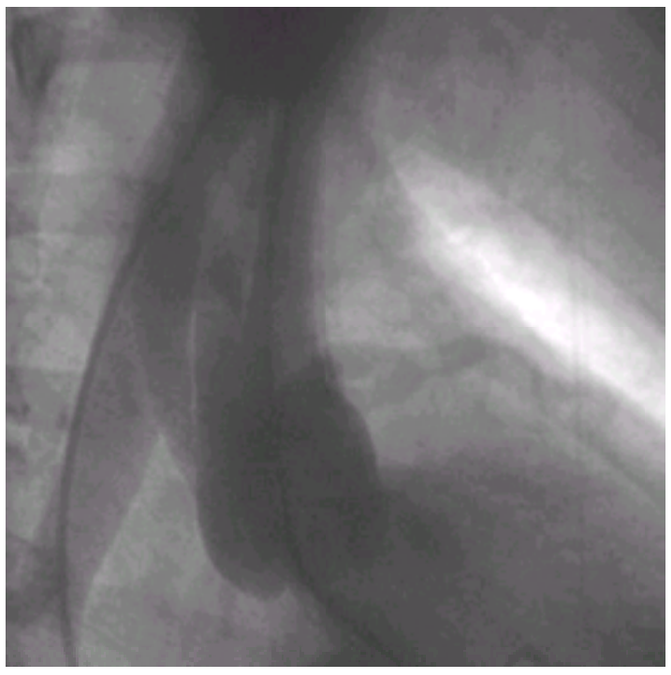
Acquired diseases of the thoracic and abdominal aorta are encountered frequently in cardiologic practice. Their clinical presentation is highly variable, ranging from occult disease to classic clinical presentations. Numerous etiologic factors, acting singly and in combination, have been identified (Table 108.1). Diagnosis is possible by noninvasive means in most patients, but some types of aortic diseases require a high index of suspicion and invasive angiographic study or arterial biopsy. Awareness of the clinical features of acquired diseases of the thoracic and abdominal aorta and familiarity with currently available diagnostic techniques are basic to their effective treatment.

Aging
Atherosclerosis
Hypertension
Infection
Inflammatory disorders
Degenerative changes
Trauma
Neoplasia

TABLE 108.1 AORTIC DISEASE: ETIOLOGY

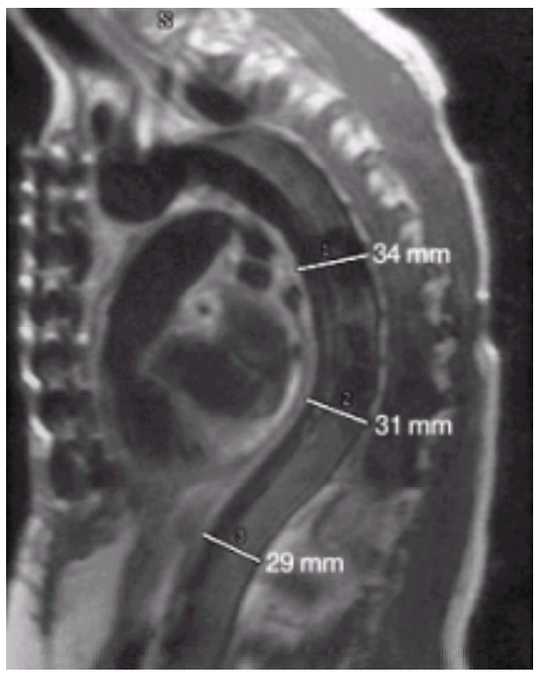
AORTIC DISSECTION

Acute dissection of the thoracic aorta is one of the most common catastrophic aortic conditions that is encountered in clinical practice. Its incidence has been reported to be approximately 2.9 in 100,000 per year (1). The variable manifestations of aortic dissection, in combination with a mortality in untreated cases of as high as 1% per hour during the first 48 hours after the onset of symptoms, underscore the importance of a high index of suspicion and prompt diagnosis and therapy (2,3 and 4). Noninvasive testing [TEE, computed tomography (CT), or magnetic resonance imaging (MRI)] allows an accurate diagnosis to be made in the majority of patients (5). Effective treatment exists, so that future improvements in initial and long-term survival in acute aortic dissection depend on increased clinical awareness, rapid noninvasive diagnosis, and the early institution of appropriate medical or surgical therapy, or both.



A 77-year-old male patient presented to the emergency department with severe chest pain and hypertension. Aortogram revealed type A aortic dissection.

Ascending aortic dissection extending into the left main. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

Pathogenesis

Aortic dissection originates at the site of an intimal tear in more than 95% of patients (2,6). Whether the intimal tear or rupture of the vasa vasorum with secondary intramural hematoma producing the intimal tear is the initial event is controversial. Nevertheless, the resultant intimal tear exposes the media to pulsatile aortic flow, creating a second or “false” aortic lumen that then dissects in the outer layer of aortic media, propagating distally and, occasionally, proximally. One feature differentiating proximal and distal aortic dissection is the greater frequency of hypertension in patients with distal dissection, a possible factor in pathogenesis (7).

The primary intimal tear is located, in decreasing order of frequency, in the ascending aorta 1 to 5 cm above the right or left Valsalva’s sinus (65%), in the proximal descending thoracic aorta just beyond the left subclavian artery origin (20%), in the transverse aortic arch (10%), and more distally in the thoracic aorta or abdominal aorta (5%) (2,6). Once initiated, the dissection usually extends distally and, occasionally, proximally for a variable distance. As the dissecting process encounters branches of the aorta, it may pass around their origins, extend into their walls, or occlude them (2,6). Reentry of the dissection through a second, more distal intimal tear may occur, usually in one of the iliac arteries. External rupture of the dissecting process into the pericardial space is the most common cause of death in aortic dissection; congestive heart failure, usually due to aortic regurgitation, is the second most common cause of death.

Predisposing Factors

Multiple risk factors for aortic dissection have been identified, the most common being advanced age, systemic hypertension, congenital abnormalities of the aortic valve, and heritable disorders of connective tissue. Aortic dissection most frequently affects patients in the fifth to seventh decades of life and is more common in men (male-female ratio, 3:1). In patients younger than 40 years, the incidence between men and women is equal due to the occurrence of aortic dissection in women during pregnancy, with approximately 50% of all aortic dissections occurring during the third trimester of pregnancy (8).

Systemic hypertension is the most frequently encountered predisposing factor for aortic dissection, being present in more than 75% of patients (2,3,9,10 and 11). Hypertension may play a role in initiating the intramural hematoma, as well as having a direct weakening effect on the aortic media (6,11). The causative role of systemic hypertension is further supported by the finding that coarctation of the aorta predisposes to aortic dissection (12). Other major risk factors for aortic dissection, especially proximal aortic dissection, are congenitally bicuspid or unicommissural aortic valves (9,11) and the congenital disorders of connective tissue such as Marfan syndrome (13) and Ehlers-Danlos syndrome.

VIDEO

Video 108.1 Coarctation of aorta (oblique). A signal-void jet is visible in the proximal descending aorta due to a short-segment narrowing representing a coarctation. Left ventricular hypertrophy is also present. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

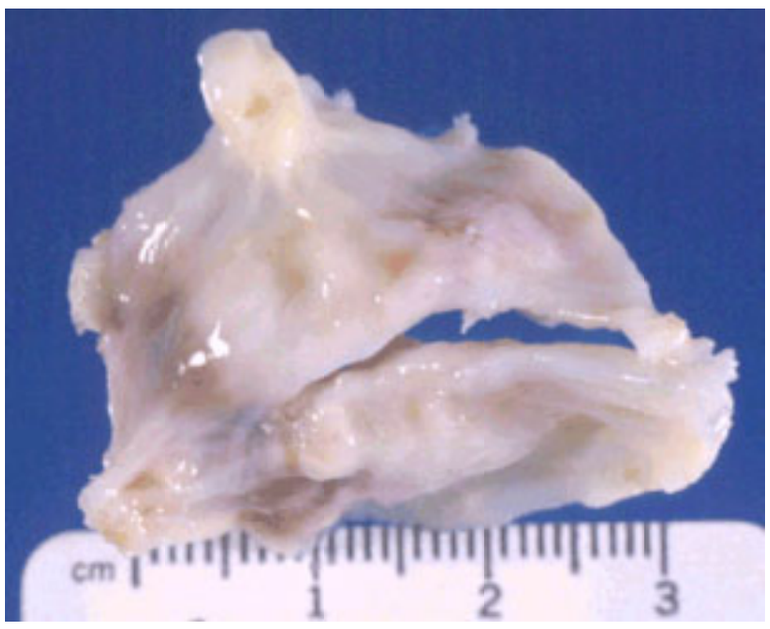
Audio 108.2 Coarctation of the aorta. Auscultation performed in a 54-year-old female patient with coarctation of the aorta, status post Dacron graft replacement of the proximal descending aorta and persistent severe graft stenosis. The mid-systolic ejection murmur is a result of residual high-grade coarctation. Left upper sternal border. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

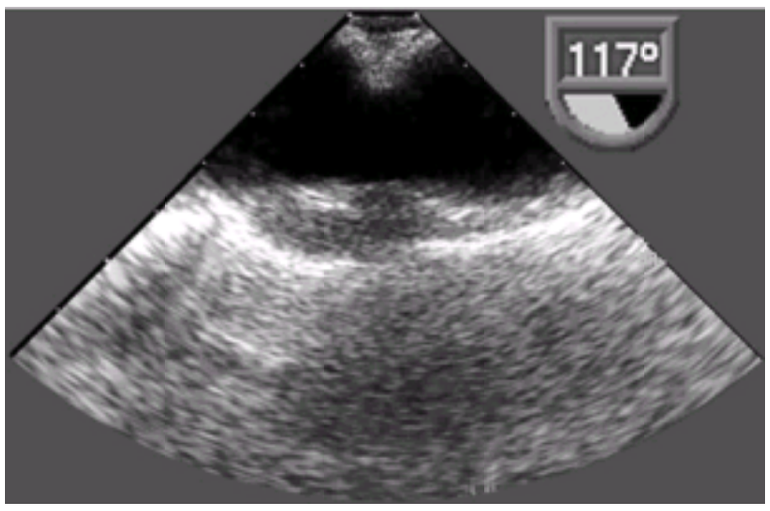
Video 108.3 Color Doppler interrogation of the coarctation demonstrating the high-velocity, turbulent flow across the focal narrowing in the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

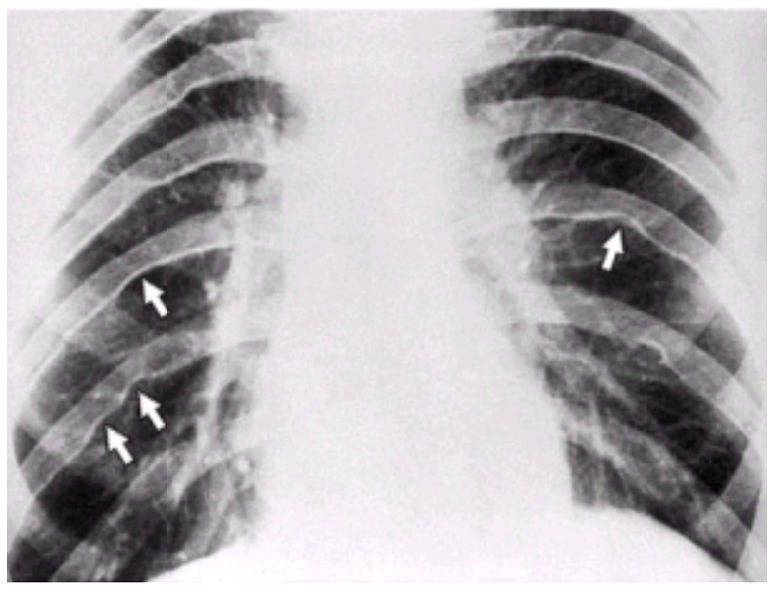
Video 108.4 A 76-year-old female patient with bicuspid aortic valve, aortic stenosis, and coarctation of aorta. Left anterior oblique aortogram revealed coarctation of the aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Bicuspid aortic valve with calcification. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



A still frame of a transesophageal echo demonstrating a coarctation of the aorta. Note the local narrowing of the aorta located at the junction of the distal arch and descending aorta. There was a 100–mm Hg pressure gradient across the coarctation as determined by continuous wave Doppler.



Chest x-ray in coarctation of the aorta. There is prominent rib notching (*white arrows*).

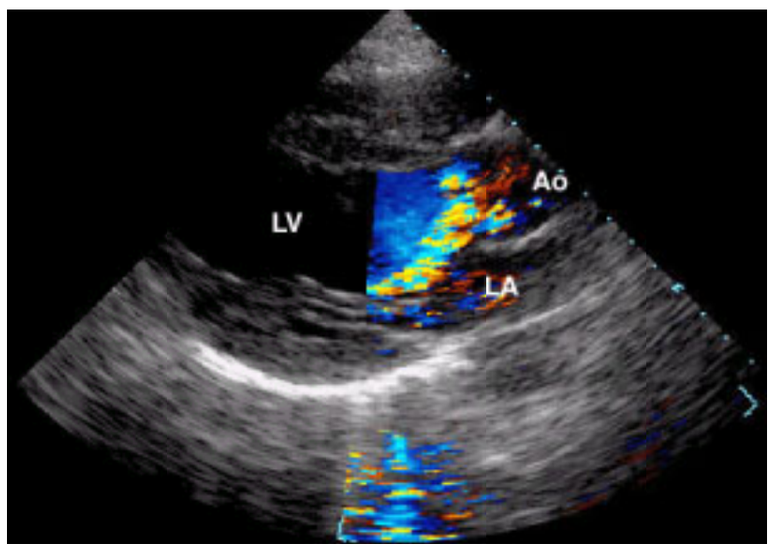
Unicuspid aortic valve (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

VIDEO

Video 108.5 A 60-degree intraoperative transesophageal echo of a patient with aortic stenosis due to a unicuspid valve (seen in short axis). Note the single commissure at the bottom of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

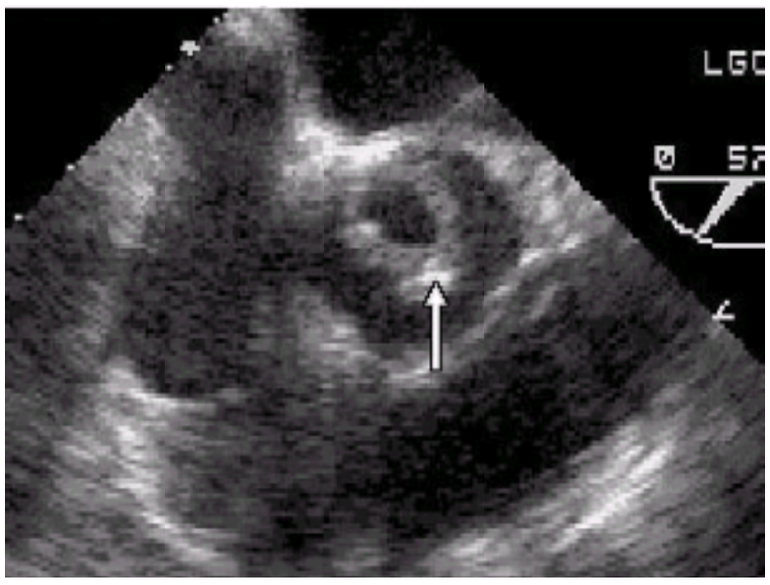
VIDEO

Video 108.6 A 49-year-old male patient with bicuspid aortic valve and severe aortic regurgitation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Parasternal long-axis view (transthoracic echo) with color Doppler demonstrating the posteriorly directed aortic insufficiency caused by prolapse of the

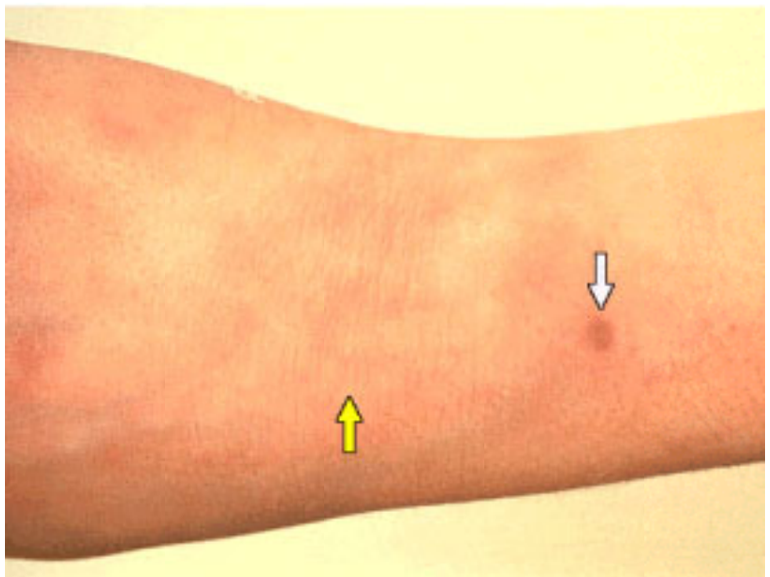
anterior leaflet of a bicuspid aortic valve. Note that the jet hits the anterior mitral leaflet.



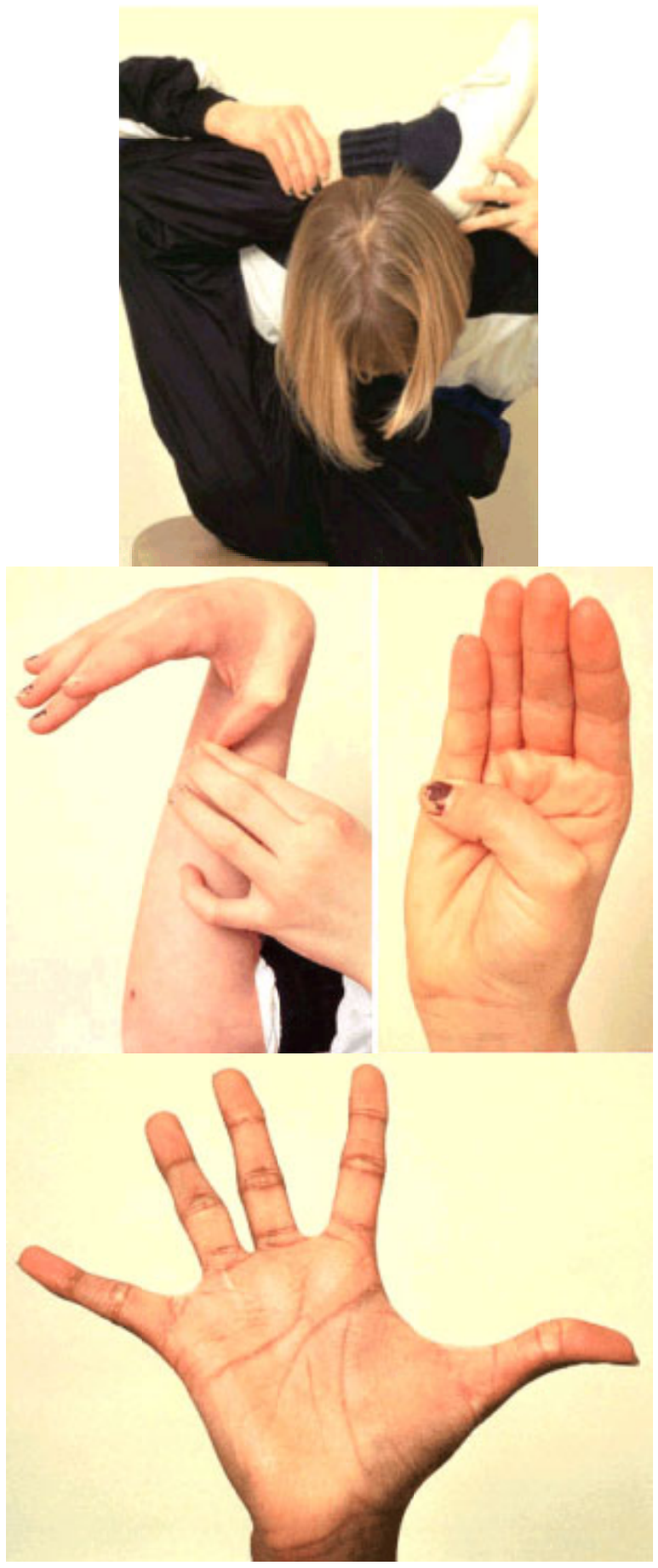
Short axis transesophageal view of a unicuspid aortic valve with aortic stenosis. The arrow designates the single commissure present in this aortic valve. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.)

Ectopia lentis. This lens dislocation is associated with Marfan syndrome.

Arachnodactylia in Marfan syndrome. The ratio of finger length to hand size is markedly increased.



Skin changes of Ehlers-Danlos syndrome. There is thin, velvety appearance of the skin (*yellow arrow*), as well as easy bruisability (*white arrow*).



Ehlers-Danlos syndrome. There is severe joint laxity and hypermobility that may produce joint dislocations (A–C).

Iatrogenic aortic dissection is an uncommon but potentially serious complication of invasive angiographic procedures and cardiac surgery. Angiographic procedures such as coronary angiography, percutaneous transluminal coronary angioplasty, intraaortic balloon insertion, and translumbar aortography have been complicated by aortic dissection (11,14,15,16). Catheter-induced dissection can originate at any location, and it is most common in Valsalva's sinus, brachiocephalic arteries, the descending thoracic aorta, the abdominal aorta, and iliac or femoral arteries. The majority of catheter-induced dissections is retrograde and tends to decrease in size over time as a result of thrombosis of the false lumen, whereas anterograde dissections tend to persist on follow-up. Nearly all iatrogenic aortic dissection can be treated medically, with serial clinical examinations and noninvasive testing used to identify those who are in need of surgical therapy (15).

Cardiac surgical procedures complicated by aortic dissection include those that require cross-clamp or cannulation of the ascending aorta, such as aortic valve replacement (11,17,18) or coronary artery bypass grafting (11,19), or both. Dissection can arise at the site of ascending aortic cannulation, aortosaphenous vein anastomosis, or aortic cross-clamp or as a result of direct arterial injury. Dissection in association with these procedures usually occurs intraoperatively and is promptly diagnosed and treated, but chronic dissection in the postoperative period has been reported (18). Aortic dissection has also been found in association with giant-cell aortitis (11,20), systemic lupus erythematosus (21), Noonan's syndrome (22), Turner's syndrome (23), fibromuscular dysplasia (10), annuloaortic ectasia (10), cocaine use (24,25), methamphetamine use, polycystic kidney disease (26), polyarteritis nodosa (27), and trauma (28).

Video 108.8 Coronary ectasia. These angiograms were obtained in a 40-year-old patient with Noonan's syndrome and no coronary risk factors. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Classification

The most widely used classification system for acute aortic dissection is that of DeBakey and associates (29), which recognizes three types of dissections (Fig. 108.1). Type I dissection arises in the ascending aorta and extends distally, type II dissection is limited to the ascending aorta, and type III dissection arises at or just distal to the origin of the left subclavian artery and extends distally or, rarely, retrogradely into the arch of the ascending aorta.

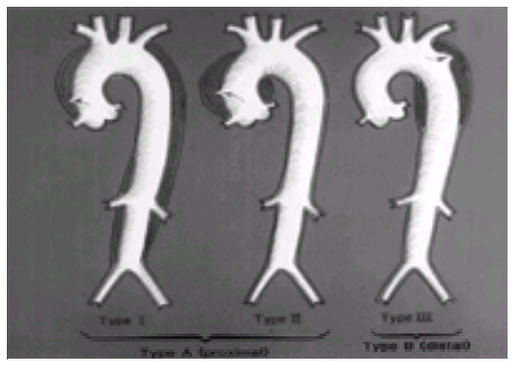


FIGURE 108.1 Classification of aortic dissection. Type I: primary tear in ascending aorta and dissection involving aortic arch and distal aorta for a variable distance. Type II: dissection involving only ascending aorta. Type III: primary tear distal to subclavian artery origin, extending distally for a variable distance. (Modified from DeBakey ME, Henly WS, Cooley DA, et al. Surgical management of dissecting aneurysms of the aorta. *J Thorac Cardiovasc Surg* 1965;49:130–149.)

For clinical purposes, because types I and II have a similar prognosis, aortic dissection can be broadly divided into those with the tear in the ascending aorta and those with the tear in the descending aorta, also called *proximal* and *distal*, respectively (30). A similar classification system, proposed by Daily and associates (31), designates all dissections that involve the ascending aorta as type A, regardless of the site of the primary intimal tear. All other dissections are designated type B.

VIDEO

Video 108.9 Aortic dissection (left anterior oblique). Type A dissection of the aorta is manifested on the cine image loop by a mobile intimal flap extending from the mid-ascending aorta to the descending thoracic aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 108.10 Aortic dissection (left anterior oblique). Type B dissection of the aorta extending distally from the isthmus, just after the left subclavian artery, to the abdominal aorta. A communication between the true and false lumen is seen in the proximal portion of the descending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

An important aspect of classification is the duration of the dissection at the time of first presentation. Dissections are categorized as “acute” if the presentation occurs within 2 weeks of onset and as “chronic” if more than 2 weeks have elapsed. The distinction is important due to the fact that approximately 65% to 75% of patients with untreated aortic dissection die in the first 2 weeks after the onset of symptoms (2).

Clinical Features

Due to variable involvement of the aorta and its branches by the dissecting process, the patient with acute aortic dissection may have clinical manifestations of ischemia of various organ systems, singly or in combination, as well as symptoms and signs of cardiac disease. The diverse presentations of aortic dissection can provide for difficult diagnosis, and misdiagnosis commonly occurs (2,11). Despite major advances in the noninvasive diagnosis of aortic dissection and in medical and surgical therapy, up to 55% of patients in reported series die without a correct antemortem diagnosis (1,2,11,32,33). Therefore, a high index of clinical suspicion in any likely setting is imperative.

The classic presentation of a patient with acute aortic dissection, occurring in up to 94% of patients, is the sudden onset of severe pain, usually beginning in the anterior chest, radiating to the back, and moving distally as the dissection progresses (1,30). The pain is most commonly described as sudden in onset with a “ripping,” “tearing,” or “stabbing” quality; this is in contrast to the crescendo nature of the discomfort of acute myocardial infarction. Patients with acute aortic dissection often appear to be in shock, although blood pressure is elevated in one-half to two-thirds of cases, especially those with distal dissection. Hypotension in aortic dissection is usually attributable to rupture of the dissection into the pericardial space or, less commonly, the pleural space or mediastinum and is more common with proximal dissection.

Although definitive diagnosis requires further noninvasive testing (see Diagnosis), the location of initial pain can help predict the site of the intimal tear (11,30,33) (*e*Table 108.1.1). It should be remembered, however, that painless dissection occurs in 14% to 21% of patients (2,11).

***e*TABLE 108.1.1** CLINICAL CLUES TO PROXIMAL VERSUS DISTAL AORTIC DISSECTION

Proximal	Distal
Initial pain in the anterior chest	Interscapular pain
Aortic diastolic murmur	Hypertension
Pericardial friction rub	Left pleural effusion
Decreased or absent blood pressure or pulses in right arm	
Decreased right carotid artery pulsation	
Evidence of myocardial ischemia or infarction on electrocardiogram	
Marfan syndrome	
Congenital abnormality of the aortic valve	

A cardiac murmur may be present, usually at the cardiac base, and may be systolic, diastolic, or both. A diastolic murmur of aortic regurgitation indicates involvement of the ascending aorta and is heard in up to 50% of patients with type I aortic dissection. Congestive heart failure, when present in association with proximal aortic dissection, is most often due to severe aortic regurgitation (9,30), but cases of congestive heart failure due to rupture of the dissecting process into the right or left atrium or right ventricle have also been reported (34,35 and 36). Myocardial infarction occurs in 1% to 2% of patients and is due to compromise of the coronary ostium by the hematoma or intimal flap. Peripheral pulse deficits are noted in approximately 40% of patients (3,30), more commonly with proximal aortic dissection. Pulse deficits may be transitory due to oscillation of the intimal flap or distal reentry of the hematoma into the true lumen. Acute lower-extremity ischemia, with or without chest pain, as a result of dissection extending into the iliac arteries occurs in 6% to 12% of patients (3,37,38) and may provide an important clue to the diagnosis (37). Other cardiovascular findings include a difference in blood pressure between the arms, tachycardia, friction rubs, bruits, pulsus paradoxus, and cardiac tamponade.

HEART SOUNDS

Audio 108.11 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border-sitting (*first clip*), Right upper sternal border-supine (*second clip*), left upper sternal border (*third clip*), and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

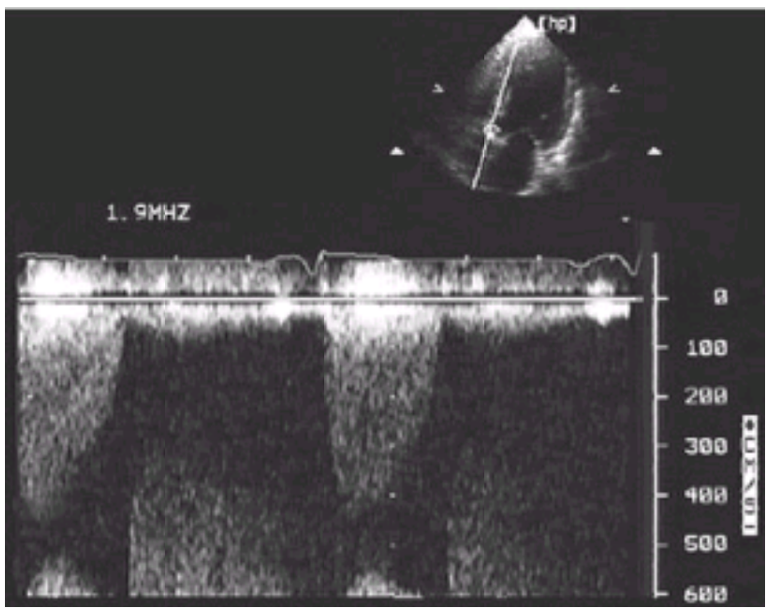
Audio 108.12 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border-sitting (*first clip*), Right upper sternal border-supine (*second clip*), left upper sternal border (*third clip*), and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 108.13 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border-sitting (*first clip*), Right upper sternal border-supine (*second clip*), left upper sternal border (*third clip*), and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 108.14 Aortic valve insufficiency. Auscultation in a 72-year-old male patient with moderate aortic insufficiency. Note the soft decrescendo early diastolic murmur heard best at the base. Right upper sternal border-sitting (*first clip*), Right upper sternal border-supine (*second clip*), left upper sternal border (*third clip*), and left lower sternal border (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



Apical continuous-wave Doppler spectrum of aortic valve disease. Note high forward velocities in systole (V_{max} 4.5 m/sec) and early peak of aortic stenosis. At the bottom, wrapped-around diastolic flow velocities from aortic regurgitation are seen.

Syncope in a patient with aortic dissection is an important event, as it usually results from rupture of the dissecting process into the pericardial space producing cardiac tamponade (11,30). Less commonly, rupture occurs into the left pleural space producing left hemothorax (11). Neurologic deficits, including cerebrovascular accident, disturbances of consciousness, ischemic paraparesis, and ischemic peripheral neuropathy, occur in more than 40% of patients, more commonly with proximal aortic dissection (1,39). Other, less-frequent findings include Horner's syndrome, a pulsatile sternoclavicular joint (40), vocal cord paralysis, hemoptysis (41), superior vena cava syndrome (42), upper airway obstruction (43), hematemesis (44), pleural effusion, unilateral pulmonary edema (45), signs of mesenteric or renal infarction, fever (46), and deep venous thrombosis (11).

Pericardial tamponade. Low QRS voltage and electrical alternans are characteristic findings of tamponade.

VIDEO

Video 108.15 Apical four-chamber view demonstrating a large pericardial effusion causing tamponade. Note the inability of the right side to fill. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

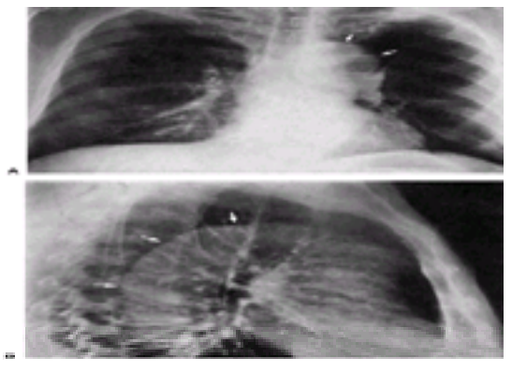
As a general rule, aortic dissection should always be considered in the differential diagnosis of a patient with unexplained syncope, stroke, congestive heart failure, acute arterial occlusion, or an abnormal aortic contour on chest radiography, even in the absence of chest pain.

Diagnosis

Routine laboratory studies are nonspecific in acute aortic dissection. A mild to moderate leukocytosis occurs in two-thirds of patients, and anemia may occur as a result of leakage of the dissection or from sequestration of blood in the false lumen. Serum lactate dehydrogenase and bilirubin levels are sometimes increased because of blood sequestered within the false lumen, but serum glutamic oxaloacetic transaminase and creatine phosphokinase are usually normal (30). Hematologic studies consistent with disseminated intravascular coagulation can also occur.

The most common electrocardiographic abnormality in patients with aortic dissection is left ventricular hypertrophy from chronic systemic hypertension (3). Acute electrocardiographic changes occur in up to 55% of patients and include ST-segment depression, T-wave changes, and ST-segment elevation, in decreasing order of frequency (47). Acute ischemic changes can occur when one or more coronary ostia becomes obstructed, either by the intimal flap or from external compression by the dissecting hematoma. The electrocardiographic changes of acute pericarditis can be seen if there has been leakage of blood into the pericardial space. Heart block resulting from proximal extension of the hematoma into the area of the atrioventricular node has also been reported (48). The chief value of the electrocardiogram is in distinguishing aortic dissection from acute myocardial infarction, especially with the current widespread use of early intravenous (i.v.) thrombolytic therapy for the latter disorder.

Chest radiography is helpful in suggesting the diagnosis of aortic dissection in more than 85% of patients, with abnormalities of the aortic silhouette being the most common finding (49,50). Additional findings include pleural effusion, mediastinal widening, displacement of intimal calcification greater than 6 mm inside the outer edge of the aortic shadow, and the radiographic findings of congestive heart failure (*e*Fig. 108.1.1). Nonetheless, it is important to remember that normal chest radiographic findings do not exclude the diagnosis of aortic dissection.



***e*FIGURE 108.1.1** Chest radiograph in a patient with type III (distal) aortic dissection. **A:** Posteroanterior view demonstrates a dilated transverse aortic arch and descending thoracic aorta (*arrows*). **B:** Lateral view demonstrates dilation of the thoracic aorta (*arrows*).

Currently available noninvasive imaging modalities that are accurate in the diagnosis of acute aortic dissection include echocardiography [combined transthoracic echocardiography (TTE) and TEE], CT, and MRI. The choice of test depends on which imaging modality is most readily available at a particular institution and the hemodynamic stability of the patient.

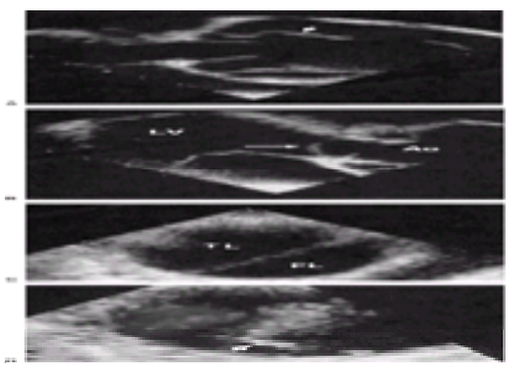
Video 108.16 Intraoperative transesophageal echo with color Doppler of an ascending aortic dissection. Note the mobile flap with the color flow separation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 108.17 Short-axis transesophageal echo view of a type I aortic dissection. Note the flap originating within the noncoronary cusp (leaflet upper left screen) and extending towards the ostium of the left main trunk. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 108.18 Intraoperative 120-degree transesophageal echo of an ascending aortic dissection. Note the large, complex flap in the ascending aorta seen originating near the origin of the right coronary artery. There is a small amount of aortic insufficiency. Flow is seen in the true lumen (*left*) whereas no flow is seen in the false lumen (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

TTE can be very useful in some patients with suspected aortic dissection. When the findings of a dilated aortic root (end diastolic diameter >42 mm), widening of the aortic walls (16–20 mm for the anterior wall and 10–13 mm for the posterior wall), and a linear undulating echo representing the intimal flap are present, the positive predictive value for TTE is 100% (51,52 and 53). Advantages of TTE are its portability; rapid “online” diagnosis; ability to identify associated aortic regurgitation and other valvular disease; and ability to assess left ventricular function, regional wall motion abnormalities, pericardial effusion, and cardiac tamponade. The diagnosis of cardiac tamponade in a patient who is suspected of having aortic dissection deserves special mention. Echocardiographically guided pericardiocentesis should be avoided in this setting because the rapid withdrawal of pericardial fluid can result in a prompt improvement in left ventricular systolic function, change in left ventricular pressure over time (dP/dT), and systolic blood pressure, producing aortic rupture (54). The patient with aortic dissection complicated by cardiac tamponade should be taken emergently to surgery for institution of cardiopulmonary bypass followed by evacuation of blood from the pericardial space. Disadvantages of TTE include difficulty in adequately visualizing the descending thoracic aorta (5) in patients with suboptimal echocardiographic “windows” due to obesity or chronic obstructive pulmonary disease.

TEE (biplane or multiplane), in combination with TTE, has a sensitivity of 99% and a specificity of 98% in the diagnosis of aortic dissection (55) and is currently the initial diagnostic test of choice in suspected acute aortic dissection. TEE is rapid, portable, and minimally invasive and can accurately determine the type and extent of dissection safely in an emergent setting, allowing effective triage of patients to either surgical or medical therapy (56,57). Color-flow Doppler imaging significantly improves the sensitivity of TEE by allowing visualization of the dissection entry site, the true and false lumina, the presence of thrombus, and associated aortic regurgitation (57) (*e*Fig. 108.1.2). The overall sensitivity of TEE is comparable with that of CT (58), MRI (5,59,60), and aortography (61) in the diagnosis of aortic dissection. Current multiplane TEE probes have largely overcome impediments in the ascending aorta that are present with monoplane and biplane transducers, although artifacts in this region continue to be a diagnostic challenge.

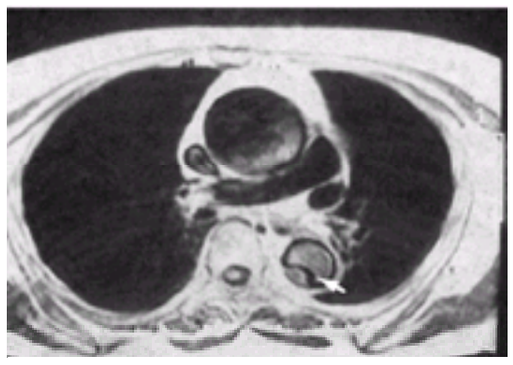


***e*FIGURE 108.1.2** Transesophageal echocardiogram in a patient with type I (proximal) aortic dissection. **A:** Longitudinal view of the ascending aorta (Ao) demonstrates

an intimal flap (*arrow*) originating in the right coronary sinus. **B:** Intimal flap prolapses through the aortic valve during diastole (*arrow*). **C:** Transverse views of the descending thoracic aorta demonstrate an intimal flap. **D:** A communication point (*arrow*) in the mid-descending thoracic aorta is readily identified with color-flow Doppler imaging. FL, false lumen; LV, left ventricle; TL, true lumen.

CT with i.v. contrast enhancement is also an accurate noninvasive screening test in patients with suspected aortic dissection (62). CT can reliably demonstrate the intimal flap, pericardial and pleural effusion, associated mediastinal hemorrhage, and involvement of the abdominal aorta; however, it often fails to demonstrate the site of entry or reentry, associated aortic regurgitation, or involvement of branches of the aorta (5). Additional disadvantages of CT include the need for contrast exposure and nonportability, limiting its use in patients with significant renal insufficiency and in hemodynamically unstable patients, respectively.

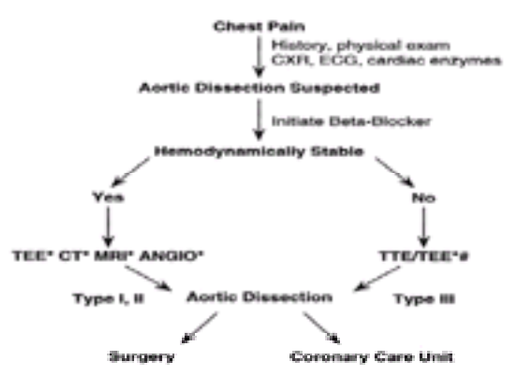
MRI is an excellent noninvasive method for diagnosing aortic dissection (63) (eFig. 108.1.3). It is superior to TEE and CT in detecting arch vessel involvement and in identifying the anastomosis in patients who are managed with surgical therapy, and it may facilitate comparison of serial studies (5,59,64). Gated spin-echo MRI accurately demonstrates the entry site and intimal flap (65) and may be the optimal method for demonstrating thrombus formation and entry site location within all segments of the aorta (66). The ability to obtain oblique and longitudinal planes of section makes MRI especially valuable in demonstrating dissection without intimal tear (5,60,67). Disadvantages of MRI include cost, examination time, reduced availability, and standard contraindications to MRI. The most important limitation of MRI in acute aortic dissection is its nonportability, limiting its use in hemodynamically unstable patients.



***e*FIGURE 108.1.3** Magnetic resonance images demonstrate type III (distal) aortic dissection. An intimal flap is present in the descending thoracic aorta (*arrow*). An ascending aortic aneurysm is also identified.

Aortography, the traditional definitive diagnostic method in aortic dissection, is able to localize the site of origin of the dissection and delineate the extent of the dissection, as well as the circulation to vital organs. Diagnostic aortographic features include opacification of the false lumen, deformity of the true lumen by the false lumen, widening of the aorta, narrowing or occlusion of branches of the aorta, and the presence of an intimal flap (68). Disadvantages of aortography include nonportability, invasive technique, exposure to ionizing radiation, the use of i.v. contrast agents, and an inherent delay in diagnosis. False-negative aortogram results can occur if there is simultaneous and equal opacification of the true and false lumina or if the false channel is very faintly opacified (69). Intravascular ultrasound, in combination with standard aortographic technique, greatly improves the accuracy of aortography, can be performed rapidly and safely, and could serve as an accessory diagnostic procedure in selected patients with suspected aortic dissection (70,71).

In view of the increased early mortality of untreated acute aortic dissection, the screening test chosen depends on which test is most readily available at a particular institution and the patient's hemodynamic status (eFig. 108.1.4). Noninvasive diagnosis of acute dissection by TEE, MRI, or CT, if readily available, is preferred, as it avoids the risks and delays that are inherent in invasive angiography (72).



***e*FIGURE 108.1.4** Initial management of suspected acute aortic dissection. ANGIO, aortography; CT, computed tomography; CXR, chest x-ray; ECG, electrocardiogram; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; #, aortogram or computed tomography if transesophageal echocardiography is not available, or rapid transfer to a tertiary facility.

Management

The initial treatment objectives in suspected aortic dissection are to control pain, reduce systemic blood pressure, and lower dP/dT to the lowest level that is compatible with maintenance of adequate visceral, renal, and cerebral perfusion (73). In hypertensive patients, treatment consists of an i.v. beta-adrenergic blocking agent, most commonly propranolol, in combination with i.v. sodium nitroprusside (eTable 108.1.2). Alternatives to propranolol include i.v. esmolol, metoprolol, or atenolol. Beta-blockade before nitroprusside therapy is essential because the latter increases the velocity of left ventricular ejection and promotes propagation of the dissection (74). Intravenous labetalol in place of a beta-blocker and sodium nitroprusside is an alternative, but it has the potential for hepatotoxicity with long-term therapy (75). In normotensive patients, propranolol, metoprolol, atenolol, or esmolol can be used alone. To assist in monitoring blood pressure and renal perfusion, an intraarterial cannula and indwelling bladder catheter are advisable.

***e*TABLE 108.1.2** PHARMACOLOGIC THERAPY OF ACUTE AORTIC DISSECTION

Hypertensive patients

Sodium nitroprusside i.v. (2.5–5.0 mg/kg/min)
with
Propranolol i.v. (1 mg q4–6h)
Goal is systolic blood pressure in the range of 110 mm Hg (or the lowest level to maintain a urine output of 25–30 mL/h) until oral medication is started
or i.v. esmolol, metoprolol, or atenolol (in place of propranolol)
or i.v. labetalol (in place of sodium nitroprusside and a beta-blocker)

Normotensive patients

Propranolol, 1 mg i.v. q4–6h or 20–40 mg orally q6h (metoprolol, atenolol, or labetalol can be used in place of propranolol)

It is generally accepted that patients with type I and II aortic dissection should undergo emergent surgical repair (76,77). Coronary angiography before surgery is not indicated, as it does not improve survival (78). Resection of the ascending aorta and replacement with Dacron represent the usual procedure in type I or type II aortic dissection (76,77). The objectives of surgery include excision of the intimal tear, obliteration of the entrance into the false lumen, repair of aortic regurgitation (if present), and restoration of patency to any major arteries that are occluded by the dissection. With associated aortic regurgitation, resuspension of the valve, if possible, is preferred. Intraoperative TEE can define the severity and mechanisms of aortic regurgitation and can assist the surgeon in identifying patients in whom valve repair is likely to be successful (79). If there is associated annuloaortic ectasia or destruction of the aortic wall, a valved conduit can be used. The coronary

arteries are reimplanted, or if they are involved by the dissection, they are reattached using vein bypass grafts anastomosed proximally to the aortic graft and distally to the uninvolved coronary arteries (77,80,81). If compromise of a branch of the aorta that supplies a vital organ is present and is not relieved by closing the false channel, direct repair or surgical replacement of that branch is indicated. Aortic fenestration may be indicated in patients with severe organ or limb ischemia complicating either acute or chronic aortic dissection. Fenestration, either surgical or percutaneous techniques, can effectively relieve the ischemia and can be performed safely in chronic aortic dissection (82,83). Inhospital mortality is approximately 14%, with patients in cardiogenic shock and those who require concomitant coronary artery bypass grafting being the highest-risk subgroup (84).

Aortic thrombus in a patient with lupus anticoagulant. A probe is placed behind the thrombus within the lumen of the aorta (*yellow arrow*).

With acute type III aortic dissection, surgery is indicated for rupture, acute expansion or impending rupture, or vascular occlusion (85). The best therapy for uncomplicated type III aortic dissection is less well defined (86). Long-term medical therapy focuses on control of blood pressure, using a beta-blocker if possible and periodic evaluation for evidence of any progression of dissection, patency of the false lumen, progression of aortic diameter to greater than 5 cm, or development of saccular aneurysm (87,88 and 89). An alternate approach is 2 to 3 weeks of pharmacologic therapy followed by surgical repair if the dissection becomes stable and the patient's general condition does not contraindicate surgery (90,91). Transluminal placement of an endovascular stent-graft device in type III aortic dissection has been successfully performed and may provide an alternative to surgery in highly selected patients in the future (92,93).

Postoperatively, continuation of beta-blockade, if possible, is essential, as hypertension and left ventricular ejection velocity play an important role in the recurrence of aortic dissection. Postoperative management includes maintenance of adequate blood pressure and serial clinical evaluations. Noninvasive testing is performed at periodic intervals to detect the development of anastomotic aneurysm or saccular aneurysm, extension of the dissection, patency of the false lumen, or progressive aortic dilation (94,95).

PENETRATING AORTIC ULCER

Penetrating aortic ulcer shares several clinical features with aortic dissection, especially type III aortic dissection, but the absence of certain clinical signs favors a diagnosis of penetrating aortic ulcer. Results of noninvasive imaging studies are usually distinctive, allowing differentiation of penetrating aortic ulcer from typical aortic dissection (96,97). Differentiation between the two disorders is important in view of the fact that the natural history of penetrating aortic ulcer is less well defined; therefore, treatment may differ from that currently used for classic aortic dissection (96,97).

Pathogenesis

Penetrating aortic ulcer refers to an atherosclerotic lesion of the thoracic aorta that undergoes ulceration that penetrates the internal elastic lamina of the thoracic aorta, resulting in formation of one of the following: intramural hematoma within the media of the aortic wall, a true saccular aneurysm, a pseudoaneurysm, or transmural aortic rupture (98) (Fig. 108.2).

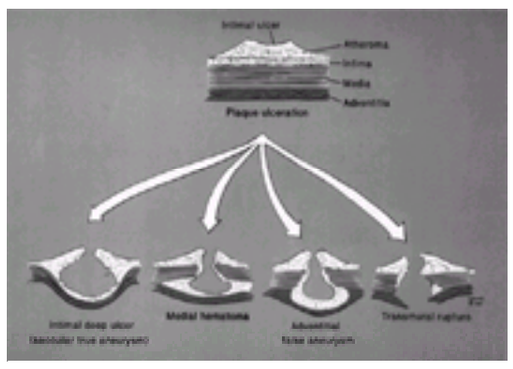
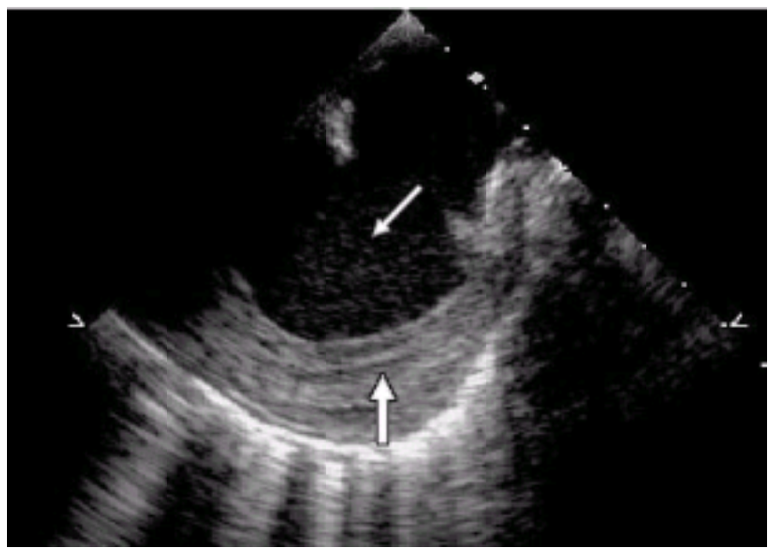


FIGURE 108.2 Pathologic consequences of penetrating atherosclerotic ulcer of the aorta. Atheromatous ulceration that burrows deeply into an atheroma can result in one of four potential outcomes (*from left to right*): a true saccular aneurysm, a medial hematoma, an adventitial false aneurysm, or transmural rupture. An intramural (medial) hematoma is the most commonly observed fate of a penetrating aortic ulcer.



Transesophageal view of the aortic arch demonstrating an arch aneurysm (*thin arrow*) with layering of thrombus inferiorly (*thick arrow*).

Penetrating aortic ulcer was first described as a rare cause of aortic dissection by Shennan in 1934 (99). Subsequently, Willius and Cragg (100) noted that some primary aortic intimal ruptures involved the more distal thoracic aorta and were associated with "ulcerating atheromatous abscesses." Multiple other case reports and small series have subsequently been published, with the majority focusing on the imaging characteristics and surgical treatment of penetrating aortic ulcer (101,102,103 and 104).

Risk Factors

Risk factors for penetrating aortic ulcer are similar to those for aortic dissection, the most common being advanced age, chronic systemic hypertension, and evidence of atherosclerotic disease (105). In contrast to aortic dissection, men and women are equally affected. Long-standing hypertension is present in the majority of patients and likely contributes to the advanced atherosclerotic disease that is universally evident. More than one-half of the patients with penetrating aortic ulcer have advanced atherosclerotic disease in other locations, including coronary artery disease, peripheral arterial occlusive disease, and cerebrovascular disease. An increased association of penetrating aortic ulcer and AAA, as well as aneurysms in other locations, has also been reported (98,101).

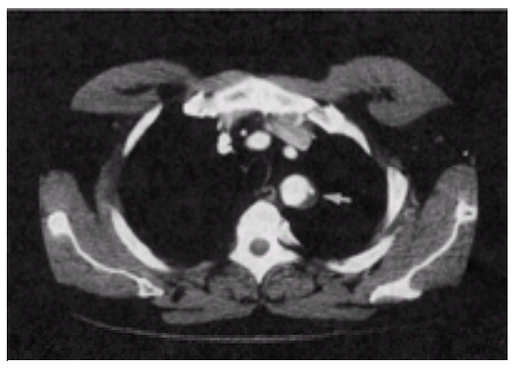
Clinical Features

The clinical presentations of penetrating aortic ulcer and acute aortic dissection are similar, the most common being an elderly patient with systemic hypertension and the acute onset of severe pain in the chest, back, and, less commonly, epigastrium. Unlike aortic dissection, the pain is rarely migratory. Because the most common site of penetrating aortic ulcer is in the descending thoracic aorta, a murmur of aortic regurgitation, pericardial friction rub, and peripheral pulse deficits are not seen. In addition, visceral vessel involvement has not been reported. Neurologic deficits are very rare, but acute lower-extremity paraplegia has been reported (98). In a patient with a history that is compatible with aortic dissection, the *absence* of physical findings suggests the diagnosis of penetrating aortic ulcer. Asymptomatic penetrating aortic ulcer does occur and is usually incidentally discovered as enlargement of the descending thoracic aorta or a hilar mass on routine chest radiography (98,101).

Laboratory Findings

Routine laboratory studies are nonspecific with penetrating aortic ulcer. The chest radiograph is the most helpful of the routine laboratory tests because it is often abnormal. It may demonstrate mediastinal widening, focal or diffuse enlargement of the descending thoracic aorta, a hilar mass, left apical mass, bilateral pleural effusion, or isolated left pleural effusion (96,97). However, normal chest radiographic findings do not exclude penetrating aortic ulcer. The most common electrocardiographic abnormality is left ventricular hypertrophy from chronic systemic hypertension.

The findings on CT, MRI, TEE, and aortography in patients with penetrating aortic ulcer are characteristic, allowing differentiation of penetrating aortic ulcer from classic aortic dissection (eFig. 108.2.1).



***e*FIGURE 108.2.1** Computed tomographic scan in a patient with penetrating atherosclerotic ulcer of the proximal descending thoracic aorta (*arrow*). Note small dimple of contrast material extending from the aortic lumen into an area of hematoma formation (the ulcer penetration site).

Management

Treatment is individualized, as the natural history of penetrating aortic ulcer and indications for surgery are not well defined. The natural history of an intramural hematoma has been shown by serial noninvasive imaging studies to follow a course of resorption of the hematoma and aortic dilation in the region of the involved aorta (97,98). Patients with an intramural hematoma should be treated medically, with special emphasis placed on control of blood pressure, preferably with a beta-adrenergic blocking agent. Ascending aortic involvement, progressive aortic dilation, persistent symptoms, or difficult-to-control hypertension is an indication for surgery. When saccular aneurysm or pseudoaneurysm is the result of a penetrating atherosclerotic ulcer of the aorta, surgery is recommended.

ANEURYSMAL DISEASE

An aneurysm can be defined as a permanent localized dilation of an artery. Because atherosclerosis is the most common cause of arterial aneurysm, aneurysmal disease and its complications are frequent clinical problems. Once initiated, an aneurysm tends to enlarge progressively. Although most aneurysms enlarge in an occult fashion, pressure of the aneurysm on surrounding structures or eventual rupture may occur. Furthermore, nonlaminar flow within the aneurysm leads to the formation of laminated thrombus, which may lead to distal embolization. Despite advances in noninvasive imaging and surgical techniques, the diverse presentations of aortic aneurysm can challenge the best of clinicians at times, making the aphorism of Sir William Osler, “There is no disease more conducive to clinical humility than aneurysm of the aorta,” (106) appropriate even today.

Thoracic Aortic Aneurysm

Atherosclerosis is the most common cause of aneurysmal disease of the aorta; thus, aneurysms are more common in men than in women (5:1) and are rare in patients who are younger than 50 years of age. Less common causes include congenital defects of the arterial wall, hypertension, tobacco use, familial tendency, inherited disorders of connective tissue, infections, arteritis, sudden deceleration, entrapment, and trauma. Perhaps less appreciated is the condition termed *annuloaortic ectasia* by Ellis et al. (107), a disorder that is more common in men and characterized by dilatation of the aortic root without other features of Marfan syndrome. These patients typically have aortic regurgitation and are prone to aortic dissection and sudden death (108). Dilatation of the aortic root causing severe aortic regurgitation can also result from poorly controlled systemic hypertension (109). Aortitis secondary to inflammatory disorders of the aorta—for example, giant-cell and Takayasu’s arteritis—can cause dilatation of the aorta, usually in the root and ascending portion, which results at times in associated aortic valve regurgitation (110). The aorta is also the most common site of infectious arteritis and mycotic aneurysm (111).

Whatever the underlying cause, the development of an aneurysm is related to weakening of the media of the artery. Once dilation begins, enlargement tends to be progressive, because lateral pressure increases with widening of the aortic lumen (Bernoulli theorem). Furthermore, wall tension at constant arterial pressure increases with increasing diameter (Laplace’s law) (112). Systemic hypertension also accelerates aneurysm expansion (113). Subtle defects in collagen and elastin, combined with an accelerated breakdown of these molecules by an increase in proteolytic enzyme activity or a decrease in the levels of protease inhibitors (or both), play a significant role in the development of aortic aneurysm (114).

Most aneurysms of the thoracic aorta are asymptomatic, being incidentally discovered on chest radiography (115,116). When symptoms develop, the aneurysm is usually large enough to encroach on surrounding structures and cause chest pain, back pain, dyspnea, dysphagia, cough, hoarseness, or stridor. When there is venous compression (eFig. 108.2.2), compression of other structures (e.g., fixation of a vocal cord), or encroachment on the chest wall, corresponding findings may be noted. The symptoms and signs of congestive heart failure may predominate when there is significant aortic regurgitation. Atheroembolism is not an infrequent clinical presentation of aortic aneurysm. As a result of slowing of flow in the peripheral portions of the aneurysm, laminated mural thrombus develops and may subsequently embolize to the distal arterial circulation (68).

***e*FIGURE 108.2.2** Unilateral neck vein distention (left internal jugular) in a patient with an aortic arch aneurysm.

VIDEO

Video 108.19 Intraoperative transesophageal echo (120-degree view) with color Doppler demonstrating aortic insufficiency due to aortic dilatation (sinuses measure 5.0 cm) causing failure of leaflet coaptation. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 108.20 Multiple gated acquisition scan of a patient with aortic insufficiency, ascending aortic aneurysm, and congestive heart failure. The ascending aorta is dilated, and there is moderate to severe left ventricular dilatation (ejection fraction approximately 30%). There is a prominent septal separation suggesting left ventricular hypertrophy. Analysis of regional wall motion reveals mild septal and posterolateral hypokinesis, moderate anterolateral and anterior hypokinesis, and inferoapical and apical dyskinesis in the anterior **(A)** and left anterior oblique **(B)** projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 108.21 Multiple gated acquisition scan of a patient with aortic insufficiency, ascending aortic aneurysm, and congestive heart failure. The ascending aorta is dilated, and there is moderate to severe left ventricular dilatation (ejection fraction approximately 30%). There is a prominent septal separation suggesting left ventricular hypertrophy. Analysis of regional wall motion reveals mild septal and posterolateral hypokinesis, moderate anterolateral and anterior hypokinesis, and inferoapical and apical dyskinesis in the anterior **(A)** and left anterior oblique **(B)** projections. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

On a plain radiograph, an aneurysm appears as a rounded or smooth density in the central portion of the chest if it is not obscured by other structures (Fig. 108.3). Unless there is calcification in its wall, the aneurysm may be difficult to differentiate from intrathoracic tumor in the central chest or from simple elongation and torsion of the aorta. Aortography has been the classic method to diagnose thoracic aortic aneurysm, but CT, particularly with i.v. contrast enhancement; MRI; and combined TTE and TEE have become the noninvasive diagnostic tests of choice (117,118,119,120 and 121).

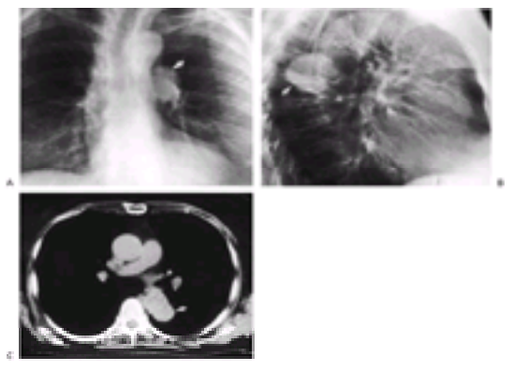


FIGURE 108.3 A: Posteroanterior chest radiograph demonstrates a left hilar mass (*arrow*). **B:** Lateral view demonstrates a mass adjacent to the proximal descending thoracic aorta (*arrow*). **C:** Computed tomographic scan demonstrates the mass to be a saccular aneurysm (*arrow*) of the proximal descending thoracic aorta.

VIDEO

Video 108.22 Ventriculography of a contained rupture of the left ventricle (false aneurysm). Contrast injection reveals a noncontractile portion of the left ventricular silhouette that fills with contrast but does not clear. This is consistent with a contained rupture of the left ventricle. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 108.23 Aortography showing an aneurysm of the ascending aorta with 3+ aortic regurgitation. The aortogram in this patient with cystic medial necrosis shows a maximum dimension of 5.4 cm. The dilation is confined to the ascending aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The prognosis of untreated thoracic aortic aneurysm is poor, with 3-year survival rates as low as 25% (122). Factors that seem to worsen the prognosis are female gender, diastolic hypertension, size greater than 6 cm, traumatic aneurysm, and associated coronary and cerebrovascular disease. The cumulative risk of rupture is 20% after 5 years (123). The 5-year risk of rupture as a function of aneurysm size at recognition is 0% for aneurysms less than 4 cm in diameter, 16% for those 4.0 to 5.9 cm, and 31% for aneurysms of 6 cm or more (123). Because of the poor prognosis for the untreated patient with a thoracic aortic aneurysm, surgical treatment is justified unless comorbid medical conditions contraindicate an operation. Based on previous natural history studies (115,116,123), the following seem to be reasonable indications for surgical treatment: (a) an aneurysm that is symptomatic, (b) an aneurysm with a diameter of 6 cm or greater, (c) an aneurysm that enlarges under

observation, and (d) an aneurysm in a person with poorly controlled systemic hypertension.

Video 108.24 Contained rupture of aorta (false aneurysm). The aorta ruptured into the pericardium, which was localized and contained by post–coronary artery bypass grafting adhesions. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 108.25 Four-chamber transesophageal view of a patient with a cystic-appearing mass on the tricuspid valve. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Audio 108.26 Ruptured sinus of Valsalva aneurysm. Auscultation performed in a 23-year-old male who presented with sudden onset of shortness of breath. Echocardiography reveals rupture of an aneurysm of the right coronary cusp into the right ventricle. The loud systolic murmur continues well into diastole. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Audio 108.27 Ruptured sinus of Valsalva aneurysm. Auscultation performed in a 23-year-old male who presented with sudden onset of shortness of breath. Echocardiography reveals rupture of an aneurysm of the right coronary cusp into the right ventricle. The loud systolic murmur continues well into diastole. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Audio 108.28 Ruptured sinus of Valsalva aneurysm. Auscultation performed in a 23-year-old male who presented with sudden onset of shortness of breath. Echocardiography reveals rupture of an aneurysm of the right coronary cusp into the right ventricle. The loud systolic murmur continues well into diastole. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Audio 108.29 Ruptured sinus of Valsalva aneurysm. Auscultation performed in a 23-year-old male who presented with sudden onset of shortness of breath. Echocardiography reveals rupture of an aneurysm of the right coronary cusp into the right ventricle. The loud systolic murmur continues well into diastole. Right upper sternal border (*first clip*), left upper sternal border (*second clip*), left lower sternal border (*third clip*), and apex (*fourth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Unless there are contraindications, elective surgical resection of thoracic aortic aneurysms that result from trauma, even when asymptomatic, is indicated because of the inability to predict rupture (124,125). Prophylactic surgical treatment of aortic root dilation greater than 5.0 cm in diameter in the person with Marfan syndrome is advisable to prevent the complications of aortic dissection and rupture (126,127).

The surgical approach to repair of an aortic aneurysm depends on its location and extent. Special problems attend operations on the thoracic aorta, in contrast to infrarenal aortic procedures. Neither the ascending nor the arch portion of the aorta should be cross-clamped for repair of an aneurysm without the use of heart-lung bypass, adjunctive hypothermia, and myocardial protection. Cross-clamping the aorta at a point just distal to the left subclavian artery involves a substantial risk (4% to 18%) of inducing severe ischemia of the spinal cord with resultant paraplegia. Risk factors for spinal cord ischemia or infarction include female gender and intraoperative hypotension (mean arterial pressure <55 mm Hg) (128). Attempts to reduce spinal cord ischemia with systemic hypothermia, rapid repair, temporary aortic shunt bypass, femoral-femoral extracorporeal circulation, intrathecal papaverine, and left atrial-to-distal arterial aortic bypass have all been used with limited success.

In general, fusiform aneurysms are opened and stripped clean of thrombus and atherosclerotic intima, after which an aortic vascular prosthesis is sutured to the luminal aspect of the proximal and distal uninvolved aorta. The less common saccular aneurysm is usually transected at its neck, and aortic integrity is reconstituted by direct suturing or by a patch of vascular graft material. If aortic annular dilatation results from proximal extension of the aortic aneurysm, thus causing aortic valvular regurgitation, repair is effected by replacing the valve and ascending aorta separately, the narrow rim of aortic root from which the coronary arteries arise being allowed to remain. Alternatively, a composite graft can be attached proximally at the annulus, after resection of the natural valve, and distally just beyond the aneurysm (129,130). The composite graft consists of a replacement aortic valve that is inserted into the proximal end of a tubular aortic vascular crimped-fabric graft. In the use of such a composite graft, buttons of the aortic wall containing the coronary ostia must be implanted into the proximal portion of the aortic graft. With technical improvements, the perioperative risk for these procedures is between 3% and 10% depending on the size and location of the aneurysm and the general condition of the patient.

Abdominal Aortic Aneurysm

Approximately three-fourths of all atherosclerotic aneurysms involve the abdominal aorta. Men are affected more frequently than women (9:1), and the majority of patients are older than 50 years. Hypertension often coexists and further contributes to aneurysm formation (7). Current smoking also increases the risk of aneurysm rupture and reduces long-term survival (131). A familial tendency for development of AAA is well established, with sex-linked and autosomal patterns of inheritance involved (132,133). First-degree male relatives of patients with AAA have a 12-fold increased risk of developing an aneurysm compared with control subjects (132). Most AAAs are infrarenal in location. Two percent to 5% are suprarenal, usually the result of distal extension of a thoracic aneurysm (thoracoabdominal aneurysm).

Video 108.30 Transesophageal echo in a patient with severe left ventricular dysfunction and a descending aortic aneurysm with severe spontaneous echo contrast within the aorta (seen in short axis). Note the significant layering of thrombus along the wall of the aneurysm (*right*). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Infectious (mycotic) aneurysms frequently involve the abdominal aorta and tend to occur at regions of diseased tissue, such as areas of atherosclerosis (134). Arterial trauma caused by accidents, surgical manipulation, i.v. drug abuse, or invasive diagnostic procedures has surpassed endocarditis as the most frequent cause of mycotic aneurysm, accounting for up to 42% of cases (134). *Salmonella* species and *Staphylococcus aureus* are the most common organisms isolated, accounting for 50% and 30% of cases, respectively (134). A less common cause of AAA that frequently goes unrecognized is trauma, usually blunt (i.e., seat belt injury), which can result in the formation of true aneurysm and pseudoaneurysm of the abdominal aorta in persons of any age.

The majority of patients with AAA are asymptomatic, emphasizing the importance of increased clinical awareness for the condition, especially when risk factors for aneurysmal disease are present. The most frequent and important physical finding in AAA is the presence of a pulsatile abdominal mass. The sensitivity of abdominal palpation for the detection of AAA is 43% overall (57% for aneurysms >4.0 cm in diameter, 29% for aneurysms <4.0 cm in diameter) (135). Previous pathologic studies have suggested that an AAA must be 4.5 cm in diameter before it can be diagnosed with any degree of accuracy on physical examination (136). In clinical practice, with time and experience, AAAs of smaller size can be palpated in most nonobese patients. A tortuous abdominal aorta, transmitted pulsation from an abdominal mass, or a horseshoe kidney anteriorly displacing the abdominal aorta are conditions that can mimic AAA on physical examination.

Miniaturized ultrasonographic machines (2.5-MHz curved array transducer connected to a compact 2.6-kg console), termed personal ultrasound imagers, now enable detection of occult AAA with a sensitivity and specificity of 91% and 96%, respectively (137,138). Ultrasound screening programs for asymptomatic AAA result in a significant reduction in mortality from all aneurysm causes (139).

When an AAA is symptomatic without rupture, the most common complaint is abdominal pain, intermittent or constant, over the preceding days or weeks. Recent-onset low back pain can occur and may be due to dissection within the aneurysm or retroperitoneal hematoma. Abdominal pain that radiates to the flank, groin, or testes may be a dominant or associated complaint. If atheroembolism from AAA has occurred, painful blue toes, livedo reticularis, hypertension, and renal insufficiency develop (eFig. 108.3.1). Less commonly, intermittent claudication from embolization of the muscular branches of the lower extremity arteries can occur.

***e*FIGURE 108.3.1** After intravenous thrombolytic therapy for acute myocardial infarction in a man with an abdominal aortic aneurysm, atheroembolism to both lower extremities occurred, causing multiple blue toes bilaterally.

Livedo reticularis. Mottled reddish discoloration of the lower extremities with accompanying multiple ulcerations associated with atheroemboli.

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene (*yellow arrow*), as well as localized skin necrosis and livedo reticularis (*white arrows*).

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene, as well as localized skin necrosis and livedo reticularis (*white arrows*).

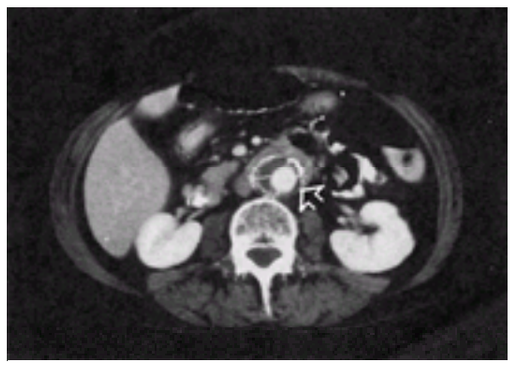
Atheroemboli. Digital necrosis resulting from severe atheroemboli.

Cholesterol emboli. Purpura secondary to cholesterol emboli are shown (*yellow arrows*).

The most frequent complication of AAA is rupture, which occurs most often when aortic diameter exceeds 5 cm (140). Rupture of an AAA is characterized by the triad of severe pain, hypotension, and a tender abdominal mass. The pain is acute in onset, constant, and severe, most commonly located in the lumbar area or diffusely throughout the abdomen with radiation into the flanks, genitals, or legs. The abdominal aorta is usually tender to palpation, and there may be peritoneal signs if free rupture into the peritoneal cavity has occurred. Findings suggestive of a ruptured AAA or contained rupture represent a true surgical emergency, and prompt diagnosis and surgical therapy are crucial to improve survival.

Less common presentations of AAA include obstructive uropathy due to ureteral compression, gastrointestinal hemorrhage when the aneurysm ruptures into the intestinal tract, high-output congestive heart failure due to an aortocaval fistula, and disseminated intravascular coagulation.

Inflammatory AAAs comprise approximately 2% to 14% of all AAAs. Patients with an inflammatory AAA classically present with abdominal or back pain, malaise, weight loss, and an elevated sedimentation rate (141,142 and 143). Obstructive uropathy is an additional presentation. Preliminary evidence suggests that inflammatory AAAs may have a familial component and that current smoking may play a role in the inflammatory process (143). The diagnosis can be established by CT or MRI (eFig. 108.3.2). Treatment is surgical grafting. The role of corticosteroid therapy is less well defined. Preliminary case reports suggest that corticosteroid therapy may facilitate surgery when severe inflammation or ureteral involvement is present and reduce inflammation after surgical resection of an inflammatory AAA (144).



***e*FIGURE 108.3.2** Computed tomographic scan of typical thick wall of inflammatory abdominal aortic aneurysm (*arrow*).

Aneurysmal disease in other locations is important to keep in mind when examining patients with AAA. Up to 30% of persons with AAA have aneurysms of other arteries, most often the iliac, femoral, and popliteal arteries. Coronary artery disease, carotid occlusive disease, and peripheral arterial occlusive disease are frequently present in patients with AAA, an important point to remember during the clinical evaluation and preoperative assessment of these patients (145). In individuals who are

selected for AAA repair, careful clinical and noninvasive assessment of associated coronary and carotid artery disease is indicated to stratify the patient's perioperative cardiac risk. The identification and surgical treatment of significant correctable coronary artery disease and carotid occlusive disease before elective resection of AAA have been shown to reduce the incidence of postoperative myocardial infarction and mortality (145).

AAA can be accurately diagnosed with ultrasonography, CT, or MRI and magnetic resonance angiography (MRA) (Fig. 108.4). Angiography is not needed to diagnose AAA, but it is useful when a juxtarenal aneurysm is suspected or when delineation of associated peripheral, renal, or visceral arterial occlusive disease is indicated before surgical repair.

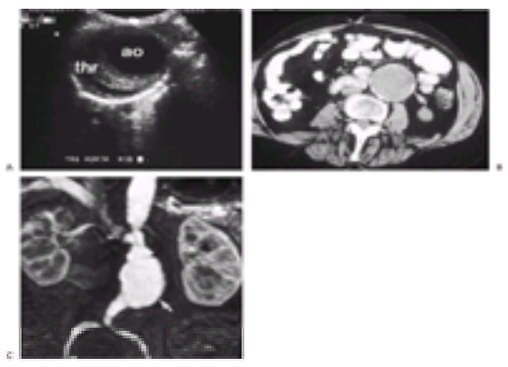


FIGURE 108.4 Noninvasive imaging in the diagnosis of abdominal aortic aneurysm. **A:** Ultrasound examination demonstrates large abdominal aortic aneurysm with large amount of laminated thrombus (thr). ao, aortic lumen. **B:** Computed tomographic study demonstrates large abdominal aortic aneurysm with calcification of the aortic wall (*arrow*). **C:** Magnetic resonance angiography demonstrates infrarenal abdominal aortic aneurysm (*arrow*).

Natural history studies of AAAs demonstrate an increase in risk of rupture when aneurysm diameter exceeds 5 cm (140,146). Elective resection and graft replacement have a surgical mortality of less than 5%, but emergent surgical treatment after the aneurysm has ruptured has a much higher mortality (145).

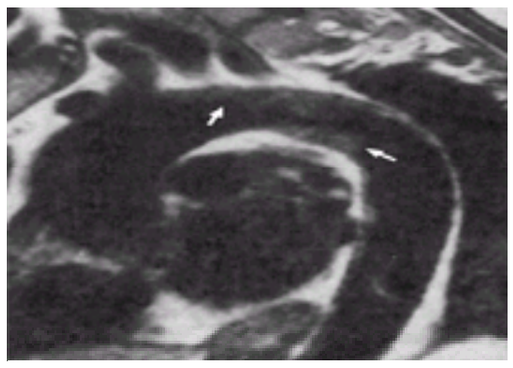
In the poor-risk patient with an aneurysm of less than 5 cm in diameter, observation of the aneurysm with serial ultrasound examinations every 3 to 6 months is appropriate. Some evidence has been found that long-term beta-adrenergic blockade may decrease the rate of expansion of AAA (147).

Endovascular repair of AAA, first reported in 1991 (148), is being used with increasing success (149,150 and 151). Advances in technology over the past 10 years and more well-defined indications have established endovascular repair of AAA as a safe and effective procedure in selected patients (151,152 and 153). With second-generation devices, the procedure is initially successful in greater than 95% of patients, with 2-year success rates that are comparable to those of standard surgical repair (151,152). Specific computed tomographic and angiographic criteria are used to determine if endovascular repair is feasible, the most common primary reasons for ineligibility being related to morphology of the aneurysm neck or abnormalities of the iliac arteries, or both. Despite the minimally invasive nature of endovascular aneurysm repair, a variety of complications occur with considerable frequency (153). Complications are more often encountered in patients with large aneurysms, advanced age, and if adjuvant procedures are required (153). Evidence of blood flow in the aneurysm sac (endoleak) occurs in up to 50% of patients but does not appear to predict patient survival or aneurysm rupture rate (152,154).

OCCLUSIVE DISEASE

Etiology

Occlusive disease of the aorta is most commonly due to advanced atherosclerosis. Additional causes include giant-cell arteritis and Takayasu's disease. Rarely, primary intimal sarcoma of the aorta can cause occlusive or embolic symptoms, or both (*e*Fig. 108.4.1).



***e*FIGURE 108.4.1** Magnetic resonance imaging demonstrates large mass (*arrows*) nearly occluding the lumen of the transverse aortic arch in a patient with cerebral, upper and lower extremity, and visceral emboli. Postmortem examination demonstrates the mass to be a primary intimal sarcoma of the aortic arch.

Severe calcific atherosclerosis of aorta. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Transesophageal echo view of the descending aorta in short axis demonstrating significant atheromatous plaque.

Atherosclerosis

Atherosclerosis in the thoracic aorta usually involves the origin of the brachiocephalic arteries, principally the left subclavian and occasionally the innominate artery. Although atherosclerotic disease of the aortic arch branches is usually asymptomatic, stenosis of the origin of the left or right subclavian artery may cause intermittent claudication of the arm of sufficient degree to warrant surgical treatment. With complete occlusion of the origin of either subclavian artery, collateral blood flow to the arm may be derived principally from the cerebral circulation via reversed flow through the ipsilateral vertebral artery, so-called subclavian steal. This results in episodes of transient cerebral ischemia, especially when the ipsilateral arm is exercised. A similar situation may occur on the right side if the obstruction occurs at the origin of the innominate artery, in which case flow in the right vertebral artery can “reverse” to enter the right subclavian artery. In addition to the symptoms of transient cerebral ischemia, physical signs of this condition include reduced arm and wrist pulses and reduced blood pressure on the affected side. Furthermore, a coronary-subclavian steal phenomenon can occur in patients who have undergone prior coronary artery bypass surgery using the internal mammary artery (IMA). When a hemodynamically significant subclavian artery stenosis is present ipsilateral to the IMA graft, flow through the IMA may reverse or “steal” during upper extremity exercise. Coronary and graft angiography demonstrate retrograde flow in the involved IMA during injection of the grafted coronary artery. The astute examiner, when palpating both radial pulses simultaneously, may also detect a delay in pulsation on the affected side (155).

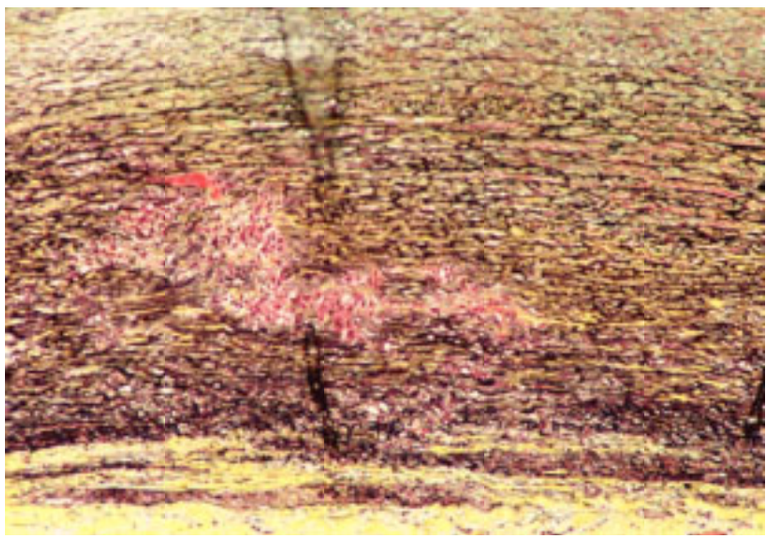
Acquired coarctation of the thoracic aorta due to focally obstructive calcific atherosclerotic disease is rare but has been reported (156). Symptomatic patients present with upper extremity hypertension and reduced blood pressure in the lower extremities, with or without intermittent claudication.

Micro- or macroemboli from atherosclerotic plaque and thrombus in the thoracic aorta are important causes of stroke and peripheral embolization. Aortic atheromas occur with a prevalence of approximately 27% in patients with previous embolic events, and aortic atheromas are also strong predictors of coronary artery disease (157,158). Assessment of thoracic aortic atherosclerotic plaque is most accurately obtained with TEE. Plaque thickness of greater than 4 mm and mobile thrombus (of any size) are associated with an increased risk of embolism (158). Embolism can occur spontaneously, in relation to invasive angiographic procedures, secondary to warfarin or thrombolytic therapy, and secondary to cardiac surgical procedures that require cardiopulmonary bypass. Treatment is surgical resection if a focal source of embolism is present and the patient’s general medical condition permits. Preliminary research suggests that warfarin may be beneficial in reducing subsequent embolic events, but further randomized trials are required (157).

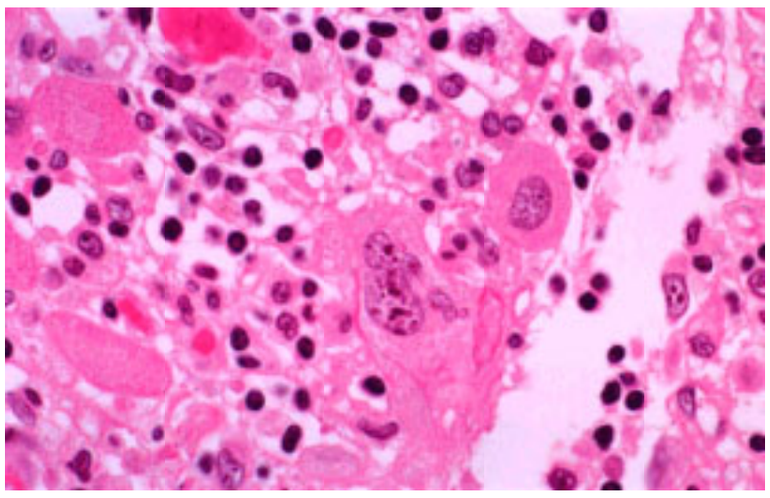
Giant-Cell Arteritis

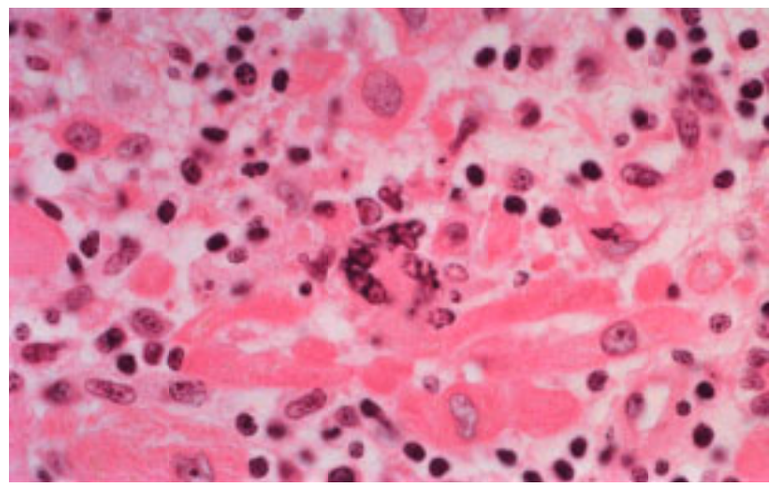
The cause of giant-cell arteritis (formerly called *temporal arteritis* or *cranial arteritis*) is unknown. The dominant clinical symptom is usually headache; the most frequent and dreaded complication is blindness. The classic physical finding is prominent, inflamed, or tender temporal arteries. Significant involvement of the aorta and large arteries is being recognized with increasing frequency.

Giant-cell arteritis is a subacute and chronic inflammatory process with local and systemic manifestations. It is generally seen in persons older than 55 years, and it is twice as common in women as in men. Involvement of the thoracic aorta and its branches may be minimal and asymptomatic, but when it is more extensive it can result in occlusion of one or more branches of the aortic arch (159), dilatation or saccular aneurysm of the aorta (160), or even aortic dissection (160).

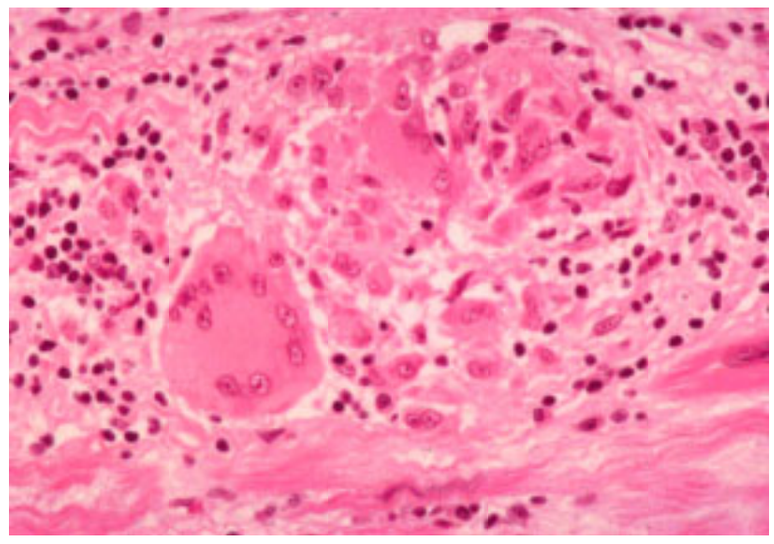


Section of aortic wall demonstrating giant cell arteritis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)





Giant cell myocarditis with apoptosis (A,B). (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)



Giant cell myocarditis. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

The diagnosis is typically established by biopsy of the superficial temporal artery. However, MRI/MRA or standard contrast angiography is required to confirm the diagnosis of aortic and branch vessel involvement and to differentiate this disorder from atherosclerotic occlusion. The ascending aorta can be dilated, and there may be thickening of its wall; involvement of branches of the arch, when present, is often bilateral, with segmental areas of smooth, tapered arterial stenosis or occlusion, or both, in the absence of atherosclerotic changes.

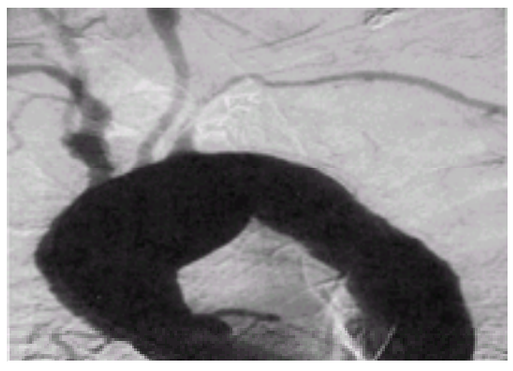
Management of the patient with aortic or large-artery involvement by giant-cell arteritis is principally by administration of corticosteroids in adequate doses (beginning with 45–60 mg prednisone daily), often in combination with methotrexate (161). Arterial changes are reversible with adequate therapy, but when pharmacologic therapy has been insufficient to suppress the arteritis, there may be progressive involvement of the aorta and resultant dissection or rupture.

Takayasu's Disease

This disorder, also called *pulseless disease* and *idiopathic medial aortopathy and arteriopathy*, is another syndrome of arteritis that involves the aorta and its branches. In contrast to patients with giant-cell arteritis, most individuals with Takayasu's disease are younger than 40 years; it also occurs more commonly in women (>80% of cases).

The early subacute phase of fever, anorexia, malaise, weight loss, night sweats, and fatigue often go unrecognized, with the diagnosis first being suspected when symptoms and signs of the occlusive phase develop. The clinical manifestations of occlusion may include cerebrovascular insufficiency, arterial insufficiency of the upper or lower extremities, or mesenteric insufficiency, depending on the location of the aortitis and arteritis. Hypertension is very common; it occurs as a result of acquired aortic coarctation or involvement of the renal arteries by the arteritis.

MRA or standard contrast aortography is of great value in the diagnosis of Takayasu's disease. Segmental narrowing of a variable length of descending or abdominal aorta or narrowing of the origin of major branches of the aorta occurs as a result of thickening of the aorta or arterial wall (*e*Fig. 108.4.2). This usually allows distinction of Takayasu's disease from other causes of the aortic arch syndrome (162). Although aneurysmal dilatation of the thoracic aorta can occur in Takayasu's disease (163), it is not common or distinctive in this disorder.



***e*FIGURE 108.4.2** Aortogram in a patient with Takayasu's disease demonstrates large ascending aortic aneurysm and long tapered stenoses of the proximal left common carotid artery (*arrowheads*) and left subclavian artery *(open arrowheads)*.

Therapy with corticosteroids, sometimes combined with anticoagulant therapy, is effective for patients in the early phase of the disease in controlling systemic symptoms and allowing return of pulses. For the patient in the later occlusive phase, surgical treatment to bypass the obstruction may be indicated to relieve hypertension caused by the acquired coarctation or renal artery stenosis (164). Similarly, other occlusive arterial lesions may require surgical treatment for relief of ischemic manifestations.

TRAUMATIC RUPTURE OF THE THORACIC AORTA

Pathogenesis

Trauma to the thoracic aorta may result from crushing injury and deceleration, as well as from penetrating injuries, or it may be iatrogenic from intraaortic procedures. Aortic rupture from sudden deceleration is the most common traumatic condition of the thoracic aorta that is encountered clinically. Rupture of the thoracic aorta as a result of sudden deceleration may vary in degree from incomplete laceration to complete transection. The injury occurs most often as a result of an automobile accident but may also occur in falls from heights or compression by heavy objects (165). With horizontal deceleration, as in automobile accidents, 80% of the aortic ruptures occur at the isthmus of the thoracic aorta just distal to the origin of the left subclavian artery and near the attachment of the ligamentum arteriosum, the point of aortic

fixation where the shearing stress is maximal (166).

Clinical Features

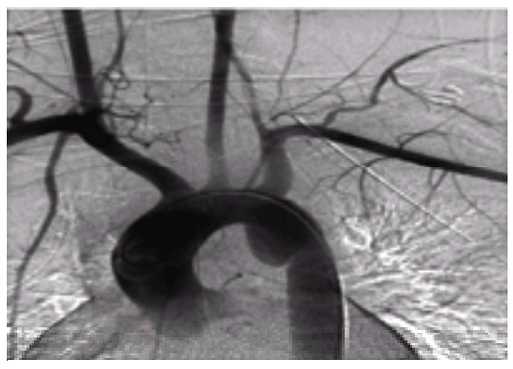
Traumatic aortic rupture should be suspected whenever an injury involves sudden deceleration or chest trauma, either blunt or penetrating. The presence of chest contusions or penetrating wounds, rib or sternal fractures (167), hypertension in the arms (168), decreased or absent pulses in the legs (169), or evidence of fluid in the left side of the chest (170) is a clue to the possibility of aortic rupture.

Radiologic Features

The only finding on radiography of the chest may be widening of the mediastinum (170). The presence of left pleural fluid in association with mediastinal widening is an even stronger clue (170). Associated rib, clavicle, or sternal fractures may also be seen.

Diagnosis

In a patient with suspected traumatic rupture of the thoracic aorta, TEE, CT, or aortography should be performed emergently to confirm the diagnosis and localize the site of aortic rupture (171,172 and 173) (*e*Fig. 108.4.3). TEE is the initial test of choice, as it permits rapid diagnosis and effective triage of patients (173). The echocardiographic signs of aortic injury are complex and may be confined to a short section of the aorta. Therefore, examination by a physician who is highly trained in echocardiography is necessary in such cases.



***e*FIGURE 108.4.3** Aortogram in a patient with traumatic rupture of the thoracic aorta demonstrates a pseudoaneurysm just distal to the left subclavian artery.

Prognosis

Most patients with traumatic aortic rupture die before they reach a hospital, but as many as 20% may survive long enough to permit diagnosis and treatment (165). Some patients survive the aortic laceration and later present with so-called chronic traumatic thoracic aortic aneurysm; approximately half of these lesions become unstable and enlarge at some time in their course, but there are no criteria to predict which will do so (124).

Treatment

In the acute setting, extreme alertness, prompt diagnosis, and immediate surgical repair are necessary. Ordinarily, end-to-end anastomosis is not feasible, and therefore a prosthetic graft is interposed after resection of the lacerated area (174).

For chronic traumatic thoracic aortic aneurysm, we and others (124,125) favor surgical treatment, even though some of these patients may survive without surgery for long periods, because of the unpredictable course of this lesion and the low morbidity and mortality of elective surgical repair.

AORTITIS

Aortitis refers to a group of disorders with diverse etiologies. Although not a particularly common primary problem, aortitis, because of its role in aortic regurgitation, aortic dissection, and aneurysmal disease, is an important disorder of the thoracic and abdominal aorta.

Video 108.31 Aortography in a patient with giant cell aortitis, a severely dilated aorta, and aortic regurgitation. After contrast injection, approximately 1+ aortic regurgitations are evident. The ascending and descending aorta are significantly enlarged (left anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Etiology

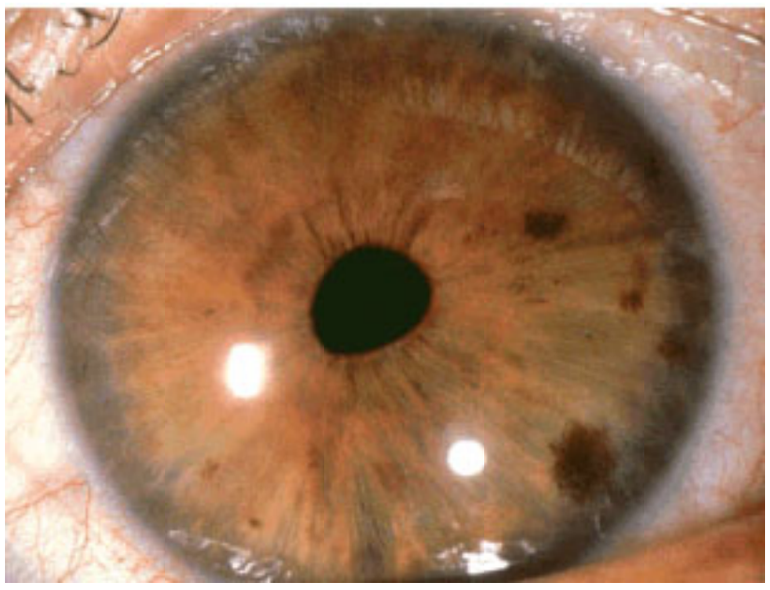
Inflammatory change can occur in the wall of the aorta in response to any type of injury. One way of classifying aortitis that involves a systematic approach to diagnosis is shown in *e*Table 108.1.3. Giant-cell arteritis and Takayasu's disease have already received attention in this chapter in the discussion of the arteritides in the section Occlusive Disease.

***e*TABLE 108.1.3** CLASSIFICATION OF AORTITIS

Nonstenosing aortitis
Infectious
Syphilitic aortitis
Infectious aortitis
Rheumatic fever
Noninfectious
Giant-cell arteritis
Takayasu's disease
Rheumatoid arthritis
Ankylosing spondylitis
Psoriatic arthritis
Enteropathic arthropathies
Relapsing polychondritis
Rheumatic fever
Reiter's syndrome
Stenosing aortitis
Takayasu's disease

Pathogenesis

Syphilitic aortitis affects the ascending aorta most commonly, the arch next, and the descending thoracic aorta least frequently. With the initial infection, the spirochetes travel to the aorta, where they produce inflammation in the media, adventitia, and vasa vasorum. Fibrosis replaces the degenerative muscle fibers; this weakens the arterial wall and produces the characteristic wrinkling of the intima as a late manifestation some 10 to 30 years after the initial infection.



Argyll-Robertson pupil.

Infections other than syphilis may cause an infectious aortitis and produce an aneurysm or involve an existing aneurysm. In the case of infectious aortitis, the primary lesion seems to be in the vasa vasorum, leading to an abscess in the arterial wall. Fusiform, saccular, or false aneurysms result. The aorta is the artery most often involved with mycotic aneurysm (175,176). The natural history of mycotic aneurysm is one of progressive expansion, thinning of the aneurysm wall, and eventual rupture.

The cause of noninfectious aortitis remains obscure. In most types, however, the aortic involvement seems to be an expression of the systemic nature of the underlying illness and vasculitis. The basic lesions involve primarily the media, and to some extent the adventitia, and are often focal, except in rheumatic fever and rheumatoid arthritis, in which intimal involvement also occurs, producing a panaortitis (177). Aortitis involving predominantly the ascending aorta has been documented in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, relapsing polychondritis, and enteropathic arthropathies. Aortic regurgitation may result from dilatation of the aortic annulus in all forms of aortitis that affect the ascending aorta. Takayasu's aortitis differs from other types in that in some patients it can produce aortic narrowing ("acquired" coarctation) involving the descending thoracic or abdominal aorta, or both.

Clinical Features

Syphilitic aortitis, unless complicated, is usually asymptomatic. Other manifestations of tertiary lues may be seen in 10% to 30% of patients. With aneurysm formation, usually saccular in type, there may be signs of compression of other mediastinal structures; rarely, bony erosion occurs. When significant aortic regurgitation develops, a diastolic murmur and signs of a widened pulse pressure are noted.

In other types of infectious aortitis ("mycotic" aneurysm), the findings are those of infectious endocarditis. Usually no specific signs of mycotic aneurysm are seen unless it encroaches on a surrounding structure or it ruptures. With other types of aortitis, the clinical signs are those of the underlying disease.

Radiographic Features

The diagnosis of aortitis is often first suspected from the findings on a chest radiograph (dilation of the ascending aorta or aneurysm). Linear calcification of the ascending aorta and not the arch is most suggestive of syphilitic aortitis. Calcification can also be seen with other types of aortitis and in atherosclerotic disease, but it does not usually involve the ascending aorta alone.

TEE, CT, MRI, and aortography are all accurate in demonstrating the extent of aortic dilatation and any aneurysmal change. Aortography or MRA is generally required to define any branch artery occlusion that may be present.

Diagnosis

The diagnosis of aortitis is usually inferred from any related clinical or chest radiographic findings, or both. Aortography can also demonstrate coronary ostial involvement in patients with syphilitic aortitis and Takayasu's disease. Further differentiation of the type of aortitis depends on associated findings of syphilis (serologic findings and characteristic calcification) or an associated systemic illness.

Prognosis

The prognosis for patients with syphilitic aortitis is about the same as that for the general population (178), and death from its complications, other than aneurysm, is unusual. The prognosis for syphilitic aortic aneurysm, on the other hand, is poor, particularly when it is large enough to cause symptoms (179).

Aortic rupture or dissection is a potential complication of giant-cell arteritis. Otherwise, the prognosis of aortitis is generally that of the underlying systemic disorder.

Treatment

The preventive value of adequate therapy of early syphilis is the most important therapeutic aspect of syphilitic aortitis. Therapy of other types of aortitis is basically that of the underlying disorder. Management of any aneurysm, aortic regurgitation, or arterial occlusive disease is the same as that for such a lesion when it is due to other causes.

MARFAN SYNDROME

Marfan syndrome is a generalized disorder of connective tissue and is relatively common, with an incidence of 1 per 20,000. The incidence of Marfan syndrome does not differ according to gender, race, or ethnicity. It is an autosomal dominant disorder with extremely variable expression (180,181 and 182). Sporadic mutations account for approximately 25% of cases. The cause of Marfan syndrome has been found to be a defect in fibrillin; the gene that encodes fibrillin is on chromosome 15q15–21 (183,184).

Clinical diagnostic criteria for Marfan syndrome depend on manifestations in the skeletal, cardiovascular, and ocular systems and the family history (185). A "marfanoid" body habitus is not diagnostic of Marfan syndrome in the absence of other characteristic features or a well-documented family history of Marfan syndrome.

The ocular abnormalities associated with Marfan syndrome include subluxation of the lenses, myopia, and retinal detachment. Ectopia lentis is the most helpful ocular finding in making a diagnosis of Marfan syndrome.

Skeletal abnormalities associated with Marfan syndrome are frequent and include tall stature, a low upper/lower segment ratio, scoliosis or kyphosis, pectus deformities, and arachnodactyly (eFig. 108.4.4). Increased joint laxity and hyperextensibility are common. The face may be long and thin, and the palate may be narrow and highly arched.

***e*FIGURE 108.4.4** Thumb sign in patient with Marfan syndrome. Note that the thumb extends beyond the fifth digit with the hand clenched in a fist.

Cardiovascular abnormalities are clinically apparent in 40% to 60% of patients with Marfan syndrome, whereas 80% to 95% of patients have cardiovascular findings by echocardiography or pathologic examination. The most common cardiovascular abnormalities are mitral valve prolapse with or without mitral regurgitation and dilation of the ascending aorta, which may result in aortic regurgitation, aortic dissection, or aortic rupture (180,185,186,187,188 and 189). Less commonly reported abnormalities are tricuspid valve prolapse and dilation of the main pulmonary artery. Cardiovascular complications, especially aortic root dilation with dissection or rupture, account for most of the early mortality in patients with Marfan syndrome. Before effective surgical techniques, most patients with Marfan syndrome died in the fourth and fifth decades of life (186,190).

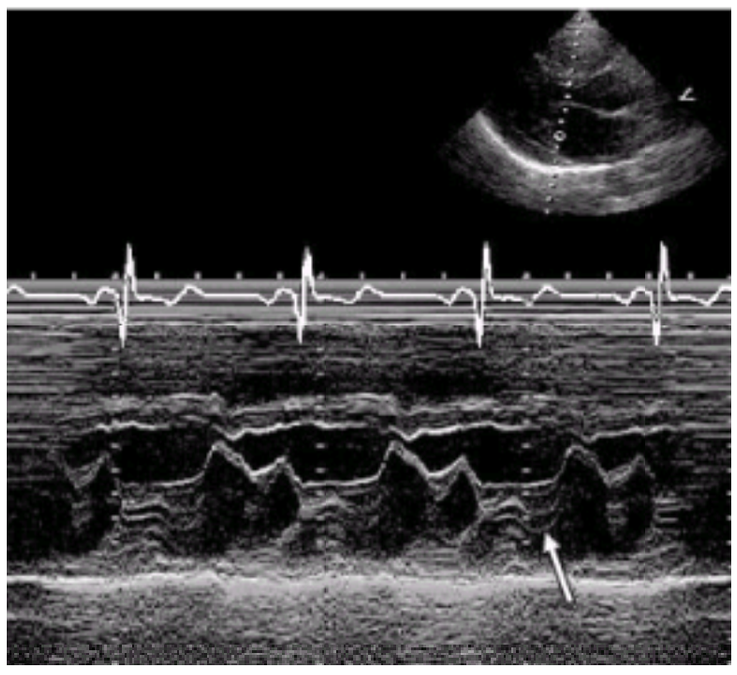
VIDEO

Video 108.32 Aortic insufficiency associated with annuloaortic ectasia of aortic root (oblique-coronal). An “onion-bulb” dilatation of the proximal ascending aorta and the sinuses of Valsalva is observed. A signal-void jet of aortic insufficiency is seen extending from the aortic valve into the left ventricular cavity during diastole. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Aortic abnormalities are found in 60% to 90% of patients (191). The prevalence of aortic root enlargement is greater in males than in females (192). Throughout life, the diameter of the aortic root is usually abnormal in proportion to body surface area in patients with Marfan syndrome; there is symmetric involvement of the sinuses of Valsalva and sinotubular ridge. Aortic dilation is usually progressive, likely due to abnormalities in aortic wall elastic properties such as increased wall stiffness (193,194). Aortic dilation may be limited to the sinuses of Valsalva or may involve the proximal and mid-ascending aorta. Generalized aortic dilation in patients with Marfan syndrome is a marker for increased risk of subsequent aortic complications (195). Dilation of the aorta is often accompanied by aortic regurgitation, and these patients often have a diastolic aortic regurgitation murmur (192). Aortic valve prolapse associated with a myxomatous aortic valve may also cause aortic regurgitation in patients without significant aortic dilation.

Aortic dissection in patients with Marfan syndrome is associated with aortic root dilatation (>6 cm) and a family history of dissection (196). Increased wall stress (Laplace’s law) in the dilated aorta may contribute to the pathogenesis of aortic dissection in these patients. Dissection most commonly involves the ascending aorta, although isolated distal dissection may also occur. Pregnancy in patients with Marfan syndrome is associated with an increased risk of aortic dissection, especially during the third trimester, parturition, and the first month postpartum (197,198).

Mitral valve prolapse and mitral regurgitation cause significant morbidity and mortality in patients with Marfan syndrome (199). Mitral regurgitation may be chronic and progressive or appear acutely if chordal rupture occurs. The finding of mitral valve prolapse in a patient with a marfanoid body habitus does not justify a diagnosis of Marfan syndrome in the absence of a positive family history or other characteristic features.



M-mode tracing of posterior leaflet mitral valve prolapse. Note the posterior displacement of the posterior mitral leaflet after the leaflets close in systole.

VIDEO

Video 108.33 Severe angiographic mitral valve prolapse with mitral regurgitation. In the angiogram there is a prolapse of the posterior leaflet accompanied by severe mitral regurgitation (4+). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 108.34 Mitral valve prolapse with severe mitral regurgitation (right anterior oblique view). *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 108.35 Intraoperative transesophageal echo showing bileaflet prolapse of the mitral valve. The color Doppler showed centrally directed mitral regurgitation. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime*

you may download it here.

The initial evaluation of patients who are suspected of having Marfan syndrome should include a chest radiograph, ophthalmologic examination (including slit lamp examination of the lenses), and echocardiography. Echocardiography is ideal in the initial evaluation of patients who are suspected of having Marfan syndrome. For the ability to accurately diagnose mitral valve prolapse and associated mitral regurgitation, aortic root dilation, aortic dissection, and aortic regurgitation, echocardiography is the test of choice in patients who are suspected of having Marfan syndrome. Echocardiography is essential for prognosis and management because no other phenotypic features predict a poor outcome (195). MRI and CT are also accurate in diagnosing aortic aneurysm and aortic dissection.

Treatment

Beta-adrenergic blockade to reduce the rate of dilation of the ascending aorta in Marfan syndrome has been shown to be beneficial (200,201,202 and 203). Progressive aortic root dilation occurs throughout life in patients with Marfan syndrome, the rate of dilation being greatest during early childhood and adolescent years. Although aortic root diameter increases over time in all patients, the rate of increase is significantly less in patients who are treated with beta-adrenergic blockade (202). Furthermore, beta-adrenergic blockade seems to improve survival without congestive heart failure, aortic regurgitation, aortic dissection, and aortic surgery (202). Therefore, patients with Marfan syndrome should begin beta-blockade therapy at the earliest age possible, and the dose should be adjusted to the largest dose that is tolerable. Atenolol has become the drug of choice for many physicians because of its relative cardioselectivity and the less frequent occurrence of adverse effects compared with lipid-soluble agents. Although no other drugs have been subjected to formal testing, verapamil, because of its negative inotropic action, is preferred in patients who cannot tolerate beta-adrenergic blocking agents (201).

Patients with aortic diameters greater than 5.0 cm have an increased risk of aortic dissection and should undergo prophylactic surgery (126). Patients with Marfan syndrome and ascending aortic aneurysm can undergo elective surgery with a low operative risk and excellent long-term survival with low morbidity. Aortic diameters less than 4 cm can be followed annually by echocardiography. Patients with aortic diameters between 4 and 5 cm should be observed more closely (every 6 to 12 months), especially if they have generalized aortic dilation and aortic regurgitation.

Video 108.36 A 120-degree postpump intraoperative transesophageal echo after placement of an aortic valve replacement conduit. The St. Jude aortic valve replacement is toward the left of the screen, and the aortic graft can be seen in the center of the screen. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Video 108.37 Postpump intraoperative echo after placement of an aortic valve homograft. Notice that the leaflets look like a native valve. The only clue that it is a homograft is the thickening at the annulus and the proximal ascending aorta due to the double thickness of the graft cuff with the native aorta. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

CONTROVERSIES AND PERSONAL PERSPECTIVES

Long-term management of type III aortic dissection continues to be an area of debate. Currently, most patients with type III aortic dissection are initially treated medically, with a beta-adrenergic blocking agent and adequate control of hypertension, and followed with noninvasive testing for the development of progressive aortic dilation and aneurysm formation, findings that might indicate the need for surgical intervention. Opinions differ about the indications for and timing of any surgical intervention in patients with “uncomplicated” type III aortic dissection. We and others currently advocate surgical therapy for patients with type III dissection after 2 to 3 weeks of pharmacologic therapy, if the patient’s general condition does not contraindicate this approach (90,91). If pharmacologic therapy does not relieve pain and stabilize the dissection, prompt surgical therapy is also indicated. Transluminal placement of an endovascular stent-graft device in type III aortic dissection has been successfully performed and may provide an alternative to surgery in highly selected patients in the future (92,204).

Debate is ongoing regarding the best noninvasive test in suspected aortic dissection. CT, MRI, and TEE, using current-generation technology, all have an exceedingly high sensitivity and specificity (>95%) in the diagnosis of aortic dissection. Currently, the diagnostic test of choice in suspected acute aortic dissection is TEE because of its rapid availability, portability, ability to provide a comprehensive cardiovascular assessment, and intraoperative applications. If TEE is not immediately available and the patient is stable hemodynamically, CT and MRI can be used as a substitute for TEE. Coronary angiography is not required in patients with acute proximal aortic dissection due to the high early mortality that is associated with this disease and inherent delays that are present with angiography (78). MRI is the preferred test in patients with chronic aortic dissection.

Equally as controversial is the treatment of patients with certain types of penetrating aortic ulcers. Although the natural history of an intramural hematoma is generally benign (i.e., resorption of the hematoma and compensatory dilation of the involved aorta) (101), the natural history of saccular aneurysm and pseudoaneurysm (due to penetrating aortic ulcer) is presently not known. Further study in this area is needed. Equally important are improved surgical techniques to decrease the risk of perioperative spinal cord ischemia and resultant paraplegia in patients undergoing thoracic aortic surgery.

The utility of beta-adrenergic blockade therapy in patients who have aneurysmal disease but not Marfan syndrome is poorly understood. The rare reports of the utility of beta-adrenergic blockade in these patients show benefit in decreasing aneurysm expansion rate, but the number of studies and patients involved are exceedingly small. Presently, our practice has been to institute a beta-blocking agent in all patients with aneurysmal disease if no contraindications to such therapy exist. Furthermore, most of these patients have concomitant coronary artery disease and systemic hypertension, which are well-established indications for beta-adrenergic blockade therapy.

Another highly controversial topic in aortic disease, especially in view of the current emphasis on cost containment in medicine, is screening for AAA. Screening programs for the general population have not been clinically or economically effective. It has been demonstrated, however, that screening certain populations who are at risk for development of an AAA (i.e., older than 70 years, hypertension, tobacco use, family history of AAA, etc.) identifies a group of patients with a significantly increased incidence of AAA compared with the general population. Targeting “high-risk” patients in future aneurysm screening programs will be more clinically meaningful and cost effective (205).

THE FUTURE

With regard to aortic dissection, continued efforts at earlier clinical recognition, allowing for more rapid diagnosis and treatment, are needed. Inclusion of aortic dissection in the differential diagnosis of patients presenting with acute chest pain is important, especially in view of the current widespread use of early i.v. thrombolytic therapy in patients with suspected acute myocardial infarction. Biochemical techniques will be integrated into the initial evaluation of patients with suspected aortic dissection. For example, elevated levels of smooth muscle myosin heavy-chain protein have been demonstrated to have a sensitivity and specificity of 91% and 98%, respectively, in patients with acute aortic dissection (206).

Based on the current size boundaries, the timing of surgical resection of aneurysms is less than perfect. For example, in patients with Marfan syndrome, an ascending aortic diameter of greater than 5 cm is associated with a small, although real, risk of rupture, and the risk increases significantly when aortic diameter exceeds 6 cm. Currently, surgery is indicated for patients with Marfan syndrome who have an ascending aortic diameter of greater than 5.5 cm, although surgery is less complicated and has less morbidity and mortality in patients with smaller aneurysms. The timing of surgical repair of AAA, in relation to aneurysm size, also requires further study. Currently, patients who are in otherwise good general health with an AAA diameter of greater than 4.5 cm are considered for *selective* surgical treatment. In the future, it is hoped that more emphasis will be placed on accurately determining aneurysm expansion rate to identify those patients with more rapid expansion rates who are at increased risk of rupture.

Increased efforts in identifying populations at risk for AAA are also clearly needed to allow more effective screening programs and identification of patients in the earlier stages of disease. Identification of less advanced aneurysmal disease may allow for earlier institution of pharmacologic therapy (i.e., beta-adrenergic blockade) and may lead to favorable alterations in the natural history of disease (i.e., decreased aneurysm expansion rate). Therapeutic agents that are targeted at the cellular level, for example, matrix metalloproteinases, may limit the growth of small AAAs. Personal ultrasound imagers will likely find increased utility in screening for aneurysmal disease and become an integral portion of the physical examination in patients who are at increased risk for development of an AAA. Earlier detection of AAA at a smaller size and careful clinical follow-up may also allow for more appropriate timing of surgical intervention and a decrease in mortality from ruptured AAA. Furthermore, the role of medical therapy (i.e., corticosteroids) in inflammatory AAA, in addition to or in place of surgical therapy, warrants further study.

Clearly, the most exciting and promising advance in the treatment of aortic disease will involve the use of percutaneous endovascular techniques to place stents, bypass grafts, and other therapeutic agents. Percutaneous placement of an endovascular stent to treat AAA, as well as thoracic aortic aneurysm, and aortic dissection may become the optimal method of treatment in the future. Furthermore, percutaneous stent or stented graft placement may allow treatment of diffuse atherosclerotic disease of the aorta in patients with atheroembolic disease who would otherwise not tolerate extensive aortic reconstructive surgery. Indications for endovascular stent placement will clearly increase in patients who cannot tolerate aortic surgery but otherwise have an acceptable prognosis. With further improvements in catheter and stent technology and, therefore, fewer initial and long-term complications, endovascular stent therapy will certainly find increasing indications.

Future improvements in imaging techniques, in particular MRA and three-dimensional TEE, will allow for more accurate diagnosis and improved preoperative planning. The ability to provide the most accurate three-dimensional information about aortic intimal flaps, aneurysm anatomy, and atherosclerotic disease will be crucial to future advancements in medical and surgical treatment of these disorders.

Improvements in imaging techniques, in particular MRA and three-dimensional TEE, will allow for more accurate and earlier diagnosis of aortic aneurysms with an associated improvement in the timing of surgical treatment. Further improvements in percutaneous endovascular techniques to place stents and bypass grafts will lead to increasing indications. In addition, therapeutic agents will be developed to effectively retard the growth rate of AAAs.

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NONINVASIVE ASSESSMENT OF VASCULAR DISEASE

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"Indicates text or graphics that appear only in the electronic versions of this text."

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OVERVIEW

This chapter reviews the application of the currently available indirect and direct methods of noninvasive testing that have been shown to be of value in the evaluation of peripheral vascular disease. The diseases considered include those most commonly seen in the practice of the cardiovascular specialist. The reader can determine which testing procedure(s) will best fit the patient population that he or she is addressing. It should also be evident how useful these testing procedures can be for evaluating the results of interventional therapy as well as the natural history of peripheral vascular disease without any form of intervention.

HISTORICAL PERSPECTIVE

Vascular diseases are broadly defined as afflictions of the arterial and venous system, the lymphatics, and the microcirculation. For the purpose of this chapter, those that involve the large- and medium-sized arteries are reviewed. The objective evaluation of peripheral vascular disease is finally reaching a mature stage. Although indirect and direct noninvasive methods were slow to be accepted, they have now become a daily part of our practice. As is noted in this chapter, there is increasing evidence that angiographic methods can be bypassed for diagnostic reasons and before surgical intervention. This is a remarkable change in practice and is one that will continue into the future. It is also evident that the natural history of vascular disease as well as the outcome following any form of intervention can be done by noninvasive means. It is no longer acceptable to document outcome based on physician interpretation alone without confirmatory studies, which are the topic of this chapter.

One of the first methods of objectively assessing arterial perfusion to the limbs was to assess the ankle systolic blood pressure and relate it to the arm systolic blood pressure [ankle/brachial index (ABI)] (1,2). This very simple determination was slow to become accepted until it was realized that it could provide an immediate indication of success or failure of arterial reconstructions. It is now a standard method to document outcome and monitor disease progression.

Before the development of ultrasonic methods, all of the approaches that were used to study the circulation were indirect. By the application of sensors to the limbs, one was able to derive physiologic information about the circulation at that site. Although the physiologic responses could be elicited, it was often difficult to relate those findings to the actual status of the disease. One example of how this information could often be misinterpreted is the instance in which a patient comes in with gangrene of the toes or forefoot but normal levels of calf blood flow. The skeptics failed to realize that blood flow levels at the calf could not be related to those found at the distal foot and toes.

Although the measurement of absolute blood flow levels has not found a very useful place in the clinical evaluation of patients, these studies have provided a valuable insight into the physiology of arterial obstruction. For example, the measurement of calf blood flow has shown how the blood flow patterns in patients with intermittent claudication are involved in the fall in ankle blood pressure and its delayed recovery with cessation of exercise (3). We now better understand the issue of postexercise hyperemia and how it relates to the severity of claudication.

Plethysmography

Plethysmography, which measures a volume change, is probably the oldest method that is used to evaluate circulation to the limbs. It comes in a variety of forms, ranging from those that completely encase the limb to the strain gauges that are applied to specific and limited segments. Historically, these were used to estimate the blood flow to a specific segment of the limb—usually the calf or forefoot (1,2,3 and 4). These measurements served as the basis for our understanding of the pathophysiology of blood flow as it is affected by arterial narrowing and occlusion. With each of these plethysmographic methods, it was possible to measure calf blood flow under a variety of circumstances. In addition, some of these methods served a dual purpose: assessment of flow and measurement of ankle and toe systolic blood

pressures (4,5).

The available plethysmographic systems were either of the volume type, in which the sensing unit would encompass the entire limb, or mercury Silastic strain gauges, which encompassed discrete circumferential segments of the limb, forefoot, or toe. The theory behind the use of such devices was verified by Whitney in 1953 (4). The Silastic strain gauge method is still in use for a variety of applications.

Ultrasound

The introduction of ultrasound undoubtedly had the greatest impact on the field of noninvasive assessment. The first development of major importance was the observation by Satomura (6) that ultrasound could be transmitted through the skin to detect frequency shifts in flowing blood. He showed that moving blood would shift the frequency of the transmitted ultrasound in a manner that could be detected and recorded. This was a remarkable observation that changed the entire picture with regard to the investigation of blood flow. Our group very quickly picked up on this method and developed the first device that could be used to detect arterial and venous blood flow from all levels of the limb (7,8). However, it had several major problems and drawbacks. It was nondirectional, and the observer could not always be sure which vessel was being interrogated by the method. However, one of its major advantages in its simplest format was that it could also be used to measure ankle systolic blood pressure. Even today, this is one of its most common applications.

One of the greatest concerns with the earliest systems was that the observer had to train his or her ear to interpret arterial and venous blood flow patterns. Although the normal and abnormal velocity patterns could be recognized, it was not possible to present the earliest systems in an understandable analog format that could be made from any desired recording site. This greatly hampered the rapid acceptance of the method.

Progress was rapid in this field, going from the simple continuous wave (CW) Doppler to the pulsed system (9), which permitted selective sampling from many depths along the path of the sound beam. In addition, it became possible to develop systems that would permit an accurate determination of the direction of blood flow (10). This innovation was quickly followed by the development of ultrasonic arteriography (11), which, by combining the pulsed Doppler with a position sensing arm, could be used to depict the anatomy of the flowing blood in any accessible arterial segment. This worked, but it was tedious to use and subject to numerous artifacts related to patient motion, depth, and anatomy of the underlying artery. It was quite clear that the best solution would be to combine the value of the ultrasonic B-mode image with a pulsed Doppler integrated into the system. This was accomplished in 1974 (12,13). Once this was done, the progress depended more on technology than anything else, and it was rapid. By the 1980s, the method was being widely applied to study disease in the large- and medium-sized vessels, wherever it was found. This was the most important development in this century, as it relates to the noninvasive study of diseases of the arterial and venous circulation. This fact will become evident as this chapter evolves.

INDIRECT NONINVASIVE TESTING

Beginning in the late 1960s, numerous indirect methods were introduced for the study of arterial and venous function (5,8,14,15,16 and 17). By definition, an indirect method is one that derives its value and information from physiologic sensors placed on a limb. These sensors can be used to obtain information on pressure and flow. From this information, it is possible to document important aspects of vascular function. All of these methods are used to measure systolic limb blood pressure, monitor digit/limb pulse volume changes, and assess (either qualitatively or quantitatively) limb blood flow.

Anatomic Considerations

Most of the observations made with the noninvasive tests to be described are useful for studying diseases of the medium-sized and large arteries and veins. By definition, these are vessels with proper names. Atherosclerosis, which is the most common of the vascular diseases that we deal with, affects vessels of this size. Structurally, the histology in general shows the same elements—an intima, media, and adventitia. Subunits such as the internal and external elastic lamina are not constant findings throughout the vascular system. In addition, the proportions of smooth muscle, elastin, and collagen also vary tremendously by location. It is these constituents that account for the varying viscoelastic properties of these vessels, be they arteries or veins. For most purposes, our studies do not include consideration of the viscoelastic elements of the circulation, but we must be aware of how important they are in the delivery aspects of blood flow to and from the various organs.

The distribution of atherosclerosis is different in diabetic patients. They have a lower incidence of aortoiliac disease but a much higher incidence below the knee as compared to the nondiabetic. The superficial femoral artery is the most common site of involvement in both groups of patients. A very important difference in diabetic patients is the high incidence of medial calcification in the tibial/peroneal arteries. This process bears no relationship to atherosclerosis but makes the measurement of ankle systolic pressures difficult if not impossible. For this reason, toe pressures should be measured in the diabetic patient (18).

One of the most important elements of the circulation that we need to appreciate is the resistance to flow offered by the various organs. The flow patterns observed are clearly dependent and different from one vascular bed to another. For example, there are three organ systems in the body that are normally low-resistance systems; that is, they require maximal blood flow at all times of the day to function properly. These are the liver, brain, and kidney. As is shown later in this chapter, these factors drastically affect the pattern of blood flow in health and in disease.

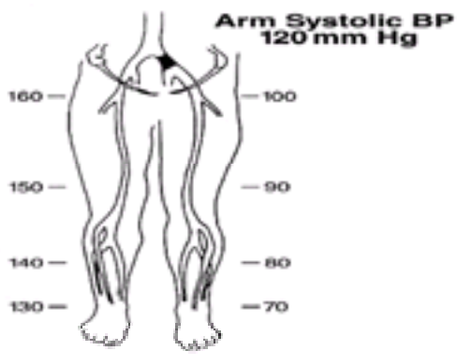
Plethysmography

For the three major types (air, mercury strain gauge, and impedance method), the principles behind each method varied, but the end point was the same (9,19,20,21 and 22). The methods were designed to measure a volume change of the limb at the point where the device was attached. The plethysmographs could be applied to any portion of the limb, including the digits. It should be noted that some plethysmographs can be used to quantitate limb blood flow at specific sites, such as the calf and the digits, but these types of data are of very little use for clinical applications. The information that is most useful is limb blood pressure (systolic), which can be obtained from the digits, ankles, below knee, above knee, and upper thigh level (5). These are often referred to as *segmental limb blood pressures*. It is also possible to use these methods to generate volume pulses from any part of the limb (20). The normal findings in a lower limb are as follows.

Systolic Blood Pressures

Systolic blood pressures are commonly expressed as absolute values or as a ratio to that recorded from the arm, often referred to as the *ABI* or *toe systolic/brachial index* (*TSPI*).

1. *Ankle.* Normally, the systolic pressure at the ankle is higher than that recorded from the arm. This gives an ABI of greater than 1.0. For clinical purposes the value that is normally taken to indicate that peripheral arterial occlusive disease (PAOD) is present is less than 0.90. The variability in the measurement is ±0.15% (23,24).
2. *Toe.* Toe measurements are most commonly taken in diabetics, in whom medial calcification of the tibial and peroneal arteries is common. When this occurs, the ABI is falsely high. The normal TSPI is greater than 0.60. The variability in measurement is ±0.17%.
3. *Segmental pressures.* It is possible to measure pressures at the ankle, calf, above knee, and upper thigh. This is done by cuffs that are placed in these locations with the sensor on the toe. The segmental pressures are used to define the level of occlusive involvement (eFig. 109.0.1). This method has been replaced by ultrasonic duplex scanning in most laboratories (5).



***e*FIGURE 109.0.1** In the presence of a left iliac artery occlusion, the left upper thigh systolic pressure is reduced. Normally, the pressure gradient between any two successive points should not exceed 20 mm Hg. BP, blood pressure.

4. *Absolute pressure levels.* It is important not only to assess the ABI and TSPI, but also to record the actual number, because it may have value from a clinical standpoint. For example, an absolute pressure of greater than 50 mm Hg is found with excellent collateral circulation. The absolute levels can also be useful in predicting when an open lesion might heal.

The ankle or toe pressures should also be measured from the arm using the same method. It is not advisable to use the stethoscopic measured arm pressure for calculation of either the ABI or the TSPI. It is now apparent that this simple measurement can be a good marker for atherosclerosis in other areas, such as the coronary/carotid artery.

Exercise Testing

The pressure recordings can be used to test the effect of exercise. Normally, the ankle systolic pressure does not decrease with moderate treadmill exercise. If occlusive disease and intermittent claudication occur, there is a drop in the ankle systolic pressure and a delayed recovery time (17,25,26 and 27). The time it takes for the ankle systolic pressure to recover is referred to as the *period of postexercise hyperemia*. It is not uncommon in cases of very severe claudication for the recovery to take more than 20 minutes.

Continuous Wave Doppler

With the development of Doppler systems, it became possible to generate information on the arterial and venous flow patterns in health and disease (8,14). The advantage of these simple systems is that they can be used at the bedside to measure ankle systolic blood pressure and assess the arterial flow patterns from the level of the tibial arteries to the external iliac artery in the leg and from the palmar circulation to the subclavian in the arm. The disadvantage of this method is that its use depends on a subjective interpretation of the audible velocity signals. However, the incorporation of this into imaging systems has produced a powerful diagnostic method that is now widely used.

TESTING PROCEDURES: ARTERIAL

Limb Blood Pressures

When a patient is first seen and suspected of having PAOD, it is necessary to measure the ABI, which provides confirmation of the presence of disease but also gives a rough index of its severity. Although presence or absence of peripheral pulses has been the major physical finding in documenting the presence of occlusive disease, this is not sufficiently sensitive or specific. That is why the simple measurement of ankle pressure and the ABI is so important. The criteria that are commonly used are as follows (28):

1. Abnormal levels are those less than 0.90.
2. An ABI of greater than 0.50 is most commonly seen with single-segment disease.
3. An ABI of less than 0.50 is commonly observed with multisegment disease.
4. For follow-up, a decrease of greater than 0.15 is consistent with disease progression. An ABI increase of greater than 0.15 is indicative of improvement in the collateral circulation.
5. If the ankle arteries are incompressible or the patient is a diabetic, the TSPI should be measured. As noted previously, this is normally greater than 0.60 (23).
6. In patients in whom it is not clear if the exercise-induced pain is due to arterial disease or some neurospinal cause, it is necessary to perform an exercise test (29). If an exercise test is performed, a normal ankle blood response is a drop of less than 20% from baseline, with recovery in less than 3 minutes. The treadmill walking time used is 2.0 mph on a 12% grade. For patients with suspected arterial disease, the maximal walking time used is 5 minutes, because this is sufficient to bring out any of the hemodynamic abnormalities. Most patients cannot walk this long even at this low workload. It is common practice to calculate the ABI after exercise, but this should not be done. The reason for this is that arm systolic pressure normally increases after exercise in proportion to the workload (17,25,26 and 27). Thus, it is only necessary to express the postexercise values in absolute units.

The most common error made by vascular laboratories is to calculate the ABI after exercise is completed. As has been noted, normally exercise induces an increase in arm systolic pressure, which, if used for the calculations, would lower the ABI, making the observer think that the testing is abnormal. After exercise, it is only necessary to measure the absolute levels of ankle systolic blood pressure.

Velocity Waveform Analysis

Because ultrasound can reach the major arteries of the upper and lower limbs, it is possible to use the CW Doppler to investigate the patterns at nearly all levels in which occlusive lesions are commonly found. Most use this method at the bedside and audibly interpret the back-scattered Doppler shift signals. It is also possible to obtain analog recordings that can provide hard copy verification. The most reliable method of analyzing the velocity patterns is by fast Fourier transform analysis. This method accurately presents the velocity information and the intensity of the back-scattered ultrasound. It is now the standard method used with Doppler ultrasound. The velocity patterns commonly observed follow.

Lower Limb

The normal velocity patterns exhibit a triphasic flow pattern from the level of the abdominal aorta to the tibial arteries at the ankle (Fig. 109.1). The three components are forward, reverse, and forward flow. If arterial occlusion is present, there will be no detectable signals from the site of involvement. Distal to the occlusion is damping of the arterial velocity patterns, with recordings showing a monophasic pattern (*e*Fig. 109.1.1). This is easily recognized by its audible characteristics.

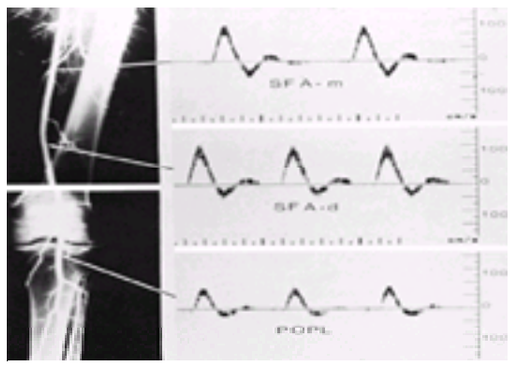
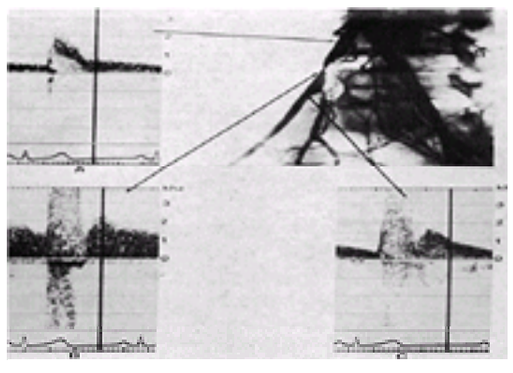


FIGURE 109.1 Hemodynamics of the normal arterial system. The normal arterial velocity patterns from the level of the abdominal aorta to the tibial arteries at the ankle are similar to those shown here. Flow is forward-reverse-forward, with a clear window beneath the systolic peak. POPL, popliteal artery; SFA-d, distal superficial femoral artery; SFA-m, medial superficial femoral artery. (From Strandness DE Jr. *Duplex scanning in vascular disorders*, 2nd ed. New York: Raven Press, 1993, with permission.)



***e*FIGURE 109.1.1** At the site of the iliac artery stenosis is a marked increase in the velocity. As one moves away from the stenosis, the peak systolic velocity decreases, and the waveform becomes monophasic. **A:** Common iliac artery. **B:** Site of stenosis. **C:** External iliac artery. (From Strandness DE Jr. *Duplex scanning in vascular disorders*, 2nd ed. New York: Raven Press, 1993, with permission.)

Upper Limb

The only differences seen in the upper limb in normal subjects relate to the reverse flow component that is observed in the radial and ulnar arteries. Up to 50% of normal subjects do not have a reverse flow component at this level. The end diastolic velocity is above zero, and the waveform itself is biphasic. This is due to the fact that resistance to flow is lower than in those with the triphasic waveform. With arterial occlusion are monophasic flow patterns, as observed in the lower limb.

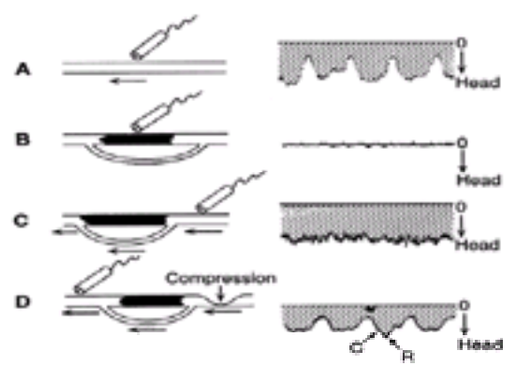
TESTING PROCEDURES: VENOUS

Acute Deep Vein Thrombosis

One of the most common vascular disorders is acute deep vein thrombosis (DVT). It affects all patient populations and is particularly common in the elderly and seriously ill patient. The major problem with DVT is the difficulty in making the diagnosis by the history and physical examination. It has been demonstrated that the bedside diagnosis is so poor that it must be established by objective means (30,31). It was to this end that indirect methods were developed to improve our recognition of this problem. The earliest methods used CW Doppler and impedance plethysmography. Their applications are as follows.

Continuous Wave Doppler

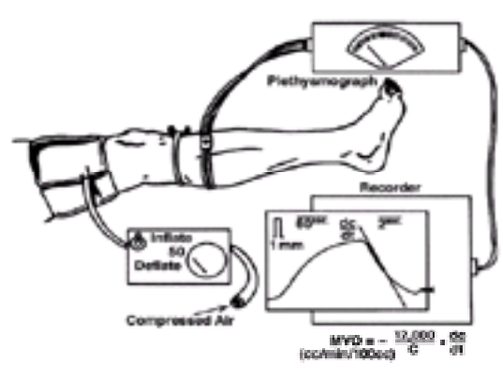
To test for acute DVT, the major deep veins (external iliac, common femoral, superficial femoral, popliteal, posterior tibial veins) are located by first identifying their companion artery. Velocity patterns in the major deep veins of the leg are phasic with respiration (30). Normally with inspiration, there is a decrease in venous flow that increases with expiration. The finding of a normal phasic flow pattern makes it very unlikely that there is an acute thrombus distal to the recording site. Of course, absence of a venous flow signal is a good sign that the vein at the site of interrogation is occluded. When listening distal to an acute occlusion, it is very common to hear continuous venous flow that no longer has a phasic flow component (32,33) (*e*Fig. 109.1.2). Its use is hampered by the subjective nature of the examination. For the experienced user, it has proved to be useful for detection of DVT of the roximal veins (popliteal to inferior vena cava). However, for calf vein thrombi, CW Doppler has a very high false-positive rate, making it unreliable in this area.



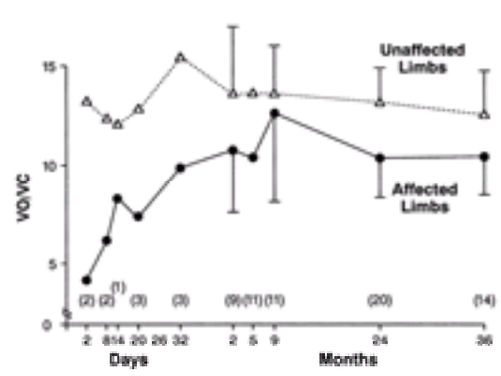
***e*FIGURE 109.1.2** Velocity patterns recorded from the normal deep veins and those affected by venous thrombosis. With the transducer over a normal vein **(A)**, flow is influenced by respiration. It decreases with inspiration and increases during expiration. With complete occlusion **(B)**, no flow is detected. With acute thrombosis and the probe placed proximal to the occlusion, flow is continuous **(C)**. With the velocity detector distal to the thrombus **(D)**, compression (C) augments flow, and release (R) results in a sudden decrease in venous flow. (From Sumner DS. Diagnosis of deep venous thrombosis. In: Rutherford RB, ed. *Vascular surgery*, 4th ed. Philadelphia: WB Saunders, 1995, with permission.)

Impedance Plethysmography

Impedance plethysmography, which has been widely tested and used as a screening test, depends on an assessment of venous outflow from the limb. This requires placing the sensor on the calf with a pneumatic cuff on the thigh (*e*Fig. 109.1.3). When the cuff is inflated to 50 mm Hg, venous volume increases. When the cuff is rapidly deflated, the rate of venous outflow can be recorded. In cases of proximal DVT, the rate of emptying is delayed (*e*Fig. 109.1.4). This method has been widely tested against venography, and it has been shown to be a useful screening test for acute DVT. The method is insensitive to venous thrombi in the calf region. In spite of its lack of sensitivity for calf vein thrombi, it has been shown that a negative impedance test is sufficient to withhold therapy.



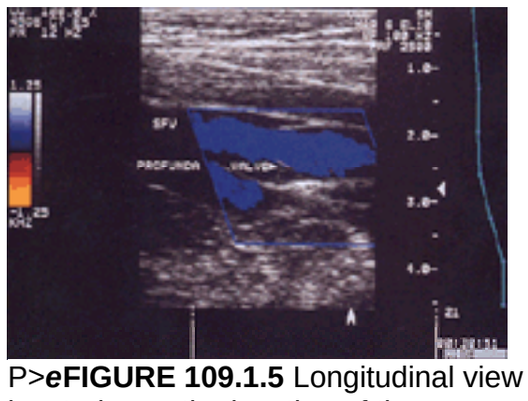
***e*FIGURE 109.1.3** Illustration of the use of a plethysmographic method to estimate the rate of venous outflow. With the thigh cuff inflated to 50 mm Hg, venous volume in the calf increases. Once it reaches a plateau, the cuff is suddenly deflated. The rate of venous outflow can be used to calculate the maximum venous outflow (MVO). In the presence of acute deep vein thrombosis, this decreases.



***e*FIGURE 109.1.4** To standardize the venous outflow data, it is useful to express the venous outflow (VO; cc per minute per 100 cc tissue) to the venous volume (VC; capacitance) at the time of cuff deflation. This is very low in patients with acute deep vein thrombosis. As thrombolysis proceeds and venous collaterals open, this tends to normalize. The numbers in parentheses reflect the numbers of patients studied at these time intervals.

Although these tests have been largely replaced by duplex scanning, they are still used in some centers and can be very helpful for the screening of patients with suspected DVT if used by personnel who understand their shortcomings.

Screening for DVT is now one of the most common examinations requested of a vascular laboratory. As the technology and study techniques have evolved, all deep veins of the lower leg can now be interrogated, including the soleal sinuses and the gastrocnemial veins. These developments provide a simple and direct way of ruling DVT in or out. The other value of this method is that it can be used to follow the progress of established DVT to monitor the rate of lysis, recanalization, and the presence of a recurrence when it occurs. In *e*Figure 109.1.5, a color Doppler longitudinal view of the junction of the common femoral/profunda femoris artery is seen. A venous valve is also visible.



P>***e*FIGURE 109.1.5** Longitudinal view of the common femoral/profunda femoris artery is shown by color Doppler. The veins are identified in blue. A valve is also seen, located near the junction of the common femoral/profunda femoris junction. SFV, superficial femoral vein.

DIRECT NONINVASIVE TESTING

Ultrasonic Duplex Scanning

The major advance in vascular testing was the development of ultrasonic duplex scanning (12,13,34,35). The method takes advantage of two ultrasonic methods, B-mode imaging and pulsed Doppler, by combining them into a single system. The major advantage of the method is that the imaging permits selective and accurate placement of the sample volume of the pulsed Doppler to sites of interest. The Doppler components of the system can now be expressed by color Doppler, power Doppler real-time fast Fourier transform spectral analysis that is used to document the velocity patterns at specific sites (36,37,38,39 and 40).

Magnetic Resonance Arteriography

Until the development of magnetic resonance arteriography (MRA), the only imaging method in common use was contrast arteriography. Because it is invasive, costly, and potentially dangerous, it is only natural that a method such as MRA would be developed. The technique that has the potential for use at all vascular beds is done with whole body imagers. Special coil designs and signal sequencing are needed and are still under evolution, but it is clear that the method will find increasing application as a potential replacement for contrast arteriography. It is possible to predict that, for certain applications, it will completely replace standard contrast studies.

Carotid Artery Screening

One of the more common problems that needs evaluation is extracranial atherosclerosis. Although there are exceptions, its most common site of involvement is the carotid bifurcation. At this site, the plaque takes its origin in the posterolateral aspect of the bulb. As it evolves, it gradually enlarges to encompass the entire bulb and undergoes degeneration to become the complicated plaque. In this form, the lesion increasingly narrows the artery, and there is frequent loss of surface covering (ulceration). At these sites, the plaque can rupture to release emboli or provide the nidus for thrombosis of the internal carotid artery to occur. Both of these events are common causes of transient ischemic attacks (TIAs) and strokes (41,42,43 and 44).

Several aspects of carotid bifurcation disease are of great interest to all cardiovascular specialists.

1. It is a common cause of stroke.
2. The results of four large, randomized clinical trials have demonstrated that carotid endarterectomy is superior to conventional medical therapy in the prevention of stroke (45,46,47,48 and 49).
3. Evidence has been found that the stroke rate following arteriography is comparable to that secondary to carotid endarterectomy.
4. The incidence of carotid disease is high in patients with coronary artery disease and peripheral artery disease.
5. Ultrasonic duplex scanning is the preferred method of screening.

RESULTS OF CLINICAL TRIALS

During the 1980s, there was considerable skepticism about the role of carotid endarterectomy in the prevention of stroke. Many prominent neurologists essentially asked for a moratorium on the operation until its efficacy had been tested by prospective clinical trials (49,50,51,52,53 and 54). As a result of this skepticism, four major trials were undertaken—two in symptomatic patients and two in asymptomatic patients. These trials are now finished; therefore, it is possible to review the results and place their conclusions in proper perspective. The major issue has now been resolved, which is that carotid endarterectomy is superior to conventional medical therapy for certain categories of lesions. However, some problems remain that affect our practice in this area. A brief summary of the results details the issues involved.

North American Symptomatic Carotid Endarterectomy Trial

The results of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) were first reported in February 1991, when a stopping rule had been reached. It was clear that carotid endarterectomy was superior to medical therapy for the prevention of stroke. At 2 years, the cumulative stroke rate in the surgical group was 9%, as compared to 26% in the medical group. This was for patients with a greater than 70% diameter reducing stenosis of the internal carotid artery. Because the role of endarterectomy was uncertain for lesser degrees of stenosis, the trial was continued, and its final results were reported in 1998. The results have been modified based on longer follow-up and showed that even the 50% diameter reducing lesions had a better result with operation than conventional medical therapy (55).

European Carotid Surgery Trial

The European Carotid Surgery Trial (ECST) also included symptomatic patients, and they reported their results at nearly the same time as did NASCET. At 2 years, the stroke rate in the surgical arm of the trial was 10.3%, as compared to 16.9% in the medical arm of the study. This, as in NASCET, only applied to patients with a greater than 70% diameter reduction. This trial continued, as did NASCET, until all ranges of stenosis severity could be examined. The final report in 1999 showed that, much like NASCET, the degree of stroke risk and also the benefit from carotid endarterectomy were based on the degree of stenosis, with the very tight lesions (between 80% and 99%) benefiting most (56).

Critical Differences between These Trials

Several facts are not appreciated and must be taken into account when the results of these two trials are compared and one attempts to place them in context for

clinical practice. These factors are as follows:

1. In NASCET, randomization took place regardless of the viewpoint of the participating surgeon and neurologist (45). In the ECST study, patients were not randomized if, in the opinion of the surgeon and neurologist, the patient was best treated by operation (45).
2. The method of measuring the degree of stenosis in the two trials was entirely different (45,46). In NASCET, the distal internal carotid artery was used as the reference normal artery; in ECST, all measurements were made from the bulb itself.

A 50% diameter reduction in ECST would be a 0% stenosis in NASCET!

It has been estimated that more than 40% of the patients with a greater than 70% stenosis in ECST would be less than 70% in NASCET. What, then, should be the cutoff point for operation in this important group given the fact that both studies advocated operation for the greater than 70% lesion? This becomes even more important when the results of the asymptomatic trials are reviewed.

1. The Veterans Asymptomatic Trial (VAT) (47). This study concluded that for patients with a 50% diameter reducing lesion, the combined events (stroke, TIAs, and death) were reduced by the application of carotid endarterectomy. For stroke alone, the *p* value was .06. This trial was criticized for considering TIAs as events. They used the distal internal carotid artery as the normal reference artery when the arteriograms were read.
2. The National Institutes of Health–supported Asymptomatic Carotid Artery Surgery Trial (ACAS) (48). This trial supported the use of endarterectomy for asymptomatic patients with a greater than 60% diameter reducing stenosis. The stroke rate in the surgical arm of the trial was 2.7%. An important finding was that the risk of stroke with arteriography was 1.2%, which was only slightly less than that occurring from operation. The relative risk reduction for stroke was 55%. The morbidity from arteriography is an extremely important consideration, because it appears to carry nearly the same risk of stroke as operation. This fact cannot be dismissed lightly, even though there are studies that have shown lower complication rates. The centers that were chosen to participate in the ACAS trial were clearly good institutions with respectable records in all aspects of the trial performance. This fact should give us the impetus to consider more seriously the role of ultrasound alone or in combination with MRA before carotid endarterectomy. If this is done, the overall cost to the health system along with a reduction in morbid events could be expected.

Important differences in trial conduct and outcome need to be emphasized.

1. In the VAT trial, oculopneumoplethysmography was also performed as a part of the screening process.
2. Because of the limited numbers of patients in VAT, stratification by degree of narrowing was not possible. In NASCET, the risk of stroke went up with increasing degrees of narrowing. For example, a 90% to 99% stenosis placed the patient at greater risk than a 70% to 79% narrowing (45).
3. In ACAS, no arteriograms were performed in the medical arm of the trial. Thus, it was not possible to stratify risk of stroke by the degree of narrowing (49).
4. The cutoff point of 60% diameter reducing stenosis in ACAS was not arrived at when a compilation of events occurred. This was a predetermined cutoff point established at the outset of the trial. This degree of diameter reduction was that needed for the oculopneumoplethysmography to become positive (48).

Impact of Clinical Trials on Clinical Approach

Although the trials all suggest that endarterectomy is of benefit in the prevention of stroke, they have also created a great deal of confusion. The following questions have arisen.

1. Who should be screened? Some answers are known: (a) All patients who have symptoms that suggest carotid artery disease, (b) patients with bruits (57), and (c) individuals who are in a high-risk category for stroke should be screened. These include patients who are undergoing coronary artery bypass grafting, those with peripheral vascular disease, type 2 diabetics with a history of cardiovascular disease, and patients with renovascular hypertension (58,59). However, many questions also remain.

Considerable disagreement is found as to who should be screened. A consortium of Canadian neurologists addressed this issue and concluded that there was very little level 1 evidence to suggest screening even for patients who are normally considered to be at risk (60). This runs contrary to most specialists who deal with atherosclerotic disease in many different arterial circulations. It is clear that the presence of disease in one of the major vascular beds (coronary, peripheral, and carotid) is very likely to be associated with disease that is potentially serious in other areas. However, there is unlikely to be good evidence to suggest that screening of the general population is of value.

2. What screening procedure should be used? The NASCET investigators have suggested that ultrasound is not reliable enough to warrant its use. They maintain that contrast arteriography remains the best available method. Unfortunately, the ultrasound data from the NASCET study were seriously flawed, because there was no attempt at quality control (61).

3. When should arteriography be done? This is important because cerebral arteriography is not only costly but dangerous as well. In recent years, there has been a shift away from its routine use even in symptomatic patients, with more reliance on duplex ultrasound. In addition, there is growing evidence that carotid endarterectomy can be safely done on the basis of ultrasound alone when it is properly performed and interpreted (62,63,64 and 65).

4. Which cases demand that an arteriogram be done? This occurs in approximately 10% of cases (62): (a) unusual anatomy (coils and kinks) in which interpretation of the ultrasound studies is difficult, (b) cases in which the disease is not confined to the bulb, and (c) instances in which so much calcium is in the bulb that it is difficult to estimate the degree of stenosis.

5. What type of arteriogram should be done, and how should it be read? Selective arteriography is the most commonly done, but it provides only limited views of the bulb. Which artery should be taken as the normal reference artery? At present, most still use the distal internal carotid artery, but one must recognize that it greatly underestimates the degree of involvement. The European group has suggested that the common carotid artery now be used as the normal reference artery, but this has been rejected by the NASCET group (66,67).

6. How can one use the conflicting data on degree of diameter reduction from the clinical trials? For example, how can a 50% or 60% diameter reduction found in the VAT (47) and ACAS (48) trials be reconciled against the higher degree of stenosis found in NASCET (45) and ECST (45)? As noted previously, this is largely related to the methodology used in terms of the ultrasound and the arteriography that was used. A fact of great importance is the intra- and interobserver variability found with all of these studies. It is not possible to define with great precision the exact degree of stenosis by any of the present means at hand. For arteriography, this can be comfortably assumed to be in the ±20% range (68). In the case of ultrasound, it has been long recognized that classification of disease into rather broad categories of clinical relevance made sense. This has proved to be true.

7. What impact is MRA going to have on this field? One must remember that it is also an arteriogram in the sense that interpretation of the presented images is very similar. In addition, the signal dropout problem remains an important issue that cannot be disregarded. This can make the estimate of the true degree of diameter reduction a very difficult problem.

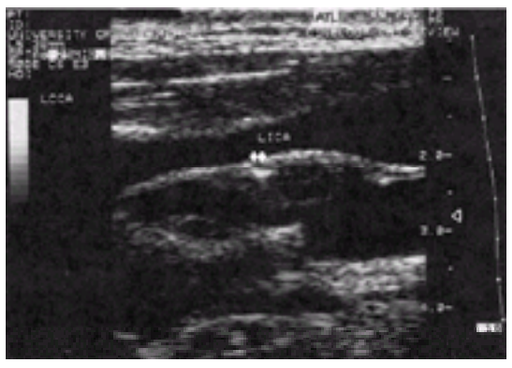
Current Clinical Approach

It is obvious that the cutoff points for each of the clinical trials is very confusing, because they seem to disagree in many respects. For example, why should a 50% or 60% diameter reduction of the carotid artery be of surgical importance in an asymptomatic patient but not apply to a symptomatic patient? This makes no sense, but that is what we are forced to live with, given the results of the randomized trials. Although calipers were used in the trials to estimate the degree of narrowing, this is not a common procedure in clinical practice.

When we introduced the use of duplex ultrasound for the evaluation of carotid artery disease, it was necessary to adapt the velocity criteria for varying degrees of stenosis (35,39,57,65). In addition, it became apparent that the method could not be used to determine precisely the degree of narrowing but could be usefully applied to determine categories of narrowing that might have relevance to clinical practice. We went through several validation trials that compared our results with cut-film selective carotid arteriograms that also included views of the aortic arch, three views of the bulb, the carotid siphon, and intracranial views (39,69,70). The categories finally arrived at (39) have been modified slightly to make them more useful clinically. The current classification scheme is as follows:

1. *Normal.* No evidence has been found on B-mode imaging of a lesion in the posterolateral aspect of the bulb. In addition, boundary layer separation has to be present.
2. *Less than 50% stenosis.* Plaque is present (with or without acoustical shadowing), but the peak systolic velocity does not exceed 125 cm per second at the site of narrowing.
3. *Narrowing of 50% to 79%.* For this category of disease, the peak systolic velocity at the site of greatest narrowing is greater than 125 cm per second, with an end

diastolic velocity of less than 140 cm per second (eFig. 109.1.6).



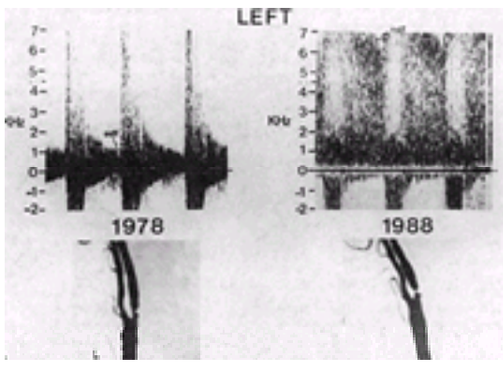
***e*FIGURE 109.1.6** This longitudinal scan of the carotid artery reveals a large heterogeneous plaque (*arrows*) in the bulb. LCCA, left common carotid artery; LICA, left internal carotid artery.

4. *Stenosis of 80% to 99%.* The end diastolic velocity exceeds 140 cm per second.
5. *Occlusion.* No detectable flow in the internal carotid artery.

How did duplex ultrasound using these criteria compare with arteriography? The best way of comparing two diagnostic tests is to calculate the kappa statistic. If there is perfect agreement, the kappa value is 1.0. If there is random distribution of values, the kappa value is 0.0. For one neuroradiologist reading the films a second time, the kappa statistic is 0.711 ± 0.054. For two neuroradiologists reading the same films, the kappa statistic is 0.568 ± 0.058. For duplex scanning and one radiologist, the kappa statistic is 0.769 ± 0.039. For most diagnostic tests used in medicine, kappa values in the range of 0.5 to 0.8 are considered to be satisfactory.

How should the data be used clinically? After several years of experience, we came to the following conclusions based on natural history studies (57,71,72,73 and 74):

1. The less than 50% diameter reducing lesions are generally of little clinical relevance and can be followed by an annual examination to document progression versus stability.
2. The 50% to 79% stenosis in an asymptomatic patient is also a relatively benign lesion, but it warrants closer follow-up. We recommend that these patients have a study performed every 6 months to assess stability of the lesion. If it progresses, the patient should be considered for endarterectomy (eFig. 109.1.7).



***e*FIGURE 109.1.7** The patient shown had his first screening examination in 1978. At that time, his carotid artery was narrowed by 50% to 79%, according to the criteria outlined. He was observed every 6 months until 1988. In the 6 months before this test, his lesion had progressed to an 80% to 99% stenosis. A carotid endarterectomy was performed at that time. (From Strandness DE Jr. *Duplex scanning in vascular disorders*, 2nd ed. New York: Raven Press, 1993, with permission.)

3. The 80% to 99% lesions are particularly dangerous and, in our view, should be considered candidates for operation.
4. The total occlusions cannot be opened surgically. However, even with an asymptomatic occlusion, the annual stroke rate on the side of the occlusion is in the range of 2% per year.

The clinical trials have posed new problems in terms of classification by ultrasound. However, it is possible to estimate the degree of stenosis defined by the trials without a major change in how the study is done. The method simply requires that the user divide the peak systolic velocity at the site of the stenosis by that found in the common carotid artery. Using this method, it has been possible to determine the 60% and 70% cutoff points defined by ACAS and NASCET.

Although one can use different cutoff points for the 60% cutoff, the author favors using a value of 3.2. This gives a positive predictive value of 85%, with a negative predictive value of 93% and overall accuracy of 89% (75).

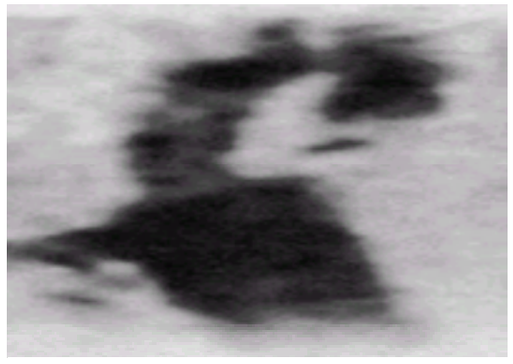
For greater than 70% stenosis, the ratio is 4.0. This provides a positive predictive value of 76%, with a negative predictive value of 96% and overall accuracy of 88% (76).

It is obvious by using receiver operator curves that different ratios can be used depending on one's personal approach to patients who might be candidates for operation. With symptomatic patients, one would not want to miss the appropriate patient. In asymptomatic patients, it is important to limit the number of invasive studies whenever possible or reasonable (75,76).

What about plaque morphology as determined by ultrasound and arteriography (42,77,78,79 and 80)? Can this be used as a surrogate finding to tell the physician which direction to go (eFig. 109.1.8)? Although it is agreed that loss of surface covering (ulceration) is a common cause for the accumulation of thrombotic debris and embolization, none of the current imaging methods is sufficiently sensitive to make them accurate enough to make this determination. Thus, one is forced at the present time to use the degree of narrowing as the sole determinant of when one should proceed with operation. Another common concept is that intraplaque hemorrhage precedes the sudden increase in size of a lesion rendering the patient symptomatic (81,82). This has also been discounted. Our own studies suggest that the most important factor to determine outcome of a stenotic lesion is the fibrous cap (83,84,85,86,87 and 88). If it remains intact, one has little to worry about. On the other hand, if it disrupts, the outcome depends on the material that is forced into the cerebral circulation. This could be thrombus, necrotic debris with cholesterol crystals, or lipid. The challenge over the next decade is to develop methods of studying the fibrous cap *in vivo*.

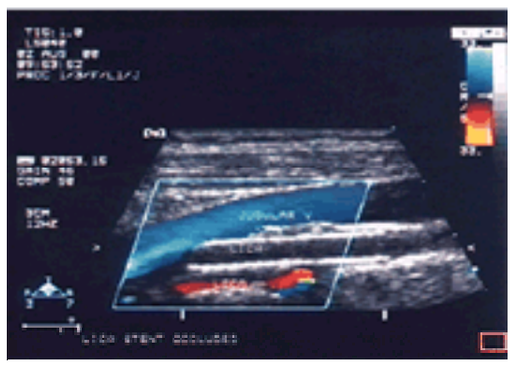
***e*FIGURE 109.1.8** A cross-sectional view of the common carotid artery. On the anterior wall is a large uniform plaque. This is a fibrous lesion that is benign. Contrast the appearance of this lesion with that shown in eFigure 109.1.6.

MRA is the latest method that is available for visualization of the carotid bifurcation. It is attractive because it is totally noninvasive and offers the opportunity of replacing conventional arteriography that will totally eliminate the risk and also lower the cost. The problem, however, is as shown in *e*Figure 109.1.9. As the degree of stenosis increases, there is often signal dropout, making it impossible to estimate the degree of diameter reduction.



***e*FIGURE 109.1.9** This magnetic resonance arteriogram (MRA) of the carotid bulb and internal carotid artery demonstrates the signal dropout commonly seen with MRA studies of stenoses. This makes it difficult to determine the degree of narrowing at that site.

Since the first edition of this book, there have been some dramatic changes in how carotid bifurcation disease might be treated. Interest in the use of stents to treat carotid bifurcation disease has increased. The procedure involves angioplasty that incorporates the stent to hold the artery in its newly distended position. Claims as to safety and efficacy vary widely, with some suggesting that this procedure will be as safe as endarterectomy and others providing a different picture. Another compounding problem is the realization that a retrieval device should be used distal to the carotid bifurcation to collect the debris that might be released when the lesion is dilated. These are all under testing. Most important, a National Institutes of Health–supported trial has been mounted to evaluate this procedure in symptomatic patients [Carotid Revascularization Endarterectomy vs. Stent Trial (CREST)]. The trial is randomized, and it is hoped that it will provide an answer to this problem. In *e*Figure 109.1.10, a color duplex study is shown visualizing the jugular vein, an internal carotid artery with a stent that is occluded (no flow seen within the stent), and a patent external carotid artery.



***e*FIGURE 109.1.10** Longitudinal view of the carotid artery with a stent in place in the internal carotid artery. The color flow shows that the left internal carotid artery (LICA) with the stent in place is occluded. The flow in the left external carotid artery (LECA) and the jugular vein is noted.

UPPER AND LOWER EXTREMITY ARTERIAL DISEASE

Arm

At the outset, it can be stated with certainty that the upper extremity is largely spared the ravages of atherosclerosis, except for the involvement of the subclavian artery at its origin. Even when the subclavian artery is totally occluded, it is unusual for this to lead to any symptoms at all. Surprisingly, arm claudication is rare, probably due to the fact that the vertebral artery, which serves as an excellent collateral source of blood to the arm, is sufficient to maintain the arm pain free even with exercise. If there is an anomalous origin of the vertebral artery from the arch of the aorta, claudication is commonly seen. However, this is rare (89).

What about the role of reverse flow in the vertebral artery and its place in the development of vertebrobasilar insufficiency? Again, although reverse flow is common in the vertebral artery with subclavian artery disease, it is rarely the cause of posterior circulation symptoms.

How does one recognize or suspect the presence of a subclavian artery stenosis or occlusion? Several clues may be found, some of which are as follows:

1. The presence of a supraclavicular bruit.
2. A differential in arm systolic pressure of 15 mm Hg or greater on the side of the disease.
3. A monophasic brachial artery velocity pattern.
4. The demonstration of a stenosis or occlusion by duplex scanning. With this method, it is also possible to document the direction of blood flow in the ipsilateral vertebral artery.

Leg

PAOD is very common in the Western world. The atherosclerosis that is responsible affects specific arteries more frequently than others and is magnified in the presence of diabetes. Although specific problems are associated with this disease, it must be recognized that it can be present without producing any symptoms at all. When it is a clinical problem, it presents in one or two ways, or both. The most common is pain with walking (intermittent claudication) or with critical ischemia (90,91). The latter is simply described as ischemia that is sufficient to warrant an amputation unless more blood can be brought to the limb.

It is important to emphasize the differences in the disease patterns between diabetics and nondiabetics. These are as follows:

1. A peripheral neuropathy is seen in up to 40% of patients with diabetes mellitus who also have PAOD (92).
2. In diabetics, there is a much higher incidence of medial calcification of the tibial and peroneal arteries (23).
3. The presence of medial calcification and the occlusive lesions of atherosclerosis are not related.
4. The occlusive lesions are much more common in the tibial and peroneal arteries of diabetics, with similar extent of involvement of the superficial femoral artery. Interestingly, less occlusive disease is found in the aorto-iliac segments in diabetic patients (92,93).

These factors are important to understand when considering the need for, or the understanding of, the noninvasive tests that are to be performed. It is necessary to realize that the indirect and direct testing procedures are of value here. It should be understood that patients with acute ischemia (due to emboli or thrombosis) demand immediate attention when compared to those with the chronic form of the disease.

Acute Limb Ischemia

When a patient has acute limb ischemia, the physician has to provide immediate action, because delays lead to progressive ischemia and tissue loss. In the past, the

majority of cases of acute ischemia were secondary to emboli from the heart. Although this still occurs, acute thrombosis in the setting of atherosclerosis or from emboli that arise from an ulcerated plaque is much more common. The common complaints in this setting are pain, paresthesias, paralysis plus pallor, and pulselessness. If the acute ischemia is critical, the physician must realize that progressive tissue death will begin within the 4- to 6-hour time frame. It is also important to realize that the muscles begin to die first, with the skin coming later.

The CW Doppler is particularly important in assessing the location of the occlusion and the extent of the available collateral circulation. As noted earlier, the normal ABI is 1.0 or greater. With acute ischemia, the following guidelines are useful:

1. An absolute systolic pressure of 50 mm Hg or greater at the ankle is reassuring evidence that the collateral circulation is adequate for tissue viability.
2. Ankle systolic pressures of less than 50 mm Hg. It is important to realize that the collateral circulation is marginal.
3. The absence of flow signals from the dorsalis pedis, posterior tibial, and peroneal arteries at the ankle is worrisome. This indicates either occlusion of these three arteries or marked compromise of the collateral inflow to the limb.
4. If the ABI of the uninvolved limb is normal, this suggests that the cause of the occlusion in the symptomatic limb may be due to emboli.
5. A survey of the major arteries (common femoral, superficial femoral, popliteal, and tibial) provides information on the most proximal level of involvement.
6. In some cases, it is helpful to carry out an ultrasonic duplex scan to document further the site of occlusion.

One of the major considerations with acute arterial occlusions relates to when and how one should intervene. Should the patient have an arteriogram and when? If the limb is severely ischemic, any delays before flow is restored can have a disastrous outcome. The physical examination of pulse level and a survey with the CW Doppler inform the physician concerning the segment(s) that are most likely occluded. Immediate operation with a confirmatory intraoperative arteriogram is a very satisfactory approach to rapid restoration of blood flow.

Chronic Limb Ischemia

Patients who present with either intermittent claudication or critical ischemia are first evaluated by the standard clinical evaluation and measurement of the ABI. If some form of intervention is going to be required, it has become a standard practice to carry out an ultrasonic duplex scan (94,95,96,97 and 98). With improvement in the technology and availability of a wide variety of transmitting frequencies and scan heads, it is now possible to assess the arterial flow from the level of the abdominal aorta to the tibial arteries at the ankle. From a clinical standpoint, the lesions that are of interest are total occlusions and stenoses that narrow the artery by more than 50% in terms of diameter reduction. The scans are done with the following guidelines in mind (94):

1. Isolated stenoses/short occlusions of the aorta/common iliac arteries are best treated by angioplasty.
2. Long occlusions of the aorto-iliac system are best treated by operative means.
3. Lesions that are distal to the inguinal ligament are best treated by surgical means.
4. Combined disease of the aorto-iliac and femoropopliteal segment can best be treated by angioplasty for the proximal lesions and bypass grafting for the below–inguinal ligament lesions.

The screening procedure used relies primarily on the following parameters for making a determination of the degree of involvement:

1. A triphasic velocity waveform is good evidence of a normal arterial system proximal to the recording site (89).
2. The degree of stenosis is estimated by noting the following changes.
3. For the stenoses that are less than 50% in terms of diameter reduction, the velocity pattern at the site of narrowing shows an increase of 30% to 100% in the peak systolic velocity with preservation of the reverse flow component (94,95,97).
4. For greater than 50% stenosis, the peak systolic velocity increases by more than 100% with loss of the reverse flow component (94,99) (Fig. 109.2).

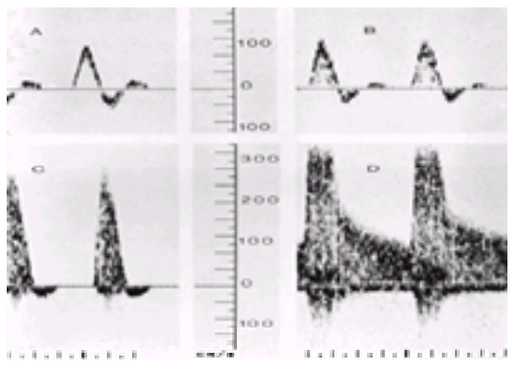


FIGURE 109.2 Velocity patterns recorded from peripheral arteries. In **A**, a normal triphasic waveform is shown. With a 1% to 19% narrowing **(B)**, the only change observed is some slight spectral broadening. When the stenosis is in the 16% to 49% diameter reducing range **(C)**, there is a peak systolic velocity change between 30% and 100% from the immediately adjacent proximal artery. Flow reversal is often preserved, but spectral broadening will be noted. With a greater than 50% stenosis **(D)**, the peak systolic velocity increases by an amount greater than 100% from the adjacent proximal artery. The reverse flow is now gone, and there is marked spectral broadening. (From Strandness DE Jr. *Duplex scanning in vascular disorders*, 2nd ed. New York: Raven Press, 1993, with permission.)

5. With total occlusion, no flow is detected.

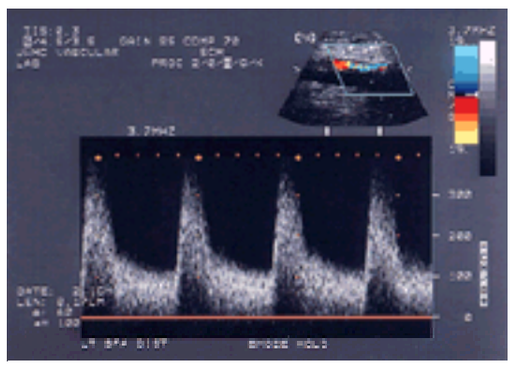
The prospective studies that have been done comparing the results with arteriography have given the results shown in Table 109.1. This scanning procedure has been useful not only in identifying the procedure that is most likely to succeed but in providing the necessary baseline data to assess the long-term outcome. Another major advantage of duplex scanning is that it is possible to carry out saphenous vein mapping. The most satisfactory method of treating lesions distal to the inguinal ligament is to use the saphenous vein. However, it is not possible to assess its suitability in terms of diameter and length without some imaging method. Duplex is ideal because it can provide both bits of information along with marking their course on the skin (100). In instances in which the leg veins may be inadequate, or if they had been previously stripped or used for other bypass procedures, it is also possible to scan the arms for suitable conduits. This procedure also is being used by cardiac surgeons, who may need to know the status of available veins for coronary bypass grafting.

Arterial segment	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Iliac	94	95	94	95
Common femoral	96	100	100	91
Profunda	33	91	40	88
Superficial femoral–proximal	95	100	100	93
Superficial femoral–mid	100	94	82	100
Superficial femoral–distal	91	85	78	94
Popliteal	91	85	78	94
All segments	87	94	88	93

TABLE 109.1 COMPARISON BETWEEN ULTRASONIC DUPLEX SCANNING AND ARTERIOGRAPHY IN DETECTING A LESS THAN OR GREATER THAN 50% DIAMETER REDUCING STENOSIS

Progress in this area is also moving rapidly, with more frequent attempts to bypass preoperative arteriography and proceed directly to the operating room for direct repair with or without concomitant use of an endovascular procedure. This approach has several advantages, which include a marked reduction in cost to the patient and health-care system as well as avoidance of the potential risks. However, this approach requires expert duplex scanning to be done that can accurately document the site(s) of involvement. This approach is clearly feasible in some situations now, and these relate to the presence of single-segment occlusive disease without significant inflow or outflow problems. In *e*Figure 109.2.1, a color Doppler view of the superficial femoral artery is shown that was taken at the site of the

narrowing. The admixture of colors plus the finding of a peak systolic velocity exceeding 300 cm per second indicate that this is a pressure- or flow-reducing lesion.



***e*FIGURE 109.2.1** Color duplex study shows the narrowing in the superficial femoral artery. The admixture of colors distal to the stenosis is consistent with a stenosis. The peak systolic velocity at the site of the stenosis is approximately 300 cm per second, which is also consistent with a hemodynamically significant stenosis.

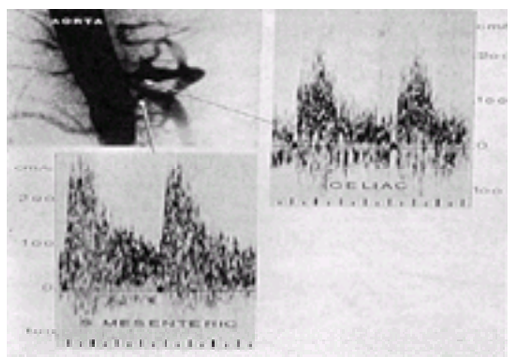
VISCERAL ARTERIAL STUDIES

The two common areas in the abdomen that are frequently the sites of atherosclerotic narrowing and occlusion are the mesenteric arteries and the renal arteries.

Mesenteric Arteries

Involvement of the mesenteric arteries (celiac, superior, and inferior mesenteric arteries) is responsible for two major clinical problems: acute mesenteric ischemia and chronic mesenteric angina (fear of food syndrome) (101,102,103,104,105 and 106). Although involvement of these arteries is common, the clinical syndromes are uncommon due to the excellent collateral circulation that exists between the major inputs to the gut. In fact, it is now well appreciated that one must have involvement of all three major vessels for intestinal angina to occur. Acute mesenteric ischemia is most often secondary to embolic occlusion and results in a dramatic clinical presentation that demands immediate attention. The urgency of this situation does not lend itself to noninvasive studies.

Chronic mesenteric angina is represented by the fear of food syndrome. Patients find that cramping abdominal pain and diarrhea develop when they eat. This results in dramatic weight loss. Although the diagnosis may be quite clear in some instances, in many cases symptoms develop that suggest the diagnosis and some independent method of evaluation is demanded. The only established method of making this diagnosis is to perform lateral aortography with visualization of the origins and the first few centimeters of the celiac and superior mesenteric arteries (eFig. 109.2.2). The advantage of duplex scanning is that the same arteries can be interrogated to assess their status. In the author's experience, if the syndrome is present, there must be very-high-grade stenoses or occlusions of both of these vessels (101,102,103,104,105 and 106). Recently, it has also been possible to assess the inferior mesenteric artery.



***e*FIGURE 109.2.2** Lateral aortogram shows high-grade lesions of the celiac and the superior mesenteric arteries. The corresponding velocity signals show marked increases in the peak systolic velocities with associated spectral broadening.

Renal Arteries

Although patients with renovascular hypertension constitute approximately 5% of the total population with hypertension, detection by noninvasive means has traditionally been difficult (107). In fact, it is agreed that the most certain method of establishing disease of the renal arteries has been arteriography. Most screening tests have not been very useful because of their poor predictive value. With the availability of lower-frequency scan heads (2.0 to 3.5 MHz) and color Doppler, it is not only possible to reach the renal arteries but to assess the presence of disease and its contribution to the parenchyma. The guidelines that have been worked out for detecting and grading the degree of stenosis are as follows:

1. The normal peak systolic velocity in the abdominal aorta at the level of the renal arteries is in the range of 100 cm per second. The variability is rather broad (±20%), making the absolute values less useful for quantitating the degree of stenosis.
2. To avoid unnecessary false-positive tests that might lead to arteriography, we elected to use a peak systolic velocity of 180 cm per second as the cutoff point for detecting narrowing. This value is 2.5 standard deviations above normal. If, at any point along the length of the renal artery, a value greater than 180 cm per second is found, the patient is classified as having renal artery stenosis (108) (Table 109.2).

Duplex	Normal	Disease	Total
Velocity <180 cm/s	9	4	13
Velocity >180 cm/s	1	60	61
Total	10	64	74

[a]Sensitivity: 94%; specificity: 90%; accuracy: 93%.

TABLE 109.2 RESULTS OF USING 180-CM-PER-SECOND PEAK SYSTOLIC VELOCITY FOR THE CUTOFF POINT OF DETECTING A RENAL ARTERY STENOSIS[a]

3. Because the development of hypertension depends on the presence of a high-grade stenosis (greater than 60% diameter reduction), it is important to have criteria for detecting this degree of narrowing. It has been found that if the ratio of the peak systolic velocity at the site of the stenosis divided by that recorded from the aorta at the level of the renal artery (the renal-aortic ratio) exceeds 3.5, the stenosis is classified as being greater than 60% in terms of diameter reduction (Table 109.3, Fig. 109.3).

Duplex	<60% diameter reduction	>60% diameter reduction	Occluded	Total
RAR <3.5	15	3	1	19
RAR >3.5	11	45	0	55
Occluded	0	0	10	10
Total	26	48	11	85

RAR, renal-aortic ratio.
[a]Sensitivity: 92%; specificity: 98%; accuracy: 91%.

TABLE 109.3 COMPARISON OF DUPLEX SCANNING VERSUS ARTERIOGRAPHY FOR DETECTION OF A GREATER THAN 60% DIAMETER REDUCING STENOSIS[a]

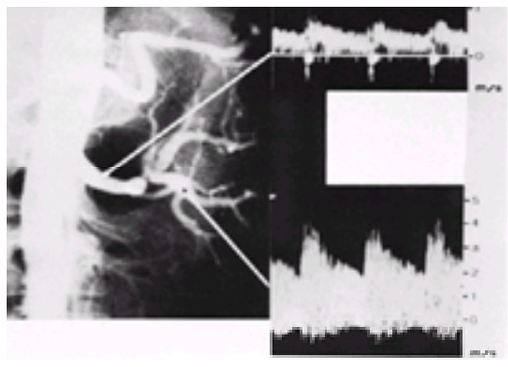


FIGURE 109.3 Velocity patterns recorded at the level of the renal hilus show a dramatic increase in peak systolic velocity (renal-aortic ratio less than 3.5). This is a case of fibromuscular hyperplasia (see text). (From Strandness DE Jr. *Duplex scanning in vascular disorders*, 2nd ed. New York: Raven Press; 1993, with permission.)

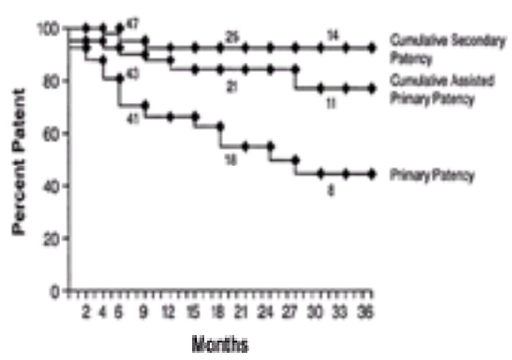
4. The inability to detect flow from the renal artery and finding a kidney less than 9.0 cm in length are taken as evidence of renal artery occlusion.
5. It is also important to measure the end diastolic ratio, which is the peak systolic velocity divided by the end diastolic velocity. The normal value is 0.34. This should be recorded from the distal renal artery and the parenchyma of the kidney itself. It reflects the parenchymal renal resistance and may be useful in predicting the response to revascularization. In patients with fibromuscular dysplasia, the end diastolic ratio is always normal, whereas in patients with renal atherosclerosis, it is often low.
6. For all follow-up studies, it is important to assess renal length. It has been shown that with greater than 60% diameter reducing lesions, there is often a loss of renal mass. This fact may well indicate the need for earlier intervention to preserve renal function (109).

Considerable progress has been made in identifying lesions in the renal artery and in predicting the long-term outcome without intervention. It is clear that the high-grade lesions not only are very prone to progress but are frequently followed by loss of renal mass (110,111). We have also come to realize the effect of parenchymal disease on the entire process and the results of intervention, be it surgical or interventional. Patients with atherosclerotic renal artery disease very commonly have arteriolar nephrosclerosis as a complicating feature. This makes the outcome of any form of intervention unpredictable. In contrast, patients with fibromuscular hyperplasia have an entirely different course. Although high-grade lesions and hypertension develop, parenchymal disease does not occur, and patients usually receive an excellent result from renal angioplasty. In addition, individuals with fibromuscular dysplasia do not progress to renal artery occlusion and do not end up in renal failure.

As with the carotid artery, there is increasing interest in the use of stents in the renal artery as the first form of intervention to be used. Several trials approved by the U.S. Food and Drug Administration are currently under way to document the role of this approach. In these trials, ultrasonic duplex scanning has become an important method of screening before intervention and a method of follow-up. Although there is general agreement that surgical repairs of the renal artery are very effective, the procedure itself carries a significant morbidity and mortality. For this reason, angioplasty and stenting deserve careful examination. If restenosis with persistence of hypertension remains a problem, this area needs to be reexamined.

Vein Graft Surveillance

It has been found that the longevity of saphenous vein grafts that are used to bypass occlusions in the leg can be increased by frequent duplex ultrasound surveillance, particularly during the first year (112,113,114 and 115). It has also been shown that up to 80% of vein grafts develop a lesion within the first 6 months. Not all of these fibromuscular lesions go on to narrow the graft progressively and lead to thrombosis, but by correcting the higher-grade lesions, the assisted secondary patency at 3 years will be in the range of 90% (eFig. 109.3.1). The criteria used to define the degree of stenosis depend on the ratio of the peak systolic velocity just proximal to a lesion divided into that found at the site of the lesion. We have found that a ratio of 3:5 is predictive of a high-grade (greater than 75% diameter reduction) stenosis that should be corrected by either transluminal angioplasty or direct surgical repair.



***e*FIGURE 109.3.1** Life table analysis of primary, cumulative assisted primary, and cumulative secondary patency rates for 61 grafts followed by ultrasonic duplex scanning to detect the development of fibromuscular dysplastic lesions (see text). (From Caps MT, Primozich JP, Bergelin RO, Strandness DE Jr. Vein graft lesions: time of onset and rate of progression. *J Vasc Surg* 1995;22:466–475, with permission.)

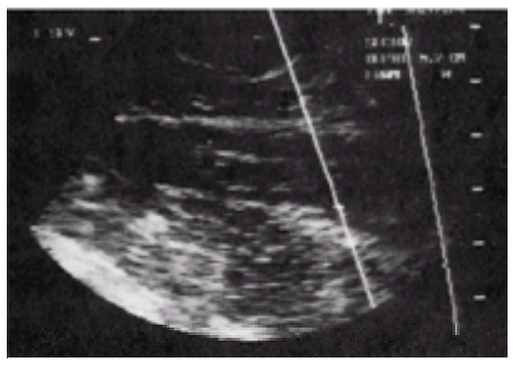
COMMONLY PERFORMED PROCEDURES: VENOUS

Screening for Acute Deep Vein Thrombosis

The introduction of duplex ultrasound with color Doppler has revolutionized our diagnostic approach to this very important area of vascular disease (116,117). This method has, in fact, eliminated the need for contrast venography, which is a real advance in this field. To be successfully applied, the method takes advantage of two modalities, the B-mode image and the flow patterns. The criteria for each segment of the venous circulation are as follows:

1. Thrombus visualization. In 50% of cases of acute DVT, the thrombus itself can be visualized (eFig. 109.3.2). Although it is tempting to try to age the thrombus on the basis of its echogenic characteristics, this must be done with care. It appears that the earlier thrombi are more uniformly echogenic, but this does not indicate the age

of the thrombus or when it may have started.



***e*FIGURE 109.3.2** Longitudinal B-mode image of the superficial femoral vein shows the presence of a large nonocclusive thrombus. (From Strandness DE Jr. *Duplex scanning in vascular disorders*, 2nd ed. New York: Raven Press; 1993, with permission.)

2. Because not all thrombi can be seen on the image, the second maneuver that is carried out is to test the compressibility of the visualized segment. If the two walls of the vein can be completely coapted, it is assumed that no thrombi are present. In some areas, compression is not feasible. These include the superficial femoral vein in the adductor canal and the iliac veins and the inferior vena cava. One must depend on thrombus visualization and the flow patterns to establish the status of these segments.

3. As noted in the section Continuous Wave Doppler, the venous flow patterns are also very useful in establishing the presence of acute DVT (118). These, as noted, are related to the spontaneity of the flow and its relationship to respiration. The one area where flow cannot be used effectively is for the deep veins of the calf. Here, flow under resting conditions is so low that spontaneous venous flow signals may not be seen even in normal subjects. The criteria for occlusion depend on compressibility and the appearance of flow with augmentation that is performed by compressing the limb distal to the site of probe placement.

4. One area of concern at the time of the original appearance of this text was the problems related to studying the veins of the calf. These are small paired veins, and with imaging alone they are often difficult to visualize. However, with the availability of color Doppler, it is now feasible to study this area as well. It is also possible to document the status of the soleal sinuses and the gastrocnemial veins.

With the availability of this testing procedure, physicians are more willing to request the test. In our early experience with this method, the positive yield for the procedure was in the range of 25% (119). The overall accuracy of the method for the detection of acute venous thrombosis is shown in Table 109.4.

	Contrast venography	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Thrombus visualization	n = 38	1938 (5)	1772 (85)	1938 (95)	1128 (57)
Incompressibility	n = 38	3038 (75)	872 (87)	3038 (98)	616 (50)

TABLE 109.4 ACCURACY OF THROMBUS VISUALIZATION AND INCOMPRESSIBILITY IN DETECTING ACUTE DEEP VEIN THROMBOSIS

This is another area that is moving rapidly, in large part due to the availability of low-molecular-weight heparin, which permits some patients with DVT to be treated as outpatients. The sensitivity of the testing has led to the question of how to deal with isolated calf vein thrombosis. Is it necessary to treat and for how long? Opinion is divided on this subject due to the fact that thrombi below the knee rarely lead to serious and fatal pulmonary embolism. What is not known relates to the role of the veins in this location to the development of the postthrombotic syndrome. This question will be answered in the years to come.

Chronic Venous Disease

Patients who require some form of evaluation represent three major categories: those with primary varicose veins, those with secondary varicose veins, and those with the postthrombotic syndrome. Distinct ultrasonic features assist in proper classification of these patients. For each of these categories, it is necessary to establish the integrity of the venous valves at all levels of the limb (superficial and deep) (120). To do this, a variety of maneuvers can be used to establish valve competency. These are as follows:

Venous stasis eczema. Stasis dermatitis as a result of chronic edema and venous incompetence. There is erythema, scaling, pigmentation, crusting, and exudation.

1. Reflux with performance of Valsalva's maneuver. By suddenly increasing intraabdominal pressure, it is possible to detect reversal of flow in veins with incompetent valves. The problem with this maneuver is that one competent valve in the iliac veins may prevent the detection of incompetence in valves in the common femoral and superficial femoral vein. It is only reliable for the common and superficial femoral veins. This method does not permit quantification of the degree of reflux.

2. For the popliteal and distal vein valves, forceful limb compression is used. The principle is the same as for Valsalva's maneuver. The sudden creation of a reverse pressure gradient promotes reflux if the valves are unable to coapt completely.

3. To provide a quantitative method, a cuff method was developed that was performed in the upright position. The procedure is as follows (121,122): (a) Cuffs are placed at the thigh, below the knee, at the ankle, and on the foot, and (b) with the patient upright and the limb to be tested non-weight bearing, the cuffs are rapidly inflated to different pressures. For example, the 24-cm thigh cuff is inflated to 80 mm Hg, the 12-cm calf and ankle cuff to 100 mm Hg, and the 7-cm foot cuff to 120 mm Hg. The key is rapid inflation and deflation. The inflation time is 3 seconds, with deflation taking only 0.3 second.

4. To document reflux, the duplex transducer is placed proximal to the cuff itself. With cuff deflation, there is a reversal of the pressure gradient, with reversal of flow attempting to replace the volume displaced by cuff inflation.

When this procedure was used on 30 normal legs, 95% of the times taken for venous valve closure were less than 0.5 second. The veins tested were the common femoral, superficial femoral, profunda femoris, popliteal, and posterior tibial at the calf and ankle level. This method has the advantage of examining the entire venous system segment by segment from the groin to the ankle. The greater and lesser saphenous veins can also be evaluated

These methods of study are used for the evaluation of the location and extent of valvular incompetence. This is particularly helpful for documenting the changes that occur with acute DVT, the effects of spontaneous thrombolysis, and the long-term sequelae of acute DVT (123,124 and 125).

Given the availability of duplex ultrasound for the sequential study of acute DVT, it became possible to follow patients on a regular basis from the time of the event to document the long-term outcome. One of the first things to be discovered was that spontaneous thrombolysis was much more common than was previously suspected and could have a dramatic effect on long-term outcome. Killewich et al. (123) found that among 21 patients followed sequentially, recanalization developed by 7 days in 44% and in 100% by 90 days. The percentage of initially involved segments that remained occluded decreased to a mean of 44% by 30 days and 14% by 90 days. This finding may well explain what Browse et al. had observed in 1981 (126). They noted that there did not appear to be any relationship between the extent of the original thrombosis and long-term outcome, namely, the development of the postthrombotic syndrome. Spontaneous lysis must play a large role in the long-term outcome.

In addition, repeat duplex ultrasound studies have permitted a look at venous valve function and its relationship to the timing of recanalization and the rate of spontaneous lysis. Markel et al. (127) and Meissner et al. (128) have clearly shown a relationship between the rate of thrombus lysis and retention of venous valve competence. Van Ramshorst et al. (124) noted a similar decrease in thrombus load in the first 6 months after the acute DVT. Recanalization with reestablishment of flow occurred in 87% of the 23 completely occluded segments.

Johnson et al. (125) examined the relationship between the dynamic changes that occur and the long-term outcome in 78 patients (83 legs) followed by sequential studies for a median of 3 years. At the time of the last visit, 49 limbs (59%) were free of symptoms. Interestingly, 12% of the previously occluded limbs had no ultrasound evidence of chronic venous disease—they were entirely normal. The 41% of limbs that had evidence of the postthrombotic syndrome had more than three times the odds of having combined reflux and residual obstruction.

These studies clearly point out the need not only for the initial screening examination, but also for a repeat study at the time of completion of therapy. It is only then that one will be able to predict the long-term outcome and advise the patient as to the lifetime outcome. These studies are also important in those patients who may come back with recurrent symptoms that are suggestive of recurrent venous thrombosis. This occurs in up to 10% of patients who are given conventional anticoagulant therapy.

CONTROVERSIES AND PERSONAL PERSPECTIVES

Is Noninvasive Testing Necessary?

When noninvasive testing for peripheral vascular disease was introduced, there was an enormous amount of resistance to this whole effort. This was largely due to the fact that the medical community had come to depend on a careful history and physical examination followed by angiography to establish the diagnosis. This became the only accepted method for planning therapy, for all vascular beds on the arterial and venous side of the circulation. The ideas and techniques for documenting the role of noninvasive testing gradually took hold and, with the introduction of ultrasonic duplex scanning, the progress and its acceptance became accelerated, and this process is continuing even today. It is my view that now, with the widespread availability of these newer devices along with trained people to use them, they are and will become even more important fixtures in our armamentarium. I do not believe that I could practice high-quality medicine without these devices and techniques.

Noninvasive Testing Alone before Surgical Intervention

We are beginning to see a revolution in the area of noninvasive testing alone before surgical intervention. It is now clear that increasing numbers of centers are starting to perform procedures such as carotid endarterectomy without the benefit of arteriography. Even a few years ago, this would have been considered heresy, and today many critics of this approach are still to be found. Why has the scene begun to change and what might be its impact? Studies have shown that contrast arteriograms are unduly costly and potentially dangerous, a fact that we all knew but were willing to accept because there was little else available (62,63). Now, it is common in centers with good quality control to perform carotid endarterectomy without the benefit of arteriography. This is going to continue into the future and will be extended to other vascular beds as well. Another striking change is the acceptance of duplex imaging alone for patients in clinical trials randomized to the surgical arm of the trial. This represents a major change.

Role of the Technologist

One of the major problems with ultrasound methods is that they are very operator dependent. The outcome of any study is entirely dependent on the skill of the examiner. Traditionally, tests performed by technologists have been finally interpreted by a physician, who either reviews the study directly or reviews hard copy output from key parts of the study. For example, for most radiologic examinations, the technologist performs the x-ray in a standard method and then gives it to the radiologist for review. This is entirely different with vascular ultrasound.

The entire examination is performed by the technologist, who follows certain guidelines, but these must be used and often modified in the context of what is being observed. In addition, the technologist must have a good grasp of regional anatomy and physiology in health and disease. At the end of each examination, the technologist has to formulate an impression based on the findings. Although this information is given to the physician for final review and approval, it is rare for the physician to change the impression of the examining technologist. This level of responsibility has caused considerable concern, particularly on the part of the radiology community members, who feel very uncomfortable from a diagnostic standpoint with the inroads made by these non-MDs. It is this level of responsibility that makes these technologists so important. They recognize their duty and level of responsibility. They generally do it very well and form the backbone of every good vascular diagnostic laboratory.

A very important step in improving quality control in this area was the establishment of the Intersocietal Commission for the Voluntary Accreditation of Vascular Laboratories. This independent reviewing body has representatives of all of the major specialty groups on its board. Certification is a very difficult job, requiring a great deal of work on the part of the laboratory that is requesting certification. Certification is for 3 years only. This program is moving forward very rapidly and will, in my view, create a ripple effect in the medical community concerning standards of performance for diagnostic methods of this type.

Role of Long-Term Studies

In cardiovascular disease, the era of treating and then discharging a patient without objective evaluation of the results must become a thing of the past. Patients who have these chronic illnesses must be under constant surveillance, and repeat studies must be performed whenever necessary to document outcome. Much of the confusion over certain forms of therapy has occurred because of the lack of objective follow-up. It now appears that we have made a major advance in attitude over the methods of follow-up. For example, in the stent trials that are currently under way, (carotid and renal) ultrasonic duplex scanning is accepted as the method. It is clear that one cannot resort to using blood pressure response alone as an index of technical and physiologic success.

The past 20 years have seen the rapid proliferation of diagnostic methods for the evaluation of vascular disease. The field has matured, and the poorer methods have been quickly replaced by more effective techniques such as ultrasonic duplex scanning. In addition, there has been a slow but deliberate movement to get away from the invasive angiographic approaches. This has been most successful in the field of acute DVT, for which venography is only rarely performed today in the United

States. As noted earlier, there are other areas, such as carotid bifurcation, in which contrast studies are being done less and less.

From a diagnostic standpoint, the only new methods that might alter the way we do business in the future revolve around intravascular ultrasound, spiral CT scanning, and magnetic resonance imaging (MRI) and angiography. These are all imaging methods that, at present, provide anatomic information alone. One fact that is not often remembered about such methods is the difficulty in quantitating the images themselves. Each of these methods has an application that can be of assistance for specific applications, some of which are as follows:

1. Intravascular ultrasound. Although currently in limited use, it appears to have found a place for the immediate evaluation of transluminal angioplasty with or without stenting. For example, after an iliac artery percutaneous transluminal angioplasty, visualization by the use of intravascular ultrasound may permit the detection of a dissection that can be corrected by the placement of a stent. Another very controversial area in which this has been recommended is for carotid artery angioplasty and stenting. Here, as in the iliac arteries, the ultrasound could be used to determine to what extent the stent has been properly placed and seated with regard to the walls of the arteries themselves. However, it is not clear even now whether this type of study is essential. It is apparent that endovascular grafting of all types is proceeding without the use of this method.

2. Spiral computed tomography (CT) can produce elegant three-dimensional displays of discrete anatomic areas such as the abdominal aorta. Here, this method was touted as being necessary as the primary diagnostic test to be done before placement of endoluminal aortic stent grafts. It provides information as to the size, location, and extent of the aneurysm itself. It can provide information as to the feasibility of placing a stent graft and its relationship to the renal arteries but as yet has not replaced conventional CT scanning. CT scanning can be used to detect paraprosthetic leaks after endovascular grafting. At the present time this constitutes one of the major problems that can occur with this form of treatment. It does have limitations that must be recognized. It requires between 100 and 200 mL contrast material and provides only limited areas of interrogation. For example, it would not be possible at the moment to extend the studies distal to the inguinal ligament, which is a disadvantage. It is also clear that color duplex imaging may be superior for the detection of endoleaks. This will be determined in the next few years.

3. It is most likely that the future will find ultrasound as the initial diagnostic study, to be followed by MRA-MRI when further diagnostic confirmation is needed. Considerable savings will still result, with absolutely no morbidity or mortality from the diagnostic studies themselves. This will be a major advance for our society.

Potential problems can be seen on the horizon that will limit the development and application of new technology. For example, the cost of new devices such as MRA will greatly limit their implementation. In addition, once they are in place within a hospital, the demand for their services will be such that it will be necessary to limit their use severely. Not enough systems will be available to satisfy the needs of the medical community. As one knows, this is all related to the availability of money and the costs of delivering health care. For example, it is very unlikely that many of the needed postoperative or postangioplasty studies will be paid for in the future. However, one would hope that those institutions that can carry out such studies will provide the necessary information to determine which categories of cases need such follow-up.

From a technological standpoint, what are some areas that badly need better data? One very important area is the morphology of the carotid bifurcation plaque. We have learned that the outcome with regard to such lesions is related to the degree of narrowing: the tighter the lesion, the more likely an adverse outcome. However, even given these facts, it is clear that most patients with similar degrees of narrowing do not have an ischemic event. The difference must lie in the morphology of the lesion. The current evidence, which appears to be consistent, is that the problem most likely lies within the fibrous cap. If it remains intact, there is little risk to the patient, but if fissuring occurs with rupture, an adverse outcome is more likely to occur. At present, there are no good methods of looking at the fibrous cap *in vivo*. Ultrasound can provide some information with regard to plaque morphology, but it is not specific enough to allow a detailed study of the fibrous cap. MRI may have some role here, but the work that needs to be done to prove its value will take a long time. The major problem will not only be a description of the lesion itself but its verification of the findings by *ex vivo* histologic confirmation. By necessity, this will have to be a method that allows three-dimensional reconstruction of the plaque.

THE FUTURE

The future will see a deliberate movement away from invasive angiographic approaches, which will be replaced by more effective methods, such as ultrasonic duplex scanning. Imaging methods such as intravascular ultrasound, spiral CT scanning, MRI, and MRA will evolve to provide more than basic anatomic function. However, cost may be an inhibiting factor in the development of these technologies.

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110

CEREBROVASCULAR DISEASE

CATHY A. SILA
ANTHONY J. FURLAN

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OVERVIEW

The term *stroke* encompasses a heterogeneous group of cerebrovascular disorders, each with its own set of clinical presentations, etiologies, and management strategies. Hypertension is the single most important risk factor for stroke. Cerebral infarction accounts for 80% to 85% of all strokes, intracerebral hemorrhage for 10% to 15%, and subarachnoid hemorrhage for 5% to 6%. Of all cerebral infarctions, 20% to 30% are due to atherothrombosis or thromboembolism from the extracranial or intracranial vessels and can be managed by carotid revascularization or antithrombotic therapy. Lacunar infarcts make up another 20% to 25%, and their treatment focuses on risk-factor management. Cardioembolic sources account for 15% to 20% of cerebral infarctions; nearly half are associated with nonvalvular atrial fibrillation (NVAF), and many warrant anticoagulation. In at least 30% of cases of cerebral infarct, the cause remains unclear. Stroke prevention typically targets high-risk patients with a transient ischemic attack (TIA) or minor stroke and includes antithrombotic therapy with aspirin, clopidogrel bisulfate, ticlopidine hydrochloride, dipyridamole, or warfarin sodium. Intervention in acute ischemic stroke is modeled after therapeutic strategies in acute myocardial infarction (MI); however, the diversity of ischemic stroke mechanisms and the risk for brain hemorrhage have impeded the development of acute therapy protocols.

GLOSSARY

Angiographically occult: Vascular abnormality that is not delineated by cerebral angiography.

Complicated migraine (migraine stroke): A neurologic deficit that replicates the symptoms of prior migraine attacks but that is not transient, with other causes of stroke having been excluded.

Lacunar: Small, 3-mm to 2-cm infarcts of the deep subcortical structures resulting from vascular occlusion of penetrating branches of the larger cerebral arteries.

Penumbra: The border zone of ischemic, but not infarcted, tissue that surrounds the infarcted core of a cerebral infarct.

Stroke: A generic term for a group of cerebrovascular disorders in which part of the brain is transiently or permanently affected by ischemia or hemorrhage, or in which one or more blood vessels of the brain are primarily affected by a pathologic process, or both.

Transient ischemic attack: Sudden, focal, painless neurologic deficit of ischemic cause resolving within 24 hours but typically clearing within 15 minutes.

HISTORICAL PERSPECTIVE

Apoplexy and Other Early Concepts

Hippocrates' aphorism on apoplexy, written in approximately 400 BC, contains what is probably the first written description of stroke (1). The term *apoplexy* is derived from the Greek *apo* (from), *pleso* (thunderstruck), and *ia* (condition).

Willis (2) contributed the word *neurology* to medicine and was one of the first to recognize the clinical importance of the collateral flow afforded by the "circle" anastomosis at the base of the brain.

Wepfer (3), in 1658, was the first to recognize that apoplexy was due to cerebral hemorrhage; however, because his was an autopsy series, he did not recognize the role of cerebral infarction. Although atherosclerosis had been described by the 1500s, it was not linked to apoplexy until the late 1600s and was not recognized as a

cause of “softening of the brain,” or infarction, until Rostan’s work (4) in 1823. The clinical manifestations of TIAs were described by Heberden in 1802 and by Cheyne in 1820 and were related to carotid artery disease by many, including Kussmaul in 1872 and Gowers in 1875 (5). Gowers, in 1875, was the first to describe retinal and cerebral embolism due to mitral stenosis and “old clots . . . contained on the auricular appendices.” Ten years later, Gowers’ textbook (6) described the difference between embolism as “the result of a morbid process elsewhere in the vascular system, commonly in the heart” and thrombosis as “a local disease of the artery by which its caliber is narrowed and its inner surface is changed . . . usually the result of atheroma or of syphilitic disease.” Chiari (7) emphasized the carotid bifurcation as a frequent site of atherosclerosis and a source of cerebral embolic symptoms in 1905, and nine years later Hunt (8) described the syndrome of internal carotid artery occlusion.

Procedural Advances

Carotid arteriography was performed after surgical exposure of the artery by Moniz (9) in 1927 and after direct carotid puncture by Loman and Myerson (10) in 1936. By the late 1960s, direct puncture techniques were replaced by Seldinger’s techniques of femoral, subclavian, or axillary puncture (11). Computerized digital subtraction technology appeared in the 1970s, providing better-quality films with less contrast and lower risk to the patient (12).

In 1951, Fisher (13) emphasized that symptoms of cerebrovascular insufficiency and internal carotid artery thrombosis were much more frequent than previously suspected, correctly predicting that such thrombosis would prove to be a major cause of apoplexy and hoping that “some day vascular surgery will find a way to bypass the occluded portion of the internal carotid artery during the period of ominous fleeting symptoms.”

Therapeutic Trials

Carotid artery surgery had its roots in the 1950s and had to evolve through the initially high postsurgical mortality that was primarily cardiac in cause (14,15,16,17,18 and 19).

Although case series extolled the benefits of anticoagulation for ischemic stroke, subsequent clinical trials reported no reduction in recurrent stroke, a variable benefit in reduction of TIAs, and a significant increase in mortality due to brain hemorrhage (20,21,22,23 and 24). Most physicians were relieved when antiplatelet therapy became available (25,26 and 27), but despite multiple multicenter, randomized, controlled trials conducted since the 1970s, the optimum dosage of aspirin to prevent stroke remains controversial (28,29,30,31,32,33,34,35,36,37,38 and 39). Insights into the variable natural history of stroke as determined by etiology and other risk factors paved the way for clinical trials focusing on more homogeneous subsets of patients, such as those with carotid bifurcation atherosclerosis, intracranial atherosclerosis, or acute middle cerebral artery occlusion.

Neuroimaging

With the development in 1972 of Hounsfield’s concept of computerizing radiographic images, the computerized tomographic (CT) scan evolved. This technique revolutionized clinical-anatomic correlation, added to the understanding of the heterogeneity of cerebrovascular disorders, and advanced a pathophysiologic approach to evaluation and treatment that is far from the naïve concept of the “cerebrovascular accident” (40,41). Magnetic resonance imaging (MRI) provided improved imaging of posterior fossa structures, permitted noninvasive assessment of the cerebral venous system, and introduced angiographic-quality images of the cervical and intracranial arteries. Diffusion-weighted and perfusion images now pursue the elusive ischemic penumbra, or noninfarcted border zone, to improve patient selection for acute stroke therapies.

Evolution to Hyperacute Therapy

Reperfusion strategies for acute ischemic stroke are similar to those developed for acute MI. Implementation of treatments for stroke has been slow due to the painless nature of symptoms, ineffective health care delivery systems, heterogeneity of stroke, and risk of brain hemorrhage.

ANATOMIC CONSIDERATIONS

Heterogeneity of Cerebrovascular Disorders

Cerebrovascular disorders are a heterogeneous group of neurologic symptoms, signs, and mechanisms of injury. The first categorization relates to whether the injury is due to vascular occlusion or rupture and defines the main subsets of stroke: cerebral ischemia and infarction, cerebral hemorrhage, and subarachnoid hemorrhage (42). Cerebral infarction typically presents acutely as a painless, focal neurologic deficit with preserved consciousness. Cerebral hemorrhage also presents as an acute, focal neurologic deficit but subacutely progresses as the hematoma expands and is accompanied by headache and altered consciousness. Subarachnoid hemorrhage also presents acutely; however, as the hemorrhage is predominantly around the brain, headache is the major complaint, and the condition is accompanied by altered consciousness when severe. Subarachnoid hemorrhage is associated with early focal findings only when aneurysmal compression of cranial nerves or concomitant intracerebral hemorrhage is present.

Epidemiology and Risk Factors

Stroke is one of the three leading causes of death in the United States and developed nations. Cerebrovascular mortality rates have been declining since the 1920s. Before the 1950s, the decline in mortality from stroke reflected changes in death certificate coding due to the recognition that most sudden deaths were related to cardiac disease rather than stroke. The rate of decline in cerebrovascular mortality was 1% per year in the 1950s and accelerated to 5% per year in the mid-1970s. The decline in cerebrovascular mortality was greater than that in cardiovascular disease in general and has been linked to declining rates of incidence of infarction and intracerebral hemorrhage, as well as to a decreased case fatality rate (43). The decline in mortality from stroke may have plateaued, however (44). A recent increase in stroke fatality rates may reflect improved case ascertainment and aging of the population. As stroke typically follows cardiovascular events by 5 to 10 years, the stroke rate may increase as survival after cardiovascular events improves.

Stroke risk factors, defined in populations at risk, provide a framework for individual patient management (45,46 and 47) (Table 110.1). Primary prevention in asymptomatic and presymptomatic individuals is the ultimate goal.

Nonmodifiable
Advanced age
Gender
Race
Family history of stroke
Modifiable
Hypertension
Transient ischemic attacks or prior stroke
Cardiac disease
Nonvalvular atrial fibrillation
Acute myocardial infarction
Valvular heart disease
Impaired myocardial function
Asymptomatic carotid artery stenosis
Hyperlipidemia
Diabetes mellitus
Cigarette smoking
Alcohol abuse
Hypercoagulable states

TABLE 110.1 RISK FACTORS FOR STROKE

Hypertension

Hypertension is the single most important risk factor for both ischemic and hemorrhagic stroke. The risk of stroke is directly related to the magnitude of elevation of both the systolic and diastolic blood pressures for both genders and all age groups (48). Stroke risk is at least threefold higher in individuals with definite hypertension (higher than 160/95) and 1.5 times higher in those with borderline hypertension. Isolated systolic hypertension increases stroke risk two to four times, even after one

controls for age and diastolic blood pressure. Improvements in detecting and managing hypertension have been linked to the observed decline in stroke mortality.

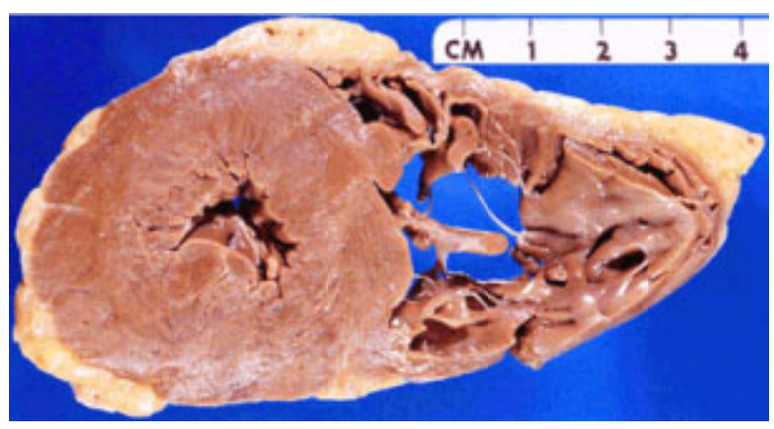
Cardiac Disease

The presence of cardiac disease, including coronary artery disease (CAD), congestive heart failure (CHF), left ventricular hypertrophy, and cardiac arrhythmias, doubles the risk of stroke. This powerful relationship between stroke and cardiac disease is attributable to a number of mechanisms. Atherothrombotic stroke shares the same risk factors as CAD, and MI is the most frequent cause of death in patients with ischemic stroke (49). Cardiogenic embolism accounts for 15% to 20% of all ischemic strokes, of which half are due to atrial fibrillation (AF). The major causes of cardiogenic cerebral embolism are NVAF, acute MI, ventricular aneurysm, rheumatic heart disease, and prosthetic cardiac valves (Table 110.2). Potential cardioembolic sources of stroke include mitral valve prolapse, patent foramen ovale, atrial septal aneurysm, spontaneous echo contrast, left atrial enlargement, aortic arch atheromatous disease, and mitral annular calcification.

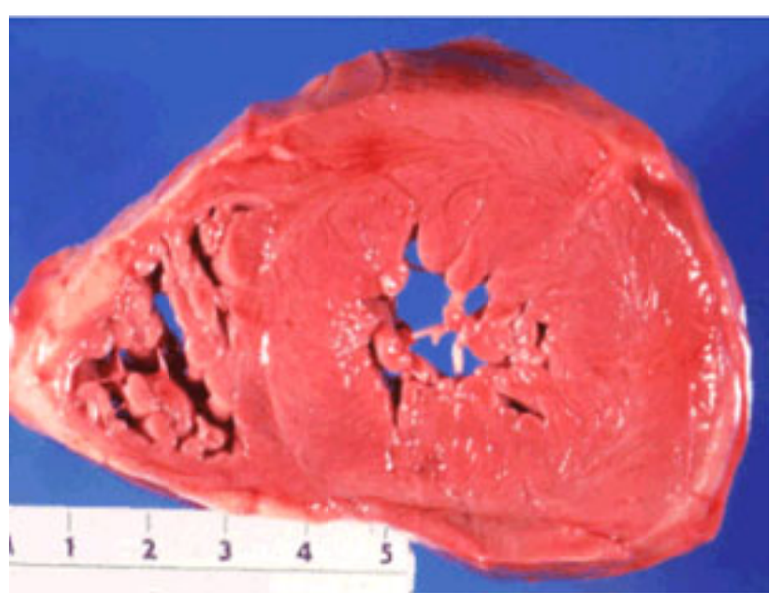
Risk factor	Increase in risk
Cardioembolic stroke	2%–4% recurrent stroke within 30 days
Atrial fibrillation	1%/yr: <65 yr, no risk factors 4.9%/yr: >65 yr, ≥1 risk factors 4.3%/yr: 65–75 yr, no risk factors 5.7%/yr: 65–75 yr, ≥1 risk factors 3.5%/yr: >75 yr, no risk factors 8.1%/yr: >75 yr, ≥1 risk factors
Acute MI	9%–11% all MI, 2%–4% anterior wall MI, 15% LV thrombus, clustered within 3 mo
LV hypertrophy on electrocardiogram	Twofold increase
Dilated cardiomyopathy	1%–3%/yr
Rheumatic mitral stenosis	5%/yr, 18-fold increase with AF, three- to sixfold increase without AF
Bioprosthetic aortic valve	0.2%–2.9%/yr stroke + systemic embolism
Bioprosthetic mitral valve	0.4%–1.9%/yr stroke + systemic embolism
Mechanical aortic valve	12.3%/yr stroke + systemic embolism
Mechanical aortic valve, anticoagulated	1.4%–3.9%/yr stroke + systemic embolism
Mechanical mitral valve	22.2%/yr stroke + systemic embolism
Mechanical mitral valve, anticoagulated	1.1%–6.5%/yr stroke + systemic embolism
Patent foramen ovale	0%–4%/yr
Cardiac morbidity for patients with rheumatic heart disease, stroke, or ischemia	5%/yr absolute

(AF, atrial fibrillation; LV, left ventricular; MI, myocardial infarction.)

TABLE 110.2 CARDIAC RISK FACTORS FOR STROKE AND CORRESPONDING INCREASE IN RISK



Left ventricular hypertrophy secondary to chronic hypertension with secondary ectasia of the right ventricle.



Massive left ventricular hypertrophy as well as concentric hypertrophic cardiomyopathy. (Courtesy of Norman Ratliff, M.D., Cardiac Pathologist at The Cleveland Clinic Foundation.)

Atrial Fibrillation

AF in patients with rheumatic mitral valve disease has long been recognized as a cause of stroke and systemic embolism. Epidemiologic studies identified the importance of chronic NVAF in the absence of rheumatic heart disease when stroke risk was increased fivefold after adjustment for other risk variables (50). The prevalence of NVAF increases with advancing age from 6.7% for those aged 50 to 59 years to 36.2% for those aged 80 to 89 years (51,52). More than one-third of ischemic strokes occurring in the elderly are in the setting of AF, and one-third of patients with AF will experience a stroke sometime during their lifetime. Clinically silent cerebral infarcts are also present on CT in more than one-third of patients with AF (53) (Fig. 110.1). The risk factors for stroke in patients with NVAF established by the Atrial Fibrillation investigators and Stroke Prevention and Atrial Fibrillation classification schemes have been combined into the $CHADS_2$ index to estimate stroke risk (54,55,56 and 57) (Table 110.3). This risk-stratification scheme assigns one point each for *C*ongestive heart failure, *H*ypertension, *A*dvanced age, and *D*iabetes and two points for prior *S*troke or TIA.

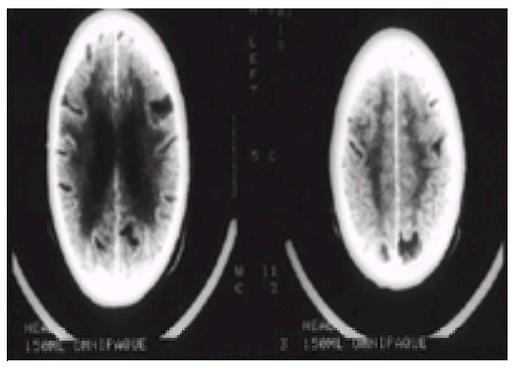


FIGURE 110.1 Small cortical infarcts and periventricular white matter disease in an octogenarian with hypertension and chronic atrial fibrillation.

Independent risk factors
Prior stroke or transient ischemic attack
Age ≥75 yr
Hypertension
Recent congestive heart failure
Diabetes mellitus
Factors posing increased risk
Female gender
Left ventricular dysfunction
Left atrial enlargement
Thrombus or "smoke" in left atrium, left atrial appendage
Mitral annular calcification
Cigarette smoking

TABLE 110.3 RISK FACTORS FOR STROKE WITH ATRIAL FIBRILLATION

Atrial fibrillation. Narrow complex QRS with irregular RR intervals. Ventricular rate is controlled.

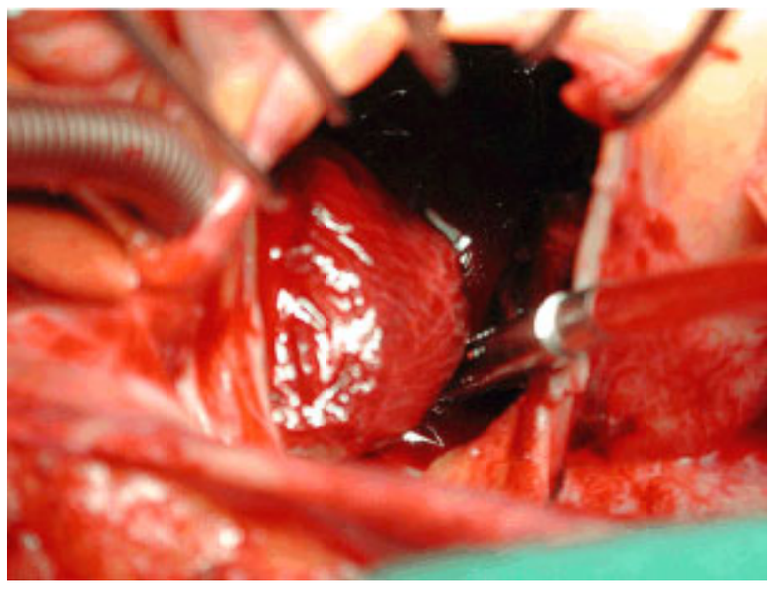
Myocardial Infarction

Before the advent of thrombolytic therapy, stroke complicated 0.8% to 5.5% of acute MIs (58,59 and 60). An embolic mechanism is supported by pathologic studies demonstrating left ventricular mural thrombi in 38% to 67% of cases, typically in the apex in patients with anteroapical infarctions (61,62). Transthoracic echocardiography (TTE) detects mural thrombi or severe wall motion abnormalities, which place patients at increased risk for embolic stroke, although embolization may occur even in the absence of detectable thrombus on echocardiography (63,64). The distribution of cerebral emboli reflects cerebral blood flow patterns, with the majority affecting the anterior circulation, particularly the middle cerebral artery. Although 90% of cerebral embolic events occur within the first 2 weeks after MI, risk for stroke continues for 4 to 6 months, with a minority of patients having a lifelong risk. Risk factors for stroke include older age, history of stroke, paroxysmal AF, anterior or apical location, impaired left ventricular function, and severity of MI as measured by levels of creatine phosphokinase, CHF, or advanced Killip class (65,66,67 and 68).

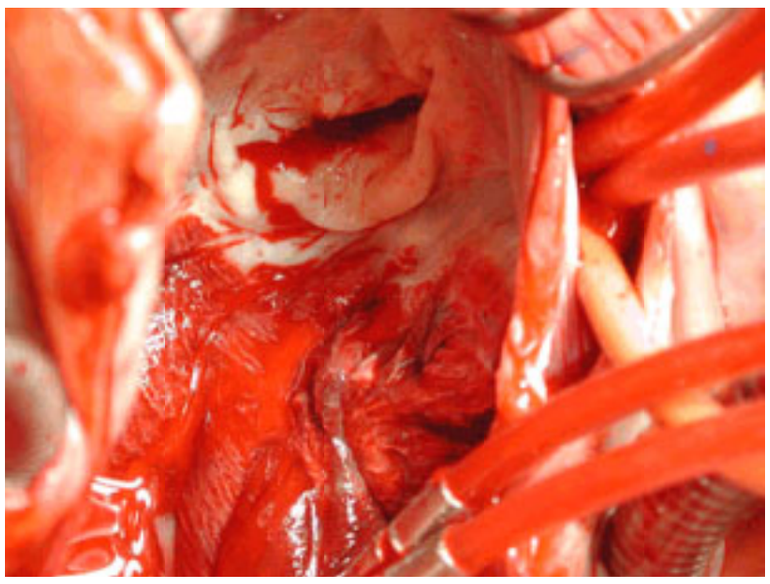
Valvular Heart Disease

Rheumatic mitral stenosis alone increases stroke risk by sixfold, and when it is associated with AF, stroke risk by increases 18-fold. Embolism occurs with all degrees of rheumatic mitral valve disease but is less frequently a complication of pure mitral regurgitation (69).

A 62-year-old female patient with mitral stenosis.



Intraoperative field looking into the left atrium of a patient with severe mitral stenosis who developed extensive clot within the left atrium. Notice the large mass in the center of the field, to the left of the opening within the left atrium. This is the largest portion of the left atrial thrombosis.



Intraoperative field looking into the left atrium after the large left atrial thrombus was resected demonstrating the rheumatic mitral valve at the top of the screen. Note the scarred, thickened, restricted mitral leaflets. This patient had severe mitral stenosis with a mean pressure gradient of 20 mm Hg across the valve and a mitral valve area of 0.7 cm^2.

VIDEO

Video 110.1 Parasternal long-axis view of a rheumatic mitral valve with thickened, restricted, doming leaflets. Severe mitral regurgitation is the primary functional problem with this valve with only mild mitral stenosis. (Reproduced with permission from the Adult Clinical Cardiology Self Assessment Program.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

VIDEO

Video 110.2 Apical four-chamber view of a patient with severe rheumatic mitral stenosis with marked thickening and doming of the mitral leaflets, with severe ALE and spontaneous echo contrast within the left atrium. Note the left ventricle remains small. Because of long-standing severe mitral stenosis, the patient has severe pulmonary hypertension with right ventricular hypertrophy and right ventricular failure and severe right atrial enlargement. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.3 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm^2. Note the loud S_1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border **(A)** and apex **(B)**. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.4 Severe mitral stenosis. Auscultation performed in a 42-year-old female patient with rheumatic mitral valve disease, leading to severe stenosis and mild regurgitation. The peak and mean diastolic gradients across the mitral valve were 14 and 9 mm Hg, respectively. The mitral valve area by pressure half-time was 0.8 cm^2. Note the loud S_1, opening snap, mid-diastolic rumble, and presystolic accentuation. Left upper sternal border **(A)** and apex **(B)**. (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.5 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral ***(fourth clip*).** (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.6 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral ***(fourth clip*).** (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.7 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral ***(fourth clip*).** (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be*

viewed with QuickTime. If you do not have QuickTime you may download it here.

HEART SOUNDS

Audio 110.8 Moderate mitral valve stenosis. Auscultation in a 42-year-old female patient with moderate mitral stenosis with peak and mean gradients of 13 and 6 mm Hg, respectively. Mitral valve area by continuity equation is 1.5 cm^2. Note the opening snap after the second heart sound. The diastolic rumbling murmur is soft and there is slight presystolic accentuation of the first heart sound. Right upper sternal border (*first clip*); left lower sternal border (*second clip*); apex, supine (*third clip*); apex, left lateral ***(fourth clip*).** (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.9 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip)*; left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.10 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip)*; left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.11 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip)*; left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.12 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip)*; left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

HEART SOUNDS

Audio 110.13 Mitral regurgitation. Auscultation in a 78-year-old female patient with severe mitral regurgitation caused by posterior mitral valve prolapse with flail at the medial scallop. Note the holosystolic murmur. The first heart sound is blunted, but remains distinct. Right upper sternal border (*first clip*); left upper sternal border (*second clip)*; left lower sternal border (*third clip*); apex, supine (*fourth clip*); and apex, left lateral (*fifth clip*). (The heart sounds were digitally acquired courtesy of equipment from Welch Allyn/Meditron and Cardionics Inc.) *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

The risk of prosthetic valve thromboembolism is higher for valves in the mitral than in the aortic position, higher for multiple prosthetic valves than for single, and higher for caged ball valves than for tilting disc or bileaflet valves. Additional risk factors for thromboembolism include prior thromboembolism, AF, CAD, an enlarged left atrium, and left atrial thrombus (70).

Impaired Myocardial Function

Clinical evidence of impaired cardiac function, including CAD and CHF, again doubles the risk for stroke. In heterogeneous groups of patients with cerebrovascular disease, 86% have angiographic evidence of CAD, which is severe in 40% as determined by noninvasive studies or cardiac catheterization (71). The neurologic presentation does not predict severity of CAD.

Transient Ischemic Attack

A TIA is a sudden, painless, focal neurologic dysfunction from a vascular cause resolving within 24 hours. This clinical definition predated CT scanning, and the median duration of a TIA is now known to be only 12 minutes. Twenty-five percent of those fulfilling the traditional criteria have evidence of cerebral infarction on CT or MRI (72). From aggregate data, TIA is associated with a 4% to 12% annual risk of stroke and a 10% to 17% annual risk of death, two-thirds of which are vascular deaths (73,74,75 and 76). The highest risk for stroke is in the first year after onset of TIA, especially in the first few months.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported nine risk factors associated with an increased risk of stroke in patients with atherosclerosis-related TIA (77,78). The 2-year risk of stroke ranged from 17% to nearly 40%, depending on the number of risk factors present (Table 110.4).

Stenosis (%)/no. of risk factors	Reduction in relative risk (%)
90–99	75
80–89	63
70–79	63
70–99	65
≥7 risk factors	78
6 risk factors	76
≤5 risk factors	38

NASCET, North American Symptomatic Carotid Endarterectomy Trial.
*Risk factors in NASCET: age >70 years; male gender; systolic blood pressure >160 mm Hg; diastolic blood pressure >90 mm Hg; symptoms within 31 days; history of stroke; stenosis >80%; plaque ulceration; history of smoking, hypertension, myocardial infarction, congestive heart failure, diabetes mellitus, claudication, or hyperlipidemia.

TABLE 110.4 REDUCTION IN RELATIVE RISK FOR IPSILATERAL STROKE AFTER ENDARTERECTOMY IN NASCET[a]

Asymptomatic Carotid Artery Stenosis

The frequency of cervical bruits increases with age and is 7% to 10% in those patients older than 65 years. Cervical bruits correlate poorly with the degree of underlying carotid artery stenosis, however, as only half of arteries with bruits harbor significant internal carotid artery stenosis and only half of the relevant stenoses produce an audible bruit. Carotid bruits and carotid plaque thickness as measured by ultrasonography are markers of systemic atherosclerosis and increased risk of vascular events, although they are not a good predictor of ipsilateral cerebral infarction. Stroke risk increases with the degree of carotid stenosis, from 1.3% per year for stenosis of less than 75% to 3.3% per year for stenosis greater than 75% (79,80). Even in the higher-risk group, however, the rate of ipsilateral cerebral infarction was only 2.5% per year, whereas the combined risk for myocardial ischemia and vascular death was 9.9% per year (81). Hence, asymptomatic carotid artery disease is a better indicator of MI and vascular death than stroke. The most important independent predictors of carotid artery stenosis are duration of cigarette smoking, hypertension, diabetes mellitus, and systolic blood pressure at the time of examination (82).

Lipid Level Abnormalities

Lipids and lipoprotein abnormalities have strong associations with coronary atherosclerosis, but their relationship to stroke is inconsistent and may be due to the heterogeneity of stroke pathogenesis. In individuals with hypertension, ischemic stroke is associated with hypercholesterolemia, but hemorrhagic stroke increases with very low cholesterol levels (83,84,85 and 86). Clinical trials carried out before the introduction of statins did not demonstrate stroke risk reduction with lipid-lowering strategies, and one trial demonstrated a paradoxical increase in hemorrhagic stroke. Trials using statin agents have demonstrated a reduction in stroke risk of from 19% to 31%, but only in high-risk patients with established cardiac disease.

The most convincing evidence that statins reduce stroke risk comes from trials of secondary prevention of heart disease in which stroke was prespecified as an end point. In the Cholesterol Reduction Prevents Ischemic Stroke trial, pravastatin sodium therapy reduced stroke incidence 31% from 3.8% to 2.6% (p = .03) without a strict relationship to cholesterol levels being noted (87). Although the Long-Term Intervention with Pravastatin in Ischemic Disease trial was prematurely terminated when mortality was significantly reduced by 23%, the 23% reduction in stroke was statistically significant (p <.022) (88). The primary prevention trials the West of Scotland Coronary Prevention Study and the Air Force/Texas Coronary Atherosclerosis Prevention Study had too few cerebrovascular end points to demonstrate any efficacy for statins in stroke prevention for middle-aged men or women with average cholesterol levels (89,90).

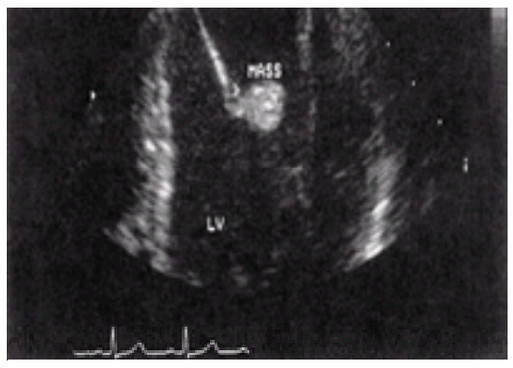
Diabetes Mellitus

Diabetes mellitus correlates strongly with hypertension, but it is an independent risk factor for cerebral infarction, especially in women, who have rates of intermittent claudication and cardiovascular complications similar to those for men. When adjusted for hypertension and diabetes, obesity is no longer an independent risk factor for stroke. The incidence of type 2 diabetes has increased dramatically, and it is a major contributor to small subcortical, or lacunar, strokes. Although aggressive treatment of hypertension among those with type 2 diabetes has been shown to reduce stroke risk, tight diabetic control has not (91). Hyperglycemia at the onset of cerebral infarction is a poor prognostic factor associated with increased infarct size (92).

Hypercoagulable States

A number of hematologic conditions collectively referred to as hypercoagulable states have been linked with an increased risk for stroke. These include elevated hematocrit, fibrinogen levels, and homocysteine levels, as well as activated protein C resistance related to the Leiden mutation and deficiencies in protein C, protein S, antithrombin III, and plasminogen.

The antiphospholipid syndrome is a heterogeneous syndrome of systemic venous and arterial thrombosis, thrombocytopenia, and recurrent fetal loss that is often, but not consistently, associated with lupus erythematosus. Rare cases of chronic, organized atrial thrombus mimicking an atrial myxoma have also been reported (*e*Fig. 110.1.1). Other manifestations include seizures, migraine, chorea, transverse myelitis, multiinfarct dementia, livedo reticularis skin patterns, and rheumatic symptoms (93,94). Laboratory test results employing phospholipid can be abnormal, including tests for anticardiolipin antibodies, antinuclear antibodies, a circulating or lupus anticoagulant, and thrombocytopenia; serologic tests for syphilis (rapid plasma reagin or VDRL) can be false-positive, and the activated partial thromboplastin time can be prolonged. Whether anticardiolipin antibodies, present in up to 8% to 15% of the elderly or in patients with other neurologic disease, interact with other risk factors to increase the risk for stroke is unknown (95).



***e*FIGURE 110.1.1** A left atrial mass mimicking an atrial myxoma in a young girl with antiphospholipid syndrome and an acute cerebral infarct. Pathologic diagnosis at resection was a chronic, organized thrombus. LV, left ventricle.

After four decades, the relationship between oral contraceptive use and stroke remains controversial. Although their use is best linked to subarachnoid hemorrhage in hypertensive women who smoke, the newer low-estrogen preparations have been associated with an increased relative risk of 1.9 for ischemic stroke. Oral contraceptive use probably acts as a risk factor only in concert with other factors, such as paradoxical embolism in women with interatrial septal abnormalities and the Leiden mutation who take oral contraceptives (96). Activated protein C resistance is acquired with oral contraceptive use and is known to increase the risk of deep venous thrombosis by three- to fourfold. Individuals who are heterozygous for the Leiden mutation have a four- to tenfold increased risk of deep venous thrombosis without oral contraceptive use and a 35-fold increased risk with oral contraceptive use. By comparison, homozygotes for the Leiden mutation have a 50- to 100-fold increased risk of deep venous thrombosis.

Genetic Factors

The familial effect of stroke predominantly reflects genetic influences of known risk factors for stroke such as hypertension, diabetes, and hyperlipidemia as well as learned behaviors of cigarette smoking, diet, and physical activity (97). However, more than 50 monogenetic disorders account for uncommon causes of stroke,

including amyloid angiopathy, coagulopathies, homocystinuria, familial cavernous malformations, saccular or berry aneurysms, and intracranial aneurysms associated with polycystic kidney disease, Ehlers-Danlos syndrome type IV, and Marfan syndrome.

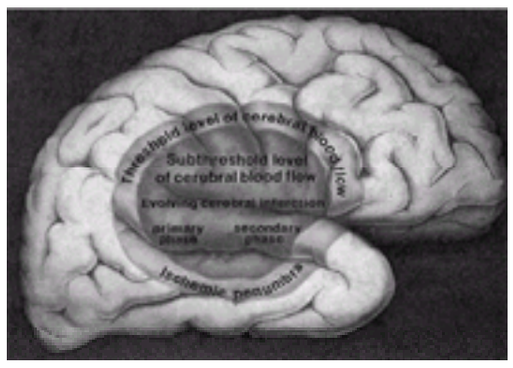
Alcohol and Tobacco Use

Consumption of modest amounts of alcohol (i.e., less than 2 oz daily) seems to reduce the risk for stroke, possibly through antiplatelet or lipid-lowering effects. High intake of alcohol increases the risk for stroke, especially for hemorrhagic stroke (98). However, hypertension, cigarette smoking, paroxysmal AF with alcoholic cardiomyopathy, and trauma are confounding factors that make the role of alcohol as an independent risk factor unclear.

Cigarette smoking increases the relative risk for both thromboembolic stroke and hemorrhagic stroke, specifically stroke from subarachnoid hemorrhage (99,100). A dose-response curve appears to exist, with risk for stroke increasing with the degree and frequency of cigarette smoking (101).

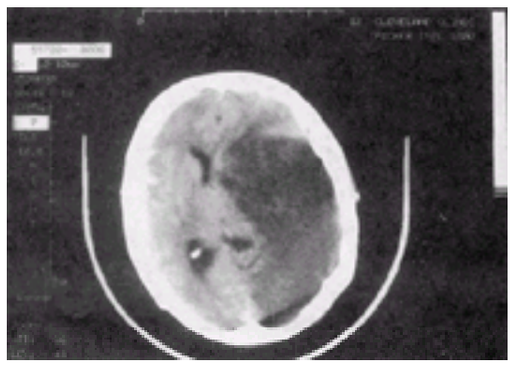
Pathophysiology of Brain Ischemia

Neuronal recovery from ischemia depends on the depth and duration of the ischemic insult, the collateral circulation, and the secondary effects of ischemic cerebral edema and metabolic derangements. In animal models, irreversible infarction occurs within 2 to 6 hours (102). Autoregulation, which maintains cerebral blood flow constant over a range of mean arterial pressures of 50 to 150 mm Hg, is disturbed in acute ischemia, and cerebral blood flow becomes passively dependent on mean arterial pressure. Aggressive management of hypertension in acute stroke, either preexisting or induced by the stroke itself, can cause extension of the infarct by lowering perfusion to the border zone (103,104) (*e*Fig. 110.1.2).



***e*FIGURE 110.1.2** Depiction of the infarcted core and the bordering “penumbra” in a middle cerebral artery distribution infarct.

The ischemic cascade consists of tissue acidosis, dysfunction of excitatory neurotransmitters (glutamate, aspartate), abnormalities of calcium homeostasis, free-radical production, cerebral edema, microcirculatory obstruction, and selective genetic expression (105). Membrane failure leads to cellular swelling from cytotoxic edema and, later, to vasogenic edema from fluid extravasation across a disrupted blood–brain barrier (*e*Fig. 110.1.3). Increased intracranial pressure (ICP) further impedes cerebral blood flow and impairs lactate clearance. Reduced microcirculatory flow results from swelling of cell processes and sludging of white and red blood cells within the arterioles and capillaries. The increase in viscosity further impairs oxygen delivery to the tissues.



***e*FIGURE 110.1.3** Cerebral edema and midline tissue shifts in a middle cerebral arterial distribution infarction.

CEREBRAL ISCHEMIA AND INFARCTION: CLINICAL PROFILE

The signs and symptoms of cerebral ischemia and infarction are related to the location and the volume of brain tissue injured as well as to the mechanism of injury. Symptoms of ischemia in the carotid territory include monocular blindness (amaurosis fugax), contralateral hemiparesis, and aphasia. These symptoms can be further divided into anterior cerebral and anterior/posterior or deep middle-cerebral artery territory symptoms (Table 110.5, Fig. 110.2, Fig. 110.3, and Fig. 110.4). Vertebrobasilar ischemia is characterized by bilateral neurologic symptoms (e.g., quadriplegia) that are frequently accompanied by vertigo, dysarthria, or diplopia (106,107 and 108). Infarction related to arteriolar or penetrator arterial occlusive disease produces several lacunar syndromes (109,110). The most common are pure motor hemiparesis, pure sensory syndrome, and ataxic hemiparesis (Table 110.6, *e*Fig. 110.4.1, *e*Fig. 110.4.2). A stereotyped pattern of symptoms suggests a focal stenosis, whereas variable symptoms referable to multiple vascular territories suggest a proximal source of embolism (e.g., heart) or a multifocal arteriopathy (e.g., vasculitis) (111).

Carotid occlusion	Manifestation
Ophthalmic artery	Amaurosis fugax (i.e., total or partial monocular blindness, usually altitudinal)
Anterior cerebral artery	Contralateral weakness involving leg more than proximal arm
Middle cerebral artery:	
Anterior branches	Contralateral motor and sensory loss, maximal for face, hand, and arm; if dominant hemisphere, nonfluent (Broca) aphasia
Posterior branches	Contralateral hemisensory loss and homonymous hemianopsia; if dominant hemisphere, fluent (Wernicke) aphasia
Deep perforating branches: lenticulostriate, anterior choroidal	Contralateral hemiparesis affecting face, arm, and leg about equally
Vertebrobasilar arterial occlusion	**Manifestation**
Bilateral symptoms	Binocular visual loss, quadriparesis, altered consciousness
Crossed symptoms	Ipsilateral cranial nerve/contralateral limbs
Combined symptoms	Dysarthria, diplopia, nausea, vomiting, vertigo, ataxia

TABLE 110.5 CLINICAL MANIFESTATIONS OF CEREBRAL ARTERIAL OCCLUSIONS

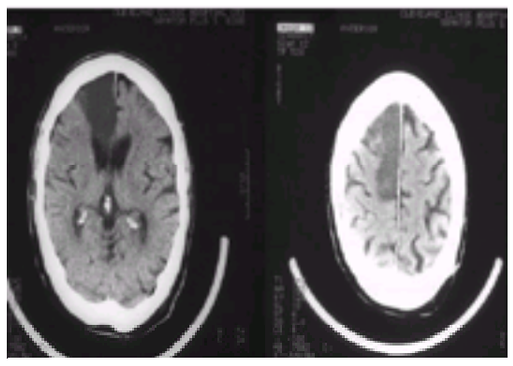


FIGURE 110.2 An anterior cerebral artery territory infarction at 7 days.

FIGURE 110.3 A chronic anterior division middle cerebral arterial infarction with encephalomalacia.

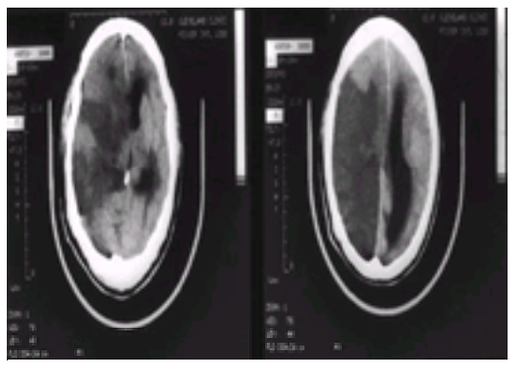
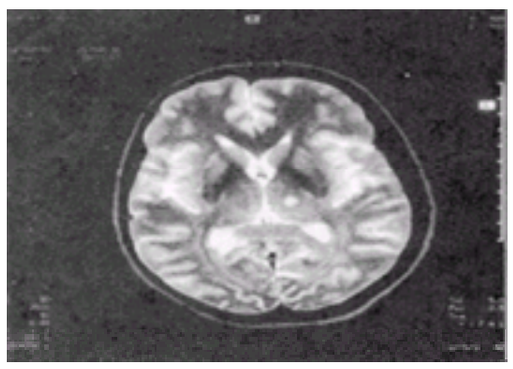


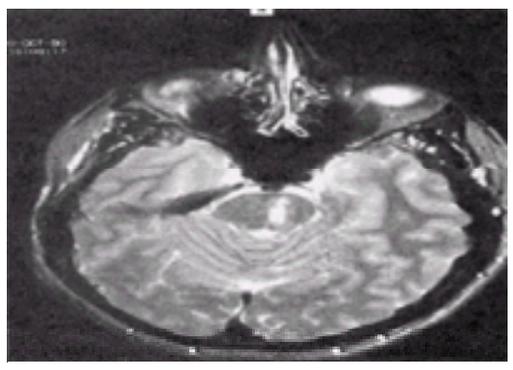
FIGURE 110.4 A carotid artery occlusion resulting in infarction of the middle and posterior cerebral artery territories that has spared the anterior cerebral artery. The midline shifts produced by the ischemic cerebral edema have resulted in hydrocephalus.

Pure motor hemiparesis: internal capsule, pons
Pure motor hemiparesis with crossed III nerve palsy: midbrain
Pure motor hemiparesis with crossed VI nerve palsy: pons
Ataxic hemiparesis: pons
Dysarthria/clumsy hand: pons or capsule
Pure sensory syndrome: ventral thalamus
Lateral medullary syndrome (Wallenberg): medulla
Sensorimotor stroke: thalamus capsule
Thalamic dementia: anterior thalamus

TABLE 110.6 LACUNAR SYNDROMES AND THEIR TYPICAL LOCATIONS

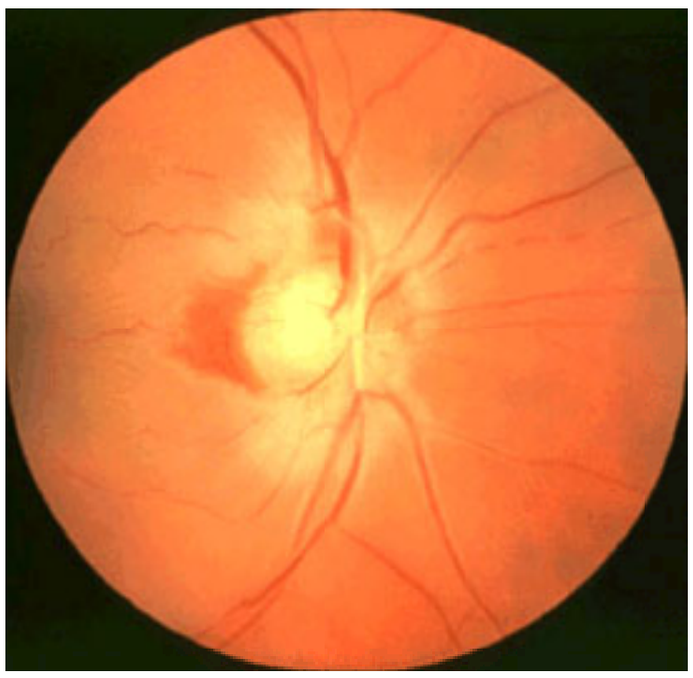


***e*FIGURE 110.4.1** Magnetic resonance image of a left thalamic lacunar infarct producing a contralateral pure sensory stroke.



***e*FIGURE 110.4.2** Magnetic resonance image of a left paramedial pontine lacunar infarct that may produce a contralateral pure motor hemiparesis or an ataxic

hemiparesis.



Central retinal artery occlusion. There are indistinct margins to the optic disc and pallor of the central retinal artery territory.

CEREBRAL ISCHEMIA AND INFARCTION: MANAGEMENT PRINCIPLES

Primary Prevention of Stroke: Strategies for Targeting High-Risk Patients

For most patients, appropriate screening consists of a thorough history and physical examination guided by knowledge of predisposing risk factors. The examination may provide important clues such as the presence of retinal Hollenhorst plaques, cervical bruits, an irregular pulse, or a cardiac murmur.

Patients with Hypertension

The efficacy of hypertension management for stroke prevention has been confirmed by a series of controlled clinical trials performed over the past 30 years. From a metaanalysis of 14 trials, a 35% to 40% reduction in stroke risk was obtained with a 5- to 6-mm Hg reduction in diastolic blood pressure over 5 years (112). Population studies have been less convincing, however, which possibly reflects less strict blood pressure control in a community setting.

The efficacy of blood pressure reduction in preventing stroke was first demonstrated in patients with severe and moderately severe diastolic hypertension (115 to 130 mm Hg) in the 1960s (113). Subsequently, the efficacy of treating mild diastolic hypertension (90 to 109 mm Hg) was demonstrated in both placebo-controlled and treatment-versus-usual-care trials (114,115). The value of treating isolated systolic hypertension (systolic pressure higher than 160 mm Hg and diastolic less than 90 mm Hg) in persons older than 60 years was demonstrated in a randomized, double-blind, placebo-controlled trial (116). Fatal and nonfatal stroke, the primary end point, was reduced by 36%, which is consistent with the 42% reduction in stroke demonstrated by previous hypertension treatment trials. Moreover, because significant numbers of elderly patients were enrolled, this trial was the first to demonstrate a benefit for treating any form of hypertension in patients aged 80 years or older.

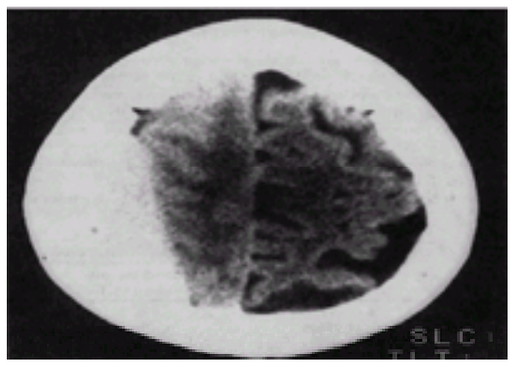
Patients with Nonvalvular Atrial Fibrillation

Oral anticoagulation had long been perceived to be such a hazardous therapy that its use was restricted to high-risk patients until pivotal clinical trials and the development and widespread adoption of the international normalized ratio (INR) method of anticoagulant monitoring established anticoagulation with warfarin as the standard of care for patients with NVAF. In the 1980s, a series of randomized clinical trials (level I evidence) addressed the prevention of cerebral and systemic embolism with long-term anticoagulant or antiplatelet therapy in patients with NVAF (117,118,119,120,121,122,123,124 and 125). A metaanalysis was conducted of data from five trials encompassing 2,461 patients followed up to 27 months. Treatment consisted of placebo, aspirin at dosages of 75 to 325 mg per day, and warfarin with an INR ranging from 1.2 to 4.5. Although the majority were in chronic fibrillation, approximately 15% of patients had paroxysmal AF. The primary end points included thromboembolic events of cerebral infarction and systemic embolism as well as hemorrhagic complications of intracranial hemorrhage (ICH), major hemorrhage (bleeding requiring hospitalization, transfusion, or surgery), and minor bleeding. Exclusion criteria typically entailed a significant bleeding history including ICH, predisposition to trauma, inability for adequate follow-up, uncontrolled hypertension, alcohol abuse, or a requirement for anticoagulant therapy.

Aggregate data from several trials including elderly patients with multiple comorbidities demonstrated a relative risk reduction of thromboembolic stroke with warfarin of 68% (range, 50% to 79%), which increased to 83% when target anticoagulation was achieved. Failure of anticoagulation to prevent stroke was associated with an INR close to 1.0 in 60% of patients. The relative risk reduction seen with aspirin, mostly at a dosage of 325 mg per day, ranges from 20% to 25%. The presence of concomitant CAD or CHF was shown to triple stroke risk, and additional clinical risk factors for stroke included prior TIA or stroke, hypertension, diabetes, and advanced age.

In the Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK) trial, one-third of the patients dropped out because of the inconvenience of monthly monitoring. The Boston Area Anticoagulation Trial for Atrial Fibrillation randomly assigned patients to receive anticoagulation or usual care in an unblinded fashion. The discretionary use of aspirin was carefully monitored, and 8 of 13 end points in the control group occurred in patients taking at least 325 mg of aspirin per day. The Stroke Prevention in Atrial Fibrillation (SPAF I) study consisted of patients (group I) randomly assigned to receive placebo, aspirin 325 mg per day, or warfarin, and patients (group II) who were warfarin ineligible but received aspirin or placebo. The study was prematurely interrupted when active treatment (aspirin or warfarin) was found significantly superior to placebo for group I patients, which left questions about the relative value of aspirin versus warfarin. SPAF II recruited additional patients and demonstrated that, although warfarin was superior to aspirin for the prevention of ischemic stroke at all ages, the benefit was nearly lost in the elderly. The 197 patients with a mean age of 80 years experienced a rate of ICH of 1.8% per year at an INR range of 2.0 to 4.0. SPAF III examined the use of low-intensity, fixed-dose warfarin therapy (INR, 1.2 to 1.5) plus aspirin 325 mg per day versus adjusted-dose warfarin (INR, 2.0 to 3.0) and was stopped prematurely when an interim analysis demonstrated that warfarin to maintain an INR of 2.0 to 3.0 was clearly superior.

Aggregate data on the complications of anticoagulant treatment showed intracerebral hemorrhage at an overall rate of 0.3% per year (eFig. 110.4.3). Major hemorrhage occurred in 1.5% per year regardless of treatment, but minor bleeding was three times more frequent in patients receiving anticoagulation therapy.



***e*FIGURE 110.4.3** This subdural hematoma occurred after a minor head injury in a patient who has received long-term anticoagulation therapy.

Recommendations for therapy from the American College of Chest Physicians Consensus Conference are based on these studies (eTable 110.6.1) and include the assessment of individual patient risk (125). The recommendations call for long-term anticoagulation with warfarin with ongoing monitoring and adjustment to achieve an INR in the range of 2.0 to 3.0, with a target of 2.5. Despite these recommendations, an estimated 75% of patients with AF are currently not receiving appropriate treatment. A more detailed discussion of AF as a risk factor for stroke can be found elsewhere in this textbook (see Chapter 64).

***e*TABLE 110.6.1** PREVENTION OF ISCHEMIC STROKE AND INCIDENCE OF HEMORRHAGIC COMPLICATIONS IN THE TREATMENT OF NONVALVULAR ATRIAL FIBRILLATION

Study (reference)	Control (%/yr)	Aspirin (%/yr) (reduction in risk, %)	Warfarin (%/yr) (reduction in risk, %)	Risk of ICH (%/yr)	Risk of major hemorrhage (%/yr)
AFASAK (118)	5.5	4.7 (15)	2.2 (58)	1	0.8
SPAF (group I, II) (120)	6.3	3.6 (42)	NA	1	1.5
SPAF (group I) (119)	7.4	NA	2.3 (67)	1	NA
BAATAF (121)	3.0	NA	0.4 (86)	1	0.8
CAFA (122)	4.6	NA	3.0 (35)	1	2.5
Aggregate data from trials above (135)	5.8	(34)	2.6 (63)	0.3	NA

AFASAK, Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation trial; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation trial; ICH, intracranial hemorrhage; NA, not available; SPAF, Stroke Prevention in Atrial Fibrillation trial.

Patients with Acute Myocardial Infarction

Three large randomized clinical trials (126,127 and 128) demonstrated that short-term anticoagulant therapy reduced stroke incidence from a rate of 2.3% to 5.0% to a rate of 0.8% to 1.7% after MI. Studies (129,130,131 and 132) assessing longer-term anticoagulant therapy after acute MI have demonstrated a reduction in embolic stroke that needs to be balanced by the increased risk for ICH. Such therapy is recommended for patients at increased risk for embolic stroke, such as those with AF, prior systemic embolism, CHF, two-dimensional echo evidence of mural thrombus, or persistent left ventricular dysfunction.

Patients with Valvular Heart Disease

Mitral Stenosis

The use of oral anticoagulation with warfarin at an INR range of 2.0 to 3.0 is recommended to prevent cerebral and systemic emboli in patients with rheumatic mitral valve disease and either chronic or paroxysmal AF or prior systemic embolism, based primarily on nonrandomized studies with historical controls (level IV evidence) (133). Even in the absence of AF, long-term anticoagulant therapy is recommended for certain subgroups, such as those with mitral stenosis associated with enlargement of the left atrium greater than 5.5 cm, those for whom left atrial spontaneous echo contrast is present, and those about to undergo balloon valvuloplasty (134).

Prosthetic Cardiac Valves

Antithrombotic therapies to prevent thromboembolic complications from prosthetic valves vary by the type of valve, valve position, and other comorbidities. For mechanical prosthetic cardiac valves, permanent anticoagulation is strongly recommended, and the relationship between efficacy and intensity of anticoagulation is often described by U-shaped curves (level III and V evidence) (135). Thromboembolic risk is higher for caged-ball and caged-disc valves than for bileaflet valves, higher for mitral valves than for aortic valves, and higher with AF or after failure of oral anticoagulant therapy alone.

Infectious Endocarditis

Although infectious endocarditis accounts for less than 1% of all embolic strokes, it requires emergent evaluation and initiation of appropriate antibiotic therapy. Neurologic complications, mostly stroke and encephalopathy, occur in 35% to 40% of patients with infectious endocarditis (136). Neuroimaging in the setting of an acute, focal neurologic deficit discloses a bland cerebral infarct in more than half, cerebral hemorrhage in 10%, and, less frequently, cerebritis or abscess. Neuroimaging in the setting of encephalopathy is typically unrevealing, but cases of bland or hemorrhagic infarction have been reported as well. The daily stroke risk before the institution of appropriate antibiotic therapy is estimated to be 6% per day; after establishment of appropriate therapy, stroke is rare (137).

The role of anticoagulation remains controversial, and data are limited to small retrospective studies (level V evidence). In the acute period, embolism is most effectively prevented by the prompt and appropriate administration of antibiotics. Anticoagulation does not appear to prevent embolism in the acute period of endocarditis affecting a native or bioprosthetic valve and increases the risk of hemorrhage. Because the subsequent risk of embolic stroke is threefold to fourfold higher in nonanticoagulated mechanical valves than in anticoagulated mechanical valves, however, the evidence favors continuation of anticoagulation for patients with mechanical valves despite an increased risk of ICH.

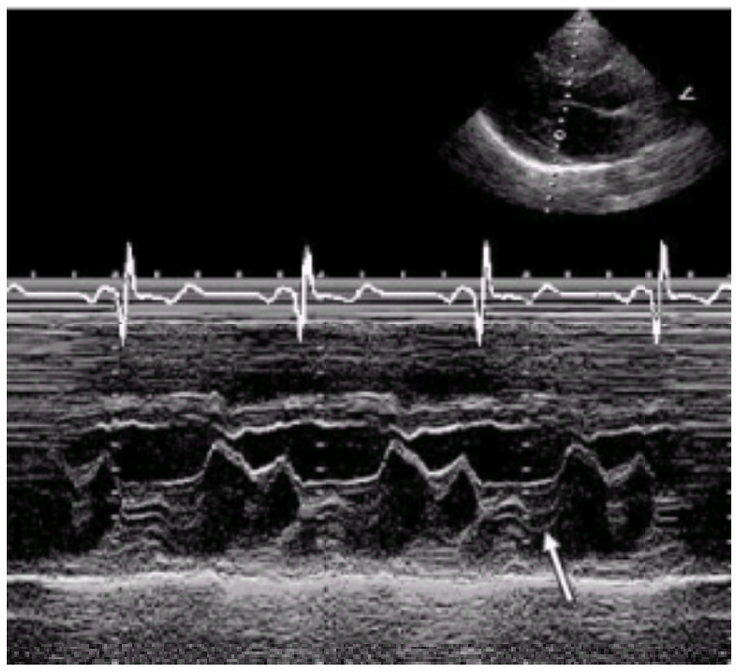
Noninfective Endocarditis

Nonbacterial thrombotic endocarditis or marantic endocarditis is a rare disorder complicating malignancies, typically mucin-producing carcinomas of the lung, colon, or pancreas. Most often diagnosed by autopsy, premorbid clinical clues include multiple organ dysfunction in the setting of arterial and venous thrombosis and ongoing disseminated intravascular coagulation. Although the treatment focuses on the underlying disease, the use of heparin sodium, but not warfarin, has been associated with benefit (level V evidence).

Libman-Sacks endocarditis is associated with inflammatory disorders such as systemic lupus erythematosus, particularly in the setting of the antiphospholipid antibody syndrome. The optimum therapy is unknown, although anticoagulation is often recommended.

Mitral Valve Prolapse

Mitral valve prolapse is identified in 1% to 10% of echocardiographic studies, with a slightly higher incidence in those with symptoms of cerebral ischemia than in controls (138). Although pathologic studies have identified platelet-fibrin aggregates on the valvular surface, mitral valve prolapse is more likely to be the cause of stroke when other risk factors are present, such as an associated atrial septal abnormality or hypercoagulable state (139). Antiplatelet therapy with aspirin, 160 to 325 mg per day, is recommended for secondary stroke prevention; anticoagulation therapy is reserved for those for whom antiplatelet therapy is ineffective (level V evidence).



M-mode tracing of posterior leaflet mitral valve prolapse. Note the posterior displacement of the posterior mitral leaflet after the leaflets close in systole.

Calcific Aortic Stenosis

Embolization of calcific debris can complicate valvuloplasty for calcific aortic stenosis (140). Although calcific emboli have been demonstrated, primarily in autopsy studies, the risk of stroke in the absence of AF remains uncertain. No evidence exists of any therapy that prevents embolization, but anticoagulation is not warranted (141).

Mitral Annular Calcification

Calcification of the mitral annulus can be identified in up to 30% of elderly patients with stroke, but it is also present in 20% of elderly patients without stroke and is associated with other risk factors such as hypertension, AF, CHF, and carotid stenosis. As with calcific aortic stenosis, its role as a cardioembolic cause of stroke and optimum therapy remains uncertain (142).

Patients with Asymptomatic Carotid Stenosis

Three early randomized trials of endarterectomy for asymptomatic carotid stenosis produced negative or inconclusive results (*e*Table 110.6.2). The Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin study (143) randomly assigned 410 patients with 50% to 90% asymptomatic internal carotid artery stenosis to receive either endarterectomy or aspirin therapy. Patients with recent MI or other severe medical diseases were excluded. No statistical difference was found in the number of neurologic deficits and deaths in the two groups. Because patients with greater than 90% stenosis were excluded, however, no conclusion could be offered about this subgroup. The Veterans Administration Asymptomatic Carotid Stenosis Trial (144) randomly assigned 444 patients with greater than 50% internal carotid artery stenosis to receive either optimal medical treatment (including aspirin) plus endarterectomy or optimal medical treatment alone. CAD was the prime determinant of operative mortality. A nonsignificant trend was seen toward a reduced incidence of ipsilateral stroke in the surgical group. The Mayo Asymptomatic Carotid Endarterectomy trial (145) was stopped early because of an excessive number of MIs in the placebo arm. Aspirin was not used in this trial.

***e*TABLE 110.6.2** TRIALS OF ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS: OUTCOMES OF STROKE AND DEATH

Study (reference)	Carotid lesion studied (% stenosis)	Medical group events (%)	Surgical group events (%)	Reduction of relative risk (%)
ACAS (146)	>60	11	5.1	53
VAACST (144)	>50	44	41	NS
MACE (145)	>50	0	8	NS
CASANOVA (143)	50 to 90	28	29	NS

ACAS, Asymptomatic Carotid Atherosclerosis Study; CASANOVA, Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin; MACE, Mayo Asymptomatic Carotid Endarterectomy; NS, not significant; VAACST, Veterans Administration Asymptomatic Carotid Stenosis Trial.

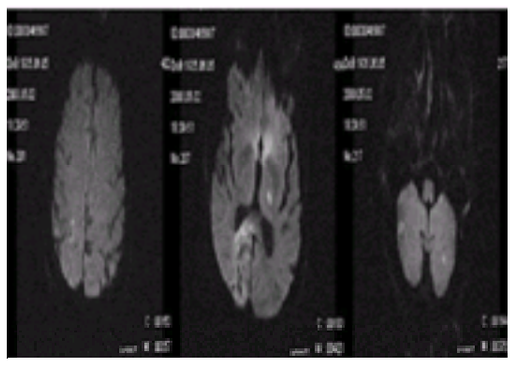
The Asymptomatic Carotid Atherosclerosis Study (ACAS) (146) randomly assigned 1,662 patients with greater than 60% internal carotid artery stenosis (determined by ultrasonography or angiography) to surgery or medical care only. Ultrasonography laboratories at participating sites underwent rigorous standardization and certification procedures to ensure the accuracy of noninvasive results (147). Despite such precautions, a 7% disagreement was seen between ultrasonography and angiography (ultrasonography positive predictive value, 93%) in ACAS. This is notable because of the increasing trend toward performing endarterectomy in asymptomatic patients based on noninvasive testing only (148,149).

ACAS was prematurely terminated after 2.7 median years of follow-up, with reported results based on Kaplan-Meier estimates of events at 5 years. The projected 5-year stroke rate in the medical group was 11.3% versus 5.6% in the surgical group. Despite the 5.7% absolute benefit demonstrated for surgery, ACAS has generated considerable controversy. Due to a higher angiographically determined complication rate in women, the benefits of surgery were seen only in men. Moreover, the rate of severe ipsilateral stroke was not reduced, and the relative efficacy of surgery by degree of stenosis (e.g., less than 90% or more than 90%) could not be determined. Concern also exists regarding the ability to replicate in the community setting the low surgical morbidity and mortality rate in ACAS (3%), which is essential for demonstrating overall efficacy (150,151,152,153 and 154).

Based on these trials, in asymptomatic patients, a conservative approach would be to recommend a prophylactic endarterectomy for those with a good 5-year life expectancy if the stenosis is greater than 80%, and the surgeon has a combined morbidity and mortality rate of less than 3%. For all others, the focus would be on medical treatment of risk factors, patient education about TIAs, and antiplatelet therapy (155,156).

Patients Undergoing Cardiovascular Procedures

Stroke complicates 2% to 5% of coronary revascularizations and up to 15% of operations that require opening of the cardiac chambers. Much of the risk is related to the cardiopulmonary bypass circuit, which can contribute to cerebral injury through a number of mechanisms, including hypoperfusion, embolization, and a provoking of a systemic inflammatory response. Additional factors include prolongation of the cardiopulmonary bypass time related to the complexity of the case, potential for embolism of valve debris, and embolism of air and particulates during mechanical de-airing of the heart. “Off-pump” coronary artery bypass surgery or the use of emboli capture devices may become the superior alternative for those at increased risk of stroke. Stroke is related to aortic arch emboli in 32%, cardiogenic emboli in 12%, hypoperfusion in 12%, and concomitant cerebrovascular disease in 11%. Stroke risk factors include atherosclerosis of the proximal aorta, hypertension, diabetes, prior cerebrovascular disease, history of neurologic disease, age older than 70 years, history of pulmonary disease, and postoperative AF (157,158 and 159). Clinically recognizable encephalopathy persisting to the fourth postoperative day occurs in 3% to 12%, although 80% of these patients recover to be able to perform normally on a simple mental status test by the time of discharge. Prospective investigations using extensive neuropsychological test batteries, however, have found that 35% to 75% of patients have impairments in cognitive function, which is severe in 20% of cases, within the first 7 to 10 days, and 10% to 30% have persistent significant deficits at 3 to 6 months. Neuroimaging studies using MRI techniques suggest that the presence of preoperative cerebral atrophy and postoperative ischemic changes manifesting as lesions on diffusion-weighted or T2-weighted MRI brain scans correlate with cognitive dysfunction, findings which support a theory of multifocal microembolism (*e*Fig. 110.4.4). Excessive alcohol consumption, postoperative AF, a history of peripheral vascular disease or prior coronary artery bypass graft, and cerebral atrophy by neuroimaging have also been reported as risk factors for cognitive decline. These identified risk factors for postoperative encephalopathy appear to reflect a patient’s “cerebral reserve” for withstanding a diffuse or multifocal ischemic insult.



***e*FIGURE 110.4.4** These diffusion-weighted magnetic resonance images demonstrate multiple acute infarcts in a patient with a prolonged encephalopathy after coronary artery bypass surgery.

Paraplegia from spinal cord infarction is a rare complication of intraaortic balloon counterpulsation support (160) (*e*Fig. 110.4.5).

***e*FIGURE 110.4.5** Magnetic resonance image depicting acute spinal cord infarction involving multiple thoracic segments.

Cerebral embolism complicates 0.1% to 1.0% of cardiac catheterizations and 0.2% to 0.3% of coronary interventions. Defects in the vertebrobasilar circulation account for 60% to 70% of cases presenting with combinations of confusional states, cortical blindness or hemianopic visual field defects, and intrinsic brainstem signs. The mechanism is generally felt to be embolic in nature, either from manipulation of the guidewire or during catheter flushing. Focal defects resolve within 48 hours in approximately half of patients; however, some strokes have been fatal. Rarely, a confusional state with headache and cortical blindness mimicking hypertensive encephalopathy or subarachnoid hemorrhage can occur. The cause is unknown, but the condition typically resolves within 48 hours with antihypertensive therapy (161,162 and 163) (*e*Fig. 110.4.6).

***e*FIGURE 110.4.6** Occipital contrast enhancement with transient cortical blindness after cardiac catheterization.

The risk of embolic stroke ranges from 1.4% to 11% for aortic valvuloplasty and 3.2% to 4.2% for mitral valvuloplasty. In the presence of an atrial thrombus, systemic embolism can result during mitral valvuloplasty, which prompted the recommendations for 3 months of anticoagulation therapy and transesophageal echocardiography before each procedure. Embolic events during aortic valvuloplasty are often highly focal, small neurologic deficits suggesting small calcific emboli (134).

The frequency of hypoxic-ischemic encephalopathy or stroke due to hypotension before insertion of a left ventricular assist device (LVAD) varies up to 25% in surgical series. Subsequent stroke from embolism of air or thrombus, or coagulopathy-related hemorrhage occurs in an additional 10% to 20% and is greater with longer durations of pump assist and during manipulation of the pump (164) ()*e*Fig. 110.4.7.

***e*FIGURE 110.4.7** Multifocal cerebral embolism after transient left ventricular assist device malfunction.

Secondary Prevention of Stroke: Prevention of Recurrent Ischemia in Patients Presenting with Transient Ischemic Attack or Major or Minor Cerebral Infarction

In patients with symptomatic retinal or cerebral ischemia, an evaluation is necessary to identify the underlying mechanism and to provide a rational basis for treatment. Depending on the clinical scenario, a complete history and physical and neurologic examination, some structural neuroimaging such as a CT scan of the brain, and basic systemic testing of blood as well as an electrocardiogram (ECG) may suffice; however, more typically, additional tests including noninvasive vascular studies, MRI, or TTE are performed (165). Additional levels of testing include cerebral angiography, transesophageal echocardiography, and assays of coagulation factors

(165a).

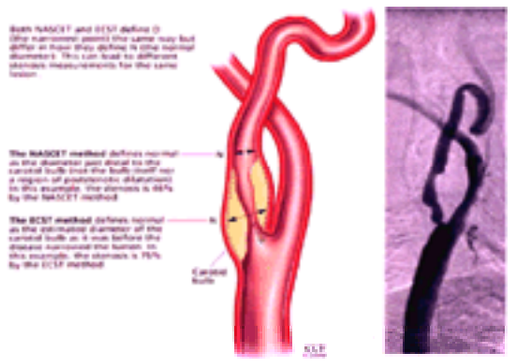
Checking for Occlusive Disease

Carotid artery screening is performed with duplex or Doppler ultrasonography. Duplex carotid ultrasonography combines b-mode anatomic imaging with a Doppler assessment of blood flow and is the preferred noninvasive study (85% sensitivity, 90% specificity). The surgical cutoff of more than 70% stenosis can be determined accurately in many laboratories. High-grade stenoses with low flow can be mistaken for occlusion and require angiographic confirmation. Doppler ultrasonography alone (70% sensitivity, 95% specificity) is an alternative screening modality at a reduced cost. Transcranial Doppler ultrasonography is used to evaluate the intracranial vasculature (166).

Magnetic resonance angiography (MRA) is noninvasive and provides a vascular image within minutes (eFig. 110.4.8). Its sensitivity and specificity are comparable to those of duplex carotid ultrasonography. MRA is also useful in evaluating intracranial circulation and the vertebrobasilar system. Besides cost, the major limitations of MRA include the fact that approximately 25% of patients are unable to tolerate the procedure because of claustrophobia and that its use is contraindicated in patients with implanted metal devices, including pacemakers, defibrillators, and certain aneurysm clips.

***e*FIGURE 110.4.8** Magnetic resonance angiography demonstrates normal intracranial cerebral circulation.

Carotid angiography is the reference diagnostic test for determining the degree of carotid artery stenosis based on NASCET and the European Carotid Surgery Trial (ECST) (eFig. 110.4.9). Serious complications occur in less than 1% to 3% of patients. Carotid angiography usually requires hospitalization, although intraarterial digital subtraction techniques and arterial closure devices allow outpatient scheduling.



***e*FIGURE 110.4.9** Measurement schemes for carotid stenosis. D, diameter of diseased narrowed lumen; ECST, European Carotid Surgery Trial; N, normal diameter; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

Performing endarterectomy based on noninvasive testing alone remains controversial, as the outcomes-based studies have used angiography as the selection reference (167). In ACAS, in which strict quality control was conducted, almost a 6% false-positive error rate was seen with ultrasonography compared with angiography. However, when ultrasonography and MRA are in agreement and intracranial MRA has excluded significant intracranial lesions, the additional expense and risks associated with angiography are difficult to justify, especially in asymptomatic patients.

Checking for a Cardiac Source of Embolism

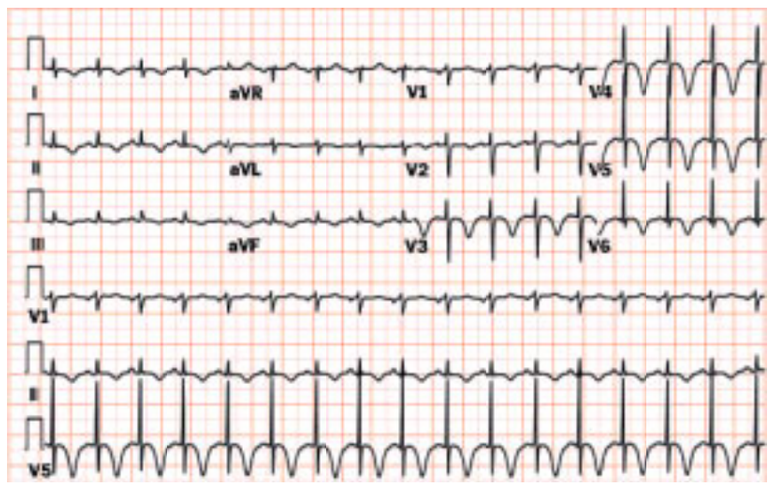
Some clinical features can clue the clinician to a proximal source of embolism, including (a) nonlacunar involvement of the cortex or cerebellum in multiple vascular territories; (b) evidence of systemic embolism, syncope, palpitations, seizures at onset, or rapid resolution of a neurologic deficit; or (c) stroke in a young patient without risk factors for premature atherosclerosis. Because emboli are more likely to lodge in the middle cerebral artery or the posterior cerebral artery, certain clinical syndromes are overrepresented, such as Wernicke aphasia, ideomotor apraxia, isolated hemianopia, or top-of-the-basilar syndrome (168). Also, because cerebral emboli spontaneously lyse in at least 30% of patients, which leads to reperfusion of the ischemic area, rapid recovery or hemorrhagic infarction also suggests an embolic mechanism. Several misconceptions about cardioembolic symptoms also warrant mention. Although repetitive ischemic symptoms referable to the same arterial territory make a proximal source less likely, cerebral emboli may travel repeatedly to the same artery, typically the middle cerebral artery. Retinal ischemia manifesting as transient monocular blindness may be the only clue to cardiac embolization. The prototypical onset is in an awake, active patient, but cardiac embolization can occur at any time of the day or night regardless of the level of activity. Although 90% of embolic strokes are maximal at onset, the remainder have a stuttering onset that reflects initial embolization with superimposed thrombus formation in a vessel with stagnant flow caused by a partially occluding embolus. A cardioembolic mechanism cannot always be inferred by the presence of a potential cardioembolic source, because an estimated 30% of patients with a cardioembolic source have concomitant cerebrovascular atherosclerosis that may also be the cause.

Echocardiography

TTE is indicated in young patients with unexplained cerebrovascular symptoms and in all patients with symptoms or signs of heart disease. In elderly patients with no evidence of heart disease, however, TTE is of limited use and is not cost effective (169,170). Transesophageal echocardiography can disclose potential cardioembolic sources of embolism, including the aortic arch, patent foramen ovale, atrial septal defects, and atrial septal aneurysms. As these conditions can be detected in up to 30% of selected populations, however, their etiologic role requires additional study (171,172,173,174 and 175).

Electrocardiographic Monitoring

ECG monitoring may reveal a variety of dysrhythmias, particularly in patients with subarachnoid hemorrhage or ICH, and should otherwise be reserved for patients with syncope or palpitations at onset, unexplained stroke, and other cardiac symptoms or signs (176,177,178 and 179).



Neurogenic T waves. These deep, symmetric T-wave inversions developed after intracranial hemorrhage.

Cerebral Angiography

The presence of branch occlusion or delayed perfusion of distal arterial branches in the absence of a more proximal arterial source of embolism suggests a more proximal source of embolism, such as the heart. Because of spontaneous clot lysis, however, angiography performed more than 24 hours after symptom onset frequently proves normal. Angiography has been useful in clinical trials investigating intraarterial delivery of thrombolytic agents after cerebral embolism.

Therapeutic Options for Patients with Transient Ischemic Attack and Stroke

Most clinical trials for stroke prevention have involved patients with TIA or minor stroke. Major treatments include antiplatelet therapy, anticoagulant therapy, and carotid endarterectomy.

Antiplatelet Therapy

Aspirin

Aspirin remains the standard preventive therapy for patients at risk for stroke. Its indications have grown from the initial U.S. Food and Drug Administration (FDA) approval in 1980, which specified its use in men with TIAs “due to fibrin platelet emboli” based on a trial in which 1,300 mg was taken daily. In a metaanalysis of 31 trials encompassing over 29,000 patients with cerebrovascular disease, the risk reduction for the combined end point of stroke, MI, or vascular death was 25%, but the major effect was from the 22% reduction in nonfatal stroke (33). Treatment was effective regardless of sex, middle or older age, or presence of hypertension or diabetes mellitus. Subgroup analyses (based on less than 400 events) in 25 trials showed no significant differences in reduction of vascular events for dosages of 75 to 150 mg (26%), 160 to 325 mg (28%), and 500 to 1,500 mg (21%), and documenting the optimum aspirin dosage would require a megatrial to avoid bias and random errors.

The United Kingdom Transient Ischemic Attack trial (34) directly compared aspirin dosages, randomly assigning patients to receive 300 mg daily or 600 mg twice daily. Although the combined end point of stroke, MI, and vascular death was reduced by 22%, the 7.7% reduction in disabling stroke and vascular death was not significant. No difference in outcomes was noted between the two dosage levels; however, the rate of gastrointestinal side effects was significantly lower in the low-dose group.

Very-low-dose aspirin was investigated in the Swedish Aspirin Low-Dose Trial, which found a statistically significant 17% relative risk reduction for the combined end point of stroke and vascular death among those taking aspirin 75 mg daily (37). The Dutch Transient Ischemic Attack Trial (36) could not demonstrate a difference in the frequency of stroke, MI, or vascular death between those taking aspirin in dosages of 30 mg per day and 283 mg per day, although major bleeding complications were slightly fewer in the lower-dosage group.

Metaanalyses provide no evidence that antiplatelet therapy reduces the risk of first stroke for “low-risk” individuals. The Physician’s Health Study addressed primary prevention of MI and stroke in a randomized trial in which asymptomatic men were treated with aspirin. The significant reduction in MI prompted premature termination of this study, unfortunately before sufficient cerebrovascular end points had occurred to allow for any meaningful statement about aspirin’s role in preventing first stroke (180).

Aspirin with Dipyridamole

Combination antiplatelet therapy with aspirin and dipyridamole was not demonstrated to be superior to treatment with aspirin alone in several trials and was largely abandoned for stroke prophylaxis until the European Stroke Prevention Study (ESPS) trials (31). ESPS I (35) followed 2,500 patients for 2 years, comparing aspirin 990 mg per day and dipyridamole 225 mg per day with placebo. The combination antiplatelet strategy achieved a 35% reduction in stroke and vascular death and a 38% reduction in fatal and nonfatal stroke over placebo but was not compared with aspirin alone. ESPS II (38) evaluated aspirin 50 mg and an extended-release formulation of dipyridamole 400 mg, either alone or in combination, versus placebo in a factorial design. The relative risk reduction for stroke was 18% for low-dose aspirin alone, 16% for dipyridamole alone, and 37% for the combination when compared with placebo. This study demonstrates the efficacy of very-low-dose aspirin and suggests that combination therapy has an additive effect, at least for stroke prevention. The combination was 23% better than low-dose aspirin alone in preventing stroke, with the predominant reduction in nonfatal stroke. None of the treatments was found to reduce the risk of MI or vascular death, but very few cardiovascular events occurred during the trial overall. The predominant side effects included gastrointestinal complaints with aspirin and headache with dipyridamole. Based on this study, the FDA approved this low-dose aspirin and high-dose extended-release dipyridamole formulation (Aggrenox) for stroke risk reduction, and the dosage of aspirin for stroke prevention in the American College of Chest Physicians guidelines was lowered to 50 mg.

Thienopyridines: Ticlopidine and Clopidogrel

Clopidogrel and ticlopidine are both thienopyridine derivatives that inhibit platelet aggregation by selectively and irreversibly inhibiting the adenosine diphosphate–dependent activation of fibrinogen binding via the glycoprotein IIb/IIIa complex. The Ticlopidine Aspirin Stroke Study (181) compared ticlopidine 250 mg twice daily with aspirin 650 mg twice daily in patients with TIAs or minor strokes. Ticlopidine reduced the overall risk for fatal or nonfatal stroke by 19% compared with aspirin, but in the first year of treatment the reduction in risk with ticlopidine proved 48% superior to that with aspirin. In the Canadian-American Ticlopidine Study (182), ticlopidine reduced recurrent stroke by 34% and reduced the combined risk for stroke, MI, or vascular death by 30% in patients with brain infarction. Ticlopidine proved effective in both men and women. Serious adverse events occurred in 2% of patients receiving both aspirin and ticlopidine, with gastrointestinal bleeding being the major side effect of aspirin. Significant neutropenia (i.e., absolute neutrophil count less than 450 per mm^3) occurred in less than 1% of ticlopidine-treated patients and almost exclusively within the first 3 months of therapy. Accordingly, a complete blood count with a differential count must be taken every 2 weeks for the first 3 months of ticlopidine therapy. Thrombotic thrombocytopenic purpura has been reported at an estimated rate of 200 to 625 cases per million ticlopidine-treated patients among those with cerebrovascular disease and after coronary interventions. As 80% of cases appeared within the first month of therapy, patients should be counseled to seek medical attention if fever, bruising, or neurologic symptoms develop (183). This safety and efficacy profile has limited the use of ticlopidine primarily to cases in which aspirin therapy has failed, although it remains under study in the African-American Antiplatelet Stroke Prevention Study.

A regimen of clopidogrel 75 mg once daily was compared to therapy with aspirin 325 mg daily in 19,185 patients with a recent stroke or MI or symptomatic peripheral vascular disease. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events study demonstrated a 9% relative risk reduction in the combined end point of stroke, MI, or vascular death for clopidogrel over aspirin (5.32% vs. 5.83%) (39). Although subset analyses were not powered to look at cerebrovascular patients separately, the major benefit was seen for patients with peripheral arterial disease, and results were not statistically significant for those patients who entered with cerebrovascular events. The 75-mg dosage of clopidogrel was selected to achieve bleeding times comparable to those with ticlopidine 250 mg twice a day. Side effects of rash and diarrhea were more frequent, but gastrointestinal symptoms and gastrointestinal bleeding were lower with clopidogrel. As the incidence of severe neutropenia was similar to that of aspirin (0.04% vs. 0.02%), hematologic monitoring is not warranted. In postmarket surveys, the risk of thrombotic thrombocytopenic purpura has been found to be 3.7 cases per million clopidogrel-treated patients against a background rate of four cases per million person-years in the general population (184,185). Given the efficacy data and superior safety profile, clopidogrel has essentially replaced ticlopidine as an aspirin alternative.

Anticoagulant Therapy

Although warfarin is used in many settings, the only clear indication for it is in the prevention of cardioembolic stroke, particularly that due to AF. A metaanalysis (186) was unable to find evidence for benefit in stroke prevention; however, the sample sizes were small, and a beneficial effect may have been missed due to a type II error.

The Warfarin-Aspirin Recurrent Stroke Study, which enrolled 2,206 patients, compared warfarin, adjusted to an INR range of 1.4 to 2.8, with aspirin 325 mg per day. The mechanism of the qualifying event was small vessel disease or lacunar stroke in 56%, cryptogenic mechanism in 26% (41% of whom had a patent foramen ovale), and large vessel stenosis or occlusion, including intracranial atherosclerosis, in 12% (186). No difference was seen in the 2-year rate of stroke and death, which reached 17.8% among those receiving warfarin and 16.0% among those given aspirin, and no differences were noted in safety, with overall low rates of major hemorrhage of 1.92% and 1.49%, respectively. Although patients who were on aspirin at the time of their qualifying event had a higher rate of recurrent events, no difference was found between those randomly assigned to receive aspirin and those assigned to receive warfarin. These data suggest that warfarin adjusted to an INR of 1.4 to 2.8 is safe but provides no additional benefit over aspirin for noncardioembolic, nonsurgical atherothrombotic causes of stroke, even in those patients for whom aspirin treatment has failed.

After a pilot retrospective case series of patients with symptomatic intracranial atherosclerosis suggested that warfarin-treated patients had lower event rates than those who received aspirin (187), the Warfarin-Aspirin Symptomatic Intracranial Disease trial was initiated to compare warfarin (INR range of 2 to 3) with aspirin 1,300 mg per day in patients with 50% or higher stenosis of the intracranial internal carotid, middle cerebral, basilar, or vertebral artery. Primarily on the basis of retrospective studies, warfarin has also been recommended for patients with the antiphospholipid syndrome who have TIA or stroke and who also have a cardiac source of stroke, recurrent deep venous thrombosis, or lupus erythematosus (188,189).

Carotid Endarterectomy for Symptomatic Carotid Stenosis

In the 1980s the Rand report (190) suggested that one-third of carotid endarterectomies were performed for inappropriate indications and that indications for another one-third were questionable. Several randomized trials (77,143,144,145 and 146,191,192 and 193) have subsequently evaluated the safety and efficacy of carotid endarterectomy (*e*Table 110.6.2, *e*Table 110.6.3, and *e*Table 110.6.4). The best indication for carotid endarterectomy is for the prevention of ipsilateral carotid territory ischemic stroke in patients with a recent TIA or minor ischemic stroke due to severe carotid bifurcation atherosclerosis. This position is supported by the results of the NASCET and ECST studies (194).

***e*TABLE 110.6.3** TRIALS OF ENDARTERECTOMY FOR SYMPTOMATIC CAROTID STENOSIS: OUTCOMES OF STROKE AND DEATH

Study (reference)	Carotid lesion studied (% stenosis)	Medical group events (%)	Surgical group events (%)	Reduction of relative risk (%)
NASCET (77,192)	>70	32	16	53
ECST (194)	>70	28	19	32
VASCST (56)	>50	10	12	NS

ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NS, not significant; VASCST, Veterans Administration Symptomatic Carotid Stenosis Trials.

***e*TABLE 110.6.4** EFFICACY OF CAROTID ENDARTERECTOMY

Clinical trial subset(% stenosis)	Surgery would need to be done on	To spare one	Duration (yr)
Symptomatic			
NASCET (70–99)	6	Ipsilateral stroke	2
	10	Major stroke or death	2
ECST (70–99)	15	Ipsilateral stroke	3
	20	Major stroke or death	3
NASCET (50–69)	12 men or 67 women	Ipsilateral stroke	5
	16 men or 125 women	Major stroke	5
ECST (<70)	No benefit	Any ipsilateral stroke	>4
NASCET (<50)	No benefit	Any ipsilateral stroke	5
VA (>50)	No benefit	Any stroke or death	(Study terminated)
	26 men	Crescendo TIA or stroke	1
Asymptomatic			
CASANOVA (50–99)	No benefit	Any stroke or death	3
VA (>50)	No benefit	Any stroke or death	4
MACE	(Study terminated, excessive myocardial infarctions)		
ACAS (³60)	17	Ipsilateral stroke or any perioperative stroke or death	5
	9	TIA, stroke, or death	5
	No benefit	Any stroke or death	5
	No benefit	Major stroke or death	5
ACST	Ongoing		

ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Stenosis Trial; CASANOVA, Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin; ECST, European Carotid Surgery Trial; MACE, Mayo Asymptomatic Carotid Endarterectomy; NASCET, North American Symptomatic Carotid Endarterectomy Trial; TIA, transient ischemic attack; VA, Veterans Administration.

North American Symptomatic Carotid Endarterectomy Trial

Starting in 1987, NASCET randomly assigned patients who had carotid territory TIA or nondisabling ischemic stroke within the past 3 months and who had ipsilateral 30% to 99% internal carotid stenosis to receive best medical management (including antiplatelet therapy) alone or with surgery. The degree of stenosis was determined by comparing the angiographic residual lumen diameter at the narrowest point to the normal vessel diameter just distal to the carotid bulb (*e*Fig. 110.4.9). The "NASCET method" has become a standard for describing carotid stenosis and differs importantly from other methods. Carotid stenosis was stratified by angiographically defined severity as moderate (30% to 69%) or severe (70% to 99%).

Severe Symptomatic Carotid Stenosis (70% to 99%). The study of the subgroup of 659 patients with 70% to 99% stenosis was prematurely terminated and the results reported in 1991 after interim analyses demonstrated a statistically significant benefit in favor of surgery. Carotid endarterectomy for severe (70% to 99%) symptomatic carotid stenosis reduced the overall rate of ipsilateral stroke from 26% to 9% (17% absolute and 65% relative risk reduction) and reduced the rate of major or fatal ipsilateral stroke from 13.1% to 2.5% (81% relative risk reduction) at 2 years. As the severity of carotid stenosis increased, so did the risk of having a stroke; as stroke risk increased, so did the benefits of surgery. Ipsilateral ischemic stroke was reduced by 12% among those with 70% to 79% stenosis, by 18% among those with 80% to 89% stenosis, and by 26% among those with 90% to 99% stenosis. The overall risk of any stroke or death was also significantly reduced from 32.3% to 15.8% (51% relative risk reduction) at 2 years.

Nine prospectively selected risk factors identified those at high risk of stroke with medical therapy alone. Among those patients with more than six of these high-risk characteristics, 39% had an ipsilateral stroke within 2 years.

Moderate Symptomatic Carotid Stenosis (30% to 69%). In 1998, the results for the 2,226 patients with moderate symptomatic carotid stenosis (30% to 69%) were published along with the long-term follow-up on the patients with severe symptomatic carotid stenosis. The relationship between the degree of carotid stenosis, risk of stroke, and expected benefit from carotid endarterectomy continued to hold.

Carotid endarterectomy for high moderate (50% to 69%) symptomatic carotid stenosis also reduced the overall rate of ipsilateral stroke from 22.2% to 15.7% (6.5% absolute and 29% relative risk reduction) at 5 years, but the benefit was marginal (p = .045). Within this subgroup, characteristics that were associated with a greater benefit from surgery included male gender, a recent stroke (rather than a TIA), recent hemispheric symptoms (rather than retinal symptoms), and failure of therapy with aspirin at 650 mg or more daily.

Endarterectomy did not benefit those with low moderate (30% to 49%) symptomatic carotid stenosis, as the overall rate of ipsilateral stroke at 5 years was not

significantly different for those who had surgery (14.9%) for those given medical therapy alone (18.7%).

Perioperative Morbidity and Mortality in the North American Carotid Endarterectomy Trial. The perioperative stroke morbidity and mortality rate in all patients with severe carotid stenosis was 5.8%, which included a major stroke and death rate of 2% and a mortality rate of less than 1%. In comparison, during the 30-day perioperative period, stroke and death occurred in 3.3% of the group receiving medical treatment. The perioperative stroke morbidity and mortality rate in all patients with moderately severe carotid stenosis was 6.7%, which included a major stroke rate of 1.6% and a mortality rate of 1.2%. In comparison, stroke and death occurred in 2.4% of the group given medical treatment within 30 days. The net increase in 30-day risk with carotid endarterectomy for patients with moderate symptomatic stenosis was 4.3% for any stroke or death and 2% for disabling stroke or death. Characteristics that doubled the risk of perioperative stroke or death included contralateral carotid occlusion, evidence of an ipsilateral cerebral infarct on CT or MRI, left-sided carotid disease, diabetes, diastolic blood pressure above 90 mm Hg, absence of a history of MI or angina, and ingestion of less than 650 mg of aspirin per day, but not age or gender.

Among patients with symptomatic carotid stenosis of more than 50%, the risk of ipsilateral stroke was highest immediately after the initial ischemic event, declined gradually to 3% per year within 2 to 3 years with medical therapy alone, then dropped rapidly to 2% per year within 10 days of carotid endarterectomy. If patients with symptomatic carotid stenosis escaped recurrent symptoms for 2 or 3 years after the index ischemic event, they had little to gain from having subsequent surgery.

European Carotid Surgery Trial

The ECST began in 1981 and allowed individual physicians to randomly assign to treatment groups 2,518 patients who had had a TIA or nondisabling stroke within the past 3 months and for whom “substantial uncertainty” existed about which treatment they should receive. This unique and inexpensive enrollment method allowed for a heterogeneous group based on individual physician preference and stratified patients by severity of carotid stenosis: less than 30%, 30% to 69%, and 70% to 99%. Like NASCET, ECST determined the degree of carotid stenosis by angiography, but the method of measurement differed in that the residual lumen diameter at the narrowest point was compared to the estimated diameter of the carotid bulb before disease. This method overestimates the stenosis compared to the NASCET method, an important point to remember when the results of the clinical trials are compared.

Results from the subgroups with 70% to 99% stenosis and less than 30% stenosis were reported in 1991. Carotid endarterectomy was beneficial only for patients with severe (70% to 99%) symptomatic carotid stenosis. For those 778 patients, carotid endarterectomy reduced the overall rate of ipsilateral stroke or death from 16.8% to 10.3% (6.5% absolute and 39% relative risk reduction) at 3 years; the rate of disabling or fatal ipsilateral stroke was reduced from 11% to 6% (45% relative risk reduction) at 3 years. The perioperative stroke morbidity and mortality rate of 7.5% included a major stroke and death rate of 3.7%. The overall rate of ipsilateral stroke at 3 years for the 374 patients with mild (less than 30%) symptomatic carotid stenosis was so small that the surgical risk outweighed any potential benefit. The overall rate of ipsilateral stroke or death at 4 years was not significantly different among those 1,599 patients with moderate (30% to 69%) symptomatic carotid stenosis that had carotid endarterectomy (16.6%) and those that had medical therapy alone (12.7%). The ECST investigators concluded that carotid endarterectomy was indicated for carotid stenosis of greater than 80%, which corresponds to 60% stenosis by the NASCET method.

When Preventive Therapies Fail: Acute Ischemic Stroke Intervention

The American Heart Association (AHA) Stroke Council has published guidelines for the management of acute ischemic stroke, which have been updated for thrombolysis (195,196 and 197,270). A critical concept is time to treatment, because intravenous thrombolytic therapy must be initiated within 3 hours of stroke onset (Table 110.7).

Treatment goal	Time (min)
Door to doctor	10
Access to stroke expertise	15
Door to computed tomographic scan done	25
Door to computed tomographic scan read	45
Door to drug (intravenous t-PA)	60
Access to neurosurgical expertise	120
Door to monitored bed	180

NINDS, National Institute of Neurological Disorders and Stroke; t-PA, tissue-type plasminogen activator.
[a]NINDS Symposium on Rapid Identification and Treatment of Acute Stroke; December 1996; Arlington, VA.

TABLE 110.7 NINDS SYMPOSIUM: ACUTE STROKE TREATMENT GOALS[a]

Standard management includes respiratory support, aspiration precautions, and prevention of deep vein thrombosis. One of the most important issues in acute stroke is hemodynamic management (103,104). An algorithm for blood pressure management in patients with acute ischemic stroke has been published by the AHA (198). If the patient has a history of hypertension, blood pressure should be kept in the mildly elevated range; some patients require higher blood pressure elevations to maintain cerebral perfusion, although this may increase the risk for cerebral edema or hemorrhage. Sustained hypertension (higher than 185/110) must be strictly avoided in patients undergoing thrombolysis. Pharmacologic agents used to decrease blood pressure should allow for minute-to-minute titration. Intravenous labetalol hydrochloride 5 to 10 mg is initially recommended when blood pressure must be lowered after acute stroke. Intravenous sodium nitroprusside is rarely required; such patients are not eligible for thrombolysis.

Aggravation of tissue acidosis from excessive anaerobic metabolism of glucose may exacerbate ischemic damage. Intravenous solutions therefore should not contain glucose, and blood glucose levels should be kept to less than 180 mg per dL and carefully monitored (92). Cerebral edema is usually maximal 3 to 7 days after cerebral infarction. Cerebral edema is best treated in an intensive care unit with ICP monitoring, osmotic dehydration, and sometimes hemicraniectomy.

Thrombolytic Therapy

Based on the National Institute of Neurological Disorders and Stroke (NINDS) trial, the FDA approved the use of intravenous tissue-type plasminogen activator (t-PA) for ischemic stroke within 3 hours of symptom onset in June 1996 (198). Intravenous t-PA within 3 hours of onset remains the only FDA-approved treatment of acute ischemic stroke. Virtually no experience has been gained with newer thrombolytic agents in acute stroke. The approval of intravenous t-PA has resulted in a much more aggressive approach to acute stroke therapy in many ways analogous to treatment of acute coronary syndromes (199). Because of the narrow therapeutic window and the risk of hemorrhage, thrombolysis in acute stroke is one of the most controversial issues in neurology today (200,201,202,203,204 and 205).

Intravenous Thrombolysis

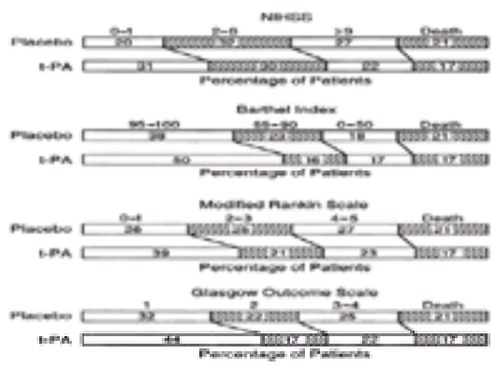
Intravenous administration has the important advantages of time, ease of administration, and widespread availability. Many small series investigating intravenous thrombolysis have been performed. A metaanalysis (206) of 12 thrombolytic trials performed since 1980 found an absolute increase in symptomatic hemorrhages of 7% [odds ratio (OR), 3.62; 95% confidence interval (CI), 2.73 to 4.80] and a 3.7% increase in death (OR, 1.36; 95% CI, 1.14 to 1.62). A significant 6.5% absolute reduction in poor outcome was seen, however; 61.5% of patients (798 of 1,297) randomly assigned to receive thrombolysis were dead or dependent compared with 65.0% (864 of 1,270) who did not receive thrombolysis (OR, 0.75; 95% CI, 0.63 to 0.88).

Seven multicenter trials of intravenous thrombolysis have been reported, four using t-PA (198,207) and three using streptokinase (208,209 and 210). The NINDS trial was a placebo-controlled, randomized trial of 0.9-mg-per-kg recombinant t-PA (rt-PA) given intravenously within 3 hours of symptom onset (eTable 110.7.1). The NINDS trial was a nonangiographic study involving 624 patients with all ischemic stroke subtypes of any degree of severity [median, National Institutes of Health Stroke Scale (NIHSS), 14]. Blood pressure was carefully controlled and maintained under 185/110 mm Hg. Patients meeting all entry criteria and treated with intravenous t-PA within 3 hours were at least 30% more likely to have minimal or no disability at 3 months than patients receiving placebo. The odds ratio of a favorable outcome with treatment was 1.7 (95% CI, 1.2 to 2.6; $p = .008$) (eFig. 110.4.10). This benefit was seen in all stroke subtypes. Post-hoc analysis failed to reveal any subgroup that did not benefit from thrombolysis, although the magnitude of improvement was less in elderly patients with severe stroke (211). Risk of symptomatic brain hemorrhage within the first 36 hours was increased tenfold: 6.4% in the group given rt-PA versus 0.6% in the group receiving placebo ($p <.001$). Although half of the brain hemorrhages were fatal, no difference was seen in overall mortality between the two treatment groups. Early CT changes and NIHSS score of greater than 20 were associated with an increased risk of symptomatic brain hemorrhage (212).

***e*TABLE 110.7.1** INCLUSION AND EXCLUSION CRITERIA FOR THE NINDS INTRAVENOUS T-PA ACUTE STROKE STUDY

Inclusion criteria
Ischemic stroke within 180 min of onset, with clearly defined time of onset
Neurologic deficit measurable on the NIH stroke scale
CT scan of the brain showing no evidence of ICH
Exclusion criteria
Stroke or serious head trauma within the preceding 3 mo
Major surgery within 14 d
History of ICH
Systolic BP >185 mm Hg or diastolic BP >110 mm Hg
Aggressive treatment required to reduce BP to the specified limits
Rapidly improving or minor neurologic symptoms
Symptoms suggestive of subarachnoid hemorrhage
GI or urinary tract hemorrhage within the previous 21 d
Arterial puncture at a noncompressible site within the previous 7 d
Seizure at the onset of stroke
Oral anticoagulation therapy
Prothrombin time >15 sec
Receipt of heparin within 48 h preceding onset of stroke, with an elevated partial thromboplastin time
Platelet count <100,000 mm^3
Glucose concentration <50 mg/dL (2.7 mmol/L) or >400 mg/dL (22.2 mmol/L)
Relative contraindications: from the FDA hearings
Severe neurologic deficit, with an NIH stroke scale score >22, especially in an elderly patient
Early signs of acute stroke on CT scan: evidence of large middle cerebral arterial involvement with hypodensity, blurring of the gray-white margins, or sulcal effacement in more than one-third of the middle cerebral artery territory

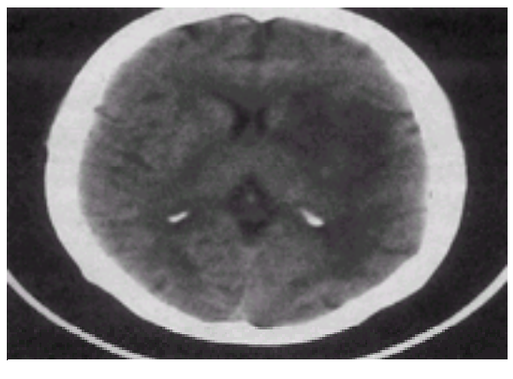
BP, blood pressure; CT, computerized tomography; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; ICH, intracranial hemorrhage; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; t-PA, tissue-type plasminogen activator.
From ref. 198.



***e*FIGURE 110.4.10** Outcomes in the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator (t-PA) acute stroke study. NIHSS, National Institutes of Health Stroke Scale.

The European Cooperative Acute Stroke Study (ECASS) was a multicenter, controlled study of the use of intravenous t-PA for acute ischemic stroke conducted at 75 centers across Europe (207). A higher dose of t-PA, 1.1 mg per kg, and a longer time window of 6 hours were used in ECASS than in NINDS. No benefit was seen in the intent-to-treat population in the primary outcome measures: the Barthel index and modified Rankin Scale score at 3 months. Parenchymal hematomas occurred in 19.8% of the group given rt-PA group and 6.5% of the group given placebo (p <.001). Mortality was also significantly worse at 90 days in the t-PA–treated patients (p = .04). Outcome was especially poor for the protocol violators who received t-PA; 42% died.

Although the intent-to-treat analysis was negative, ECASS defined a “target” population by excluding protocol violators, mainly patients with extensive early infarct signs on CT (eFig. 110.4.11). In the target population, a significant improvement was seen in the 90-day Rankin score in t-PA–treated patients (p = .035). Also, when the NINDS statistical methodology is applied to the ECASS intent-to-treat data set, a significant increase in favorable outcome is seen in rt-PA–treated patients, similar in degree to that seen in the NINDS study (OR, 1.5; 95% CI, 1.1 to 2.0; p = .008) (213).



***e*FIGURE 110.4.11** Computed tomographic scan showing early signs of infarction: hypodensity involving most of the left middle cerebral artery territory (from a stroke of 6 hours’ duration).

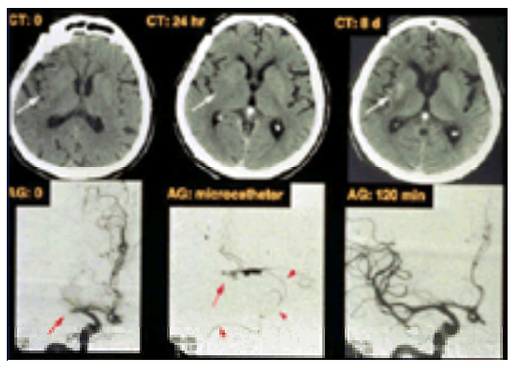
The ECASS II trial (214) again used a time window of 6 hours but reduced the intravenous t-PA dose to 0.9 mg per kg (as in the NINDS trial). Care was taken to ensure accurate CT interpretation by having all participating sites undergo CT training sessions. Blood pressure was also more tightly controlled. The parenchymal hemorrhage rate in patients receiving intravenous t-PA (11.8%) was lower than that seen in the initial trial, although it was four times higher than in placebo-treated patients (3.1%). Protocol deviations declined to 9%. The percentage of patients achieving the primary outcome measure of minimal or no disability (modified Rankin score of 0 or 1 at 90 days) was not significantly different for patients receiving t-PA (40.3%) and for controls (36.6%) (p = .277). A post-hoc analysis, however, did demonstrate a significant increase in the percentage of patients with slight to no disability (modified Rankin score of less than 2) for patients receiving t-PA.

The Alteplase Thrombolysis for Acute Noninterventional Therapy trial was designed to test whether the time window for intravenous t-PA administration could be extended to 3 to 5 hours from symptom onset (215). Inclusion and exclusion criteria for this multicenter randomized trial were very similar to those of the NINDS trial except for the time window and the exclusion of patients who had early infarct signs over one-third of the middle cerebral artery territory (a lesson from ECASS). This trial was halted prematurely after 63% of the planned patients were enrolled when an interim analysis indicated that treatment was unlikely to prove beneficial. Symptomatic ICH occurred in 7% of t-PA-treated patients versus 1.1% of those given placebo (p <.001). The Alteplase Thrombolysis for Acute Noninterventional Therapy trial, together with the ECASS I and ECASS II trials, suggest no or minimal beneficial effect of intravenous t-PA given beyond 3 hours to unselected patients with acute ischemic stroke.

The three streptokinase trials, Multicenter Acute Stroke Trial—Italy, Multicenter Acute Stroke Trial—Europe, and Australian Streptokinase Trial, were earlier trials that all used the cardiac dose of streptokinase, 1.5 million U. All three trials were prematurely halted due to the increased frequency of often fatal ICH in the streptokinase-treated patients and the lack of overall benefit.

Intraarterial Thrombolysis

The use of intraarterial thrombolysis has been reported in roughly 800 patients with acute stroke in contrast to the over 3,900 patients treated intravenously in randomized trials alone (206,214,215 and 216). Intraarterial thrombolysis requires interventional neuroradiology facilities that are not widely available and delays the time to initiation of the thrombolytic infusion. However, recanalization rates are 20% to 30% higher with local intraarterial infusion than with systemic intravenous infusion. The difference is most apparent in occlusions of larger vessels, such as the internal carotid artery or mainstem middle cerebral artery, which have larger thrombus loads. Because a lower thrombolytic dose is used, intraarterial thrombolysis may decrease systemic lytic effects. Intraarterial therapy also allows mechanical manipulation, which can speed clot lysis (eFig. 110.4.12).



***e*FIGURE 110.4.12** The initial angiogram (AG:0) reveals a proximal middle cerebral artery occlusion; there is no evidence of early infarction on the corresponding computed tomography (CT) scan. As the microcatheter is advanced into the middle cerebral artery, filling defects are appreciated. With intra-arterial thrombolysis, middle cerebral artery reperfusion is confirmed on the 2-hour AG. The follow-up CT scan at 24 hours demonstrates early infarction in the inferior striatum that undergoes asymptomatic hemorrhagic conversion by 8 days.

The Prolyse in Acute Cerebral Thromboembolism Trial (PROACT I) and PROACT II are the only randomized, controlled trials of intraarterial thrombolysis for acute ischemic stroke (216,217). The PROACT I trial was a phase I/II safety study that randomly assigned 46 patients with angiographically documented M1 or M2 segment middle cerebral artery occlusions to receive either 6 mg of recombinant prourokinase (rproUK) or placebo directly into the thrombus face within 6 hours of stroke onset. Recanalization was significantly higher in the rproUK-treated group, 57.7% versus 14.3%. Symptomatic brain hemorrhage within 24 hours occurred in 15.4% of the patients given rproUK and 7.1% of the patients receiving placebo. The brain hemorrhage rate was cut to 6.7% (similar to that with intravenous rt-PA) when the dose of concomitant heparin was reduced, but this also resulted in a lowered recanalization rate.

The follow-up phase III efficacy trial, PROACT II, used a 9-mg dose of rproUK and the reduced heparin regimen. A significant improvement was noted in the primary outcome, defined as modified Rankin score of 0 to 2 (slight or no neurologic disability) at 90 days. Symptomatic ICH occurred in 10% of patients receiving rproUK and 2% of control patients. Although the hemorrhage rate was higher than in the NINDS trial, PROACT II patients had a higher stroke severity (median NIHSS of 17 vs. 14) and a longer time before treatment (median of 5.3 vs. 1.5 hours) than in the NINDS trial. Recombinant prourokinase is not yet FDA approved.

A pilot study has explored combined intravenous and intraarterial thrombolytic therapy (218) in an attempt to optimize both time to treatment and recanalization rates. Although a combined approach resulted in more complete middle cerebral artery recanalizations, the risk of major hemorrhagic complications was increased. Further study is needed to determine the risks versus benefits of this approach.

Vertebrobasilar Thrombolysis

Because of a poor natural history (219,220), intraarterial thrombolysis has been preferred in patients with acute basilar artery occlusion. Basilar artery occlusions have a high incidence of residual atherostenosis, which often requires adjuvant therapies including angioplasty, stenting, and antithrombotic and antiplatelet therapy.

In a compilation of reported cases of vertebrobasilar thrombolysis, the mortality among patients for whom recanalization failed was 90% compared to 31% among patients achieving at least partial reperfusion. Good outcomes are strongly associated with recanalization after thrombolytic therapy. The majority of patients who successfully recanalized had outcomes of moderate disability or better, whereas less than 14% of patients whose vessels remained occluded achieved such outcomes. Recanalization depends on the location of the occlusion. Distal occlusions have higher recanalization rates than proximal occlusions. Emboli, which often lodge in the distal basilar artery, are easier to lyse than atherosclerosis-related thrombi, the usual cause of caudal basilar occlusions (221,222). Short-segment occlusions are easier to lyse than longer-segment occlusions (221). Patients who are younger have higher recanalization rates (223,224), probably due to the increased incidence of embolic occlusions seen in this setting.

The time window for thrombolysis may be longer in the posterior circulation. The presence of coma or tetraparesis for several hours portends poor prognosis, despite recanalization (220,221,224). These symptoms do not preclude survival, however, and recovery has been documented after successful recanalization in such patients (221,223,225,226).

The rates of hemorrhagic transformation after vertebrobasilar thrombolysis appear less than those after thrombolysis in the anterior circulation. The average rate of symptomatic brain hemorrhage is approximately 6.5% in such cases compared to 8.3% in cases involving the carotid circulation. The lower hemorrhagic transformation may be due to higher ischemic tolerance in the posterior circulation, improved collaterals, or an increased density of white matter tracts (227).

Risks of Hemorrhagic Transformation

Several series have found no relationship between recanalization and hemorrhage risk, although these series usually refer to early as opposed to delayed recanalization (220,226,228,229,230,231 and 232). The amount of ischemic damage is a key factor in the development of hemorrhage after thrombolysis. Early CT changes and severity of initial deficit, both indicators of the extent of ischemic damage, are currently some of the best predictors of hemorrhagic transformation (199,207,233).

Several factors have been associated with hemorrhage after thrombolysis for both stroke and MI, including thrombolytic dose (230,234), blood pressure (19,230,235,236 and 237), advanced age, and prior head injury (199,230,234,235,238,239). Age was the most important identifiable risk factor in one of the largest series investigating thrombolysis-related ICH (238). Because of the increased risk in elderly patients, an upper age limit was initially placed on patients being considered for coronary thrombolysis. These patients were found still to benefit from treatment, and the generally accepted age limit has increased. The strong relationship between advanced age and hemorrhage was demonstrated again in the NINDS and ECASS trials. At this time, no strict age cutoff exists for administering thrombolytics for stroke. Physicians need to take into account the increased risk of hemorrhage in patients aged 75 and older when making the decision to initiate thrombolysis.

Intracerebral hemorrhage after thrombolysis for stroke can occur at sites distant from the ischemic region (207,212,230). These hemorrhages may have similar pathogenesis to those occurring after coronary thrombolysis. Cerebral amyloid angiopathy has been reported as a causative factor for hemorrhages after thrombolysis for MI (240). This well-known cause of spontaneous hemorrhage in the elderly is associated with dementia of the Alzheimer's type, and elderly demented patients may have a particularly increased risk with thrombolytic therapy. Hemorrhage into an arteriovenous malformation and unsuspected ischemic infarction have also been reported as causes of postlysis ICH (240).

Thrombolysis in the Community Setting

Several phase IV series of t-PA use in experienced stroke centers have been published (241,242 and 243) that demonstrate similar rates of symptomatic ICH as seen in the NINDS trial. In the Cleveland metropolitan area, only 1.8% of all ischemic stroke patients admitted to hospitals and 10% arriving within 3 hours of symptom onset received intravenous t-PA (244). A systematic audit of t-PA use in Cleveland, performed in 1997 to 1998, found a higher symptomatic ICH rate (15.7%) (244), which suggests that the efficacy seen in clinical trials and experienced centers may not necessarily be replicated in communities. The presence of protocol deviations is

associated with higher rates of symptomatic ICH (243). Major early signs of infarction on CT portend a worse prognosis and increased hemorrhage risk; such patients probably should not receive intravenous rt-PA. These signs can be missed (207,217,245). In a study of the accuracy of interpretation of head CT scans by emergency physicians, only 43% correctly recognized a remote infarction as being old. Their ability to detect early CT changes was 0% for scans rated as “difficult” and 46% for scans rated as “intermediate” in difficulty (245).

Use of Ancrod

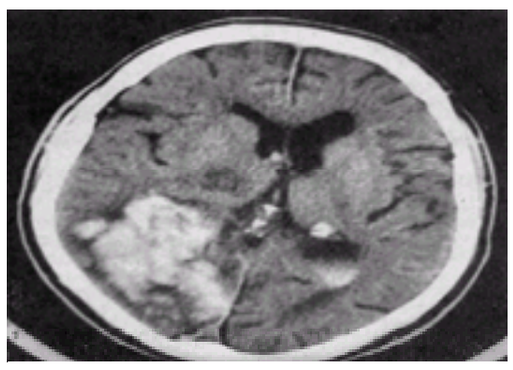
The defibrinogenating agent ancrod, derived from Malayan pit viper venom, has been studied in acute stroke (246). The positive results of the Stroke Treatment with Ancrod Trial were not replicated in a European study.

Anticoagulation and Antiplatelet Therapy

Heparin Therapy

Although many physicians believe that heparin may be useful in situations of acute ischemic stroke, data on its efficacy are insufficient or conflicting (247,248,249,250,251,252,253,254,255,256,257,258,259,260,261 and 262). Progressing stroke can be due to progression of occlusion, reembolization, reduced collateral perfusion, or reperfusion with hemorrhagic transformation (262a,263), as well as hemorrhagic transformation of the infarct, cerebral edema, or metabolic derangements (264,265 and 266). Once a fluctuating course is identified, further clinical worsening occurs in at least one-third of patients (267,268).

The risks of hemorrhagic transformation of a bland infarct (eFig. 110.4.13) and hemorrhage-related clinical worsening have been related to (a) advanced age, (b) hypertension, (c) embolic mechanism, (d) size of infarct on CT or clinical deficit, (e) early anticoagulant therapy for large infarcts, (f) use of a loading bolus, and (g) excessive prolongation of the activated partial thromboplastin time. Again, however, no consensus exists about the relative importance of these factors or their predictive value (263,269).



***e*FIGURE 110.4.13** Spontaneous hemorrhagic transformation of a cardioembolic infarction in the territory of the posterior cerebral artery.

The AHA guidelines (270) for managing acute ischemic stroke strongly recommend the prophylactic administration of heparin or low-molecular-weight heparins or heparinoids to prevent deep venous thrombosis in immobilized patients with acute stroke when no contraindication exists to the use of antithrombotic drugs. The guidelines could not offer any other recommendations for use of heparin, however, stating “until more data are available, the use of heparin remains a matter of preference of the treating physician. It should be understood that the use of heparin (or the lack of its administration) may not alter the outcome of a patient with acute ischemic stroke.”

In the first megatrial of stroke therapy and the largest study of early intervention in acute stroke, the International Stroke Trial (271) evaluated the risks and benefits of subcutaneous heparin (25,000 U per day or 10,000 U per day), with or without aspirin 300 mg per day, and placebo for 14 days in 19,436 patients with acute thrombotic or embolic stroke of less than 48 hours’ duration. Significantly fewer in-hospital deaths and recurrent strokes occurred among patients treated with aspirin. No early benefit was found for heparin, in part because the 0.9% reduction in recurrent ischemic stroke was offset by a 0.8% increase in symptomatic hemorrhagic stroke, mostly in those who received the higher heparin dosage. Taking CT scans before beginning heparin and monitoring coagulation were not required, however, which has sparked debate in the interpretation of the results. The Chinese Acute Stroke Trial studied the use of aspirin in 21,106 patients with acute ischemic stroke of less than 18 hours’ duration (272). Taken together, these megatrials found that administration of 160–300 mg of aspirin begun within 48 hours of acute ischemic stroke is significantly superior to placebo and reduces absolute early mortality by 0.5% to 0.6% and recurrent ischemic stroke by 0.5% to 1.1% while increasing the risk of symptomatic hemorrhagic stroke by a nonsignificant 0.1% to 0.2%.

With the present information, the prudent approach would be to begin aspirin therapy in all patients with acute ischemic stroke. Heparin may be used, but only in highly selected patients believed to be at risk for recurrent embolism or progressive thrombosis.

The use of heparin is contraindicated for 24 hours after delivery of intravenous t-PA for acute stroke. The risk of major hemorrhage, especially ICH, is increased when heparin is combined with thrombolytic agents, and the risk progressively increases as the activated partial thromboplastin time is prolonged beyond 80 seconds (273).

Use of Low-Molecular-Weight Heparin

Researchers have investigated the use of low-molecular-weight heparin in treating acute ischemic stroke (274). The Fraxiparine in Stroke Study (275) reported improved neurologic outcome at 6 months that was not present at 3 months in patients treated with low-molecular-weight heparin compared to those treated with placebo. Although this study has generated much interest, its methodologies have been criticized and its results must be interpreted with caution. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) evaluated the heparinoid Org 10172 in a randomized trial of the treatment of acute ischemic stroke. No overall benefit was found, and the rate of intracerebral hemorrhage in patients with more severe strokes was significant (NIHSS higher than 14). Subgroup analysis suggested a trend toward benefit for those patients with acute stroke due to large vessel atherosclerosis (276).

Glycoprotein IIb/IIIa Receptor Antagonism

The glycoprotein IIb/IIIa receptor is the final common pathway for platelet binding to fibrinogen and has demonstrated efficacy in prevention of thrombus formation in acute coronary syndromes and interventional procedures. In acute ischemic stroke, a dose-escalation study demonstrated that abciximab is safe when given as a 0.25-mg-per-kg bolus and 0.125-mg-per-kilogram-per-minute infusion (277). A phase II trial, Abciximab (ReoPro) in Acute Ischemic Stroke, is under way to test its use in treating acute ischemic stroke of less than 6 hours’ duration. The role of IIb/IIa agents in stroke prevention is less clear, as several prevention trials with oral IIb/IIIa agents have been stopped early due to increased mortality rates and lack of apparent efficacy.

Controversies and Personal Perspectives

Choice of Antithrombotic Therapy

The optimum dosage of aspirin for preventing stroke has become less controversial. Dosages from 50 mg to 325 mg have their advocates and a few trials still are using 650 mg to 1,300 mg. The FDA has approved aspirin in doses of 50 mg to 325 mg for the prevention of stroke and TIAs. A metaanalysis found no significant effect of aspirin dose on stroke risk reduction (278).

Treatment of patients who remain symptomatic on aspirin is still controversial. An increasing number of alternatives to aspirin are available. Despite the lack of definitive evidence that clopidogrel specifically reduces the risk of stroke, it has replaced ticlopidine for most cerebrovascular indications. Combinations of antiplatelet agents likely will soon supplant single-agent therapy. Although the 50-mg aspirin plus 400-mg extended-release dipyridamole formulation has significant benefit for stroke risk reduction, the lack of demonstrated cardiovascular risk reduction is problematic in patients with multisystem atherosclerosis. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial (279) suggests that the combination of clopidogrel and aspirin is safe and effective for coronary risk reduction, and this combination is being specifically studied in the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient

Ischemic Attack or Ischemic Stroke (MATCH) trial. The Warfarin Aspirin Symptomatic Intracranial Disease study and the SPAF study demonstrated that antiplatelet or antithrombotic efficacy varies depending on the cause of the patient's cerebrovascular symptoms and on other poorly understood variables. These findings suggest that, in the future, therapy may well be determined by a number of selective factors.

Carotid Revascularization and Endovascular Therapies

Clinical trials have clarified the role of endarterectomy in symptomatic patients, but recommendations for asymptomatic patients remain controversial. The authors' conservative recommendations are based on (a) the particular cerebral event to be prevented (i.e., TIAs vs. all strokes vs. severe ipsilateral strokes), (b) the patient group in which such an event is to be prevented (e.g., men vs. women), and (c) the cost at which such prevention is to be achieved, both in terms of negative outcomes and economics. The lack of standard reporting of endarterectomy complication rates among surgeons and the performance of endarterectomy based on noninvasive testing alone are causes of concern. Carotid artery stenting has been proposed as an alternative to endarterectomy in cases of postradiation therapy carotid stenosis, restenosis after endarterectomy, and stenosis in high-risk patients with severe comorbidities, as well as in symptomatic, surgically inaccessible intracranial stenoses (280,281 and 282). Despite glowing case reports, however, the poor results with carotid angioplasty in the reported randomized trials should provoke a cautious advance of the technique, improved patient selection, then proof of equivalent efficacy in controlled clinical trials before it is widely embraced (283,284).

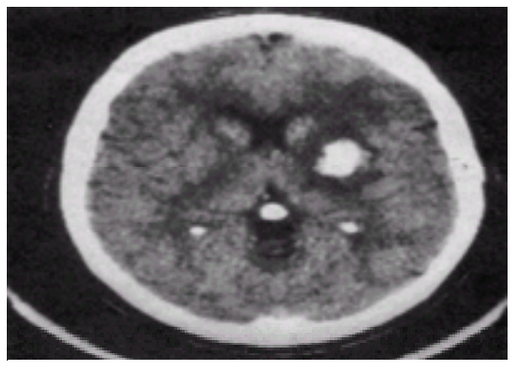
Endovascular techniques for aneurysm obliteration continue to carry substantial complication rates and uncertain longevity but are emerging as promising alternatives to aneurysm surgery ready for comparison in a clinical trial (285,286 and 287). Angioplasty is emerging as a promising treatment for vasospasm secondary to subarachnoid hemorrhage when standard medical therapy has failed (288,289,290 and 291).

CEREBRAL HEMORRHAGE: CLINICAL PROFILE

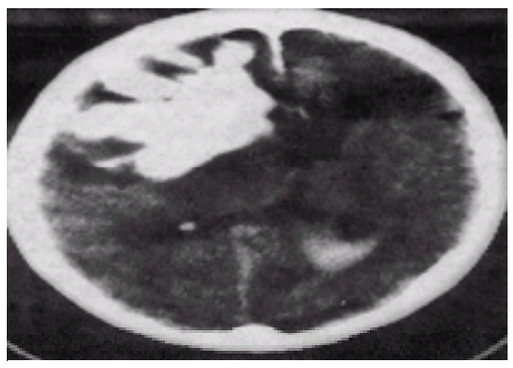
Nontraumatic ICHs are referred to as *primary* or *spontaneous* when no evidence is seen of an underlying cause, and as *secondary* when they occur because of a vascular malformation or aneurysm, coagulopathy, primary or metastatic tumor, or granuloma (292). Although time to diagnosis and overall mortality have improved with neuroimaging techniques and hypertension therapy, early mortality remains high at 30% to 40%.

The sites of bleeding are related to the cause. For primary ICH, 50% occur in the deep nuclei (putamen, 35%; thalamus, 10%; caudate nucleus, 5%), 30% occur in the lobar white matter, and 20% occur in the posterior fossa (cerebellum, 15%; brainstem, 5%) (293). Although ICHs related to coagulopathies are more frequently confluent, single, and lobar in location, tremendous variability can be found, with multiple hemorrhages and blood fluid levels within the hematomas (294,295).

Arterial hemorrhage into the brain parenchyma presents acutely with focal neurologic deficits that reflect the location and size of the hemorrhage and with generalized symptoms of headache, vomiting, and depressed consciousness that are related to an abrupt rise in ICP (296). Seizures occur in 10% to 40% of cases, most within 48 hours. Putamenal hemorrhage presents with a contralateral hemiparesis, relatively mild hemisensory loss, and forced head and eye deviation toward the side of the bleed (eFig. 110.4.14). Aphasia is associated with dominant hemisphere hemorrhage and a neglect syndrome with nondominant hemisphere involvement. Caudate nucleus hemorrhage is usually associated with memory disturbances, hemiparesis, and gaze deviation; however, small hemorrhages that decompress rapidly into the ventricular system may not produce any discernible focal neurologic deficits and can easily be mistaken for subarachnoid hemorrhages. Thalamic hemorrhage presents with prominent hemisensory loss, hemiparesis, forced downward deviation, paralysis of upgaze and convergence, retraction nystagmus, ptosis, and small unreactive pupils. Aphasia and neglect may be seen with larger hemorrhages. Hemorrhage into the frontal lobe produces hemiparesis and frontal headache (eFig. 110.4.15). Temporal hemorrhage produces superior quadrantic field defects, dysphasia or memory disturbance, and temporal or postauricular pain. Parietal hemorrhage produces hemisensory loss, behavioral disturbance, inferior quadrantic or hemianopic field defects, and temporal-parietal headache. Occipital hemorrhage produces a hemianopic visual field defect and an occipital or retroorbital headache (297). Cerebellar hemorrhage typically presents with generalized headache, nausea, and vomiting with truncal and gait ataxia that may be overlooked when violently ill patients are confined to a cart or bed. Nystagmus and appendicular ataxia may be associated findings. Decompression into the fourth ventricle is often associated with neck stiffness, but the danger of continued hemorrhage is the rapid development of brainstem compression heralded by irregular respirations, hemodynamic instability, and coma. Most brainstem hemorrhages occur within the pons. Large hemorrhages frequently manifest as locked-in syndrome, pinpoint reactive pupils, and coma. Small pontine hemorrhages may produce ataxic hemiparesis or sensorimotor stroke and more laterally located pontine hemorrhages usually manifest as abnormal extraocular movements such as ipsilateral gaze palsy, intranuclear ophthalmoplegia, and miosis.



***e*FIGURE 110.4.14** A hypertensive putamenal intracerebral hemorrhage.



***e*FIGURE 110.4.15** A massive intracerebral hemorrhage involving the frontal lobe.

Hypertension

Arterial hypertension is blamed for 70% to 90% of primary ICHs related to rupture of small perforating arteries damaged by lipohyalinosis and microaneurysm formation (298,299).

Amyloid Angiopathy

Beta-amyloid protein deposits within the media and adventitia of small meningeal and cortical vessels produce vascular fragility, which leads to lobar hemorrhages that tend to be multiple or recurrent. The most common cause of nonhypertensive hemorrhage in the elderly, amyloid angiopathy is also implicated in ICH complicating thrombolysis (300,301 and 302) (Fig. 110.5).

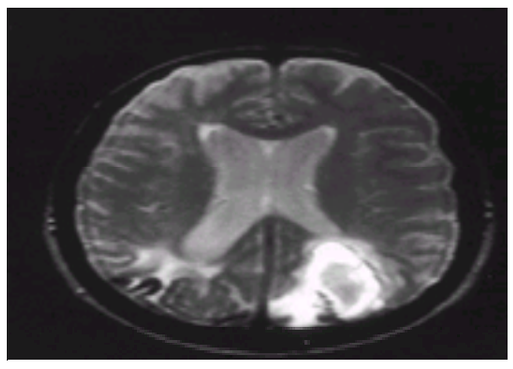


FIGURE 110.5 Residual hemosiderin in the right occipital lobe from a remote hemorrhage and subacute blood in the left occipital lobe in a patient with amyloid angiopathy.

Arteriovenous Malformation or Tumor

A history of seizures, headache, personality change, or subtle focal neurologic complaints suggests hemorrhage into a previously unrecognized vascular malformation or into a primary or metastatic brain tumor (303,304 and 305). Most ICHs are surrounded by an area of hypointensity on CT scanning that represents vasogenic edema; however, edema out of proportion to the size of the hematoma suggests hemorrhage into an underlying tumor such as glioblastoma multiforme or oligodendroglioma, or a metastatic adenocarcinoma, melanoma, choriocarcinoma, or hypernephroma. Abnormal vascular patterns on enhanced CT or MRI or areas of calcification suggest an underlying vascular malformation.

Coagulopathy-Induced Intracranial Hemorrhage

Anticoagulant-related ICHs account for 9% of all ICHs, and typically occur in patients on long-term or excessive oral anticoagulation. Other risk factors include increasing age, poorly controlled hypertension, and, probably, underlying cerebral amyloid angiopathy (306).

ICH is the most feared complication of thrombolytic therapy for acute ischemic stroke as well as a rare but serious complication of thrombolytic treatment of acute MI, peripheral vascular disease, and pulmonary embolism. Risk factors include advanced age, hypertension, low body weight, underlying hypertensive cerebrovascular disease, and amyloid angiopathy. Although hemorrhages are most commonly confluent, solitary, and lobar, the spectrum includes multiple, deep, or infratentorial hemorrhages, and associated subdural, intraventricular, and subarachnoid bleeding (235,238) (Fig. 110.6).

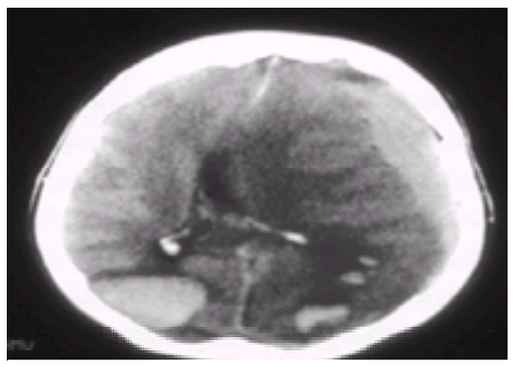


FIGURE 110.6 Complex multiple intracranial hemorrhages after coronary thrombolysis for acute myocardial infarction.

Drug-Related Intracranial Hemorrhage

Recreational drugs associated with ICH include the sympathomimetics, most commonly cocaine; amphetamines; and phencyclidine (307). Phenylpropanolamine has now been removed from appetite suppressants and cough and cold remedies, after it was associated with hemorrhagic stroke in women (308,309). An underlying structural cause, such as underlying arteriovenous malformation or aneurysm, is common, and rare cases of occlusive vasculopathy that mimics vasculitis have been described.

CEREBRAL HEMORRHAGE: MANAGEMENT PRINCIPLES

Stabilization of the Patient

The airway may be compromised by bulbar weakness in the setting of depressed consciousness. Acute hypertension is common in acute stroke but particularly dangerous in patients with intracranial bleeding and warrants aggressive treatment to limit hemorrhage extension (310). Target blood pressures for elderly or hypertensive patients (systolic pressure of 150 mm Hg) are more liberal than those for young or nonhypertensive patients (systolic pressure of less than 120 mm Hg) to limit the risk of cerebral hypoperfusion, which may occur with overzealous management in patients with impaired cerebral autoregulation (307). In patients with increased ICP, however, blood pressure management must be individualized to maintain cerebral perfusion pressure at levels above 45 to 50 mm Hg (311).

Blood should be drawn immediately for determination of coagulation parameters, including platelet count, prothrombin time, partial thromboplastin time, and bleeding time, and defects should be corrected rapidly as hemorrhage expansion can continue over the first 8 to 24 hours (312). If a focal neurologic deficit with altered mental status occurs within 24 hours of thrombolytic therapy, the event should be presumed to be an ICH until proven otherwise. Immediately stopping all thrombolytic, antithrombotic, and antiplatelet therapy while stabilizing the patient and obtaining laboratory coagulation testing should be the first consideration. Reversal of the coagulation disturbance should begin while emergency CT scanning is awaited to evaluate the neurologic event.

Medical complications are related to the severity of the hemorrhage and account for part of the morbidity. Cardiac arrhythmias, usually supraventricular tachyarrhythmias, and subendocardial ischemia may complicate ICH, especially in patients with subarachnoid bleeding (177,178 and 179). Continuous ECG monitoring and serial cardiac enzyme testing should be considered. Invasive cardiac monitoring with a Swan-Ganz catheter may be necessary if management of blood pressure and fluids is complicated by cardiac decompensation (313). If a seizure is suspected or documented, the patient should be rapidly loaded with anticonvulsants, although some clinicians recommend prophylactic anticonvulsant therapy in the acute period. Increased ICP may require more intensive monitoring by a transducer placed in either the subdural or epidural space, or, if obstructive hydrocephalus is present, by intraventricular catheter, which is diagnostic as well as therapeutic (314,315 and 316). The benefit of corticosteroid therapy in ICH has never been confirmed, and their use remains controversial (317,318).

Neuroimaging

Intracerebral bleeding should be confirmed by a noncontrast CT scan of the brain, which provides a highly accurate determination of hematoma size and location as well as other complicating factors, such as shift of intracranial structures relating to herniation and obstructive hydrocephalus (238,312). MRI is sensitive to small amounts of heme and may indicate a multifocal vasculopathy (amyloid, cavernous malformations) or underlying tumor. Lumbar puncture is rarely useful for diagnosis and is potentially hazardous in the presence of an intracranial mass lesion. Cerebral angiography is indicated when a vascular malformation, aneurysm, or vasculitis is suspected.

Surgical Evacuation for Intracranial Hemorrhage

Surgical evacuation for ICH should be considered before neurologic deterioration leads to coma and irreversible brainstem damage, although patient selection remains highly controversial. Symptomatic cerebellar ICHs are usually evacuated because of the unpredictable course and risk of rapid and progressive brainstem compression, producing respiratory arrest and death. Accessible subcortical ICHs, particularly those involving the nondominant hemisphere or noneloquent areas of the brain, are also amenable to surgical evacuation, and such evacuation should be considered in patients who present with relatively preserved neurologic function that subsequently begin to deteriorate (319). Surgical therapy does not improve outcome with ICHs affecting basal ganglia and the brainstem, and advanced age, large hematoma volume, and a depressed level of consciousness on evaluation are consistent predictors of poor neurologic outcome (320,321).

SUBARACHNOID HEMORRHAGE: CLINICAL PROFILE

Despite major advances in neurosurgical techniques over the past two decades, the acute mortality of approximately 10% continues to pose the major obstacle to treatment of subarachnoid hemorrhage. An additional 50% of patients die within 3 months, and of those who survive, more than half are left with a major neurologic or neurocognitive disability and a diminished quality of life (322,323).

The most common symptom of subarachnoid hemorrhage is a headache of noteworthy severity, ranging from the thunderclap prodromal headache with a minor leak to the sudden, severe, often exertional headache present in 45% of patients (324,325 and 326). Syncope at onset results from global cerebral hypoperfusion when the rupture causes a precipitous spike in ICP that approaches the mean arterial pressure and thus reduces cerebral perfusion pressure. Clinical grading of the patient based on headache and mental status is important in predicting prognosis and chance of recovery. The most commonly used scale is the Hunt and Hess classification scheme (*e*Table 110.7.2).

***e*TABLE 110.7.2** HUNT AND HESS CLASSIFICATION OF SUBARACHNOID HEMORRHAGE

Grade I:	Asymptomatic or minimal headache and slight nuchal rigidity
Grade II:	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
Grade III:	Drowsiness, confusion, or mild focal deficit
Grade IV:	Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity, and vegetative disturbance
Grade V:	Deep coma, decerebrate rigidity, moribund appearance

A CT scan of the brain without contrast performed within 24 hours shows positive findings in 92% but by 48 hours bears only a 75% chance of demonstrating cisternal or subarachnoid blood (Fig. 110.7). If no hemorrhage is seen, a lumbar puncture is recommended to establish the diagnosis. Selective intraarterial cerebral angiography remains the standard for diagnosis and planning of a therapeutic surgical or endovascular approach (327,328).

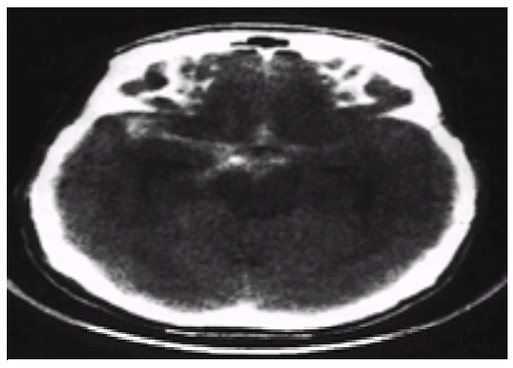
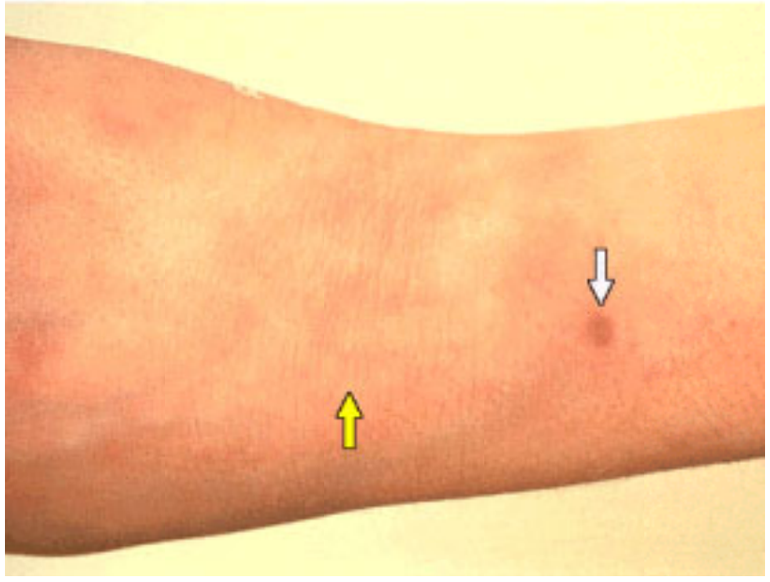


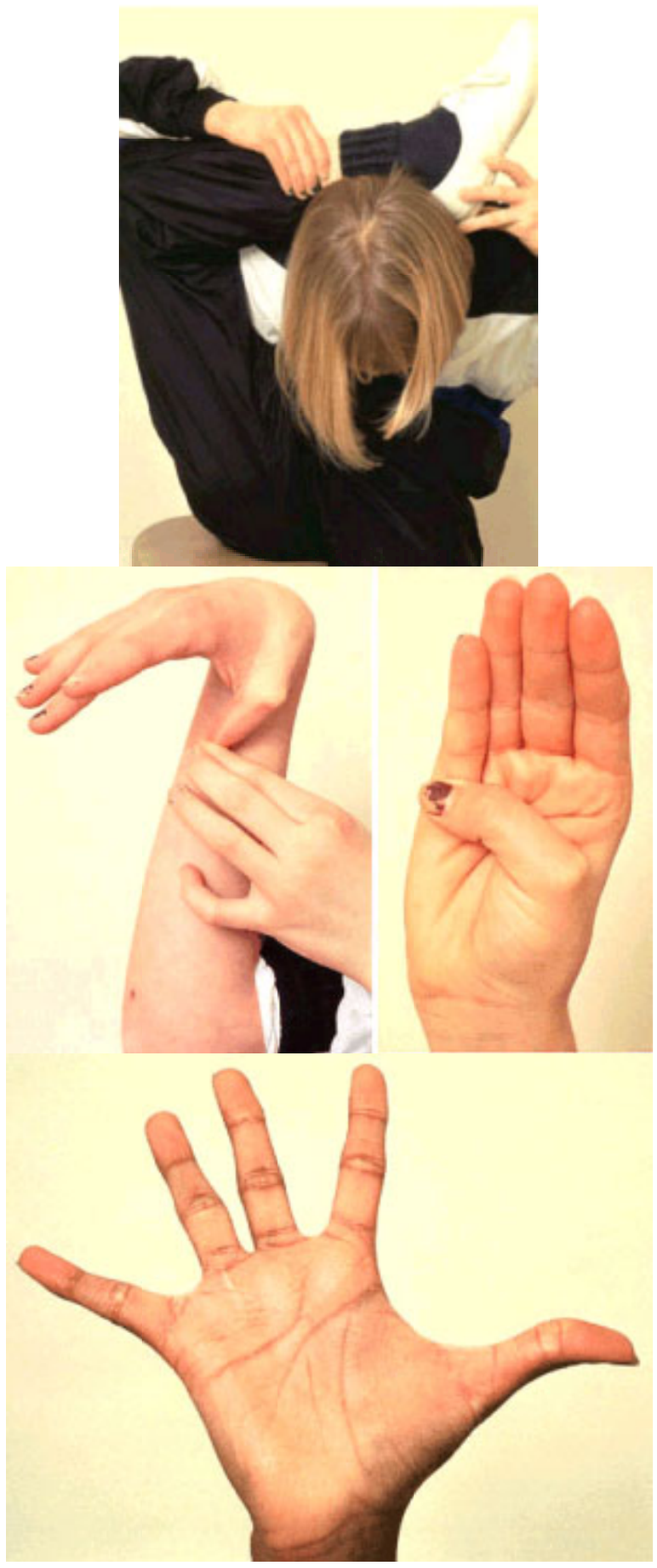
FIGURE 110.7 Computed tomographic scan showing cisternal blood in acute subarachnoid hemorrhage.

Aneurysms

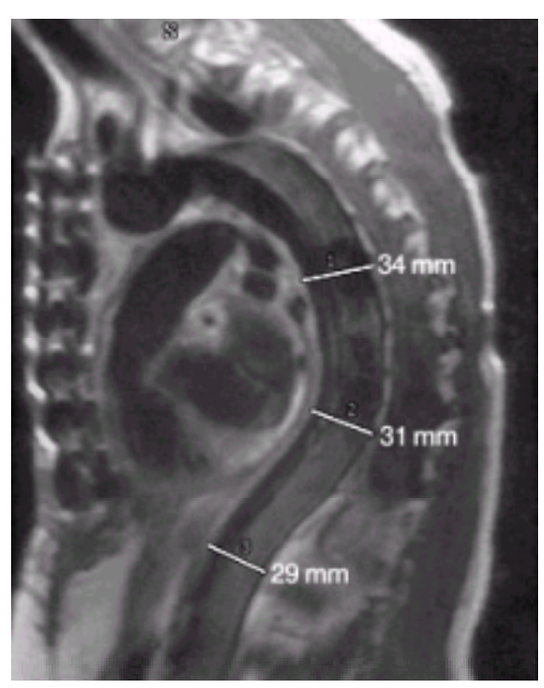
Most intracranial aneurysms are *saccular* and are believed to be outpouchings of the arterial wall as a result of a congenital defect in the muscular layer, a degenerative process in the internal elastic membrane, or a combination of both processes. They most frequently occur at bifurcations, branch and bending points within the arterial tree, with the majority at the base of the brain on the circle of Willis. They are associated with polycystic kidney disease, coarctation of the aorta, Ehlers-Danlos syndrome, neurofibromatosis, fibromuscular dysplasia, and arteriovenous malformations (329,330).



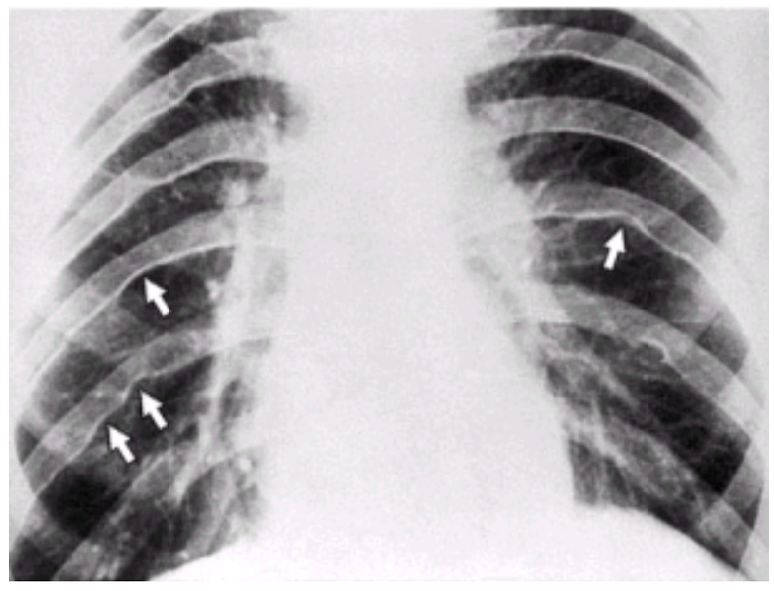
Skin changes of Ehlers-Danlos syndrome. There is thin, velvety appearance of the skin (*yellow arrow*), as well as easy bruisability (*white arrow*).



Ehlers-Danlos syndrome. There is severe joint laxity and hypermobility that may produce joint dislocations (A–C).

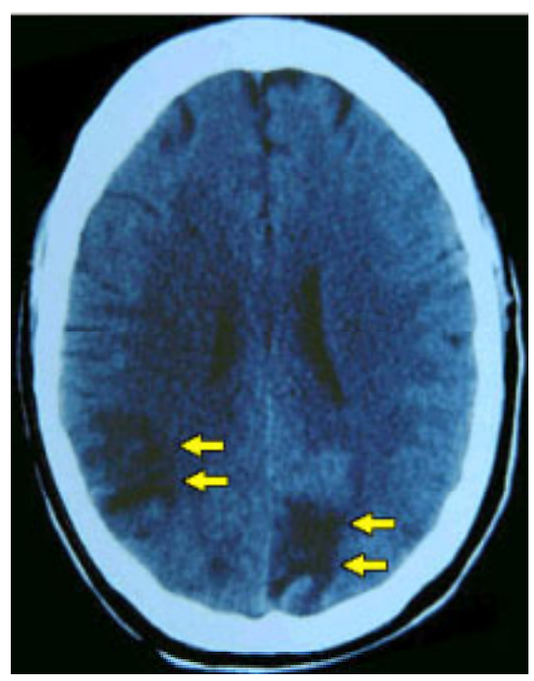


Magnetic resonance scan of the thoracic aorta in Marfan syndrome. There is dilation of the descending aorta with an average diameter of approximately 3 cm.

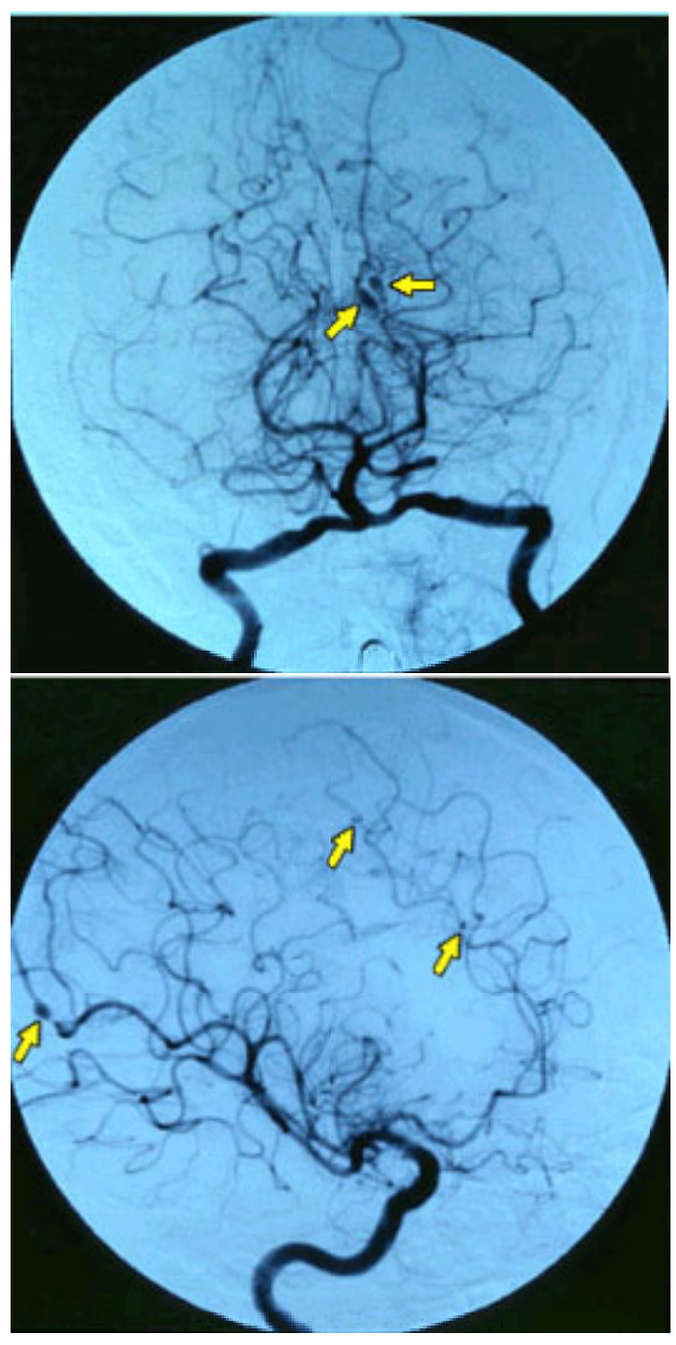


Chest x-ray in coarctation of the aorta. There is prominent rib notching (*white arrows*).

Mycotic aneurysms are a complication of subacute bacterial endocarditis in which an infective embolus produces a local arteritis and septic degeneration of the vessel wall. The true incidence of mycotic aneurysms is unknown and would require cerebral angiography in a large series of patients with subacute bacterial endocarditis to ascertain. The location of such aneurysms at peripheral cerebral branch sites and their small size defy adequate visualization by any currently available noninvasive neuroimaging technique, including MRA (327). The neurologic profile most suggestive of a possible mycotic aneurysm is a focal neurologic deficit consistent with cerebral embolism. In patients who have successfully completed their full course of appropriate antibiotic therapy, the risk for late mycotic aneurysm rupture is estimated to be less than 3% (136,137).



Ruptures mycotic aneurysms. Several areas of hypodensity representing ruptured mycotic aneurysms as a result of endocarditis (*arrows*).



Mycotic aneurysms from infective endocarditis. Localized aneurysmal dilatation of cerebral vessels as a result of endocarditis (*arrows*, A,B).

Atherosclerotic aneurysms are tortuous vessels that are most frequently located in the vertebrobasilar system; however, they can affect the major intracranial internal carotid branches. Symptoms are produced by mass effect, ischemia from branch artery occlusions, and obstructive hydrocephalus but rarely from rupture (Fig. 110.8).

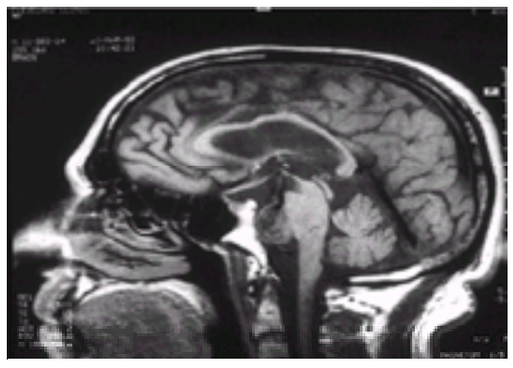
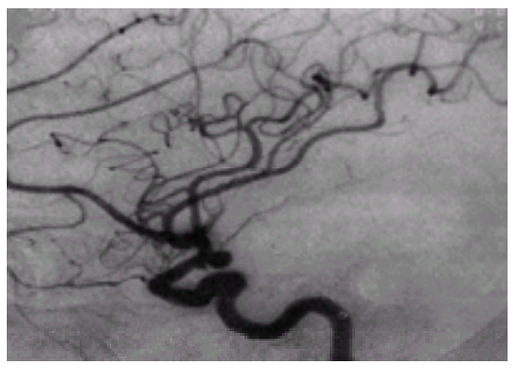


FIGURE 110.8 Magnetic resonance image demonstrating a large fusiform basilar arterial aneurysm producing brainstem compression and transient ischemic attacks.

Unruptured Saccular Intracranial Aneurysms

The risk of rupture of incidental or symptomatic unruptured aneurysms is 1% to 2% per year (331,332 and 333). Factors that increase this risk include aneurysm size, multiplicity, location, and the patient's age. The median diameter of a ruptured aneurysm is 7 mm, with most being 5 to 10 mm. This translates into the common practice of considering surgery for any aneurysm larger than 5 mm (332,334,335 and 336) (eFig. 110.8.1).



***e*FIGURE 110.8.1** Lateral carotid arteriogram showing a posterior communicating arterial aneurysm.

Aneurysms rarely present with symptoms other than rupture with subarachnoid hemorrhage, but when they do, they can pose a diagnostic challenge. Enlargement and thrombosis can produce a mass effect, causing headache and focal neurologic signs appropriate to the structures involved. The most recognized syndromes include (a) a painful third nerve palsy with ptosis, mydriasis, and loss of pupillary light reflex with an expanding aneurysm at the origin of the posterior communicating artery; (b) a painful unilateral visual loss with diplopia due to an ophthalmic artery aneurysm; or (c) vertigo, brainstem signs, and hydrocephalus with an atherosclerotic fusiform vertebrobasilar aneurysm. Giant aneurysms also on rare occasions may embolize intraaneurysmal thrombotic material and may present as TIA or stroke.

SUBARACHNOID HEMORRHAGE: MANAGEMENT PRINCIPLES

Subarachnoid hemorrhage carries the highest mortality of all stroke and warrants highly specialized management (337,338 and 339). The introduction of microsurgical techniques has substantially reduced operative morbidity and mortality, but nonoperative complications of rebleeding, vasospasm, and hydrocephalus continue to contribute to the poor outcome in many patients (339,340,341 and 342).

Rebleeding occurs in 30% of patients, is highest in the first 3 weeks, and carries a much higher morbidity and mortality risk (343). Transient episodes of hypertension have often been observed to precede and to perhaps precipitate rebleeding, but antihypertensive treatment per se has not been shown to improve outcome (344). Nevertheless, precautions for patients with aneurysm include a combination of bed rest, analgesia, stool softeners, dim lighting, and strict visitor limitations; in short, avoidance of any stimulus that may cause agitation or excitement and result in a rise in blood pressure. The optimal blood pressure range in the post–subarachnoid hemorrhage period remains undefined but generally is within approximately 5% of the premorbid range.

Vasospasm

Vasospasm is clinically present in approximately 30% of patients, although angiographic evidence is present in approximately 70% (345,346). Symptoms of a focal neurologic deficit with a depression of consciousness usually begin between the third and fifth days after subarachnoid hemorrhage and peak between the fifth and fourteenth days, resolving over a period of weeks. Transcranial Doppler ultrasonography is useful in diagnosis and helps guide hypervolemic, hypertensive therapy (347,348). Hyponatremia often parallels the time course of vasospasm, is due to natriuresis or cerebral salt wasting and volume contraction mediated by atrial natriuretic factor, and is managed with intravascular administration of isotonic fluids (349,350). Oral nimodipine, 60 mg every 4 hours started within 4 days of the hemorrhage and continuing for 21 days, has been shown to reduce poor outcome due to vasospasm for patients of good neurologic condition after the ictus (i.e., Hunt and Hess grades I, II, and III) (351,352,353,354,355 and 356).

Medical Comorbidities

Subarachnoid hemorrhage is often accompanied by a massive rise in circulating levels of catecholamines that results in subendocardial ischemia, infarction, and arrhythmias. Premature ventricular complexes, bradyrhythmias, or supraventricular tachycardias occur in up to 90% of patients; however, potentially malignant arrhythmias such as atrioventricular dissociation, idioventricular arrhythmias, and ventricular tachycardia occur in 20% to 40% of patients. Arrhythmias are most frequent in the first 48 hours after subarachnoid hemorrhage, are often associated with QTc prolongation or hypokalemia, and may lead to sudden death.

Common pulmonary complications of subarachnoid hemorrhage include aspiration pneumonia and pulmonary edema. Pulmonary edema after subarachnoid hemorrhage may be due to elevated cardiac filling pressures or may be neurogenic, to which pulmonary capillary tight junction disruption is postulated as an important contributor.

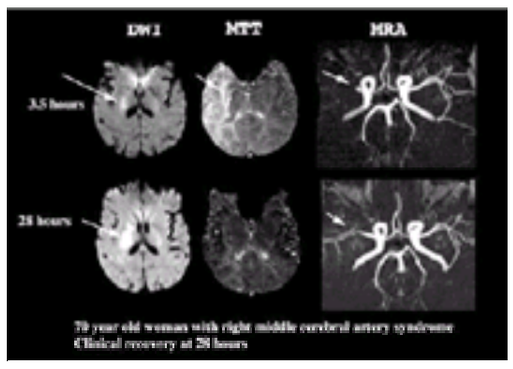
Hydrocephalus complicates 20% of cases and when acute and untreated, carries a grave prognosis. Hydrocephalus more frequently develops insidiously, resulting in impaired consciousness, lower limb spasticity, and increased ICP. Ventricular drainage is recommended for symptomatic patients; however, catheterization carries a risk for rebleeding and infection, and catheter patency may be difficult to maintain (357,358 and 358a).

Seizure-like events are more common at the ictus but may also occur in a delayed fashion and carry a potential risk for rebleeding. Use of prophylactic anticonvulsants in the early posthemorrhage period is recommended; however, long-term continuation is not necessary if the patient has been seizure free (359).

FUTURE DIRECTIONS

Advances in neuroimaging may refine patient selection for thrombolysis and other treatment strategies. Currently, a noncontrast CT scan is performed to exclude a hemorrhage or mass that can mimic stroke, as ischemic changes of sulcal effacement and blurring of the gray-white distinction are rarely seen before 3 hours after ictus. Diffusion-weighted MRI detects the random movements of water protons, which rapidly become restricted in ischemic tissue. Areas destined for infarction can be demonstrated on diffusion-weighted imaging sequences within several hours, expand to reflect ischemic edema, and then contract to correlate closely with T2-weighted images of the ultimate infarct volume. Perfusion MRI is a qualitative map of brain perfusion generated after a bolus of contrast. The demonstration of the penumbra of potentially salvageable tissue represented by the difference between the perfusion imaging and diffusion-weighted imaging regions is believed to have implications for

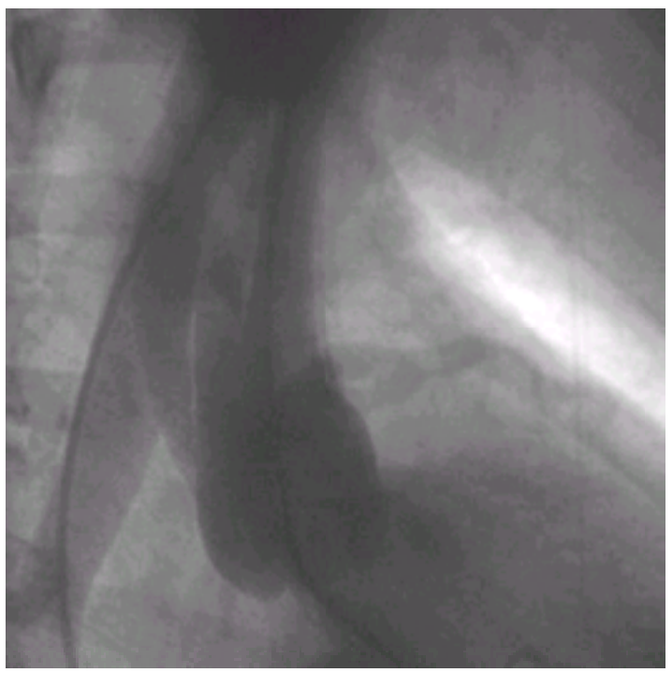
determining the true window of opportunity for reperfusion therapy (360,361). The addition of MRA of the extracranial and intracranial circulation would rapidly complete the assessment of vascular anatomy and collateral supply (*e*Fig. 110.8.2).



***e*FIGURE 110.8.2** Diffusion-weighted magnetic resonance image (DWI) depicting a small area in the basal ganglia of completed infarction with perfusion imaging sequences indicating a large area of middle cerebral artery distribution cortex at risk for infarction in the setting of a middle cerebral artery occlusion. Arterial recanalization with reperfusion of the middle cerebral artery occlusion reverses the perfusion abnormality. MRA, magnetic resonance angiogram; MTT, mean transit time.

Reperfusion will remain a core treatment strategy in acute ischemic stroke. Thrombolysis is in its infancy for treating cerebrovascular disease. New thrombolytic agents and delivery techniques that will improve reperfusion rates while limiting the risk of serious cerebral hemorrhage may well emerge. Thrombolytic agents with shorter half-lives and even more clot specificity are under development. Adjunctive agents such as platelet IIb/IIIa receptor antibodies may enhance recanalization; however, the risk of intracerebral hemorrhage limits their use to more than the coronary circulation.

Endovascular therapies provide many therapeutic opportunities. Advances in catheter design may permit recanalization of large vessel occlusions previously resistant even to direct intraarterial thrombolysis. A variety of mechanical strategies for clot removal in patients with acute stroke are under investigation. These range from lasers to high-pressure saline jet technology to simple snare devices. The theoretical advantages of these approaches include more rapid and complete clot removal and minimization of the use of thrombolytic agents.



A 77-year-old male patient presented to the emergency department with severe chest pain and hypertension. Aortogram revealed type A aortic dissection.

Numerous neuroprotective agents, many with dramatic effects in animal models, have made their way into clinical trials and onto a long list of efficacy failures for human stroke (362,363,364,365,366,367,368,369,370,371,372 and 373). Moderate to profound hypothermia, in use for decades as a means of protecting tissue during cardiovascular and neurovascular procedures, has been shown to decrease infarct volume and extend the time required for tissue damage to occur (therapeutic window). Complications include cardiac arrhythmias, pneumonia, and sepsis, and in patients with large hemispheric infarcts, the cerebral edema may just be delayed only to recur during rewarming. Two clinical trials are addressing hypothermia for cerebral protection. The Cooling for Acute Ischemic Brain Damage (COOL AID) trial focuses on moderate hypothermia in acute ischemic stroke of less than 12 hours' duration using an intravenous heat-exchange catheter that obviates the need for sedation, paralysis, and intubation (374). Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) uses intraoperative surface cooling in patients with aneurysmal subarachnoid hemorrhage.

THE FUTURE

A better understanding of the risk factors specific for each stroke subtype will advance preventive strategies. Endovascular interventions will evolve and mature, combined with thrombolysis for acute ischemic stroke, as an alternative to surgery for aneurysms and vascular malformations and in the treatment of inaccessible occlusive disease. Stroke health care delivery systems will continue to evolve to allow better patient access to care.

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DISEASE OF PERIPHERAL VESSELS

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OVERVIEW

Although their primary focus remains in the diagnosis and treatment of cardiac disorders, many cardiovascular specialists are no longer limiting themselves to treatment of coronary artery disease (CAD) but instead are adopting a "global vascular management" strategy for their patients. This approach has been promulgated by institutions setting up divisions of vascular medicine under two premises. First, the peripheral vasculature makes up the largest single "organ system" in the body—one that is complex and fascinating in its biology and dynamic in its function. The peripheral vessels hold many biologic secrets that, when unlocked, will open doors for new therapies for both noncoronary and coronary diseases. Second, both patients and medical science could benefit from the perspective and knowledge gained from a medical (as opposed to surgical) subspecialty whose sole focus encompasses the evaluation and management of vascular disease.

Cardiovascular specialists can no longer realistically limit their focus to the coronary vasculature. The coronary and noncoronary circulations are interdependent; they commonly coexist and may each cause disabling or life-threatening symptoms. Furthermore, they are affected by the same disease processes and often require similar treatment modalities. The approaches to treatment of one often depend on the other. For example, patients requiring vascular surgery generally have higher cardiac risk than those undergoing nonvascular surgery because of the increased prevalence of CAD in this group. Likewise, many patients under treatment for CAD are disabled by symptomatic peripheral arterial disease (PAD); post–myocardial infarction patients with claudication may not be able to be appropriately rehabilitated without treatment of their PAD.

Toward that end, the ensuing chapter is designed to provide a brief overview of the major disease states that occur in the peripheral arteries, as well as a synopsis of current treatment for each condition. The principal focus of the chapter, however, is on the management of *atherosclerotic* PAD. By far the most common disorder of lower extremities encountered by North American physicians, it afflicts more than 20% of men and women combined older than the age of 75 years (1). An aging population guarantees that the prevalence will continue to increase. Significant technological advances, especially in percutaneous therapies, over the past 10 years now enable safer and more efficacious treatment of atherosclerotic PAD. Knowledge about the range of therapeutic options available, and in which patients to apply them, is critical to the optimal management of these patients.

DISEASE STATES OF THE PERIPHERAL ARTERIES

Atherosclerosis

PAD, or arteriosclerosis obliterans, is the most common cause of symptomatic obstruction in the peripheral arterial tree. The pathophysiologic basis of PAD is identical to that of coronary artery atherosclerosis; the same risk factors are also associated, including tobacco smoking, diabetes mellitus, hypertension, hyperlipidemia, a positive family history, and advanced age. The estimated prevalence of PAD in people age 65 years or older is 20%; this estimate may, in fact, be conservative due to the presence of a large number of patients who have either asymptomatic disease or in whom the symptoms are not recognized as being due to arterial obstruction. The latter group, those in whom PVD symptoms are overlooked or falsely attributed to other etiologies (deconditioning, arthritis), make up an important subset who, if appropriately diagnosed, might benefit from available treatments.

The clinical presentation of patients with PAD is highly variable and depends on the involved vascular territory. Lower extremity symptoms range from mild discomfort during intense exercise to the presence of constant rest discomfort, painful ulceration, or frank gangrene. Claudication is described variably as pain, tightness, aching, soreness, hardness, or heaviness that occurs in the calf, buttocks, hips, or arch of the foot during ambulation and resolves with rest, similar to the pattern of exertional angina in CAD. Although intermittent claudication can be mild and nondisabling, it can become severely disabling. Pain at rest occurs if the impairment of blood flow is severe enough that oxygen and nutrient supply falls below the resting requirements of the distal tissue. Where the level of tissue ischemia is severe, cell injury and

death will occur, leading to tissue breakdown, clinically manifested as ulceration or gangrene. Neither of these is likely to resolve without restoration of nutrient (usually pulsatile) flow to the affected extremity. Similar symptoms occur in the hand or forearm of patients with severe atherosclerosis of vessels supplying the upper extremities.

As is the case in CAD, symptoms related to PAD rarely occur until the atherosclerotic process has narrowed the vessel diameter by at least 50%. However, the presence of one or more lesions with 50% or more narrowing does not imply that the patient will be symptomatic. Indeed, a large number of patients with PAD remain asymptomatic, even in the presence of severe and extensive disease. Patients with complete occlusion of the major blood supply to a limb or organ may have no symptoms if an ample collateral supply is present. Rutherford et al., by defining the signs and symptoms according to their intensity and combining these with noninvasive data, developed a series of categories to describe the severity of chronic limb ischemia (Table 111.1) (2). Such standardization has greatly enhanced the ability of investigators to perform meaningful comparative analyses of treatment strategies. Furthermore, it has facilitated decision making for clinicians regarding optimal therapy for a given level of limb ischemia.

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic	Normal treadmill/stress test
	1	Mild claudication	Completes treadmill exercise,[a] ankle pressure after exercise <50 mm Hg but >25 mm Hg less than brachial
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete treadmill exercise and ankle pressure after exercise <50 mm Hg
II	4	Ischemic rest pain	Resting ankle pressure <40 mm Hg; ankle or metatarsal pulse volume recording flat or barely pulsatile; toe pressure <40 mm Hg
	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure <40 mm Hg; flat or barely pulsatile ankle or metatarsal pulse volume recording; toe pressure <30 mm Hg
III	6	Major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5

[a] 5 minutes at 2 mph on a 12% incline

Adapted from Rutherford RB, Flanigan DP, Gupchis RV. Suggested standards for reports dealing with lower extremity ischemia. J Vasc Surg 1986;4:80–94.

TABLE 111.1 CLINICAL CATEGORIES OF CHRONIC LIMB ISCHEMIA

Natural History of Peripheral Arterial Disease

An important consideration in any treatment strategy of patients with PAD is the natural history of both symptomatic and asymptomatic disease. The uninterrupted clinical course of lower extremity arterial disease is usually one of slow progression of symptoms over time (3). Approximately 70% of patients will remain unchanged or even less symptomatic after 5 to 10 years; less than 30% will progress to require intervention; and less than 10% will need amputation. Patients with diabetes mellitus, who comprise a large percentage of patients with PAD, are a unique subgroup in terms of prognosis and natural history of the disease. Diabetics have a higher likelihood of developing critical limb ischemia; indeed, their amputation rate is seven times greater than in nondiabetic patients with PAD.

Therapy for Atherosclerotic Peripheral Arterial Disease

The goals of therapy are to maintain functional status, reduce or eliminate ischemic symptoms, and prevent progression of disease. Insofar as PAD is a marker for systemic atherosclerosis, a secondary goal is to reduce the incidence of coronary and cerebrovascular events. Therapeutic options include conservative measures, percutaneous intervention, and surgery. With respect to noninvasive measures, risk factor modification (cessation of smoking is paramount) should thus be an important part of any treatment plan and may reduce progression of disease. Because limb ischemia may stimulate collateral growth, formal exercise training in a supervised setting may increase claudication-free walking distance by approximately twofold in patients with mild or moderate symptoms. Those with severe claudication, rest pain, or tissue loss (e.g., Rutherford category of 3 or more) are less likely to benefit from exercise.

Patients with PAD should receive drug treatment for coexisting disease (e.g., hypertension), risk factor modification (e.g., hyperlipidemia), and prophylaxis against thrombotic events associated with atherosclerosis (e.g., antiplatelet drugs), predominantly to reduce associated cardiac and cerebrovascular morbidity and mortality. No pharmacologic agent has proved efficacious enough to produce significant improvement in symptoms of PAD to gain widespread acceptance or use. Two established drugs, however, have gained U.S. Food and Drug Administration approval. Pentoxifylline (Trental), a rheolytic agent, has shown up to a 21% increase over placebo in walking distance; patients most likely to benefit were those with symptoms for longer than 1 year and an ankle-brachial index of less than 0.80. However, most investigators agree that Trental is of little overall value in the treatment of symptomatic PAD (4). Cilostazol (Pletal), a phosphodiesterase III inhibitor with vasodilator and antiplatelet activity, more recently gained approval and has demonstrated benefit in some patients. In randomized trials, cilostazol led to a 47% increase in walking distance compared with placebo (13%) and improved quality of life (5). Prostaglandins have been used in several studies of patients with critical limb ischemia with some success (6). A number of vasodilator (e.g., calcium channel blockers, alpha-adrenergic antagonists), antiplatelet (e.g., aspirin, ticlopidine, clopidogrel) (7), and metabolic agents (L-carnitine, L-arginine) (8) have been studied, but none has been conclusively demonstrated to improve symptoms related to PAD.

Another novel form of “medical” or “noninvasive” therapy currently under investigation in early phase I and II clinical trials is the use of growth factors to treat critical limb ischemia (9,10). The premise behind this treatment is that the obstructed main vessel may not require recanalization if flow can be augmented by the development of more collateral vessels, a process termed *therapeutic angiogenesis*. Angiogenic cytokines (e.g., vascular endothelial growth factor and basic fibroblast growth factor) can be administered as recombinant protein or as gene encoding for that protein, either by direct intravascular infusion or site-specific intramuscular injection.

Invasive therapy, including percutaneous revascularization and surgery, is the most effective therapy for immediate relief of symptoms related to PAD. Major advances in recent years have facilitated less invasive treatment modalities. The latter two-thirds of this chapter are devoted to the implementation of these new techniques and their results vis-à-vis surgical therapy.

Atheroembolism

Atheroembolism is a particularly malignant consequence of advanced atherosclerotic PAD. It is caused by embolization of micro- or macroscopic friable or ulcerated atherosclerotic plaque debris, liberated from the proximal arterial tree, either spontaneously or after provocation by direct surgical or catheter manipulation. Atheroembolism may result in ischemia or infarction of the tissue supplied by the small arteries and capillaries to which the debris travels. Atheroembolism to the lower extremities may be focal, in which one or more toes are involved (causing the so-called blue toe syndrome) or diffuse, causing bilateral livedo reticularis, cyanosis, and pain; ischemia may progress to painful ulceration and gangrene, depending on the embolic load and the status of the underlying vasculature. Involvement of the renovascular bed may result in deterioration of renal function.

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene (*yellow arrow*), as well as localized skin

necrosis and livedo reticularis (*white arrows*).

Atheroemboli. Embolization of cholesterol, fibrin, and platelet debris results in digital necrosis and gangrene, as well as localized skin necrosis and livedo reticularis (*white arrows*).

Atheroemboli. Digital necrosis resulting from severe atheroemboli.

The treatment strategy for atheroembolism includes conservative local measures for the affected tissue and, importantly, appropriate steps to avoid future embolic events. These steps might include antiplatelet therapy and avoidance of future surgical and catheter manipulation near the presumed source of embolization, such as the abdominal aorta. Occasionally, especially in the case of recurrent atheroembolism, exclusion of the embolic source, either via percutaneous or surgical means, is recommended.

Other Disease States

Several other disease states involve the peripheral vessels; these include the vasculitic syndromes, thromboangiitis obliterans (TAO; Buerger's disease), vasospastic disorders, and the hypercoagulable states.

Vasculitis

The vasculitic syndromes (11) have in common the presence of vessel wall inflammation, but otherwise they are quite heterogeneous in their pathophysiology, clinical presentation, and consequences. The systemic necrotizing vasculitides (polyarteritis nodosa, Wegener's granulomatosis, essential cryoglobulinemia) and the hypersensitivity vasculitides can occasionally cause symptoms of claudication but more often are associated with cutaneous manifestations or signs and symptoms of organ involvement. In contrast, patients with Takayasu's disease not infrequently present during the chronic phase with upper and/or lower extremity claudication or with hypertension related to abdominal aortic coarctation and renal artery stenosis (RAS). Interventional treatment may sometimes alleviate the obstruction in these cases.

Thromboangiitis Obliterans (Buerger's Disease)

TAO is an aggressive form of inflammatory vasculitis, affecting predominantly the small- and medium-sized arteries and veins of the upper and lower extremities; it occurs in young (younger than 50 years old) predominantly male smokers and is associated with inflammatory thrombosis of extremity vessels (12). The etiology of TAO is poorly understood, but tobacco smoking clearly plays a central causative role. Patients typically present with an ischemic ulceration of one or more digits, which may progress to gangrene. They may have associated arch, foot, or calf claudication; cold sensitivity; and/or episodic superficial thrombophlebitis. The disease almost always involves two or more limbs; an abnormal Allen's test is present in two-thirds of patients. Proximal vessels in patients with TAO are normal, but angiography often demonstrates occlusion of small distal branches.

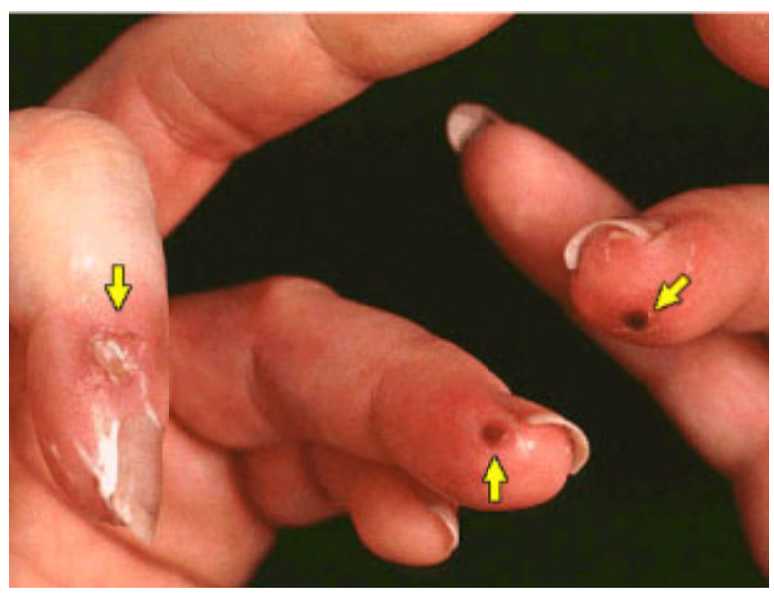
Buerger's disease (arteriosclerosis obliterans). Ulcers and gangrene from atherosclerosis involving the lower-extremity vasculature.

Buerger's disease (thromboangiitis obliterans). This inflammatory occlusive vascular disorder of small and medium-sized arteries and veins results in digital gangrene (*yellow arrows*), as well as skin ulceration (*white arrows*).

Several other diseases can mimic TAO, so excluding these other entities in the differential diagnosis is essential. Therapy for TAO consists primarily of (a) absolute cessation of smoking, (b) appropriate treatment of ulcers, including amputation if needed, and (c) palliation of symptoms. Judicious use of vasodilators, aspirin, anticoagulants, prostanoids, and sympathectomy may be appropriate in certain cases. Invasive treatment, both surgical and percutaneous, has little or no role in the treatment of TAO. The cornerstone of treatment is complete cessation of cigarette smoking, which generally leads to quiescence of the disease and eliminates need for repeated amputations (3). More recently, a strategy of intramuscular vascular endothelial growth factor gene transfer has been used successfully to eliminate rest pain and heal ischemic ulcers in patients with TAO (13).

Vasospastic Diseases

Vasospastic conditions, including Raynaud's phenomenon and others, can produce transient ischemic symptoms in the extremities, particularly involving digits. Most of these abnormalities are related to or exacerbated by cold exposure. Raynaud's may occur as an idiopathic phenomenon, in association with a number of collagen vascular, hypercoagulable, malignant, ischemic, drug-related, or metabolic syndromes (1).



Raynaud's disease. Ulcers and gangrene on the fingertips are shown (*arrows*) caused by vasospasm and abnormalities of digital vessels. Associated cardiac findings are coronary vasospasm and primary pulmonary hypertension.

Although most "attacks" are mild, patients with severe Raynaud's will occasionally present with ulceration or gangrene due to prolonged vasospasm. Treatment of Raynaud's and other vasospastic disorders is aimed at measures both local (e.g., warming the extremity) and pharmacologic that facilitate vasodilation.

Hypercoagulable States

A variety of hypercoagulable syndromes have been identified over the past two decades. Certain of these (e.g., hyperhomocysteinemia) are associated with premature onset of peripheral atherosclerosis and, secondarily, predisposition to thrombosis. Others, including the so-called primary hypercoagulable states (e.g., antithrombin III deficiency and protein C or S deficiency) and antiphospholipid syndrome, predispose patients to early thrombosis of arterial grafts and veins. The therapeutic approach to these patients includes early recognition of the abnormality and judicious use of anticoagulants and/or antiplatelet agents (14).

Acute Limb Ischemia

Acute limb ischemia most commonly occurs as a result of embolic arterial occlusion; the embolic source is cardiac in more than three-fourths of cases, and atrial fibrillation is responsible for the vast majority. *In situ* thrombosis of diseased native extremity vessels occurs less frequently; when spontaneous thrombosis does occur, especially in the absence of an underlying high-grade stenosis, the possibility of a previously unrecognized hypercoagulable state must be entertained. Bypass graft thrombosis with or without underlying impediment to flow is another frequent cause of acute limb ischemia.

Diagnosis

The clinical presentation of acute limb ischemia is typically dramatic, with acute onset of severe pain followed shortly thereafter by paresthesia and, ultimately, motor dysfunction (e.g., paralysis). On examination the extremity is cool, pale, and pulseless. Rutherford and colleagues described a series of clinical categories of acute limb ischemia (Table 111.2), with well-defined diagnostic criteria that help determine whether the affected limb is viable, in imminent jeopardy (e.g., "threatened"), or already irreversibly damaged (15). Whether a given patient will present with one category or another depends on many factors, including the duration of occlusion, the level and etiology of the occlusion, the status of the underlying vessels, and general factors (blood pressure, cardiac output, presence/absence of diabetes, oxygen saturation). Paradoxically, it is often the patient with less underlying PAD who develops the most severe ischemia—for example, the patient with atrial fibrillation and normal peripheral vessels who embolizes to the common femoral or popliteal arteries. The presence of better-developed collaterals in the patient with preexisting PAD can be protective.

Category	Description	Capillary return	Muscle weakness	Sensory loss	Doppler signals	
					Arterial	Venous
Viable	Not immediately threatened	Intact	None	None	Audible (ankle pressure >30 mm Hg)	Audible
Threatened	Salvageable if promptly treated	Intact, slow	Mild, partial	Mild, incomplete	Inaudible	Audible
Irreversible	Major tissue loss, amputation regardless of treatment	Absent (marbling)	Profound, paralysis	Profound, anesthetic	Inaudible	Inaudible

Adapted from Rutherford RB, Flanigan DP, Gupta SK. Suggested standards for reports dealing with lower extremity ischemia. J Vasc Surg 1986;4:80–94.

TABLE 111.2 CLINICAL CATEGORIES OF ACUTE LIMB ISCHEMIA

Therapy

Patients with acute limb ischemia, especially those with threatened limbs, require immediate attention and an accelerated effort to restore nutrient flow to the jeopardized limb. Treatment for each patient is individualized, as discussed later in this chapter. Options include surgical or catheter-based thrombectomy, bypass, thrombolytic therapy, or direct percutaneous recanalization.

CURRENT THERAPEUTIC APPROACH TO PERIPHERAL ARTERIAL DISEASE

Role of Catheter-Based Interventions

Since the pioneering work of Dotter, Judkins, Gruentzig, and others (16,17), technical innovations have resolved many of the limitations (large-profile balloons, stiff guidewires, and poor imaging equipment), and consequently reduced the hazards associated with the early years of percutaneous transluminal angioplasty (PTA). Catheter profiles have been streamlined, limiting complications related to vascular access. Novel materials for balloon and guidewire construction have facilitated passage through occluded vessels and permitted routine access to more remote vascular sites with less risk and greater efficacy. Directional and rotational atherectomy and laser irradiation now enable “debulking” of atheroma. Endovascular stents have dramatically improved both short-term and long-term outcomes of PTA (18,19,20 and 21). Foremost among improvements in imaging techniques has been the introduction of intravascular ultrasound (IVUS), digital enhancement of conventional contrast images, and magnetic resonance imaging.

Market forces and changes in population demographics have also made percutaneous revascularization increasingly attractive. Providers and insurers recognize that PTA, performed as a “same-day” procedure, is a potentially cost-saving approach. Patients favor using less-invasive techniques, even if the symptomatic improvement may not be as durable or the degree of revascularization not as complete; lower-risk partial revascularization by percutaneous means may suffice to treat symptoms and indeed may be preferable to higher-risk attempts at complete surgical revascularization. This philosophy is exemplified in the treatment of infrapopliteal disease in high-risk patients with limb-threatening ischemic ulceration, where even short-term restoration of antegrade flow by PTA can result in ulcer healing and the potential for long-term limb salvage, thereby providing a viable alternative to surgery in these patients (22). Finally, as the population ages, the prevalence of PAD is increasing, thus compelling health care providers to optimize treatment strategies. People older than age 65 years, the stage when vascular disease achieves its peak prevalence, now constitute nearly 15% of the population, a figure expected to double in the next 35 years. Judicious treatment of older patients disabled by PAD may enable them to experience the well-documented benefits of exercise and physical activity. In consideration of these goals, the availability of effective, “less invasive” percutaneous options for revascularization in this group of patients with a high-risk profile due to comorbid conditions has led to a reevaluation of the threshold for intervention.

The increasing popularity of percutaneous revascularization as first-line therapy for patients with PAD underscores the need for vascular specialists to have a comprehensive understanding of the mechanisms of angioplasty, indications for intervention, expected outcome, and potential complications of a given revascularization procedure.

Imaging in Percutaneous Angioplasty

Conventional contrast angiography remains the time-honored approach for lesion characterization. It is, however, limited by the fact that it depicts the vessel lumen only; plaque and vessel wall are viewed as a “negative imprint” on the contrast-filled lumen (23). Although this allows for characterization of lumen topography, irregularities within the vessel wall may only be inferred from the negative imprint. Furthermore, contrast angiography is limited to a single planar view per injection; as such, information regarding the circumferential nature of the plaque is not provided.

VIDEO

Video 111.1 Normal iliac-femoral run-off after distal aortography. In this example, cineangiography of a distal aortic injection is illustrated with brisk run-off in the iliac and femoral systems. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*

Pathologic evaluation of dilated vessels typically discloses plaque fractures and stretching of the arterial wall; the exact contribution of these, versus plaque compression and other factors that might augment lumen area, remains controversial. Most *in vivo* attempts to identify the mechanisms responsible for successful (or unsuccessful) PTA have been limited by the lack of ability to adequately assess the morphology and geometry of a lesion before and after treatment, and at the time of restenosis using standard angiographic imaging methods.

Intravascular Ultrasound

IVUS has become a very useful adjunctive imaging technique to contrast angiography by providing a cross-sectional view of the vessel similar to a histologic section, thereby addressing many of the angiographic limitations. IVUS is unequivocally superior to contrast angiography in its ability to demonstrate detailed characteristics at the interface of the lumen and vessel wall as well as within the plaque. Indeed, experimental and clinical experience indicates that IVUS images correlate remarkably well with histologic examination; IVUS is exquisitely sensitive in detecting details that are angiographically “silent” (Fig. 111.1 and Fig. 111.2) (24,25). For instance, angiographically normal sites that are adjacent to target lesions almost always demonstrate disease when imaged by IVUS. Similarly, calcified plaque, characterized by “acoustic shadowing,” is detected by IVUS in a majority of vessels undergoing angioplasty, a feature grossly underappreciated by angiography (26). Similarly, angiographically normal-appearing vessels are often found by IVUS to have diffuse plaque deposition, indicating a much more advanced stage of atherosclerosis than would have been presumed otherwise.

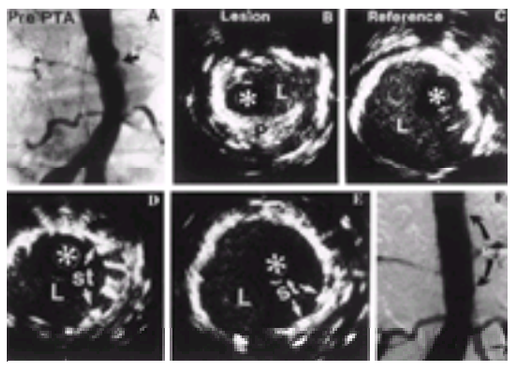


FIGURE 111.1 Superior imaging of eccentric aortic lesion by intravascular ultrasound (IVUS) compared with angiography. This 63-year-old woman presented with accelerated bilateral buttocks claudication, occurring at 1 to 2 blocks. **A:** Conventional anteroposterior angiography failed to disclose any significant stenosis; mild irregularity (*arrow*) was seen within the distal aorta. After discovering a large pressure gradient (see Fig. 111.4), IVUS examination was performed. **B:** IVUS image depicting focal eccentric plaque (P) narrowing the lumen (L) in distal aorta. **C:** IVUS from reference site distal to stenosis depicts normal lumen dimensions. **D:** Although lumen (L) is now enlarged compared with pre-percutaneous transluminal angioplasty (PTA), IVUS after 9-mm PTA/stent demonstrates stent underexpansion, with all struts (st) between 2 and 5 o'clock not in apposition to the arterial wall. **E:** IVUS after 12-mm PTA demonstrates complete expansion of stent, with all struts (st) now completely apposed to arterial wall and overall lumen (L) area further increased. **F:** Angiogram after 12-mm PTA shows slight decrease in luminal irregularity where stent has been redilated (*arrows*). *, IVUS catheter.

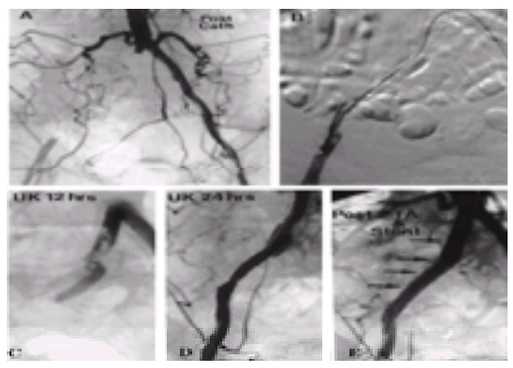


FIGURE 111.4 Thrombolysis, percutaneous transluminal angioplasty (PTA), and stent deployment in a patient with acute onset of right lower extremity ischemia after diagnostic cardiac catheterization (Cath). **A:** Baseline arteriogram demonstrates lengthy fresh occlusion of right common iliac artery, with reconstitution of common femoral artery by collaterals. **B:** Occlusion crossed in antegrade fashion from contralateral side and infusion of urokinase (UK) begun via Mewissen catheter and Katzen wire. **C:** After 12 hours of UK, common and external iliac arteries are now partially patent but have extensive dissection, residual thrombus, and blind cul-de-sac. Thrombolytic therapy therefore continued. **D:** After 24 hours of UK, vessel is now patent and thrombus resolved, but extensive dissection remains. **E:** After deployment of two Palmaz stents (*arrows*), the iliac artery is widely patent, with amelioration of dissection and elimination of the cul-de-sac. The patient remains asymptomatic 18 months later.

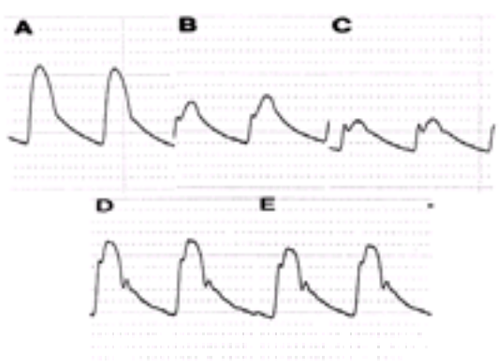


FIGURE 111.2 Intraarterial transstenotic pressure gradient before and after percutaneous transluminal angioplasty in the patient from Figure 111.3. **A:** Baseline blood pressure from aorta proximal to lesion. **B:** Pressure obtained simultaneously from aorta distal to lesion demonstrates 30-mm Hg peak gradient, which becomes exacerbated after administration of intraarterial nitroglycerin **(C)**. Proximal **(D)** and distal **(E)** aortic pressures after percutaneous transluminal angioplasty/stent are nearly identical, indicating hemodynamic improvement.

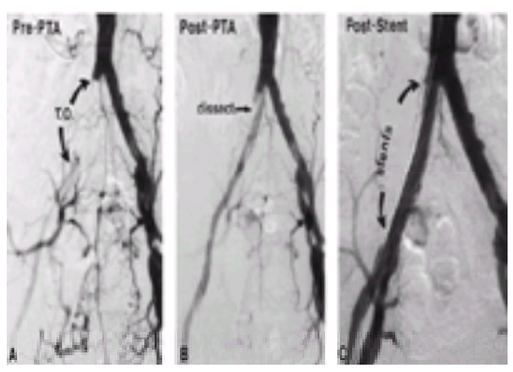


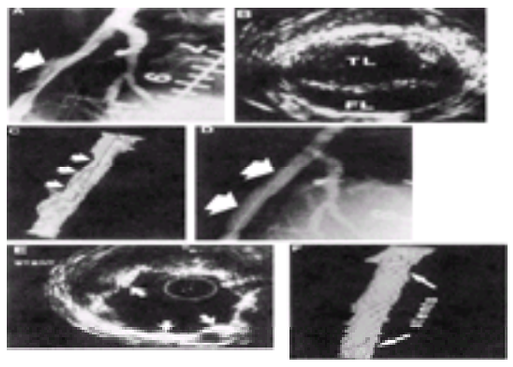
FIGURE 111.3 Percutaneous transluminal angioplasty (PTA) and stent deployment in chronically occluded right common iliac artery. **A:** Baseline angiogram demonstrates 5-cm total occlusion (T.O.) of right common iliac artery with reconstitution of external and internal iliac arteries. Occlusion was crossed using combination of angled and straight Glidewires, buttressed by a 4-Fr. catheter. **B:** Post-PTA angiogram demonstrating patent common iliac artery with extensive dissection (dissect.). **C:** Final angiogram after deployment of two Palmaz stents. Common iliac artery is widely patent. Baseline mean gradient of 37 mm Hg was reduced to 1 mm Hg. Patient is asymptomatic 4 years later.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) has been increasingly used for assessment of the lower limb vasculature over the past decade. A metaanalysis of 34 MRA studies published in the past 8 years (27) showed that MRA was highly accurate for assessment of all lower extremity arteries, specifically for detection of stenoses greater than 50%, and three-dimensional gadolinium enhancement improved the diagnostic performance. Advancement in techniques has resulted in comparable accuracy of MRA to conventional arteriography or digital subtraction angiography for assessment of lower extremity arteries, particularly the infrapopliteal vessels. Nevertheless, until randomized trials are performed that compare outcomes of distal bypass surgery or infrapopliteal angioplasty based on arteriography and MRA, it will be unclear which modality is preferred.

Mechanisms of Angioplasty and Related Techniques

Plaque fracture, plaque compression, and stretching of arterial wall components all likely play a role in enhancing luminal dimensions. IVUS has provided new insight into the effects of angioplasty and other revascularization techniques (28). For example, observations from IVUS suggest that plaque fracture and/or dissection is associated with balloon dilation in the majority of angiographically and hemodynamically successful procedures (24). Vessels in which directional atherectomy (DA) is performed demonstrate less prominent plaque-arterial wall disruption; instead, the perimeter of the neolumen is typically smooth and uninterrupted, with discrete "bites" corresponding to individual passes of the cutting blade. Signs of arterial wall trauma, including severe disruption, are most completely ameliorated on IVUS images recorded after delivery of an endovascular stent (eFig. 111.2.1) (29).



***e*FIGURE 111.2.1** Amelioration of post–percutaneous transluminal angioplasty dissection of external iliac artery using stents. **A:** Post–percutaneous transluminal angioplasty angiogram demonstrates extensive dissection (*arrow*) in external iliac artery. **B:** Representative intravascular ultrasound frame shows extent of arterial wall trauma, with large dissection flap interposed between true lumen (TL) and false lumen (FL). **C:** Three-dimensional reconstruction of serial intravascular ultrasound images creates a "cast" of the vascular lumen, narrowed by dissection and encroaching false lumen (*arrows*). **D:** Angiogram after deployment of two Palmaz stents (*arrows*) shows improved patency, but the interface between stent and vessel wall is not delineated. **E:** Intravascular ultrasound image from stent site demonstrates amelioration of arterial wall pathology with effacement of dissection by expanded stent. Struts identified by arrows. **F:** Three-dimensional cast of stented iliac artery now depicts uniform dimensions throughout length of vessel, with resolution of luminal narrowing. Cobblestoned appearance of struts is evident.

ANATOMIC REGIONS OF INTEREST

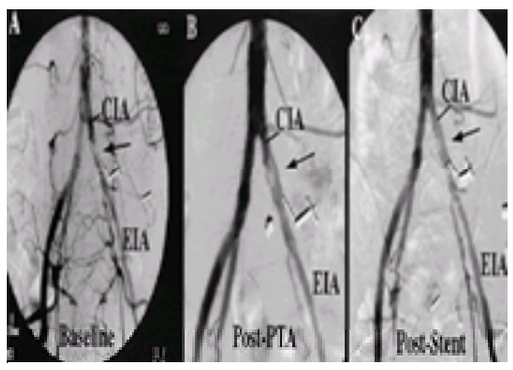
Therapy for certain sites within the peripheral circulation, particularly those previously considered to be inaccessible by the percutaneous approach, is evolving rapidly. Likelihood of success and chances for clinical improvement vary in degree according to the region of interest and extent of disease. However, because the management of an individual lesion in a particular patient depends on a number of factors, any classification or categorizing of recommendations is difficult (30). Weighted consideration of these individual issues is therefore required to determine, for any given combination of lesions, the appropriateness of nonsurgical revascularization (Table 111.3).

TABLE 111.3 REVASCULARIZATION STRATEGY FOR VARIOUS LOCATIONS (AS OF 2001)

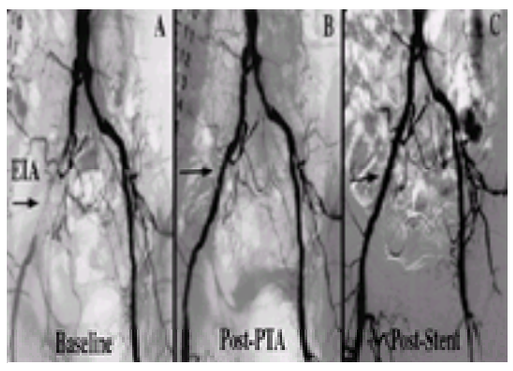
AORTOILIAC OBSTRUCTIVE DISEASE

Most stenotic disease in the infrarenal abdominal aorta and iliac arteries is atherosclerotic in origin. The excellent procedural and long-term results of aortoiliac PTA, enhanced by stenting, are so predictable that the physical finding of a diminished femoral pulse is a useful sign for identifying patients who are likely to derive benefit.

Aortoiliac revascularization is thus recommended for (a) relief of symptomatic lower extremity ischemia, including claudication, rest pain, ulceration or gangrene, or embolization causing blue toe syndrome (*e*Fig. 111.2.2) (31); (b) restoration and/or preservation of inflow to the lower extremity in the setting of preexisting or anticipated distal bypass (*e*Fig. 111.2.3) (32,33); (c) procurement of access to more proximal vascular beds for anticipated invasive procedures (e.g., cardiac catheterization/percutaneous transluminal coronary angioplasty, intraaortic balloon insertion) (34); and (d) rescue of flow-limiting dissection complicating access for other invasive procedures (*e*Fig. 111.2.4).

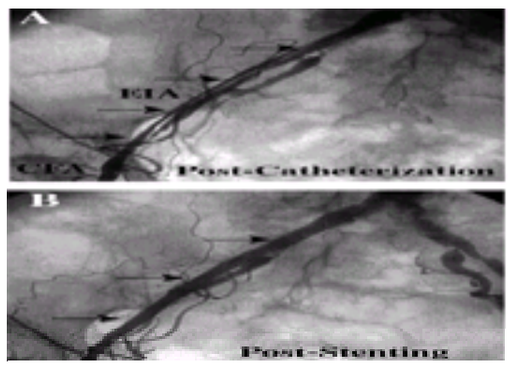


***e*FIGURE 111.2.2** Percutaneous transluminal angioplasty (PTA)/stent for iliac stenosis in a 54-year-old patient with Rutherford category 2 claudication and blue toe syndrome. **A:** Baseline angiogram demonstrates a focal stenosis in the left common iliac artery (CIA) resulting from a large, calcified, and ulcerated plaque (*arrow*) that was the likely source of the distal embolization. **B:** Persistence of the plaque (*arrow*) after balloon angioplasty; a suboptimal result despite some increase in luminal diameter. Rock-like calcium plaque remains a source of emboli. **C:** Exclusion of calcified plaque burden and restoration of full luminal patency after deployment of endovascular stent (*arrow*). EIA, external iliac artery.



***e*FIGURE 111.2.3** Percutaneous revascularization of external iliac artery (EIA) occlusion in a 75-year-old patient with distal disease and a nonhealing ulcer. Patient had significant coronary artery disease and previous abdominal surgery. Surgical risk of abdominal vascular reconstruction was therefore reduced by strategy of sequential percutaneous transluminal angioplasty (PTA)/stent and surgical distal bypass. **A:** Access obtained in the ipsilateral common femoral artery and the occlusion traversed

with a Glidewire. Angiography, in the left anterior oblique projection, demonstrates a lengthy (5 cm) occlusion of the right EIA (*arrow*), moderate disease of the contralateral common iliac artery, and right superficial femoral artery occlusion. **B:** Luminal patency was restored with balloon angioplasty (*arrow*). **C:** Final angiography after stent deployment demonstrates excellent result (*arrow*). Femoropopliteal bypass facilitated healing of the ulcer and resolution of symptoms.



***e*FIGURE 111.2.4** Eighty-four-year-old woman complaining of increasing right leg pain and coolness during cardiac catheterization. **A:** After cardiac catheterization, iliac angiogram demonstrates flow-limiting, lengthy spiral dissection (*arrows*). **B:** Flow was restored after treatment with percutaneous transluminal angioplasty and Wallstent (*arrow*). When encountering new symptoms of lower extremity ischemia during catheterization, angiographic delineation of the cause is preferable to removing the sheath and hoping for restoration of flow. EIA, external iliac artery.

Isolated Aortic Lesions

Isolated aortic lesions are relatively uncommon. Early reports of PTA for atherosclerotic aortic disease had been mostly limited to discrete, focal lesions of less than 2 cm in length (35). Successful dilation of these lesions was accomplished using either side-by-side simultaneously inflated balloons or a single large balloon, with favorable results in greater than 90% (36).

Aortoiliac Stenosis

Percutaneous therapy represents the first line of therapy for aortoiliac stenoses. Acute technical and clinical success of PTA alone for iliac stenoses exceeds 90%, and 1- and 5-year patency rates range from 75% to 95% and 55% to 85%, respectively (30,37). Stents have been shown to rescue the flow-limiting complications, reduce the acute recoil, and improve on the immediate hemodynamic results of PTA for aortoiliac stenoses, with acute technical success rates of 90% to 100% (eFig. 111.2.1 and Fig. 111.3) (30,38,39,40,41,42,43,44 and 45). Significant improvements in long-term patency have also been achieved in patients randomized to PTA and stent versus PTA alone: The angiographic patency (93%) in patients studied at 5-year follow-up rivals the best clinical patency reported at a similar time interval in patients undergoing operative revascularization (21,30).

Aortoiliac Occlusion

The approach to iliac occlusion is in evolution, moving from a predominantly surgically oriented therapy, to consideration of thrombolysis preceding PTA, and now toward a preference for primary PTA/stenting. There are two specific considerations in this regard. The first is the enhanced ability to traverse the segment of occluded artery (even chronic occlusions) by advancements in guidewire (e.g., hydrophilic) and catheter technologies (46) and novel technical approaches, such as the so-called pull-through technique (Fig. 111.3 and Fig. 111.4) (47), a combination that has yielded an extremely high procedural success rate, especially in lengthy occlusions. The second issue concerns the specter of acute limb-threatening ischemia resulting from distal embolization in direct (nonlytic) recanalization of iliac occlusions, previously reported to occur with alarming frequency (48). The current incidence of embolization in this setting is exceedingly low, especially if a strategy of initial underdilation followed by stent deployment is used; the stent provides a scaffold, which, in theory, affixes the thrombus/plaque to the vessel wall, thus reducing the likelihood of distal embolization. The exception is the case of documented recent thrombosis, where use of thrombolytic therapy is unequivocally indicated (Fig. 111.4) (49,50 and 51). The extent to which lytic therapy may further optimize the treatment of less acute iliac occlusions by exposing an underlying lesion and converting an occlusion to a stenosis remains to be defined.

PTA alone for aortoiliac occlusions has less favorable results than for stenoses; the technical success rate of PTA of segmental (external or common) iliac occlusions is 80% to 85% (37,52) and long-term patency rates are close to 80% at 1 year and 55% at 5 years (53). Consequently, stenting is the preferred primary therapy for aortoiliac occlusions (40,44,53); indeed, a strategy of primary stent deployment for aortoiliac disease has been adopted by many investigators (43,45,54). A metaanalysis (55) of more than 2,100 patients showed greater immediate success rate (96% vs. 91%) and higher 4-year patency rates (61% vs. 54%) for stents than for PTA alone; stents also reduced the relative risk of 4-year failure by nearly 39% over PTA alone. Disease severity and relative proximal locations also have a positive influence on the outcome of revascularization by stenting (42). In patients with only focal aortoiliac or common iliac lesions, the rates for complete relief of symptoms and 3-year persistent clinical benefit approach 90% and 95%, respectively, compared with 85% and 98% for patients with external iliac disease and 60% and 60% for patients with multilevel infrainguinal disease.

Use of Aortoiliac Percutaneous Transluminal Angioplasty/Stenting in Conjunction with Surgery

In some patients with claudication and in rare patients with limb ischemia, the iliac lesion typically coexists with more distal disease (56); in such cases, initial treatment of the iliac obstruction is based on the premise that improving inflow will secondarily improve outflow, either via the profunda in the case of an occluded superficial femoral artery (SFA) or by increasing the head of perfusion pressure to that segment of the infrapopliteal circulation that remains patent. Sometimes, this may obviate the need for reconstruction more distally. Implicit in this strategy are the lesser degree of technical difficulty, high incidence of procedural success, and low rate of restenosis associated with iliac PTA, compared with that for more distal segments.

A similar strategy underlies the preparatory role of iliac angioplasty in patients undergoing surgical revascularization for treatment of distal disease (eFig. 111.2.3) (56,57). Percutaneous revascularization of an iliac lesion may be required to facilitate patency of a downstream femoral-popliteal conduit designed to bypass an occluded SFA. Alternatively, in patients with coexistent coronary heart disease, the proximal anastomosis may be adjusted one level caudal, thereby reducing the risk associated with operative revascularization. For example, in the patient with a lengthy unilateral occlusion of one iliac artery and less extensive obstruction of the contralateral side, higher-risk aortofemoral bypass surgery may be obviated by percutaneous treatment of the less diseased iliac artery, followed by a cross-femoral graft to the contralateral femoral artery.

One additional issue regarding percutaneous treatment of aortoiliac disease deserves specific comment. This concerns the role of percutaneous revascularization in modifying the treatment of patients with cardiac disease, in whom abdominal-level surgery is associated with a marked increase in cardiac morbidity and mortality (58). Work from several groups (59,60 and 61) has demonstrated the feasibility of intraluminal insertion of stent-graft prostheses for the treatment of abdominal aortic aneurysms (AAAs).

Current Recommendations for the Treatment of Aortoiliac Disease

PTA is generally applied to more focal disease of the distal aorta, common iliac arteries, and external iliac arteries. The current consensus (30) is that stents are appropriate for use in aortoiliac disease in the following instances: for significant elastic recoil after PTA based on residual pressure gradient causing insufficient hemodynamic result; in flow-limiting dissection; for lengthy or complex lesions where balloon angioplasty has been shown to yield suboptimal results and for which primary stenting may give more satisfactory results; for restenotic aortoiliac lesion after previously performed PTA; in reconstruction of the aortoiliac bifurcation; for iliac artery ulceration associated with symptoms; for revascularization of “donor artery,” in preparation for more distal cross-femoral or femoral-to-distal bypass; and as primary therapy for aortoiliac chronic occlusion. Several issues, however, remain outstanding. First, the role of primary stent deployment for *uncomplicated* iliac lesions is yet to be defined. Many interventionalists believe this strategy is warranted, given the positive aspects and the absence of significant complications associated with stenting at this level. Second, the usefulness and cost-effectiveness of multiple stents also remain to be established.

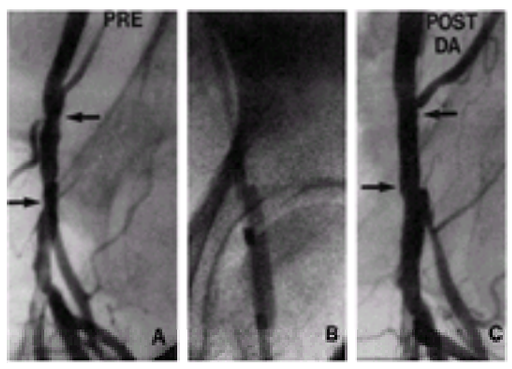
ABDOMINAL AORTIC ANEURYSM

Open surgical repair remains the current gold standard for treatment of AAAs. The operative mortality of resection is between 1.4% and 7.6% (59) and rises significantly for patients with symptomatic aneurysms. A substantial number of patients (15%) with AAA greater than or equal to 5 cm in diameter have comorbid conditions or unsuitable anatomy for repair. Such patients have a poor prognosis: a fivefold chance of rupture when the diameter exceeds 6 cm and a 5-year survival rate of 18% (62). Rapid advances have been made with endovascular devices, allowing high-risk patients with aneurysmal disease involving the abdominal aorta and other sites to benefit from the availability of less invasive therapy. Currently, more than 5,000 stent-graft procedures worldwide have been performed for AAA exclusion. The Guidant/EVT and Medtronic AVE AneuRx devices received U.S. Food and Drug Administration approval in 1999. Other devices include Boston Scientific Vanguard, Medtronic AVE Talent, Cook Zenith, Corvita Endograft, and Gore Prograft. D'Ayala and colleagues (61) reported a success rate of 74% to 100% in 767 patients, endoleaks in 14% (one-third sealed spontaneously), and 8% requiring conversion to open procedures; overall mortality was 4%. Two other studies report experience with the AneuRx stent-graft (60) and a combination of bifurcated Mintec and Boston Scientific Vanguard devices (59), achieving technical success in 80% to 90%, endoleaks in 10% to 20%, and morbidity rates of 10% to 15%. Current limitations include the obligatory sacrifice of one or both internal iliac arteries and the large-caliber device (12 Fr. to 28 Fr.), which requires access by femoral artery cutdown. Situations that may not be appropriate for stent-grafting include aneurysms with a short or absent proximal neck and severe angulation at the origin of the aneurysm. The use of stent-graft technology to treat iliac aneurysms has also been very successful (63).

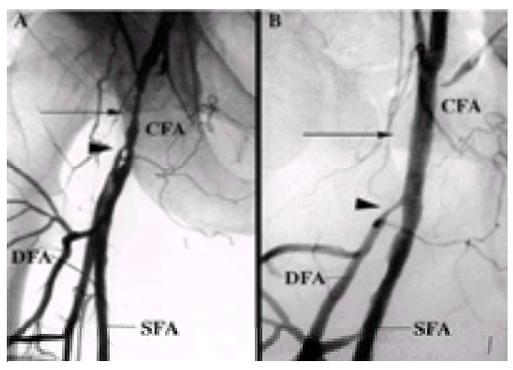
COMMON FEMORAL AND PROFUNDA FEMORIS ARTERIES

Revascularization of the common femoral artery (CFA) has long been considered to be exclusively surgical for several reasons. Access is easily achieved through a local incision and often under local anesthesia, the results of endarterectomy or patch angioplasty are outstanding, and this vessel has the propensity to demonstrate elastic recoil.

Lesions of the CFA may be accessed without great difficulty and results of PTA or DA can be quite favorable (*e*Fig. 111.4.1). Lesion characteristics play a significant role in determining the success of PTA (*e*Fig. 111.4.2). In general, the more calcification that is present, the less responsive is the CFA lesion to PTA, particularly lesions extending into the origins of the superficial femoral and profunda femoris arteries. However, the concern that PTA-induced plaque fractures could propagate into the common femoral bifurcation, leading to potential compromise of both the SFA and profunda, implicitly suggests that PTA of the CFA must be undertaken with considerable caution. The biggest impediments to successful long-term outcome after CFA revascularization are recoil and restenosis. There are no long-term studies, but the restenosis rate is widely accepted to be greater than 50%. The use of stents in the CFA is ill advised, as their placement may preclude future surgical procedures or compromise future attempts at percutaneous access.



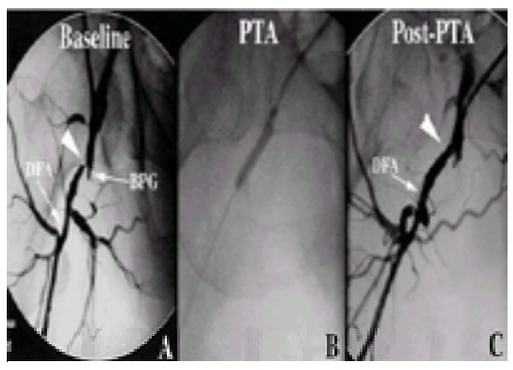
***e*FIGURE 111.4.1** Directional atherectomy (DA) of common femoral artery stenosis. **A:** Severe left common femoral artery stenosis *arrows*) in an elderly female with coronary artery disease. **B:** DA catheter placed via retrograde puncture. **C:** Angiogram post-DA demonstrating improved patency. Arrows indicate site of previous stenosis.



***e*FIGURE 111.4.2** Balloon angioplasty (percutaneous transluminal angioplasty) of common femoral artery in a patient with multiple previous right leg surgical interventions, resulting in severe scarring of right groin. **A:** High-grade, diffuse stenosis (*arrow*) in right common femoral artery (CFA) extending to the origins (*arrowhead*) of the profunda femoris (DFA) and superficial femoral artery (SFA). Revascularization with percutaneous transluminal angioplasty was performed via the contralateral approach. **B:** Final angiogram demonstrates excellent patency of the CFA and proximal SFA, with mild recoil at the origin of the DFA. Patient's claudication symptoms resolved, and he continues to be minimally symptomatic 4 years later. Arrow indicates previous site of stenosis; arrowhead indicates origin of the DFA.

The profunda femoris, or deep femoral, artery is the main source of collaterals to the lower extremity. In occlusion of the SFA the deep femoral artery alone becomes responsible for maintaining viability of the lower extremity (64). Traditionally, bypass surgery (endarterectomy and patch angioplasty) is performed for occlusive disease in the deep femoral artery, which almost always occurs in conjunction with ostial SFA disease. Technically satisfactory results of profunda PTA have been described (65). However, because of the potential for jeopardizing the limb, in the event that the vessel dissects or occludes, caution should be exercised when considering PTA in the profunda.

For the present, PTA is reserved for situations of severe ischemia (Rutherford category 4, 5, or 6) and for situations in which surgery is contraindicated (*e*Fig. 111.4.3). Stenting in the profunda is usually reserved for cases of true flow-limiting dissection after balloon angioplasty, wherein patency of the vessel and viability of the limb might be threatened without maintaining an open vessel.



***e*FIGURE 111.4.3** Balloon angioplasty [percutaneous transluminal angioplasty (PTA)] for profunda femoris disease in a 50-year-old patient with multiple previous

percutaneous interventions, including endovascular stenting, for recurrent femoropopliteal bypass graft occlusion (chronic superficial femoral artery occlusion). A below-knee amputation was ultimately required for critical limb ischemia. **A:** Critical stenosis (*arrow*) of the profunda femoris artery (DFA) causing stump ischemia and chronic occlusion of a femoropopliteal graft (BPG). **B:** Balloon angioplasty performed at low inflation pressure using the antegrade approach. **C:** Final angiographic image demonstrating restoration of luminal patency.

SUPERFICIAL FEMORAL AND POPLITEAL ARTERIES

Previous experience has failed to document any significant differences in either acute or long-term results for percutaneous revascularization of the SFA versus the popliteal artery; accordingly, both are herein considered together under the heading of SFA.

In contrast to aortoiliac disease, disease in the SFA/popliteal arteries typically occurs in older patients and is associated more closely with the presence of CAD (66), and symptoms are two or more times more frequent. Patients with SFA/popliteal disease usually present with calf claudication. Less frequently, the presenting sign is critical limb ischemia; proximal SFA occlusion alone may be associated with only mild claudication, and in some patients, no claudication at all in the presence of well-developed profunda collaterals.

Stenoses of the Superficial Femoral Artery or Popliteal Artery

The acute procedural success that may be currently achieved using conventional guidewires and standard PTA in SFA stenoses is similar to that reported for iliac stenoses, approaching 100%. Long-term patency in the SFA, however, is clearly inferior to that which may be expected in iliac stenoses; from pooled data among patients undergoing PTA of femoral-popliteal stenoses, primary patency rates at 1, 3, and 5 years were, on average, 60%, 50%, and 45%, respectively (67,68,69 and 70). Variability in long-term results is due in part to the multiple lengths and morphologies of SFA lesions selected for treatment, including a mixture of stenoses and occlusions. In one of the more comprehensive reports, using a prospective analysis of PTA of 208 lesions in 140 limbs, Matsi and colleagues reported an overall acute angiographic success rate of 88% and a successful immediate clinical outcome in 91% of SFA lesions (70). Systematic, prospective long-term follow-up of all study patients using ankle-brachial indices and clinical symptoms revealed 1-, 2-, and 3-year primary patency rates of 47%, 44%, and 43%, respectively. Secondary patency was 63% at 1 year and 59% at both 2 and 3 years.

Predictors of long-term patency after SFA/popliteal PTA include claudication as the presenting symptom, a more severe lesion at baseline, stenosis versus occlusion, concentric morphology, fewer stenoses, two- to three-vessel runoff, absence of residual stenosis after angioplasty, and restoration of an ankle-brachial index to greater than 0.9 at 24 hours postprocedure (67,70,71). Factors that negatively influence long-term patency include the presence of diabetes, threatened limb loss, or diffuse atherosclerotic vascular disease (71).

A variety of other technologies have been investigated as means of improving long-term patency and reducing restenosis in the SFA. DA has the unique capability of resecting intact atherosclerotic plaque, which can be used for a variety of laboratory analyses (72), including prospectively identifying those patients likely to develop restenosis (73). In patients with short, eccentric lesions, particularly those lesions resistant to balloon dilation, and for fibrotic lesions with significant recoil (e.g., graft anastomoses), DA (with or without adjunctive PTA) seems to offer satisfactory acute results, similar to those for PTA (74,75 and 76). Currently, however, there is no evidence to support the use of DA as a means of preventing restenosis (76).

Rotational atherectomy (77,78) has not thus far been demonstrated to have an advantage for SFA/popliteal revascularization, save for those rare patients in whom the extent of calcific deposits renders the lesion refractory to alternative techniques. In the smaller popliteal artery, it is possible that the debulking effect of rotational atherectomy may ultimately prove to offer some benefit over balloon angioplasty alone. The role of laser angioplasty in SFA/popliteal revascularization remains controversial and unproven. A variety of laser sources have been investigated for this application (79,80 and 81), but trials thus far have demonstrated no definitive benefit of this device at this level.

In contrast to the documented benefits achieved by use of endovascular stents for iliac PTA, experience thus far in the SFA has been less favorable. Although preliminary, nonrandomized studies using the Palmaz stent (82) and the Wallstent (83,84) demonstrated modest improvement in intermediate-term patency, primary 1-year and 3-year patency rates of 22% to 81% and 18% to 72%, respectively, have been reported (85,86 and 87); restenosis caused by intimal hyperplasia in the stented segment is quite common in the first 3 to 6 months (86). More recently, pooled data from 11 studies (585 patients) of stents in both femoropopliteal stenoses and occlusions revealed technical success, 1- and 3-year patency rates of 98%, 67%, and 58%, respectively (30). Furthermore, the use of stents in the SFA has been complicated by an unpredictable incidence of subacute thrombosis (85). However, there appears to be an acute hemodynamic benefit of femoropopliteal stenting for treatment of a flow-limiting dissection and for failed balloon angioplasty (30,86) despite a lack of encouraging long-term benefits. The descriptions of deformation or compression of stents placed within the adductor canal (88) suggest that balloon-expandable stents should be avoided in favor of self-expandable stents. Future studies will determine whether the newer Nitinol self-expanding stents offer any advantage over the previous stainless steel designs, as is widely believed to be the case.

Occlusion of the Superficial Femoral Artery or Popliteal Artery

Among patients studied angiographically for consideration of revascularization, occlusions are more prevalent than stenoses. Two technical advances have facilitated treatment of SFA occlusions, even lengthy (more than 10 cm) or chronically occluded segments. The first is the use of hydrophilic wires. At our institution, the Glidewire was used to attempt percutaneous revascularization of 109 SFA total occlusions and was successfully advanced across the occluded segment in 107 (98%); PTA alone or in combination with DA and/or laser angioplasty was then used to complete percutaneous revascularization in all 107 patients (46). Improvements in ankle-brachial index (from 0.48 pre- to 0.82 postrevascularization) and in Rutherford class (one grade or more) were observed in 94% at 1-month follow-up. This experience was noteworthy for two reasons in particular. First, 50 lesions measured 5 to 10 cm in length and 21 were more than 20 cm long; consequently, mean occlusion length (9.8 cm) exceeded that reported in most previous series. Second, IVUS examination during these procedures demonstrated a subintimal route of recanalization in approximately one-third of patients (89).

The second advance is the use of thrombolytic therapy (Fig. 111.5), which has been proven effective, even for some patients with chronic total occlusions, because occlusion of the lower extremity arteries is typically characterized by a lengthy, gelatin-like thrombus superimposed on a high-grade atherosclerotic lesion. In such cases, lytic therapy can be effective in converting a long occlusion to one that is either shorter or no longer occlusive and thereby more amenable to mechanical revascularization. The efficacy of this approach underwent systematic multicenter investigation in patients with lower extremity occlusions who were randomized to lytic versus operative therapy in the Surgery and Thrombolysis for Ischemia of the Lower Extremity (STILE) Trial (90). Data from the STILE Trial suggest that successful recanalization of *chronic* SFA occlusions using thrombolytic agents (tissue plasminogen activator or urokinase) is technically feasible and, in many instances, associated with an excellent outcome. However, reestablishing patency by this approach is less reliable for lengthy or “flush” total occlusions than surgical bypass, and for these lesions the outcomes of surgery are more durable. The use of thrombolytic therapy for “acute” occlusions (14 days’ duration or less) appears to be more favorable (Fig. 111.5 and eFig. 111.5.1). Both the STILE Trial and a similar randomized investigation executed by Ouriel and associates (91) demonstrated that, for acute or subacute occlusions, thrombolysis and surgery were equivalent in terms of restoration of patency and limb salvage. In addition, there was a significant reduction in the frequency of both in-hospital complications and 12-month mortality in patients receiving thrombolysis versus those treated surgically. Thus, there is compelling evidence to support a strategy of primary thrombolysis for acute occlusions of the SFA.

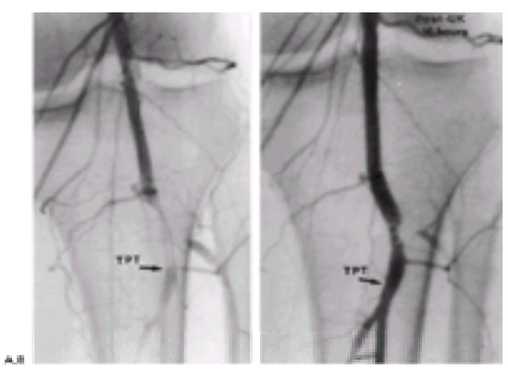
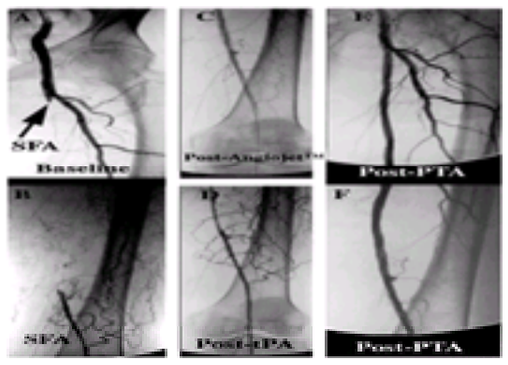


FIGURE 111.5 A: Acute embolic occlusion in an elderly woman with chronic atrial fibrillation. **B:** Rest pain resolved promptly after administration of urokinase (UK).

Patency was restored to tibioperoneal trunk (TPT). The patient remains asymptomatic 4 years later.



***e*FIGURE 111.5.1** Thrombolysis, rheolytic thrombectomy, and percutaneous transluminal angioplasty (PTA) for acute limb ischemia in an 87-year-old woman with erythrocytosis. Baseline angiogram demonstrates occlusion **(A)** of the proximal superficial femoral artery (SFA), with reconstitution via collaterals from the profunda **(B)** at the adductor canal. The occlusion was traversed with a Glidewire and partially recanalized **(C)** with rheolytic thrombectomy (Angiojet). Luminal patency was reestablished with thrombolytic therapy (tPA), revealing moderate disease in the mid-SFA **(D)**. After balloon angioplasty, final angiographic images **(E)** and **(F)** demonstrated widely patent SFA with normal flow/caliber.

Preliminary use of rheolytic thrombectomy devices (92,93) (Angiojet; Possis Medical Systems, Minneapolis, MN) either in lieu of or in conjunction with thrombolytic therapy has demonstrated encouraging results for treatment of acute and chronic thrombus in the SFA/popliteal (as well as other sites) and highlighted the potential for this device to reduce procedure time, hospital stay, and risks associated with prolonged infusion of thrombolytic therapy (*e*Fig. 111.5.1).

The extent to which favorable acute procedural results in patients with chronic total occlusion will ultimately extend the role of percutaneous revascularization remains to be defined. Certainly for patients with nonhealing lesions or threatened limb loss in whom the risks of surgery are considered prohibitive, or in whom veins are unavailable for distal bypass, percutaneous revascularization of even lengthy occluded segments may facilitate healing. In similar types of patients with rest pain or severe claudication, PTA may be used to achieve pain relief at a lower risk than conventional surgical reconstruction. For patients with less severe symptoms, improved ability to revascularize does not in and of itself constitute a sufficient basis for routine invasive therapy.

One further issue concerning femoral arterial revascularization deserves additional specific comment. This involves embolic complications apparently related to ulcerated or thrombotic lesions of the SFA, the so-called blue toe syndrome. Emboli in such patients were initially inferred to result from friable plaque morphology that posed an unacceptable risk for percutaneous revascularization. It is now clear such patients can be effectively treated by PTA with stenting or DA with a high degree of procedural success and an acceptably low risk of further embolic complications (94,95 and 96).

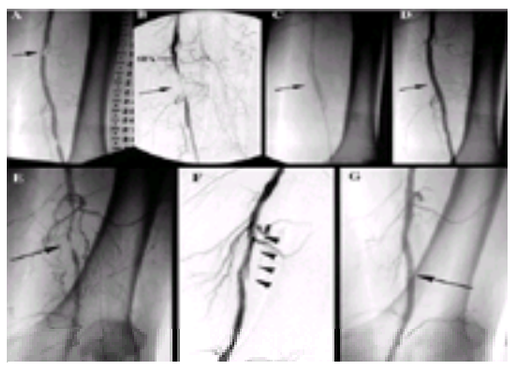
Restenosis

An important caveat in the management of patients with symptomatic SFA/popliteal disease is the issue of restenosis. Despite excellent acute procedural success using conventional guidewires and standard PTA, restenosis continues to be a frustrating and expensive consequence of this otherwise efficacious intervention, complicating the clinical course of up to 60% of patients. Its occurrence raises fundamental questions as to whether the biology and pathophysiology of plaque formation in the SFA/popliteal artery is in some way different from that in other vessels. Furthermore, even though stents may ameliorate the acute flow-limiting complications of SFA PTA, they have been thus far shown to have no significant impact on long-term patency.

Several promising strategies lie on the horizon for treating this vexing problem. First is the concept of gene transfer of angiogenic cytokines. Isner and colleagues effectively transferred genetic material to promote healing of the disrupted endovascular surface after PTA, and preclinical studies have shown reduction of restenosis by the facilitated healing response (97,98). An ongoing phase I trial in humans undergoing SFA/popliteal PTA has thus far demonstrated encouraging results, although these finding are very preliminary (99). Second, the concept of endovascular brachytherapy (100), which is currently being tested in coronary arteries, is also undergoing studies (PARIS Trial) in conjunction with SFA/popliteal PTA and showing encouraging preliminary results. Finally, drug-eluting stents, currently under investigation in coronary arteries, will likely have a role in reducing restenosis in peripheral vessels as well.

Current Recommendations for Superficial Femoral and Popliteal Disease

The acute technical success of balloon angioplasty for SFA/popliteal stenosis or occlusion is currently in the range of 90%. The principal factors in long-term patency are the status of the runoff vessels and the presence of occlusion. Long-term patency of 50% can be anticipated at 5 years; this is significantly less than that of iliac angioplasty. Thus, the threshold for intervention below the inguinal ligament should be higher. However, for patients with claudication severe enough to warrant intervention, PTA is the preferred initial treatment. This applies to both stenoses and occlusions that are amenable to revascularization. Lengthy, flush occlusions of the SFA may not be approachable. Endovascular stents as a primary approach are not indicated. However, at present they have a limited role in salvage of acute PTA failures or complications (*e*Fig. 111.5.2). For chronic critical ischemia, or even acute limb-threatening ischemia, surgery is the preferred modality. However, one caveat to that is in the case of patients in whom the need for coronary bypass grafting is anticipated; in these patients, as long as instrumentation does not preclude future surgical intervention, PTA may be preferred to preserve the leg veins for future coronary bypass surgery.



***e*FIGURE 111.5.2** Stents deployed for complication of balloon angioplasty to the superficial femoral artery after balloon dilation in patients with claudication. **A:** Baseline angiography disclosed a focal lesion (*arrow*) in the mid–superficial femoral artery (SFA). **B:** Balloon angioplasty resulted in flow-limiting dissection and occlusion (*arrow*). **C:** Deployment of self-expanding endovascular stent (*arrow*) was required. **D:** Final angiography demonstrated complete patency (*arrow*) and normal flow. **E:** Baseline angiography in a second patient disclosed focal critical stenosis (*arrow*) in the SFA at the adductor canal with patent popliteal artery. **F:** Balloon angioplasty resulted in a lengthy flow-limiting dissection (*arrowheads*). **G:** A VascuCoil endovascular prosthesis (*arrow*) was deployed repairing the dissection and preserving luminal patency. Patient has remained asymptomatic at 2 years' follow-up.

INFRAPOPLITEAL ARTERIES

Published clinical experience involving percutaneous revascularization of the anterior tibial, tibioperoneal trunk, posterior tibial, and peroneal arteries, although dating to the time of Dotter and Judkins' original work (17), has nevertheless been far more limited than that described for aortoiliac and SFA sites. This is related to several issues, including the fact that claudication is rarely due to isolated disease of the infrapopliteal arteries; knee-to-foot patency of one of the three major branches is generally regarded as sufficient to prevent critical lower limb ischemia; restenosis rates in these vessels have typically been the highest of any of the lower extremity

sites; and obstructive disease in these arteries is often occlusive or diffuse and complicated by heavy calcific deposits. Furthermore, diabetics have a high incidence of infrapopliteal disease, which is associated with diffusely atretic vessels that respond poorly to balloon dilation.

The ability to treat infrapopliteal disease has improved with technological advances, and the application of techniques used for coronary arterial revascularization has consequently resulted in a more widespread application of percutaneous revascularization for infrapopliteal disease (101). Despite this, many of the patients treated with infrapopliteal angioplasty to date have been those who were too high risk or otherwise unqualified for bypass surgery. The latter is still considered to be the standard of care for patients with critical limb ischemia due to infrapopliteal disease. Regardless of the conduit (reversed vein, *in situ* vein, or prosthetic material), patency rates are nonetheless inferior to those of more proximal reconstruction. It is conceivable that the long-term clinical outcome of percutaneous therapy may ultimately equal that of distal bypass grafting. Over the past decade, reports have documented that stenotic and even short occlusions of one or more infrapopliteal arteries can be revascularized percutaneously with a high degree of efficacy and at extraordinarily low risk (102,103) both for critical limb ischemia and for claudication. These studies have demonstrated technical and clinical success rates in the range of 80% to 95% (the success rate in stenoses is superior to that in occlusions).

It must be emphasized that the goals of infrapopliteal revascularization often differ from those of above-the-knee therapy and vary with clinical presentation. In most patients with claudication, for example, below-knee angioplasty is not necessary, as treatment of coexisting proximal disease alone is often sufficient for symptomatic relief. There is a subset of patients who claudicate due solely to infrapopliteal disease for whom percutaneous therapy is becoming more popular. Such a strategy should be reserved, at least for the present, for patients who have severe symptoms (Rutherford category 3). Infrapopliteal PTA may also be justified in claudicants who undergo proximal revascularization (either with surgery or PTA), in whom the runoff is severely impaired, as outflow may be the principal determinant of long-term patency for femoropopliteal revascularization. In patients with rest pain or ischemic ulceration, restoration of uninterrupted patency of at least one of the three major infrapopliteal arteries is generally required to obviate symptoms and/or heal a distal ischemic lesion. In this group of patients, aggressive application of percutaneous revascularization may achieve extremely gratifying results, even in patients with calcified and/or lengthy total occlusions (Fig. 111.6).

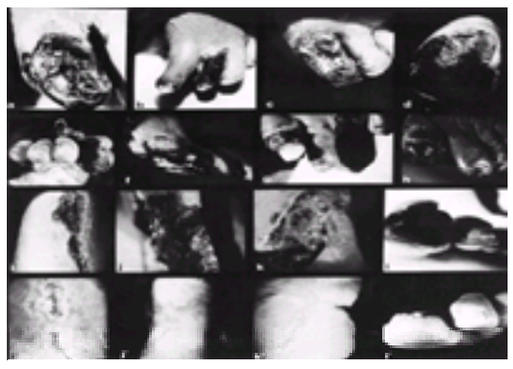


FIGURE 111.6 Composite figure showing the extent of severely ischemic alterations that typically develop before patients or their physicians seek medical consultation regarding the basis for these findings and possible treatment options. In most of these cases, amputation ultimately was required. For the patient whose limbs were photographed at the time of initial presentation in **i** through **l**, the corresponding photographs **i'** through **l'** demonstrate the appearance after percutaneous revascularization. These patients illustrate one of the most difficult groups of patients seen by specialists in vascular medicine. Earlier diagnosis and institution of therapy clearly are required to prevent the development of such extensive disease if the risk of amputation in these patients is to be reduced. It should be recognized, however, that when the extent of disease has reached even this degree, amputation and bypass surgery are not the only available treatment options. Percutaneous revascularization often may be successful in rescuing limbs of these patients; regardless of the subsequent incidence of restenosis, in the absence of recurrent foot, ankle, or lower leg trauma, such lesions will often remain clinically silent after satisfactory healing.

One point concerning percutaneous infrapopliteal revascularization requires special emphasis: the incidence of restenosis—which remains high—should not be a factor in the decision to use a percutaneous approach for what is, in many of these patients, a short-term problem. If uninterrupted patency of even one vessel can be achieved, the improvement in antegrade nutrient flow is typically adequate to facilitate limb salvage. Once healed, most patients will do satisfactorily, even in the face of documented reocclusion or restenosis. This strategy is further supported by the fact that both short- and long-term outcomes of distal surgical reconstruction for infrapopliteal disease are likewise imperfect (104). It is also conceivable that both of these revascularization strategies will be supplemented in many instances by the strategy of therapeutic angiogenesis (10,105,106).

When performing infrapopliteal PTA, care should be taken to ensure that subsequent surgical options are not compromised. For example, overdilation and disruption of a distal, previously uncompromised vessel may prohibit subsequent bypass to that site. Rotational atherectomy or excimer laser angioplasty can be useful as adjunctive therapy to angioplasty, particularly for lesions that have unfavorable morphology, such as total occlusions, heavy calcification, and ostial disease. Endovascular stents are not currently recommended for infrapopliteal vessels.

BYPASS GRAFTS

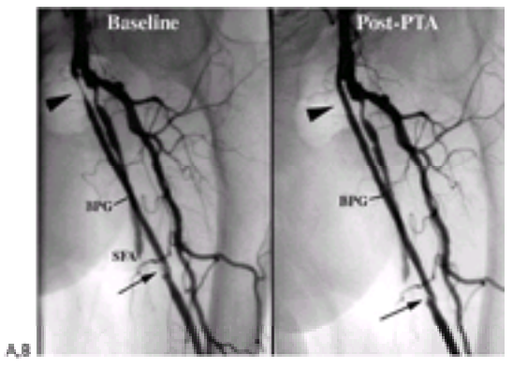
Stenosis in a lower extremity bypass graft can threaten the patency of the graft and shorten its life. Stenosis that occurs within the first few weeks of graft placement usually indicates a technical problem best treated by surgical graft revision. Graft failure within months to 1 year can be due to myointimal hyperplasia, atherosclerosis, or progressive fibrosis of a poor venous conduit. Other factors contributing to graft failure include the presence of poor inflow or poor outflow, low cardiac output, presence of a hypercoagulable state, compression of the graft due to compromised patient positions, and external compression of the graft by sclerosis and fibrosis. Prosthetic conduits are more likely to present with abrupt occlusion, whereas native venous conduits tend to present with a progressive downhill course. Of course, even in the case of the latter, abrupt thrombosis and acute limb ischemia can occur.

Graft failure or impending graft failure is often not heralded by increasing clinical symptoms. Accordingly, a strategy of regular graft surveillance using duplex ultrasonography is paramount to preserving patency and extending the life of the graft and optimizing the results of revascularization therapy (107). For impending graft failure, either detected by duplex ultrasonography or increasing symptoms, immediate arteriography is recommended, followed by either surgical or percutaneous revascularization.

Percutaneous revascularization represents an alternative to operative reconstruction for failing or failed native or prosthetic conduits. Nonsurgical revascularization has several obvious advantages: It saves the patient the morbidity and additional hospitalization associated with a repeat surgical procedure; it does not require the availability or use of additional native veins; and in certain cases it may obviate the need to use prosthetic materials for distal reconstruction, an application for which such materials have been shown to confer lower patency rates (108,109).

The published results of PTA of *stenotic* lower extremity bypass grafts are extremely variable. Series in the surgical literature suggest that, although PTA can be acutely successful, the long-term patency is inferior to that associated with surgical revision (110,111). Our own approach to stenotic grafts is to make at least one attempt at percutaneous revascularization. This approach is derived from consideration of several issues. First, percutaneous revascularization of stenotic grafts is most often technically straightforward. Second, the risk of serious complications is low. Third, the contribution of adjunctive diagnostic and therapeutic techniques, including IVUS, DA, and endovascular stents, to preservation of graft patency remains essentially untested. Fourth, surgical revision itself is complicated by imperfect long-term patency (56,112,113).

Currently, PTA is recommended for cases of graft stenosis with myointimal hyperplasia, vein fibrosis, sclerotic valves, focal proximal (eFig. 111.6.1) or distal anastomotic lesions of a femoropopliteal or femorotibial graft, and short-segment lesions (3 cm or less), particularly if the vein size is greater than or equal to 3.5 mm and the lesion is more than 3 months out from surgery (114). Lengthy lesions (especially more than 10 cm) and stenoses associated with anastomotic aneurysms are recommended to undergo surgical revision. Furthermore, in the presence of a proximal or distal anastomotic lesion, it is conceivable that the lesion may be resistant to balloon dilation alone. In these cases, DA is a useful tool for salvaging the graft and improving the outcome of the percutaneous intervention (115). Reported technical success rates in excess of 90% and 2-year patency rates of 80% compare favorably to balloon angioplasty and surgical revision. Although stents have been used in failing vein grafts, this strategy has not yet been studied in any formal trials.



***e*FIGURE 111.6.1 A:** Right anterior oblique view of critical stenosis (*arrowhead*) at origin of femoropopliteal graft (BPG) and moderate irregular lesion (*arrow*) at distal end of jump-graft placed during previous graft revision. The superficial femoral artery (SFA) is occluded proximally. Lesions were detected during routine surveillance (patient asymptomatic). Due to proximity of lesions to ipsilateral common femoral artery, contralateral access may be preferred. **B:** After percutaneous transluminal angioplasty (PTA), stenoses are eliminated, but regular surveillance will be essential to prevent graft failure. Arrowhead indicates location of original stenosis; arrow indicates location of original lesion.

The approach to *occluded* lower extremity bypass conduits varies widely from institution to institution. Revascularization strategy should be based on consideration of numerous factors, including degree of ischemia present, type of graft material (e.g., prosthetic or autogenous vein), age of the graft, level of obstruction and accessibility for catheter-directed thrombolysis, presumed etiology of occlusion, and presence of comorbid conditions. Often, determination of the factor(s) responsible for graft failure is not possible before reestablishing enough flow to visualize the graft angiographically. Review of previous angiograms, including previous baseline (pregraft) and immediate postgrafting ("completion") studies, often provides a clue as to the factors that may have contributed to thrombosis. In cases of early graft failure (e.g., less than 3 months), reexamination of the angiograms for signs of technical or anatomic problems is crucial. Findings such as inadequate inflow to the graft due to proximal atherosclerosis, absence of adequate distal runoff vessels, mild residual narrowing at proximal or distal anastomotic sites, and presence of residual venous side branches are all potential sources of graft compromise that can have been underestimated or unrecognized altogether. Reevaluation of the patient's clinical and hematologic parameters is equally important: It is not unusual to detect an occult hypercoagulable state, such as protein C or S deficiency, which predisposed the patient to graft thrombosis.

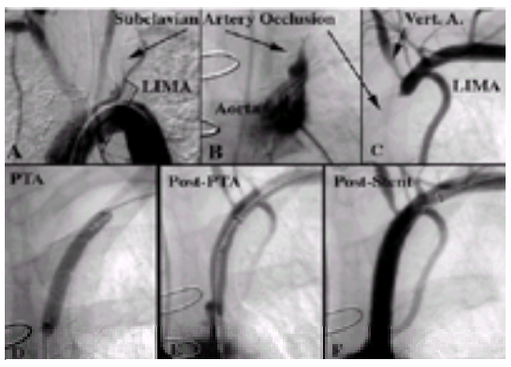
Decisions regarding revascularization of an occluded graft should be made in conjunction with vascular surgical colleagues. Thrombosis of a very recently placed graft (e.g., less than 1 month) usually suggests the presence of an underlying anatomic or technical issue that is better treated by surgical thrombectomy and revision. The exception to that is the prosthetic graft (especially infrainguinal), which may thrombose spontaneously in the absence of obvious pathology, presumably because of the presence of thrombogenic foreign material. In these patients, even with recently placed grafts, prompt initiation of catheter-directed thrombolytic therapy may rapidly restore patency and enable angiographic evaluation and treatment of flow-limiting lesions. If none is detected, aggressive treatment with combined anticoagulation and antiplatelet agents is initiated in an attempt to prevent recurrent spontaneous thrombosis. Patients presenting with acute or subacute thromboses (less than 14 days) are best treated with catheter-directed thrombolysis (49,91). An alternative is balloon embolectomy, although this strategy may be associated with a higher morbidity and mortality over the ensuing year (91). Catheter-directed thrombolysis also remains an option for late or delayed (more than 3 months) occlusion of autogenous vein grafts. Angiography after successful elimination of thrombus often identifies a stenosis—anastomotic or elsewhere—that may have been primarily responsible for the graft occlusion. Treatment of the stenotic site with balloon angioplasty or DA can successfully restore long-term patency.

SUBCLAVIAN AND INNOMINATE ARTERIES

The vast majority of disease in these vessels is due to atherosclerosis. However, giant cell arteritis, Takayasu's arteritis, and fibromuscular disease (FMD) can also cause clinically relevant disease (116,117 and 118). Clinical indications for subclavian revascularization are symptomatic ischemia of the posterior fossa (e.g., vertebral-basilar insufficiency) or upper extremity, with or without subclavian steal syndrome; preservation of flow, in which thrombosis or progressive stenosis could have devastating consequences, especially in the case of coronary artery bypass graft surgery using the internal mammary arteries (e.g., ischemia in left internal mammary artery/right internal mammary artery territory with or without coronary-subclavian steal syndrome) (*e*Fig. 111.6.2); preservation of inflow to axillary graft or dialysis conduit; and "blue digit" syndrome (embolization to fingers). Routine examination (measurement of cuff pressure and palpation of pulses in both upper extremities plus auscultation over the supra- and subclavicular areas) uncovers patients with asymptomatic subclavian disease. Initially, such patients do not require treatment but should be followed closely for progression or development of related symptoms. Noninvasive testing with duplex ultrasound is essential, with determination of the direction of flow in the vertebral arteries (antegrade or retrograde, the latter indicating the presence of a steal syndrome) and documentation as to the presence or absence of carotid disease.

VIDEO

Video 111.2 Severe stenosis of left subclavian artery. In this selective angiogram, a severe atherosclerotic narrowing with the left subclavian artery is evident. This lesion is proximal to the origin of the left internal mammary artery. In patient's with subclavian stenosis, angina can be produced despite a normal left internal mammary and left anterior descending bypass graft. *This video must be viewed with QuickTime. If you do not have QuickTime you may download it here.*



***e*FIGURE 111.6.2** Subclavian artery revascularization for disabling upper limb claudication, subclavian steal syndrome, and coronary steal syndrome in an elderly patient. **A:** Arch aortogram discloses short segment occlusion of the left subclavian artery (SCA) 1 cm from the origin, with reconstitution distally. Retrograde filling of the left internal mammary artery (LIMA) is also present. **B:** Selective cannulation of SCA demonstrates a "beak-like" obstruction. **C:** Angiography via brachial artery access demonstrates reconstitution via thoracic collaterals proximal to the left internal mammary artery and vertebral artery (Vert. A.). **D:** Percutaneous transluminal angioplasty (PTA) was performed after the lesion was traversed with a Glidewire from the arm and resulted in restoration of luminal patency with residual stenosis. **E:** Stent deployment was successfully performed proximal to the vertebral artery to include the origin of the SCA. **F:** Subclavian and coronary steal syndromes resolved, as did upper limb claudication.

Angioplasty of the subclavian and innominate arteries is now considered first-line therapy for focal subclavian stenoses, with reported technical success and complication rates of more than 90% and less than 10%, respectively (119,120). Recent series using primary stenting indicate that stenting may further improve the results (121,122), which already compare favorably to surgical alternatives. Complications are generally minor and infrequent but include problems related to femoral or brachial access, inadvertent "jailing," dissection, and embolization of the vertebral or left internal mammary artery (123). PTA has potential advantages over surgery: It eliminates the need for general anesthesia, shortens hospital stay, is less invasive, and reduces overall morbidity. It also avoids concern about potential stenosis in the carotid artery, which serves as the donor for carotid-subclavian bypass.

In contrast, despite a lower chance of success (50% to 75%) and increased potential to embolize thrombus or atheroma into the cerebral, upper extremity, or coronary

circulation, PTA for subclavian occlusions has been shown to be technically feasible (124) and, based on the favorable results of several investigators (125,126), appears to be an appropriate strategy for symptomatic patients. Furthermore, primary stenting (both balloon expandable and self-expanding) has also emerged as an appropriate initial strategy for symptomatic patients (126,127). One multicenter retrospective analysis compared primary subclavian stenting with surgical reconstruction and demonstrated lower rates of stroke, mortality, complications, and recurrence for the stent group (128).

Restenosis within subclavian arteries occurs in 10% to 20% of patients. Stent compression should be treated by balloon reexpansion and placement of a self-expanding stent within the old device. A special category of patients with subclavian obstruction—those with so-called coronary subclavian steal syndrome—respond quite nicely to PTA and stent deployment. In such patients, restoration of antegrade flow into the carotid and internal mammary artery can be life-saving (*e*Fig. 111.6.2) (129).

CAROTID ARTERIES

Atherosclerotic disease predominates at the common carotid bifurcation, a site easily accessible for surgical carotid endarterectomy (CEA). Indeed, revascularization of carotid arteries has, until recently, been considered to be exclusively within the purview of surgery. Since the first CEA more than 30 years ago, the associated morbidity, mortality, cost, and patient inconvenience associated with this procedure have been reduced considerably, such that CEA is currently recognized as the gold standard of therapy for patients deemed to require carotid revascularization. Supporting this are the landmark North American Symptomatic Carotid Endarterectomy Trial and Asymptomatic Carotid Artery Study trials demonstrating that surgical endarterectomy, when performed for carotid bifurcation disease by experienced vascular surgeons on appropriately selected patients, is effective in reducing the likelihood of stroke compared with medical therapy (130,131).

Carotid balloon angioplasty (CPTA) was performed as early as 1983, but due to the excellent results associated with CEA and concerns about the potential for distal embolization (132) and vessel recoil/thrombosis, the use of PTA for carotid disease (especially at the bifurcation) was limited to single-center anecdotal reports. Currently most institutions reserve percutaneous treatment of carotid arteries for those circumstances wherein the surgical risk is increased (133,134,135 and 136), such as in patients with either high cervical stenosis (i.e., under the angle of the mandible) or stenosis within the proximal common carotid artery near the aortic arch, which would require extensive intrathoracic surgery. In addition, patients with prior neck irradiation or radical neck dissection and those with restenosis at a previous endarterectomy site have also been considered appropriate for percutaneous intervention because of the increased risk of surgery in these subsets. Successful PTA, especially with the adjunctive use of endovascular stents, in these high-risk patients has led to consideration of the possibility that the less invasive, percutaneous approach might be applied more widely for carotid artery disease (Fig. 111.7).

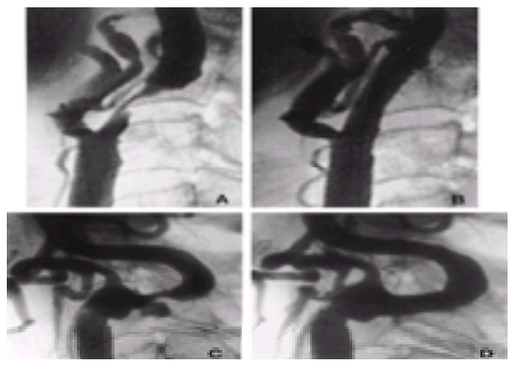
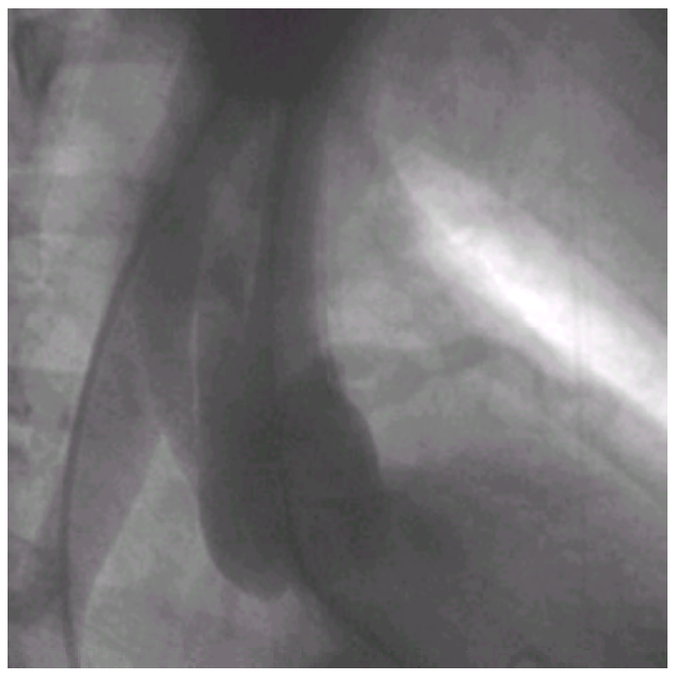


FIGURE 111.7 Bilateral carotid artery revascularization with balloon angioplasty and stent deployment in an 82-year-old asymptomatic male with “isolated hemispheres.” **A:** High-grade stenosis of right internal carotid artery. **B:** Status post-percutaneous transluminal angioplasty and Wallstent deployment, with marked improvement and only mild residual narrowing. Wallstent extends into common carotid artery. No significant compromise in external carotid artery. **C:** High-grade, ulcerated stenosis in proximal left internal carotid artery, revascularized 4 weeks after percutaneous transluminal angioplasty of the right side. **D:** Status post percutaneous transluminal angioplasty and Palmaz stent deployment in proximal left internal carotid artery. Excellent result with no residual stenosis. Both procedures were uneventful, and the patient remains asymptomatic at 1-year follow-up.



A 77-year-old male patient presented to the emergency department with severe chest pain and hypertension. Aortogram revealed type A aortic dissection.

The work of Roubin, Iyer, Yadav, Vitek (133,137,138), and others (139) demonstrated superior results of primary (as opposed to provisional) stenting (CPTA/stent) in carotid arteries, possibly due to more complete effacement of the plaque and associated ulcerations, reduction in elastic recoil, and restoration of laminar flow. Intermediate-term results demonstrate comparable safety (particularly the risk of neurologic events) and efficacy to CEA, especially when taking into account the selection of patients in higher-risk categories (lesion site, comorbid conditions) (140,141,142 and 143) (Fig. 111.8). Although technologic advances in stents, sheaths/guiding catheters, and diagnostic catheters may have contributed to the improved results, the reduction in events is principally due to increased operator experience and refinements in selection criteria.

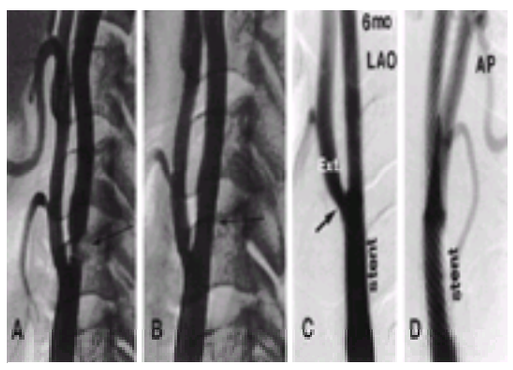
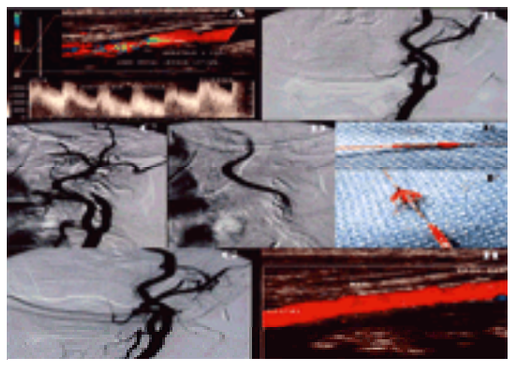


FIGURE 111.8 Carotid stent deployment in an 82-year-old patient with highly unstable angina on intravenous nitroglycerin, awaiting coronary artery bypass graft. Contralateral internal carotid artery is completely occluded, and both vertebral arteries are 95% narrowed. **A:** Before percutaneous transluminal angioplasty, internal carotid artery has severe, ulcerated, focal stenosis (*arrow*). **B:** After percutaneous transluminal angioplasty and deployment of Wallstent. Stenosis now ameliorated (*arrow*); flow improved into internal carotid artery. External carotid artery (Ext.) is minimally compromised. Patient subsequently underwent uneventful coronary artery

bypass graft 1 day after percutaneous transluminal angioplasty. Left anterior oblique (LAO) **(C)** and anteroposterior (AP) **(D)** angiograms of right carotid artery 6-month status post Wallstent deployment demonstrate widely patent carotid artery. In **(C)**, Wallstent covers origin (*arrow*) of external carotid artery, which remains patent. Minimal neointimal growth within stent is seen in anteroposterior view. Patient remains free of neurologic and cardiac symptoms 14 months later.

Subsequently, prospective randomized trials have been initiated to compare the percutaneous versus surgical modalities to identify the role for CPTA/stenting. CAVATAS (144) enrolled 504 patients (253 CEA, 251 CPTA) and reported comparable 30-day major stroke and mortality rates between surgery and angioplasty. The Carotid Revascularization Endarterectomy Versus Stent Trial, a large National Institutes of Health–sponsored multicenter study, promises ultimately to provide more definitive information regarding the role of CPTA/stenting, at least in patients with symptomatic disease (145,146).

It remains to be determined what will be the best stent design for use in the carotid arteries. Despite initial excellent results with balloon-expandable Palmaz biliary stents (139,140), the infrequent but troublesome occurrence of stent compression (147) has led most investigators to favor the use of self-expanding stents that are lower profile, flexible, and able to be placed accurately. There are also tremendous enthusiasm and anticipation surrounding the development of distal protection devices to avoid embolization during carotid angioplasty (eFig. 111.8.1). Clinical trials in Europe (148) and early investigational studies in the United States have shown promising results with devices involving the use of a distal trap, or umbrella, encasing a filter, which collects particulate debris. It is anticipated that these will significantly reduce the embolic complications associated with CPTA/stenting.



***e*FIGURE 111.8.1** Carotid percutaneous transluminal angioplasty and stenting with distal protection in a 78-year-old man. **A:** Duplex ultrasound with color Doppler flow demonstrates critical stenosis in the left internal carotid artery with diastolic flow velocities of more than 350 cm per second (systolic velocities were more than 500 cm per second). **B:** Selective left common carotid angiography in the anteroposterior projection demonstrated more than 90% lesion in the proximal left internal carotid artery. **C:** Angiography after percutaneous transluminal angioplasty and stent deployment revealed slow flow (TIMI-2) distal to the instrumented site. **D:** Later images demonstrated haziness in the region of the carotid siphon at the site where the distal protection device was located. **E:** The Angioguard distal protection device still constrained after removal from the patient. **F:** Particulate matter visible within the umbrella of the device. **G:** Final angiographic image after removal of the distal protection device demonstrating excellent luminal patency and normal distal antegrade flow. **H:** Duplex ultrasound 4 weeks after stent.

VERTEBRAL AND BASILAR ARTERIES

Vertebral artery stenosis is a common finding in patients undergoing arch or subclavian angiography. Although the vertebral artery is usually easy to access, revascularization is indicated only in patients with indisputable symptoms of vertebral basilar insufficiency that include diplopia, dysarthria or global aphasia, dizziness or vertigo, and altered state of consciousness. In rare instances, a patient with an obstructed carotid may present with classic carotid, as opposed to vertebral, ischemia. In such cases, if the vertebral artery gives rise to collaterals (via posterior communicating artery), PTA of the stenotic vertebral lesion is justified. The significant downside of failed or complicated vertebral PTA (including potentially fatal brainstem CVA) makes case selection critical. Before undertaking vertebral intervention, therefore, it is important to define the pattern of intracerebral blood flow and collateral circulation (with MRA or four-vessel angiography).

Intervention in the basilar artery is considered to be even more hazardous because it is a “terminal vessel,” responsible alone for perfusion to a number of critical central nervous system areas, especially the brainstem. Accordingly, basilar artery PTA is reserved for the rare instances in which patients present with symptoms unequivocally related to a critical stenosis or acute occlusion. Revascularization in the latter case often requires use of thrombolytic therapy and can produce dramatic recovery of patients who were previously near death. Given the high stakes involved in vertebral-basilar instrumentation, neurology should be involved in any decisions regarding therapy for the posterior cerebral circulation.

RENAL ARTERIES

The primary goals of renal artery revascularization are to improve control of hypertension; preserve or restore renal function; or treat the physiologic effects of severe RAS, which include congestive heart failure (CHF), recurrent flash pulmonary edema, and angina. Associated secondary benefits may include reduction in antihypertensive medications, ability to more safely administer angiotensin-converting enzyme inhibitors in patients with chronic CHF or cardiomyopathy, and, occasionally, elimination of the need for dialysis.

Since Gruentzig first reported successful application of balloon catheters for renal angioplasty (149), controversy has persisted regarding which lesions to treat by PTA, with or without stent deployment, versus surgery, and at what threshold revascularization should be recommended. The paucity of controlled trials comparing medical therapy, surgery, and PTA precludes formulation of conclusions regarding the relative merits of each strategy. Nevertheless, percutaneous revascularization offers an attractive alternative to surgical bypass or endarterectomy, which are more invasive and associated with higher morbidity. However, when analyzing indications and results, it is important to distinguish between lesion etiology—fibromuscular dysplasia (FMD) and atherosclerotic disease, the latter being much more common—and lesion location (ostial, mid-vessel, or branch). Additional considerations include the condition of the adjacent aorta and the presence of comorbid conditions, such as CAD.

Fibromuscular Disease

Surgical revascularization for severe hypertension due to FMD is exemplary in the hands of surgeons with extensive experience (150), but the role of surgery has nonetheless declined for this entity, a reflection of the fact that PTA alone is quite effective. For lesions localized within the main renal artery or its primary branches, studies report acute technical success in excess of 90%, initial clinical success (elimination or significant reduction in hypertension at 6-month follow up) of 85% to 90%, 5-year recurrence rates of less than 10%, and long-term clinical benefit in 80% to 90% (151,152 and 153). Hence, the threshold for PTA in patients with FMD is relatively low; patients with persistent, even modest, hypertension on medications should be treated, especially if they are young, so as to avoid the long-term consequences of hypertension.

The experience with PTA for FMD involving branch vessels and/or aneurysmal disease is limited. Although surgical revascularization is still advocated using extracorporeal reconstruction of the branch vessels, reports of technical and clinical outcomes approaching 85% suggest that PTA may offer an effective alternative treatment (154); the decision to attempt PTA on smaller branch vessels, however, must be weighed against the potential to cause dissection, thrombosis, and loss of the kidney.

The use of endovascular stents has not generally been advocated in FMD patients for two main reasons. First, the results with balloon angioplasty alone for FMD have been excellent, with lower recurrence rates than atherosclerotic disease. Second, the biologic effects and long-term consequences of placing stents in these lesions are unknown. Nonetheless, there have been anecdotal reports of stenting for refractory or recurrent FMD lesions.

Atherosclerotic Renal Artery Stenosis

Percutaneous treatment of atherosclerotic RAS has been less gratifying than that of FMD. However, balloon angioplasty can provide a safe and effective modality for renal revascularization, with a favorable risk-benefit ratio. In a pooled analysis of multiple early studies, percutaneous transluminal renal artery angioplasty (PTRA)

resulted in improved renal function in 43% of patients, stabilization in 35%, and continued worsening (e.g., no beneficial effect of PTRA) in 22% (155) but was hampered by a high restenosis rate, which approached 70% at 6 to 12 months, primarily related to the predilection for immediate and delayed elastic recoil as a result of the high prevalence (approximately 80% to 90%) of thick, calcified aorto-ostial plaque. The mortality rate in most series is less than 1%; contrast-related and atheroembolic events are surprisingly infrequent; and the majority of reported complications is related to vascular access.

On the other hand, primary surgical revascularization in appropriately selected good surgical candidates has shown to be effective both with respect to restoration of patency and favorable clinical outcome (preservation of renal function and reduction of hypertension) (155,156), and although the associated mortality can be significant (between 2% and 17%) (155,157,158), progression of surgical experience and technique (using extraanatomic bypass techniques) has resulted in significant reduction in mortality rates (150,159).

Weibull and colleagues, in one of the only randomized prospective trials, compared PTRA (without stenting) with surgical reconstruction in 58 patients 70 years old or younger with unilateral aorto-ostial (within 1 cm of the aorta) atherosclerotic RAS (160). There was no statistically significant difference in acute outcome. At 24 months, the primary patency in the PTRA group was only 62%, but secondary patency (90%), achieved by repeat PTRA or surgery, was comparable to that of patients initially randomized to surgery (97%). Results with regard to cure or improvement in hypertension were also similar, as was the frequency of complications. They concluded that a strategy of initial treatment with PTRA is indicated for RAS, with close clinical follow-up and additional PTRA or surgical revascularization for cases of initial failure or restenosis. Based on their data and using this strategy, one can expect that approximately 60% of patients will not require additional treatment after initial PTRA; of those with recurrent symptoms, 50% will require repeat PTRA, the other 50% surgery. Interestingly, over the 2-year study period, 14% of patients developed a new stenosis in the contralateral nonrandomized renal artery, necessitating additional treatment. This makes the case for less invasive initial therapy even more compelling.

The factor that is most predictive of initial failure or recurrence after PTRA alone is lesion location: Balloon dilation of stenoses located at the ostium are generally associated with an acute success rate of 50% or less and high restenosis rates (152,153,161). Although modifications in angioplasty technique, such as use of guiding catheters (162) and enhancement in imaging using IVUS (163), may facilitate PTRA, it is likely that the major limitation to successful dilation of ostial lesions will continue to be the elastic recoil of plaque, which is partially aortic in origin. Recent experiences using stents during PTRA to augment lumen size and reduce recoil, particularly for ostial stenoses, have clearly demonstrated much more complete amelioration of the stenosis and transstenotic pressure gradient compared with balloon angioplasty alone (Fig. 111.9) (164,165). Blum and colleagues, in a study of stent deployment for failed angioplasty of ostial lesions (166), reported 11% restenosis (more than 50% stenosis), 92% secondary patency at 60 months, 16% reversal of and 62% improvement in hypertension, and stability of renal function even in patients with baseline renal dysfunction. Palmaz (167) analyzed results from renal artery stenting in eight series (mean follow-up of 10.9 months); hypertension was improved in 56% or cured in 10%; renal function improved in 27% and stabilized (e.g., no further deterioration) in 38%; restenosis occurred in approximately 16% of patients; and major complications occurred in 4.9%. These results support the routine use of stents for renal ostial stenoses.

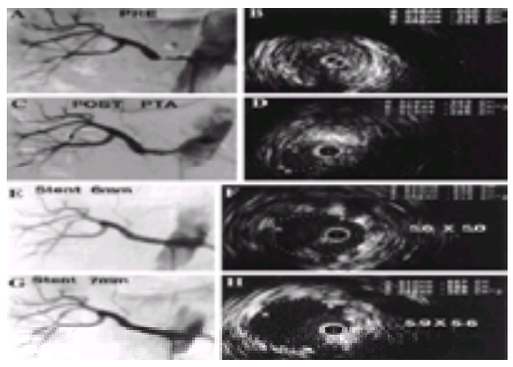


FIGURE 111.9 Percutaneous transluminal angioplasty (PTA) of the proximal renal artery lesion, guided by intravascular ultrasound (IVUS). **A:** Baseline angiogram depicts severe proximal renal artery stenosis. **B:** Corresponding IVUS image shows plaque abutting catheter circumferentially. **C:** Post-PTA, irregular lumen with plaque fracture and residual stenosis. **D:** IVUS post-PTA shows only modest enlargement of the lumen. **E:** Deployment and dilation of a Palmaz stent with a 6-mm balloon; angiographic result much improved over PTA alone. **F:** IVUS shows doubling in lumen diameter over PTA alone. However, in spite of excellent angiographic appearance, IVUS shows that the diameter of the treated segment is still less than the “reference segment.” **G:** After inflation with a 7-mm balloon, the angiographic result is slightly better. **H:** IVUS now shows the size of stented vessel is equal to that of the reference segment. This case highlights the usefulness of IVUS in renal angioplasty.

Complications related to balloon angioplasty and/or stenting of renal arteries occur in less than 10% of patients and commonly relate to access. The most feared complication, which probably occurs more frequently than is clinically appreciated, is that of atheroembolism into either renal vascular or peripheral vascular beds. Other complications of percutaneous renal revascularization include dissection of the renal artery or the wall of the aorta, acute or delayed thrombosis, and rupture of the renal artery.

Current Recommendations for the Treatment of Renal Artery Stenosis

The percutaneous approach is the initial choice of therapy for atherosclerotic renal artery stenosis. Furthermore, the evidence is overwhelming that stents, whether used primarily or provisionally, greatly enhance the results of PTA. Surgery is reserved for patients in whom PTA is less suitable, such as those with branch vessel disease, total occlusions, and stenosis in a renal artery that arises from within an AAA. The question remains of when revascularization should be undertaken. In considering this issue, 40% of patients with atherosclerotic renal artery stenosis will progress over 5 to 10 years. Furthermore, a small subset of patients (10% to 20%) will demonstrate deterioration in renal function immediately after revascularization, presumably due to cholesterol embolization or contrast toxicity. Patients with progressive renovascular disease—in association with steady decline in renal function, hypertension that is accelerated or difficult to control, or CHF—will generally benefit from renal revascularization. Patients who have recently developed end-stage renal disease, partly or wholly due to RAS, may also benefit from revascularization (158,168); PTRA may enable such patients to discontinue or avoid imminent dialysis (Fig. 111.10).

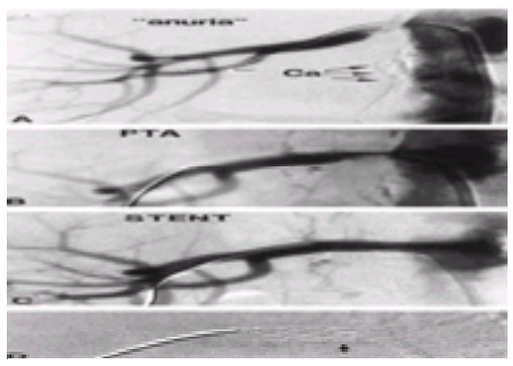


FIGURE 111.10 “Salvage” renal angioplasty and stent deployment in a woman with recent onset of renal failure, anuria, and severe, refractory congestive heart failure requiring intubation. **A:** Baseline angiogram obtained after traversing subtotal occlusion of right renal artery with guidewire. Aorta is very heavily calcified (Ca), and left renal artery is occluded; left kidney is nonfunctional. **B:** Status post balloon angioplasty alone [percutaneous transluminal angioplasty (PTA)] for this heavily calcified ostial stenosis; extensive recoil is evident. **C:** Vessel widely patent after stent deployment. Not significantly obstructive. **D:** Stent configuration without contrast demonstrates minor dimple (*arrow*) along inferior border caused by resistant aortic plaque. Patient began making urine immediately while on the angiographic table. Dialysis was discontinued immediately, and the patient left the hospital with a creatinine of 1.2 off dialysis 4 days after stent deployment. She remains off dialysis 1 year later.

Certain factors stand out as predictors of successful outcome. For patients with hypertension, the clinical factors predictive of a successful outcome include rapid acceleration of previously well-controlled hypertension or presence of malignant hypertension, hypertension in association with flash pulmonary edema,

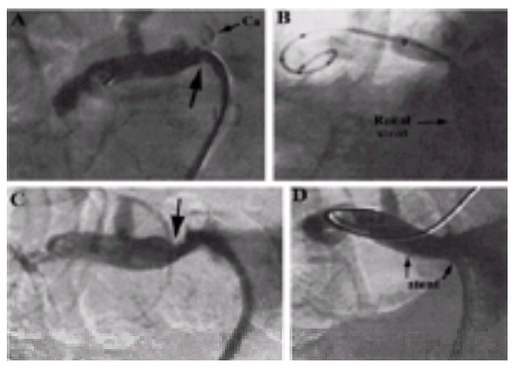
contemporaneous rise in creatinine, and development of azotemia in response to angiotensin-converting enzyme inhibitors, administered for control of hypertension. In patients with CHF, those with episodic flash pulmonary edema (as opposed to gradual fluid retention), especially in the absence of ischemic coronary disease or left ventricular dysfunction, are more likely to respond. PTRA and stents, like surgery (158,169), can be used successfully to restore or "salvage" renal function and eliminate the need for dialysis (170,171). More commonly than actually getting patients off dialysis, PTRA/stenting can slow the progression of renal dysfunction in patients with RAS (172). However, one cannot always predict which individuals with RAS, renal ischemia, and severe azotemia (creatinine of more than 2) are going to respond; factors predictive of success include recent rapid rise in creatinine unexplained by other factors, azotemia resulting from angiotensin-converting enzyme inhibitors, and absence of diabetes or other causes of intrinsic kidney disease. One strongly predictive factor is the presence of "global renal ischemia," wherein the entire functioning renal mass is subtended by bilateral critical stenoses or a severe unilateral lesion in the case of a solitary kidney. These patients can present with any combination of hypertension, congestive cardiac failure, or impaired renal function but invariably exhibit a favorable clinical response to successful intervention (173).

Some patients are less likely to benefit from renal artery revascularization. It is questionable whether patients with mild or moderate hypertension that is well-controlled medically, who also have unilateral RAS and normal renal function, will benefit from revascularization. Such patients should probably be followed longitudinally, with careful reevaluation of renal function and kidney size and control of blood pressure. Likewise, patients with severe baseline renal insufficiency secondary to nephrosclerosis (e.g., in diabetes), with superimposed RAS, are unlikely to benefit from revascularization. It is often difficult to discern what portion of the renal failure or hypertension is due to intrinsic kidney disease versus ischemic dysfunction. Hemodynamic variables such as an absent or minimal pressure gradient or renal size (less than 8 cm in length) may also help predict an unfavorable response to PTA.

MESENTERIC ARTERIES

Stenosis of mesenteric vessels is a frequent finding during routine angiographic studies of the abdominal aorta, but ischemic consequences of those stenoses occur infrequently, often with a subtle presentation not easily ascribed to mesenteric ischemia. The classic but uncommon syndrome of postprandial abdominal pain, gas, diarrhea, food avoidance, and weight loss is most likely to occur in the setting of severe global compromise of blood supply to the mesentery, such as from occlusion of two out of three mesenteric vessels and a critical stenosis in the third. There are syndromes with lesser degrees of ischemia wherein patients will present with variable symptoms, including mild postprandial aching or discomfort, diarrhea, nausea, or gaseousness, in which two mesenteric vessels are patent, but both with severe narrowing. Occasionally, even a single critically narrowed vessel can cause these symptoms.

As is the case with many other vascular sites, the standard of therapy for mesenteric disease has been surgical (endarterectomy or bypass), with a 6% mortality rate (174). In the current era, however, PTA can be effective in restoring acute patency, although restenosis rates are 50% or more because of the ostial location of these lesions (eFig. 111.10.1). Although prospective studies have yet to be done regarding long-term outcome after PTA/stenting, early indications suggest that stents reduce acute recoil and may lead to a better long-term patency (175,176 and 177). The biggest dilemma in patients with mesenteric disease is deciding who is likely to benefit. Certainly, the incidental finding of a mesenteric vessel during routine angiography for other reasons does not necessarily indicate the need for treatment. A conservative approach is indicated in situations in which symptoms of mesenteric ischemia are absent. At the other extreme, the percutaneous approach is ill advised in patients with acute mesenteric ischemia, in whom bowel infarction has already taken place. These patients are better served by surgical repair and intestinal resection.

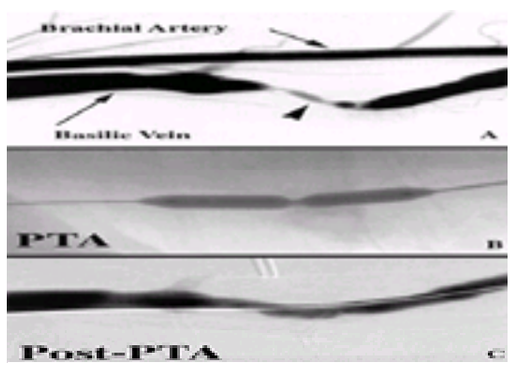


***e*FIGURE 111.10.1** Percutaneous transluminal angioplasty and stenting of celiac artery in a 68-year-old woman with severe intestinal angina and weight loss. **A:** Selective angiogram shows critical ostial stenosis (*large arrow*) due to calcific plaque (Ca). **B:** Waist (*large arrow*) in balloon at 8 atmospheres. Renal stent, placed 18 months earlier, is seen "on end." **C:** Recoil leaves residual stenosis (*arrow*) after percutaneous transluminal angioplasty. **D:** Stenosis alleviated after stent (Palmaz) deployed.

HEMODIALYSIS CONDUITS

More than 120,000 patients are dependent on hemodialysis, and recent evidence shows an increase of 10% per year (178). Nowadays, with the expanding dialysis population enjoying an increased life expectancy, preservation of vascular access sites has become increasingly important. Repeated large-gauge needle punctures, increased sheer forces and intraluminal pressure during dialysis, and postdialysis compression of puncture sites are all factors that may contribute to the high incidence of stenosis and thrombosis in dialysis conduits, be they arteriovenous fistulas or Gore Tex grafts. Arteriovenous fistulas tend to develop fibrous strictures at, and proximal to, sites of repeated puncture. Gore Tex grafts develop stenoses principally localized to the venous and arterial anastomoses; accumulation of pseudointima within the body of the graft may also predispose to graft failure. Surgical revision typically involves several days of hospitalization and placement of temporary access. A more important consequence of surgical revision, however, is the use of proximal vein, which may limit options for future surgical management. PTA has played an increasingly important role in maintaining the functional status of hemodialysis access conduits. The use of PTA for dialysis conduits requires a different perspective from PTA at other sites: Because the patency of dialysis conduits is problematic, regardless of whether surgery or other approaches are used, restenosis is tolerated at a higher frequency than in nearly all other circumstances.

Percutaneous treatment of stenotic or occluded grafts or fistulae is usually technically straightforward (eFig. 111.10.2). Acute success rates of 70% to 95% have been reported (178,179 and 180). However, primary restenosis rates are higher than for PTA in most other vascular beds, up to 60% and 80% at 1 and 2 years, respectively (180,181). *Secondary* patency, however, has been quite acceptable (more than 70% at 2 years) in series in which the investigators closely monitored graft function and performed early angiography and repeat PTA in cases of recurrent stenosis (180). Thus, although the average graft may remain functional only for 4 to 6 months after a single PTA, as opposed to 14 to 18 months after surgical revision (178), close monitoring of graft function and appropriately timed intervention can enhance the results of the percutaneous strategy and delay the need for graft revision.



***e*FIGURE 111.10.2** Percutaneous revascularization [percutaneous transluminal angioplasty (PTA)] of a hemodialysis conduit (arteriovenous fistula) in an elderly patient with chronic renal failure. **A:** Diagnostic fistulogram, obtained because of poor dialysis efficiency (high venous pressures) demonstrated a high-grade focal stenosis (*arrowhead*) in the mid-portion of the basilic vein. **B:** Angioplasty was performed using a noncompliant balloon. **C:** Final angiographic image demonstrated acute technical success with resolution of the stenosis and minimal elastic recoil.

Angioplasty of offending lesions in dialysis conduits often requires use of high-pressure (up to 20 atmospheres) inflation because of the fibrotic nature of the strictures within the venous system and at the graft anastomosis. IVUS is particularly useful for determining the reference diameter and quantifying the extent of recoil (182). Even aggressive angioplasty using oversized balloons, however, is often insufficient, in which case adjunctive treatment with DA may be useful to “cut” the fibrous band. Endovascular stents have also been investigated, but their role remains to be determined.

As suggested by several studies (178,179,183), management of dialysis conduits requires the cooperative efforts of a team consisting of nephrologists, vascular surgeons, and interventionalists. The nephrologists and dialysis nursing staff must pay close attention to the hemodynamic function of access sites during dialysis. Increase in venous pressure, decrease in arterial flow, increase in recirculation, and poor dialysis efficiency are all occurrences that should trigger the request for a diagnostic angiogram. Focal stenoses can be treated initially using PTA and, for resistant lesions, DA. Thereafter, patients should be monitored particularly closely, as one can expect a high incidence of restenosis. Repeated percutaneous interventions, in the interest of preserving the access site and avoiding the need to sacrifice additional vein, are appropriate. However, in cases of recurrent early failure and/or extensive graft degeneration, surgical revision becomes necessary.

CONTROVERSIES AND PERSONAL PERSPECTIVES

In general, the same rigorous standards that have been applied to studies evaluating management strategies in CAD have not thus far been applied to studies of peripheral artery revascularization (15). The development by Rutherford, Becker, and others of uniform standards for reporting results of interventions paves the way for the performance of prospective multicenter trials, which should enable more accurate comparison between various treatment strategies (2).

When Is It Appropriate to Revascularize?

The spectrum of thresholds for intervention is very broad, ranging from practitioners who will refer only PAD patients with advanced ischemia (Rutherford category 4) to those who consider lifestyle-limiting claudication grounds for considering revascularization. The former (conservative) approach is based on the premise that (a) this disease is not generally life-threatening and usually not limb-threatening; (b) any intervention uses up scarce health care dollars and limited resources; (c) the results of both PTA and surgery are imperfect; (d) complications can occur and are not entirely predictable; and (e) patients can occasionally be rendered worse off after (failed) intervention. However, an approach to patients solely based on these premises ignores the progress made in recent years treating PAD; the therapeutic armamentarium for and clinical experience with percutaneous revascularization has markedly improved the prospects of patients with PAD. In the bygone era, there was little reason to perform diagnostic angiography unless surgery was indicated, justifiably so given the risks of major reconstructive surgery in a high-risk population with coronary and cerebrovascular disease, thereby restricting surgery to patients with altogether disabling claudication or threatened limb loss.

In the current era, intervention at an earlier stage of symptomatic disability is possible due to the lower risks and lower costs of nonsurgical revascularization. As has been pointed out by Kumpe and Rutherford (184), “[T]he advantages to the patient able to undergo angioplasty rather than surgery . . . are lower initial morbidity and mortality, no need for general anesthesia, shorter hospital stay, [and] less trauma.” This is true even when one adds to the morbidity of PTA that of diagnostic angiography. Complications of PTA are for the most part minor and typically do not require surgical treatment (185). Access-related events account for most complications [2% to 8% in most series (184,185 and 186)]; these range from the less serious and more common (e.g., groin hematoma) to the serious but rare (e.g., retroperitoneal hematoma) (187). The incidence of complications at the angioplasty site—1% to 7% in most series (185,186,188)—is similar to that in percutaneous transluminal coronary angioplasty, and consists principally of acute occlusion; as with PTA, many of these can be managed with lytic or adjunctive mechanical therapy, including stents, so that the need for emergent surgery due to a jeopardized limb is rare. Distal embolization has been reported in up to 5% of cases (186). Most, however, are clinically silent (185), and even those that might be potentially problematic can often be obviated pre-PTA or treated successfully post-PTA by judicious use of lytic therapy.

It is nevertheless true that both the risks and cost of percutaneous revascularization increase with the complexity and extent of anatomic involvement. The decision to revascularize the patient with claudication in 2001 must therefore take into account two principal considerations. The first is the patient’s symptoms. Reduction in pulse amplitude or inability to palpate one or more pulses on physical examination altogether supports a vascular basis for the patient’s complaints. Noninvasive testing (189,190 and 191) continues to represent an indispensable and necessary initial step in the evaluation of PAD; importantly, failure to detect an abnormal ankle-brachial index at rest does not exclude the presence of severe obstruction, particularly in diabetic or other patients with calcified, noncompressible arteries. Exercise or alternative stress testing may be required to elicit hemodynamic evidence of symptomatic vascular obstructions. Duplex (189), including color-flow (191), examinations may help to clarify such discrepancies. Angiographic examination, however, is still required to define the second consideration, namely the full extent and complexity of the anatomic basis for symptomatic disability, although current advancements in magnetic resonance imaging allow a noninvasive approach.

Once having clarified the anatomic basis for claudication, the recommendation to advise percutaneous revascularization is then individualized. Two patients, for example, may be similarly limited, and in both, the degree of limitation may be inadequate to justify the risks of vascular surgical reconstruction. Diagnostic angiography may suggest that percutaneous revascularization has a high likelihood of technical success in one patient who may thus be a suitable candidate for percutaneous revascularization. In the second patient, certain risks and a complex of anatomic factors suggesting a low likelihood of acute or long-term success may dictate that only surgical revascularization would constitute effective therapy, in which case it may be appropriate to defer the risk of surgery until the patient is more critically disabled. Angiography may thus critically raise or lower the threshold for recommending that an intervention be performed. In previous days, when higher-risk and higher-cost surgery represented the sole option to medical and exercise therapy, it could be reasonably argued that the decision to proceed with angiography could come down to consideration of symptomatic disability only. The option of performing lower-risk and lower-cost PTA, however, implies that the threshold for responding to a given level of symptomatic disability may be raised or lowered, depending on the extent and complexity of anatomic findings.

Should the patient treated by percutaneous revascularization return with clinical evidence of restenosis, repeat percutaneous intervention is probably indicated for the same reasons that led to the recommendation for the original procedure. A certain proportion of these patients—as has been clearly documented in certain patients undergoing one or more repeat coronary angioplasty procedures (192,193)—will achieve a satisfactory long-term result after the second intervention. In those who fail repeated percutaneous attempts to achieve long-term patency, the decision to undergo surgical revascularization may involve a reassessment of the patient’s anatomy and clinical status.

Who Should Decide on the Revascularization Strategy, and Who Should Perform Percutaneous Interventions?

This controversy deserves but a few short lines. The concepts that are promulgated by some individuals within various specialties (vascular surgery: “our disease”; radiology: “our procedures”; cardiology: “our patients”) have no place in the workup and management of patients with PAD. Justification for so-called turf wars is difficult to find and seems to be based mainly on issues only tangentially related to patient care, at best. Such “battles” preclude cross-fertilization and exchange of knowledge and ideas among specialties. As such, patient care stands to suffer from the underuse of resources that could have been helpful.

The ideal approach to management of PAD, a truly multidisciplinary disease, requires coordinated input from experts in cardiology, vascular surgery, radiology, and vascular medicine. Formal or informal multidisciplinary vascular conferences provide an invaluable forum for exchange of knowledge and information, as well as an opportunity to develop management strategies for individual patients.

Regarding the performance of percutaneous interventions, such skills are not “specialty specific.” Whoever has acquired a good fund of knowledge and has fulfilled the requirements set forth by their institution, requirements presumably that are based more or less on the published guidelines of American College of Cardiology/American Heart Association, should be capable of performing the procedures for which he or she is trained.

THE FUTURE

As the population ages and patients are surviving with their heart disease, physicians are now grappling with the increased prevalence and disabling effects of vascular disease at other arterial sites, including carotids, renals, and lower extremities. Over the next 10 years, cardiologists will become much more aware and knowledgeable about PAD and involved in management issues related to this disease. Concurrently, detection and recognition of PAD will increase. The available treatment options, both conservative and invasive, will expand as well. Intensive efforts will be devoted to prevent the onset and halt the progression of vascular disease using powerful new lipid-lowering agents and aggressive risk factor modification. Similar resources will be used to prevent secondary recurrence after successful initial treatment. New innovative pharmaceutical agents currently under development may prove to be effective in treatment of intermittent claudication.

Invasive therapy for PAD will continue to shift toward a predominantly percutaneous, as opposed to surgical, approach. As interventions become more effective and safer, the threshold for treatment will be lowered and the number of percutaneous interventions will rise, probably dramatically. Restenosis, which remains the greatest enigma of percutaneous revascularization, will continue to complicate outcomes. However, the use of endovascular stents, which have already had a favorable impact on restenosis in coronary and iliac arteries, will be applied routinely to other vascular sites, including renal, carotid, vertebral mesenteric, aortic, and femoropopliteal vessels.

Meanwhile, additional promising strategies to reduce restenosis, including genetic and molecular manipulations and x-ray therapy, will be refined and will augment the beneficial impact of endovascular stents, further reducing the incidence of restenosis. The use of sophisticated imaging techniques, such as IVUS, MRA, and spinal computed tomography, will facilitate diagnosis and enhance the results of revascularization. These will also enable complex percutaneous procedures (e.g., exclusion of aneurysms by stent-grafting) to be performed with less risk and optimal results. Although novel treatment modalities will continue to be developed, third-party payors will require more rigorous documentation of outcomes using standardized measures that have not previously seen widespread application in PAD studies. There remains a concern that scrutiny by third-party payors and reduction in resources will stifle creative new research. As a consequence of the emphasis on risk factor modification, the aging of the population, and the shift toward catheter-based therapies, cardiologists will become increasingly involved with management of PAD. Finally, for patients who previously may have had to opt for amputation in the absence of viable options for conventional revascularization, the possibility of encouraging the formation of new vascular conduits by introducing angiogenic factors may offer these patients new hope for limb salvage. Indeed, if the angiogenesis trials and other molecular investigations currently under way produce favorable results, this could profoundly alter the way we approach both peripheral vascular and cardiovascular disease.

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112

RENAL ARTERY DISEASE

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OVERVIEW

Renal artery stenosis (RAS) is most commonly due to either fibromuscular dysplasia (FMD) or atherosclerosis. The former predominates in young women, whereas the latter is almost exclusively seen in individuals over the age of 55. Frequently, RAS is discovered incidentally during imaging studies for other reasons (atrophic or small kidney), or at autopsy. Incidental RAS is quite common (1,2), whereas renovascular hypertension occurs in only 1% to 5% of all patients with hypertension (3). The predominant clinical manifestation of FMD is hypertension. The hypertension can frequently be cured or significantly improved with percutaneous transluminal angioplasty (PTA). The predominant clinical manifestations of atherosclerotic RAS include hypertension, renal failure (ischemic nephropathy), and recurrent episodes of congestive heart failure and flash pulmonary edema (4,5).

The presence of anatomic RAS does not necessarily establish that the hypertension or renal failure is caused by the RAS. Many patients have had essential (primary) hypertension for years and then develop atherosclerotic RAS later in life. In patients with long-standing hypertension, it is unlikely to achieve a cure of the hypertension with surgical or percutaneous intervention. However, 50% to 80% of patients do experience improvement in blood pressure control (4,6,7,8,9 and 10). Ischemic nephropathy or flash pulmonary edema only occurs in the presence of bilateral renal artery disease or disease to a solitary functioning kidney. Percutaneous or surgical revascularization can lead to improvement or stabilization in renal function and improvement in congestive heart failure if the patients are selected carefully (8,11). Screening tests for RAS have improved considerably over the last decade. Although captopril renography was used almost exclusively in the past, duplex ultrasound of the renal arteries or magnetic resonance angiography (MRA) has replaced other modalities as the screening test of choice in many centers. Rarely does an arteriogram have to be performed for diagnostic purposes only.

Management of RAS consists of three possible strategies: medical management, surgical management, or percutaneous therapy with balloon angioplasty and stent implantation. The treatment of choice to control hypertension in patients with fibromuscular disease is percutaneous angioplasty. Renal artery stenting has replaced surgical revascularization for most patients with atherosclerotic disease who require an intervention.

HISTORICAL PERSPECTIVE

Richard Bright first demonstrated an association between hypertension and the kidney. In 1934, Goldblatt and colleagues (12) demonstrated that hypertension could be produced in dogs by constriction of one renal artery [two-kidney, one-clip (2K-1C) model], or both renal arteries or one renal artery if the contralateral kidney was removed (one-kidney, one-clip model). Houssay and Taquini (13) identified a pressor substance that may have been causing the hypertension, and Braun-Menendez and Fasciolo (14) named the substance *hypertensin*. They also demonstrated that this substance was formed in the blood by the actions of renin, an enzyme secreted by the ischemic kidney (15). Page demonstrated that renin produced a pressor substance that he called *angiotonin* (16). Shortly thereafter, it was noted that hypertensin and angiotonin were the same, and the substance was renamed *angiotensin*. Angiotensin was first isolated by Skeggs in 1954 (17), and its amino acid sequence described by Elliott and Peart in 1956 (18).

PATHOPHYSIOLOGY

Experimental Models of Renovascular Hypertension

Pickering clarified the difference between renovascular hypertension and RAS: "The demonstration of a RAS in a hypertensive patient does not necessarily establish a diagnosis of renovascular hypertension, because essential hypertension may accelerate the development of atheromatous plaques, which do not necessarily have any functional significance. Ideally, it is necessary to demonstrate that there is also renal ischemia, since this is thought to be the stimulus that raises the blood pressure, and leads to a decline of renal function" (19). Most investigators believe that there must be at least a 70% reduction in luminal diameter for a RAS to cause either hypertension or ischemic nephropathy (5,20,21).

Animal models for renovascular hypertension have helped to elucidate the pathophysiology of hypertension in patients with RAS (20,22,23 and 24). The renin-angiotensin-aldosterone system plays an important role, as shown in Figure 112.1 (10). In animals, the 2K-1C model is the classic model for renin-mediated hypertension and is analogous to unilateral RAS in humans. The one-kidney, one-clip model of renovascular hypertension is a model for volume-mediated hypertension and is analogous to bilateral RAS or RAS to a solitary functioning kidney in humans. Although the acute phases of both of these models are similar, different events occur in the chronic phase.

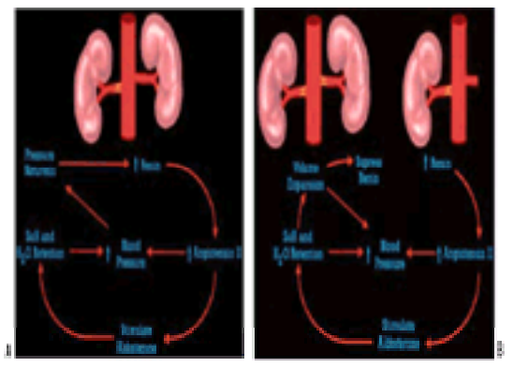


FIGURE 112.1 Pathogenesis of renovascular hypertension in unilateral **(A)** and bilateral **(B)** renal artery stenosis. (From Olin JW, Novick AC. Renovascular disease. In: Young JR, Olin JW, Bartholomew JR, eds. *Peripheral vascular diseases*, 2nd ed. St. Louis: Mosby, 1996:321–342, with permission.)

In the 2K-1C model (unilateral RAS), decreased renal blood flow stimulates the production of renin (Fig. 112.1A). Renin cleaves the proenzyme angiotensinogen to form angiotensin I and, in the presence of angiotensin-converting enzyme (ACE), is converted to angiotensin II. Angiotensin II has several important functions: (1) It elevates blood pressure directly by causing systemic vasoconstriction; (2) it stimulates aldosterone secretion, causing sodium reabsorption and potassium and hydrogen ion secretion in the cortical collecting duct; and (3) it changes the intrarenal hemodynamics, such as diminishing glomerular filtration, by decreasing glomerular capillary surface area and redistributing intrarenal blood flow. The salt and water retention (caused by excess aldosterone production) is rapidly excreted by the contralateral (normal) kidney by pressure natriuresis. This produces a cycle of renin-dependent hypertension (25,26 and 27).

Administration of an ACE inhibitor blocks this cycle and early in the course of renovascular hypertension returns the blood pressure to normal. There is decreased blood flow to the kidney with the clipped (stenotic) artery, increased renin secretion from the ischemic kidney, and suppressed renin secretion from the unaffected contralateral kidney in the 2K-1C model. It is important to differentiate the acute events from the more chronic events. Rats with the 2K-1C model of Goldblatt's hypertension have a rapid increase in plasma renin activity shortly after clipping the renal artery. When an ACE inhibitor or angiotensin receptor blocker (ARB) is administered, the blood pressure immediately declines (20,28). In the chronic phase, the blood pressure remains elevated, even though the plasma renin activity returns to baseline. When an ACE inhibitor or ARB is administered, the blood pressure does not immediately decline but takes 5 to 7 days (29) to return to normal. The delayed blood pressure response suggests that the blood pressure is no longer primarily caused by the direct effects of angiotensin II but involves some degree of salt retention as well. Reasons that have been proposed for this delayed response of an ACE inhibitor and ARB in 2K-1C Goldblatt's hypertension include a delay in drug penetration to sites of angiotensin II action such as the brain (30,31), and some functional effects of prolonged angiotensin II are transcriptionally mediated. This leads to the expression of nicotine adenine diphosphate oxidase, which provides a memory of past angiotensin II effects, thus sustaining the hypertension (32).

In the one-kidney, one-clip model of renovascular hypertension, there is a similar decrease in blood flow to the affected kidney(s), acutely causing the secretion of renin and synthesis of angiotensin II and aldosterone (Fig. 112.1B) (10). Angiotensin II directly elevates blood pressure, and aldosterone causes salt and water retention. In this model there is not a normal kidney that can *sense* the elevated blood pressure; therefore, pressure natriuresis does not occur. The increased aldosterone causes sodium and water retention and volume expansion. The expanded plasma volume suppresses plasma renin activity, thus converting the animal from renin-mediated hypertension to volume-mediated hypertension (28,33). During this stage, administration of an ACE inhibitor or ARB does not decrease blood pressure or change renal blood flow (35). Dietary restriction of sodium or administration of diuretics returns the subject to a renin-mediated form of hypertension and restores sensitivity to an ACE inhibitor or ARB. Functional renal insufficiency may occur in humans when ACE inhibitors are administered to patients with bilateral RAS or RAS to a solitary kidney, especially in the volume-contracted state.

The time course for the chronic phase to occur may be weeks in the one-kidney, one-clip rat model, whereas it may take up to 4 months in the 2K-1C rat model (34). In the 2K-1C model, loss of renin sensitivity in the chronic state may also occur and is caused by an inability of the contralateral (normal) kidney to excrete an increased sodium load when the blood pressure is increased (pressure natriuresis). This attenuation may occur due to changes in intrarenal hemodynamics and structural changes in the microvasculature of the kidney (35). For example, nephrosclerosis commonly occurs in patients with long-standing hypertension. If this patient later develops unilateral RAS, he or she may behave like a patient with bilateral disease since the contralateral kidney would not be able to excrete a salt load normally. Numerous other mechanisms have been shown to be important to varying degrees in the generation and maintenance of hypertension in animals and patients with RAS (23,38). Several newer concepts regarding the renin-angiotensin system have emerged. These include local production of angiotensins in various vascular beds, the discovery of biologically active peptides other than angiotensin II, and the identification of multiple angiotensin receptor subtypes. In addition, there is a body of evidence accumulating that nitric oxide, an endothelium-dependent vasodilator, plays an important role in blood pressure regulation (36). Endothelium-derived constricting factors (prostaglandin H_2 and thromboxane A_2) and endothelium-derived relaxing factors (nitric oxide) are both important in regulating vascular tone in the renal circulation (37).

Pathophysiologic Differences between Unilateral and Bilateral Stenosis

Whereas unilateral RAS closely resembles the 2K-1C model in animals, patients with bilateral RAS or RAS to a solitary functioning kidney probably have components of both renin-mediated and volume-mediated hypertension. Patients with bilateral disease may have high, normal, or low renin values depending on their volume status (38,39). Therefore, peripheral venous measurement of plasma renin activity is not a useful screening test for RAS.

There are three pieces of evidence that there is volume expansion in patients with bilateral disease: The cardiac output is usually higher than in patients with unilateral disease (40), recurrent pulmonary edema occurs almost exclusively in patients with bilateral disease or disease to a solitary functioning kidney (11,41,42), and restoration of blood flow to patients with bilateral disease or disease to a solitary functioning kidney is often accompanied by prompt diuresis (43).

Pathophysiology of Ischemic Nephropathy

There are numerous reports suggesting that patients who develop azotemia while receiving ACE inhibitors have bilateral RAS, RAS to a solitary kidney, or decompensated congestive heart failure in the sodium-depleted state (44,45,46,47,48 and 49).

There are two mechanisms by which renal functional impairment may occur with the use of antihypertensive agents. The first may occur with any antihypertensive agent when a critical perfusion pressure is reached below which the kidney no longer receives adequate perfusion. This has been shown by the infusion of sodium nitroprusside in patients with high-grade bilateral RAS. When the critical perfusion pressure was reached, the urine output, renal blood flow, and glomerular filtration rate declined and later returned to normal when the blood pressure increased above this critical perfusion pressure (44). The exact pressure necessary to perfuse a kidney with RAS varies with the degree of stenosis and is different among different patients.

The second mechanism is confined to patients receiving ACE inhibitor or ARB agents and may occur despite no significant change in blood pressure (49). Patients with high-grade bilateral RAS or RAS to a solitary kidney may be highly dependent on angiotensin II for glomerular filtration. This is particularly common in patients who receive a combination of ACE inhibitor and diuretic (50) or in patients who are placed on a sodium-restricted diet (51). Under these circumstances, the constrictive effect of angiotensin II on the efferent arteriole allows for the maintenance of normal transglomerular capillary hydraulic pressure, thus allowing glomerular filtration to remain normal in the presence of markedly diminished blood flow (Fig. 112.2). In this instance, glomerular filtration is highly dependent on angiotensin II. When an ACE inhibitor is administered, the efferent arteriolar tone is no longer maintained, and glomerular filtration is therefore decreased. A similar situation occurs in patients with decompensated congestive heart failure who are sodium depleted (47). Hricik and associates (51) demonstrated the important role that sodium balance plays in the azotemia associated with bilateral RAS or RAS to a solitary functioning kidney (*e*Table 112.0.1). When an ACE inhibitor alone was given, there was no change in renal function. However, if the patient was sodium depleted and then an ACE inhibitor was administered, the patient developed acute renal failure. This was rapidly reversed with the administration of intravenous fluids.

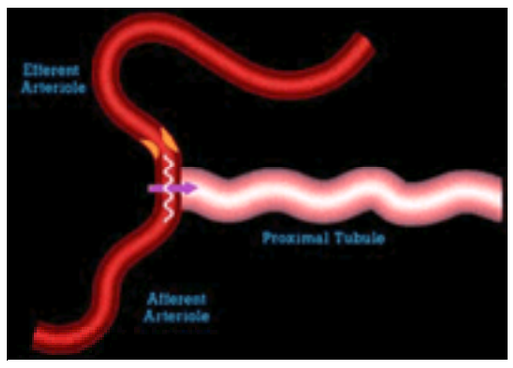


FIGURE 112.2 Patients with high-grade bilateral renal artery stenosis or renal artery stenosis to a solitary kidney may be highly dependent on the efferent arteriolar constriction caused by angiotensin II in preserving transglomerular capillary hydraulic pressure (*arrow*) and glomerular filtration rate. When an angiotensin-converting enzyme inhibitor is given, the efferent arteriole dilates, transglomerular capillary hydraulic pressure is not maintained, and blood is shunted from the afferent arteriole to the efferent arteriole, bypassing glomerular filtration.

***e*TABLE 112.0.1** ROLE OF SODIUM BALANCE IN RENAL INSUFFICIENCY CAUSED BY ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

	Sodium depletion (day 1)	**Sodium depletion plus captopril (day 2)**	**Sodium repletion (day 4)**	**Sodium repletion plus captopril (day 5)**
Weight (kg)	73.6	73.9	75.2	76.8
Serum creatinine (mg/dL)	1.5	3.6	1.6	1.6
Inulin clearance (mL/min)	73.0	37.0	62.0	53.0
Para-aminohippurate clearance (mL/min)	339.0	238.0	420.0	386.0

From Hricik D, Browning PJ, Kopelman R, et al. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenosis or renal-artery stenosis to a solitary kidney. *N Engl J Med* 1983;308:373, with permission.

There have been several animal studies suggesting that ACE inhibitor–induced acute renal failure may not be functional or reversible. Grone and Helmchen (52) have demonstrated that after 14 days of treatment with enalapril in rats with 2K-1C renovascular hypertension, proximal tubular atrophy occurred. This was not demonstrated in rats treated with dihydralazine. Jackson and colleagues (53) demonstrated more marked irreversible fibrotic atrophy in the clipped kidney in animals receiving enalapril compared with those receiving minoxidil or no antihypertensive treatment. These data have led some investigators (54) to suggest that the tubular interstitial changes represented a form of “disuse atrophy” due to hypofiltration.

Pathology of Renovascular Disease

Shanley suggested that loss of renal mass, loss of nephrons, and renal atrophy predominate in the pathologic picture of patients with renovascular disease (55). There is a point at which many of these changes are reversible, and the goal of management is to identify the patients early and treat them to prevent progressive renal failure. Prolonged ischemia leads to wrinkling and collapse of the glomerular capillaries (56). Long-standing renovascular disease is associated with small cortical infarcts and significant thickening, hyalinosis, and endothelial damage of the arterioles (57). Atheromatous embolization has also been associated with renovascular disease (58). The compilation of injury leads to cortical scarring, interstitial fibrosis, tubular collapse, and destruction of the renal architecture.

Systemic and glomerular pressure plays an important role in renal injury in patients with renovascular disease. In the 2K-1C model of renovascular hypertension, the unclipped kidney demonstrates significantly more vascular and glomerular damage than the clipped kidney (59,60). It is not clear whether this is due to a direct hemodynamic effect of the elevated blood pressure or the mitogenic and hypertrophic effects of angiotensin.

Nephrotic syndrome has been occasionally reported in patients with renovascular disease. There are observations that the nephrotic syndrome remits after correction of the RAS (61,62,63,64 and 65). The exact mechanism of nephrotic range proteinuria in renal artery disease is not well defined (66,67).

ANATOMIC CONSIDERATIONS

Atheromatous Lesions

Approximately 90% of all renovascular lesions are secondary to atherosclerosis (5). Although atherosclerotic RAS may occasionally be isolated to the renal artery alone, it is more commonly a manifestation of generalized atherosclerosis involving the aorta, coronary, cerebral, and peripheral vessels. Atherosclerotic RAS most often occurs at the ostium or the proximal 2 cm of the renal artery (Fig. 112.3). Distal arterial or branch involvement is distinctly uncommon (10).

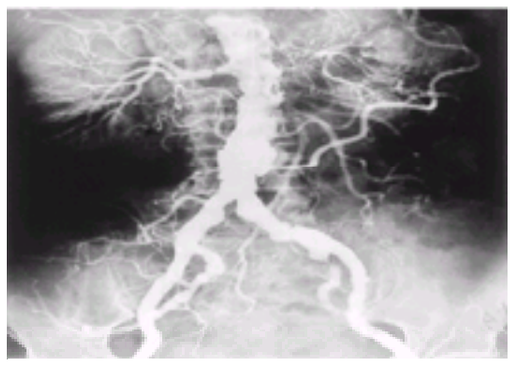


FIGURE 112.3 Aortogram showing severe proximal stenosis of the right renal artery. The left renal artery is occluded. Note the severe atherosclerosis in the aorta and iliac arteries. There is a large wandering artery of Drummond, indicating severe stenosis or occlusion of the superior mesenteric artery.

Fibromuscular Dysplasia

FMD is a nonatherosclerotic, noninflammatory disease that most commonly affects the renal arteries and is the second most common cause of RAS. The most common clinical presentation is that of hypertension in a young woman. FMD has been demonstrated in virtually every vascular bed. Renal artery involvement occurs in 60% to 75% of patients with FMD, followed by cervicocranial arteries in 25% to 30%, visceral arteries in 9%, and arteries of the extremities in approximately 5% of patients (68). It may present as a systemic disease (affecting a combination of the carotids, mesenteric, subclavian, and extremity vessels) in up to 28% of patients (69). The diagnosis is rarely made pathologically, but is usually determined by its typical angiographic appearance (Fig. 112.4). Although atherosclerosis involves the origin and proximal portion of the renal arteries, FMD characteristically involves the distal two-thirds of the artery and may involve the branches (70).

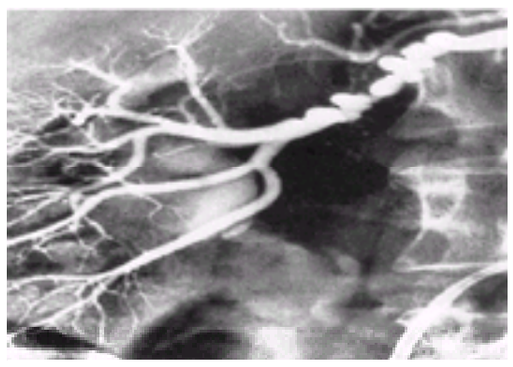


FIGURE 112.4 This renal arteriogram demonstrates typical medial fibroplasias of the renal artery. The “string of beads” appearance of the renal artery involves the distal portion of the main renal artery, and the “beads” are larger than the normal diameter of the artery. (From Olin JW, Novick AC. Renovascular disease. In: Young JR, Olin JW, Bartholomew JR, eds. *Peripheral vascular diseases*, 2nd ed. St. Louis: Mosby, 1996:321–342, with permission.)

The lesions of FMD are thought to be congenital dysplasias with maldevelopment of the fibrous, muscular, and elastic tissues of the renal artery. They are subcategorized according to the layer of the arterial wall involved (71). This classification is important since each type of fibrous dysplasia has distinct histologic and angiographic features, and each type occurs in a different clinical setting (Table 112.1).

Classification	Frequency	Pathology	Angiographic appearance
Medial dysplasia			
Medial fibroplasia	75–80%	Alternating areas of thinned media and thickened fibromuscular ridges containing collagen; internal elastic membrane may be lost in some areas.	“String of beads” appearance in which the diameter of the “beading” is larger than the diameter of the artery
Perimedial fibroplasia	10–15%	Extensive collagen deposition in the outer half of the media.	“Beading” in which the “beads” are smaller than the diameter of the artery
Medial hyperplasia	1–2%	True smooth muscle cell hyperplasia without fibrosis.	Concentric smooth stenosis (similar to intimal disease)
Intimal fibroplasia	<10%	Circumferential or eccentric deposition of collagen in the intima. No lipid or inflammatory component; internal elastic lamina fragmented or duplicated.	Concentric focal band; long smooth narrowing
Adventitial (periarterial) fibroplasia	<1%	Dense collagen replaces the fibrous tissue of the adventitia and may extend into surrounding tissue.	

From Begelman SM, Olin JW. Fibromuscular dysplasia. *Curr Opin Rheumatol* 2000;12:41–47, with permission.

TABLE 112.1 CLASSIFICATION OF FIBROMUSCULAR DYSPLASIA

Medial FMD has been further divided into medial hyperplasia (the only type in which there is true smooth muscle hyperplasia), perimedial dysplasia, and medial fibroplasia. Medial fibroplasia is the histologic finding in nearly 80% of all cases of FMD. It tends to occur in 25- to 50-year-old women and often involves both renal arteries. It has a “string of beads” appearance angiographically, with the “bead” diameter larger than the proximal, unaffected artery (Fig. 112.4). The areas of stenosis are often overshadowed by contrast medium in the microaneurysms, making the degree of actual stenosis difficult to assess. This beading is due to thickening of the media, interspersed by areas of aneurysmal dilatation. Microscopically, the internal elastic membrane is focally variably thinned and lost. Within the alternating thickened areas much of the muscle is replaced by collagen, hence the term *medial fibroplasia*. In other areas, thinning of the media occurs to the point of complete loss, and microaneurysms can be seen as saccules lined by only the external elastica. In extreme cases, giant aneurysms may be found in association with medial fibroplasia. Progression to total occlusion is rare in this subtype. Medial fibroplasia responds well to PTA.

Perimedial fibroplasia occurs predominantly in 15- to 30-year-old women. Of all fibrous lesions 10% to 15% are perimedial fibroplasias (10). These tightly stenotic lesions only occur in the renal artery and consist pathologically of a collar of dense collagen enveloping the renal artery for variable lengths and thicknesses. The collagen is deposited in the outer border of the media and usually replaces a considerable portion of it; in some areas of collagen it may completely replace the media.

The arteriogram of perimedial fibroplasia may give the appearance of arterial beading, but careful observation shows that the caliber of the normal segment of the vessel is not exceeded by the “bead.” This fact, along with the frequent occurrence of external collateral circulation, differentiates this lesion angiographically from that of medial fibroplasia. Perimedial fibroplasia produces severe stenosis and, although complicating thrombosis or dissection is relatively uncommon, progressive obstruction with ischemic renal atrophy occurs frequently.

Medial hyperplasia is an extremely rare disease, accounting for only 1% to 2% of fibrous lesions, and tends to occur in children and young adults. This is the only renal arterial disease in which true hyperplasia of the smooth muscle cell is present. The renal artery shows a concentric thickening of its wall with a mixture of proliferating smooth muscle and fibrous tissue in variable quantity. Arteriographically, medial hyperplasia appears as a smooth stenosis of the renal artery or its branches and, from a radiographic standpoint, may be indistinguishable from intimal fibroplasia. Most patients with this disease develop progressive vascular obstruction.

Intimal fibroplasia occurs in children and young adults and accounts for approximately 10% of the total number of fibrous lesions. This lesion is characterized by a circumferential accumulation of collagen inside the internal elastica lamina (72). Disruption and duplication of the elastica interna occur more often in younger patients, with dissecting hematomas as a complication in some patients. Intimal fibroplasia with complicating medial dissection is characterized pathologically by large dissecting channels in the outer one-half of the media. Arteriography in intimal fibroplasia reveals either a smooth long area of narrowing or a concentric band-like focal stenosis usually involving the midportion of the vessel or its branches. Dissecting hematomas may distort the area of the stenosis. Progressive renal artery obstruction and ischemic atrophy of the involved kidney may occur. Although intimal fibroplasia most commonly affects the renal arteries, this may also occur as a generalized disorder with concomitant involvement of the carotid, upper and lower extremities, and mesenteric vessels and may mimic a necrotizing vasculitis (73).

Some investigators consider the moyamoya syndrome to be a variant of FMD. In the moyamoya syndrome, there is RAS associated with abnormalities of the cerebral circulation. These may include stenoses of the carotid or intracranial arteries with an associated network of collateral vessels, the so-called puff of smoke appearance. There is an increased risk of intracerebral hemorrhage when these cerebrovascular abnormalities occur along with hypertension (74,75 and 76).

Miscellaneous Causes of Renovascular Disease

Renal Artery Aneurysms

Renal artery aneurysms may require surgical treatment when they are the cause of significant hypertension or to obviate the risk of rupture. The latter is of greatest concern with aneurysms that are larger than 2 cm in diameter and noncalcified, particularly when they occur in premenopausal women because of the predisposition for aneurysmal rupture during pregnancy (77,78). According to the classification of Poutasse (79), there are four basic types of renal artery aneurysms: saccular, fusiform, dissecting, and intrarenal.

Saccular aneurysms, which account for approximately 75% of renal artery aneurysms, are the most common. They generally occur at the bifurcation of the renal artery, perhaps due to an inherent weakness in the wall of the artery at this point. These aneurysms may become involved with secondary atherosclerotic degeneration, intramural calcification, or both. There are several mechanisms by which saccular aneurysms may be causally related to hypertension. These include compression or displacement of renal artery branches with resulting ischemia, aneurysmal erosion into a renal vein with formation of an arterial venous fistula, mural thrombus formation within the aneurysm with peripheral renal embolization, and the association of some aneurysms with stenosing fibrous renal artery disease. It is also well appreciated that saccular aneurysms can cause hypertension in the absence of these sequelae, most likely because of relative renal ischemia caused by the turbulent flow of blood as it passes through the aneurysmally dilated arterial segment. Fusiform renal artery aneurysms are almost always associated with stenosing fibrous renal artery disease. The latter is the cause for the severe hypertension generally seen in these patients. Fusiform aneurysms actually represent a severe poststenotic dilation of the renal artery. Dissecting renal artery aneurysms are most often a complication of intimal fibroplasia or atherosclerosis. These are often manifested clinically by the sudden onset of pain that stimulates renal colic and the development of gross or microscopic hematuria, which is quite common. In some patients, the

dissection in the wall of the vessel may reenter the lumen more distally. In other patients, total arterial occlusion with renal infarction may ensue.

Intrarenal arterial aneurysms are of mixed origin and may be congenital, posttraumatic, iatrogenic, neoplastic, or associated with polyarteritis nodosa. Intrarenal aneurysms that occur following blunt trauma or closed renal biopsy occasionally resolve spontaneously with expectant management. Intrarenal aneurysms do have the propensity for rupture, and surgical treatment may be indicated if their diameter is greater than 2 cm.

Other causes of renovascular disease include Takayasu's arteritis, atheroemboli, thromboemboli, spontaneous renal artery dissection, arteriovenous malformations or fistulas, trauma (e.g., from radiation, lithotripsy, direct injury, or surgery), and neurofibromatosis. Retroperitoneal fibrosis producing external compression has also been associated with RAS.

CLINICAL ASPECTS OF RENAL ARTERY STENOSIS

Primary or essential hypertension is present in over 60 million Americans. Renovascular disease and renal parenchymal disease are the most common secondary causes of hypertension after obesity, excess alcohol ingestion, drug abuse, and oral contraceptives. Patients with atherosclerotic RAS have the usual risk factors for atherosclerosis. Past or present smoking is especially common in patients with renovascular disease (80,81). There is conflicting information on the prevalence of RAS in blacks. Although Keith et al. reported that renovascular disease was much more common in whites than it was in blacks (82), others (83) have shown that the prevalence of renovascular hypertension is similar in blacks and whites. Blacks with primary (essential) hypertension are more likely to have severe hypertension leading to vital organ damage [i.e., stroke, end-stage renal disease (ESRD)] than whites.

Although the effect of atherosclerosis on the coronary and carotid arteries is well recognized, involvement of the renal arteries is frequently overlooked. It is known that patients with atherosclerotic RAS succumb prematurely from myocardial infarction and stroke (8,84,85 and 86). Therefore, early diagnosis and treatment are of vital importance to avoid premature morbidity and mortality.

Prevalence of Renal Artery Stenosis

Although there are excellent prevalence data in specific patient populations (i.e., those with coronary artery disease, aortic aneurysm, peripheral arterial disease), the prevalence of RAS in the general population is not known. Not all cases of RAS are clinically significant. Dustan et al. (87) reviewed 149 aortograms and found that approximately one-half of patients with greater than or equal to 50% RAS did *not* have hypertension.

The prevalence of atherosclerotic RAS has been reported in several autopsy series. Holley et al. (88) examined 295 consecutive patients and found RAS (defined as greater than or equal to 50% stenosis) in 53%. The prevalence increased to 74% when only those individuals older than 70 were considered. Likewise, Schwartz et al. (89) prospectively studied 154 consecutive patients at autopsy. They found RAS in 24% of all patients and in 86% of patients age 75 or older. More recently, 297 patients greater than 40 years old with autopsy-proven myocardial infarction were examined for evidence of atherosclerotic RAS (90). Significant stenosis (greater than 75% luminal narrowing) was documented in 12% of patients. Because atherosclerosis increases with age, it is understandable why the prevalence of atherosclerotic RAS would be greater among the elderly.

Several series have looked at the prevalence of renovascular disease in patients who have atherosclerotic disease elsewhere (91,92,93,94 and 95). To determine the prevalence of atherosclerotic RAS, we studied 395 consecutive patients who had undergone arteriography as part of an evaluation for an abdominal aortic aneurysm, aortoiliac occlusive disease, and peripheral arterial disease. In addition, 78 patients had an aortogram performed for suspected RAS (*e*Table 112.1.1) (1). These patients did not have the usual clinical clues to suggest RAS. High-grade bilateral renal artery disease was present in approximately 13% of patients. In the 319 patients reported in six different studies, 44% of patients had bilateral RAS (9). Other studies have shown that 22% to 59% of patients with peripheral arterial disease have significant RAS (96).

***e*TABLE 112.1.1** PREVALENCE OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS

³50% stenosis	Abdominal aortic aneurysm (n = 109)	Aortoiliac occlusive disease (n = 21)	Peripheral arterial disease (n = 189)	Renal artery stenosis (n = 76)
All patients	41 (38%)	7 (33%)	74 (39%)	53 (70%)[a]
Diabetic patients	6 (50%)	1 (33%)	34 (50%)[b]	10 (71%)
Nondiabetic patients	35 (36%)	6 (33%)	40 (33%)	43 (69%)[a]

[a]$p<.001$.
[b]$p<.02$.
From Olin JW, Melia M, Young JR, et al. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am J Med* 1990;88:46N–51N, with permission.

It has also been established that RAS is common in patients with coronary artery disease (97,98). Harding et al. (2) performed abdominal aortography at the time of cardiac catheterization in 1,235 patients and found that 30% had renal artery disease. Only one-half of the patients had documented luminal narrowing of at least 50%. It has also been shown that patients with RAS are more likely to have significant carotid or peripheral arterial disease (99,100,101 and 102). Louie and associates demonstrated that 46% of patients with greater than 60% RAS had greater than 50% carotid stenosis (100).

Some studies report disease prevalence for individuals in whom there are clinical clues to suggest the presence of RAS. This increases the pretest probability for underlying RAS and, as one would suspect, increases the prevalence of the disease. For example, we have demonstrated that 70% of patients with a suggestive history of RAS were found to have significant disease (1). The prevalence of renovascular hypertension was found to be high in patients with accelerated or malignant hypertension (103).

Natural History of Renal Artery Stenosis

Knowledge of the natural history of atherosclerotic renovascular disease is extremely important in the subsequent management of patients with RAS. Most natural history studies reported in the literature were retrospective studies. It is not only important to study anatomic end points (i.e., progression of stenosis), but also clinical end points (i.e., frequency of chronic renal failure and ESRD). These clinical end points have been lacking in many reports.

Anatomic Progression of Renal Artery Stenosis

In 1984, Schreiber and colleagues (107) retrospectively evaluated the angiograms of 169 patients: 85 patients had atherosclerotic renovascular disease, 75 patients had fibrous renal arterial disease, and 9 patients had components of both atherosclerosis and fibrous disease (*e*Table 112.1.2) (104,105 and 106). Of the 85 patients with atherosclerosis, 37 patients (44%) were found to have anatomic progression of RAS on repeat angiography, and 14 patients (16%) progressed to complete occlusion. The mean angiographic follow-up was 52 months (range, 12 to greater than 60 months). The rate of progression to total occlusion occurred more frequently (39%) when there was greater than 75% stenosis on the initial renal arteriogram.

***e*TABLE 112.1.2** NATURAL HISTORY OF ATHEROSCLEROTIC RENAL ARTERY STENOSIS

Series	Year	Reference	Follow-up (mo)	No. of patients	Progression no. (%)	Occlusion no. (%)
Wollenweber et al.	1998	104	3–88	30	21 (70)	—
Meaney et al.	1968	105	6–120	39	14 (36)	3 (8)
Dean et al.	1981	106	6–102	35	10 (29)	4 (11)
Schreiber et al.	1984	107	12–60+	85	37 (44)	14 (16)[a]
Tollefson et al.	1991	108	15–180	48	34 (71)	7 (15)
Total				237	116 (49)	28 (14)

[a]The rate of occlusion occurred in 39% of patients when the stenosis was ³75%.
From Rimmer JM, Gennari FJ. Atherosclerotic renovascular disease and progressive renal failure. *Ann Intern Med* 1993;118:712–719, with permission.

Tollefson et al. (108) studied 48 patients with 194 sequential aortograms over a mean period of 4.5 years. The renovascular disease progressed in 53% of the 79 vessels (34 of 48 patients, or 71%). Seven renal arterial stenoses in seven patients (15%) progressed to complete occlusion. Crowley et al. (109) assessed progression in 1,189 patients who had undergone renal angiography at the time of cardiac catheterization and later had a repeat cardiac catheterization. The disease progressed in 11.1%.

Zierler et al. (110,111) used renal duplex ultrasound to prospectively study anatomic progression of atherosclerotic renovascular disease. This study classified the RAS as follows: *normal* [peak systolic velocity (PSV) <180 cm per second and renal aortic ratio (RAR) <3.5]; *less than 60% stenosis* (PSV greater than or equal to 180 cm per second, RAR <3.5); *greater than or equal to 60% stenosis* (PSV greater than or equal to 180 cm per second, RAR greater than or equal to 3.5); and *occlusion* (no signal detected). If the renal arteries were normal, only 8% progressed over 36 months. However, at 3 years, 48% of patients progressed from less than 60% stenosis to greater than or equal to 60% stenosis. The four renal arteries that progressed to occlusion all had greater than or equal to 60% stenosis at the initial visit. Progression of RAS occurred at an average rate of 7% per year for all categories of baseline disease combined.

Clinical End Points

Several studies have evaluated clinical end points (deterioration of renal function, loss of renal mass, survival) as they relate to patients with progressive RAS. Dean et al. (106) evaluated 41 patients with atherosclerotic renovascular disease and renovascular hypertension randomly selected for nonoperative management. Serial renal function studies were performed prospectively on these 41 patients with a mean follow-up of 28 months (range, 6 to 102 months). Nineteen of 41 patients (46%) experienced an increase in serum creatinine between 25% and 120%, and the glomerular filtration rates dropped 25% to 50% in 12 (29%) patients. Fourteen patients (37%) experienced a reduction in renal length of more than 10%. Although not a direct measure of renal function, loss of renal mass has been associated with a loss of renal function.

The effect of RAS on kidney size has been well studied (112,113). Using duplex ultrasound, Caps and colleagues (113) prospectively followed 204 kidneys in 122 patients with known RAS for a mean of 33 months. The 2-year cumulative incidence of renal atrophy was 5.5%, 11.7%, and 20.8% in kidneys with a baseline renal artery disease classification of normal, less than 60% stenosis, and greater than or equal to 60% stenosis (p = .009, log rank test).

However, a question that has really never been satisfactorily answered is how common is atherosclerotic RAS as a cause of ESRD? Scoble et al. (114) found that atherosclerotic renovascular disease was the cause of ESRD in 14% of patients starting dialysis therapy. Mailloux and colleagues (86) reviewed the causes of ESRD in 683 patients over a 20-year period. Eighty-three patients (12%) had documented RAS as a cause of ESRD. Because these investigators only performed arteriography in patients in whom they highly suspected RAS, it is entirely possible that the true incidence of RAS as a cause of ESRD was seriously underestimated. RAS should be searched for in every patient starting dialysis if a clear-cut etiology for the ESRD is not known.

Connolly et al. (84) showed that the 2-year actuarial *renal* survival (percent of patients remaining off dialysis) was 97.3% for patients with unilateral RAS, 82.4% in patients with bilateral RAS, and 44.7% in patients who have stenosis or occlusion to a solitary functioning kidney. Patients on dialysis have a shortened life expectancy. The average life expectancy in a patient with ESRD greater than age 65 is only 2.7 years (115,116). The survival estimates are even worse if the patient has atherosclerotic renovascular disease as the cause of ESRD. Mailloux and associates (86) have shown that median survival for patients with renovascular disease was 25 months compared with 55 months in patients with malignant hypertension and 133 months for patients with polycystic kidney disease. The 2-year survival on dialysis in patients with renovascular disease was 56%, 5-year survival 18%, and 10-year survival only 5%. These data underscore the fact that patients with atherosclerotic RAS who progress to ESRD and require dialysis have extremely high mortality.

In addition, the mere presence of RAS, even before developing ESRD, portends a poor prognosis. Patient survival decreases as the severity of RAS increases (117), with 2-year survival rates of 96% in patients with unilateral RAS, 74% in patients with bilateral RAS, and 47% in patients with stenosis or occlusion to a solitary functioning kidney. Dorros and associates (9) demonstrated that as the serum creatinine increases, the survival decreases in patients with atherosclerotic RAS. The 3-year probability of survival was 92 ± 4% for patients with a serum creatinine less than 1.4 mg per dL, 74 ± 8% for patients with a serum creatinine of 1.5 to 1.9 mg per dL, and 51 ± 8% for patients with a serum creatinine greater than or equal to 2.0 mg per dL.

Long-term survival was investigated at Duke University in a cohort of 1,235 patients who underwent abdominal aortography at the time of cardiac catheterization. The 4-year survival rate of subjects without RAS was 88% versus 67% for those with RAS (117).

Clinical Clues to the Diagnosis of Renal Artery Stenosis

A multicenter study was performed to determine a set of clinical characteristics that would identify individuals with a higher likelihood of having hypertension due to renal arterial disease (118). The clinical clues to suggest renal artery disease have changed considerably since that time (Table 112.2) (9).

Onset of hypertension after the age of 55
Exacerbation of previously well-controlled hypertension
Malignant hypertension
Resistant hypertension
Epigastric bruit (systolic/diastolic)
Unexplained azotemia
Azotemia while receiving angiotensin-converting enzyme inhibitors or angiotensin-receptor blocking agents
Atrophic kidney or discrepancy in size between the two kidneys
Recurrent congestive heart failure or "flash" pulmonary edema
Atherosclerosis elsewhere

TABLE 112.2 CLINICAL CLUES TO THE DIAGNOSIS OF RENAL ARTERY STENOSIS

Hypertension

- What was the age of onset?
- Has the hypertension suddenly become more difficult to control?
- Did the patient have malignant or accelerated hypertension?
- Does the patient have resistant hypertension?

Individuals who develop hypertension between the ages of 30 and 55 usually have primary (essential) hypertension. If the initial diagnosis of hypertension is made before the age of 30, it is usually due to FMD. Because atherosclerosis occurs in older individuals, it is usually the cause of RAS after the age of 55. It is not uncommon for patients to have years of primary hypertension and as they age, develop atherosclerotic RAS. This cohort of patients may have had well-controlled blood pressure that suddenly became more difficult to control. Accelerated or malignant hypertension has also been associated with a high prevalence of RAS. Davis and colleagues (103) demonstrated that renovascular hypertension was present in 32% of 76 white patients and 11% of 29 black patients studied with grade III or IV hypertensive retinopathy. *Resistant hypertension* is defined as failure to normalize blood pressure less than 140/90 mm Hg (119) after a good medical regimen consisting of at least three drugs with different mechanisms of action. The diagnosis of renovascular disease should be strongly considered in patients with resistant hypertension.

Physical Examination

- Does the patient have evidence of atherosclerosis elsewhere?
- Does the patient have an epigastric bruit?

In general, the physical examination is of limited help. Evidence of coronary, cerebral, or peripheral arterial disease is associated with a higher likelihood of renal artery disease due to the systemic nature of atherosclerosis. Although a systolic abdominal bruit is common and nonspecific, the presence of a systolic/diastolic bruit, especially over the epigastrium, may point to underlying renal artery disease (120). The presence of a diastolic component to the bruit indicates that the degree of narrowing of the artery is severe since there is continued flow during diastole (120). A systolic/diastolic bruit more often occurs in patients with fibromuscular disease (53%) than in patients who have atherosclerotic disease (12.5%) (121). Hunt et al. found a systolic/diastolic bruit in one-third of patients with atherosclerotic renovascular disease and in 75% of patients with fibromuscular disease (122). The presence of a bruit is helpful, but the absence does not exclude the diagnosis of either atherosclerotic renovascular disease or FMD.

Renal Function

- Are the kidneys of differing sizes?
- Has the patient ever developed azotemia associated with ACE inhibitors or angiotensin II receptor blocking agents?
- Does the patient have unexplained azotemia?
- Is the patient receiving dialysis without a clear cause for end-stage renal disease?

Gifford et al. (123) found that 71% of patients (53 of 75 patients) with an atrophic kidney had severe stenosis or complete occlusion of the renal artery ipsilateral to the small kidney. Three studies have shown that if there is a discrepancy in the size between the two kidneys or if one kidney is atrophic, there is a 60% chance that the contralateral renal artery (normal-sized kidney) is severely stenotic (10,124). Therefore, the presence of an atrophic kidney or a discrepancy in size between the two kidneys demands a thorough investigation for the presence of renovascular disease.

There are numerous reports suggesting that patients who develop azotemia while receiving ACE inhibitors have bilateral RAS, RAS to a solitary kidney, or decompensated congestive heart failure in the sodium-depleted state (44,45,46,47 and 48). The mechanisms have been discussed in detail earlier in this chapter.

Congestive Heart Failure and Pulmonary Edema

- Does the patient have unexplained congestive heart failure?
- Has the patient had recurrent episodes of “flash” pulmonary edema?

Recurrent congestive heart failure and flash pulmonary edema not related to ischemic heart disease can result from bilateral RAS (or unilateral RAS to a single functioning kidney). In our renal artery stent series, 39 patients (19% of all patients undergoing renal artery stent implantation from 1991 to 1997) had recurrent episodes of congestive heart failure or flash pulmonary edema as the primary indication for renal artery stenting (11). Although it is not completely understood, the mechanism of congestive heart failure may be related in part to the inability to use ACE inhibitors or ARBs, direct toxic effects of angiotensin II on myocardial function, or the inability to adequately control volume.

DIAGNOSIS OF RENOVASCULAR DISEASE

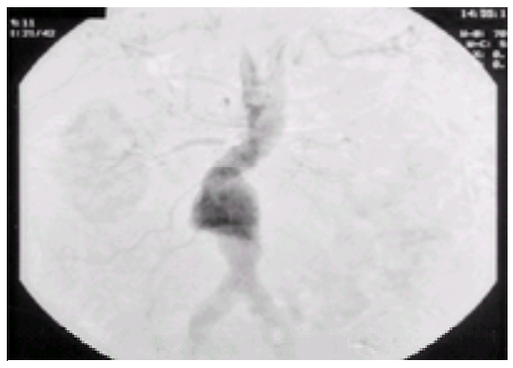
The ideal imaging procedure should (a) identify the main renal arteries as well as accessory or polar vessels; (b) localize the site of stenosis or disease; (c) provide evidence for the hemodynamic significance of the lesion; and (d) identify associated pathology (i.e., abdominal aortic aneurysm, renal mass, and so forth) that may have an effect on the treatment of the renal artery disease (124,125). The most sensitive and specific methods to identify RAS include the noninvasive imaging techniques such as duplex ultrasound, computed tomographic (CT) angiography, and MRA. Although intravenous digital subtraction angiography was used in the past, it no longer is used because of the large contrast loads required and poor image quality.

Arteriography

Angiography, the gold standard for arterial imaging, is rarely required to make the *diagnosis* of RAS. Usually one or more of the noninvasive modalities can accurately make the diagnosis. Exceptions to this general rule may occur in patients with FMD that primarily affects the branches of the renal arteries and patients with renal artery aneurysms. Angiography or intraarterial digital subtraction angiography has several distinct advantages as an imaging modality. All portions of the renal artery, including the intrarenal branches, can be well visualized. In addition, accessory renal arteries can be identified, and one can determine kidney size and gross function (the presence of a nephrogram). However, angiography is invasive and costly compared with other imaging modalities. Although not common, complications associated with angiography include access site complications such as a hematoma, pseudoaneurysm, arterial venous fistula, as well as acute renal failure from contrast-induced nephrotoxicity and atheromatous embolization to the kidneys, bowel, or lower extremities. Therefore, angiography is a poor *screening* test for RAS, but an excellent confirmatory test once it has been decided that revascularization (PTA, stent, surgery) is indicated.

It is important to recognize that the renal arteries often come off of the aorta posteriorly and, therefore, oblique views of the aorta may be needed to visualize the origins of the renal arteries well. Pressure gradients should also be obtained to confirm the physiologic significance of a given lesion.

CO_2 angiography provides an alternative to conventional angiography or digital-subtraction angiography using iodinated contrast agents (eFig. 112.4.1). This may be particularly useful in patients with renal insufficiency in whom contrast exposure may accelerate decline of renal function. When compared with angiography, CO_2 angiography demonstrates a sensitivity of 83% and a specificity of 99% (126,127). CO_2 is rapidly eliminated via the lungs, allowing repeated injections without increased risk of toxicity. The disadvantages of using CO_2 can be related to the buoyancy, compressibility, and solubility of the gas. Due to its buoyancy, CO_2 does not optimally visualize posteriorly placed structures. Large boluses may be necessary to completely displace the blood from the vessel and obtain quality images. This may be difficult because the compressibility of the gas can make injection difficult, and CO_2 dissolves rapidly in the blood; thus, the image degrades in a few seconds (127,128). Although the use of CO_2 does prevent nephrotoxicity from contrast, the patient can still develop atheromatous embolization (from catheter manipulation in the aorta or renal artery) to the kidney. The major drawback from using CO_2 as a contrast agent is that the resolution and clarity are not as good as with iodinated contrast.



***e*FIGURE 112.4.1** CO_2 angiogram demonstrates a small infrarenal abdominal aortic aneurysm, occluded left renal artery, and severe stenosis of the right renal artery.

We do not advocate the use of CO_2 angiography as a screening test for RAS. However, once the diagnosis of RAS is made by some other imaging modality, CO_2 angiography is useful to identify the origins of the renal arteries. When using CO_2 alone or with a small amount of contrast, one can perform an angioplasty and stent placement (129,130). The use of gadolinamide as a contrast agent either alone or with CO_2 in patients with renal insufficiency is becoming more common (131). Gadolinium provides excellent images and may supplant the use of CO_2 in the future.

Renal Arteriography at the Time of Cardiac Catheterization

Because RAS is so common in patients with coronary artery disease, some physicians recommend the routine performance of an aortogram on the “way out” after performing a cardiac catheterization (2,132). We are opposed to routine “drive-by angiography” at the time of cardiac catheterization. It adds additional time and contrast to the procedure. In addition, the quality of the images is often suboptimal. There may not be adequate views of the origin of the renal arteries, especially when they arise posteriorly from the aorta.

However, if the patient has a clear-cut indication for intervention (inability to control the blood pressure with a good antihypertensive regimen, jeopardy of renal function, or recurrent episodes of congestive heart failure), and the clinician is prepared to perform angioplasty and stenting should significant RAS be discovered, then an

aortogram at the time of cardiac catheterization is not an unreasonable approach.

Knowing that the patient has RAS adds nothing to the patient's overall management other than to tempt the angiographer to stent this renal artery lesion in the absence of accepted clinical indications. This has been termed the *renal oculosten(t)otic reflex* (133).

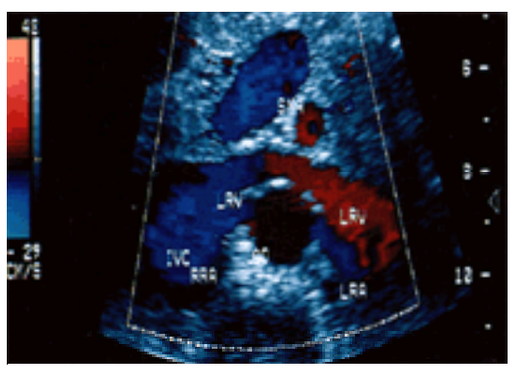
Direct Screening Tests

Evaluation of the renal arteries is essential in acute or chronic renal failure, poorly controlled hypertension, or recurrent congestive heart failure that is not directly caused by myocardial ischemia (134). Imaging modalities are also useful to screen for restenosis after percutaneous or surgical revascularization of the renal arteries. Every patient who has undergone percutaneous intervention for RAS should be put in a surveillance program to detect restenosis. Technological advances in spiral CT angiography and MRA provide aortic and renal artery imaging that compares well with the quality and accuracy of angiography. In fact, MRA has virtually replaced diagnostic angiography for the evaluation of aortic and renal artery disease. Factors such as the patient's body habitus, the degree of renal impairment, and cost may help to determine which screening test is used. However, institutional experience and expertise are perhaps the most important factors determining which of the noninvasive imaging studies is used as a screening test for renovascular disease.

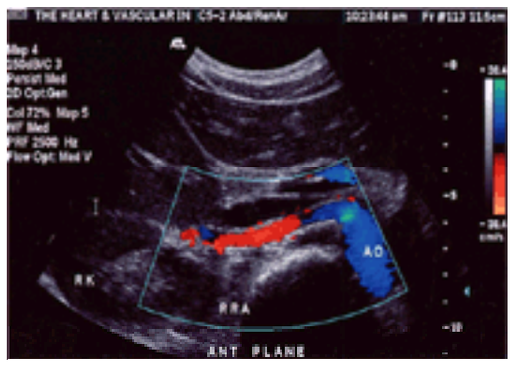
Duplex Ultrasonography

Duplex ultrasonography is an excellent test to detect RAS. It is the least expensive of the imaging modalities and provides useful information about the degree of stenosis, the kidney size, and other associated disease processes, such as obstruction, and may even predict which patients can expect an improvement in blood pressure control or renal function after renal artery angioplasty and stenting (135). The location and degree of stenosis can accurately be determined by duplex ultrasound of the renal artery. Duplex ultrasound can be performed without altering the antihypertensive regimen and does not require contrast agents that may have an adverse effect on renal function.

Duplex ultrasonography combines B-mode ultrasound and Doppler examination. Improvements in ultrasound hardware, software, and transducer technology are responsible for improved visualization of the arteries and more precise Doppler interrogation of the entire artery. Renal artery ultrasound should be performed from both an anterior (*e*Fig. 112.4.2) and oblique [or posterior (flank)] (*e*Fig. 112.4.3) approach. In the longitudinal (long-axis) view, the peak systolic flow velocity in the aorta is recorded at the level of the renal arteries. The aortic velocity and the highest renal artery PSV are used to calculate the RAR.

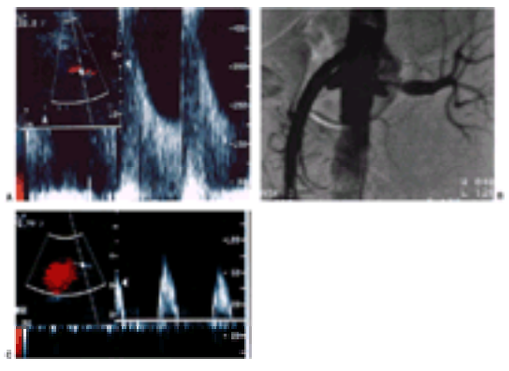


***e*FIGURE 112.4.2** Duplex ultrasound demonstrating the anatomic relationship of the renal arteries, left renal vein (LRV), and superior mesenteric artery (SMA). AO, aorta; IVC, inferior venous cava; LRA, left renal artery; RRA, right renal artery.



***e*FIGURE 112.4.3** Normal renal artery duplex of right renal artery from a flank view. Note excellent visualization of the right renal artery from the origin to the distal portion. AO, aorta; RK, right kidney; RRA, right renal artery.

The renal arteries are best visualized in a transverse (short-axis) view. *e*Figure 112.4.4 demonstrates a high-grade stenosis of the left renal artery before (A and B) and after (C) renal artery stent implantation. Using the B-mode image and a 60-degree angle of insonance, the arteries are interrogated with pulse wave Doppler. The Doppler should be swept through the artery from its origin to the renal hilum. This allows the examiner to survey the artery for velocity shifts along the entire course of the renal artery. Velocities should be recorded at the origin, proximal, mid-, and distal arterial segments. From an oblique approach, the renal artery can be visualized at the renal hilum and followed to the aorta (*e*Fig. 112.4.3). By studying the patient from an anterior and an oblique approach, Doppler velocity measurements are obtained in two views, ensuring that a focal stenosis is not missed and that the angle of insonation is correct. Because medial fibroplasia most often occurs in the mid- to distal renal artery, the oblique approach is particularly good for identifying these entities. It is important to note that segmental Doppler interrogation (spot-checking) of the renal artery velocities is inadequate and often leads to an inaccurate result (136,137).



***e*FIGURE 112.4.4 A:** Renal artery duplex ultrasound from the anterior approach. The Doppler is placed in the proximal left renal artery. The peak systolic velocity is 485 cm per second and the end diastolic velocity (*arrow*) is 210 cm per second, indicating a stenosis of greater than 80% of the left renal artery. **B:** The aortogram shows a total occlusion of the right renal artery and a severe eccentric stenosis of the left renal artery with poststenotic dilatation. **C:** Duplex of the left renal artery after a renal artery stent was placed. Note normal velocities compared with prestenting.

Overall, when compared with angiography, duplex ultrasound has a sensitivity and specificity of 84% to 98% and 62% to 99%, respectively, when used to diagnose RAS (138,139,140,141,142 and 143). We performed a prospective study comparing duplex ultrasound with angiography (*e*Table 112.2.1) (143). If the end diastolic

velocity was greater than or equal to 150 cm per second, then the degree of stenosis was likely to be greater than or equal to 80% (143).

***e*TABLE 112.2.1** COMPARISON OF DUPLEX ULTRASOUND WITH ARTERIOGRAPHY[a]

	Stenosis by arteriography				
Stenosis by ultrasound	0–59%	60–79%	80–99%	100%	Total
0–59%	62	0	1	1	64
60–99%	1	31	67	0	99
100%	0	1	1	22	24
Total	63	32	69	23	187

[a]Sensitivity, 0.98; specificity, 0.98; positive predictive value, 0.99; and negative predictive value, 0.97.
From Olin JW, Piedmonte MR, Young JR, et al. The utility of duplex ultrasound scanning of the renal arteries for diagnosing significant renal artery stenosis. *Ann Intern Med* 1995;122:833–838, with permission.

The RAR, the ratio of the PSV in the renal arteries to the PSV in the aorta, is used to classify the degree of stenosis. A three-category classification scheme is commonly used: 0% to 59% stenosis, 60% to 99% stenosis, and total occlusion (*e*Table 112.2.2). When the aortic velocity is less than 40 cm per second or greater than 100 cm per second, the RAR is not an accurate representation of the degree of stenosis. In these instances, if the PSV is greater than 200 cm per second and turbulence is present on color flow, the stenosis would be classified as 60% to 99%. When there is a discrepancy in kidney size of 2.0 cm or greater, the ultrasonographer should search carefully for the presence of RAS or an occluded renal artery.

***e*TABLE 112.2.2** DUPLEX ULTRASOUND CRITERIA FOR RENAL ARTERY STENOSIS

Stenosis	**Duplex criteria**
<60% stenosis	Renal-to-aortic ratio <3.5
60–99% stenosis	Renal-to-aortic ratio ³3.5 and peak systolic velocity >200 cm/sec
Occlusion	No flow signal from renal artery; low-amplitude parenchymal signal ± small kidney

The acceleration time, acceleration index, and resistive index have been used by some investigators to diagnose RAS. These measurements are obtained by Doppler examination in the renal parenchyma. The Doppler measurements are made with a 0-degree angle to obtain the best Doppler waveform possible. Acceleration time, measured in milliseconds, is the time from the onset of the upstroke of the arterial wave to the systolic peak. The acceleration index is the slope of the acceleration adjusted by the transmitted frequency. The resistive index is calculated as the (PSV – end diastolic velocity)/PSV (144) and is a measure of the resistance within the renal circulation. An elevated resistive index may be present in renal parenchymal disease (142) and the resistive index may be influenced by some antihypertensive drugs and age. It is not useful for predicting the degree of RAS. In our noninvasive vascular laboratory, we rely on the RAR and PSV in the main renal arteries to determine the degree of stenosis. Parameters such as the acceleration time and acceleration index may provide corroborative evidence, but are not often used to diagnose RAS.

A recent study used Doppler ultrasonography to predict the outcome of therapy in patients with RAS (136). One hundred thirty-eight patients with greater than 50% RAS underwent renal artery angioplasty or surgery for blood pressure control or preservation of renal function. A renal resistance index of at least 80 accurately identified patients in whom angioplasty or surgery was not associated with improved blood pressure, renal function, or kidney survival. Ninety-seven percent of patients with an increased renal resistance index demonstrated no improvement in blood pressure, and 80% had no improvement in renal function. The authors suggest that the increased resistive index identifies structural abnormalities in the small vessels of the kidney. Such small vessel disease has been seen with long-standing hypertension associated with nephrosclerosis or glomerulosclerosis (145). If this study is confirmed, it could provide a method for predicting which patients will improve after percutaneous intervention.

Renal artery duplex is an excellent test for the follow-up of RAS after percutaneous therapy or surgical bypass (*e*Fig. 112.4.4C) (7,146,147 and 148). Unlike MRA and CT angiography (which may be affected by artifact or scatter produced by the stent), ultrasound transmission through the stent is not a problem. Hudspeth et al. (147) compared angiography with duplex ultrasound for follow-up of RAS after angioplasty and demonstrated a sensitivity and specificity of 69% and 98%, respectively, for detecting stenosis greater than 60%. All patients who have undergone percutaneous intervention should be placed in a surveillance program in an attempt to identify restenosis and treat it before the artery occludes. After PTA and stent implantation, a renal artery duplex should be obtained at 6 months, 12 months, and yearly thereafter.

The sensitivity of identifying accessory renal arteries is approximately 67%. If there is a high index of suspicion for RAS and the duplex examination fails to reveal a significant stenosis, one may suspect an accessory vessel as the culprit.

Computed Tomographic Angiography

CT angiography can produce excellent images of the abdominal vasculature (*e*Fig. 112.4.5). The angiography protocol is performed using a peripheral intravenous iodinated contrast bolus of 100 to 150 mL followed by limited spiral CT. Typically, scanning intervals of 1 to 2 mm are used for image acquisition.

***e*FIGURE 112.4.5** Computed tomographic angiogram showing a low takeoff of an accessory left renal artery.

After the initial axial images are acquired, several different software programs are commercially available to reformat the data into two-dimensional and three-dimensional reconstruction images. The most commonly used reformatting techniques are the shaded surface display, maximal intensity projection, and volume rendering.

Depending on the techniques used, CT angiography has a sensitivity and specificity for detecting RAS of 59% to 96% and 82% to 99%, respectively, when compared with conventional angiography (149,150,151,152,153 and 154). In some techniques, when the stenosis is severe, discontinuity of arteries may be seen on reconstruction images due to partial volume averaging. However, CT angiography with real-time interactive volume rendering had a specificity of 99%, whereas maximum intensity projection had a specificity of 87% (152).

Because a limited CT scan of the abdomen is often performed before CT angiography, additional anatomic information may be available. This includes information regarding associated calcification, aortic aneurysm or dissection, and renal or adrenal pathology. During the examination of 50 hypertensive patients, Beregi et al. (149) identified five unexpected abnormalities in patients free of renal artery disease; two patients had bilateral adrenal hyperplasia (primary aldosteronism), one patient had papillary adenocarcinoma, and two patients had abdominal aortic aneurysms.

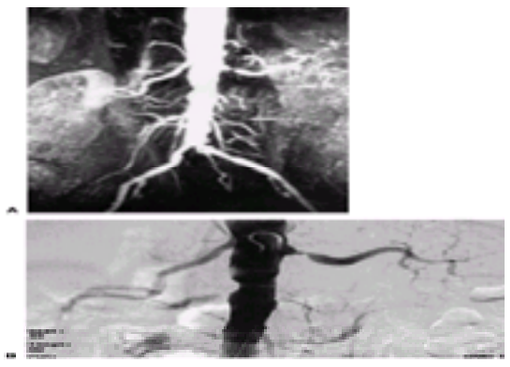
There are some technical limitations of the procedure. The protocol parameters for table speed, time delay to image acquisition, and scan volume may vary between institutions. It is important to understand how some of these parameters may affect the accuracy of the procedure. If the time delay is insufficient or if an inadequate volume of contrast is infused, the opacification of the vessels may be suboptimal. This could be interpreted erroneously as a stenosis or occlusion. The scan volume must include the entire renal artery from the aorta to the hilum to avoid missing a stenosis in the distal portion of the artery. In addition, an adequate length of scan volume is required so that accessory arteries arising in the distal aorta are not overlooked. Beregi et al. (149) used a 6-cm scan volume and failed to identify 7 of 32 accessory renal arteries because they originated outside the scan area. Conversely, Kim et al. (152) used a variable scan range based on the patient's height and

detected 27 of 28 accessory arteries identified by intraarterial digital subtraction angiography.

CT angiography may not be suitable for all patients. The required contrast volume is significant. In the patient with renal insufficiency, CT angiography is not an ideal screening test for RAS. Similar to renal duplex, CT angiography may be limited in obese patients. Patients must be able to suspend respiration during image acquisition since respiratory artifact may significantly degrade the image quality. CT angiography is generally well tolerated by most individuals. The gantry is open, thus claustrophobia is not commonly a limiting factor.

Magnetic Resonance Angiography

Like CT angiography, MRA provides excellent imaging of the abdominal vasculature and associated anatomic structures (eFig. 112.4.6). The examination does not require nephrotoxic contrast agents and therefore provides a good alternative to CT angiography in patients with renal insufficiency, congestive heart failure, or a contrast allergy. In general, the procedure is similar to CT angiography. The examination is performed with the patient supine. The patient must be able to cooperate and refrain from breathing during contrast-enhanced sequences or the quality of the study may be compromised.



***e*FIGURE 112.4.6 A:** Magnetic resonance angiogram demonstrating a severe stenosis of the left renal artery and a normal right renal artery. **B:** Arteriography of the same renal artery at the time of renal artery stenting.

Each examination should begin with acquisition of routine T1- and T2-weighted images to evaluate the kidneys, adrenal glands, and associated soft tissues. Time-of-flight and phase contrast are noncontrast techniques commonly used for vascular imaging. Software is available for both two-dimensional and three-dimensional imaging. The initial source images are completed in approximately 20 minutes. The reformatting process usually requires an additional 30 to 45 minutes. Maximum intensity projection and multiplanar reconstructions are the most commonly used postprocessing algorithms.

When compared with angiography, MRA has demonstrated a sensitivity of 90% to 100% and a specificity of 76% to 94% (155,156,157,158 and 159). However, MRA does not have the same sensitivity and specificity in patients with FMD.

Contrast-enhanced MRA provides a superior quality study when compared with noncontrast studies. Gadolinium chelate is the contrast agent of choice. Other contrast agents are under development and may improve the current imaging techniques. Unlike ionic and nonionic iodinated contrast agents, gadolinium is not nephrotoxic and can be used safely in patients with renal insufficiency. The imaging time is substantially shortened, and 20- to 40-second acquisition times are not uncommon. This eliminates some artifact created by gross patient movement (160). Signal strength is increased, providing for better visualization of distal small caliber vessels (161). Unlike flow-based techniques (time-of-flight, phase contrast), areas of slow flow or turbulence may be better visualized. The signal depends only on gadolinium concentration in the vessel. Thus, flow-related artifacts are almost entirely avoided. Thornton et al. (161) compared breath-hold MRA with conventional digital subtraction angiography in 42 patients. They demonstrated a sensitivity of 100% and a specificity of 98% for detecting greater than 50% stenosis. Overall MRA revealed 85 of 87 renal arteries, 20 of 20 stenoses, and 5 of 5 occlusions. The two arteries not identified were accessory vessels. Other studies have demonstrated a sensitivity and specificity between 91% and 100% and 79% and 98%, respectively (162,163,174).

In addition to the technical considerations of MRA, there are several other considerations in choosing MRA as a screening or diagnostic test. At most centers, the cost of performing MRA exceeds that of duplex ultrasonography or CT angiography. In addition, some patients are not good candidates for the examination. Patients with metallic implants—such as some mechanical heart valves, cerebral aneurysm clips, and electrically activated implants (pacemakers, spinal cord stimulators)—are not able to be studied. Most patients with inferior vena cava filters can be safely studied. Claustrophobia is a common problem. The scan time can be significantly shortened with the use of gadolinium. If patients are still apprehensive, they can usually be premedicated with a sedative hypnotic agent.

Indirect Screening Tests

Intravenous Urography

The rapid sequence intravenous pyelogram to screen for the presence of RAS was first described in the early 1960s (164). In the Cooperative Study of Renovascular Hypertension (165), 11.4% of patients with essential hypertension had an abnormal intravenous urogram, and 17% of patients with significant RAS documented by arteriography had a normal intravenous urogram. A false-positive rate of up to 41% has been reported (166,167). Therefore, this test should no longer be used to screen for RAS.

Peripheral Plasma Renin Activity

Maxwell et al. (168) reviewed 540 patients reported in the literature to assess the value of plasma renin activity in the diagnosis of renovascular hypertension. There was a sensitivity of 57% and a specificity of 66%. The false-negative and false-positive rates were extremely high at 43% and 34%, respectively. The PRA did not predict which patients benefited from renal revascularization. Elevated plasma renin activity may be present in approximately 15% of patients with essential hypertension and patients with bilateral disease or disease to a solitary functioning kidney may have normal or low PRA. Therefore, PRA should not be used as a reliable screening test for renovascular disease.

Captopril Test

In an attempt to increase the utility of measuring plasma renin activity, Muller and colleagues administered captopril, 50 mg orally, and obtained PRA 60 minutes later. The criteria that they found to be the most reliable for distinguishing patients with renovascular hypertension are a postcaptopril renin of more than 12 ng per mL per hour, an absolute increase of 10 ng per mL per hour or more, and a percent increase of 150% or more, or 400% if the baseline renin is below 3 (169). The overall sensitivity is approximately 61%, and specificity is 86% (170). This test can be affected by volume status, position of the patient during the test, and medications the patient is taking. The test is less accurate in azotemic patients and in African-American patients (171). The captopril test is not an ideal screening test and is rarely used anymore.

Renal Vein Renin Measurements

Renal vein renin measurements are not a useful test to screen for RAS. However, measurement of renin produced from the renal vein of the kidney with RAS compared with the renal vein of the healthy kidney has been used as a method for predicting which patients may benefit from intervention such as surgery, percutaneous angioplasty, or stent placement. Technical factors can interfere with the interpretation of the results and therefore limit the utility of the test. Ideally, patients should be off all medications that can either stimulate or suppress renin for a period of at least 3 days. Blood should be taken from the right and left renal vein and the inferior vena cava above and below the renal veins as a baseline. Either 40 mg of furosemide or 25 mg of captopril should then be administered and repeat blood samples taken 30 minutes later. If these guidelines are followed, renal vein renin measurements may be accurate in predicting in whom a *cure* of renovascular hypertension may occur with revascularization (172,173).

A renal vein renin ratio of 1.5:1 or greater with suppression of renin production by the contralateral (nonstenotic) kidney is considered a positive renal vein renin

response (174,175). Hughes et al. (173) demonstrated that when a renal vein renin ratio greater than 1.4:1 was combined with a duration of hypertension of less than 5 years, 19 of 20 patients (95%) had a cure of their renovascular hypertension. Several reports have now been published that show that renal vein renin lateralization does not predict which patient will have an *improvement* in blood pressure after surgical revascularization or percutaneous intervention (176,177,178 and 179).

Nuclear Imaging Modalities

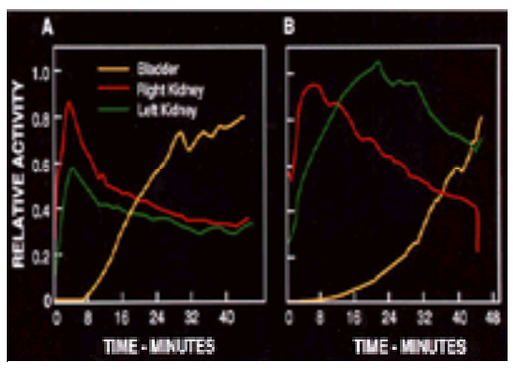
Radionuclide imaging techniques are a noninvasive and safe way of evaluating renal blood flow and excretory function. However, the renal flow scan has unacceptably high false-positive and false-negative rates (180). When an ACE inhibitor such as captopril is added to isotope renography, the sensitivity and specificity of the test improve considerably, especially for patients with unilateral RAS. In most instances of unilateral RAS, the glomerular filtration rate of the stenotic kidney falls by approximately 30% after captopril administration (181,182). In contrast, the contralateral normal kidney exhibits an increase in glomerular filtration rate, urine flow, and salt excretion despite a reduction in systemic blood pressure. These expected physiologic changes within the stenotic and contralateral kidneys are the basis of the asymmetry of renal function following ACE inhibition detected by renal scintigraphy (183,184 and 185).

Oral hydration (water, 10 mL per kg) is encouraged the morning of the test. A peripheral venous catheter for sampling, injection, or both is inserted, and baseline blood pressure is measured and repeated at 15- to 20-minute intervals. Captopril (25 to 50 mg orally crushed) is administered and a conventional radionuclide study of the kidneys is begun 60 minutes after captopril.

The majority of captopril renography studies to date has been performed with technetium-99m (Tc-99m) diethylenetriaminepentaacetic acid (DTPA), Tc-99m mercaptoacetyltriglycine (Tc-MAG_3), or [^{131}I]OIH using a medium-energy collimator and conventional software (186,187). DTPA is the preferred agent because it is excreted by the kidneys by glomerular filtration and it provides an index of renal perfusion and kidney size.

However, Tc-99m-MAG_3, which is excreted by the kidney similar to PAH or OIH, has become clinically available for renography and has been systematically studied. Tc-99m-MAG_3 may become the radionuclide of choice because it offers both the advantageous technetium-labeling characteristics and optimal renal handling and excretion. Tc-99m-MAG_3 for captopril renography has shown good results, especially in patients with azotemia because of its higher extraction capabilities (188,189). The one drawback of Tc-99m-MAG_3 is cost compared with the other two radionuclide agents.

The Consensus Report on Captopril Renography suggested that both the scintigraphic images and computer-generated time-activity curves provided information about renal size, perfusion, and excretory capacity (183). The diagnostic criteria to suggest RAS were (a) delayed time to maximal activity (T_{max}) (greater than or equal to 11 minutes after captopril); (b) significant asymmetry of peak activity of each kidney; (c) marked cortical retention of the radionuclide after captopril; and (d) marked reduction in calculated glomerular filtration rate of the ipsilateral kidney after ACE (eFig. 112.4.7).



***e*FIGURE 112.4.7** Captopril renogram demonstrating unilateral left renal artery stenosis. **A:** Tc-99m diethylenetriamine pentaacetic acid (DTPA) time-activity curves during baseline. **B:** Tc-99m DTPA time-activity curves following captopril stimulation. (From Nally JV. Provocative captopril testing in the diagnosis of renovascular hypertension. *Urol Clin North Am* 1994;21:232, with permission.)

Geyskes, Oei, and colleagues (190) demonstrated that captopril renography accurately identified those patients with significant unilateral RAS and was predictive of a successful outcome in 13 of 15 patients who underwent percutaneous balloon dilatation of the renal artery. eTable 112.2.3 represents a synopsis of the captopril renography studies in hypertensive patients suspected of renovascular disease (184,186,189,190,191,192,193,194,195,196,197 and 198). Overall, the accuracy of captopril renography in identifying patients with renovascular disease appears quite acceptable with a sensitivity approximately 85% to 90% (range, 45 to 94) and specificity approximately 93% to 98% (range, 81 to 100). Those patients with unilateral disease and normal renal function would be best suited for a captopril renogram.

***e*TABLE 112.2.3** SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUE OF CAPTOPRIL RENOGRAPHY

Investigators	No. of patients studied	No. of patients with renal artery stenosis	Radionuclide	Sensitivity (%)	Specificity (%)	Predictive value
Geyskes et al. (190)	34	15	^{131}I OIH	80	100	Yes, 12/15
Sfakianakis et al. (191)	31	16	^{131}I OIH	67	100	—
			Tc-DTPA	48		
Erbsloh-Moller et al. (192)	40	28	^{131}I OIH	96	95	Yes, 10/11
Svetkey et al. (83)	6	11	Tc-DTPA	74	44	—
			^{131}I OIH	71	41	
Setaro et al. (185)	90	44	Tc-DTPA	91	94	Yes, 15/18
Mann et al. (193)	55	35	Tc-DTPA	94	95	No, 8/19
			^{131}I OIH	83	85	
Fommei et al. (189)	472	259	Tc-DTPA (380)	83	91	Yes, 40/43
			Tc-DTPA (74)	83	100	
Dondi (188)	102	54	Tc-MAG_3	90	92	Yes
Elliott et al. (194)	100	59	Tc-pertechnetate	92	80	Yes, 51/53
van Jaarsveld et al. (195)	505	263	DTPA and MAG_3	68	90	
Mittal et al. (196)	86	45	DTPA	82	98	100% (positive predictive value), 85% (negative predictive value or no predictive value)
Miralles et al. (197)	60	44	?	87	87	74% (positive predictive value), 94% (negative predictive value or no predictive value)
Johansson et al. (198)	98	18	DTPA	68	92	

From Nally JV, Barton DP. Contemporary approach to the diagnosis and evaluation of renovascular hypertension. *Urol Clin North Am* 2001 (in press), with permission.

The presence of significant azotemia or bilateral RAS may adversely affect the accuracy of captopril renography. Many investigators have excluded patients with serum creatinine exceeding 2.5 to 3.0 mg per dL. In patients with a serum creatinine greater than or equal to 1.5 mg per dL and less than or equal to 3.0 mg per dL, Fommei et al. (189) reported a reduction in the positive predictive value from 88% to 57% while there was a minimum reduction in sensitivity and specificity in patients with serum creatinine of 1.5 mg per dL.

It is controversial whether the captopril renogram can predict which patients will exhibit a cure or improvement in blood pressure after revascularization (186,190,192,195,196). There are no reliable data using the captopril renogram to predict whether revascularization will result in preservation or improvement in renal function.

Although the captopril renogram was once the noninvasive diagnostic test of choice for patients with RAS, it is now relegated to a secondary screening modality because the quality of the images of duplex ultrasound, MRA, and CT angiography are excellent.

PRINCIPLES OF MANAGEMENT

There has been a paradigm shift in management of atherosclerotic renal artery stenosis. Before 1990, if a patient met the criteria for intervention, surgical renal artery revascularization was almost always performed. However, since the introduction of stents, surgical revascularization is rarely performed solely for the treatment of renal artery disease. Despite advances in the technical aspects of angioplasty and stent implantation, there has been a paucity of controlled clinical trials assessing the role of renal artery angioplasty and stenting to control hypertension or preserve renal function. Because of a lack of controlled clinical trials, there remains some controversy as to the most appropriate treatment of atherosclerotic renal artery disease.

The four modalities currently available for the treatment of RAS are medical therapy, percutaneous balloon angioplasty, angioplasty with stent placement, and surgical revascularization. For the purpose of this discussion, *revascularization* is defined as restoration of blood flow to the kidney. This includes both percutaneous as well as surgical techniques. The etiology of the lesion, the patient's comorbidities, and the technical expertise of the treating physician must be taken into consideration when considering the type of treatment that will be employed.

The following items are the indications for revascularization:

- At least a 70% stenosis of one or both renal arteries *and*
- Inability to adequately control the blood pressure despite a good antihypertensive regimen *or*
- Chronic renal insufficiency not related to another clear-cut cause (disease should be bilateral or stenosis to a solitary functioning kidney). The treatment of an elevated serum creatinine with unilateral disease is controversial, and there are no good clinical trials to help guide the clinician (199).
- Dialysis-dependent renal failure in a patient without a definite cause of ESRD (200,201 and 202).
- Recurrent congestive heart failure or flash pulmonary edema not attributable to a cardiac cause (11,46,203).

In all patients, risk factor modification is important. Patients should be advised to stop smoking, lose weight, and exercise. Control of diabetes and appropriate management of hyperlipidemia are equally important. Because the majority of lesions is attributable to atherosclerosis or FMD, comments regarding therapy focus on these two diseases.

Medical Therapy

All patients with hypertension should be treated medically, even if they undergo intervention. Antiplatelet agents should be prescribed to help to lower the extremely high cardiovascular morbidity and mortality that occur in this patient population. Many patients have superimposed essential hypertension and will still require medications long term. Despite the etiology, the guidelines of the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure should be followed (204). Patients with unilateral disease often have renin-mediated hypertension. They should be placed on an ACE inhibitor or an ARB. Beta-blockers, which block renin secretion, and calcium channel blockers, which may counteract the direct effects of angiotensin II on the smooth muscle wall, are also first-line therapy. In individuals with bilateral disease or disease to a solitary functioning kidney, ACE inhibitors or ARBs should be used with caution, because this class of drugs can precipitate acute renal failure.

Patients with RAS who are treated solely with medical therapy should be carefully followed for progression of disease. This should include three important strategies:

- Follow the blood pressure closely and work to achieve a goal blood pressure within the guidelines of Sixth Joint National Committee.
- Follow the renal function every 3 months. If the serum creatinine begins to rise and there is no other explanation, consider revascularization.
- Place the patient into a surveillance program with serial duplex ultrasound imaging. The kidney size, volume, and severity of the stenosis can be closely followed. If the patient begins to lose volume to the affected kidney, consider revascularization.

Percutaneous Transluminal Angioplasty

PTA for RAS was first performed successfully by Gruntzig in 1978 (205). PTA has become widely used to treat individuals with renovascular disease. Technical success reflects the immediate outcome of the intervention (i.e., angiographic result and improvement in the pressure gradient), whereas long-term success is related to improvement in clinical parameters (i.e., blood pressure, renal function, and congestive heart failure).

PTA is the treatment of choice for FMD. Stenting is generally not indicated for patients with FMD because they respond so well to PTA alone. Sos et al. (206) performed PTA in 31 patients with FMD and demonstrated a technical success rate of 87.1%. Blood pressure was cured in 59.3% and improved in 33.3%. The cure or improvement in blood pressure was maintained in 93% of patients over an average follow-up of 16 months. Ramsay and Waller (207) reviewed ten published series of patients with FMD and reported that the hypertension was cured in 50% and improved in 42%. In a series of 85 lesions in 66 patients, PTA was technically successful in 100%. There was an 8% late recurrence rate at a mean of 15.7 months. Blood pressure was cured in 39% and improved in 59% of patients over a mean follow-up period of 39 months (208). Fourteen of these patients were treated for both hypertension and preservation of renal function. Before PTA, the mean serum creatinine was 2.4 mg per dL and after PTA the serum creatinine was 1.7 mg per dL (mean follow-up of 33 months). This represented an overall improvement of renal function in 86% of individuals.

Although the trend toward greater success for lesions due to FMD than atherosclerosis has been duplicated in many studies, the degree of overall cure has not been consistently demonstrated. A large retrospective series from the Mayo Clinic evaluated 105 patients with FMD who underwent PTA. While PTA resulted in blood pressure improvement in 85%, only 22% were classified as "cured" (mean follow-up of 42.7 months) (209).

Most studies looking at PTA in patients with FMD have concentrated on disease in the main renal artery. However, intimal, medial, and perimedial fibroplasia may occur in the branch renal arteries as well. In the past, surgical reconstruction has been the primary therapeutic modality to treat these lesions. However, with better catheter and balloon technology, virtually all of these lesions can be treated with PTA, even in the small renal artery branches (210). In 25 branch renal artery lesions, the technical success of dilatation was 84%. At 6 months, stenosis recurred in only 9%, all of which were successfully redilated.

The larger majority of patients with RAS has underlying atherosclerosis. Unlike FMD, disease due to atherosclerosis is found in the proximal arterial segment and, even more often, at the ostium of the artery. Ostial lesions respond poorly to PTA alone.

The ten-case series reviewed by Ramsay and Waller (207) included 464 atherosclerotic lesions. Technically successful angioplasty was performed for 391 lesions. Overall, blood pressure was cured in 19% and improved in an additional 52%. Bonelli et al. (209) retrospectively reviewed 190 atherosclerotic renal artery lesions that had undergone PTA and reported a cure rate of only 8.4%. The technical success rate was 81.6% and was higher for those lesions that occurred in the main branch as opposed to the origin of the renal artery (82.4% vs. 60.4%). In another larger series of atherosclerotic lesions (n = 289), technical failure rate was 8%, with a primary patency of 57% and a secondary patency of 77% (211). Blood pressure was cured in 8% and improved in 59%.

Several studies have looked at PTA to restore renal function. Rimmer and Gennari (9) reviewed several studies in which angioplasty was performed in azotemic patients. Renal function improved in 25% to 53% of patients (212,213,214,215,216 and 217).

In general, PTA is less effective for treating ostial lesions than nonostial disease (213,218,219). Canzanello et al. (216) evaluated 100 consecutive patients with high-grade atherosclerotic RAS. Technical success was achieved in 76%, 74%, and 68% of patients with unilateral RAS, bilateral RAS, or RAS to a solitary kidney, respectively. Of the technical successes, 59% of patients had a sustained improvement in blood pressure control over a mean follow-up of 22 months. Most blood pressure failures and most restenoses occurred in the ostial group. Only 25% of patients with ostial disease had blood pressure improvement. One study showed that PTA can be performed safely as an outpatient procedure (220).

Comparison of Medical Therapy and Percutaneous Transluminal Angioplasty

There are three randomized prospective trials comparing medical management with angioplasty for blood pressure control in patients with atherosclerotic RAS. Each of the three studies has significant drawbacks precluding any definite conclusions. Plouin et al. (221) randomized 49 patients with unilateral RAS and found no significant difference in blood pressure control at 6 months (140/81 mm Hg in the PTA group vs. 141/84 mm Hg in the medical therapy–alone group). However, patients in the angioplasty group required less antihypertensive medication. In the medical group, 7 of 26 patients developed refractory hypertension and subsequently underwent

PTA.

Webster et al. (222) randomized 55 of 135 eligible patients (44%) and followed them for 6 months. A significant fall in blood pressure from baseline occurred in the patients with bilateral RAS who were randomized to PTA (152/83 mm Hg in the PTA group vs. 171/91 mm Hg in the medical therapy group). This difference was not seen in patients with unilateral RAS.

The largest randomized, prospective study was published by van Jaarsveld et al. (223). One hundred six patients with angiographically documented RAS were randomly assigned to PTA or medical therapy and had blood pressure and renal function assessed at 3 and 12 months. Baseline blood pressure was 179/104 mm Hg and 180/103 mm Hg in the angioplasty and drug therapy groups, respectively. At 3 and 12 months, there was no significant difference in blood pressure control between the two groups, but the PTA group was on fewer antihypertensive medications. There were several rather serious problems with this study (224). Forty-four percent of patients randomized to medical therapy crossed over to the balloon angioplasty group, resulting in dilution of the long-term outcome differences. In spite of this, the initial angioplasty group required less antihypertensive therapy than the medical group (p <.001). There was a favorable trend to all primary outcome events, and with the small sample size we calculated that the chance of a type II error was substantial. Perhaps most importantly, the authors chose a 50% diameter reduction as the cut-off for “hemodynamically significant” renal artery lesions despite the fact that the evidence is clear that a lesion of at least 70% stenosis is required to cause significant hypertension or a decrement in renal function (5). Only 57% of patients had stenosis of greater than 70%.

The primary problems with PTA alone are that a good technical result is virtually impossible with ostial lesions (221) and the restenosis rate is high (211,225).

Renal Artery Stents

Due to the high restenosis rate with angioplasty alone, endovascular stents offer a significant advantage over PTA in patients with atherosclerotic disease, especially those with ostial stenosis. The degree of stenosis poststenting approaches zero and most dissection flaps caused by PTA alone are successfully sealed with stents (Fig. 112.5). Despite the widespread use of stents in thousands of renal arteries since the late 1980s, there is still no U.S. Food and Drug Administration approval of these devices for the renal circulation.

FIGURE 112.5 A: Severe stenosis to the right renal artery. **B:** Excellent angiographic result after stent placement.

There are a few important technical caveats when stenting the renal arteries:

- The shortest stent to adequately cover the lesion should be used.
- The stent must extend 1 to 2 mm into the aorta in patients with ostial disease.
- The stent must be fully expanded. A common problem encountered is to underdeploy the stent. It may be worthwhile to do the first 15 to 20 cases with intravascular ultrasound to be certain the stent is adequately expanded. It is also important to make sure that no postprocedure pressure gradient exists.

Rees and colleagues (226), using the Palmaz stent for ostial atherosclerotic RAS, achieved technical success in 27 of 28 patients. Sixty-four percent of patients had their blood pressure cured or improved, and 10 of 14 patients had stabilization of renal function. However, restenosis occurred in 7 of the 18 patients studied (39%). In those patients with greater than 15% residual stenosis, all 4 patients had restenoses, whereas in those patients with less than 15% residual stenosis, only 3 of 14 (21%) patients had restenoses.

White, Ramee, and associates (227) evaluated the safety and efficacy of renal artery stent implantation in patients with lesions that did not respond well to angioplasty alone. Balloon-expandable stents were placed in 100 consecutive patients (133 renal arteries). The technical success (as assessed by quantitative angiography) was 99%. The mean blood pressure values were 173 ± 25/88 ± 17 mm Hg before stent implantation and 146 ± 20/77 ± 12 mm Hg 6 months after renal artery stenting (p <.01). Angiographic follow-up in 67 patients (mean, 8.7 ± 5.0 months) demonstrated restenosis (greater than 50%) in 15 (19%) patients.

Dorros and colleagues (8) performed Palmaz-Schatz stent revascularization in 163 consecutive patients (202 arteries) with poorly controlled hypertension or jeopardy of renal function. The immediate technical success rate was 99%. One hundred forty-five patients were followed for more than 6 months. The mean blood pressure was 166 ± 26/86 ± 14 mm Hg at baseline and 148 ± 22/80 ± 11 mm Hg after 4 years of follow-up.

Blum et al. (7) prospectively placed a Palmaz stent in 68 patients (74 lesions) with ostial RAS and suboptimal PTA. All patients were hypertensive and 20 had mild or severe renal dysfunction. Stents were placed due to elastic recoil (63 arteries), post-PTA dissection (1 artery), or late restenosis (10 arteries) with 100% technical success rate. Five-year patency was 84.5% (mean follow-up was 27 months). Restenosis occurred in 8 of 74 arteries (11%), but after reintervention the secondary 5-year patency rate was 92.4%. Blood pressure was cured or improved in 78% of patients. There was no significant change in the serum creatinine values after stent implantation.

Comparison of Percutaneous Transluminal Angioplasty and Endovascular Therapy with Stenting

The first randomized, prospective study comparing angioplasty alone with angioplasty and stenting was published (228): Eighty-five patients with ostial lesions were randomized to receive PTA alone (42 patients, 51 arteries) or PTA and stent (42 patients, 52 arteries). Secondary stent implantation was allowed if the PTA failed immediately or during the first 6 months of therapy. The primary technical success rate (individual arteries) was 57% for PTA group and 88% for PTA with stent group. At 6 months, the primary patency was 29% for the PTA group and 75% for the stent group. Because this was an intention-to-treat analysis and 12 patients underwent stenting in the PTA group, there were no clinical differences between the two groups.

A publication of 163 patients (200 arteries) with atherosclerotic RAS evaluated the patency rates in patients undergoing PTA alone and those undergoing PTA and stent implantation. For ostial disease, the 12-month primary patency rate for PTA was 21 of 33 arteries (34%) and for PTA and stent was 4 of 21 arteries (80%) (p = .002) (229).

A metaanalysis of 14 studies compared the technical and clinical effect of renal artery PTA and stent implantation (Table 112.3) (7,8,228,229,230,231,232,233,234,235,236,237,238 and 239). The stent patients had a higher technical success rate and a lower restenosis rate when compared with patients only receiving PTA (98% vs. 77% and 17% vs. 26%; p <.001). The mean follow-up was 17 months for patients receiving a stent and 19 months for PTA patients. Complications of renal artery stent placement are shown in *e*Table 112.3.1. Hypertension was improved or cured in 69% of patients, and renal function improved or stabilized in 68% of patients. It should be noted that the complication rate varies considerably between centers, and high-volume centers generally can perform renal artery stenting with minimal morbidity and mortality. Although all studies reported use of an antithrombotic agent during the procedure and most patients were discharged on an antiplatelet agent, the regimens varied.

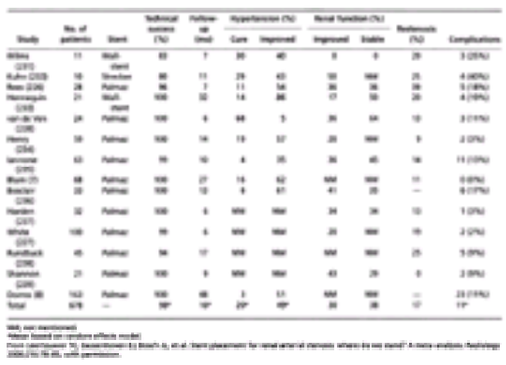


TABLE 112.3 CLINICAL AND ANGIOGRAPHIC FOLLOW-UP IN PATIENTS WHO UNDERWENT RENAL ARTERY STENT PLACEMENT

***e*TABLE 112.3.1** COMPLICATIONS ASSOCIATED WITH RENAL ARTERY STENT IMPLANTATION (N = 678 PATIENTS, 799 TREATED ARTERIES)[a]

Complication	Number	Percent
Renal failure	34	4.3
Segmental renal infarction	9	1.1
Perinephric hematoma	9	1.1
Renal artery thrombosis or occlusion	6	0.8
Stent misplacement	5	0.6
Proteinuria	2	0.3
Sepsis	1	0.1
Brachial arterial occlusion	1	0.1
Mismatch of stent and vessel	1	0.1
Cholesterol embolism to lower extremities	1	0.1
Dissection of iliac artery	1	0.1
Brachial artery bleeding	1	0.1
Total major complications	71	8.9
Hematoma and access site complications	40	5.0
Total minor complications	40	5.0

[a]The mortality was 1.0% (95% confidence interval, 0 to 2). The complication rate varied considerably across studies.

From Leertouwer TC, Gussenhoven EJ, Bosch JL, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology* 2000;216:78–85, with permission.

Two studies evaluated the effect that renal artery stent implantation had on preserving renal function (237,240). Both studies used the reciprocal of the serum creatinine to determine the rate of decline or improvement in renal function. Harden et al. (237) placed renal artery stents in 32 patients (33 arteries) and reported that renal function improved or stabilized in 22 (69%) patients. In 25 patients with complete follow-up, Watson and associates (240) demonstrated that all exhibited a negative slope to the reciprocal of the serum creatinine. After stent placement, the slopes were positive in 18 patients and less negative in 7 patients.

Surgical Revascularization

Surgical revascularization has been used much less frequently than in the past. This is due in large part to the excellent technical results that can be achieved with angioplasty and stents. As previously noted, many patients can now undergo renal artery stent implantation as an outpatient procedure at a fraction of the cost of surgical revascularization.

Current indications for surgical revascularization include the following items:

- Patients with branch disease from FMD that cannot be adequately treated with balloon angioplasty (241).
- Patients with recurrent stenosis after stenting; however, this has been extremely rare in our experience (11).
- Patients who require simultaneous aortic surgery (abdominal aortic aneurysm repair or symptomatic aortoiliac disease); even in this circumstance, it may be advisable to stent the renal artery first and then proceed with aortic reconstruction. The mortality of aortic replacement and renal artery revascularization is higher than either procedure alone (242).

A variety of surgical revascularization techniques are available for treating patients with significant renal artery disease. Aortorenal bypass with autogenous saphenous vein was an excellent method in patients with a nondiseased abdominal aorta (243,244). However, severe aortic disease almost always accompanies atherosclerotic RAS. Polytetrafluoroethylene aortorenal bypass grafts have been successfully employed usually when an autogenous graft is not available (245). Renal endarterectomy also continues to be used to treat atherosclerotic renal artery disease. Patients with complex branch renal artery lesions can be managed with extracorporeal microvascular reconstruction and autotransplantation (246,247).

In older patients, severe atherosclerosis of the abdominal aorta may render an aortorenal bypass or endarterectomy technically difficult and potentially hazardous to perform. In such cases, alternate surgical approaches often allow renal revascularization to be safely and effectively accomplished while avoiding operation on a badly diseased aorta. The most effective alternate bypass techniques have been a splenorenal bypass for left renal revascularization (248,249) and a hepatorenal bypass for right renal revascularization (250). The absence of occlusive disease involving the origin of the celiac artery is an important prerequisite for these operations. Significant celiac artery stenosis may occur in up to 50% of patients with atherosclerotic RAS (251). This information underscores the importance of obtaining preoperative lateral aortography to evaluate the celiac artery origin in patients who are being considered for hepatorenal or splenorenal bypass. The supraceliac or lower thoracic aorta for renal revascularization has also been used successfully in patients with significant aortic disease (252,253). The supraceliac aorta is often relatively disease free in such patients and can be used to achieve renovascular reconstruction with an interposition saphenous vein graft.

Reports from several large centers have demonstrated that surgical renal revascularization can be performed with operative mortality of 2.1% (243), 3.1% (254), 3.4% (255), and 6.1% (256) in patients with atherosclerotic RAS. The mortality is increased with bilateral simultaneous renal revascularizations or when renal revascularization is performed with aortic replacement (257,258). Most studies have indicated a high technical success rate for surgical vascular reconstruction with postoperative thrombosis or stenosis rates of less than 10% (243,259). In patients with fibrous dysplasia, 50% to 60% are cured, 30% to 40% are improved, and the failure rate is less than 10% (243,256). In patients undergoing revascularization for atherosclerotic renovascular hypertension, the cure rate is lower. *e*Table 112.3.2 and *e*Table 112.3.3 demonstrate the results of surgical revascularization on blood pressure control and preservation of renal function (243,249,256,257 and 258,260).

***e*TABLE 112.3.2** RESULTS OF SURGICAL REVASCULARIZATION FOR THE TREATMENT OF RENOVASCULAR HYPERTENSION

Series	No. of patients	No. cured (%)	No. improved (%)	No. failed (%)
Van Bockel (1987) (247)	105	19 (18)	64 (61)	22 (21)
Novick (1987) (241)	180	55 (31)	110 (61)	15 (8)
Libertino (1988) (260)	86	38 (44)	44 (51)	4 (5)
Hansen (1992) (254)	152	22 (15)	116 (75)	14 (10)
Total	523	134 (26)	334 (64)	55 (10)

Adapted from Olin JW, Novick AC. Renovascular disease. In: Young JR, Olin JW, Bartholomew JR, eds. *Peripheral vascular diseases*, 2nd ed. St. Louis: Mosby, 1996:321–342, with permission.

***e*TABLE 112.3.3** RESULTS OF SURGICAL REVASCULARIZATION FOR ATHEROSCLEROTIC ISCHEMIC NEPHROPATHY

Series	No. of patients	No. improved (%)	No. stable (%)	No. deteriorated (%)
Novick (1987) (241)	161	93 (58)	50 (31)	18 (11)
Hallet (1987) (258)	91	20 (22)	48 (53)	23 (25)
Hansen (1992) (254)	70	34 (49)	25 (36)	11 (15)
Bredenberg (1992) (255)	40	22 (55)	10 (25)	8 (20)
Libertino (1992) (256)	91	45 (49)	31 (35)	15 (16)
Total	453	214 (47)	164 (36)	75 (17)

Adapted from Olin JW, Novick AC. Renovascular disease. In: Young JR, Olin JW, Bartholomew JR, eds. *Peripheral vascular diseases*, 2nd ed. St. Louis: Mosby, 1996:321–342, with permission.

Comparison of Surgery and Percutaneous Transluminal Angioplasty

The only randomized prospective trial comparing PTA with surgical revascularization was conducted by Weibull and colleagues (261). Fifty-eight patients with a blood pressure of at least 160/100 mm Hg and significant unilateral RAS were assigned to have either surgery or PTA of the renal artery. Technical result, primary patency (at 24 months), and secondary patency were 83%, 75%, and 90% for the group randomized to PTA and 97%, 96%, and 97% for the surgically treated group. Surgery resulted in the improvement or cure of high blood pressure in 86% of patients, whereas PTA cured or improved blood pressure in 90% of patients. Improved or cured renal function was documented in 83% of individuals after PTA and 72% after surgery. Ultimately, 17% of patients in the PTA group required surgical intervention.

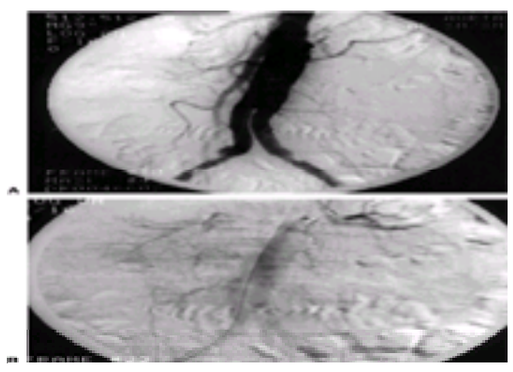
Patient Selection for Intervention to Preserve Renal Function

One can often identify those patients in whom such disease poses a significant threat to overall renal function. Patients who are at a markedly increased risk are those with greater than 75% bilateral RAS or severe stenosis to a single functioning kidney. In this patient subgroup, the risk of total occlusion of the renal artery is significant, and if this occurs, the clinical outcome is a critical decrease in functioning renal mass with resulting renal failure (21,46,86,108,114,201,204).

The benefit of undertaking revascularization for preservation of renal function in patients with unilateral RAS and a normal contralateral renal artery is not established. If the contralateral kidney is anatomically and functionally normal, revascularization for this purpose is clearly not warranted. If the opposite kidney is functioning but involved with some type of parenchymal disorder, revascularization of the ischemic kidney may benefit some patients, but specific indications for this approach are not well defined.

Complete occlusion of the renal artery most often eventuates in irreversible ischemic damage of the involved kidney. However, in some patients with gradual arterial occlusion, the viability of the kidney can be maintained through the development of collateral arterial supply (262,263). There are certain clues that may help to predict renal salvageability in patients with an occluded renal artery:

- Angiographic demonstration of late filling of the distal renal arterial tree by collateral vessels on the side of total arterial occlusion (eFig. 112.5.1) (264)
- Renal size of 8 to 9 cm
- Function of the involved kidney on a renal flow scan
- The presence of a nephrogram after a contrast arteriogram
- A renal biopsy showing well-preserved glomeruli and an absence of significant glomerulosclerosis



***e*FIGURE 112.5.1 A:** Patient underwent an aortoiliac bypass graft with a swing graft to the left renal artery 6 months before this angiogram. Note that the bypass graft is occluded. The right renal artery has a long-standing occlusion. **B:** Distal late reconstitution of the left renal artery. The patient underwent catheter-directed urokinase infusion, and flow to the left kidney was reestablished (not shown). (From Olin JW, Young JR, Graor RA. Thrombolytic therapy for renal artery occlusions. *Cleve Clin J Med* 1989;56:432–438, with permission.)

Revascularization to preserve renal function in patients with atherosclerotic RAS is most likely to be beneficial in patients with less severe renal impairment (serum creatinine less than 3.0 mg per dL) (265,266). When the serum creatinine is greater than 4.0 mg per dL, there is a greater chance that significant parenchymal renal disease exists along with main RAS. The most common underlying parenchymal renal disease in patients with RAS is severe nephrosclerosis or atheromatous embolization.

Some patients may develop acute renal failure shortly after the initiation of antihypertensive therapy (54,267). Acute renal failure in this setting is often a manifestation of perfusion-dependent renal function due to underlying RAS. Prompt intervention to relieve renal arterial obstruction can prevent permanent renal damage in patients with this type of severe acute renal insufficiency.

In addition to the absolute level of renal function, the rate of decline in overall renal function is an important determinant of the outcome following intervention in atherosclerotic ischemic renal disease. Dean and associates demonstrated that patients with a rapid deterioration in the glomerular filtration rate during the 6 months preceding surgical revascularization achieved the greatest benefit in terms of postoperative improvement in renal function (268).

There are several anecdotal reports showing that restoration of renal function in patients with totally occluded renal arteries with either endovascular therapy or surgical revascularization is feasible (269). Kaylor et al. (201) reported on nine patients who were on dialysis from 1 week to 13 months secondary to atherosclerotic RAS. Reversal of end-stage renal failure occurred in all nine patients with surgical revascularization. The serum creatinine at 1 month ranged from 1.1 to 4.2 mg per dL, with a mean of 2.5 mg per dL. Hansen and colleagues (202) have also shown that it is possible to restore renal function with surgical revascularization in some patients who have been on chronic hemodialysis therapy. From 1987 to 1993, 340 patients underwent surgical renal revascularization. Twenty patients were receiving hemodialysis before renal artery repair. Hemodialysis was discontinued in 16 of the 20 patients (80%). Two of the 16 patients resumed dialysis 4 and 6 months after surgery. A favorable response in this series occurred in those patients who had a relatively rapid decline in their glomerular filtration rate in the 14 weeks preceding renal revascularization. If a rapid decline occurred, there was a statistically significant likelihood of having the patient discontinue treatment. However, if there was a slow decrease in glomerular filtration rate over weeks to months, the chances of becoming dialysis independent were quite small. The long-term survival was better in those who were dialysis independent compared with those who required ongoing dialysis therapy. There were only two late deaths among the 14 patients not receiving dialysis compared with five late deaths among the six patients who continued to receive dialysis after surgical revascularization (p <.01).

Revascularization for Control of Congestive Heart Failure or Flash Pulmonary Edema

There have been numerous reports demonstrating that surgical or endovascular revascularization is indicated for the treatment of congestive heart failure or flash pulmonary edema in some patients (11,41,42,201,205,270,271). This subgroup of patients most often has significant bilateral RAS or RAS to a single functioning kidney. The left ventricular systolic function may be normal or impaired (11). We reported 39 patients who underwent renal artery stent implantation for control of congestive heart failure (11). This represented 19% of our renal artery stent population. In this series, 18 (46%) patients had bilateral RAS and 21 (54%) patients had stenosis to a solitary functioning kidney. Renal artery stent implantation was technically successful in all 39 patients. The blood pressure was improved in 72% of patients. Renal function was improved in 51%, stable in 26%, and the renal function deteriorated in 23% of patients. The mean number of hospitalizations for congestive heart failure before stenting was 2.37 ± 1.42 (range, 1 to 6) and poststenting was 0.30 ± 0.65 (range, 0 to 3; p <.001). Seventy-seven percent of patients had no further hospitalizations after renal artery stenting over a mean follow-up period of 21.3 months. It was anecdotally noted that some patients were unable to be diuresed despite large doses of loop diuretics before stenting. Several patients began diuresing in the angiography suite immediately following stent placement.

The mechanism by which RAS causes congestive heart failure and pulmonary edema is not well defined. The improvement poststenting may in part be related to the ability to use ACE inhibitors, especially for those with impaired left ventricular function and the ability to better control volume.

CONTROVERSIES AND PERSONAL PERSPECTIVES

There have been many advances in the diagnosis of RAS in the last decade. In addition, catheter, balloon, and stent technology have revolutionized the treatment of renal artery disease. Whereas surgical revascularization was the treatment of choice a decade ago, endovascular stent implantation is now used to treat virtually all patients with RAS who require treatment. There is a large body of literature supporting the use of angioplasty and stent implantation for atherosclerotic RAS. However,

there is a paucity of randomized prospective trials comparing renal artery stents with medical therapy and surgical revascularization. There will probably never be a randomized trial comparing stents with surgical bypass, because most clinicians now believe that that would not be ethical. Although there is compelling evidence to suggest that stent implantation can improve or at least stabilize renal function in many patients, there remain 15% to 20% of patients in whom renal function deteriorates after percutaneous intervention. Reasons for this deterioration include contrast injury, atheromatous embolization, or perhaps the renal failure was not caused by the RAS per se, but some other etiology (i.e., nephrosclerosis). It is often difficult to predict which patients will exhibit a decline in renal function after percutaneous intervention. The time has come for a prospective, controlled, randomized trial comparing renal artery stent implantation with medical therapy for preservation of renal function. This trial should randomize three distinct groups: bilateral RAS greater than 75%; RAS (greater than 75%) to a single functioning kidney; and unilateral RAS (greater than 75%) with an elevated serum creatinine level.

Just because the renal artery obstruction can be corrected safely does not mean that it should be corrected. Despite better balloons, catheters, and stents and better training in endovascular techniques, the temptation to dilate a RAS because it is there should be suppressed. Percutaneous renal intervention should be performed for one of three indications: to better control the blood pressure in patients with suboptimal control despite a good antihypertensive regimen, preserve renal function, or treat congestive heart failure.

THE FUTURE

Over the last decade, renal artery angioplasty and stenting have become much safer because of better equipment and more experienced operators. However, renal function does not improve or may even worsen in 15% to 20% of patients undergoing stent implantation, and blood pressure is not improved in 20% to 50% of patients after intervention. Two important advances will occur in the future: more accurate ways to predict response to therapy (i.e., identify the patient most likely to demonstrate improvement in blood pressure control and preservation of renal function), and protection of the kidneys during the procedure. The first will occur by measuring such parameters as the resistive index and functional flow reserve. The second will occur with emboli protection devices similar to those used in the carotid and coronary circulations.

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